UNIVERSITY OF CALIFORNIA

Santa Barbara

Conjugate Additions of sp^2 Hybridized Nitrogen Nucleophiles to *ortho*-Quinone Methides

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

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September 2022

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Acknowledgements

First I would like to thank Professor Thomas R. R. Pettus for his guidance throughout my graduate school study. He has given enough room for messing up, trial and errors, as well as how to proceed in research projects. His dedication in teaching, especially the way he gives challenges to his students, has impacted my teaching style as well.

I would also like to thank my other committee members, Professor Armen Zakarian, Professor Bruce H. Lipshutz and Professor Lior Sepunaru, for their time and advice. I also thank Dr. Hongjun Zhou for his help in NMR experiments, Dr. Dmitriy Uchenik and Dr. Felix Grun (UCI) for their help in HRMS analysis.

Finally, I thank all the past group members, KC Chen, Derek Yang and Ivan Hernandez, for their help in my research projects. It has been a good exepreince working with them, and I wish them the best for their future career.

Curriculum Vitae

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Publications

1. "Catalytic Asymmetric 1,6-Conjugate Addition of *para*-Quinone Methides: Formation of All-Carbon Quaternary Stereocenters". Wang, Z.; Wong, Y. F.; Sun,* J. *Angew. Chem., Int. Ed.* **2015**, *54*, 13711-13714.

2. "Chiral Phosphoric Acid Catalyzed Asymmetric Addition of Naphthols to para-Quinone Methides" Wong, Y. F.; Wang, Z.; Sun,* J. *Org. Biomol. Chem.* **2016**, *14*, 5751-5754.

3. "A One-Pot Oxidation/Cycloaddition Cascade Synthesis of 2,4-Diaryl Chromans via ortho-Quinone Methides" Wong, Y. F.; Wang, Z.; Hong, X.; Sun,* J. *Tetrahedron* **2016**, *72*, 2748-2751.

4. "Remote Cooperative Group Strategy Enables Ligands for Accelerative Asymmetric Gold Catalysis" Wang, Z.; Nicolini, C.; Hervieu, C.; Wong, Y. F.; Zanoni, G.; Zhang,* L. *J. Am. Chem. Soc.* **2017**, *139* (45), 16064-16067.

5. "Nucleophilic Imines and Electrophilic *o*-Quinone Methides, a Three-Component Assembly of Assorted 3,4-Dihydro-2H-1,3-benzoxazines". Chen, P. †; Wong, Y. F. †; Yang, D.; Pettus,* T. R. R. *Org. Lett*. **2019**, *21*, 19, 7746-7749. († denotes equal contribution)

6. "Enantioselective Additions of Imines to *o*-Quinone Methides" Wong, Y. F.; Pettus,* T. R. R. (manuscript in preparation)

7. "Nucleophilic Addition of 4,5-Dihydrooxazole Derivatives to Base Generated *o*-Quinone Methides; a new four component reaction" Wong, Y. F.; Hernandez, I.; Pettus,* T. R. R. (manuscript in preparation)

8. "Synthesis of Naturally Racemic Marilines A-C through Multi-Component Reactions Involving *o*-QMs and Various Nitrogen Nucleophiles" Wong, Y. F.; Hernandez, I.; Pettus,* T. R. R. (manuscript in preparation)

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Abstract

Conjugate Additions of sp^2 Hybridized Nitrogen Nucleophiles to *ortho*-Quinone Methides

by

Yuk Fai Wong

Ortho-quinone methides (*o*-QMs) are highly reactive electrophiles, which have been well used in chemical synthesis. Our group developed a base-promoted method to generate *o*-QMs *in-situ*. In this thesis, novel conjugate additions of sp^2 hybridized nitrogen nucleophiles towards *o*-QMs will be discussed. In the first part of this presentation, a three-component synthesis of 3,4-dihydro-2H-1,3-benzoxazines is described. This reaction demonstrates an unusual reactivity of imines as nitrogen nucleophiles in the event of C-N bond formation. In the second part, conjugate addition of dihydrooxazoles derivatives is presented. The reaction is believed to proceed through long-lived iminium intermediates. Subsequent stereoelectronically controlled, regioselective hydrolysis generates a variety of benzylic amino-esters as kinetic products. Potential application in synthesis of natural products will be discussed. Lastly, the on-going development of a recoverable chiral auxiliary that enables asymmetric syntheses of bnenzylic amines via benzoxazines is described.

Table of Contents

List of Abbreviations

α = alpha

β = beta

δ = delta/chemical shift

Å = angstrom

Ac = acetyl

Ar = aryl

aq = aqueous

Bn = benzyl

Boc = *tert*-Butyloxycarbonyl

b.p. = boiling point

$CDCl_3$ = deuterated chloroform

CD_2Cl_2 = deuterated dichloromethane

d = doublet

DCE = 1,2-dichloroethane

DCM = dichloromethane

DMAP = 4-dimethylaminopyridine

DMF = *N*,*N*-dimethylformamide

DMS = dimethyl sulfate

DMSO = dimethyl sulfoxide

d.r. = diastereomeric ratio

dppp = 1,3-bis(diphenylphosphino)propane

E = electrophile

e.e. = enantiomeric excess

ESI = electrospray ionization

EVE = ethyl vinyl ether

equiv = equivalents

Et = ethyl

gem = geminal

HRMS = high-resolution mass spectrometry

Im = imidazolyl

i-Pr = isopropyl

LAH = lithium aluminum hydride

m = multiplet

M = molarity

MS = molecular sieves/mass spectrometry

m/z = mass-to-charge ratio

Me = methyl

n-Bu = *n*-butyl

NMR = nuclear magnetic resonance

Nu = nucleophile

o- = *ortho*-

o-QM = *ortho*-quinone methide

p- = *para*-

ppm = parts per million

py = pyridine

Ph = phenyl

q = quartet

quint = quintet

R = alkyl

R_f = retention factor

RT = room temperature

s = singlet

salen = *N,N'*-ethylenebis(salicylimine)

sex = sextet

sept = septet

t = triplet

TBS = *tert*-butyldimethylsilyl

TMOA = trimethyl orthoacetate

Tf = trifluoromethylsulfonyl

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin-layer chromatography

TMEDA = *N,N,N',N'*-tetramethylethylenediamine

t-Bu = *tert*-butyl

TsOH = *p*-toluenesulfonic acid

X = halides

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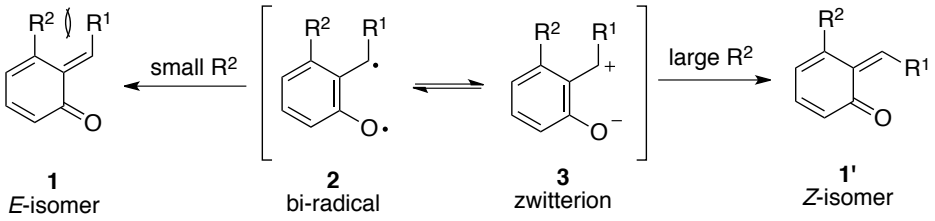
Chapter 1. Background

1.1 Background of *ortho*-Quinone Methides (*o*-QMs)

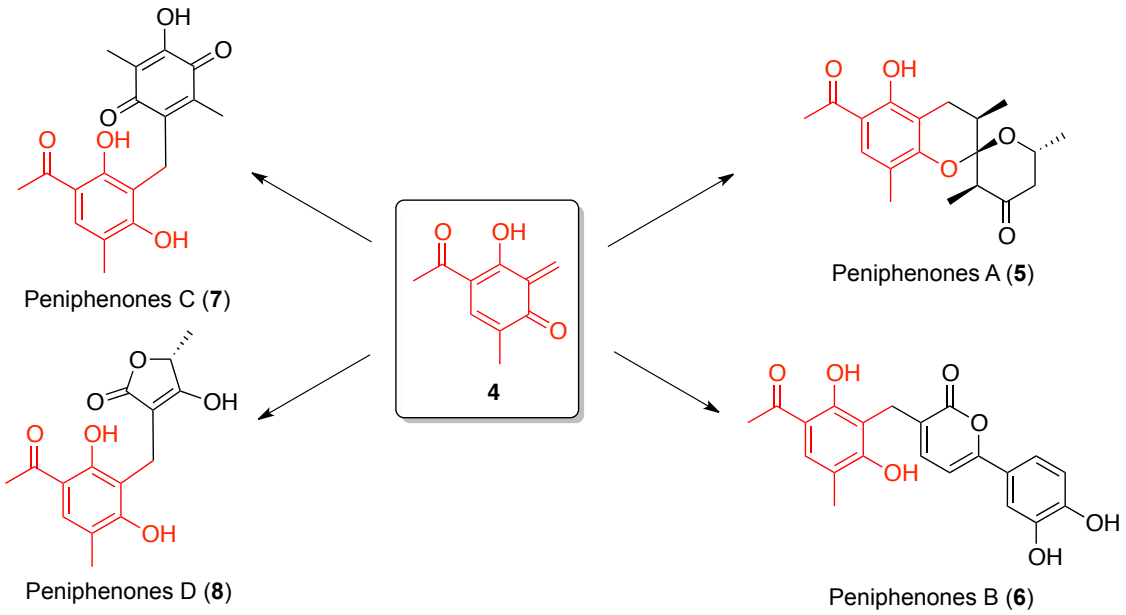
Ortho-quinone methides **1** and **1'** (*o*-QMs) are highly reactive intermediates due to their thermodynamic drive to re-establish aromaticity (Scheme 1). Their bi-radical (**2**) and zwitterionic (**3**) characters allow facile isomerization between their *E* and *Z* isomers **1** and **1'**. Thermodynamic distribution between the two isomers depends on steric hindrance from adjacent group R^2. *E*-isomer is preferred if R^2 is smaller than carbonyl. Larger R^2 substituents can cause the *Z*-isomer to predominate.[1-2]

Scheme 1. Canonical representations of *o*-QMs



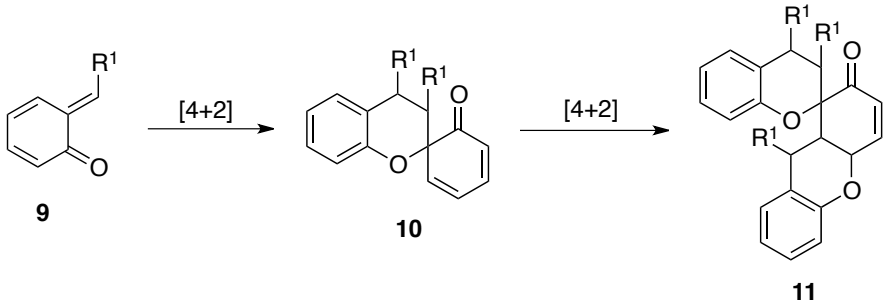
o-QMs have been proposed as intermediates in biosyntheses of several natural products.[1] For example, the *o*-QM **4** is believed to be the common intermediate in biosyntheses of Peniphenones A-D (**5-8**), a series of natural products isolated from Mangrove Fungus *Penicillium dipodomyicola* HN4-3A (Scheme 2).[3]

Scheme 2. Proposed biosynthesis of Peniphenones A-D.



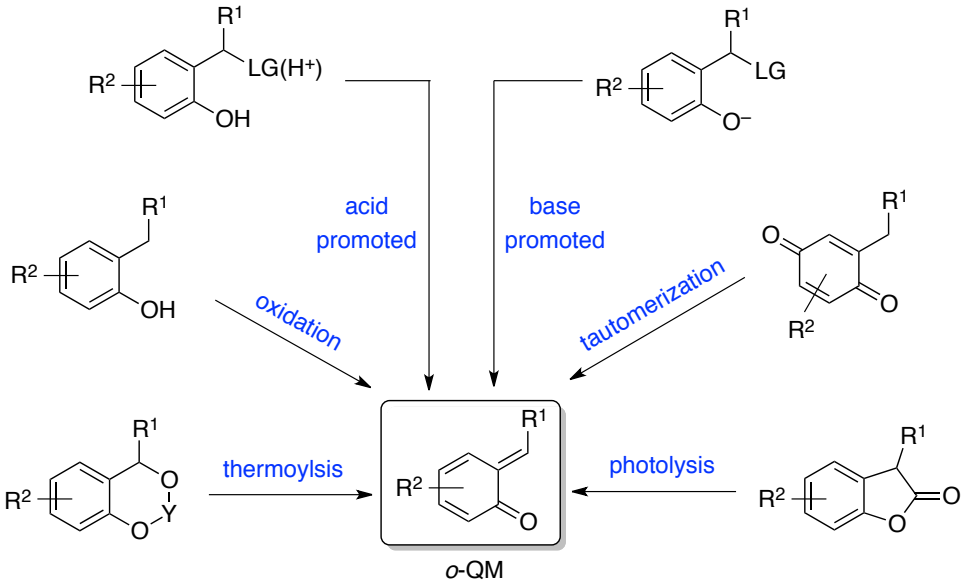
Despite their natural occurrence, the instability of *o*-QMs poses challenge for their synthetic utility. Even at relatively low concentration, *o*-QMs like **9** undergo rapid dimerization and trimerization, forming **10** and **11** respectively via a sequence of [4+2] cycloadditions (Scheme 3).[4] Therefore, gradual and controlled generation of an *o*-QM, such that the concentration of reactive *o*-QM is low at any given time, proves essential.

Scheme 3. Dimerization and trimerization of *o*-QMs.



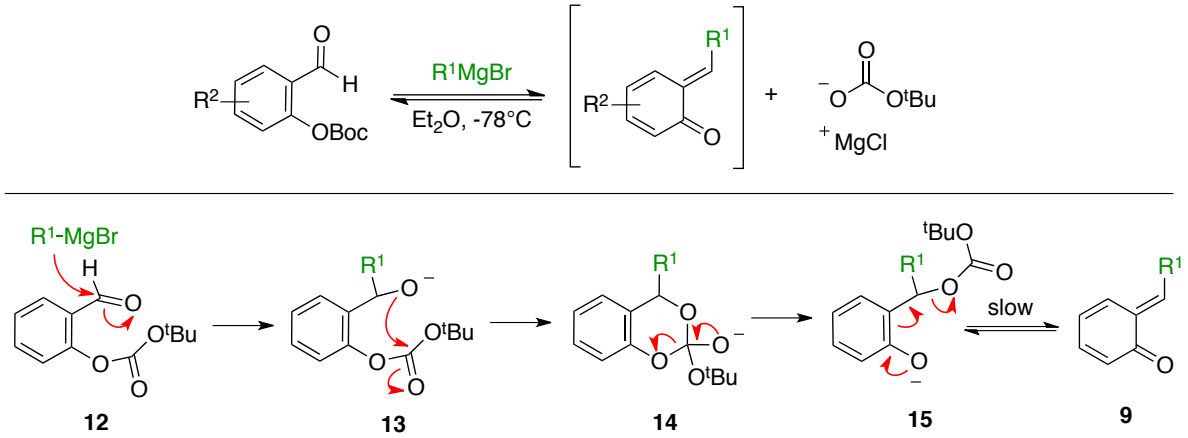
A number of methods for generating *o*-QMs have been developed over the past century. Most of them can be categorized as thermolysis, oxidation, as well as acid or base promoted β -eliminations. Other less utilized methods include tautomerization and photolysis (Scheme 4).[5] Applicability of each method is often limits their compatibility in subsequent reactions.

Scheme 4. Past methods to generate *o*-QMs.



Some time ago, our group developed a method that enables controlled, low temperature generation of *o*-QMs under basic condition (Scheme 5).[6] The method involves a cascade of reactions driven by relative stabilities of anions and likely involves several equilibria. The multicomponent cascade reaction begins with nucleophilic addition of a Grignard reagent to an *ortho*-OBoc salicylaldehyde, such as **12**. The benzylic alkoxide **13** undergoes intramolecular cyclization to form **14**, which collapses to provide a more stable phenoxide **15**. Subsequent β-elimination generates the desired *o*-QM **9**. It is believed that magnesium ion is critical for the final slow β-elimination and maintaining an equilibria.[7]

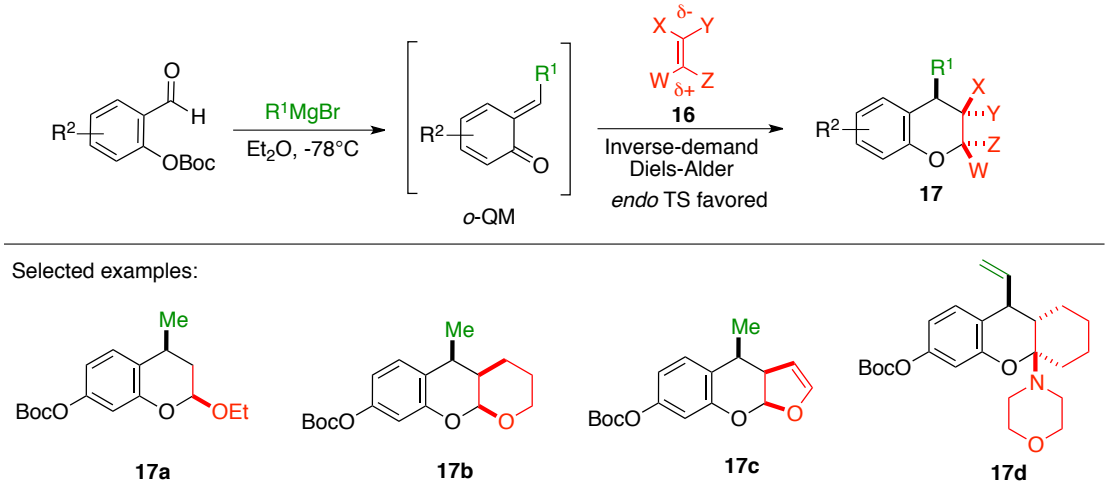
Scheme 5. Cascade pathway to generate *o*-QMs.



1.2 Reactivity of *o*-QMs

Electron deficiency of the diene moiety in *o*-QM allows them to undergo reaction with electron rich dienophiles, such as **16**, via an inverse demand Diels-Alder reaction (Scheme 6). *o*-QM generated by our cascade pathway had been intercepted using variety of electron-rich alkenes, including an assortment of enol ethers, enamines and furans.[8] The three-component, one-pot reactions generate chroman adducts **17** with *d.r.* greater than 95:5 in most cases, favoring *cis* products from *endo* transition state.

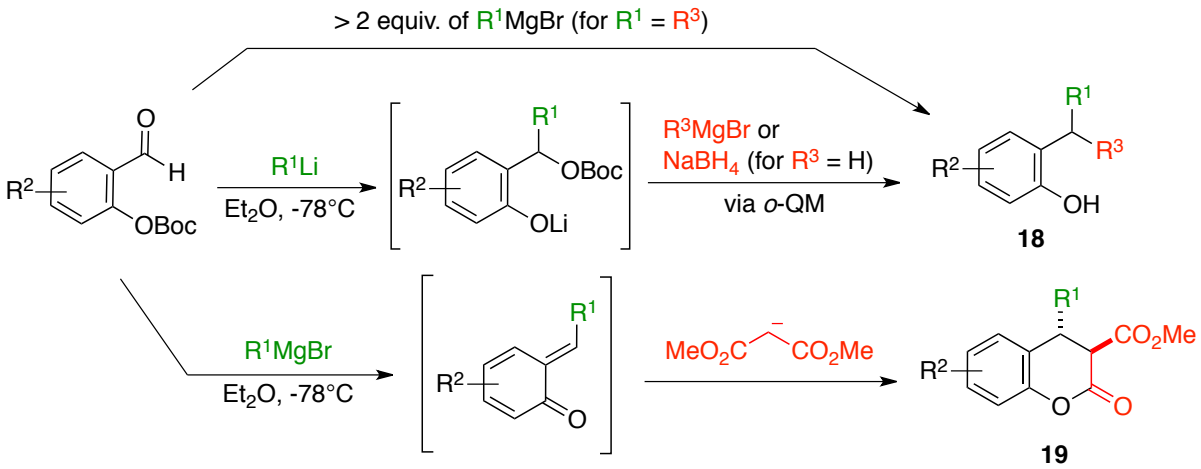
Scheme 6. Examples of Diels-Alder reaction between *o*-QMs and polarized alkenes.



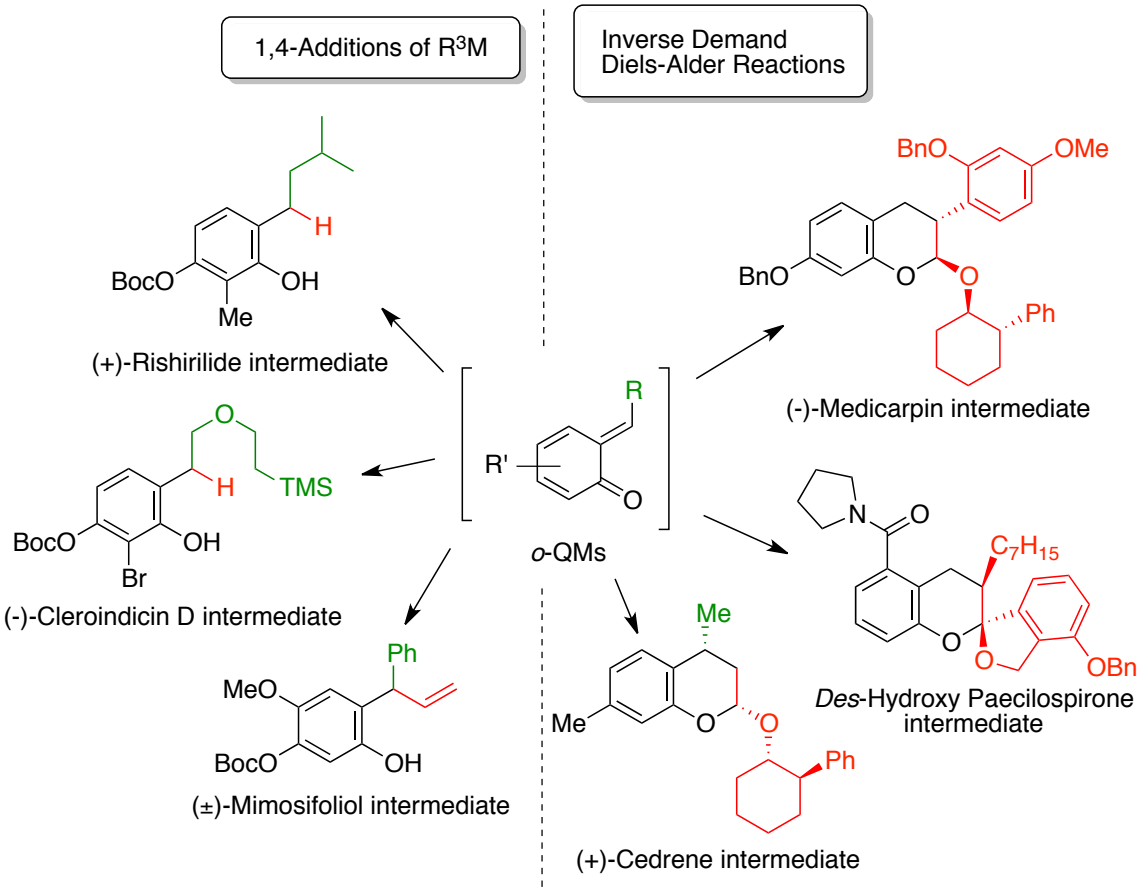
Besides Diels-Alder reaction, the *o*-QMs can also undergo 1,4-addition when a second nucleophile is added (Scheme 7). These nucleophiles include second Grignard reagents and sodium borohydride.[9] Thus, a wide range of *ortho*-branched and unbranched alkyl substituted phenols **18** can be synthesized in one-pot. In

addition, sodium malonate has been used as a nucleophile to yield lactones resembling **19** as final product.[9b] These reactivity of *o*-QMs have been utilized in total syntheses of of a variety of racemic or enantioenriched forms of natural products (scheme 8).[5,9c-d]

Scheme 7. Examples of conjugate addition to *o*-QMs.



Scheme 8. Applications of our *o*-QM chemistry in natural product syntheses.



1.3 Conjugate Addition of Nitrogen Nucleophiles to *o*-QMs

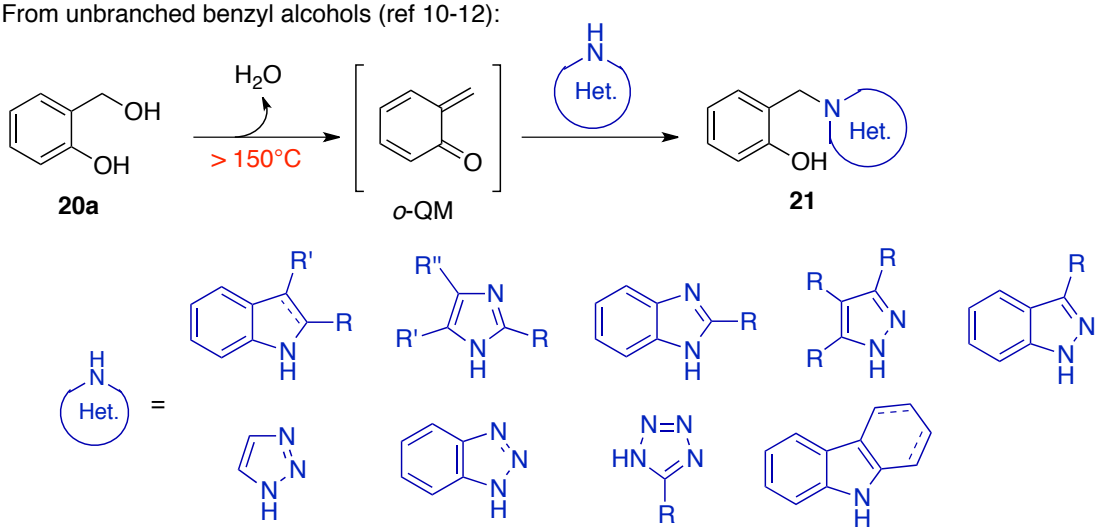
Despite the rich chemistry mentioned in previous section, most nucleophiles which were used to capture *o*-QMs are carbon-based. The addition of heteroatom nucleophiles, in particular nitrogen nucleophiles, remains quite limited. Below, we summarize all of the examples of nitrogen nucleophiles known to intercept *o*-QMs in the literature. Each method can be categorized based upon the *o*-QM generation method used, as well as by the class of precursor deployed.

1.3.1 *o*-QMs Derived from Benzyl Alcohols

2-(hydroxymethyl)phenols **20** are the most commonly used precursor to generate *o*-QMs. With heat or acid, reversible β-elimination of water generates *o*-QM for subsequent reaction. Temperature of above 150 °C is often necessary for unbranched benzyl alcohol **20a** (Scheme 9a). Wu demonstrated a diversity-oriented synthetic strategy through 1,4-addition of different families of nitrogen-containing heterocycles to *o*-QMs.[10] Their Nucleophiles they used include imidazole, triazole, indoline, benzimidazole, indazole, benzotriazole, indole, carbazole and tetrahydrocarbazole. Similar conditions have been employed by Klimochkin and López for addition of tetrazoles[11] and azoles[12]. The use of bases in several of these processes helps sequester the proton from the nitrogen atom after its union with the *o*-QM.

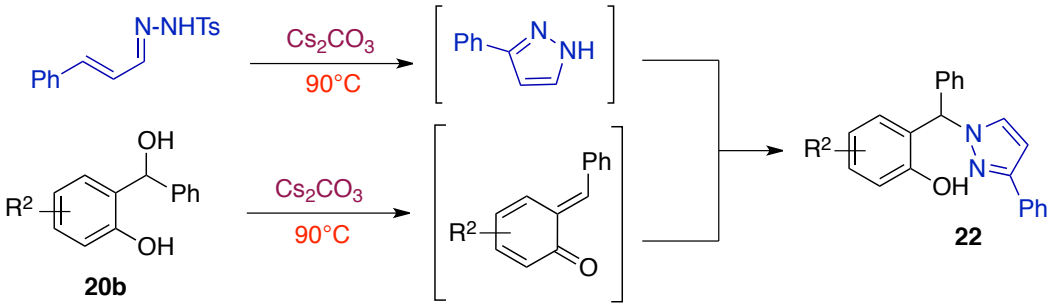
Scheme 9. Examples where *o*-QMs derived from benzyl alcohols.

(a) From unbranched benzyl alcohols (ref 10-12):

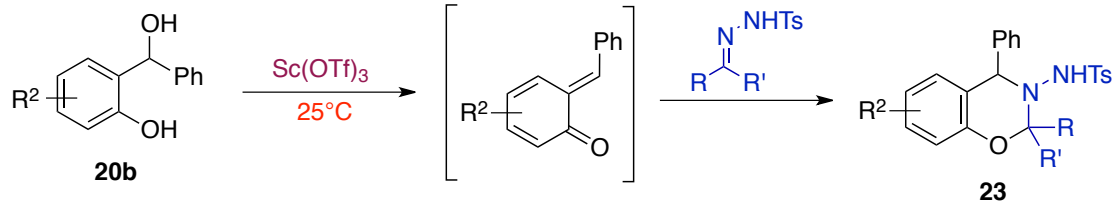


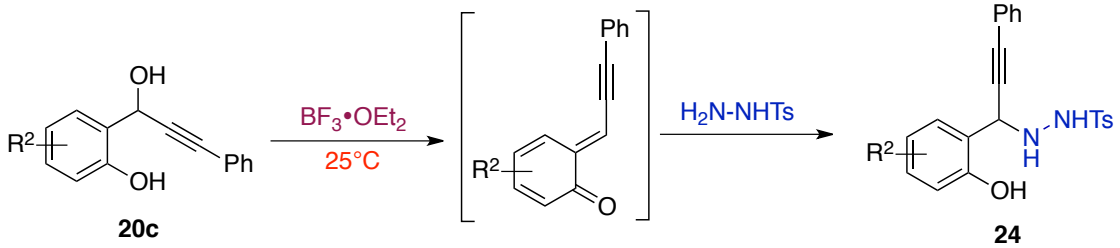
(b) From branched benzyl alcohols (ref 13-15):

- With Proton Scavenger:



- Lewis Acid Promoter:





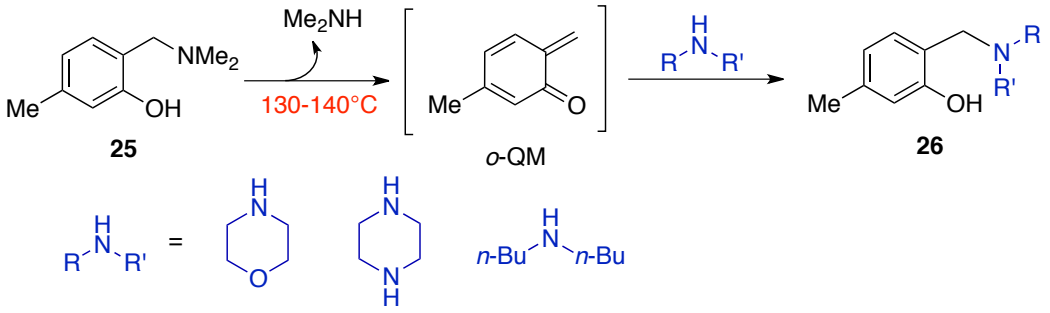
Branched benzyl alcohols, with substituents that conjugate with the incipient *o*-QM in particular, proceed at lower temperature (scheme 9b)s. Kang reported an interesting cascade synthesis of *N*-benylpyrazoles using Cs_2CO_3 as proton scavenger.[13] Cyclization of *N*-tosylhydrazone in base generates pyrazole *in-situ*. On the other hand, *o*-hydroxybenzyl alcohol **20b** undergoes facile elimination to form *o*-QM *in-situ*. Conjugate addition of the pyrazole to *o*-QM and proton scavenging furnishes the final product **22**.

Acid promoted methods are seldom used in nitrogen addition, since Lewis acid promoters can deactivate nucleophilicity of nitrogen atom, or, in an opposite sense, basic nitrogen can deactivate the acid promoter. As a result, the scope of nucleophile is limited to those with non-basic nitrogen and non-labile under acidic conditions, favoring Lewis acids that favor oxygen coordination over nitrogen coordination. Tang reported a formal [4+2] cycloaddition of *N*-tosylhydrazones with *o*-QMs generated from $Sc(OTf)_3$ mediated dehydration of **20b**.[14] Du, on the other hand, employed $BF_3{\cdot}OEt_2$ as Lewis acid catalyst for β-elimination, followed by conjugate addition of various tosylhydrazides to yield intermediate **24**, which underwent subsequent cyclization.[15]

1.3.2 *o*-QMs Derived from Benzyl Amines

Besides benzyl phenols, elimination of dimethylamine from 2-(aminomethyl)phenol **25** have been used similarly to generate *o*-QMs. Wilkins observed exchange of amine moieties by heating **25** with morpholine, piperazine and di-*n*-butylamine at 130°C to 140°C (scheme 10) as dimethylamine is expelled from vessel.[16]

Scheme 10. Examples where *o*-QMs derived from benzyl amines.



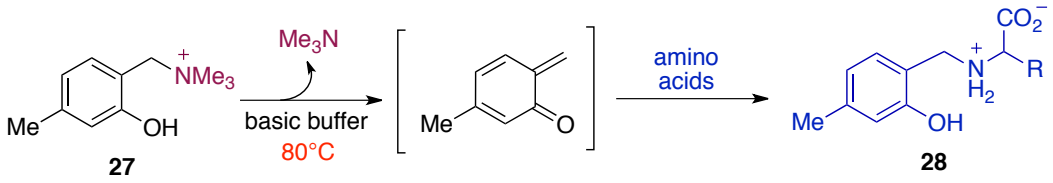
1.3.3 *o*-QM Precursors with a Benzylic Leaving Group

Temperatures required to generate *o*-QM can be lowered to near room temperature by using better leaving groups at benzylic position. Mella demonstrated that (2-hydroxybenzyl)trimethylammonium salt **27** to be a precursor (scheme 11a).[17] Expulsion reactions with amino acids occur at a much lower temperature compared to those in scheme 9. In addition, acetates[18-19], sulfinates[20] and halides[21] have been used as leaving groups (scheme 11b-d). There are several reports of *o*-QMs generated at 25-65°C under these conditions, and subsequently trapped by nitrogen nucleophiles such as azide, aqueous ammonia, dialkyl amines, anilines and pyridines.

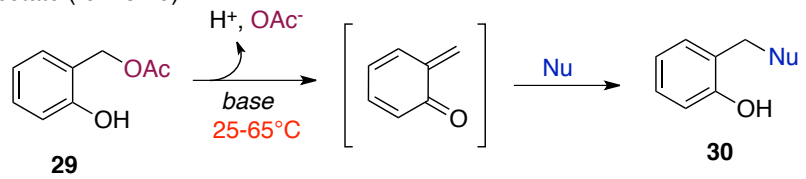
However more reactive *o*-QM precursors have to be generated *in-situ* at even low temperatures. For example, Varvounis demonstrated *o*-QMs can be formed *in-situ* by desilylation and β-elimination of silyl protected *o*-hydroxybenzyl nitrate esters at -78°C (scheme 11e).[22]

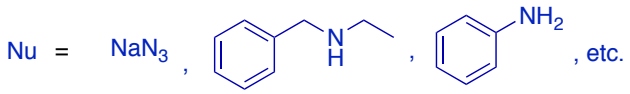
Scheme 11. Examples of *o*-QM precursors with a benzylic leaving group.

(a) From trimethylammonium salt (ref 17):

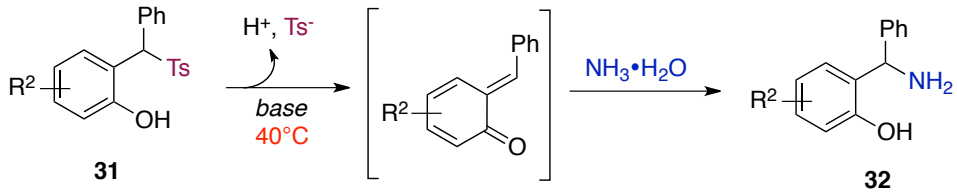


(b) From acetate (ref 18-19):

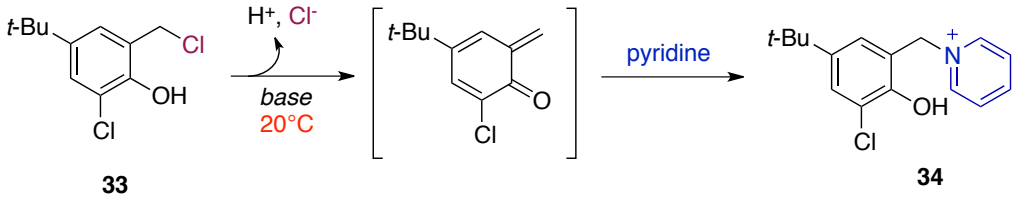




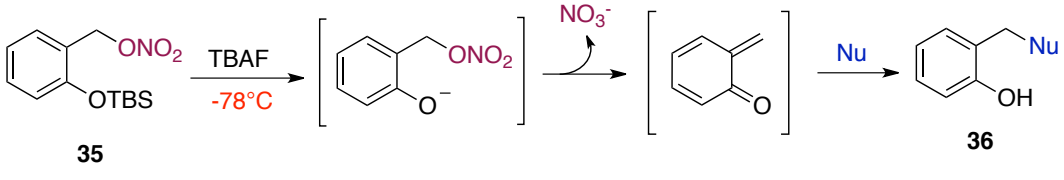
(c) From sulfinates (ref 20):

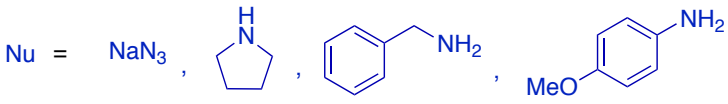


(d) From chlorides (ref 21):



(e) From nitrate esters (ref 22):



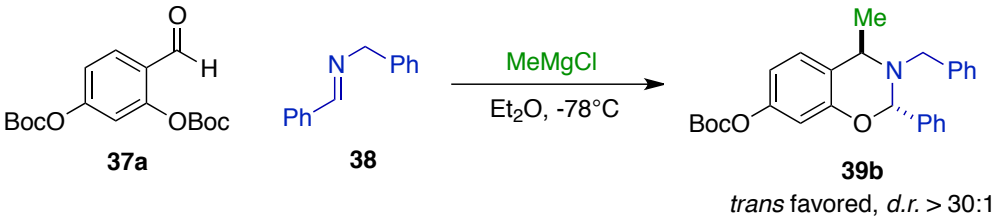


1.4 Motivations for this Research Project

It should be noted that the methods of nitrogen addition summarized in previous section suffer from several limitations. First, the benzylic substituent of *o*-QM has to be installed in a separate step. Second, most of these methods either require high temperature, or need precursors that take several steps to prepare. Third, asymmetric addition of nitrogen nucleophiles to *o*-QMs are extremely scarce.[20,23] We believe our cascade reaction to generate *o*-QMs at low temperature might provide a solution to enable researchers to circumvent these limitations.

Back in 2002, we reported a single example of formal [4+2] cycloaddition between *o*-QM and imine **38** (scheme 12).[8a] However, instead of *cis* product expected from *endo* transition state, a *trans* product was observed. Fifteen years later, we set out to revisit the addition of imines to *o*-QMs to better understand this stereochemical discrepancy, with the goal of understanding the underlying transition state in chapter 2, where we have greatly expanded the scope of imines. Reactions with other nitrogen nucleophiles, such as dihydrooxazine derivatives and anilines, will be covered in chapter 3. The development of chiral auxiliary that enable diastereoselective reactivity will be presented in chapter 4 of this thesis.

Scheme 12. Formal [4+2] cycloaddition between *o*-QM and imine.



37a **38** **39b**

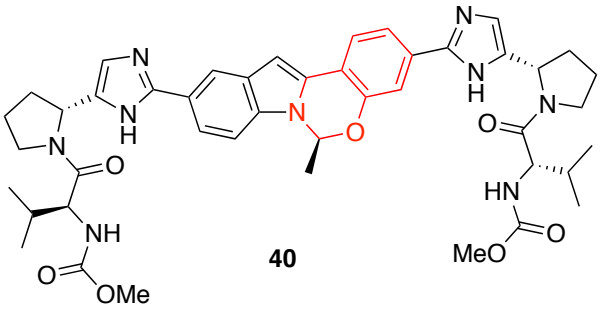
trans favored, *d.r.* > 30:1

Chapter 2. Conjugate Addition of Imines to *o*-QMs

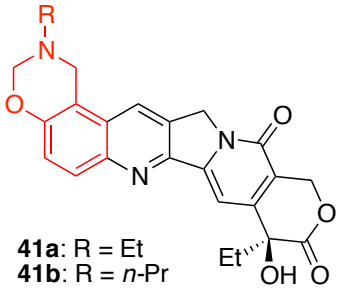
2.1 Introduction

3,4-Dihydro-2*H*-1,3-benzoxazines are an important class of heterocycles. Many of these derivatives exhibit diverse biological activities (scheme 13). Elbasvir (**40**) is a potent and selective NS5a inhibitor and is used to treat chronic hepatitis C virus infection.[24] Camptothecin derivatives **41a-b** show great potency against cancer cell lines.[25] Other benzoxazines were found to have anti-fungal[26], pesticides[27], anti-bacterial[28] and anti-inflammatory[29] activities.

Scheme 13. Some biological active molecules with benzoxazine core.



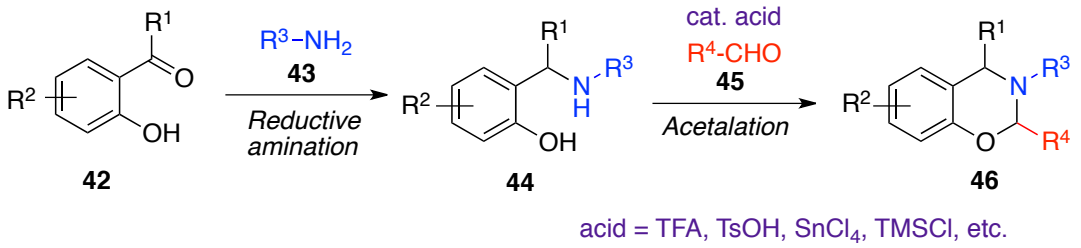
40



41a: R = Et
41b: R = *n*-Pr

Given their biological importance, various conditions have been developed to synthesize benzoxazine derivatives. The most general strategy is two-step synthesis (scheme 14).[26,30] This method begins with reductive amination between salicylaldehyde **42** and primary amine **43**. The benzyl amine **44** that is formed undergoes acid-catalyzed acetalation with aldehyde **45** to give the benzoxazine **46**. Various Brønsted and Lewis acids have been used as catalysts for this acetalation. Despite being most general procedure previously known, none of these benzoxazine products display a substituent on the 4-position. Moreover, the process does not employ an *o*-QM intermediate.

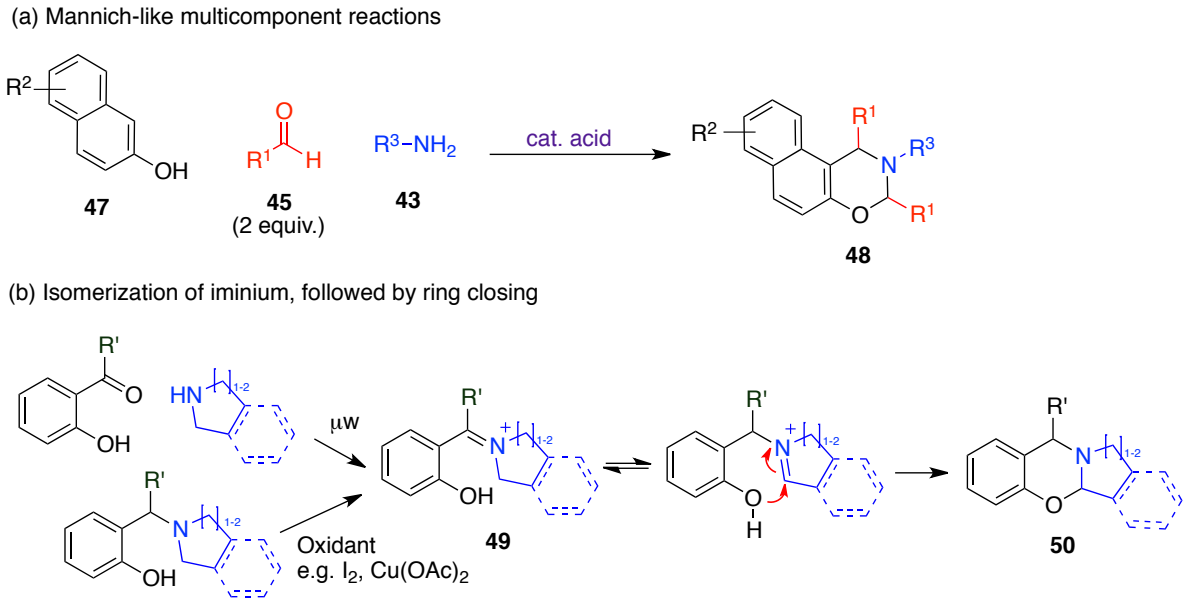
Scheme 14. Traditional two-step synthesis of benzoxazine derivatives.



Seeking to reduce number of steps required to assemble the benzoxazine core, several one-pot reactions have been developed. Most of these fall into two categories. The first strategy is Mannich-like multicomponent condensation between phenol **47**, primary amine **43** and two equivalents of aldehyde **45** (scheme 15a).[31] The second strategy utilizes iminium **49** formed *in-situ* from condensation or oxidation (scheme 15b).[32] The iminium undergoes isomerization, which then cyclizes to give benzoxazine **50**. However, both strategies suffer from limited scope.

The Mannich-like condensation works with electron-rich phenols or naphthols only. In addition, double incorporation of the same aldehyde results in identical substituent at the 2 and 4-position of benzoxazine. Isomerization of iminium is regioselective only for a limited scope of amines.

Scheme 15. Reported one-pot synthesis of benzoxazine derivatives.



Most of these reported strategies, as described above, are performed under acidic and/or thermodynamic conditions. Our single example of formal [4+2] cycloaddition between *o*-QM and imine (scheme 12) provided a new strategy to synthesize benzoxazine derivatives. To the best of our knowledge, it is the first one-pot synthesis, and proceeds under basic condition at low temperature.

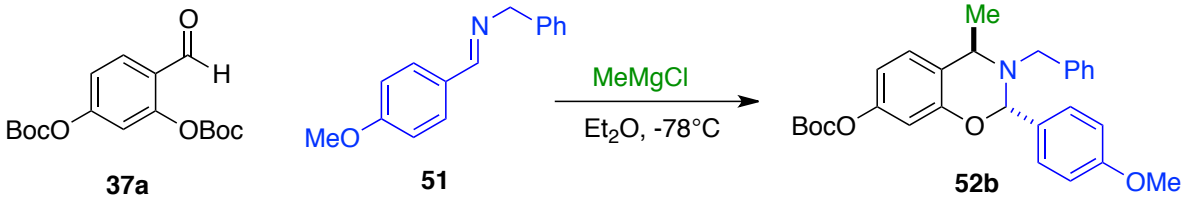
2.2 Condition Optimization

Despite having reported an example, the yield of benzoxazine adduct was inconsistent in our hands. Even with standard Schlenk line techniques, the crude NMR yield was found to fluctuate considerably and even depended upon the environmental humidity of the experiment. We believe these fluctuations were due to water adhering to aldehyde and imine deployed into reaction flask. The excess of five equivalents of imine, as used in original procedure, further increased the chance of introducing water into reaction.

Aldehyde **37a** and imine **51** were chosen to be model substrates for condition optimization. To minimize amount of water introduced, we reduced amount of imine to 1.1 equivalents (entry 1). Moreover, to ensure the aldehydes and imines were scrupulously dry, they were prepared as 1 M solution in dry toluene stored over 4Å molecular sieves (entry 2). However, only minor improvement in the yield of adduct **52b** was observed. We next turned our attention to other water scavengers, such as trimethyl orthoacetate (TMOA).[33] We envisioned TMOA reacts with one equivalent of water to give methyl acetate and methanol, thereby removing trace amount of water left in imines and aldehydes. Unfortunately, addition of TMOA alone gave almost no improvement (entry 3). We believe methanol produced disrupted the reaction. To our delight, the use of both TMOA and 4Å molecular sieves gave great enhancement in yield (entry 4). It appears that 4Å molecular sieves removes methanol more efficiently than water. Storage of these solutions in dessicator overnight before use proved to promote the yield (yield 5). With all these

modifications, crude NMR yield of adduct becomes more consistent and usually falls into the range of 80-90%.

Table 1. Condition optimization of formal [4+2] cycloaddition between *o*-QM and Imine.[a]



37a **51** **52b**

Entry	4Å MS[b]	TMOA[c]	NMR yield[d]
1	X	X	13%
2	√	X	39%
3	X	√	20%
4	√	√	67%
5[e]	√	√	88%

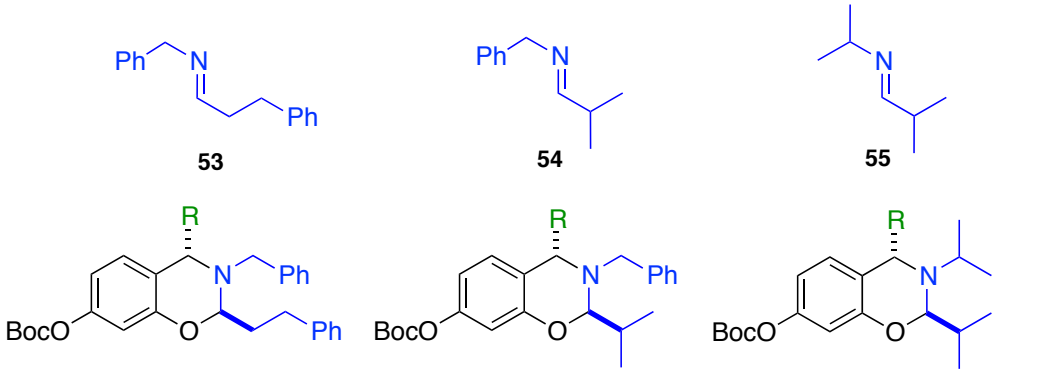
[a] Reaction condition: **37a** (0.1 mmol, 1 M solution in toluene), **51** (0.11 mmol, 1 M solution in toluene), MeMgCl (0.105 mmol, 2.6 M solution in THF), in 1 mL of Et_2O at -78°C. [b] 100 mg per mL of toluene [c] 5% by mass of aldehyde or imine dissolved. [d] Determined by adding 1.0 equiv of CH_2Br_2 as internal standard in crude product. [e] Both solutions were stored in desiccator overnight before use.

2.3 Substrate Scope

With a consistent process, we proceeded to explore the scope of reactivity among imines. These were divided into four categories, which depended on nature of substituents attached to the nitrogen and carbon atoms of the respective imines.

2.3.1 Class I Imines

Class I imines contained aliphatic substituents on both the nitrogen and the carbon atoms (figure 1). With imines **53**-**55**, we were able to obtain the desired benzoxazines **56**-**58** in NMR yields ranging from 63% to 95%. Yields for isolated adducts (61% to 94%) were generally 2% to 10% lower than their respective NMR yields and reflect the instability of the adducts toward chromotagraphy. Comparable yields between **56** and **57** demonstrate that steric encumbrances on carbon side of imine are well tolerated. However, steric features on the nitrogen side (adducts **58**) were found to result in lower yield and stereoselectivity.



56a: R = -Ph, 81% yield
56b: R = -Me, 83% yield[x]

57a: R = -Ph, 95% yield
57b: R = -Me, 82% yield[x]

58a: R = -Ph, 63% yield[y]
58b: R = -Me, 72% yield
(*trans*:*cis* = 5:1)

Figure 1. Adducts from class I imines. [x] NOE analysis. [y] 2 equiv of imine used.

Only the corresponding *trans* stereoisomers were observed for adducts **56** and **57**. This *trans* configuration was experimentally established by NOE experiments. However the congested *bis*-isopropyl adduct **58b** did show a very small amount of the *cis* isomer (*trans*:*cis* = 5:1). These two diastereomers show distinctive ^{1}H NMR chemical shifts for their respective benzylic protons ($\Delta\delta = +0.15$ ppm, *trans* vs *cis*).

2.3.2 Class II Imines

Next, we examined class II imines, which have an aryl group on the nitrogen residue and an alkyl group on carbon (figure 2). Again, imines **59** and **60** gave adducts **61**-**62** as single, *trans* diastereomer (established again by NOE experiments). The yields of these adducts were lower than those in class I. Comparing these two adducts, we found electron withdrawing and donating groups on aryl ring of imine had little effect on yields or diastereoselectivity. These adducts proved to be more unstable toward silica gel chromotagraphy.

2.3.3 Class III Imines

We next examined *bis*-arylated class III imines **63**-**65**, in which both carbon and nitrogen atoms of imine were arylated (figure 3). These imines did not give satisfactory results. The NMR yields of adducts were estimated to be between 15% to 31%. These adducts were even more unstable than the preceding adducts. As a result we were unable to fully characterize these adducts.

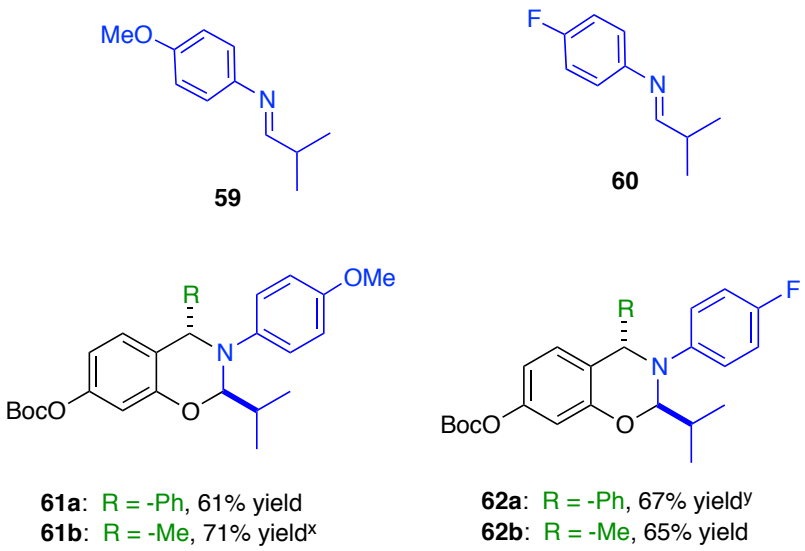


Figure 2. Adducts from class II imines. [x] NOE analysis. [y] 2 equiv of imine used.

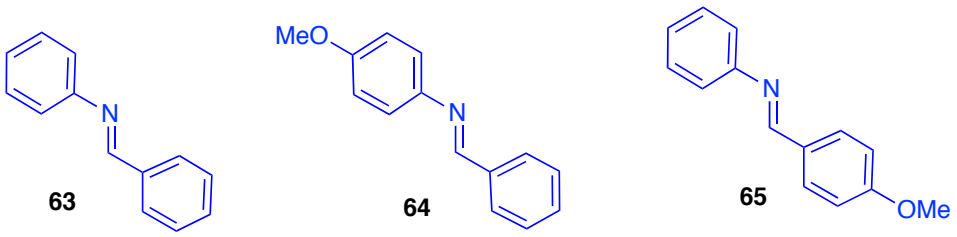


Figure 3. Unproductive class III imines tested.

2.3.4 Class IV Imines

Lastly, we examined class IV imines **38, 51, 66-72**, which have aliphatic group on the nitrogen side and an aryl groups on carbon side of the respective imines (figure 4). Most of the adducts **39, 52, 73-81** were formed in reasonable yields. Even though these adducts were found to be less stable than class I adducts on silica gel, they were considerably more stable than class II and III. Hence purification by chromatography was possible. Imines with electron-withdrawing groups on carbon side (**66**) required two equivalents of imines to be deployed in order to obtain a respectable yield. Comparing the yields for adducts **39** and **74** indicated that inductive effects from the aliphatic nitrogen side of the imine had little effect upon reaction outcome. On the other hand, sterics near nitrogen atom (**69**) severely lowered the yield of the respective adduct. Attempts to relieve sterics encumbrances near the carbon side by using mesityl derivative (**70**) led to no improvement.

In all cases, *E*-imines produced exclusively *trans* adducts (*trans*:*cis* > 30:1) as established by NOE experiments. The use of cyclic (*Z*)-imine **72** predominately afforded the corresponding *cis* diastereomer in a ratio of *trans*:*cis* = 1:5 for both methyl and phenyl adducts **79a** and **79b**.

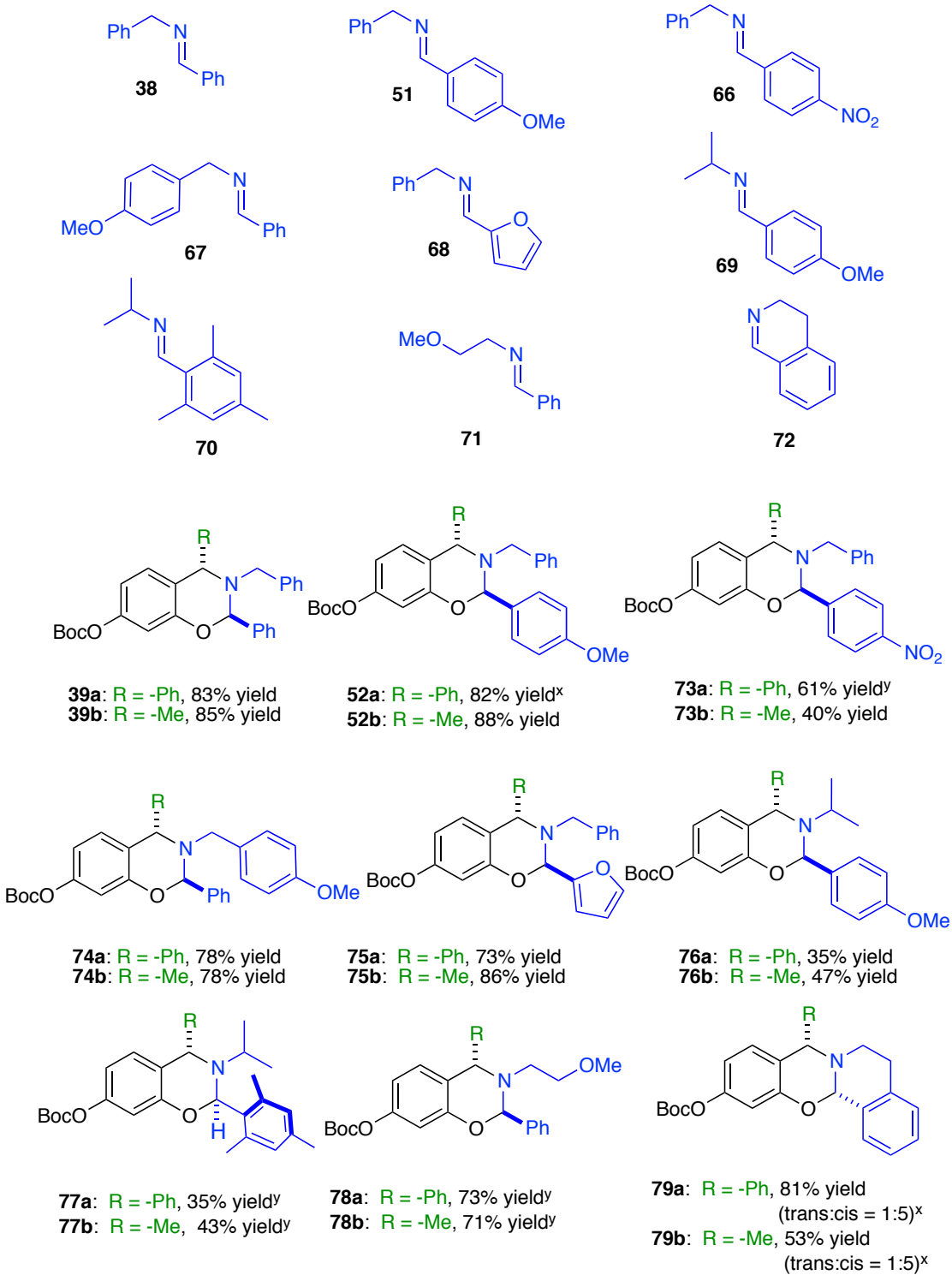


Figure 4. Adducts from class IV imines. [x] NOE analysis. [y] 2 equiv of imine used.

2.4 Comparison to Thermodynamic Methods

We were also interested to know if our one-pot assembly of the benzoxazine proved more efficient and general over the traditional two-step synthesis under thermodynamic conditions (scheme 14). We prepared benzyl amines **44** by reductive amination between salicylaldehyde **42a** and primary amine **43**, followed by acid-catalyzed acetalation with aldehyde **45**. This thermodynamic method again favors the *trans* diastereomer as major product, just as our *o*-QM chemistry. However, the sequence proceeds in lower overall yields (scheme 16, **57b** and **52b**). Moroever, the thermodynamic method failed to afford adducts **58d** and **76b**, presumably due to unfavorable sterics of isopropyl group on nitrogen to the subsequent cyclization. The two-step thermodynamic process also failed to provide N-arylated adduct **61b**. To the best of our knowledge, there have been no prior report of a synthesis of an 3-*N*-arylated 1,3-benzoxazines with substituents on both 2 and 4 positions using the traditional two-step thermodynamic method. We believe aryl groups on the nitrogen may provide stronger even more steric issues in these systems.

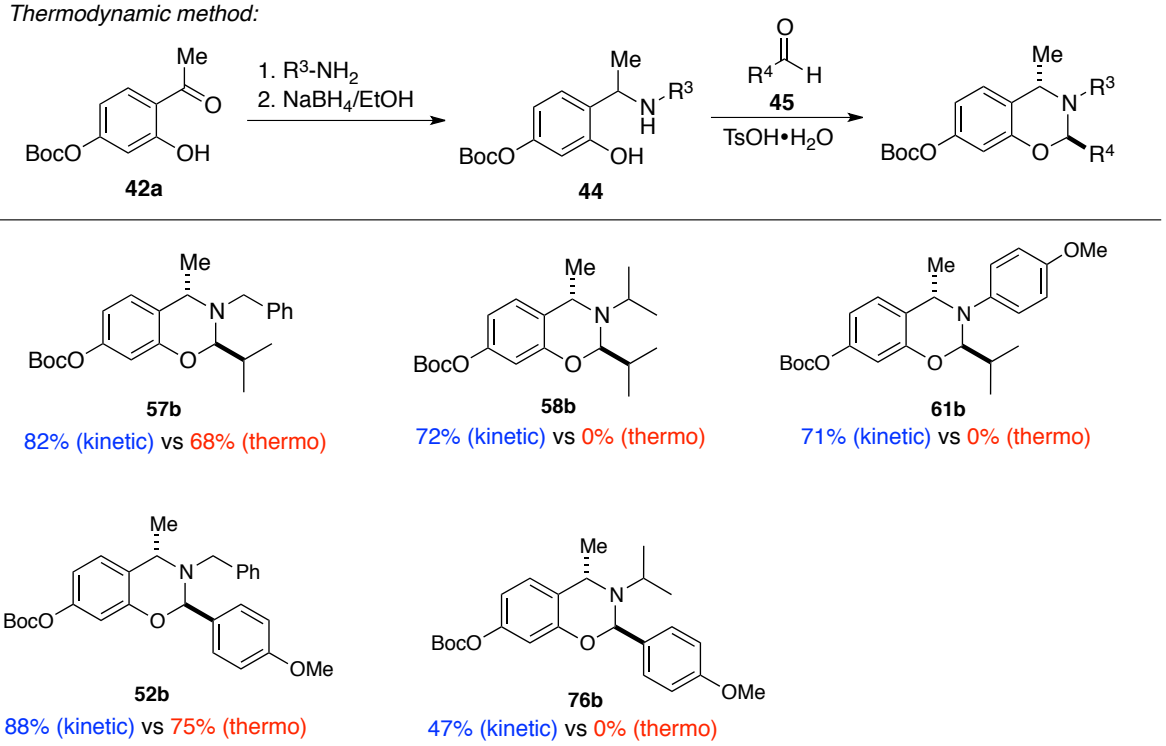
2.5 Mechanistic Insights

2.5.1 Ruling out Concerted Mechanism

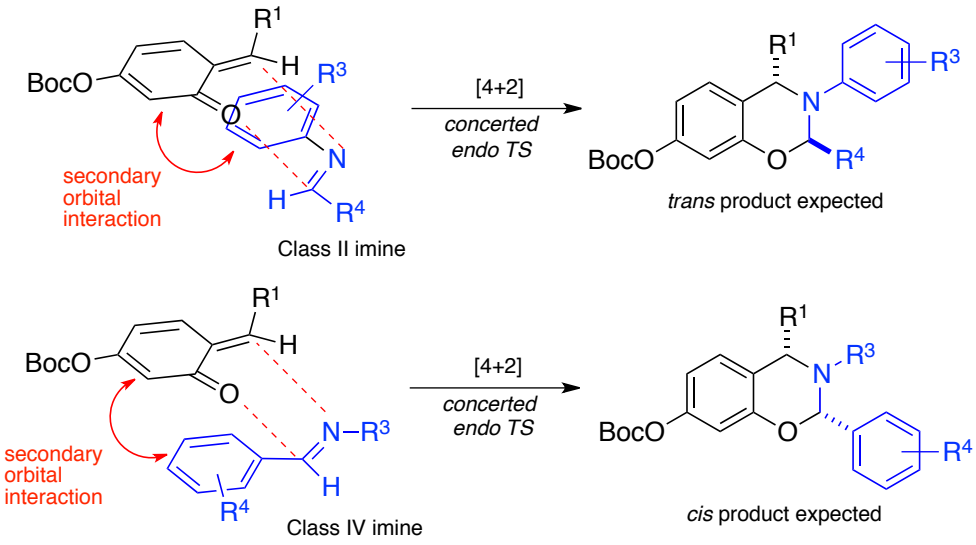
From our previous considerable experiences with enol ethers undergo reactions with o-QMs (scheme 6), this new imine reaction appears to be an inverse demand Diels-Alder cycloadditions. However, a concerted [4+2] cycloaddition transition state contradicted the stereochemical outcomes observed for imine nucleophiles. First, the imine reaction is highly diastereoselective even for bis-aliphatic (class I) imines, where secondary orbital effects are absent from both aliphatic substituents. Second, both N-arylated (class II) and C-arylated (class IV) *E*-imines favor *trans* products. These two classes of imines should have afforded different diastereomers, as the secondary orbital effects from aryl ring should work in opposite directions (scheme 17).

One might argue the preference of *trans* product across all classes of imines result from equilibration over time when the mixture warms up to room temperature. However, we ruled out this possibility by allowing our adduct **61b**, prepared using our *o*-QM method, to reflux in deuterated chloroform. Degradation in diastereomeric ratio (from *trans*:*cis* > 30:1 to 1:1) was observed to occur. This would seem to prove that diastereoselectivity observed was not due to thermodynamics.

Scheme 16. Preparation of benzoxazines using two step thermodynamic process and comparison with our one-pot kinetic method.



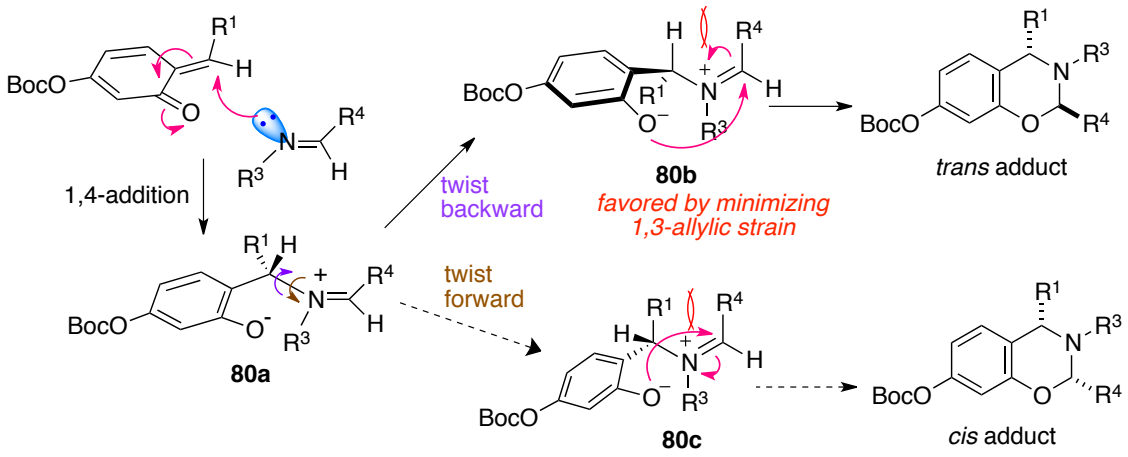
Scheme 17. Expected stereochemical outcome of class II and IV imines from concerted mechanism.



2.5.2 Stepwise Mechanism Proposed

We next considered the possibility of a stepwise mechanism (scheme 18). The reaction begins with nitrogen atom of imine participating in a 1,4-conjugate addition with the *o*-QM to result in the iminium species **80a**. A phenolate cyclization follows via a twist yield the benzoxazine adduct. However, the direction of twist determines whether a *trans* or *cis* product is formed. The strong preference of *trans* adduct from *E*-imine is dictated by the preferred twist and ensuing facial selectivity of phenolate's attack onto the iminium carbon. The iminium species likely adopts the conformation shown in **80b** due to 1,3-allylic strain, and this in turn dictates the most efficient twisting motion. In addition, close proximity of phenolate oxygen and iminium carbon helps stabilize the initial iminium intermediate. Consequently, the phenolate prefers to attack from top face of iminium carbon, which yields *trans* product. This stepwise mechanism predicts stereochemistry consistent with our observations.

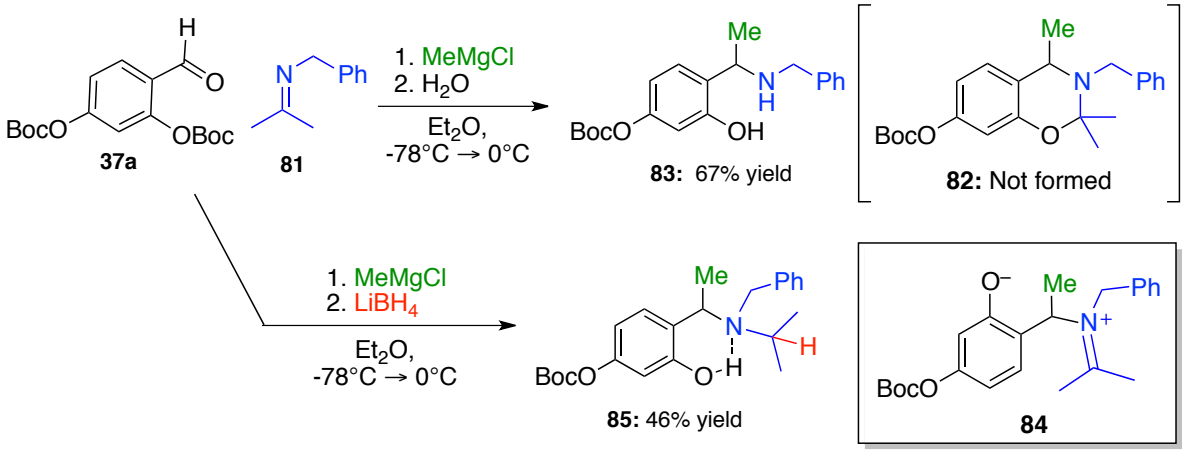
Scheme 18. Stepwise mechanism proposed for imine additions.



2.5.3 Further Mechanistic Evidence from Trisubstituted Imines

We also attempted to carry out this new reaction with trisubstituted imine **81** using the same protocol. To our surprise, instead of benzoxazine **82** as expected, benzylic amine **83** was cleanly formed upon aqueous work-up (scheme 19). We believe the phenolate cyclization, which is required to form the benzoxazine, is deterred by more sterically encumbered environment around iminium carbon. This supposition is further supported by reduction of supposed iminium intermediate **84** by lithium tetraborohydride, which was shown to result in benzylic tertiary amine **85.** These observations provided additional speculative evidence on the presence of iminium intermediate produced in a stepwise mechanism as proposed in the previous sections.

Scheme 19. Outcomes with trisubstituted acyclic imines.



2.5.4 Imines as Nitrogen Nucleophiles

The stepwise mechanism we proposed demonstrates an unusual reactivity of imine, in which nitrogen atom serves as nucleophile for C-N bond formation. Imines are usually activated by addition of Lewis acids for subsequent attack of carbon nucleophiles.[34] On contrary, the use of imine as nucleophile towards carbon electrophiles was less explored. While Staudinger's β-lactam synthesis is one of such example[35], the reaction often proceed via Umpolung fashion, where the ketene is first converted into a nucleophilic zwitterionic enolate by addition of an amine or phosphine, followed by subsequent addition to an electron deficient imine[36]. Other examples include *N*-acyl iminiums formed by acylation of Schiff bases.[37, 38] Our use of *o*-QM provided an additional example of carbon electrophile for such uncommon reactivity.

2.6 Conclusion

In conclusion, we developed a straightforward one-pot synthesis of an assortment of 3,4-Dihydro-2*H*-1,3-benzoxazines in high diastereoselectivity. We showed this method can deliver more sterically challenging adducts that are not accessible by traditional thermodynamic processes. The stepwise mechanism proposed, which involves 1,4-conjugate addition of imine to *o*-QM followed by cyclization, explains *trans*-selectivity observed successfully. This mechanism also shows an uncommon reactivity of imines, where imine nitrogen serves as nucleophile in the event of C-N bond formation. Our findings shed light on the development of enantioselective version of this reaction, which will be covered in chapter 4 of this thesis.

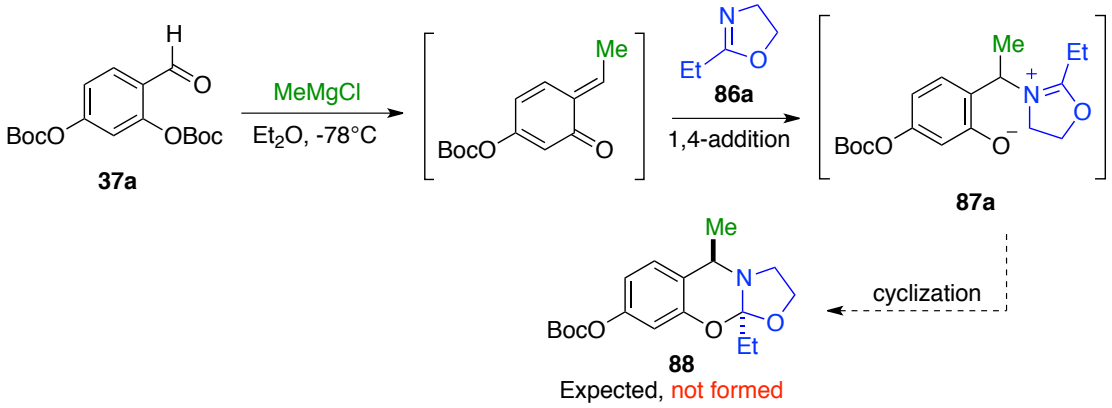
Chapter 3. Conjugate Addition of 4,5-Dihydrooxazole Derivatives to *o*-QMs

3.1 Introduction

We have described the conjugate additions of imines to *o*-QMs in the previous chapter. Building upon our these findings, we set out to explore reactivity of other sp^2 nitrogen nucleophiles, and 4,5-dihydrooxazoles came to our attention. We postulated that resonance donation from oxygen atom would enhance their nucleophilicity at nitrogen atom. However, when dihydrooxazoles **86a** was submitted to our standard reaction condition, the tricyclic 1,3-benzoxazine adduct **88** expected was not observed (scheme 20).

We then paused to examine the supposed iminium intermediate **87a**. From our previous study on trisubstituted imines (section 2.5.3), we believe that phenolate cyclization is hindered by the steric environment around the iminium carbon, and resonance donation from oxygen further deactivates **87a** from cyclization.

Scheme 20. Addition of dihydrooxazoles to *o*-QM.



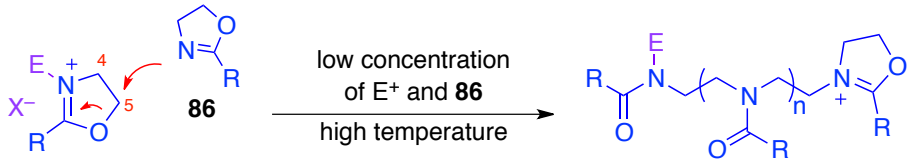
On the other hand, our literature search shows that oxazolium species resembling **87a** exhibit two major modes of reactivity. In most cases, an attack of a nucleophile at 5-position initiate an irreversible dihydrooxazole ring opening. There has been a plethora of similar examples of cationic ring opening polymerization of dihydrooxazole derivatives (scheme 21a).[39] The addition of small amount of electrophilic initiator, including Bronsted or Lewis acids, alkylation or acylation reagents, enabled continuous ring opening by another dihydrooxazole molecule to form a living polymer **89a**. Such polymerization is thermodynamically driven by the formation of an amide. Apart from polymerization, ring opening by other nucleophiles, such as aryl rings[40], secondary amines[41] and halides[42], at 5-position have also been reported (scheme 21b-d).

Alternatively, in the presence of opportunistic water, a solitary report denotes that the oxazolium species can be intercepted by water at 2-position to yield the hemi-orthoamide intermediates **90**, which undergoes further ring opening to exclusively form the amino-ester **91** under kinetic conditions (scheme 22a)[43]. The more thermodynamically stable amide product, **92**, is reported to form over time under basic conditions.[43b-e]

From literature reports above, we envisioned that when the dihydrooxazole **86a** was submitted to our *o*-QM generation protocol, the oxazolium intermediate **87a** undergoes one or more pathways similar to scheme 21-22, and form products resembling **89**, **91** or **92**. Thus, we began by examining products generated upon aqueous quenching under kinetic and basic conditions.

Scheme 21. Reported ring openings of oxazolium species at 5-position.

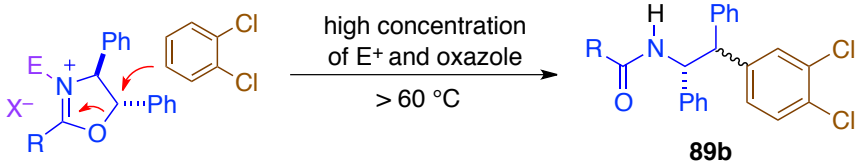
(a) By another dihydrooxazole (ref 39):



$E^+ X^-$ = acyl chlorides, TMS-I, MeI, TfOH, *etc.*

89a
living polymer

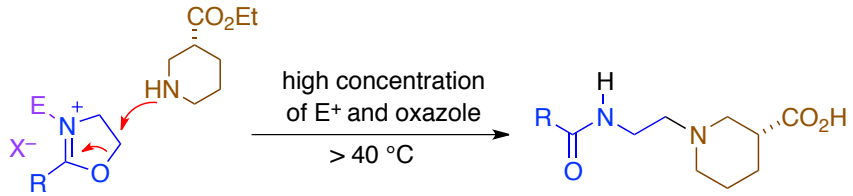
(b) By aryl ring (ref 40):



$E^+ X^- = CF_3SO_3H$

89b
61% yield, R = -Et
86% *de*

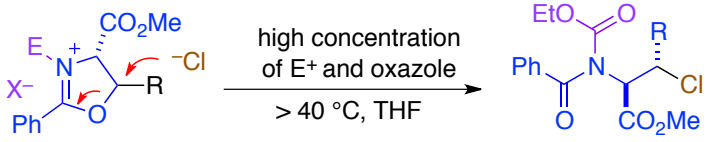
(c) By amine (ref 41):



$E^+ X^- = TsOH$

89c
>50% yield, R = *p*-F-C_6H_4

(d) By chloride (ref 42):



$E^+ X^-$ = ClCOEt

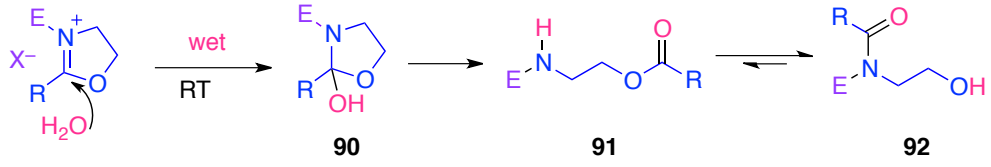
89d
85% yield, R = -H

3.2 Kinetic Hydrolysis of Oxazolium Species

When the reaction mixtures containing **87** were treated with aqueous $NaHCO_3$ solution, the amino-esters **94** formed exclusively (scheme 22b). This suggested that the oxazolium intermediates undergo kinetic hydrolysis similar to that shown in scheme 22a. The structure was assigned based on the following observations: 1) ^{1}H-NMR spectra show benzylic methine resonances of below 4.0 ppm in most of our adducts. The methine resonances of benzylic amides resembling **92** are generally above 5.0 ppm. 2) The ^{1}H-NMR of adducts showed no broad peaks due to rotamers. Thus, the opportunistic water that intercepted oxazolium species can be considered as forth reactant in our multi-component reaction. So, we proceeded to explore the scope of this new four-component reaction.

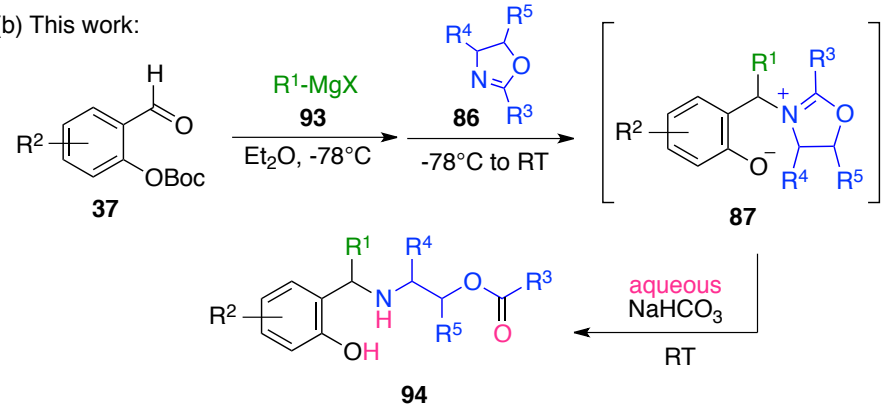
Scheme 22. Interception of oxazolium species with opportunistic water.

(a) Hydrolysis of imidate salts by opportunistic water (ref 43):



$E^+ X^-$ = acyl chlorides, Me-I, Me-OTf, mandelic acid, *etc*

(b) This work:



3.2.1 Scope of Aromatic Cores

We began by altering the position of substituents in *o*-Boc salicaldehydes **37** (figure 5). The trend of yields observed was consistent with our previous observations. Aromatic cores with electron-donating substituents at 2 to 5 positions (**37a-d**) generate more stable *o*-QMs, which provide better control for subsequent reactions. These more stable o-QMs provided the adducts **94a-e** in good to moderate yields. On the other hand, aldehyde **37e** produces an *o*-QM without any substituents. This more reactive non-substituted *o*-QM is more prone to self-destruction, and hence led to a lower yield of the desired adduct.

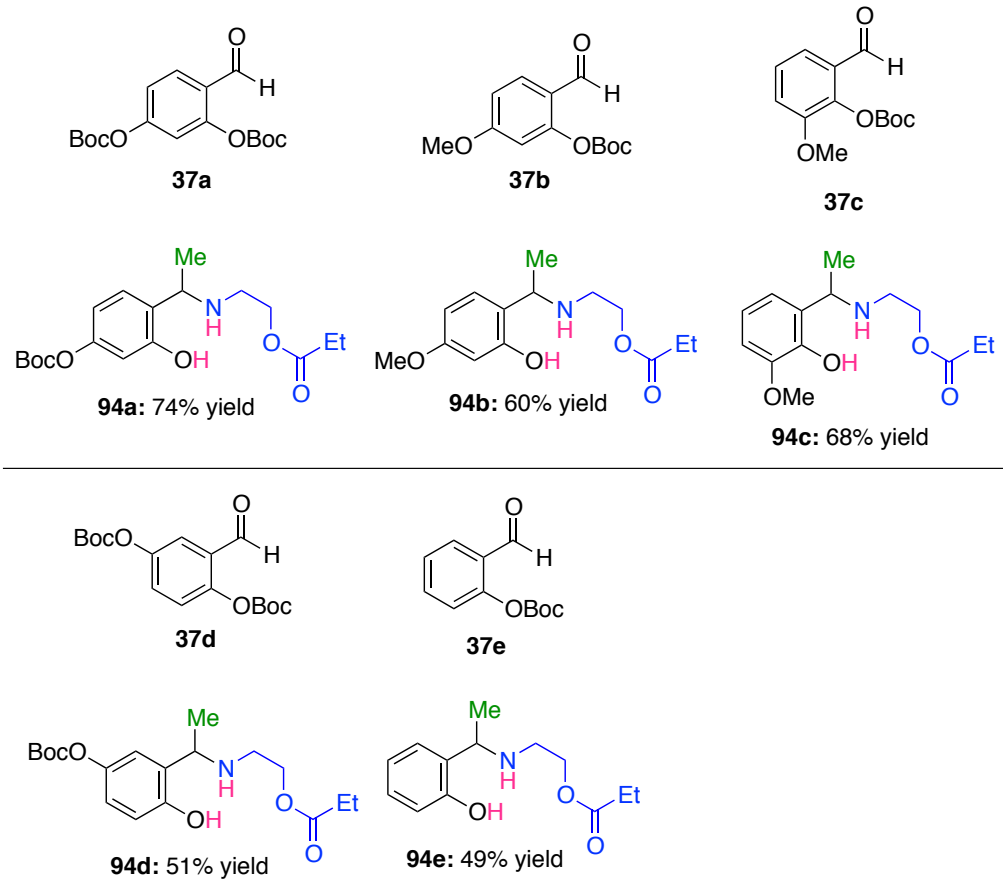


Figure 5. Scope of aromatic cores for *o*-QM generation.

3.2.2 Scope of Grignard Reagents

We next varied the Grignard reagents **93** used to generate *o*-QMs (figure 6). Reactions with longer straight chain alkyl magnesium bromides (**93b-c**) proceeded smoothly to provide adducts **94f-g**. Phenylmagnesium bromide (**93d**) was found to be equally effective. Heterocycles like piperidine, which were attached elsewhere on the Grignard reagent (**93e**), were well tolerated under our mild reaction conditions.

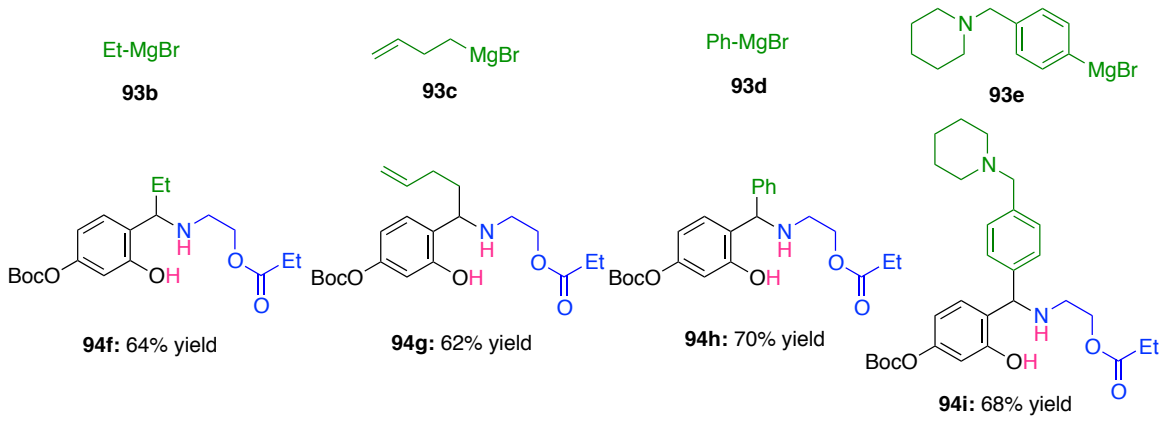


Figure 6. Scope of Grignard reagents for *o*-QM generation.

3.2.3 Scope of Dihydrooxazole Derivatives

We then examined an assortment of dihydrooxazole derivatives **86** in our reaction conditions. The trend among yields of adducts (figure 7), together with unsuccessful cases are shown in figure 8. These revealed some undesirable features in dihydrooxazoles. For example, branched substituents at 2-position (**86c**) results in lower yield of adduct (**94k**). Similarly, furyl oxazole **86d** produced a low yield of adduct **94l**, while the phenyl analog **86i** was unproductive. These observations seem to suggest that steric encumbrance adjacent to nucleophilic

nitrogen atom is undesirable. We believe these steric effects have two consequences: 1) obstructing the nitrogen atom's attack of the oxazoles towards *o*-QMs, and 2) hindering the addition of water to oxazolium intermediate as it is formed. The six-membered ring analog, **86e-f**, produced corresponding adducts **94m-n** smoothly. We also attempted distereoselective addition by placing methyl groups on 4 or 5 positions of dihydrooxazole ring (**86g-h**). Unfortunately, these nucleophiles provided little diastereoselectivity (**94o-p**).

It is noteworthy that dihydrooxazoles **86k-n** failed to yield any similar adducts. We attribute this to an incompatibility of their acidic protons, either at benzylic positions or 2-position of oxazole ring, with our basic condition. In addition, the aromatic analog (**86n**) was unproductive, as the hydrolysis of corresponding oxazolium species requires disruption of aromatic system.

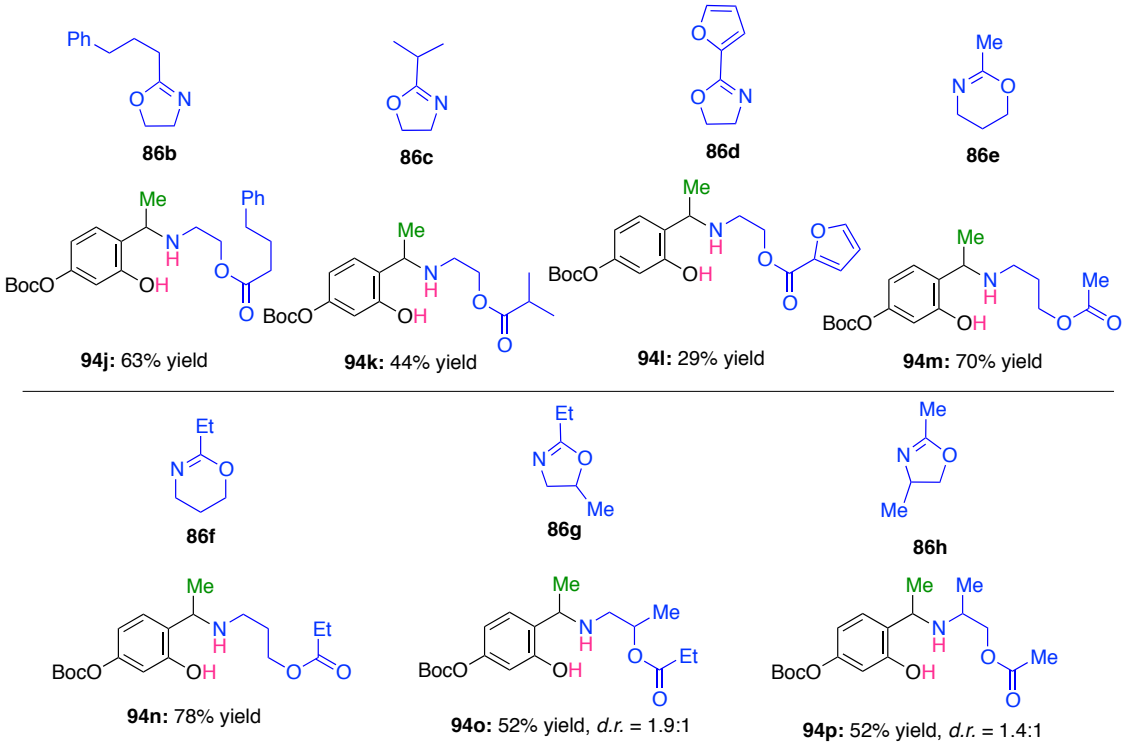


Figure 7. Scope of successful dihydrooxazole derivatives.

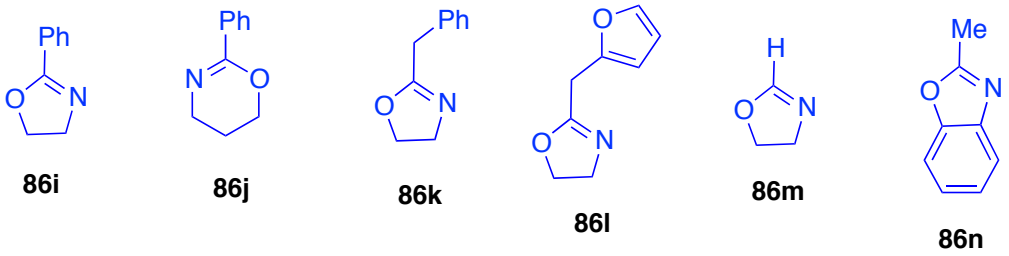


Figure 8. List of unsuccessful dihydrooxazole derivatives.

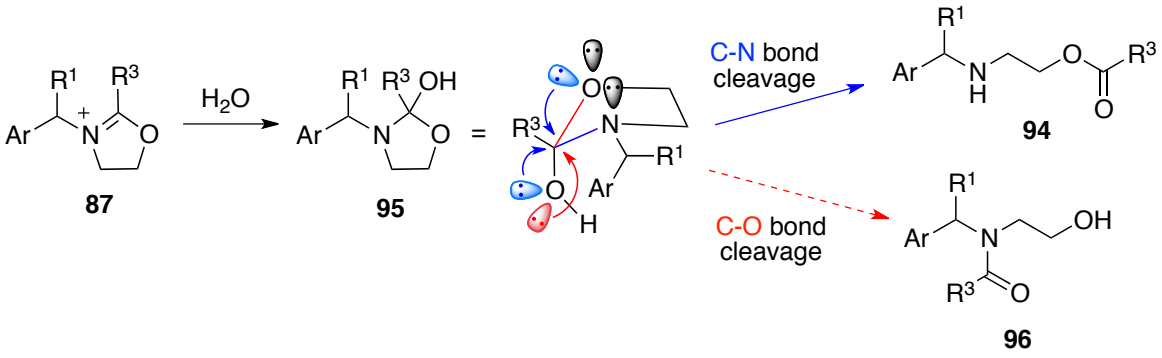
3.3 Mechanistic Studies

3.3.1 Origin of Regioselectivity in Hydrolysis

We speculate that if a reaction mixture containing dihydrooxazolium ion **87** comes into contact with water during work-up, then opportunistic water attacks the oxazolium species at 2-position to form hemi-orthoamide intermediate **95** (scheme 23). This intermediate can subsequently collapse to form either the amino-ester **94** or the more thermodynamically stable amide **96**. The exclusive formation of **94**, which is observed, can be explained by invoking the stereoelectronic model first proposed by Deslongchamps.[43d-f] Under kinetic condition, intermediate **95** adopts the most stable conformation shown, in which hydroxy group is placed in axial position due to anomeric effect, while the benzyl residue on nitrogen is placed in equatorial alignment. The energy barrier for C-N bond cleavage is thus lowered by alignment of the two oxygen lone pair orbitals in antiperiplanar fashion to C-N bond ($n_{\mathrm{O}} \rightarrow \sigma^{*}_{\mathrm{C-N}}$ interactions). In contrast, there is only one stereoelectronic interaction ($n_{\mathrm{O}} \rightarrow \sigma^{*}_{\mathrm{C-O}}$) for C-O bond cleavage. As a result, the amino-ester **94** is formed in a kinetically more favorable event. Apart from stereoelectronic arguments, we suspect

phenol in close proximity to basic nitrogen and may serve to assist cleavage of C-N bond through general acid catalysis.

Scheme 23. Kinetic preference in hydrolysis of oxazolium intermediate.



3.3.2 Direct Observation of Oxazolium Salt

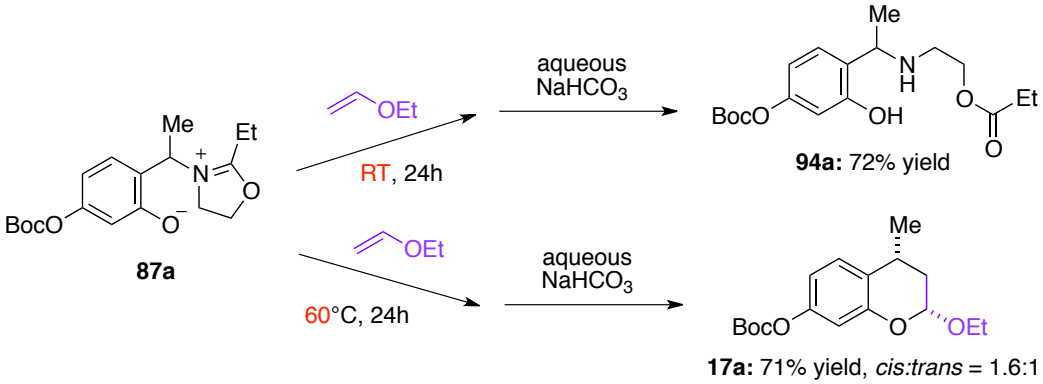
The oxazolium intermediate **87a**, which is formed before aqueous work-up, was subsequently found to be much longer-lived than other *o*-QM precursors along our cascade pathway. The salt appears stable for at least 48 hours in Et_2O at room temperature. We attempted to obtain direct spectroscopic evidence of the oxazolium salt by removing Et_2O directly without aqueous work-up. Crude ^{1}H-NMR in CD_2Cl_2 did not show any signals from expected 1,3-benzoxazine **88** or amino-ester **94a**. Comparing the crude ^{1}H-NMR with that of **94a** shows that protons adjacent to nitrogen in ethanolamine moiety have shifted downfield by 0.98 ppm, which is consistent with our proposed oxazolium salt **87a**.

3.4 Other Reactions Utilizing Oxazolium Salts

3.4.1 Oxazolium Salts as *o*-QM Precursors

Next, we attempted to utilize the intermediate dihydrooxazolium salts for reactions other than kinetic hydrolysis. Since the dihydrooxazole moiety is a good leaving group, we envisioned these oxazolium salts might serve as another class of *o*-QM precursors. To verify this hypothesis, we introduced ethyl vinyl ether (EVE) into the crude reaction mixture containing **87a** (scheme 24). When the mixture was stirred at room temperature for another 24 hours and worked up under aqueous conditions, the same amino-ester **94a** was obtained in comparable yield. However, when an identical mixture of **87a** and EVE was heated to 60°C for 24 hours, a [4 + 2] benzopyran adduct **17a** was isolated in 71% yield, with *cis*:*tran* = 1.6:1. These observations reveal that, while oxazolium salt **87a** is stable at room temperature, it remains an effective *o*-QM precursors at some elevated temperature between room temperature to 60°C.

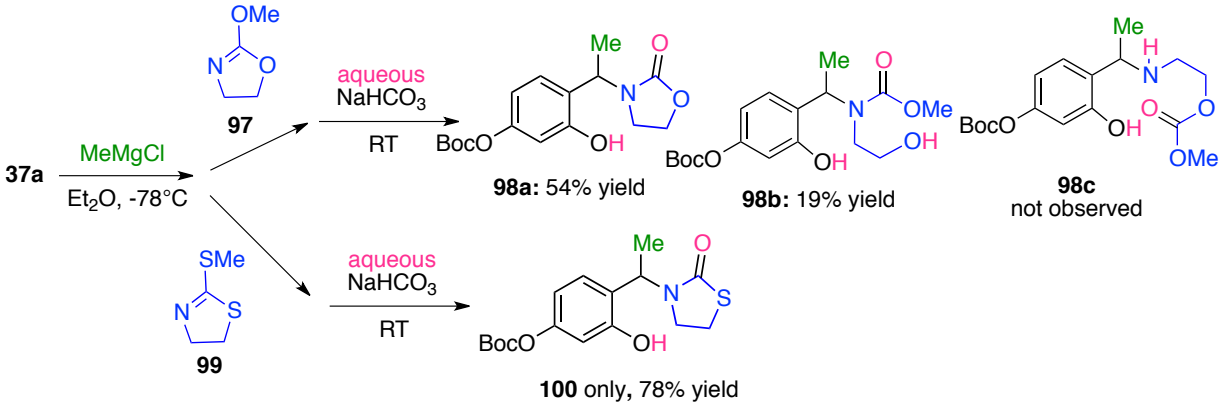
Scheme 24. Oxazolium salt as o-QM precursor.



3.4.2 Other Pathways for Hydrolysis

To explore plausible new pathways for collapse from the hemi-orthoamide intermediate **95**, 2-methoxy-4,5-dihydrooxazole (**97**), which possessed a good leaving methoxy group at 2-position, was deployed (scheme 25). In this case, the methoxy group became the preferential leaving group, so that the oxazolidinone **98a** formed in 54% yield, together with carbonate **98b** in 19% yield. Much to our surprise, none of the carbonate **98c** was observed. Similarly, using 2-(methylthio)-4,5-dihydrothiazole **99** as nucleophile, we observed that the reaction afforded the thiazolidin-2-one **100** exclusively in 78% yield. The improved selectivity is presumably due to thiomethyl being a better leaving group than an oxygen substituent.

Scheme 25. Reactions of 2-methoxydihydrooxazole and 2-(methylthio)-dihydrothiazole.

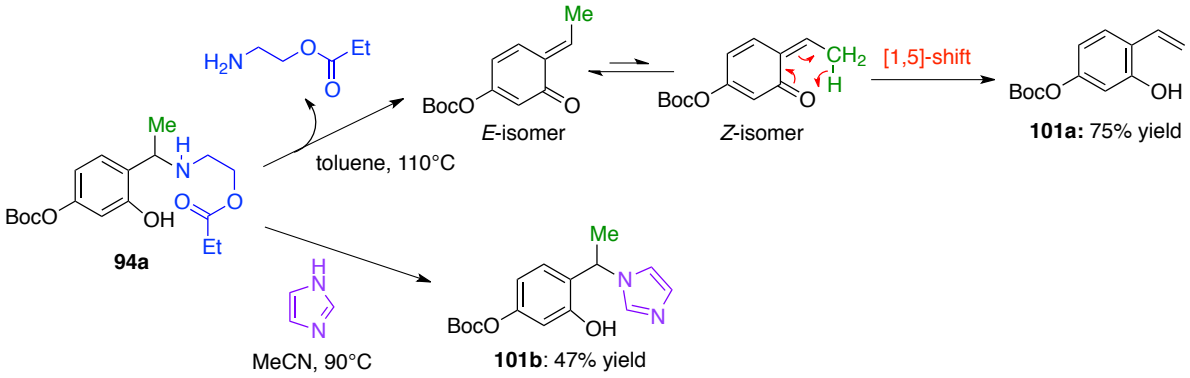


3.5 Transformations of Amino-ester Adducts

Among the amino-ester adducts **94** emerging from our four-component reaction several additional interesting transformations were observed (scheme 26). For example, styrene **101a** was formed in 75% yield when toluene solution of **94a** was heated at 110°C for 24 hours. We believe the reaction proceeds via reversible expulsion of ethanolamine moiety to form predominantly *E*-isomer of *o*-QM. However, under these elevated temperatures, part of the *E*-isomer is converted to less stable *Z*-isomer (scheme 1), and the ensuing [1,5] sigmatropic shift generates the observed product consuming all of the starting *E*-isomer.

We believe this finding shows our amino-ester adducts are yet another class of *o*-QM precursor. As further evidence of *o*-QM formation, we were able to trap the *o*-QM formed with imidazole to form adduct **101b**. To compare the tendency of amino-esters and oxazolium salts to form *o*-QM, a mixture of **94a** and EVE was heated at 60°C for 24 hours. No indications of [4+2] benzopyran adduct **17a** was observed in ^{1}H-NMR upon analysis of the crude reaction mixture. This observation suggests that our amino-ester products require higher temperature, somewhere between 60°C to 110°C, to generate *o*-QMs effectively, higher than the zwitterion precursor **87a**.

Scheme 26. Some transformations of our amino-ester adduct.



3.6 Applications in Natural Product Syntheses

Our new four-component reaction enables the facile introduction of a benzylic ethanolamine moiety in a single step. We thus imagined this robust tool might be applicable in the syntheses of several natural products with this structural motif (figure 9). For example, (±)-Stritida B & C (**102a-b**) are the first reported examples of pyridocarbazole alkaloids with N-2-hydroxyethyl moiety.[44] (+)-Hispidacine (**103**), on the other hand, is an 8,4'-oxyneolignan alkaloid with vasorelaxant activity, featuring unusual incorporation of 2-hydroxyethylamine moiety.[45] Meanwhile (±)-Irexine (**104**) is a newly produced isoindolinone metabolite of *I. lacteus* in the coculture with *P. oryzae*. However, we chose to demonstrate the potential application of our new 4-component reaction by total synthesis of mariline B (**105**), a naturally occurring racemic phthalimidine isolated from the sponge derived fungus *Stachylidium sp*.[46]

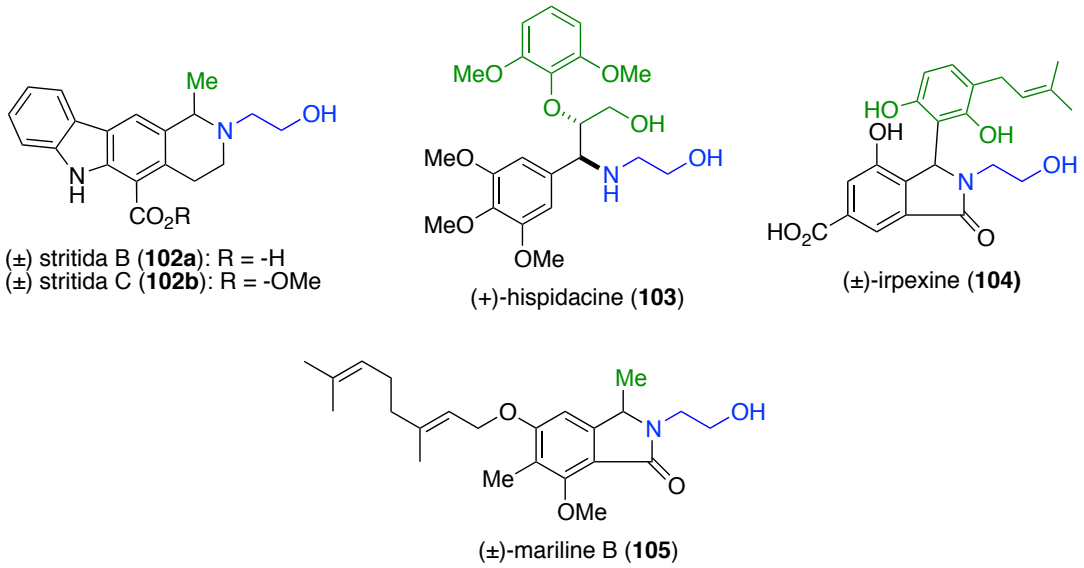
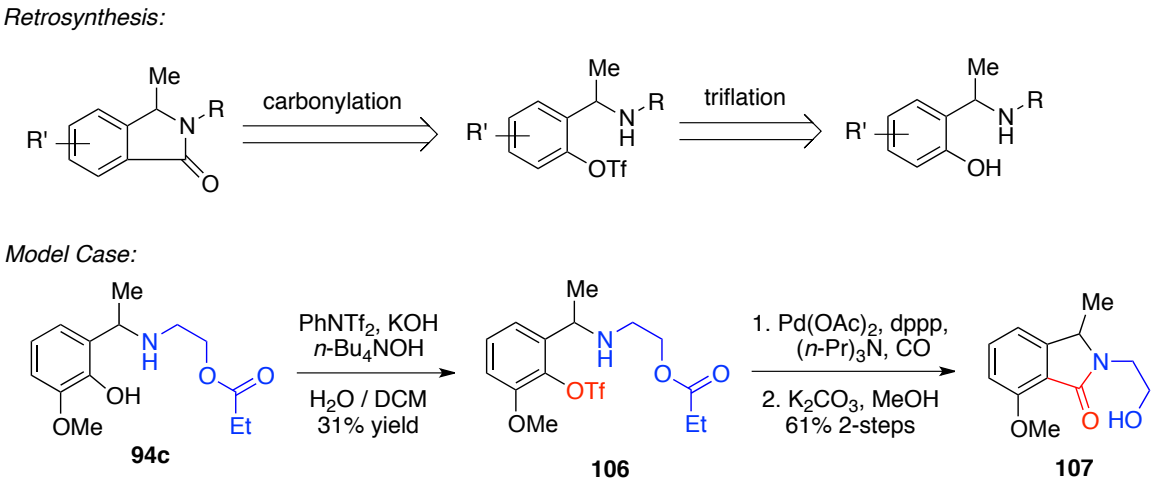


Figure 9. Potential natural product applications.

3.6.1 A Model Case of Mariline B

We supposed that the phthalimidine core could be constructed using a Buchwald-Hartwig variant of carbonylation. However, this strategy requires a selective triflation of phenol in the presence of benzylic secondary amine (scheme 27). We set out by synthesizing the phthalimidine **107** from the amino-ester **94c** as a model study. We accomplished the selective oxygen triflation required using biphasic conditions first developed by Sonesson.[47] Unfortunately, the yield of desired triflate **106** was only moderate (31%). Nevertheless, the palladium catalyzed carbonylation chemistry,[48] and ensuing one-pot saponification afforded the desired phthalimidine **107** in a satisfactory yield.

Scheme 27. Synthesizing model case of mariline B.

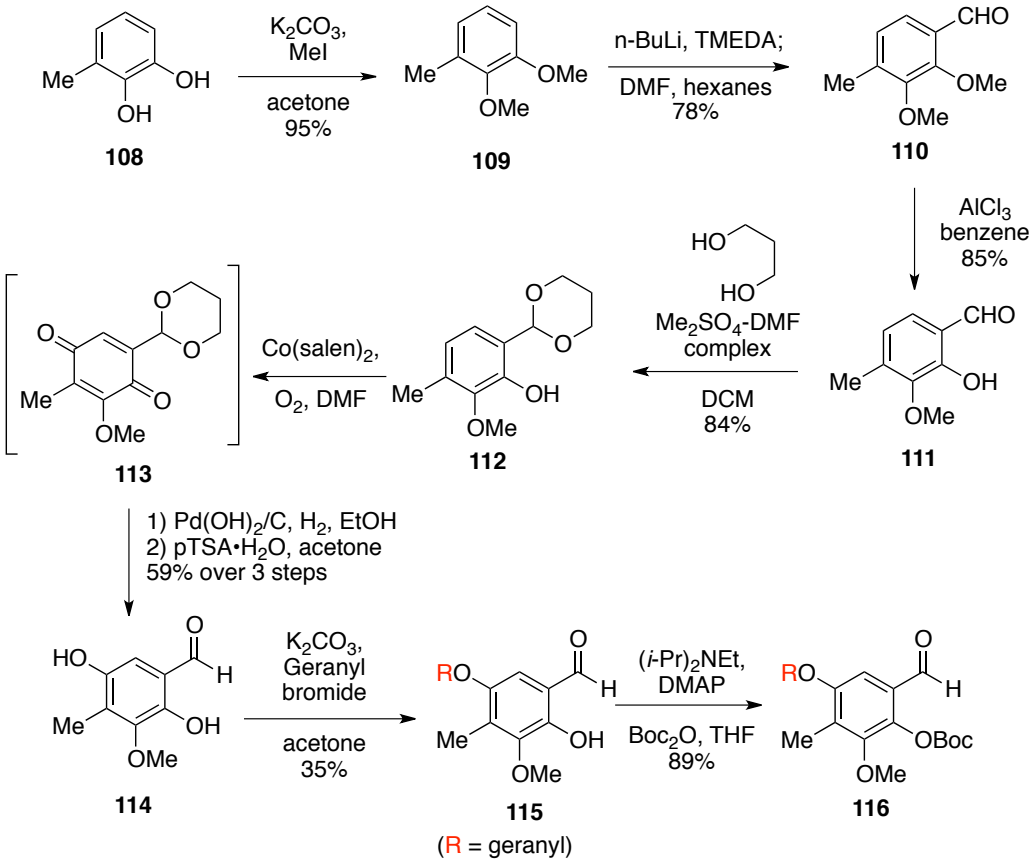


3.6.2 Total Synthesis of Mariline B

The rapid success of two-pot procedure in previous section prompted us to carry out the actual synthesis of (±)-mariline B. The synthesis of aromatic core began with the commercially available 3-methylbenzene-1,2-diol **108** (scheme 28). Standard Williamson ether synthesis with methyl iodide afforded *bis*-ether **109** in excellent yield. *Ortho*-lithiation and subsequent treatment with DMF smoothly afforded aldehyde **110**. Selective deprotection of the methyl ether in close proximity to the carbonyl group by $AlCl_3$ produced the desired salicylaldehyde **111**.[49] However, the electron-withdrawing carbonyl group hindered oxidation to quinone in the next step. Thus, the aldehyde was first protected as the acetal **112**. Aerobic *para*-oxidation using the convenient and well-known $Co(salen)_2$ catalyst smoothly afforded the *p*-quinone **113**.[50] This crude material was then submitted to hydrogenation using Pearlman's catalyst, followed by deprotection of the acetal to give the salicylaldehyde **114**. At this juncture, selective alkylation of phenol at 5-

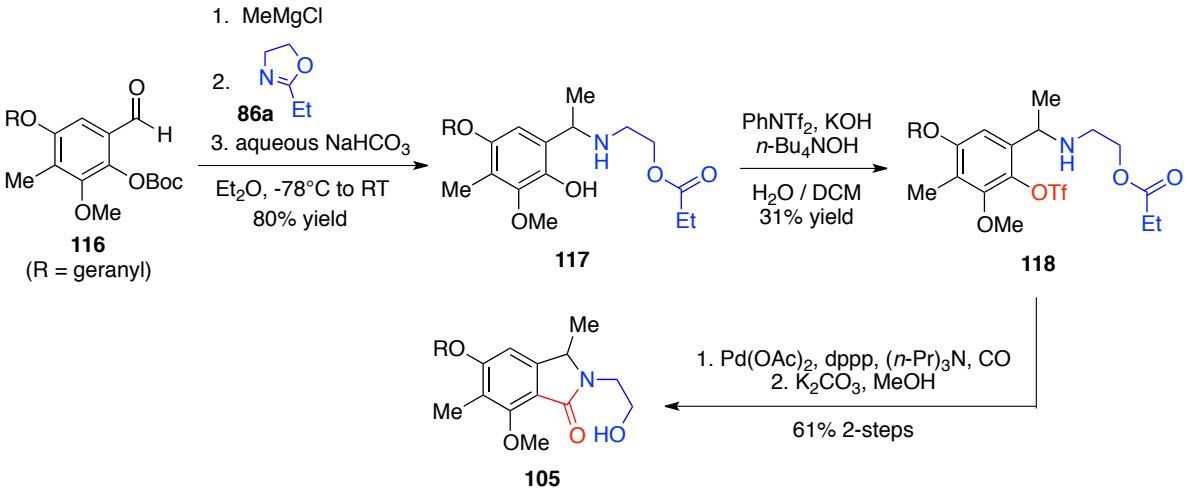
position with geranyl bromide afforded the desired ether **115** in moderate yield. Finally, standard protection of the phenol at 2-position using Boc_2O afforded the *o*-Boc salicylaldehyde **116**, as needed.

Scheme 28. Synthesis of salicylaldehyde precursor **116**.

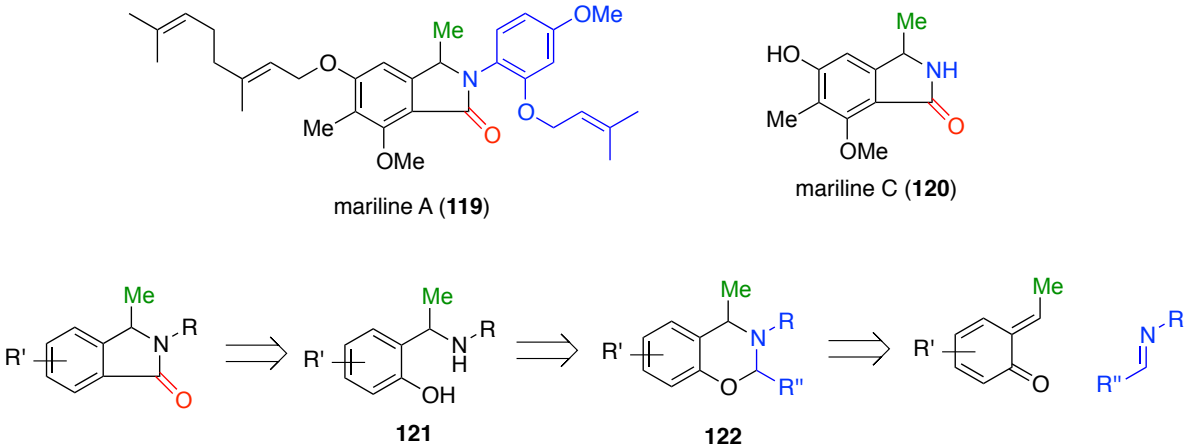


To complete the synthesis, the *o*-Boc salicylaldehyde **116** was next submitted to our four-component reaction using methylmagnesium chloride, the dihydrooxazole **86a**, and opportunistic water to afford amino-ester **117** in very satisfactory yield (scheme 29). Following the same triflation sequence as before, mariline B (**105**) was obtained.

Scheme 29. Synthesis of mariline B using our four-component reaction.



Scheme 30. Retrosyntheses of mariline A and C.



3.6.3 Plausible Adaptions to the Syntheses of (±)-Marilines A and C

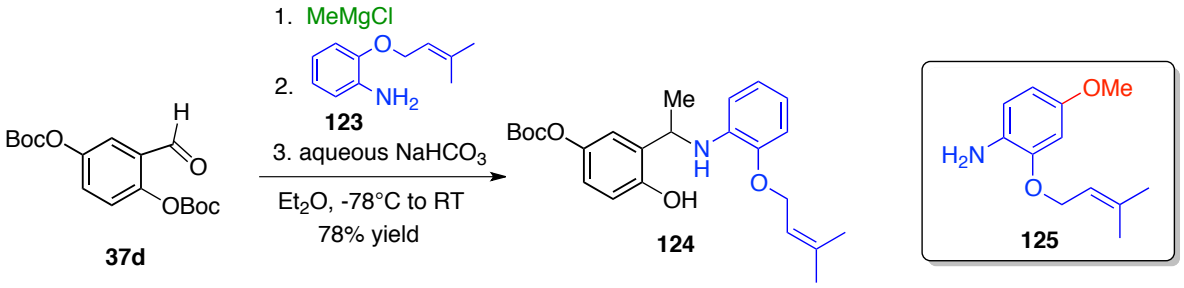
We next turned our attention to the remaining two natural products, marilines A and C (**119-120**, scheme 30). We imagined that they could be accessed from the benzyl amines **121**, which could be obtained by hydrolysis of the requisite benzoxazines **122**. In other words, we speculated that the reaction of imines to *o*-QMs described in chapter 2 could be applied to these other natural products.

First, we prepared the benzyl amine **124** as a model case. As we have seen in chapter 2, *bis*-aryl imines are unreactive under our low-temperature conditions (section 2.3.2). Hence, we required a class II imine in order to install *N*-aryl group needed to construct mariline A. However, we found that *neither* condensation of aniline **123** with straight chain propionaldehyde *nor* the branched chain isobutyraldehyde afforded the desired imine, presumably due to facile imine-enamine tautomerization. Nevertheless, we found the free aniline **123** could be directly used as nucleophile with the *o*-QM generated by our method. In this manner the desired benzyl amine **124** was smoothly formed in 78% yield (scheme 31). We speculate that application of the same triflation and carbonylation sequence with aldehyde **116** and aniline **125** should provide a total synthesis of mariline A.

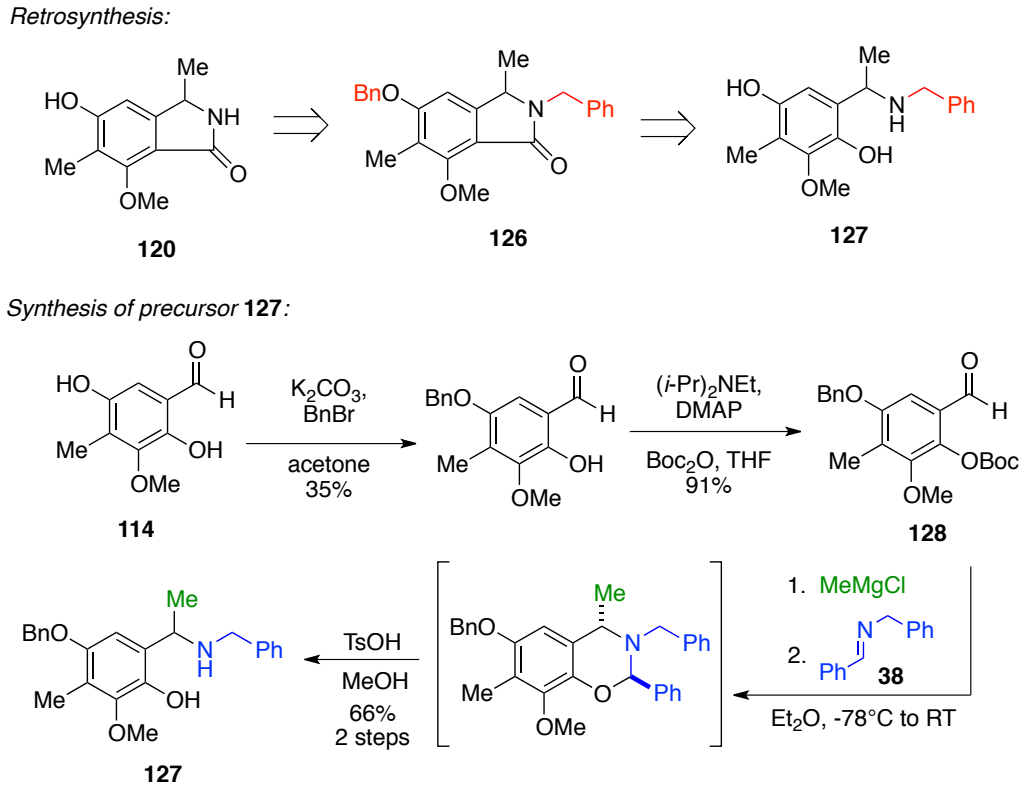
We next explored the possibility of synthesizing mariline C. We imagined that the *bis*-benzyl variant **126** serving as a precursor (scheme 32). It presumably can be accessed from the benzyl amine **127** using the same triflation and carbonylation sequence. Thus, we prepared the *o*-Boc salicylaldehyde **128** by selective benzylation of phenol **114** followed by standard protection with Boc_2O. In the light of direct addition of aniline we had just observed, we first attempted to perform similar

addition using a free benzylamine as the nucleophile. Unfortunately, no desired adduct **127** was observed. Instead, we found that if the classic imine **38** was deployed, then hydrolysis of the adduct afforded **127** in one-pot and in good yield. Execution of the carbonylation sequence is expected to yield mariline C.

Scheme 31. Synthesis of a model benzyl alcohol precursor to mariline A.



Scheme 32. Potential synthesis of mariline C.



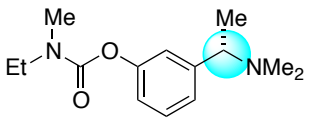
3.7 Conclusion

In conclusion, we have developed a *novel* four-component reaction that provides a variety of structurally diverse products. The mechanism involves an unusual zwitterionic oxazolium that undergoes regioselective hydrolysis. We have shown the zwitterion to be an *o*-QM precursor that is long-lived at room temperature. This new *o*-QM precursor might provide many more transformations that are not accessible with our OBoc triggered generation method. We futher anticipated the oxazolium species itself can be utilized in other useful transformations, such as ring opening by assorted nucleophiles at 2 or 5 positions. Finally, we have demonstrated the utility of our four-component reaction in several natural product applications.

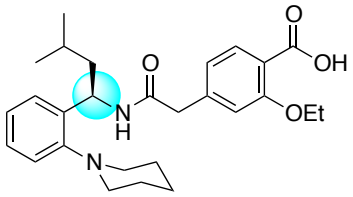
Chapter 4. Asymmetric Addition of Nitrogen Nucleophiles to *o*-QMs

4.1 Introduction

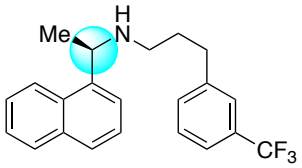
Chiral benzylic amines are common subunits in a wide range of biologically active molecules, natural products and pharmaceuticals (figure 10).[51] For example, the anti-dementia agent Rivastigmine (**129**) is used in treatment of Alzheimer's and Parkinson's diseases.[52] Repaglinide (**130**) is a drug used in the treatment of type 2 diabetes.[53] Cinacalcet (**131**) is a medication used to treat hyperparathyroidism in patients with chronic kidney diseases.[52] The preparation of enantioenriched benzyl amine is of particular importance. Moreover, very often only one particular enantiomer has desired biological effect, while the opposite enantiomer is inactive or affords an undesirable effect. Unfortunately, only a few robust synthetic methods have been developed for the creation of enantioenriched benzylic amine stereocenters.



Rivastigmine (**129**)



Repagilinide (**130**)

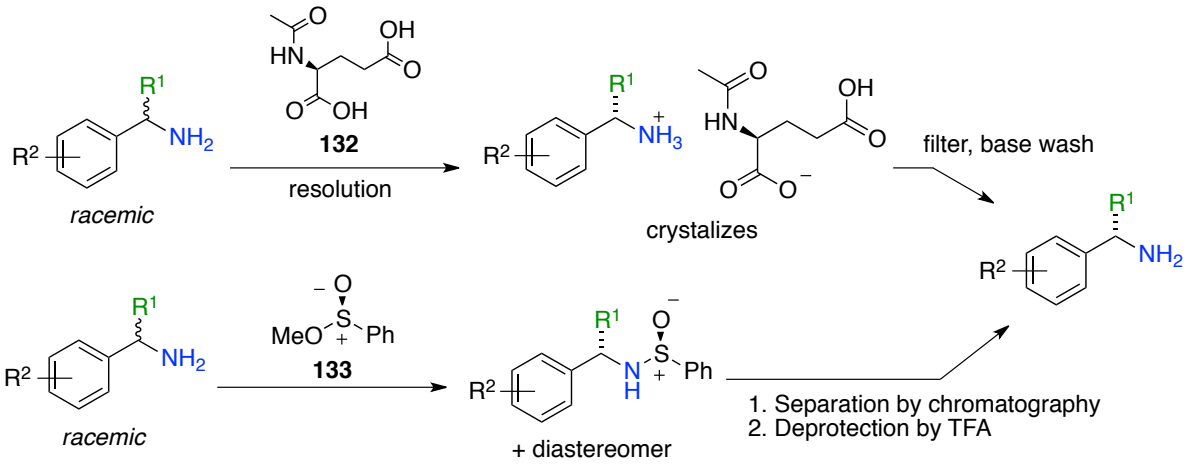


Cinacalcet (**131**)

Figure 10. Examples of pharmaceutical molecules bearing chiral benzylic amine units.

Chiral resolution of racemic mixture is still the most general method to obtain chiral amines (scheme 33). The racemate is allowed to react with chiral resolving agents **132-133** to afford mixture of two diastereomers, which can be separated by selective crystallization or column chromatography.[54] An obvious shortcoming of this method is that the undesired, opposite enantiomer is simply discarded after resolution.

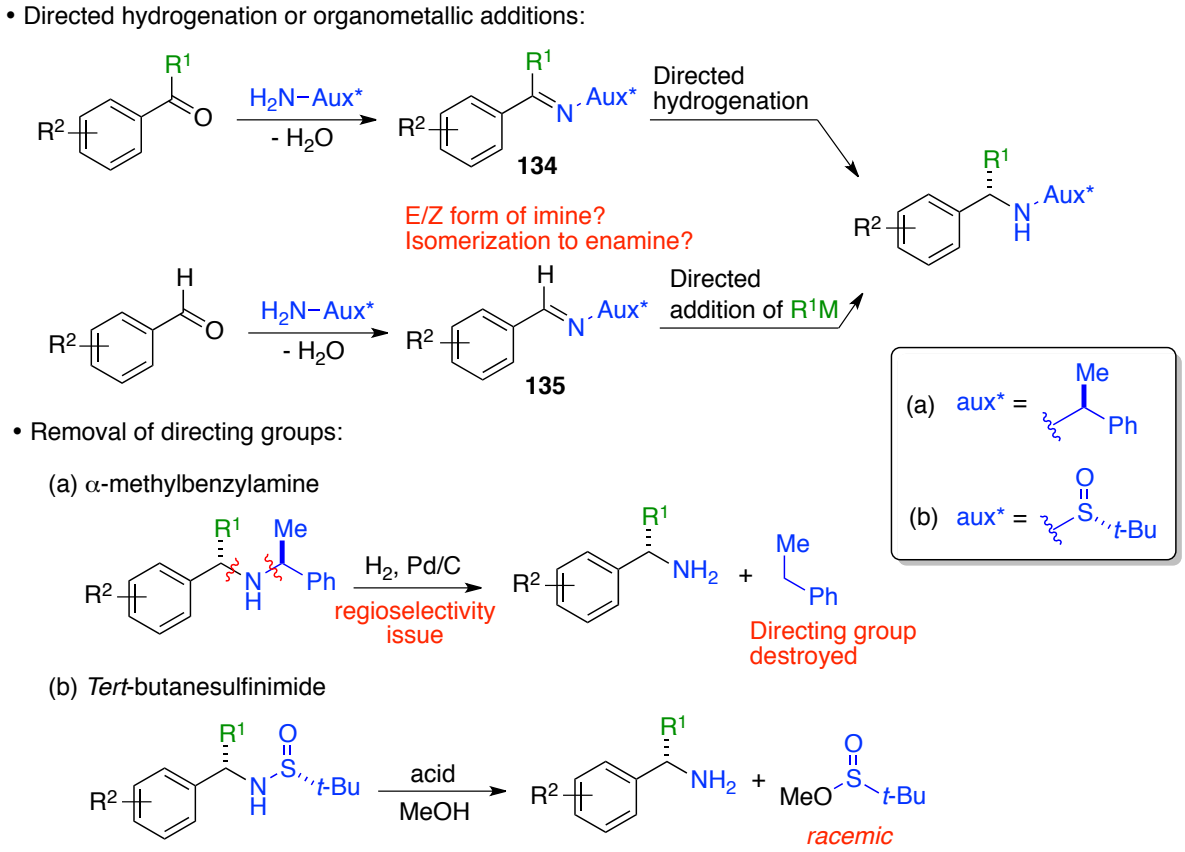
Scheme 33. Preparation of enantioenriched benzyl amines by chiral resolutions.



To remedy this deficiency, two types of directing groups, namely α-methylbenzylamines and *tert*-butanesulfinimides have been developed (scheme 34). Both of them are used to prepare imines **134-135** with stereocenter alpha to nitrogen, which allows directed reduction or addition by organometallic reagents.[55] However, the removal and recovery of these auxiliaries are problematic. In the case of α-methylbenzylamines, removing directing group by hydrogenolysis is hardly

regioselective, and the directing group is destroyed upon removal. For sulfinimides, the chiral directing group becomes racemic under acidic hydrolysis condition.

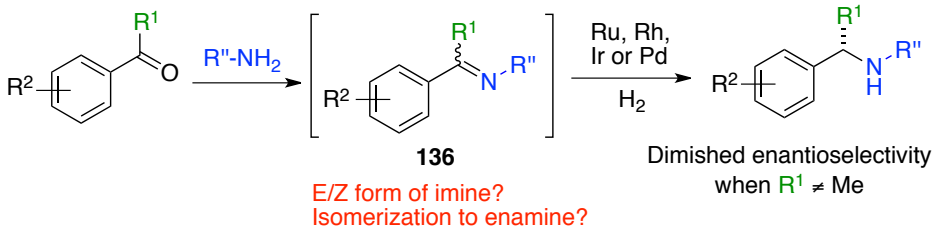
Scheme 34. Asymmetric synthesis of chiral benzylic amines using directing groups.



There are also several report on catalytic asymmetric hydrogenation of enamines (scheme 35).[56] However, the scope of substrate is limited to acetophenone (R^1 = -CH_3). Deviations from acetophenone core leads to vastly lower enantiomeric excess due to imine-enamine isomerization of intermediates resembling **136**. To the best of our knowledge, a recoverable chiral auxiliary that enabled the preparation of chiral benzylic amines is unknown. We therefore speculated that by proper design of chiral imine from a chiral aldehyde, asymmetric

addition of nitrogen nucleophiles to *o*-QM might provide a new method to prepare chiral benzylic amines.

Scheme 35. Catalytic asymmetric hydrogenation of enamines.



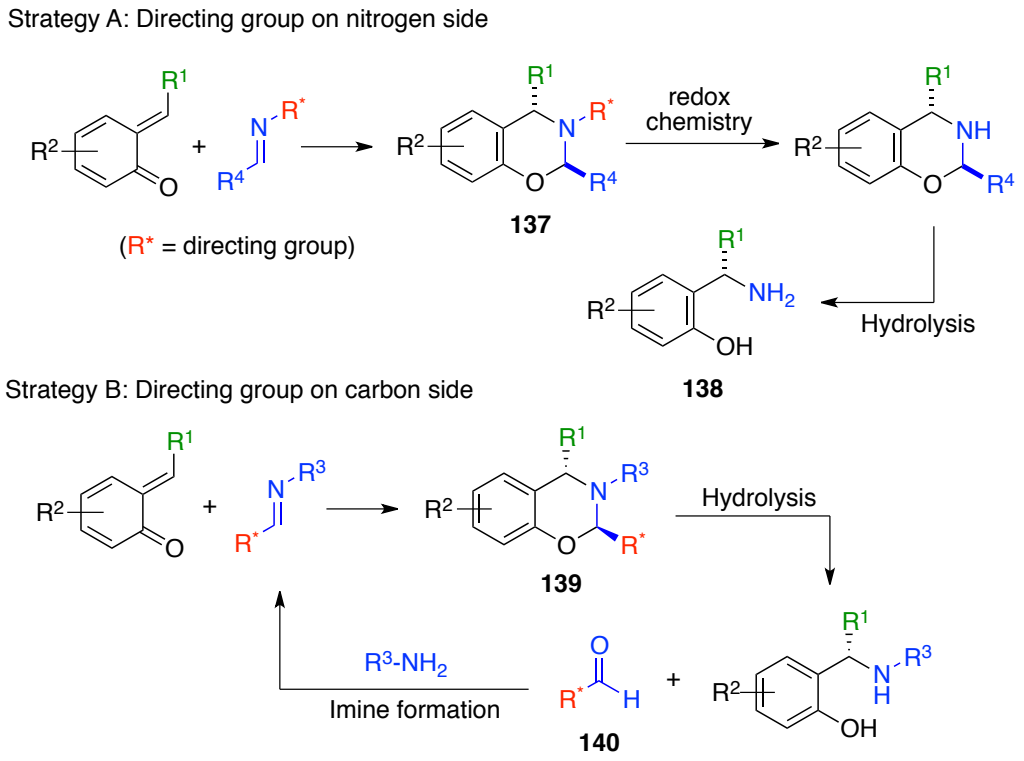
4.2 Designs of Chiral Auxiliaries for Asymmetric Additions

4.2.1 General Design Strategies

We hypothesized that diastereoselective addition of a nitrogen nucleophile to an *o*-QM could be accomplished by attaching some directing group to either nitrogen side of the imine (strategy A, scheme 36) or upon its carbon side (strategy B). Each strategy would requires different conditions to remove the initial directing group. For strategy A, once the benzoxazine **137** is formed, the chiral directing group can be selectively removed using redox chemistry. Subsequent hydrolysis should afford the desired chiral benzylic amine **138**. In the case of strategy B, the directing group on the aldehyde **140** could be easily recovered upon hydrolysis of benzoxazine **139**. The latter strategy presented several potential advantages over those summarized in section 4.1. *First*, there would be no regioselectivity issue when the directing group was removed. *Second*, a directing group on the aldehyde is neither destroyed nor racemized, and could be recycled in subsequent imine

formation reactions. Third, our multicomponent *o*-QM procedure enables quick one-pot access to a structurally diverse array of amines. Thus, strategy B was of particular interest.

Scheme 36. Two general design strategies of chiral auxiliaries.

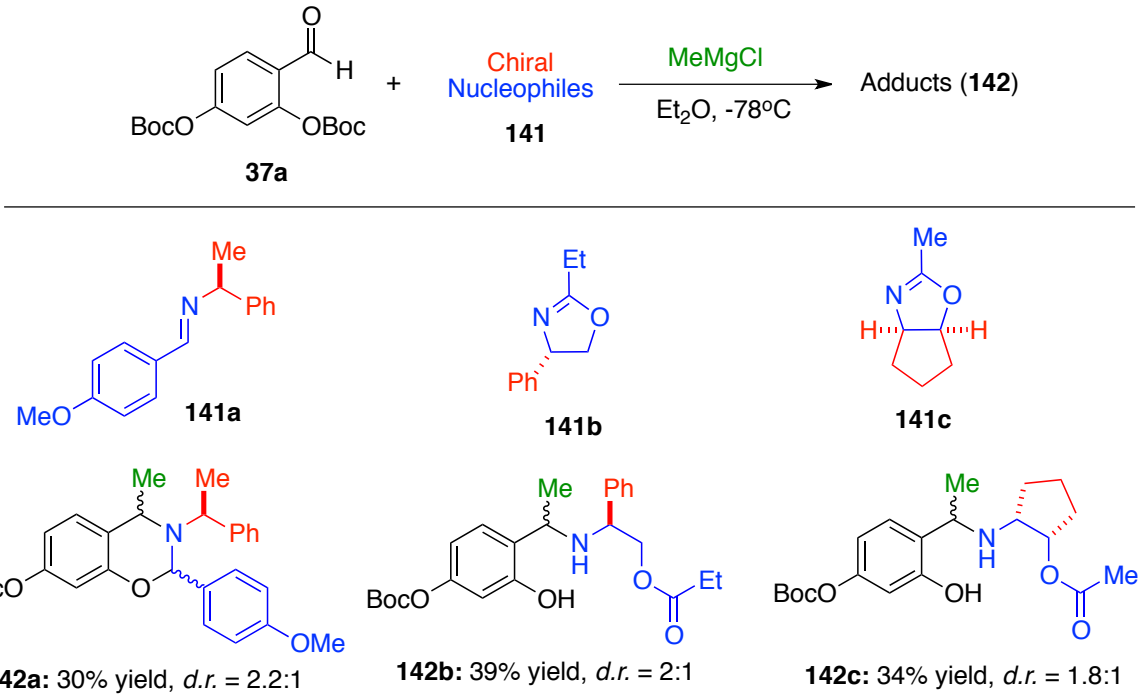


4.2.2 Strategy A: Directing Groups Near Nucleophilic Nitrogen

Nevertheless, we began by exploring chiral nucleophiles with directing groups near nitrogen atom (scheme 37). Inspired by directing groups used in asymmetric hydrogenations, we prepared the imine **141a** derived from α-methylbenzylamine. As we have seen in section 2.3.4, branching adjacent to nitrogen resulted in lower yields of the desired benzoxazine adduct **142a**. Moreover, much to our surprise, this chiral imine provided a low diastereoselectivity of 2.2:1.

To improve the yield among potential chiral adducts, we turned our attention to dihydrooxazoles, with the hope that resonance donation from oxygen atom could make these components more nucleophilic. Having observed that compound **86h** afford very little diastereoselectivity (section 3.2.3), we next explored dihydrooxazoles with larger substituents at their 4-position. With a phenyl group (**141b**), the diastereomeric ratio (*d.r.*) was slightly improved to around a 2:1 ratio (**142b**), albeit in a slightly lower yield due to greater steric encumbrance near nitrogen. Whereas, the bicyclic analog **141c** afforded the adduct **142c** with slightly lower yield and diastereomeric ratio. All of these attempts seemed to suggest that placing a directing group near the nitrogen atom failed to afford appreciable diastereoselectivity during the initial 1,4-conjugate addition with the *o*-QM.

Scheme 37. Some chiral nitrogen nucleophiles explored under strategy A.



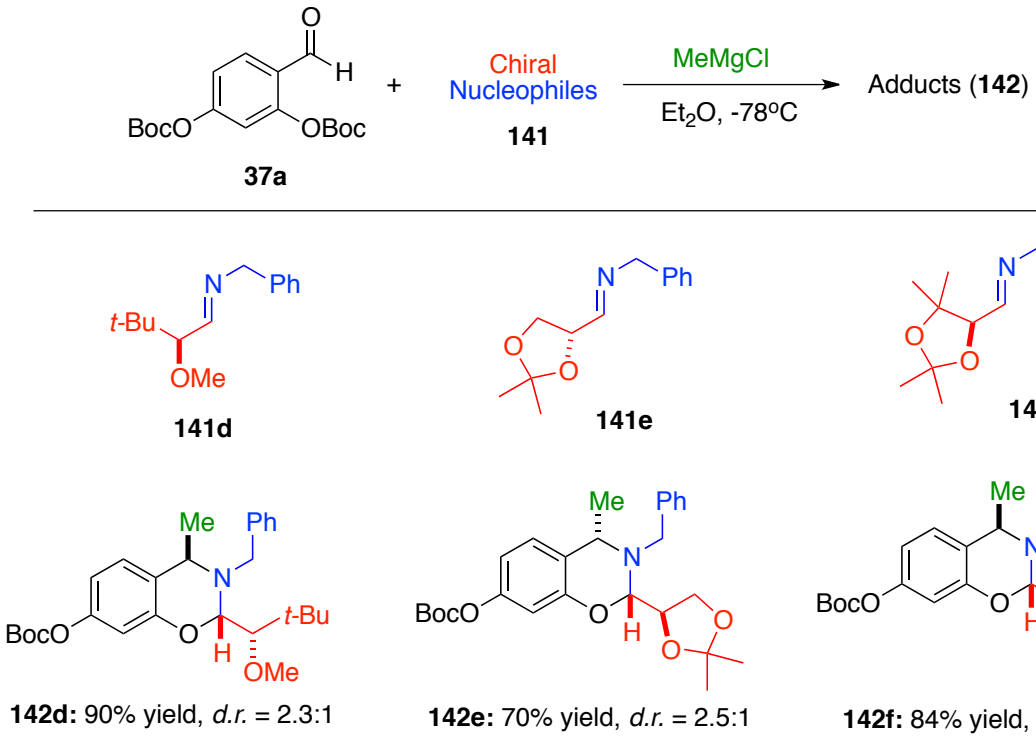
4.2.3 Strategy B: Directing Groups Near Carbon of Imines

We next explored strategy B, which involved placing a directing group on the carbon side of the starting imine. However, the requisite starting chiral aldehydes, which would possess a stereocenter at the α position, are notorious for facile racemization though either acid or base catalyzed keto-enol tautomerization. We therefore began with imine **141d** (scheme 38),[57] as the α-methoxy substituent discourages tautomerization by destabilizing the enol form and ensuring that the aldehyde remain configurationally stable. This imine gave an excellent yield of benzoxazine **142d** with an encouraging *d.r.* of 2.3:1. Continuing along, we prepared imine **141e** from readily available glyceraldehyde acetonide.[58] We were pleased that there was a slight improvement in diastereoselectivity of adduct **142e**. Theorizing that this was indeed a linear 1,4 conjugate addition, we were delighted to find that installation of *gem*-dimethyl group at β position (**141f**) afforded the benzoxazine **142f** in excellent yield and as single diastereomer. The relative configuration of **142f** was confirmed by X-ray diffraction analysis of its crystal.

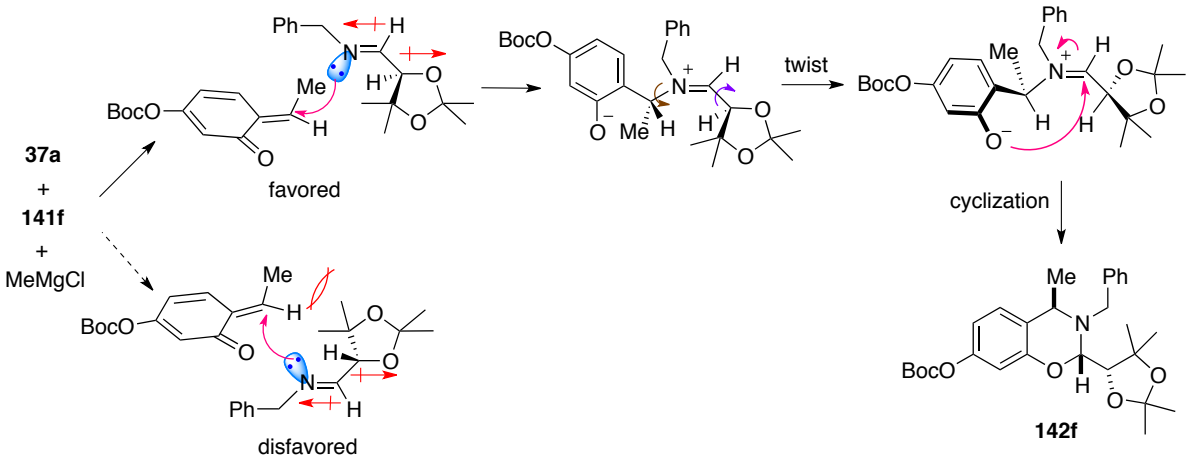
A stereochemical model that foretold of this improved selectivity is shown in scheme 39. We speculated that during conjugate addition, the C-O bond at α position is aligned anti-periplanar to imine C=N bond. In this manner, cancellation of the two dipole moments helps to minimize the overall energy of this transition state. As we have seen in section 2.5.2, a forward twist is favorable for minimizing 1,3-allylic strain. Thus, two consecutive diastereotopic moves, the intial addition and the direction of rotation for cyclization, provide the benzoxazine product as single

diastereomer. Thus, the relative configuration between the existing and created stereocenters in our adduct **142f** agrees with our stereochemical model.

Scheme 38. Some chiral imines explored under strategy B.



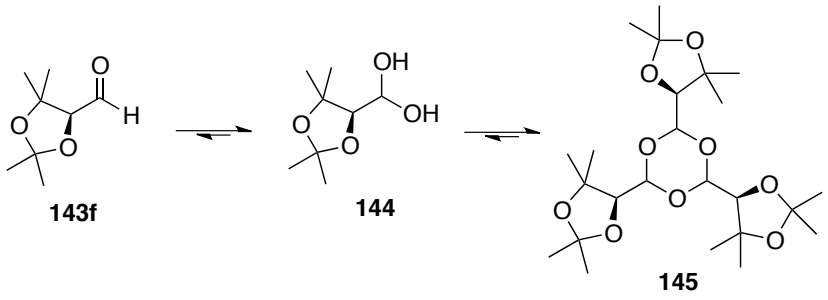
Scheme 39. Plausible stereochemical model of asymmetric addition.



4.3 Improving Recovery of Chiral Aldehyde

Despite providing excellent diastereoselectivity, we realized the aldehyde **143f** (scheme 40) was problematic to recover upon hydrolysis of benzoxazine adduct: *First*, its ketal functionality proves sensitive to the *aqueous* acidic condition required to hydrolyze the benzoxazine. *Second*, the α-alkoxy aldehyde readily form its corresponding hydrate **144** provides the trimer **145** in less than an hour at room temperature. Third, we find the recovered aldehyde to be quite unstable on silica gel chromatography.

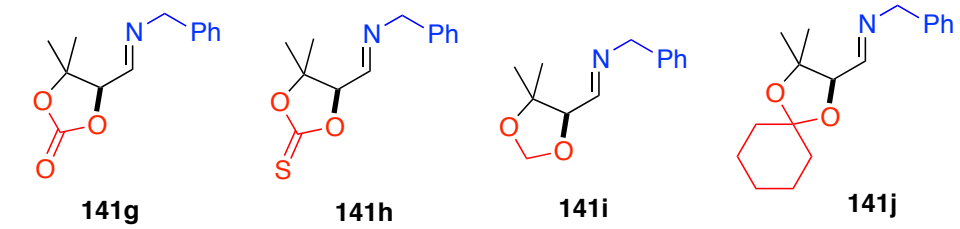
Scheme 40. Hydration and trimerization of aldehyde **143f**.



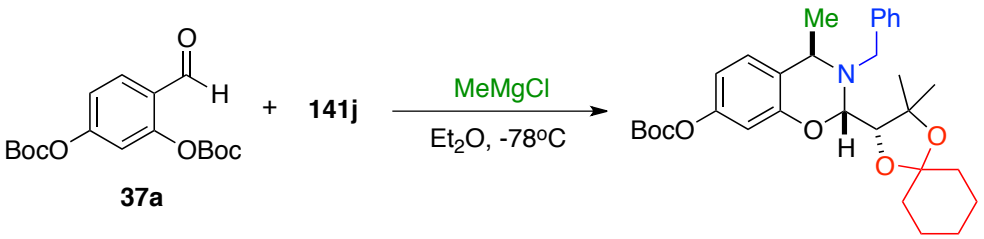
We attempted to solve the first problem by investigating more acid-stable functionalities, such as carbonate (**141g**, scheme 41) and thiocarbonate (**141h**), attached to the 1,2-diol moiety of aldehyde. Unfortunately, these compounds were even less stable than **143f**. They could only be formed *in-situ* and used in subsequent imine formation in one-pot. We believed that perhaps these electron-withdrawing groups had increased their tendency to form hydrate and thus facilitated trimerization upon work-up. The methylene acetal analog **141i** did not

provide any noticeable improvement, presumably because the more hydrophilic nature led to an increased tendency of corresponding aldehyde to form hydrate. We next prepared the corresponding cyclohexylidene ketal analog **141j**. To our delight, the starting aldehyde **143j** proves quite stable at room temperature for more than a week and easily traverses chromatography on silica gel. Moreover, submission of the ensuing imine **141j** to our *o*-QM condition afforded the expected benzoxazine **142j** as in single diastereomer! These observations demonstate that **142j** can be used as a recoverable chiral auxiliary upon hydrolysis of the benzoxazine, thereby providing a new route for enantioselective access to these kinds of important chiral benzylic amines.

Scheme 41. Other chiral imine analogs explored.



141g **141h** **141i** **141j**



37a

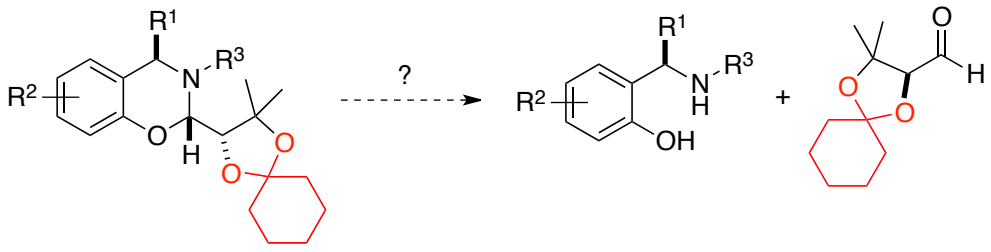
142j: 78% yield, *d.r.* > 20:1

4.4 Future Directions

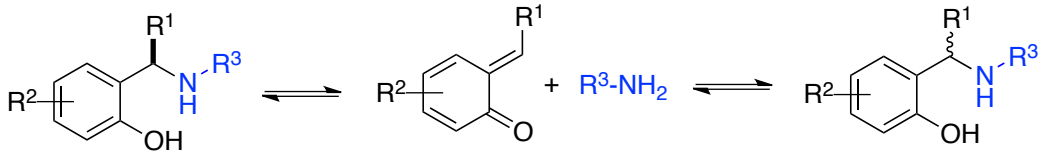
With a stable, recoverable aldehyde, we can develop streamlined conditions for benzoxazine hydrolysis (scheme 42a). We believe the use of solid resin acid catalyst, such as Amberlyst® 15, can affect rapid and selective hydrolysis as required. Another challenge will be to determine if racemization can occur after hydrolysis after formation of the corresponding resulting benzyl amine **146** after hydrolysis (scheme 42b) via *o*-QM reformation and readdition. However, to the best of our knowledge this process requires elevated temperatures. Moreover, protection of phenol would be expected to further mitigate this problem, if it were to arise. Finally, it would be desirable to greatly expand the scope of reaction to include other versatile Grignard reagents containing other functional groups, thereby providing quick access to enantiomerically enriched benzylic amines that are not accessible with current catalytic methods that can only address methylated derivatives.

Scheme 42. Potential challenges in hydrolysis of benzoxazines.

(a) Selective hydrolysis of benzoxazines:



(b) Potential racemization:



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Experimentals

1. General Techniques

In reactions where water was not present as a solvent, reagent, or byproduct, the glassware was flame dried, and the reactions were carried out under an inert atmosphere of nitrogen. Reactions were monitored by analytical thin-layer chromatography on EMD silica gel 60 F254 plates; visualization was effected by ultraviolet light (254 nm), *p*-anisaldehyde or potassium permanganate stains. Solvents were removed using a rotary evaporator. If the product was non-volatile, trace solvents were removed at a reduced pressure of approximately 2 mmHg.

All purchased chemicals were used without purification unless otherwise stated. Dichloromethane, acetonitrile, hexanes and triethylamine was distilled from CaH_2. Diethyl ether, tetrahydrofuran, benzene and toluene were distilled from sodium and benzophenone. Deuterated chloroform was stored over anhydrous potassium carbonate and 4Å molecular sieves before use.

^1H NMR spectra were recorded at 400, 500, or 600 MHz on *Varian* or *Bruker* instruments with the solvent resonance of $CDCl_3$ (7.26 ppm), CD_2Cl_2 (5.32 ppm), CD_3OD (3.31 ppm) and DMSO-d_6 (2.50 ppm). ^{13}C NMR spectra were recorded at 500 or 600 MHz instruments with a solvent resonance of $CDCl_3$ (77.0 ppm). High resolution mass spectra (HRMS) were obtained by electrospray ionization/time-of-flight experiments.

2. Experimental Procedures

2.1 Synthesis of *o*-Boc Salicyaldehydes 37

General Procedure A

To a solution of phenol (10 mmol) in THF (50 mL) was slowly added NaH (0.48 g, 12 mmol, 1.2 equiv., 60% dispersion in mineral oil) at 0°C. After stirring for 10 minutes, Boc_2O (3.27 g, 15 mmol, 1.5 equiv.) was added. The mixture was stirred at room temperature for 13 hours. It was then quenched with saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with ethyl acetate (40 mL $\times$ 3). Organic layers were combined, washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 20:1 $\rightarrow$ 3:1) to afford pure products.

** In the case of bis-phenols (**37a** and **37d**), the amount of NaH and Boc_2O were doubled to afford bis-protected products.*

2.2 Synthesis of Achiral Imines

General Procedure B

At room temperature, aldehyde (20 mmol) and amine (20 mmol) were dissolved in dichloromethane (60 mL). Trimethyl orthoacetate (20 mmol, 2.4 mL) was added. The mixture was stirred overnight. The mixture was then concentrated *in vacuo*, and purified by vacuum distillation to afford the respective imine.

General Procedure C

At room temperature, aldehyde (20 mmol) and amine (20 mmol) were dissolved in dichloromethane (60 mL). Anhydrous magnesium sulfate (4 g) was added, and the suspension was stirred overnight. Magnesium sulfate was removed by filtration, and the solvents were removed *in vacuo*. The residue was then purified by either recrystallization or vacuum distillation.

General Procedure D

Amine (20 mmol) was placed in a round-bottom flask equipped with an addition funnel. The flask was cooled to 0°C using an ice-water bath. With stirring, aldehyde was added dropwise through addition funnel over 2 hours. The mixture was then warmed to room temperature. Several pellets of KOH were added. Stirring was continued for 30 minutes. Aqueous layer formed at bottom was removed using a pipette. Several additional pellets of KOH were added, and the mixture was left overnight. Finally, the liquid was purified by vacuum distillation to afford pure imines.

(*E*)-*N*-benzyl-3-phenylpropan-1-imine (53) was synthesized according to general procedure D as colorless oil (b.p. = 122 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (tt, *J* = 4.6, 1.3 Hz, 1H), 7.33-7.27 (m, 4H), 7.26-7.23 (m, 2H), 7.22-7.19 (m, 4H), 4.57 (s, 2H), 2.92 (t, *J* = 7.9 Hz, 2H), 2.67-2.64 (m, 2H). Our characterization data matched prior literature data.[1]

(*E*)-*N*-benzyl-2-methylpropan-1-imine (54) was synthesized according to general procedure B as colorless oil (b.p. = 59 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (dt, *J* = 5.5, 1.5 Hz, 1H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 3H), 4.56 (s, 2H),

[1] Tian, H.; Yu, X.; Li, Q.; Wang, J.; Xu, Q. *Adv. Synth. Catal*. **2012**, *354*, 2671-2677.

2.50 (sept d, *J* = 6.5, 5.5 Hz, 1H), 1.12 (d, *J* = 6.5 Hz, 6H). Our characterization data matched prior literature data.[2]

(*E*)-2-methyl-*N*-(propan-2-yl)propan-1-imine (55) was synthesized according to general procedure B as colorless oil (b.p. = 100 ^{o}C under 760 torr). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 5.7 Hz, 1H), 3.23 (sept, *J* = 6.4 Hz, 1H), 2.39 (sept d, *J* = 6.8, 5.7 Hz, 1H), 1.13 (d, *J* = 6.4 Hz, 6H), 1.05 (d, *J* = 6.8 Hz, 6H). Our spectral characterization matched prior literature data.[3]

(*E*)-*N*-(4-methoxyphenyl)-2-methylpropan-1-imine (59) was synthesized according to general procedure B as yellow oil (b.p. = 122 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (d, *J* = 5.0 Hz, 1H), 7.02 (d, *J* = 9 Hz, 2H), 6.87 (d, *J* = 9 Hz, 2H), 3.81 (s, 3H), 2.61 (sept, *J* = 6.9 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 6H). Our characterization data matched prior literature data.[4]

(*E*)-*N*-(4-fluorophenyl)-2-methylpropan-1-imine (60) was synthesized according to general procedure C as colorless oil (b.p. = 37 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (d, *J* = 4.8 Hz, 1H), 7.04-6.96 (m, 4H), 2.62 (heptd, *J* = 6.9, 4.8 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 161.0 (d, $J_{C\text{-}F}$ = 241 Hz), 148.5, 122.1 (d, $J_{C\text{-}F}$ = 6.5 Hz), 115.8 (d, $J_{C\text{-}F}$ = 22.3 Hz), 34.8, 19.2. HRMS (ESI) Unstable under HRMS conditions.

(*E*)-*N*,1-diphenylmethanimine (63) was synthesized according to general procedure C. Purified by recrystallization from hot hexanes. Yellow solid. ^{1}H NMR

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[2] Chen, M. Z.; McLaughlin, M.; Takahashi, M.; Tarselli, M. A.; Yang, D.; Umemura, S.; Micalizio, G. C. *J. Org. Chem.* **2010**, *75*, 8048-8059.

[3] Mandal, D.; Dolai, R.; Chrysochos, N.; Kalita, P.; Kumar, R.; Dhara, D.; Maiti, A.; Narayanan, R. S.; Rajaraman, G.; Schulzke, C.; Chandrasekhar, V.; Jana, A. *Org. Lett.* **2017**, *19*, 5605-5608.

[4] Anderson, J. C.; Kalogirou, A. S.; Porter M. J.; Tizzard. G. J. *Beilstein J. Org. Chem.* **2013**, *9*, 1737-1744.

(500 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.92-7.91 (m, 2H), 7.50-7.47 (m, 3H), 7.42-7.39 (m, 2H), 7.26-7.21 (m, 3H). Our characterization data matched prior literature data.[5]

(*E*)-*N*-(4-methoxyphenyl)-1-phenylmethanimine (64) was synthesized according to general procedure C. Purified by recrystallization from hot hexanes. White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.93-7.91 (m, 2H), 7.50-7.48 (m, 3H), 7.27 (d, *J* = 9.0 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H). Our characterization data matched prior literature data.[6]

(*E*)-1-(4-methoxyphenyl)-*N*-phenylmethanimine (65) was synthesized according to general procedure C. Purified by recrystallization from hot hexanes. Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.85 (d, *J* = 9.2, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.23-7.18 (m, 3H), 6.99 (d, *J* = 9.2, 2H), 3.88 (s, 3H). Our characterization data matched prior literature data.[7]

(*E*)-*N*-benzyl-1-phenylmethanimine (38) was synthesized according to general procedure B as colorless oil (b.p. = 105 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.80-7.78 (m, 2H), 7.44-7.40 (m, 3H), 7.34 (t, *J* = 4.5 Hz, 4H), 7.28-7.25 (m, 1H), 4.84 (s, 2H). Our characterization data matched prior literature data.[8]

(*E*)-*N*-benzyl-1-(4-methoxyphenyl)methanimine (51) was synthesized according to general procedure B as colorless oil that solidified upon storage (b.p. = 135 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.73 (d, *J* = 9 Hz, 2H),

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[5] Schaufelberger, F.; Timmer, B. J. J.; Ramström, O. *Chem. Eur. J.* **2018**, *24*, 101-104.
[6] Monopoli, A.; Cotugno, P.; Iannone, F.; Ciminale, F.; Dell'Anna, M. M.; Mastrorilli, P.; Nacci, A. *Eur. J. Org. Chem.* **2014**, *27*, 5925-5931.
[7] Vayer, M.; Morcillo, S. P.; Dupont, J.; Gandon, V.; Bour, C. *Angew. Chem. Int. Ed.* **2018**, *57*, 3228-3232.
[8] Lawson, J. R.; Wilkins, L. C.; Melen, R. L.; *Chem. Eur. J.* **2017**, *23*, 10997-11000.

7.36-7.33 (m, 4H), 7.27-7.24 (m, 1H), 6.93 (d, *J* = 9 Hz, 2H), 4.80 (s, 2H), 3.85 (s, 3H). Our characterization data matched prior literature data.[9]

(*E*)-*N*-benzyl-1-(4-nitrophenyl)methanimine (66) was synthesized according to general procedure C. Purified by recrystallization from a mixture of hexanes, dichloromethane, diethyl ether and ethyl acetate. Yellow solid.^{1}H NMR (600 MHz, $CDCl_3$): δ 8.47 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.39-7.34 (m, 4H), 7.31-7.28 (m, 1H), 4.89 (s, 2H). Our characterization data matched prior literature data. [8]

(*E*)-*N*-[(4-methoxyphenyl)methyl]-1-phenylmethanimine (67) was synthesized according to general procedure B as colorless oil (b.p. = 148 ^{o}C under 2 torr). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.79-7.76 (m, 2H), 7.43-7.40 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.77 (s, 2H), 3.80 (s, 3H). Our characterization data matched prior literature data.[10]

(*E*)-*N*-benzyl-1-(furan-2-yl)methanimine (68) was synthesized according to general procedure B as yellow oil (b.p. = 116 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.52 (d, *J* = 0.9 Hz, 1H), 7.35-7.32 (m, 3H), 7.28-7.25 (m, 2H), 6.78 (d, *J* = 3.4 Hz, 1H), 6.48 (dd, *J* = 3.4, 1.7 Hz, 1H), 4.79 (s, 2H). Our characterization data matched prior literature data. [7]

(*E*)-1-(4-methoxyphenyl)-*N*-(propan-2-yl)methanimine (69) was synthesized according to general procedure B as colorless oil (b.p. = 68 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.67 (d, *J* = 9 Hz, 2H), 6.91 (d, *J* = 9 Hz,

[9] Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 6579-6587.
[10] Guimond, N.; Fagnou, K.; *J. Am. Chem. Soc.* **2009**, *131*, 12050-12051.

2H), 3.84 (s, 3H), 3.50 (sept, *J* = 6.3 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 6H). Our characterization data matched prior literature data.[11]

(*E*)-*N*-(propan-2-yl)-1-(2,4,6-trimethylphenyl)methanimine (70) was synthesized according to general procedure B as colorless oil (b.p. = 60 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (s, 1H), 6.84 (s, 2H), 3.51 (sept, *J* = 6.3 Hz, 1H), 2.34 (s, 6H), 2.26 (s, 3H), 1.28 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.3, 138.3, 136.9, 131.9, 129.1, 62.8, 24.6, 21.2, 20.3. HRMS (ESI) m/z calculated for $C_{13}H_{20}N$ $[M+H]^+$: 190.1596; found 190.1605.

(*E*)-*N*-(2-methoxyethyl)-1-phenylmethanimine (71) was synthesized according to general procedure B as colorless oil (b.p. = 60 ^{o}C under 2 torr). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.75-7.73 (m, 2H), 7.42-7.39 (m, 3H), 3.80 (t, *J* = 6.0 Hz, 2H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.38 (s, 3H). Our characterization data matched prior literature data.[12]

***N*-benzylpropan-2-imine (81)** was synthesized according to general procedure C as colorless oil (b.p. = 68 ^{o}C under 2 torr).^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34-7.31 (m, 4H), 7.24-7.22 (m, 1H), 4.46 (s, 2H), 2.09 (s, 3H), 1.94 (s, 3H). Our characterization data matched prior literature data.[13]

3,4-Dihydroisoquinoline (72). At room temperature, 1,2,3,4-tetrahydroisoquinoline (2.66 g, 20 mmol) was dissolved in dichloromethane (100 mL). Freshly recrystallized *N*-bromosuccinimide (3.92 g, 22 mmol, 1.1 equiv.) was added

[11] Koyama, Y.; Gudeangadi, P. G. *Chem. Commun.* **2017**, *53*, 3846-3849
[12] Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817-12819.
[13] Paul, B.; Chakrabarti, K.; Kundu, S. *Dalton Trans.* **2016**, *45*, 11162-11171.

portionwise over 20 minutes. The solution was stirred at room temperature for 45 minutes. 30% NaOH solution was added, and the two-phase mixture was stirred for additional one hour. The organic layer was separated and washed with water (50 mL), and then extracted by 1M HCl (100 mL). The acidic aqueous layer was washed with dichloromethane (50 mL), and then carefully neutralized by 28% ammonium hydroxide solution until pH was close to 9. The oil precipitated out was extracted by dichloromethane (100 mL x 2), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by vacuum distillation (b.p. = 58 ^{o}C under 2 torr) to afford pure imine **72** as colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.34 (t, *J* = 2.1 Hz, 1H), 7.36 (td, *J* = 7.3, 1.7 Hz, 1H), 7.31-7.29 (m, 1H), 7.27 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 3.79-3.76 (m, 2H), 2.76 (t, *J* = 7.7 Hz, 2H). Our characterization data matched prior literature data.[14]

2.3 Three-Component Assembly of 3,4-Dihydro-2*H*-1,3-benzoxazines

General Procedure E

A flame-dried round-bottomed flask was charged with pure imine under nitrogen atmosphere. The imine was dissolved in appropriate amount of dry toluene to make up a 1.0 M of solution. Trimethyl orthoacetate (5% by mass of imine) was added, followed by 4Å molecular sieves. The solution was stored in desiccator overnight before use. The *o*-Boc salicylaldehyde **37a** was diluted as 1.0 M solution in dry toluene under nitrogen similarly.

[14] Huang, B.; Tian, H.; Lin, S.; Xie, M.; Yu, X.; Xu, Q. *Tet. Lett.* **2013**, *54*, 2861-2864

Imine (0.1 mL, 0.1 mmol, 1.0 M in toluene, 1 equiv. unless otherwise specified) was added to a stirred solution of **37a** (0.1 mL, 0.1 mmol, 1.0 M in toluene, 1 equiv.) in Et_2O (1 mL) at room temperature. Grignard reagent (PhMgCl or MeMgCl solutions in THF, 1.05 equiv.) was added to the mixture at -78 ºC. The reaction mixture was allowed to warm to room temperature over six hours then quenched with pH 2.6 buffer solution (1 mL) and stirred for 2 hours at room temperature. The aqueous solution was extracted with Et_2O (3 x 1 mL) then the combined organic solution was washed with saturated sodium bicarbonate solution (3 x 1 mL). Saturated sodium bisulfite solution (1 mL) was added to the combined organic solution and stirred for 1.5 hours at room temperature. The aqueous solution was extracted with Et_2O (3 x 1 mL), then the combined organic solution was washed with brine (1 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford crude product. Crude NMR yields were determined by dibromomethane as internal standard. Purification by flash column chromatography (SiO_2, eluent: 1% triethylamine in hexane) was performed to afford pure product when specified.

***Trans*-3-benzyl-2-phenethyl-4-phenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (56a).** Prepared according to the general procedure E. 81% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (48.61 mg, 78% isolated yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.25-7.22 (m, 1H), 7.16-7.15 (m, 3H), 7.06-7.02 (m, 3H), 6.99 (d, *J* = 6.3 Hz, 2H), 6.88 (d, *J* = 7.1 Hz, 2H), 6.83 (d, *J* = 8.3 Hz,

1H), 6.70 (d, *J* = 2.1 Hz, 1H), 6.66 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.73 (s, 1H), 4.68 (t, *J* = 6.6 Hz, 1H), 4.17 (d, *J* = 14.0 Hz, 1H), 3.38 (d, *J* = 14.0 Hz, 1H), 2.62-2.58 (m, 2H), 2.12-2.02 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.0, 152.2, 150.9, 143.3, 141.4, 139.3, 131.0, 129.4, 129.3, 128.7, 128.6, 128.5, 128.2, 127.5, 127.3, 126.0, 117.3, 113.5, 109.8, 85.7, 83.8, 60.6, 49.7, 33.7, 31.3, 27.9. HRMS (ESI) m/z calculated for $C_{34}H_{35}NO_4Na$ $[M+Na]^+$: 544.2464; found 544.2460 R_f = 0.6 (hexanes/ethyl acetate = 9:1).

***Trans*-3-benzyl-4-methyl-2-phenethyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl tert-butyl carbonate (56b).** Prepared according to the general procedure E. 83% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (32 mg, 70% isolated yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34-7.23 (m, 9H), 7.17-7.12 (m, 2H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.64 (s, 1H), 4.88 (t, *J* = 6.6 Hz), 4.14 (d, *J* = 14.9 Hz, 1H), 3.68 (q, *J* = 7.1 Hz), 3.34 (d, *J* = 14.8 Hz, 1H), 2.87-2.74 (m, 2H), 2.24 (m, *J* = 8.9, 6.7 Hz, 1H), 2.15 (m, *J* = 13.7, 8.7, 6.5 Hz, 1H), 1.52 (s, 9H), 1.29 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.3, 152.3, 150.2, 141.5, 139.7, 129.3, 128.8, 128.7, 128.7, 128.3, 127.2, 126.3, 122.8, 113.7, 109.8, 85.7, 83.7, 53.4, 49.6, 33.7, 31.7, 30.0, 28.0, 24.0. HRMS (ESI) m/z calculated for $C_{29}H_{34}NO_4$ $[M+H]^+$: 460.2488; found 460.2473 R_f = 0.5 (hexanes/ethyl acetate = 9:1).

***Trans*-3-benzyl-2-isopropyl-4-phenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl tert-butyl carbonate (57a).** Prepared according to the general procedure E. 95% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (43.38 mg, 94% isolated yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (d, *J* =

7.4 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.68 (s, 1H), 4.13 (d, *J* = 9.5 Hz, 1H), 4.09 (d, *J* = 13.9 Hz, 1H), 3.35 (d, *J* = 13.9 Hz, 1H), 2.16-2.09 (m, 1H), 1.51 (s, 9H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.0, 152.3, 150.9, 143.4, 139.2, 131.1, 129.3, 129.0, 128.7, 128.1, 127.5, 127.2, 117.2, 113.3, 109.9, 91.7, 83.7, 59.9, 49.4, 29.5, 28.0, 19.7, 18.3. HRMS (ESI) m/z calculated for $C_{29}H_{33}NO_4Na$ $[M+Na]^+$: 482.2307; found 482.2316. R_f = 0.6 (hexanes/ethyl acetate = 9:1).*Trans*-stereochemistry assignment was confirmed by nOe analysis.

***Trans*-3-benzyl-2-isopropyl-4-methyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl tert-butyl carbonate (57b).** Prepared according to the general procedure E. 82% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (25 mg, 72% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.29 (m, 4H), 7.25 (d, *J* = 5.2 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.44 (d, *J* = 9.3 Hz, 1H), 4.09 (d, *J* = 15.0 Hz, 1H), 3.69 (q, *J* = 7.0 Hz, 1H), 3.37 (d, *J* = 15.0 Hz, 1H), 2.21 (dp, *J* = 9.4, 6.6 Hz, 1H), 1.56 (s, 9H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 6.5 Hz,), 1.05 (d, *J* = 6.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.5, 152.3, 150.2, 129.3, 128.6, 128.2, 127.1, 122.8, 113.6, 109.8, 91.9, 83.7, 52.9, 49.5, 29.7, 28.0, 23.9, 20.1, 18.6. HRMS (ESI) m/z calculated for $C_{24}H_{32}NO_4$ $[M+H]^+$: 398.2331; found 398.2336. R_f = 0.4 (hexanes/ethyl acetate = 9:1). *Trans*-stereochemistry assignment was confirmed by nOe analysis.

***Tert*-butyl (*trans*-2,3-diisopropyl-4-phenyl-3,4-dihydro-2H- benzo[*e*][1,3]oxazin-7-yl) carbonate (58a).** Prepared according to the general procedure E using two equivalents of **55**. 63% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (30.43 mg, 61% isolated yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21-7.18 (m, 4H), 7.13 (t, *J* = 6.6 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.63-6.60 (m, 2H), 4.94 (s, 1H), 4.04 (d, *J* = 9.5 Hz, 1H), 3.51-3.44 (m, 1H), 2.15-2.09 (m, 1H), 1.49 (s, 9H), 1.28 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.68 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.3, 152.2, 150.6, 144.6, 129.5, 128.9, 128.1, 126.8, 121.0, 112.6, 110.1, 92.8, 83.6, 54.6, 45.7, 29.3, 27.9, 23.4, 21.3, 20.0, 18.5. HRMS (ESI) m/z calculated for $C_{25}H_{33}NO_4Na$ $[M+Na]^+$: 434.2307; found 434.2310. R_f = 0.6 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl(*trans*-2,3-diisopropyl-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (58b).** Prepared according to the general procedure E. 72% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (22 mg, 63% isolated yield, inseparable mixture of diastereomers, *dr* = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) 7.00 (d, *J* = 8.3 Hz, 1H), 6.63 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 4.33 (d, *J* = 9.5 Hz, 1H), 3.98 (q, *J* = 6.9 Hz, 1H), 3.39 (p, *J* = 6.7 Hz, 1H), 2.22 (dp, *J* = 9.4, 6.6 Hz, 1H), 1.54 (s, 9H), 1.38 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 152.3, 149.8, 127.8, 126.3, 112.9, 109.9, 92.9, 83.5, 46.7, 45.7, 29.2, 27.9, 24.8, 22.9, 20.4, 20.3, 18.8. HRMS (ESI) m/z calculated for $C_{20}H_{32}NO_4$ $[M+H]^+$: 350.2331; found 350.2343. R_f = 0.4

(hexanes/ethyl acetate = 9:1). *Trans*-stereochemistry of major isomer was confirmed by nOe analysis.

***Tert*-butyl(*trans*-2-isopropyl-3-(4-methoxyphenyl)-4 phenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl)carbonate (61a).** Prepared according to the general procedure E. 61% crude NMR yield. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.8 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.9 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.64 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.08 (s, 1H), 4.26 (d, *J* = 9.7 Hz, 1H), 3.69 (s, 3H), 1.95-1.89 (m, 1H), 1.51 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.63 (d, *J* = 6.6 Hz, 3H). **R_f** = 0.5 (hexanes/ethyl acetate = 9:1). *Trans*-stereochemistry assignment was confirmed by nOe analysis.

***Tert*-butyl(*trans*-2-isopropyl-3-(4-methoxyphenyl)-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl)carbonate (61b).** Prepared according to the general procedure E. 71% crude NMR yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.13-7.12 (m, 2H), 6.92 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.79-6.70 (m, 3H), 6.66 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.57 (d, *J* = 9.7 Hz, 1H), 4.08 (q, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 2.00 (dp, *J* = 9.6, 6.6 Hz, 1H), 1.56 (m, 12H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H). **R_f** = 0.4 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl(*trans*-3-(4-fluorophenyl)-2-isopropyl-4-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (62a).** Prepared according to the general procedure E using two equivalents of **60**. 67% crude NMR yield. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.7 Hz, 2H), 7.29-7.27 (m, 4H), 7.23-7.21 (m, 1H), 6.90-6.86 (m, 3H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.10 (s, 1H), 4.27

(d, *J* = 9.7 Hz, 1H), 1.98-1.93 (m, 1H), 1.50 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.61 (d, *J* = 6.6 Hz, 3H). $\mathbf{R_f}$ = 0.6 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl((2R,4S)-3-(4-fluorophenyl)-2-isopropyl-4-methyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (62b).** Prepared according to the general procedure E. 65% crude NMR yield. $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 9:1). *Trans*-stereochemistry of major isomer was confirmed by nOe analysis.

***Trans*-3-benzyl-2,4-diphenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (39a).** Prepared according to the general procedure E. 83% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (34.97 mg, 71% isolated yield).**^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.26-7.25 (m, 3H), 7.24-7.16 (m, 5H), 7.13-7.12 (m, 3H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.75 (s, 1H), 4.82 (s, 1H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.28 (d, *J* = 14.0 Hz, 1H), 1.52 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.5, 152.2, 151.1, 143.5, 139.2, 138.0, 131.2, 129.3, 129.2, 128.6, 128.4, 128.3, 128.2, 127.4 (2C), 126.6, 117.4, 113.9, 110.3, 85.9, 83.7, 59.7, 49.7, 28.0. **HRMS (ESI)** m/z calculated for $C_{32}H_{31}NO_4Na$ $[M+Na]^+$: 516.2151; found 516.2164. $\mathbf{R_f}$ = 0.6 (hexanes/ethyl acetate = 9:1).

***Trans*-3-benzyl-4-methyl-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazin-7-yl *tert*-butyl carbonate (39b).** Prepared according to the general procedure E. 83% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (37 mg, 85% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.33-7.10 (m, 6.84H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.86-6.85 (m, 1H), 6.72 (dt, *J* = 8.3, 1.7 Hz, 1H), 6.05 (s, 1H), 3.82 (q, *J* =7.0 Hz, 1H),

3.78 (d, *J* = 14.9 Hz, 1H), 3.30 (d, *J* = 14.8 Hz, 1H), 1.55 (s, 9H), 1.51 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.8, 152.3, 150.3, 139.6, 138.3, 129.3, 128.6, 128.5, 128.3, 128.2, 127.1, 126.7, 123.0, 114.2, 110.3, 86.1, 83.8, 52.5, 49.9, 28.0, 24.2. **HRMS (ESI)** m/z calculated for $C_{27}H_{30}NO_4$ $[M+H]^+$: 432.2175; found 432.2189. **R_f** = 0.5 (hexanes/ethyl acetate = 9:1). *Trans*-stereochemistry assignment was confirmed by nOe analysis.

***Trans*-3-benzyl-2-(4-methoxyphenyl)-4-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (52a).** Prepared according to the general procedure E. 82% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (31.43 mg, 60% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.26-7.25 (m, 3H), 7.21-7.17 (m, 4H), 7.14-7.12 (m, 3H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.73 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.71 (s, 1H), 4.81 (s, 1H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.71 (s, 3H), 3.25 (d, *J* = 14.0 Hz, 1H), 1.52 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.5, 155.6, 152.2, 151.1, 143.5, 139.4, 131.2, 130.1, 129.3, 129.1, 128.6, 128.3, 127.8, 127.4, 117.4, 113.8 (2C), 110.3 (2C), 85.8, 83.9, 59.7, 55.5, 49.5, 27.7. **HRMS (ESI)** m/z calculated for $C_{33}H_{33}NO_5Na$ $[M+Na]^+$: 546.2256; found 546.2263. **R_f** = 0.5 (hexanes/ethyl acetate = 9:1). *Trans*-stereochemistry assignment was confirmed by nOe analysis.

***Trans*-3-benzyl-2-(4-methoxyphenyl)-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (52b).** Prepared according to the general procedure E. 88% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (34 mg, 73% isolated yield). **^{1}H NMR** (500

MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 4.4 Hz, 3H), 7.25-7.18 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.04 (s, 1H), 3.84 (q, *J* = 7 Hz, 1H), 3.82 (s, 3H), 3.81 (d, *J* = 14.8 Hz, 1H), 3.30 (d, *J* = 14.8 Hz, 1H), 1.58 (s, 9H), 1.53 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.6, 154.9, 150.3, 139.7, 130.4, 129.3, 128.5, 128.3, 127.9, 127.0, 123.0, 114.1, 114.0, 110.2, 86.0, 83.8, 55.5, 52.4, 49.7, 30.0, 28.0, 24.2. **HRMS (ESI)** m/z calculated for $C_{28}H_{32}NO_5$ $[M+H]^+$: 462.2281; found 462.2295. **R_f** = 0.5 (hexanes/ethyl acetate = 9:1).

***Trans*-3-benzyl-2-(4-nitrophenyl)-4-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (73a).** Prepared according to the general procedure E using two equivalents of **66**. 61% crude NMR yield. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.27-7.26 (m, 2H), 7.24-7.22 (m, 4H), 7.18-7.16 (m, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.95-6.94 (m, 2H), 6.78 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.78 (s, 1H), 4.86 (s, 1H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.33 (d, *J* = 13.9 Hz, 1H), 1.53 (s, 9H). **R_f** = 0.6 (hexanes/ethyl acetate = 9:1).

***Trans*-3-benzyl-4-methyl-2-(4-nitrophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl tert-butyl carbonate (73b).** Prepared according to the general procedure E. 40% crude NMR yield. **R_f** = 0.5 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl(*trans*-3-(4-methoxybenzyl)-2,4-diphenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (74a).** Prepared according to the general procedure E. 78% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (40.03 mg, 76% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.28 (m 2H), 7.25-7.23

(m, 3H), 7.21-7.18 (m, 3H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.81 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.80 (s, 1H), 4.89 (s, 1H), 3.79-3.76 (m, 4H), 3.29 (d, *J* = 13.7 Hz, 1H), 1.59 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.1, 155.5, 152.2, 151.1, 143.6, 138.1, 131.1, 130.4, 129.1, 128.4, 128.3, 128.1, 127.4, 126.6, 117.5, 114.0, 113.9, 110.3 (2C), 85.9, 83.9, 59.4, 55.5, 49.0, 28.0. **HRMS (ESI)** m/z calculated for $C_{33}H_{34}NO_5$ $[M+H]^+$: 524.2437; found 524.2427. **R_f** = 0.5 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl(*trans*-3-(4-methoxybenzyl)-4-methyl-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl)carbonate (74b).** Prepared according to the general procedure E. 78% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (34 mg, 73% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.7 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.75 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.07 (s, 1H), 3.85 (q, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 3.73 (d, *J* = 14.4 Hz, 1H), 3.26 (d, *J* = 14.5 Hz, 1H), 1.58 (s, 9H), 1.52 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 158.8, 154.8, 152.3, 150.3, 138.4, 131.5, 129.4, 129.3, 128.5, 128.2, 126.7, 123.1, 114.1, 113.9, 110.2, 86.7, 83.8, 55.5, 52.1, 49.1, 28.0, 24.1. **HRMS (ESI)** m/z calculated for $C_{28}H_{32}NO_5$ $[M+H]^+$: 462.2281; found 462.2276. **R_f** = 0.5 (hexanes/ethyl acetate = 9:1).

***Trans*-3-benzyl-2-(furan-2-yl)-4-phenyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazin-7-yl *tert*-butyl carbonate (75a).** Prepared according to the general procedure E. 73% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (33.45 mg, 69% isolated yield).**^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35-7.33

(m, 3H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.22-7.21 (m, 3H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.73 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.49 (d, *J* = 3.3 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.79 (s, 1H), 4.79 (s, 1H), 3.99 (d, *J* = 14.1 Hz, 1H), 3.39 (d, *J* = 14.1 Hz, 1H), 1.52 (s, 9H).**^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.0, 152.1, 151.1, 150.3, 142.8, 139.1, 131.1 (2C), 129.3, 129.2, 128.6, 128.4, 127.6, 127.5, 117.5, 114.1, 110.5, 110.3, 109.2, 83.9, 82.7, 59.7, 50.9, 28.0. **HRMS (ESI)** m/z calculated for $C_{30}H_{30}NO_5$ $[M+H]^+$: 484.2124; found 484.2126. **R_f** = 0.6 (hexanes/ethyl acetate = 9:1).

***Trans*-3-benzyl-2-(furan-2-yl)-4-methyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl tert-butyl carbonate (75b).** Prepared according to the general procedure E. 86% crude NMR yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.34-7.28 (m, 4H), 7.23 (t, *J* = 7.1 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.75 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.60 (d, *J* = 3.2 Hz, 1H), 6.41 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.09 (s, 1H), 4.00 (d, *J* = 14.8 Hz, 1H), 3.83, (q, *J* = 6.9 Hz, 1H), 3.40 (d, *J* = 14.7 Hz, 1H), 1.57 (s, 9H), 1.51 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.4, 152.2, 150.4, 150.4, 142.8, 139.4, 129.3, 128.5, 128.4, 127.2, 122.7, 114.4, 110.6, 110.2, 109.2, 83.8, 82.8, 52.4, 50.9, 27.9, 23.9. **HRMS (ESI)** m/z calculated for $C_{25}H_{28}NO_5$ $[M+H]^+$: 422.1967; found 422.1964. **R_f** = 0.5 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl (*trans*-3-isopropyl-2-(4-methoxyphenyl)-4-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (76a).** Prepared according to the general procedure E. < 10% crude NMR yield. **R_f** = 0.4 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl (*trans*-3-isopropyl-2-(4-methoxyphenyl)-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (76b).** Prepared according to the general procedure E. 47% crude NMR yield. $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl(*trans*-3-isopropyl-2-mesityl-4-phenyl-3,4-dihydro- 2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (77a).** Prepared according to the general procedure E using two equivalents of **70**. 35% crude NMR yield. $\mathbf{R_f}$ = 0.5 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl (*trans*-3-isopropyl-2-mesityl-4-methyl-3,4- di-hydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (77b).** Prepared according to the general procedure E using two equivalents of **70**. 43% crude NMR yield. $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl (*trans*-3-(2-methoxyethyl)-2,4-diphenyl-3,4- dihydro-2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (78a).** Prepared according to the general procedure E using two equivalents of imine **71**. 73% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (35.99 mg, 65% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 4H), 7.21-7.17 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.74 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.56 (s, 1H), 5.21 (s, 1H), 3.44 (m 1H), 3.40-3.37 (m, 1H), 3.20 (s, 3H), 2.75 (dt, *J* = 14.2, 5.7 Hz, 1H), 2.54-2.49 (m, 1H), 1.51 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.7, 152.1, 151.0, 143.8, 138.0, 131.1, 129.2, 128.4, 128.3, 128.0, 127.4, 126.7, 117.9, 113.7, 110.4, 86.1, 83.8, 73.2, 62.5, 58.9, 45.1, 28.0. **HRMS (ESI)** m/z calculated for

$C_{28}H_{31}NO_5Na$ $[M+Na]^+$: 484.2100; found 484.2107. $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl(*trans*-3-(2-methoxyethyl)-4-methyl-2-phenyl- 3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (78b).** Prepared according to the general procedure E using two equivalents of imine **71**. 71% crude NMR yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 1.4 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 6.74 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.92 (s, 1H), 4.09 (q, *J* = 7.0 Hz, 1H), 3.32 (t, *J* = 6.1 Hz, 2H), 3.19 (s, 3H), 2.76 (dt, *J* = 14.1, 6.3 Hz, 1H), 2.41 (dt, *J* = 14.1, 5.9 Hz, 1H), 1.58 (d, *J* = 7.1 Hz, 3H), 1.57 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.0, 152.2, 150.3, 138.3, 129.1, 128.4, 128.1, 126.9, 123.5, 114.0, 110.2, 86.2, 83.7, 72.7, 58.9, 54.7, 46.0, 28.0, 24.2. **HRMS (ESI)** m/z calculated for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2124; found 400.2133. $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 9:1).

***Tert*-butyl (*cis*-8-phenyl-5,6,8,13a-tetrahydrobenzo[5,6] [1,3]oxazino[2,3-a]isoquinolin-11-yl) carbonate (79a).** Prepared according to the general procedure E. 81% crude NMR yield (inseparable diastereomers, *cis*/*trans* = 5:1). The residue was purified by flash column chromatography as a yellow oil (34.89 mg, 81% isolated yield of two isomers). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 4.3 Hz, 4H), 7.20-7.17 (m, 3H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.68 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 5.44 (s, 1H), 4.87 (s, 1H), 3.27 (td, *J* = 11.6, 3.8 Hz, 1H), 3.16 (td, *J* = 14.2, 6.2 Hz, 1H), 2.95 (dt, *J* = 11. 0, 5.5 Hz, 1H), 2.80 (dd, *J* = 16.0, 3.1 Hz, 1H), 1.48 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.0, 152.1, 151.1, 142.9, 135.1, 133.0, 130.1, 129.2, 129.0, 129.0,

128.9, 128.4, 127.6, 126.3, 116.8, 113.3, 110.1, 83.7, 82.8, 64.6, 45.4, 29.5, 27.9. **HRMS (ESI)** m/z calculated for $C_{27}H_{27}NO_4$ $[M+H]^+$: 430.2018; found 430.2020. $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 9:1). *Cis*-stereochemistry of major product was confirmed by nOe analysis.

***Tert*-butyl (*cis*-8-methyl-5,13a-dihydro-6H,8H-benzo [5,6][1,3]oxazino[2,3-a]isoquinolin-11-yl) carbonate (79b).** Prepared according to the general procedure E. 53% crude NMR yield (inseparable diastereomers, *cis*/*trans* = 5:1). **^{1}H NMR** (500 MHz, $CDCl_3$) Major diastereomer: δ 7.40 (d, *J* = 7.4 Hz, 1H), 7.34-7.27 (m, 2H), 7.21-7.09 (m, 2H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.71 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.65 (d, *J* = 2.3 Hz), 5.81 (s,1H), 3.85 (q, *J* = 7.0 Hz, 1H), 3.29 (td, *J* = 11.7, 4.1 Hz, 1H), 3.15 (ddd, *J* = 14.6, 12.5, 6.4 Hz, 1H), 2.89-2.72 (m, 2H), 1.58 (d, *J* = 4.7 Hz, 3H), 1.54 (s, 9H). $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 9:1). *Cis*-stereochemistry of major product was confirmed by nOe analysis.

2.4 Thermodynamic Method of Synthesizing 1,3-Benzoxazines

General Procedure F

Amine (8 mmol) was added to a stirred solution of **42a** (4 mmol) in dry methanol (10 mL) at room temperature and stirred at the same temperature overnight. Yellow solids formed were collected by filtration and rinsed with cold methanol. The crude imine was directly used for the next step without purification. $NaBH_4$ (1 mmol) was added to a stirred solution of imine in dry methanol (10 mL) at 0°C. The reaction mixture was allowed to slowly warm to room temperature, then quenched with water (10 mL) and extracted with dichloromethane (3 x 5 mL). The

combined organic solution was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography was performed to afford pure benzylic amine **44a** to **44c**.

In a sealed-tube, aldehyde (0.2 mmol) was added to a stirred solution of benzylic amine (**44a** to **44c**, 0.1 mmol) in benzene (1 mL) at room temperature. Then TsOH (15 mol%) was added to the mixture. The reaction mixture was refluxed overnight and allowed to cool to room temperature then quenched with saturated sodium bisulfite solution. Organic layer was washed with saturated sodium bisulfite solution (10 x 1 mL). The aqueous solution was extracted with Et_2O (3 x 1 mL), then the combined organic solution was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford crude product. Crude NMR yields were determined by dibromomethane as internal standard for crude product.

***Tert*-butyl (3-hydroxy-4-(1-(isopropylamino)ethyl)phenyl) carbonate (44a)** was synthesized according to general procedure F as brown solid (m.p. = 99.4-99.9 ^{O}C). **1H-NMR** (400 MHz, $CDCl_3$): δ 6.90 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.56 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.06 (q, *J* = 6.7 Hz, 1H), 2.84 (sep, *J* = 6.3 Hz, 1H), 2.53 (q, *J* = 7.2 Hz, 1H), 1.55 (s, 9H), 1.40 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.64, 151.95, 151.01, 128.01, 124.70, 111.47, 109.88, 83.24, 55.64, 46.44, 27.66, 23.25, 22.93, 21.71. **HRMS (ESI)** m/z calculated for $C_{16}H_{25}NO_4$ $[M+H]^+$: 296.1862; found 296.1860. $\mathbf{R_f}$ = 0.35 (hexanes/ethyl acetate = 3:1).

***Tert*-butyl (3-hydroxy-4-(1-((4-methoxyphenyl)amino)ethyl)phenyl) carbonate (44b)** was synthesized according to general procedure F as light brown solid (m.p. = 149.1-149.4 ^{O}C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.36 (bs, OH), 7.06 (d, *J* = 8.3 Hz, 1H), 6.76 (s, 4H), 6.68 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 4.43 (q, *J* = 6.7 Hz, 1H), 3.73 (s, 3H), 3.56 (bs, NH), 1.57 (d, *J* = 6.8 Hz, 3H), 1.55 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.59, 154.79, 151.83, 151.17, 139.40, 127.62, 124.90, 118.66, 114.63, 112.44, 110.12, 83.42, 56.79, 55.51, 27.67, 22.44. **HRMS (ESI)** m/z calculated for $C_{20}H_{25}NO_5$ $[M+Na]^+$: 382.1631; found 382.1640. **R_f** = 0.30 (hexanes/ethyl acetate = 3:1).

4-(1-(Benzylamino)ethyl)-3-hydroxyphenyl *tert*-butyl carbonate (44c) was synthesized according to general procedure F as colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.31 (m, 2H), 7.31-7.27 (m, 3H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 2.7 Hz), 6.62 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.00 (q, *J* = 6.7 Hz, 1H), 3.84 (d, *J* = 13.1 Hz), 3.66 (d, *J* = 12.9 Hz, 1H), 1.56 (s, 9H), 1.45 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.39, 152.11, 151.42, 138.49, 128.86, 128.73, 128.57, 128.48, 127.74, 123.99, 112.02, 110.16, 110.12, 83.52, 58.19, 51.71, 27.86, 22.68. **HRMS (ESI)** m/z calculated for $C_{20}H_{25}NO_4$ $[M+H]^+$: 344.1862; found 344.1868. **R_f** = 0.30 (hexanes/ethyl acetate = 3:1).

2.5 Adducts with Trisubstituted Imine 81

4-(1-(Benzylamino)ethyl)-3-hydroxyphenyl *tert*-butyl carbonate (83): Imine **81** (0.1 mL, 0.1 mmol, 1.0 M in toluene) was added to a stirred solution of **37a** (0.1 mL, 0.1 mmol, 1.0 M in toluene) in Et_2O (1 mL) at room temperature. MeMgCl (0.1

mmol, 3.0 M solution in THF, 0.03 mL) was added to the mixture at -78 ºC. The reaction mixture was allowed to warm to room temperature over 6 hours then quenched with aqueous $NaHCO_3$ solution (1 mL). The aqueous solution was extracted with Et_2O (3 x 1mL), then the combined organic solution was washed with brine (1mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, eluent: hexanes/EtOAc = 3:1) to afford pure **83** as yellow oil (23.01 mg, 67% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35-7.33 (m, 2H), 7.30-7.27 (m, 3H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.62 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.99 (q, *J* = 6.7 Hz, 1H), 3.84 (d, *J* = 13.0 Hz, 1H), 3.65 (d, *J* = 13.0 Hz, 1H), 1.56 (s, 9H), 1.44 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 158.3, 152.1, 151.6, 138.2, 128.9, 128.8, 128.7, 127.9, 123.8, 112.2, 110.2, 83.6, 58.2, 51.7, 27.9, 22.5. **HRMS (ESI)** m/z calculated for $C_{20}H_{26}NO_4$ $[M+H]^+$: 344.1842; found 344.1856. **R_f** = 0.4 (hexanes/ethyl acetate = 3:1).

4-(1-(Benzyl(isopropyl)amino)ethyl)-3-hydroxyphenyl *tert*-butyl carbonate (85): Imine **81** (0.1 mL, 0.1 mmol, 1.0 M in toluene) was added to a stirred solution of bis-(2,4-tert-butoxycarbonyloxy)-benzaldehyde (0.1 mL, 0.1 mmol, 1.0 M in toluene) in Et_2O (1 mL) at room temperature. MeMgCl (0.1 mmol, 3.0 M solution in THF, 0.03 mL) was added to the mixture at -78 ºC. The reaction mixture was allowed to warm to 0 ºC over 4 hours. $LiBH_4$ (0.2 mmol, 2.0 M solution in THF, 0.1 mL) was added at 0 ºC. The mixture was then allowed to warm to room temperature over two hours. The reaction was quenched carefully with aqueous NH_4Cl solution (2 mL), stirred for one hour until gas evolution ceased. The aqueous solution was extracted with Et_2O

(3 x 1mL), then the combined organic solution was washed with brine (1mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, eluent: hexanes/EtOAc = 9:1) to afford pure **85** as yellow oil (23.01 mg, 46% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.59-6.58 (m, 2H), 4.10 (q, *J* = 7.2 Hz, 1H), 3.77-3.74 (m, 2H), 3.14 (sept, *J* = 7.2 Hz, 1H), 1.53 (s, 9H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.6, 152.1, 151.5, 129.4, 129.3, 128.94, 128.86, 127.6, 127.5, 111.8, 109.5, 83.5, 56.7, 51.5, 49.7, 28.6, 27.9, 20.5, 16.2. **HRMS (ESI)** m/z calculated for $C_{23}H_{32}NO_4$ $[M+H]^+$: 386.2331; found 386.2337. **R_f** = 0.3 (90% hexane 10% ethyl acetate).

2.6 Synthesis of Dihydrooxazole Derivatives 86

General Procedure G

At room temperature, anhydrous $ZnCl_2$ (140 mg, 1 mmol, 2 mol%) was suspended in anhydrous nitrile (55 mmol, 1.1 equiv). To this suspension, aminoalcohol (50 mmol, 1.0 equiv) was added dropwise with stirring. The mixture was heated at 95 °C for 48 hours. The crude mixture was purified by vacuum distillation to afford pure product. The product was further dried by another vacuum distillation over CaH_2 before use.

General Procedure H

A sealed tube was charged with a mixture of aminoalcohol (20 mmol, 1.0 equiv), triethyl orthoester (24 mmol, 1.2 equiv) and glacial acetic acid (70 μL, 1.2

mmol, 6 mol%) in DCE (60 mL). The tube was heated at 95 °C for 16 hours. The mixture was cooled to room temperature, quenched with saturated $NaHCO_3$ solution (20 mL), extracted with dichloromethane (4 × 50 mL). Organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by vacuum distillation over CaH_2 to afford pure, anhydrous product.

General Procedure I

A solution of amido alcohol (15.0 mmol) in dry chloroform (80 mL) was cooled to 0 °C. $SOCl_2$ (1.85 mL, 25.5 mmol, 1.7 equiv) was added dropwise using a dropping funnel. The mixture was warmed to room temperature and stirred for 16 hours. The reaction was quenched with 1M Na_2CO_3 solution (20 mL), extracted with chloroform (3 × 10 mL). Organic phases were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude chloride was taken up in dry ethanol (15 mL). Pellets of NaOH (3.61 g, 90.0 mmol, 6.0 equiv) was then added. The mixture was heated at 50 °C for 16 hours. The white salt precipitated was removed by filtering through a pad of Celite. The filtrate was concentrated *in vacuo*, then taken up in chloroform (40 mL). The solution was washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was distilled over CaH_2 to afford pure, anhydrous product.

2-Ethyl-4,5-dihydrooxazole (86a). Obtained from Alfa Aesar. It was further dried by vacuum distilled over CaH_2 (b.p. = 65 °C at 60 Torr) before use.

2-(3-Phenylpropyl)-4,5-dihydrooxazole (86b). Prepared according to the general procedure I. The crude product was purified by vacuum distillation (b.p. = 74 °C at Torr) as a colorless oil (0.79 g, 28% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.24 - 7.30 (m, 3H), 7.15 - 7.21 (m, 2H), 4.20 (t, *J* = 9.5 Hz, 2H), 3.77 - 3.85 (m, 2H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.97 (quin, *J* = 7.6 Hz, 2H). Our characterization data match with prior literature data.[15]

2-Isopropyl-4,5-dihydrooxazole (86c). Prepared according to the general procedure G. The crude product was purified by vacuum distillation (b.p. = 68 °C at Torr) as a colorless oil (1.70 g, 30% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.21 (t, *J* = 9.5 Hz, 2H), 3.81 (t, *J* = 9.3 Hz, 2H), 2.56 (sept, *J* = 7.0 Hz, 1H), 1.19 (d, *J* = 7.0 Hz, 6H). Our characterization data match with prior literature data.[16]

2-(Furan-2-yl)-4,5-dihydrooxazole (86d). Prepared according to the general procedure G. The crude product was purified by recrystallization using ethyl acetate and hexanes as white solid (2.19 g, 32% isolated yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 1.2 Hz, 1H), 6.95 (d, *J* = 3.1 Hz, 1H), 6.48 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.41 (t, *J* = 9.4 Hz, 2H), 4.06 (t, *J* = 9.6 Hz, 2H). Our characterization data match with prior literature data.[17]

2-Methyl-5,6-dihydro-4H-1,3-oxazine (86e). Prepared according to the general procedure G. The crude product was purified by vacuum distillation (b.p. = 65 °C at 60 Torr) as a colorless oil (1.98 g, 40% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ

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4.13 (t, *J* = 4.7 Hz, 2H), 3.32 (br s, 2H), 1.87 (s, 3H), 1.86-1.80 (m, 2H). Our characterization data match with prior literature data.[18]

2-Ethyl-5,6-dihydro-4H-1,3-oxazine (86f). Prepared according to the general procedure G. The crude product was purified by vacuum distillation (b.p. = 78 °C at ~60 mmHg) as a colorless oil (3.17 g, 56% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.13 (t, *J* = 5.4 Hz, 2H), 3.35 (t, *J* = 5.7 Hz, 2H), 2.13 (q, *J* = 7.7 Hz, 2H), 1.84 (quin, *J* = 5.7 Hz, 2H), 1.08 (t, *J* = 7.7 Hz, 3H). Our characterization data match with prior literature data.[19]

2-Ethyl-5-methyl-4,5-dihydrooxazole (86g). Prepared according to the general procedure G. The crude product was purified by vacuum distillation (b.p. = 70 °C at 60 Torr) as a colorless oil (1.75 g, 31% isolated yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.70-4.55 (m, 1H), 3.90 (dd, *J* = 13.7, 9.4 Hz, 1H), 3.36 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.26 (q, *J* = 7.2 Hz, 2H), 1.31 (d, *J* = 6.7 Hz, 3H), 1.17 (t, *J* = 7.4 Hz, 3H). Our characterization data match with prior literature data of (*R*) and (*S*) enantiomers.[20]

2,4-Dimethyl-4,5-dihydrooxazole (86h). Prepared according to the general procedure H. The crude product was purified by vacuum distillation (b.p. = 65 °C at 60 Torr) as a colorless oil (0.14 g, 5% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.33 (t, *J* = 9 Hz, 1H) 4.16 - 4.10 (m, 1H), 3.76 (t, *J* = 8 Hz, 1H) 1.97 (s, 3H) 1.24 (d, *J* = 6.5 Hz, 3H). Our characterization data match with prior literature data.[21]

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2-Phenyl-4,5-dihydrooxazole (86i). Prepared according to the general procedure G. The crude product was purified by vacuum distillation (b.p. = 95 °C at 2 Torr) as a colorless oil (3.61 g, 49% isolated yield). The oil solidified into white solid upon standing at room temperature. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.00-7.88 (m, 2 H), 7.52-7.44 (m, 1H), 7.44-7.37 (m, 2H), 4.44 (t, *J* = 9.6 Hz, 2H), 4.06 (t, *J* = 9.6 Hz, 2H). Our characterization data match with prior literature data.[22]

2-Phenyl-5,6-dihydro-4H-1,3-oxazine (86j). Prepared according to the general procedure G. The crude product was purified by vacuum distillation (b.p. = 120 °C at 2 mmHg) as a colorless oil (3.06 g, 38% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.90-7.86 (m, 2H), 7.42-7.38 (m, 1H), 7.38-7.33 (m, 2H), 4.36 (t, *J* = 5.6 Hz, 2H), 3.61 (t, *J* = 5.9 Hz, 2H), 1.98 (quin, *J* = 5.7 Hz, 2H). Our characterization data match with prior literature data.[23]

2-Benzyl-4,5-dihydrooxazole (86k). Prepared according to the general procedure I. The crude product was purified by vacuum distillation (b.p. = 100 °C at 2 mmHg) as a colorless oil (1.18 g, 49% isolated yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.14 (m, 5H), 4.24 (t, *J* = 9.8 Hz, 2H), 3.84 (t, *J* = 9.6 Hz, 2H), 3.62 (s, 2H). Our characterization data match with prior literature data.[24]

4,5-Dihydrooxazole (86m). Prepared according to the general procedure I. The crude product was purified by distillation (b.p. = 96 °C at 760 mmHg) as an orange oil (50 mg, 5% isolated yield). **^{1}H NMR** (600 MHz, CD_3OD): 8.07 (s, 1H), 3.61 (t, *J* =

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5.4 Hz, 2H) 3.58 (t, *J* = 5.4 Hz, 2H). Our characterization data match with prior literature data.[25]

2-Phenyl-5,6-dihydro-4H-1,3-oxazine (86n). 2-Aminophenol (5.00 g, 46 mmol) was suspended in a solution of triethyl orthoacetate (7.80 g, 48.1 mmol, 1.05 equiv.) and ammonium chloride (367 mg, 3.87 mmol, 15 mol%) in water (100 mL). The mixture was refluxed for 16 hours. After cooling to room temperature, the aqueous layer was extracted with ethyl acetate (3 × 70 mL). Organic phases were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was first purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 3:1), then dried by vacuum distillation over CaH_2 (b.p. = 75°C under 2 torr) as yellow oil (1.41 g, 23% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.68-7.62 (m, 1H), 7.49-7.44 (m, 1H), 7.32-7.27 (m, 2H), 2.64 (s, 3H). **R_f** = 0.6 (hexanes/ethyl acetate = 1:1). Our characterization data match with prior literature data.[26]

2-Methoxy-4,5-dihydrooxazole (97). Trimethyloxonium tetrafluoroborate (5.61 g, 38 mmol) was suspended in dry dichloromethane (15 mL) at 0°C. A solution of oxazolidin-2-one (3.00 g, 34.5 mmol) in dichloromethane (15 mL) was added. The mixture was stirred at room temperature for 16 hours before quenching with cold aqueous sodium carbonate solution. The aqueous layer was extracted with dichloromethane (3 × 20 mL). Organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by

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distillation over CaH_2 (b.p. = 97°C under 760 torr) as colorless oil (1.58 g, 45% isolated yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.41 (t, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.80 (t, *J* = 8.8 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 164.5, 69.0, 57.5, 51.6.

2-(Methylthio)-4,5-dihydrothiazole (99). To a solution of thiazolidine-2-thione (2.85 g, 24 mmol) in methanol (15 mL) was added methyl iodide (3.39 g, 24 mmol). The mixture was refluxed for 1 hour. After cooling to room temperature, diethyl ether was added slowly. White crystalline solid precipitated was collected by vacuum filtration. The solid was dissolved in 15% NaOH solution (24 mL), and extracted with chloroform (3 × 20 mL). Organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by distillation over CaH_2 (b.p. = 54°C under 2 torr) as colorless oil (1.60 g, 50% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.23 (t, *J* = 8.0 Hz, 2H), 3.43 (t, *J* = 8.0 Hz, 2H), 2.58 (s, 3H). Our characterization data match with prior literature data.[27]

2.7 Four-Component, Conjugate Addition of Dihydrooxazole Derivatives to *o*-QMs

General Procedure J

To a flame-dried Schlenk tube was charged with *o*-OBoc aldehyde solution (0.1 mL, 0.1 mmol, 1.0 M in toluene) and dry Et_2O (1 mL). Grignard reagent (1.05 equiv) was added to the mixture at -78 ºC. The mixture was allowed to stir at the same temperature for 10 minutes before addition of dihydrooxazole solution (0.2 mL, 0.2 mmol, 1.0 M in toluene, 2 equiv.). The mixture was allowed to warm to room

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temperature over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (1 mL), extracted with Et_2O (3 × 1mL). Organic layers were combined, washed with brine (1 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1) to afford pure products.

2-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)ethyl propionate (94a). Prepared according to the general procedure J. Yellow oil (26.1 mg, 74% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.58 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.26 (ddd, *J* = 11.7, 6.4, 3.5 Hz, 1H), 4.11 (ddd, *J* = 11.3, 7.1, 3.8 Hz, 1H), 3.94 (q, *J* = 6.8 Hz, 1H), 2.92-2.80 (m, 2H), 2.37 (q, *J* = 7.7 Hz, 2H), 1.54 (s, 9H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.15 (t, *J* = 7.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.3, 158.1, 151.9, 151.3, 128.4, 123.7, 111.9, 110.0, 83.3, 62.9, 58.2, 45.9, 27.7, 27.4, 22.3, 9.0. **HRMS (ESI)** m/z calculated for $C_{18}H_{28}NO_6$ $[M+H]^+$: 354.1917; found 354.1923. **R_f** = 0.2 (hexanes/ethyl acetate = 3:1).

2-((1-(2-Hydroxy-4-methoxyphenyl)ethyl)amino)ethyl propionate (94b). Prepared according to the general procedure J. Yellow oil (16.0 mg, 60% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.84 (d, *J* = 8.3 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 6.35 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.27 (ddd, *J* = 11.4, 6.5, 3.7 Hz, 1H), 4.12 (ddd, *J* = 11.3, 7.1, 3.8 Hz, 1H), 3.92 (q, *J* = 6.6 Hz, 1H), 3.75 (s, 3H), 2.94-2.79 (m, 2 H), 2.37 (q, *J* = 7.5 Hz, 2H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.16 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.4, 160.2, 158.2, 128.7, 118.4, 105.2, 102.2, 62.9, 58.0,

55.2, 45.7, 27.4, 22.4, 9.0. **HRMS (ESI)** m/z calculated for $C_{14}H_{21}NO_4Na$ $[M+Na]^+$: 290.1368; found 290.1377. $\mathbf{R_f}$ = 0.2 (hexanes/ethyl acetate = 3:1).

2-((1-(2-Hydroxy-3-methoxyphenyl)ethyl)amino)ethyl propionate (94c). Prepared according to the general procedure J. Yellow oil (18.2 mg, 68% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ6.78 (dd, *J*=8.0, 1.4 Hz, 1 H), 6.74 (t, *J* = 7.8 Hz, 1H), 6.59 (dd, *J* = 7.7, 1.4 Hz, 1H), 4.28 (ddd, *J* = 11.5, 5.9, 3.8 Hz, 1H), 4.11 (ddd, *J* = 11.6, 7.4, 4.0 Hz, 1H), 3.97 (q, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 2.94-2.79 (m, 2H), 2.37 (q, *J* = 7.5 Hz, 2H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.15 (t, *J* = 7.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.3, 148.2, 146.3, 126.5, 120.1, 118.8, 110.6, 63.0, 58.5, 55.8, 46.0, 27.4, 22.3, 9.0. **HRMS (ESI)** m/z calculated for $C_{14}H_{22}NO_4$ $[M+H]^+$: 268.1549; found 268.1547. $\mathbf{R_f}$ = 0.3 (hexanes/ethyl acetate = 1:1).

2-((1-(5-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)ethyl propionate (94d). Prepared according to the general procedure J. Yellow oil (18.0 mg, 51% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.93 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 1H), 4.26 (ddd, *J* = 11.4, 6.3, 3.5 Hz, 1H), 4.12 (ddd, *J* = 11.5, 7.3, 3.5 Hz, 1H), 3.92 (q, *J* = 6.8 Hz, 1H), 2.95-2.79 (m, 2H), 2.37 (q, *J* = 7.7 Hz, 2H), 1.54 (s, 9H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.16 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.3, 154.7, 152.4, 143.4, 126.5, 121.0, 120.6, 117.3, 83.2, 62.9, 58.4, 46.0, 27.7, 27.4, 22.0, 9.0. **HRMS (ESI)** m/z calculated for $C_{18}H_{28}NO_6$ $[M+H]^+$: 354.1917; found 354.1923. $\mathbf{R_f}$ = 0.1 (hexanes/ethyl acetate = 3:1).

2-((1-(2-Hydroxyphenyl)ethyl)amino)ethyl propionate (94e). Prepared according to the general procedure J. Yellow oil (11.6 mg, 49% isolated yield). **^{1}H NMR** (600

MHz, $CDCl_3$): δ 7.14 (td, *J* = 8.0, 1.7 Hz, 1H), 6.95 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.77 (td, *J* = 7.4, 0.9 Hz, 1H), 4.27 (ddd, *J* = 11.6, 6.5, 3.5 Hz, 1H), 4.12 (ddd, *J* = 11.4, 7.2, 3.7 Hz, 1H), 3.96 (q, *J* = 6.7 Hz, 1H), 2.94-2.80 (m, 2H), 2.37 (q, *J* = 7.5 Hz, 2H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.16 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.4, 157.1, 128.5, 128.1, 126.1, 119.2, 116.8, 62.9, 58.7, 45.9, 27.4, 22.3, 9.0. **HRMS (ESI)** m/z calculated for $C_{13}H_{19}NO_3Na$ $[M+Na]^+$: 260.1263; found 260.1259. **R_f** = 0.3 (hexanes/ethyl acetate = 3:1).

2-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)propyl)amino)ethyl propionate (94f). Prepared according to the general procedure J. Yellow oil (20 mg, 54% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.90 (d, *J* = 8.3 Hz, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.60 (dd, *J* = 8.2, 2.3 Hz, 1 H), 4.33-4.27 (m, 1H), 4.15-4.09 (m, 1H), 3.69 (t, *J* = 7.0 Hz, 1H), 2.89 (t, *J* = 5.0 Hz, 2H), 2.37 (q, *J* = 7.7 Hz, 2H), 1.89-1.76 (m, 2H), 1.54 (s, 9H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.4, 157.7, 151.8, 151.6, 129.7, 128.9, 111.9, 110.0, 83.4, 64.6, 45.8, 27.7, 27.7, 27.4, 10.7, 9.0. **R_f** = 0.2 (hexanes/ethyl acetate = 3:1).

2-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)pent-4-en-1-yl)amino)ethyl propionate (94g). Prepared according to the general procedure J. Yellow oil (24.4 mg, 62% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.0 Hz, 1H), 6.70 (br s, 1H), 6.61 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.76 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.03 (dd, *J* = 17.4, 1.7 Hz, 1H), 5.00 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.30 (dt, *J* = 11.8, 5.0 Hz, 1H), 4.13 (dt, *J* = 12.2, 4.9 Hz, 1H), 3.83 (t, *J* = 6.8 Hz, 1H), 2.89 (t, *J* = 5.0 Hz, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 1.55 (s, 9H), 1.15 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.5, 157.7, 151.8, 151.7, 137.2, 129.7, 115.7

(2C unresolved), 112.0, 110.1, 83.5, 62.5, 62.2, 45.8, 30.2, 27.7 (2C unresolved), 27.4, 9.0. **R_f** = 0.3 (hexanes/ethyl acetate = 3:1).

2-(((4-((*Tert*-butoxycarbonyl)oxy)-2 hydroxyphenyl)(phenyl)methyl)amino)ethyl propionate (94h). Prepared according to the general procedure J. Yellow oil (29.1 mg, 70% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.70 (d, *J* = 1.7 Hz, 1H), 6.55 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.93 (s, 1H), 4.30 (ddd, *J* = 11.7, 5.9, 4.0 Hz, 1H), 4.17 (ddd, *J* = 11.5, 7.0, 4.2 Hz, 1H), 3.01-2.91 (m, 2 H), 2.36 (q, *J* = 7.4 Hz, 2H), 1.54 (s, 9H), 1.15 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.3, 158.5, 151.8, 151.6, 129.6, 129.3, 129.1, 128.5, 128.1, 127.4, 122.0, 112.0, 110.2, 83.4, 66.8, 62.6, 46.3, 27.7, 9.0. **HRMS (ESI)** m/z calculated for $C_{23}H_{30}NO_6$ $[M+H]^+$: 416.2073; found 416.2068. **R_f** = 0.4 (hexanes/ethyl acetate = 3:1).

2-(((4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)(4-(piperidin-1-ylmethyl)phenyl)methyl)amino)ethyl propionate (94i). Prepared according to the general procedure J. Yellow oil (34.9 mg, 68% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.91 (s, 1H), 4.30 (ddd, *J* = 11.7, 6.2, 3.7 Hz, 1H), 4.16 (ddd, *J* = 11.5, 7.1, 4.0 Hz, 1H), 3.55 (br s, 2H), 3.01-2.88 (m, 2H), 2.46 (br s, 4H), 2.36 (q, *J* = 7.7 Hz, 2H), 1.64 (br s, 4H), 1.54 (s, 9H), 1.46 (br s, 2H), 1.14 (t, *J* = 7.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.3, 158.4, 151.8, 151.6, 130.5, 129.6, 127.4, 121.9, 112.1, 110.3, 83.5, 66.7, 62.7, 54.0, 46.4, 31.7, 29.7, 27.7 (2C unresolved), 27.4, 24.9, 23.7, 9.0. **HRMS (ESI)** m/z calculated

for $C_{29}H_{41}N_2O_6$ $[M+H]^+$: 513.2964; found 513.2955. $\mathbf{R_f}$ = 0.1 (hexanes/ethyl acetate = 1:1).

2-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)ethyl 4-phenylbutanoate (94j). Prepared according to the general procedure J. Yellow oil (28.0 mg, 63% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31-7.21 (m, 2H), 7.22-7.17 (m, 3H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.61-6.57 (m, 2H), 4.25 (ddd, *J* = 11.4, 6.3, 3.5 Hz, 1H), 4.09 (ddd, *J* = 11.5, 7.3, 3.8 Hz, 1H), 3.94 (q, *J* = 6.6 Hz, 1H), 2.91-2.79 (m, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.36 (t, *J* = 7.7 Hz, 2H), 1.98 (quin, *J* = 7.5 Hz, 2H), 1.55 (s, 9H), 1.44 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 173.3, 158.0, 151.9, 151.3, 141.2, 128.5, 128.5, 128.4, 126.0, 123.7, 111.9, 110.0, 83.4, 62.9, 58.3, 45.8, 35.1, 33.4, 27.7, 26.3, 22.3. **HRMS (ESI)** m/z calculated for $C_{25}H_{34}NO_6$ $[M+H]^+$: 444.2386; found 444.2397. $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 3:1).

2-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)ethyl isobutyrate (94k). Prepared according to the general procedure J. Yellow oil (16.1 mg, 44% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.92 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.59 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.26 (ddd, *J* = 11.6, 6.3, 3.7 Hz, 1H), 4.11 (ddd, *J* = 11.4, 7.0, 4.2 Hz, 1H), 3.97 (q, *J* = 6.8 Hz, 1H), 2.94-2.80 (m, 2H), 2.59 (sept, *J* = 7.0 Hz, 1H), 1.54 (s, 9H), 1.45 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 8.0 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 177.0, 157.9, 151.9, 151.4, 128.5 (2C unresolved), 111.9, 110.0, 83.4, 62.7, 58.1, 45.8, 33.9, 27.7, 22.1, 19.0. **HRMS (ESI)** m/z calculated for $C_{19}H_{30}NO_6$ $[M+H]^+$: 368.2073; found 368.2068. $\mathbf{R_f}$ = 0.3 (hexanes/ethyl acetate = 3:1).

2-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)ethyl furan-2-carboxylate (94l). Prepared according to the general procedure J. Yellow oil (11.4 mg, 29% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.60 (d, *J* = 0.6 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.53 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.48 (ddd, *J* = 11.5, 6.6, 3.5 Hz, 1H), 4.34 (ddd, *J* = 11.3, 7.1, 3.8 Hz, 1H), 4.00 (q, *J* = 6.7 Hz, 1H), 3.01 (ddd, *J* = 13.5, 6.9, 3.3 Hz, 1H), 2.95 (ddd, *J*=13.3, 6.5, 3.8 Hz, 1H), 1.55 (s, 9H), 1.46 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 158.5, 158.0, 151.9, 151.3, 146.6, 144.2, 128.5, 123.6, 118.6, 112.0, 112.0, 110.1, 83.4, 63.4, 58.2, 49.2, 45.8, 27.7. **HRMS (ESI)** m/z calculated for $C_{20}H_{26}NO_7$ $[M+H]^+$: 392.1709; found 392.1708. **R_f** = 0.2 (hexanes/ethyl acetate = 3:1).

3-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)propyl acetate (94m). Prepared according to the general procedure J. Yellow oil (24.7 mg, 70% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.90 (d, *J* = 8.3 Hz, 1H), 6.59 (d, *J* = 2.1 Hz, 1H), 6.57 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.16 (dt, *J* = 11.7, 6.0 Hz, 1H), 4.07 (dt, *J* = 11.7, 6.0 Hz, 1H), 3.90 (q, *J* = 6.6 Hz, 1H), 2.74-2.62 (m, 2H), 2.03 (s, 3H), 1.89-1.77 (m, 2H), 1.54 (s, 9H), 1.42 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.1, 158.2, 151.9, 151.2, 128.3, 124.0, 111.7, 109.9, 83.3, 62.2, 58.7, 44.2, 28.7, 27.7, 22.5, 20.9. **HRMS (ESI)** m/z calculated for $C_{18}H_{28}NO_6$ $[M+H]^+$: 354.1917; found 354.1913. **R_f** = 0.2 (hexanes/ethyl acetate = 3:1).

3-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)propyl propionate (94n). Prepared according to the general procedure J. Yellow oil (28.6 mg, 78% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.90 (d, *J* = 8.3 Hz, 1H),

6.61-6.52 (m, 2H), 4.17 (dt, *J* = 11.7, 6.0 Hz, 1H), 4.08 (dt, *J* = 11.7, 6.1 Hz, 1H), 3.90 (q, *J* = 6.6 Hz, 1H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.30 (q, *J* = 7.7 Hz, 2H), 1.89-1.77 (m, 2H), 1.54 (s, 9H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.5, 158.2, 151.9, 151.2, 128.3, 124.0, 111.7, 109.8, 83.3, 62.1, 58.7, 44.2, 28.7, 27.7, 27.5, 22.5, 9.1. **HRMS (ESI)** m/z calculated for $C_{19}H_{30}NO_6$ $[M+H]^+$: 368.2073; found 368.2073. **R_f** = 0.2 (hexanes/ethyl acetate = 3:1).

1-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)propan-2-yl propionate (94o). Prepared according to the general procedure J. Yellow oil (19.1 mg, 52% isolated yield, d.r. = 1.9:1, inseparable diastereomers). **HRMS (ESI)** m/z calculated for $C_{19}H_{30}NO_6$ $[M+H]^+$: 368.2073; found 368.2063. **R_f** = 0.2 (hexanes/ethyl acetate = 3:1).

Major Diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.0 Hz, 1H), 6.61-6.57 (m, 2H), 5.02-4.94 (m, 1H), 3.90-3.87 (m, 1H), 2.77-2.66 (m, 2H), 2.42-2.29 (m, 2H), 1.54 (s, 9H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.14 (t, *J* = 7.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.0, 158.0, 151.9, 151.3, 128.4, 123.9, 111.8, 110.0, 83.4, 70.1, 68.4, 58.7, 52.0, 27.7, 22.2, 18.1, 9.1.

Minor Diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.0 Hz, 1H), 6.61-6.57 (m, 2H), 5.14-5.07 (m, 1 H), 4.94 - 5.02 (m, 1H), 3.94-3.90 (m, 1H), 2.78-2.68 (m, 2H), 2.42-2.29 (m, 2H), 1.54 (s, 9H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.16 (q, *J* = 7.7

Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.3, 158.1, 151.9, 151.4, 128.4, 123.7, 111.8, 110.0, 83.5, 71.3, 70.1, 58.1, 51.8, 27.8, 22.4, 17.9, 9.1.

2-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)propyl acetate (94p). Prepared according to the general procedure D. Yellow oil (29.4 mg, 42% isolated yield, *d.r.* = 1.4:1, inseparable diastereomers). **HRMS (ESI)** m/z calculated for $C_{18}H_{28}NO_6$ $[M+H]^+$: 354.1917; found 354.1906. **R_f** = 0.2 (hexanes/ethyl acetate = 3:1).

Major Diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.93 (d, *J* = 8.4 Hz), 6.65 (s, 1H), 6.61 - 6.58 (m, 1H), 4.23 (dd, *J* = 11.4, 3.6 Hz, 1H), 4.14-4.10 (m, 1H), 3.95 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.04 (sex, *J* = 6 Hz, 1H), 2.10 (s, 3H), 1.54 (s, 9H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.9, 157.9, 151.8, 151.4, 128.3, 123.8, 112.0, 110.1, 83.4, 65.4, 55.7, 49.7, 27.7, 22.0, 20.8, 17.6.

Minor Diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.94 (d, *J* = 7.8 Hz), 6.70 (s, 1H), 6.61-6.58 (m, 1H), 4.14-4.10 (m, 1H), 4.06 – 4.03 (m, 2H), 2.98 (sex, *J* = 6 Hz, 1H), 2.09 (s, 3H), 1.54 (s, 9H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.19 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.0, 157.6, 151.8, 151.6, 128.6, 123.8, 112.2, 110.2, 83.4, 66.9, 55.5, 50.0, 27.7, 21.8, 20.8, 17.6.

2.8 Cross-over Experiments

Direct Observation of **87a**: To a flame-dried Schlenk tube was charged with aldehyde **37a** solution (0.1 mL, 0.1 mmol, 1.0 M in toluene) and dry Et_2O (1 mL).

Methylmagnesium chloride (0.04 mL, 0.105 mmol, 2.6M solution in THF, 1.05 equiv) was added to the mixture at -78 ºC. The mixture was allowed to stir at the same temperature for 10 minutes before addition of dihydrooxazole solution (0.2 mL, 0.2 mmol, 1.0 M in toluene, 2 equiv.). The mixture was allowed to warm to room temperature over 16 hours. Et_2O and dihydrooxazole **86a** were removed *in vacuo*. The residue was taken up in dry CD_2Cl_2 and transferred into a NMR tube under argon atmosphere.

***5-((Tert-butoxycarbonyl)oxy)-2-(1-(2-ethyl-4,5-dihydrooxazol-3-ium-3-yl)ethyl)phenolate magnesium bromide* (87a)**.

Characteristic shifts: **^{1}H NMR** (600 MHz, CD_2Cl_3): δ 4.30 (3H, C***H*$_2$**O + Ar-C***H*-CH_3), 3.86 (2H, C***H*$_2$**N), 2.44 (2H, C***H*$_2$-CH_3).

Cross-over Experiment with EVE at room temperature: To a Schlenk tube containing crude solution of **87a** in Et_2O was added ethyl vinyl ether (0.5 mL). The mixture was allowed to stir for another 24 hours. The solution was thenquenched with saturated $NaHCO_3$ solution (1 mL), extracted with Et_2O (3 × 1mL). Organic layers were combined, washed with brine (1 mL), dried over anhydrous Na_2SO_4, and concentrated. NMR analysis of this crude product showed the presence of **94a**, but no indication of **17a**.

Cross-over Experiment with EVE at 70ºC: A sealed tube under argon atmosphere was charged with crude solution of oxazolium ion **87a**. To this solution was added 0.5 mL of ethyl vinyl ether at room temperature. The mixture was heated to 70 ºC for 24 hours. The solution was quenched with saturated $NaHCO_3$ solution (1 mL), extracted with Et_2O (3 × 1mL). Organic layers were combined, washed with

brine (1 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1) to afford pure products as yellow oil (19.8 mg, 70% isolated yield, d.r. = 1.6:1, inseparable isomers).

Tert-butyl (2-ethoxy-4-methylchroman-7-yl) carbonate **(17a)**. $\mathbf{R_f}$ = 0.6 (hexanes/ethyl acetate = 9:1).

Major, cis Isomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.3 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 5.18 (dd, *J* = 7.1, 2.6 Hz, 1H), 4.02-3.94 (m, 1H), 3.65-3.57 (m, 1H), 2.99-2.93 (m, 1H), 2.18-2.11 (m, 1H), 1.79-1.68 (m, 1H), 1.55 (s, 9H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H). This *cis* isomer has been reported. Our characterization data match with prior literature data.[28]

Minor, trans Isomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.01 (d, *J* = 9.0 Hz, 1H), 6.41 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 5.16 (dd, *J* = 7.1, 2.6 Hz, 1H), 4.02-3.94 (m, 1H), 3.65-3.57 (m, 1H), 2.94-2.87 (m, 1H), 2.18-2.11 (m, 1H), 1.79-1.68 (m, 1H), 1.55 (s, 9H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H).

2.9 Other Pathways of Hydrolysis of Iminium 87a

Conjugate addition of **97**: To a flame-dried Schlenk tube was charged with aldehyde **37a** solution (0.1 mL, 0.1 mmol, 1.0 M in toluene) and dry Et_2O (1 mL). Methylmagnesium chloride (0.04 mL, 0.105 mmol, 2.6M solution in THF, 1.05 equiv)

[28] Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122* (27), 6502–6503.

was added to the mixture at -78 ºC. The mixture was allowed to stir at the same temperature for 10 minutes before addition of **97** solution (0.2 mL, 0.2 mmol, 1.0 M in toluene, 2 equiv.). The mixture was allowed to warm to room temperature over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (1 mL), extracted with Et_2O (3 × 1mL). Organic layers were combined, washed with brine (1 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 10:1→1:1).

Tert-butyl (3-hydroxy-4-(1-(2-oxooxazolidin-3-yl)ethyl)phenyl) carbonate **(98a)**. White solid (17.5 mg, 54% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 6.70 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.30 (q, *J* = 7.3 Hz, 1H), 4.39-4.25 (m, 2H), 3.65-3.56 (m, 1H), 3.38-3.28 (m, 1H), 1.60 (d, *J* = 7.3 Hz, 3H), 1.54 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.0, 156.1, 151.8, 151.7, 126.7, 122.8, 112.7, 111.3, 83.6, 62.9, 45.5, 39.9, 27.6, 16.4. **HRMS (ESI)** m/z calculated for $C_{16}H_{21}NO_6Na$ $[M+Na]^+$: 346.1266; found 346.1274. **R_f** = 0.1 (hexanes/ethyl acetate = 3:1).

Methyl (1-(4-((tert-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)(2-hydroxyethyl)carbamate **(98b)**. White solid (6.7 mg, 19% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.72 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.52 (q, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.44-3.29 (m, 4H), 1.59-1.57 (m, 3 H), 1.56-1.53 (m, 12 H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.2, 152.0, 151.6, 126.8, 123.3, 112.7, 110.8, 83.7, 53.8, 48.3, 44.0, 40.8, 27.7, 17.4. **R_f** = 0.3 (hexanes/ethyl acetate = 3:1).

Conjugate addition of **99**: To a flame-dried Schlenk tube was charged with aldehyde **37a** solution (0.1 mL, 0.1 mmol, 1.0 M in toluene) and dry Et_2O (1 mL). Methylmagnesium chloride (0.04 mL, 0.105 mmol, 2.6M solution in THF, 1.05 equiv) was added to the mixture at -78 ºC. The mixture was allowed to stir at the same temperature for 10 minutes before addition of **99** solution (0.2 mL, 0.2 mmol, 1.0 M in toluene, 2 equiv.). The mixture was allowed to warm to room temperature over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (1 mL), extracted with Et_2O (3 × 1mL). Organic layers were combined, washed with brine (1 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1).

Tert-butyl (3-hydroxy-4-(1-(2-oxothiazolidin-3-yl)ethyl)phenyl) carbonate **(100)**. White solid (24.2 mg, 71% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.7 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.51 (q, *J* = 7.0 Hz, 1H), 3.74 (ddd, *J* = 9.6, 8.2, 4.5 Hz, 1H), 3.41-3.34 (m, 1H), 3.30 (dt, *J* = 10.7, 8.4 Hz, 1H), 3.17 (ddd, *J* = 10.8, 8.0, 4.5 Hz, 1H), 1.62 (d, *J* = 7.3 Hz, 3H), 1.55 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 175.2, 156.1, 151.9, 151.7, 126.7, 122.5, 112.7, 111.3, 83.7, 46.0, 43.8, 27.7, 25.8, 16.6. **HRMS (ESI)** m/z calculated for $C_{16}H_{21}NO_5SNa$ $[M+Na]^+$: 362.1038; found 362.1056. $\mathbf{R_f}$ = 0.1 (hexanes/ethyl acetate = 3:1).

2.10 Transformations of Amino-ester 94a

Elimination to styrene: A solution of **94a** (70.6 mg, 0.2 mmol) in toluene (2.0 mL) was refluxed for 24 hours, then concentrated *in vacuo*. The residue was purified by column chromatography to afford pure **101a** as white solid (35.4 mg, 75% isolated yield).

***Tert*-butyl (3-hydroxy-4-vinylphenyl) carbonate (101a)**. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.7 Hz, 1H), 6.86 (dd, *J* = 17.7, 11.1 Hz, 1H), 6.73 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 5.68 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.33 (dd, *J* = 11.3, 1.2 Hz, 1H), 5.31 (br s, 1H), 1.56 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 153.4, 151.7, 151.0, 130.8, 127.9, 122.7, 115.9, 113.7, 109.0, 83.8, 27.7. **HRMS (ESI)** Dimerized in ESI condition, m/z calculated for dimer $C_{26}H_{32}O_8Na$ $[2M+Na]^+$: 495.1995; found 495.2018. $\mathbf{R_f}$ = 0.5 (hexanes/ethyl acetate = 3:1).

Trapping *o*-QM with imidazole: A solution of **94a** (5.0 mg, 0.014 mmol) in acetonitrile (2.0 mL) was added imidazole (1.0 mg, 0.014 mmol, 1.0 equiv). The solution was stirred at 90 ºC for 5 days, then concentrated *in vacuo*. The residue was purified by column chromatography to afford pure **101b** as yellow oil (2.0 mg, 47% isolated yield).

4-(1-(1H-Imidazol-1-yl)ethyl)-3-hydroxyphenyl *tert*-butyl carbonate (101b). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.69 (br s, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.00 (br s, 1H), 6.95 (s, 1H), 6.76 (s, 1H), 6.67 (dd, *J* = 8.5, 1.9 Hz, 1H), 5.72 (q, *J* = 6.7 Hz, 1H), 1.84 (d, *J* = 7.0 Hz, 3H), 1.53 (s, 9H). $\mathbf{R_f}$ = 0.5 (DCM/MeOH = 9:1).

2.11 Synthesis of Model Case of Mariline B

To a solution of adduct **94c** (15.0 mg, 0.1 mmol) in dichloromethane (1 mL) was added 2M NaOH solution (0.5 mL), followed by tetrabutylammonium hydroxide (5.2 mg, 10 mol%, 50% solution in water) and bis(trifluoromethanesulfonyl)aniline (53.6 mg, 0.15 mmol, 1.5 equiv). The biphasic mixture was stirred at room temperature for 16 hours. The mixture was then diluted with more dichloromethane (2 mL). The aqueous layer was extracted with dichloromethane (3 × 2 mL). The combined organic layers was dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent: hexanes:ethyl acetate = 10:1→5:1) to afford **106** as yellow oil (12.4 mg, 31% isolated yield). A Schlenk tube was charged with **106** (12.4 mg, 0.031 mmol) in toluene (0.5 mL) under nitrogen atmosphere. To this solution was added tri-*n*-propylamine (8.9 mg, 0.062 mmol, 2.0 equiv), $Pd(OAc)_2$ (0.7 mg, 0.0031 mmol, 10 mol%) and dppp (1.3 mg, 0.0031 mmol, 10 mol%). The solution was purged with a balloon of carbon monoxide gas for 3 minutes, after which the balloon was left attached to the Schlenk tube. The solution was heated at 100 ºC for 16 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate (1 mL) and water (1 mL). Aqueous layer was extracted with ethyl acetate (3 × 1 mL). The organic layers were combined, washed with brine (1 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was taken up in methanol (1 mL), potassium carbonate (12.9 mg, 0.093 mmol, 3 equiv) was added. The suspension was stirred for 30 minutes, after which the suspension was filtered. The filtrate collected was concentrated and purified by column chromatography (SiO_2, eluent: hexanes/ethyl

acetate = 1:1→100% ethyl acetate) to afford **107** as yellow oil (4.2 mg, 61% isolated yield).

2-(2-Hydroxyethyl)-7-methoxy-3-methylisoindolin-1-one (107). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.52-7.46 (m, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 4.53 (q, *J* = 6.6 Hz, 1H), 3.97 (s, 3H), 3.91-3.83 (m, 2H), 3.81-3.75 (m, 1H), 3.57 (ddd, *J* = 14.6, 6.4, 3.7 Hz, 1H), 1.46 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.3, 150.0, 136.3, 133.5, 118.5, 114.0, 110.2, 62.6, 57.1, 55.8, 44.8, 18.5. $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 3:1).

2.12 Total Synthesis Mariline B

1,2-Dimethoxy-3-methylbenzene (109): To a solution of 3-methylcatechol **108** (5.00 g, 40 mmol) in acetone (40 mL) was added K_2CO_3 (19.0 g, 136 mmol, 3.4 equiv.), followed by methyl iodide (22.9 g, 160 mmol, 4.0 equiv.). The mixture was allowed to reflux for 48 hours. Upon completion, the mixture was filtered. The filtrate collected was concentrated *in vacuo*, and was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 10:1) to afford pure product as colorless oil (6.03 g, 95% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.95 (t, *J* = 7.9 Hz, 1H), 6.79-6.73 (m, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 2.28 (s, 3H). $\mathbf{R_f}$ = 0.7 (hexanes/ethyl acetate = 3:1). Our characterization data match with prior literature data.[29]

[29] Movahhed, S.; Westphal, J.; Kempa, A.; Schumacher, C. E.; Sperlich, J.; Neudörfl, J.; Teusch, N.; Hochgürtel, M.; Schmalz, H. *Eur. J. Chem.* **2021**, *27* (45), 11574-11579.

2,3-Dimethoxy-4-methylbenzaldehyde (110): To a fame-dried round bottom flask was charged with a solution of **109** (6.00 g, 39 mmol) and TMEDA (1.15 g, 9.75 mmol, 0.25 equiv) in hexanes (150 mL). *n*-BuLi (40 mL, 1.2M solution in pentane, 46.8 mmol, 1.2 equiv) was added over 30 mins at room temperature. The resulting suspension was stirred at room temperature for 24 hours before cooling to 0 ºC. DMF (5.79 g, 78 mmol, 2.0 equiv) was added dropwise. The solution was allowed to warm to room temperature and stirred for 1 hour. The reaction was then quenched with water (5 mL), followed by addition of 2M HCl solution until pH of aqueous layer was close to 7. Aqueous layer was extracted with Et_2O (3 × 250 mL). Organic layers were combined, washed with brine (200 mL), dried over anhydrous Na2SO4, and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 9:1) to give afford pure product as yellow oil (5.48 g, 78% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.33 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.00 (dt, *J* = 8.0, 0.8 Hz, 1H), 4.00 (s, 3H), 3.86 (s, 3H), 2.32 (s, 3H). $\mathbf{R_f}$ = 0.3 (hexanes/ethyl acetate = 9:1). Our characterization data match with prior literature data.[29]

2-Hydroxy-3-methoxy-4-methylbenzaldehyde (111): To a solution of **110** (6.99 g, 38.8 mmol) in benzene (60 mL) was added $AlCl_3$ (6.21 g, 46.6 mmol, 1.2 equiv) in two portions. The suspension was reflexed for 30 minutes. After cooling to room temperature, the reaction was quenched with 1M $NaHSO_4$ solution (50 mL). The biphasic mixture was allowed to stir at room temperature until all solid dissolved. The aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were

combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 20:1) to give afford pure product as yellow oil (5.48 g, 85% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 11.15 (s, 1H), 9.83 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 196.0, 154.7, 146.1, 140.9, 128.1, 121.8, 120.3, 60.0, 16.8. **R_f** = 0.3 (hexanes/ethyl acetate = 9:1).

6-(1,3-Dioxan-2-yl)-2-methoxy-3-methylphenol (112): To a Schlenk flask charged with DMF (6.28 g, 86 mmol) was added dimethyl sulfate (10.84g, 86 mmol) dropwise at 50 ºC. The mixture was then stirred at 80 ºC for 2 hours to obtain DMF-DMS complex. To a separate flask charged with a solution of **111** (6.10 g, 36 mmol) in DCM (20 mL) was added 1,3-propanediol (8 mL), followed by the DMF-DMS complex prepared above. The mixture was allowed to stir at room temperature for 24 hours. The reaction was quenched by slow addition of Et_3N (6 mL) at 0 ºC. The viscous diol layer was extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with NaOAc saturated $NaHSO_3$ solution (20 mL), followed by NaOAc saturated NaCl solution (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 3:1, with 1% Et_3N by volume) to give afford pure product as orange oil (6.78 g, 84% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.92 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.67 (s, 1H), 4.31-4.26 (m, 2H), 4.04-3.97 (m, 2H), 3.82 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 147.8, 146.2, 132.5,

122.2, 121.7, 121.5, 101.5, 67.5, 60.2, 46.1, 25.7, 15.9. $\mathbf{R_f}$ = 0.3 (hexanes/ethyl acetate = 3:1).

2,5-Dihydroxy-3-methoxy-4-methylbenzaldehyde (114): To a solution of **112** (6.23 g, 27.8 mmol) in DMF (100 mL) was added $Co(salen)_2$ (578 mg, 1.7 mmol, 6 mol%). The solution was first saturated with oxygen gas, then an oxygen balloon was connected to the flask. The solution was allowed to stir at room temperature for 48 hours. Upon completion, the solution was diluted with water (300 mL) and Et_2O (300 mL). The aqueous layer was extracted with more Et_2O (3 × 200 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated to afford the crude *p*-quinone **113**. This crude quinone was re-dissolved in ethyl acetate (130 mL), to which $Pd(OH)_2/C$ (360 mg) was added. A hydrogen balloon was connected, and the suspension was allowed to stir at room temperature for 18 hours. The mixture was then filtered through Celite pad. The filtrate was concentrated *in vacuo* to afford the crude hydroquinone, which was taken up in a mixture of acetone (90 mL) and water (5 mL) immediately. TsOH monohydrate (252 mg, 2.8 mmol, 10 mol%) was added. The mixture was allowed to stir at room temperature for 24 hours. The solution was quenched with Et_3N (1 mL) and concentrated. The residue was extracted with ethyl acetate (4 × 50 mL). The organic layers were combined, washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 3:1) to give afford pure product as brown solid (2.99 g, 59% isolated yield over 3 steps). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.70

(s, 1 H), 9.76 (s, 1H), 6.73 (s, 1H), 3.89 (s, 3H), 2.25 (s, 3H). $\mathbf{R_f}$ = 0.6 (hexanes/ethyl acetate = 1:1).

(*E*)-5-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-2-hydroxy-3-methoxy-4-methylbenzaldehyde (115): To a solution of **114** (608 mg, 3.34 mmol) in acetone (20 mL) was added K_2CO_3 (923 mg, 6.68 mmol, 2.0 equiv), followed by geranyl bromide (871 mg, 4.01 mmol, 1.2 equiv). The mixture was stirred at room temperature for 24 hours, after which it was filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 30:1) to give afford pure product as yellow oil (372 mg, 35% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.27 (s, 1H), 7.02 (s, 1H), 5.50 (td, *J* = 7.4, 1.2 Hz, 1H), 5.31 (br s, 1H), 5.08-5.04 (m, 1H), 4.61 (d, *J* = 7.7 Hz, 2H), 3.88 (s, 3H), 2.22 (s, 3H), 2.11-2.00 (m, 4H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H). $\mathbf{R_f}$ = 0.3 (hexanes/ethyl acetate = 9:1).

(*E*)-*Tert*-butyl (4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-6-formyl-2-methoxy-3-methylphenyl) carbonate (116): To a solution of **115** (372 mg, 1.17 mmol) and Hünig's base (75.0 mg, 0.58 mmol, 0.5 equiv) in DCM (20 mL) was added DMAP (4.3 mg, 0.035 mmol, 3 mol%), followed by Boc_2O (255 mg, 1.17 mmol, 1.0 equiv). The solution was stirred at room temperature for 16 hours. The reaction was quenched with water (5 mL). The aqueous layer was extracted with DCM (3 × 10 mL). Organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, eluent:

hexanes/ethyl acetate = 30:1) to give afford pure product as yellow oil (436 mg, 89% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.13 (s, 1H), 7.08 (s, 1H), 5.46 (td, *J* = 6.5, 1.0 Hz, 1H), 5.12-5.05 (m, 1H), 4.58 (d, *J* = 6.5 Hz, 2H), 3.81 (s, 3H), 2.22 (s, 3H), 2.16-2.04 (m, 4H), 1.74 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.57 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 188.0, 155.6, 151.4, 151.2, 141.4, 140.7, 131.8, 129.6, 126.5, 123.7, 119.1, 105.0, 84.3, 65.7, 61.1, 39.5, 27.6, 26.3, 25.7, 17.7, 16.7, 10.1. **R_f** = 0.4 (hexanes/ethyl acetate = 9:1).

(*E*)-2-((1-(5-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-2-hydroxy-3-methoxy-4-methylphenyl)ethyl)amino)ethyl propionate (117): To a flame-dried Schlenk flask was charged with a solution of **116** (236 mg, 0.57 mmol) in dry Et_2O (6 mL). Methylmagnesium chloride (0.23 mL, 0.60 mmol, 2.6M solution in THF, 1.05 equiv) was added to the mixture at -78 ºC. The mixture was allowed to stir at the same temperature for 10 minutes before addition of **86a** solution (1.14 mL, 0.2 mmol, 1.0 M in toluene, 2 equiv.). The mixture was allowed to warm to room temperature over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (3 mL), extracted with Et_2O (3 × 5 mL). Organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1) to afford pure product as yellow oil (198 mg, 80% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.29 (s, 1H), 5.48 (t, *J* = 5.9 Hz, 1H), 5.10 (t, *J* = 6.8 Hz, 1H), 4.43 (d, *J* = 6.6 Hz, 2H), 4.30-4.25 (m, 1H), 4.12 (ddd, *J* = 11.3, 7.1, 3.8 Hz, 1H), 3.90 (q, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 2.93-2.82 (m, 2H), 2.37 (q, *J* = 7.7 Hz, 2H), 2.14 (s,

3H), 2.13-2.04 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.16 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.3, 150.0, 146.9, 144.0, 140.2, 131.7, 123.9, 123.3, 120.6, 120.3, 107.7, 66.3, 62.9, 60.1, 58.7, 45.9, 39.5, 30.3, 27.4, 26.4, 25.7, 22.2, 17.7, 16.6, 9.1. **R_f** = 0.1 (hexanes/ethyl acetate = 3:1).

(*E*)-5-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-2-(2-hydroxyethyl)-7-methoxy-3,6-dimethylisoindolin-1-one (105): Synthesized from **117** analogous to procedure used to prepare **107**. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.92 (s, 1H), 5.51 (t, *J* = 6.6 Hz, 1H), 5.10 (t, *J* = 6.6 Hz, 1H), 4.74-4.59 (m, 3H), 3.98 (s, 3H), 3.85 (dt, *J* = 14.0, 5.5 Hz, 1H), 3.71 (m, 2H), 3.33 (dt, *J* = 14.0, 5.5 Hz, 1H), 2.15-2.11 (m, 4H), 2.09 (s, 3H), 1.76 (s, 3H), 1.63 (s, 3H), 1.58 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H). **R_f** = 0.1 (hexanes/ethyl acetate = 1:1).

2.13 Model Case Studies of Marilines A and C

***Tert*-butyl (4-hydroxy-3-(1-((2-((3-methylbut-2-en-1-yl)oxy)phenyl)amino)ethyl)phenyl) carbonate (124):** To a flame-dried Schlenk tube was charged with a solution of **37d** (33.8 mg, 0.1 mmol) in dry Et_2O (1 mL). Methylmagnesium chloride (0.04 mL, 0.105 mmol, 2.6M solution in THF, 1.05 equiv) was added to the mixture at -78 ºC. The mixture was allowed to stir at the same temperature for 10 minutes before addition of **123** solution (0.11 mL, 0.11 mmol, 1.0 M in toluene, 1.1 equiv.). The mixture was allowed to warm to room temperature

over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (1 mL), extracted with Et_2O (3 × 1 mL). Organic layers were combined, washed with brine (1 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 10:1→3:1) to afford pure product as orange oil (32.4 mg, 78% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.99-6.95 (m, 2H), 6.86-6.74 (m, 5H), 5.52-5.45 (m, 1H), 4.60-4.51 (m, 2H), 4.44 (q, *J* = 6.8 Hz, 1H), 1.81 (s, 3H), 1.74 (s, 3H), 1.61 (d, *J* = 6.7 Hz, 3H), 1.56 (s, 9H). **R_f** = 0.1 (hexanes/ethyl acetate = 9:1).

4-(Benzyloxy)-6-formyl-2-methoxy-3-methylphenyl *tert*-butyl carbonate (128): Synthesized from **114** analogous to procedure used to prepare **115** and **116**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.14 (s, 1H), 7.47-7.29 (m, 5H), 7.17 (s, 1H), 5.11 (s, 2H), 3.83 (s, 3H), 2.28 (s, 3H), 1.57 (s, 9H). **R_f** = 0.6 (hexanes/ethyl acetate = 3:1).

6-(1-(Benzylamino)ethyl)-4-(benzyloxy)-2-methoxy-3-methylphenol (127): To a flame-dried Schlenk flask was charged with a solution of **128** (186 mg, 0.5 mmol) and 38 (0.55 mL, 0.55 mmol, 1.0 M in toluene, 1.1 equiv) in dry Et_2O (5 mL). Methylmagnesium chloride (0.2 mL, 0.53 mmol, 2.6M solution in THF, 1.05 equiv) was added to the mixture at -78 ºC. The mixture was allowed to warm to room temperature over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (5 mL), extracted with Et_2O (3 × 5 mL). Organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was re-dissolved in methanol (5 mL). TsOH monohydrate (4.8 mg, 0.025

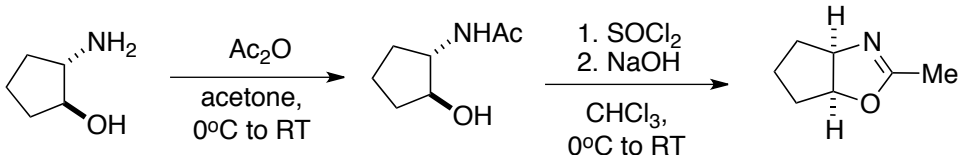
mmol, 5 mol%) was added. The solution was stirred at room for 10 hours. The reaction was quenched with Et_3N (0.1 mL). The mixture was concentrated in vacuo, then purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1) to afford pure product as yellow oil (125 mg, 66% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ7.45 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.34-7.27 (m, 6H), 6.41 (s, 1H), 5.00 (s, 2H), 3.96 (q, *J* = 6.3 Hz, 1H), 3.87 (s, 3H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 2.22 (s, 3H), 1.47 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 149.7, 147.0, 144.4, 138.4, 137.7, 128.6, 128.4, 128.4, 127.6, 127.4, 127.2, 123.6, 120.4, 107.6, 71.1, 60.1, 58.5, 51.5, 22.3, 9.1. **R_f** = 0.2 (hexanes/ethyl acetate = 3:1).

2.14 Syntheses of Chiral Nitrogen Nucleophiles

(*S*,*E*)-*N*-(4-Methoxybenzylidene)-1-phenylethanamine (141a). At room temperature, 4-methoxybenzaldehyde (2.72 g, 20 mmol) and (*S*)-1-phenylethanamine (2.42 g, 20 mmol) were dissolved in dichloromethane (60 mL). Anhydrous magnesium sulfate (4 g) was added, and the suspension was stirred overnight. Magnesium sulfate was removed by filtration, and the solvents were removed *in vacuo*. The residue was then purified by vacuum distillation (b.p. = 97 ^oC under 2 torr) over CaH_2 to afford pure product as colorless oil (3.20 g, 67% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.51 (q, *J* = 6.5 Hz, 1H), 3.84 (s, 3H), 1.58 (d, *J* = 6.7 Hz, 3H). The

opposite enantiomer is reported. Our characterization data match with prior literature data.[30]

(*S*)-2-Ethyl-4-phenyl-4,5-dihydrooxazole (141b). A sealed tube was charged with a mixture of (*S*)-2-amino-2-phenylethanol (1.50 g, 10 mmol), triethyl orthopropionate (2.31 g, 12 mmol, 1.2 equiv) and glacial acetic acid (25 µL, 0.4 mmol, 4 mol%) in DCE (20 mL). The tube was heated at 95 °C for 16 hours. The mixture was cooled to room temperature, quenched with saturated $NaHCO_3$ solution (5 mL), extracted with dichloromethane (4 × 15 mL). Organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by vacuum distillation (b.p. = 75 ^oC under 2 torr) over CaH_2 to afford pure, anhydrous product as as colorless oil (0.81 g, 46% isolated yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.30 (m, 2H), 7.30-7.21 (m, 3H), 5.16 (t, *J* = 9.2 Hz, 1H), 4.60 (dd, *J* = 10.0, 8.4 Hz, 1H), 4.08 (t, *J* = 8.2 Hz, 1H), 2.41 (q, *J* = 7.7 Hz, 2H), 1.27 (t, *J* = 7.4 Hz, 3H). Our characterization data match with prior literature data.[31]



S1 **S2** **141c**

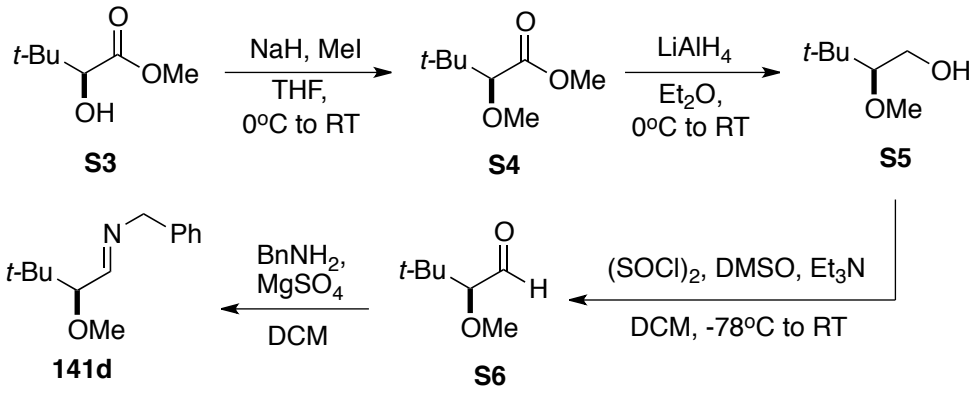
***N*-((1*S*,2*S*)-2-Hydroxycyclopentyl)acetamide (S2).** To a solution of **S1** (2.02 g, 20 mmol) in acetone (20 mL) was added acetic anhydride (2.04 g, 20 mmol, 1.0 equiv)

[30] Huang, L.; Zhang, Y.; Staples, R. J.; Huang, R. H.; Wulff, W. D. *Eur. J. Chem.* **2012**, *18* (17), 5302-5313.
[31] Shen, J.; Ikeda, N.; Bi, W.; Satoh, K.; Kamigaito, M.; Okamoto, Y. *Journal of Polymer Science Part A: Polymer Chemistry* **2018**, *57* (3), 441-447.

slowly at 0°C. The mixture was warmed to room temperature and stirred for 2 hours. Upon completion, the solution was diluted with saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The resulting mixture was extracted with 9:1 mixture of chloroform and isopropanol (5 × 20 mL). Organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product (2.75 g, 91% yield). This crude product was used directly in next step without purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.73 (br s, 1H), 3.97 (q, *J* = 6.8 Hz, 1H), 3.87-3.77 (m, 1H), 2.19-2.09 (m, 1H), 2.07-1.99 (m, 1H), 2.02 (s, 3H), 1.87-1.75 (m, 1H), 1.75-1.61 (m, 2H), 1.47-1.34 (m, 1H). **R_f** = 0.4 (DCM/MeOH = 9:1).

(3a*R*,6a*S*)-2-Methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]oxazole (141c). To a solution of **S2** (2.05 g, 14.3 mmol) in chloroform (10 mL) was added thionyl chloride (7.32 g, 61.5 mmol, 4.3 equiv) slowly at 0°C. The mixture was warmed to room temperature, stirred for 2 hours, and concentrated *in vacuo*. The residue was dissolved in 1M NaOH solution (50 mL). The resulting solution was extracted with Et_2O (4 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by vacuum distillation over CaH_2 (b.p. = 90 ^oC under 60 torr) to afford pure product (1.09 g, 61% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.90 (dd, *J* = 6.9, 5.6 Hz, 1H), 4.48 (t, *J* = 7.0 Hz, 1H), 1.98-1.91 (m, 4H), 1.88-1.82 (m, 1H), 1.67-1.53 (m, 3H), 1.50-1.38 (m, 1H). Our characterization data match with prior literature data.[32]

[32] Yeung; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128* (30), 9644-9645.



***(S)*-Methyl 2-methoxy-3,3-dimethylbutanoate (S4).** A suspension of NaH (1.13 g, 30 mmol, 1.5 equiv, 60% in oil) in THF (30 mL) was cooled to 0°C. To this suspension was added a solution of **S3** (2.80 g, 20 mmol) in THF (10 mL). The mixture was stirred at 0°C for 20 minutes before the addition of methyl iodide (4.02 g, 30 mmol, 1.5 equiv). The mixture was then warmed to room temperature and stirred for 3 hours. Upon completion, the reaction was quenched with saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated. This crude product was used directly in next step without purification (2.84 g, 89% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.41 (s, 1H), 3.34 (s, 3H), 0.97 (s, 9H). Our characterization data match with prior literature data.[33]

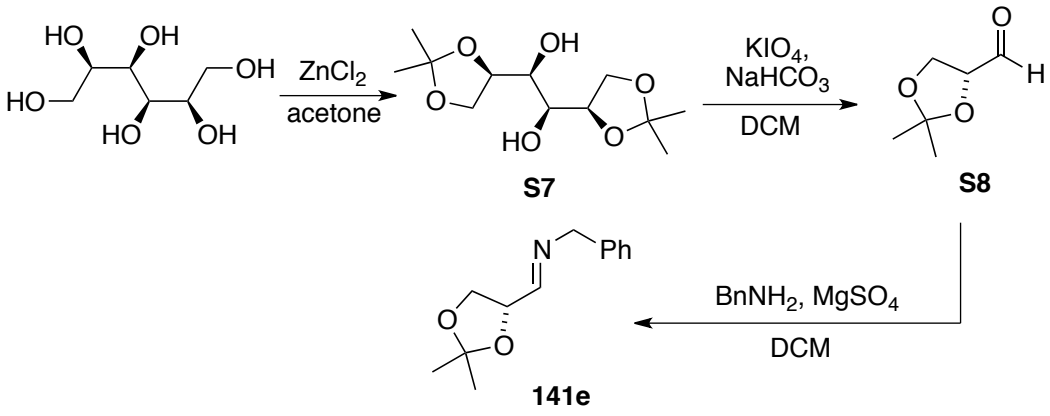
(*S*)-2-Methoxy-3,3-dimethylbutan-1-ol (S5). A suspension of $LiAlH_4$ (0.62 g, 16.2 mmol, 1.3 equiv) in Et_2O (30 mL) was cooled to 0°C. To this suspension was added a solution of **S4** (2.00 g, 12.5 mmol) in Et_2O (30 mL). The mixture was then warmed to room temperature and stirred for 16 hours. Upon completion, the reaction was

[33] Nitsch, D.; Huber, S. M.; Pöthig, A.; Narayanan, A.; Olah, G. A.; Prakash, G. K. S.; Bach, T. *J. Am. Chem. Soc.* **2014**, *136* (7), 2851-2857

quenched with methanol (5 mL), followed by saturated Rochelle's salt solution (50 mL). The biphasic mixture was stirred until both layers turned clear. The aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. This crude product was used directly in next step without purification (1.25 g, 76% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.76 (ddd, *J* = 11.5, 7.9, 3.5 Hz, 1H), 3.58 (ddd, *J* = 11.6, 7.3, 4.7 Hz, 1H), 3.54 (s, 3H), 2.90 (dd, *J* = 7.5, 3.4 Hz, 1H), 0.92 (s, 9H). Our characterization data match with prior literature data.[33]

(*S*)-2-Methoxy-3,3-dimethylbutanal (S6). A solution of oxalyl chloride (3.00 g, 23.6 mmol, 2.0 equiv) in DCM (70 mL) was cooled to -78°C. To this solution, DMSO (3.69 g, 47.2 mmol, 4.0 equiv) was added slowly. The suspension was stirred for 10 minutes before the addition of a solution of **S5** (1.56 g, 11.8 mmol) in DCM (10 mL). The mixture was stirred at -78°C for 30 minutes, after which Et_3N (7.16 g, 70.8 mmol, 6.0 equiv) was added. The solution was warmed to room temperature over 1 hour. The reaction was quenched with water (40 mL). The aqueous layer was extracted with DCM (3 × 40 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 20:1) to afford pure product as colorless oil (1.10 g, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.73 (d, *J* = 3.1 Hz, 1H), 3.40 (s, 3H), 3.07 (d, *J* = 3.5 Hz, 1H), 1.00 (s, 9H). **R_f** = 0.5 (hexanes/ethyl acetate = 9:1). Our characterization data match with prior literature data.[33]

(*S,E*)-N-(2-Methoxy-3,3-dimethylbutylidene)-1-phenylmethanamine (141d). At room temperature, **S6** (1.25 g, 9.6 mmol) and benzylamine (1.02 g, 9.6 mmol) were dissolved in dichloromethane (50 mL). Anhydrous magnesium sulfate (2 g) was added, and the suspension was stirred overnight. Magnesium sulfate was removed by filtration, and the solvents were removed *in vacuo*. The residue was then purified by vacuum distillation (b.p. = 75 ^{o}C under 2 torr) over CaH_2 to afford pure product as colorless oil (1.22 g, 58% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.66 (dt, *J* = 7.0, 1.4 Hz, 1H), 7.35-7.28 (m, 2H), 7.28-7.20 (m, 3H), 4.65 (q, *J* = 13.6 Hz, 2H), 3.31 (s, 3H), 3.26 (d, *J* = 7.0 Hz, 1H), 0.93 (s, 9H).



(1*S*,2*S*)-1,2-bis((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (S7). To a solution of D-mannitol (5.47 g, 30 mmol) in acetone (50 mL) was added anhydrous $ZnCl_2$ (11.45 g, 84 mmol, 2.8 equiv). The suspension was stirred at room temperature for 10 hours until it turned into a clear solution. The reaction was quenched with saturated K_2CO_3 solution (50 mL). The mixture was stirred at room temperature for 30 minutes. The white precipitate was filtered by vacuum filtration. The filtrate was extracted with DCM (3 × 50 mL). The organic layers were

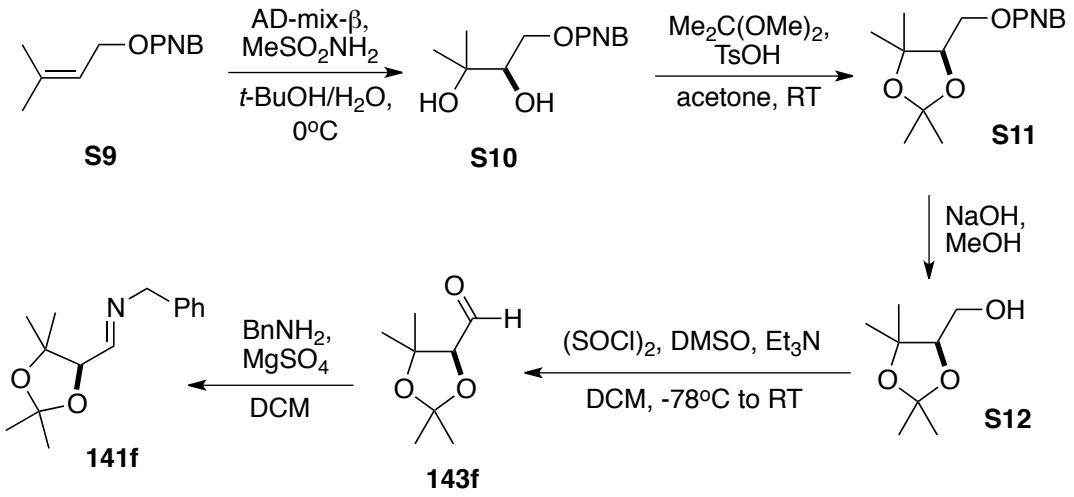
combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by recrystallization from DCM and hexanes to afford pure product as white crystals (5.25 g, 67% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.20 (q, *J* = 6.5 Hz, 2H), 4.12 (dd, *J* = 8.7, 6.3 Hz, 2H), 3.97 (dd, *J* = 8.7, 5.9 Hz, 2H), 3.77-3.73 (m, 2H), 2.54 (d, *J* = 6.6 Hz, 2H), 1.42 (s, 6H), 1.36 (s, 6H). Our characterization data match with prior literature data.[34]

(*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (S8). To a solution of **S7** (4.50 g, 17.2 mmol) in DCM (50 mL) was added saturated $NaHCO_3$ solution (2 mL), followed by $NaIO_4$ (3.68 g, 17.2 mmol, 1.0 equiv). The biphasic mixture was stirred at room temperature for 2 hours. Upon completion, anhydrous Na_2SO_4 was added, and the mixture was stirred for 1 hour. The solid was removed by filtration. The filtrate was concentrated to afford crude product as colorless oil. This crude product was used directly in next step without purification (4.07 g, 91% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.72 (d, *J* = 1.8 Hz, 1H), 4.38 (ddd, *J* = 7.3, 4.9, 1.8 Hz, 1H), 4.19-4.16 (m, 1H), 4.12-4.09 (m, 1H), 1.49 (s, 3H), 1.42 (s, 3H). Our characterization data match with prior literature data.[34]

(*S*,*E*)-*N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-1-phenylmethanamine (141e). At room temperature, **S8** (2.98 g, 22.9 mmol) and benzylamine (2.46 g, 22.9 mmol) were dissolved in dichloromethane (70 mL). Anhydrous magnesium sulfate (5 g) was added, and the suspension was stirred overnight. Magnesium sulfate was removed by filtration, and the solvents were removed *in vacuo*. The residue was then purified by vacuum distillation (b.p. = 80 ^oC under 2 torr) over CaH_2 to afford

[34] Lees, N. R.; Han, L.; Byrne, M. J.; Davies, J. A.; Parnell, A. E.; Moreland, P. E. J.; Stach, J. E. M.; van der Kamp, M. W.; Willis, C. L.; Race, P. R. *Angew. Chem. Int. Ed.* **2019**, *58* (8), 2305-2309.

pure product as colorless oil (2.78 g, 51% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.77 (dt, *J* = 5.2, 1.0 Hz, 1H), 7.36-7.31 (m, 2H), 7.28-7.23 (m, 3H), 4.66-4.61 (m, 3H), 4.21 (dd, *J* = 8.3, 7.0 Hz, 1H), 3.97 (dd, *J* = 8.5, 6.1 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H).



(*R*)-2,3-dihydroxy-3-methylbutyl 4-nitrobenzoate (S10). AD-mix-β (76.4 g) and methanesulfonamide (4.06 g, 42.6 mmol, 1.0 equiv) were dissolved in biphasic mixture of *tert*-butanol (240 mL) and water (240 mL). The orange slurry was cooled to 0^{o}C before addition of **S9** (10.00 g, 42.6 mmol). The mixture was stirred at 0^{o}C for 48 hours. Upon completion, the reaction was quenched with Na_2SO_3 solid (64.2 g, 510 mmol, 12 equiv) at 0 ^{o}C. The mixture was warmed to room temperature and stirred for one hour. The aqueous layer was extracted ethyl acetate (3 × 200 mL). The organic layers were combined, washed brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 2:1) to afford pure product as yellow solid (9.60 g, 85% isolated yield, 88% *e.e.*). This pure product was further recrystallized

using hexanes and Et_2O to further improve enantiopurity of product (7.00 g, 62% yield, >95% *e.e.*). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 2H), 8.23 (d, *J* = 8.6 Hz, 2H), 4.59 (dd, *J* = 11.3, 2.7 Hz, 1H), 4.38 (dd, *J* = 11.5, 8.4 Hz, 1H), 3.84 (dd, *J* = 8.4, 2.5 Hz, 1H), 1.35 (s, 3H), 1.30 (s, 3H). **R_f** = 0.3 (hexanes/ethyl acetate = 1:1). Our characterization data match with prior literature.[35]

(*R*)-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)methyl 4-nitrobenzoate (S11). To a solution of **S10** (4.80 g, 17.8 mmol) in acetone (90 mL) was added 2,2-dimethoxypropane (7.42 g, 71.2 mmol, 4 equiv) and TsOH (120 mg, 1.1 mmol, 6 mol%). The mixture was stirred at room temperature for 16 hours. Upon completion, the reaction was quenched with Et_3N (4 mL), after which the solution was concentrated. The residue was redissolved in a mixture of water (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, washed brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 20:1) to afford pure product as yellow solid (4.92 g, 90% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.30 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H), 4.49-4.42 (m, 2H), 4.14-4.12 (m, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.22 (s, 3H). **R_f** = 0.3 (hexanes/ethyl acetate = 9:1).

(*R*)-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)methanol (S12). To a solution of **S11** (4.90 g, 16.1 mmol) in methanol (40 mL) was added 20% NaOH solution (25 mL). The mixture was stirred at room temperature for one hour. The solution was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined,

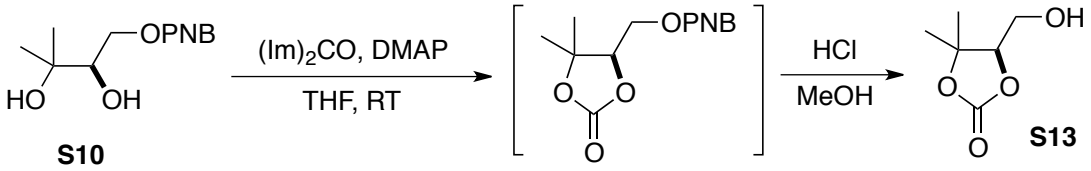
[35] Noe, M. C.; Letavic, M. A.; Snow, S. L. *Org. React.* **2005**, 109-625.

washed brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1) to afford pure product as colorless oil (2.50 g, 99% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.91 (dd, *J* = 7.8, 3.7 Hz, 1H), 3.77 (ddd, *J* = 11.6, 7.6, 4.2 Hz, 1H), 3.66 (ddd, *J* = 11.5, 7.7, 3.8 Hz, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.12 (s, 3H). **R_f** = 0.3 (hexanes/ethyl acetate = 3:1). Our characterization data match with prior literature.[36]

(*S*)-2,2,5,5-tetramethyl-1,3-dioxolane-4-carbaldehyde (143f). A solution of oxalyl chloride (2.06 g, 16.3 mmol, 1.3 equiv) in DCM (60 mL) was cooled to -78°C. To this solution, DMSO (2.34 g, 47.2 mmol, 2.4 equiv) was added slowly. The suspension was stirred for 10 minutes before the addition of a solution of **S12** (2.00 g, 12.5 mmol) in DCM (30 mL). The mixture was stirred at -78°C for 30 minutes, after which Et_3N (5.11 g, 50.0 mmol, 4.0 equiv) was added. The solution was warmed to room temperature over 1 hour. The reaction was quenched with water (40 mL). The aqueous layer was extracted with DCM (3 × 50 mL). The organic layers were combined, washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated to afford crude product as colorless oil (1.73 g, 88% yield). The crude product is used in next step immediately without purification. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.72 (d, *J* = 2.4 Hz, 1H), 4.08 (d, *J* = 2.1 Hz, 1H), 1.55 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.20 (s, 3H). **R_f** = 0.4 (hexanes/ethyl acetate = 3:1). Our characterization data match with prior literature.[37]

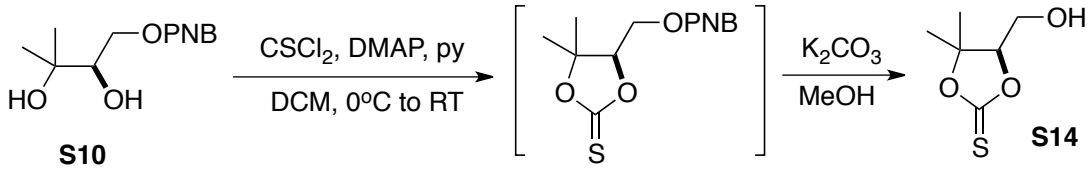
[36] Serra, S. *Tetrahedron: Asymmetry.* **2014**, *25* (23), 1561-1572.
[37] Krief, A.; Froidbise, A. *Tetrahedron.* **2004**, *60* (35), 7637-7658.

(*R*,*E*)-1-phenyl-*N*-((2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)methylene)methanamine (141f). At room temperature, **143f** (1.50 g, 9.5 mmol) and benzylamine (1.02 g, 9.5 mmol, 1.0 equiv) were dissolved in dichloromethane (70 mL). Anhydrous magnesium sulfate (3 g) was added, and the suspension was stirred overnight. Magnesium sulfate was removed by filtration, and the solvent was removed *in vacuo*. The residue was then purified by vacuum distillation (b.p. = 95°C under 2 torr) over CaH_2 to afford pure product as colorless oil (1.40 g, 60% isolated yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (dt, *J* = 5.5, 1.2 Hz, 1H), 7.36-7.31 (m, 2H), 7.29-7.24 (m, 3H), 4.66 (d, *J* = 6.3 Hz, 2H), 4.32 (d, *J* = 5.5 Hz, 1H), 1.51 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.15 (s, 3H).



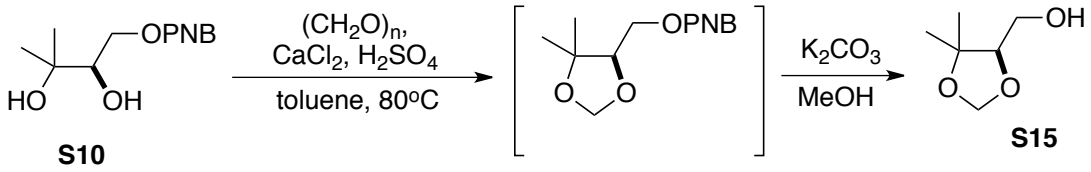
(*R*)-5-(hydroxymethyl)-4,4-dimethyl-1,3-dioxolan-2-one (S13). To a solution of **S10** (325 mg, 1.23 mmol) in THF (15 mL) was added 1,1-carbonyldiimidazole (400 mg, 2.46 mmol, 2 equiv) and DMAP (15 mg, 0.12 mmol, 10 mol%). The solution was stirred at room temperature for 20 hours. Upon completion, the reaction was quenched with saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was redissolved in methanol (2 mL). To this solution HCl solution (0.4 mL, 0.4 mmol, 20 mol%, 1M solution in methanol) was added. The solution was stirred at room temperature for 2 hours before quenching with $NaHCO_3$ solution (1 mL). The aqueous layer was

extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 3:1) to afford pure product as colorless oil (202 mg, 53% isolated yield over 2 steps). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.35 (dd, *J* = 5.9, 4.7 Hz, 1H), 3.91 (dd, *J* = 12.3, 5.7 Hz, 1H), 3.83 (dd, *J* = 12.1, 3.5 Hz, 1H), 1.83 (br s, 1H), 1.55 (s, 3H), 1.48 (s, 3H). **R_f** = 0.2 (hexanes/ethyl acetate = 1:1).

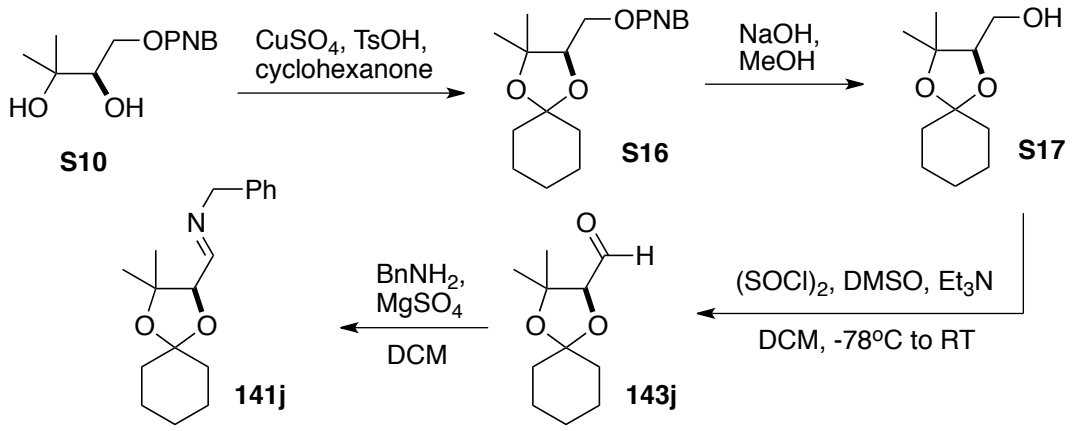


(*R*)-5-(hydroxymethyl)-4,4-dimethyl-1,3-dioxolane-2-thione (S14). A solution of **S10** (744 mg, 2.82 mmol), DMAP (34.5 mg, 0.282 mmol, 10 mol%) and pyridine (446 mg, 5.64 mmol, 2 equiv) in DCM (6 mL) was cooled to 0°C. With vigorous stirring, thiophosgene (324 mg, 2.82 mmol, 1 equiv) was added dropwise over 5 minutes. The solution was warmed to room temperature and stirred for 16 hours, after which the solution was concentrated *in vacuo*. The residue was diluted with brine (10 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was taken up in methanol (10 mL), potassium carbonate (1.95 mg, 14.1 mmol, 5 equiv) was added. The suspension was stirred for 30 minutes, after which the suspension was filtered. The filtrate collected was concentrated and purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 2:1) to afford pure product

as orange oil (123 mg, 27% isolated yield over 2 steps). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.53 (br s, 1H), 3.91 (m, 2H), 1.60 (s, 3H), 1.54 (s, 3H). **R_f** = 0.2 (hexanes/ethyl acetate = 1:1).



(*R*)-(5,5-dimethyl-1,3-dioxolan-4-yl)methanol (S15). To a solution of **S10** (813 mg, 3.08 mmol) in toluene (20 mL) was added paraformaldehyde (508 mg, 16.9 mmol, 5 equiv), anhydrous $CaCl_2$ (683 mg, 6.16 mmol, 2 equiv) and concentrated H_2SO_4 (181 mg, 1.85 mmol, 0.6 equiv). The mixture was stirred at 80 ^oC for 20 hours. Upon completion, the mixture was carefully quenched with $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was taken up in methanol (15 mL), potassium carbonate (2.13 mg, 15.4 mmol, 5 equiv) was added. The suspension was stirred for 30 minutes, after which the suspension was filtered. The filtrate collected was concentrated and purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 2:1) to afford pure product as colorless oil (113 mg, 28% isolated yield over 2 steps). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.10 (s, 1H), 4.97 (s, 1H), 3.73-3.61 (m, 3H), 1.33 (s, 3H), 1.19 (s, 3H). **R_f** = 0.5 (hexanes/ethyl acetate = 1:1).



(*R*)-(3,3-dimethyl-1,4-dioxaspiro[4.5]decan-2-yl)methyl 4-nitrobenzoate (S16). To a solution of **S10** (7.55 g, 28.6 mmol) was added cyclohexanone (3.26 g, 34.3 mmol, 1.2 equiv), anhydrous $CuSO_4$ (7.30 g, 45.8 mmol, 1.6 equiv) and TsOH monohydrate (272 mg, 1.43 mmol, 5 mol%). The mixture was stirred at room temperature for 20 hours. Upon completion, the reaction was quenched with Et_3N (0.5 mL). The mixure was stirred for 5 minutes, filtered through a pad of Celite, and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 9:1) to afford pure product as yellow solid (7.29 g, 73% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 2H), 8.23 (d, *J* = 8.7 Hz, 2H), 4.52-4.40 (m, 2H), 4.11 (dd, *J* = 6.6, 5.2 Hz, 1H), 1.72-1.56 (m, 8H), 1.45-1.33 (m, 5H), 1.22 (s, 3H). **R_f** = 0.6 (hexanes/ethyl acetate = 3:1).

(*R*)-(3,3-dimethyl-1,4-dioxaspiro[4.5]decan-2-yl)methanol (S17). To a solution of **S16** (7.00 g, 20.0 mmol) in methanol (50 mL) was added 20% NaOH solution (30 mL). The mixture was stirred at room temperature for one hour. The solution was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, washed brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2: eluent: hexanes/ethyl

acetate = 2:1) to afford pure product as colorless oil (3.60 g, 90% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.89 (dd, *J* = 7.7, 3.8 Hz, 1H), 3.76 (dd, *J* = 11.4, 7.8 Hz, 1H), 3.64 (dd, *J* = 11.4, 3.9 Hz, 1H), 1.66-1.56 (m, 8H), 1.44-1.33 (m, 2H), 1.31 (s, 3H), 1.11 (s, 3H). **R_f** = 0.1 (hexanes/ethyl acetate = 3:1).

(*S*)-3,3-dimethyl-1,4-dioxaspiro[4.5]decane-2-carbaldehyde (143j). A solution of oxalyl chloride (2.28 g, 18.0 mmol, 1.3 equiv) in DCM (60 mL) was cooled to -78°C. To this solution, DMSO (2.60 g, 33.3 mmol, 2.4 equiv) was added slowly. The suspension was stirred for 10 minutes before the addition of a solution of **S17** (2.78 g, 13.9 mmol) in DCM (30 mL). The mixture was stirred at -78°C for 30 minutes, after which Et_3N (5.60 g, 55.4 mmol, 4.0 equiv) was added. The solution was warmed to room temperature over 1 hour. The reaction was quenched with water (40 mL). The aqueous layer was extracted with DCM (3 × 50 mL). The organic layers were combined, washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 3:1) to afford pure product as colorless oil (2.00 g, 73% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.73 (d, *J* = 2.3 Hz, 1H), 4.05 (d, *J* = 2.3 Hz, 1H), 1.81-1.58 (m, 8H), 1.49-1.43 (m, 1H), 1.42 (s, 3H), 1.39-1.35 (m, 1H), 1.19 (s, 3H). **R_f** = 0.5 (hexanes/ethyl acetate = 3:1).

(*R*,*E*)-*N*-((3,3-dimethyl-1,4-dioxaspiro[4.5]decan-2-yl)methylene)-1-phenylmethanamine (141j). At room temperature, **143j** (2.00 g, 10.1 mmol) and benzylamine (1.08 g, 10.1 mmol, 1.0 equiv) were dissolved in dichloromethane (80 mL). Anhydrous magnesium sulfate (4 g) was added, and the suspension was stirred overnight. Magnesium sulfate was removed by filtration, and the solvent was

removed *in vacuo*. The residue was then purified by vacuum distillation (b.p. = 130°C under 2 torr) over CaH_2 to afford pure product as colorless oil (1.52 g, 52% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 5.7 Hz, 1H), 7.36-7.31 (m, 2H), 7.29-7.24 (m, 3H), 4.69 (d, *J* = 13.8 Hz, 1H), 4.62 (d, *J* = 13.8 Hz, 1H), 4.30 (d, *J* = 5.7 Hz, 1H), 1.77-1.53 (m, 9H), 1.46-1.37 (m, 1H), 1.35 (s, 3H), 1.15 (s, 3H).

2.15 Diastereoselective Additions of Nitrogen Nucleophiles

General Procedure K

Chiral nucleophile **141** (0.15 mL, 0.15 mmol, 1.0 M in toluene, 1.5 equiv. unless otherwise specified) was added to a stirred solution of **37a** (0.1 mL, 0.1 mmol, 1.0 M in toluene) in Et_2O (1 mL) at room temperature. Methylmagnesium chloride (0.04 mL, 0.105 mmol, 2.6M solution in THF, 1.05 equiv) was added to the mixture at -78 ºC. The reaction mixture was allowed to warm to room temperature over 16 hours then quenched with $NaHCO_3$ solution (1 mL). The aqueous layer was extracted with Et_2O (3 x 1mL) then the combined organic layers was washed with brine (1 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford crude product. Crude NMR yields were determined by dibromomethane as internal standard. Purification by flash column chromatography was performed to afford pure product when specified.

***Tert*-butyl (2-(4-methoxyphenyl)-4-methyl-3-((*S*)-1-phenylethyl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (142a).** Prepared according to the general

procedure K. 30% crude NMR yield. The residue was directly hydrolyzed to give corresponding benzylic amine.

***Tert*-butyl (3-hydroxy-4-(1-(((*S*)-1-phenylethyl)amino)ethyl)phenyl) carbonate (142a').** The crude 1,3-benzoxazine **142a** was dissolved in methanol TsOH monohydrate (9.6 mg, 0.05 mmol, 5 mol%) was added. The solution was stirred at room for 10 hours. The reaction was quenched with Et_3N (0.2 mL). The mixture was concentrated in vacuo, then purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1) to afford pure product as yellow oil (8.9 mg, 25% isolated yield, inseparable mixture of diastereomers, *dr* = 2.2:1). $\mathbf{R_f}$ = 0.2 (hexanes/ethyl acetate = 3:1).

Major diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.13 (m, 5H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 2.3 Hz, 1H), 6.56 (dd, *J* = 8.2, 2.2 Hz, 1H), 3.70 (q, *J* = 6.7 Hz, 1H), 3.64 (q, *J* = 6.7 Hz, 1H), 1.56 (s, 9H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.32 (d, *J* = 6.7 Hz, 3H).

Minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.13 (m, 5H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 2.1 Hz, 1H), 6.56 (dd, *J* = 8.2, 2.2 Hz, 1H), 3.99 (q, *J* = 6.8 Hz, 1H), 3.91 (q, *J* = 6.5 Hz, 1H), 1.55 (s, 9H), 1.46 (d, *J* = 6.5 Hz, 3H), 1.41 (d, *J* = 6.5 Hz, 3H).

(2*S*)-2-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)-2-phenylethyl propionate (142b). Prepared according to the general procedure K. The residue was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 4:1→1:1) to afford pure product as yellow oil (16.8 mg, 39% isolated yield,

inseparable mixture of diastereomers, *dr* = 2:1). $\mathbf{R_f}$ = 0.3 (hexanes/ethyl acetate = 3:1).

Major diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39-7.16 (m, 5H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.57-6.55 (m, 1H), 4.27 (dd, *J* = 11.5, 8.0 Hz, 1H), 4.17 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.87 (br s, 1H), 3.68 (q, *J* = 6.7 Hz, 1H), 2.44-2.34 (m, 2H), 1.56 (s, 9H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.24 (t, *J* = 7.7 Hz, 3H).

Minor diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39-7.16 (m, 5H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.57-6.55 (m, 1H), 4.60 (dd, *J* = 10.1, 8.4 Hz, 1H), 4.37 (dd, *J* = 11.1, 4.2 Hz, 1H), 4.25-4.22 (m, 1H), 3.97 (q, *J* = 6.6 Hz, 1H), 2.44-2.34 (m, 2H), 1.54 (s, 9H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.27 (t, *J* = 7.5 Hz, 3H).

(1*S*,2*R*)-2-((1-(4-((*Tert*-butoxycarbonyl)oxy)-2-hydroxyphenyl)ethyl)amino)cyclopentyl acetate (142c). Prepared according to the general procedure K. The residue was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 4:1→1:1) to afford pure product as yellow oil (12.9 mg, 34% isolated yield, *dr* = 1.8:1). $\mathbf{R_f}$ = 0.3 (hexanes/ethyl acetate = 3:1).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, *J* = 7.8 Hz, 1H), 6.62-6.54 (m, 2H), 5.24 (t, *J* = 4.3 Hz, 1H), 3.91 (q, *J* = 6.7 Hz, 1H), 3.11-3.00 (m, 1H), 2.12 (s, 3H), 1.97-1.82 (m, 2H), 1.80-1.70 (m, 2H), 1.55-1.50 (m, 2H), 1.61 (s, 9H), 1.37 (d, *J* = 6.7 Hz, 3H).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.2 Hz, 1H), 6.62-6.55 (m, 2H), 5.07 (t, *J* = 4.1 Hz, 1H), 4.00 (q, *J* = 6.7 Hz, 1H), 3.10-3.00 (m, 1H), 2.09 (s, 3H), 1.93-1.84 (m, 1H), 1.84-1.67 (m, 3H), 1.56-1.50 (m, 2 H), 1.55 (s, 3H), 1.43 (d, *J* = 6.7 Hz, 3H).

(2*S*)-3-Benzyl-2-((*S*)-1-methoxy-2,2-dimethylpropyl)-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (142d). Prepared according to the general procedure K. The residue was purified by column chromatography (SiO_2, eluent: 1% triethylamine in hexane) to afford pure product as yellow oil (41.0 mg, 90% isolated yield, inseparable mixture of diastereomers, *dr* = 2.3:1). **R_f** = 0.6 (hexanes/ethyl acetate = 9:1).

Major diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.18 (m, 5H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 2.4 Hz, 1H), 6.66-6.63 (m, 1H), 4.97 (d, *J* = 4.5 Hz, 1H), 4.66 (d, *J* = 15.3 Hz, 1H), 3.81-3.73 (m, 1H), 3.60 (s, 3H), 3.52 (d, *J* = 15.3 Hz, 1H), 3.30 (d, *J* = 4.5 Hz, 1H), 1.55 (s, 9H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.06 (s, 9H).

Minor diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.18 (m, 5H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 6.67-6.66 (m, 1H), 4.94 (d, *J* = 7.3 Hz, 1H), 4.18 (d, *J* = 15.3 Hz, 1H), 3.81-3.73 (m, 1H), 3.60 (s, 3H), 3.52 (d, *J* = 15.3 Hz, 1H), 3.15 (d, *J* = 7.3 Hz, 1H), 1.55 (s, 9H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H).

(2*S*)-3-Benzyl-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (142e). Prepared according to the

general procedure K. The residue was purified by column chromatography (SiO_2, eluent: 1% triethylamine in hexane) to afford pure product as yellow oil (31.9 mg, 70% isolated yield, inseparable mixture of diastereomers, *dr* = 2.5:1). $\mathbf{R_f}$ = 0.6 (hexanes/ethyl acetate = 9:1).

Major diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.16 (m, 5H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.66-6.58 (m, 2H), 4.85 (d, *J* = 7.3 Hz, 1H), 4.40 (q, *J* = 5.8 Hz, 1H), 4.16-4.04 (m, 2H), 3.95-3.88 (m, 1H), 3.70 (q, *J* = 6.7 Hz, 1H), 3.32 (d, *J* = 14.3 Hz, 1H), 1.49 (s, 9H), 1.42-1.29 (m, 9H).

Minor diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.16 (m, 5H), 6.84-6.63 (m, 3H), 4.77 (d, *J* = 7.7 Hz, 1H), 4.50 (q, *J* = 7.3 Hz, 1H), 4.16-4.04 (m, 2H), 4.02-4.00 (m, 1H), 3.62 (q, *J* = 7.0 Hz, 1H), 3.43 (d, *J* = 15.0 Hz, 1H), 1.49 (s, 9H), 1.42-1.29 (m, 9H).

(2*S*,4*R*)-3-Benzyl-4-methyl-2-((*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (142f). Prepared according to the general procedure K. The residue was purified by column chromatography (SiO_2, eluent: 1% triethylamine in hexane) to afford pure product as yellow oil (36.3 mg, 75% isolated yield, single diastereomer). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.3 Hz, 2H), 7.31-7.29 (m, 2H), 7.25-7.23 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.64 (d, *J* = 1.8 Hz, 1H), 5.00 (d, *J* = 8.3 Hz, 1H), 4.26 (d, *J* = 13.9 Hz, 1H), 4.10 (d, *J* = 8.7 Hz, 1H), 3.79 (q, *J* = 7.0 Hz, 1H), 3.37 (d, *J* = 14.3 Hz, 1H), 1.55 (s, 9H), 1.48 (s, 6H), 1.40 (d, *J* = 7.0 Hz, 3 H),

1.30 (s, 3 H), 1.29 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 154.2, 152.2, 150.2, 139.5, 129.2, 129.0, 128.5, 127.2, 123.1, 114.2, 109.7, 107.9, 84.6, 83.8, 81.1, 79.2, 52.9, 50.6, 28.9, 27.9, 27.7, 27.1, 23.6, 23.3. **HRMS (ESI)** m/z calculated for $C_{28}H_{38}NO_6$ $[M+H]^+$: 484.2699; found 484.2717. **R_f** = 0.6 (hexanes/ethyl acetate = 9:1). Relative stereochemistry was confirmed by X-ray diffraction of its crystal. The X-ray data have been deposited at the Cambridge Crystallographic Data Center (Deposition number 1936973).

(2*S*,4*R*)-3-Benzyl-2-((*S*)-3,3-dimethyl-1,4-dioxaspiro[4.5]decan-2-yl)-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (142j). Prepared according to the general procedure K. The residue was purified by column chromatography (SiO_2, eluent: 1% triethylamine in hexane) to afford pure product as yellow solid (40.8 mg, 78% isolated yield, single diastereomer). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.27-7.23 (m, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.70 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 5.02 (d, *J* = 8.7 Hz, 1H), 4.30 (d, *J* = 14.3 Hz, 1H), 4.10 (d, *J* = 8.3 Hz, 1H), 3.76 (q, *J* = 7.0 Hz, 1H), 3.38 (d, *J* = 14.3 Hz, 1H), 1.78-1.60 (m, 6H), 1.56 (s, 9H), 1.54-1.42 (m, 7H), 1.40 (d, *J* = 7.0 Hz, 3H), 1.30 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 154.1, 152.0, 150.0, 139.6, 129.0, 128.6, 128.2, 126.9, 123.0, 113.8, 109.6, 108.1, 84.4, 83.6, 80.4, 78.7, 52.5, 50.2, 38.4, 36.1, 27.8, 27.7, 25.1, 24.1, 23.9, 23.6, 23.5. **R_f** = 0.6 (hexanes/ethyl acetate = 9:1).

3. X-ray Diffraction Data of Compound 142f

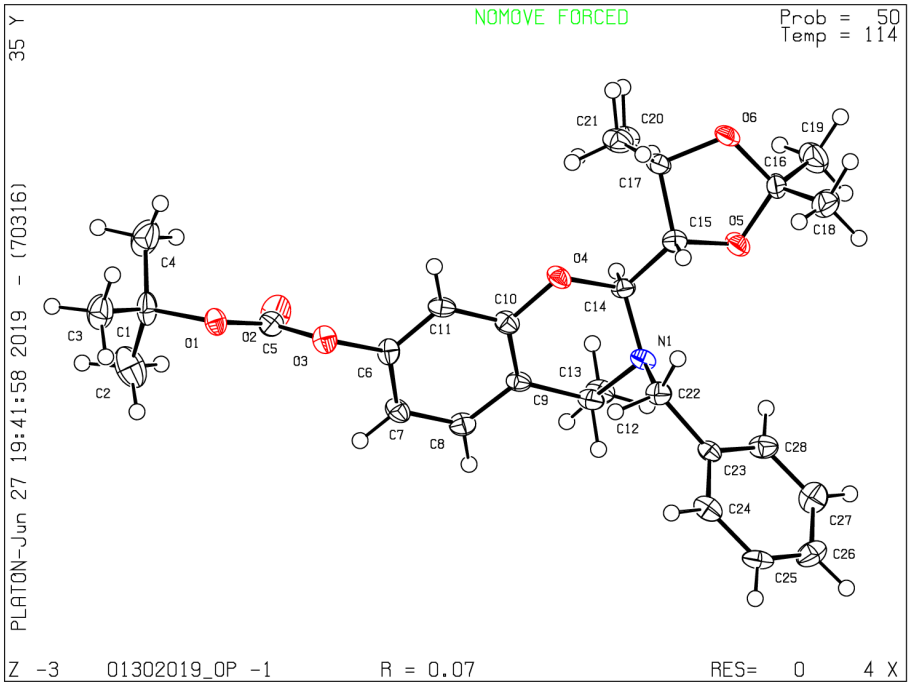


Table S1. Crystal data.

$C_{28}H_{37}NO_6$	Z = 2
M_r = 483.58	F(000) = 520
Triclinic, P1	D_x = 1.224 Mg m^{-3}
a = 8.195 (7) Å	Mo Kα radiation, λ = 0.71073 Å
b = 11.797 (10) Å	Cell parameters from 1266 reflections
c = 14.501 (12) Å	θ = 2.6–21.1°
α = 104.13 (3)°	μ = 0.09 mm^{-1}
β = 100.44 (3)°	T = 114 K
γ = 97.93 (3)°	Needle, colorless
V = 1312.3 (19) Å^3	0.25 × 0.05 × 0.05 mm

Table S2. Data Collection.

Bruker Kappa Apex II diffractometer	R_{int} = 0.061
Absorption correction: multi-scan *SADABS*	θ_{max} = 24.8°, θ_{min} = 1.5°
T_{min} = 0.568, T_{max} = 0.745	h = −9→9
7975 measured reflections	k = −13→11
4461 independent reflections	l = −16→17
2421 reflections with I > 2σ(I)	

Table S3. Data Refinement.

Refinement on F^2	0 restraints
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.067	H-atom parameters constrained
$wR(F^2)$ = 0.194	$w = 1/[\sigma^2(F_o^2) + (0.093P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
S = 0.97	$(\Delta/\sigma)_{max} < 0.001$
4461 reflections	$\Delta\rho_{max}$ = 0.28 e Å^{-3}
324 parameters	$\Delta\rho_{min}$ = −0.45 e Å^{-3}

Table S4. Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	−0.2352 (5)	0.8075 (4)	0.6354 (3)	0.0288 (10)
C2	−0.3776 (6)	0.6992 (4)	0.5871 (3)	0.0464 (13)
H2A	−0.3972	0.6832	0.5160	0.070*
H2B	−0.4812	0.7153	0.6082	0.070*
H2C	−0.3456	0.6297	0.6061	0.070*

C3	−0.2016 (6)	0.8345 (4)	0.7458 (3)	0.0364 (11)
H3A	−0.1719	0.7649	0.7655	0.055*
H3B	−0.3033	0.8535	0.7678	0.055*
H3C	−0.1080	0.9027	0.7752	0.055*
C4	−0.2646 (7)	0.9161 (4)	0.6028 (3)	0.0452 (13)
H4A	−0.1648	0.9797	0.6316	0.068*
H4B	−0.3632	0.9428	0.6240	0.068*
H4C	−0.2850	0.8964	0.5315	0.068*
C5	−0.0551 (5)	0.7433 (3)	0.5248 (3)	0.0222 (9)
C6	0.1417 (5)	0.6659 (3)	0.4408 (2)	0.0198 (9)
C7	0.0597 (5)	0.5529 (3)	0.3839 (3)	0.0231 (9)
H7	−0.0318	0.5107	0.4015	0.028*
C8	0.1141 (5)	0.5035 (3)	0.3018 (3)	0.0227 (9)
H8	0.0582	0.4264	0.2623	0.027*
C9	0.2485 (5)	0.5628 (3)	0.2746 (2)	0.0190 (9)
C10	0.3262 (5)	0.6770 (3)	0.3335 (3)	0.0216 (9)
C11	0.2724 (5)	0.7293 (3)	0.4162 (3)	0.0211 (9)
H11	0.3250	0.8074	0.4552	0.025*
C12	0.3152 (5)	0.5046 (3)	0.1876 (3)	0.0223 (9)
H12	0.3254	0.4225	0.1918	0.027*
C13	0.1959 (5)	0.4911 (3)	0.0904 (3)	0.0260 (10)
H13A	0.1810	0.5699	0.0837	0.039*
H13B	0.0861	0.4438	0.0878	0.039*
H13C	0.2437	0.4507	0.0370	0.039*
C14	0.4936 (5)	0.6942 (3)	0.2176 (3)	0.0192 (9)
H14	0.4047	0.7103	0.1680	0.023*
C15	0.6617 (5)	0.7688 (3)	0.2203 (3)	0.0208 (9)
H15	0.7535	0.7536	0.2687	0.025*

C16	0.8191 (5)	0.8261 (3)	0.1202 (3)	0.0248 (10)
C17	0.6698 (5)	0.9027 (3)	0.2377 (3)	0.0218 (9)
C18	0.9957 (5)	0.8007 (4)	0.1483 (3)	0.0399 (12)
H18A	1.0139	0.7898	0.2140	0.060*
H18B	1.0798	0.8679	0.1474	0.060*
H18C	1.0072	0.7282	0.1017	0.060*
C19	0.7810 (6)	0.8435 (4)	0.0191 (3)	0.0406 (12)
H19A	0.7834	0.7698	−0.0292	0.061*
H19B	0.8661	0.9082	0.0151	0.061*
H19C	0.6687	0.8639	0.0059	0.061*
C20	0.5083 (5)	0.9357 (3)	0.1889 (3)	0.0288 (10)
H20A	0.5287	1.0211	0.1940	0.043*
H20B	0.4174	0.9170	0.2215	0.043*
H20C	0.4753	0.8902	0.1200	0.043*
C21	0.7262 (5)	0.9726 (3)	0.3450 (3)	0.0294 (10)
H21A	0.8350	0.9553	0.3730	0.044*
H21B	0.6415	0.9494	0.3802	0.044*
H21C	0.7384	1.0580	0.3508	0.044*
C22	0.6162 (5)	0.5275 (3)	0.2565 (3)	0.0221 (9)
H22A	0.5733	0.5154	0.3136	0.027*
H22B	0.7201	0.5897	0.2807	0.027*
C23	0.6586 (5)	0.4133 (3)	0.2028 (3)	0.0177 (8)
C24	0.7068 (5)	0.3311 (3)	0.2511 (3)	0.0232 (9)
H24	0.7029	0.3443	0.3179	0.028*
C25	0.7602 (5)	0.2305 (3)	0.2049 (3)	0.0263 (10)
H25	0.7916	0.1754	0.2396	0.032*
C26	0.7675 (5)	0.2108 (3)	0.1083 (3)	0.0306 (10)
H26	0.8060	0.1427	0.0760	0.037*

C27	0.7184 (5)	0.2907 (4)	0.0591 (3)	0.0318 (11)
H27	0.7212	0.2766	−0.0079	0.038*
C28	0.6652 (5)	0.3910 (3)	0.1055 (3)	0.0269 (10)
H28	0.6327	0.4454	0.0702	0.032*
N1	0.4883 (4)	0.5685 (3)	0.1939 (2)	0.0199 (7)
O1	−0.0740 (3)	0.7749 (2)	0.61562 (17)	0.0224 (7)
O2	−0.1497 (4)	0.7423 (3)	0.45156 (19)	0.0343 (8)
O3	0.1010 (3)	0.7146 (2)	0.53052 (17)	0.0239 (7)
O4	0.4616 (3)	0.7428 (2)	0.31412 (17)	0.0231 (6)
O5	0.6936 (3)	0.7338 (2)	0.12458 (18)	0.0252 (7)
O6	0.8050 (3)	0.9318 (2)	0.19091 (18)	0.0257 (7)

Table S5. Atomic displacement parameters (Å^2)

	U11	U22	U33	U12	U13	U23
C1	0.021 (2)	0.045 (3)	0.028 (2)	0.014 (2)	0.0116 (19)	0.013 (2)
C2	0.031 (3)	0.069 (4)	0.037 (3)	−0.001 (3)	0.005 (2)	0.018 (3)
C3	0.040 (3)	0.048 (3)	0.027 (2)	0.016 (2)	0.013 (2)	0.012 (2)
C4	0.064 (4)	0.054 (3)	0.035 (3)	0.034 (3)	0.025 (3)	0.021 (2)
C5	0.018 (2)	0.023 (2)	0.023 (2)	0.0017 (18)	0.0016 (19)	0.0041 (18)
C6	0.022 (2)	0.025 (2)	0.0094 (19)	0.0031 (18)	0.0013 (17)	0.0017 (16)
C7	0.019 (2)	0.023 (2)	0.024 (2)	−0.0031 (18)	0.0036 (18)	0.0057 (18)
C8	0.022 (2)	0.018 (2)	0.022 (2)	−0.0022 (18)	0.0002 (18)	0.0001 (17)
C9	0.024 (2)	0.015 (2)	0.015 (2)	0.0000 (17)	0.0013 (17)	0.0037 (16)
C10	0.020 (2)	0.021 (2)	0.020 (2)	−0.0009 (18)	0.0018 (18)	0.0046 (17)
C11	0.022 (2)	0.015 (2)	0.021 (2)	−0.0022	−0.0014	0.0037 (16)

				(17)	(18)	
C12	0.027 (2)	0.017 (2)	0.021 (2)	−0.0003 (18)	0.0034 (18)	0.0062 (17)
C13	0.027 (2)	0.022 (2)	0.022 (2)	−0.0031 (18)	−0.0010 (18)	0.0026 (17)
C14	0.025 (2)	0.014 (2)	0.018 (2)	0.0030 (17)	0.0042 (18)	0.0038 (16)
C15	0.021 (2)	0.020 (2)	0.021 (2)	0.0030 (17)	0.0025 (18)	0.0053 (17)
C16	0.024 (2)	0.022 (2)	0.029 (2)	0.0006 (18)	0.0150 (19)	0.0020 (18)
C17	0.027 (2)	0.017 (2)	0.021 (2)	−0.0007 (18)	0.0065 (18)	0.0062 (17)
C18	0.035 (3)	0.025 (2)	0.057 (3)	0.002 (2)	0.021 (2)	0.000 (2)
C19	0.055 (3)	0.035 (3)	0.030 (3)	−0.004 (2)	0.020 (2)	0.005 (2)
C20	0.030 (3)	0.022 (2)	0.034 (2)	0.0028 (19)	0.005 (2)	0.0096 (19)
C21	0.038 (3)	0.022 (2)	0.023 (2)	−0.0033 (19)	0.004 (2)	0.0038 (17)
C22	0.026 (2)	0.021 (2)	0.018 (2)	0.0030 (18)	0.0024 (18)	0.0059 (17)
C23	0.014 (2)	0.017 (2)	0.017 (2)	−0.0041 (16)	−0.0006 (16)	0.0034 (16)
C24	0.019 (2)	0.026 (2)	0.018 (2)	−0.0053 (18)	−0.0046 (18)	0.0066 (17)
C25	0.025 (2)	0.016 (2)	0.035 (3)	−0.0016 (18)	0.000 (2)	0.0113 (18)
C26	0.027 (3)	0.022 (2)	0.036 (3)	0.0057 (19)	0.001 (2)	−0.0007 (19)
C27	0.034 (3)	0.036 (3)	0.023 (2)	0.008 (2)	0.003 (2)	0.006 (2)
C28	0.034 (3)	0.022 (2)	0.026 (2)	0.0053 (19)	0.004 (2)	0.0093 (18)
N1	0.0192 (18)	0.0177 (17)	0.0215 (18)	−0.0008 (14)	0.0018 (14)	0.0075 (14)
O1	0.0225	0.0285	0.0163	0.0034 (12)	0.0057 (12)	0.0059 (12)

	(16)	(16)	(15)			
O2	0.0329 (18)	0.0475 (19)	0.0212 (16)	0.0143 (15)	−0.0007 (14)	0.0084 (14)
O3	0.0227 (16)	0.0293 (16)	0.0169 (14)	0.0025 (12)	0.0024 (12)	0.0041 (12)
O4	0.0257 (16)	0.0187 (14)	0.0207 (14)	−0.0059 (12)	0.0073 (12)	0.0020 (11)
O5	0.0273 (16)	0.0215 (15)	0.0245 (15)	−0.0036 (12)	0.0092 (13)	0.0045 (12)
O6	0.0318 (17)	0.0167 (15)	0.0283 (16)	−0.0033 (12)	0.0128 (13)	0.0057 (12)

Table S6. Bond Lengths (Å)

C1—O1	1.483 (5)	C15—O5	1.430 (4)
C1—C4	1.504 (6)	C15—C17	1.527 (5)
C1—C3	1.519 (5)	C15—H15	1.0000
C1—C2	1.530 (6)	C16—O5	1.413 (5)
C2—H2A	0.9800	C16—O6	1.442 (4)
C2—H2B	0.9800	C16—C19	1.512 (6)
C2—H2C	0.9800	C16—C18	1.522 (6)
C3—H3A	0.9800	C17—O6	1.445 (5)
C3—H3B	0.9800	C17—C21	1.524 (5)
C3—H3C	0.9800	C17—C20	1.530 (5)
C4—H4A	0.9800	C18—H18A	0.9800
C4—H4B	0.9800	C18—H18B	0.9800
C4—H4C	0.9800	C18—H18C	0.9800
C5—O2	1.192 (4)	C19—H19A	0.9800
C5—O1	1.322 (4)	C19—H19B	0.9800
C5—O3	1.362 (5)	C19—H19C	0.9800

C6—C11	1.370 (5)	C20—H20A	0.9800
C6—C7	1.387 (5)	C20—H20B	0.9800
C6—O3	1.407 (4)	C20—H20C	0.9800
C7—C8	1.371 (5)	C21—H21A	0.9800
C7—H7	0.9500	C21—H21B	0.9800
C8—C9	1.392 (5)	C21—H21C	0.9800
C8—H8	0.9500	C22—N1	1.471 (4)
C9—C10	1.398 (5)	C22—C23	1.502 (5)
C9—C12	1.514 (5)	C22—H22A	0.9900
C10—O4	1.376 (5)	C22—H22B	0.9900
C10—C11	1.386 (5)	C23—C28	1.383 (5)
C11—H11	0.9500	C23—C24	1.387 (5)
C12—N1	1.488 (5)	C24—C25	1.382 (5)
C12—C13	1.522 (5)	C24—H24	0.9500
C12—H12	1.0000	C25—C26	1.377 (6)
C13—H13A	0.9800	C25—H25	0.9500
C13—H13B	0.9800	C26—C27	1.374 (5)
C13—H13C	0.9800	C26—H26	0.9500
C14—N1	1.431 (5)	C27—C28	1.380 (5)
C14—O4	1.463 (4)	C27—H27	0.9500
C14—C15	1.518 (5)	C28—H28	0.9500
C14—H14	1.0000		

Table S7. Bond Angles (º)

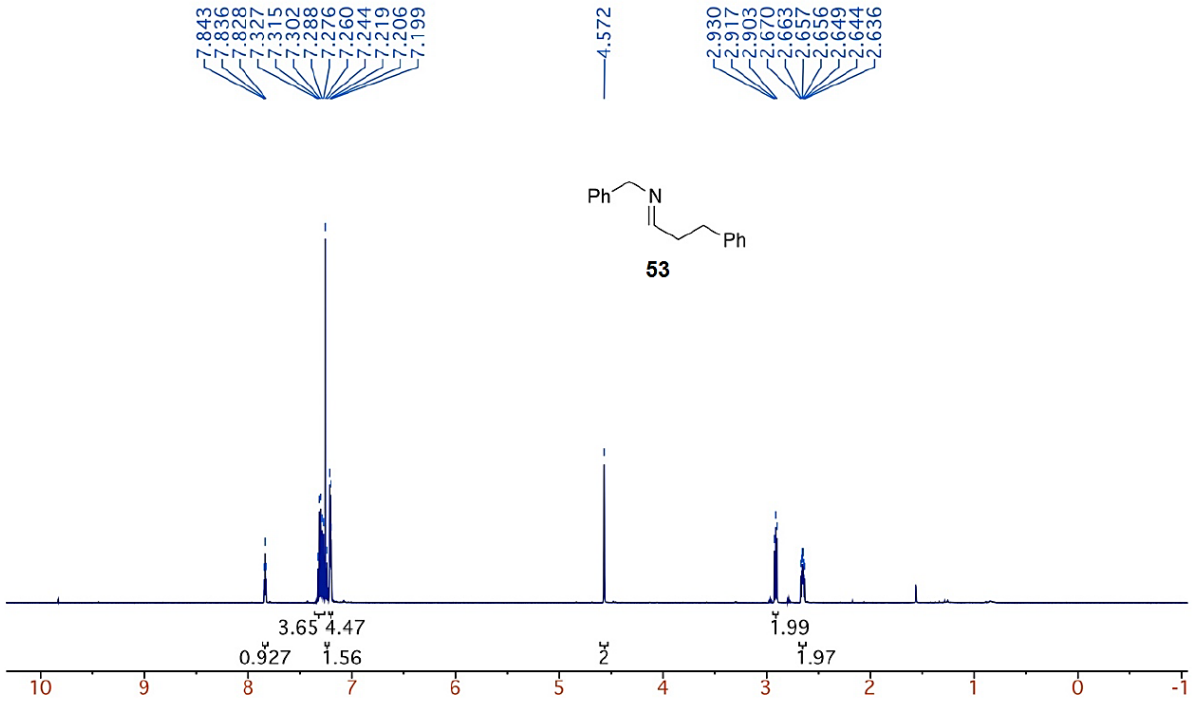
O1—C1—C4	110.4 (3)	O5—C16—O6	106.2 (3)
O1—C1—C3	101.7 (3)	O5—C16—C19	108.5 (3)
C4—C1—C3	111.1 (4)	O6—C16—C19	109.6 (3)
O1—C1—C2	108.7 (3)	O5—C16—C18	111.5 (3)

C4—C1—C2	113.5 (4)	O6—C16—C18	108.2 (3)
C3—C1—C2	110.8 (4)	C19—C16—C18	112.7 (4)
C1—C2—H2A	109.5	O6—C17—C21	107.4 (3)
C1—C2—H2B	109.5	O6—C17—C15	100.4 (3)
H2A—C2—H2B	109.5	C21—C17—C15	113.5 (3)
C1—C2—H2C	109.5	O6—C17—C20	109.7 (3)
H2A—C2—H2C	109.5	C21—C17—C20	111.1 (3)
H2B—C2—H2C	109.5	C15—C17—C20	114.0 (3)
C1—C3—H3A	109.5	C16—C18—H18A	109.5
C1—C3—H3B	109.5	C16—C18—H18B	109.5
H3A—C3—H3B	109.5	H18A—C18—H18B	109.5
C1—C3—H3C	109.5	C16—C18—H18C	109.5
H3A—C3—H3C	109.5	H18A—C18—H18C	109.5
H3B—C3—H3C	109.5	H18B—C18—H18C	109.5
C1—C4—H4A	109.5	C16—C19—H19A	109.5
C1—C4—H4B	109.5	C16—C19—H19B	109.5
H4A—C4—H4B	109.5	H19A—C19—H19B	109.5
C1—C4—H4C	109.5	C16—C19—H19C	109.5
H4A—C4—H4C	109.5	H19A—C19—H19C	109.5
H4B—C4—H4C	109.5	H19B—C19—H19C	109.5
O2—C5—O1	128.8 (4)	C17—C20—H20A	109.5
O2—C5—O3	125.4 (4)	C17—C20—H20B	109.5
O1—C5—O3	105.8 (3)	H20A—C20—H20B	109.5
C11—C6—C7	121.9 (4)	C17—C20—H20C	109.5
C11—C6—O3	117.9 (3)	H20A—C20—H20C	109.5
C7—C6—O3	120.0 (3)	H20B—C20—H20C	109.5
C8—C7—C6	118.3 (4)	C17—C21—H21A	109.5
C8—C7—H7	120.8	C17—C21—H21B	109.5

C6—C7—H7	120.8	H21A—C21—H21B	109.5
C7—C8—C9	122.2 (4)	C17—C21—H21C	109.5
C7—C8—H8	118.9	H21A—C21—H21C	109.5
C9—C8—H8	118.9	H21B—C21—H21C	109.5
C8—C9—C10	117.5 (3)	N1—C22—C23	111.9 (3)
C8—C9—C12	121.9 (3)	N1—C22—H22A	109.2
C10—C9—C12	120.6 (3)	C23—C22—H22A	109.2
O4—C10—C11	116.2 (3)	N1—C22—H22B	109.2
O4—C10—C9	122.3 (3)	C23—C22—H22B	109.2
C11—C10—C9	121.4 (4)	H22A—C22—H22B	107.9
C6—C11—C10	118.6 (3)	C28—C23—C24	117.5 (4)
C6—C11—H11	120.7	C28—C23—C22	121.2 (3)
C10—C11—H11	120.7	C24—C23—C22	121.1 (3)
N1—C12—C9	110.4 (3)	C25—C24—C23	122.0 (4)
N1—C12—C13	112.4 (3)	C25—C24—H24	119.0
C9—C12—C13	113.1 (3)	C23—C24—H24	119.0
N1—C12—H12	106.9	C26—C25—C24	119.6 (4)
C9—C12—H12	106.9	C26—C25—H25	120.2
C13—C12—H12	106.9	C24—C25—H25	120.2
C12—C13—H13A	109.5	C27—C26—C25	119.2 (4)
C12—C13—H13B	109.5	C27—C26—H26	120.4
H13A—C13—H13B	109.5	C25—C26—H26	120.4
C12—C13—H13C	109.5	C26—C27—C28	121.0 (4)
H13A—C13—H13C	109.5	C26—C27—H27	119.5
H13B—C13—H13C	109.5	C28—C27—H27	119.5
N1—C14—O4	113.1 (3)	C27—C28—C23	120.8 (4)
N1—C14—C15	115.0 (3)	C27—C28—H28	119.6
O4—C14—C15	103.9 (3)	C23—C28—H28	119.6

N1—C14—H14	108.2	C14—N1—C22	116.3 (3)
O4—C14—H14	108.2	C14—N1—C12	110.0 (3)
C15—C14—H14	108.2	C22—N1—C12	111.0 (3)
O5—C15—C14	107.0 (3)	C5—O1—C1	119.8 (3)
O5—C15—C17	102.6 (3)	C5—O3—C6	115.7 (3)
C14—C15—C17	117.0 (3)	C10—O4—C14	114.0 (3)
O5—C15—H15	109.9	C16—O5—C15	105.8 (3)
C14—C15—H15	109.9	C16—O6—C17	109.1 (3)
C17—C15—H15	109.9		

4. NMR Spectra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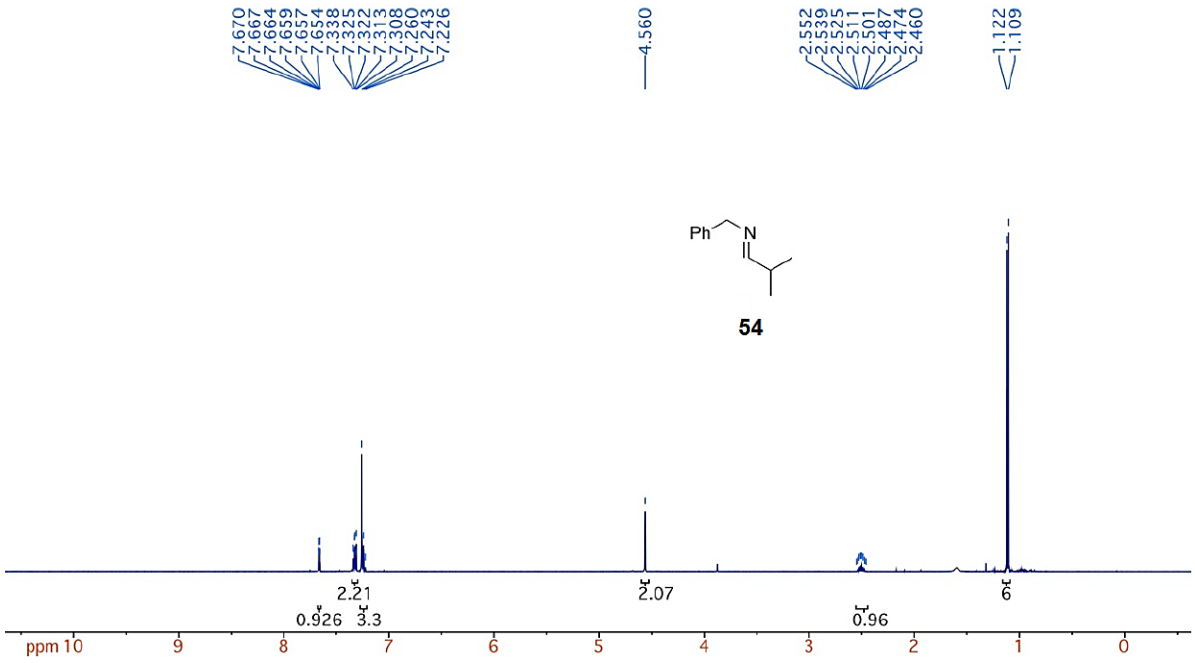
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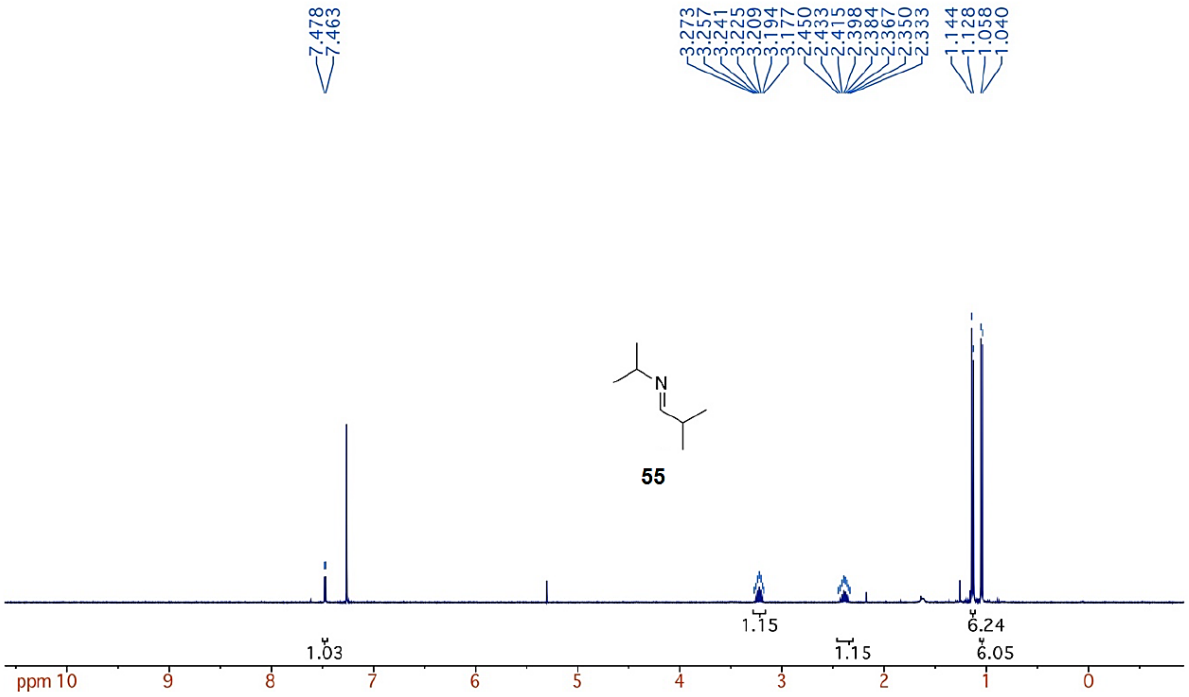
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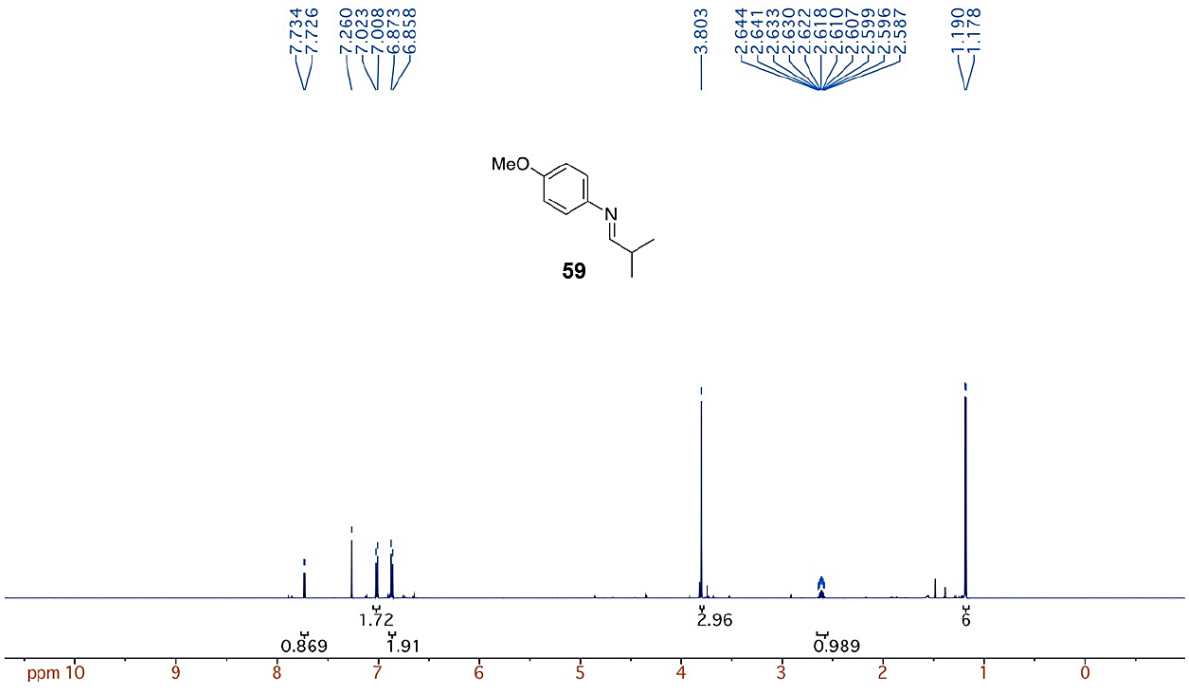
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6.858
3.803
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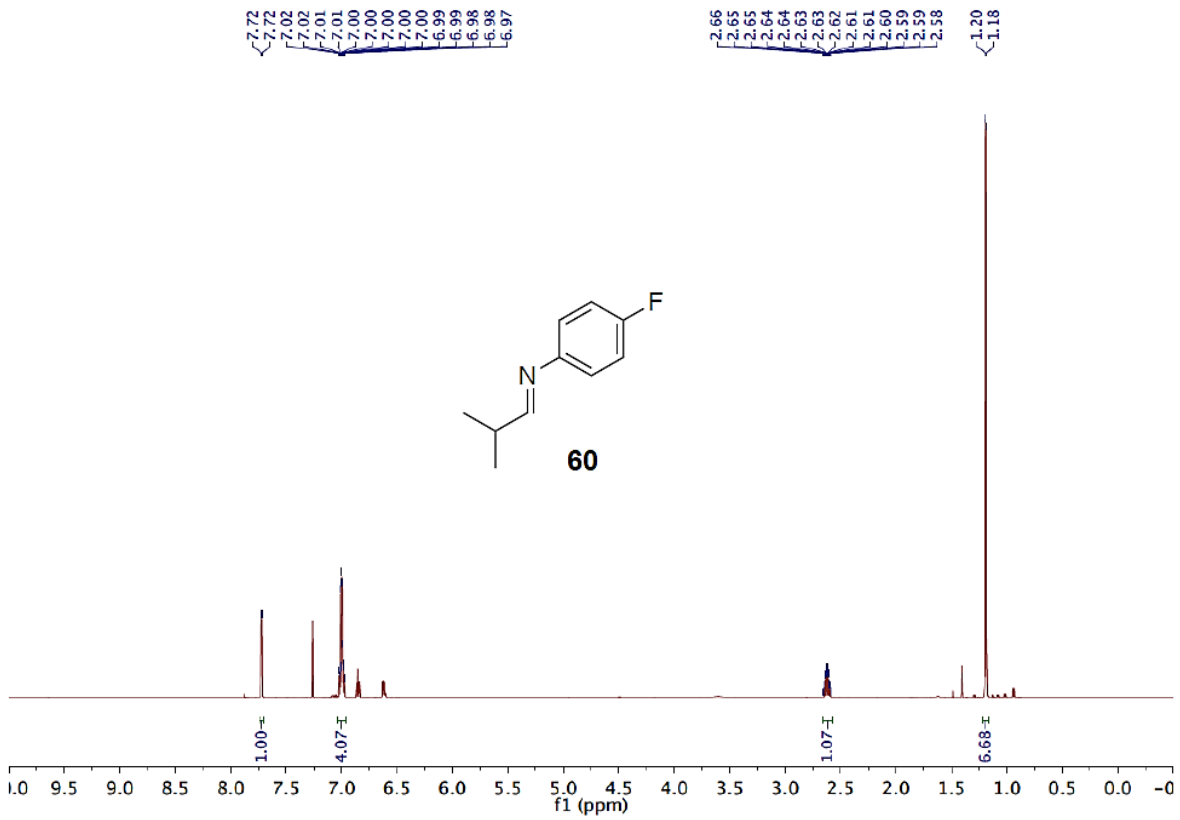
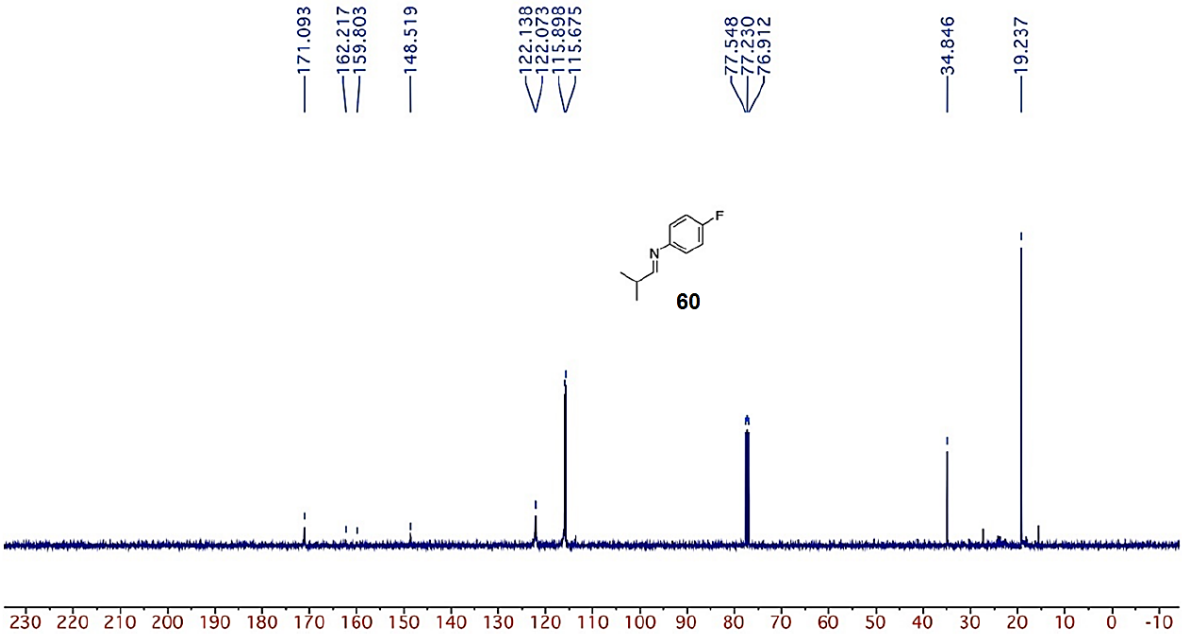
2.630
2.622
2.618
2.610
2.607
2.599
2.596
2.587
1.190
1.178
MeO
N
59
0.869
1.72
1.91
2.96
0.989
6
ppm 10
9
8
7
6
5
4
3
2
1
0


7.72
7.72
7.02
7.02
7.01
7.01
7.00
7.00
7.00
7.00
7.00
6.99
6.99
6.98
6.98
6.97
2.66
2.65
2.65
2.64
2.64
2.63
2.63
2.62
2.61
2.61
2.60
2.59
2.59
2.58
1.20
1.18
F
N
60
1.00
4.07
1.07
6.68
f1 (ppm)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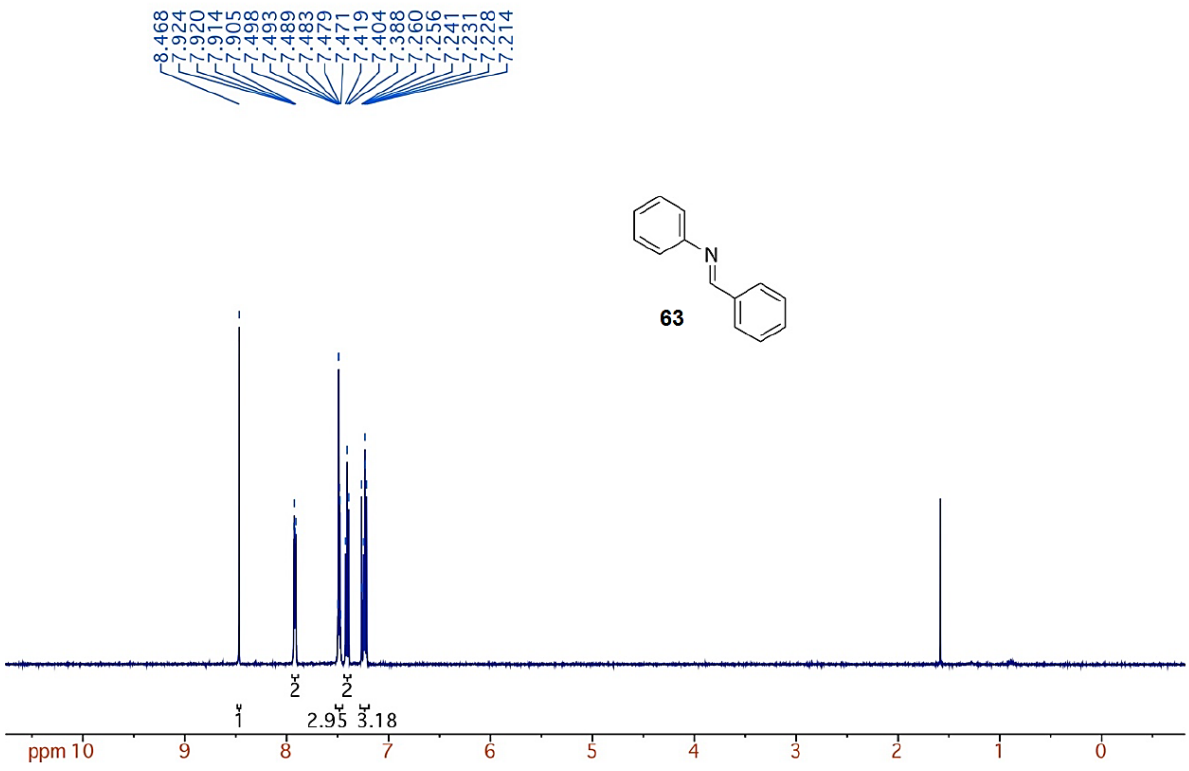
162.217
159.803
148.519
122.138
122.073
115.898
115.675
77.548
77.230
76.912
34.846
19.237
F
N
60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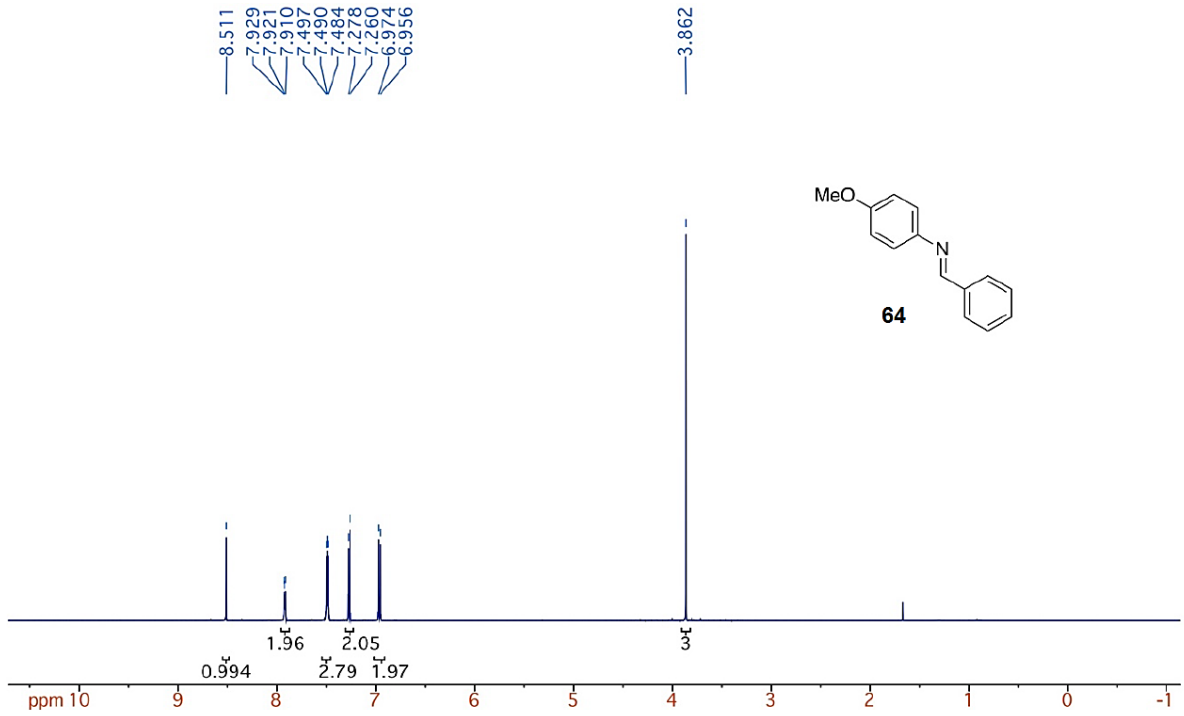
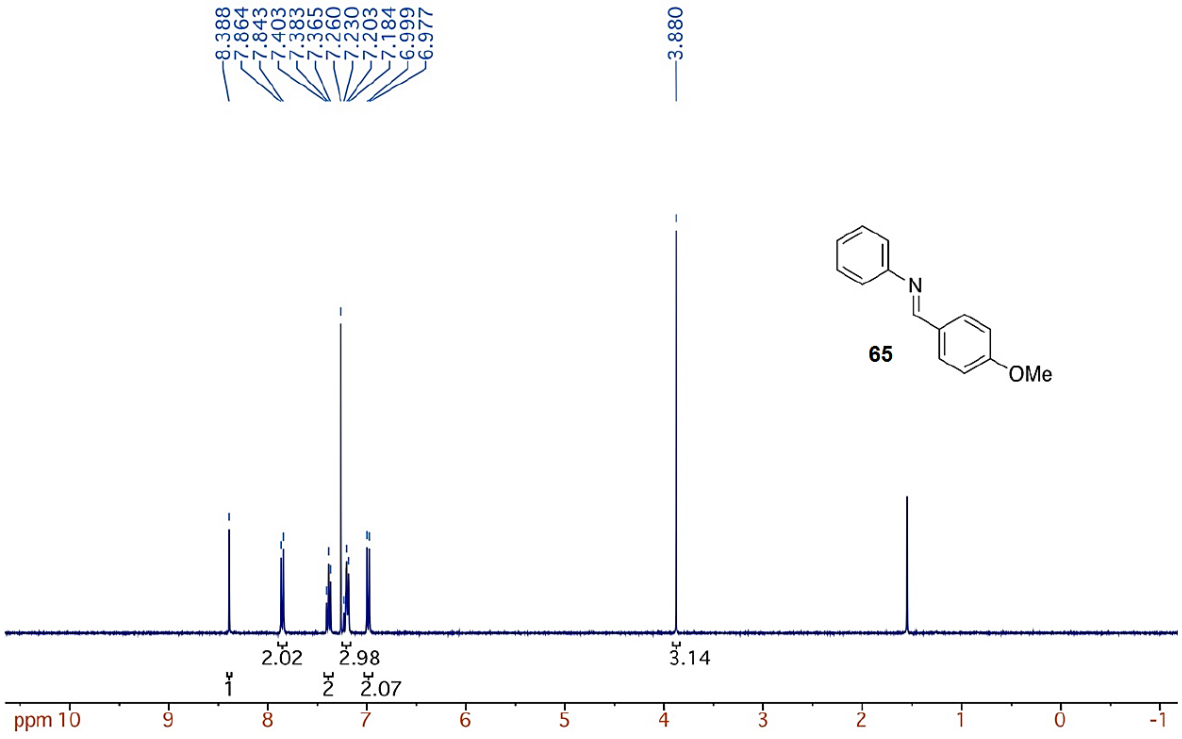
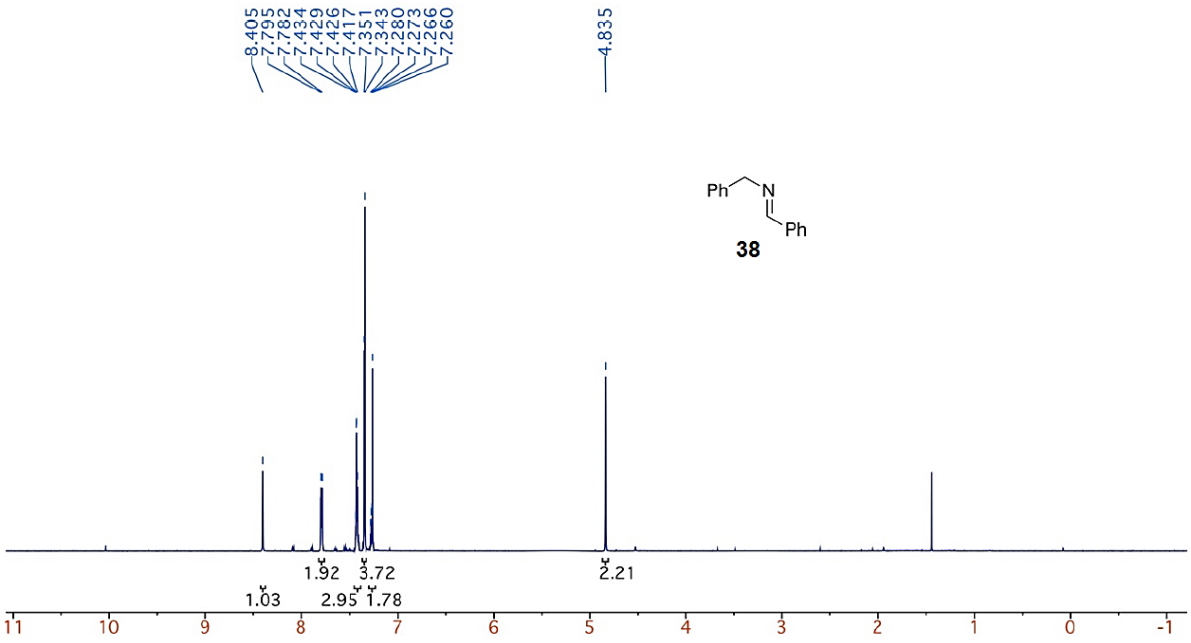
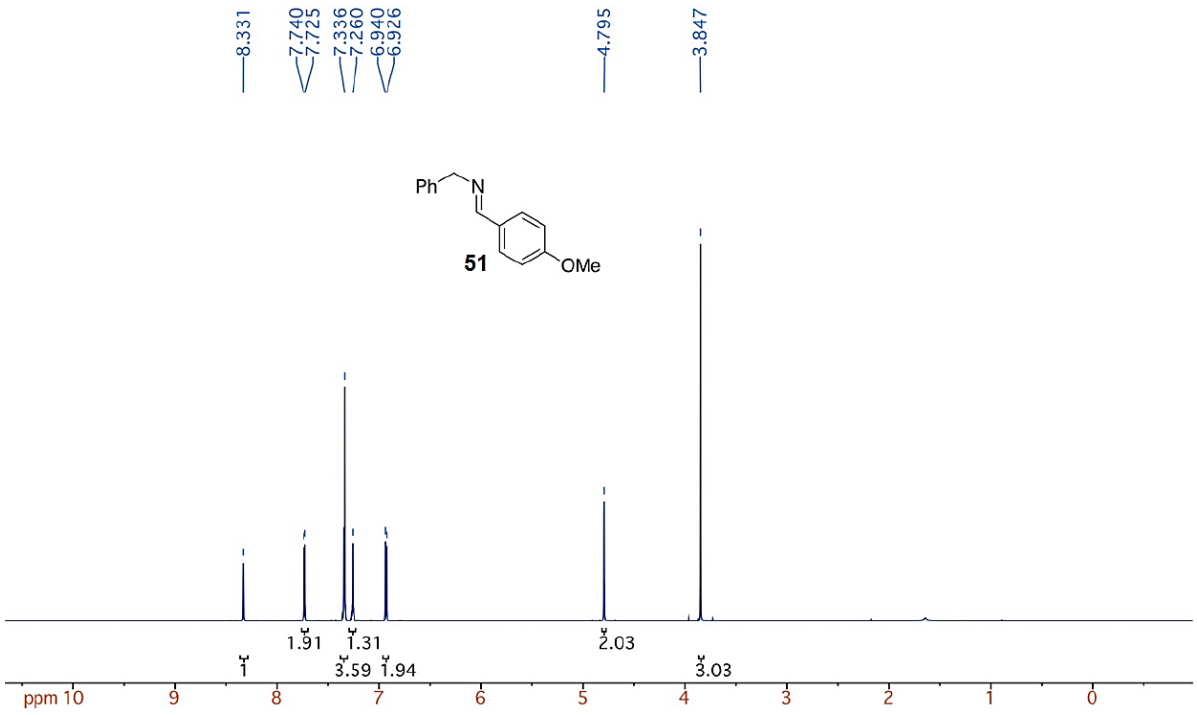
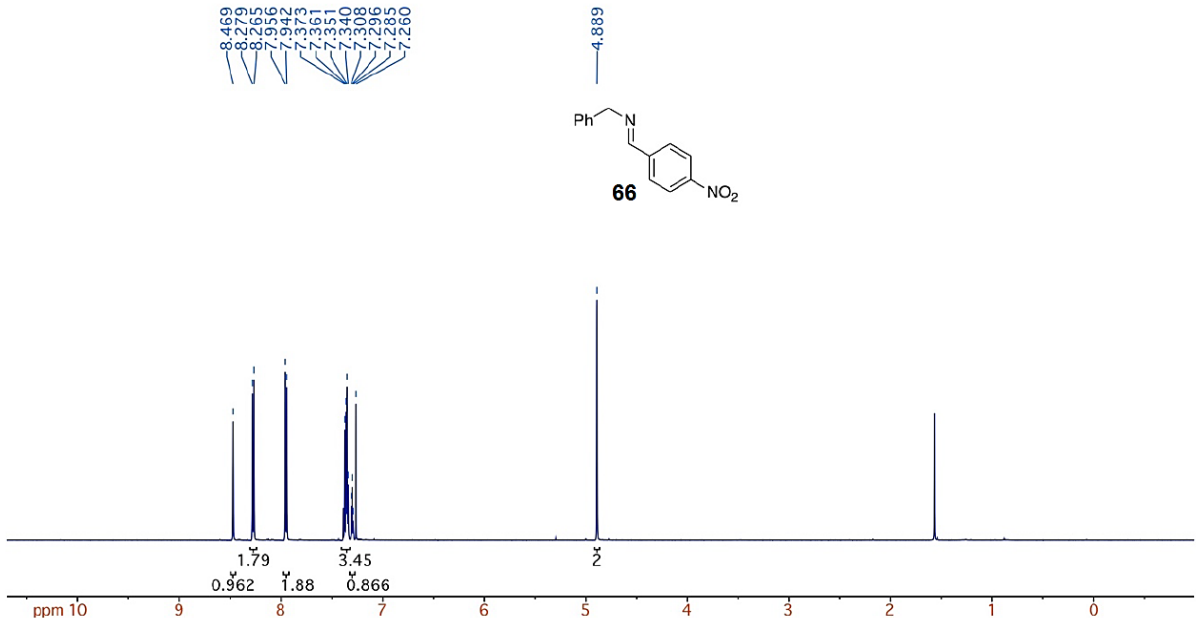
7.924
7.920
7.914
7.905
7.498
7.493
7.489
7.483
7.479
7.471
7.419
7.404
7.388
7.260
7.256
7.241
7.231
7.228
7.214
63
1
2
2
2.95
3.18
ppm 10
9
8
7
6
5
4
3
2
1
0

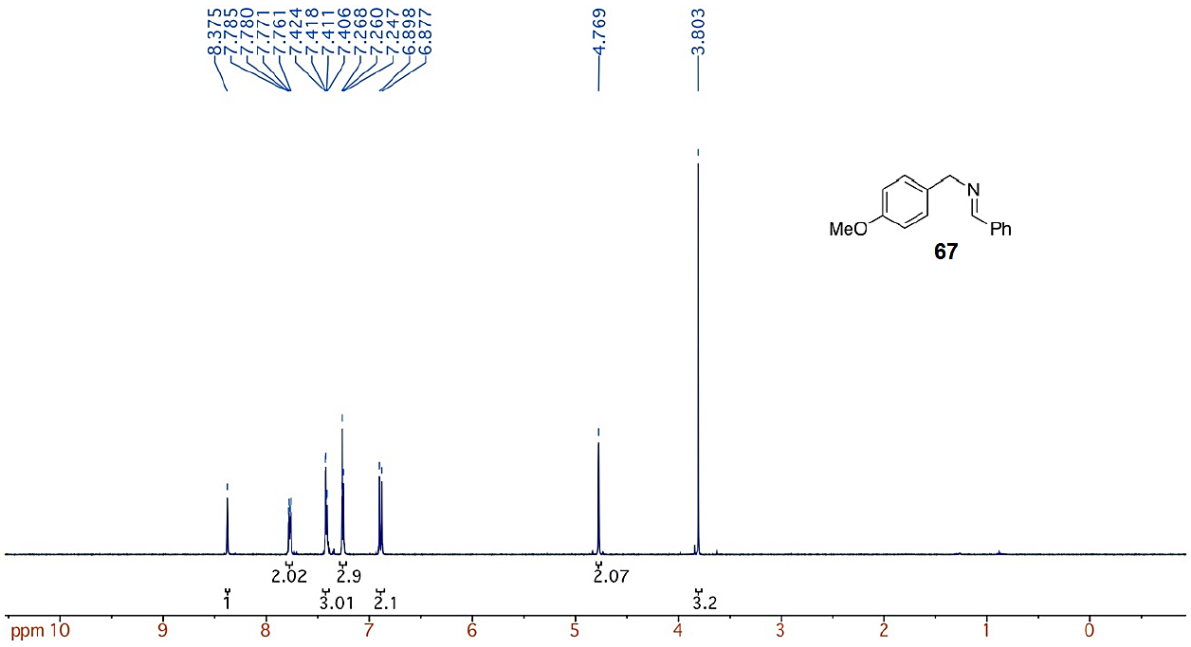

8.511
7.929
7.921
7.910
7.497
7.490
7.484
7.278
7.260
6.974
6.956
3.862
MeO
64
0.994
1.96
2.05
2.79
1.97
3
ppm 10
9
8
7
6
5
4
3
2
1
0
-1

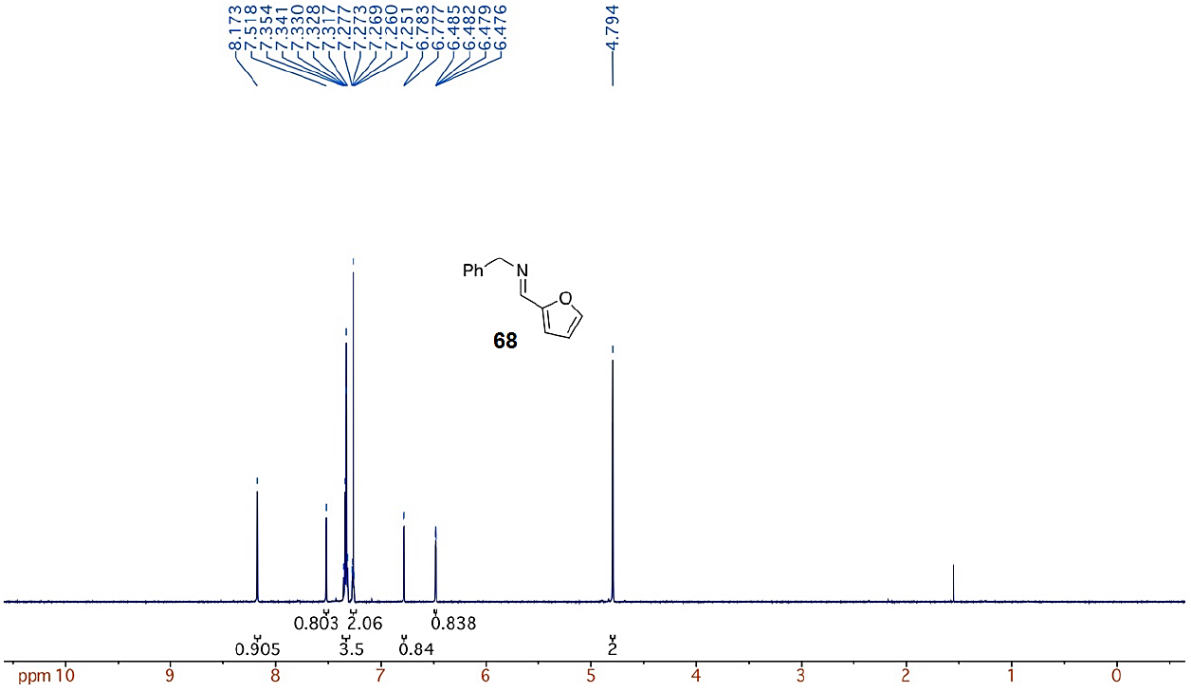

8.388
7.864
7.843
7.403
7.383
7.365
7.260
7.230
7.203
7.184
6.999
6.977
3.880
N
OMe
65
2.02
2.98
3.14
1
2
2.07
ppm 10
9
8
7
6
5
4
3
2
1
0
-1

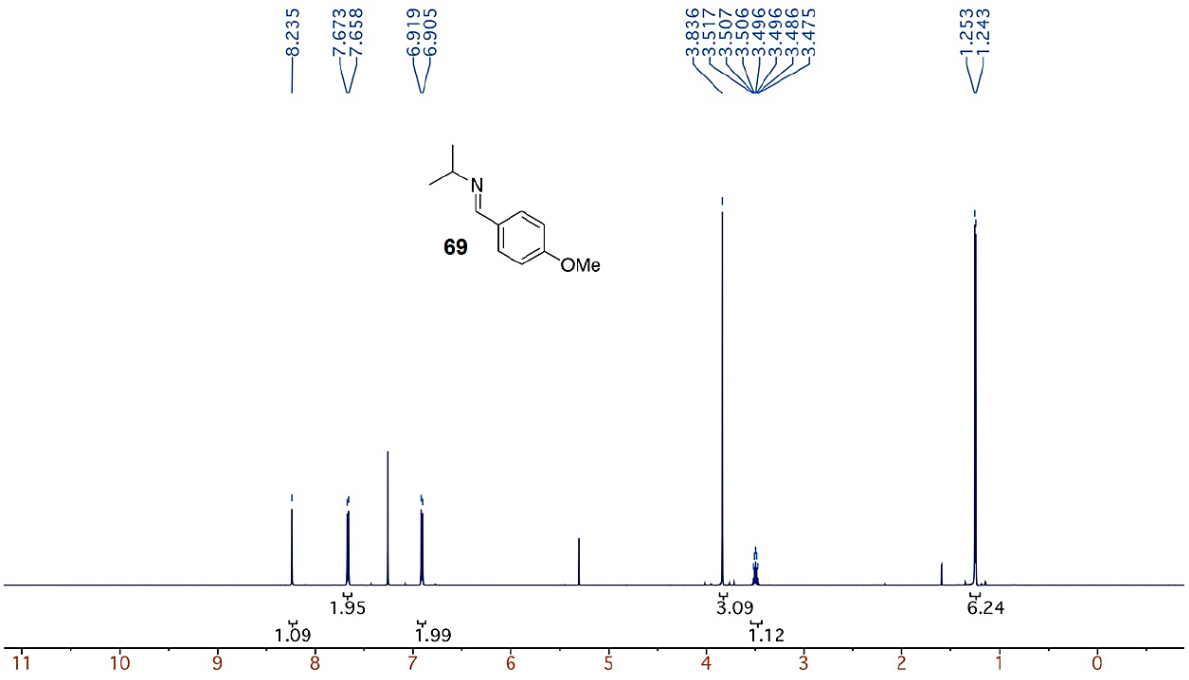

8.405
7.795
7.782
7.434
7.429
7.426
7.417
7.351
7.343
7.280
7.273
7.266
7.260
4.835
Ph
N
Ph
38
1.92
3.72
2.21
1.03
2.95
1.78
11
10
9
8
7
6
5
4
3
2
1
0
-1

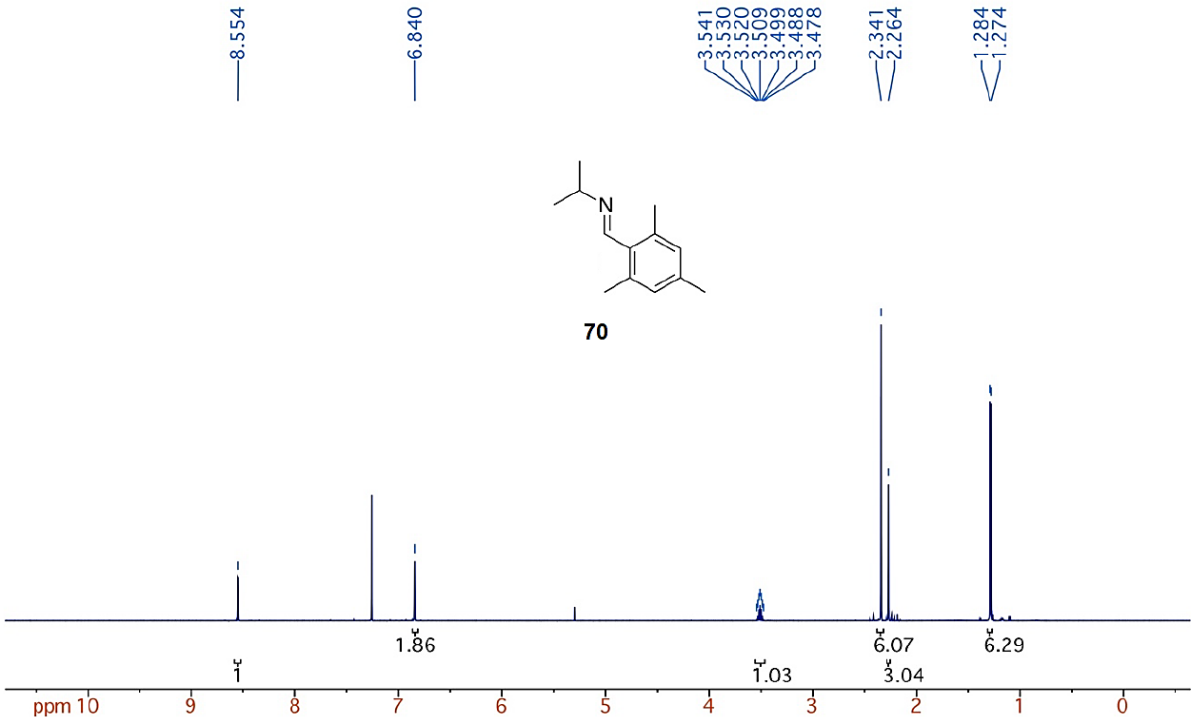

8.331
7.740
7.725
7.336
7.260
6.940
6.926
4.795
3.847
Ph
N
OMe
51
1.91
1.31
2.03
1
3.59
1.94
3.03
ppm 10
9
8
7
6
5
4
3
2
1
0

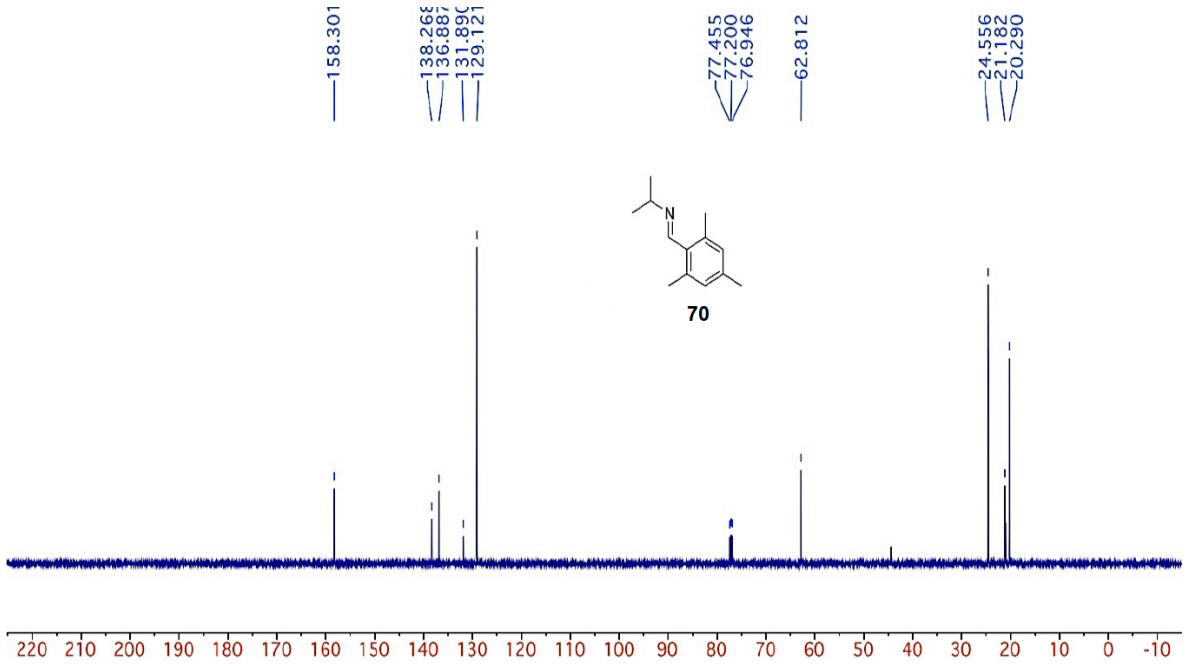

8.469
8.279
8.265
7.956
7.942
7.373
7.361
7.351
7.340
7.308
7.296
7.285
7.260
4.889
Ph
N
NO2
66
1.79
3.45
2
0.962
1.88
0.866
ppm 10
9
8
7
6
5
4
3
2
1
0

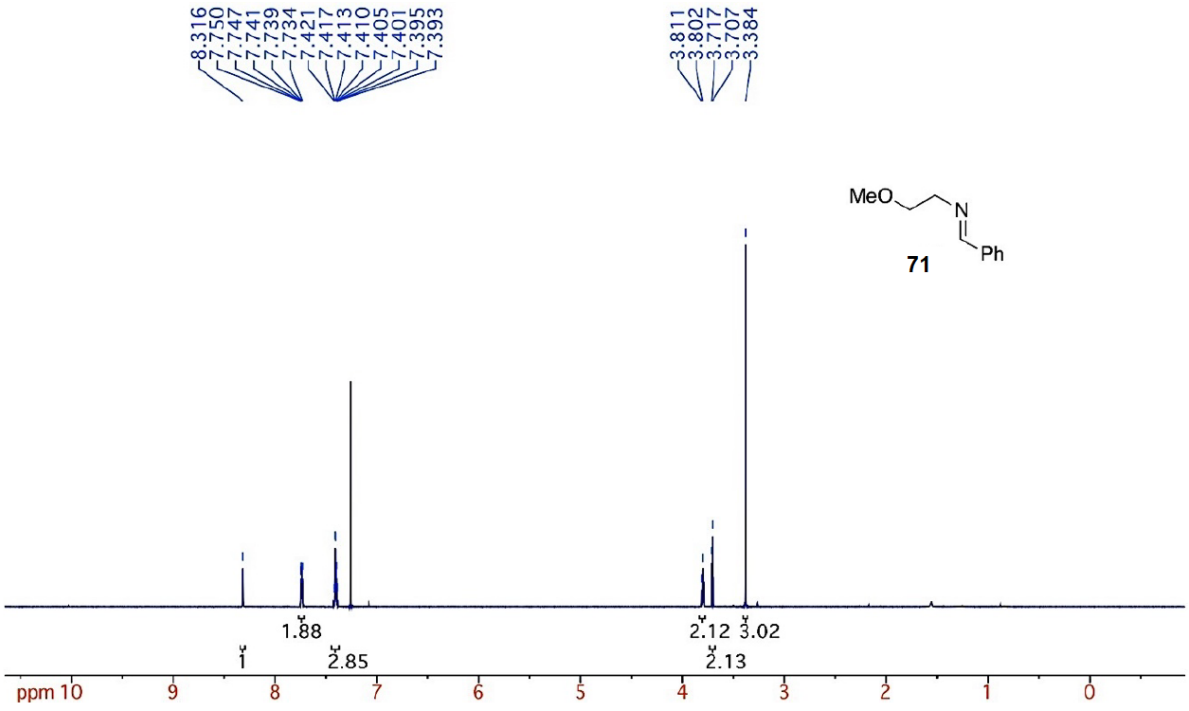

8.375
7.785
7.780
7.771
7.761
7.424
7.418
7.411
7.406
7.268
7.260
7.247
6.898
6.877
4.769
3.803
MeO
N
Ph
67
2.02
2.9
2.07
1
3.01
2.1
3.2
ppm 10
9
8
7
6
5
4
3
2
1
0

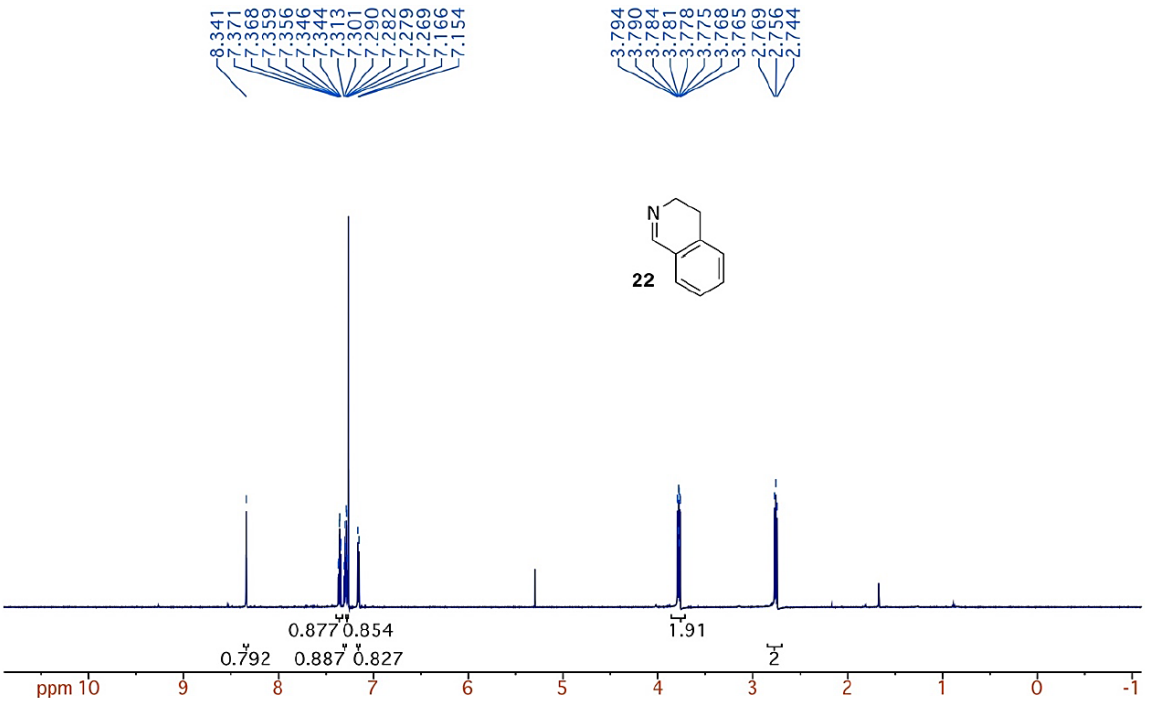

8.173
7.518
7.354
7.341
7.330
7.328
7.317
7.277
7.273
7.269
7.260
7.251
6.783
6.777
6.485
6.482
6.479
6.476
4.794
Ph
N
O
68
0.803
2.06
0.838
0.905
3.5
0.84
2
ppm 10
9
8
7
6
5
4
3
2
1
0

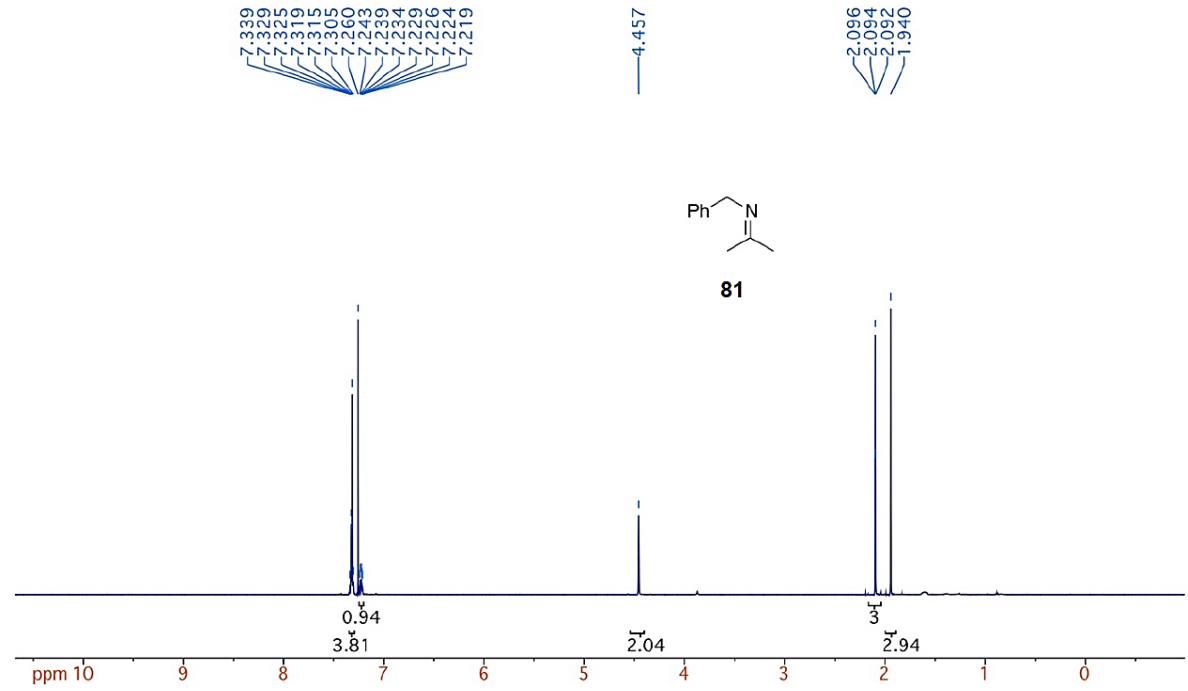

8.235
7.673
7.658
6.919
6.905
3.836
3.517
3.507
3.506
3.496
3.496
3.486
3.475
1.253
1.243
N
69
OMe
1.95
3.09
6.24
1.09
1.99
1.12
11
10
9
8
7
6
5
4
3
2
1
0

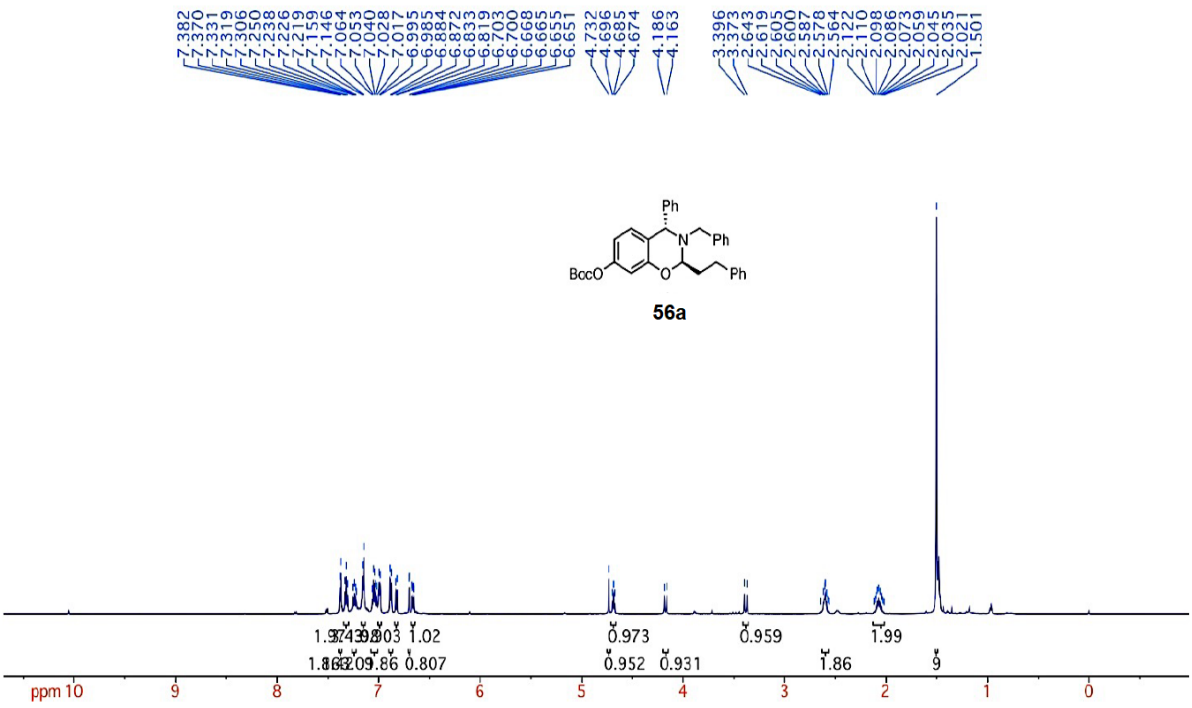

8.554
6.840
3.541
3.530
3.520
3.509
3.499
3.488
3.478
2.341
2.264
1.284
1.274
N
70
1.86
6.07
6.29
1
1.03
3.04
ppm 10
9
8
7
6
5
4
3
2
1
0

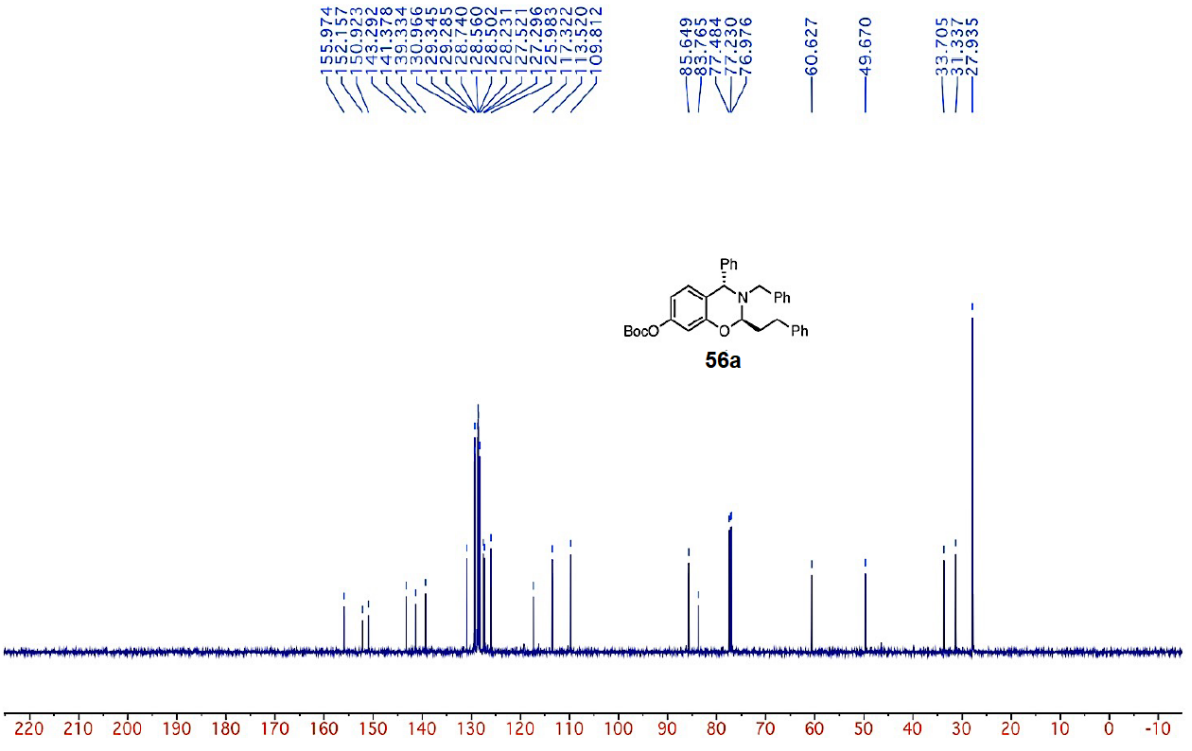

158.301
138.268
136.887
131.890
129.121
77.455
77.200
76.946
62.812
24.556
21.182
20.290
N
70
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

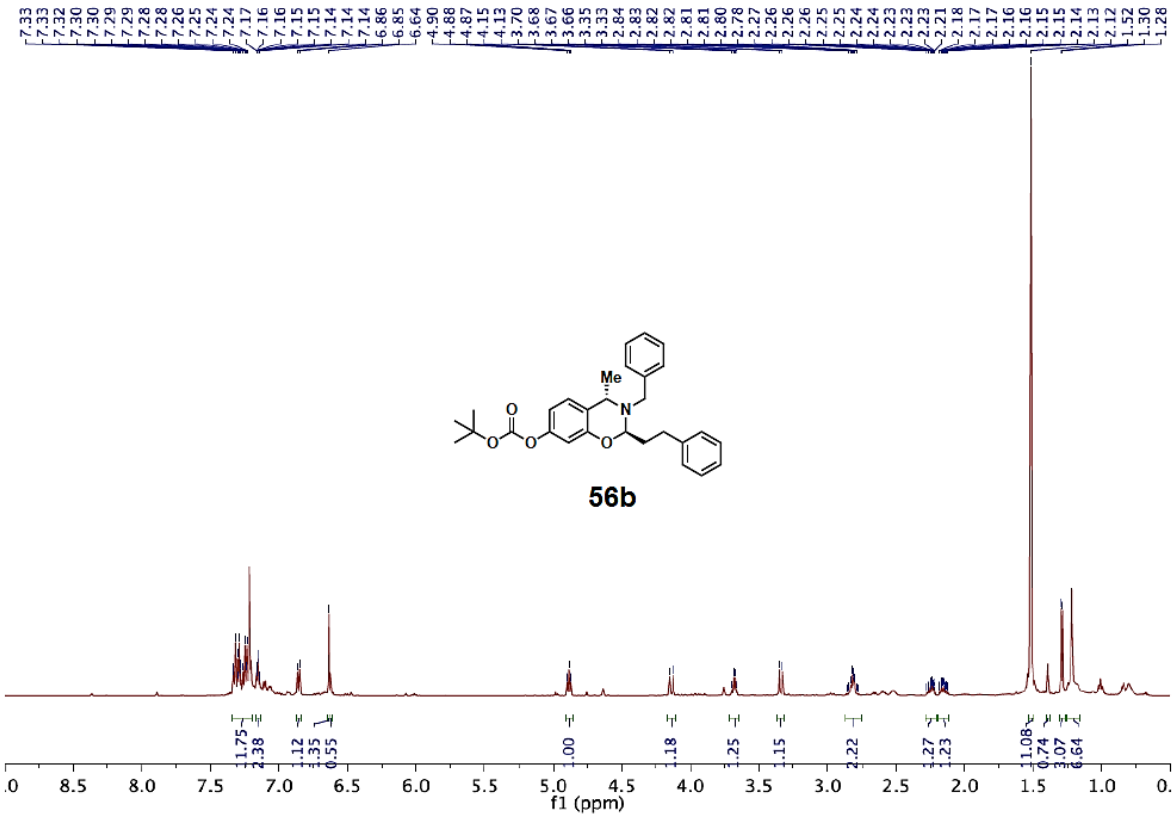

8.316
7.750
7.747
7.741
7.739
7.734
7.421
7.417
7.413
7.410
7.405
7.401
7.395
7.393
3.811
3.802
3.717
3.707
3.384
MeO
N
Ph
71
1.88
1
2.85
2.12
3.02
2.13
ppm 10 9 8 7 6 5 4 3 2 1 0

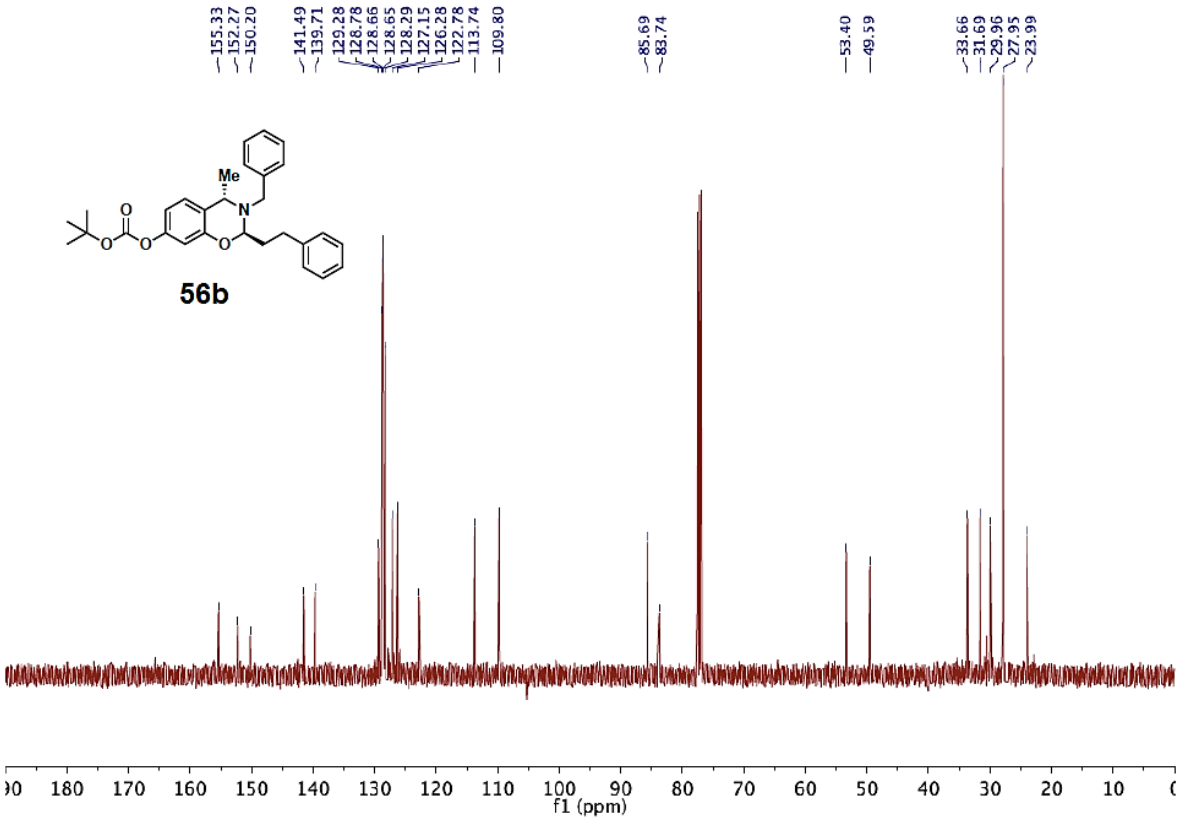

8.341
7.371
7.368
7.359
7.356
7.346
7.344
7.313
7.301
7.290
7.282
7.279
7.269
7.166
7.154
3.794
3.790
3.784
3.781
3.778
3.775
3.768
3.765
2.769
2.756
2.744
N
22
0.877
0.854
1.91
0.792
0.887
0.827
2
ppm 10
9
8
7
6
5
4
3
2
1
0
-1

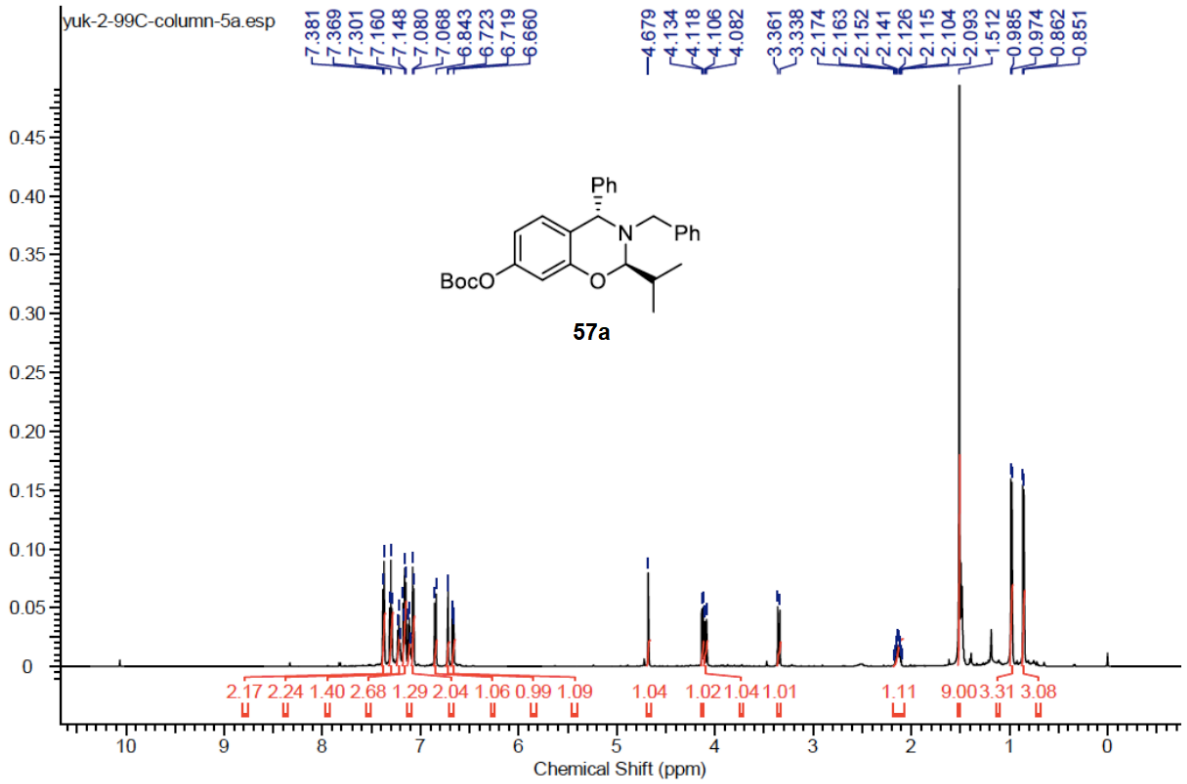

7.339
7.329
7.325
7.319
7.315
7.305
7.260
7.243
7.239
7.234
7.229
7.226
7.224
7.219
4.457
2.096
2.094
2.092
1.940
Ph
N
81
0.94
3.81
2.04
3
2.94
ppm 10
9
8
7
6
5
4
3
2
1
0

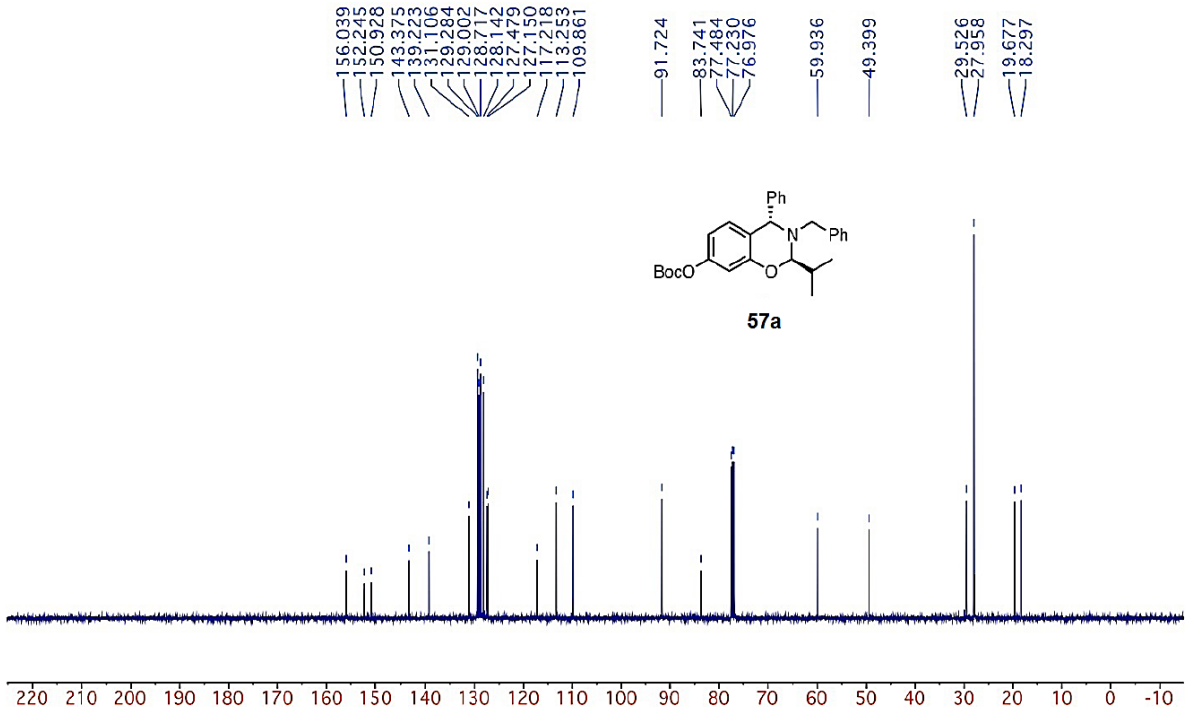

7.382
7.370
7.331
7.319
7.306
7.250
7.238
7.226
7.219
7.159
7.146
7.064
7.053
7.040
7.028
7.017
6.995
6.985
6.884
6.872
6.833
6.819
6.703
6.700
6.668
6.665
6.655
6.651
4.732
4.696
4.685
4.674
4.186
4.163
3.396
3.373
2.643
2.619
2.605
2.600
2.587
2.578
2.564
2.122
2.110
2.098
2.086
2.073
2.059
2.045
2.035
2.021
1.501
Ph
N
Ph
BccO
O
Ph
56a
1.02
0.973
0.959
1.99
0.807
0.952
0.931
1.86
9
ppm 10
9
8
7
6
5
4
3
2
1
0

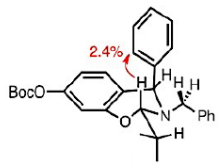

155.974
152.157
150.923
143.292
141.378
139.334
130.966
129.345
129.285
128.740
128.560
128.502
128.231
127.321
127.296
125.983
117.322
113.520
109.812
85.649
83.765
77.484
77.230
76.976
60.627
49.670
33.705
31.337
27.935
Ph
N
Ph
BocO
O
Ph
56a
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


Me
N
O
O
O
O
56b
f1 (ppm)

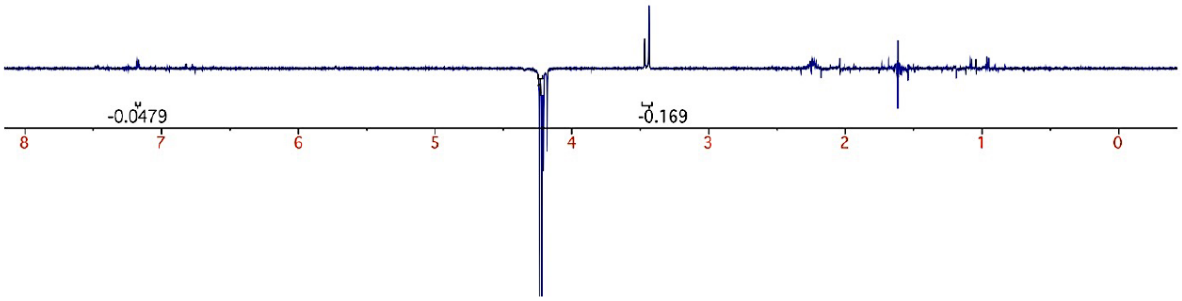

Me
N
O
O
O
O
56b
f1 (ppm)

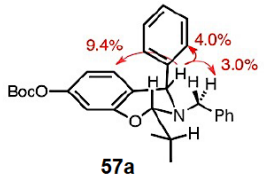

yuk-2-99C-column-5a.esp
7.381
7.369
7.301
7.160
7.148
7.080
7.068
6.843
6.723
6.719
6.660
4.679
4.134
4.118
4.106
4.082
3.361
3.338
2.174
2.163
2.152
2.141
2.126
2.115
2.104
2.093
1.512
0.985
0.974
0.862
0.851
Ph
N
Ph
BocO
O
57a
2.17 2.24 1.40 2.68 1.29 2.04 1.06 0.99 1.09
1.04
1.02 1.04 1.01
1.11
9.00 3.31 3.08
Chemical Shift (ppm)


156.039
152.245
150.928
143.375
139.223
131.106
129.284
129.002
128.717
128.142
127.479
127.150
117.218
113.253
109.861
91.724
83.741
77.484
77.230
76.976
59.936
49.399
29.526
27.958
19.677
18.297
Ph
N
Ph
BocO
O
57a

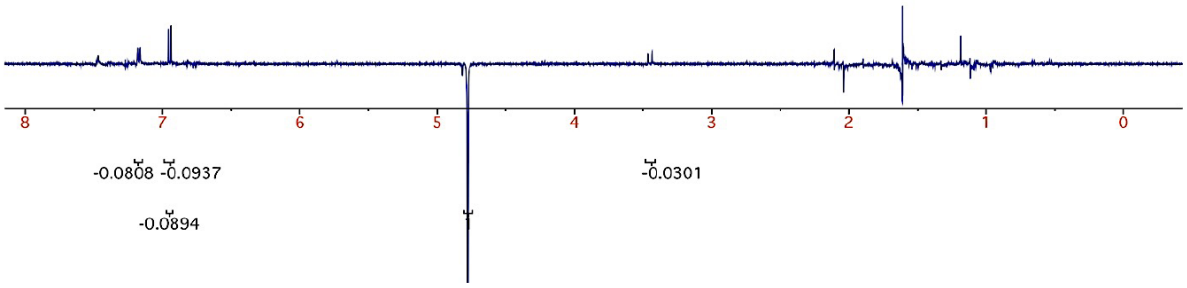

2.4%
BocO
H
H
H
N
Ph
O
H

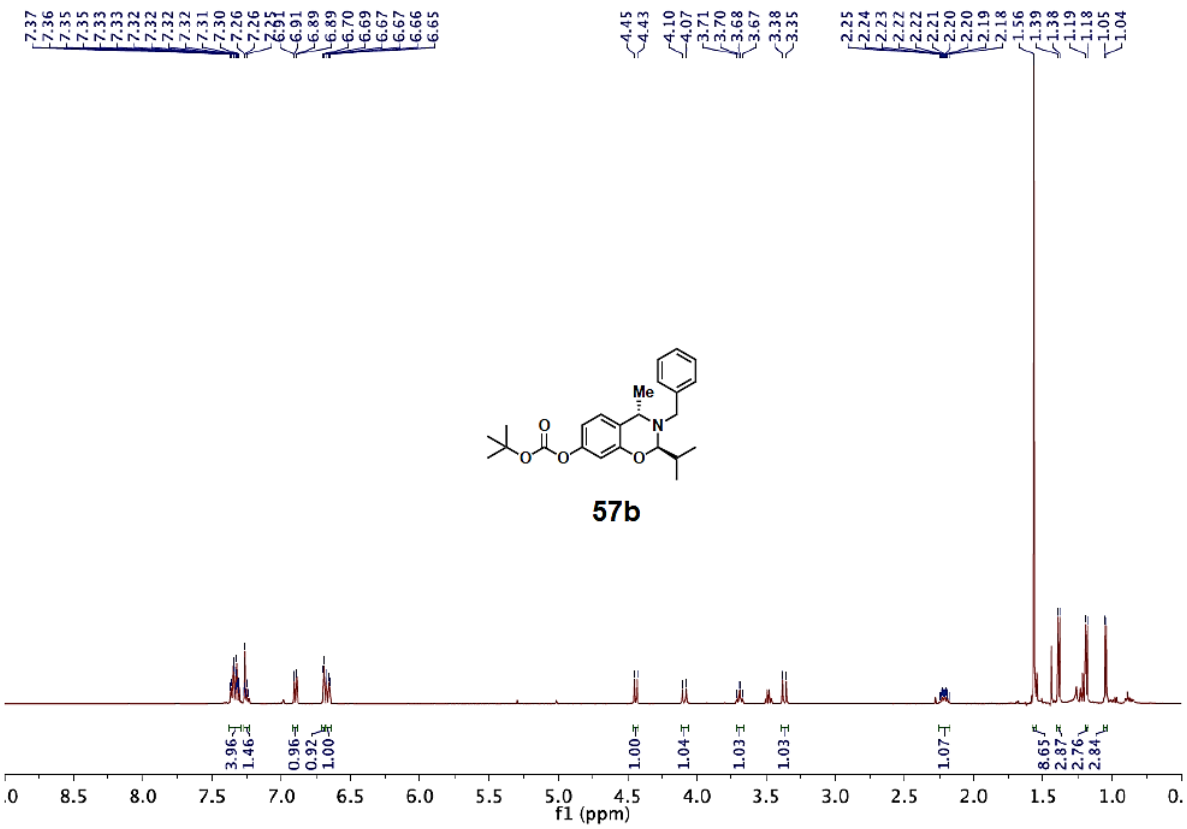
57a

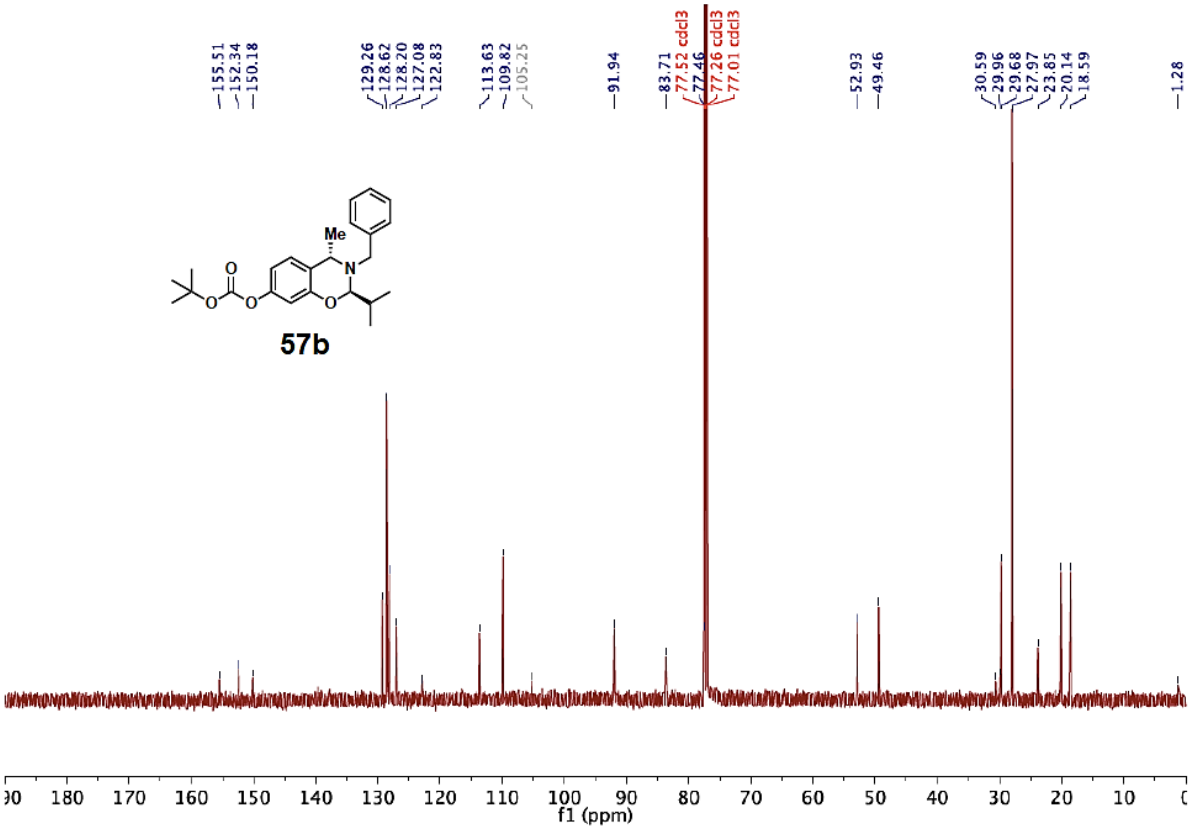

-0.0479
-0.169
8
7
6
5
4
3
2
1
0

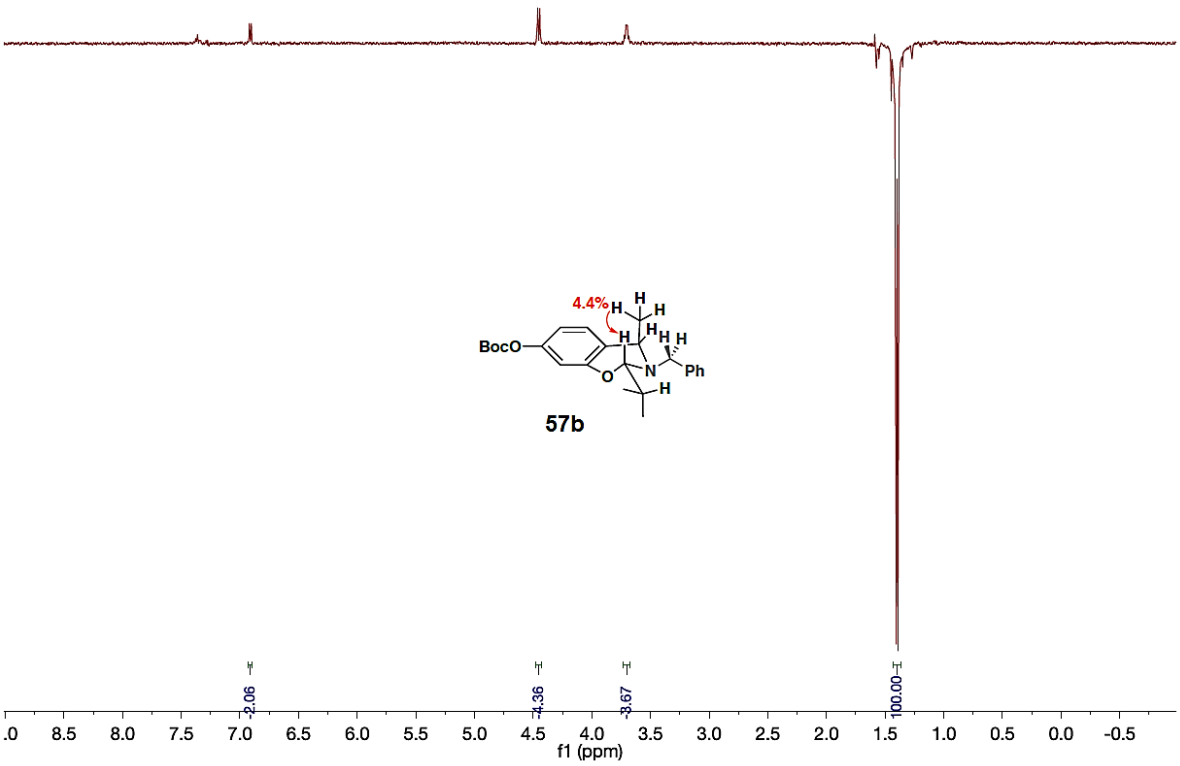

9.4%
4.0%
3.0%
BocO
H
H
H
N
Ph
O
H

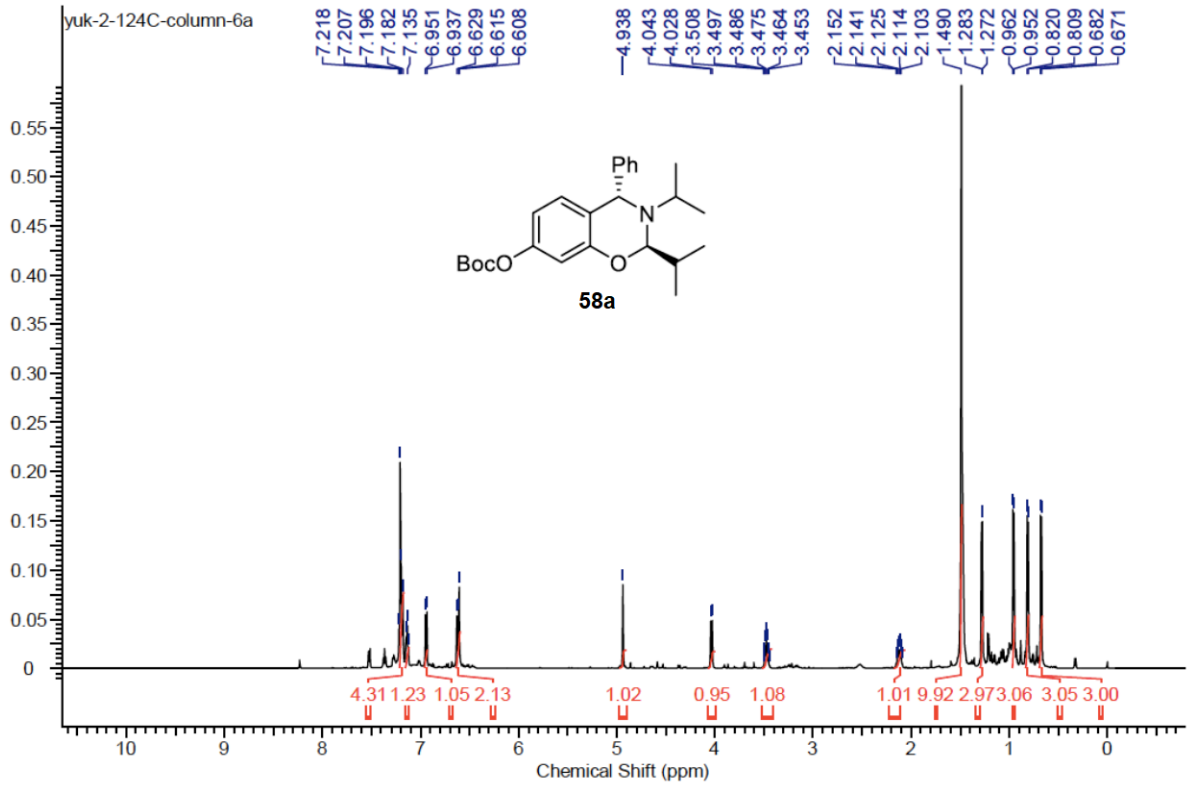
57a

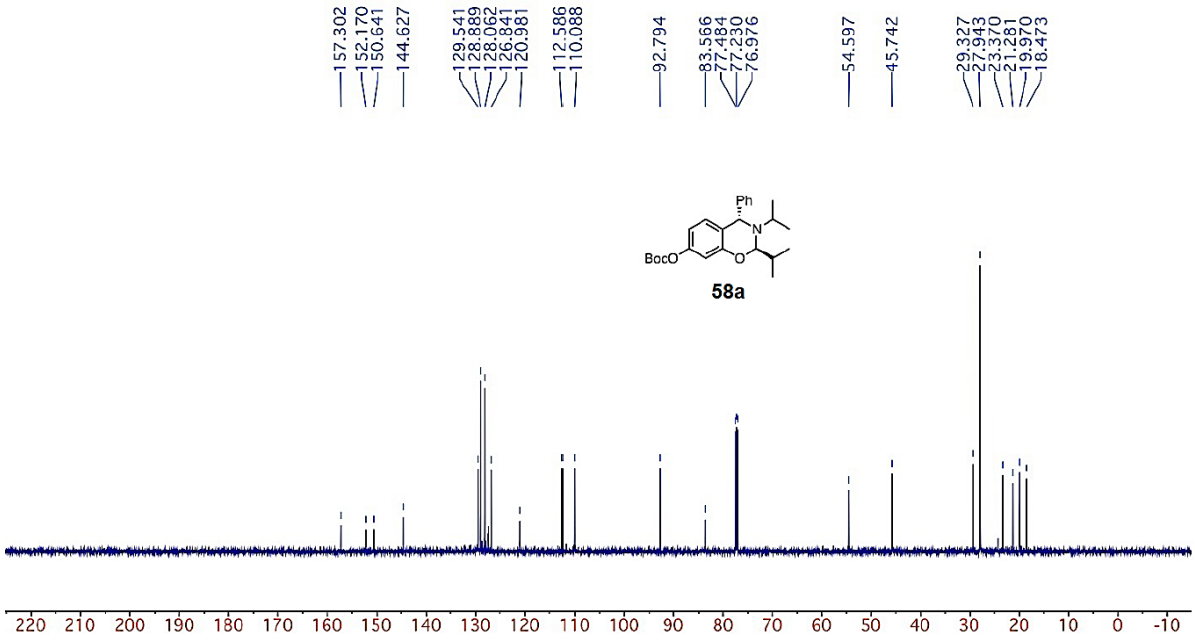

8
7
6
5
4
3
2
1
0
-0.0808
-0.0937
-0.0894
-0.0301

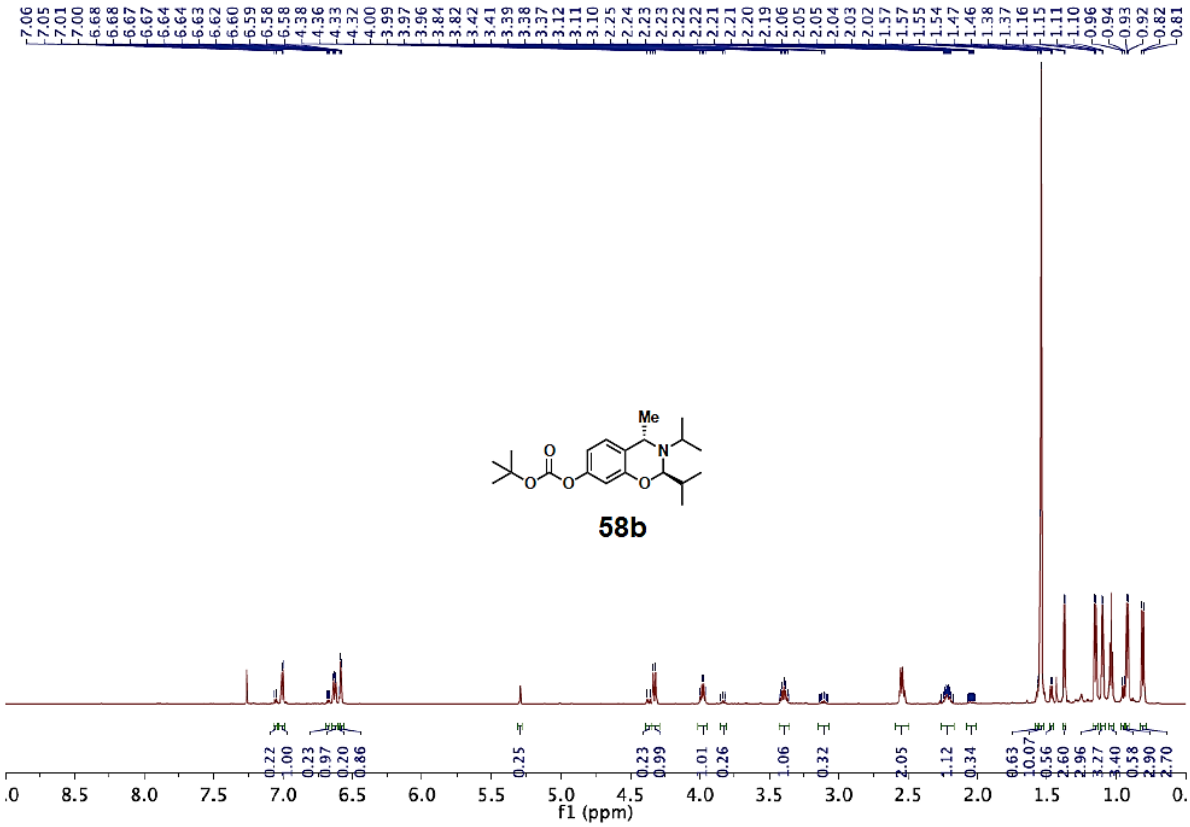

7.37
7.36
7.35
7.35
7.33
7.33
7.32
7.32
7.32
7.32
7.31
7.30
7.26
7.26
6.91
6.89
6.89
6.70
6.69
6.67
6.67
6.66
6.65
4.45
4.43
4.10
4.07
3.71
3.70
3.68
3.67
3.38
3.35
2.25
2.24
2.23
2.22
2.22
2.21
2.20
2.20
2.19
2.18
1.56
1.39
1.38
1.19
1.18
1.05
1.04
Me
N
O
O
O
57b
3.96
1.46
0.96
0.92
1.00
1.00
1.04
1.03
1.03
1.07
8.65
2.87
2.76
2.84
f1 (ppm)

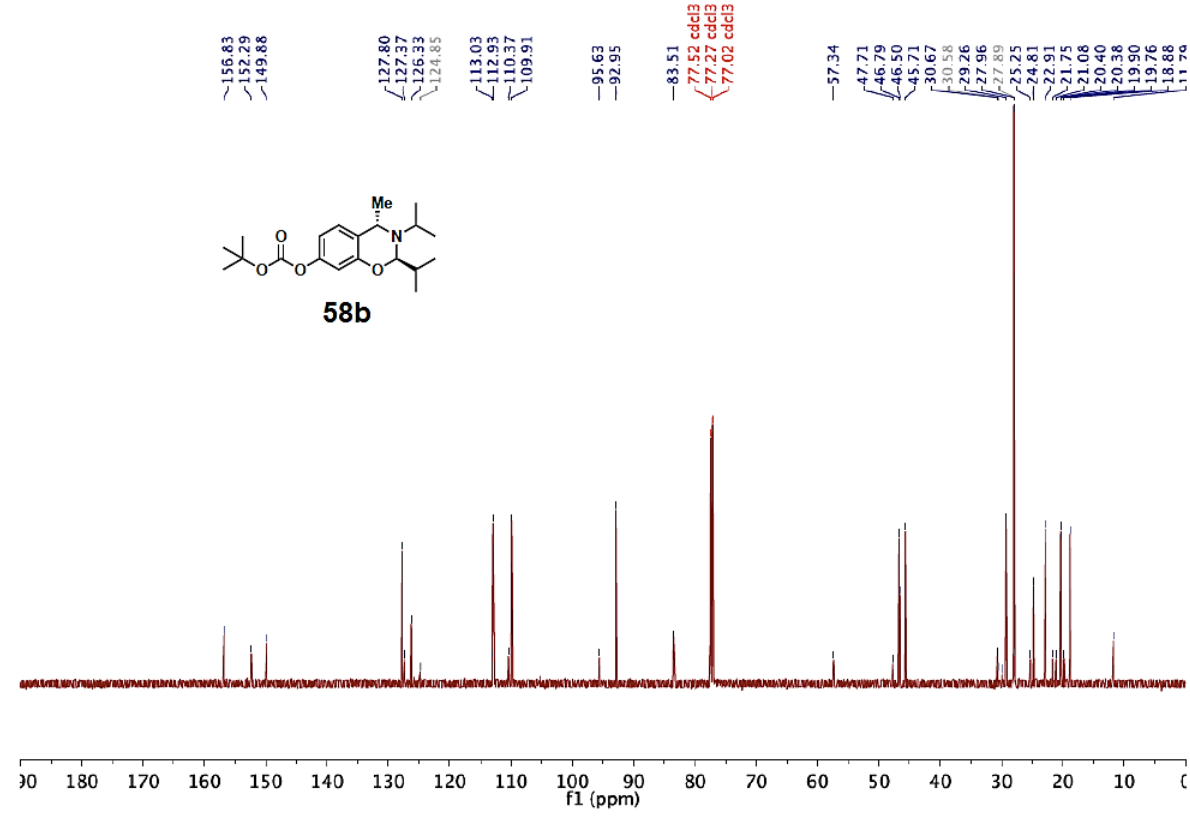

155.51
152.34
150.18
129.26
128.62
128.20
127.08
122.83
113.63
109.82
105.25
91.94
83.71
77.52 cdcl3
77.46
77.26 cdcl3
77.01 cdcl3
52.93
49.46
30.59
29.96
29.68
27.97
23.85
20.14
18.59
1.28
Me
N
O
O
O
57b
f1 (ppm)

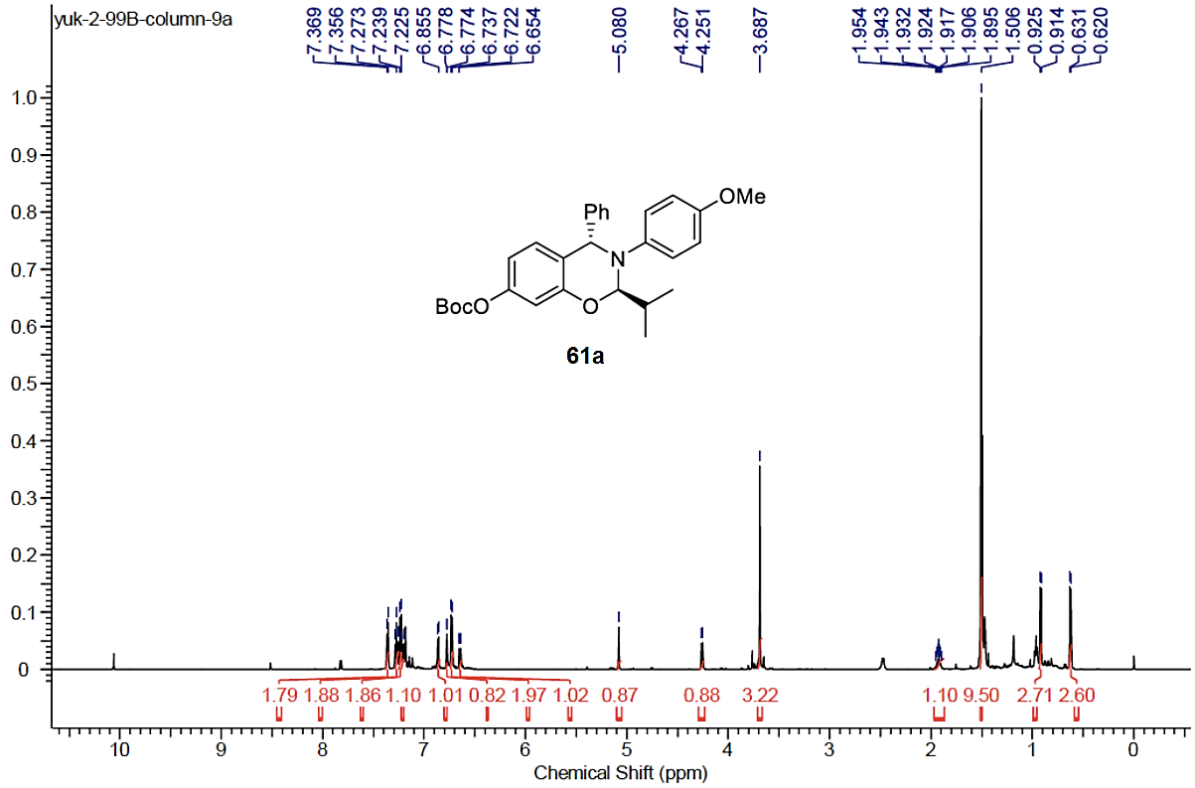

4.4%
BocO
O
N
Ph
H
57b
2.06
4.36
3.67
100.00
f1 (ppm)

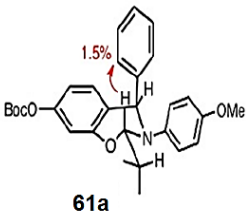

yuk-2-124C-column-6a
7.218
7.207
7.196
7.182
7.135
6.951
6.937
6.629
6.615
6.608
4.938
4.043
4.028
3.508
3.497
3.486
3.475
3.464
3.453
2.152
2.141
2.125
2.114
2.103
1.490
1.283
1.272
0.962
0.952
0.820
0.809
0.682
0.671
Ph
N
O
BocO
58a
4.31 1.23 1.05 2.13
1.02
0.95
1.08
1.01 9.92 2.97 3.06 3.05 3.00
Chemical Shift (ppm)

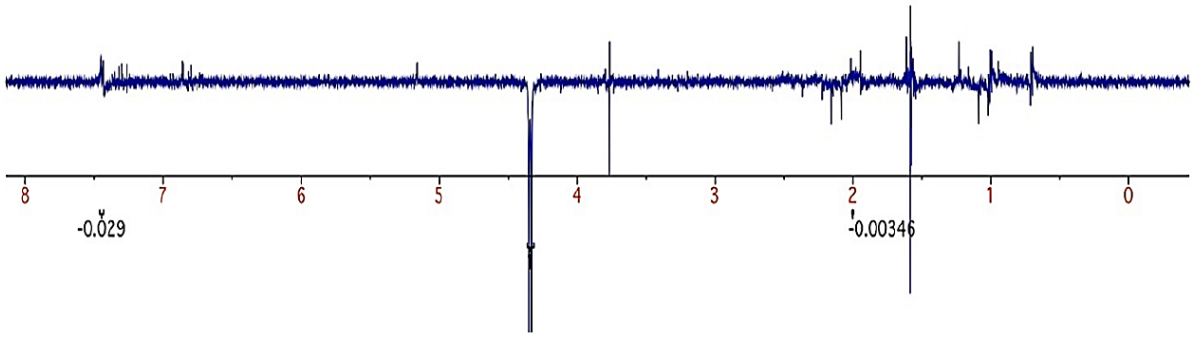

157.302
152.170
150.641
144.627
129.541
128.889
128.062
126.841
120.981
112.586
110.088
92.794
83.566
77.484
77.230
76.976
54.597
45.742
29.327
27.943
23.370
21.281
19.970
18.473
Ph
N
O
BocO
58a

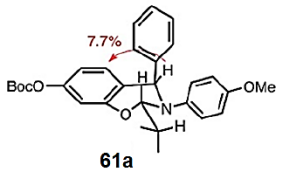

Me
58b
f1 (ppm)


Me
58b
f1 (ppm)

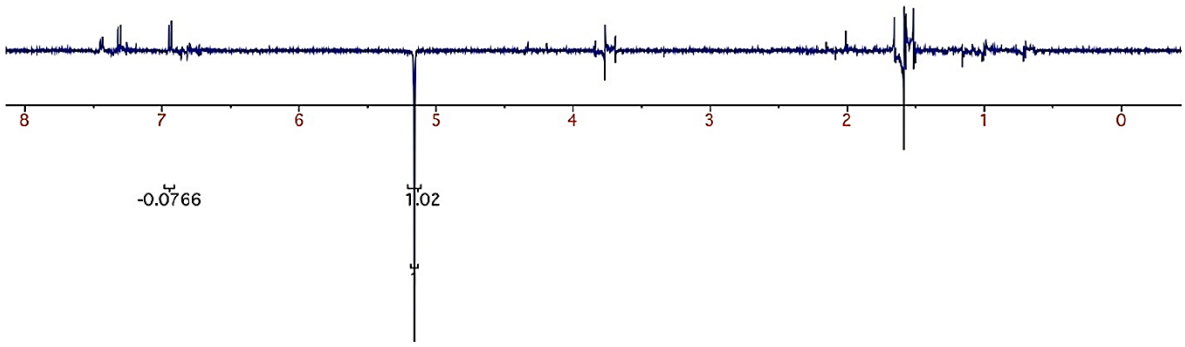

yuk-2-99B-column-9a
7.369
7.356
7.273
7.239
7.225
6.855
6.778
6.774
6.737
6.722
6.654
5.080
4.267
4.251
3.687
1.954
1.943
1.932
1.924
1.917
1.906
1.895
1.506
0.925
0.914
0.631
0.620
Ph
OMe
N
O
BocO
61a
1.79 1.88 1.86 1.10 1.01 0.82 1.97 1.02 0.87 0.88 3.22 1.10 9.50 2.71 2.60
Chemical Shift (ppm)

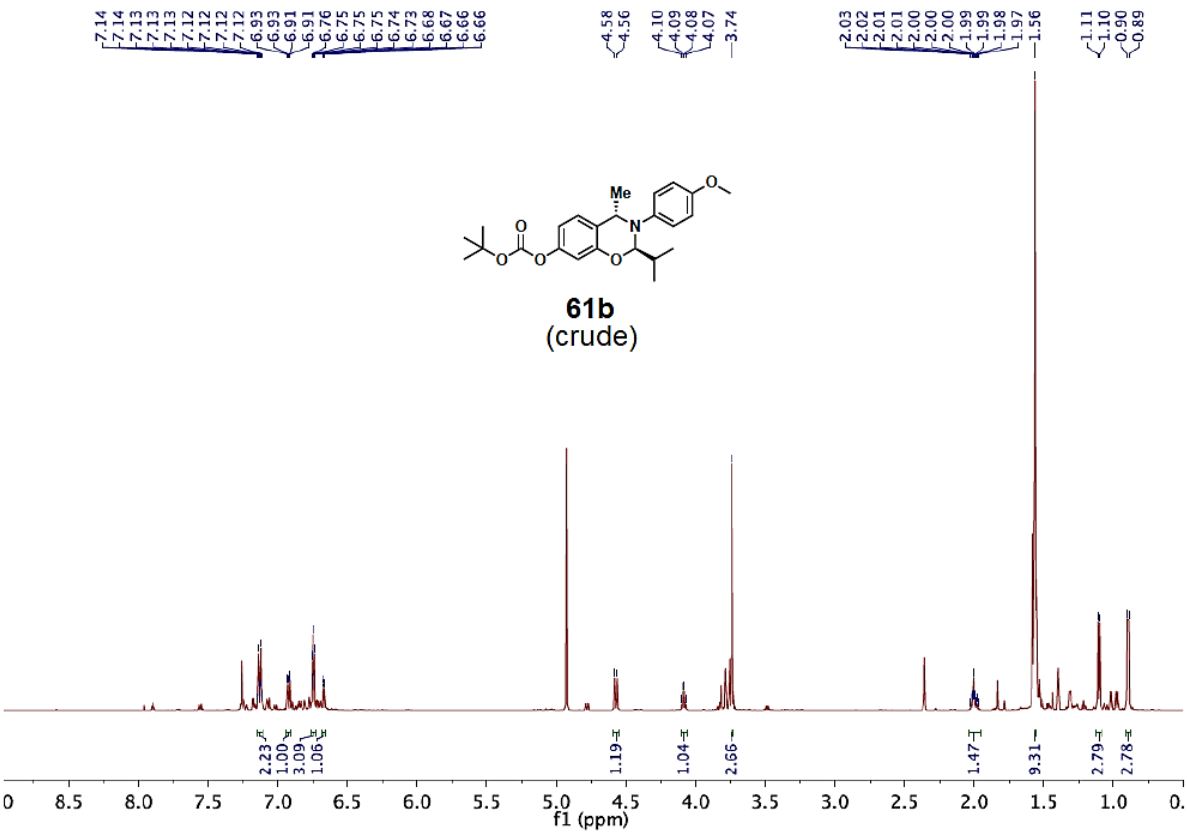

1.5%
H
H
BocO
OMe
O
N
H
61a


-0.029
-0.00346

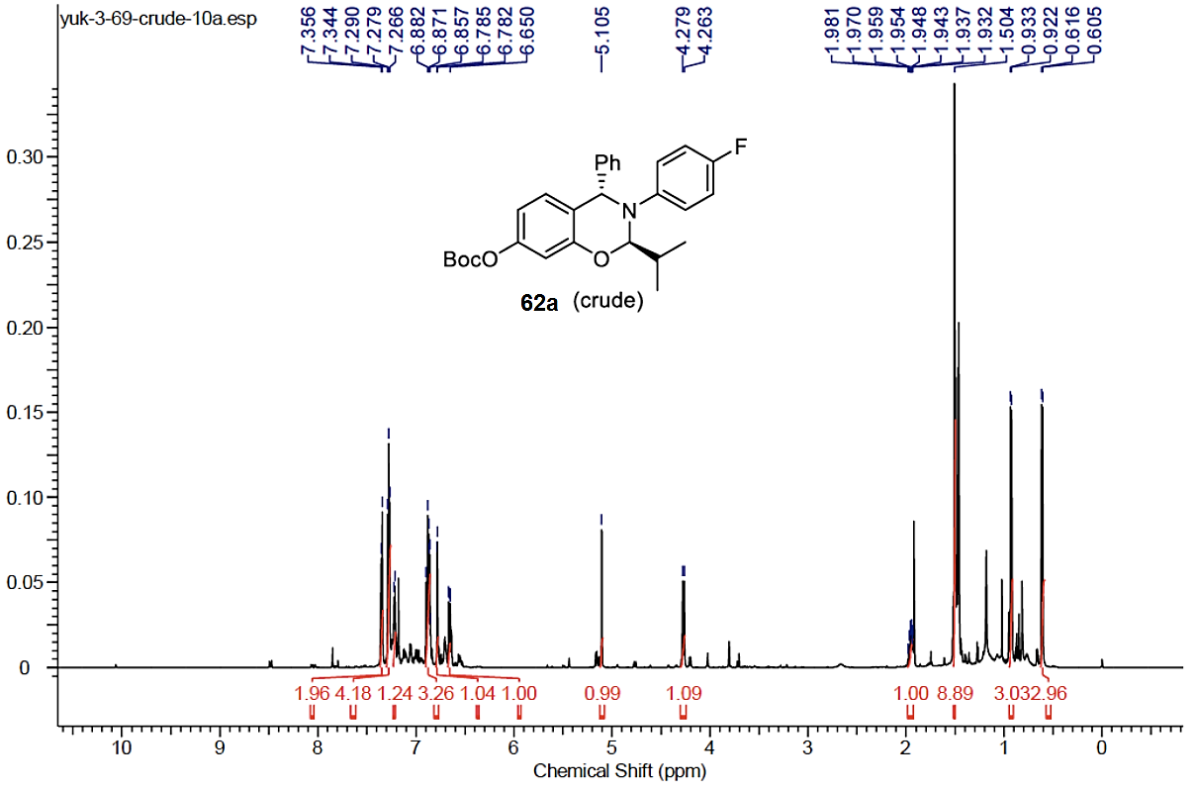


61a

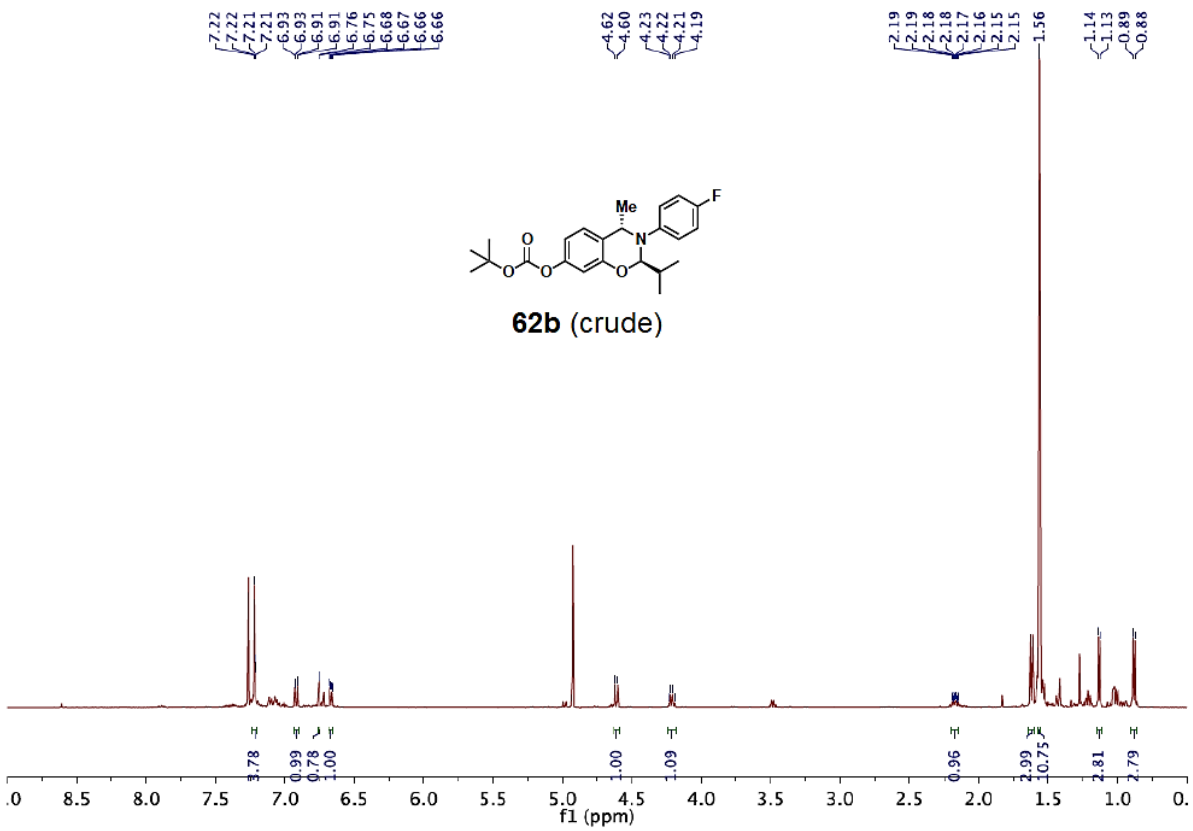




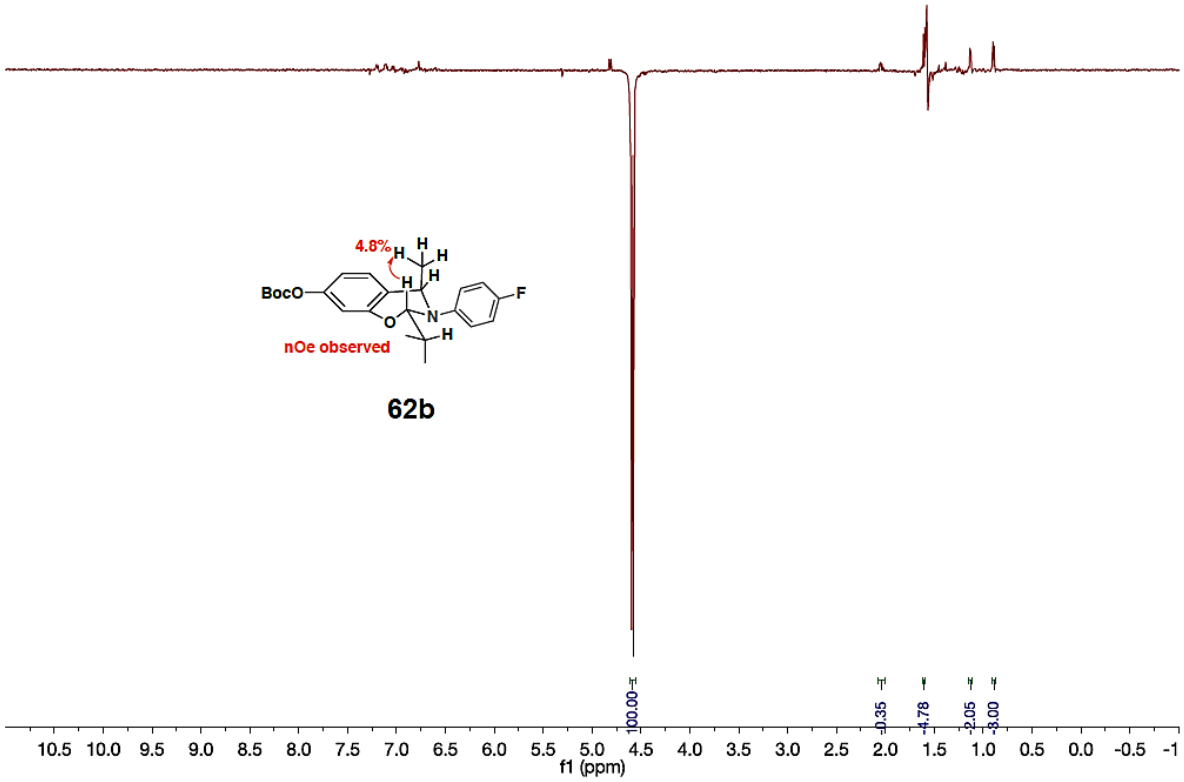
61b
(crude)

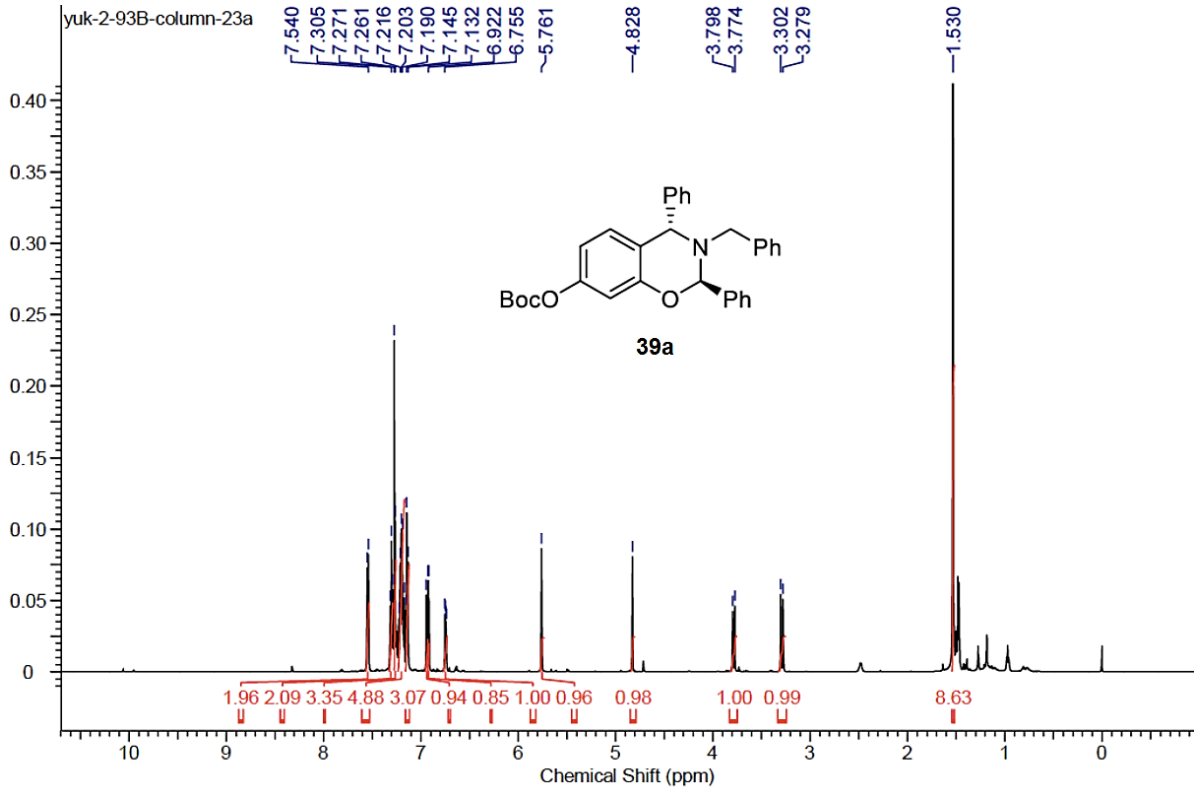


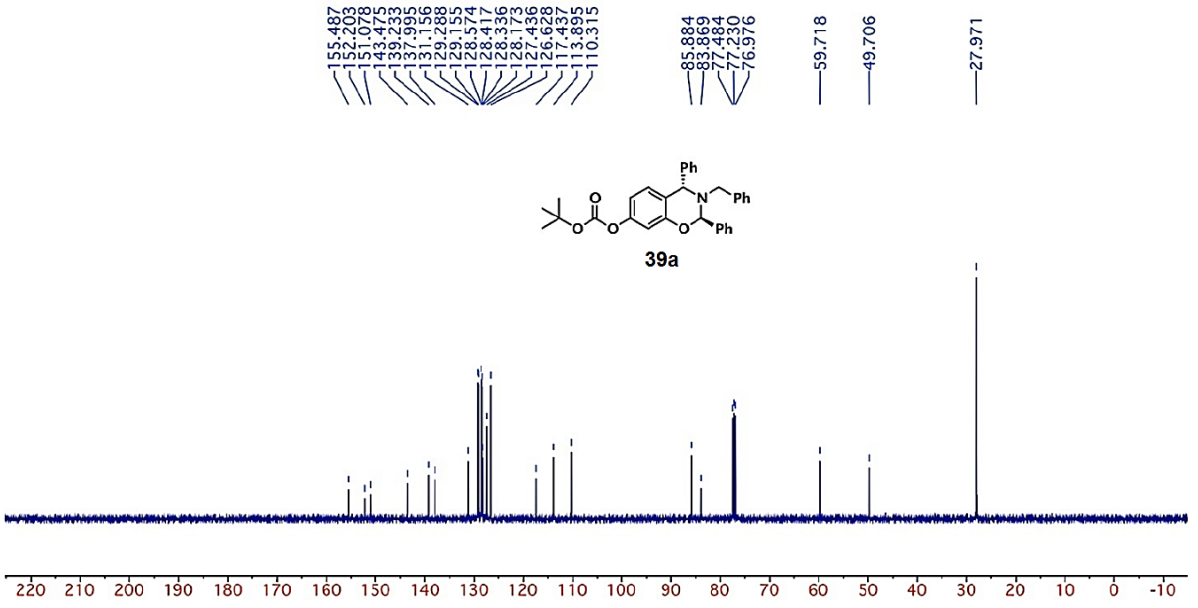
62a (crude)

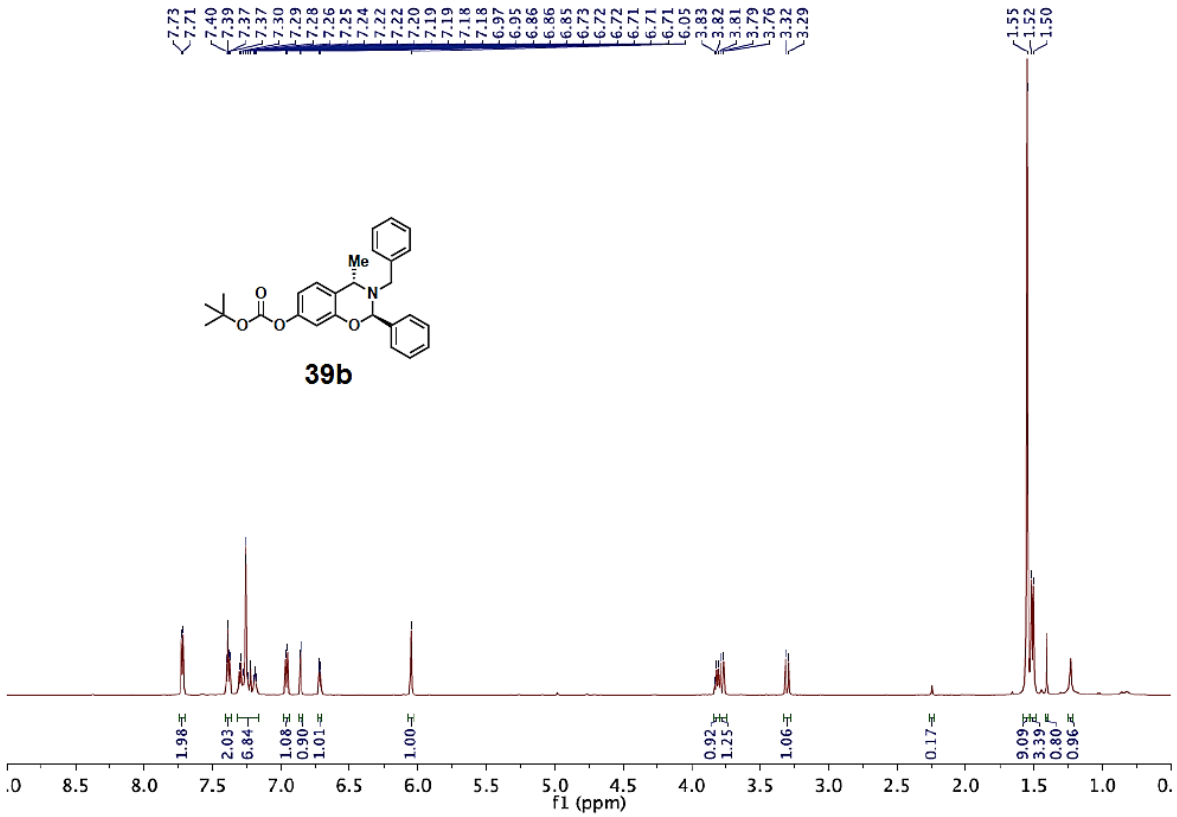


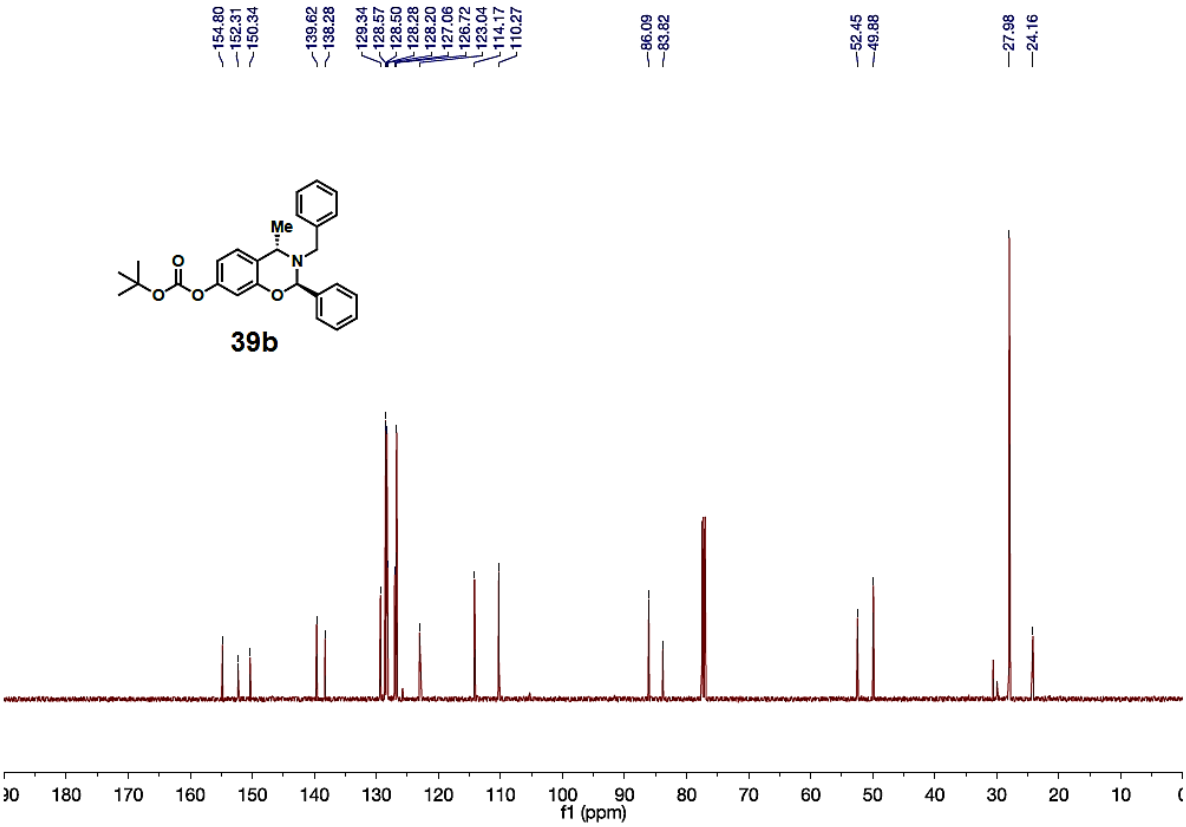
62b (crude)

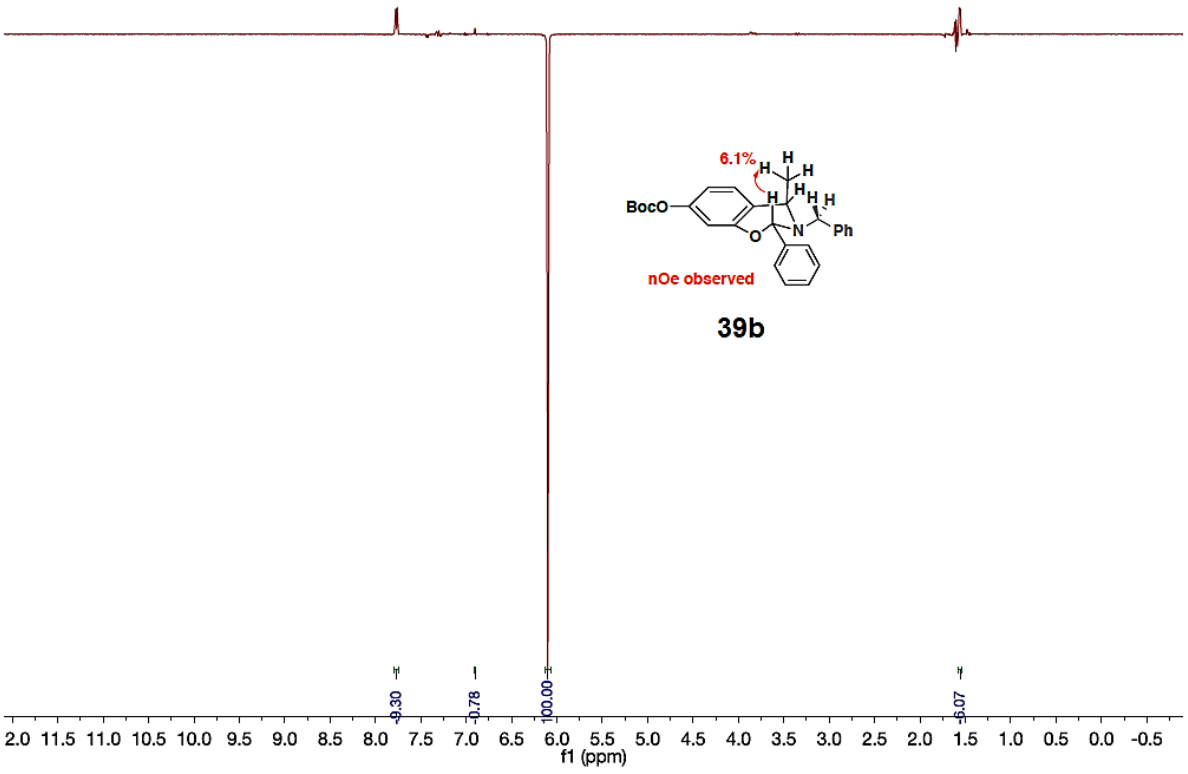

4.8%
BocO
F
O
N
nOe observed
62b
100.00
0.35
4.78
2.05
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

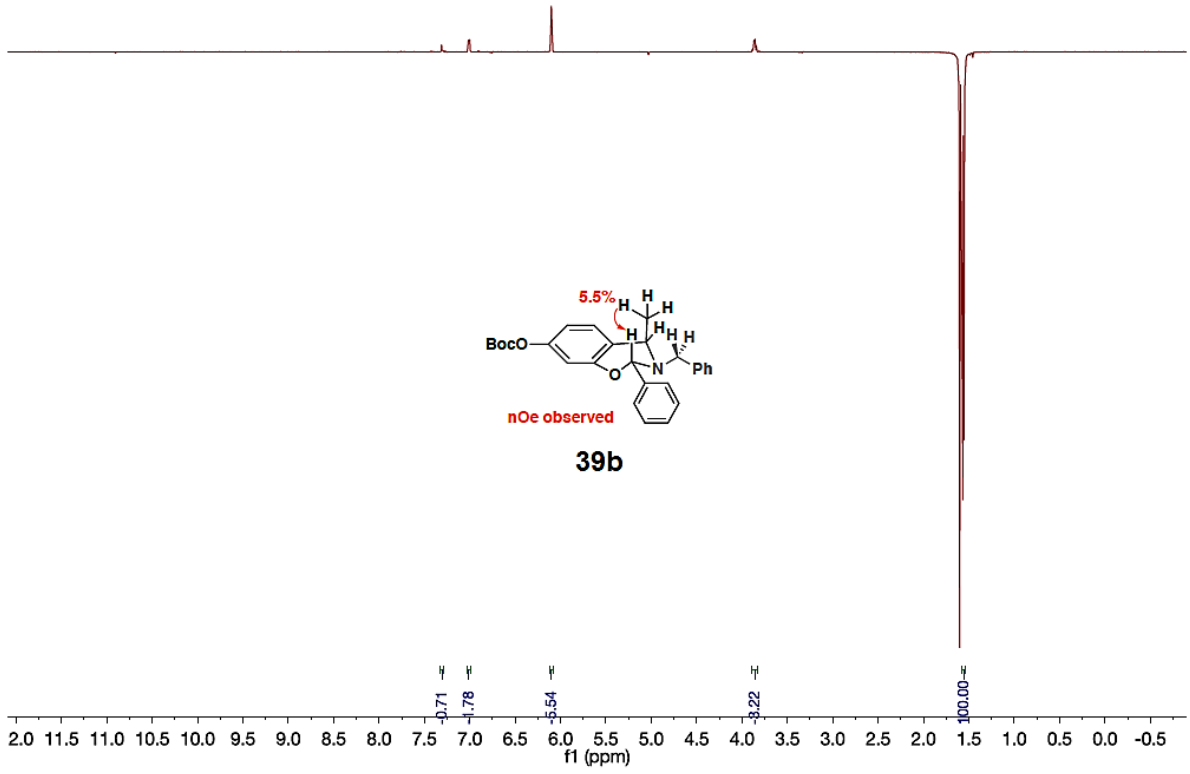

yuk-2-93B-column-23a
7.540
7.305
7.271
7.261
7.216
7.203
7.190
7.145
7.132
6.922
6.755
5.761
4.828
3.798
3.774
3.302
3.279
1.530
Ph
N
Ph
BocO
O
Ph
39a
1.96 2.09 3.35 4.88 3.07 0.94 0.85 1.00 0.96 0.98 1.00 0.99 8.63
Chemical Shift (ppm)

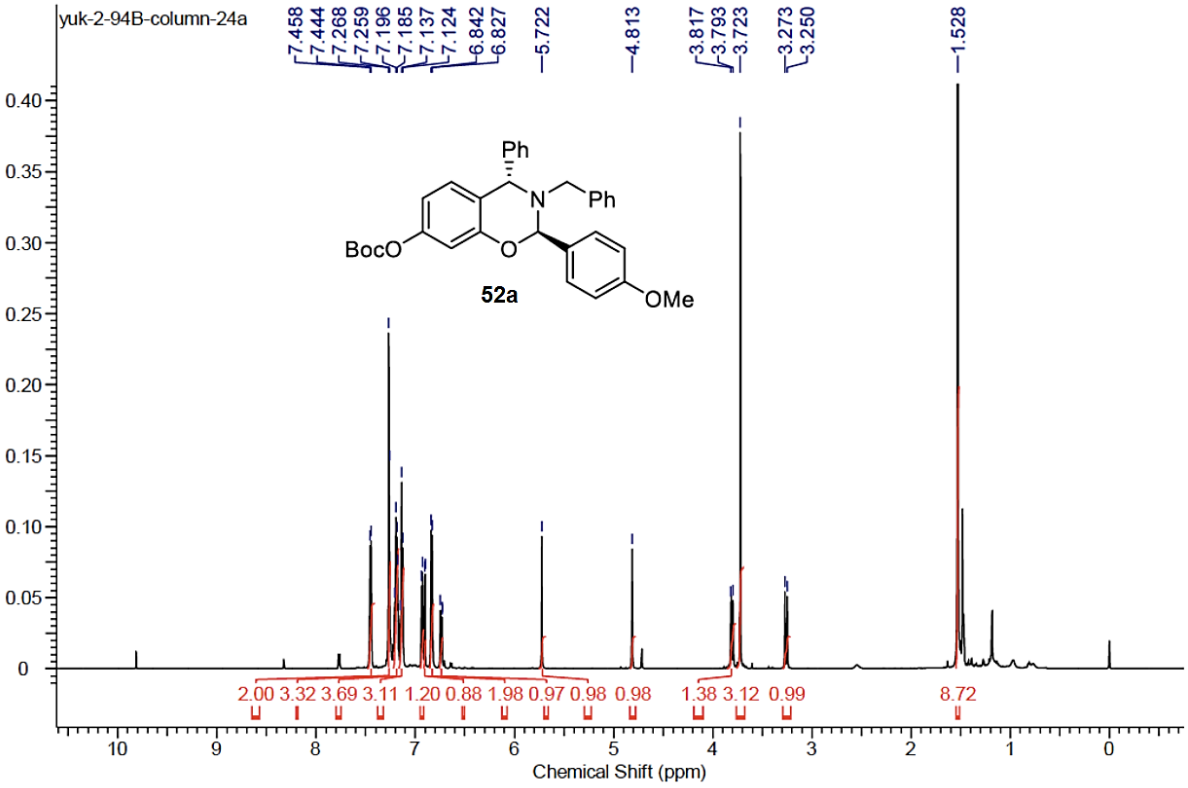

155.487
152.203
151.078
143.475
139.233
137.995
131.156
129.288
129.155
128.574
128.417
128.336
128.173
127.436
126.628
117.437
113.895
110.315
85.884
83.869
77.484
77.230
76.976
59.718
49.706
27.971
Ph
N
Ph
O
O
O
Ph
39a

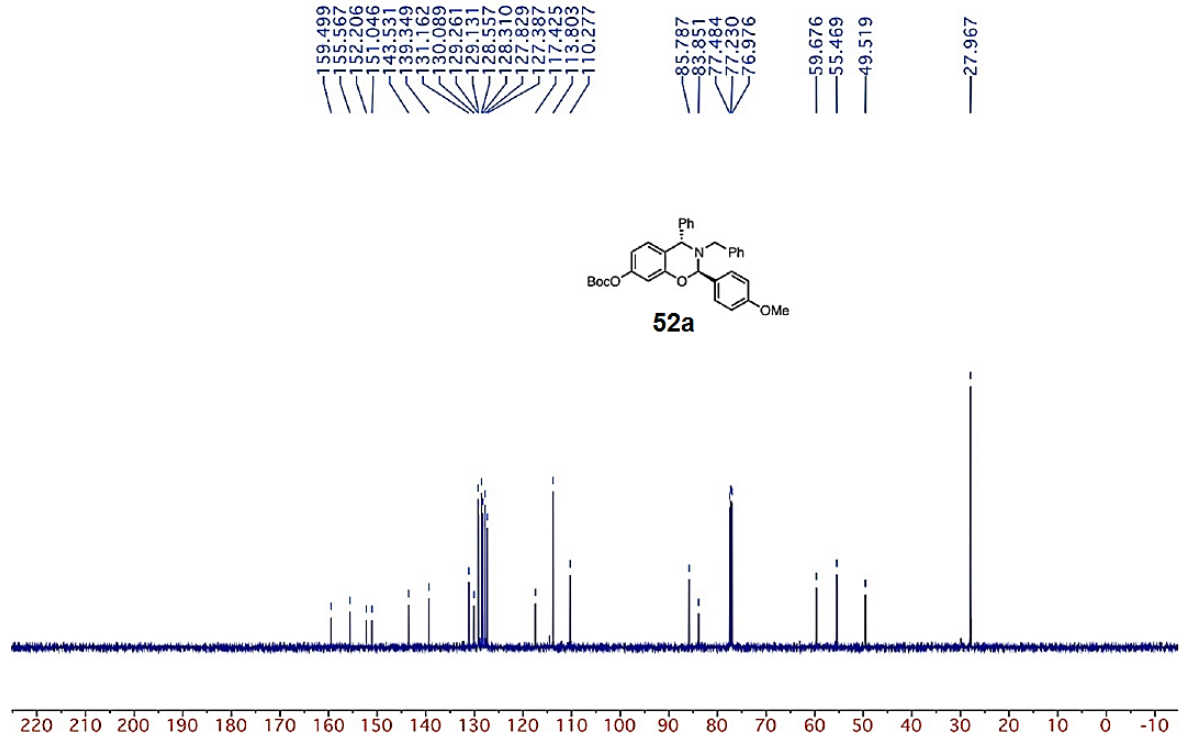

7.73
7.71
7.40
7.39
7.37
7.37
7.30
7.29
7.28
7.26
7.25
7.24
7.22
7.22
7.20
7.19
7.19
7.18
7.18
6.97
6.95
6.86
6.86
6.85
6.73
6.72
6.72
6.71
6.71
6.71
6.05
3.83
3.82
3.81
3.79
3.76
3.32
3.29
1.55
1.52
1.50
Me
N
O
O
O
O
39b
1.98
2.03
6.84
1.08
0.90
1.01
1.00
0.92
1.23
1.06
0.17
9.09
3.39
0.80
0.96
f1 (ppm)

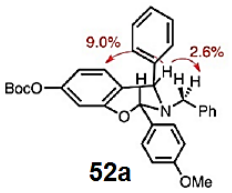

154.80
152.31
150.34
139.62
138.28
129.34
128.57
128.50
128.28
128.20
127.06
126.72
123.04
114.17
110.27
86.09
83.82
52.45
49.88
27.98
24.16
Me
N
O
O
O
O
39b
f1 (ppm)


6.1%
BocO
Ph
nOe observed
39b
9.30
0.78
100.00
6.07
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

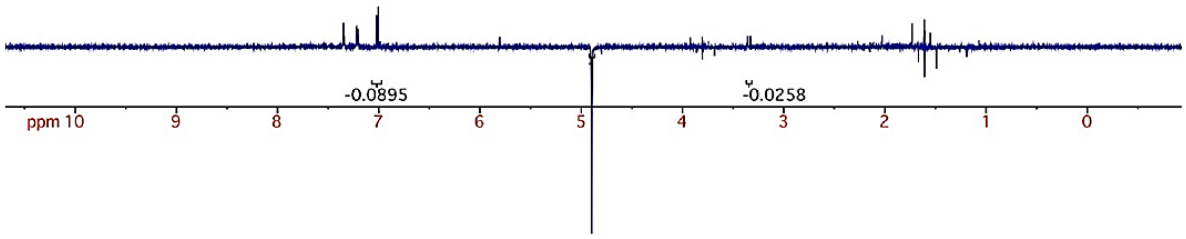

5.5%
BocO
Ph
nOe observed
39b
0.71
1.78
5.54
3.22
100.00
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

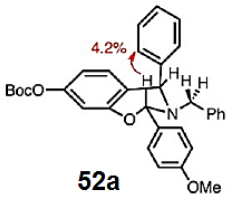

yuk-2-94B-column-24a
7.458
7.444
7.268
7.259
7.196
7.185
7.137
7.124
6.842
6.827
5.722
4.813
3.817
3.793
3.723
3.273
3.250
1.528
Ph
N
Ph
BocO
O
OMe
52a
2.00 3.32 3.69 3.11 1.20 0.88 1.98 0.97 0.98 0.98 1.38 3.12 0.99 8.72
Chemical Shift (ppm)


159.499
155.567
152.206
151.046
143.531
139.349
131.162
130.089
129.261
129.131
128.557
128.310
127.829
127.387
117.425
113.803
110.277
85.787
83.851
77.484
77.230
76.976
59.676
55.469
49.519
27.967
Ph
N
Ph
BocO
O
OMe
52a

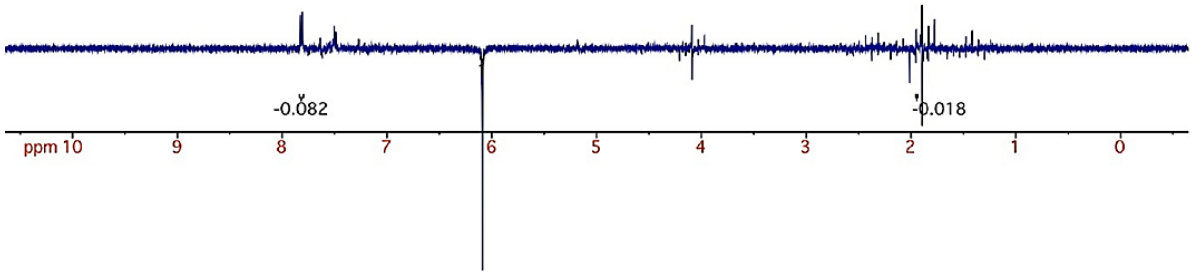

9.0%
2.6%
BocO
Ph
OMe

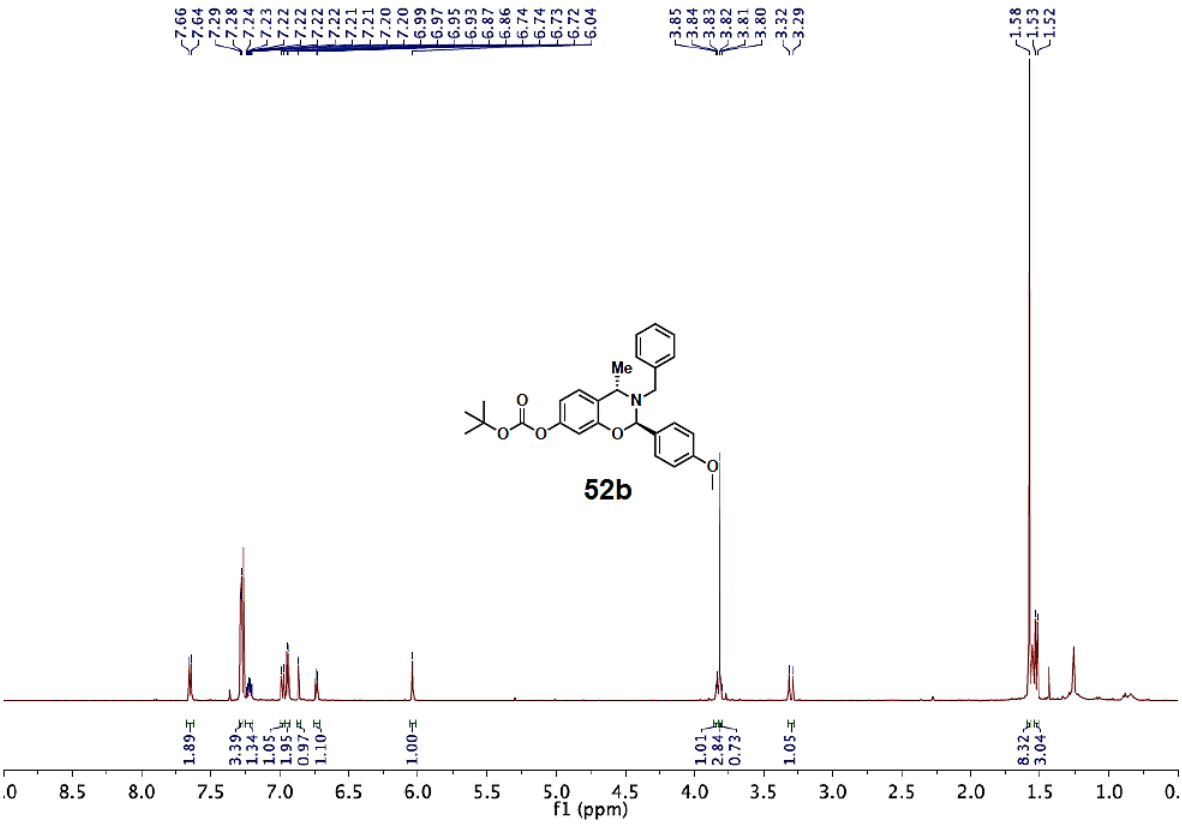
52a

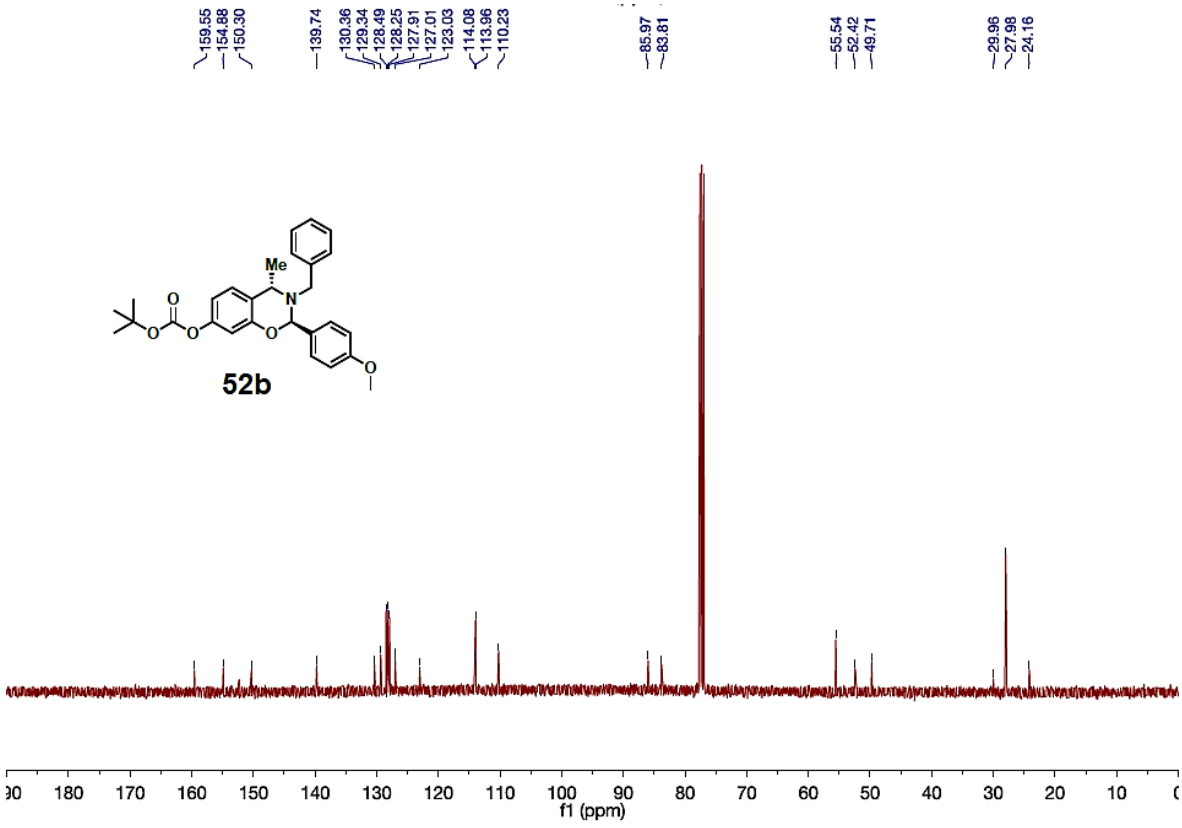

-0.0895
-0.0258
ppm 10
9
8
7
6
5
4
3
2
1
0

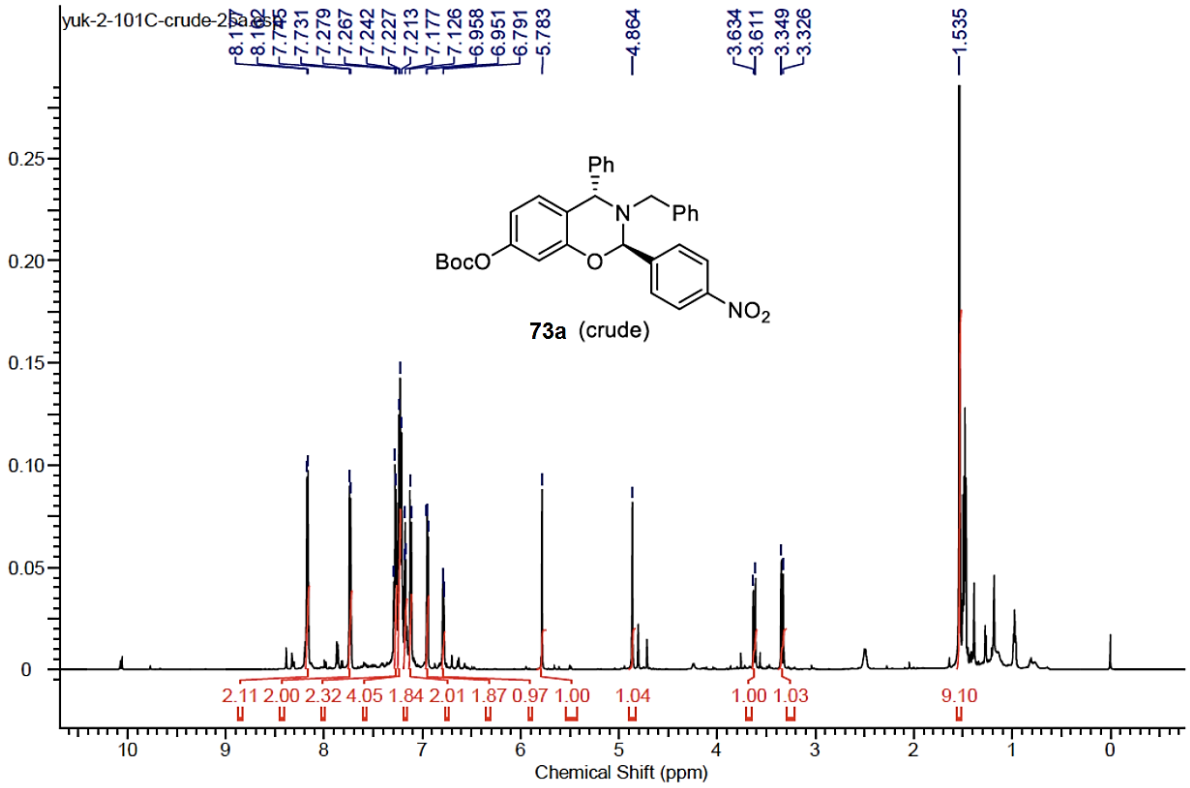

4.2%
BocO
Ph
OMe

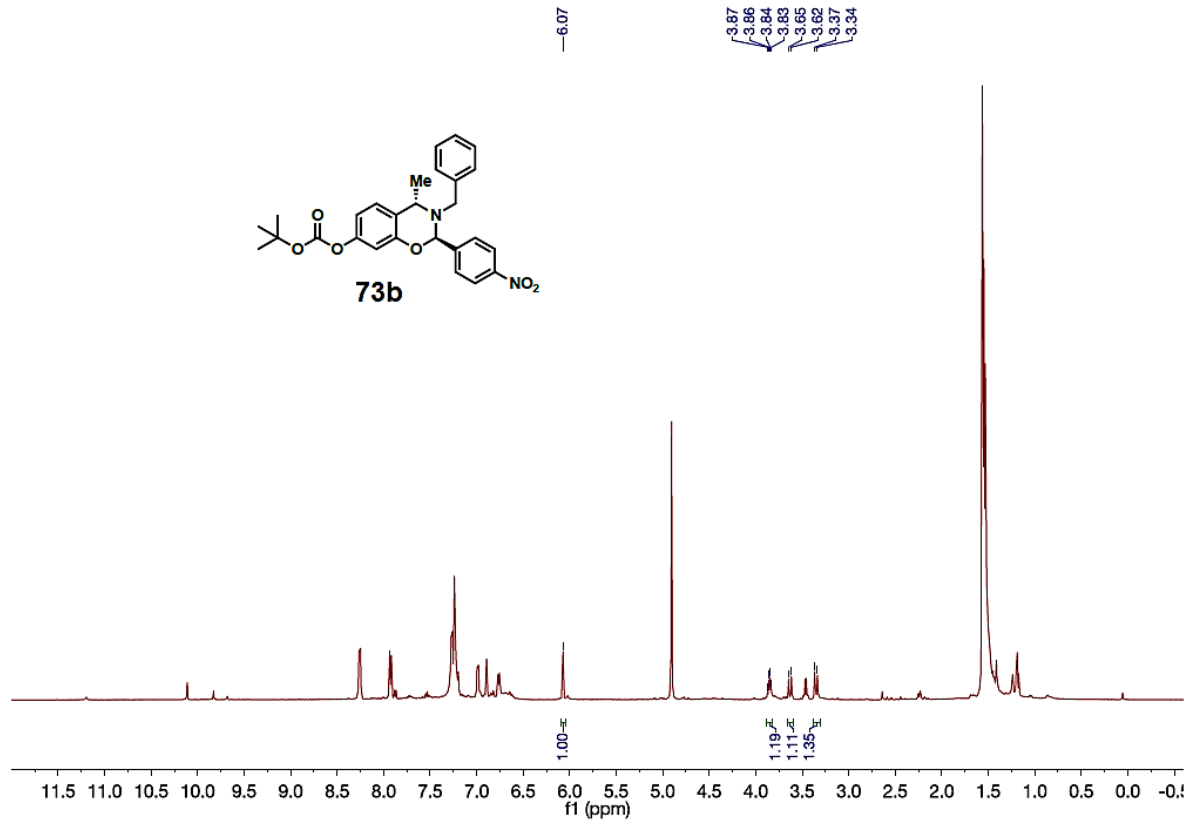
52a

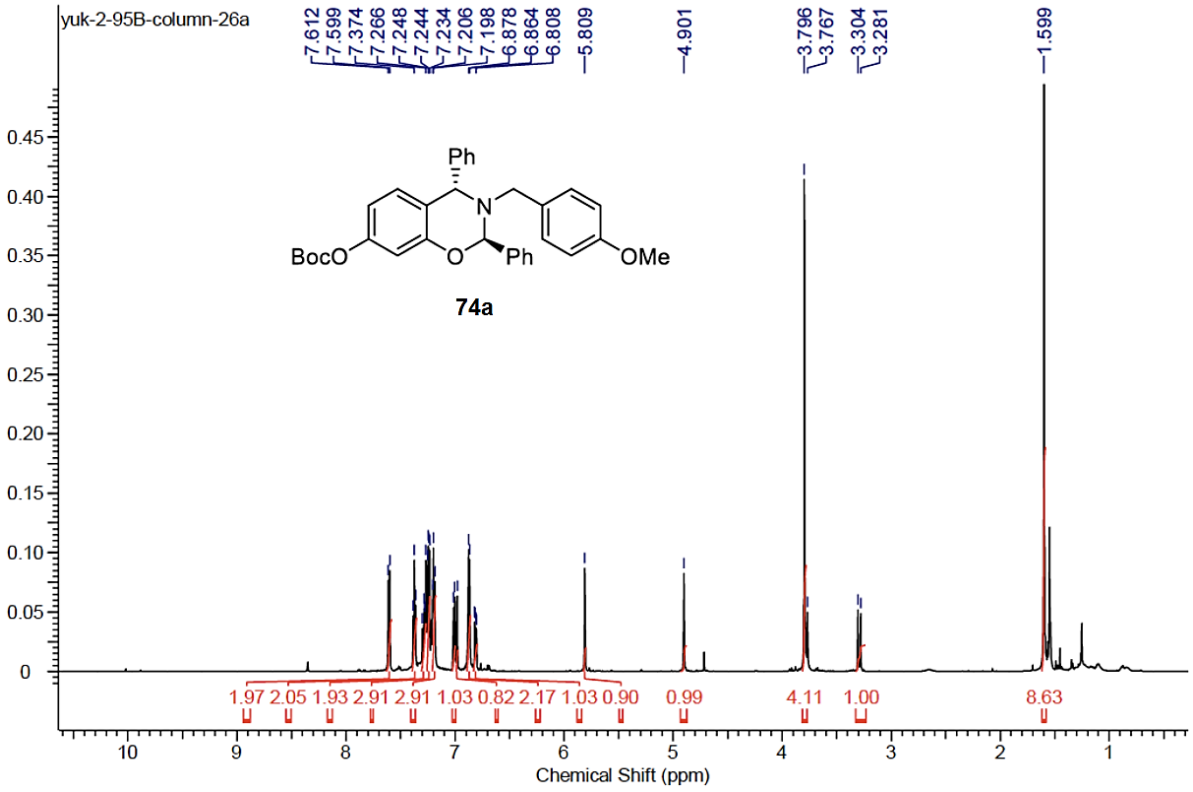

-0.082
-0.018
ppm 10
9
8
7
6
5
4
3
2
1
0

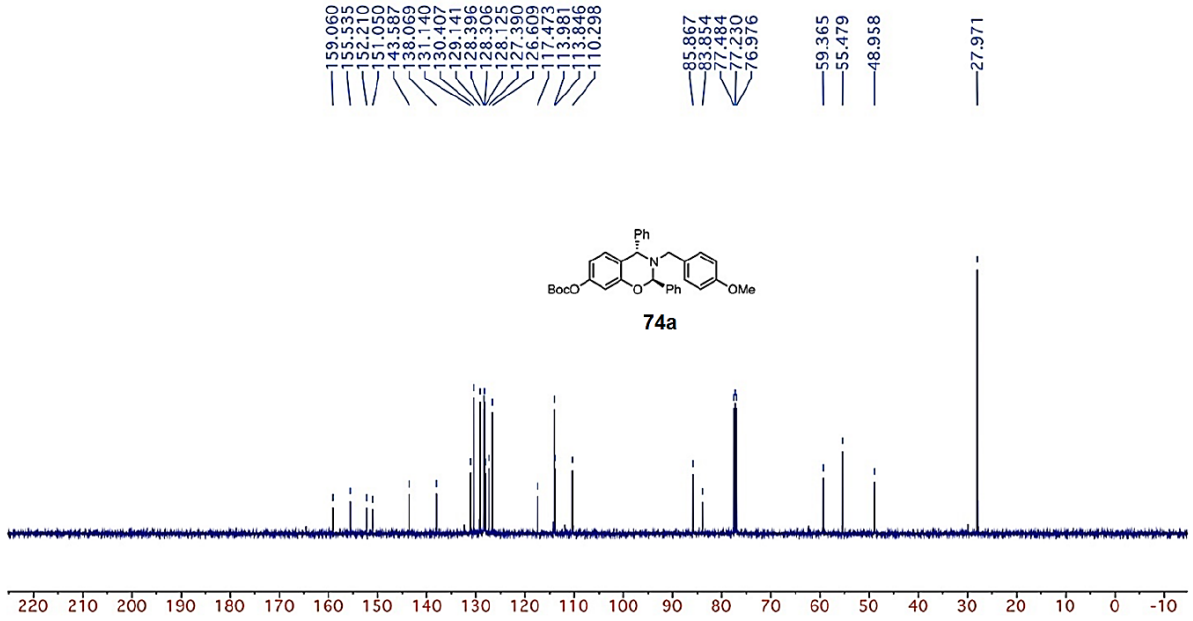

7.66
7.64
7.29
7.28
7.24
7.23
7.22
7.22
7.22
7.22
7.21
7.21
7.20
7.20
6.99
6.97
6.95
6.93
6.87
6.86
6.74
6.74
6.73
6.72
6.04
3.85
3.84
3.83
3.82
3.81
3.80
3.32
3.29
1.58
1.53
1.52
Me
N
O
O
O
O
O
52b
1.89
3.39
1.34
1.05
1.95
0.97
1.10
1.00
1.01
2.84
0.73
1.05
8.32
3.04
f1 (ppm)

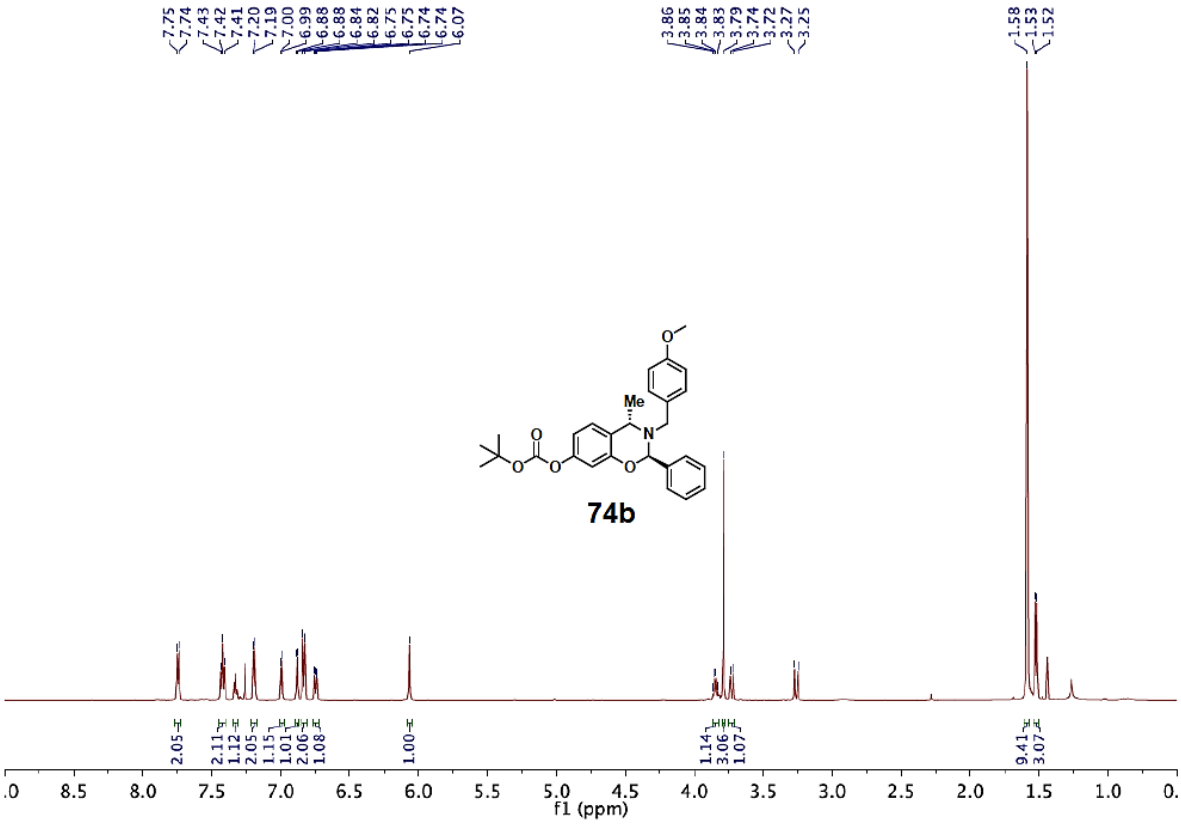

159.55
154.88
150.30
139.74
130.36
129.34
128.49
128.25
127.91
127.01
123.03
114.08
113.96
110.23
85.97
83.81
55.54
52.42
49.71
29.96
27.98
24.16
Me
N
O
O
O
O
O
52b
f1 (ppm)

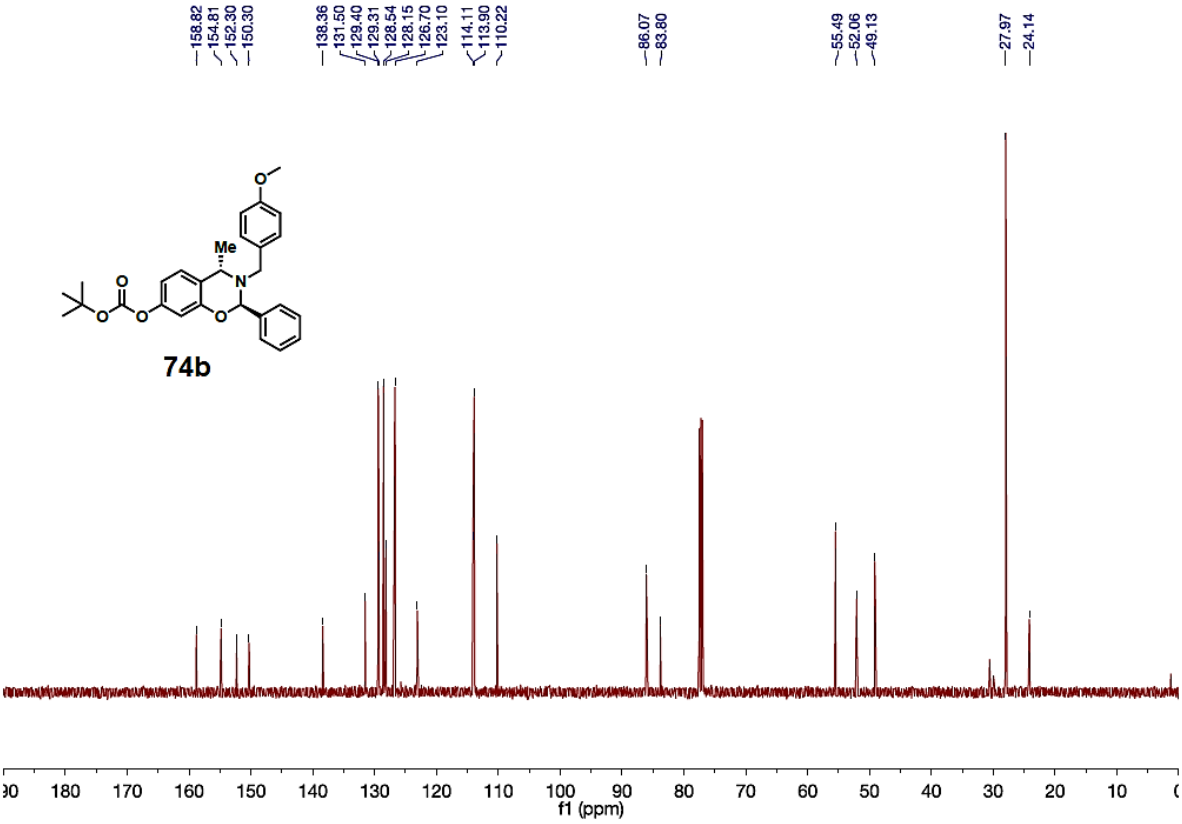

yuk-2-101C-crude-2
8.182
8.162
7.745
7.731
7.279
7.267
7.242
7.227
7.213
7.177
7.126
6.958
6.951
6.791
5.783
4.864
3.634
3.611
3.349
3.326
1.535
Ph
N
Ph
BocO
O
NO2
73a (crude)
2.11 2.00 2.32 4.05 1.84 2.01 1.87 0.97 1.00 1.04 1.00 1.03 9.10
Chemical Shift (ppm)

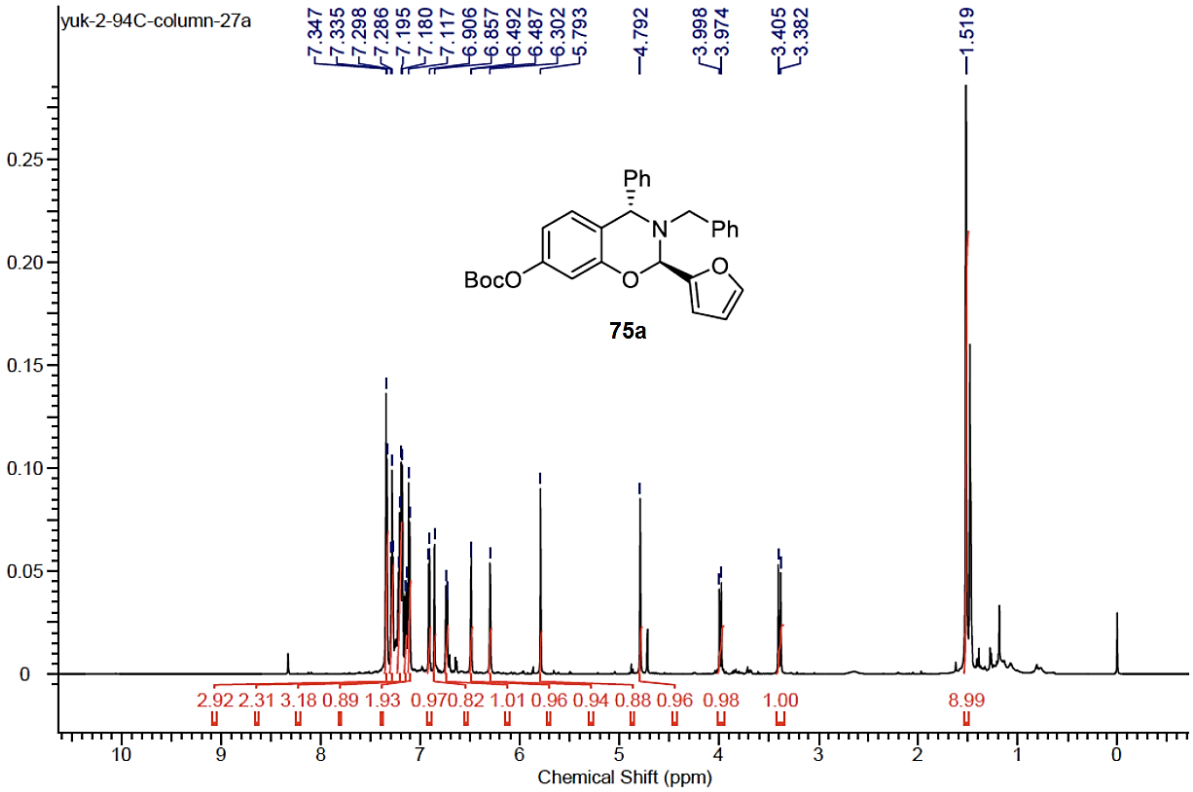

6.07
3.87
3.86
3.84
3.83
3.65
3.62
3.37
3.34
Me
N
O
O
O
O
NO2
73b
1.00
1.19
1.11
1.35
f1 (ppm)

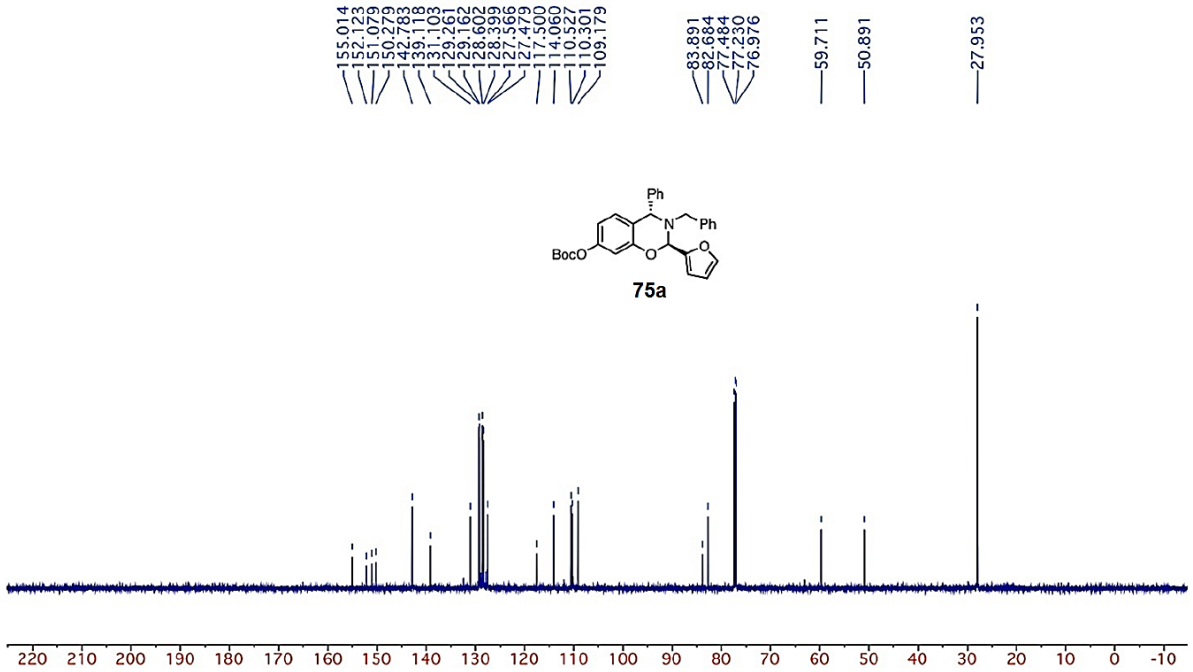

yuk-2-95B-column-26a
7.612
7.599
7.374
7.266
7.248
7.244
7.234
7.206
7.198
6.878
6.864
6.808
5.809
4.901
3.796
3.767
3.304
3.281
1.599
Ph
N
BocO
O
Ph
OMe
74a
1.97 2.05 1.93 2.91 2.91 1.03 0.82 2.17 1.03 0.90
0.99
4.11
1.00
8.63
Chemical Shift (ppm)

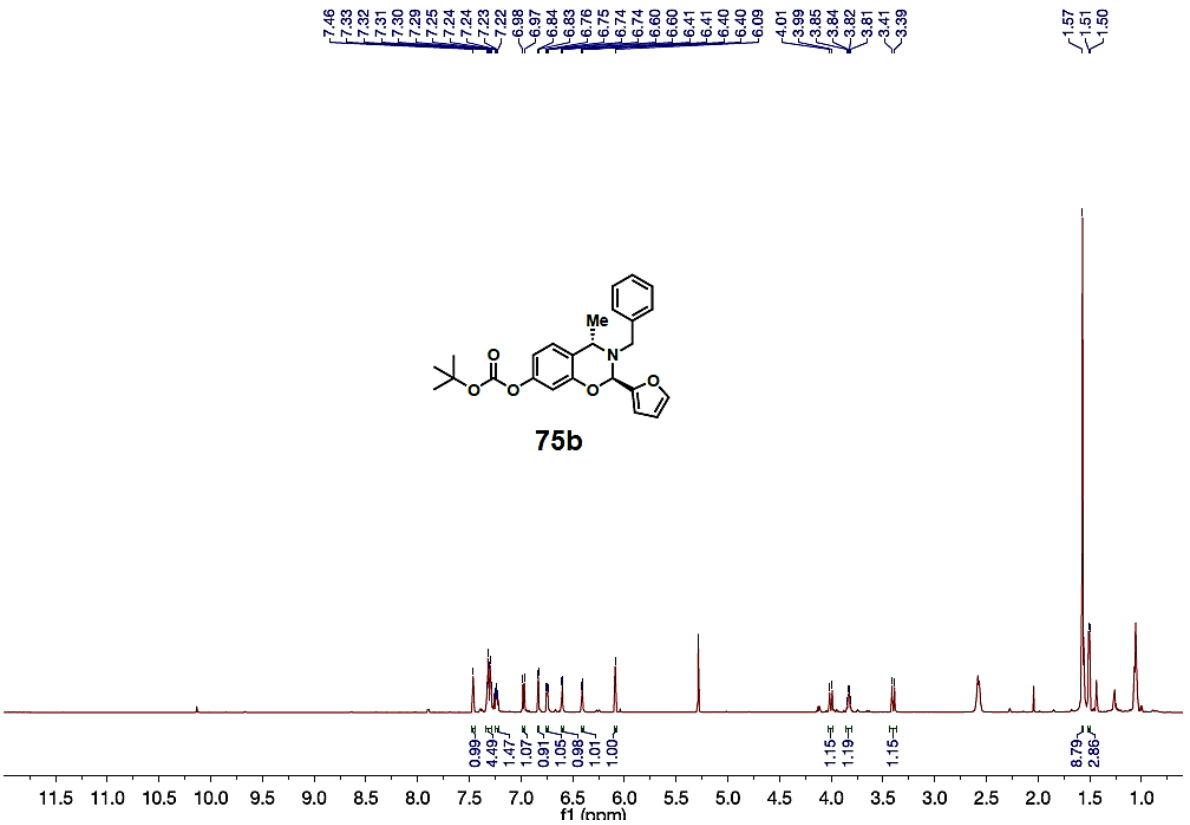

159.060
155.535
152.210
151.050
143.587
138.089
131.140
130.407
129.141
128.396
128.306
128.125
127.390
126.609
117.473
113.981
113.846
110.298
85.867
83.854
77.484
77.230
76.976
59.365
55.479
48.958
27.971
Ph
N
BocO
O
Ph
OMe
74a

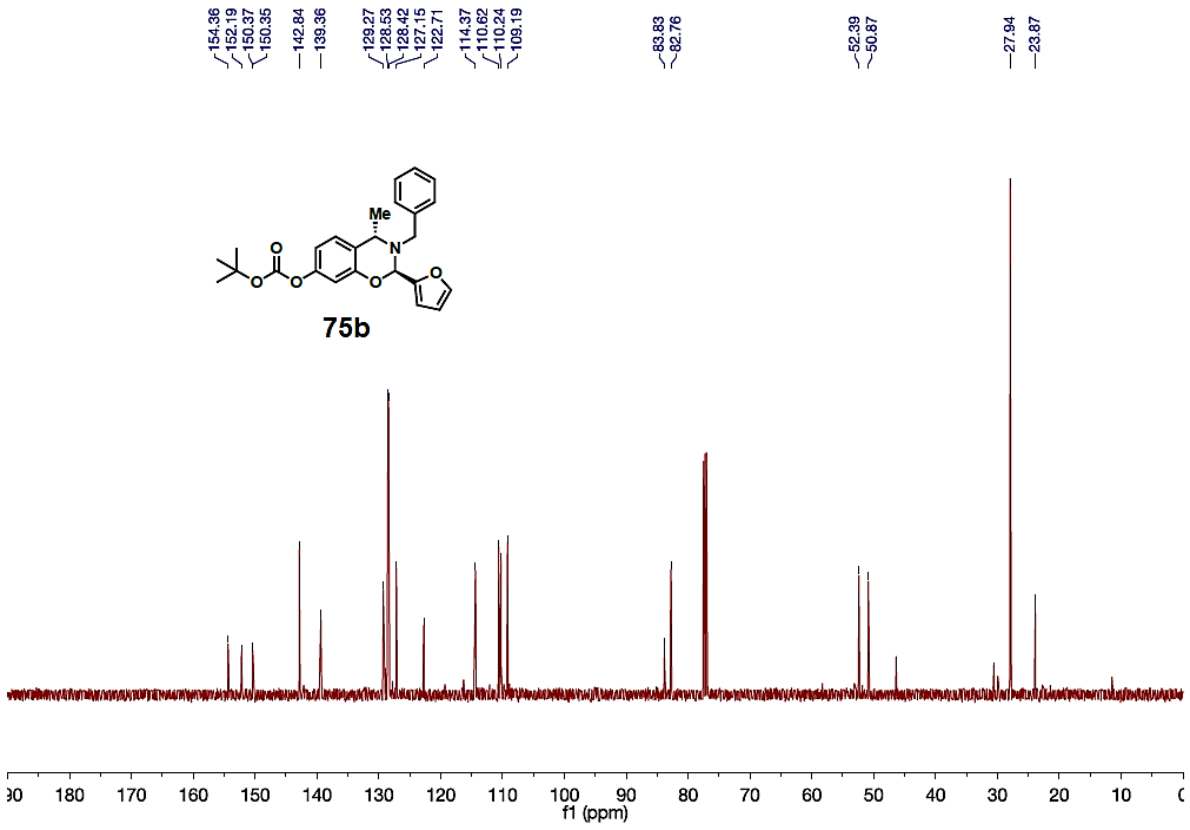

7.75
7.74
7.43
7.42
7.41
7.20
7.19
7.00
6.99
6.88
6.84
6.82
6.75
6.74
6.07
3.86
3.85
3.84
3.83
3.79
3.74
3.72
3.27
3.25
1.58
1.53
1.52
Me
74b
2.05
2.11
1.12
2.05
1.15
1.01
2.06
1.08
1.00
1.14
3.06
1.07
9.41
3.07
f1 (ppm)

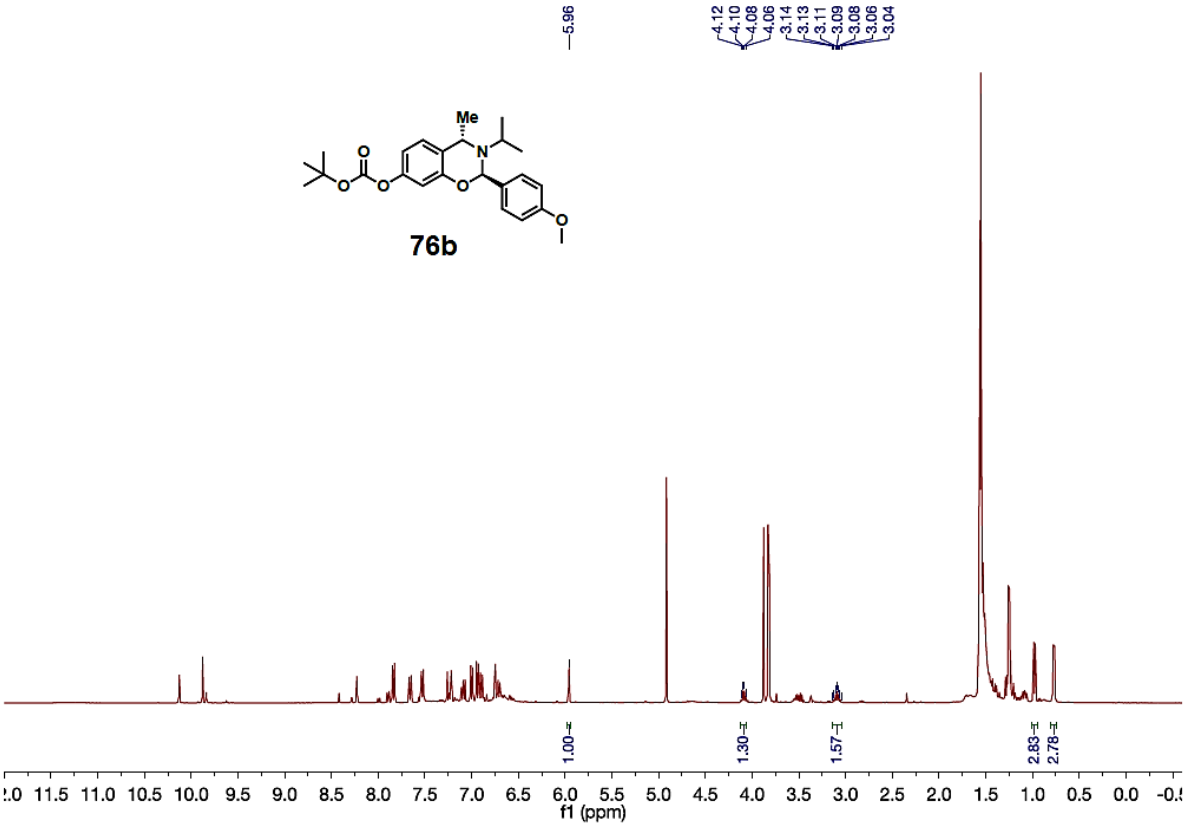

158.82
154.81
152.30
150.30
138.36
131.50
129.40
129.31
128.54
128.15
126.70
123.10
114.11
113.90
110.22
86.07
83.80
55.49
52.06
49.13
27.97
24.14
Me
74b
f1 (ppm)

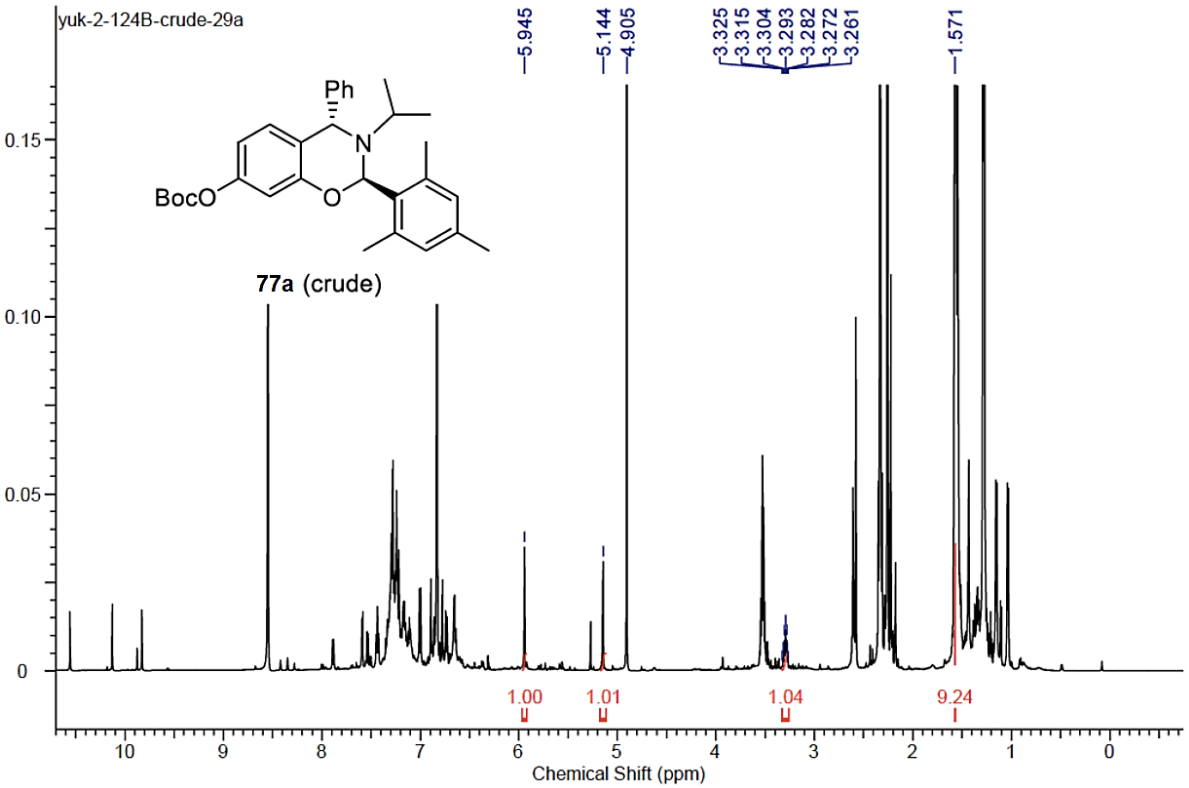

yuk-2-94C-column-27a
7.347
7.335
7.298
7.286
7.195
7.180
7.117
6.906
6.857
6.492
6.487
6.302
5.793
4.792
3.998
3.974
3.405
3.382
1.519
Ph
N
Ph
BocO
O
O
75a
2.92 2.31 3.18 0.89 1.93 0.97 0.82 1.01 0.96 0.94 0.88 0.96 0.98 1.00 8.99
Chemical Shift (ppm)

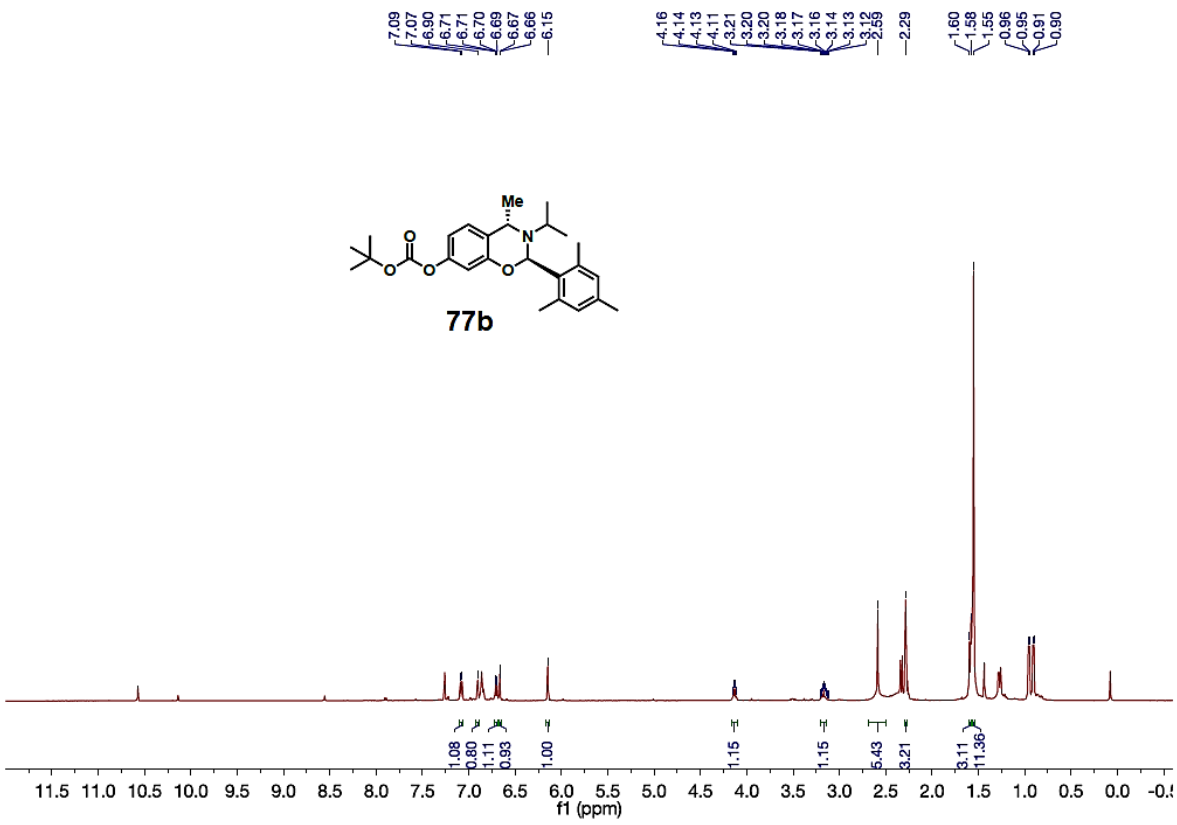

155.014
152.123
151.079
150.279
142.783
139.118
131.103
129.261
129.162
128.602
128.399
127.566
127.479
117.500
114.060
110.527
110.301
109.179
83.891
82.684
77.484
77.230
76.976
59.711
50.891
27.953
Ph
N
Ph
BocO
O
O
75a

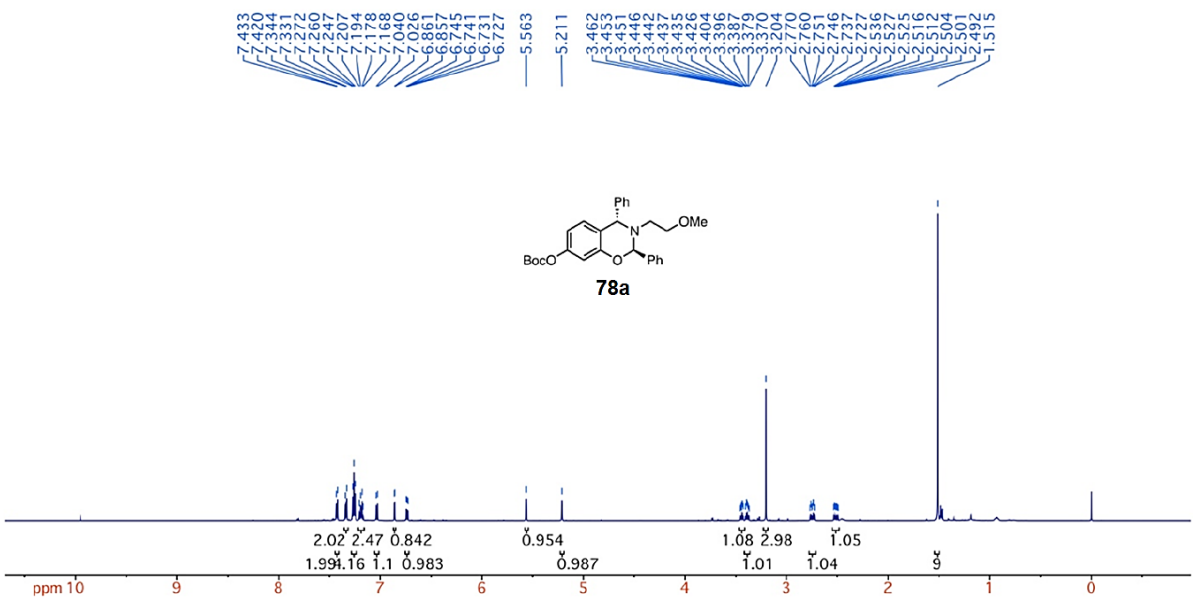

7.46
7.33
7.32
7.31
7.30
7.29
7.25
7.24
7.24
7.23
7.22
6.98
6.97
6.84
6.83
6.76
6.75
6.74
6.74
6.60
6.60
6.41
6.41
6.40
6.40
6.09
4.01
3.99
3.85
3.84
3.82
3.81
3.41
3.39
1.57
1.51
1.50
Me
N
O
O
O
O
O
75b
0.99
4.49
1.47
1.07
0.91
1.05
0.98
1.01
1.00
1.15
1.19
1.15
8.79
2.86
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

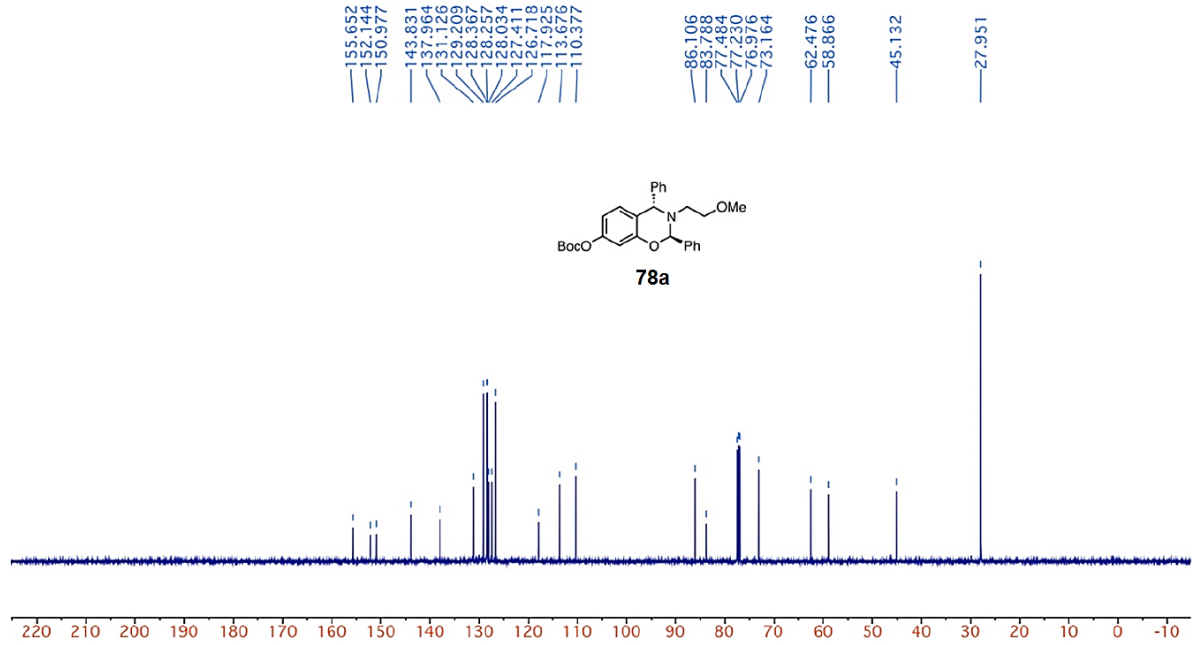

154.36
152.19
150.37
150.35
142.84
139.36
129.27
128.53
128.42
127.15
122.71
114.37
110.62
110.24
109.19
83.83
82.76
52.39
50.87
27.94
23.87
Me
N
O
O
O
O
O
75b
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

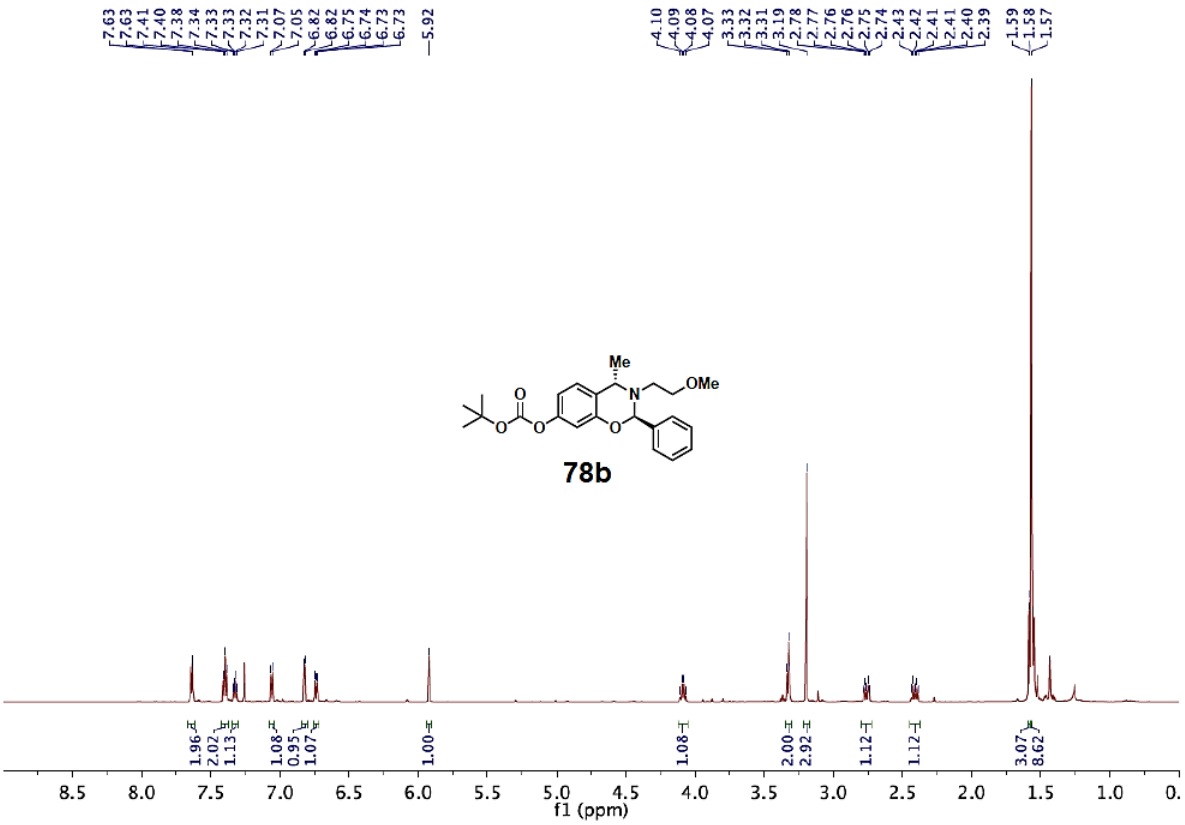

5.96
4.12
4.10
4.08
4.06
3.14
3.13
3.11
3.09
3.08
3.06
3.04
Me
N
O
O
O
O
76b
1.00
1.30
1.57
2.83
2.78
f1 (ppm)

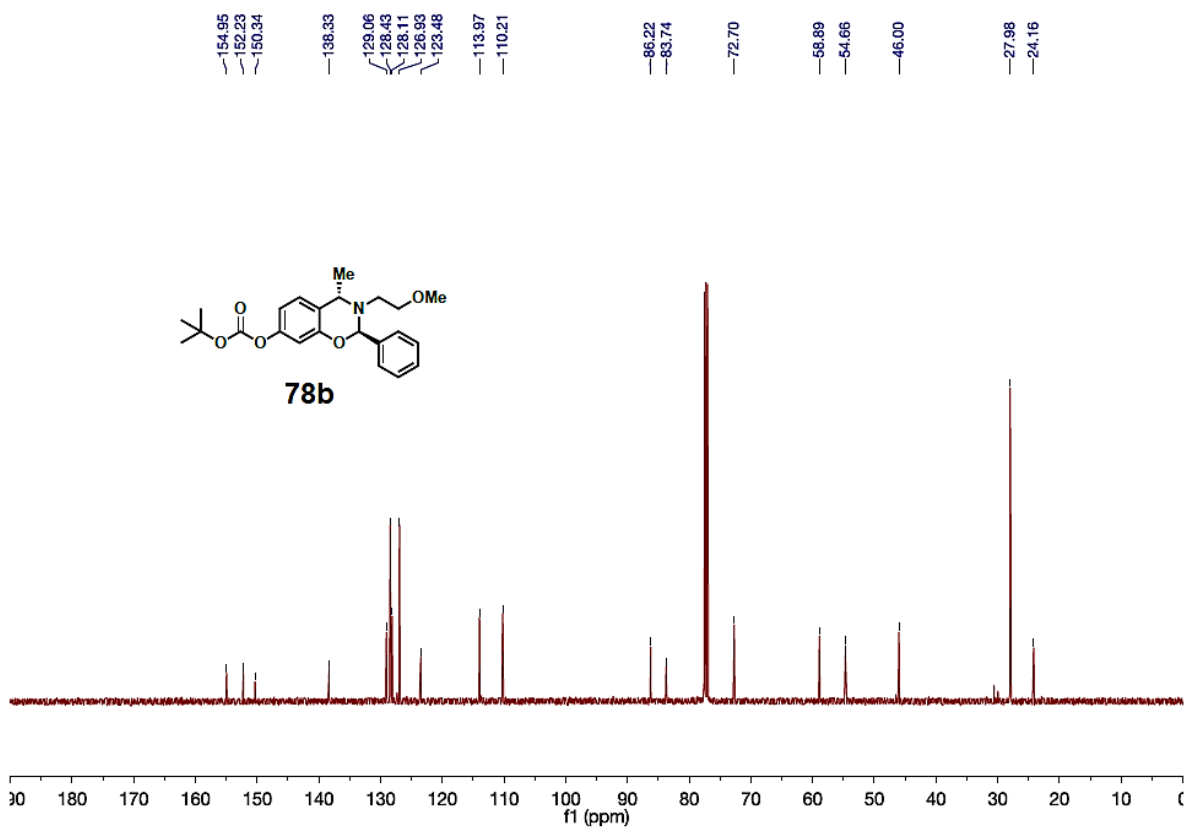

yuk-2-124B-crude-29a
5.945
5.144
4.905
3.325
3.315
3.304
3.293
3.282
3.272
3.261
1.571
Ph
N
BocO
O
77a (crude)
0.15
0.10
0.05
0
1.00
1.01
1.04
9.24
Chemical Shift (ppm)

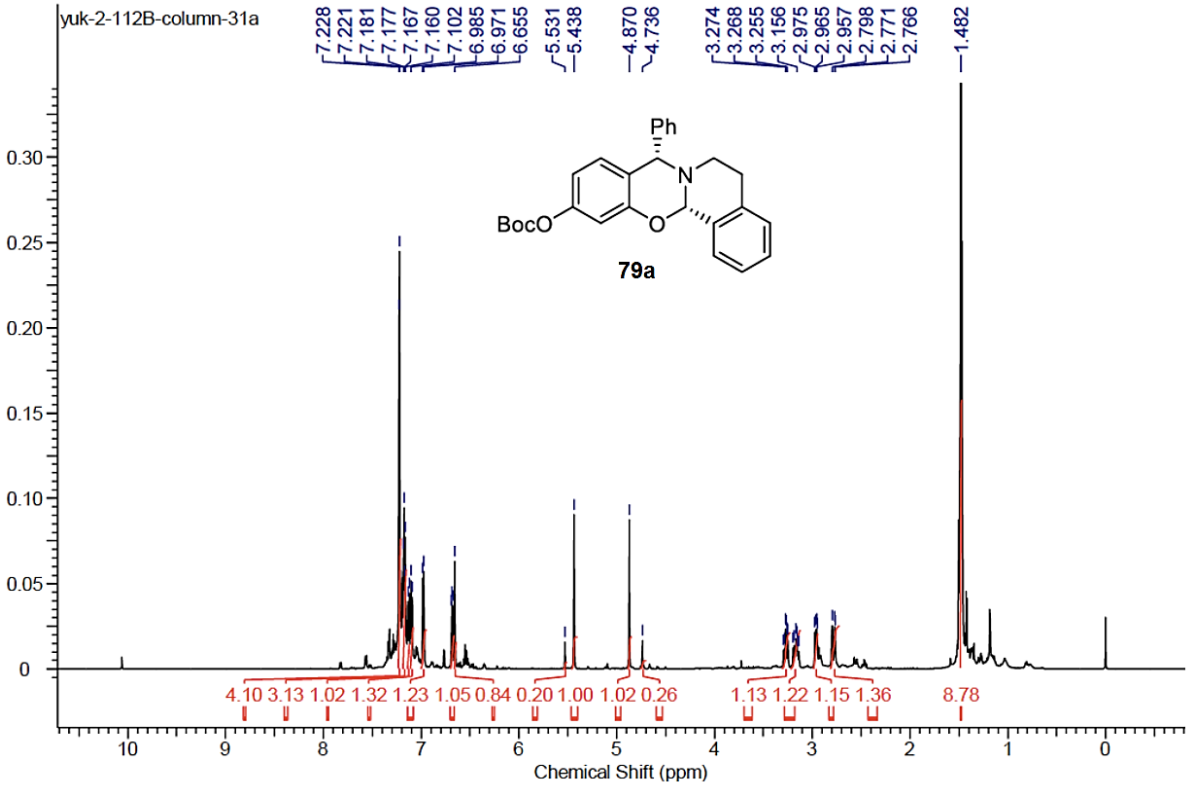

7.09
7.07
6.90
6.71
6.71
6.70
6.69
6.67
6.66
6.15
4.16
4.14
4.13
4.11
3.21
3.20
3.20
3.18
3.17
3.16
3.14
3.13
3.12
2.59
2.29
1.60
1.58
1.55
0.96
0.95
0.91
0.90
Me
N
O
O
O
O
77b
1.08
0.80
1.11
0.93
1.00
1.15
1.15
5.43
3.21
3.11
11.36
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

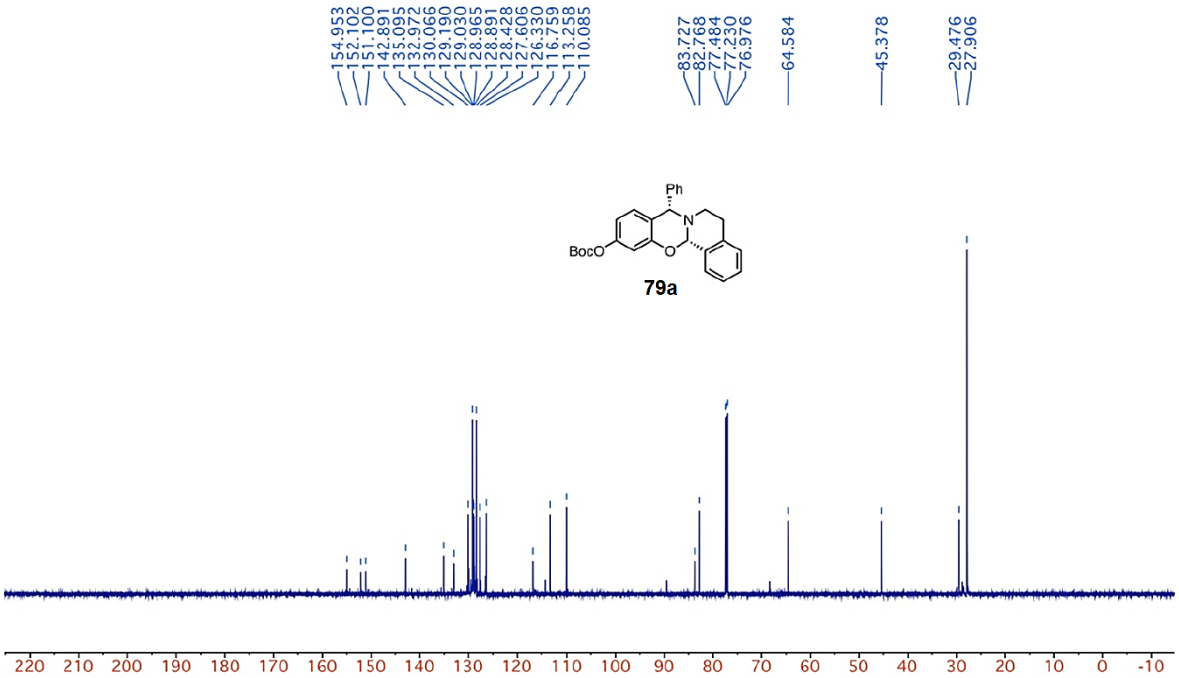

7.433
7.420
7.344
7.331
7.272
7.260
7.247
7.207
7.194
7.178
7.168
7.040
7.026
6.861
6.657
6.745
6.741
6.731
6.727
5.563
5.211
3.462
3.453
3.451
3.446
3.442
3.437
3.435
3.426
3.404
3.396
3.387
3.379
3.370
3.204
2.770
2.760
2.751
2.746
2.737
2.727
2.536
2.527
2.525
2.516
2.512
2.504
2.501
2.492
1.515
Ph
N
OMe
BocO
O
Ph
78a
2.02 2.47 0.842
1.99 1.16 1.1 0.983
0.954
0.987
1.08 2.98 1.05
1.01 1.04
ppm 10 9 8 7 6 5 4 3 2 1 0

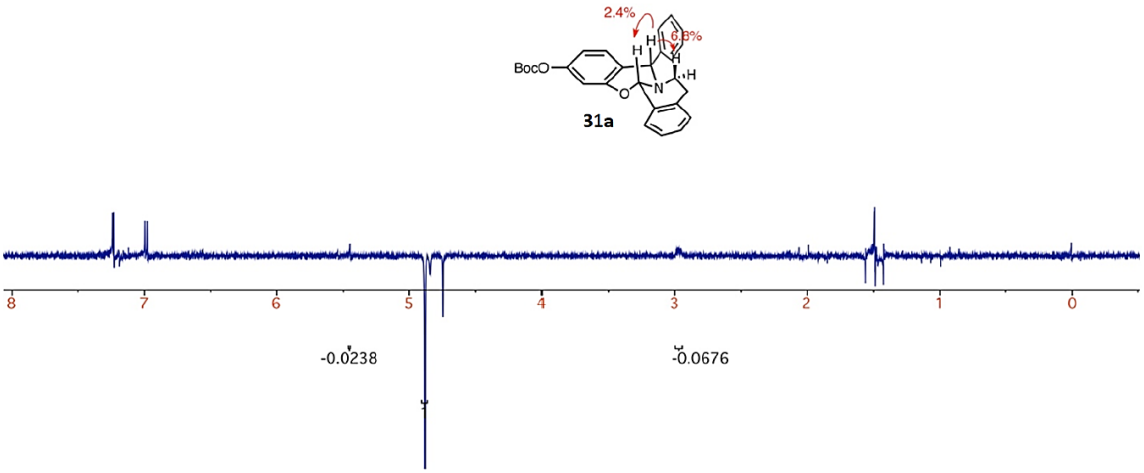

155.652
152.144
150.977
143.831
137.964
131.126
129.209
128.367
128.257
128.034
127.411
126.718
117.925
113.676
110.377
86.106
83.788
77.484
77.230
76.976
73.164
62.476
58.866
45.132
27.951
Ph
N
OMe
BocO
O
Ph
78a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

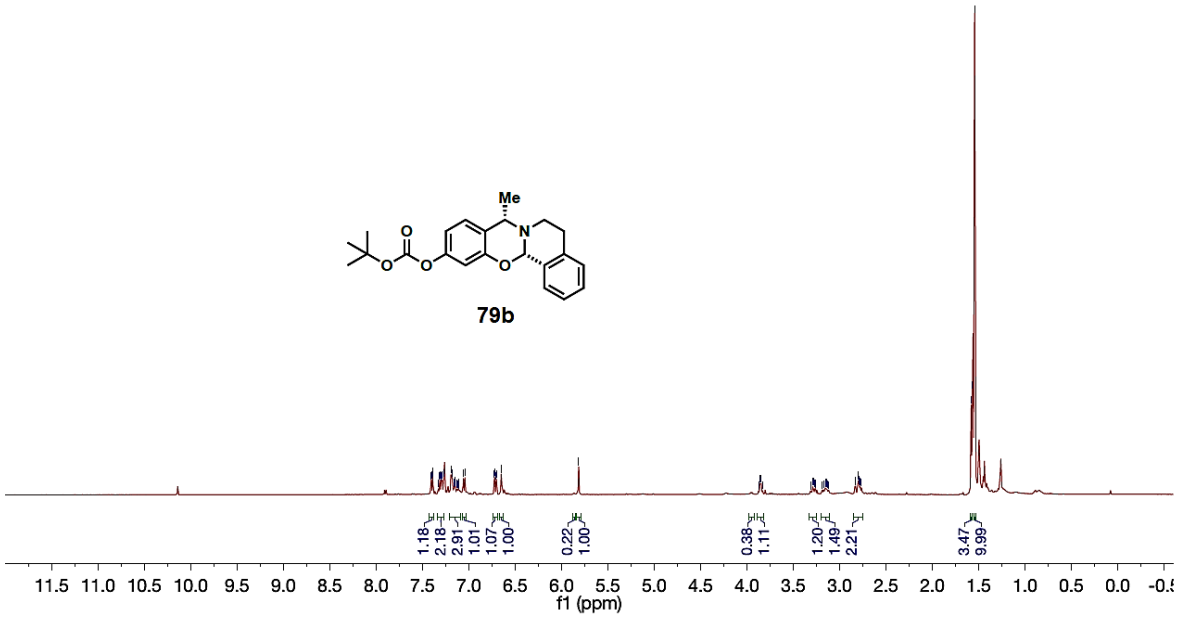

7.63
7.63
7.41
7.40
7.38
7.34
7.33
7.33
7.32
7.31
7.07
7.05
6.82
6.82
6.75
6.74
6.73
6.73
5.92
4.10
4.09
4.08
4.07
3.33
3.32
3.31
3.19
2.78
2.77
2.76
2.76
2.75
2.74
2.43
2.42
2.41
2.41
2.40
2.39
1.59
1.58
1.57
Me
OMe
78b
1.96
2.02
1.13
1.08
0.95
1.07
1.00
1.08
2.00
2.92
1.12
1.12
3.07
8.62
f1 (ppm)

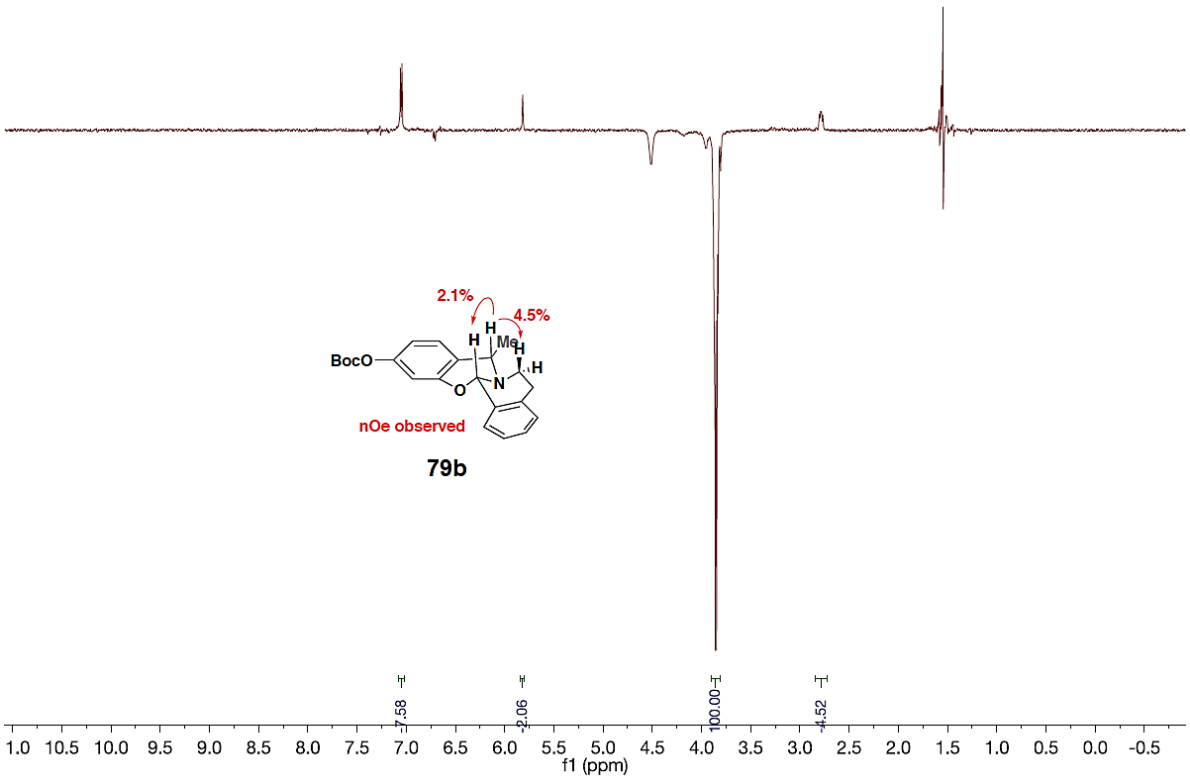

154.95
152.23
150.34
138.33
129.06
128.43
128.11
126.93
123.48
113.97
110.21
86.22
83.74
72.70
58.89
54.66
46.00
27.98
24.16
Me
OMe
78b
f1 (ppm)

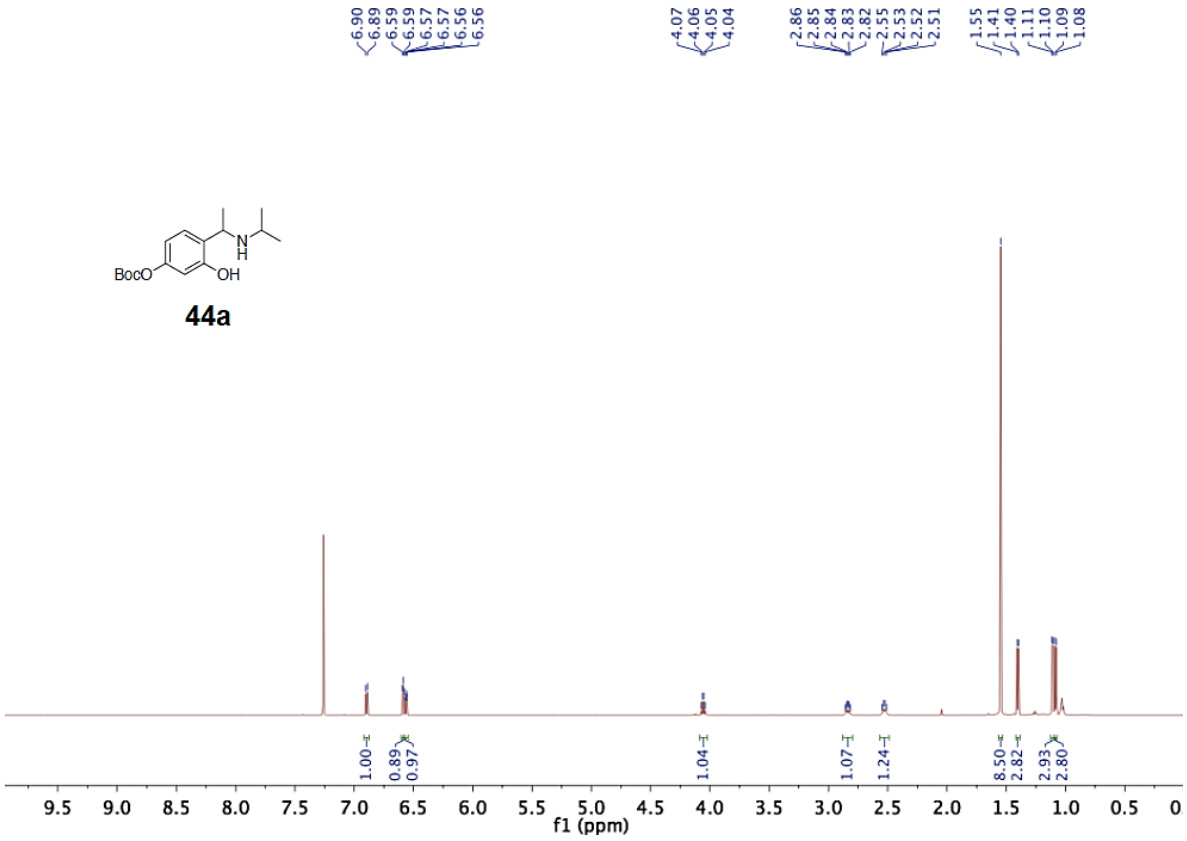

yuk-2-112B-column-31a
7.228
7.221
7.181
7.177
7.167
7.160
7.102
6.985
6.971
6.655
5.531
5.438
4.870
4.736
3.274
3.268
3.255
3.156
2.975
2.965
2.957
2.798
2.771
2.766
1.482
Ph
N
O
BocO
79a
4.10 3.13 1.02 1.32 1.23 1.05 0.84 0.20 1.00 1.02 0.26 1.13 1.22 1.15 1.36 8.78
Chemical Shift (ppm)

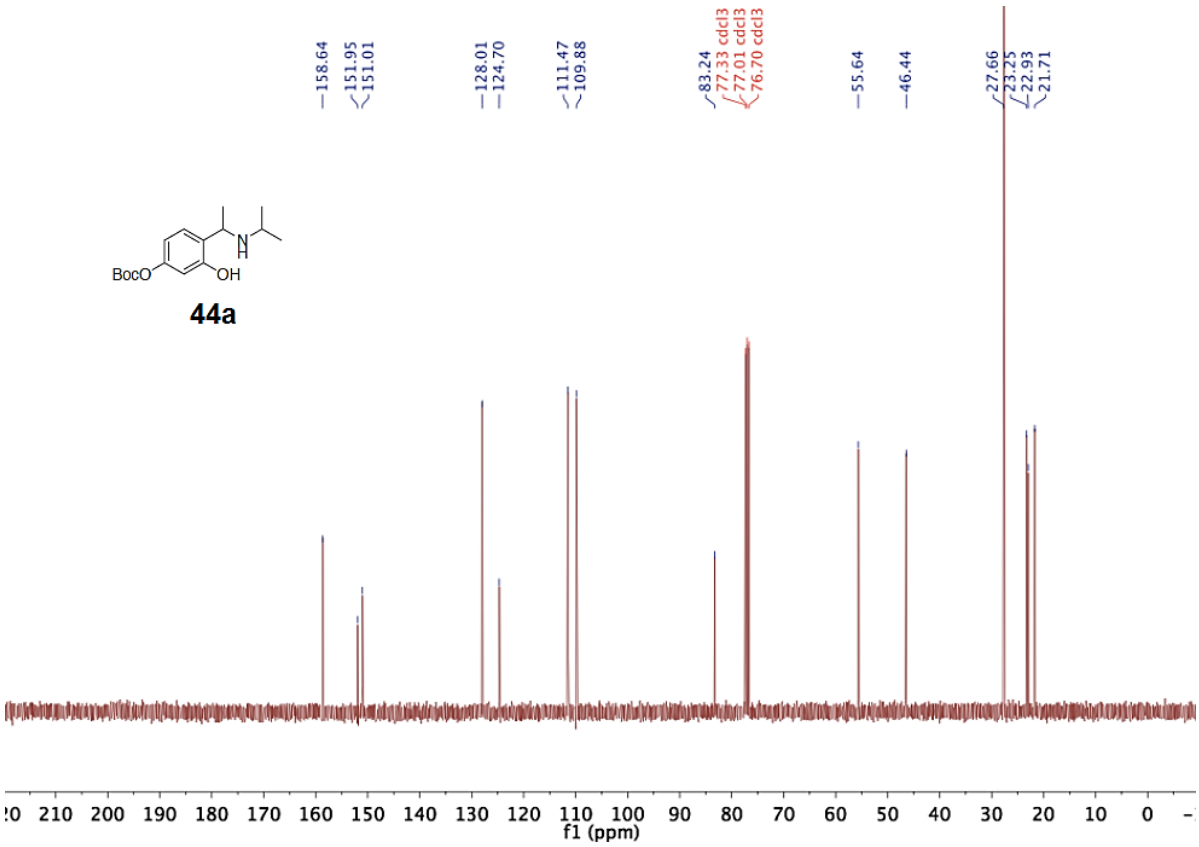

154.953
152.102
151.100
142.891
135.095
132.972
130.066
129.190
129.030
128.965
128.891
128.428
127.606
126.330
116.759
113.258
110.085
83.727
82.768
77.484
77.230
76.976
64.584
45.378
29.476
27.906
Ph
N
O
BocO
79a

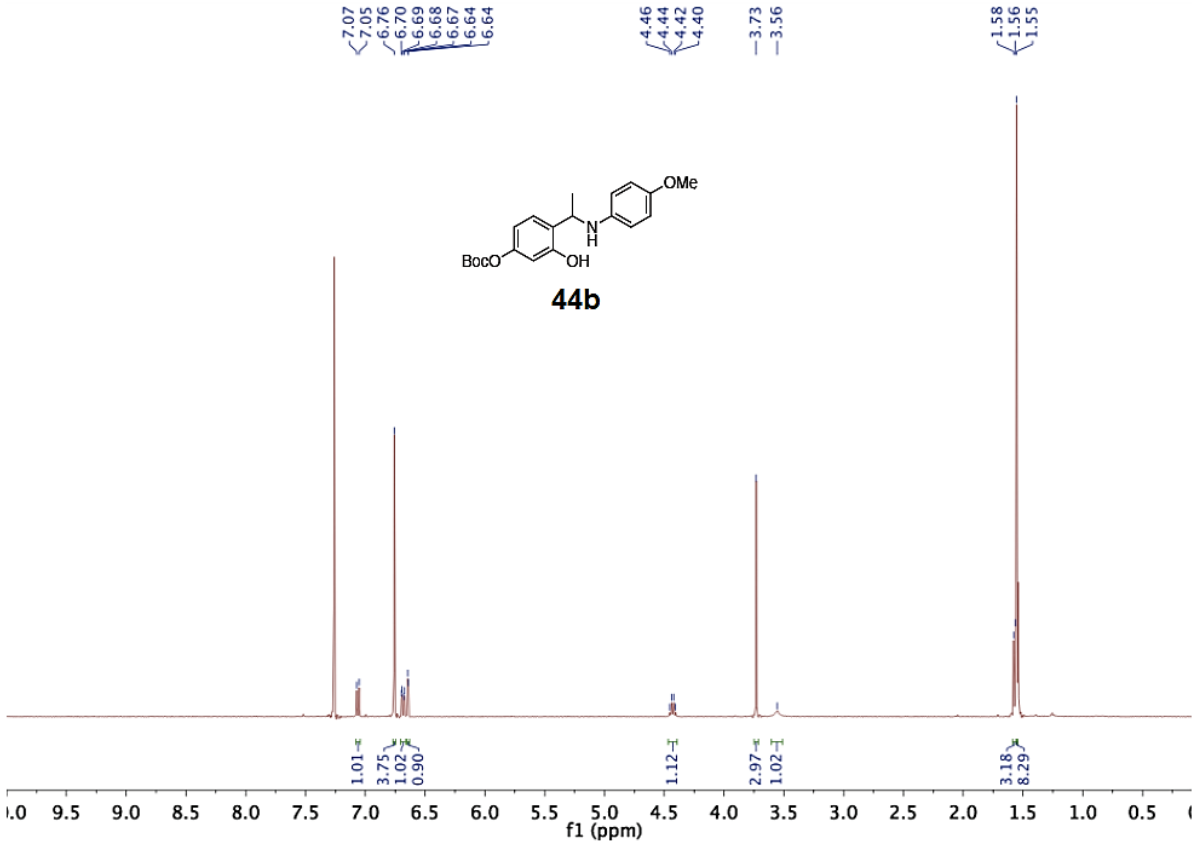

2.4%
6.8%
BocO
H
H
H
N
O
31a
8
7
6
5
4
3
2
1
0
-0.0238
-0.0676

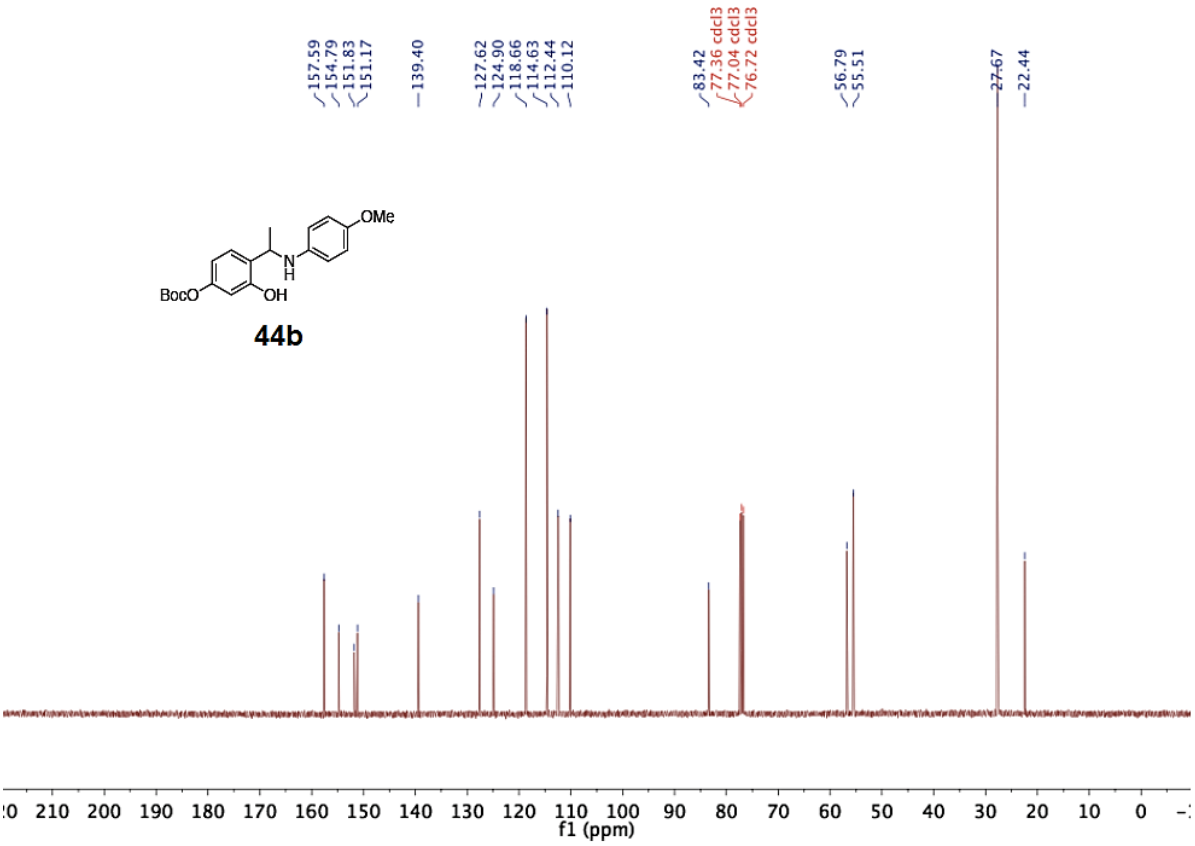

Me
O
O
O
N
O
79b
1.18
2.18
2.91
1.01
1.07
1.00
0.22
1.00
0.38
1.11
1.20
1.49
2.21
3.47
9.99
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

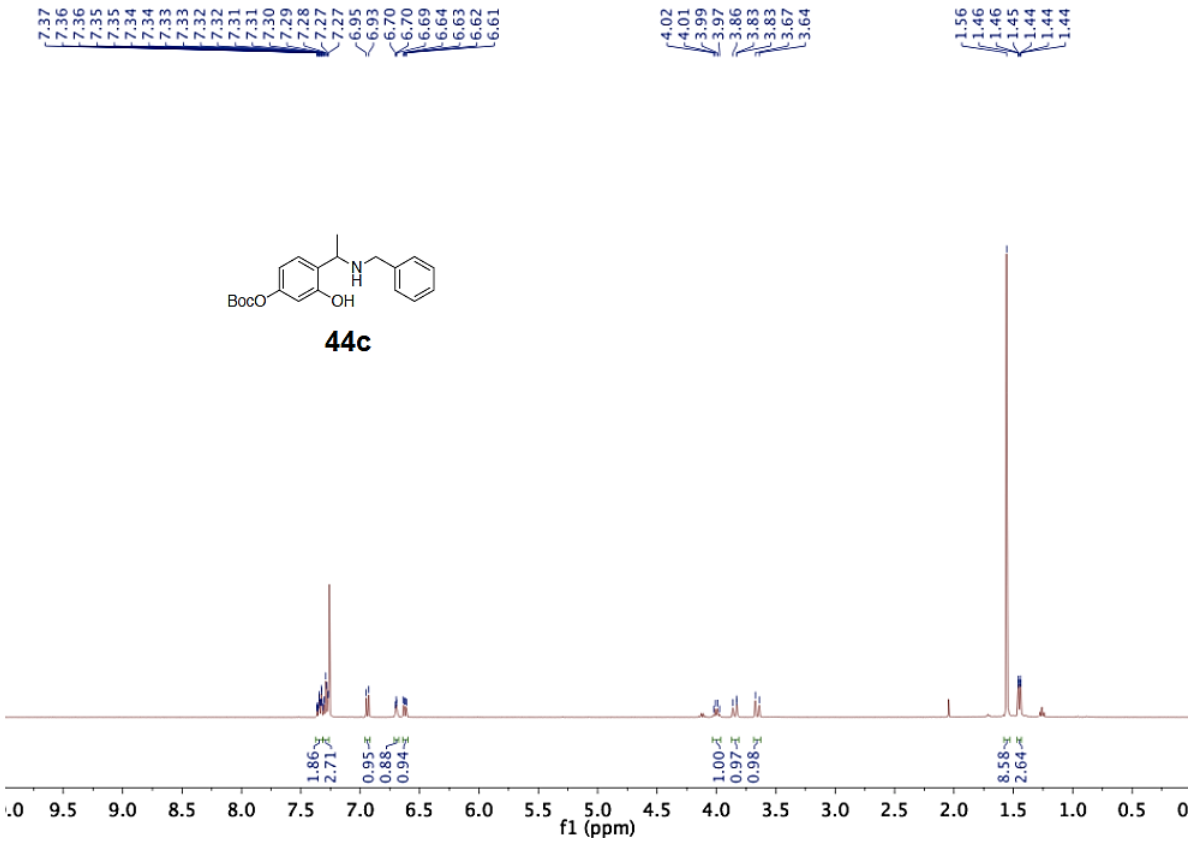

2.1%
4.5%
H
H
Me
H
H
BocO
N
O
nOe observed
79b
7.58
2.06
100.00
4.52
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

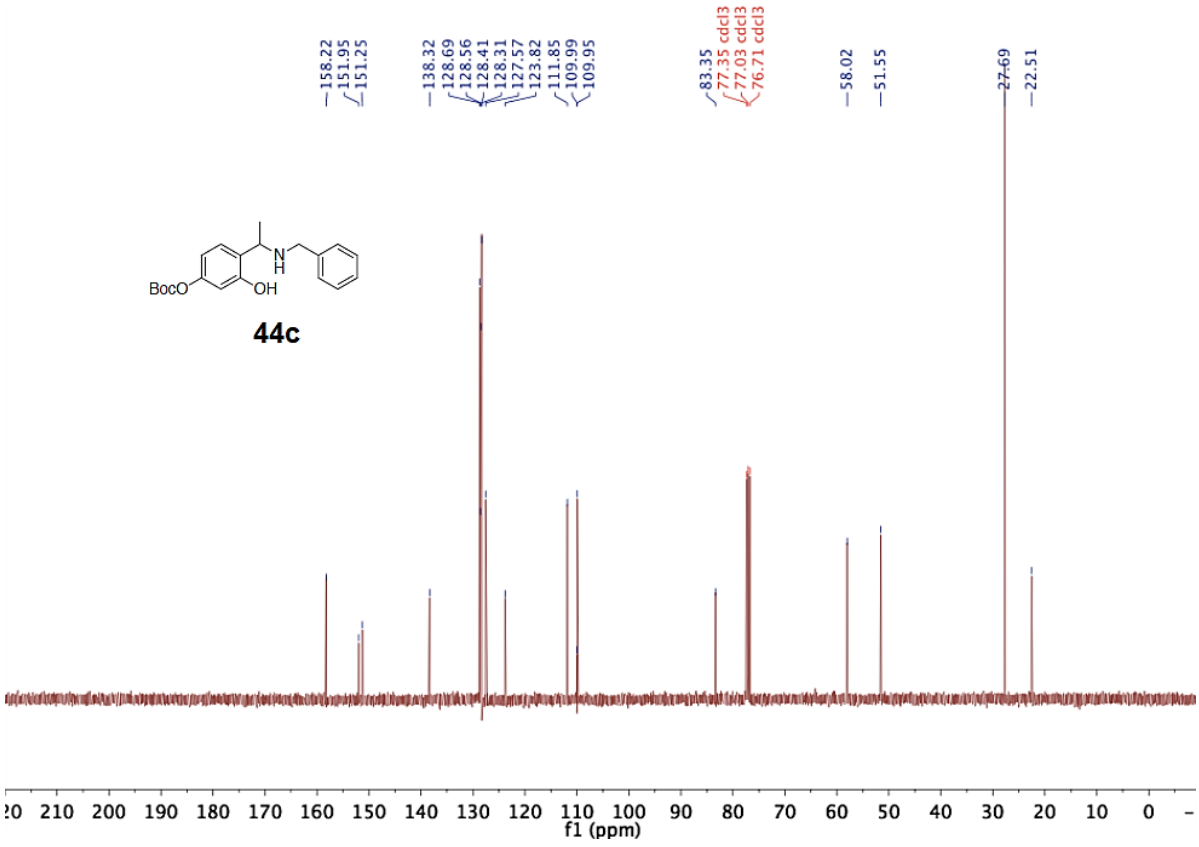

6.90
6.89
6.59
6.59
6.57
6.57
6.56
6.56
4.07
4.06
4.05
4.04
2.86
2.85
2.84
2.83
2.82
2.55
2.53
2.52
2.51
1.55
1.41
1.40
1.11
1.10
1.09
1.08
BocO
OH
44a
1.00
0.89
0.97
1.04
1.07
1.24
8.50
2.82
2.93
2.80
f1 (ppm)

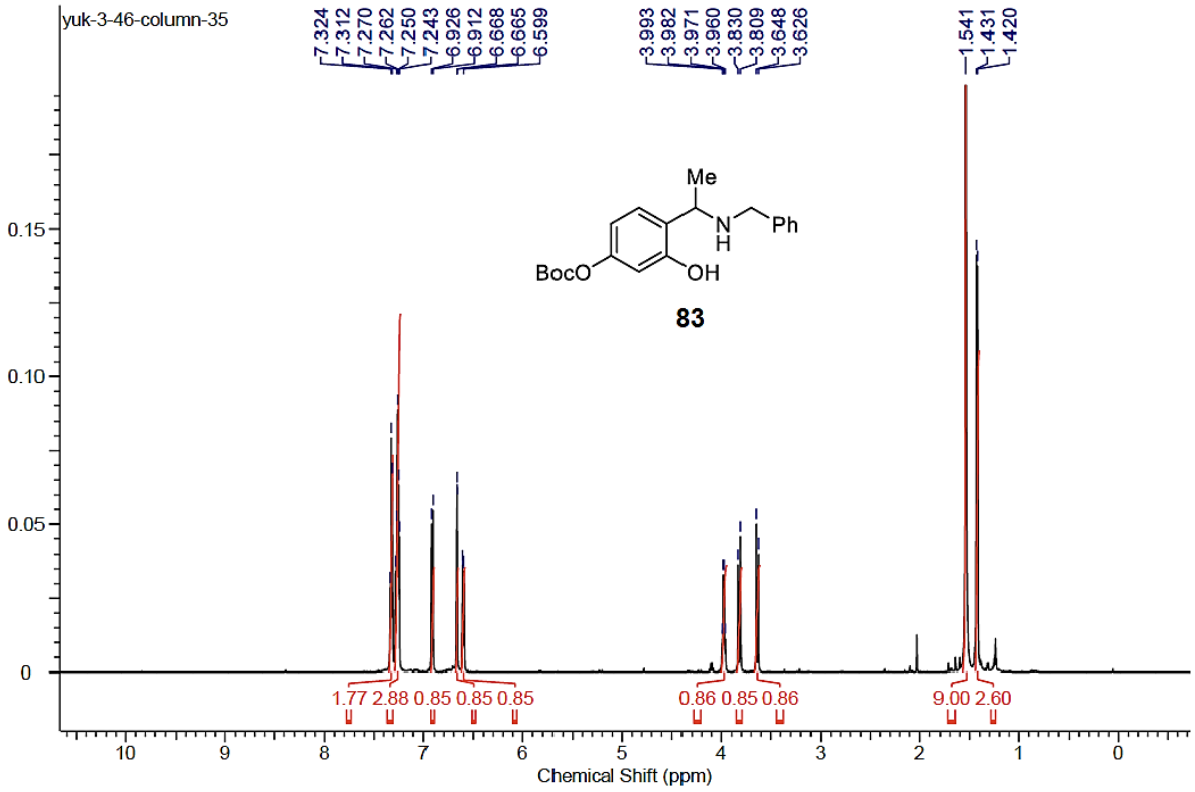

158.64
151.95
151.01
128.01
124.70
111.47
109.88
83.24
77.33 cdcl3
77.01 cdcl3
76.70 cdcl3
55.64
46.44
27.66
23.25
22.93
21.71
BocO
OH
44a
f1 (ppm)

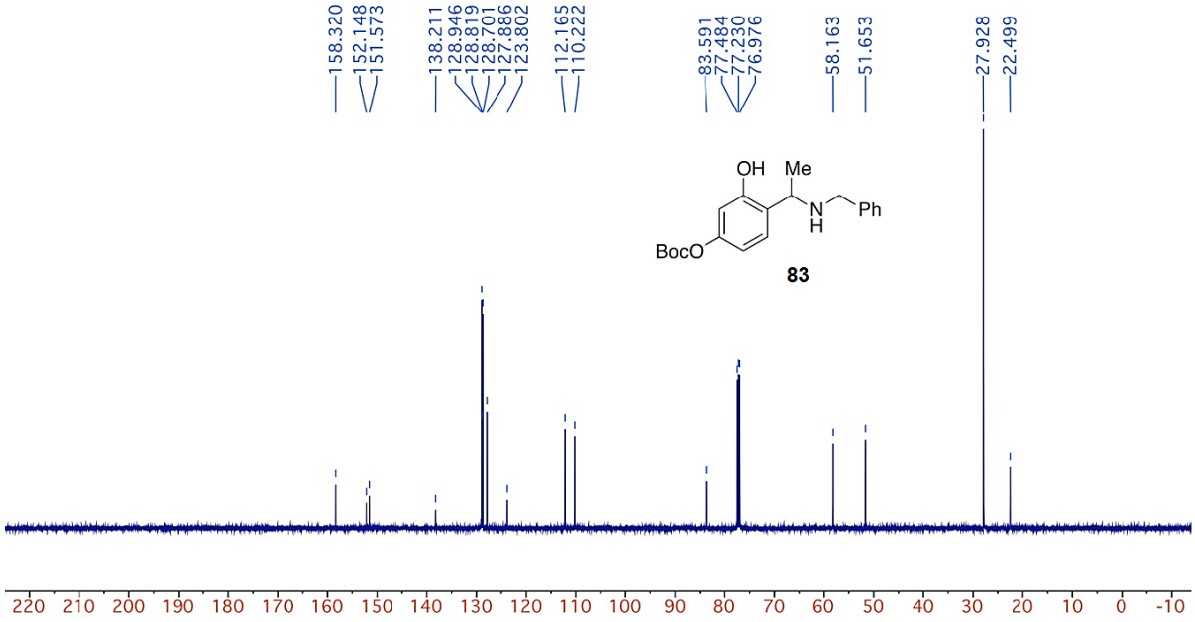

7.07
7.05
6.76
6.70
6.69
6.68
6.67
6.64
6.64
4.46
4.44
4.42
4.40
3.73
3.56
1.58
1.56
1.55
OMe
N
H
BocO
OH
44b
1.01
3.75
1.02
0.90
1.12
2.97
1.02
3.18
8.29
f1 (ppm)

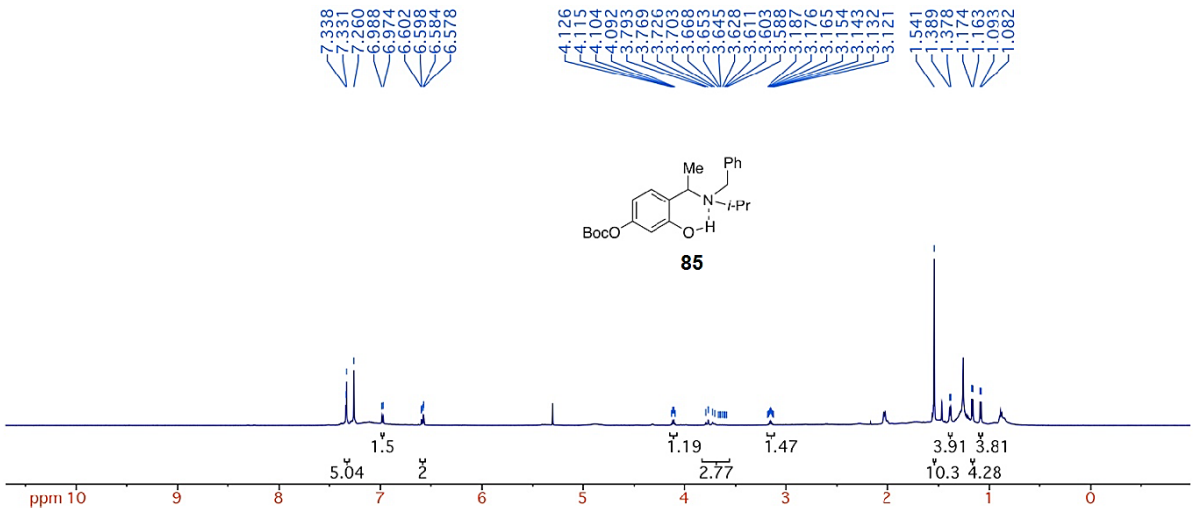

157.59
154.79
151.83
151.17
139.40
127.62
124.90
118.66
114.63
112.44
110.12
83.42
77.36 cdcl3
77.04 cdcl3
76.72 cdcl3
56.79
55.51
27.67
22.44
OMe
N
H
BocO
OH
44b
f1 (ppm)


7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.29
7.28
7.27
7.27
6.95
6.93
6.70
6.70
6.69
6.64
6.63
6.62
6.61
4.02
4.01
3.99
3.97
3.86
3.83
3.83
3.67
3.64
1.56
1.46
1.46
1.45
1.44
1.44
1.44
BocO
OH
N
H
44c
1.86
2.71
0.95
0.88
0.94
1.00
0.97
0.98
8.58
2.64
f1 (ppm)


158.22
151.95
151.25
138.32
128.69
128.56
128.41
128.31
127.57
123.82
111.85
109.99
109.95
83.35
77.35 cdcl3
77.03 cdcl3
76.71 cdcl3
58.02
51.55
27.69
22.51
BocO
OH
N
H
44c
f1 (ppm)


yuk-3-46-column-35
7.324
7.312
7.270
7.262
7.250
7.243
6.926
6.912
6.668
6.665
6.599
3.993
3.982
3.971
3.960
3.830
3.809
3.648
3.626
1.541
1.431
1.420
Me
N
H
Ph
BocO
OH
83
0.15
0.10
0.05
0
1.77 2.88 0.85 0.85 0.85
0.86 0.85 0.86
9.00 2.60
10 9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)


158.320
152.148
151.573
138.211
128.946
128.819
128.701
127.886
123.802
112.165
110.222
83.591
77.484
77.230
76.976
58.163
51.653
27.928
22.499
OH
Me
N
H
Ph
BocO
83
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


7.338
7.331
7.260
6.988
6.974
6.602
6.598
6.584
6.578
4.126
4.115
4.104
4.092
3.793
3.769
3.726
3.703
3.668
3.653
3.645
3.628
3.611
3.603
3.588
3.187
3.176
3.165
3.154
3.143
3.132
3.121
1.541
1.389
1.378
1.174
1.163
1.093
1.082
Me
Ph
N
i-Pr
H
O
BocO
85
1.5
2
1.19
1.47
3.91
3.81
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10.3
4.28
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8
7
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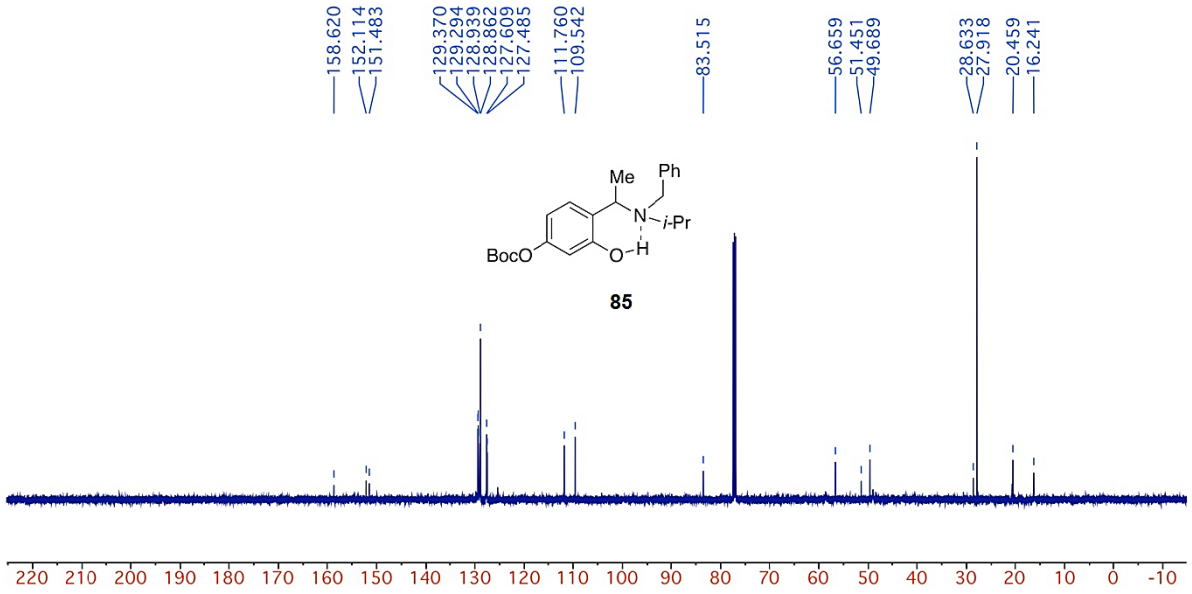
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152.114
151.483
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128.862
127.609
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111.760
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83.515
56.659
51.451
49.689
28.633
27.918
20.459
16.241
Me
Ph
N
i-Pr
H
O
BocO
85
220
210
200
190
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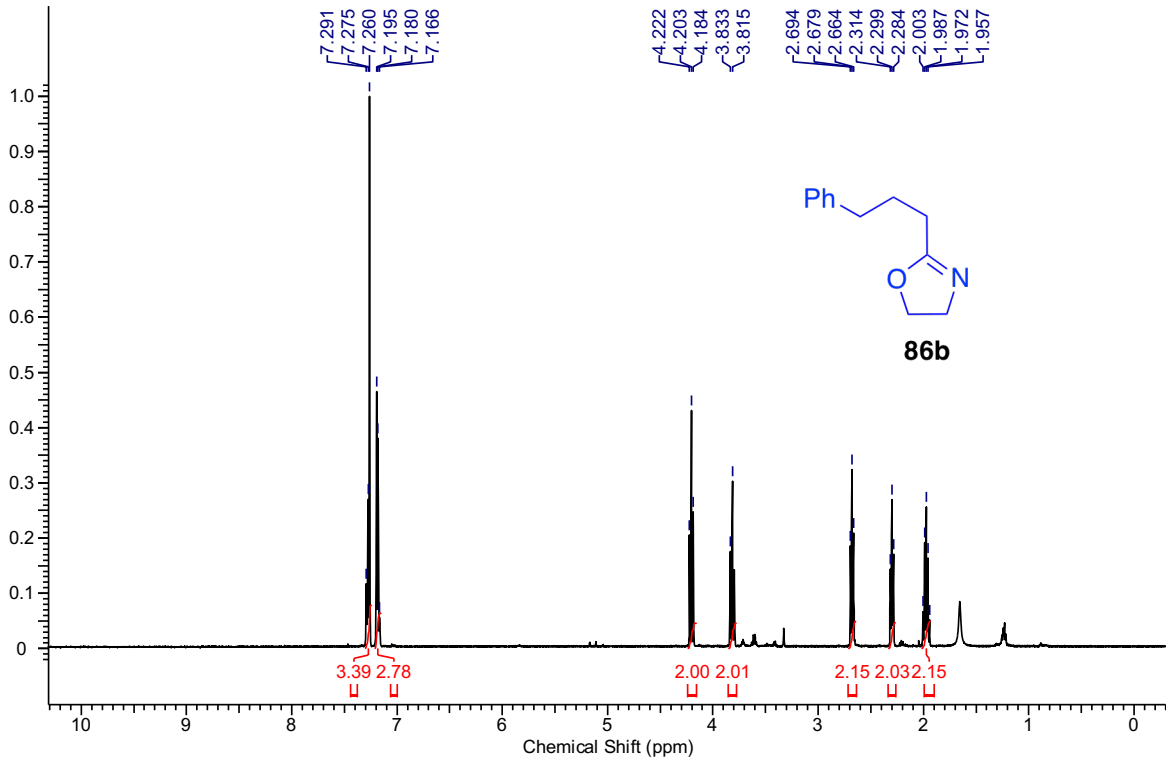
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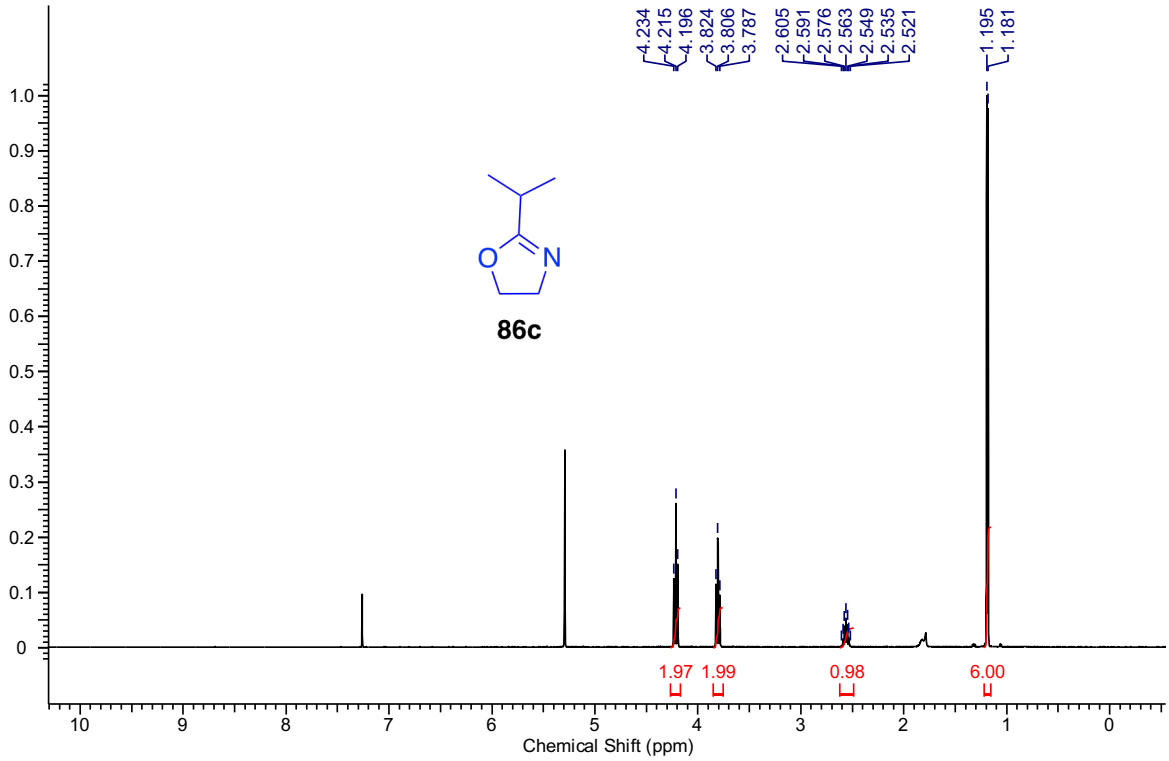
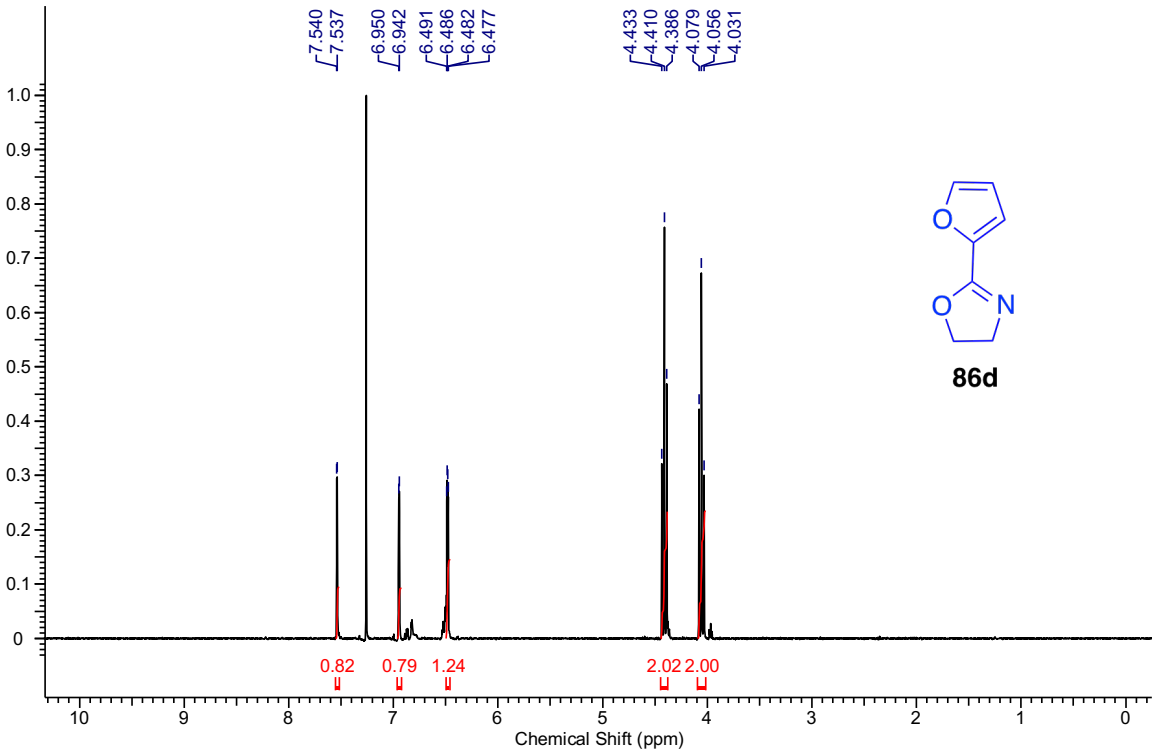
7.275
7.260
7.195
7.180
7.166
4.222
4.203
4.184
3.833
3.815
2.694
2.679
2.664
2.314
2.299
2.284
2.003
1.987
1.972
1.957
Ph
O
N
86b
3.39 2.78
2.00 2.01
2.15 2.03 2.15
Chemical Shift (ppm)


4.234
4.215
4.196
3.824
3.806
3.787
2.605
2.591
2.576
2.563
2.549
2.535
2.521
1.195
1.181
O
N
86c
1.97 1.99
0.98
6.00
Chemical Shift (ppm)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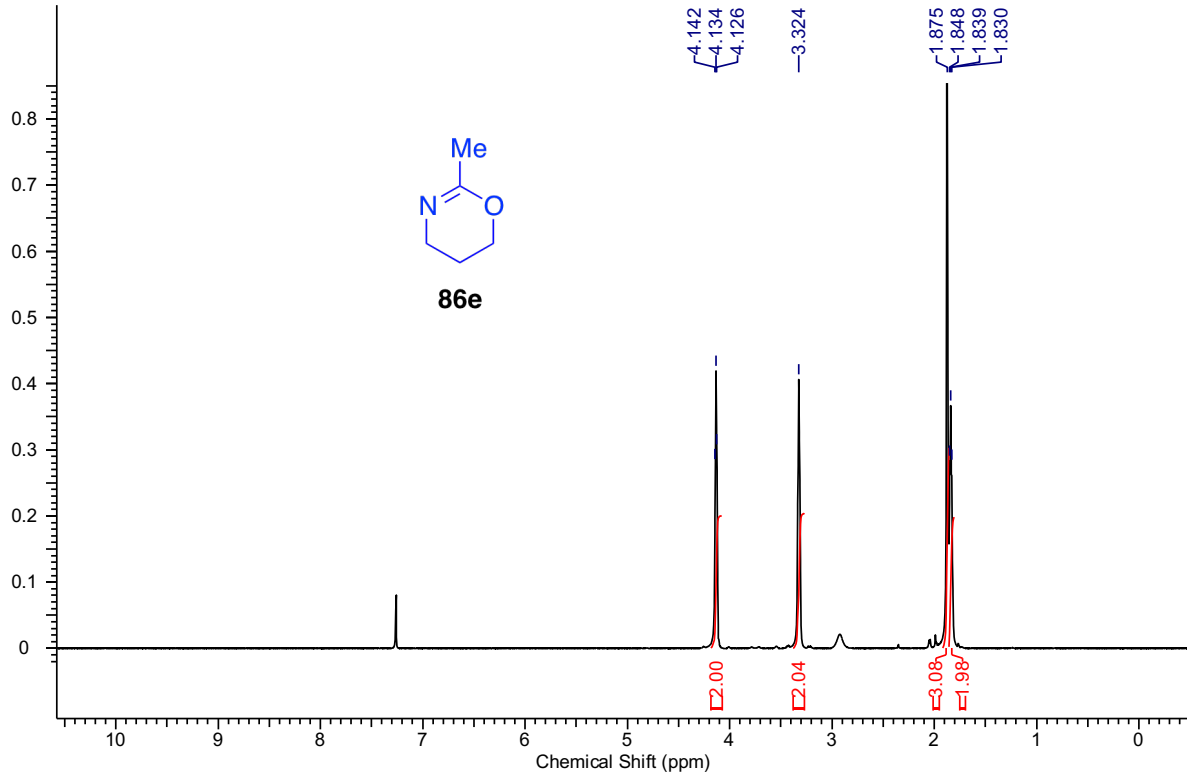
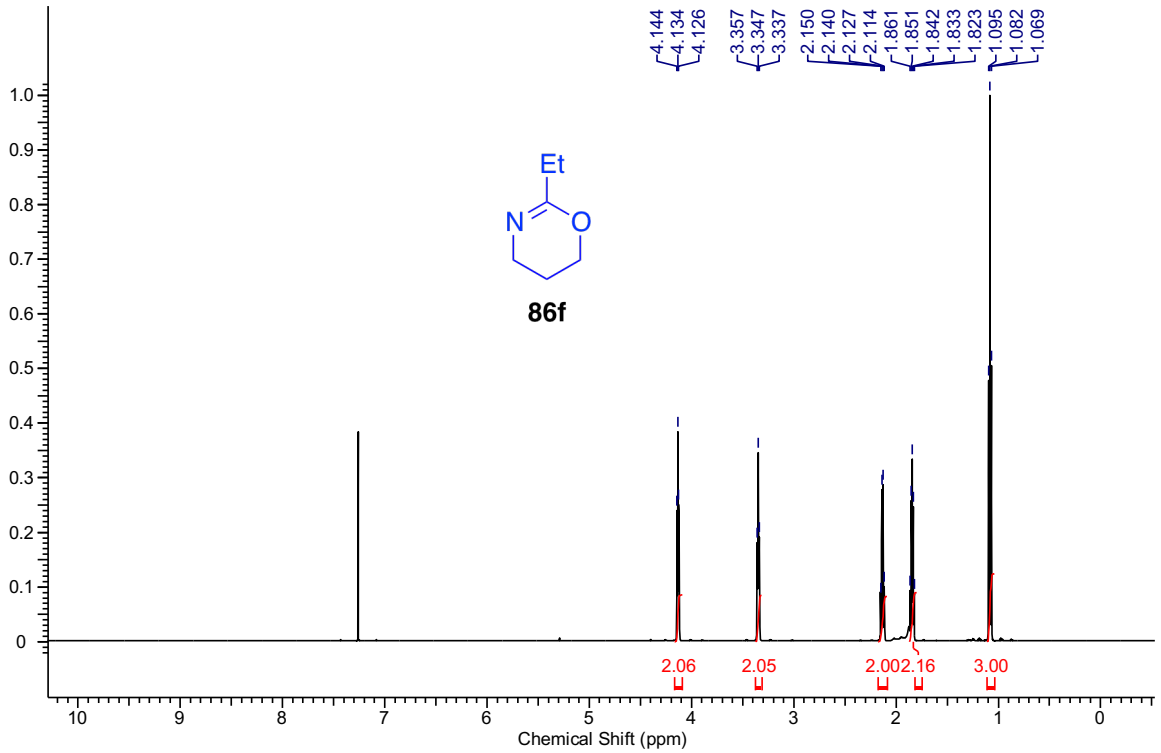
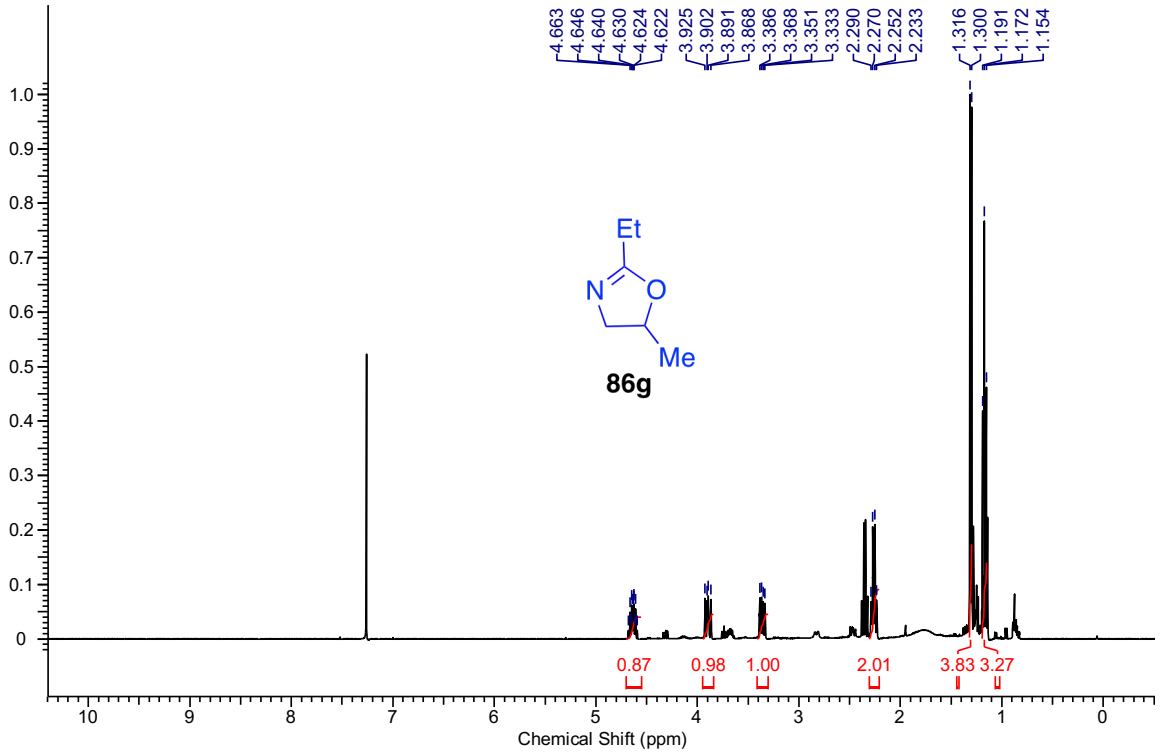
7.537
6.950
6.942
6.491
6.486
6.482
6.477
4.433
4.410
4.386
4.079
4.056
4.031
0.82
0.79
1.24
2.02
2.00
Chemical Shift (ppm)
86d


4.142
4.134
4.126
3.324
1.875
1.848
1.839
1.830
Me
86e
2.00
2.04
3.08
1.98
Chemical Shift (ppm)


4.144
4.134
4.126
3.357
3.347
3.337
2.150
2.140
2.127
2.114
1.861
1.851
1.842
1.833
1.823
1.095
1.082
1.069
Et
N
O
86f
2.06
2.05
2.00
2.16
3.00
Chemical Shift (ppm)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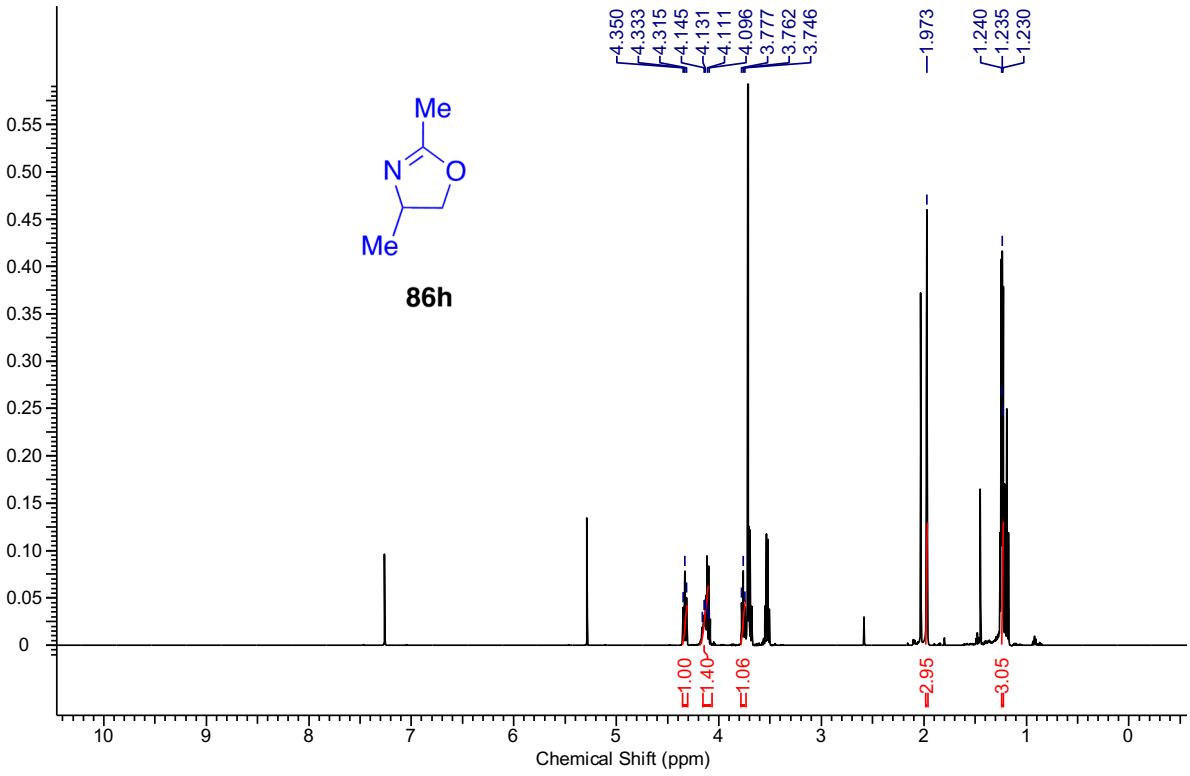
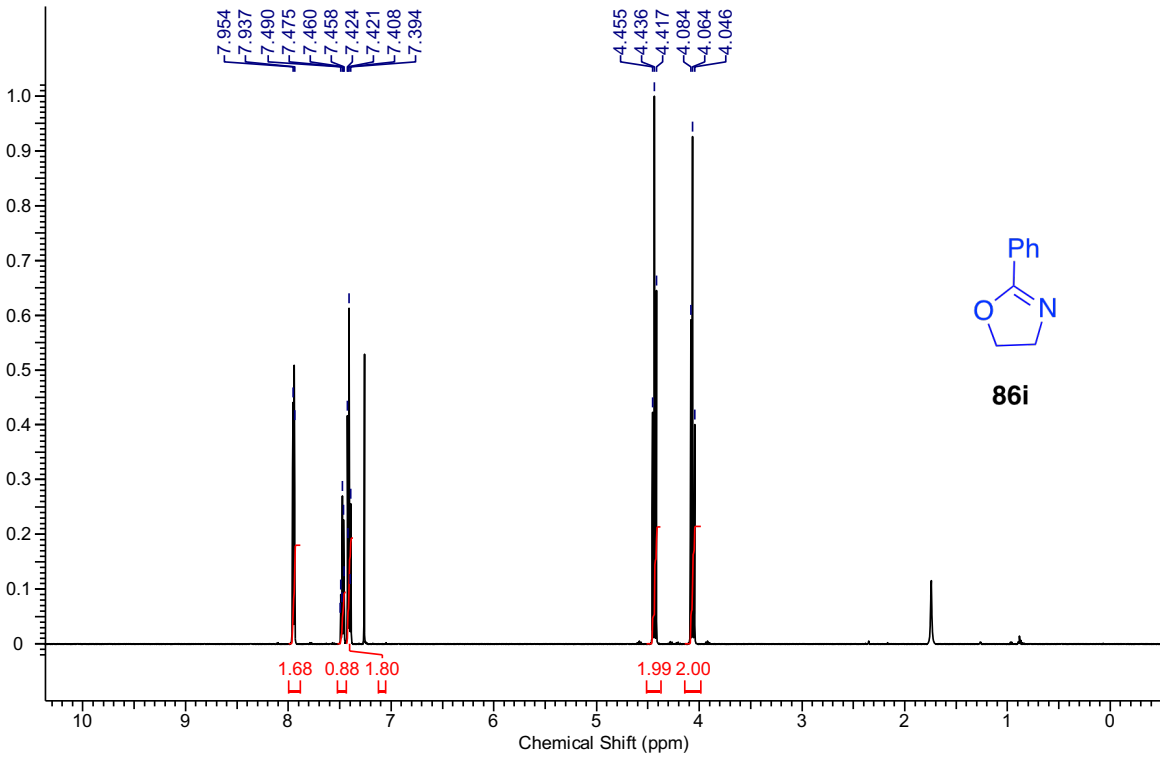
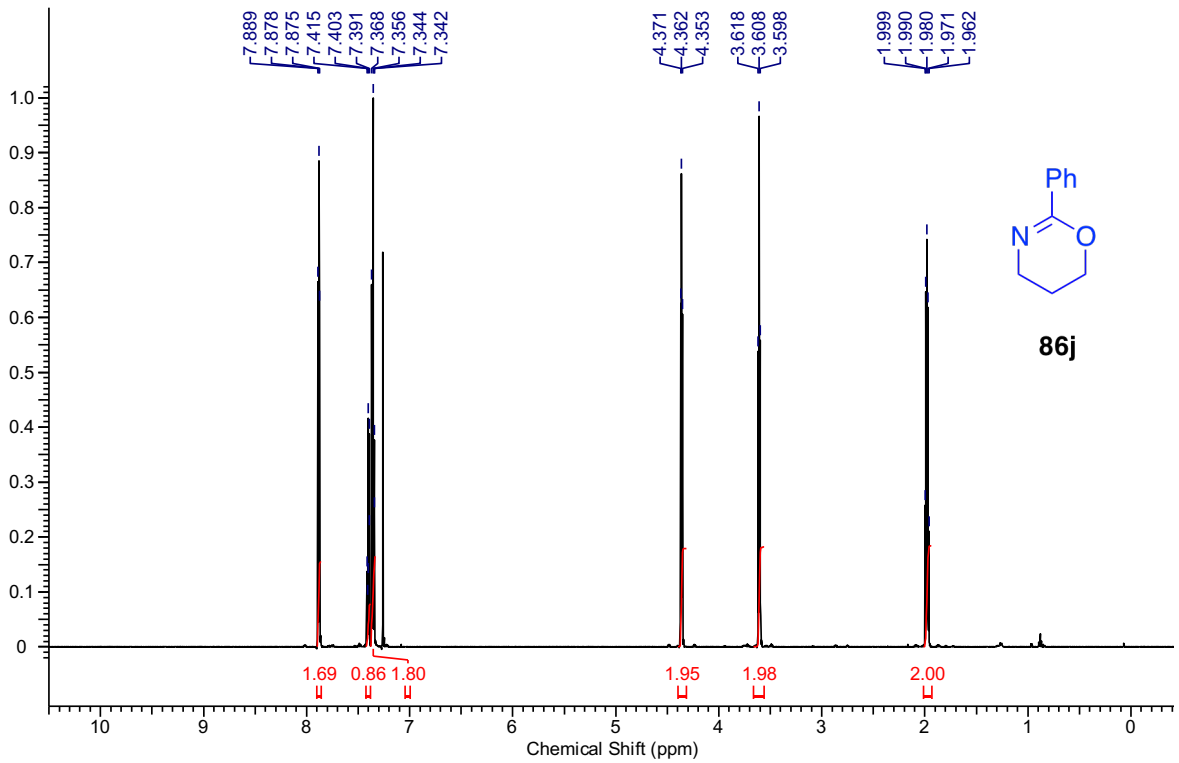
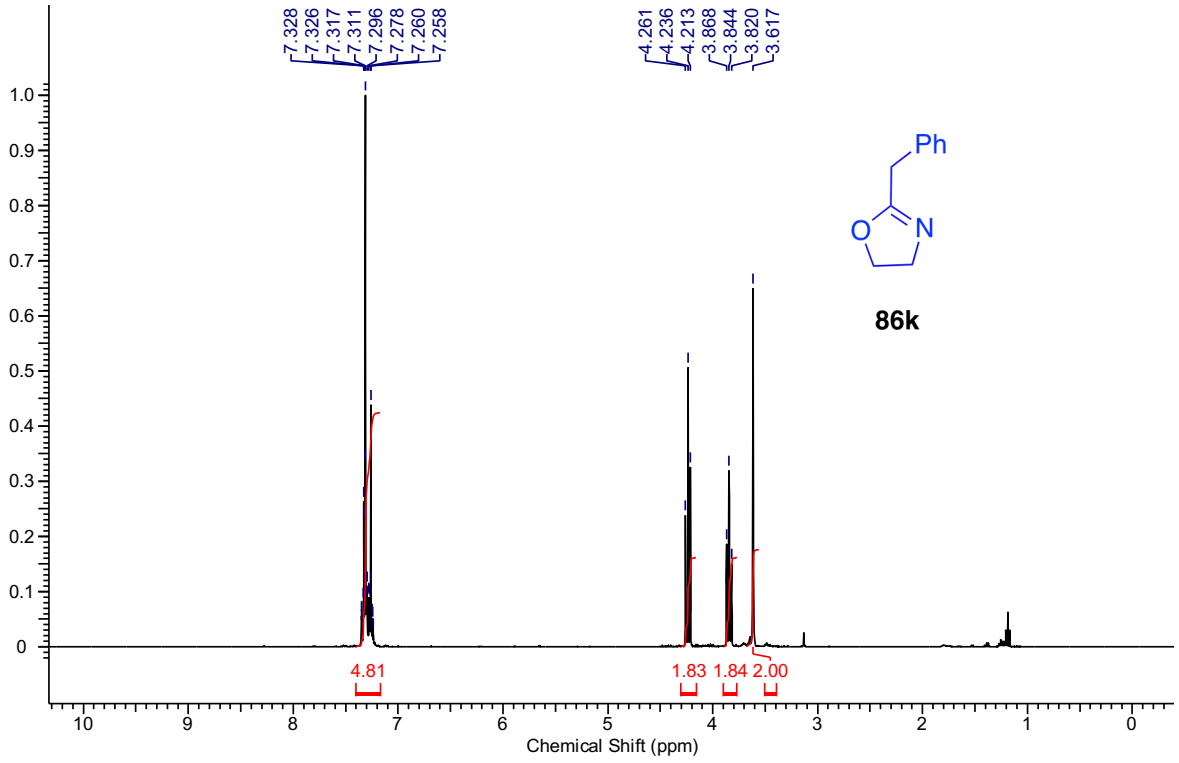
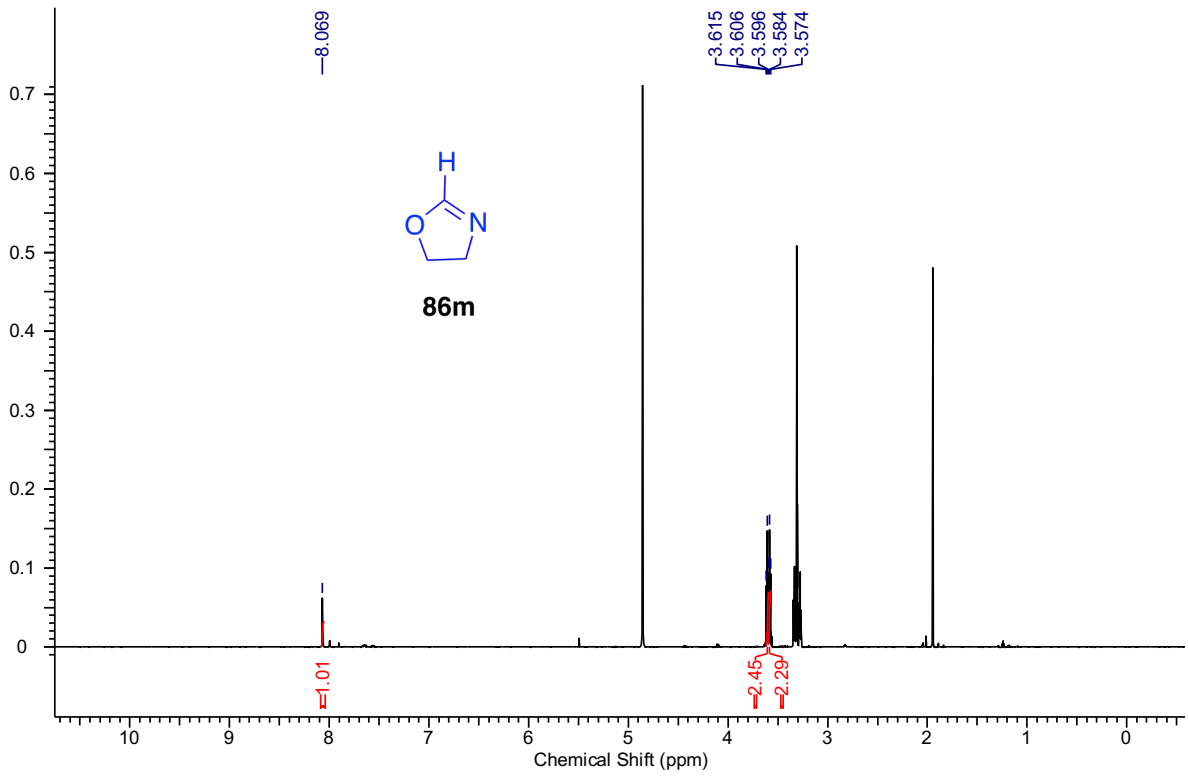
4.646
4.640
4.630
4.624
4.622
3.925
3.902
3.891
3.868
3.386
3.368
3.351
3.333
2.290
2.270
2.252
2.233
1.316
1.300
1.191
1.172
1.154
Et
N
O
Me
86g
0.87
0.98
1.00
2.01
3.83
3.27
Chemical Shift (ppm)

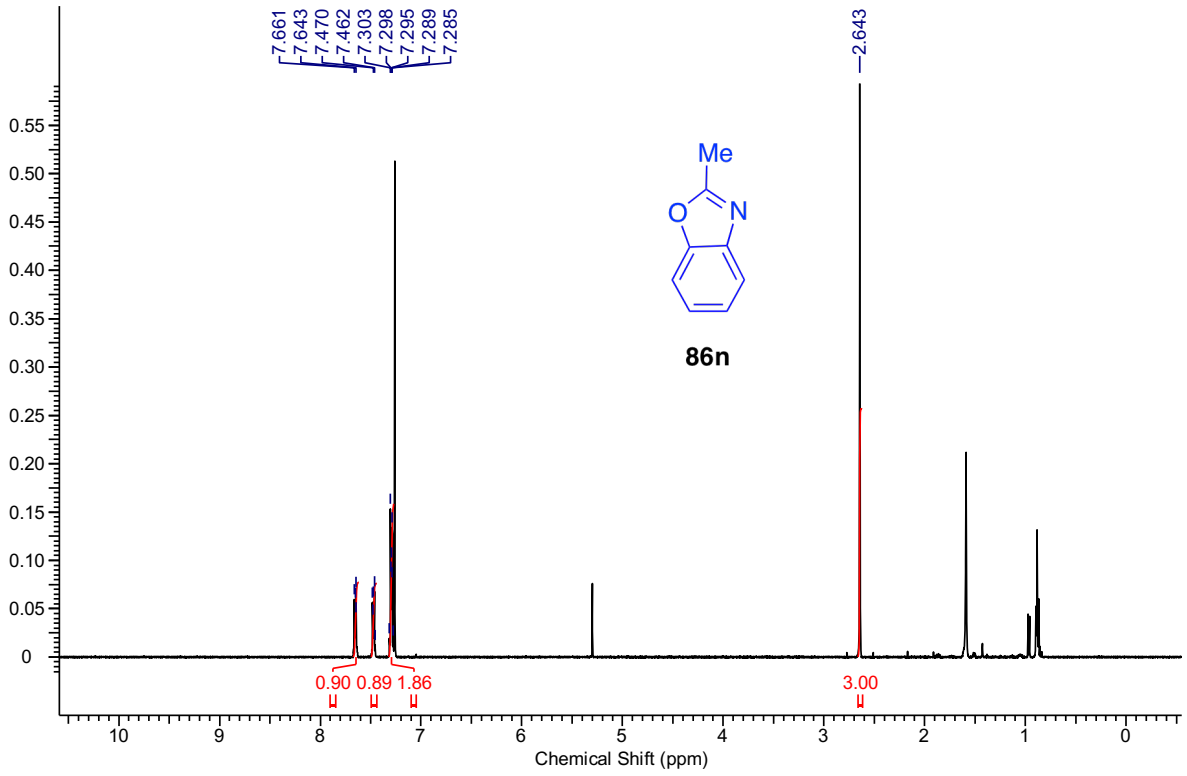

4.350
4.333
4.315
4.145
4.131
4.111
4.096
3.777
3.762
3.746
1.973
1.240
1.235
1.230
Me
N
O
Me
86h
1.00
1.40
1.06
2.95
3.05
Chemical Shift (ppm)

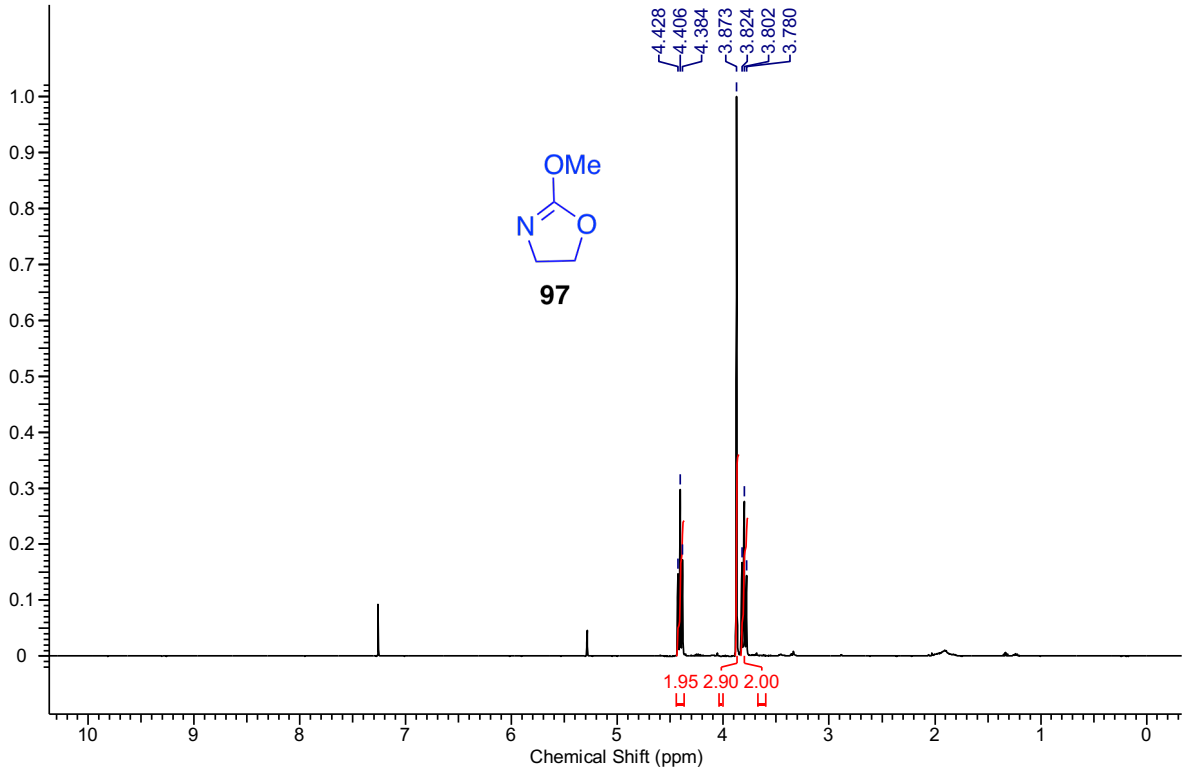

7.954
7.937
7.490
7.475
7.460
7.458
7.424
7.421
7.408
7.394
4.455
4.436
4.417
4.084
4.064
4.046
Ph
O
N
86i
1.68
0.88
1.80
1.99
2.00
Chemical Shift (ppm)

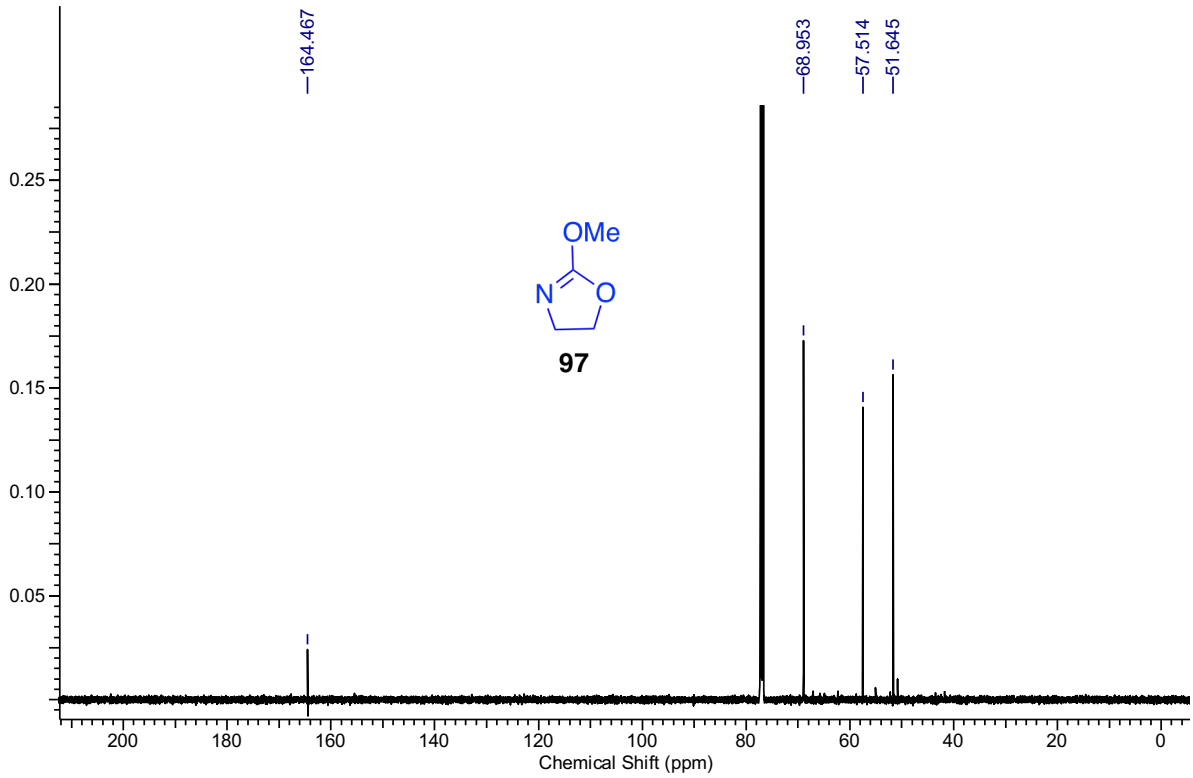

7.889
7.878
7.875
7.415
7.403
7.391
7.368
7.356
7.344
7.342
4.371
4.362
4.353
3.618
3.608
3.598
1.999
1.990
1.980
1.971
1.962
Ph
N
O
86j
1.69
0.86
1.80
1.95
1.98
2.00
Chemical Shift (ppm)

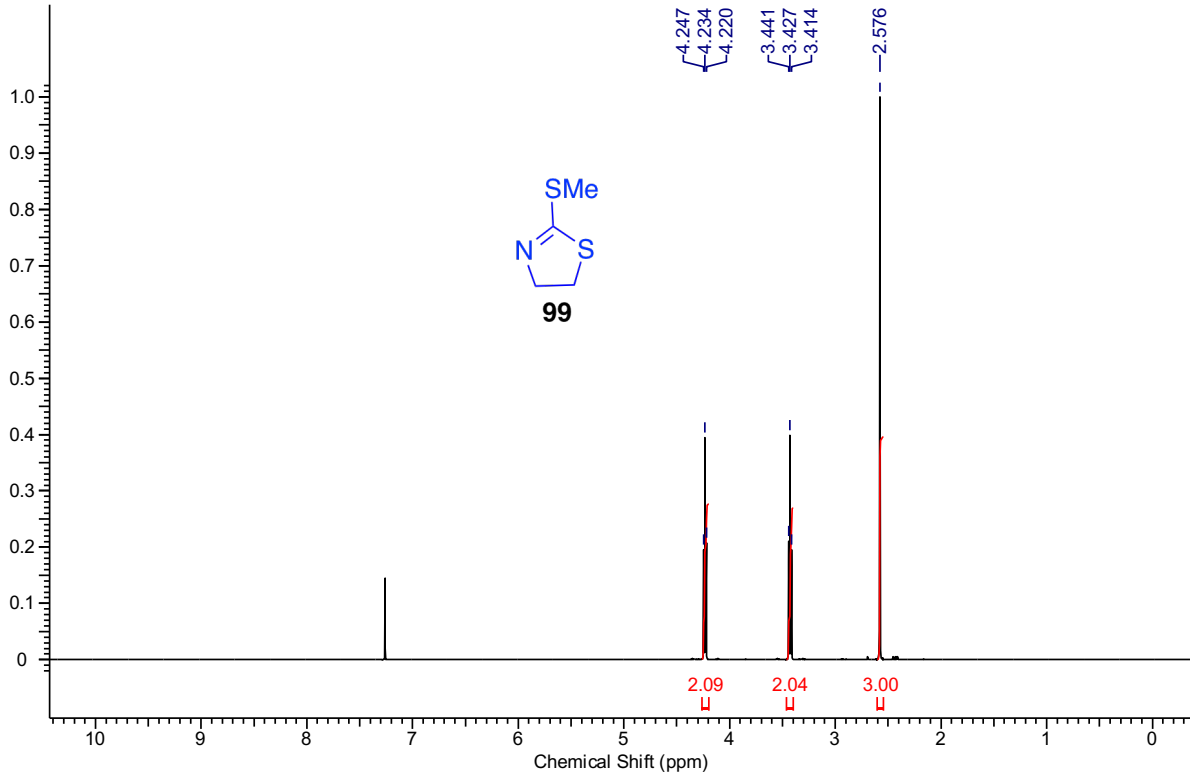

7.328
7.326
7.317
7.311
7.296
7.278
7.260
7.258
4.261
4.236
4.213
3.868
3.844
3.820
3.617
Ph
O
N
86k
4.81
1.83
1.84
2.00
Chemical Shift (ppm)

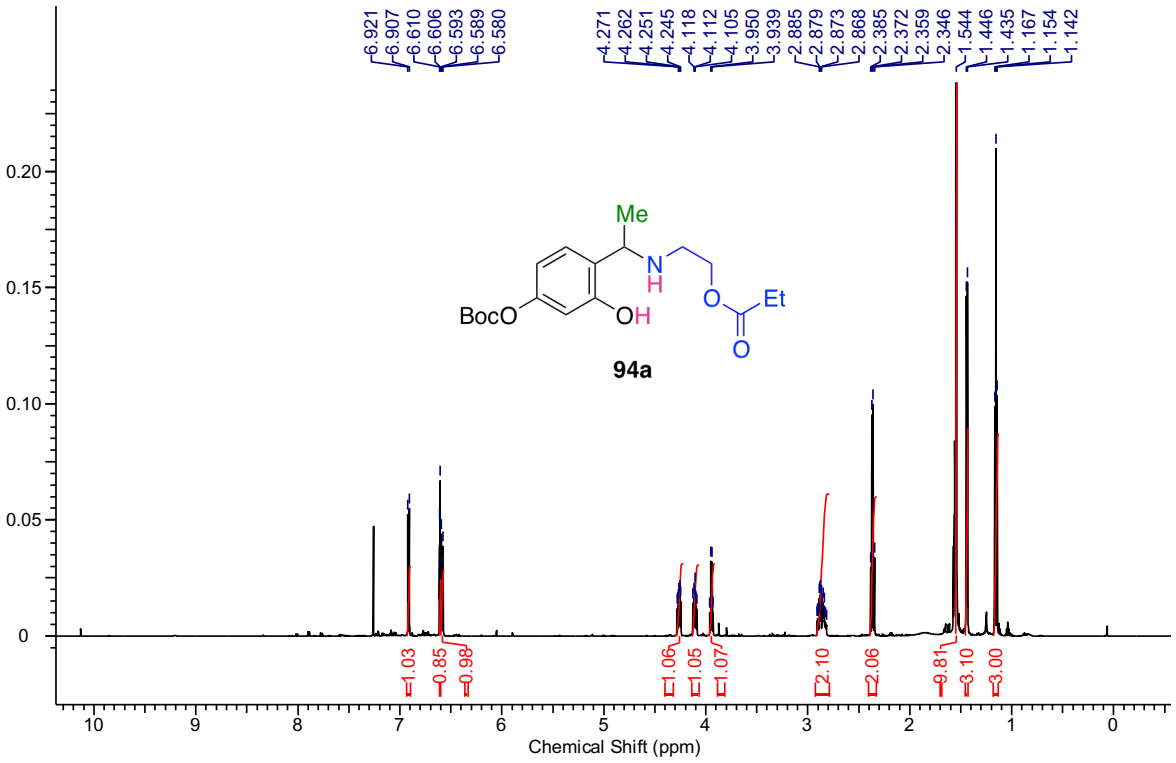

8.069
3.615
3.606
3.596
3.584
3.574
H
O
N
86m
1.01
2.45
2.29
Chemical Shift (ppm)


7.661
7.643
7.470
7.462
7.303
7.298
7.295
7.289
7.285
2.643
Me
O
N
86n
0.90 0.89 1.86
3.00
Chemical Shift (ppm)


4.428
4.406
4.384
3.873
3.824
3.802
3.780
OMe
N
O
97
1.95 2.90 2.00
Chemical Shift (ppm)


164.467
68.953
57.514
51.645
OMe
N
O
97
0.25
0.20
0.15
0.10
0.05
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


4.247
4.234
4.220
3.441
3.427
3.414
2.576
SMe
N
S
99
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2.09
2.04
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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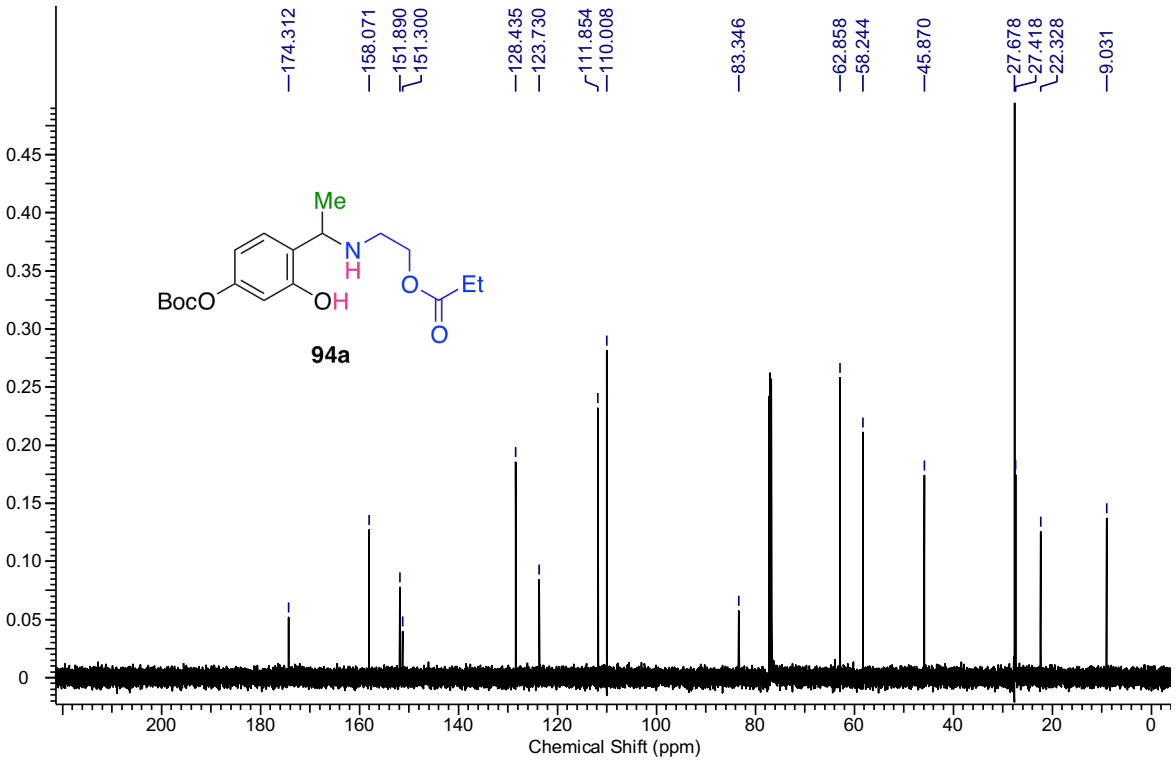
6.907
6.610
6.606
6.593
6.589
6.580
4.271
4.262
4.251
4.245
4.118
4.112
4.105
3.950
3.939
2.885
2.879
2.873
2.868
2.385
2.372
2.359
2.346
1.544
1.446
1.435
1.167
1.154
1.142
Me
N
H
O
Et
BocO
OH
O
94a
1.03
0.85
0.98
1.06
1.05
1.07
2.10
2.06
9.81
3.10
3.00
Chemical Shift (ppm)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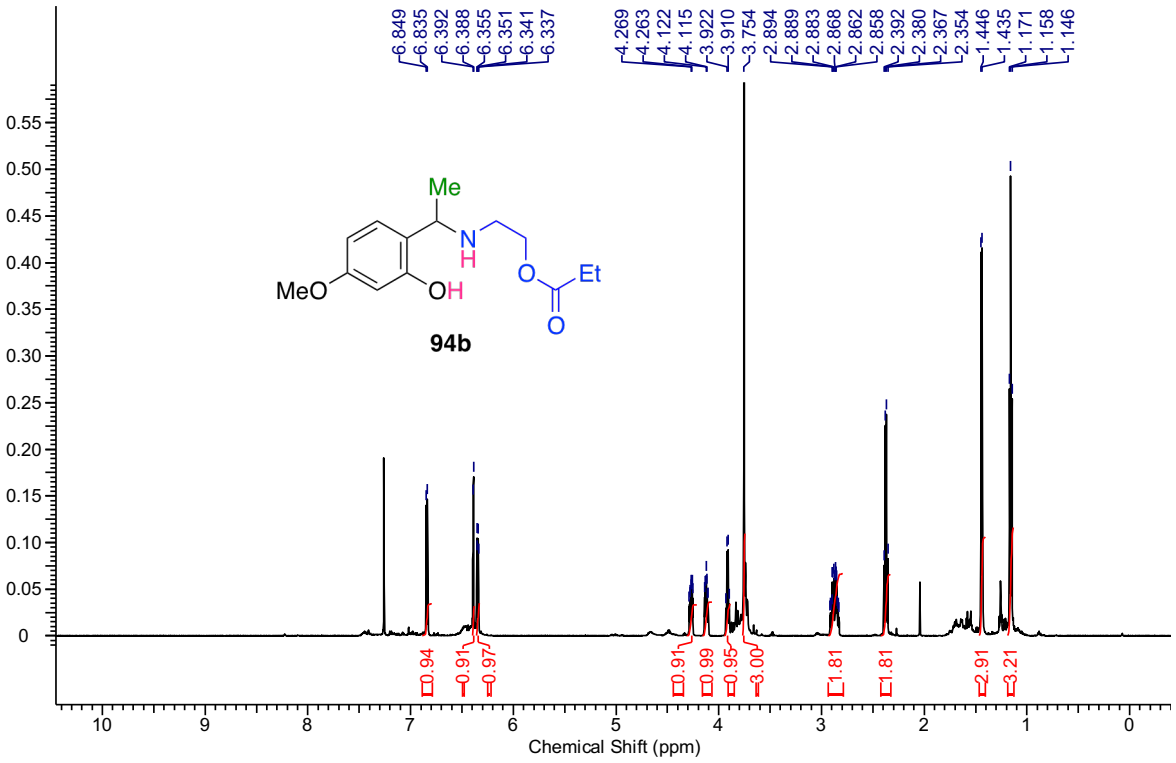
151.890
151.300
128.435
123.730
111.854
110.008
83.346
62.858
58.244
45.870
27.678
27.418
22.328
9.031
Me
N
H
O
Et
BocO
OH
O
94a
Chemical Shift (ppm)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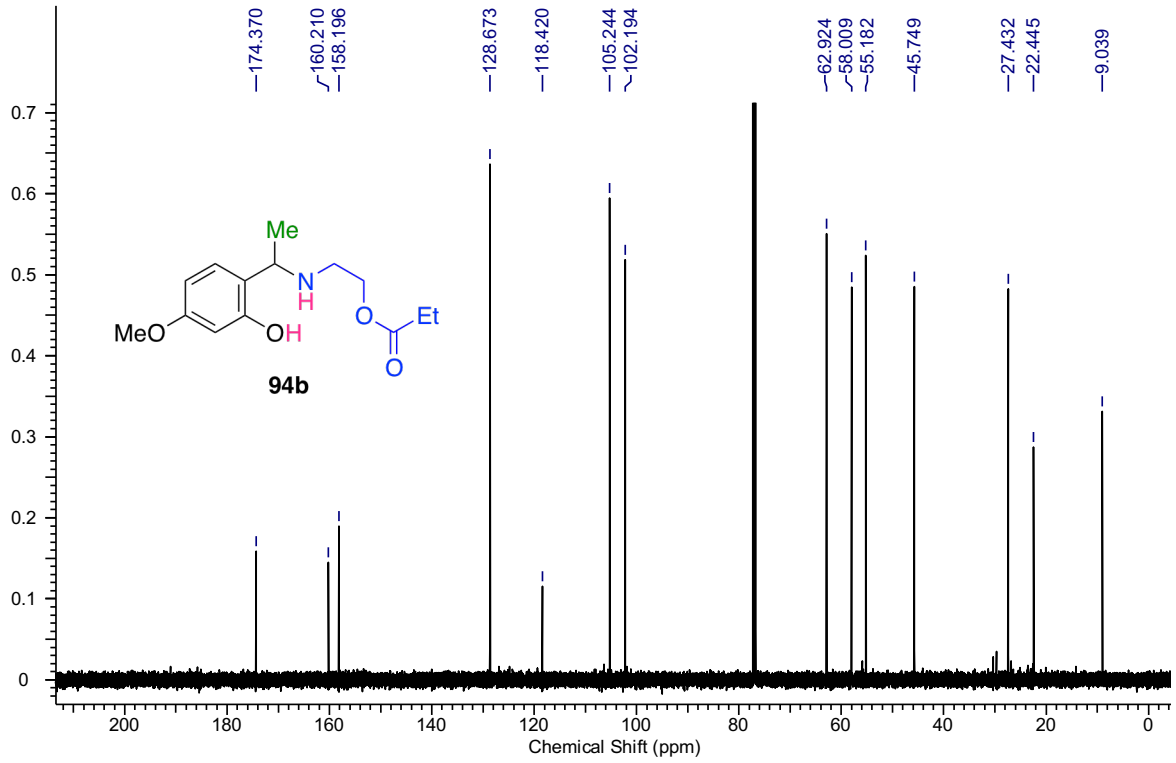
6.392
6.388
6.355
6.351
6.341
6.337
4.269
4.263
4.122
4.115
3.922
3.910
3.754
2.894
2.889
2.883
2.868
2.862
2.858
2.392
2.380
2.367
2.354
1.446
1.435
1.171
1.158
1.146
Me
N
H
MeO
OH
O
Et
O
94b
0.94
0.91
0.97
0.91
0.99
0.95
3.00
1.81
1.81
2.91
3.21
Chemical Shift (ppm)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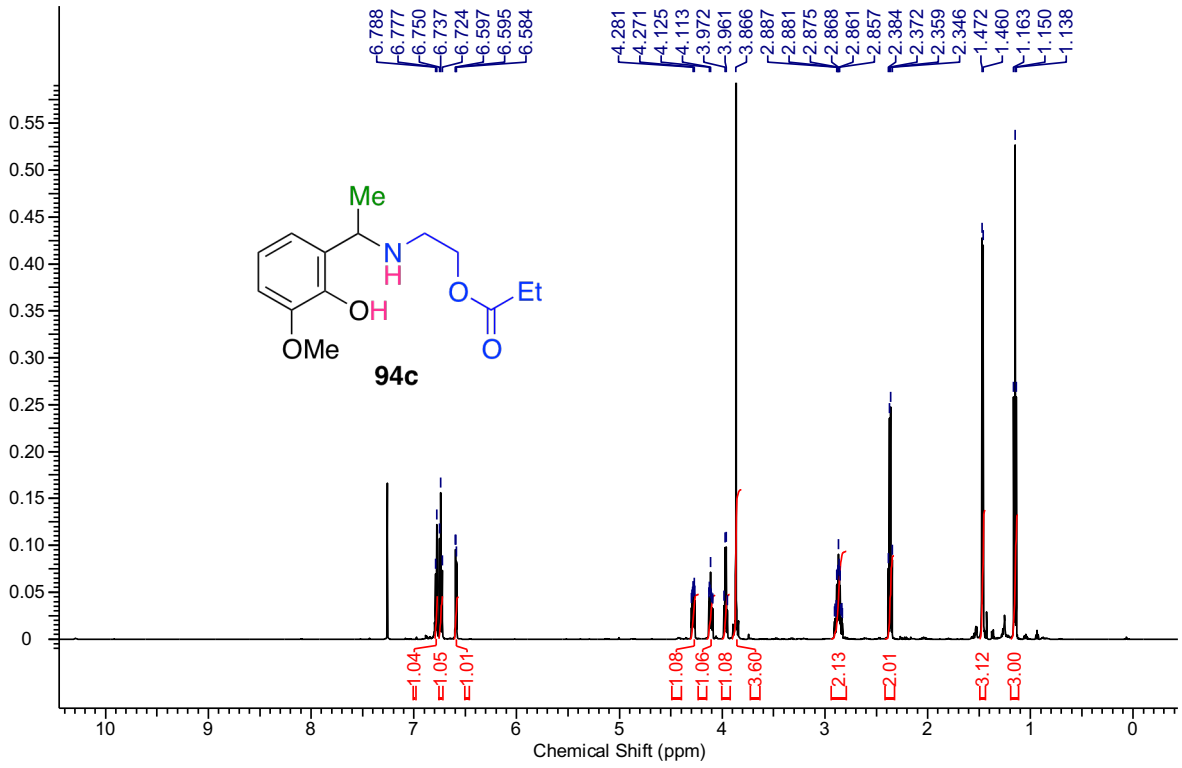
158.196
128.673
118.420
105.244
102.194
62.924
58.009
55.182
45.749
27.432
22.445
9.039
Me
N
H
MeO
OH
O
Et
O
94b
Chemical Shift (ppm)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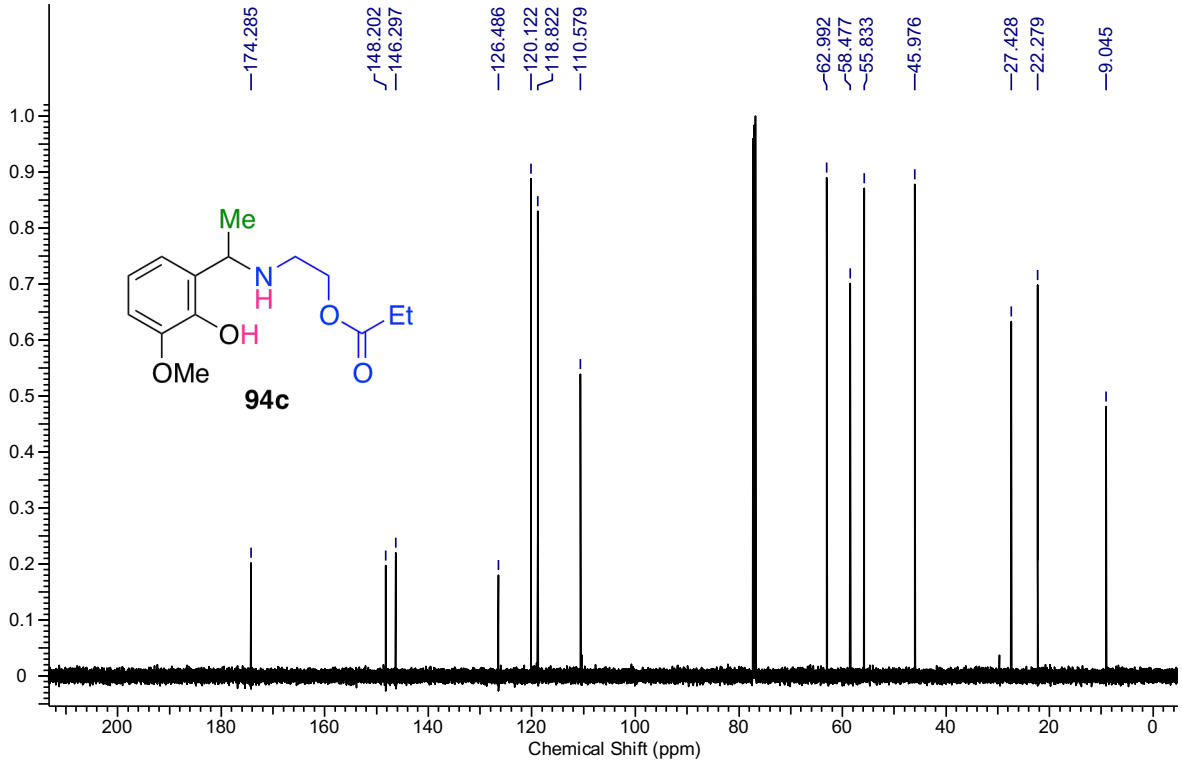
6.595
6.584
4.281
4.271
4.125
4.113
3.972
3.961
3.866
2.887
2.881
2.875
2.868
2.861
2.857
2.384
2.372
2.359
2.346
1.472
1.460
1.163
1.150
1.138
1.04
1.05
1.01
1.08
1.06
1.08
3.60
2.13
2.01
3.12
3.00
Me
N
H
O
Et
OH
OMe
O
94c
Chemical Shift (ppm)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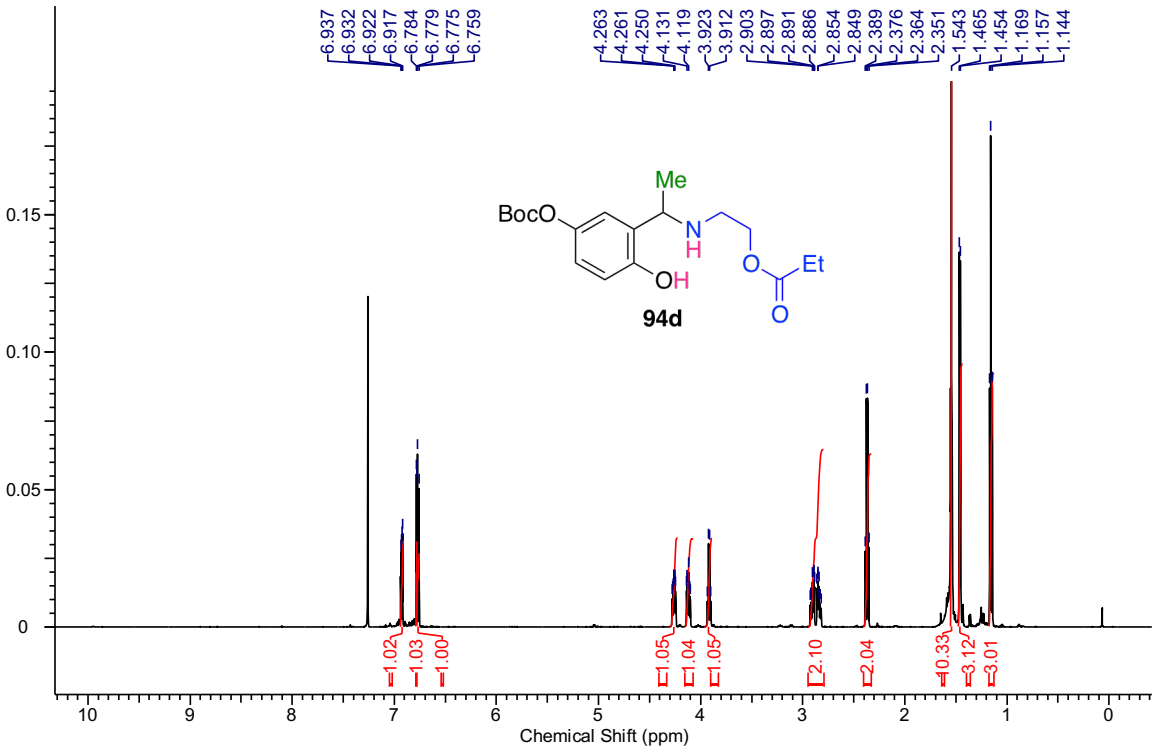
126.486
120.122
118.822
110.579
62.992
58.477
55.833
45.976
27.428
22.279
9.045
Me
N
H
O
Et
OH
OMe
O
94c
Chemical Shift (ppm)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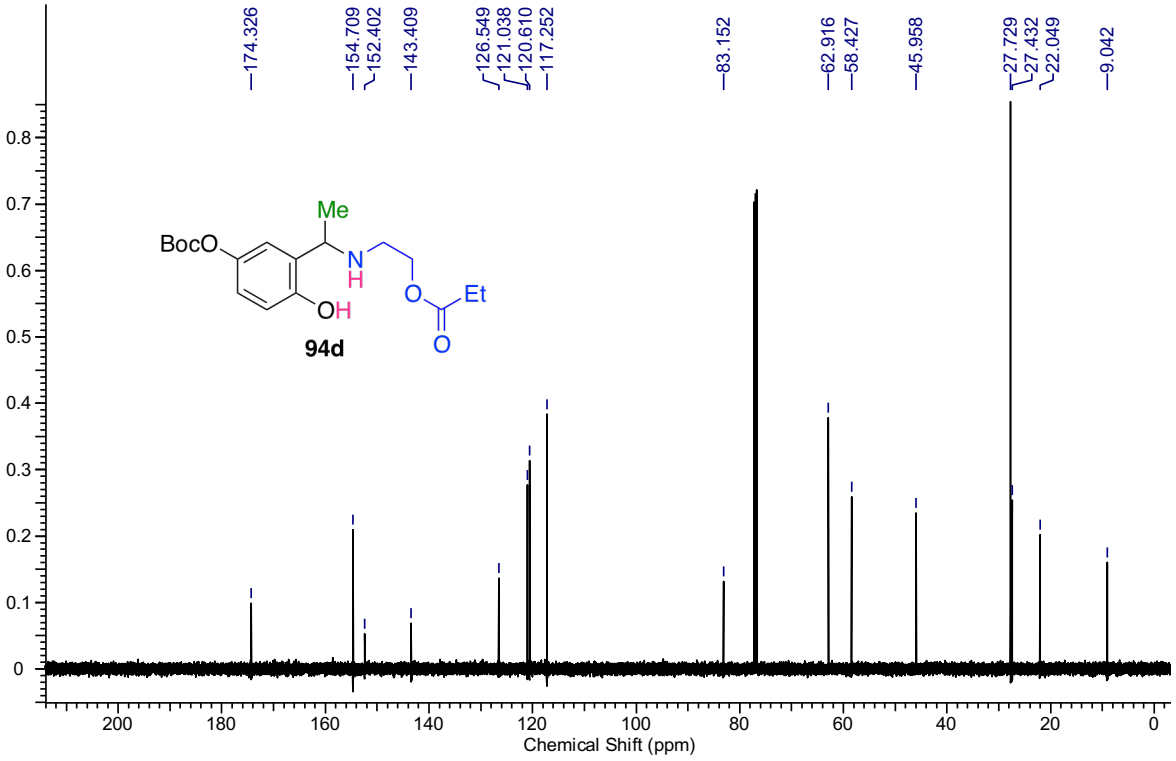
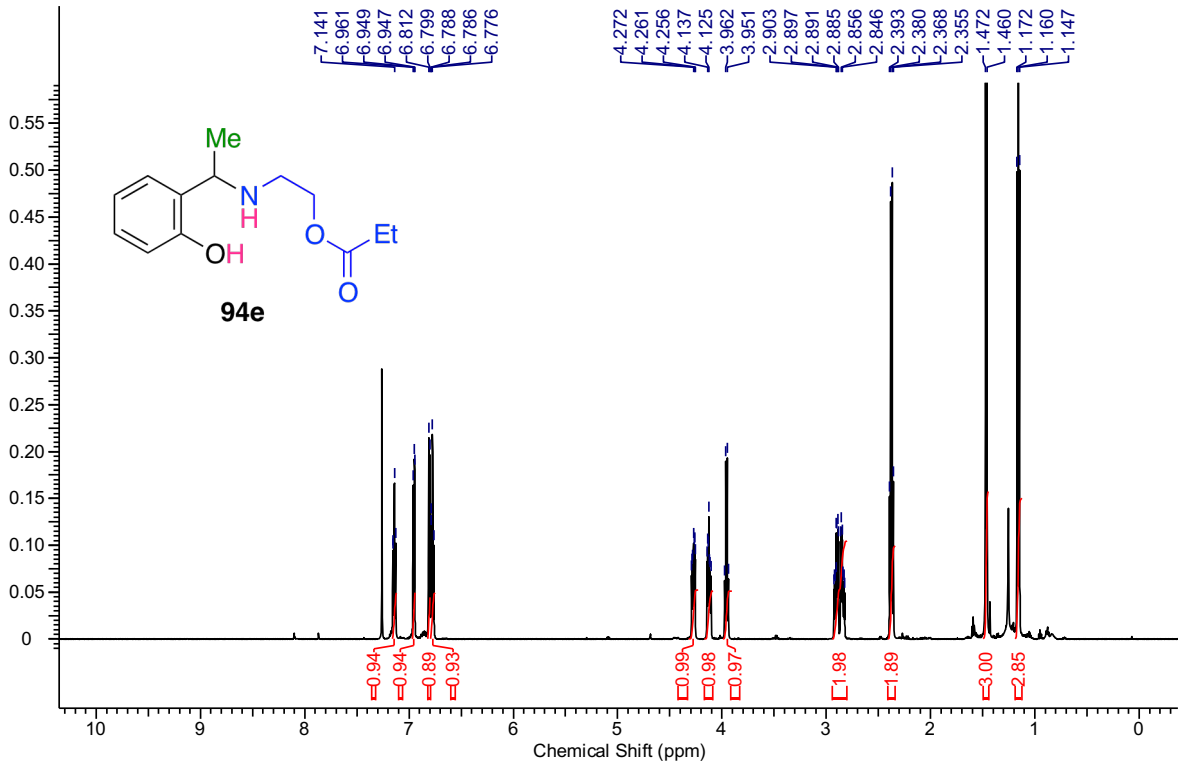
6.784
6.779
6.775
6.759
4.263
4.261
4.250
4.131
4.119
3.923
3.912
2.903
2.897
2.891
2.886
2.854
2.849
2.389
2.376
2.364
2.351
1.543
1.465
1.454
1.169
1.157
1.144
Me
BocO
N
H
OH
O
Et
O
94d
1.02
1.03
1.00
1.05
1.04
1.05
2.10
2.04
10.33
3.12
3.01
Chemical Shift (ppm)


174.326
154.709
152.402
143.409
126.549
121.038
120.610
117.252
83.152
62.916
58.427
45.958
27.729
27.432
22.049
9.042
Me
BocO
N
H
OH
O
Et
O
94d
Chemical Shift (ppm)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6.788
6.786
6.776
4.272
4.261
4.256
4.137
4.125
3.962
3.951
2.903
2.897
2.891
2.885
2.856
2.846
2.393
2.380
2.368
2.355
1.472
1.460
1.172
1.160
1.147
Me
N
H
O
OH
Et
O
94e
0.94
0.94
0.89
0.93
0.99
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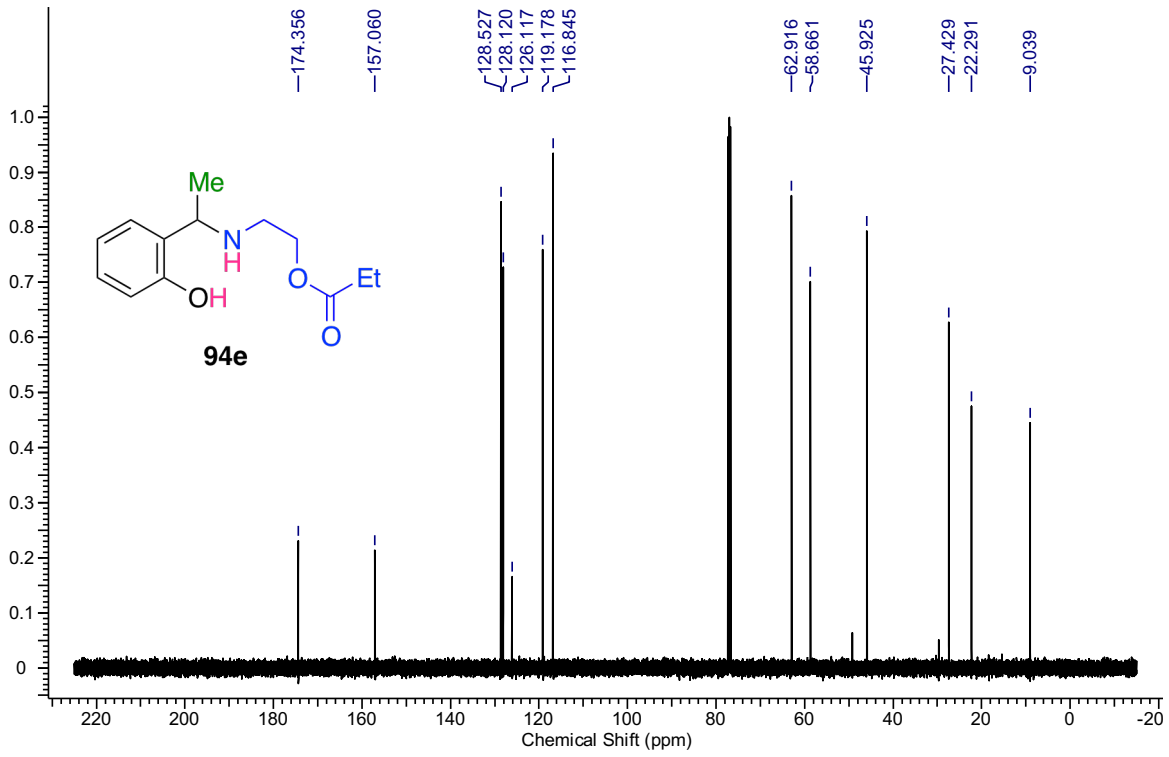
1.89
3.00
2.85
Chemical Shift (ppm)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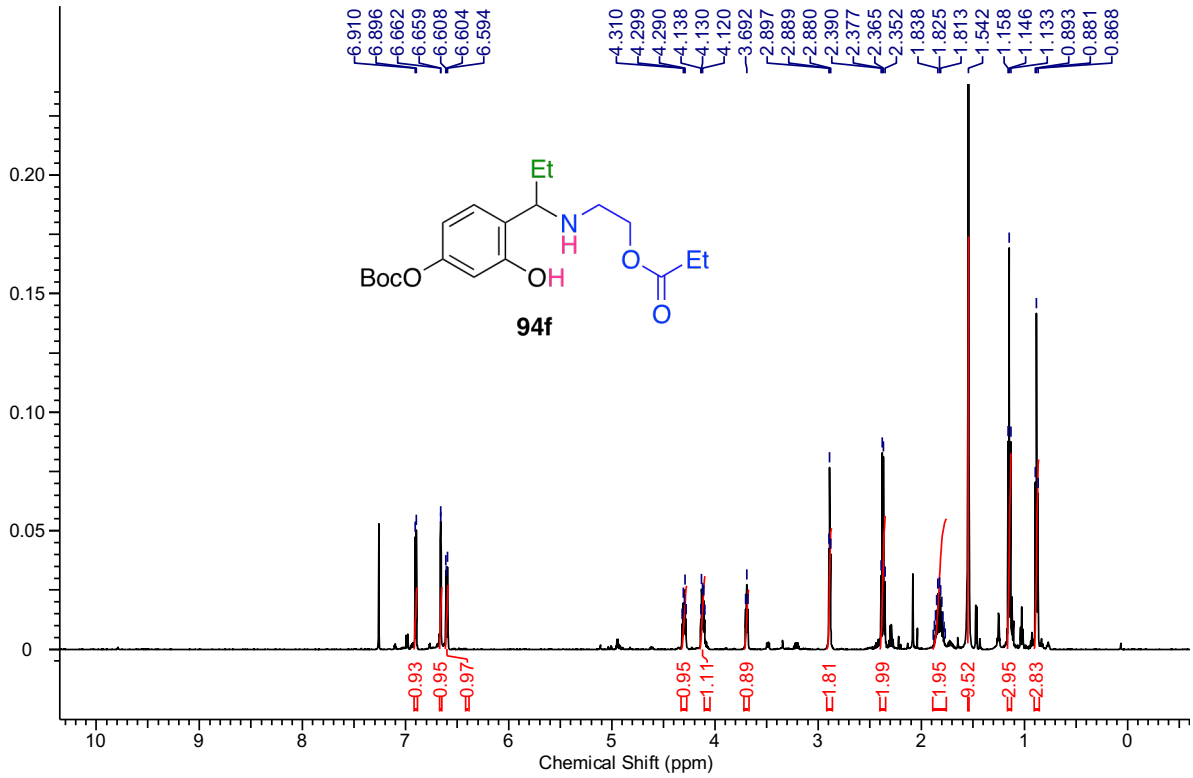
119.178
116.845
62.916
58.661
45.925
27.429
22.291
9.039
Me
N
H
O
OH
Et
O
94e
Chemical Shift (ppm)


6.910
6.896
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6.659
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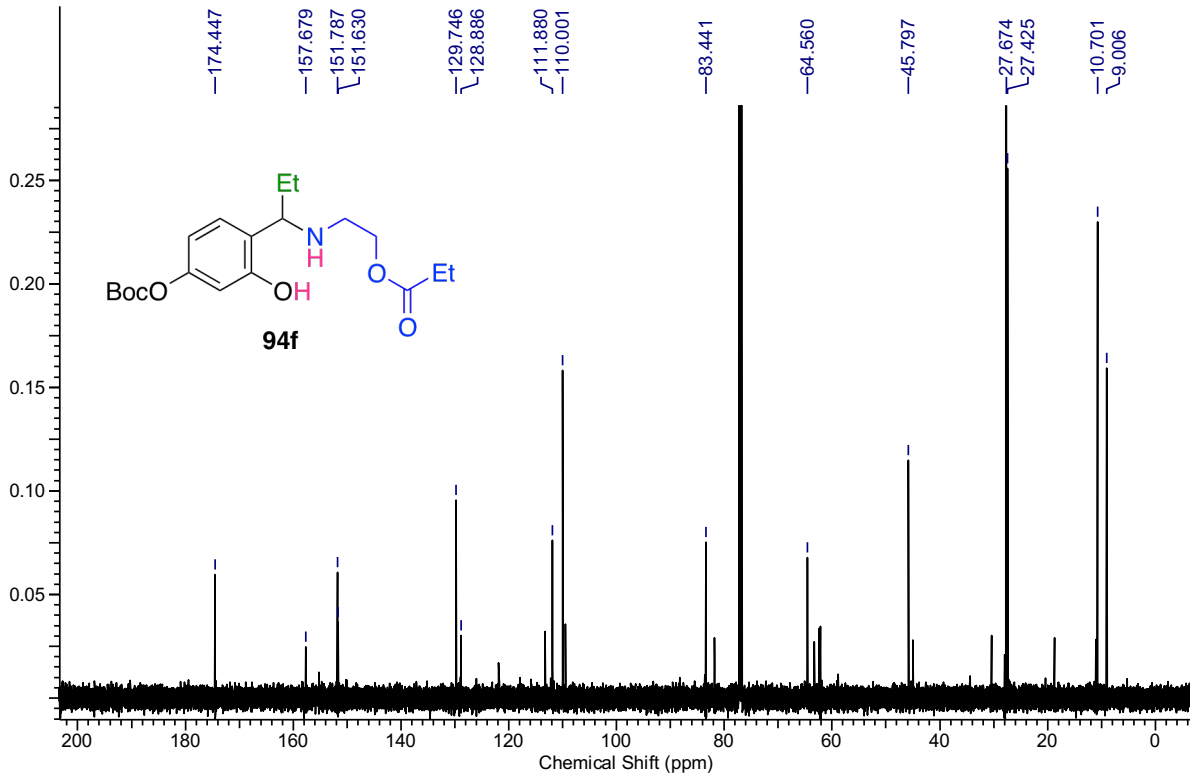
6.604
6.594
4.310
4.299
4.290
4.138
4.130
4.120
3.692
2.897
2.889
2.880
2.390
2.377
2.365
2.352
1.838
1.825
1.813
1.542
1.158
1.146
1.133
0.893
0.881
0.868
Et
N
H
BocO
OH
O
Et
O
94f
0.93
0.95
0.97
0.95
1.11
0.89
1.81
1.99
1.95
9.52
2.95
2.83
Chemical Shift (ppm)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151.630
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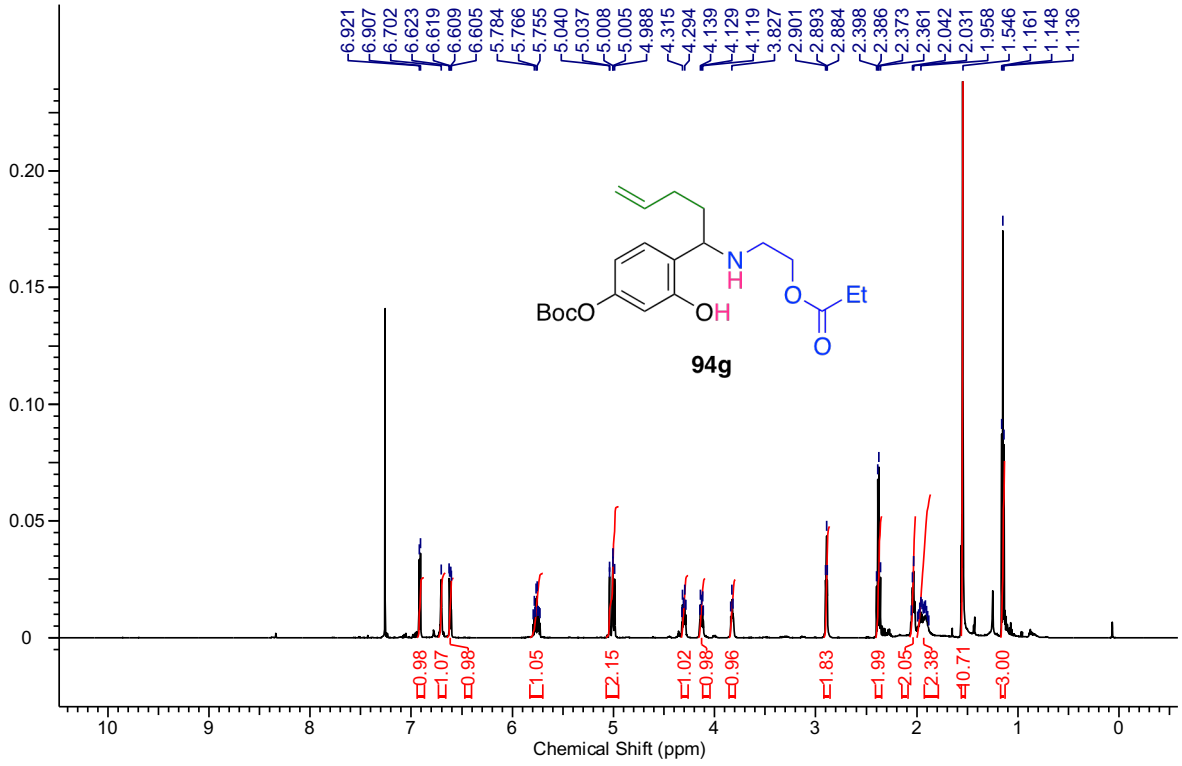
128.886
111.880
110.001
83.441
64.560
45.797
27.674
27.425
10.701
9.006
Et
N
H
BocO
OH
O
Et
O
94f
Chemical Shift (ppm)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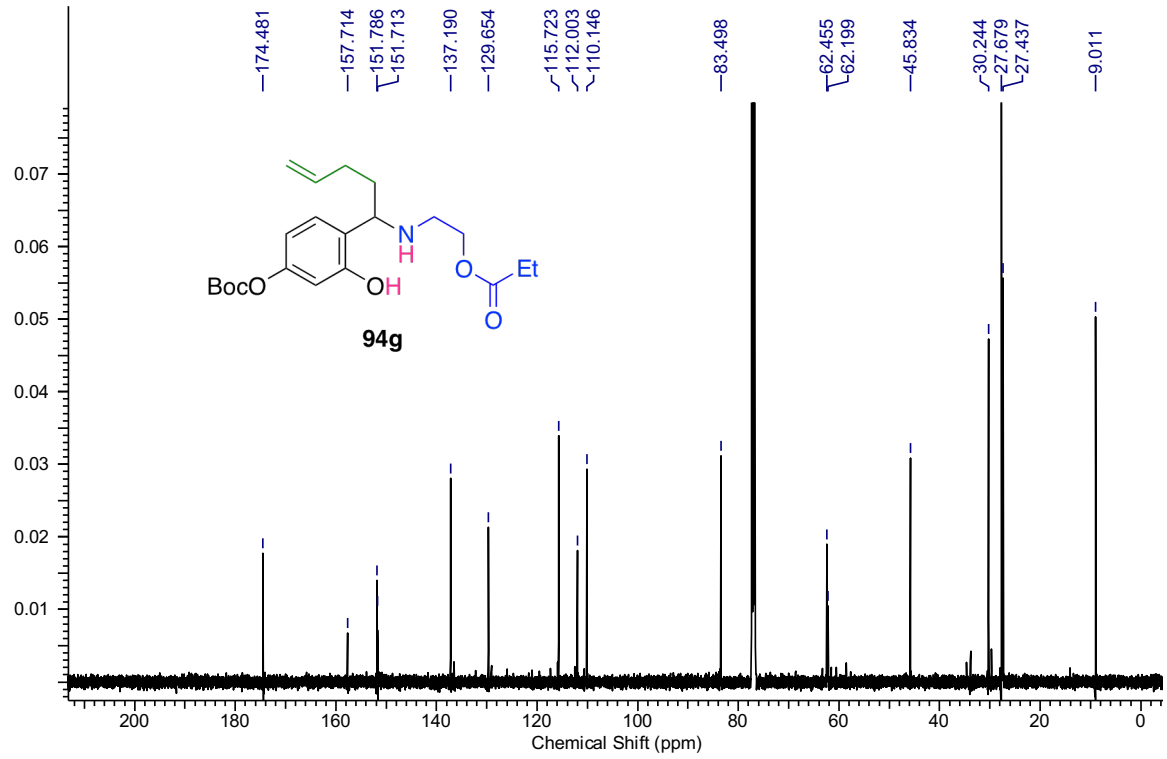
6.907
6.702
6.623
6.619
6.609
6.605
5.784
5.766
5.755
5.040
5.037
5.008
5.005
4.988
4.315
4.294
4.139
4.129
4.119
3.827
2.901
2.893
2.884
2.398
2.386
2.373
2.361
2.042
2.031
1.958
1.546
1.161
1.148
1.136
BocO
OH
N
H
O
Et
O
94g
0.98
1.07
0.98
1.05
2.15
1.02
0.98
0.96
1.83
1.99
2.05
2.38
10.71
3.00
Chemical Shift (ppm)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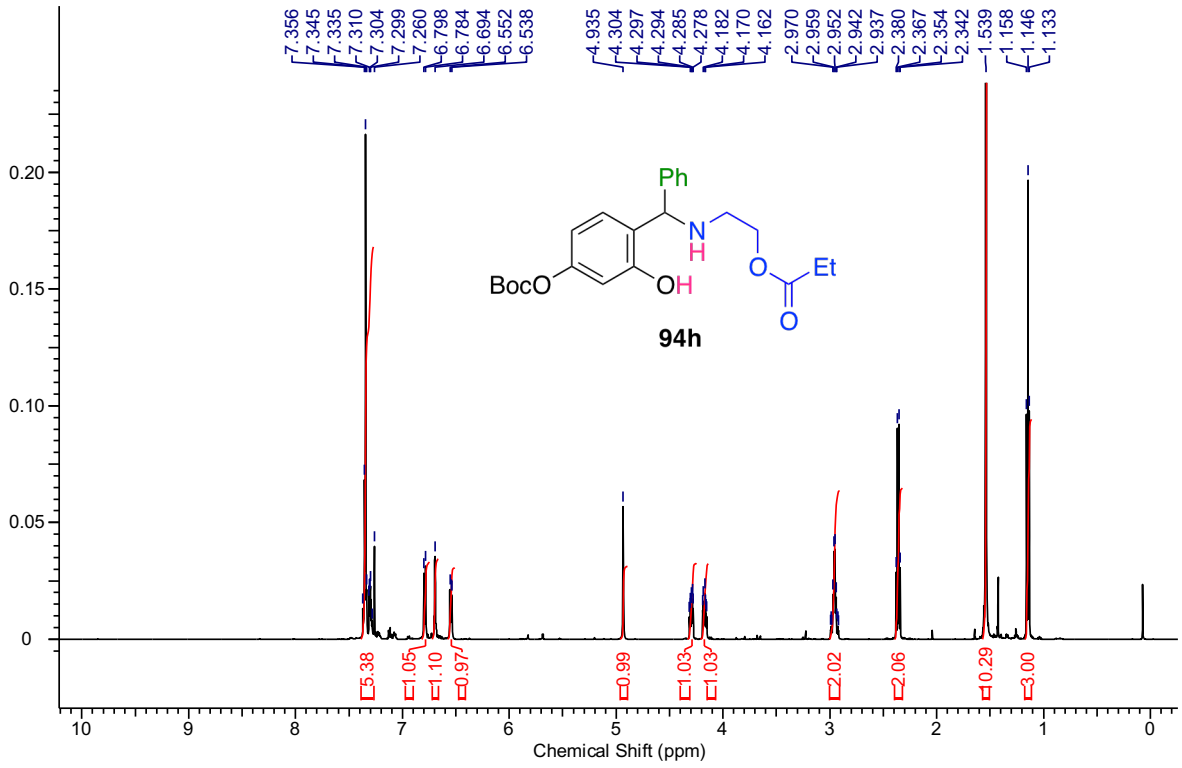
157.714
151.786
151.713
137.190
129.654
115.723
112.003
110.146
83.498
62.455
62.199
45.834
30.244
27.679
27.437
9.011
BocO
OH
N
H
O
Et
O
94g
Chemical Shift (ppm)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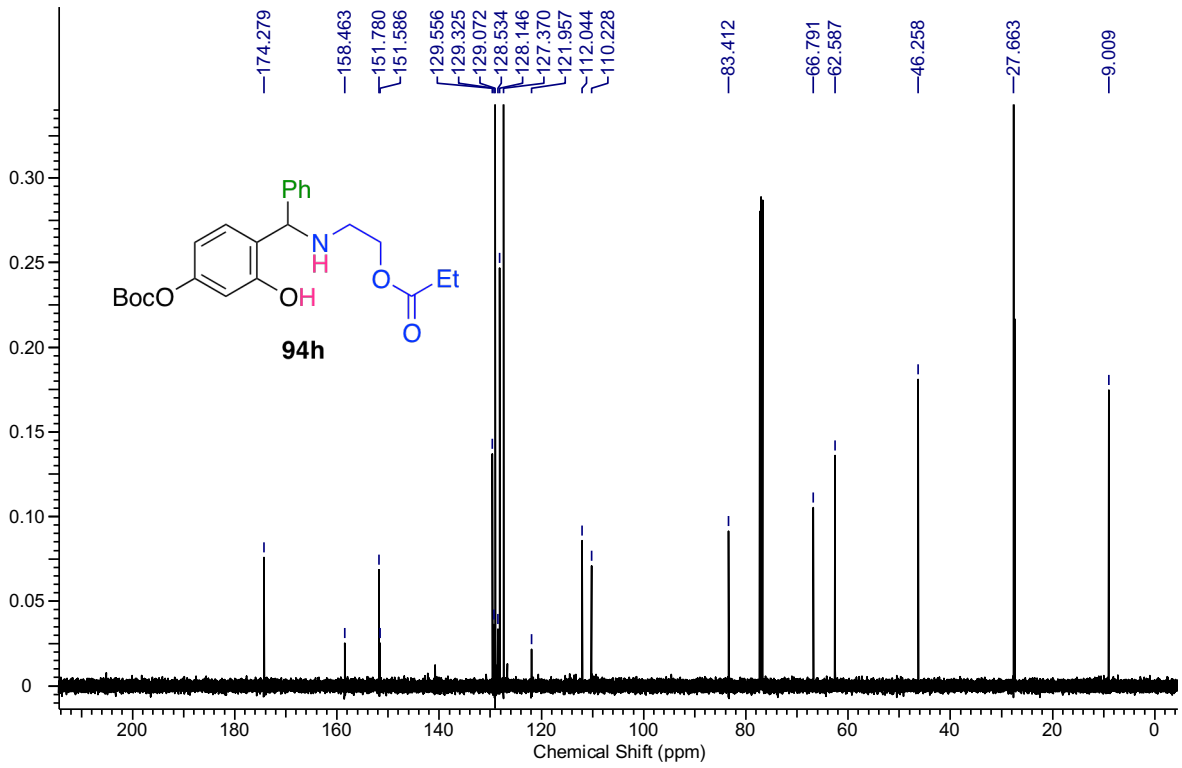
7.345
7.335
7.310
7.304
7.299
7.260
6.798
6.784
6.694
6.552
6.538
4.935
4.304
4.297
4.294
4.285
4.278
4.182
4.170
4.162
2.970
2.959
2.952
2.942
2.937
2.380
2.367
2.354
2.342
1.539
1.158
1.146
1.133
Ph
N
H
BocO
OH
O
Et
O
94h
5.38
1.05
1.10
0.97
0.99
1.03
1.03
2.02
2.06
10.29
3.00
Chemical Shift (ppm)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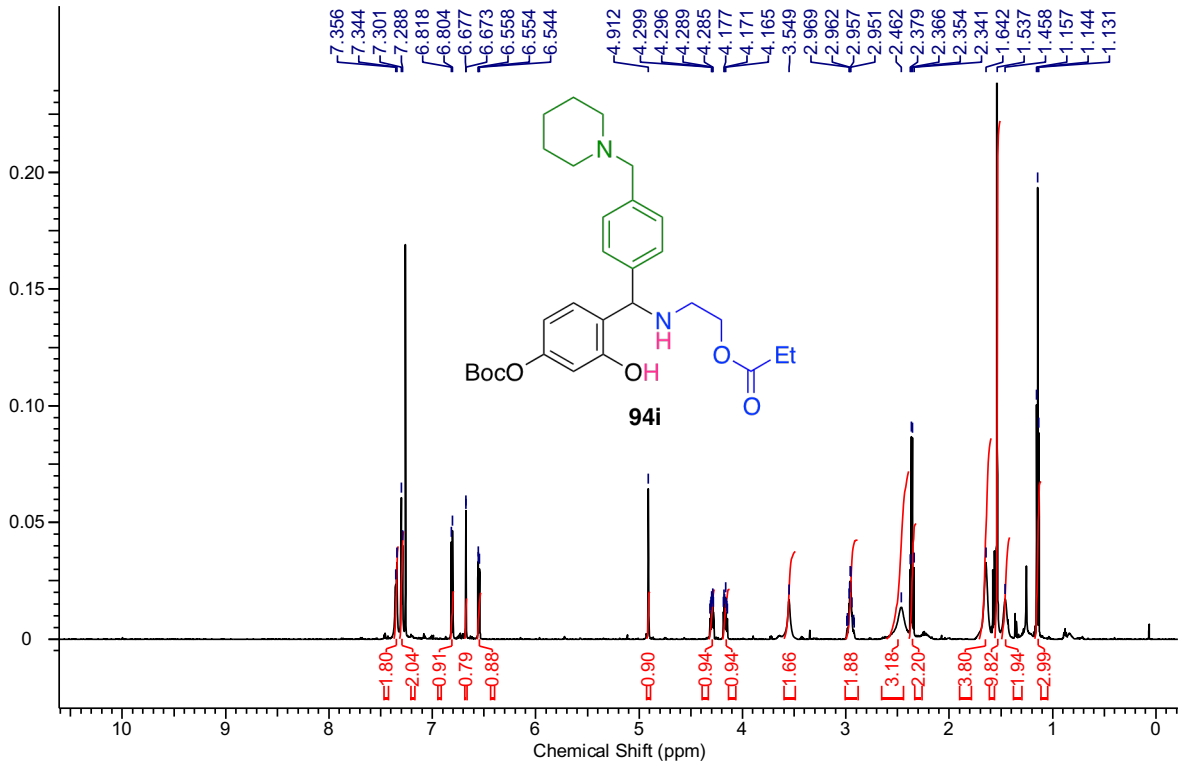
158.463
151.780
151.586
129.556
129.325
129.072
128.534
128.146
127.370
121.957
112.044
110.228
83.412
66.791
62.587
46.258
27.663
9.009
Ph
N
H
BocO
OH
O
Et
O
94h
Chemical Shift (ppm)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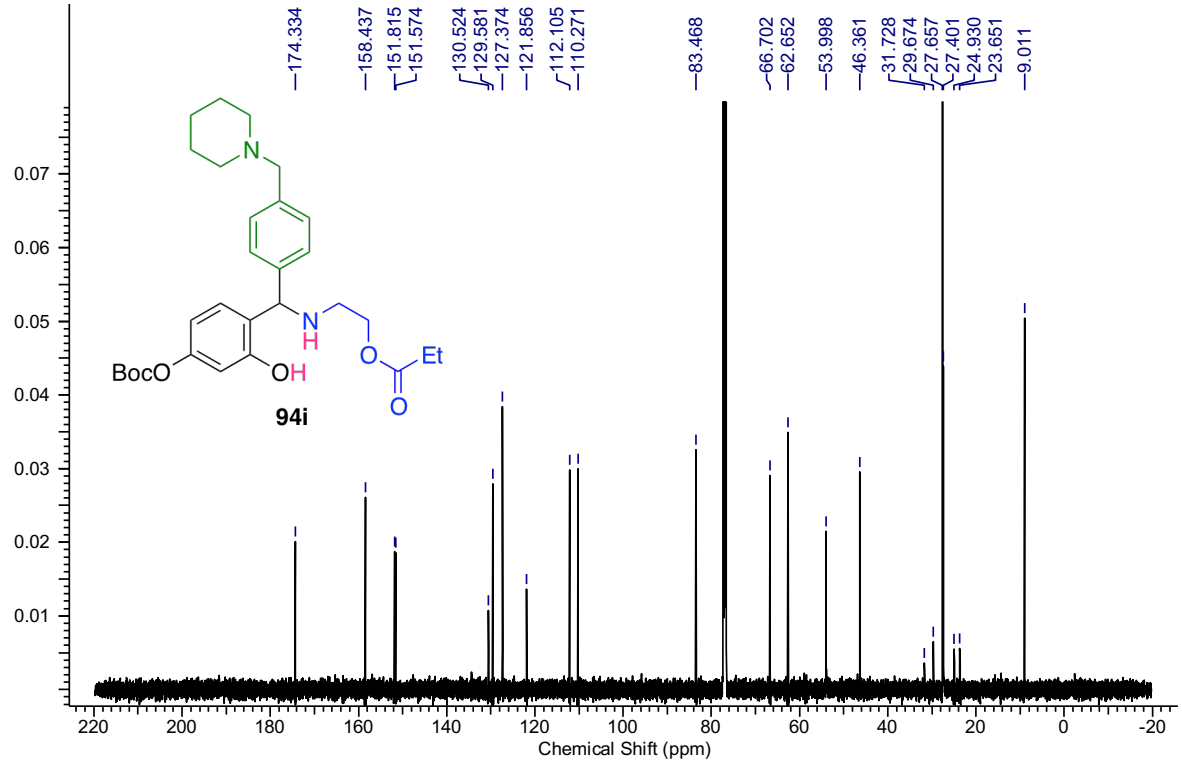
7.344
7.301
7.288
6.818
6.804
6.677
6.673
6.558
6.554
6.544
4.912
4.299
4.296
4.289
4.285
4.177
4.171
4.165
3.549
2.969
2.962
2.957
2.951
2.462
2.379
2.366
2.354
2.341
1.642
1.537
1.458
1.157
1.144
1.131
1.80
2.04
0.91
0.79
0.88
0.90
0.94
0.94
1.66
1.88
3.18
2.20
3.80
9.82
1.94
2.99
BocO
OH
Et
94i
Chemical Shift (ppm)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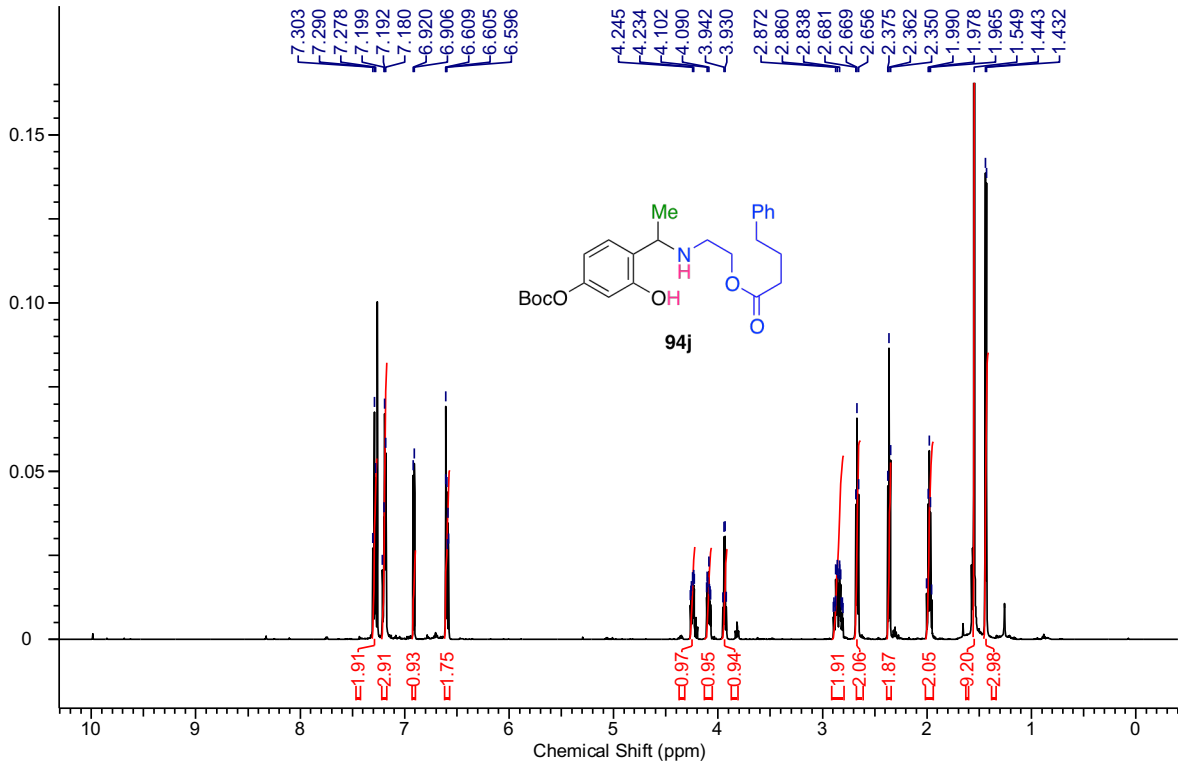
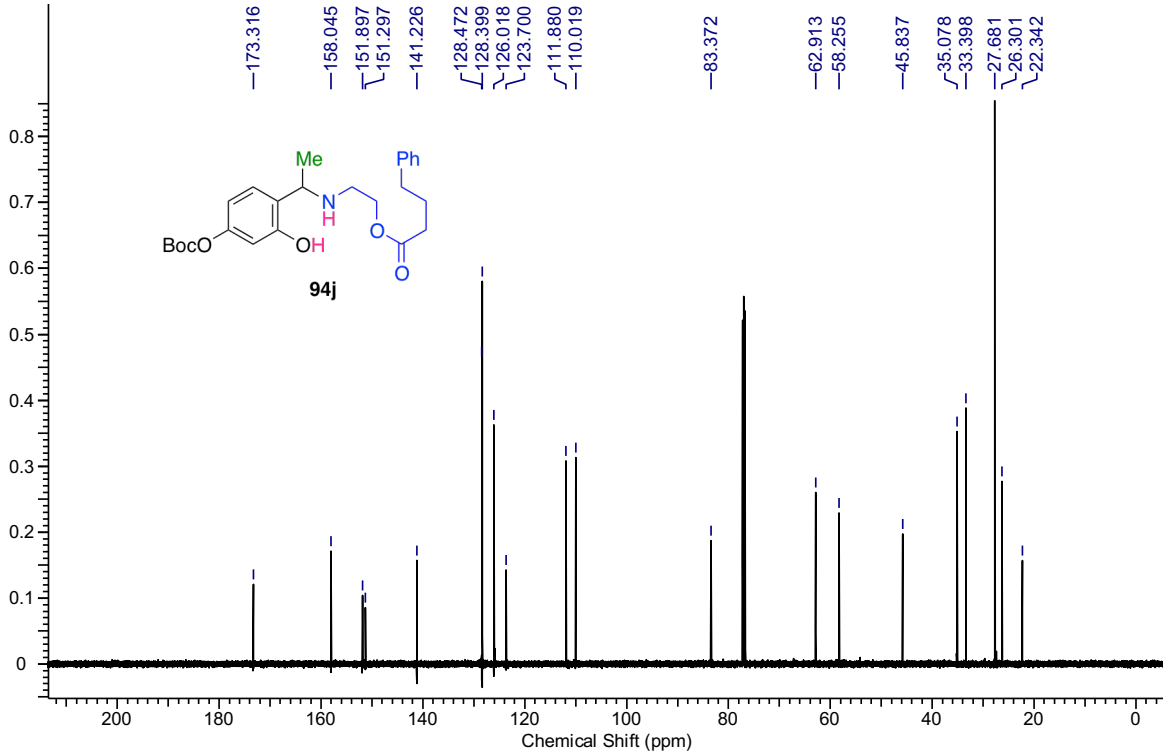
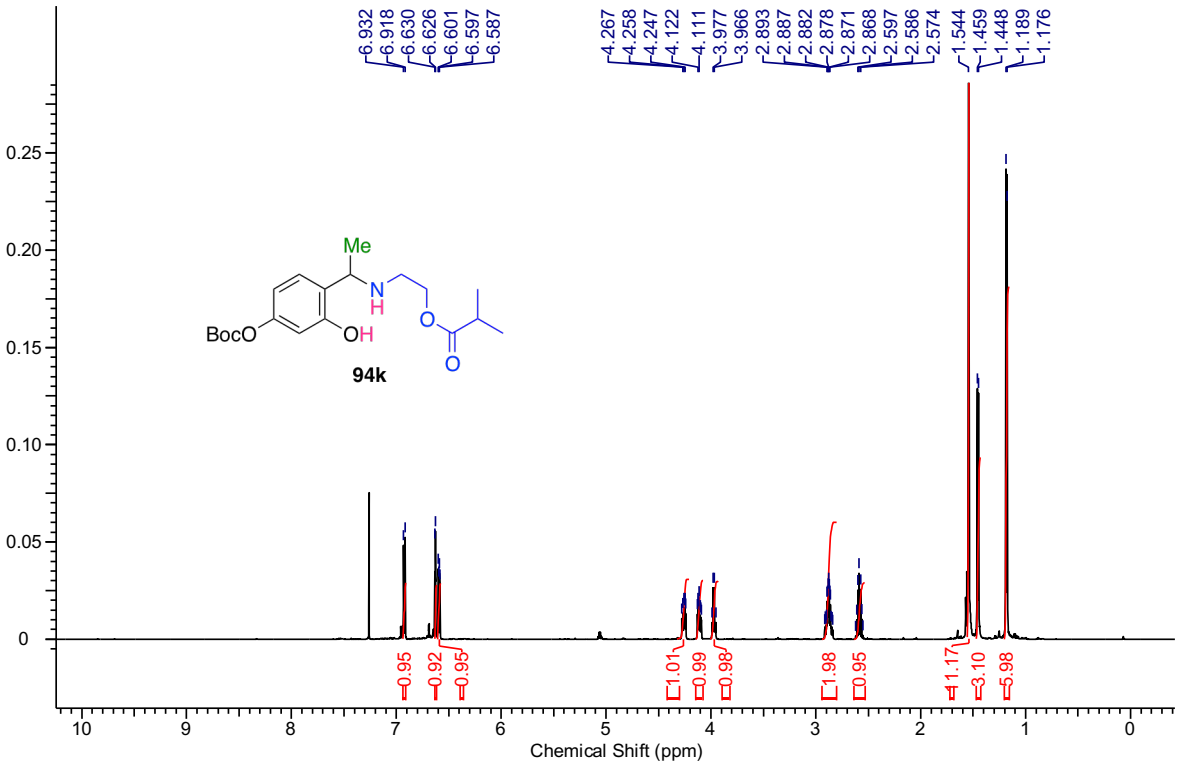
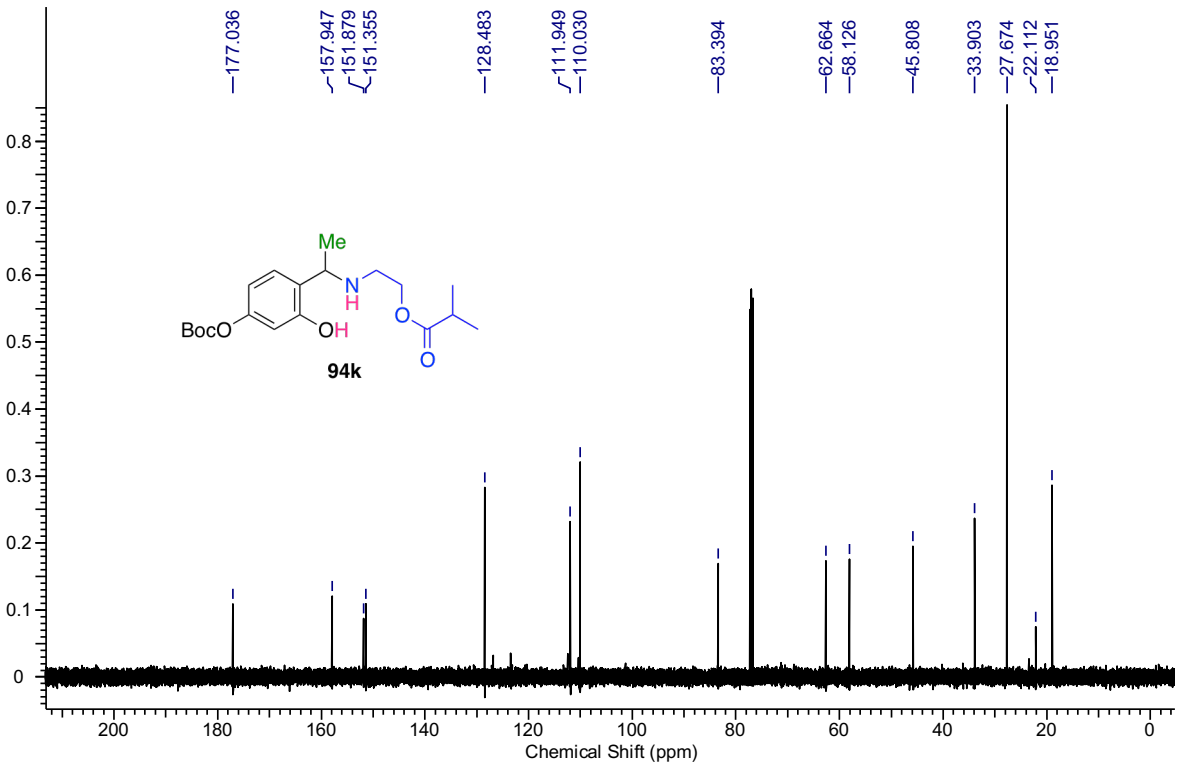
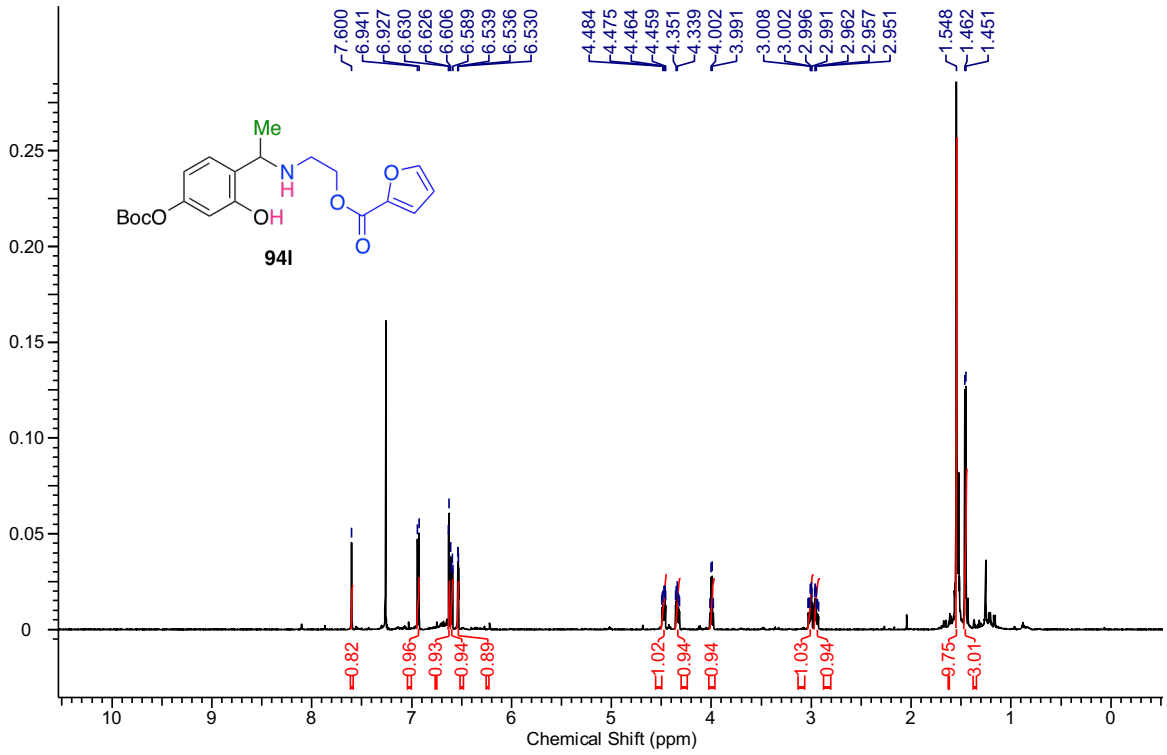
158.437
151.815
151.574
130.524
129.581
127.374
121.856
112.105
110.271
83.468
66.702
62.652
53.998
46.361
31.728
29.674
27.657
27.401
24.930
23.651
9.011
BocO
OH
Et
94i
Chemical Shift (ppm)

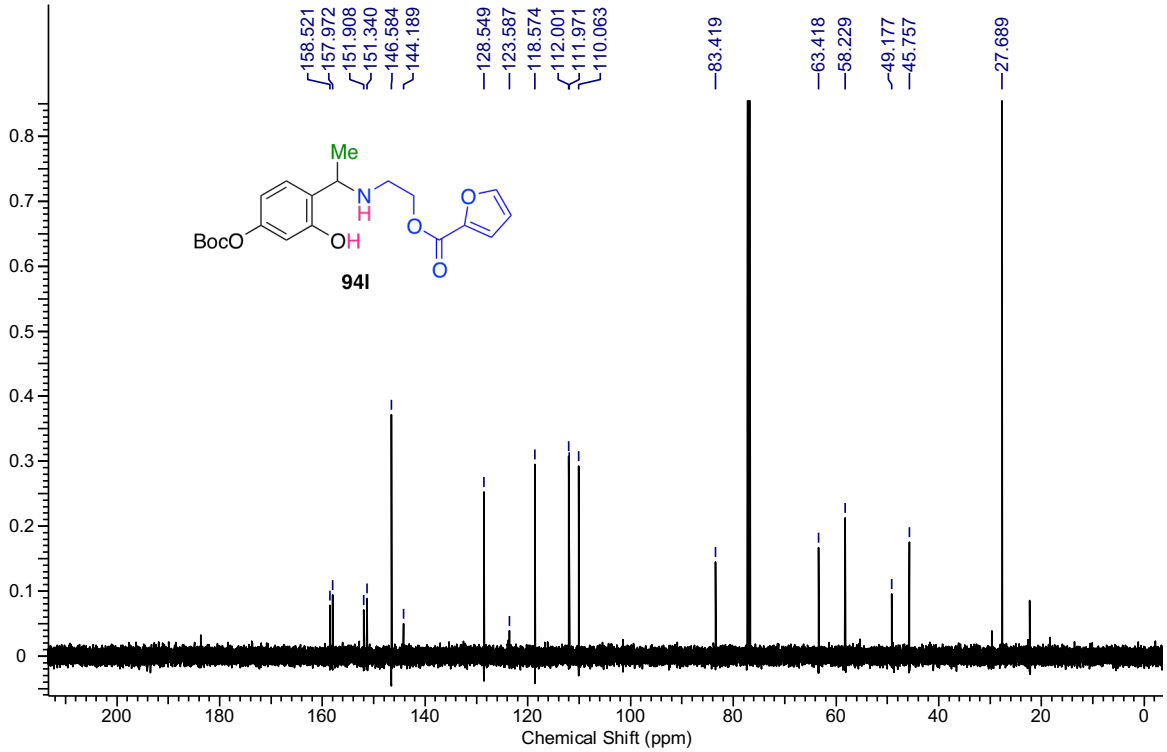

7.303
7.290
7.278
7.199
7.192
7.180
6.920
6.906
6.609
6.605
6.596
4.245
4.234
4.102
4.090
3.942
3.930
2.872
2.860
2.838
2.681
2.669
2.656
2.375
2.362
2.350
1.990
1.978
1.965
1.549
1.443
1.432
Me
Ph
N
H
O
BocO
OH
O
94j
1.91
2.91
0.93
1.75
0.97
0.95
0.94
1.91
2.06
1.87
2.05
9.20
2.98
Chemical Shift (ppm)

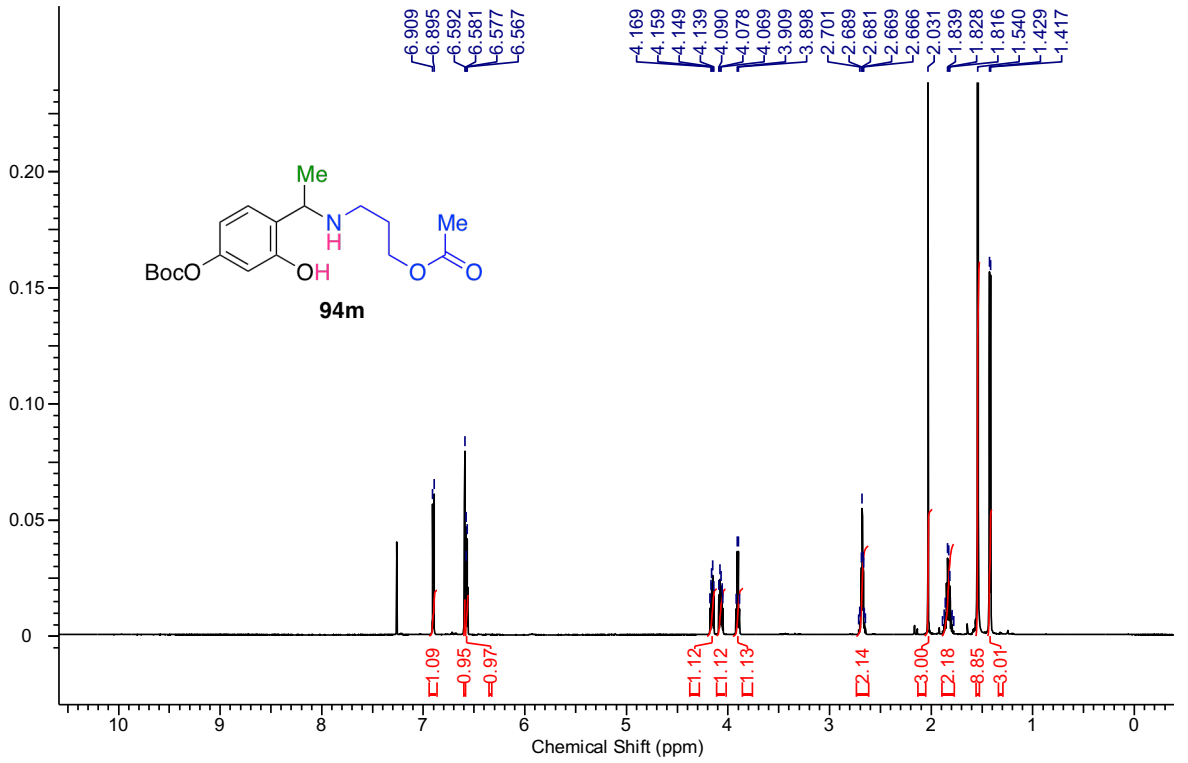

173.316
158.045
151.897
151.297
141.226
128.472
128.399
126.018
123.700
111.880
110.019
83.372
62.913
58.255
45.837
35.078
33.398
27.681
26.301
22.342
Me
Ph
N
H
O
BocO
OH
O
94j
Chemical Shift (ppm)

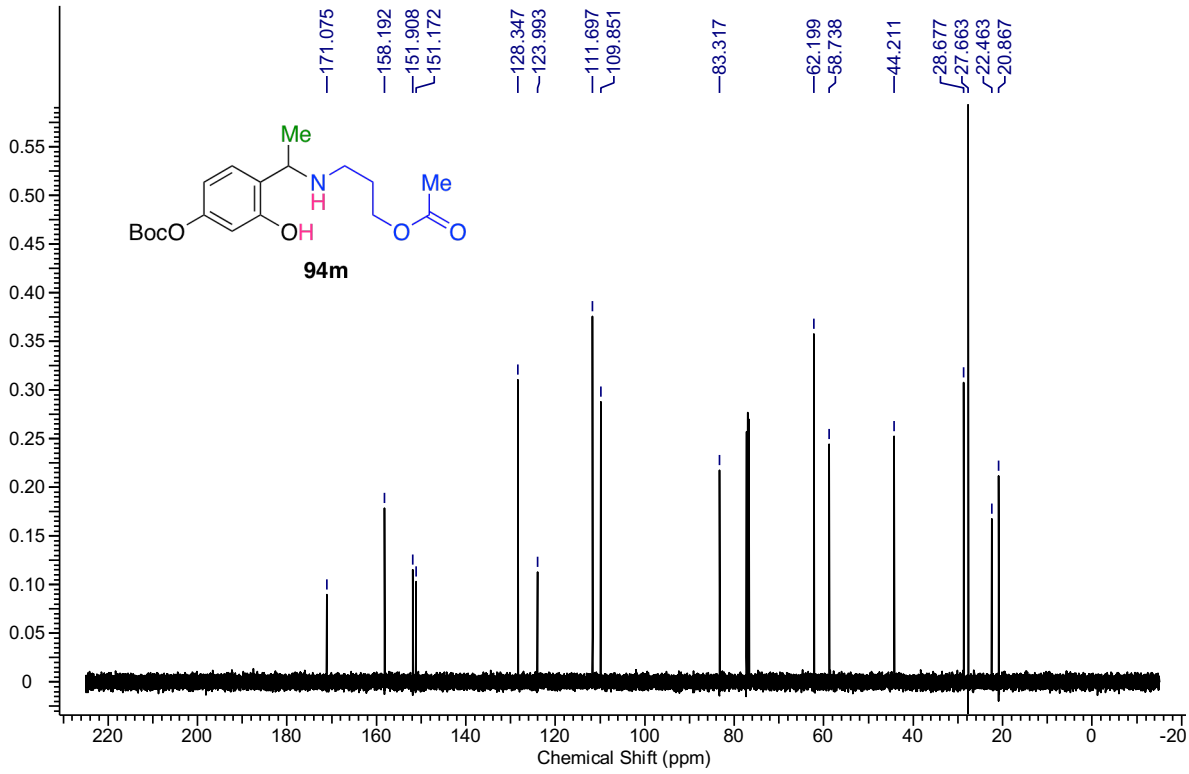

6.932
6.918
6.630
6.626
6.601
6.597
6.587
4.267
4.258
4.247
4.122
4.111
3.977
3.966
2.893
2.887
2.882
2.878
2.871
2.868
2.597
2.586
2.574
1.544
1.459
1.448
1.189
1.176
Me
N
H
BocO
OH
O
O
94k
0.95
0.92
0.95
1.01
0.99
0.98
1.98
0.95
11.17
3.10
5.98
Chemical Shift (ppm)


177.036
157.947
151.879
151.355
128.483
111.949
110.030
83.394
62.664
58.126
45.808
33.903
27.674
22.112
18.951
Me
N
H
BocO
OH
O
O
94k
Chemical Shift (ppm)


7.600
6.941
6.927
6.630
6.626
6.606
6.589
6.539
6.536
6.530
4.484
4.475
4.464
4.459
4.351
4.339
4.002
3.991
3.008
3.002
2.996
2.991
2.962
2.957
2.951
1.548
1.462
1.451
Me
N
H
O
BocO
OH
O
O
94l
0.82
0.96
0.93
0.94
0.89
1.02
0.94
0.94
1.03
0.94
9.75
3.01
Chemical Shift (ppm)


158.521
157.972
151.908
151.340
146.584
144.189
128.549
123.587
118.574
112.001
111.971
110.063
83.419
63.418
58.229
49.177
45.757
27.689
Me
N
H
O
BocO
OH
O
O
94l
Chemical Shift (ppm)


6.909
6.895
6.592
6.581
6.577
6.567
4.169
4.159
4.149
4.139
4.090
4.078
4.069
3.909
3.898
2.701
2.689
2.681
2.669
2.666
2.031
1.839
1.828
1.816
1.540
1.429
1.417
Me
N
H
Me
BocO
OH
O
O
94m
1.09
0.95
0.97
1.12
1.12
1.13
2.14
3.00
2.18
8.85
3.01
Chemical Shift (ppm)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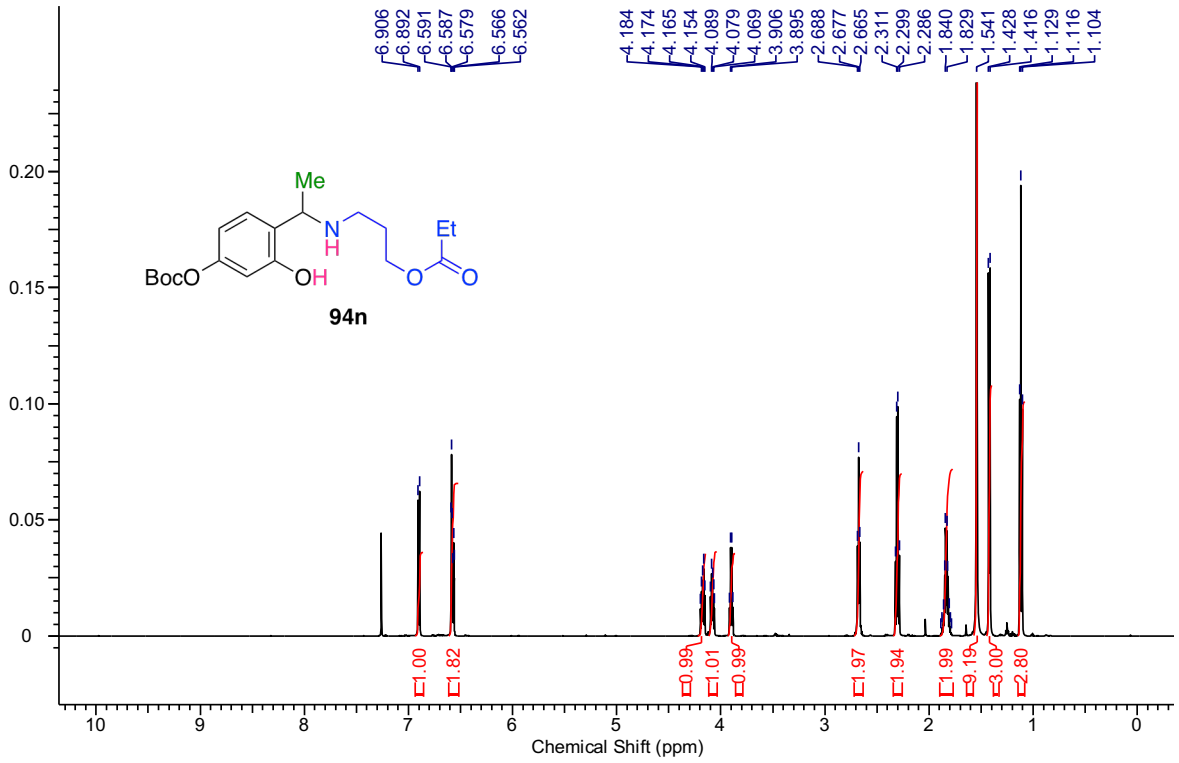
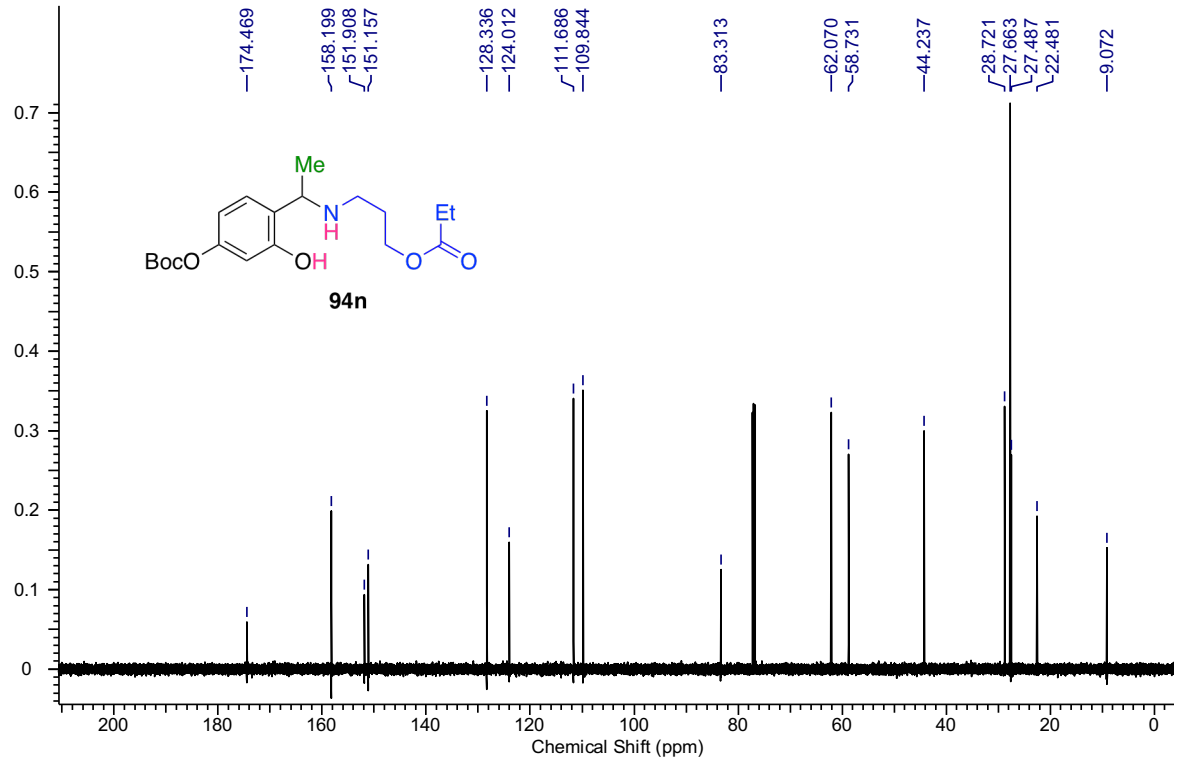
151.908
151.172
128.347
123.993
111.697
109.851
83.317
62.199
58.738
44.211
28.677
27.663
22.463
20.867
Me
N
H
Me
BocO
OH
O
O
94m
Chemical Shift (ppm)


6.906
6.892
6.591
6.587
6.579
6.566
6.562
4.184
4.174
4.165
4.154
4.089
4.079
4.069
3.906
3.895
2.688
2.677
2.665
2.311
2.299
2.286
1.840
1.829
1.541
1.428
1.416
1.129
1.116
1.104
Me
N
H
Et
BocO
OH
O
O
94n
1.00
1.82
0.99
1.01
0.99
1.97
1.94
1.99
9.19
3.00
2.80
Chemical Shift (ppm)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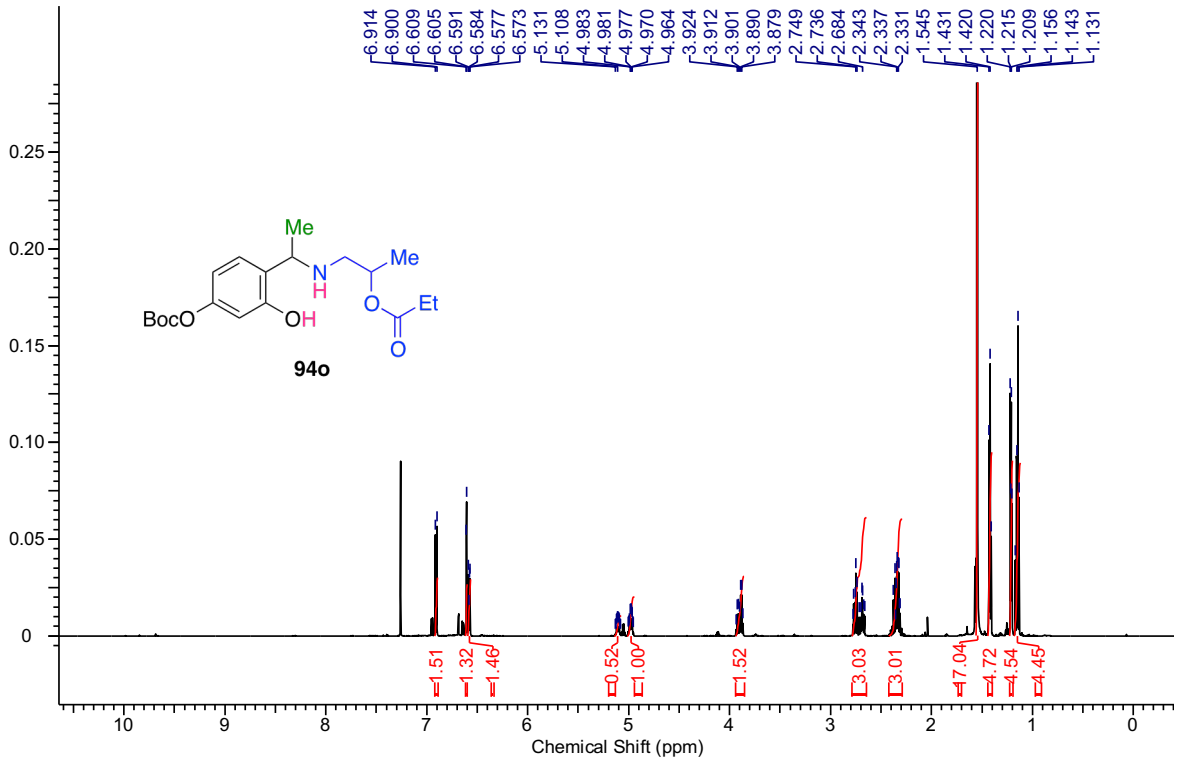
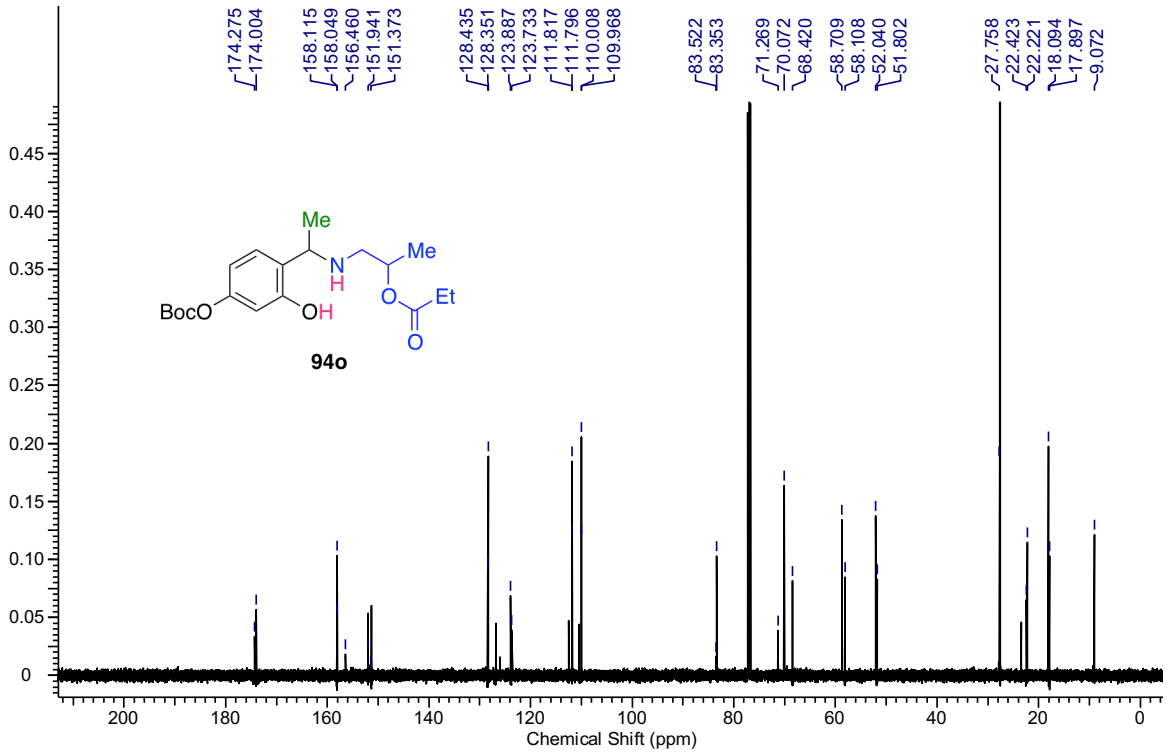
151.908
151.157
128.336
124.012
111.686
109.844
83.313
62.070
58.731
44.237
28.721
27.663
27.487
22.481
9.072
Me
N
H
Et
BocO
OH
O
O
94n
Chemical Shift (ppm)


6.914
6.900
6.609
6.605
6.591
6.584
6.577
6.573
5.131
5.108
4.983
4.981
4.977
4.970
4.964
3.924
3.912
3.901
3.890
3.879
2.749
2.736
2.684
2.343
2.337
2.331
1.545
1.431
1.420
1.220
1.215
1.209
1.156
1.143
1.131
Me
N
H
Me
O
Et
O
BocO
OH
94o
1.51
1.32
1.46
0.52
1.00
1.52
3.03
3.01
17.04
4.72
4.54
4.45
Chemical Shift (ppm)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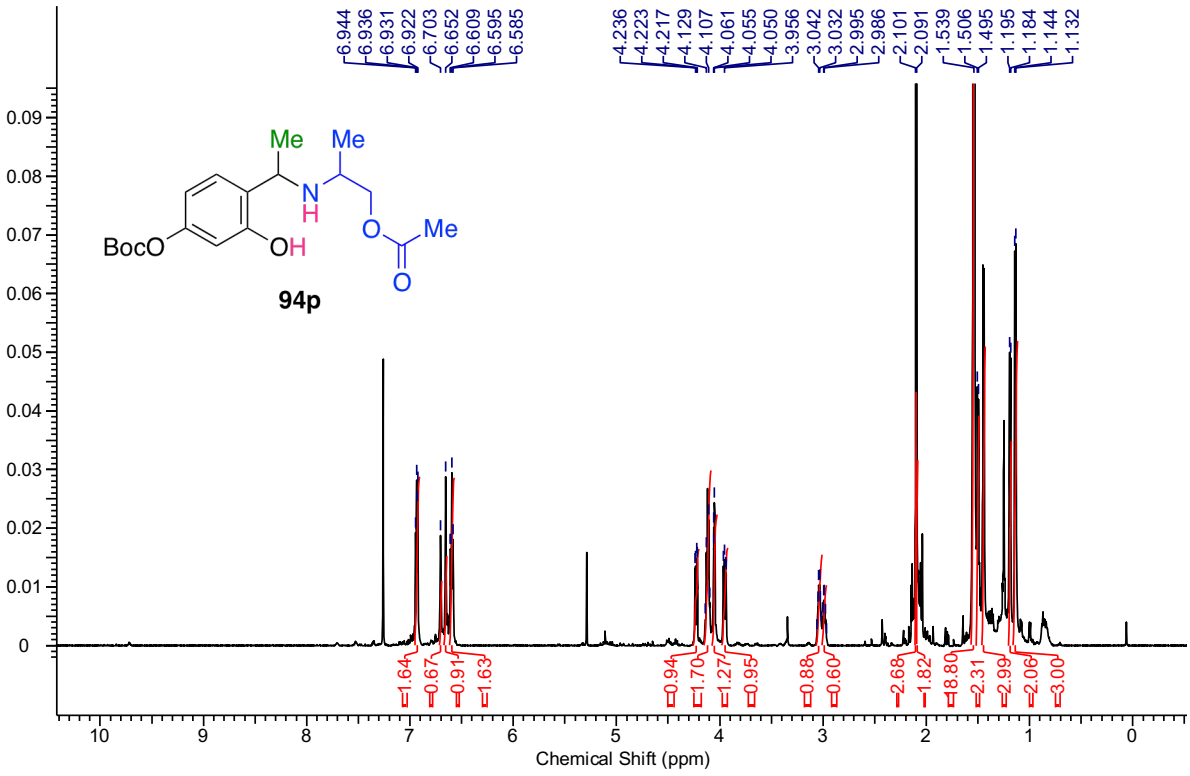
158.115
158.049
156.460
151.941
151.373
128.435
128.351
123.887
123.733
111.817
111.796
110.008
109.968
83.522
83.353
71.269
70.072
68.420
58.709
58.108
52.040
51.802
27.758
22.423
22.221
18.094
17.897
9.072
Me
N
H
Me
O
Et
O
BocO
OH
94o
Chemical Shift (ppm)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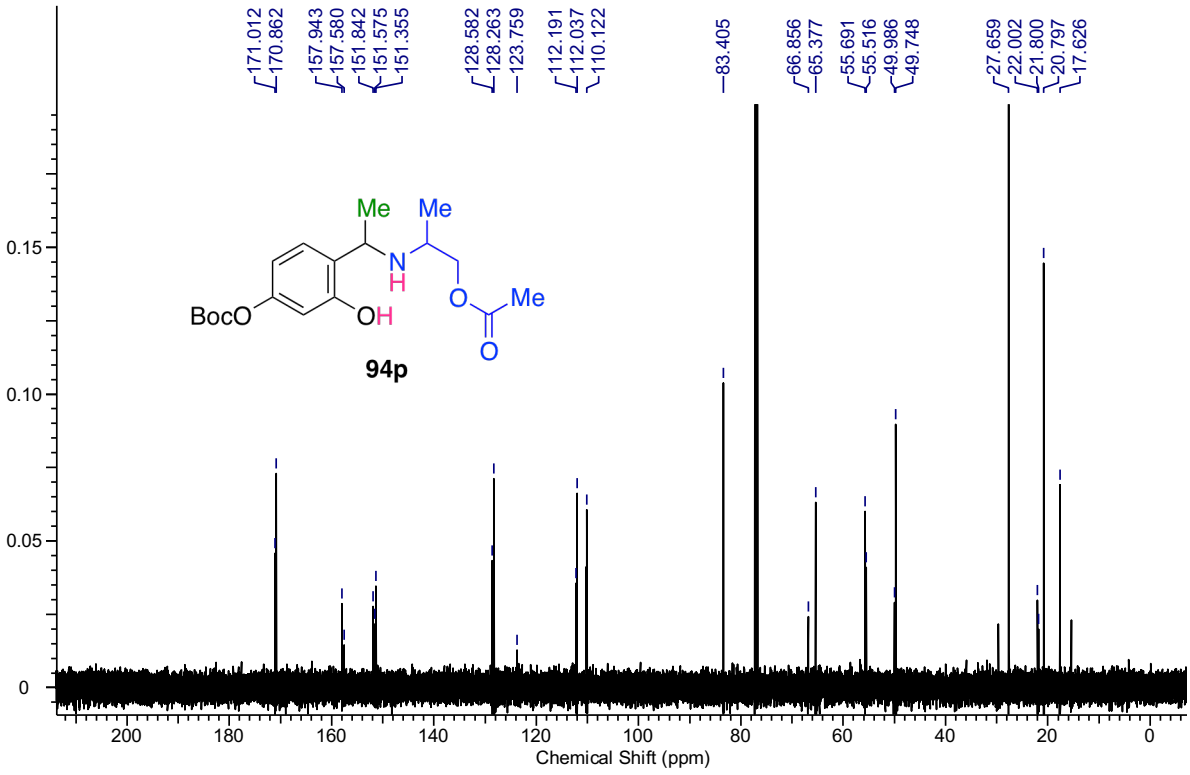
6.931
6.922
6.703
6.652
6.609
6.595
6.585
4.236
4.223
4.217
4.129
4.107
4.061
4.055
4.050
3.956
3.042
3.032
2.995
2.986
2.101
2.091
1.539
1.506
1.495
1.195
1.184
1.144
1.132
Me
Me
N
H
O
Me
BocO
OH
O
94p
1.64
0.67
0.91
1.63
0.94
1.70
1.27
0.95
0.88
0.60
2.68
1.82
18.80
2.31
2.99
2.06
3.00
Chemical Shift (ppm)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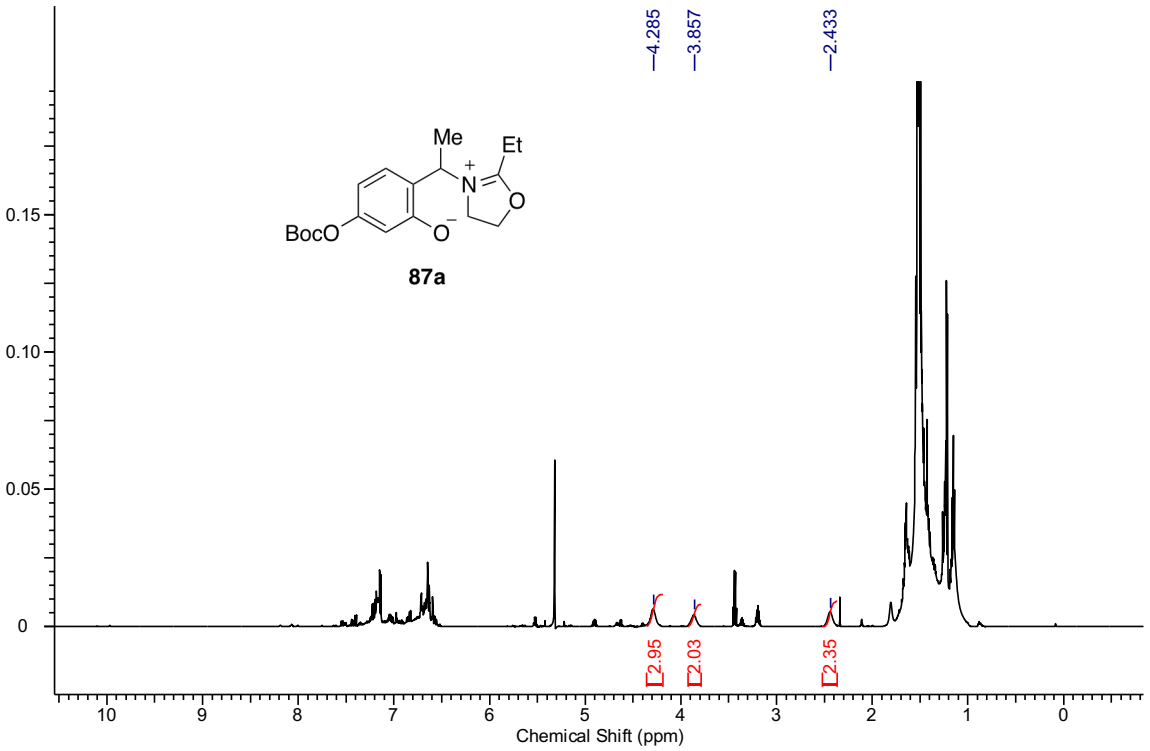
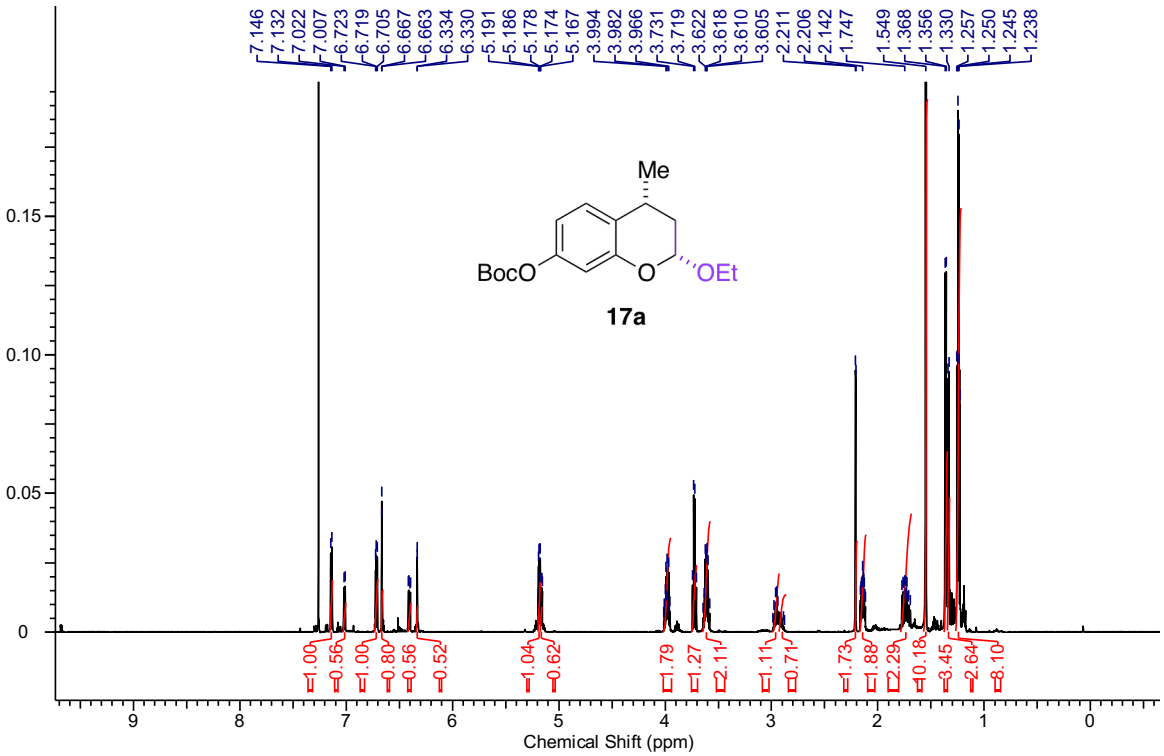
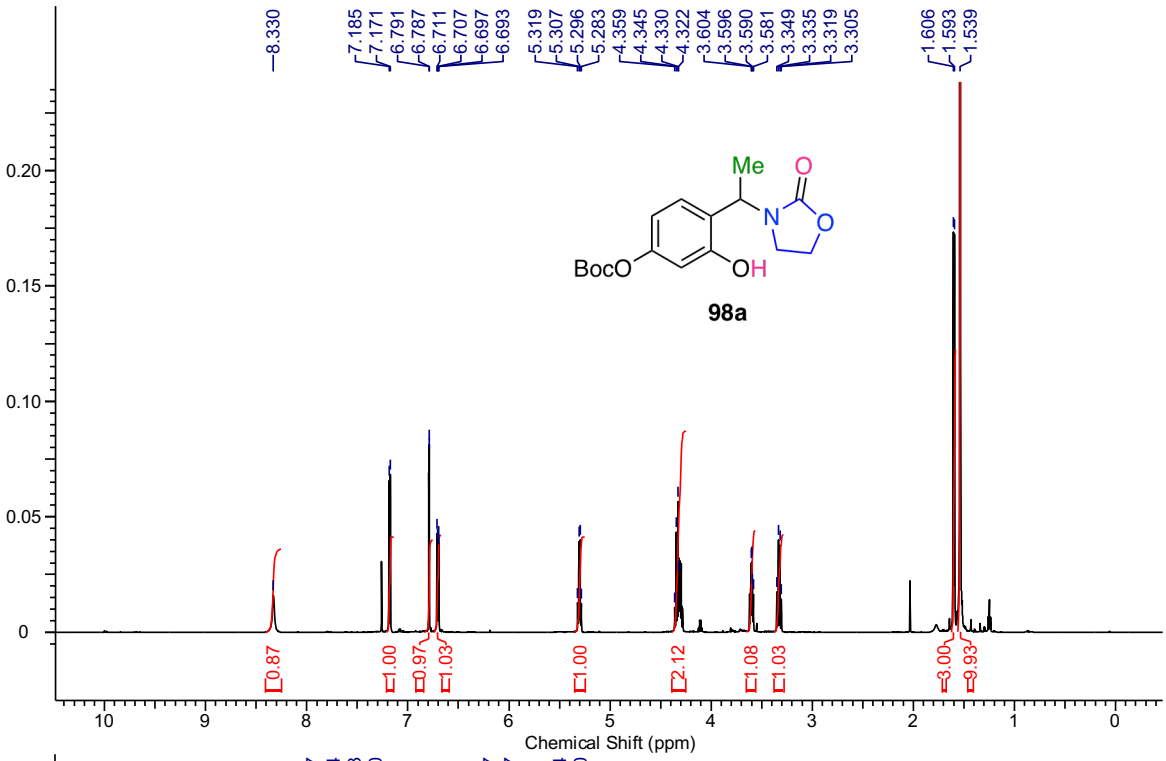
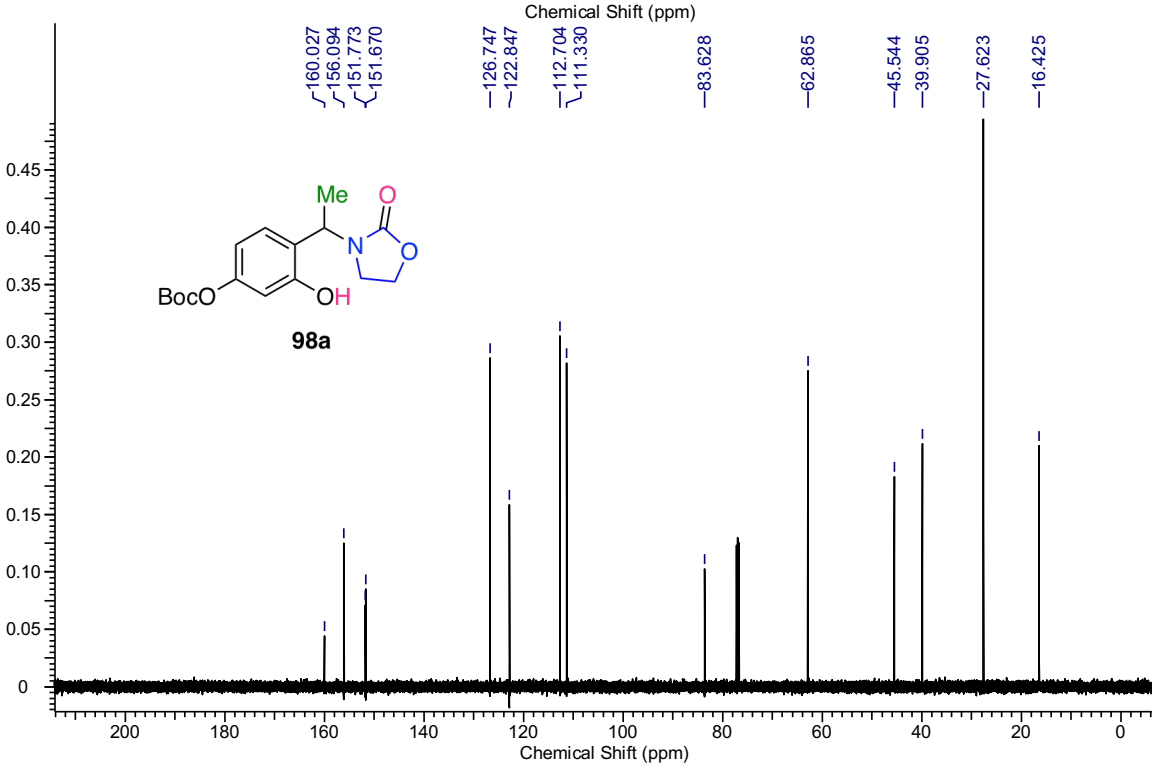
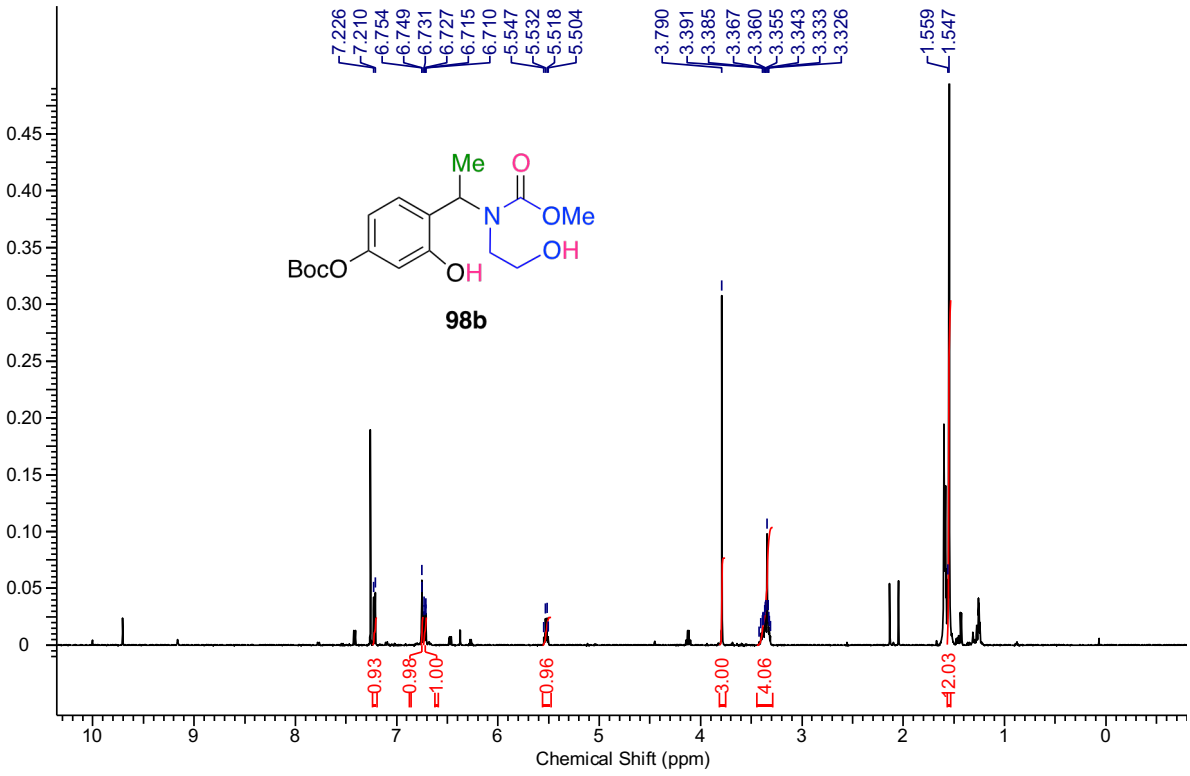
170.862
157.943
157.580
151.842
151.575
151.355
128.582
128.263
123.759
112.191
112.037
110.122
83.405
66.856
65.377
55.691
55.516
49.986
49.748
27.659
22.002
21.800
20.797
17.626
Me
Me
N
H
O
Me
BocO
OH
O
94p
Chemical Shift (ppm)

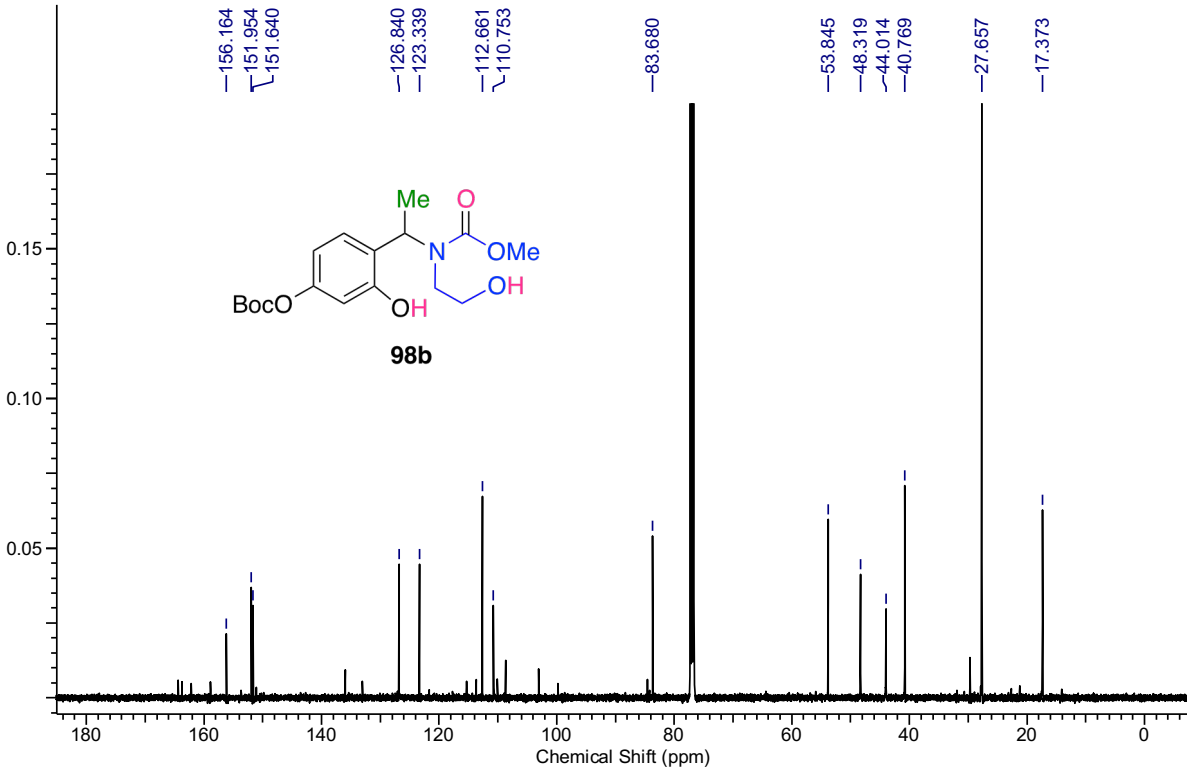

4.285
3.857
2.433
Me
Et
N
O
BocO
O
87a
0.15
0.10
0.05
0
2.95
2.03
2.35
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

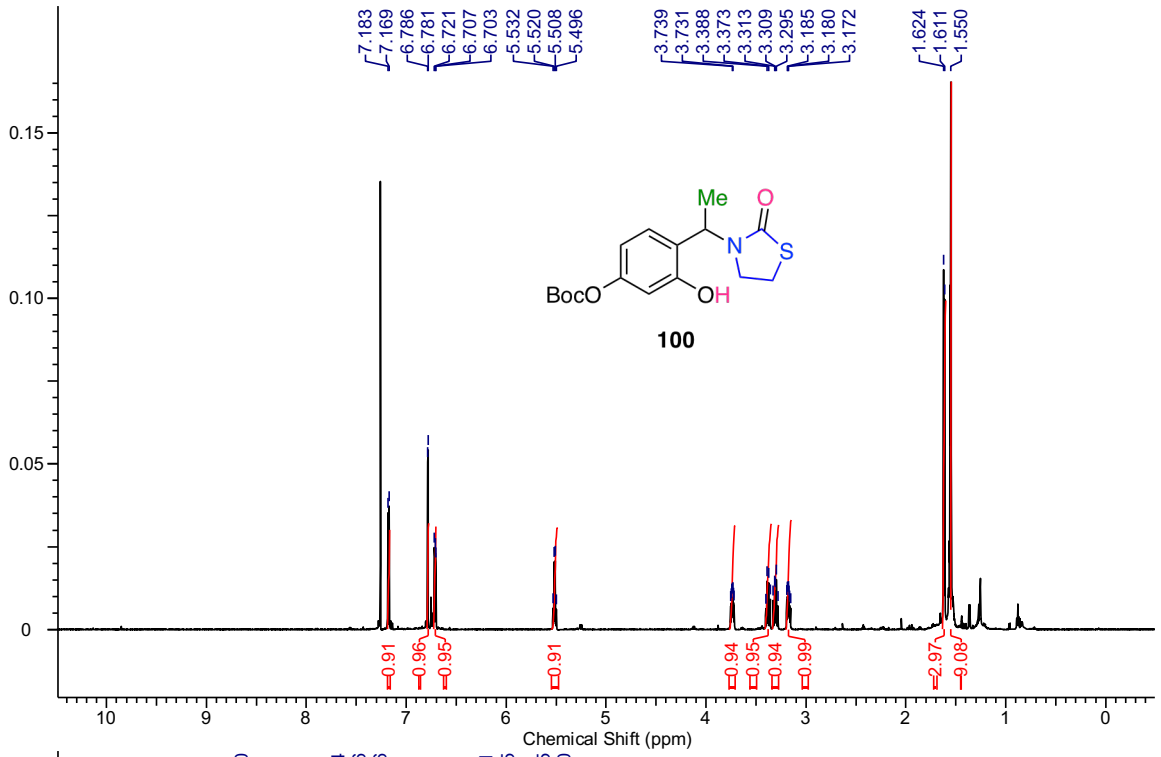

7.146
7.132
7.022
7.007
6.723
6.719
6.705
6.667
6.663
6.334
6.330
5.191
5.186
5.178
5.174
5.167
3.994
3.982
3.966
3.731
3.719
3.622
3.618
3.610
3.605
2.211
2.206
2.142
1.747
1.549
1.368
1.356
1.330
1.257
1.250
1.245
1.238
Me
BocO
O
OEt
17a
0.15
0.10
0.05
0
1.00
0.56
1.00
0.80
0.56
0.52
1.04
0.62
1.79
1.27
2.11
1.11
0.71
1.73
1.88
2.29
10.18
3.45
2.64
8.10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

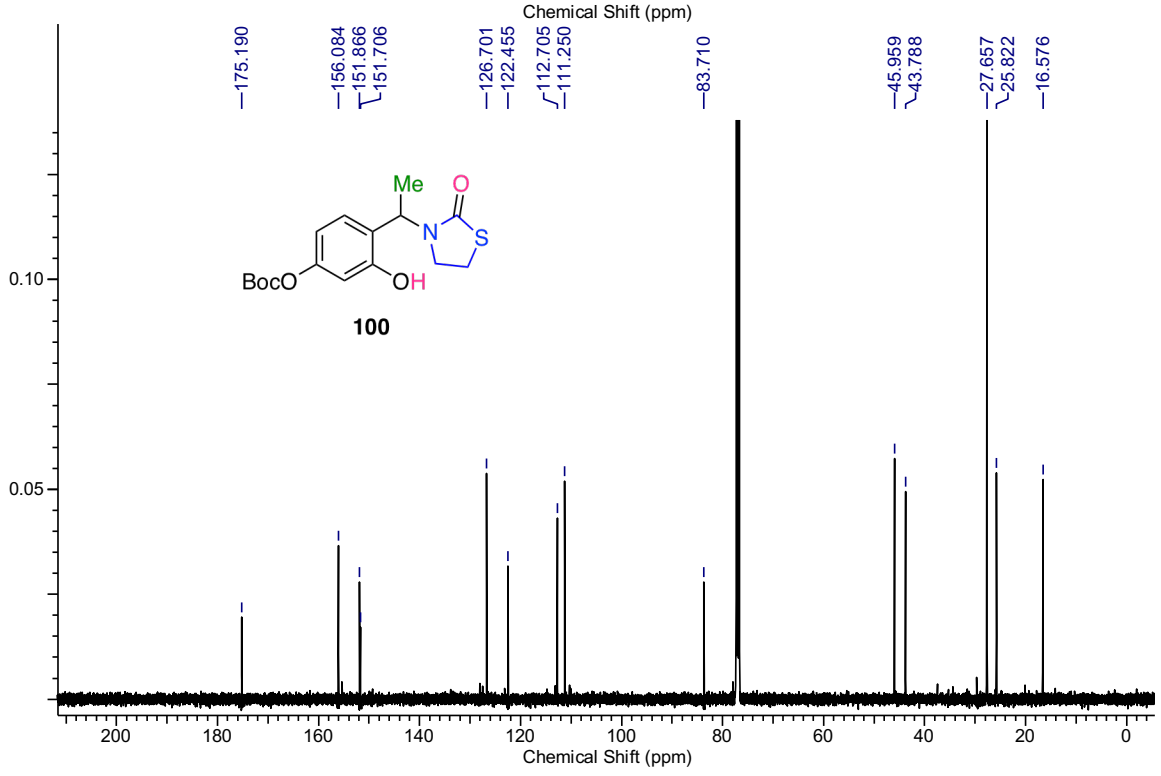

8.330
7.185
7.171
6.791
6.787
6.711
6.707
6.697
6.693
5.319
5.307
5.296
5.283
4.359
4.345
4.330
4.322
3.604
3.596
3.590
3.581
3.349
3.335
3.319
3.305
1.606
1.593
1.539
Me
O
N
O
BocO
OH
98a
0.87
1.00
0.97
1.03
1.00
2.12
1.08
1.03
3.00
9.93
Chemical Shift (ppm)

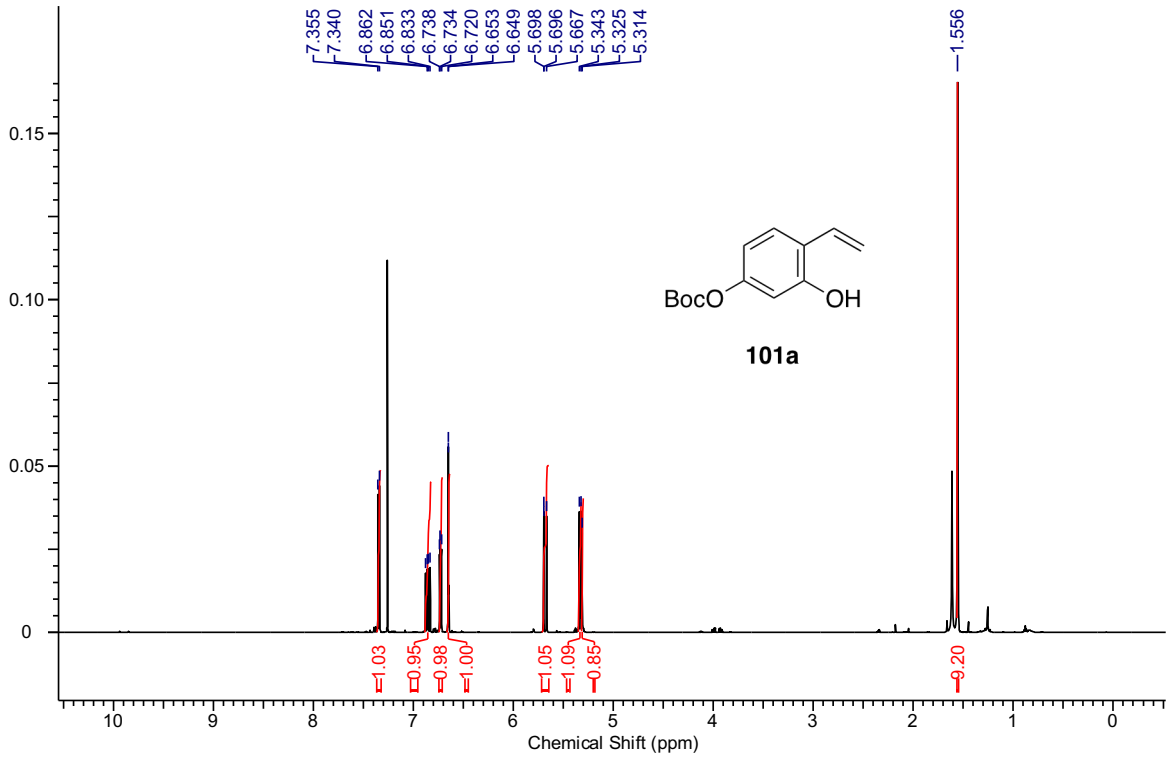

160.027
156.094
151.773
151.670
126.747
122.847
112.704
111.330
83.628
62.865
45.544
39.905
27.623
16.425
Me
O
N
O
BocO
OH
98a
Chemical Shift (ppm)

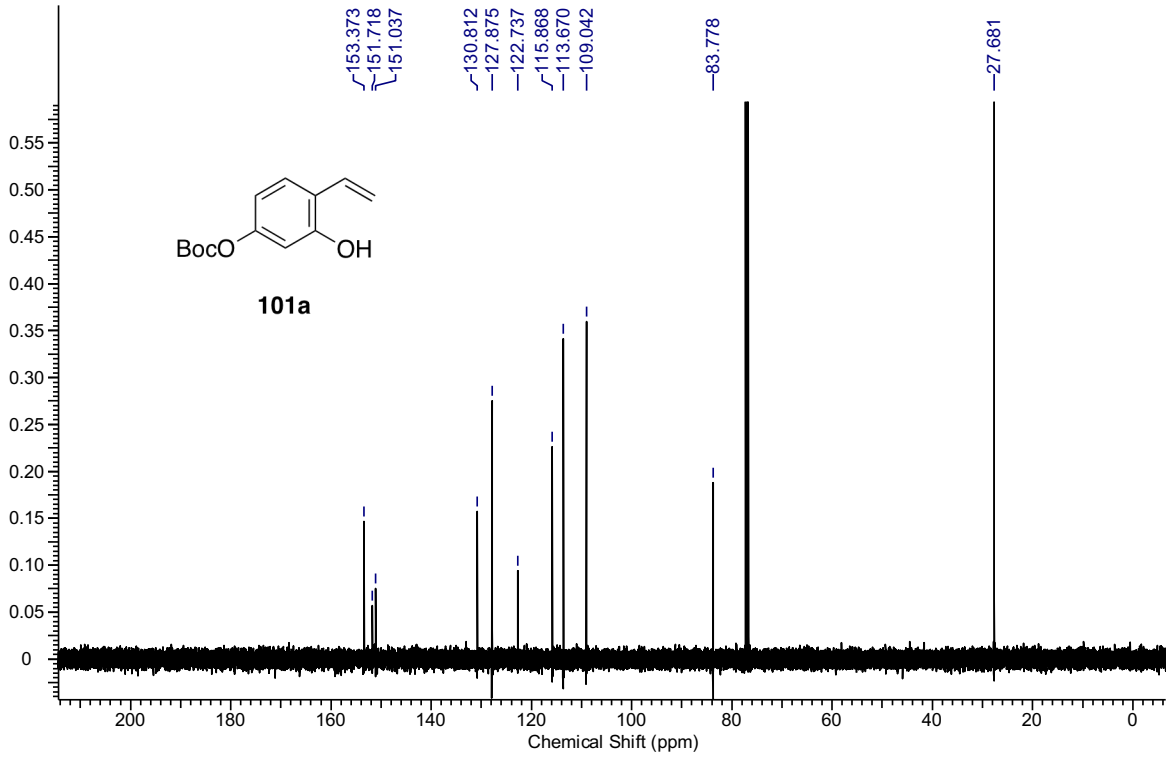

7.226
7.210
6.754
6.749
6.731
6.727
6.715
6.710
5.547
5.532
5.518
5.504
3.790
3.391
3.385
3.367
3.360
3.355
3.343
3.333
3.326
1.559
1.547
Me
O
N
OMe
OH
BocO
OH
98b
0.93
0.98
1.00
0.96
3.00
4.06
12.03
Chemical Shift (ppm)

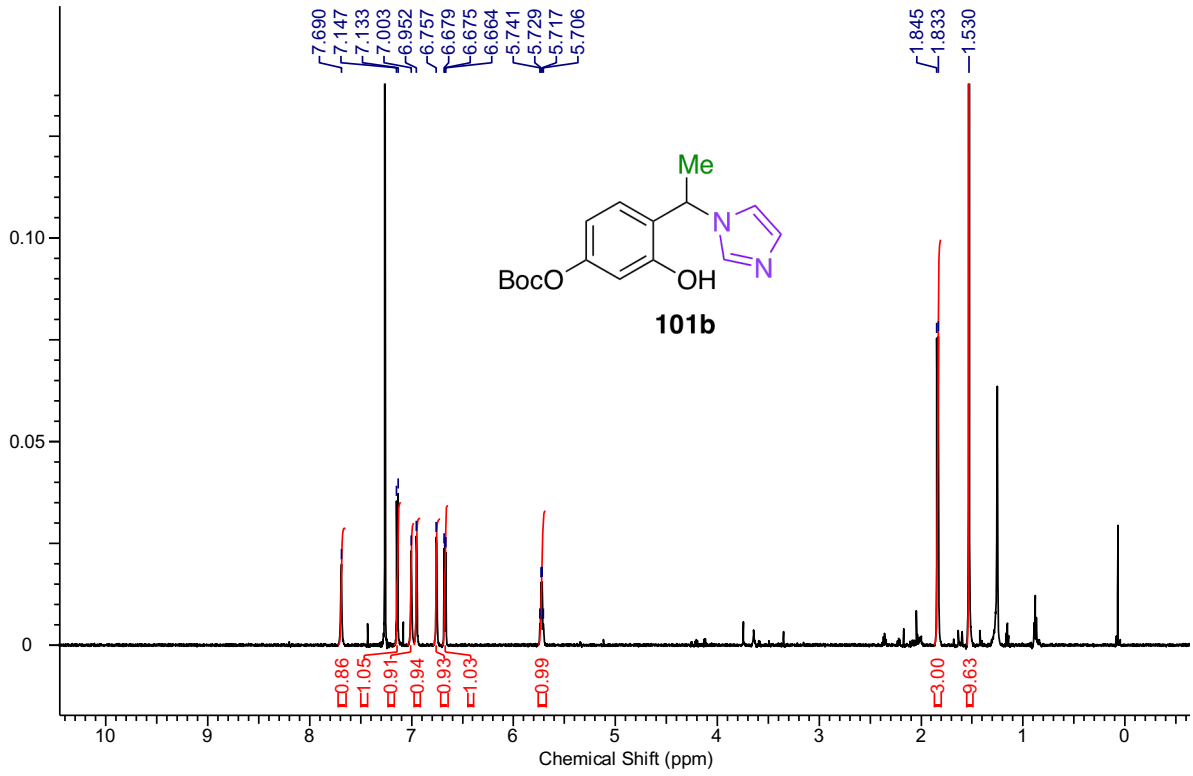

156.164
151.954
151.640
126.840
123.339
112.661
110.753
83.680
53.845
48.319
44.014
40.769
27.657
17.373
Me
O
N
OMe
OH
BocO
OH
98b
Chemical Shift (ppm)

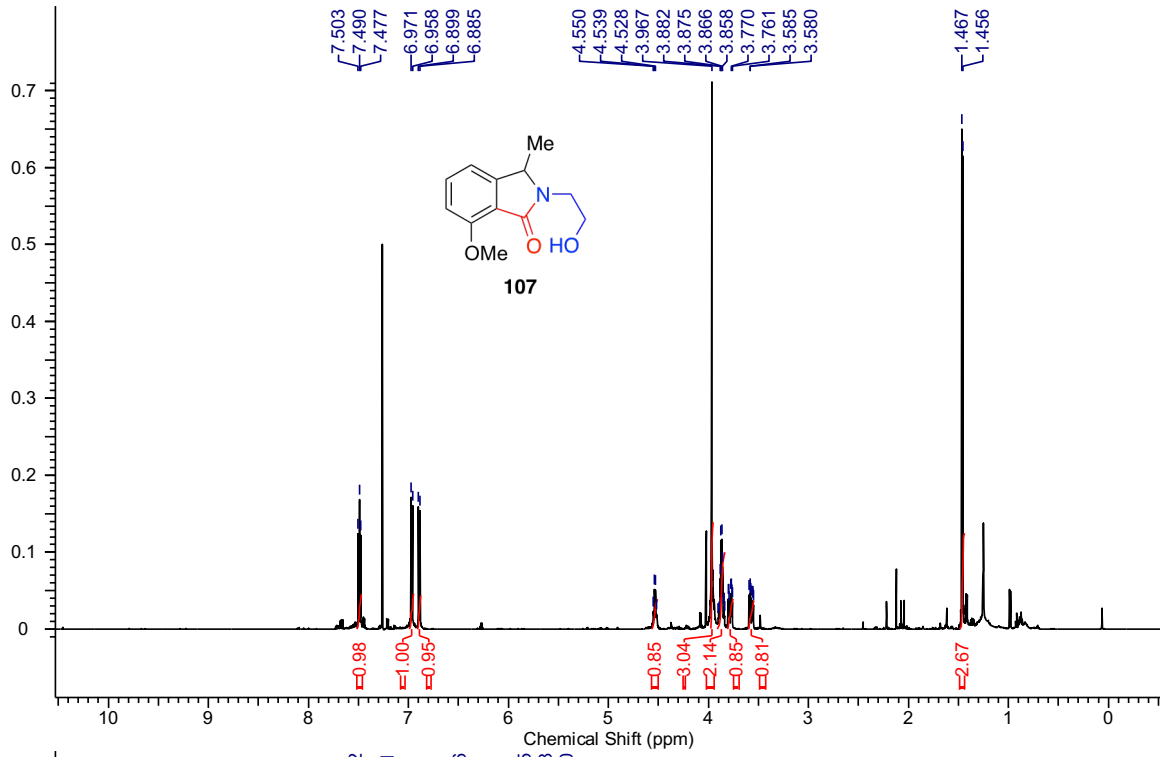

7.183
7.169
6.786
6.781
6.721
6.707
6.703
5.532
5.520
5.508
5.496
3.739
3.731
3.388
3.373
3.313
3.309
3.295
3.185
3.180
3.172
1.624
1.611
1.550
Me
O
N
S
BocO
OH
100
0.91
0.96
0.95
0.91
0.94
0.95
0.94
0.99
2.97
9.08
Chemical Shift (ppm)

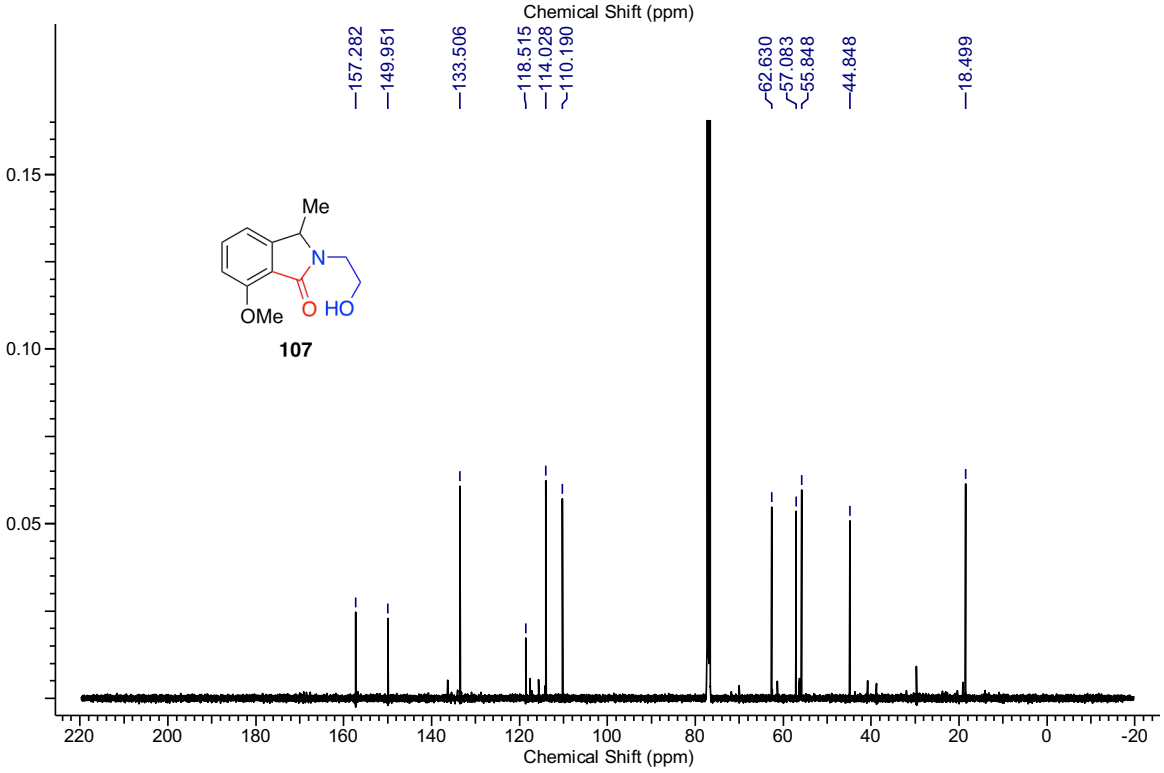

175.190
156.084
151.866
151.706
126.701
122.455
112.705
111.250
83.710
45.959
43.788
27.657
25.822
16.576
Me
O
N
S
BocO
OH
100
Chemical Shift (ppm)

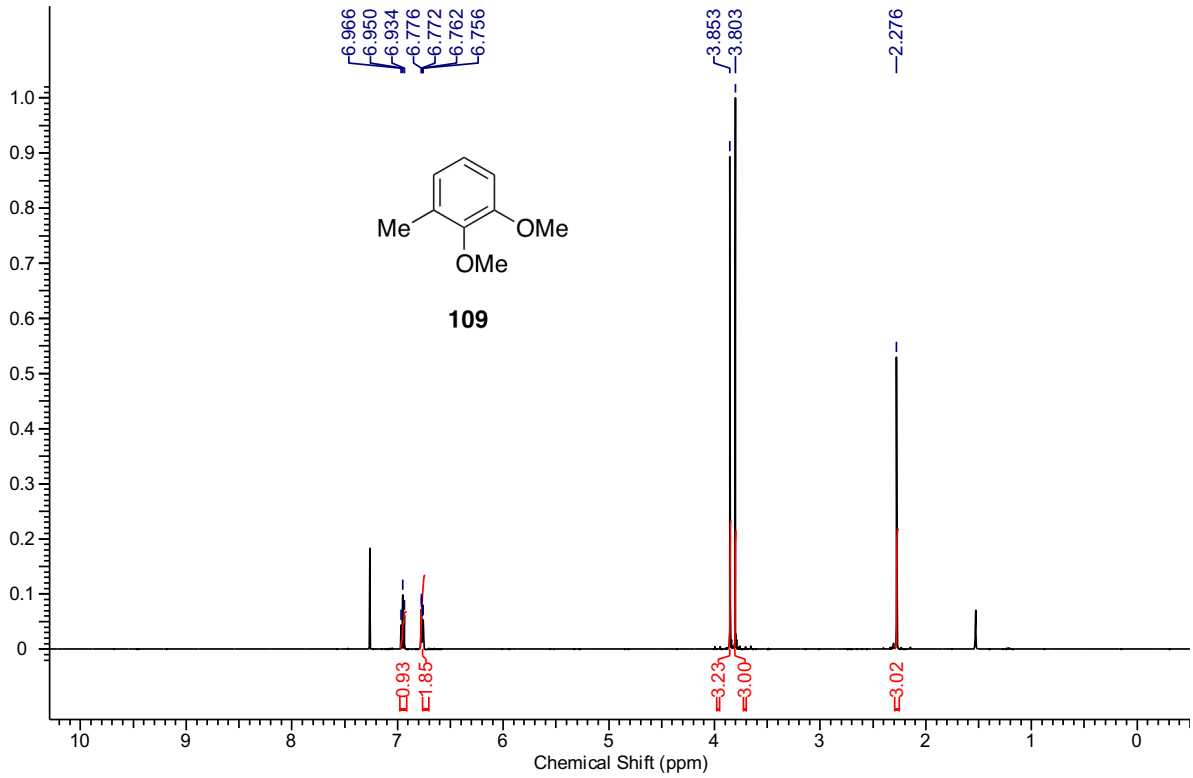

7.355
7.340
6.862
6.851
6.833
6.738
6.734
6.720
6.653
6.649
5.698
5.696
5.667
5.343
5.325
5.314
1.556
BocO
OH
101a
1.03
0.95
0.98
1.00
1.05
1.09
0.85
9.20
Chemical Shift (ppm)

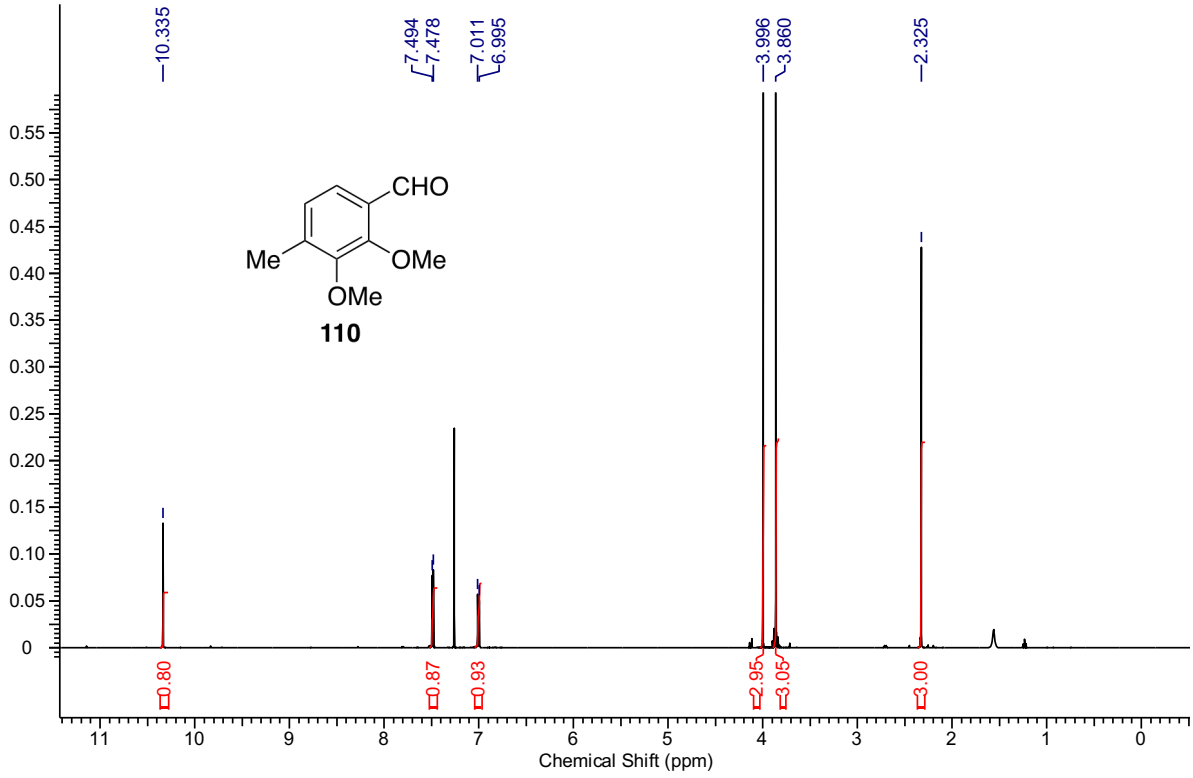

153.373
151.718
151.037
130.812
127.875
122.737
115.868
113.670
109.042
83.778
27.681
BocO
OH
101a
Chemical Shift (ppm)

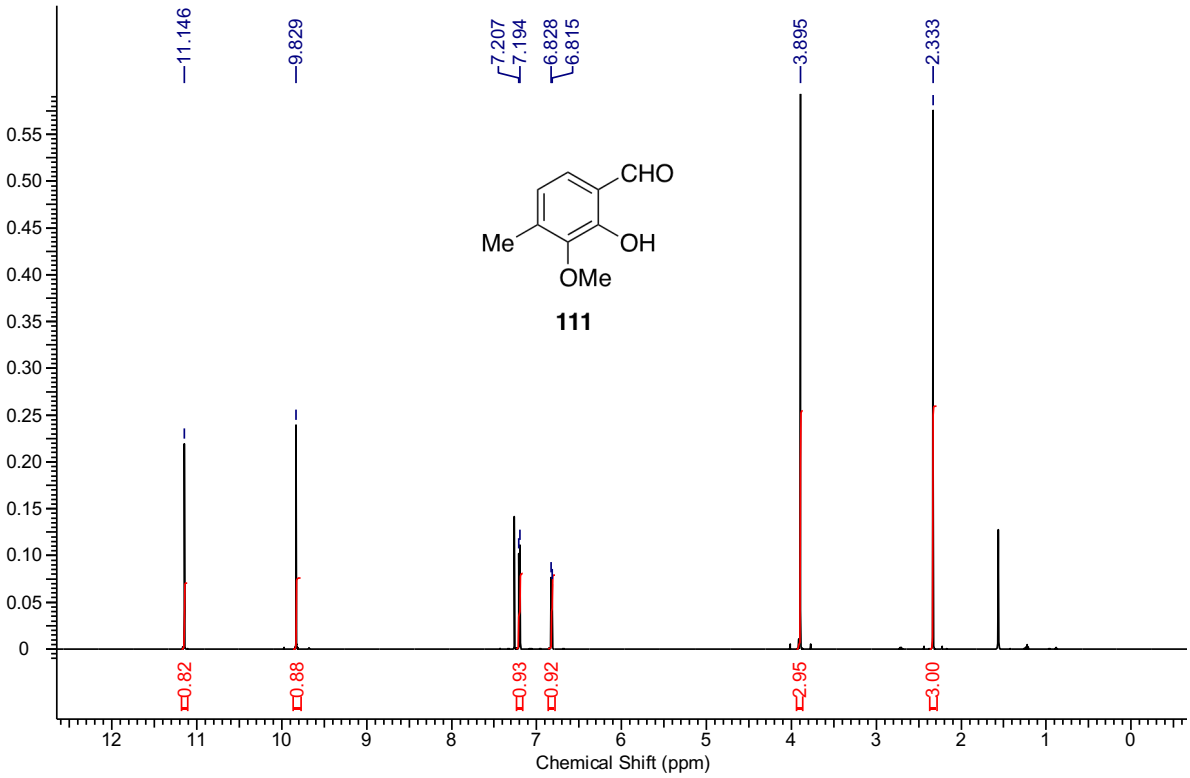

7.690
7.147
7.133
7.003
6.952
6.757
6.679
6.675
6.664
5.741
5.729
5.717
5.706
1.845
1.833
1.530
Me
N
N
BocO
OH
101b
0.10
0.05
0
0.86
1.05
0.91
0.94
0.93
1.03
0.99
3.00
9.63
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

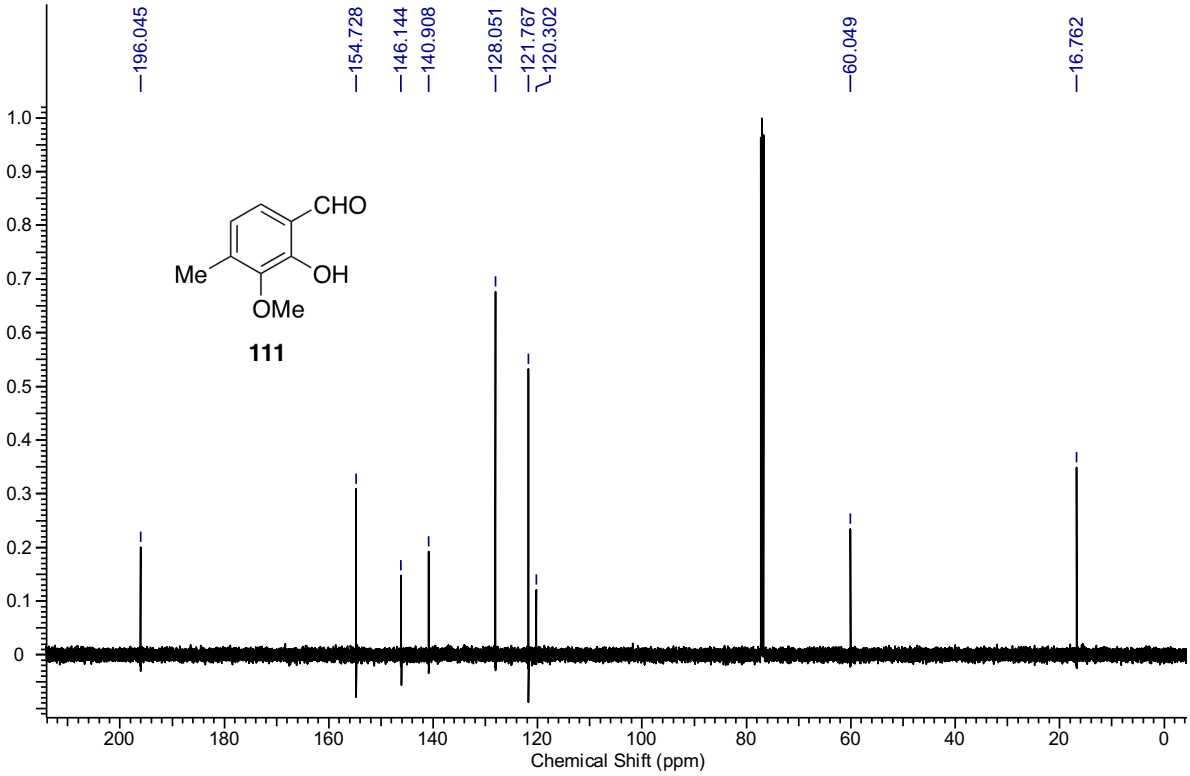

7.503
7.490
7.477
6.971
6.958
6.899
6.885
4.550
4.539
4.528
3.967
3.882
3.875
3.866
3.858
3.770
3.761
3.585
3.580
1.467
1.456
Me
N
O
HO
OMe
107
0.98
1.00
0.95
0.85
3.04
2.14
0.85
0.81
2.67
Chemical Shift (ppm)

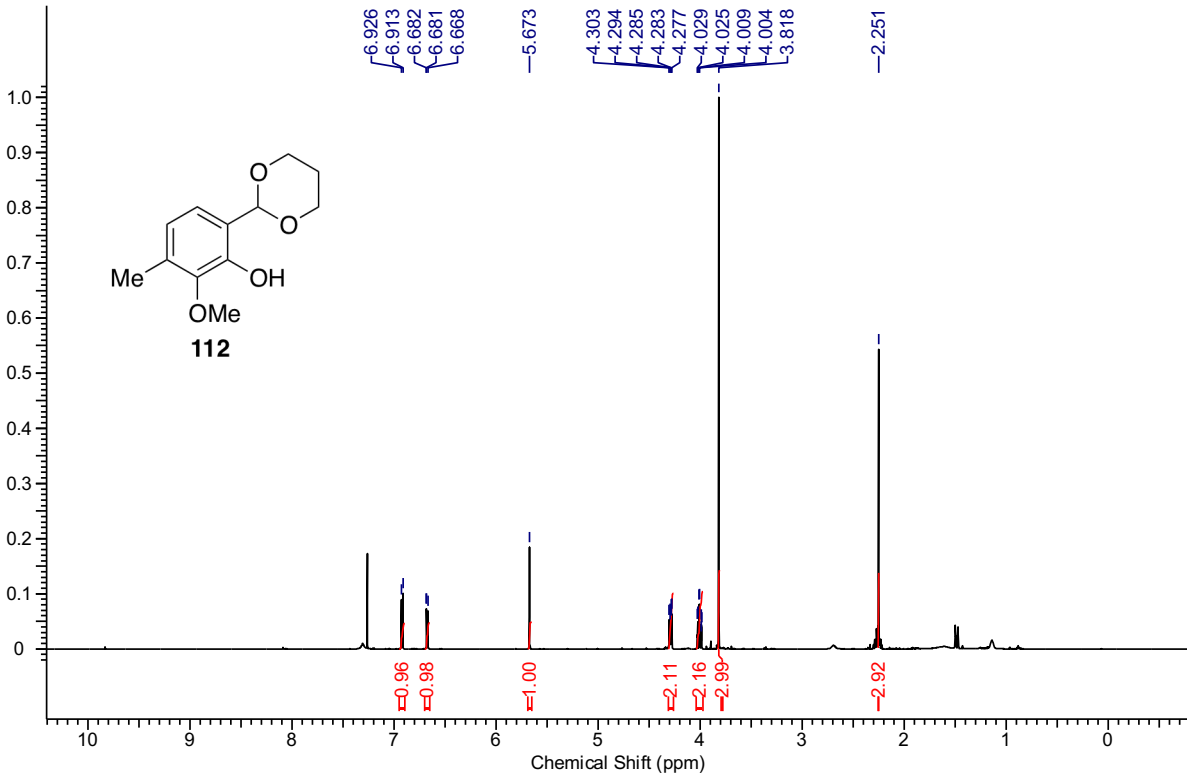

157.282
149.951
133.506
118.515
114.028
110.190
62.630
57.083
55.848
44.848
18.499
Me
N
O
HO
OMe
107
Chemical Shift (ppm)

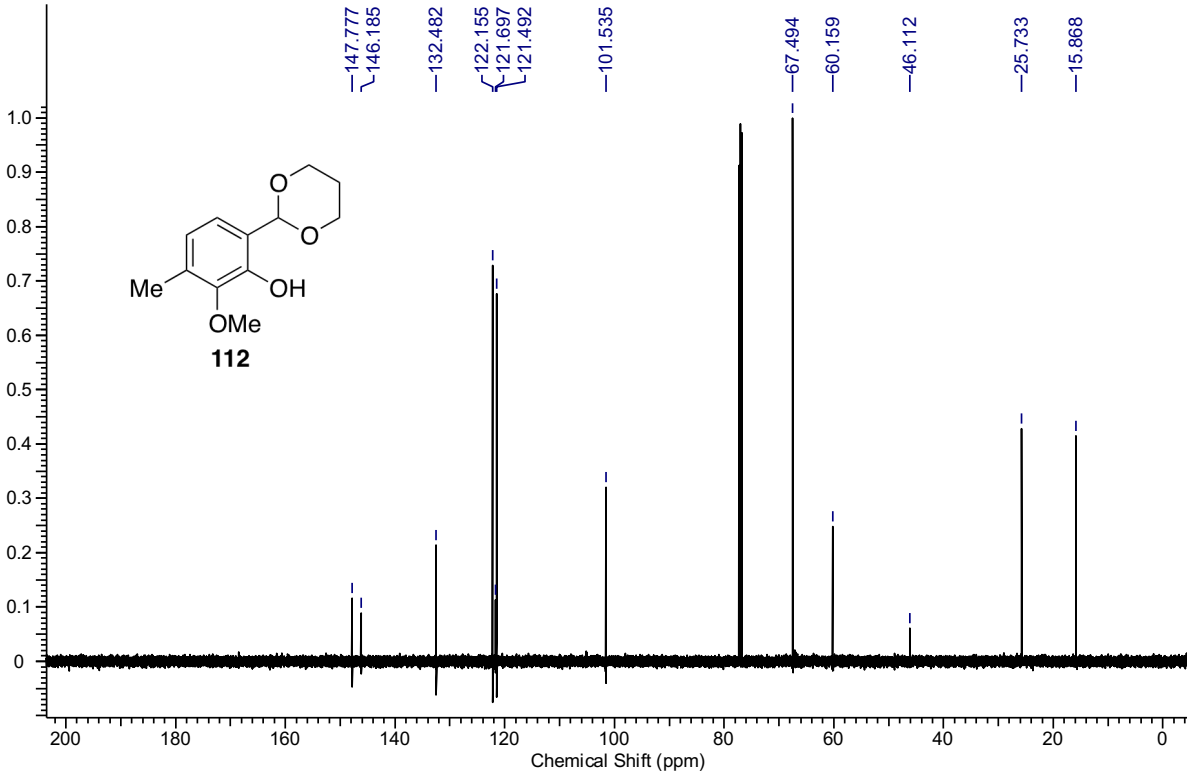

6.966
6.950
6.934
6.776
6.772
6.762
6.756
3.853
3.803
2.276
Me
OMe
OMe
109
0.93
1.85
3.23
3.00
3.02
Chemical Shift (ppm)

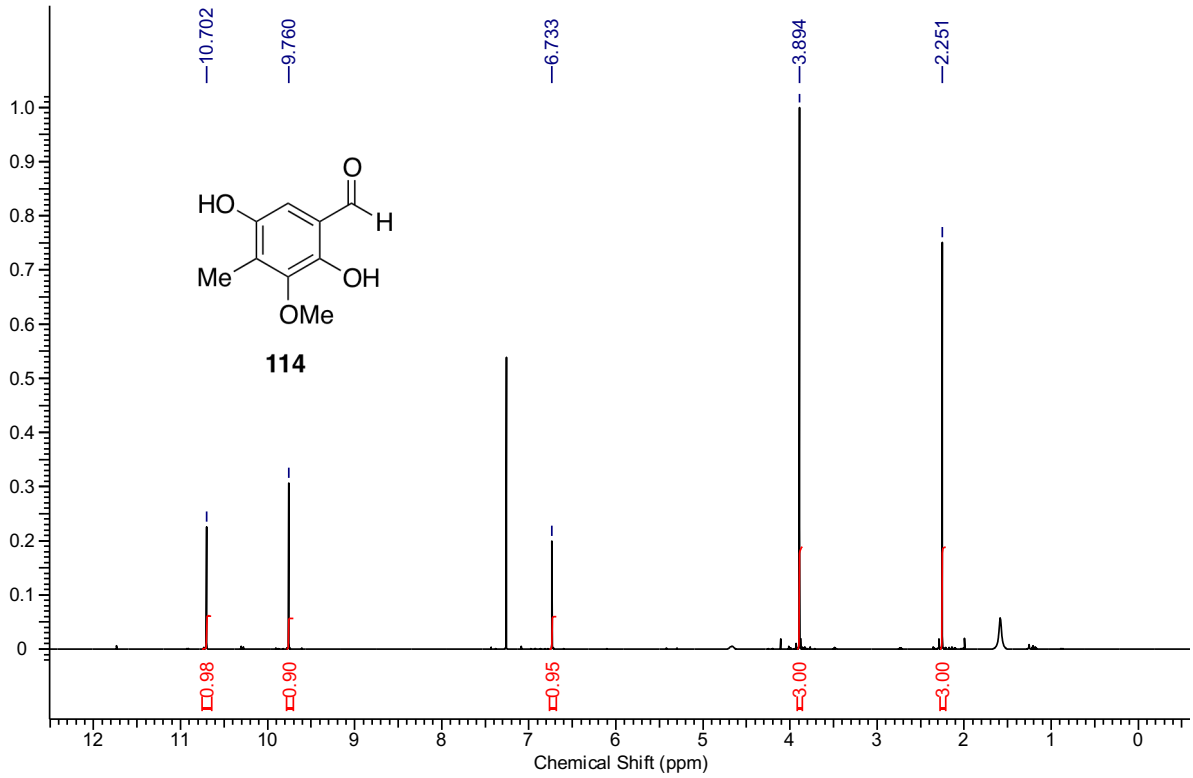

10.335
7.494
7.478
7.011
6.995
3.996
3.860
2.325
CHO
Me
OMe
OMe
110
0.80
0.87
0.93
2.95
3.05
3.00
Chemical Shift (ppm)

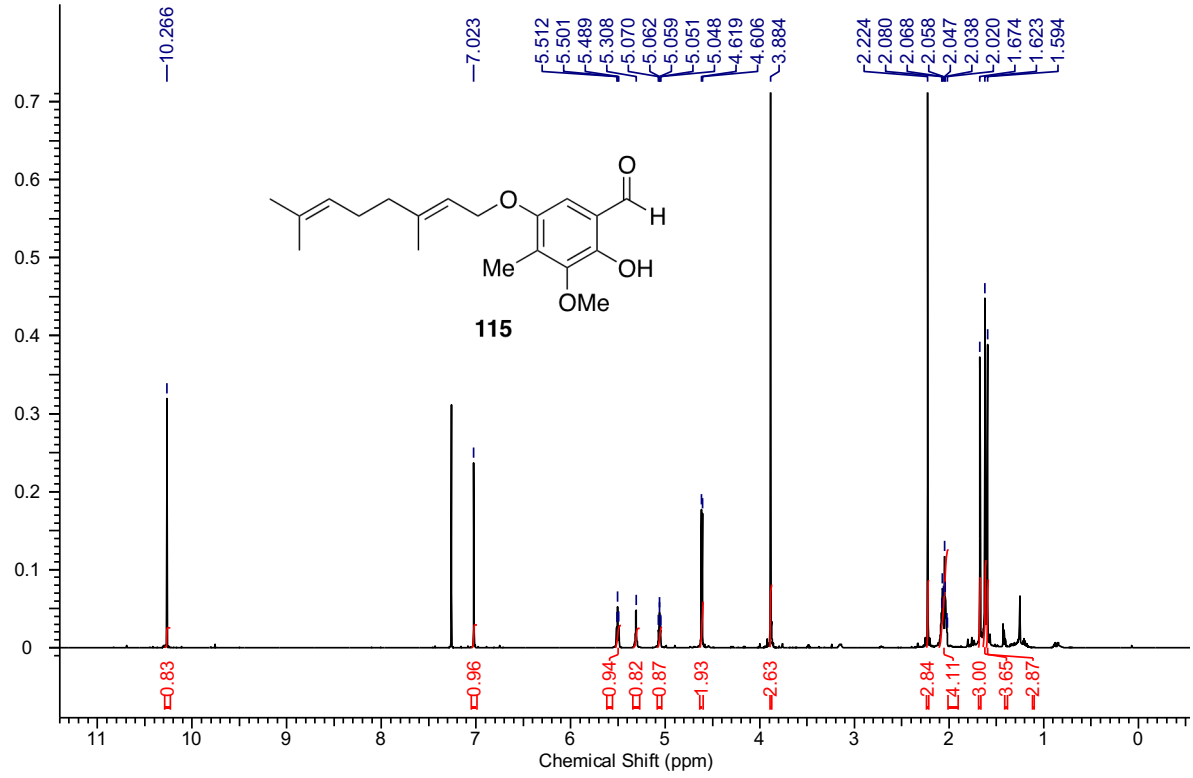

11.146
9.829
7.207
7.194
6.828
6.815
3.895
2.333
CHO
Me
OH
OMe
111
0.82
0.88
0.93
0.92
2.95
3.00
Chemical Shift (ppm)

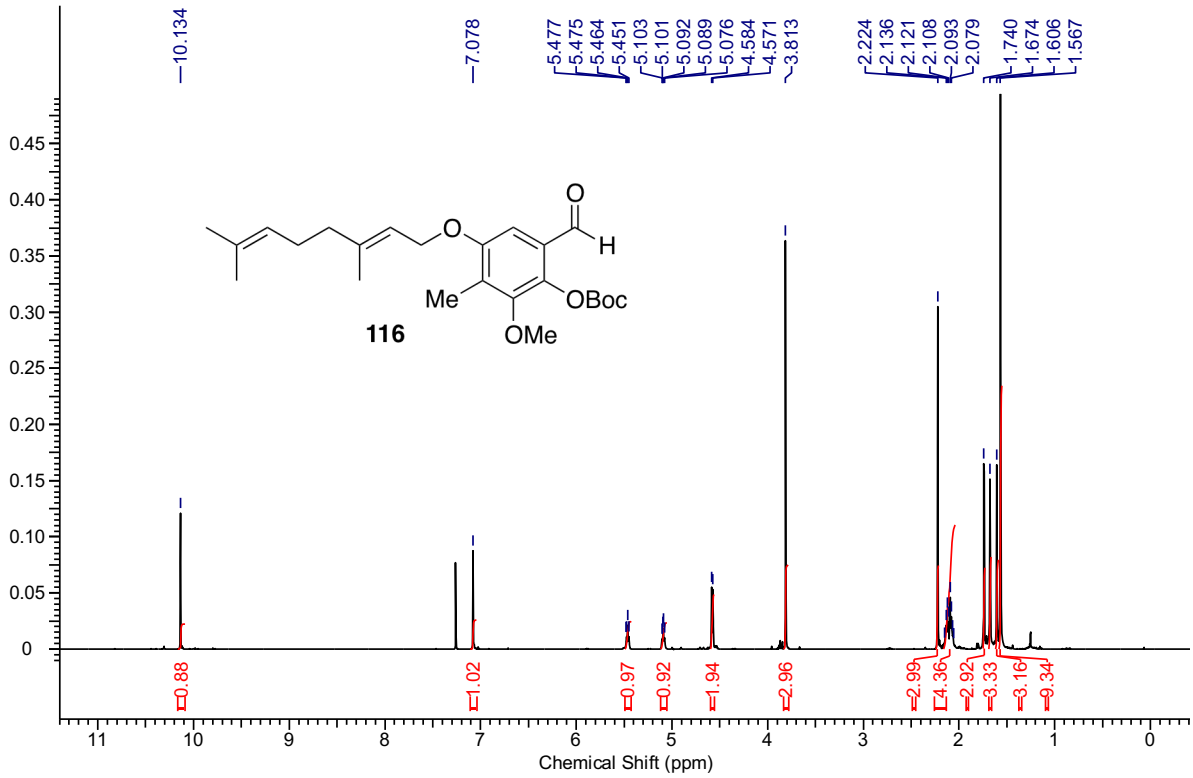

196.045
154.728
146.144
140.908
128.051
121.767
120.302
60.049
16.762
CHO
Me
OH
OMe
111
Chemical Shift (ppm)

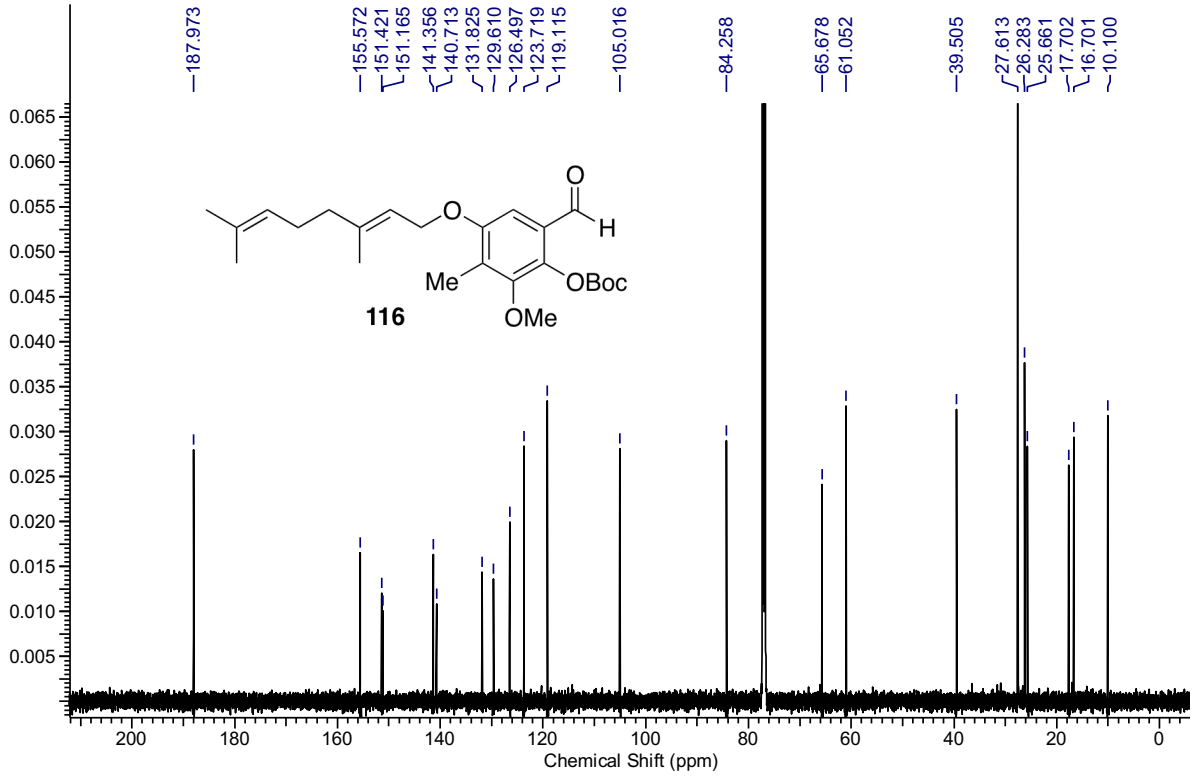

6.926
6.913
6.682
6.681
6.668
5.673
4.303
4.294
4.285
4.283
4.277
4.029
4.025
4.009
4.004
3.818
2.251
Me
OH
OMe
112
0.96
0.98
1.00
2.11
2.16
2.99
2.92
Chemical Shift (ppm)

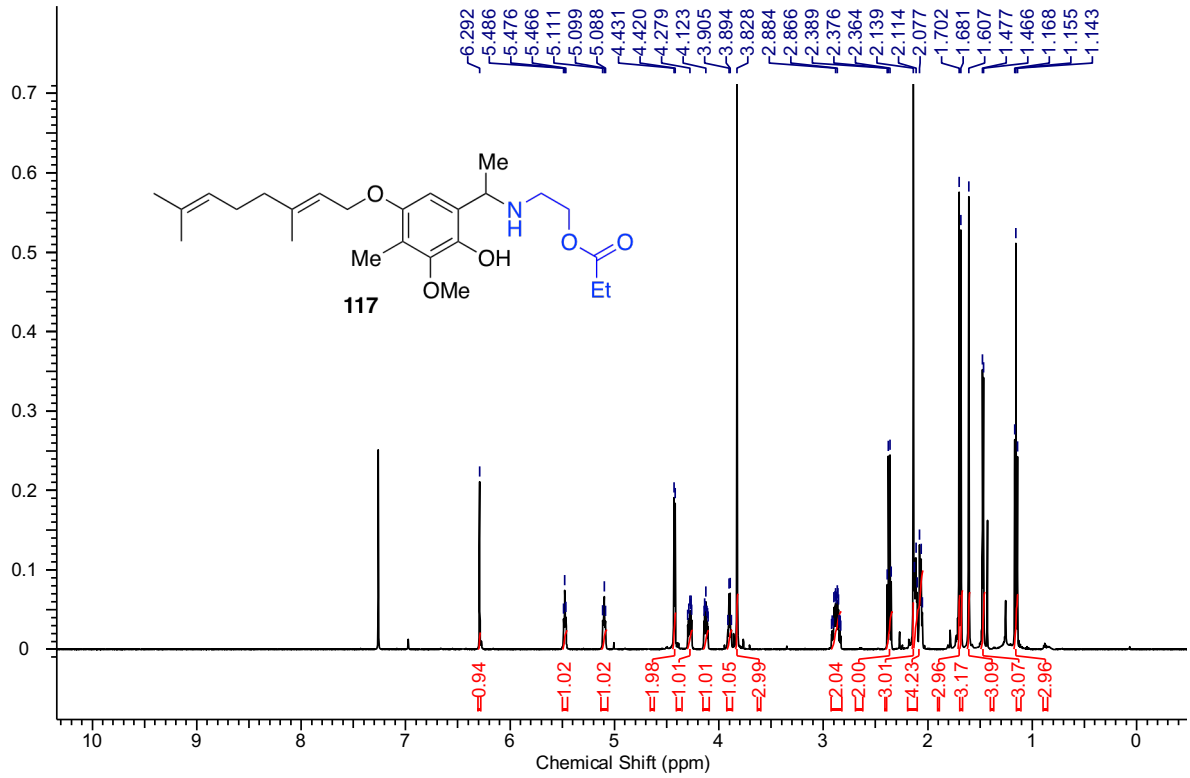

147.777
146.185
132.482
122.155
121.697
121.492
101.535
67.494
60.159
46.112
25.733
15.868
Me
OH
OMe
112
Chemical Shift (ppm)

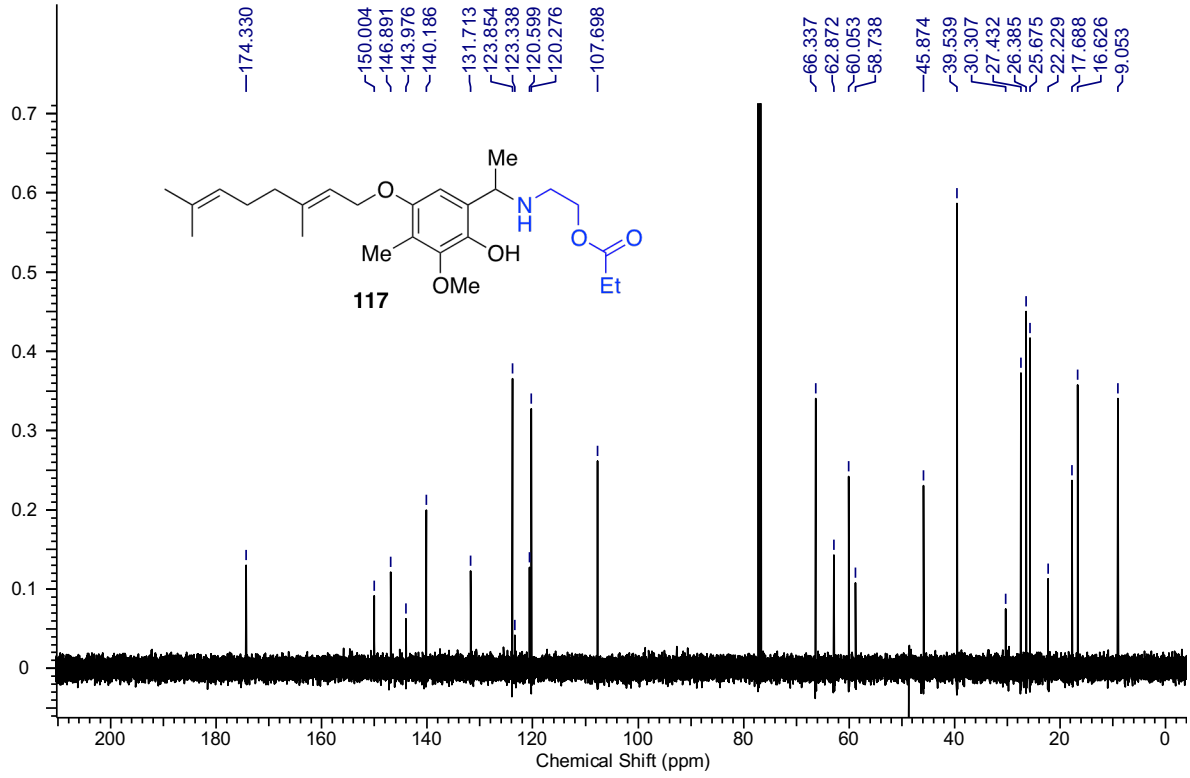

10.702
9.760
6.733
3.894
2.251
HO
O
H
Me
OH
OMe
114
0.98
0.90
0.95
3.00
3.00
Chemical Shift (ppm)

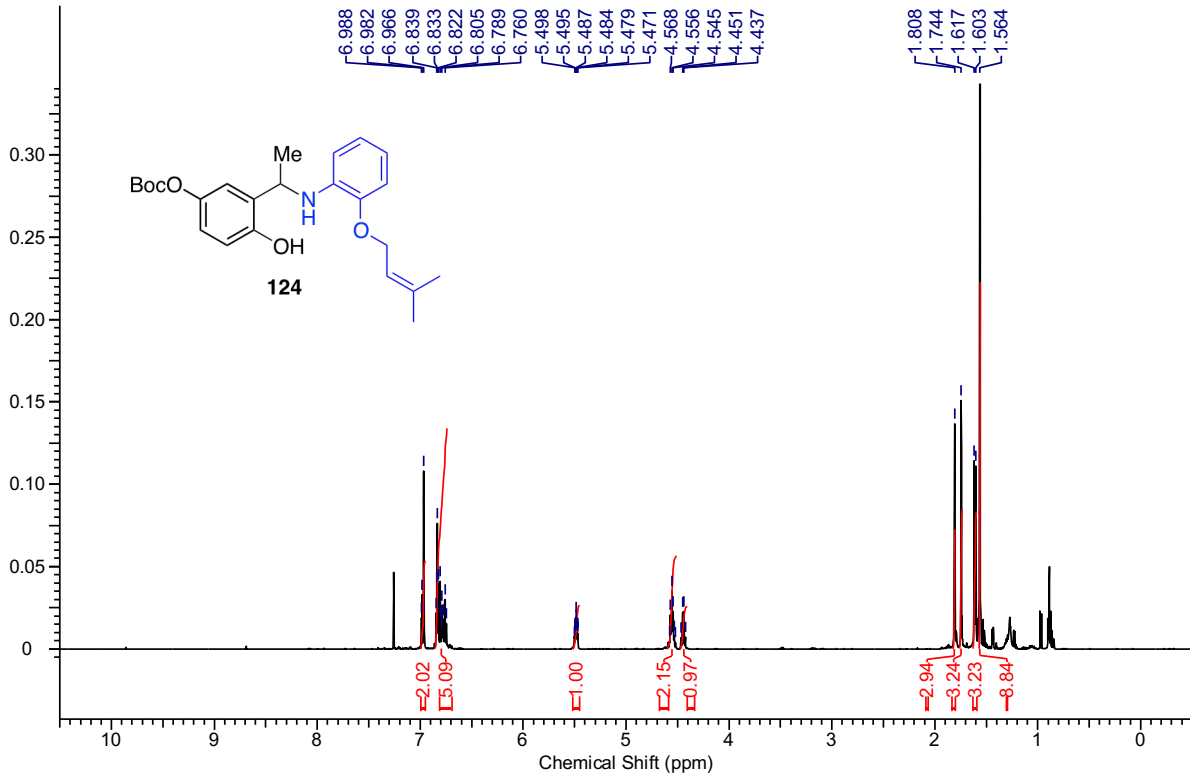

10.266
7.023
5.512
5.501
5.489
5.308
5.070
5.062
5.059
5.051
5.048
4.619
4.606
3.884
2.224
2.080
2.068
2.058
2.047
2.038
2.020
1.674
1.623
1.594
O
H
O
Me
OH
OMe
115
0.83
0.96
0.94
0.82
0.87
1.93
2.63
2.84
4.11
3.00
3.65
2.87
Chemical Shift (ppm)

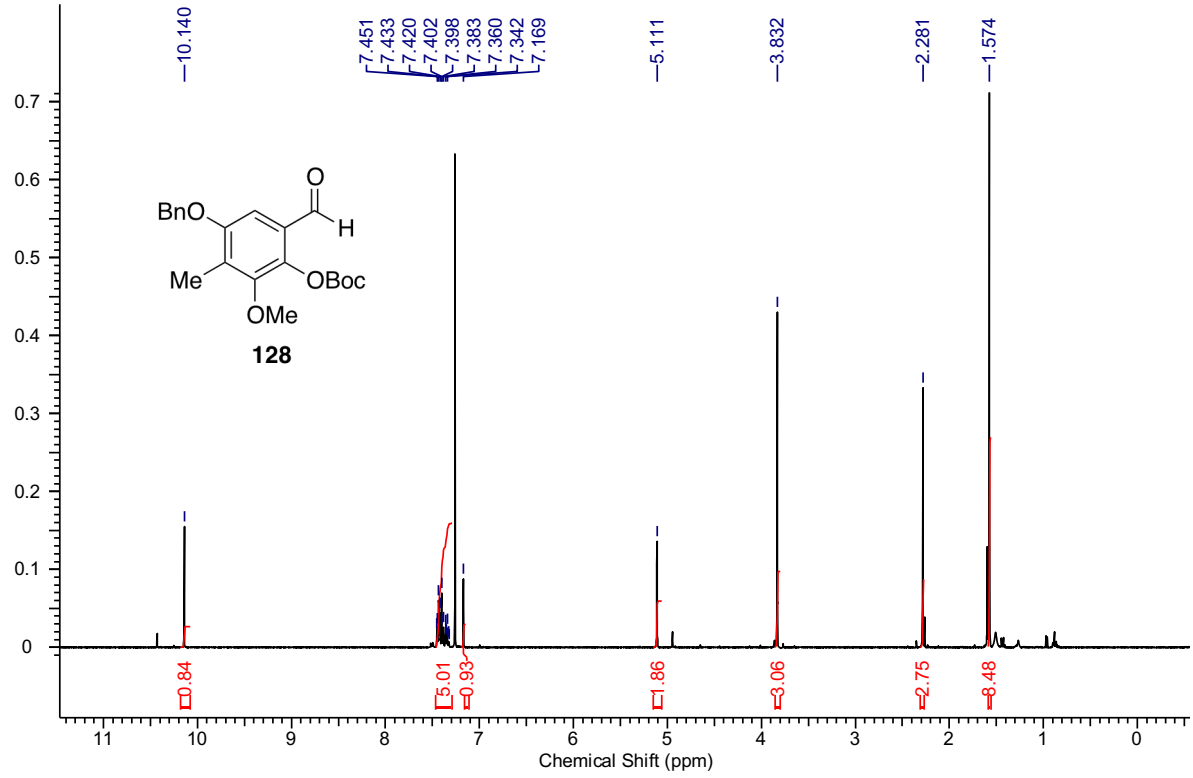

10.134
7.078
5.477
5.475
5.464
5.451
5.103
5.101
5.092
5.089
5.076
4.584
4.571
3.813
2.224
2.136
2.121
2.108
2.093
2.079
1.740
1.674
1.606
1.567
O
H
O
Me
OBoc
OMe
116
0.88
1.02
0.97
0.92
1.94
2.96
2.99
4.36
2.92
3.33
3.16
9.34
Chemical Shift (ppm)

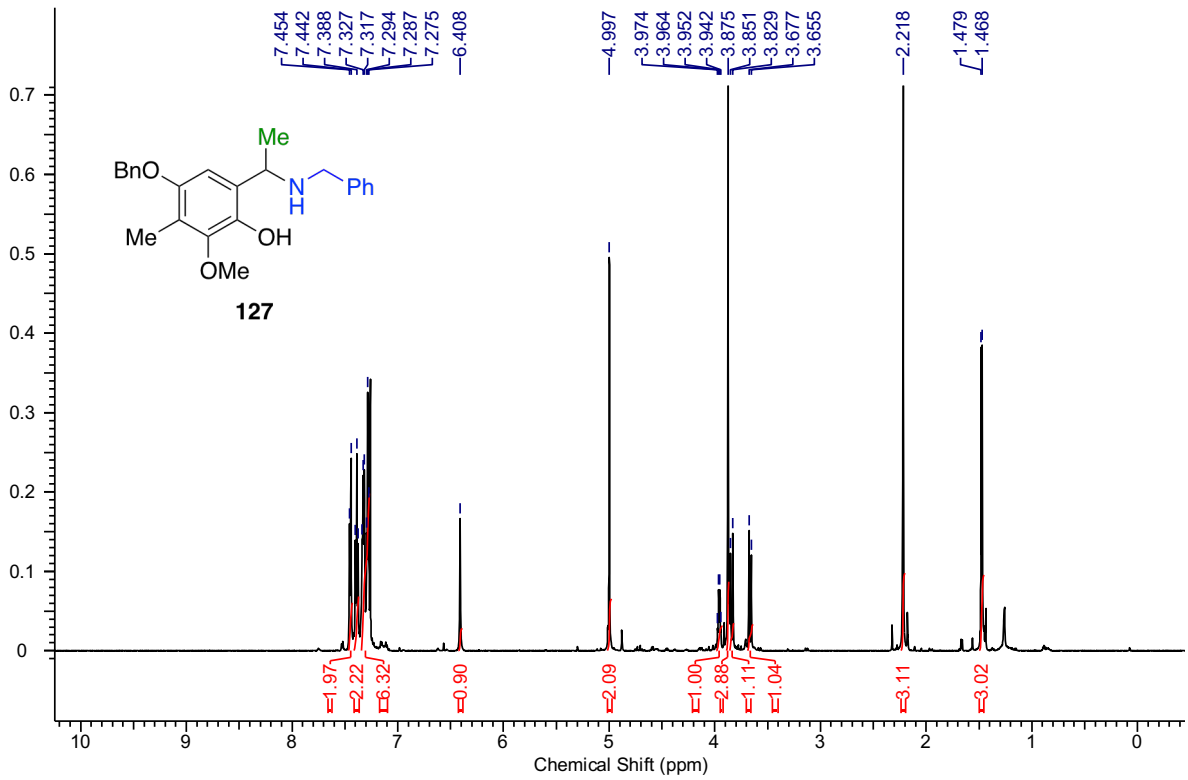

187.973
155.572
151.421
151.165
141.356
140.713
131.825
129.610
126.497
123.719
119.115
105.016
84.258
65.678
61.052
39.505
27.613
26.283
25.661
17.702
16.701
10.100
O
H
O
Me
OBoc
OMe
116
Chemical Shift (ppm)


6.292
5.486
5.476
5.466
5.111
5.099
5.088
4.431
4.420
4.279
4.123
3.905
3.894
3.828
2.884
2.866
2.389
2.376
2.364
2.139
2.114
2.077
1.702
1.681
1.607
1.477
1.466
1.168
1.155
1.143
Me
O
N
H
Me
OH
OMe
O
O
Et
117
0.94
1.02
1.02
1.98
1.01
1.01
1.05
2.99
2.04
2.00
3.01
4.23
2.96
3.17
3.09
3.07
2.90
Chemical Shift (ppm)


174.330
150.004
146.891
143.976
140.186
131.713
123.854
123.338
120.599
120.276
107.698
66.337
62.872
60.053
58.738
45.874
39.539
30.307
27.432
26.385
25.675
22.229
17.688
16.626
9.053
Me
O
N
H
Me
OH
OMe
O
O
Et
117
Chemical Shift (ppm)


6.988
6.982
6.966
6.839
6.833
6.822
6.805
6.789
6.760
5.498
5.495
5.487
5.484
5.479
5.471
4.568
4.556
4.545
4.451
4.437
1.808
1.744
1.617
1.603
1.564
Me
BocO
N
H
O
OH
124
2.02
5.09
1.00
2.15
0.97
2.94
3.24
3.23
8.84
Chemical Shift (ppm)


10.140
7.451
7.433
7.420
7.402
7.398
7.383
7.360
7.342
7.169
5.111
3.832
2.281
1.574
O
H
BnO
Me
OBoc
OMe
128
0.84
5.01
0.93
1.86
3.06
2.75
8.48
Chemical Shift (ppm)


7.454
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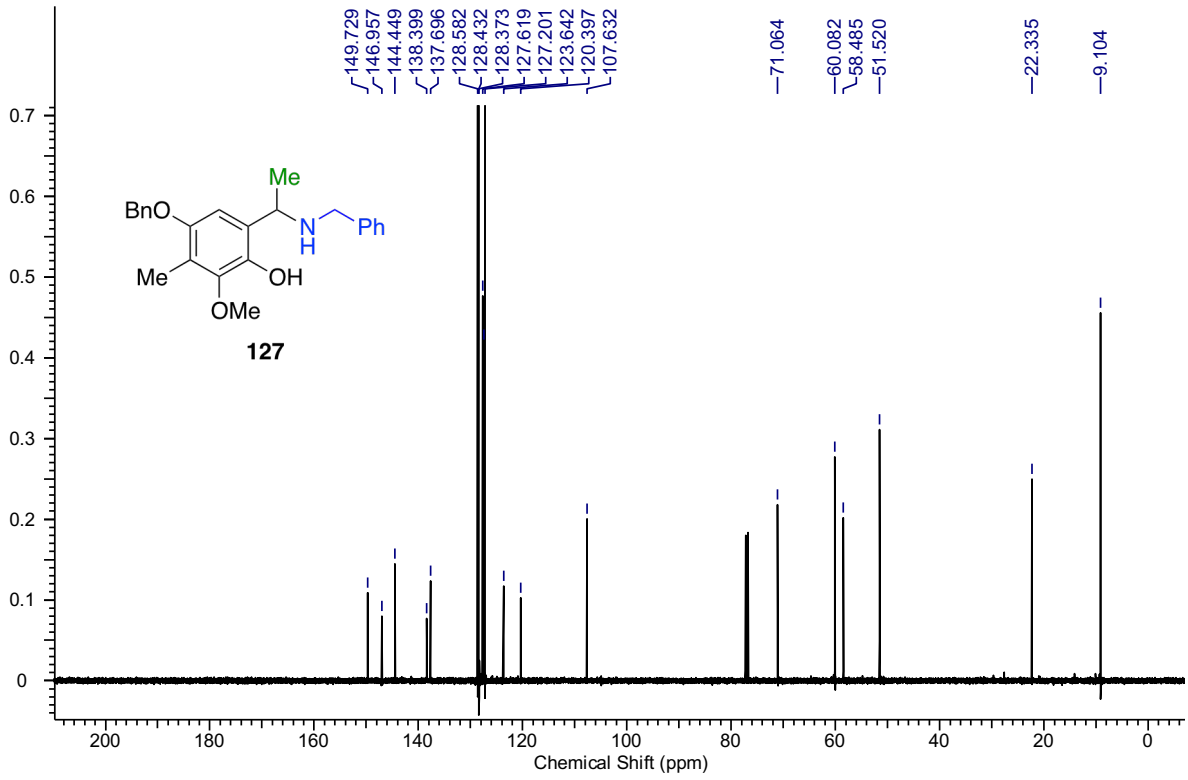
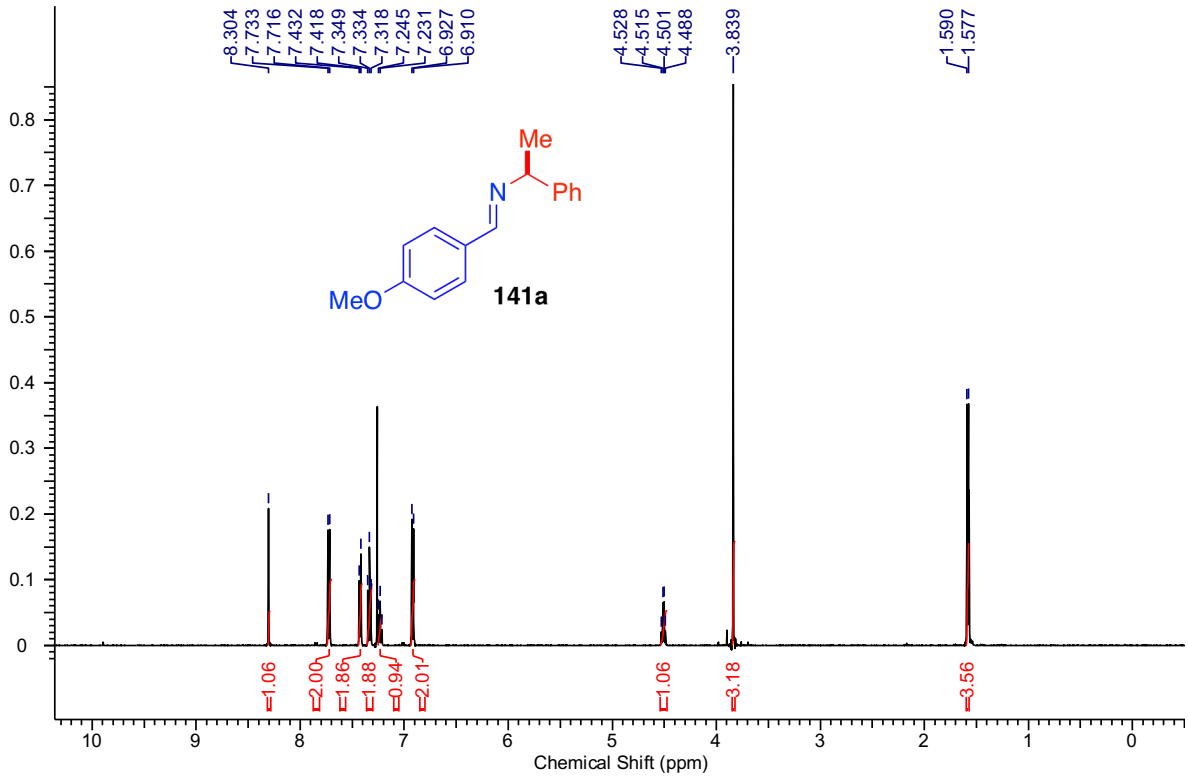
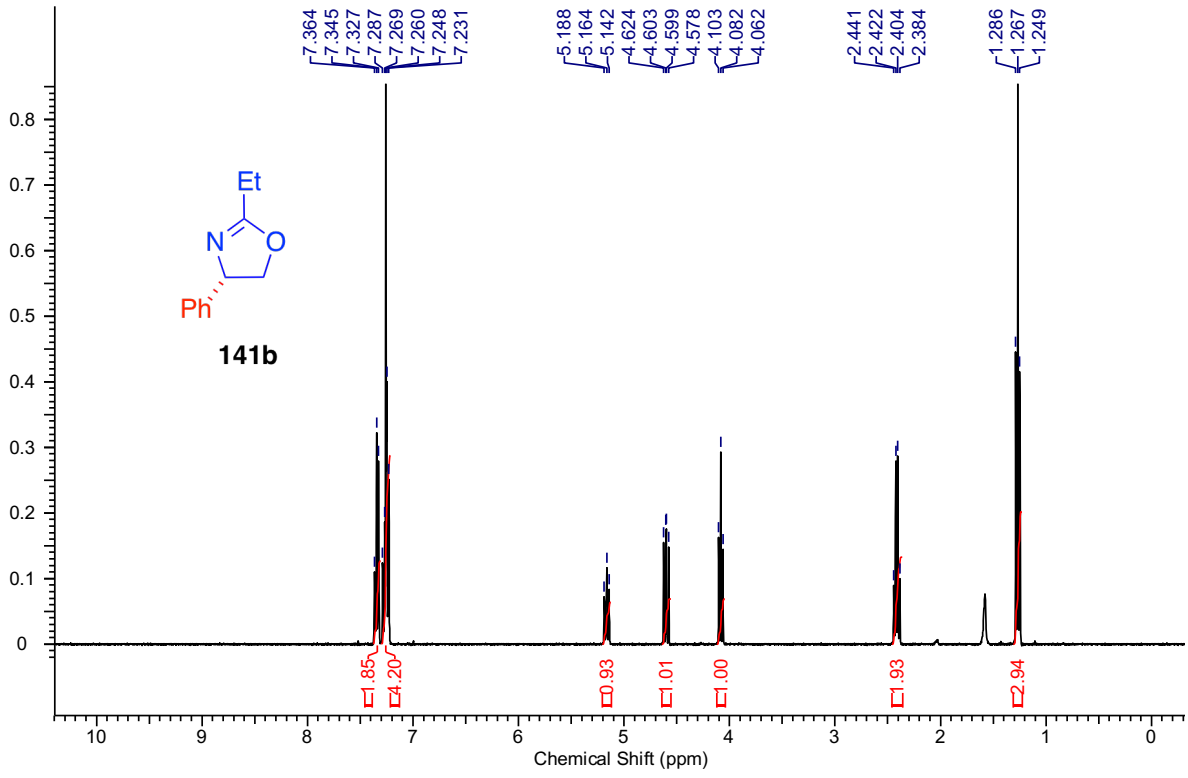
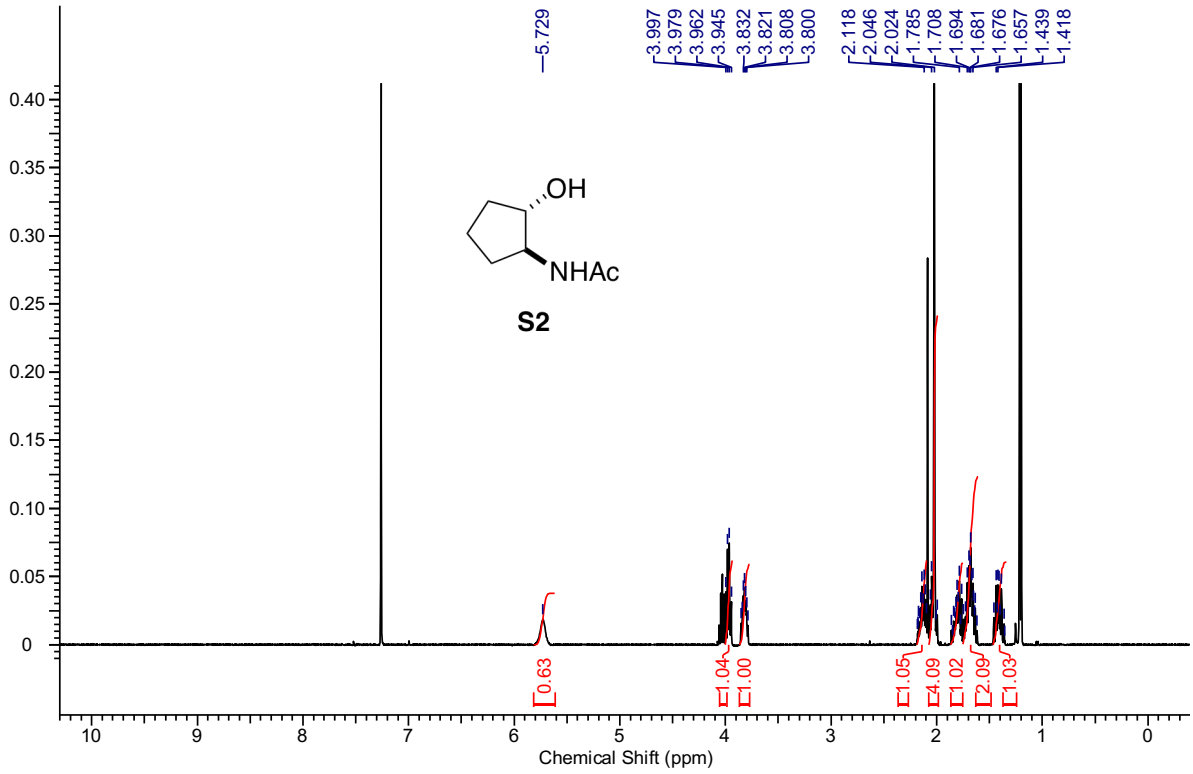
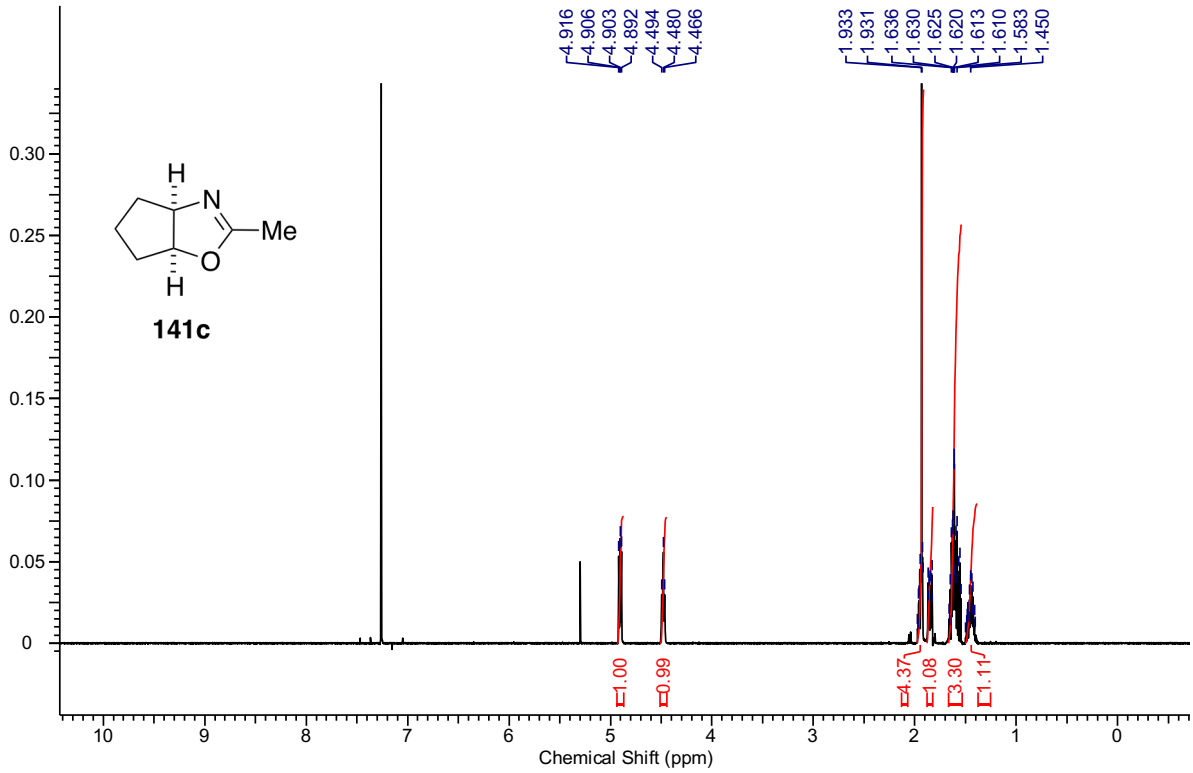
7.388
7.327
7.317
7.294
7.287
7.275
6.408
4.997
3.974
3.964
3.952
3.942
3.875
3.851
3.829
3.677
3.655
2.218
1.479
1.468
Me
BnO
N
H
Ph
Me
OH
OMe
127
1.97
2.22
6.32
0.90
2.09
1.00
2.88
1.11
1.04
3.11
3.02
Chemical Shift (ppm)

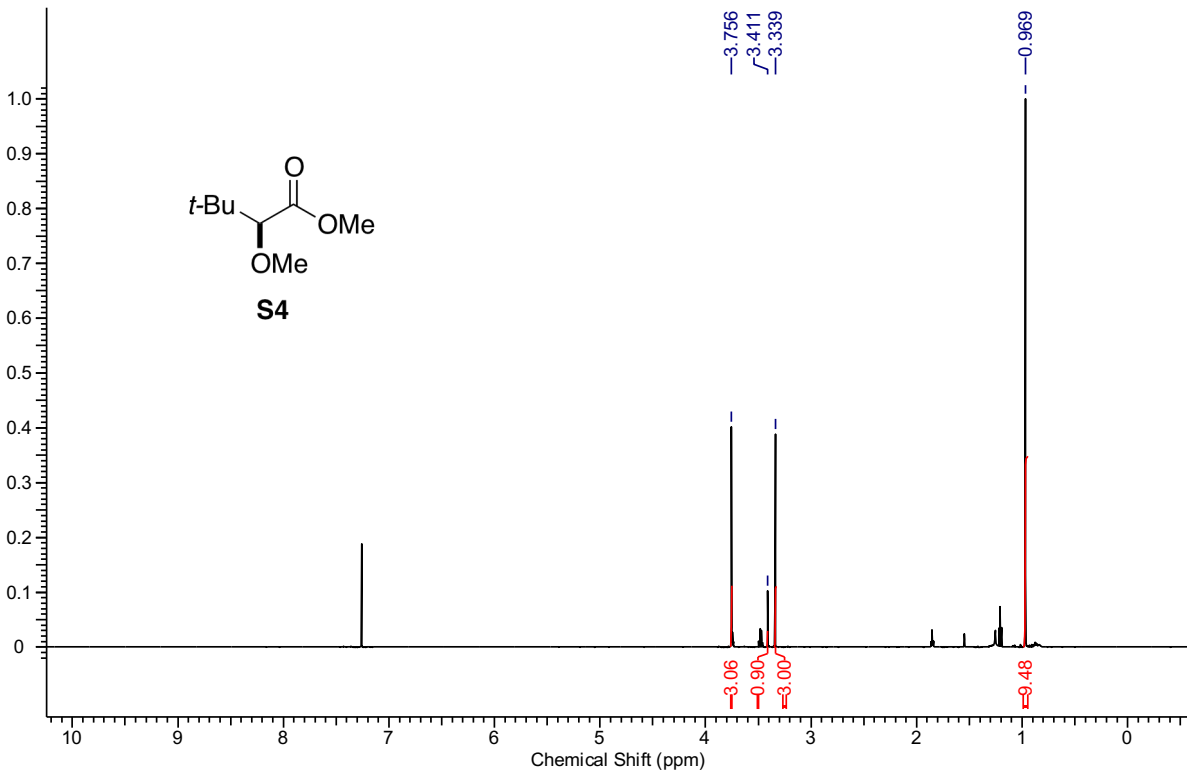

149.729
146.957
144.449
138.399
137.696
128.582
128.432
128.373
127.619
127.201
123.642
120.397
107.632
71.064
60.082
58.485
51.520
22.335
9.104
Me
BnO
N
H
Ph
Me
OH
OMe
127
Chemical Shift (ppm)

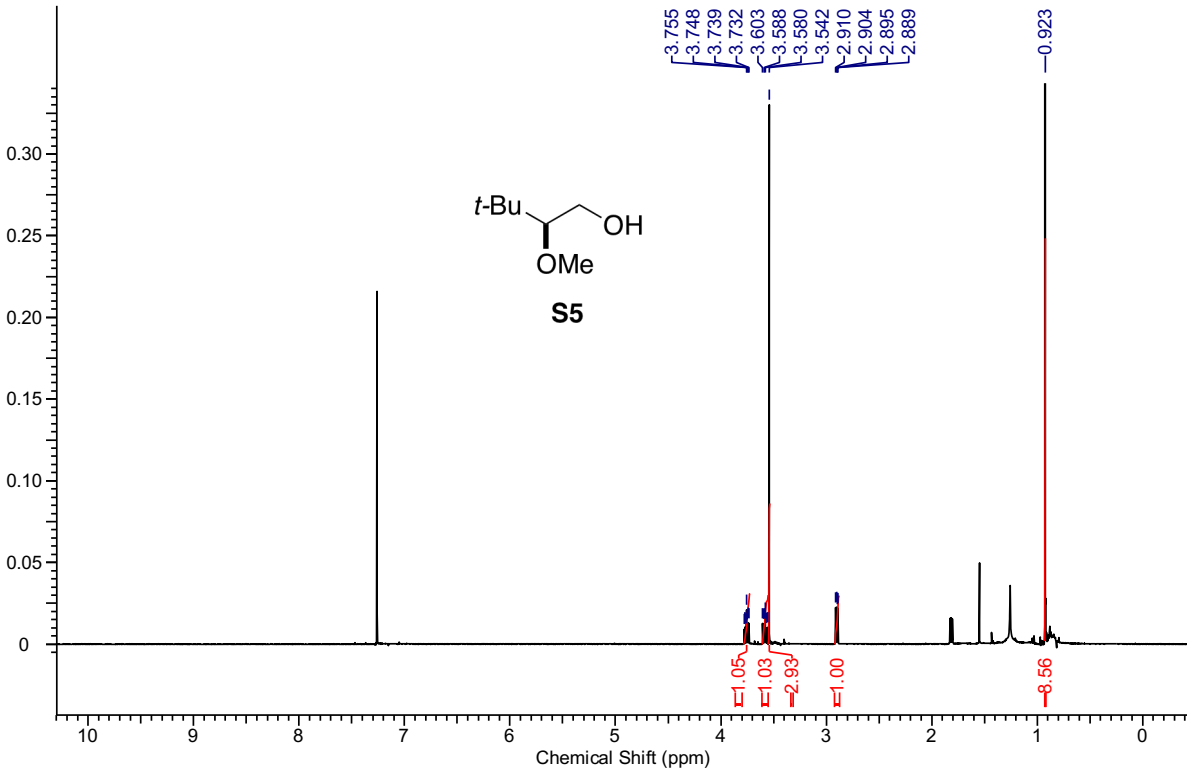

8.304
7.733
7.716
7.432
7.418
7.349
7.334
7.318
7.245
7.231
6.927
6.910
4.528
4.515
4.501
4.488
3.839
1.590
1.577
Me
N
Ph
MeO
141a
1.06
2.00
1.86
1.88
0.94
2.01
1.06
3.18
3.56
Chemical Shift (ppm)

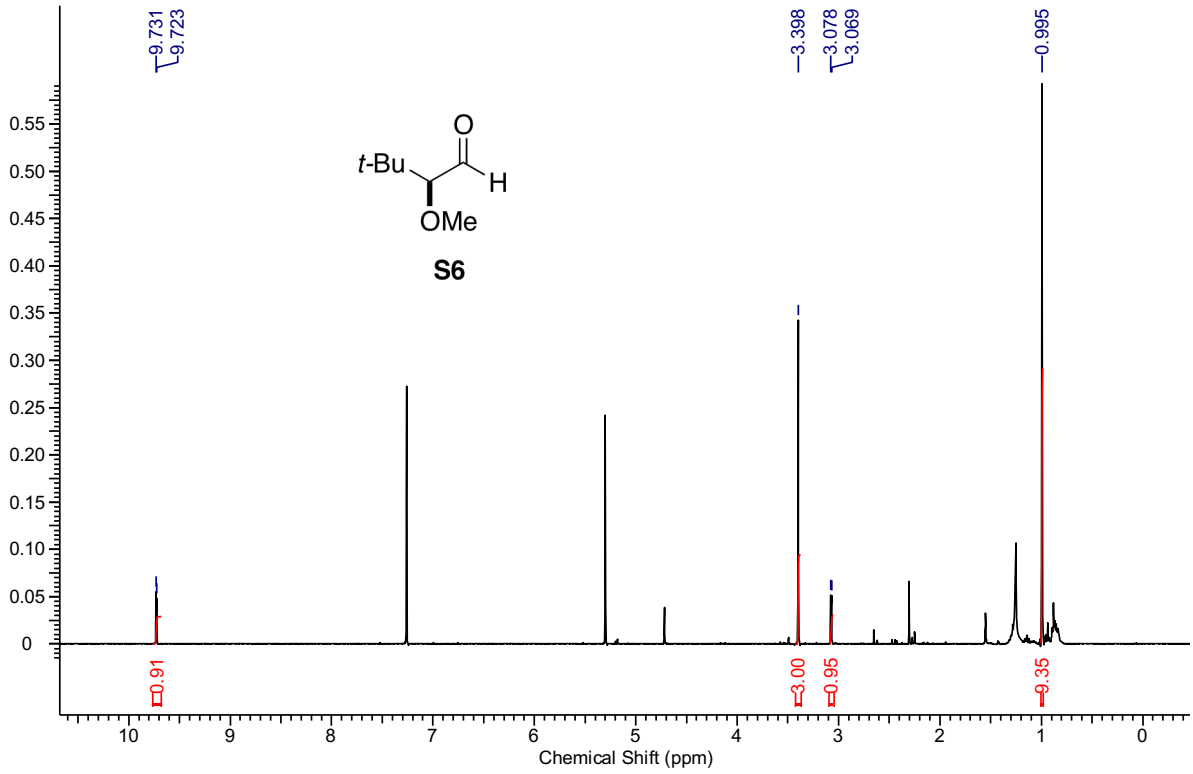

7.364
7.345
7.327
7.287
7.269
7.260
7.248
7.231
5.188
5.164
5.142
4.624
4.603
4.599
4.578
4.103
4.082
4.062
2.441
2.422
2.404
2.384
1.286
1.267
1.249
Et
N
O
Ph
141b
1.85
4.20
0.93
1.01
1.00
1.93
2.94
Chemical Shift (ppm)

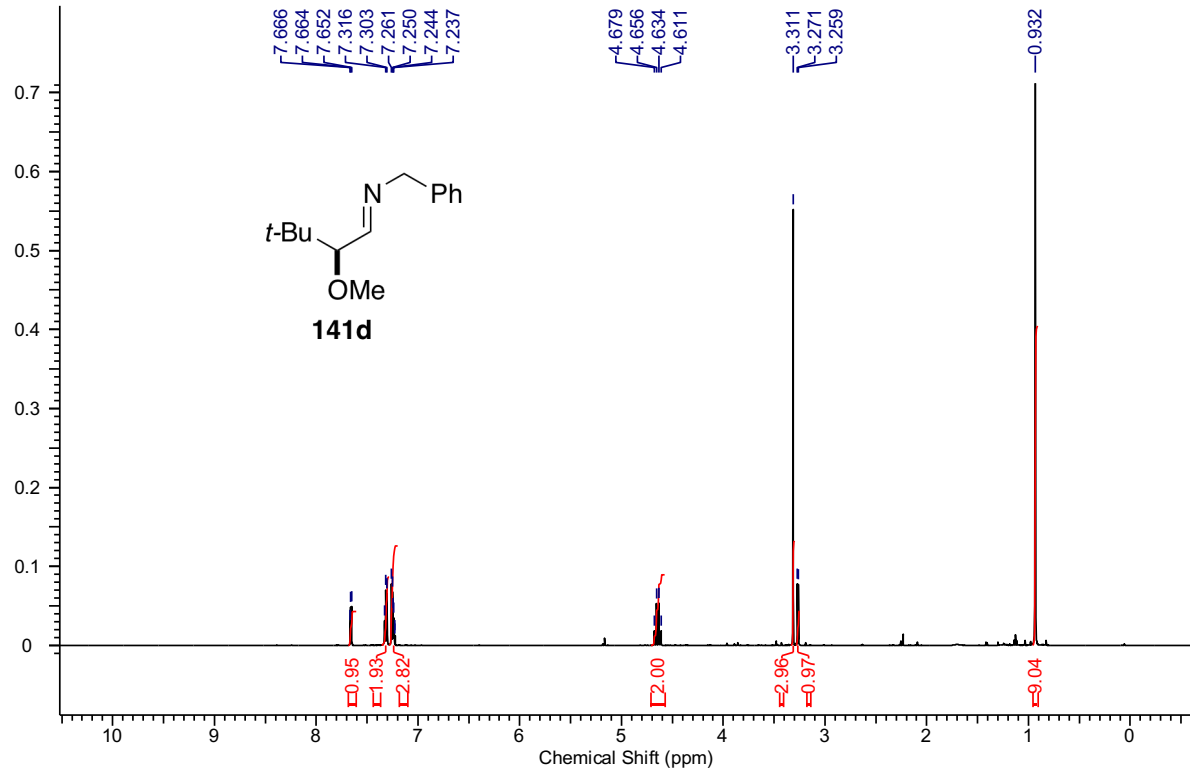

5.729
3.997
3.979
3.962
3.945
3.832
3.821
3.808
3.800
2.118
2.046
2.024
1.785
1.708
1.694
1.681
1.676
1.657
1.439
1.418
OH
NHAc
S2
0.63
1.04
1.00
1.05
4.09
1.02
2.09
1.03
Chemical Shift (ppm)

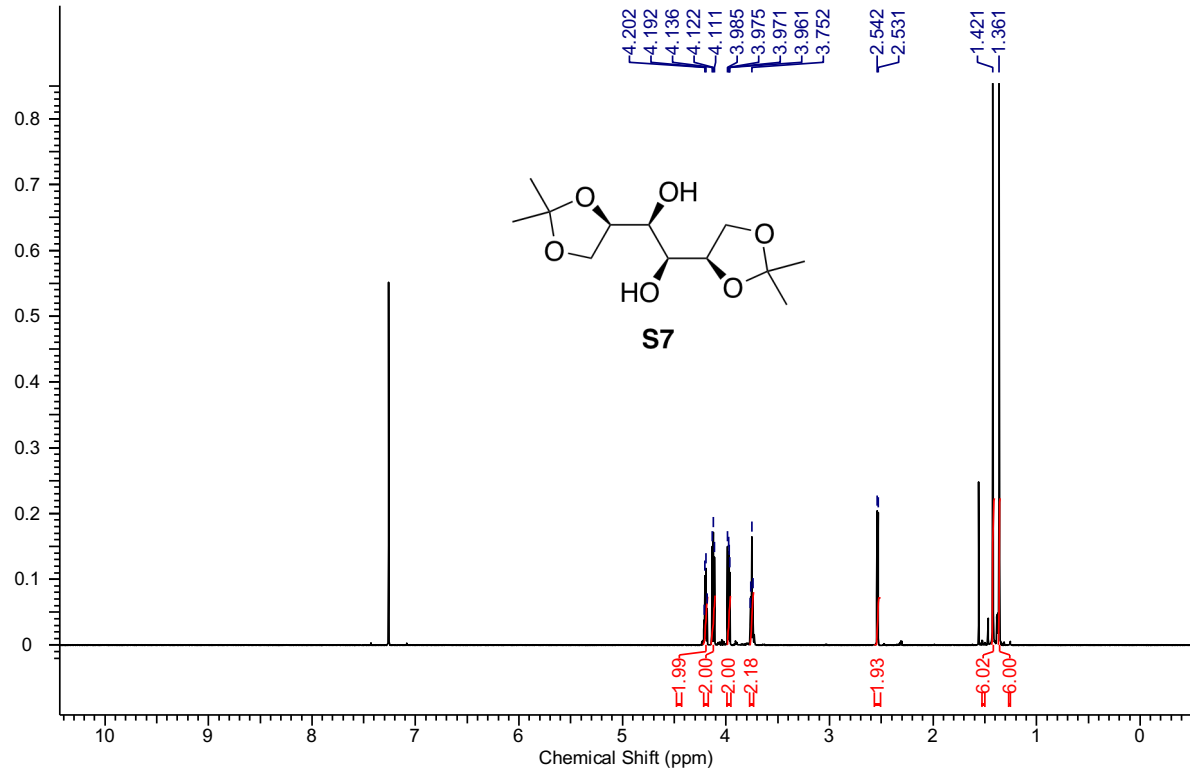

4.916
4.906
4.903
4.892
4.494
4.480
4.466
1.933
1.931
1.636
1.630
1.625
1.620
1.613
1.610
1.583
1.450
H
N
Me
O
H
141c
1.00
0.99
4.37
1.08
3.30
1.11
Chemical Shift (ppm)

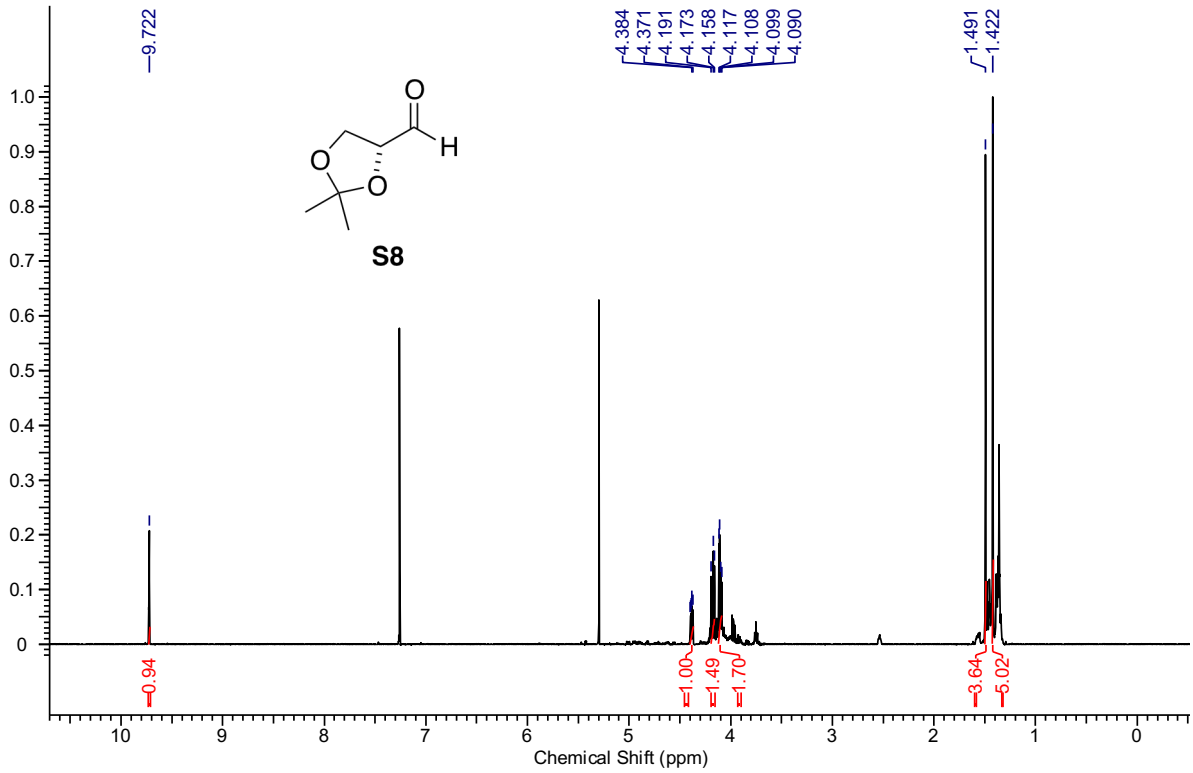

3.756
3.411
3.339
0.969
t-Bu
O
OMe
OMe
S4
3.06
0.90
3.00
9.48
Chemical Shift (ppm)

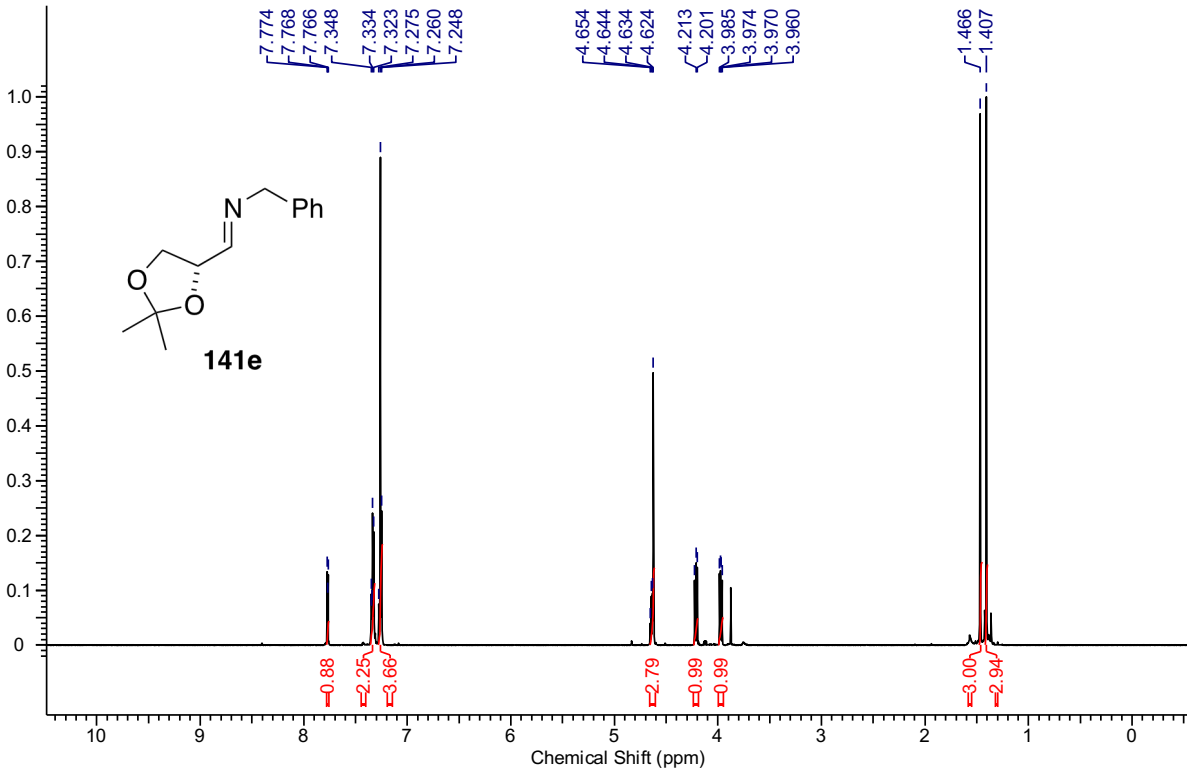

3.755
3.748
3.739
3.732
3.603
3.588
3.580
3.542
2.910
2.904
2.895
2.889
0.923
t-Bu
OH
OMe
S5
1.05
1.03
2.93
1.00
8.56
Chemical Shift (ppm)

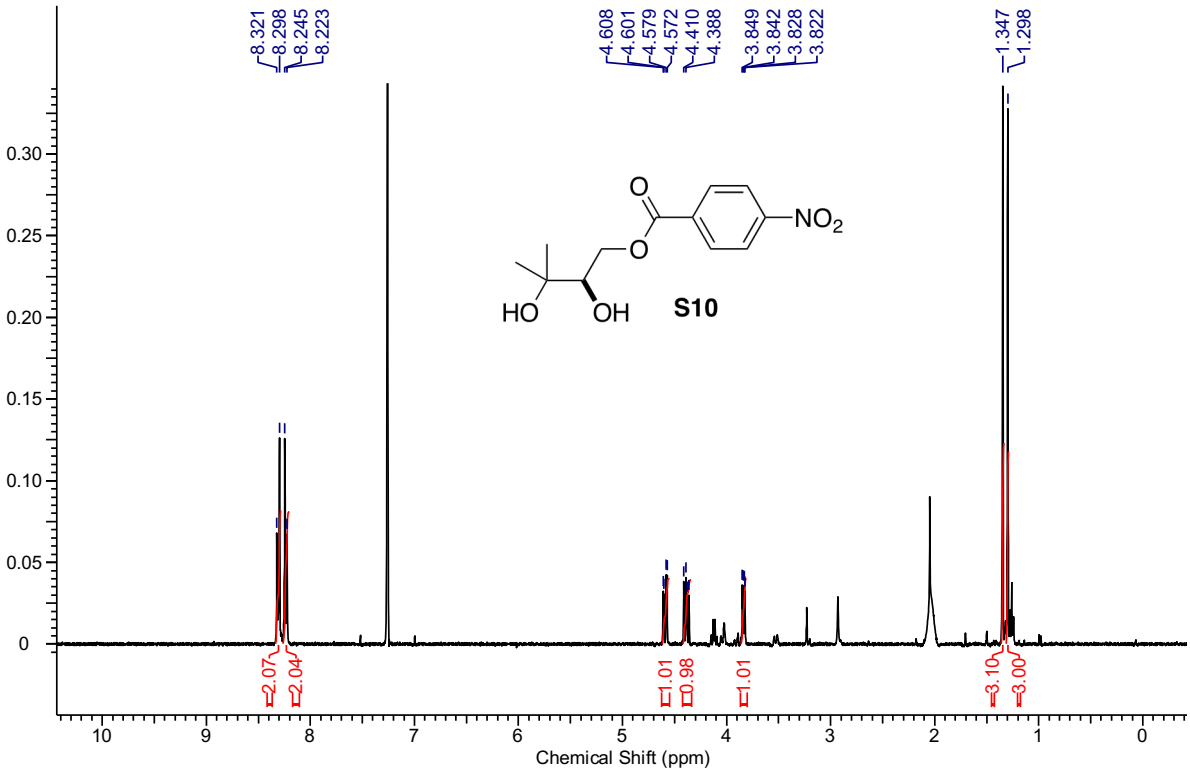

9.731
9.723
3.398
3.078
3.069
0.995
t-Bu
O
H
OMe
S6
0.91
3.00
0.95
9.35
Chemical Shift (ppm)

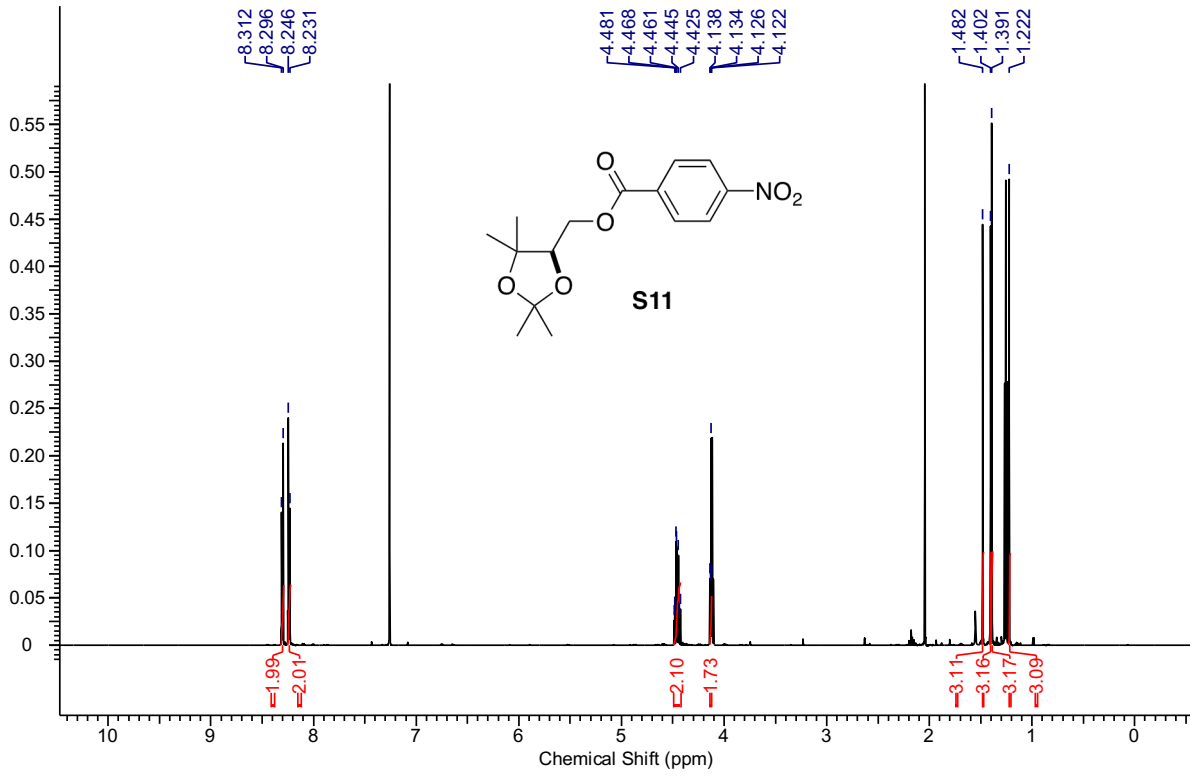

7.666
7.664
7.652
7.316
7.303
7.261
7.250
7.244
7.237
4.679
4.656
4.634
4.611
3.311
3.271
3.259
0.932
N
Ph
t-Bu
OMe
141d
0.95
1.93
2.82
2.00
2.96
0.97
9.04
Chemical Shift (ppm)

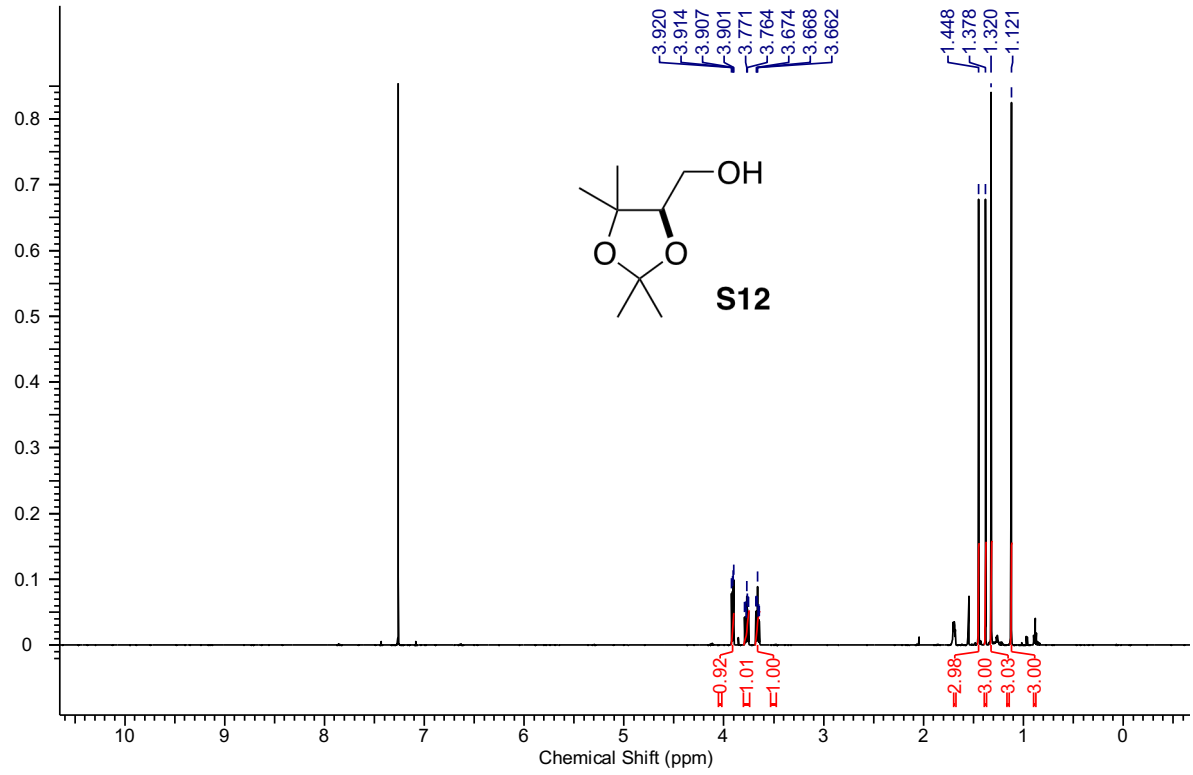

4.202
4.192
4.136
4.122
4.111
3.985
3.975
3.971
3.961
3.752
2.542
2.531
1.421
1.361
OH
HO
O
O
O
O
S7
1.99
2.00
2.00
2.18
1.93
6.02
6.00
Chemical Shift (ppm)

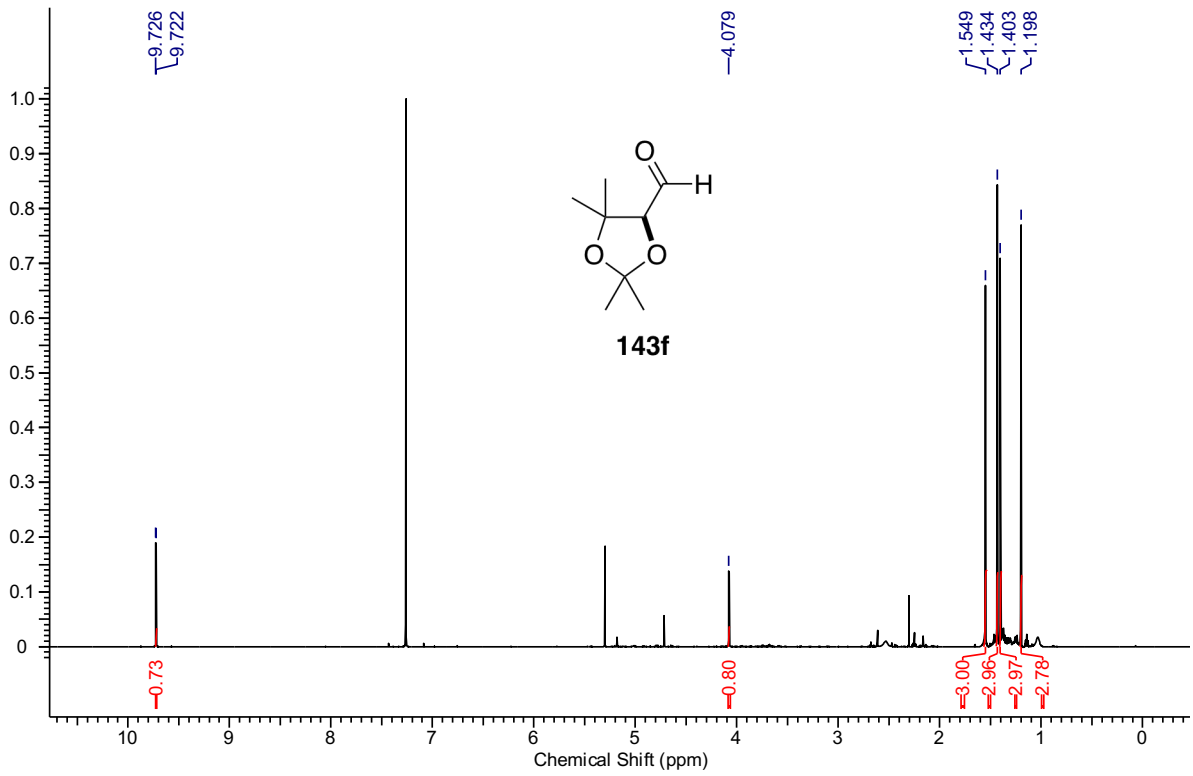

9.722
4.384
4.371
4.191
4.173
4.158
4.117
4.108
4.099
4.090
1.491
1.422
O
H
O
O
S8
0.94
1.00
1.49
1.70
3.64
5.02
Chemical Shift (ppm)

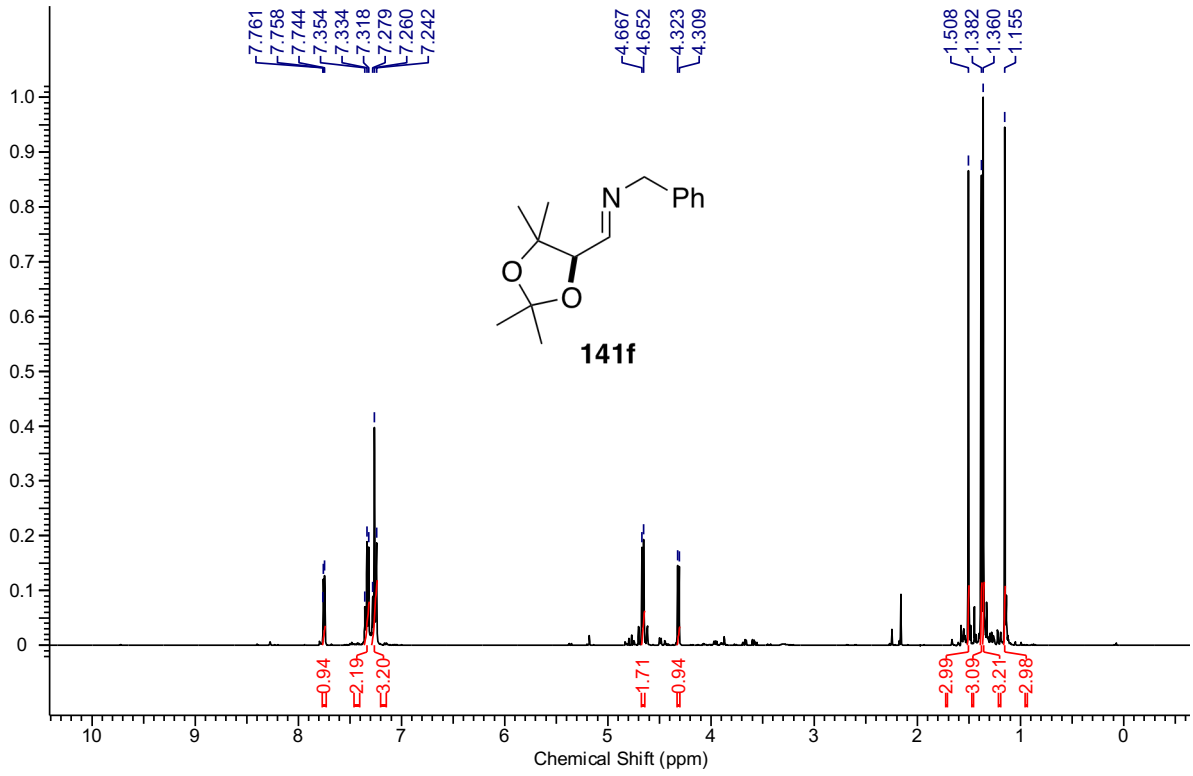

7.774
7.768
7.766
7.348
7.334
7.323
7.275
7.260
7.248
4.654
4.644
4.634
4.624
4.213
4.201
3.985
3.974
3.970
3.960
1.466
1.407
N
Ph
O
O
141e
0.88
2.25
3.66
2.79
0.99
0.99
3.00
2.94
Chemical Shift (ppm)

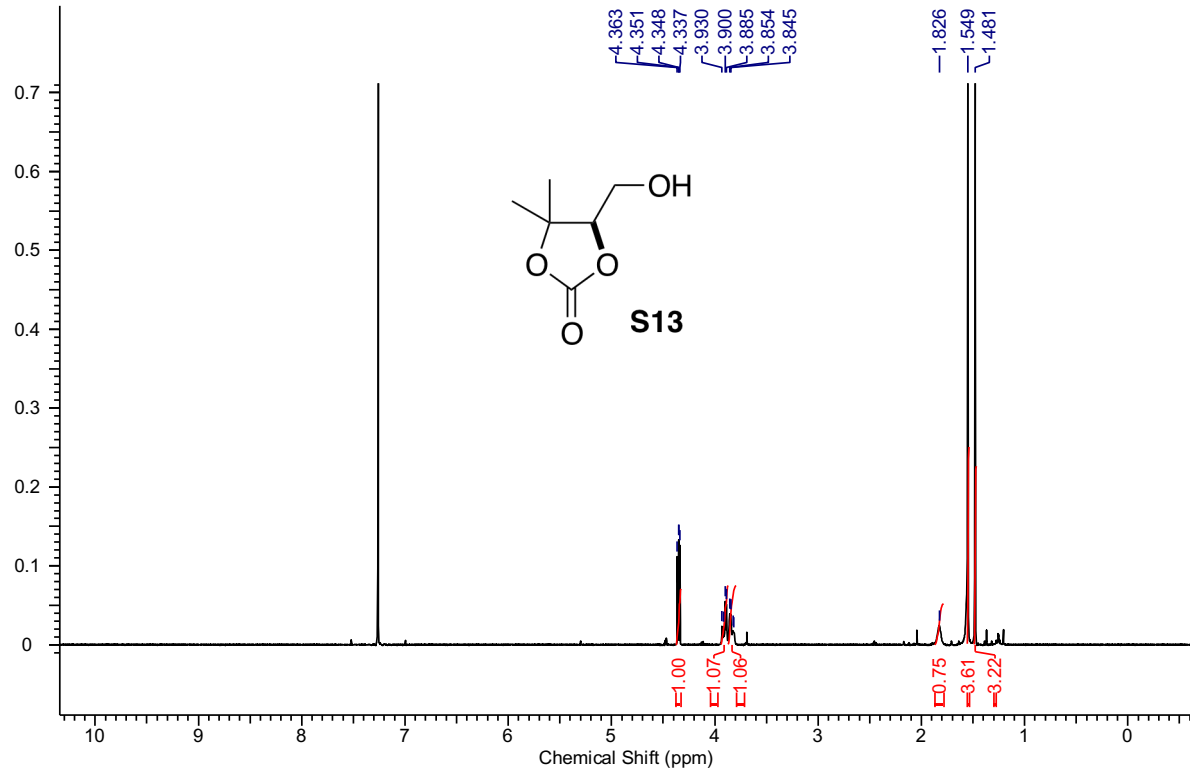

8.321
8.298
8.245
8.223
4.608
4.601
4.579
4.572
4.410
4.388
3.849
3.842
3.828
3.822
1.347
1.298
O
O
NO2
HO
OH
S10
2.07
2.04
1.01
0.98
1.01
3.10
3.00
Chemical Shift (ppm)

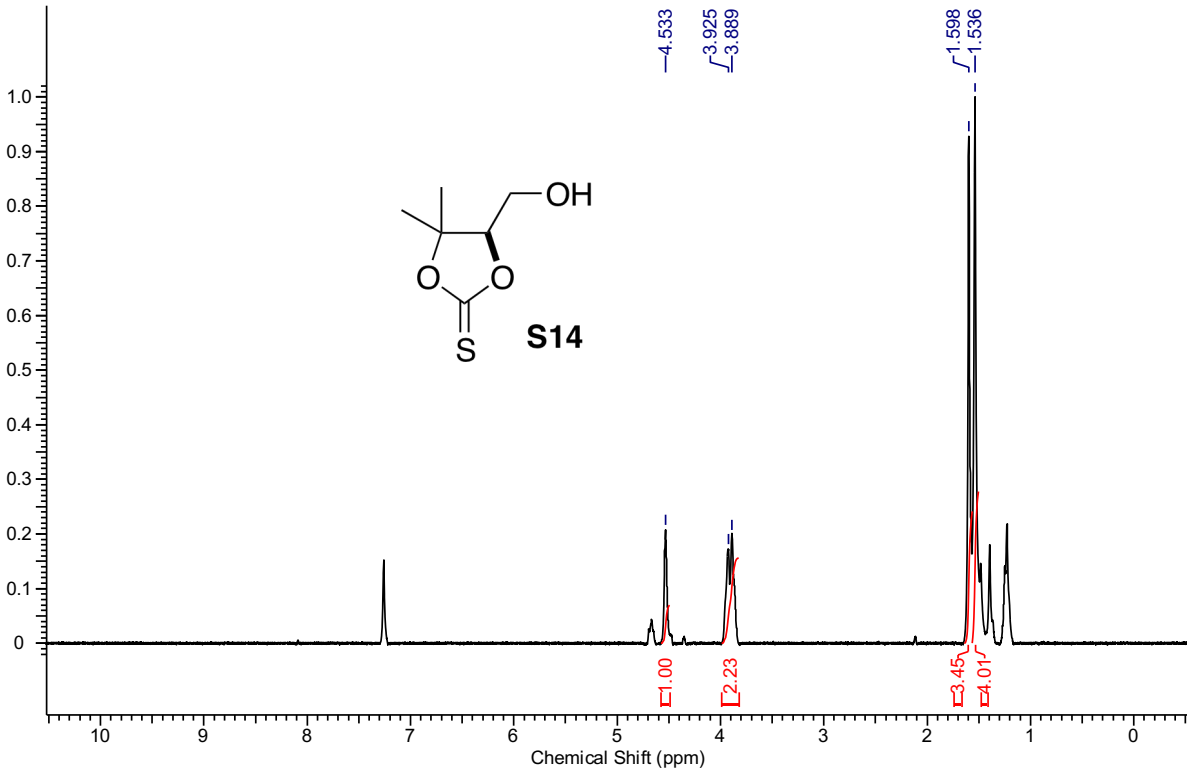

8.312
8.296
8.246
8.231
4.481
4.468
4.461
4.445
4.425
4.138
4.134
4.126
4.122
1.482
1.402
1.391
1.222
O
O
NO2
O
O
S11
1.99
2.01
2.10
1.73
3.11
3.16
3.17
3.09
Chemical Shift (ppm)

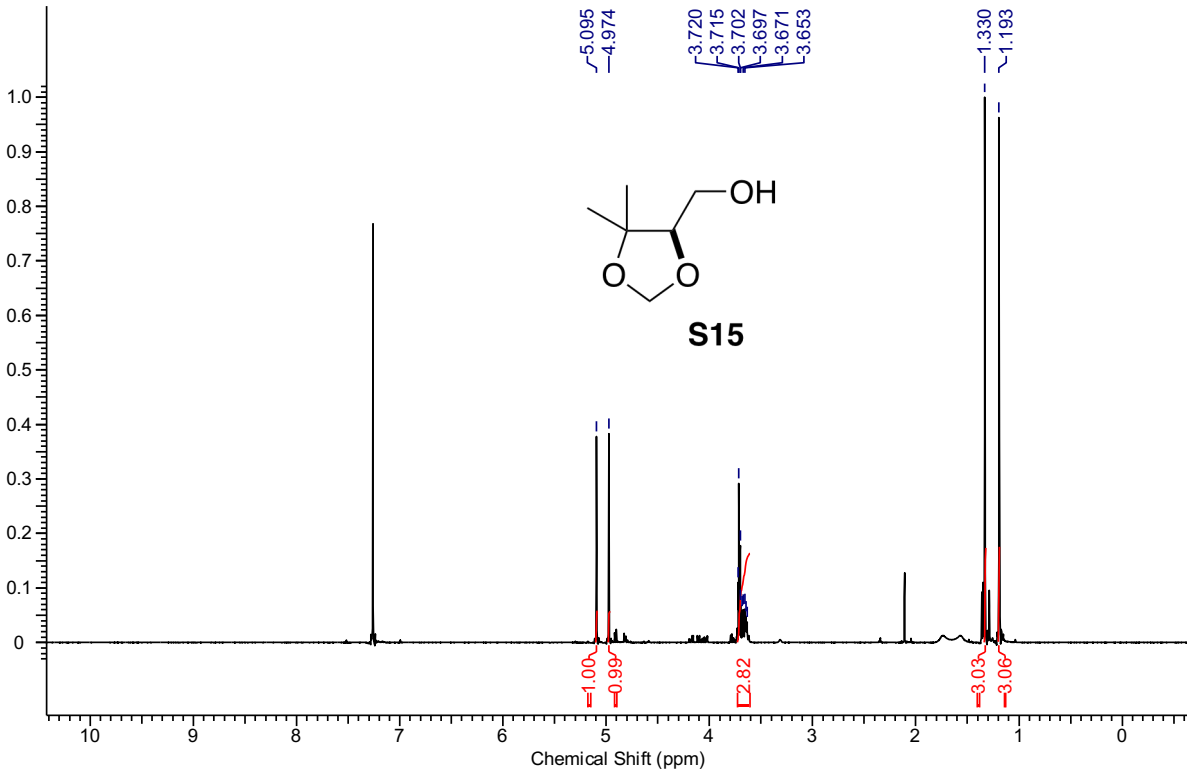

3.920
3.914
3.907
3.901
3.771
3.764
3.674
3.668
3.662
1.448
1.378
1.320
1.121
OH
O
O
S12
0.92
1.01
1.00
2.98
3.00
3.03
3.00
Chemical Shift (ppm)

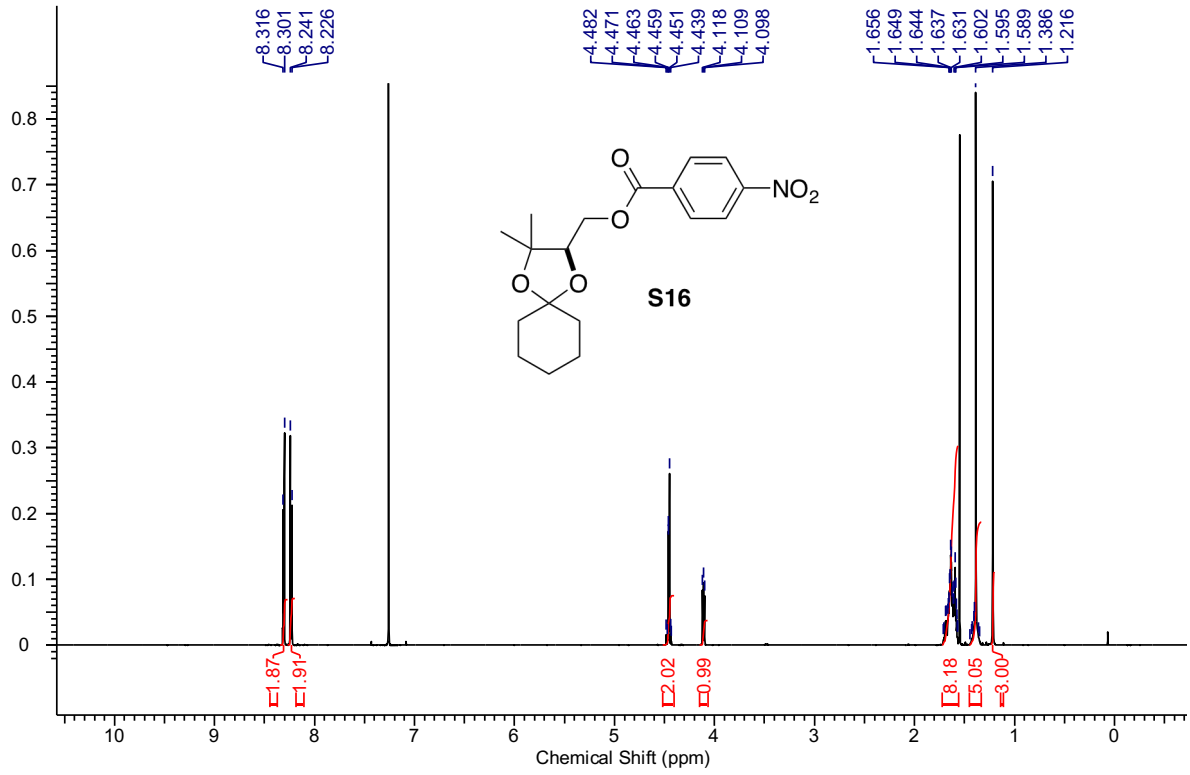

9.726
9.722
4.079
1.549
1.434
1.403
1.198
143f
0.73
0.80
3.00
2.96
2.97
2.78
Chemical Shift (ppm)

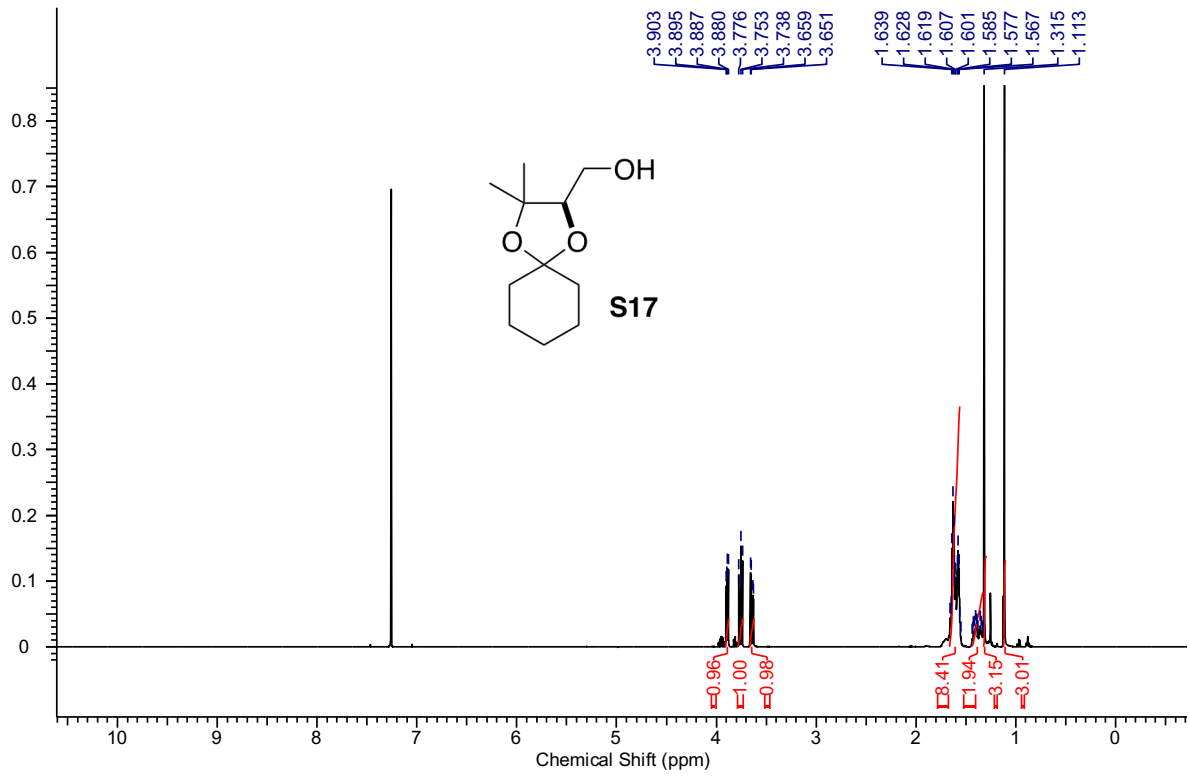

7.761
7.758
7.744
7.354
7.334
7.318
7.279
7.260
7.242
4.667
4.652
4.323
4.309
1.508
1.382
1.360
1.155
N
Ph
O
O
141f
0.94
2.19
3.20
1.71
0.94
2.99
3.09
3.21
2.98
Chemical Shift (ppm)

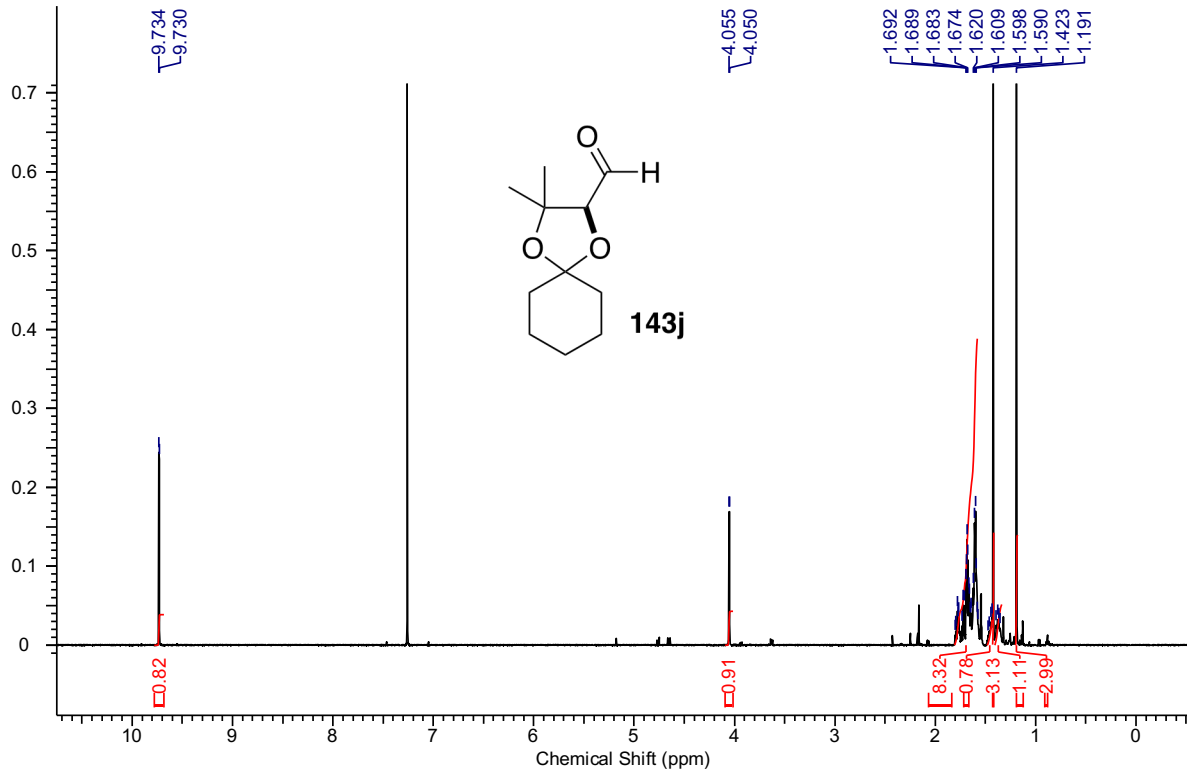

4.363
4.351
4.348
4.337
3.930
3.900
3.885
3.854
3.845
1.826
1.549
1.481
OH
O
O
O
S13
1.00
1.07
1.06
0.75
3.61
3.22
Chemical Shift (ppm)

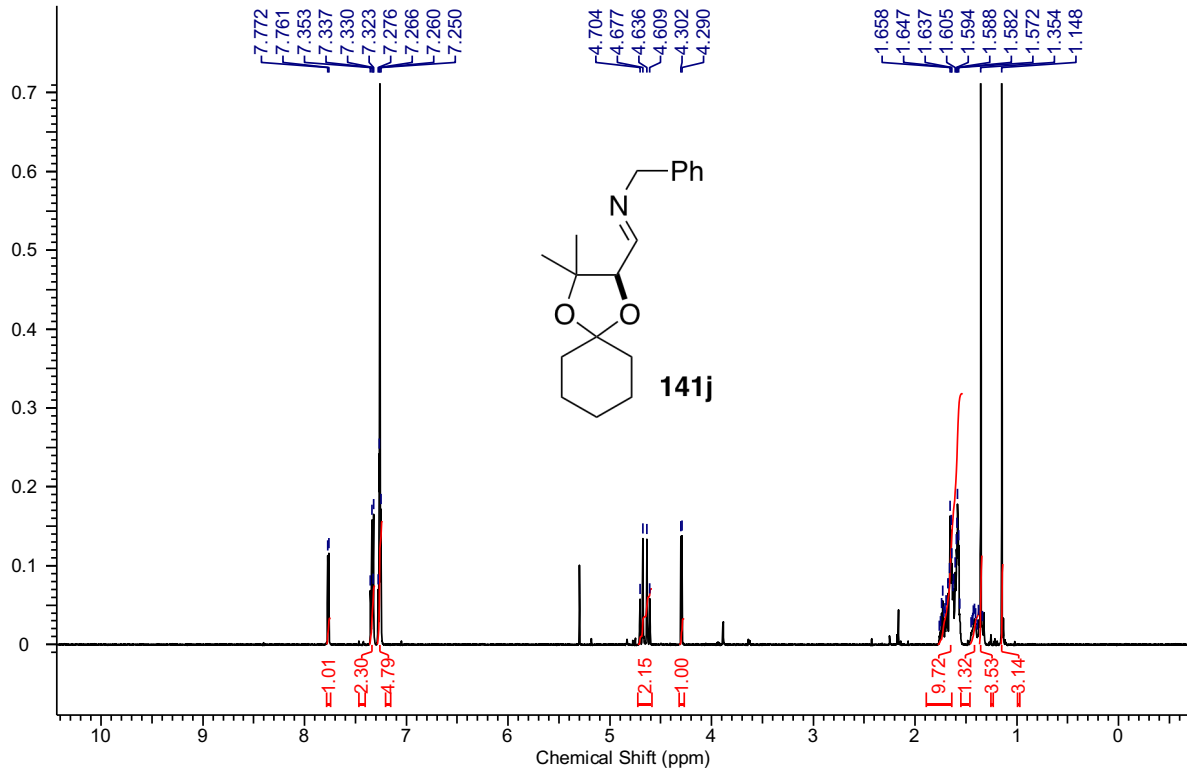

4.533
3.925
3.889
1.598
1.536
OH
O
O
S
S14
1.00
2.23
3.45
4.01
Chemical Shift (ppm)

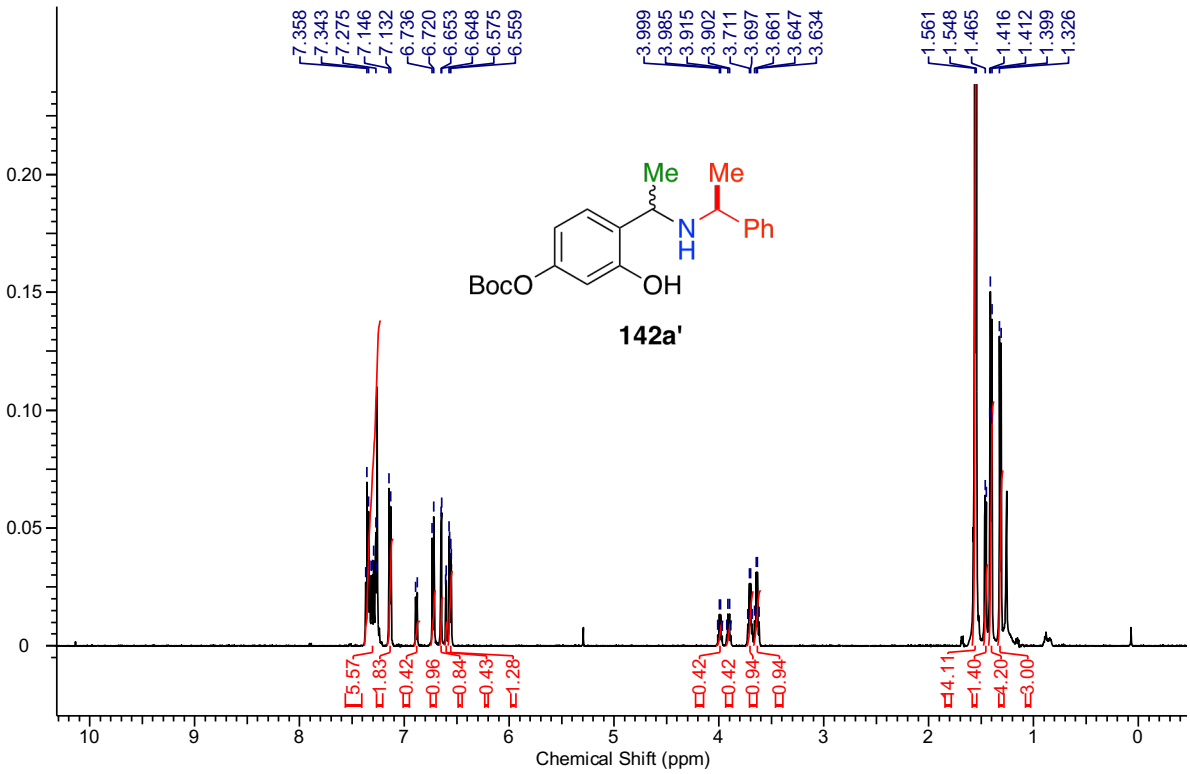

5.095
4.974
3.720
3.715
3.702
3.697
3.671
3.653
1.330
1.193
OH
O
O
S15
1.00
0.99
2.82
3.03
3.06
Chemical Shift (ppm)

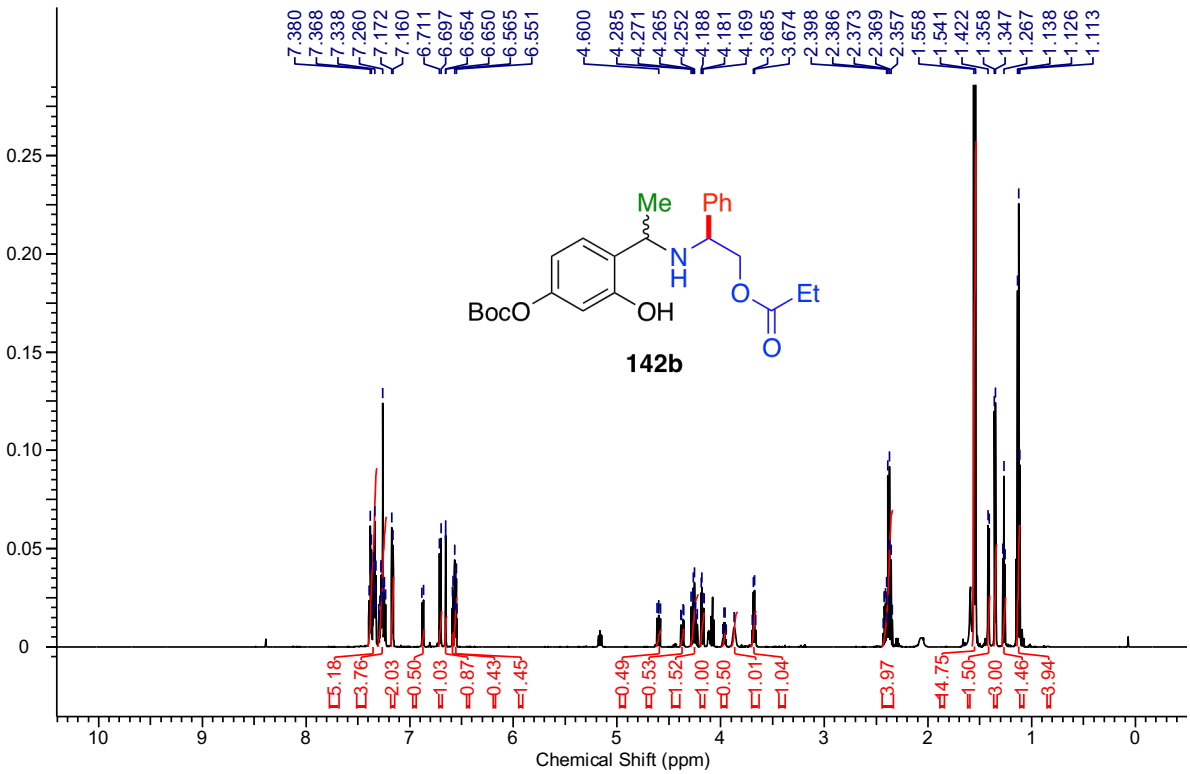

8.316
8.301
8.241
8.226
4.482
4.471
4.463
4.459
4.451
4.439
4.118
4.109
4.098
1.656
1.649
1.644
1.637
1.631
1.602
1.595
1.589
1.386
1.216
O
O
NO2
O
O
S16
1.87
1.91
2.02
0.99
8.18
5.05
3.00
Chemical Shift (ppm)

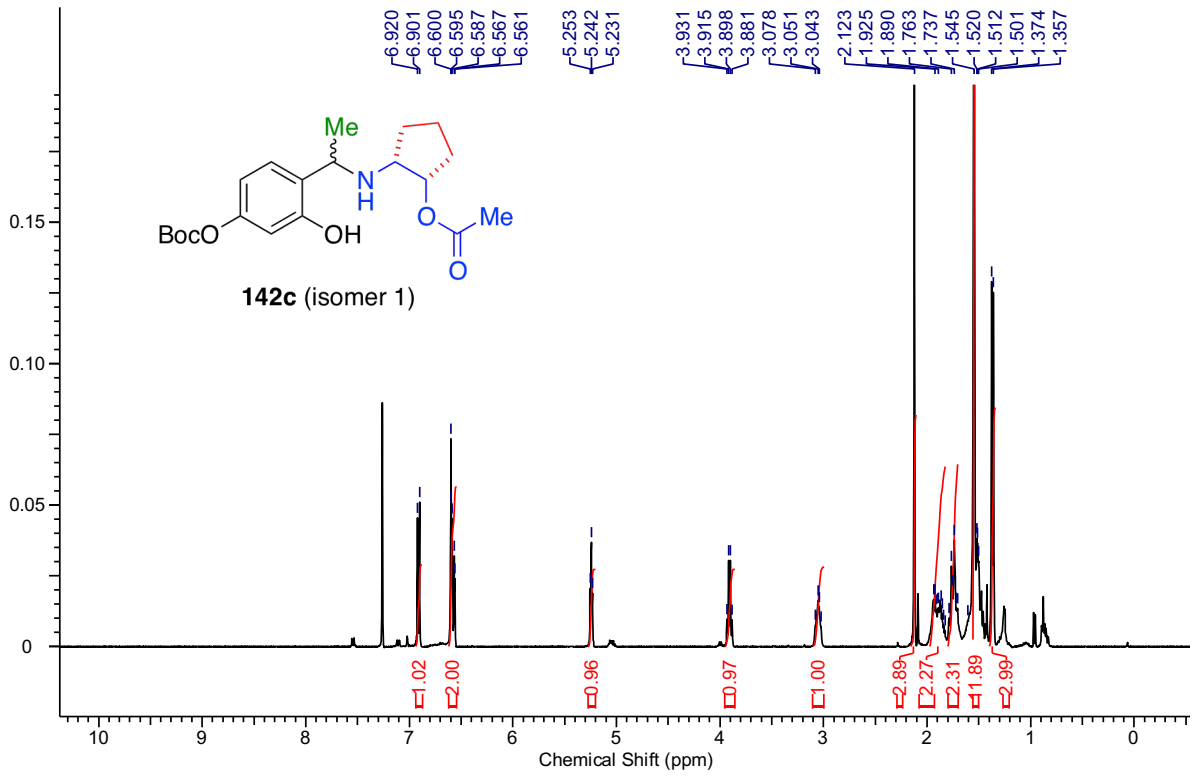

3.903
3.895
3.887
3.880
3.776
3.753
3.738
3.659
3.651
1.639
1.628
1.619
1.607
1.601
1.585
1.577
1.567
1.315
1.113
OH
O
O
S17
0.96
1.00
0.98
8.41
1.94
3.15
3.01
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

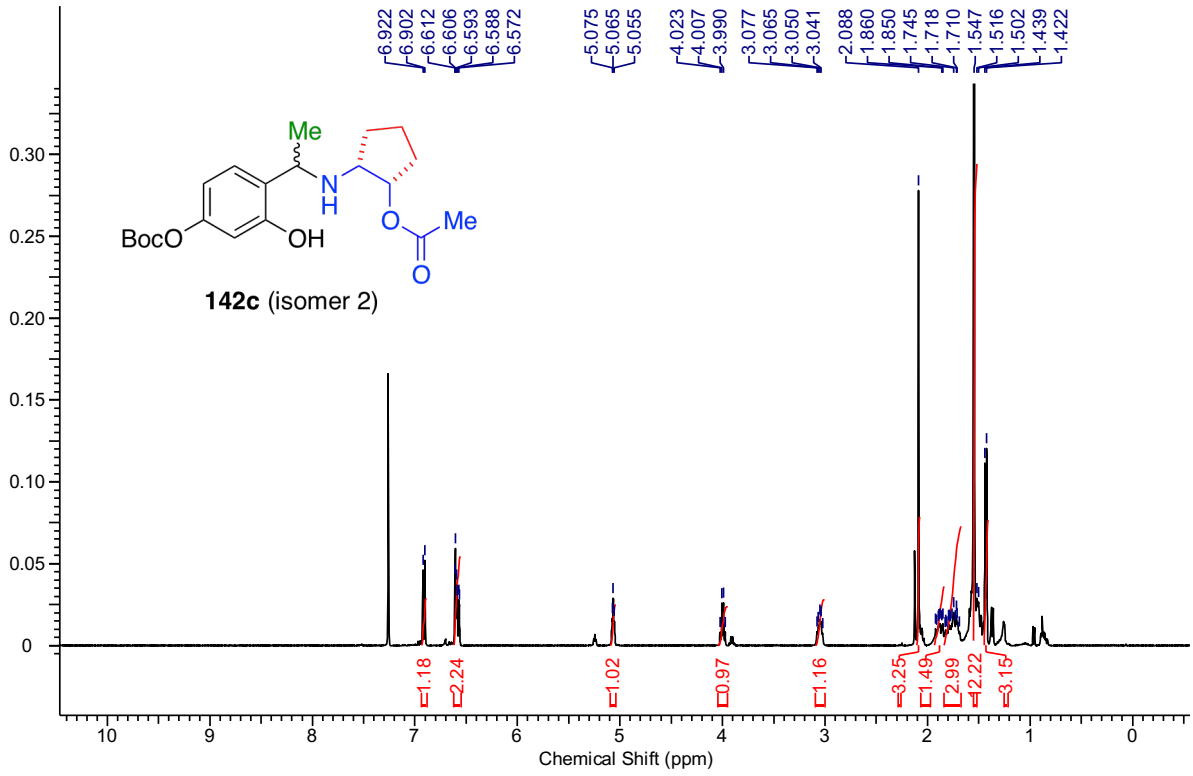

9.734
9.730
4.055
4.050
1.692
1.689
1.683
1.674
1.620
1.609
1.598
1.590
1.423
1.191
O
H
O
O
143j
0.82
0.91
8.32
0.78
3.13
1.11
2.99
Chemical Shift (ppm)

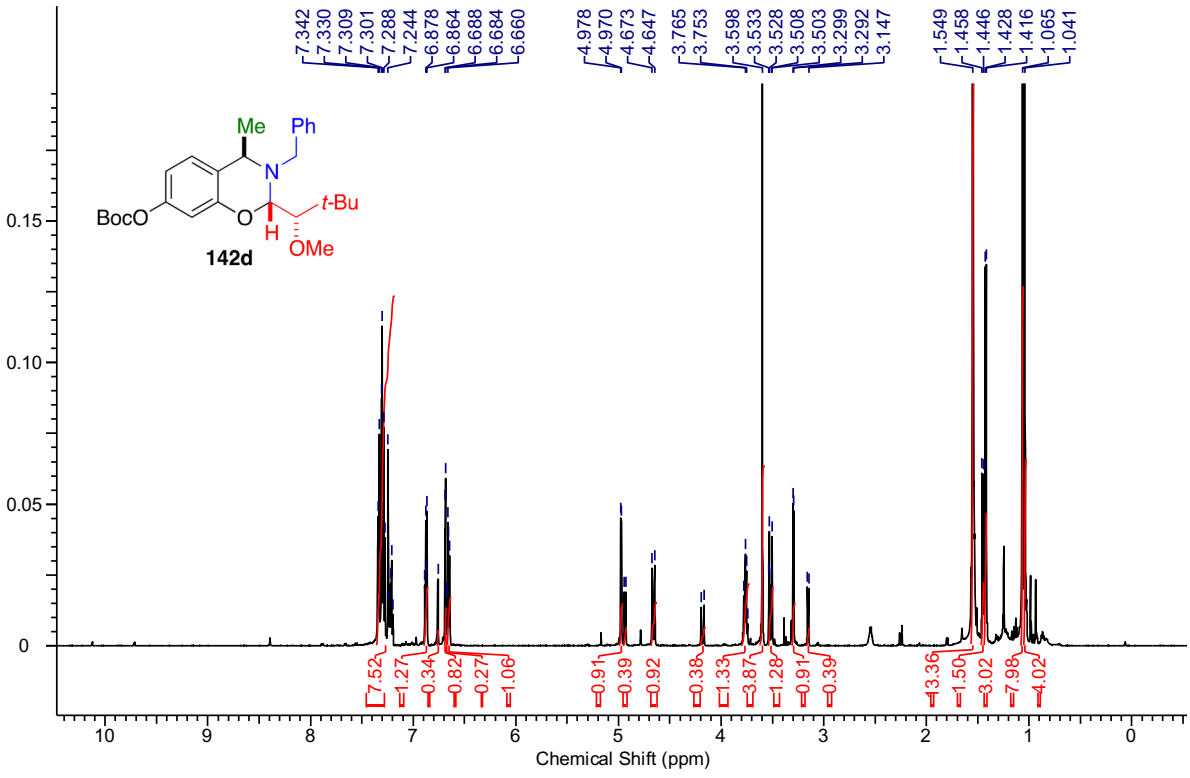

7.772
7.761
7.353
7.337
7.330
7.323
7.276
7.266
7.260
7.250
4.704
4.677
4.636
4.609
4.302
4.290
1.658
1.647
1.637
1.605
1.594
1.588
1.582
1.572
1.354
1.148
Ph
N
O
O
141j
1.01
2.30
4.79
2.15
1.00
9.72
1.32
3.53
3.14
Chemical Shift (ppm)

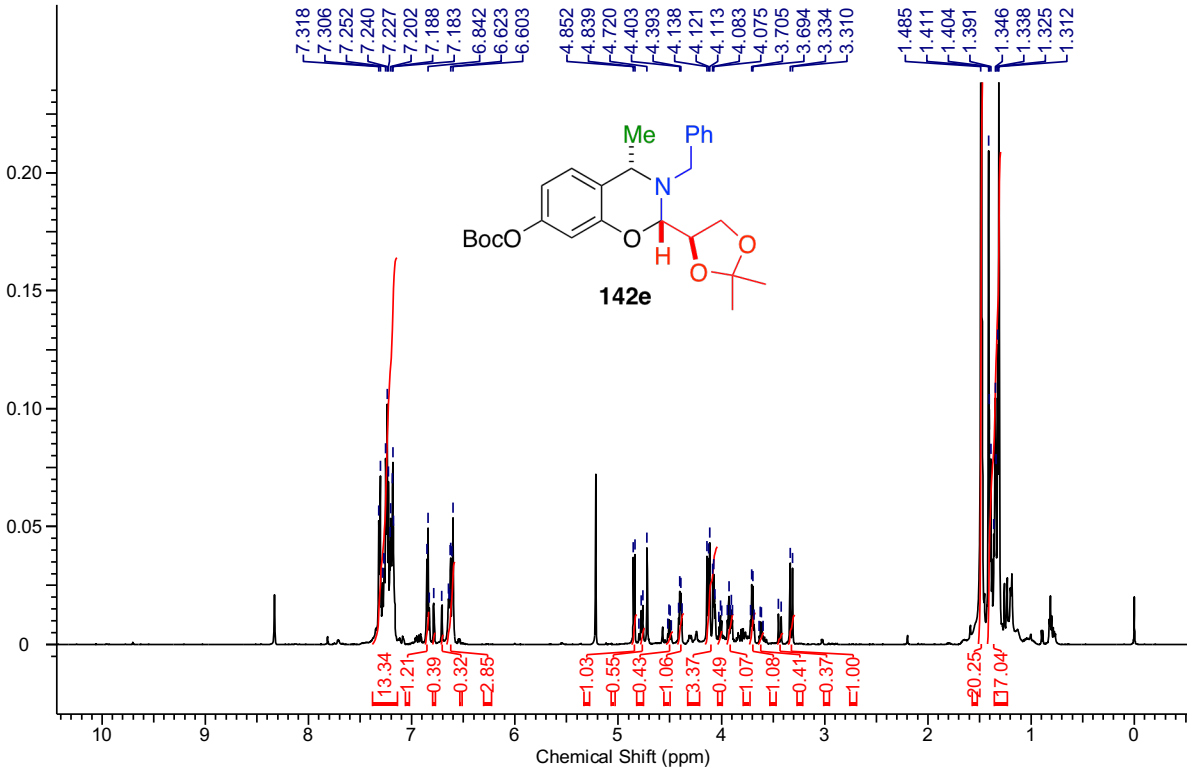

7.358
7.343
7.275
7.146
7.132
6.736
6.720
6.653
6.648
6.575
6.559
3.999
3.985
3.915
3.902
3.711
3.697
3.661
3.647
3.634
1.561
1.548
1.465
1.416
1.412
1.399
1.326
Me
Me
N
H
Ph
BocO
OH
142a'
5.57
1.83
0.42
0.96
0.84
0.43
1.28
0.42
0.42
0.94
0.94
14.11
1.40
4.20
3.00
Chemical Shift (ppm)

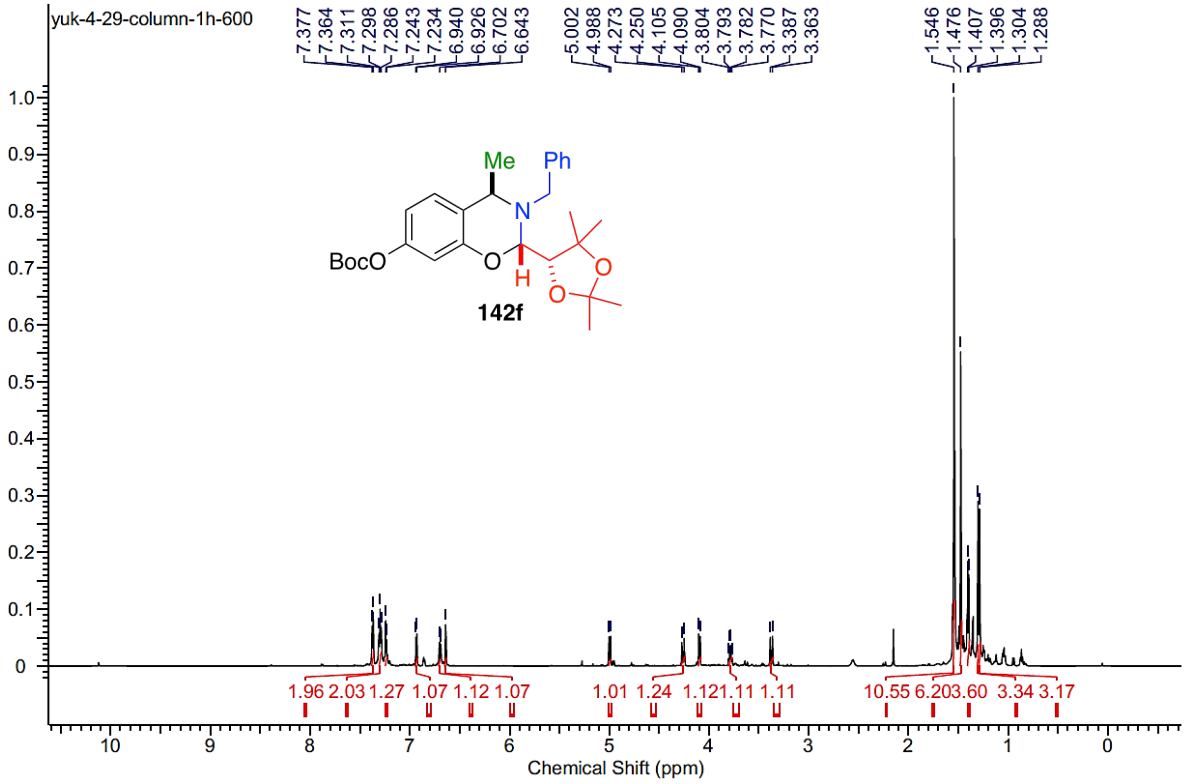

7.380
7.368
7.338
7.260
7.172
7.160
6.711
6.697
6.654
6.650
6.565
6.551
4.600
4.285
4.271
4.265
4.252
4.188
4.181
4.169
3.685
3.674
2.398
2.386
2.373
2.369
2.357
1.558
1.541
1.422
1.358
1.347
1.267
1.138
1.126
1.113
Me
Ph
N
H
O
Et
O
BocO
OH
142b
5.18
3.76
2.03
0.50
1.03
0.87
0.43
1.45
0.49
0.53
1.52
1.00
0.50
1.01
1.04
3.97
4.75
1.50
3.00
1.46
0.94
Chemical Shift (ppm)

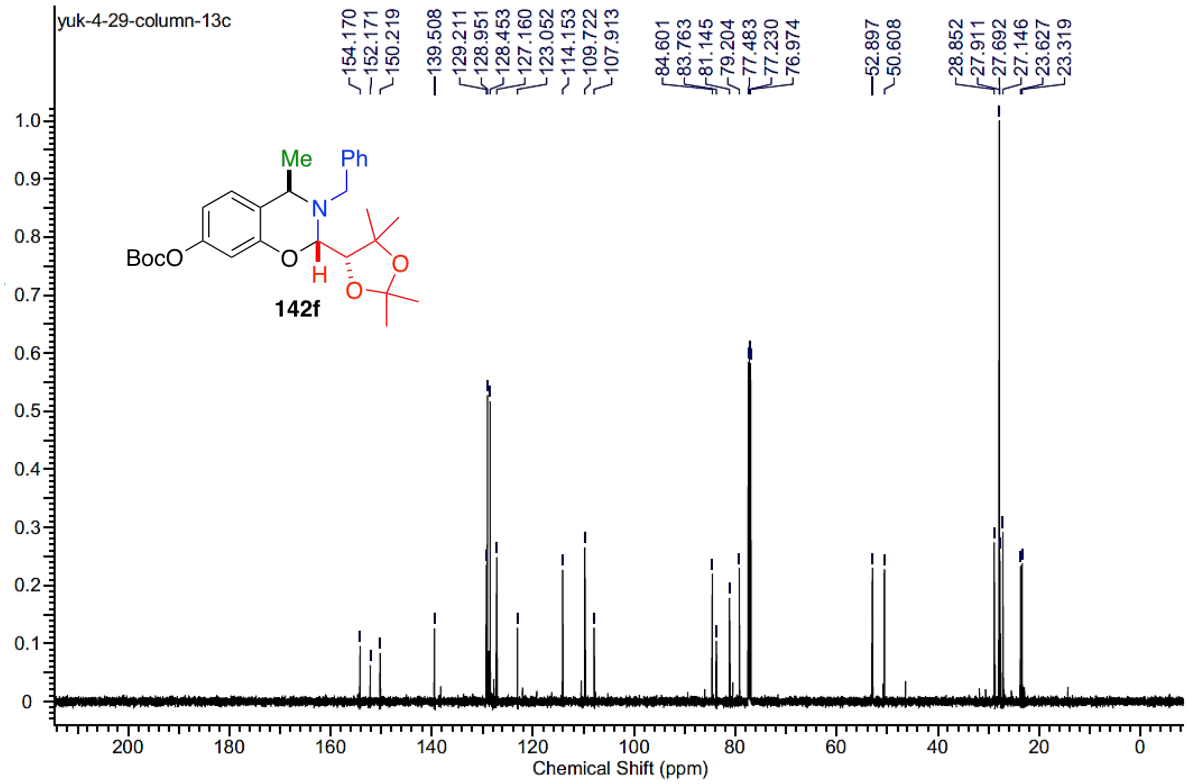

6.920
6.901
6.600
6.595
6.587
6.567
6.561
5.253
5.242
5.231
3.931
3.915
3.898
3.881
3.078
3.051
3.043
2.123
1.925
1.890
1.763
1.737
1.545
1.520
1.512
1.501
1.374
1.357
Me
N
H
O
Me
O
BocO
OH
142c (isomer 1)
0.15
0.10
0.05
0
1.02
2.00
0.96
0.97
1.00
2.89
2.27
2.31
1.89
2.99
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

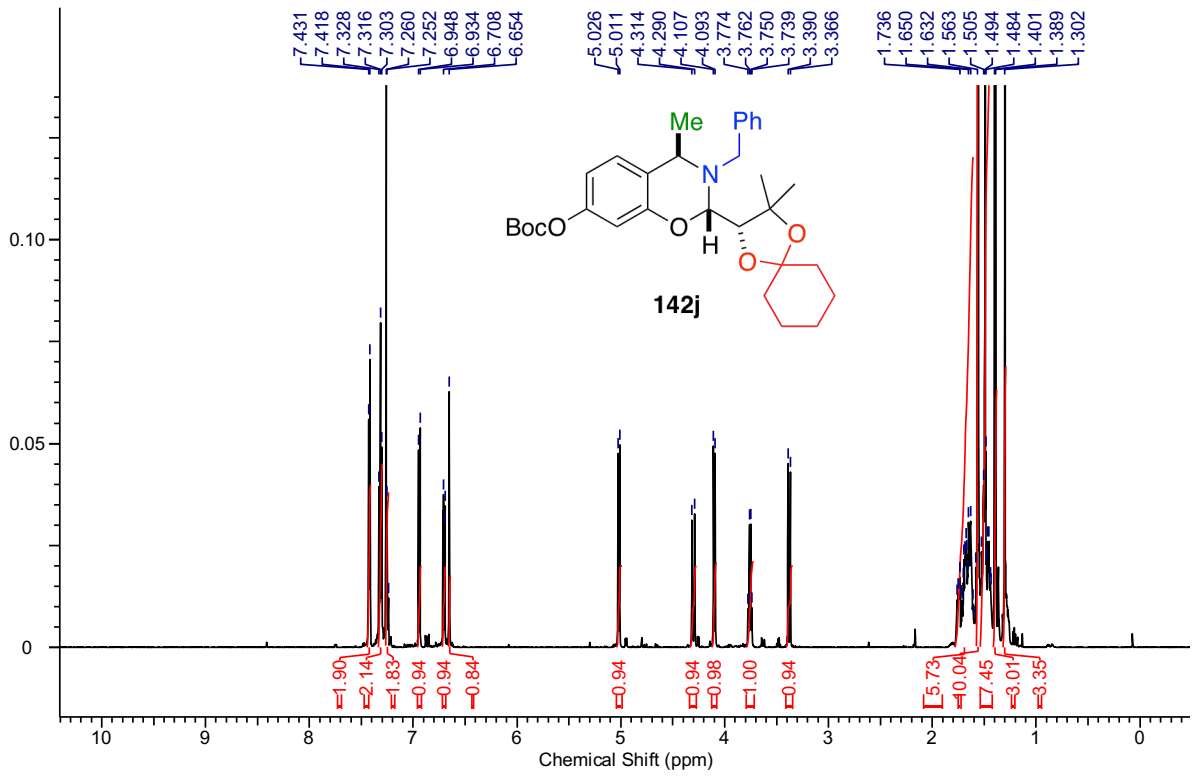

6.922
6.902
6.612
6.606
6.593
6.588
6.572
5.075
5.065
5.055
4.023
4.007
3.990
3.077
3.065
3.050
3.041
2.088
1.860
1.850
1.745
1.718
1.710
1.547
1.516
1.502
1.439
1.422
Me
N
H
O
Me
O
BocO
OH
142c (isomer 2)
0.30
0.25
0.20
0.15
0.10
0.05
0
1.18
2.24
1.02
0.97
1.16
3.25
1.49
2.99
12.22
3.15
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

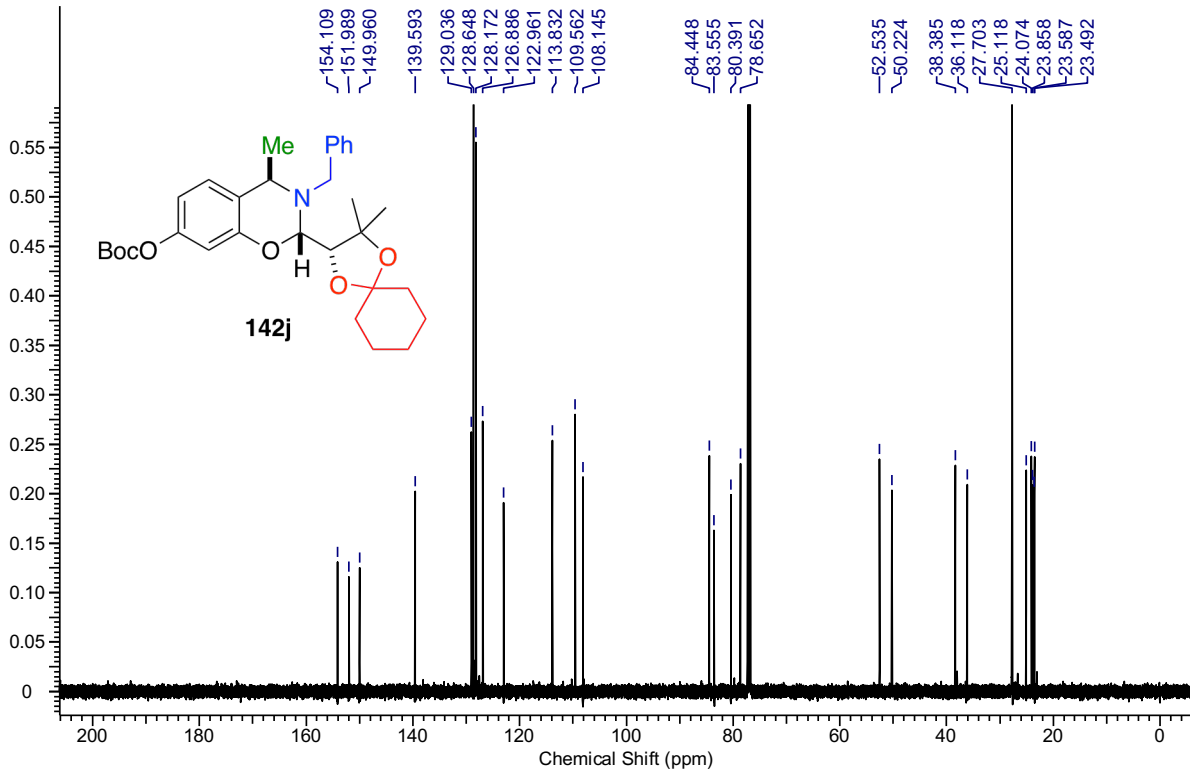

Me
Ph
N
BocO
O
H
t-Bu
OMe
142d
Chemical Shift (ppm)


Me
Ph
N
BocO
O
H
O
O
142e
Chemical Shift (ppm)


yuk-4-29-column-1h-600
7.377
7.364
7.311
7.298
7.286
7.243
7.234
6.940
6.926
6.702
6.643
5.002
4.988
4.273
4.250
4.105
4.090
3.804
3.793
3.782
3.770
3.387
3.363
1.546
1.476
1.407
1.396
1.304
1.288
Me
Ph
N
BocO
O
H
O
O
142f
1.96 2.03 1.27 1.07 1.12 1.07
1.01 1.24 1.12 1.11 1.11
10.55 6.20 3.60 3.34 3.17
Chemical Shift (ppm)


yuk-4-29-column-13c
154.170
152.171
150.219
139.508
129.211
128.951
128.453
127.160
123.052
114.153
109.722
107.913
84.601
83.763
81.145
79.204
77.483
77.230
76.974
52.897
50.608
28.852
27.911
27.692
27.146
23.627
23.319
Me
Ph
N
BocO
O
H
O
O
142f
Chemical Shift (ppm)


7.431
7.418
7.328
7.316
7.303
7.260
7.252
6.948
6.934
6.708
6.654
5.026
5.011
4.314
4.290
4.107
4.093
3.774
3.762
3.750
3.739
3.390
3.366
1.736
1.650
1.632
1.563
1.505
1.494
1.484
1.401
1.389
1.302
Me
Ph
N
BocO
O
H
O
O
142j
0.10
0.05
0
1.90
2.14
1.83
0.94
0.94
0.84
0.94
0.94
0.98
1.00
0.94
5.73
10.04
7.45
3.01
3.35
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


154.109
151.989
149.960
139.593
129.036
128.648
128.172
126.886
122.961
113.832
109.562
108.145
84.448
83.555
80.391
78.652
52.535
50.224
38.385
36.118
27.703
25.118
24.074
23.858
23.587
23.492
Me
Ph
N
BocO
O
H
O
O
142j
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)