Design of New Methods for the Synthesis of α-Amino Esters

A Thesis Submitted for the Degree of

Doctor of Philosophy

by

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June-2016

Declaration

I hereby declare that the matter embodied in this thesis entitled "***Design of New Methods for the Synthesis of α-Amino Ester***" is the result of investigations carried out by me at the New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore India under the supervision of **Prof. Sridhar Rajaram** and that it has not been submitted elsewhere for the award of any degree or diploma.

In keeping with the general practice in reporting the scientific observations, due acknowledgment has been made whenever the work described is based on the findings of other investigators. Any omission that might have occurred due to oversight or error in judgment is regretted.

Mr. G. Ramana Reddy
(Ph.D. student)

Certificate

I hereby certify that the matter embodied in this thesis entitled "***Design of New Methods for the Synthesis of α-Amino Ester***" has been carried out by **Mr. G. Ramana Reddy** at the New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India under my supervision and that it has not been submitted elsewhere for the award of any degree or diploma.

Prof. Sridhar Rajaram
(Research Supervisor)

Acknowledgment

First of all, I would like to thank my research supervisor, Prof. Sridhar Rajaram for his mentorship and guidance. I am obliged to him for directing me in each and every step of my projects. The experimental techniques I have learnt from him have been immensely useful throughout my Ph.D. career.

I would like to thank my parents for their unconditional love and without them nothing would have been possible. I thank my wife for her unconditional support. I am happy to be blessed with a daughter during the final stages of my Ph.D. and I also thank my older brother and his family.

I take this opportunity to acknowledge Bharat Ratna Prof. C. N. R. Rao for providing excellent facilities in the department.

I want to take this opportunity to acknowledge the course instructors: Prof. Subi Jacob George, Prof. T. Govindaraju, Prof. Balram, and Prof. Siddhartha Sharma.

I am grateful to my labmates, Mr. Arjun Kumar Chittoory, Mr. Sunil Kumar Kandappa, Ms. Debopreeti Mukherjee, Mr. Chaitanya Krishna, Mr. M. S. Ramesh, and Ms. Anusha S. Avadhani.

I thank Anand and Ankit for proofreading part of my thesis and I would like to thank Ms. Vinutha Lakshman for proofreading and editing my thesis.

I thank all my friends at JNCASR for making my stay a pleasant and enjoyable one. I thank the JNCASR administrative staff, hostel staff, and health center staff for making our stay hassle free.

I would also like to thank Mr. Shiva, Mr. Mahesh, and Mr. Vasu for their help in the characterization of the various compounds.

I thank CSIR for granting me fellowship during my Ph.D.

Thesis Synopsis

Design of New Methods for the Synthesis of α-Amino Esters

Non-proteinogenic α-amino acids are important in catalysis, medicinal chemistry, and biology. Chemical synthesis of these amino acids has been accomplished by several means including hydrogenation, alkylation of glycine imino esters, and Strecker reaction. Important amino acids like *tert*-leucine and phenylglycine derivatives cannot be synthesized using either hydrogenation or alkylation, whereas this is achieved in Strecker chemistry using toxic cyanide anion. To avoid the use of cyanide, an approach to amino acid synthesis that reverses the polarity of reactants in Strecker chemistry has been developed. In this approach, a benzyl-aryl carbonate is used as a carboxyl synthon. This is activated by a nucleophile (DABCO) to generate an activated acyl group and a phenoxide. The phenoxide deprotonates the nitroalkane to generate a nitronate anion which attacks the activated acyl group to generate α-nitroesters. The α-nitroesters were readily reduced to α-amino esters.

Nitronate anion is an ambident nucleophile that can react either through the oxygen atom or carbon atom. An important feature of this protocol is the reaction of nitronate anion with the activated acyl group through the carbon atom. Earlier reports from other groups have shown that nitronate anion prefers to react through the oxygen atom with similar electrophiles like chloroformates and isocyanate to yield nitrile oxides. The reactivity preference of nitronate anions has been explained previously using the HSAB principle. However, the reaction of nitronate anions with chloroformates and isocyanates to yield nitrile oxides cannot be explained by the HSAB principle. Mayr and coworkers have proposed that nitronate anions have a kinetic preference for reacting through the oxygen atoms; in certain cases, the kinetic product is unstable and the thermodynamically stable product is formed by reaction through carbon center. The

formation of nitrile oxide proceeds through the kinetically favorable oxygen attack. To obtain the product of carbon attack, the formation of kinetic product has to be rendered reversible. In our case, the use of a nucleophilic base, DABCO accomplishes this. In the process, we have added to the experimental support for Mayr's hypothesis. The reaction conditions for the synthesis of α-nitro esters were optimized to give high yields. Reactions can be performed in gram-scale without extensive purification of starting material and the product can be obtained in 85% yield and 93% purity after simple extractive workup.

To further understand this reaction, mechanistic studies were initiated. These studies showed that the transiently generated phenoxide was indeed the deprotonating agent. Further, it has been shown that the attack through the carbon atom is rendered irreversible by deprotonation of the product by DABCO. While exploring the scope of various carbonates, it was observed that cation-π interactions play a key role in the activation of carbonate. Indeed, only benzyl-aryl carbonates are useful for these reactions. The activation of these stable carbonates with nucleophiles is an important reaction as these can easily replace the more reactive acid anhydrides in several important reactions. To quantify the role of cation-π interactions, a model reaction that proceeds through the same transition state, viz., the nucleophile mediated hydrolysis of carbonates was used. Using this, rate constants for the hydrolysis carbonates with varying substitution pattern on the benzene ring were obtained. A comparison of the rate constant clearly supports a role for cation-π interactions. A key finding of this study is that an electron donating group on the benzene stabilizes tetra-substituted ammonium ions more than naphthalene. This is in contrast to theoretical studies that have shown that alkali metal cations bind more strongly to naphthalene than phenol. To confirm that nucleophilic attack is indeed the rate determining step, the hydrolysis of carbonates was

performed with DMAP, a weaker nucleophile. These reactions were indeed slower, thereby supporting our hypothesis. Additionally, rate constants were also obtained for carbonates with various phenoxy substituents. This shows that varying the phenoxy group could be an additional handle for tuning the reactivity of benzyl-aryl carbonates. Application of these findings to other reactions is currently in progress.

Finally, a novel method for the synthesis of β-hydroxy-α-amino acids was developed. This was accomplished using a simple aldol reaction between glycine amine esters and an aldehyde. Earlier work in this direction had shown that the reaction is reversible in the case of aromatic aldehydes. Additionally, although good yields and selectivity were obtained for non-aromatic aldehydes, the catalysts required long syntheses. We have shown that these reactions can be performed with reasonable selectivity using a commercially available dimeric cinchona alkaloid catalyst. The reaction scope is restricted to electron-deficient aromatic aldehydes.

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List of Abbreviations

Aq	:	Aqueous
BOC	:	*tert*-Butoxycarbonyl
Bn	:	Benzyl
Bz	:	Benzoyl
Cbz	:	Carbobenzyloxy
DABCO	:	1,4-Diazabicyclo[2,2,2]octane
DBU	:	1,8-Diazabicyclo[5.4.0]]undec-7-ene
DCM	:	Dichloromethane
DMSO	:	Dimethyl sulfoxide
DMAP	:	4-Dimethylaminopyridine
EtOAc	:	Ethyl acetate
Equiv	:	Equivalent
IR	:	Infrared spectroscopy
LDA	:	Lithium diisopropyl amide
M.P.	:	Melting point
NMR	:	Nuclear magnetic resonance
NOBIN	:	2-hydroxy-2'-amino-1,1'-binaphthyl
Nu	:	Nucleophile
TADDOL	:	(4*S*,5*S*)-2,2-dimehtyl-α,α,*α*', *α*'-tetraphenyl-1,3-dioxolane-4,5-dimethanol
Teoc	:	Trimethylsilylethoxycarbonyl
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography

Chapter 1

Synthesis of α-Amino Acids

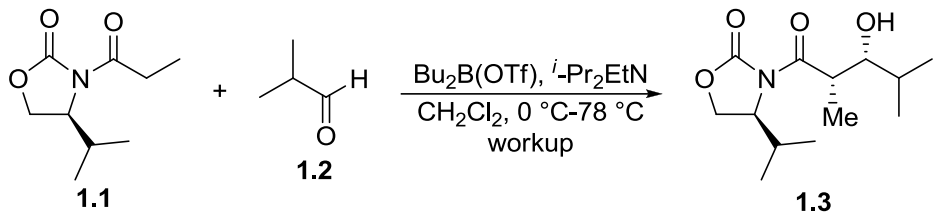
1.1 Introduction

Amino acids are an important class of molecules that have applications in a wide variety of research areas. In the realm of biology, α-amino acids are the building blocks of all proteins. Apart from this, they also act as neurotransmitters, signaling molecules, and antibiotics. Overall, these compounds constitute the second largest component of human muscles, tissues, and cells. One of the important roles of proteins is the catalysis of biochemical reactions. These are accomplished by enzymes, a subset of proteins. Chemists have attempted to mimic these catalysts in the laboratory. In this pursuit, α-amino acids have been transformed into numerous chiral auxiliaries, catalysts, and ligands. Additionally, α-amino acids have found utility in materials science as well as in medicinal chemistry. Due to their importance in diverse fields, ready access to the α-amino acids is essential. This has been accomplished using a variety of approaches. In this chapter, the application of α-amino acids in asymmetric synthesis and medicinal chemistry are described briefly. Following this, we detail some of the important chemical approaches to the synthesis of α-amino acids.

1.2 *α*-Amino Acids in Asymmetric Synthesis

α-Amino acids can be readily reduced to 1,2-amino alcohols. Derivatives of 1,2-amino alcohols have been used extensively as chiral auxiliaries. Oxazolidinones have been used by Evans and coworkers[1] as chiral auxiliaries for the preparation of aldol adduct in an enantiomerically pure form (Scheme 1.1).

Scheme 1.1 Oxazolidinone as a Chiral Auxiliary: Evans Aldol Reaction



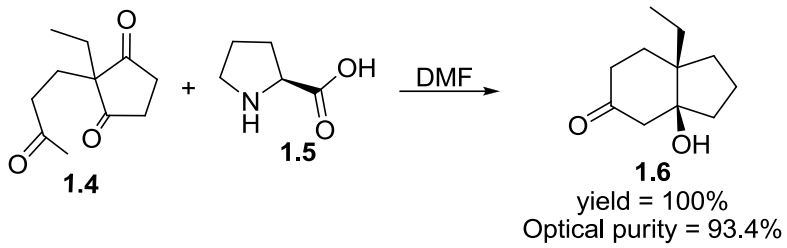
1.2.1 α*-Amino Acids as Catalysts*

α-Amino acids by themselves have been used as catalysts for enantioselective reactions. An asymmetric Robinson annulation using α-amino acid (proline) as organocatalyst has been reported by two groups independently. Hajos and Parrish have used proline (3 mol%) as a catalyst for carrying out the Robinson annulation of triketone **1.4** and isolated the intermediate ketol in 100% yield and 93.4% optical purity[2] (Scheme 1.2). On the other hand, Wiechert and coworkers reported a direct conversion of this ketol to enone[3]. This is used in the synthesis of steriods and terpenoids[4]. Apart from this, proline has also been used as catalyst for intermolcular aldol reactions[5], Michael reactions,[6] and Mannich reactions[7]. Other derivatives of α-amino acids such as cyclic peptides[8] and Schiff bases[9] have been used as organocatalysts in a variety of reactions.

1.2.2 α*-Amino Acid Derivatives as Ligands*

Bis-oxazolines, which are derivatives of α-amino acids, have been used extensively as ligands in metal catalyzed enantioselective reactions. Metal complexes of bis-oxazolines have been used as enantioselective catalysts in allylic substitution, [10] allylic oxidation,[11] Diels-Alder reactions,[12] and Mukaiyama aldol reactions.[13] Schiff bases derived from α-amino acid have been used as ligands for the asymmetric Strecker reaction by Hoveyda and coworkers.[14]

Scheme 1.2 Proline Catalyzed Intramolecular Aldol Reaction



1.3 α-Amino Acids as Medicinally Active Molecules

α-Amino acids which are not encoded into peptides are referred to as non-proteinogenic or non-ribosomal α-amino acids.[15] Some of these α-amino acids are found in ribosomally-synthesized peptides, due to post-translational modification. Marine sponges, bacteria, fungi, plants, and many diverse organisms are the sources of peptides with unusual α-amino acids. These peptides have diverse biological activity and are utilized as antibiotics, immunosupressants, anti-cancer drugs, siderophores, antivirals, anti-inflammatories, and insecticides.

Cyclic α-amino acids isolated from complex alkaloids such as castanospermine[16], slaframine[17], detoxinine[18], telomycin,[19] and polyhydroxylated alkaloids[20] are known as potent glycosidase inhibitors. The analogs of cyclic α-amino acids serve as lead compounds in the development of antiviral agents[21]. In addition to this, cyclic α-amino acids induce conformational constraints in peptides. This has been used for studying the effects of conformation on ligand-receptor interactions.[22]

Cyclosporine A is a cyclic non-ribosomal peptide. It contains 11 α-amino acids and along with a d-amino acid that is generally not seen in nature[23]. Cyclosporine has been extensively used as an immunosuppressive agent for people receiving organ transplants. This drug is also used for the treatment of autoimmune diseases such as psoriasis and rheumatoid arthritis.

Medical researchers have found that l-DOPA is active against Parkinson's disease and it has been used since early 1960.[24] In addition, l-α-methyl-DOPA is used as an antihypertensive drug. Pencillamine, a metabolite of penicillin is on the list of essential medicines issued by World Health Organization[25]. This is used as an immunosuppressant to treat rheumatoid arthritis.

Synthetic α-amino acids such as d-*p*-hydroxyphenylglycine (d-HPG) and d-phenylglycine are produced in several thousand tons per year for the synthesis of antibiotics such as ampicillin and amoxicillin.[26] α-Amino Acids are also part of other drugs such as Ramipril (angiotensin-converting enzyme inhibitor), atazanavir (HIV-protease inhibitor), fluvalinate (insecticide), arsenal (herbicide), and fenamidone (fungicide). Apart from this, α-amino acids have found utility in cosmetics, nutritional supplements, and as feedstock in farming.

Considering the utility of α-amino acids as mentioned above, their synthesis is of great importance. The most common approaches for the preparation of α-amino acids are extraction, fermentation, enzymatic catalysis and chemical synthesis.

1.4 Extraction

Extraction of α-amino acid from protein hydrolysate is used in the production of l-serine, l-proline, l-hydroxy-proline, and l-tyrosine. Large scale production of α-amino Acids using this process is a difficult task and this has led to a search for alternatives.

1.5 Fermentation

The increase in demand for mono sodium glutamate, a flavor enhancer, led to the development of fermentation approaches for the production of α-amino acids. Fermentation is a very simple process and requires a culture medium containing a carbon source such as sugarcane syrup along with nitrogen, sulfur, phosphorus, and trace element

sources. A culture of the production strain is added to the fermentation tank and stirred under particular conditions (temperature, pH, aeration, etc.). The amino acid produced by the microorganism is collected in the recovery section of the fermentation plant. *α*-Amino acids such as l-lysine, l-threonine, l-tryptophan, l-phenylalanine, l-arginine, l-histidine, l-isoleucine, and l-serine can be prepared by fermentation in an economical way. However, attempts for cost-effective production of methionine, a sulfur containing α-amino acid, have not been successful.[27]

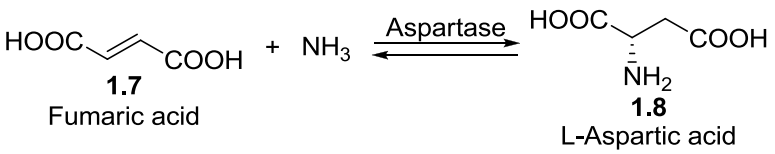
1.6 Enzymatic Resolution

Biocatalytic resolution of racemic α-amino acids is an economically viable process for the preparation of optically pure α-amino acids at an industrial scale. The racemic α-amino acids obtained from Strecker reaction were resolved by employing the Aclyase process.[28] The maximum yield in this process is only 50%. In special cases where Dynamic Kinetic Resolution (DKR) is employed, a theoretical yield of 100% is possible. Alternatively, a theoretical yield of 100% can be obtained by employing enzyme catalyzed asymmetric synthesis.

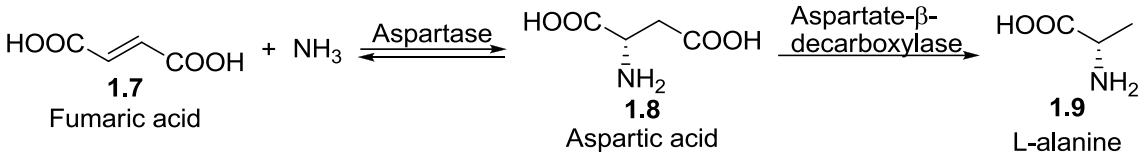
1.7 Ammonia Lyase Processes

l-Aspartate ammonia lyase (aspartase) is one such process for the large scale preparation of l-aspartic acid. This is synthesized from inexpensive fumaric acid by the addition of ammonia (Scheme 1.3).[29] l-aspartic acid is extensively used in the food industry (mainly in Japan). l-Alanine is mainly used in enteral and parenteral nutrition and is also used as a food additive due to its sweet taste and bacteriostatic properties. This is produced by the decarboxylation of aspartic acid by aspartate-β-decarboxylase(Scheme 1.4).[30] About 500 tons of this amino acid is produced annually.

Scheme 1.3 Enzyme Catalyzed Asymmetric Synthesis



Scheme 1.4 l-Alanine Synthesis via Chemo Enzymatic Asymmetric Synthesis

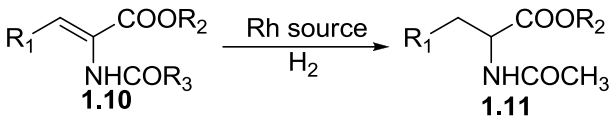


A large number of non-coded α-amino acids have found applications in many fields including catalysis and medicinal chemistry. These non-coded α-amino acids are not easily accessed by the bio-chemical methods mentioned above. Chemical methods of synthesis provide the most efficient means to access these amino acids. A large amount of effort has gone into developing novel methods for the synthesis of α-amino acids. Among these, the methods that have the widest scope are hydrogenations, alkylation of glycine imine esters, and the Strecker reaction.

1.8 Asymmetric Hydrogenation:

The enantioselective hydrogenation of enamides is one of the earliest methods for the preparation of scalemic α-amino acids and is employed by industries. A large number of ligands have been used for the asymmetric hydrogenation of enamides. Table 1.1 shows some of the efficient ligands (>95% ee) for the asymmetric hydrogenation of enamides. Typically, cationic Rhodium complexes and low hydrogen pressures are employed. Substrate to catalyst ratio as high as 50000:1 has been employed without any effect on selectivity and yields.

Table 1.1 Asymmetric Hydrogenation of Enamides



1.10 **1.11**

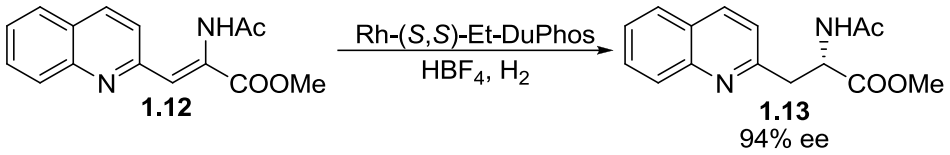
A:R1 = H, R_2 = CH_3, R_3 = CH_3
B: R1 = Ph, R_2 = H, R_3 = CH_3
C: R1 = Ph, R_2 = CH_3, R_3 = CH_3
D: R1 = Ph, R_2 = CH_3, R_3 = C_6H_5

ligand	subs	S/C ratio	reaction conditions	%ee (config)	ref
(*R,R*)-DIPAMPP	C	1000	MeOH, 50 °C, 3 atm H_2	97 (*R*)	41b
(*R,R*)-NORPHOS	B	95	MeOH, rt, 1.1 atm H_2	96 (*R*)	44
(*R,R*)-PYRPHOS	C	50000	MeOH, rt, 61 atm H_2	96.5 (*S*)	38
(*S*)-BINAP	D	100	EtOH, rt, 3 atm H_2	100 (*S*)	45
(*S,S*)-Et-Du Phos	A	50440	MeOH, rt, 2 atm H_2	>99 (*S*)	39
(*S,S,R, R*)-Tang Phos	C	10000	MeOH, rt, 1.3 atm H_2	99.8 (*S*)	40
(*S*)-MonoPhos	A	20	EtOAc, rt, 1 atm H_2	99.6 (*R*)	43

Chiral ligands such as PYRPHOS,[31] EtDuPhos,[32] TangPhos,[33] DPAMPP,[34] BoPhoz,[35] MonoPhos,[36] NORPHOS,[37] and BINAP[38] have been used to obtain high levels of enantio-induction.

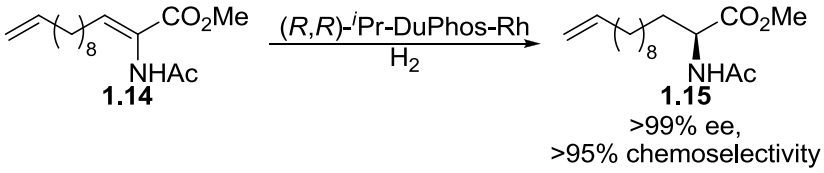
Asymmetric hydrogenation of enamides containing coordinating groups such as pyridine is sluggish since pyridine coordinates with the metal and the catalytic activity of metal decreases. This problem can be partially solved by using tetrafluoroboric acid in the reaction mixture. [39] Tetrafluoroboric acid protonates the Lewis basic site and prevents coordination of the Lewis basic site to the metal center. Additionally, the conjugate base is a non-coordinating counter ion and does not bind rhodium. Tiffin and coworkers have developed a protocol for the asymmetric hydrogenation of quinoline enamide using this approach (Scheme 1.5) and have obtained quinolylalanine in 94% ee.[40] However, this method failed to give good enatiomeric excess (ee) in the preparation of 2-pyridylalanine and isoquinolylalanine.

Scheme 1.5 Asymmetric Hydrogenation of Quinoline Enamide



In the case of substrates with more than one double bond, asymmetric hydrogenation with the EtDuphos system is highly chemoselective. This could be due to the chelation of the active Rh complex through the alkene and the carbonyl oxygen of the N-acyl group. This directs the hydrogenation preferentially to the enamide double bond (Scheme 1.6).[41] Hydrogenation of α,γ-dieneamides with an Et-Duphos-Rh catalyst gave the required α-amino acid in over 98% chemoselectivity.[42] The stereochemistry at the α,β double bound is critical for obtaining good enantioselectivity with the Z-isomer giving very high ees. On the other hand, with the E-isomer, yields are low and enantioselectivity is poor.[43] The major drawbacks of this methodology are that substrates with strong coordinating groups are not tolerated and α,α-disubstituted amino acids cannot be prepared using this methodology.

Scheme 1.6 Chemoselective Hydrogenation of Double Bond

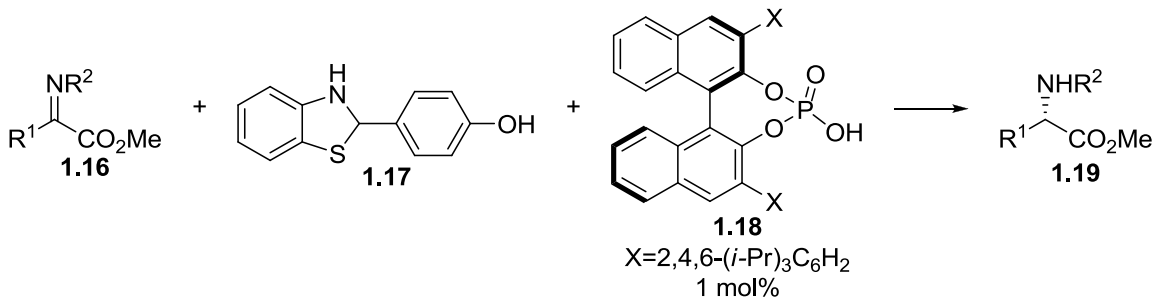


Hydrogenation of imine esters is an alternative procedure for the preparation of α-amino acids. Unlike hydrogenation of C-C double bonds and ketones, the stereoselective hydrogenation of imines is not easy owing to the rapid inter-conversion of E and Z isomers.[44] This has precluded the extensive use of this method for the preparation of α-amino acids. However, several methods that give reasonable results have been developed. Liu and coworkers have shown that iridium catalyzed asymmetric hydrogenation of oximes bearing an ester gave excellent enantioselectivities (up to 93%

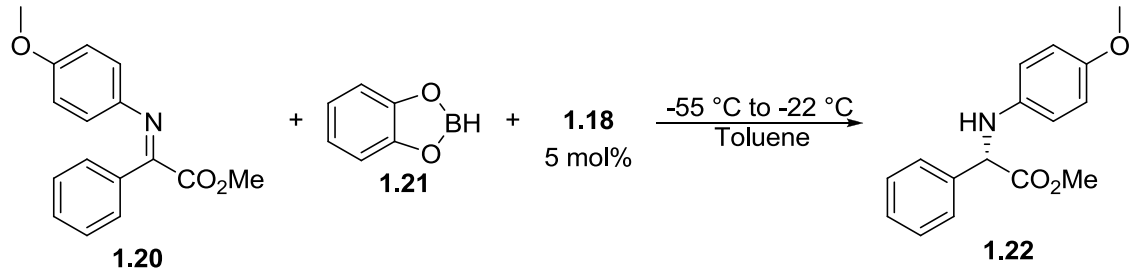
ee). However, the yields were low (19%).[45] Alternatively, hydrosilylation of C-N double bond of nitrone ester with a ruthenium catalyst gave an ee of 91% with a yield of 21%.[46] Uneyama and coworker have reported on the Pd catalyzed reduction of α-fluorinated iminesters with good enantioselectivity (ee: 61%-91%) and good yields (75%-99%) in product. However, this methodology is applicable only to α-fluorinated iminesters.[47] N-Phosphinyl iminoesters have been reduced with dimethylphenyl silane as the reducing agent in the presence of Re(V)-oxo complex as the catalyst with good yields and enantioselectivity (yield: 47%-83%, ee: 95%-99%). This method is limited to α-phenyl phosphinoyl iminester.[48]

Due to the limitations of metal catalyzed reduction of iminoesters, several groups have sought organocatalytic approaches for the synthesis of α-amino esters. Hantzsch esters have been used as a hydrogen source for the asymmetric reduction of *β,γ*-akynyl-α-imino esters in the presence of chiral phosphoric acid as chiral catalyst.[49] The You and Antilla groups have independently reported on this approach to α-amino esters, which gave good ees and yields with various substrates.[50] However, purifying the α-amino ester from the reaction mixture which contained a pyridine derivative as the by product was a difficult task. Benothiazoline has also been used as a hydride source for the asymmetric hydrogenation of iminesters in the presence of chiral Brønsted acid. However, purification of product from byproducts is problematic with this reagent as well.[51] This problem was overcome by introducing a hydroxyl group on the aryl ring (Scheme1.7). Boranes have also been employed for the asymmetric reduction of iminesters in the presence of chiral Brønsted acid catalyst. In this case, the products were obtained in near quantitative yields with ees reaching 94% (Scheme 1.8).[52]

Scheme 1.7 Bezothiazoline Mediated Reduction of Imine esters



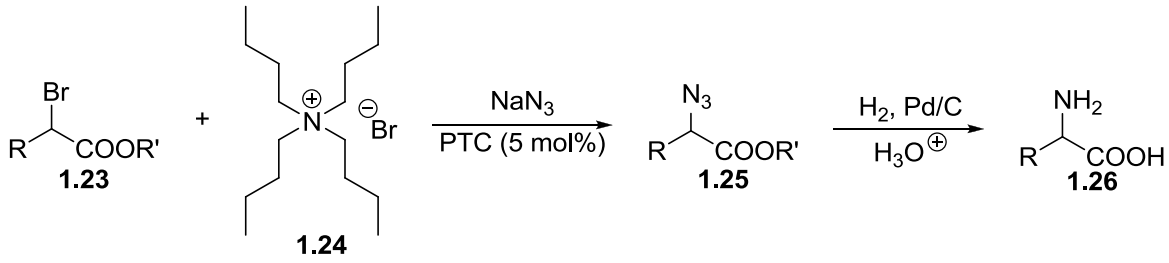
Scheme 1.8 Borane Mediated Reduction of Imine esters



1.9 Asymmetric Alkylation:

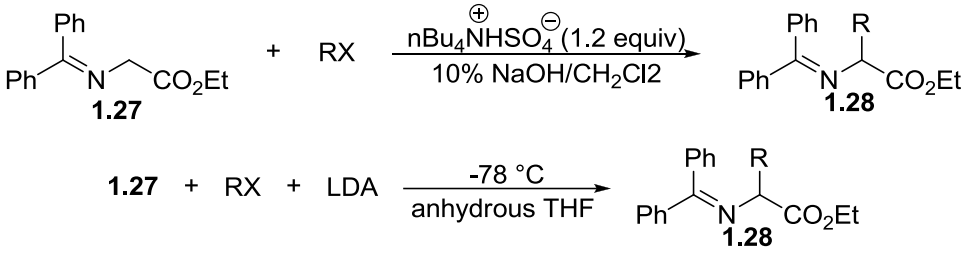
The amination of α-halogenated esters was one of the earliest methods employed for the preparation of α-amino esters. Nakajima and coworkers pioneered the use of phase-transfer catalysis for the nucleophilic substitution reaction between α-bromoesters and sodium azide. Reduction of the azido ester resulted in the formation of α-amino acids (Scheme 1.9).[53]

Scheme 1.9 Nucleophilic Substitution of Azide



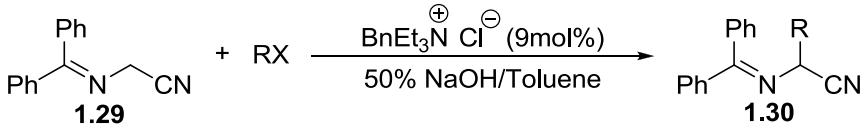
An alternate approach was developed by O'Donnell and coworkers wherein glycine imine esters were used as the substrate.[54] Alkylation of these imine esters was carried out in the presence of phase transfer catalysts to yield α-amino esters. This avoids the use of azide, a reagent prone to explosion. Apart from the use of phase transfer catalysts, alkylations have also been carried out under anhydrous conditions. In the case of anhydrous conditions, organic bases like lithium diisopropylamide were used at -78 °C for generating the anion. This was followed by the addition of an alkyl halide (Scheme 1.10).[54]

Scheme 1.10 Alkylation of Glycine Imine esters.



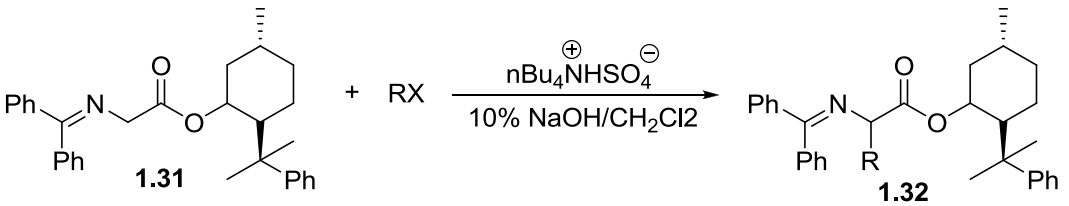
Alternatively, the anion of glycine imine esters can be obtained by employing a phase transfer reagent. The experimental conditions for employing phase transfer catalysts are simple, mild, and use an environmentally benign reagent. This method can be easily employed for large scale reactions. Initially, the O´Donnell group reported on the alkylation of benzophenone imine of aminonitrile **1.29** in the presence of benzyltriethylammonium chloride as a phase transfer catalyst (Scheme 1.11).[55] Ion exchange of the chloride with NaOH resulted in the transfer of the highly basic hydroxide anion to the organic phase. This facilitated the deprotonation of the aminonitrile.

Scheme 1.11 Alkylation of Imine nitriles

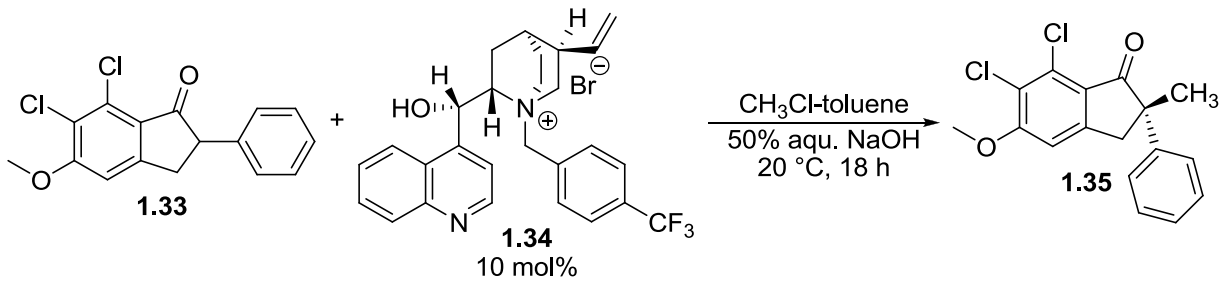


Based on this work, Langström *et.al* employed (-)-8-phenylmenthol as a chiral auxiliary for the diastereoselective alkylation of glycine imine esters under phase transfer conditions (Scheme 1.12).[56] However, the diastereoselectivity of the reaction was not great. Later on, Nájera and Guillena employed an imidazolidinone as the chiral auxiliary and improved the diastereoselectivity.[57] Engaging a chiral phase transfer catalyst for the preparation of α-amino acids would be an attractive alternative methodology. Initial attempts for asymmetric alkylation of active methylene compounds were not successful. In related work, the Merck group used benzyl cinchoninium bromide as a chiral phase transfer catalyst for the methylation of 6,7-dichloro-5-methoxy-2- phenyl-1-indanone and obtained an ee of 92% (Scheme 1.13).[58] Based on this work, O´Donnell attempted the alkylation of glycine imine ester with benzyl cinchoninium chloride and obtained the α-amino acid in moderate selectivity (scheme 1.14). The opposite enantiomer of α-amino acid could be obtained by simply switching the catalyst from cinchonine to cinchonidine. Recrystallization of alkylated product followed by hydrolysis for deprotection led to the formation of α-amino acid with enantioselectivity greater than 99% ee and with an overall yield of 50%. (Scheme 1.14).[59]

Scheme 1.12 Diastereselective Alkylation of Imine Ester



Scheme 1.13 Asymmetric Alkylation of Indanone derivative



Scheme 1.14 Asymmetric Alkylation of Glycine Imine Ester

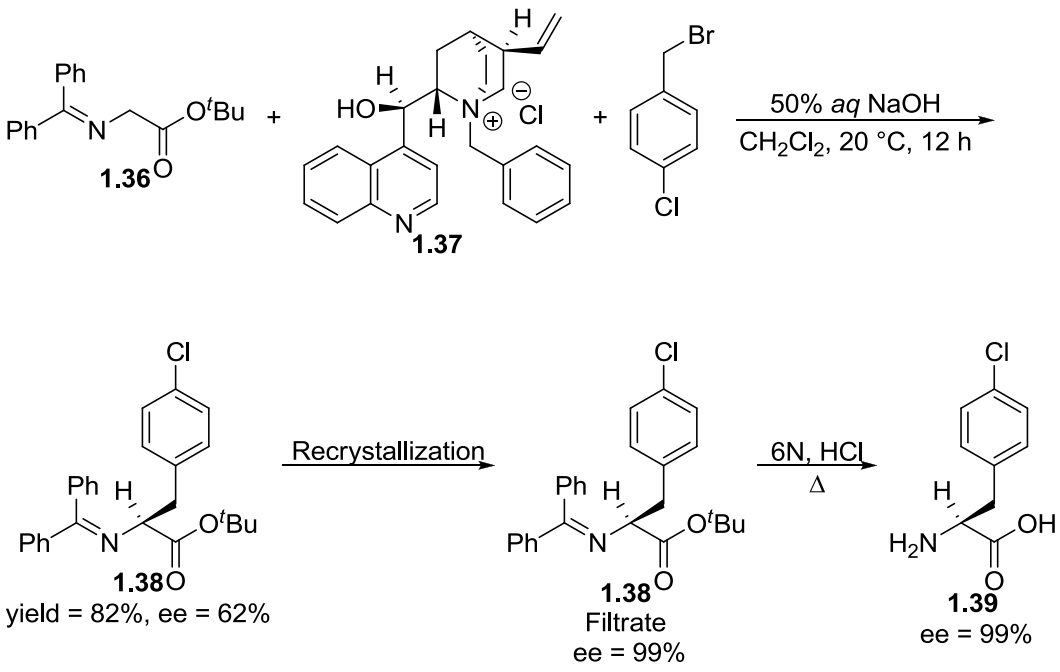
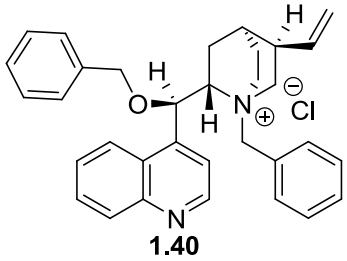


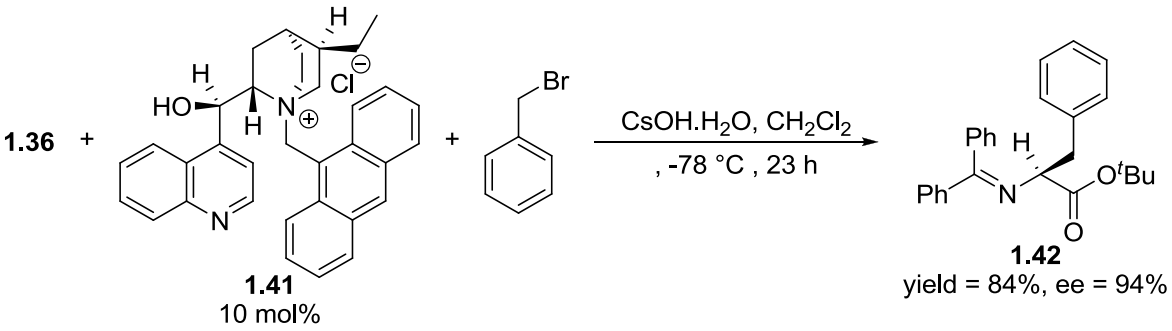
Figure 1.1 O-Alkylated Cinchona Salt Formed in the Reaction Mixture



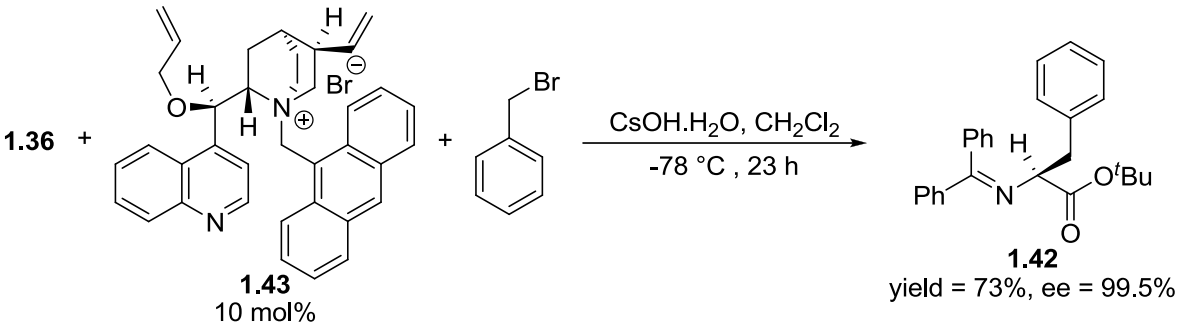
Under the reaction conditions, the catalyst was converted to the O-benzylated product (Figure 1.1). O'Donnell has shown that this is the catalytically active species.[60] The chiral catalyst employed by O´Donnell can be obtained with ease and the starting materials for the preparation of catalyst are cheap. The only disadvantage is that the product is obtained with moderate selectivity. However, recrystallization of the adduct led to greater than 99% ee, albeit with a reduction in yield.

In a quest to obtain better enantiselectivities, Lygo and Wainwright had screened catalysts with bulkier groups like anthracenylmethyl and dihydro anthracenylmethyl instead of benzyl group. The dihydroanthracenylmethyl cinchonine salt gave up to 94% ee and 85% yield (Scheme 1.15).[61] In an effort to improve ees, Corey and coworkers employed O-allyl-N-anthracenylmethyl cinchonidinium salt as chiral phase transfer catalyst and solid $CsOH.H_2O$ as base in DCM solvent. Due to the absence of water, the reactions could be performed at lower temperatures.[58,59] When glycine imine ester was treated with benzyl bromide at -78 °C under these conditions, the product was obtained in 99.5% ee and 73% yield (Scheme 1.16).[62]

Scheme 1.15 Dihydrocinchonidine Salt as Phase Transfer Catalyst



Scheme 1.16 Solid Liquid Phase Transfer Catalyst



The development of dimeric cinchona alkaloid ligands for the Sharpless asymmetric dihydroxylation increased the substrate scope and selectivity. Inspired by this, Jew and coworkers prepared three dimeric ammonium salts from α,α'-dibromo-*o*-xylene, α,α'-dibromo-*m*-xylene and α,α'-dibromo-*p*-xylene. Among these, the catalyst obtained from *m*-xylene was the most efficient (Scheme 1.17).[63] Further, a trimeric

catalyst was prepared (Figure 1.2) and employed for the asymmetric alkylation of glycine imine ester with different halides and obtained good enantiselectivities and yields. The authors believe that the glycine enolate in the reaction mixture would be on the A site rather than on the B site due to the steric hindrance from the cinchona alkaloid unit on the B site (Figure 1.2).

Scheme 1.17 Dimeric Cinchona Alkaloid Catalytic System

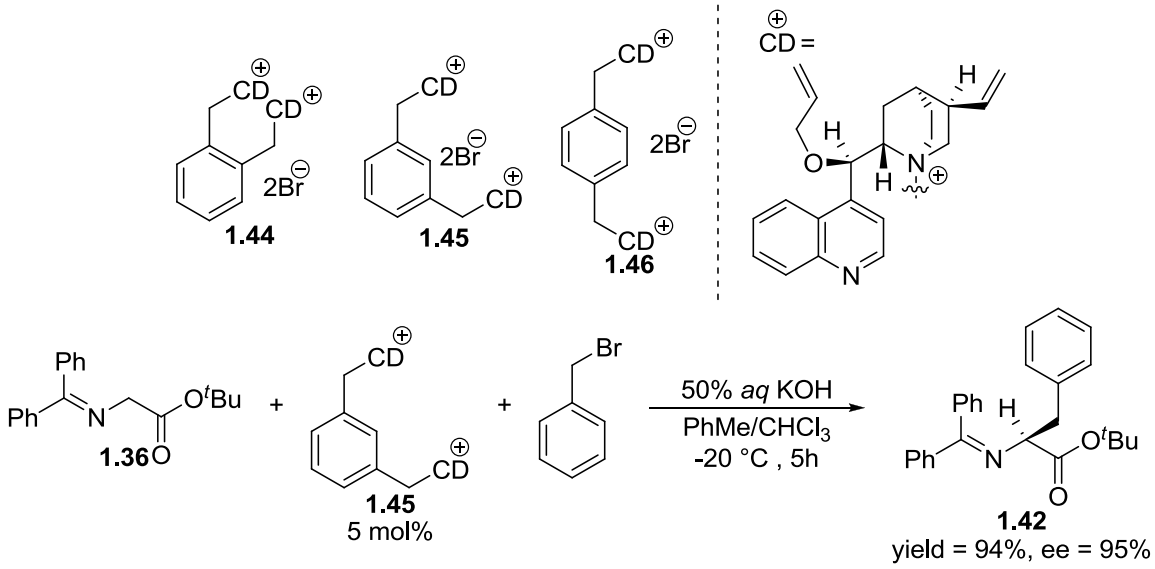
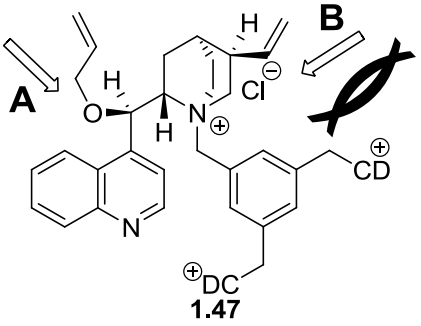


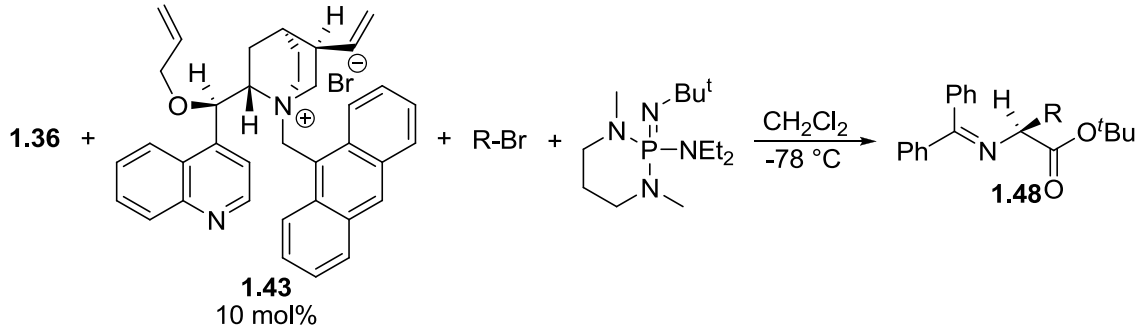
Figure 1.2. Jew's Trimeric Catalyst.



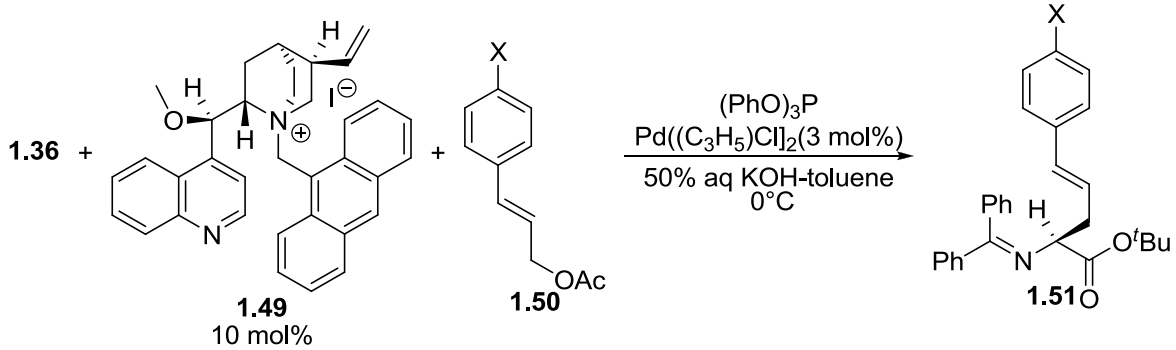
Heterogeneous reactions typically require efficient stirring for maximum efficiency. In the case of these phase transfer catalysts, it has been observed that stirring is not necessary for optimal yield or ee. However, the reaction is slower in the absence of stirring. O´Donnell and coworkers have employed Schwesinger bases along with chiral phase transfer catalyst for the asymmetric alkylation of glycine imine esters under

homogeneous conditions. The Schwesinger base generates small amounts of the ester enolate which immediately reacts with the alkyl halide and drives the equilibrium in the forward direction (Scheme 1.18).[64] For large scale enantioselective synthesis of α-amino acids, easily available and reusable catalysts like polymer bound catalysts are preferred. Nájera and coworkers prepared a Merrifield resin bound phase transfer catalyst by N-alkylation of cinchonine and cichonidine. They have used these reusable catalysts for asymmetric alkylation of glycine imine esters under phase transfer conditions. In this case, the enantioselectivities were moderate.[65] Cahard and coworkers improved the selectivity greatly by attaching Merrifield resin on the hydoxyl group of cinchonine alkaloid.[66] Takemoto reported asymmetric alkylation of glycine imine esters with allylic acetate mediated by the combination of Pd catalyst and chiral phase transfer catalyst (Scheme 1.19). [67]

Scheme 1.18 Alkylation of Glycine Imine Ester under Homogeneous Conditions

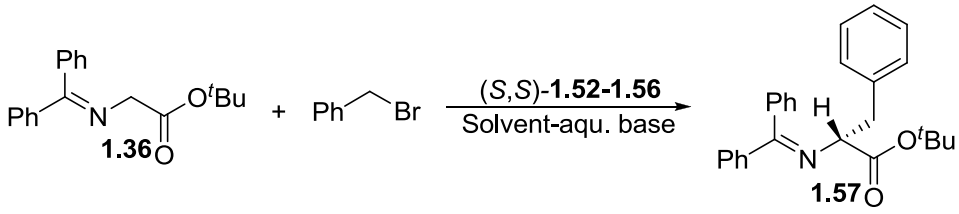


Scheme 1.19 Pd Catalyst Mediated Alkylation of Glycine Imine Ester



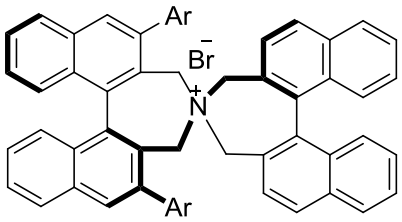
In all of the above reactions, the chiral phase transfer catalyst was derived from cinchona alkaloids. The alkyl group on the nitrogen is the only moiety that can be easily varied in these systems. Thus, the catalyst structure is not easily amenable to rational tuning. To overcome this problem, Maruoka and coworkers designed C_2-symmetric chiral phase transfer catalyst derived from commercially available *S*-binaphthol. Based on this scaffold, they prepared five catalysts by varying substituents at the 3,3'-positions of one of the binaphthyl unit of the catalyst and these catalyst were screened for the alkylation of glycine imine ester (Table 1.2). When the catalyst **1.52** was employed, the corresponding alkylated product was obtained in 76% yield with 73% ee (Table 1.2, entry 1). By employing the catalyst **1.53**, the product was obtained in 41% yield with 81% ee (Table 1.2, entry 2). This shows that aromatic substitution at 3,3'-position on one of the binaphthyl helped greater enantioselection. When toluene was used as the solvent and reaction temperature was reduced to 0 °C, the enantioselectivity of the product increased (88% ee, Table 1.2, entry 3). The reaction was completed in 30 min when 50% aq. KOH was used (Table 1.2, entry 4). As the steric size on the catalyst at 3,3'-position increased, enantioselectivity of the product increased (Table 1.2, entry 5 and 6). When the catalyst **1.56** was employed the selectivity of the product reached 99% ee, but the yield was low (Table1.2, entry 8). This could be due to the oxidation of enolate anion of glycine imine ester with the aerobic oxygen. This was rectified by performing the reaction under argon atmosphere (Table 1.2, entry 9). Moreover, the catalyst loading could be reduced to 0.2 mol% without a detrimental effect on selectivity (Table 1.2, entry 10).[68] The reactions under phase transfer conditions are generally carried out with mechanical stirring. In order to obtain sufficient reaction rate, the reaction mixture was stirred vigorously at higher rpm. This resulted in reproducibility problems and inefficiency in the case of large scale reactions.

Table 1.2 Screening of Maruoka Catalysts for Various Substrates



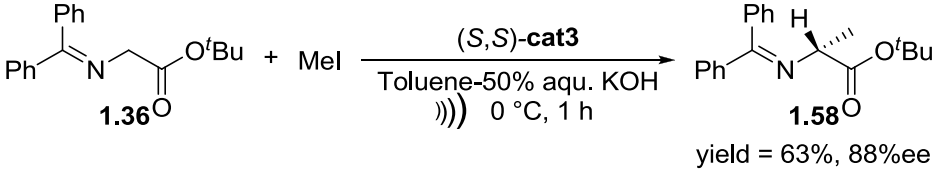
entry	catalyst	mol%	solvent	base	condition °C, h	% yield	%ee
1	**1.52**	1	benzene	50% NaOH	rt, 10	76	73
2	**1.53**	1	benzene	50% NaOH	rt, 10	43	81
3	**1.53**	1	toluene	50% NaOH	0, 5	62	88
4	**1.53**	1	toluene	50% KOH	0, 0.5	82	89
5	**1.54**	1	toluene	50% KOH	0, 0.5	95	96
6	**1.55**	1	toluene	50% KOH	0, 0.5	91	98
7	**1.55**	0.2	toluene	50% KOH	0, 12	81	98
8	**1.56**	1	toluene	50% KOH	0, 2	79	99
9	**1.56**	1	toluene	50% KOH	0, 12	90	99[a]
10	**1.56**	0.2	toluene	50% KOH	0, 48	72	99[a]

[a] Under argon atmosphere



(S,S)-**1.52**(Ar = H), **1.53** (Ar = Ph), **1.54** (Ar = β-Np)
1.55 (Ar = 3,5-Ph_2-Ph), **1.56** (Ar = 3,4,5-F_3-Ph)

Scheme 1.20 Effect of Ultrasonication on Reaction Rate

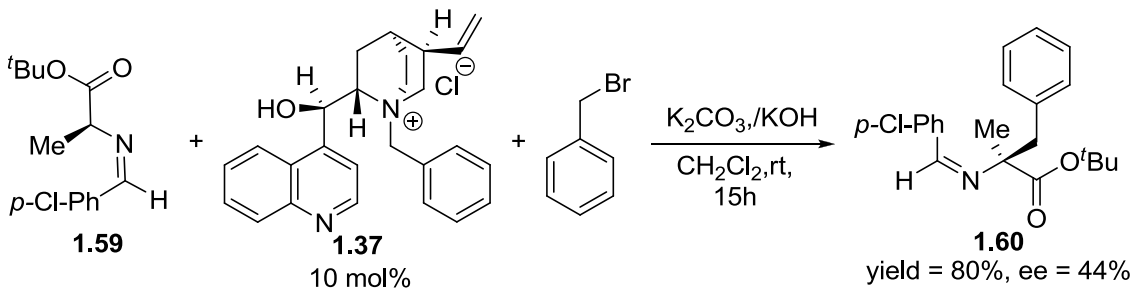


yield = 63%, 88%ee

Ultrasonication has gained importance in this regard and has been applied in a number of heterogeneous reactions.[69] Along the same lines, Maruoka employed ultrasonication for the alkylation of glycine imine ester under phase transfer conditions and observed that the rate increased by eight times compared to normal stirring conditions (Scheme 1.20).[70]

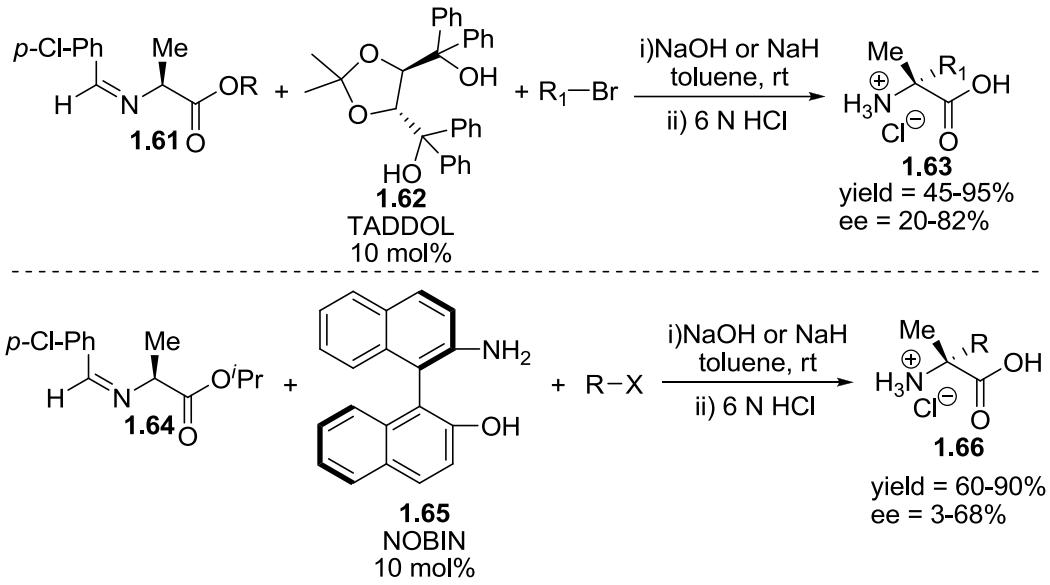
Non-proteinogenic α,α-disubstituted α-amino acids are an important class of α-amino acids. These compounds when incorporated into peptides reduce the conformation space available for the peptide. In their original report, O´Donnell and coworkers accomplished the monoalkylation of glycine imine ester **1.27** in the presence of chiral phase transfer catalysts. It was shown that the *p*K_a of the monoalkylated species was significantly higher than the reactant and this prevented racemization of the product as well as formation of the dialkylated product.[71] The monolkylated product is likely to experience $A^{1,3}$ strain during deprotonation and this prevents dialkylation. It was hypothesized that an aldimine would not experience this strain and is therefore likely to undergo dialkylation. To test this, a Schiff base was prepared from alanine *tert*-Butyl ester and 4-chloro benzaldehyde (**1.59**). Alkylation of this substrate was performed using chiral phase transfer catalyst. Examination of different bases showed that the best result was obtained by using mixture of K_2CO_3 and KOH (Scheme 1.21).[72]

Scheme 1.21 Alkylation of Monoalkylated Glycine Imine Ester with Phase Transfer Catalyst

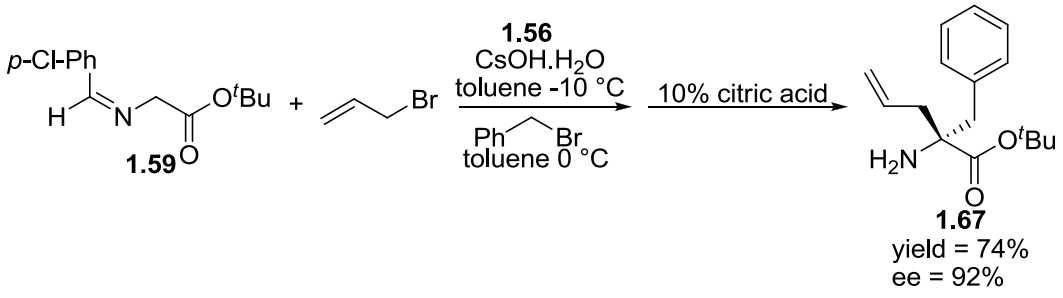


Chiral catalysts like TADDOL (**1.62**) and NOBIN (**1.65**) promoted selective alkylation of alanine-derived imine in the presence presence of solid NaOH or NaH at room temperature (Scheme 1.22).[73] When a stoichiometric amount of TADDOL was used, better enantioselectivities were obtained. Further, Maruoka and coworkers envisioned sequential addition of alkylating reagents to the glycine Schiff base of aryl aldehyde in the presence of a phase transfer catalyst obtained from binapthol. This reaction was performed by treating the Schiff base with an allylbromide in the presence of the binapthol-derived catalyst. $CsOH.H_2O$ was used as a base the reaction was performed in toluene at -10 °C for 3.5 h. Then, benzyl bromide was added at 0 °C and stirred at this temperature for 0.5 h and this led to the formation of dialkylated product (Scheme 1.23).

Scheme 1.22 Alkylation of Monoalkylated Glycine Imine Ester with Organocatalyst



Scheme 1.23 One Pot Dialkylation of Glycine Imine Ester



Asymmetric hydrogenation and asymmetric alkylation methodologies suffer from limited substrate scope. They cannot be employed for preparing α-aryl-α-amino acids and α-quaternary amino acids. Moreover, the catalysts used in these reactions are expensive. Some of these limitations can be overcome by employing Strecker reaction.

1.10 Strecker Reaction

The Strecker reaction is one of the oldest known methods for the synthesis of α-amino acid. This method is employed for the synthesis of α-amino acids in industries (Scheme 1.24).[74] Recently, several groups have reported on an enantioselective version of this reaction. Lipton and coworkers have shown that a cyclic dipeptide could catalyze a Strecker reaction.[75] The reaction gave good ees for a very limited set of substrates. Along with the development of enantioselective reactions, one of the key areas of research has been directed towards finding alternatives to HCN. Hydrogen cyanide is an extremely toxic reagent and is difficult to handle under ambient conditions as it boils at 25 °C. Hence, many alternative cyanide reagents were developed for the Strecker reaction. Jacobsen and coworkers have reported on employing trimethylsilyl cyanide (TMSCN) as cyanide source in the presence of a thiourea catalyst for the preparation of optically pure α-amino acids through Strecker reaction. They screened several thiourea catalysts for hydrocyanation of imines and found that in the case of **1.76** high yields and enantioselectivties were obtained for the product (Table 1.3).[76]

Scheme 1.24 Strecker Reaction

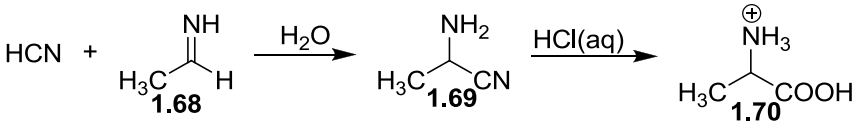
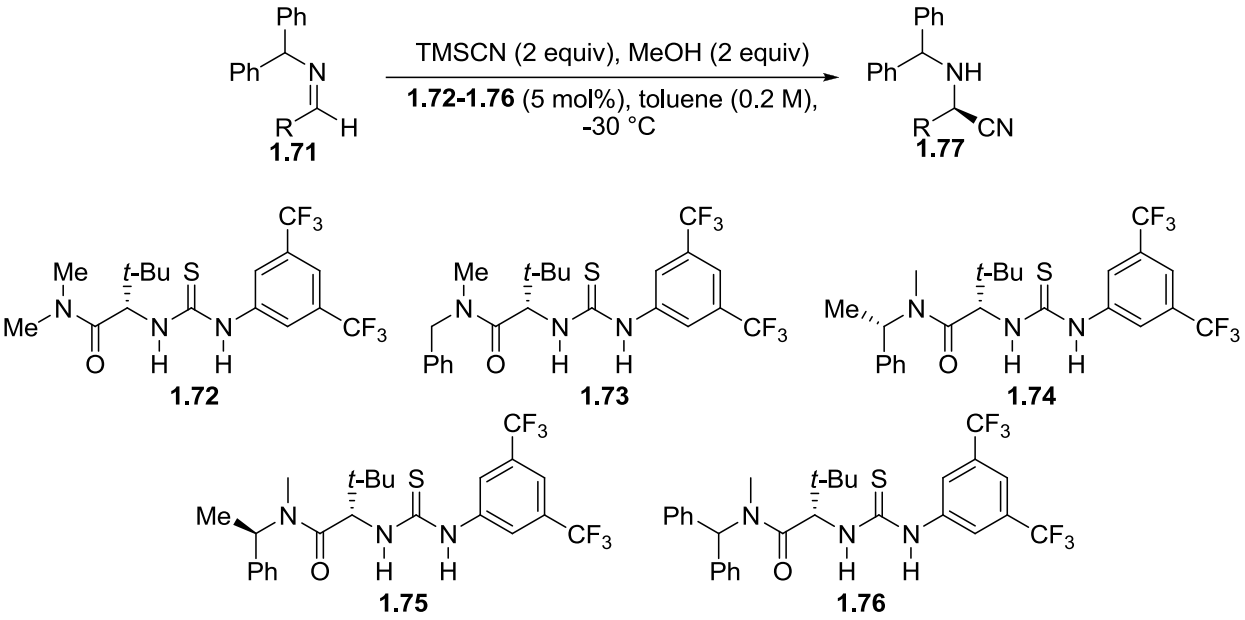


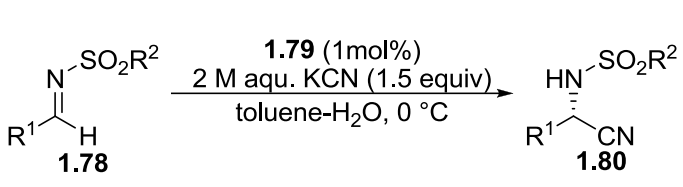
Table 1.3 TMSCN as Cyanating Reagent



Entry	Catalyst	Enantiomeric excess (%) R = *t*-Bu	Enantiomeric excess (%) R = C_6H_5
1	**1.72**	-14	41
2	**1.73**	30	86
3	**1.74**	58	90
4	**1.75**	77	97
5	**1.76**	93	98

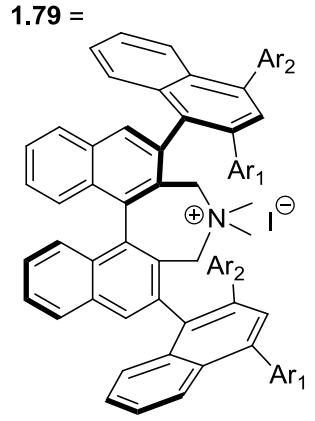
The substrate scope for this reaction was broad and includes imines derived from aliphatic aldehydes and cycloalkyl aldehydes. When TMSCN was used, certain reactions were carried out at lower temperature. Further, TMSCN is expensive and generates stoichiometric amount of cyanide upon reacting with alcohol. This limits its applicability to large scale reactions. Alternatively, Maruoka and coworkers used inexpensive KCN as a source of cyanide for the hydrocyantion of imines in the presence of a phase transfer catalyst (Scheme 1.25). This method is restricted to aliphatic aldimines.[77] When quinine was employed as a catalyst, only aromatic substrates were tolerated. This was in contrast to reactions carried out with phase transfer catalysts (Scheme 1.26).[78]

Scheme 1.25 Phase Transfer Catalyst Employed Asymmetric Strecker Reaction



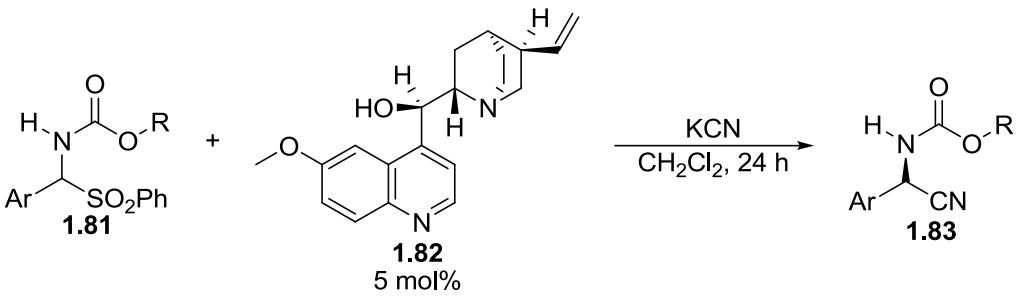
R^1	yield%	ee%
i-Pr	88	97
$Ph(CH_2)_2$	85	93
$(CH_3)_2CHCH_2$	82	88
t-Bu	94	94

R^2=Mesityl



Ar_1=Ar_2=*p*-CF_3-C_6H_4

Scheme 1.26 Quinine Catalyzed Asymmetric Strecker Reaction



For large scale reactions, Jacobsen and coworkers employed catalyst **1.76** under biphasic conditions. Using this method they were successful in preparing *R*-tert-leucine and related compounds in multi-gram scale (Scheme 1.27).[83] *R*-tert-leucine is found in medicinally active molecules like atazanavir and in ligands like (*S*)-*t*-Bu-Phox which is used in asymmetric catalysis.

Toru and coworkers have employed diethyl aluminum cyanide as a cyanide source for the stereoselective preparation of α-amino acids using a Strecker reaction. They have employed different chiral additives for carrying out the reaction (Figure 1.3). When the reaction was carried out in the absence of chiral catalyst at -78 °C, only trace amount of product was obtained (Table1 1.4, entry 1).

Scheme 1.27 Large Scale Preparation of α-Amino Acid

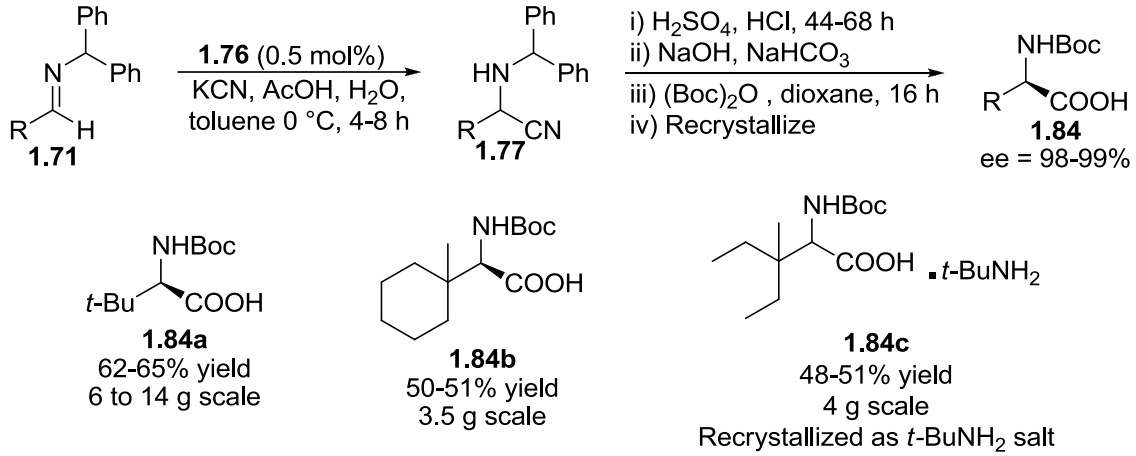
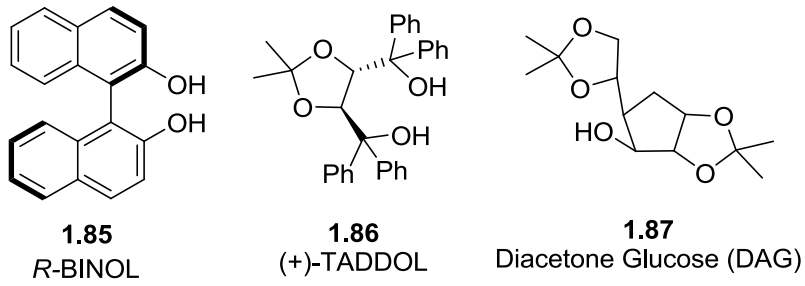


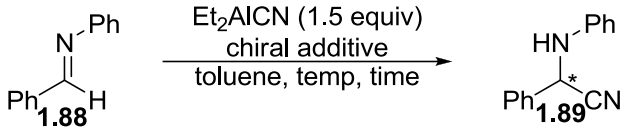
Figure 1.3 Catalyst Screened for Asymmetric Strecker Reaction with Et_2AlCN



However, when the reaction was performed in the presence of **1.85**, **1.86**, and **1.87** (Table 1.4, entry 2, 3, 4), the reaction proceeded smoothly and was completed in 0.5 h. While the products were obtained in good yields, the enantioselectivities were moderate. The product was formed with good optical purity when **1.85 (**1.2 equivalent) and Et_2AlCN (1.5 equivalent) were used (Table 1.4, entry5). Surprisingly, when 4.5 equivalent of **1.85** was used the product was obtained with the opposite configuration (Table 1.4, entry 6).[79]

In the case of Et_2AlCN and TMSCN, reactions were performed under anhydrous conditions as this reagent decomposes in the presence of moisture. Kobayashi and coworkers reported on the use of stable tributyltin cyanide reagent as cyanide source in the Strecker reaction. The tributyltin cyanide is stable in aqueous solutions and the reaction was catalyzed by scandium triflate.

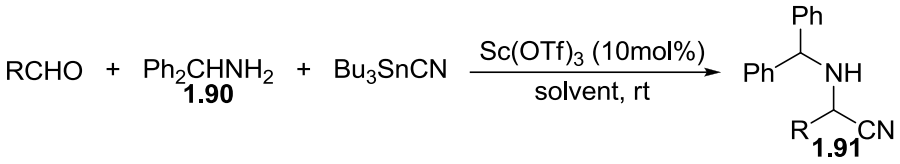
Table 1.4 Optimization of Asymmetric Strecker Reaction with Et_2AlCN



Entry	Chiral additive	Temp	Time (min)	yield (%)	ee (%)
1	None	-78 °C	90	Trace	-
2	**1.85** (1.5 equiv)	-78 °C	30	90	48
3	**1.86** (1.5 equiv)	-78 °C	30	91	35
4	**1.87** (3.0 equiv)	-78 °C	30	96	22
5	**1.85** (1.2 equiv)	-78 °C	30	96	61
6	**1.85** (4.5 equiv)	-78 °C	360	97	-52

Initially, the reaction was performed in a 1:1 mixture of acetonitrile and toluene as solvent with in situ formation of the imine. Under these conditions, the highest yield of 84% was obtained with the benzaldehyde. The reaction does not require any dehydrating agent.[80] When the reaction was performed in water, there was no effect on yield (Table 1.5**)**. The reaction is compatible with aromatic as well as alkyl aldehydes (Table 1.5). The use of organo-tin reagents is limited by their toxicity. However, in this method all the tin reagents from the reaction mixture are recovered during workup. Alternatively, List and coworkers have reported on the use of acetyl cyanide as cyanide source for the asymmetric reaction.[81]

Table 1.5 Strecker Reaction with Bu_3SnCN



1.90 **1.91**

Entry	R	yield (%) [in MeCN-toluene (1:1)]	yield(%) in H_2O
1	Ph	88	88
2	PhCH=CH	83	84
3	2-Furyl	88	89
4	$PhCH_2$	94	79
5	Bu	84	94
6	c-C_6H_{11}	86	94

In earlier work, Dornow and Lüpfert reported on the use of benzoyl cyanide as cyanide source for the preparation of α-amino nitriles by Strecker reaction.[82] This reaction works in the presence of catalytic amount of triethyl amine. Based on this, List and coworkers have screened several oraganocatalysts (Figure 1.4) for the hydrocyanation of aldimines. Quinine catalyzes the reaction readily and the product was obtained in 70% yield with very little selectivity (Table 1.6 entry 1). When the reaction was performed in the presence of phenyl phosphinic acid, the yield increased from 70% to 88%. Following this, they screened binol-based Brønsted acids and found that the reaction (Table 1.6, entry 3) proceeded with moderate ees. When an achiral thiourea catalyst was used, the product was obtained in almost quantitative yield (Table 1.6, entry 4). Screening of chiral thiourea catalysts (Table 1.6) showed that with Jacobsen catalyst, the product was obtained in almost enantimerically pure form (Table 1.6, entry 7). Both aliphatic and aromatic aldimines gave the corresponding α-amino nitrile products in good yields and enantioselectivities.

Figure 1.4 Catalysts Screened by Benjamin List

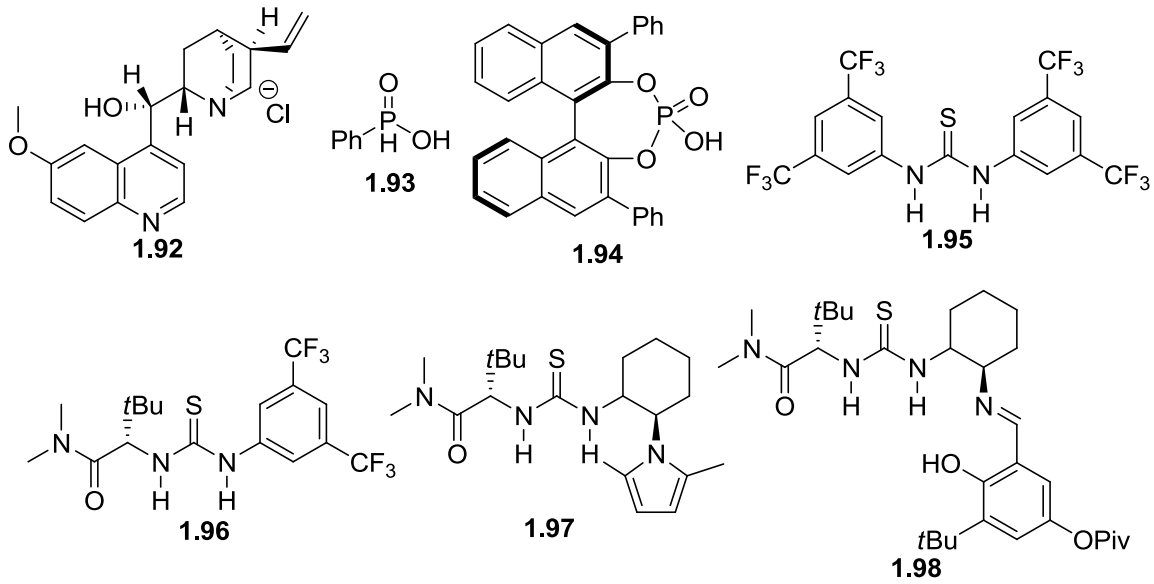
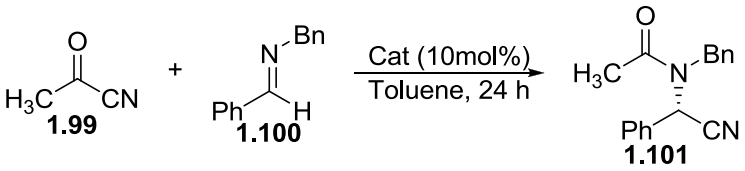


Table 1.6 Screening of Catalysts



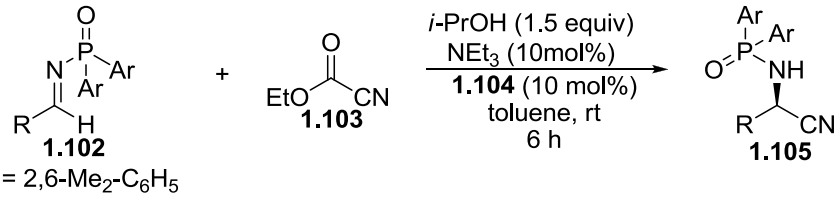
Entry	Catalyst	Temp	yield (%)[a]	e.r
1	**1.92**	0 °C	70	52:48
2	**1.93**	0 °C	88	-
3	**1.94**	-40 °C	95	61:39
4	**1.95**	0 °C	98	-
5	**1.96**	-40 °C	99	60:40
6	**1.97**	-40 °C	99	97:3
7	**1.98**	-40 °C	98	>99:1

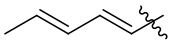
[a]Determined by GC

In a quest for alternative cyanide sources that are safe to handle, Yamamato and Abell have attempted to use ethylcyanoformate as cyanide source for the asymmetric Strecker reaction.[83] Cyanoformate reacts with a nucleophile and releases cyanide anion. Typically, triethylamine was used for this purpose. In the presence of a chiral aluminium catalyst, a variety of aldimines was subjected to hydrocyanation (Table 1.7). It was found that substrates with electron-withdrawing groups on the aromatic ring and larger aromatic aldimines required longer reaction times (Table 1.7, entry 3-5). Heteroaromatic aldimines were also tolerated and gave the corresponding α-amino nitrile product in good yields and enantioselectivities (Table 1.7). In the case of unsaturated and aliphatic aldimines, the more nucleophilic DMAP was needed (Table 1.7, entry 6-7). The catalyst employed was also suited for the hydrocyanation of ketimines. Ricci and coworkers employed cyanohydrins as cyanide source for the preparation of α-amino nitriles using Strecker reaction. Using a cinchona alkaloid based phase transfer catalyst, an enantioselective reaction was achieved.[84] The hydroxy group on the cinchona alkaloid was necessary for asymmetric induction (Table 1.8, entry 3). This method is compatible only with aliphatic α-amido sulfones.

The above mentioned alternative cyanide sources are safer to handle compared to hydrogen cyanide employed in the Strecker reaction. However, most of these reagents are prepared from hydrogen cyanide. In the next chapter, we describe our approach towards a cyanide-free Strecker reaction.

Table 1.7 Ethylcyanoformate as Cyanating Reagent



entry	R	yield (%)[a]	ee (%)
1	Ph	96	97
2	4-Br-C_6H_4	92	94
3[b]	4-Cl-C_6H_4	88	93
4[b]	4-F-C_6H_4	85	94
5[b]	1-Naphthyl	82	95
6	2-furyl	99	96
7[c]		85	90
8[c]	*t*-Bu	94	90

[a]Isolate yield. [b]Reaction was allowed to run for 14 h
[c]DMAP was used as nucleophilic catalyst

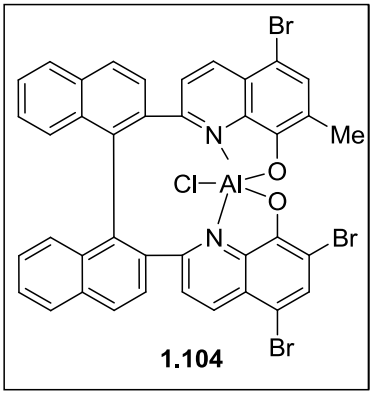
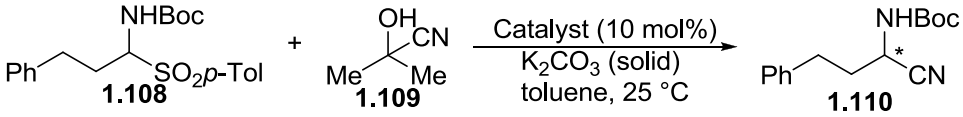
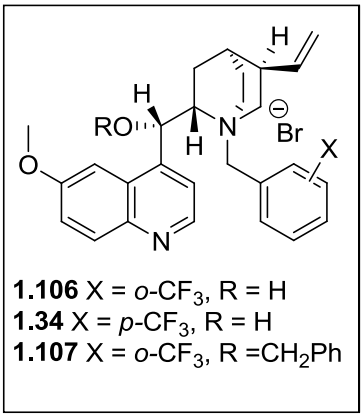


Table 1.8 Cyanohydrins as Cyanating Reagent



entry	catalyst	time	yield (%)	ee (%)
1	**1.106**	5 h	95	60
2	**1.34**	5 h	89	16
3	**1.107**	5 h	90	0



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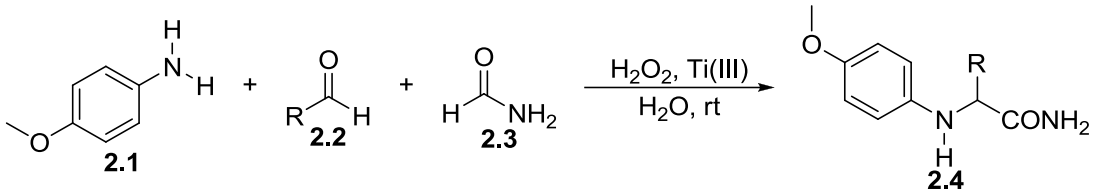
Chapter 2

Controlling Ambident Reactivity of Nitronate Anions with Aryl Alkyl Carbonate: Synthesis of α-Amino Esters

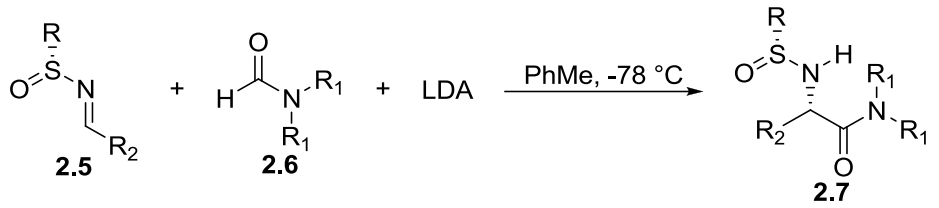
2.1 Introduction

Proteinogenic and non-proteinogenic α-amino acids have found utility in various fields like catalysis,[1] medicinal chemistry,[2] and materials science.[3] Proteinogenic amino acids are readily obtained from natural sources, while chemical synthesis is one of the best ways for obtaining non-proteinogenic amino acids. Amongst the various methods that have been used for the synthesis of α-amino acids,[4] the Strecker reaction has one of the broadest substrate scopes.[4] As mentioned in the previous chapter, the Strecker reaction uses cyanide as a one-carbon synthon. Nucleophilic attack of the cyanide on an imine results in the formation of an α-amino nitrile. Hydrolysis of the nitrile group results in the formation of an α-amino acid. A major drawback of this approach is the toxicity of cyanide. This has led to alternative approaches wherein cyanide is generated *in situ*. As summarized in the previous chapter, these included the use of acyl cyanide,[5] cyanohydrins,[6] and trimethylsilyl cyanide.[7] In order to completely avoid the use of cyanide, several groups have looked at alternative one-carbon synthons. In this context, the Porta group has used formamide as a carboxyl equivalent in a radical version of the Strecker reaction (Scheme 2.1a).[8] In a different approach, Reeves and coworkers used

Scheme 2.1a Preparation of α-Amino Acids Using Formamide



Scheme 2.1b Preparation of α-Amino Acids Using Formamide and Strong Base

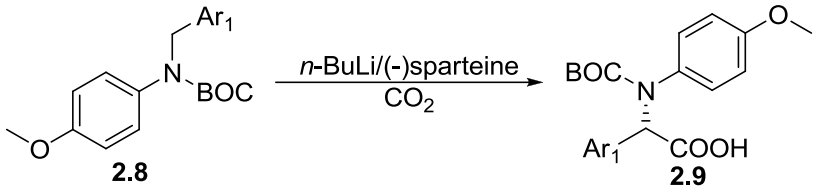


carbamoyl lithium as a one-carbon synthon (Scheme 2.1b).[9] To obtain optically enriched amino acids, a chiral sulfoxide is used as the chiral auxiliary and the corresponding *N*-sufinyl imines are used as the electrophile. This reaction requires the use of three equivalents of a strong base and the reaction has to be carried out at low temperatures.

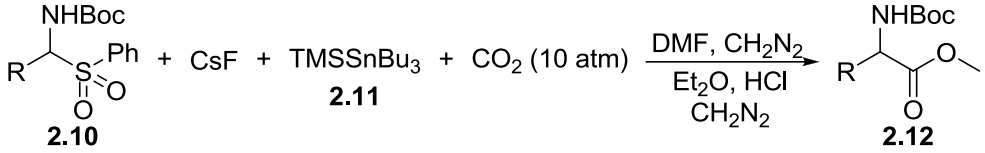
2.2 Carbon dioxide as Carboxyl Equivalent

A more convenient and direct one-carbon synthon is carbon dioxide. The carbon atom in carbon dioxide is electrophilic as seen in its reaction with Grignard reagents. This is in contrast to Strecker reactions where cyanide, the carboxyl equivalent, is a nucleophile. Therefore, when carbon dioxide is used as the carboxyl equivalent, the imine or imine equivalent has to be nucleophilic (i.e.) a reversal of polarity is needed. Several groups have attempted this and the most notable among the earlier work is the synthesis of protected aryl-glycines by Beak and coworkers (Scheme 2.2).[10] In this method, a doubly protected benzylamine was deprotonated with a strong base and treated with carbon dioxide to yield aryl-glycines. An enantioselective reaction was performed using stoichiometric amounts of sparteine as a chiral ligand. More recently, the Mita and Sato groups have used α-amino sulfones as imine equivalents.[11]

Scheme 2.2 Preparation of α-Amino Acids Using Carbon dioxide as Carboxylate Equivalent



Scheme 2.3 Preparation of α-Amino Acids Using Carbon dioxide and Bis-metal Reagent



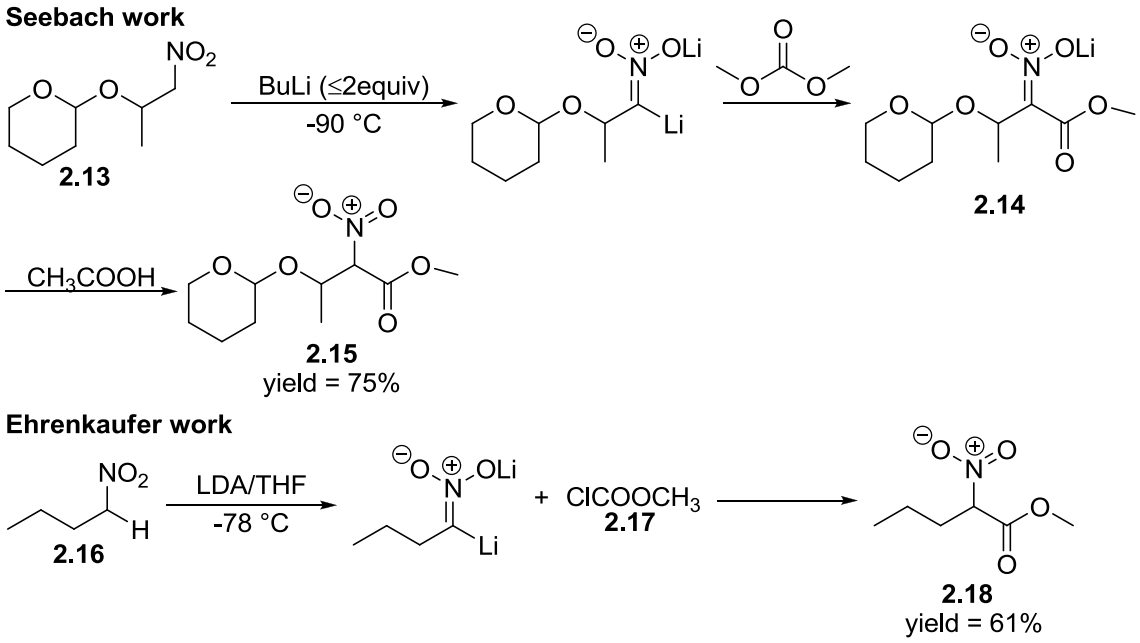
Carbanions were generated from these sulfones using bis-metal reagents. Further reaction with carbon dioxide resulted in the formation of α-aryl and α-vinyl amino acids. Quenching of the carbanion by a proton shunt is a potential problem in this reaction and is controlled by faster reactivity with carbon dioxide (Scheme 2.3). In most cases, 10 atm pressure of carbon dioxide was required although lower pressures could be used in some cases. In an alternative approach, the Radosevich group has shown that carbanions generated reductively from imines can react with carbon dioxide to yield α-amino acids.[12] In all of these approaches, an imine is treated with moisture sensitive reagents to generate an unstable α-aza-carbanion. A much easier way to generate these carbanions is through the deprotonation of nitroalkanes. Reaction of the nitronate anions with electrophilic carboxyl equivalents can generate α-nitro esters. These can be readily reduced to the corresponding α-amino acids.[13]

2.3 α-Nitro Esters

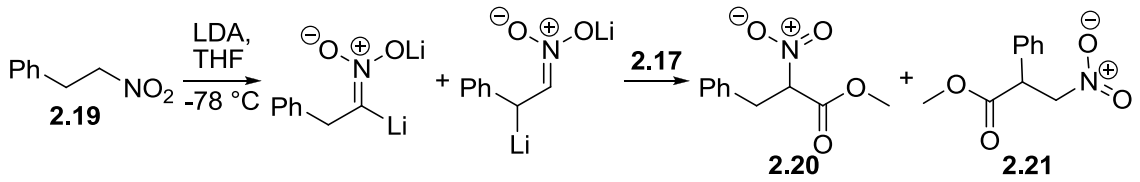
The synthesis of α-nitro esters using carbonate and nitroalkanes has been explored by several groups. Finkbeiner and coworkers had shown that magnesium methyl carbonate can be used as a one carbon synthon in combination with nitroalkanes to generate α-nitro esters, albeit in low yields.[14] Later work has shown that for the

successful generation of nitro esters, dianions of nitroalkanes are required. The Seebach group has shown that dialkyl carbonates can react with dianions of nitroalkanes to give α-nitro esters (Scheme 2.4).[15] Ehrenkaufer and Ram have shown that chloroformates react with dianions of nitroalkanes to generate α-nitro esters (Figure 2.4).[16] The nitro esters can be readily reduced to give α-amino esters. Both of these methods use two equivalents of a strong base at low temperatures to generate the dianion. A general drawback with formation of dianions is that the second deprotonation can proceed in a non-regioselective manner. Thus, in the case of β-phenyl nitroethane, the second deprotonation gives a mixture of anions with deprotonation occurring at either the α or β carbon (Scheme 2.5).

Scheme 2.4 Preparation of α-Nitro Esters via Dinitronate Anion

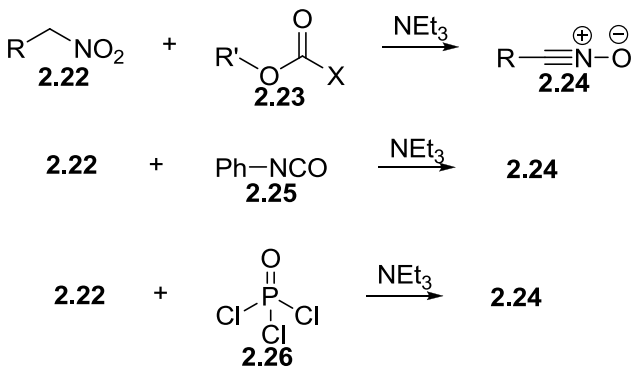


Scheme 2.5 Dinitronate Anion Reaction with β-Phenyl Nitro Ethane

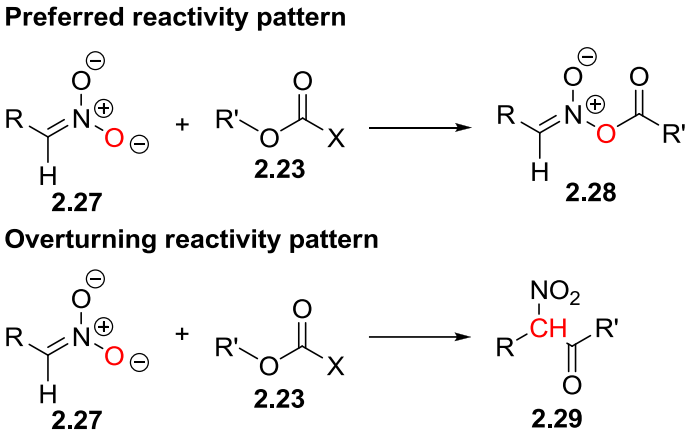


Both of these anions react with the carbonate resulting in the formation of an inseparable mixture of regioisomeric nitro esters. Therefore, this method is unsuitable for the formation of β-aryl-α-amino acids like phenylalanine. Formation of dianion is required to force reactivity through the carbon atom of the ambident nitronate anion. The mono-anion preferentially reacts with electrophiles through the oxygen atom. Indeed, it is well known that the nitronate anions react with electrophiles like choloroformates, carbonates, isocyanates, and pentavalent chlorophosphines to yield nitrile oxides (Scheme 2.6).[17] These are obtained by oxygen attack on the electrophile followed by an elimination reaction. An exception has been reported in the case of an intramolecular reaction. Here, the nitronate anion reacts with isocyanate to give the corresponding nitroamide in low yields.[18] Our interest in the synthesis of α-nitro esters stemmed from our desire to develop a safe and scalable alternative to the Strecker reaction. For this purpose, we decided to explore the possibility of using carbonates as our carboxyl equivalent and nitroalkanes as the source of α-aza-carbanion. To accomplish this, we had to overturn the preferred reactivity pattern of nitronate anions and generate α-nitro esters under mildly basic conditions that are safe and scalable (Scheme 2.7). As this reaction proceeds through mono-anionic species β-aryl-α-amino acids can be readily synthesized using this procedure. The nitro esters were readily reduced to obtain the corresponding α-amino esters (vide infra).

Scheme 2.6 Mono-nitronate anion Reaction with Electrophiles



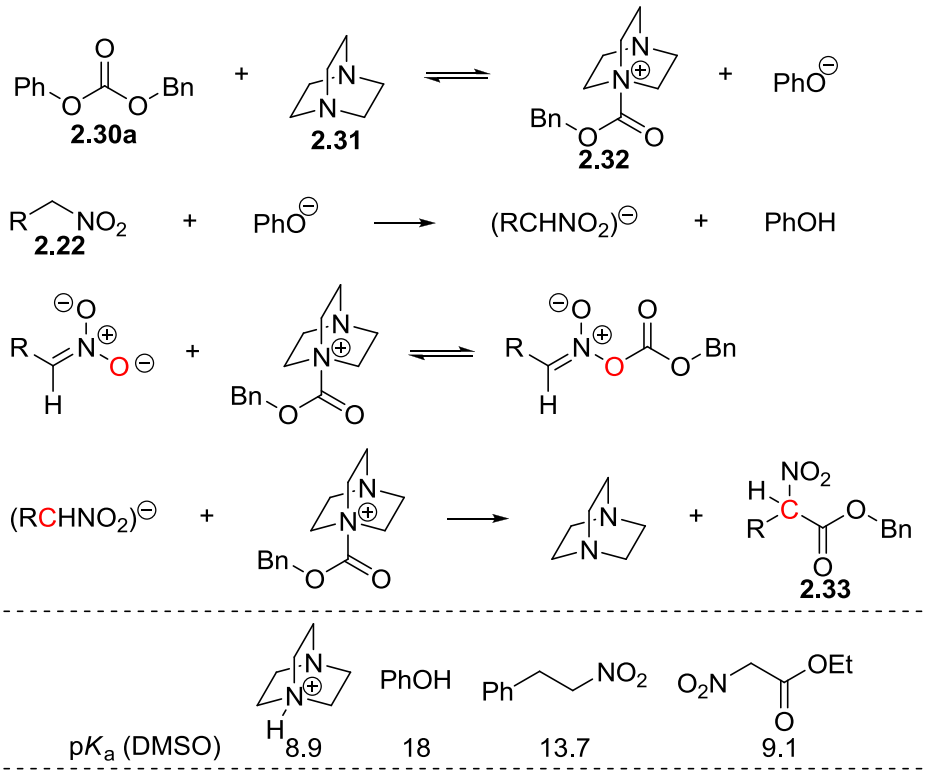
Scheme 2.7 Mono-nitronate Anion Reaction at Carbon Centre



2.4 Initial Hypothesis:

We hypothesized that unsymmetrical carbonates like benzyl phenyl carbonate can be activated by a strong nucleophile like DABCO (Scheme 2.8). Attack of a nucleophile on the carbonyl carbon would lead to the release of a phenoxide and an activated acyl group. As shown from the pK_a values of the corresponding conjugate acids, phenoxide is a much stronger base than DABCO.[19] The transiently generated phenoxide was expected to deprotonate the nitroalkane to generate a nitronate anion (Scheme 2.8). Reaction of the nitronate anion with the activated acyl group through the carbon atom was expected to lead to the formation of the α-nitro ester. The unsymmetrical carbonate was chosen keeping in mind that the carbonate had to be activated only once. A second activation would lead to the formation of unwanted side products. Therefore, we chose benzyl phenyl carbonate which has a single good leaving group. The corresponding product from this group would have a benzyloxy carbonyl group, which would not be susceptible to nucleophilic attack. DABCO was also expected to play a role in preventing the formation of nitrile oxides. The reaction of nitronate anion through its oxygen atom with the activated acyl group would lead to the formation of a nitronocarbonate. Deprotonation of this species would lead to the formation of nitrile oxide.

Scheme 2.8 Initial Hypothesis

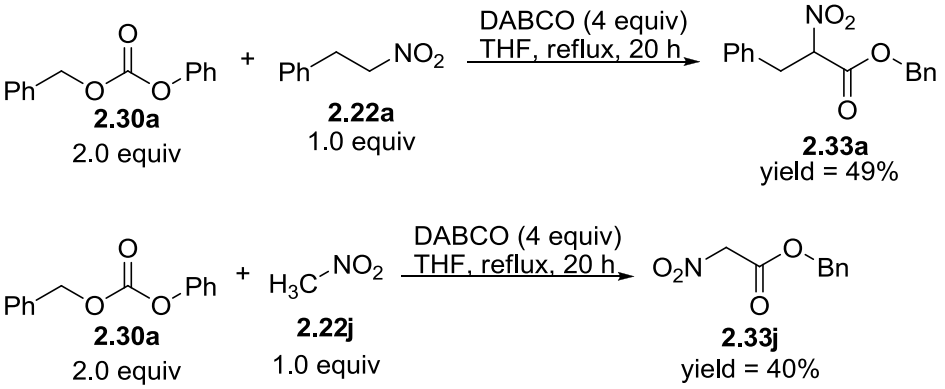


This would be prevented by nucleophilic attack of DABCO on the nitronocarbonate, which would regenerate the nitronate anion. In essence, the presence of DABCO would ensure that reaction through oxygen atom was reversible. On the other hand, reaction through the carbon atom was expected to be irreversible for two reasons: (i) the carbonyl group in the nitro ester was expected to be less electrophilic and (ii) the nitro ester was expected to be deprotonated by DABCO (vide infra).

2.5 Results and Discussions

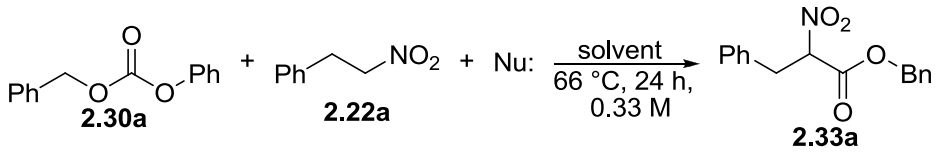
To test our hypothesis, a mixture of 2-phenyl nitroethane (**2.22a**), benzyl phenyl (**2.30a**), and DABCO (**2.31**) was refluxed in THF for 20 hours.[20] After purification of the reaction mixture by column chromatography, we were able to isolate the required product (**2.33a**) in 49% yield (Scheme 2.9). Under similar conditions, a reaction was carried out with nitromethane as the substrate and the corresponding nitro ester (**2.33j**) was isolated in 40% yield.

Scheme 2.9 Testing Our Hypothesis



To further optimize this reaction, we decided to screen various nucleophiles. Reactions were performed with various nucleophiles using 2-phenyl nitroethane as the substrate and either THF or DMSO as the solvent. The percent conversion of the starting materials was measured by GC/MS using an internal standard and the results are shown in Table 2.1. While pyridine, DMAP and imidazole were competent nucleophiles, the highest conversion was observed with DABCO in both THF and DMSO.

Table 2.1 Nucleophile Screen

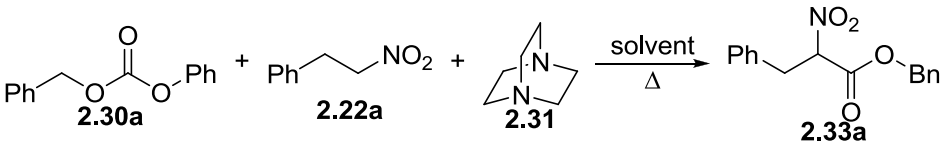


entry	solvent	Nu:	% conversion
1	THF	Pyridine	0
2	THF	Imidazole	48
3	THF	DMAP	83
4	**THF**	**DABCO**	**88**
5	DMSO	DMAP	0
6	DMSO	Pyridine	53
7	DMSO	Imidazole	67
8	**DMSO**	**DABCO**	**99**

Reaction condition: carbonate 2 eq, Nu: 4 eq, 70 °C, time 24 h, DMSO (0.33M), product conversion was determined by GC/MS

We then tried to identify the optimal solvent for this reaction using **2.22a** as the substrate, **2.30a** as the carbonate, and DABCO as the nucleophile. Reactions were performed with various solvents and the isolated yields after column chromatography are shown in Table 2.2. While ethyl acetate gave the best yields among the various solvents, the highest yield (76%) was obtained when the reaction was performed in the absence of solvents. The initially hypothesized mechanism (Scheme 2.8) involves cationic intermediates and is likely to have cationic transition states. Based on this, it appeared that addition of a small amount of DMSO might speed up the reaction as it is known to stabilize cations. Indeed, addition of three equivalents of DMSO reduced the reaction time by half while a nominal increase in yield was observed. Additionally, we were able to reduce the amount of DABCO to two equivalents. In contrast to earlier reports,[15,16] the products obtained in our reactions are single regioisomers. This is due to the fact that in our method the reaction proceeds through a mono-nitronate anion.

Table 2.2 Solvent Screen



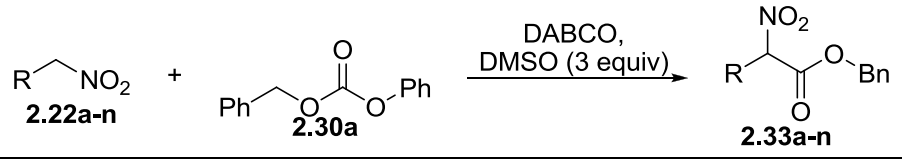
Entry	solvent	temp	time [h]	% yield[b]
1	Tetrahydrofuran	66 °C	20	49
2	Acetonitrile	50 °C	64	58
3	Ethyl Acetate	50 °C	64	64
4	Chlorobenzene	50 °C	64	58
5	Ethyl Acetate	60 °C	59	64
6	DMSO[c]	70 °C	2.5	52
7	Isopropyl Acetate	60 °C	67	59
8	**Neat[d]**	**60 °C**	**12**	76
9	**DMSO[d,e]**	**60 °C**	**5**	77

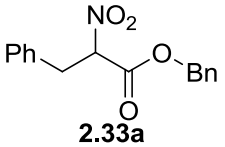
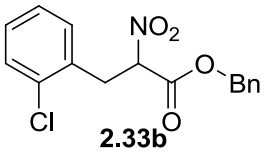
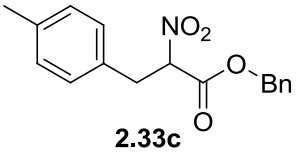
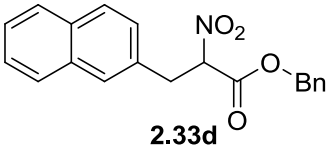
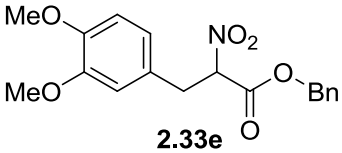
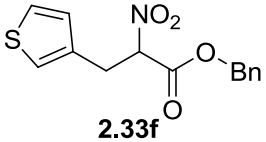
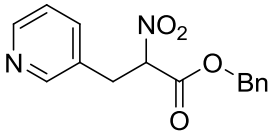
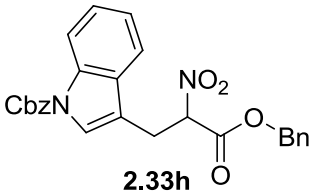
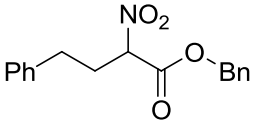
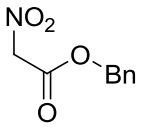
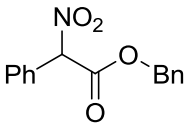
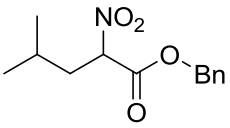
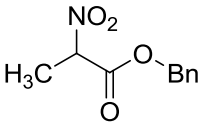
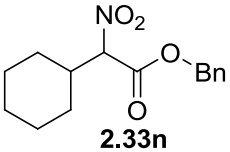
[a]Conditions: **2.30a** (2.0 equiv), **2.31** (4.0 equiv), ~ 0.66 M of **2.22a**. [b]Yield of product after column chromatography. [c]~0.33 M of **2.22a**,[d]**2.30a** (3.0 equiv), **2.31** (2.0 equiv). [e]DMSO (3.0 equiv).)

With the optimized reaction in hand, we decided to explore the substrate scope of the reaction (Table 2.3). When 2-(2-chlorophenyl) nitroethane and 2-(2-naphthyl) nitroethane were used as substrates, the corresponding products were obtained in good yields (Table 2.3, **2.33b** & **2.33d**). This showed that the presence of electron-withdrawing groups and the presence of the bulky naphthyl ring did not negatively impact the yield of the reaction. For substrates with an electron-donating substituent on the aromatic and nucleophilic aromatic substrates, we anticipated that the aromatic ring might also act as a nucleophile and lead to formation of unwanted side products. In reactions with substrates **2.22c**, **2.22e**, and **2.22f**, the corresponding products were isolated in good yields and none of the unwanted side products were observed.

Nitrogen containing heterocycles are found in a number of biologically active compounds. A potential problem with these substrates is the nucleophilicity of the nitrogen atom. Heterocycles with an 'NH' group might react irreversibly with the activated electrophile,[21] whereas heterocyles wherein the nitrogen is not attached to hydrogen might react reversibly. To test these two cases, we chose substrates **2.22g** and **2.22h**. In the case of the substrate 3-(2-nitroethyl)-1*H*-indole, we found that the indole nitrogen reacts with the activated electrophile and a mixture of products was obtained. Protection of the indole nitrogen with a Cbz-group (Table 2.3, **2.33h**) led to isolation of clean product. This shows that nitrogen containing heterocycles can be used as substrates in this reaction as long as the nitrogen is protected. In the case of pyridyl substrate **2.33g**, we obtained the product in 52% yield. Pyridylalanines have found extensive use in medicinal chemistry.[22] To test whether the pyridyl group in the substrate can act as a nucleophile, we performed a control reaction in the absence of DABCO (Scheme 2.10). In this case, we did not obtain any of the required product.

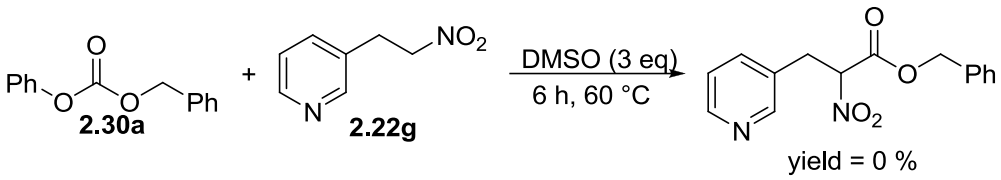
Table 2.3 Substrate Scope



 **2.33a** time: 5 h yield: 77%	 **2.33b** time: 5 h yield: 73%	 **2.33c** time: 7 h yield: 72%
 **2.33d** time: 8.5 h yield: 71%	 **2.33e** time: 8 h yield: 64%[a]	 **2.33f** time: 7.5 h yield: 75%[a]
 **2.33g** time: 6 h yield: 52%	 **2.33h** time: 4.5 h yield: 70%[b]	 **2.33i** time: 6 h yield: 34%[a]
 **2.33j** time: 16.5 h yield: 65%	 **2.33k** time: 8 h yield: 7%[b]	 **2.33l** time: 20 h yield: 16%
 **2.33m** time: 12 h yield: 0%	 **2.33n** time: 4 h yield: 0%	

All yields are averages of two runs. Conditions: **2.22a-n** (1.0 equiv), **2.30a** (3.0 equiv), DABCO (2.0 equiv), 60 ^{o}C. [a] 3.5 equiv of **2.30a** was used. [b] reaction was run at 45 ^{o}C with 3.5 equiv of **2.30a.**[c] yield for single run

Scheme 2.10. Control Reaction in the Absence of DABCO



Substrate	recovered %
nitro alkane	84
carbonate	97

Homophenylalanine is an amino acid found in the inhibitor of angiotensin-converting enzyme.[23] We were able to synthesize the corresponding nitro ester **2.33i**, albeit in low yield using our method. In the case of phenyl nitromethane (**2.33k**), we obtained the corresponding nitro ester in very low yields. The higher acidity of the benzylic 'CH' proton probably led to more rapid formation of nitrile oxides.[24] With nitromethane as a substrate, we obtained benzyl nitroacetate in 65% yield (Table 2.3, **2.33j**). Surprisingly, with nitroethane as substrate, we did not observe formation of nitro ester (Table 2.3, **2.33m**). However, 3-methyl-1-nitrobutane was tolerated and product was obtained in low yield (Table 2.3, **2.33l**) and in the case of 2-cyclohexyl nitroethane, we failed to obtain the required product (Table 2.3, **2.33n**).

With the nitro esters in hand, we focused on the reduction of nitro group to amine group. The Johnston and Shibasaki groups have reported on the reduction of nitro groups by using $NaBH_4$ in combination with either $CoCl_2$ or $NiCl_2$.[25] For our substrates, these reactions failed to give the corresponding amino esters (Scheme 2.11). We also attempted a Pd/C catalyzed reduction of the nitro group. In this case, we obtained 2-phenylnitroethane as the product (Scheme 2.11).[26] Kozlowski and coworkers have shown that nitro esters can be readily reduced to the corresponding amino esters using Zn and acetic acid.[13] Using these conditions, we were able to reduce nitro esters (**2.33a-2.33i**) in excellent yields (Table 2.4).

Scheme 2.11 Attempted Reduction of Nitro Ester

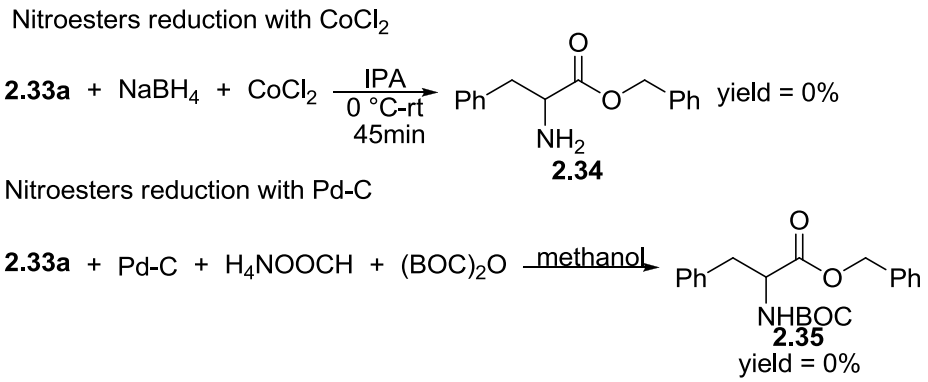
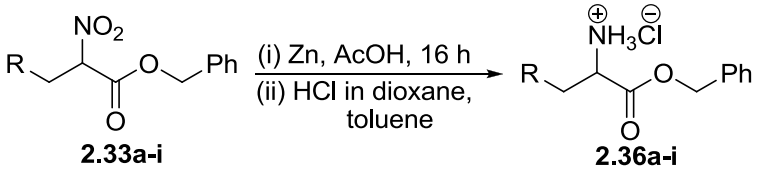
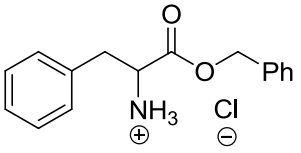
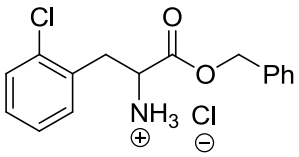


Table 2.4 Reduction of α-Nitro Esters

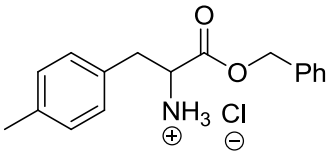




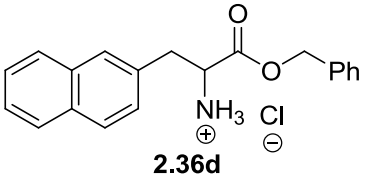
2.36a
Yield = 88%



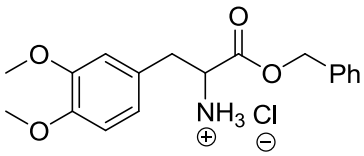
2.36b
Yield = 84%



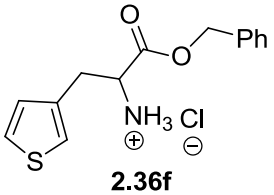
2.36c
Yield = 85%



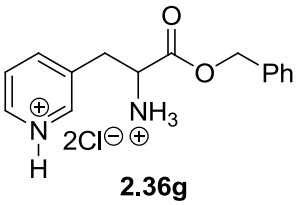
2.36d
Yield = 84%



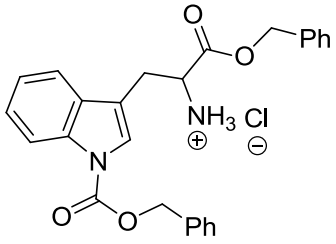
2.36e
Yield = 82%



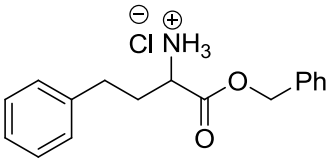
2.36f
Yield = 85%



2.36g
Yield = 88%



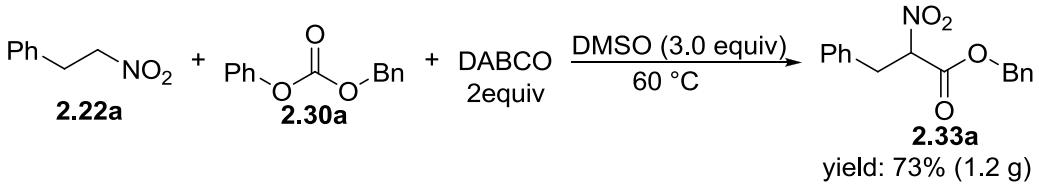
2.36h
Yield = 77%



2.36i
Yield = 83%

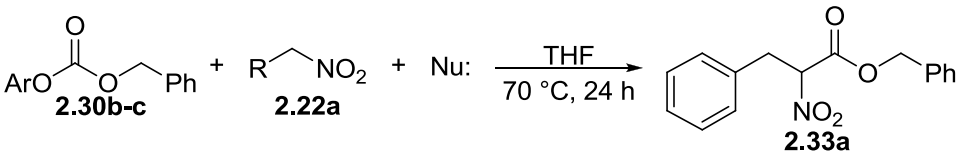
To test the practicality of our method, we decided to perform a gram-scale reaction with 2-phenylnitroethane as the substrate. An important consideration for practicality is the ease of accessing reactants. For the smaller scale reactions reported in Table 2.3, we used benzyl phenyl carbonate that had been purified by column chromatography. In case of the large scale reaction, we decided to use material obtained by distillation, which had ~9% by mass of dibenzyl carbonate as impurity. Using this material, we performed the gram-scale reaction under standard conditions. After a simple extractive workup, we were able to obtain the product in ~85% yield and ~93% purity. Further purification of the product by chromatography resulted in isolation of ~1.2 g (73%) of product (Scheme 2.12).

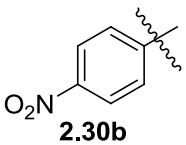
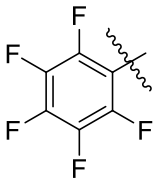
Scheme 2.12 Gram Scale preparation of α-Nitro Ester



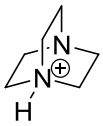
A key part of our reaction design was the generation of a stronger base from the reaction of a weak base and a carbonate. We had hypothesized that the nucleophilic attack of DABCO on carbonate **2.30a** would generate a phenoxide which would in turn deprotonate the nitroalkane (Scheme 2.8). To confirm that phenoxide is the base, we synthesized carbonates **2.30b** and **2.30c**. Based on the reported pK_a values of the corresponding phenols in DMSO,[19] the phenoxides generated from these carbonates would be unable to deprotonate nitroalkanes. On the other hand, if DABCO acts as the deprotonating agent, the reaction should proceed as before. Reactions carried out with these carbonates failed to yield any nitro ester product, thereby confirming that phenoxides act as the base (Table 2.4).

Table 2.4 Identifying Basic Reagent in the Reaction Mixture

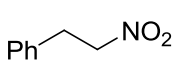


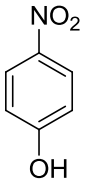
Ar	Nu:	% yield
 2.30b	Pyridine	0
	DABCO	0
	Imidazole	0
	DMAP	0
 2.30c	Pyridine	0
	DABCO	0
	Imidazole	0
	DMAP	0

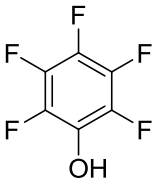
Reported pK_as (DMSO)


8.93

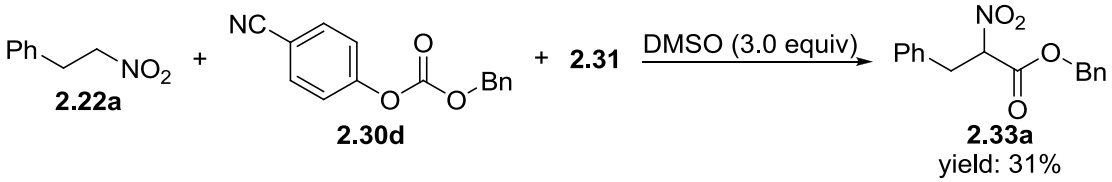
PhOH
18


13.7


10.8

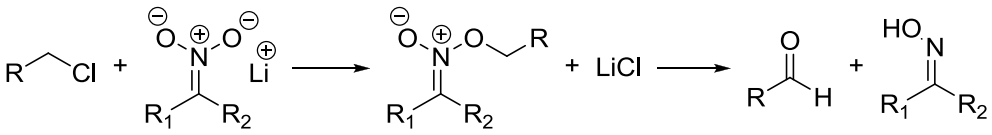

8.9

Scheme 2.13 α-Nitro Ester Preparation



Further, reactions were carried out with the 4-cyanophenyl carbonate (**2.33d**) where pK_a of phenoxide ion is 13.2. In this case, the reaction proceeded at a much faster rate but the yield was lower (Scheme 2.13). The reactivity pattern of nitronate anion in this reaction is different from what has been reported previously. Nitronate anions are ambident nucleophiles that can react either through oxygen atom or the carbon atom. Understanding and controlling the reactivity of ambident nucleophiles is a long-standing problem in organic chemistry. The reactivity of ambident nucleophiles can be tuned empirically by varying the reaction conditions. Hass and Bender, in their pioneering work, had shown that nitronate anions react with alkyl halides to generate aldehydes.[27] This was postulated to proceed through an oxygen attack as shown in Scheme 2.14.

Scheme 2.14 Nitronate Anion Reaction with Alkyl Halides

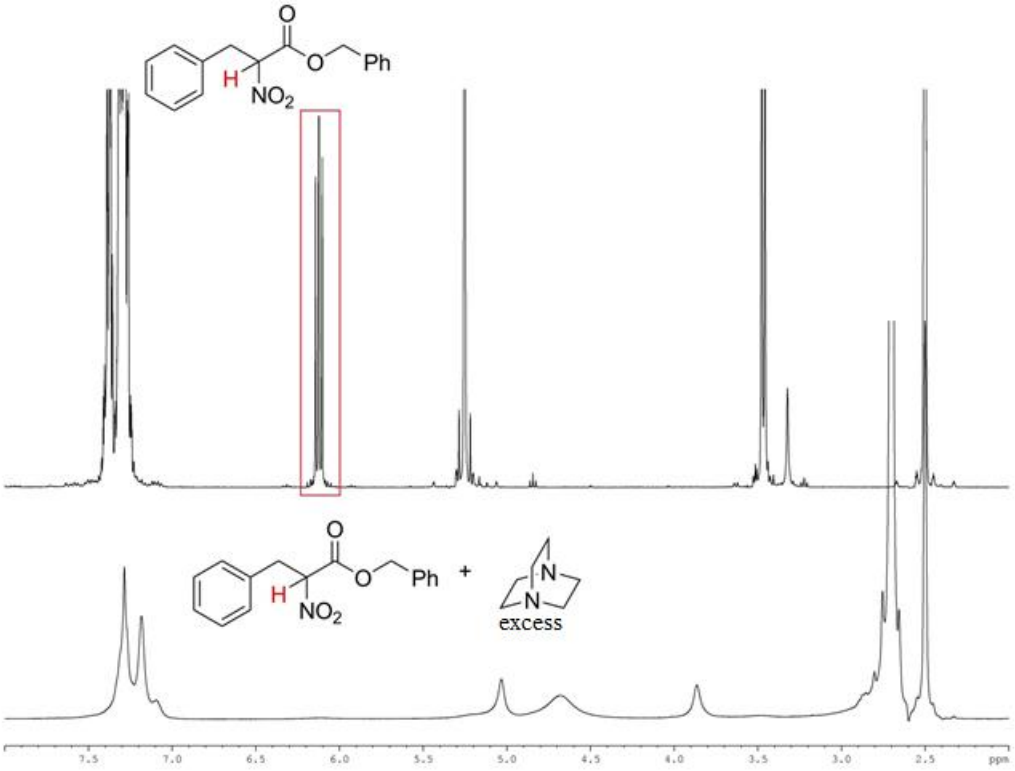


Later, Kornblum and coworkers generalized this and showed that in some cases the nitronate esters obtained from the attack of oxygen can be isolated.[28] Generally, in reactions of nitronate anions with alkyl halides, the dominant pathway is reaction through the oxygen atom with the exception of 4-nitrobenzylchloride.[29] Hamilton and coworkers attempted to overturn this preferred reactivity by complexing the nitronate anion with a guanidine.[30] This failed to give the product of carbon attack. Reactivity through carbon has been accomplished under radical conditions by the Katritzky[31] and Watson groups.[32] Yamataka and coworkers have performed DFT calculations on the reactivity of nitronate anions with methyl brosylate.[33] This showed that the barrier for reactivity through the oxygen atom is ~10 kcal/mol lower than the barrier for reactivity through carbon atom.

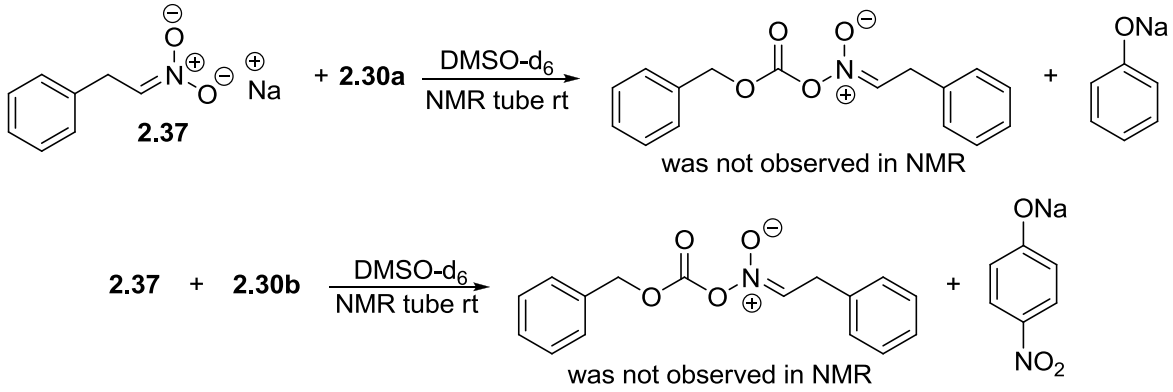
In contrast to these reactions, nitronate anions appear to react exclusively through the carbon atom in the case of imines and aldehydes. The apparent dichotomy in reactivity has been explained using the Hard and Soft Acids and Bases (HSAB) concept.[34] In this explanation, the softer carbon center of the nitronate anion is expected to react with softer π–electrophiles while the harder oxygen center reacts with harder electrophiles like alkyl halides. On the basis of this explanation, it would be expected that nitronate anions would react through the carbon atom with softer π–electrophiles like chloroformates and carbonates.[17] However, with the exception of a single report,[18] the preferred reactivity in these cases is through the oxygen atom. Indeed, this is precisely the reason that the Seebach[15] and Ehrenkaufer[16] groups have used harsh bases to generate dianions. In contrast to other reports on the reactions of nitronate anions, we observed the product of reactivity through carbon atom.

Mayr and coworkers have proposed an alternate theory that explains the reactivity of nitronate anions with various electrophiles on the basis of the reversibility of attack through the oxygen atom.[35] They have postulated that the barrier for reaction of nitronate anion through oxygen is lower than that for reaction through carbon atom for all electrophiles. In cases where the reaction through oxygen atom is reversible, the product of carbon attack is observed. On the basis of this, we propose that in our reaction[20] as well as in reactions reported previously,[18] the kinetic product from oxygen attack is formed initially. In the case of previous reports (Scheme 2.6), subsequent deprotonation leads to the formation of nitrile oxides. The key difference between our work and the previous reports is the use of a nucleophilic base. In our reaction, the presence of a nucleophile renders the oxygen attack reversible and regenerates the nitronate anion. Reaction of the nitronate anion irreversibly through the carbon atom generates the α-nitro ester. The irreversibility of the reaction through carbon atom is likely due to reduced electrophilicity of the ester and deprotonation of the product by DABCO. A NMR experiment was performed by mixing four equivalents of DABCO with one equivalent of **2.33a** (Figure 2.7). In the absence of DABCO, the ^{1}HNMR showed a peak at 6.12 ppm that was assigned to the α-hydrogen of the nitro ester. The peak at 5.27 ppm was assigned to the benzyloxy group in the ester while the peak at 3.47 was assigned to the benzyl group adjacent to the α-proton. In the NMR with DABCO, the α-proton has disappeared while the benzylic groups have shifted. This showed complete deprotonation of the product by DABCO, thereby reducing the electrophilicity of the ester. To study the role of DABCO more precisely, we have attempted to observe peaks corresponding to nitronocarbonate compound in ^{1}H NMR. We attempted this by treating the nitronate anions with various carbonates and monitored the reaction regularly by ^{1}H NMR (Scheme 2.15). However, these efforts were not successful.

Figure 2.7 Deprotonation of α-Nitro Ester by DABCO



Scheme 2.15 Attempts to Study the Role of DABCO



2.6 Conclusions

In conclusion, we have developed a safe and scalable alternative to the Strecker reaction using benzyl phenyl carbonate as the carboxyl equivalent. Activation of the carboxyl equivalent by DABCO leads to the transient generation of a much stronger base that deprotonates the nitroalkane. Studies with carbonates that generate weaker bases show that phenoxide is the base. Optimization of the nucleophile and solvent led to

reaction with good substrate scope. Aromatic groups with both electron-donating and electron-withdrawing groups were tolerated. Nitrogen containing heterocycles with an 'NH' required protection of the nitrogen to obtain clean reactivity. All of the nitro esters were readily reduced to the corresponding amino esters in high yields using a mixture of zinc and acetic acid. The scalability of the reaction was evaluated by performing a gram-scale reaction with substrate **2.22a**. Importantly, the presence of minor amounts of dibenzyl carbonate as an impurity in benzyl phenyl carbonate was tolerated. An intriguing aspect of our reaction in comparison to earlier work is the formation of products from the attack of the carbon atom of nitronate anion. We postulate that this is due to the use of DABCO, which attacks the product of oxygen attack and regenerates the nitronate anion. Our reaction provides a good example of controlling the ambident reactivity of nitronate. Additionally, the generation of a strong base and an activated electrophile is likely to be useful in other reactions.

2.7 Experimental Section

All glassware was dried overnight in an oven at 120 °C prior to use. Reactions were carried out under argon atmosphere using standard Schlenk techniques and were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed using silica gel of mesh size 230–400. Grease-free solvents for flash column chromatography were obtained by distillation. Unless otherwise noted, all chemicals obtained from commercial sources were used without further purification. 1,4-diazabicyclo[2.2.2]octane (DABCO) was dried azeotropically with benzene. Infrared spectra were recorded using Bruker IFS 66V/S FTIR instrument. ^{1}H and ^{13}C NMRs were recorded on a Bruker AVANCE-400 (400 MHz) Fourier transform NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with respect to the residual solvent peak: $CDCl_3$ (^{1}H NMR: 7.27 ppm, ^{13}C

{^{1}H} NMR: 77.16 ppm); DMSO-d_6 (^{1}H NMR: 2.50 ppm, ^{13}C {^{1}H} NMR: 39.52 ppm); D_2O (^{1}H NMR: 4.79 ppm). ^{13}C NMRs were recorded at 100 MHz using proton decoupling. DMSO-d_6 was added as an internal standard to ^{13}C samples taken in D_2O. HRMS were recorded using Agilent Q-TOF spectrometer. Melting point was measured using hot plate melting point apparatus from Techno Instruments.

General Procedure for the Synthesis of Nitroesters:

A thick walled tube with a Teflon screw cap was charged with nitroalkane (1 mmol) and benzyl phenyl carbonate (680 mg, 3 mmol). The tube was flushed with argon and dimethyl sulfoxide (DMSO) (210 µL, 2.95 mmol) was added followed by DABCO (224 mg, 2 mmol). The tube was capped and immersed in an oil bath at 60 °C. The reaction mixture was stirred at this temperature and the progress of the reaction was monitored by TLC.

Workup Procedure:

Method A

After completion of reaction (by TLC), the reaction mixture was cooled to 0 °C and quenched with 1 M $KHSO_4$ (6 mL). This was further stirred at room temperature till a suspension was formed. The suspension was transferred to a separatory funnel containing 15 mL of 1 M $KHSO_4$. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined ether layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography.

Method B

1. After completion of reaction by TLC, the reaction mixture was cooled to 0 °C and quenched with 1 M $KHSO_4$ (6 mL). This was further stirred at room temperature till a suspension was formed. The suspension was transferred to a separatory funnel containing

15 mL of 1 M $KHSO_4$. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were concentrated in a 250 mL round bottom flask.

2. To the material obtained in step 1, 1 M K_2CO_3 (25 mL) was added and stirred at room temperature for 15 min. After this, de-ionized water (75 mL) was added and stirred at room temperature for 15 min.

3. This aqueous layer was washed with hexanes (3 × 20 mL). The combined hexanes layers were concentrated. The hexanes layers contains small quantities of compound.

4. The aqueous layer was acidified with 1 M $KHSO_4$ and extracted with diethyl ether (3 × 40 mL).

5. Steps 2 through 4 (except concentration of hexanes layers) were repeated using the material obtained from step 3 with the following quantities of reagents: 1 M K_2CO_3 (10 mL), de-ionized water (30 mL), hexanes (3 × 20 mL), and diethyl ether (2 × 20 mL).

6. The first and second lot of ether layers were combined, dried over Na_2SO_4, concentrated, and purified by flash column chromatography.

Benzyl 2-nitro-3-phenylpropanoate (2.33a)

The general procedure was carried out with method B as workup procedure. Time: 5 h.

Column Chromatography:

Approximately 45 mL of silica was packed into a column using 30% dichloromethane (DCM) in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 700 mL of 30% DCM in hexanes was eluted and collected in 25 mL fractions. Fractions 13 – 24 contained product. These fractions were concentrated and dried under high vacuum to give 220 mg of product (yield: 78%, average yield over two runs: 77%).

Characterization:

Pale yellow liquid; R_f: 0.27 in 10% ethyl acetate (EtOAc) in hexanes; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 – 7.23 (m, 10H), 6.12 (dd, *J* = 8.2, 7.4 Hz, 1H), 5.27 (d, *J* = 12.4 Hz, 1H), 5.23 (d, *J* = 12.4 Hz, 1H), 3.47 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz $CDCl_3$): 164.1, 134.3, 134.0, 129.1, 129.0, 128.9, 128.6, 127.9, 89.2, 68.7, 36.4; IR (film): 3066 (aromatic C-H), 3032 (aromatic C-H), 1749 (carbonyl), 1559 (N-O), 1496 (aromatic C=C), 1453 (aromatic C=C),1363 (N-O), 1267 (C-O) cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{16}H_{14}NO_4^-$ 284.0928; Found 284.0932.

*Procedure for Gram-scale Synthesis of **2.33a**:*

A 25 mL Schlenk flask was charged with nitroalkane (900 mg, 5.95 mmol) and phenyl benzyl carbonate (4.43 g, 17.9 mmol, 91% purity). The flask was flushed with argon and DMSO (1.27 mL, 17.9 mmol) was added followed by DABCO (1.34 g, 11.9 mmol). The Schlenk flask was immersed in an oil bath at 60 °C and the reaction mixture was stirred at this temperature for 5 h.

Workup Procedure for Gram-scale Synthesis of 2.33a:

1. After 5 h, the reaction mixture was cooled to 0 °C and quenched with 1 M $KHSO_4$ (15 mL). This was further stirred at room temperature till a suspension was formed. The suspension was transferred to a separatory funnel containing 200 mL of 1 M $KHSO_4$ and diethyl ether (100 mL). The aqueous layer was further extracted with diethyl ether (2 × 75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated.

2. The material from step 1 was distilled under high vacuum at 160 °C to remove a large portion of the phenol.

3. To the residual material obtained in step 2, 1 M K_2CO_3 (150 mL) was added and stirred at room temperature for 15 min. After this, de-ionized water (450 mL) was added and stirred at room temperature for 15 min.

4. This aqueous layer was washed with hexanes (3 × 120 mL). The combined hexanes layers were concentrated. The hexanes layers contains small quantities of compound.

5. Step 3 through 4 (except concentration of hexane layers) were repeated using the material obtained from step 4 with the following quantities of reagents 1 M K_2CO_3 (60 mL), water (180 mL), and hexanes (3 × 50 mL).

6. The combined aqueous layers from step 4 and 5 were acidified with 4.5 M HCl (80 mL) and extracted with dichloromethane (3 × 120 mL). The combined DCM layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography.

Column Chromatography:

Approximately 200 mL of silica was packed into a column using 3% EtOAc in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 1,250 mL of 3% EtOAc in hexanes was eluted followed by elution with 300 mL of 15% EtOAc in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 45 – 55 contained product. These fractions were concentrated and dried under high vacuum to give 1.24 g of product (yield: 73%, average yield over two runs: 73%).

Benzyl 3-(2-chlorophenyl)-2-nitropropanoate(2.33b)

The general procedure was carried out with method B as workup procedure. Time: 5 h.

Column Chromatography:

Approximately 45 mL of silica was packed into a column using 25% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 500 mL of 25% DCM in hexanes was eluted followed by elution with 200 mL of 40% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 11 – 27 contained

product. These fractions were concentrated and dried under high vacuum to give 236 mg of product (yield = 74%, average yield over two runs = 73%).

Characterization:

Pale yellow liquid; R_f: 0.30 in 10% EtOAc in hexanes; ^{1}H NMR:(400 MHz, DMSO-d_6): δ 7.48 – 7.46 (m, 1H), 7.42 – 7.28 (m, 8H), 6.07 (dd, *J* = 9.3, 6.3 Hz, 1H), 5.28 (d, *J* = 12.3 Hz, 1H), 5.24 (d, *J* = 12.3 Hz, 1H), 3.69 (dd, *J* = 14.7, 9.3 Hz, 1H), 3.60 (dd, *J* = 14.7, 6.3 Hz, 1H); ^{13}C NMR (100 MHz $CDCl_3$): 163.9, 134.3, 134.2, 131.9, 131.7, 130.0, 129.7, 129.0, 128.9, 128.5, 127.5, 86.9, 68.8, 34.6; IR (film): 3066 (aromatic C-H), 3034 (aromatic C-H), 1752 (carbonyl), 1561 (N-O), 1445 (aromatic C=C), 1364 (N-O), 1266 (C-O) cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{16}H_{13}ClNO_4^-$ 318.0539; Found 318.0547.

Benzyl 2-nitro-3-p-tolylpropanoate (2.33c)

The general procedure was carried out with method B as workup procedure. Time: 7 h.

Column Chromatography:

Approximately 60 mL of silica was packed into a column using 30% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 600 mL of 30% DCM in hexanes was eluted followed by elution with 300 mL of 40% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 16 – 24 contained product. These fractions were concentrated and dried under high vacuum to give 214 mg of product (yield = 72%, average yield over two runs = 72%).

Characterization:

Pale yellow liquid; R_f: 0.30 in 10% EtOAc in hexanes; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 – 7.29 (m, 5H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.08 (dd, *J* = 8.5, 7.2 Hz, 1H), 5.25 (s, 2H), 3.43 – 3.41 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (100

MHz $CDCl_3$): 164.1, 137.6, 134.3, 130.9, 129.8, 129.0, 128.9, 128.8, 128.5, 89.3, 68.7, 36.0, 21.2; IR (film): 3032 (aromatic C-H), 2923 (alkane C-H), 1751 (C=O), 1561 (N-O), 1516 (aromatic C=C), 1365 (N-O), 1268 (C-O) cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{17}H_{16}NO_4^-$ 298.1085; Found 298.1097.

Benzyl 3-(naphthalen-2-yl)-2-nitropropanoate(2.33d)

The general procedure was carried out with method A as workup procedure. Time: 8.5 h.

Column Chromatography:

Approximately 45 mL of silica was packed into a column using 30% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 800 mL of 30 % DCM in hexanes was eluted and collected in 25 mL fractions. Fractions 12 – 24 contained compound and dibenzyl carbonate. Fractions 25 – 31 contained a small amount of phenol and compound. Fractions 12 – 31 were combined, concentrated, and purified by flash column chromatography. Approximately 48 mL of silica was packed into a column using 3% EtOAc in hexanes as the solvent. The material obtained from the first column was adsorbed on silica and loaded on the column. Approximately 600 mL of 3% EtOAc in hexanes was eluted followed by elution with 200 mL of 5% EtOAc in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 13 – 28 contained product. These fractions were concentrated and dried under high vacuum to give 239 mg of product (yield = 72%, average yield over two runs = 71%).

Characterization:

Pale yellow liquid; R_f: 0.10 in 10 % EtOAc in hexanes; ^1H NMR (400 MHz, DMSO-d_6): δ 7.94 – 7.83 (m, 3H), 7.78 (s, 1H), 7.54 – 7.47 (m, 3H), 7.35 – 7.25 (m, 5H), 6.25 (dd, J = 8.7, 7.0 Hz, 1H), 5.26 (s, 2H), 3.67 – 3.65 (m, 2H); ^{13}C NMR (100 MHz $CDCl_3$): 164.1, 134.2, 133.6, 132.9, 131.4, 128.99, 128.98, 128.8, 128.5, 128.2, 127.9,

127.8, 126.6, 126.5, 126.4, 89.1, 68.8, 36.6; IR (film): 1750 (C=O), 1560 (N-O), 1364 (N-O), 1267 (C-O), 1196 (C-O), 1169 (C-O) cm^{-1}; HRMS (ESI) m/z $(M–H)^-$ Calcd. for $C_{20}H_{16}NO_4^-$ 334.1085; Found 334.1081.

Benzyl 3-(3,4-dimethoxyphenyl)-2-nitropropanoate(2.33e)

The general procedure was carried out with method A as workup procedure. In this reaction 3.5 mmol of benzyl phenyl carbonate was used. Time: 8 h.

Column Chromatography:

Approximately 70 mL of silica was packed into a column using 15% EtOAc in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 400 mL of 15% EtOAc in hexanes was eluted followed by elution with 300 mL of 74% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 15 – 20 contained product. These fractions were concentrated and dried under high vacuum at 130 °C for overnight to give 220 mg of product (yield = 64%, average yield over two runs = 64%).

Characterization:

Red viscous liquid; R_f: 0.15 in 15% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.34 (m, 3H), 7.30 – 7.28 (m, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.73 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.69 (d, *J* = 1.9 Hz, 1H), 5.36 (dd, *J* = 9.2, 6.1 Hz, 1H), 5.24 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.52 (dd, *J* = 14.6, 9.2 Hz, 1H), 3.43 (dd, *J* = 14.6, 6.1 Hz, 1H); ^{13}C NMR (100 MHz $CDCl_3$): 164.1, 149.3, 148.8, 134.3, 129.0, 128.9, 128.5, 126.3, 121.3, 112.1, 111.6, 89.4, 68.7, 56.0, 36.1; IR (film): 1751 (C=O), 1561 (N-O), 1458 (aromatic C=C), 1516 (aromatic C=C), 1367 (N-O), 1262 (C-O) cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{18}H_{18}NO_6^-$ 344.1140; Found 344.1150.

Benzyl 2-nitro-3-(thiophen-3-yl)propanoate(2.33f)

The general procedure was carried out with method B as workup procedure. In this reaction 3.5 mmol of benzyl phenyl carbonate was used. Time: 7.5 h.

Column Chromatography:

Approximately 80 mL of silica was packed into a column using 25% DCM in hexanes as the solvent. The material obtained from workup was loaded on column after dissolution in a minimum amount of this solvent. Approximately 800 mL of 25% DCM in hexanes was eluted followed by elution with 400 mL of 30% DCM in hexanes and 600 mL of 40% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 42 – 59 contained product, fractions 60 – 65 contained compound and phenol. Fractions 42 – 59 were concentrated and dried under high vacuum to give product 210 mg. Mixed fractions were concentrated and kept under high vacuum at 60 °C for 8 h to obtain a further 10 mg of pure product (yield = 76%, average yield over two runs = 75%).

Characterization:

Yellow liquid; R_f: 0.33 in 10 % EtOAc in hexanes; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.49 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.42 – 7.32 (m, 6H), 7.06 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.12 (dd, *J* = 9.6, 5.8 Hz, 1H), 5.26 (s, 2H), 3.54 (dd, *J* = 15.0, 9.6 Hz, 1H), 3.44 (dd, *J* = 14.9, 5.7 Hz, 1H); ^{13}C NMR (100 MHz $CDCl_3$): 164.0, 134.3, 134.0, 129.0, 128.9, 128.6, 127.8, 126.8, 123.7, 88.5, 68.8, 31.0; IR (film): 3107 (aromatic C-H), 3034 (aromatic C-H), 2963 (aromatic C-H), 1749 (C=O), 1558 (N-O), 1454 (aromatic C=C), 1363 (N-O), 1267 (C-O), 1155 (C-O) cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{14}H_{12}SNO_4^-$ 290.0493; Found 290.0503.

Benzyl 2-nitro-3-(pyridin-3-yl)propanoate (2.33g)

Procedure:

A thick-walled glass tube with a Teflon screw cap was charged with nitroalkane (151 mg, 1 mmol) and benzyl phenyl carbonate (680 mg, 3 mmol). The tube was flushed with argon and then DMSO (210 µL, 2.95 mmol) was added followed by DABCO (224 mg, 2 mmol). The tube was capped and immersed in an oil bath at 60 °C. The reaction mixture was stirred at this temperature and the progress of the reaction was monitored by TLC. After completion of reaction (6 h), the reaction mixture was cooled to 0 °C and quenched with 1 M HCl (6 mL). This was further stirred at room temperature till a suspension was formed. The suspension was transferred to a separatory funnel containing 4 mL of 1 M HCl. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The acidic layer was quenched with saturated $NaHCO_3$ solution and extracted with DCM (4 × 30 mL). The combined DCM layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography.

Column Chromatography:

Approximately 40 mL of silica was packed into a column using 40% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 600 mL of 40% EtOAc in hexanes was eluted and collected in 25 mL fractions. Fractions 11 – 22 contained product. These fractions were concentrated and dried under high vacuum to give 147.4 mg of product (yield = 52%, average yield over two runs = 52%).

Characterization:

Pale yellow liquid; R_f: 0.20 in 50% EtOAc in hexanes; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (d, *J* = 1.9 Hz, 1H), 8.47 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.71 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.41 – 7.30 (m, 6H), 6.20 (dd, *J* = 8.3, 7.2 Hz, 1H), 5.29 – 5.23 (m, 2H),

3.52 – 3.50 (m, 2H); ^{13}C NMR (100 MHz DMSO-d_6): 164.0, 150.1, 148.6, 136.6, 134.6, 130.2, 128.5, 128.2, 123.5, 88.0, 67.9, 32.5; IR (film): 1752 (C=O), 1561(N-O), 1426 (aromatic C=C), 1366 (N-O) cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{15}H_{13}N_2O_4^-$ 285.0881; Found 285.0888.

Benzyl 3-(3-(benzyloxy)-2-nitro-3-oxopropyl)-1H-indole-1-carboxylate (2.33h)

Procedure:

A 10 mL Schlenk flask was charged with benzyl phenyl carbonate (343 mg, 1.5 mmol) and the flask was flushed with argon. The Schlenk flask was further charged with nitroalkane (163 mg, 0.5 mmol), DMSO (110 µL, 1.5 mmol), and DABCO (112mg, 1 mmol) while maintaining a positive pressure of argon. The flask was then immersed in an oil bath at 45 °C and the reaction mixture was stirred at this temperature for 4.5 h. It was then cooled to 0 °C and diethyl ether (3 mL) was added followed by 1 M $KHSO_4$ (5 mL). The contents were warmed to room temperature and stirred till a suspension was formed. It was then transferred to a separatory funnel containing 15 mL of 1 M $KHSO_4$. The aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined ether layers were dried over Na_2SO_4 and concentrated. The material obtained was distilled under high vacuum at 150 °C to remove large portion of phenol. The residual material in the distillation flask was further purified by flash column chromatography.

Column Chromatography:

Approximately 85 mL of silica was packed into a column using 40% DCM in hexanes as the solvent. The residual material obtained after distillation was adsorbed on silica and loaded on the column. Approximately 350 mL of 40% DCM in hexanes was eluted followed by elution with 800 mL of 45% DCM in hexanes, 700 mL of 50% DCM in hexanes, and 400 mL of DCM. The eluted solvent was collected in 25 mL fractions. Fractions 57 – 86 contained compound. These fractions were concentrated and dried

under high vacuum to give 162 mg of product (yield = 71%, average over two runs = 70%).

Characterization:

White solid; Mp = 174 – 176 °C; R_f: 0.57 in 60% DCM in hexanes; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.66 (s, 1H), 7.54 – 7.51 (m, 2H), 7.46 – 7.27 (m, 8H), 7.23 – 7.20 (m, 2H), 6.22 (dd, *J* = 9.2, 6.4 Hz, 1H), 5.46 (s, 2H), 5.21 (s, 2H), 3.67 (dd, *J* = 15.3, 9.0 Hz, 1H), 3.55 (dd, *J* = 15.2, 6.4 Hz, 1H); ^{13}C NMR (100 MHz DMSO-d_6): 164.2, 149.9, 135.2, 134.7, 134.6, 129.4, 128.6, 128.5, 128.4, 128.3, 128.0, 124.9, 124.3, 123.0, 119.4, 114.7, 114.2, 87.0, 68.4, 67.8, 25.2; IR (film): 1743 (C=O), 1562 (N-O), 1455 (aromatic C=C), 1398 (aromatic C=C), 1361 (N-O), 1250 (C-O) cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{21}H_{26}N_2O_6^-$ 457.1405; Found 457.1414.

Benzyl 2-nitro-4-phenylbutanoate (2.33i)

The general procedure was carried out with method B as workup procedure. In this reaction, 3.5 mmol of benzyl phenyl carbonate was used. Time: 6 h.

Column Chromatography:

Approximately 40 mL of silica was packed into a column using 30% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 800 mL of 30% DCM in hexanes was eluted and collected in 25 mL fractions. Fractions 11 – 21 contained product. Fractions 22 – 24 contained product contaminated with phenol. Fractions 11 – 24 were concentrated and dried under high vacuum at 60 °C for 5 h to give 106 mg of product (yield = 35%, average yield over two runs = 34%).

Characterization:

Pale yellow liquid; R_f : 0.33 in 10% EtOAc in hexanes; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44–7.35 (m, 5H), 7.32 – 7.28 (m, 2H), 7.23 – 7.18 (m, 3H), 5.72 (dd, *J* = 8.6, 5.5 Hz, 1H), 5.26 (s, 2H), 2.70 – 2.56 (m, 2H), 2.48 – 2.31 (m, 2H); ^{13}C NMR (100 MHz $CDCl_3$): 164.5, 139.0, 134.5, 129.0, 128.94, 128.91, 128.7, 128.5, 127.0, 87.2, 68.6, 32.0, 31.7; IR (film): 3029 (aromatic C-H), 1751 (C=O), 1560 (N-O), 1454 (aromatic C=C),, 1371 (N-O), 1357 (alkane C-H) cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{17}H_{16}NO_4^-$ 298.1085; Found 298.1094.

Benzyl 2-nitroacetate (2.33j)

The general procedure was used with method A as workup procedure. Time: 16.5 h.

Column Chromatography:

Approximately 40 mL of silica was packed into a column using 30% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 800 mL of 30% DCM in hexanes was eluted and collected in 25 mL fractions. Fractions 15 – 18 contained product. Fractions 19 – 32 contained product contaminated with phenol. Fractions 15 – 32 were concentrated and dried under high vacuum at 60 °C for 5 h to give 103 mg of product (yield = 52%, average yield over two runs =49.5 %).

Characterization:

Pale yellow liquid; R_f : 0.4 in 50% DCM in hexanes. ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.38 (m, 5H), 5.30 (s, 2H), 5.20 (s, 2H).

Benzyl 2-nitro-2-phenylacetate (2.33k)

The general procedure was carried out with method A as workup procedure. Time: 8 h.

Column Chromatography:

Approximately 45 mL of silica was packed into a column using 30% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 700 mL of 30% DCM in hexanes was eluted and collected in 12 mL fractions. Fractions 32 – 40 contained product. These fractions were concentrated and dried under high vacuum to give 15 mg of product (yield = 7%). The ^{1}H NMR data of the product was in agreement with the literature values.

Benzyl 4-methyl-2-nitropentanoate (2.33l)

The general procedure was carried out with method B as workup procedure. Time: 6 h.

Column Chromatography:

Approximately 40 mL of silica was packed into a column using 30% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 400 mL of 30% DCM in hexanes was eluted and collected in 25 mL fractions. Fractions 6 – 15 contained product. These fractions were concentrated and dried under high vacuum to give 41 mg of product (yield = 16, average yield over two runs =16 %).

Characterization:

Pale yellow liquid; R_f : 0.36 in 30% DCM in hexanes; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41–7.33 (m, 5H), 5.25 – 5.21 (m, 3H), 5.26 (s, 2H), 2.33 – 2.25 (m, 1H), 1.98 – 1.91 (m, 1H), 1.67 – 1.57 (m, 1H), 0.98 (d, *J* = 1.9 Hz, 3H), 0.96 (d, *J* = 1.8 Hz, 3H); ^{13}C NMR (100 MHz $CDCl_3$): 164.9, 134.5, 129.0, 128.9, 128.5, 86.9, 68.6, 38.9, 25.2, 22.6, 21.5; IR (film): 2965 (alkane C-H), 1750 (C=O), 1559 (N-O), 1174 (C-O), 696 (aromatic C-H) cm^{-1}; ; HRMS (ESI) m/z $(M–H)^-$ Calcd. for $C_{13}H_{16}NO_4^-$ 250.1085; Found 250.1091.

General Procedure for Reduction of Nitro Esters:

A 10 mL round bottomed flask was charged with α-nitro ester (0.5 mmol) and 2.5 mL of glacial acetic acid. Zinc dust (200 mg, 3 mmol) was added to this solution in four portions over 30-minute intervals. The reaction mixture was stirred for 16 h at room temperature and quenched with saturated K_2CO_3. The obtained suspension was filtered through a celite pad and the filtrate was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. It was then dissolved in toluene (1mL) and cooled to 0 °C. At this temperature, 4 M HCl (200 μL) in dioxane was added and reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was removed and the solid residue was dried under vacuum. The dried solid was washed with a 1:1 mixture of EtOAc and hexanes (50 mL) followed by distilled hexanes (30 mL) and dried once again under high vacuum to get pure product.

1-(Benzyloxy)-1-oxo-3-phenylpropan-2-aminium chloride (2.36a)

General procedure was employed with **2.33a** (140 mg, 0.49 mmol) and **2.36a** was obtained as a white solid (126 mg, yield = 88%).

Characterization:

Mp = 174 – 176 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (br s, 3H), 7.37 – 7.33 (m, 3H), 7.30 – 7.19 (m, 7H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 4.29 (dd, *J* = 7.9, 5.5 Hz, 1H), 3.25 (dd, *J* = 13.9, 5.5 Hz, 1H), 3.10 (dd, *J* = 13.9, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 168.8, 134.8, 134.7, 129.4, 128.5, 128.4, 128.31, 128.26, 127.2, 67.0, 53.2, 35.9 cm^{-1}; IR (KBr): 3141 (N-H), 2830 (alkane C-H), 1745 (C=O), 1606 (N-H), 1493 (aromatic C=C), 1456 (aromatic C=C), 1373 (alkane C-H), 1234 (C-O); HRMS (ESI) m/z M^+ Calcd. for $C_{16}H_{18}NO_2^+$ 256.1332; Found 256.1329.

1-(Benzyloxy)-3-(2-chlorophenyl)-1-oxopropan-2-aminium chloride (2.36b)

General procedure was employed with **2.33b** (144 mg, 0.45 mmol) and **2.36b** was obtained as a white solid (123 mg, yield = 84%).

Characterization:

Mp = 152 – 154 °C; ^{1}H NMR (400 MHz, D_2O): δ 7.53 – 7.45 (m, 4H), 7.38 – 7.24 (m, 5H), 5.27 (s, 2H), 4.54 (dd, *J* = 8.0, 7.2 Hz, 1H), 3.50 (dd, *J* = 14.1, 8.1 Hz, 1H), 3.40 (dd, *J* = 14.1, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, D_2O): 170.8, 135.8, 135.4, 133.3, 133.1, 131.43, 131.35, 130.6, 130.4, 130.3, 129.3, 70.3, 54.2, 35.4; IR (KBr): 2830 (br) (N-H),1744 (C=O), 1498 (aromatic C=C), 1477 (aromatic C=C), 1228 (C-O) cm^{-1}; HRMS (ESI) m/z M^+ Calcd. for $C_{16}H_{17}ClNO_2^+$ 290.0942; Found 290.09352.

1-(Benzyloxy)-1-oxo-3-p-tolylpropan-2-aminium chloride (2.36c)

General procedure was employed with **2.33c** (143 mg, 0.47 mmol) and **2.36c** was obtained as a white solid (124 mg, yield = 84%).

Characterization:

Mp = 173 – 175 °C (dec); ^{1}H NMR (400 MHz, D_2O): δ 7.52 – 7.48 (m, 3H), 7.40 – 7.37 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 5.32 (d, 12.0 Hz, 1H), 5.25 (d, 12.0 Hz, 1H), 4.44 (t, *J* = 6.7 Hz, 1H), 3.28 (dd, *J* = 14.3, 6.4 Hz, 1H), 3.23 (dd, *J* = 14.6, 7.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, D_2O): 171.0, 139.6, 135.9, 131.9, 131.3, 130.9, 130.6, 130.43, 130.40, 70.0, 55.6, 36.9, 21.8; IR (KBr): 2855 (br) (N-H), 1736 (C=O), 1489 (aromatic C=C), 1249 (C-O), 1231 (C-O) cm^{-1}; HRMS (ESI) m/z M^+ Calcd. for $C_{17}H_{20}NO_2^+$ 270.1489; Found 270.1487.

1-(Benzyloxy)-3-(naphthalen-2-yl)-1-oxopropan-2-aminium chloride (2.36d)

General procedure was employed with **2.33d** (160 mg, 0.47 mmol) and **2.36d** was obtained as a white solid (137 mg, yield = 84%).

Characterization:

Mp = 174 – 176 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (br s, 3H), 7.92 – 7.79 (m, 3H), 7.73 (s, 1H), 7.54 – 7.49 (m, 2H), 7.37 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.13 (d, *J* = 7.5 Hz, 2H), 5.13 (s, 2H), 4.44 – 4.41 (m, 1H), 3.45 – 3.40 (m, 1H), 3.28 (dd, *J* = 14.0, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): 170.0, 136.0, 135.0, 134.3, 132.6, 129.9, 129.8, 129.7, 129.59, 129.57, 128.8, 128.7, 127.9, 127.5, 127.3, 69.2, 55.1, 37.7; IR (KBr): 2868 (br) (N-H), 1741 (C=O), 1489 (aromatic C=C), 1228 (C-O) cm^{-1}; HRMS (ESI) m/z M^+ Calcd. for $C_{20}H_{20}NO_2^+$ 306.1489; Found 306.1488.

1-(Benzyloxy)-3-(3,4-dimethoxyphenyl)-1-oxopropan-2-aminium chloride (2.36e)

General procedure was employed with **2.33e** (150 mg, 0.43 mmol) and **2.36e** was obtained as a white solid (125 mg, yield = 82%).

Characterization:

Mp = 151 – 153 °C; ^{1}H NMR (400 MHz, D_2O): δ 7.44 – 7.35 (m, 3H), 7.22 – 7.20 (m, 2H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 6.67 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 4.40 (dd, *J* = 7.8, 6.3 Hz, 1H), 3.78 (s, 3 H), 3.67 (s, 3H), 3.22 (dd, *J* = 14.3, 6.2 Hz, 1H), 3.09 (dd, *J* = 14.3 Hz, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, D_2O): 171.0, 149.8, 149.3, 135.9, 130.5, 130.3, 130.0, 128.0, 123.6, 114.1, 113.5, 69.9, 57.11, 57.08, 55.5, 37.0; IR (KBr): 2834 (br) (N-H), 1750 (C=O), 1519 (aromatic C=C), 1266 (C-O) cm^{-1}; HRMS (ESI) m/z M^+ Calcd. for $C_{18}H_{22}NO_4^+$ 316.1543; Found 316.1541.

1-(Benzyloxy)-1-oxo-3-(thiophen-3-yl)propan-2-aminium chloride (2.36f)

General procedure was employed with **2.33f** (145 mg, 0.48 mmol) and **2.36f** was obtained as a white solid (122 mg, yield = 85%).

Characterization:

Mp = 172 – 174 °C; ^{1}H NMR (400 MHz, D_2O): δ 7.55 – 7.44 (m, 6H), 7.193 – 7.187 (m, 1H), 6.89 (d, *J* = 5.0 Hz, 1H), 5.36 (d, *J* = 12.0 Hz, 1H), 5.30 (d, *J* = 12.0 Hz, 1H), 4.47 (t, *J* = 6.3 Hz, 1H), 3.35 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, D_2O): 170.9, 136.1, 134.9, 130.7, 130.5, 130.4, 129.6, 129.0, 126.3, 70.2, 55.0, 31.6; IR (KBr): 2909 (br) (N-H), 1735 (C=O), 1492 aromatic (C=C), 1230 (C-O) cm^{-1}; HRMS (ESI) m/z M^+ Calcd. for $C_{14}H_{16}SNO_2^+$ 262.0896; Found 262.0890.

1-(Benzyloxy)-1-oxo-3-(pyridin-3-yl)propan-2-amine dihydrochloride (2.36g)

General procedure was employed with **2.33g** (119 mg, 0.41 mmol). In this reaction, 500 µL of 4N HCl was used and **2.36g** was obtained as a faint green solid (122 mg, yield = 89%).

Characterization:

Highly hygroscopic; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 – 8.79 (m, 5H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.90 (dd, *J* = 7.7, 5.7 Hz, 1H), 7.42 – 7.30 (m, 5H), 5.21 (s, 2H), 4.58 (m, 1H), 3.44 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): 168.2, 146.6, 142.7, 140.5, 135.2, 134.8, 128.5, 128.4, 128.3, 126.8, 67.4, 52.2, 32.1; IR (KBr): 2948 (br) (N-H), 2883 (N-H)(br), 2838 (N_H) (br), 1746 (C=O), 1221 (C-O) cm^{-1}; HRMS (ESI) m/z M^+ Calcd. for $C_{15}H_{17}N_2O_2^+$ 257.1285; Found 257.1291.

1-(Benzyloxy)-3-(1-(benzyloxycarbonyl)-1H-indol-3-yl)-1-oxopropan-2-aminium chloride (2.36h)

General procedure was employed with **2.33h** (100 mg, 0.21 mmol). Product **2.36h** was obtained as a pale yellow solid (78.1 mg, yield = 77%).

Characterization:

Mp = 156 – 158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.98 (br s, 3H), 8.03 (br s, 1H), 7.63 – 7.30 (m, 7H), 7.21 – 7.10 (m, 5H), 6.93 (br s, 2H), 5.25 (s, 2H), 4.89 (s, 2H), 4.55

(br s, 1H), 3.58 – 3.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.1, 150.8, 135.5, 135.1, 134.3, 130.0, 128.8, 128.7, 128.5, 128.4, 128.2, 125.5, 125.0, 123.2, 119.3, 115.4, 114.2, 68.8, 68.2, 53.3, 26.5; IR (KBr): 3490 (br) (N-H), 2967 (br) (N-H), 2907 (aromatic C-H), 1728 (C=O), 1753 (C=O), 1455 (aromatic C=C), 1398 (alkane C-H), 1357 (alkane C-H), 1259 (C-O), 1244 (C-O) cm^{-1}; HRMS (ESI) m/z M^+ Calcd. for $C_{26}H_{25}N_2O_4^+$ 429.1809; Found 429.1806.

1-(benzyloxy)-1-oxo-4-phenylbutan-2-aminium chloride (2.36i)

General procedure was employed with **2.33i** (98 mg, 0.32 mmol). Product **2.36i** was obtained as a white solid (82.9 mg, yield = 83%).

Characterization:

Mp = 140 – 142 °C; ^{1}H NMR (400 MHz, D_2O): 7.54 – 7.44 (m, 5H), 7.40 – 7.29 (m, 3H), 7.21 – 7.20 (m, 1H), 5.30 (d, *J* = 12.0 Hz, 1H), 5.24 (d, *J* = 12.0 Hz, 1H), 4.19 (t, *J* = 6.2 Hz, 1H), 2.81 – 2.74 (m, 1H), 2.66 – 2.59 (m, 1H), 2.36 – 2.20 (m, 2H); ^{13}C NMR (100 MHz, D_2O): 171.3, 141.3, 136.3, 130.6, 130.5, 130.4, 130.3, 130.0, 128.3, 70.0, 53.8, 33.0, 31.6; IR (KBr): 2955 (br) (N-H), 2934 (N-H) (br), 2920 (N-H) (br), 1748 C=O), 1524, (aromatic C=C), 1238 (C-O) cm^{-1}; HRMS (ESI) m/z M^+ Calcd. for $C_{17}H_{20}NO_2^+$ 270.1489; Found 270.1489.

Benzene, (2-acinitroethyl)-, Sodium derivative (2.37)

Procedure:

A 50 mL round bottomed flask was charged with 60% suspension of sodium hydride (120 mg, 3 mmol) in mineral oil. The suspension was washed twice with dry hexane under argon to remove mineral oil. It was then re-suspended in 10 mL of dry THF and the round bottom flask was immersed in ice bath. 1-Nitro-2-phenyl ethane (450 mg, 2.97 mmol) was dissolved in 3 mL of THF and the solution was cannulated to the suspension of sodium hydride at 0 °C. The reaction mixture was allowed to warm to

room temperature and stirred for 4h. The solvent was removed and the solid residue obtained was washed with Ethanol and dried under high vacuum to obtain 254.1 mg of compound (yield = 53.7 %).

1-Nitro-2-phenylethane (2.22a)

Procedure:

A 100 mL round bottomed flask was charged with trans-β-nitrostyrene (1.5 g, 10.05 mmol), glacial acetic acid (1.2 mL, 20.96 mmol), and DMSO (8 mL). The flask was immersed in a water bath and $NaBH_4$ (620 mg, 16.3 mmol) was added portion-wise to the flask. After addition of $NaBH_4$, the reaction mixture was stirred for 30 min. It was then diluted with EtOAc (100 mL). The EtOAc solution was washed successively with de-ionized water (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL). It was then dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography. R_f: 0.27 in 10% EtOAc in hexanes.

Column Chromatography:

Approximately 80 mL of silica was packed into a column using 5% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 800 mL of 5% EtOAc in hexanes was eluted and collected in 25 mL fractions. Fractions 10 – 28 contained product. These fractions were concentrated and dried under high vacuum to give 1.23 g of product (yield = 81%). The ^{1}H NMR data of the product was in agreement with the literature values.[36]

2-(o-Chlorophenyl)nitroethane (2.22b)

Procedure:

A 50 mL round bottomed flask was charged with 2-chlorobenzaldehyde (1.5 g, 9.64 mmol), MeOH (3 mL), and nitromethane (520 µL, 9.68 mmol). The flask was immersed in an ice bath and 5 M NaOH (2 mL) was added. The reaction mixture was

stirred at 0 °C for 4 h. It was then added to a beaker containing concentrated HCl (3 mL) in crushed ice and a clear solution was obtained. The aqueous layer was extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in a mixture of DMSO (17 mL) and glacial acetic acid (1.4 mL, 24.45 mmol). This solution was kept in a water bath and $NaBH_4$ (1.09 g, 28.68 mmol) was added portion-wise. After this, the reaction mixture was stirred for 30 min. It was then diluted with EtOAc (50 mL). The organic layer was washed successively with de-ionized water (50 ml), saturated $NaHCO_3$ (50 mL), and brine (50 mL). It was then dried over Na_2SO_4 and concentrated. The material obtained was purified by flash column chromatography. R_f: 0.25 in 15% EtOAc in hexanes.

Column chromatography:

Approximately 120 mL of silica was packed into a column using 15% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 800 mL of 15% DCM in hexanes was eluted and collected in 25 mL fractions. Fractions 11 – 19 contained compound. These fractions were concentrated and dried under high vacuum to give 398 mg of product (yield = 16%). The ^1H NMR data of the product was in agreement with the literature.[37]

2-(p-Tolyl)-1-nitroethane (2.22c)

This was synthesized using the procedure for preparing **3b**, with the following quantities: p-tolualdehyde (3 mL, 25.4 mmol), MeOH (8 mL), nitromethane (1.4 mL, 26 mmol), concentrated HCl (6 mL), DMSO (17 mL), glacial acetic acid (2 mL, 34.9 mmol), and $NaBH_4$ (2.62 g, 68.9 mmol). R_f: 0.12 in 15 % DCM in hexanes.

Column Chromatography:

Approximately 120 mL of silica was packed into a column using 15 % DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. The column was eluted with 15 % DCM in hexanes and the eluant was collected in 25 mL fractions. Fractions 21 – 68 contained compound. These fractions were concentrated and dried under high vacuum to give 1.36 g of product (yield = 33%). The ^{1}H NMR data of the product was in agreement with the literature.[38]

2-(2-Nitroethyl)-naphthalene (2.22d)

This was synthesized using the procedure for preparing **3b**, with the following quantities: 2-naphthaldehyde (2 g, 12.8 mmol), MeOH (3.5 mL), nitromethane (690 μL, 12.8 mmol), 5 M NaOH (3.5 mL), concentrated HCl (3 mL), DMSO (6 mL), glacial acetic acid (2.2 mL, 38.4 mmol), and $NaBH_4$ (2.7 g, 71 mmol). R_f: 0.12 in 15 % DCM in hexanes.

Column Chromatography:

Approximately 130 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. The column was eluted with 20% DCM in hexanes and the eluent was collected in 25 mL fractions. Fractions 20 – 80 contained compound. These fractions were concentrated and dried under high vacuum to give 1.28 g of product (yield = 50%). The ^{1}H NMR data of the product was in agreement with the literature.[39]

(3, 4-Dimethoxyphenyl)-β-nitrostyrene

Procedure:

A 100 mL round bottomed flask was charged with 3, 4-dimethoxy benzaldehyde (5 g, 30 mmol), MeOH (30 mL) and nitromethane (1.6 mL, 30.1 mmol). The flask was immersed in an ice bath and 5 M NaOH (3.0 mL) was added. The reaction mixture was stirred at 0 °C for 5 h. It was then added to a solution of concentrated HCl (34 mL) in de-ionized water (34 mL) at 0 °C. The precipitate obtained was filtered, washed with 1:1mixture of EtOH in water solution (20 mL) and dried under high vacuum to give 5.18 g of product (yield = 82%).

(3, 4-Dimethoxyphenyl)-1-nitroethane (2.22e)

Procedure:

A 250 mL flask was charged with (3, 4-dimethoxyphenyl)-β-nitrostyrene (5.1 g, 24.7 mmol), MeOH (55 mL) and DCM (55 mL). The flask was immersed in an ice bath and $NaBH_4$ (2.3 g, 52.6 mmol) was added portion-wise. The reaction mixture was stirred at 0 °C for 30 min and 70 mL of de-ionized water was added. The aqueous layer was extracted with DCM (4 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The material obtained was purified by flash column chromatography. R_f: 0.20 in 20% EtOAc in hexanes

Column Chromatography:

Approximately 120 mL of silica was packed into a column using 20% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,600 mL of 20% EtOAc in hexanes was eluted and collected in 25 mL fractions. Fractions 20 – 52 contained product. These fractions were concentrated and dried under high vacuum to give 1.44 g of product (yield = 28%). The ^{1}H NMR data of the product was in agreement with the literature.[377]

(3-Thiophene)-1-nitroethane (2.22f)

This was synthesized using the procedure for preparing **3b**, with the following quantities: thiophene-3-aldehyde (920 mg, 8.2 mmol), MeOH (15 mL), nitromethane (480 μL, 9 mmol), 10 M NaOH (900 μL), concentrated HCl (20 mL), DMSO (7 mL), glacial acetic acid (940 μL, 16.4 mmol), and $NaBH_4$ (500 mg, 13.1 mmol). R_f: 0.27 in 10 % EtOAc in hexanes.

Column Chromatography:

Approximately 120 mL of silica was packed into a column using 5% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,200 mL of 5% EtOAc in hexanes was eluted and collected in 25 mL fractions. Fractions 19 – 45 contained product. These fractions were concentrated and dried under high vacuum to give 449.2 mg of product (yield = 35%). The ^{1}H NMR data of the product was in agreement with the literature values.[40]

Pyridine 3-(2-nitroethyl) (2.22g)

Procedure:

A 100 mL round bottomed flask was charged with 3-pyridinecarboxaldehyde (2 mL, 21.3 mmol), nitromethane (1.6 mL, 29.8 mmol) and 26 mL of 1:1 mixture of THF and ^{t}BuOH. The flask was immersed in an ice bath and potassium tert-butoxide (150 mg, 1.34 mmol) was added. After completion of reaction (2 h) by TLC, de-ionized water (12 mL) was added to the reaction mixture. The aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined ether layers were dried over Na_2SO_4 and concentrated in 100 mL round bottomed flask. To the residue, DCM (50 mL), 4-dimethylaminopyridine (DMAP, 190 mg, 1.55 mmol) and acetic anhydride (2.2 mL, 23.27 mmol) were added. The reaction mixture was stirred at room temperature for 2 h and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with

DCM. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in a mixture of DMSO (25 mL) and glacial acetic acid (2.9 mL, 50.65 mmol). This solution was kept in a water bath and $NaBH_4$ (1.2 g, 31.5 mmol) was added portion-wise. After this, the reaction mixture was stirred for 30 min. It was then diluted with EtOAc (70 mL). The organic layer was washed successively with de-ionized water (70 mL), saturated $NaHCO_3$ solution (70 mL), and brine (70 mL). It was then dried over Na_2SO_4 and concentrated. The material obtained was purified by flash chromatography. R_f: 0.10 in 30% EtOAc in hexanes.

Column chromatography:

Approximately 110 mL of silica was packed into a column using 30% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1200 mL of 30% EtOAc in hexanes was eluted and collected in 25 mL fractions. Fractions 20 – 34 contained compound. These fractions were concentrated and dried under high vacuum to give 371 mg of product (yield = 11%). The ^{1}H NMR data of the product was in agreement with the literature.[41]

N-(Benzyloxycarbonyl) indole-3-carbaldehyde

Procedure:

A 100 mL two neck round bottomed flask was charged with sodium hydride (1.7 g, 42.5 mmol, 60% suspension in mineral oil) and THF (50 mL). The flask was immersed in an ice bath and indole-3-carboxaldehyde (5 g, 34.4 mmol) was added portion-wise. The reaction mixture was warmed to 40 °C and stirred for 30 min. It was then cooled to 0 °C and benzyl chloroformate (12 mL, 35.16 mmol) was added drop wise. After this, the reaction mixture was allowed to warm to room temperature and stirred for 16 h. To the reaction mixture, de-ionized water (50 mL) was added. The aqueous layer was extracted with DCM (3 × 50mL). The combined DCM layers were dried over

Na_2SO_4 and concentrated. The material obtained was purified by flash column chromatography on silica gel. R_f: 0.50 in 15% EtOAc in hexanes.

Column Chromatography:

Approximately 140 mL of silica was packed into a column using 10% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 2000 mL of 10% EtOAc in hexanes was eluted and collected in 15 mL fractions. Fractions 32 – 88 contained product. These fractions were concentrated and dried under high vacuum to give 3.61 g of product (yield = 38%). The ^{1}H NMR data of the product was in agreement with the literature.[42]

N-(Benzylloxycarbonyl) indole-3-nitroethane (2.22h)

Procedure:

A 50 mL round bottomed flask was charged with N-(Benzyloxycarbonyl) indole-3-carbaldehyde (2.4 g, 8.7 mmol), ammonium acetate (1.70 g, 21.8 mmol), glacial acetic acid (18 mL) and nitromethane (1.5 mL, 27.9 mmol). The reaction mixture was refluxed for 45 min and transferred to a separatory funnel containing ice cold water (200 mL). The aqueous layer was extracted with DCM (4 × 50 mL). The combined DCM layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in a mixture of DMSO (5 mL) and glacial acetic acid (610 µL, 10.65 mmol). This solution was kept in a water bath and $NaBH_4$ (320 mg, 8.42 mmol) was added portion-wise. After this, the reaction mixture was stirred for 30 min. It was then diluted with EtOAc (70 mL). The organic layer was washed successively with de-ionized water (70 mL), saturated $NaHCO_3$ (70 mL), and brine (70 mL). It was then dried over Na_2SO_4 and concentrated. The material obtained was purified by flash column chromatography.

Column Chromatography:

Approximately 100 mL of silica was packed into a column using 6% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,700 mL of 6% EtOAc in hexanes was eluted and collected in 25 mL fractions. Fractions 29 – 53 contained compound. These fractions were concentrated and dried under high vacuum to give 1.16 g of product (yield = 40%).

Characterization:

Pale yellow solid; Mp = 80 – 83 °C; R_f: 0.12 in 10 % EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): 8.20 (d, *J* = 7.1 Hz, 1H), 7.58 – 7.28 (m, 9H), 5.46 (s, 2H), 4.68 (t, *J* = 7.3 Hz, 2H), 3.44 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 150.7, 135.7, 135.1, 129.6, 128.9, 128.7, 125.3, 123.5, 123.3, 118.5, 115.7, 74.7, 69.0, 23.2; IR (film): 1735 (C=O), 1552 aromatic (C=C), 1455 (N-O), 1399 (alkane C-H), 1252 (C-O), 1090 (C-O) cm^{-1}; HRMS (ESI) m/z M^+ Calcd. for $C_{18}H_{17}N_2O_4^+$ 325.1181; Found 325.1172.

3-Phenylnitropropane (2.22i)

This was synthesized using the procedure for preparing **3b**, with the following quantities: 2-phenylacetaldehyde (4.2 mL, 37.1 mmol), MeOH (9 mL), nitromethane (2 mL, 37.2 mmol), 13 M NaOH (3.6 mL), concentrated HCl (9 mL), DMSO (34 mL), glacial acetic acid (4.6 mL, 80.35 mmol) and $NaBH_4$ (2 g, 52.63 mmol). R_f: 0.27 in 10% EtOAc in hexanes.

Column Chromatography:

Approximately 100 mL of silica was packed into a column using 18% DCM in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,200 mL of 18% DCM in hexanes was eluted and collected in 25 mL fractions. Fractions 18 – 39 contained compound. These fractions

were concentrated and dried under high vacuum to give 665 mg of product (yield = 11%). The ^{1}H NMR data of the product was in agreement with the literature.[43]

3-Methyl-1-nitrobutane (2.22l)

Procedure:

This was synthesized using the procedure for preparing **3b**, with the following quantities: isobutyraldehyde (3.4 mL, 38.2 mmol), MeOH (9 mL), nitromethane (2 mL, 37.2 mmol), 13 M NaOH (3.6 mL), concentrated HCl (18 mL), DMSO (38 mL), glacial acetic acid (4.5 mL, 78.6 mmol) and $NaBH_4$ (2.3 g, 61.63 mmol). The material obtained after workup was distilled under vacuum (25 mm of Hg) at 130 °C to give 911 mg of pure compound (yield = 34.5%). The ^{1}H NMR of the product was in agreement with the literature.[44]

(2-Nitroehtyl)cyclohexane (2.22n)

This was synthesized using the procedure for preparing **3b**, with the following quantities: cyclohexane carbaldehyde (3.1 mL, 25.6 mmol), MeOH (7 mL), nitromethane (1.5 mL, 27.9 mmol), 13 M NaOH (3.6 mL), concentrated HCl (10 mL), DMSO (26 mL), glacial acetic acid (3 mL, 52.4 mmol) and $NaBH_4$ (1.2 g, 31.57 mmol). The material obtained after workup was purified by column chromatography.

Column Chromatography:

Approximately 120 mL of silica was packed into a column using 30% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 600 mL of 40% DCM in hexanes was eluted and collected in 25 mL fractions. Fractions 13 – 20 contained compound. These fractions were concentrated and dried under high vacuum to give 1.24 g of product (yield = 38.5%). The ^{1}H NMR of the product was in agreement with the literature.[388]

Benzyl phenyl carbonate (2.30a)

Procedure:

A 50 mL round bottomed flask was charged with phenol (4.68 g, 49.7 mmol), DCM (50 mL) and pyridine (4 mL, 49.6 mmol). The flask was immersed in an ice bath and benzyl chloroformate (17 mL, 49.81 mmol) was added drop-wise. The reaction mixture was allowed to warm up to room temperature and stirred overnight. After this the reaction mixture was transferred to a separatory funnel and diluted with DCM (50 mL). The organic layer was washed successively with de-ionized water (50 mL), 5% NaOH (50 mL), 1 M HCl (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The material obtained was purified by flash column chromatography. R_f: 0.47 in 50% DCM in hexanes.

Column Chromatography:

Approximately 150 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 500 mL of 20% DCM in hexanes was eluted followed by elution with 1,200 mL of 25% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 21 – 63 contained product. These fractions were concentrated and dried under high vacuum to give 6.46 g of product (yield: 57%). The ^{1}H NMR data of the product was in agreement with the literature values.[45]

Benzyl-4-nitrophenyl carbonate (2.30b)

Method employed for the preparation of benzyl phenyl carbonate was used with the following quantities: 4-nitrophenol (700 mg, 5.0 mmol), benzyl chloroformate (1.7 mL, 5.0mmol), pyridine (0.41 mL, 5.0 mmol), and DCM (15 mL).

Column Chromatography:

Approximately 60 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 600 mL of 60% DCM in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 4 – 21 contained product. These fractions were concentrated and dried under high vacuum to give 1.1 g of product (yield: 78.7%).

Characterization:

Crystalline white solid; R_f: 0.2 in 50% DCM in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 – 8.26 (m, 2H), 7.47 – 7.38 (m, 7H), 5.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 152.6, 145.6, 134.3, 129.2, 128.9, 128.8, 125.4, 121.9, 71.1; IR (film): 1769 (C=O), 1502 (N-O), 1252 (C-O), 757 , 705, 477 cm^{-1}.

Benzyl perfluorophenyl carbonate (2.30c):

Method employed for the preparation of benzyl phenyl carbonate was used with the following quantities: 2,3,4,5,6-pentafluorophenol (930 mg, 5.0 mmol), benzyl chloroformate (1.7 mL, 5.0mmol), pyridine (0.41 mL, 5.0 mmol), and DCM (15 mL).

Column Chromatography:

Approximately 60 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 200 mL of 5% DCM in hexanes was eluted followed by elution with 400 mL of 20% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 11 – 18 contained product. These fractions were concentrated and dried under high vacuum to give 825 mg of product (yield: 51.4%). The ^{1}H NMR, data of the product was in agreement with the literature.[46]

Benzyl-4-cyanophenyl carbonate (2.30d)

Method employed for the preparation of benzyl phenyl carbonate was used with the following quantities: 4-cyanophenol (3 g, 25.9 mmol), benzyl chloroformate (14 mL, 41.0mmol), pyridine (3.2 mL, 39.7 mmol), and DCM (30 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,400 mL of 1% EtOAc in hexanes was eluted followed by elution with 1,000 mL of 30% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 60 – 98 contained product. These fractions were concentrated and dried under high vacuum to give 4.95 g of product (yield: 75.6%).

Characterization:

Crystalline white solid; R_f: 0.36 in 30% DCM in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 – 7.69 (m, 2H), 7.47 – 7.39 (m, 5H), 7.36 – 7.32 (m, 2H), 5.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 152.7, 134.4, 133.9, 129.2, 128.9, 128.8, 118.2, 110.1, 119.5, 71.1; IR (film): 2226 (CN), 1763 (C=O), 1495 (aromatic (C=C), 1212 (C-O), 736, 805, 547 cm^{-1}.

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Chapter 3

Cation-π Interactions in the Activation of Benzyl Phenyl Carbonates

3.1 Introduction

In the previous chapter, the development of a cyanide-free synthesis of α-amino esters was described. The activation of benzyl phenyl carbonate using a nucleophile is a key step in this reaction. Benzyl phenyl carbonate acts as a one-carbon synthon for the carboxyl group and is retained in the product as a benzyl ester. To obtain the corresponding α-amino acids, the ester group has to be transformed to the carboxylic acid. Benzyl esters can be reductively cleaved under a variety of conditions to obtain the corresponding carboxylic acids (Scheme 3.1).[1] In order to have flexibility in the conversion of amino esters into carboxylic acids, we decided to explore other carbonates as one-carbon synthons (Figure 3.1). Our initial target was to use *t*-butyl phenyl carbonate as the one-carbon synthon. Using this carbonate in our synthesis of α-amino acids was expected to yield a *t*-butyl ester as product (Scheme 3.2). *t*-Butyl esters can be readily converted to the corresponding carboxylic acid under acidic conditions.[2] We thought that this would be especially useful in the case of substrates that may be sensitive to reductive conditions. Therefore, during our initial optimization of the α-amino ester synthesis we looked at *t*-butyl phenyl carbonate (**3.1b**) as a potential one-carbon synthon.

Scheme 3.1 Reduction of Benzyl Esters

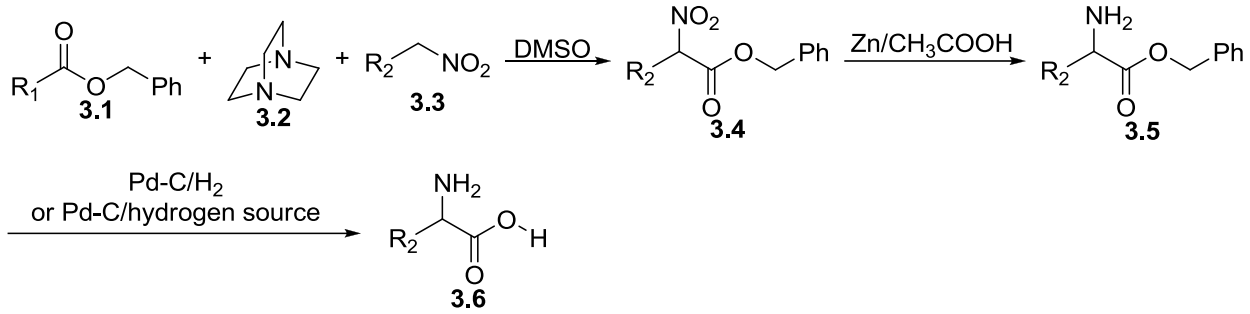
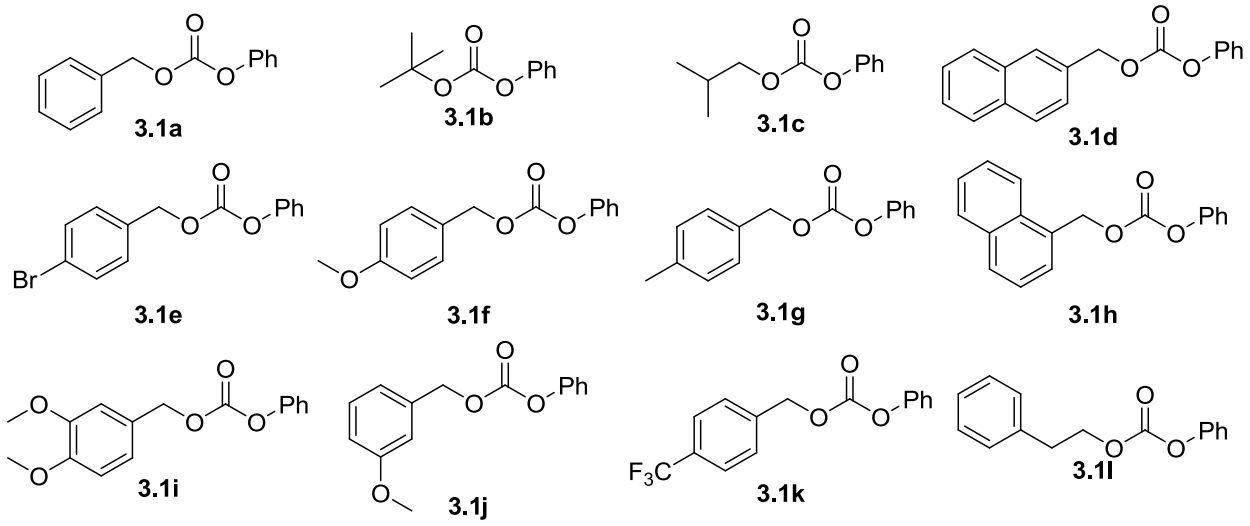
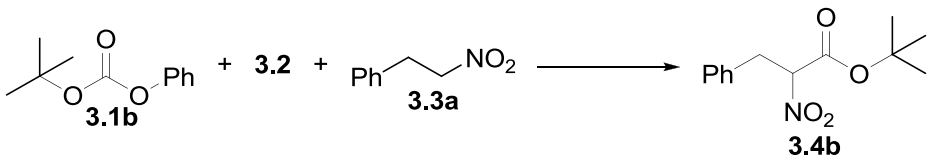


Figure 3.1 List of Carbonates Screened

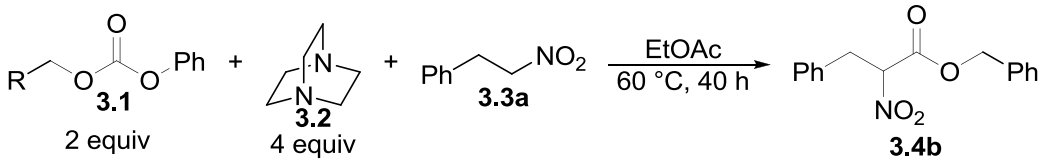


Scheme 3.2 α-Nitro Ester Preparation from *t*-Butyl Phenyl Carbonate



To test this, we carried out a reaction at 60 °C with 2-phenyl nitroethane as the substrate and ethyl acetate as the solvent (Table 3.1). Under these conditions, we did not observe the formation of *t*-butyl ester. Indeed, we were able to recover both the carbonate and the 2-phenyl nitroethane in good yield. Under identical conditions, benzyl phenyl carbonate gave a 64% yield of the benzyl ester product. We hypothesized that the difference in reactivity was due to the larger size of the *t*-butyl carbonate.

Table 3.1 Effect of Carbonates on yields of α-Nitro Ester



entry	carbonate	% yield	% nitro alkane recovered	% carbonate recovered
1	**3.1b**	0	85	> 95
2	**3.1c**	0	86	> 95
3	**3.1a**	64	0	0

To test our hypothesis, we synthesized the less hindered isobutyl phenyl carbonate (**3.1c**). Once again we failed to observe formation of the corresponding ester and we were able to recover the starting materials in good yield (Table 3.1). These experiments clearly showed that the benzyl group had a key role to play in the nucleophilic activation of carbonates.

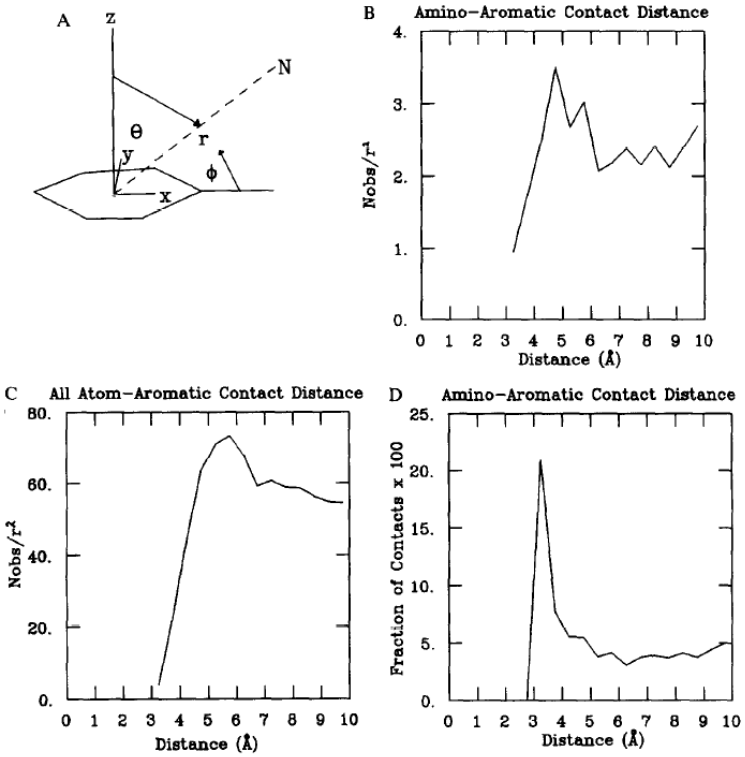
Based on the mechanism proposed in the previous chapter, it seemed plausible that the benzyl group might be involved in the stabilization of cationic transition states and intermediates. The nucleophilic activation of a carbonate generates an activated acyl group and a phenoxide anion. In tandem, these two species can be used in a number of important reactions. For example, the nucleophilic activation of carbonates has been used in an enantioselective *O*- to *C*-carboxyl transfer by Smith and coworkers.[3] Carbonates have also been used by Lou and coworkers to trap the product of reaction between glycine imine esters and aryl aldehydes.[4] This is an extremely useful reaction that generates β-hydroxy-α-amino acids as the product. The isolation of the aldol product in these reactions is complicated by the reversible nature of the reaction.[5] To facilitate isolation of the aldol adduct, the hydroxyl group in the product is trapped using a carbonate. Apart from this, activation of acyl groups using chiral nucleophiles has also been used in kinetic resolutions.[6] In these reactions, the activated acyl group is generated from moisture sensitive acid anhydrides and acid chlorides. On the other hand, in our

method, we generate activated acyl groups from stable carbonates and this is likely to be useful in a number of reactions. The key role of cation-π interactions in this activation step is explored in detail in this chapter.

3.2 Cation-π Interactions

Cation-π interactions were originally hypothesized to be key interactions in the stabilization of protein structure by Petsko and coworkers.[7] In their analysis of 33 protein crystal structures, they found that positively charged ammonium cations were often in close contact with the aromatic side chains of amino acids (Figure 3.2). For most of the structures, the distance between the aromatic residue and the cation was in the range of 3.4 to 6 Å. This suggested that the interaction between a cation and an aromatic side chain was a stabilizing interaction.

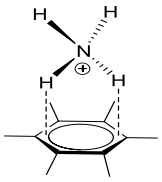
Figure 3.2 Ammonium Cations Interaction with π Electron Cloud of Aromatic ring in Proteins. Reprinted with Permission from Elsevier. Permission no. 3882871415382.



A) Coordinate axis for the definition of polar coordinate system (*r, θ, ϕ*). B)The distance distribution function for amino aromatic contacts (<10Å). C)The distance distribution function for all protein atom aromatic contacts (<10Å). D) The frequency of amino aromatic contacts (<10Å) displayed as a percentage of all protein aromatic contacts.

Along similar lines, Kebarle and coworkers have shown that potassium cation interacts more strongly with benzene than with water.[8] Later work shows that other alkali metal ions also exhibit stronger binding affinities for aromatic groups.[9] Thermochemical measurement by Meot-Ner and Deakyne showed that ammonium ions also have strong interactions with π-systems.[10] In pioneering studies, Dougherty and coworkers showed that the interaction of cations with cyclophane based receptors is stronger than solvation in aqueous media.[11] A number of cyclophanes were synthesized and their binding affinities with various cations were studied in water as well as organic solvents.[12] On the basis of these studies, it has been proposed that a major contributing factor to cation-π interactions is an electrostatic interaction between the quadruple dipole of the aromatic ring and the charge on the cation. A study of electrostatic potential maps shows that stronger cation-π interactions are observed in aromatic systems with greater negative charge at their center. Consistent with this, a study of substituent effects on the strength of cation-π interactions shows that the best correlations are obtained with σ_m parameters.[13] The σ_m parameter is a reflection of the inductive contribution of a substituent. In the case of ammonium ions, a greater degree of positive charge is present on the hydrogens attached to the nitrogen. Several studies have shown that the optimal orientation for cation-π interaction involves a 'bidentate' binding mode wherein two hydrogen atoms interact with benzene (Figure 3.3). As a result, the cationic portion is no longer focused at the center of the aromatic system. Indeed Sussman and coworkers have shown that in the case of ammonium ion, the hydrogens are oriented towards the carbons that carry the greatest degree of negative charge.[14] This would suggest a Hammett correlation with σ_p parameters. The resonance contribution of each substituent is reflected in σ_p parameters. Our study of cation-π interactions in the activation of carbonates could potentially clarify this.

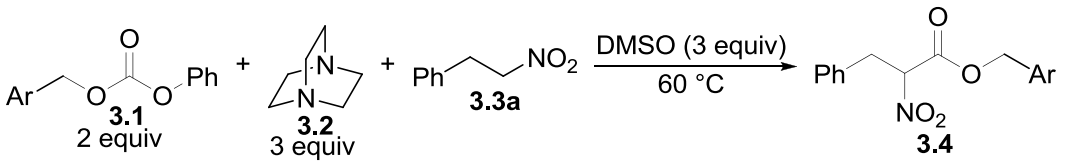
Figure 3.3 Ammonium Cation Interaction with Benzene



3.3 Hydrolysis as a Model Reaction

Our initial experiments (Table 3.1) suggested that benzyl groups play an important role in the synthesis of α-nitro ester. To clarify this, we synthesized carbonates with various substitution patterns (Figure 3.1). Among these we selected three carbonates and evaluated their performance in the synthesis of α-nitro esters (Table 3.2). Using 2-phenylnitroethane as the substrate. We performed reactions with various carbonates under the standard conditions reported in Chapter 2. All of the reactions were monitored by thin layer chromatography (TLC) and reactions were quenched upon complete consumption of starting materials. Our study showed that the reaction with *p*-methoxy benzyl phenyl carbonate (**3.1f**) was faster than the reaction with benzyl phenyl carbonate (**3.1a**). Although the reaction was faster, the yield of the isolated product was lower. This was most likely due to the formation of nitrile oxide and furoxane side products.[15] We were unable to isolate and characterize these products.

Table 3.2 α-Nitro Ester Preparation by Employing Different Carbonates



entry	carbonate	product	time[a]	% yield
1	**3.1a**	**3.4a**	5 h	77
2	**3.1d**	**3.4d**	5 h	74
3	**3.1e**	**3.4e**	3 h	70
4	**3.1f**	**3.4f**	1 h	48

[a]Reactions were quenched after complete consumption of starting materials.

The faster reaction with carbonate **3.1f** indicated a possible role for cation-π interactions in these reactions. To quantify the increase in reaction rate with variation in benzyl group, we wanted to evaluate the rate constant for consumption of carbonate. However, the divergent yields precluded the possibility of quantifying the rate acceleration through kinetic studies on these reactions. Therefore, we sought a model reaction that would potentially proceed through a similar transition state. Keeping this in mind, we decided to use the DABCO mediated hydrolysis of carbonates as our model reaction. The activation of benzyl aryl carbonate with DABCO generates a phenoxide and an activated acyl group. The activated acyl group reacts with a nitronate anion in the case of α-nitroester formation. In case of our model reaction, it was expected to react with water and yield benzyl hydrogen carbonate as the product. Decomposition of this product would result in the formation of the corresponding benzyl alcohol. DMSO was chosen as the solvent for this study as it was used as an additive in the synthesis of α-nitroesters.

3.4 Results and Discussion

Nucleophile mediated hydrolysis provides a convenient alternative to nitro ester synthesis for clarifying the role of benzyl group. Comparison of the rate constant for hydrolysis of various carbonates can give us an estimate of the transition state stabilization provided by the benzyl group. For this purpose, we synthesized the carbonates shown in Figure 3.1. To obtain rate constants, we studied the nucleophile mediated hydrolysis under pseudo-first order conditions. For convenient monitoring, all reactions were performed in an NMR tube with a carbonate concentration of ~0.03 M and a DABCO concentration of ~0.15 M. An 80:20 mixture of DMSO-d_6 and D_2O was used as the solvent and naphthalene was used as an internal standard. Reactions were performed by immersing the NMR tube in an oil bath maintained at 40 °C. For

monitoring the reaction, the NMR tube was periodically removed from the oil bath and immersed in ice water for a few minutes. Following this, the NMR spectra were recorded at 25 °C. The percentage of extant carbonate (C_t) was measured at each time point by comparing its integration with the internal standard. Pseudo-first order rate constants were obtained from a plot of $\ln(100/C_t)$ vs time (Figure 3.4). All reactions were performed in triplicate and the average rate constants along with the standard deviations are shown in Table 3.3.

We began our studies with the hydrolysis of benzyl phenyl carbonate under standard conditions. The reactions reached ~92% conversion over ~1900 minutes and a plot of $\ln(100/C_t)$ vs time gave excellent straight line fits (Figure 3.4). From this, an average rate constant, $k = 1.4\times10^{-3}$/min was obtained. To understand the role of benzyl group, we performed the hydrolysis of the isobutyl phenyl carbonate **3.1c** under identical conditions. An average rate constant of 8.8×10^{-5}/min was obtained for this reaction. The 16-fold rate acceleration for the hydrolysis of carbonate **3.1a** over carbonate **3.1c** can be rationalized by the hypothetical reaction pathway shown in Scheme 3.3. We hypothesize that the observed rate acceleration is due to stabilization of the transition state for nucleophilic attack of DABCO on the carbonate. This is likely due to cation-π interactions between the acyl-ammonium cation and the benzene ring.

Figure 3.4 Plot of $\ln(100/C_t)$ vs Time for the Hydrolysis of **1a** with DABCO

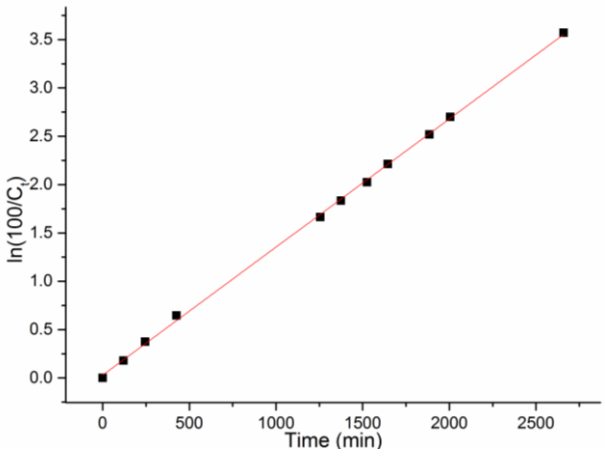
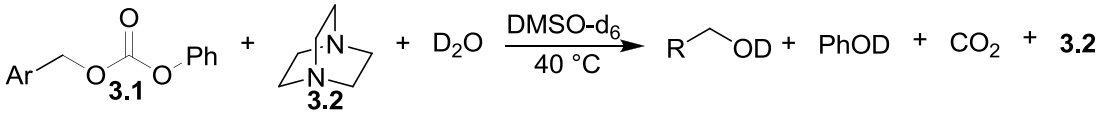


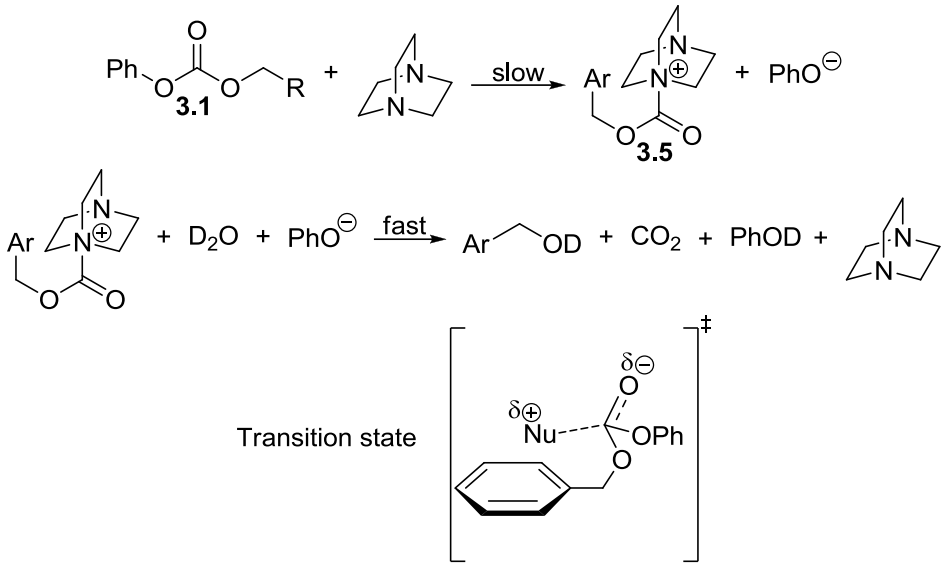
Table 3.3 Rate Constants for Hydrolysis of Different Benzyl Aryl Carbonates



entry	carbonate	rate constant k (min^{-1})[a]	standard deviation	relative rate
1	**3.1c**	$8.8x10^{-5}$	$8.1x10^{-6}$	1
2	**3.1a**	$1.4x10^{-3}$	$6.2x10^{-5}$	16
3	**3.1d**	$2.0x10^{-3}$	$9.9x10^{-5}$	23
4	**3.1e**	$1.5x10^{-3}$	$6.5x10^{-5}$	17
5	**3.1f**	$4.5x10^{-3}$	$1.0x10^{-4}$	51
6	**3.1g**	$2.3x10^{-3}$	$4.9x10^{-5}$	26
7	**3.1h**	$2.9x10^{-3}$	$1.6x10^{-4}$	33
8	**3.1i**	$3.9x10^{-3}$	$1.5x10^{-4}$	44
9	**3.1j**	$1.2x10^{-3}$	-	14
10	**3.1k**	$9.3x10^{-4}$	$9.3x10^{-4}$	11

[a] Reactions were performed in an NMR tube immersed in an oil bath maintained at 40 °C. For monitoring the reactions, the NMR tube was immersed in an ice bath for a few minutes followed by recording of spectra at 25 °C. All reactions were repeated thrice and the average k is reported. For standard deviations see supporting information.

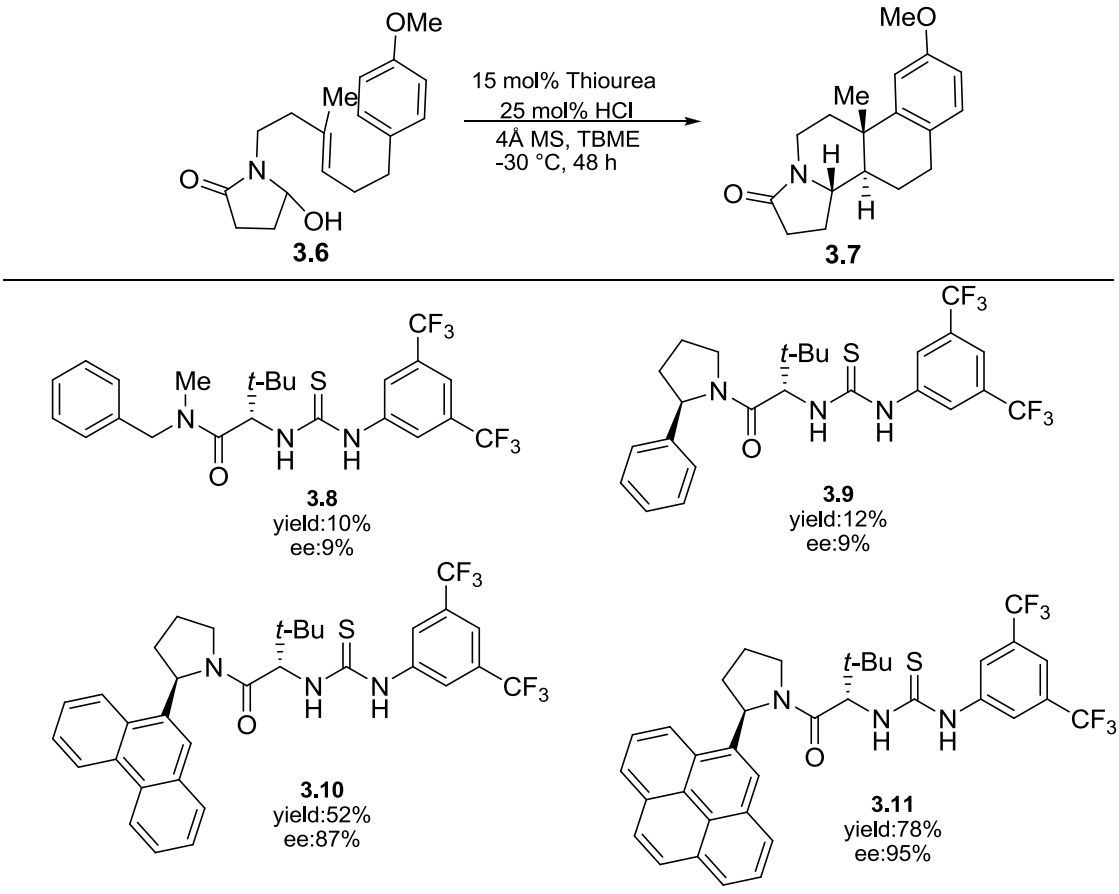
Scheme 3.3 Hypothetical Reaction Pathway for Hydrolysis of Benzyl Phenyl Carbonate



As mentioned earlier, cation-π interactions were expected to be sensitive to the substituent pattern on the benzyl group. To test this, we carried out the hydrolysis of various carbonates shown in Figure 3.1. Theoretical calculation of binding energy in the gas phase have shown that toluene binds tetramethyl ammonium ions more strongly than benzene by 0.5 kcal/mol.[16] On the other hand, thermochemical measurements by Meot-Ner and Deakyne have shown that the difference in binding energy for these systems is 0.1 kcal/mol.[10] On the basis of these studies, we expected that the transition state for hydrolysis of the 4-methylbenzyl carbonate **3.1g** will be ~0.1 to 0.5 kcal/mol more stable than the transition state for hydrolysis of **3.1a**. This was expected to lead to a faster hydrolysis. In line with our expectation, the rate constant for hydrolysis of **3.1g** was higher ($k = 2.3\times10^{-3}$/min) than the rate constant for hydrolysis of carbonate **3.1a** ($k = 1.4\times10^{-3}$/min). A comparison of the rate constants showed that the transition state for hydrolysis of carbonate **3.1g** was 0.3 kcal/mol more stable than the corresponding transition state for hydrolysis of carbonate **3.1a**. With respect to hydrolysis of isobutyl phenyl carbonate **3.1c**, a 26-fold rate acceleration was observed. We then studied the hydrolysis of other carbonates shown in Figure 3.3. The 4-bromobenzyl phenyl carbonate (**3.1e**) hydrolyzed at the same rate as benzyl phenyl carbonate ($k = 1.5\times10^{-3}$/min). This showed that the bromo group does not have a large influence in cation-π interactions. A larger π-surface area is expected to show greater cation-π interaction.[17] Jacobsen and coworkers have used this in the design of thiourea catalysts for enantioselective cationic cyclization (Scheme 3.4).[18] Catalyst **3.11** with a larger π-surface area than catalyst **3.8** gave higher enantioselectivity for the cationic cyclization. This is possibly due to greater stabilization of the favored cationic transition state. Similarly, for our hypothetical reaction pathway (Scheme 3.3) a carbonate with a larger π-surface is expected to stabilize the transition state and lead to faster reaction. Consistent with this, the hydrolysis of

naphthalenemethyl phenyl carbonates (**3.1d** and **3.1h**) were faster. Interestingly, the positional isomers showed different rates of hydrolysis with carbonate **3.1h** hydrolyzing faster (relative rate ≈ 33) than carbonate **3.1d** (relative rate ≈ 23). This is possibly due to unfavorable steric interaction in transition state for the hydrolysis of carbonate **3.1d**.

Scheme 3.4 π-Electron Surface Effect on the Enantioselectivity and Yield



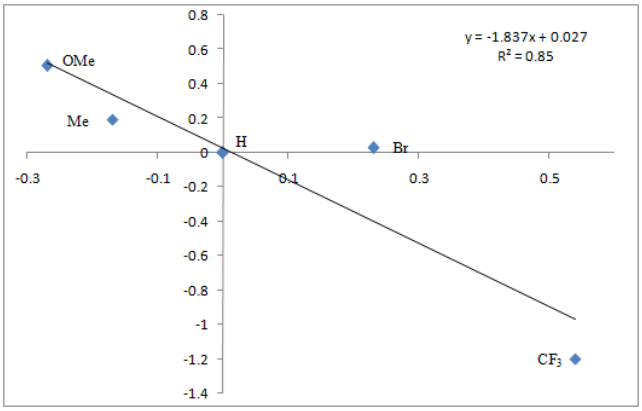
The fastest hydrolysis was observed for carbonate **3.1f** with a rate constant of 4.5×10^{-3}/min and relative rate of ~51. This showed that the hydrolysis is accelerated by electron-donating groups on the aromatic system and is consistent with our hypothetical transition state. Based on this observation, we expected the hydrolysis of dimethoxybenzyl carbonate **3.1i** to be even faster. Somewhat surprisingly, the hydrolysis was slower with a relative rate of ~44. We posited that this could be due to unfavorable steric interactions between the meta substituent and the ammonium cation. Consistent with our hypothesis, the hydrolysis of 3-methoxy benzyl carbonate **3.1j** was considerably

slower with a rate constant of 1.2×10^{-3}/min and a relative rate of ~14. To study the effect of an electron-withdrawing group on the aromatic system, we studied the hydrolysis of the 4-trifluoromethyl carbonate **3.1k**. Electron withdrawing groups are expected to diminish the cation-π interaction and based on our proposed transition state, a lower rate of hydrolysis was expected. Indeed the hydrolysis of carbonate **3.1k** proceeded at a slower rate with a rate constant of 9.3×10^{-4}/min and a relative rate of ~11. The strength of cation-π interactions is dependent on the distance between the cationic group and aromatic system. An increase in the distance between the interacting species is expected to lower the cation-π interactions.[19] We probed this with carbonate **3.1l** wherein the cation and the aromatic system are separated by an extra methylene group in comparison to carbonate **3.1a**. Hydrolysis of this carbonate was very slow and only ~13% of the carbonate was consumed in 720 minutes. Once again this is consistent with our proposed transition state.

We resorted to Hammett correlations to systematically analyze the effect of substituents on the rate of hydrolysis. For this purpose, we chose carbonates **3.1a**, **3.1e**, **3.1f**, **3.1g**, and **3.1k** as substituents on these carbonates have well-defined σ values.[20] Plotting the logarithm of relative rate with respect to **3.1a** vs various σ parameters (Figure 3.5) showed that the best linear fits were obtained with σ_p and σ_p^- values (R^2 = 0.85 and 0.88 respectively). For Hammett correlations, R^2 values above 0.8 are deemed acceptable.[21] The corresponding ρ values were -1.84 and -1.66, respectively. The negative value for ρ clearly shows the buildup of positive charge in the transition state. Although the magnitude of ρ is somewhat small, a survey of the literature shows that similar values have been reported earlier. For example, the ρ value for hydrolysis of $ArCH_2Cl$ is -1.87, while a ρ of -1.41 is seen in the oxidation of benzyl alcohols.[22] A more detailed list has been provided by Hammett.[22a]

Figure 3.5 Hammet Plots with Various σ Parameters: a) Correlation with σ_p. b) Correlation with σ_p-. c) Correlation with σ_{p+}. d) Correlation with σ_m.

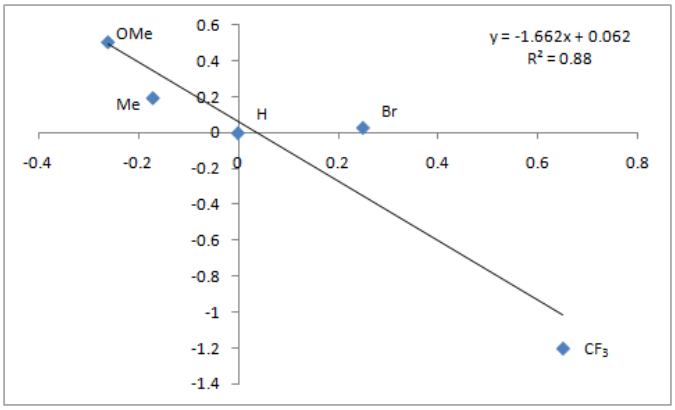
a)



$\log(k_x/k_H)$

σ_p

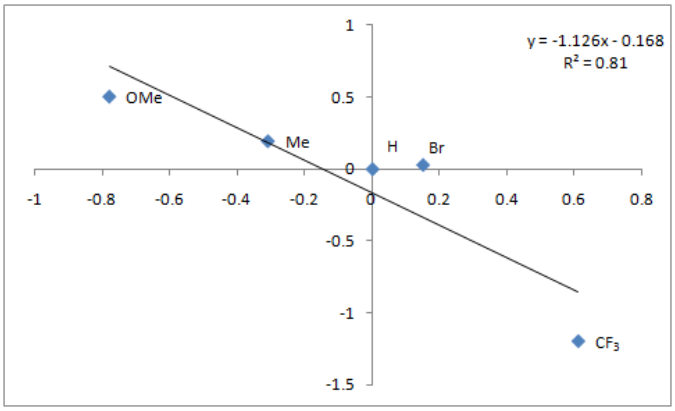
b)



$\log(k_x/k_H)$

σ_p^-

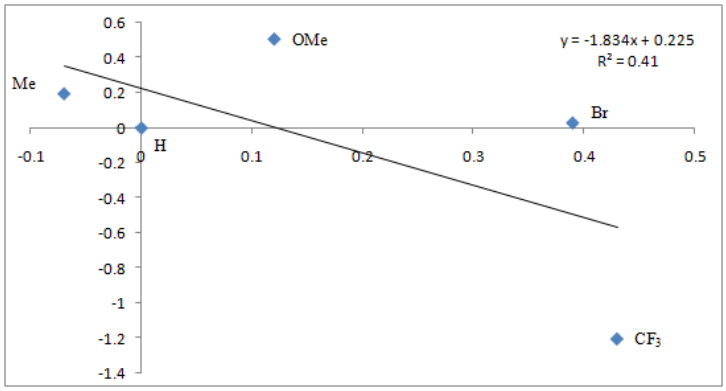
c)



$\log(k_x/k_H)$

σ_p^+

d)



$\log(k_x/k_H)$

σ_m

Theoretical studies have shown that cation-π interactions are diminished in the presence of solvents.[23] Therefore, solvent shielding is probably one of the reasons for the smaller magnitude of ρ seen in our reaction. Most importantly, we did not obtain good fits when we tried to correlate the logarithm of relative rate with σ_m values. The low R^2 values show that there is no meaningful correlation. This is in contrast to studies by Dougherty wherein correlations for binding Na^+ were obtained with σ_m values for the substituents.[13] The σ_m parameter provides a measure of their inductive effect and the correlation may be a reflection of the fact that the Na^+ is positioned close to the centroid of the aromatic system. On the other hand, σ_p values provide a measure of the resonance effects associated with the substituent. Sussman and coworkers have shown that a bidentate mode of binding is preferred for the interaction of ammonium cations with benzene rings.[14] In this mode of binding, the hydrogens are positioned closest to the carbon atoms that have greater negative charge. As mentioned earlier, the bidentate mode of binding is likely to be more sensitive to σ_p. Our studies clearly show that in the case of acyl trialkyl ammonium cation, the best correlations are obtained with σ_p values and not with σ_m values.

The hypothetical reaction pathway shown in Scheme 3.3 suggests that the hydrolysis reaction would be slower with a weaker nucleophile. To test this, we

performed the hydrolysis reaction with DMAP. Mayr and coworkers have shown that DMAP is a weaker nucleophile than DABCO.[24] Indeed, to get appreciable rates of hydrolysis, the reactions had to be carried out at 60 °C.[25] When we plotted $\ln(100/C_t)$ vs time, we did not obtain straight lines (Figure 3.6). Therefore, we were unable to compare the pseudo-first order rate constants for various carbonates and get a quantitative idea about the effect of substituents. However, a qualitative idea about the role of substituents was obtained by comparing the time taken for the hydrolysis to reach ~90% completion (Table 3.4). Broadly, trends similar to the DABCO mediated hydrolysis were seen. The 4-methoxybenzyl (**3.1f**) and naphthalenemethyl carbonates (**3.1d** and **3.1h**) were hydrolyzed at a faster rate compared to **3.1a**. Significantly, the isomeric naphthalenemethyl carbonates hydrolyzed at similar rates. DMAP is likely to orient parallel to the aromatic ring of the benzyl group and is therefore unlikely to experience steric interaction with the aromatic substituents (Figure 3.7). The fastest rate of hydrolysis was once again seen with the 4-methoxybenzyl carbonatate (**3.1f**). In contrast to the DABCO mediated reaction, the hydrolysis of the dimethoxybenzyl carbonate (**3.1i**) and 4-methoxybenzyl carbonate (**3.1f**) proceeded at similar rates. The orientation of DMAP probably prevents steric interaction with the meta group.

Figure 3.6 Plot of $\ln(100/C_t)$ Vs Time for The Hydrolysis of **1a** with DABCO Nucleophile

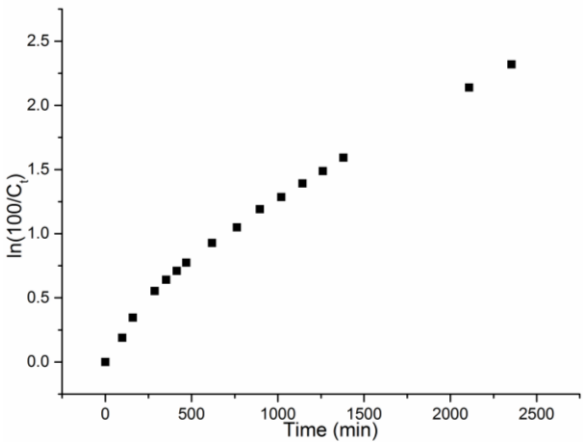
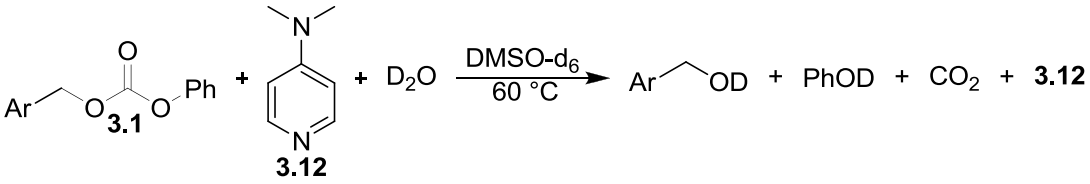


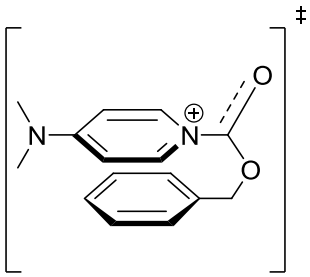
Table 3.4 Hydrolysis of Carbonate with DMAP as Nucleophile



entry	carbonate	time (approx. 90% completion)[a]	
		Run 1	Run 2
1	**3.1a**	39 h (90%)	41 h (90%)
2	**3.1d**	20 h (89%)	20 h (89%)
3	**3.1f**	6.5 h (92%)	6.2 h (89%)
4	**3.1h**	19 h (90%)	21 h (91%)
5	**3.1i**	5 h (92%)	5 h (90%)

[a] Reactions were performed at 60 °C and monitored as mentioned in Table 3.3.

Figure 3.7 Orientation of Acylpyridinium Ion



The hydrolysis reactions were also used to evaluate the role of the leaving group, (i.e.), the phenoxide moiety on the activation of benzyl phenyl carbonate (Figure 3.8). In these studies, the results are along expected lines and carbonates with less basic phenoxy groups are hydrolyzed faster (Table 3.5). A comparison of the relative rates shows that when the pK_a of the conjugate acid of the leaving group is reduced by ~2 units, a four-fold increase in the rate constant is observed. This is similar to the rate acceleration observed when the benzyl group is replaced by a 4-methoxybenzyl group.

Figure 3.8 List of Different Phenyl Carbonates Screened

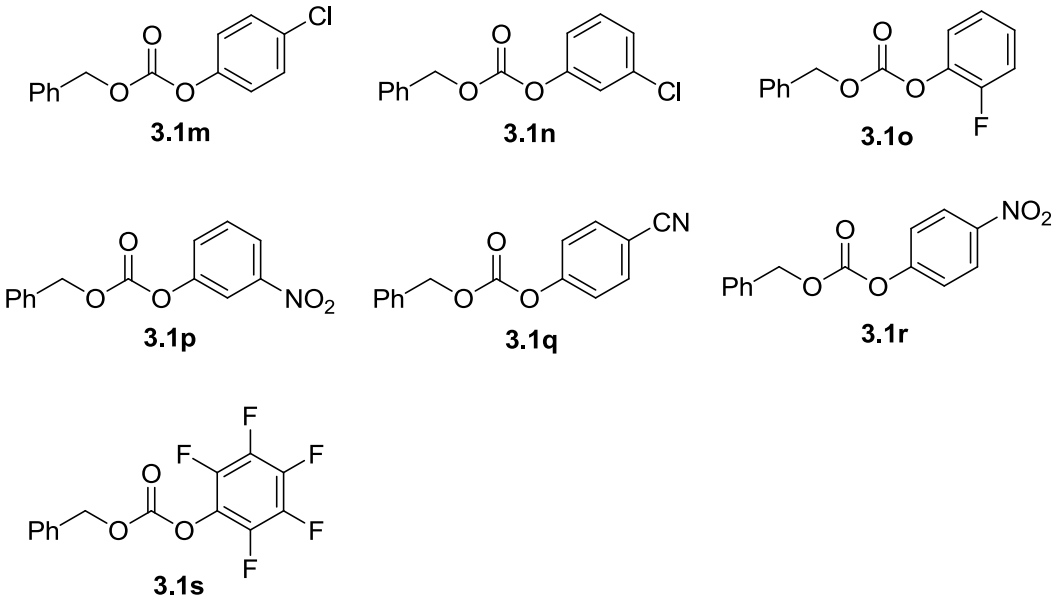
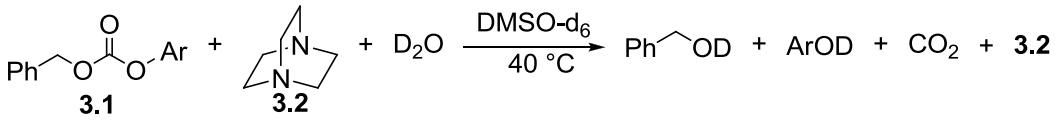


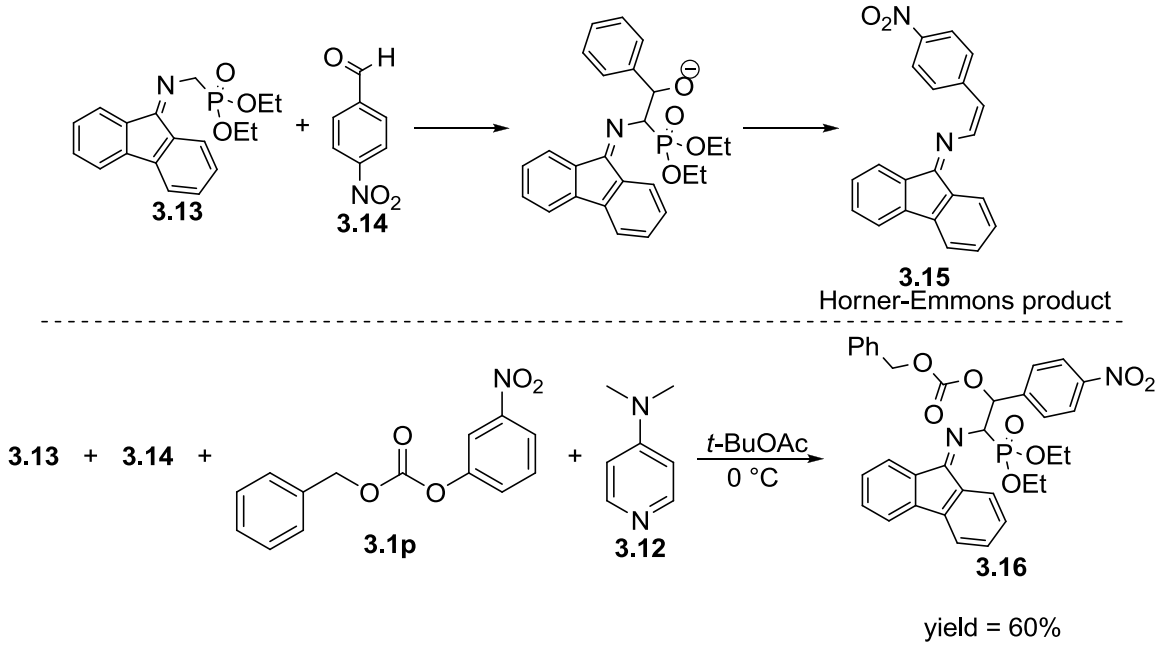
Table 3.5 Hydrolysis of Various Phenyl Carbonates with DABCO.



entry	carbonate	pK_a (ArOH)	rate constant k (min^{-1})	relative rate
1	**3.1a**	18	1.4×10^{-3}	1
2	**3.1m**	16.7	3.2×10^{-3}	2.3
3	**3.1n**	15.8	5.4×10^{-3}	3.9
4	**3.1o**	15.6	5.4×10^{-3}	3.9
5	**3.1p**	14.4	very fast	-
6	**3.1q**	13.2	very fast	-
7	**3.1r**	10.8	very fast	-
8	**3.1s**	8.9	very fast	-

Based on the above results, it is clear that the cation-π interactions play an important role in activating benzyl phenyl carbonates. Using this approach, activated acyl groups can be readily accessed using benzyl phenyl carbonates without taking recourse to the less stable acid anhydrides. As mentioned earlier, this can be useful in a number of reactions. In our laboratory, we are using this approach for the synthesis of β-hdyroxy-α-amino phosphonates (Scheme 3.5) from imine phosphonates. Obtaining good yields in this reaction is challenging due to the formation of α,β-unsaturated imine phosphonates as side products through a Horner-Emmons reaction.[26] This unwanted side reaction can be avoided by trapping the hydroxyl group of β-hydroxy-α-amino phosphonates with an activated acyl group. Good yields of the product have been obtained using DMAP and benzyl 3-nitrophenyl carbonates.

Scheme3.5 Preparation of β-Hydroxy α-Amino Acids Using Carbonates as Trapping Reagent



3.5 Conclusions

In this chapter, we have reported our studies on the nucleophile mediated hydrolysis of benzyl aryl carbonates under pseudo-first order conditions. Excellent straight line fits were obtained for plots of $\ln(100/C_t)$ vs time for the reactions mediated by DABCO. Comparison of the rate constant for hydrolysis of isobutyl phenyl carbonate with various substituted benzyl carbonates showed that cation-π interactions play an important role in hydrolysis. A Hammett analysis by plotting the logarithm of the relative rate with respect to carbonate **3.1a** vs various σ parameters have shown that best correlations were obtained with σ_p and σ_p^- values. This is in contrast to earlier work from the Dougherty group wherein correlation with σ_m values were seen for the binding of Na^+ with aromatic systems. The difference in the binding mode of Na^+ and the acylammonium cation is possibly the reason for this variation. This is one of the important outcomes of our study. When DMAP, a weaker nucleophile than DABCO, was used, the hydrolysis reactions had to be carried out at 60 °C to get appreciable rates. This further supports the idea that the nucleophile attack on the carbonate is the rate determining step. However, in these reactions, a plot of $\ln(100/C_t)$ vs time did not give proper straight line fits. Therefore, the effect of substituents could only be studied in a qualitative manner by comparing the times required to reach ~90% conversion of carbonates. In this case as well, trends similar to the DABCO mediated reactions were observed. The nucleophilic activation of benzyl phenyl carbonate leads to generation of a strong base along with an activated acyl group. Typically, activated acyl groups are generated from the much more reactive acid anhydrides, whereas in our approach this can be generated from stable and easy-to-purify carbonates. Currently, this is being used to develop a synthesis of β-hydroxy-α-amino phosphonates in our group. Future work will involve application of this approach to the development of other reactions.

3.6 Experimental Section

All glassware was dried overnight in an oven at 120 °C prior to use. Reactions were carried out under argon atmosphere using standard Schlenk techniques and were monitored by TLC using silica gel TLC plates. Flash column chromatography was performed using silica gel of mesh size 230–400. Grease-free solvents for flash column chromatography were obtained by distillation. Unless otherwise noted, all chemicals obtained from commercial sources were used without further purification. Infrared spectra were recorded using an FT-IR Spectrometer. ^{1}H and ^{13}C NMRs were recorded on a 400 MHz and 100 MHz Fourier Transform NMR spectrometer, respectively. Chemical shifts are reported in parts per million (ppm) with respect to the residual solvent peak. For ^{1}H NMRs recorded in $CDCl_3$, the residual solvent peak at 7.27 ppm was used for calibration. For $\{^{1}H\}$ ^{13}C NMRs recorded in $CDCl_3$, the residual solvent peak at 77.16 ppm was used for calibration. For ^{1}H NMRs recorded in DMSO-d_6, the residual solvent peak at 2.50 ppm was used for calibration. For $\{^{1}H\}$ ^{13}C NMRs recorded in DMSO-d_6, the residual solvent peak at 39.5 ppm was used for calibration. HRMS were recorded using a Q-TOF mass analyzer. Melting points were measured using melting point apparatus.

General Procedure for the Synthesis of Carbonates:

Method A

A round bottomed flask was charged with phenol (1 equiv), dichloromethane (DCM), and pyridine (1.26 equiv). The flask was immersed in an ice bath and benzyl chloroformate (1.3 equiv) was added drop-wise. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was transferred to a separatory funnel and diluted with DCM. The organic layer was washed successively with de-ionized water, 5% NaOH, 1 M HCl, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The material obtained was purified by flash column chromatography.

Method B

A round bottomed flask was charged with the required benzyl alcohol (1 equiv), DCM, and pyridine (1.26 equiv). The flask was immersed in an ice bath and phenyl chloroformate (1.3 equiv) was added drop-wise. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was transferred to a separatory funnel and diluted with DCM. The organic layer was washed successively with de-ionized water, 5% NaOH, 1 M HCl, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The material obtained was purified by flash column chromatography.

Benzyl phenyl carbonate (3.1a)

Method A was employed with the following quantities: phenol (4.68 g, 49.7 mmol), benzyl chloroformate (2.93 M solution in toluene, 22 mL (64.7 mmol), pyridine (5 mL, 62.5mmol), and DCM (50 mL).

Column Chromatography:

Approximately 150 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 500 mL of 20% DCM in hexanes was eluted followed by elution with 1200 mL of 25% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 21 – 63 contained product. These fractions were concentrated and dried under high vacuum to give 6.46 g of product (yield: 57%). The ^{1}H NMR of the product was in agreement with the literature.[27]

tert-Butyl phenyl carbonate (3.1b):

Method B was employed with the following quantities: *tert*-butyl alcohol (3.4 mL, 35.55 mmol), phenyl chloroformate (5.8 mL, 46.2 mmol), pyridine (3.7 mL, 45.9 mmol), and DCM (35 mL).

Column Chromatography:

Approximately 130 mL of silica was packed into a column using 2% ethyl acetate (EtOAc) in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 800 mL of 2% EtOAc in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 6 – 27 contained product. These fractions were concentrated and dried under high vacuum to give 4.1 g of product (yield: 88%). The ^{1}H NMR data of the product was in agreement with the literature.[28]

2-Methylpropyl phenyl carbonate (3.1c):

Method A was modified by replacing benzyl chloroformate with isobutylchloroformate and the following quantities were used: isobutyl chloroformate (3 mL, 23.1 mmol), phenol (3.24 g, 34.4 mmol), pyridine (3.5 mL, 43.4 mmol), and DCM (35 mL).

Column Chromatography:

Approximately 100 mL of silica was packed into a column using 25% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 1000 mL of 25% DCM in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 4 – 29 were concentrated and dried under high vacuum to give 3.1 g of product (yield: 69%).

Characterization:

Colorless liquid; R_f: 0.36 in 10% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.37 (m, 2H), 7.27 – 7.17 (m, 3H), 4.05 (d, *J* = 6.7 Hz, 2H), 2.07 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 151.3, 129.6, 126.1, 121.2, 74.9, 28.0, 19.0; IR (film): 1758 (C=O), 1237 (C-O), 1204 (C-O), 768 cm^{-1}; HRMS (ESI): m/z $(M+Na)^+$ Calcd. for $C_{11}H_{14}NaO_3^+$ 217.0841, Found 217.0832.

Naphthalen-2-ylmethyl phenyl carbonate (3.1d):

Method B was employed with the following quantities: naphthalene-2-ylmethanol (4 g, 25.32 mmol), phenyl chloroformate (4.8 mL, 38.26 mmol), pyridine (2.7 mL, 33.5 mmol), and DCM (25 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 1.1% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,600 mL of 1.1% EtOAc in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 34 – 62 contained product. These fractions were concentrated and dried under high vacuum to give 2.03 g of product (yield: 29%).

Characterization:

Pale brown crystalline solid; Mp = 45 – 46 °C; R_f: 0.2 in 2.5% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.5 Hz, 1H), 7.93 – 7.90 (m, 2H), 7.65 – 7.54 (m, 3H), 7.49 (dd, *J* = 7.1, 8.2 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.25 – 7.17 (m, 3H), 5.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 151.3, 133.9, 131.0, 130.5, 130.0, 129.6, 128.9, 128.2, 127.0, 126.22, 126.17, 125.4, 123.6, 121.2, 68.7; IR (film): 1763 (C=O), 1244 (C-O), 1212 (C-O), 976, 772 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ Calcd. for $C_{18}H_{14}NaO_3^+$ 301.0841, Found 301.0838.

4-Bromobenzyl phenyl carbonate (3.1e):

Method B was employed with the following quantities: 4-bromobenzyl alcohol (3.41 g, 18.22 mmol), phenyl chloroformate (3.5 mL, 27.8 mmol), pyridine (2 mL, 24.8 mmol), and DCM (20 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 25% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 1,300 mL of 25% DCM in hexanes was eluted and collected in 25 mL fractions. Fractions 8 – 53 contained product. The fractions were concentrated. However, the isolated compound contained di-phenyl carbonate. This mixture was purified by column chromatography using 110mL silica. Approximately 1200 mL of 0.77% EtOAc in hexanes was eluted followed by 300 mL of DCM and 25 mL fractions were collected. Fractions 45 – 61 contained pure compound. These fractions were concentrated and dried under high vacuum to give 2.6 g of product (yield: 46%).

Characterization:

Pale yellow liquid; R_f: 0.13 in 30% DCM in hexanes; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.63 - 7.61 (m, 2H), 7.46 – 7.41 (m, 4H), 7.31 – 7.23 (m, 3H), 5.25 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.9, 150.7, 134.5, 131.5, 130.5, 129.6, 126.2, 121.8, 121.2, 68.9; IR (film): 1759 (C=O), 1492 (aromatic C=C), 1201 (C-O), 1012 (C-O), 772, 496 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ Calcd. for $C_{14}H_{11}BrNaO_3^+$ 328.9789, Found 328.9787.

4-Methoxybenzyl phenyl carbonate (**3.1f**):

Method B was employed with the following quantities: 4-methoxybenzyl alcohol (4 g, 28.95 mmol), phenyl chloroformate (4.7 mL, 37.46 mmol), pyridine (3 mL, 37.2 mmol), and DCM (30 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 0.7% EtOAc in hexanes as the solvent. The material obtained from workup was loaded on the column

after dissolution in a minimum amount of this solvent. Approximately 1100 mL of 0.7% EtOAc in hexanes was eluted followed by elution with 400 mL of 30% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 33 – 53 contained pure product. These fractions were concentrated and dried under high vacuum to give 5.07 g of product (yield: 68%). The ^{1}H NMR data of the product was in agreement with the literature.[27]

4-Methylbenzyl phenyl carbonate (3.1g):

Method B was employed with the following quantities: 4-methylbenzyl alcohol (2 g, 16.37 mmol), phenyl chloroformate (2.7 mL, 21.5 mmol), pyridine (1.6 mL, 19.9 mmol), and DCM (16 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 1% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,100 mL of 1% EtOAc in hexanes was eluted followed by elution with 500 mL of 15% EtOAc in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 3 – 20 contained product. These fractions were concentrated and dried under high vacuum to give 2.88 g of product (yield: 73%). The ^{1}H NMR, data of the product was in agreement with the literature.[29]

Naphthalen-1-ylmethyl phenyl carbonate (3.1h):

Method B was employed with the following quantities: naphthalene-1-ylmethanol (1.73 g, 10.9 mmol), phenyl chloroformate (1.7 mL, 13.5 mmol), pyridine (1 mL, 12.4 mmol), and DCM (10 mL).

Column Chromatography:

Approximately 90 mL of silica was packed into a column using 1% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and

loaded on the column. Approximately 1,400 mL of 1% EtOAc in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 26 – 44 contained product. These fractions were concentrated and dried under high vacuum to give 1.79 g of product (yield: 59%).

Characterization:

Crystalline white solid; Mp = 43 – 44 °C; R_f: 0.4 in 5% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.2 Hz, 1H), 7.93 – 7.90 (m, 2H), 7.65 – 7.54 (m, 3H), 7.49 (dd, *J* = 7.6, 8.2 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.25 – 7.18 (m, 3H), 5.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 151.2, 133.8, 131.6, 130.3, 129.8, 129.5, 128.8, 128.1, 126.8, 126.1, 126.0, 125.3, 123.5, 121.0, 68.6; IR (film): 1757 (C=O), 1246 (C-O), 1206 (C-O), 1068, 974, 771, 686; HRMS (ESI) m/z $(M+Na)^+$ Calcd. for $C_{18}H_{14}NaO_3^+$ 301.0841, Found 301.0835.

3,4-Dimethoxybenzyl phenyl carbonate (3.1i):

Method B was employed with the following quantities: 3,4-dimethoxybenzyl alcohol (3.068 g, 18.24 mmol), phenyl chloroformate (3.5 mL, 27.9 mmol), pyridine (1.9 mL, 23.6 mmol), and DCM (18 mL).

Column Chromatography:

Approximately 100 mL of silica was packed into a column using 8% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 900 mL of 8% EtOAc in hexanes was eluted followed by elution with 300 mL of 15% EtOAc in hexanes and 200 mL of 20% EtOAc in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 25 – 49 contained product. These fractions were concentrated and dried under high vacuum to give 4.18 g of product (yield: 80%).

Characterization:

Crystalline white solid; Mp = 47 – 48 °C; R_f: 0.16 in 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 - 7.36 (m, 2H), 7.27 – 7.17 (m, 3H), 7.04 – 6.98 (m, 2H), 6.89 – 6.87 (m, 1H), 5.22 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 151.3, 149.7, 149.2, 129.6, 127.4, 126.2, 121.9, 121.2, 112.1, 111.2, 70.7, 56.1; IR (film): 1739 (C=O), 1247 (C-O), 1023 (C-O), 748, 705 cm^{-1}; Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.88; H, 5.62.

3-Methoxybenzyl phenyl carbonate (3.1j):

Method B was employed with the following quantities: 3-methoxybenzyl alcohol (960 µL, 7.72 mmol), phenyl chloroformate (1.2 mL, 9.6 mmol), pyridine (800 µL, 9.93 mmol), and DCM (8 mL).

Column Chromatography:

Approximately 80 mL of silica was packed into a column using 3% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 600 mL of 3% EtOAc in hexanes was eluted followed by elution with 400 mL of 8% EtOAc in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 14 – 25 contained product. These fractions were concentrated and dried under high vacuum to give 1.39 g of product (yield: 70%).

Characterization:

White viscous liquid; R_f: 0.16 in 5% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.37 (m, 2H), 7.34 – 7.30 (m, 1H), 7.25 – 7.18 (m, 3H), 7.04 – 6.91 (m, 3H), 5.26 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 153.8, 151.3, 136.4, 129.9, 129.6, 126.2, 121.2, 120.8, 114.6, 113.9, 70.3, 55.4; IR (film): 1755 (C=O), 1590 (aromatic C=C), 1205 (C-O), 1039 (C-O), 685, 504 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ Calcd. for $C_{15}H_{14}NaO_4^+$ 281.0790; Found: 281.0790.

4-Trifluoromethylbenzyl phenyl carbonate (3.1k):

Method B was employed with the following quantities: 4-trifluoromethylalcohol (650 mg, 3.69 mmol), phenyl chloroformate (700 µL, 5.1 mmol), pyridine (420 µL, 5.21 mmol), and DCM (6 mL)

Column Chromatography:

Approximately 96 mL of silica was packed into a column using 2% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,400 mL of 2% EtOAc in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 39 – 56 contained product. These fractions were concentrated and dried under high vacuum to give 611 mg of product (yield: 56%).

Characterization:

Crystalline white solid; Mp = 62 – 64 °C; R_f: 0.16 in 2% EtOAc in hexanes; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.32 – 7.25 (m, 3H), 5.38 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.1, 152.0, 141.1, 130.9, 129.8, 127.5, 126.7 (q, *J* = 3.6 Hz), 124.0, 122.4, 70.0; IR (film): 1750 (C=O), 1275 (C-O), 1105 (C-O), 1066, 715 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ Calcd. for $C_{15}H_{11}F_3O_3Na^+$ 319.0558; Found: 319.0557.

Phenyl-2-phenylethyl carbonate (3.1l):

Method B was employed with the following quantities: 2-phenylethanol (4 mL, 33.3 mmol), phenyl chloroformate (5.4 mL, 43.04mmol), pyridine (3.4 mL, 42.2 mmol), and DCM (30 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 0.7% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and

loaded on the column. Approximately 1,100 mL of 0.7% EtOAc in hexanes was eluted followed by elution of 1100 mL of 30% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 45 – 84 contained product. These fractions were concentrated and dried under high vacuum to give 6.63 g of product (yield: 82%).

Characterization:

Amorphous white solid; Mp = 79 – 80 °C ;R_f: 0.16 in 2.5% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.33 (m, 4H), 7.29 – 7.28 (m, 2H), 7.26 – 7.23 (m, 2H), 7.17 – 7.14 (m, 2H), 4.47 (t, *J* = 7.1 Hz, 2H), 3.07(t, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 151.1, 137.0, 129.5, 129.0, 128.6, 126.8, 126.0, 121.1, 69.0, 35.1 ; IR (film): 1751 (C=O), 1486 (aromatic C=C), 1262 (C-O), 969, 757, 704, 501 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ Calcd. for $C_{15}H_{14}NaO_3^+$ 265.0840, Found 265.0835.

Benzyl-4-chlorophenyl carbonate (3.1m):

Method B was employed with the following quantities: 4-chlorophenol (3 g, 23.3 mmol), benzyl chloroformate (12 mL, 35.2mmol), pyridine (2.9 mL, 36.0 mmol), and DCM (20 mL).

Column Chromatography:

Approximately 130 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 1200 mL of 20% DCM in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 13 – 40 contained product. These fractions were concentrated and dried under high vacuum to give 6.63 g of product (yield: 69%). The ^{1}H NMR, data of the product was in agreement with the literature.[27]

Benzyl-3-chlorophenyl carbonate (3.1n):

Method B was employed with the following quantities: 3-chlorophenol (3 mL, 28.4 mmol), benzyl chloroformate (15 mL, 43.9mmol), pyridine (3.5 mL, 43.4 mmol), and DCM (30 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 800 mL of 20% DCM in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 9 – 30 contained product. These fractions were concentrated and dried under high vacuum to give 2.48 g of product (yield: 82%).

Characterization:

Pale yellow liquid; R_f: 0.36 in 30% DCM in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.37 (m, 5H), 7.34 – 7.30 (m, 1H), 7.26 – 7.23 (m, 2H), 7.12 – 7.10 (m, 1H), 5.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 151.6, 134.7, 134.6, 130.3, 128.9, 128.8, 128.6, 126.4, 119.5, 70.6; IR (film): 1759 (C=O), 1590 (aromatic C=C), 1208 (C-O), 878, 697, 445 cm^{-1}.

Benzyl-2-fluorophenyl carbonate (3.1o):

Method B was employed with the following quantities: 2-fluorophenol (2.5 mL, 28.0 mmol), benzyl chloroformate (15 mL, 43.9mmol), pyridine (3.4 mL, 42.2 mmol), and DCM (20 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 2,000 mL of 20%

DCM in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 61 – 80 contained product. These fractions were concentrated and dried under high vacuum to give 5.33 g of product (yield: 76%).

Characterization:

White crystalline solid;R_f: 0.17 in 50% DCM in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.38 (m, 5H), 7.26 – 7.12 (m, 4H), 5.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 153 (d, *J* = 3.2 Hz), 138.8, 138.7, 134.7, 129.0, 128.8, 128.6, 127.5 (d, *J* = 7.2 Hz), 124.6 (d, *J* = 4.1 Hz), 123.5 (*J* = 18.2 Hz), 71.0; IR (film): 1755 (C=O), 1499 (aromatic C=C), 1251 (C-O), 744, 579 cm^{-1}.

Benzyl-3-nitrophenyl carbonate (3.1p):

Method B was employed with the following quantities: 3-nitrophenol (3 g, 21.6 mmol), benzyl chloroformate (11 mL, 32.2mmol), pyridine (2.6 mL, 32.2 mmol), and DCM (20 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1500 mL of 0.77% EtOAc in hexanes was eluted followed by elution with 500 mL of 30% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 61 – 79 contained product. These fractions were concentrated and dried under high vacuum to give 5.13 g of product (yield: 87%).

Characterization:

Pale yellow crystalline solid; R_f: 0.17 in 50% DCM in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 – 8.11 (m, 2H), 7.60 – 7.54 (m, 2H), 7.48 – 7.40 (m, 5H), 5.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 151.5, 148.9, 134.6, 134.4, 130.3, 129.2,

128.9, 128.8, 127.5, 121.1, 117.0, 71.1; IR (film): 1747 (C=O), 1531 (aromatic C=C), 1216 (C-O), 961, 805, 720, 480 cm^{-1}.

Benzyl-4-cyanophenyl carbonate (3.1q):

Method B was employed with the following quantities: 4-cyanophenol (3 g, 25.9 mmol), benzyl chloroformate (14 mL, 41.0mmol), pyridine (3.2 mL, 39.7 mmol), and DCM (30 mL).

Column Chromatography:

Approximately 110 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,400 mL of 1% EtOAc in hexanes was eluted followed by elution with 1,000 mL of 30% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 60 – 98 contained product. These fractions were concentrated and dried under high vacuum to give 4.95 g of product (yield: 75.6%).

Characterization:

Crystalline white solid; R_f: 0.36 in 30% DCM in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 – 7.69 (m, 2H), 7.47 – 7.39 (m, 5H), 7.36 – 7.32 (m, 2H), 5.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 152.7, 134.4, 133.9, 129.2, 128.9, 128.8, 118.2, 110.1, 119.5, 71.1; IR (film): IR (film): 2226 (CN), 1763 (C=O), 1495 (aromatic C=C), 1212 (C-O), 736, 805, 547 cm^{-1}.

Benzyl-4-nitrophenyl carbonate (3.1r):

Method B was employed with the following quantities: 4-nitrophenol (700 mg, 5.0 mmol), benzyl chloroformate (1.7 mL, 5.0mmol), pyridine (0.41 mL, 5.0 mmol), and DCM (15 mL).

Column Chromatography:

Approximately 60 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 600 mL of 60% DCM in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 4 – 21 contained product. These fractions were concentrated and dried under high vacuum to give 1.1 g of product (yield: 78.7%).

Characterization:

Crystalline white solid;R_f: 0.2 in 50% DCM in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 – 8.26 (m, 2H), 7.47 – 7.38 (m, 7H), 5.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 152.6, 145.6, 134.3, 129.2, 128.9, 128.8, 125.4, 121.9, 71.1; IR (film): 1769 (C=O), 1502 (aromatic C=C), 1252 (C-O), 757, 705, 477 cm^{-1}.

Benzyl perfluorophenyl carbonate (3.1s):

Method B was employed with the following quantities: 2,3,4,5,6-pentafluorophenol (930 mg, 5.0 mmol), benzyl chloroformate (1.7 mL, 5.0mmol), pyridine (0.41 mL, 5.0 mmol), and DCM (15 mL).

Column Chromatography:

Approximately 60 mL of silica was packed into a column using 20% DCM in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 200 mL of 5% DCM in hexanes was eluted followed by elution with 400 mL of 20% DCM in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 11 – 18 contained product. These fractions were concentrated and dried under high vacuum to give 825 mg of product (yield: 51.4%). The ^{1}H NMR, data of the product was in agreement with the literature.[30]

General Procedure for the Synthesis of Nitroesters:

A thick-walled glass tube with a Teflon screw cap was charged with phenylnitroethane (1equiv) and aryl phenyl carbonate (3 equiv). The tube was flushed with argon and dimethyl sulfoxide (3 equiv) was added followed by 1,4-diazabicyclo [2.2.2] octane (DABCO) (2 equiv). The tube was capped and immersed in an oil bath at 60 °C. The reaction mixture was stirred at this temperature and the progress of the reaction was monitored by TLC.

Workup procedure:

After completion of reaction by TLC, the reaction mixture was cooled to 0 °C and quenched with 1 M $KHSO_4$. This was further stirred at room temperature till a suspension was formed. The suspension was transferred to a separatory funnel containing 15 mL of 1 M $KHSO_4$. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined ether layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography.

Benzyl 2-nitro-3-phenylpropanoate (3.4a):

The general procedure was employed with the following quantities: 2-phenylnitro ethane (100 mg, 0.66 mmol), 1a (455 mg, 2.0 mmol), DABCO (150 mg, 1.33 mmol), and DMSO (140 µL, 2.0 mmol). Time: 5 h.

Column Chromatography:

Approximately 50 mL of silica was packed into a column using 25% DCM in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of this solvent. Approximately 800 mL of 25% DCM in hexanes was eluted followed by elution with 400 mL of 40% DCM in hexanes. The eluted solvent was collected in 12 mL fractions. Fractions 58 – 67 contained product, diphenyl carbonate and phenyl benzyl carbonate. Fractions 68 – 71 contained

pure product. Fractions 58 – 67 were concentrated and purified by column chromatography. Approximately 40 mL of silica was packed into a column using 3% EtOAc in hexanes as the solvent. The mixed fractions from the first column was adsorbed on silica and loaded on the column. Approximately 450 mL of 3% EtOAc in hexanes was eluted followed by elution with 100 mL of 50% DCM in hexanes. The eluted solvent was collected in 12 mL fractions. Fractions 36 – 38 contained product. The fractions containing pure product from column I and column II were concentrated and dried under high vacuum to give 149 mg of product (yield: 78%). The ^{1}H NMR, data of the product was in agreement with the literature.[31]

Naphthalen-2-ylmethyl 2-nitro-3-phenylpropanoate (3.4d):

The general procedure was employed with the following quantities: 2-phenylnitro ethane (75 mg, 0.5 mmol), 1d (415 mg, 1.5 mmol), DABCO (112 mg, 1 mmol), and DMSO (110 μL, 1.5 mmol). Time: 5 h.

Column Chromatography:

Approximately 45 mL of silica was packed into a column using 3% EtOAc in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 700 mL of 3% EtOAc in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 15 – 22 contained product. These fractions were concentrated and dried under high vacuum to give 135 mg of product. The obtained product contained 7.5 mol% of bis-(naphthalene-2-ylmehtyl) carbonate as impurity. Yield: 74% (based on ^{1}H NMR).

Characterization:

Brown viscous liquid; R_f: 0.23 in 5% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 – 7.86 (m, 3H), 7.59 – 7.43 (m, 5H), 7.26 – 7.24 (m, 3H), 7.15 – 7.12 (m, 2H), 5.70 (s, 2H), 5.37 (dd, *J* = 6.2, 9.1 Hz, 1H), 3.56 (dd, *J* = 9.1, 14.4 Hz, 1H), 3.46 (dd,

J = 6.2, 14.4 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 133.93, 133.90, 131.7, 130.2, 129.8, 129.1, 129.0, 128.96, 128.3, 127.9, 127.1, 126.3, 125.3, 123.3, 89.1, 67.2, 36.4; IR (film): 1747 (C=O), 1562 (aromatic C=C), 1202 (C-O), 1170 (C-O), 859, 777, 701 cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{20}H_{16}NO_4^-$, 334.1084, Found, 334.1081.

4-Bromobenzyl 2-nitro-3-phenylpropanoate (3.4e):

The general procedure was employed with the following quantities: 2-phenylnitro ethane (75 mg, 0.5 mmol), 1e (456 mg, 1.5 mmol), DABCO (112 mg, 1 mmol), and DMSO (110 µL, 1.5 mmol).

Time: 3 h.

Column Chromatography:

Approximately 45 mL of silica was packed into a column using 25% toluene in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 1,300 mL of 25% toluene in hexanes was eluted. The eluted solvent was collected in 25 mL fractions. Fractions 35 – 49 contained product. These fractions were concentrated and dried under high vacuum to give 127 mg of product (yield: 70%).

Characterization:

Brown viscous liquid; R_f. 0.16 in 50% DCM in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.48 (m, 2H), 7.33 – 7.28 (m, 3H), 7.19 – 7.13 (m, 4H), 5.37 (dd, *J* = 6.3, 9.1 Hz, 1H), 5.17 (s, 2H), 3.57 (dd, *J* = 9.1, 14.5 Hz, 1H), 3.48 (dd, *J* = 6.3, 14.5 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 133.9, 133.3, 132.1, 130.2, 129.2, 129.0, 128.0, 123.2, 89.1, 67.9, 36.4; IR (film): 1747 (C=O), 1562 (aromatic C=C), 1202 (C-O), 1170 (C-O), 859, 777, 701 cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{16}H_{13}BrNO_4^-$, 362.0033, Found 362.0028.

4-Methoxybenzyl 2-nitro-3-phenylpropanoate (3.4f):

The general procedure was employed with the following quantities: 2-phenylnitro ethane (75 mg, 0.5 mmol), 1f (384 mg, 1.5 mmol), DABCO (112 mg, 1 mmol), and DMSO (110 µL, 1.5 mmol). Time: 1 h

Column Chromatography:

Approximately 45 mL of silica was packed into a column using 60% toluene in hexanes as the solvent. The material obtained from workup was adsorbed on silica and loaded on the column. Approximately 400 mL of 60% toluene in hexanes was eluted followed by the elution of 400 mL of 70% toluene in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 16 – 22 contained product. These fractions were concentrated and dried under high vacuum to give 82 mg of product. The obtained product contains 7.5 mol% of bis-(4-methoxybenzyl) carbonate as impurity. Yield: 48% (based on ^{1}H NMR).

Characterization:

Brown viscous liquid; R_f. 0.16 in 30% DCM in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.27 (m, 3H), 7.25 – 7.15 (m, 4H), 6.89 – 6.87 (m, 2H), 5.34 (dd, *J* = 6.0, 9.2 Hz, 1H), 5.17 (s, 2H), 3.81 (s, 3H), 3.54 (dd, *J* = 9.4, 14.5 Hz, 1H), 3.45 (dd, *J* = 6.0, 14.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 160.3, 134.1, 130.6, 129.1, 129.0, 127.9, 126.4, 114.3, 89.3, 68.7, 55.5, 36.4; IR (film): 1747 (C=O), 1614, 1558 (N-O), 1513 (N-O), 1250 (C-O), 1174 (C-O), 1028, 826, 701 cm^{-1}; HRMS (ESI) m/z $(M-H)^-$ Calcd. for $C_{17}H_{16}NO_5^-$, 314.1034, Found 314.1024.

Hydrolysis of Carbonates with DABCO:

A 1 mL volumetric flask was charged with 1mg of naphthalene (as an internal standard) and 0.03 mmol (1 equiv) of carbonate. To this 600 µL of DMSO-d_6 was added. Carbonate and naphthalene were dissolved in the solvent followed by the addition of 200

µL of D_2O. To this, 5.1 equiv (± 7%) of DABCO was added and the solution was made up to the mark using DMSO. The solution was immediately transferred to a clean NMR tube and ^1H NMR spectra were recorded at regular intervals.

Note: For hydrolysis of carbonate 1c, the ASCII files of NMR were exported to origin and integration of peaks was performed in origin.

Hydrolysis of Carbonates with DMAP:

A 1mL volumetric flask was charged with 1mg of naphthalene (as an internal standard)[32] and 0.03 mmol (1 equiv) of carbonate. To this 600 µL of DMSO-d_6 was added. Carbonate and naphthalene were dissolved in the solvent followed by the addition of 200 µL of D_2O. To this, 5 equiv (± 2%) of DMAP was added and the solution was made up to the mark using DMSO. The solution was immediately transferred to a clean NMR tube and ^1H NMR spectra were recorded at regular intervals.

3.7 References

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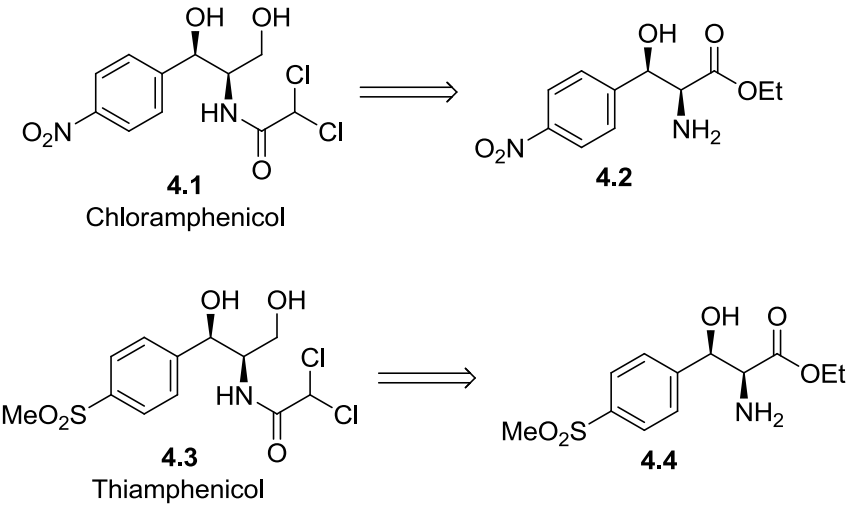
Chapter 4

Enantioselective Synthesis of β-Hydroxy-α-Amino Acids

4.1 Introduction

The synthesis of modified α-amino acids has been addressed by several groups due to their importance in a variety of fields. Among these amino acids, one of the most important class is β-hydroxy-α-amino acids. Among proteinogenic amino acids, serine and threonine have a β-hydroxyl group. The hydroxyl group in serine plays a key role in the catalytic activity of serine proteases.[1] Phosphorylation of the hydroxyl group in serine and threonine is an important way of modulating protein function. The multiple roles played by these amino acids has led to the synthesis of non-natural β-hydroxy-α-amino acids for applications in peptidomimetics.[2] Apart from this, several non-proteinogenic β-hydroxy-α-amino acids have found applications in medicinal chemistry. For example, phenyl serine has been used as an antiviral agent.[3] β-Hydroxy-α-amino acids are also found in antibiotics like vancomycin and teicoplanin.[4] Antibiotics like chloramphenicol and thiamphenicol can be readily prepared from the corresponding β-hydroxy-α-amino acids as shown in Scheme 4.1.[5] The wide application of these amino acids has driven the development of synthetic methods targeted towards their ready access. In this chapter, we discuss the advantages and disadvantages of these methods and report on our efforts in the development of a simple approach to a subset of these amino acids.

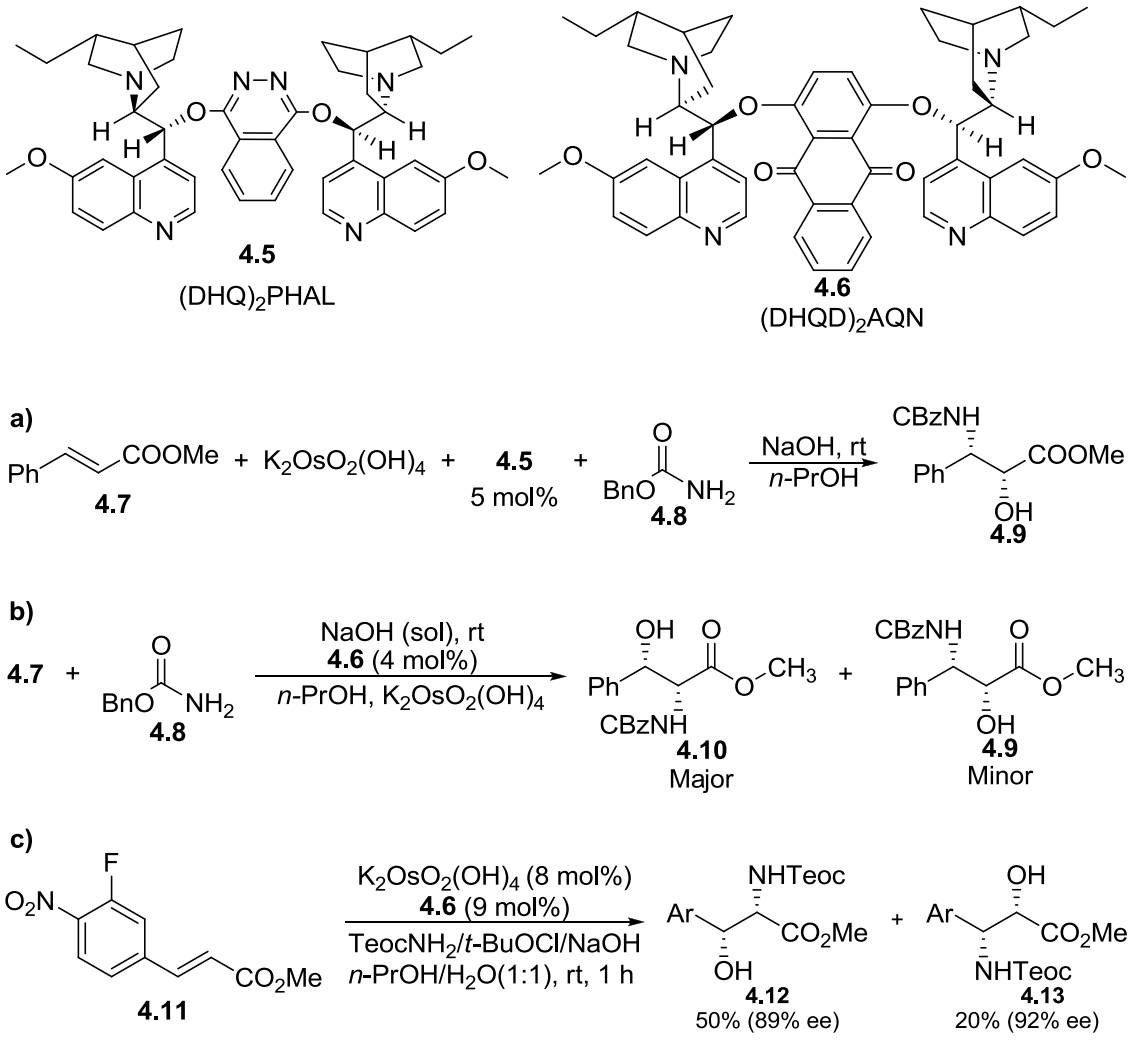
Scheme 4.1 Retrosynthesis of Chlormphenicol and Thiamphenicol



4.2 Metal Catalyzed Amino Hydroxylation

The Sharpless dihydroxylation introduced the idea of enantioselective vicinal functionalization. Amino hydroxylation reaction is an extension of this idea. Sharpless and coworkers have shown that osmium catalyzed amino hydroxylation of cinnamate esters with $(DHQ)_2PHAL$ as the ligand gave α-hydroxy-β-amino acid as the major regioisomer (Scheme 4.2a).[6] In this reaction, benzyl carbamate is oxidized with t-butyl hypochlorite to yield the N-Cl carbamate, which acts as the nitrogen source. The regiochemical outcome of the reaction could be switched by using $(DHQ)_2AQN$ as the ligand and this led to the isolation of β-hydroxy-α-amino acids as the product (Scheme 4.2b).[7] Moderate regioselectivities ranging from 2:1 to 4:1 were obtained under these conditions. The reaction is non-selective when cinnamates with electron-withdrawing substituents on the benzene ring are used. These substrates are particularly useful for the synthesis of antibiotics like chloramphenicol and thiamphenicol. Joullié and coworkers sought to address the poor regioselectivity in this substrate class by varying the nitrogen source.[8] Using Teoc-carbamate as the nitrogen source, a regioisomer ratio of 5:2 was obtained for one of their substrates (Scheme 4.2c).

Scheme 4.2 Sharpless Amino Hydroxylation

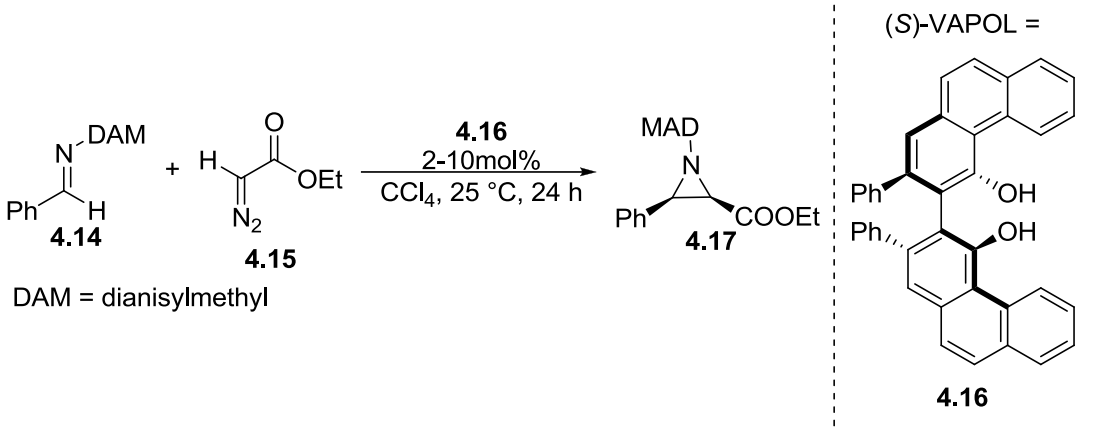


Although the diastereomers were separable by chromatography, the low regioselectivity of this reaction remains a problem. Additionally, osmium is an expensive and toxic metal and therefore, several groups have looked at alternative approaches to this problem.

4.3 Ring opening of Aziridines

Regioselective ring opening of aziridines derived from cinnamates is a potential route to β-hydroxy-α-amino acids. Enantioselective aziridination of cinnamates was reported by Wulff and coworkers using a catalyst derived from $B(OPh)_3$ and chiral biaryl diols (VAPOL or VANOL) (Scheme 4.3).[9]

Scheme 4.3 Aziridination of Imines

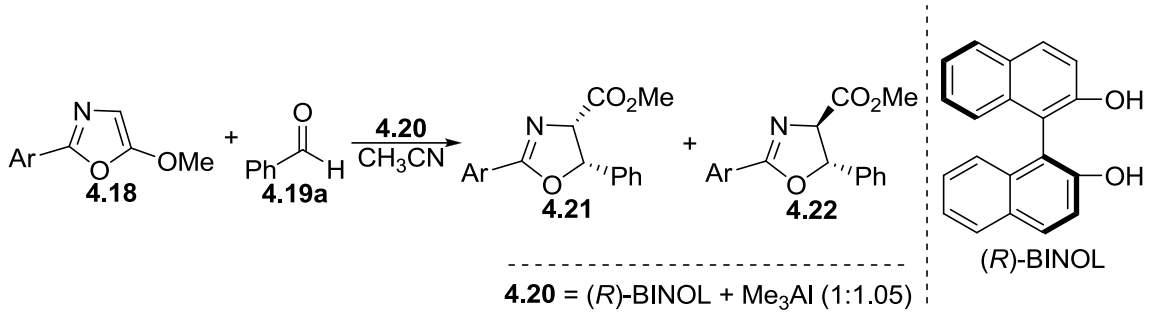


The aziridination proceeds with excellent enantioselectivity. In a later report, the regioselective ring opening of the aziridine to yield β-hydroxy-α-amino acids was disclosed.[5] This methodology was used to synthesize chloramphenicol in an enantioselective manner. Although chloramphenicol was synthesized in an efficient manner using this approach, the use of diazoacetate as the reagent remains a significant drawback. Ethyl diazoacetate can undergo explosive decomposition and therefore, this method is not suited for large scale preparations.

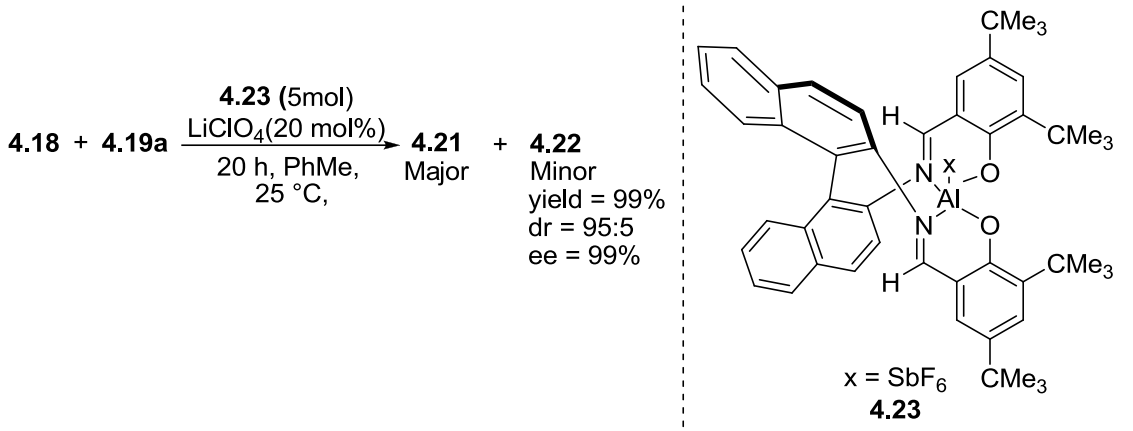
4.4 Aldol Reactions

Stereoselective aldol reactions of acetate and propionate esters have been developed by a number of groups. Direct application of these methods with glycine is not feasible due to the presence of the NH_2 group. To overcome this, several groups have resorted to the use of protected glycine esters and glycine equivalents. Suga and Ibata have reported on the use of 5-methoxy oxazole as the glycine source in their preparation of β-hydroxy-α-amino acids (Scheme 4.4).[10] The methoxy oxazole reacts with aldehydes in the presence of a Lewis acid to yield oxazolines as the product. Hydrolysis of the oxazolines results in the formation of β-hydroxy-α-amino acids. A chiral aluminum complex derived from BINOL was used as the catalyst and good diastereoselectivities were obtained. However, only moderate enantioselectivities were

Scheme 4.4 Aldol Reaction of Aldehydes and 5-Alkoxyoxazoles



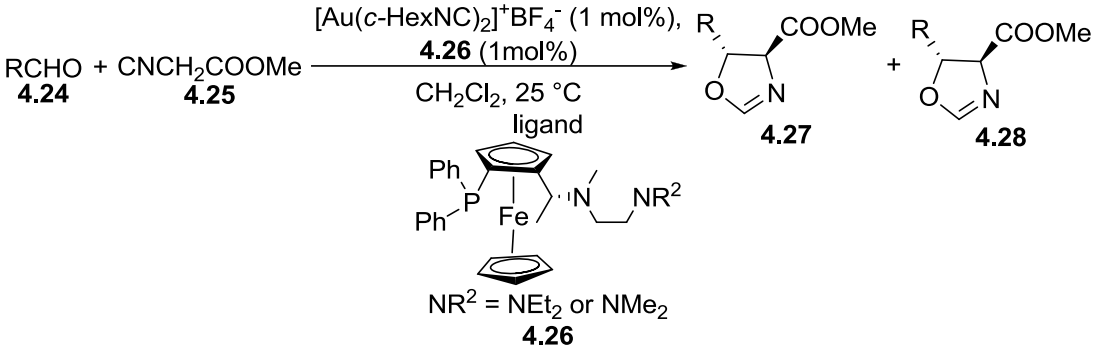
Scheme 4.5 Chiral Aluminum Complex Catalyzed Aldol Reaction of Aldehydes and 5-Alkoxyoxazoles



achieved and a high catalyst loading was required (30 mol%). Improvements to this system were reported by Evans and coworkers using an axially chiral aluminum-salen complex.[11] Excellent selectivities were observed with this system at low catalyst loadings (Scheme 4.5). However, the hydrolysis of the oxazoline to the corresponding β-hydroxy-α-amino acids was not reported.

Methyl isocyanoacetate has also been used as a glycine equivalent for the synthesis of β-hydroxy-α-amino acids. Ito and coworkers have shown that gold complexes of chiral ferrocenyl phoshphines are excellent catalysts for the reaction of aldehydes with methyl cyanoacetate (Scheme 4.6).[12]

Scheme 4.6 Gold Catalyzed Oxazolines Preparation

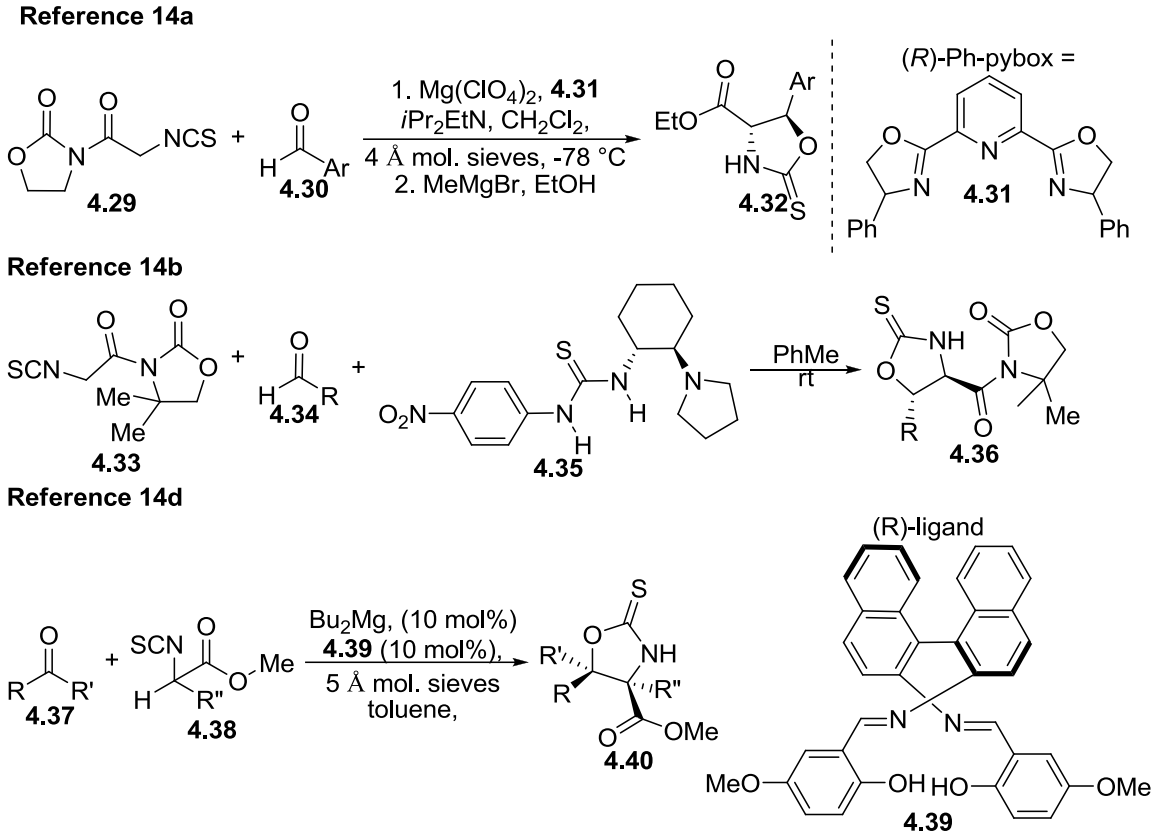


The resulting oxazolines were readily hydrolyzed to the corresponding syn-diastereomer of β-hydroxy-α-amino acids. More recently, Dixon and the coworkers have reported on a similar reaction that is catalyzed by a chiral silver complex. [13] In spite of the excellent selectivity, the toxicity and instability of methyl isocyanoacetate is a major disadvantage of this reaction.

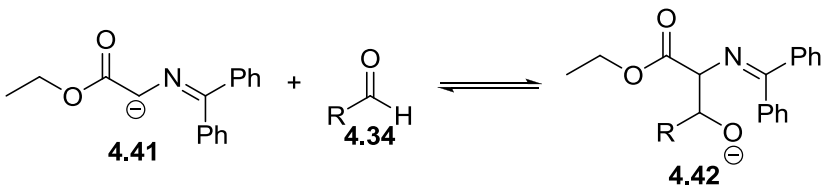
Isothiocyanato imides have also been used by a number of groups for the synthesis of β-hydroxy-α-amino acids.[14] The Willis group reported on the enantioselective synthesis of oxazolidine thiones from aldehydes and isothiocyanatoacetate using a chiral magnesium complex (Scheme 4.7).[14a] In a similar approach, the Seidel group showed that this can be accomplished using a bifunctional thiourea catalyst (Scheme 4.7).[14b,c] This was later extended to α-ketoesters. Shibsaki and coworkers have shown that reactions with ketones can be catalyzed effectively using a magnesium-salen complex (Scheme 4.7).[14d] Although, high enantioselectivities have been obtained with these reactions, the hydrolysis of oxazolidine thiones are extremely challenging especially in the presence of esters.[15]

Imine esters of glycine were introduced by O'Donnel as convenient glycine equivalent for the synthesis of modified amino acids.[16] The enhanced acidity of the α-proton coupled with the easy removal of the imine group has led to the wide application of this species as a glycine equivalent. Aldol reactions of imine esters with aldehydes are

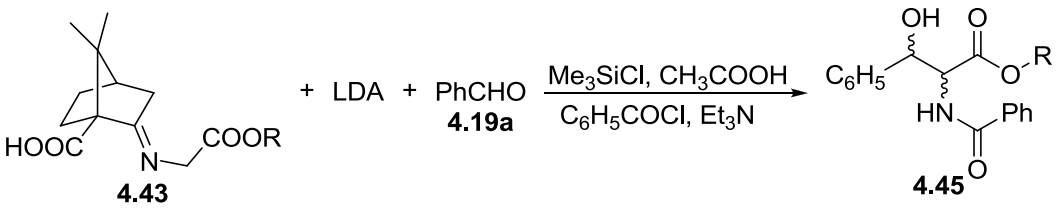
Scheme 4.7 Preparation of Oxazlidine Thione



Scheme 4.8 Reversible of Aldehydes to Anion of Imine Esters



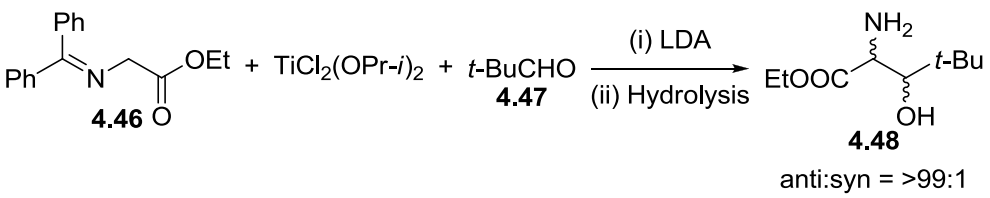
Scheme 4.9 Diastereoselective Aldol Reaction



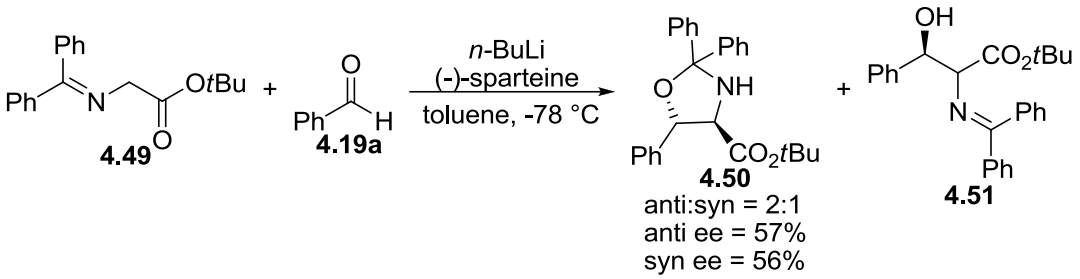
a potentially simple way of accessing β-hydroxy-α-amino acids. However, this reaction is plagued by poor selectivity and the formation of retroaldol products during hydrolysis (Scheme 4.8). One of the earliest attempts at an enantioselective reaction used ketopinic acid as the chiral auxiliary.[17] Modest levels of diastereoselectivity were obtained in this reaction (Scheme 4.9).

Benzophenone imine esters are the most commonly used glycine imine esters. The titanium enolate of these imine esters were shown to react with aldehydes in a diastereoselective manner by Tatsukawa and coworkers (Scheme 4.10).[18] The strong Lewis acidity of titanium was thought to activate the aldehyde. In the same report, a soft enolization approach was also reported with lithium and DBU. In this case, the product was obtained with very low diastereoselectivity. Molinksi and coworkers generated chiral lithium enolates from imine esters using a mixture of BuLi and (-)-Sparteine.[19] The reaction proceeded with modest diastereoselection and the authors were able to isolate the diastereomers and measure the individual ees (Scheme 4.11). Amongst various methods for deprotonation of benzophenone imine esters, the most commonly employed method uses a chiral phase transfer catalyst. Cinchona alkaloid based catalysts have been developed by several groups[20] for the enantioselective alkylation of glycine imine esters. However, in the case of aldol reactions, these catalysts are not very effective, especially, when aromatic aldehydes are used as substrates. Miller and Gasparski, showed that when *N*-benzyl cinchoninium chloride was used as the phase transfer catalyst, only modest amounts of diastereoselection were observed with very little ee (Scheme 4.12).[21]

Scheme 4.10 Lewis Acid Mediated Aldol Reaction



Scheme 4.11 Asymmetric Aldol Reaction Mediated by (-)-Sparteine

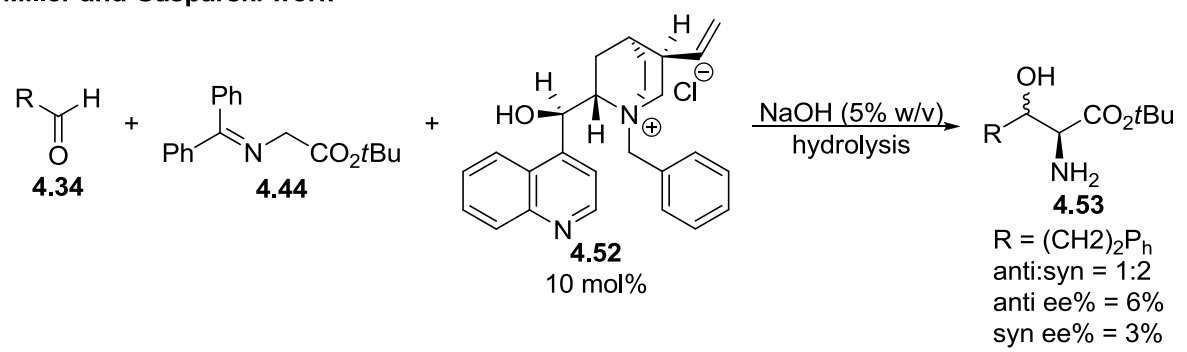


An improvement on this approach was reported by Castle group using the Park-Jew catalyst (Scheme 4.12).[22] Here good enantioselectivities were observed while only modest diastereoselectivities were observed. Maruoka and coworkers introduced spiro ammonium phase transfer catalyst based on axially chiral biaryl derivatives (Scheme 4.12). In their original report,[23] excellent enantioselectivities were observed with modest levels of diastereoselection. However, Castle and coworkers reported that they were unable to reproduce these results due to the reversibility of this reaction.[22] In a later report, Maruoka and coworkers showed that by buffering the reaction conditions with ammonium chloride, the reversibility of the aldol reaction could be controlled.[24] In all these reactions, the anti-diastereomer is the major product. A major drawback of this protocol is that reactions with aromatic aldehydes do not give good yields and selectivity. Moreover, Maruoka's phase transfer catalysts require long synthetic sequences.

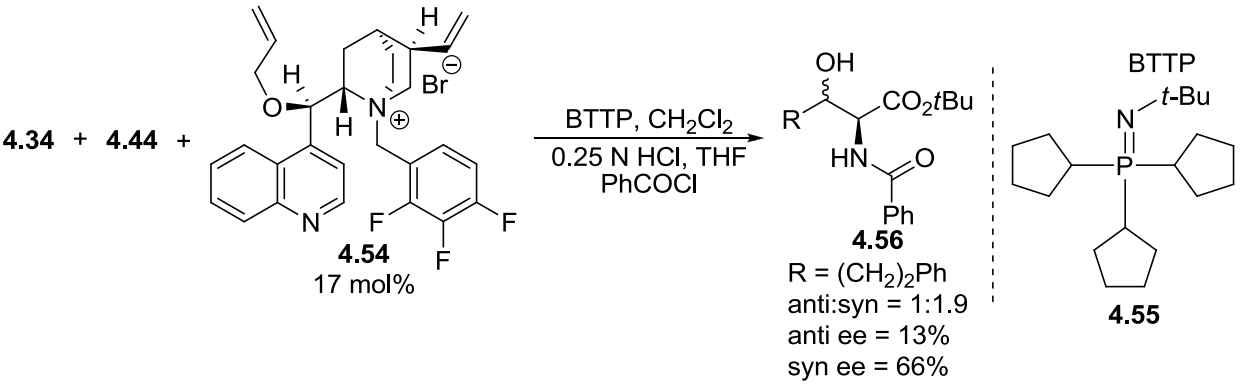
In order to access the syn-diastereomer, Trost and Miege used a zinc catalyst with a chiral semi-aza crown ligand (Scheme 4.13).[25] The products were isolated after an in situ reduction with $NaBH_3CN$ followed by hydrogenative cleavage of the benzhydryl group using Pd/C as the catalyst. Here again, the synthesis of the chiral ligand requires long synthetic sequences and aromatic aldehydes are not good substrates. Recently, Lou and coworkers have developed a silver catalyzed method for this aldol reaction.[26] The β-hydroxy-α-amino acid is trapped with diboc-carbonate to prevent the retro-aldol reaction.

Scheme 4.12 Phase Transfer Catalyst Mediated Asymmetric Aldol Reaction

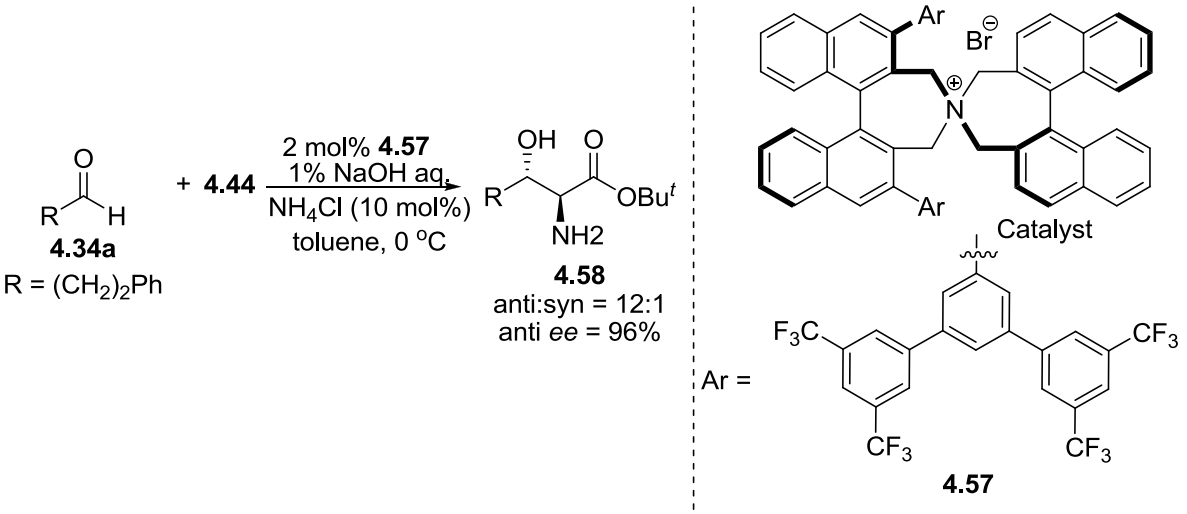
Miller and Gasparski work



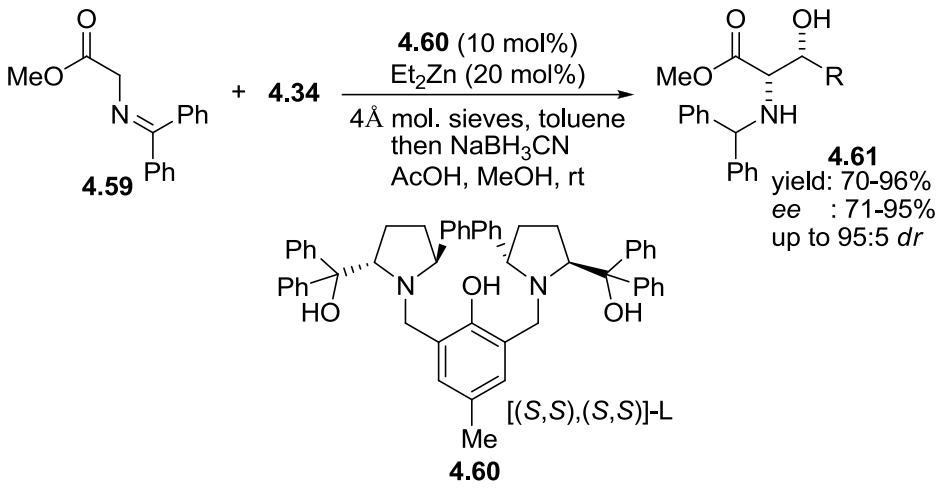
Srikanth and Castle work



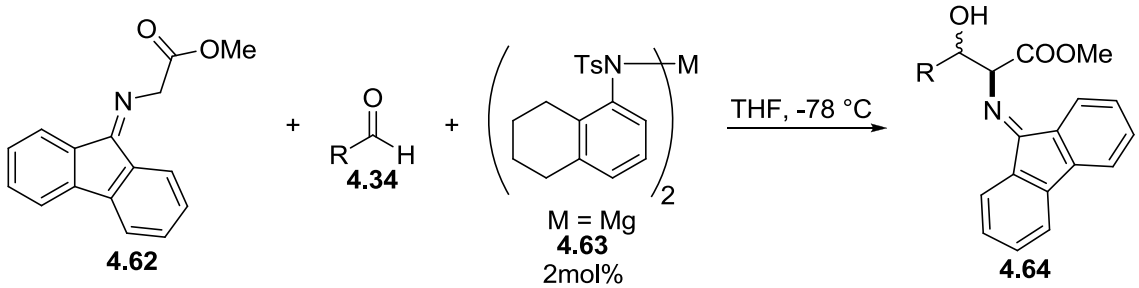
Maruoka work



Scheme 4.13 Enanatioselective β-Hydroxy-α-Amino acid Preparation



Scheme 4.14 Aldol Reaction of Flurenone Imine

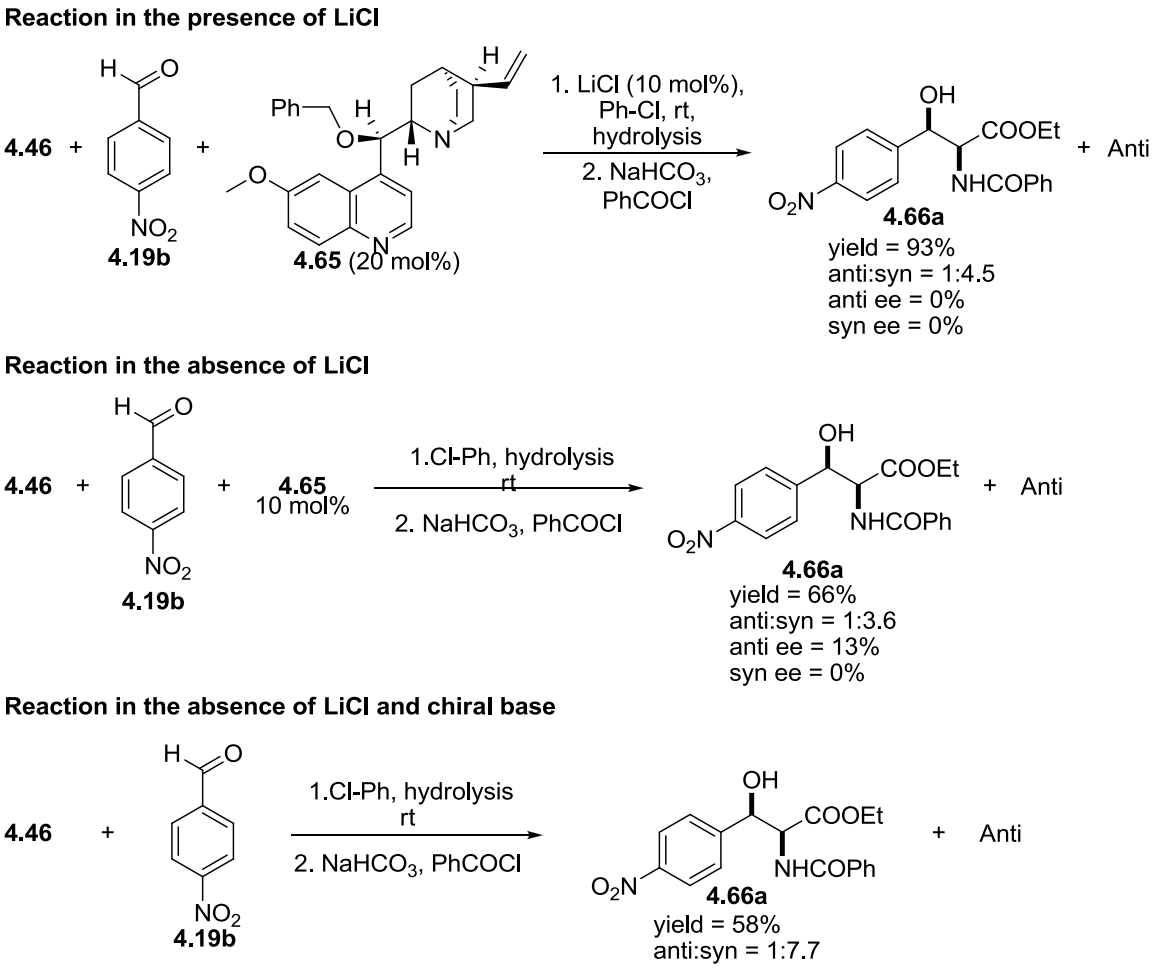


Apart from these, Kobayashi and coworkers have reported on a magnesium catalyzed aldol reaction with fluorenone imine (Scheme 4.14). The reaction proceeds in a diastereoselective manner.[27] In both of these cases, the Lewis acid activates the aldehyde. Keeping these limitations in mind, we decided to look for a simple method for the enantioselective synthesis of β-hydroxy-α-amino acids that would accommodate aryl aldehydes as substrates.

4.5 Results and Discussions

The work of Lou[26] and Kobayashi[27] along with earlier work by Tatsukawa[19] inspired us to evaluate a soft enolization approach for the synthesis of β-hydroxy-α-amino acid. In our initial effort, we studied the reaction of imine ester **4.46** with nitrobenzaldehyde using LiCl as the Lewis acid and *O*-benzylquinine as the base. With chlorobenzene as the solvent, the reaction was performed at room temperature.

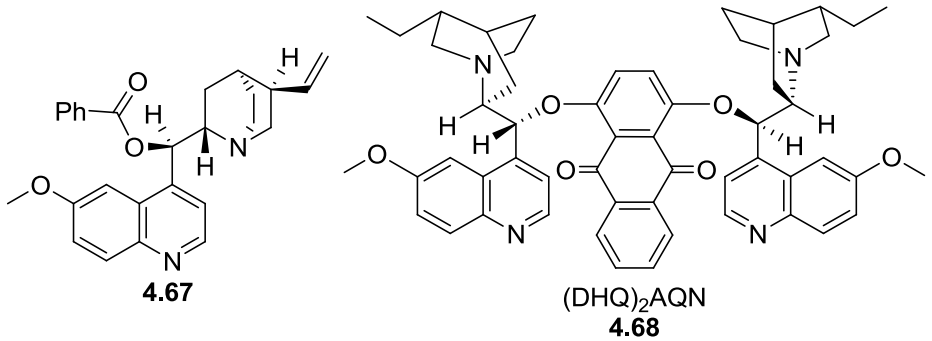
Scheme 4.15 Initial Screening of Quinine catalysts



Direct hydrolysis of the aldol product followed by reaction with benzoyl chloride led to the isolation of the N-benzoyl product **4.66a** in 93% yield (Scheme 4.15). The diastereomer ratio was determined by ^{1}HNMR to be 1(anti):4.5 (syn). The diastereomers were assigned by comparison with literature NMR.[28] In spite of the use of a chiral base, the aldol products were obtained as a racemic mixture. We then ran a control reaction in the absence of LiCl. In this case, the product was obtained in 66% yield with a diastereomer ratio of 1:3.6 (Scheme 4.15). The major diastereomer did not show any enantio enrichment while the minor diastereomer was obtained in 13% enantiomeric excess (ee). Surprisingly, when the reaction was performed in the absence of LiCl and cinchona alkaloid, the product was obtained in 58% yield with a diastereomer ratio of 1:7.7. This result stands in sharp contrast to the reports by Kobayashi[27] and Lou,[26]

wherein a Lewis acid catalyst was used for a diastereoselective reaction. Our work shows that aldol reaction of glycine imine ester **4.46** with an electron deficient aryl aldehyde can proceed in a diastereoselective manner even in the absence of catalysts. On the basis of these results, we decided to screen cinchona alkaloid catalysts with various substituents on the oxygen atom and the results are summarized in Table 4.1. When we switched to *O*-benzoylquinine, we obtained the product in 45% yield with a diastereomer ratio of 1:1.2. The major diastereomer was obtained in 4.6% ee, while the minor diastereomer was obtained as a racemic mixture. Encouraged by this initial result, we tried the commercially available dimeric cinchona alkaloid $(DHQ)_2AQN$ as the catalyst. In this case, the reaction was performed at 4 °C and the product was obtained as a near equal mixture of diastereomers (1:1.2). Interestingly, ee for the minor diastereomer was found to be 30%, while the major diastereomer was obtained as a racemic mixture.

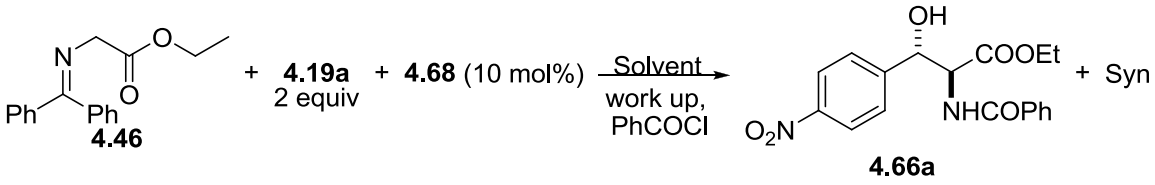
Table 4.1 Screening of Cinchona Alkaloid Based Catalyst



Entry	Catalyst	Solvent	Temp	Time	yield%	dr anti:syn	ee% anti (syn)
1	**4.65**	Cl-Ph	rt	4 d	45	1:2	4.6 (0)
2	**4.67**	Cl-Ph	rt	2 d	45	1:1.2	0 (4.6)
3	**4.68**	Cl-Ph	4 °C	3 d	51	1:1.2	30 (0)

To further optimize this reaction, we performed a solvent screen at 4 °C and the results are summarized in Table 4.2. Based on this study, we identified isopropyl acetate as the optimal solvent (entry 5). When the reaction was carried out with this solvent the product was obtained in 37% yield with a diastereomer ratio of 4.5:1 and ee of 47%. A dramatic improvement in the yield and a moderate improvement in ee were observed when 4 Å molecular sieves were used (entry 6) as an additive. Under these conditions, the product was obtained in 80% yield (diastereomer ratio, 2.7:1; 60% ee).

Table 4.2 Solvent Screen



Entry	Solvent	Temp	Time	yield%	dr anti:syn	ee% anti (syn)
1	THF	4 °C	5 d	51	1.64:1	36(0)
2	DMF	4 °C	5.5 d	69	1.5:1	32(0)
3	Toluene	4 °C	5.5 d	34	10:1	45(0)
4	Isopropanol	4 °C	5.5 d	28	1:1	12(7)
5	Isopropyl acetate	4 °C	5.5 d	37	4.5:1	47(0)
6	Isopropyl acetate[a]	4 °C	5.5 d	80	2.7:1	60(0)
7	EtOAc[a]	4 °C	5.5 d	61	5:1	61(0)

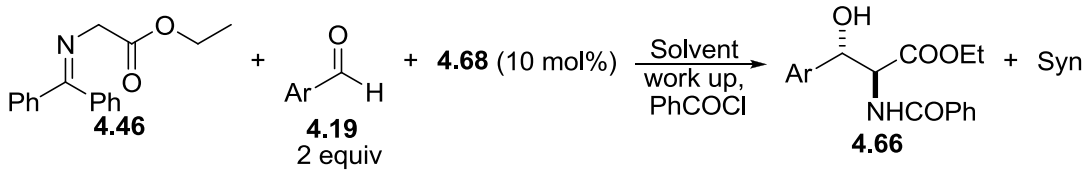
a) 100mg of 4 Å molecular sieves were added

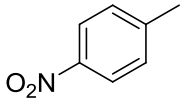
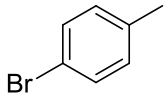
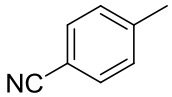
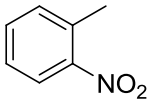
When the reaction was tried at -25 °C we failed to observe formation of any product. We also tried to improve the ee by performing reactions with benzophenone imines of glycine benzyl ester and glycine t-butyl ester. In the case of benzyl ester we were unable to isolate pure products, while in the case of t-butyl ester we did not observe product formation. The highest ee (71%) for an aldol reaction of glycine imine esters with an aromatic aldehyde was reported by Trost[25] for the reaction of **4.59** with

benzaldehyde. This reaction yields the syn-diastereomer after a two-step removal of the benzophenone group. In the case of the Maruoka catalyst, the yields and ees have been reported only for alkyl aldehydes.[24] The catalyst systems used by Maruoka and Trost require long synthetic sequences. By contrast, our method uses a commercially available catalyst and the product is isolated in a relatively simple manner. Therefore, even with the slightly lower ee, our method constitutes a simple and straightforward way of obtaining β-hydroxy-α-amino acids.

The scope of the reaction was evaluated using other electron deficient aromatic aldehydes (Table 4.3). When 4-bromobenzaldehyde was used as the substrate, the corresponding product was obtained in 42% yield with a diastereomer ratio of 3.6: 1. The major diastereomer was obtained in 74% ee and minor diastereomer was obtained in 25% ee. This is one of the highest ees for an aldol reaction of glycine imine ester with aromatic aldehydes. With p-cyanobenzaldehyde the product was obtained in 62% yield (diastereomer ratio, 4.3:1; ee: 50%). In the case of 2-nitro benzaldehyde, the product was obtained in 65% yield (diastereomer ratio 1:3.4). The major diastereomer was obtained in 0% ee and the minor diastereomer was obtained in 35% ee. Under our reaction conditions we failed to observe any reaction when benzaldehyde was used as a substrate. Although the reaction appears to work only with electron deficient aldehydes, it could still be a useful reaction for the synthesis of antibiotics like chloramphenicol and thiamphenicol. Apart from this, the β-hydroxy-α-amino acids found in teicoplanin and vancomycin can be potentially synthesized using this approach. Therefore, this is a very useful method in spite of its limitations.

Table 4.3 Substrate Scope

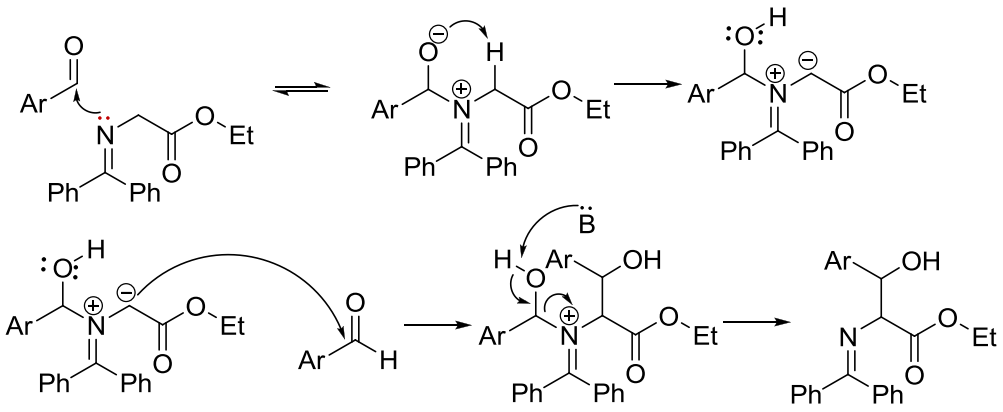


Entry	Ar	product	yield%	dr Anti:Syn	ee% Anti (Syn)
1		**4.66a**	80	2.7:1	60 (0)
2		**4.66b**	43	3.6:1	74 (25)
3		**4.66c**	62	4.3:1	50 (0)
4		**4.66d**	65	3.4:1	0 (35)

An interesting aspect of both the catalyzed and uncatalyzed reaction is the mechanism for deprotonation of the imine ester. The pK_a of the imine ester has been found to be 18.7 in DMSO.[29] The pK_a of protonated amines, on the other hand, is usually in the range of 9-11. For protonated imines, the pK_a is expected to be even lower as the nitrogen is in sp^2 hybridization. Based on these values, it is unlikely that the imine nitrogen in **4.46** can act as the base in the uncatalyzed reaction. Further, the ^{1}HNMR of the imine ester does not show any evidence of tautomerism. Indeed, the tautomer of this compound has been independently synthesized by the Johnston group and does not appear to show the presence of **4.46**.[30] Therefore, the source of base required for deprotonation is not clear. A possible source of base for this reaction is from the reversible attack of the imine nitrogen on the carbonyl carbon. The transiently generated alkoxide can then deprotonate the imine via a 5-membered transition state (Scheme 4.16). The resulting anion can then react with another molecule of aldehyde to form the β-hydroxy-α-amino

acids. Reaction of aldehydes with amines to generate alkoxides that can act as catalyst is well precedented. The hydrolysis of α-amino esters using an aldehyde catalyst has been reported by Hay and coworkers.[31] Commeyras and coworkers have used a similar approach for the hydrolysis of an amide bond. [32] Neighboring group participation from an adjacent aldehyde has been posited by Bender and coworkers in their study of hydrolysis of methyl o-formylbenzoate.[33] Suh and coworkers have shown that covering silica surfaces with aldehydes can generate artificial proteases.[34] In all of these reactions, the generation of an alkoxide from aldehyde has been proposed as the key step. Thus, although the proposed mechanism of the uncatalyzed reaction is unusual, it has literature precedence. In a similar vein, the catalyzed reaction is likely to proceed from the attack of the nucleophilic nitrogen of $(DHQ)_2AQN$ on the aldehyde carbon. This would potentially generate a chiral base for the deprotonation of imine ester (Scheme 4.16).

Scheme 4.16. Hypothesis for Generating Imine Anion.



4.6 Conclusion

In conclusion, a simple method for the enantioselective synthesis of β-hydroxy-α-amino acids from electron deficient aldehydes has been developed. Unlike earlier methods that use difficult-to-prepare catalysts, our method utilizes a simple commercially available catalyst. The products are obtained with moderate enantioselectivity. Importantly, we have shown that these reactions proceed in a diastereoselective manner

even in the absence of a catalyst. Although the substrate scope is restricted to electron deficient aromatic aldehydes, these represent an important class of substrate. The mechanism of the reaction probably involves the transient formation of an alkoxide from the reaction of an aldehyde with a nucleophile. Further studies are underway to harness this system for other reactions.

4.7 Experimental Section

All glassware was dried overnight in an oven at 120 °C prior to use. Reactions were monitored by TLC using silica gel TLC plates. Flash column chromatography was performed using silica gel of mesh size 230–400. Grease-free solvents for flash column chromatography were obtained by distillation. Unless otherwise noted, all chemicals obtained from commercial sources were used without further purification. Infrared spectra were recorded using an FT-IR Spectrometer. ^{1}H and ^{13}C NMRs were recorded on a 400 MHz Fourier Transform NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with respect to the residual solvent peak. For ^{1}H NMRs recorded in $CDCl_3$, the residual solvent peak at 7.27 ppm was used for calibration. For $\{^{1}H\}$ ^{13}C NMRs recorded in $CDCl_3$, the residual solvent peak at 77.16 ppm was used for calibration. For ^{1}H NMRs recorded in DMSO-d_6, the residual solvent peak at 2.50 ppm was used for calibration. For $\{^{1}H\}$ ^{13}C NMRs recorded in DMSO-d_6, the residual solvent peak at 39.5 ppm was used for calibration. ^{13}C NMRs were recorded at 100 MHz using proton decoupling. HRMS were recorded using Q-TOF mass analyzer. Melting points were measured using melting point apparatus. Compound **4.46** was prepared, following the literature procedure.[35] The ^{1}H NMR data of the product (**4.46**) was in agreement with the literature.[36] Compound **4.65** was prepared, following the literature procedure.[37] Compound **4.66** was prepared, following the literature procedure.[38]

General Procedure for the Synthesis of Benzoyl Protected β-Hydroxy-α-Amino acid:

A 5 mL vial was charged with **4.46** (50 mg, 0.19 mmol) and 100 mg of 4 Å molecular sieves. The vial was flushed with argon followed by addition of isopropyl acetate (1 mL).. The vial was immersed in an ice bath and $(DHQ)_2AQN$ (10 mol%) was added followed by addition of aldehyde (2 equiv).. The vial was then kept in a refrigerator (maintained at 4 °C) for 5.5 days. The reaction mixture was transferred to a round bottomed flask and diluted with THF (4 mL). The flask was cooled to 0 °C and 1 N HCl was added. The reaction mixture was stirred at 0 °C for 1 h. After dilution of the reaction mixture with 10 mL of DI water, the aqueous layer was washed with diethyl ether (3×20 mL). The aqueous layer was basified with saturated sodium bicarbonate solutionand theproduct was extracted with DCM (4×20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in a mixture of of water and dioxane (0.5 mL water, 4.5 mL dioxane). To this, $NaHCO_3$ (56 mg, 0.7 mmol) was added followed by benzoyl chloride (100 µL, 0.9 mmol) and the reaction mixture was stirred at room temperature for 1 h. It was then diluted with saturated $NaHCO_3$ (20 mL) solution and the compound was extracted with DCM (4×20 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography.

Phenylalanine,* N-*benzoyl-β-hydroxy-4-nitro-ethylester (4.66a):

The general procedure was employed with the following quantities: **4.46** (50 mg**,** 0.19 mmol), 4-nitrobenzaldehyde (56 mg, 0.37 mmol), $(DHQ)_2AQN$ (18 mg, 0.02 mmol), benzoyl chloride (100 µL, 0.9 mmol), $NaHCO_3$ (56 mg, 0.7 mmol), isopropyl acetate (1 mL) (1 mL), and dioxane:water (4.5 mL:0.5 mL).

Column Chromatography:

Approximately 40 mL of silica was packed into a column using 20% EtOAc in hexanes as the solvent. The material obtained from workup was loaded on the column after

dissolution in a minimum amount of DCM. Approximately 400 mL of EtOAc in hexanes was eluted followed by elution with 300 mL of 40% EtOAc in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 18 – 25 contained product. These fractions were concentrated and dried under high vacuum to give 53 mg of product (yield: 80%). The ^{1}H NMR of the product was in agreement with the literature.[28]

Phenylalanine,* N-*benzoyl-β-hydroxy-4-bromo-ethylester (4.66b):

The general procedure was employed with the following quantities: **4.46** (56 mg**,** 0.20 mmol), 4-bromo benzaldehyde (155 mg, 0.83 mmol), $(DHQ)_2AQN$ (18 mg, 0.02 mmol), benzoyl chloride (100 µL, 0.9 mmol), $NaHCO_3$ (56 mg, 0.7 mmol), isopropyl acetate (1 mL) (1 mL), and dioxane:water (4.5 mL:0.5 mL).

Column Chromatography:

Approximately 40 mL of silica was packed into a column using 20% EtOAc in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of DCM. Approximately 400 mL of 20% EtOAc in hexanes was eluted followed by elution with 100 mL of 40% EtOAc in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 8 – 16 contained product. These fractions were concentrated and dried under high vacuum to give 35 mg of product (yield: 42%). Obtained product is a mixture of diastereomers in the ratio of 4:1.

Characterization:

White solid; R_f: 0.33 in 40% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ. 7.77 – 7.75 (maj. dia., m, 2h), 7.73 – 7.10 (min. dia., m, int. (0.6), 2H), 7.58 – 7.52 (min. dia., m, int. (0.6), 5h), 7.50 – 7.1 (maj. dia., m, int. (0.6), 2H), 7.37 (min. dia., d, , *J* = 8.5 Hz, int. (0.8), 2h), 7.16 (maj. dia., d, , *J* = 8.4 Hz, 2h), 6.94 (maj. dia., d, , *J* = 6.2 Hz, 1h), 6.88 (min. dia., d, , *J* = 8.7 Hz, int. (0.25), 1h), 5.38 (maj. dia., br s, 1h), 5.33 (min. dia., br s, int. (0.24), 1h), 5.18 (maj. dia., dd, *J* = 3.1, 6.5 Hz, 1H), 5.05 (min. dia., dd, *J* = 8.6, 3.3 Hz, int. (0.28) 1H), 4.87 (maj. dia., d, , *J* = 5.6 Hz, 1H), 4.29 – 4.19 (mixture of dia.,

m, int. (2.8), 4H), 1.33 – 1.25 (mixture of dia., m, int. (4..78), 6H) ; ^{13}C NMR (100 MHz $CDCl_3$): 169.3, 169.1, 138.5, 133.0, 132.5, 132.1, 131.7, 131.6, 129.0, 128.8, 127.9, 127.8, 127.3, 127.2, 122.2, 75.2, 73.9, 62.6, 62.2, 59.9, 58.6, 14.2; IR (film1743 (C=O), 1631 (N-H amide), 1534 (N-H amide), 1488 (aromatic C=C), 1067 (C-O), 689 (C=O) cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ Calcd. for $C_{18}H_{19}BrNO_4^+$ 392.0497; Found 392.0494.

Phenylalanine,* N-*benzoyl-β-hydroxy-4-nitrile-ethylester (4.66c):

The general procedure was employed with the following quantities: **6** (56 mg**,** 0.20 mmol), 4-nitrile benzaldehyde (110 mg, 0.83 mmol), $(DHQ)_2AQN$ (18 mg, 0.02 mmol), benzoyl chloride (100 µL, 0.9 mmol), $NaHCO_3$ (56 mg, 0.7 mmol), isopropyl acetate (1 mL) and dioxane:water (4.5 mL:0.5 mL).

Column Chromatography:

Approximately 40 mL of silica was packed into a column using 20% EtOAc in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of DCM. Approximately 400 mL of 20% EtOAc in hexanes was eluted followed by elution with 300 mL of 40% EtOAc in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 16 – 24 contained product. These fractions were concentrated and dried under high vacuum to give 44 mg of product (yield: 62%). The ^{1}H NMR of the product was in agreement with the literature.**Error! Bookmark not defined.**

Phenylalanine,* N-*benzoyl-β-hydroxy-2-nitro-ethylester (4.66d):

The general procedure was employed with the following quantities: **6** (56 mg**,** 0.20 mmol), 3-nitro benzaldehyde (127 mg, 0.84 mmol), $(DHQ)_2AQN$ (18 mg, 0.02 mmol), benzoyl chloride (100 µL, 0.9 mmol), $NaHCO_3$ (56 mg, 0.7 mmol), isopropyl acetate (1 mL), and dioxane:water (4.5 mL:0.5 mL).

Column Chromatography:

Approximately 40 mL of silica was packed into a column using 20% EtOAc in hexanes as the solvent. The material obtained from workup was loaded on the column after dissolution in a minimum amount of DCM. Approximately 400 mL of 20% EtOAc in hexanes was eluted followed by elution with 300 mL of 40% EtOAc in hexanes. The eluted solvent was collected in 25 mL fractions. Fractions 15 – 26 contained product. These fractions were concentrated and dried under high vacuum to give 43 mg of product (yield: 65%). Obtained product contains minor impurities.

Characterization:

Yellow solid; R_f: 0.26 in 40% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ. 8.07 – 8.05 (maj. dia., m, 1h), 7.95 – 7.92 (min. dia., m, int. (0.4), 1H), 7.84 – 7.82 (m, int. (1.5), 2h), 7.69 – 7.37 (mixture of dia., m, int. (10.15), 14H), 7.03-7.01 (mixture of dia., m, int. (1.33), 2h), 6.06 (maj. dia., d, , J = 2.5 Hz, 1h), 5.92 (min. dia., d, J = 4.9 Hz, int. (0.25), 1h), 5.41 (maj. dia., dd, J = 2.6, 8.9 Hz, 1H), 5.19 (min. dia., dd, J = 4.9, 7.6 Hz, int. (0.27) 1H), 4.33 – 4.16 (mixture of dia., m, int. (2.5), 4H), 1.33 – 1.24 (mixture of dia., m, int. (4.8), 6H); ^{13}C NMR (100 MHz $CDCl_3$): 170.3, 170.2, 168.2, 167.7, 147.5, 136.2, 133.8, 133.5, 133.0, 132.3, 132.0, 129.5, 129.1, 129.0, 128.8, 128.7, 127.2, 127.1, 125.1, 124.6, 70.5, 70.3, 62.6, 62.3, 59.0, 57.2, 14.2, 14.0; IR (film): 1742 (C=O), 1628 (N-H amide), 1520 (N-H amide), 1347 (C-O), 1220 (C-O) cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ Calcd. for $C_{18}H_{19}N_2O_6^+$ 359.1243; Found 359.1232.

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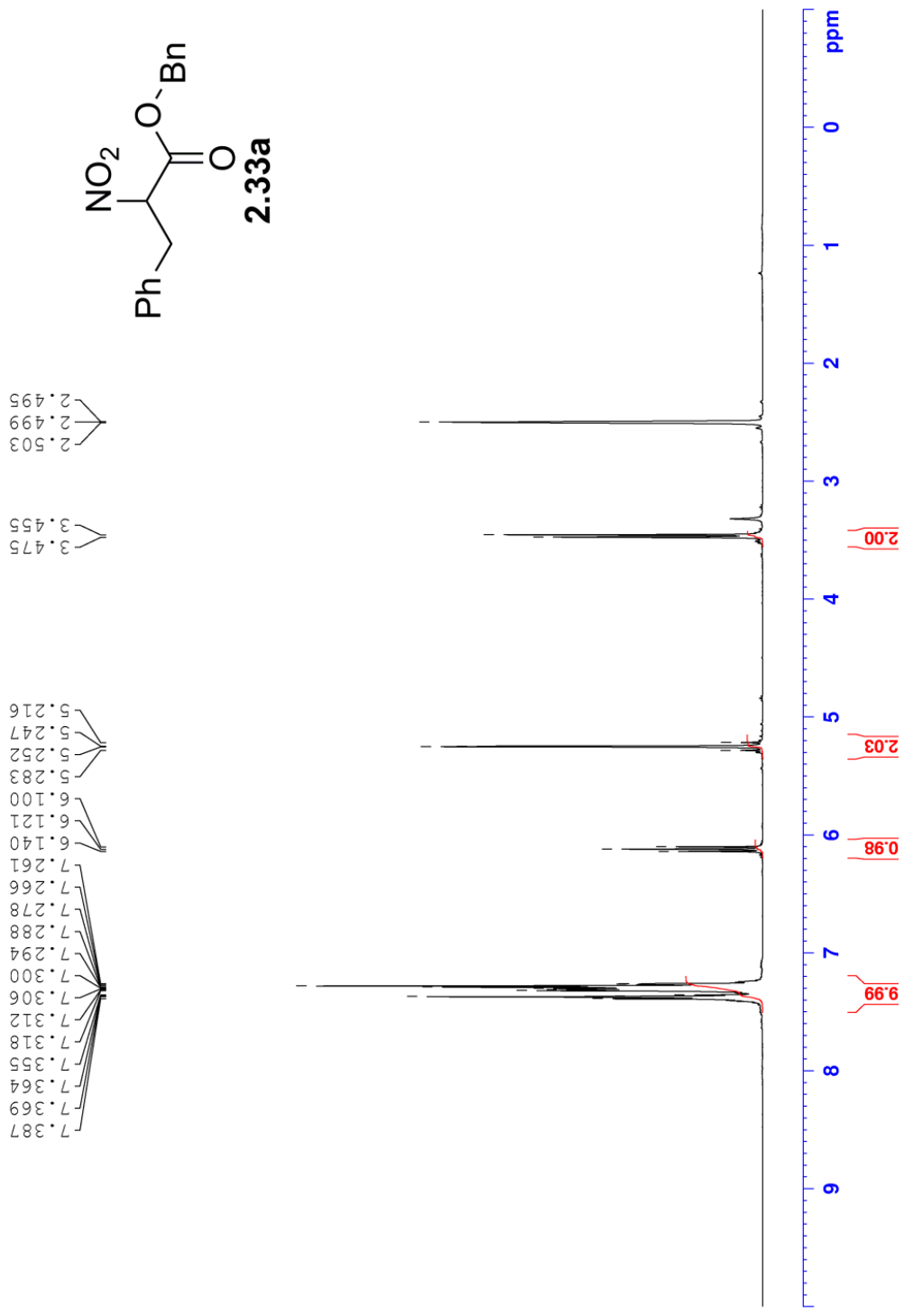
APPENDIX I

NMRs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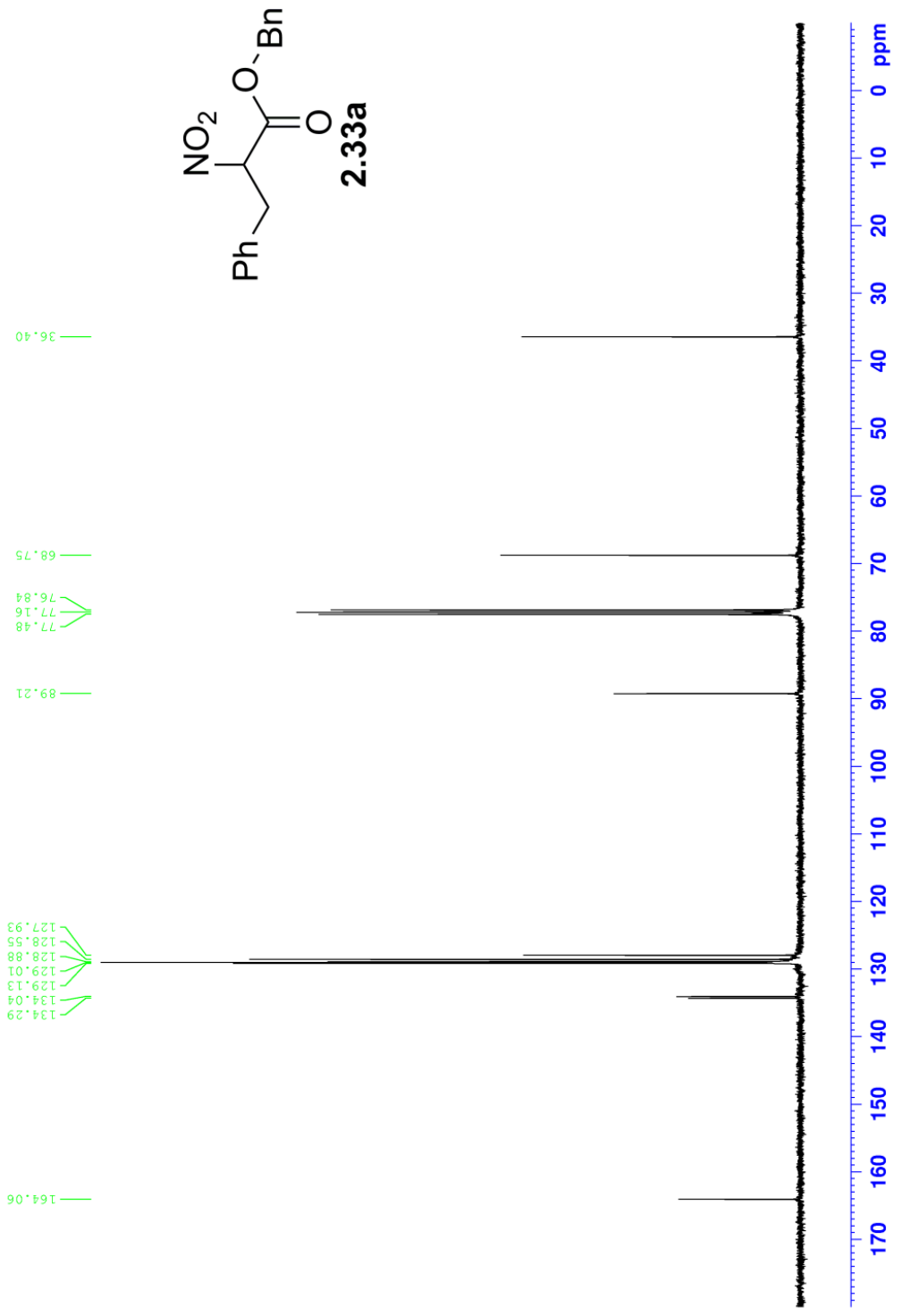
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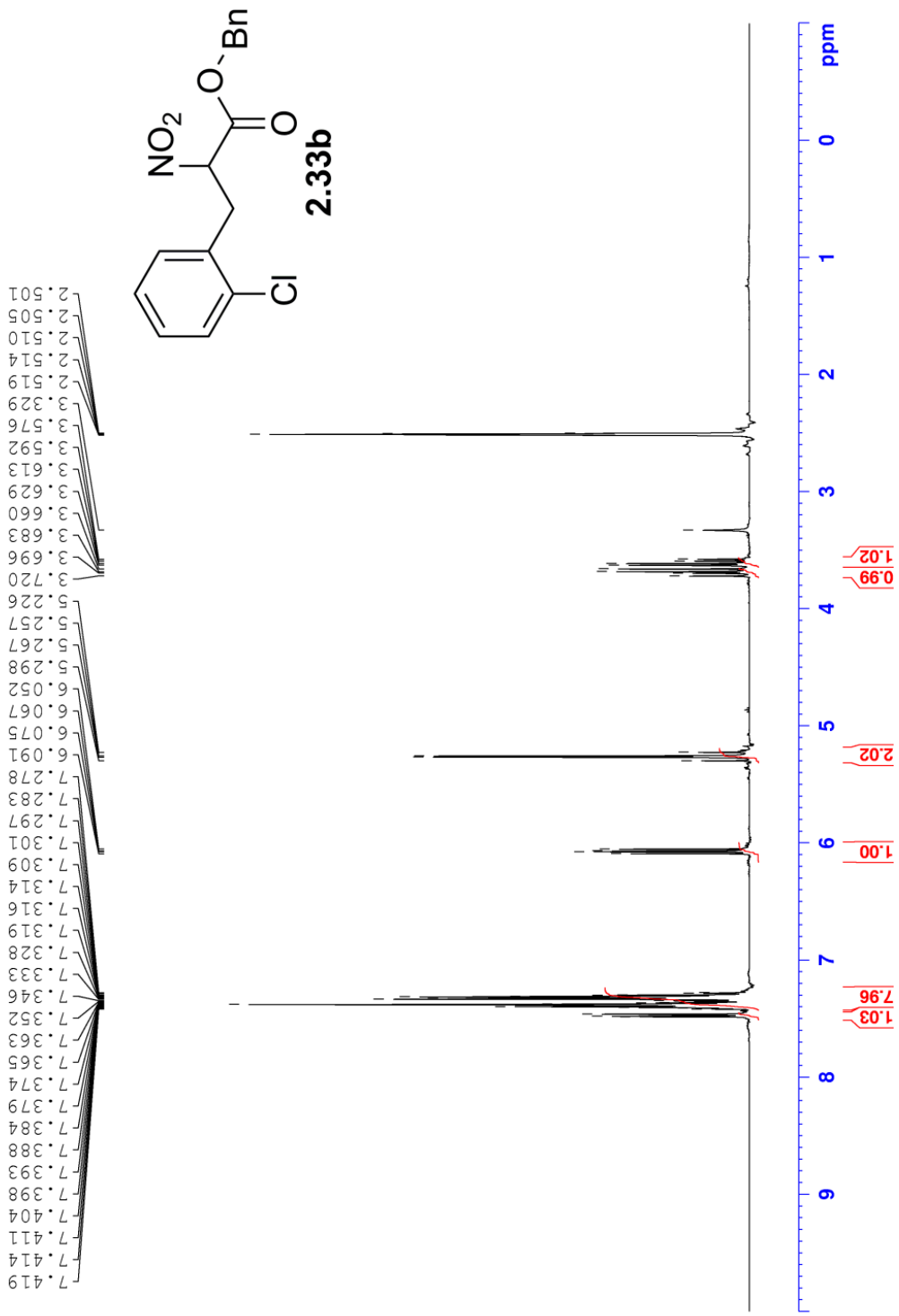
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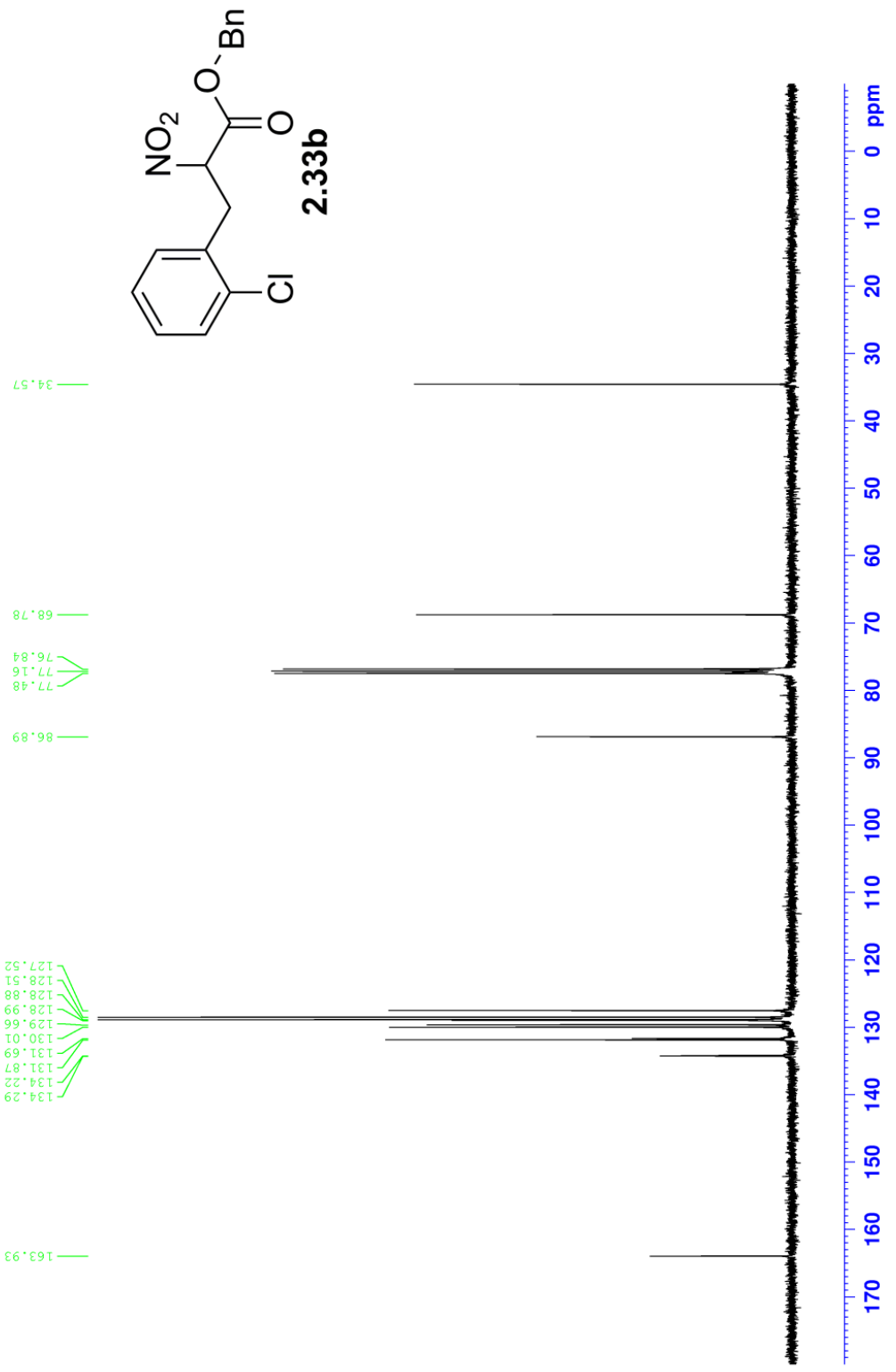
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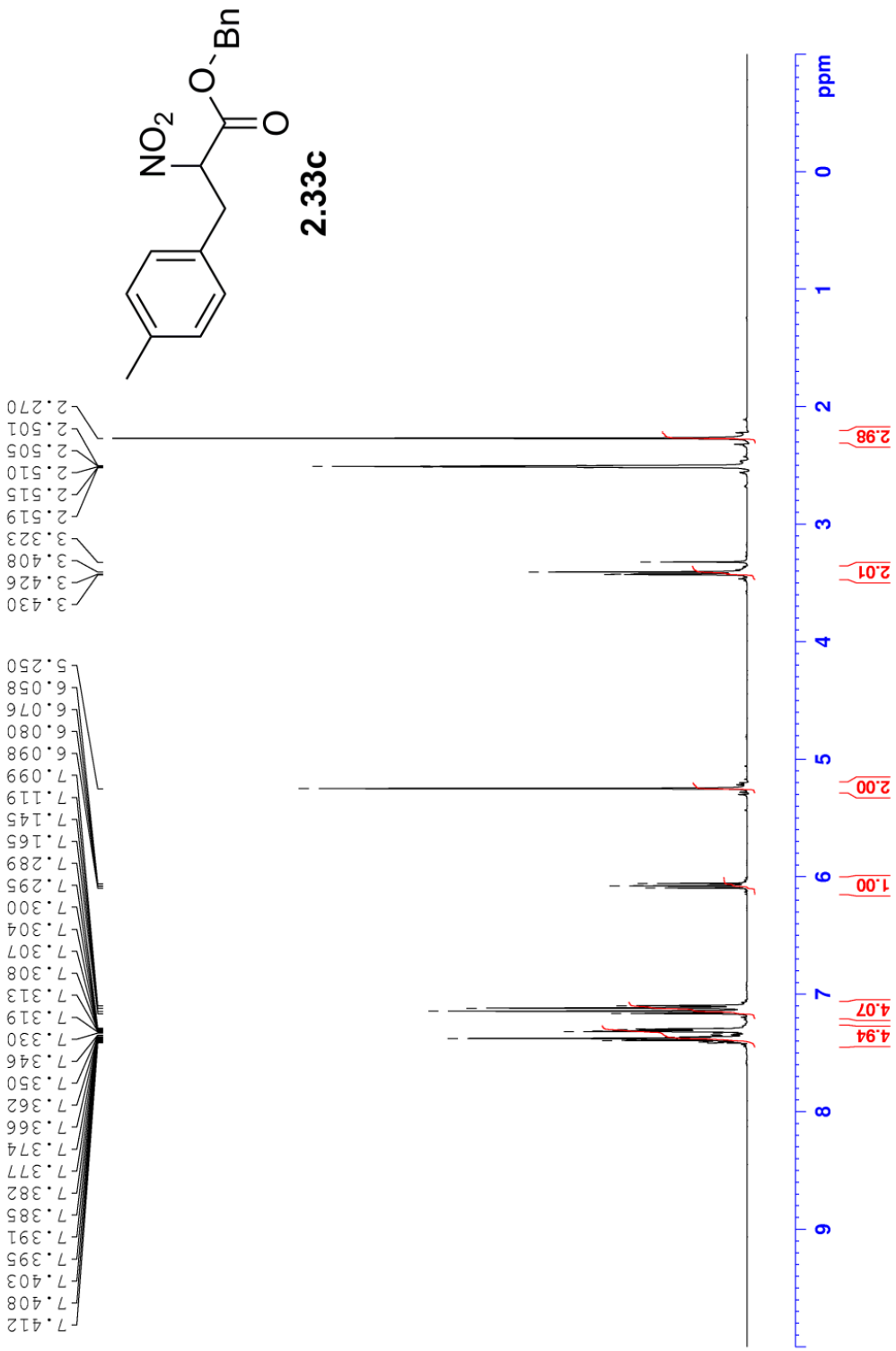
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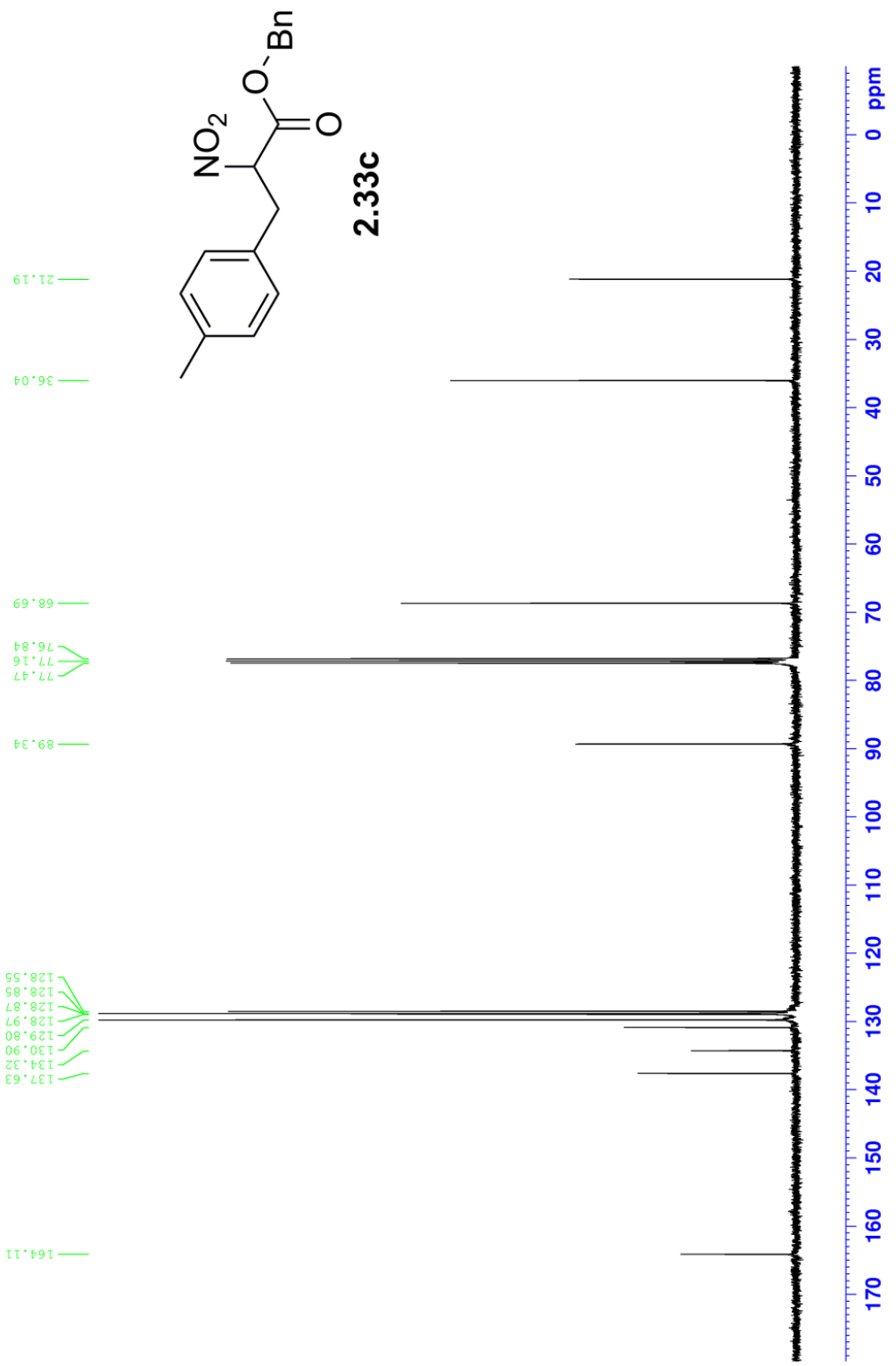
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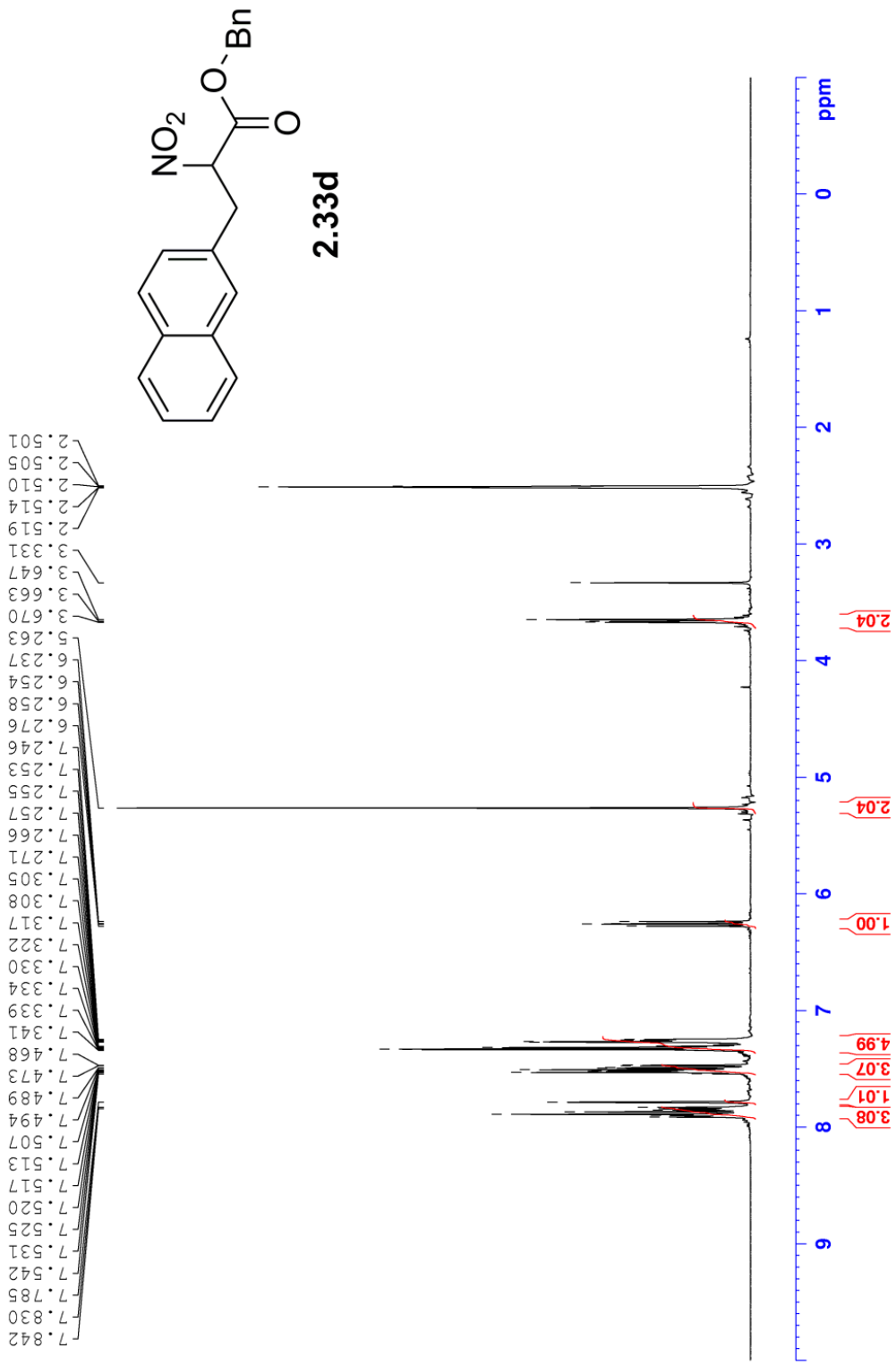
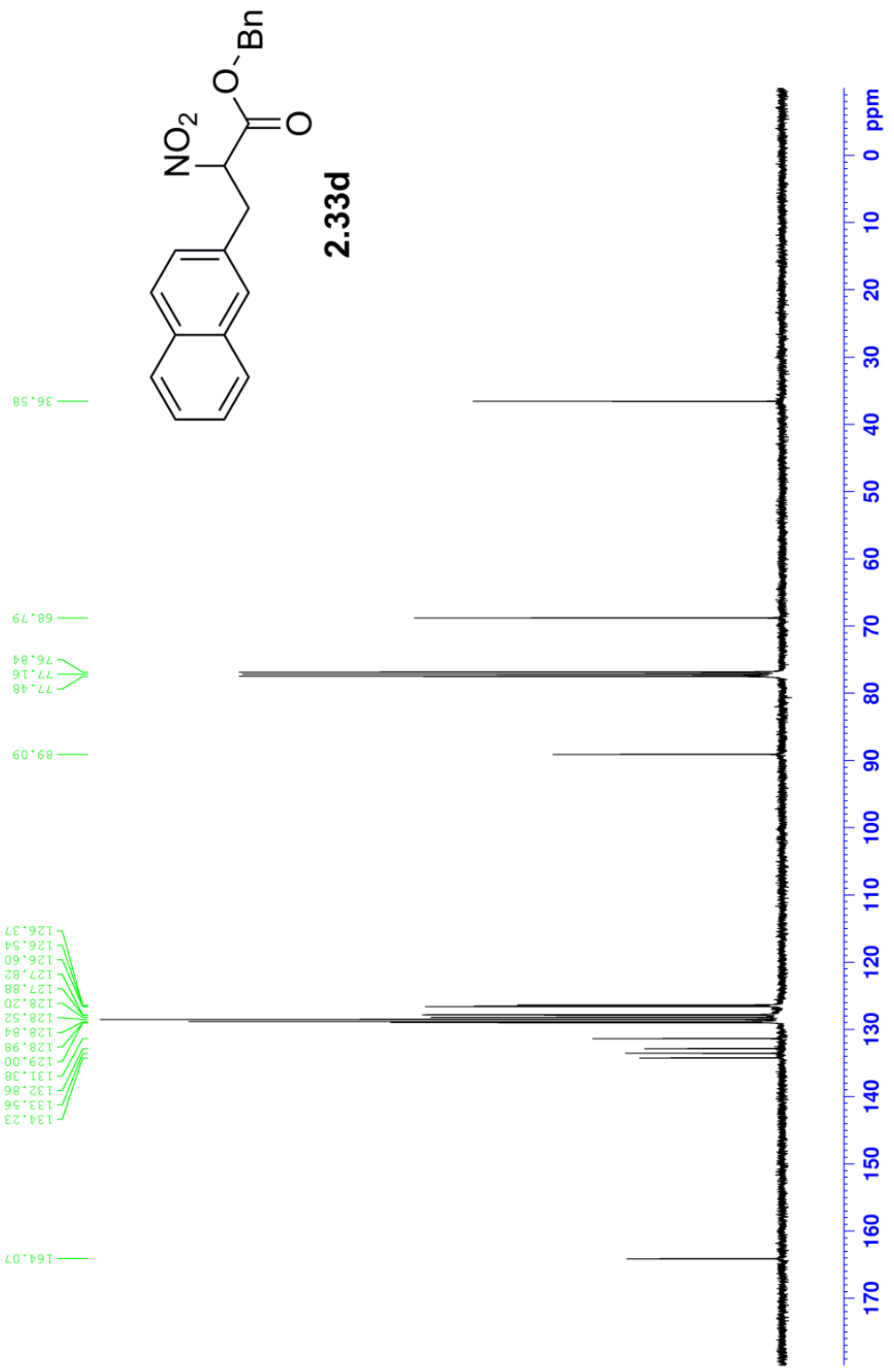

2.33d
NO2
O
O
Bn
ppm
0
1
2
3
4
5
6
7
8
9
2.04
2.04
1.00
4.99
3.07
1.01
3.08
2.501
2.505
2.510
2.514
2.519
3.331
3.647
3.663
3.670
5.263
6.237
6.254
6.258
6.276
7.246
7.253
7.255
7.257
7.266
7.271
7.305
7.308
7.317
7.322
7.330
7.334
7.339
7.341
7.468
7.473
7.489
7.494
7.507
7.513
7.517
7.520
7.525
7.531
7.542
7.785
7.830
7.842


O
Bn
O
NO2
2.33d
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68.79
76.84
77.16
77.48
89.09
126.37
126.54
126.60
127.82
127.88
128.20
128.52
128.84
128.98
129.00
131.38
132.86
133.56
134.23
164.07
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20
30
40
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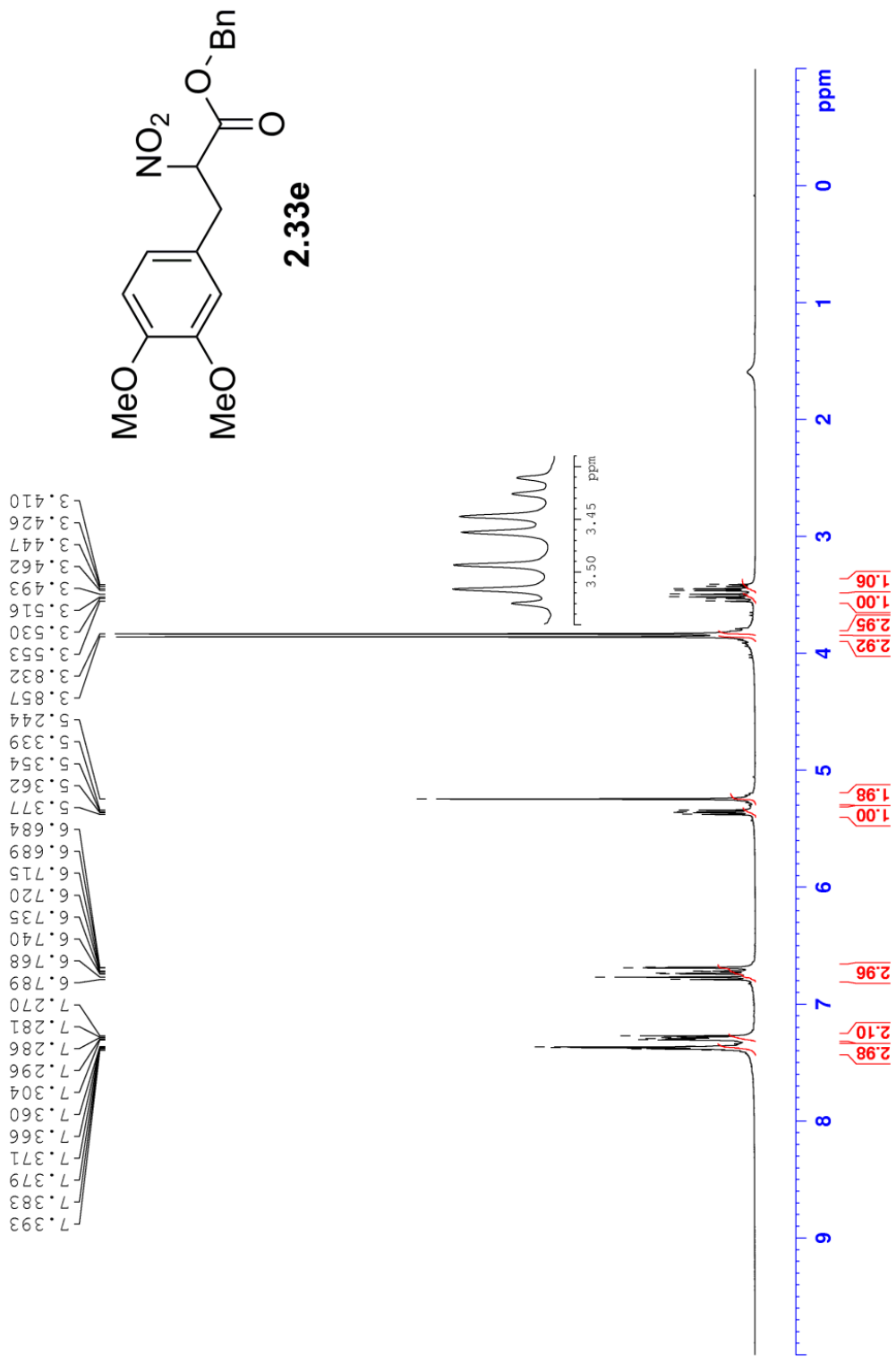
90
100
110
120
130
140
150
160
170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MeO
NO2
O
O
Bn
2.33e
3.50
3.45
ppm
7.393
7.383
7.379
7.371
7.366
7.360
7.304
7.296
7.286
7.281
7.270
6.789
6.768
6.740
6.735
6.720
6.715
6.689
6.684
5.377
5.362
5.354
5.339
5.244
3.857
3.832
3.553
3.530
3.516
3.493
3.462
3.447
3.426
3.410
2.98
2.10
2.96
1.00
1.98
2.92
2.95
1.00
1.06
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1
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3
4
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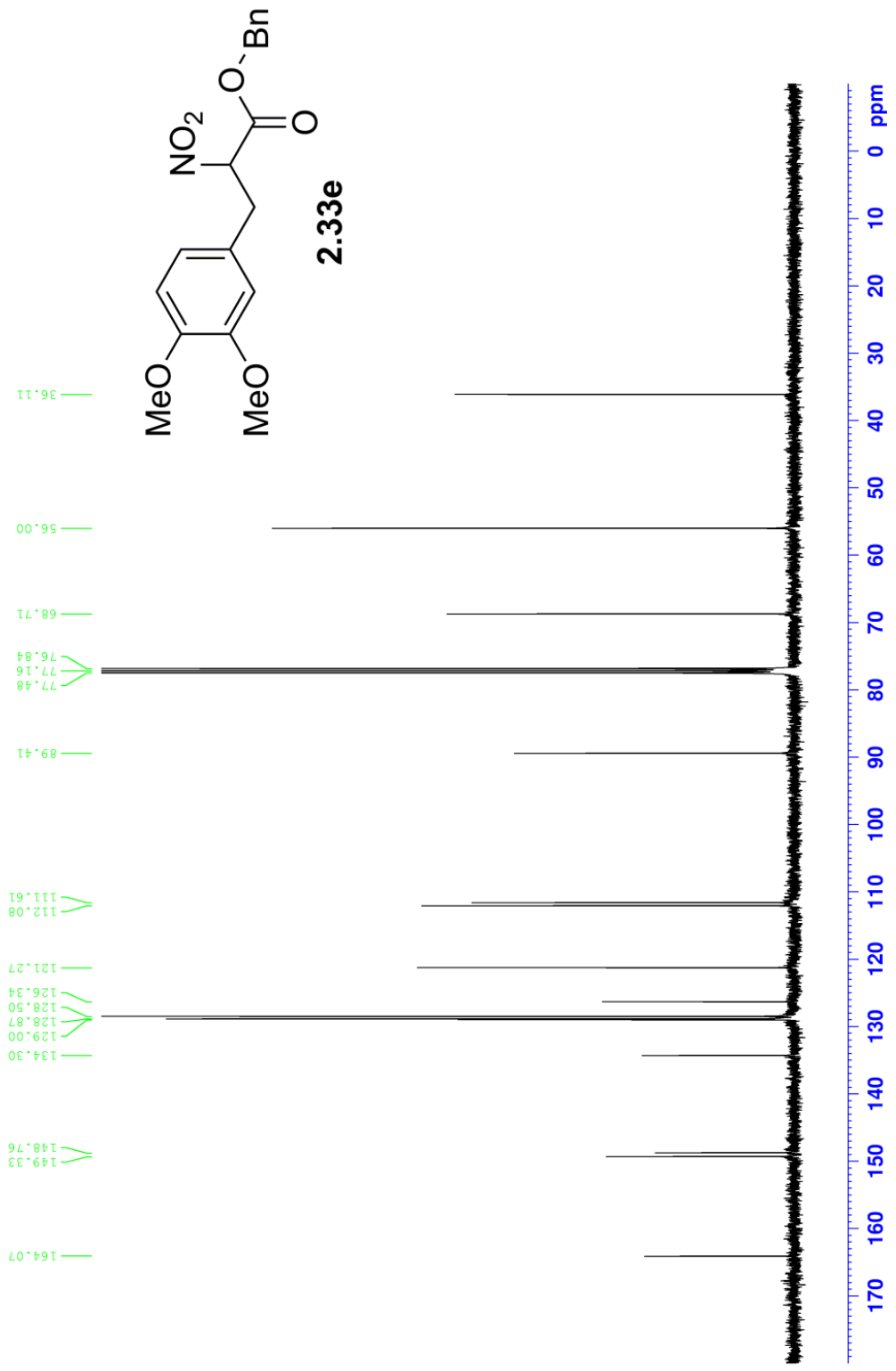
6
7
8
9
ppm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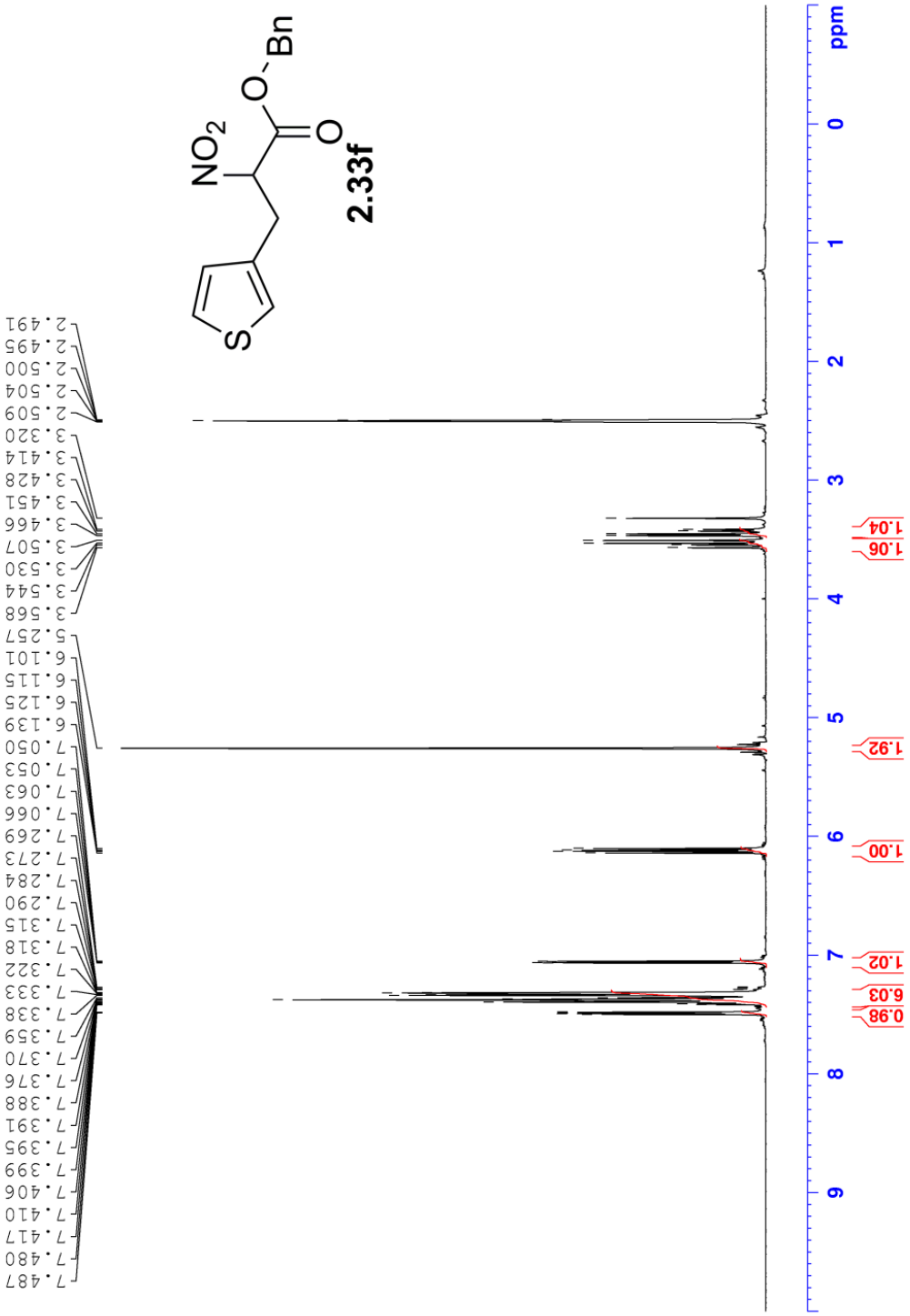
MeO
NO2
O
O
Bn
2.33e
36.11
56.00
68.71
76.84
77.16
77.48
89.41
111.61
112.08
121.27
126.34
128.50
128.87
129.00
134.30
148.76
149.33
164.07
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
ppm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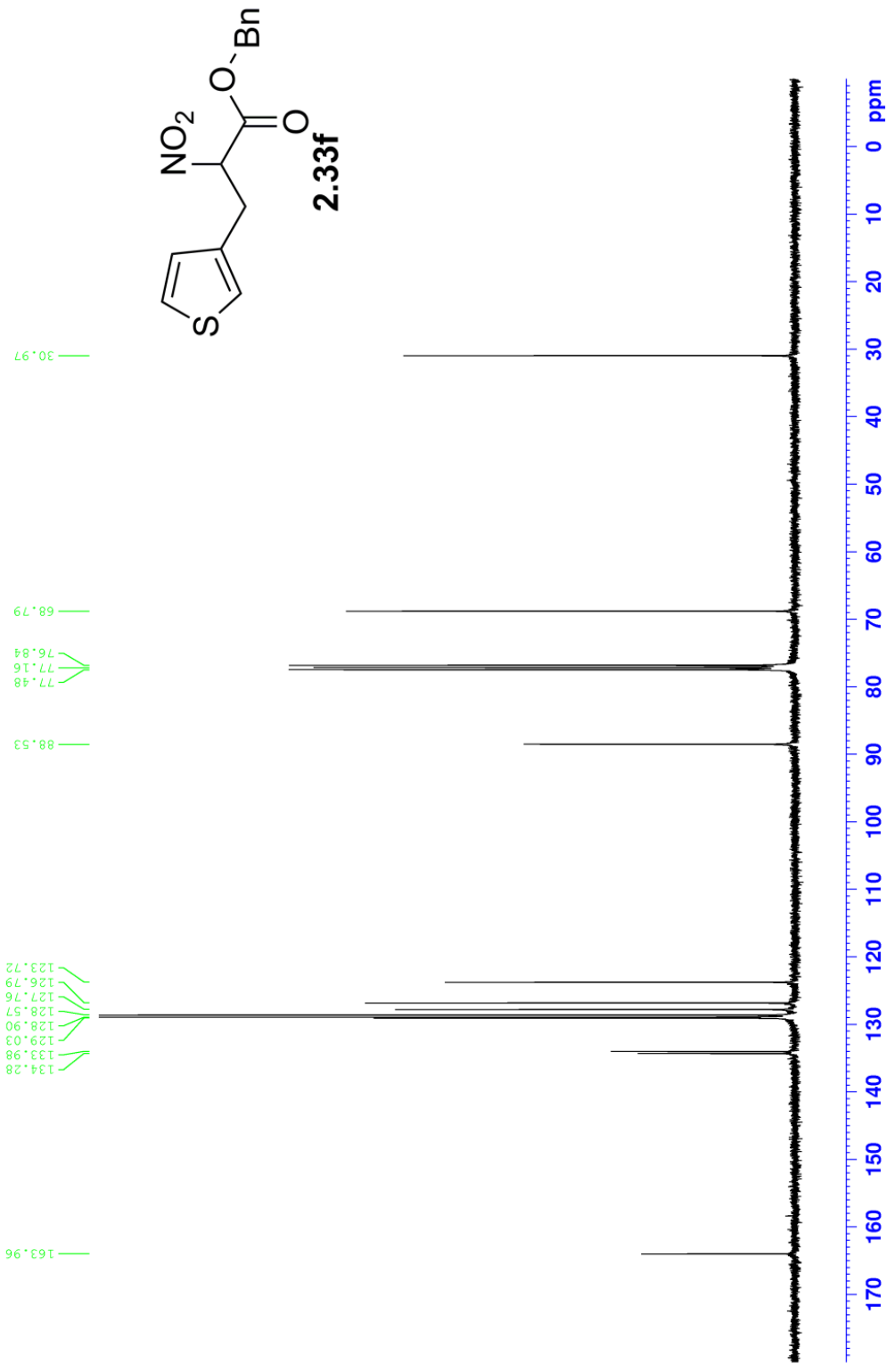
NO2
O
O
Bn
S
ppm
0
1
2
3
4
5
6
7
8
9
1.04
1.06
1.92
1.00
1.02
6.03
0.98
7.487
7.480
7.417
7.410
7.406
7.399
7.395
7.391
7.388
7.376
7.370
7.359
7.338
7.333
7.322
7.318
7.315
7.290
7.284
7.273
7.269
7.066
7.063
7.053
7.050
6.139
6.125
6.115
6.101
5.257
3.568
3.544
3.530
3.507
3.466
3.451
3.428
3.414
3.320
2.509
2.504
2.500
2.495
2.491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O
O
Bn
S
2.33f
30.97
68.79
76.84
77.16
77.48
88.53
123.72
126.79
127.76
128.57
128.90
129.03
133.98
134.28
163.96
0 ppm
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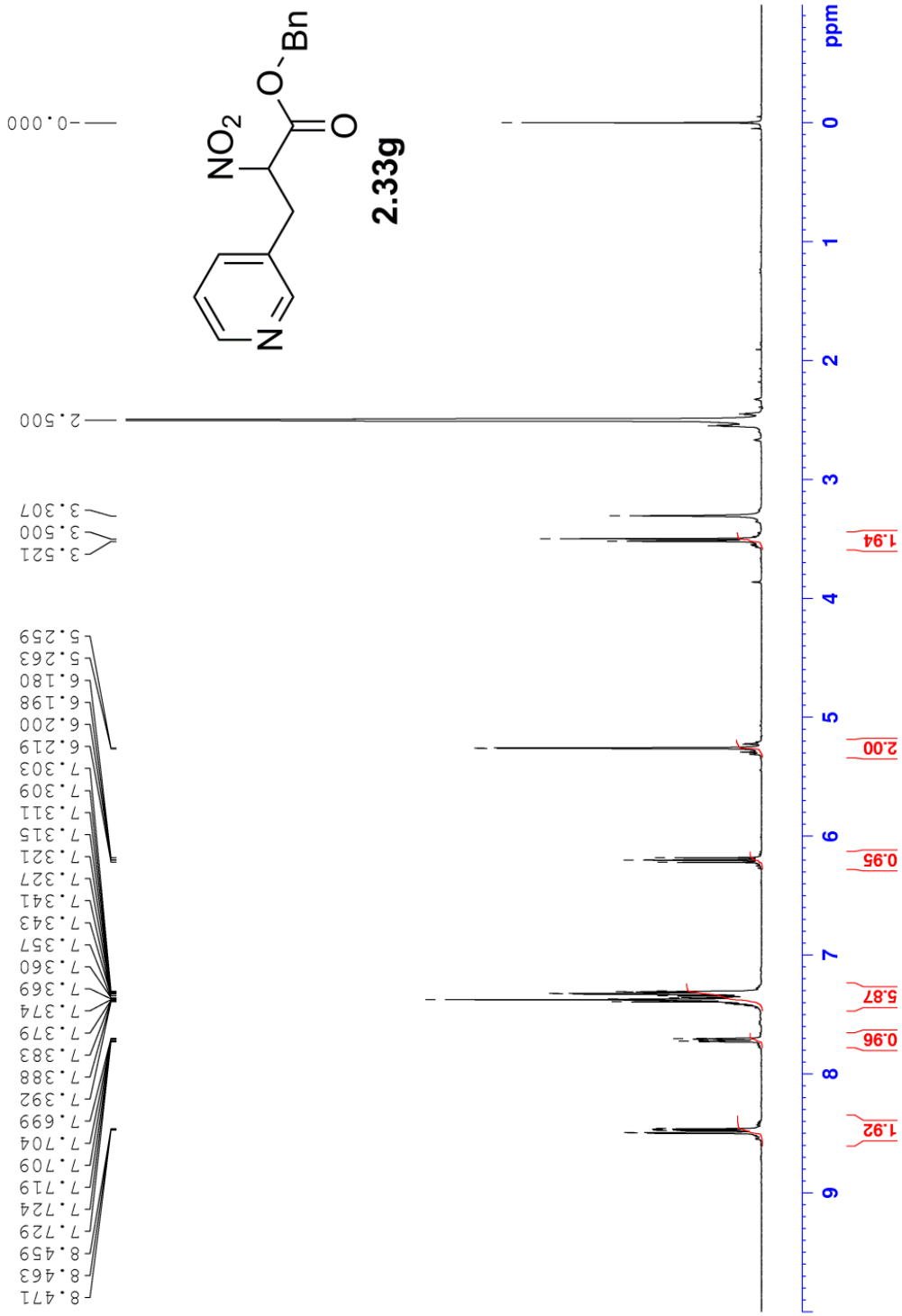
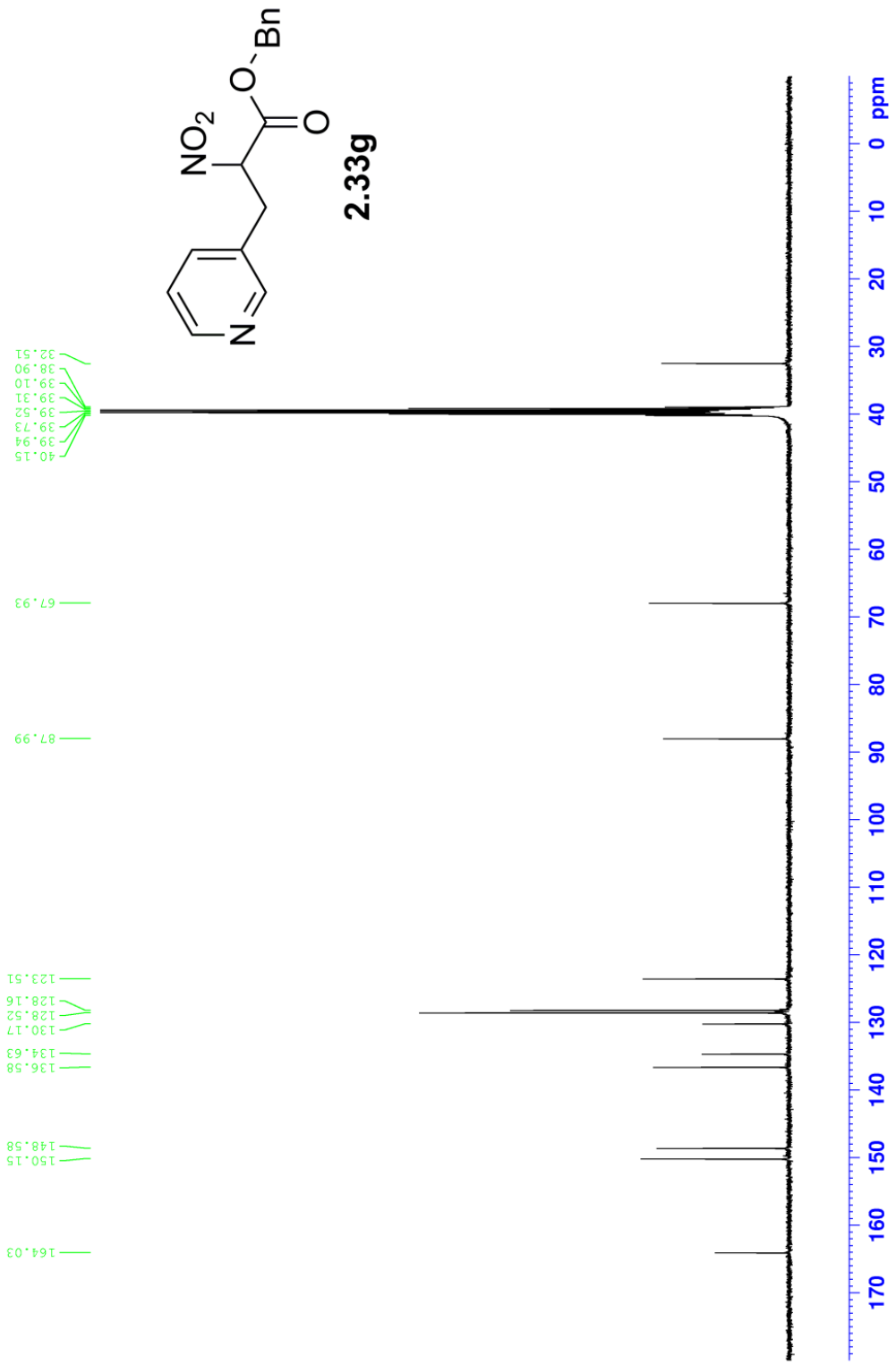
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170


2.33g
NO2
O
O
Bn
N
ppm
0
1
2
3
4
5
6
7
8
9
1.94
2.00
0.95
5.87
0.96
1.92
0.000
2.500
3.307
3.500
3.521
5.259
5.263
6.180
6.198
6.200
6.219
7.303
7.309
7.311
7.315
7.321
7.327
7.341
7.343
7.357
7.360
7.369
7.374
7.379
7.383
7.388
7.392
7.699
7.704
7.709
7.719
7.724
7.729
8.459
8.463
8.471


2.33g
NO2
O
O
Bn
N
32.51
38.90
39.10
39.31
39.52
39.73
39.94
40.15
67.93
87.99
123.51
128.16
128.52
130.17
134.63
136.58
148.58
150.15
164.03
0 ppm
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20
30
40
50
60
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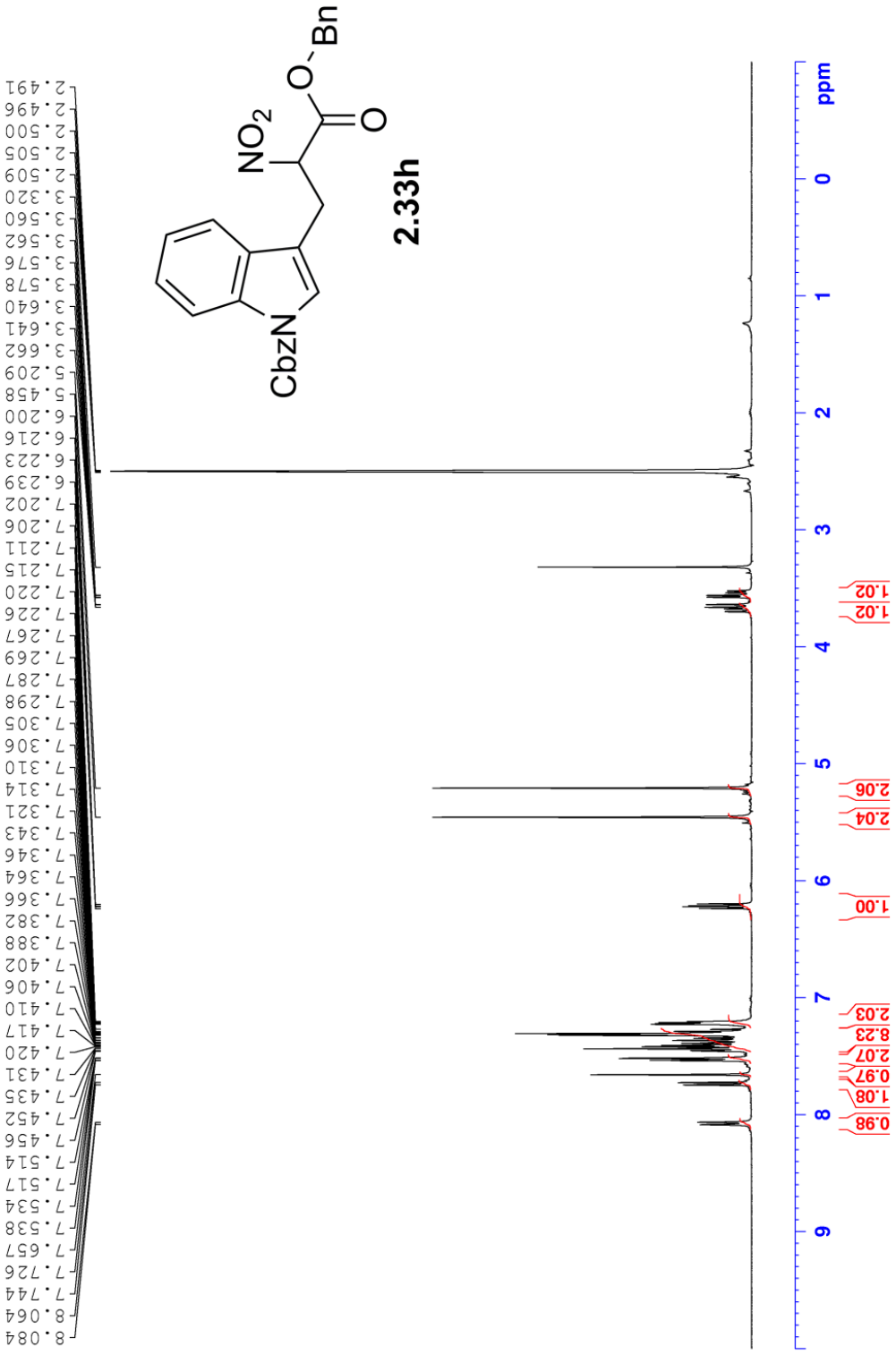
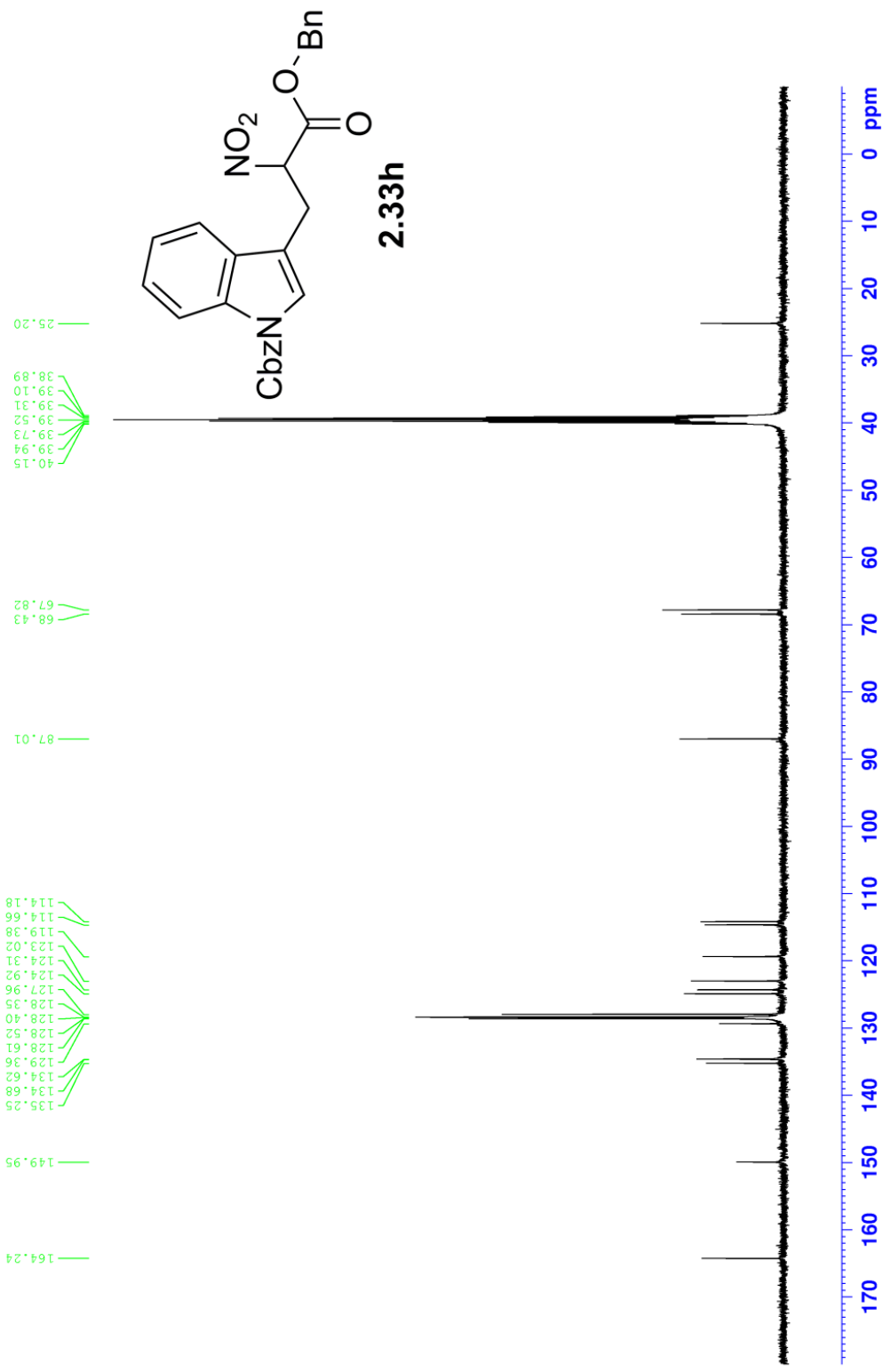
80
90
100
110
120
130
140
150
160
170


2.33h
CbzN
NO2
O
O
Bn
ppm
0
1
2
3
4
5
6
7
8
9
1.02
1.02
2.06
2.04
1.00
2.03
8.23
2.07
0.97
1.08
0.98


2.33h
CbzN
NO2
O
O
Bn
25.20
38.89
39.10
39.31
39.52
39.73
39.94
40.15
67.82
68.43
87.01
114.18
114.66
119.38
123.02
124.31
124.92
127.96
128.35
128.40
128.52
128.61
129.36
134.62
134.68
135.25
149.95
164.24
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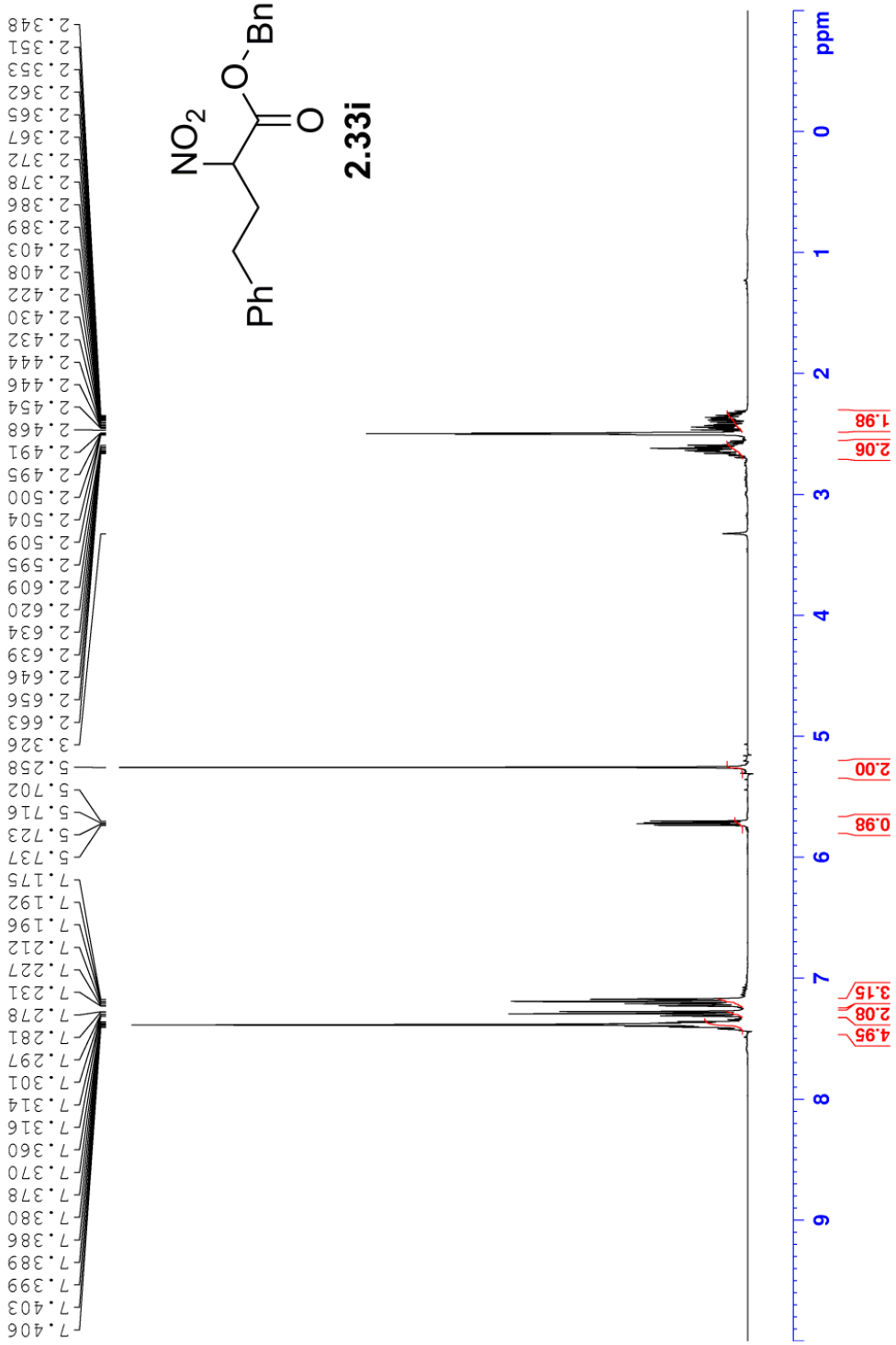
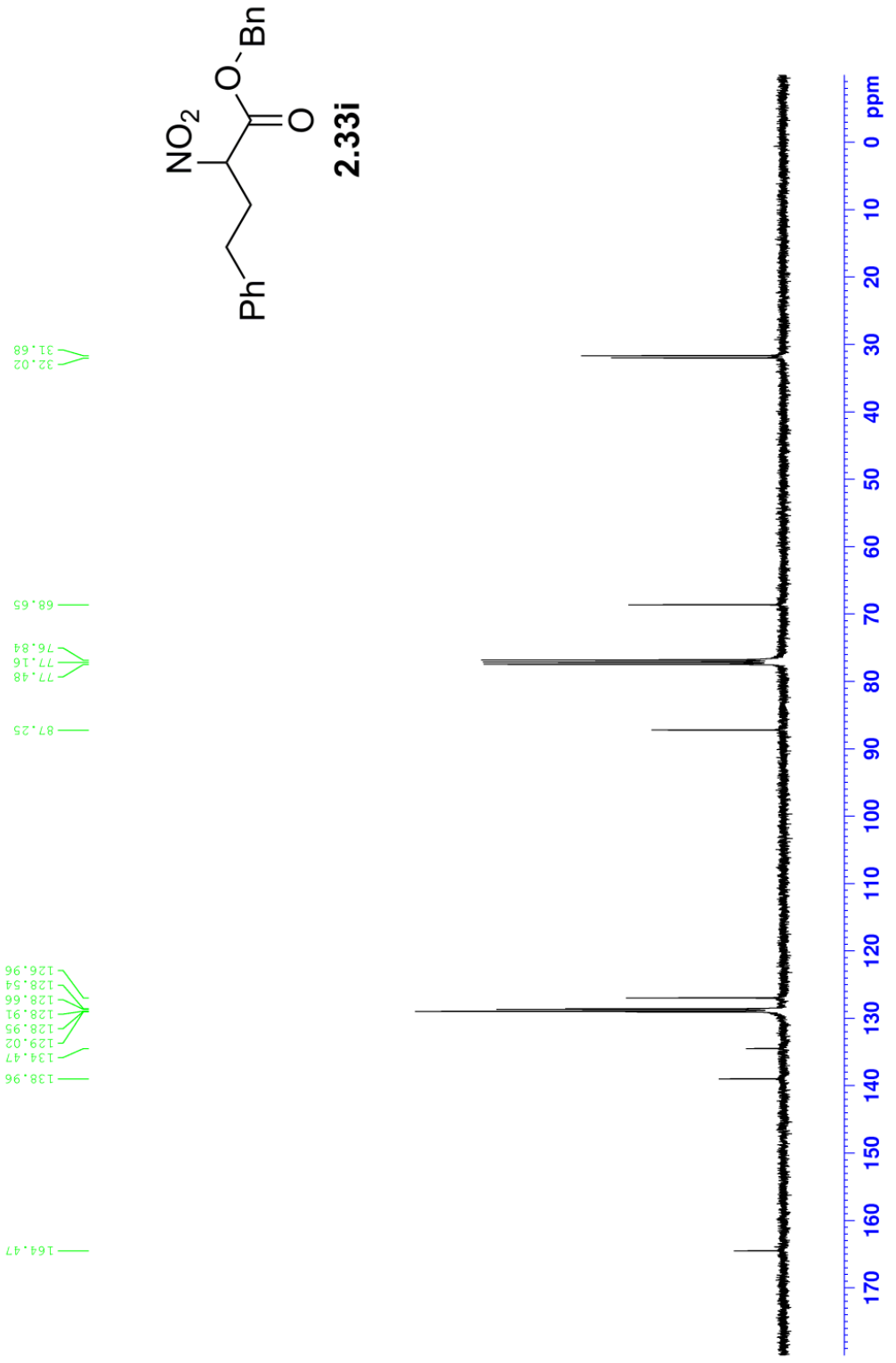
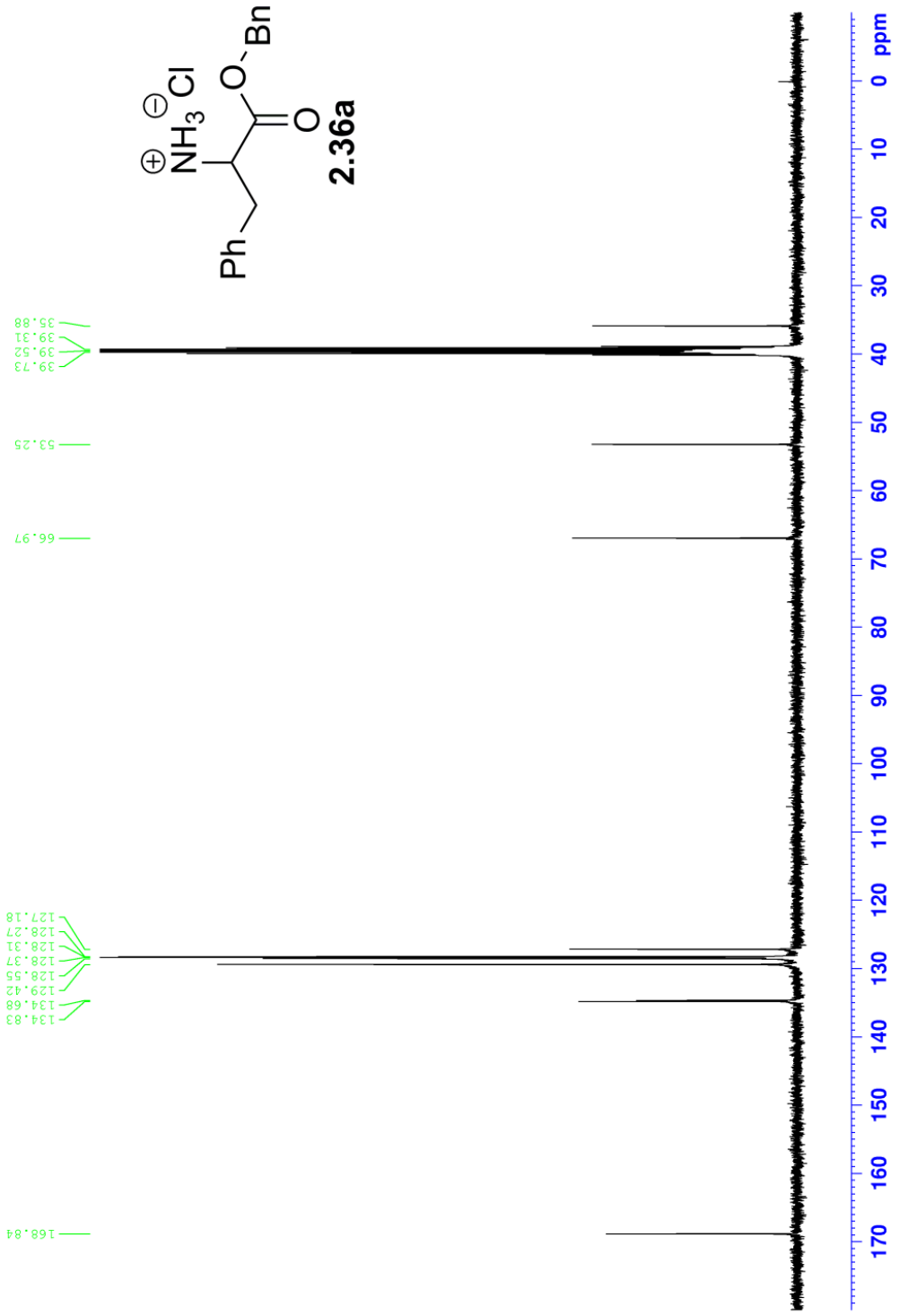
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170


NO2
O
O
Bn
Ph
2.33i
ppm
0
1
2
3
4
5
6
7
8
9
1.98
2.06
2.00
0.98
4.95
2.08
3.15
2.348
2.351
2.353
2.362
2.365
2.367
2.372
2.378
2.386
2.389
2.403
2.408
2.422
2.430
2.432
2.444
2.446
2.454
2.468
2.491
2.495
2.500
2.504
2.509
2.595
2.609
2.620
2.634
2.639
2.646
2.656
2.663
3.326
5.258
5.702
5.716
5.723
5.737
7.175
7.192
7.196
7.212
7.227
7.231
7.278
7.281
7.297
7.301
7.314
7.316
7.360
7.370
7.378
7.380
7.386
7.389
7.399
7.403
7.406


NO2
O
O
Bn
Ph
2.33i
31.68
32.02
68.65
76.84
77.16
77.48
87.25
126.96
128.54
128.66
128.91
128.95
129.02
134.47
138.96
164.47
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
ppm

2.36a
Ph
Bn
O
NH3 Cl
ppm
0
1
2
3
4
5
6
7
8
9
1.00
1.00
1.00
2.00
3.02
7.02
2.96
2.491
2.495
2.500
2.505
2.509
3.072
3.092
3.107
3.127
3.228
3.242
3.263
3.277
4.277
4.290
4.296
4.310
5.087
5.118
5.128
5.159
7.186
7.191
7.203
7.210
7.232
7.238
7.247
7.256
7.260
7.268
7.272
7.281
7.285
7.339
7.345
7.353
7.356
8.826


Ph
NH3 Cl
O
O
Bn
2.36a
35.88
39.31
39.52
39.73
53.25
66.97
127.18
128.27
128.31
128.37
128.55
129.42
134.68
134.83
168.84
0 ppm
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20
30
40
50
60
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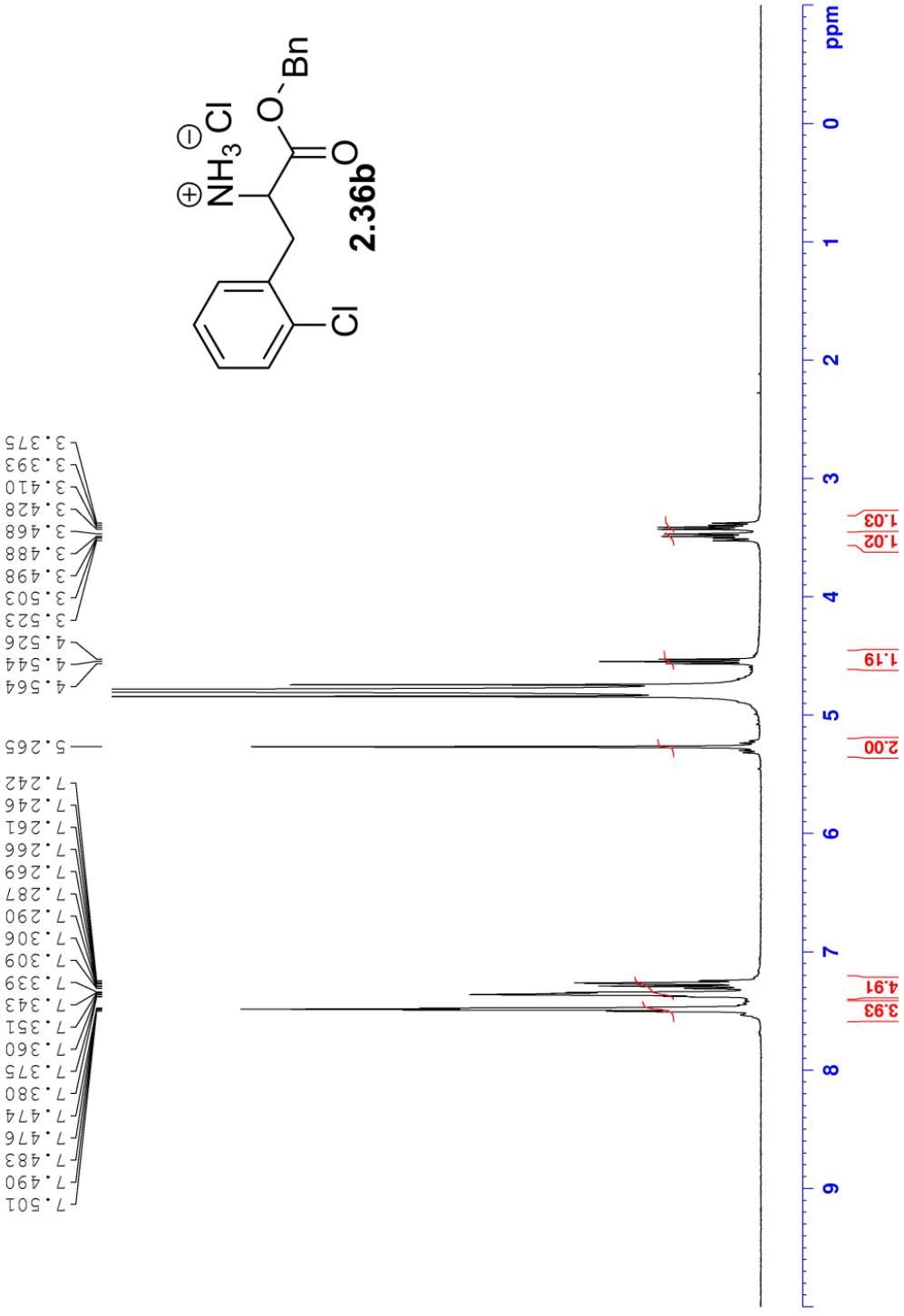
80
90
100
110
120
130
140
150
160
170


2.36b
Cl
Bn
ppm
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2
3
4
5
6
7
8
9
1.03
1.02
1.19
2.00
4.91
3.93
7.501
7.490
7.483
7.476
7.474
7.380
7.375
7.360
7.351
7.343
7.339
7.309
7.306
7.290
7.287
7.269
7.266
7.261
7.246
7.242
5.265
4.564
4.544
4.526
3.523
3.503
3.498
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3.468
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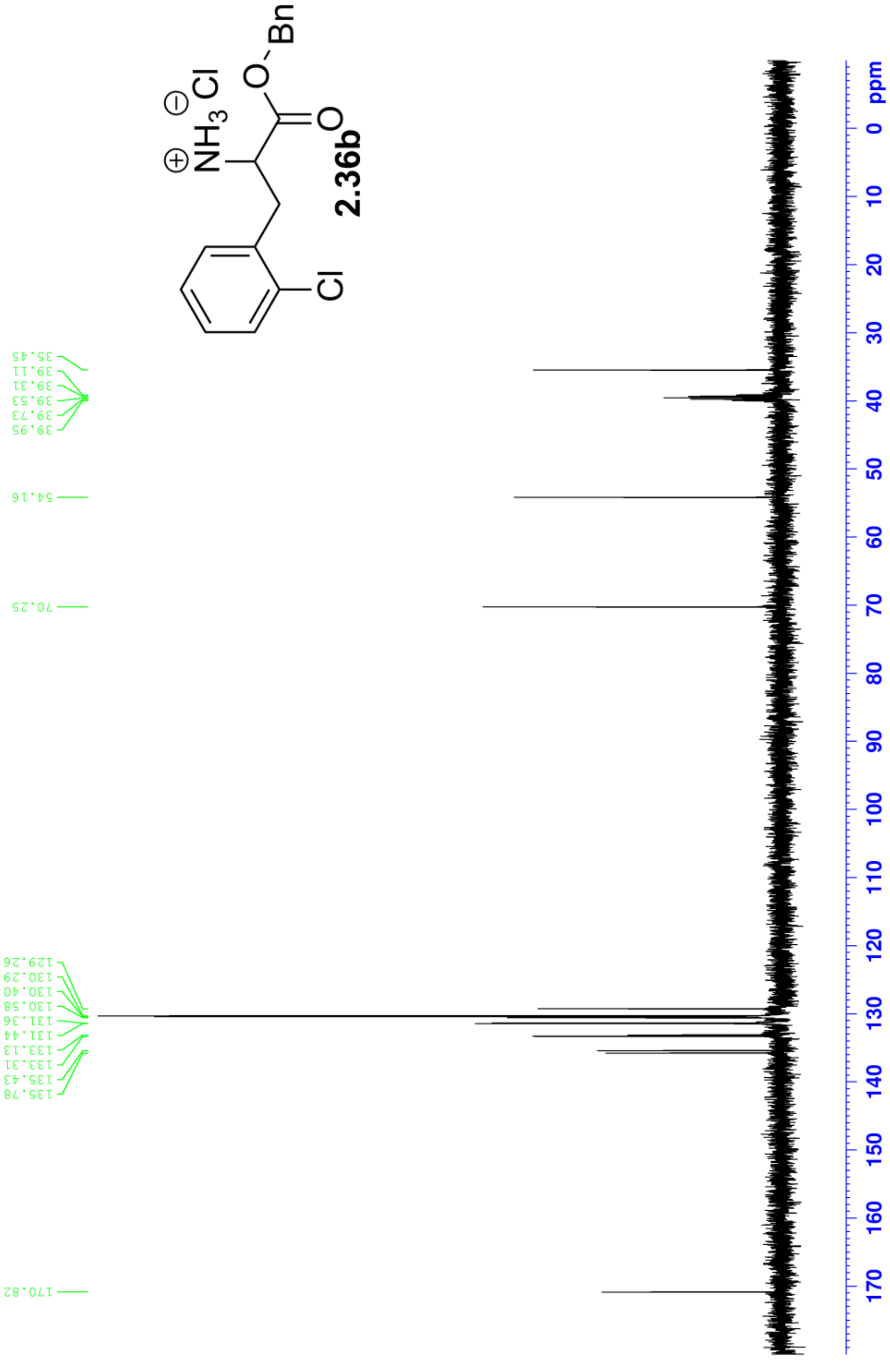
3.410
3.393
3.375



2.36b
35.45
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39.31
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39.73
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54.16
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130.58
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133.31
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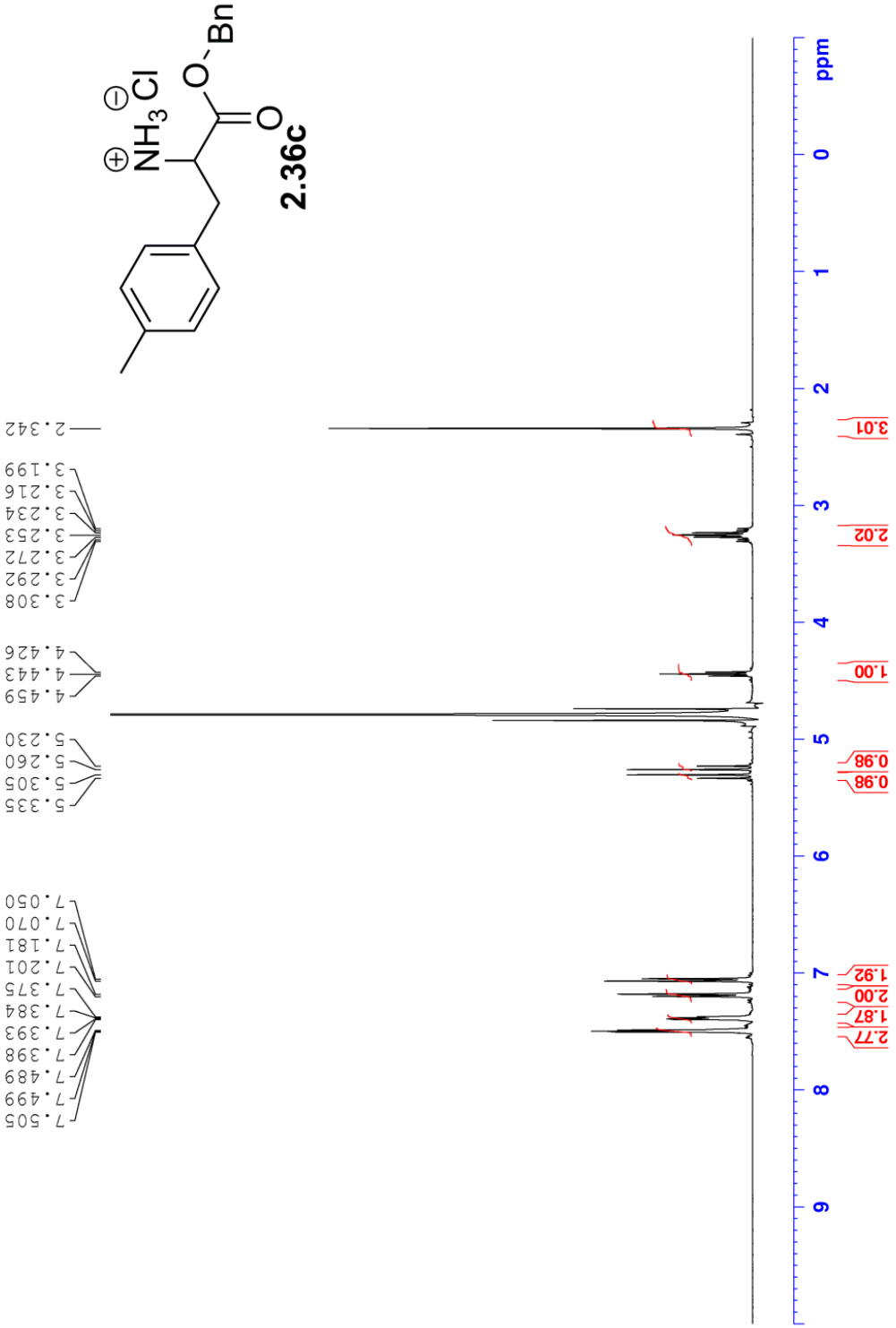
170.82
ppm


2.36c
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3.199
3.216
3.234
3.253
3.272
3.292
3.308
4.426
4.443
4.459
5.230
5.260
5.305
5.335
7.050
7.070
7.181
7.201
7.375
7.384
7.393
7.398
7.489
7.499
7.505
3.01
2.02
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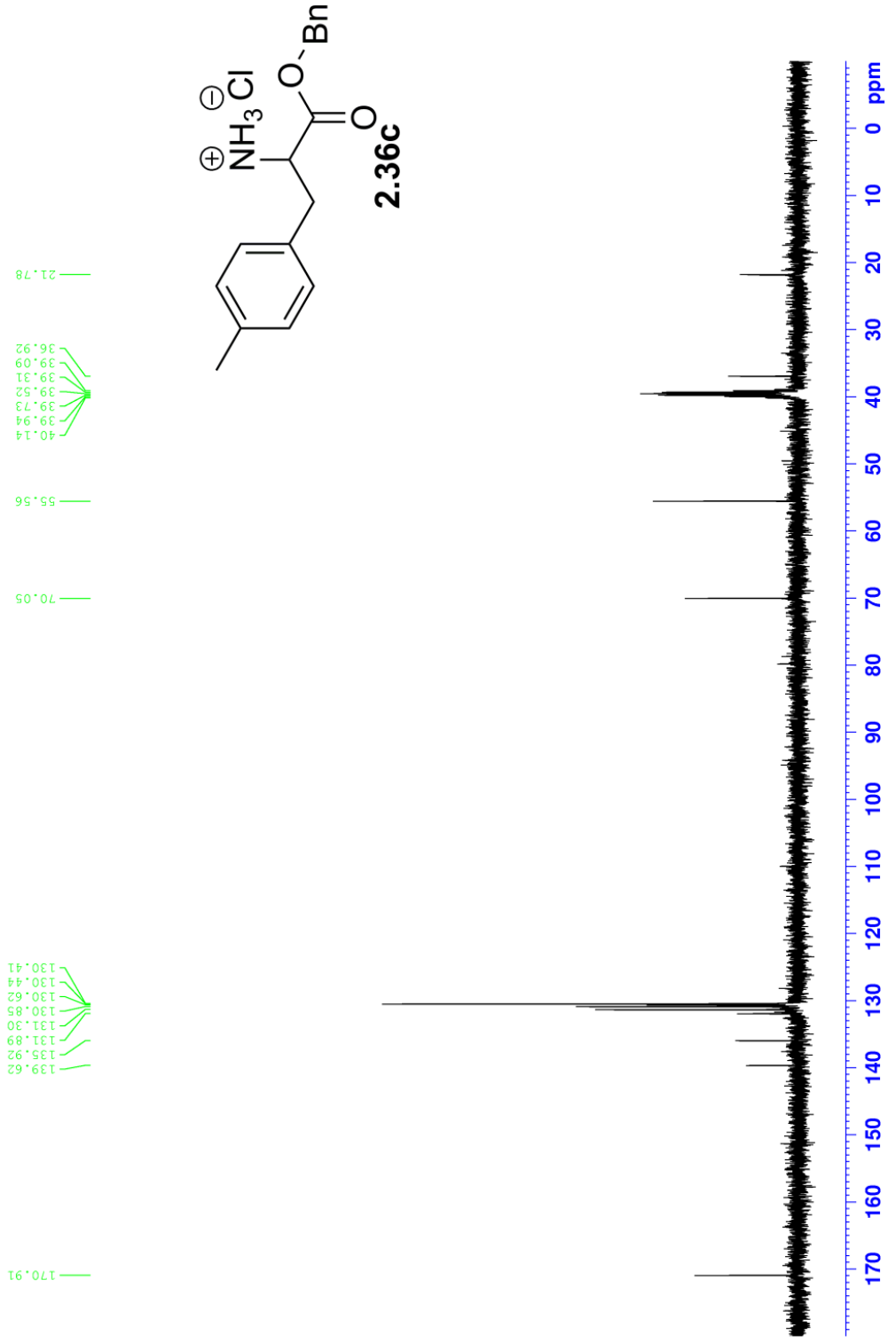
1.92
2.00
1.87
2.77
ppm


2.36c
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39.09
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39.52
39.73
39.94
40.14
55.56
70.05
130.41
130.44
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130.85
131.30
131.89
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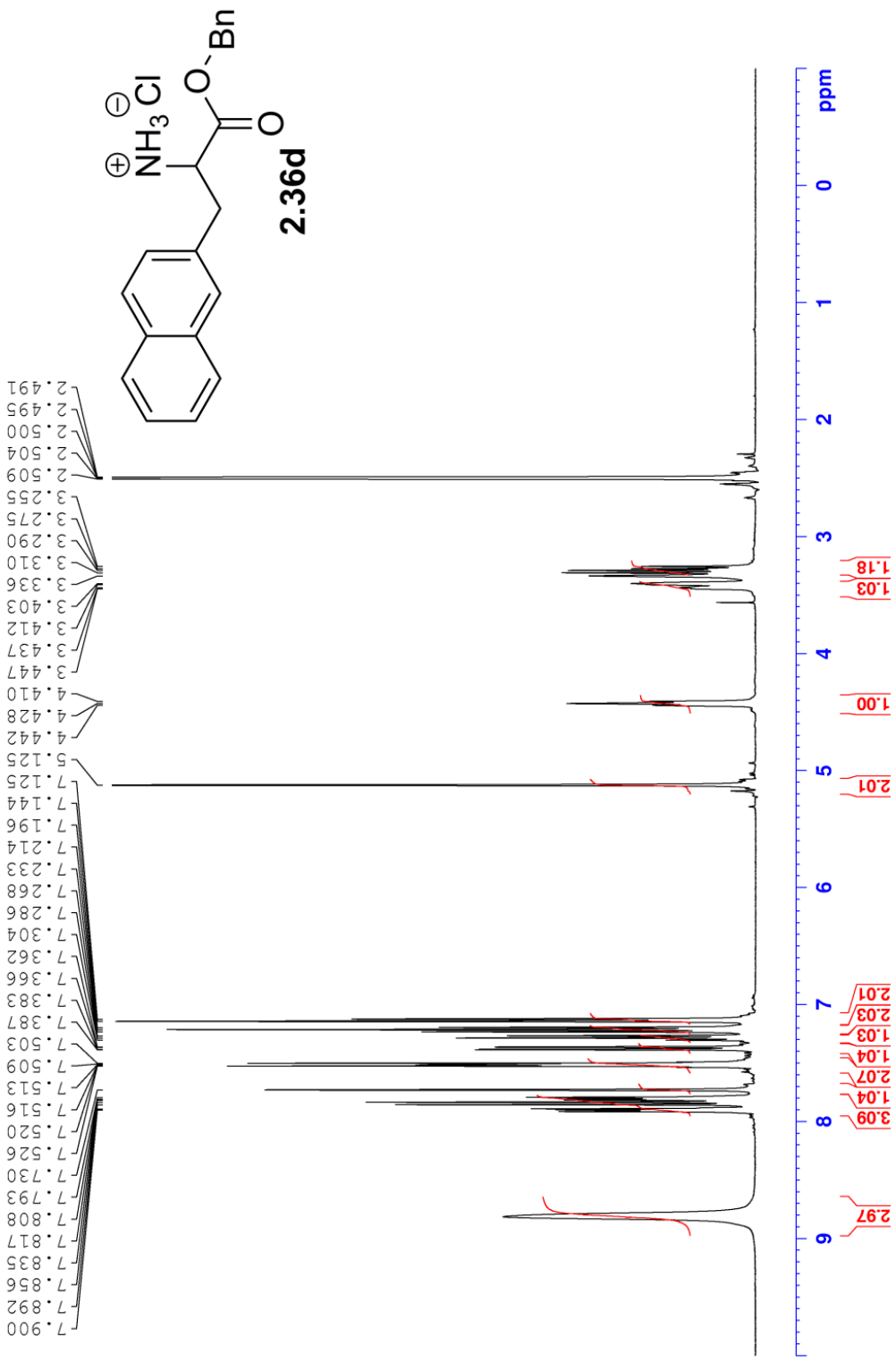
139.62
170.91
0 ppm


2.36d
Bn
O
O
NH_3 Cl
ppm
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1
2
3
4
5
6
7
8
9
2.97
3.09
1.04
2.07
1.04
1.03
2.03
2.01
1.00
2.01
1.03
1.18
7.900
7.892
7.856
7.835
7.817
7.808
7.793
7.730
7.526
7.520
7.516
7.513
7.509
7.503
7.387
7.383
7.366
7.362
7.304
7.286
7.268
7.233
7.214
7.196
7.144
7.125
5.125
4.442
4.428
4.410
3.447
3.437
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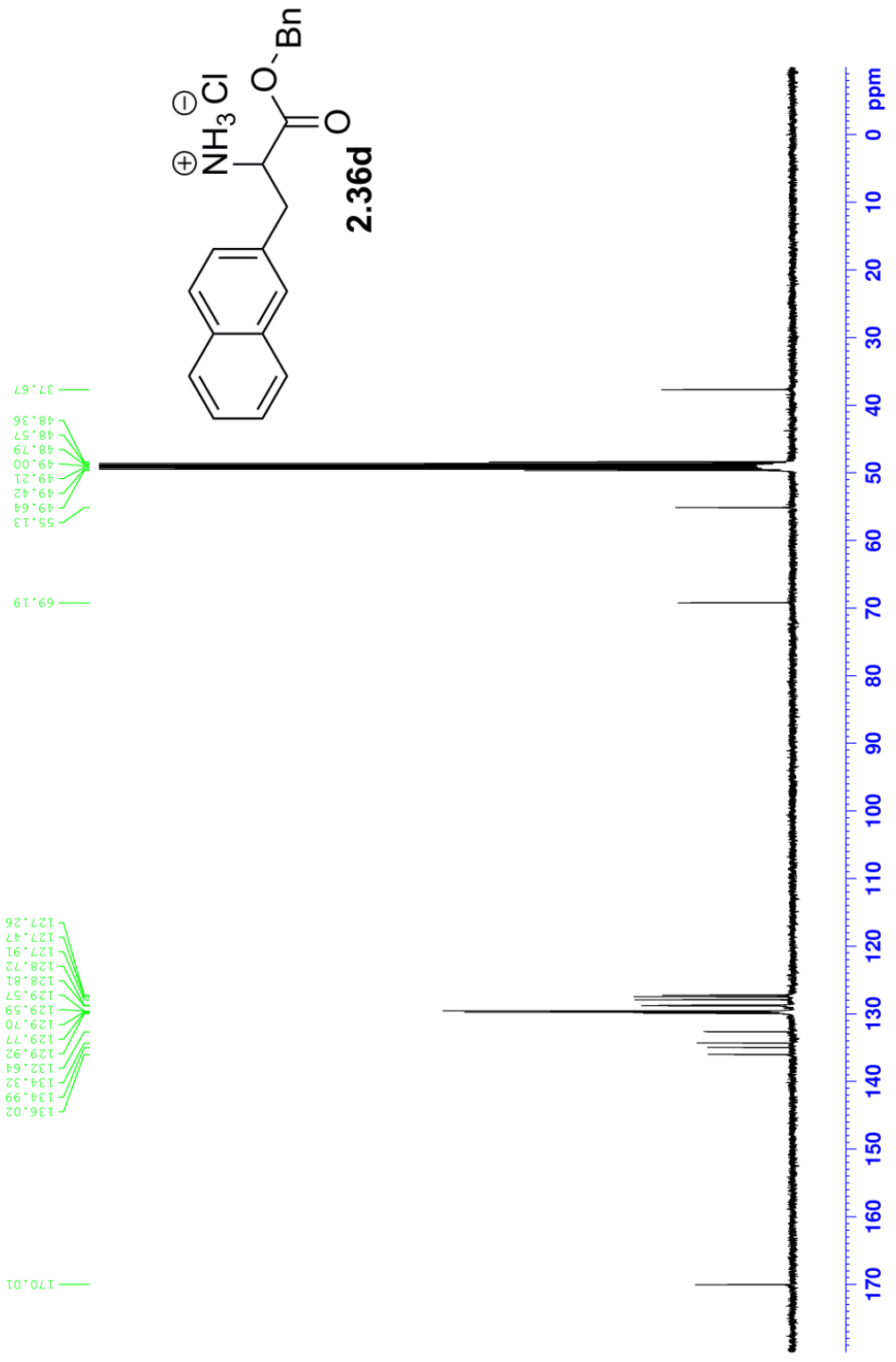
3.310
3.290
3.275
3.255
2.509
2.504
2.500
2.495
2.491


2.36d
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48.36
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49.42
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55.13
69.19
127.26
127.47
127.91
128.72
128.81
129.57
129.59
129.70
129.77
129.92
132.64
134.32
134.99
136.02
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20
30
40
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60
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80
90
100
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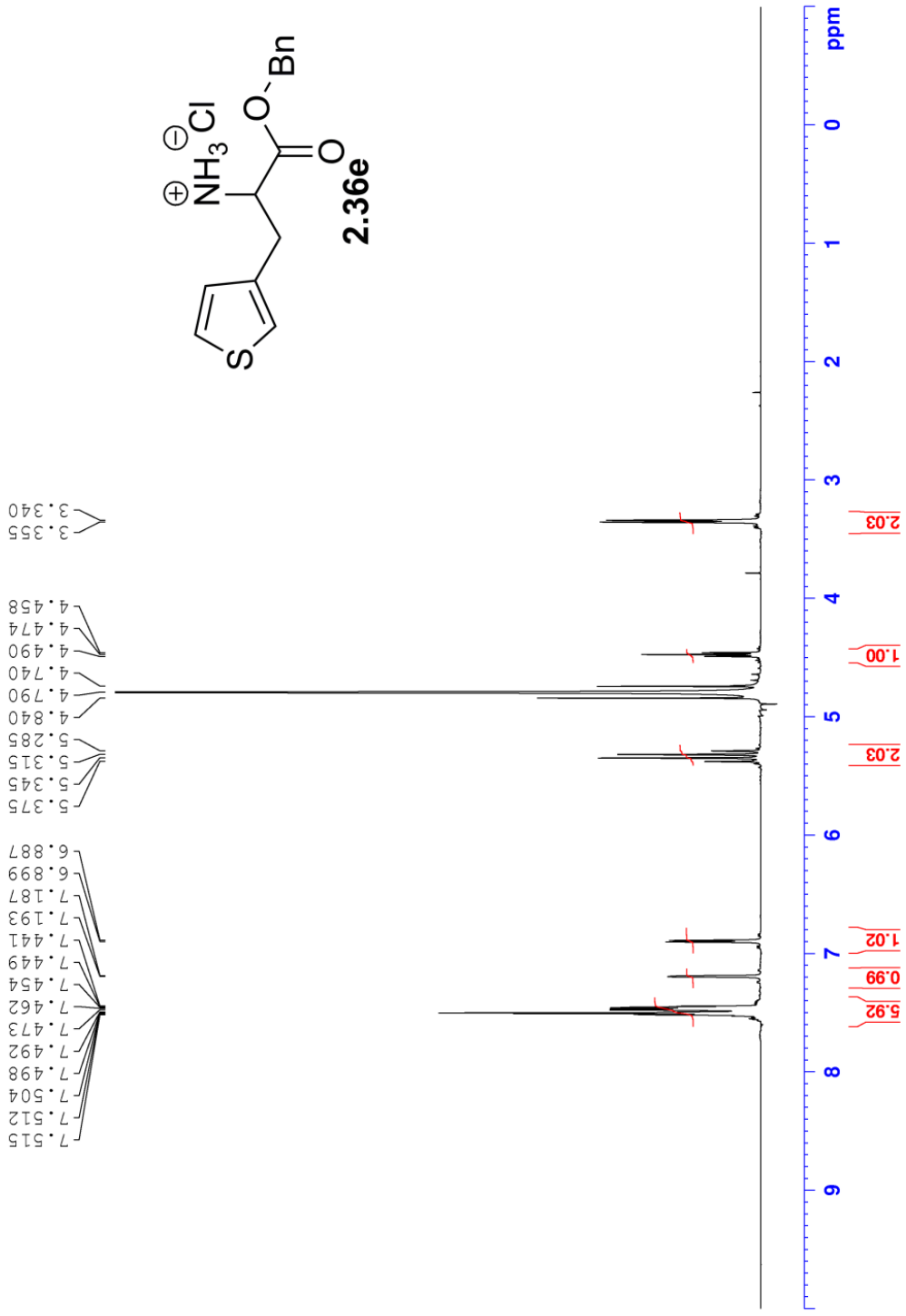
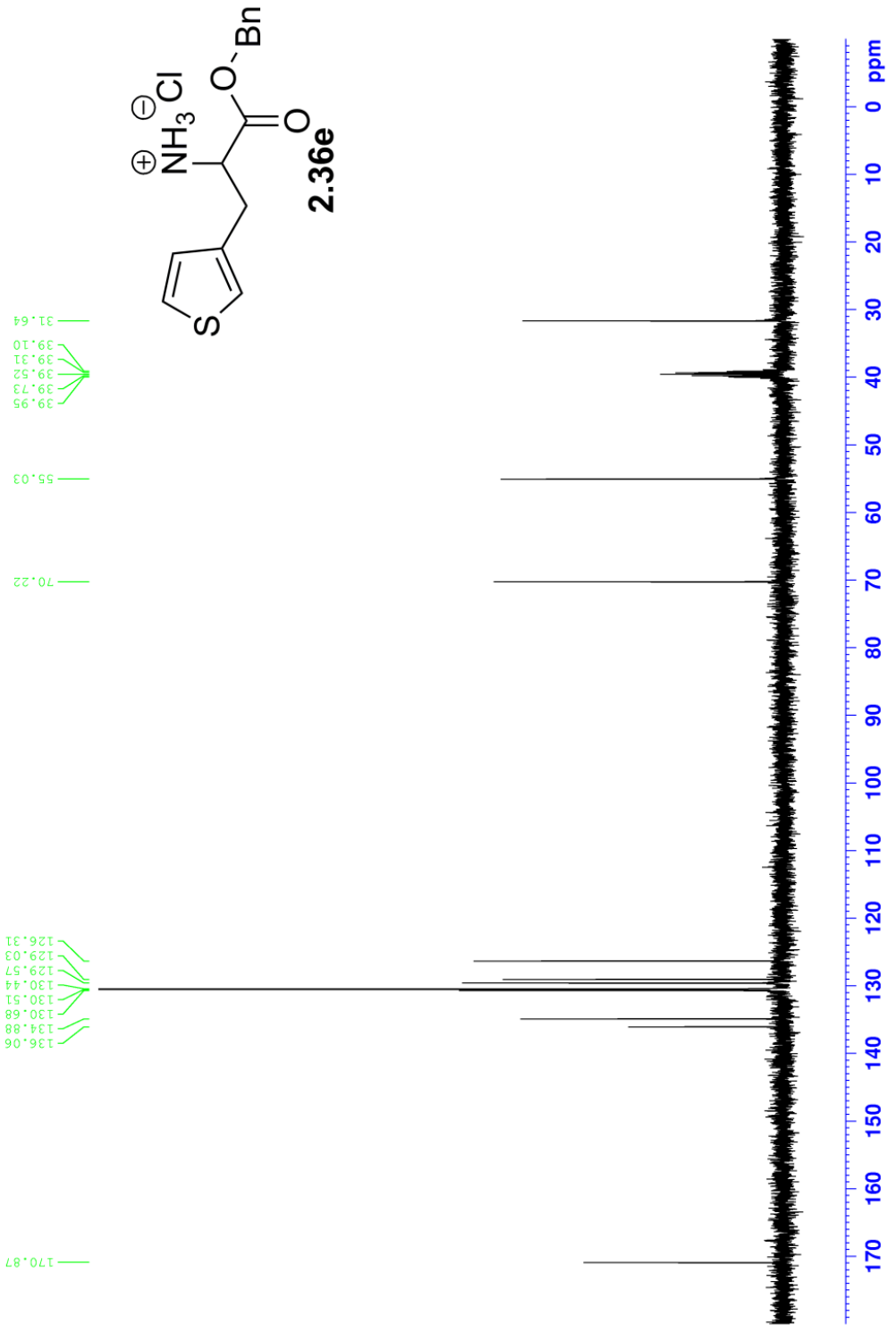
150
160
170


2.36e
3.355
3.340
4.458
4.474
4.490
4.740
4.790
4.840
5.285
5.315
5.345
5.375
6.887
6.899
7.187
7.193
7.441
7.449
7.454
7.462
7.473
7.492
7.498
7.504
7.512
7.515
ppm
0
1
2
3
4
5
6
7
8
9
2.03
1.00
2.03
1.02
0.99
5.92


2.36e
31.64
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39.31
39.52
39.73
39.95
55.03
70.22
126.31
129.03
129.57
130.44
130.51
130.68
134.88
136.06
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20
30
40
50
60
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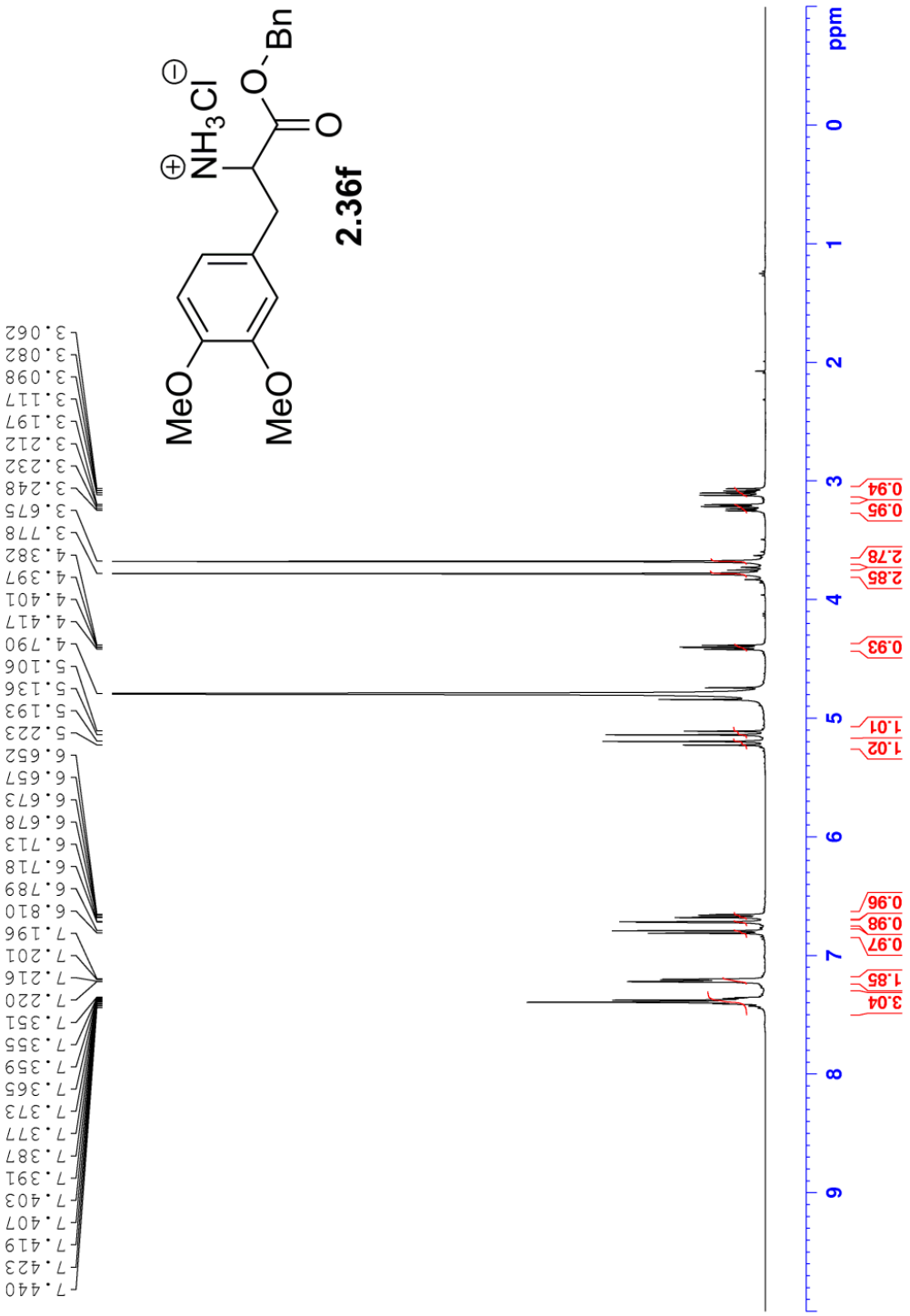
80
90
100
110
120
130
140
150
160
170


2.36f
MeO
MeO
Bn
ppm
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1
2
3
4
5
6
7
8
9
0.94
0.95
2.78
2.85
0.93
1.01
1.02
0.96
0.98
0.97
1.85
3.04
7.440
7.423
7.419
7.407
7.403
7.391
7.387
7.377
7.373
7.365
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7.355
7.351
7.220
7.216
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7.196
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6.789
6.718
6.713
6.678
6.673
6.657
6.652
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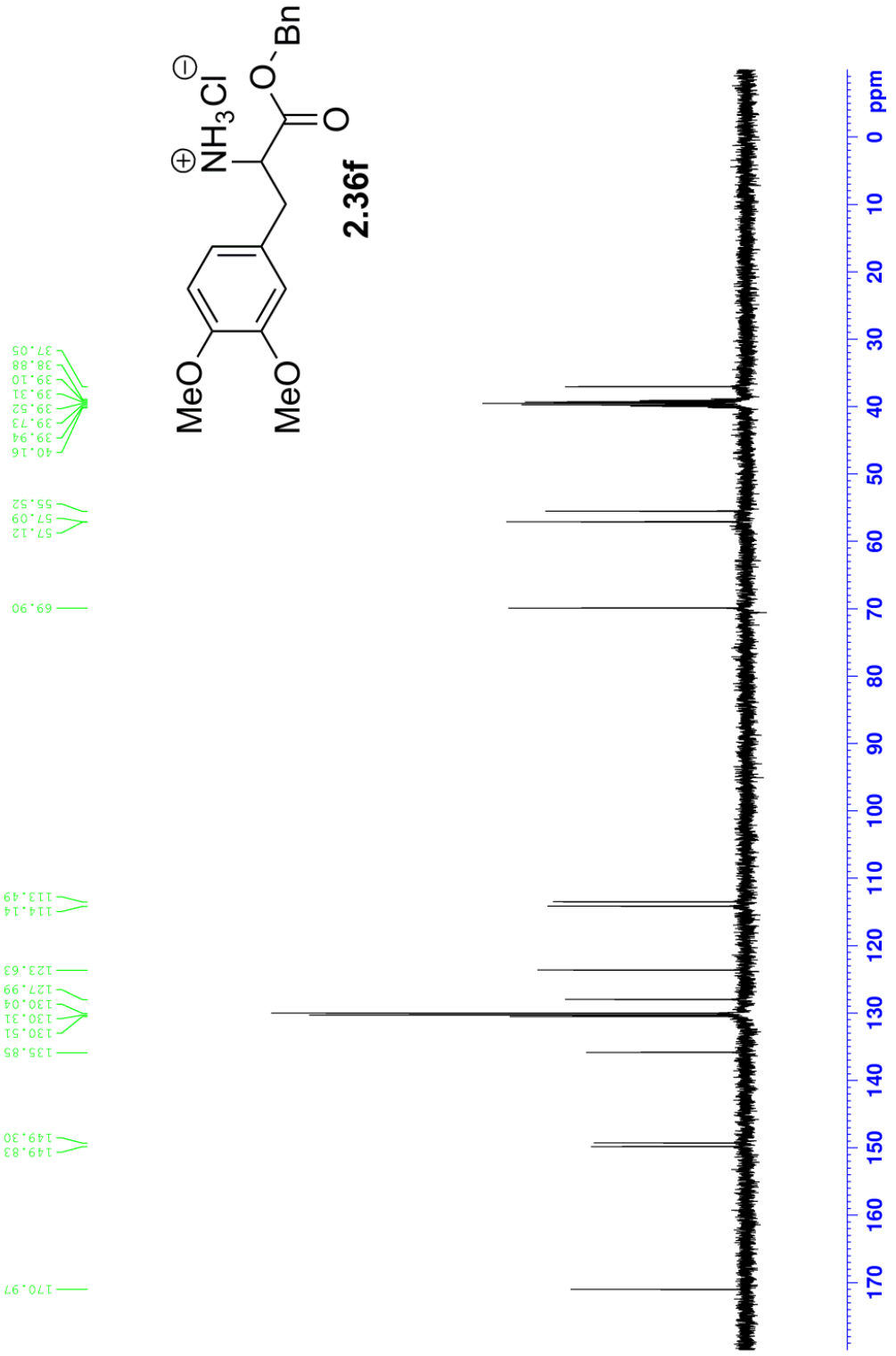
5.193
5.136
5.106
4.790
4.417
4.401
4.397
4.382
3.778
3.675
3.248
3.232
3.212
3.197
3.117
3.098
3.082
3.062


MeO
MeO
NH3Cl
O
O
Bn
2.36f
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38.88
39.10
39.31
39.52
39.73
39.94
40.16
55.52
57.09
57.12
69.90
113.49
114.14
123.63
127.99
130.04
130.31
130.51
135.85
149.30
149.83
170.97
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20
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40
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60
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80
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100
110
120
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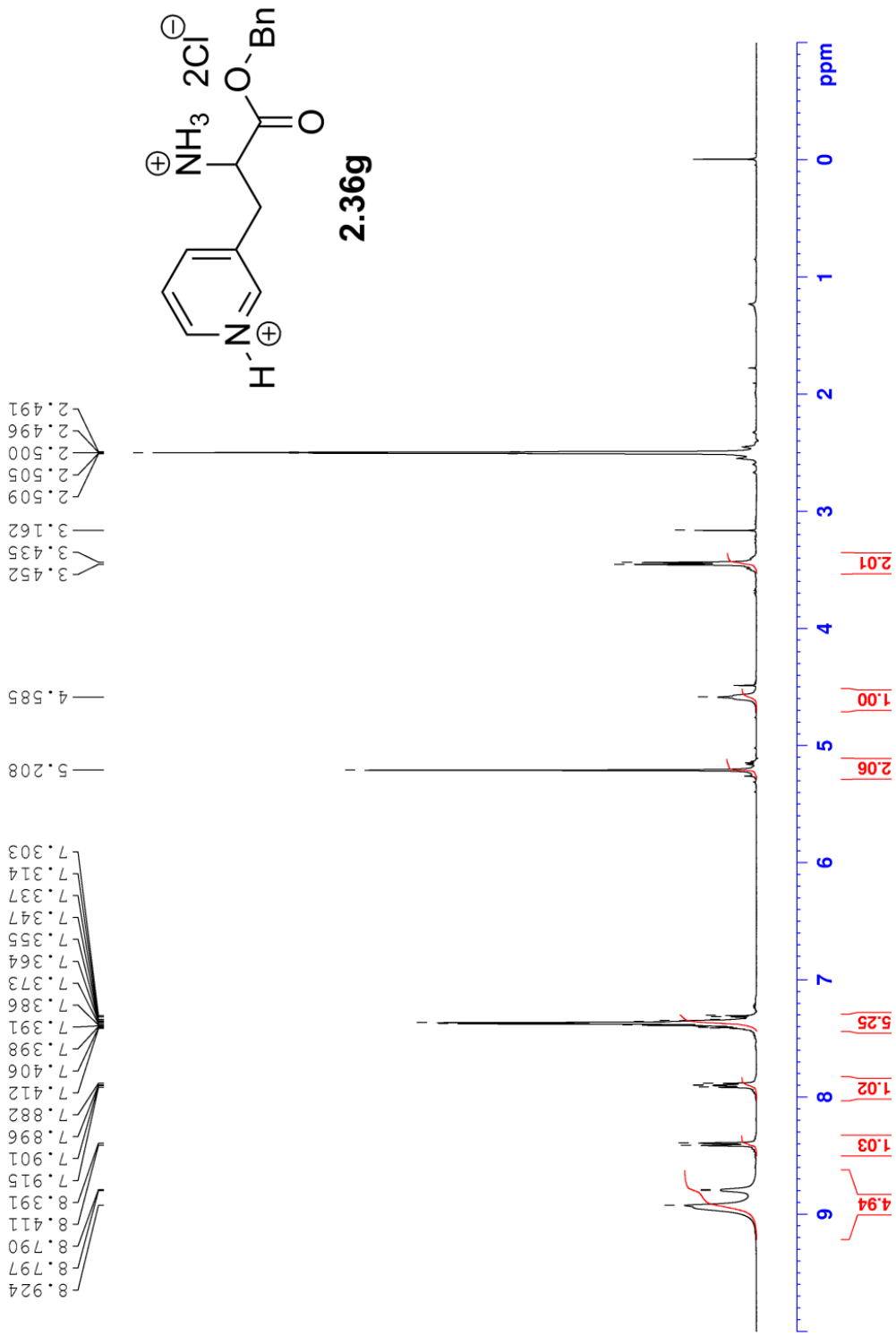
140
150
160
170


2.36g
2Cl
Bn
NH3
O
N
H
ppm
0
1
2
3
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5
6
7
8
9
2.01
1.00
2.06
5.25
1.02
1.03
4.94
2.491
2.496
2.500
2.505
2.509
3.162
3.435
3.452
4.585
5.208
7.303
7.314
7.337
7.347
7.355
7.364
7.373
7.386
7.391
7.398
7.406
7.412
7.882
7.896
7.901
7.915
8.391
8.411
8.790
8.797
8.924


2.36g
32.15
38.90
39.10
39.31
39.52
39.73
39.94
40.15
52.16
67.36
126.80
128.32
128.41
128.49
134.84
135.19
140.52
142.72
146.61
168.19
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

2.36h
CbzN
NH3 Cl
O
O
Bn
8.979
8.025
7.630
7.592
7.428
7.358
7.337
7.319
7.300
7.282
7.270
7.207
7.189
7.171
7.160
7.139
7.114
7.098
6.926
5.250
4.886
4.554
3.581
3.473
1.93
0.82
1.81
2.00
1.83
5.05
6.96
1.03
2.65
ppm


2.36h
CbzN
O
O
Bn
NH3
Cl
26.45
53.25
68.25
68.78
76.84
77.16
77.48
114.17
115.42
119.27
123.22
124.97
125.50
128.25
128.45
128.47
128.71
128.81
129.96
134.25
135.12
135.49
150.79
169.13
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60
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100
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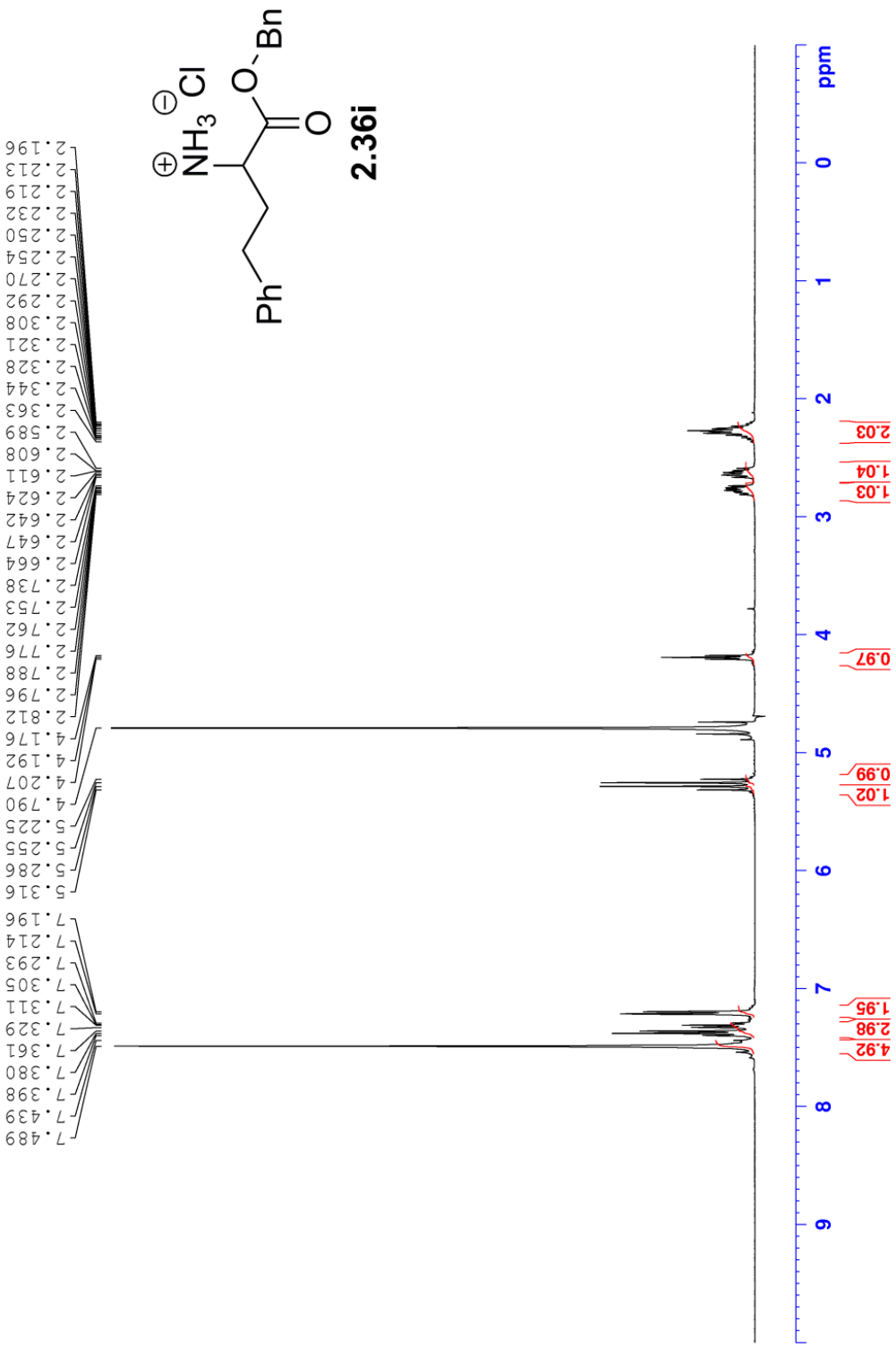
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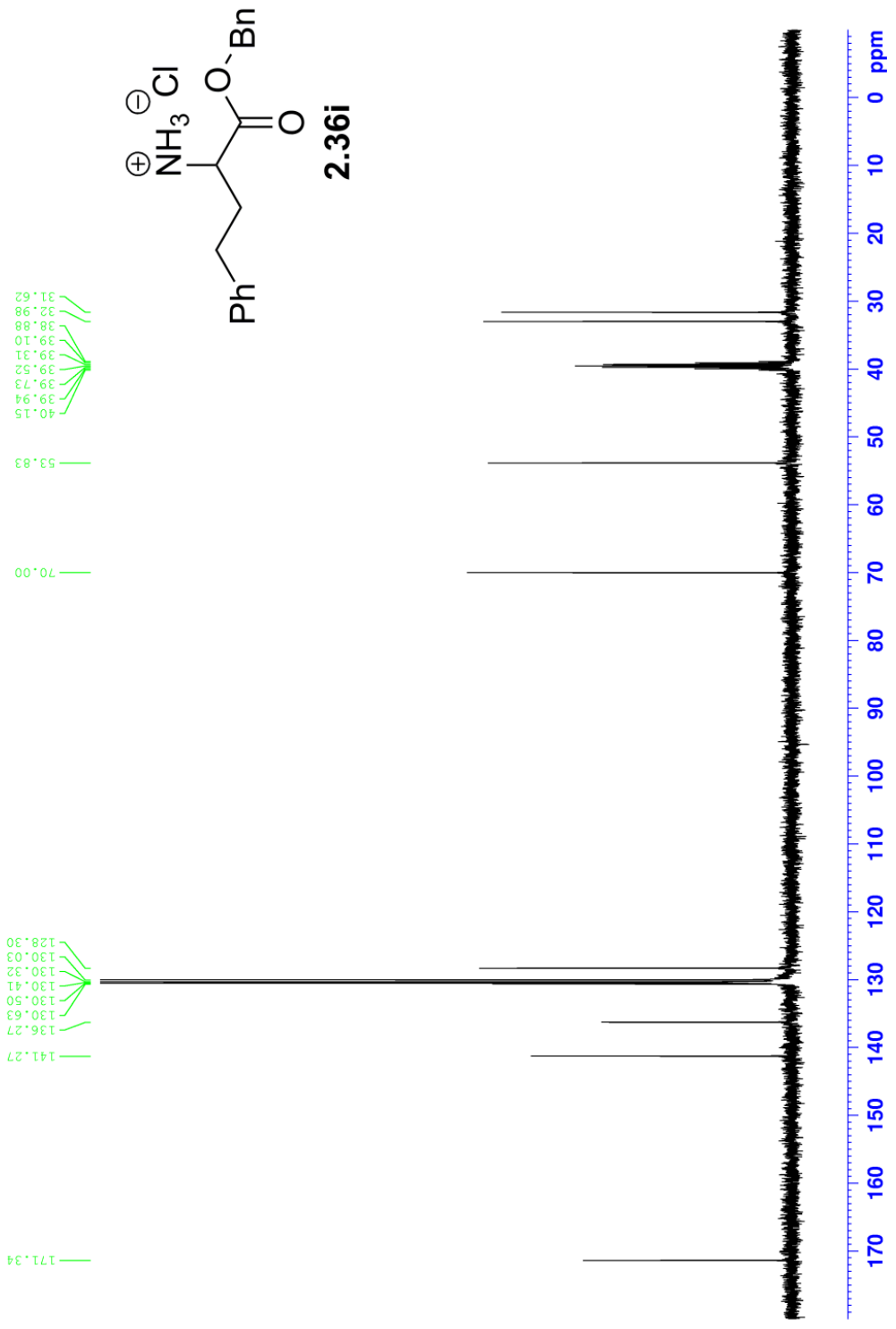
2.213
2.219
2.232
2.250
2.254
2.270
2.292
2.308
2.321
2.328
2.344
2.363
2.589
2.608
2.611
2.624
2.642
2.647
2.664
2.738
2.753
2.762
2.776
2.788
2.796
2.812
4.176
4.192
4.207
4.790
5.225
5.255
5.286
5.316
7.196
7.214
7.293
7.305
7.311
7.329
7.361
7.380
7.398
7.439
7.489
NH3 Cl
O
O
Bn
Ph
2.36i
ppm
0
1
2
3
4
5
6
7
8
9
2.03
1.03
1.04
0.97
1.02
0.99
4.92
2.98
1.95


2.36i
Ph
Bn
O
O
NH3 Cl
31.62
32.98
38.88
39.10
39.31
39.52
39.73
39.94
40.15
53.83
70.00
128.30
130.03
130.32
130.41
130.50
130.63
136.27
141.27
171.34
0 ppm
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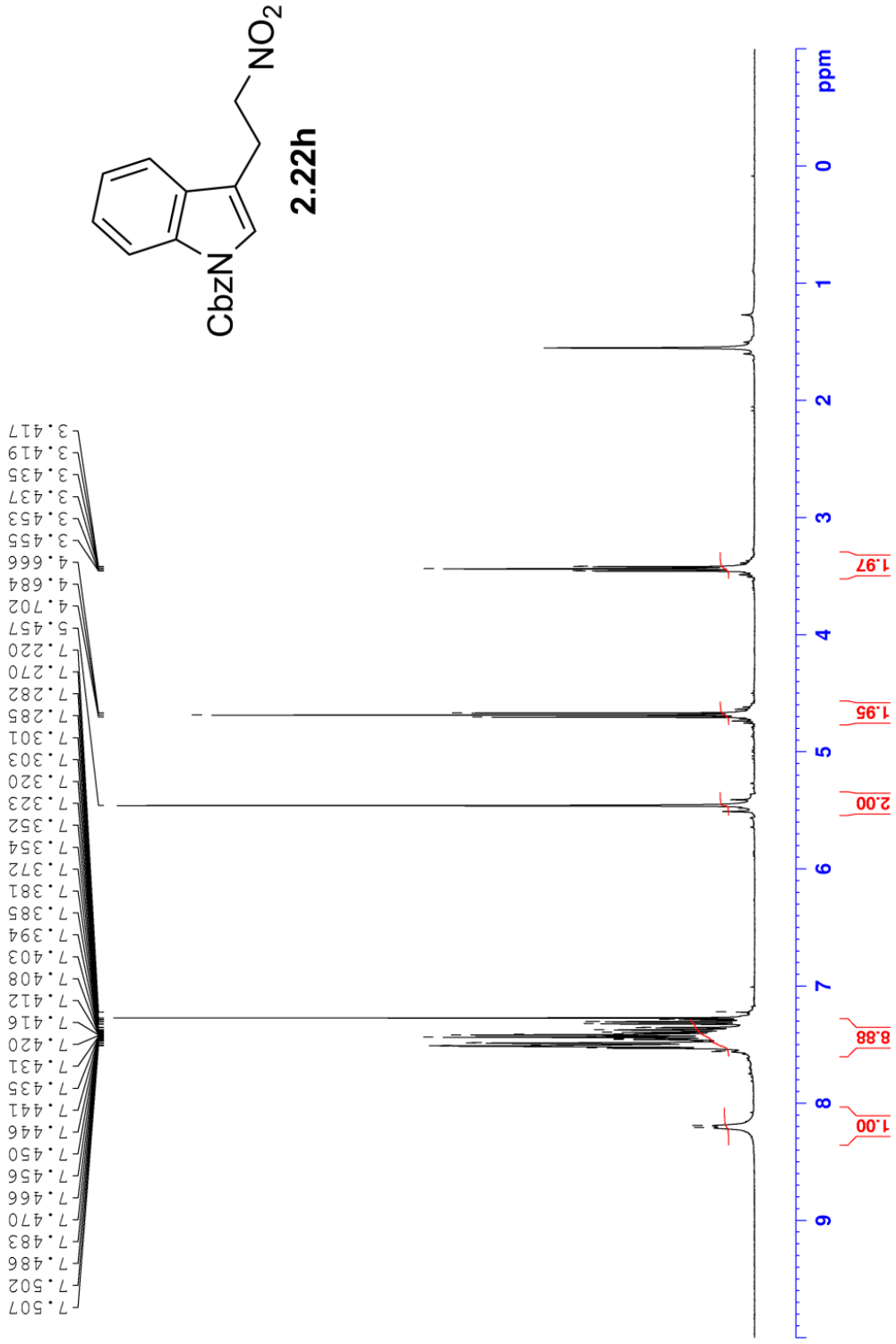
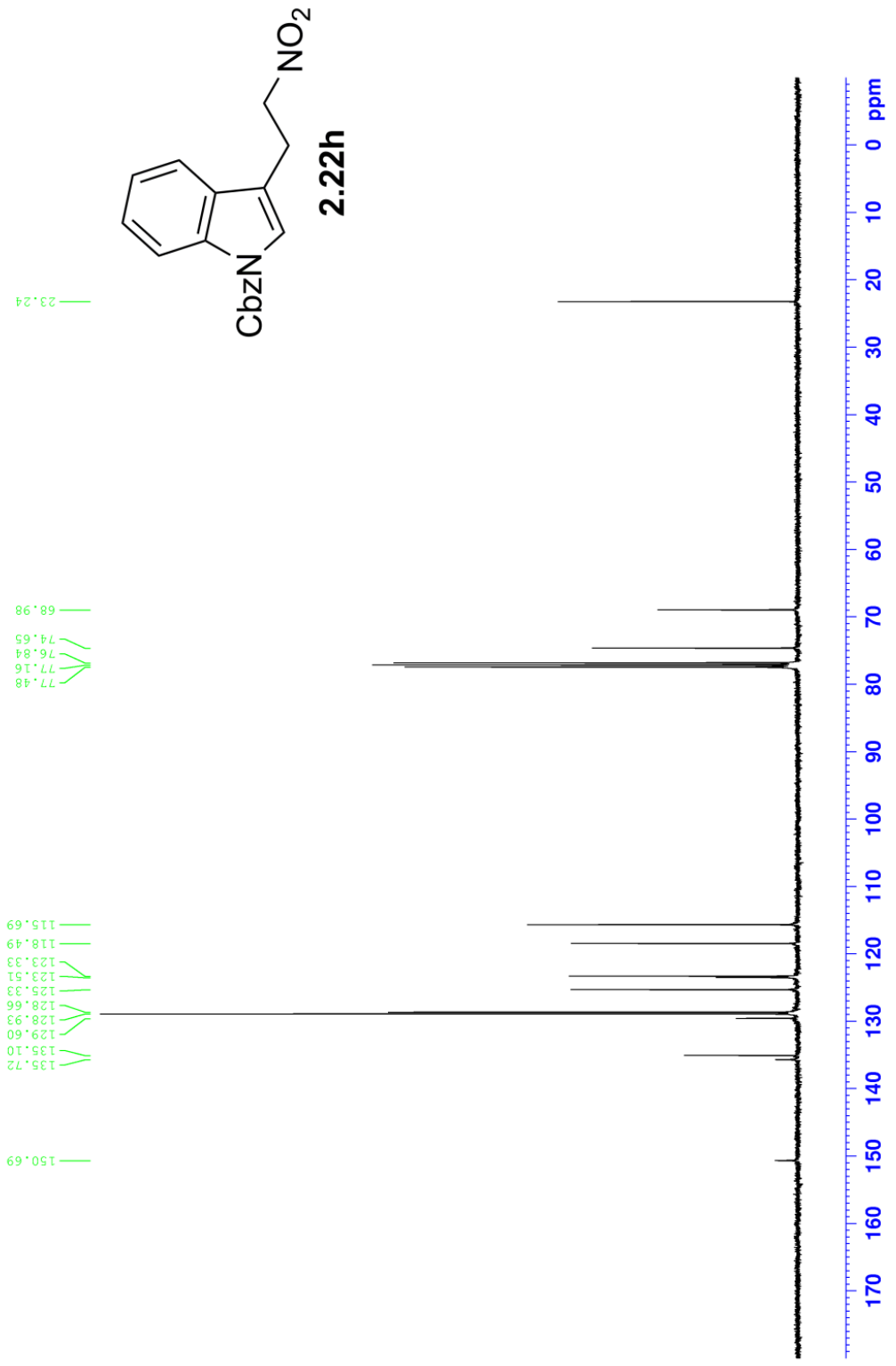
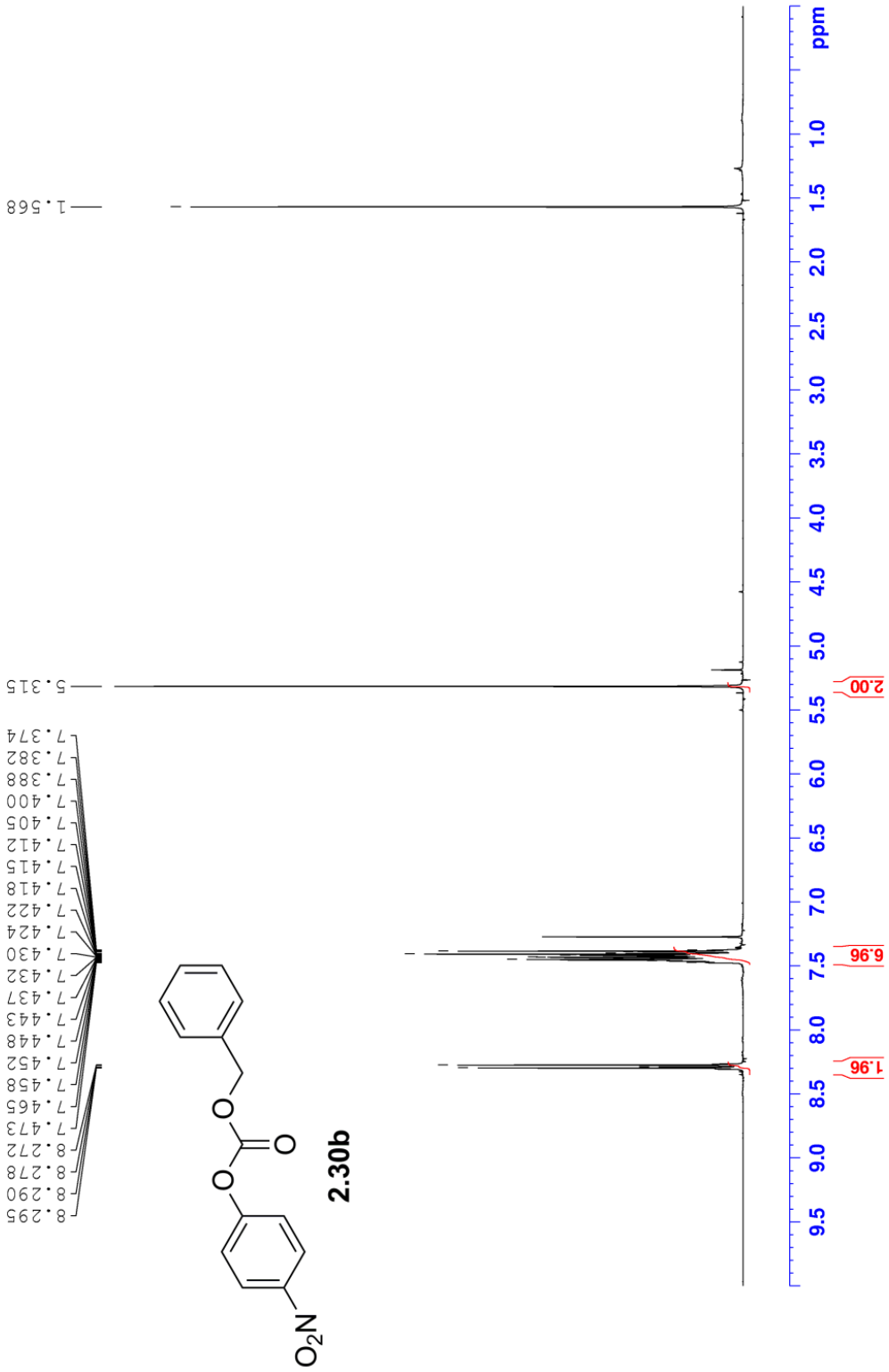
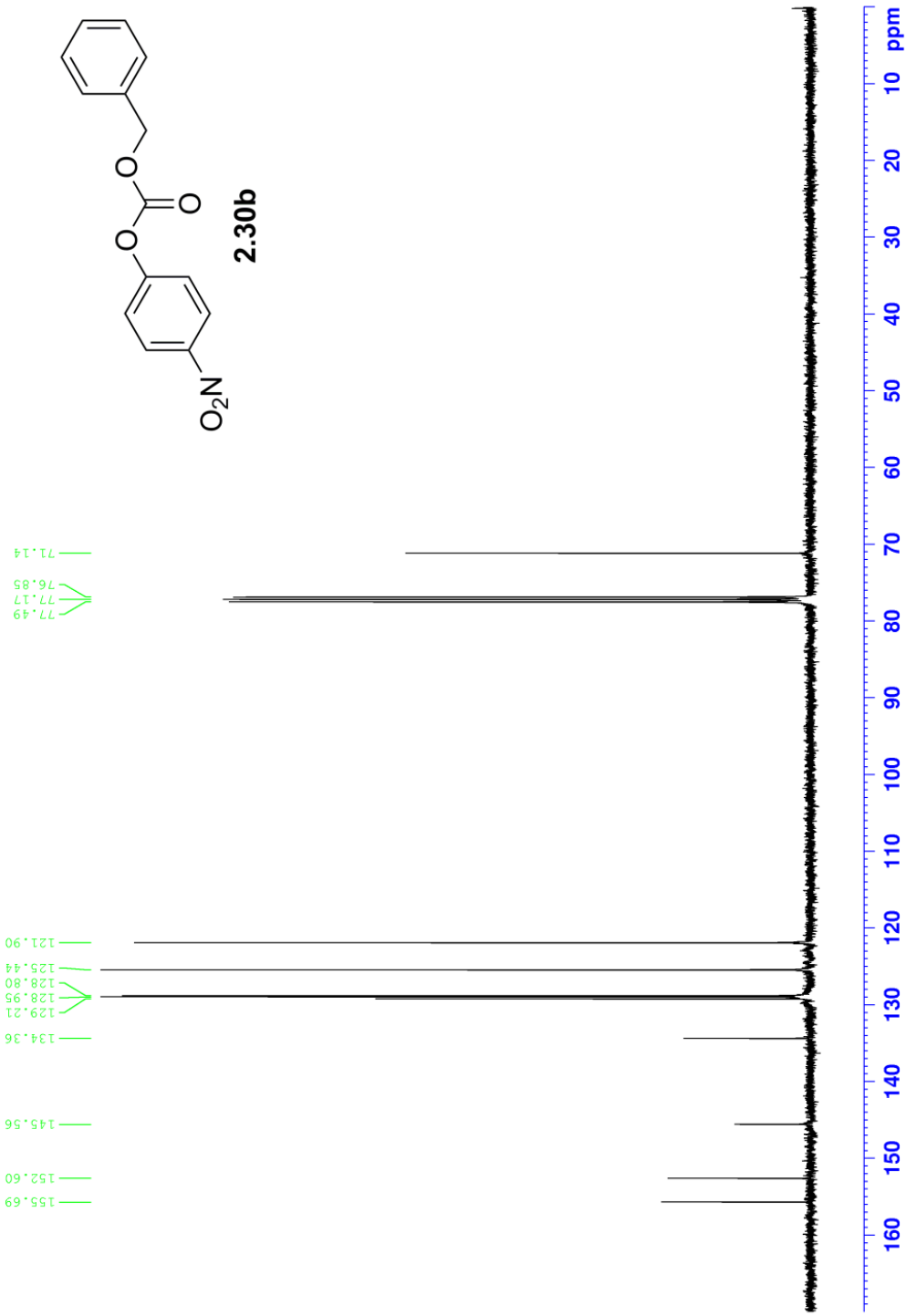
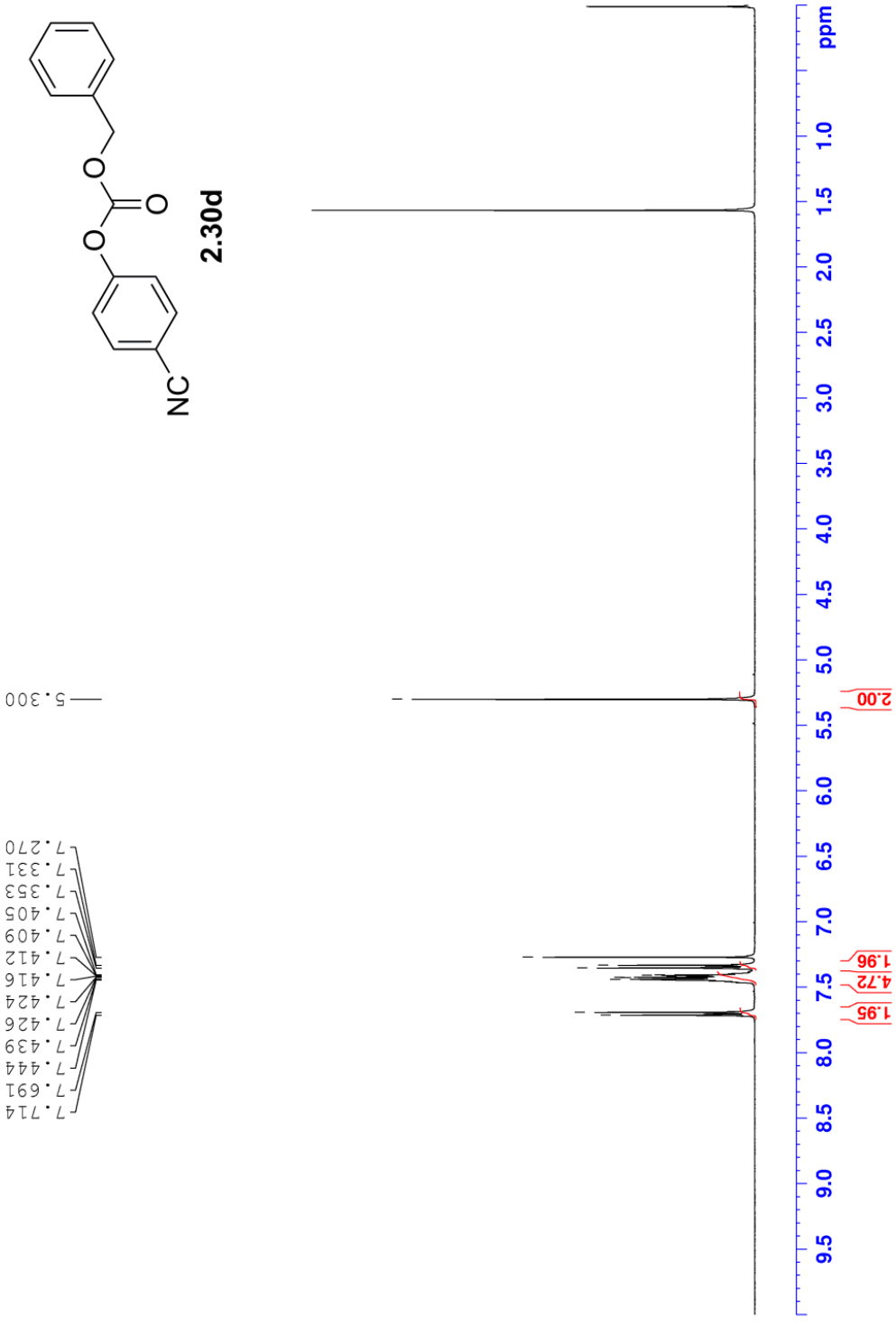
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

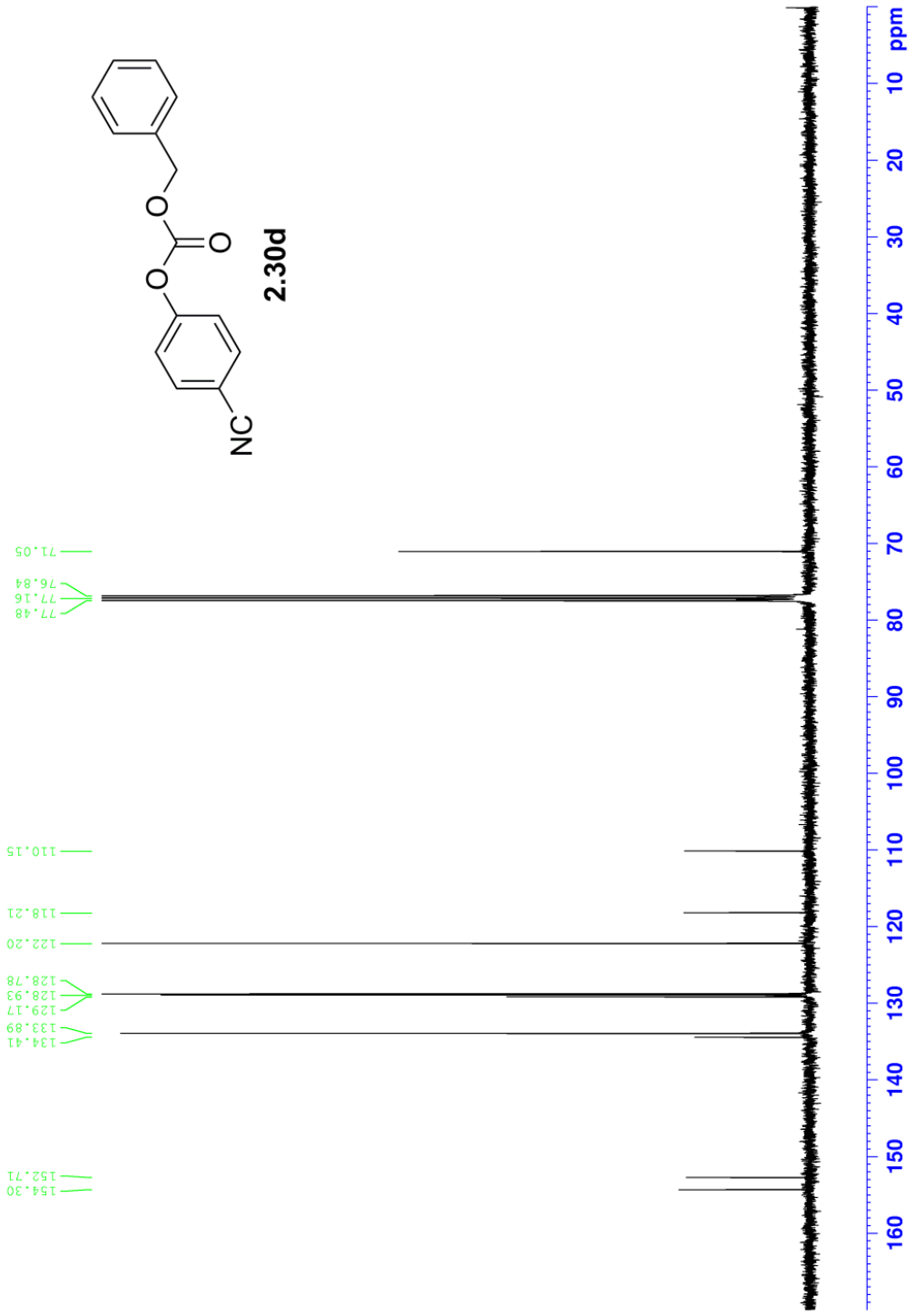

NO2
CbzN
2.22h
ppm
0
1
2
3
4
5
6
7
8
9
1.97
1.95
2.00
8.88
1.00
3.417
3.419
3.435
3.437
3.453
3.455
4.666
4.684
4.702
5.457
7.220
7.270
7.282
7.285
7.301
7.303
7.320
7.323
7.352
7.354
7.372
7.381
7.385
7.394
7.403
7.408
7.412
7.416
7.420
7.431
7.435
7.441
7.446
7.450
7.456
7.466
7.470
7.483
7.486
7.502
7.507

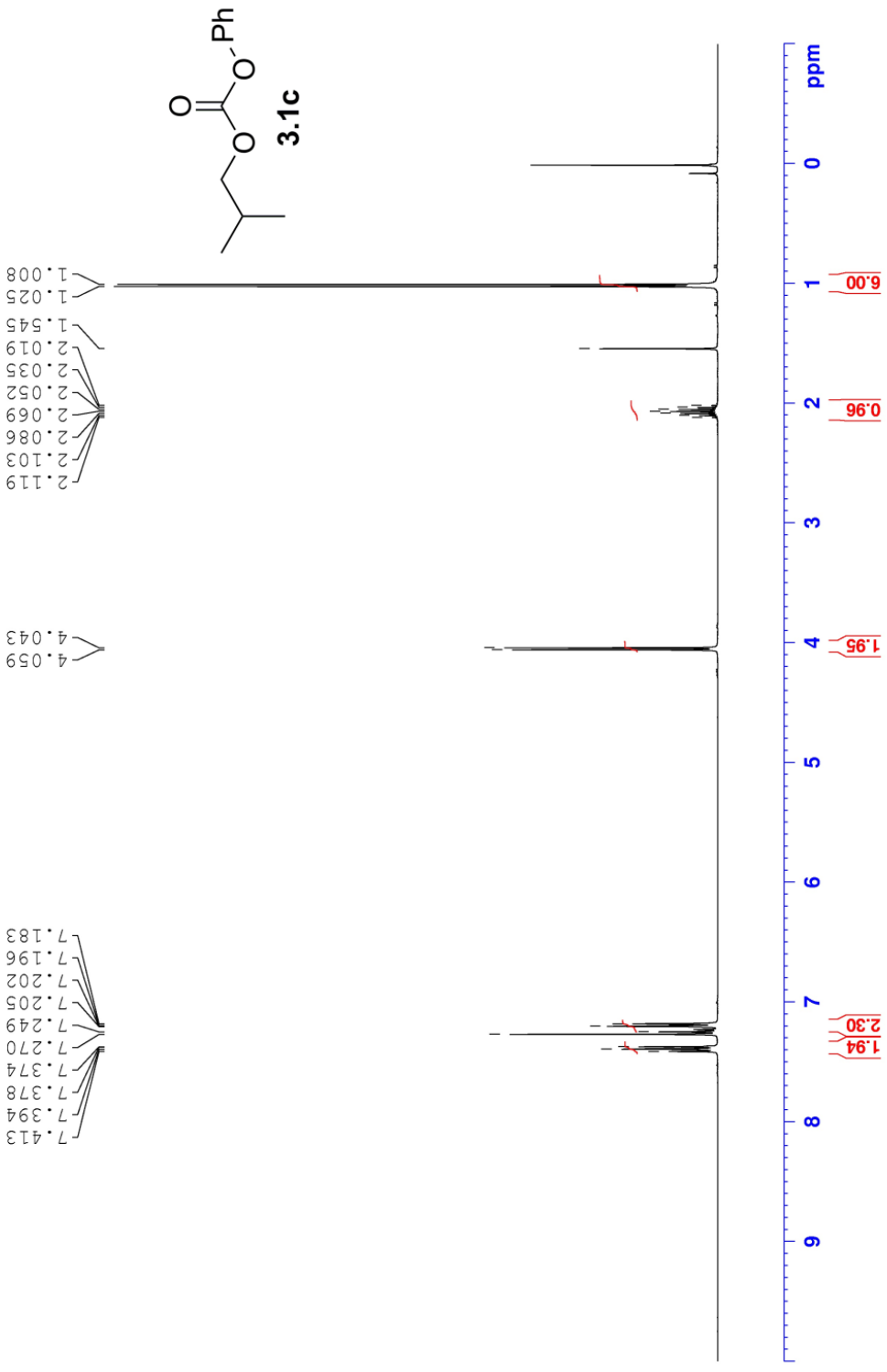

NO2
CbzN
2.22h
23.24
68.98
74.65
76.84
77.16
77.48
115.69
118.49
123.33
123.51
125.33
128.66
128.93
129.60
135.10
135.72
150.69
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

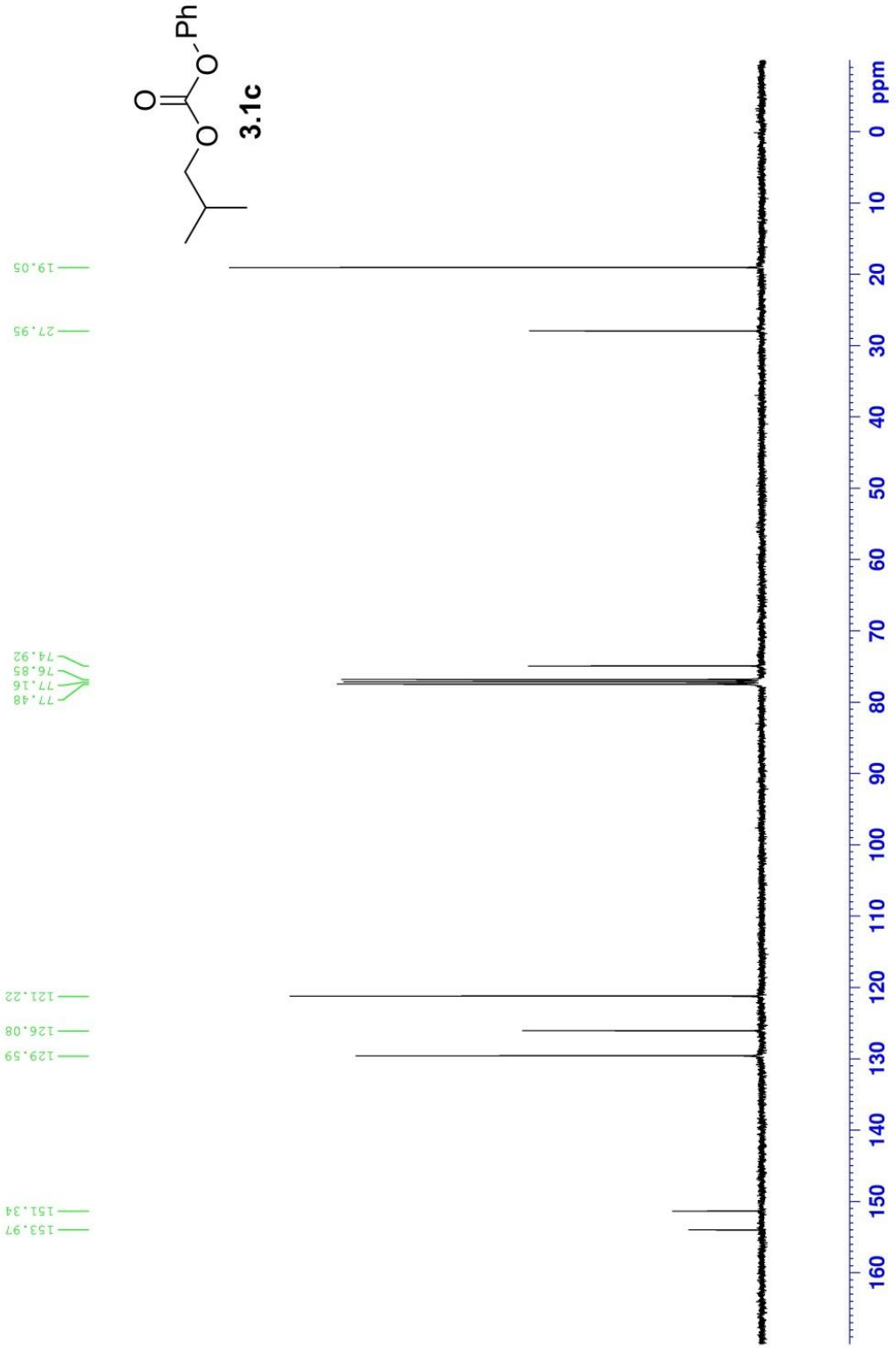

1.568
5.315
7.374
7.382
7.388
7.400
7.405
7.412
7.415
7.418
7.422
7.424
7.430
7.432
7.437
7.443
7.448
7.452
7.458
7.465
7.473
8.272
8.278
8.290
8.295
2.30b
O2N
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
2.00
6.96
1.96


2.30b
O2N
O
O
O
71.14
76.85
77.17
77.49
121.90
125.44
128.80
128.95
129.21
134.36
145.56
152.60
155.69
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160

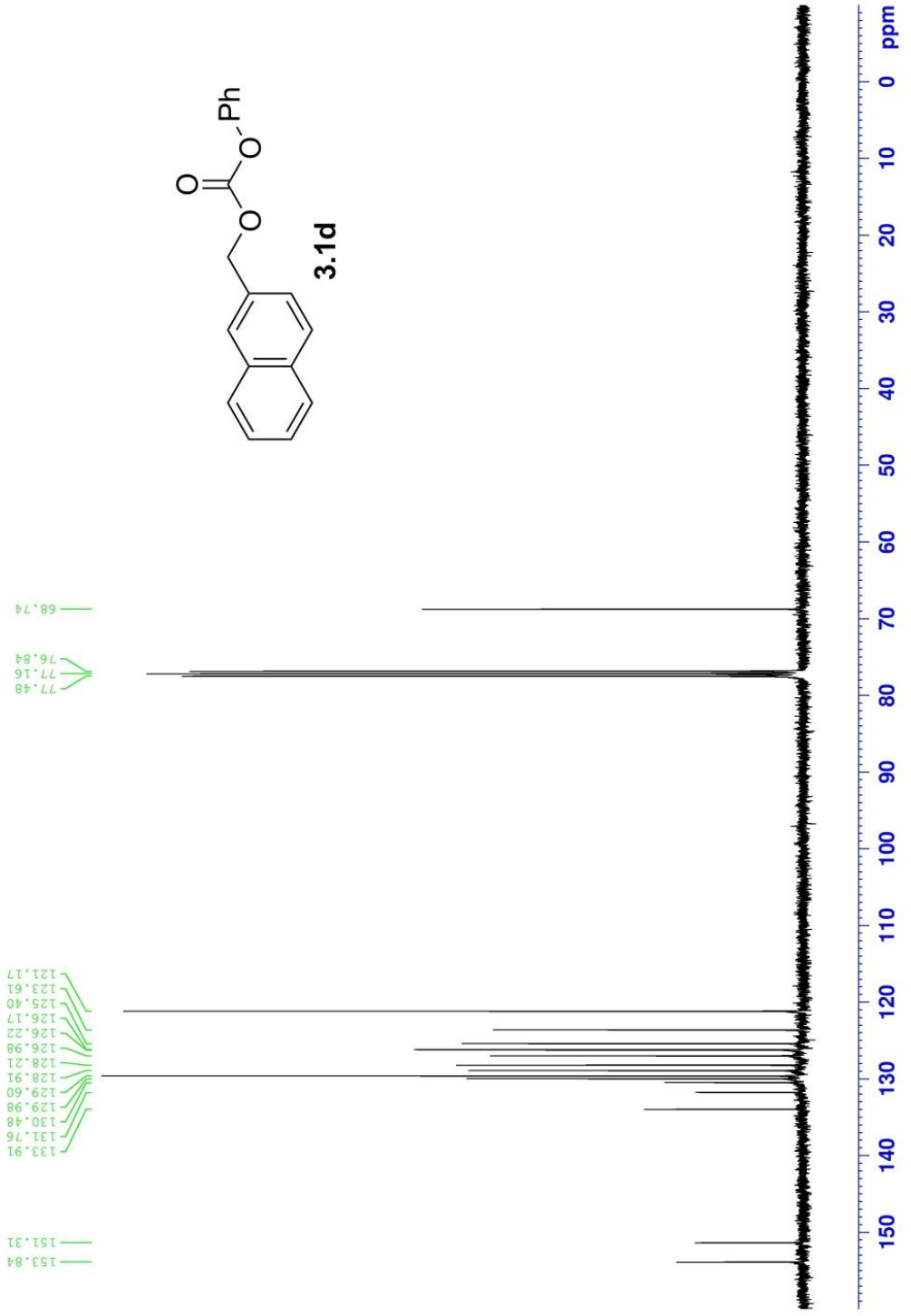

2.30d
NC
O
O
O
5.300
7.714
7.691
7.444
7.439
7.426
7.424
7.416
7.412
7.409
7.405
7.353
7.331
7.270
2.00
1.96
4.72
1.95
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

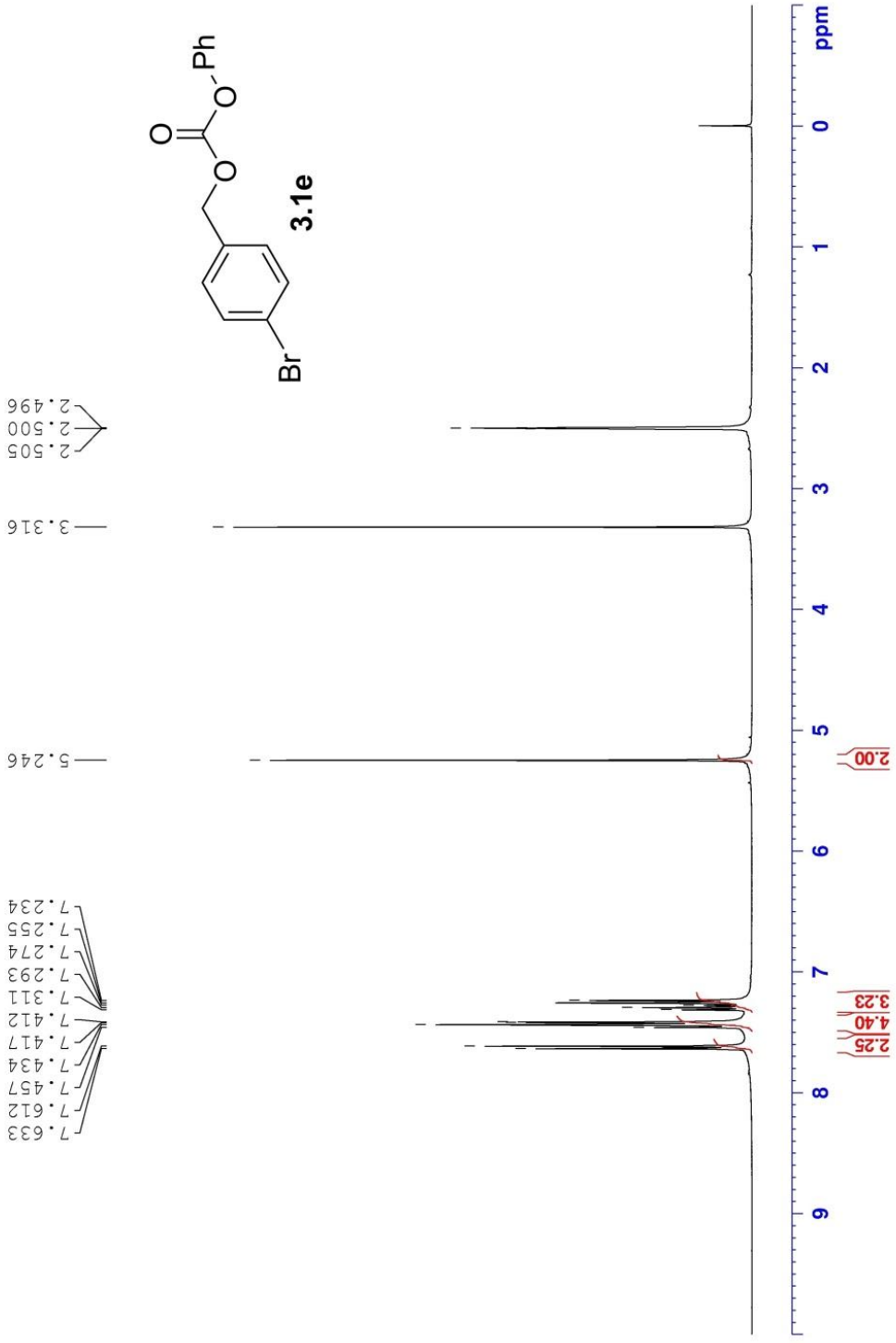

2.30d
NC
O
O
O
71.05
76.84
77.16
77.48
110.15
118.21
122.20
128.78
128.93
129.17
133.89
134.41
152.71
154.30
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160

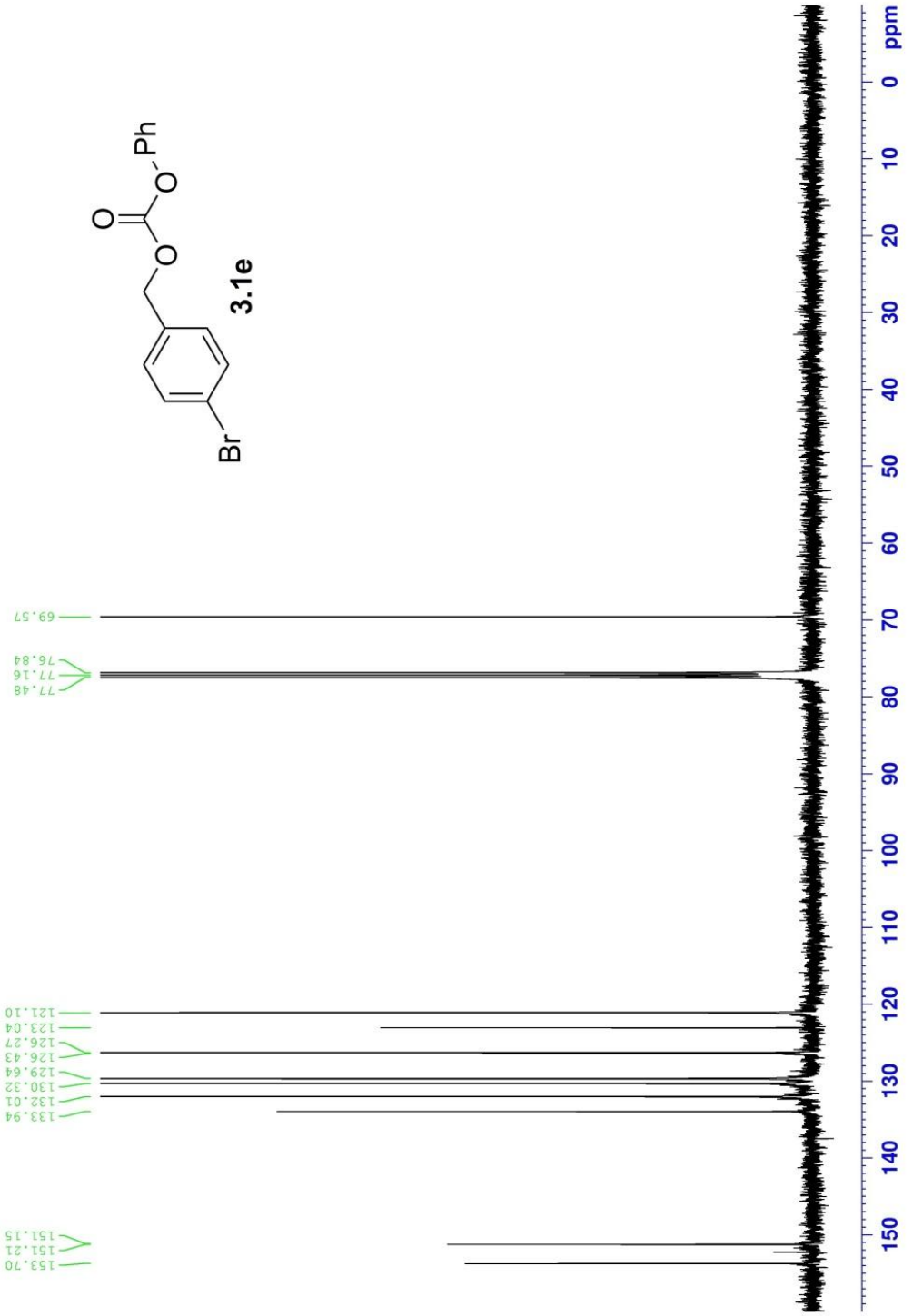

3.1c
Ph
O
O
O
ppm
0
1
2
3
4
5
6
7
8
9
6.00
0.96
1.95
1.94
2.30
1.008
1.025
1.545
2.019
2.035
2.052
2.069
2.086
2.103
2.119
4.043
4.059
7.183
7.196
7.202
7.205
7.249
7.270
7.374
7.378
7.394
7.413

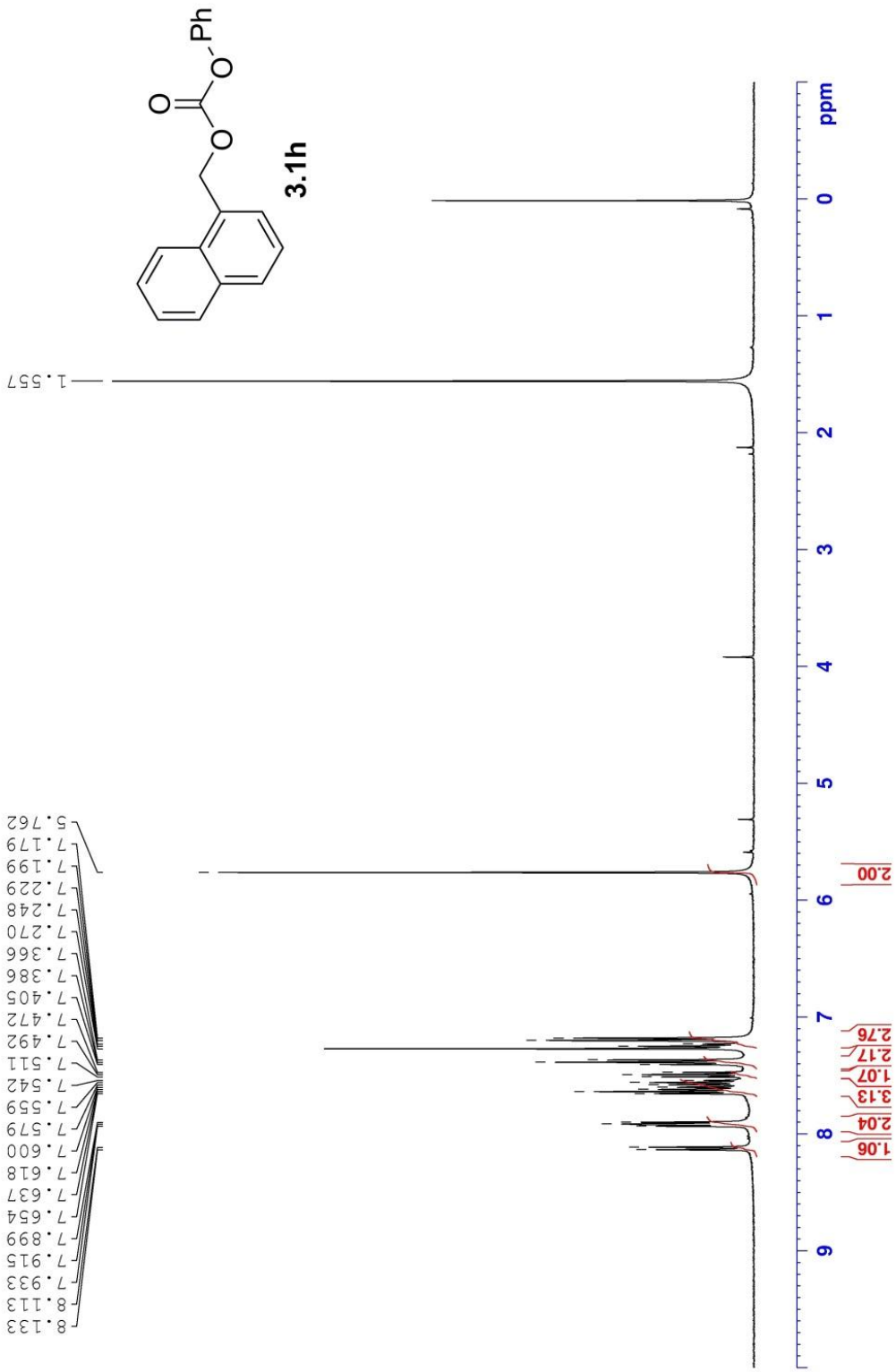

O
O
O
Ph
3.1c
19.05
27.95
74.92
76.85
77.16
77.48
121.22
126.08
129.59
151.34
153.97
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160

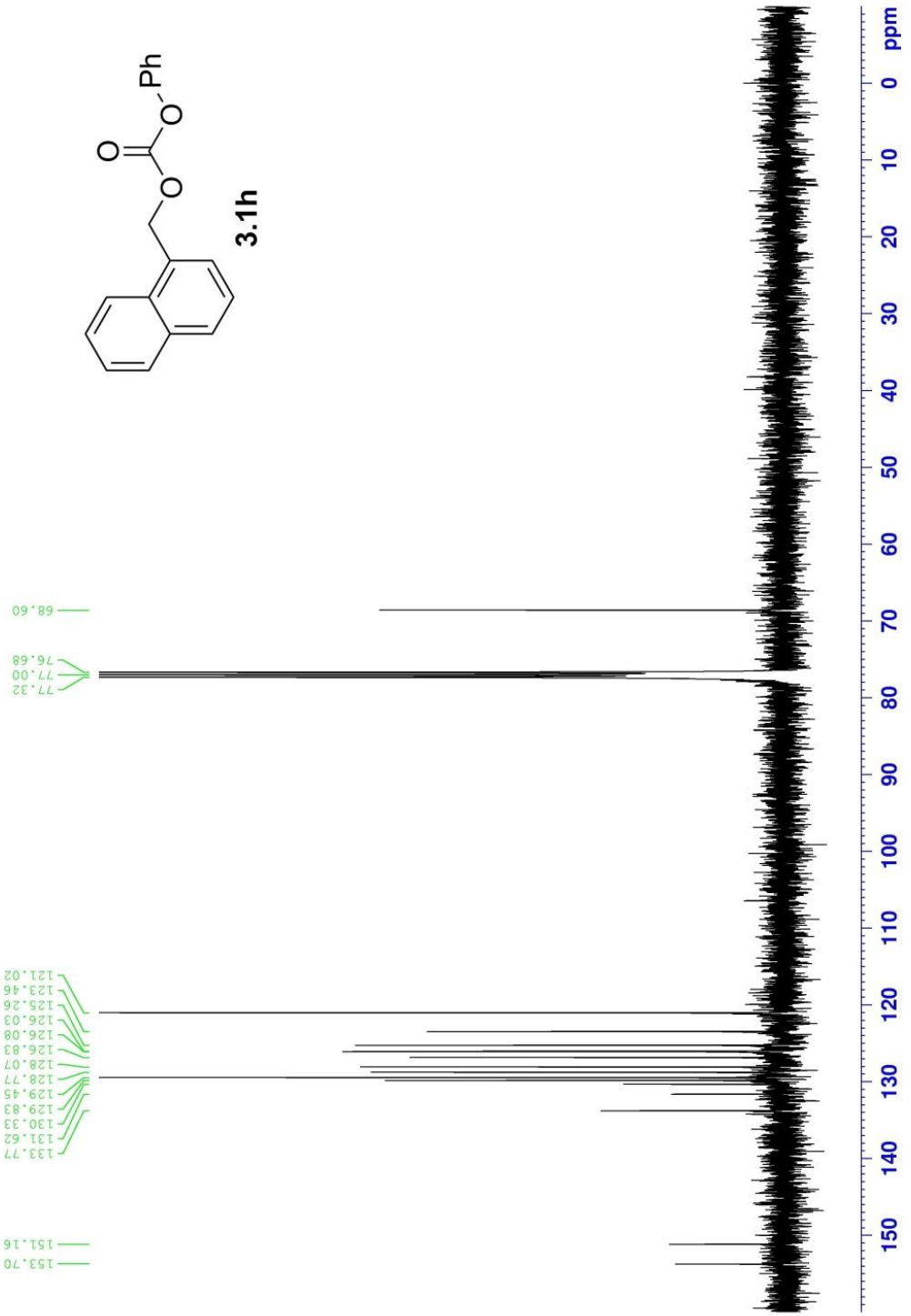
7.618
7.615
7.601
7.597
7.580
7.577
7.562
7.559
7.557
7.542
7.539
7.510
7.492
7.490
7.472
7.405
7.400
7.386
7.370
7.366
7.360
7.248
7.232
7.230
7.227
7.202
7.198
7.193
7.182
7.180
7.178
7.171
5.762
O
O
O
Ph
3.1d
ppm
0
1
2
3
4
5
6
7
8
9
2.00
0.98
1.97
3.95
1.98
2.65

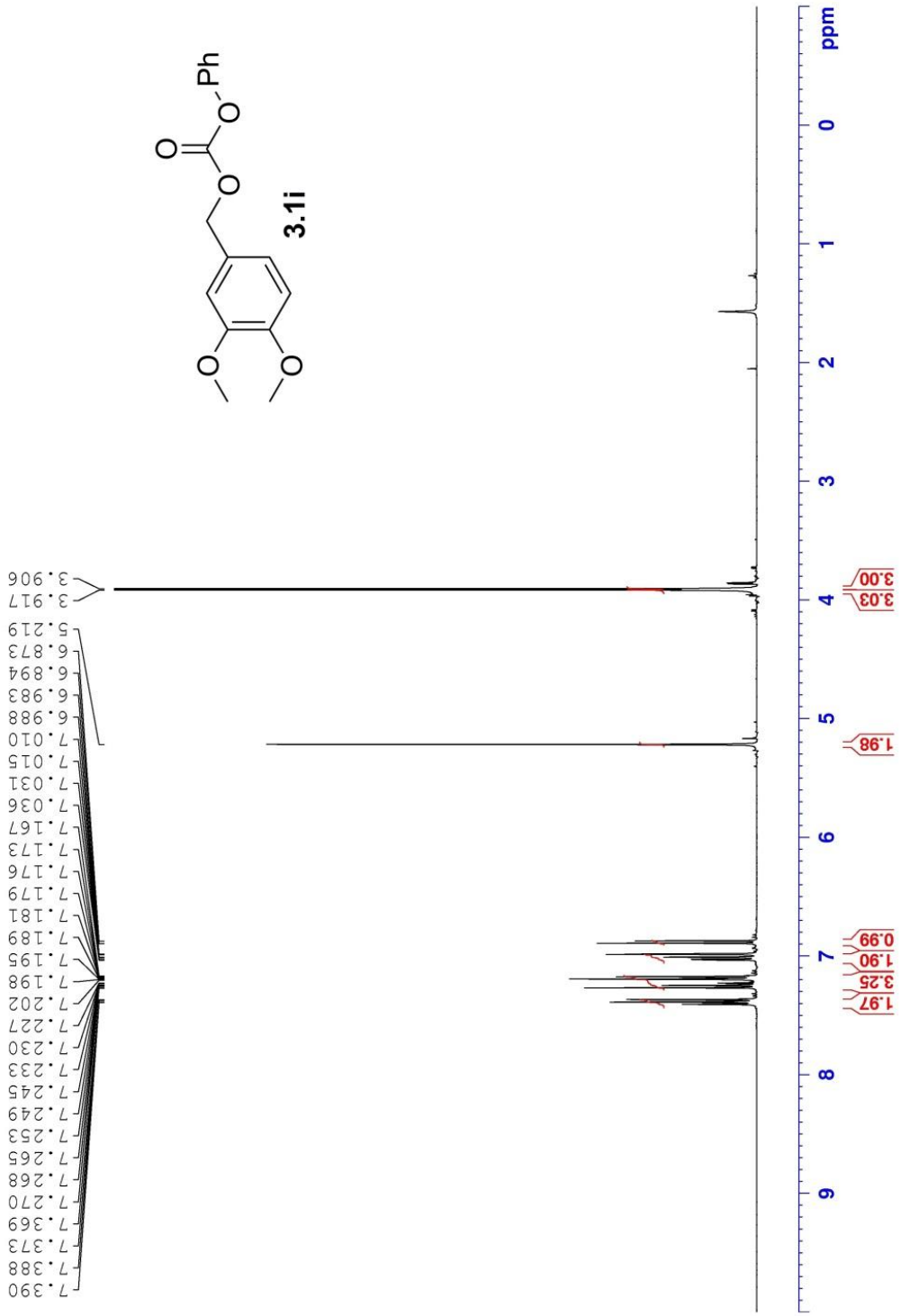

3.1d
153.84
151.31
133.91
131.76
130.48
129.98
129.60
128.91
128.21
126.98
126.22
126.17
125.40
123.61
121.17
77.48
77.16
76.84
68.74
ppm


3.1e
Ph
O
O
O
Br
ppm
0
1
2
3
4
5
6
7
8
9
2.00
3.23
4.40
2.25
2.496
2.500
2.505
3.316
5.246
7.234
7.255
7.274
7.293
7.311
7.412
7.417
7.434
7.457
7.612
7.633


O
O
Ph
O
Br
3.1e
69.57
76.84
77.16
77.48
121.10
123.04
126.27
126.43
129.64
130.32
132.01
133.94
151.15
151.21
153.70
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


3.1h
Ph
O
O
O
1.557
8.133
8.113
7.933
7.915
7.899
7.654
7.637
7.618
7.600
7.579
7.559
7.542
7.511
7.492
7.472
7.405
7.386
7.366
7.270
7.248
7.229
7.199
7.179
5.762
2.00
2.76
2.17
1.07
3.13
2.04
1.06
ppm


3.1h
Ph
O
O
O
68.60
76.68
77.00
77.32
121.02
123.46
125.26
126.03
126.08
126.83
128.07
128.77
129.45
129.83
130.33
131.62
133.77
151.16
153.70
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm


3.1i
Ph
O
O
O
O
O
ppm
0
1
2
3
4
5
6
7
8
9
3.00
3.03
1.98
0.99
1.90
3.25
1.97
3.917
3.906
7.390
7.388
7.373
7.369
7.270
7.268
7.265
7.253
7.249
7.245
7.233
7.230
7.227
7.202
7.198
7.195
7.189
7.181
7.179
7.176
7.173
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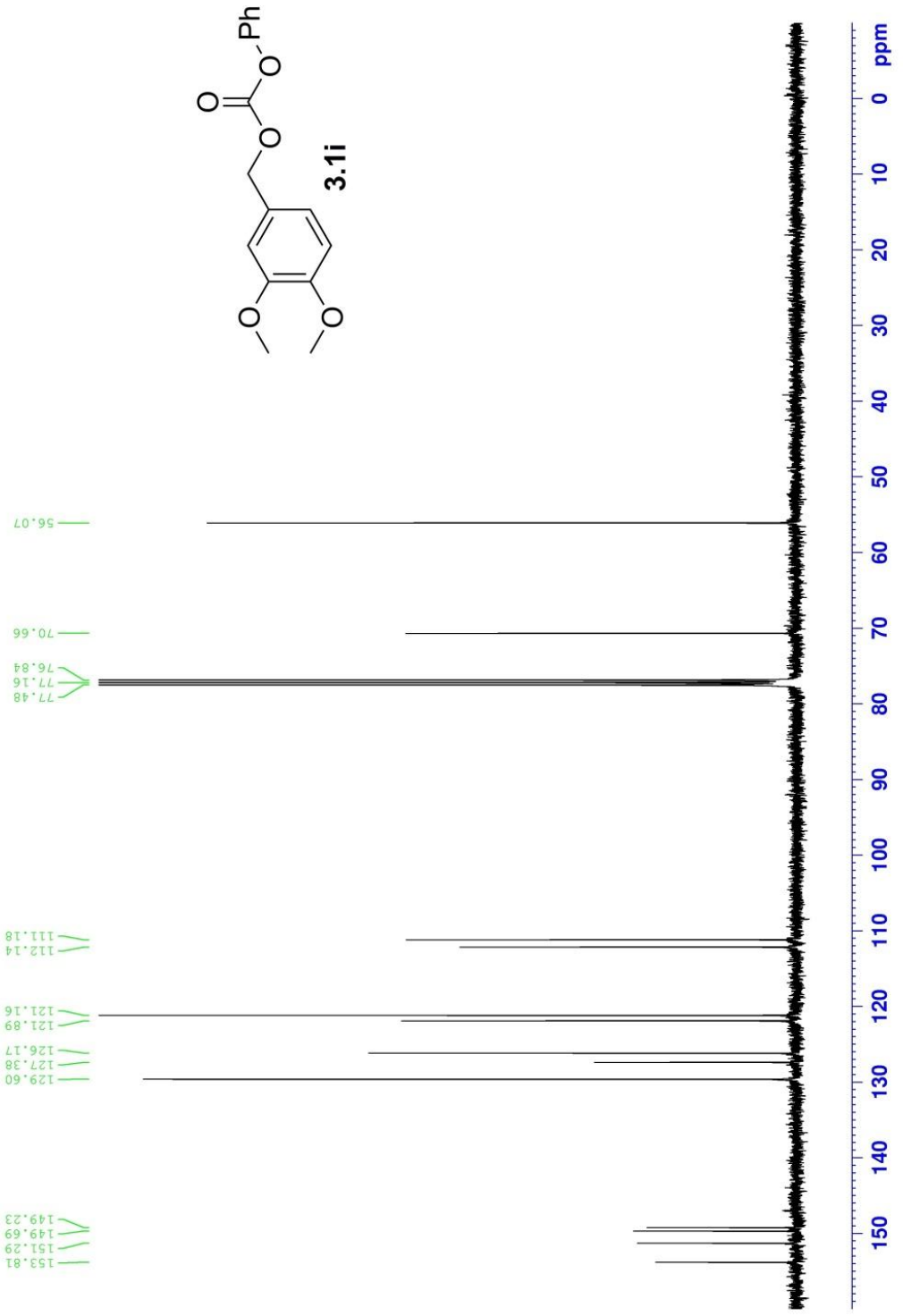
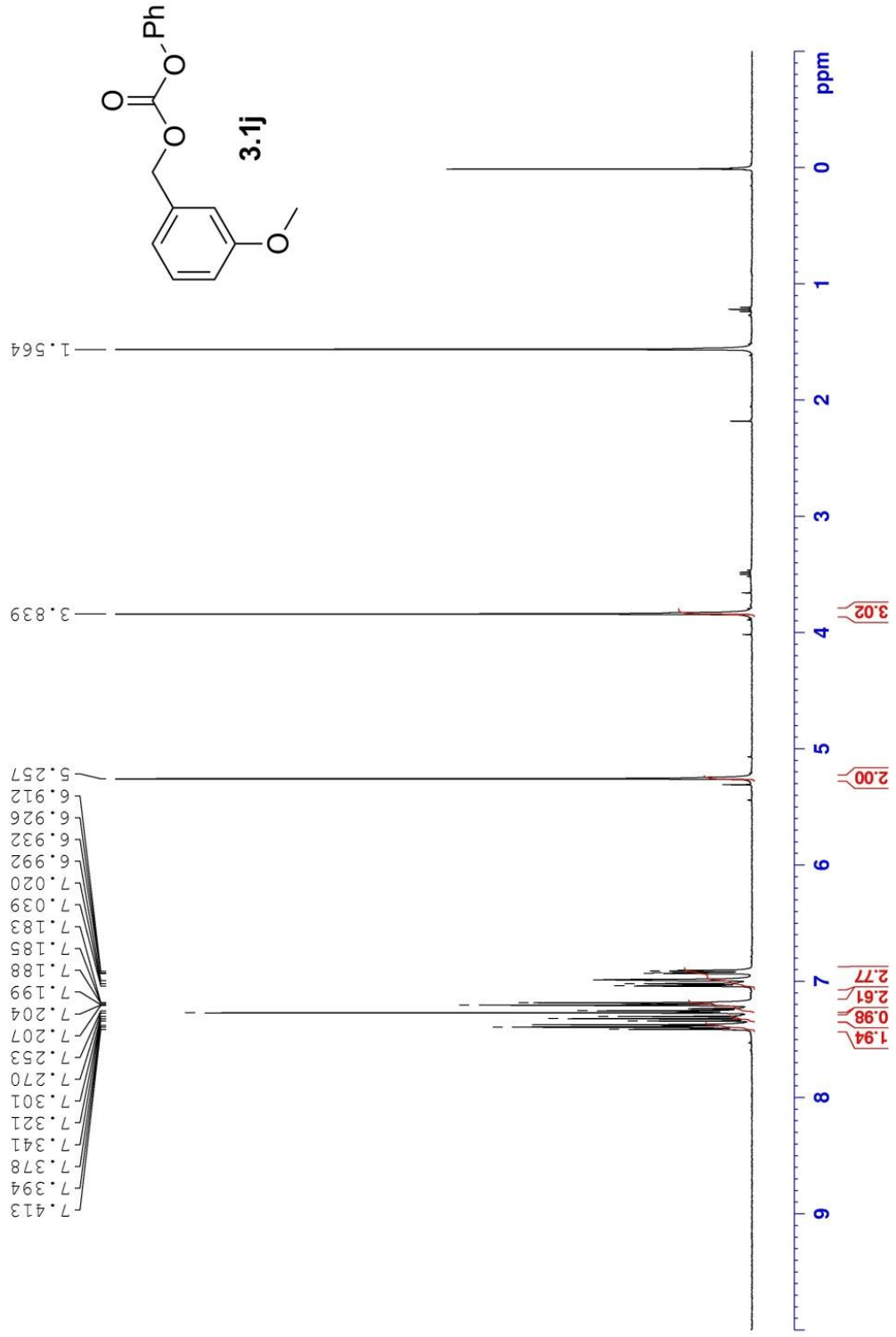
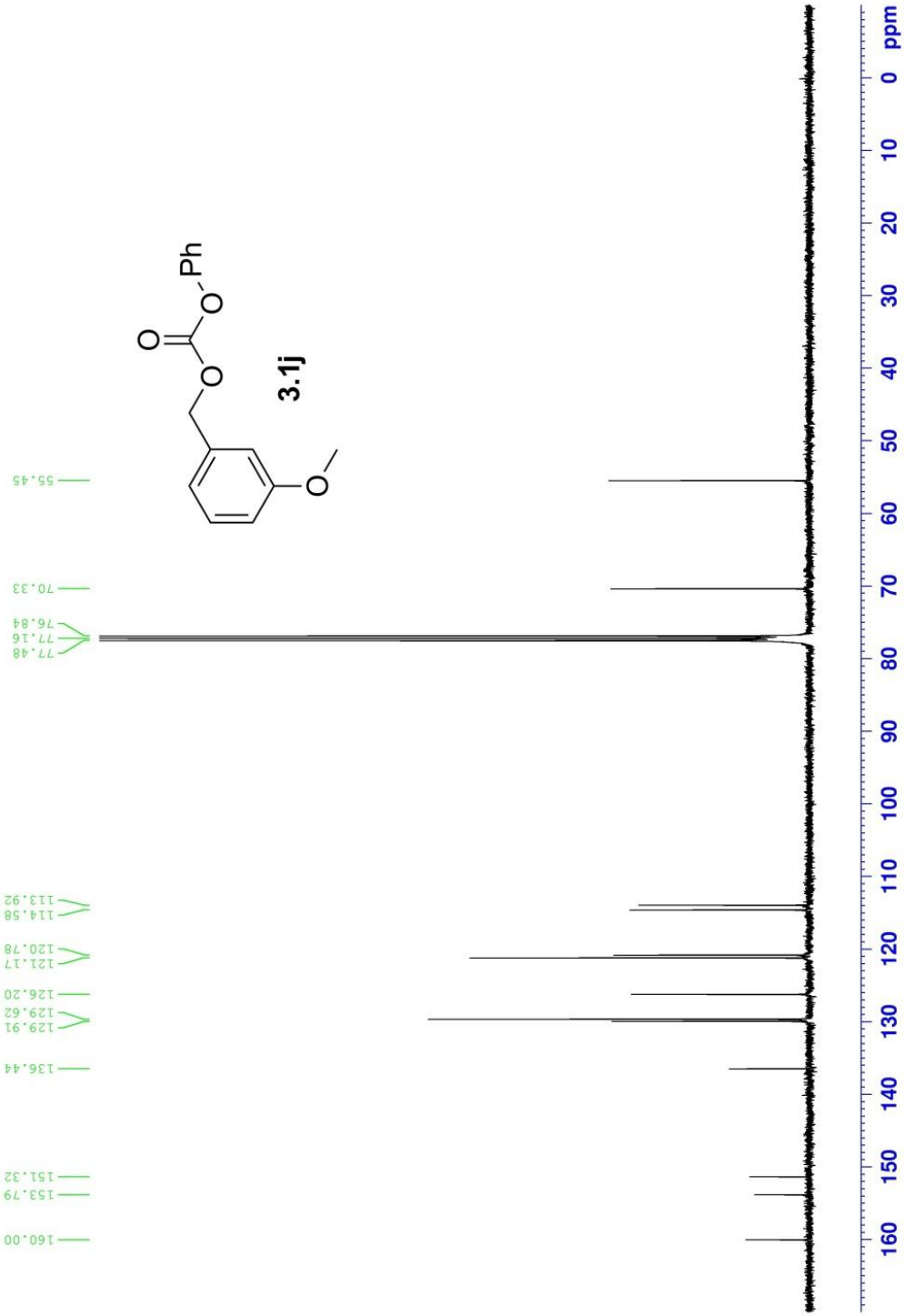
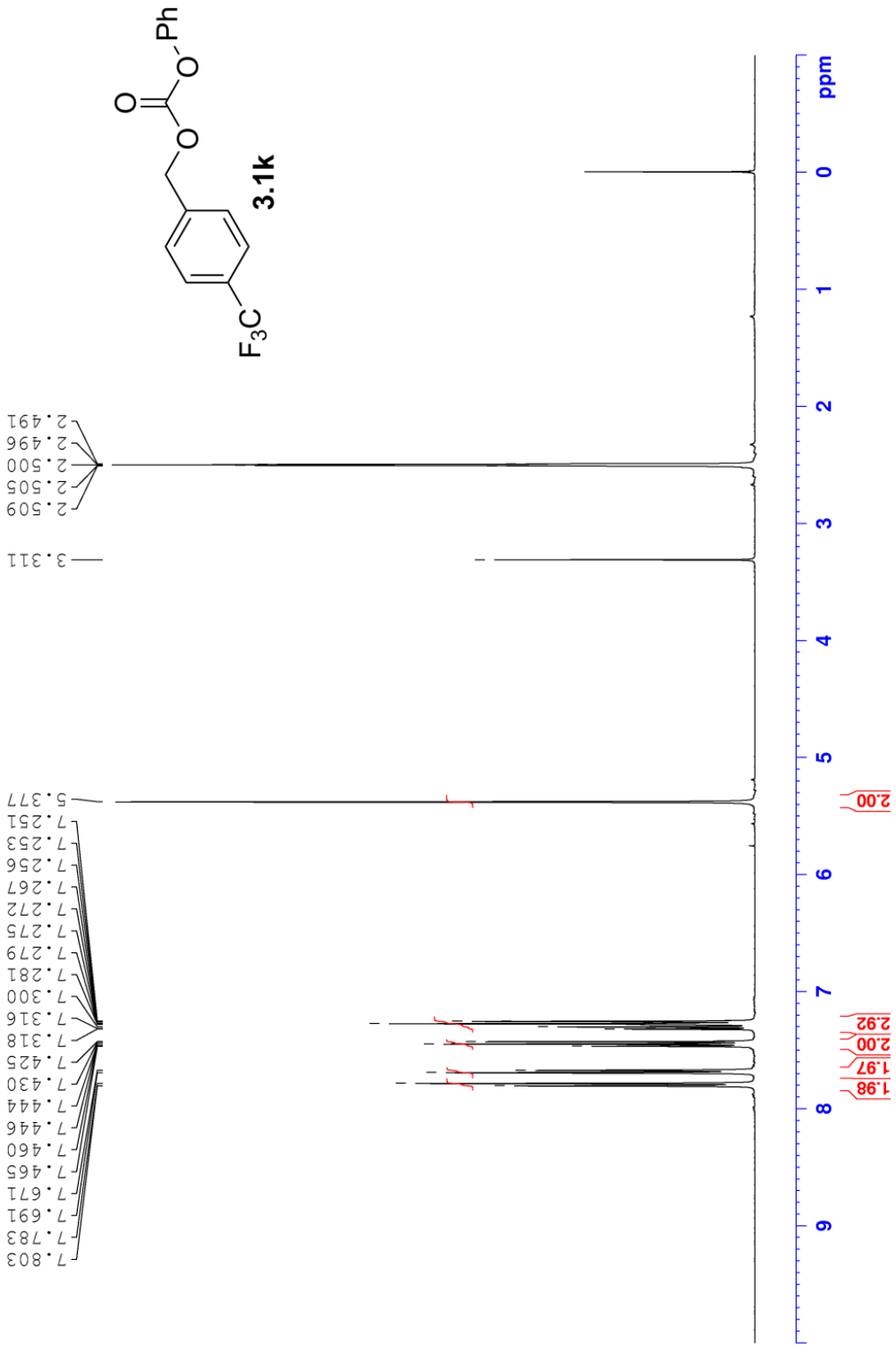
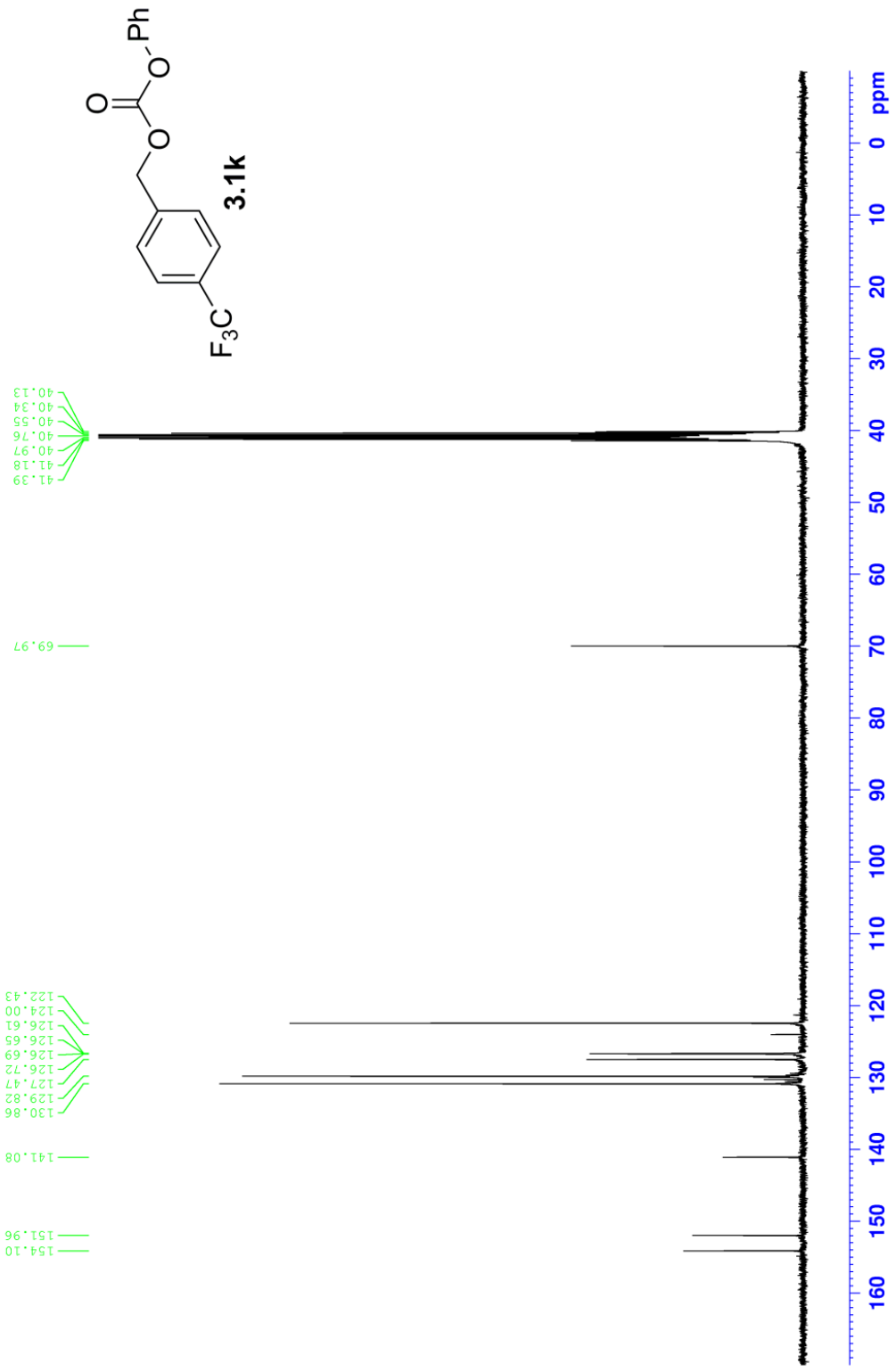
6.983
6.894
6.873
5.219

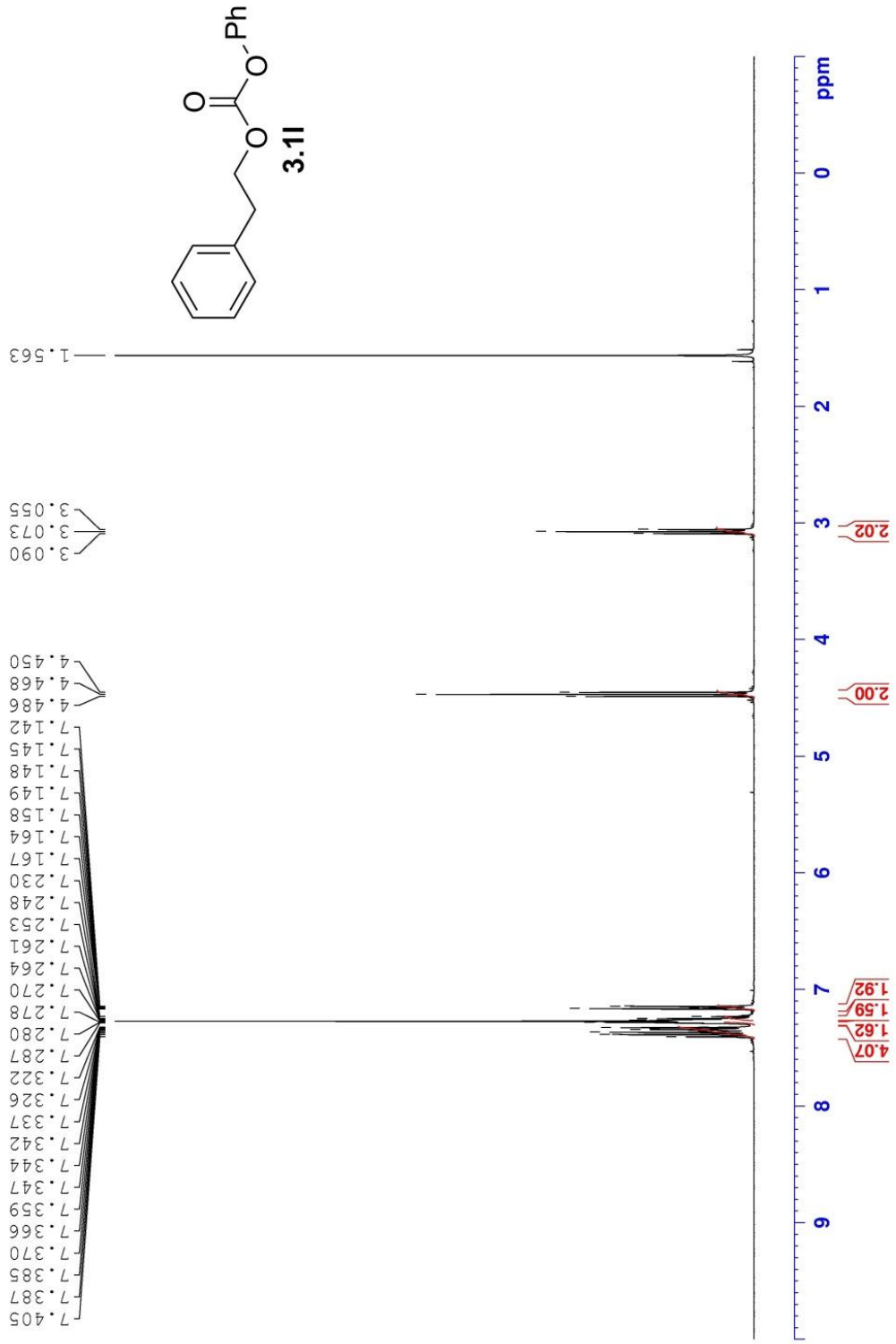

3.1i
56.07
70.66
76.84
77.16
77.48
111.18
112.14
121.16
121.89
126.17
127.38
129.60
149.23
149.69
151.29
153.81
ppm

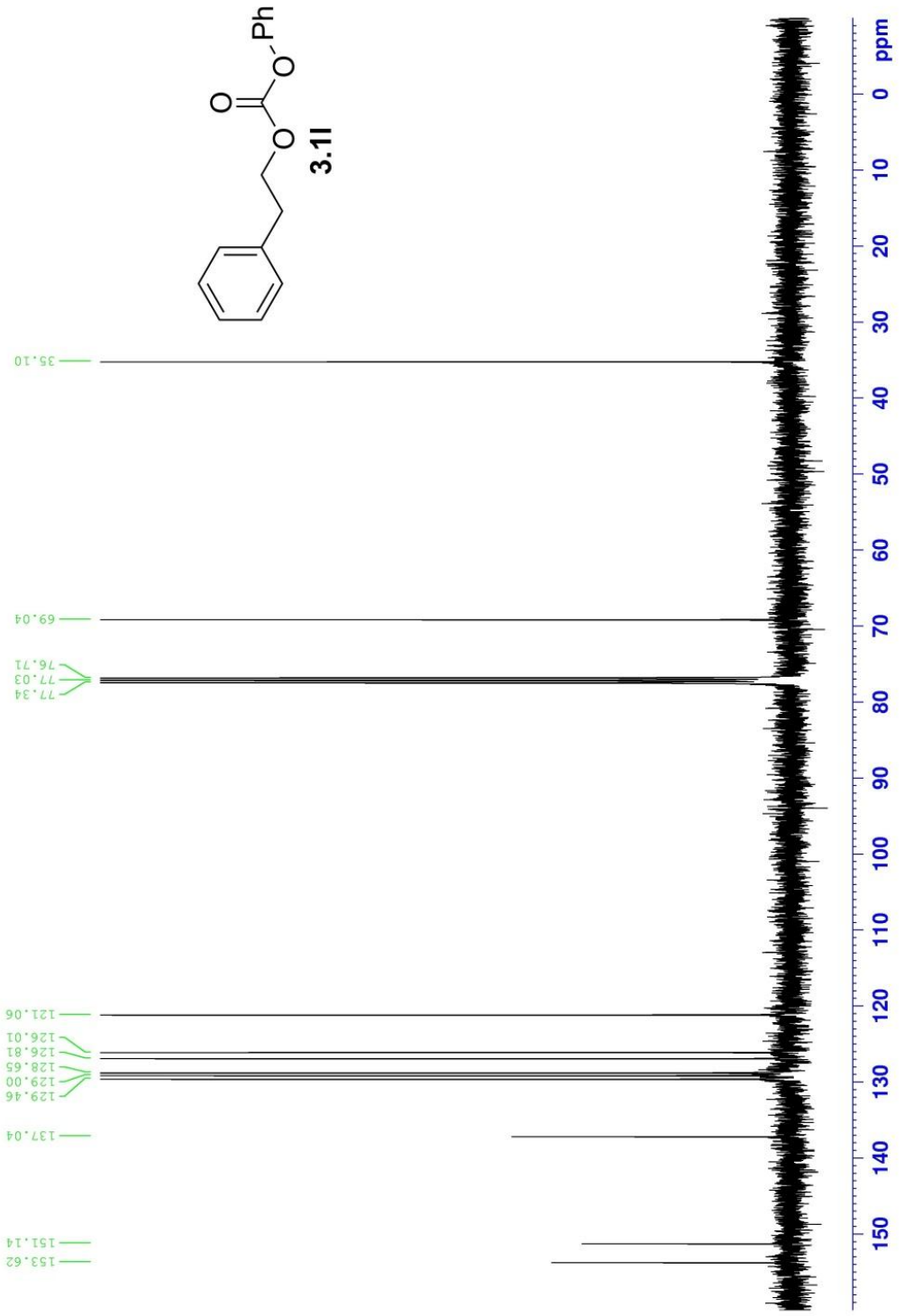

3.1j
O
O
Ph
O
O
ppm
0
1
2
3
4
5
6
7
8
9
1.564
3.839
5.257
6.912
6.926
6.932
6.992
7.020
7.039
7.183
7.185
7.188
7.199
7.204
7.207
7.253
7.270
7.301
7.321
7.341
7.378
7.394
7.413
3.02
2.00
2.77
2.61
0.98
1.94


3.1j
55.45
70.33
76.84
77.16
77.48
113.92
114.58
120.78
121.17
126.20
129.62
129.91
136.44
151.32
153.79
160.00
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160


3.1k
F3C
O
O
O
Ph
ppm
0
1
2
3
4
5
6
7
8
9
2.00
2.92
2.00
1.97
1.98
2.491
2.496
2.500
2.505
2.509
3.311
5.377
7.251
7.253
7.256
7.267
7.272
7.275
7.279
7.281
7.300
7.316
7.318
7.425
7.430
7.444
7.446
7.460
7.465
7.671
7.691
7.783
7.803


Ph
O
O
O
F3C
3.1k
40.13
40.34
40.55
40.76
40.97
41.18
41.39
69.97
122.43
124.00
126.61
126.65
126.69
126.72
127.47
129.82
130.86
141.08
151.96
154.10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm


3.11
Ph
O
O
O
ppm
0
1
2
3
4
5
6
7
8
9
1.563
3.090
3.073
3.055
4.450
4.468
4.486
2.02
2.00
4.07
1.62
1.59
1.92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O
O
O
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69.04
76.71
77.03
77.34
121.06
126.01
126.81
128.65
129.00
129.46
137.04
151.14
153.62
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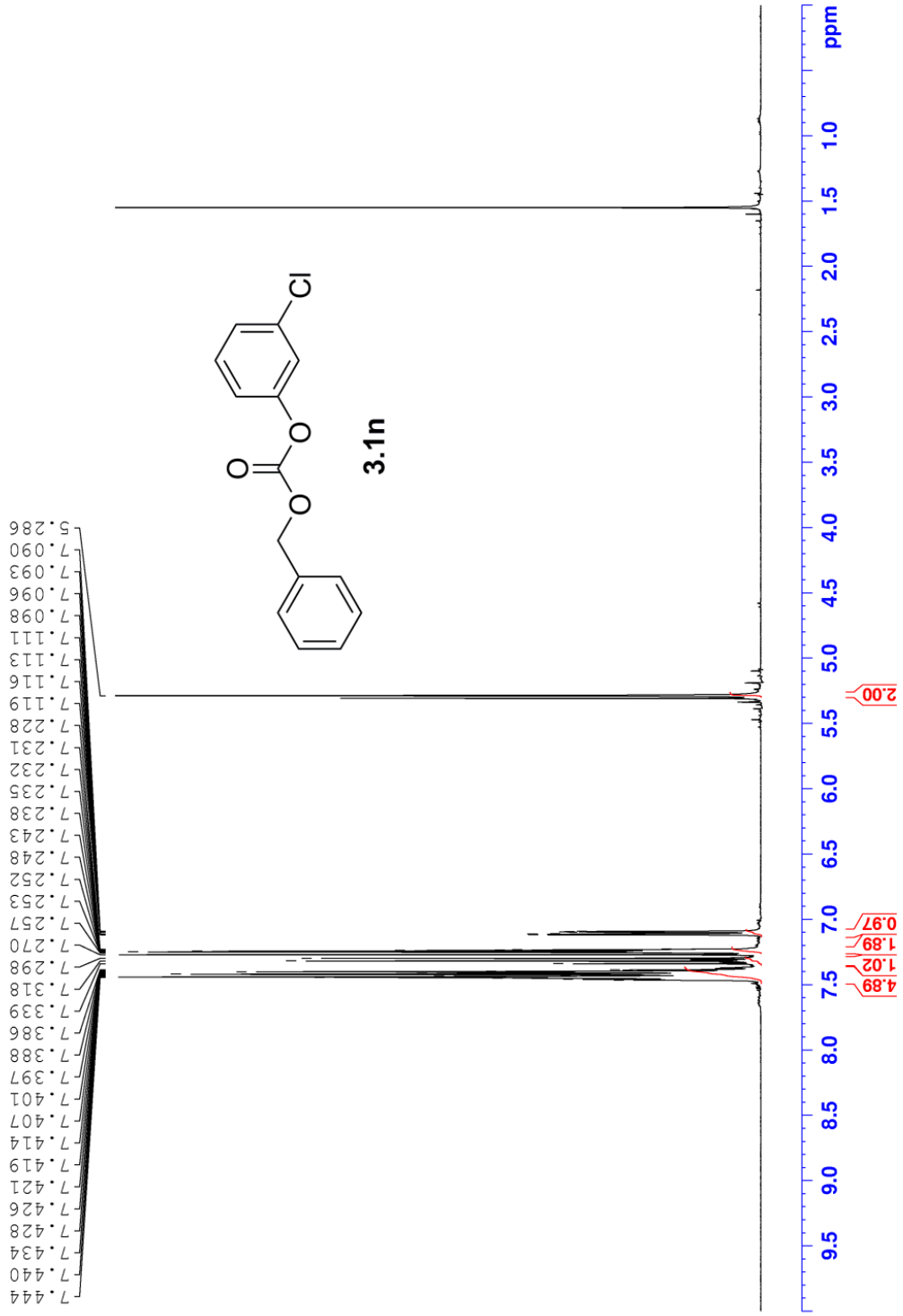
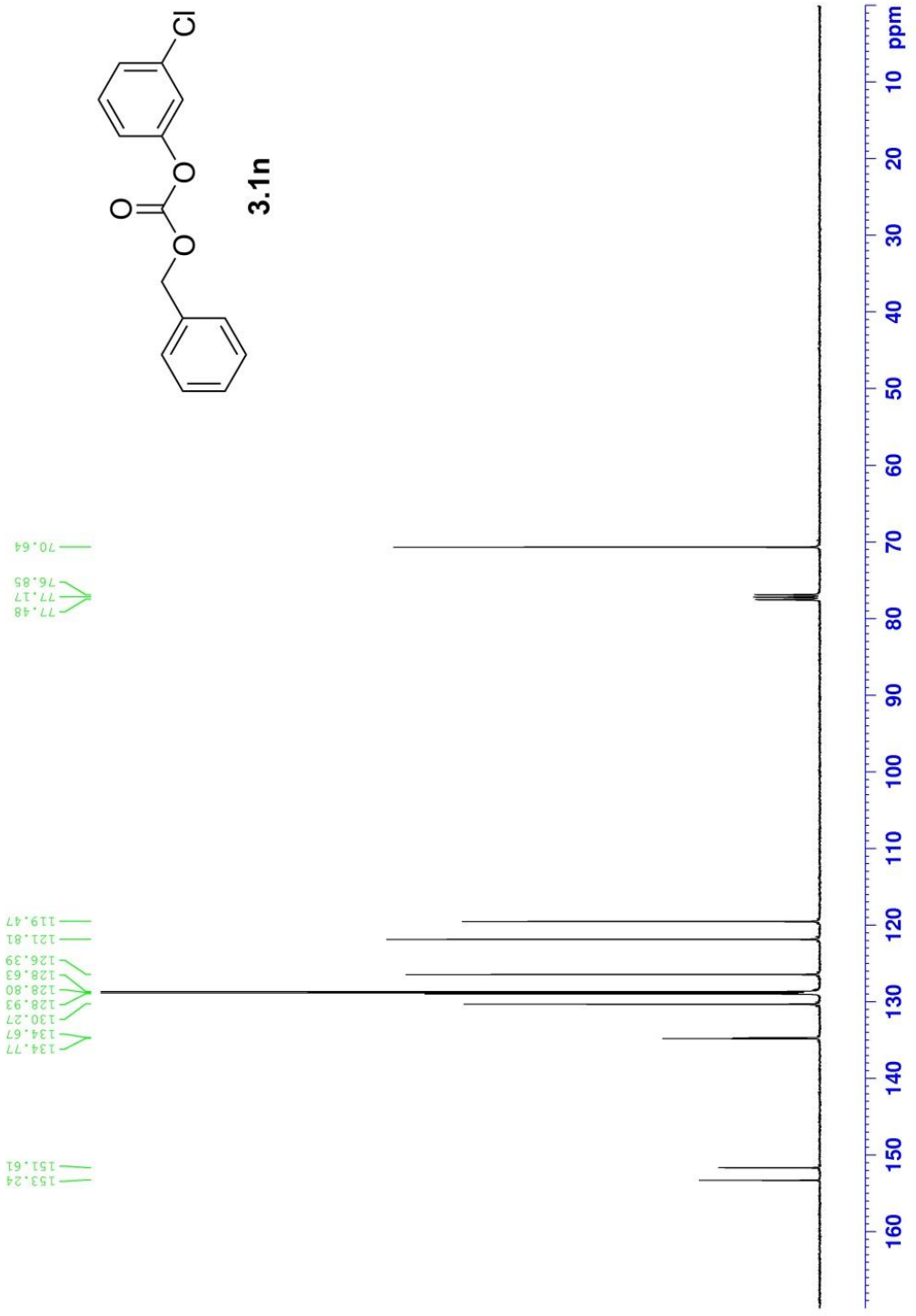
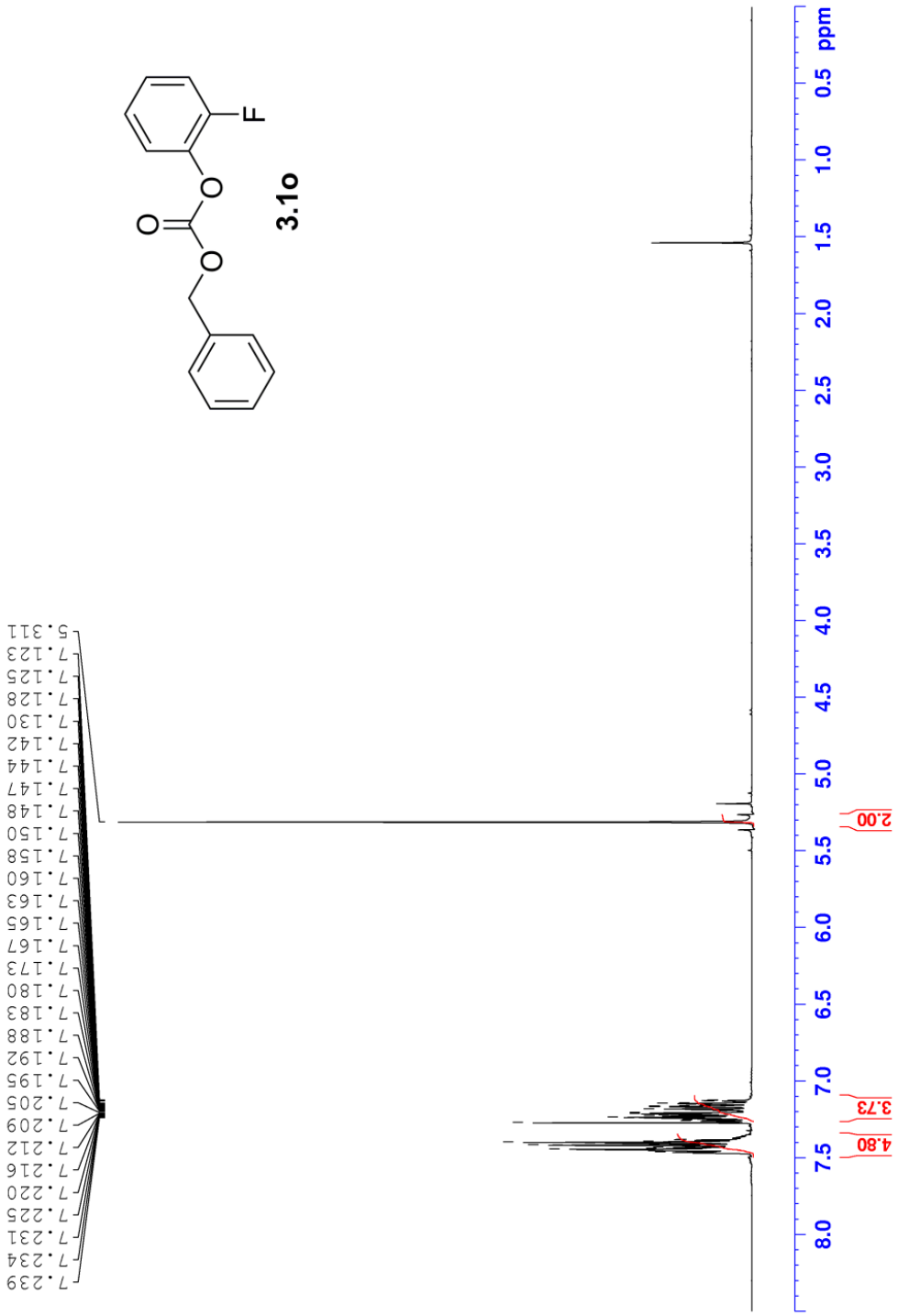
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm


3.1n
Cl
O
O
O
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
4.89
1.02
1.89
0.97
2.00
7.444
7.440
7.434
7.428
7.426
7.421
7.419
7.414
7.407
7.401
7.397
7.388
7.386
7.339
7.318
7.298
7.270
7.257
7.253
7.252
7.248
7.243
7.238
7.235
7.232
7.231
7.228
7.119
7.116
7.113
7.111
7.098
7.096
7.093
7.090
5.286


Cl
O
O
O
3.1n
153.24
151.61
134.77
134.67
130.27
128.93
128.80
128.63
126.39
121.81
119.47
77.48
77.17
76.85
70.64
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160


3.1o
F
O
O
O
ppm
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1.5
2.0
2.5
3.0
3.5
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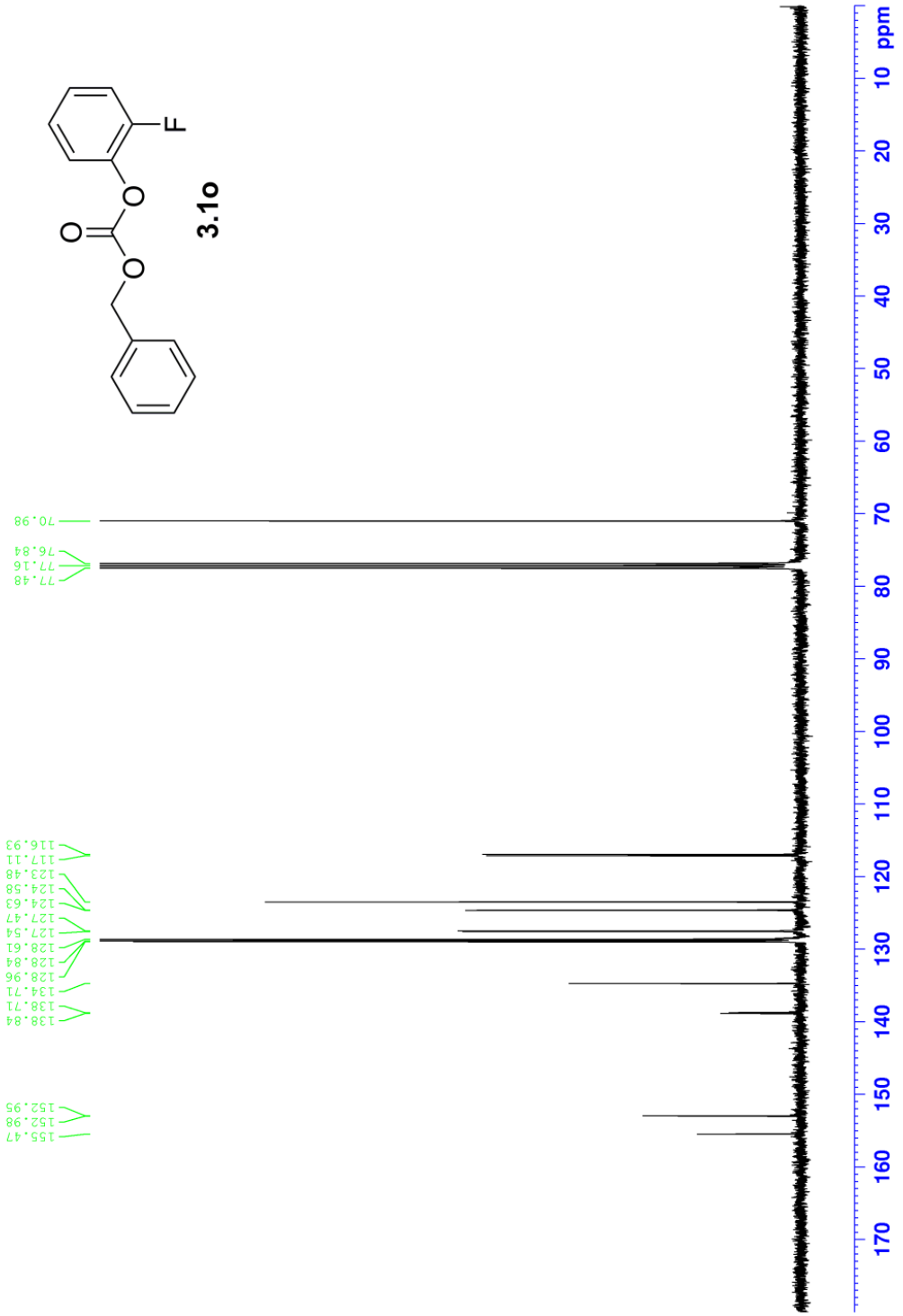
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
2.00
3.73
4.80
5.311
7.123
7.125
7.128
7.130
7.142
7.144
7.147
7.148
7.150
7.158
7.160
7.163
7.165
7.167
7.173
7.180
7.183
7.188
7.192
7.195
7.205
7.209
7.212
7.216
7.220
7.225
7.231
7.234
7.239


F
O
O
O
3.1o
70.98
76.84
77.16
77.48
116.93
117.11
123.48
124.58
124.63
127.47
127.54
128.61
128.84
128.96
134.71
138.71
138.84
152.95
152.98
155.47
10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
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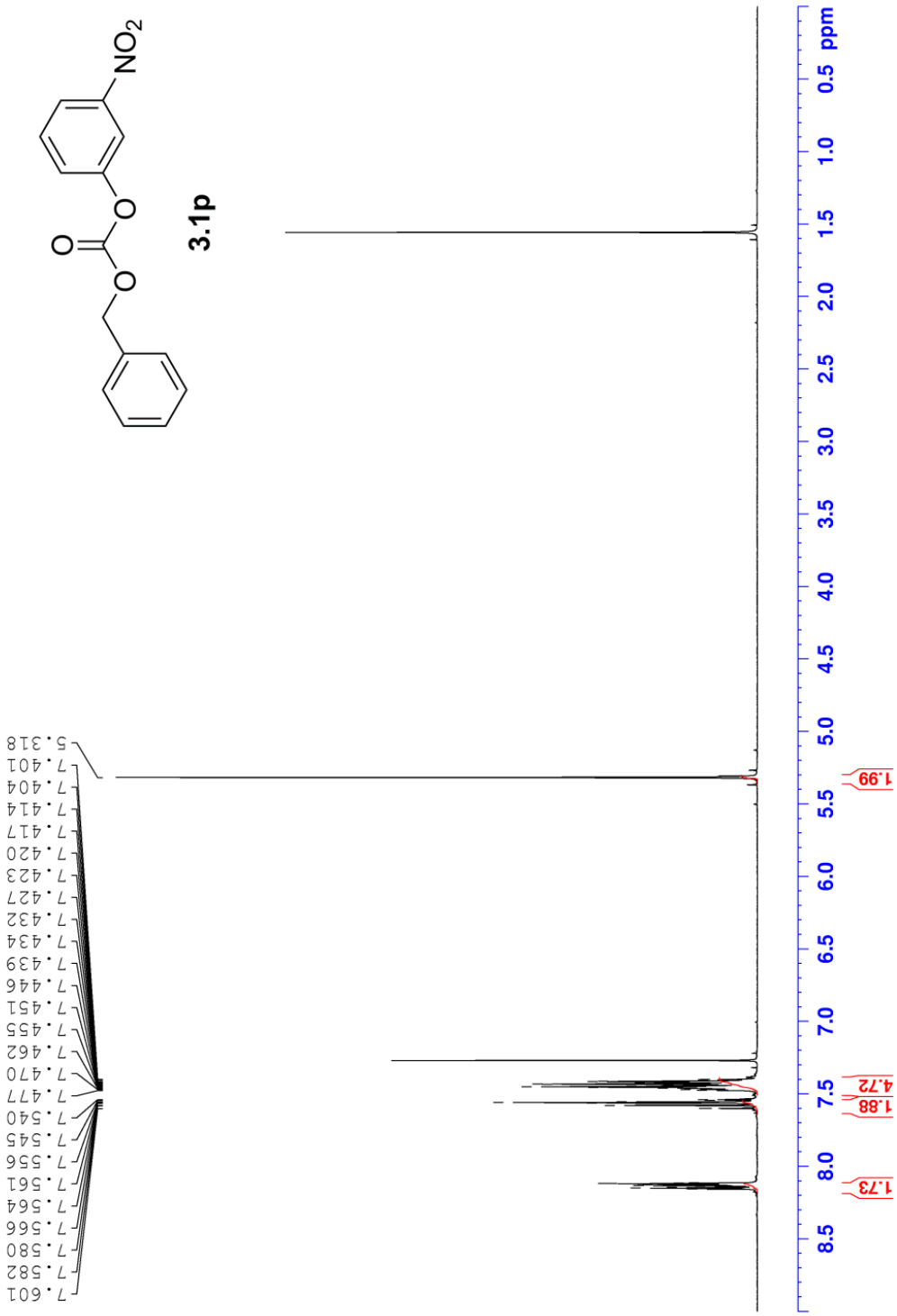
160
170


NO2
O
O
O
3.1p
5.318
7.401
7.404
7.414
7.417
7.420
7.423
7.427
7.432
7.434
7.439
7.446
7.451
7.455
7.462
7.470
7.477
7.540
7.545
7.556
7.561
7.564
7.566
7.580
7.582
7.601
1.99
4.72
1.88
1.73
ppm


NO2
O
O
O
3.1p
71.14
76.85
77.17
77.49
117.00
121.11
127.51
128.80
128.94
129.19
130.27
134.41
148.94
151.49
153.03
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160

1.560
3.433
3.448
3.469
3.484
3.533
3.555
3.569
3.592
5.308
5.349
5.365
5.372
5.387
5.701
7.123
7.128
7.136
7.138
7.146
7.239
7.244
7.252
7.256
7.270
7.441
7.458
7.466
7.478
7.492
7.495
7.509
7.513
7.522
7.527
7.531
7.534
7.540
7.544
7.547
7.555
7.563
7.567
7.572
7.584
Ph
NO2
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O
3.4d
2.18
0.96
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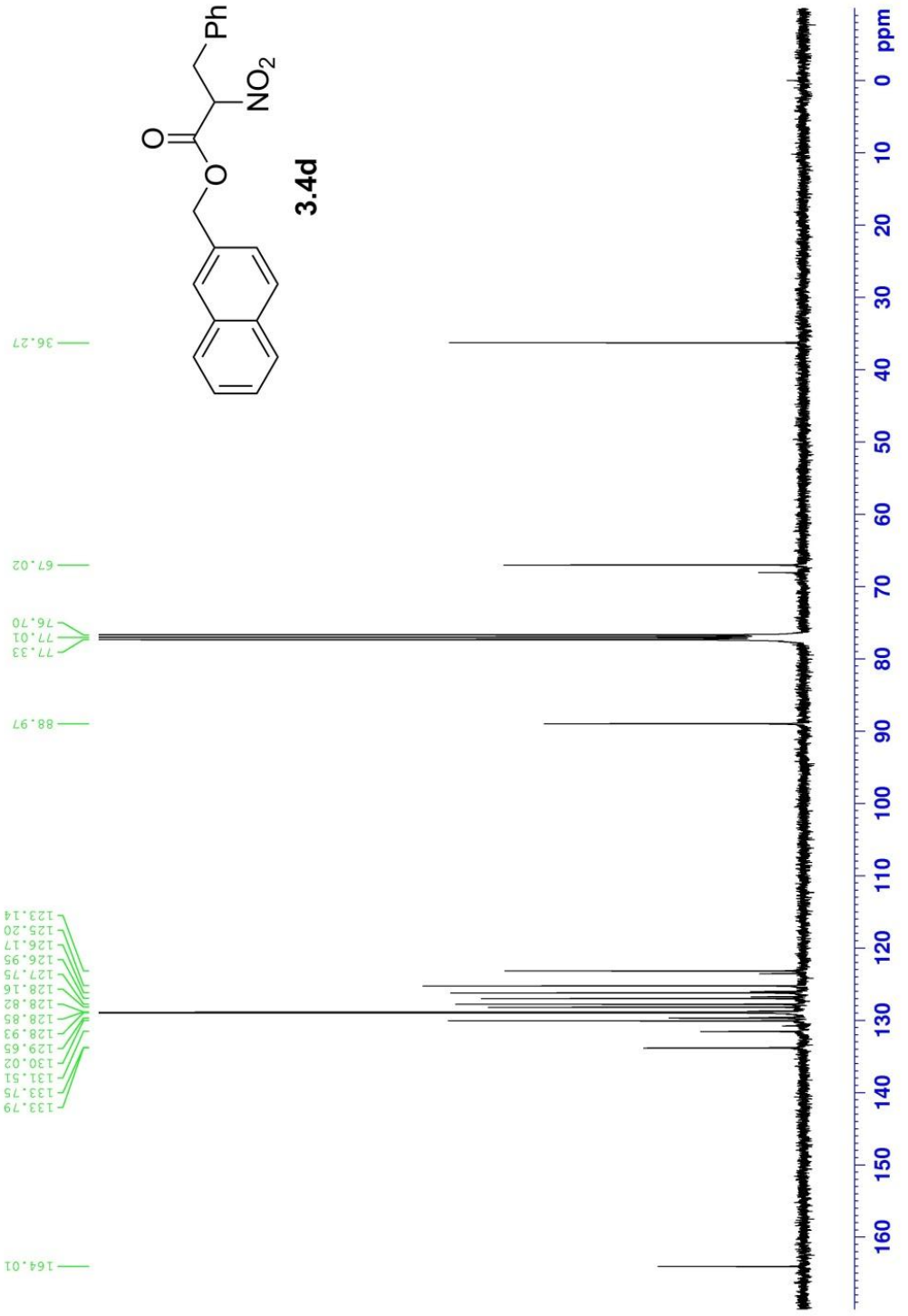
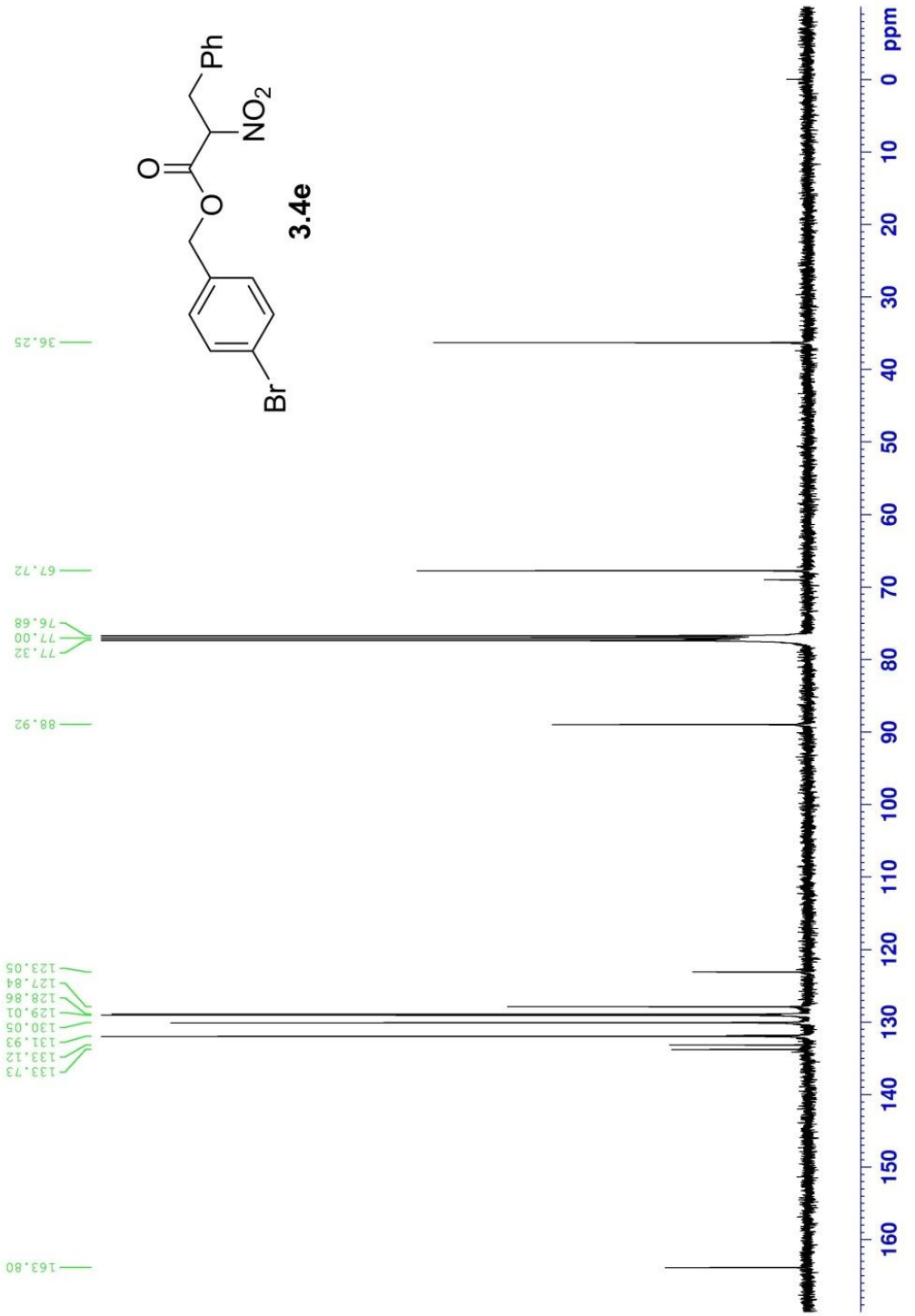
1.96
2.78
4.70
3.29
ppm


Ph
NO2
O
O
3.4d
36.27
67.02
76.70
77.01
77.33
88.97
123.14
125.20
126.17
126.95
127.75
128.16
128.82
128.85
128.93
129.65
130.02
131.51
133.75
133.79
164.01
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160

7.518
7.511
7.507
7.495
7.490
7.484
7.270
5.388
5.373
5.365
5.350
5.179
5.120
3.602
3.579
3.566
3.543
3.504
3.489
3.468
3.453
2.366
1.552
2.23
3.06
4.24
1.00
2.09
2.13
ppm
Ph
NO2
O
O
Br
3.4e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O
Br
3.4e
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67.72
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77.00
77.32
88.92
123.05
127.84
128.86
129.01
130.05
131.93
133.12
133.73
163.80
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160

Ph
NO2
O
O
O
3.4f
1.543
3.814
3.574
3.550
3.538
3.514
3.478
3.463
3.442
3.427
5.356
5.341
5.333
5.318
5.165
7.287
7.270
7.257
7.256
7.242
7.221
7.172
7.168
7.153
6.892
6.871
ppm
0
1
2
3
4
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6
7
8
9
1.08
1.09
3.57
2.00
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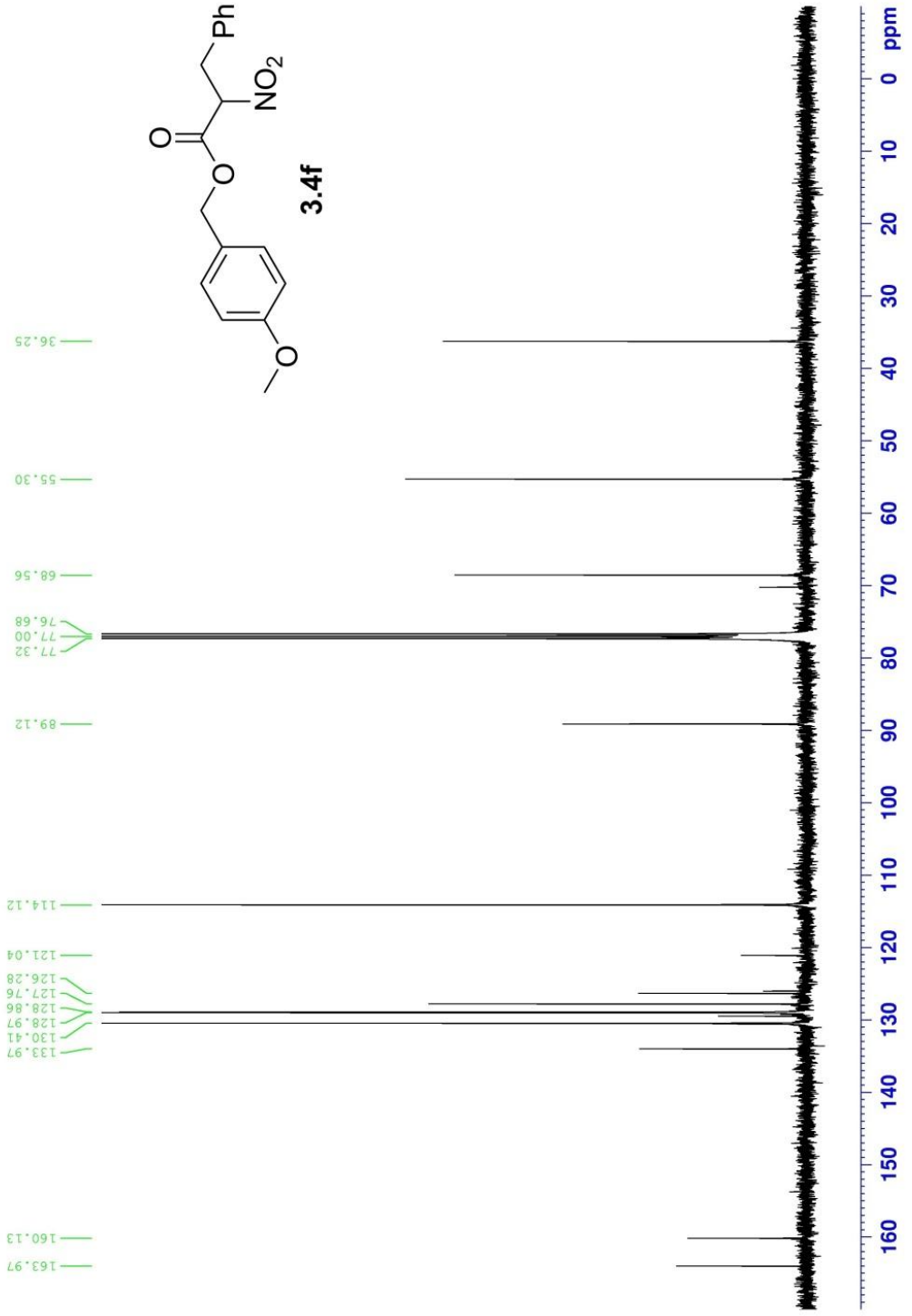
2.09
2.27
6.90


Ph
NO2
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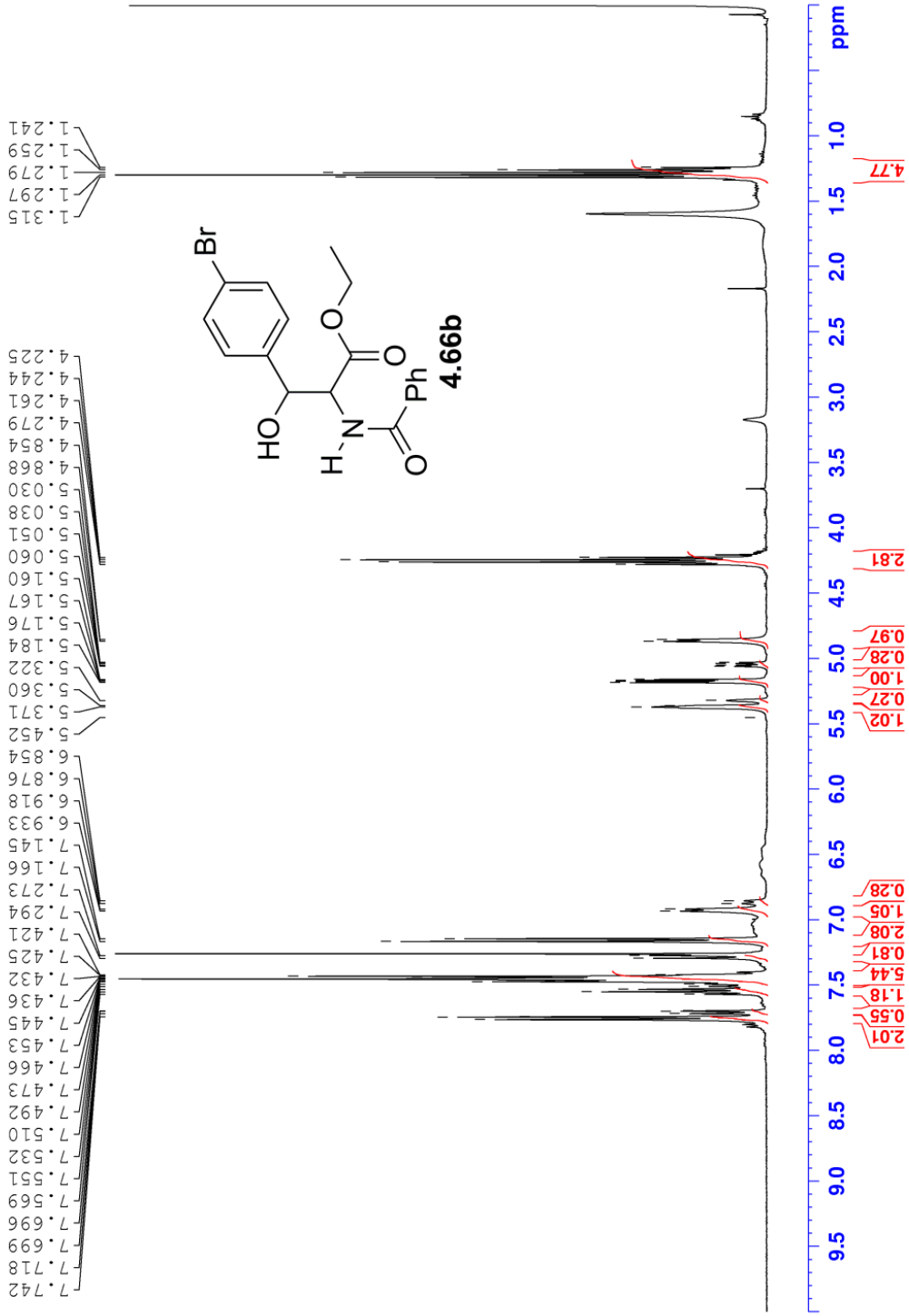
O
O
3.4f
36.25
55.30
68.56
76.68
77.00
77.32
89.12
114.12
121.04
126.28
127.76
128.86
128.97
130.41
133.97
160.13
163.97
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160


Br
HO
H
N
O
O
Ph
O
4.66b
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
4.77
2.81
0.97
0.28
1.00
0.27
1.02
0.28
1.05
2.08
0.81
5.44
1.18
0.55
2.01
1.241
1.259
1.279
1.297
1.315
4.225
4.244
4.261
4.279
4.854
4.868
5.030
5.038
5.051
5.060
5.160
5.167
5.176
5.184
5.322
5.360
5.371
5.452
6.854
6.876
6.918
6.933
7.145
7.166
7.273
7.294
7.421
7.425
7.432
7.436
7.445
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7.492
7.510
7.532
7.551
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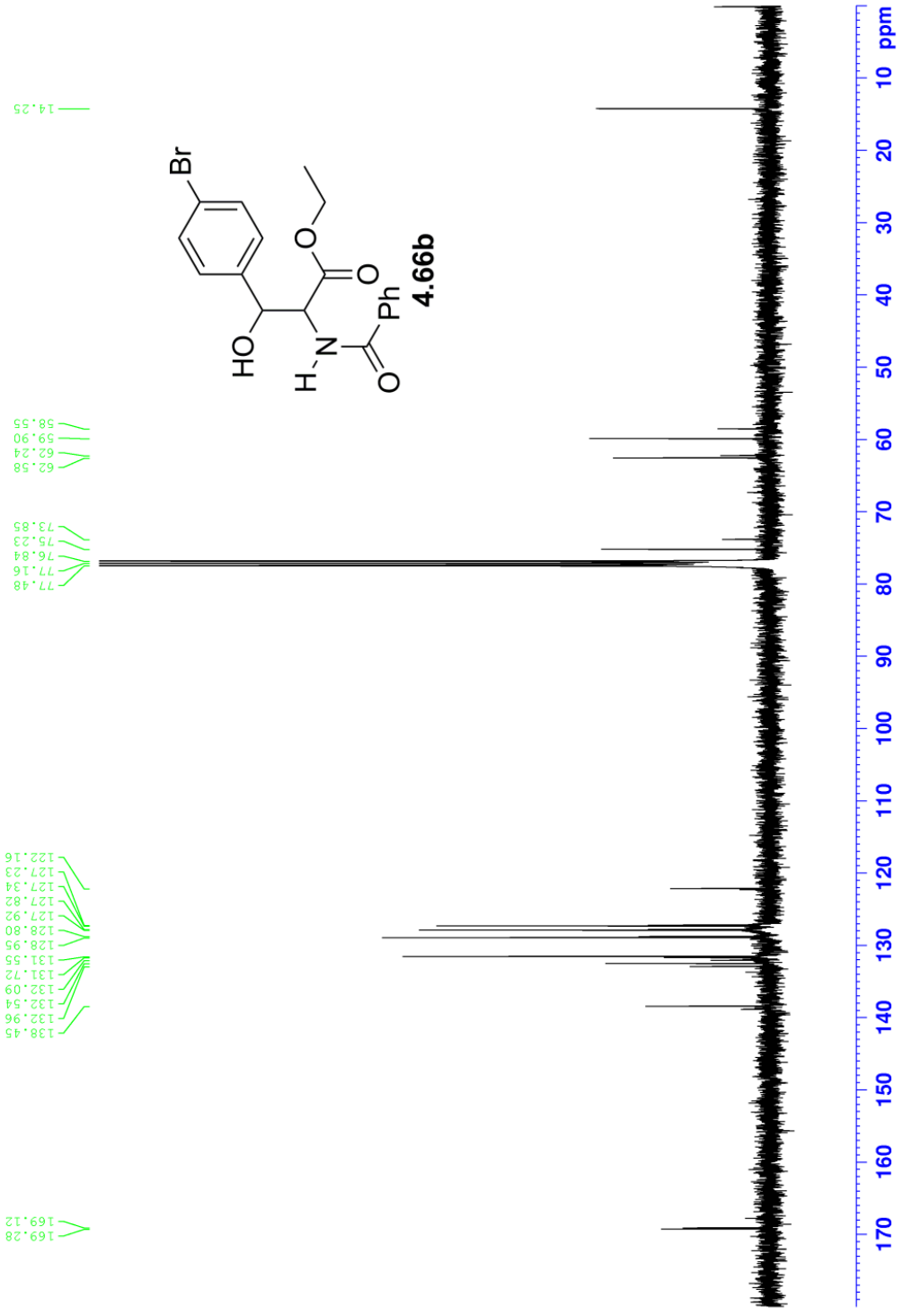
7.742


Br
HO
H
N
O
O
O
Ph
4.66b
14.25
58.55
59.90
62.24
62.58
73.85
75.23
76.84
77.16
77.48
122.16
127.23
127.34
127.82
127.92
128.80
128.95
131.55
131.72
132.09
132.54
132.96
138.45
169.12
169.28
170
160
150
140
130
120
110
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90
80
70
60
50
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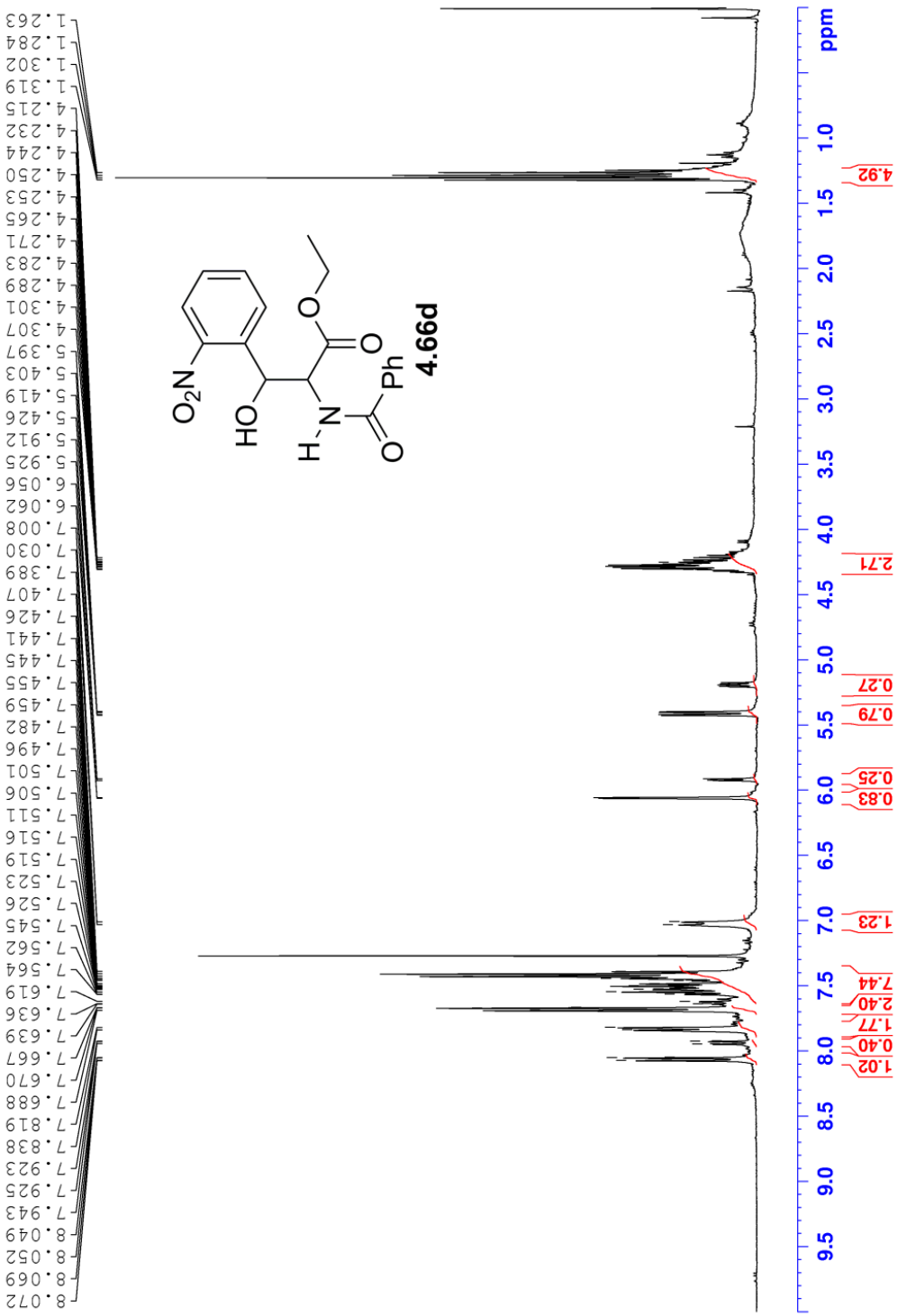
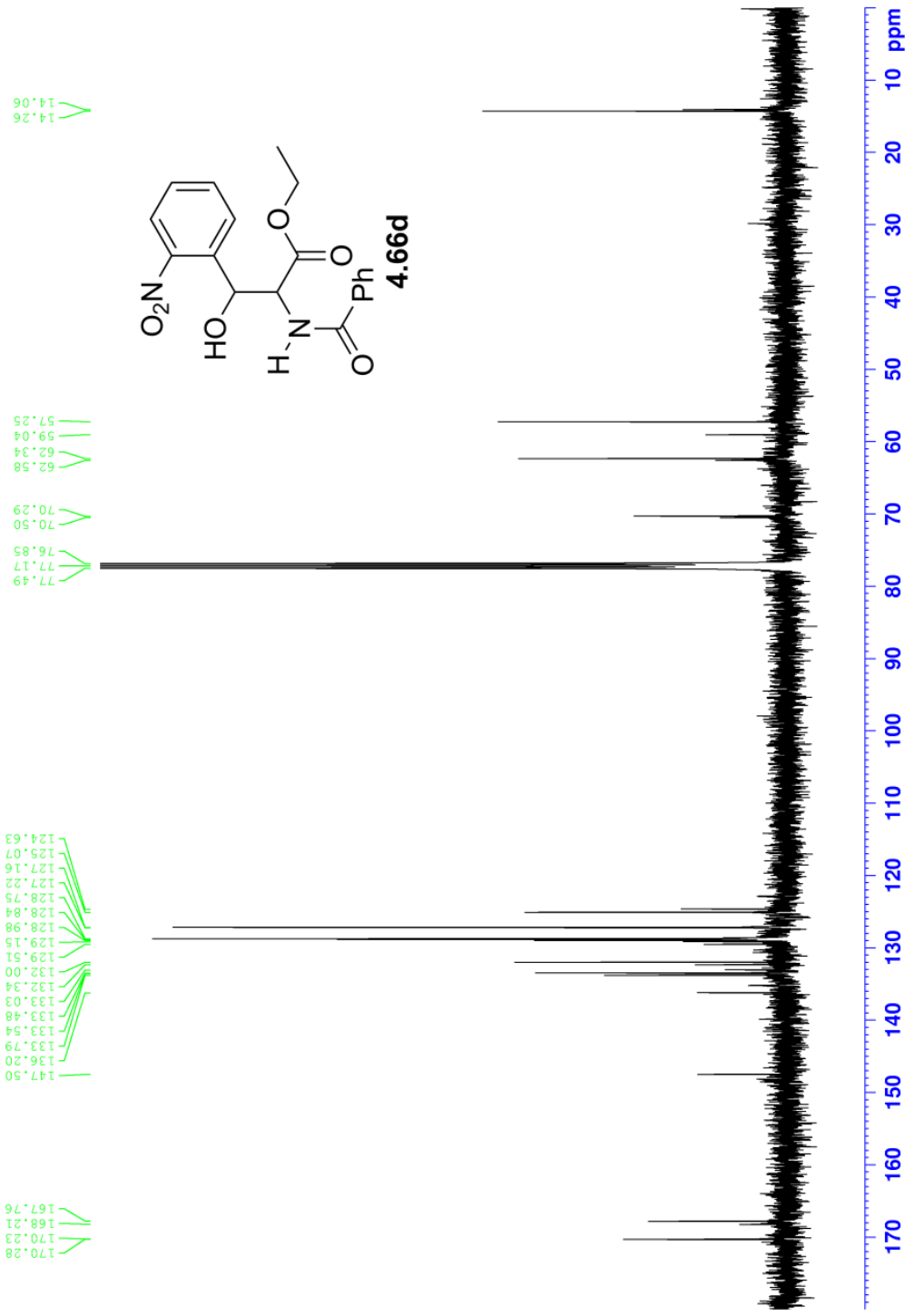
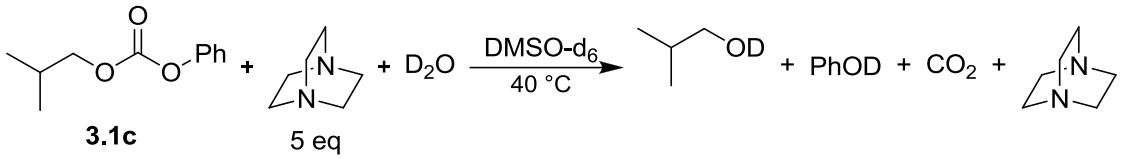
30
20
10
ppm


4.66d
O2N
HO
H
N
O
Ph
O
O
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
4.92
2.71
0.27
0.79
0.83
0.25
1.23
7.44
2.40
1.77
0.40
1.02


4.66d
14.06
14.26
57.25
59.04
62.34
62.58
70.29
70.50
76.85
77.17
77.49
124.63
125.07
127.16
127.22
128.75
128.84
128.98
129.15
129.51
132.00
132.34
133.03
133.48
133.54
133.79
136.20
147.50
167.76
168.21
170.23
170.28
ppm

APPENDIX II

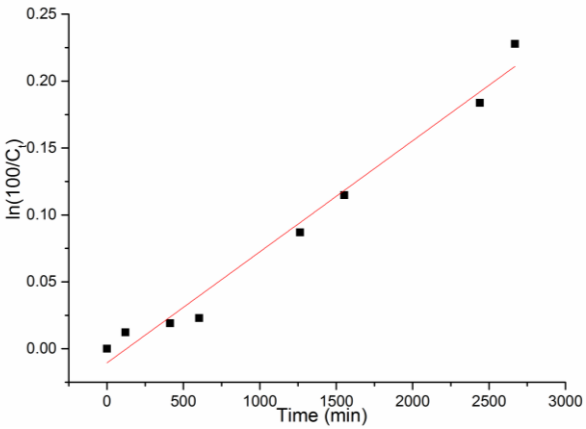
KINETIC PLOTS



3.1c 5 eq

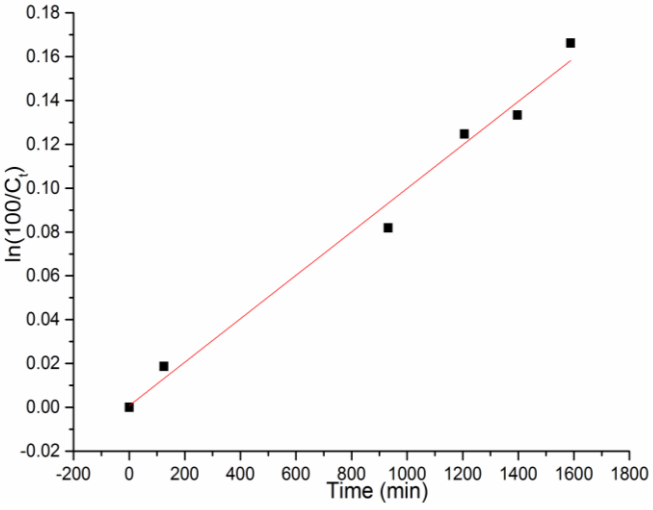
Run 1: $k = 8.3 \times 10^{-5}$/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
120	98.8	0.012
412	98.1	0.020
603	97.7	0.023
1263	91.7	0.090
1553	89.2	0.114
2440	83.2	0.184
2669	79.6	0.228



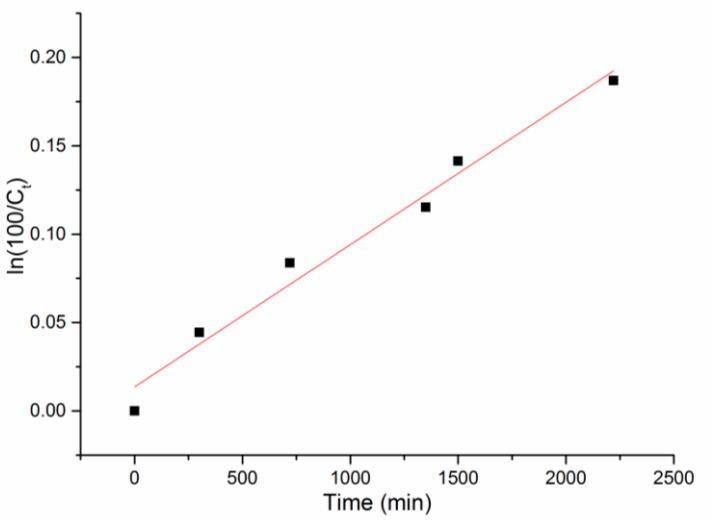
Run 2: $k = 9.9 \times 10^{-5}$/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
125	98.2	0.019
932	92.1	0.082
1206	88.3	0.125
1397	87.5	0.133
1588	84.7	0.166

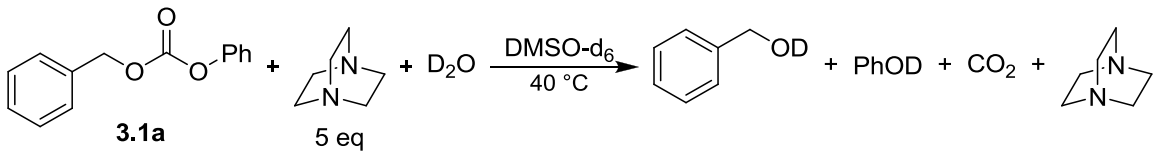


Run 3: k = 8.1×10^{-4}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
300	94.3	0.044
720	92.0	0.083
1350	89.1	0.115
1500	86.8	0.141
2220	82.9	0.187

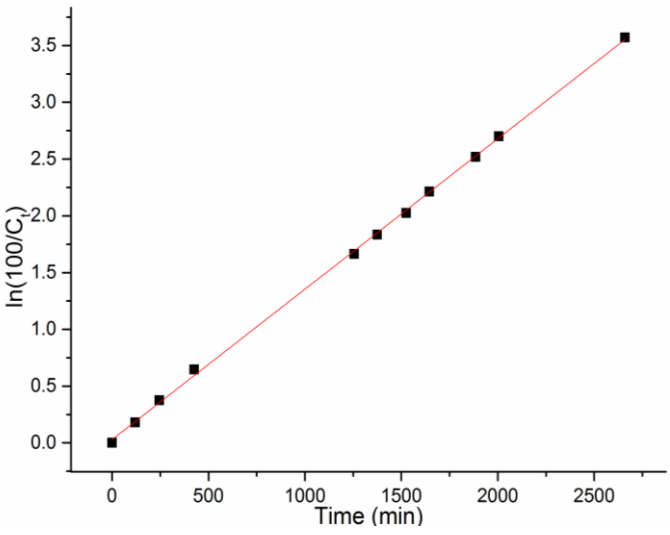


Average: k = 8.8×10^{-5}/min
Standard deviation = 8.1×10^{-6}



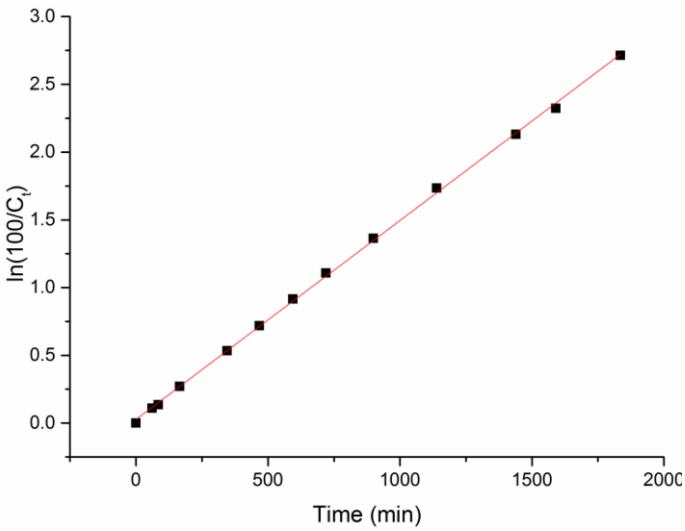
Run 1: k = 1.3×10^{-3}/min

Time(min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
120	83.6	0.18
245	68.7	0.38
425	52.4	0.65
1255	18.9	1.66
1375	16.0	1.83
1525	13.2	2.02
1645	10.9	2.21
1885	8.1	2.51
2005	6.7	2.70
2660	2.8	3.57



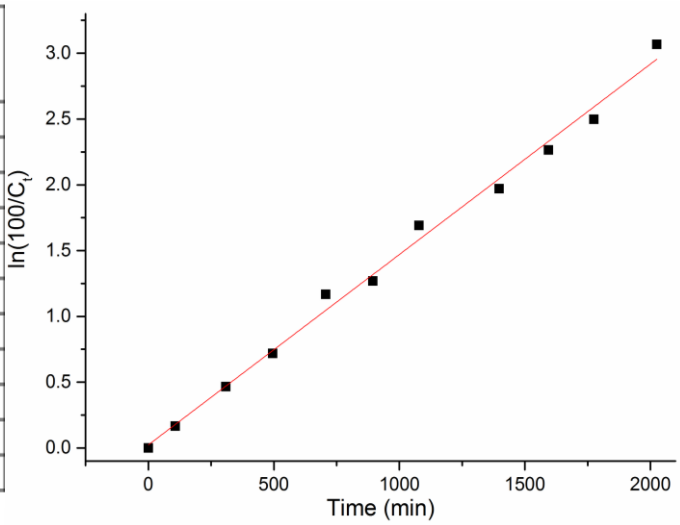
Run 2: k = 1.5×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
61	89.5	0.11
85	87.3	0.14
165	76.3	0.27
345	58.6	0.53
467	48.8	0.72
594	40.0	0.92
719	33.0	1.11
899	25.5	1.36
1139	17.6	1.73
1439	11.9	2.13
1591	9.8	2.32
1835	6.6	2.71

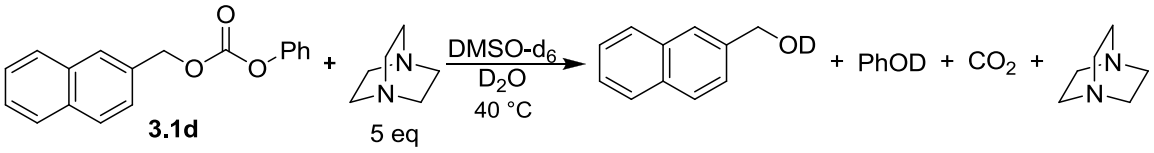


Run 3: k = 1.5×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
107	84.7	0.17
309	62.7	0.47
495	48.8	0.72
706	31.1	1.17
894	28.1	1.27
1078	18.4	1.69
1397	13.9	1.97
1594	10.4	2.27
1775	8.2	2.50
2025	4.6	3.07

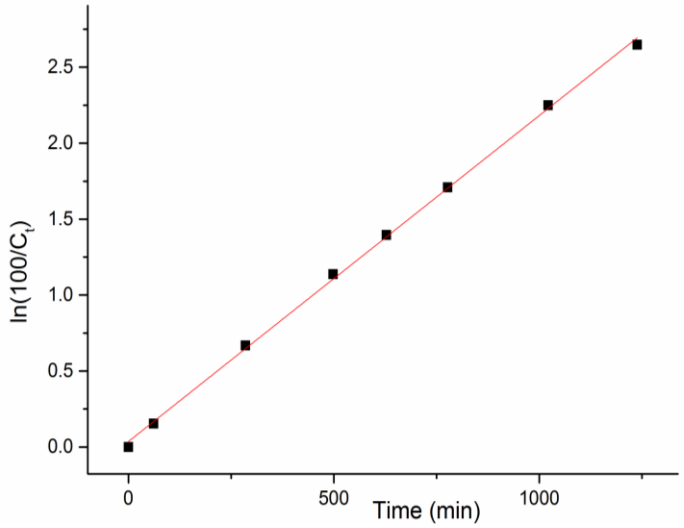


Average: k = 1.4×10^{-3}/min
Standard deviation = $6.2\times10^{-}$



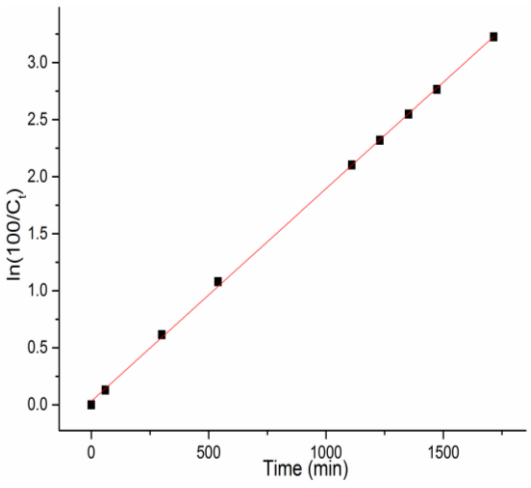
Run 1: k = 2.1×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
61	85.8	0.15
285	51.2	0.67
498	32.0	1.14
628	24.7	1.40
777	18.1	1.71
1022	10.5	2.24
1239	7.1	2.65



Run 2: k = 1.9×10^{-3}/min

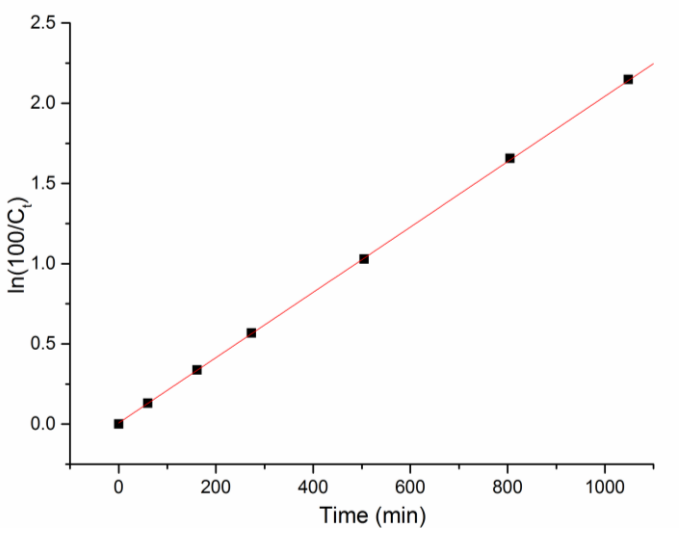
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
60	87.9	0.13
300	54.2	0.61
540	34.0	1.08
1110	12.2	2.10
1230	9.8	2.32
1352	7.8	2.55
1473	6.2	2.77
1715	4.0	3.23

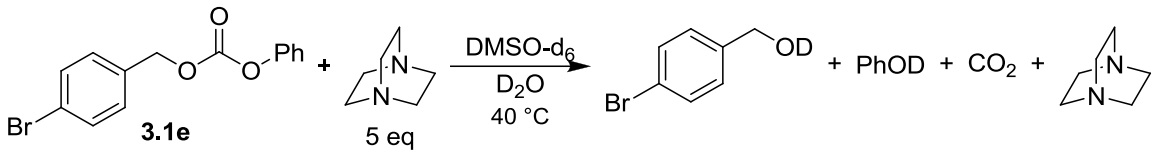


Run 3: k = 2.0×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
60	87.7	0.13
161	71.4	0.34
273	56.7	0.57
505	35.7	1.03
805	19.1	1.66
1048	11.7	2.15
1138	9.9	2.31

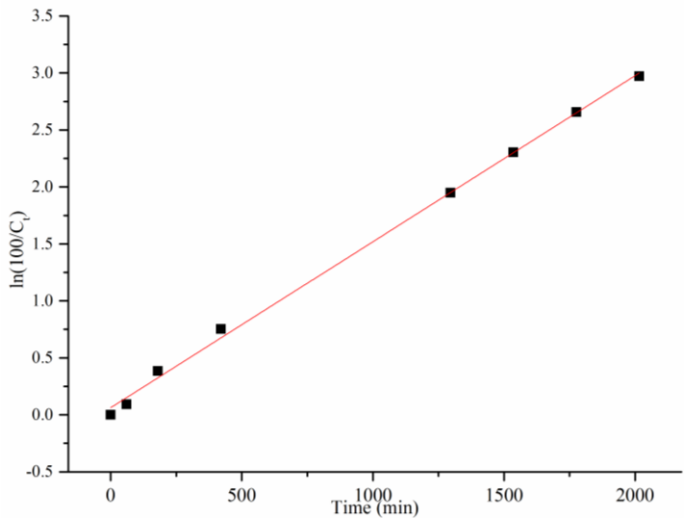
Average: k = 2.0×10^{-3}/min
Standard deviation = 9.9×10^{-5}





Run 1: k = 1.5×10^{-3}/min

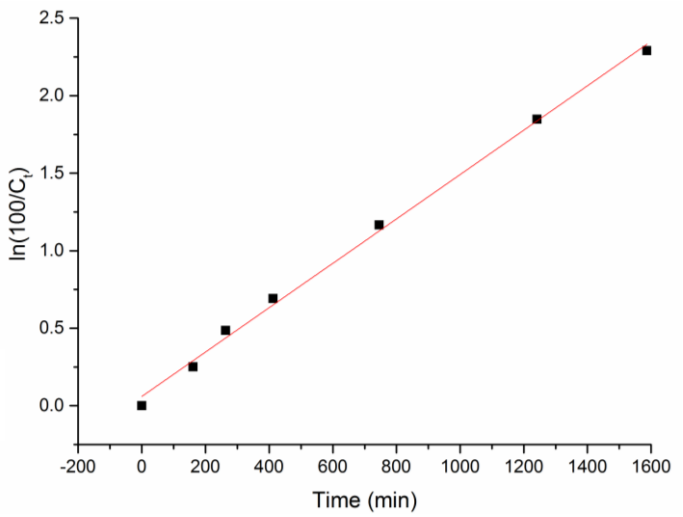
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
60	91.1	0.09
180	68.1	0.38
420	47.1	0.75
1296	14.2	1.95
1536	10.0	2.30
1776	7.0	2.66
2016	5.1	2.97

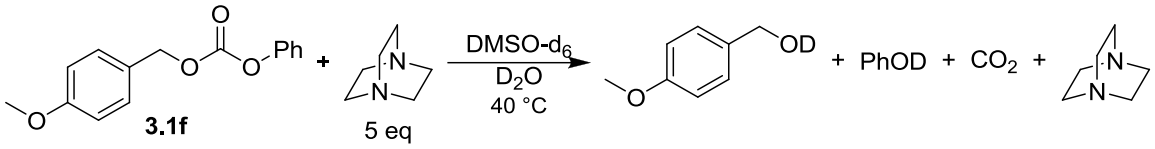


Run 3: k = 1.4×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
161	77.8	0.25
263	61.5	0.49
412	50.1	0.69
746	31.2	1.17
1242	15.8	1.85
1587	10.1	2.29

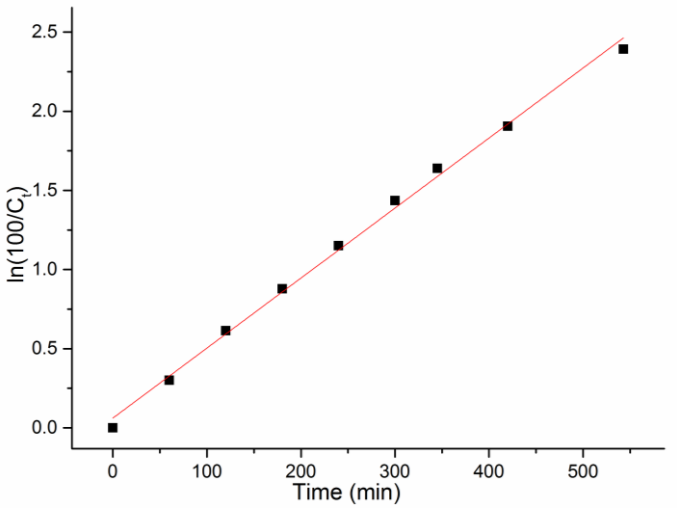
Average: k = 1.5×10^{-3}/min
Standard deviation = 6.5×10^{-5}





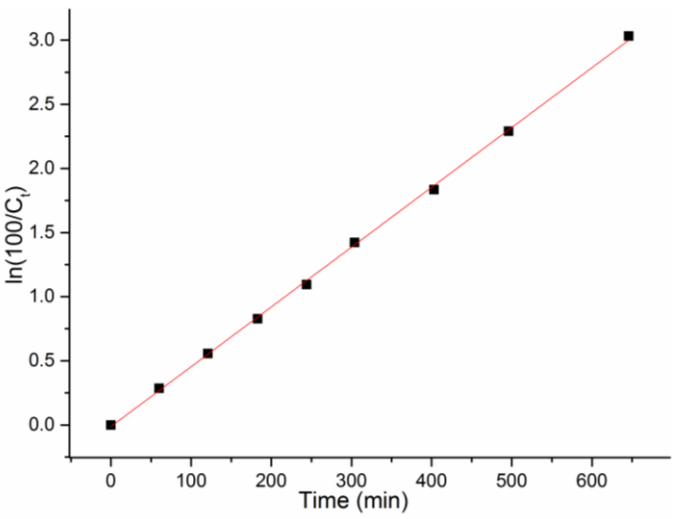
Run 1: k = 4.4×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
60	74.0	0.30
120	54.1	0.61
180	41.6	0.88
240	31.6	1.15
300	23.8	1.44
345	19.4	1.64
420	14.9	1.91
543	9.1	2.40



Run 3: $k = 4.7\times10^{-3}$/min

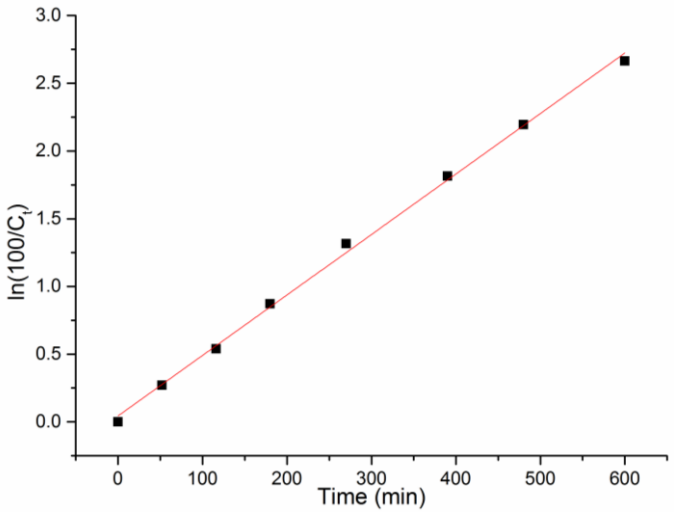
Time (min)	% Carbonate Unreacted (C_t)	$\ln(100/C_t)$
0	100	0
60	75.1	0.29
121	57.3	0.56
183	43.7	0.83
244	33.5	1.09
304	24.1	1.42
403	16.0	1.84
496	10.1	2.29
646	4.8	3.03

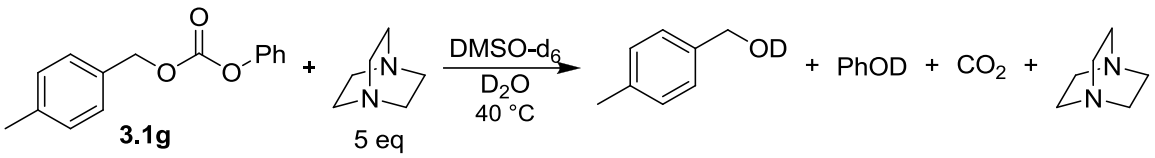


Run 3: $k = 4.5\times10^{-}$/min

Time (min)	% Carbonate Unreacted (C_t)	$\ln(100/C_t)$
0	100	0
52	76.2	0.27
116	58.3	0.54
180	41.8	0.87
270	26.8	1.32
390	16.3	1.81
480	11.1	2.19
600	7.0.	2.66

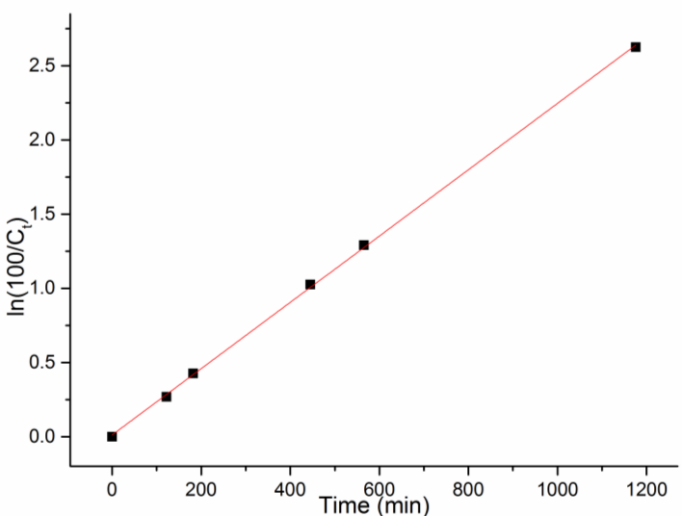
Average: $k = 4.5\times10^{-3}$/min
Standard deviation = 1.0×10^{-4}





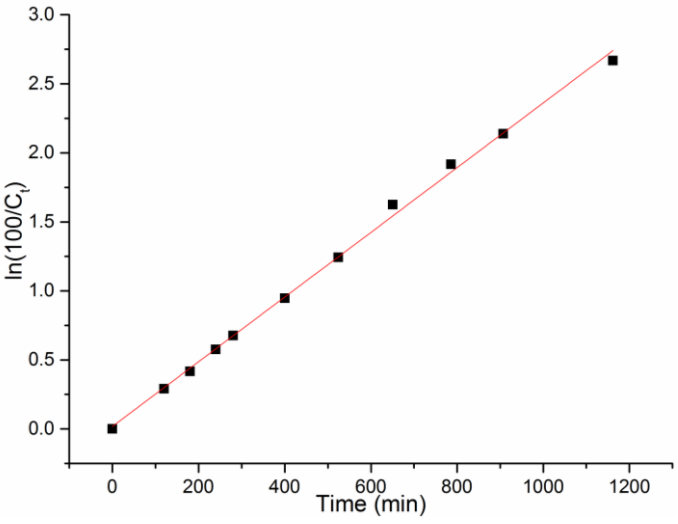
Run 1: k = 2.2×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
122	76.4	0.27
182	65.3	0.43
445	35.8	1.03
565	27.5	1.29
1176	7.2	2.62



Run 2: k = 2.3×10^{-3}/min

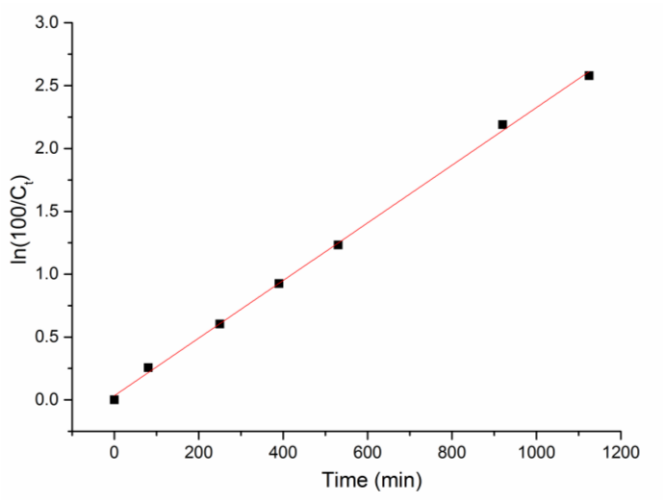
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
120	74.8	0.29
180	65.9	0.42
240	56.2	0.58
280	50.9	0.68
400	38.8	0.95
524	28.8	1.24
651	19.7	1.62
786	14.7	1.92
907	11.8	2.14
1162	6.9	2.67

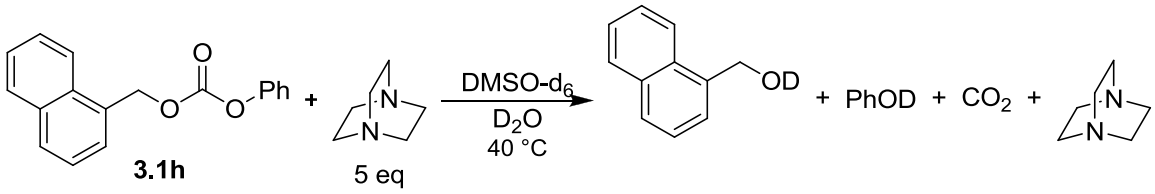


Run 3: k = 2.3×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
80	77.4	0.26
250	54.7	0.60
390	39.6	0.93
530	29.2	1.23
920	11.2	2.19
1125	7.6	2.58

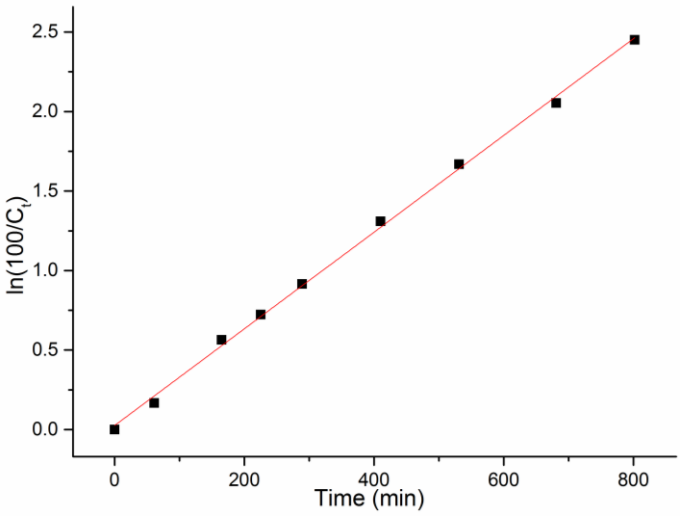
Average: k = 2.3×10^{-3}/min
Standard deviation = 4.9×10^{-5}





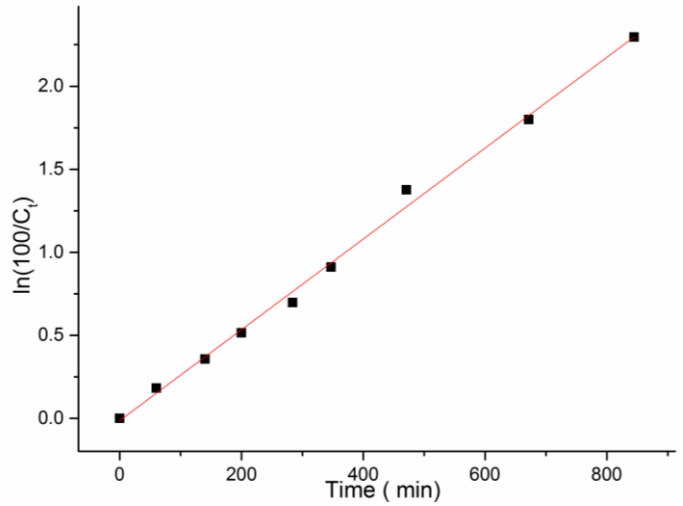
Run 1: k = 3.0×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
61	84.7	0.17
165	56.9	0.56
225	48.5	0.72
289	40.0	0.92
410	27.0	1.31
531	18.8	1.67
681	12.8	2.05
802	8.6	2.45



Run 2: k = 2.7×10^{-3}/min

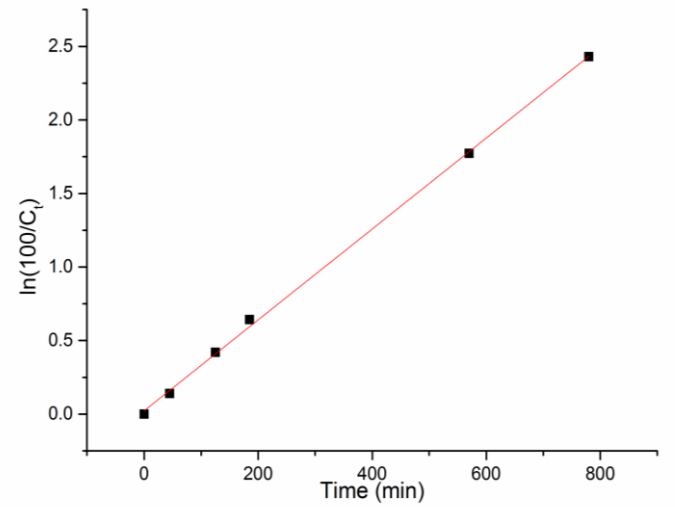
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
60	83.34	0.18
140	70	0.36
200	59.74	0.52
284	49.8	0.70
347	40.2	0.91
471	25.26	1.38
672	16.55	1.80
845	10.07	2.30

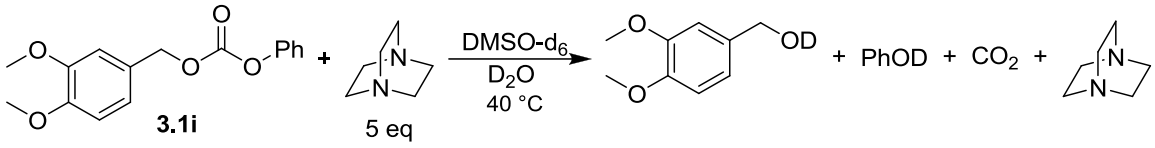


Run 3: k = 3.1×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
45	87.0	0.14
125	65.7	0.42
185	52.6	0.64
570	17.0	1.77
780	8.8	2.43

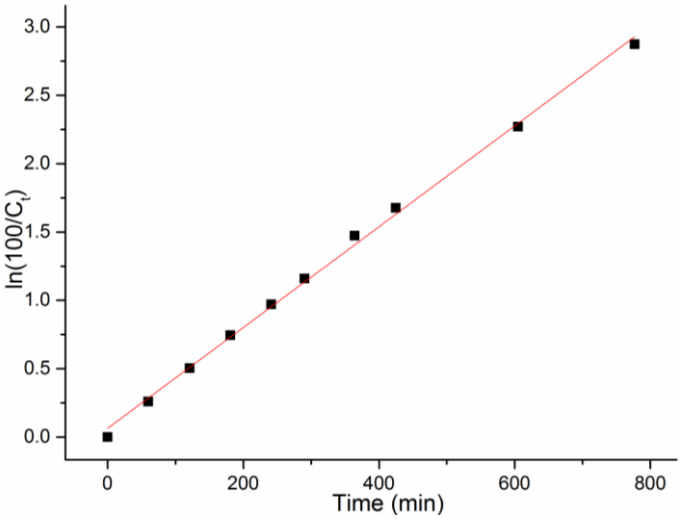
Average: k = 2.9×10^{-3}/min
Standard deviation = 1.6×10^{-4}





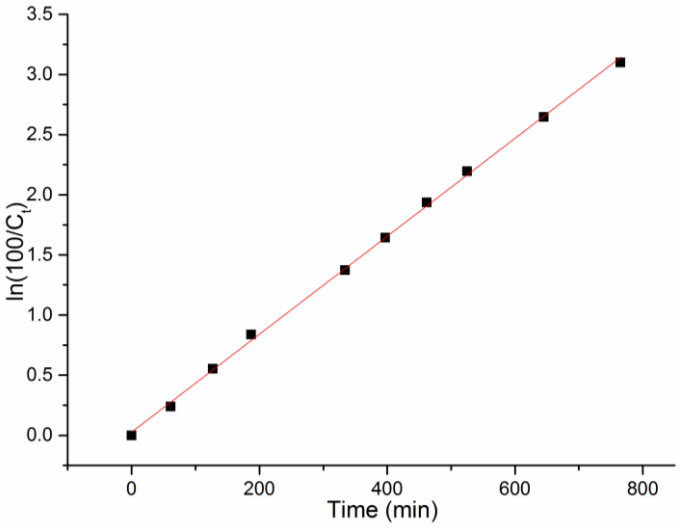
Run 1: k = 3.7×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
60	77.2	0.26
121	60.4	0.50
181	47.5	0.75
241	37.9	0.97
290	31.4	1.16
364	22.9	1.47
425	18.7	1.68
605	10.3	2.27
777	5.7	2.87



Run 2: k = 4.1×10^{-3}/min

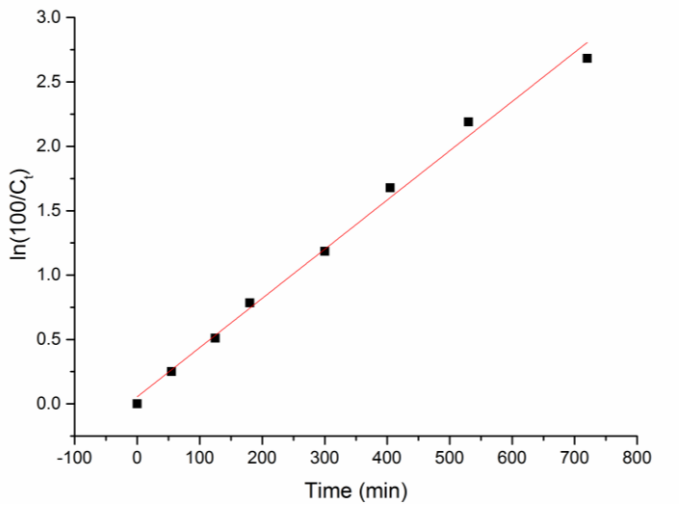
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
61	78.8	0.24
127	57.5	0.55
187	43.2	0.84
334	25.3	1.37
397	19.3	1.64
462	14.4	1.94
525	11.1	2.20
645	7.1	2.65
765	4.5	3.10

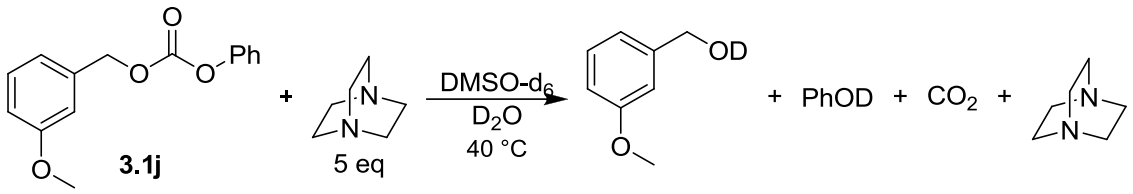


Run 3: k = 3.8×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
55	77.8	0.25
125	60.0	0.51
180	45.6	0.78
300	30.6	1.19
405	18.7	1.68
530	11.2	2.19
720	6.8	2.68

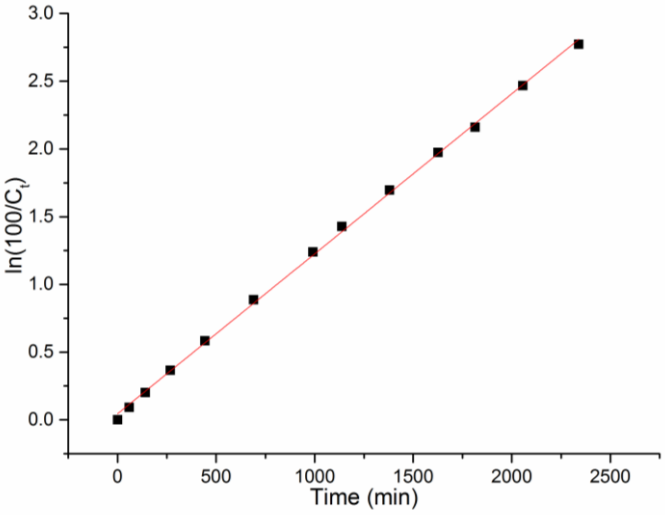
Average: k = 3.9×10^{-3}/min
Standard deviation = 1.5×10^{-4}





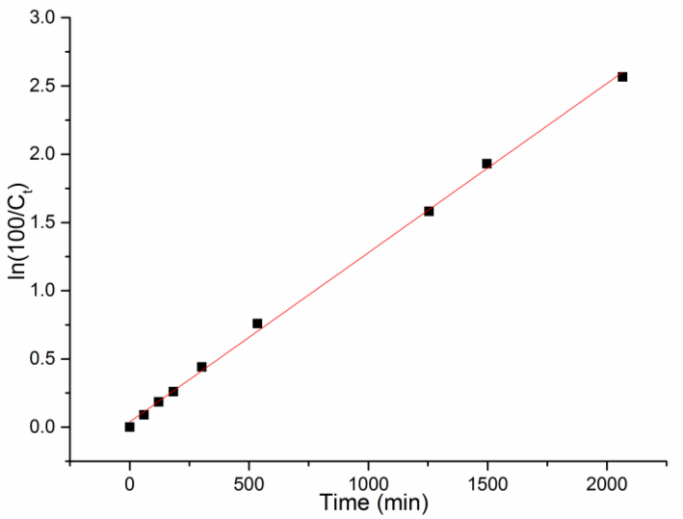
Run 1: k = 1.2×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
60	91.3	0.09
141	81.8	0.20
267	69.3	0.36
443	55.8	0.58
690	41.2	0.89
991	28.9	1.24
1138	24.0	1.43
1380	18.3	1.70
1626	13.9	1.97
1814	11.5	2.16
2056	8.5	2.47
2340	6.2	2.77



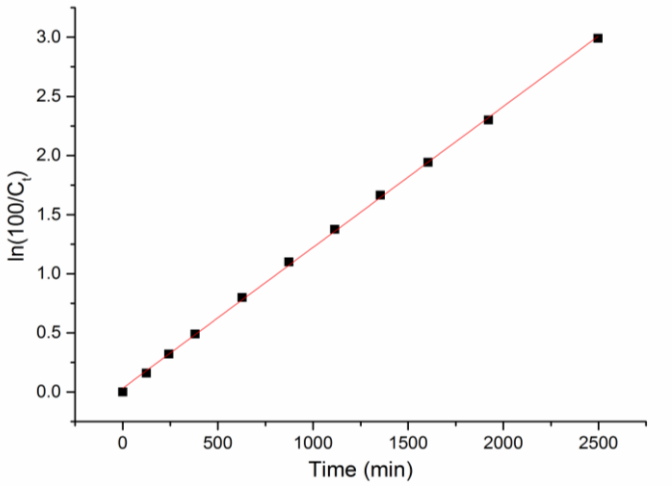
Run 2: k = 1.2 × 10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
60	91.4	0.09
122	83.1	0.18
183	77.1	0.26
303	64.3	0.44
536	46.9	0.76
1255	20.6	1.58
1497	14.5	1.93
2066	7.7	2.57

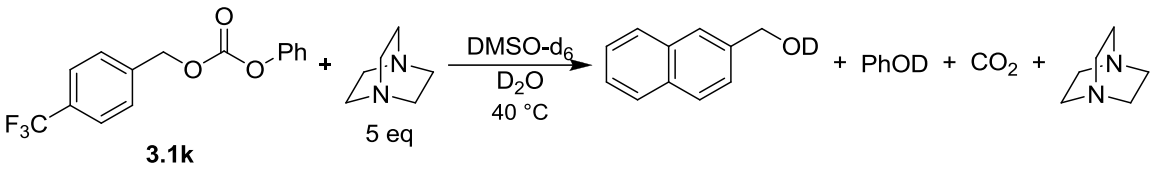


Run 3: k = 1.2×10^{-3}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
124	85.2	0.16
243	72.6	0.32
381	61.3	0.49
628	45.0	0.80
873	33.3	1.10
1114	25.3	1.38
1354	18.9	1.66
1605	14.3	1.94
1922	10.0	2.30
2498	5.0	3.00

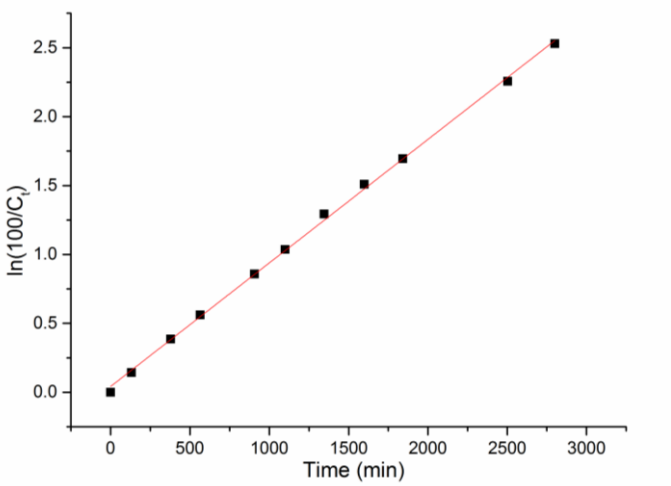


Average: k = 1.2×10^{-3}/min



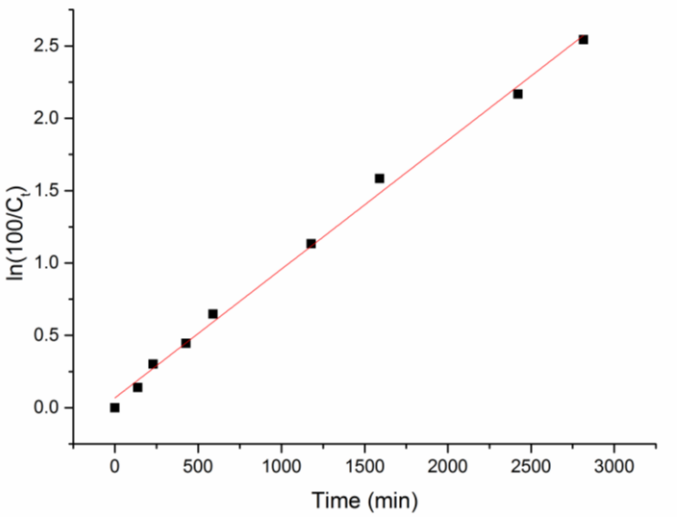
Run 1: k = 9.0×10^{-4}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
131	86.6	0.14
378	68.0	0.39
564	57.1	0.56
907	42.4	0.86
1100	35.5	1.04
1346	27.4	1.29
1600	22.1	1.51
1842	18.4	1.69
2504	10.5	2.26
2801	8.0	2.53



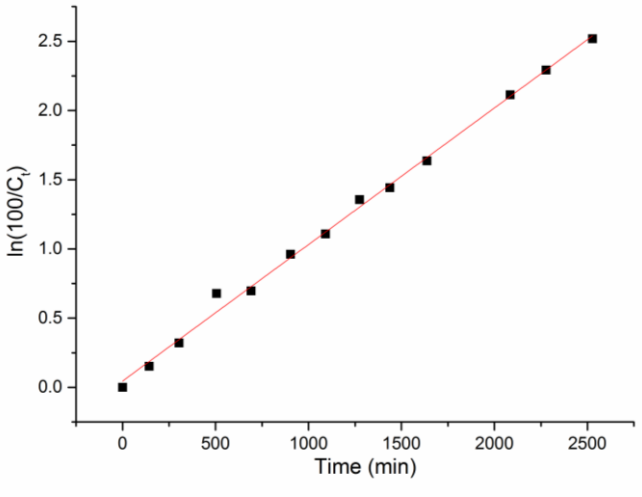
Run 2: k = 8.9×10^{-4}/min

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
138	86.9	0.14
229	73.9	0.30
427	64.1	0.44
589	52.4	0.65
1179	32.2	1.13
1591	20.5	1.58
2421	11.4	2.17
2815	7.9	2.54

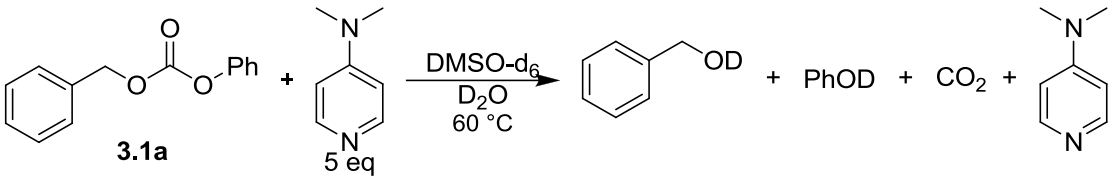


Run 3: $k = 9.9\times10^{-4}$/min

Time (min)	% Carbonate Unreacted (C_t)	$\ln(100/C_t)$
0	100	0
144	85.9	0.15
304	72.6	0.32
506	50.8	0.68
692	49.8	0.70
903	38.3	0.96
1091	33.0	1.11
1275	25.8	1.36
1438	23.6	1.44
1638	19.5	1.64
2085	12.1	2.11
2278	10.1	2.29
2528	8.7	2.52

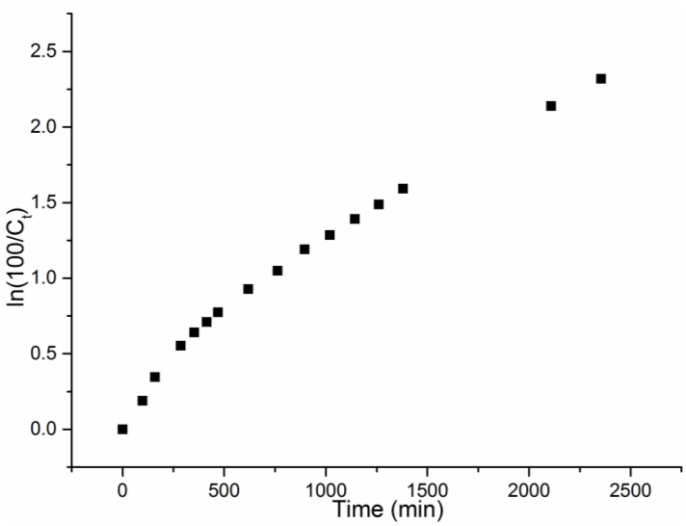


Average: $k = 9.3\times10^{-4}$/min
Standard deviation = 4.1×10^{-5}



Run 1

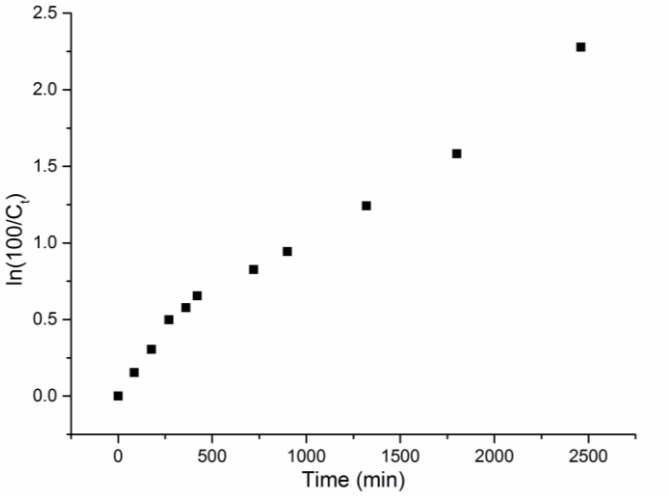
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
98	82.8	0.19
160	70.8	0.35
286	57.6	0.55
353	52.7	0.64
414	49.2	0.71
469	46.1	0.77
619	39.6	0.93
763	35.0	1.05
896	30.4	1.19
1020	27.6	1.29
1143	24.9	1.39
1261	22.6	1.49
1380	20.3	1.59
2109	11.8	2.14
2355	9.8	2.32



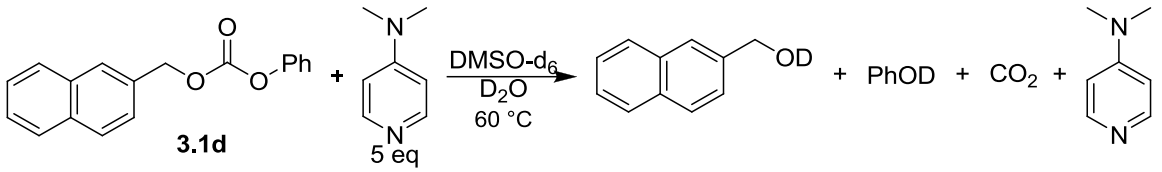
Time (approx. 90% completion) = 39 h (90%)

Run 2

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
86	85.7	0.15
177	73.7	0.30
270	60.8	0.50
360	56.1	0.58
420	52.0	0.65
720	43.8	0.83
900	38.9	0.94
1320	28.8	1.24
1800	20.6	1.59
2460	10.2	2.28

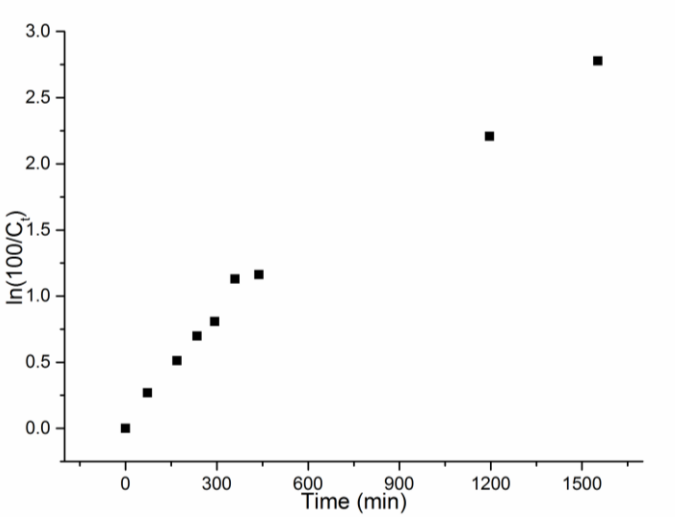


Time (approx. 90% completion) = 41 h (90%)



Run 1

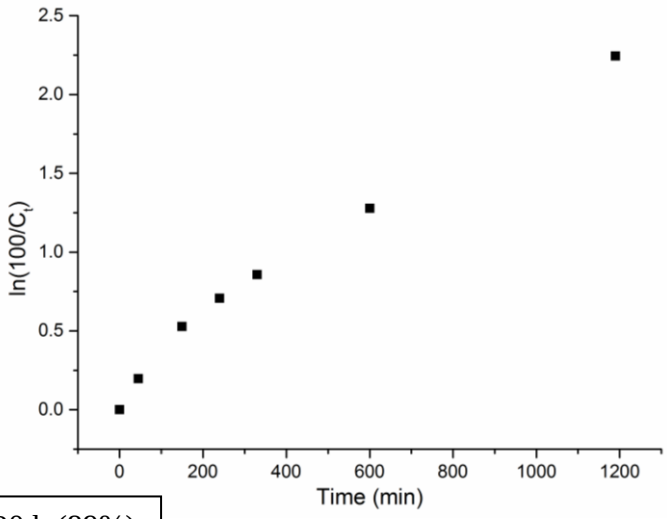
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
72	76.4	0.27
169	59.9	0.51
235	49.7	0.70
293	44.6	0.81
360	32.3	1.13
438	31.3	1.16
1196	11.0	2.21
1552	6.2	2.78



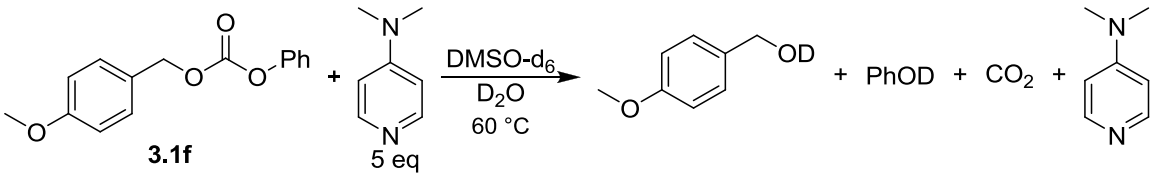
Time (approx. 90% completion) = 20 h (89%)

Run 2

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
45	82.0	0.20
150	58.9	0.53
240	49.3	0.71
330	42.4	0.86
600	27.9	1.28
1190	10.6	2.24

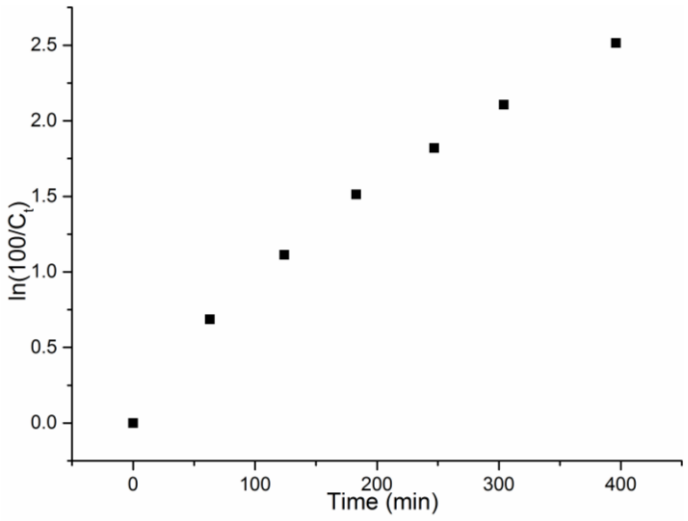


Time (approx. 90% completion) = 20 h (89%)



Run 1

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
63	50.4	0.69
124	32.8	1.11
183	22.0	1.51
247	16.2	1.82
304	12.2	2.11
396	8.1	2.51
432	6.5	2.74

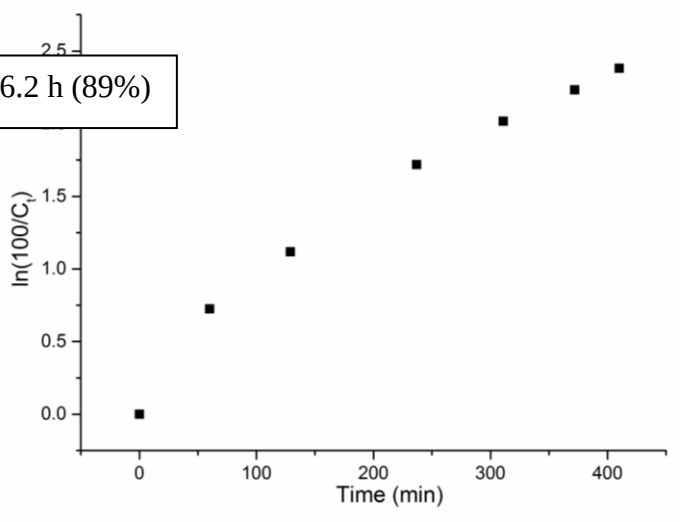


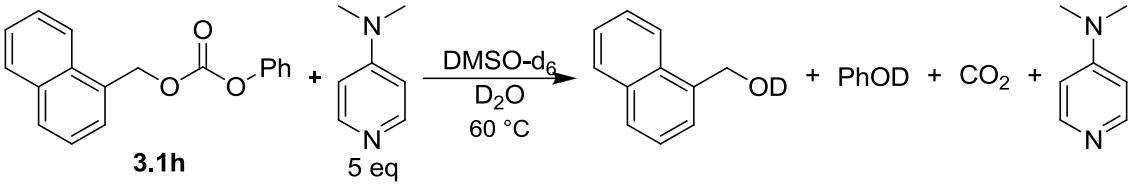
Time (approx. 90% completion) = 6.5 h (92%)

Run 2

	% Carbonate	
60	48.4	0.73
129	32.7	1.12
237	17.9	1.72
311	13.3	2.02
372	10.7	2.23
410	9.2	2.38

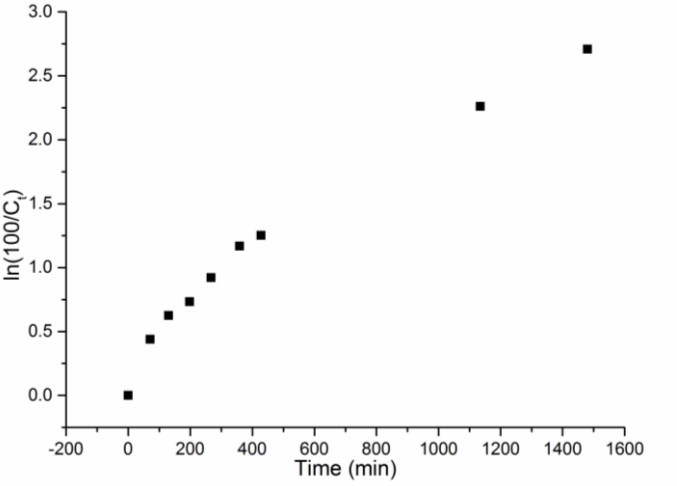
Time (approx. 90% completion) = 6.2 h (89%)





Run 1

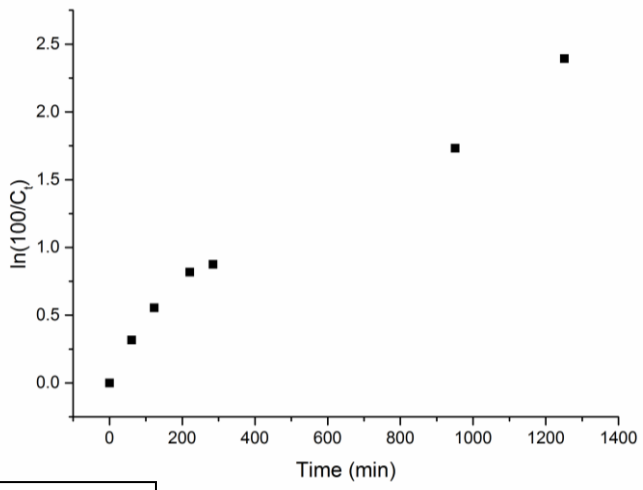
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
71	64.4	0.44
130	53.5	0.63
198	48.1	0.73
267	39.8	0.92
359	31.0	1.17
428	28.6	1.25
1135	10.4	2.26
1480	6.7	2.71



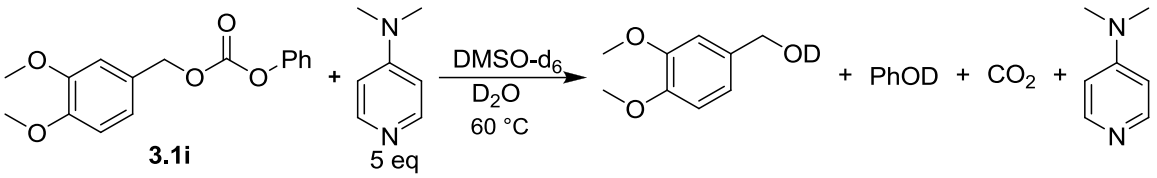
Time (approx. 90% completion) = 19 h (90%)

Run 2

Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
61	72.9	0.32
123	57.5	0.55
221	44.1	0.82
285	41.7	0.87
951	17.7	1.73
1251	9.1	2.39

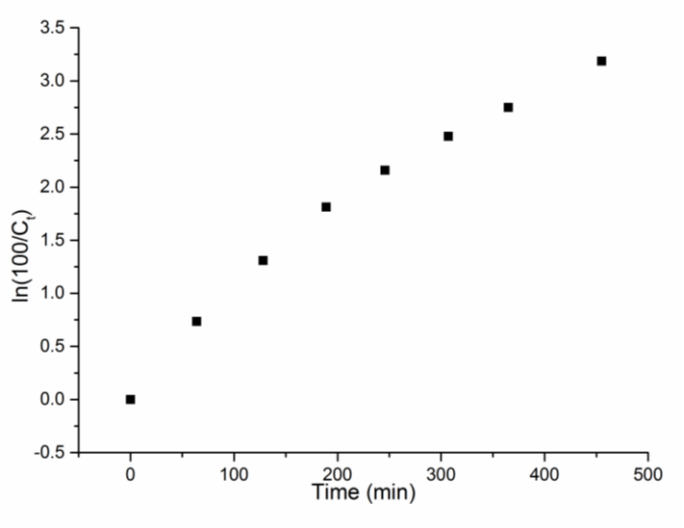


Time (approx. 90% completion) = 21 h (91%)



Run 1

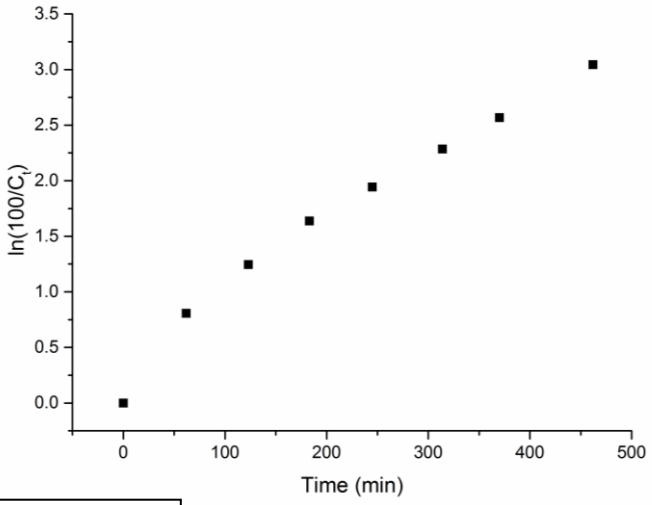
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
64	48.0	0.74
128	27.0	1.31
189	16.3	1.81
246	11.6	2.16
307	8.4	2.48
365	6.4	2.75
455	4.1	3.19



Time (approx. 90% completion) = 5 h (92%)

Run 2

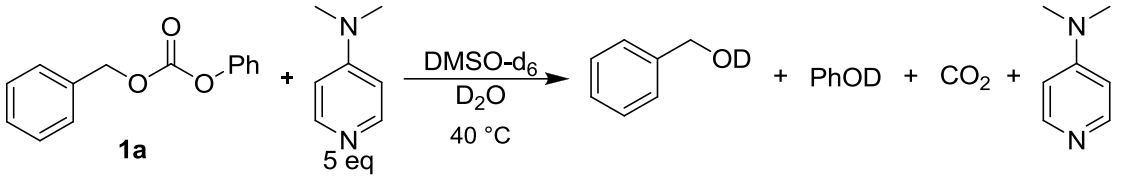
Time (min)	% Carbonate Unreacted (C_t)	ln(100/C_t)
0	100	0
62	44.7	0.81
123	28.8	1.25
183	19.4	1.64
245	14.3	1.94
314	10.2	2.28
370	7.7	2.57
462	4.8	3.04



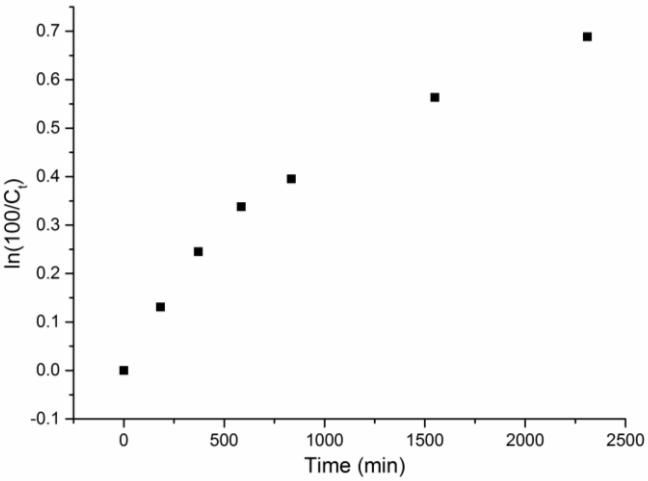
Time (approx. 90% completion) = 5 h (90%)

Hydrolysis of benzyl-phenyl carbonate with DMAP at 40 °C:

The hydrolysis of benzyl-phenyl carbonate with DMAP was performed at 40 °C using the procedure shown in the experimental section. The half life for this reaction is ~39 hrs as can be seen from the data (*Vide Infra*). For the hydrolysis carried out with DABCO under otherwise identical conditions the half life is 8 hours. This reduction in half life is more than what would be expected from the presence of a second nitrogen group in DABCO.



Time (min)	% Carbonate Unreacted (C_t)	$\ln(100/C_t)$
0	100	0
183	87.7	0.13
372	78.3	0.25
585	71.3	0.34
835	67.4	0.40
1550	56.9	0.56
2310	50.2	0.69

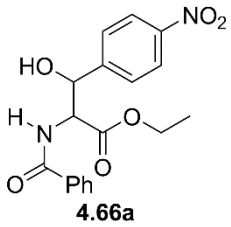


APPENDIX III

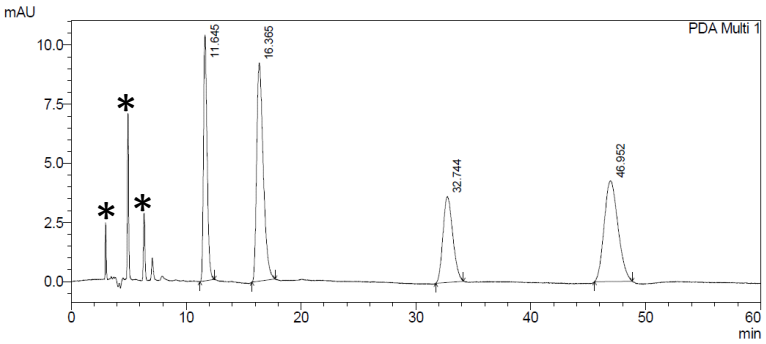
HPLC TRACES

Column: Phenomenex Cellulose1 (hexanes:2-propanol 88:12, 1.0 mL/min)

Racemic sample



4.66a



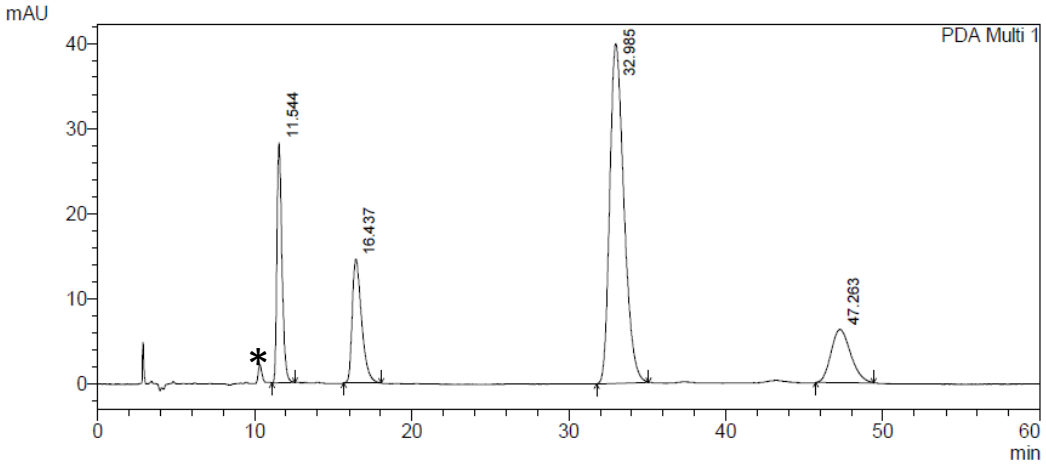
PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.645	227574	10409	19.491	37.797
2	16.365	368922	9230	31.596	33.516
3	32.744	215849	3636	18.486	13.204
4	46.952	355266	4264	30.427	15.484
Total		1167611	27539	100.000	100.000

*Impurities

Chiral Sample



1 PDA Multi 1/254nm 4nm

PeakTable

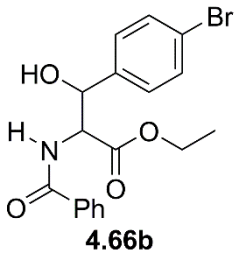
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.544	633114	28185	14.798	31.736
2	16.437	603111	14548	14.096	16.381
3	32.985	2500862	39837	58.452	44.856
4	47.263	541374	6241	12.653	7.028
Total		4278460	88810	100.000	100.000

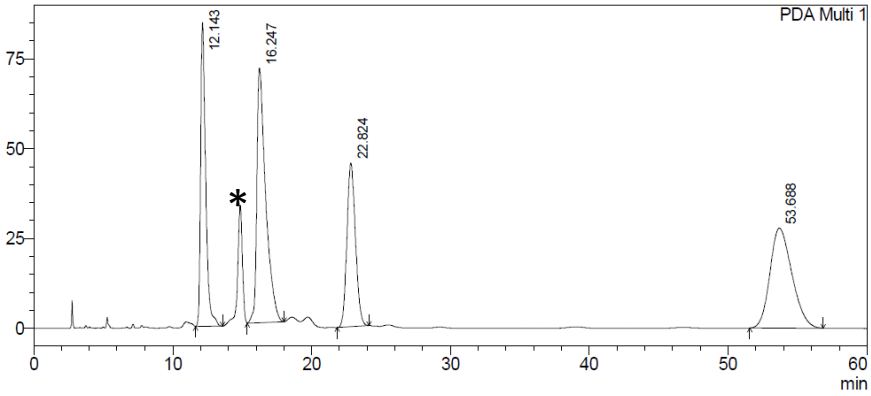
*Impurities

Column: Phenomenex Cellulose1 (hexanes:2-propanol 90:10, 1.0 mL/min)

Racemic sample



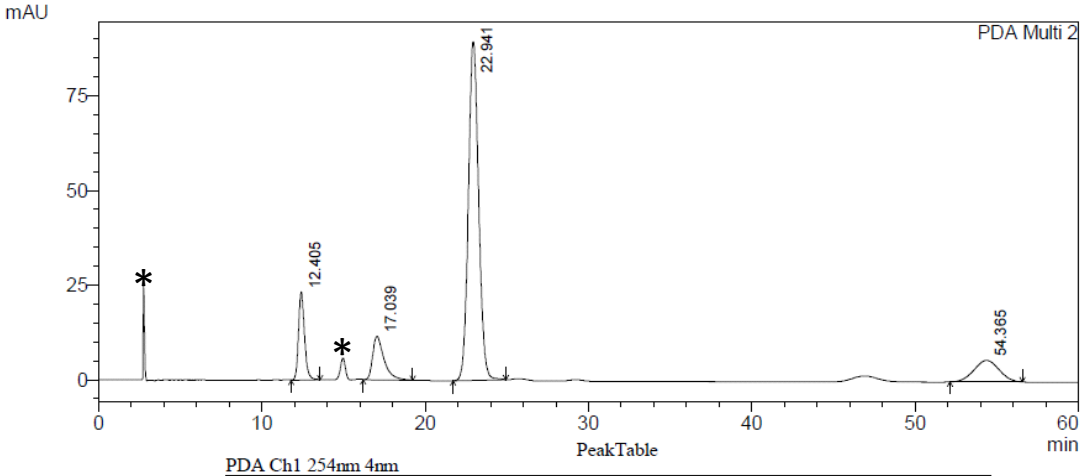
4.66b



Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.143	2145501	84473	20.818	36.941
2	16.247	3147077	70808	30.536	30.965
3	22.824	1951512	45551	18.936	19.920
4	53.688	3061958	27839	29.710	12.174
Total		10306048	228671	100.000	100.000

*Impurities

Chiral sample



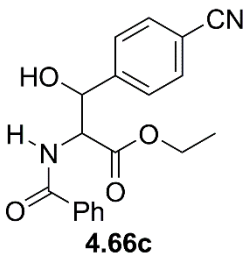
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.396	89373	3578	11.108	18.601
2	17.058	50463	1235	6.272	6.420
3	22.942	592079	13751	73.586	71.488
4	54.354	72694	672	9.035	3.491
Total		804610	19236	100.000	100.000

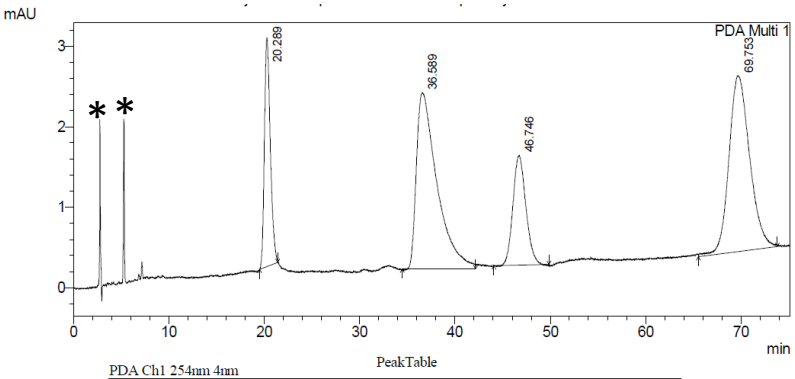
*Impurities

Column: Phenomenex Cellulose1 (hexanes:2-propanol 90:10, 1 mL/min

Racemic sample



4.66c



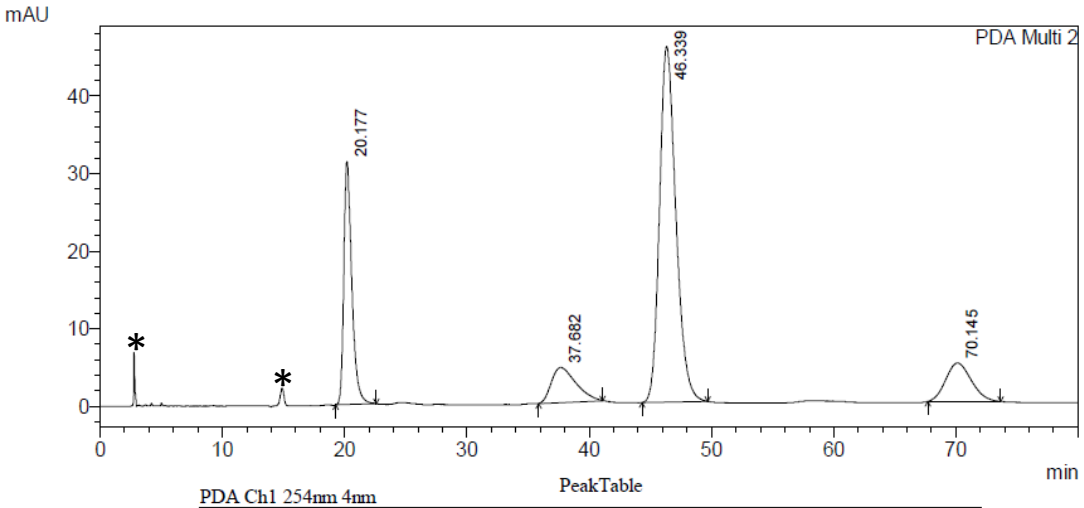
PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.289	122473	2844	13.473	33.114
2	36.589	327936	2190	36.075	25.496
3	46.746	128146	1368	14.097	15.927
4	69.753	330495	2187	36.356	25.463
Total		909051	8588	100.000	100.000

*Impurities

Chiral sample



PeakTable

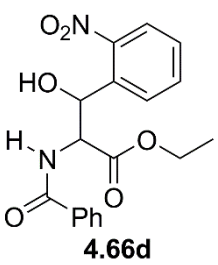
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.174	272689	6234	21.708	37.883
2	37.806	82304	549	6.552	3.333
3	46.339	826226	9114	65.773	55.382
4	70.149	74958	560	5.967	3.402
Total		1256178	16457	100.000	100.000

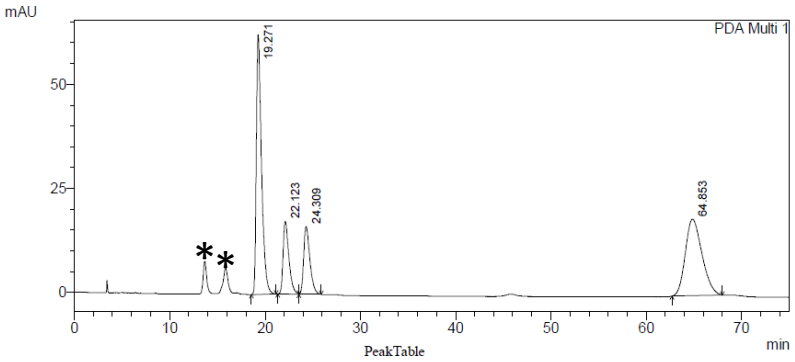
*Impurities

Column: Phenomenex Cellulose1 (hexanes:2-propano 88:12, 0.8 mL/min)

Racemic sample



4.66d

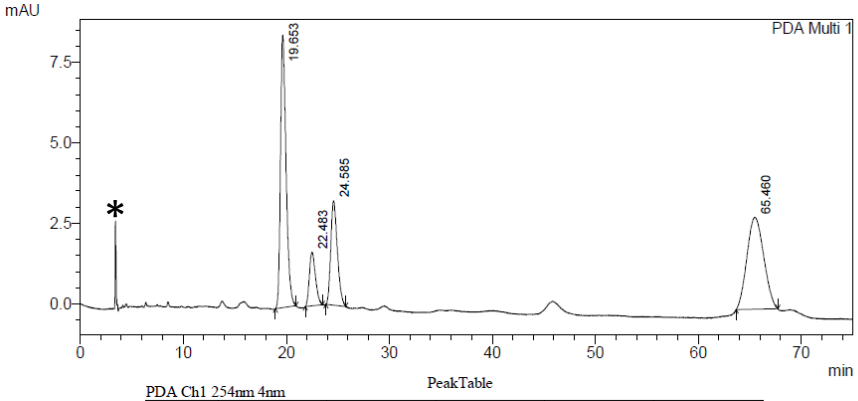


PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.271	2356067	62472	38.818	54.427
2	22.123	736512	17537	12.135	15.279
3	24.309	736604	16334	12.136	14.231
4	64.853	2240290	18439	36.911	16.064
Total		6069473	114781	100.000	100.000

*Impurities

Chiral sample



PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.653	318409	8466	37.234	52.144
2	22.483	68805	1675	8.046	10.315
3	24.585	143804	3239	16.816	19.949
4	65.460	324146	2856	37.905	17.592
Total		855164	16236	100.000	100.000

*Impurities