UNIVERSITY OF CALIFORNIA

Santa Barbara

General Method for the Construction of *ortho*-*tert*-Butyl Phenols & 3,4-Dihydro-*2H*-1,3-benzoxazines *via* Base-Promoted *ortho*-Quinone Methide Chemistry; A Review of Generation of aza-*ortho*-Quinone Methide and Its Applications

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

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June 2022

The dissertation of Kazaf KC Chan is approved.

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March 2022

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Acknowledgements

Special thanks to Prof. Tom Pettus for accepting me into his group, creating great projects and supporting my research. His commitment to student is incredible and selfless. You are an awesome and tough mentor.

I would like to thank Prof. Mahdi Abu-Omar, Prof. Javier Read de Alaniz and Prof. Liming Zhang for not only being part of my committees but also for their optimistic attitudes about school and life. The professional atmosphere they created was greatly appreciated.

Thank my bust buddy ever, Boss, for showing up in my life and your unconditional love and emotional support during all these difficult times.

The past and present Pettus group deserves many thanks. You all provide great work to move *ortho*-quinone methide projects forward.

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"Nucleophilic Imines and Electrophilic *o*-Quinone Methides, a Three-Component Assembly of Assorted 3,4-Dihydro-*2H*-1,3-benzoxazines"

Organic Letters **2019**, *21*, 7746-7749.

"An Anesthetic Drug Demonstration and an Introductory Antioxidant Activity Experiment with Eugene, the Sleepy Fish"

Journal of Chemical Education **2016**, *93(1)*, 202-205.

"Synthetic Anthocyanidins and Their Antioxidant Properties"

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Abstract

General Method for the Construction of

ortho-*tert*-Butyl Phenols & 3,4-Dihydro-*2H*-1,3-benzoxazines

via Base-Promoted *ortho*-Quinone Methide Chemistry;

A Review of Generation of aza-*ortho*-Quinone Methide and Its Applications

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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*, which is subsequently used for [4+2] cycloadditions with a dienophile and 1,4-conjugated additions with a nucleophile. In this thesis, I would like to discuss two new methods for synthesizing privilege structures using our base-promoted *o*-QM chemistry.

In the first part of this thesis, a new general process for construction of a variety of *ortho*-*tert*-butyl phenols *via o*-QMs is presented. In addition, other known methods for construction of *ortho*-*tert*-butyl phenols were also evaluated regarding to their regioselectivity, efficiency and functional group tolerance. By comparison, we concluded that our *o*-QM chemistry provides better yields and also tolerate an assortment of functional groups for delivering *ortho*-*tert*-butyl phenols.

In the second part of this thesis, a one-pot method for combining three separate components leading to a variety of *N*-substituted 3,4-dihydro-*2H*-1,3-benzoxazines is

described. This method involves the addition of a Grignard reagent to an *ortho*-OBoc salicylaldehyde derivative in the presence of an imine. With an assortment of imines tested, 15 examples of *N*-substituted 3,4-dihydro-*2H*-1,3-benzoxazines are presented, including the diastereoselective incorporation of racemic imines.

In the third part of this thesis, I would like to discuss about aza-*ortho*-quinone methides (aza-*o*-QMs), an analogue of *o*-QMs. Aza-*o*-QMs are very similar to *o*-QMs for their highly electrophilicity. Nevertheless, aza-*o*-QMs are far less explored comparing to *o*-QMs. Therefore, I would like to use my experience in *o*-QMs to propose a more general method for base-promoted aza-*o*-QMs generation and its future applications suitable for our group.

List of Abbreviations

Ac_2O = acetic anhydride

aza-*o*-QM = aza-*ortho*-quinone methide

$BF_3 \cdot Et_2O$ = boron trifluoride diethyrate

BnCl = benzyl chloride

-Boc = *tert*-butyl carbonate

Boc_2O = di-*tert*-butyl dicarbonate

CH_2Cl_2 or DCM = dichloromethane

CH_3CN = acetonitrile

CH_3CO_2H = acetic acid

-CHO = aldehyde

$ClCH_2CH_2Cl$ or DCE = 1,2-dichloroethane

CO_2 = carbon dioxide

CSA = camphorsulfonic acid

DMAP = 4-dimethylaminopyridine

-Et = ethyl

Et_2O = diethyl ether

Et_3N = triethylamine

EtOH = ethanol

H_2O = water

HCl = hydrochloric acid

K_2CO_3 = potassium carbonate

MeI = methyl iodide

MeMgBr = methylmagnesium bromide

MeMgCl = methylmagnesium chloride

MeOH = methanol

MsCl = methanesulfonyl chloride

$NaBH_4$ = sodium borohydride

NaH = sodium hydride

$NaHCO_3$ = sodium bicarbonate

n-Bu = butyl

-OEt = ethoxy

o-QM = *ortho*-quinone methide

-Ph = phenyl

PhMgBr = phenylmagnesium bromide

PhMgCl = phenylmagnesium chloride

t-Bu = *tert*-butyl

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TMSOTf = trimethylsilyl triflate

TABLE OF CONTENTS

Chapter 1

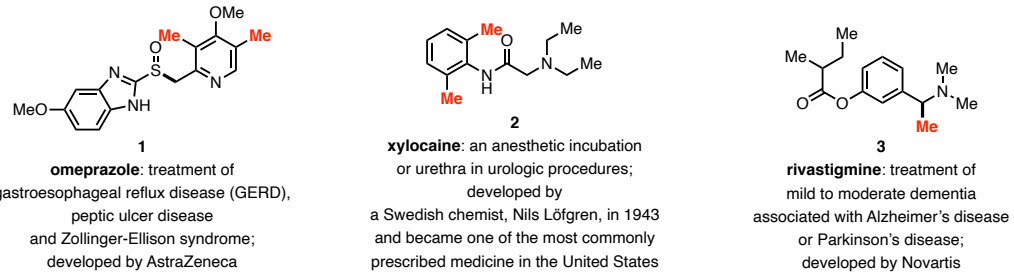
Base-Promoted *ortho*-Quinone Methide Chemistry

Generation of *ortho-tert*-Butyl Phenols,

A Privilege Structure

1.1 A tert-Butyl Function Group ortho to an Oxygen Substituent on Aromatic Rings in Medicinal Chemistry

Often an aromatic compound displaying a methyl residue is identified from a high throughput screen (HTS) of its biological potency, which is usually known as "Methyl Effects" in drug discovery (Figure 1).[1] "Methyl Effects" refer to the binding potency, where the change of *C-H* to *C-Me* improves the IC_{50} value of a drug candidate more than 100-fold.[1a] Examples that show the "Methyl Effects" are in Figure 1. Compound **1** (Figure 1) was developed by AstraZeneca for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease and Zollinger-Ellison syndrome.[2] Compound **2** (Figure 1) has become one of the most commonly prescribed medicines used as an anesthetic incubation or urethra in urological procedures, and it was developed by a Swedish chemist, Nils Löfgren, in 1946.[3] Compound **3** (Figure 1) was developed by Novartis for the treatment of mild to moderate dementia that is associated with Alzheimer's disease or Parkinson's disease.[4]



1
omeprazole: treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease and Zollinger-Ellison syndrome; developed by AstraZeneca

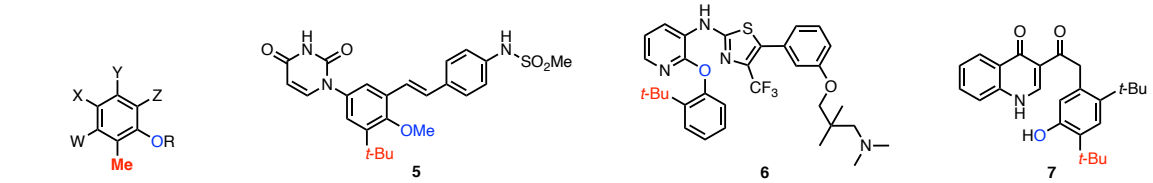
2
xylocaine: an anesthetic incubation or urethra in urologic procedures; developed by a Swedish chemist, Nils Löfgren, in 1943 and became one of the most commonly prescribed medicine in the United States

3
rivastigmine: treatment of mild to moderate dementia associated with Alzheimer's disease or Parkinson's disease; developed by Novartis

Figure 1. Small-molecule drugs contain C-Me group

However, when a methyl substituent is positioned *ortho* to an oxygen substituent on an aromatic ring, as in compound **4** (Figure 2), it makes the methyl residue oxidatively vulnerable. One possible solution is to replace the methyl residue with a more oxidatively stable *tert*-butyl residue.[5] There are more than a few examples that imbedded a *tert*-butyl residue amongst many pharmaceutical ingredients. Compound **5** (Figure 2) was disclosed as

a potent NS5B polymerase inhibitor that has been explored as a treatment for Hepatitis C Virus (HCV) by AbbVie.[6] Similar *tert*-butyl phenolic skeletons have been studied by Roche for numerous therapeutic applications.[7] Bristol-Myers Squibb (BMS) has further investigated this *ortho-tert*-butyl phenol structural motif and reported compound **6** (Figure 2) as a $P2Y_1$ antagonist for chronic treatment of antithrombotic.[8] Therefore, it is important to have an efficient and robust strategy for the construction of *ortho-tert*-butyl phenols. Nevertheless, it was not until Vertex's adoption of our base-promoted *ortho*-quinone methide (*o*-QM) chemistry to deliver ivacaftor (**7**)[9] (Figure 2) and its deuterated counterpart[10] on industrial scale that we were aware the challenges that have been posted for this *ortho-tert*-butyl phenol structural motif, which will be discussed in section 1.2. We were also honored to see the usefulness of *o*-QM chemistry and its power to solve the long standing problem – building an *ortho-tert*-butyl phenol.



4
HTS lead compound
oxidatively vulnerable Me residue

5
ABT-072: potent NS5B polyemerase inhibitor, treatment for HCV;
scaffolds researched by AbbVie and Roche

6
2-Aminothiazole derivatives: $P2Y_1$ antagonist, chronic treatment for antithrombotic;
scaffolds researched by Bristol-Myers Squibbs

7
ivacaftor: CFTR potentiator, treatment of cystic fibrosis;
developed by Vertex

Figure 2. Small-molecule drugs contain *tert*-butyl group *ortho* to phenols

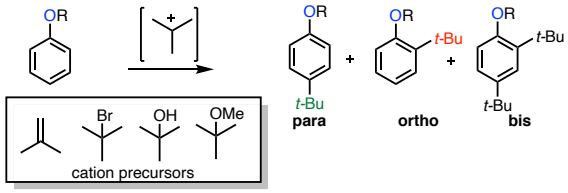
In this chapter, I will share the pre-existing methods for construction of *ortho-tert*-butyl phenols along with their respective strengths and drawbacks. At the end, I will introduce our developed *o*-QM chemistry for the synthesis of *ortho-tert*-butyl phenols.

1.2 Methods for Construction of ortho-tert-Butyl Phenol Derivatives

1.2.1 Friedel-Crafts Alkylation/tert-Butylation

Friedel-Crafts alkylation has been used widely for the introduction of *tert*-butyl groups onto various anisole derivatives (Scheme 1).[11] However, this strategy is limited with poor

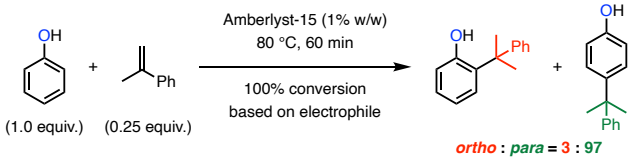
ortho-regiocontrol. Furthermore, the introduction of additional electron donating groups would only futher complicate these *ortho*-regiocontrol problems. In order to resolve these issues, many researchers have investigated a variety of *tert*-butyl cation precursors in conjunction with various Lewis acid promoters.



Scheme 1. Isomeric mixtures and bis-tert-butylation resulted from Friedel-Crafts alkylation

1.2.1.1 Sharma's Condition

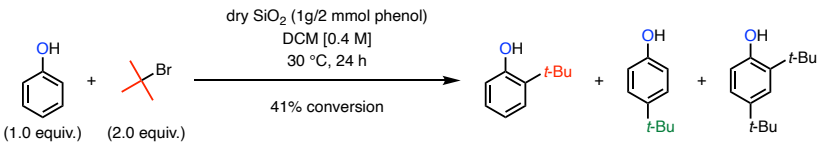
In 1991, Sharma *et. al.* found that Amberlyst-15 provided the greatest amount of the corresponding *para*-*tert*-alkylation product (97 : 3) with the absence of *bis*-*tert*-alkylation product (Scheme 2). They claimed that Amberlyst-15 outperformed *p*TSA, $AlCl_3$ and many other Lewis acids investigated.[12a] Nevertheless, none of their results provided an advantage condition to generate *ortho*-*tert*-alkylation product regioselectively.



Scheme 2. Sharma's condition for Friedel-Craft alkylation, para-product is dominant

1.2.1.2 Tsukamoto's Condition

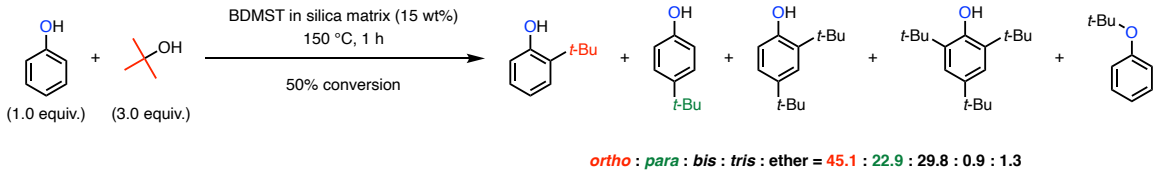
In 1986, Tsukamoto *et. al.* reported that the highest *ortho* yielding expamples by using *tert*-butyl bromide impregnated onto dry silica gel.[12b] However, the reaction only resulted in 41% overall conversion with a distribution of 58% *ortho* : 32% *para* : 10% *bis* products (Scheme 3).



Scheme 3. Tsukamoto's condition for Friedel-Craft alkylation, *ortho*-product is dominant along with *para*- and *bis*- side products

1.2.1.3 Gagea's Condition

Gagea *et. al.* reported to utilize *tert*-butyl dimethylsilyltrifluoromethane sulfonate (BDMST), a Lewis acid, for the synthesis of *ortho-tert*-butyl phenols, napthols[12c] and hydroquinones.[12d] However, poor regiocontrol was still present along with only 50% conversion yield (Scheme 4).



Scheme 4. Gagea's condition for Friedel-Craft alkylation, *ortho*-product is dominant along with *para*-, *bis*-, *tris*- and ether side products

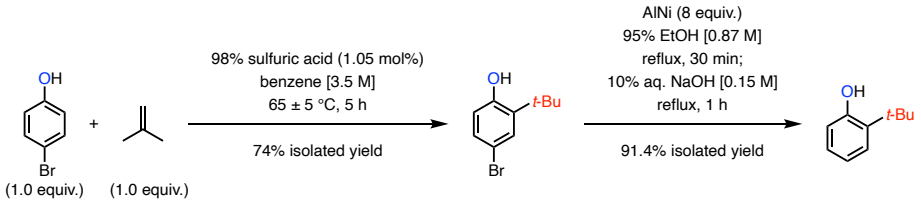
1.2.1.4 Pezzotta's Condition

More recently, Pezzotta *et. al.* reported to use Keggin-type phosphotungstic acid ($H_3PW_{12}O_{40}$) immobilized on Santa Barbara Amorphous SBA-15 to conduct regioselective *tert*-butylation on resorcinol using methyl *tert*-butyl ether as a cationic precursor.[12e] Nevertheless, only 20% conversion of resorcinol was observed with a mixture of *mono-ortho-tert*-butyl resorcinol and *bis-ortho-tert*-butyl resorcinol in 42:58 ratio.

1.2.1.5 Hart's Condition

Given the above and other studies[11], it is apparent that cationic alkylation regimes fail to provide much of synthetic utility. Nevertheless, Hart reported that a successful regioselective *ortho-tert*-butylation on phenols can be carried out with 74% yield if the

para-site is blocked with a deactivating group, like a bromo substituent (Scheme 5).[12e] Isobutylene was used a cationic precursor and sulfuric acid was used as a Brøsted acid. Upon the isolation of *ortho-tert*-butyl *para*-bromo phenol, the bromo substituent can be reductively removed by Raney nickel-aluminum alloy in alkaline solutions to afford the desired *ortho-tert*-butyl phenol in 67.6% over 2 steps. In the meantime, the regioselective introduction of the bromo group for a desired precursor can also become another dilemma.



Scheme 5. Hart's condition for Friedel-Craft alkylation on *para*-substituted phenol

1.2.2 Addition of *t*-Bu$^-$ or *t*-Bu$^\cdot$ to Carbonyl Compounds

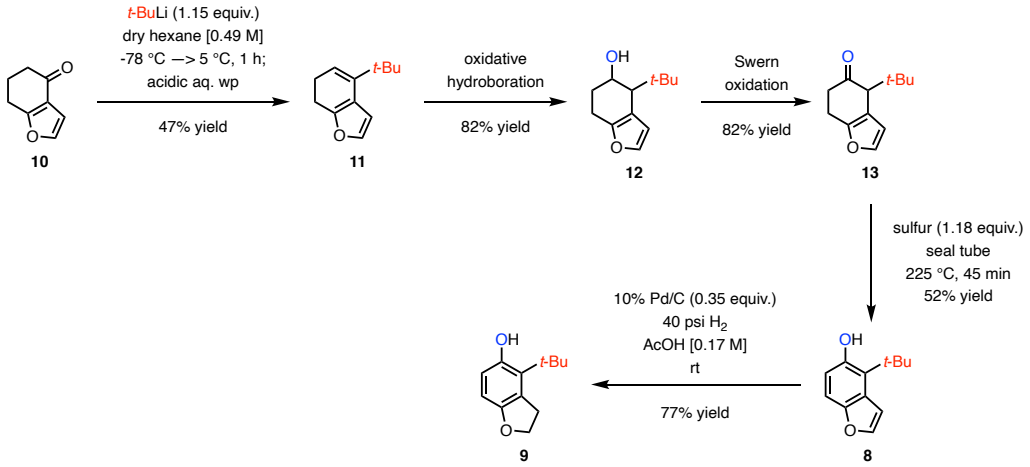
Usage of *tert*-butyl anions or radicals for the formation of a carbon-carbon bond is challegning. Nervertheless, there are a few examples where this strategy has proven effective for *ortho*-functionalized phenols using carbonyl and alkene substrates.

1.2.2.1 Hammond's Method: Addition of *t*-Bu$^-$ to Carbonyl Compounds

In 1988, Hammond *et. al.* synthesized 5-benzofuranol derivatives, which shows promoising antioxidant based inhibitors of 5-lipoxygenase.[13] However, the pre-exiting methods cannot provide the synthesis of desired compound **8** and its hydrogenated counterpart, compound **9** (Scheme 6). Therefore, Hammond *et. al.* has developed a new synthetic route, which is to use a *tert*-butyl anion in one of the four-step sequence for the synthesis of these two *ortho-tert*-butyl phenol derivatives of interest.[14]

Hammond observed that a *tert*-butyl anionic nucleophile participated in a desired 1,2-addtion with the vinylogous ester carbonyl (**10**). Upon an acidic aqueous work-up, the

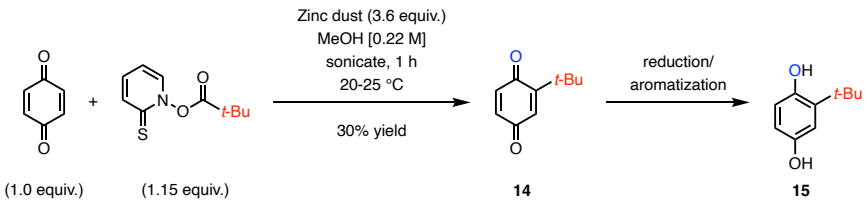
resulting tertiary alchol was elminated *via* E1 mechanism resulting in the cyclohexene intermediate (**11**). Further oxidative hydroboration of compound **11** afforded the secondary alcohol (**12**), which is then oxidized by Swern oxidation condition to afford the ketone (**13**). Compound **13** was treated with sulfur at high temperature to promote the enolization of **13** followed by the dehydrogenation, which afforded the desired compound **8** in only 16% overall yield. Further hydrogenation of compound **8** over Pd/C allows the formation of compound **9** in only 13% overall yield.[14]



Scheme 6. Hammond's method: introduction of a *tert*-butyl group by using a *tert*-butyl anion nucleophile performs a 1,2-addition on vinylougous ester carbonyls

1.2.2.2 Barton's Method: Addition of *t*-Bu· to Quinones

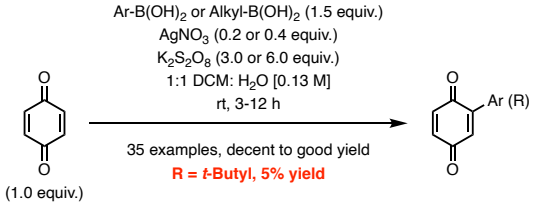
Barton *et. al.* used a pivaylate ester, which is derived from carboxylic acids and *N*-hydroxy-2-thiopyridinones, participated in a 1,4-conjugated radical addition with 1,4-quinones (Scheme 7) to afford the quinone (**14**).[15] Nevertheless, only 30% of compound **14** was collected, while 45% of *tert*-butylated benzoquinone was reported. For a less hinder radical than a *tert*-butyl group, higher yielding was also observed. Upon further reduction, a hydroquinone product (**15**) can be obtained.[16]



Scheme 7. Barton's method: introduction of a *tert*-butyl group by using a *tert*-butyl radical performs a 1,4-conjugated addition on quinones

1.2.2.3 Baran's Method: Addition of *t*-Bu· to Quinones

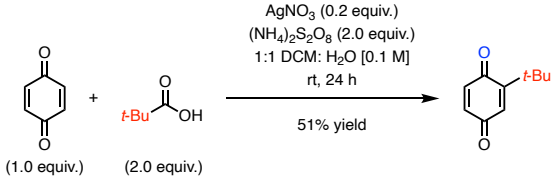
Similar to Barton's method, Baran *et. al.* also reported the use of a *tert*-butyl radical on quinones. An aryl/alkyl radical was generated from reaction between silver nitrate and a boronic acid, then *para*-quinone reacts with the aryl/alkyl radical followed by reoxidation to result in a functionalized quinone.[17a] Baran has proved that this method is useful for a variety of aryl/alkyl boronic acids, but failed to do so with a more hindered *tert*-butyl radical (Scheme 8).



Scheme 8. Baran's method: C-H Functionlization of quinones with boronic acids, nucleophilic radical addition to quinones followed by *in situ* reoxidation

1.2.2.4 Baxter's Method: Addition of *t*-Bu· to Quinones

Baxter *et. al.* subsequently described a slightly modified procedure that leads to a similar *tert*-butyl quinone in 51% yield with the direct use of a *tert*-butylcarboxylic acid (Scheme 9).[17b]



Scheme 9. Baxter's method: C-H Functionlization of quinones with carboxylic acids, nucleophilic radical addition to quinones followed by *in situ* reoxidation

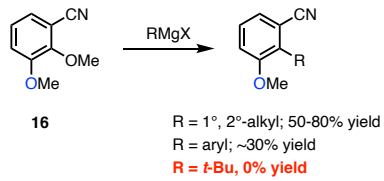
Although none of the previously described methods in Section 1.2.2 provide high yielding for the introduction of *tert*-butyl residues, they have proven to be extraordinaryly useful for incorporation of less congested alkyl/aryl groups onto *para*-quinones.

1.2.3 *t*-Bu$^-$ *Ipso* S_NAr of Aryl Methoxy and *t*-Butylsulfoxide Moieties

Ipso S_NAr reactions have also been studied for *tert*-butylation on aromatic rings. Several methods will be discussed in the following subsection 1.2.3.1-1.2.3.2.

1.2.3.1 *t*-Bu$^-$ *Ipso* S_NAr of Aryl Methoxy Moieties

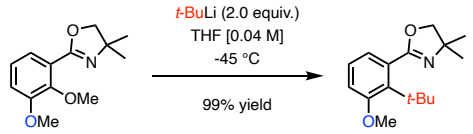
In 1949, Richtzenhain *et. al.* described the addition of various Grignard reagents to 2,3-dimethoxy benzonitriles (**16**). Althougth reactions proceeded in 50-80% yields with primary and secondary Grignard reagents, when aryl Grignards were used, only ~30% yields were observed. As for the case of *tert*-butyl Grignard, the reaction completely failed (Scheme 10).[18a] The low yielding is most likely due to Grignards also reacting with the nitrile group, which can lead to undesired side reactions.



Scheme 10. Richtzenhain's condition: Griginard regeants *Ipso* S_NAr on aryl methoxy with nitrile directing group

In the 1970s, Meyers reported to use an aryl oxazoline (**17**) as a surrogate to the earlier benzonitrile system. The reaction proved to be useful even for the introduction of a *tert*-butyl anion nucelophile, which results in 99% yield (Scheme 11).[18b,c] Nevertheless, further transformation of oxazolines to carboxylic acids only results in 45% yield in alkaline

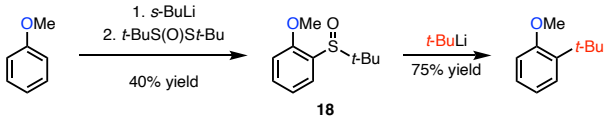
conditions and complete removal of the *tert*-butyl group in acidic conditions due to *tert*-butyl group being acid-labile.



Scheme 11. Meyers's condition: Griginard/organolithium regeants *Ipso* S_NAr on aryl methoxy with oxazoline directing group

1.2.3.2 *t*-Bu- Anions *Ipso* S_NAr of Aryl *tert*-Butyl Sulfoxide Moieties

More recently, Clayden *et. al.* described aryl *tert*-butyl sulfoxides undergo *Ipso* S_NAr reactions with organolithium nucleophiles. Remarkably, these reactions proceed with both electron withdrawing groups (oxzolines or amides) and moderate electron donating groups (methoxys).[19] Examples with electron withdrawing groups afforded greater overall yields across the two-step synthesis. Indeed, 75% yield in the anisole example is extraordinary. Nevertheless, the construction of the respective sulfoxide precursor (**18**) proves to be deficient with 40% yield, which leads to an inefficient overall process.



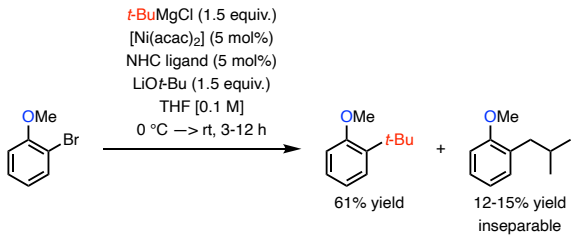
Scheme 12. Meyers's method: organolithium regeants *Ipso* S_NAr on aryl *t*-butylsulfoxides with both electron withdrawing groups (oxazolines or amides) and moderate electron donating groups (methoxy)

1.2.4 Metal Mediated Cross Coupling of Aryl Bromides

Metal mediated cross couplings have also been investigated for introduction of *tert*-butyl group on aromatic rings. This method has been shown to proceed moderately well, despite the risk of β-hydride elimination.[20]

In the meantime, there are two obstacles one must consider before implementing this strategy. First, halogenated materials with *ortho* electron donating groups (hydroxy, methoxy, *etc*.) often prove to be resistant to oxidative insertion.[21] Second, regioselective *ortho*-bromination of phenols, and particularly onto anisoles, can prove to be very challenging.[22]

If the desired halogenated precursors can be obtained, then copper, nickel, iron and chromium species have proved to be effective in cross couplings with various *tert*-butyl nucleophiles.[23] For example, Glorius *et. al.* recently reported the successful cross couplings between *ortho*-bromo anisole with a *tert*-butyl magnesium chloride in the presence of a *N*-heterocyclic carbenes (NHC) catlayst to produce *ortho-tert*-butyl anisole with 61% yield. However, this method also leads to a 12-15% inseparable *iso*-butyl isomer (Scheme 13).[24]



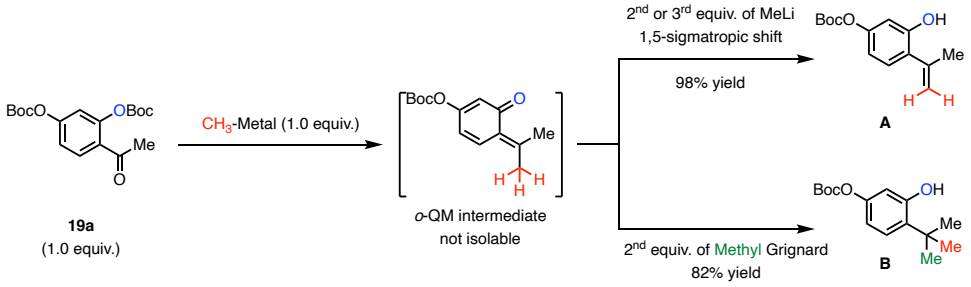
Scheme 13. Glorius's condition: Nickel-catalyzed cross-coupling of aryl bromides with *tert*-butyl Grignard reagents utilizing NHCs

1.2.5 Development of *ortho-tert*-Butylation of Phenols *via* Base-Promoted *o*-QMs at Low Temperature

1.2.5.1 Pettus Group History on Synthesis of *ortho-tert*-Butylation of Phenols (2000-2017)

In 2000, our group published a communication revealing a general method to access *o*-QM intermediates under basic conditions.[25a] It was a ground-breaking process because this method enables the formation of *o*-QMs and allow *o*-QMs to engage with assorted carbon

nucleophiles at low temperature for the first time (Scheme 14). Although the construction of *ortho*-*tert*-butyl phenols was not the main focus, a solitary example delivering the phenol (**B**) from the *ortho*-OBoc acetophenone (**19a**) was demonstrated.

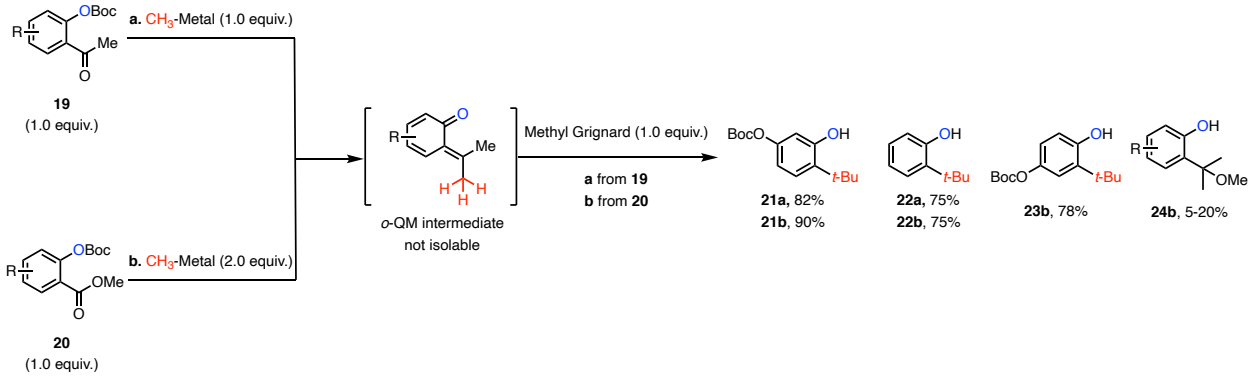


Scheme 14. Pettus's condition: construction of *ortho*-alkyl phenols *via* base-promoted *o*-QM at low temperature from *ortho*-OBoc acetophenones

In this early study of organometallic nucleophiles, three important conclusions were made. First, from screening acyl residues, which enabled a controlled *o*-QM formation, a *tert*-butyloxycarbonate (Boc) was shown to be superior in both formation and subsequent reactions from among methoxycarbonate, acetyl and pivalate alternatives. Second, from screening several solvents, a dilute solutioin of diethyl ether provided superior yields comparing to THF, benzene and toluene. This is because diethyl ether possibly have effects in the Schlenk equilibrium. Third, application of an organomagnesium reagent proved indispensable in delivering the *tert*-butylated product(s) (**B**), as the corresponding organolithium led to the corresponding styrene products (**A**), which is presumably due to 1,5-sigmatropic shift (Scheme 14).

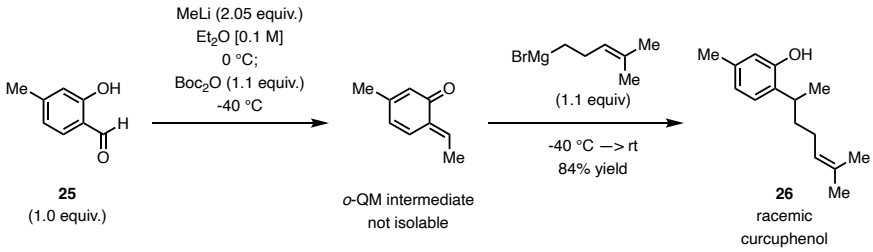
Expanding upon this earlier work, in 2001, our group investigated *ortho*-OBoc acetopheones (**19**) and *ortho*-OBoc methyl benzoates (**20**) resulting in the *tert*-butylated compounds (Scheme 15, **21**-**23**).[25b] In both cases, these one-pot transformations were conducted in diethyl ether with 2 to 3 equivalents of methyl magnesium chloride. However,

ortho-OBoc methyl benzoates afforded the undesired methyl benzyl ethers (**24b**) in about 5-20% yield along with the desired *tert*-butyl adducts (**21**-**23**).



Scheme 15. Pettus's condition: construction of *ortho*-alkyl phenols *via* base-promoted *o*-QM at low temperature from *ortho*-OBoc acetophenos and *ortho*-OBoc methyl benzoates

Some years later, while persuing the racemic curcuphenol (**26**) from benzaldehyde (**25**), our group explored a slight modification to the original protocol, whereby 2 equivalents of methyl lithium were deployed to cause both phenol deprotonation and methyl addition, followed by introduction of Boc_2O. Then the addition of an organomagnesium reagent induced *o*-QM formation and incorportaion of the side chain (Scheme 16).[25c] However, this modification for *tert*-butyl formation was never tested.

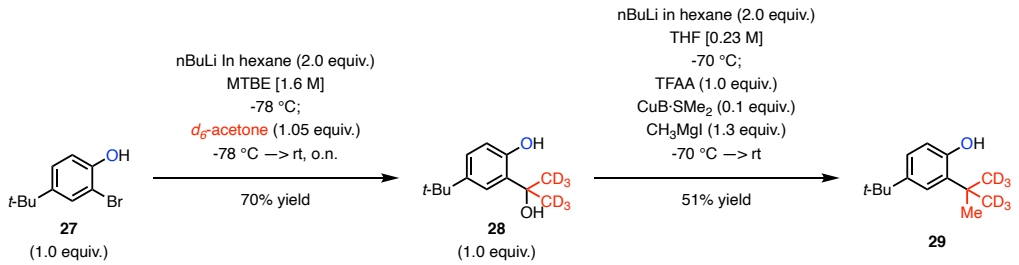


Scheme 16. Pettus's condition: construction of racemic curcuphenol *via* one-pot base-promoted *o*-QM at low temperature from 5-methylsalicylaldehyde

1.2.5.2 Vertex's Adoption of Our *o*-QM Chemistry on Synthesis of Ivacaftor & *d9*-Ivacaftor

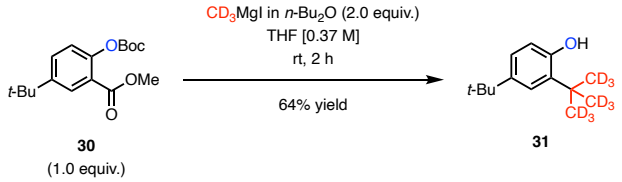
In 2017, Vertex informed us that due to the pitfalls of other *tert*-butylation methods, they were testing our *o*-QM chemistry for preparation of ivacaftor (**7**). In 2020, they reported some of their findings in regards to a deuterated derivatives.[26]

Their tactics closely mirror our earlier work. However, their evaluations were more thorough and exhaustive, resulting in some additional observations and refinements. First, after preparing the diol (**28**) from the aryl bromide (**27**), they surveyed several additional acylation reagents, including PivCl and BzCl. They reported that trifluoroacetic anhydride (TFAA) to be equal, if not superior to our original selection of Boc_2O for the conversion of the diol (**28**) into the *ortho-tert*-butyl phenol (Scheme 17, **29**). Moreover, their entire sequence began from the aryl bromide (**27**), which could be carried out in a one-pot reaction if so desired. However, due to the reactivity of *o*-QM intermediate, a nucleophilic trap needed to be immediately available and a one-pot reaction would become challening by using aryl bromide as the precursor upon scale-up. Second, they indicated that CuBr-SMe_2 as a metal additive improved the overall yield by possibly stabilizing *o*-QM intermediates (Scheme 17).



Scheme 17. Vertex's condition: construction of *ortho-tert*-butyl phenol derivative *via* a two-pot base-promoted *o*-QM at low temperature from aryl bromides

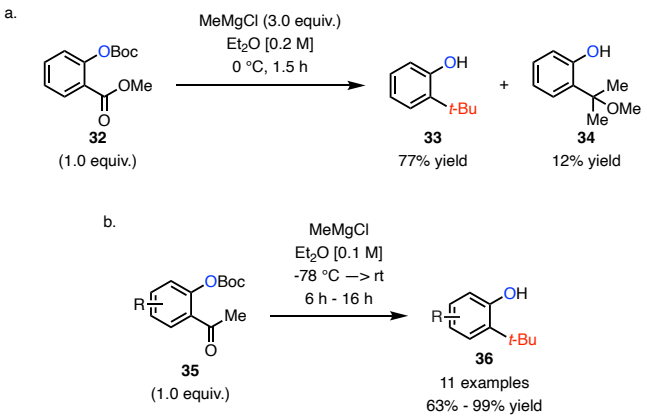
Third, they indicated that a solvent mixture comprised of *n*-butyl ether and THF to be slightly better than our original choice of diethyl ether. They implemented this change with the ester (**30**) to arrive at the deuterated *tert*-butyl derivative (**31**) in 64% yiled for an over-than-ten-kilogram scale (Scheme 18). Lastly, they suggested that organomagnesium iodides, which are easier to prepare on industrial scale, performed slightly better than other organomagnesium halides in THF as a cosolvent (Scheme 18). They further postulated that this was perhaps due to perturbation in the Schlenk equilibrium as a $MgI_2 \cdot THF$ insoluble complex formed leading to a beneficial system containing the more reactive $(CD_3)_2Mg$.



Scheme 18. Vertex's condition: construction of *ortho*-d_9-*tert*-butyl phenol derivative *via* a one-pot base-promoted *o*-QM from *ortho*-OBoc methyl benzoate

1.2.5.3 Substrate Scope Study of Our ortho-Quinone Methide Chemistry for Construction of ortho-tert-Butyl Phenols

Given the importance of *ortho*-*tert*-butyl phenol structrual motif, we decided to examine a few additional cases to better establish our method's scope. Our results indicated that when an *ortho*-OBoc methyl benzoate (**32**) was used, 77% of desired *ortho*-*tert*-butyl phenol (**33**) along with 12% of undesired methyl benzyl ether byproduct (**34**) were obtained (Scheme 19, a), which is comparable with our previous results, as well as reported by Vertex. Therefore, we decided to focus our attention upon *ortho*-OBoc acetophenones (**35**) as our starting materials (Scheme 19, b).



Scheme 19. a) construction of *ortho-tert*-butyl phenols *via* a one-pot base-promoted *ortho*-Quinone Methide from *ortho*-OBoc methyl benzoate
b) construction of *ortho-tert*-butyl phenols *via* a one-pot base-promoted *ortho*-Quinone Methide from *ortho*-OBoc acetophenones

As shown in Table 1, the *ortho-tert*-butyl phenols (**36a-k**) were all preapred following our traditional protocol (Scheme 19, b) from their corresponding *ortho*-OBoc acetophenones (**35a-k**). Toleration of several new functional groups was demonstrated to include methoxy (**36a-c**), halogen (**36d**), heteroaromatic (**36e**), unprotected phenol (**36f**) and amide (**36g**) residues, as well as reactions upon naphthalene (**36h**) and benzofuran (**36i-j**) cores. Higher relative yields amongst the various products likely reflect greater stability of *o*-QM intermediates. Of special note, we found that the reaction proceeds with an unprotected phenol (**35f**) and amide (**35g**) functionality yielding compounds **36f** and **36g** respectiviely. This could be achieved by providing an additional equivalent of methyl Grignard for deprotonation of the acidic Ar-X-H. In addition, we also found that when the starting material is the *bis-ortho*-OBoc acetophenone (**35k**), our method can deliver four methyl residues to arrive at the *bis-ortho-tert*-butyl resorcinol (**36k**) in a 63% yield.

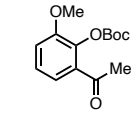
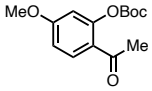
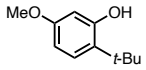
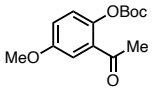
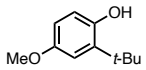
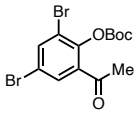
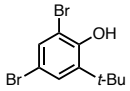
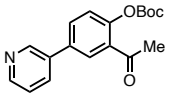
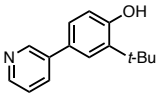
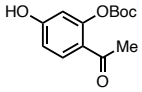
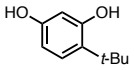
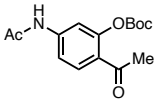
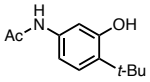
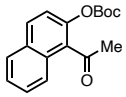
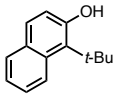
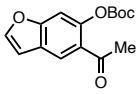
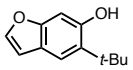
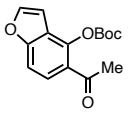
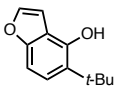
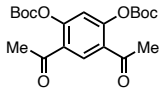
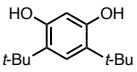
ortho-OBoc acetophenones		MeMgCl (equiv.)	*ortho-tert*-butylated product		product isolated yield
35a		3.0	**36a**		84%
35b		3.0	**36b**		85%
35c		3.0	**36c**		90%
35d		3.0	**36d**		81%
35e		2.2	**36e**		68%
35f		3.0	**36f**		78%
35g		3.0	**36g**		93%
35h		3.0	**36h**		99%
35i		2.2	**36i**		90%
35j		3.0	**36j**		88%
35k		5.0	**36k**		65%

Table 1. Substrate scope study: construction of *ortho-tert*-butyl phenol derivatives *via* base-promoted *o*-QM method from *ortho*-OBoc acetophenone derivates at low temperature

1.3 Conclusion

We hope our review of methods for *ortho-tert*-butylation on phenols has illuminated the difficulties surrounding the construction of this medically useful structural motif as well as offered a potential solution. As we have disclosed that although Friedel-Crafts alkylation is by far the most conventional method for installing an *ortho-tert*-butyl group on phenols, the

poor regioselectivity resulted in low efficiency regardless of many existing conditions (Section 2.1). For addition of *tert*-butyl anions or radicals on carbonyl compounds, the synthesis yield is compromised due to long synthetic routes or introducing a hinder radical nucleophile (Section 2.2). For *tert*-butyl anion *Ipso* S_NAr on aryl methoxide or sulfoxide precursors, the synthesis yield is diminished when preparing the appropriate precursors (Section 2.3). Although metal mediated cross coupling of a *tert*-butyl group with an aryl bromide seems to be promising, but one must consider the difficulty to install a bromo group regioselectively, which is another conundrum in synthesis (Section 2.4). We found that when an *ortho*-OBoc acetophenone is deployed in base-promoted *o*-QM method with methyl Grignards, the reaction provides the corresponding *ortho*-*tert*-butyl phenols with good substrate scope and in high efficiency. Therefore, we present our method as a useful new tool for synthetic chemists.

Chapter 2

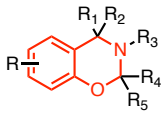
Base-Promoted *ortho*-Quinone Methide Chemistry

Generation of 3,4-Dihydro-*2H*-1,3-benzoxazines,

A Privilege Structure

2.1 3,4-Dihydro-2H-1,3-benzoxazines

A benzoxazine is an *N*,*O*-heterobicyclic structure that consists of a benzene ring annulated to an oxazine ring. The different isomeric structures depend on the relative positions between the oxygen and nitrogen atoms as well as the degree of oxidation of the oxazine ring system. This chapter is focused on 3,4-dihydro-*2H*-1,3-benzoxazine derivatives (Figure 3), given that 3,4-dihydro-*2H*-1,3-benzoxazine derivatives are a significant class of heterocycles with remarkable biological activities, such as herbicides and agricultural microbicides, and diverse pharmacological activities, such as anti-tumor agents, anti-retroviral therapy, anti-tubercular activity, anti-bacterial activity, anti-inflammatory activity, anti-convulsant activity, *etc*.[27] For example, elbasvir was developed by Merck and is a potent inhibitor for the HCV NS5A protein, which is used in combination with grazoprevir for the treatment of the HCV NS3/4A (Figure 3).[28] Therefore, efforts are continuing for the development of novel synthetic methods and this chapter builds on the previous work using *o*-QM chemistry with a different nucleophiles for the construction of 3,4-dihydro-*2H*-1,3-benzoxazine derivatives.



3,4-Dihydro-*2H*-1,3-benzoxazines

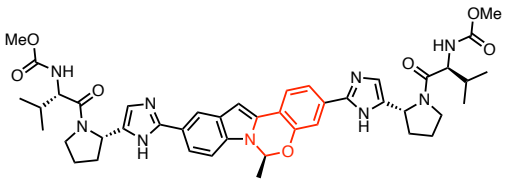
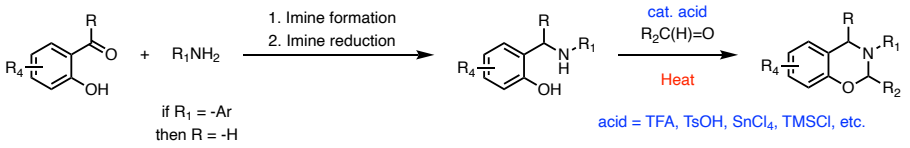


Figure 3. Elbasvir, treatment of hepatitis C virus, developed by Merck

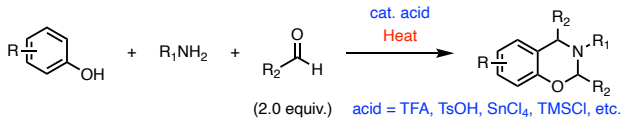
2.2 Previous Syntheses of 3,4-Dihydro-*2H*-1,3-benzoxazines

In general, there are three common methods for the generation of 3,4-dihydro-*2H*-1,3-benzoxazine. In this section, I will discuss about each method and compare their benefits and disadvantages. In 1944, Cope *et. al.* reported the first synthesis of 3,4-dihydro-*2H*-1,3-benzoxazine monomers (Scheme 21).[29] Their method started from reductive amination using a primary amine and an aldehyde to form an *ortho*-hydroxybenzylamine, also known as a Mannich base. Then the Mannich base incorporates with an aldehyde to undergo condensation with an acid catalyst to form 3,4-dihydro-*2H*-1,3-benzoxazines. However, this thermodynamic method fails to enable the incorporation of substituent at the 4-position if R_1 = -Ar, which is due to imine-enamine tautomerization. In addition, this method also requires acid-stable functional group amongst all reactants.



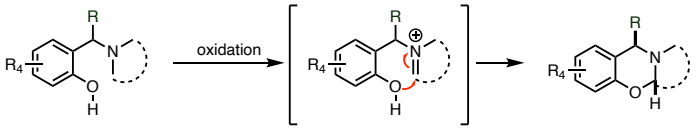
Scheme 21. Three-step thermodynamic synthesis of 3,4-dihydro-*2H*-1,3-benzoxazines from salicylaldehyde derivatives

The most widely adopted route to synthesize 3,4-dihydro-*2H*-1,3-benzoxazines was developed by Burke *et. al.* in 1949, which is to utilize a Mannich-like acid-catalyzed multicomponent condensation reaction of phenols, primary amines and aldehydes (Scheme 22).[30] This method begins with a phenol derivative to perform nucleophilic addition onto an iminium formed under acidic conditions. While it reverses the order of events to avoid the reduction step, it only works well with electron-rich phenol derivatives. In addition, this method results in double incorporation of the same aldehydes, and therefore limits the substrate scope study.



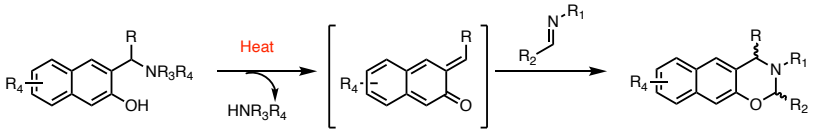
Scheme 22. Mannich-like acid catalyzed multicomponent condensation reaction for the synthesis of 3,4-dihydro-*2H*-1,3-benzoxazines from electron-rich phenol derivatives

Seeking to improve upon the previous thermodynamic methods, in the 2010s, a few examples reported to use cross-dehydrogenative coupling method to induce the formation of 3,4-dihydro-*2H*-1,3-benzoxazine derivatives (Scheme 23).[31] This method would allow the method to conduct at lower temperature comparing to the previous thermodynamic methods.[31d] begins with a Mannich base and is limited to only employ the symmetric cyclic-tertiary amines.



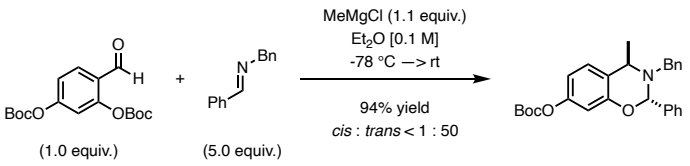
Scheme 23. Intramolecular oxidative α-functionalization of a cyclic trisubstituted amine from Mannich base to induce cross-dehydrogenative coupling to form 3,4-dihydro-*2H*-1,3-benzoxazines

While there have been a few other reports utilizing *o*-QMs for the synthesis of 3,4-dihydro-*2H*-1,3-benzoxazines, most involved a more stable polycyclic *o*-QM derivative that were thermally generated from their corresponding Mannich bases (Scheme 24).[32]



Scheme 24. Thermal-induced method to generate stabilized *ortho*-quinone methide derivatives from a Mannich base and undergo reaction with imine to form 3,4-dihydro-*2H*-1,3-benzoxazines

To the best of our knowledge, our report in 2002 is the first demonstration of *mono*-cyclic *o*-QMs undergoing diastereoselective reactions with imines to a 3,4-dihydro-*2H*-1,3-benzoxazine (Scheme 25).[33]



Scheme 25. Base-promoted method to generate *o*-QMs *in-situ* and undergoes diastereoselective reactions with imines to form a 3,4-dihydro-*2H*-1,3-benzoxazine

2.3 *o*-QM Background and State-of-The-Art

As mentioned in Chapter 1, our group has been studying *o*-QMs because of their awesome electrophilicity as a useful synthons for construction of molecules that are interesting to the chemistry society. In this section, *o*-QMs properties will be discussed in addition to their usage. *o*-QMs display a cyclohexadiene core with an exocyclic methylene and a carbonyl residue *ortho* to each other (Figure 4).[34] *o*-QMs' overall stability depends on a combination of structural and electronic effects.[35] In general, extended conjugation and substitution with electron donating groups allow *o*-QMs less reactive and more likely to be isolable. Nevertheless, *o*-QMs display a greater dipole and prove to be less stable and more reactive than the isomeric *para*-quinone methides. In general, most *o*-QMs are non-isolable and tend to self-destruct through polymerization or reactions with any unintended nucleophiles.[36] In addition, chiral catalysts tend to further diminish *o*-QMs' stability, which usually leads to a more rapid self-destruction than the more useful asymmetric induction. Sterics also play in a significant role in controlling the methylene geometry, which in turn affect the stereochemistry of subsequent products.

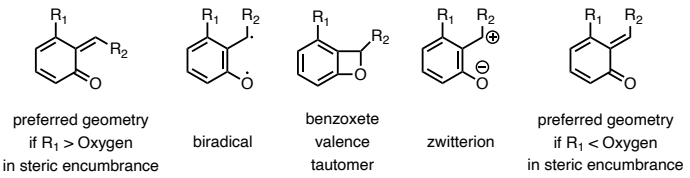
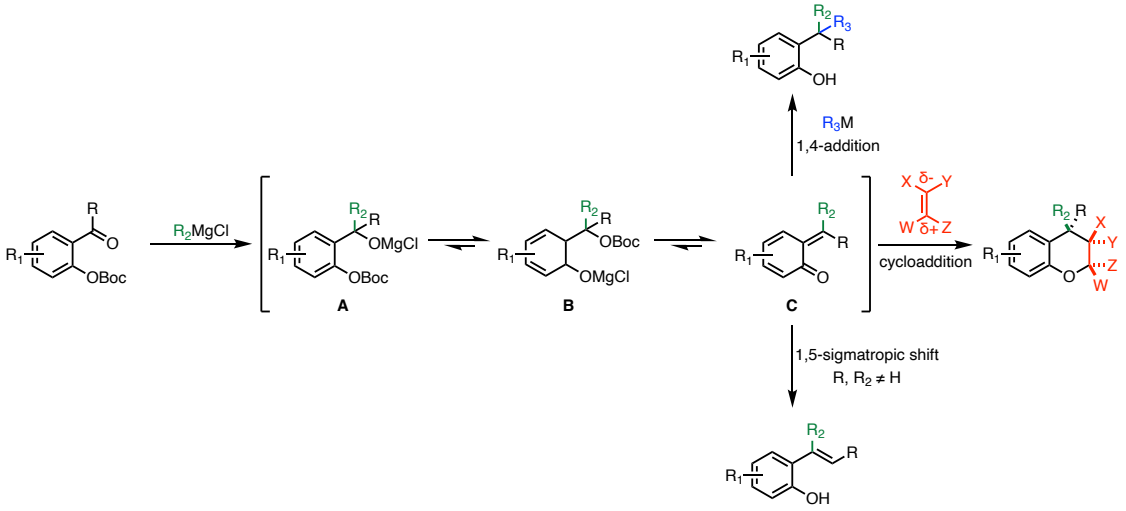


Figure 4. Possible representation of *ortho*-quinone methides

About two decades ago, our group discovered a base-promoted method to generate *o*-QMs at low temperature *in situ* from readily available *ortho*-OBoc salicylaldehyde derivatives (Scheme 26).[34] This novel cascade reaction includes both generation of *o*-QMs and their subsequent reactions. The overall transformation was initiated by the addition of an organometallic reagent, usually a Grignard reagent, which resulted in the formation of a benzyloxy alkoxide (Scheme 26, **A**). Intramolecular migration of Boc residue from the neighboring phenol produced a magnesium phenoxide (Scheme 26, **B**) that undergo β-elimination of the transferred Boc residue to form an *o*-QM (Scheme 26, **C**) as an intermediate for immediate further reactions. This new level of domestication enabled our group to employ *o*-QMs for the first time in a range of application including the previous mentioned *ortho-tert*-butyl phenol formations *via* a 1,4-conjugated addition (Chapter 1) and other diastereoselective reactions (Scheme 26).



Scheme 26. Base-promoted method for generation of *o*-QM *in-situ* and its applications

2.4 Imines' Reactivities

Seeking to explore other possible nucleophiles to react with *o*-QMs, imines brought to our interest given that the single example presented in Scheme 25. Imines have become one

of the most useful nitrogen-containing building blocks for the synthesis of many bioactive nitrogen-containing compounds.[37] The popularity of using imines as building blocks may due to two possible factors: 1) imines' reactivities are based on substrates that are used and 2) there are a variety of commercial available amines and aldehydes, which can lead to a great access to different imines and therefore lead to a diverse molecular scaffolds.[38a]

Possible reactivities of imines are shown in Figure 5. Imines can serve as either aza-dienes[38,39] or dienophiles[38,40] in cycloaddition reactions. Imines can also behave like carbonyls in the presence of a good carbon-nucleophile to provide Mannich-type products. Imines indeed usually serve as excellent electrophiles in the present of a Lewis/Brøsted acid.[38,41]

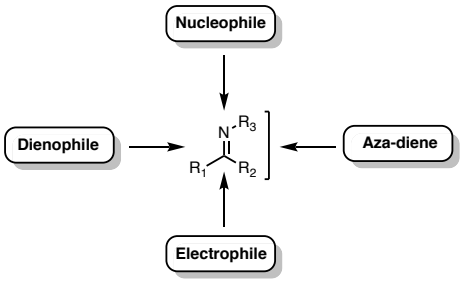
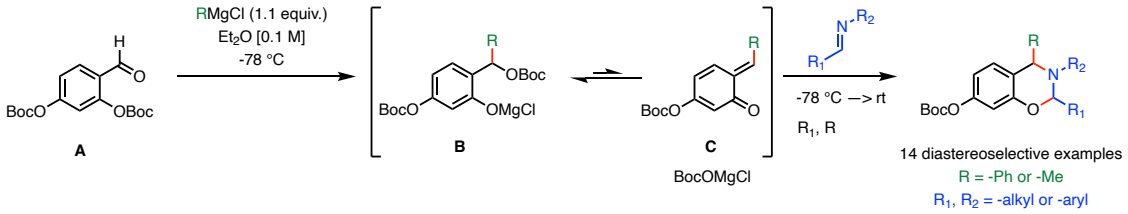


Figure 5. Imines' Reactivity Profiles

On the other hand, imines can also serve as nucleophiles due to their electron-rich nitrogen atoms.[38] Though, this reactivity of imines was less explored. Staudinger β-lactam construction is an example of using imines as a nucleophile.[42a-c] Nevertheless, it is commonly used in Umpolung fashion that an electrophilic ketene is first converted into a nucleophilic zwitterionic enolate by addition of an amine or a phosphine. The resulted intermediates undergo subsequent addition to an electron deficient imine.[42d] Indeed, beyond a few examples of *N*-acyliminiums formed by acylation of Schiff bases,[43] we could find very few examples of imines serving as nucleophiles to form C-N bonds.[44]

2.5 New Procedure

Building upon our past experiences, we proposed that an imine would engage with an *o*-QM to provide an assortment of diastereoselective *N*-substituted 3,4-dihydro-*2H*-1,3-benzoxazines in a one-pot reaction (Scheme 27) that is more straightforward than other processes as discussed above. We chose to focus on the reactivity of two *o*-QMs (Scheme 27, **C**, R = -Ph or -Me) prepared *in-situ* at low concentrations *via* the intermediates (Scheme 27, **B**), which was generated from the aldehyde (Scheme 27, **A**) by addition of the appointed Grignard reagent. We knew the two examined *o*-QMs displayed remarkable different reactivity profiles. Phenylated *o*-QMs prove to be less reactive due to extended conjugation and therefore more stereoselective in reactions with nucleophiles comparing with methylated *o*-QMs. In addition, given our past investigations of *o*-QMs with different substituents and their reactions with a range of nucleophiles, we expected to be able to extrapolate our findings for these two *o*-QM species to many other systems.



Scheme 27. General method: base-promoted method to generate *o*-QM *in-situ* from *ortho*-OBoc salicylaldehyde derivatives and subsequent reaction with imines for the diastereoselective synthesis of 3,4-dihydro-*2H*-1,3-benzoxazines

2.5.1 Substrate Scope Study

For all substrate scope study described below, I first tested all classes of imines with the methylated *o*-QM. Once I was able to obtain a decent to good yields from the reactions, my lab mate, Yuk Fai, would continue my work with the same type of imines to react with the phenylated *o*-QM. Therefore, we can compare both the reactivities and stereoselectivities of

two major different *o*-QMs to extrapolate our understanding of this novel reaction. Our combination of effort contributed to the publication in *Organic Letters* in 2019.[45]

2.5.1.1. Class I Imines, Bis-alkyl Substituted Imines

We began by examining Class I imines **37-39** (Table 2). Class I imines contained aliphatic substituents on both nitrogen and carbon atoms of the imine functionality. Using the method described above (Scheme 27), we were able to obtain the corresponding 3,4-dihydro-*2H*-1,3-benzoxazines **37a,b-39a,b** in 61-94% isolated yields. In contrast, 63-95% crude NMR yields were calculated by using an external ^{1}H NMR standard, CH_2Br_2. The crude NMR yields result in 1-13% higher than their respective isolated yields. In our opinion, the crude NMR yield measurements were much more useful for interpreting structural and electronic effects on a reaction's outcome, while the isolated yields revealed 3,4-dihydro-*2H*-1,3-benzoxazines' overall stability.

Both compounds **37a,b** and **38a,b** were observed to form as a single diastereomer as determined by ^{1}H NMR (presumably > 99:1).[46] Subsequent NOE NMR experiments established that the major stereoisomer possessed a *trans* configuration regarding the R and R_1 substituents. Only *bis*-isopropyl imine leads to product **39a-Me** with a small amount of the corresponding *cis* stereoisomer (**39a-Me**, *trans* : *cis* = 5 : 1). These diastereomers displayed distinctive and useful ^{1}H NMR chemical shifts for their corresponding H_A and H_B protons, which enabled the rapid assignment for 3,4-dihydro-*2H*-1,3-benzoxazines' diastereomeric protons ($\Delta\delta$ for H_A +0.15 ppm, *trans vs. cis* and $\Delta\delta$ for H_B -0.04 ppm, *trans vs. cis*).

While compound **38a,b** proved that sterics are tolerated on imine's carbon-side for Class I imines, compound **39a,b** revealed that increasing sterics on imine's nitrogen-side of Class I

imines could either result in a lower-yield reaction (**39b-Ph**) or a less diastereoselective reaction (**39a-Me**).

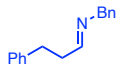
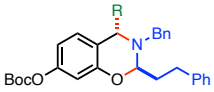
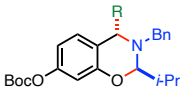
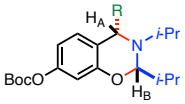
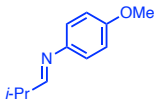
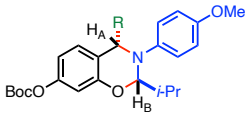
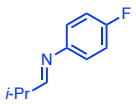
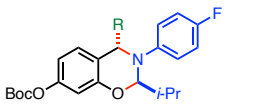
Imine Class		Imines	Benzoxazine Products	Benzoxazine Crude Product Yields[a] and dr	Benzoxazine Isolated Product Yields
Class I	37			**37a-Me**: 83% yield, single diastereomer **37b-Ph**: 81% yield, single diastereomer	**37a-Me**: 70% yield, single diastereomer **37b-Ph**: 78% yield, single diastereomer
	38			**38a-Me**: 82% yield, single diastereomer[c] **38b-Ph**: 95% yield, single diastereomer[c]	**38a-Me**: 72% yield, single diastereomer[c] **38b-Ph**: 94% yield, single diastereomer[c]
	39			**39a-Me**: 72% yield, dr(*trans* : *cis*) 5 : 1[c] **39b-Ph**: 63% yield, single diastereomer[b]	**39a-Me**: 63% yield, dr(*trans* : *cis*) 5 : 1[c] **39b-Ph**: 61% yield, single diastereomer[b]
Class II	40			**40a-Me**: 71% yield, single diastereomer **40b-Ph**: 61% yield, single diastereomer[c]	**40a-Me**: N/A **40b-Ph**: N/A
	41			**41a-Me**: 65% yield, single diastereomer[c] **41b-Ph**: 67% yield, single diastereomer[b]	**41a-Me**: N/A **41b-Ph**: N/A

Table 2. Results from Class I-II imines. a) Crude NMR yields were estimated using CH_2Br_2 as an external NMR standard. b) 2 equivalents of imines were used. c) NOE NMR analysis was performed.

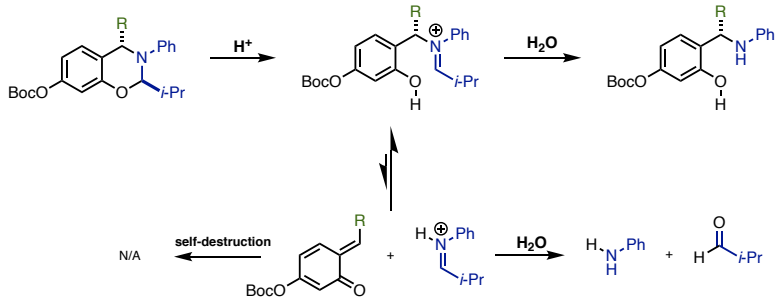
2.5.1.2 Class II Imines, N-Aryl C-Alkyl Substituted Imines

Next, we examined Class II imines **40** and **41** (Table 2). The respective 3,4-dihydro-*2H*-1,3-benzoxazines **40a,b** and **41a,b** were again observed to form as a single diastereomer assumed to be > 99:1 by ^{1}H NMR.[46] These 3,4-dihydro-*2H*-1,3-benzoxazine products formed in slightly lower yield than those observed for the prior examples **37a,b-39a,b** (Table 2). This observation might due to nitrogen's electron-density delocalizes through the adjacent aromatic rings, which leads to a less-reactive class of imines comparing to Class I imines. Both electron-donating and electron-withdrawing groups on the *N*-aryl portion of the imines had little effect on reaction outcomes.

The *trans* stereochemical arrangement of the R and R_1 substituents was again deduced by NOE NMR analysis. Refluxing **40a-Me** in deuterated chloroform was found to degrade

the diastereomeric ratio from *trans* : *cis* > 99:1 to 1:1, which can be explained by possible acid-promoted ring-chain tautomerization of 3,4-dihydro-*2H*-1,3-benzoxazines.[47] The resulted diastereomers again displayed different ^{1}H NMR chemical shifts for their corresponding H_A and H_B that facilitated the assignment ($\Delta\delta$ for H_A +0.60 ppm, *trans vs. cis* and $\Delta\delta$ for H_B -0.20 ppm, *trans vs. cis*).

In addition, due to these 3,4-dihydro-*2H*-1,3-benzoxazine products proved to be unstable toward purification using column chromatography, we were unable to purify them further. This could be explained by the possible acidity and moisture nature of silica gel, which in the presence of a free proton even under a mild acidic condition, 3,4-dihydro-*2H*-1,3-benzoxazines can undergo ring-chain tautomerization, and if water-moisture is present, the chain form of 3,4-dihydro-*2H*-1,3-benzoxazines can further undergo hydrolysis or possible reverse formation of *o*-QMs that can undergo self-destruction (Scheme 28). Nevertheless, their corresponding crude products proved to be sufficiently pure for NMR characterization.



Scheme 28. 3,4-Dihydro-*2H*-1,3-benzoxazine adducts from Class II imines are not stable for purification *via* column chromatography due to free-protons environment

2.5.1.3 Class III Imines, Bis-aryl Substituted Imines

Class III imines **42-44** contains aryl substituents on both the nitrogen and carbon atoms of imines, led to disappointing results (Figure 6). We estimated only 15-31% of the possible corresponding 3,4-dihydro-*2H*-1,3-benzoxazine products were formed based on ^{1}H NMR analysis with external standard, CH_2Br_2. We suspected that due to full conjugation of

imines, imines' electronic density was delocalized reactivity and therefore dropped significantly, which would lead to low yields for all three imines tested. In addition, 3,4-dihydro-*2H*-1,3-benzoxazine products proved to be even more unstable than the adducts **40a,b-41a,b** from Class II imines described above (Table 2). Although we were unable to thoroughly characterized and identify the products' structural information, we speculated that products were decomposed during column chromatography as described in Scheme 28, but due to full conjugation of iminium, it further lower the stability of ring conformation and prefer to stay as the chain conformation. Upon water residue present, chain conformation would be hydrolyzed.

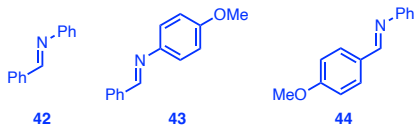


Figure 6. Class III imines

2.5.1.4 Class IV Imines, N-Alkyl C-Aryl Substituted Imines

Next, we examined Class IV imines **45-53**, which displayed an assorted aliphatic groups on the nitrogen atom and various aryl substituents on the carbon atom of their respective imines (Table 3). Almost all of the corresponding 3,4-dihydro-*2H*-1,3-benzoxazine products **45a,b-53a,b** formed in decent to good yields (Table 3). While these 3,4-dihydro-*2H*-1,3-benzoxazine adducts were less stable than those from Class I imines (**37a,b-39a,b**, Table 2), they proved to be more stable that those found from Class II imines (**40a,b-41a,b**, Table 2). The corresponding isolated yields will be found in the experimental section. The *trans* diastereomer was again produced exclusively in nearly all of the cases (*trans* : *cis* > 99:1) except **53a,b**.

Results for imines **45** and **46** prompted that inductive electronic effects in the aliphatic portion of the imine had little influence on imines' reactivity, as the yields for products **45a,b** and **46a,b** were similar. On the other hand, results for imine **47** and **49** suggested that electronic effects in the aromatic portion of the imine played a significant role in imines' reactivities, as the yields for products **47a,b** were over 80%, while the yields for products **49a,b** were lower than 65% even with the use of 2 equivalents of imines for reaction as for **49b-Ph**. Steric encumbrance in the aliphatic portion of the imine, chiefly when near the nitrogen atom, as in imines **50** and **51**, was found to severely impede the formation of products **50a,b** and **51a,b**. The mesityl derivative providing no improvement as shown for **51a,b**.[48] The Z-configured cyclic imine **53** afforded the *cis* diastereomer as the preferred diastereomer (*trans* : *cis* 1 : 5) for both the methyl adduct **53a-Me** and the phenyl adduct **53b-Ph** as established by NOE NMR analysis and coupling data ($\Delta\delta$ for H_A +0.10 ppm, *trans vs. cis* and $\Delta\delta$ for H_B +0.05 ppm, *trans vs. cis*). We note that others, who have reported structures resembling compound **53b-Ph** constructed through orthogonal procedure involving oxidation of the corresponding Mannich base, may have mistakenly assigned these products as their corresponding *trans* diastereomer.[31a]

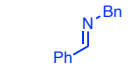
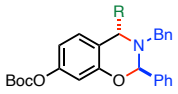
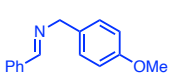
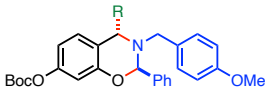
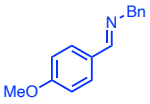
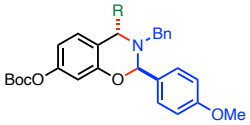
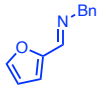
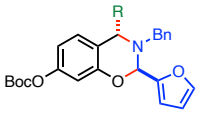
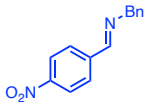
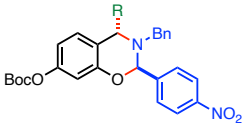
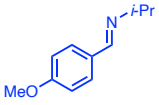
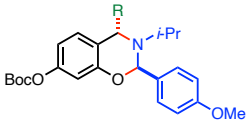
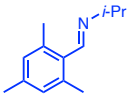
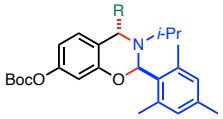
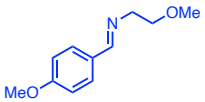
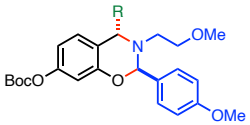
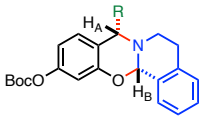
	Imines	Benzoxazine Products	Benzoxazine Crude Product Yields[a] and dr
45			**45a-Me**: 85% yield, single diastereomer[c] **45b-Ph**: 83% yield, single diastereomer
46			**46a-Me**: 78% yield, single diastereomer **46b-Ph**: 78% yield, single diastereomer
47			**47a-Me**: 88% yield, single diastereomer **47b-Ph**: 82% yield, single diastereomer[c]
48			**48a-Me**: 86% yield, single diastereomer **48b-Ph**: 73% yield, single diastereomer
49			**49a-Me**: 40% yield, single diastereomer **49b-Ph**: 61% yield, single diastereomer[b]
50			**50a-Me**: 47% yield, single diastereomer **50b-Ph**: <10% yield, single diastereomer[b]
51			**51a-Me**: 43% yield, single diastereomer[b] **51b-Ph**: 35% yield, single diastereomer[b]
52			**52a-Me**: 71% yield, single diastereomer[b] **52b-Ph**: 73% yield, single diastereomer[b]
53			**53a-Me**: 53% yield, single diastereomer[c] **53b-Ph**: 81% yield, single diastereomer[c]

Table 3. Results from Class IV imines. a) Crude NMR yields were estimated using CH_2Br_2 as an external NMR standard. b) 2 equivalents of imines were used. c) NOE NMR analysis was performed. d) **45b-Me** was previously prepared by our group as shown in reference 33.

2.5.2 Study of Kinetic vs. Thermodynamic Methods

We were also curious to determine if our one-step kinetic *o*-QM chemistry is favorable compared with the traditional thermodynamic method (Scheme 21). Therefore, we synthesized a Mannich base from an *ortho*-hydroxyacetophenone derivative with a primary amine by reductive amination, then treated with the appropriate aldehyde to yield desired

3,4-dihydro-*2H*-1,3-benzoxazine adducts (Table 4). The thermodynamic method is reported to generally favor the *trans* diastereomer as the major isomer, just as our kinetic *o*-QM method had.[49] However, the thermodynamic process cannot access structures resembling 3,4-dihydro-*2H*-1,3-benzoxazine adduct **53a,b**, due to the introduction of piperidine followed by reduction affords a tertiary amine, and therefore it cannot further participate in the formation of the corresponding 3,4-dihydro-*2H*-1,3-benzoxazine.

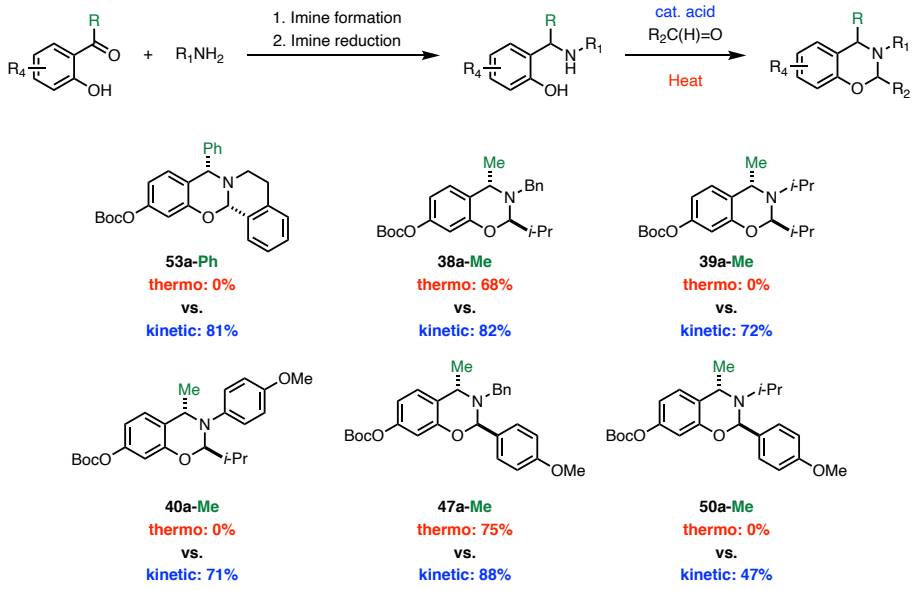


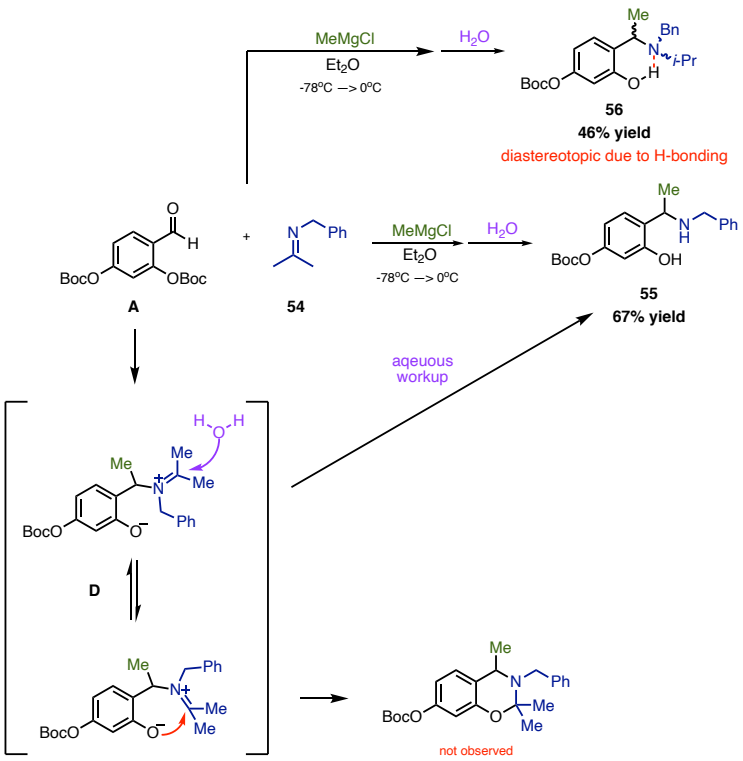
Table 4. Preparation of 3,4-dihydro-*2H*-1,3-benzoxazines using the multistep thermodynamic method and comparison with our kinetic *ortho*-quinone methide chemistry

In our hands, the traditional thermodynamic process afforded adducts **38a-Me** and **47a-Me** in lower yields with diastereoselectivity identical to our kinetic method. However, in our hands, the thermodynamic method failed to yield adducts **39a-Me** and **50a-Me**, which we suspect the steric encumbrance of the isopropyl residue prevents adduct formation in these examples. In addition, an exhaustive literature search reveals no examples of 3-*N*-isopropylated 3,4-dihydro-*2H*-1,3-benzoxazines displaying any substituents at both 2- and 4-positions. Though only adducts with substituents at either 2- or 4- position were prepared. We were also surprised by our inability to prepare adduct **40a-Me** using the thermodynamic

process. However, a thorough literature search reveals no examples of 3-*N*-arylated 3,4-dihydro-*2H*-1,3-benzoxazines displaying substituents at both 2- and 4- positions being prepared in this manner. Similar to cases for **39a-Me** and **50a-Me**, only adducts with substituents at either 2- or 4- position were prepared. These three failing examples might suggest the stronger steric effects are operating from *N*-substituted benzylic amine systems.

2.5.3 Substrate Scope Study of Trisubstituted Acyclic Aliphatic Imines

We also tested the reaction of a trisubstituted acyclic aliphatic imines **54** with both methylated and phenylated *o*-QMs (Scheme 29). Though the usage of phenyl magnesium chloride with the aldehyde **A** in the presence of imines **54** failed to afford anything identifiable, which we suspect this is due to the phenylated *o*-QM is less reactive than the methylated *o*-QM. The reaction with methyl magnesium chloride afforded the disubstituted benzylic amine **55** without the presence of other side products upon aqueous workup. We speculate the different outcomes could be due to methylated *o*-QM is substantially more reactive, while the more sterically encumbered nature of intermediate **D** prevents the phenoxide perform ring-closing onto the iminium. In order to further prove 3,4-dihydro-*2H*-1,3-benzoxazine product was not accidently hydrolyzed during aqueous workup, we therefore conduct the same reaction but with lithium borohydride as the quenching agent. Our hypothesis was supported by the sequential addition of lithium borohydride to the reaction mixture before aqueous workup, which resulted in a trisubstituted benzylic amine **56** as a 1:1 mixture of diastereomers.[50] Both results indicate that the highly possible formation of iminium *in-situ*, which will further assist our mechanism proposal.



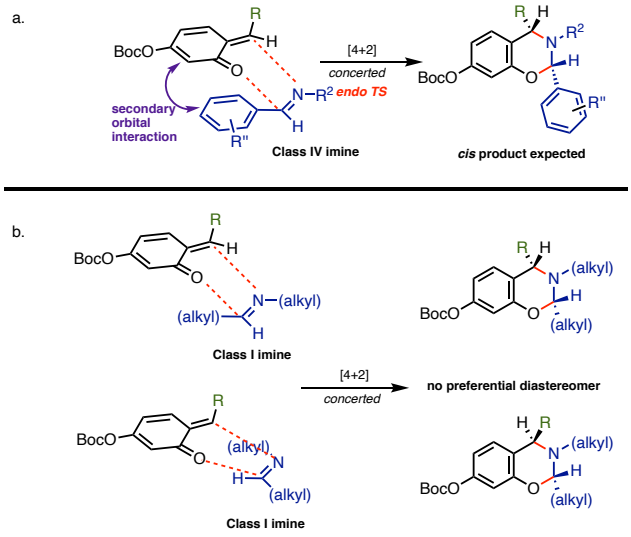
Scheme 29. Base-promoted *o*-QMs react with trisubstituted aliphatic acyclic imines resulted in no 3,4-dihydro-*2H*-1,3-benzoxazines, but substituted benzylic amines

2.6 Mechanism Proposal

2.6.1 Inverse-Demand Diels-Alder Reaction Mechanism

At first, we speculate whether *o*-QMs would undergo inverse-demand Diels-Alder reaction with imines, as we have observed for reactions between *o*-QMs and enol ethers.[34] However, due to secondary orbital interactions between *o*-QMs and Class IV imines, we should expect to observe the *cis*-diastereomer as the preferred stereoisomer (Scheme 30, a). In addition, both Class II (Table 2) and Class IV (Table 3) *E*-imines afforded *trans* diastereomers. These different imine classes should have favored dissimilar diastereomers as their secondary orbital effects work in opposite directions. However, as we have observed from our substrate scope study for all class of disubstituted imines, as long as an *E*-imine is used, a *trans*-diastereomer would form as the major diastereomer. This was proved by NOE

NMR analysis. As for Class I imines (Table 2), secondary orbital interactions would be scarce, and therefore we should not expect to see a preferential diastereomeric ratio (Scheme 30, b). Nevertheless, this is also against our observation of stereochemistry based on our experimental results. Moreover, in the case of a trisubstituted imine, we were able to selectively hydrolyze or reduce intermediate **D** before cyclization (Scheme 29). Therefore, we suggest that our reaction does not follow inverse-demand Diels-Alder reaction mechanism.

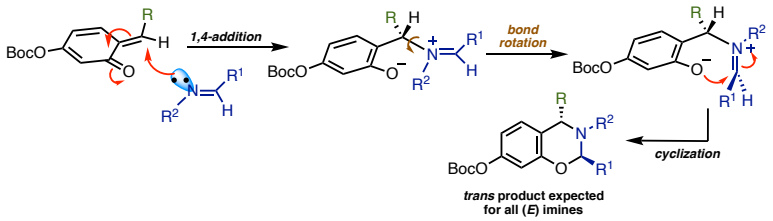


Scheme 30. Proposed mechanism: inverse-demand Diels-Alder reactions against our observed stereochemistry

2.6.2 Step-wise Reaction Mechanism: 1,4-Conjugated Addition, Follow by Cyclization

We then propose that imines serve as a nucleophile instead of a dienophile to undergo reaction with *o*-QMs, which follows a step-wise mechanism (Scheme 31). The reaction is starting from the lone pair of electrons on imine's nitrogen atom undergoes a 1,4-conjugated addition onto the *o*-QM and results in a carbon-functionalized iminium species. Due to 1,3-allylic strain between the methylene's hydrogen and the substituents on iminium's carbon-

side, the iminium intermediate rotate *via* the C-N bond. Upon close proximity, the phenolate undergoes cyclization onto the iminium. This mechanism allows the formation of *trans* diastereomer of 3,4-dihydro-*2H*-1,3-benzoxazine preferentially. We will further utilize this proposed mechanism to design chiral auxiliary for an enantioselective reaction.

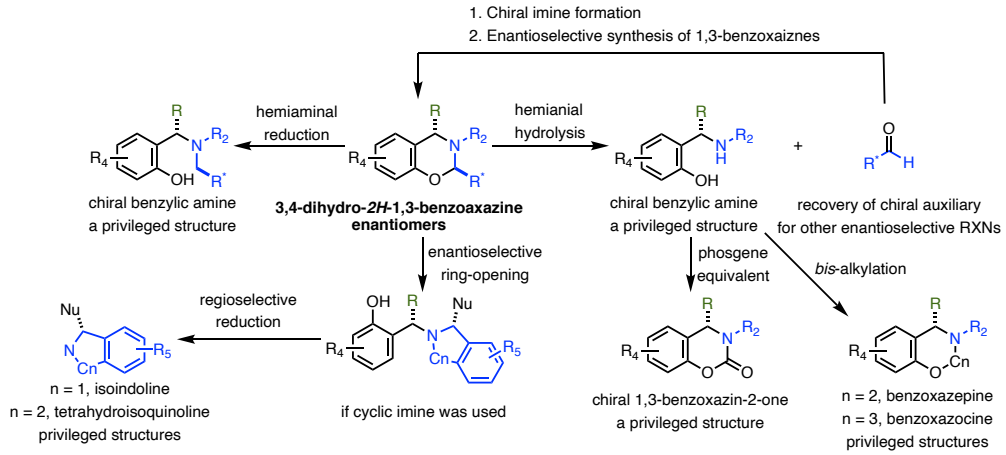


Scheme 31. Proposed mechanism: step-wise reaction, 1,4-conjugated addition followed by cyclization

2.7 Future Applications

Recently, our group has been working on developing a recoverable chiral auxiliary for an enantioselective synthesis of 3,4-dihydro-*2H*-1,3-benzoxazines and achieved in major progress. The detailed of chiral auxiliary design will be disclosed and discussed by my lab mate, Yuk Fai. Given the successful work of an enantioselective synthesis, I believe there are many further applications of utilizing 3,4-dihydro-*2H*-1,3-benzoxazine structural motif (Scheme 32) besides its own diversified usage in medicinal chemistry.[27,28] For example, upon the successful enantioselective synthesis of 3,4-dihydro-*2H*-1,3-benzoxazines, it can undergo hemiaminal hydrolysis to generate a chiral disubstituted benzylic amine, which is a privileged structure, as well as the recovery of chiral auxiliary for other enantioselective reactions. A chiral disubstituted benzylic amine can further form 1,3-benzoxazin-2-one with a phosgene equivalent.[51] Moreover, a chiral disubstituted benzylic amine can also undergo dialkylation for the formation of benzoxazepine (7-membered heterocyclic privileged structure) and benzoxazocine (8-membered heterocyclic privileged structure).[51] A 3,4-dihydro-*2H*-1,3-benzoxazine enantiomer can also undergo hemiaminal reduction to afford a

chiral trisubstituted benzylic amine, which is another privileged structure.[52] Enantioselective ring-opening by a nucleophile at the hemiaminal position, followed by regioselective reduction would eventually lead to isoindoline or tetrahydroisoquinoline, which are another scaffolds of privileged structures.[53]



Scheme 32. Future applications of chiral 3,4-dihydro-*2H*-1,3-benzoxazines

2.8 Conclusion

In conclusion, we have developed a straightforward one-pot method that delivers an assortment of 3,4-dihydro-*2H*-1,3-benzoxazines. It is our assertion that this method provides a greater range and scope compared to the previous described methods for construction of this structural motif. Our studies further show that this method can deliver very encumbered systems that cannot be prepared by current thermodynamic methods. While this reaction may appear to be an inverse demand Diels-Alder cycloaddition, we believe it instead to follow a stepwise mechanism. Lastly, our findings provide a road map for implementation of this method in future enantioselective applications, which we believe are needed for construction of a variety of privileged structures with great medicinal value.

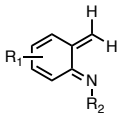
Chapter 3

A Review of Aza-*ortho*-Quinone Methide:

Generation, Limitation and Applications

3.1 Introduction

A 6-methylene-2,4-cyclohexadien-1-imine such as **57** (Figure 7) is referred as aza-*ortho*-quinone methides (aza-*o*-QMs). Just like *o*-QMs, aza-*o*-QMs are also highly unstable and reactive intermediates due to the driving forcing of rearomatization.



57
aza-*o*-QMs

Figure 7. Structure of aza-*ortho*-quinone methides

Aza-*o*-QMs were first proposed by Smolinsky in 1961.[54] The cycloaddition product arising from aza-*o*-QM intermediates were experimentally observed by Burgess and McCullagh in 1966.[55] However, despite the general knowledge of aza-*o*-QMs, these intermediates still lie outside the synthetic mainstream. Although their assorted functional groups suggest abundant synthetic potential, it was not until 1999, when Steinhagen and Corey employed these useful synthons to form a series of tetrahydroquinoline derivatives through inter- and intramolecular Diels-Alder reactions, that aza-*o*-QMs attracted extensive attention.[56] Since then, aza-*o*-QMs have been playing a more important role in organic synthetic chemistry as powerful building blocks for tetrahydroquinolines and their derivatives. Nevertheless, fewer aza-*o*-QMs have been utilized as intermediates and applied than their oxygen-containing analogues *o*-QMs to various reactions in total syntheses. We speculate that this omission is a consequence of aza-*o*-QM reactivity, which mandates their *in-situ* formation and subsequent consumption. Therefore, their range of potential reactions were severely limited. In this review, we describe the methods by which aza-*o*-QMs are prepared, the benefits and limitations associated with each method. We will also propose a

possible novel method for preparation of aza-*o*-QMs that allow a more versatile reactions in the future.

3.2 Scope of This Review

Because of the transient nature of aza-*o*-QMs, it is more difficult to prepare a comprehensive review than we first expected. Conventional structure searching methods failed to produce a comprehensive overview of their chemistry as these intermediates are usually deduced rather than isolated. Therefore, we relied upon a combination of a word search for "aza-*ortho*-quinone methide", "1-methylene-6-iminocyclohexa-2,4-diene", "aza-*ortho*-xylylene" and "*ortho*-quinone methylene imine" using the *Scifinder*® and the *Web of Science*® databases. Along with research into the reactivity of aza-*o*-QMs, many methods to prepare these intermediates have been developed over the past few decades, which have been reviewed by Wojciechowski[57] and Gao *et. al.*[58] Therefore, in this review, we describe the methods by which aza-*o*-QMs are prepared, the benefits and limitations associated with each method. These methods mainly include thermolysis,[59-68] photolysis,[69-73] metal-catalyzed facilitation,[75-88] 1,4-elimination process (fluoride-induced,[89] acid-promoted[90-95] and base-promoted[96-103]) (Figure 8).

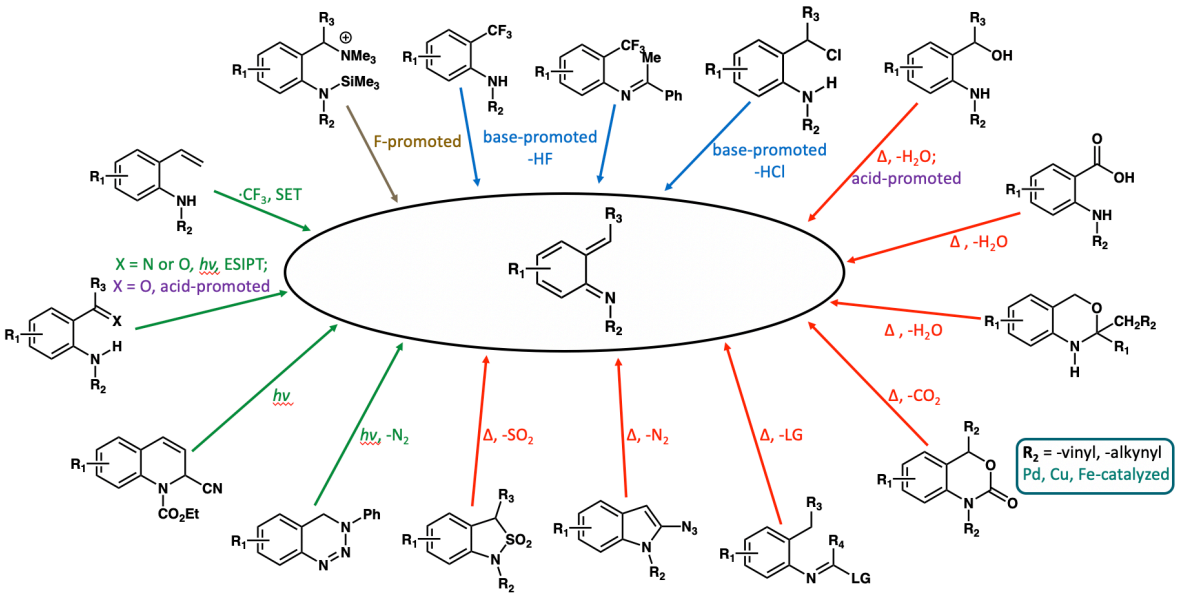
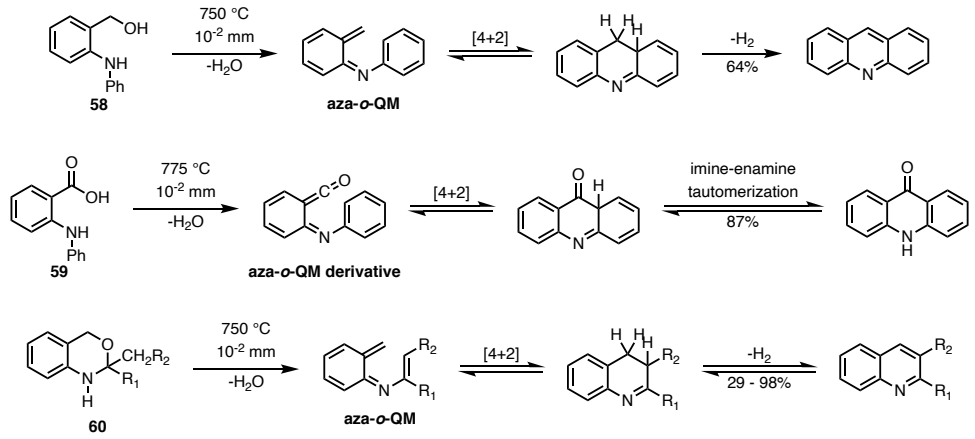


Figure 8. Methods for aza-*ortho*-quinone methides generation

3.3 Thermal Initiation

Thermolysis has been the method of choice among synthetic chemists for generating aza-*o*-QMs before the 2000s. Scheme 33-39 shows the precursors that were utilized.[59-68] It should be noted that all thermal generation techniques preclude the application of nucleophiles that are thermally unstable. In addition, most can result in corruption of stereochemistry in reactions that can lead to diastereomeric mixtures. With any given precursor, there is a substantial temperature range for initiation, which depends on the substituents. In general, if the process involves significant non-bonded interactions, then the temperature requirements are higher, while extended conjugation or other stabilizing factors lowers the overall temperature requirements. All of these precursors (**58-72**) prove highly successful when the aza-*o*-QM is consumed in a subsequent intramolecular reaction. Application of each towards intermolecular reactions, however, is significantly more challenging because of the tendency toward dimerization.[57]

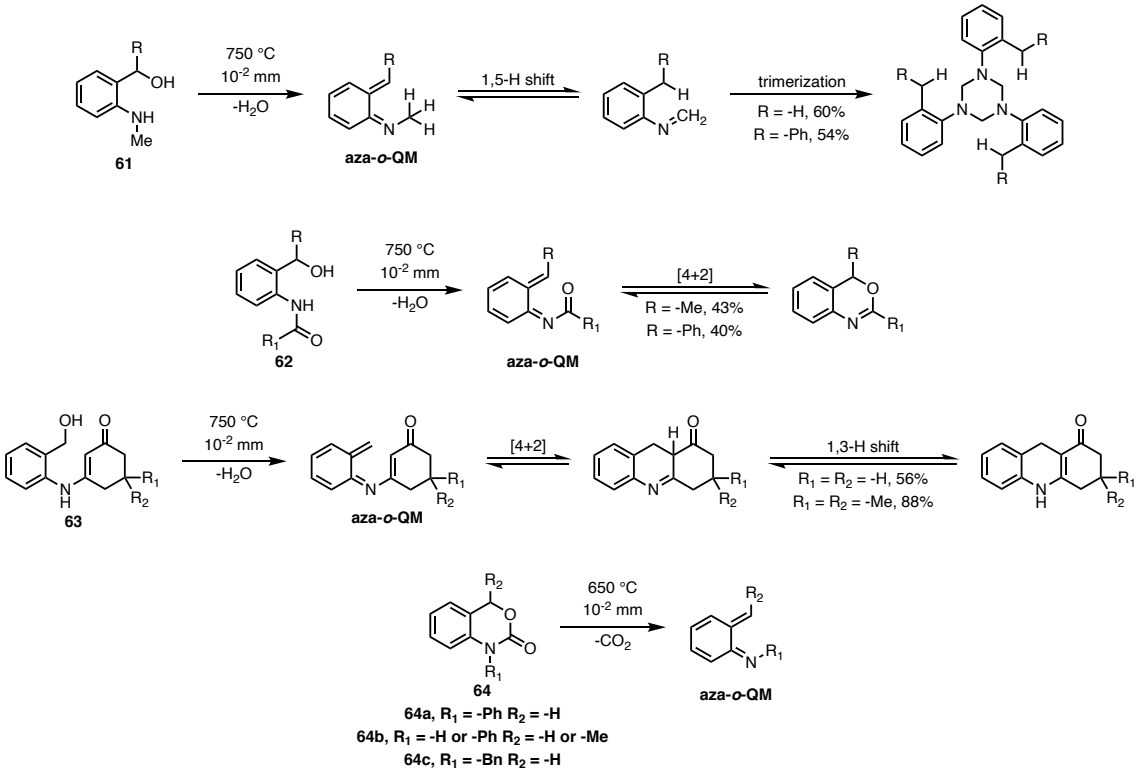
In 1980, Boekelheide *et. al.* reported the first generation of aza-*o*-QMs under flash vacuum pyrolysis/thermolysis (FVP/T) condition.[59] Precursors such as an *ortho*-amino benzylalcohol (**58**), its benzylic acid derivative (**59**), as well as its 1,3-benzoxazine derivatives (**60**) by the elimination of a water molecule (Scheme 33). Due to the available dienophile from the corresponding precursors, the highly reactive aza-*o*-QM can immediately undergo intramolecular IMDA and therefore form the heterocyclic structures with decent to good yield. Meanwhile, intermolecular IMDA reaction was unsuccessful due to aza-*o*-QMs tend to undergo dimerization or polymerization.[57] Boekelheide's work set the foundation of FVP/T condition for later-on development of aza-*o*-QM generation under thermolysis condition.

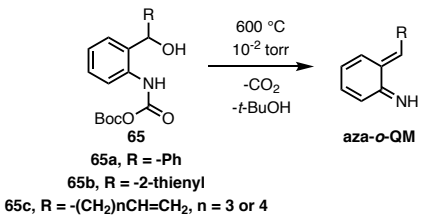


Scheme 33. Boekelheide's flash vacuum pyrolysis/thermolysis condition for generation of aza-*ortho*-quinone methides followed by intramolecular inverse-demand Diels Alder reactions

Inspiring by Boekelheide's work, Storr *et. al.* decided to explored other *o*-amino benzylalcohol derivatives (Scheme 34, **61-65**).[60] Storr found that in the absence of an available dienophile (**61**), aza-*o*-QM would undergo 1,5-hydride shift to result in an imine intermediate, which would undergo immediate trimerization.[60a] Acylated anilines (**62**) and enamines (**63**) were also tested. Interestingly, an electron-deficient carbonyl or an enone can

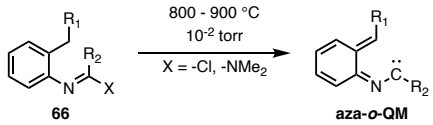
also undergo intramolecular IMDA with aza-*o*-QMs, though lower yields were observed from the carbonyl examples.[60a] The usage of 1,3-benzoxazinones (**64**) for generation of aza-*o*-QMs lowers FVP/T condition by 100 °C due to the easier removal of a carbon dioxide molecule from precursors.[60a] In addition, 1,3-benzoxazinones (**64**) are much more stable than *o*-amino benzylalcohol derivatives. Subsequently, Storr also reported *N*-Boc-protected *o*-amino benzylalcohols (**65**) can further lower FVP/T condition by another 50 °C due to the easier remover of Boc-protecting and hydroxyl groups.[60b] A carbon dioxide and a *t*-BuOH molecules were proposed to be removed under FVP/T condition. All above mentioned conditions stay true that if an intramolecular dienophile available, then the reaction would undergo intramolecular IMDA reaction to form a [4+2] product. Otherwise, a 1,5-hydride shift product would form and followed by immediate trimerization of the corresponding imine formed *in-situ*.





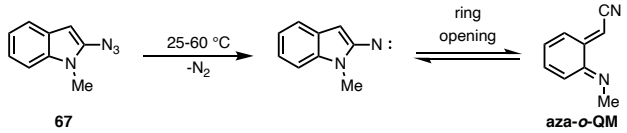
Scheme 34. Storr's flash vacuum pyrolysis/thermolysis condition for generation of aza-*ortho*-quinone methides from various *ortho*-amino benzylalcohol derivatives

In 1987, Storr *et. al.* explored a different type of aza-*o*-QM precursor, *N*-phenyl imine derivatives with a leaving group on imine's carbon-side (Scheme 35, **66**).[61] It was suspected that a carbene-like species was generated *in-situ*, which is first reported using FVP/T condition.



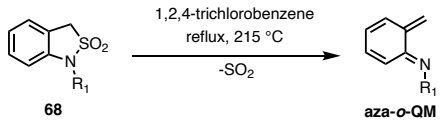
Scheme 35. Storr's flash vacuum pyrolysis/thermolysis condition for generation of aza-*ortho*-quinone methides from phenyl formimidoyl chloride or formamidine precursors

Thus far, generation of aza-*o*-QMs can only be done using the technique of FVP/T, which requires low-pressure. Therefore, implementation of FVP/T for large-scale synthesis is problematic. For later research, scientists have been focusing on exploring a precursor that can generate aza-*o*-QMs at relatively lower temperature in the absence of low-pressure reaction condition. In 1989, Zanirato *et. al.* reported the thermal ring-opening of 2-azido-1-methylindole (**67**) to generate aza-*o*-QMs *in-situ* (Scheme 36).[62] Though this method indeed lower the reaction temperature to 25-60 °C, it's known that azido compounds are explosive and therefore need to handle with extra precaution.



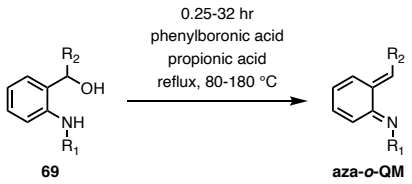
Scheme 36. Zanirato's thermolysis condition for generation of aza-*ortho*-quinone methides from 2-azido-1-methylindole

Wojciechowski *et. al.* thermolysis condition contributed some good work to show the decrease of reaction temperature by using cheletropic SO_2 extrusion of benzosultams (Scheme 37, **68**).[63] However, this thermolysis condition would only allow the introduction of other thermal-stable dienophiles to the system.



Scheme 37. Wojciechowski's thermolysis condition for generation of aza-*ortho*-quinone methides using cheletropic SO_2 extrusion

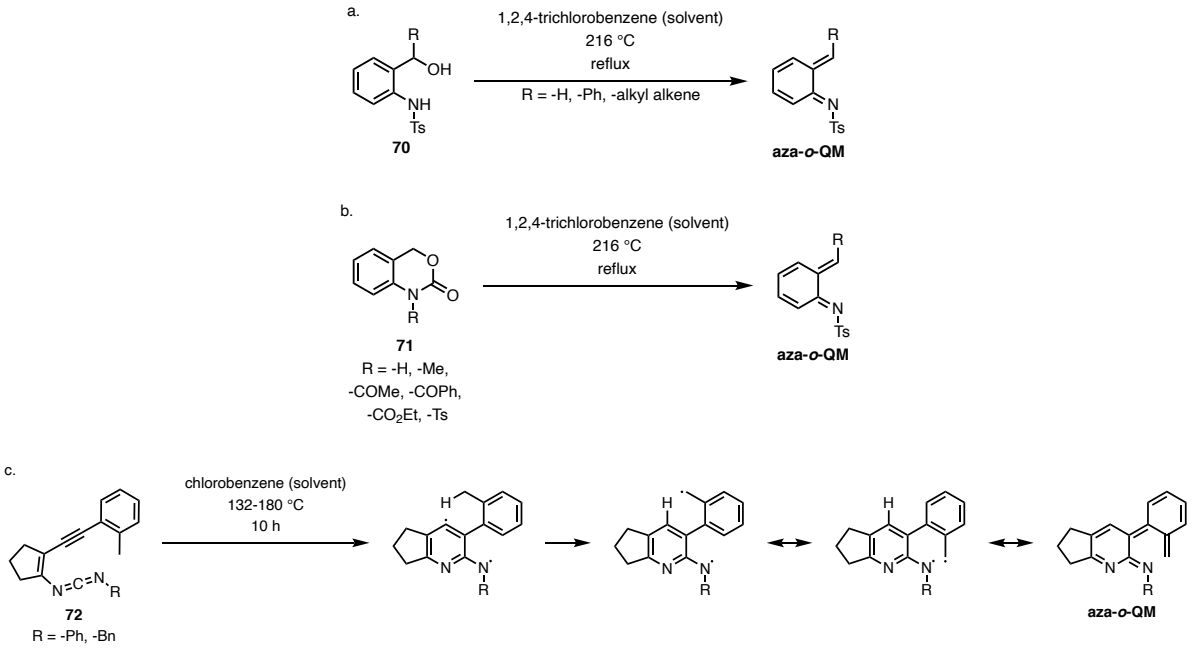
In the meantime, Lau *et. al.* reported the usage of a Lewis acid, boronic acid, would allow the reduction of reaction temperature to 80-180 °C with *o*-amino benzylalcohol derivatives (Scheme 38, **69**)[64] comparing to above mentioned FVP/T conditions with similar *o*-amino benzylalcohol precursors (Scheme 33-34). Martín *et. al.* adapted Lau's method and apply for intermolecular IMDA reaction between aza-*o*-QM and C_{60} in 1998.[65]



Scheme 38. Lau's thermolysis condition for generation of aza-*ortho*-quinone methides using a Lewis acid to lower reaction temperature

In addition to Lau's thermolysis condition, Ferraccioli,[66] Ohno[67] and Wang[68] independently studied other aza-*o*-QM precursors that can reduce the reaction temperature. Ferraccioli *et. al.* reported the usage of an electron-withdrawing protecting group, a tosyl group, on *o*-amino benzylalcohols (**70**) can lower reaction temperature (Scheme 39a).[66] Ohno *et. al.* reported an *N*-electron-withdrawing-group substituted 1,3-benzoxazinone (**71**)

can also lower reaction temperature (Scheme 39b).[67] In the meantime, Wang *et. al.* reported the usage of an enyne-carbodimmide precursor (**72**) that can undergo a thermo-initiated cascade reaction to generate aza-*o*-QM *via* radical mechanism (Scheme 39c) to promote reagent reactivities and subsequently lower reaction temperature.[6]



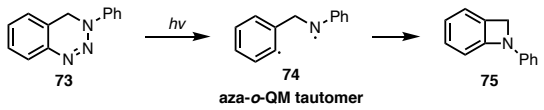
Scheme 39. Other aza-*ortho*-quinone methide precursors that lead to lower reaction temperature

3.4 Photochemical Facilitation

Similar to thermolysis condition described in section 3.3, photolysis approaches can practically undergo in neutral conditions and often proceed with the release of small molecules. On the other hand, photolysis approaches significantly reduces the temperatures required for aza-*o*-QM generation for many of the precursors shown in section 3.3. Another major differences between thermolysis and photolysis is that aza-*o*-QMs generated by photolysis can undergo [2+2] cycloaddition to form benzoazetines in the absence of trapping reagents, while thermolysis cannot.[57] In many cases, excitation with light can induce aza-*o*-QMs to form at ambient or even lower temperatures. Therefore, in principle, photochemical

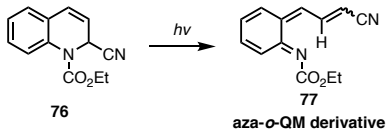
initiation allows the development of diastereoselective reactions for aza-*o*-QMs. In practice, however, photochemical generation is not widely used synthetically due to two problems. First, many precursors remain unstable and difficult to purify. Second, most precursors require high energy (short λ) to facilitate formation of aza-*o*-QMs. With high-energy light, many functional groups and nucleophilic partners can be excited into a reactive state in addition to aza-*o*-QM precursors. Therefore, undesired side reactions would occur and photolysis limit a wide range of substituents and solvents.

In 1966, Burgess and McCullagh reported the first evidence of aza-*o*-QM formation by irradiating 3-phenyl-*4H*-benzo-1,2,3-triazine (**73**) in benzene solution with UV-light to form *N*-phenylbenzoazetine (Scheme 40, **75**).[55] Compound **75** suggests the formation of a 1,4-biradical (**74**), which is a tautomer of aza-*o*-QM. Compound **75** was also tested for generation of aza-*o*-QM in the same report under photolysis condition and proved to be successful, which is a reversible reaction between **75** and **74**. Later on, Smith *et. al.* discovered a previous-mentioned thermo-precursor benzosultams (**68**) can also lead to compound **75** formation under photolysis condition.[69]



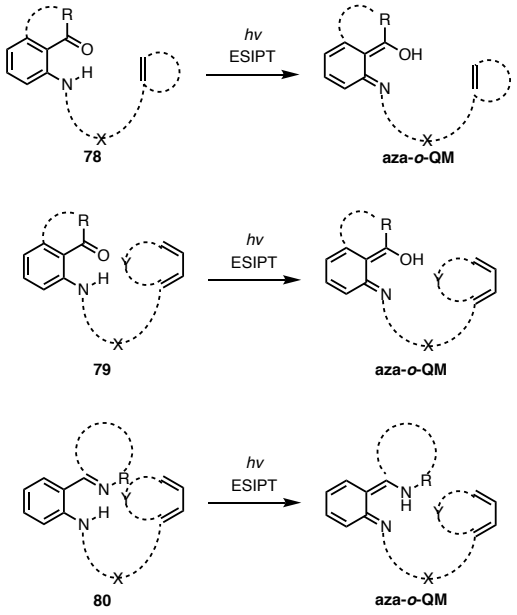
Scheme 40. First evidence of aza-*ortho*-quinone methide formation, discovered by Burgess and McCullagh

Nevertheless, photolysis approaches for generation of aza-*o*-QMs remain unexplored for almost a decade until Ikeda *et. al.* discovered a different aza-*o*-QM precursor. They reported the usage of an ethyl 2-nitrile 1,2-dihydroquinoline-*N*-carboxylate (**76**) under photolysis condition to generate benzoazahexatriene intermediates (**77**), which is a derivative of aza-*o*-QMs (Scheme 41).[70]



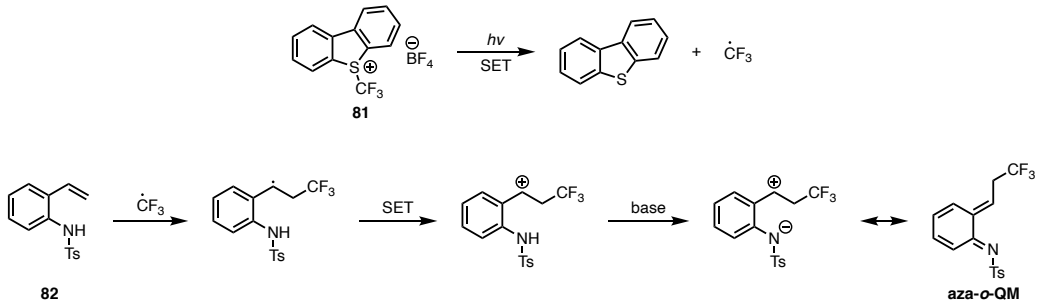
Scheme 41. Photolysis of ethyl 2-nitrile 1,2-dihydroquinoline-*N*-carboxylate for the generation of aza-*ortho*-quinone methide derivative, benzoazahexatriene

Later on, inspired by the well documented generation of *o*-QMs *via* an excited-state intramolecular proton transfer (ESIPT),[71] Kutaeladze *et. al.* studied photogeneration of aza-*o*-QMs from *ortho*-ketone substituted aniline (**78** & **79**) or *ortho*-imine substituted aniline (**80**) *via* ESIPT (Scheme 41).[72] Their methods demonstrated the first diastereoselective synthesis of a mixture of intramolecular [4+2] and [4+4] reactions under photolysis condition. Though the regioselective problem remains to be solved.



Scheme 42. Kutaeladze's method for generation of aza-*ortho*-quinone methide *via* excited-state intramolecular proton transfer

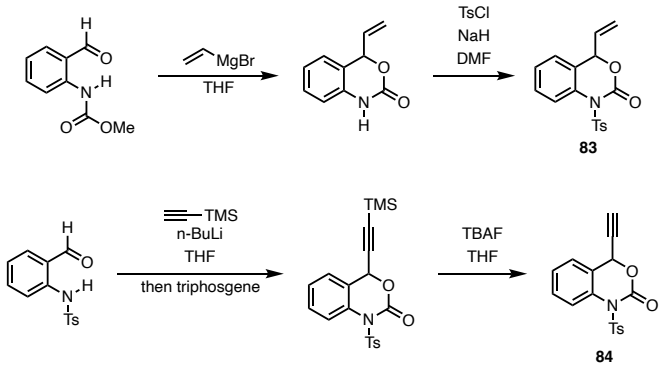
Xiao, Chen and Rao collaboratively developed a photochemical-generation of aza-*o*-QMs *via* single-electron transfer (SET), which allows a more benefit for synthetic potential. They use the Umemoto reagent (**81**) as CF_3 radical sources and *N*-tosyl-2-vinylanilines (**82**) as aza-*o*-QMs photo-precursor (Scheme 43).[73] In the presence of a base, like Cs_2CO_3, NaOAc or $NaHPO_4$, an aza-*o*-QM intermediate is formed and can undergo various intermolecular reactions with coupling partners that are stable under photochemical condition and resulting into good regio- and diastereoselectivity.



Scheme 43. Single-electron transfer approach for generation of aza-*ortho*-quinone methide

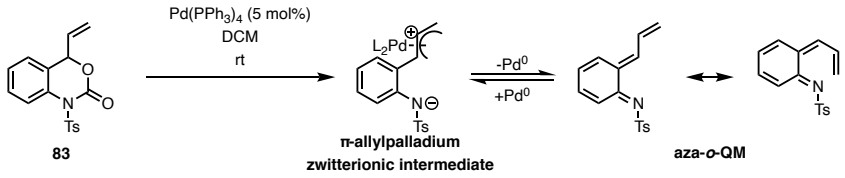
3.5 Metal-Catalyzed Facilitation

Metal-catalyzed generation of active zwitterionic intermediates, such as π-allylpalladium intermediates, copper-allenylidene intermediates and iron-enyl intermediates, under mild conditions have been reported in recent years.[74-88] The zwitterionic intermediates can be conceived as a functionally equivalent of the aza-*o*-QMs. The analogues of highly reactive intermediate aza-*o*-QMs are generated from benzoxazinones, which were used in thermal cycloaddition reactions as mentioned in section 3.3. Thus far, only two benzoxazinones (Scheme 44, **83** & **84**)[74] are reported to well-tolerate metal-catalyzed condition for subsequent [4+n] cycloadditions (n=1-4) and 1,4 conjugated-addition.



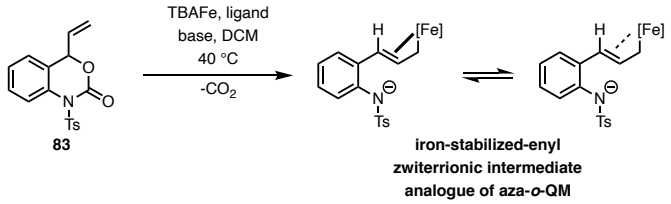
Scheme 44. Synthesis of aza-*ortho*-quinone methide metal-catalyzed precursors

In 2008, Tung *et. al.* first reported to use a benzoxazinone (**83**) in the presence of Pd(0) catalyst to generate a π-allylpalladium zwitterionic intermediate (Scheme 45).[75a] Subsequently, Tung,[75] Lu, Xiao,[76] Jørgensen,[77] Glorius,[78] Shi,[79] Guo,[80] Zhai,[81] Ashfeld,[82] and Du[83] have been using this π-allylpalladium zwitterionic intermediate for assortment of [4+n] cycloadditions (n = 1-4) and 1,4-conjugated addition with decent to good yield and diastereoselectivity.



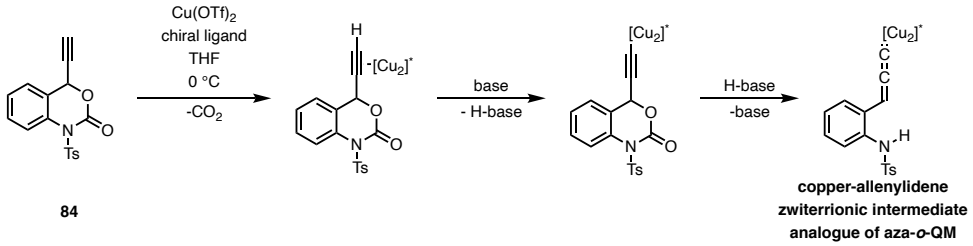
Scheme 45. Pd-catalyzed generation of π-allylpalladium zwitterionic intermediates, analogues of aza-*ortho*-quinone methides

In 2016, Lu, Lan and Xiao reported an alternative iron catalyst for the generation of iron-stabilized-enyl zwitterionic intermediate using aza-*o*-QM precursor (**83**) for subsequent [4+1] reaction with sulfur ylides (Scheme 46),[84] which is a lower-cost version of previous mentioned Pd-catalyzed reaction.[76a]



Scheme 46. Fe-catalyzed generation of Fe-enyl zwitterionic intermediates, analogues of aza-*ortho*-quinone methides

In the same year, Lu and Xiao further developed an ethynyl derivative of benzoxazinone (**84**) that can form Cu-allenylidene intermediates, a formal copper-containing 1,4-dipole, under mild conditions by reacting with Cu catalysts (Scheme 47).[85] This method was further developed by Gong,[86] Wu[87] and Deng[88] for [4+2] cycloaddition reactions with proper synthons.



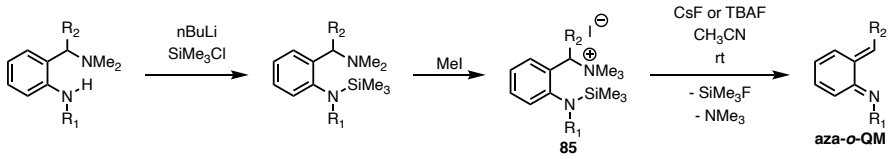
Scheme 47. Cu-catalyzed generation of Cu-allenylidene zwitterionic intermediates, analogues of aza-*ortho*-quinone methides

3.6 1,4-Elimination Process

The most frequently used method to generate aza-*o*-QMs is through a 1,4-elimination process. There are three sub-category reactions under 1,4-elimination process, including fluoride-promoted, acid-promoted and base-promoted reaction.[89-103] All three sub-category reactions require a suitable leaving group in order to generate aza-*o*-QMs *in-situ*. In addition, due to the readily-available aza-*o*-QM intermediates, these reactions can occur at ambient or even lower temperature and therefore allow a wider reactivities with varieties of nucleophiles and dienophiles.

3.6.1 Fluoride-Promoted 1,4-Elimination

For fluoride-promoted 1,4-elimination process, given the aza-*o*-QM precursors (**85**) proved to be unstable, limited syntheses were only reported by Saegusa *et. al.* (Scheme 48).[89]

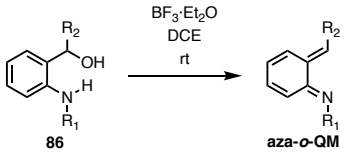


Scheme 48. Fluoride-promoted 1,4-elimination process developed by Saegusa *et. al.*

3.6.2 Acid-Promoted 1,4-Elimination

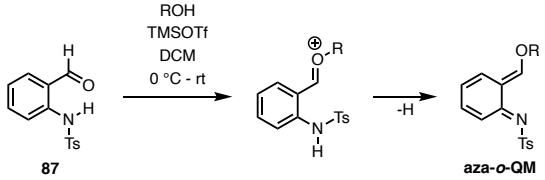
Many of the thermal processes can be induced to occur at lower temperatures by the addition of a Lewis/Brønsted acid due to *ortho*-amino benzylalcohols are acid-labile. Nevertheless, acidic conditions reduce the range of nucleophiles that can be used due to nucleophilicity is diminished under this condition.[90-95]

In 1996, Lau *et. al.* reported the first example harnessing a Lewis acid, $BF_3 \cdot Et_2O$, to induce 1,4-elimiantion of water molecule from *ortho*-amino benzyl alcohols (**86**) and generate aza-*o*-QMs *in-situ* for subsequent intermolecular reactions (Scheme 49).[90] The same precursor was used in thermolysis and by addition of a Lewis acid, Lau *et. al.* showed that the reaction temperature is significantly reduced and therefore enhances reactions' diastereoselectively. Since Lau's report, many Lewis/Brønsted acids were tested, such as $FeCl_3$, $ZnCl_2$, 4 Å molecular sieves,[91] TFA,[92] phosphoric acid[93] and $In(OTf)_3$,[94] result in competitive results. With the use of a chiral Brøsted acid, such as a chiral phosphoric acid, lead to enantioselective reactions.[93]



Scheme 49. First acid-promoted 1,4-elimination process developed by Lau *et. al.*

Recently, Gharpure and Vishwakarma reported to use of a different aza-*o*-QM precursor (**87**, a derivative of a photolysis precursor) in the presence of TMSOTF, a Lewis acid, and resulted in intermolecular reactions with decent to good diastereoselectivity (Scheme 50).[95]



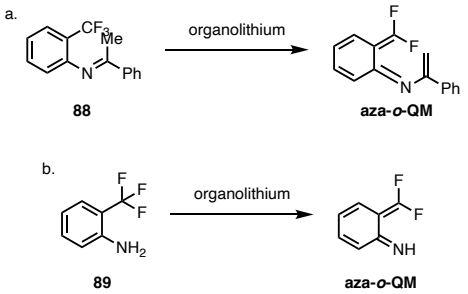
Scheme 50. Acid-promoted aza-*ortho*-quinone methide generation from *ortho*-amino benzaldehyde derivatives

3.6.3 Base-Promoted 1,4-Elimination

There is one noteworthy benefit for base-promoted 1,4-elimination process. Most nucleophiles by nature, tolerate basic conditions to some degree, which cannot be achieved by thermolysis, photolysis or acid-promoted protocols. Therefore, in principle, a low-temperature base-promoted process should encompass a greater range of substituents in reactants than alternative protocols.

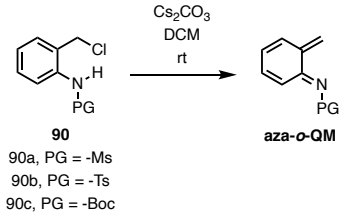
Strekowski *et. al.* reported to use a base-promoted 1,4-elimination of HF from 2-(trifluoromethyl)phenyl ketimine (Scheme 51a, **88**)[96] and 2-(trifluoromethyl)aniline (Scheme 51b, **89**)[97] to generate a difluoro aza-*o*-QM intermediate. These reactive difluoro aza-*o*-QMs enter into reactions, such as 1,4-conjugated additions of nucleophiles and electrocyclizations. This process allows the possibility of the recurrence of the elimination and addition steps, which results in the complete replacement of the fluorine atoms in the final product. Despite all the efforts undertaken, there are no reports on the intermolecular

[4+2] cycloadditions. In addition, the above-mentioned 2-(trifluoromethyl)aniline derivatives (**88** & **89**) are easily hydrolyzed to the corresponding 2-aminobenzoic acids in basic media, which contributes to a higher level of difficulty when handling these precursors.[57]



Scheme 51. Base-promoted 1,4-elimination of HF to generate aza-*ortho*-quinone methide reported by Strekowski *et. al.*

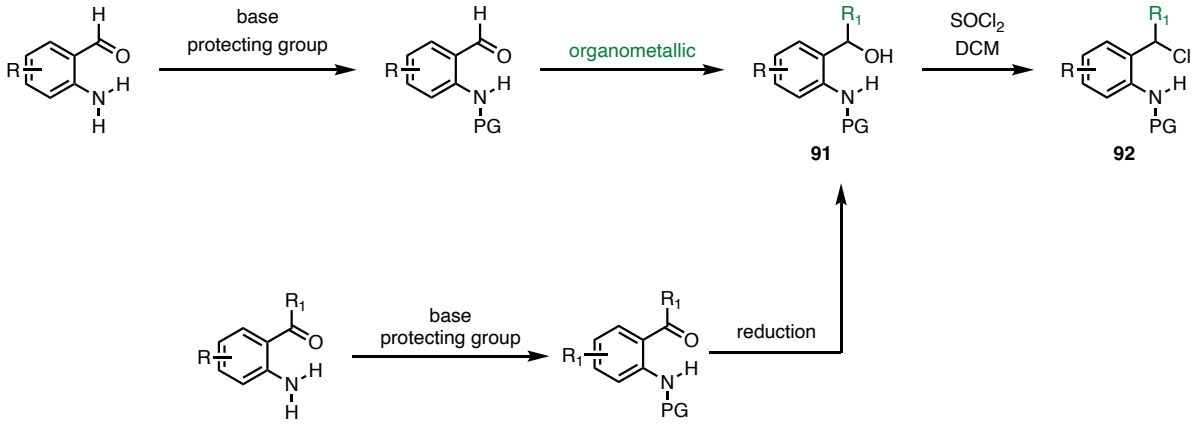
The simplest method for generating of aza-*o*-QMs was developed by Steinhagen and Corey.[56] Readily available *N*-protected 2-(chloromethyl)aniline derivatives (**90**) were subjected to a base-promoted 1,4-elimination of HCl (Scheme 52). The resulting aza-*o*-QM intermediates were ready to react with π-electron-rich olefins, such as vinyl ethers and acetylenes, for intramolecular and intermolecular [4+2] cycloadditions with good regio- and diastereoselectivity. Since then, many reports were followed with this methodology with minor changes of bases and solvents for intermolecular and intramolecular cyclizations[98-101] and nucleophilic additions.[102]



Scheme 52. Base-promoted 1,4-elimination of HCl to generate aza-*ortho*-quinone methide reported by Steinhagen and Corey

3.7 Future Applications

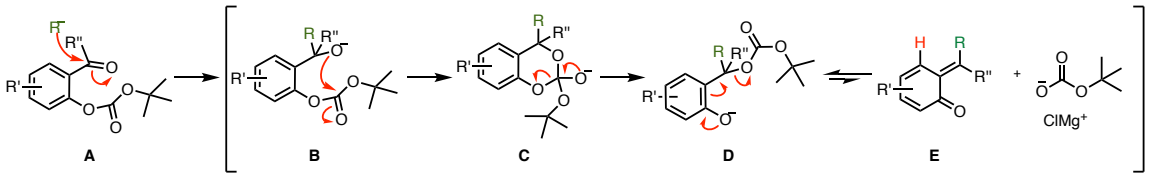
Although Steinhagen and Corey's base-promoted 1,4-elimination method are well used for a variety of intra- and intermolecular cycloadditions and nucleophilic additions, one major problem still underlies. As mentioned before, benzylalcohol derivatives, such as benzylchloride (**92**), are not stable and ready for hydrolysis. In addition, for every benzylic substituted benzylchloride precursor, it requires the transformation from benzylic substituted benzylalcohol (Scheme 53, **91**).[103] Therefore, it is necessary to develop a precursor that is more stable and hopefully allows one-pot multicomponent synthesis.



Scheme 53. General synthesis of benzylic-substituted benzylchloride

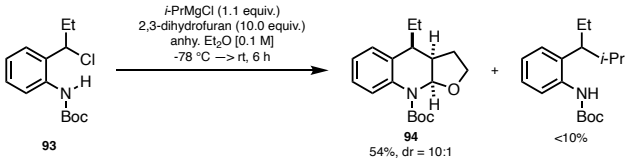
Based on our group's experience in *o*-QMs, we learned that *o*-QM is formed following a sequence of events begins with a nucleophilic addition of an organometallic reagent to an *o*-OBoc salicylaldehyde (Scheme 54, **A**) the resulting benzyloxy anion **B** attacks the -OBoc carbonate to form a cyclic intermediate **C**, which collapses to form a more stable phenoxide **D** upon -Boc migration. Under certain circumstances, β-elimination of the -OBoc residue produces an *o*-QM **E**. Cascade incursion is both metal and temperature dependent, presumably reflecting the strength of the oxygen-metal bond and the electrophilicity of the metal cation. For example, an aluminum reagent proceeds to intermediate **B**; whereas, a

lithium reagent continues to intermediate **D**. A magnesium reagent facilitates the final conversion to **E**, an unfavorable event which is energetically offset by entropy, the Lewis acidity of Mg^{2+} and CO_2 expulsion.[25b]



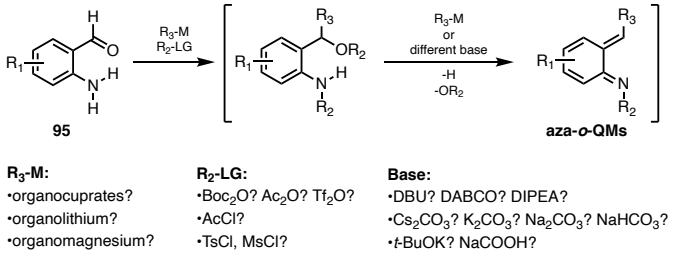
Scheme 54. *ortho*-Quinone methides cascade

Thus far, I have adapted our Grignard-promoted *o*-QM generation method on benzylchloride precursor (**93**) with promising results. In the presence of *i*-PrMgCl and 2,3-dihydrofuran, ethyl-substituted benzylchloride (**93**) is transformed to a [4+2] cycloaddition product (**94**) with decent yield and diastereoselectivity (Scheme 55).



Scheme 55. Preliminary results

Hereby, I would like to propose a possible novel method for generation of aza-*o*-QMs, which is similar to our base-promoted *o*-QMs chemistry (Scheme 56). An *ortho*-amine benzaldehyde (**95**) is subjected as an aza-*o*-QM precursor, with the proper organometallic reagent, leaving group and base in desire solvent, I hypothesized that aza-*o*-QMs can be generated *in-situ* and ready for subsequent cycloadditions and 1,4-conjugated addition reactions. In the future, our group should test out a varieties of organometallic reagents, such as organocuprates, organolithiums, and organomagnesiums; potential leaving groups, such as, -Boc, -Ac, -Tf, -Ts and -Ms; other bases, such as DBU, DABCO, Hünig's base, Cs_2CO_3, K_2CO_3, Na_2CO_3, $NaHCO_3$, *t*-BuOK and sodium formate.



Scheme 56. Future directions for base-promoted aza-*ortho*-quinone methide generations

References

1. a) Schönherr, H.; Cernak, T. "Profound Methyl Effects in Drug Discovery and a Call for New C-H Methylation Reactions." *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.
   b) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. "The Methylation Effect in Medicinal Chemistry." *Chem. Rev.* **2011**, *111*, 5215-5246.

2. Lindberg, P.; Brändström, A.; Wallmark, B.; Mattsson, H.; Rikner, L.; Hoffmann, K.-J. "Omeprazole: The First Proton Pump Inhibitor." *Med. Res. Rev.* **1990**, *10(1)*, 1-54.

3. a) Collinsworth, K. A.; Kalman, S. M.; Harrison, D. C. "The Clinical Pharmacology of Lidocaine as an Antiarrhythmic Drug." *Circulation* **1974**, *50*, 1217-1230.
   b) Foo, I.; Macfarlane, A. J. R.; Srivastava, D.; Bhaskar, A.; Barker, H.; Knaggs, R.; Eipe, N.; Smith, A. F. "The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety." *Anaesthesia* **2021**, *76*, 238-250.

4. a) Enz, A.; Amstutz, R.; Boddeke, H.; Gmelin, G.; Malanowski, J. "Chapter 53: Brain selective inhibition of acetylcholinesterase: a novel approach to therapy for Alzheimer's disease." *Progress in Brain Research* **1993**, *98*, 431-438.
   b) Chaudhury, S. S.; Sinha, K.; Das Mukhopadhyay, C. "Intranasal route: The green corridor for Alzheimer's disease therapeutics." *J. Drug Deliv. Sci. Technol.* **2021**, *66*, 102791.

5. Barnes-Seeman, D.; Jain, M.; Bell, L.; Ferreira, S.; Cohen, S.; Chen, X.-H.; Amin, J.; Snodgrass, B.; Hatsis, P. "Metabolically Stable *tert*-Butyl Replacement." *ACS Med. Chem. Lett.* **2013**, *4*, 514-516.

6. Randolph, J. T.; Krueger, A. C.; Donner, P. L.; Pratt, J. K.; Liu, D.; Motter, C. E.; Rockway, T. W.; Tufano, M. D.; Wagner, R.; Lim, H. B.; Beyer, J. M.; Mondal, R.; Panchal, N. S.; Colletti, L.; Liu, Y.; Koev, G.; Kati, W. M.; Hernandez, L. E.; Beno, D. W. A.; Longenecker, K. L.; Stewart, K. D.; Dumas, E. O.; Molla, A.; Maring, C. J. "Synthesis and Biological Characterization of Aryl Uracil Inhibitors of Hepatitis C Virus NS5B Polymerase: Discovery of ABT-072, a *trans*-Stilbene Analog with Good Oral Bioavailability." *J. Med. Chem.* **2018**, *61*, 1153-1163.

7. Talamas, F. X.; Abbot, S. C.; Anand, S.; Brameld, K. A.; Carter, D. S.; Chen, J.; Davis, D.; de Vincente, J.; Fund, A. D.; Gong, L.; Harris, S. F.; Inbar, P.; Labadie, S. S.; Lee, E. K.; Lemoine, R.; Le Pogam, S.; Leveque, V.; Li, J.; McIntosh, J.; Nájera, I.; Park, J.; Railkar, A.; Rajyaguru, S.; Sangi, M.; Schoenfeld, R. C.; Staben, L. R.; Tan, Y. T.; Taygerly, J. P.; Villaseñor, A. G.; Weller, P. E. "Discovery of *N*-[4-[6-*tert*-Butyl-5-methoxy-8-(6-methoxy-2-oxo-1*H*-pyridin-3-yl)-3-quinolyl]phenyl]methanesulfonamide (RG7109), a Potent Inhibitor of the Hepatitis C Virus NS5B Polymerase." *J. Med. Chem.* **2014**, *57*, 1914-1931.

8. Pi, Z.; Sutton, J.; Lloyd, J.; Hua, J.; Price, L.; Wu, Q.; Chang, M.; Zheng, J.; Rehfuss, R.; Huang, C. S.; Wexler, R. R.; Lam, P. Y. S. "2-Aminothiazole based $P2Y_1$ antagonists as novel antiplatelet agents." *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4206-4209.

9. Hadida, S.; Van Goor, F.; Zhou, J.; Arumugam, V.; McCartney, J.; Hazlewood, A.; Decker, C.; Negulescu, P.; Grootenhuis, P. D. J. "Discovery of *N*-(2,4-Di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (VX-770, Ivacaftor), a Potent and Orally Bioavailable CFTR Potentiator." *J. Med. Chem.* **2014**, *57*, 9776-9775.

10. Looker, A. R.; Wilde, N.; Ryan, M. P.; Roeper, S.; Ye, Z.; Lewandowski, B. L. "Utilizing *o*-Quinone Methide Chemistry: Synthesis of d_9-Ivacaftor." *J. Org. Chem.* **2020**, *85*, 501-507.

11. Rueping, M.; Nachtsheim, B. J. "A review of new developments in the Friedel-Crafts alkylation – From green chemistry to asymmetric catalysis." *Beilstein J. Org. Chem.* **2010**, *6* (6), 1-24.

12. a) Chaudhuri, B.; Sharma, M. M. "Alkylation of Phenol with α-Methylstyrene, Propylene, Butenes, Isoamylene, 1-Octene, and Diisobutylene: Heterogeneous vs Homogeneous Catalysts." *Ind. Eng. Chem. Res.* **1991**, *30*, 227-231.
b) Kamitori, Y.; Hojo, M.; Masuda, R.; Izumi, T.; Tsukamoto, S. "Silica Gel as an Effective Catalyst for the Alkylation of Phenols and Some Heterocyclic Aromatic Compounds." *J. Org. Chem.* **1984**, *49*, 4161-4165.
c) Gagea, B. C.; Parvulescu, A. N.; Parvulescu, V. I.; Auroux, A.; Grange, P.; Poncelet, G. "Alkylation of phenols and naphthol on silica immobilized triflate derivatives." *Catal. Letters* **2003**, *91(1-2)*, 141-144.
d) Gagea, B. C.; Parvulescu, A. N.; Poncelet, G.; Pârvulescu, V. I. "Alkylation of hydroquinone with *tert*-butanol over silica-immobilized triflate derivatives." *Catal. Letters* **2005**, *105(3-4)*, 219-222.
e) Pezzotta, C.; Fleury, G.; Soetens, M.; Van der Perre, S.; Denayer, J. F. M.; Riant, O.; Gaigneaux, E. M. "Improving the selectivity to 4-*tert*-butylresorcinol by adjusting the surface chemistry of heteropolyacid-based alkylation catalysts." *J. Catal.* **2018**, *359*, 198-211.
f) Hart, H. "*o*-*t*-Butylphenol." *J. Am. Chem. Soc.* **1948**, *71*, 1966-1967.

13. Cashman, J. R. "Leukotriene Biosynthesis Inhibitors." *Pharm. Res.* **1985**, 253-261.

14. Zambias, R. A.; Caldwell, C. G.; Kopka, I. E.; Hammond, M. L. "A Convenient Synthesis of 4-*tert*-Butyl-5-benzofuranols and Dihydrobenzofuranols." *J. Org. Chem.* **1988**, *53*, 4135-4137.

15. Barton, D. H. R.; Sas, W. "THE INVENTION OF RADICAL REACTIONS. PART XIX. THE SYNTHESIS OF VERY HINDERED QUINONES." *Tetrahedron* **1990**, *46(10)*, 3419-3430.

16. Baschieri, A.; Amorati, R.; Valgimigli, L.; Sambri, L. "1-Methyl-1,4-cyclohexadiene as a Traceless Reducing Agent for the Synthesis of Catechols and Hydroquinones." *J. Org. Chem.* **2019**, *84*, 13655-13664.

17. a) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. "Practical C-H Functionalization of Quinones with Boronic Acids." *J. Am. Chem. Soc.* **2011**, *133*, 3292-3295.
b) Hamsath, A.; Galloway, J. D.; Baxter, R. D. "Quinone C-H Alkylations *via* Oxidative Radical Processes." *Synthesis* **2018**, *50*, 2915-2923.

18. a) Richtzenhain, H.; Nippus, P. "Substitutionsreaktionen mit metallorganischem Verbindungen, IV. Mitteil.: Die Grignardierung methoxylhaltiger aromatischer Nitrile." *Chem. Ber.* **1949**, *82*, 408-417 and references cited therein.
b) Meyers, A. I.; Mihelich, E. D. "Oxazolines. XXII. Nucleophilic Aromatic Substitution on Aryl Oxazolines. An Efficient Approach to Unsymmetrically Substituted Biphenyls and *o*-Alkyl Benzoic Acids." *J. Am. Chem. Soc.* **1975**, *97(25)*, 7383-7385.
c) Meyers, A. I.; Gabel, R.; Mihelich, E. D. "Nucleophilic Aromatic Substitution on *o*-(Methoxy)aryloxazolines. A Convenient Synthesis of *o*-Alkyl-, *o*-Alkylidene-, and *o*-Arylbenzoic Acids." *J. Org. Chem.* **1978**, *43(7)*, 1372-1379.

19. Clayden, J.; Stimson, C. C.; Keenan, M. "Contra-Friedel-Crafts *tert*-butylation of substituted aromatic rings *via* directed metalation and sulfinylation." *Chem. Commun.* **2006**, 1393-1394.

20. a) Rudolph, A.; Lautens, M. "Secondary Alkyl Halides in Transition-Metal-Catalyzed Cross-Coupling Reactions." *Angew. Chem. Int. Ed.* **2009**, *48*, 2656-2670.
b) Campeau, L.-C.; Hazari, N. "Cross-Coupling and Related Reactions: Connecting Past Success to the Development of New Reactions for the Future.

21. Ando, S.; Mawatari, M.; Matsunaga, H.; Ishizuka, T. "An *N*-heterocyclic carbene-based nickel catalyst for the Kumada-Tamao-Corriu coupling of aryl bromides and tertiary alkyl Grignard reagents." *Tetrahedron Lett.* **2016**, *57*, 3287-3290.

22. Pearson, D. E.; Wysong, R. D.; Breder, C. V. "The *ortho* Bromination of Phenols." *J. Org. Chem.* **1967**, *32(7)*, 2358-2360.

23. a) Frisch, A. C.; Beller, M. "Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides." *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688.
b) Schröter, S.; Stock, C.; Bach, T. "Regioselective cross-coupling reactions of multiple halogenated nitrogen-, oxygen-, and sulfur-containing heterocycles." *Tetraheron* **2005**, *61*, 2245-2267.
c) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. "Ni- or Cu-Catalyzed Cross-Coupling Reaction of Alkyl Fluorides with Grignard Reagents." *J. Am. Chem. Soc.* **2003**, *125*, 5646-5647.

d) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. "Cross-coupling of alkyl halides with Grignard reagents using nickel and palladium complexes bearing η^3-allyl ligand as catalysts." *Chem. Commun.* **2007**, 825-827.
For copper reagents: e) Bell, T. W.; Hu, L.-Y.; Patel, S. V. "Alkylation of Heteroaryl Halides by 2:1 Grignard Reagent/Cu(I) Mixtures. Synthesis of Alkylated Octahydrodibenzo[*b,j*][1,10]phenanthrolines." *J. Org. Chem.* **1987**, *52*, 3847-3850.
f) Hintermann, L.; Xiao, L.; Labonne, A. "A General and Selective Copper-Catalyzed Cross-Coupling of Tertiary Grignard Reagents with Azacyclic Electrophiles." *Angew. Chem. Int. Ed.* **2008**, *47*, 8246-8250.
g) Langlois, J.-B.; Alexakis, A. "Dynamic kinetic asymmetric transformation in copper catalyzed allylic alkylation." *Chem. Commun.* **2009**, 3868-3870.
For nickel reagents: h) Hayashi, T.; Konishi, M.; Yokota, K.; Kumada, M. "CROSS-COUPLING OF TERTIARY ALKYL GRIGNARD REAGENTS WITH β-BROMOSTYRENE CATALYZED BY DICHLORO[1,1'-BIS(DIPHENYLPHOSPHINO)FERROCENE]NICKEL(II)." *Chem. Lett.* **1980**, 767-768.
i) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. "Nickel-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Alkyl Halides and Tosylates: Remarkable Effect of 1,3-Butadienes." *J. Am. Chem. Soc.* **2002**, *124*, 4222-4223.
j) Glorius, F. "Asymmetric Cross-Coupling of Non-Activated Secondary Alkyl Halides." *Angew. Chem. Int. Ed.* **2008**, *47*, 8347-8349.
k) Vechorkin, O.; Proust, V.; Hu, X. "Functional Group Tolerant Kumada-Corriu-Tamao Coupling of Nonactivated Alkyl Halides with Aryl and Heteroaryl Nucleophiles: Catalysis by a Nickel Pincer Complex Permits the Coupling of Functionalized Grignard Reagents." *J. Am. Chem. Soc.* **2009**, *131*, 9756-9766.
For iron reagents: l) Cahiez, G.; Avedissian, H. "Highly Stereo- and Chemoselective Iron-Catalyzed Alkenylation of Organomagnesium Compounds." *Synthesis* **1998**, 1199-1205.
m) Cahiez, G.; Foulgoc, L.; Moyeux, A. "Iron-Catalyzed Oxidative Heterocoupling Between Aliphatic and Aromatic Organozinc Reagents: A Novel Pathway for Functionalized Aryl-Alkyl Cross-Coupling Reactions." *Angew. Chem. Int. Ed.* **2009**, *48*, 2969-2972.
For chromium reagents: n) Liu, P.; Chen, C.; Cong, X.; Tang, J.; Zeng, X. "Chromium-catalyzed *para*-selective formation of quaternary carbon centers by alkylation of benzamide derivatives." *Nature Comm.* **2018**, *9*, 4637.

24. Lohre, C.; Dröge, T.; Wang, C.; Glorius, F. "Nickel-Catalyzed Cross-Coupling of Aryl Bromides with Tertiary Grignard Reagents Utilizing Donor Functionalized N-Heterocyclic Carbenes (NHCs)." *Chem. Eur. J.* **2011**, *17*, 6052-6055.

25. a) Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. "New Construction of Ortho Ring-Alkylated Phenols via Generation and Reaction of Assorted *o*-Quinone Methides." *J. Am. Chem. Soc.* **2000**, *122*, 6502-6503.
b) Jones, R. M.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. "A Mild Anionic Method for Generation *o*-Quinone Methides: Facile Preparations of *Ortho*-Functionalized Phenols." *J. Org. Chem.* **2001**, *66*, 3435-3441.

c) Green, J. C.; Pettus, T. R. R. "An Oxidative Dearomatization-Induced [5+2] Cascade Enabling the Synthesis of α-Cedrene, α-Pipitzol, and *sec*-Cedrenol." *J. Am. Chem. Soc.* **2011**, *133*, 1603-1608.

26. Looker, A. R.; Wilde, N.; Ryan, M. P.; Roeper, S.; Ye, Z.; Lewandowski, B. L. "Utilizing *o*-Quinone Methide Chemistry: Synthesis of d_9-Ivacaftor." *J. Org. Chem.* **2020**, *85*, 501-507.

27. a) Augelli-Szafran, C. E.; Jaen, J. C.; Moreland, D. W.; Nelson, C. B.; Penvose-Yi, J. R.; Schwarz, R. D. "IDENTIFICATION AND CHARACTERIZATION OF m4 SELECTIVE MUSCARINIC ANTAGONISTS." *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1991-1996.
b) Böhme, T. M.; Augelli-Szafran, C. E.; Hallak, H.; Pugsley, T.; Serpa, K.; Schwarz, R. D. "Synthesis and Pharmacology of Benzoxazines as Highly Selective Antagonists at M_4 Muscarinic Receptors." *J. Med. Chem.* **2002**, *45*, 3094-3102.
c) Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. "Preparation of Enantiopure Substituted Piperidines Containing 2-Alkene or 2-Alkyne Chains: Application to Total Syntheses of Natural Quinolizidine-Alkaloids." *J. Org. Chem.* **2010**, *75*, 1911-1916.
d) Mathew, B. P.; Kumar, A.; Sharma, S.; Shukla, P. K.; Nath, M. "An eco-friendly synthesis and antimicrobial activities of dihydro-*2H*-benzo- and naphtho-1,3-oxazine derivatives." *Eur. J. Med. Chem.* **2010**, *45*, 1502-1507.
e) Verma, V.; Singh, K.; Kumar, D.; Klapötke, T. M.; Stierstorfer, J.; Narasimhan, B.; Qazi, A. K.; Hamid, A.; Jaglan, S. "Synthesis, antimicrobial and cytotoxicity study of 1,3-disubstituted-*1H*-naphtho[1,2-e][1,3]oxazines." *Eur. J. Med. Chem.* **2012**, *56*, 195-202.
f) Joule, J. A. "Natural Products Containing Nitrogen Heterocycles – Some Highlights 1990 – 2015." *Adv. Heterocycl. Chem.* **2016**, *119*, 81-106.
g) Prandi, C.; Occhiato, E. G. "From synthetic control to natural products: a focus on *N*-Heterocyles." *Pest. Manag. Sci.* **2019**, *75*, 2385-2402.
h) Sharaf El-Din, N. A. E.-L. "3,4-Dihydro-*2H*-1,3-benzoxazines and their oxo-derivatives – Chemistry and bioactivities." *J. Serb. Chem. Soc.* **2021**, *86(3)*, 213-246.

28. Lawitz, E.; Gane, E.; Pearlman, B.; Tam, E.; Ghesquiere, W.; Guyader, D.; Alric, L.; Bronwicki, J.-P.; Lester, L.; Sievert, W.; Ghalib, R.; Balart, L.; Sund, F.; Lagging, M.; Dutko, F.; Shaughnessy, M.; Hwang, P.; Howe, A. Y. M.; Wahl, J.; Robertson, M.; Barr, E.; Haber, B. "Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomized, open-label phase 2 trial." *Lancet* **2015**, *385*, 1075-1086.

29. Holly, F. W.; Cope, A. C. "Condensation Products of Aldehydes and Ketones with *o*-Aminobenzyl Alcohol and *o*-Hydroxybenzylamine." *J. Am. Chem. Soc.* **1944**, *66(11)*, 1875-1879.

30. a) Burke, W. J. "3,4-Dihydro-1,3,2H-Benzoxazines. Reaction of *p*-Substituted Phenols with N,N-Dimethylolamines." *J. Am. Chem. Soc.* **1949**, *71(2)*, 609-612.
b) Burke, W. J.; Murdock, K. C.; Ec, G. "Condensation of Hydroxyaromatic Compounds with Formaldehyde and Primary Aromatic Amines." *J. Am. Chem. Soc.* **1954**, *76(6)*, 1677-1679.
c) Desai, R. B. "Mannich Reaction with Hydroxycoumarins." *J. Org. Chem.* **1961**, *26(12)*, 5251-5253.
d) Fields, D. L.; Miller, J. B.; Reynolds, D. D. "Mannich-Type Condensation of Hydroquinone, Formaldehyde, and Primary Amines." *J. Org. Chem.* **1962**, *27(8)*, 2749-2753.
e) Burke, W. J.; Glennie, E. L. M.; Weatherbee, C. "Condensation of Halophenols with Formaldehyde and Primary Amines." *J. Org. Chem.* **1964**, *29(4)*, 909-912.

31. a) Deb, M. L.; Dey, S. S.; Bento, I.; Barros, M. T.; Maycock, C. D. "Copper-Catalyzed Regioselective Intramolecular Oxidative α-Functionalization of Tertiary Amines: An Efficient Synthesis of Dihydro-1,3-Oxazines." *Angew. Chem. Int. Ed.* **2013**, *52*, 9791-9795.
b) Mahato, S.; Haldar, S.; Jana, C. K. "Diastereoselective α-C-H functionalization of aliphatic *N*-heterocycles: an efficient route to ring fused oxazines." *Chem. Commun.* **2014**, *50*, 332-334.
c) Mahato, S.; Haque, M. A.; Dwari, S.; Jana, C. K. "Divergent reaction: metal & oxidant free direct C-H aryloxylation and hydride free formal reductive *N*-benzylation of N-heterocycles." *RSC Adv.* **2014**, *4*, 46214-46217.
d) Waghmode, N. A.; Kalbandhe, A. M.; Thorat, P. B.; Karade, N. N. "Metal-free new synthesis of 1,3-naphthoxazines via intramolecular cross dehydrogenative-coupling reaction of 1-(α-aminoalkyl)-2-naphthols using hypervalent iodine(III) reagent." *Tetra. Lett.* **2016**, *57*, 680-683.
e) Gupta, K. S. V.; Ramana, D. V.; Vinayak, B.; Sridhar, B.; Chandrasekharam, M. "Copper-catalyzed regio and diastereoselective three-component C-N, C-C and C-O bond forming reaction: oxidative sp^3 C-H functionalization." *New J. Chem.* **2016**, *40*, 6389-6395.
f) Deb, M. L.; Pegu, C. D.; Borpatra, P. J.; Saikia, P. J.; Baruah, P. K. "Catalyst-free multi-component cascade C-H-functionalization in water using molecular oxygen: an approach of 1,3-oxazines." *Green Chem.* **2017**, *19*, 4036-4042.
g) Borpatra, P. J.; Deb, M. L.; Baruah, P. K. "Visible light-promoted metal-free intramolecular cross dehydrogenative coupling approach to 1,3-oxazines." *Tetra. Lett.* **2017**, *58*, 4006-4010.

32. a) Von Strandtmann, M.; Cohen, M. P.; Shavel, Jr. J. "Reaction of Phenolic Mannich Bases with Imines and Oximes. Synthesis of Fused Ring Systems Containing 1,3-Oxazines." *J. Heterocycl. Chem.* **1969**, *6(3)*, 429-431.
b) Szatmári, I.; Barta, P.; Tóth, G.; Balázs, A.; Halász, J.; Fülöp, F. "Synthesis and Conformational Behaviour of Enantiomeric Naphthoxazinoquinoxalinone Derivatives." *Eur. J. Org. Chem.* **2017**, 5537-5545.

c) Szatmári, I.; Barta, P.; Csámpai, A.; Fülöp, F. "Synthesis and detailed conformational analysis of new naphthoxazino[2,3-*a*]benz[*c*]azepine and naphthoxazino[2,3-*a*]thieno[3,2-*c*]pyridine." *Tetrahedron* **2017**, *73*, 4790-4804.

33. Jones, R. M.; Selenski, C.; Pettus, T. R. R. "Rapid Syntheses of Benzopyrans from *o*-OBoc Salicylaldehydes and Salicyl alcohols: A Three-Component Reaction." *J. Org. Chem.* **2002**, *67*, 6911-6915.

34. Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. "The Domestication of *ortho*-Quinone Methides." *Acc. Chem. Res.* **2014**, *47*, 3655-3664.

35. Weinert, E. E.; Dondi, R.; Colloredo-Melz, S.; Frankenfield, K. N.; Mitchell, C. H.; Freccero, M.; Rokita, S. E. "Substituents on Quinone Methides Strongly Modulate Formation and Stability of Their Nucleophilic Adducts." *J. Am. Chem. Soc.* **2006**, *128*, 11940-11947.

36. Van De Water, R. W.; Pettus, T. R. R. "*o*-Quinone methides: intermediates underdeveloped and underutilized in organic synthesis." *Tetrahedron* **2002**, *58*, 5367-5405.

37. a) Robinson, R. "LXIII. – A Synthesis of Tropinone." *J. Chem. Soc. Trans.* **1917**, *111*, 762-768.
b) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. "Synthesis of diverse heterocyclic scaffolds via tandem additions to imine derivatives and ring-forming reactions." *Tetrahedron* **2009**, *65*, 6454-6469.
c) Touré, B. B.; Hall, D. G. "Natural Product Synthesis Using Multicomponent Reaction Strategies." *Chem. Rev.* **2009**, *109*, 4439-4486.

38. a) Layer, R. W. "THE CHEMISTRY OF IMINES." *Chem. Rev.* **1963**, *63(5)*, 489-510.
b) Choudhury, L. H.; Parvin, T. "Recent advances in the chemistry of imine-based multicomponent reactions (MCRs)." *Tetrahedron* **2011**, *67*, 8213-8228.

39. Glinkerman, C. M.; Boger, D. L. "Catalysis of Heterocyclic Azadiene Cycloaddition Reactions by Solvent Hydrogen Bonding: Concise Total Synthesis of Methoxatin." *J. Am. Chem. Soc.* **2016**, *138*, 12408-12413.

40. a) Heintzelman, G. R.; Meigh, I. R.; Mahajan, Y. R.; Weinreb, S. M. "DIELS-ALDER REACTIONS OF IMINO DIENOPHILES." *Org. React.* **2005**, *65*, 141-599.
b) Hatanaka, Y.; Nantaku, S.; Nishimura, Y.; Otsuka, T.; Sekikaw, T. "Catalytic enantioselective aza-Diels-Alder reactions of unreacted acyclic 1,3-dienes with aryl-, alkenyl-, and alkyl substituted imines." *Chem. Commun.* **2017**, *53*, 8996-8999.

41. a) Dai, L.-X.; Lin, Y.-R.; Hou, X.-L.; Zhou, Y.-G. "Stereoselective reactions with imines." *Pure Appl. Chem.* **1999**, *71(6)*, 1033-1040.
b) Royer, J.; Bonin, M.; Micouin, L. "Chiral Heterocycles by Iminium Ion Cyclization." *Chem. Rev.* **2004**, *104*, 2311-2352.

42. a) Staudinger, H. "Diphenylketen." *Justus Liebigs Ann. Chem.* **1907**, *356*, 51-123.
b) Jiao, L.; Liang, Y.; Xu, J. "Origin of the Relative Stereoselectivity of the β-Lactam Formation in the Staudinger Reaction." *J. Am. Chem. Soc.* **2006**, *128*, 6060-6069.
c) Cossío, F. P.; Arrieta, A.; Sierra, M. A. "The Mechanism of the Ketene-Imine (Staudinger) Reaction in Its Centennial: Still an Unsolved Problem?" *Acc. Chem. Res.* **2008**, *41(8)*, 925-936.
d) Pitts, C. R.; Lectka, T. "Chemical Synthesis of β-Lactams: Asymmetric Catalysis and Orhter Recent Advances." *Chem. Rev.* **2014**, *114*, 7930-7953.

43. a) Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K. "Direct Imine Acylation: Rapid Access to Diverse Heterocyclic Scaffolds." *Org. Lett.* **2013**, *15(2)*, 258-261.
b) Unsworth, W. P.; Coulthard, G.; Kitsiou, C.; Taylor, R. J. K. "Direct Imine Acylation for Molecular Diversity in Heterocyclic Synthesis." *J. Org. Chem.* **2014**, *79*, 1368-1376.

44. a) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. "CO_2 Incorporation Reaction Using Arynes: Straightforward Access to Benzoxazinone." *J. Am. Chem. Soc.* **2006**, *128*, 11040-11041.
b) Martin, S. F. "Recent applications of imines as key intermediates in the synthesis of alkaloids and novel nitrogen heterocycles." *Pure Appl. Chem.* **2009**, *81(2)*, 195-204.
c) Maji, B.; Mayr, H. "Nucleophilic Reactivities of Schiff Bases." Z. *Naturforsch.* **2013**, *68b*, 693-699.
d) Funes-Ardoiz, I.; González, J.; Santamaría, J.; Sampedro, D. "Understanding the Mechanism of the Divergent Reactivity of Non-Heteroatom-Stabilized Chromium Carbene Complexes with Furfural Imines: Formation of Benzofurans and Azetines." *J. Org. Chem.* **2016**, *81*, 1565-1570.
e) Gu, R.; Flidrova, K.; Lehn, J.-M. "Dynamic Covalent Metathesis in the C=C/C=N Exchange between Knoevenagel Compounds and Imines." *J. Am. Chem. Soc.* **2018**, *140*, 5560-5568.

45. Chan, K. K.; Wong, Y. F.; Yang, D.; Pettus, T. R. R. "Nucleophilic Imines and Electrophilic *o*-Quinone Methides, a Three-Component Assembly of Assorted 3,4-Dihydro-*2H*-1,3-benzoxazines." *Org. Lett.* **2019**, *21*, 7746-7749.

46. Adams, R. W.; Byrne, L.; Király, P.; Foroozandeh, M.; Paudel, L.; Nilsson, M.; Clayden, J.; Morris, G. A. "Diastereomeric ratio determination by high sensitivity band-selective pure shift NMR spectroscopy." *Chem. Commun.* **2014**, *50*, 2512-2514.

47. Fülöp, F.; Pihlaja, K.; Mattinen, J.; Bernáth, G. "Ring-Chain Tautomerism in 1,3-Oxazines." *J. Org. Chem.* **1987**, *52*, 3821-3825.

48. Trotter, J. "STERIC INHIBITION OF RESONANCE." *Can. J. Chem.* **1959**, *37*, 1487-1490.

49. Neuvonen, K.; Pihlaja, K. "Studies on the Benzoxazine Series. Part 1. Preparation and ^{1}H and ^{13}C Nuclear Magnetic Resonance Structure Study of Some Substituted 3,4-Dihydro-*2H*-1,3-benzoxazines." *J. Chem. Soc. Perkin Trans. II* **1988**, 461-467.

50. Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. "Solvent-Free Asymmetric Aminoalkylation of Electron-Rich Aromatic Compounds: Stereoselective Synthesis of Aminoalkylnaphthols by Crystallization-Induced Asymmetric Transformation." *J. Org. Chem.* **2001**, *66*, 4759-4765.

51. Muthengi, A.; Zhang, X.; Dhawan, G.; Zhang, W.; Corsini, F.; Zhang, W. "Sequential (3+2) cycloaddition and (5+n) annulation for modular synthesis of dihydrobenzoxazines, tetrahydrobenzoxazepines and tetrahydrobenzoxazocines." *Green Chem.* **2018**, *20*, 3134-3139.

52. Wei, H.; Yin, L.; Luo, H.; Li, X.; Chan, A. S. C. "Structural Influence of Chiral Tertiary Aminonaphthol Ligands on the Asymmetric Phenyl Transfer to Aromatic Aldehydes." *Chirality* **2011**, *23(3)*, 222-227.

53. a) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. "Nonracemic Betti Base as a New Chiral Auxiliary: Application to Total Syntheses of Enantiopure (*2S*,*6R*)-Dihydropinidine AND (*2S*,*6R*)-Isosolenopsins." *J. Org. Chem.* **2005**, *70*, 1897-1900.
b) Cheng, G.; Wang, X.; Zhu, R.; Shao, C.; Xu, J.; Hu, Y. "Total Synthesis of (-)-Cocaine and (-)-Ferruginine." *J. Org. Chem.* **2011**, *76*, 2694-2700.
c) Mahato, S.; Jana, C. K. "Iterative direct $C_{(sp3)}$-H functionalization of amines: diastereoselective divergent syntheses of α,α'-disubstituted alicyclic amines." *Org. Biomol. Chem.* **2017**, *15*, 1655-1660.

54. Smolinsky, G. "The Vapor Phase Pyrolysis of Several Substituted Azidobenzenes." *J. Org. Chem.* **1961**, *26(10)*, 4108-4110.

55. Burgess, E. M.; McCullagh, L. "N-Phenylbenzoazetine." *J. Am. Chem. Soc.* **1966**, *88(7)*, 1580-1581.

56. a) Steinhagen, H.; Corey, E. J. "A Convenient and Versatile Route to Hydroquinolines by Inter- and Intramolecular Aza-Diels-Alder Pathways." *Angew. Chem. Int. Ed.* **1999**, *38(13/14)*, 1928-1931.
b) Steinhagen, H.; Corey, E. "A Simple Convergent Approach to the Synthesis of the Antiviral Agent Virantmycin." *Org. Lett.* **1999**, *1(5)*, 823-824.

57. Wojciechowski, K. "Aza-*ortho*-xylylenes in Organic Synthesis." *Eur. J. Org. Chem.* **2001**, 3587-3605.

58. Yang, B.; Gao, S. "Recent advances in the application of Diels-Alder reactions involving *o*-quinodimethanes, aza-*o*-quinone methides and *o*-quinone methides in natural product total synthesis." *Chem. Soc. Rev.* **2018**, *47*, 7926-7953.

59. Mao, Y.-L.; Boekelheide, V. "Nitrogen Analogues of *o*-Xylylenes." *J. Org. Chem.* **1980**, *45(8)*, 1547-1548.

60. a) Bowen, R. D.; Davies, D. E.; Fishwick, C. W. G.; Glasbey, T. O.; Noyce, S. J.; Storr, R. C. "GENERATION AND REACTIONS OF AZAXYLYLENES." *Tetrahedron. Lett.* **1982**, *23(43)*, 4501-4504.
b) Fishwick, C. W. G.; Storr, R. C.; Manley, P. W. "A Simple Route to C-Functionalised Azaxylylenes and Diazaxylylenes." *J. Chem. Soc., Chem. Commun.* **1984**, 1304-1305.
c) Hodgetts, I.; Noyce, S. J.; Storr, R. C. "CATALYSIS IN FLASH VACUUM PYROLYSIS." *Tetrahedron Lett.* **1984**, *25(47)*, 5435-5438.
d) Barker, S. J.; Jones, G. B.; Randles, K. R.; Storr, R. C. "FLASH VACUUM PYROLYSIS OF 1-ALLYLBENZOTRIAZOLES AND DIHYDROBENZOXAZINES: FORMATION OF QUINOLINES." *Tetrahedron Lett.* **1988**, *29(8)*, 953-954.

61. Randles, K. R.; Storr, R. C. "FORMATION OF INDOLES AND QUINOLINES BY FLASH VACUUM PYROLYSIS." *Tetrahedron Lett.* **1987**, *28(45)*, 5555-5558.

62. Foresti, E.; Spagnolo, P.; Zanirato, P. "Synthesis and Thermal Ring-Cleavage Fragmentation of 2-Azido-1-methylindole and 2-Azidobenzo[*b*]furan." *J. Chem. Soc. Perkin Trans. I* **1989**, 1354-1356.

63. a) Wojciechowski, K. "Synthesis of 1,2,3,4-Tetrahydroquinoline-2,3-dicarboxylic Acid Derivatives." *Synlett* **1991**, 571-572.
b) Wojciechowski, K. "New Synthesis of 2-Phenylindene Derivatives." *Synth. Comm.* **1993**, *23(17)*, 2415-2422.
c) Wojciechowski, K. "Reactions of Aza-*ortho*-xylylenes Generated from 2,1-Benzisothiazoline 2,2-Dioxides." *Tetrahedron* **1993**, *49(33)*, 7277-7286.
d) Wojciechowski, K. "[1,5] Hydrogen Shift in Aza-*ortho*-xylylenes Generated from 3-Alkyl-2,1-benzisothiazoline 2,2-Dioxides." *Tetrahedron* **1993**, *49(44)*, 10017-10026.
e) Wojciechowski, K.; Kosiński, S. "Generation and Reactions of Heteroanalogues of Aza-*ortho*-xylylenes." *Tetrahedron Lett.* **1997**, *38(26)*, 4667-4670.
f) Kosiński, S.; Wojciechowski, K. "Reactions of Pyridine Analogues of Aza-*ortho*-xylylenes Generated from 1,3-Dialkylpyridosultams." *Eur. J. Org. Chem.* **2000**, 1263-1270.
g) Wojciechowski, K.; Kosiński, S. "Reactions of Pyridine Analogues of Aza-*ortho*-xylylenes Generated from 1,3-Dihydroisothiazolo[4,3-*b*]pyridine 2,2-Dioxides (Pyridosultams) – Formation of 2:1 Adducts with *N*-Phenylmaleimide." *Eur. J. Org. Chem.* **2002**, 947-954.
h) Modrzejewska, H.; Wojciechowski, K. "Synthesis and reactions of 3-alkylsulfanyl-1,3-dihydro-2,1-benzisothiazole 2,2-dioxides." *Tetrahedron* **2005**, *61*, 8848-8854.

64. a) Migneault, D.; Bernstein, M. A.; Lau, C. K. "Preparation of *ortho*-hydroxyalkylanilines as *ortho*-quinone methide imine precursors via an aminoborane complex." *Can. J. Chem.* **1995**, *73*, 1506-1513.

b) Wiebe, J. M.; Caillé, A. S.; Trimble, L.; Lau, C. K. "Syntheses of Quinolines, Dihydro- and Tetrahydroquinolines via *ortho*-Quinone Methide Imine intermediate." *Tetrahedron* **1996**, *52(36)*, 11705-11724.
c) Zakrzewski, P.; Gowan, M.; Trimble, L. A.; Lau, C. K. "*ortho*-Hydroxyalkylation of Aminopyridines: A Novel Approach to Heterocycles." *Synthesis* **1999**, *11*, 1893-1902.

65. Martín, N.; Martínez-Grau, A.; Sánchez, L.; Seoane, C.; Torres, M. "The First Hetero-Diels-Alder Reaction of C_{60} with 1-Azadienes. Synthesis of Tetrahydropyrido[2',3':1,2][60]fullerene Derivatives." *J. Org. Chem.* **1998**, *63(22)*, 8074-8076.

66. Consonni, R.; Croce, P. D.; Ferraccioli, R.; La Rosa, C. "Diels-Alder reactions of *N*-sulfonyl substituted aza-*ortho*-xylylenes generated from the corresponding 1,4-dihydro-*2H*-3,1-benzoxazin-2-one derivatives." *J. Chem. Soc., Perkin Trans. I* **1996**, 1809-1814.

67. Ohno, M.; Sato, H.; Eguchi, S. "Synthesis of Fullerotetrahydroquinolines by Cycloaddition Reaction of C_{60} with Aza-*ortho*-xylylenes." *Synlett* **1999**, *2*, 207-209.

68. Li, H.; Petersen, J. L.; Wang, K. K. "Cascade Cyclizations via *N*,4-Didehydro-2-(phenylamino)pyridine Biradicals/Zwitterions Generated from Enyne-Carbodiimides." *J. Org. Chem.* **2003**, *68*, 5512-5518.

69. Lancaster, M.; Smith, D. J. H. "Preparation and Some Reactions of Benzazetidines." *J. Chem. Soc. Chem. Comm.* **1980**, 471-472.

70. a) Ikeda, M.; Matsugashita, S.; Ishibashi, H.; Tamura, Y. " Photochemical Reactions of 1,2-Dihydroquinolines." *J. Chem. Soc. Chem. Comm.* **1973**, 922-923.
b) Ikeda, M.; Matsugashita, S.; Tabusa, F.; Ishibashi, H.; Tamura, Y. "Photochemical Synthesis of 2,3-Homoindoles." *J. Chem. Soc. Chem. Comm.* **1974**, 433-434.
c) Ikeda, M.; Matsugashita, S.; Tabusa, F.; Ishibashi, H.; Tamura, Y. "Photo-isomerisation of 1-Acetyl-2-cyano-1,2-dihydroquinolines to *N*-Acetylbenzoazetines." *J. Chem. Soc. Chem. Comm.* **1975**, 575-576.

71. Hagg, R.; Wirz, J. "The Photoenolization of 2-Methylacetophenone and Related Compounds." *Helv. Chim. Acta* **1977**, *60(8)*, 2595-2607.

72. a) Mukhina, O. A.; Bhuvan Kumar, N. N.; Arisco, T. M.; Valiulin, R. A.; Metzel, G. A. Kutateladze, A. G. "Rapid Photoassisted Access to N,O,S-Polyheterocycles with Benzoazocine and Hydroquinoline Cores: Intramolecular Cycloadditions of Photogenerated Azaxylylenes." *Angew. Chem. Int. Ed.* **2011**, *50*, 9423-9428.
b) Mukhina, O. A.; Bhuvan Kumar, N. N.; Arisco, T. M.; Valiulin, R. A.; Metzel, G. A. Kutateladze, A. G. "Rapid Photoassisted Access to N,O,S-Polyheterocycles with Benzoazocine and Hydroquinoline Cores: Intramolecular Cycloadditions of Photogenerated Azaxylylenes." *Angew. Chem. Int. Ed.* **2011**, *123*, 9595-9600.

c) Bhuvan Kumar, N. N.; Mukhina, O. A.; Kutateladze, A. G. "Photoassisted Synthesis of Enantiopure Alkaloid Mimics Possessing Unprecedented Polyheterocyclic Cores." *J. Am. Chem. Soc.* **2013**, *135*, 9608-9611.
d) Nandurkar, N. S.; Bhuvan Kumar, N. N.; Mukhina, O. A.; Kutateladze, A. G. "Photoassisted Access to Enantiopure Conformationally Locked Ribofuranosylamines Spiro-Linked to Oxazolidino-Diketopiperazines." *ACS Comb. Sci.* **2013**, *15*, 73-76.
e) Cronk, W. C.; Mukhina, O. A.; Kutateladze, A. G. "Intramolecular Photoassisted Cycloadditions of Azaxylylenes and Postphotochemical Capstone Modifications via Suzuki Coupling Provide Access to Complex Polyheterocyclic Biaryls." *J. Org. Chem.* **2014**, *79*, 1235-1246.
f) Mukhina, O. A.; Cronk, W. C.; Bhuvan Kumar, N. N.; Chandra Sekhar, M.; Samanta, A.; Kutateladze, A. G. "Intramolecular Cycloadditions of Photogenerated Azaxylylenes: An Experimental and Theoretical Study." *J. Phys. Chem. A* **2014**, *118*, 10487-10496.
g) Mukhina, O. A.; Bhuvan Kumar, N. N.; Cowger, T. M.; Kutateladze, A. G. "Photoassisted Diversity-Oriented Synthesis: Accessing 2,6-Epoxyazocane (Oxamorphan) Cores." *J. Org. Chem.* **2014**, *79*, 10956-10971.
h) Bhuvan Kumar, N. N.; Kuznetsov, D. M.; Kutateladze, A. G. "Intramolecular Cycloadditions of Photogenerated Azaxylylenes with Oxadiazoles Provide Direct Access to Versatile Polyheterocyclic Ketopiperazines Containing a Spiro-oxirane Moiety." *Org. Lett.* **2015**, *17*, 438-441.
i) Umstead, W. J.; Mukhina, O. A.; Kutateladze, A. G. "Conformationally Constrained Penta(hetero)cyclic Molecular Architectures by Photoassisted Diversity-Oriented Synthesis." *Eur. J. Org. Chem.* **2015**, 2205-2213.
j) Mukhina, O. A.; Kuznetsov, D. M.; Cowger, T. M.; Kutateladze, A. G. "Amino Azaxylylenes Photogenerated from *o*-Amido Imines: Photoassisted Access to Complex Spiro-Poly-Heterocycles." *Angew. Chem. Int. Ed.* **2015**, *54*, 11516-11520.
k) Kuznetsov, D. M.; Mukhina, O. A.; Kutateladze, A. G. "Photoassisted Synthesis of Complex Molecular Architectures: Dearomatization of Benzenoid Arenes with Aza-*o*-xylylenes via an Unprecedented [2+4] Reaction Topology." *Angew. Chem. Int. Ed.* **2016**, *55*, 6988-6991.
l) Kuznetsov, D. M.; Kutateladze, A. G. "Step-Economical Photoassisted Diversity-Oriented Synthesis: Sustaining Cascade Photoreactions in Oxalyl Anilides to Access Complex Polyheterocyclic Molecular Architectures." *J. Am. Chem. Soc.* **2017**, *139*, 16584-16590.

73. a) Liu, Y.-Y.; Yu, X.-Y.; Chen, J.-R.; Qiao, M.-M.; Qi, X.; Shi, D.-Q.; Xiao, W.-J. "Visible-Light-Driven Aza-*ortho*-quinone Methide Generation for the Synthesis of Indoles in a Multicomponent Reaction." *Angew. Chem. Int. Ed.* **2017**, *56*, 9527-9531.
b) Liang, D.; Rao, L.; Xiao, C.; Chen, J.-R. "Intramolecular Hetero-Diels-Alder Reactions of Photogenerated aza-*ortho*-Quinone Methides with Aldehydes." *Org. Lett.* **2019**, *21*, 8783-8788.
c) Liang, D.; Tan, L.-P.; Xiao, W.-J.; Chen, J.-R. "Inverse-electron-demand [4+2] cycloaddition of photogenerated aza-*ortho*-quinone methides with 1,3,5-triazinanes: access to perfluoroalkylated tetrahydroquinazolines." *Chem. Commun.* **2020**, *56*, 3777-3780.

74. Li, T.-R.; Wang, Y.-N.; Xiao, W.-J.; Lu, L.-Q. "Transition-metal-catalyzed cyclization reactions using vinyl and ethynyl benzoxazinones as dipole precursors." *Tetrahedron Lett.* **2018**, *59*, 1521-1530.

75. a) Wang, C.; Tunge, J. A. "Asymmetric Cycloadditions of Palladium-Polarized Aza-*o*-xylylenes." *J. Am. Chem. Soc.* **2008**, *130*, 8118-8119.
b) Wang, C.; Pahadi, N.; Tunge, J. A. "Decarboxylative cyclizations and cycloadditions of palladium-polarized aza-*ortho*-xylylenes." *Tetrahedron* **2009**, *65*, 5102-5109.

76. a) Li, T.-R.; Tan, F.; Lu, L.-Q.; Wei, Y.; Wang, Y.-N.; Liu, Y.-Y.; Yang, Q.-Q.; Chen, J.-R.; Shi, D.-Q.; Xiao, W.-J. "Asymmetric trapping of zwitterionic intermediates by Sulphur ylides in a palladium-catalysed decarboxylation-cycloaddition sequence." *Nat. Comm.* **2014**, *5*, 5500.
b) Wei, Y.; Lu, L.-Q.; Li, T.-R.; Feng, B.; Wang, Q.; Xiao, W.-J.; Alper, H. "P,S Ligands for the Asymmetric Construction of Quaternary Stereocenters in Palladium-Catalyzed Decarboxylative [4+2] Cycloadditions." *Angew. Chem. Int. Ed.* **2016**, *55*, 2200-2204.
c) Li, M.-M.; Wei, Y.; Liu, J.; Chen, H.-W.; Lu, L.-Q.; Xiao, W.-J. "Sequential Visible-Light Photoactivation and Palladium Catalysis Enabling Enantioselective [4+2] Cycloadditions." *J. Am. Chem. Soc.* **2017**, *139*, 14707-14713.
d) Wang, Y.-N.; Wang, B.-C.; Zhang, M.-M.; Gao, X.-W.; Li, T.-R.; Lu, L.-Q.; Xiao, W.-J. "Hydrogen Bond Direction Enables Palladium-Catalyzed Branch- and Enantioselective Allylic Aminations and Beyond." *Org. Lett.* **2017**, *19*, 4094-4097.

77. Leth, L. A.; Glaus, F.; Mezza, M.; Fu, L.; Thøgersen, M. K.; Bitsch, E. A.; Jørgensen, K. A. "Decarboxylative [4+2] Cycloaddition by Synergistic Palladium and Organocatalysis." *Angew. Chem. Int. Ed.* **2016**, *55*, 15272-15276.

78. a) Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. "Cooperative N-Heterocyclic Carbene/Palladium-Catalyzed Enantioselective Umpolung Annulations." *J. Am. Chem. Soc.* **2016**, *138*, 7840-7843.
b) Guo, C.; Janssen-Müller, D.; Fleige, M.; Lerchen, A.; Daniliuc, C. G.; Glorius, F. "Mechanistic Studies on a Cooperative NHC Organocatalysis/Palladium Catalysis System: Uncovering Significant Lessons for Mixed Chiral Pd(NHC)(PR_3) Catalyst Design." *J. Am. Chem. Soc.* **2017**, *139*, 4443-4451.

79. a) Mei, G.-J.; Bian, C.-Y.; Li, G.-H.; Xu, S.-L.; Zheng, W.-Q.; Shi, F. "Catalytic Asymmetric Construction of the Tryptanthrin Skeleton via an Enantioselective Decarboxylative [4+2] Cyclization." *Org. Lett.* **2017**, *19*, 3219-3222.
b) Mei, G.-J.; Li, D.; Zhou, G.-X.; Shi, Q.; Cao, Z.; Shi, F. "A catalytic asymmetric construction of a tetrahydroquinoline-based spirooxindole framework *via* a diastereo- and enantioselective decarboxylative [4+2] cycloaddition." *Chem. Commun.* **2017**, *53*, 10030-10033.

80. Wang, C.; Li, Y.; Wu, Y.; Wang, Q.; Shi, W.; Yuan, C.; Zhou, L.; Xiao, Y.; Guo, H. "Enantioselective Construction of Tetrahydroquinazoline Motifs via Palladium-

Catalyzed [4+2] Cycloaddition of Vinyl Benzoxazinones with Sulfamate-Derived Cyclic Imines." *Org. Lett.* **2018**, *20*, 2880-2883.

81. Duan, S.; Cheng, B.; Duan, X.; Bao, B.; Li, Y.; Zhai, H. "Synthesis of *cis*-5,5a,6,10b-Tetrahydroindeno[2,1-*b*]indoles through Palladium-Catalyzed Decarboxylative Coupling of Vinyl Benzoxazinanones with Arynes." *Org. Lett.* **2018**, *20*, 1417-1420.

82. Tucker, Z. D.; Hill, H. M.; Smith, A. L.; Ashfeld, B. L. "Diverting β-Hydride Elimination of a π-Allyl Pd^{II} Carbene Complex for the Assembly of Disubstituted Indolines via a Highly Diastereoselective (4+1)-Cycloaddition." *Org. Lett.* **2020**, *22*, 6605-6609.

83. Ma, Y.-H.; Meng, F.-X.; Wang, R.-N.; Fan, Y.-X.; Su, Q.-Q.; Du, J.-Y. "Diastereoselective Palladium-Catalyzed [4+1] Cycloadditions of 4-Vinyl-1,4-dihydro-*2H*-3,1-benzoxazin-2-ones with In Situ Formed Carbenes." *Synthesis* **2022**, *54*, 499-505.

84. Wang, Q.; Qi, X.; Lu, L.-Q.; Li, T.-R.; Yuan, Z.-G.; Zhang, K.; Li, B.-J.; Lan, Y.; Xiao, W.-J. "Iron-Catalyzed Decarboxylative (4+1) Cycloadditions: Exploiting the Reactivity of Ambient Iron-Stabilized Intermediates." *Angew. Chem. Int. Ed.* **2016**, *55*, 2840-2844.

85. Wang, Q.; Liu, T.-R.; Lu, L.-Q.; Li, M.-M.; Zhang, K.; Xiao, W.-J. "Catalytic Asymmetric [4+1] Annulation of Sulfur Ylides with Copper-Allenylidene Intermediates." *J. Am. Chem. Soc.* **2016**, *138*, 8360-8363.

86. Song, J.; Zhang, Z.-J.; Gong, L.-Z. "Asymmetric [4+2] Annulation of C1 Ammonium Enolates with Copper Allenylidenes." *Angew. Chem. Int. Ed.* **2017**, *56*, 5212-5216.

87. Lu, X.; Ge, L.; Cheng, C.; Chen, J.; Cao, W.; Wu, X. "Enantioselective Cascade Reaction for Synthesis of Quinolinones through Synergistic Catalysis Using Cu-Pybox and Chiral Benzotetramisole as Catalysts." *Chem. Eur. J.* **2017**, *23*, 7689-7693.

88. Jin, J.-H.; Wang, H.; Yang, Z.-T.; Yang, W.-L.; Tang, W.; Deng, W.-P. "Asymmetric Synthesis of 3,4-Dihydroquinolin-2-ones via a Stereoselective Palladium-Catalyzed Decarboxylative [4+2] Cycloaddition." *Org. Lett.* **2018**, *20*, 104-107.

89. a) Ito, Y.; Miyata, S.; Nakatsuka, M.; Saegusa, T. "Synthesis of Nitrogen-Containing Polycycles on the Basis of a New Method of *o*-Quinone Methide Imine Generation." *J. Am. Chem. Soc.* **1981**, *103*, 5250-5251.
    b) Ito, Y.; Nakajo, E.; Nakatsuka, M.; Saegusa, T. "A NEW APPROACH TO GEPHYROTOXIN." *Tetrahedron Lett.* **1983**, *24(28)*, 2881-2884.
    c) Ito, Y.; Nakajo, E.; Saegusa, T. "Intermolecular Cycloadditions of *o*-Quinone Methide *N*-Alkylimines with Electron Deficient Olefins." *Syn. Comm.* **1986**, *16(9)*, 1073-1080.

90. a) Caillé, A. S.; Trimble, L.; Berthelette, C.; Lau, C. K. "*ortho*-Quinone Methide Imine: Generation and Diels-Alder Reaction at Room Temperature" *Synlett.* **1996**, 699-671.

b) Zakrzewski, P.; Gowan, M.; Trimble, L. A.; Lau, C. K. "*ortho*-Hydroxyalkylation of Aminopyridines: A Novel Approach to Heterocycles." *Synthesis* **1999**, *11*, 1893-1902.

91. Fan, J.; Wan, C.; Sun, G.; Wang, Z. "Cascade Synthesis of 3-Quinolinecarboxylic Ester via Benzylation/Propargylation – Cyclization." *J. Org. Chem.* **2008**, *73*, 8608-8611.

92. Robertson, F. J.; Kenimer, B. D.; Wu, J. "Direct annulation and alkylation of indoles with 2-aminobenzyl alcohols catalyzed by TFA." *Tetrahedron* **2011**, *67*, 4327-4332.

93. a) Li, G.; Liu, H.; Lv, G.; Wang, Y.; Fu, Q.; Tang, Z. "Enantioselective Organocatalytic Transfer Hydrogenation of 1,2-Dihydroquinoline through Formation of Aza-*o*-xylylene." *Org. Lett.* **2015**, *17*, 4125-4127.
b) Liao, H.-H.; Chatupheeraphat, A.; Hsiao, C.-C.; Atodiresei, I.; Rueping, M. "Asymmetric Brøsted Acid Catalyzed Synthesis of Triarylmethanes – Construction of Communesin and Spiroindoline Scaffolds." *Angew. Chem. Int. Ed.* **2015**, *54*, 15540-15544.
c) Chatupheeraphat, A.; Liao, H.-H.; Mader, S.; Sako, M.; Sasai, H.; Atodiresei, I.; Rueping, M. "Asymmetric Brøsted Acid Catalyzed Substitution of Diaryl Methanols with Thiols and Alcohols for the Synthesis of Chiral Thioethers and Ethers." *Angew. Chem. Int. Ed.* **2016**, *55*, 4803-4807.
d) Kretzschmar, M.; Hodík, T.; Schneider, C. "Brøsted Acid Catalyzed Addition of Enamides to *ortho*-Quinone Methide Imines – An Efficient and Highly Enantioselective Synthesis of Chiral Tetrahydroacridines." *Angew. Chem. Int. Ed.* **2016**, *55*, 9788-9792.
e) Hodík, T.; Schneider, C. "Brøsted acid-catalyzed, enantioselective synthesis of 1,4-dihydroquionline-3-carboxylates *via in situ* generated *ortho*-quinone methide imines." *Org. Biomol. Chem.* **2017**, *15*, 3706.
f) Yu, Y.; Li, J.; Jiang, L.; Zhang, J.-R.; Zu, L. "Catalytic Enantioselective Aza-pinacol Rearrangement." *Angew. Chem. Int. Ed.* **2017**, *56*, 9217-9221.
g) Yu, Y.; Li, J.; Jiang, L.; Zhang, J.-R.; Zu, L. "Catalytic Enantioselective Aza-pinacol Rearrangement." *Angew. Chem. Int. Ed.* **2017**, *129*, 9345-9349.
h) Hodík, T.; Schneider, C. "A Highly Enantio- and Diastereoselective Synthesis of Spirocyclic Dihydroquinolones via Domino Michael Addition-Lactamization of *ortho*-Quinone Methide Imines." *Chem. Eur. J.* **2018**, *24*, 18082-18088.
i) Liao, H.-H.; Hsiao, C.-C.; Atodiresei, I.; Rueping, M. "Multiple Hydrogen-Bond Activation in Asymmetric Brøsted Acid Catalysis." *Chem. Eur. J.* **2018**, *24*, 7718-7723.
j) Kretzschmar, M.; Hofmann, F.; Moock, D.; Schneider, C. "Intramolecular Aza-Diels-Alder Reactions of *ortho*-Quinone Methide Imines: Rapid, Catalytic, and Enantioselective Assembly of Benzannulated Quinolizidines." *Angew. Chem. Int. Ed.* **2018**, *57*, 4774-4778.
k) Yue, C.; Na, F.; Fang, X.; Cao, Y.; Antilla, J. C. "Chiral Phosphoric Acid-Catalyzed Asymmetric Synthesis of Hetero-triarylmethanes from Racemic Indolyl Alcohols." *Angew. Chem. Int. Ed.* **2018**, *57*, 11004-11008.
l) Li, L.-Z.; Wang, C.-S.; Guo, W.-F.; Mei, G.-J.; Shi, F. "Catalytic Asymmetric [4+2] Cycloaddition of in Situ Generated *o*-Quinone Methide Imines with *o*-Hydroxystyrenes: Diastereo- and Enantioselective Construction of Tetrahydroquinoline Frameworks." *J. Org. Chem.* **2018**, *83*, 614-623.

m) Zhou, J.; Xie, H. "A Brøsted acid-promoted asymmetric intramolecular allylic amination of alcohols." *Org. Biomol. Chem.* **2018**, *16*, 380-383.
n) Hofmann, F.; Gärtner, C.; Kretzschmar, M.; Schneider, C. "Asymmetric Synthesis of Fused Tetrahydroquinolines via Intramolecular Aza-Diels-Alder Reaction of *ortho*-Quinone Methide Imines." *Synthesis* **2022**, *54*, 1055-1080.

94. Luo, M.; Chen, J.; Yu, L.; Wei, W. "Concise Synthesis of Polycyclic Indoline Scaffolds through an In^{III}-Catalyzed Formal [4+2] Annulation of 2,3-Disubstituted Indoles with *o*-Aminobenzyl Alcohols." *Eur. J. Org. Chem.* **2017**, 2652-2660.

95. Gharpure, S. J.; Vishwakarma, D. S. "Lewis Acid Catalyzed Intramolecular [4+2] Cycloaddition of In Situ Generated Aza-Quinone Methides for the Stereoselective Synthesis of Furo/pyrano[3,2-*c*]tetrahydroquinolines." *Eur. J. Org. Chem.* **2020**, 6887-6891.

96. a) Strekowski, L.; Wydra, R. L.; Cegla, M. T.; Czarny, A.; Harden, D. B.; Patterson, S. E.; Battiste, M. A.; Coxon, J. M. "An Unusual Base-Mediated Cyclization of Ketimines Derived from 2-(Trifluoromethyl)aniline That Involves the Trifluoromethyl Group: An Expedient Route to 2-Arylquinolines." *J. Org. Chem.* **1990**, *55(16)*, 4777-4779.
b) Strekowski, L.; Mokrosz, J. L.; Honkan, V. A.; Czarny, A.; Cegla, M. T.; Wydra, R. L.; Patterson, S. E.; Schinazi, R. F. "Synthesis and Quantitative Structure-Activity Relationship Analysis of 2-(Aryl or Heteroaryl)quinoline-4-amines, a New Class of Anti-HIV-1 Agents." *J. Med. Chem.* **1991**, *34*, 1739-1746.
c) Strekowski, L.; Patterson, S. E.; Janda, L.; Wydra, R. L.; Harden, D. B.; Lipowska, M.; Cegla, M. T. "Further Studies on the Cyclization of Aromatic Azomethines Ortho-Substituted with a Trifluoromethyl Group: Synthesis of 2,4-Di- or 2,3,4-Trisubstituted Quinolines." *J. Org. Chem.* **1992**, *57*, 196-201.

97. a) Hojjat, M.; Kiselyov, A. S.; Strekowski, L. "An Activated Trifluoromethyl Group as a Novel Synthon for a Substituted Vinyl Function: Facile Synthesis of 2-(Substituted 1-Alkenyl)anilines." *Syn. Comm.* **1994**, *24(2)*, 267-272.
b) Strekowski, L.; Kiselyov, A. S.; Hojjat, M. "The *o*-Amino-Trifluoromethyl Functionality as a Novel Synthon for 4-Fluoroquinolines." *J. Org. Chem.* **1994**, *59*, 5886-5890.

98. [4+2] Cycloadditions:
a) Avemaria, F.; Vanderheiden, S.; Bräse, S. "The aza-xylylene Diels-Alder approach for the synthesis of naturally occurring 2-alkyl tetrahydroquinolines." *Tetrahedron* **2003**, *59*, 6785-6796.
b) Lee, A.; Younai, A.; Price, C. K.; Izquierdo, J.; Mishra, R. K.; Scheidt, K. A. "Enantioselective Annulations for Dihydroquinolones by in Situ Generation of Azolium Enolates." *J. Am. Chem. Soc.* **2014**, *136*, 10589-10592.
c) Jiang, S.-P.; Lu, W.-Q.; Liu, Z.; Wang, G.-W. "Synthesis of Fullerotetrahydroquinolines via [4+2] Cycloaddition Reaction of [60]Fullerene with in Situ Generated Aza-*o*-quinone Methides." *J. Org. Chem.* **2018**, *83*, 1959-1968.

d) Zheng, Y.; Tu, L.; Li, N.; Huang, R.; Feng, T.; Sun, H.; Li, Z.; Liu, J. "Inverse-Electron-Demand [4+2]-Cycloaddition of 1,3,5-triazinanes: Facile Approaches to Tetrahydroquinazolines." *Adv. Synth. Catal.* **2019**, *361*, 44-48.
e) Lei, L.; Yao, Y.-Y.; Jiang, L.-J.; Lu, X.; Liang, C.; Mo, D.-L. "Synthesis of Furo[3,2-*b*]quinolines and Furo[2,3-*b*:4,5-*b'*]diquinolines through [4+2] Cycloaddition of Aza-*o*-Quinone Methides and Furans." *J. Org. Chem.* **2020**, *85*, 3059-3070.
f) Lei, L.; Liang, Y.-F.; Liang, C.; Qin, J.-K.; Pan, C.-X.; Su, G.-F.; Mo, D.-L. "Copper(I)-catalyzed [4+2] cycloaddition of aza-*ortho*-quinone methides with bicyclic alkenes." *Org. Biomol. Chem.* **2021**, *19*, 3379-3383.
g) Ji, H.; He, C.; Gao, H.; Fu, W.; Xu, J. "DBU-Promoted Formal [4+2] Annulation Reactions of *o*-Chloro-methyl Anilines with Azlactones." *Synthesis* **2021**, *53*, 1349-1355.

99. [4+1] Cycloadditions:
a) Yang, Q.-Q.; Xiao, C.; Lu, L.-Q.; An, J.; Tan, F.; Li, B.-J.; Xiao, W.-J. "Synthesis of Indoles through Highly Efficient Cascade Reactions of Sulfur Ylides and *N*-(*ortho*-Chloromethyl)aryl Amides." *Angew. Chem. Int. Ed.* **2012**, *51*, 9137-9140.
b) Huang, H.; Yang, Y.; Zhang, X.; Zeng, W.; Liang, Y. "Transition-metal-free approach to synthesis of indolines from *N*-(*ortho*-chloromethyl)aryl amides and indonium ylides." *Tetraheron Lett.* **2013**, *54*, 6049-6052.
c) Dou, X.; Yao, W.; Zhou, B.; Lu, Y. "Asymmetric synthesis of 3-spirocyclopropyl-2-oxindoles *via* intramolecular trapping of chiral aza-*ortho*-xylylenes." *Chem. Commun.* **2013**, *49*, 9224-9226.
d) Yang, Q.-Q.; Wang, Q.; An, J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. "Construction of Optically Active Indolines by Formal [4+1] Annulation of Sulfur Ylides and *N*-(*ortho*-Chloromethyl)aryl Amides." *Chem. Eur. J.* **2013**, *19*, 8401-8404.
e) Todd Hovey, M.; Check, C. T.; Sipher, A. F.; Scheidt, K. A. "N-Heterocyclic-Carbene-Catalyzed Synthesis of 2-Aryl Indoles." *Angew. Chem. Int. Ed.* **2014**, *53*, 9603-9607.
f) Kuang, Y.; Shen, B.; Dai, L.; Yao, Q.; Liu, X.; Lin, L.; Feng, X. "Diastereodivergent asymmetric Michael-alkylation reactions using chiral *N,N'*-dioxide/metal complexes." *Chem. Sci.* **2018**, *9*, 688-692.
g) Zhang, X.; Pan, Y.; Liang, P.; Ma, X.; Jiao, W.; Shao, H. "An Effective Method for the Synthesis of 1,3-Dihydro-*2H*-indazoles via N-N Bond Formation." *Adv. Synth. Catal.* **2019**, *361*, 5552-5557.
h) Gui, H.-Z.; Wu, X.-Y.; Wei, Y.; Shi, M. "A Formal Condensation and [4+1] Annulation Reaction of 3-Isothiocyanato Oxindoles with Aza-*o*-Quinone Methides." *Adv. Synth. Catal.* **2019**, *361*, 5466-5471.
i) Jong, J. A. W.; Bao, X.; Wang, Q.; Zhu, J. "Formal [4+1] Cycloaddition of *o*-Aminobenzyl Chlorides with Isocyanides: Synthesis of 2-Amino-3-Substituted Indoles." *Helv. Chim. Acta* **2019**, *102*, e1900002.
j) Hua, T.-B.; Chao, F.; Wang, L.; Yan, C.-Y.; Xiao, C.; Yang, Q.-Q.; Xiao, W.-J. "Tandem Phospha-Michael Addition/*N*-Acylation/Intramolecular Wittig Reaction of aza-*o*-Quinone Methides: Approaches to 2,3-Disubstituted Indoles." *Adv. Synth. Catal.* **2020**, *362*, 2615-2619.

k) Yan, X.; Liu, C.-F.; An, X.-T.; Ge, X.-M.; Zhang, Q.; Pang, L.-H.; Bao, X.; Fan, C.-A. "Copper-Catalyzed (4+1) Cascade Annulation of Terminal Alkynes with 2-(Tosylmethyl)anilines: Synthesis of 2,3-Disubstituted Indoles." *Org. Lett.* **2021**, *23*, 8905-8909.
l) Kawai, K.; Uno, H.; Fujimoto, D.; Shibata, N. "Transition-Metal Free Catalytic Synthesis of Trifluoromethyl Indolines by [4+1] Cycloaddition of Trifuloromethyl Benzoxazinones with Sulfur Ylides." *Helv. Chim. Acta* **2021**, *104*, e2000217.

100. [4+3] Cycloadditions:
a) Zhan, G.; Shi, M.-L.; He, Q.; Du, W.; Chen, Y.-C. "[4+3] Cycloadditions with Bromo-Substituted Morita-Baylis-Hillman Adducts of Isatins and *N*-(*ortho*-Chloromethyl)aryl Amides." *Org. Lett.* **2015**, *17*, 4750-4753.
b) Zhi, Y.; Zhao, K.; Shu, T.; Enders, D. "Synthesis of Benzotriazepine Derivatives via [4+3] Cycloaddition of Aza-*o*-quinone Methide Intermediates and Azomethine Imines." *Synthesis* **2016**, *48*, 238-244.
c) Wang, L.; Li, S.; Blümel, M.; Philipps, A. R.; Wang, A.; Puttreddy, R.; Rissanen, K.; Enders, D. "Asymmetric Synthesis of Spirobenzazepinones with Atroposelectivity and Spiro-1,2-Diazepinones by NHC-Catalyzed [3+4] Annulation Reactions." *Angew. Chem. Int. Ed.* **2016**, *55*, 11110-1114.
d) Wang, L.; Li, S.; Blümel, M.; Philipps, A. R.; Wang, A.; Puttreddy, R.; Rissanen, K.; Enders, D. "Asymmetric Synthesis of Spirobenzazepinones with Atroposelectivity and Spiro-1,2-Diazepinones by NHC-Catalyzed [3+4] Annulation Reactions." *Angew. Chem. Int. Ed.* **2016**, *128*, 11276-11280.
e) Liu, J.-Y.; Lu, H.; Li, C.-G.; Liang, Y.-M.; Xu, P.-F. "Lewis Base and Brøsted Base Dual-Catalyzed Formal [4+3] Cycloaddition Reaction: Synthesis of Aza-Spirocycloheptane Oxindole." *Synlett* **2016**, *27*, 1287-1291.
f) Guo, Z.; Jia, H.; Liu, H.; Wang, Q.; Huang, J.; Guo, H. "A [4+3] Annulation Reaction of aza-*o*-Quinone Methides with Arylcarbohydrazonoyl Chlorides for Synthesis of 2,3-Dihydro-*1H*-benzo[*e*][1,2,4]triazepines." *Org. Lett.* **2018**, *20*, 2939-2943.
g) Meng, Z.; Yang, W.; Zheng, J. "[4+3]-Cycloaddition of aza-*o*-quinone methides and azomethine imines to make 1,2,4-triazepines." *Tetrahedron Lett.* **2019**, *60*, 1758-1762.
h) Wang, X.; Li, Z.; Feng, C.; Zhen, Q.; Guo, M.; Yao, Y.; Zou, X.; Wang, P.; Hou, Y.; Gong, P. "A [4+3] Cycloaddition Reaction of Aza-*ortho*-quinone Methides with C,N-Cyclic Azomethine Imines for Synthesis of 1,2,4-Triazepines." *Synlett* **2021**, *32*, 2090-2096.
i) Zhang, L.; Fang, L.; Huang, H.; Wang, C.; Gao, F.; Wang, Z. "Synthesis of Benzo[*e*][1,4]thiazepines by Base-Induced Formal [4+3] Annulation Reaction of Aza-*o*-quinone Methides and Pyridinium 1,4-Zwitterionic Thiolates." *J. Org. Chem.* **2021**, *86*, 18156-18163.
j) Wang, C.-C.; Liu, X.-H.; Wang, X.-L.; Cui, H.-P.; Ma, Z.-W.; Ding, D.; Liu, J.-T.; Meng, L.; Chen, Y.-J. "Synthesis of Functionalized 4,1-Benzothiazepines via a [4+3] Annulation between Aza-*o*-Quinone Methides and Pyridinium 1,4-Zwitterionic Thiolates." *Adv. Synth. Catal.* **2022**, *364*, 296-301.

101. [3+2] Cycloadditions:
Jia, H.; Liu, H.; Guo, Z.; Huang, J.; Guo, H. "Tandem [3+2] Cycloaddition/1,4-Addition Reaction of Azomethine Ylides and Aza-*o*-quinone Methides for Asymmetric Synthesis of Imidazolidines." *Org. Lett.* **2017**, *19*, 5236-5239.

102. 1,4-Additions:
a) Liu, X.; Wang, K.; Guo, W.; Liu, Y.; Li, C. "An organic-base catalyzed asymmetric 1,4-addition of tritylthiol to *in situ* generated aza-*o*-quinone methides at the H_2O/DCM interface." *Chem. Commun.* **2019**, *55*, 2668-2671.
b) Liu, R.; Wei, Y.; Shi, M. "Rhodium(III)-Catalyzed C-H Benzylation of Indole's C3 Position with Aza-*o*-Quinone Methides." *Adv. Synth. Catal.* **2020**, *362*, 3649-3654.

103. a) Pang, X.; Lou, Z.; Li, M.; Wen, L.; Chen, C. "Tandem Arylation/Friedel-Crafts Reactions of *o*-Acylanilines with Diaryliodonium Salts: A Modular Synthesis of Acridine Derivatives." *Eur. J. Org. Chem.* **2015**, 3361-3369.
b) Butin, A. V.; Smirnov, S. K.; Stroganova, T. A.; Bender, W.; Krapivin, G. D. "Simple route to 3-(2-indolyl)-1-propanones via a furan recyclization reaction." *Tetrahedron* **2007**, *63*, 474-491.

Experimental

4.1 General Information

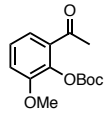
In reactions where water was not present as a solvent, reagent, or byproduct, glassware was flame dried, and the reactions were carried out under an inert atmosphere of nitrogen. Reactions were monitored by analytical thin-layer chromatography on EMD silica gel 60 F254 plates; visualization was effected 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 pressure of approximately 2 mmHg.

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

^{1}H-NMR spectra were recorded at 400, 500, or 600 MHz instruments with the solvent resonance of $CDCl_3$ (7.26 ppm). ^{13}C-NMR spectra were recorded at 500 or 600 MHz instruments with a solvent resonance of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded on an FTIR-8300 Fourier transform infrared spectrometer with neat sample. High resolution mass spectra (HRMS) were obtained by electrospray ionization/time-of-flight experiments.

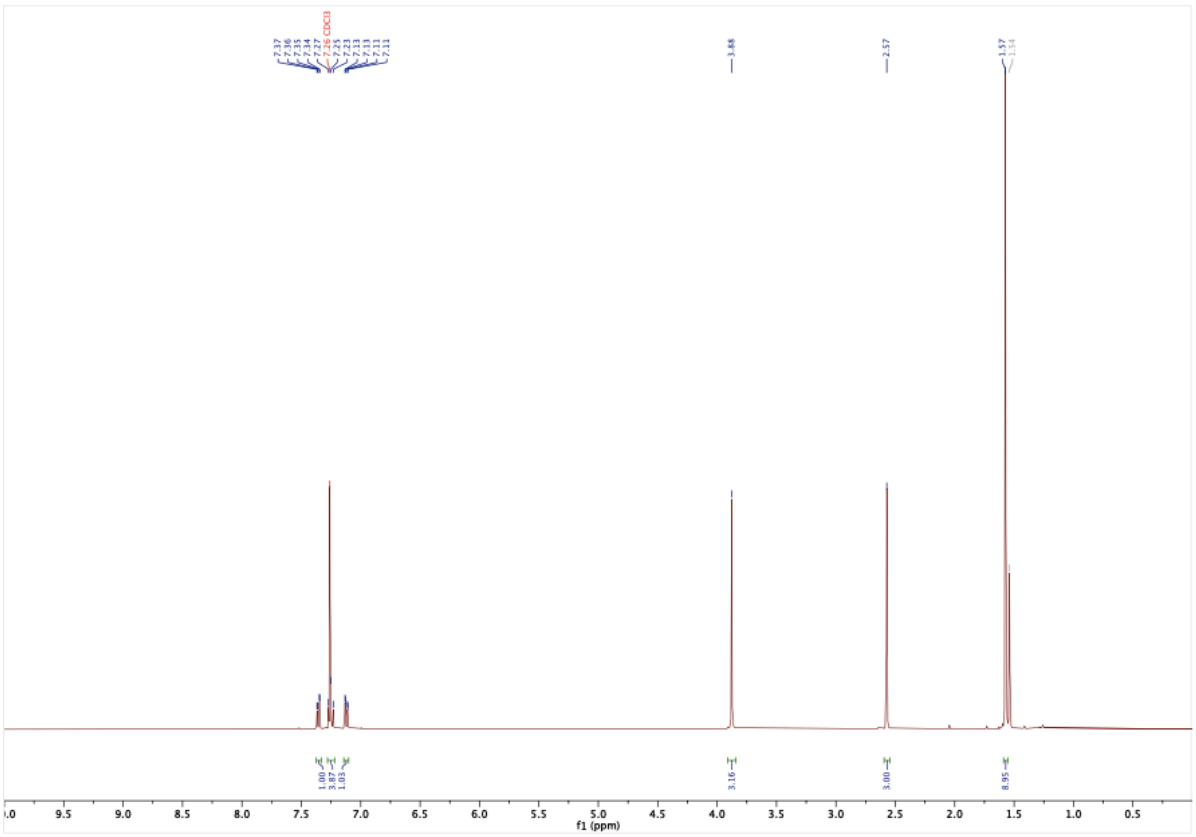
4.2 Synthesis of Boc-Protected Acetophenones

4.2.1 General Procedure A



35a

To a 100 mL round-bottom flask, charged with acetophenone (2.7 g, 20 mmol) in THF (40 mL, 0.2 M) was added 60% NaH (0.53 g, 1.1 equivalent) at 0 °C, then di-*tert*-butyl dicarbonate (4.8 g, 1.1 equivalent) was added. The reaction was slowly warm to room temperature overnight. The completion of reaction is analyzed by TLC. The reaction mixture was quenched with 0.1 M HCl (40 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (ethyl acetate–hexane, 1:9) to afford the corresponding Boc-protected acetophenone (**35a**, 3.6 g, 86% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 7.9, 1.5 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.12 (dd, J = 8.2, 1.5 Hz, 1H), 3.88 (s, 3H), 2.57 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.76, 152.22, 151.04, 139.39, 132.43, 126.45, 121.21, 116.15, 84.03, 56.50, 30.35, 27.79. HRMS (ESI+) m/z calculated for $C_{14}H_{18}O_5$ $[M+Na]^+$: 289.1052; found 289.1051.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7.36
7.35
7.34
7.27
7.26
CDCl3
7.25
7.23
7.13
7.12
7.11
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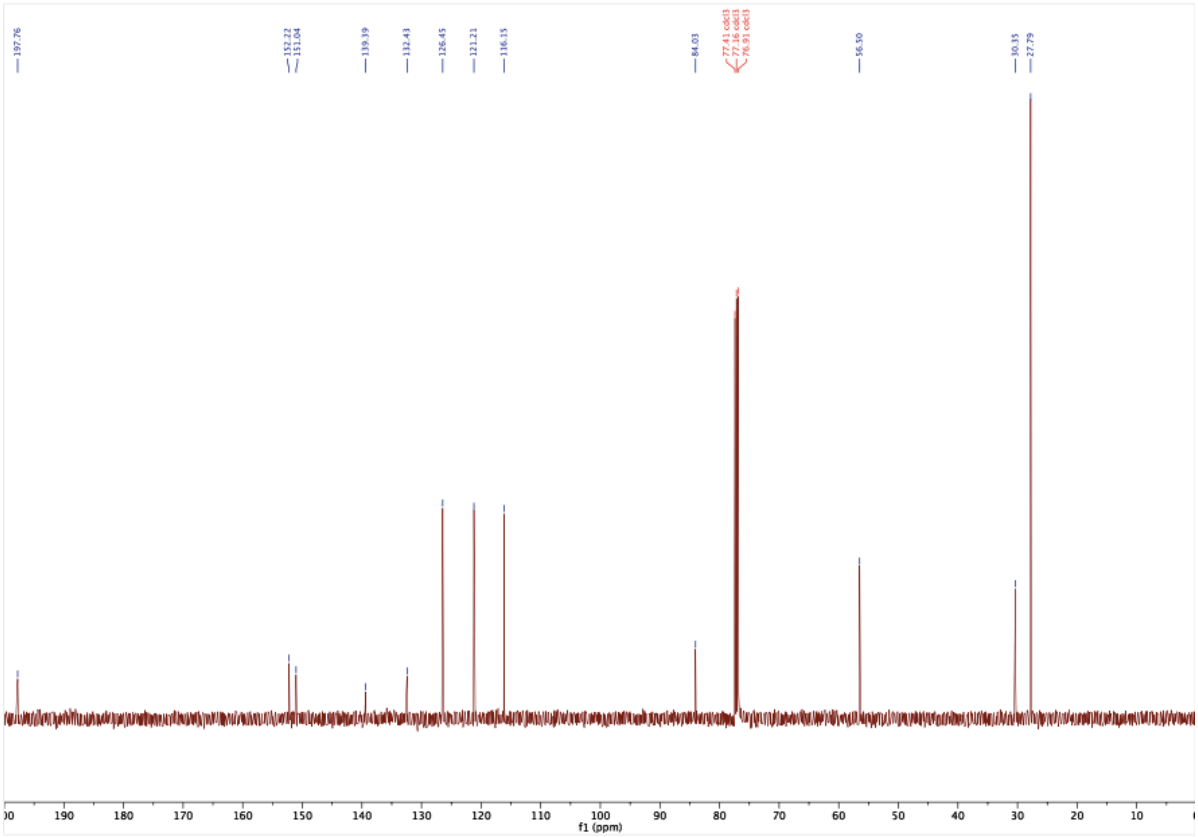
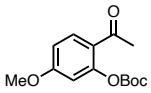
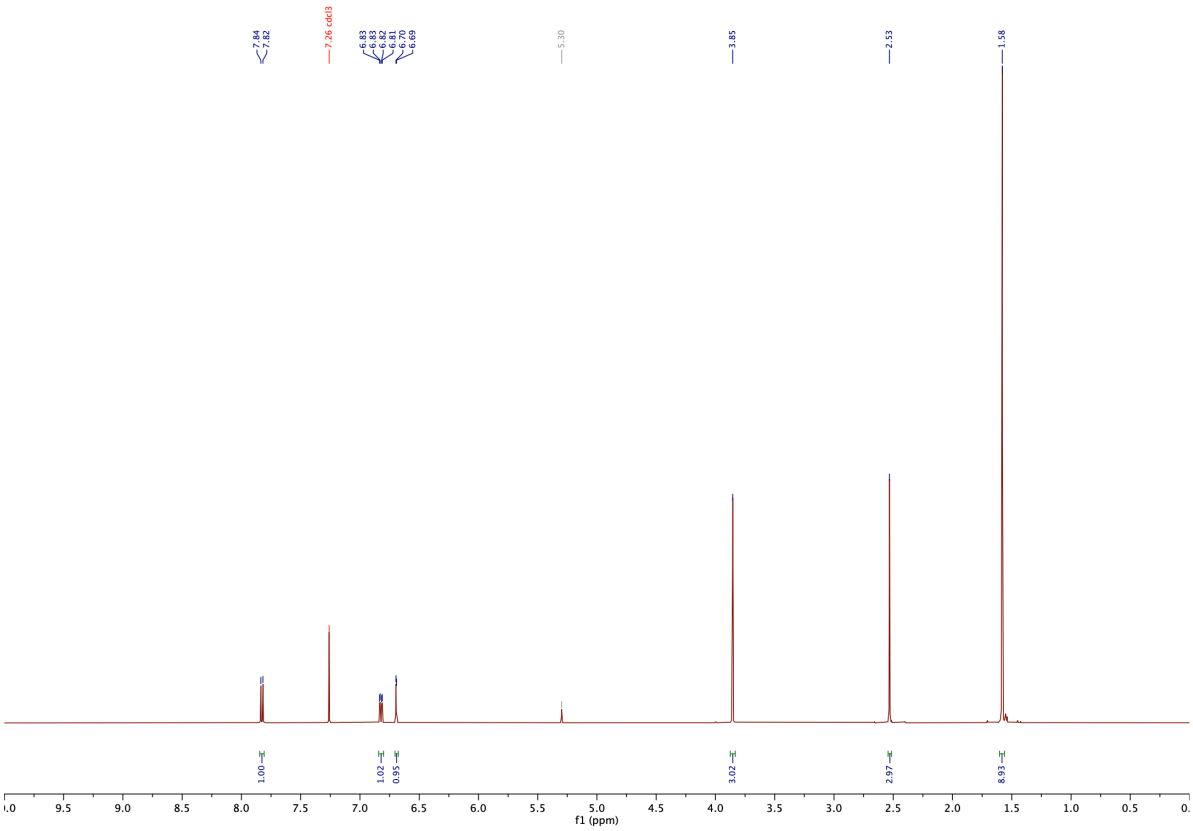
3.87
1.03
3.16
3.00
8.95
f1 (ppm)


197.76
152.22
151.04
139.39
132.43
126.45
121.21
116.15
84.03
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
56.50
30.35
27.79
f1 (ppm)



35b

Compound **35b** was synthesized according to general procedure A: (ethyl acetate–hexane, 1:9), 80% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.8 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 3H), 2.53 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.91, 163.87, 151.73, 151.49, 132.51, 123.54, 111.97, 109.17, 84.17, 55.87, 29.34, 27.87. HRMS (ESI+) m/z calculated for $C_{14}H_{18}O_5$ $[M+Na]^+$: 289.1052; found 289.1051.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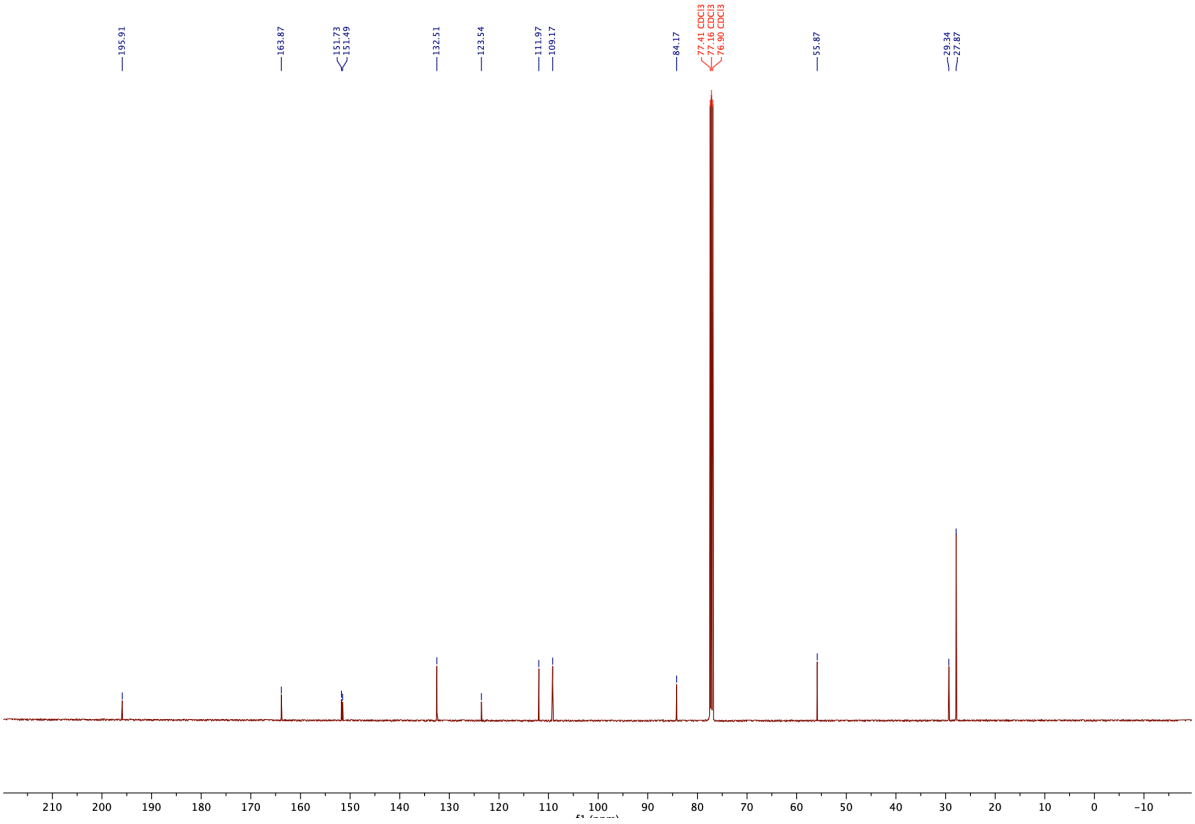
7.82
7.26 cdcl3
6.83
6.83
6.82
6.82
6.81
6.70
6.69
5.30
3.85
2.53
1.58
1.00
1.02
0.95
3.02
2.97
8.93
f1 (ppm)


195.91
163.87
151.73
151.49
132.51
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77.41 CDCl3
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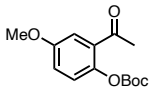
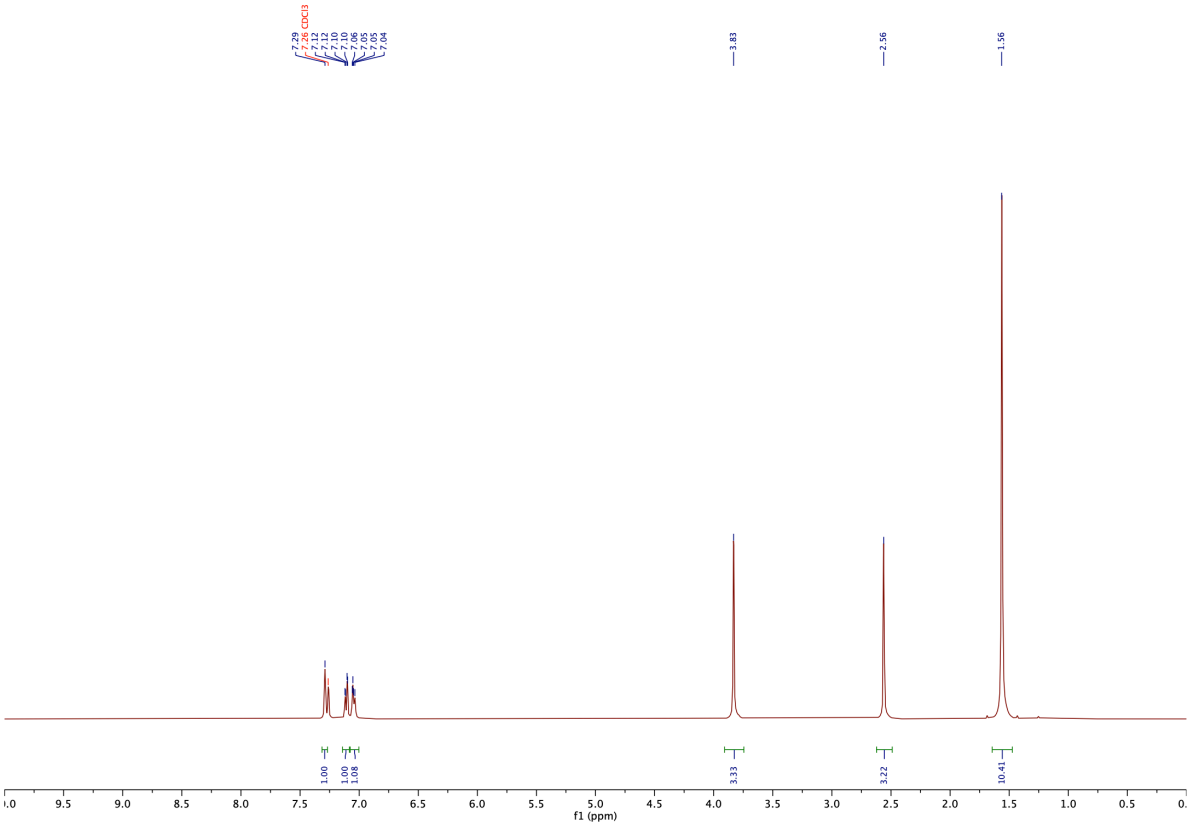
76.90 CDCl3
55.67
29.34
27.87



35c

Compound **35c** was synthesized according to general procedure A: (ethyl acetate–hexane, 1:9), 80% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (s, 1H), 7.11 (dd, J = 8.9, 2.4 Hz, 1H), 7.05 (dd, J = 7.0, 4.2 Hz, 2H), 3.83 (s, 3H), 2.56 (s, 3H), 1.56 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 197.41, 157.30, 152.06, 143.31, 131.67, 124.65, 119.18, 114.56, 84.11, 55.95, 29.85, 27.84. HRMS (ESI+) m/z calculated for $C_{14}H_{18}O_5$ $[M+Na]^+$: 289.1052; found 289.1048.


7.29
7.26 CDCl3
7.12
7.12
7.10
7.10
7.06
7.05
7.04
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2.56
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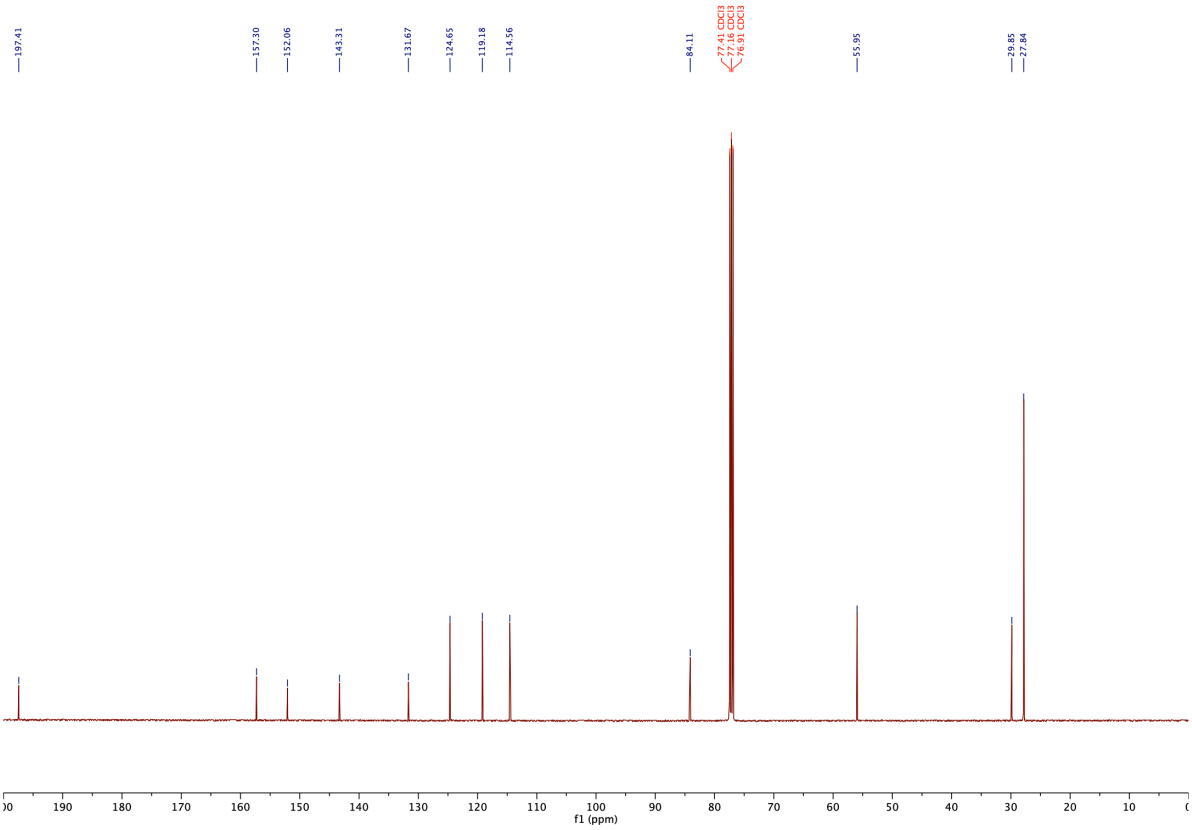
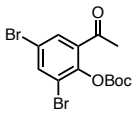
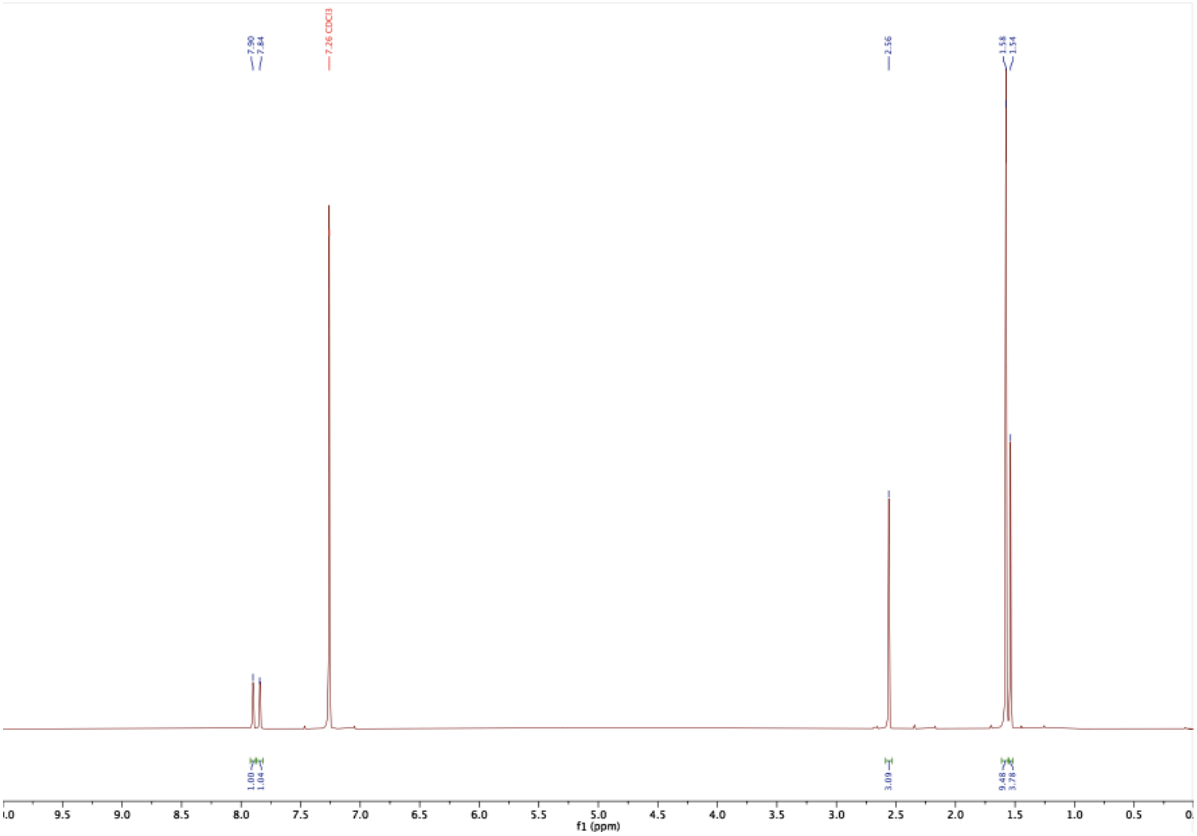
1.08
3.33
3.22
10.41
f1 (ppm)

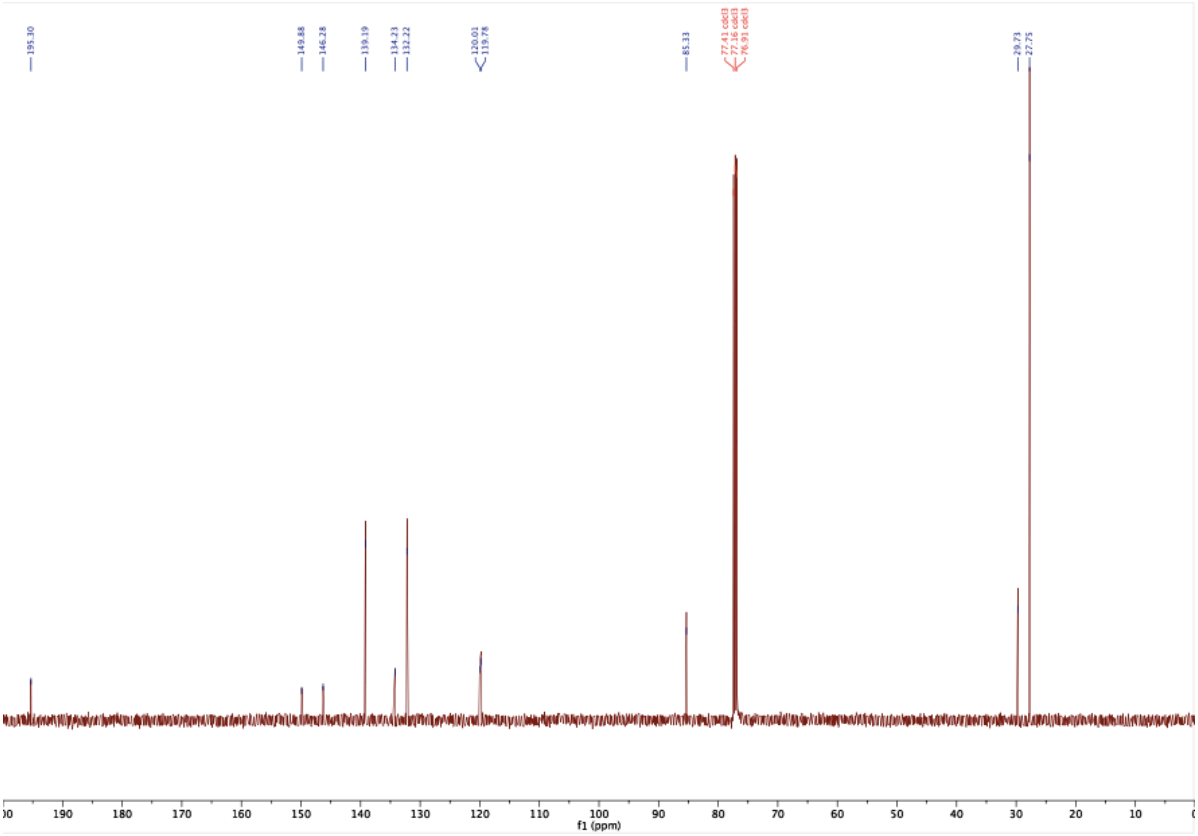

197.41
157.30
152.06
143.31
131.67
124.65
119.18
114.56
84.11
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
55.95
29.85
27.84
f1 (ppm)



35d

Compound **35d** was synthesized according to general procedure A: (ethyl acetate–hexane, 1:9), 80% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.84 (s, 1H), 2.56 (s, 3H), 1.58 (s, 9H), 1.54 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.30, 149.88, 146.28, 139.19, 134.23, 132.22, 120.01, 119.78, 85.33, 29.73, 27.75. HRMS (ESI+) m/z calculated for $C_{13}H_{14}Br_2O_4$ $[M+Na]^+$: 416.9137; found 416.9134.


7.90
7.84
7.26 CDCl3
2.56
1.58
1.54
1.00
1.04
3.09
9.48
3.78
f1 (ppm)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146.28
139.19
134.23
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120.01
119.76
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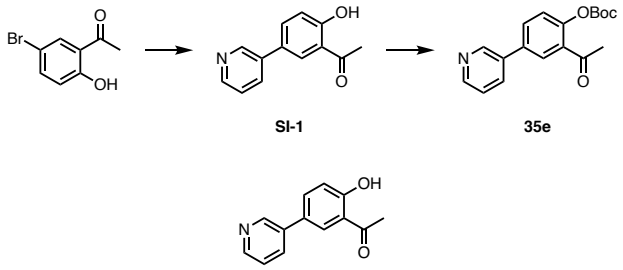
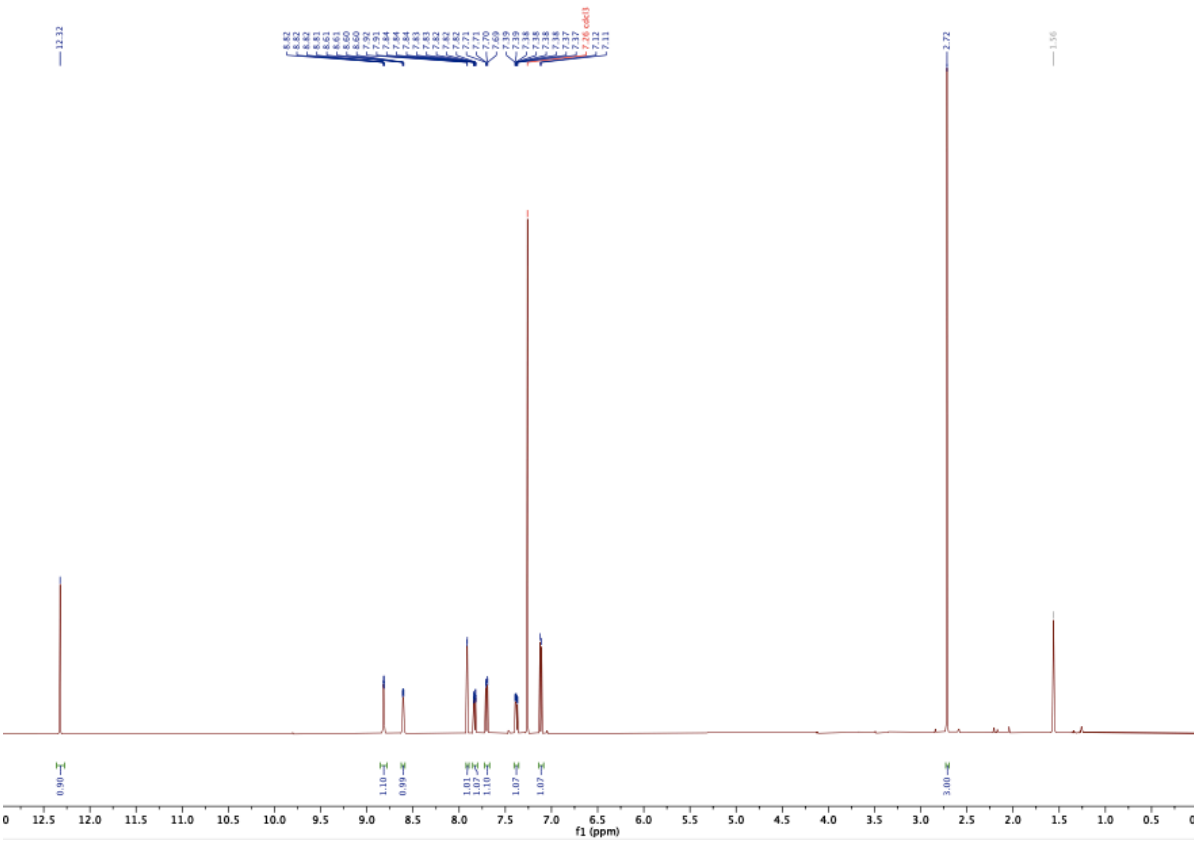
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
29.73
27.75
f1 (ppm)



SI-1

To a Schlenk flask containing a magnetic stir bar was added 5'-bromo-2'-hydroxyacetophenone (1.0 g, 4.8 mmol) and purged with N_2. To the flask was added a solution of $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol, 2.5 mol%) in N_2-degassed dimethoxyethane (8 mL, 0.015 M) and aqueous Na_2CO_3 (2.2 g, 21 mmol, 4.0 equivalent, 2 M in N_2-degassed d.I. H_2O solution), and purged with N_2. The resultant solution was stirred at room temperature for 5 minutes, then a slurry of 3-pyridinylboronic acid (0.79 g, 6.4 mmol, 1.25 equivalent) in N_2-degassed EtOH (8 mL, 0.81 M) was added. The flask was purged with N_2 and the mixture was heated to 90 °C and stirred at 90 °C overnight. The completion of reaction is analyzed by TLC. The solution was cooled to room temperature and filtered through a pad of Celite, washed with DCM (30 mL). The filtrate was washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (1% TEA in ethyl acetate-hexane, 1:3) to yield product **SI-1** (0.80 g, 4.2 mmol, 88% isolated yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.32 (s, 1H), 8.82 (dd, J = 2.5, 0.9 Hz, 1H), 8.61 (dd, J = 4.8, 1.6 Hz, 1H), 7.91 (d, J = 2.3 Hz, 1H), 7.83 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.70 (dd, J = 8.6, 2.3 Hz, 1H), 7.38 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 2.72 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.49, 162.47, 148.55, 148.00, 135.56, 135.21, 133.99, 129.23, 128.95, 123.71, 120.06, 119.47, 26.82. HRMS (ESI+) m/z calculated for $C_{13}H_{11}NO_2$ $[M+H]^+$: 214.0868; found 214.0872.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8.82
8.82
8.82
8.81
8.61
8.61
8.60
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7.91
7.84
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7.83
7.83
7.82
7.82
7.72
7.71
7.70
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7.39
7.39
7.38
7.38
7.38
7.37
7.26 cdcl3
7.12
7.11
2.72
1.56
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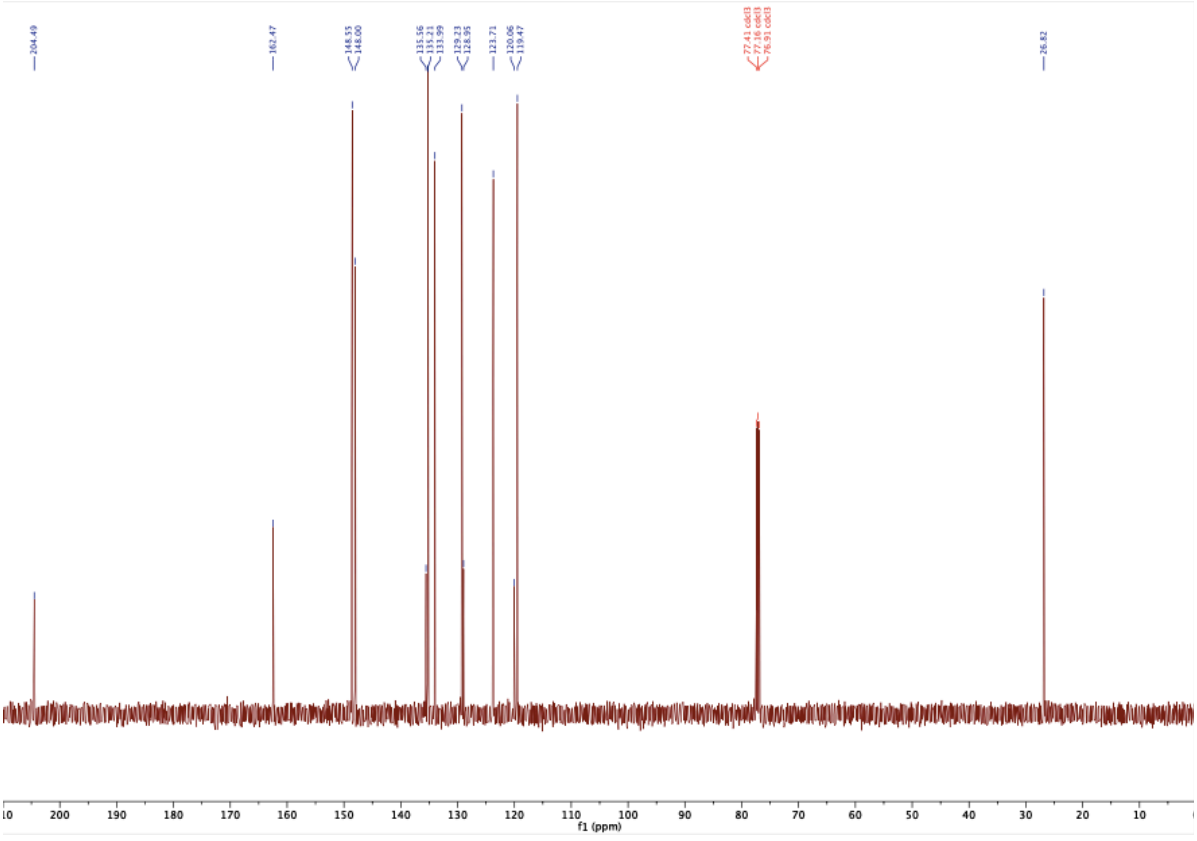
1.10
0.99
1.01
1.07
1.10
1.07
1.07
3.00
f1 (ppm)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162.47
146.55
148.00
135.56
133.21
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128.23
126.95
123.71
120.06
119.47
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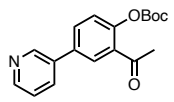
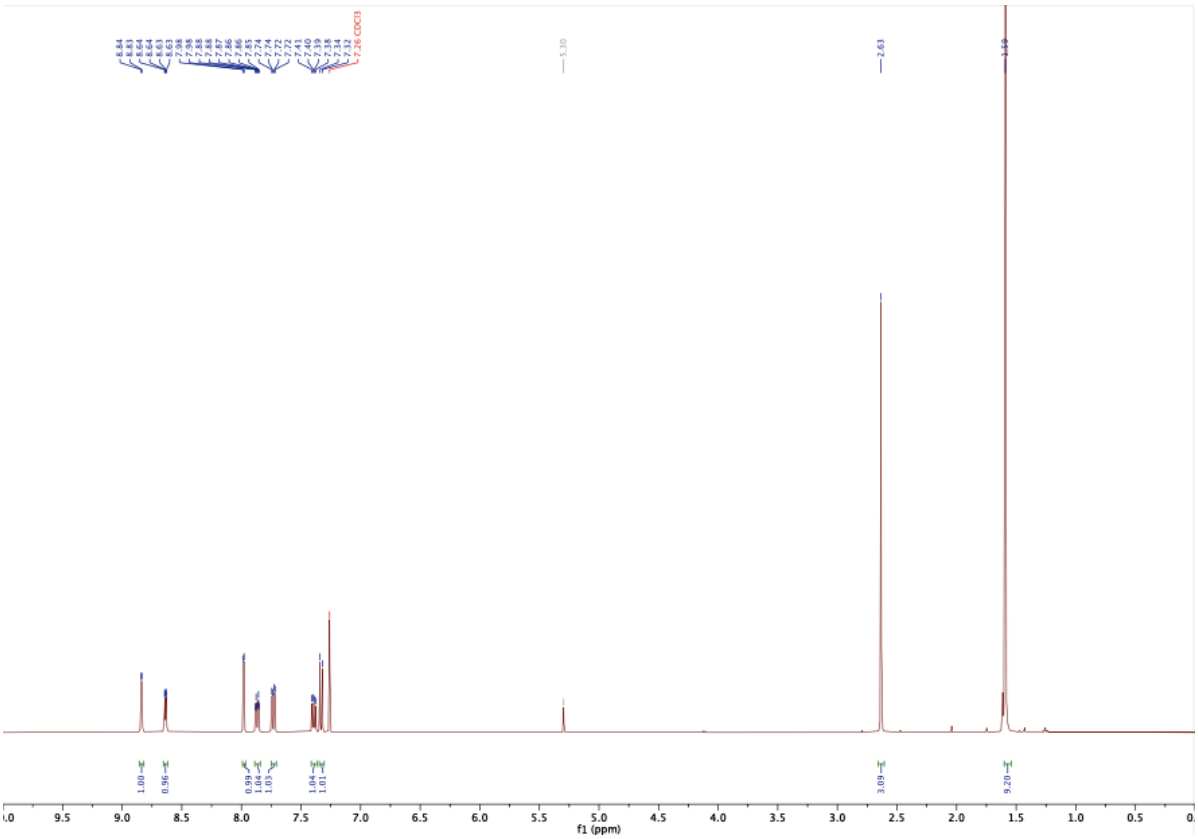
77.16 cdcl3
76.91 cdcl3
26.82
f1 (ppm)



35e

The Boc-protection of **SI-1** (0.80 g, 3.8 mmol) would follow *General Procedure A* to obtain Boc-protected product **35e**. The crude product was purified by flash column chromatography (1% TEA in ethyl acetate-hexane, 1:1) to yield product **35e** (1.13 g, 3.6 mmol, 96% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 2.4 Hz, 1H), 8.64 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.98 (d, *J* = 2.3 Hz, 1H), 7.87 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.73 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.39 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 2.63 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.26, 151.45, 149.45, 149.15, 148.24, 136.06, 135.05, 134.44, 131.86, 131.74, 128.92, 124.43, 123.73, 84.53, 29.85, 27.75. HRMS (ESI+) m/z calculated for $C_{18}H_{19}NO_4$ $[M+Na]^+$: 336.1212; found 336.1211.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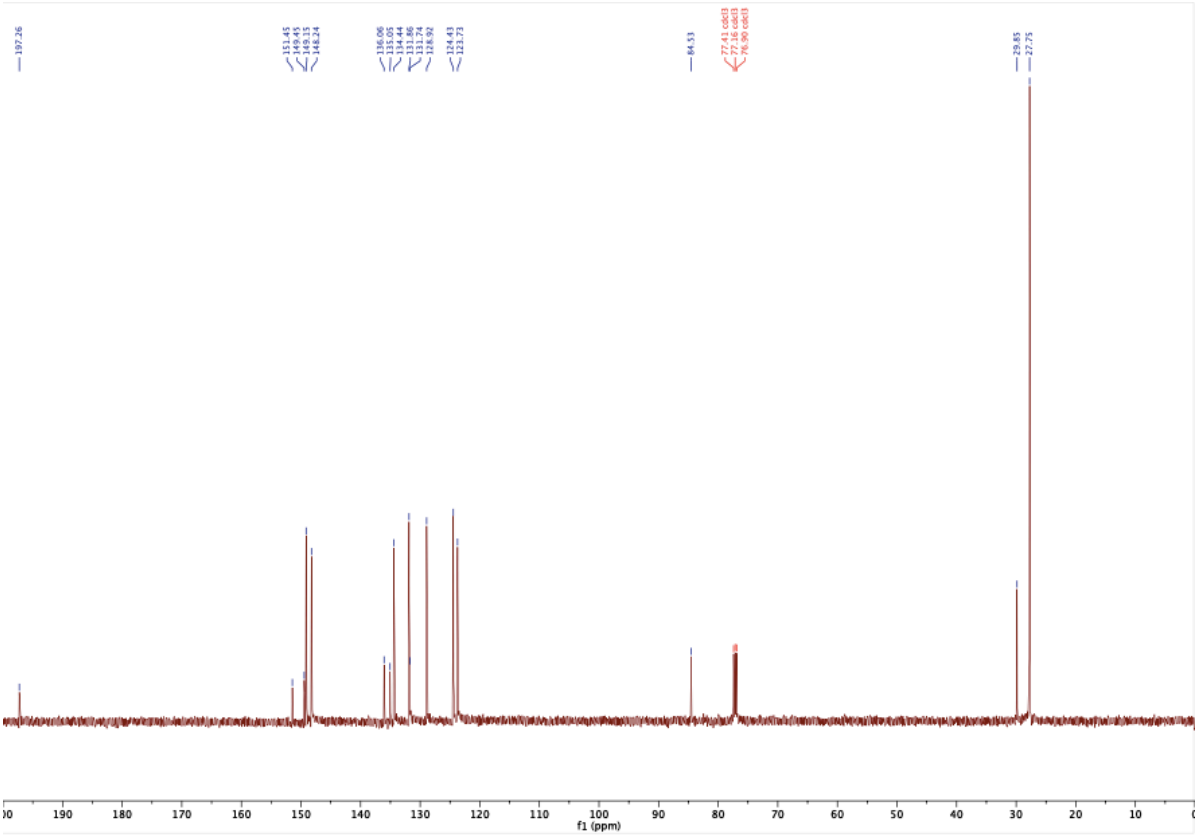
8.65
8.64
8.64
8.63
8.63
7.88
7.88
7.88
7.87
7.86
7.85
7.74
7.74
7.72
7.72
7.41
7.40
7.39
7.38
7.34
7.32
7.26 CDCl3
5.30
2.63
1.63
1.00
0.96
0.99
1.04
1.03
1.04
1.01
3.09
9.20
f1 (ppm)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149.15
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131.74
128.92
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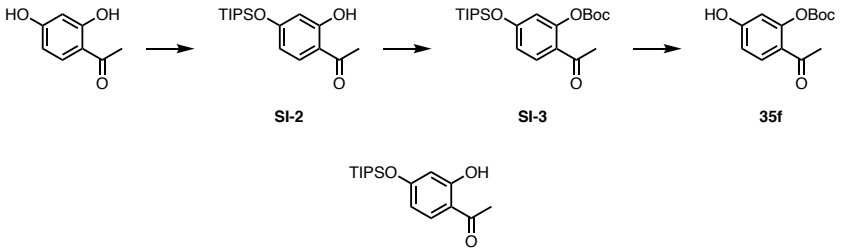
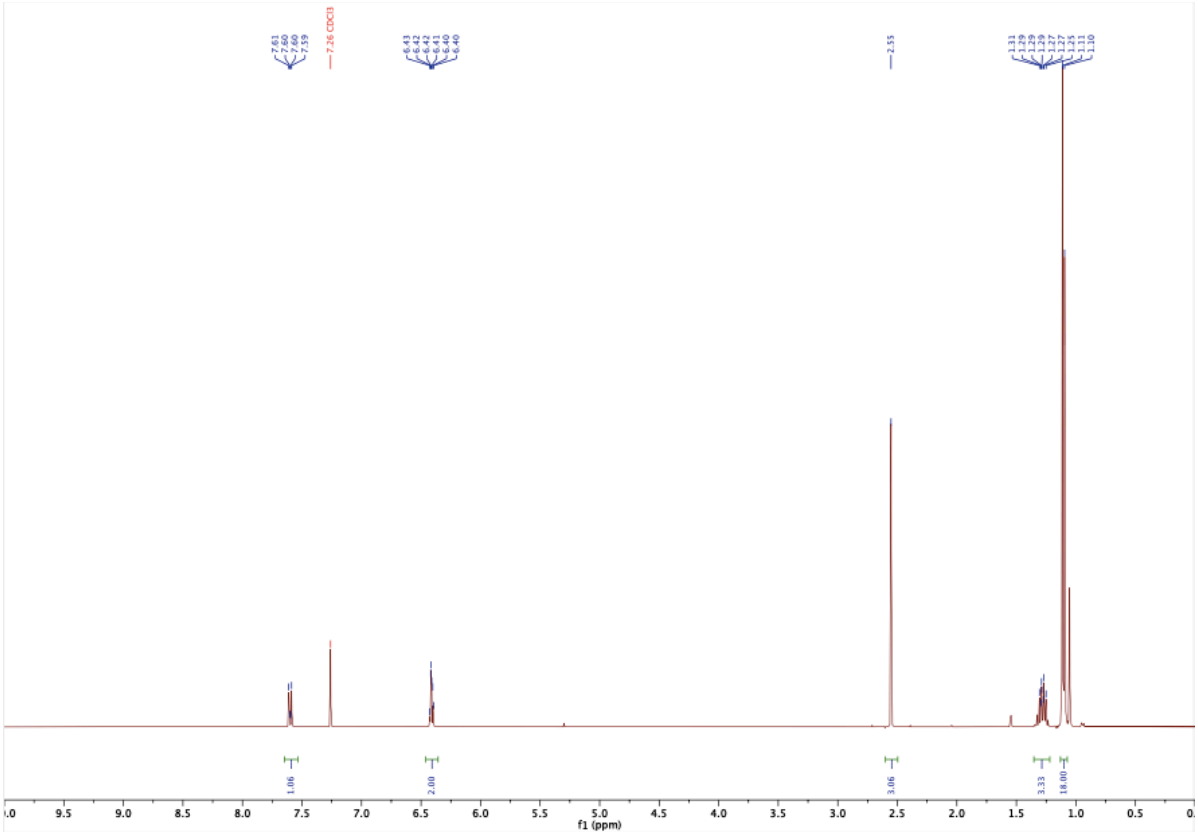
123.73
84.53
77.41 cdcl3
77.16 cdcl3
76.90 cdcl3
29.85
27.75
f1 (ppm)



SI-2

To a 100 mL round bottom flask, charged with 2',4'-dihydroxyacetophenone (3.5 g, 23 mmol) in dry DCM (46 mL, 0.5 M) was added imidazole (3.5 g, 52 mmol, 2.2 equivalent), DMAP (0.28 g, 2.3 mmol, 0.1 equivalent) and TIPSCl (5.4 mL, 25.3 mmol, 1.1 equivalent) at room temperature. The reaction mixture was stirred at room temperature overnight. The completion of reaction is analyzed by TLC. The reaction mixture was diluted with DCM (50 mL) and quenched with sat. NH_4Cl solution (50 mL). The resulting solution was extracted with DCM (3 x 20 mL). The combined organic fractions were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate-hexane, 1:9) to yield product **SI-2** (7.44 g, 23 mmol, 100% isolated yield). ^1H NMR (400 MHz, $CDCl_3$): δ 12.58 (s, 1H), 7.63-7.56 (m, 1H), 6.45-6.37 (m, 2H), 2.55 (s, 3H), 1.31-1.25 (m, 3H), 1.10 (d, J = 7.3 Hz, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.73, 165.04, 163.55, 132.51, 114.63, 112.28, 108.06, 26.38, 17.98, 12.83. HRMS (ESI+) m/z calculated for $C_{17}H_{28}O_3Si$ $[M+H]^+$: 309.1886; found 309.1890.


7.61
7.60
7.60
7.59
7.26 CDCl3
6.43
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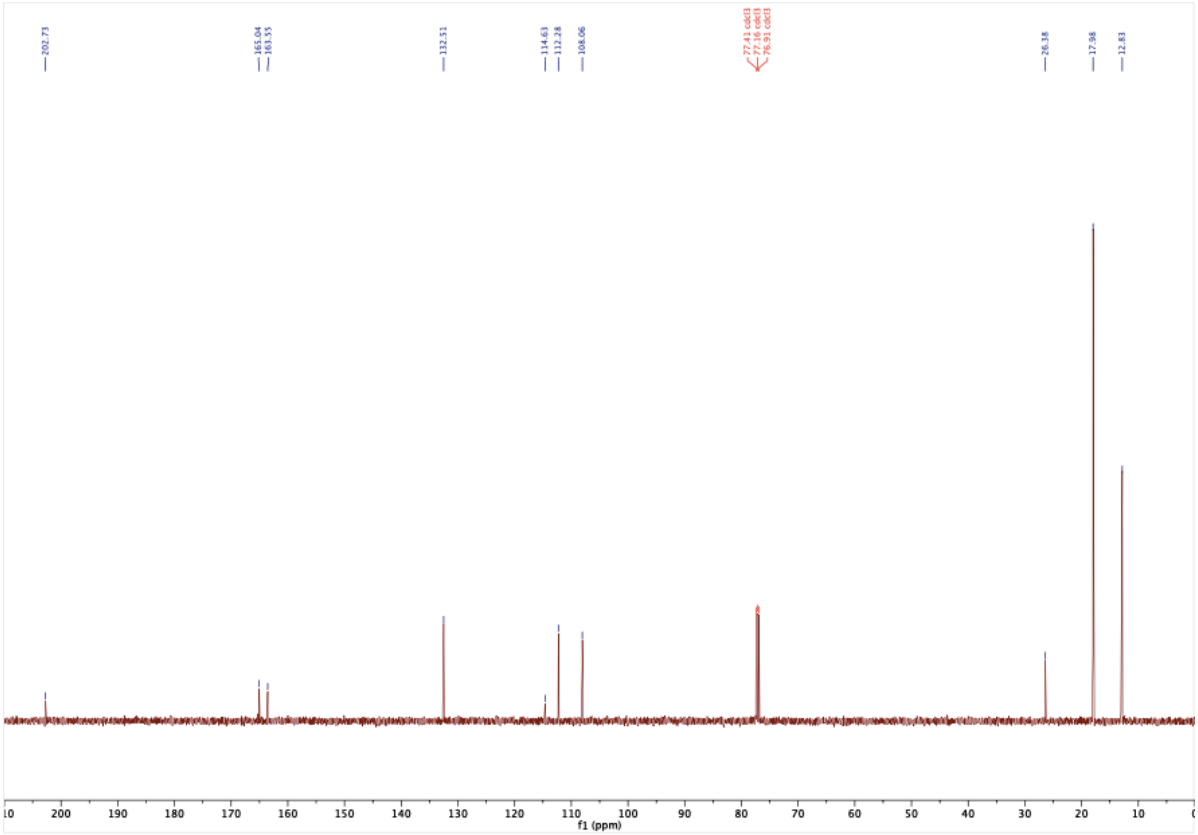
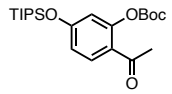
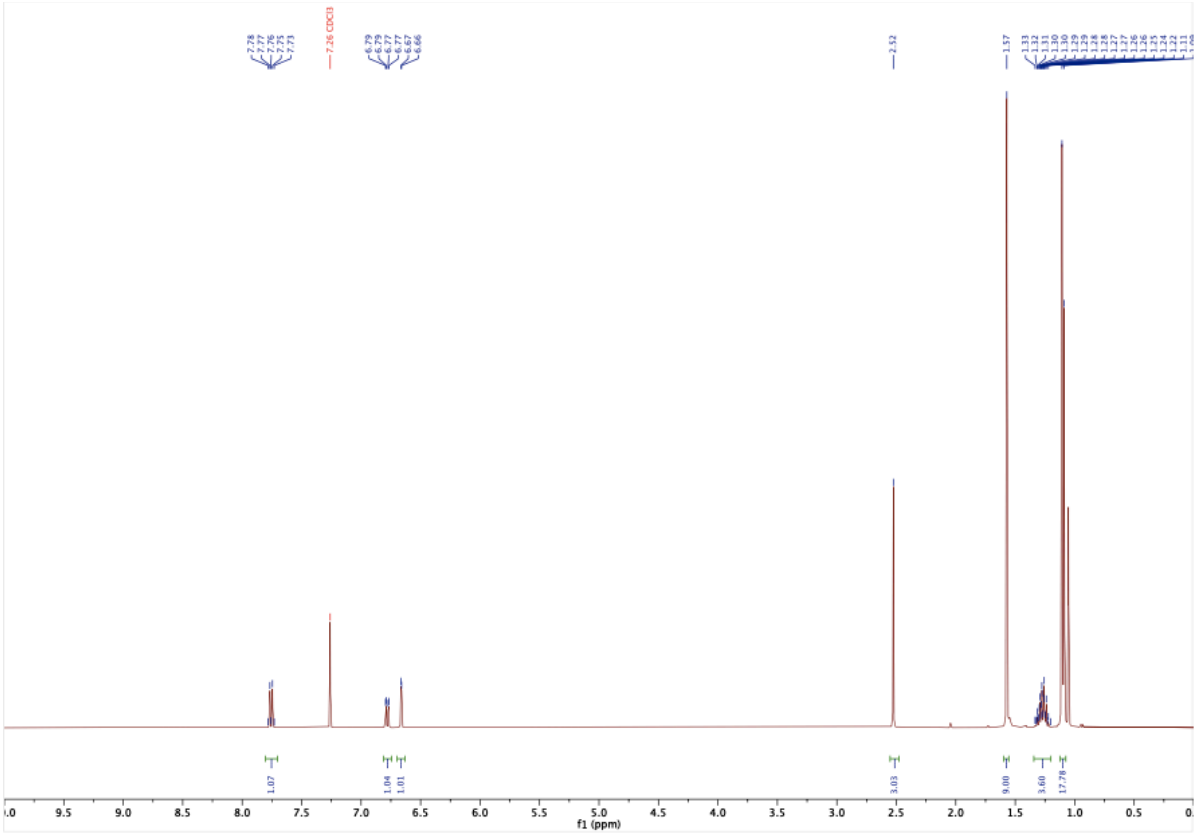
6.42
6.41
6.40
6.40
2.55
1.31
1.29
1.29
1.28
1.27
1.27
1.15
1.11
1.10
1.06
2.00
3.06
3.33
18.00
f1 (ppm)


202.73
165.04
163.55
132.51
114.63
112.28
108.06
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
26.38
17.98
12.83
f1 (ppm)



SI-3

The Boc-protection of **SI-2** (7.1 g, 23 mmol) would follow *General Procedure A* to obtain Boc-protected product **SI-3**. The crude product was purified by flash column chromatography (ethyl acetate-hexane, 1:20) to yield product **SI-3** (8.0 g, 20 mmol, 86% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.66 (d, *J* =2.4 Hz, 1H), 2.52 (s, 3H), 1.57 (s, 9H), 1.36-1.20 (m, 3H), 1.10 (d, *J* = 7.4 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.06, 160.97, 151.58, 151.33, 132.29, 123.95, 117.47, 115.23, 84.05, 29.37, 27.87, 17.96, 12.78. HRMS (ESI+) m/z calculated for $C_{17}H_{28}O_3Si$ $[M+Na]^+$: 431.2230; found 431.2226.


7.78
7.77
7.76
7.75
7.73
7.26 CDCl3
6.79
6.79
6.77
6.77
6.67
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1.07
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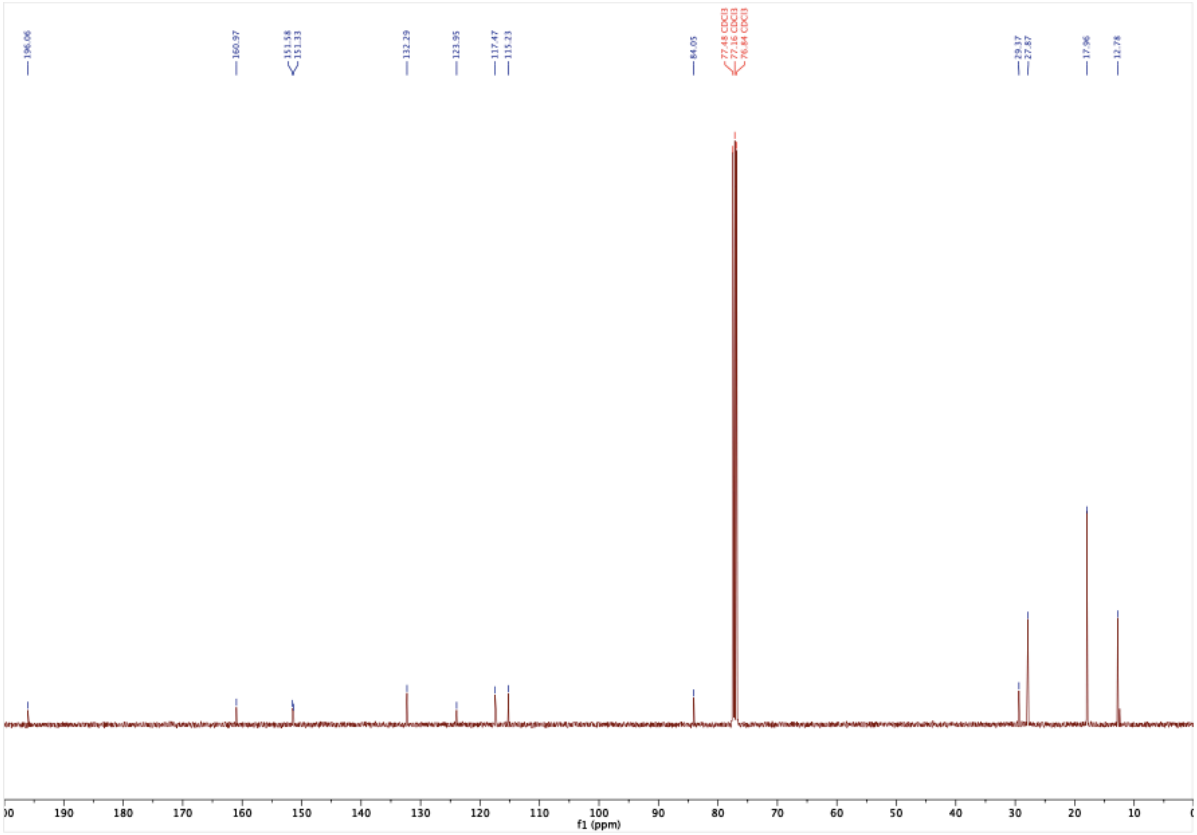
3.03
9.00
3.60
17.78
f1 (ppm)


196.06
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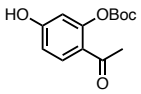
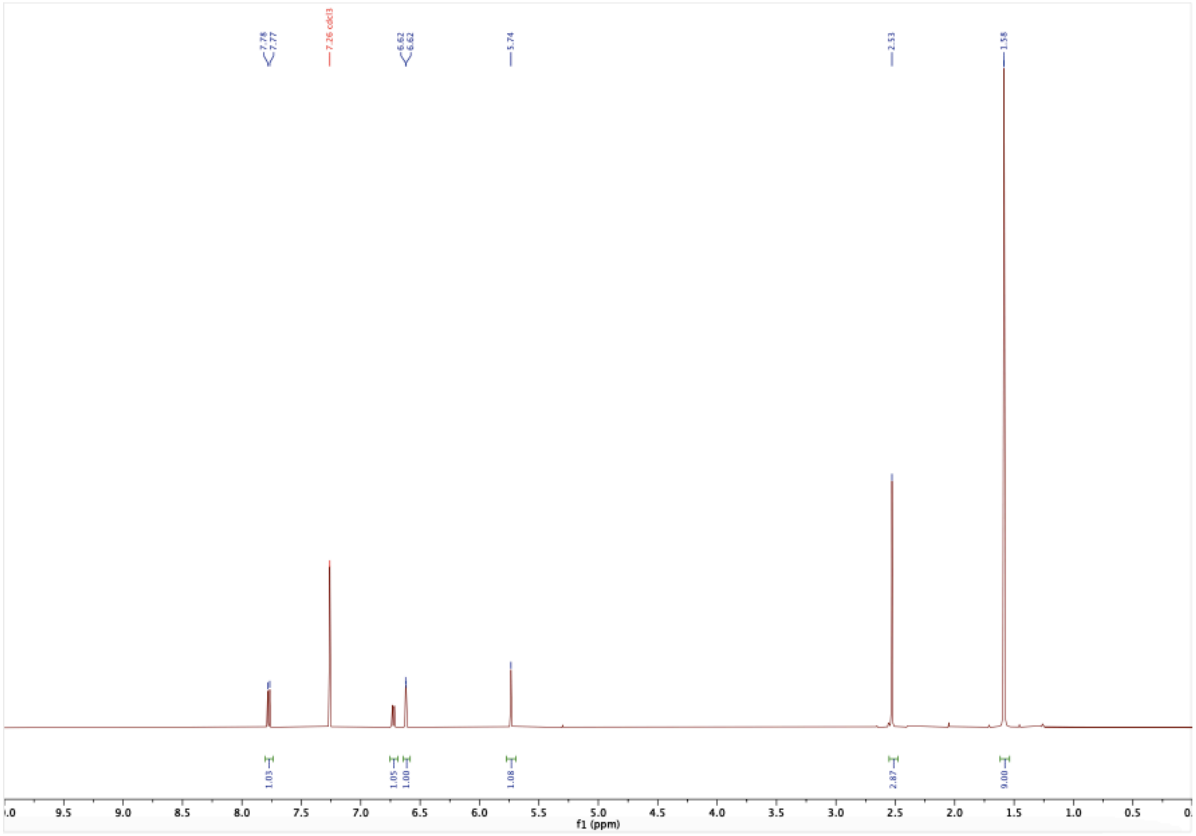
151.33
132.29
123.95
117.47
115.23
84.05
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
29.37
27.87
17.96
12.78
f1 (ppm)



35f

To a 25 mL round bottom flask, charged with **SI-3** (0.98 g, 2.4 mmol) was added TBAF (2.7 mL, 2.7 mmol, 1.1 equivalent, 1 M solution in THF) at room temperature. The reaction mixture was stirred at room temperature overnight. The completion of reaction is analyzed by TLC. The reaction mixture was diluted with EtOAc (5 mL) and quenched with sat. NH_4Cl solution (5 mL). The resulting solution was extracted with EtOAc (3 x 5 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate-hexane, 1:3) to yield product **35f** (0.53 g, 2.1 mmol, 86% isolated yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 8.6 Hz, 1H), 6.73 (dd, J = 8.6, 2.5 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 5.74 (s, 1H), 2.53 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.51, 161.03, 151.90, 151.62, 132.94, 123.16, 113.54, 111.09, 84.63, 29.23, 27.87. HRMS (ESI+) m/z calculated for $C_{13}H_{16}O_5$ $[M+Na]^+$: 275.0895; found 275.0900.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6.82
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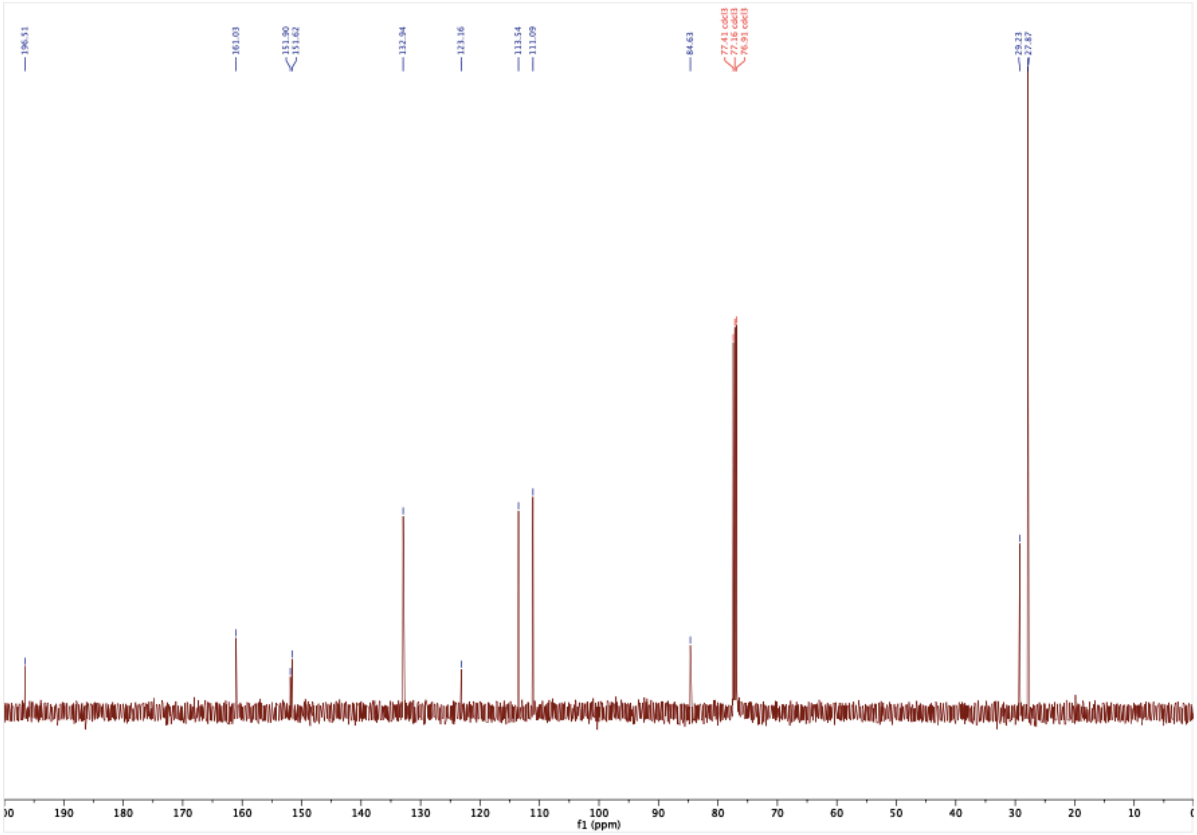
1.58
1.03
1.05
1.00
1.08
2.87
9.00
f1 (ppm)


196.51
161.03
151.90
151.62
132.94
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111.09
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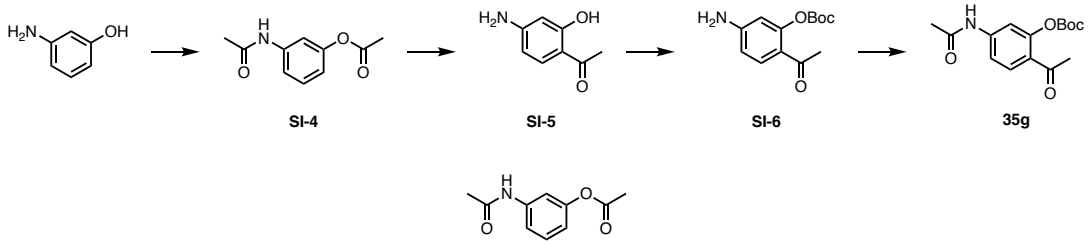
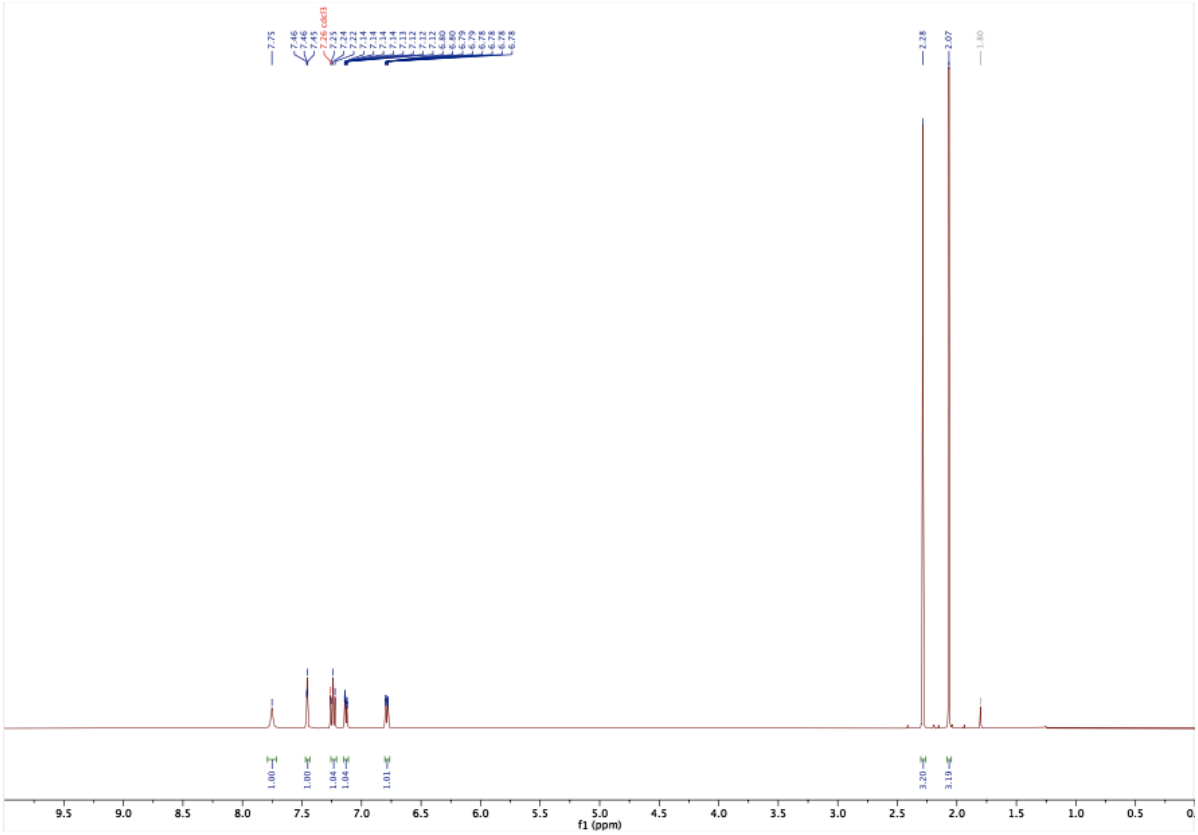
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
29.23
27.87
f1 (ppm)



SI-4

To a 50 mL seal-tube, charged with 3-aminophenol (1 g, 9.2 mmol) in EtOAc (6.3 mL, 1.47 M) was added NaOH pellets (0.91 g, 22.8 mmol, 2.49 equivalent) and acetic anhydride (3.1 mL, 32.5 mmol, 3.55 equivalent). The reaction mixture was sealed and refluxed at 80 °C for 20 hours. The completion of reaction is analyzed by TLC. The resulting reaction mixture was filtered through Frit and the residue was washed with EtOAc (4 x 10 mL). The filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate-hexane, 5:1) to yield product **SI-4** (1.1 g, 5.8 mmol, 63% isolated yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (s, NH), 7.46 (t, *J* = 2.2 Hz, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.13 (ddd, *J* = 8.2, 2.1, 1.0 Hz, 1H), 6.79 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 2.28 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.00, 168.74, 151.03, 139.38, 129.63, 117.09, 113.45, 24.54, 21.24. HRMS (ESI+) m/z calculated for $C_{10}H_{11}NO_3$ $[M+Na]^+$: 216.0637; found 216.0636.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7.45
7.45
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7.14
7.13
7.12
7.12
6.80
6.80
6.79
6.79
6.78
6.78
6.78
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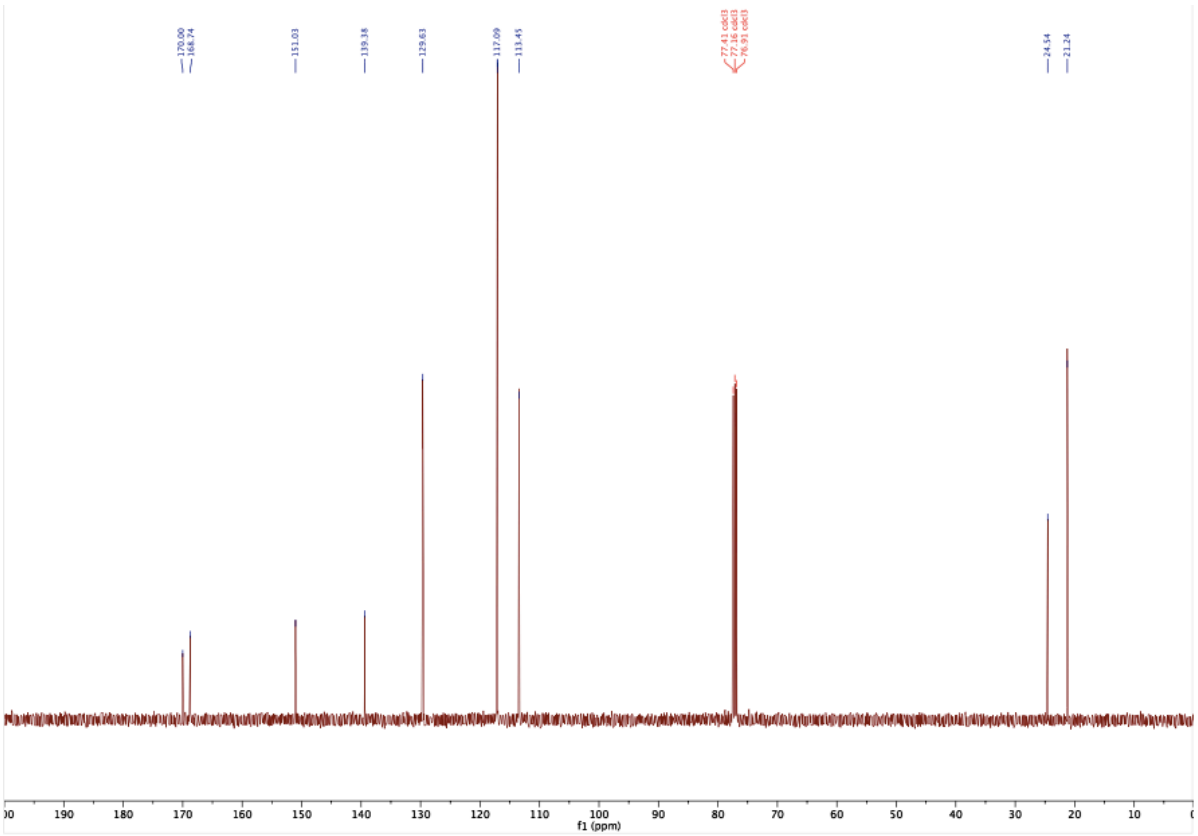
1.04
1.01
3.20
3.19
f1 (ppm)


170.00
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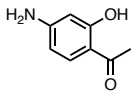
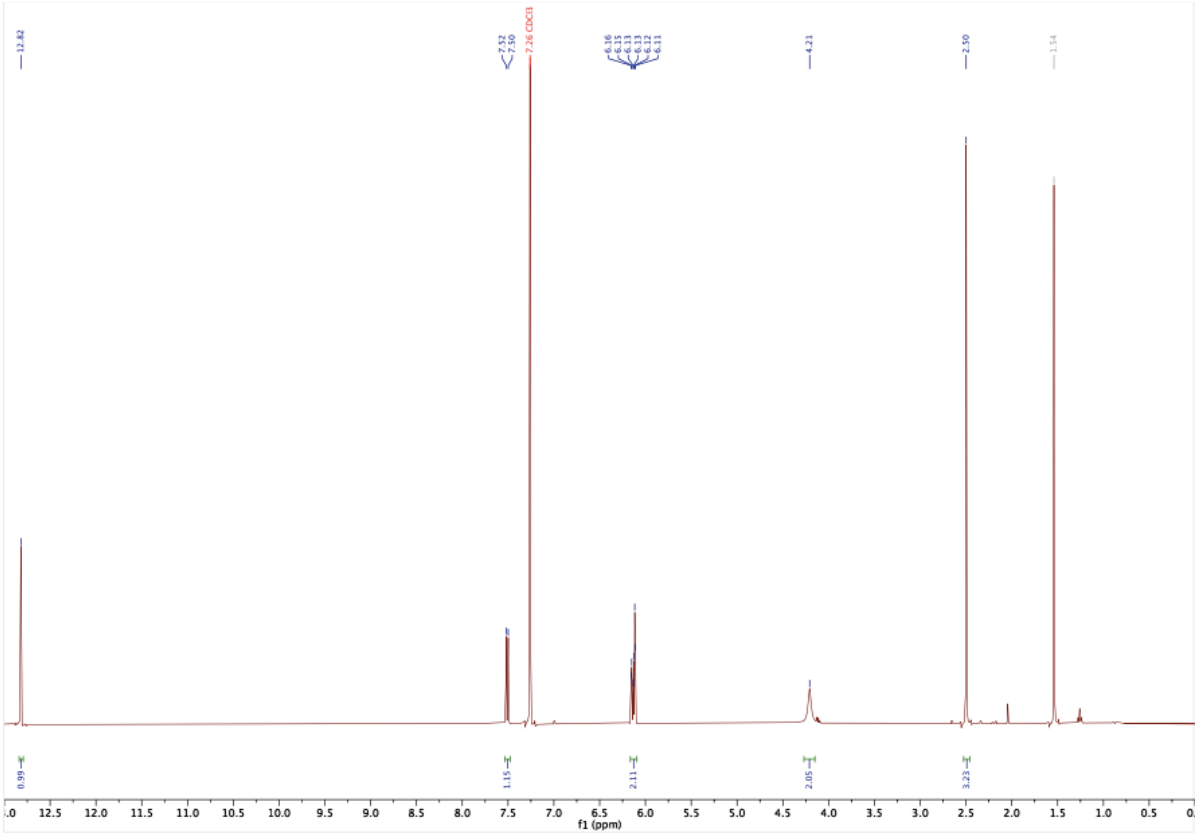
139.38
129.63
117.09
113.45
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
24.54
21.24
f1 (ppm)



SI-5

To a 100 mL seal-tube, charged with **SI-4** (1.1 g, 5.8 mmol) and anhydrous $AlCl_3$ (3.87 g, 29 mmol, 5.0 equivalent). The reaction mixture was heated at 135 °C for 20 hours then cooled to room temperature. At 0 °C, cold d.I. H_2O (50 mL) was added slowly to the reaction mixture and stirred at 50 °C until all solids disappeared. The resulting solution was extracted with EtOAc (4 x 20 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. 6 N aq. HCl (7.5 mL, 0.78 M) was added to above crude mixture and heated at 50 °C for 20 hours then cooled to room temperature. The reaction mixture was extracted with EtOAc (4 x 10 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (1% TEA in ethyl acetate-hexane, 1:3 → 1:1) to yield condensed product **SI-5** (0.68 g, 4.5 mmol, 78% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.82 (s, OH), 7.51 (d, J = 8.5 Hz, 1H), 6.18 – 6.09 (m, 2H), 4.21 (s, NH_2), 2.50 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.56, 165.32, 154.24, 133.07, 112.17, 106.63, 100.72, 25.87. HRMS (EI+) m/z calculated for $C_8H_9NO_2$ [M^+]: 151.0633; found 151.0627.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6.16
6.15
6.13
6.13
6.12
6.12
6.11
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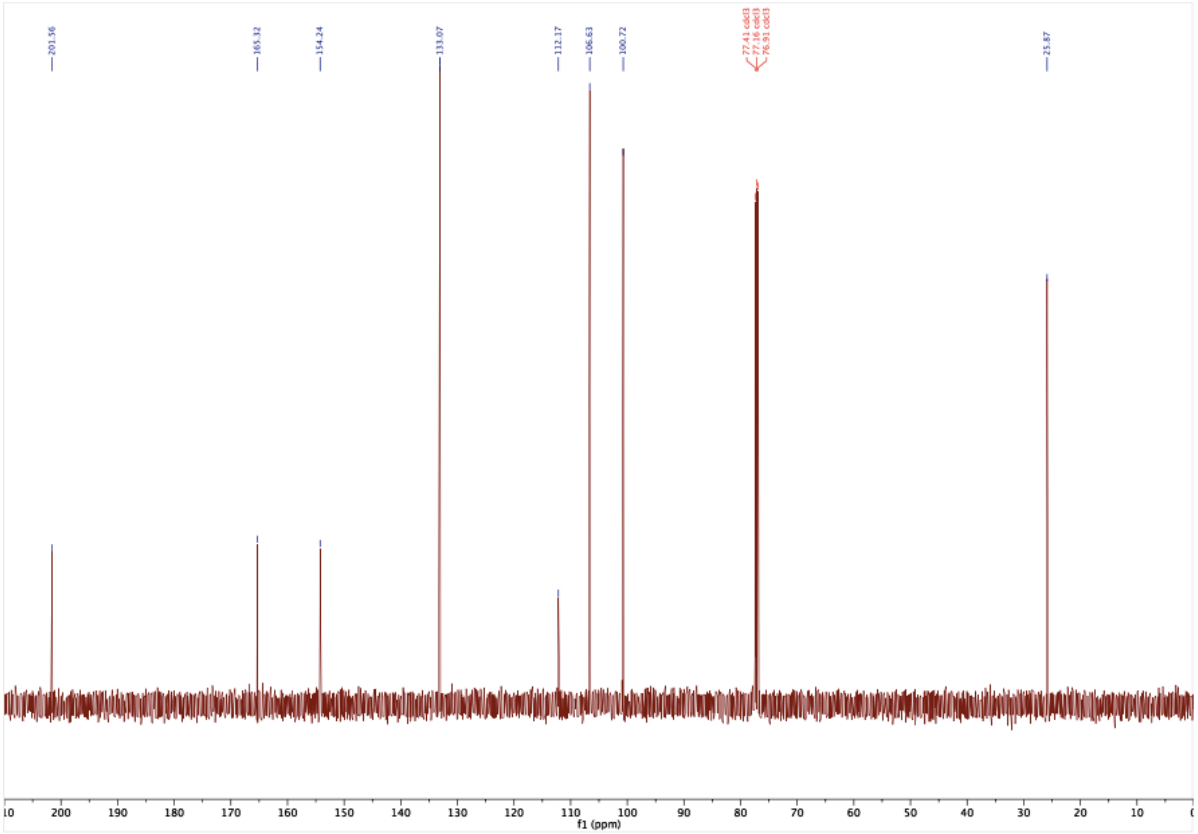
2.59
1.54
0.99
1.15
2.11
2.05
3.23
f1 (ppm)


201.56
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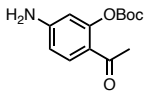
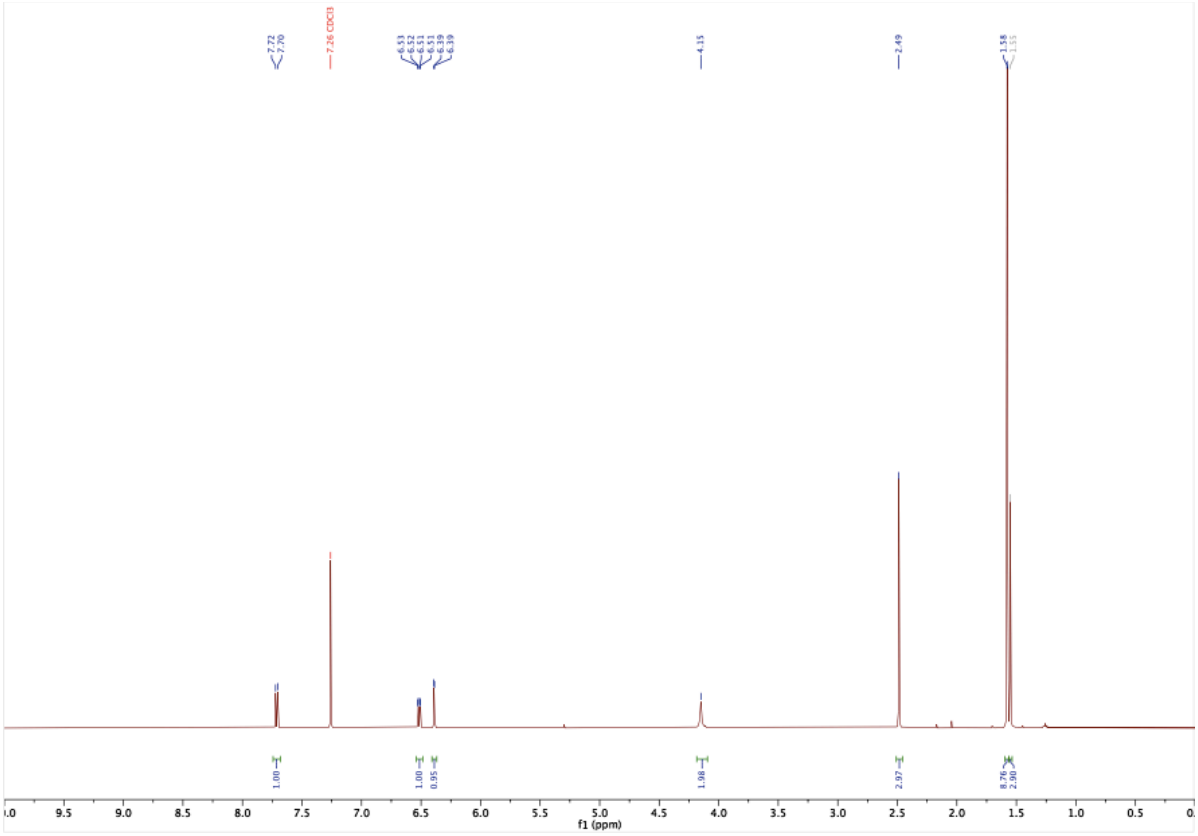
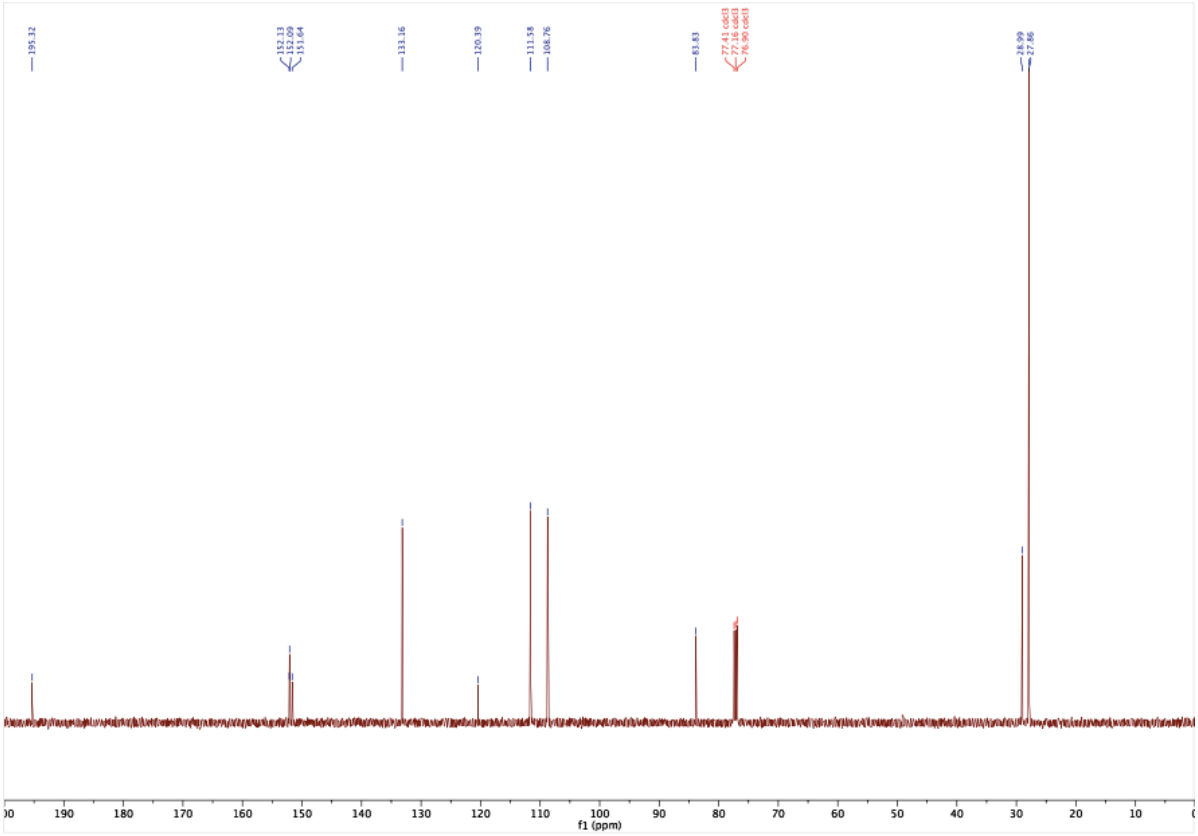
106.63
100.72
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
25.87
f1 (ppm)

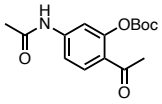


SI-6

The Boc-protection of **SI-5** (0.40 g, 2.7 mmol) would follow *General Procedure A* to obtain Boc-protected product **SI-6**. The crude product was purified by flash column chromatography (1% TEA in ethyl acetate-hexane, 1:3 → 1:1) to yield condensed product **SI-6** (0.57 g, 2.3 mmol, 84% isolated yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.5 Hz, 1H), 6.52 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.39 (d, *J* = 2.3 Hz, 1H), 4.15 (s, NH_2), 2.49 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.32, 152.13, 152.09, 151.64, 133.16, 120.39, 111.58, 108.76, 83.83, 28.99, 27.86. HRMS (ESI+) m/z calculated for $C_{13}H_{17}NO_4$ $[M+Na]^+$: 274.1055; found 274.1059.

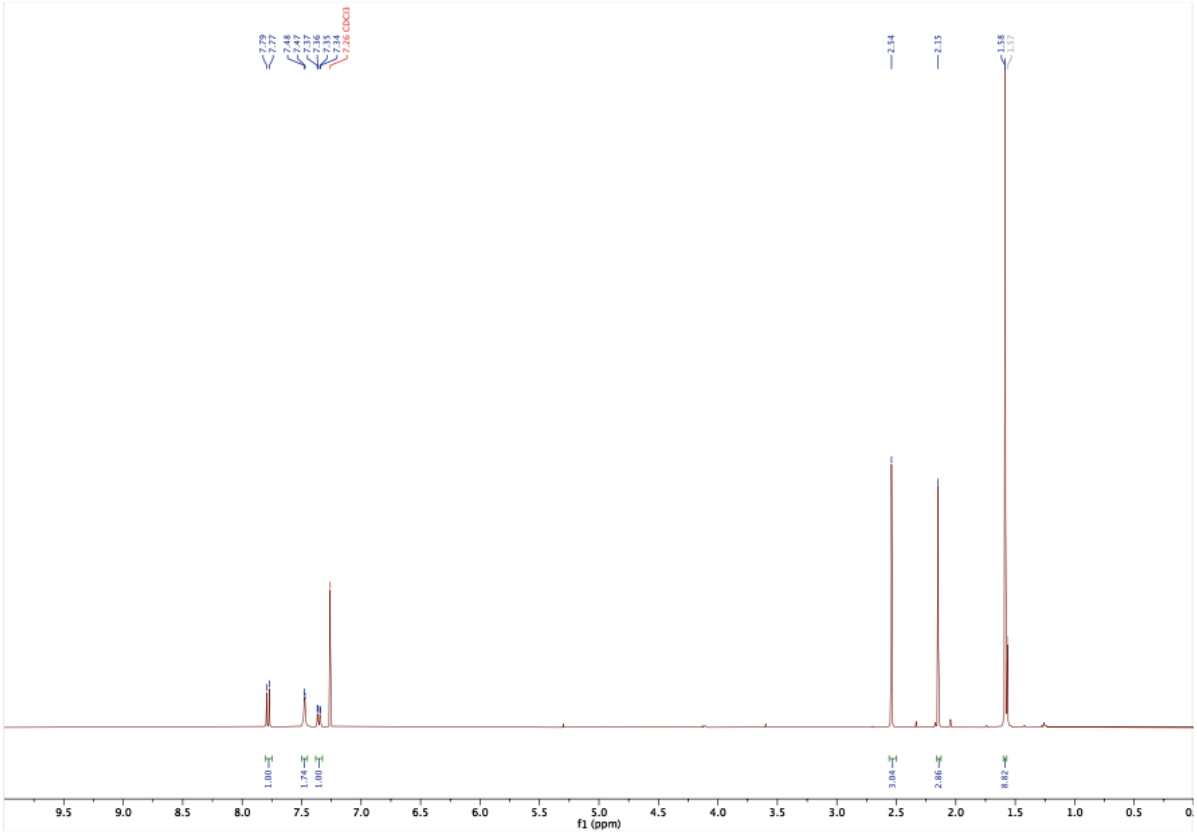

7.72
7.70
7.26 CDCl3
6.53
6.52
6.51
6.51
6.39
6.39
4.15
2.49
1.58
1.55
1.00
1.00
0.95
1.98
2.97
8.76
2.90
f1 (ppm)

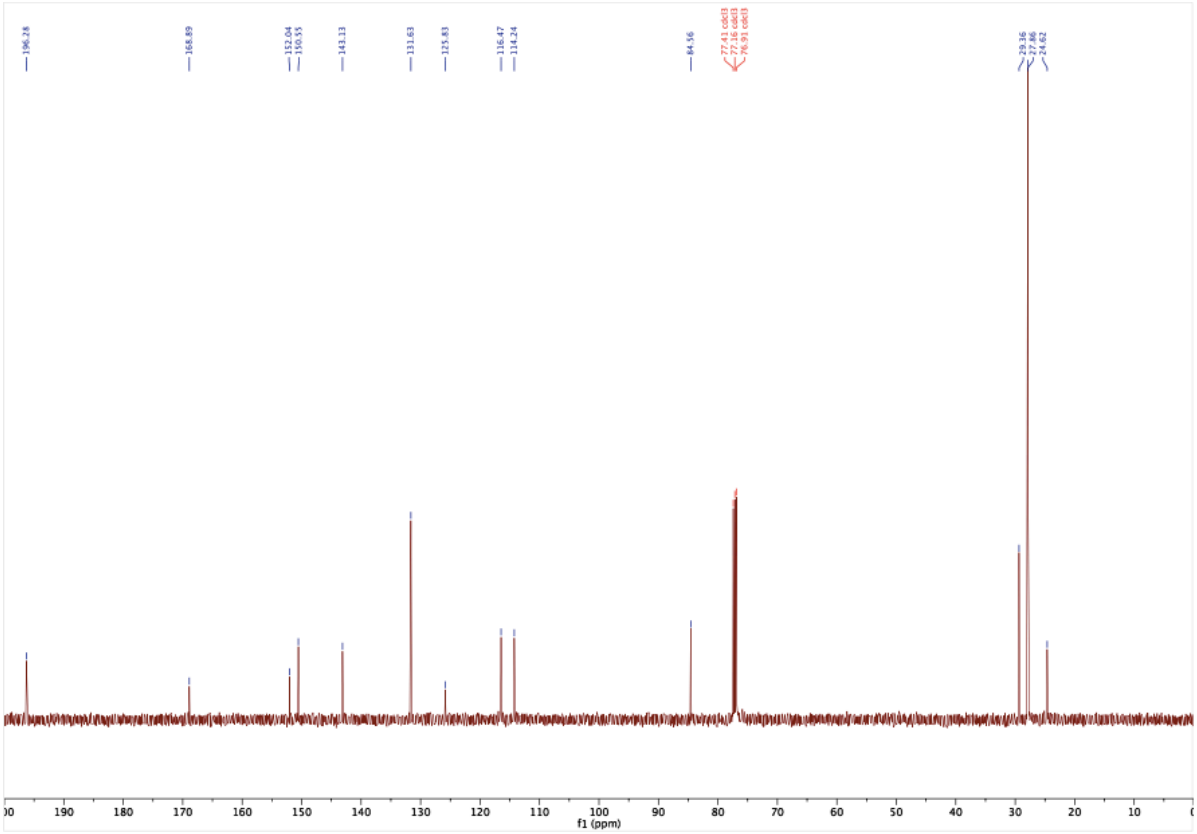

195.32
152.33
152.09
151.64
133.16
120.39
111.58
108.76
83.83
77.41 cdcl3
77.16 cdcl3
76.90 cdcl3
28.99
27.86
f1 (ppm)

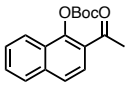


35g

To a 100 mL round bottom flask, charged with **SI-6** (0.57 g, 2.3 mmol) in dry DCM (23 mL, 0.1 M) was added dry triethylamine (0.64 mL, 4.6 mmol, 2.0 equivalent). At 0 °C, acetyl chloride (0.33 mL, 4.6 mmol, 2.0 equivalent) was added dropwise to the reaction solution. The reaction mixture was stirred at 0 °C and slowly warm to room temperature overnight. The completion of reaction is analyzed by TLC. At 0 °C, sat. NH_4Cl solution (30 mL) was added slowly to the reaction mixture. The resulting solution was extracted with DCM (3 x 10 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate-hexane, 1:1) to yield product **35g** (0.53 g, 1.8 mmol, 79% isolated yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 2.1 Hz, AR-H & NH), 7.36 (dd, J = 8.6, 2.1 Hz, 1H), 2.54 (s, 3H), 2.15 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.28, 168.89, 152.04, 150.55, 143.13, 131.63, 125.83, 116.47, 114.24, 84.56, 29.36, 27.86, 24.62. HRMS (ESI+) m/z calculated for $C_{15}H_{19}NO_5$ $[M+Na]^+$: 316.1161; found 316.1157.

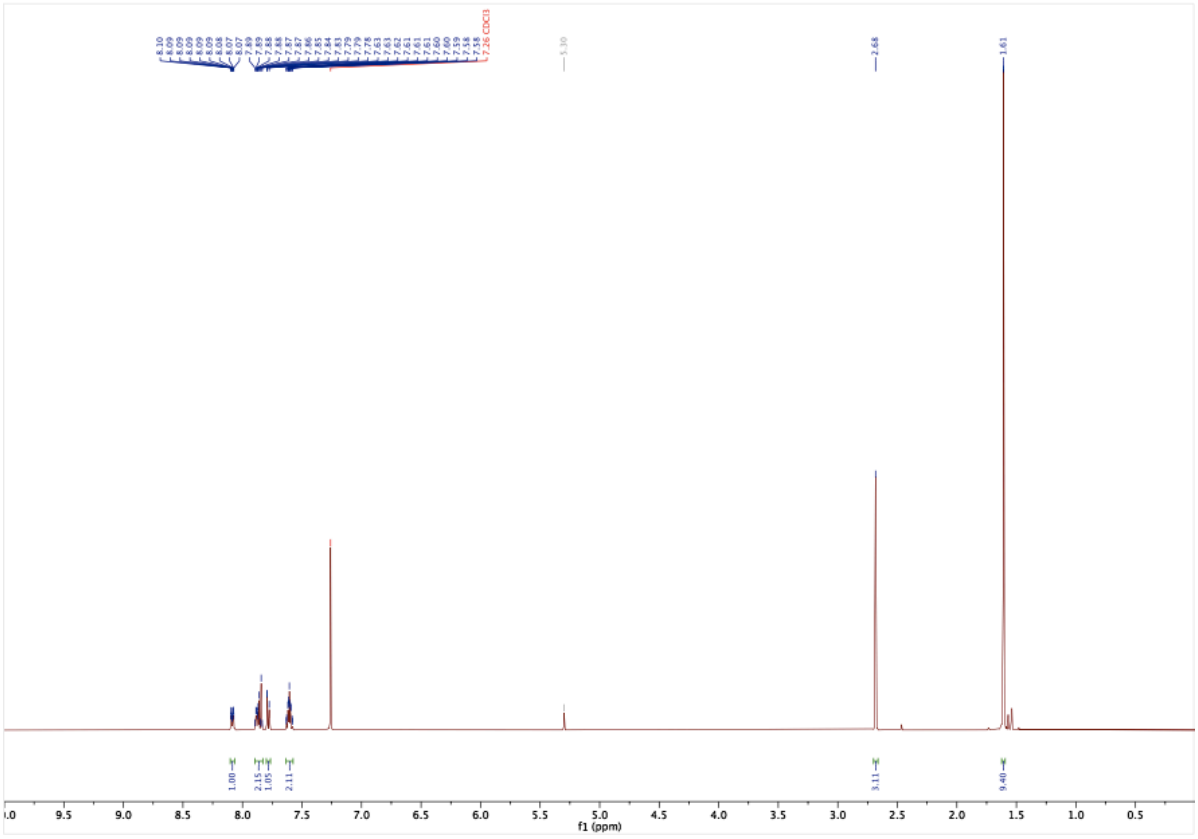

7.79
7.77
7.48
7.47
7.37
7.36
7.35
7.34
7.26 CDCl3
2.54
2.15
1.58
1.00
1.74
1.00
3.04
2.86
8.82
f1 (ppm)

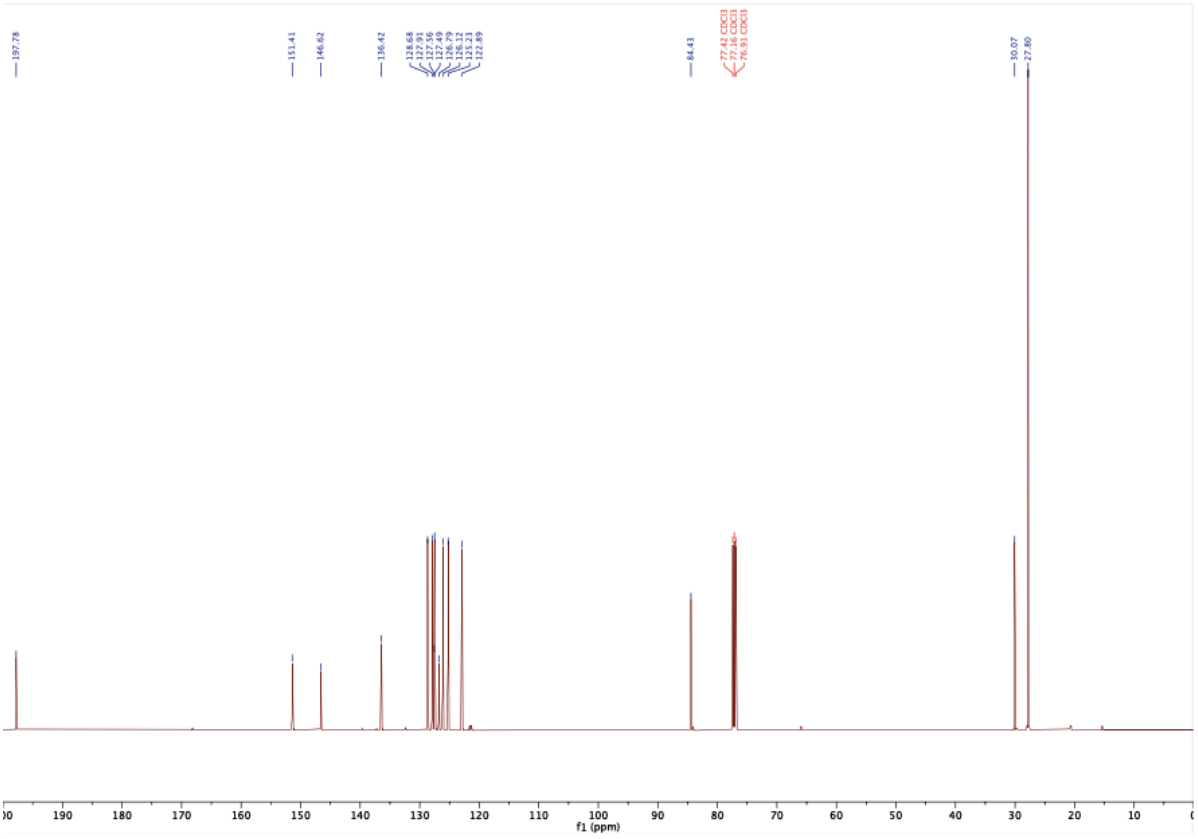

196.28
168.89
152.04
150.55
143.13
131.63
125.83
116.47
114.24
84.56
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
29.36
27.86
24.62
f1 (ppm)

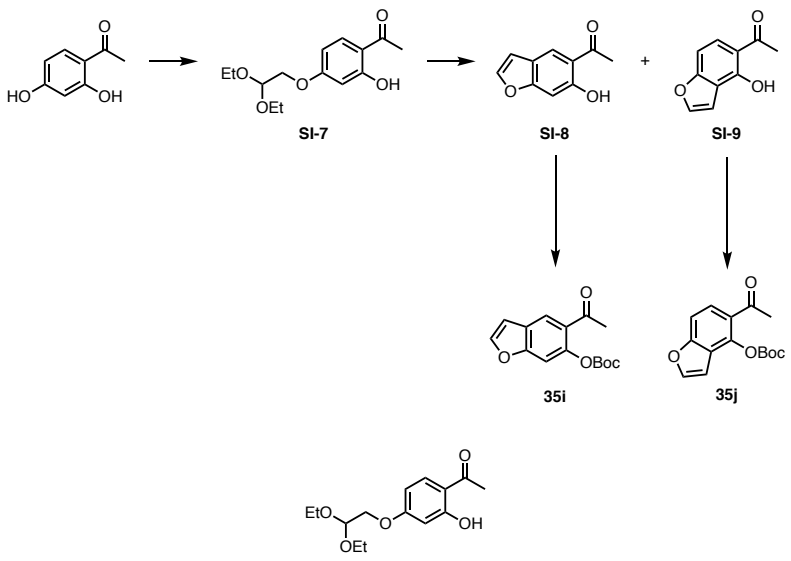


35h

Compound **35h** was synthesized according to general procedure A: (ethyl acetate–hexane, 1:9), 80% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11-8.05 (m, 1H), 7.91-7.82 (m, 2H), 7.81-7.76 (m, 1H), 7.65-7.56 (m, 2H), 2.68 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.78, 151.41, 146.62, 136.42, 128.68, 127.91, 127.56, 127.49, 126.79, 126.12, 125.23, 122.89, 84.43, 30.07, 27.80. HRMS (ESI+) m/z calculated for $C_{17}H_{18}O_4$ $[M+Na]^+$: 309.1103; found 309.1102.

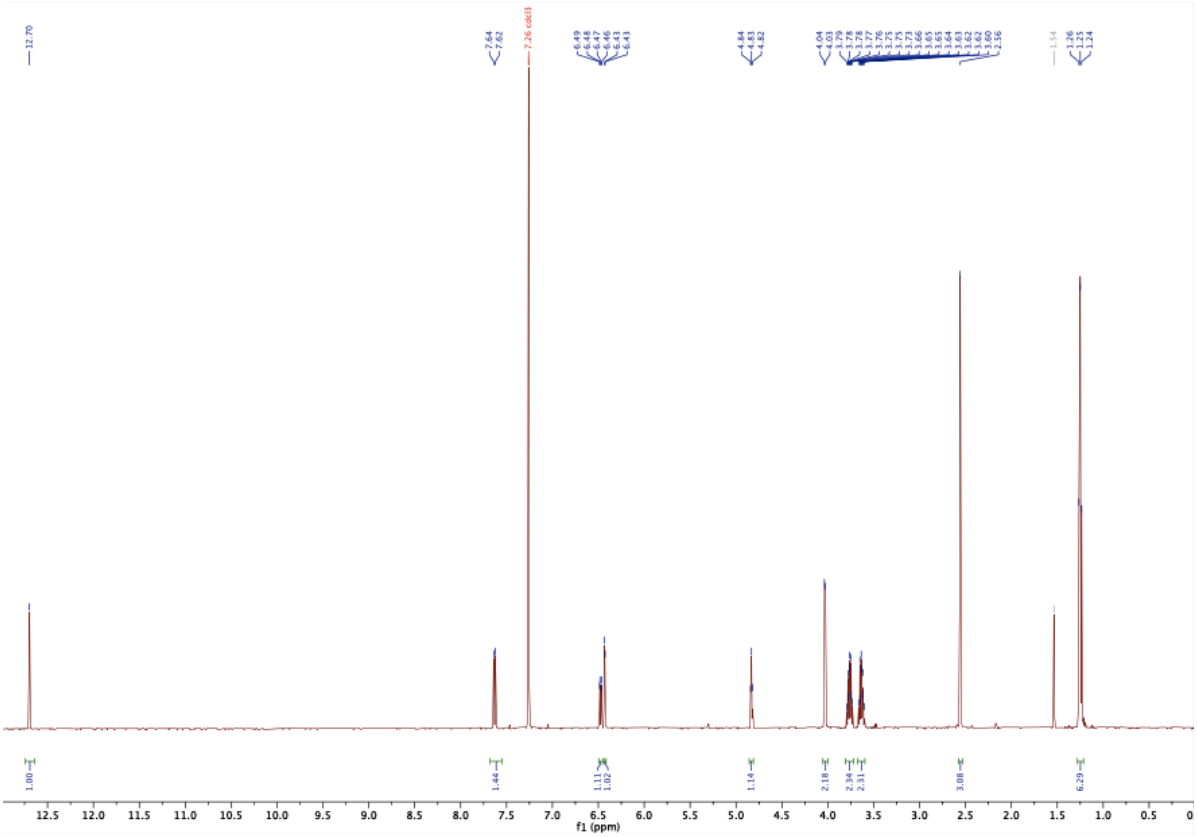

f1 (ppm)


f1 (ppm)



SI-7

To a 100 mL round-bottom flask, charged with 2',4'-dihydroxyacetophenone (8.4 g, 55 mmol) in DMF (55 mL, 1 M) was added potassium carbonate (7.6 g, 1.0 equivalent) and bromoacetaldehyde diethyl acetal (11 g, 1.0 equivalent). The reaction mixture was refluxed at 160 °C for 6 hours. The completion of reaction is analyzed by TLC. The reaction mixture was quenched with d.I. H_2O (40 mL) and extracted with Et_2O (3 x 30 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate-hexane, 1:3) to yield alkylated product **SI-7** (7.0 g, 26 mmol, 47% isolated yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.70 (s, OH), 7.63 (d, J = 8.9 Hz, 1H), 6.48 (dd, J = 8.9, 2.4 Hz, 1H), 6.43 (d, J = 2.5 Hz, 1H), 4.83 (t, J = 5.2 Hz, 1H), 4.03 (d, J = 5.2 Hz, 2H), 3.76 (dq, J = 8.8, 7.0 Hz, 2H), 3.63 (dq, J = 9.1, 7.0 Hz, 2H), 2.56 (s, 3H), 1.25 (t, J = 7.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.75, 165.27, 165.17, 132.48, 114.31, 107.95, 101.88, 100.27, 68.76, 62.93, 26.40, 15.47. HRMS (EI+) m/z calculated for $C_{14}H_{20}O_5$ $[M+Na]^+$: 291.1208; found 291.1204.


12.70
7.64
7.62
7.26 cdcl3
6.49
6.48
6.47
6.46
6.45
6.43
4.84
4.83
4.82
4.04
4.03
3.79
3.78
3.78
3.77
3.76
3.75
3.75
3.73
3.66
3.66
3.65
3.64
3.64
3.63
3.62
3.62
3.60
3.56
1.54
1.26
1.25
1.24
1.00
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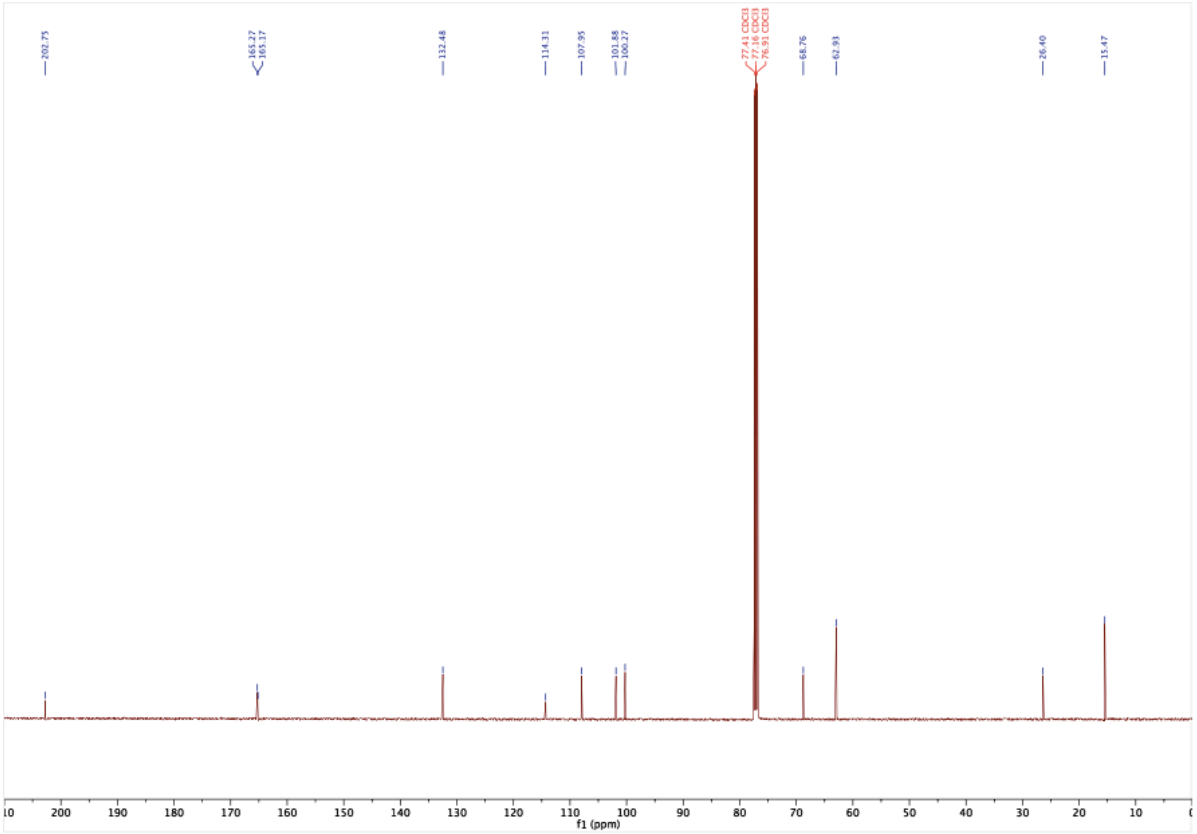
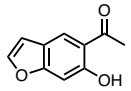
1.11
1.02
1.14
2.18
2.34
2.31
3.08
6.29
f1 (ppm)

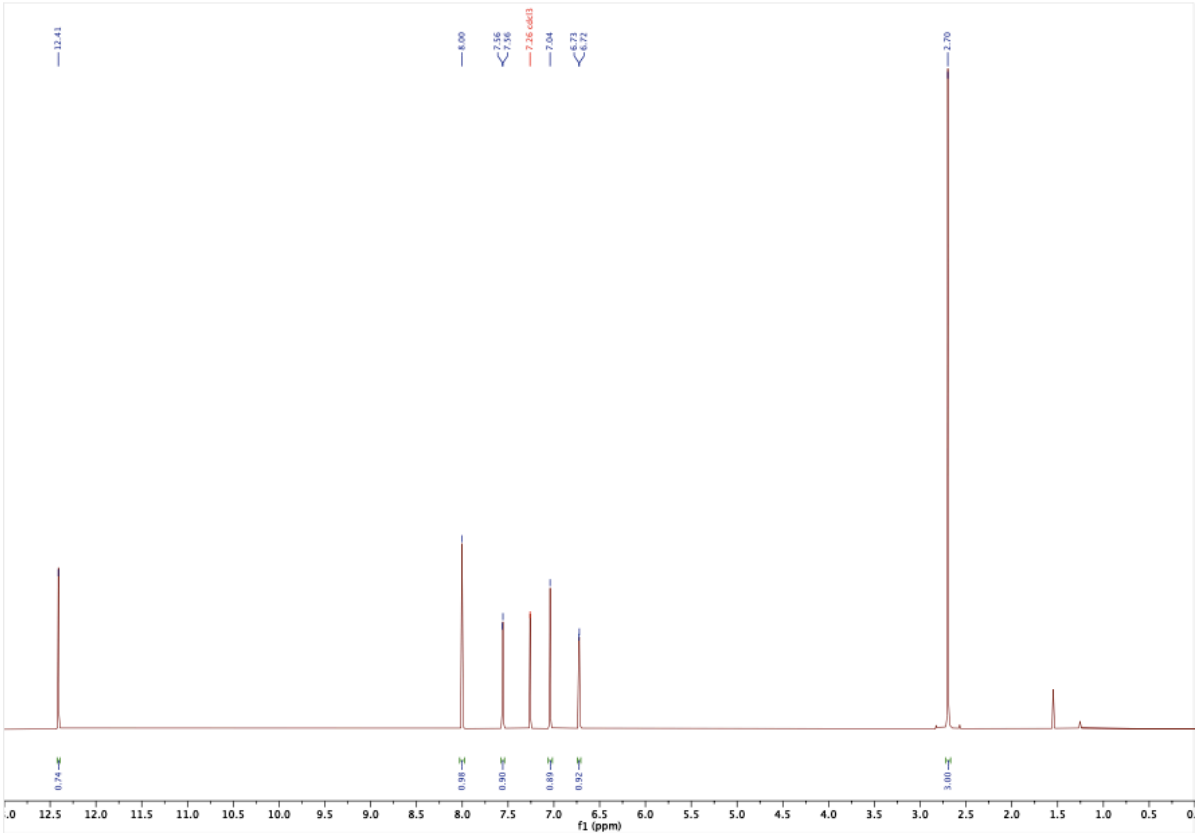

202.75
165.27
165.17
132.48
114.31
107.95
101.88
100.27
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
68.76
62.93
26.40
15.47
f1 (ppm)

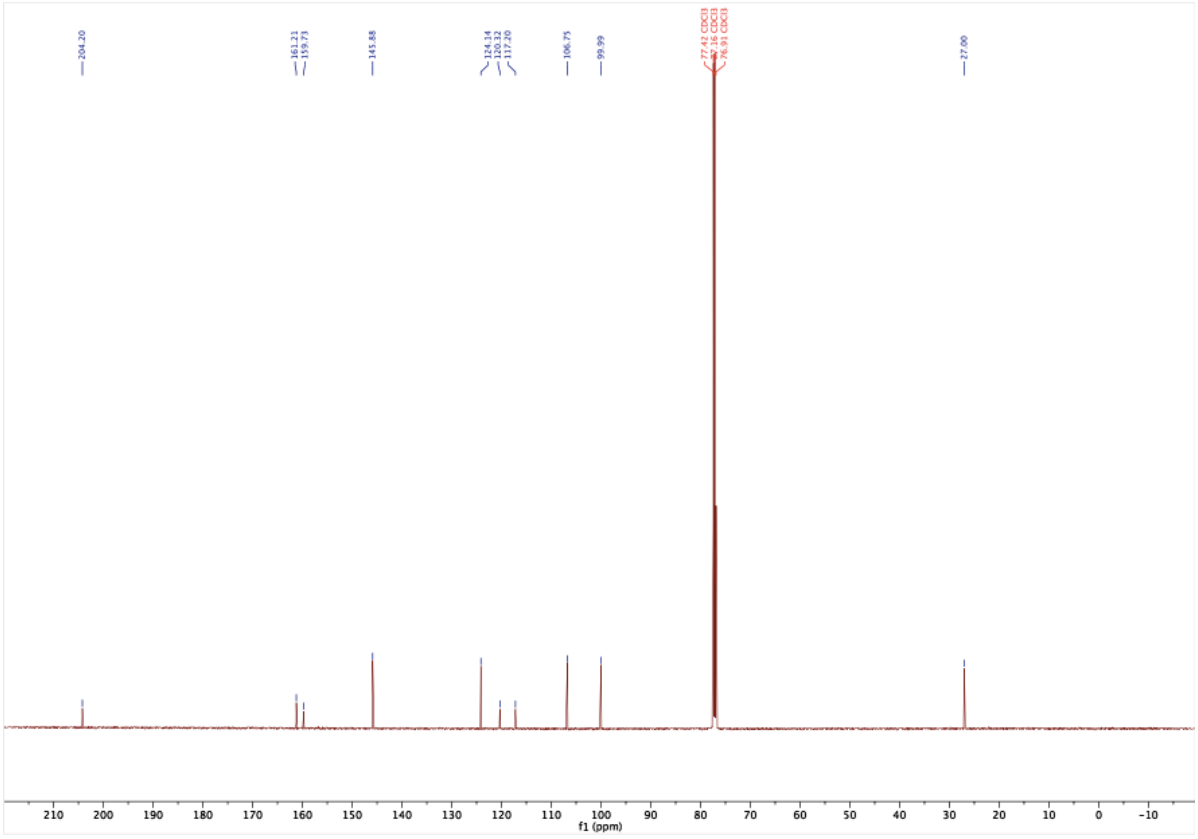
To a 100 mL round bottom flask, charged with **SI-7** (6.4 g, 24 mmol) in dry toluene (48 mL, 0.2 M) was added amberlyst-15 (0.8 g, 12.5% m/m). The reaction mixture was refluxed with a Dean-Stark at 120 °C for 8 hours. The completion of reaction is analyzed by TLC. The resulting reaction mixture was filtered through Frit and the resin was washed with Et_2O. The filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate-hexane, 1:10) to yield condensed product **SI-8** (1.1 g, 6.0 mmol, 25% isolated yield) and **SI-9** (1.6 g, 8.9 mmol, 37% isolated yield).

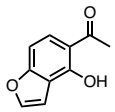


SI-8

SI-8, ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.41 (s, OH), 8.00 (s, 1H), 7.56 (d, J = 2.3 Hz, 1H), 7.04 (s, 1H), 6.72 (dd, J = 2.3, 1.0 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.20, 161.21, 159.73, 145.88, 124.14, 120.32, 117.20, 106.75, 99.99, 27.00. HRMS (EI+) m/z calculated for $C_{10}H_8O_3$ [M^+]: 176.0473; found 176.0466.

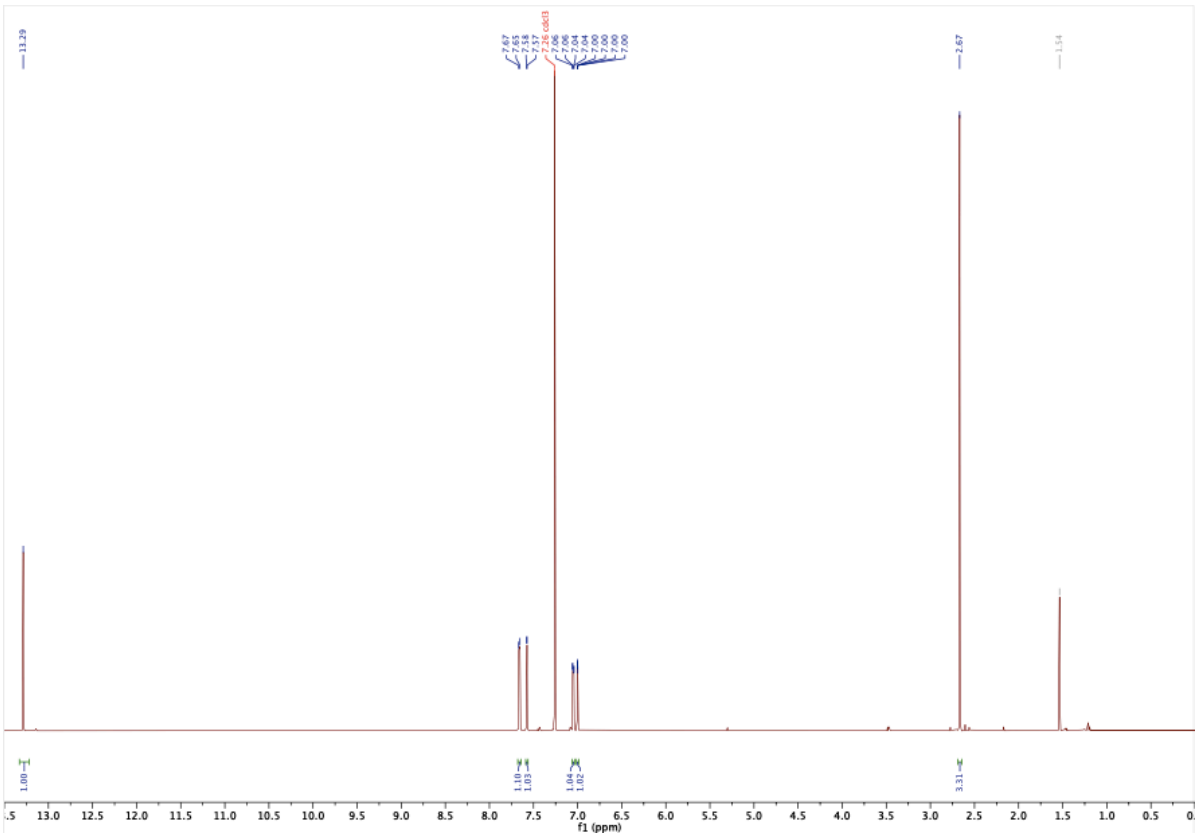

12.41
8.00
7.66
7.66
7.26 cdcl3
7.04
6.73
6.72
2.70
0.74
0.98
0.90
0.89
0.92
3.00
f1 (ppm)

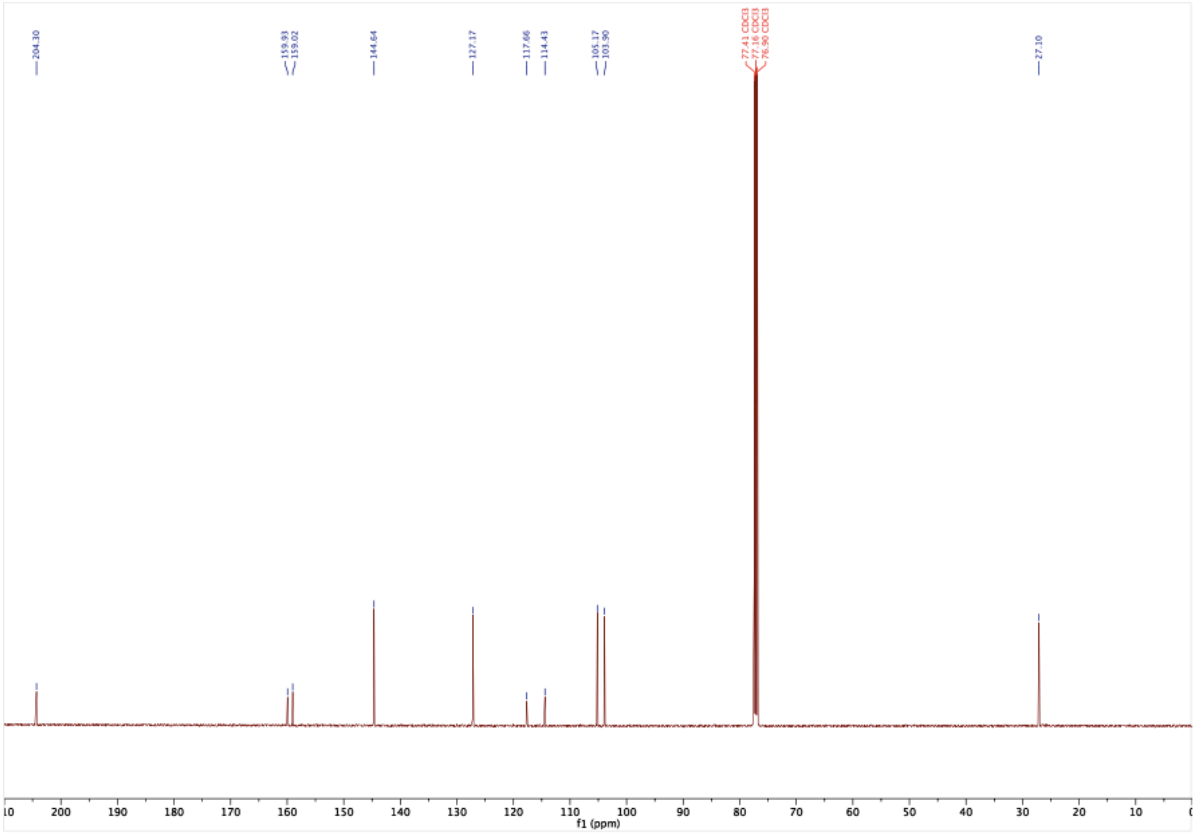

204.20
161.21
159.73
145.88
124.14
120.32
117.20
106.75
99.99
77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
27.00
f1 (ppm)



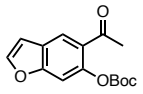
SI-9

SI-9, ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.29 (s, OH), 7.66 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.05 (dd, J = 8.9, 0.9 Hz, 1H), 7.00 (dd, J = 2.2, 0.9 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.30, 159.93, 159.02, 144.64, 127.17, 117.66, 114.43, 105.17, 103.90, 27.10. HRMS (EI+) m/z calculated for $C_{10}H_8O_3$ [M^+]: 176.0473; found 176.0479.


11.29
7.67
7.65
7.18
7.16
7.06
7.06
7.04
7.04
7.00
7.00
7.00
7.00
2.67
1.54
1.00
1.10
1.03
1.04
1.02
3.31
f1 (ppm)

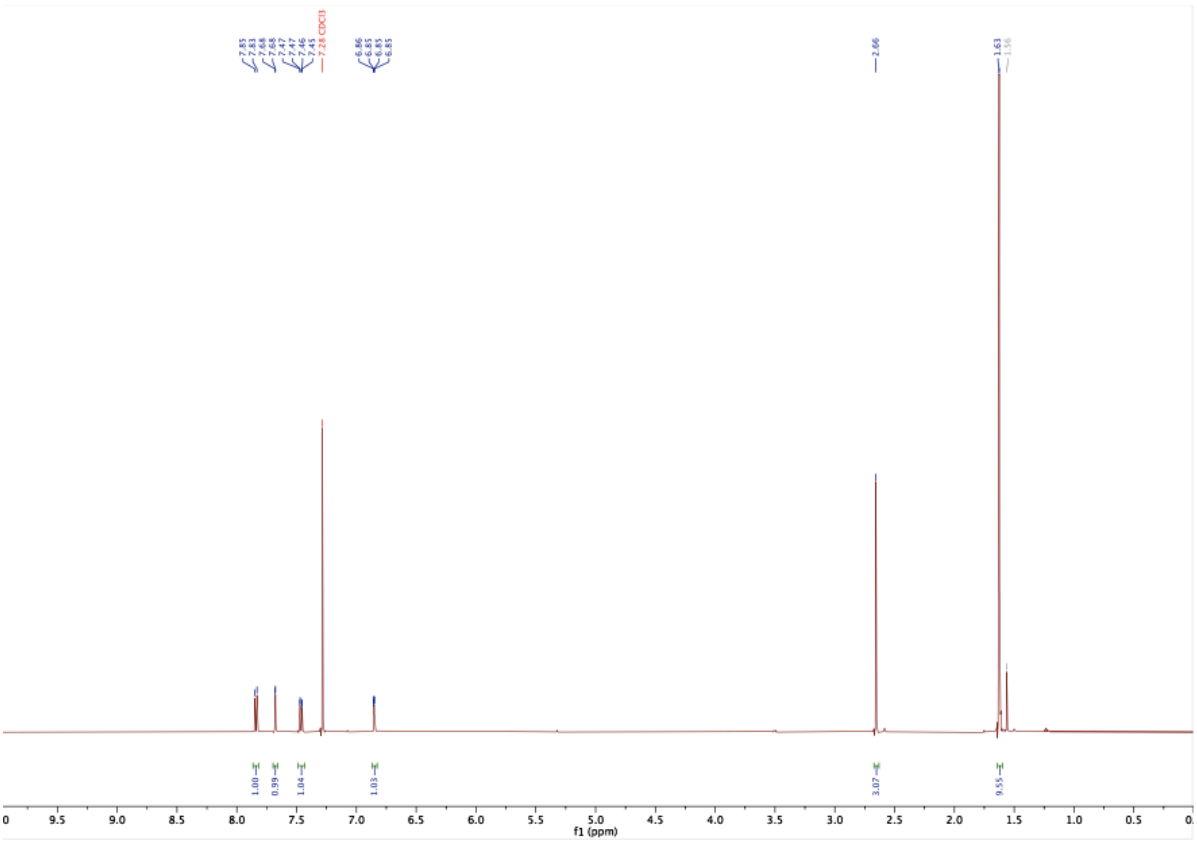

204.30
159.93
159.02
144.64
127.17
117.66
114.43
105.17
103.90
77.41 CDCl3
77.16 CDCl3
76.90 CDCl3
27.10
f1 (ppm)

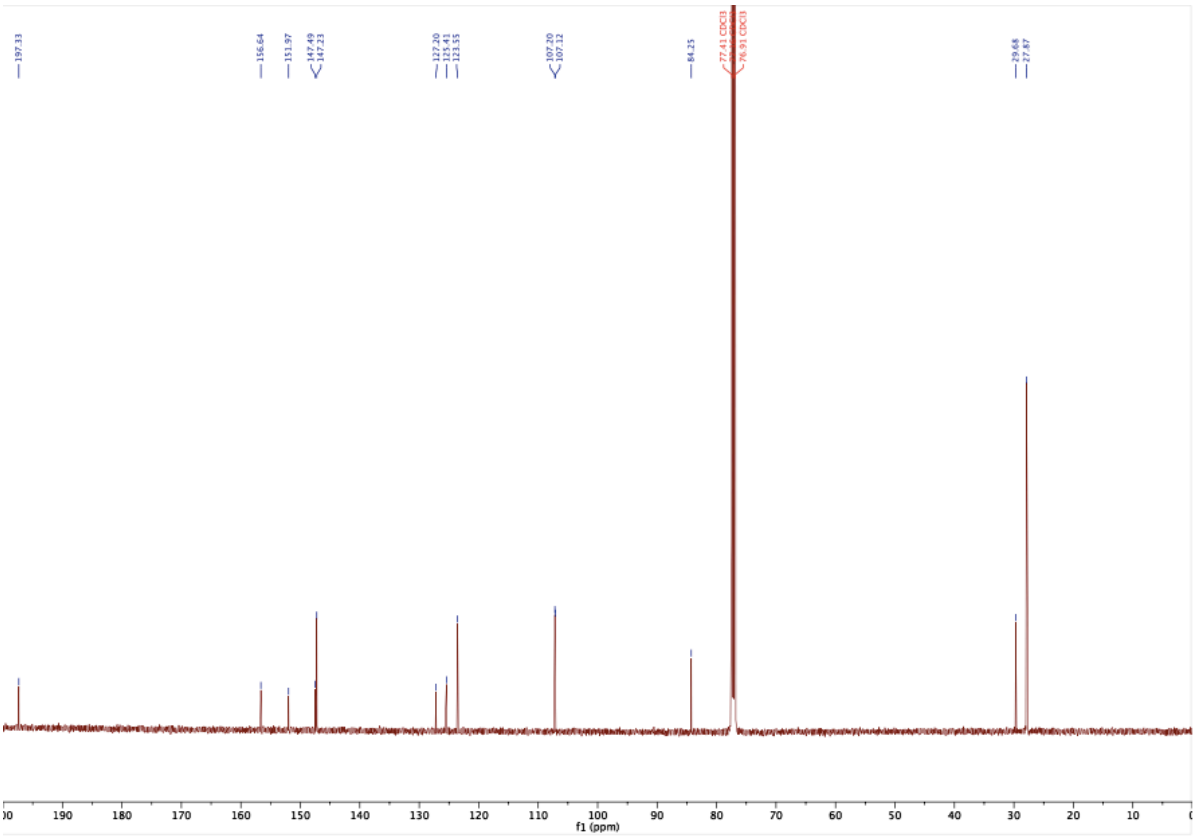
The Boc-protection of **SI-8** (0.88 g, 5 mmol) and **SI-9** (0.88 g, 5 mmol) would follow *General Procedure A* to obtain Boc-protected product **35i** (1.2 g, 90% isolated yield) and **35j** (1.2 g, 90% isolated yield).

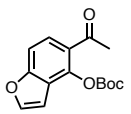


35i

Compound **35i**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.69 (d, *J* =2.3 Hz, 1H), 7.35 (d, *J* = 0.9 Hz, 1H), 6.84 (dd, J = 2.2, 1.0 Hz, 1H), 2.63 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.33, 156.64, 151.97, 147.49, 147.23, 127.20, 125.41, 123.55, 107.20, 107.12, 84.25, 29.68, 27.87. HRMS (EI+) m/z calculated for $C_{15}H_{16}O_5$ $[M+Na]^+$: 299.0895; found 299.0898.

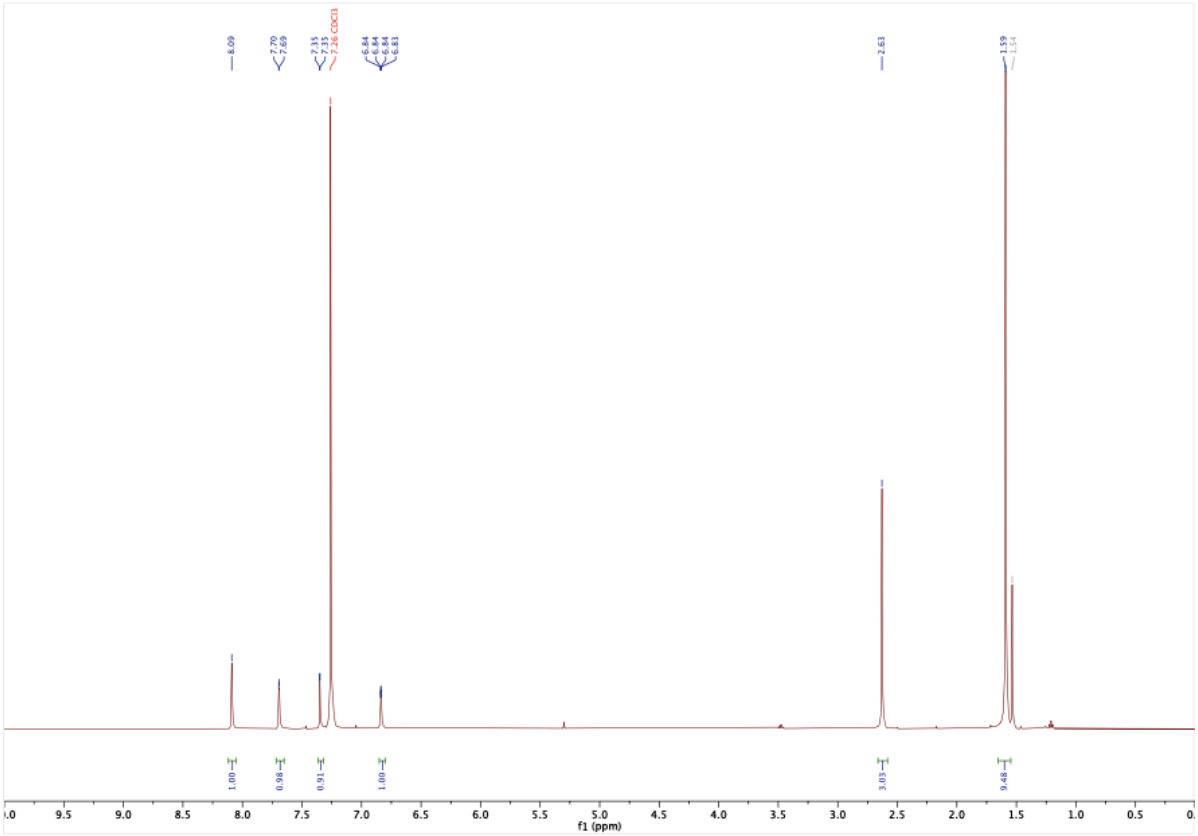

7.85
7.83
7.68
7.66
7.47
7.47
7.46
7.44
7.26 CDCl3
6.86
6.85
6.85
6.83
2.66
1.63
1.56
1.00
0.99
1.04
1.03
3.07
9.55
f1 (ppm)

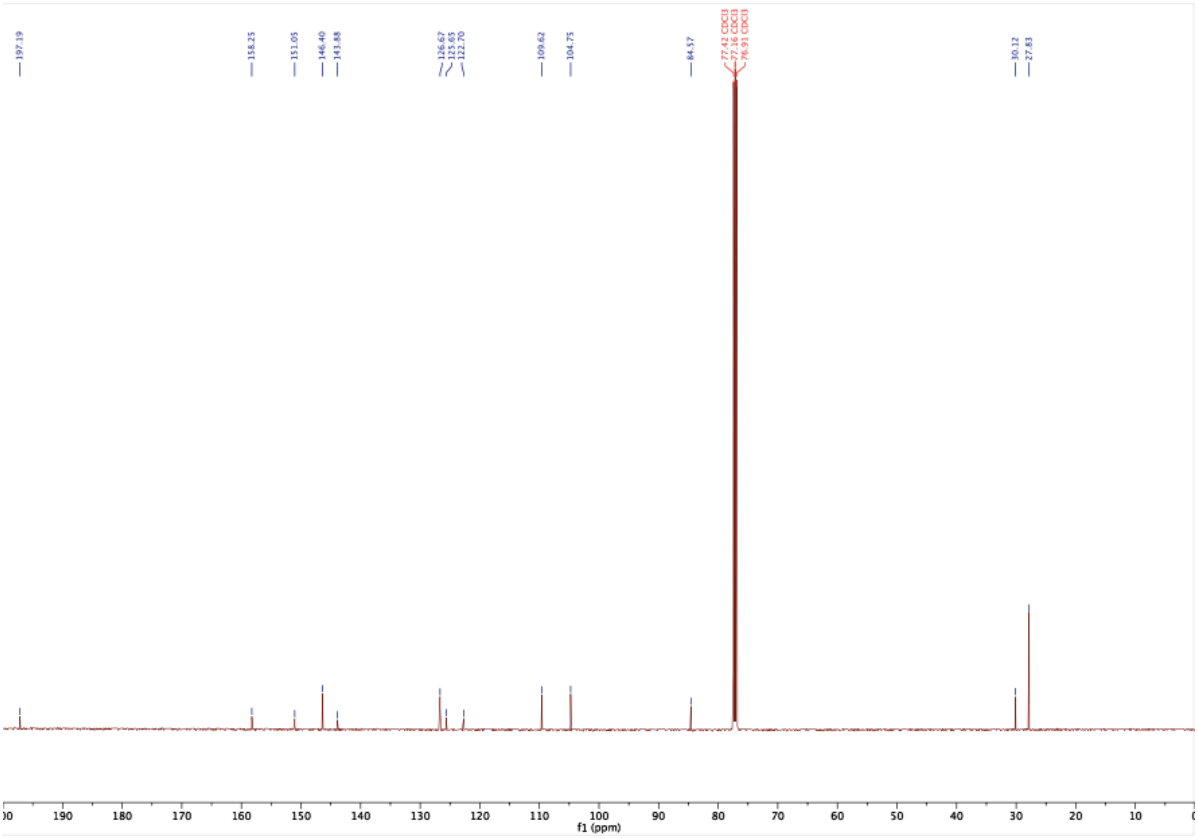

197.33
156.64
151.97
147.49
147.23
127.20
125.41
123.55
107.20
107.12
84.25
77.41 CDCl3
77.00 CDCl3
76.91 CDCl3
29.68
27.07
f1 (ppm)



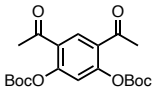
35j

Compound **35j**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.46 (dd, *J* = 8.7, 1.0 Hz, 1H), 6.85 (dd, *J* = 2.3, 1.0 Hz, 1H), 2.66 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 197.19, 158.25, 151.05, 146.40, 143.88, 126.67, 125.65, 122.70, 109.62, 104.75, 84.57, 30.12, 27.83. HRMS (EI+) m/z calculated for $C_{15}H_{16}O_5$ $[M+Na]^+$: 299.0895; found 299.0894.


8.09
7.70
7.69
7.35
7.26 CDCl3
6.84
6.84
6.84
6.83
2.63
1.59
1.54
1.00
0.98
0.91
1.00
3.03
9.48
f1 (ppm)

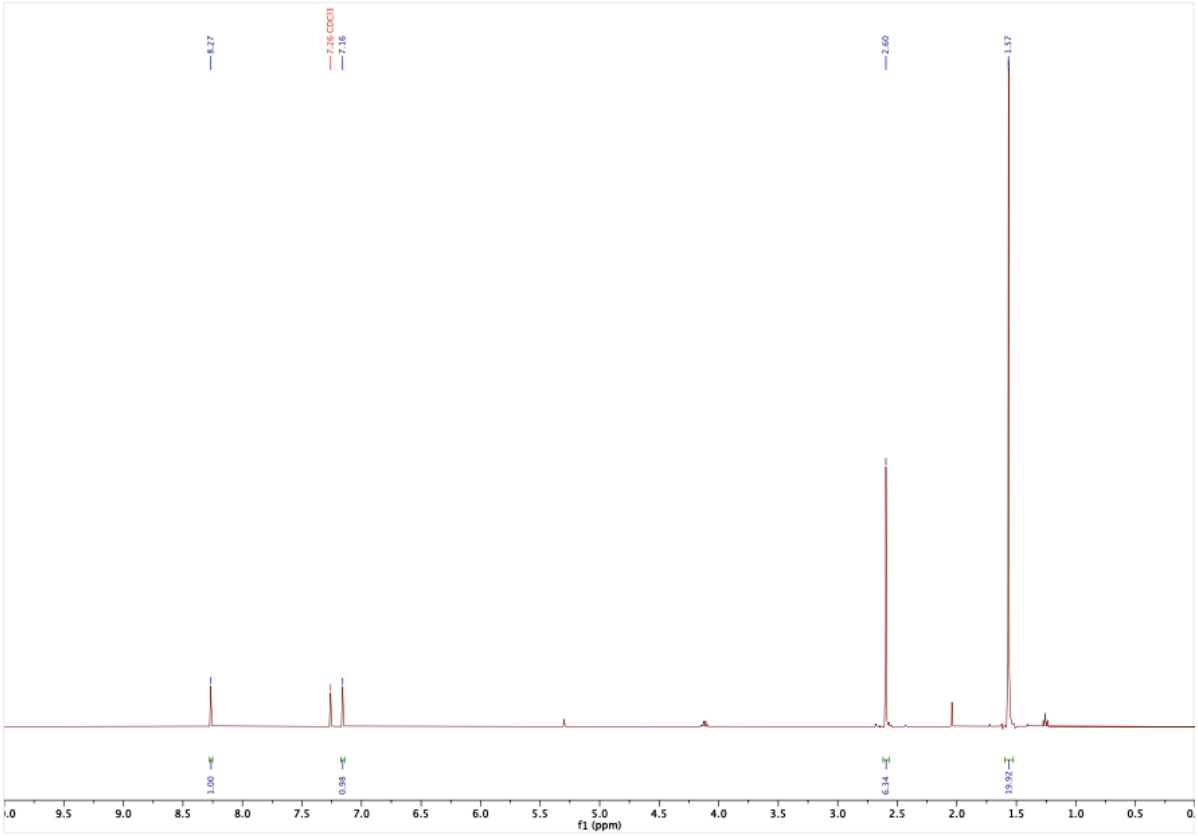

197.19
158.25
151.05
146.40
143.88
126.67
125.65
122.70
109.62
104.75
84.57
77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
30.12
27.83
f1 (ppm)

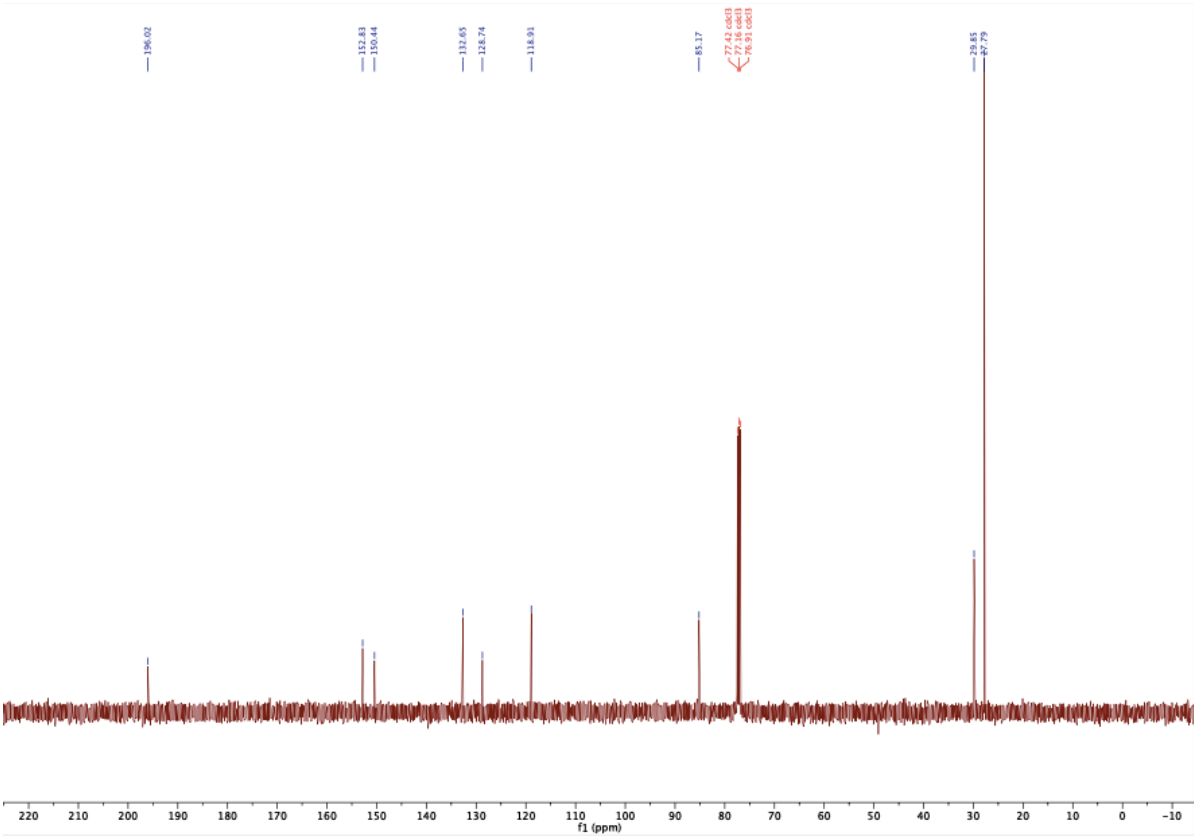
4.2.2 General Procedure B



35k

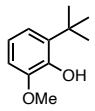
To a 100 mL round bottom flask, charged with 4,6-diacetylresorcinol (0.58 g, 3 mmol) in dry THF (30 mL, 0.1 M) was added 60% NaH (0.26 g, 6.6 mmol, 2.2 equivalent) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Boc_2O (1.44 g, 6.6 mmol, 2.2 equivalent) was added to the reaction solution. The reaction mixture was stirred at 0 °C and slowly warm to room temperature overnight. The completion of reaction is analyzed by TLC. At 0 °C, 0.1 N HCl aqueous solution (30 mL) was added slowly to the reaction mixture. The resulting solution was extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate-hexane, 1:3) to yield product **35k** (1.14 g, 2.6 mmol, 86% isolated yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.16 (s, 1H), 2.60 (s, 6H), 1.57 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.02, 152.83, 150.44, 132.65, 128.74, 118.91, 85.17, 29.85, 27.79. HRMS (ESI+) m/z calculated for $C_{20}H_{26}NO_8$ $[M+Na]^+$: 417.1525; found 417.1530.


8.27
7.26 CDCl3
7.16
2.60
1.57
1.00
0.98
6.34
19.92
f1 (ppm)


196.02
152.83
150.44
132.65
128.74
118.91
85.17
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
29.85
29.79
f1 (ppm)

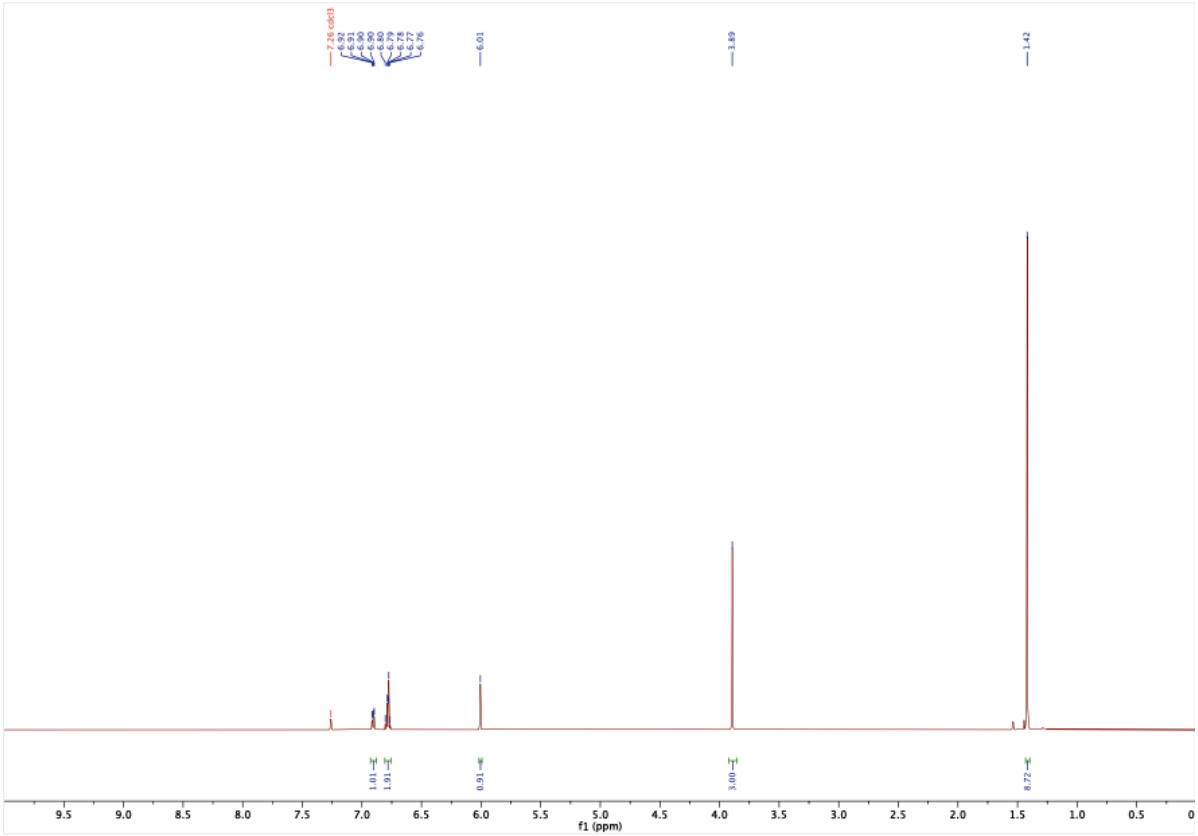
4.3 Synthesis of *ortho-tert*-Butyl Phenols

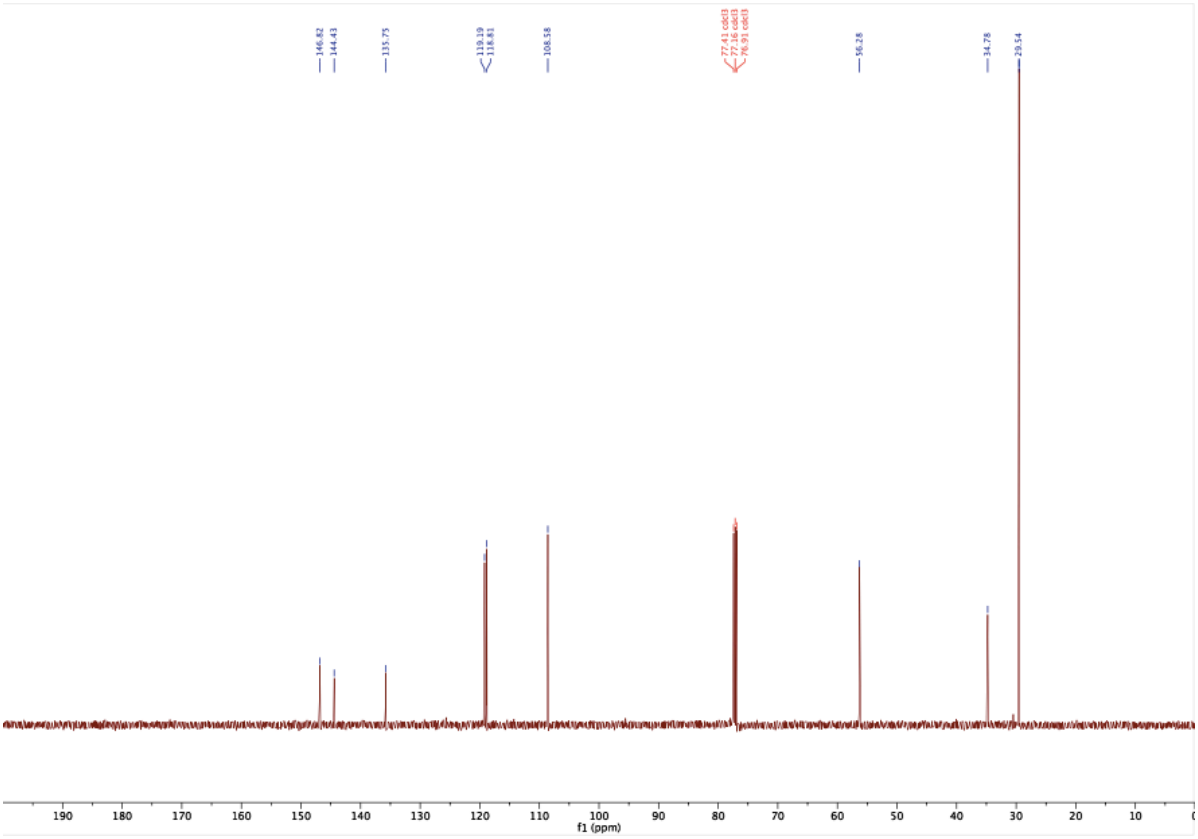
4.3.1 General Procedure C

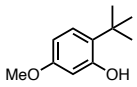


36a

A dry, nitrogen flushed, 10-mL Schlenk flask, equipped with a magnetic stir bar was charged with **35a** (100 mg) in dry Et_2O (3.8 mL, 0.1 M) was added MeMgCl (0.42 mL, 2.69 M, 1.13 mmol, 3.0 equivalent) dropwise at -78 °C. The reaction was allowed to slowly warm to room temperature overnight. The reaction was quenched with 1 M aq. NH_4Cl (3 mL) and extracted with Et_2O (4 x 1 mL). The combined organic fractions were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate–hexane, 1:9) to yield the *t*-butylated phenols **36a** (56.9 mg, 84% isolated yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (dd, J = 6.7, 2.8 Hz, 1H), 6.82 – 6.74 (m, 2H), 6.01 (s, OH), 3.89 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.82, 144.43, 135.75, 119.19, 118.81, 108.58, 56.28, 34.78, 29.54. HRMS (EI+) m/z calculated for $C_{11}H_{16}O_2$ [M^+]: 180.1150; found 180.1149.

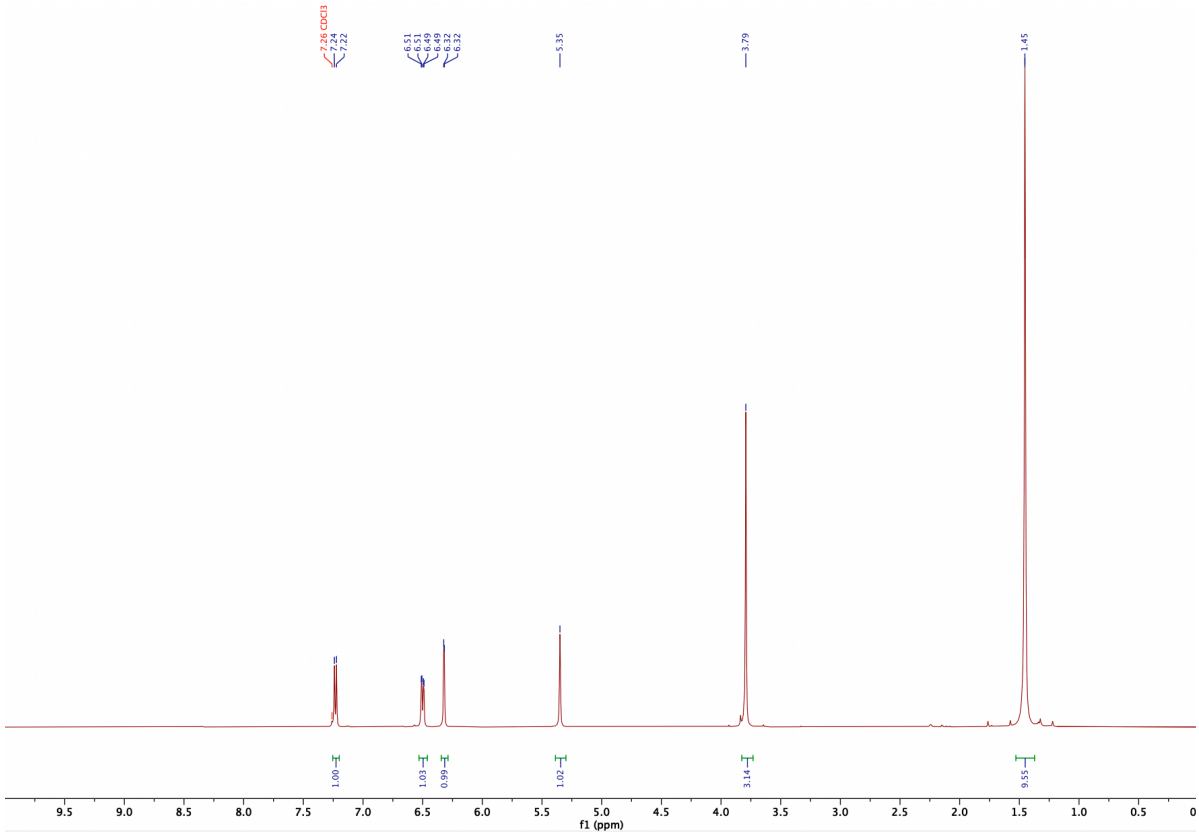

7.26 cdcl3
6.91
6.90
6.90
6.80
6.80
6.79
6.78
6.77
6.76
6.01
3.89
1.42
1.01
1.91
0.91
3.00
8.72
f1 (ppm)

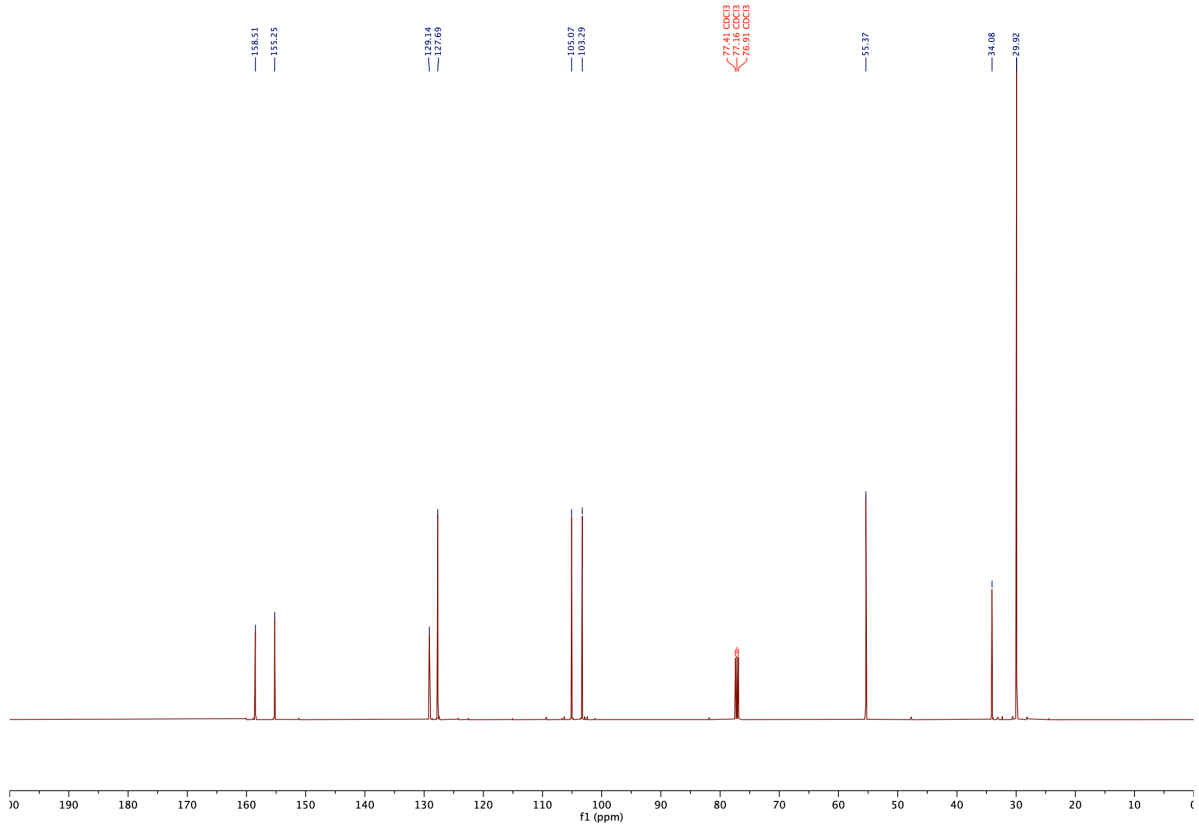

146.82
144.43
135.75
119.19
118.81
108.58
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
56.28
34.78
29.54
f1 (ppm)

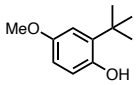


36b

Compound **36b** was synthesized according to general procedure C: (ethyl acetate–hexane, 1:3), 53.0 mg, 84% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, J = 8.6 Hz, 1H), 6.50 (dd, J = 8.8, 2.6 Hz, 1H), 6.32 (d, J = 2.6 Hz, 1H), 5.35 (s, 1H), 3.79 (s, 3H), 1.45 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 158.51, 155.25, 129.14, 127.69, 105.07, 103.29, 55.37, 34.08, 29.92. HRMS (ESI-) m/z calculated for $C_{11}H_{16}O_2$ $[M]^+$: 180.1150; found 180.1143.

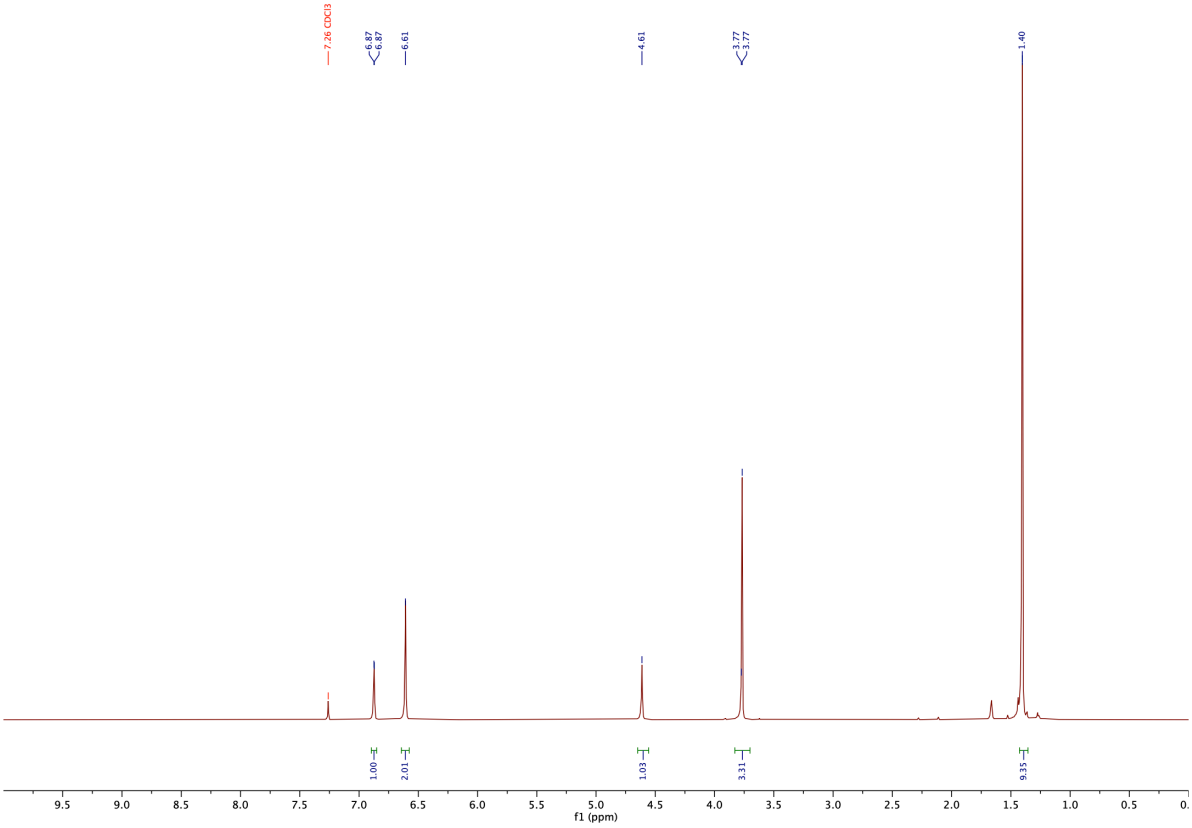

7.26 CDCl3
7.24
7.22
6.51
6.51
6.49
6.49
6.32
6.32
5.35
3.79
1.45
1.00
1.03
0.99
1.02
3.14
9.55
f1 (ppm)

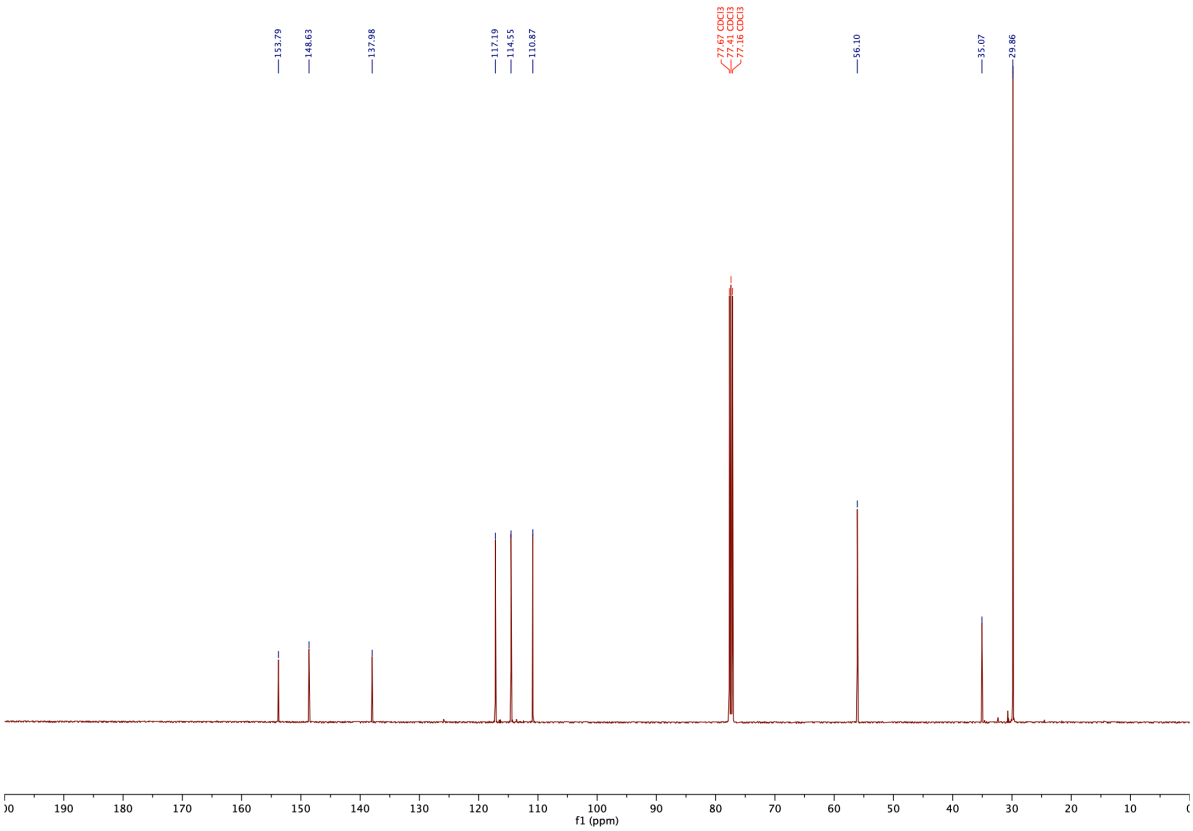

158.51
155.25
129.14
127.69
105.07
103.29
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
55.37
34.08
29.92
f1 (ppm)

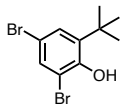


36c

Compound **36c** was synthesized according to general procedure C: (ethyl acetate–hexane, 1:3), 53.0 mg, 85% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89 – 6.85 (m, 1H), 6.61 (s, 1H), 4.61 (s, 1H), 3.77 (s, 3H), 1.40 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.79, 148.63, 137.98, 117.19, 114.55, 110.87, 56.10, 35.07, 29.86. HRMS (ESI-) m/z calculated for $C_{11}H_{16}O_2$ $[M]^+$: 180.1150; found 180.1144.

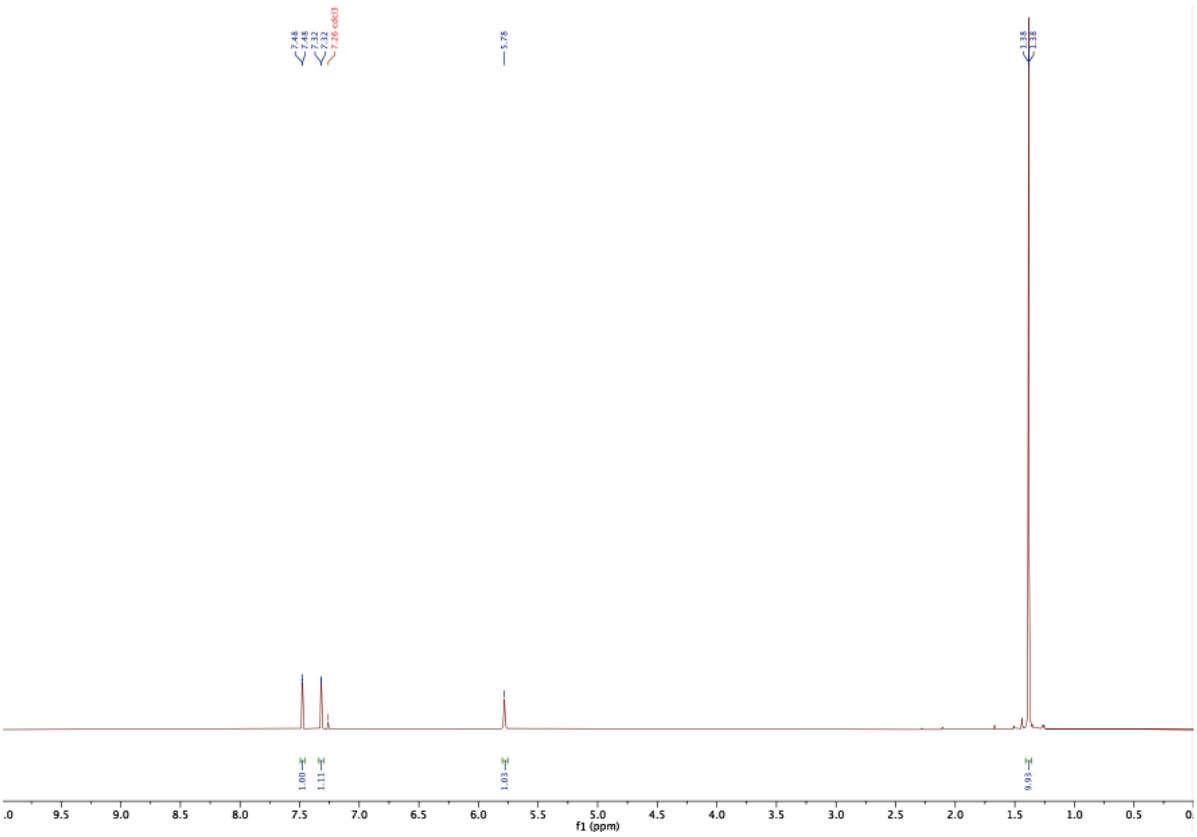

7.26 CDCl3
6.87
6.87
6.61
4.61
3.77
3.77
1.40
1.00
2.01
1.03
3.31
9.35
f1 (ppm)

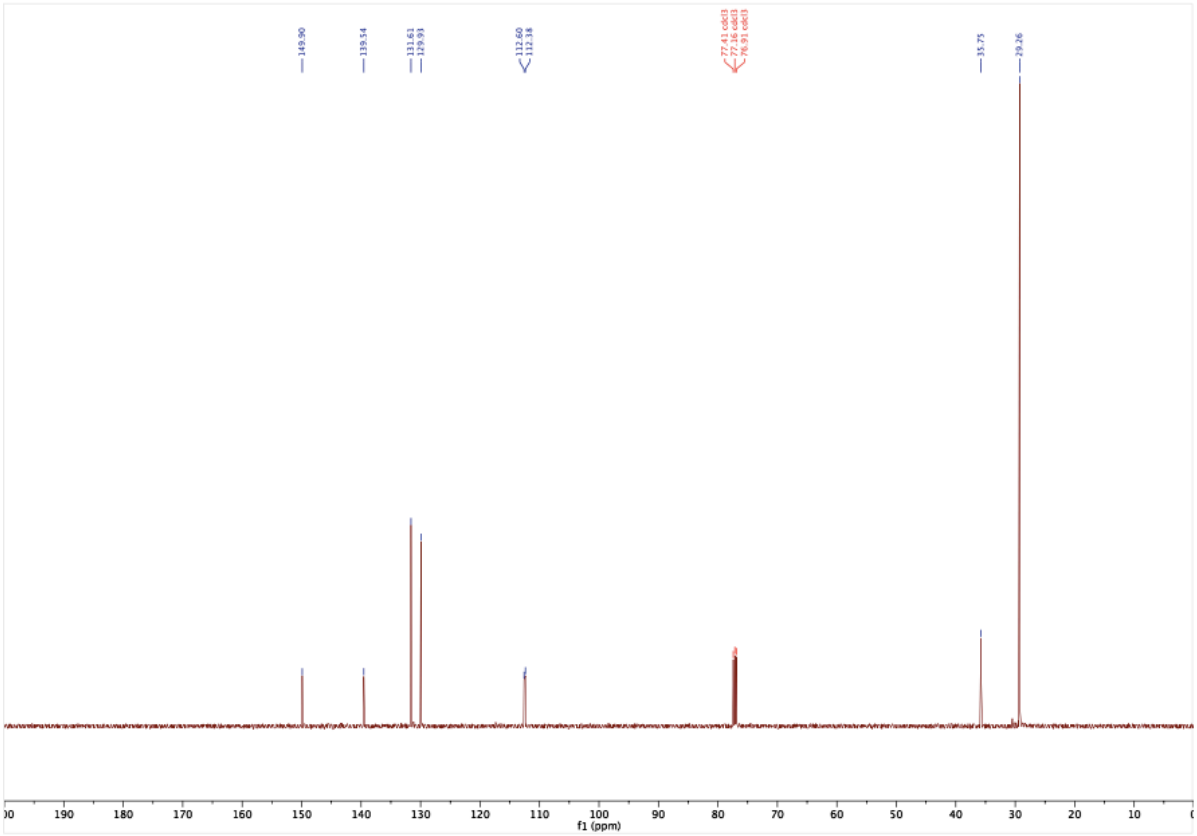

153.79
148.63
137.98
117.19
114.55
110.87
77.67 CDCl3
77.41 CDCl3
77.16 CDCl3
56.10
35.07
29.86
f1 (ppm)

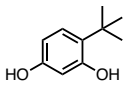


36d

Compound **36d** was synthesized according to general procedure C: (ethyl acetate–hexane, 1:3), 63.3 mg, 81% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, J = 2.4, 0.7 Hz, 1H), 7.32 (dd, J = 2.3, 0.7 Hz, 1H), 5.78 (s, OH), 1.38 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 149.90, 139.54, 131.61, 129.93, 112.60, 112.38, 35.75, 29.26. HRMS (ESI-) m/z calculated for $C_{10}H_{12}Br_2O$ $[M-H]^-$: 306.9156; found 306.9150.

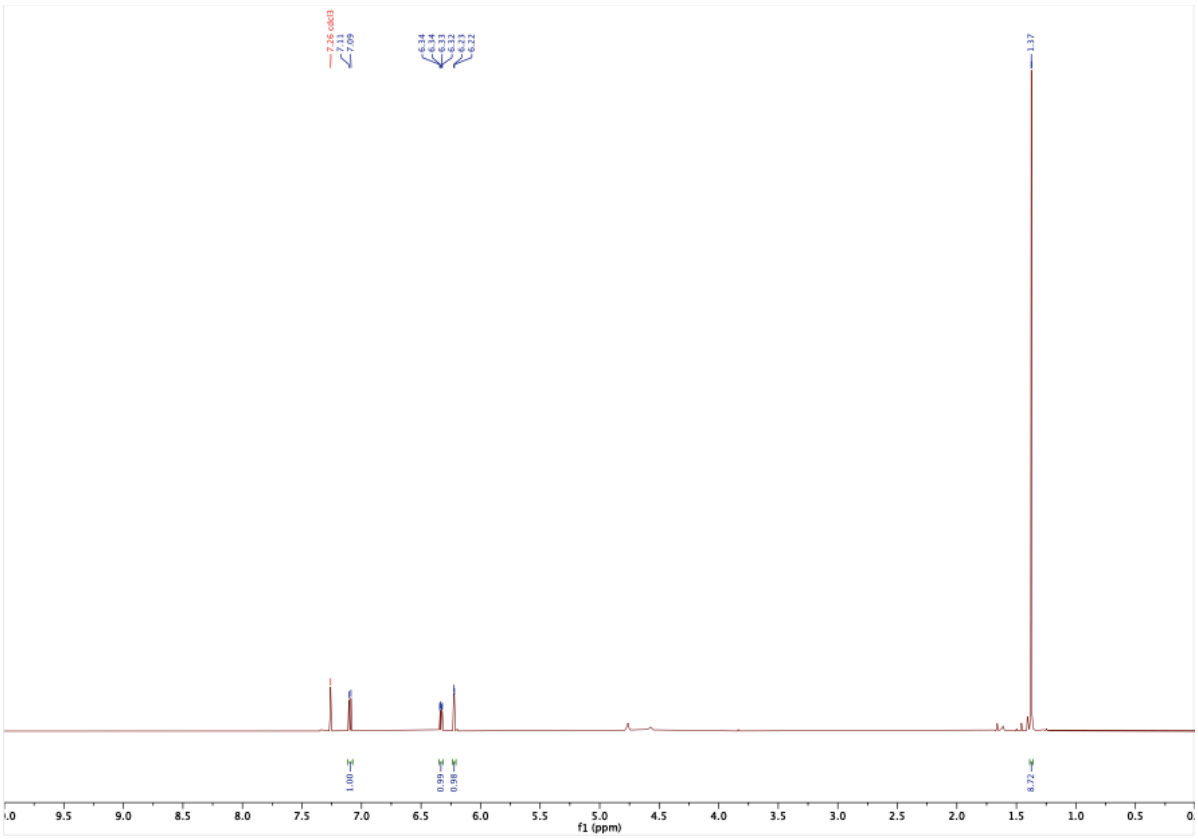

7.48
7.48
7.32
7.32
7.26 cdcl3
5.78
1.38
1.38
1.00
1.11
1.03
9.93
f1 (ppm)

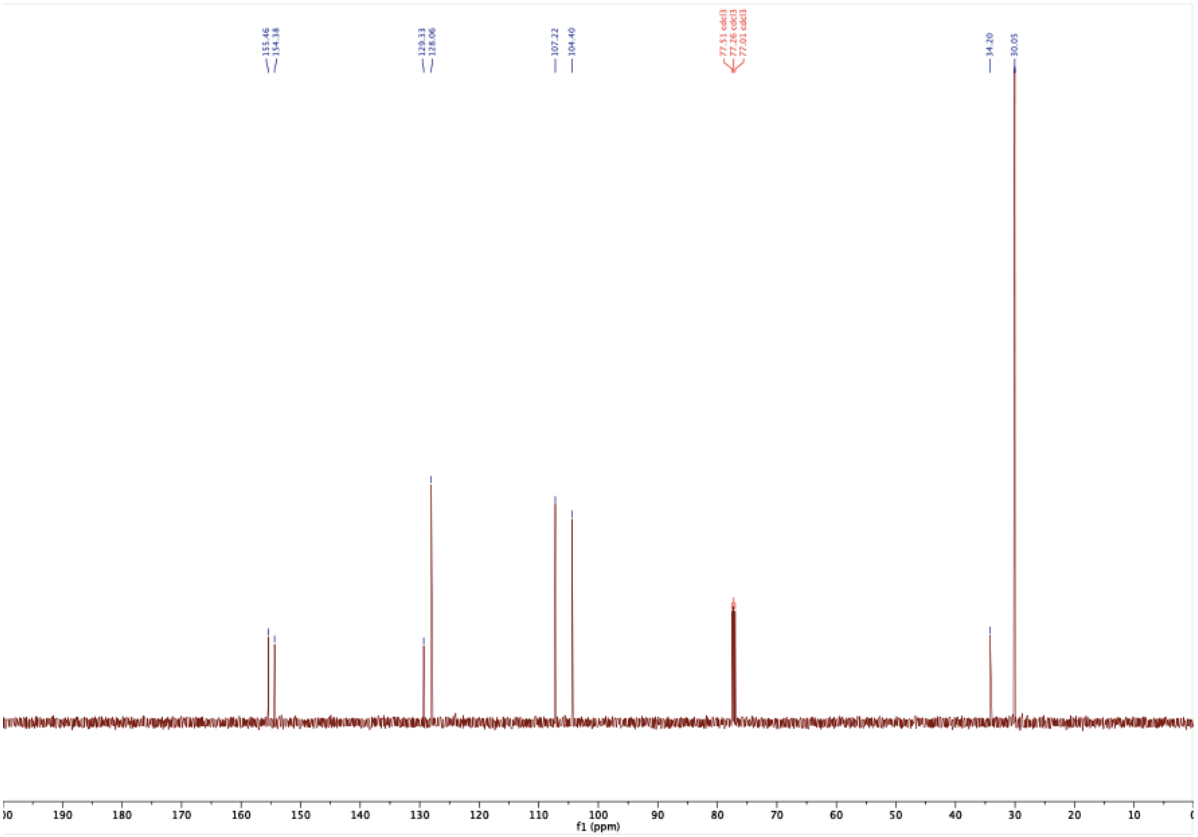

149.90
139.54
131.61
129.93
112.60
112.38
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
35.75
29.26
f1 (ppm)

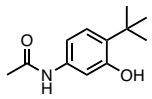


36f

Compound **36f** was synthesized according to general procedure C: (ethyl acetate–hexane, 1:3), 78.3 mg, 78% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.4 Hz, 1H), 6.33 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.22 (d, *J* = 2.6 Hz, 1H), 1.37 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.36, 154.28, 129.23, 127.96, 107.12, 104.30, 34.10, 29.95. HRMS (ESI+) m/z calculated for $C_{10}H_{14}O_2$ $[M]^+$: 166.0994; found 166.0994.

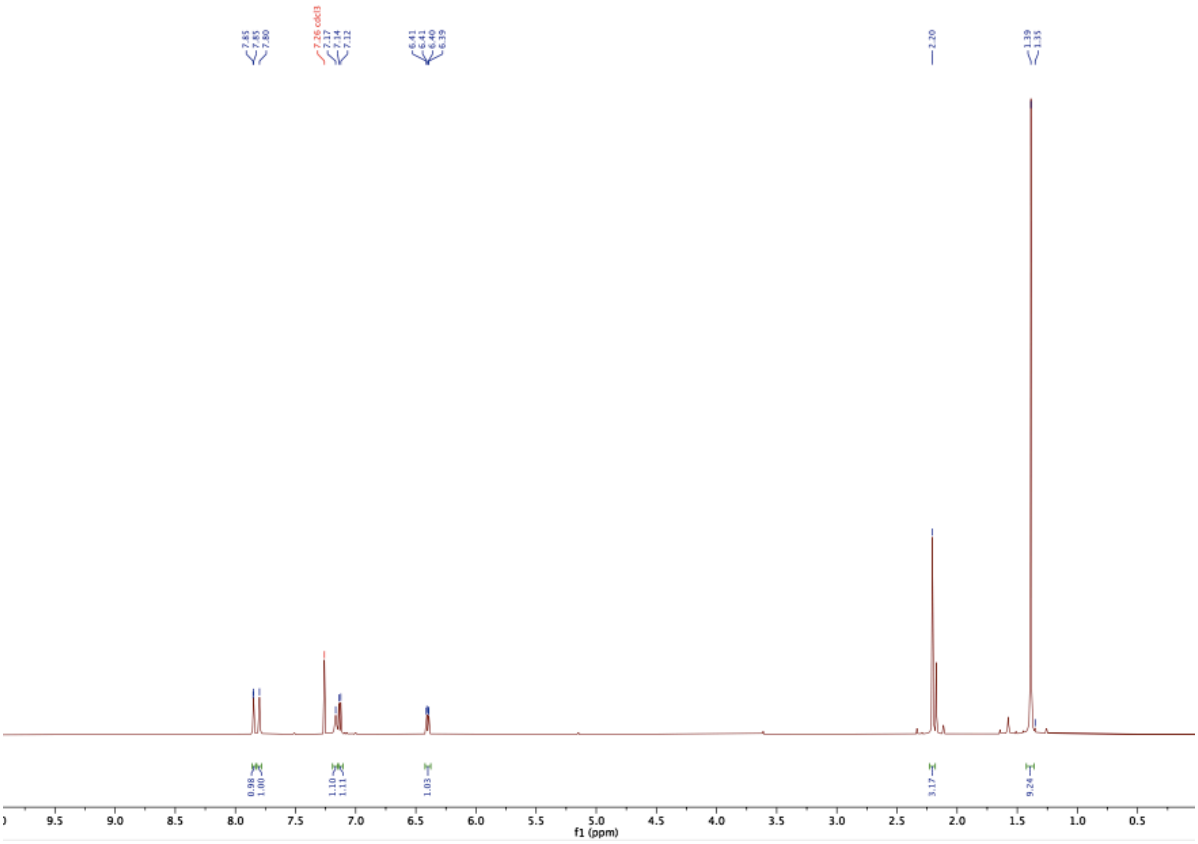

7.26 cdcl3
7.11
7.09
6.34
6.34
6.33
6.32
6.23
6.22
1.37
1.00
0.99
0.98
8.72
f1 (ppm)

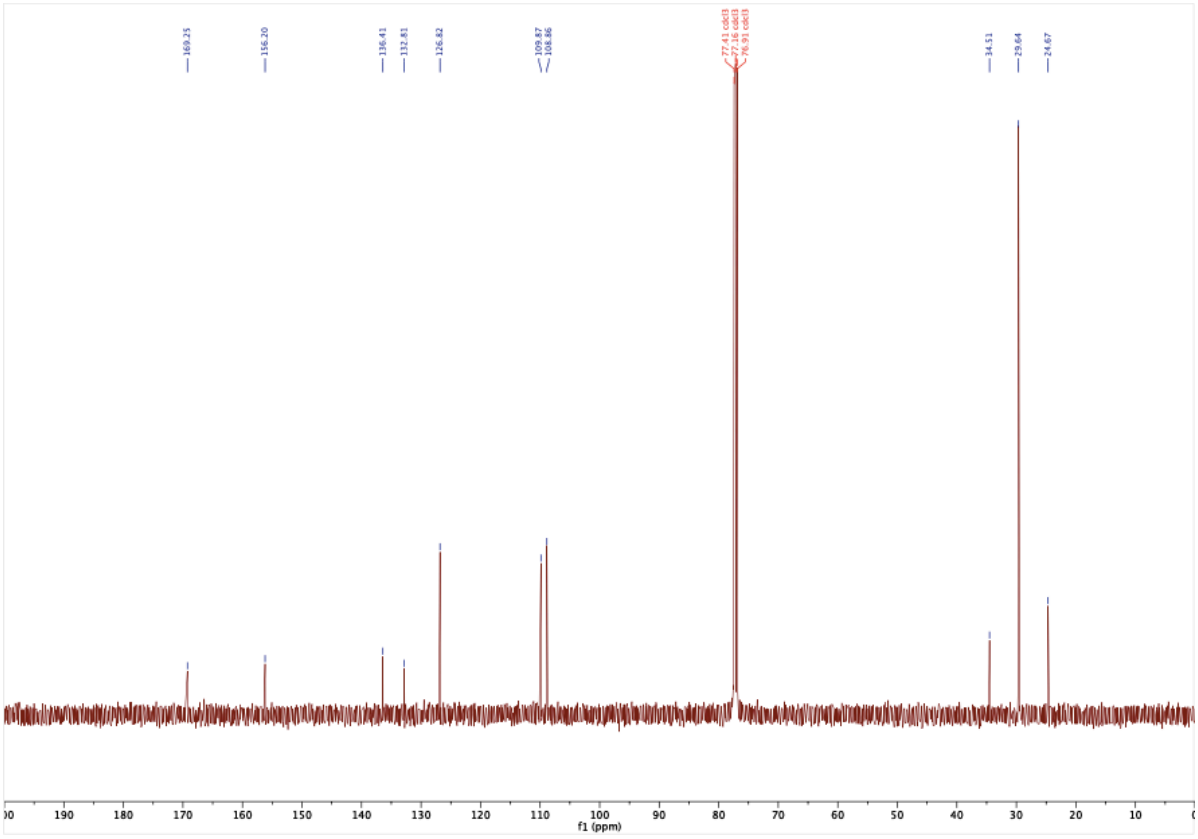

155.46
154.38
129.33
128.06
107.22
104.40
77.31 cdcl3
77.06 cdcl3
76.81 cdcl3
34.20
30.05
f1 (ppm)

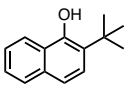


36g

Compound **36g** was synthesized according to general procedure C: (ethyl acetate–hexane, 1:1), 65.8 mg, 93% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 2.3 Hz, 1H), 7.80 (s, 1H), 7.17 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.40 (dd, *J* = 8.3, 2.3 Hz, 1H), 2.20 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.25, 156.20, 136.41, 132.81, 126.82, 109.87, 108.86, 34.51, 29.64, 24.67. HRMS (ESI+) m/z calculated for $C_{12}H_{17}NO_2$ $[M+Na]^+$: 230.1157; found 230.1154.

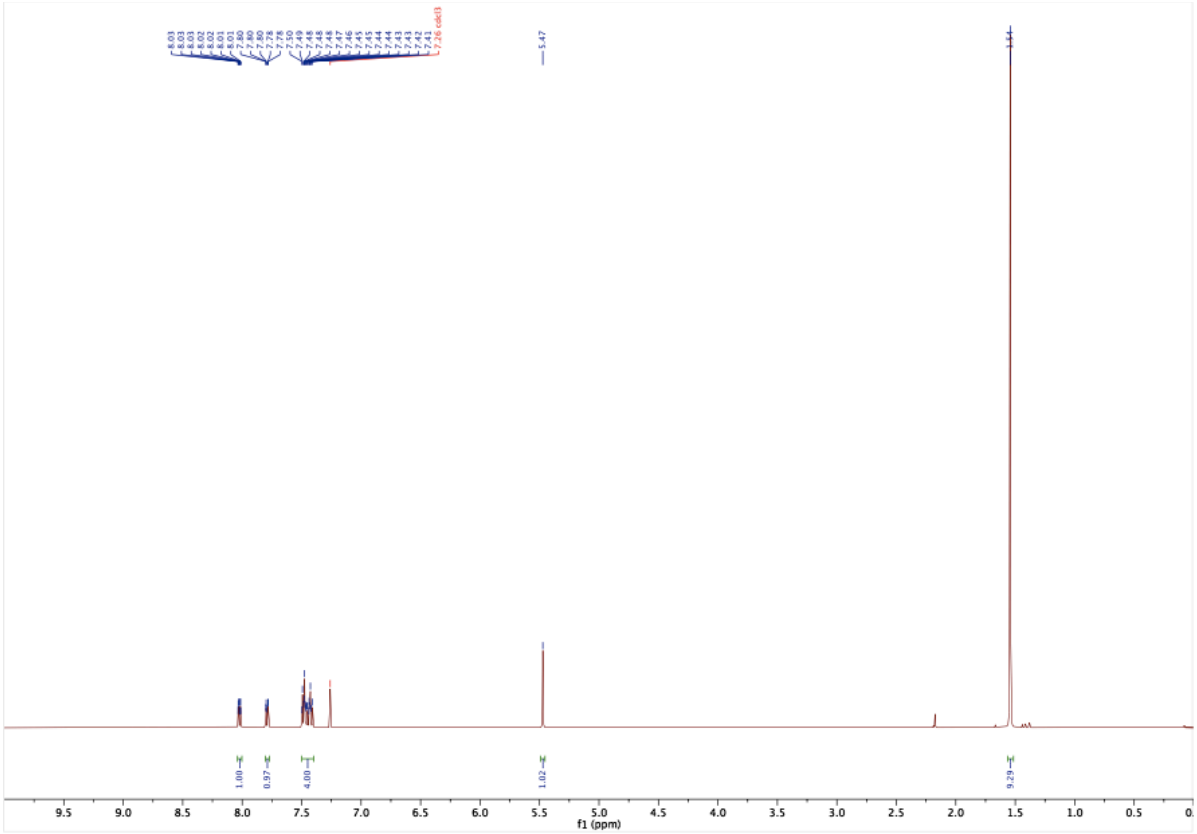

7.85
7.85
7.80
7.26 cdcl3
7.17
7.14
7.12
6.41
6.41
6.40
6.39
2.20
1.39
1.35
0.98
1.00
1.10
1.11
1.03
3.17
9.24
f1 (ppm)

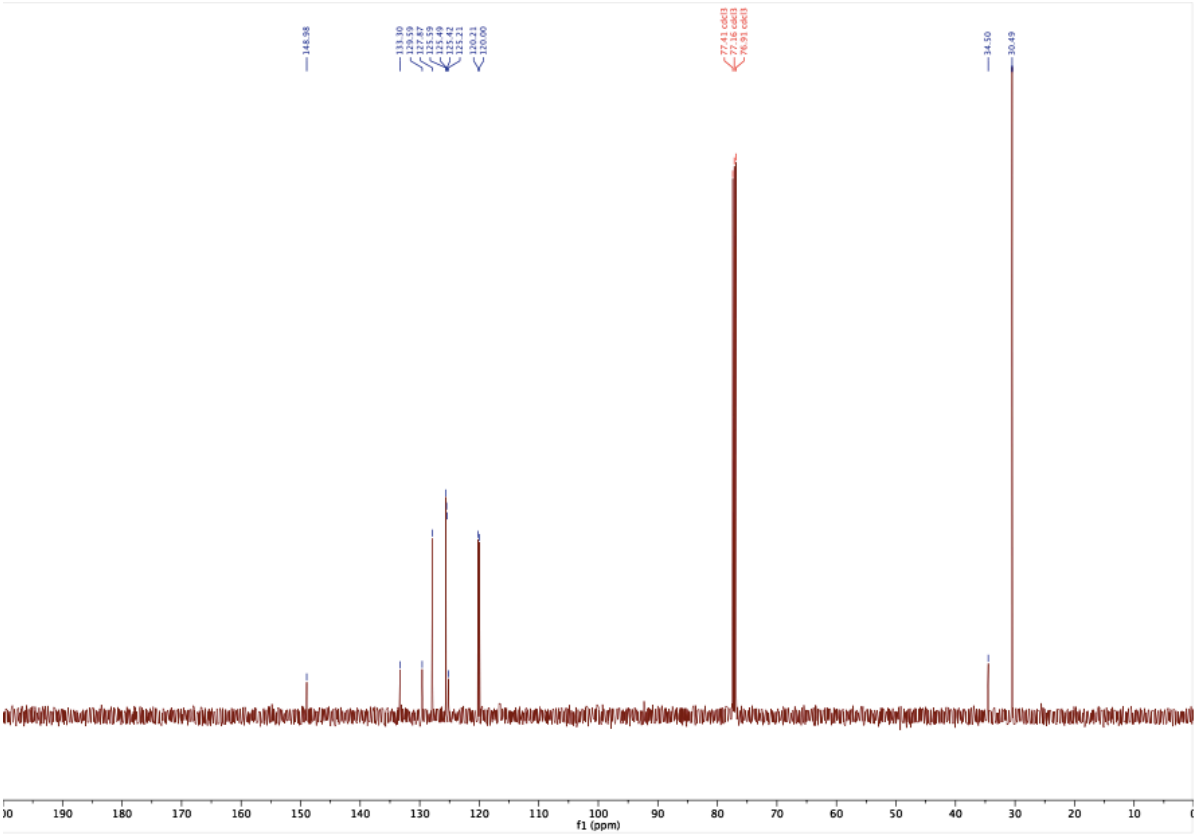

169.25
156.20
136.41
132.81
126.82
109.87
108.86
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
34.51
29.64
24.67
f1 (ppm)

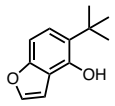


36h

Compound **36h** was synthesized according to general procedure C: (ethyl acetate–hexane, 1:3), 69.2 mg, 99% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 – 7.99 (m, 1H), 7.82 – 7.76 (m, 1H), 7.51 – 7.39 (m, 4H), 5.47 (s, OH), 1.54 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.98, 133.30, 129.59, 127.87, 125.59, 125.49, 125.42, 125.21, 120.21, 120.00, 34.50, 30.49. HRMS (EI+) m/z calculated for $C_{14}H_{16}O$ [M^+]: 200.1201; found 200.1203.

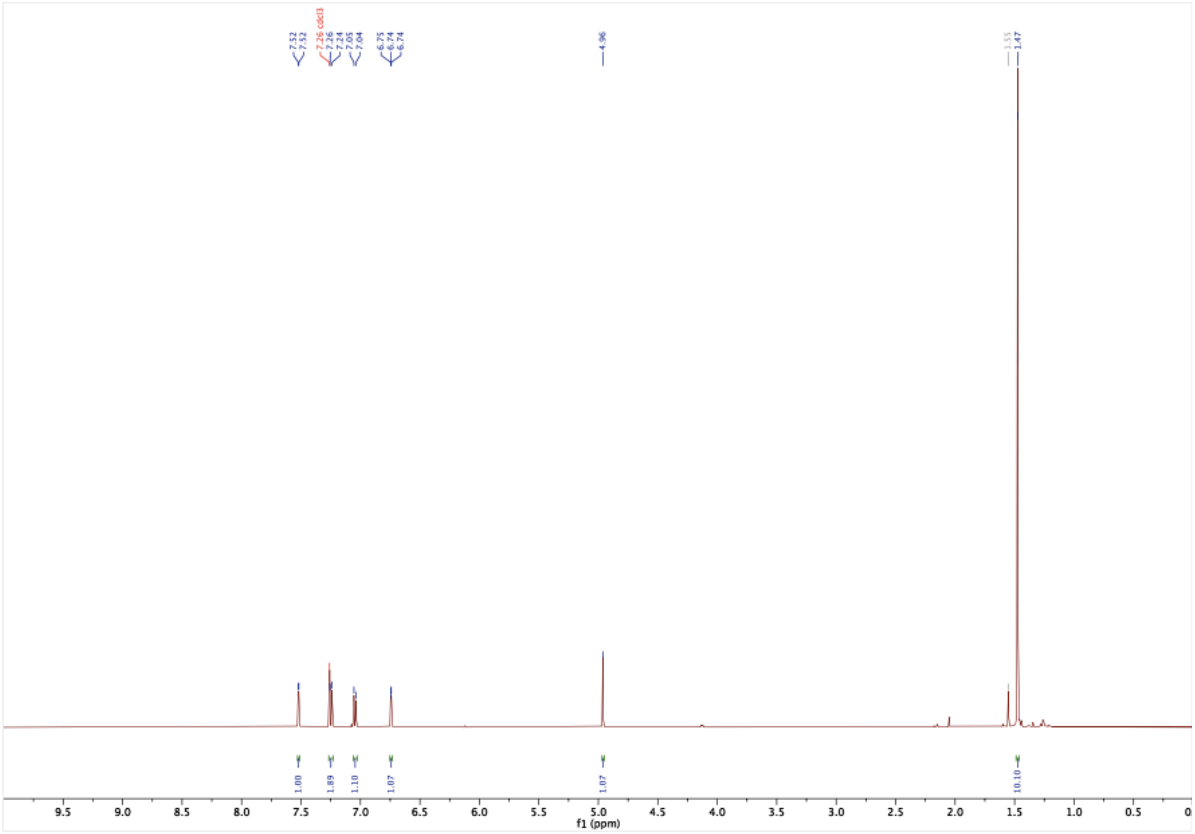

8.03
8.03
8.03
8.02
8.02
8.02
8.01
8.01
7.80
7.80
7.79
7.78
7.50
7.49
7.48
7.48
7.48
7.47
7.47
7.46
7.45
7.45
7.44
7.44
7.43
7.43
7.42
7.41
7.26 cdcl3
5.47
1.44
1.00
0.97
4.00
1.02
9.29
f1 (ppm)

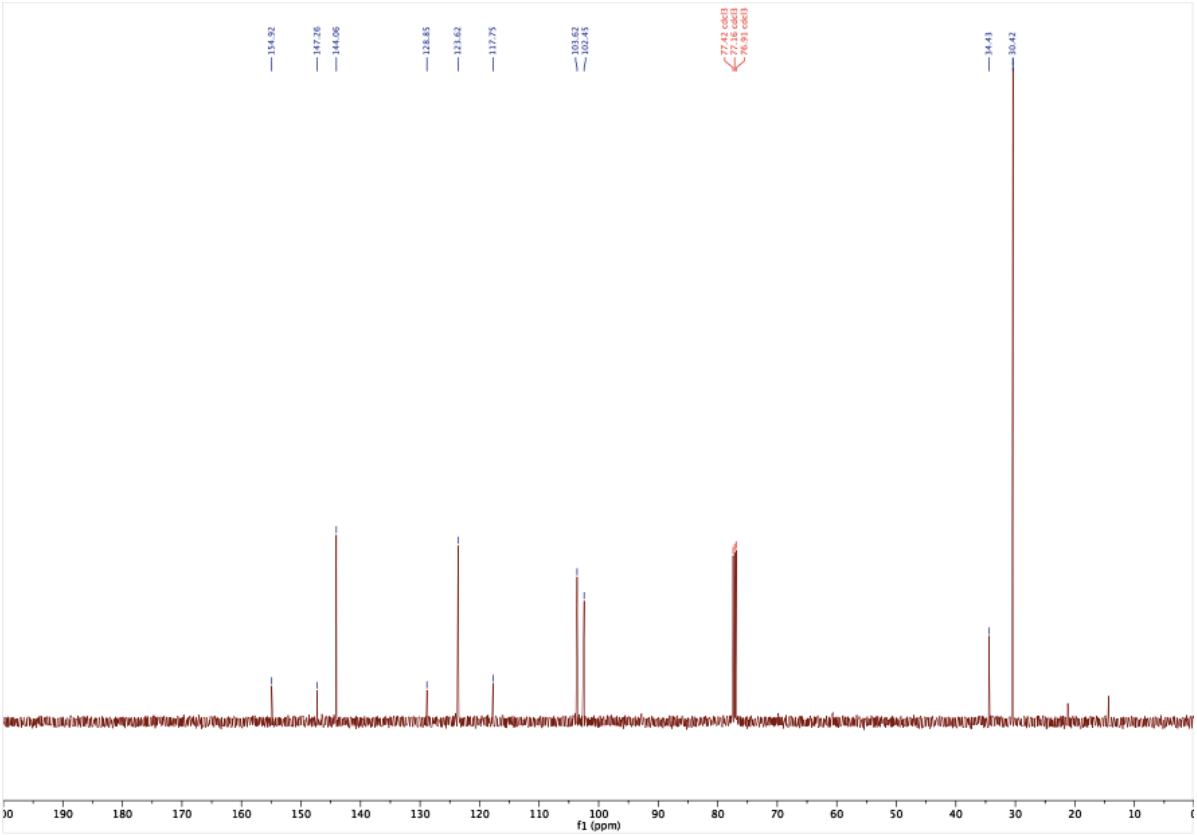

148.98
133.10
129.99
127.87
125.59
125.49
125.42
125.21
120.21
120.00
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
34.50
30.49
f1 (ppm)



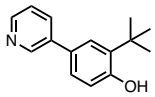
36j

Compound **36j** was synthesized according to general procedure C: (ethyl acetate–hexane, 1:3), 60.6 mg, 88% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 2.3 Hz, 1H), 7.28 – 7.22 (m, 1H, overlap with NMR solvent), 7.05 (dt, *J* = 8.7, 0.9 Hz, 1H), 6.74 (dt, *J* = 2.0, 0.9 Hz, 1H), 4.96 (s, OH), 1.47 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.92, 147.26, 144.06, 128.85, 123.62, 117.75, 103.62, 102.45, 34.43, 30.42. HRMS (EI+) m/z calculated for $C_{12}H_{14}O_2$ [M^+]: 190.0994; found 190.0995.


7.52
7.52
7.26 cdcl3
7.26
7.24
7.05
7.04
6.75
6.74
6.74
4.96
1.55
1.47
1.00
1.89
1.10
1.07
1.07
10.10
f1 (ppm)

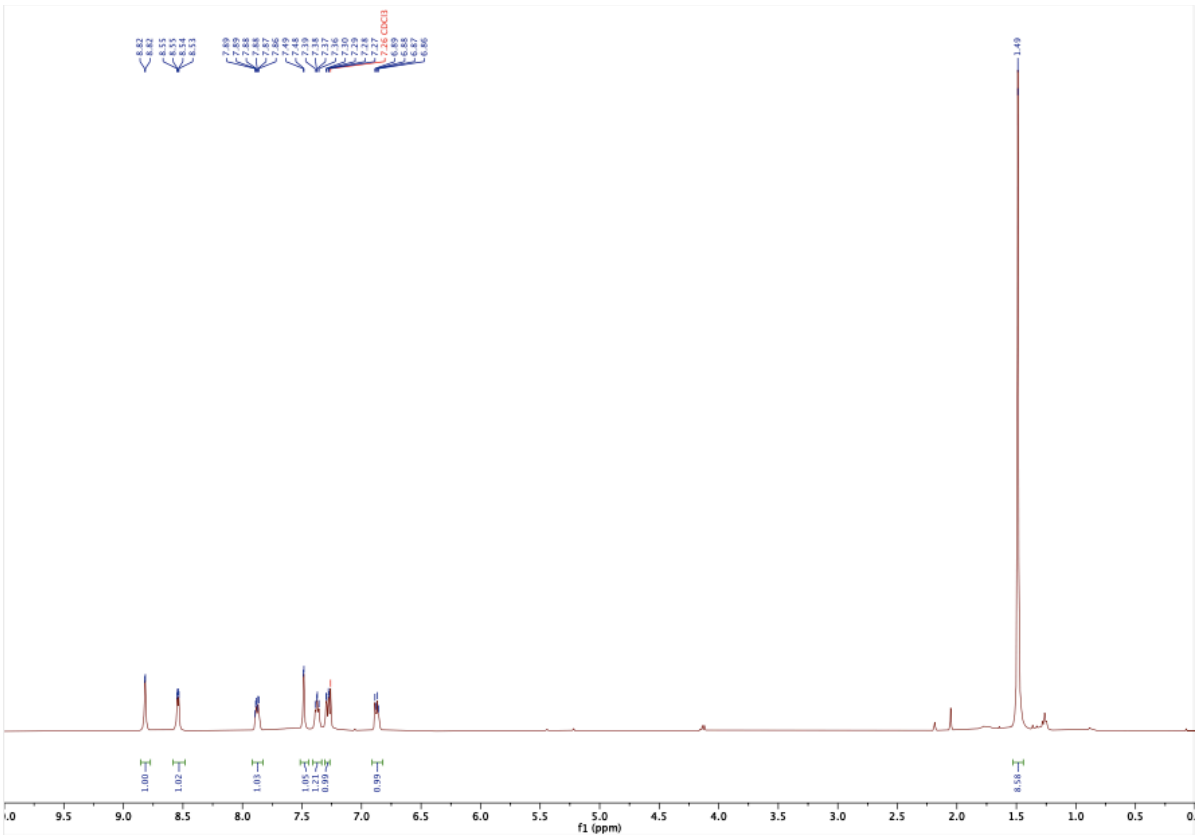

154.92
147.26
144.06
128.85
123.62
117.75
103.62
102.45
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
34.43
30.42
f1 (ppm)

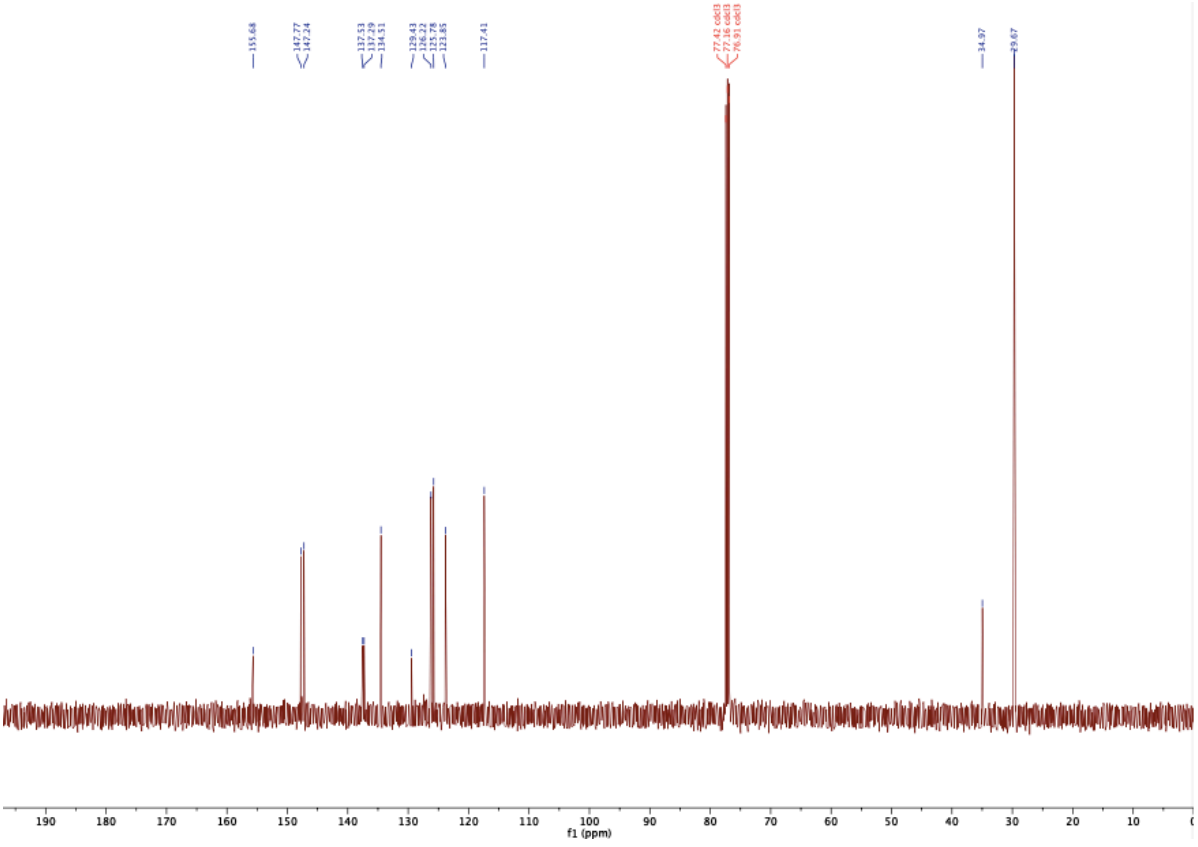
4.3.2 General Procedure D

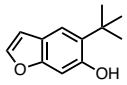


36e

A dry, nitrogen flushed, 10-mL Schlenk flask, equipped with a magnetic stir bar was charged with **35e** (0.2 mL, 0.5 M in dry toluene, 0.1 mmol) in dry Et_2O (1 mL, 0.1 M) was added MeMgCl (0.16 mL, 2.74 M, 0.44 mmol, 2.2 equivalent) dropwise at -78 °C. The reaction was stirred and allowed to slowly warm to room temperature overnight. The reaction was quenched with 1 M aq. NH_4Cl (1 mL) and extracted with Et_2O (3 x 1 mL). The combined organic fractions were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography (1% TEA in ethyl acetate–hexane, 1:3), 49.3 mg, 68% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, *J* = 2.3 Hz, 1H), 8.56 – 8.52 (m, 1H), 7.92 – 7.84 (m, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.37 (dd, *J* = 7.9, 5.0 Hz, 1H), 7.29 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.87 (dd, *J* = 8.2, 4.1 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.68, 147.77, 147.24, 137.53, 137.29, 134.51, 129.43, 126.22, 125.78, 123.85, 117.41, 34.97, 29.67. HRMS (ESI+) m/z calculated for $C_{15}H_{17}NO$ $[M+H]^+$: 228.1388; found 228.1389.

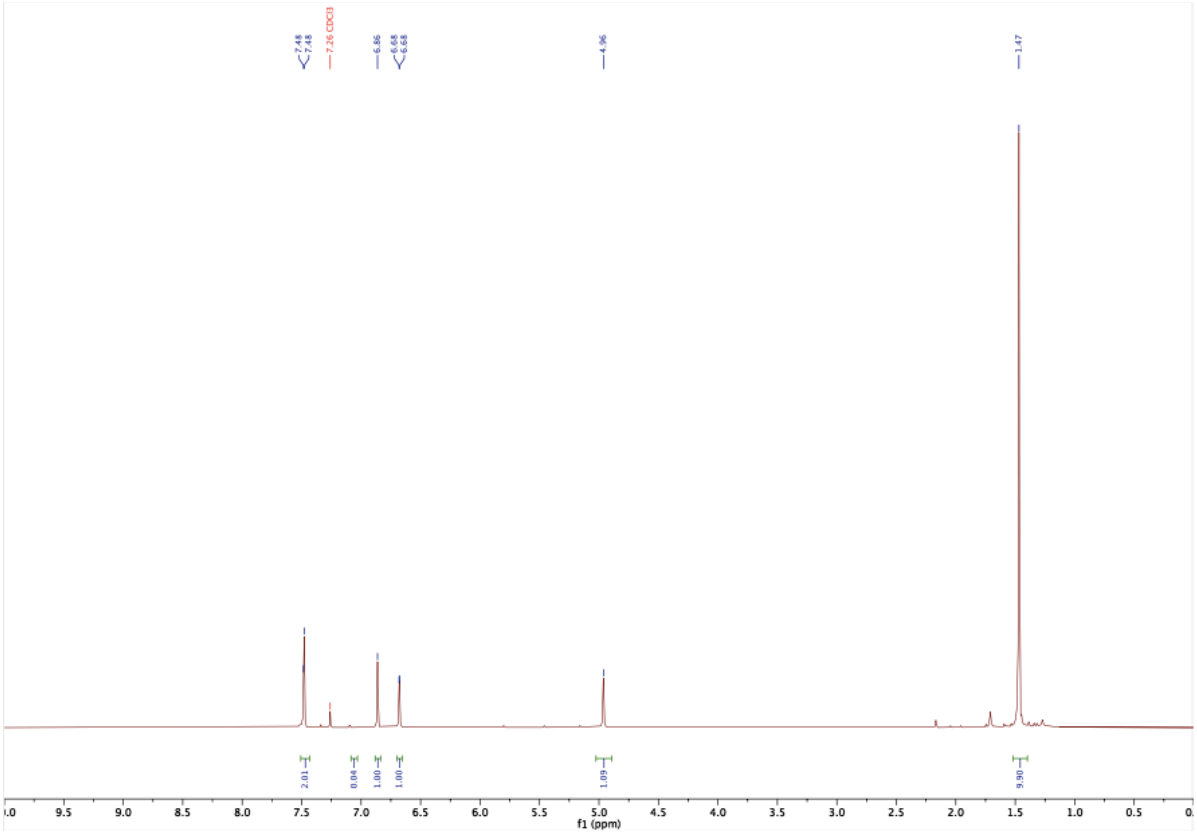

8.82
8.82
8.55
8.55
8.54
8.53
7.89
7.89
7.88
7.88
7.87
7.86
7.49
7.48
7.39
7.38
7.37
7.36
7.30
7.29
7.28
7.27
CDCl3
6.89
6.88
6.87
6.86
1.49
1.00
1.02
1.03
1.05
1.21
0.89
0.99
8.58
f1 (ppm)

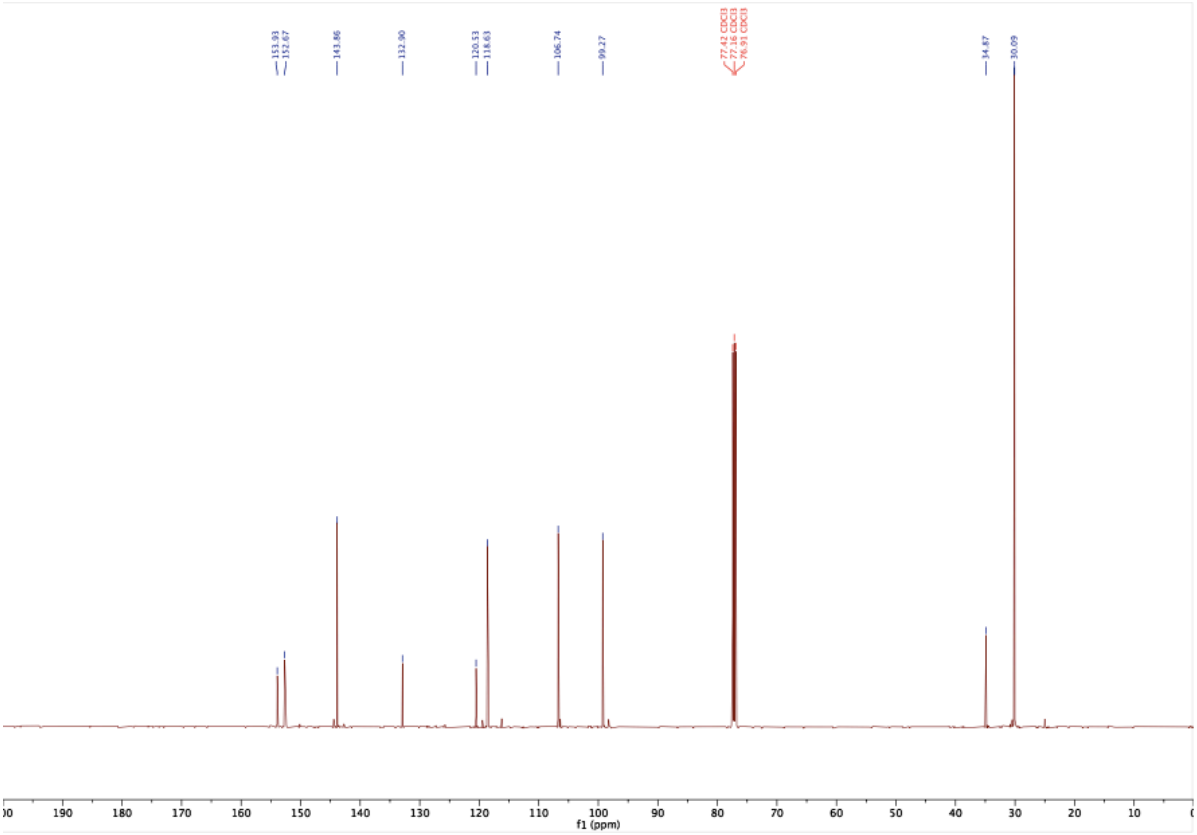

155.68
147.77
147.24
137.53
137.39
134.51
129.41
126.22
125.78
123.85
117.41
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
34.97
29.67
f1 (ppm)



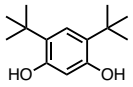
36i

Compound **36i** was synthesized according to general procedure D: (ethyl acetate–hexane, 1:3) to yield the *t*-butylated phenols **36i** (17.1 mg, 90% isolated yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (m, 2H), 6.86 (s, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 4.96 (s, OH), 1.47 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.93, 152.67, 143.86, 132.90, 120.53, 118.63, 106.74, 99.27, 34.87, 30.09. HRMS (EI+) m/z calculated for $C_{12}H_{14}O_2$ [M^+]: 190.0994; found 190.0986.


7.48
7.48
7.26 CDCl3
6.86
6.68
6.68
4.96
1.47
2.01
0.04
1.00
1.00
1.09
9.90
f1 (ppm)

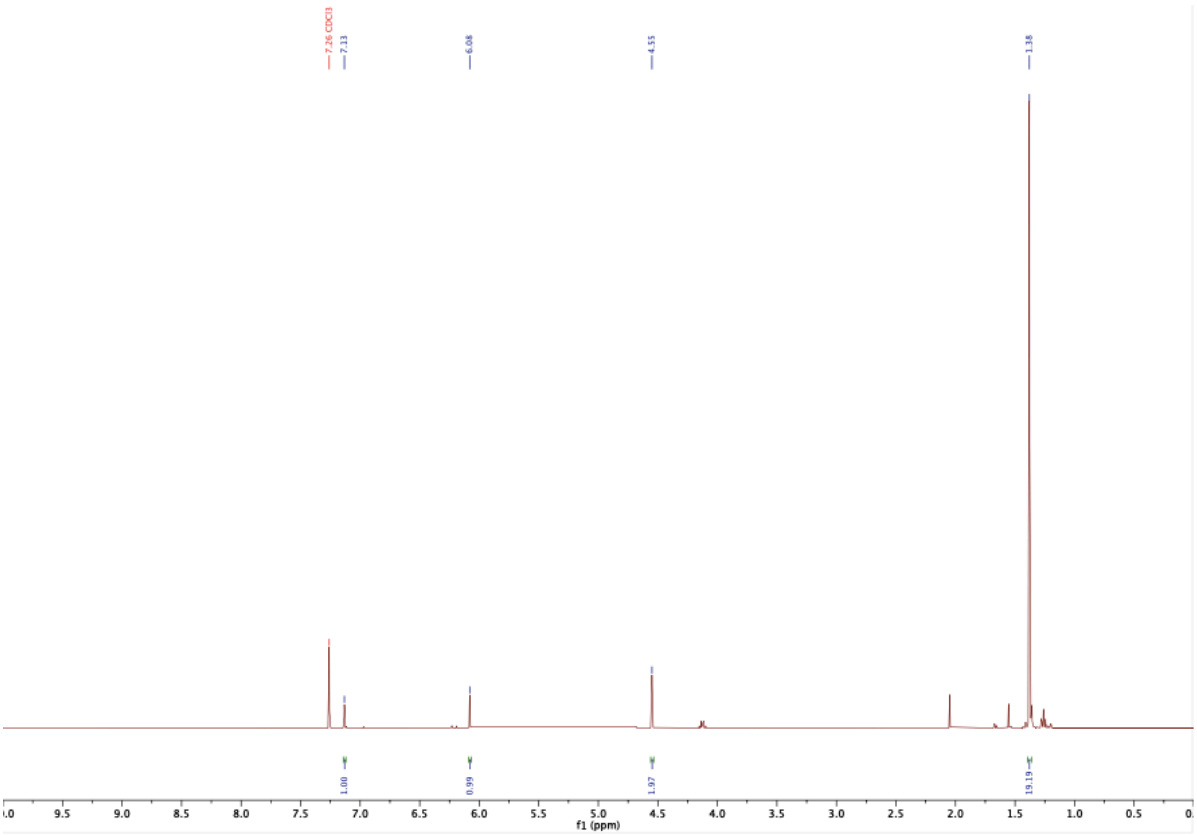

153.93
152.67
143.86
132.90
120.53
118.63
106.74
99.27
77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
34.87
30.09
f1 (ppm)

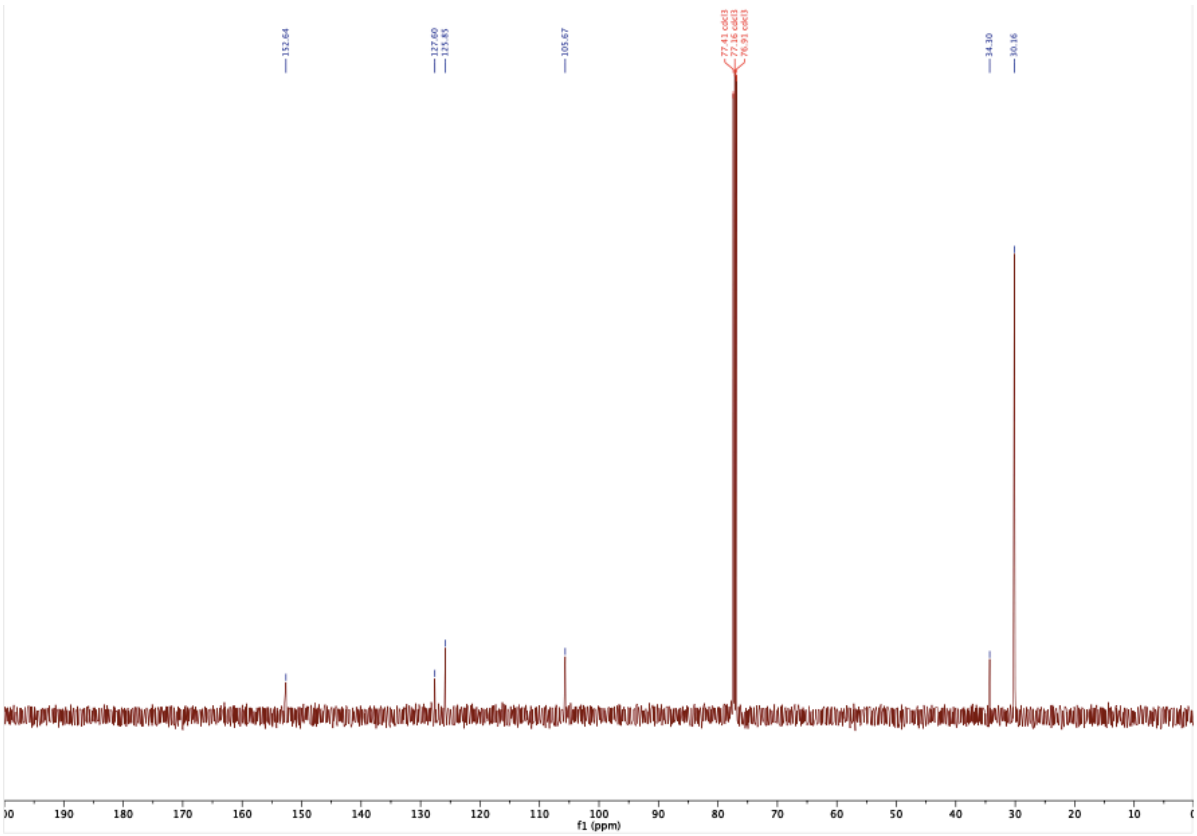
4.3.3 General Procedure E



36k

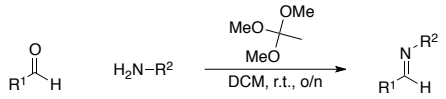
A dry, nitrogen flushed, 10-mL Schlenk flask, equipped with a magnetic stir bar was charged with **35k** (0.7 mL, 0.72 M in dry toluene, 0.50 mmol) in dry Et_2O (5 mL, 0.1 M) was added MeMgCl (0.94 mL, 2.69 M, 2.5 mmol, 5.0 equivalent) dropwise at -78 °C. The reaction was stirred and allowed to slowly warm to room temperature overnight. The reaction was quenched with 1 M aq. NH_4Cl (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate–hexane, 1:3) to yield the *t*-butylated phenols **36k** (72.6 mg, 65% isolated yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 (s, 1H), 6.08 (s, 1H), 4.55 (s, 2H, OH), 1.38 (s, 17H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.64, 127.60, 125.85, 105.67, 77.41, 77.16, 76.91, 34.30, 30.16. HRMS (EI+) m/z calculated for $C_{10}H_{22}O_2$ [M^+]: 222.1620; found 222.1627.


7.26 CDCl3
7.13
6.08
4.55
1.38
1.00
0.99
1.97
19.19
f1 (ppm)


152.64
127.60
125.85
105.67
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
34.30
30.16
f1 (ppm)

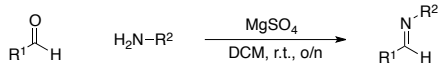
4.4 Synthesis of Acyclic (*E*)-Imines

4.4.1 General Procedure E



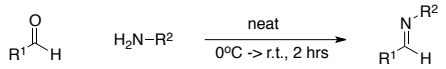
At room temperature, aldehyde (20 mmol) and amine (20 mmol) were dissolved in dichloromethane (60 mL). Trimethyl orthoacetate (20 mmol, 2.4 mL) was added. The mixture was stirred overnight. The mixture was then concentrated *in vacuo*, and finally purified by vacuum distillation (2 torr) to afford pure imines.

4.4.2 General Procedure F



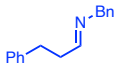
At room temperature, aldehyde (20 mmol) and amine (20 mmol) were dissolved in dichloromethane (60 mL). Anhydrous magnesium sulfate (4 g) was added, and the suspension was stirred overnight. Magnesium sulfate was removed by filtration, and solvents were removed *in vacuo*. The residue left was purified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

4.4.3 General Procedure G



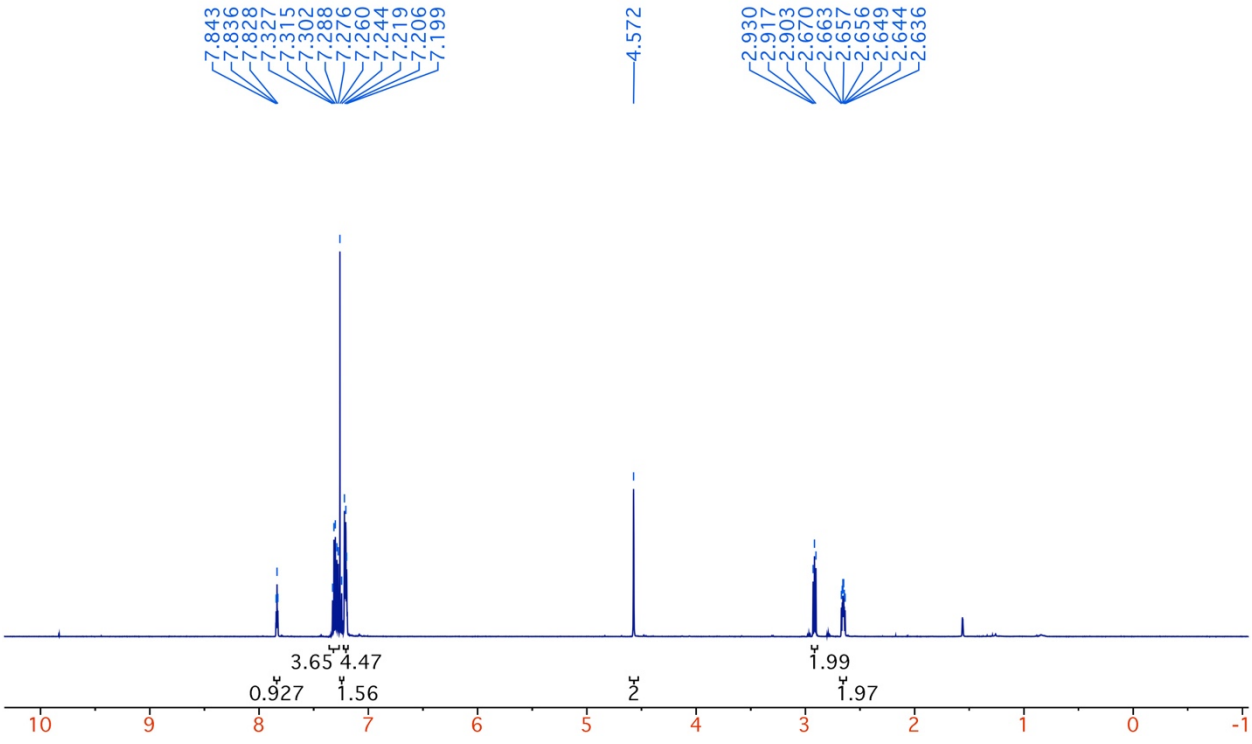
Amine (20 mmol) was placed in a round-bottom flask equipped with an addition funnel. The flask was cooled to 0 ˚C using an ice-water bath. With stirring, aldehyde (24 mmol) was added dropwise through addition funnel over 2 hours. The mixture was then warmed to room temperature. Several pellets of KOH 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.



37

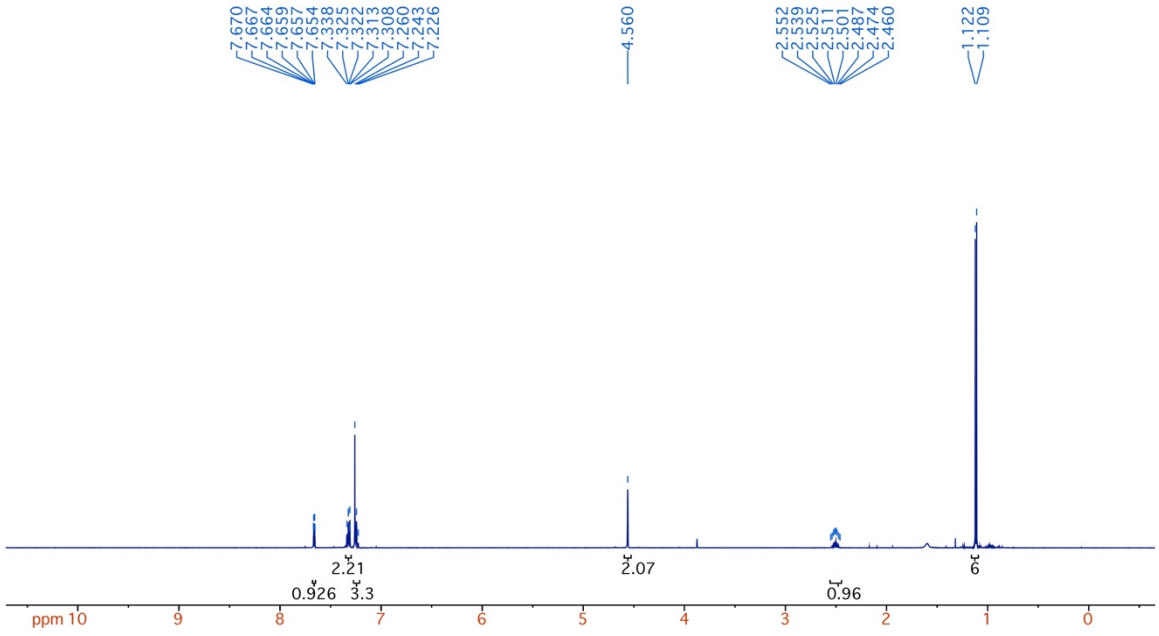
(*E*)-*N*-benzyl-3-phenylpropan-1-imine (37) was synthesized according to general procedure C as colorless oil (b.p. = 122 °C under 2 torr). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.84 (tt, *J* = 4.6, 1.3 Hz, 1H), 7.33-7.27 (m, 4H), 7.26-7.23 (m, 2H), 7.22-7.19 (m, 4H), 4.57 (s, 2H), 2.92 (t, *J* = 7.9 Hz, 2H), 2.67-2.64 (m, 2H). Imine **37** has been reported. Our characterization data match the literature data.[1]



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

38

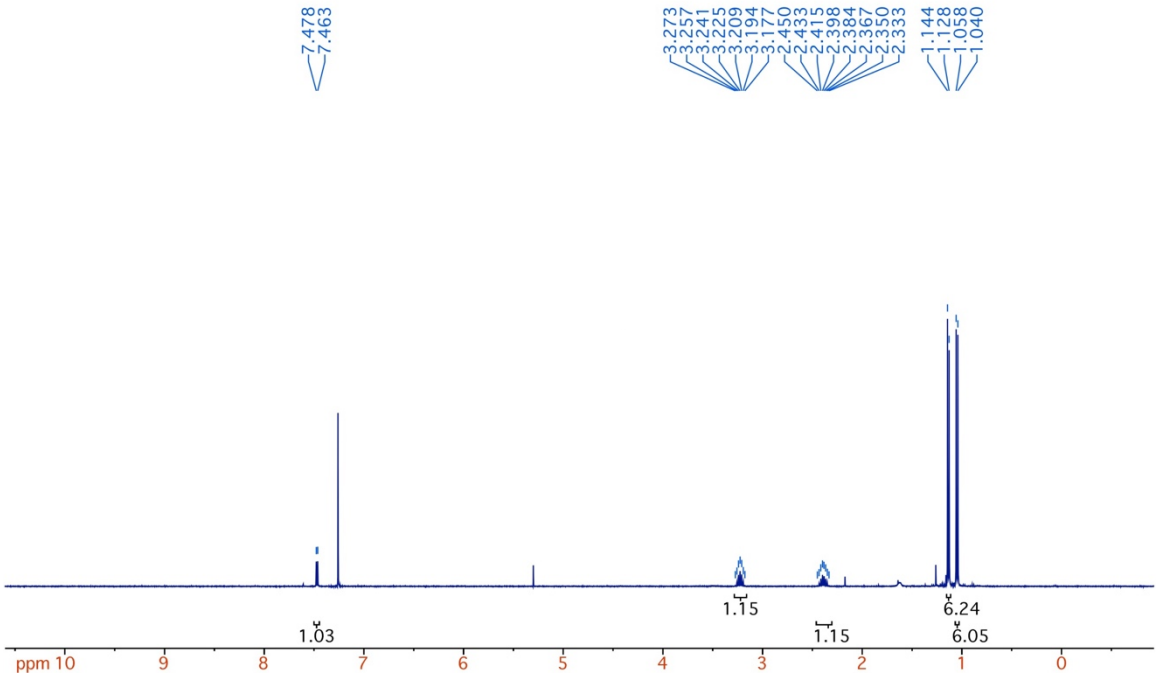
(*E*)-*N*-benzyl-2-methylpropan-1-imine (38) was synthesized according to general procedure A as colorless oil (b.p. = 59 °C under 2 torr). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.66 (dt, *J* = 5.5, 1.5 Hz, 1H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 3H), 4.56 (s, 2H), 2.50 (sept d, *J* = 6.5, 5.5 Hz, 1H), 1.12 (d, *J* = 6.5 Hz, 6H). Imine **38** has been reported. Our characterization data match the literature data.[2]



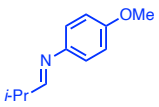
[2] Chen, M. Z.; McLaughlin, M.; Takahashi, M.; Tarselli, M. A.; Yang, D.; Umemura, S.; Micalizio, G. C. *J. Org. Chem.* **2010**, *75*, 8048-8059.

39

(*E*)-2-methyl-*N*-(propan-2-yl)propan-1-imine (39) was synthesized according to general procedure A as colorless oil (b.p. = 100 °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). Imine **39** has been reported. Our characterization data match the literature data.[3]

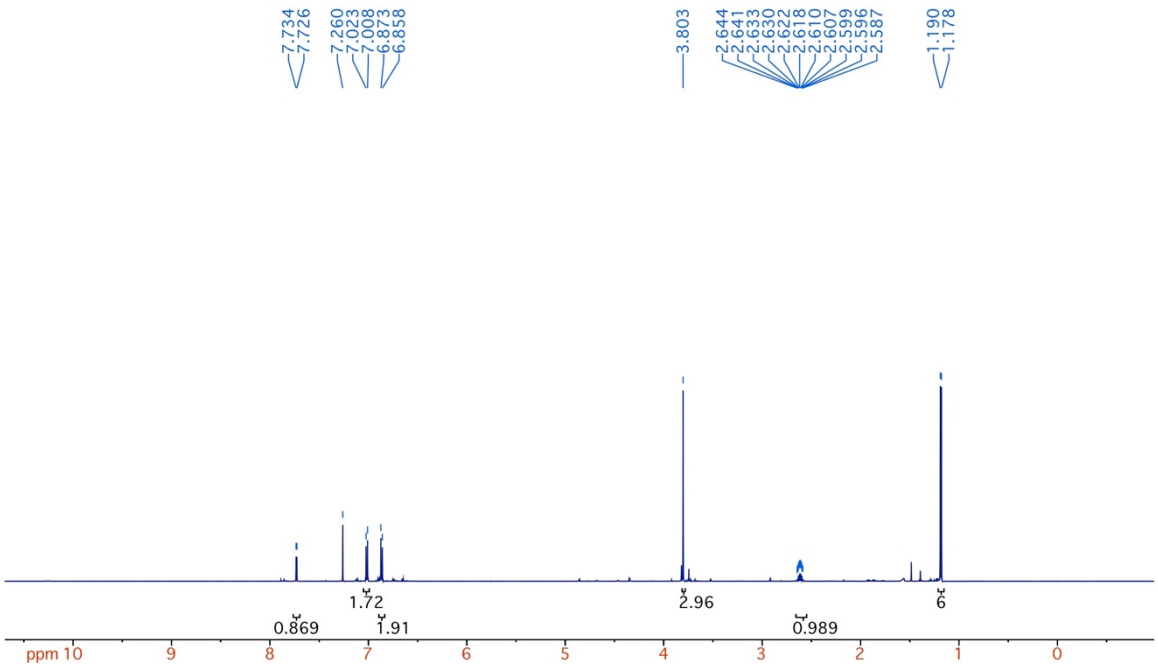


[3] Mandal, D.; Dolai, R.; Chrysochos, N.; Kalita, P.; Kumar, R.; Dhara, D.; Maiti, A.; Narayanan, R. S.; Rajaraman, G.; Schulzke, C.; Chandrasekhar, V.; Jana, A. *Org. Lett.* **2017**, *19*, 5605-5608.

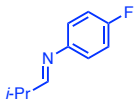


40

(*E*)-*N*-(4-methoxyphenyl)-2-methylpropan-1-imine (40) was synthesized according to general procedure A as yellow oil (b.p. = 122 °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). Imine **40** has been reported. Our characterization data match the literature data.[4]

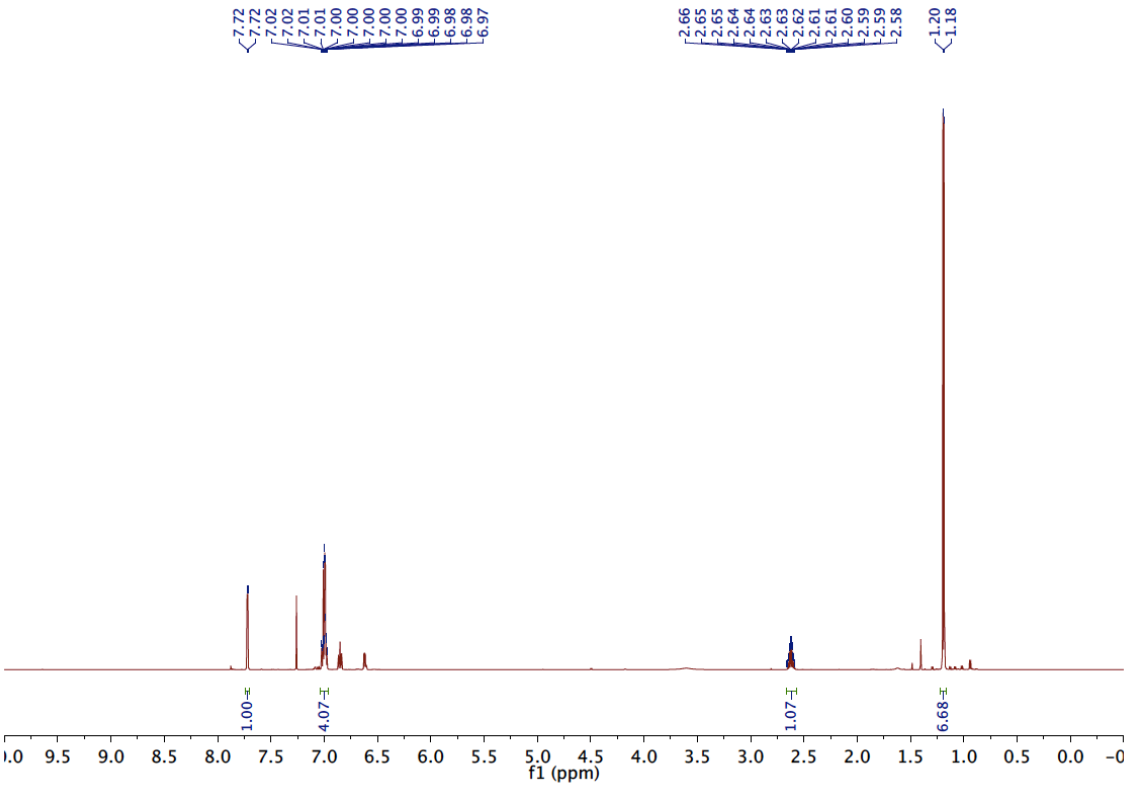


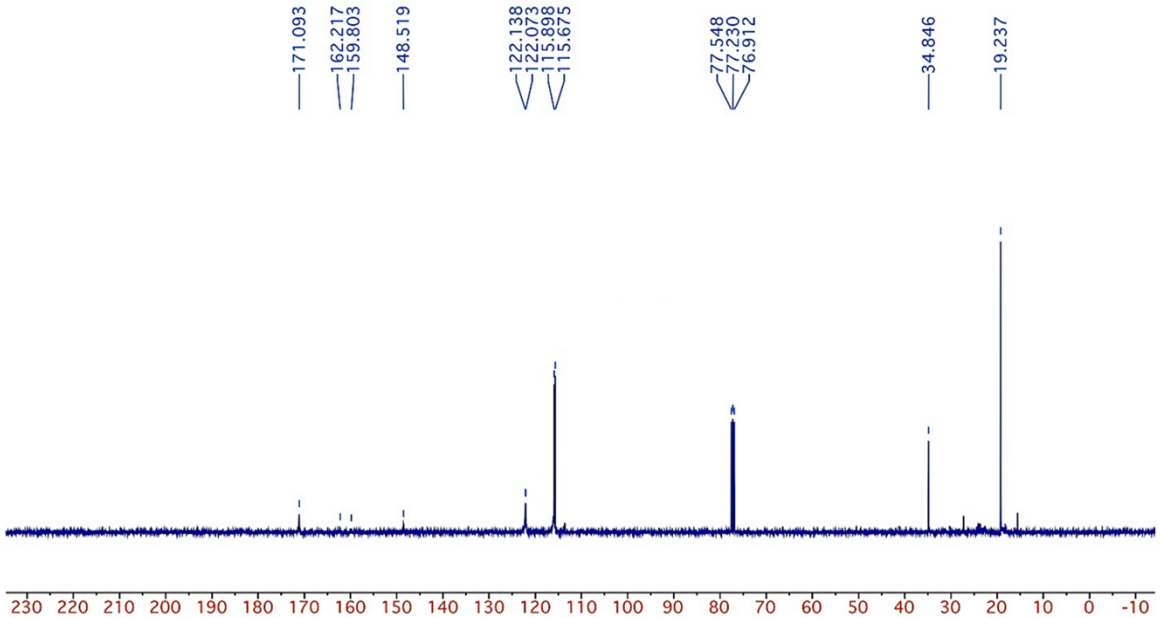
[4] Anderson, J. C.; Kalogirou, A. S.; Porter M. J.; Tizzard. G. J. *Beilstein J. Org. Chem.* **2013**, *9*, 1737-1744.



41

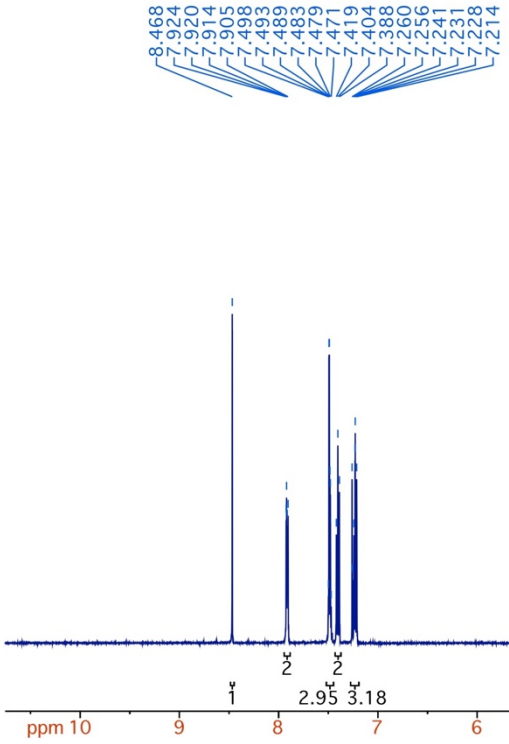
(*E*)-*N*-(4-fluorophenyl)-2-methylpropan-1-imine (41) was synthesized according to general procedure B as colorless oil (b.p. = 37 °C under 2 torr). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.72 (d, J = 4.8 Hz, 1H), 7.04-6.96 (m, 4H), 2.62 (heptd, J = 6.9, 4.8 Hz, 1H), 1.19 (d, J = 6.9 Hz, 7H). **^{13}C 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.


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
1.00
4.07
1.07
6.68
f1 (ppm)

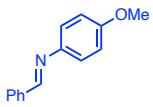

171.093
162.217
159.803
148.519
122.138
122.073
115.898
115.675
77.548
77.230
76.912
34.846
19.237

42

(*E*)-*N*,1-diphenylmethanimine (42) was synthesized according to general procedure B. Purified by recrystallization from hot hexanes. Yellow solid. **^{1}H-NMR** (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). Imine **42** has been reported. Our characterization data match the literature data.[5]

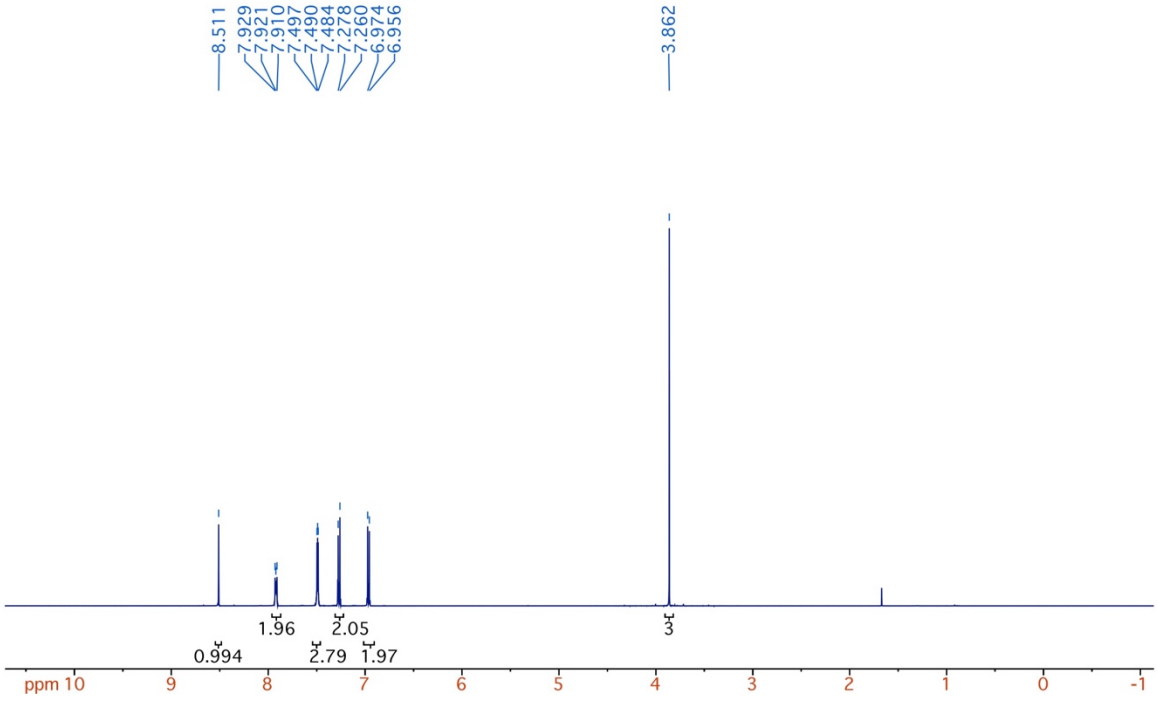


[5] Schaufelberger, F.; Timmer, B. J. J.; Ramström, O. *Chem. Eur. J.* **2018**, *24*, 101-104.

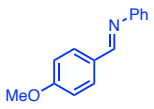


43

(*E*)-*N*-(4-methoxyphenyl)-1-phenylmethanimine (43) was synthesized according to general procedure B. 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). Imine **43** has been reported. Our characterization data match the literature data.[6]

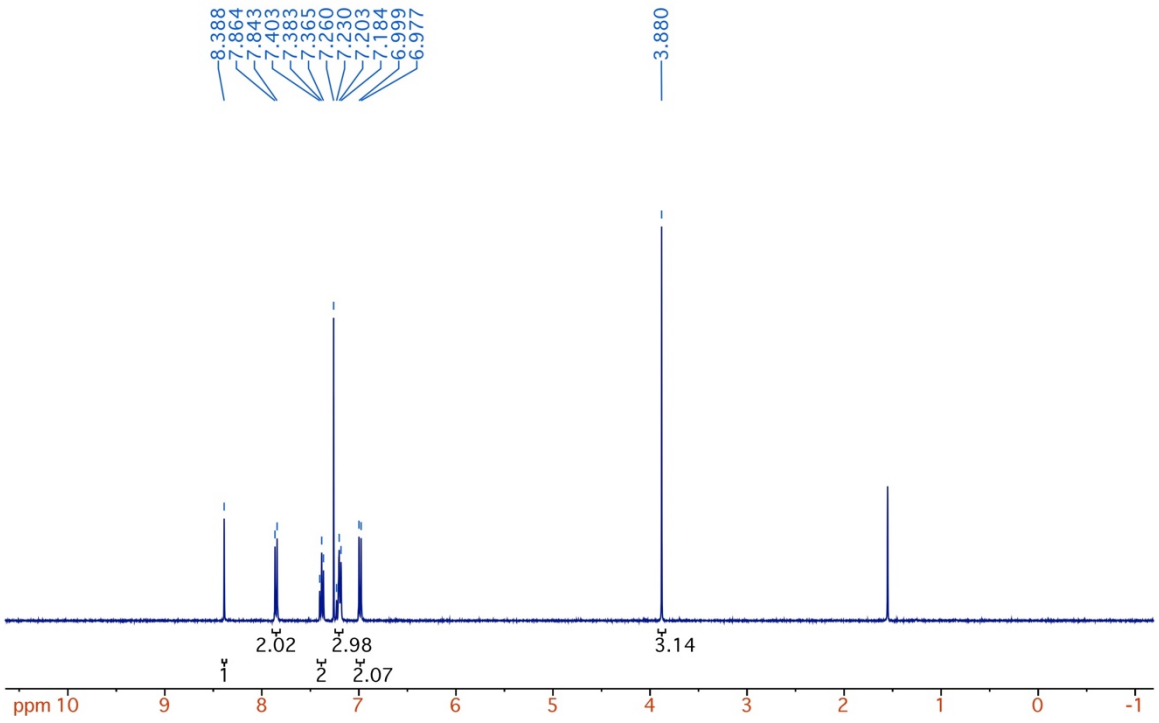


[6] Monopoli, A.; Cotugno, P.; Iannone, F.; Ciminale, F.; Dell'Anna, M. M.; Mastrorilli, P.; Nacci, A. *Eur. J. Org. Chem.* **2014**, *27*, 5925-5931.



44

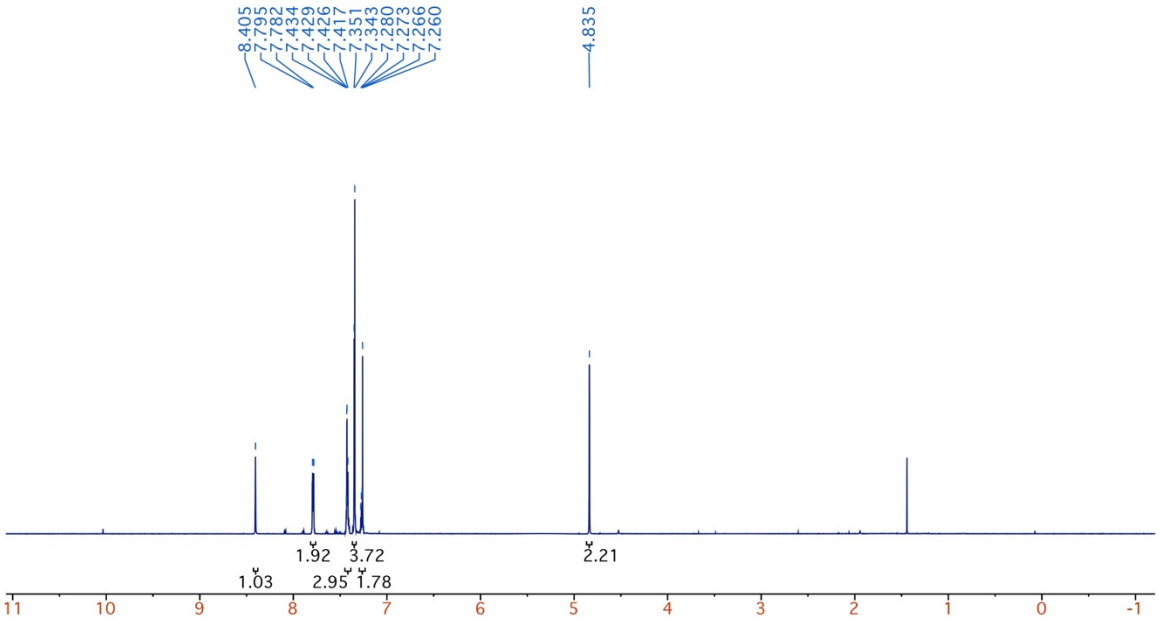
(*E*)-1-(4-methoxyphenyl)-*N*-phenylmethanimine (44) was synthesized according to general procedure B. Purified by recrystallization from hot hexanes. Yellow solid. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.85 (d, *J* = 9.2, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.23-7.18 (m, 3H), 6.99 (d, *J* = 9.2, 2H), 3.88 (s, 3H). Imine **44** has been reported. Our characterization data match the literature data.[7]



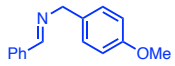
[7] Vayer, M.; Morcillo, S. P.; Dupont, J.; Gandon, V.; Bour, C. *Angew. Chem. Int. Ed.* **2018**, *57*, 3228-3232.

45

(*E*)-*N*-benzyl-1-phenylmethanimine (45) was synthesized according to general procedure A as colorless oil (b.p. = 105 °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). Imine **45** has been reported. Our characterization data match the literature data.[8]

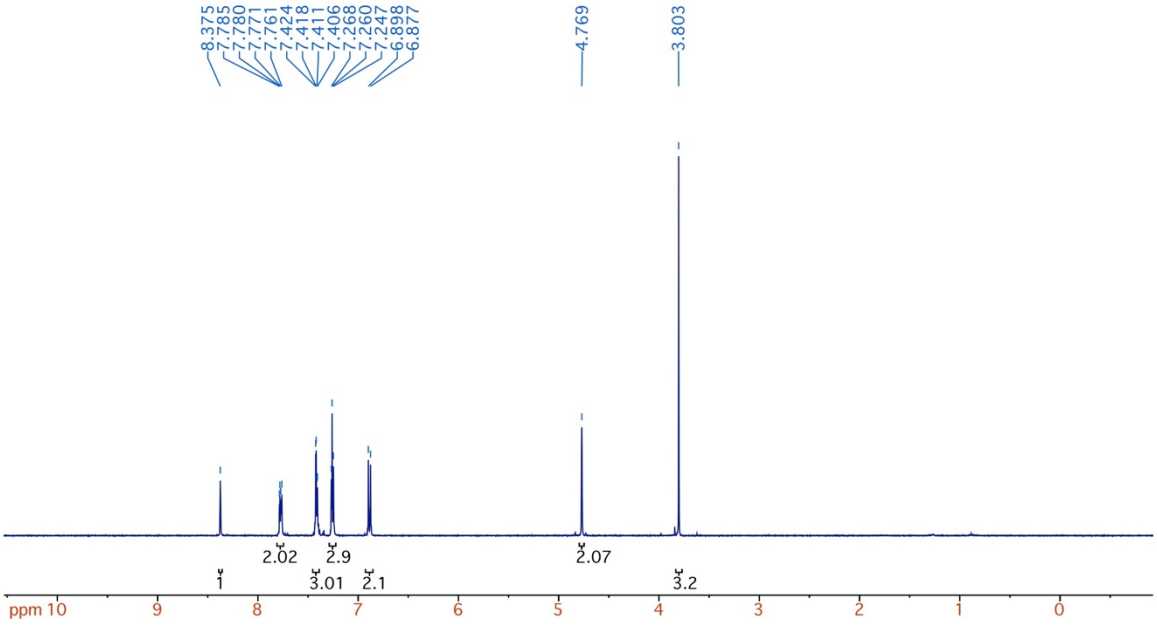


[8] Lawson, J. R.; Wilkins, L. C.; Melen, R. L.; *Chem. Eur. J.* **2017**, *23*, 10997-11000.

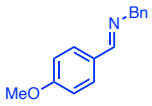


46

(*E*)-*N*-[(4-methoxyphenyl)methyl]-1-phenylmethanimine (46) was synthesized according to general procedure A as colorless oil (b.p. = 148 °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). Imine **46** has been reported. Our characterization data match the literature data.[9]

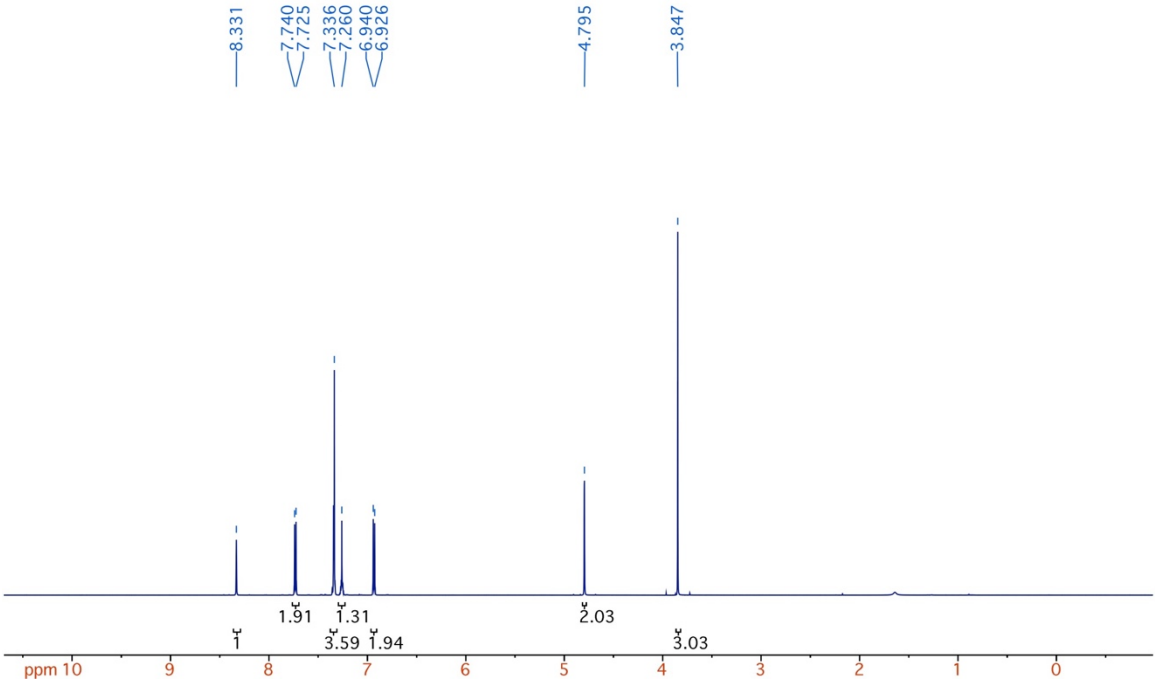


[9] Guimond, N.; Fagnou, K.; *J. Am. Chem. Soc.* **2009**, *131*, 12050-12051.

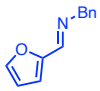


47

(*E*)-*N*-benzyl-1-(4-methoxyphenyl)methanimine (47) was synthesized according to general procedure A as colorless oil that solidified upon storage (b.p. = 135 °C under 2 torr). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.73 (d, *J* = 9 Hz, 2H), 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). Imine **47** has been reported. Our characterization data match the literature data.[10]

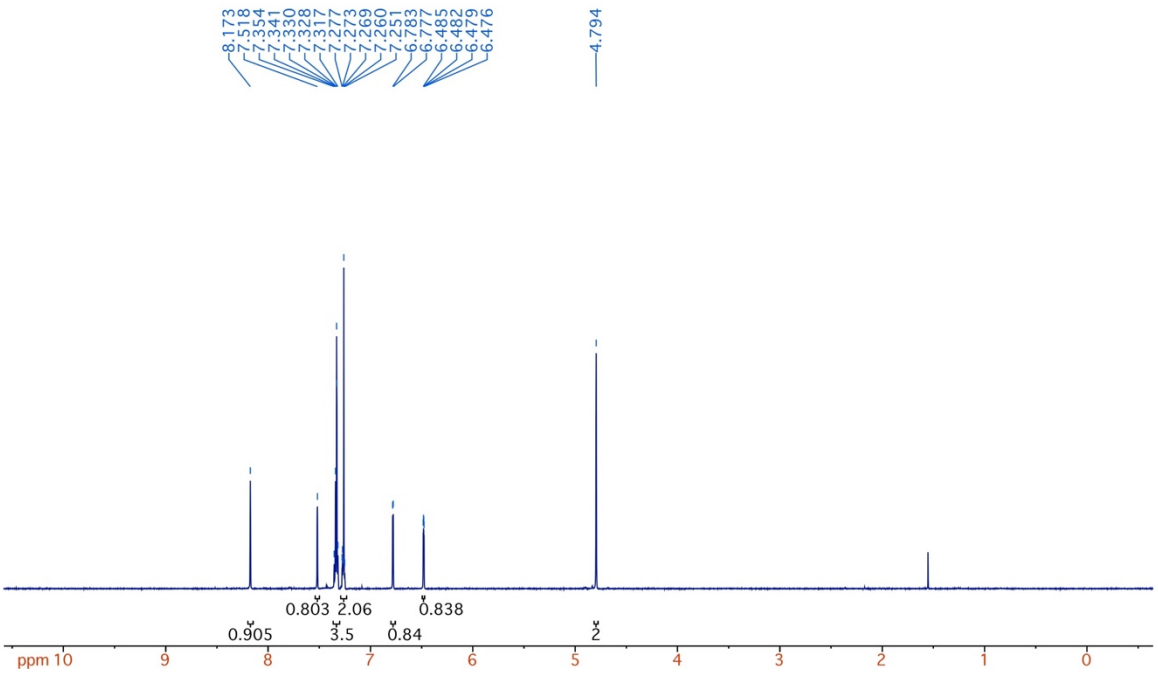


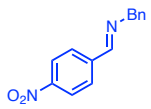
[10] Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 6579-6587.



48

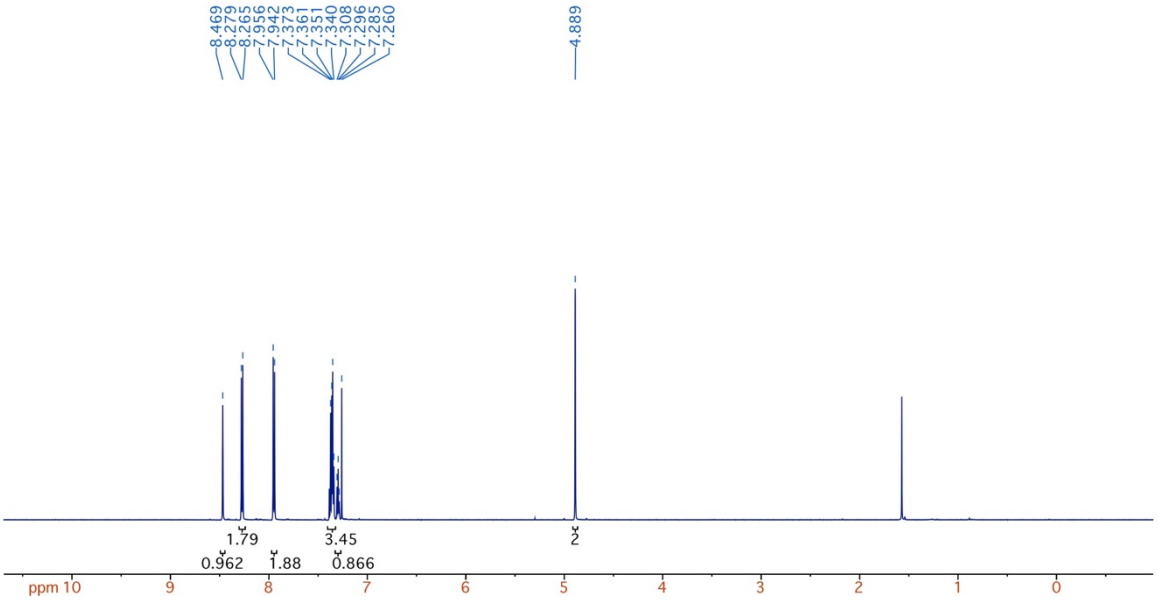
(*E*)-*N*-benzyl-1-(furan-2-yl)methanimine (48) was synthesized according to general procedure A as yellow oil (b.p. = 116 °C under 2 torr). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.52 (d, *J* = 0.9 Hz, 1H), 7.35-7.32 (m, 3H), 7.28-7.25 (m, 2H), 6.78 (d, *J* = 3.4 Hz, 1H), 6.48 (dd, *J* = 3.4, 1.7 Hz, 1H), 4.79 (s, 2H). Imine **48** has been reported. Our characterization data match the literature data.[7]

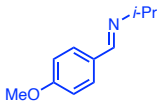




49

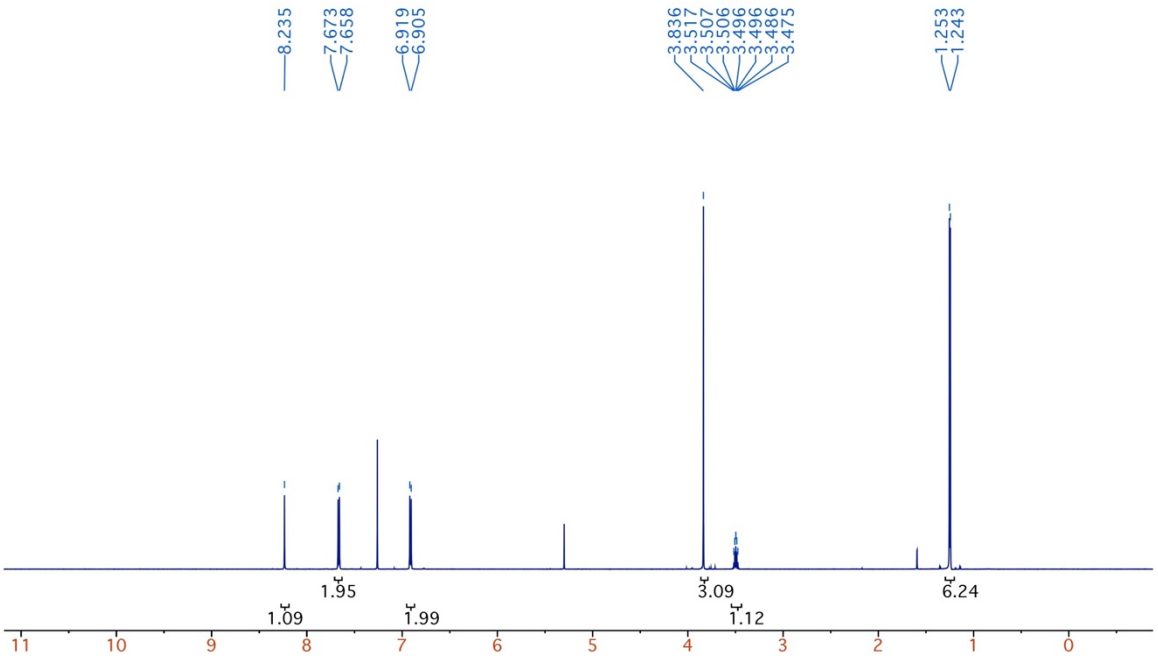
(*E*)-*N*-benzyl-1-(4-nitrophenyl)methanimine (49) was synthesized according to general procedure B. Purified by recrystallization from a mixture of hexanes, dichloromethane, diethyl ether and ethyl acetate. Yellow solid. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.47 (s, 1H), 8.27 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H), 7.39-7.34 (m, 4H), 7.31-7.28 (m, 1H), 4.89 (s, 2H). Imine **49** has been reported. Our characterization data match the literature data.[8]



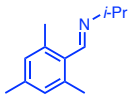


50

(*E*)-1-(4-methoxyphenyl)-*N*-(propan-2-yl)methanimine (50) was synthesized according to general procedure A as colorless oil (b.p. = 68 °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, 2H), 3.84 (s, 3H), 3.50 (sept, *J* = 6.3 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 6H). Imine **50** has been reported. Our characterization data match the literature data.[11]

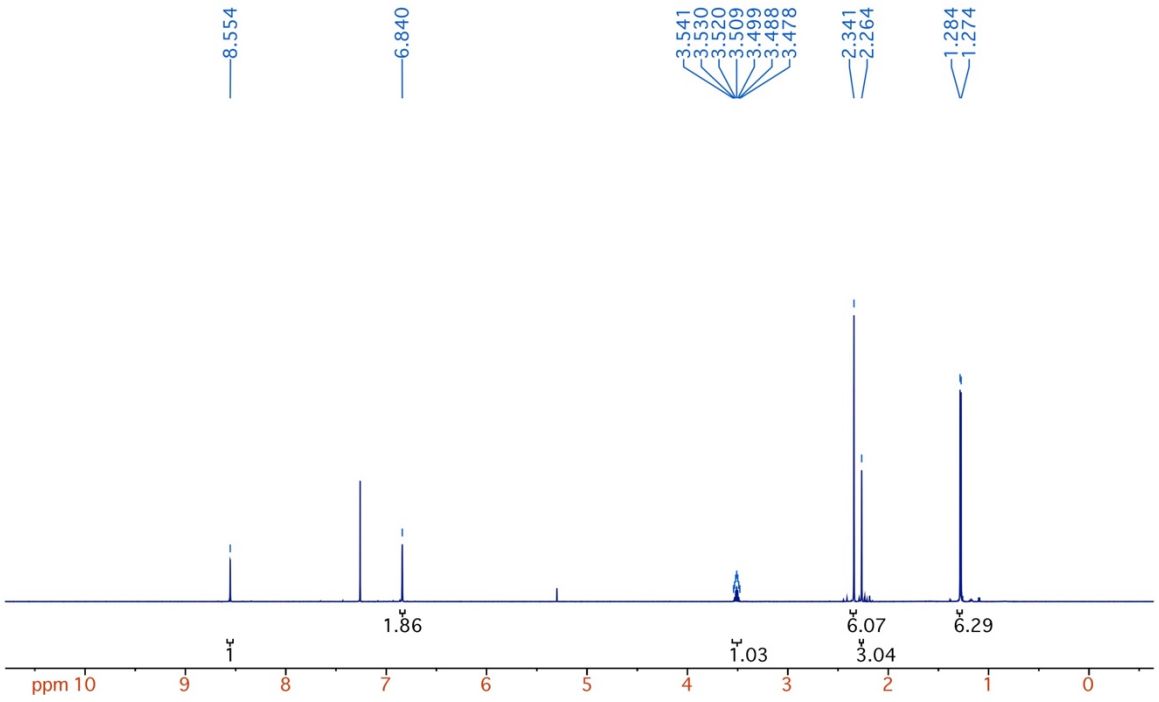


[11] Koyama, Y.; Gudeangadi, P. G. *Chem. Commun.* **2017**, *53*, 3846-3849



51

(*E*)-*N*-(propan-2-yl)-1-(2,4,6-trimethylphenyl)methanimine (51) was synthesized according to general procedure A as colorless oil (b.p. = 60 °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.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3.541
3.530
3.520
3.509
3.499
3.488
3.478
2.341
2.264
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1.274
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1.03
3.04
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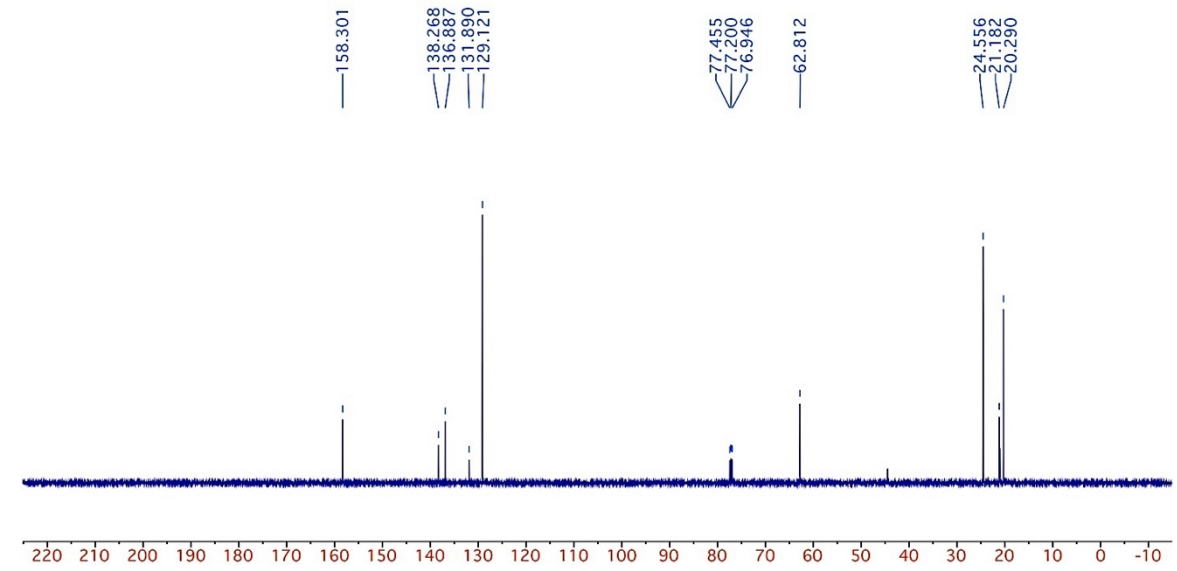
9
8
7
6
5
4
3
2
1
0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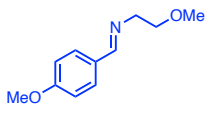
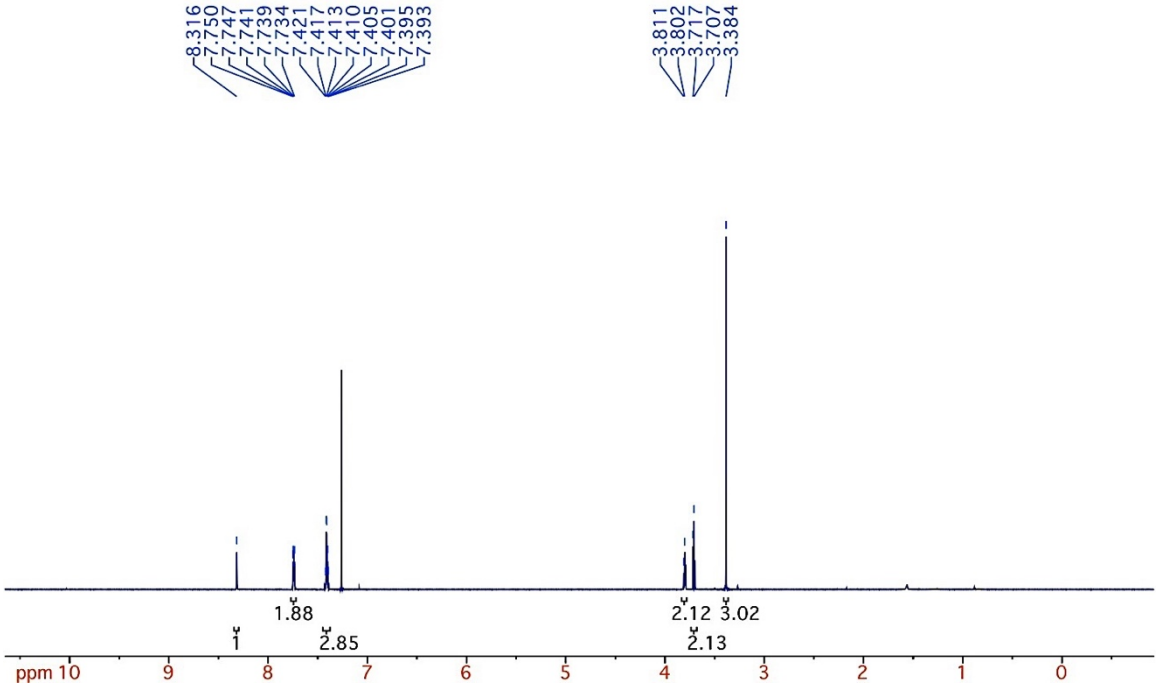
136.887
131.890
129.121
77.455
77.200
76.946
62.812
24.556
21.182
20.290
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



52

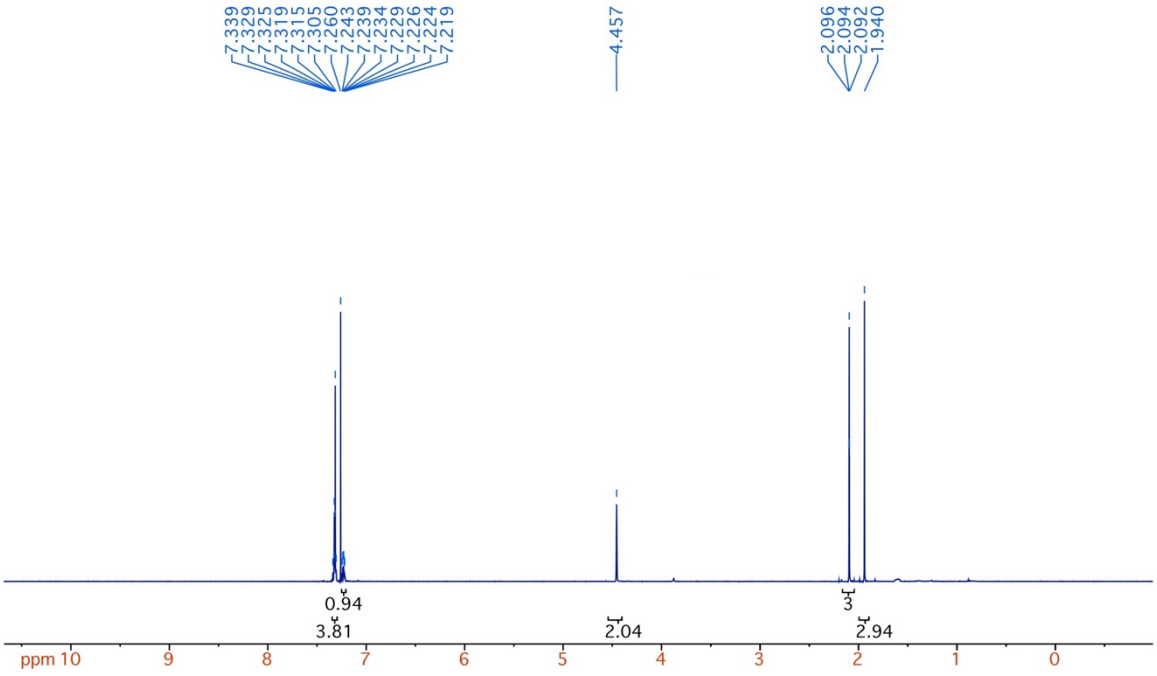
(*E*)-*N*-(2-methoxyethyl)-1-phenylmethanimine (52) was synthesized according to general procedure A as colorless oil (b.p. = 60 °C under 2 torr). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.75-7.73 (m, 2H), 7.42-7.39 (m, 3H), 3.80 (t, *J* = 6.0 Hz, 2H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.38 (s, 3H). Imine **52** has been reported. Our characterization data match the literature data.[12]



[12] Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817-12819.

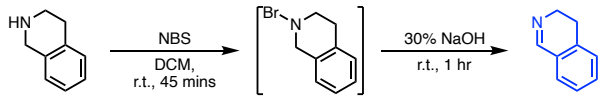
54

***N*-benzylpropan-2-imine (54)** was synthesized according to general procedure B as colorless oil (b.p. = 68 °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, 2H), 3.84 (s, 3H), 3.50 (sept, *J* = 6.3 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 6H). Imine **54** has been reported. Our characterization data match the literature data.[13]



[13] Paul, B.; Chakrabarti, K.; Kundu, S. *Dalton Trans.* **2016**, *45*, 11162-11171.

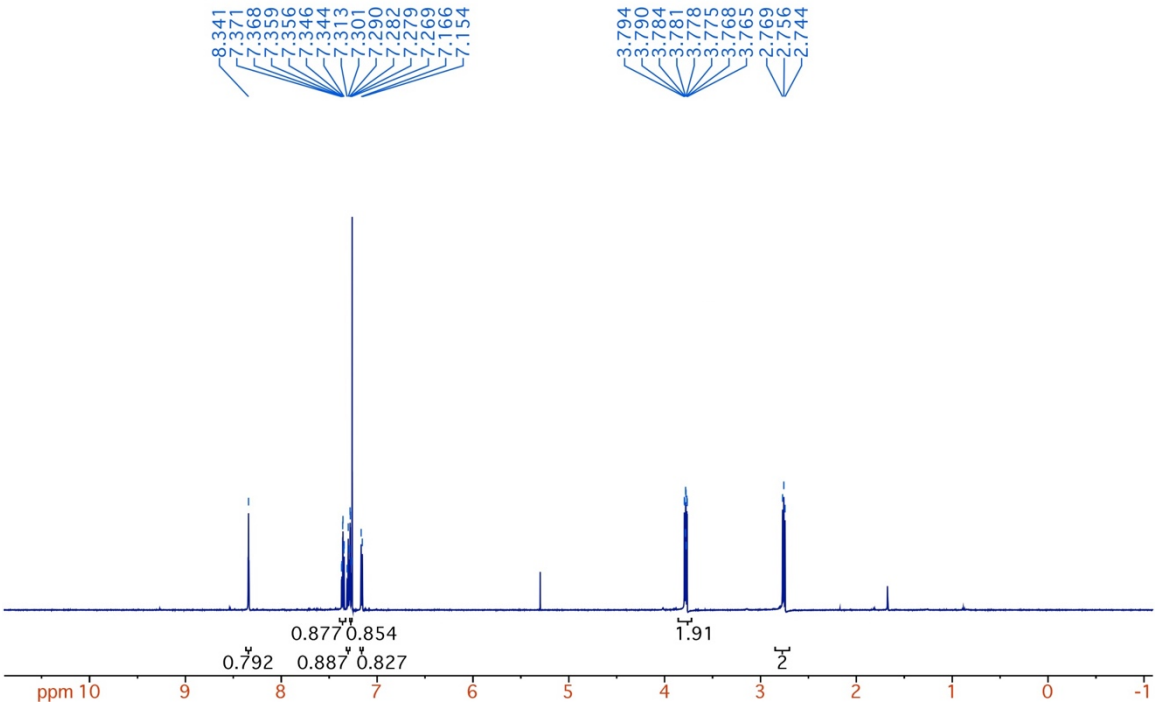
4.5 Synthesis of Cyclic (*Z*)-Imines



53

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, 1.1 equiv) was added 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 **24** 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). Imine **53** has been reported. Our characterization data match the literature data.[14]

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


8.341
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7.359
7.356
7.346
7.344
7.313
7.301
7.290
7.282
7.279
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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
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

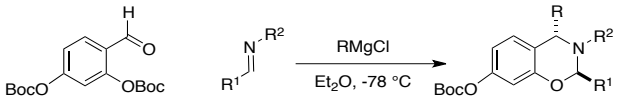
4.6 Preparation of Imines and Aldehydes Substrate Solutions

All the imines synthesized in part II were diluted as 1.0 M solution in toluene as follows:

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) were added, followed by 4Å molecular sieves. The solution was stored in desiccator overnight before use.

The aldehyde substrate, bis-(2,4-tert-butoxycarbonyloxy)-benzaldehyde, was prepared according to our previous report.[15] The pure aldehyde was diluted as 1.0 M solution in dry toluene under nitrogen similarly.

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



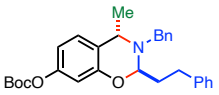
4.7.1 General Procedure H

Imine (0.1 mL, 0.1 mmol, 1.0 M in toluene, 1 equiv. unless otherwise specified) was added to a stirred solution of bis-(2,4-tert-butoxycarbonyloxy)-benzaldehyde (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 (1mL) and stirred for 2 hours at room temperature. The aqueous solution was extracted with Et_2O (3 x 1mL) then the combined organic solution was washed with saturated sodium bicarbonate solution (3 x 1mL). Saturated sodium bisulfite solution (1mL) was added to the combined organic solution and stirred for 1.5 hours at room temperature.* The aqueous

[15] Jones, R. M.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. *J. Org. Chem.* **2001**, *66*, 3435-3441.

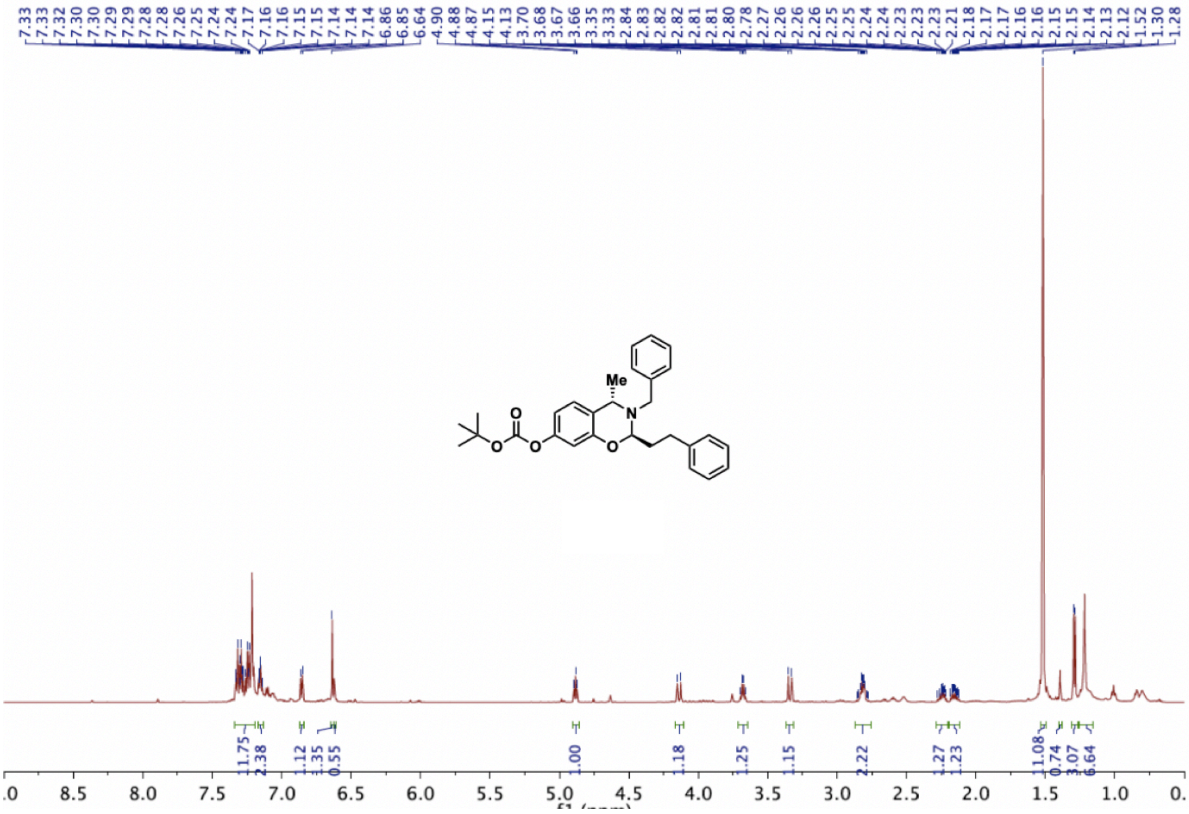
solution was extracted with Et_2O (3 x 1mL), then the combined organic solution was washed with brine (1mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford crude product. Crude NMR yields were determined by adding 5 μL of dibromomethane as internal standard to this crude product. Purification by flash column chromatography (SiO_2, eluent: 1% triethylamine in hexane) was performed to afford pure product when specified.

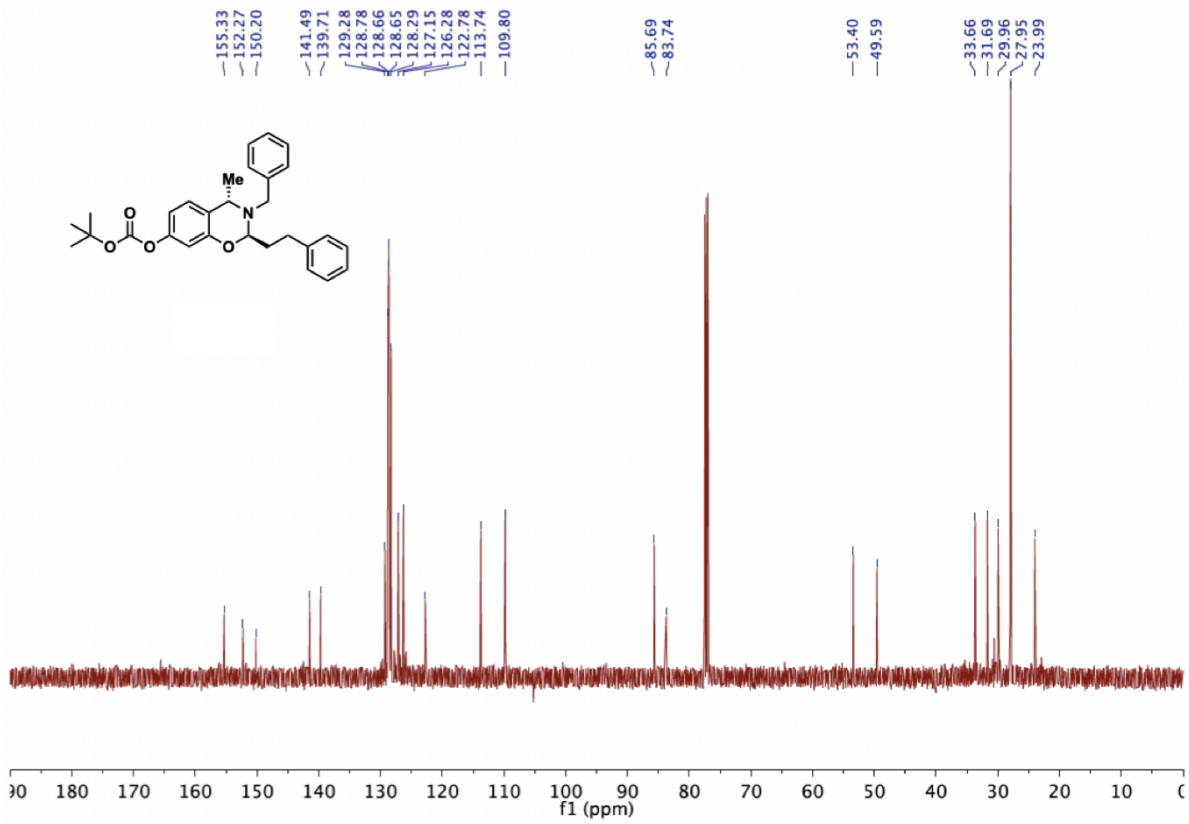
*****_This step is not necessary for compounds_ ***38a-b***_,_ ***39a-b***_,_ ***40a-b***_,_ ***41a-b*** _and_ ***12***_, as the aldehydes can be removed easily by vacuum (2 torr)._

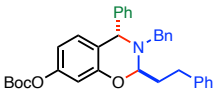


37a-Me

(±)-*trans*-3-benzyl-4-methyl-2-phenethyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl tert-butyl carbonate (37a-Me). Prepared according to the general procedure H. 83% Hcrude 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 (90% hexane 10% ethyl acetate).

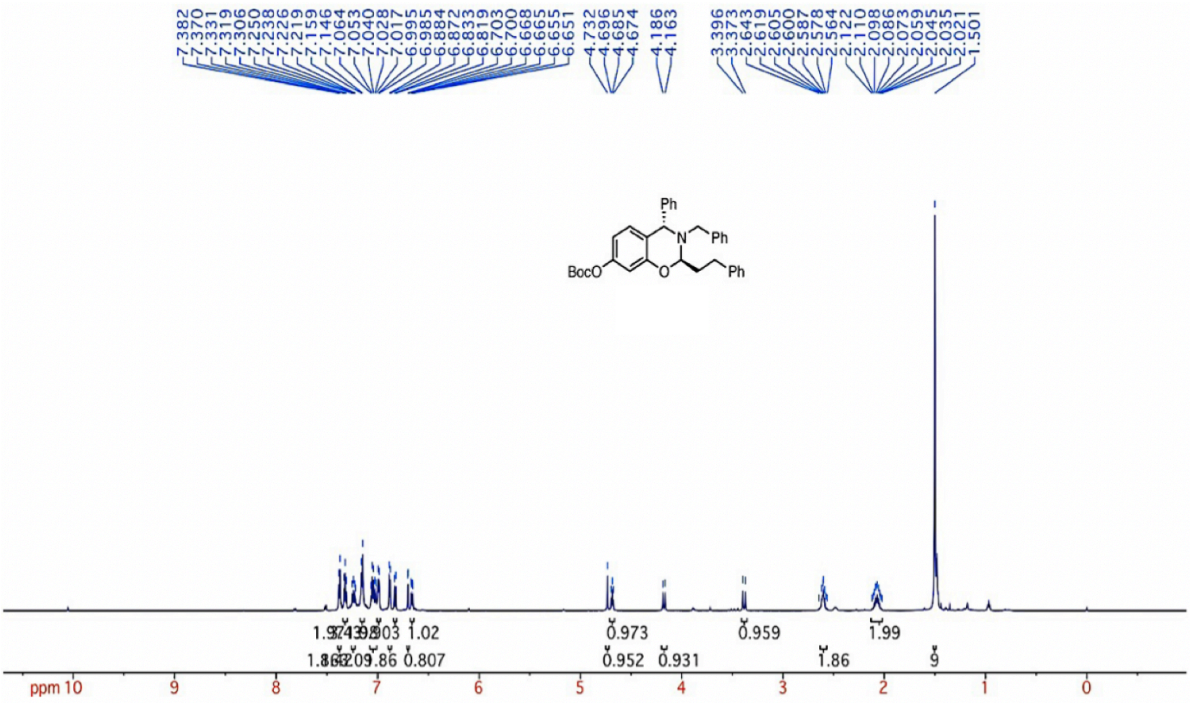

7.33 7.33 7.32 7.30 7.30 7.29 7.29 7.28 7.28 7.26 7.25 7.24 7.24 7.17 7.16 7.16 7.15 7.15 7.14 7.14 7.14 6.86 6.85 6.64
4.90 4.88 4.87 4.15 4.13 3.70 3.68 3.67 3.66 3.35 3.33 2.84 2.83 2.82 2.82 2.81 2.81 2.80 2.78 2.27 2.26 2.26 2.26 2.25 2.24 2.24 2.23 2.23 2.21 2.18 2.17 2.17 2.16 2.16 2.15 2.15 2.14 2.13 2.12 1.52 1.30 1.28
Me
N
O
O
O
11.75 2.38 1.12 1.35 0.55 1.00 1.18 1.25 1.15 2.22 1.27 1.23 11.08 0.74 3.07 6.64
f1 (ppm)

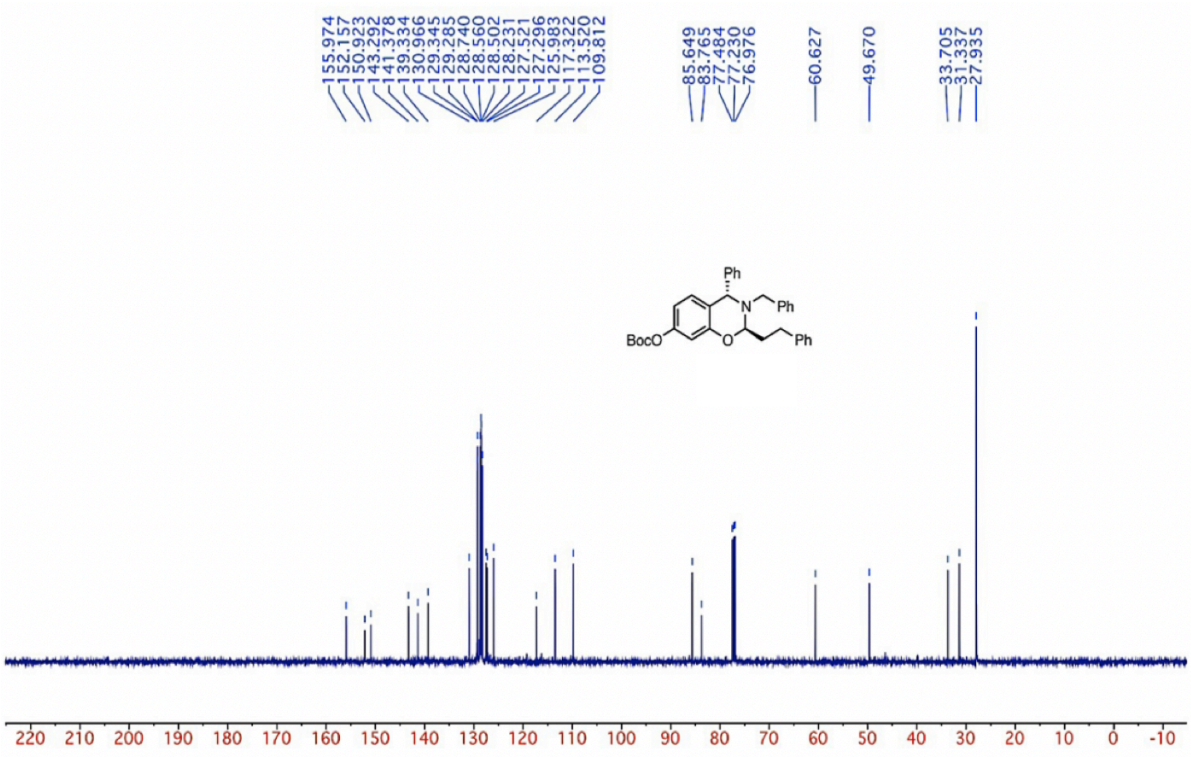

155.33 152.27 150.20 141.49 139.71 129.28 128.78 128.66 128.65 128.29 127.15 126.28 122.78 113.74 109.80 85.69 83.74 53.40 49.59 33.66 31.69 29.96 27.95 23.99
Me
N
O
O
O
f1 (ppm)

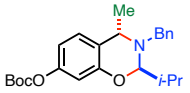


37b-Ph

(±)-*trans*-3-benzyl-2-phenethyl-4-phenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (37b-Ph). Prepared according to the general procedure H. 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 (90% hexane 10% ethyl acetate).


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
3.343
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
BocO
O
Ph
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

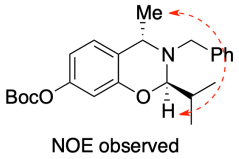

155.974
152.157
150.923
143.292
141.378
139.334
130.966
129.345
129.285
128.740
128.560
128.502
128.231
127.521
127.296
125.983
117.322
113.520
109.812
85.649
83.765
77.484
77.230
76.976
60.627
49.670
33.705
31.337
27.935
Ph
N
Ph
BocO
O
Ph
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

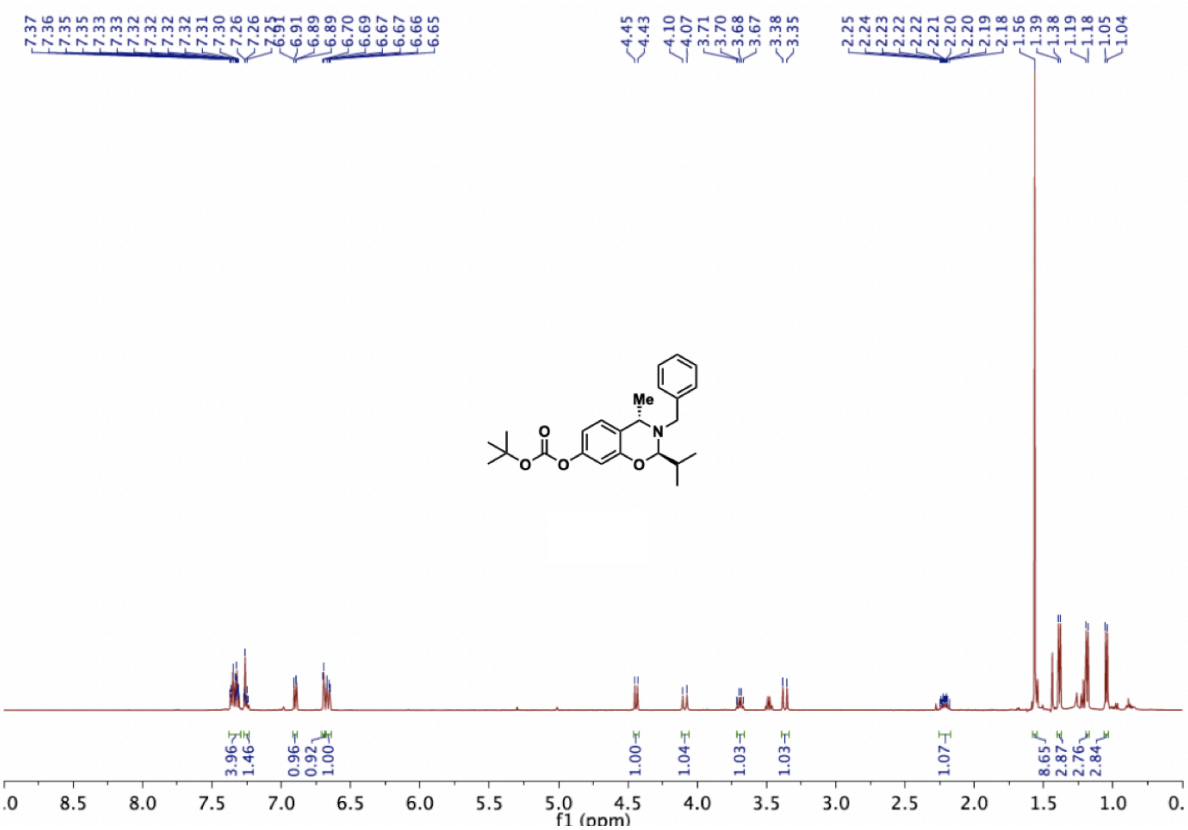


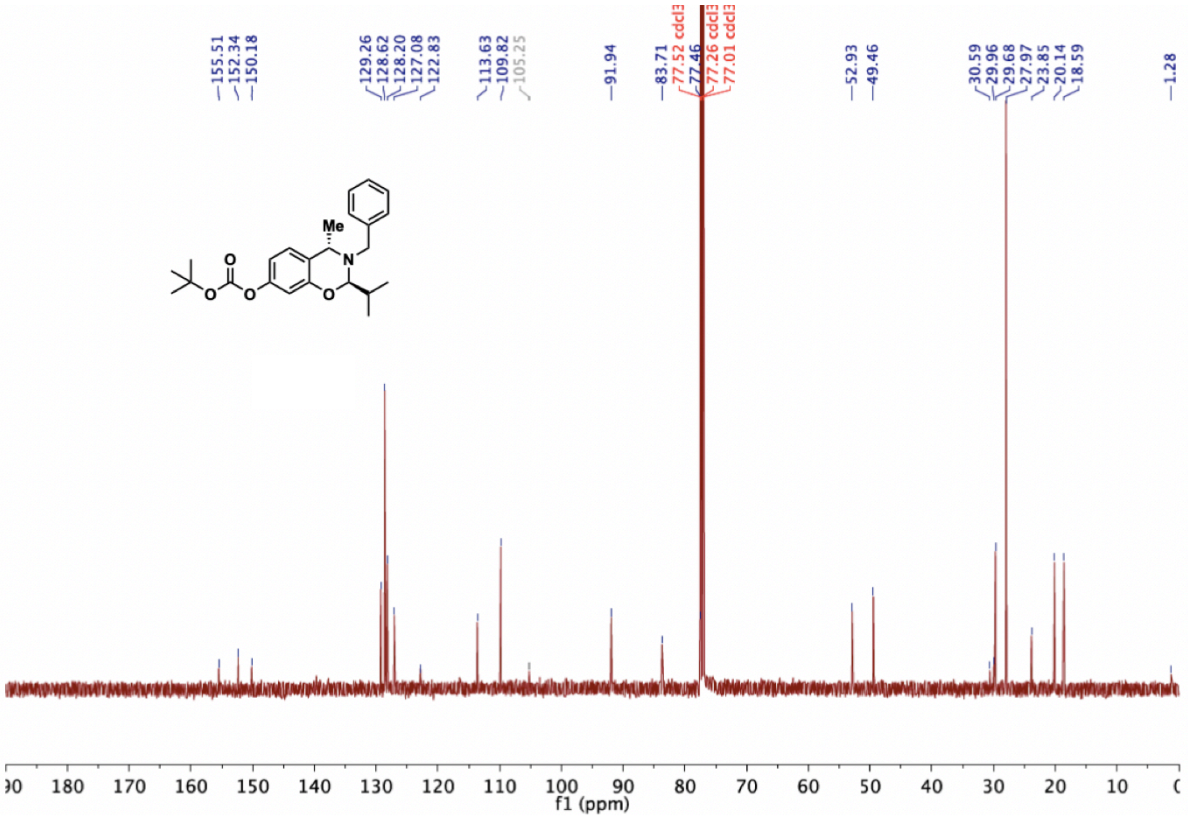
38a-Me

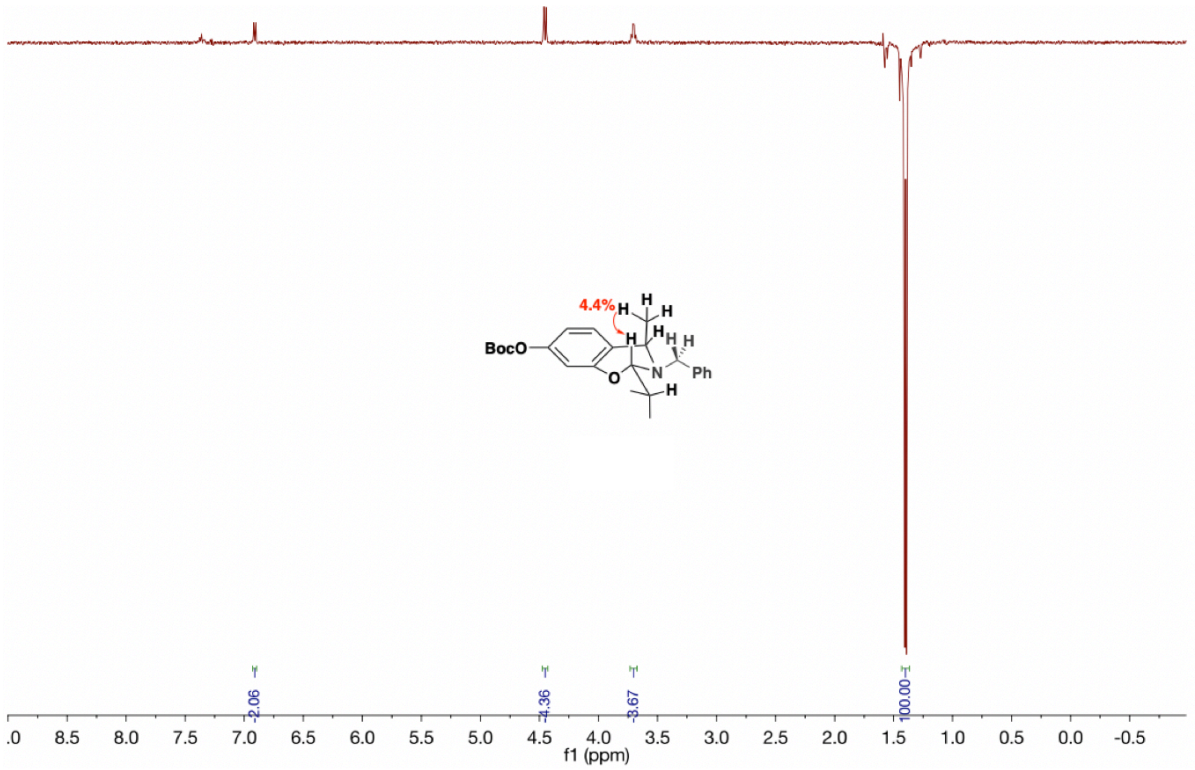
(±)-*trans*-3-benzyl-2-isopropyl-4-methyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl tert-butyl carbonate (38a-Me). Prepared according to the general procedure H. 82% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (25 mg, 72% isolated yield). **^{1}H NMR** (400 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 (90% hexane 10% ethyl acetate).

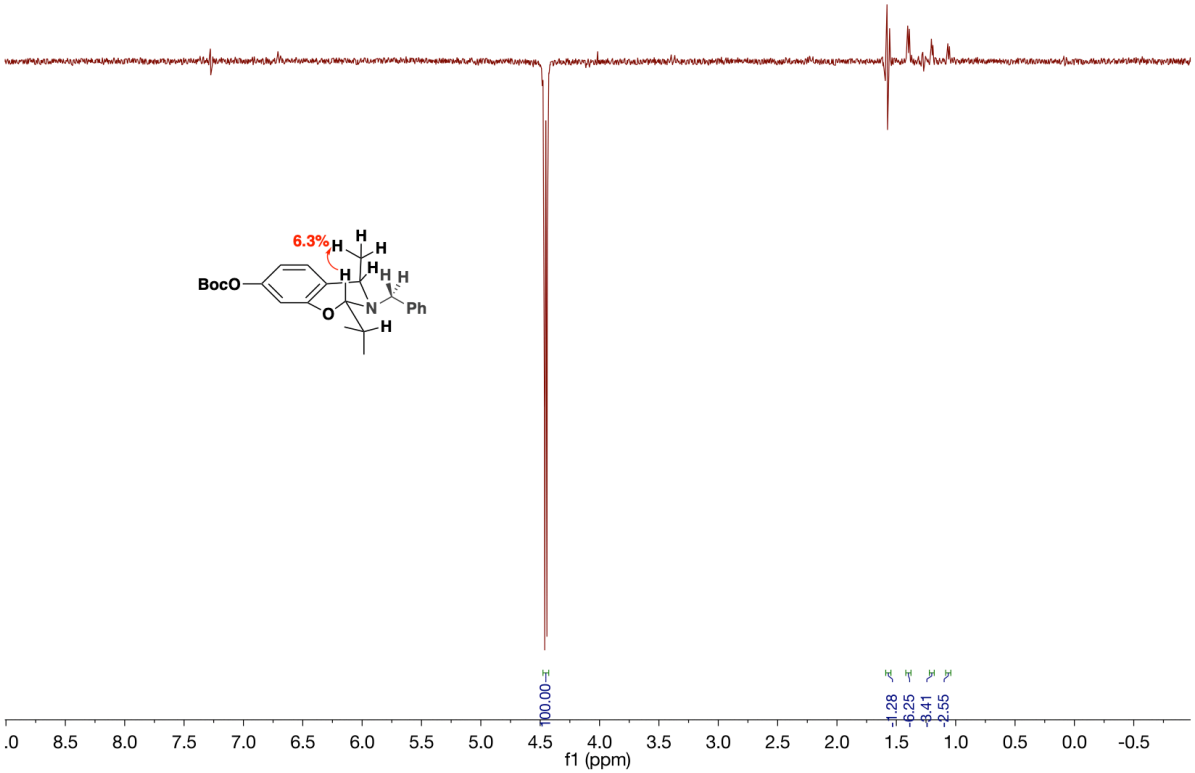
Trans-stereochemistry assignment was confirmed by nOe analysis.

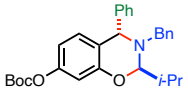



7.37 7.36 7.35 7.35 7.33 7.33 7.32 7.32 7.32 7.32 7.31 7.30 7.26 7.26 6.91 6.89 6.89 6.70 6.69 6.67 6.67 6.66 6.65
4.45 4.43 4.10 4.07 3.71 3.70 3.68 3.67 3.38 3.35
2.25 2.24 2.23 2.22 2.22 2.21 2.20 2.20 2.19 2.18 1.56 1.39 1.38 1.19 1.18 1.05 1.04
Me
N
O
3.96 1.46 0.96 0.92 1.00 1.00 1.04 1.03 1.03 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 77.26 77.01 52.93 49.46 30.59 29.96 29.68 27.97 23.85 20.14 18.59 1.28
Me
N
O
f1 (ppm)


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

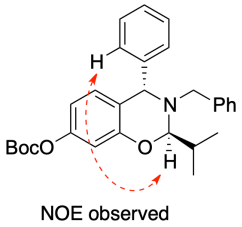

6.3%
BocO
O
N
Ph
100.00
1.28
6.25
8.41
2.55
f1 (ppm)

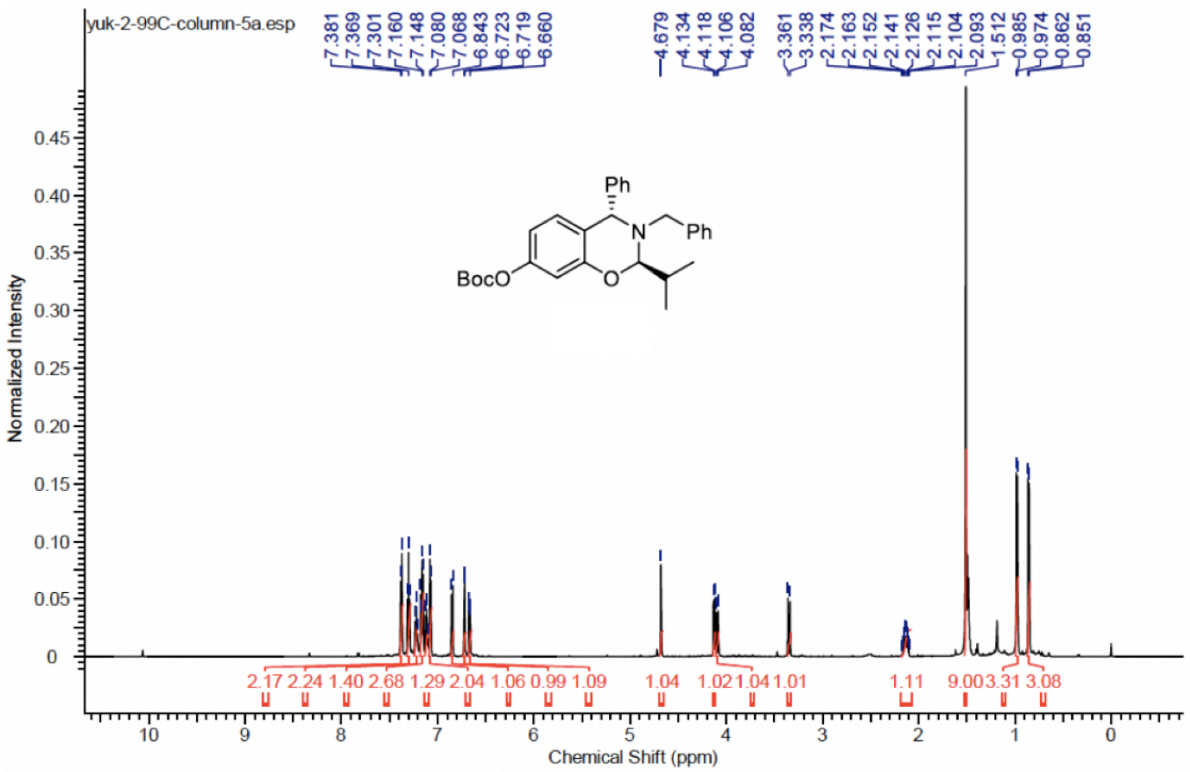


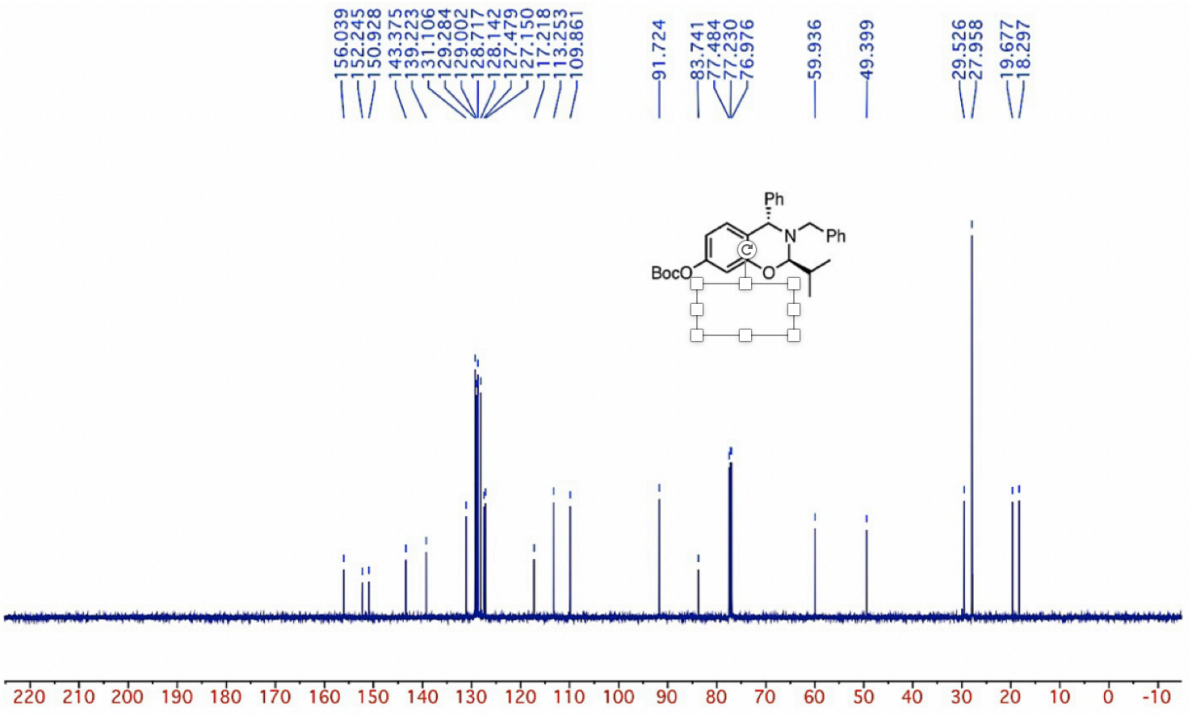
38b-Ph

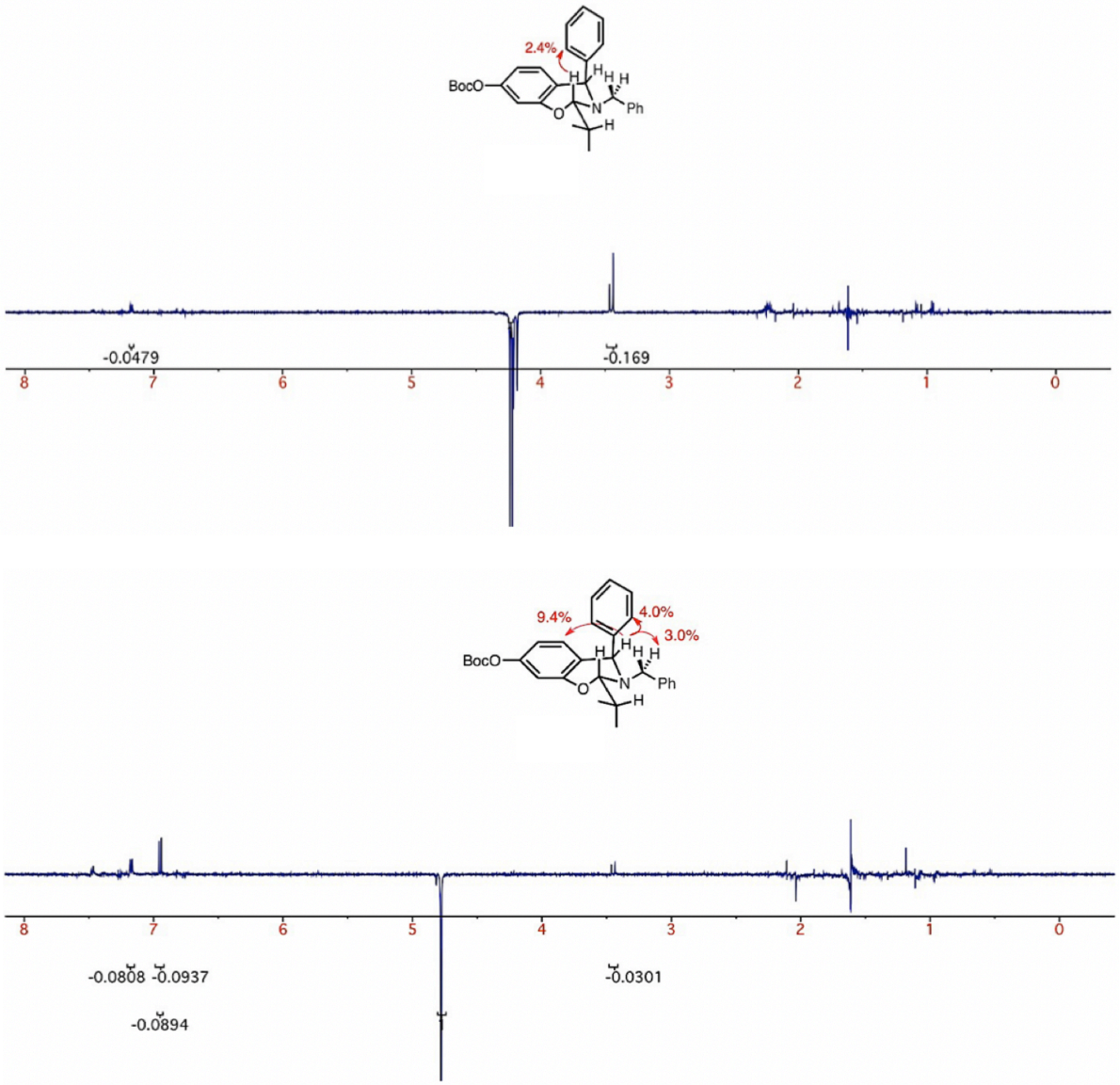
(±)-*trans*-3-benzyl-2-isopropyl-4-phenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl tert-butyl carbonate (38b-Ph). Prepared according to the general procedure H. 95% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (43.38 mg, 94% isolated yield). **^{1}H NMR** (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 (90% hexane 10% ethyl acetate).

Trans-stereochemistry assignment was confirmed by nOe analysis.

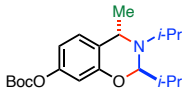



yuk-2-99C-column-5a.esp
7.381
7.369
7.301
7.160
7.148
7.080
7.068
6.843
6.723
6.719
6.660
4.679
4.134
4.118
4.106
4.082
3.361
3.338
2.174
2.163
2.152
2.141
2.126
2.115
2.104
2.093
1.512
0.985
0.974
0.862
0.851
Ph
N
Ph
BocO
O
Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
2.17 2.24 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
10
9
8
7
6
5
4
3
2
1
0
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
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


2.4%
BocO
Ph
-0.0479
-0.169
8
7
6
5
4
3
2
1
0

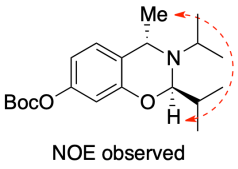
9.4%
4.0%
3.0%
BocO
Ph
8
7
6
5
4
3
2
1
0
-0.0808
-0.0937
-0.0894
-0.0301



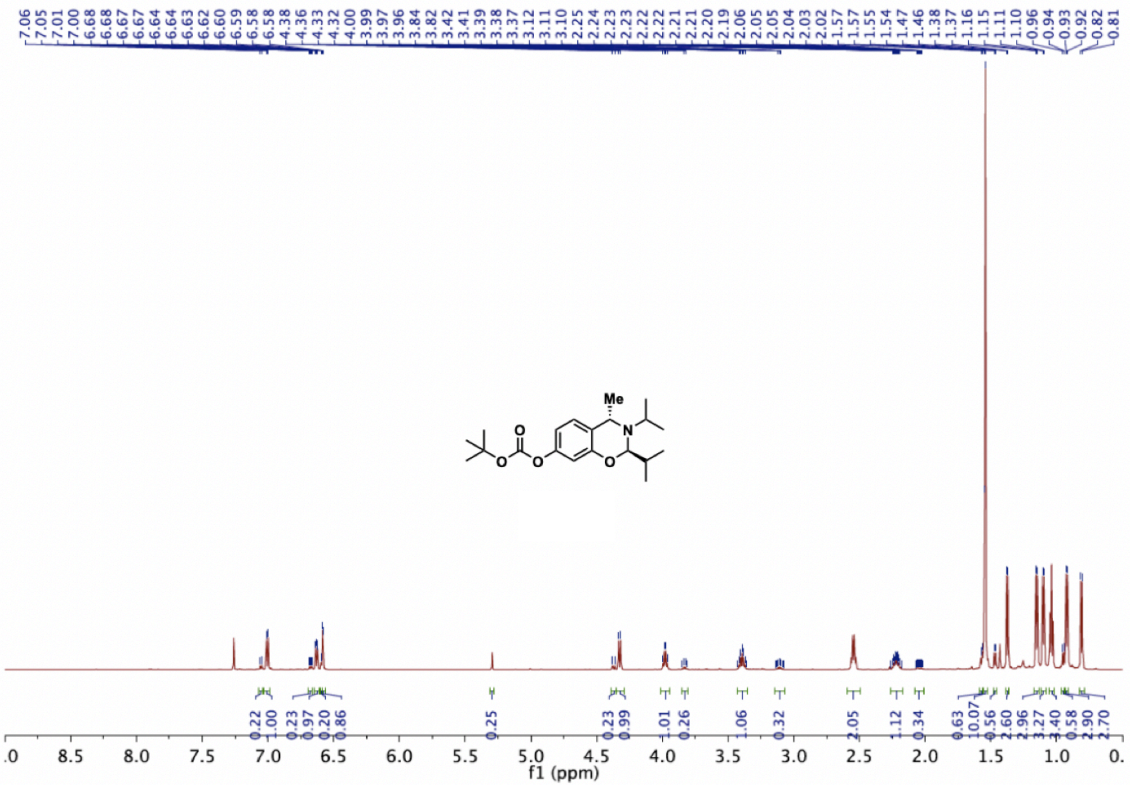
39a-Me

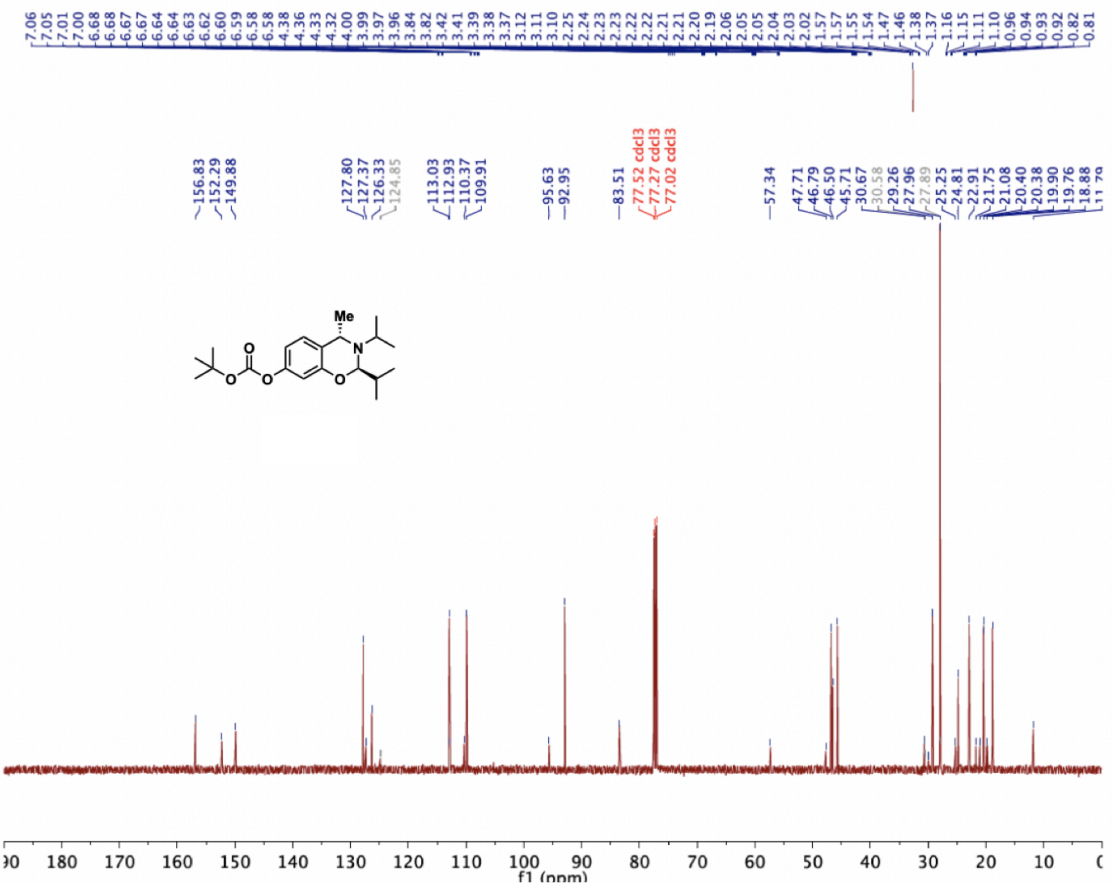
(±)-*tert*-butyl (*trans*-2,3-diisopropyl-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (39a-Me). Prepared according to the general procedure H using two equivalents of imines. 72% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (22 mg, 63% isolated yield, inseparable mixture of diastereomers, *dr* = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) *cis*-isomer: δ7.05 (d, *J* = 8.4 Hz, 1H), 6.68 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.59 (d, *J* = 1.2 Hz, 1H), 4.37 (d, *J* = 10.4 Hz, 1H), 3.83 (q, *J* = 7.1 Hz, 1H), 3.11 (p, *J* = 6.6 Hz, 1H), 2.04 (dp, *J* = 10.3, 6.5 Hz, 1H), 1.57 (d, *J* = 5.8 Hz, 3H), 1.55 (s, 9H), 1.47 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). *trans*-isomer: 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, $CDCl_3$) *cis*-isomer: δ (3 unresolved quaternary carbons) 127.3, 124.8, 113.0, 110.3, 95.6, 77.4, 57.3, 47.6, 30.6, 27.8, 25.2, 21.7, 21.0, 19.9, 19.7. *trans*-isomer: 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 (90% hexane 10% ethyl acetate).

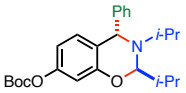
Trans-stereochemistry of major isomer was confirmed by nOe analysis.



NOE observed

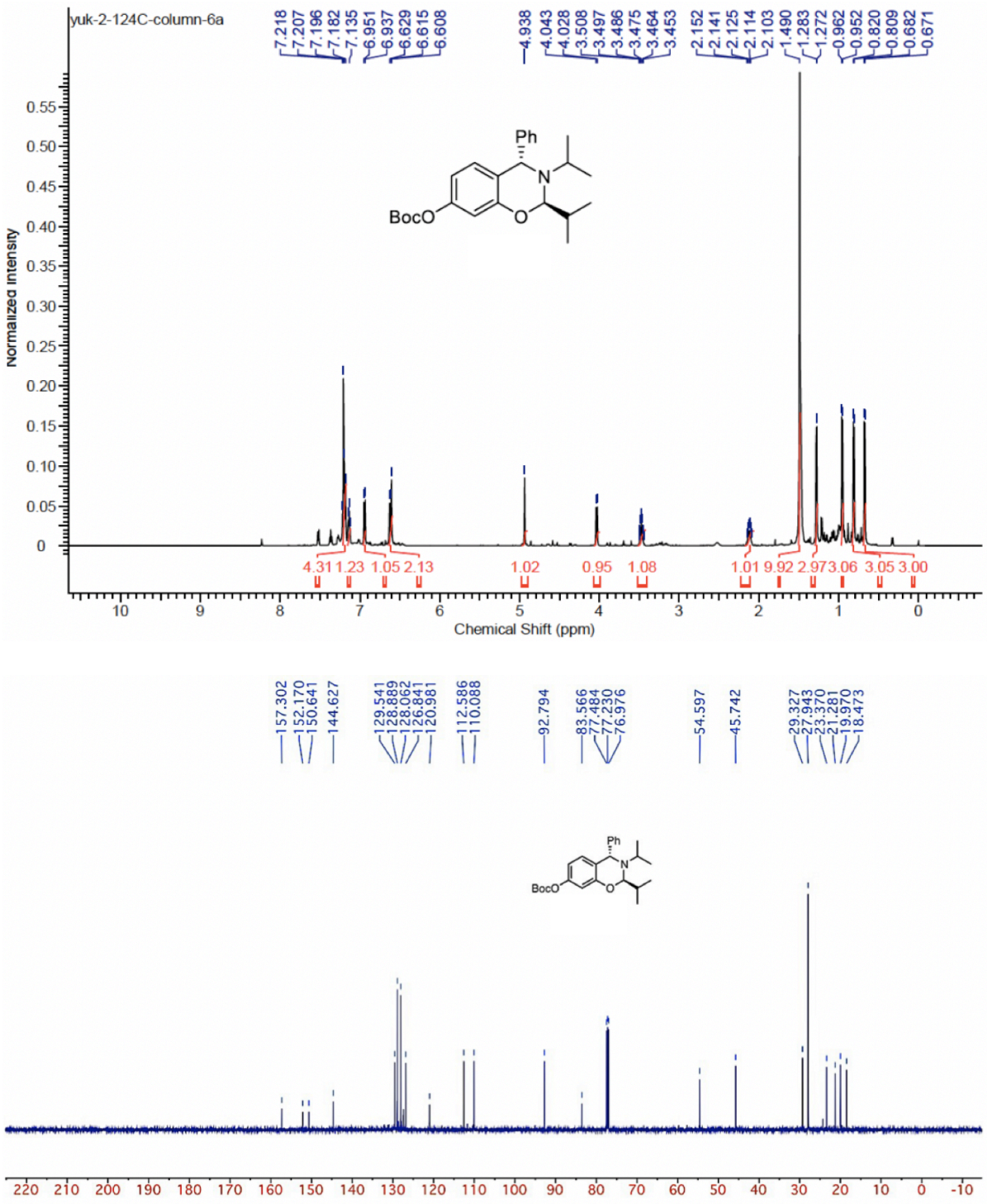

Me
f1 (ppm)


Me
77.52 cdd3
77.27 cdd3
77.02 cdd3
f1 (ppm)



39b-Ph

(±)-*tert*-butyl (*trans*-2,3-diisopropyl-4-phenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (39b-Ph). Prepared according to the general procedure H using two equivalents of imines. 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 (90% hexane 10% ethyl acetate).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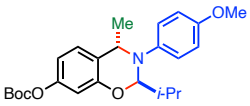
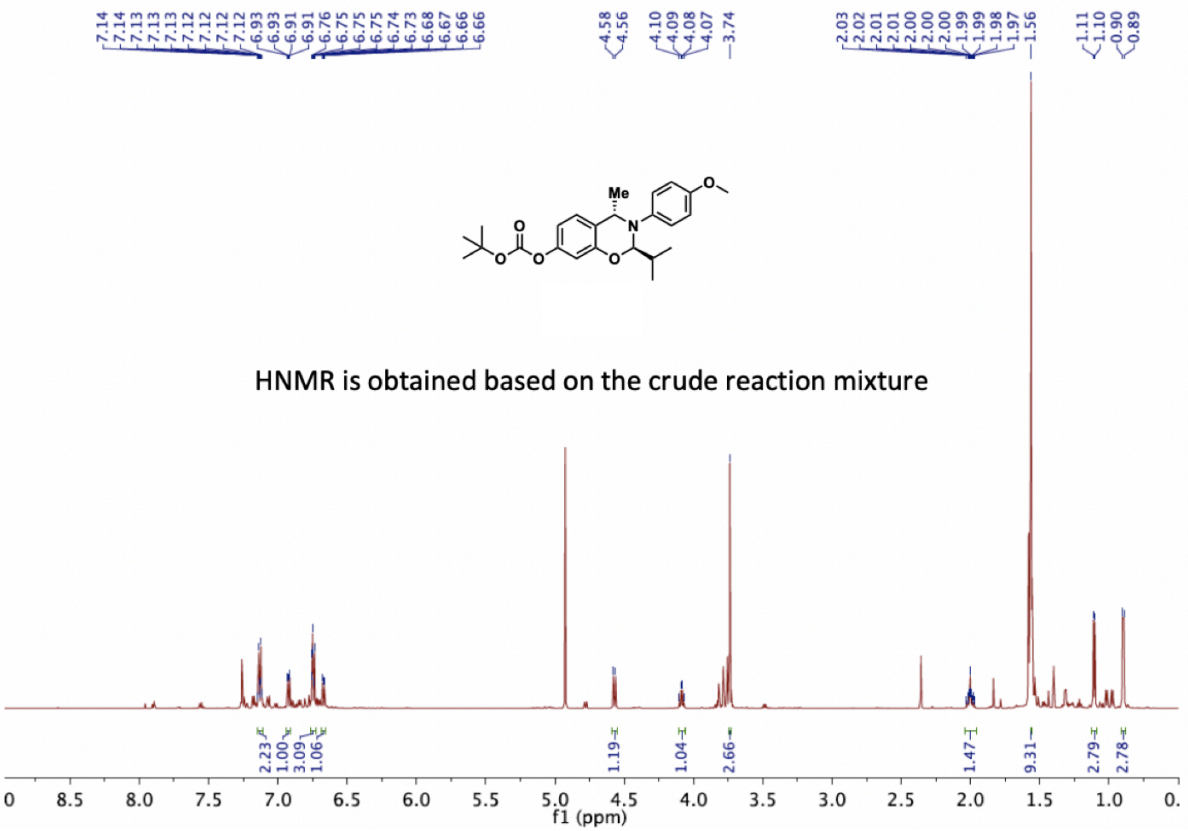
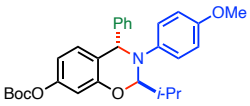
7.207
7.196
7.182
7.135
6.951
6.937
6.629
6.615
6.608
4.938
4.043
4.028
3.508
3.497
3.486
3.475
3.464
3.453
2.152
2.141
2.125
2.114
2.103
1.490
1.283
1.272
0.962
0.952
0.820
0.809
0.682
0.671
Ph
N
O
BocO
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
4.31 1.23 1.05 2.13
1.02
0.95
1.08
1.01 9.92 2.97 3.06 3.05 3.00
10
9
8
7
6
5
4
3
2
1
0
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
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10



40a-Me

(±)-*tert*-butyl(*trans*-2-isopropyl-3-(4-methoxyphenyl)-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (40a-Me). Prepared according to the general procedure H. 71% crude NMR yield. $\mathbf{R_f}$ = 0.4 (90% hexane 10% ethyl acetate).

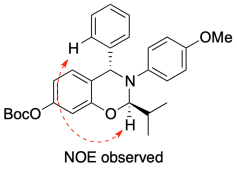


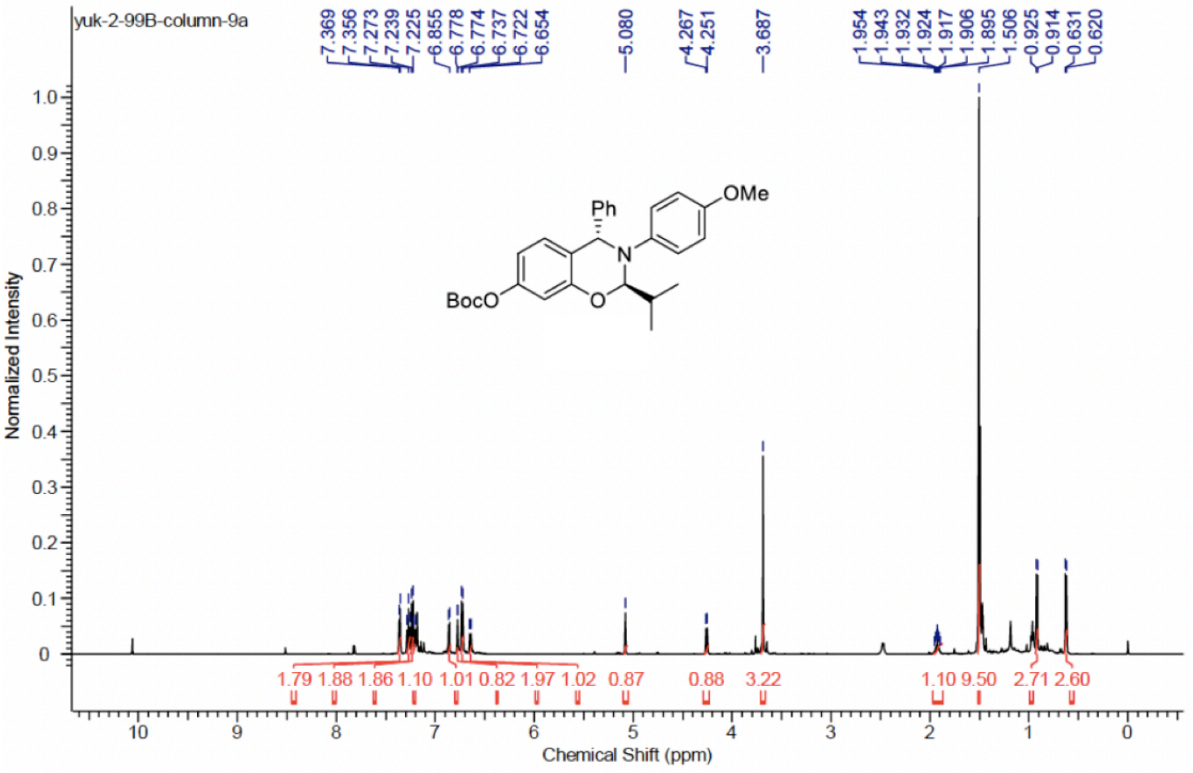


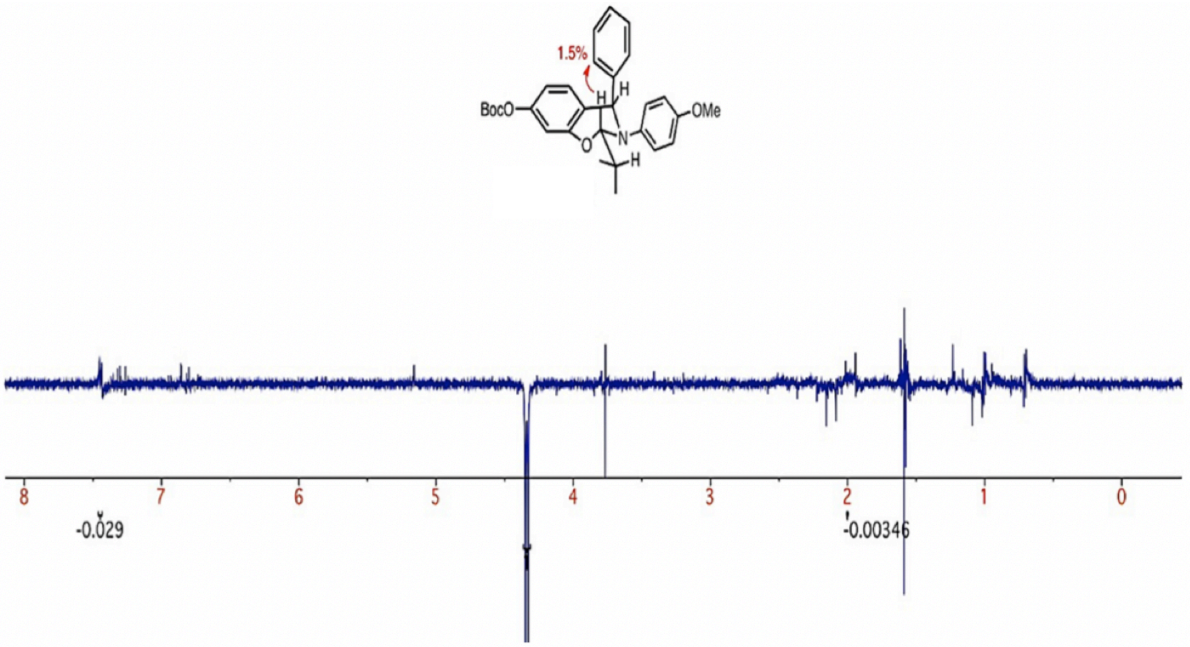
40b-Ph

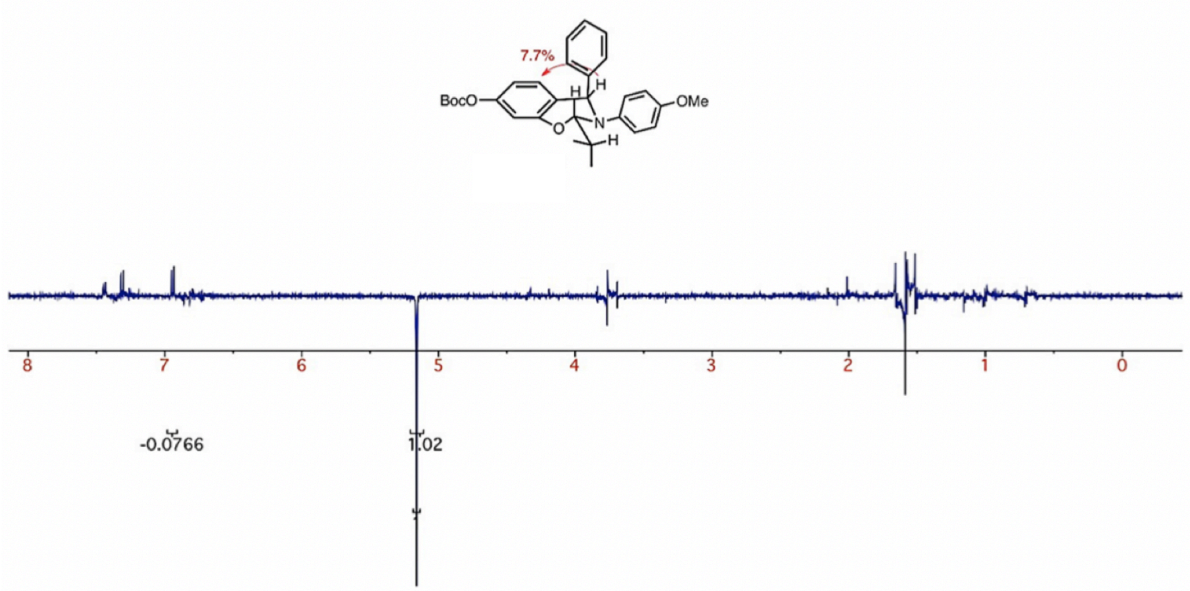
(±)-*tert*-butyl(*trans*-2-isopropyl-3-(4-methoxyphenyl)-4-phenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (40b-Ph). Prepared according to the general procedure H. 61% crude NMR yield. $\mathbf{R_f}$ = 0.5 (90% hexane 10% ethyl acetate).

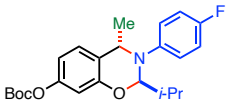
Trans-stereochemistry assignment was confirmed by nOe analysis.






1.5%
BocO
OMe
H
H
O
N
H
8
7
6
5
4
3
2
1
0
-0.029
-0.00346

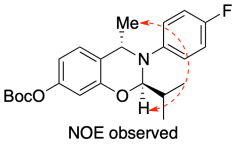

7.7%
BocO
OMe
H
H
O
N
H
8
7
6
5
4
3
2
1
0
-0.0766
1.02

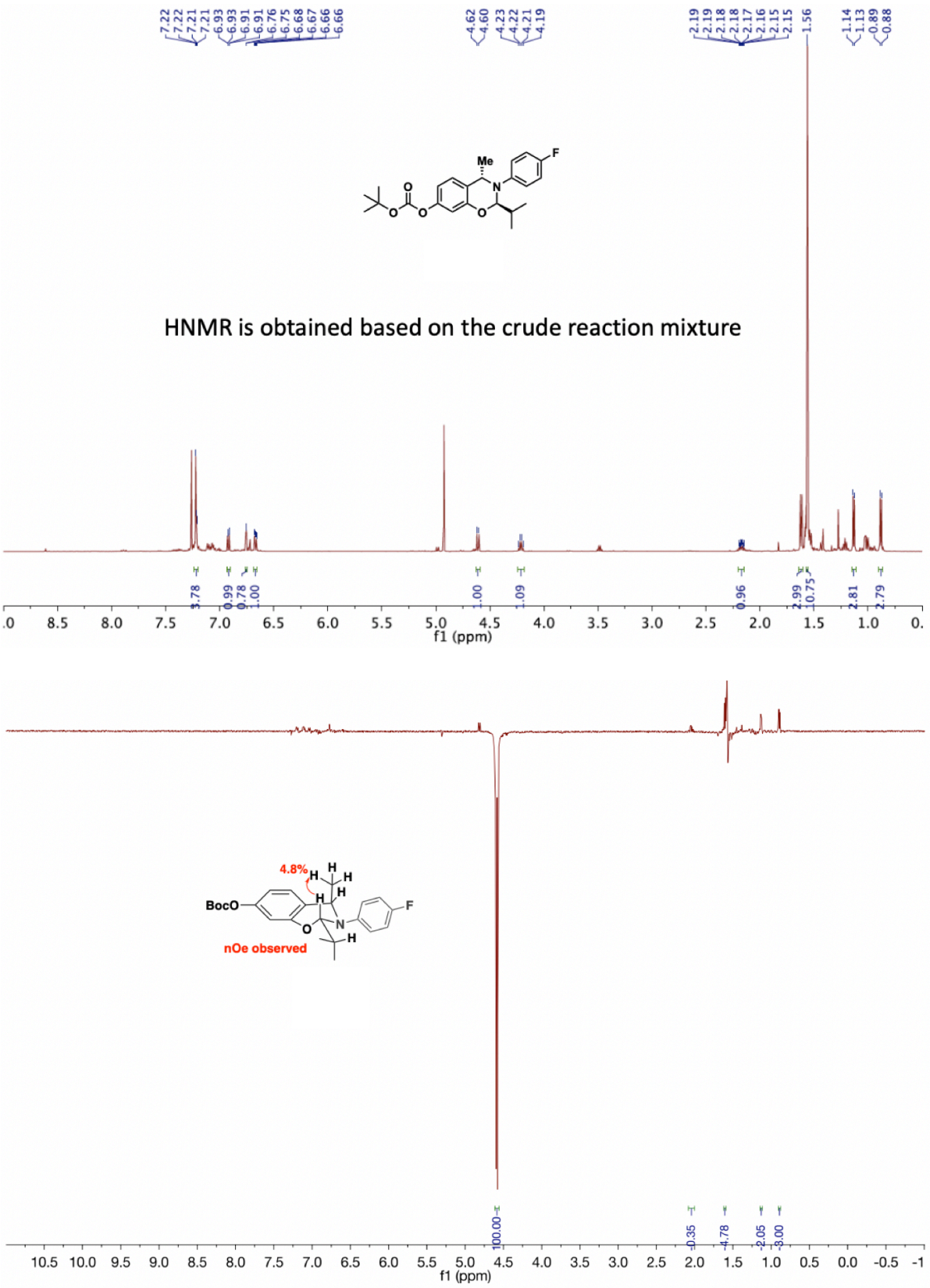


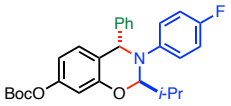
41a-Me

(±)-*tert*-butyl((2R,4S)-3-(4-fluorophenyl)-2-isopropyl-4-methyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (41a-Me). Prepared according to the general procedure H. 65% crude NMR yield. $\mathbf{R_f}$ = 0.4 (90% hexane 10% ethyl acetate).

Trans-stereochemistry assignment was confirmed by nOe analysis.

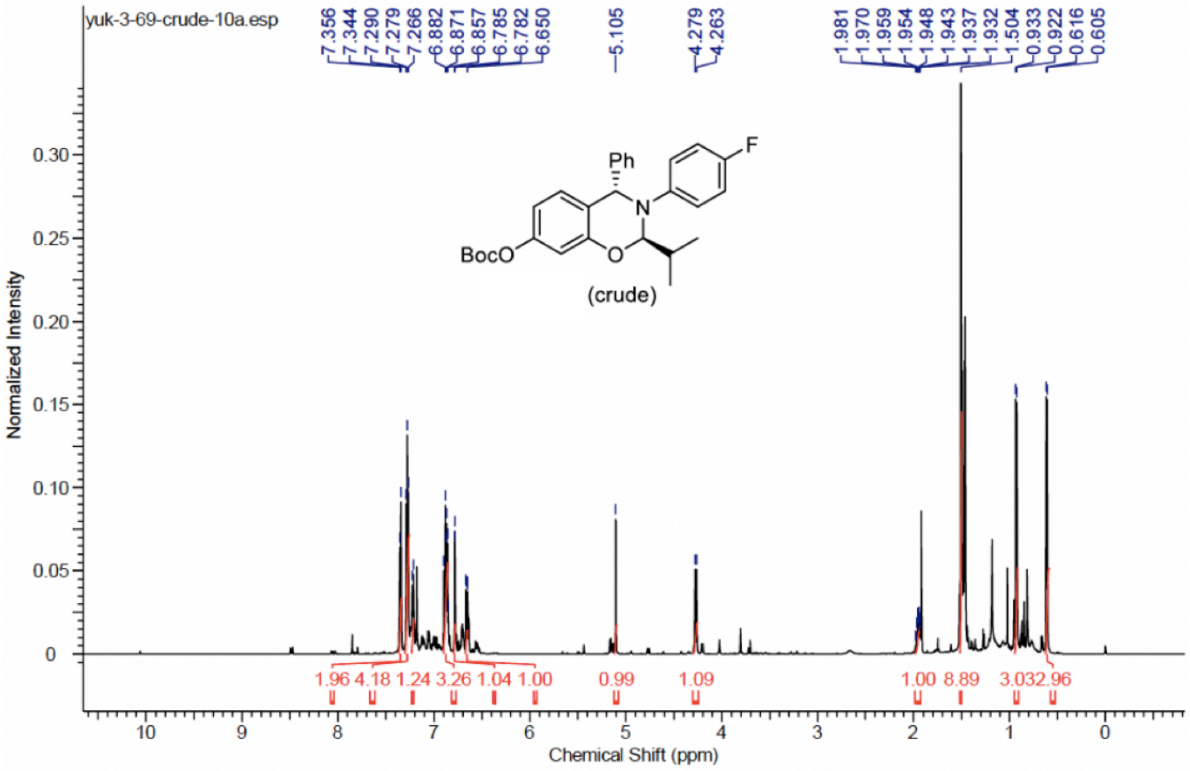


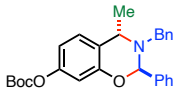

HNMR is obtained based on the crude reaction mixture
f1 (ppm)
4.8%
BocO
nOe observed
f1 (ppm)



41b-Ph

(±)-*tert*-butyl(*trans*-3-(4-fluorophenyl)-2-isopropyl-4-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (41b-Ph). Prepared according to the general procedure H. 67% crude NMR yield. $\mathbf{R_f}$ = 0.6 (90% hexane 10% ethyl acetate).

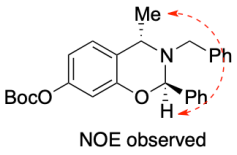


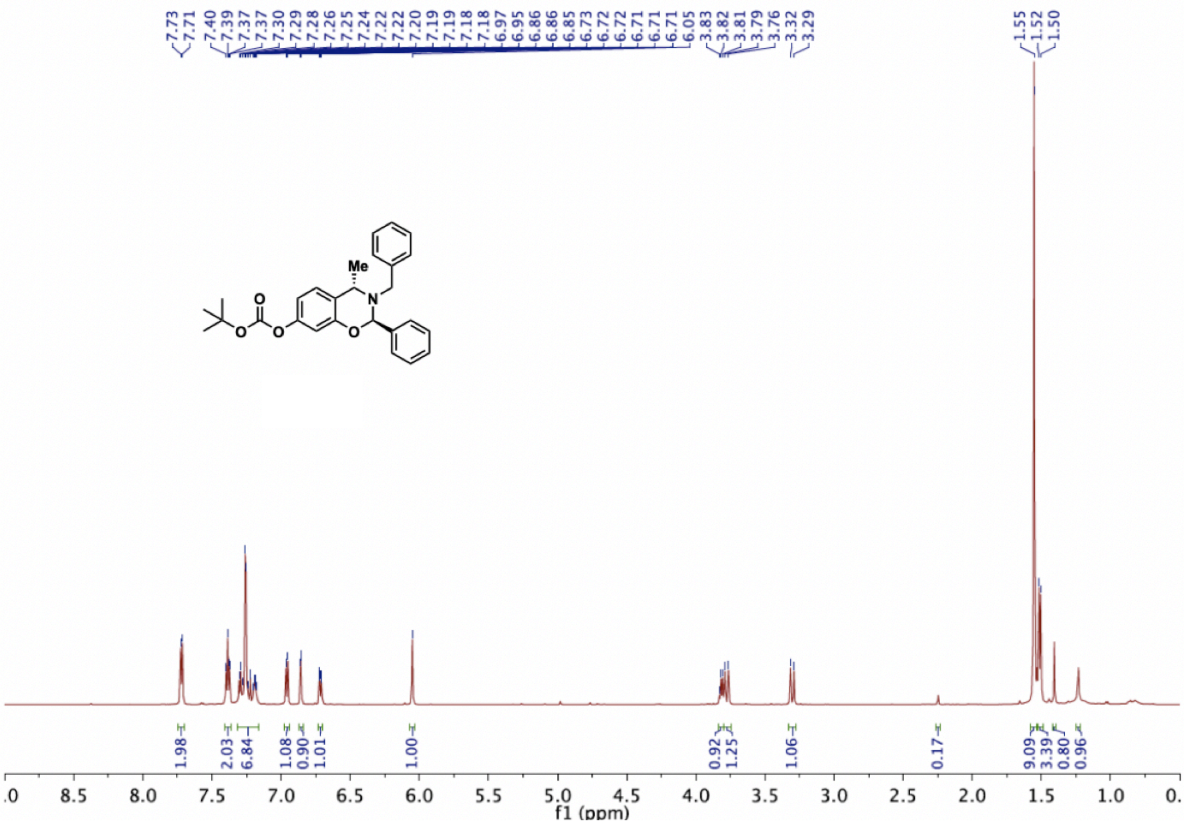


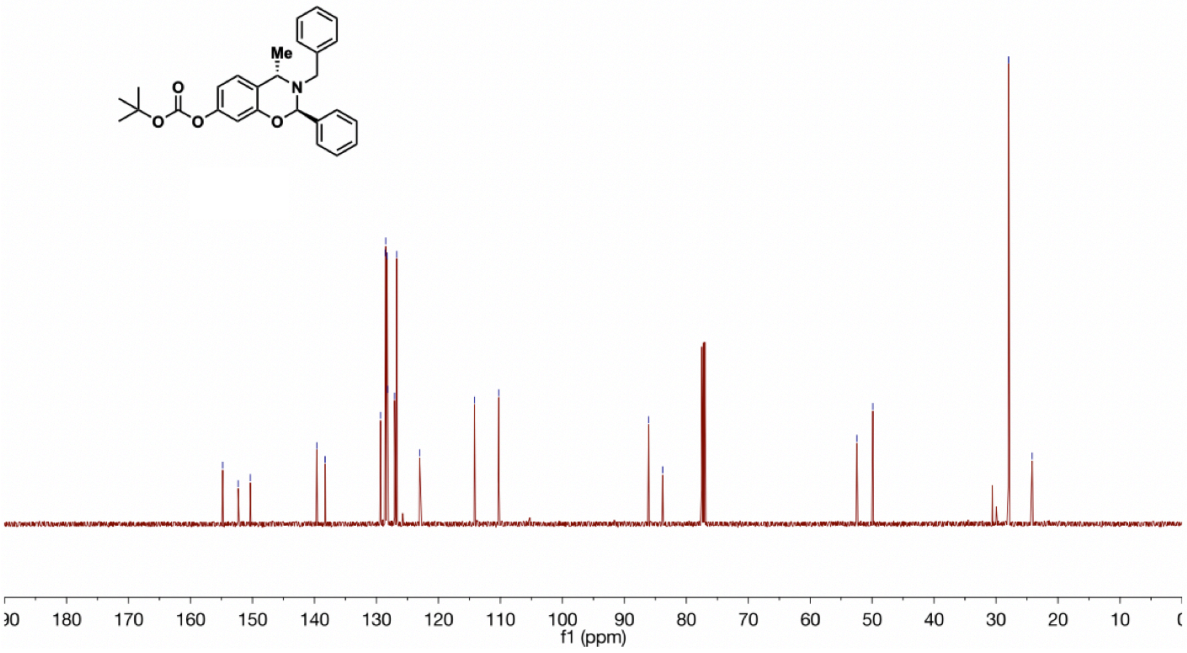
45a-Me

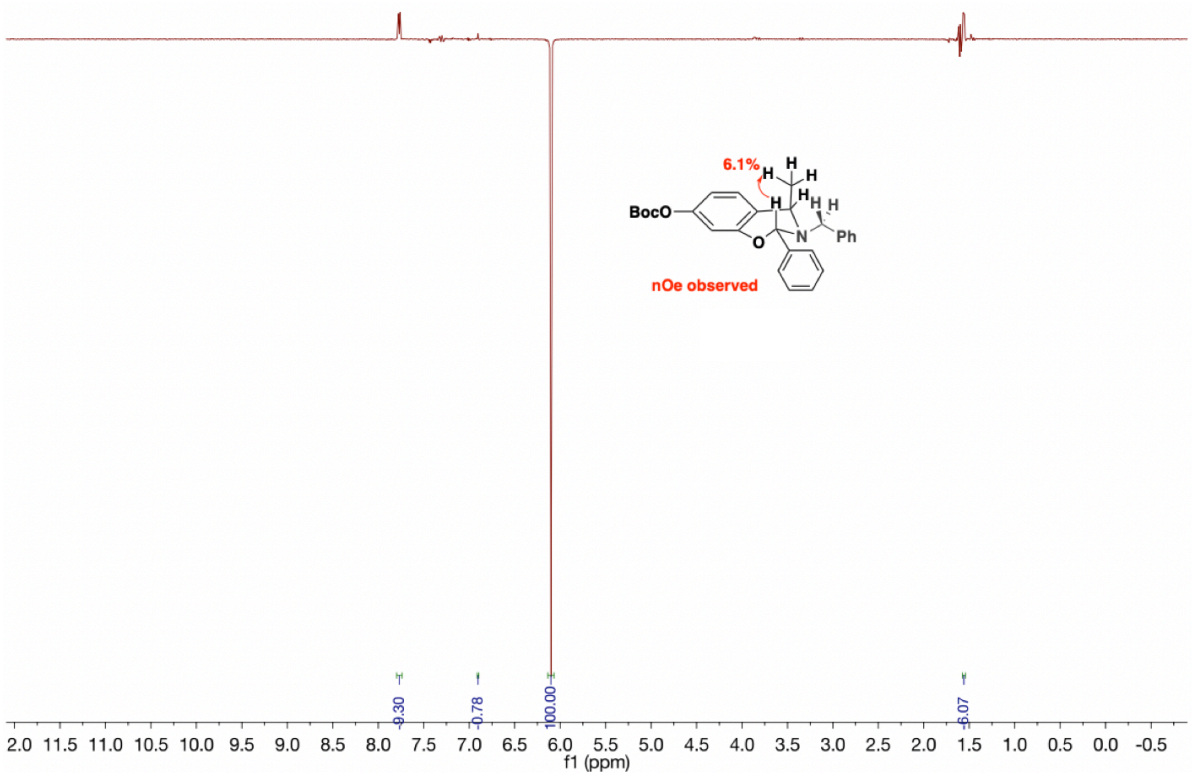
(±)-*trans*-3-benzyl-4-methyl-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (45a-Me). Prepared according to the general procedure H. 83% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (37 mg, 85% isolated yield). **^{1}H NMR** (600 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 (90% hexane 10% ethyl acetate).

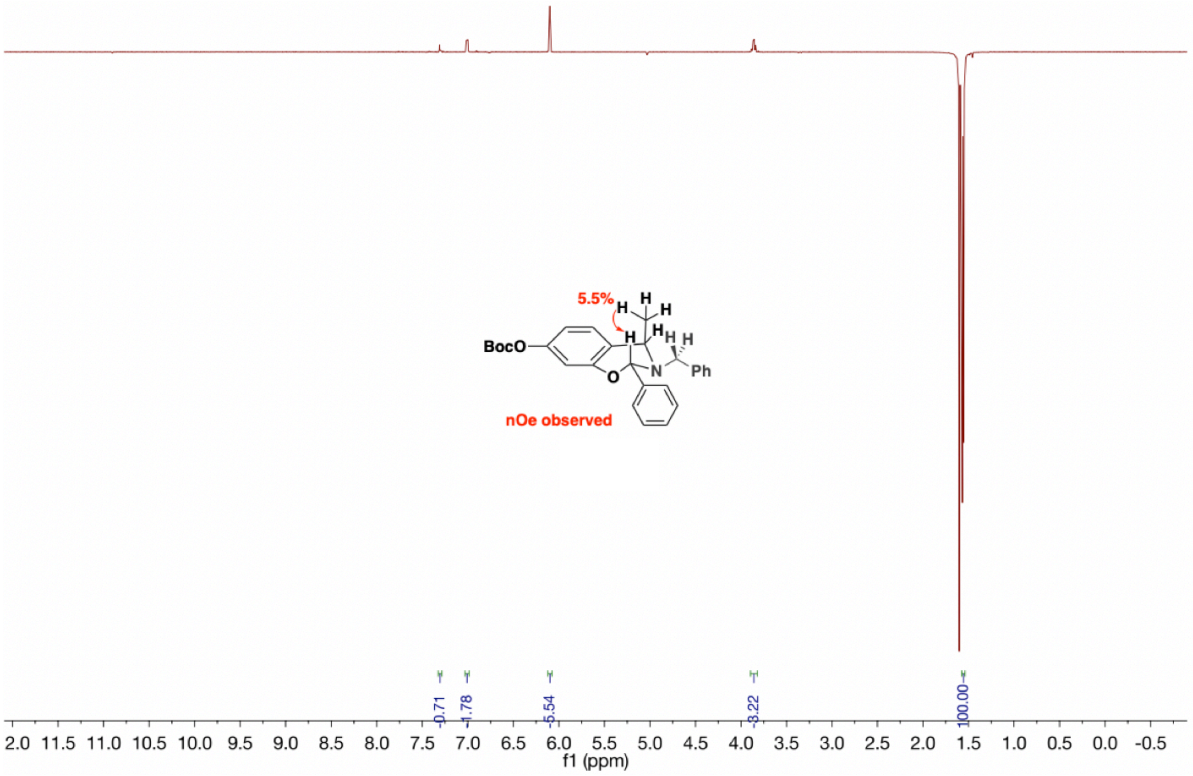
Trans-stereochemistry assignment was confirmed by nOe analysis.

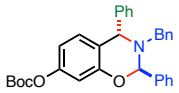



7.73
7.71
7.40
7.39
7.37
7.37
7.30
7.29
7.28
7.26
7.25
7.24
7.22
7.22
7.20
7.19
7.19
7.18
7.18
6.97
6.95
6.86
6.86
6.85
6.73
6.72
6.72
6.71
6.71
6.71
6.05
3.83
3.82
3.81
3.79
3.76
3.32
3.29
1.55
1.52
1.50
Me
N
O
O
O
1.98
2.03
6.84
1.08
0.90
1.01
1.00
0.92
1.25
1.06
0.17
9.09
3.39
0.80
0.96
f1 (ppm)


Me
N
O
O
O
f1 (ppm)

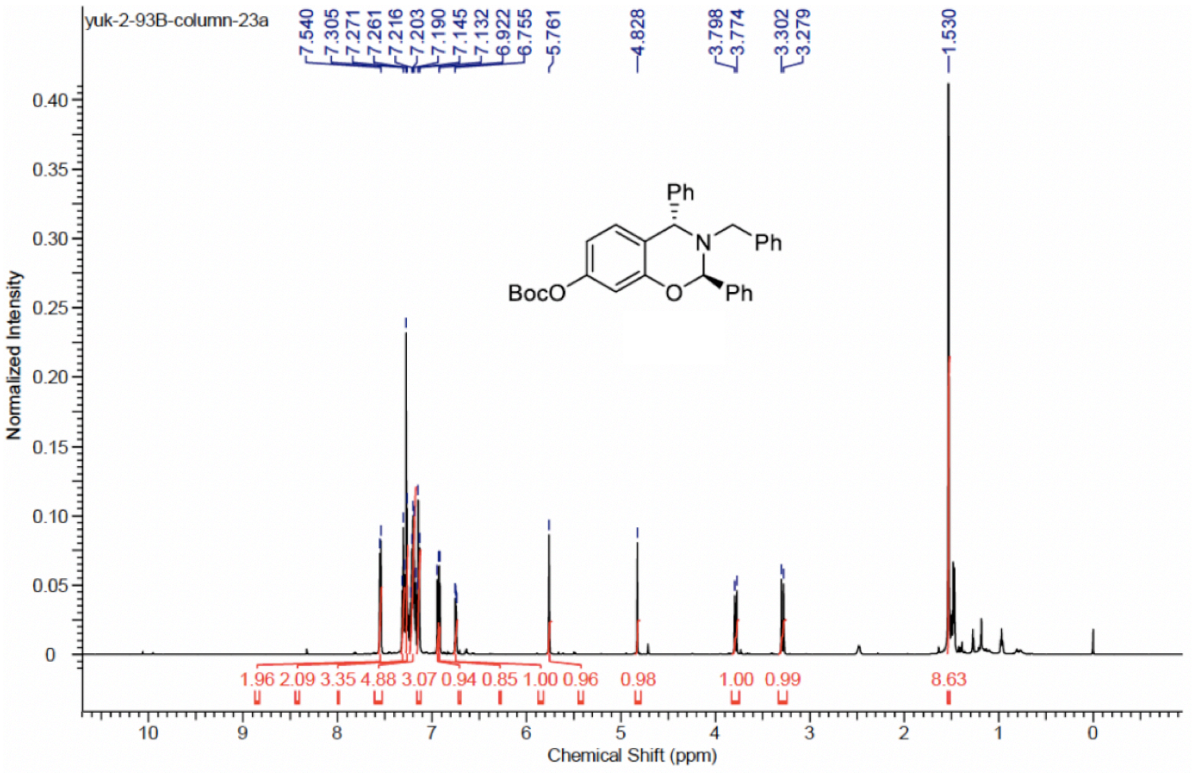

6.1%
BocO
O
N
Ph
nOe observed
9.30
0.78
100.00
9.07
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

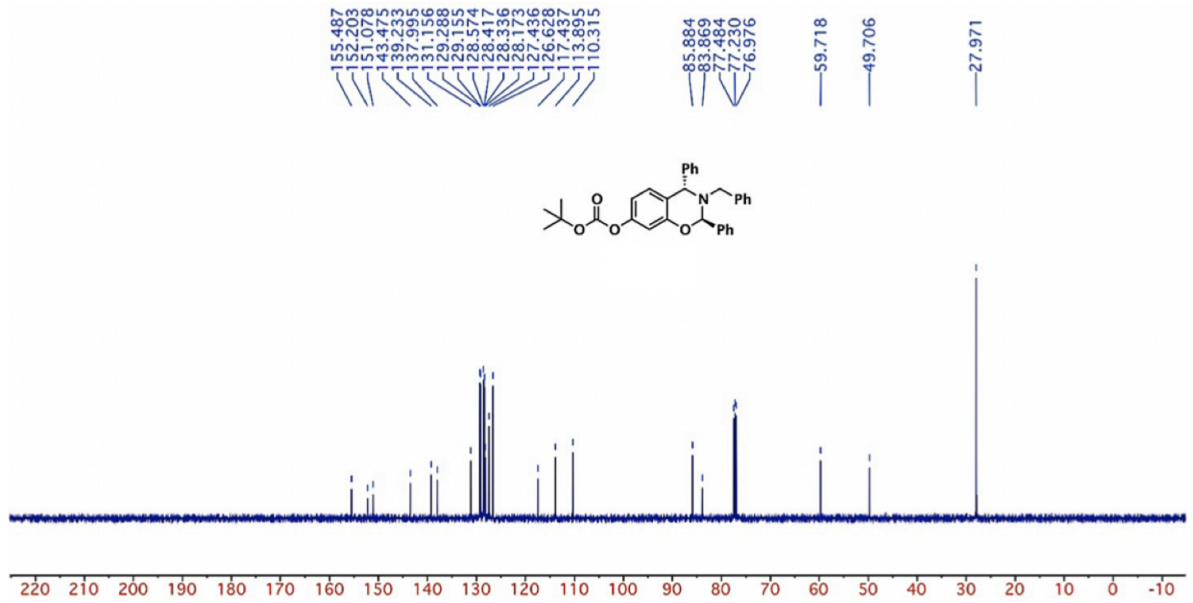

5.5%
BocO
O
N
Ph
nOe observed
0.71
1.78
5.54
3.22
100.00
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

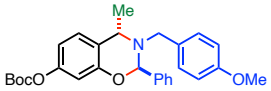


45b-Ph

(±)-*trans*-3-benzyl-2,4-diphenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (45b-Ph). Prepared according to the general procedure H. 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. **R_f** = 0.6 (90% hexane 10% ethyl acetate).

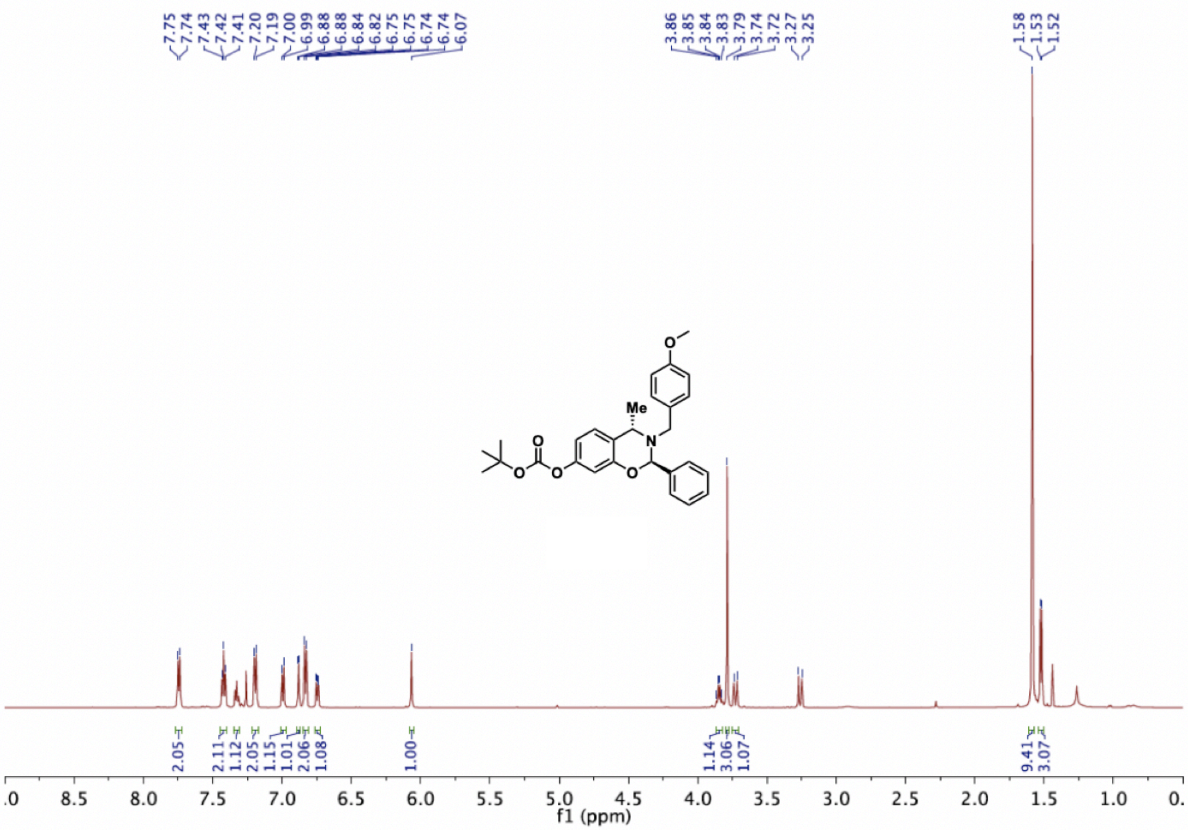

yuk-2-93B-column-23a
7.540
7.305
7.271
7.261
7.216
7.203
7.190
7.145
7.132
6.922
6.755
5.761
4.828
3.798
3.774
3.302
3.279
1.530
Normalized Intensity
Chemical Shift (ppm)
1.96 2.09 3.35 4.88 3.07 0.94 0.85 1.00 0.96 0.98 1.00 0.99 8.63
Ph
N
Ph
BocO
O
Ph

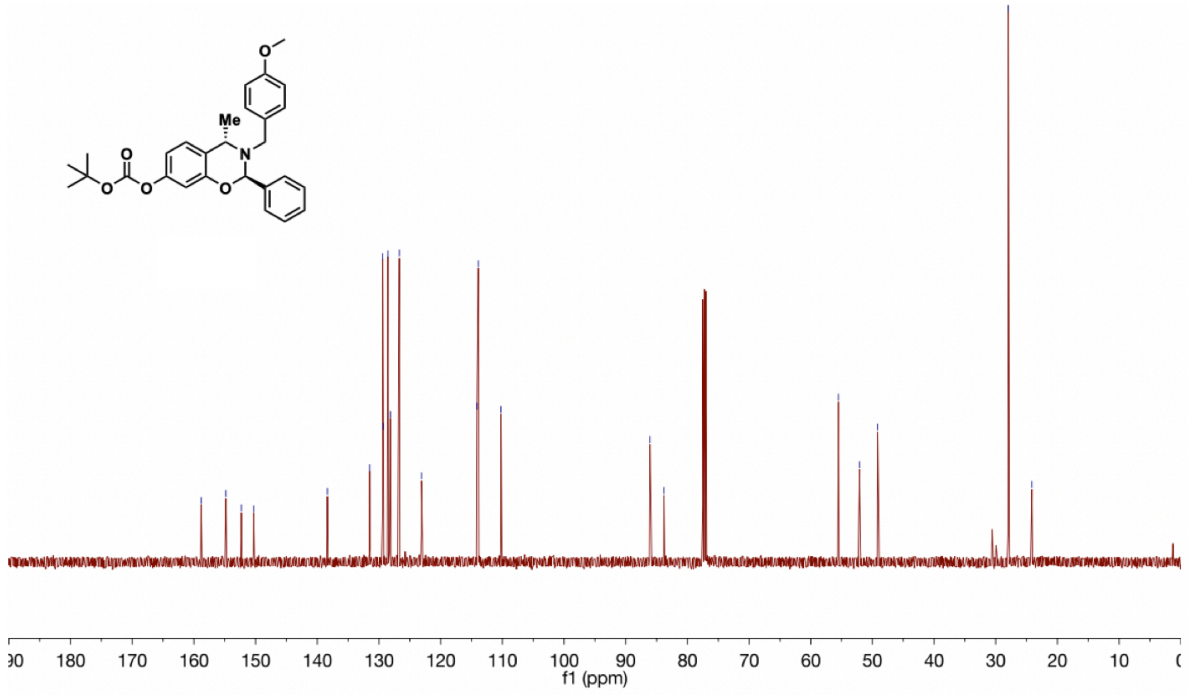

155.487
152.203
151.078
143.475
139.233
137.995
131.156
129.288
129.155
128.574
128.417
128.336
128.173
127.436
126.628
117.437
113.895
110.315
85.884
83.869
77.484
77.230
76.976
59.718
49.706
27.971
Ph
N
Ph
O
O
O
Ph

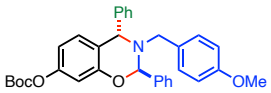


46a-Me

(±)-*tert*-butyl(*trans*-3-(4-methoxybenzyl)-4-methyl-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (46a-Me). Prepared according to the general procedure H. 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 (90% hexane 10% ethyl acetate).

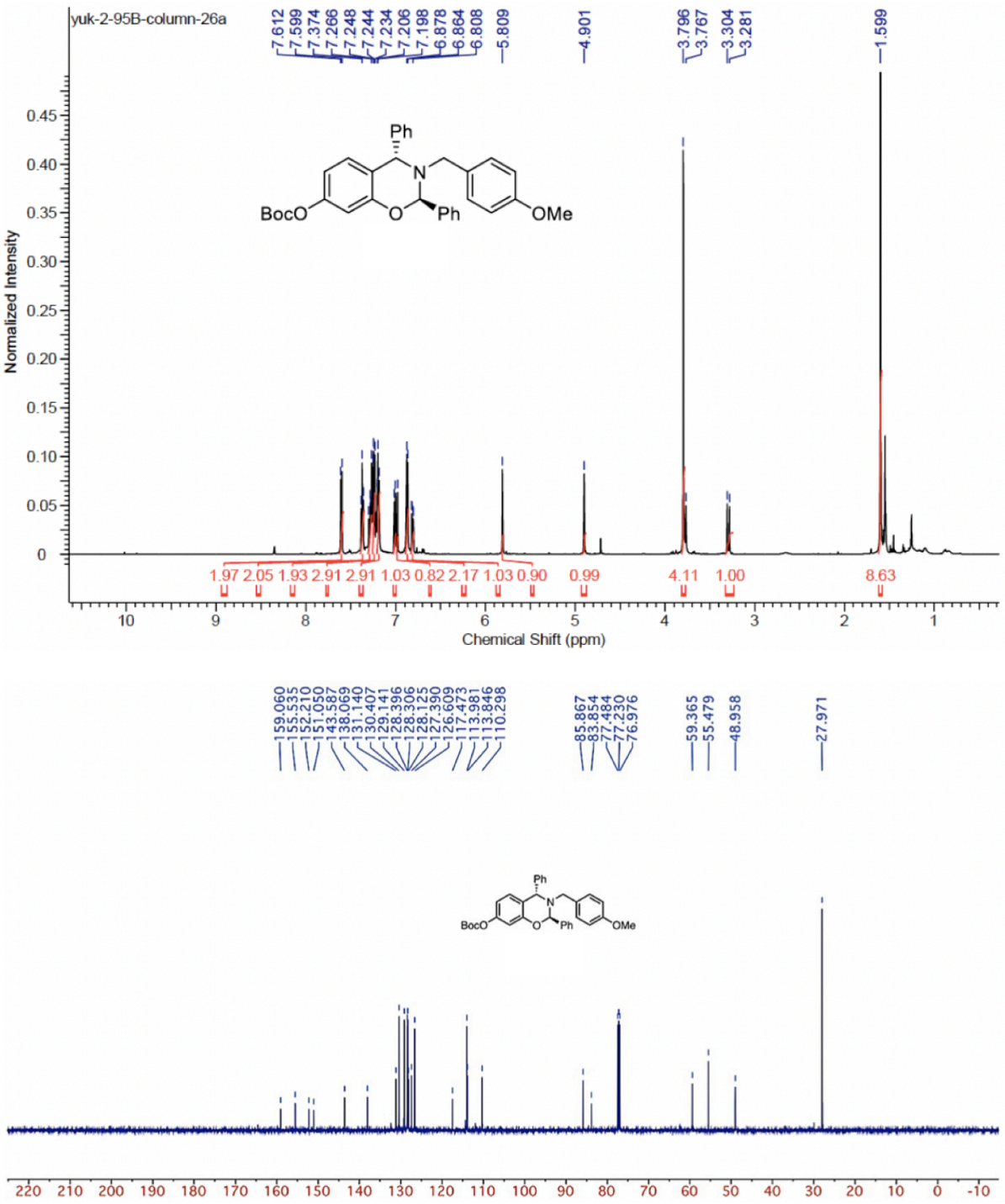

7.75
7.74
7.43
7.42
7.41
7.20
7.19
7.00
6.99
6.88
6.88
6.84
6.82
6.75
6.75
6.74
6.74
6.07
3.86
3.85
3.84
3.83
3.79
3.74
3.72
3.27
3.25
1.58
1.53
1.52
Me
O
N
O
O
O
2.05
2.11
1.12
2.05
1.15
1.01
2.06
1.08
1.00
1.14
3.06
1.07
9.41
3.07
f1 (ppm)

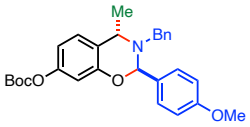

Me
O
N
O
O
O
f1 (ppm)



46b-Ph

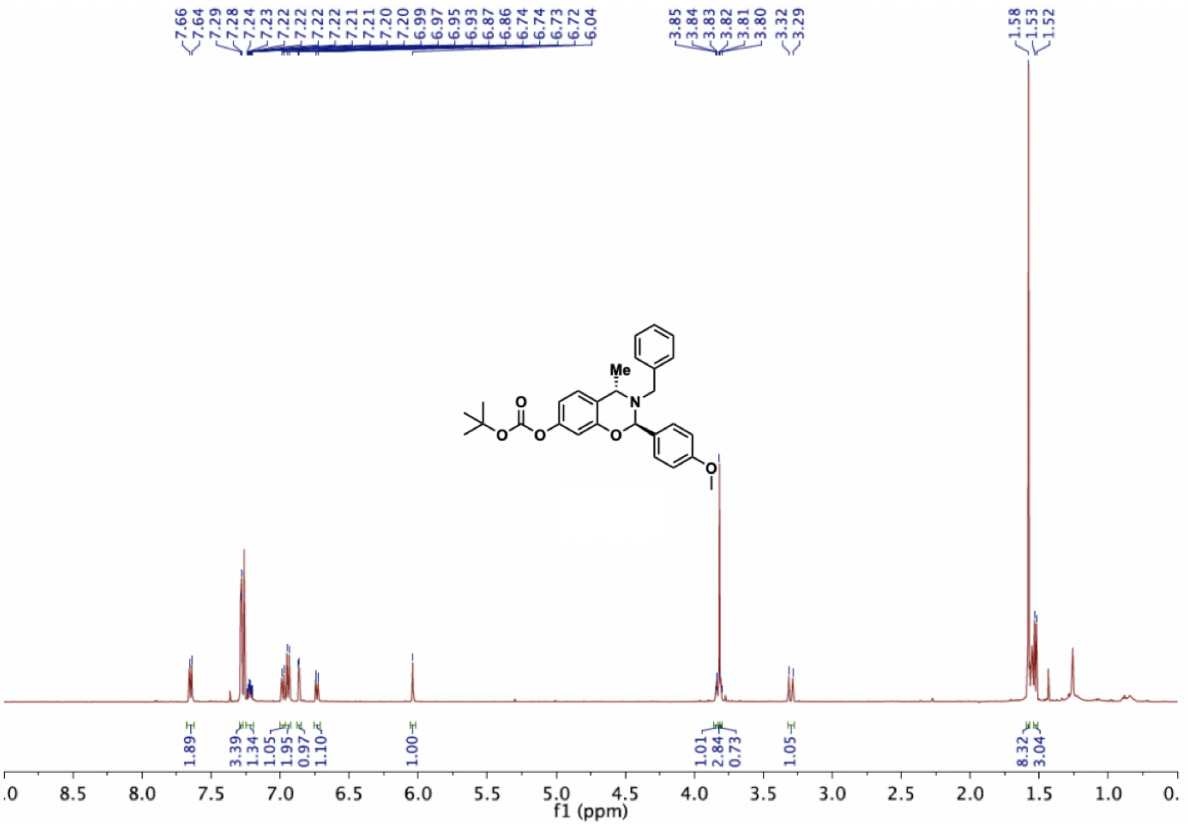
(±)-*tert*-butyl(*trans*-3-(4-methoxybenzyl)-2,4-diphenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (46b-Ph). Prepared according to the general procedure H. 78% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (40.03 mg, 76% isolated yield). **^{1}H 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. $\mathbf{R_f}$ = 0.5 (90% hexane 10% ethyl acetate).

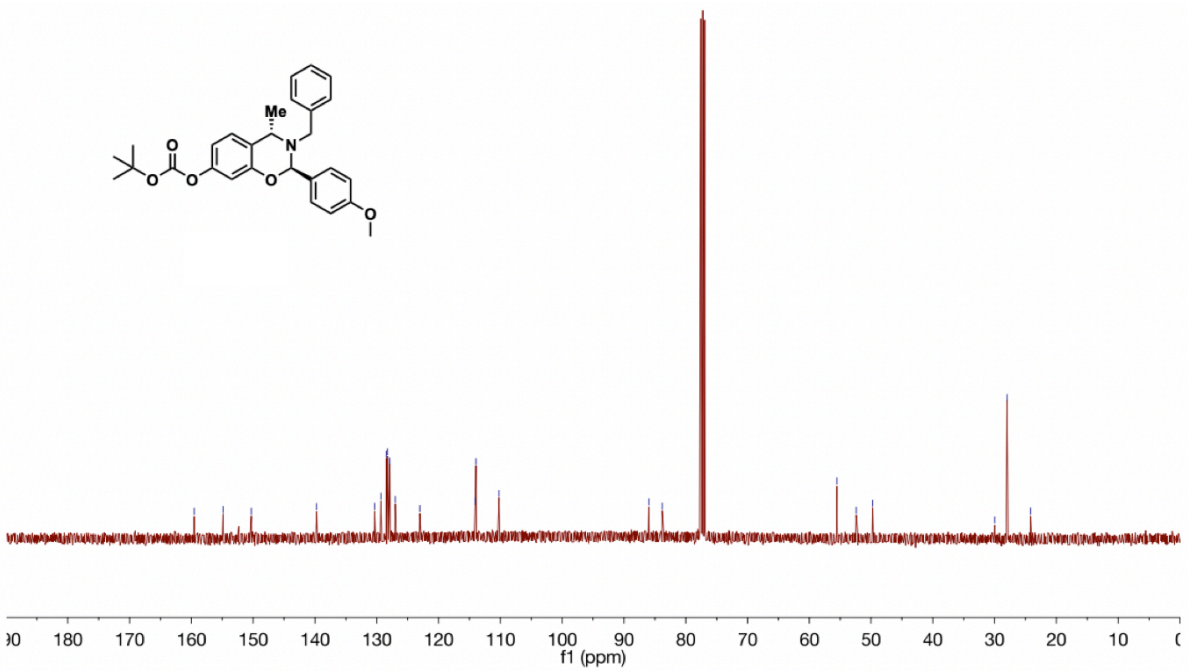

yuk-2-95B-column-26a
7.612
7.599
7.374
7.266
7.248
7.244
7.234
7.206
7.198
6.878
6.864
6.808
5.809
4.901
3.796
3.767
3.304
3.281
1.599
Ph
N
BocO
O
Ph
OMe
Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.97 2.05 1.93 2.91 2.91 1.03 0.82 2.17 1.03 0.90 0.99 4.11 1.00 8.63
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)
159.060
155.535
152.210
151.050
143.587
138.069
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
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

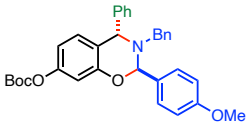


47a-Me

(±)-*tert*-butyl(*trans*-3-(4-methoxybenzyl)-4-methyl-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (47a-Me). Prepared according to the general procedure H. 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 (90% hexane 10% ethyl acetate).


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
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)

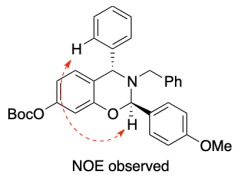

Me
N
O
O
O
O
f1 (ppm)

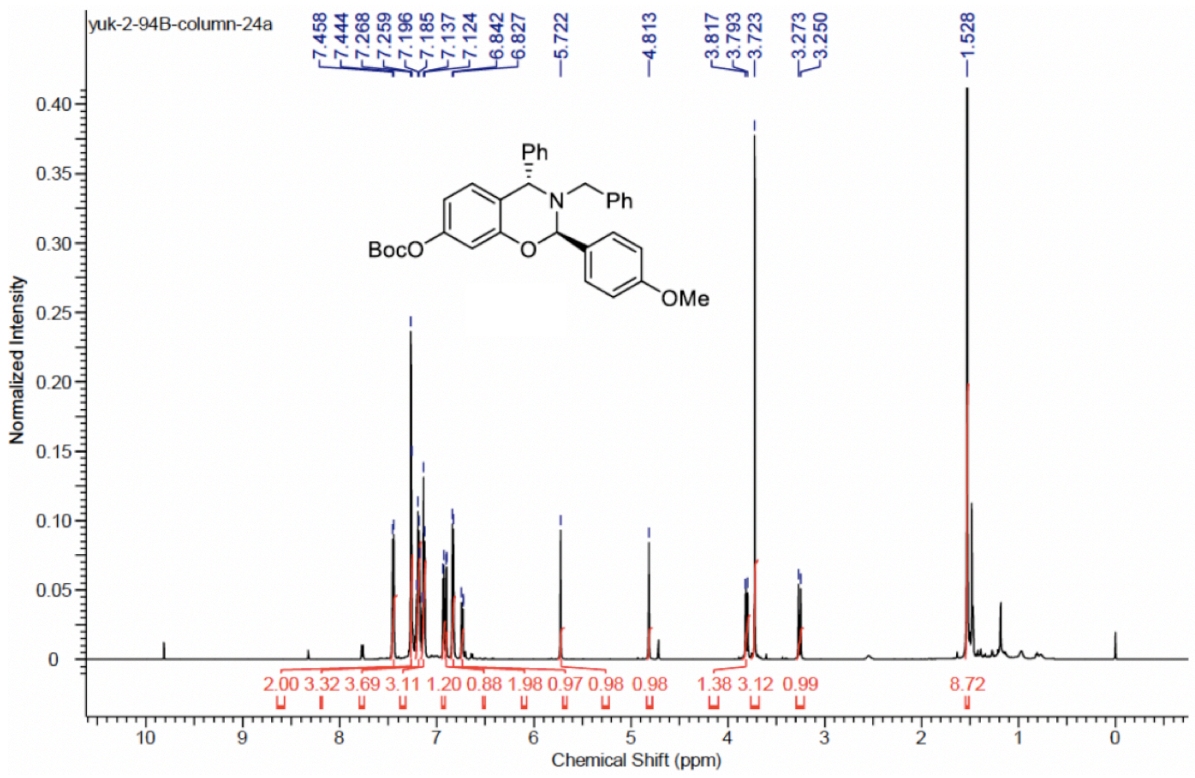


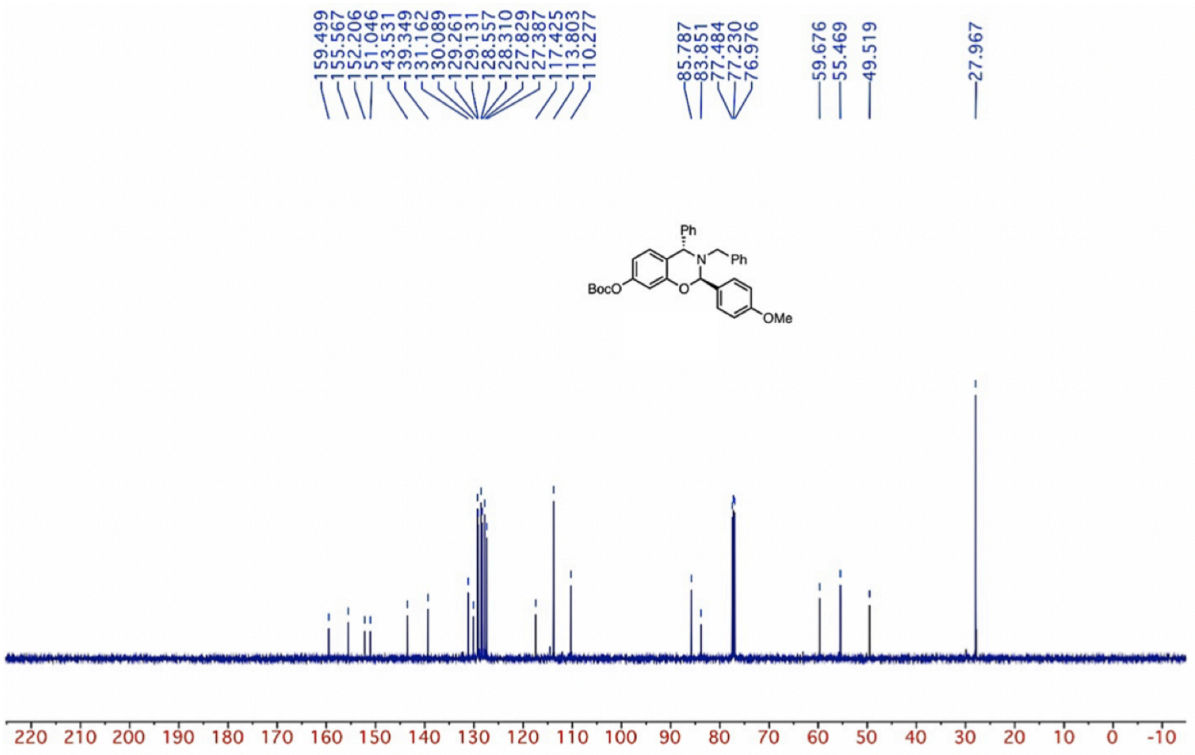
47b-Ph

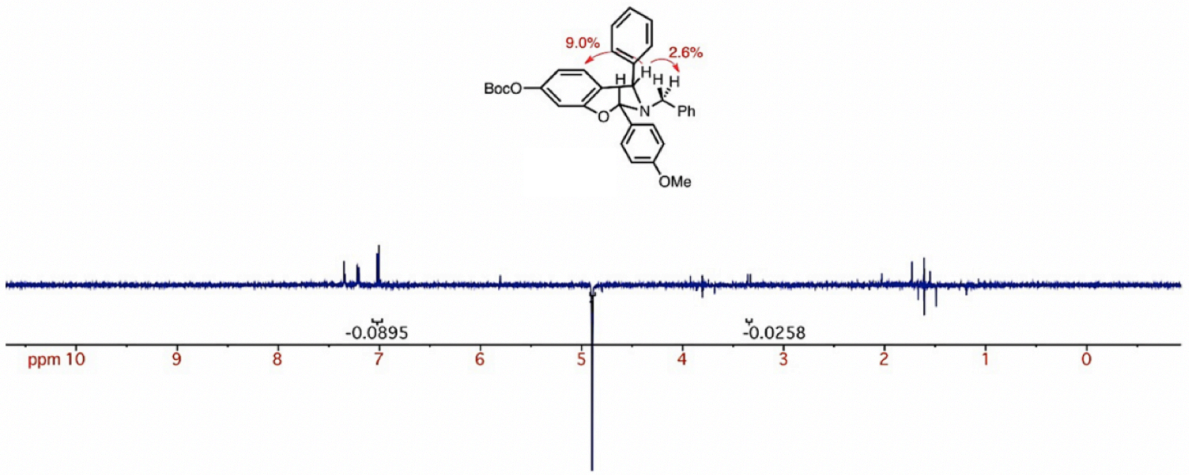
(±)-*tert*-butyl(*trans*-3-(4-methoxybenzyl)-2,4-diphenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (47b-Ph). Prepared according to the general procedure H. 78% crude NMR yield. The residue was purified by flash column chromatography as a yellow oil (40.03 mg, 76% isolated yield). **^{1}H 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 (90% hexane 10% ethyl acetate).

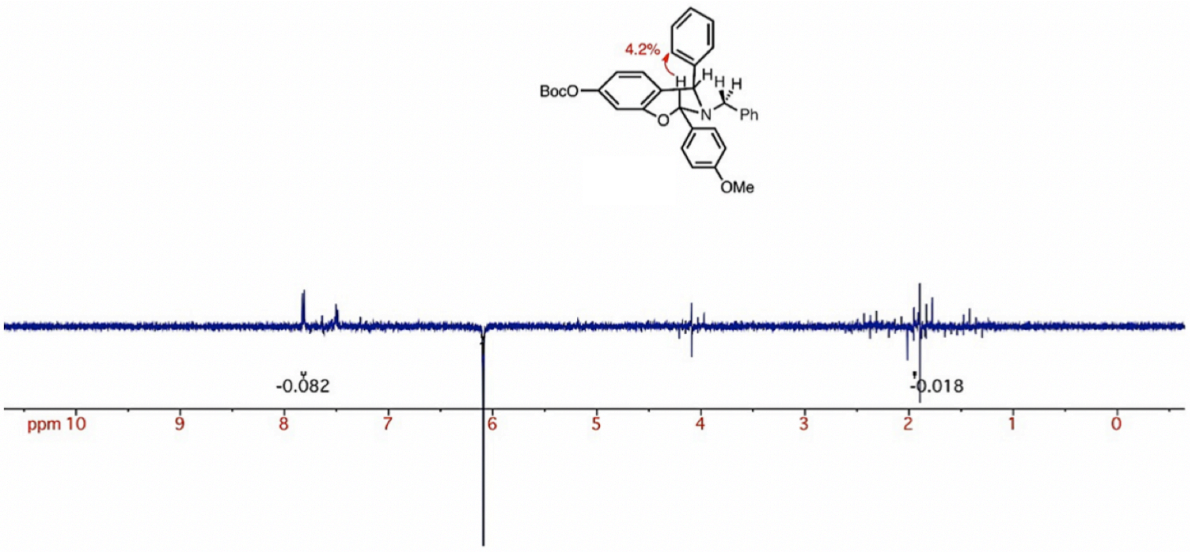
Trans-stereochemistry assignment was confirmed by nOe analysis.

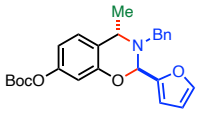



yuk-2-94B-column-24a
7.458
7.444
7.268
7.259
7.196
7.185
7.137
7.124
6.842
6.827
5.722
4.813
3.817
3.793
3.723
3.273
3.250
1.528
Ph
N
Ph
BocO
O
OMe
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
2.00 3.32 3.69 3.11 1.20 0.88 1.98 0.97 0.98 0.98 1.38 3.12 0.99 8.72
10 9 8 7 6 5 4 3 2 1 0
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
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

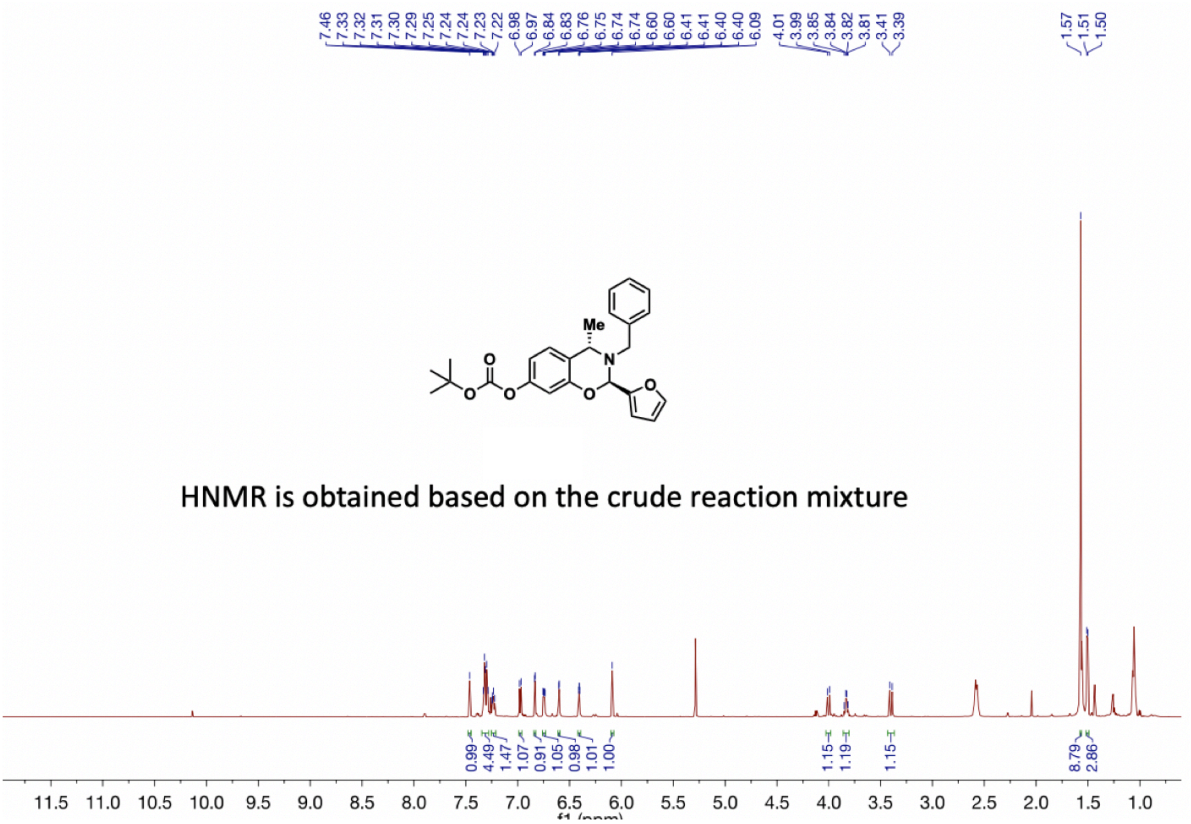

9.0%
2.6%
BocO
H
H
H
N
Ph
O
OMe
-0.0895
-0.0258
ppm 10
9
8
7
6
5
4
3
2
1
0

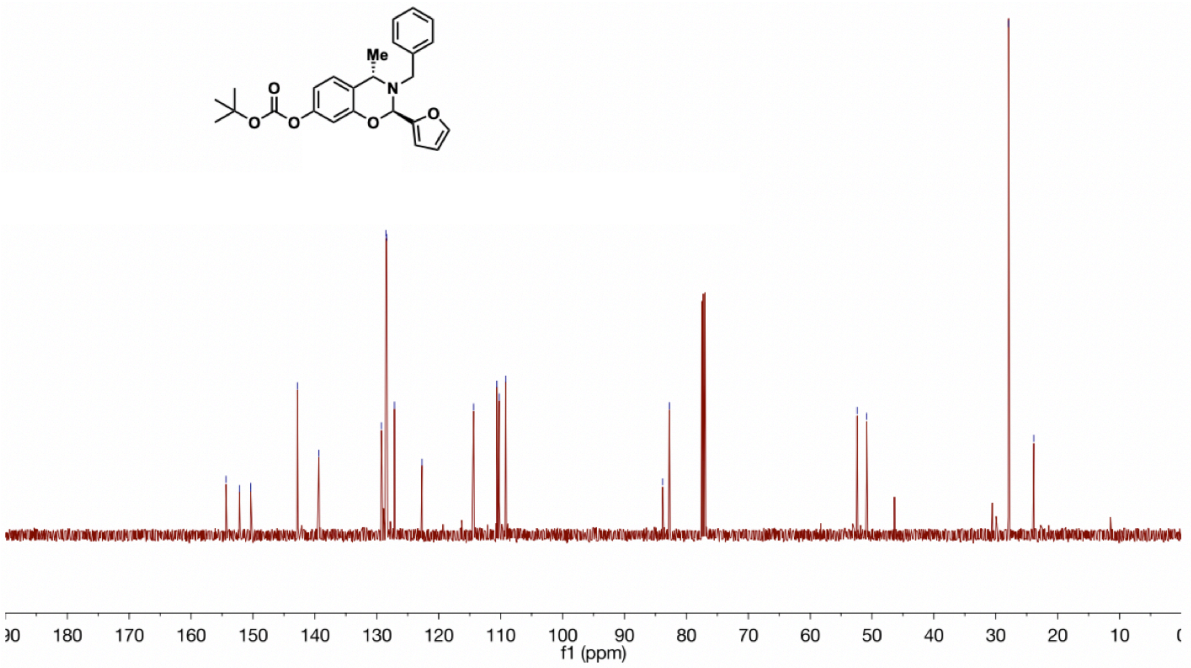

4.2%
BocO
H
H
H
N
Ph
O
OMe
-0.082
-0.018
ppm 10
9
8
7
6
5
4
3
2
1
0

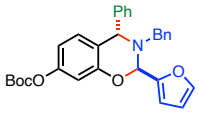


48a-Me

(±)-*trans*-3-benzyl-2-(furan-2-yl)-4-methyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl tert-butyl carbonate (48a-Me). Prepared according to the general procedure H. 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. $\mathbf{R_f}$ = 0.5 (90% hexane 10% ethyl acetate).

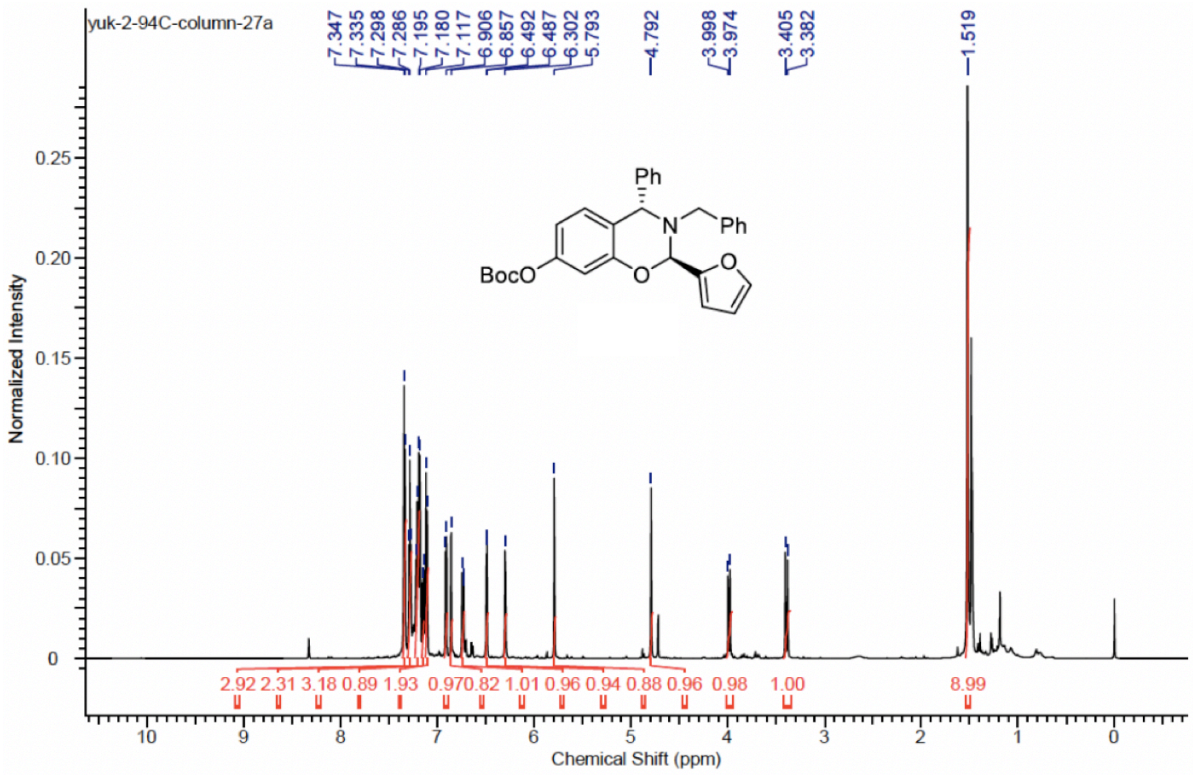

7.46
7.33
7.32
7.31
7.30
7.29
7.25
7.24
7.24
7.23
7.22
6.98
6.97
6.84
6.83
6.76
6.75
6.74
6.74
6.60
6.60
6.41
6.41
6.40
6.40
6.09
4.01
3.99
3.85
3.84
3.82
3.81
3.41
3.39
1.57
1.51
1.50
Me
N
O
O
O
O
HNMR is obtained based on the crude reaction mixture
0.99
4.49
1.47
1.07
0.91
1.05
0.98
1.01
1.00
1.15
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)

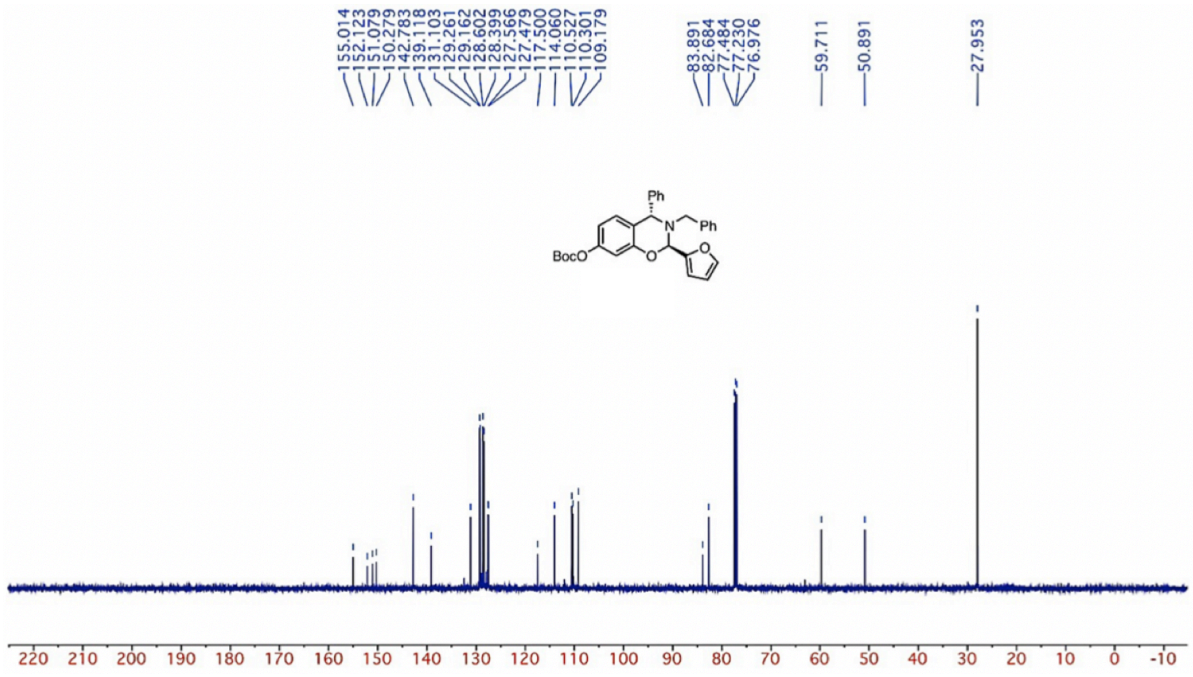

Me
N
O
O
O
O
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

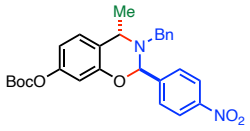


48b-Ph

(±)-*trans*-3-benzyl-2-(furan-2-yl)-4-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (48b-Ph). Prepared according to the general procedure H. 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. $\mathbf{R_f}$ = 0.6 (90% hexane 10% ethyl acetate).

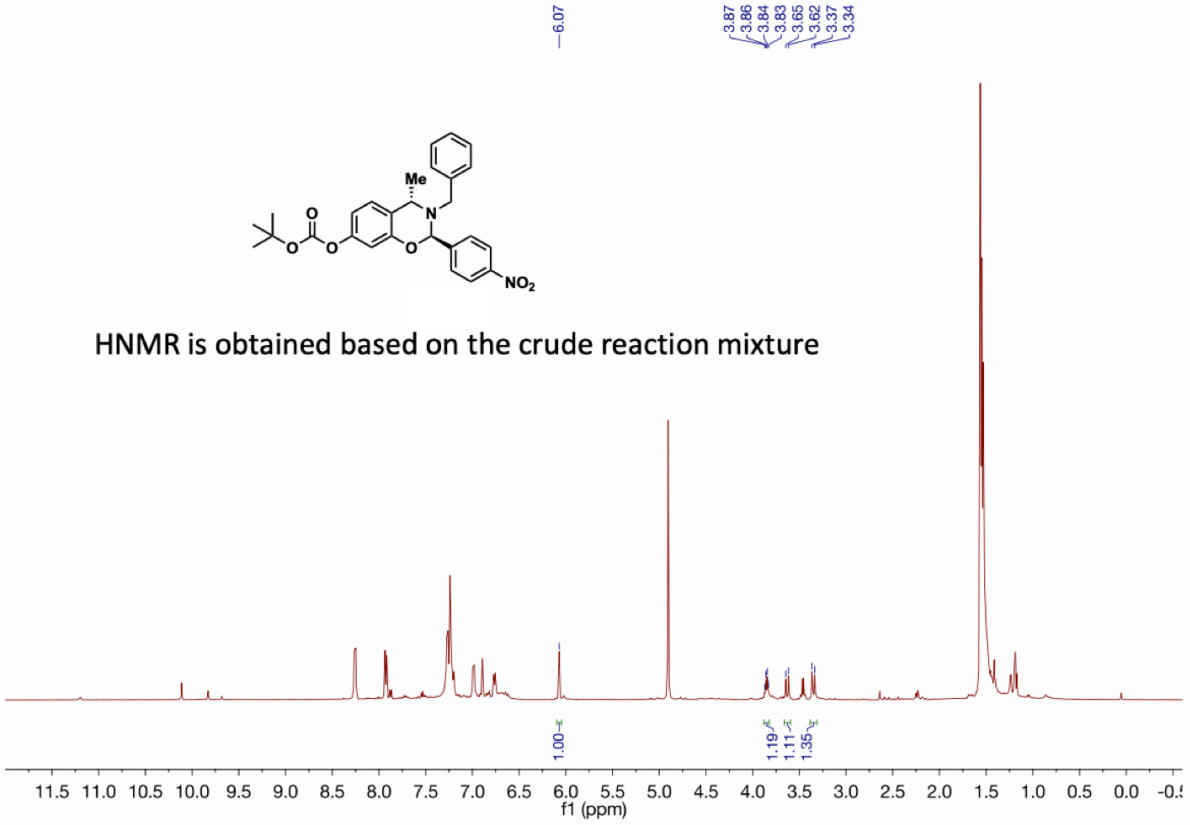

yuk-2-94C-column-27a
7.347
7.335
7.298
7.286
7.195
7.180
7.117
6.906
6.857
6.492
6.487
6.302
5.793
4.792
3.998
3.974
3.405
3.382
1.519
Ph
N
Ph
BocO
O
O
Normalized Intensity
0.25
0.20
0.15
0.10
0.05
0
2.92 2.31 3.18 0.89 1.93 0.97 0.82 1.01 0.96 0.94 0.88 0.96 0.98 1.00 8.99
10 9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)

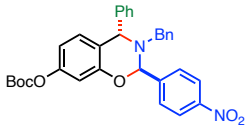

155.014
152.123
151.079
150.279
142.783
139.118
131.103
129.261
129.162
128.602
128.399
128.356
127.596
127.479
117.500
114.060
110.527
110.301
109.179
83.891
82.684
77.484
77.230
76.976
59.711
50.891
27.953
Ph
N
Ph
BocO
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10



49a-Me

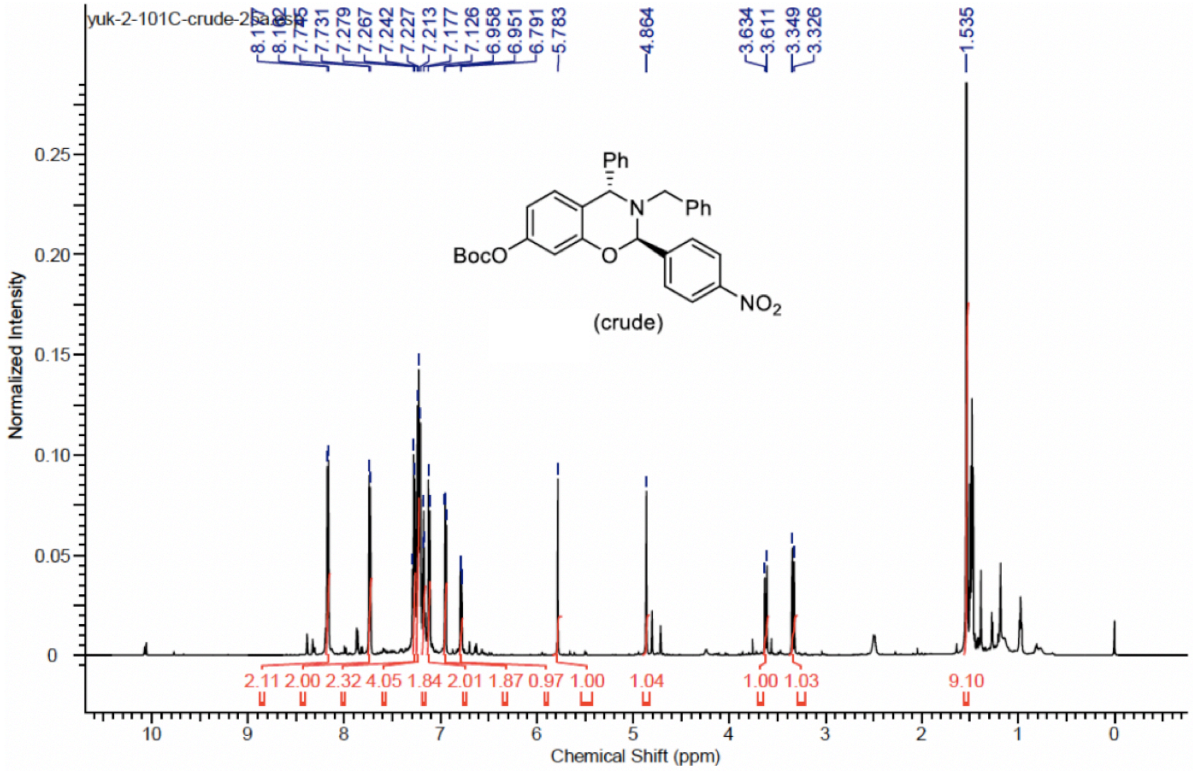
(±)-*trans*-3-benzyl-4-methyl-2-(4-nitrophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl tert-butyl carbonate (49a-Me). Prepared according to the general procedure H. 40% crude NMR yield. $\mathbf{R_f}$ = 0.5 (90% hexane 10% ethyl acetate).

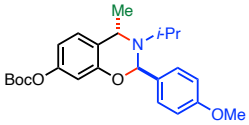




49b-Ph

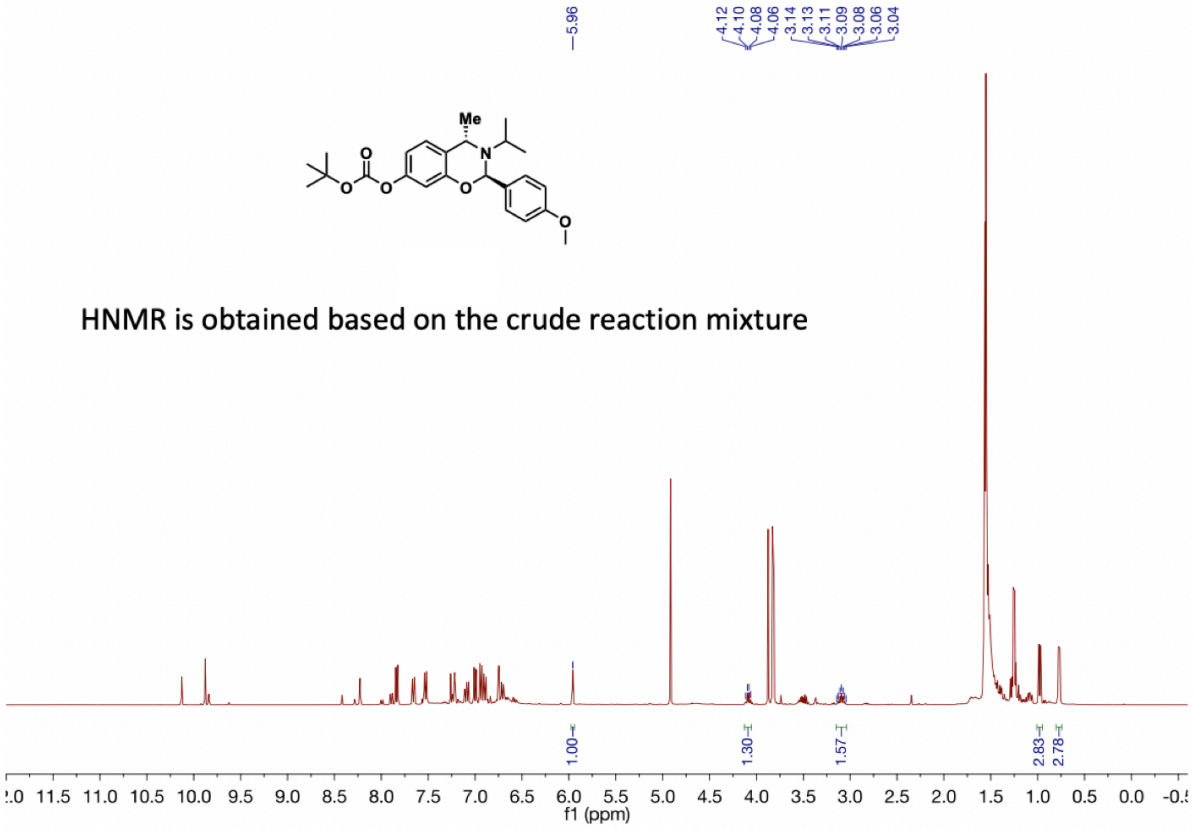
(±)-*trans*-3-benzyl-2-(4-nitrophenyl)-4-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl *tert*-butyl carbonate (49b-Ph). Prepared according to the general procedure H using two equivalents of imines. 61% crude NMR yield. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 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 (90% hexane 10% ethyl acetate).

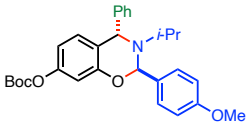




50a-Me

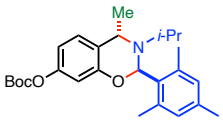
(±)-*tert*-butyl(*trans*-3-isopropyl-2-(4-methoxyphenyl)-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (50a-Me). Prepared according to the general procedure H. 47% crude NMR yield. $\mathbf{R_f}$ = 0.4 (90% hexane 10% ethyl acetate).





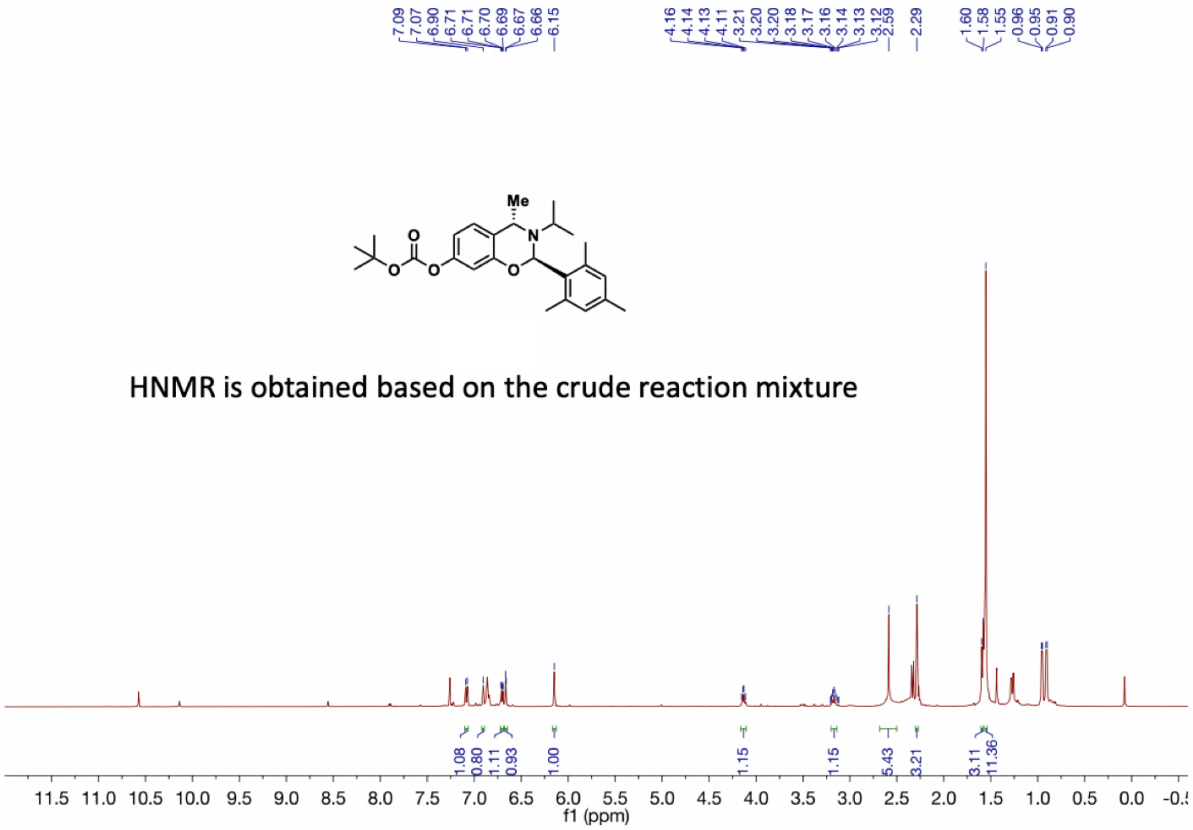
50b-Ph

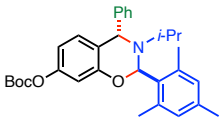
(±)-*tert*-butyl (*trans*-3-isopropyl-2-(4-methoxyphenyl)-4- phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (50b-Ph). Prepared according to the general procedure H. <10% crude NMR yield. $\mathbf{R_f}$ = 0.4 (90% hexane 10% ethyl acetate).



51a-Me

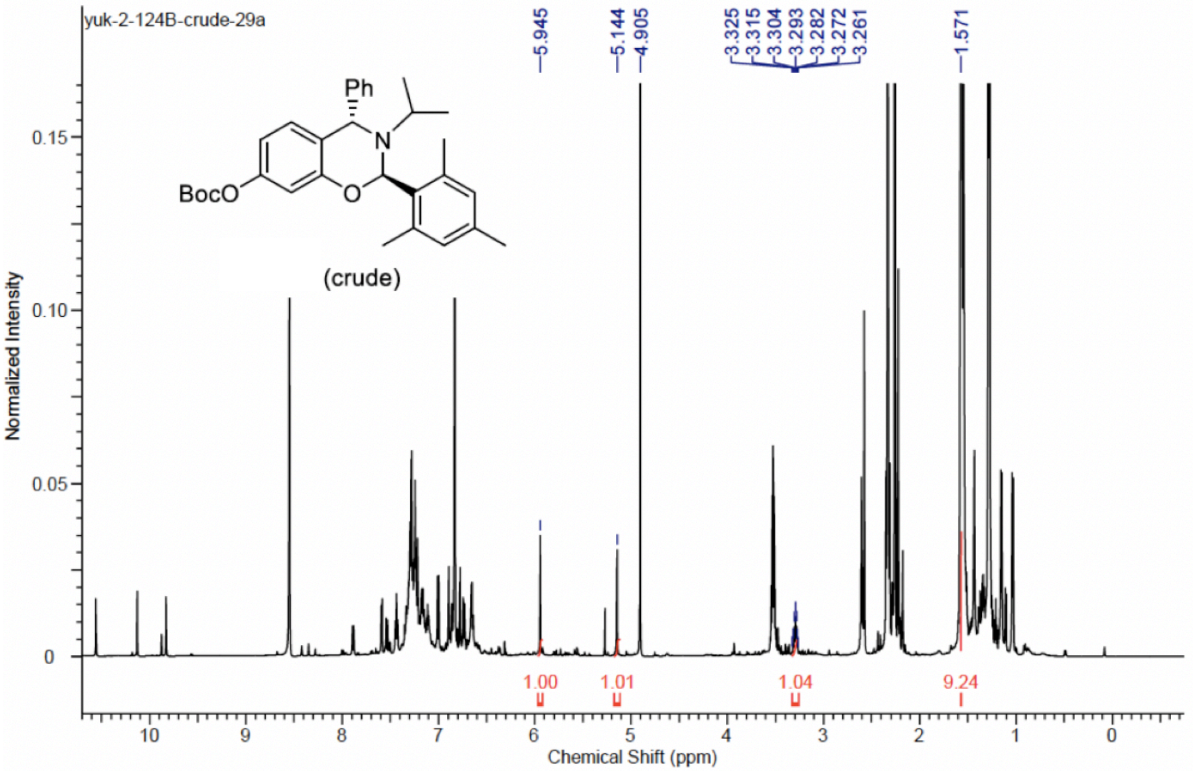
(±)-*tert*-butyl (*trans*-3-isopropyl-2-mesityl-4-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-7-yl) carbonate (51a-Me). Prepared according to the general procedure H. 43% crude NMR yield. $\mathbf{R_f}$ = 0.4 (90% hexane 10% ethyl acetate).

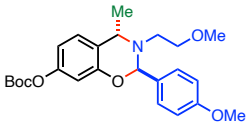




51b-Ph

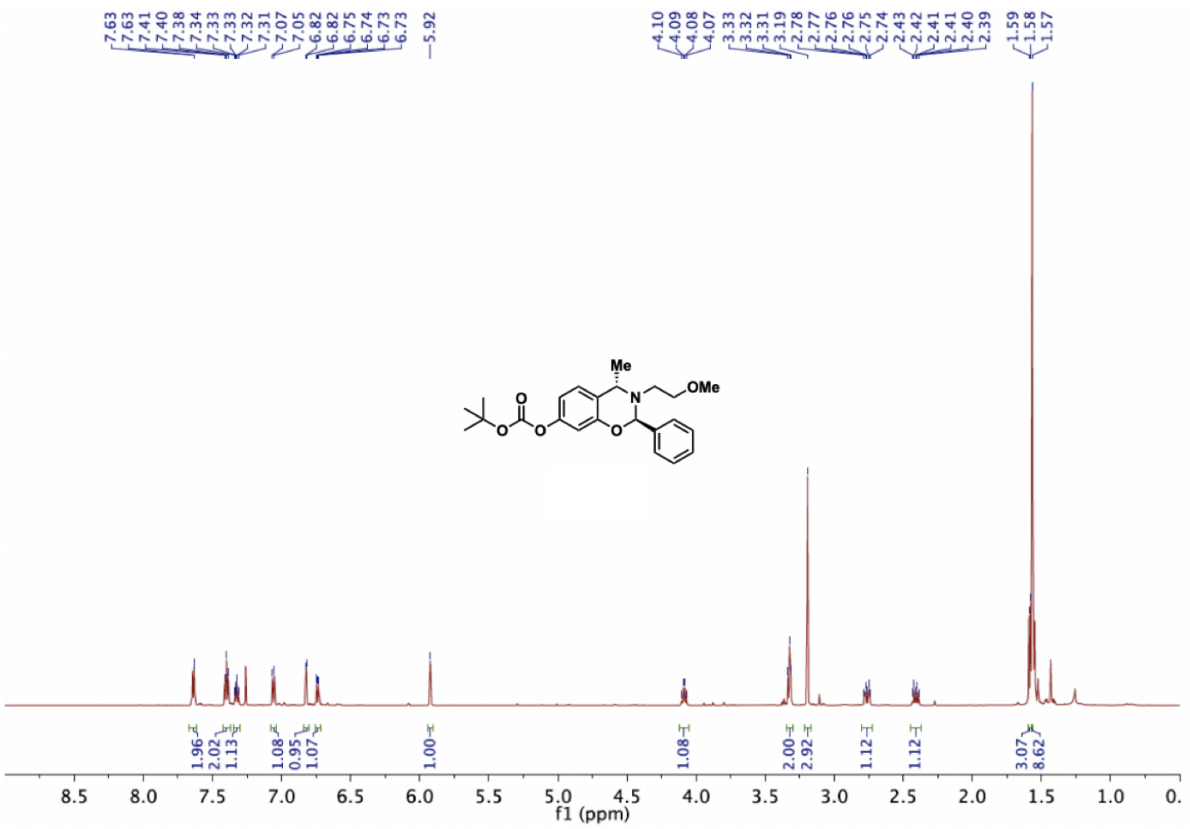
(±)-*tert*-butyl (*trans*-3-isopropyl-2-mesityl-4-phenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (51b-Ph). Prepared according to the general procedure H. 35% crude NMR yield. $\mathbf{R_f}$ = 0.5 (90% hexane 10% ethyl acetate).

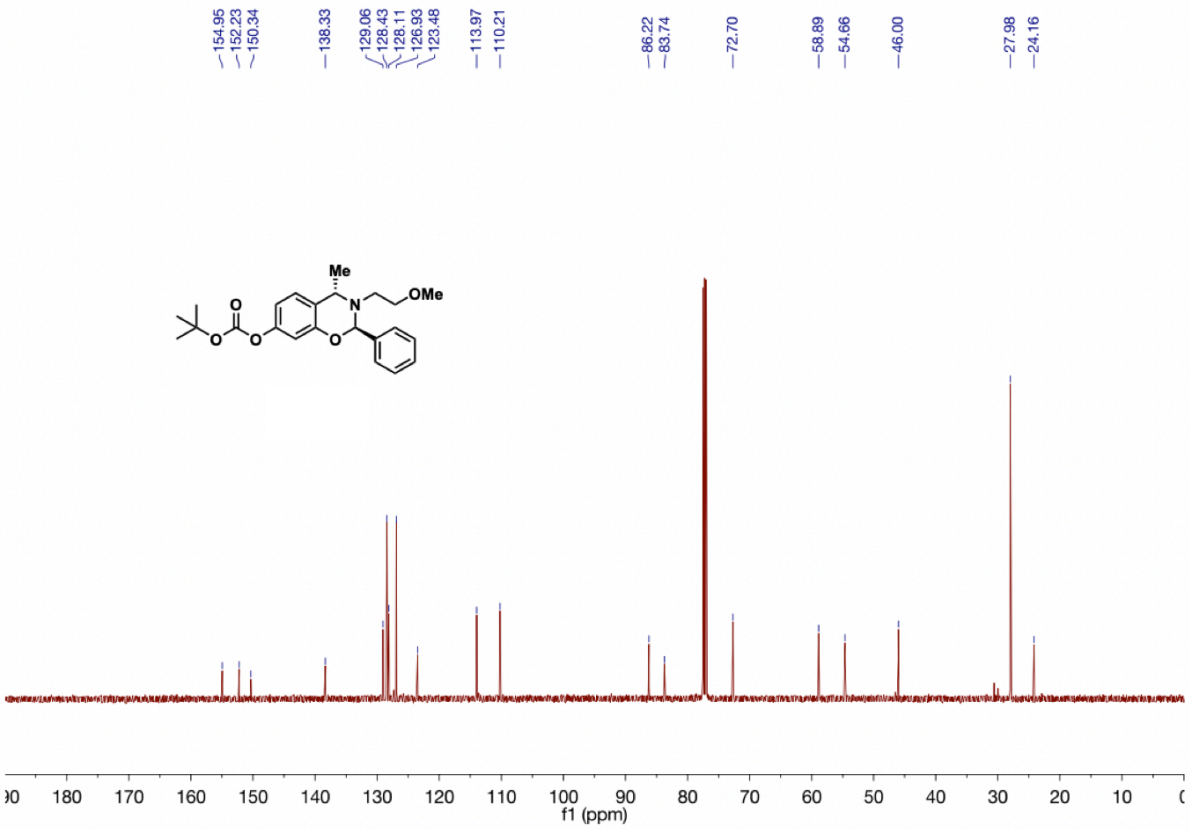


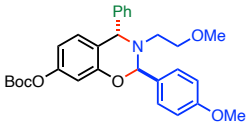


52a-Me

(±)-*tert*-butyl (*trans*-3-(2-methoxyethyl)-4-methyl-2-phenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (52a-Me). Prepared according to the general procedure H using two equivalents of imine. 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. **R_f** = 0.4 (90% hexane 10% ethyl acetate).

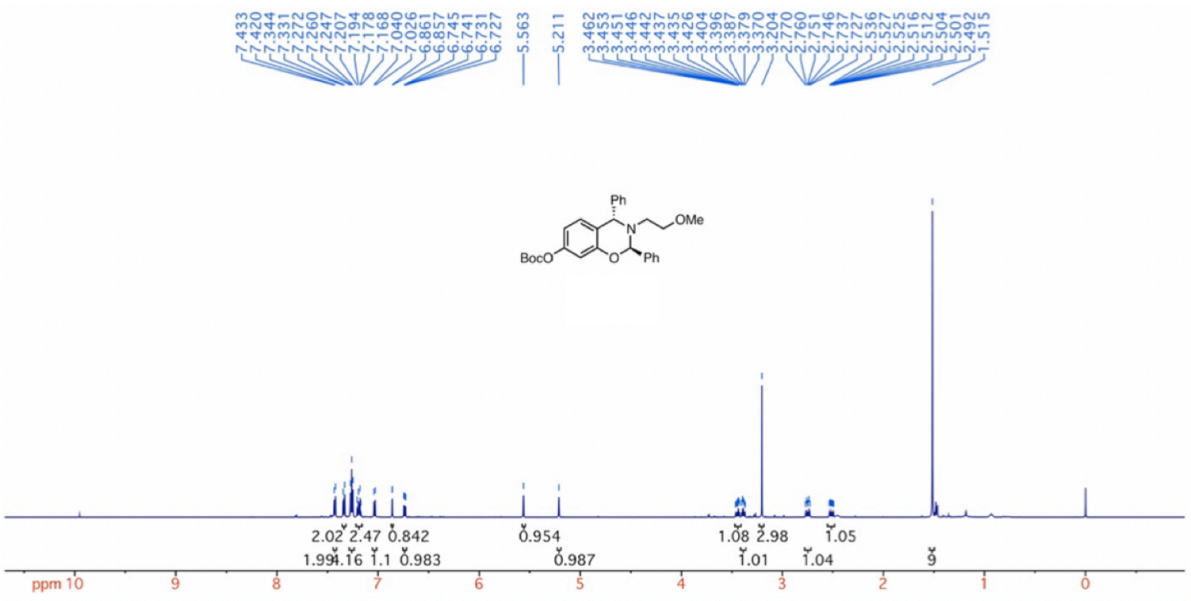

7.63
7.63
7.41
7.40
7.38
7.34
7.33
7.33
7.32
7.31
7.07
7.05
6.82
6.82
6.75
6.74
6.73
6.73
5.92
4.10
4.09
4.08
4.07
3.33
3.32
3.31
3.19
2.78
2.77
2.76
2.76
2.75
2.74
2.43
2.42
2.41
2.41
2.40
2.39
1.59
1.58
1.57
Me
N
OMe
O
O
O
1.96
2.02
1.13
1.08
0.95
1.07
1.00
1.08
2.00
2.92
1.12
1.12
3.07
8.62
8.5
8.0
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)

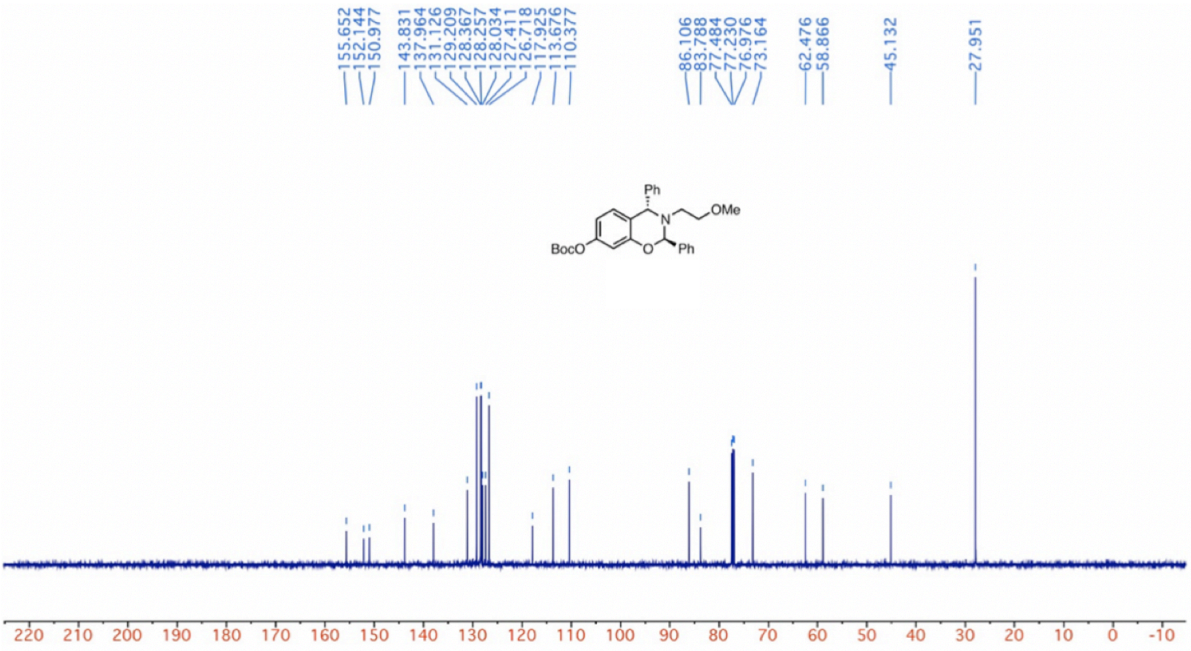

154.95
152.23
150.34
138.33
129.06
128.43
128.11
126.93
123.48
113.97
110.21
86.22
83.74
72.70
58.89
54.66
46.00
27.98
24.16
Me
N
OMe
O
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

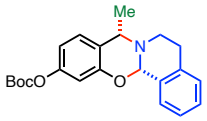


52b-Ph

(±)-*tert*-butyl (*trans*-3-(2-methoxyethyl)-2,4-diphenyl-3,4-dihydro-2H-benzo[*e*][1,3]oxazin-7-yl) carbonate (52b-Ph). Prepared according to the general procedure H using two equivalents of imine. 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 (90% hexane 10% ethyl acetate).


7.433
7.420
7.344
7.331
7.262
7.260
7.247
7.207
7.194
7.178
7.168
7.040
7.026
6.861
6.557
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
2.525
2.516
2.512
2.504
2.501
2.492
1.515
Ph
OMe
N
BocO
O
Ph
2.02 2.47 0.842
0.954
1.08 2.98 1.05
1.99 1.16 1.1 0.983
0.987
1.01 1.04 9
ppm 10 9 8 7 6 5 4 3 2 1 0

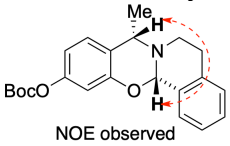

155.652
152.144
150.977
143.831
137.964
131.126
129.209
128.567
128.357
128.034
127.411
126.718
117.925
113.676
110.377
86.106
83.788
77.484
77.230
76.976
73.164
62.476
58.866
45.132
27.951
Ph
OMe
N
BocO
O
Ph
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

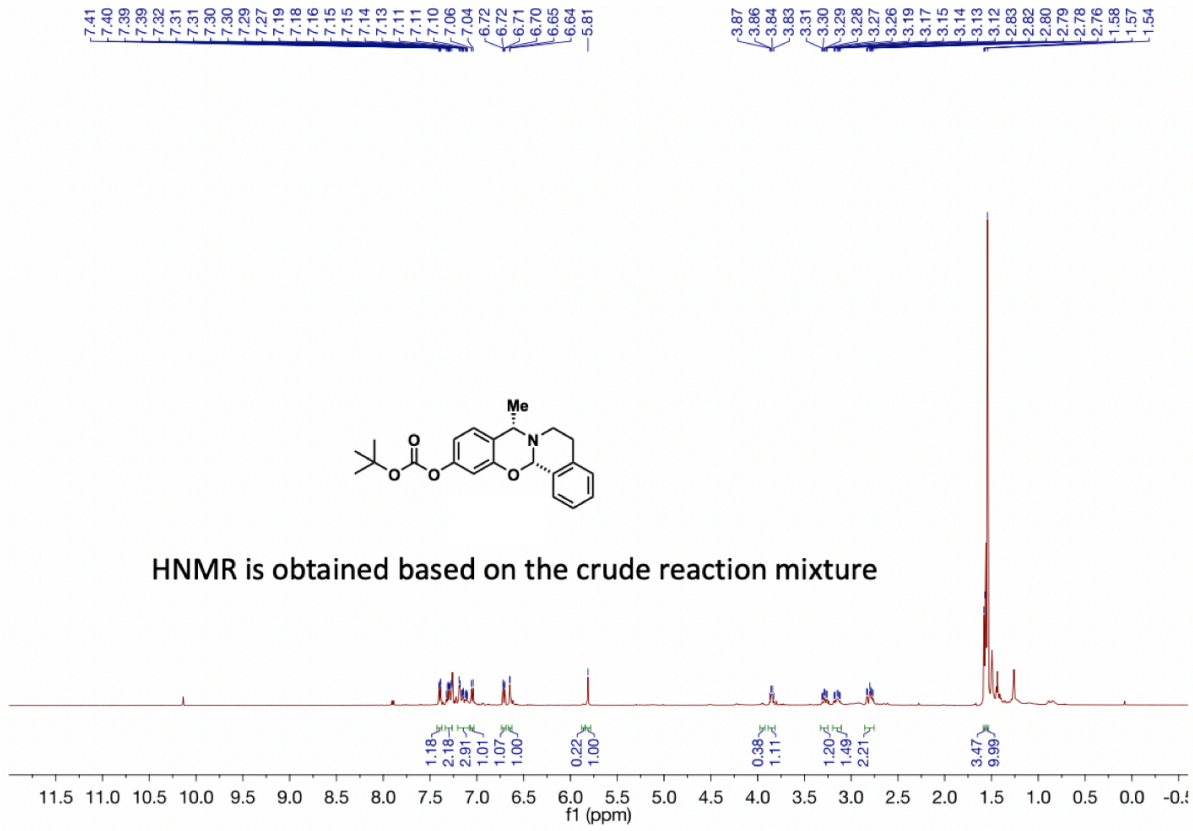


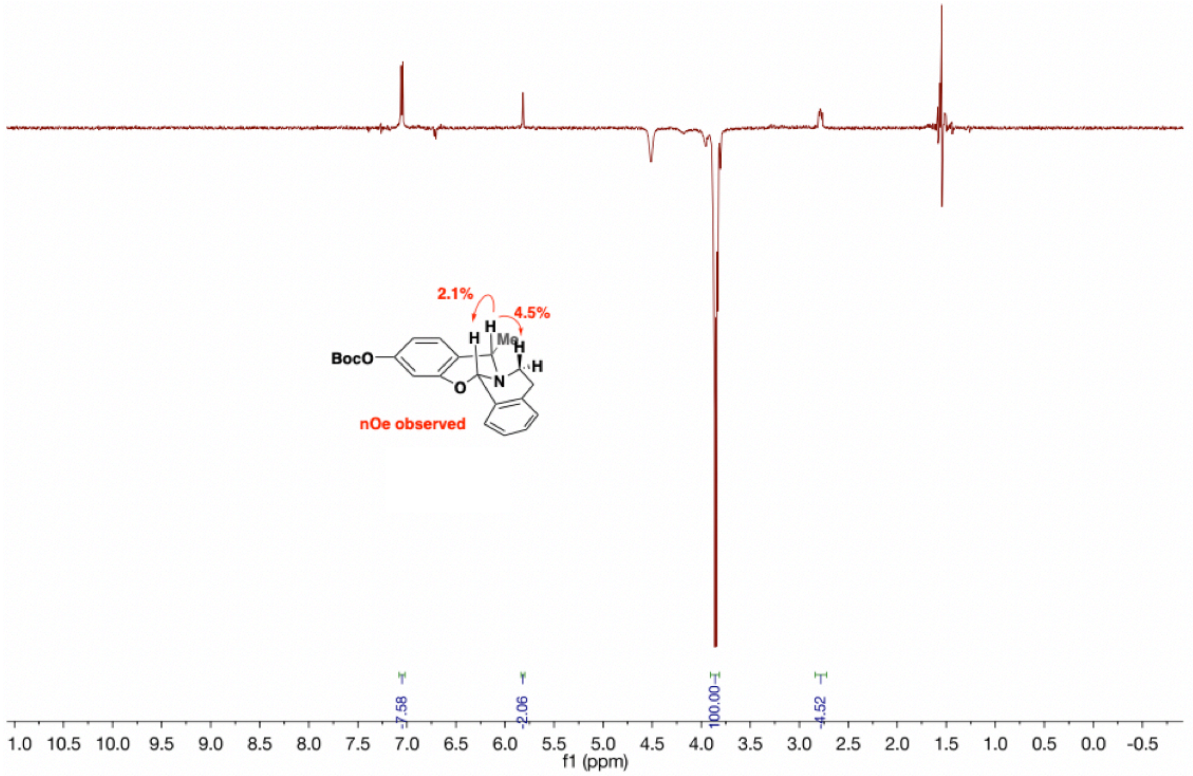
53a-Me

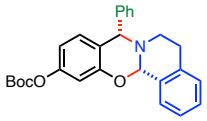
(±)-*tert*-butyl (*cis*-8-methyl-5,13a-dihydro-6H,8H-benzo[5,6][1,3]oxazino[2,3-a]isoquinolin-11-yl) carbonate (53a-Me). Prepared according to the general procedure H. 53% crude NMR yield (*dr* = 5:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.4 Hz, 1H), 7.34-7.27 (m, 2H), 7.21-7.09 (m, 2H), 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). **R_f** = 0.4 (90% hexane 10% ethyl acetate).

Cis-stereochemistry of major product was confirmed by nOe analysis.




Me
HNMR is obtained based on the crude reaction mixture
f1 (ppm)

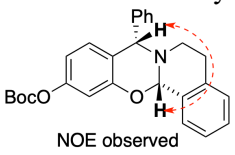

2.1%
4.5%
BocO
nOe observed
f1 (ppm)

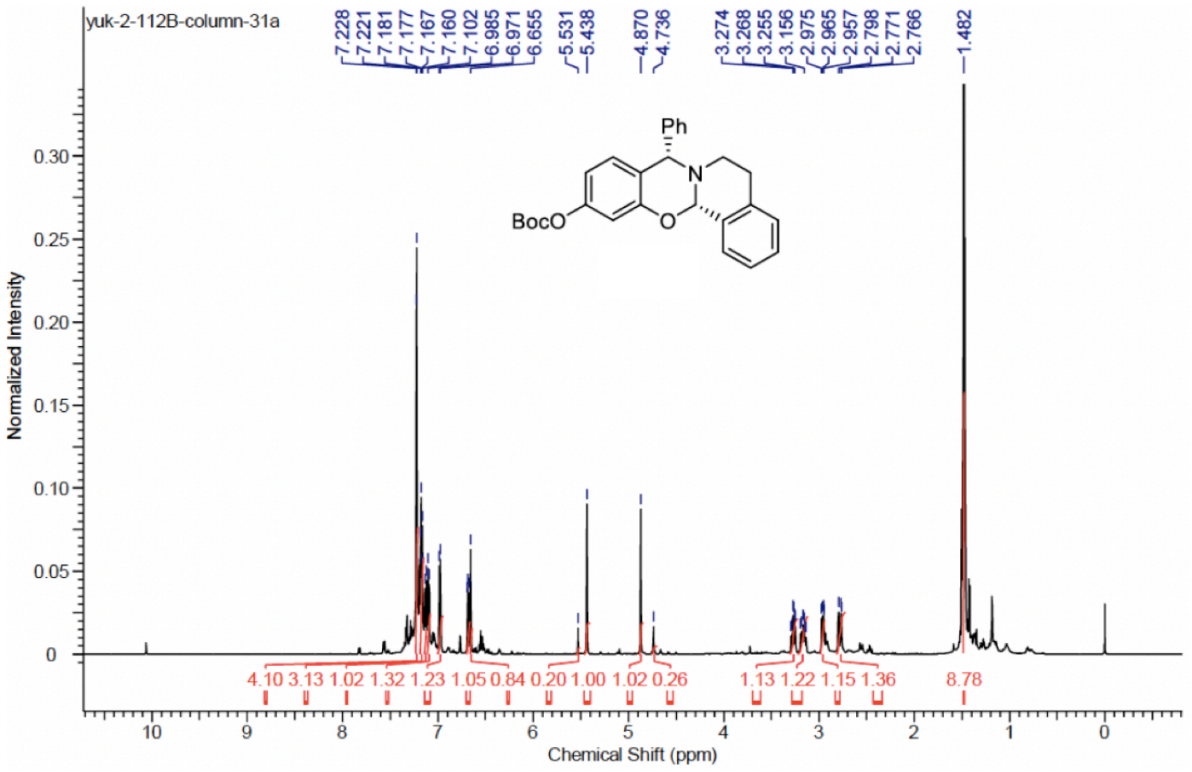


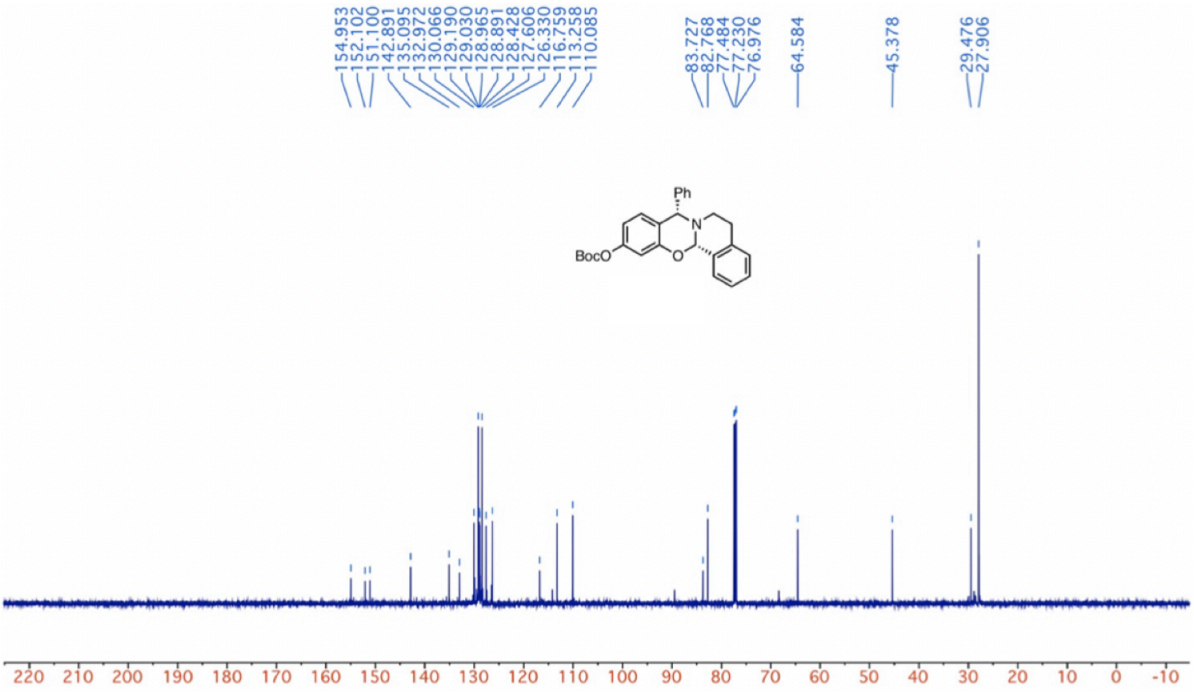
53b-Ph

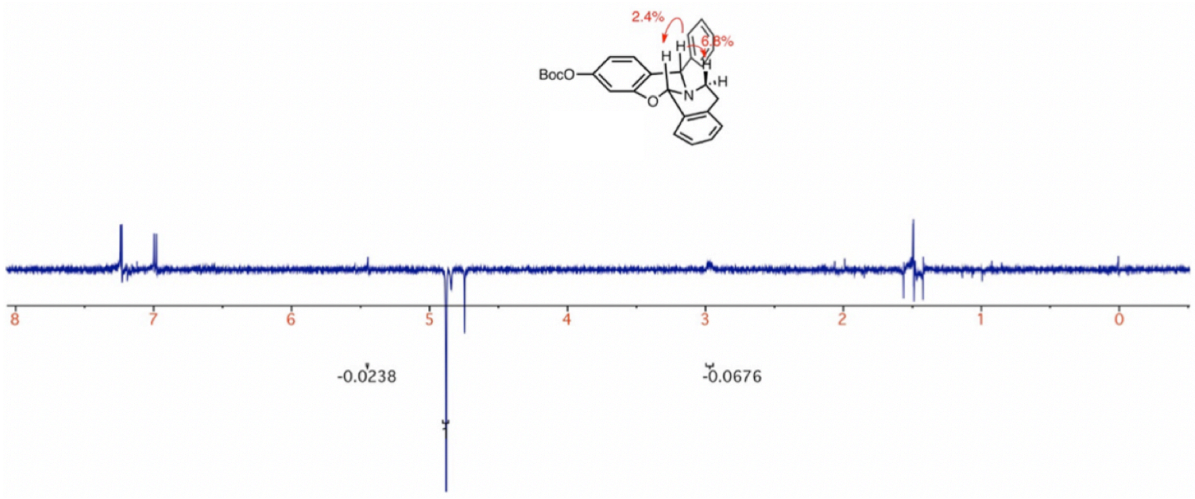
(±)-*tert*-butyl (*cis*-8-phenyl-5,6,8,13a-tetrahydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-11-yl) carbonate (53b-Ph). Prepared according to the general procedure H. 81% crude NMR yield (inseparable diastereomers, *cis*/*trans* = 5:1). The residue was purified by flash column chromatography as a yellow oil (34.89 mg, 81% isolated yield of two isomers). **^{1}H NMR** (500 MHz, $CDCl_3$): δ7.22 (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 $C_{27}H_{27}NO_4$ $[M]^+$: 430.2018; found ??. **R_f** = 0.4 (90% hexane 10% ethyl acetate).

Cis-stereochemistry of major product was confirmed by nOe analysis.

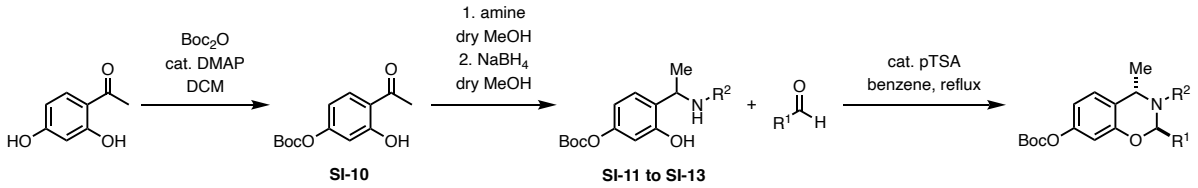



yuk-2-112B-column-31a
7.228
7.221
7.181
7.177
7.167
7.160
7.102
6.985
6.971
6.655
5.531
5.438
4.870
4.736
3.274
3.268
3.255
3.156
2.975
2.965
2.957
2.798
2.771
2.766
1.482
Ph
N
O
BocO
Normalized Intensity
0.30
0.25
0.20
0.15
0.10
0.05
0
4.10 3.13 1.02 1.32 1.23 1.05 0.84 0.20 1.00 1.02 0.26
1.13 1.22 1.15 1.36
8.78
10
9
8
7
6
5
4
3
2
1
0
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
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


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

4.8 Thermodynamic Method of Synthesizing 3,4-Dihydro-2H-1,3-benzoxazines

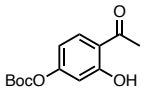


4.8.1 General Procedure I

Amine (8 mmol, 2.0 equiv) was added to a stirred solution of **SI-1** (4 mmol, 1.0 equiv) in dry MeOH (10 mL) at room temperature and stirred at the same temperature overnight. Yellow solids formed were collected by filtration and rinsed with cold MeOH. Crude product, imine, was dried under reduced pressure and directly used for the next step without purification. $NaBH_4$ (1 mmol, 1.0 equiv) was added to a stirred solution of imine (4 mmol, 1.0 equivalence) in dry MeOH (10 mL) at 0^o C. The reaction mixture was allowed to slowly warm to room temperature, then quenched with deionized water (10 mL) and extracted with DCM (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 **SI-2** to **SI-4**.

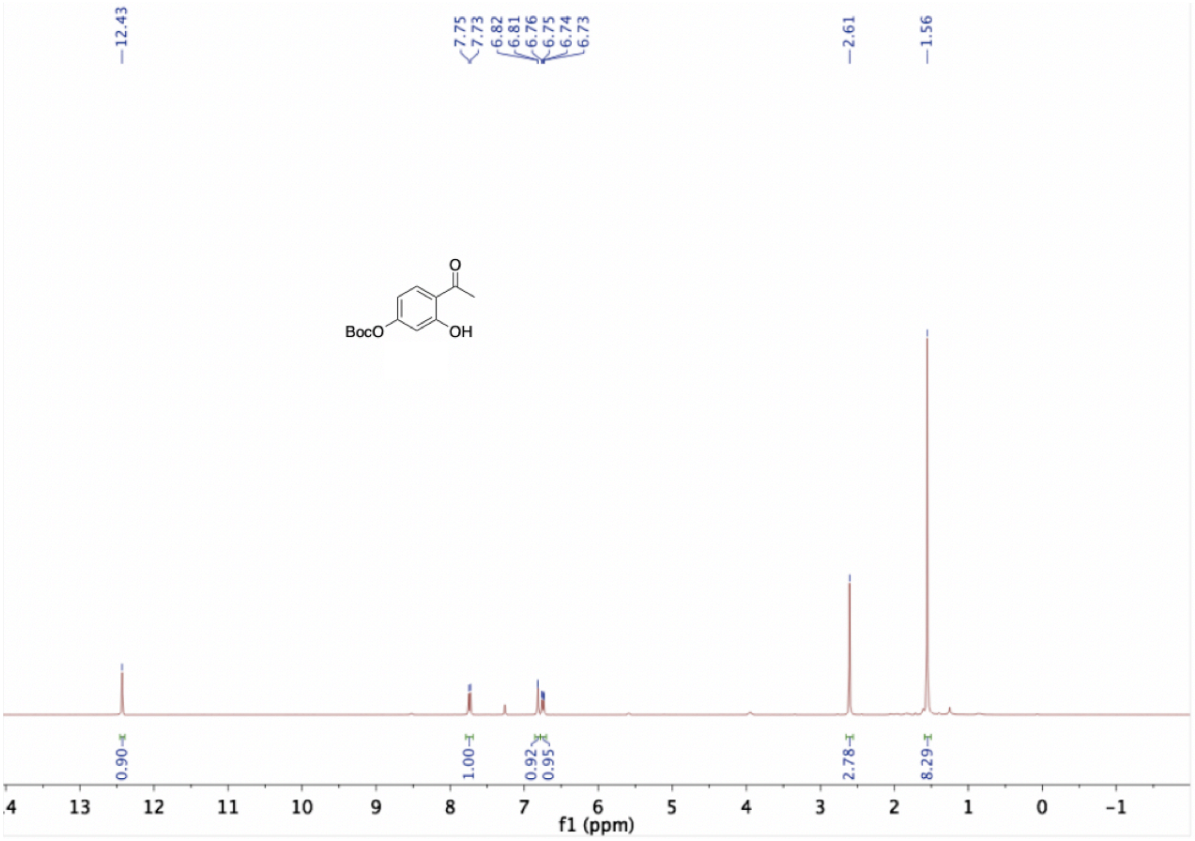
In a sealed-tube, aldehyde (0.2 mmol, 2.0 equiv) was added to a stirred solution of benzylic amine (**SI-2** to **SI-4**, 0.1 mmol, 1.0 equiv) in benzene (1 mL) at room temperature. Then pTSA (15 mol%) was added to the mixture. The reaction mixture was refluxed overnight and allowed to cool to room temperature 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

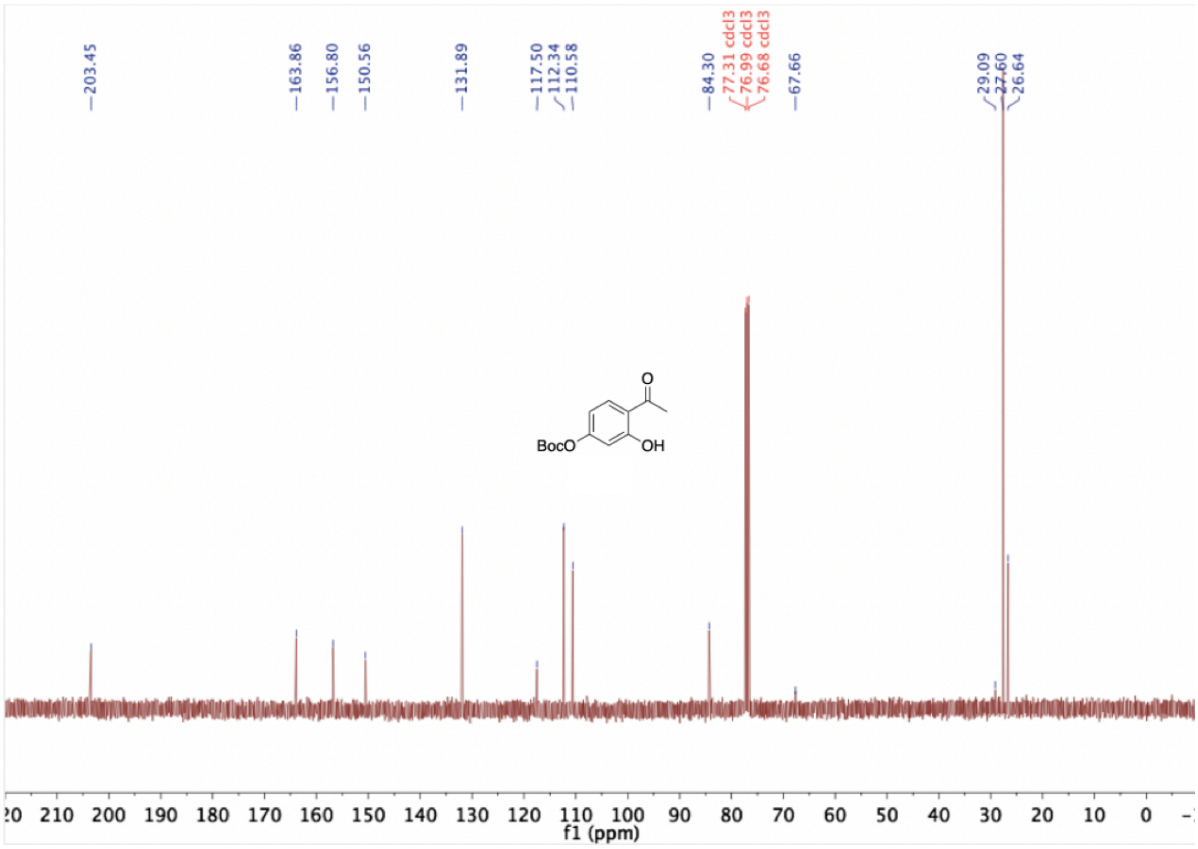
dibromomethane (3.5 μL for adducts) as internal standard for crude product. No purification was needed since these are known compounds by general procedure H.

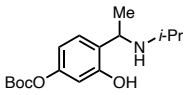


SI-10

4-Acetyl-3-hydroxyphenyl tert-butyl carbonate (SI-1) To a suspension of 2,4-dihydroxyacetophenone (10 mmol, 1.0 equiv) in DCM (20 mL) was added Boc_2O (15 mmol, 1.5 equiv) and DMAP (1 mmol, 10 mol%) at room temperature. The suspended solids eventually went into solution over an 18 h period and the resulting mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (90% hexane 10% ethyl acetate) to give ketone SI-1 (2.5 g, 78%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.43 (s, OH), 7.74 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 2.3 Hz, 1H), 6.75 (dd, J = 8.7, 2.3 Hz, 1H), 2.62 (s, 3H), 1.56 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.45, 163.86, 156.80, 150.56, 131.89, 117.50, 112.34, 110.58, 84.30, 67.66, 29.09, 27.60, 26.64. **HRMS (ESI)** m/z calculated for $C_{13}H_{16}O_5$ $[M+Na+MeOH]^+$: 307.1158; found 307.1158. **R_f** = 0.4 (90% hexane 10% ethyl acetate).

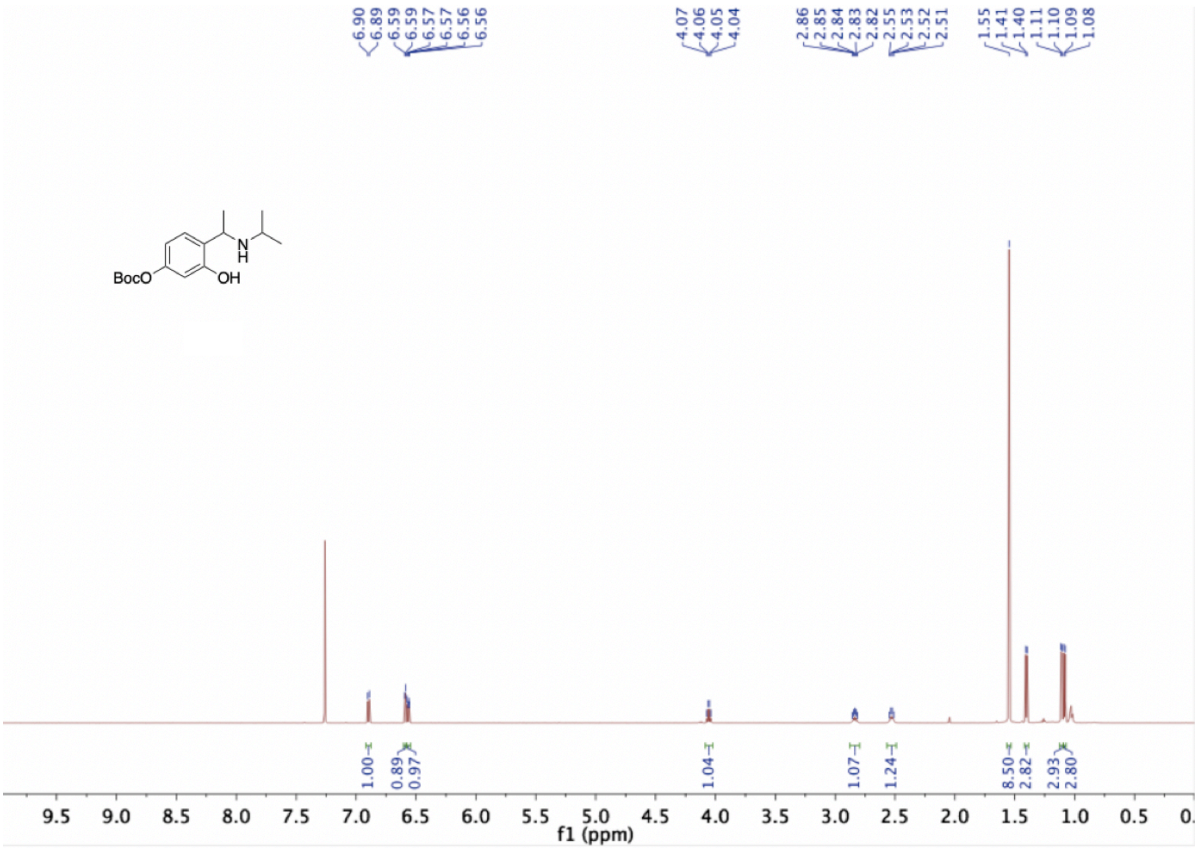

12.43
7.75
7.73
6.82
6.81
6.76
6.75
6.74
6.73
2.61
1.56
O
BocO
OH
0.90
1.00
0.92
0.95
2.78
8.29
f1 (ppm)

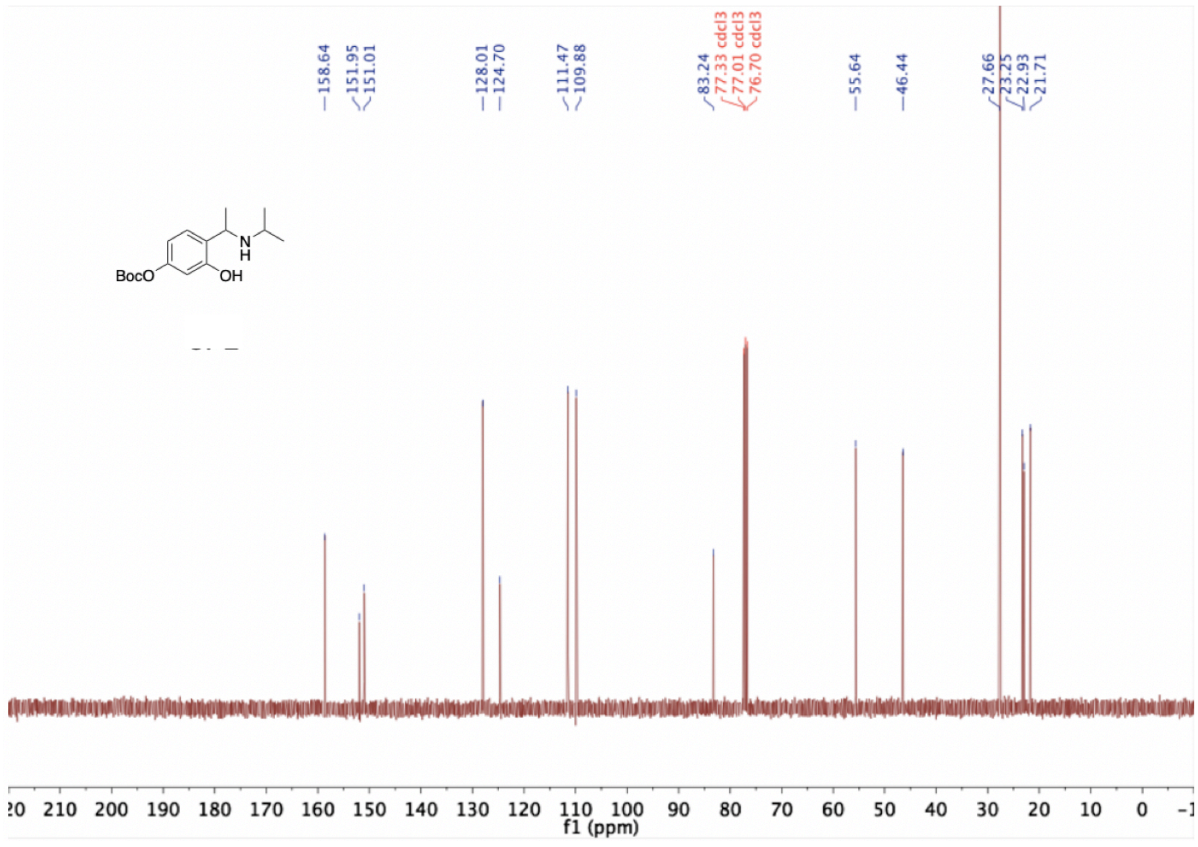

203.45
163.86
156.80
150.56
131.89
117.50
112.34
110.58
84.30
77.31 cdcl3
76.99 cdcl3
76.68 cdcl3
67.66
29.09
27.60
26.64
O
BocO
OH
f1 (ppm)

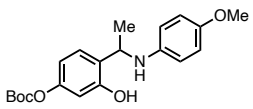


SI-11

***Tert*-butyl (3-hydroxy-4-(1-(isopropylamino)ethyl)phenyl) carbonate (SI-2)** was synthesized according to general procedure I 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 (75% hexane 25% ethyl acetate).

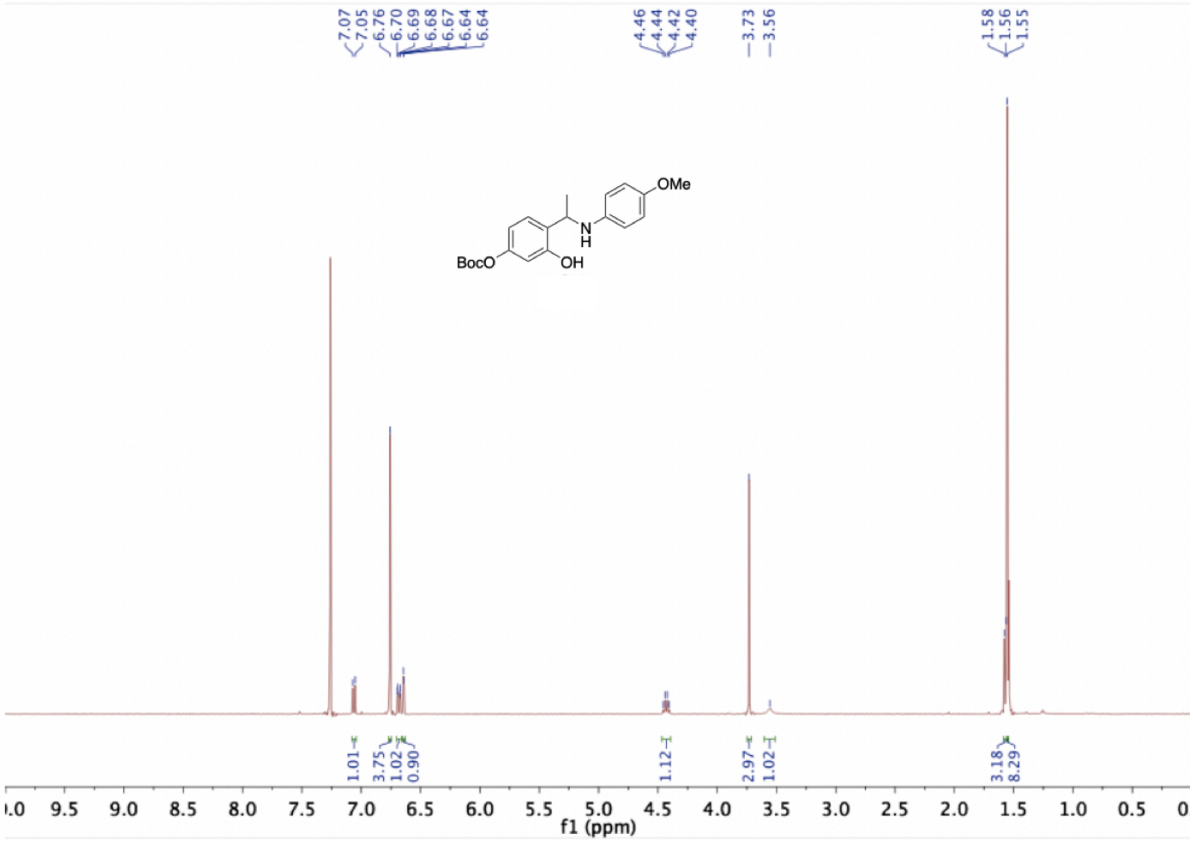

6.90
6.89
6.59
6.59
6.57
6.57
6.56
6.56
4.07
4.06
4.05
4.04
2.86
2.85
2.84
2.83
2.82
2.55
2.53
2.52
2.51
1.55
1.41
1.40
1.11
1.10
1.09
1.08
BocO
OH
N
H
1.00
0.89
0.97
1.04
1.07
1.24
8.50
2.82
2.93
2.80
f1 (ppm)

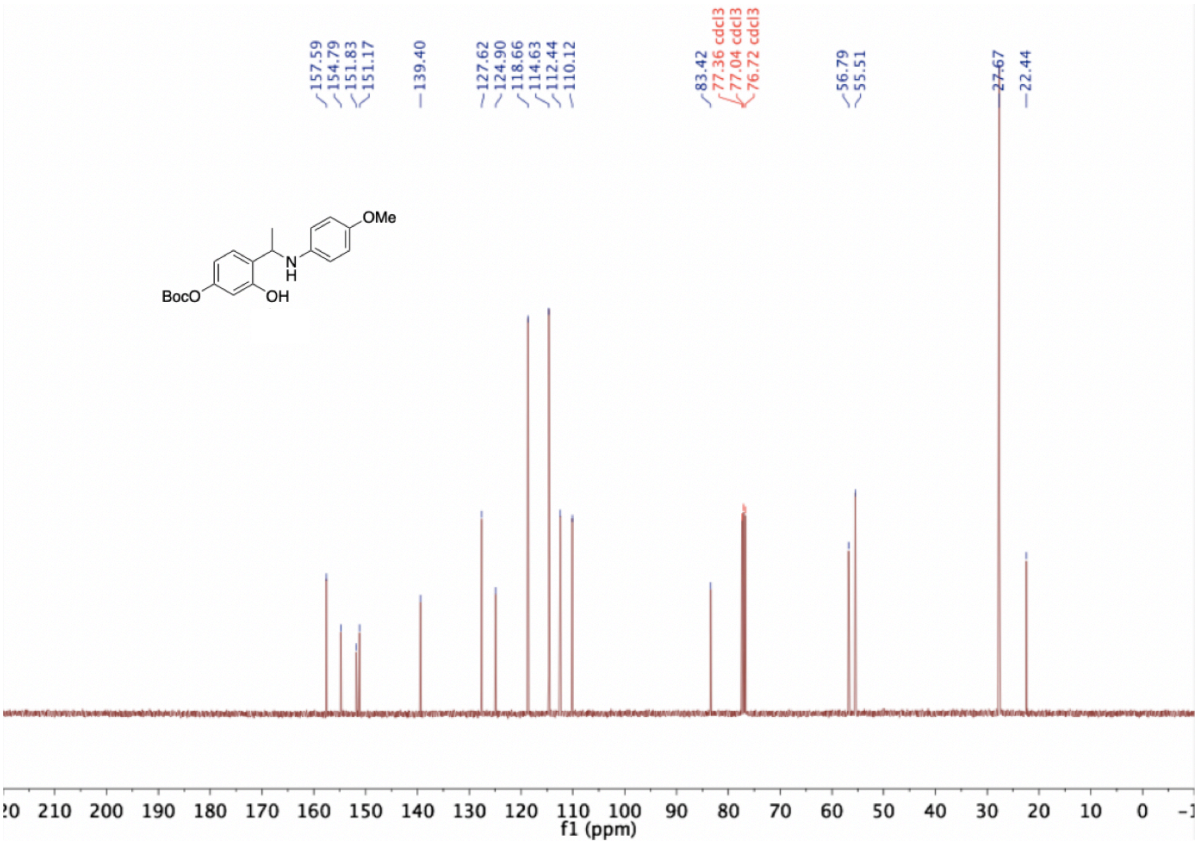

158.64
151.95
151.01
128.01
124.70
111.47
109.88
83.24
77.33 cdcl3
77.01 cdcl3
76.70 cdcl3
55.64
46.44
27.66
23.25
22.93
21.71
BocO
OH
N
H
f1 (ppm)



SI-12

***Tert*-butyl (3-hydroxy-4-(1-((4-methoxyphenyl)amino)ethyl)phenyl) carbonate (SI-3)** was synthesized according to general procedure I 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. $\mathbf{R_f}$ = 0.30 (75% hexane 25% ethyl acetate).


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
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
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56.79
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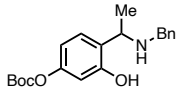
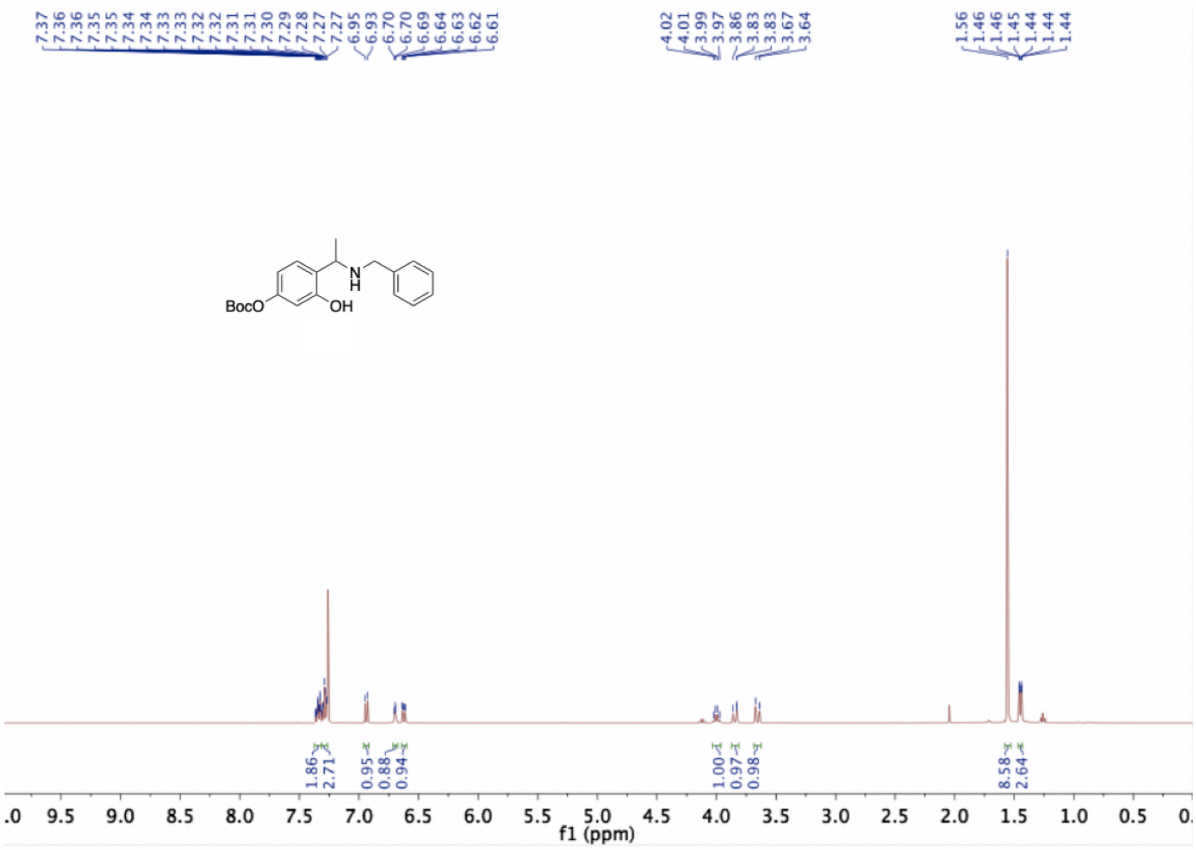
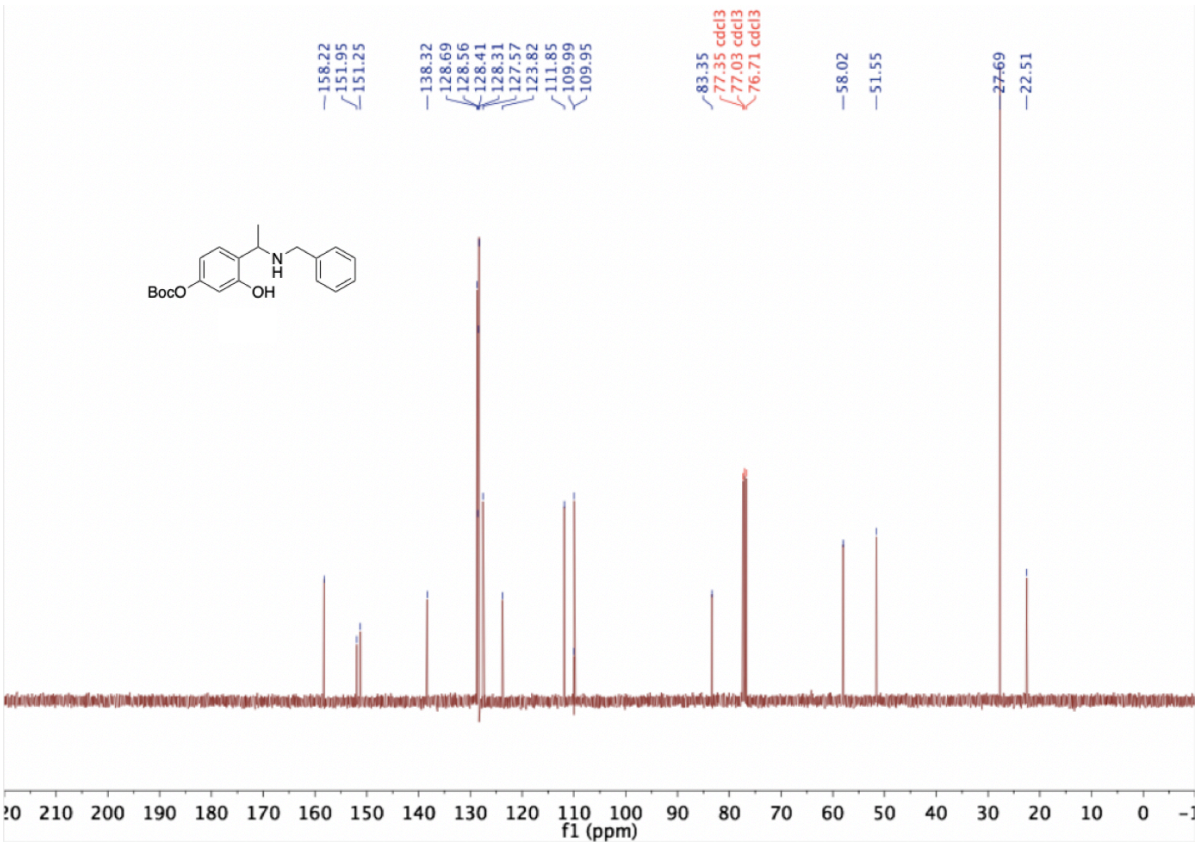
27.67
22.44
OMe
N
H
BocO
OH
f1 (ppm)



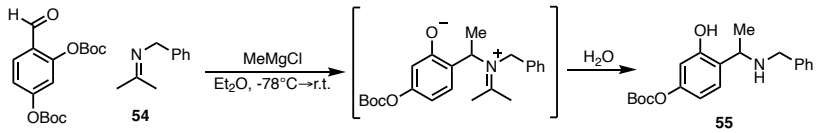
SI-13

4-(1-(benzylamino)ethyl)-3-hydroxyphenyl *tert*-butyl carbonate (SI-4) was synthesized according to general procedure I 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. $\mathbf{R_f}$ = 0.30 (75% hexane 25% ethyl acetate).

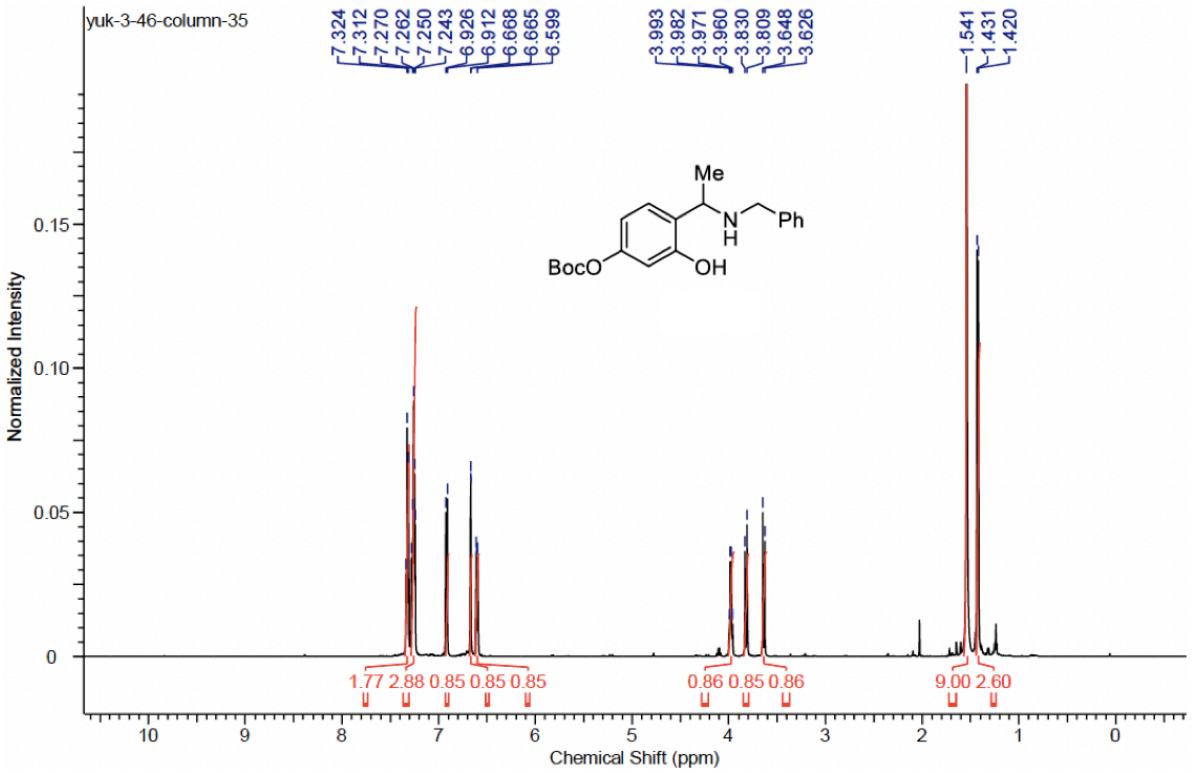

7.37 7.36 7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.30 7.29 7.28 7.27 7.27 6.95 6.93 6.70 6.70 6.69 6.64 6.63 6.62 6.61
4.02 4.01 3.99 3.97 3.86 3.83 3.83 3.67 3.64
1.56 1.46 1.46 1.45 1.44 1.44 1.44
BocO
OH
N
H
1.86 2.71 0.95 0.88 0.94 1.00 0.97 0.98 8.58 2.64
f1 (ppm)


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
f1 (ppm)

4.9 Trisubstituted Imine Studies



(±)-4-(1-(benzylamino)ethyl)-3-hydroxyphenyl *tert*-butyl carbonate (55). Imine **54** (0.1 mL, 0.1 mmol, 1.0 M in toluene, 1 equiv.) was added to a stirred solution of bis-(2,4-tert-butoxycarbonyloxy)-benzaldehyde (0.1 mL, 0.1 mmol, 1.0 M in toluene, 1 equiv.) in Et_2O (1 mL) at room temperature. MeMgCl (3.0 M solution in THF, 0.03 mL, 1.0 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 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 **55** 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. $\mathbf{R_f}$ = 0.4 (75% hexane 25% ethyl acetate).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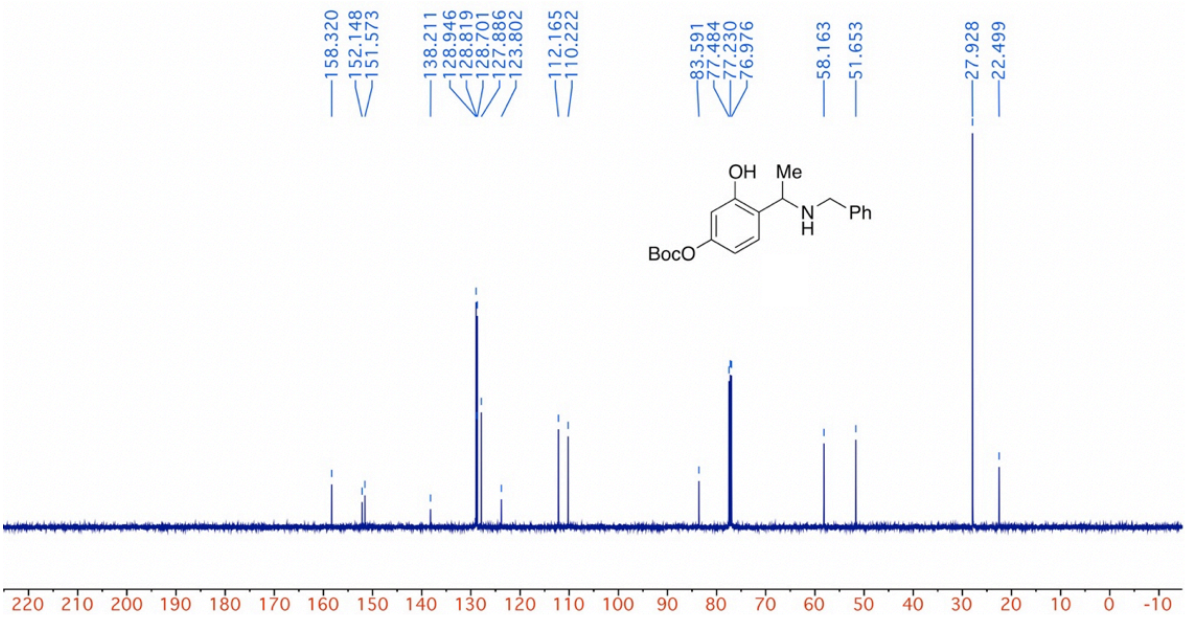
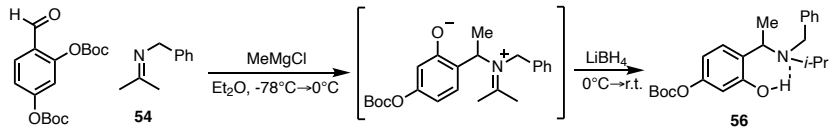
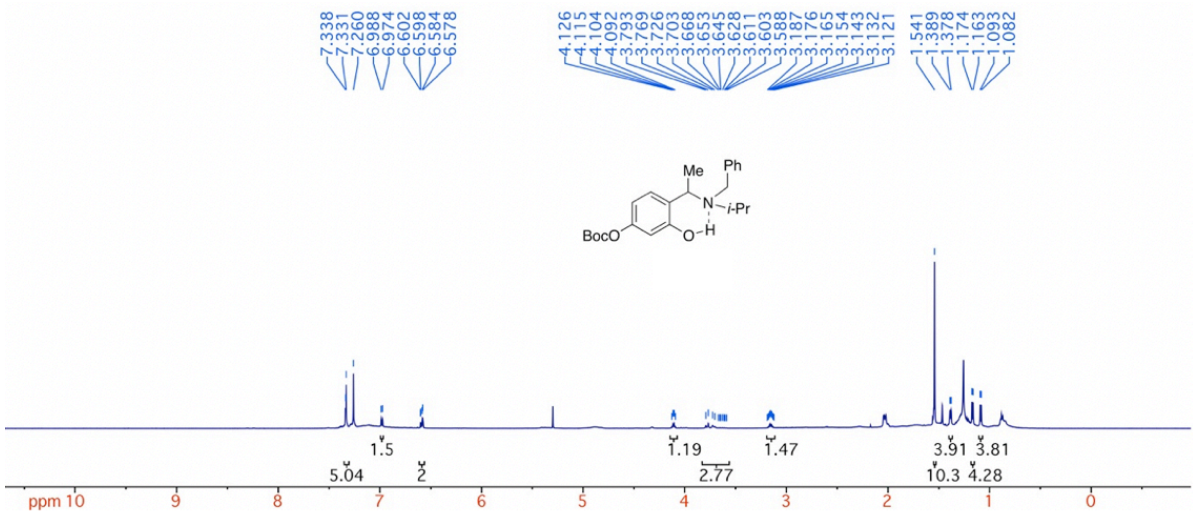
7.324
7.312
7.270
7.262
7.250
7.243
6.926
6.912
6.668
6.665
6.599
3.993
3.982
3.971
3.960
3.830
3.809
3.648
3.626
1.541
1.431
1.420
Me
N
H
Ph
BocO
OH
Normalized Intensity
0.15
0.10
0.05
0
1.77 2.88 0.85 0.85 0.85
0.86 0.85 0.86
9.00 2.60
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


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
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



(±)-4-(1-(benzyl(isopropyl)amino)ethyl)-3-hydroxyphenyl *tert*-butyl carbonate (56). Imine **54** (0.1 mL, 0.1 mmol, 1.0 M in toluene, 1 equiv.) was added to a stirred solution of bis-(2,4-tert-butoxycarbonyloxy)-benzaldehyde (0.1 mL, 0.1 mmol, 1.0 M in toluene, 1 equiv.) in Et_2O (1 mL) at room temperature. MeMgCl (3.0 M solution in THF, 0.03 mL, 1.0 equiv.) was added to the mixture at -78 ºC. The reaction mixture was allowed to warm to 0 ºC over four hours. $LiBH_4$ (2.0 M solution in THF, 0.1 mL, 2.0 equiv.) 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 **56** as yellow oil (23.01 mg, 46% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) major diastereomer: 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, $CDCl_3$) major diastereomer: 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).


7.338
7.331
7.260
6.988
6.974
6.602
6.598
6.584
6.578
4.126
4.115
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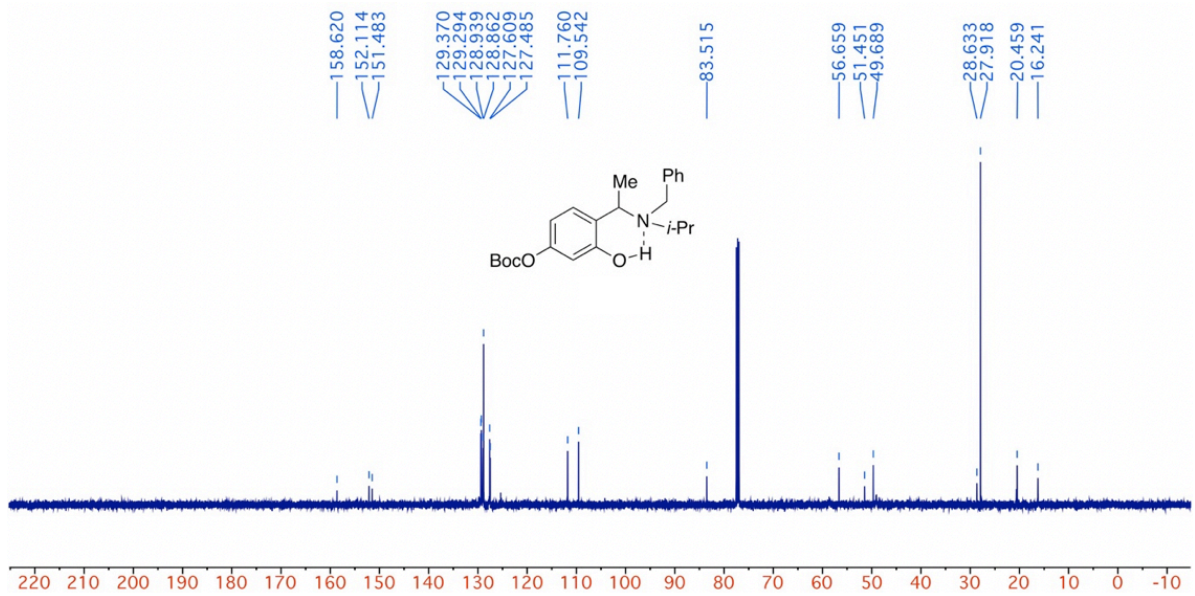
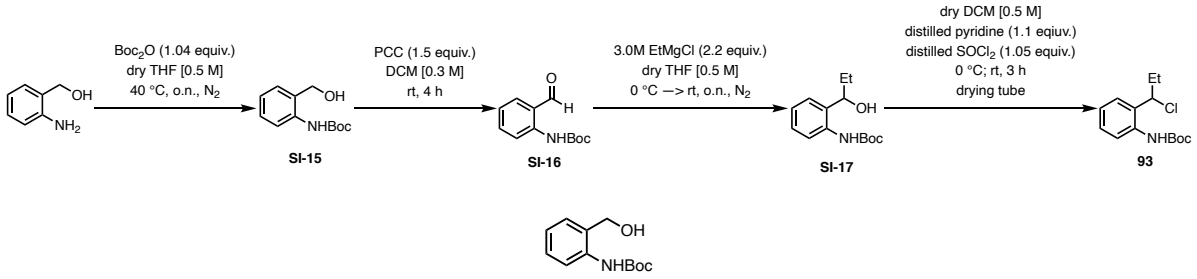
3.793
3.769
3.726
3.703
3.668
3.653
3.645
3.628
3.611
3.603
3.588
3.187
3.176
3.165
3.154
3.143
3.132
3.121
1.541
1.389
1.378
1.174
1.163
1.093
1.082
Me
Ph
N
i-Pr
H
BocO
O
1.5
5.04
2
1.19
2.77
1.47
3.91
3.81
10.3
4.28
ppm 10
9
8
7
6
5
4
3
2
1
0

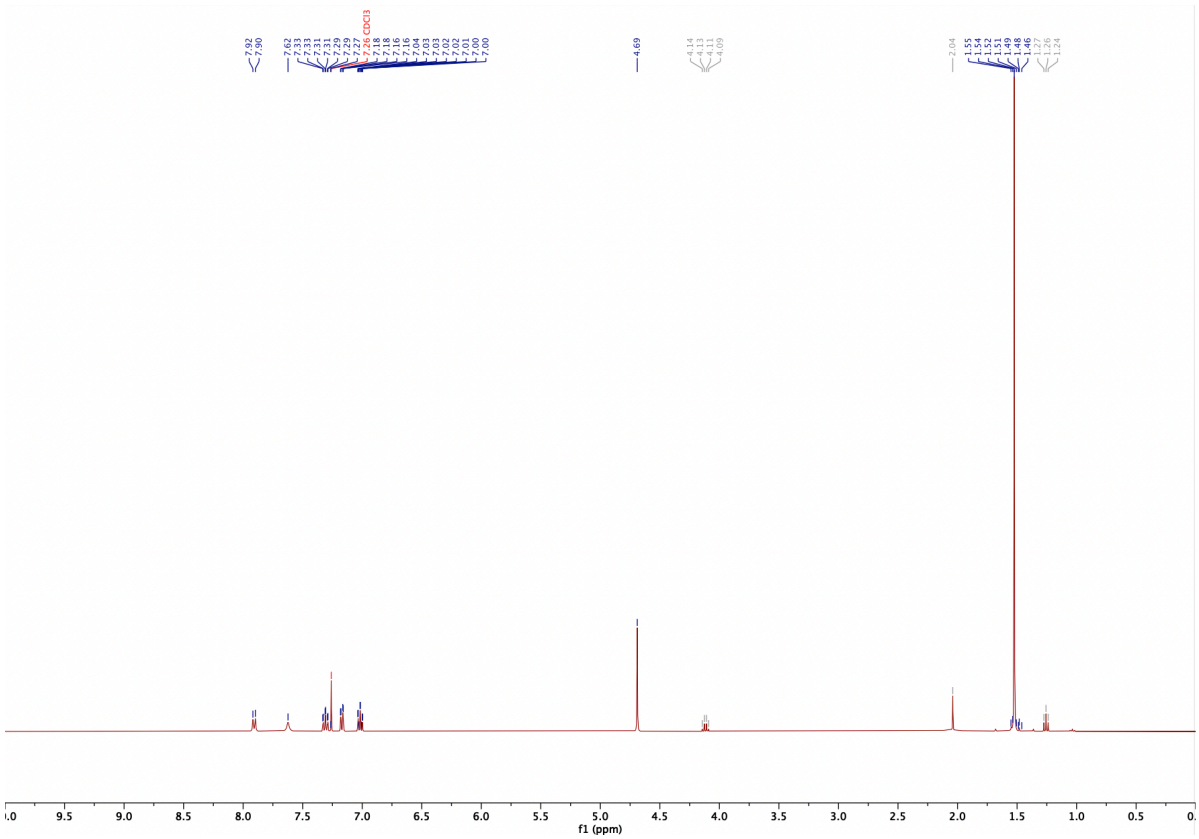

158.620
152.114
151.483
129.370
129.294
128.939
128.862
127.609
127.485
111.760
109.542
83.515
56.659
51.451
49.689
28.633
27.918
20.459
16.241
Me
Ph
N
i-Pr
H
BocO
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

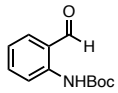
4.8 Preliminary Results of Base-Promoted Aza-*ortho*-Quinone Methide Method



SI-15

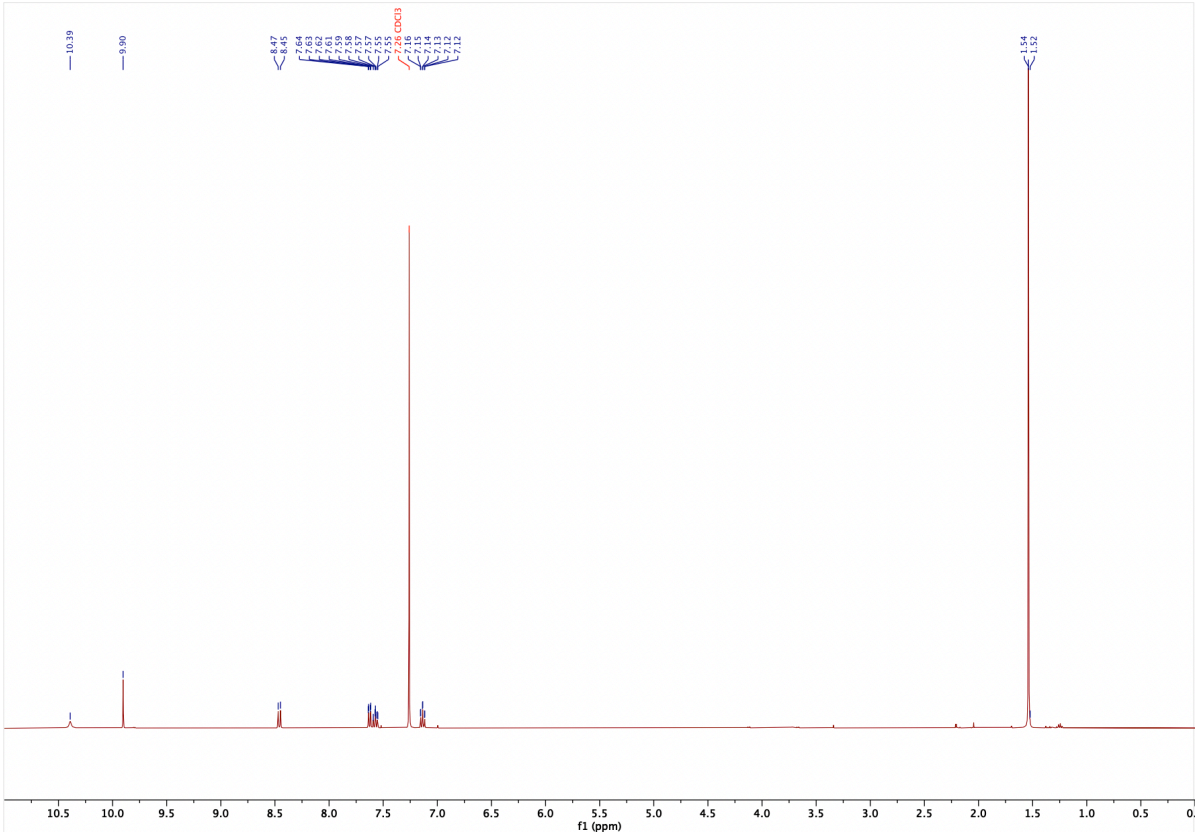
To a 100 mL round-bottom flask, charged with 2-amino benzylic alcohol (1.9 g, 15.4 mmol) in THF (31 mL, 0.5 M) was added di-*tert*-butyl dicarbonate (3.5 g, 1.04 equivalent). The reaction was stirred at 40 °C under nitrogen atmosphere overnight. The completion of reaction is analyzed by TLC. The reaction mixture was quenched with 0.1 M HCl (40 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (ethyl acetate–hexane, 1:3) to afford the corresponding **SI-15** (3.3 g, 97% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.31 (td, J = 7.8, 1.7 Hz, 1H), 7.17 (dd, J = 7.5, 1.6 Hz, 1H), 7.02 (td, J = 7.5, 1.2 Hz, 1H), 4.69 (s, 2H), 1.52 (s, 9H).

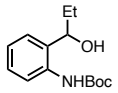

7.92
7.90
7.62
7.33
7.33
7.31
7.31
7.29
7.29
7.27
7.27
7.26 CDCl3
7.18
7.18
7.16
7.16
7.04
7.03
7.03
7.02
7.02
7.01
7.00
7.00
4.69
4.14
4.13
4.11
4.09
2.04
1.55
1.54
1.52
1.51
1.49
1.48
1.46
1.27
1.26
1.24
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



SI-16

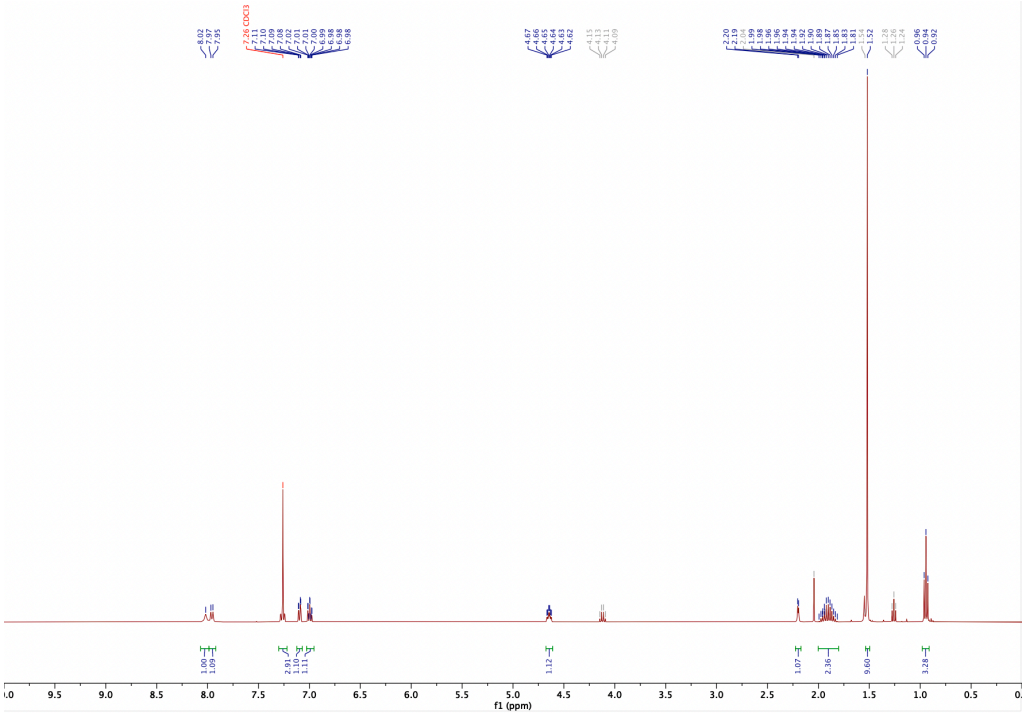
To a 250 mL round-bottom flask, charged with **SI-15** (3.3 g, 14.9 mmol) in DCM (50 mL, 0.3 M) was added pyridinium chlorochromate (4.8 g, 1.5 equivalent). The reaction was stirred at room temperature over 4 hours. The completion of reaction is analyzed by TLC. The reaction mixture was filtered through Celite and washed with DCM. The combined organic solutions were concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (ethyl acetate–hexane, 1:3) to afford the corresponding **SI-16** (3 g, 91% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 9.90 (s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 7.63 (dd, J = 7.7, 1.7 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.14 (td, J = 7.5, 1.0 Hz, 1H), 1.54 (s, 9H).

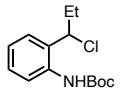




SI-17

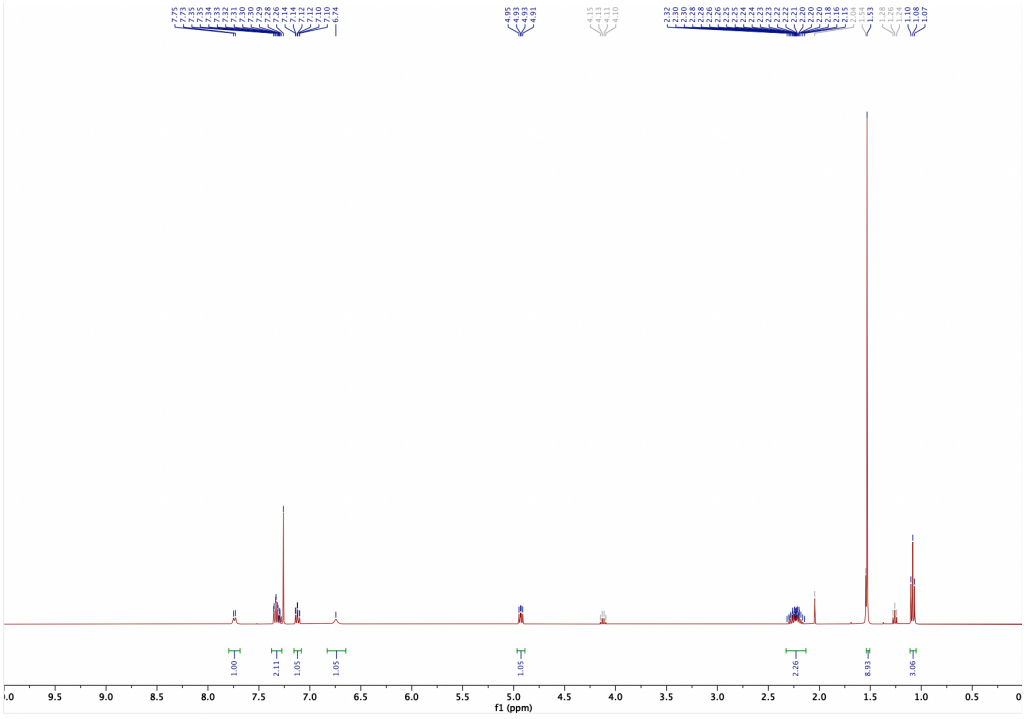
To a 100 mL round-bottom flask, charged with **SI-16** (3.0 g, 13.6 mmol) in dry THF (28 mL, 0.5 M) at 0 °C was added 3 M ethyl magnesium chloride (10 mL, 2.2 equivalent). The reaction was stirred at 0 °C under nitrogen atmosphere and slowly warmed to room temperature overnight. The completion of reaction is analyzed by TLC. The reaction mixture was quenched with 0.1 M HCl (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (ethyl acetate–hexane, 1:3) to afford the corresponding **SI-17** (2.3 g, 66% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.10 (dd, J = 7.6, 1.6 Hz, 1H), 7.00 (td, J = 7.5, 1.2 Hz, 1H), 4.64 (td, J = 7.0, 3.4 Hz, 1H), 2.20 (d, J = 3.7 Hz, OH), 1.90 (qt, J = 13.8, 7.2 Hz, 2H), 1.52 (s, 9H), 0.94 (t, J = 7.4 Hz, 1H).

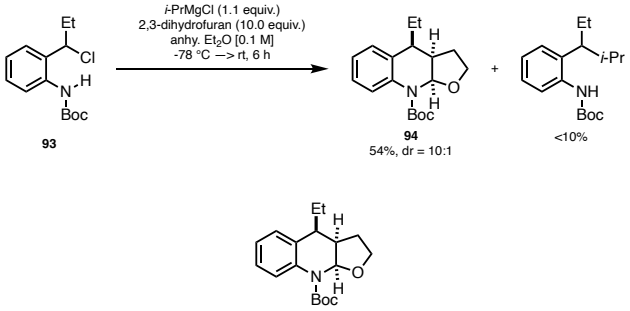




93

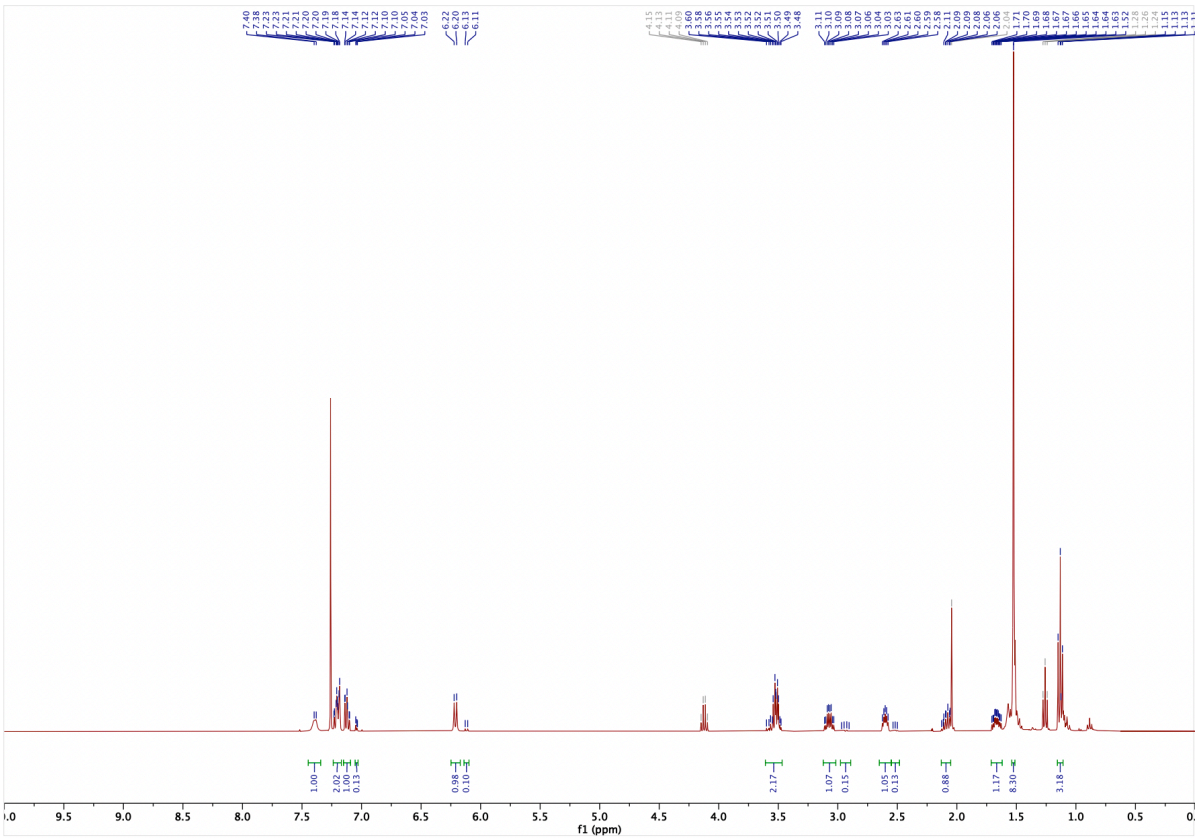
To a 100 mL round-bottom flask, charged with **SI-17** (2.3 g, 9.0 mmol) in dry DCM (18mL, 0.5 M) at 0 °C was added distilled pyridine (0.8 mL, 1.1 equivalent) and thionyl chloride (0.69 mL, 1.05 equivalent). The reaction was stirred at 0 °C for 3 hours. The completion of reaction is analyzed by TLC. The reaction mixture was quenched with sat. $NaHCO_3$ solution (30 mL) and extracted with DCM (3 x 10 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (ethyl acetate–hexane, 1:7) to afford the corresponding **93** (1.6 g, 64% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 1H), 7.32 (m, 2H), 7.12 (td, J = 7.6, 1.3 Hz, 1H), 6.74 (s, 1H), 4.93 (dd, J = 8.5, 6.1 Hz, 1H), 2.34 – 2.12 (m, 2H), 1.53 (s, 9H), 1.08 (t, J = 7.3 Hz, 3H).

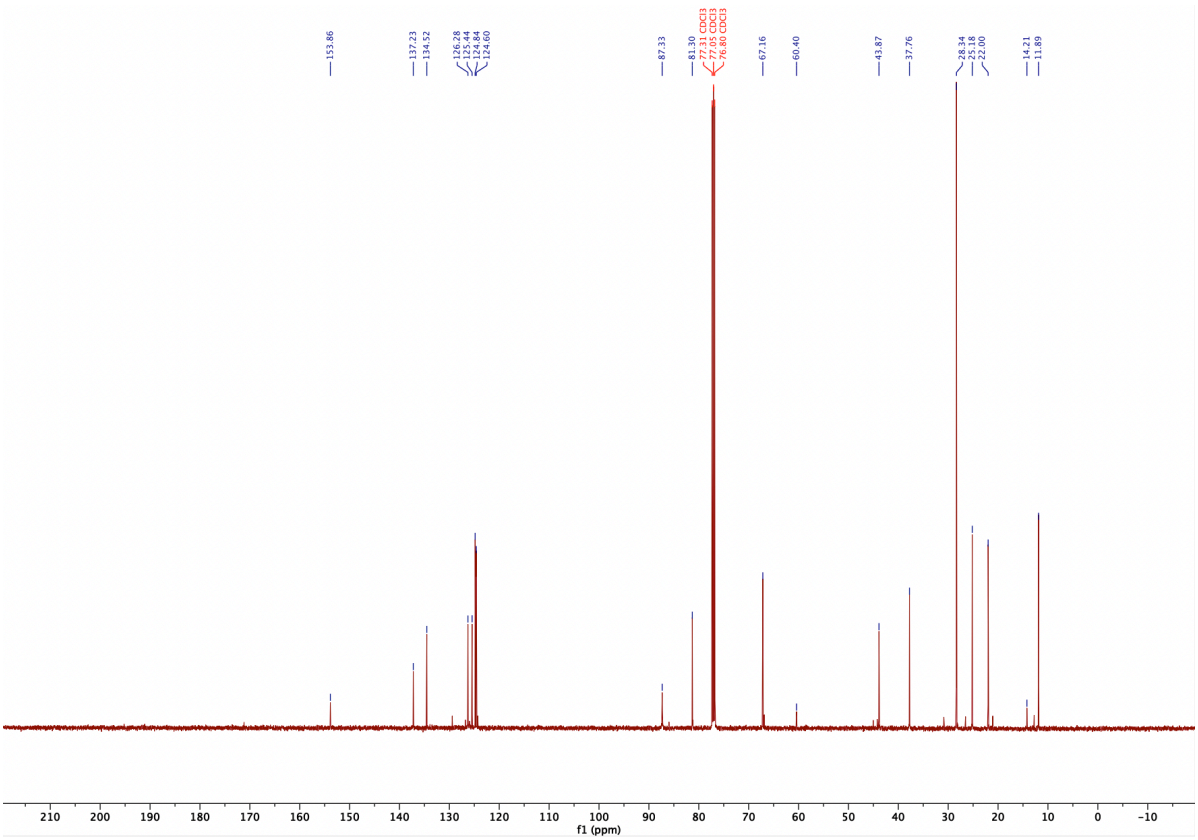




94

To a 10 mL Schlenk tube, charged with distilled 2,3-dihydrofuran (0.25 mL, 10.0 equivalent) in dry Et_2O (3.3 mL, 0.1 M) at -78 °C was added *i*PrMgCl (1.1 equivalent) and **93** (0.328 mmol, 0.5 M in dry toluene with 5% TMOA). The reaction was stirred at -78 °C and slowly warm to room temperature over 6 hours. The reaction mixture was quenched with sat. $NaHCO_3$ solution (1 mL) and extracted with EtOAc (3 x 1 mL). The combined organic fractions were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (ethyl acetate–hexane, 1:9) to afford the corresponding **94** (53.7 mg, 54% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.1 Hz, 1H), 7.24 – 7.17 (m, 2H), 7.12 (td, J = 7.4, 1.3 Hz, 1H), 6.21 (d, J = 8.7 Hz, 1H), 3.5 (m, 2H), 3.07 (qd, J = 9.0, 4.2 Hz, 1H), 2.60 (dt, J = 9.6, 5.0 Hz, 1H), 2.13 – 2.05 (m, 1H), 1.67 (dddd, J = 12.6, 9.5, 6.1, 3.9 Hz, 1H), 1.52 (s, 9H), 1.13 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.86, 137.23, 134.52, 126.28, 125.44, 124.84, 124.60, 87.33, 81.30, 67.16, 60.40, 43.87, 37.76, 28.34, 25.18, 22.00, 14.21, 11.89.


f1 (ppm)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134.52
126.28
124.84
124.60
87.33
81.30
77.31 CDCl3
77.05 CDCl3
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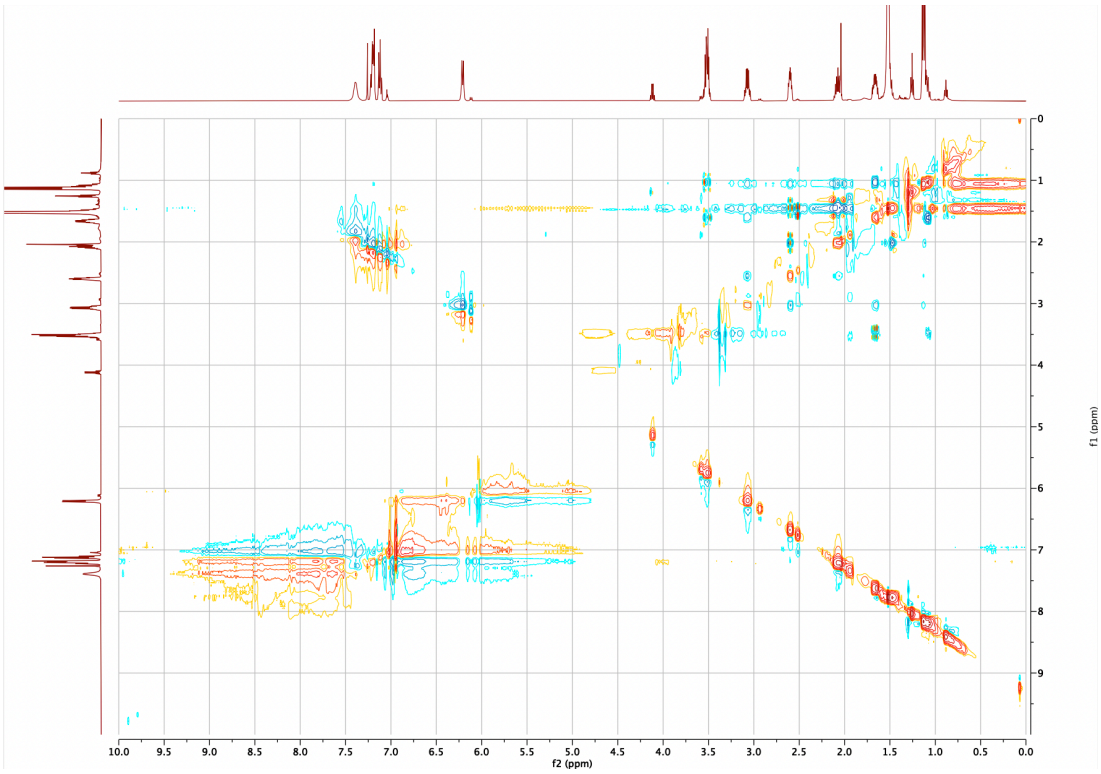
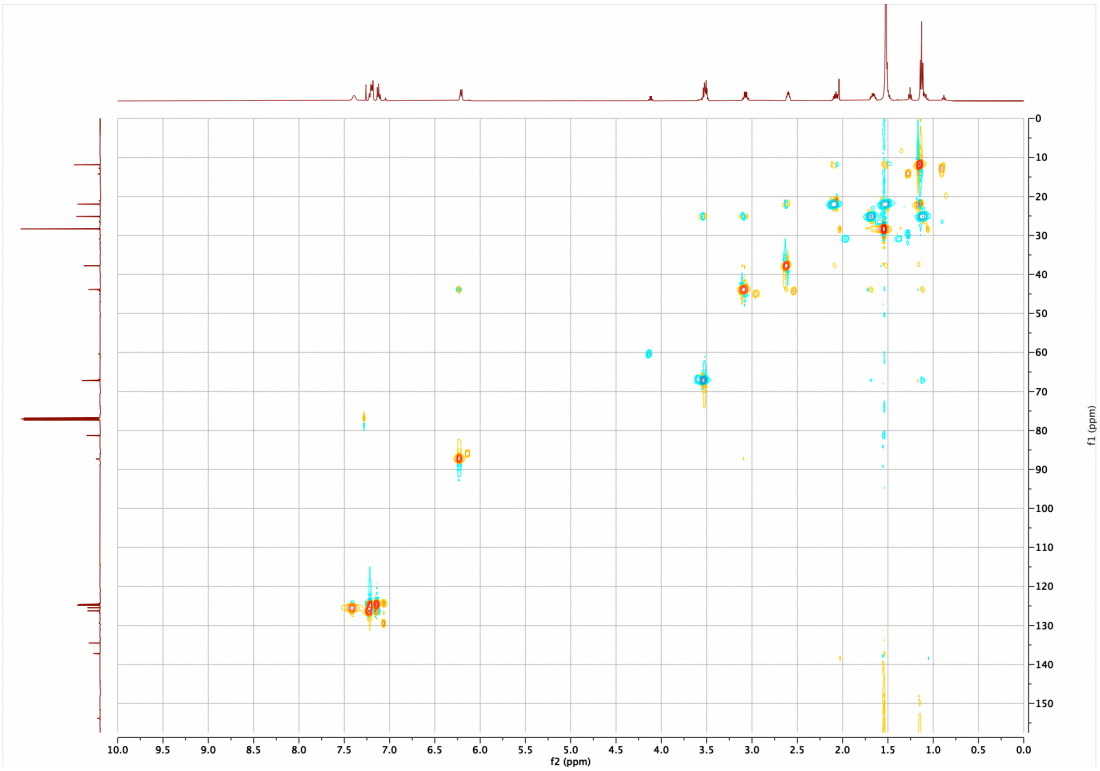
25.18
22.00
14.21
11.89
f1 (ppm)



2D NOESY



2D HSQC