EXPLORING NEW REACTIVITIES OF ACTIVATED ISOCYANIDES TO ACCESS DIVERSE NITROGEN HETEROCYCLES

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Declaration

I hereby declare that this thesis is my original work and it has been written by me in its entirety, under the supervision of Prof. Dr. Zhao Yu, Chemistry Department, National University of Singapore, between Aug 2012 and May 2016.

I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.

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Name	Signature	Date

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Summary

The development of efficient and economical processes for the preparation of valuable nitrogen heterocycles remains an important goal in synthetic organic and medicinal chemistry. Along these lines, activated isocyanides (or α-acidic isocyanides) have proven to be a versatile functionality to react with carbonyls, imines, activated alkenes/alkynes, *etc*. to produce a wide range of heterocyclic compounds. The main theme of my Ph.D. studies has been the development of new transformations of activated isocyanides to access diverse heterocyclic structures, with a focus on the development of catalytic asymmetric variants.

In chapter 1, the catalytic asymmetric reactions of activated isocyanides with various electrophiles, including carbonyl compounds, imines, activated alkenes, and azodicarboxylates were summarized to give a general background of this field.

In chapter 2, we reported for the first time that aryl esters could react with isocyanoacetates to yield oxazoles. Based on this discovery, we developed a novel complexity-generating method: both functionalities in readily available α-imino esters undergo [3+2] cyclization reaction with isocyanoacetates to give directly linked oxazole-imidazolines under silver catalysis. The asymmetric variant has also been realized with the Dixon-type ligand to produce these compounds in high diastereo- and enantiopurity.

In chapter 3, the divergent [3+2] cyclization reaction of activated isocyanides with allenoates was described for the first time. Under different catalytic systems, we

realized the cycloaddition using either of the two C=C bonds in the allene structure. While Ag catalysis led to an unprecedented enantioselective synthesis of 3*H* pyrroles and related *N*-heterocycles, a simple procedure using catalytic amount of PPh_3 produced a wide range of polysubstituted 1*H* pyrroles in high efficiency.

In chapter 4, we presented an unexpected Ag-catalyzed three-component reaction of 3-formylchromones, amines and isocyanoacetates, leading to the formation of 1,2,4-trisubstituted pyrroles. Importantly, mechanistic studies revealed that this unusual transformation was initiated by 1,4-conjugate addition of amine to 3-formyl chromone instead of imine condensation, representing a new reaction pathway in isocyanoacetate-based multicomponent reactions.

In chapter 5, an interesting and effective catalyst-controlled chemo-divergent cascade reaction of *para*-quinone methide-aryl esters with activated isocyanides was developed for the first time. While Ag catalysis led to the formation of tricyclic ketals with three continuous stereogenic centers in pure form, structurally diverse triarylmethanes were obtained exclusively under Cu catalysis.

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List of Schemes

List of Abbreviations

Ac	Acetyl
Å	Ångström
Ar	Aryl
Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
Bn	Benzyl
Bu	Butyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
DCE	1,2-Dichloroethane
DIPEA	*N*,*N*-Diisopropylethylamine
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppe	1,1-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppm	1,1-Bis(diphenylphosphino)methane
dppp	1,3-Bis(diphenylphosphino)propane
d.r.	Diastereomeric ratio

ee	Enantiomeric excess
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EWG	Electron-withdrawing group
EDG	Electron-donating group
EI	Electron ionization
ESI	Electrospray ionization
FG	Functional group
h	Hour
HRMS	High resolution mass spectrometry
HPLC	High-performance liquid chromatography
i-Pr	Isopropyl
m/z	Mass-to-charge ratio
Me	Methyl
Mes	Mesitylene
mmol	Millimole
MP	Melting point
MS	Molecular seives
n.d.	Not determined
NMR	Nuclear magnetic resonance
Nu	Nucleophile

n.r.	No reaction
Ph	Phenyl
Pr	Propyl
r.t.	Room temperature
TBAF	*tetra*-n-Butylammonium fluoride
TBAB	*tetra*-n-Butylammonium bromide
t-Bu	*tert*-Butyl
TEA	Triethylamine
Tf	Trifluorosulfonyl
TMS	Trimethylsilyl
TMEDA	Tetramethylethylenediamine
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
Ts	*p*-Toluenesulfonyl

List of Publications

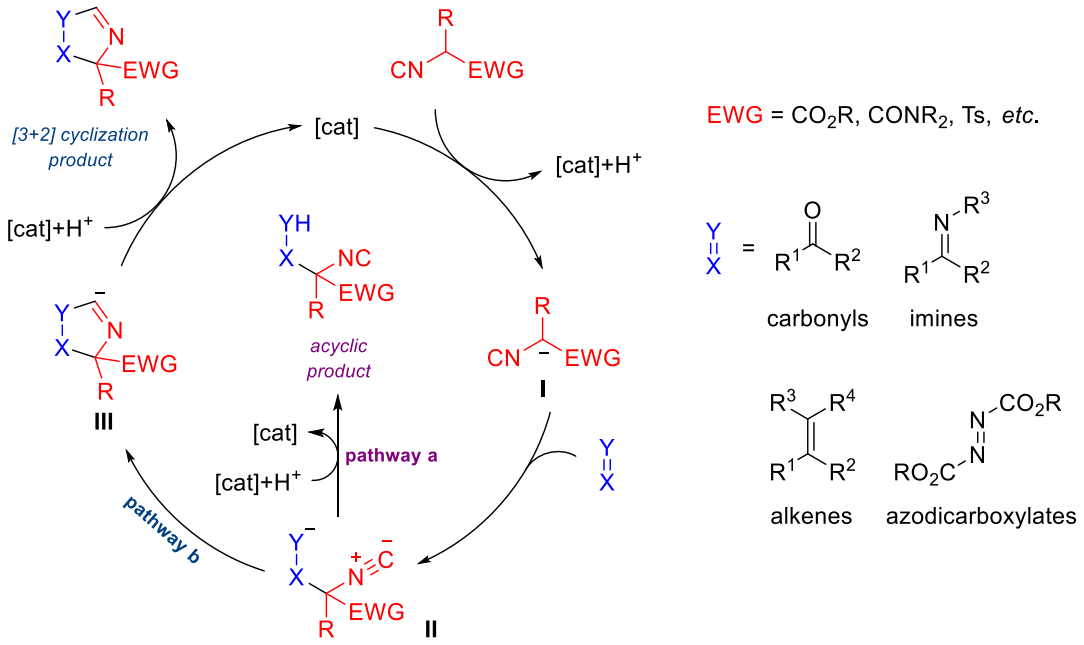
1. "Divergent Synthesis of Tricyclic Ketals and Triarylmethanes from Catalytic Cascade Reactions of Activated Isocyanides," **J.-Y. Liao**, Q. Ni, Y. Zhao, **2016**, *submitted*.
2. "Synthesis of Polysubstituted Pyrroles from Ag-Catalyzed Three-Component Reactions of Isocyanoacetates" **J.-Y. Liao**, W. J. Yap, J. Wu, M. W. Wong, Y. Zhao, **2016**, *manuscript in preparation*.
3. "Catalytic Divergent Synthesis of 3*H* or 1*H* Pyrroles by [3+2] Cyclization of Allenoates with Activated Isocyanides," **J.-Y. Liao**, P.-L. Shao, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 628-631.
4. "Highly Diastereo- and Enantioselective Ag-Catalyzed Double [3+2] Cyclization of α-Imino Esters with Isocyanoacetate," P.-L. Shao, **J.-Y. Liao**, Y. A. Ho, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 5435-5439.

Chapter 1 Catalytic Asymmetric Reactions of Activated Isocyanides

1.1 Introduction

Heterocyclic compounds, in particular nitrogen heterocycles are one of the most abundant and useful classes of chemical substances, which are commonly presented in natural products, biologically active structures as well as drug related compounds.[1] As a result of the importance of these molecules, their preparation has always been a hot topic in organic synthesis. Along these lines, activated isocyanides (or α-acidic isocyanides) have been identified as irreplaceable building blocks to deliver a wide of nitrogen heterocycles, such as oxazolines, imidazolines and 1,2,4-triazolines. The divergent reactivity of activated isocyanides is resulted from the unique divalent properties of the isocyanide group, which could serve both as an electrophile and a nucleophile.

Scheme 1.1 General Mechanism for the Reaction of Activated Isocyanides with Electrophiles



Over the past few decades, great efforts have been made to develop highly efficient methods for the construction of nitrogen heterocycles by employing activated isocyanides.[2] In this review, we will summarize the catalytic asymmetric reactions of activated isocyanides with various electrophiles, including carbonyl compounds, imines, activated alkenes and azodicarboxylates. A general mechanism is described in Scheme 1.1. Typically, all these reactions start with the formation of α-carbanion **I** from the deprotonation of activated isocyanide. The nucleophilic addition of this carbanion to the electrophile takes place to generate intermediate **II**. After the formation of **II**, there are two possibilities: 1) Direct protonation of **II** gives the acyclic product with regeneration of the catalyst (pathway a); 2) Addition of the newly formed anion in **II** to the isocyanide generates intermediate **III** followed by protonation to give the [3+2] cyclization product (pathway b). The selectivity of these two pathways depends on the nature of substrates used as well as the reaction conditions. The content of this review is organized based on the different types of electrophiles.

1.2 Reaction with Carbonyl Compounds

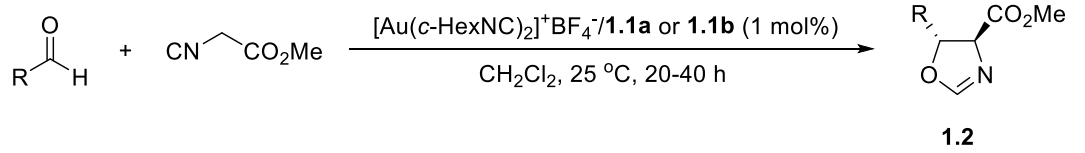
Typically, only [3+2] cycloaddition products (in this case, oxazolines) could be obtained from the reaction of activated isocyanides with carbonyl compounds, as the resulting alkoxide (refer to intermediate **II**, Scheme 1.1) has a strong tendency to cyclize.

1.2.1 Transition-Metal Catalysis

1.2.1.1 Gold(I) Catalysis

In 1986, Ito and co-workers reported the first enantioselective synthesis of oxazoline from the reaction of isocyanoacetate with aldehydes, catalyzed by a chiral ferrocenylphosphine-Au(I) complex (Scheme 1.2).[3] Since then, this Au(I)-catalyzed aldol reaction has been thoroughly investigated and become a valuable method for the preparation of chiral oxazolines and their β-hydroxyamino acids derivatives.[4]

Scheme 1.2 Au(I)-Catalyzed Aldol Reaction of Isocyanoacetates (Ito and Hayashi, 1986)



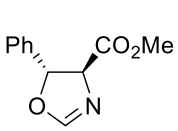
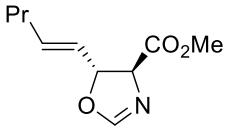
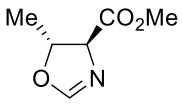
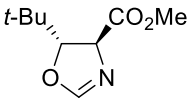
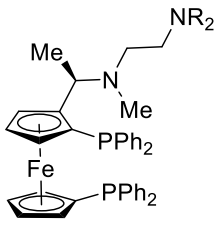
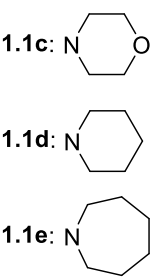
			
1.2a 98%, 8:1 d.r. 96% ee	**1.2b** 97%, 4:1 d.r. 87% ee	**1.2c** 100%, 5:1 d.r. 72% ee	**1.2d** 100%, >20:1 d.r. 97% ee

Figure 1.1 Chiral Ferrocenylphosphine Ligands Used in Au(I) Catalysis



1.1

NR_2 = **1.1a**: NMe_2
1.1b: NEt_2

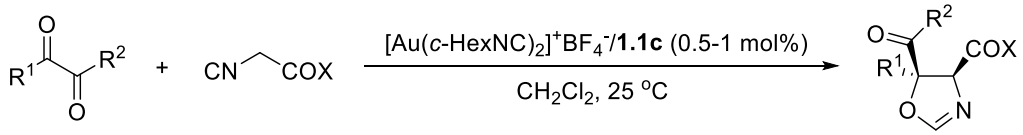


In an effort to expand the scope of this catalytic system, various chiral ferrocenylphosphine ligands were synthesized and evaluated, for which **1.1a-e** were proved to be highly effective (Figure 1.1).

Detailed studies were performed to explain the origin of stereoselectivity of this Au(I)-system.[5] In addition to isocyanoacetates, other types of substrates, such as isocyanoacetamides[4f, 6] and (isocyanomethyl)phosphonates[7] were also employed in this reaction.

Notably, this catalytic system could be applied to ketones as well (Scheme 1.3).[8] However, the level of stereoselectivity (both diastereo- and enantioselectivity) was generally lower than the reaction with aldehydes. Furthermore, it was limited to activated ketone substrates, such as α-ketoesters and α-diketones.

Scheme 1.3 Au(I)-Catalyzed Aldol Reaction of Activated Ketones (Ito and Hayashi, 1989)

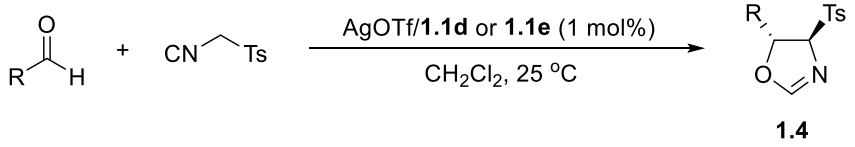


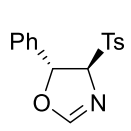
1.3a 90%, 3:1 d.r. 82% ee	**1.3b** >99%, 7:1 d.r. 90% ee	**1.3c** >99%, 4:1 d.r. 42% ee	**1.3d** 92%, 1:1 d.r. 75% ee

1.2.1.2 Silver(I) Catalysis

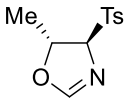
Except for gold, other transition metals such as silver has also been investigated in the asymmetric aldol reaction of activated isocyanides with aldehydes. The pioneer work was reported by Ito and co-workers using tosylmethyl isocyanide in 1990 (Scheme 1.4).[9] In this reaction, the chiral ferrocenylphosphine ligand **1.1d** or **1.1e** was introduced to give the corresponding oxazolines in up to 86% ee. Aromatic, aliphatic as well as α,β-unsaturated aldehydes were all tolerated. This catalytic system was also applicable to the aldol reaction of isocyanoacetates.[10]

Scheme 1.4 Ag(I)-Catalyzed Aldol Reaction of Tosylmethyl Isocyanide (Ito, 1990)

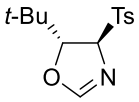




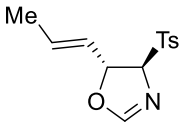
1.4a
96%, >20:1 d.r.
83% ee



1.4b
94%, >20:1 d.r.
83% ee



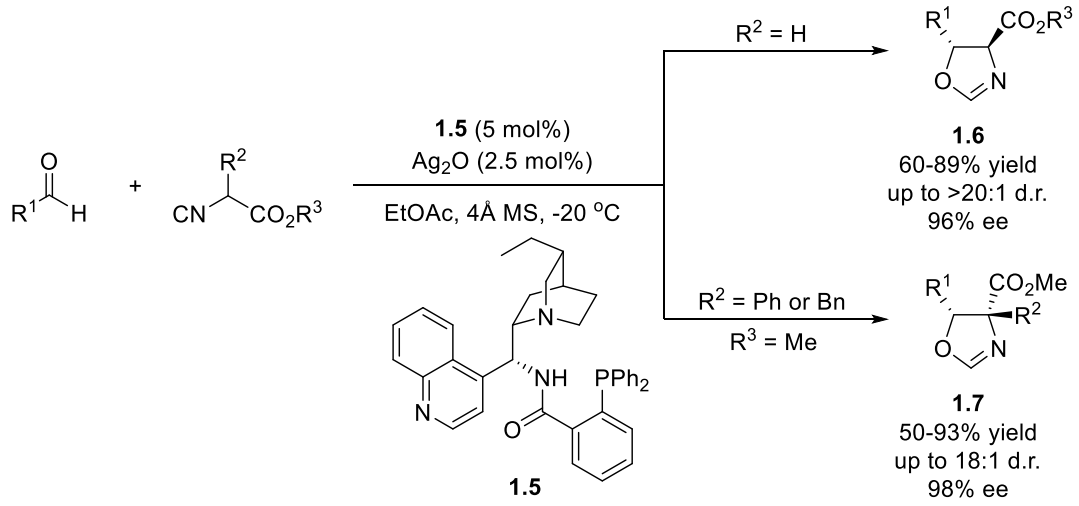
1.4c
97%, >20:1 d.r.
85% ee



1.4d
96%, >20:1 d.r.
85% ee

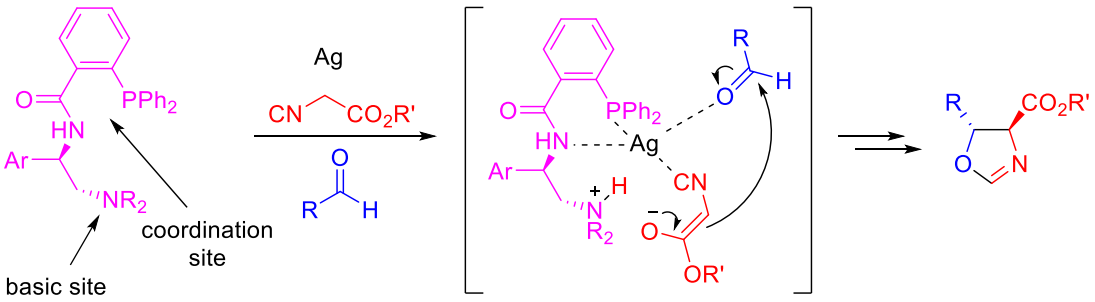
In 2011, a new class of chiral amino phosphine ligands derived from *cinchona* alkaloids was developed by the Dixon group.[11] In combination with Ag_2O, these ligands performed as effective catalysts for the synthesis of enantiomerically enriched oxazolines. Both mono-and disubstituted isocyanoacetates were tested to give the corresponding products in high stereoselectivities (Scheme 1.5).

Scheme 1.5 Ag(I)-Catalyzed Aldol Reaction of Isocyanoacetates (Dixon, 2011)



A catalyst activation mode was proposed. As shown in Figure 1.2, the coordination of isocyanide to silver (as Lewis acid) enhances the acidity of the α-proton thus facilitates the deprotonation by the quinuclidine nitrogen (as Brønsted base) to generate enolate; in the meantime, the aldehyde is activated by silver as well to promote the nucleophilic addition of the enolate.

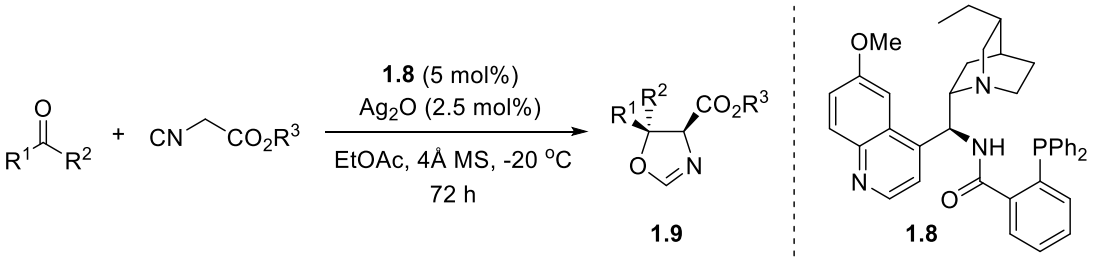
Figure 1.2 Proposed Catalyst Activation Mode

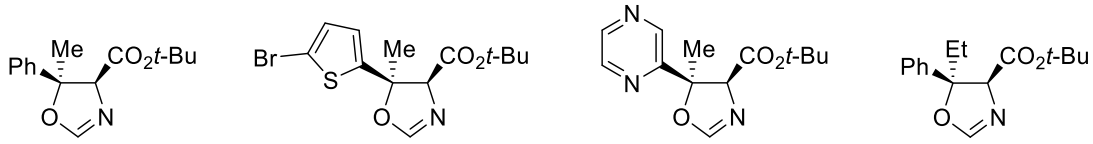


This Ag(I)-catalyzed asymmetric aldol reaction could be applied to the synthesis of complex structures, for instance, biologically active (-)-chloramphenicol.[12]

In addition to aldehydes, ketones were also tested in this system by the same group.[13] Various alkyl aryl ketones were examined to give the corresponding highly functionalized oxazolines in good to excellent stereoselectivities (Scheme 1.6). It is noteworthy that this is the first asymmetric aldol reaction of isocyanoacetates with unactivated ketones and is complementary to Ito and Hayashi's work[8].

Scheme 1.6 Ag(I)-Catalyzed Aldol Reaction of Unactivated Ketones (Dixon, 2015)





1.9a
84%, 16:1 d.r.
88% ee

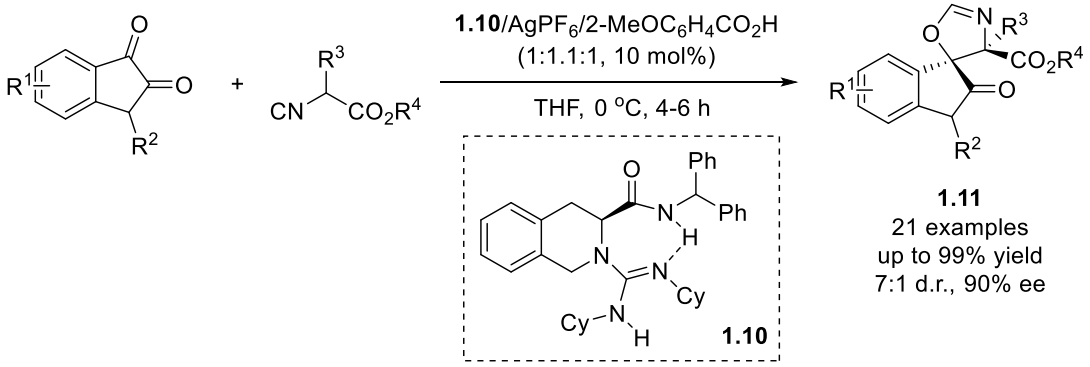
1.9b
78%, 7:1 d.r.
86% ee

1.9c
75%, 10:1 d.r.
82% ee

1.9d
76%, 9:1 d.r.
98% ee

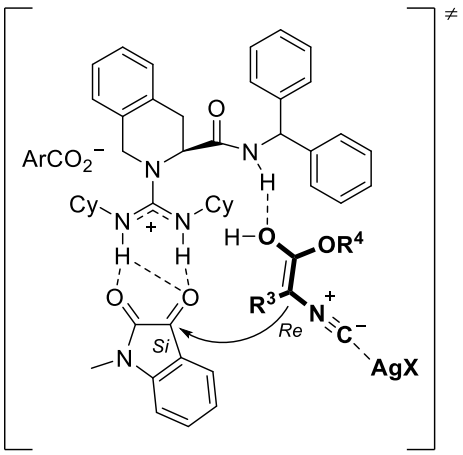
Functionalized ketones, such as isatins were investigated in the transition-metal catalyzed aldol reaction of isocyanoacetates as well. In 2015, a cooperative chiral guanidine/silver(I) catalytic system was developed to realize the asymmetric reaction of isocyanoacetates with isatins.[14] Series of spirooxindole oxazolines with two adjacent stereocenters were obtained in moderate to good stereoselectivities (Scheme 1.7).

Scheme 1.7 Asymmetric Aldol Reaction with Isatins (Liu and Feng, 2015)



A transition state was proposed, where both of the two substrates were activated by the catalysts (Figure 1.3). The coordination of isocyanide coordinates to silver increases the acidity of the α-proton. Simultaneously, the guanidinium salt, generated *in situ* from the reaction of guanidine catalyst **1.10** with the Brønsted acid, activates isatin through organized multiple hydrogen-bonding interactions. This transition state results in the attack of isocyanoacetate from its *Re*-face to the *Si*-face of isatin, leading to the construction of two adjacent stereocenters. Subsequent intramolecular cyclization affords the spriocyclic skeletons.

Figure 1.3 Proposed Transition State

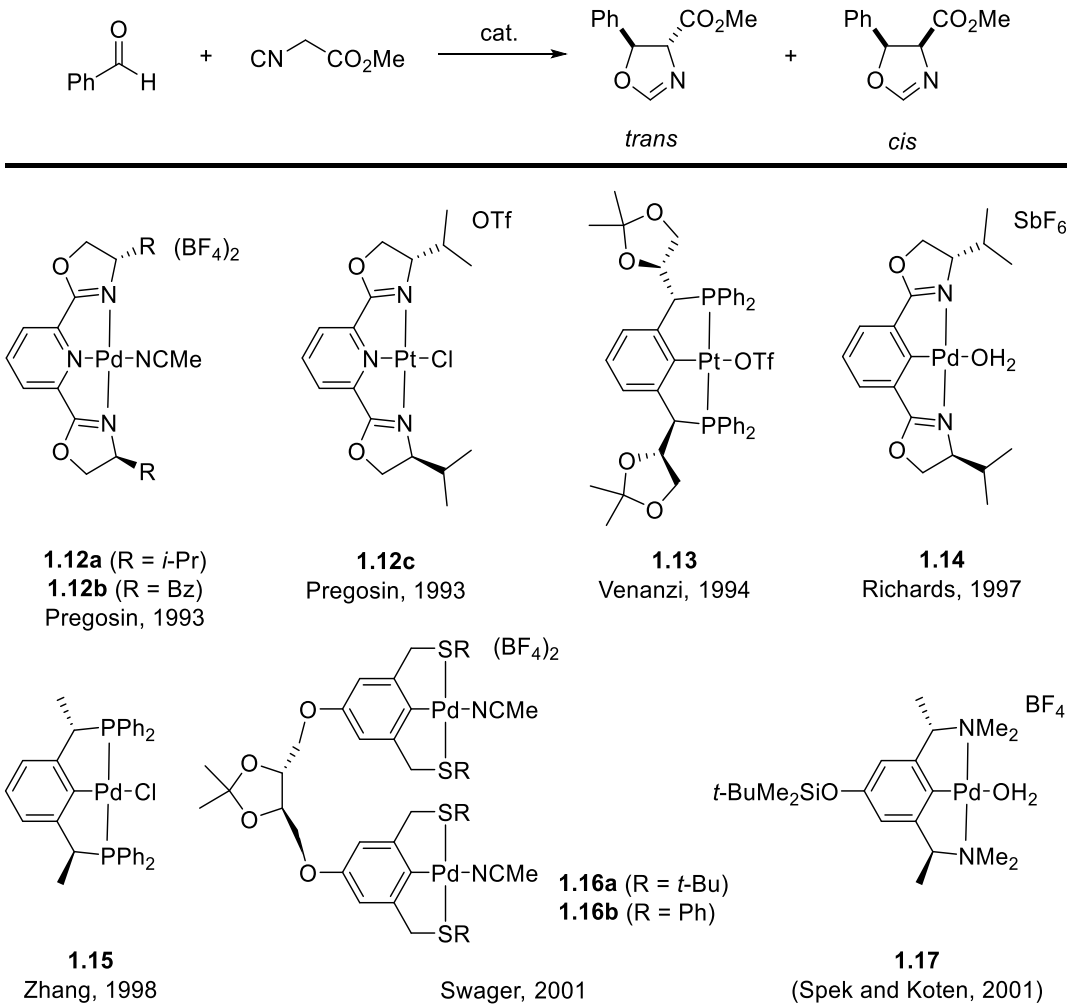


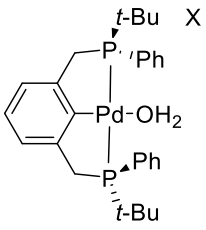
1.2.1.3 Palladium(II) and Platinum(II) Catalysis

Other than gold and silver complexes, chiral palladium and platinum complexes have also been evaluated in the asymmetric aldol reaction of isocyanoacetates with aldehydes.

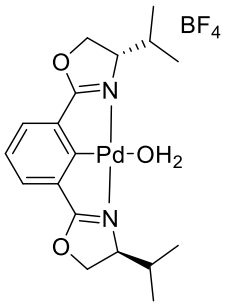
The first example was described by Pregosin and co-workers in 1993.[15] In this study, chiral Pd(II) and Pt(II)-complexes **1.12a-c** were tested in the reaction of methyl isocyanoacetate with benzaldehyde. All these complexes showed high efficiency but with poor stereoselectivity (Scheme 1.8).

Scheme 1.8 Chiral Pd- and Pt-Complexes Applied in Asymmetric Aldol Reaction

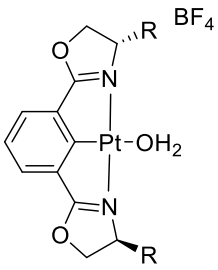




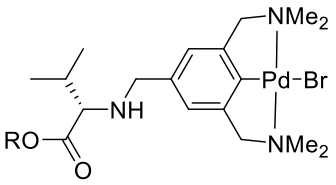
1.18a (X = BF_4)
1.18b (X = OTf)
Spek and Koten, 2001



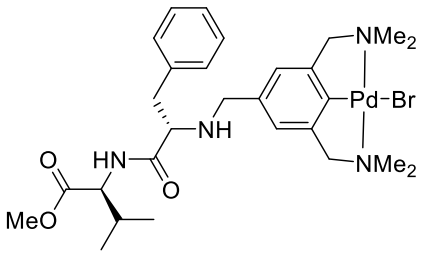
1.19
Motoyama, 2002



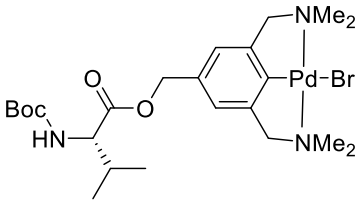
1.20a (R = *i*-Pr)
1.20b (R = Bn)
Motoyama, 2002



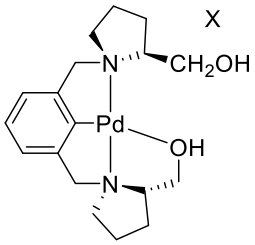
1.21a (R = Me)
1.21b (R = H)
Koten, 2002



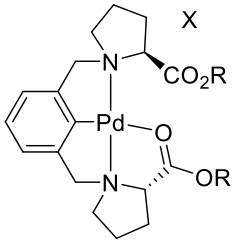
1.21c
Koten, 2002



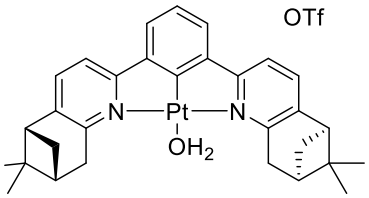
1.21d
Koten, 2002



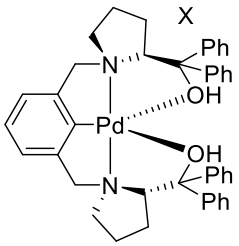
1.22a (X = PF_6)
1.22b (X = BF_4)
Gebbink, 2006



1.23a (R = Me, X = BF_4)
1.23b (R = Me, X = PF_6)
1.23c (R = Bn, X = BF_4)
1.23d (R = Bn, X = PF_6)
Koten and Gebbink, 2006



1.24
Ahn, 2006



1.25a (X = PF_6)
1.25b (X = BF_4)
Gebbink, 2008

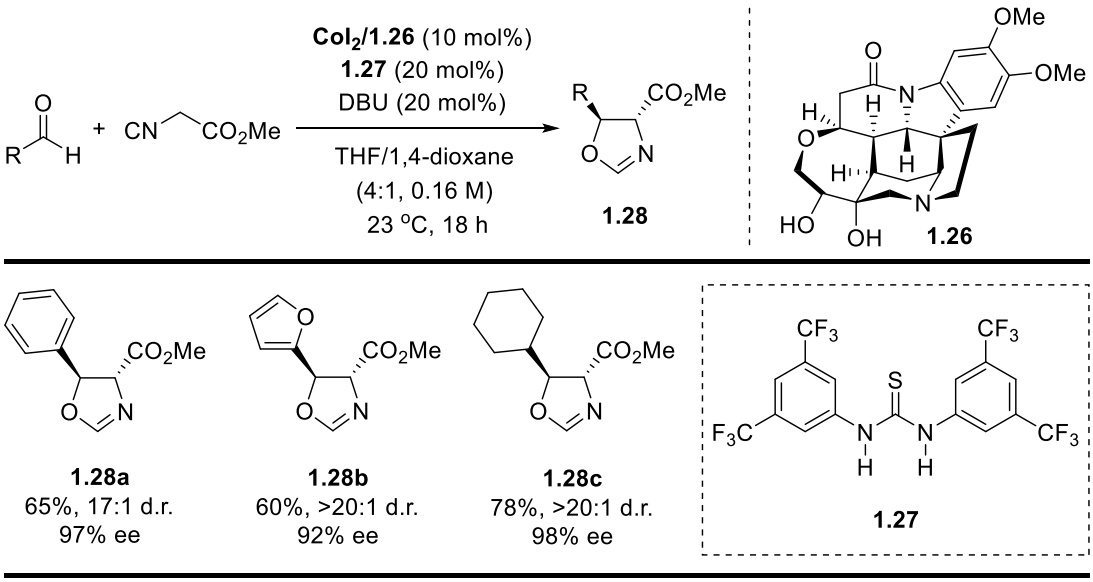
From then on, a variety of chiral Pd(II)- and Pt(II)-complexes[16] have been examined in this reaction (Scheme 1.8). Typically, high yields could be obtained, suggesting that Pd(II) and Pt(II) might be alternatives to Au(I) and Ag(I) and worth consideration in the future. The formation of *trans*-diastereomers was preferred.

However, no catalyst achieved acceptable level of diastereo- and enantioselectivity. The poor stereoselectivity probably resulted from the displacement of the chiral ligand from the metal with isocyanoacetate.[17] Hence, the development of an effective chiral Pd(II) or Pt(II)-complex regarding to high stereoselcvity is extremely desired.

1.2.1.4 Cobalt(II) catalysis

In 2011, the Oh group developed a cooperative catalytic system involving a chiral Co(II)-catalyst and an achiral thiourea co-catalyst for the asymmetric aldol reaction of isocyanoacetates (Scheme 1.9).[18] Aryl, heteroaryl, and alkyl aldehydes were all tolerated to give the corresponding oxazolines in good to excellent stereoselectivities.

Scheme 1.9 Thiourea/Co(II) Cooperatively Catalyzed Asymmetric Aldol Reaction (Oh, 2011)



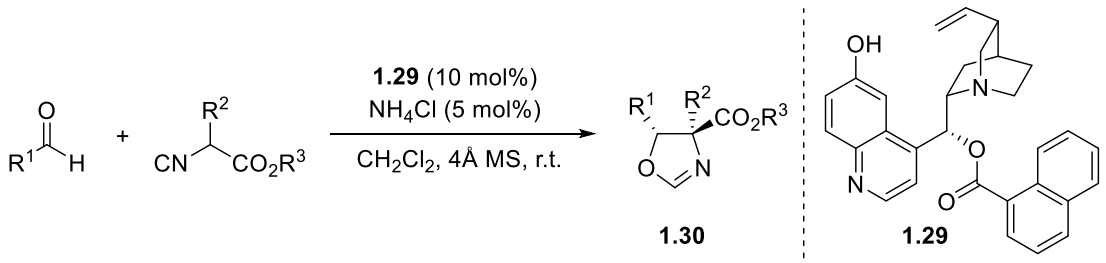
It is worth noting that in this system, isocyanide does not coordinate to metal

(different from Au and Ag); instead, it is activated by the thiourea **1.27** through a strong anion-bonding interaction. This interaction potentially disturbs the intrinsic metal-isocyanide complexation and might be critical to the stereocontrol.[18] To be noted, this is the only example of Co(II)-catalyzed asymmetric reaction of activated isocyanides.

1.2.2 Organocatalysis

In contrast to transition-metal catalyzed asymmetric aldol reactions of activated isocyanides, only a few organocatalytic variations have been developed.

Scheme 1.10 Organocatalytic Asymmetric Aldol Reaction of Isocyanoacetates (Gong, 2009)



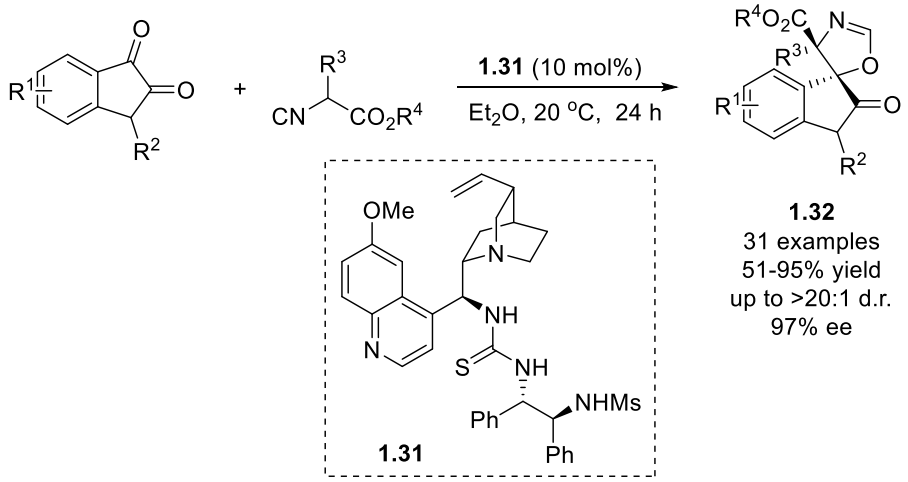
1.30a	**1.30b**	**1.30c**	**1.30d**
94%, 6:1 d.r.	44%, 2:1 d.r.	30%, 2:1 d.r.	89%, 13:1 d.r.
78% ee	74% ee	89% ee	31% ee

In 2009, Gong and co-workers reported the first organocatalytic stereoselective synthesis of oxazolines by employing a *cinchona* alkaloid derivative as catalyst

(Scheme 1.10).[19] Generally, electron-poor benzaldehydes worked fairly well, whereas electron-neutral as well as aliphatic aldehydes resulted in low yields even with prolonged reaction time. Monosubstituted isocyanoacetate could also be used to give the desired product, albeit with moderate enantioselectivity.

In addition to aldehydes, ketones have also been applied in organocatalytic asymmetric aldol reaction of activated isocyanides. In 2013, Zhao and co-workers described a stereoselective [3+2] cycloaddition reaction of isocyanoacetates with isatins catalyzed by a *cinchona* alkaloid-derived thiourea catalyst.[20] Spirooxindole oxazolines with two adjacent quaternary stereocenters were obtained in good yields with good to excellent stereoselectivities (Scheme 1.11).

Scheme 1.11 Organocatalytic Asymmetric Reaction of Isocyanoacetates with Isatins (Zhao and Shi, 2013)



In this system, isocyanoacetate was deprotonated by the quinuclidine nitrogen of catalyst **1.31**, leading to the formation of hydrogen-bonding interaction between the

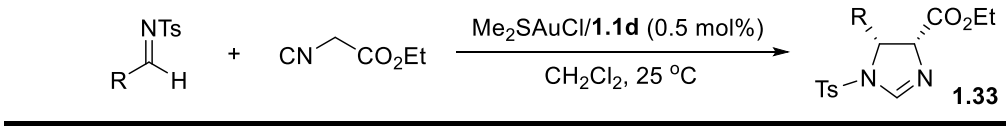
enolate and the tertiary amine. In the meantime, isatin was activated through multiple hydrogen bonds formed between the two carbonyl groups of isatin and the hydrogen-bonding donor moiety of **1.31**. Other than hydrogen-bonding interactions, concurrent π-π stacking between the two substrates might be responsible for the stereoselectivity as well.[20]

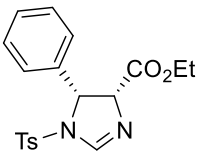
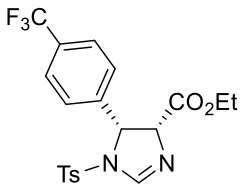
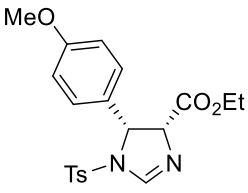
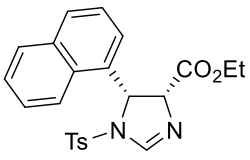
1.3 Reaction with Imines

In most cases, [3+2] cycloaddition products (in this case, imidazolines) were obtained from the reaction of activated isocyanides with imines (refer to pathway b, Scheme 1.1). However, acyclic adducts (refer to pathway a) could also be generated depending on the specific reaction environment.

1.3.1 Transition-Metal Catalysis

Scheme 1.12 Au(I)-Catalyzed Enantioselective Synthesis of Imidazolines (Lin, 1999)



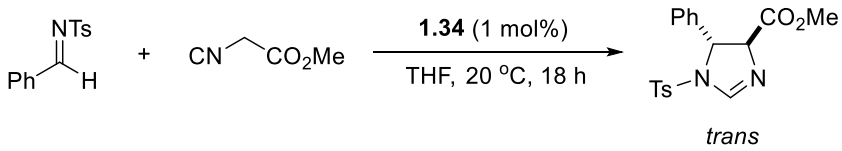
			
1.33a 85%, 12:1 d.r. 61% ee	**1.33b** 82%, 9:1 d.r. 46% ee	**1.33c** 89%, >20:1 d.r. 58% ee	**1.33d** 79%, 12:1 d.r. 58% ee

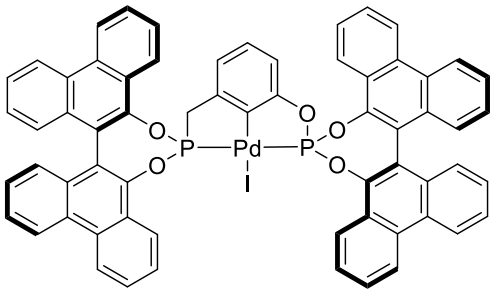
The first transition-metal catalyzed enantioselective synthesis of imidazolines

from isocyanoacetates and imines was described in 1999 by Lin and co-workers, employing a chiral ferrocenylphosphine-Au(I) complex similar to Ito and Hayashi's system (Scheme 1.12).[21] However, only moderate enantioselectivities were obtained.

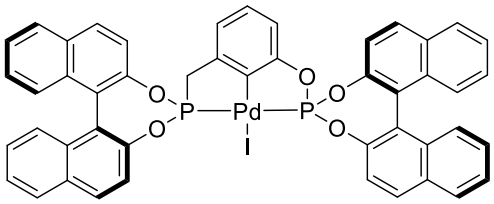
Palladium(II)-pincer complexes **1.34a-d** were identified as efficient catalysts for the reaction of isocyanoacetates with imines as well (Scheme 1.13).[22] In contrast to Lin's report, this system showed a tendency for the selective formation of *trans*-diastereomer (up to 4:1 *trans*/*cis*).

Scheme 1.13 Pd(II)-Pincer Complexes Catalyzed Synthesis of Imidazolines (Szabó, 2008)

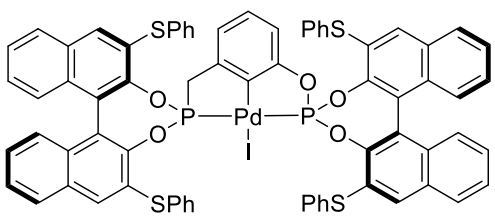




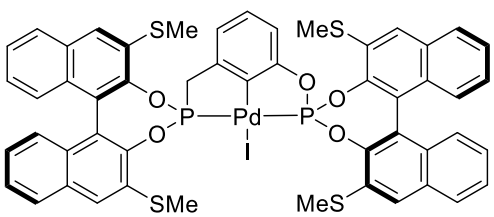
1.34a
98%, 1:1 d.r.



1.34b
98%, 4:1 d.r.



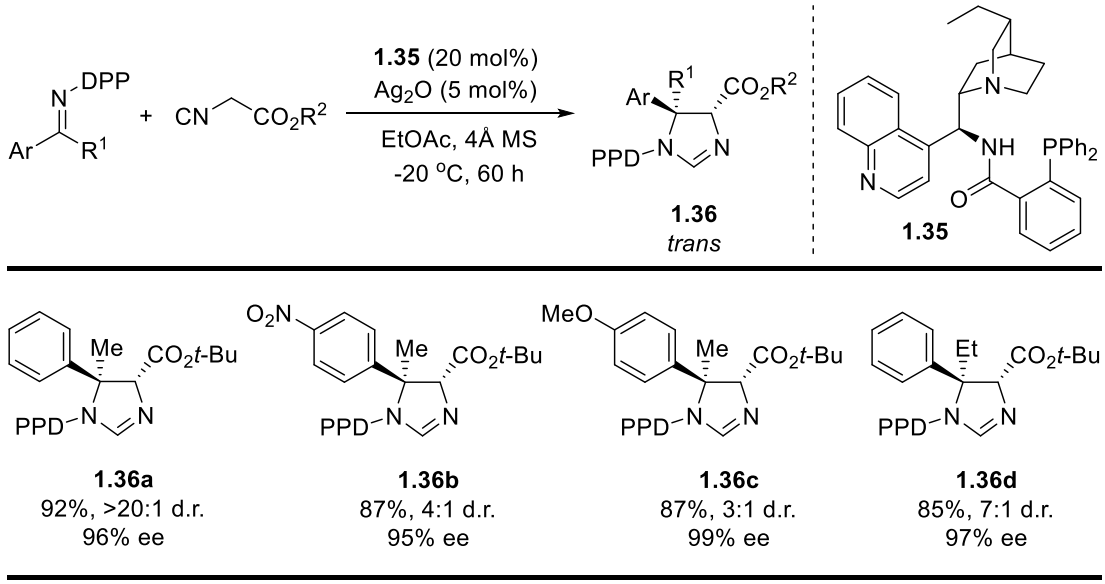
1.34c
98%, 4:1 d.r.



1.34d
98%, 2:1 d.r.

In 2014, the Dixon group reported the asymmetric reaction of isocyanoacetates with ketimines by employing their own catalytic system[11, 13] (Scheme 1.14).[23] In this study, various *N*-diphenylphosphinoyl (DPP)-protected ketimines and isocyanoacetates were evaluated to give *trans*-imidazolines in high yields with good to excellent stereoselectivities. Moreover, the cleavage of DPP group was realized by using a 1.0 M solution of HCl in dichloromethane at room temperature without any loss of the stereoselectivity.

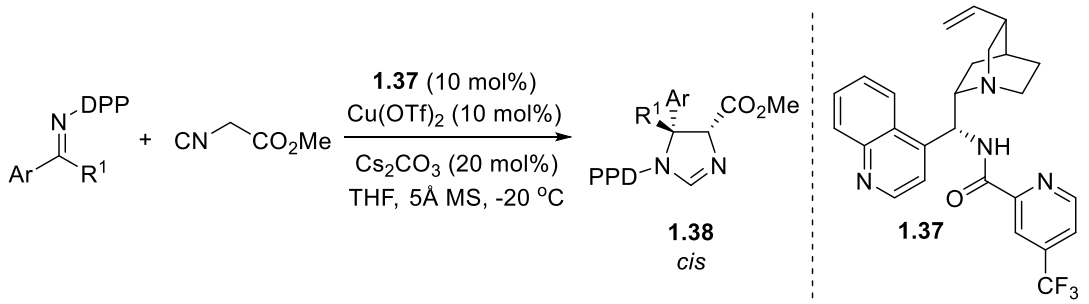
Scheme 1.14 Ag(I)-Catalyzed Reaction of Isocyanoacetates with Ketimines (Dixon, 2014)



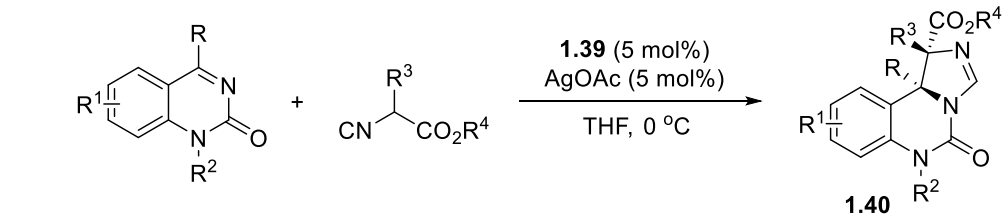
Alternatively, this Mannich-type reaction could be realized by introducing a chiral Cu(II) catalyst (Scheme 1.15).[24] In general, this catalytic system offered a *cis*-selective synthesis of imidazolines, which is different from Dixon's work[23]. However, when dialkyl substituted ketimines were applied, the corresponding

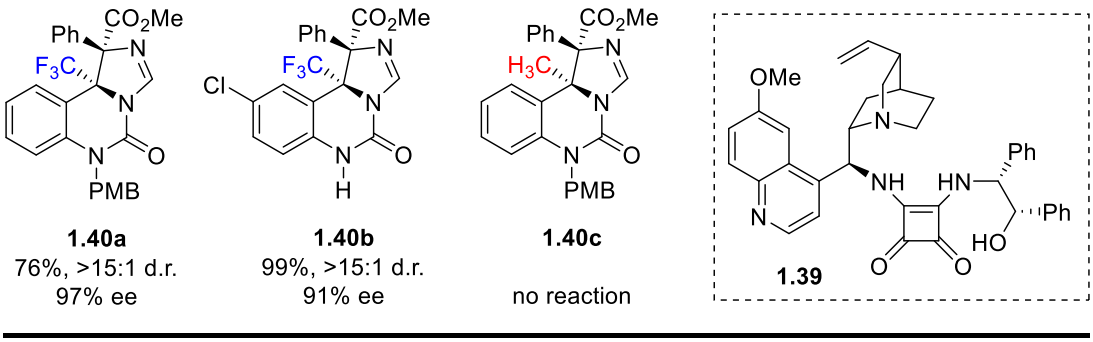
trans-diastereomers were produced preferably.

Scheme 1.15 Cu(II)-Catalyzed Reaction of Isocyanoacetates with Ketimines (Nakamura, 2014)



Scheme 1.16 Asymmetric Reaction of Isocyanoacetates with Cyclic Trifluoromethyl Ketimines (Zhao and Shi, 2014)

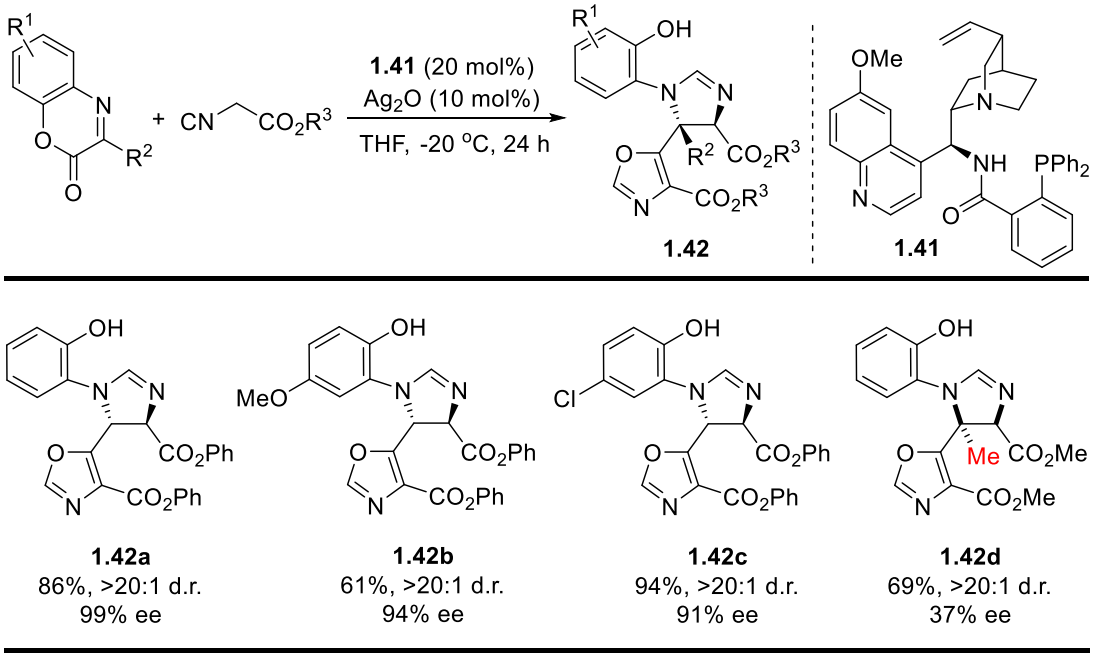




Cyclic ketimines have also been investigated in this filed. In 2014, Zhao and co-workers reported an asymmetric reaction of isocyanoacetates with cyclic trifluoromethyl ketimines cooperatively catalyzed by a hydrogen-bonding donor

catalyst and silver acetate.[25] A variety of tetrahydroimidazo-[1,5-*c*]quinazoline derivatives were constructed in excellent yields with good to excellent stereoselectivities (Scheme 1.16). However, this reaction was limited to trifluoromethyl-substituted substrates. The replacement of the trifluoromethyl group with a methyl group resulted in no reaction under the optimal conditions.

Scheme 1.17 Double [3+2] Cyclization of Isocyanoacetates with α-Imino Esters (Zhao, 2014)



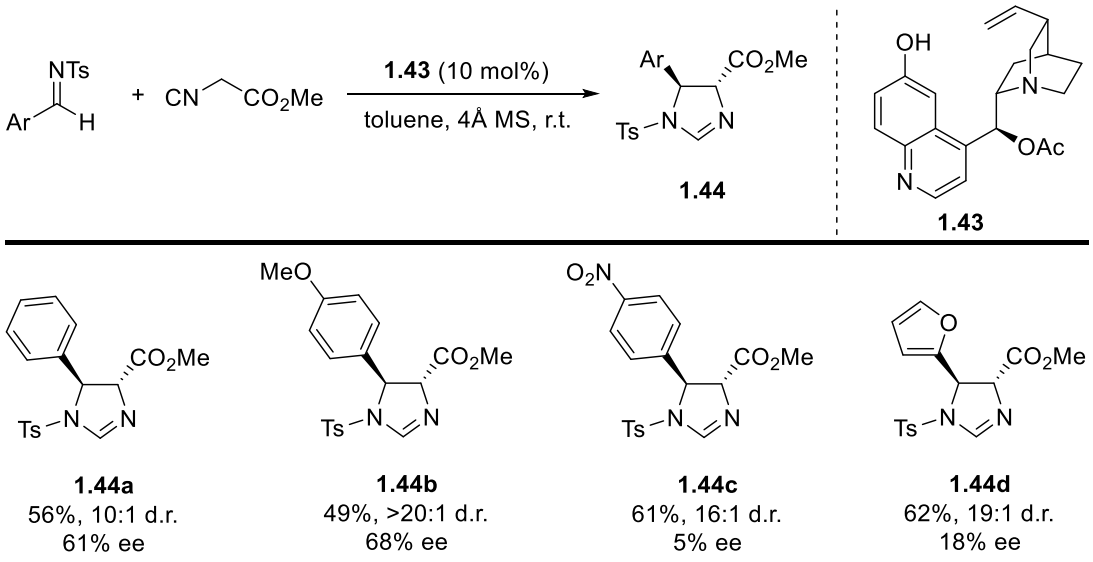
Except for ketimines, the reaction of isocyanoacetates with aldimines was investigated as well. In 2014, Zhao and co-workers developed a Ag(I)-catalyzed reaction of isocyanoacetates with α-imino esters (Scheme 1.17).[26] In this reaction, both functionalities of α-imino esters underwent [3+2] cyclization with isocyanoacetates to produce directly linked oxazole-imidazolines. The asymmetric

variant of this transformation was realized by introducing a Dixon-type chiral ligand[11, 13, 23] **1.41**. Generally, α-imino esters with different substituents on the aryl ring were well tolerated, while ketimines turned out to be difficult substrates for the enantiocontrol.

In order to better understand the mechanism, kinetic studies were performed, showing that the two cyclization reactions were stepwise (imine reacted first) and the enantioselectivity was determined in the first step. Based on this finding, this catalytic system was applied to the preparation of mono [3+2] cyclization adducts. Additionally, three-component reactions of two different isocyanoacetates with α-imino esters were also realized.

1.3.2 Organocatalysis

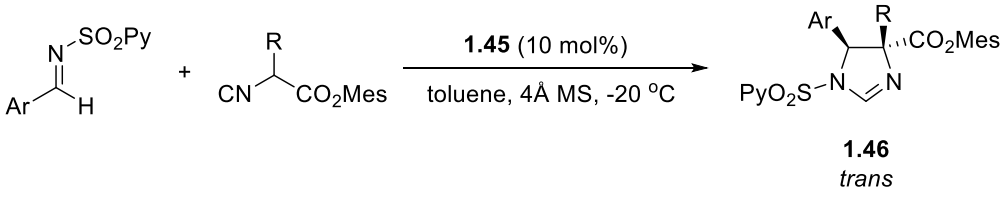
Scheme 1.18 Chiral Brønsted Base-Catalyzed Reaction of Isocyanoacetates with Imines (Lu and Chan, 2010)



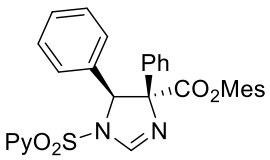
The first organocatalytic asymmetric reaction of isocyanoacetate with *N*-sulfonylimines was reported by Lu and co-workers in 2010 (Scheme 1.18).[27] A variety of *cinchona* alkaloid-derived Brønsted bases were examined in this reaction and **1.43** was determined to be the optimal choice. However, only moderate yields and enantioselectivities were obtained.

In 2012, Nakamura and co-workers achieved the highly enantioselective synthesis of *trans*-imidazolines (up to 96% ee) by employing a chiral thiourea catalyst (Scheme 1.19).[28] In this study, the pyridinesulfonyl group in the imine substrates proved to be essential for the high stereoselectivity through hydrogen-bonding interaction towards the catalyst. The removal of this group could be realized by using magnesium in methanol without compromising stereoselectivity.

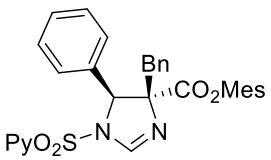
Scheme 1.19 Chiral Thiourea-Catalyzed Reaction of Isocyanoacetates with 2-Pyridinesulfonyl Imines (Nakamura and Shibata, 2012)



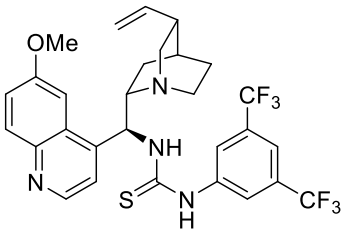
1.46
trans



1.46a
98%, >20:1 d.r.
82% ee



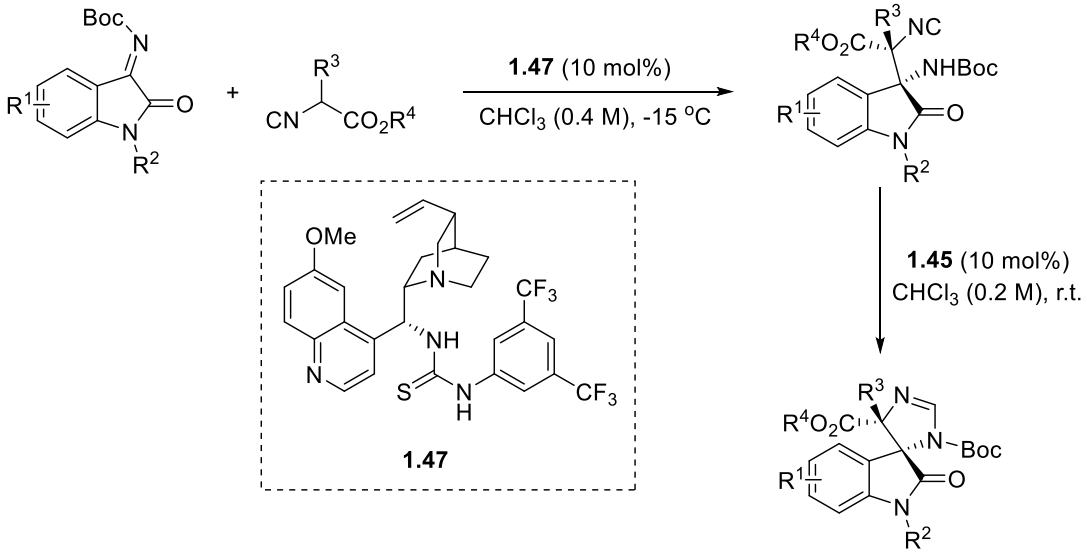
1.46b
79%, >20:1 d.r.
80% ee



1.45

In an effort to expand the substrate scope, isatin-derived ketimines were employed in the reaction with isocyanoacetates (Scheme 1.20).[29] In this study, a chiral thiourea **1.47** was used as the catalyst to achieve the stereoselective synthesis of Mannich adducts. Furthermore, these products could be transformed to functionalized spirooxindole imidazolines in high yields and without any loss of stereoselectivities by introducing another chiral thiourea catalyst **1.45**.

Scheme 1.20 Chiral Thiourea-Catalyzed Reaction of Isocyanoacetates with Isatin-Derived Ketimines (Zhao, 2015)



1.4 Reaction with Activated Alkenes

In general, the reaction of activated isocyanides with activated alkenes affords acyclic Michael addition adduct (refer to pathway a, Scheme 1.1) or [3+2] cycloaddition product (refer to pathway b, Scheme 1.1) depending on the nature of substrates used and the reaction conditions. This section is organized according to the

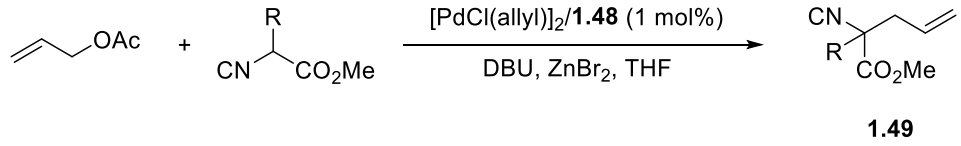
two reaction pathways.

1.4.1 Michael Addition

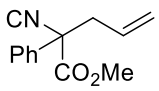
1.4.1.1 Transition-Metal Catalysis

In 1987, Ito and co-workers reported the first palladium-catalyzed enantioselective allylation of isocyanoacetates with allylic acetates (Scheme 1.21).[30] By employing a chiral ferrocenylphosphine ligand **1.48**, up to 39% ee was obtained. To be noted, this is the only example of transition-metal catalyzed asymmetric Michael addition of activated isocyanides.

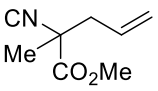
Scheme 1.21 Palladium-Catalyzed Enantioselective Allylation of Isocyanoacetates (Ito and Hayashi, 1987)



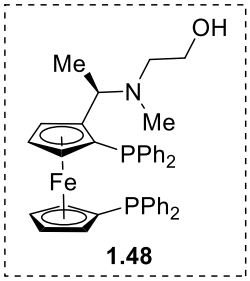
1.49



1.49a
55%, 39% ee



1.49b
35%, 20% ee



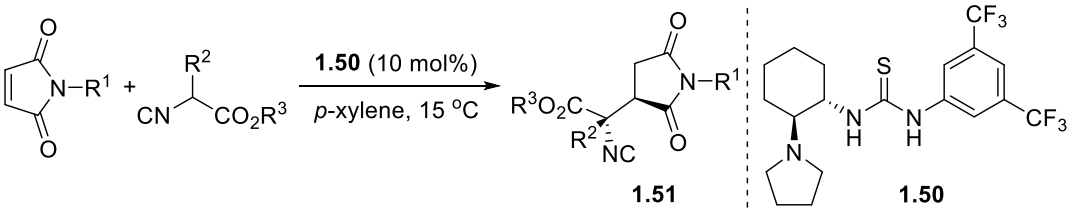
1.48

1.4.1.2 Organocatalysis

In 2012, Xu and co-workers presented the first organocatalytic asymmetric Michael addition of isocyanoacetates to maleimides catalyzed by a bifunctional

tertiary amine thiourea catalyst (Scheme 1.22).[31] Generally, the use of *N*-arylmaleimides resulted in better stereoselectivities than *N*-alkyl substituted substrates. In addition, the α-substituent of isocyanoacetates was essential to the stereoselectivity. When changing from phenyl to benzyl or methyl, only moderate diastereo- and enantioselectivities were obtained even with higher catalyst loading. This reaction could also be catalyzed by *cinchona* alkaloid or cyclohexane-1,2-diamine derived squaramide catalysts.[32]

Scheme 1.22 Asymmetric Michael Addition of Isocyanoacetates to Maleimides (Xu and Wang, 2012)

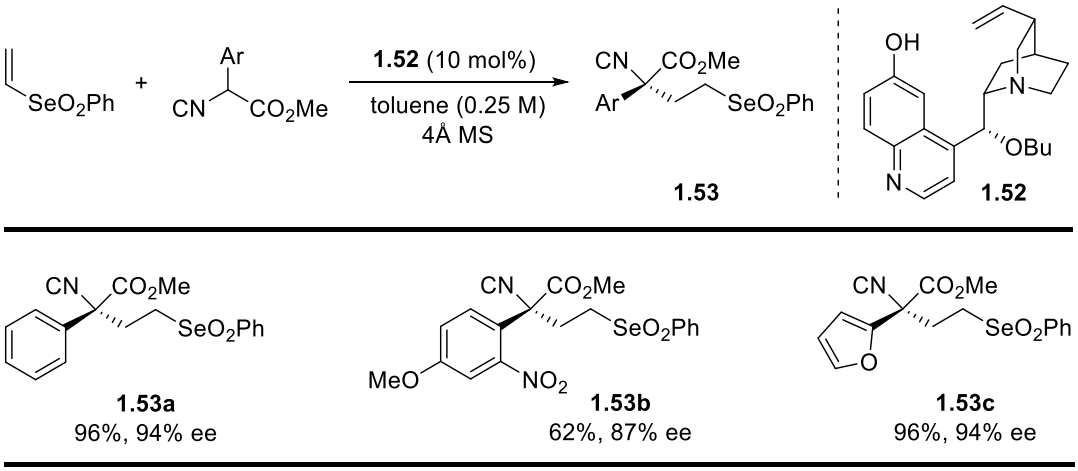


1.51a	1.51b	1.51c	1.51d
93%, >20:1 d.r.	74%, 6:1 d.r.	71%, 1.2:1 d.r.	65%, 1.2:1 d.r.
94% ee	60% ee	58% ee	54% ee

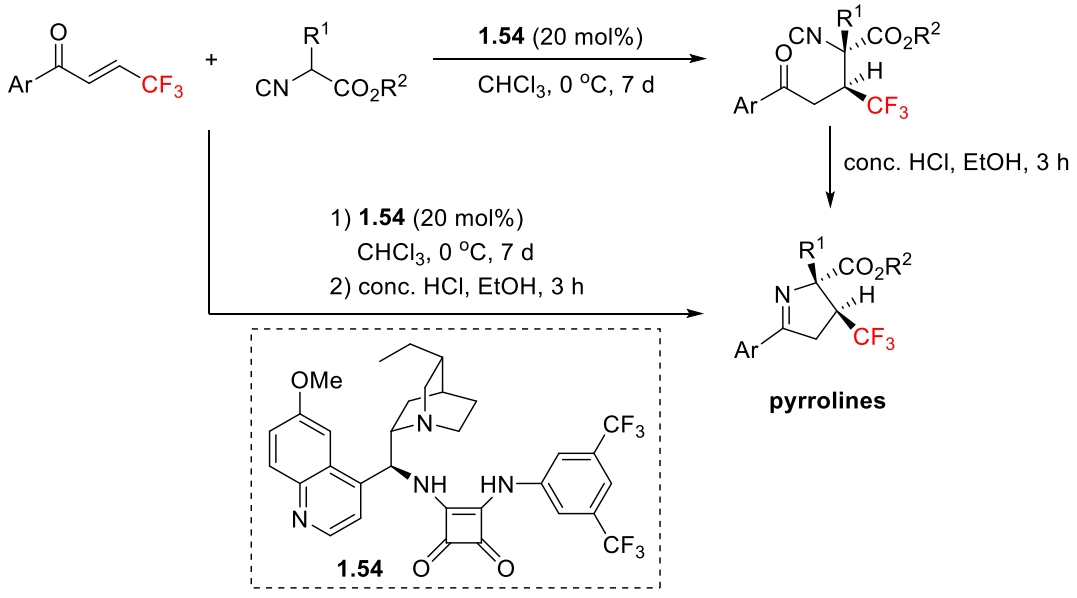
Complementary to cyclic substrates, acyclic activated alkenes were investigated. In 2013, Zhu and co-workers developed a chiral Brønsted base catalyzed enantioselective alkylation of isocyanoacetates with vinyl phenylselenone, affording enantioenriched α,α-disubstituted isocyanoacetates (Scheme 1.23).[33] Both aryl- and heteroaryl-substituted isocyanoacetates were well tolerated in this reaction. The

resulting Michael adduct **1.53b** was used as a starting material to complete the total synthesis of (+)-trigonoliimine A. Moreover, this catalytic system was applied to the one-pot enantioselective synthesis of 1,3-oxazinan-2-ones.[34]

Scheme 1.23 Asymmetric Alkylation of Isocyanoacetates with Vinyl Phenylselenone (Zhu, 2013)

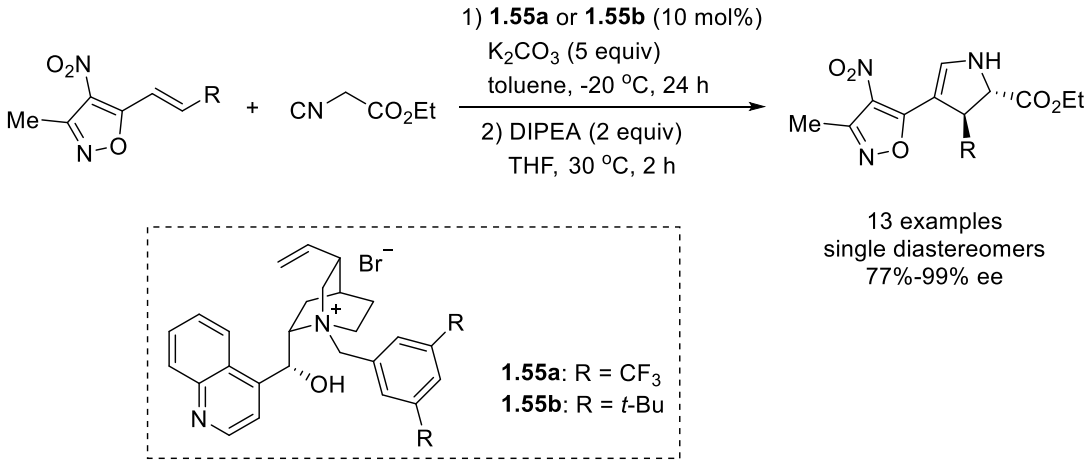


Scheme 1.24 Asymmetric Michael Addition of Isocyanoacetates to β-Trifluoromethylated Enones (Zhao and Shi, 2015)



In 2015, Zhao and Shi employed a *cinchona* alkaloid-derived squaramide catalyst to achieve the asymmetric Michael addition of isocyanoacetates to β-trifluoromethylated enones, affording the corresponding structures in excellent stereoselectivities (Scheme 1.24).[35] These adducts could be easily transformed into highly functionalized pyrrolines. Alternatively, these pyrrolines could be prepared directly from isocyanoacetates and β-trifluoromethylated enones through a one-pot procedure.

Scheme 1.25 Asymmetric Michael Addition of Isocyanoacetates to Styrylisoxazoles and Subsequent Cyclization (Adamo, 2015)



Phase-transfer catalysts have also been employed in the asymmetric Michael addition of isocyanoacetates to activated alkenes. In 2015, Adamo and co-workers described an asymmetric reaction of styrylisoxazoles and ethyl isocyanoacetate under phase-transfer catalysis, affording enantiomerically enriched Michael addition adducts in high enantioselectivities (Scheme 1.25).[36] Subsequent cyclization of these

compounds led to the formation of 2,3-dihydro-pyrroles in perfect diastereo-selectivities.

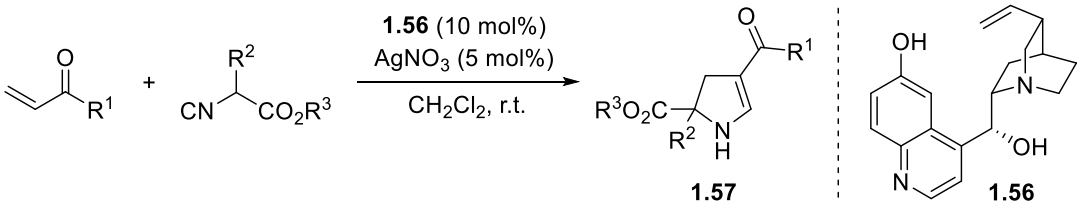
A similar catalytic system was developed by the same research group to accomplish the asymmetric Michael addition of ethyl isocyanoacetate to (*Z*)-3-substituted-2-(4-pyridyl)-acrylonitriles.[37]

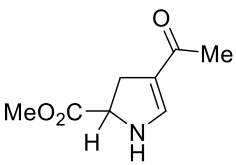
1.4.2 [3+2] Cycloaddition

1.4.2.1 Transition-Metal Catalysis

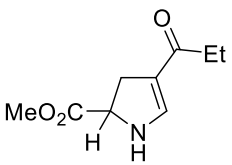
In 2011, Escolano and co-workers reported the first asymmetric [3+2] cyclization reaction of isocyanoacetates with α,β-unsaturated ketones, leading to the construction of 2,3-dihydropyrroles (Scheme 1.26).[38] However, only moderate yields and enantioselectivities were achieved.

Scheme 1.26 Asymmetric [3+2] Cycloaddition of Isocyanoacetates with α,β-Unsaturated Ketones (Escolano, 2011)

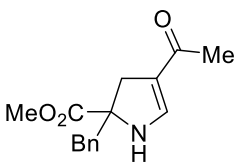




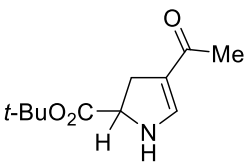
1.57a
58%, 60% ee



1.57b
49%, 74% ee

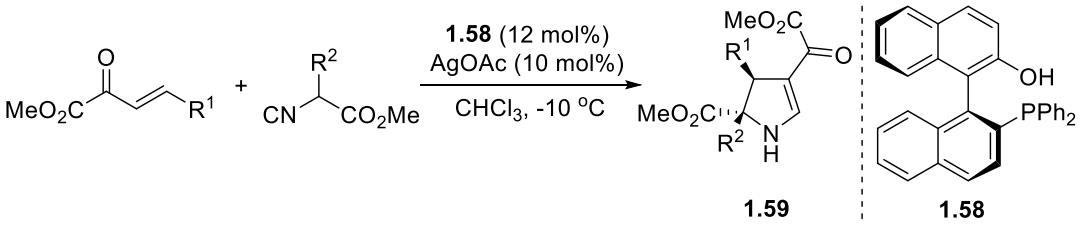


1.57c
85%, 16% ee



1.57d
59%, 58% ee

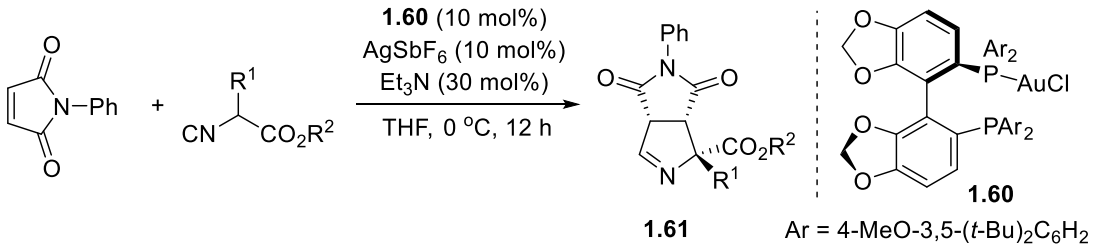
Scheme 1.27 Asymmetric [3+2] Cycloaddition of Isocyanoacetates with 2-Oxobutenoate Esters (Gong, 2011)

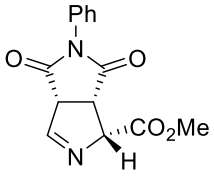


1.59a	1.59b	1.59c	1.59d
90%, 3:1 d.r.	90%, 2:1 d.r.	93%, 4:1 d.r.	78%, 3:1 d.r.
92% ee	93% ee	98% ee	96% ee

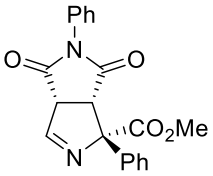
At almost the same time, the Gong group presented an asymmetric [3+2] cycloaddition of isocyanoacetates with 2-oxobutenoate esters catalyzed by a chiral silver complex (Scheme 1.27).[39] Various 2-oxobutenoate esters and α-aryl substituted isocyanoacetates were tested in this reaction. Generally, the corresponding 2,3-dihydropyrroles were formed in high yields and enantioselectivities with moderate diastereoselectivities. It is noteworthy that a crystal structure of this Ag-complex was obtained, in which the phosphorus coordinates to silver, while the hydroxyl proton forms a hydrogen-bond with one of the acetate oxygens.

Scheme 1.28 Au(I)-Catalyzed [3+2] Cycloaddition of Isocyanoacetates with Phenylmaleimide (Adrio and Carretero, 2012)

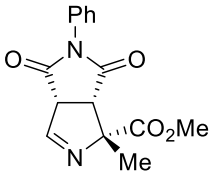




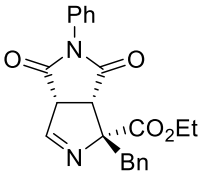
1.61a
70%, >19:1 d.r.
78% ee



1.61b
55%, >20:1 d.r.
92% ee



1.61c
65%, >20:1 d.r.
85% ee



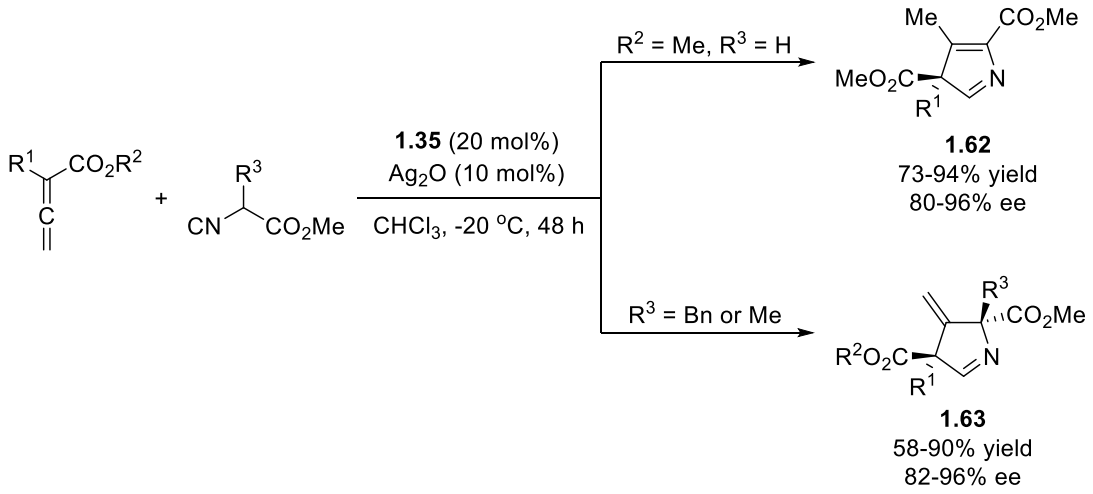
1.61d
54%, >20:1 d.r.
83% ee

Instead of acyclic alkenes, cyclic substrates such as maleimides (previously recognized as Michael acceptors)[31-32] have also been applied in the asymmetric [3+2] cyclization reaction with isocyanoacetates.[40] In the presence of Au(I)-complex **1.60**, the corresponding bicyclic pyrrolines were generated in high stereoselectivities (Scheme 1.28). In general, the use of disubstituted isocyanoacetates resulted in higher enantioselectivities than monosubstituted substrates. This reaction could also be realized by using a cooperative catalytic system.[41]

In 2015, Zhao and co-workers reported the cyclization of allenoates with isocyanoacetates for the first time, affording a wide range of nitrogen heterocycles under silver catalysis (Scheme 1.29).[42] The asymmetric variant was also developed by employing a Dixon-type chiral ligand[11, 13, 23, 26] **1.35**. In general, the use of monosubstituted isocyanoacetates resulted in the formation of highly substituted 3*H* pyrroles **1.62** in high yields with good to excellent enantioselectivities. It is worth noting that this is the first enantioselective synthesis of this class of heterocycles. In

contrast, highly functionalized pyrrolines **1.63** possessing an exocyclic olefin were constructed when disubstituted isocyanoacetates were employed. The formation of **1.63** not only expanded the scope of this catalytic system but also provided strong support for the formation of 3*H* pyrroles through a [3+2] cyclization/1,3-H shift sequence.

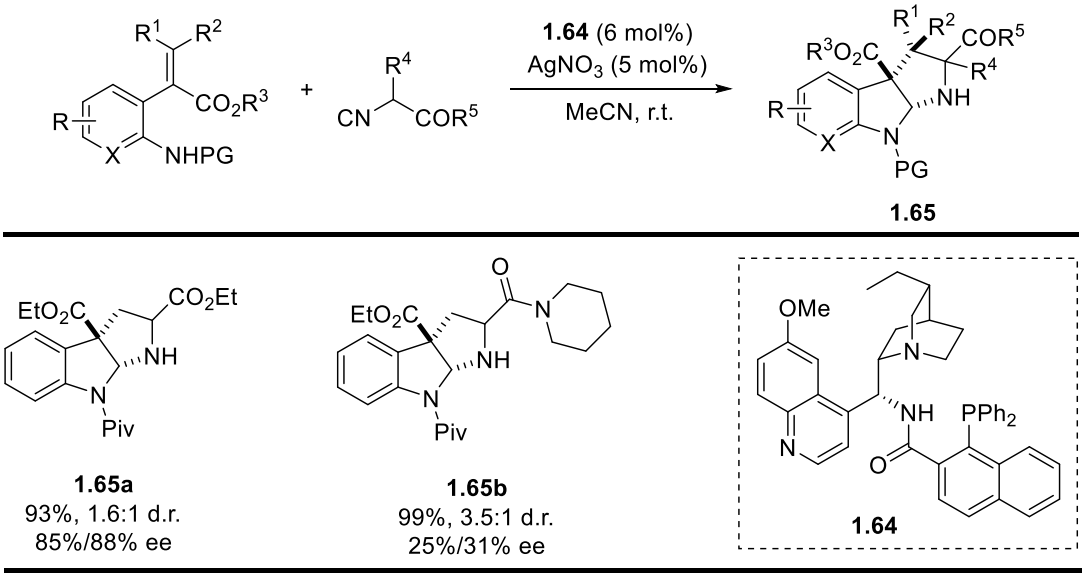
Scheme 1.29 Ag(I)-Catalyzed [3+2] Cycloaddition of Isocyanoacetates with Allenoates (Zhao, 2015)



Very recently, an asymmetric cascade reaction of isocyanoacetates was developed by introducing a Dixon-type chiral ligand[11, 13, 23, 26, 42] **1.64** with $AgNO_3$.[43] A variety of *cis*-3a,8a-hexahydropyrrolo[2,3-*b*]indoles (HPIs) were obtained from the reaction of activated isocyanides with 2-(2-amidophenyl)acrylates (Scheme 1.30). Isocyanoacetates and isocyanoacetamides were employed in this reaction. Generally, good overall yields could be obtained but with moderate stereoselectivities. In terms of reaction mechanism, this reaction starts with the generation of cyclic imine

intermediates through [3+2] cyclization of activated isocyanides with the olefin moiety. Subsequent intramolecular nucleophilic addition of the amino group to the newly formed imines results in the formation of tricyclic frameworks.

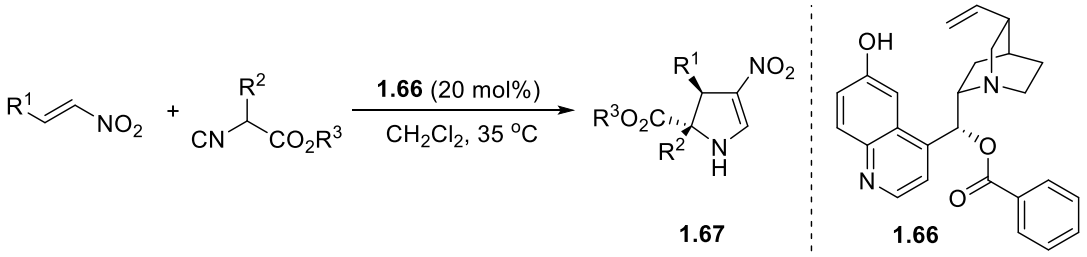
Scheme 1.30 Ag(I)-Catalyzed Asymmetric Cascade Reaction of Activated Isocyanides (Xie, 2016)

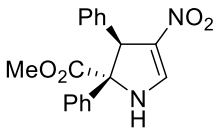


1.4.2.2 Organocatalysis

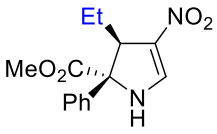
The first organocatalytic asymmetric [3+2] cyclization reaction of isocyanoacetates with nitroolefins was developed by the Gong group in 2008 (Scheme 1.31).[44] Various *cinchona* alkaloid-derived Brønsted bases were evaluated in this reaction and **1.66** was determined to be optimal choice. Under the standard conditions, a number of highly functionalized 2,3-dihydropyrroles were generated with high stereoselectivities. Both aryl- and alkyl-substituted nitroolefins were well tolerated in this system.

Scheme 1.31 Chiral Brønsted Base Catalyzed [3+2] Cycloaddition of Isocyanoacetates with Nitroolefins (Gong, 2008)

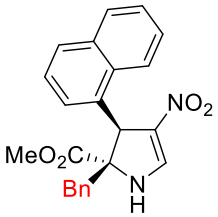




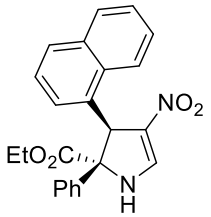
1.67a
68%, 19:1 d.r.
97% ee



1.67b
51%, 10:1 d.r.
97% ee



1.67c
64%, 5:1 d.r.
90% ee

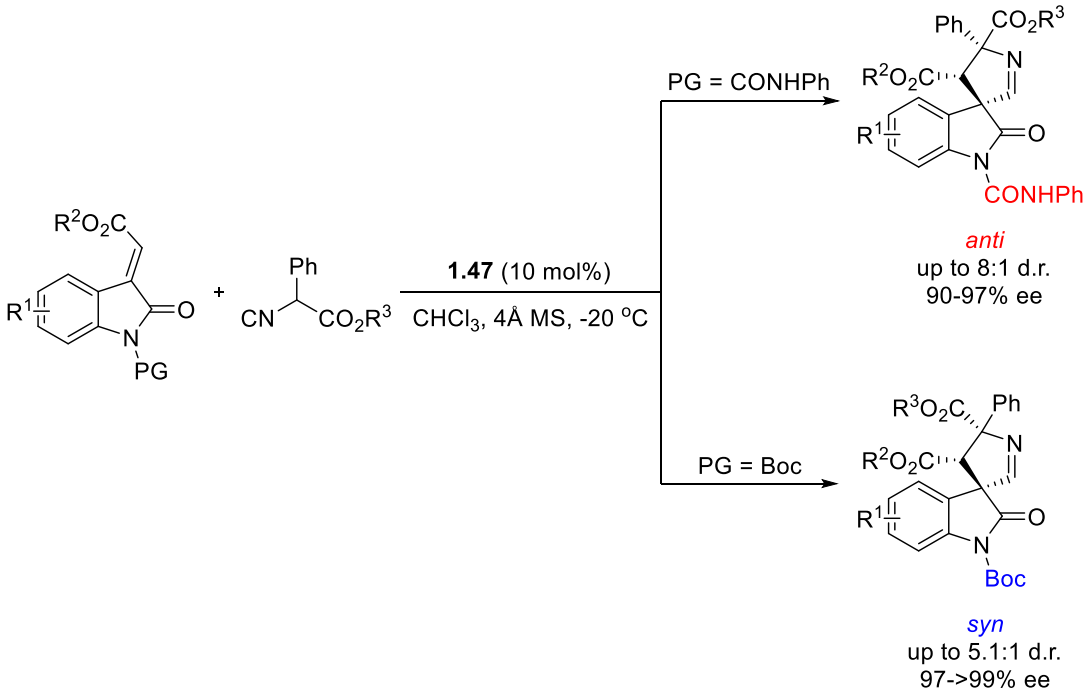


1.67d
85%, 8:1 d.r.
92% ee

Isatin-derived alkenes have also been studied in the [3+2] cycloaddition reactions. In 2012, Xu and co-workers described a stereoselective cyclization reaction of isocyanoacetates with methyleneindolinones by introducing a quinine-derived bifunctional thiourea-tertiary amine catalyst (Scheme 1.32).[45] Various 3,3'-pyrrolidinyl spirooxindoles were obtained in moderate diastereoselectivities with excellent enantioselectivities. Notably, only by changing the protecting groups on the alkene substrates, different diastereomers could be generated. The use of *N*-phenyl amide protected methyleneindolinones resulted in the selective formation of *anti*-diastereomers, whereas *syn*-isomers were generated preferably by employing *N*-*tert*-butoxycarbonyl (*N*-Boc) protected substrates. This method represents a new entry to substrate-induced diastereodivergent reactions. However, the origin of this

selectivity is not clear.

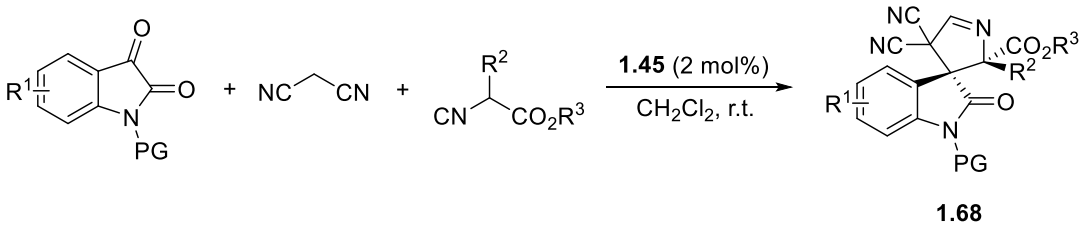
Scheme 1.32 Diastereodivergent Cyclization of Isocyanoacetates with Methyleneindolinones (Xu and Wang, 2012)

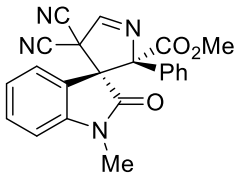


In the same year, an asymmetric three-component reaction of isatins, malononitrile and isocyanoacetates was developed by Yan and co-workers (Scheme 1.33).[46] A variety of enantioenriched 3,3'dihydropyrryl spirooxindoles were obtained. The *N*-protecting group and α-substituent of isocyanoacetates proved to be crucial to the reactivity and stereoselectivity. Except for malononitrile, other analogous nucleophiles such as methyl cyanoacetate, diethyl malonate and ethyl nitroacetate, were also evaluated in this reaction. However, no desired product was observed. This three-component reaction proceeds through the formation of isatylidene malononitrile *via* the Knoevenagel condensation of isatin and malononitrile, followed by [3+2]

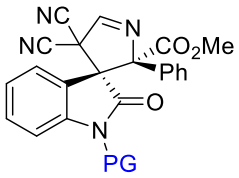
cycloaddition with isocyanoacetates.

Scheme 1.33 Asymmetric Three-Component Reaction of Isatins, Malononitrile and Isocyanoacetates (Yan, 2012)

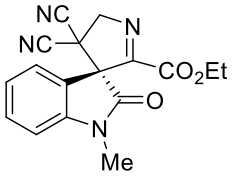




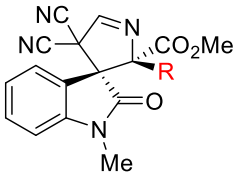
1.68a
92%, 3.5:1 d.r.
97%/94% ee



1.68b
(PG = Ac or Boc)
no reaction



1.68c
80%
11% ee



1.68d
(R = *i*-Pr or Bn)
no reaction

The *in situ* utilization of the imine functionality, generated from formal [3+2] cyclization of isocyanoacetates with activated alkenes, would not only expand the scope of this cycloaddition reaction but also result in the construction of complex structures in a single step manner.

In 2014, the Smith group developed an enantioselective synthesis of pyrroloindolines through a cascade reaction of isocyanoacetates under phase-transfer catalysis (Scheme 1.34).[47] By incorporating an amino group into the alkene substrates, the imine intermediates could be trapped by intramolecular nucleophilic addition to give the tricyclic architectures. Interestingly, when treating with *tetra*-*n*-butyl ammonium bromide (TBAB) and K_2CO_3, pyrroloindoline **1.70** could be

transformed into a spriocyclic scaffold **1.71** without any loss of stereoselectivity. The spirocycle **1.71** was probably formed through ring opening of the indoline ring with subsequent amide formation from the addition of the urea nitrogen to the benzylic ester (Figure 1.4).

Scheme 1.34 Asymmetric Cascade Reaction of Isocyanoacetates under Phase-Transfer Catalysis (Smith, 2014)

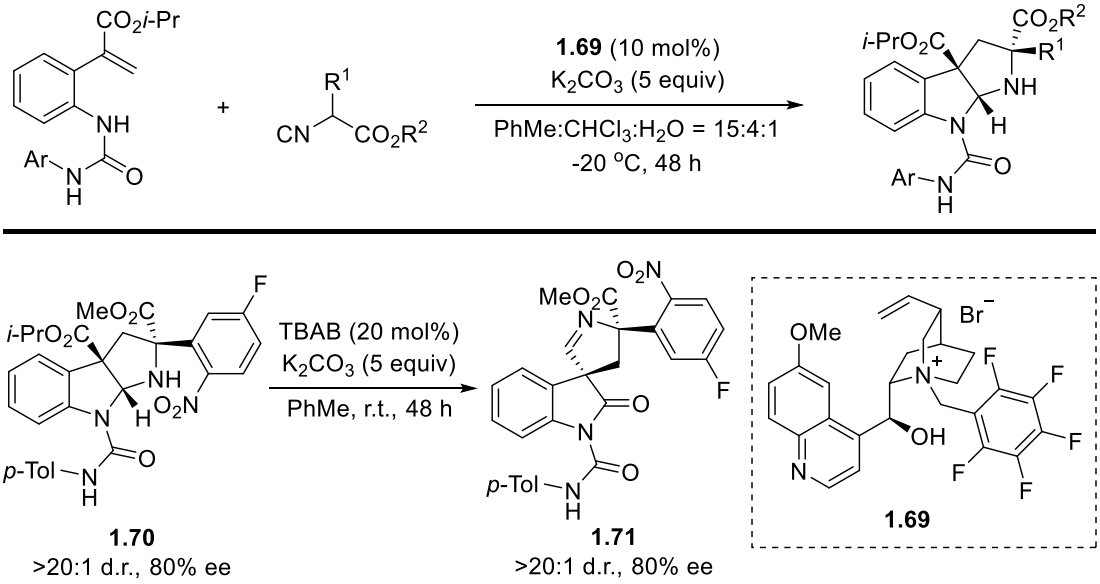
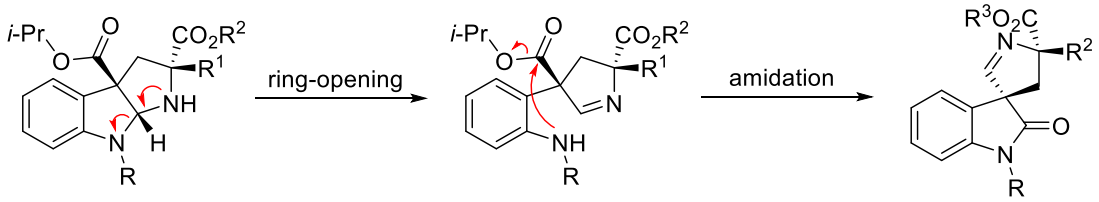


Figure 1.4 Proposed Mechanism for the Formation of Spirocycle



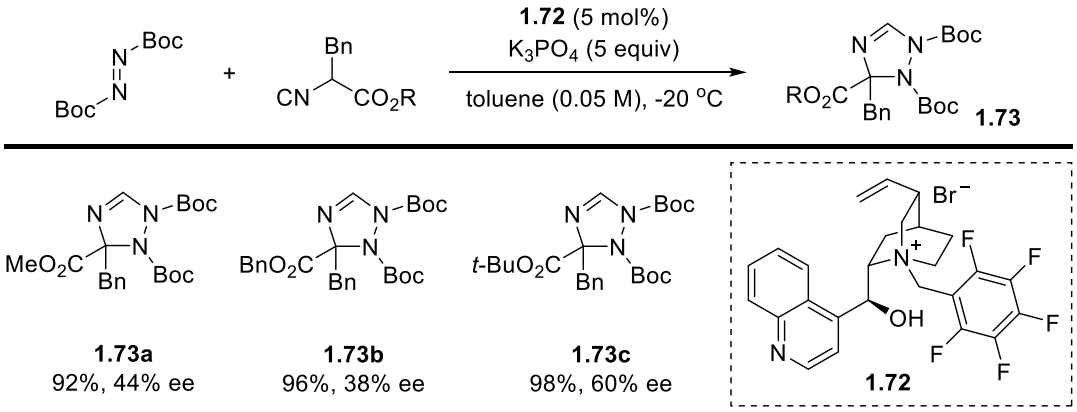
1.5 Reaction with Azodicarboxylates

In addition to carbonyl compounds, imines and activated alkenes,

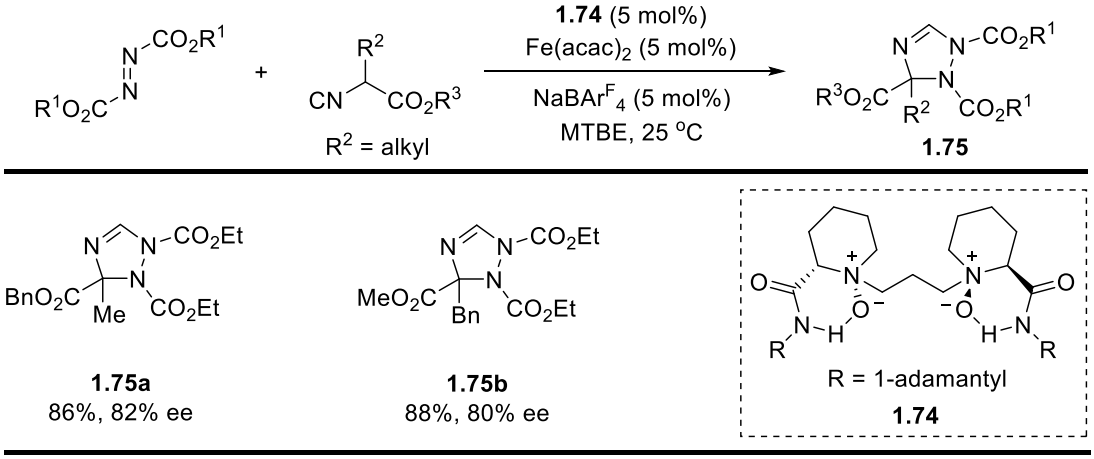
azodicarboxylates have also been investigated in the asymmetric reaction with activated isocyanides, leading to the construction of enantioenriched 1,2,4-triazolines (refer to pathway b, Scheme 1.1).

The pioneer work was reported by Jørgensen and co-workers employing a *cinchonine*-derived phase-transfer catalyst (Scheme 1.35).[48] Excellent yields but moderate enantioselectivities (only up to 60% ee) were obtained.

Scheme 1.35 Asymmetric [3+2] Cyclization of Isocyanoacetates with Azodicarboxylates (Jørgensen, 2011)

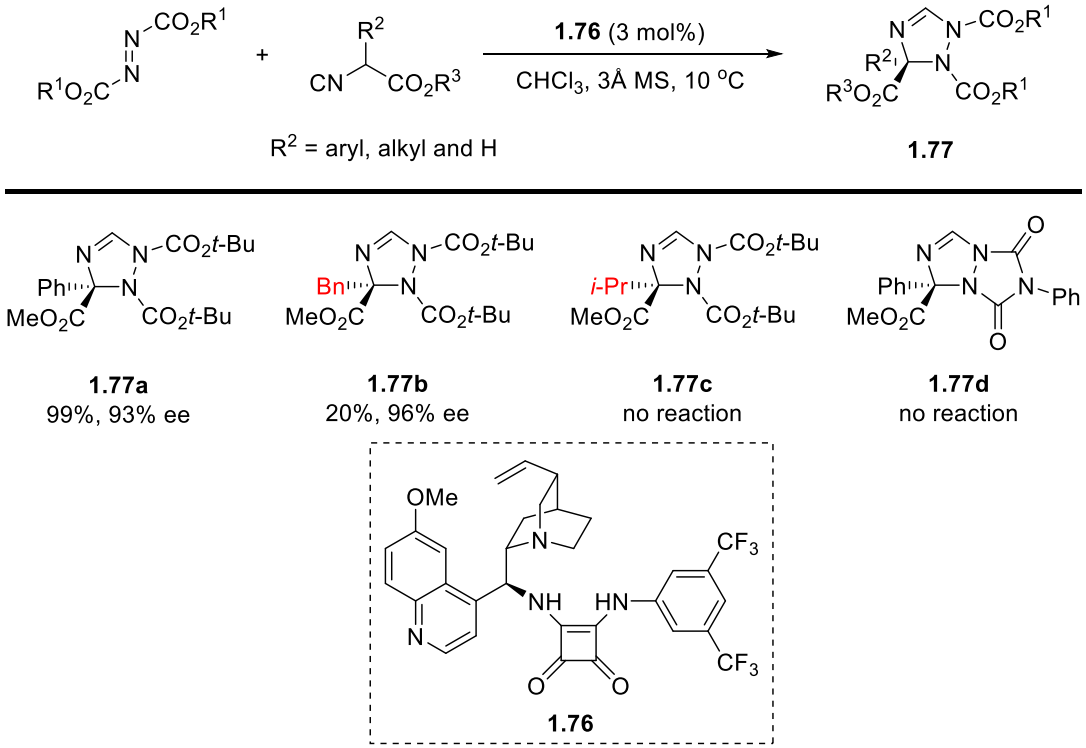


Scheme 1.36 Fe(II)-Catalyzed Enantioselective Synthesis (Liu and Feng, 2013)



A chiral *N,N'*-dioxide/Fe(II) complex was employed to achieve the highly enantioselective synthesis of 1,2,4-triazolines (Scheme 1.36).[49] Various alkyl-substituted isocyanoacetates and azodicarboxylates bearing different esters were examined, affording the corresponding adducts in high yields and enantioselectivities. However, the absolute configuration of the products was not assigned.

Scheme 1.37 Asymmetric Synthesis of 1,2,4-Triazolines (Zhao and Shi, 2013)



Alternatively, this reaction cloud be realized by using a *cinchona* alkaloid-derived squaramide catalyst (Scheme 1.37).[50] In contrast to Liu and Feng's report, the use of alkyl-substituted isocyanoacetates resulted in low yields or no reaction under the standard conditions. Moreover, cyclic substrate was investigated in this reaction, but with no desired product formation.

1.6 Conclusion and Outlook

In summary, in the past few decades, catalytic asymmetric reactions of activated isocyanides have been explored with the development of a number of catalytic systems. Different types of electrophiles, including carbonyl compounds, imines, activated alkenes and azodicarboxylates have been employed, affording a wide range of enantiomerically enriched molecules.

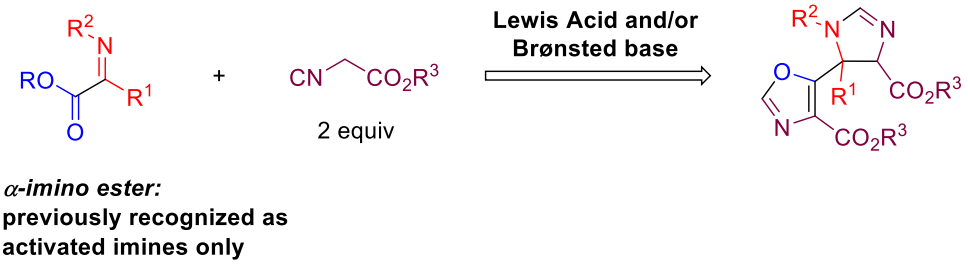
Despite of these great achievements, limitations still remained. For instance, only five-membered ring structures could be accessed through the cyclization reactions. The development of new catalytic system for the stereoselective synthesis of medium ring (such as 6 or 7-membered) skeletons is in high demand. Although multicomponent reactions (MCRs) and cascade reactions have proven to be the most useful strategies for the construction of complex scaffolds, only a few examples of these types[26, 43, 46-47] are presented in this filed. Future studies should focus on the exploration of new reactivities of activated isocyanides in order to address these limitations. Additionally, the application of these existing methods in the synthesis of natural products or bioactive complex molecules should be considered.

Chapter 2 Highly Diastereo- and Enantioselective Ag-Catalyzed Double [3+2] Cyclization of α-Imino Esters with Isocyanoacetate

2.1 Introduction

The generation of complexity and diversity in molecular structure in an efficient and economical fashion is an important goal in organic synthesis and chemical biology,[51] for which cascade reactions[52] and multicomponent reactions (MCRs)[53] have proven to be the most powerful approaches. Along these lines, isocyanoacetates (as functionalized isocyanides)[2, 54] have found wide application not only in classical Passerini and Ugi type MCRs, but also proven to be a versatile functionality to react with various electrophiles, such as carbonyls,[3, 8, 10-11, 18-19] imines,[21, 27-28, 55] α,β-unsaturated carbonyls,[31, 39-40, 44] activated alkenes/alkynes,[56] *etc*. to deliver a wide range of nitrogen heterocycles. The combination of these reactions with further functionalization of the products in a tandem fashion has also been thoroughly studied, in particular by the Zhu Group to produce more complex scaffolds.[57]

Scheme 2.1 Double Cyclization with Both Imine and Ester Functionalities



α-imino ester:
previously recognized as activated imines only

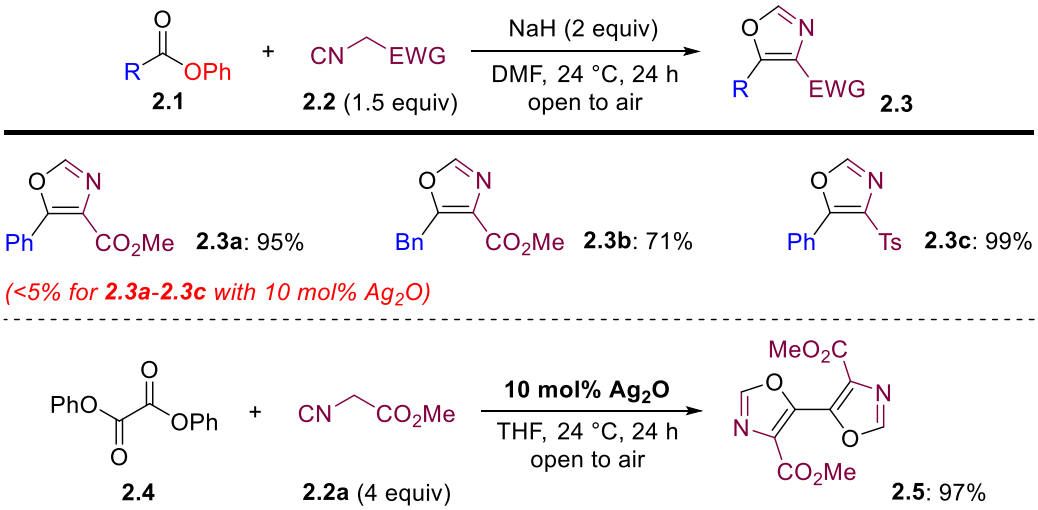
We present here a conceptually different complexity-generating method, *i.e.*, both functionalities in α-imino esters (previsouly recognized as activated imines only) undergo cyclization with isocyanoacetate to give directly linked oxazole-imidazolines[58] under silver catalysis (Scheme 2.1). The asymmetric variant

has also been developed by employing Dixon-type catalyst[11] to produce these compounds in high diastereo- and enantiopurity, which can be further converted to other valuable, highly functionalized entities.

2.2 Project Design

Our attention was drawn to this possibility of double cyclization during our initial attempts of oxazole formation from the reaction between isocyanoacetates and esters, which should be more functional group tolerant and easier to handle than the use of strong acylating reagents such as acid chlorides (Scheme 2.2).[2] Such a combination, however, was known to fail to react even under harsh conditions, due to the low reactivity of the enolate derived from isocyanoacetate towards ester.[59] We argued that the use of aryl esters could be beneficial, as the better leaving group of aryloxide (compared with simple alkoxide from alkyl esters) should facilitate the addition of the enolate to the ester.

Scheme 2.2 Oxazole Formation from Aryl Esters



Indeed, this led to the efficient synthesis of oxazole from different aryl esters **2.1** and activated isocyanides **2.2** (methyl isocyanoacetate or toluenesulfonylmethyl isocyanide) by the use of stoichiometric strong base (71-99% yield for **2.3a**-**2.3c** with the use of 2 equiv of NaH). For oxalate **2.4**, interestingly, the bis-oxazole **2.5** could be generated with excellent yield by using a much milder Ag-catalyzed procedure, which, on the other side, failed to yield **2.3a**-**2.3c** at all. Clearly there is a synergetic effect between the ester functionalities in **2.4**, which led us to consider substrates bearing different functionalities that could mutually activate each other for the reaction with isocyanoacetate to give complex molecules.

2.3 Results and Discussion

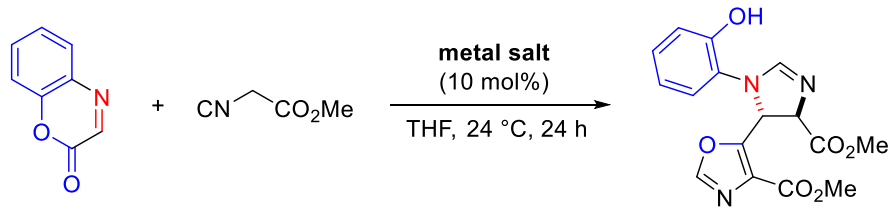
2.3.1 Optimization of Reaction Conditions

To demonstrate this idea, the readily available cyclic α-imino ester **2.6a** was chosen as the model substrate due to its unique α-imino aryl ester structure.[60] Notably, the proposed double cyclization with both imine and aryl ester moieties with isocyanoacetate will be entirely atom-economical as the product incorporates all portions from the starting materials. It is also worth noting that the reaction of isocyanoacetates (or isocyanoacetamides) with imines is known to follow divergent pathways to produce either imidazoline[21, 27-28, 55d] or oxazole (initiated by isocyanide addition to activated imines).[55a-c] These factors, combined with the reaction at the aryl ester functionality, could in principle lead to a complex mixture.

As shown in Table 2.1, a variety of metal salts of different levels of basicity or

Lewis acidity was evaluated for the reaction of **2.6a** and **2.2a** at ambient temperature. Gratifyingly, the desired double [3+2] cyclization product **2.7a** could be obtained cleanly (>20:1 d.r.) when Cu and Ag salts possessing strong basicity were used, with Ag_2O and Ag_2CO_3 being the optimal choices (99% yield). In contrast, other Zn or Au salts and even strong Lewis acids such as $BF_3{\cdot}OEt_2$ or $Sc(OTf)_3$ failed to promote the reaction. This led us to speculate that this may be a base-catalyzed process, in which the Mannich reactivity of **2.2a** predominates to yield imidazoline with concomitant oxazole formation from reaction with the aryl ester moiety.

Table 2.1 Metal Salt Screening for Double [3+2] Cyclization of **2.6a** and **2.2a**[a-b]

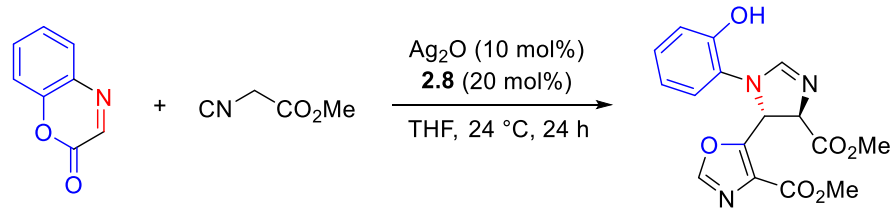


2.6a **2.2a** (2 equiv) *rac*-**2.7a**

entry	metal salt	yield (%)[b]	entry	metal salt	yield (%)[b]
1	Cu_2O	72	**7**	**Ag_2O**	**99**
2	$Cu(OAc)_2$	40	**8**	**Ag_2CO_3**	**99**
3	$CuCl_2$	<2	9	$AgBF_4$	<2
4	$ZnCl_2$	<2	10	AgOTf	<2
5	$AuCl_3$	<2	11	$BF_3{\cdot}OEt_2$	<2
6	AgOAc	90	12	$Sc(OTf)_3$	<2

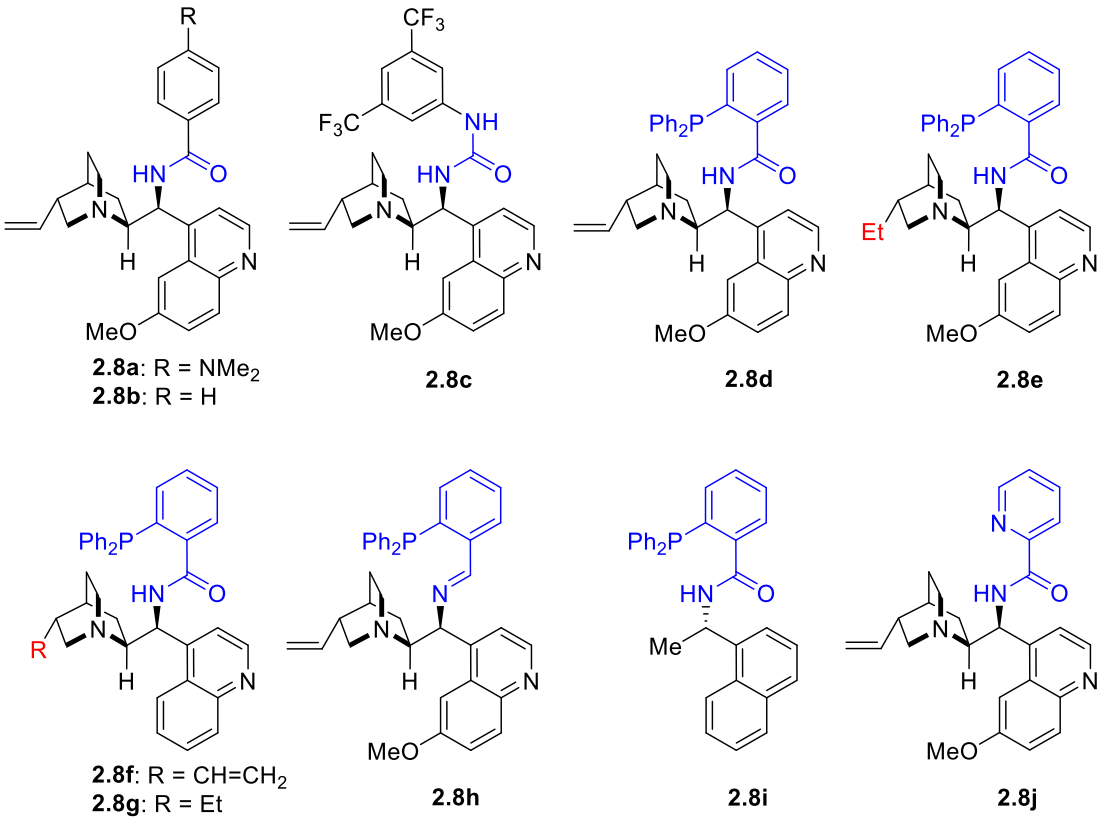
[a] The reactions were carried out in air at ambient temperature for 24 h. [b] Isolated yields.

Table 2.2 Ligand Screening for Enantioselective Double [3+2] Cyclization[a-c]



2.6a **2.2a** (2 equiv) **2.7a**

entry	**2.8**	yield (%)[b]	ee (%)[c]	entry	**2.8**	yield (%)[b]	ee (%)[c]
1	**2.8a**	95	<2	6	**2.8f**	99	72
2	**2.8b**	98	<2	7	**2.8g**	99	58
3	**2.8c**	67	<2	8	**2.8h**	95	14
4	**2.8d**	**99**	**81**	9	**2.8i**	95	-3
5	**2.8e**	99	79	10	**2.8j**	99	<2



[a] Carried out in air for 24 h. [b] Isolated yields. [c] Determined by HPLC analysis.

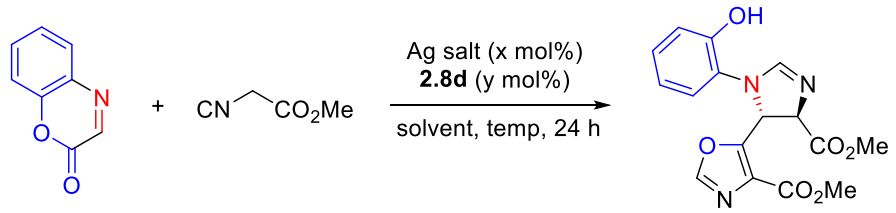
With an efficient reaction in hand, we turned our attention to the development of an asymmetric variant by evaluating Cu or Ag complexes supported by various chiral ligands. After extensive experimentation, Ag_2O turned out to be the most promising choice of metal salt, the screening data of which with different chiral ligands is summarized in Table 2.2. Initially we focused on simple quinine amides we recently disclosed for silicon activation and Cu catalysis,[61] which, to our disappointment, led to no asymmetric induction at all (entries 1-3).

Inspired by the recent report from the Dixon group on enantioselective isocyanoacetate aldol reaction catalyzed by Ag complex with a new family of *cinchona*-derived amino phosphine ligands,[11, 23] we tested the related **2.8d**-**2.8g** for our reaction. The use of quinine-derived phosphine **2.8d** with Ag_2O gratifyingly yielded **2.7a** with a good ee of 81% (entry 4). Modification on the structure of **2.8d** as reported by the Dixon group (reduction to **2.8e** or use of *cinchonidine*-derived **2.8f**-**2.8g**)[11] unfortunately all led to lower ee (entries 5-7). The structurally related imine **2.8h** was also tested, which proved to be much less selective (entry 8). The simple chiral phosphine-containing amide **2.8i** was not enantioselective at all, implying the importance of quinuclidine moiety for the asymmetric induction in addition to the phosphine amide moiety (entry 9). Finally, the use of pyridyl-containing **2.8j**[62]yielded racemic product (entry 10).

Further optimization of reaction conditions was carried out (Table 2.3). With the optimal ligand identified, the use of Ag_2CO_3 instead of Ag_2O resulted in a lower 67% ee (entry 1). Various solvents were examined next (entries 2-6) and THF was proved

to be the optimal choice. To our delight, lowering the reaction temperature led to a dramatic increase in the enantioselectivity. When the reaction was carried out at -20 ^{o}C, **2.7a** was obtained in excellent 99% yield with 98% ee (entry 8). Decreased catalyst loading of 5 mol% Ag_2O with 10 mol% **2.8d** yielded **2.7a** in high 97% yield but with a lower ee of 90% (entry 9).

Table 2.3 Further Optimization of Reaction Conditions[a-d]



2.6a **2.2a** (2 equiv) **2.7a**

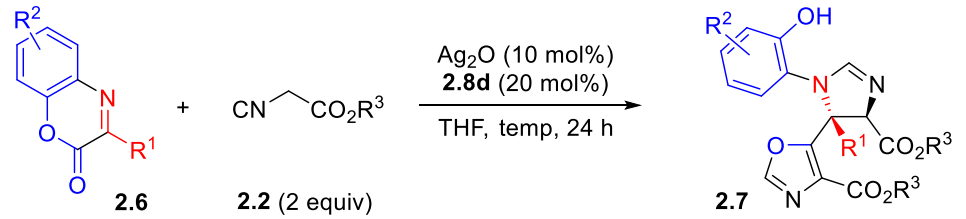
entry	Ag salt (x)	**2.8d** (y)	solvent	temp (^{o}C)	yield (%)[b]	ee (%)[c]
1	Ag_2CO_3 (10)	20	THF	24	96	67
2	Ag_2O (10)	20	EtOAc	24	85	73
3	Ag_2O (10)	20	TBME	24	<2	n.d.[d]
4	Ag_2O (10)	20	Et_2O	24	<2	n.d.[d]
5	Ag_2O (10)	20	CH_2Cl_2	24	65	75
6	Ag_2O (10)	20	toluene	24	<5	n.d.[d]
7	Ag_2O (10)	20	THF	0	98	83
8	**Ag_2O (10)**	**20**	**THF**	**-20**	**99**	**98**
9	Ag_2O (5)	10	THF	-20	97	90

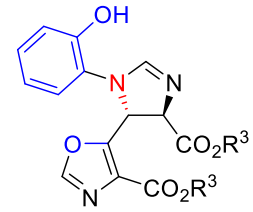
[a] Carried out in air for 24 h. [b] Isolated yields. [c] Determined by HPLC analysis. [d] n.d. = not determined.

2.3.2 Substrate Scope

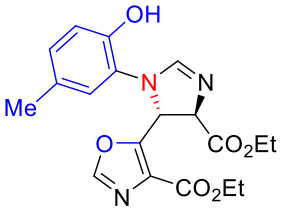
With the optimal reaction conditions in hand, the substrate scope of this system was studied next (Scheme 2.3). It is worth noting that in almost all cases perfect diastereoselectivity was obtained for product **2.7** with an *anti*-diamine moiety.

Scheme 2.3 Scope for Enantioselective Double [3+2] Cyclization of **2.6** and **2.2**[a-d]

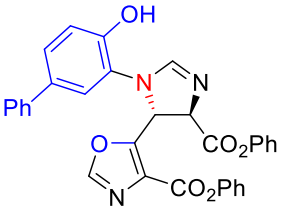




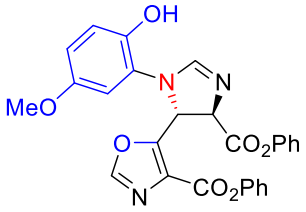
2.7a (R^3 = Me): 99%, 98% ee
2.7b (R^3 = Et): 89%, 97% ee
2.7c (R^3 = *i*-Pr): 95%, 92% ee[b]
2.7d (R^3 = *t*-Bu): 85%, 91% ee[c]
2.7e (R^3 = Ph): 86%, 99% ee[c]



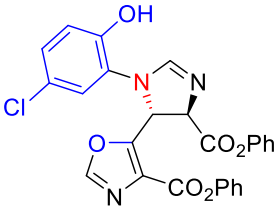
2.7f: 87%, 94% ee



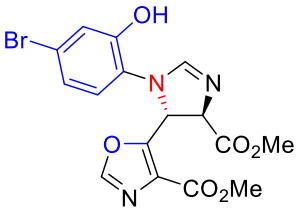
2.7g: 68%, 95% ee[c]



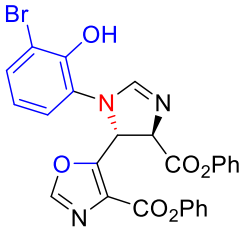
2.7h: 61%, 94% ee[d]



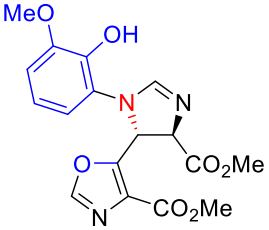
2.7i: 94%, 91% ee[d]



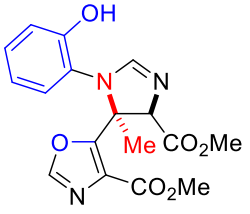
2.7j: 61%, 99% ee[c]



2.7k: 76%, 95% ee[d]



2.7l: 90%, 99% ee



2.7m: 69%, 37% ee[b]

[a] -20 °C. [b] 24 °C. [c] -20 °C for 12 h, then 0 °C for 12 h. [d] 0 °C.

As shown, isocyanoacetates bearing different ester groups were all suitable substrates to produce **2.7a**-**2.7e** in uniformly high yields and excellent ee (91-99%). Different substitution patterns on the aryl ring (*para*-, *meta*- and *ortho*-) could be well-tolerated to form highly functionalized imidazolines with different phenol units with excellent enantioselectivity (**2.7f**-**2.7l**). Ketimines turned out to be difficult substrates for the double cyclization. A mixture of mono [3+2] cycloaddition product (with imine) and the desired product **2.7m** was obtained for methyl substituted ketimine. Surprisingly a different *syn*-diastereomer was formed, with a lower ee of 37%.

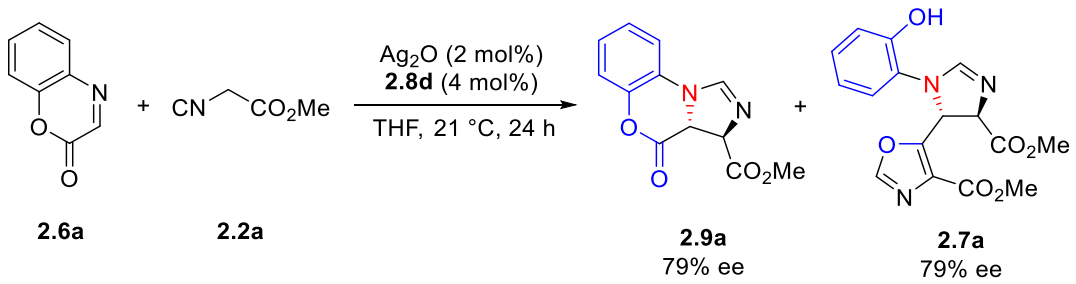
It is noteworthy that the current catalytic system is simple to perform with catalysts that can be easily prepared from inexpensive starting materials. The reactions were set up open to air with no need for exclusion of air or moisture. The level of diastereo- and enantioselectivity compares favorably with previously reported Mannich reaction of isocyanoacetate with imines,[27-28, 55d] with the additional advantage of complexity generation from concomitant imidazoline and oxazole formation.

2.3.3 Mechanistic Study

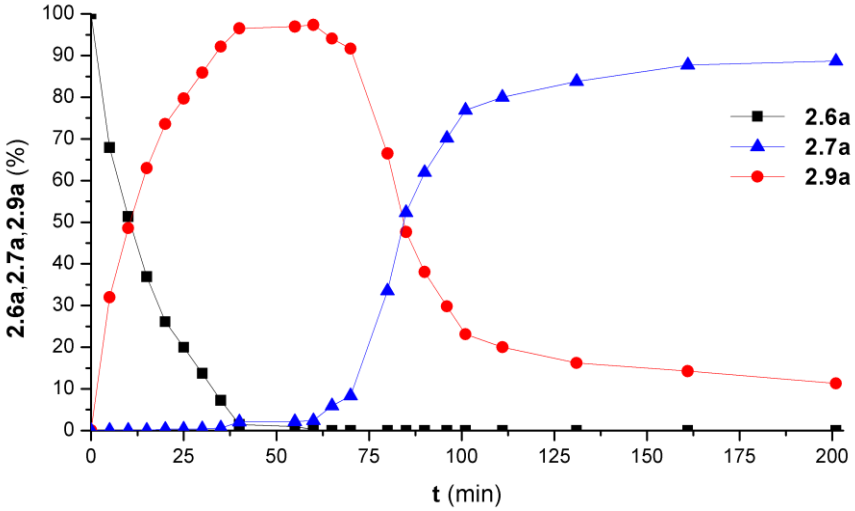
In an effort to better understand the mechanism of the system, the kinetics of the reaction between **2.6a** and **2.2a** was monitored by NMR (Scheme 2.4). With a lower catalyst loading and in turn decreased reaction rate, the two cyclization reactions were identified to be stepwise. Strikingly, an essentially full conversion of **2.6a** to mono

cyclization product **2.9a** was observed within 60 min at 21 °C before the formation of **2.7a** started to expedite. As expected, the enantioselectivity was determined at the first step; **2.9a** and **2.7a** were obtained with the same 79% ee.

Scheme 2.4 NMR Studies Revealed a Stepwise Reaction Profile



2.6a **2.2a** **2.9a** 79% ee **2.7a** 79% ee



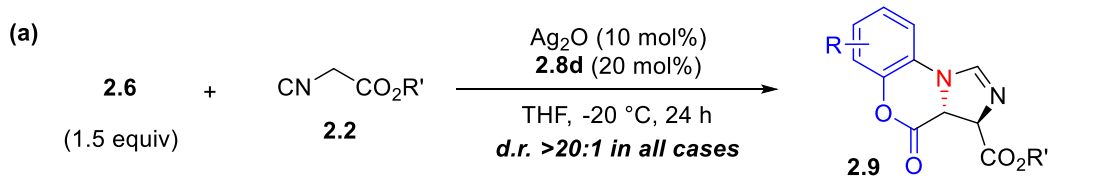
2.3.4 Isolation of Mono [3+2] Cyclization Products and Three-Component Reactions

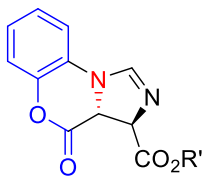
While the nature of this stepwise reaction profile necessitates further investigation, it provided more possibilities for our methodology to produce structurally different compounds.

As shown in Scheme 2.5 (part a), the mono [3+2] cyclization products **2.9a-g**

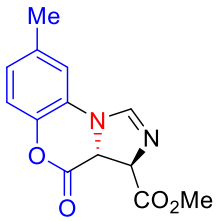
could be isolated in high yield with good to excellent ee when the reaction was carried out at -20 °C with **2.2** as the limiting reagent. Alternatively, a three-component reaction of two different isocyanoacetates with **2.6a** could also be realized (part b); **2.2e** and **2.2a** were added sequentially to yield **2.7n** in 67% yield with 97% ee. In addition, the use of disubstituted isocyanoacetates such as **2.2f** could lead to a smooth [3+2] cycloaddition with **2.6a**, which was followed by the cyclization of **2.2a** with the ester unit in the intermediate to yield **2.7o** with 73% yield and a slightly lower ee of 71%. X-ray analysis of **2.7o** further confirmed the directly linked oxazole-imidazoline structure of the products.

Scheme 2.5 Isolation of Intermediates or Three-Component Reactions

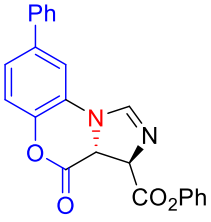




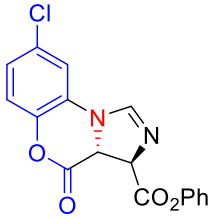
2.9a (R' = Me): 84%, 97% ee
2.9b (R' = Ph): 92%, 99% ee



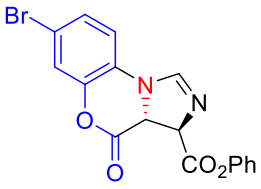
2.9c
92%, 97% ee



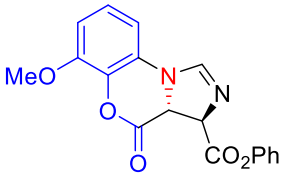
2.9d
86%, 93% ee



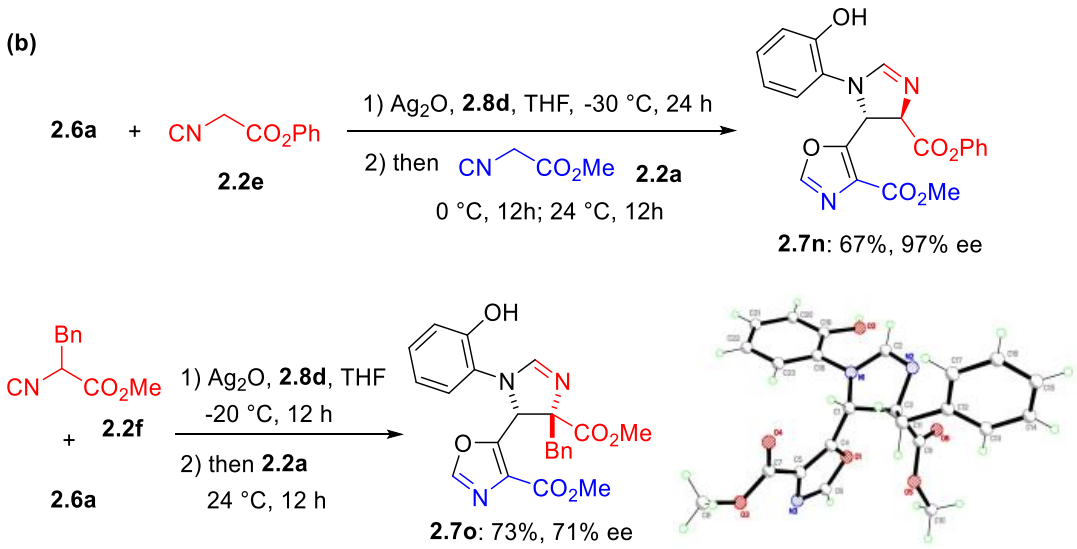
2.9e
90%, 95% ee



2.9f
84%, 96% ee

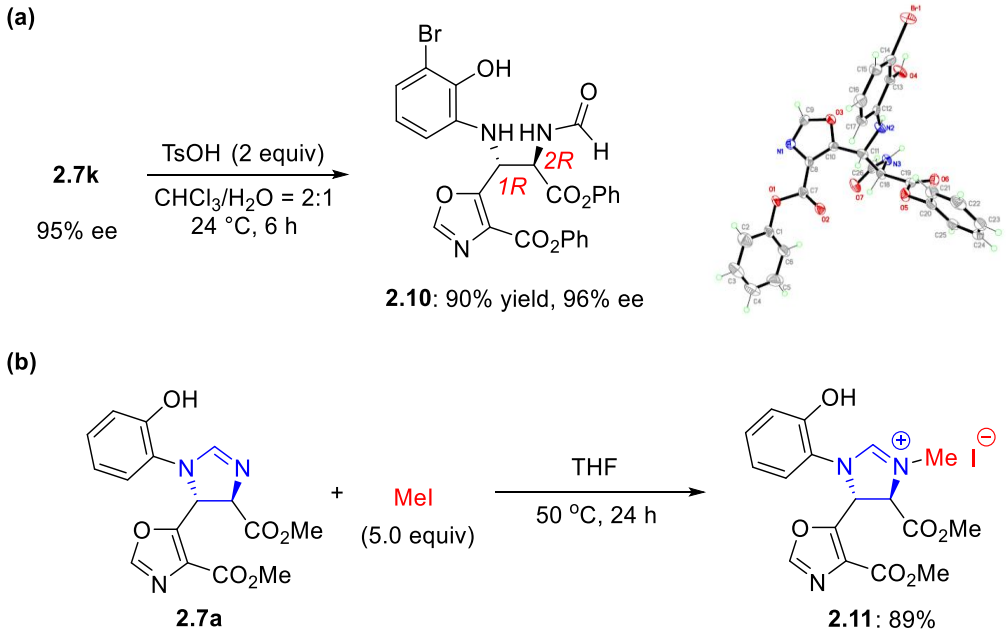


2.9g
85%, 96% ee



2.3.5 Derivatization

Scheme 2.6 Derivatization of **2.7** to α,β-Diamino Esters and Imidazolinium Salt



The products of this reaction can be easily transformed into useful entities in asymmetric catalysis. The imidazoline moiety could be readily hydrolyzed under

acidic conditions to yield highly functionalized α,β-diamino esters such as **2.10** in high yield without any loss of stereoselectivity (part a, Scheme 2.6), X-ray analysis of which confirmed the relative and absolute configuration of products **2.7**. Formamide **2.10** has been identified to be highly efficient Lewis base catalyst for the addition of allyltrichlorosilane to aliphatic aldehydes, a process that was seriously hampered in most previous systems due to chloride addition to aldehyde.[61a] Systematic optimization is ongoing with compounds **2.7a**-**m** and related analogs, the results of which will be reported in due course.

Alternatively, **2.7a** was converted to the imidazolinium salt **2.11** in high yield upon treatment with alkylating reagent such as methyl iodide (part b, Scheme 2.6). The application of related compounds as bidentate NHC-phenoxide ligand in enantioselective catalysis has been beautifully demonstrated by the Hoveyda group.[63] The unique structure bearing multiple functionalities in our products may provide new opportunities in asymmetric catalysis.

2.4 Conclusion

In summary, we reported for the first time that aryl esters could react with isocyanoacetates to yield oxazoles. Based on this discovery, we have developed a novel complexity-generating method, in which both functionalities of α-imino esters undergo stereoselective [3+2] cyclization with isocyanoacetates to produce directly linked oxazole-imidazolines and in turn highly functionalized α,β-diamino esters and imidazolinium salts in high diastereo- and enantiopurity.

2.5 Experimental Section

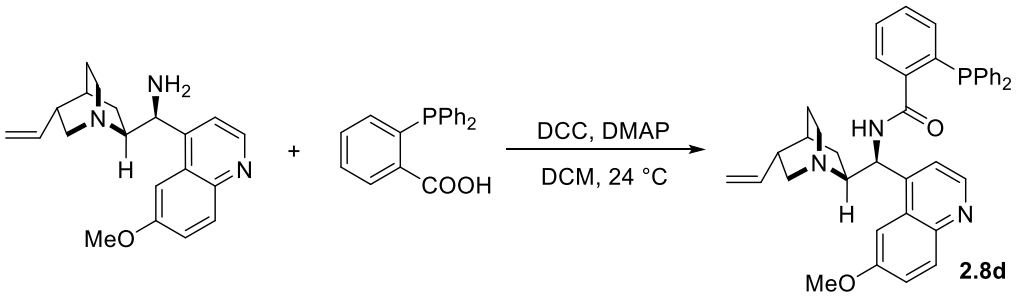
2.5.1 General Information

^{1}H and **^{13}C NMR** spectra were recorded on a Bruker AFC 300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: ^{1}H (chloroform δ 7.26; DMSO δ 2.50), ^{13}C (chloroform δ 77.0; DMSO δ 39.5). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz) and integration. Melting point (**MP**) was obtained on Buchi B-540. For thin layer chromatography (**TLC**), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. High resolution mass spectra (**HRMS**) were obtained on a Finnigan/MAT 95XL-T spectrometer. **Optical rotations** were recorded on an mrc AP81 automatic polarimeter. Enantiomeric excesses (**ee**) were determined by HPLC analysis on Agilent HPLC units, including the following instruments: pump, LC-20AD; detector, SPD-20A; column, Chiralcel OD-H, Chiralpak AD-H, AS-H and IE.

Unless otherwise noted, all the reactions were carried out in air. Dichloromethane, diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were dried over a Pure Solv solvent purification system. Deuterated solvents were purchased from Cambridge Isotope Laboratories and used as received without further purification. Methyl isocyanoacetate (**2.2a**) and ethyl isocyanoacetate (**2.2b**) were purchased from Alfa Aesar company. *tert*-Butyl isocyanoacetate (**2.2d**)[64] and methyl 2-isocyano-3-

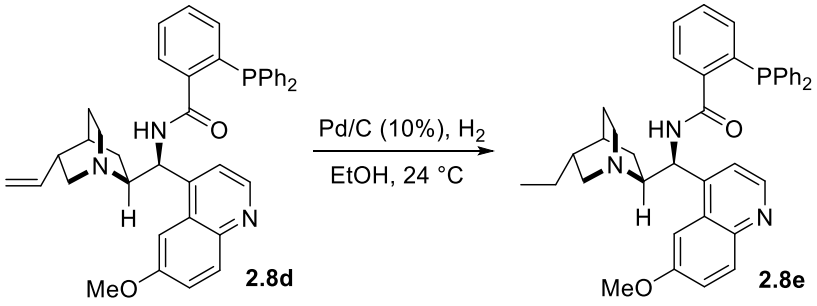
phenylpropanoate (**2.2f**)[65] were prepared by literature procedures. Other chemicals were purchased from commercial suppliers and used as received without further purification.

2.5.2 Synthesis of Ligand



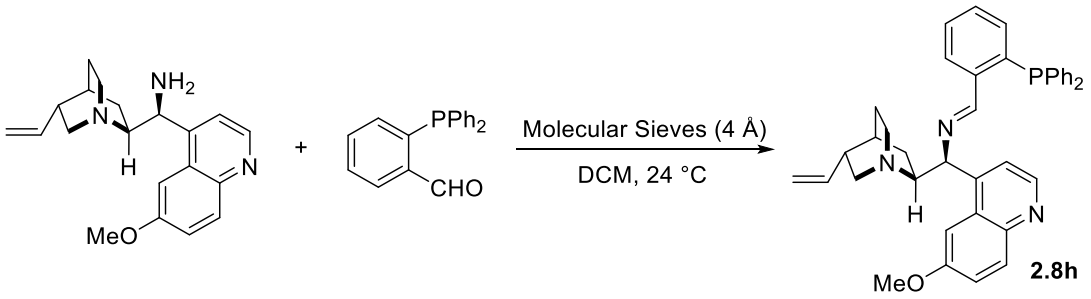
To the solution of 9-amino(9-deoxy) *epi*-quinine (2.00 g, 6.19 mmol) in anhydrous CH_2Cl_2 (100 mL) was added 2-(diphenylphosphino)benzoic acid (2.10 g, 6.81 mmol), 4-dimethylaminopyridine (151 mg, 1.20 mmol) and *N*,*N'*-dicyclohexyl-carbodiimide (1.40 g, 6.81 mmol). The reaction mixture was stirred at ambient temperature for 24 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate 1:3) to yield 3.4 g (90%) of **2.8d** as a white solid. **Optical Rotation**: $[\alpha]_D^{25}$ = -7.2 (c 0.3, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.65 (d, *J* = 4.4 Hz, 1H), 8.02 (d, *J* = 9.5 Hz, 1H), 7.75 (s, 1H), 7.68-7.66 (m, 1H), 7.38-7.32 (m, 3H), 7.29-7.24 (m, 9H), 7.19-7.16 (m, 4H), 6.94-6.92 (m, 1H), 5.76-5.69 (m, 1H), 5.51 (br s, 1H), 4.99-4.95 (m, 2H), 3.96 (s, 3H), 3.17-3.12 (m, 2H), 3.04 (br s, 1H), 2.67-2.56 (m, 2H), 2.27-2.23 (m, 1H), 1.64-1.63 (m, 1H), 1.60-1.54 (m, 1H), 1.46-1.42 (m, 1H), 0.92-0.89 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) (C-P coupling not removed): δ 168.6, 157.5, 147.3, 144.5, 141.3, 141.2, 141.1, 137.1, 137.0, 136.8,

136.7, 135.4, 135.3, 134.0, 133.5, 133.4, 133.4, 133.3, 131.3, 129.9, 128.5, 128.5, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 121.4, 114.2, 102.1, 55.7, 55.5, 40.8, 39.3, 27.7, 27.2, 26.0; **^{31}P NMR** (202 MHz, $CDCl_3$): δ -10.2; **MP**: 172-173 °C; **HRMS** (ESI): m/z calcd. for $[C_{39}H_{39}N_3O_2P, M+H]^+$: 612.2774; found: 612.2801.



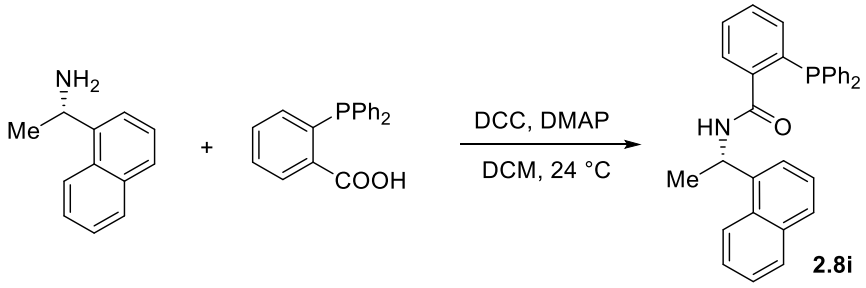
To the solution of **2.8d** (0.60 g, 0.98 mmol) in EtOH (30 mL) was added 10% Pd/C (60 mg). The reaction mixture was stirred under a hydrogen atmosphere for 12 h at ambient temperature, and then filtered through celite washing with EtOH (3×20 mL). The filtrate was concentrated and purified by flash chromatography (hexanes/ethyl acetate 1:3) to yield 540 mg (90%) of **2.8e** as a white solid. **Optical Rotation**: $[\alpha]_D^{25}$ = -13.9 (c 0.3, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.66 (d, *J* = 4.5 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 2.5 Hz, 1H), 7.67-7.65 (m, 1H), 7.40-7.36 (m, 2H), 7.32-7.25 (m, 10H), 7.22-7.15 (m, 4H), 6.95-6.92 (m, 1H), 5.43 (br s, 1H), 3.99 (s, 3H), 3.14-3.09 (m, 2H), 2.96 (br s, 1H), 2.63-2.58 (m, 1H), 2.27-2.24 (m, 1H), 1.63-1.57 (m, 2H), 1.51-1.46 (m, 1H), 1.42-1.39 (m, 1H), 1.37-1.32 (m, 1H), 1.26-1.20 (m, 2H), 0.92-0.88 (m, 1H), 0.82 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) (C-P coupling not removed): δ 168.8, 157.6, 147.4, 144.6, 141.6, 141.3, 137.3, 137.2, 136.9, 136.8, 135.5, 135.4, 134.1, 133.7, 133.6, 133.5,

133.4, 131.4, 130.0, 128.6, 128.6, 128.4, 128.4, 128.3, 128.3, 128.2, 121.4, 102.2, 57.5, 55.6, 41.0, 37.2, 28.5, 27.3, 25.9, 25.1, 11.9; **^{31}P NMR** (202 MHz, $CDCl_3$): δ -10.3; **MP**: 111-112 °C; **HRMS** (ESI): calcd. for $[C_{39}H_{41}N_3O_2P, M+H]^+$: 614.2931; found: 614.2954.



To the solution of 9-amino(9-deoxy) *epi*-quinine (323 mg, 1.00 mmol) in anhydrous CH_2Cl_2 (50 mL) were added 2-(diphenylphosphino)benzaldehyde (290 mg, 1.00 mmol) and molecular sieves (4 Å) (1.00 g). The reaction mixture was stirred at ambient temperature for 24 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate 1:1) to yield 488 mg (82%) of **2.8h** as a pale yellow solid. **Optical Rotation**: $[\alpha]_D^{25}$ = -23.2 (c 0.3, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.04 (d, *J* = 5.7 Hz, 1H), 8.70 (d, *J* = 4.4 Hz, 1H), 8.12-8.10 (m, 1H), 8.04 (d, *J* = 9.5 Hz, 1H), 7.76 (s, 1H), 7.43-7.34 (m, 6H), 7.30-7.25 (m, 3H), 7.21-7.21 (m, 5H), 6.85-6.83 (m, 1H), 5.80-5.73 (m, 1H), 5.00-4.94 (m, 2H), 4.82 (d, *J* = 9.5 Hz, 1H), 4.02 (s, 3H), 3.53-3.48 (m, 1H), 3.11-3.06 (m, 1H), 2.98-2.92 (m, 1H), 2.68-2.64 (m, 1H), 2.47-2.42 (m, 1H), 2.23-2.18 (m, 1H), 1.61-1.59 (m, 1H), 1.49-1.46 (m, 2H), 1.37-1.32 (m, 1H), 0.84-0.80 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) (C-P coupling not removed): δ 159.9, 159.7, 157.4, 147.6, 145.4, 144.8, 141.9, 139.2, 139.1, 137.3,

137.2, 136.4, 136.3, 136.2, 134.1, 134.0, 133.9, 133.7, 133.1, 131.6, 130.4, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.0, 128.0, 127.9, 121.4, 121.2, 114.1, 102.5, 60.1, 56.3, 55.6, 40.5, 39.8, 28.2, 27.9, 25.8; **^{31}P NMR** (202 MHz, $CDCl_3$): δ -13.1; **MP**: 71-73 °C; **HRMS** (ESI): calcd. for $[C_{39}H_{39}N_3OP, M+H]^+$: 569.2825; found: 569.2842.



2.8i

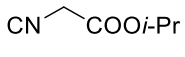
To the solution of (*S*)-1-(naphthalen-1-yl)ethanamine (342 mg, 2.00 mmol) in anhydrous CH_2Cl_2 (10 mL) were added 2-(diphenylphosphino)benzoic acid (765 mg, 2.50 mmol), 4-dimethylaminopyridine (24.4 mg, 0.20 mmol) and *N*,*N*'-dicyclohexyl-carbodiimide (618 mg, 3.00 mmol). The reaction mixture was stirred at ambient temperature for 12 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate 4:1) to yield 910 mg (99%) of **2.8i** as a white solid. **Optical Rotation**: $[\alpha]_D^{25}$ = + 43.7 (c 0.3, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.59-7.56 (m, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.38-7.29 (m, 11H), 7.25-7.21 (m, 2H), 6.97-6.95 (m, 1H), 6.26 (d, *J* = 7.6 Hz, 1H), 6.08-6.02 (m, 1H), 1.60 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) (C-P coupling not removed): δ 167.9, 141.7, 141.5, 138.0, 137.1, 137.0, 136.7, 136.6, 135.6, 135.4, 134.1, 133.9, 133.8, 133.8, 133.7, 131.1, 130.1, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.5, 128.2, 128.0,

127.9, 126.5, 125.8, 125.1, 123.7, 122.6, 45.3, 20.4; **^{31}P NMR** (202 MHz, $CDCl_3$): δ -10.2; **MP**: 73-75 °C; **HRMS** (ESI), m/z calcd. for [$C_{31}H_{27}NO$, M+H]$^+$: 460.1825; found: 460.1839.

2.5.3 Synthesis of Isocyanoacetate 2.2

2.2c and **2.2e** were synthesized according to the procedure reported by Zhu.[66]

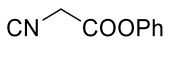
Isopropyl isocyanoacetate (2.2c, known compound[67]**)**



2.2c

Pale yellow oil, 67% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.13-5.06 (m, 1H), 4.17 (s, 2H), 1.28 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 163.3, 160.9, 70.9, 43.7, 21.5.

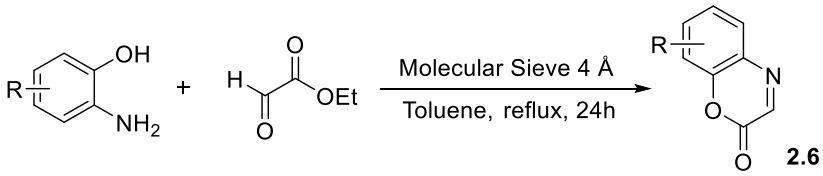
Phenyl isocyanoacetate (2.2e)



2.2e

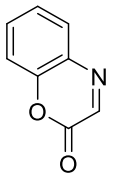
Brown wax, 49% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (t, *J* = 8.2 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.15-7.13 (m, 2H), 4.47 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 162.5, 162.0, 149.9, 129.6, 126.6, 120.9, 43.5. **HRMS** (EI), m/z calcd. for [$C_9H_7NO_2$, M]: 161.0477; found: 161.0476.

2.5.4 Synthesis of α-Imino Esters 2.6



General Procedure. The mixture of *o*-aminophenol (15 mmol), ethyl glyoxalate (6.0 mL, 30 mmol) and 4 Å MS (4 g) in toluene (100 mL) was refluxed for 24 h, and filtered through Celite washing with ethyl acetate. The filtrate was concentrated, purified by flash chromatography (hexanes/ethyl acetate 10:1) to afford **2.6**.

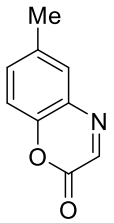
2*H*-Benzo[*b*][1,4]oxazin-2-one (2.6a, known compound[60]**)**



2.6a

Yellow solid, 56% yield, **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.81 (dd, *J* = 8.2 Hz, 1.9 Hz, 1H), 7.57-7.54 (m, 1H), 7.41-7.37 (m, 1H), 7.32 (dd, *J* = 8.2 Hz, 1.3Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.3, 146.3, 146.3, 132.1, 131.2, 129.6, 125.7, 116.8.

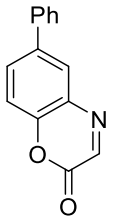
6-Methyl-2*H*-benzo[*b*][1,4]oxazin-2-one (2.6b)



2.6b

Yellow solid, 44% yield. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.08 (s, 1H), 7.59 (d, *J* = 1.3 Hz, 1H), 7.35 (dd, *J* = 8.9 Hz, 1.9 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 2.45 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.5, 146.2, 144.1, 135.6, 132.9, 130.9, 129.4, 116.3, 20.7; **MP**: 125-127 °C; **HRMS** (EI), m/z calcd. for [$C_9H_7NO_2$, M]: 161.0477; found: 161.0480.

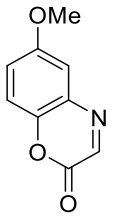
6-Phenyl-2*H*-benzo[*b*][1,4]oxazin-2-one (2.6c)



2.6c

Yellow solid, 84% yield. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.15 (s, 1H), 8.02 (d, *J* = 2.5 Hz, 1H), 7.78 (dd, *J* = 8.2 Hz, 1.9 Hz, 1H), 7.63-7.61 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.43-7.38 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.2, 146.6, 145.5, 139.1, 138.8, 131.3, 130.7, 129.1, 128.0, 127.7, 127.0, 117.0; **MP**: 108-109 °C; **HRMS** (EI), m/z calcd. for [$C_{14}H_9NO_2$, M]: 223.0633; found: 223.0635.

6-Methoxy-2*H*-benzo[*b*][1,4]oxazin-2-one (2.6d)

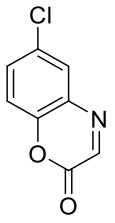


2.6d

Yellow solid, 76% yield. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.13 (s, 1H), 7.29-7.28 (m,

2H), 7.17-7.15 (m, 1H), 3.91 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.0, 152.5, 146.6, 140.3, 131.5, 119.9, 117.3, 111.5, 55.9; **MP**: 132-133 °C; **HRMS** (EI), m/z calcd. for [$C_9H_7NO_3$, M]: 177.0426; found: 177.0424.

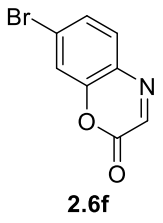
6-Chloro-2*H*-benzo[*b*][1,4]oxazin-2-one (2.6e)



2.6e

Yellow solid, 27% yield. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.13 (s, 1H), 7.80 (d, *J* = 3.6 Hz, 1H), 7.52 (dd, *J* = 14.5 Hz, 3.8 Hz, 1H), 7.27 (d, *J* = 14.6 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 151.6, 147.4, 144.8, 131.9, 131.6, 130.8, 129.0, 117.9; **MP**: 123-125 °C; **HRMS** (EI), m/z calcd. for [$C_8H_4ClNO_2$, M]: 180.9931; found: 180.9923.

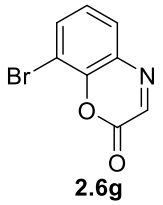
7-Bromo-2*H*-benzo[*b*][1,4]oxazin-2-one (2.6f)



2.6f

Yellow solid, 91% yield. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.09 (d, *J* = 2.6 Hz, 1H), 7.65 (dd, *J* = 8.9 Hz, 3.2 Hz, 1H), 7.51-7.47 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 146.5, 146.3, 130.5, 130.1, 129.1, 125.8, 120.0; **MP**: 139-140 °C; **HRMS** (EI), m/z calcd. for [$C_8H_4BrNO_2$, M]: 224.9425; found: 224.9426.

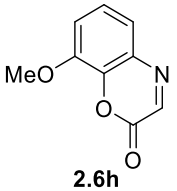
8-Bromo-2*H*-benzo[*b*][1,4]oxazin-2-one (2.6g)



2.6g

Yellow solid, 62% yield. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.09 (s, 1H), 7.77-7.75 (m, 2H), 7.28 (t, *J* = 7.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 146.7, 143.7, 135.5, 132.1, 128.9, 126.1, 110.0; **MP**: 115-116 °C; **HRMS** (EI), m/z calcd. for [$C_8H_4BrNO_2$, M]: 224.9425; found: 224.9429.

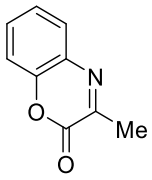
8-Methoxy-2*H*-benzo[*b*][1,4]oxazin-2-one (2.6h)



2.6h

Yellow solid, 59% yield. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.11 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.30 (t, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 3.97 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.8, 147.1, 146.6, 136.1, 131.8, 125.0, 121.0, 114.1, 56.5; **MP**: 144-145 °C; **HRMS** (EI), m/z calcd. for [$C_9H_7NO_3$, M]: 177.0426; found: 177.0421.

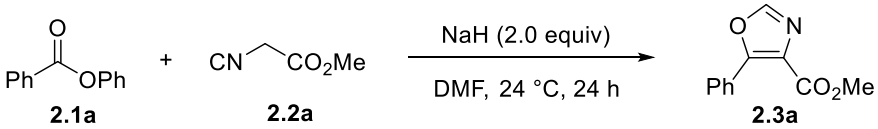
3-Methyl-2*H*-benzo[*b*][1,4]oxazin-2-one (2.6i, known compound[68]**)**



2.6i

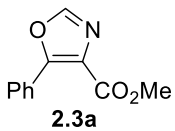
The general procedure outlined above was followed (using ethyl pyruvate). Yellow solid, 59% yield. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.71 (dd, *J* = 8.2 Hz, 1.3Hz, 1H), 7.48-7.45 (m, 1H), 7.36-7.33 (m, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 2.57 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.1, 153.1, 146.5, 131.1, 130.4, 128.5, 125.4, 116.3, 21.2.

2.5.5 Oxazole Formation from Aryl Esters



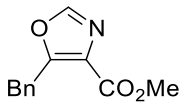
General procedure. To a 10 mL vial charged with **2.1a** (19.8 mg, 0.1 mmol) were added anhydrous DMF (1 mL) and **2.2a** (14 µL, 0.15 mmol). NaH (60% dispersion in mineral oil) (8 mg, 0.2 mmol) was added at 0 ^{o}C. The reaction mixture was stirred at ambient temperature for 24 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate 2:1) to yield 19.3 mg (95%) of **2.3a**.

Methyl 5-phenyloxazole-4-carboxylate (2.3a, known compound[69]**)**



White solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.09-8.07 (m, 2H), 7.91 (s, 1H), 7.50-7.47 (m, 3H), 3.95 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 162.4, 155.7, 148.9, 130.5, 128.5, 128.4, 126.6, 126.3, 52.3.

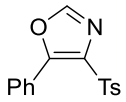
Methyl 5-benzyloxazole-4-carboxylate (2.3b, known compound[70]**)**



2.3b

The general procedure outlined above was followed (using phenyl 2-phenylacetate). Colorless syrup, 71% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.33-7.23 (m, 5H), 4.40 (s, 2H), 3.94 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 162.4, 158.0, 149.3, 135.8, 128.7, 127.1, 127.0, 52.1, 31.9.

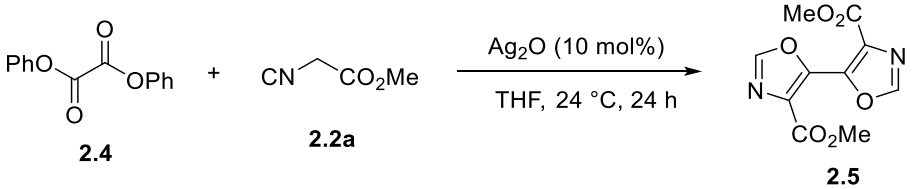
5-Phenyl-4-tosyloxazole (2.3c, known compound[71]**)**



2.3c

The general procedure outlined above was followed (using *p*-toluenesulfonylmethyl isocyanide). White solid, >99% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.99-7.97 (m, 2H), 7.90 (d, *J* = 8.2, 2H), 7.85 (s, 1H), 7.52-7.50 (m, 3H), 7.32 (d, *J* = 8.2, 2H), 2.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.7, 149.2, 145.0, 137.1, 135.6, 130.9, 129.8, 129.0, 128.6, 128.3, 125.5, 21.7.

Dimethyl [5,5'-bioxazole]-4,4'-dicarboxylate (2.5, known compound[72]**)**



2.4 **2.2a** **2.5**

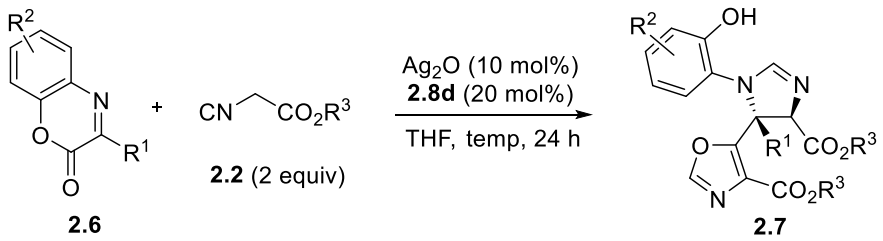
To a 10 mL vial charged with **2.4** (24.2 mg, 0.100 mmol) and Ag_2O (2.3 mg, 0.010 mmol) was added anhydrous THF (1 mL) and **2.2a** (36 µL, 0.40 mmol). The

reaction mixture was stirred at ambient temperature for 24 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate 2:1) to yield 24.5 mg (97%) of **2.5** as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.08 (s, 2H), 3.87 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 160.6, 151.7, 141.4, 133.0, 52.6.

2.5.6 Metal Salt Screening for Double [3+2] Cyclization of 2.6a and 2.2a

General procedure. To a 10 mL vial charged with metal salt (0.010 mmol) and **2.6a** (14.7 mg, 0.100 mmol) were added anhydrous THF (1 mL) and **2.2a** (18 μL, 0.200 mmol) at the ambient temperature. The reaction mixture was stirred for 24 h, and then concentrated and purified by flash chromatography (hexanes/ethyl acetate) to afford the product **2.7a**.

2.5.7 Double [3+2] Cyclization of Isocyanoacetate with Cyclic α-Imino Ester



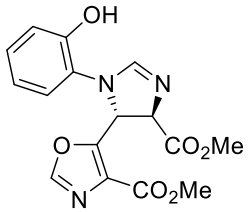
General procedure. To a 10 mL vial charged with **2.8d** (12 mg, 0.020 mmol) and Ag_2O (2.3 mg, 0.010 mmol) was added anhydrous THF (1 mL). The mixture was stirred at ambient temperature for 5 min, then cyclic α-imino ester **2.6** (0.1 mmol) and isocyanoacetate **2.2** (0.2 mmol) were added at the given temperature. The reaction mixture was stirred at the given temperature for the given time, and then concentrated,

purified by flash chromatography (hexanes/ethyl acetate) to afford the product **2.7**.

Racemic sample of **2.7** for the standard of chiral HPLC spectra was prepared using 10 mol% Ag_2O as catalyst.

2.5.8 Characterization of Compounds

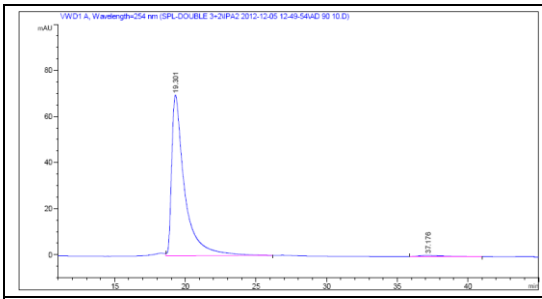
Methyl 5-((4*R*,5*R*)-1-(2-hydroxyphenyl)-4-(methoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7a)



2.7a

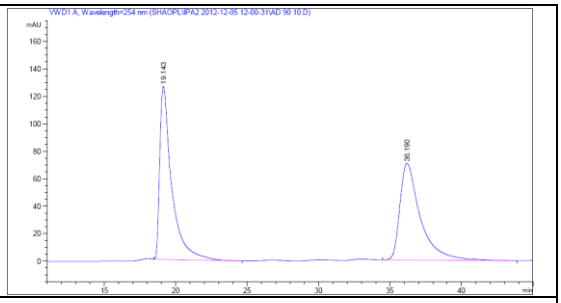
The general procedure outlined above was followed (**2.6a** and **2.2a** were added in one portion, stirred at -20 ^oC for 24 h). Colorless wax, 99% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 1.9 Hz, 1H), 7.85 (s, 1H), 6.99-6.93 (m, 3H), 6.73-6.70 (m, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 4.93 (dd, *J* = 7.9 Hz, 1.9 Hz 1H), 3.90 (s, 3H), 3.78 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.6, 161.4, 156.3, 154.4, 150.7, 150.6, 129.9, 126.6, 124.8, 122.2, 119.9, 117.1, 72.2, 57.3, 52.9, 52.4; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{16}N_3O_6, M+H]^+$: 346.1034; found: 346.1047.

Optical Rotation: $[\alpha]^{25}_D$ = -85.9 (c = 0.2, $CHCl_3$). The absolute configuration of **2.7a** was assigned by analogy to **2.7k**. 98% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 19.3 min for major isomer, t_R = 37.2 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

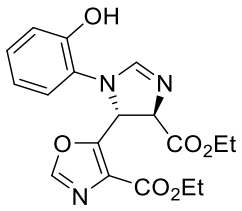
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.301	VB	0.9136	4460.52734	69.79208	98.7704
2	37.176	BB	1.4221	55.52840	4.59415e-1	1.2296



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.143	MM T	0.9660	7314.19971	126.19489	50.2438
2	36.190	MM T	1.6989	7243.22559	71.05961	49.7562

Ethyl 5-((4*R*,5*R*)-4-(ethoxycarbonyl)-1-(2-hydroxyphenyl)-4,5-dihydro-1*H*–imidazol-5-yl)oxazole-4-carboxylate (2.7b)

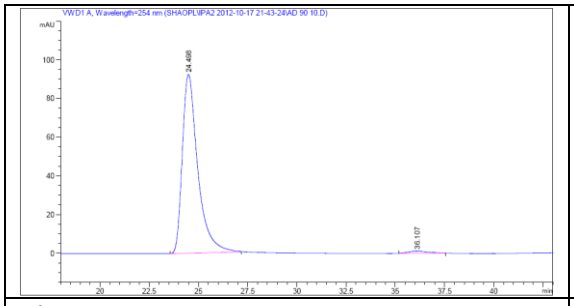


2.7b

The general procedure outlined above was followed (**2.6a** and **2.2b** were added in one portion, stirred at -20 ^{o}C for 24 h). Colorless wax, 89% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.84 (s, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.97-6.92 (m, 2H), 6.73-6.69 (m, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 4.91 (dd, *J* = 7.6 Hz, 1.3 Hz, 1H), 4.41-4.36 (m, 2H), 4.30-4.21 (m, 2H), 1.37 (t, *J* = 7.3 Hz, 3H), 1.25 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.1, 161.0, 156.3, 154.2, 150.6, 150.6, 130.2, 126.5, 124.8, 121.9, 119.8, 117.1, 72.3, 62.2, 61.7, 57.3, 14.1, 13.9; **HRMS** (ESI): m/z calcd. for $[C_{18}H_{20}N_3O_6, M+H]^+$: 374.1347; found: 374.1354.

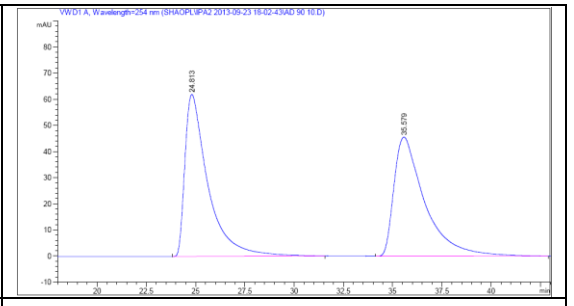
Optical Rotation: $[\alpha]^{25}_D$ = -40.3 (c = 0.2, $CHCl_3$). The absolute configuration of **2.7b** was assigned by analogy to **2.7k**. 97% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R =

24.5 min for major isomer, t_R = 36.1 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

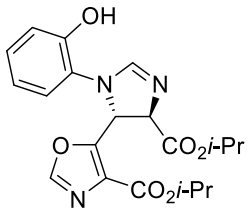
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	24.498	BB	0.8060	5036.03613	98.3967
2	36.107	BB	0.8849	82.05785	1.6033



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.813	BB	1.1208	5051.02930	62.04259	50.3641
2	35.579	BB	1.4738	4978.00195	45.62827	49.6359

Isopropyl 5-((4*R*,5*R*)-1-(2-hydroxyphenyl)-4-(isopropoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7c)

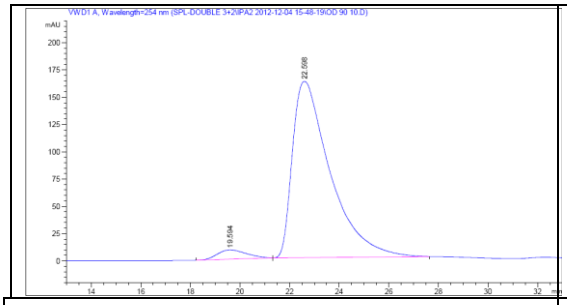


2.7c

The general procedure outlined above was followed (**2.6a** and **2.2c** were added in one portion, stirred at ambient temperature for 24 h). Colorless wax, 95% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 1.9 Hz, 1H), 7.83 (s, 1H), 7.06-7.05 (m, 1H), 6.99-6.93 (m, 2H), 6.73-6.70 (m, 1H), 6.43 (d, *J* = 7.6 Hz, 1H), 5.28-5.26 (m, 1H), 5.13-5.11 (m, 1H), 4.87 (dd, *J* = 7.6 Hz, 1.9 Hz, 1H), 1.37 (d, *J* = 3.8 Hz, 3H), 1.36 (d, *J* = 3.8 Hz, 3H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.7, 160.5, 156.2, 153.9, 150.6, 130.5, 126.4, 124.8, 121.9, 119.7, 117.2, 72.3, 70.0, 69.6, 57.3, 21.7, 21.7, 21.6, 21.5; **HRMS** (ESI): m/z calcd. for

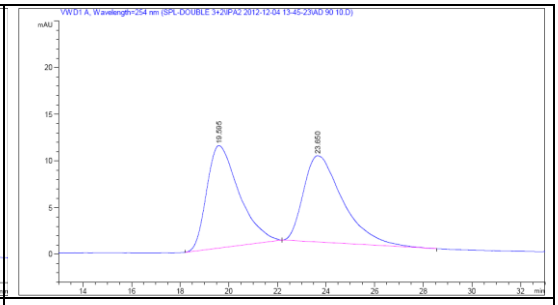
$[C_{20}H_{24}N_3O_6, M+H]^+$: 402.1660; found: 402.1657.

Optical Rotation: $[\alpha]^{25}_D$ = -69.8 (c = 0.2, $CHCl_3$). The absolute configuration of **2.7c** was assigned by analogy to **2.7k**. 92% ee (HPLC condition: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 19.6 min for minor isomer, t_R = 22.6 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

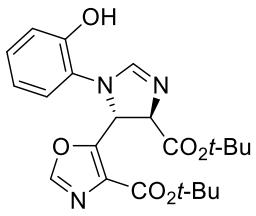
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.594	BB	1.1760	700.05212	8.58854	3.9309
2	22.598	BB	1.5617	1.71088e4	161.66019	96.0691



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.595	BB	1.3264	1012.36371	10.98300	49.3561
2	23.650	BB	1.4782	1038.77637	9.24290	50.6439

***tert*-Butyl 5-((4*R*,5*R*)-4-(tert-butoxycarbonyl)-1-(2-hydroxyphenyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7d)**

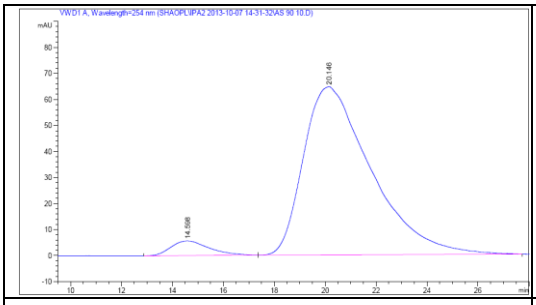


2.7d

The general procedure outlined above was followed (**2.6a** was added in one portion; **2.2d** in anhydrous THF (1 mL) was added *via* syringe pump over 2 h at -20 °C, stirred at -20 °C for 12 h, and then 0 °C for 12 h). Colorless wax, 85% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 1.3 Hz, 1H), 7.81 (s, 1H), 7.04-7.02 (m, 1H), 6.98-6.95

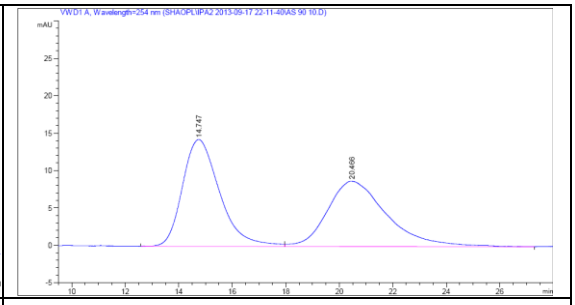
(m, 2H), 6.73-6.69 (m, 1H), 6.32 (d, J = 7.0 Hz, 1H), 4.80 (dd, J = 7.0 Hz, 1.3 Hz, 1H), 1.57 (s, 9H), 1.48 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.5, 160.0, 156.1, 153.4, 150.9, 150.5, 131.2, 126.7, 124.9, 122.5, 119.7, 117.2, 83.2, 83.0, 73.0, 57.5, 28.1, 27.9; **HRMS** (ESI): m/z calcd. for $[C_{22}H_{28}N_3O_6, M+H]^+$: 430.1973; found: 430.1981.

Optical Rotation: $[\alpha]^{25}_D$ = -38.2 (c = 0.2, $CHCl_3$). The absolute configuration of **2.7d** was assigned by analogy to **2.7k**. 91% ee (HPLC condition: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 14.6 min for minor isomer, t_R = 20.1 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

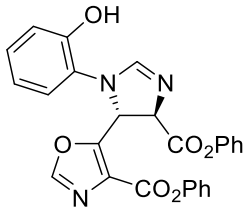
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.598	BB	1.2168	584.65033	5.62402	4.6718
2	20.146	BB	2.1580	1.19297e4	64.61401	95.3282



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.747	BV	1.4910	1374.56702	14.27983	50.5251
2	20.466	VB	2.2756	1345.99670	8.74558	49.4749

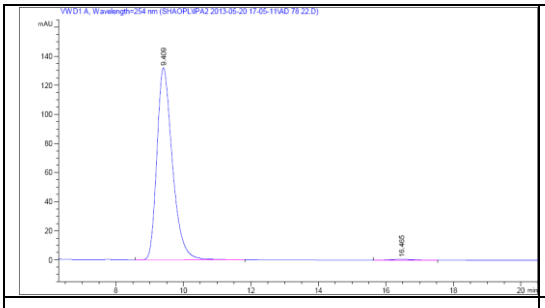
Phenyl 5-((4*R*,5*R*)-1-(2-hydroxyphenyl)-4-(phenoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7e)



2.7e

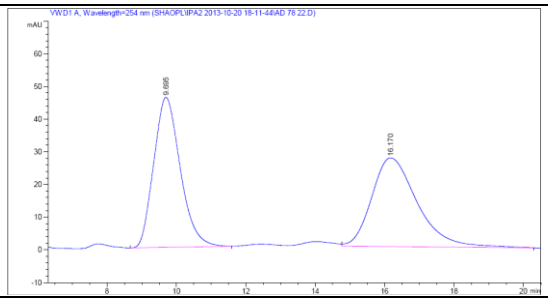
The general procedure outlined above was followed (**2.6a** was added in one portion; **2.2e** in anhydrous THF (1 mL) was added *via* syringe pump over 2 h at -20 °C, stirred at -20 °C for 12 h, and then 0 °C for 12 h). Colorless wax, 86% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 10.03 (s, 1H), 8.59 (s, 1H), 7.81 (d, *J* = 1.9, 1H), 7.46 (t, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.04-7.02 (m, 1H), 6.99-6.96 (m, 1H), 6.89-6.87 (m, 1H), 6.77-6.73 (m, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 5.27 (dd, *J* = 6.9 Hz, 1.9 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 169.1, 159.2, 156.1, 155.1, 152.3, 150.3, 150.2, 149.7, 129.6, 129.5, 128.1, 126.3, 126.1, 126.0, 125.5, 122.7, 121.6, 121.4, 119.4, 116.4, 73.8, 56.9; **HRMS** (ESI), m/z calcd. for [$C_{26}H_{20}N_3O_6$, M+H]$^+$: 470.1347; found: 470.1357.

Optical Rotation: $[\alpha]^{25}_D$ = -74.9 (c = 0.4, $CHCl_3$). The absolute configuration of **2.7e** was assigned by analogy to **2.7k**. 99% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 78:22, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 9.4 min for major isomer, t_R = 16.5 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

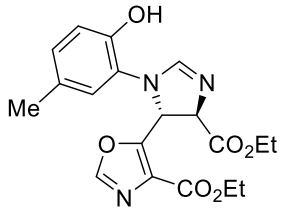
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.409	BB	0.4835	4203.58252	132.01898	99.4116
2	16.465	BB	0.5747	24.88129	5.14059e-1	0.5884



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.695	BV	0.6889	2436.57837	45.93020	49.6168
2	16.170	VV	1.0662	2474.21729	27.13749	50.3832

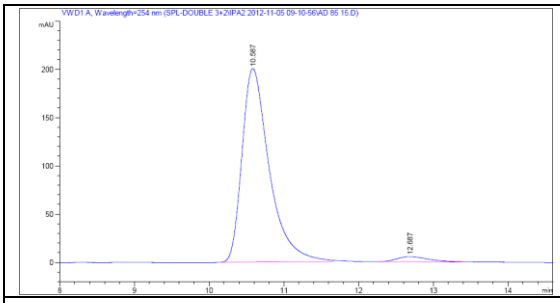
Ethyl 5-((4*R*,5*R*)-4-(ethoxycarbonyl)-1-(2-hydroxy-5-methylphenyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7f)



2.7f

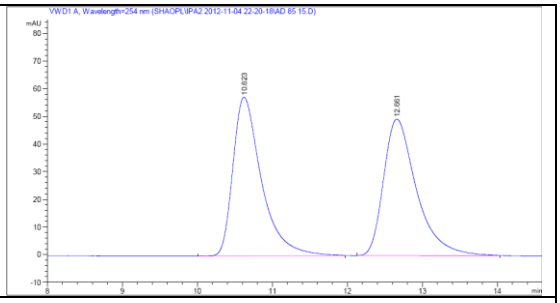
The general procedure outlined above was followed (**2.6b** and **2.2b** were added in one portion, stirred at -20 ºC for 24 h). White solid, 87% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 1.3 Hz, 1H), 7.84 (s, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 1.3 Hz, 1H), 6.73 (dd, *J* = 8.2 Hz, 1.3 Hz, 1H), 6.44 (d, *J* = 7.6 Hz, 1H), 4.90 (dd, *J* = 7.6 Hz, 1.9 Hz, 1H), 4.39 (q, *J* = 7.3 Hz, 2H), 4.30-4.21 (m, 2H), 2.14 (s, 3H), 1.39 (t, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.2, 161.0, 156.2, 154.3, 150.6, 148.0, 130.2, 129.1, 126.8, 124.4, 122.2, 116.9, 72.3, 62.1, 61.7, 57.1, 20.3, 14.1, 14.0; **MP**: 82-33 °C; **HRMS** (ESI): m/z calcd. for $[C_{19}H_{22}N_3O_6$, M+H$]^+$: 388.1503; found: 388.1489.

Optical Rotation: $[\alpha]^{25}_D$ = -31.6 (c = 0.3, $CHCl_3$). The absolute configuration of **2.7f** was assigned by analogy to **2.7k**. 94% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 85:15, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 10.6 min for major isomer, t_R = 12.7 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

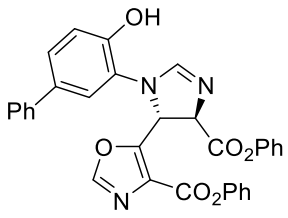
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	10.587	BB	0.3845	5088.42676	96.9903
2	12.687	BB	0.4531	157.89868	3.0097



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	10.623	BB	0.3911	1520.15027	50.2853
2	12.661	BB	0.4454	1502.89966	49.7147

Phenyl 5-((4*R*,5*R*)-1-(4-hydroxy-[1,1'-biphenyl]-3-yl)-4-(phenoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7g)

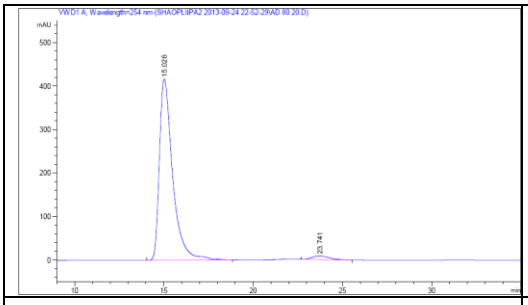


2.7g

The general procedure outlined above was followed (**2.6c** and **2.2e** were added in one portion, stirred at -20 °C for 12 h, and then 0 °C for 12 h). Colorless wax, 68% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): 10.21 (s, 1H), 8.61 (s, 1H), 7.94 (d, J = 1.9 Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.42-7.35 (m, 5H), 7.31-7.26 (m, 5H), 7.11-7.04 (m, 4H), 6.95 (d, J = 8.9 Hz, 1H), 6.64 (d, J = 7.0 Hz, 1H), 5.30 (dd, J = 7.6 Hz, 1.9 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 169.1, 159.3, 156.1, 154.8, 152.4, 150.3, 149.6, 149.5, 139.5, 131.6, 129.5, 129.5, 128.8, 128.3, 126.7, 126.2, 126.1, 125.8, 123.9, 121.5, 121.4, 120.3, 116.9, 73.7, 56.6; **HRMS** (ESI): m/z calcd. for [$C_{32}H_{22}N_3O_6$, M-H]$^-$: 544.1514; found: 544.1500.

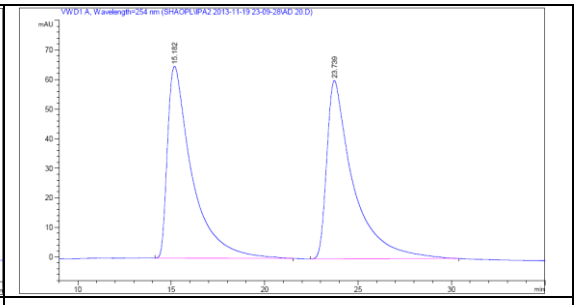
Optical Rotation: $[\alpha]^{25}_D$ = -42.8 (c = 0.3, $CHCl_3$). The absolute configuration of

2.7g was assigned by analogy to **2.7k**. 95% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 15.0 min for major isomer, t_R = 23.7 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

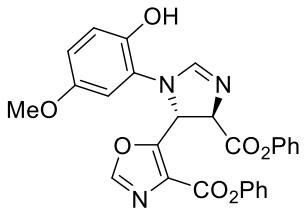
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.026	BB	0.7432	2.14352e4	416.67993	97.5840
2	23.741	BB	0.7652	530.70471	8.10686	2.4160



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.182	BB	1.0952	5904.03320	64.81410	49.9267
2	23.739	BB	1.1586	5921.36914	60.32958	50.0733

Phenyl 5-((4*R*,5*R*)-1-(2-hydroxy-5-methoxyphenyl)-4-(phenoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7h)

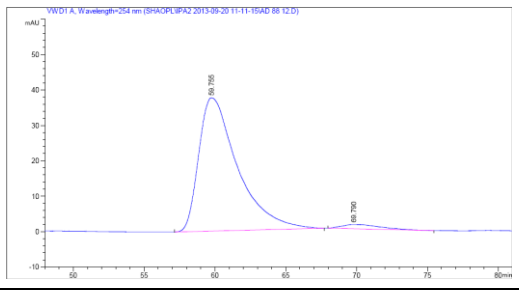


2.7h

The general procedure outlined above was followed (**2.6d** was added in one portion, **2.2e** in anhydrous THF (1 mL) was added *via* syringe pump over 2 h at 0 °C, stirred at 0 °C for 24 h). Colorless wax, 61% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): 9.54 (s, 1H), 8.60 (s, 1H), 7.89 (d, *J* = 1.9 Hz, 1H), 7.48-7.44 (m, 2H), 7.40-7.37 (m, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.20-7.18 (m, 2H), 7.08-7.07 (m, 2H), 6.79-6.77 (m, 1H), 6.63 (d, *J* = 3.2 Hz, 1H), 6.56-6.54 (m, 2H), 5.26 (dd, *J* = 7.6

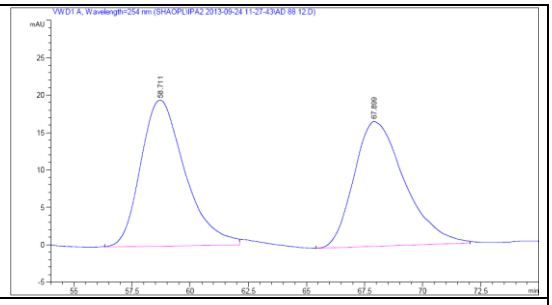
Hz, 1.9 Hz, 1H), 3.61 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 169.0, 159.3, 156.0, 154.6, 152.3, 152.2, 150.3, 149.7, 143.3, 129.6, 129.5, 128.2, 126.3, 126.1, 125.9, 121.6, 121.4, 116.9, 110.2, 107.6, 73.6, 56.6, 55.3; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{20}N_3O_7, M-H]^-$: 498.1307; found: 498.1291.

Optical Rotation: $[\alpha]^{25}_D$ = -88.8 (c = 0.2, $CHCl_3$). The absolute configuration of **2.7h** was assigned by analogy to **2.7k**. 94% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 88:12, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 59.8 min for major isomer, t_R = 69.8 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

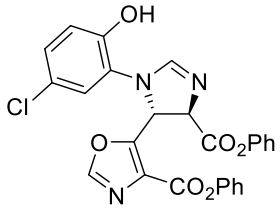
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	59.755	BB	2.2274	7158.41748	37.66283	96.8554
2	69.790	BB	2.2680	232.41103	1.20296	3.1446



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	58.711	VV	1.5526	2588.82593	19.54324	50.6735
2	67.899	BV	1.7677	2520.00708	16.69835	49.3265

Phenyl 5-((4*R*,5*R*)-1-(5-chloro-2-hydroxyphenyl)-4-(phenoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7i)

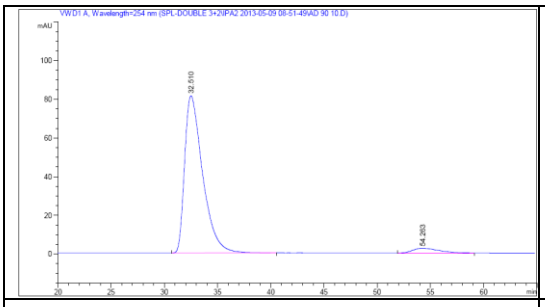


2.7i

The general procedure outlined above was followed (**2.2e** was added in one portion;

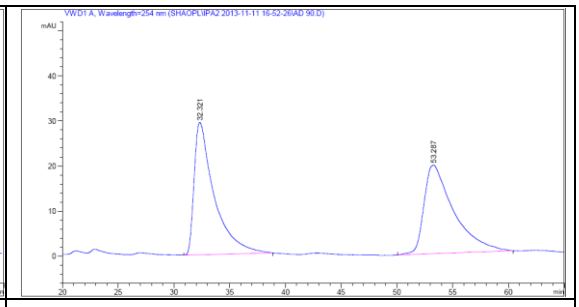
2.6e in anhydrous THF (1 mL) was added *via* syringe pump over 2 h at 0 °C, stirred at 0 °C for 24 h). Colorless wax, 94% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): 10.38 (s, 1H), 8.61 (s, 1H), 7.93 (d, J = 1.9 Hz, 1H), 7.48-7.45 (m, 2H), 7.40-7.37 (m, 2H), 7.34-7.31 (m, 1H), 7.28-7.25 (m, 1H), 7.22-7.20 (m, 2H), 7.16 (d, J = 2.5 Hz, 1H), 7.09-7.07 (m, 2H), 7.01-6.99 (m, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.59 (d, J = 7.0 Hz, 1H), 5.31 (dd, J = 7.6 Hz, 1.9 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 168.9, 159.3, 155.7, 154.2, 152.4, 150.3, 149.7, 148.6, 129.6, 129.5, 128.3, 126.8, 126.3, 126.1, 125.0, 122.5, 121.6, 121.4, 121.3, 117.6, 73.8, 56.5; **HRMS** (ESI): m/z calcd. for $[C_{26}H_{19}ClN_3O_6, M+H]^+$: 504.0957; found: 504.0954.

Optical Rotation: $[\alpha]^{25}_D$ = -81.9 (c = 0.3, $CHCl_3$). The absolute configuration of **2.7i** was assigned by analogy to **2.7k**. 91% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 32.5 min for major isomer, t_R = 54.3 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

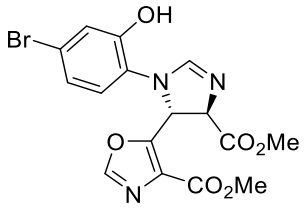
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.510	BB	1.8094	9551.39551	81.25585	95.6977
2	54.263	BB	2.0202	429.40646	2.50208	4.3023



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.321	BB	1.4622	3664.33765	29.37829	50.1292
2	53.287	BB	2.1657	3645.45605	19.66513	49.8708

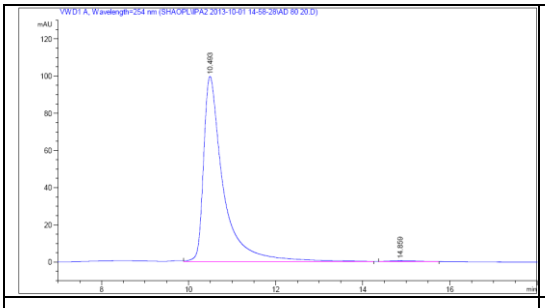
Methyl 5-((4*R*,5*R*)-1-(4-bromo-2-hydroxyphenyl)-4-(methoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7j)



2.7j

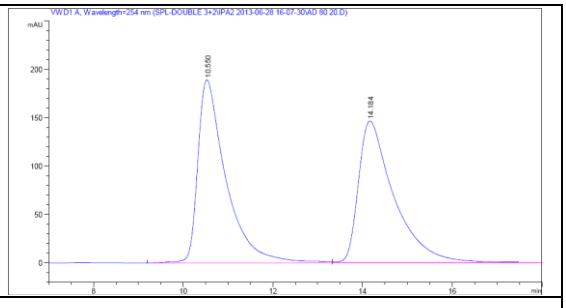
The general procedure outlined above was followed (**2.6f** added in one portion; **2.2a** in anhydrous THF (1 mL) was added *via* syringe pump over 2 h at -20 °C, stirred at -20 °C for 12 h, and then 0 °C for 12 h). Colorless wax, 61% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): 10.51 (s, 1H), 8.43 (s, 1H), 7.74 (s, 1H), 6.97 (s, 1H), 6.88 (s, 2H), 6.25 (d, J = 7.6 Hz, 1H), 4.86 (d, J = 7.6 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.7, 161.1, 154.7, 154.0, 151.9, 150.9, 128.5, 125.3, 123.3, 122.0, 118.8, 116.7, 73.5, 56.5, 52.4, 52.0; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{15}BrN_3O_6, M+H]^+$: 424.0139; found: 424.0144.

Optical Rotation: $[\alpha]^{25}_D$ = -37.4 (c = 0.3, $CHCl_3$). The absolute configuration of **2.7j** was assigned by analogy to **2.7k**. 99% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 10.5 min for major isomer, t_R = 14.9 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

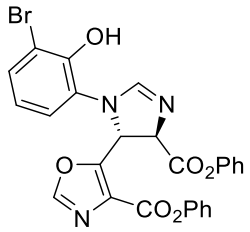
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.493	VB	0.4453	3107.58398	99.52293	99.5644
2	14.859	BB	0.4970	13.59722	3.20152e-1	0.4356



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.550	BV	0.6532	8255.38379	189.15004	50.4291
2	14.184	VB	0.8055	8114.88818	146.67126	49.5709

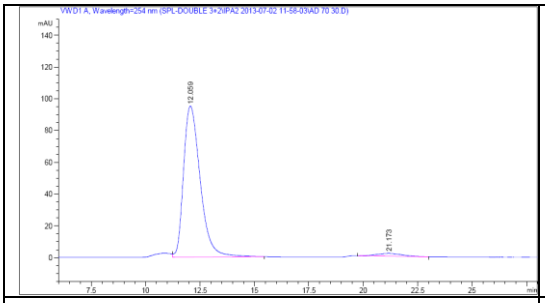
Phenyl 5-((4*R*,5*R*)-1-(3-bromo-2-hydroxyphenyl)-4-(phenoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7k)



2.7k

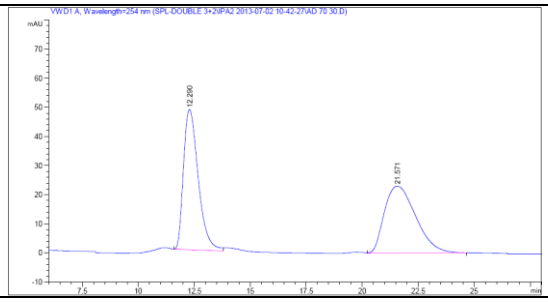
The general procedure outlined above was followed (**2.6g** was added in one portion; **2.2e** in anhydrous THF (1 mL) was added *via* syringe pump over 2 h at 0 °C, stirred at 0 °C for 24 h). Colorless wax, 76% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): 9.76 (brs, 1H), 8.60 (s, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.45 (t, J = 7.9 Hz, 2H), 7.39 (t, J = 7.9 Hz, 2H), 7.35-7.30 (m, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.18-7.16 (m, 2H), 7.09-7.04 (m, 3H), 6.77 (t, J = 7.9 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 5.34 (dd, J = 7.0 Hz, 1.9 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 168.9, 159.2, 155.5, 154.9, 152.4, 150.3, 149.6, 147.6, 129.8, 129.6, 129.5, 128.6, 128.4, 126.2, 126.0, 123.0, 121.7, 121.4, 121.4, 112.6, 73.8, 56.9; **HRMS** (ESI): m/z calcd. for $[C_{26}H_{17}BrN_3O_6, M-H]^-$: 546.0306; found: 546.0305.

Optical Rotation: $[\alpha]^{25}_D$ = -74.1 (c = 0.3, $CHCl_3$). The absolute configuration of **2.7k** was assigned by conversion to **2.10** followed by X-ray analysis. 95% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 70:30, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 12.1 min for major isomer, t_R = 21.2 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

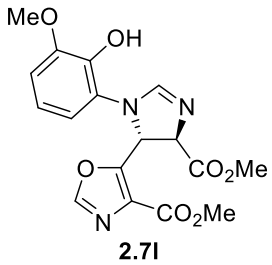
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.059	VB	0.8267	5054.38770	95.00580	97.3455
2	21.173	BB	0.9498	137.82619	1.70741	2.6545



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.290	BV	0.7110	2201.28711	48.09238	49.5846
2	21.571	VV	1.4714	2238.17358	22.99872	50.4154

Methyl 5-((4*R*,5*R*)-1-(2-hydroxy-3-methoxyphenyl)-4-(methoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7l)

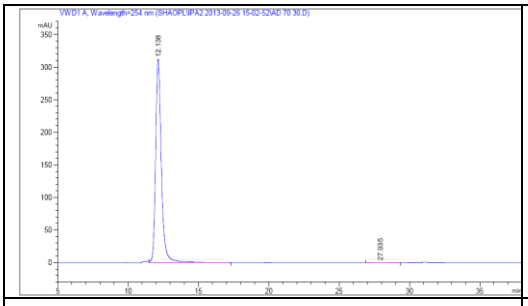


2.7l

The general procedure outlined above was followed (**2.6h** was added in one portion; **2.2a** in anhydrous THF (1 mL) was added *via* syringe pump over 2 h at -20 °C, stirred at -20 °C for 24 h). Colorless wax, 90% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.79 (s, 1H), 7.75 (d, *J* = 1.9 Hz, 1H), 6.70-6.67 (m, 1H), 6.61-6.59 (m, 2H), 6.42 (d, *J* = 8.2 Hz, 1H), 4.87 (dd, *J* = 7.6 Hz, 1.9 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.7, 161.4, 155.0, 154.6, 150.4, 147.5, 138.3, 129.6, 124.7, 119.7, 113.6, 107.4, 73.6, 56.8, 56.1, 52.8, 52.3; **HRMS** (ESI), m/z calcd. for $[C_{17}H_{18}N_3O_7, M+H]^+$: 376.1139; found: 376.1148.

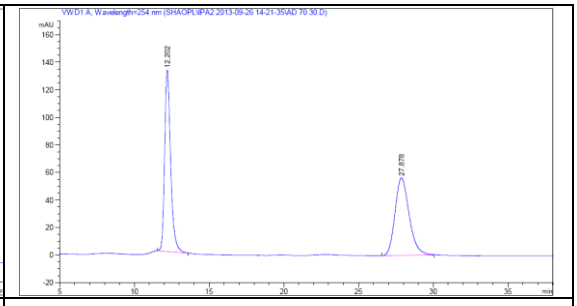
Optical Rotation: $[\alpha]^{25}_D$ = -67.8 (c = 0.5, $CHCl_3$). The absolute configuration of **2.7l** was assigned by analogy to **2.7k**. 99% ee (HPLC condition: Chiralpak AD-H

column, *n*-hexane/*i*-PrOH = 70:30, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 12.1 min for major isomer, t_R = 27.9 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

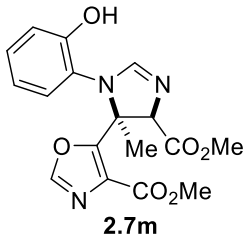
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.138	VB	0.4274	8871.85449	312.33362	99.5599
2	27.935	BV	0.8218	39.21745	5.59443e-1	0.4401



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.202	BV	0.4059	3691.80981	131.75467	49.9021
2	27.878	VV	0.7722	3706.30200	56.21597	50.0979

Methyl 5-((4*R*,5*R*)-4-(ethoxycarbonyl)-1-(2-hydroxyphenyl)-5-methyl-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7m)

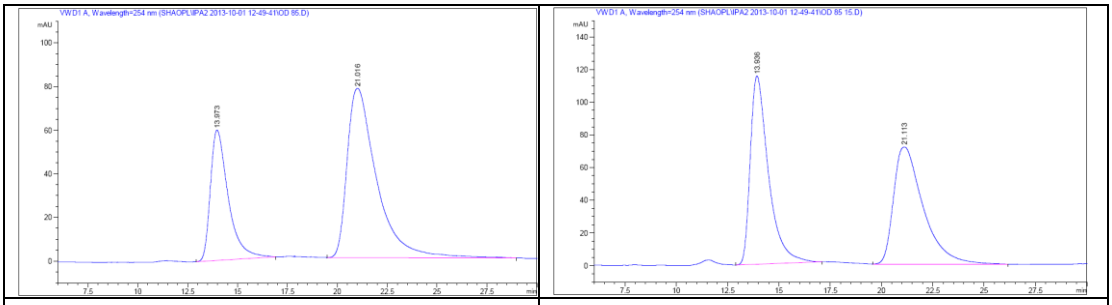


2.7m

The general procedure outlined above was followed (**2.6i** was added in one portion; **2.2a** in anhydrous THF (1 mL) was added *via* syringe pump over 2 h at ambient temperature, stirred at ambient temperature for 24 h). Colorless wax, 69% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): 9.88 (s, 1H), 8.49 (s, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.05-7.02 (m, 1H), 6.87 (dd, J = 7.9 Hz, 1.3 Hz, 1H), 6.66-6.63 (m, 1H), 6.43 (dd, J = 7.9 Hz, 1.6 Hz, 1H), 5.23 (d, J = 2.2 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 1.33 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 169.7, 161.5, 158.6, 155.6, 153.6, 150.5, 127.9, 127.6, 127.1, 124.5, 119.3, 116.4, 78.5, 68.4, 52.1, 51.7, 16.5; **HRMS** (ESI), m/z

calcd. for $[C_{17}H_{18}N_3O_6, M+H]^+$: 360.1190; found: 360.1206.

Optical Rotation: $[\alpha]^{25}_D$ = +29.8 (c = 0.20, $CHCl_3$). 37% ee (HPLC condition: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 85:15, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 14.0 min for minor isomer, t_R = 21.0 min for major isomer).



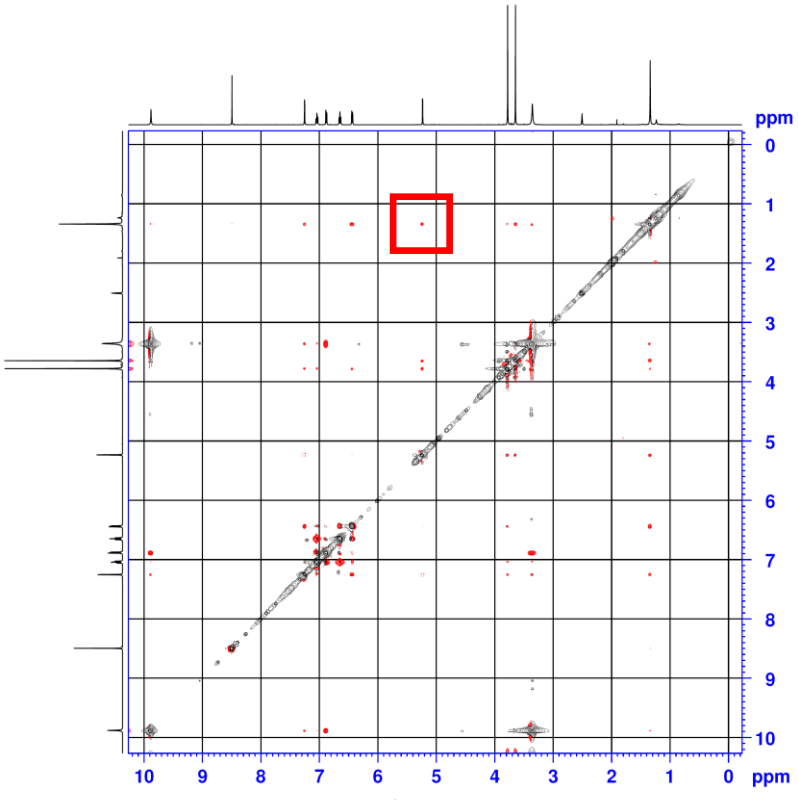
Signal 1: VWD1 A, Wavelength=254 nm

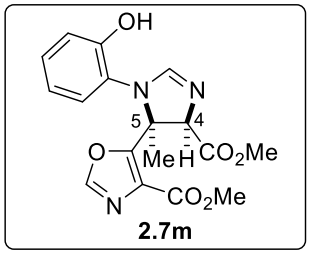
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.973	BB	0.9248	3715.35498	59.80088	31.7186
2	21.016	BB	1.5017	7998.12500	77.65199	68.2814

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.936	BB	0.9164	7096.37256	115.24377	49.7086
2	21.113	BB	1.4703	7179.58447	71.69635	50.2914

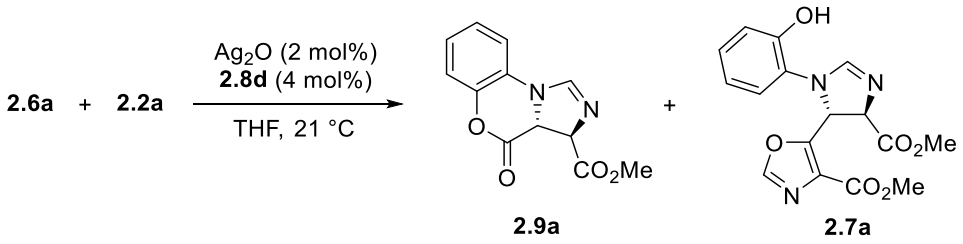
Figure 2.1 NOESY Spectrum of **2.7m**





The *cis* relative configuration of **2.7m** was determined by the NOE correlation between the H at **C-4** and Me group at **C-5** (Figure 2.1). The absolute configuration was not determined.

2.5.9 NMR Studies Revealed a Stepwise Reaction Profile

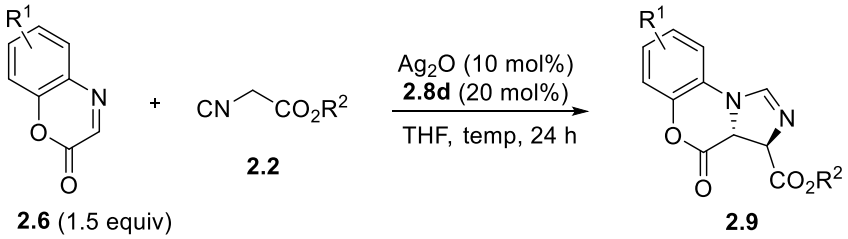


To a 50 mL round-bottom flask charged with **2.8d** (44 mg, 0.072 mmol) and Ag_2O (8.3 mg, 0.036 mmol) was added anhydrous THF (18 mL). The mixture was stirred at 21°C for 5 min, then **2.6a** (265 mg, 1.80 mmol) and **2.2a** (324 μL, 3.60 mmol) were added in one portion. The reaction mixture was stirred at 21 °C for the given time. Real time conversion was determined by ^{1}H NMR (500 MHz).

entry	time (min)	**2.6a** (%)	**2.9a** (%)	**2.7a** (%)
1	0	100	0	0
2	5	67.94	31.99	0.07

3	10	51.34	48.59	0.07
4	15	36.94	62.99	0.07
5	20	26.12	73.58	0.30
6	25	19.99	79.69	0.32
7	30	13.72	85.91	0.38
8	35	7.22	92.18	0.60
9	40	1.44	96.53	2.03
10	55	0.92	96.96	2.12
11	60	0.23	97.40	2.37
12	65	0	94.09	5.91
13	70	0	91.68	8.32
14	80	0	66.50	33.5
15	85	0	47.67	52.33
16	90	0	38.05	61.95
17	96	0	29.82	70.18
18	101	0	23.12	76.88
19	111	0	20.00	80.00
20	131	0	16.20	83.80
21	161	0	14.25	87.75
22	201	0	11.32	88.68

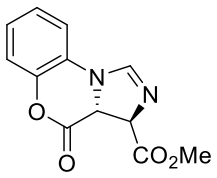
2.5.10 Mono [3+2] Cyclization of 2.6 and 2.2



General procedure. To a 10 mL vial charged with **2.8d** (12 mg, 0.020 mmol) and Ag_2O (2.3 mg, 0.010 mmol) was added anhydrous THF (1 mL). After the mixture was stirred at ambient temperature for 5 min, **2.6** (0.150 mmol) was added. When the reaction mixture was cooled to -20 ^oC, **2.2** (0.100 mmol) in anhydrous THF (1 mL) was added *via* syringe pump over 2 h. The reaction mixture was stirred at the given temperature for the given time, and then concentrated, purified by flash chromatography (hexanes/ethyl acetate) to afford the product **2.9**.

Racemic sample of **2.9** for the standard of chiral HPLC spectra was prepared using 10 mol% Ag_2O as catalyst.

(3*R*,3a*R*)-methyl 4-oxo-3a,4-dihydro-3*H*-benzo[*b*]imidazo[1,5-*d*][1,4]oxazine-3-carboxylate (2.9a)

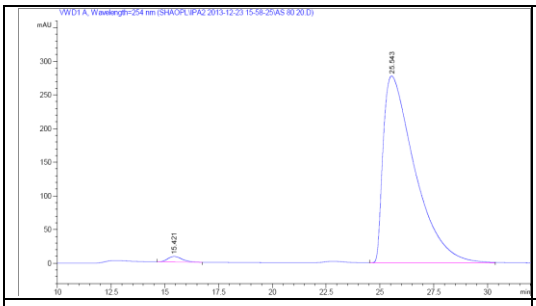


2.9a

The general procedure outlined above was followed (stirred at -20 ^oC for 24 h). Colorless wax, 84% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 2.5 Hz, 1H),

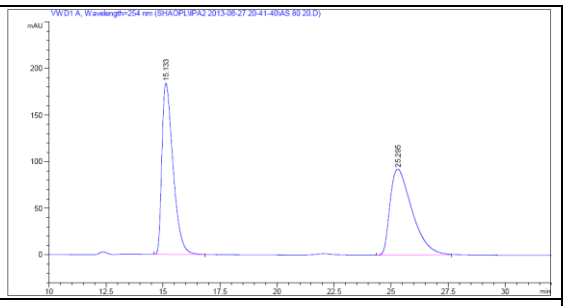
7.21-7.19 (m, 1H), 7.17-7.13 (m, 3H), 5.27 (dd, *J* = 7.0 Hz, 1.9 Hz, 1H), 4.85 (d, *J* = 7.0 Hz, 1H), 3.83 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.1, 163.9, 151.0, 142.5, 125.5, 125.5, 123.3, 118.3, 117.8, 73.0, 56.9, 53.2; **HRMS** (ESI), m/z calcd. for $[C_{12}H_{11}N_2O_4, M+H]^+$: 247.0713; found: 247.0722.

Optical Rotation: $[\alpha]^{25}_D$ = -90.3 (c = 0.2, $CHCl_3$). The absolute configuration of **2.9a** was assigned by analogy. 97% ee (HPLC condition: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 15.4 min for minor isomer, t_R = 25.5 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

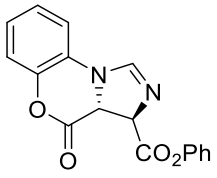
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.421	BB	0.5380	381.55423	8.30528	1.3335
2	25.543	BV	1.1957	2.82316e4	277.43130	98.6665



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.133	VV	0.4528	6209.27100	183.73260	50.1031
2	25.295	BV	0.7844	6183.71826	92.27117	49.8969

(3*R*,3a*R*)-phenyl 4-oxo-3a,4-dihydro-3*H*-benzo[*b*]imidazo[1,5-*d*][1,4]oxazine-3-carboxylate (2.9b)

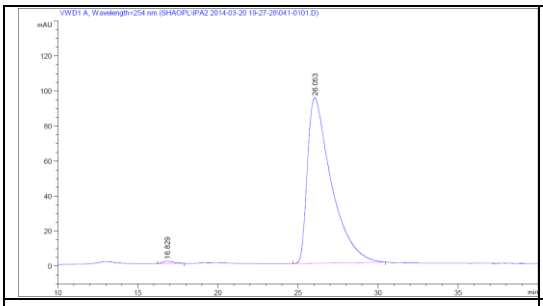


2.9b

The general procedure outlined above was followed (stirred at -20 ºC for 12 h, and then 0 ºC for 12 h). Colorless wax, 92% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ

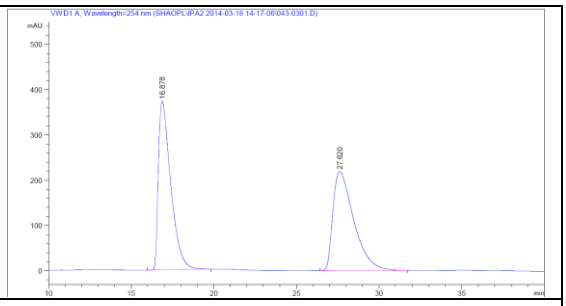
7.86 (d, J = 2.5 Hz, 1H), 7.55-7.53 (m, 1H), 7.48-7.45 (m, 2H), 7.32-7.29 (m, 1H), 7.24-7.20 (m, 4H), 7.18-7.15 (m, 1H), 5.33 (dd, J = 6.9 Hz, 1.9 Hz, 1H), 5.25 (d, J = 7.6 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 168.8, 164.0, 153.0, 150.3, 142.0, 129.6, 126.2, 125.0, 124.4, 123.9, 121.5, 118.5, 117.1, 72.5, 56.7; **HRMS** (ESI), m/z calcd. for $[C_{17}H_{13}N_2O_4, M+H]^+$: 309.0870; found: 309.0879.

Optical Rotation: $[\alpha]^{25}_D$ = -42.6 (c = 0.3, $CHCl_3$). The absolute configuration of **2.9b** was assigned by analogy. 99% ee (HPLC condition: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 16.8 min for minor isomer, t_R = 26.1 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

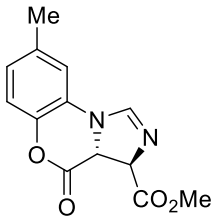
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.829	VV	0.5733	65.16469	1.32957	0.6620
2	26.053	BB	1.2074	9778.12793	94.55898	99.3380



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.878	BB	0.7139	1.94054e4	372.44482	50.3363
2	27.620	BB	1.0208	1.91461e4	219.03615	49.6637

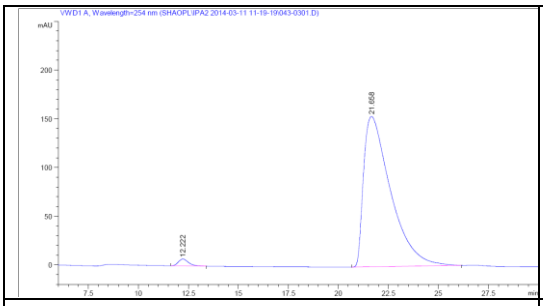
(3*R*,3a*R*)-methyl 8-methyl-4-oxo-3a,4-dihydro-3*H*-benzo[*b*]imidazo[1,5-*d*][1,4]oxazine-3-carboxylate (2.9c)



2.9c

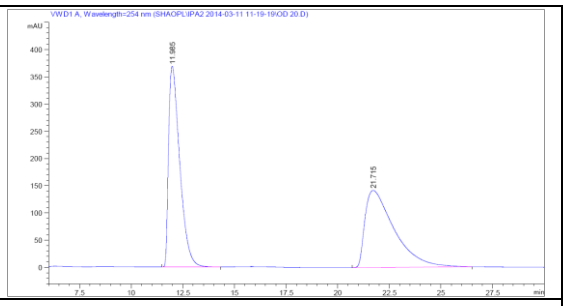
The general procedure outlined above was followed (stirred at -20 ºC for 24 h). Colorless wax, 92% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.74 (t, J = 1.3 Hz, 1H), 7.32 (d, J = 1.3 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.95-6.93 (m, 1H), 5.02-5.01 (m, 2H), 3.75 (s, 3H), 2.30 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.4, 164.3, 152.3, 139.9, 134.5, 124.7, 123.5, 118.5, 116.7, 72.5, 56.6, 52.6, 20.4; **HRMS** (ESI), m/z calcd. for $[C_{13}H_{12}N_2NaO_4, M+Na]^+$: 283.0689; found: 283.0700.

Optical Rotation: $[\alpha]^{25}_D$ = -63.3 (c = 0.2, $CHCl_3$). The absolute configuration of **2.9c** was assigned by analogy. 97% ee (HPLC condition: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 12.2 min for minor isomer, t_R = 21.7 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

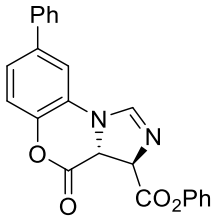
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.222	BB	0.4108	243.75261	6.95628	1.6509
2	21.658	BB	1.1007	1.45208e4	154.32559	98.3491



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.985	BB	0.5470	1.38519e4	368.55515	49.9177
2	21.715	BB	1.1518	1.38976e4	141.50586	50.0823

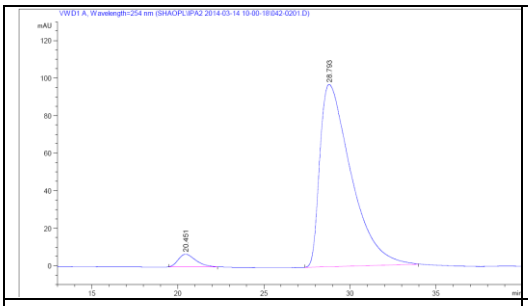
(3*R*,3a*R*)-phenyl 4-oxo-8-phenyl-3a,4-dihydro-3*H*-benzo[*b*]imidazo[1,5-*d*][1,4]oxazine-3-carboxylate (2.9d)



2.9d

The general procedure outlined above was followed (stirred at -20 ºC for 24 h). Colorless wax, 86% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.04 (d, J = 1.9 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.50-7.44 (m, 5H), 7.39 (t, J = 7.3 Hz, 1H), 7.33-7.29 (m, 2H), 7.24 (d, J = 7.6 Hz, 2H), 5.39 (dd, J = 7.6 Hz, 1.9 Hz, 1H), 5.31 (d, J = 7.6 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 168.8, 163.9, 153.0, 150.3, 141.4, 138.8, 137.2, 129.7, 128.9, 127.7, 126.7, 126.3, 124.2, 122.4, 121.5, 117.5, 116.5, 72.6, 56.7; **HRMS** (ESI), m/z calcd. for $[C_{23}H_{16}N_2NaO_4, M+Na]^+$: 407.1002; found: 407.1004.

Optical Rotation: $[\alpha]^{25}_D$ = -47.5 (c = 0.3, $CHCl_3$). The absolute configuration of **2.9d** was assigned by analogy. 93% ee (HPLC condition: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R =20.5 min for minor isomer, t_R = 28.8 min for major isomer).



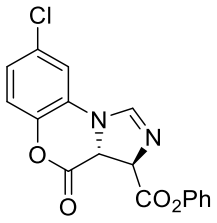
Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.451	BB	0.8133	467.71527	6.72137	3.6821
2	28.793	BV	1.4711	1.22345e4	97.09574	96.3179

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.820	BB	1.1208	3.77616e4	488.78107	50.2777
2	27.941	BB	1.6111	3.73446e4	277.75418	49.7223

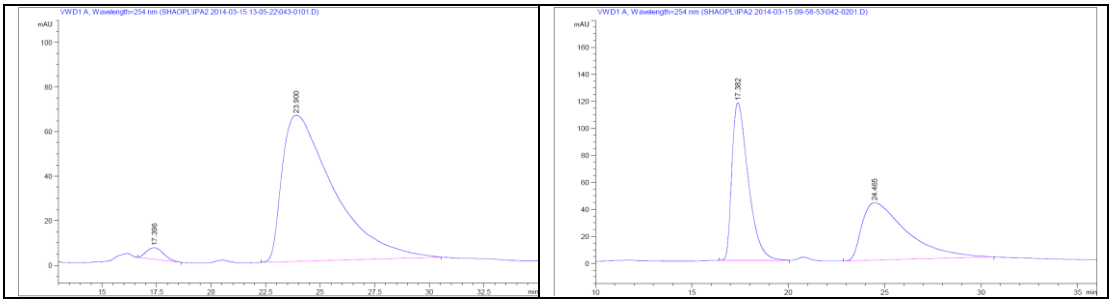
(3*R*,3a*R*)-phenyl 8-chloro-4-oxo-3a,4-dihydro-3*H*-benzo[*b*]imidazo[1,5-*d*][1,4]oxazine-3-carboxylate (2.9e)



2.9e

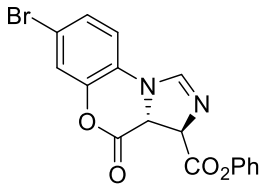
The general procedure outlined above was followed (stirred at -20 ºC for 24 h). Colorless wax, 90% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.91 (d, *J* = 1.9 Hz, 1H), 7.73 (d, *J* = 2.6 Hz, 1H), 7.48-7.45 (m, 2H), 7.33-7.30 (m, 1H), 7.26-7.21 (m, 3H), 7.19-7.16 (m, 1H), 5.33 (dd, *J* = 7.6 Hz, 1.9 Hz, 1H), 5.25 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 168.7, 163.4, 152.5, 150.3, 140.7, 129.7, 128.7, 126.3, 125.1, 123.6, 121.5, 118.6, 117.9, 72.6, 56.2; **HRMS** (ESI), m/z calcd. for $[C_{17}H_{12}ClN_2O_4, M+H]^+$: 343.0480; found: 343.0492.

Optical Rotation: $[\alpha]^{25}_D$ = -57.9 (c = 0.3, $CHCl_3$). The absolute configuration of **2.9e** was assigned by analogy. 95% ee (HPLC condition: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 17.4 min for minor isomer, t_R = 23.9 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm							Signal 1: VWD1 A, Wavelength=254 nm						
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.396	BB	0.6341	281.56860	5.19099	2.5494	1	17.382	BV	0.6903	6869.41211	116.78278	50.0899
2	23.900	BB	1.9156	1.07631e4	65.61199	97.4506	2	24.465	BB	1.8806	6844.75488	42.49585	49.9101

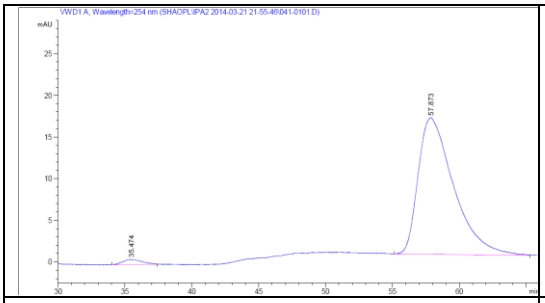
(3*R*,3a*R*)-phenyl 7-bromo-4-oxo-3a,4-dihydro-3*H*-benzo[*b*]imidazo[1,5-*d*][1,4]oxazine-3-carboxylate (2.9f)



2.9f

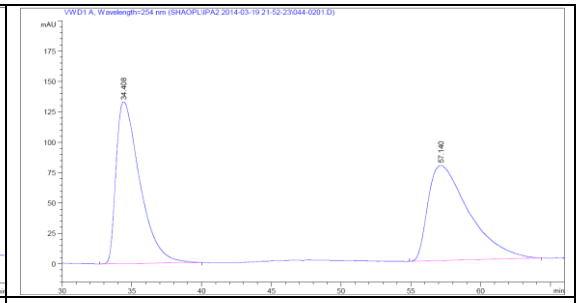
The general procedure outlined above was followed (stirred at -20 °C for 12 h, and then 0 °C for 12 h). Colorless wax, 84% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.86 (d, *J* = 1.9 Hz, 1H), 7.52-7.50 (m, 2H), 7.48-7.45 (m, 2H), 7.42-7.40 (m, 1H), 7.32-7.29 (m, 1H), 7.22-7.20 (m, 2H), 5.32 (dd, *J* = 7.6 Hz, 1.9 Hz, 1H), 5.24 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 168.7, 163.3, 152.7, 150.2, 142.6, 129.6, 127.6, 126.3, 123.5, 121.5, 119.9, 115.0, 72.6, 56.4; **HRMS** (ESI), m/z calcd. for $[C_{17}H_{12}BrN_2O_4, M+H]^+$: 386.9975; found: 386.9983.

Optical Rotation: $[\alpha]^{25}_D$ = -46.6 (c = 0.3, $CHCl_3$). The absolute configuration of **2.9f** was assigned by analogy. 96% ee (HPLC condition: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 34.3 min for minor isomer, t_R = 55.8 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

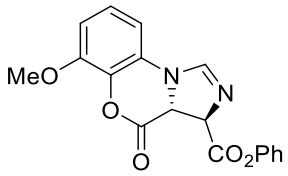
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.474	VV	1.1758	62.33090	6.20569e-1	2.0177
2	57.873	BV	2.1646	3026.91235	16.40534	97.9823



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.408	BB	1.3850	1.57443e4	132.90932	49.6591
2	57.140	BB	2.3811	1.59605e4	78.29883	50.3409

(3*R*,3a*R*)-phenyl 6-methoxy-4-oxo-3a,4-dihydro-3*H*-benzo[*b*]imidazo[1,5-*d*][1,4]oxazine-3-carboxylate (2.9g)

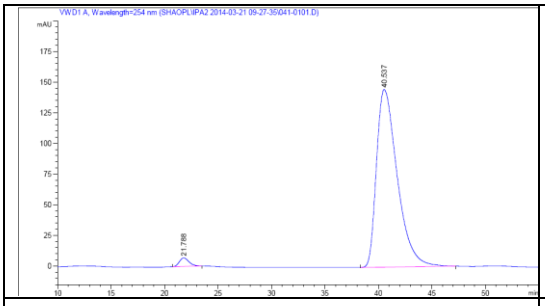


2.9g

The general procedure outlined above was followed (stirred at -20 °C for 12 h, and then 0 °C for 12 h). Colorless wax, 85% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.85 (d, J = 1.9 Hz, 1H), 7.46 (t, J = 8.2 Hz, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.32-7.29 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.09 (m, 1H), 6.90-6.88 (m, 1H), 5.33 (dd, J = 6.9 Hz, 1.9 Hz, 1H), 5.21 (d, J = 7.0 Hz, 1H), 3.86 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 168.8, 163.6, 152.9, 150.3, 147.6, 131.2, 129.6, 126.3, 124.8, 124.7, 121.5, 110.2, 107.8, 72.4, 56.5, 56.1; **HRMS** (ESI), m/z calcd. for [$C_{18}H_{15}N_2O_5$, M+H]$^+$: 339.0975; found: 339.0985.

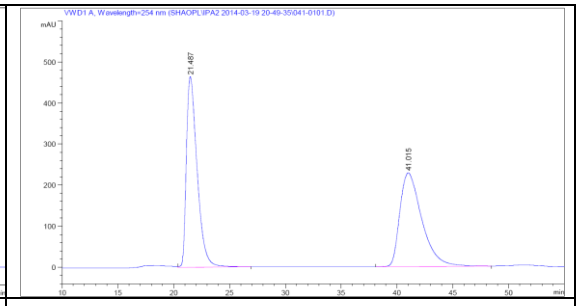
Optical Rotation: $[\alpha]^{25}_D$ = -58.9 (c = 0.2, $CHCl_3$). The absolute configuration of **2.9g** was assigned by analogy. 96% ee (HPLC condition: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 75:25, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 21.8 min

for minor isomer, t_R = 40.5 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

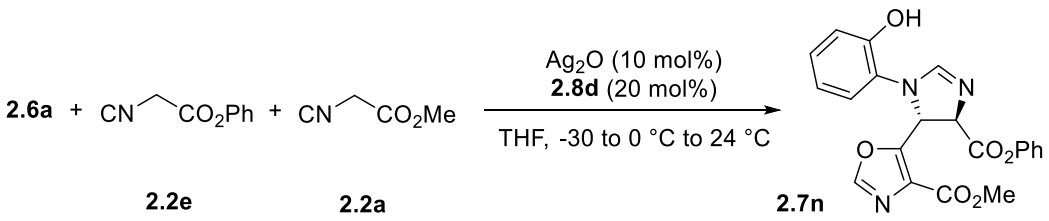
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.788	BB	0.7315	430.33716	6.88248	2.1540
2	40.537	BB	1.5779	1.95485e4	144.86101	97.8460



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.487	VB	1.0092	3.10002e4	464.15204	49.9156
2	41.015	BB	1.9321	3.11051e4	228.22420	50.0844

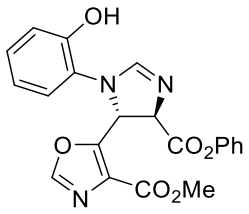
2.5.11 Three-Component Reaction of Different Isocyanoacetates with 2.6a



To a 10 mL vial charged with **2.8d** (12 mg, 0.020 mmol) and Ag_2O (2.3 mg, 0.010 mmol) was added anhydrous THF (1 mL). After the mixture was stirred at ambient temperature for 5 min, **2.6a** (14.7 mg, 0.100 mmol) was added. When the reaction mixture was cooled to -30 °C, **2.2e** (16.1 mg, 0.100 mmol) in anhydrous THF (1 mL) was added *via* syringe pump over 2 h. The reaction mixture was stirred for 24 h at -30 °C, and then **2.2a** (9.0 µL, 0.100 mmol) was added in one portion. The reaction mixture was stirred for 12 h at 0 °C and another 12 h at ambient temperature, concentrated and purified by flash chromatography to afford **2.7n**.

Methyl 5-((4*R*,5*R*)-1-(2-hydroxyphenyl)-4-(phenoxycarbonyl)-4,5-dihydro-1*H*-im

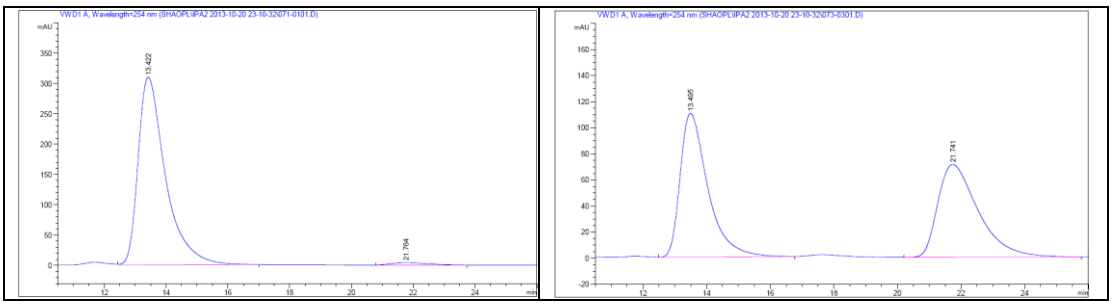
idazol-5-yl)oxazole-4-carboxylate (2.7n)



2.7n

Colorless wax, 67% yield. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.0 (s, 1H), 8.48 (s, 1H), 7.80 (d, J = 3.0 Hz, 1H), 7.46 (t, J = 13.0 Hz, 2H), 7.30 (t, J = 12.2 Hz, 1H), 7.18 (d, J = 12.6 Hz, 2H), 6.98-6.91 (m, 2H), 6.86-6.83 (m, 1H), 6.73-6.68 (m, 1H), 6.43 (d, J = 12.9 Hz, 1H), 5.16 (dd, J = 12.6 Hz, 3.1 Hz, 1H), 3.79 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 169.2, 161.3, 155.0, 154.9, 152.0, 150.4, 150.1, 129.6, 128.7, 126.1, 125.8, 125.4, 122.3, 121.5, 119.4, 116.4, 73.5, 56.6, 52.0; **HRMS** (ESI): m/z calcd. for $[C_{21}H_{18}N_3O_6, M+H]^+$: 408.1190; found: 408.1203.

Optical Rotation: $[\alpha]^{25}_D$ = -76.8 (c = 0.3, $CHCl_3$). The absolute configuration of **2.7n** was assigned by analogy to **2.7k**. 97% ee (HPLC condition: Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 13.4 min for major isomer, t_R = 21.8 min for minor isomer).

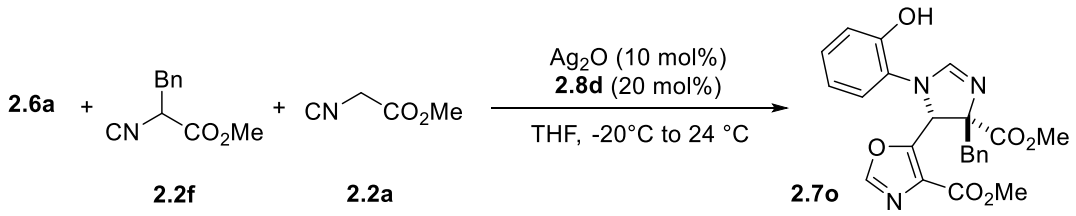


Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.422	VB	0.7614	1.89334e4	309.07520	98.3356
2	21.764	BB	0.9441	320.45358	3.96532	1.6644

Signal 1: VWD1 A, Wavelength=254 nm

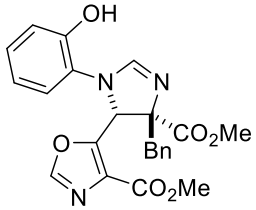
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.495	VB	0.8718	6644.24854	110.13220	51.4477
2	21.741	BB	1.0710	6270.30859	71.22929	48.5523



2.2f **2.2a** **2.7o**

To a 10 mL vial charged with **2.8d** (12 mg, 0.020 mmol) and Ag_2O (2.3 mg, 0.010 mmol) was added anhydrous THF (1 mL). After the mixture was stirred at ambient temperature for 5 min, **2.6a** (14.7 mg, 0.100 mmol) was added. When the reaction mixture was cooled to -20 °C, **2.2f** (18.9 mg, 0.100 mmol) in anhydrous THF (1 mL) was added *via* syringe pump over 2 h. The reaction mixture was stirred for 12 h at -20 °C, and then **2.2a** (9.0 µL, 0.100 mmol) was added in one portion. The reaction mixture was stirred for 12 h at ambient temperature, concentrated and purified by flash chromatography to afford **2.7o**.

Methyl 5-(4-benzyl-1-(2-hydroxyphenyl)-4-(methoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)oxazole-4-carboxylate (2.7o)

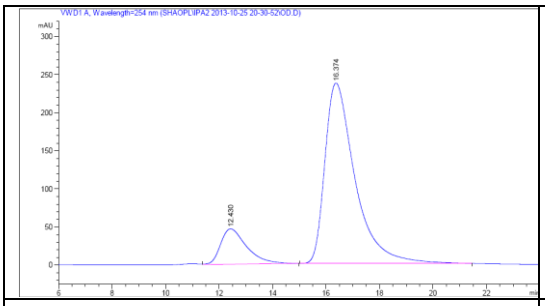


2.7o

White solid, 73% yield. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.35 (s, 1H),

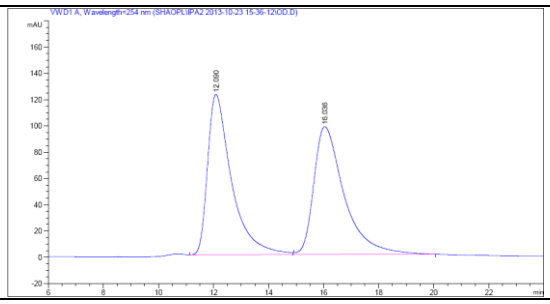
7.68 (s, 1H), 7.31-7.25 (m, 4H), 7.22-7.19 (m, 1H), 6.87-6.84 (m, 1H), 6.77-6.75 (m, 1H), 6.72-6.71 (m, 1H), 6.64-6.60 (m, 1H), 6.18 (s, 1 H), 3.89 (s, 3H), 3.31 (s, 3H), 3.29 (d, *J* = 13.2 Hz, 1H), 3.21 (d, *J* = 13.2 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.8, 161.3, 154.2, 153.0, 151.6, 149.7, 135.5, 130.6, 129.2, 127.7, 126.7, 125.5, 125.3, 121.7, 119.2, 116.2, 82.5, 60.9, 52.0, 51.8, 44.8; **MP**: 199-200 °C; **HRMS** (ESI), m/z calcd. for $[C_{23}H_{22}N_3O_6, M+H]^+$: 436.1503; found: 436.1503.

Optical Rotation: $[\alpha]^{25}_D$ = +61.5 (c = 0.3, $CHCl_3$). 71% ee (HPLC condition: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 12.4 min for minor isomer, t_R = 16.4 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.430	VB	0.7952	3154.73560	46.55003	14.5153
2	16.374	BB	0.9255	1.85791e4	236.90318	85.4847

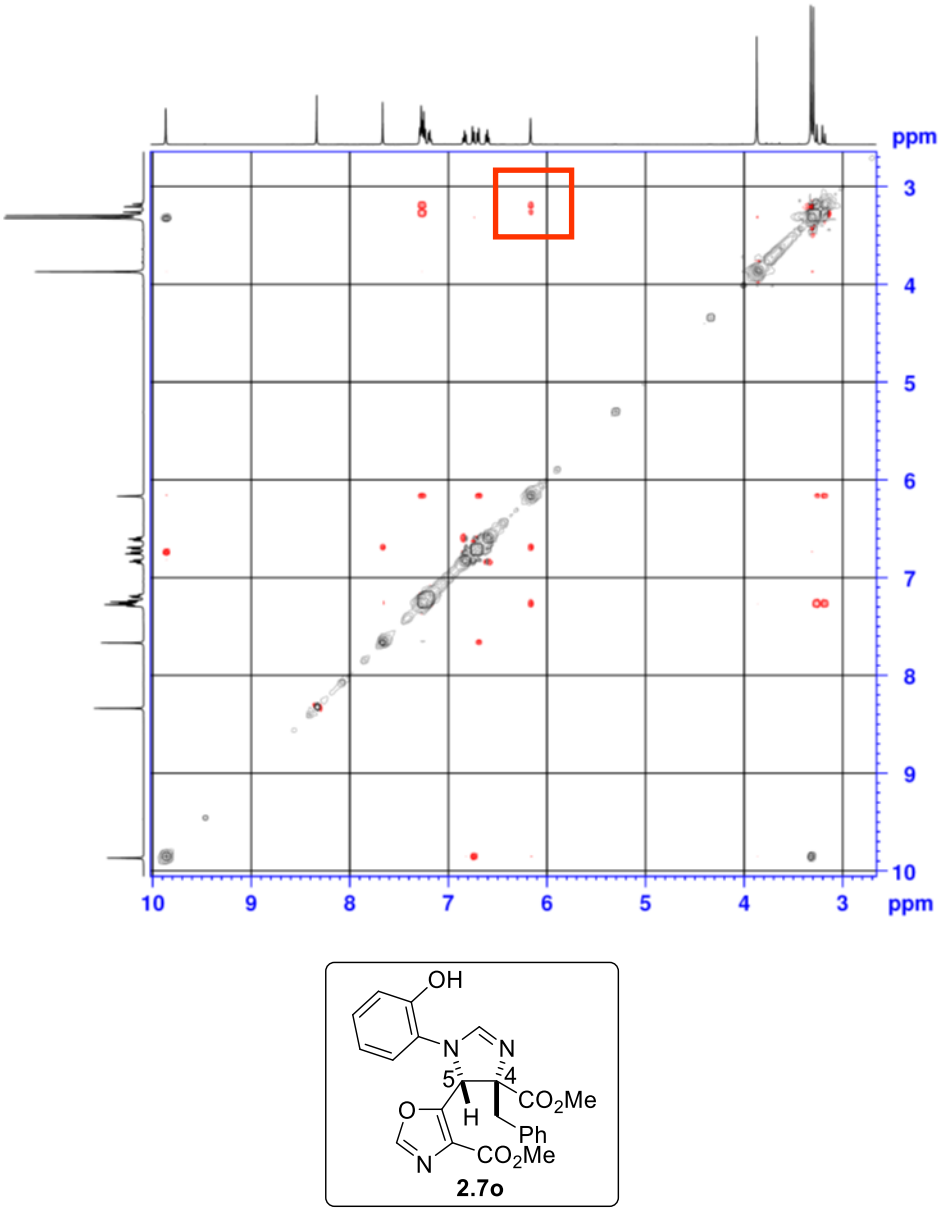


Signal 1: VWD1 A, Wavelength=254 nm

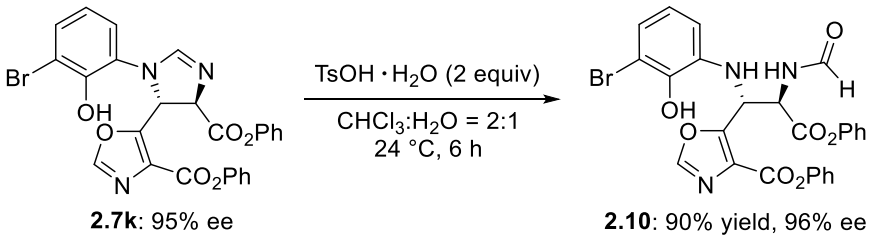
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.090	BV	0.7061	7356.43066	121.97366	49.6755
2	16.036	VV	0.8956	7452.52832	97.30054	50.3245

The *cis* relative configuration of **2.7o** was determined by the NOE correlation between the CH_2 of benzyl group at **C-4** and the H at **C-5** (Figure 2.2), and reconfirmed by X-ray crystallographic analysis of a single crystal of **2.7o**.

Figure 2.2 NOESY Spectrum of **2.7o**



2.5.12 Hydrolysis to α,β-Diamino Ester



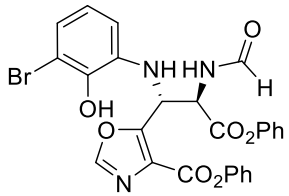
2.7k: 95% ee

2.10: 90% yield, 96% ee

p-Toluenesulfonic acid monohydrate (21 mg, 0.11 mmol) was added to the

mixture of **2.7k** (30 mg, 0.055 mmol, 95% ee), $CHCl_3$ (2 mL) and H_2O (1 mL). The reaction mixture was stirred at ambient temperature for 6 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate, 1/2) to yield 28 mg (90%) of **2.10**.

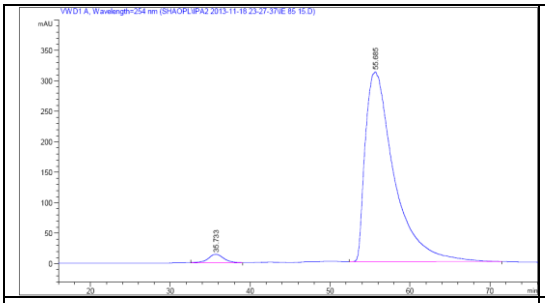
Phenyl 5-((1*R*,2*R*)-1-((3-bromo-2-hydroxyphenyl)amino)-2-formamido-3-oxo-3-phenoxypropyl)oxazole-4-carboxylate (2.10)



2.10

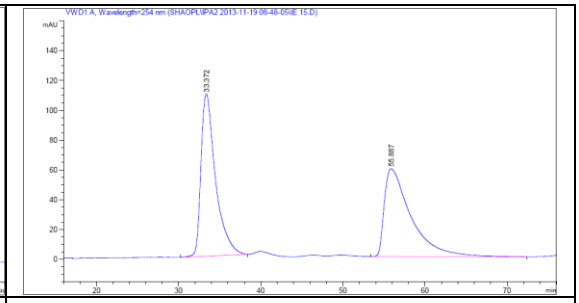
White solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.37 (d, J = 8.2 Hz, 1H), 9.21 (s, 1H), 8.62 (s, 1H), 8.16 (s, 1H), 7.50 (t, J = 7.9 Hz, 2H), 7.40 (t, J = 8.2 Hz, 2H), 7.36-7.31 (m, 3H), 7.27 (t, J = 7.3 Hz, 1H), 6.97 (d, J = 7.6 Hz, 2H), 6.84-6.83 (m, 1H), 6.67-6.64 (m, 2H), 6.05-5.99 (m, 2H), 5.54 (dd, J = 8.9 Hz, 5.1 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 167.4, 161.6, 159.7, 156.4, 152.0, 150.0, 149.8, 141.3, 137.8, 129.7, 129.7, 127.8, 126.3, 126.3, 122.0, 121.7, 121.4, 121.2, 111.4, 110.3, 53.3, 50.9; **MP**: 185-186 °C; **HRMS** (ESI), m/z calcd. for $[C_{26}H_{20}BrN_3NaO_7, M+Na]^+$: 588.0377; found: 588.0372.

Optical Rotation: $[\alpha]^{25}_D$ = -79.3 (c = 0.1, Acetone). 96% ee (HPLC condition: Chiralpak IE column, *n*-hexane/*i*-PrOH = 85:15, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 35.7 min for minor isomer, t_R = 55.7 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

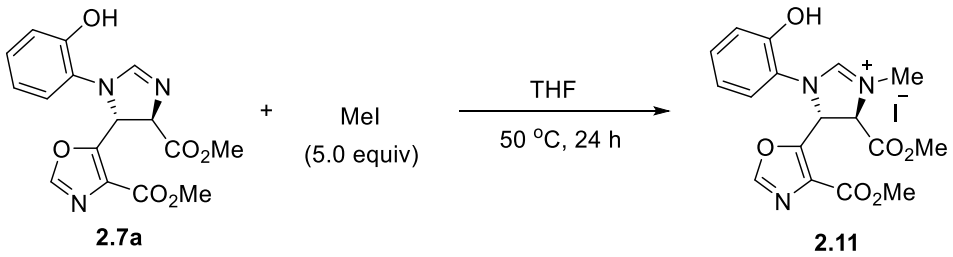
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.733	BB	1.5339	1800.62817	13.71305	2.2467
2	55.685	BB	2.9480	7.83461e4	311.74097	97.7533



Signal 1: VWD1 A, Wavelength=254 nm

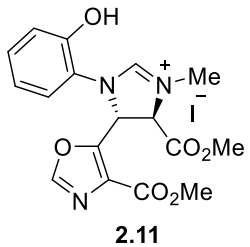
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.372	BB	1.8354	1.33777e4	108.72894	50.1417
2	55.887	BB	3.1279	1.33021e4	58.96596	49.8583

2.5.13 Imidazolinium Salt Formation



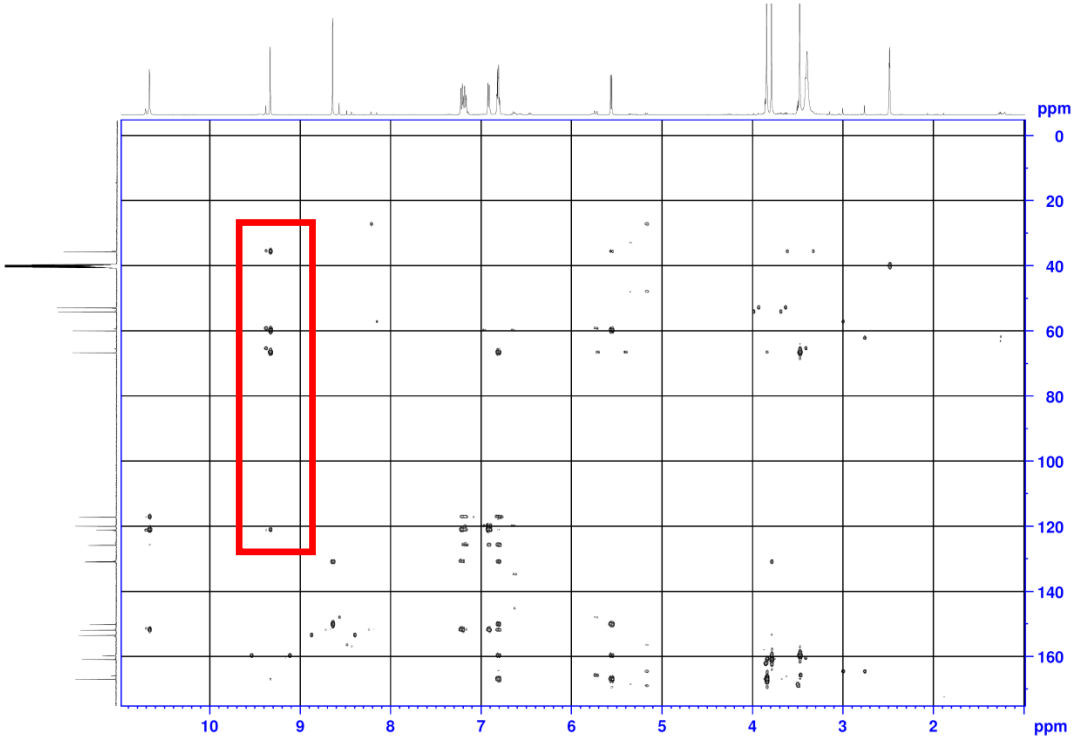
Methyl iodide (40 µL, 0.650 mmol) was added to the solution of **2.7a** (45 mg, 0.130 mmol) in anhydrous THF (2 mL). The reaction mixture was stirred at 50 °C for 24 h and then concentrated. The ratio of isomers (5:1) was determined by ^{1}H NMR. The residue was purified by flash chromatography (MeOH/ethyl acetate, 1/5) to give 56 mg (89%) of **2.11**.

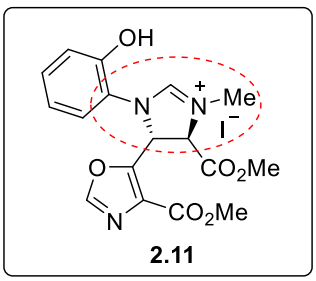
1-(2-Hydroxyphenyl)-4-(methoxycarbonyl)-5-(4-(methoxycarbonyl)oxazol-5-yl)-3-methyl-4,5-dihydro-1*H*-imidazol-3-ium iodide (2.11)



Pale yellow solid. **^{1}H NMR** (500 MHz, DMSO-d_6, major isomer): δ 10.69 (s, 1H), 9.34 (s, 1H), 8.66 (s, 1H), 7.24-7.16 (m, 2H), 6.93 (dd, J = 8.2 Hz, 1.3 Hz, 1H), 6.84-6.81 (m, 2H), 5.58 (d, J = 7.0 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.49 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6, major isomer): δ 166.5, 160.4, 159.2, 153.0, 151.4, 149.7, 130.5, 130.3, 125.3, 120.6, 119.4, 116.7, 66.1, 59.4, 53.6, 52.3, 35.1; **MP**: 86-88 °C; **HRMS** (ESI), m/z calcd. for $[C_{17}H_{18}N_3O_6]^+$ (cation): 360.1190; found: 360.1205. The structure of **2.11** was confirmed by HMBC analysis (Figure 2.3).

Figure 2.3 HMBC Spectrum of **2.11**





2.11

2.5.14 X-ray Crystallographic Analysis and Determination of Configuration of the Products

The absolute configuration of **2.10** (**1*R*,2*R***) was assigned by X-ray crystallographic analysis of a single crystal of **2.10** (Figure 2.4). The crystal was prepared from the solution of **2.10** in ethyl acetate at ambient temperature. The absolute configuration of **2.7k** (**4*R*,5*R***) was deduced. The configurations of **2.7a-2.7j**, **2.7l** were assigned by analogy.

Figure 2.4 X-ray Structure of **2.10**

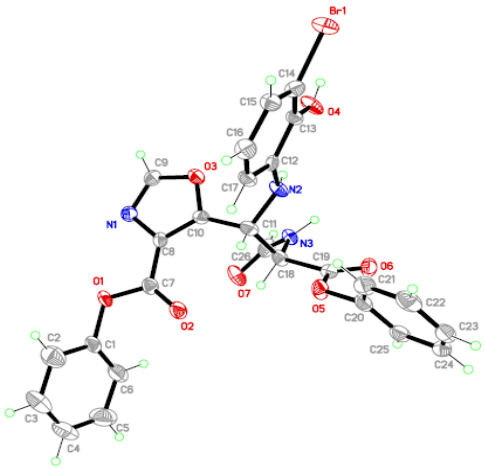


Table 2.4 Crystal Data and Structure Refinement for **2.10**

Identification code	**2.10**
Empirical formula	$C_{30}H_{28}BrN_3O_9$
Formula weight	654.46
Temperature	100(2) K
Wavelength	1.54178 Å

Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.1252(15) Å	α = 90°
	b = 13.217(2) Å	β = 90°
	c = 22.607(4) Å	γ = 90°
Volume	3025.3(8) $Å^3$	
Z	4	
Density (calculated)	1.437 Mg/m^3	
Absorption coefficient	2.350 mm^{-1}	
F(000)	1344	
Crystal size	0.290 x 0.190 x 0.080 mm^3	
Theta range for data collection	3.874 to 68.196°	
Index ranges	-12<=h<=10, -14<=k<=15, -12<=l<=27	
Reflections collected	16789	
Independent reflections	5418 [R(int) = 0.0328]	
Completeness to theta = 67.679°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7531 and 0.6432	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5418 / 3 / 399	
Goodness-of-fit on F^2	1.152	
Final R indices [I>2sigma(I)]	R1 = 0.0593, wR2 = 0.1643	

R indices (all data)	R1 = 0.0626, wR2 = 0.1678
Absolute structure parameter	0.035(8)
Extinction coefficient	n/a
Largest diff. peak and hole	1.987 and -0.612 e.Å^{-3}

The relative configuration of **2.7o** was assigned by X-ray crystallographic analysis of a single crystal of **2.7o** (Figure 2.5). The crystal was prepared from the solution of **2.7o** in dimethyl sulfoxide (DMSO) at ambient temperature.

Figure 2.5 X-ray Structure of **2.7o**

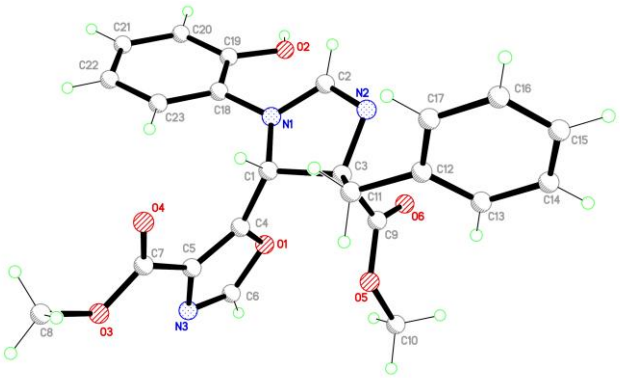


Table 2.5 Crystal Data and Structure Refinement for **2.7o**

Identification code	**2.7o**
Empirical formula	$C_{23}H_{21}N_3O_6$
Formula weight	435.43
Temperature	100(2) K
Wavelength	0.71073 Å

Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 9.3056(3) Å	α = 90°
	b = 10.5189(3) Å	β = 95.9360(11)°
	c = 21.2002(8) Å	γ = 90°
Volume	2064.05(12) $Å^3$	
Z	4	
Density (calculated)	1.401 Mg/m^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	912	
Crystal size	0.240 x 0.120 x 0.100 mm^3	
Theta range for data collection	2.164 to 28.283°	
Index ranges	-12<=h<=12, -14<=k<=14, -28<=l<=28	
Reflections collected	43940	
Independent reflections	5123 [R(int) = 0.0302]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.7142	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5123 / 0 / 295	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0390, wR2 = 0.0910	

R indices (all data)	R1 = 0.0492, wR2 = 0.0958
Absolute structure parameter	0.035(8)
Extinction coefficient	n/a
Largest diff. peak and hole	0.366 and -0.214 e.Å^{-3}

Chapter 3 Catalytic Divergent Synthesis of 3*H* or 1*H* Pyrroles by [3+2] Cyclization of Allenoates with Activated Isocyanides

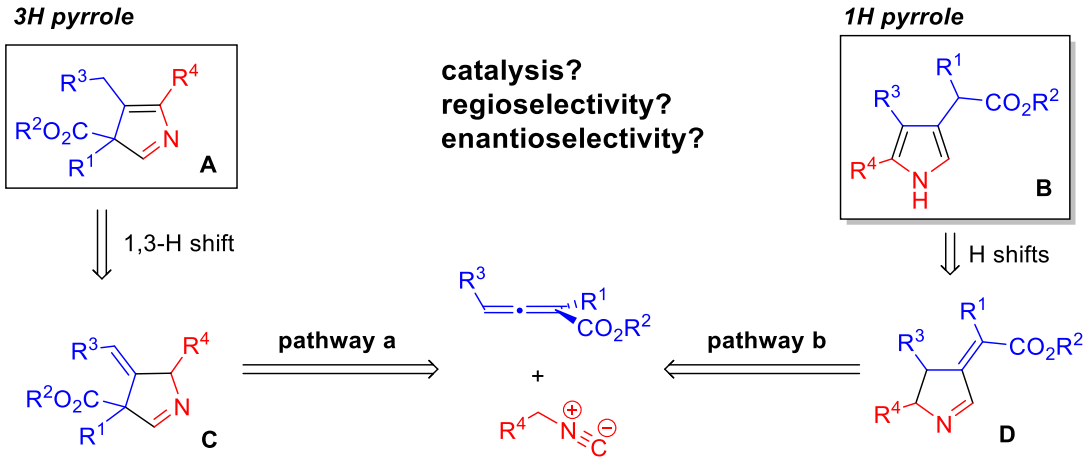
3.1 Introduction

The development of efficient and atom economical processes for the preparation of valuable heterocycles remains an important goal in synthetic organic chemistry. In particular, the construction of pyrroles, one of the most abundant and useful classes of *N*-heterocycle,[73] is still under active investigation for which transition metal-catalyzed cyclization strategies have proven highly fruitful.[74] In contrast, the isomeric non-aromatic 3*H* pyrroles (**A** in Scheme 3.1) have been poorly studied due to their difficult access, although some of them have been shown to possess *anti*-tumor or *anti*-microbial activities.[75] The few previously reported syntheses of 3*H* pyrrole were either low yielding to produce mixture of isomers, or required harsh reaction conditions and suffered from narrow substrate scope.[76] To the best of our knowledge, no enantioselective synthesis of this class of heterocycle has been reported.

Activated isocyanides such as isocyanoacetates have proven to be a versatile functionality to undergo cyclization with various π-systems for heterocycle synthesis.[2, 53a, 54] In particular, substituted pyrroles can be obtained from the reaction of isocyanoacetate with nitroalkenes (as in Barton-Zard pyrrole synthesis),[77] alkynoates (catalyzed by copper reported from the groups of Yamamoto[56a] and de Meijere[56b]), and even simple terminal alkynes (catalyzed by silver reported by the groups of Bi[78] and Lei[79]). Based on our group's continuous interest in isocyanoacetate chemistry,[26] we became interested in the reaction between isocyanoacetate and allenoate,[80] and we envisioned such a combination of two versatile functionalities may lead to an efficient synthesis of difficult-to-access 3*H*

pyrroles.

Scheme 3.1 3*H* or 1*H* Pyrrole from Reaction of Allenoates with Activated Isocyanides



As illustrated in Scheme 3.1, the [3+2] cyclization of isocyanoacetate and allenoate may proceed with different regioselectivity to generate intermediates **C** or **D** (or other isomers). Once **C** is formed, it should undergo facile 1,3-H shift to produce 3*H* pyrrole **A**. While 3*H* pyrroles without 3,3-disubstitution is known to readily rearrange to 1*H* pyrroles through 1,3-H shift driven by aromatization, compound **A** bearing a quaternary carbon can be produced as a stable compound. Alternatively, intermediate **D** will most likely undergo multiple H-shifts to produce 1*H* pyrrole **B**.

The focus of this study was whether an efficient catalytic method could be developed that will allow regio- and stereoselective synthesis of 3*H* or 1*H* pyrroles. Herein we report operationally simple procedures using silver or phosphine catalysis to deliver these products as well as related *N*-heterocycles from allenoates and

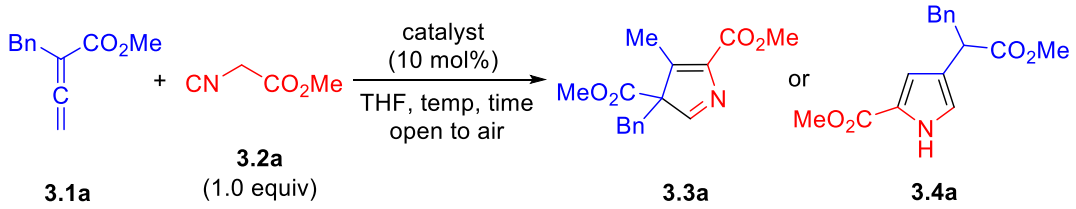
activated isocyanides in high efficiency and stereoselectivity.

3.2 Results and Discussion

3.2.1 Identification of Divergent Reaction Profile

The readily available allenoate **3.1a** and isocyanoacetate **3.2a** were chosen as the model substrates. Various metal salts with strong basicity that could deprotonate the isocyanoacetate to deliver the enolate reactivity of **3.2a** were evaluated; selected data are summarized in Table 3.1.

Table 3.1 Identification of Divergent Reaction Profile[a-b]



3.1a **3.2a** (1.0 equiv) **3.3a** **3.4a**

entry	metal	ligand	temp (°C)	time (h)	**3a**:**4a** yield (%)[b]
1	Cu_2O	/	0	12	10: <2
2	Ag_2O	/	0	24	24: <2
3	Ag_2CO_3	/	0	24	37: <2
4	Ag_2CO_3	/	24	3	19: <2
5	Ag_2CO_3	PPh_3	24	1	**55**: <2
6	/	PPh_3	24	24	<2: **18**

[a] The reactions were carried out open to air. [b] Isolated yields.

At 0 °C, we were excited to observe that the desired product **3.3a** could be obtained by using copper or silver salts, albeit with low yield due to the formation of other side products (entries 1-3). When the reaction was carried out at ambient temperature using Ag_2CO_3, however, the reaction was messy to yield **3.3a** in only 19% (entry 4). In an effort to modulate the reactivity between **3.1a** and **3.2a**, the addition of ligands such as PPh_3 was examined, which to our delight led to a higher yield of **3.3a** (55%, entry 5). It is noteworthy that under these conditions no product corresponding to pathway b (Scheme 3.1) was observed. Inspired by the recent advances of phosphine catalysis of allenes with various electrophiles,[81] we also tested the control reaction using only PPh_3 as the catalyst. Intriguingly, 2,4-disubstituted pyrrole **3.4a** was formed as the exclusive product, albeit in low yield (entry 6).[56a] This observation represents an interesting example of catalyst-controlled divergent reaction.[82]

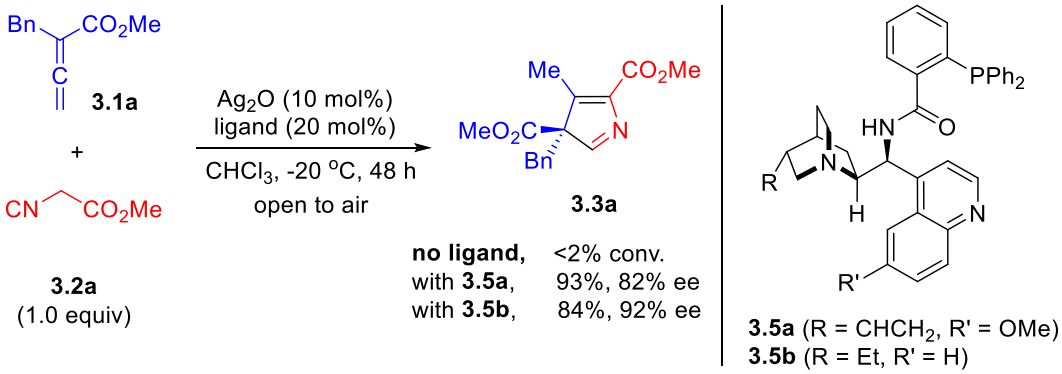
3.2.2 Silver-Catalyzed [3+2] Cyclization

3.2.2.1 Optimization of Reaction Conditions

The observation of dramatic ligand effect prompted us to examine a wide range of ligands and in particular chiral ones aiming towards an efficient as well as enantioselective synthesis of 3*H* pyrroles bearing all-carbon quaternary center.[83] In particular, the Dixon group has introduced *cinchona* alkaloid-based phosphine ligands for highly enantioselective Ag-catalyzed aldol and Mannich reactions of isocyanoacetates.[11, 23] In our hands, this family of catalysts proved remarkably

effective for highly enantioselective double [3+2] cyclization of isocyanoacetate with α-imino esters[26] as well as for 3*H* pyrrole synthesis after extensive screening of different catalysts. It is noteworthy that a dramatic ligand acceleration effect was observed with this catalytic system so that a lower temperature of -20 °C could be employed to produce **3.3a** in high yield and ee (Scheme 3.2).

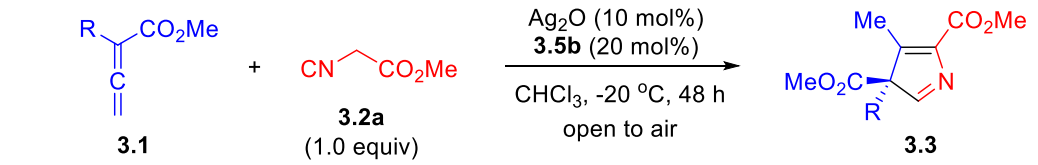
Scheme 3.2 Optimization of Ag-Catalyzed Enantioselective Cyclization

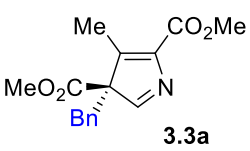


3.2.2.2 Substrate Scope

The scope of this simple catalytic procedure proved to be broad (Scheme 3.3). Various allenoates **3.1** underwent smooth reaction with **3.2a** in a 1:1 ratio at -20 °C. 3*H* Pyrrole **3.3** with different 3-substituents including benzyl derivatives (**3.3a**-**3.3j**), allyl (**3.3k**) and alkyl (**3.3l**, **3.3m**) groups were all obtained in high yield (73-94%) with good to excellent ee (80-96%). 3*H* Pyrroles have been utilized as aza-diene for Diels-Alder reaction before;[76e] in our studies we have also identified new reactivity involving addition to the imine moiety. Details along these lines will be reported in due course.

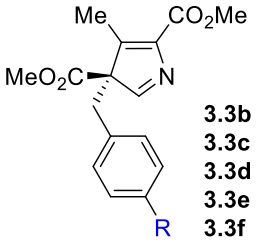
Scheme 3.3 Enantioselective Synthesis of 3*H* Pyrrole[a-c]



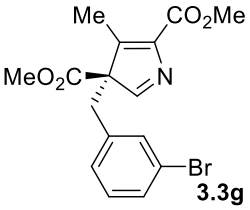


3.3a

84%, 92% ee
(77%, 440 mg, 88% ee)[c]

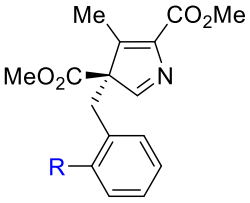


3.3b (R = Me): 92%, 94% ee
3.3c (R = OMe): 74%, 91% ee
3.3d (R = Br): 87%, 88% ee
3.3e (R = F): 92%, 96% ee
3.3f (R = CF_3): 88%, 91% ee

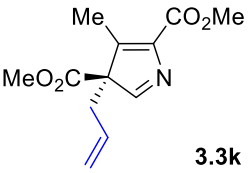


3.3g

94%, 87% ee

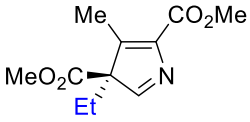


3.3h (R = Me): 84%, 96% ee
3.3i (R = Br): 90%, 96% ee
3.3j (R = CF_3): 85%, 94% ee



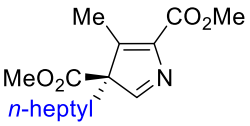
3.3k

88%, 83% ee



3.3l

73%, 80% ee



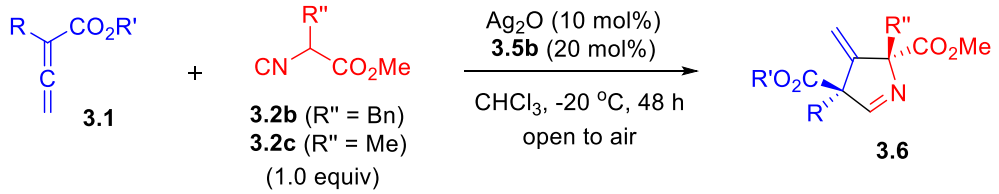
3.3m

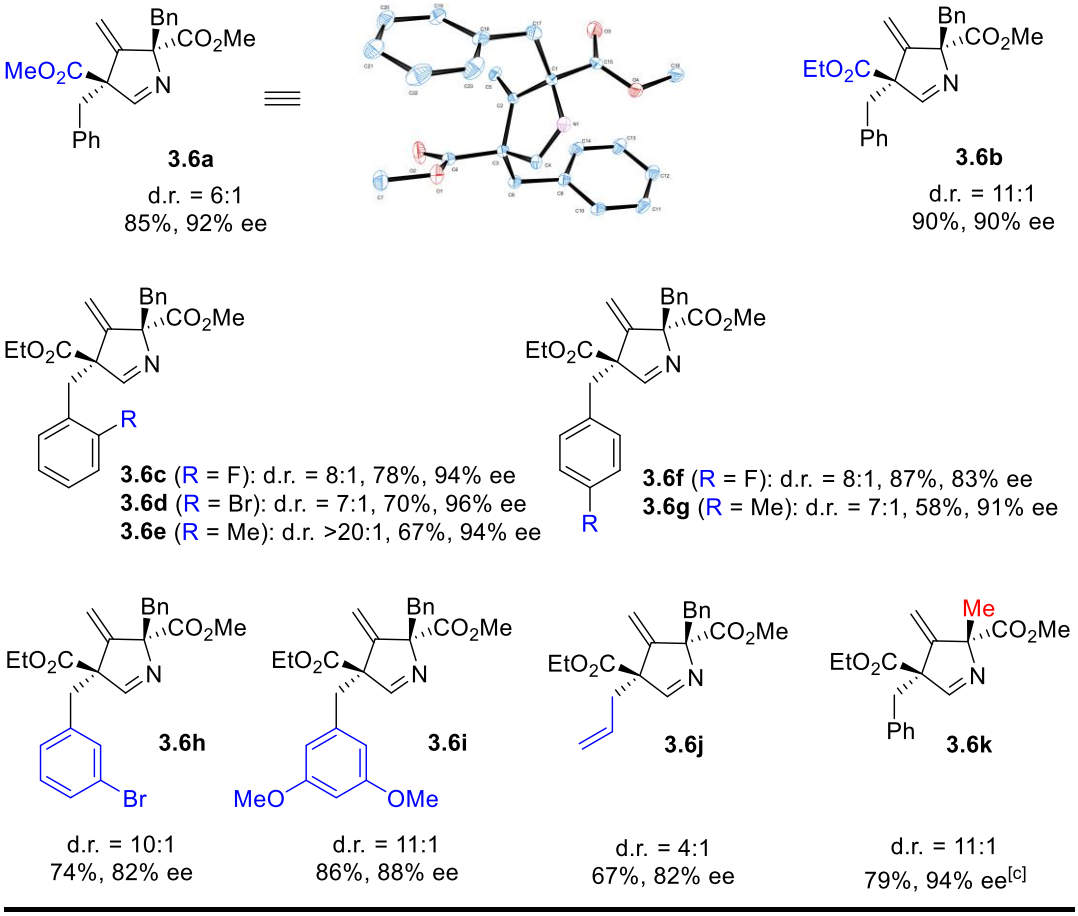
89%, 93% ee

[a] Carried out at -20 °C for 48 h. [b] Isolated yields. [c] 2 mmol-scale reaction.

To further extend the scope of this catalytic system, the reaction of **3.1a** with disubstituted isocyanoacetate **3.2b** was examined under the same conditions (Scheme 3.4). Gratifyingly, the direct [3+2] cyclization product **3.6a** possessing an exocyclic olefin (corresponding to **C** in Scheme 3.1) was obtained in high yield and 92% ee, with a good d.r. of 6:1 (85% isolated major diastereomer). The formation of **3.6a** not only provided strong support for the mechanism of formation of 3*H* pyrrole **3.3** through [3+2] cyclization followed by 1,3-H shift (that is not possible in the case of **3.6a**), but also highlighted the versatility of our method to prepare *N*-heterocycles bearing multiple quaternary stereocenters.[83]

Scheme 3.4 Cyclization of Disubstituted Isocyanoacetates[a-c]





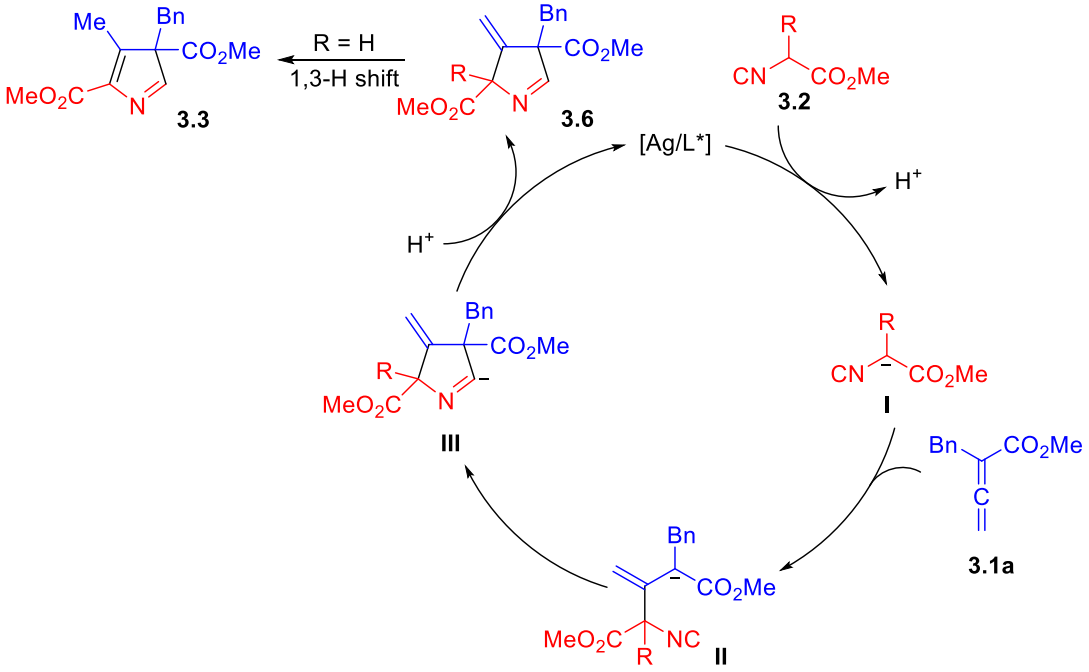
[a] The reactions were carried out at -20 °C under ambient atmosphere for 48 h. [b] Isolated yields of the major diastereomer. [c] The reaction time was 7 days.

The same set of conditions could be used to produce a wide range of heterocycles **3.6** (Scheme 3.4). The use of ethyl ester analog of **3.1a** led to **3.6b** in higher d.r. and similar ee. Various substituted benzyl groups (**3.6c**-**3.6i**) as well as allyl substituent (**3.6j**) on the allenoate structure could be tolerated to yield the products in high yield

and selectivity (82-96% ee; d.r. up to >20:1). Finally, use of methyl-substituted isocyanoacetate **3.2c** yielded **3.6k** in excellent stereoselectivity as well. In all cases, the yields refer to that of the isolated major diastereomer. The relative and absolute configuration of **3.6a** was unambiguously assigned by single crystal X-ray analysis and those of other products were assigned by analog. It is also worth noting that all the reactions were carried out under ambient atmosphere; exclusion of air or moisture was not required.

3.2.2.3 Proposed Mechanism

Scheme 3.5 Proposed Mechanism for the Formation of **3.3** and **3.6**



This method represents a new entry to Ag-catalyzed reactions of isocyanoacetates. As illustrated by the proposed mechanism in Scheme 3.5, intermediate **I** formed by

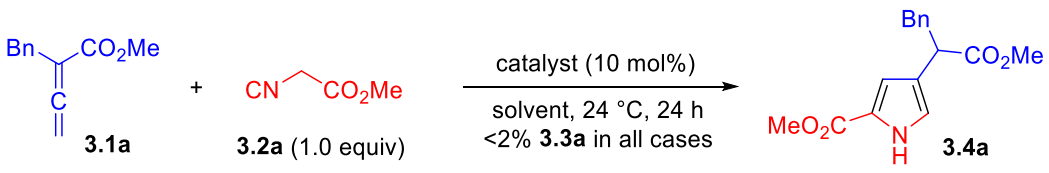
deprotonation of isocyanoacetate **3.2** would attack allenoate **3.1a** to generate **II**. Subsequent intramolecular cyclization and protonation affords formal [3+2] cyclization product **3.6**. When substituent R is proton, it would undergo facile 1,3-H shift to produce 3*H* pyrrole **3.3**.

3.2.3 Phosphine-Catalyzed [3+2] Cyclization

3.2.3.1 Optimization of Reaction Conditions

Recognizing the synthetic utility of conversion of readily available allenoates to polysubstituted pyrroles, we decided to optimize the PPh_3-catalyzed reaction (entry 6, Table 3.1); selected data are summarized in Table 3.2. Various trialkylphosphines (*e.g.* PCy_3), diarylmonoalkyl-phosphines (*e.g.* $Ph_2PCH_2PPh_2$) and triarylphosphines were examined (entries 1-4), and the simple and inexpensive PPh_3 was determined to be the optimal choice. After screening of reaction conditions, a dramatic solvent effect was discovered. Chloroform proved superior to all others leading to a highly efficient synthesis of **3.4a** (entry 5). Decreased catalyst loading of 5 mol% PPh_3 resulted in a lower yield of 78% (entry 9). It is worth noting that under these conditions no product corresponding to pathway a (Scheme 3.1) was observed.

Table 3.2 Optimization of Phosphine Catalysis[a-d]



entry	catalyst	solvent	yield (%)[b]
1	PCy_3	CH_2Cl_2	15
2	$PPh_2CH_2PPh_2$	CH_2Cl_2	52
3	P(*o*-tol)$_3$	CH_2Cl_2	n.r.[c]
4	PPh_3	CH_2Cl_2	53
5	**PPh_3**	**$CHCl_3$**	**90**
6	PPh_3	THF	18
7	PPh_3	Et_2O	25
8	PPh_3	toluene	17
9[d]	PPh_3	$CHCl_3$	78

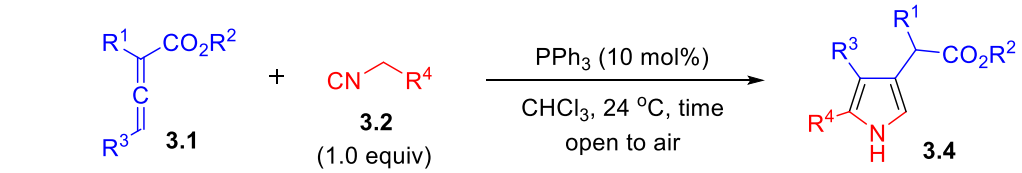
[a] The reactions were carried out at ambient temperature in air for 24 h. [b] Isolated yields. [c] n.r. = no reaction. [d] 5 mol% PPh_3 was used.

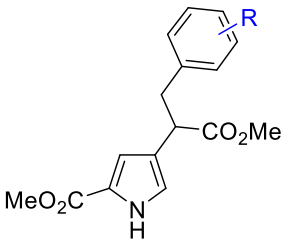
3.2.3.2 Substrate Scope

Using this catalytic protocol, a wide range of di- and tri-substituted pyrroles could be accessed (Scheme 3.6). Different substituents on allenoates were well tolerated (**3.4a**-**3.4p**). Different isocyanoacetates as well as tosylmethylisocyanide could also be used to produce **3.4q**, **3.4r** and **3.4s**-**3.4w** in good to high yield. The high efficiency of this process, coupled with the operational simplicity (use of cheap PPh_3 as catalyst and running reactions open to air), makes it an attractive method for pyrrole synthesis. The related 2,4-disubstituted pyrroles such as Pyrrolostatin[84] are important targets in medicinal chemistry and the current method provides a rapid access to the core

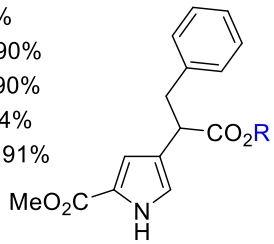
structure of those compounds.

Scheme 3.6 Pyrrole Synthesis by PPh_3 Catalysis[a-f]

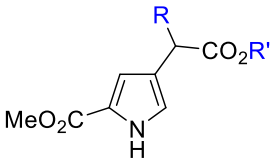




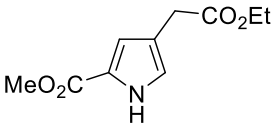
3.4a (R = H): 24 h, 90%
3.4b (R = 4-Br): 17 h, 90%
3.4c (R = 3-Br): 17 h, 90%
3.4d (R = 4-F): 17 h, 94%
3.4e (R = 4-Me): 17 h, 91%



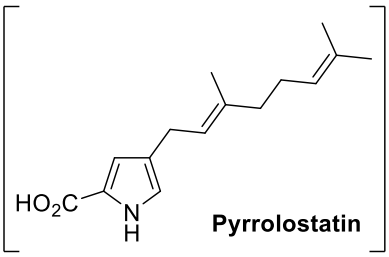
3.4f (R = Et): 18 h, 95%
3.4g (R = *i*-Pr): 16 h, 93%
(>98%, 1.26 g)[c]
3.4h (R = *t*-Bu): 72 h, 95%
3.4i (R = Cy): 36 h, 93%

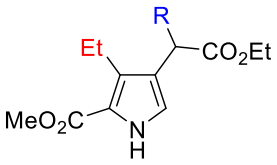


3.4j (R = Me, R' = Bn): 23 h, 75%
3.4k (R = Et, R' = Me): 23 h, 84%
3.4l (R = Allyl, R' = Me): 16 h, 81%
3.4m (R = CH_2CO_2Me, R' = Me): 16 h, 86%

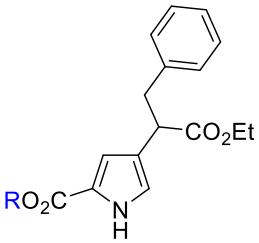


3.4n: 43 h, 56%[d]

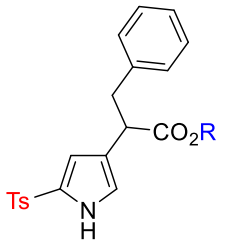




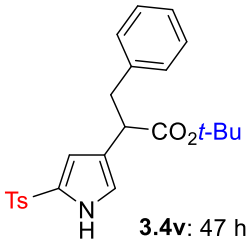
3.4o (R = H): 41 h, 59%[d]
3.4p (R = Bn): 95 h, 39%[e]



3.4q (R = Et): 20 h, 97%
3.4r (R = *t*-Bu): 89 h, 82%[d]

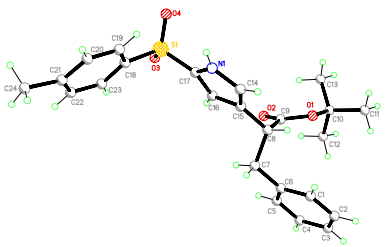


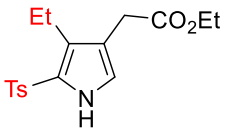
3.4s (R = Me): 23 h, 79%
3.4t (R = Et): 18 h, 83%
3.4u (R = *i*-Pr): 23 h, 86%



3.4v: 47 h, 71%[d]

≡





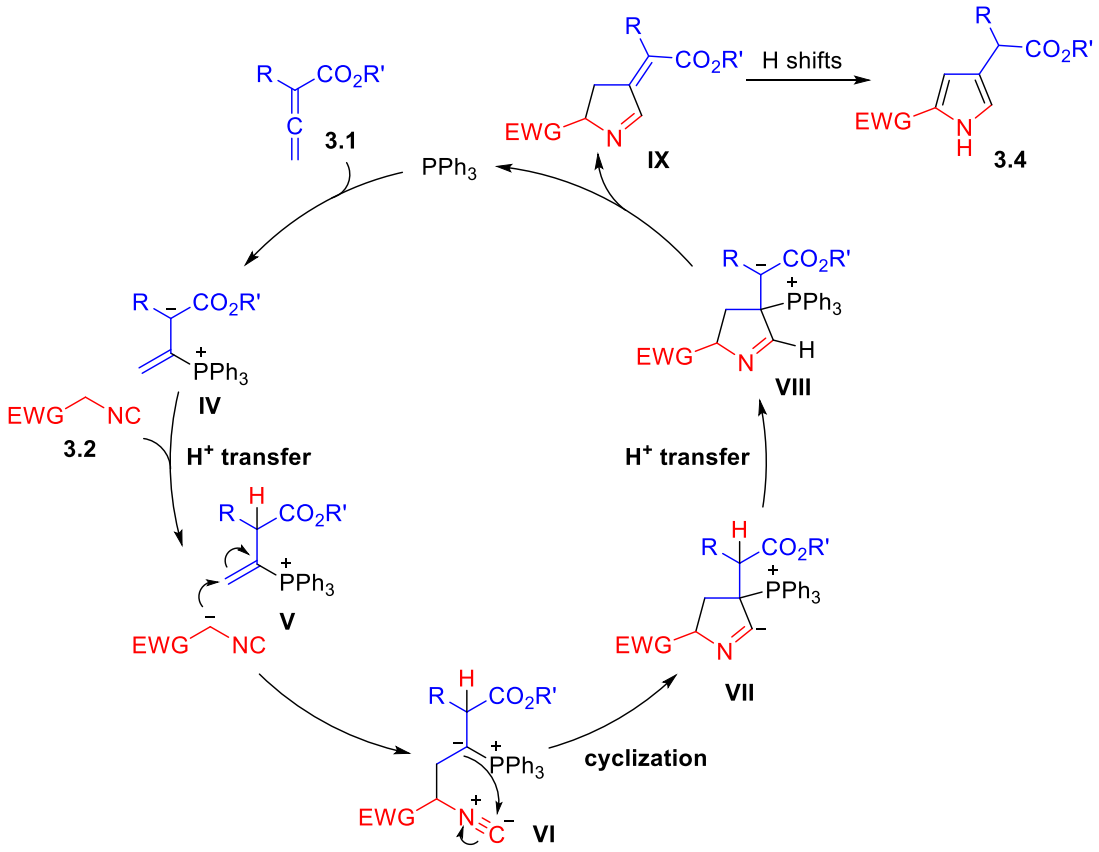
3.4w: 95 h, 58%[f]

[a] Carried out at ambient temperature in air. [b] Isolated yields. [c] 4 mmol-scale reaction for 24 h. [d] 20 mol% PPh_3. [e] 50 mol% PPh_3. [f] 30 mol% PPh_3.

3.2.3.3 Proposed Mechanism

This method represents a new entry to phosphine-catalyzed umpolung reactions.[85]

Scheme 3.7 Proposed Mechanism for the Formation of **3.4**

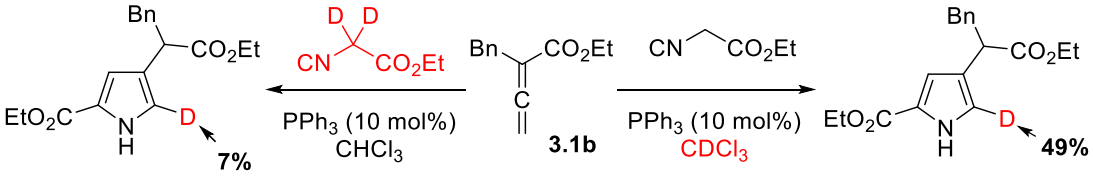


As illustrated by the proposed mechanism in Scheme 3.7, intermediate **IV** formed by addition of PPh_3 to **3.1** is reported to be capable of deprotonating Brønsted acidic substrates such as malonate to generate analogs of ion pair **V** and then ylide **VI**.[85a, 85b] With an isocyanide functionality in this case, the ylide is believed to undergo cyclization to generate **VII**. Proton transfer followed by elimination of phosphine then yields **IX** that is eventually transformed to the final product **3.4**.

3.2.3.4 Mechanistic Study

In an effort to better understand the reaction profile, deuterium labeling studies were carried out. As shown in Scheme 3.8, while the use of D_2-isocyanoacetate led to surprisingly low deuterium labeling on the pyrrole ring, the use of $CDCl_3$ resulted in significant deuterium labeling (49% *vs*. 7%). This interesting observation suggests that proton transfer (**VII** to **VIII** in Scheme 3.7) is facilitated by chloroform bearing a slightly acidic proton by proton shuffling, which is consistent with the dramatic solvent effect (Table 3.2).[86]

Scheme 3.8 Deuterium Labeling Studies



3.3 Conclusion

In conclusion, we have developed the divergent [3+2] cyclization reaction of allenoates with activated isocyanides for the first time. Under different catalytic systems, we realized the cycloaddition using either of the two C=C bonds in the allene structure. While Ag catalysis led to an unprecedented enantioselective synthesis of 3*H* pyrroles and other related *N*-heterocycles, a simple procedure using PPh_3 produced a wide range of polysubstituted 1*H* pyrroles in high efficiency. Current efforts are focused on the application of the current catalytic systems to the preparation of other types of *N*-heterocycles.

3.4 Experimental Section

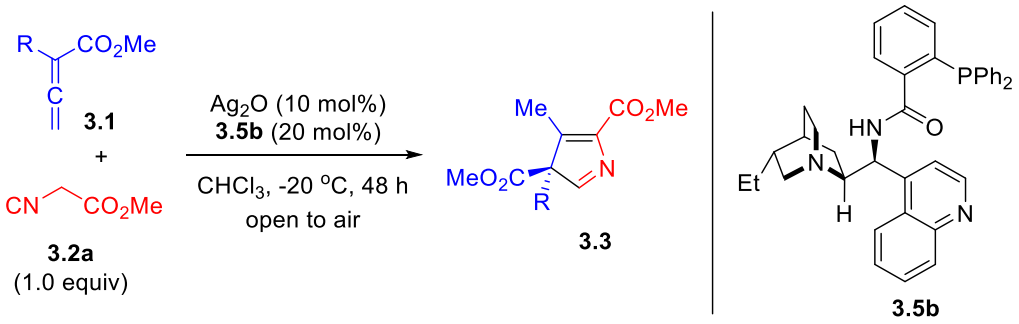
3.4.1 General Information

^{1}H and **^{13}C NMR** spectra were recorded on a Bruker AFC 300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: ^{1}H (chloroform δ 7.26; DMSO δ 2.50; Acetone δ 2.05), ^{13}C (chloroform δ 77.0; DMSO δ 39.5; Acetone δ 29.8, 206.3). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets), coupling constants (Hz) and integration. ^{19}F NMR was measured at 282 MHz, and $CFCl_3$ (0 ppm) was used as an external standard. Melting point (**MP**) was obtained on Buchi B-540. For thin layer chromatography (**TLC**), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. High resolution mass spectra (**HRMS**) were obtained on a Finnigan/MAT 95XL-T spectrometer. **Optical rotations** were recorded on an mrc AP81 automatic polarimeter. Enantiomeric excesses (**ee**) were determined by HPLC analysis on Agilent HPLC units, including the following instruments: pump, LC-20AD; detector, SPD-20A; column, Chiralcel OD-H, Chiralpak AD-H, AS-H and IA, IB, IC, IE.

Unless otherwise noted, all the reactions were carried out open to air. Dichloromethane, diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were dried over a Pure Solv solvent purification system. Deuterated solvents were purchased from Cambridge Isotope Laboratories and used as received without further

purification. Methyl isocyanoacetate (**3.2a**), ethyl isocyanoacetate and tosylmethyl isocyanide isocyanide were purchased from Alfa Aesar company and used without further purification. *tert*-Butyl isocyanoacetate[64] and all allenoates were prepared according to literature procedures.[87] Other chemicals were purchased from commercial suppliers and used as received without further purification.

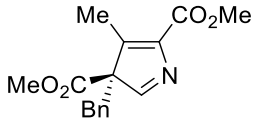
3.4.2 Ag-Catalyzed Enantioselective [3+2] Cyclization of 3.1 and 3.2a



General procedure. To a 10 mL vial charged with **3.5b**[11] (12 mg, 0.020 mmol) and Ag_2O (2.3 mg, 0.010 mmol) was added anhydrous $CHCl_3$ (0.5 mL). The mixture was allowed to stir at ambient temperature for 5 min, then allenoate **3.1** (0.10 mmol) was added in one portion. After the mixture was cooled to -20 °C, isocyanoacetate **3.2a** (0.10 mmol) in anhydrous $CHCl_3$ (0.5 mL) was added *via* syringe pump over 2 h. The reaction mixture was stirred at -20 °C for 48 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate) to afford the product **3.3**.

3.4.3 Characterization of Compounds 3.3

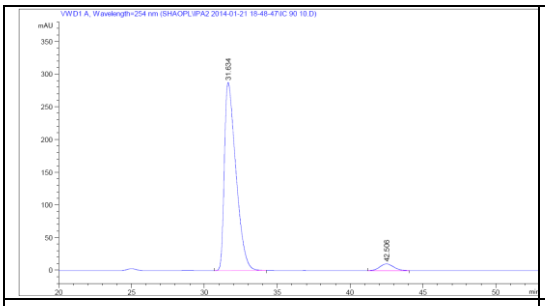
(*S*)-dimethyl 3-benzyl-4-methyl-3*H*-pyrrole-3,5-dicarboxylate (3.3a)



3.3a

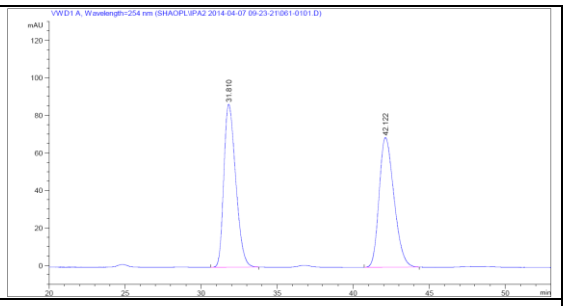
The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 84% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.21 (s, 1H), 7.21-7.17 (m, 3H), 7.10-7.09 (m, 2H), 3.69 (s, 3H), 3.63 (d, J = 13.9 Hz, 1H), 3.63 (s, 3H), 3.19 (d, J = 13.9 Hz, 1H), 2.29 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.4, 167.3, 162.7, 148.0, 141.9, 134.3, 129.2, 127.9, 127.0, 74.5, 53.0, 51.4, 36.5, 11.4; **HRMS** (ESI): m/z calcd. for [$C_{16}H_{16}NO_4$, M-H]$^-$: 286.1085; found: 286.1071.

Optical Rotation: $[\alpha]^{25}_D$ = 86.5 (c = 0.4, $CHCl_3$). The absolute configuration of **3.3a** was assigned by analogy to **3.6a**. 92% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 31.6 min for major isomer, t_R = 42.5 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

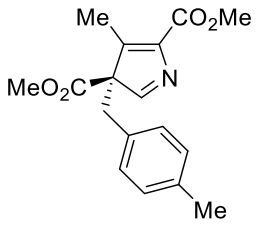
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.634	BB	0.7456	1.58397e4	287.81726	95.9517
2	42.506	BB	0.7651	668.29987	10.25111	4.0483



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.810	BB	0.6368	4713.68213	86.90087	50.0736
2	42.122	BB	0.7943	4699.83398	69.16246	49.9264

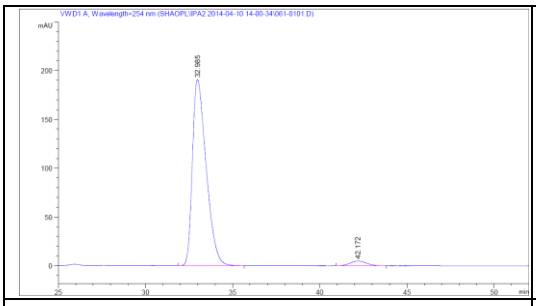
(*S*)-dimethyl 4-methyl-3-(4-methylbenzyl)-3*H*-pyrrole-3,5-dicarboxylate (3.3b)



3.3b

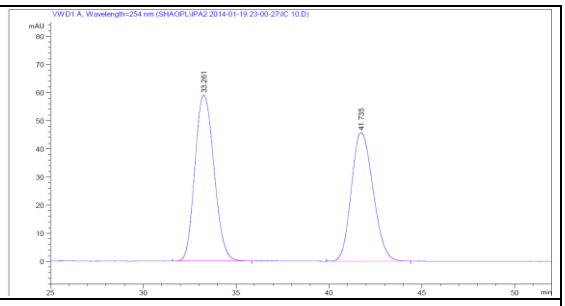
The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 92% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.19 (s, 1H), 7.01-6.96 (m, 4H), 3.69 (s, 3H), 3.63 (s, 3H), 3.58 (d, J = 13.9 Hz, 1H), 3.13 (d, J = 13.9 Hz, 1H), 2.28 (s, 3H), 2.21 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.5, 167.3, 162.7, 148.1, 141.8, 136.1, 131.2, 129.1, 128.5, 74.6, 53.0, 51.5, 36.2, 20.6, 11.4; **HRMS** (ESI): m/z calcd. for [$C_{17}H_{18}NO_4$, M-H]$^-$: 300.1241; found: 300.1243.

Optical Rotation: $[\alpha]^{25}_D$ = 82.8 (c = 0.3, $CHCl_3$). The absolute configuration of **3.3b** was assigned by analogy to **3.3a**. 94% ee (HPLC condition: Chiralcel IC column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 33.0 min for major isomer, t_R = 42.2 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

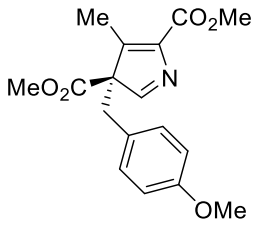
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.985	BB	0.7958	1.04640e4	190.81758	97.0669
2	42.172	BB	0.7611	316.18893	4.86621	2.9331



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.261	BB	1.0634	4229.10645	59.06289	53.2572
2	41.735	BB	1.2138	3711.79834	45.78618	46.7428

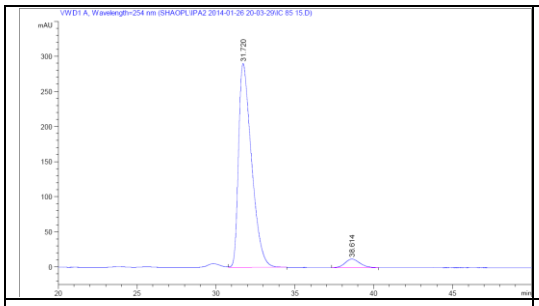
(*S*)-dimethyl 3-(4-methoxybenzyl)-4-methyl-3*H*-pyrrole-3,5-dicarboxylate (3.3c)



3.3c

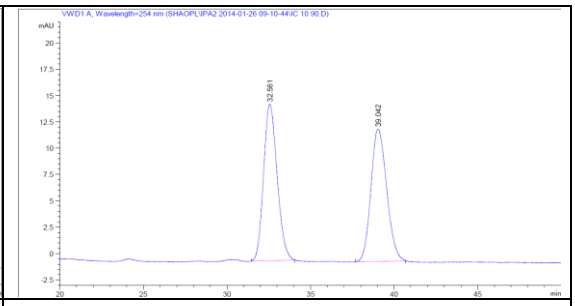
The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 74% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.19 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 3.63 (s, 3H), 3.56 (d, *J* = 13.8 Hz, 1H), 3.11 (d, *J* = 13.8 Hz, 1H), 2.28 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.5, 167.3, 162.7, 158.1, 148.1, 141.8, 130.3, 126.1, 113.3, 74.7, 54.9, 53.0, 51.5, 35.8, 11.4; **HRMS** (ESI): m/z calcd. for $[C_{17}H_{18}NO_5, M\text{-}H]^-$: 316.1190; found: 316.1191.

Optical Rotation: $[\alpha]^{25}_D$ = 62.2 (c = 0.3, $CHCl_3$). The absolute configuration of **3.3c** was assigned by analogy to **3.3a**. 91% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 85:15, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 31.7 min for major isomer, t_R = 38.6 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

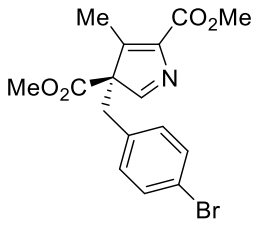
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.720	VB	0.7740	1.66209e4	290.27914	95.5570
2	38.614	VB	0.7531	772.80615	11.99587	4.4430



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.561	BB	0.6573	836.99536	14.87837	50.3487
2	39.042	BV	0.7671	825.40228	12.59414	49.6513

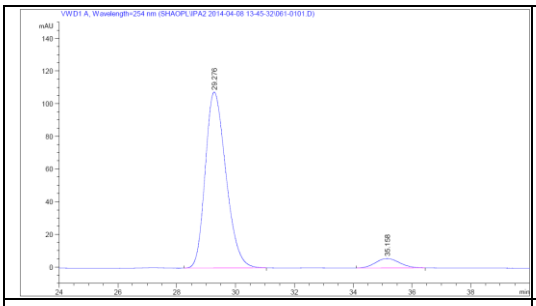
(*S*)-dimethyl 3-(4-bromobenzyl)-4-methyl-3*H*-pyrrole-3,5-dicarboxylate (3.3d)



3.3d

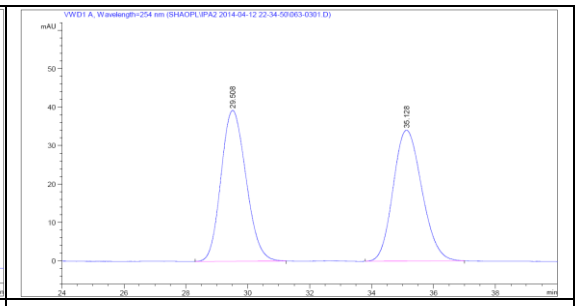
The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 87% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.38 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 3.70 (s, 3H), 3.63 (s, 3H), 3.61 (d, J = 13.8 Hz, 1H), 3.20 (d, J = 13.5 Hz, 1H), 2.28 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.3, 167.1, 162.6, 147.8, 142.0, 133.7, 131.5, 130.8, 120.3, 74.2, 53.1, 51.5, 35.5, 11.4; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{16}BrNNaO_4, M+Na]^+$: 388.0155; found: 388.0165.

Optical Rotation: $[\alpha]^{25}_D$ = 64.3 (c = 0.3, $CHCl_3$). The absolute configuration of **3.3d** was assigned by analogy to **3.3a**. 88% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 29.3 min for major isomer, t_R = 35.2 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

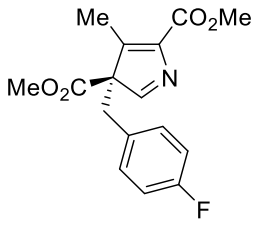
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.276	BB	0.5883	5255.60645	107.80663	94.1710
2	35.158	BB	0.6601	325.31232	5.76726	5.8290



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.508	BB	0.6565	2200.97900	39.26047	50.0668
2	35.128	BB	0.7533	2195.10376	34.06339	49.9332

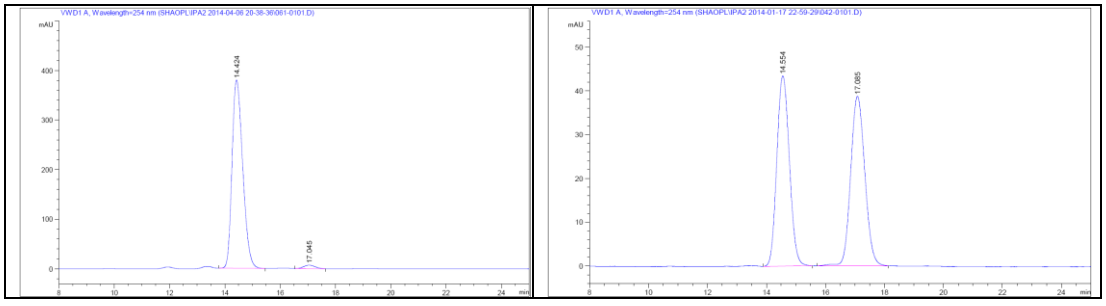
(*S*)-dimethyl 3-(4-fluorobenzyl)-4-methyl-3*H*-pyrrole-3,5-dicarboxylate (3.3e)



3.3e

The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1.5:1). Colorless syrup, 92% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.15-7.12 (m, 1H), 7.03-6.99 (m, 1H), 3.69 (s, 3H), 3.63 (d, *J* = 13.9 Hz, 1H), 3.63 (s, 3H), 3.20 (d, *J* = 13.9 Hz, 1H), 2.28 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.4, 167.2, 162.7, 161.2 (d, *J* = 241.4 Hz), 147.8, 142.0, 131.2 (d, *J* = 8.2 Hz), 130.4 (d, *J* = 2.7 Hz), 114.6 (d, *J* = 21.0 Hz), 74.4, 53.0, 51.5, 35.5, 11.4; **^{19}F NMR** (282 MHz, DMSO-d_6): δ -115.52; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{16}FNNaO_4, M+Na]^+$: 328.0956; found: 328.0971.

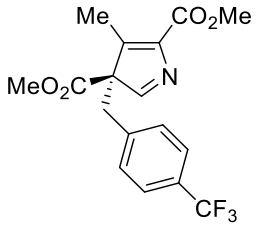
Optical Rotation: $[\alpha]^{25}_D$ = 39.4 (c = 0.7, $CHCl_3$). The absolute configuration of **3.3e** was assigned by analogy to **3.3a**. 96% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 14.4 min for major isomer, t_R = 17.0 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm						
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.424	VV	0.3722	1.01607e4	379.69833	98.0730
2	17.045	VV	0.3357	199.64679	6.96355	1.9270

Signal 1: VWD1 A, Wavelength=254 nm						
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.554	BB	0.3528	1283.29382	43.42076	49.8580
2	17.085	BB	0.3940	1290.60278	38.70964	50.1420

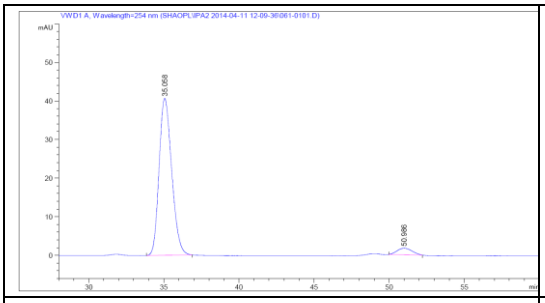
(*S*)-dimethyl 4-methyl-3-(4-(trifluoromethyl)benzyl)-3*H*-pyrrole-3,5-dicarboxylate (3.3f)



3.3f

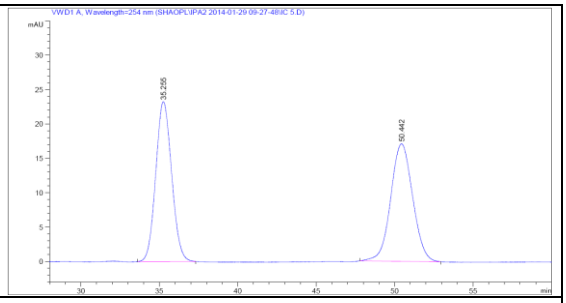
The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 88% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 3.73 (d, J = 13.2 Hz, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.32 (d, J = 14.5 Hz, 1H), 2.30 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.2, 167.1, 162.6, 147.7, 142.1, 139.2, 130.1, 127.6 (q, J = 31.9 Hz), 124.7 (q, J = 4.6 Hz), 124.2 (q, J = 270.5 Hz), 74.2, 53.1, 51.5, 35.7, 11.3; **^{19}F NMR** (282 MHz, DMSO-d_6): δ -60.94; **HRMS** (ESI): m/z calcd. for $[C_{17}H_{16}F_3NNaO_4, M+Na]^+$: 378.0924; found: 378.0932.

Optical Rotation: $[\alpha]^{25}_D$ = 50.2 (c = 0.3, $CHCl_3$). The absolute configuration of **3.3f** was assigned by analogy to **3.3a**. 91% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 35.1 min for major isomer, t_R = 51.0 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

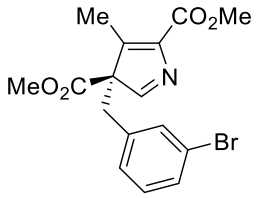
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.058	BB	0.6813	2367.87354	40.64016	95.2682
2	50.986	BB	0.8120	117.60919	1.70441	4.7318



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.255	BB	0.8260	1637.85962	23.24649	49.6986
2	50.442	BB	1.1438	1657.72803	17.07239	50.3014

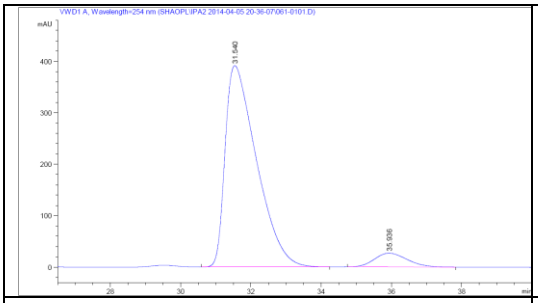
(*S*)-dimethyl 3-(3-bromobenzyl)-4-methyl-3*H*-pyrrole-3,5-dicarboxylate (3.3g)



3.3g

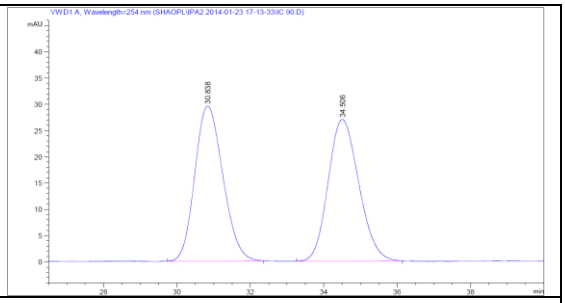
The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 94% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.24 (s, 1H), 7.38-7.33 (m, 2H), 7.16 (t, J = 7.9 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 3.70 (s, 3H), 3.63 (d, J = 13.9 Hz, 1H), 3.64 (s, 3H), 3.23 (d, J = 13.3 Hz, 1H), 2.28 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.2, 167.1, 162.6, 147.7, 142.1, 137.0, 132.0, 130.0, 128.3, 121.0, 74.2, 53.1, 51.5, 35.5, 11.4; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{16}BrNNaO_4, M+Na]^+$: 388.0155; found: 388.0159.

Optical Rotation: $[\alpha]^{25}_D$ = 48.2 (c = 0.3, $CHCl_3$). The absolute configuration of **3.3g** was assigned by analogy to **3.3a**. 87% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 31.5 min for major isomer, t_R = 35.9 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

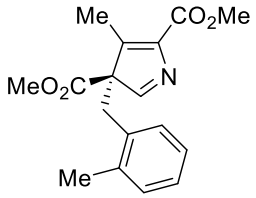
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.540	BB	0.8147	2.42107e4	391.13046	93.3785
2	35.936	BB	0.7560	1716.79358	26.63470	6.6215



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.838	BB	0.6224	1567.05066	29.51832	50.0318
2	34.506	BB	0.6783	1565.05554	26.97815	49.9682

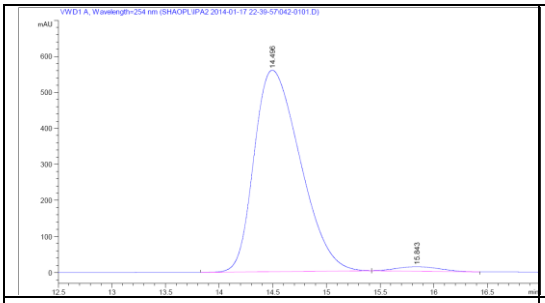
(*S*)-dimethyl 4-methyl-3-(2-methylbenzyl)-3*H*-pyrrole-3,5-dicarboxylate (3.3h)



3.3h

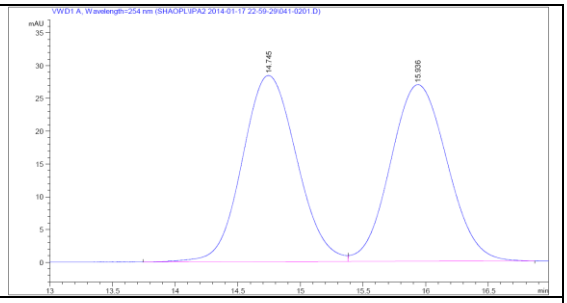
The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 84% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.06 (s, 1H), 7.13-7.08 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 3.62 (d, J = 14.4 Hz, 1H), 3.07 (d, J = 14.2 Hz, 1H), 2.32 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.1, 167.5, 162.8, 148.2, 141.6, 136.1, 133.1, 130.4, 129.2, 127.2, 125.5, 74.5, 53.1, 51.5, 33.4, 19.4, 11.5; **HRMS** (ESI): m/z calcd. for $[C_{17}H_{18}NO_4, M\text{-}H]^-$: 300.1241; found: 300.1233.

Optical Rotation: $[\alpha]^{25}_D$ = 52.5 (c = 0.3, $CHCl_3$). The absolute configuration of **3.3h** was assigned by analogy to **3.3a**. 96% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 14.5 min for major isomer, t_R = 15.8 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

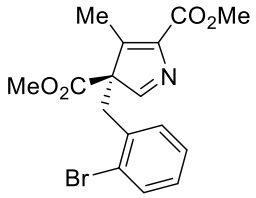
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.496	BB	0.4175	1.66658e4	559.06122	97.9664
2	15.843	BB	0.3237	345.96002	12.49807	2.0336



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.745	BV	0.3617	855.85681	28.39102	50.2045
2	15.936	VB	0.3712	848.88342	26.93318	49.7955

(*S*)-dimethyl 3-(2-bromobenzyl)-4-methyl-3*H*-pyrrole-3,5-dicarboxylate (3.3i)

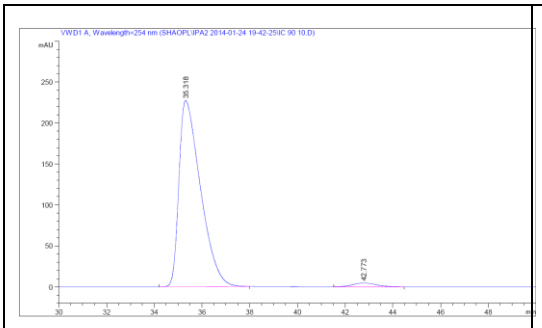


3.3i

The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 90% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.56 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.26-7.22 (m, 1H), 7.17-7.14 (m, 1H), 7.11 (dd, J = 7.6 Hz, 1.7 Hz, 1H), 3.80 (d, J = 14.0 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.35 (d, J = 14.0 Hz, 1H), 2.34 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 169.1, 167.0, 162.7, 147.7, 142.0, 134.0, 132.8, 131.0, 129.4, 127.5, 124.4, 74.3, 53.3, 51.6, 36.0, 11.6; **HRMS** (ESI), m/z calcd. for $[C_{16}H_{16}BrNNaO_4, M+Na]^+$: 388.0155; found: 388.0148.

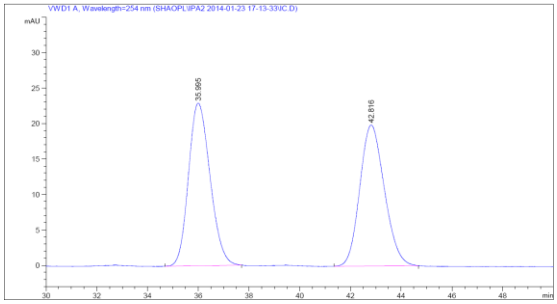
Optical Rotation: $[\alpha]^{25}_D$ = 71.3 (c = 0.4, $CHCl_3$). The absolute configuration of **3.3i** was assigned by analogy to **3.3a**. 96% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 35.3 min

for major isomer, t_R = 42.8 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

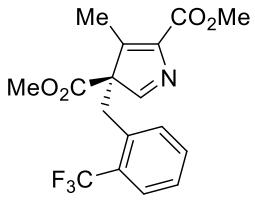
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.318	BB	0.7422	1.42154e4	227.28114	97.8621
2	42.773	BB	0.7938	310.54532	4.57593	2.1379



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.995	VB	0.6902	1355.59167	22.94728	50.3227
2	42.816	BB	0.7874	1338.20361	19.89107	49.6773

(*S*)-dimethyl 4-methyl-3-(2-(trifluoromethyl)benzyl)-3*H*-pyrrole-3,5-dicarboxylate (3.3j)

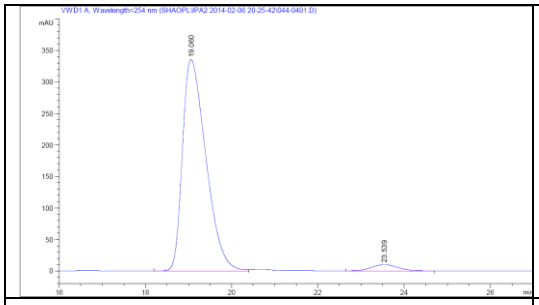


3.3j

The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 85% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 3.82 (d, *J* = 14.8 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 3.35 (d, *J* = 14.8 Hz, 1H), 2.32 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 169.5, 167.1, 162.7, 148.1, 142.3, 133.2, 132.3, 130.3, 127.9, 127.1 (q, *J* = 29.2 Hz), 126.1 (q, *J* = 5.5 Hz), 124.3 (q, *J* = 272.4 Hz), 73.7, 53.4, 51.6, 31.7, 11.3; **^{19}F NMR** (282 MHz, DMSO-d_6): δ -56.90; **HRMS** (ESI): m/z calcd. for $[C_{17}H_{16}F_3NO_4, M-H]^-$: 354.0959;

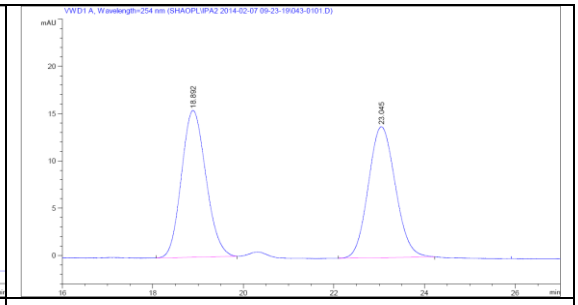
found: 354.0952.

Optical Rotation: $[\alpha]^{25}_{D}$ = -31.6 (c = 0.3, $CHCl_3$). The absolute configuration of **3.3j** was assigned by analogy to **3.3a**. 94% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 19.1 min for major isomer, t_R = 23.5 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

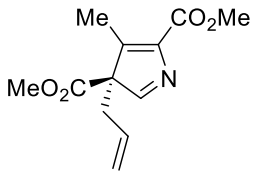
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.060	BV	0.5726	1.26316e4	335.23303	96.8317
2	23.539	BB	0.4947	413.29828	9.86670	3.1683



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.892	BB	0.4418	582.71259	15.52738	50.3647
2	23.045	BB	0.4851	574.27374	13.85384	49.6353

(*S*)-dimethyl 3-allyl-4-methyl-3*H*-pyrrole-3,5-dicarboxylate (3.3k)

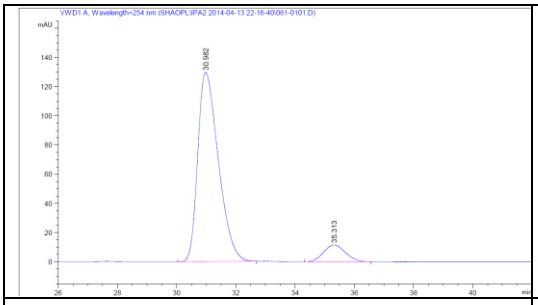


3.3k

The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 88% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.11 (s, 1H), 5.30-5.22 (m, 1H), 5.12 (dd, *J* = 17.0 Hz, 1.2 Hz, 1H), 4.98-4.96 (m, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 2.99 (dd, *J* = 13.8 Hz, 6.7 Hz, 1H), 2.61 (dd, *J* = 13.8 Hz, 7.6 Hz, 1H), 2.16 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.4, 167.1, 162.9, 148.4, 141.6, 130.5, 119.5, 73.3, 53.0, 51.5, 34.4, 11.0; **HRMS** (ESI), m/z calcd. for

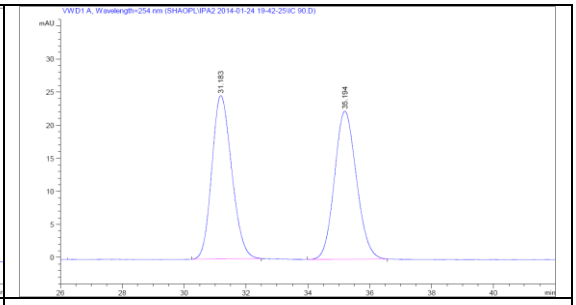
$[C_{12}H_{15}NNaO_4, M+Na]^+$: 260.0893; found: 260.0900.

Optical Rotation: $[\alpha]^{25}_D$ = 5.1 (c = 0.2, $CHCl_3$). The absolute configuration of **3.3k** was assigned by analogy to **3.3a**. 83% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 31.0 min for major isomer, t_R = 35.3 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

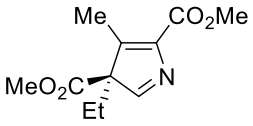
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.982	BB	0.5979	6260.72607	129.64581	91.3071
2	35.313	BB	0.6045	596.05530	11.54218	8.6929



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.183	BV	0.5227	1101.27893	24.69826	49.8963
2	35.194	BB	0.5778	1105.85596	22.38541	50.1037

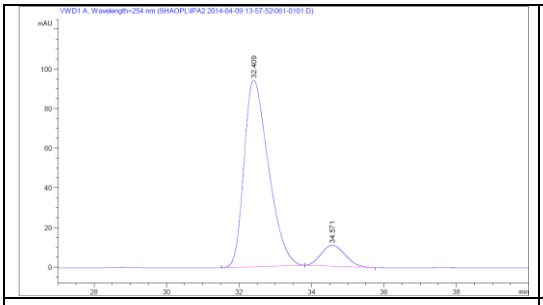
(*S*)-dimethyl 3-ethyl-4-methyl-3*H*-pyrrole-3,5-dicarboxylate (3.3l)



3.3l

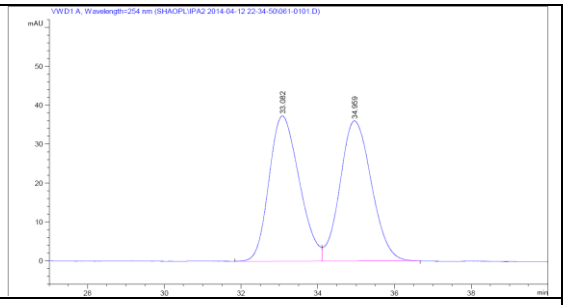
The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 73% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.12 (s, 1H), 3.78 (s, 3H), 3.61 (s, 3H), 2.31-2.24 (m, 1H), 2.14 (s, 3H), 1.88-1.81 (m, 1H), 0.58 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 171.0, 167.7, 162.9, 148.5, 141.5, 74.3, 52.9, 51.5, 23.9, 10.8, 7.9; **HRMS** (ESI): m/z calcd. for $[C_{11}H_{15}NNaO_4, M+Na]^+$: 248.0893; found: 248.0905.

Optical Rotation: $[\alpha]^{25}_{D}$ = 6.5 (c = 0.2, $CHCl_3$). The absolute configuration of **3.3l** was assigned by analogy to **3.3a**. 80% ee (HPLC condition: Chiralpak IC column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 32.4 min for major isomer, t_R = 34.6 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

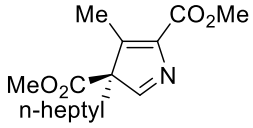
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.409	BB	0.5500	4408.55322	94.11761	90.1395
2	34.571	BB	0.5357	482.25842	10.53631	9.8605



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.082	BV	0.6426	2048.76660	37.34404	49.9184
2	34.959	VB	0.6665	2055.46509	36.06234	50.0816

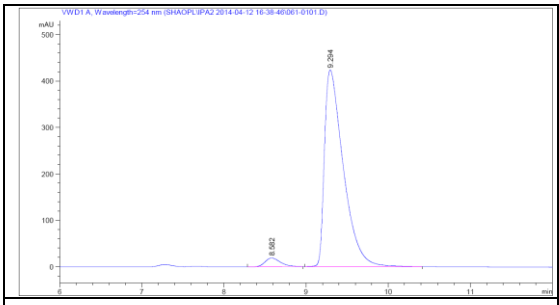
(*S*)-dimethyl 3-heptyl-4-methyl-3*H*-pyrrole-3,5-dicarboxylate (3.3m)



3.3m

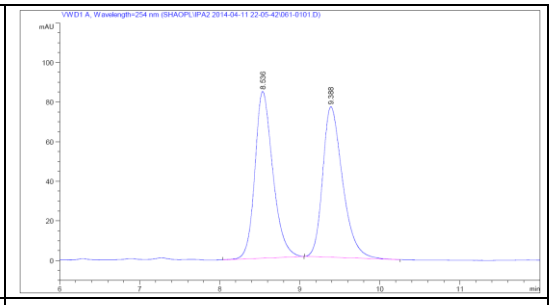
The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 1:1). Colorless syrup, 89% yield. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.14 (s, 1H), 3.78 (s, 3H), 3.61 (s, 3H), 2.24-2.18 (m, 1H), 2.15 (s, 3H), 1.81-1.75 (m, 1H), 1.25-1.18 (m, 8H), 0.91-0.86 (m, 2H), 0.83 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 171.1, 167.6, 162.9, 148.6, 141.3, 73.9, 52.9, 51.5, 31.1, 30.6, 28.9, 28.2, 23.2, 22.0, 13.8, 10.9; **HRMS** (ESI), m/z calcd. for [$C_{16}H_{25}NNaO_4$, M+Na]$^+$: 318.1676; found: 318.1679.

Optical Rotation: $[\alpha]^{25}_D$ = +21.1 (c = 0.3, $CHCl_3$). The absolute configuration of **3.3m** was assigned by analogy to **3.3a**. 93% ee (HPLC condition: Chiralcel IB column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 8.6 min for minor isomer, t_R = 9.3 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

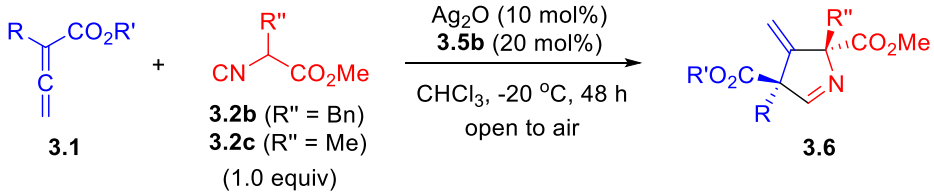
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.582	BB	0.1613	241.54588	18.80792	3.4665
2	9.294	BB	0.2308	6726.39209	423.50473	96.5335



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.536	BB	0.2189	1307.48840	84.11266	49.9077
2	9.388	BB	0.2259	1312.32678	76.00854	50.0923

3.4.4 Ag-Catalyzed Enantioselective Cyclization of Disubstituted Isocyanoacetate

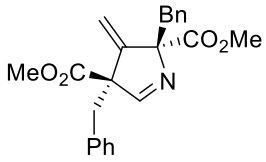


General procedure. To a 10 mL vial charged with **3.5b** (12 mg, 0.020 mmol) and Ag_2O (2.3 mg, 0.010 mmol) was added anhydrous $CHCl_3$ (0.5 mL). The mixture was allowed to stir at ambient temperature for 5 min, then allenoate **3.1** (0.10 mmol) was added in one portion. After the mixture was cooled to -20 °C, isocyanoacetate **3.2b** or **3.2c** (0.10 mmol) in anhydrous $CHCl_3$ (0.5 mL) was added *via* syringe pump over 2 h. The reaction mixture was stirred at -20 °C for 48 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate) to afford the product **3.6**. The pure major

diastereomer was isolated and characterized.

3.4.5 Characterization of Compounds 3.6

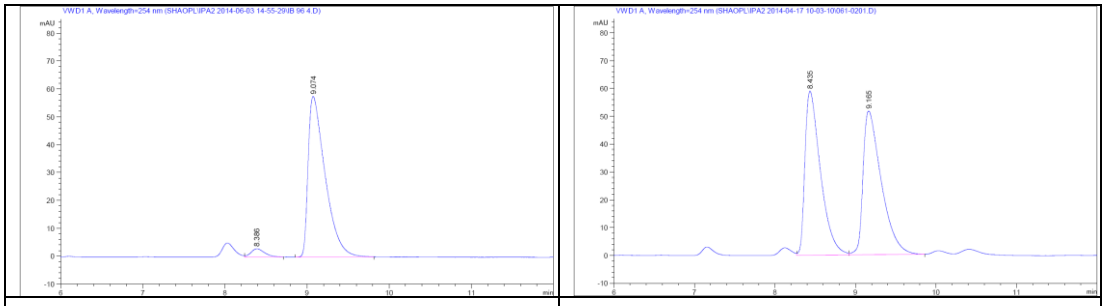
(2*R*,4*S*)-dimethyl 2,4-dibenzyl-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarbox ylate (3.6a)



3.6a

6:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). White solid, 85% yield. **MP**: 87-89 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-*d*$_6$): δ 7.65 (s, 1H), 7.23-7.18 (m, 3H), 7.17-7.14 (m, 3H), 7.01-6.98 (m, 4H), 5.65 (s, 1H), 5.60 (s, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 3.31 (d, *J* = 15.1 Hz, 1H), 3.26 (d, *J* = 13.2 Hz, 1H), 3.00 (d, *J* = 13.9 Hz, 1H), 2.91 (d, *J* = 13.3 Hz, 1H); **^{13}C NMR** (125 MHz, DMSO-*d*$_6$): δ 170.9, 170.1, 166.9, 147.3, 135.3, 135.2, 130.8, 130.0, 128.0, 127.3, 126.7, 126.2, 112.5, 84.9, 66.4, 52.6, 52.4, 44.1, 42.7; **HRMS** (ESI): m/z calcd. for [$C_{23}H_{24}NO_4$, M+H]$^{+}$: 378.1700; found: 378.1711.

Optical Rotation: $[\alpha]^{25}_{D}$ = 51.6 (c = 1.0, $CHCl_3$). 92% ee (HPLC condition: Chiralpak IB column, *n*-hexane/*i*-PrOH = 96:4, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 8.4 min for minor isomer, t_R = 9.1 min for major isomer).



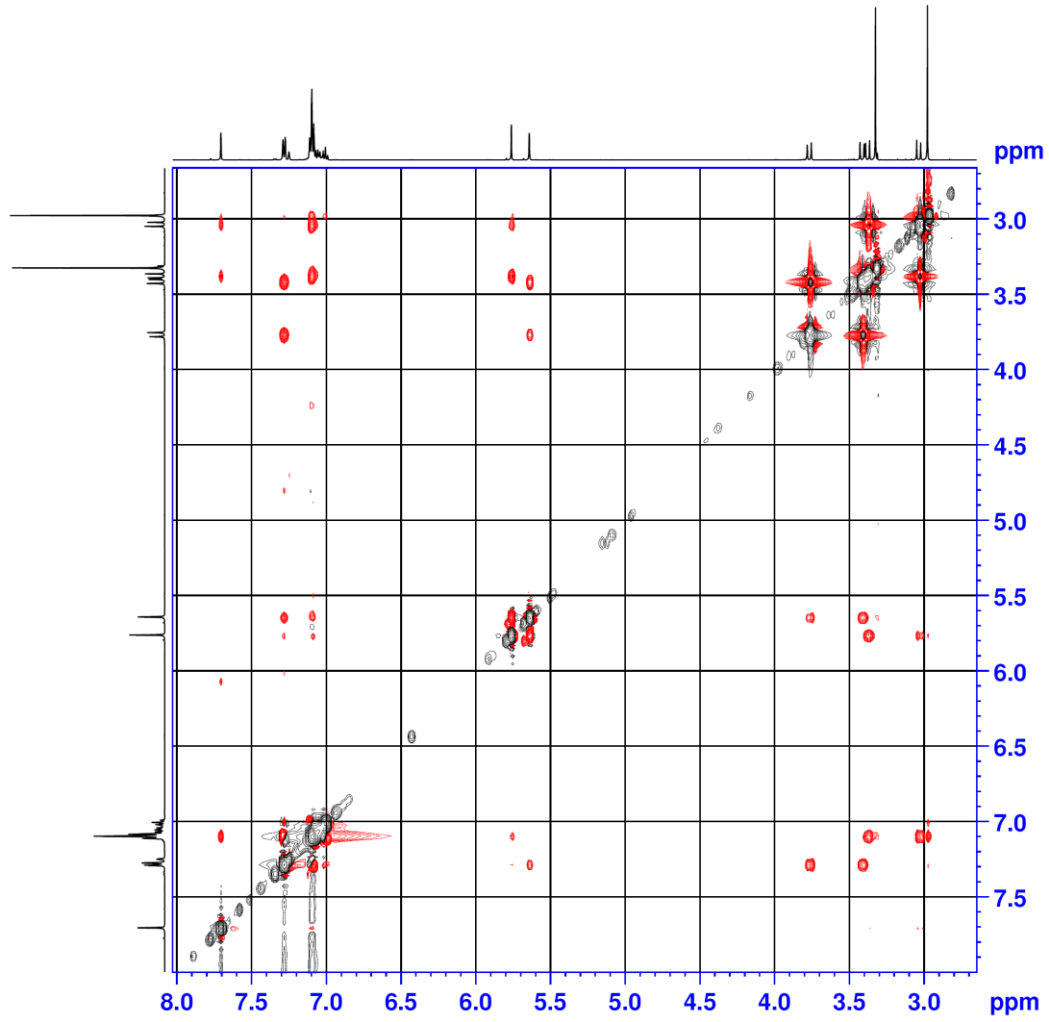
Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.386	VV	0.1386	34.94751	2.99643	4.0403
2	9.074	BV	0.1942	830.03448	57.65868	95.9597

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.435	VV	0.1914	791.58527	58.97248	49.2947
2	9.165	VB	0.2054	814.23706	51.72694	50.7053

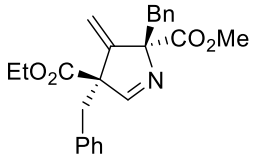
Figure 3.1 NOESY Spectrum of **3.6a**



The *trans* relative configuration of **3.6a** was determined by the NOE (Figure 3.1),

and reconfirmed by X-ray crystallographic analysis of a single crystal of **3.6a** (Figure 3.2).

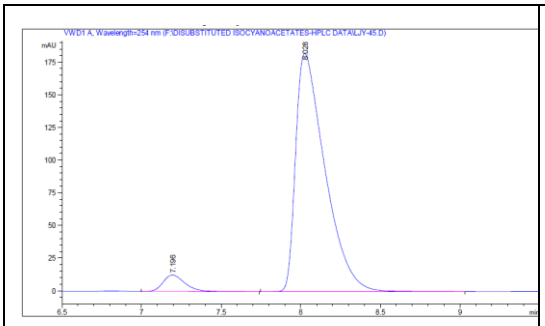
(2*R*,4*S*)-4-ethyl-2-methyl-2,4-dibenzyl-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (3.6b)



3.6b

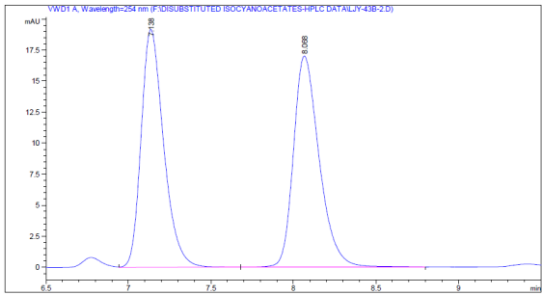
11:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.23-7.01 (m, 10H), 5.74 (s, 1H), 5.71 (s, 1H), 3.99-3.88 (m, 1H), 3.75-3.65 (m, 1H), 3.52 (s, 3H), 3.43 (d, *J* = 13.5 Hz, 1H), 3.29 (d, *J* = 13.4 Hz, 1H), 3.10 (d, *J* = 13.5 Hz, 1H), 2.92 (d, *J* = 13.4 Hz, 1H), 1.03 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.6, 170.0, 167.5, 147.5, 135.3, 135.1, 131.2, 130.1, 128.2, 127.5, 126.9, 126.4, 112.9, 85.3, 66.7, 61.6, 52.7, 45.0, 44.4, 13.7; **HRMS** (ESI): m/z calcd. for $[C_{24}H_{26}NO_4, M+H]^+$: 392.1856; found: 392.1867.

Optical Rotation: $[\alpha]^{23}_D$ = 38.2 (c = 0.5, $CHCl_3$). The absolute configuration of **3.6b** was assigned by analogy to **3.6a**. 90% ee (HPLC condition: Chiralpak IB column, *n*-hexane/*i*-PrOH = 96:4, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 7.2 min for minor isomer, t_R = 8.0 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

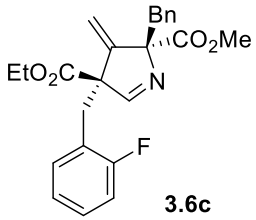
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.196	VB	0.1464	120.59810	12.63223	4.9254
2	8.028	BV	0.1900	2327.91309	182.03169	95.0746



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.138	VB	0.1458	181.94548	19.15106	49.6595
2	8.068	BB	0.1645	184.44064	16.99959	50.3405

(2*R*,4*S*)-4-ethyl 2-methyl 2-benzyl-4-(2-fluorobenzyl)-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (3.6c)

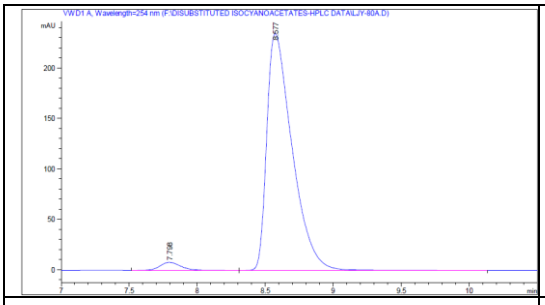


3.6c

8:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 78% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.69 (d, *J* = 2.6 Hz, 1H), 7.20-6.90 (m, 9H), 5.78 (s, 1H), 5.71 (s, 1H), 4.03-3.92 (m, 1H), 3.84-3.73 (m, 1H), 3.46-3.27 (m, 5H), 3.12-2.99 (m, 2H), 1.10 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.6, 169.8, 166.9, 161.1 (d, *J* = 246.2 Hz), 147.0, 135.3, 132.7 (d, *J* = 4.1 Hz), 131.1, 129.0 (d, *J* = 8.3 Hz), 127.6, 126.5, 123.7 (d, *J* = 3.7 Hz), 122.3 (d, *J* = 15.8 Hz), 115.4 (d, *J* = 22.5 Hz), 113.4, 85.3, 66.7, 61.8, 52.7, 45.5, 36.3, 13.7; **HRMS** (ESI): m/z calcd. for $[C_{24}H_{25}FNO_4, M+H]^+$: 410.1762; found: 410.1777.

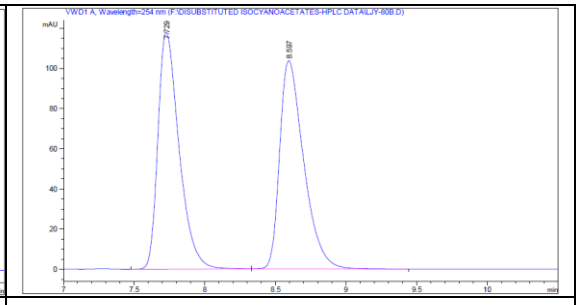
Optical Rotation: $[\alpha]^{25}_D$ = 37.6 (c = 0.3, $CHCl_3$). The absolute configuration of

3.6c was assigned by analogy to **3.6a**. 94% ee (HPLC condition: Chiralpak IB column, *n*-hexane/*i*-PrOH = 96:4, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 7.8 min for minor isomer, t_R = 8.6 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

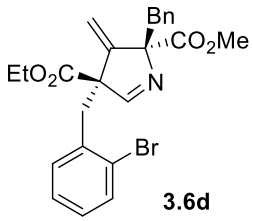
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.798	VV	0.1635	86.97683	8.08093	2.7800
2	8.577	VB	0.1949	3041.72290	234.71327	97.2200



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.729	BB	0.1577	1223.94080	117.80592	49.9724
2	8.597	BB	0.1802	1225.29333	103.65217	50.0276

(2*R*,4*S*)-4-ethyl 2-methyl 2-benzyl-4-(2-bromobenzyl)-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (3.6d)

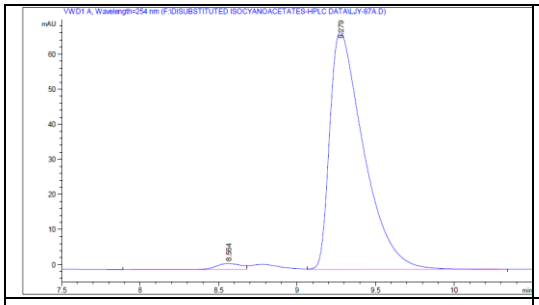


3.6d

7:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 70% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.56-7.43 (m, 1H), 7.16-7.06 (m, 8H), 5.78 (d, *J* = 3.3 Hz, 2H), 4.02-3.91 (m, 1H), 3.78-3.66 (m, 1H), 3.52 (s, 3H), 3.45 (dd, *J* = 13.6, 6.2 Hz, 2H), 3.24 (d, *J* = 13.7 Hz, 1H), 3.10 (d, *J* = 13.5 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.6, 169.9, 166.8, 147.4, 135.2, 133.1, 132.0, 131.1, 128.7, 127.5, 127.1, 126.4, 125.4, 113.5, 85.2, 77.2, 66.8, 61.8, 52.6, 45.2, 42.9, 13.7;

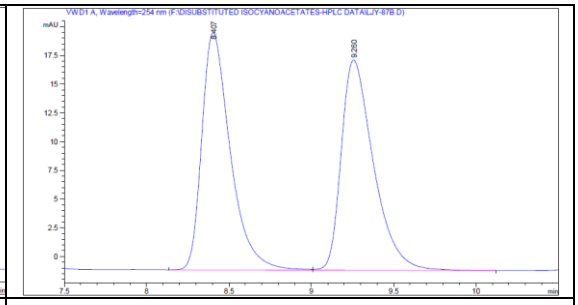
HRMS (ESI): m/z calcd. for $[C_{24}H_{25}BrNO_4, M+H]^+$: 470.0961; found: 470.0964.

Optical Rotation: $[\alpha]^{22}_D$ = 22.1 (c = 0.3, $CHCl_3$). The absolute configuration of **3.6d** was assigned by analogy to **3.6a**. 96% ee (HPLC condition: Chiralpak IB column, *n*-hexane/*i*-PrOH = 96:4, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 8.6 min for minor isomer, t_R = 9.3 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

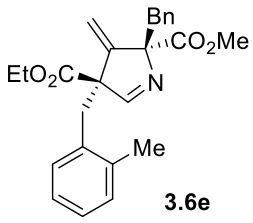
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.564	BV	0.1687	19.25164	1.71770	1.8614
2	9.279	VB	0.2245	1015.00482	67.67448	98.1386



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.407	BV	0.1842	248.20226	20.61120	49.9459
2	9.260	VB	0.2055	248.73956	18.26922	50.0541

(2*R*,4*S*)-4-ethyl 2-methyl 2-benzyl-4-(2-methylbenzyl)-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (3.6e)

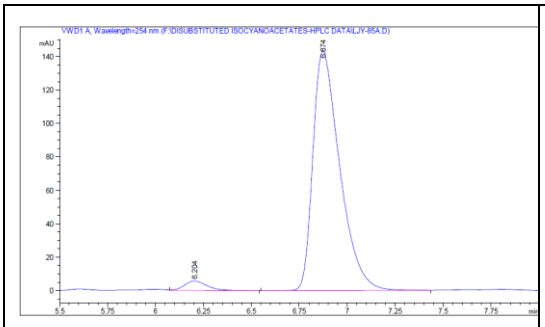


3.6e

>20:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless wax, 67% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.22-6.98 (m, 9H), 5.75 (s, 1H), 5.69 (s, 1H), 4.00-3.89 (m, 1H), 3.72-3.55 (m, 4H), 3.48 (d, *J* = 13.5 Hz, 1H), 3.30 (d, *J* = 13.8 Hz, 1H), 3.15 (d, *J* = 13.6 Hz, 1H), 3.02 (d, *J* = 13.8 Hz, 1H), 2.25 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 3H); **^{13}C**

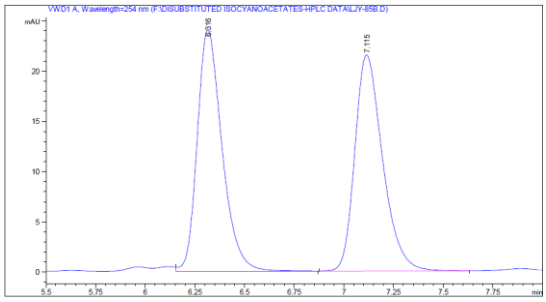
NMR (75 MHz, $CDCl_3$): δ 171.8, 170.3, 168.0, 148.3, 136.6, 135.3, 133.9, 131.3, 130.6, 130.2, 127.5, 127.2, 126.4, 125.8, 112.7, 85.3, 66.7, 61.6, 52.7, 44.4, 41.3, 19.7, 13.7; **HRMS** (ESI): m/z calcd. for $[C_{25}H_{28}NO_4, M+H]^+$: 406.2013; found: 406.2024.

Optical Rotation: $[\alpha]^{24}_D$ = 36.5 (c = 0.3, $CHCl_3$). The absolute configuration of **3.6e** was assigned by analogy to **3.6a**. 94% ee (HPLC condition: Chiralpak IB column, *n*-hexane/*i*-PrOH = 96:4, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 6.2 min for minor isomer, t_R = 6.9 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

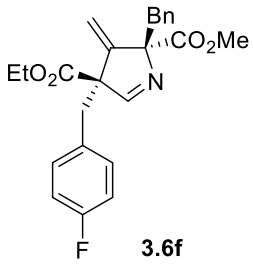
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.204	VB	0.1237	45.94837	5.66917	3.1898
2	6.874	BV	0.1486	1394.52600	143.15509	96.8102



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.316	VB	0.1316	207.96281	24.02143	49.8745
2	7.115	BB	0.1483	209.00940	21.51010	50.1255

(2*R*,4*S*)-4-ethyl 2-methyl 2-benzyl-4-(4-fluorobenzyl)-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (3.6f)

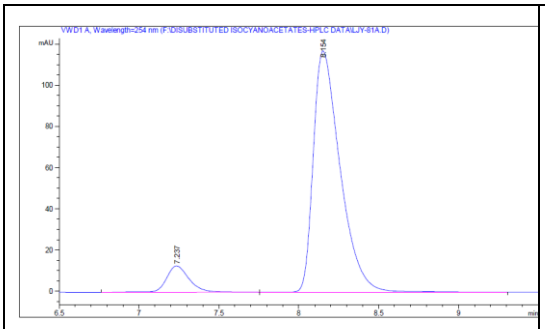


3.6f

8:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 87% yield. **^{1}H NMR** (300 MHz,

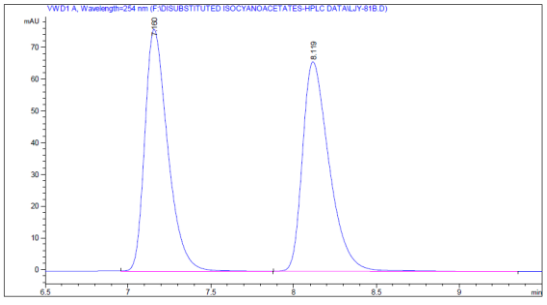
$CDCl_3$): δ 7.62 (s, 1H), 7.21-6.97 (m, 7H), 6.92-6.86 (m, 2H), 5.75 (s, 1H), 5.69 (s, 1H), 4.00-3.90 (m, 1H), 3.80-3.66 (m, 1H), 3.52 (s, 3H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.26 (d, *J* = 13.6 Hz, 1H), 3.08 (d, *J* = 13.5 Hz, 1H), 2.92 (d, *J* = 13.6 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.6, 169.9, 167.2, 162.0 (d, *J* = 245.5 Hz), 147.3, 135.2, 131.8 (d, *J* = 8.0 Hz), 131.1, 130.9 (d, *J* = 3.3 Hz), 127.6, 126.5, 115.1 (d, *J* = 21.3 Hz), 113.1, 85.4, 66.8, 61.7, 52.7, 45.3, 43.3, 13.8; **HRMS** (ESI): m/z calcd. for $[C_{24}H_{25}FNO_4, M+H]^+$: 410.1762; found: 410.1769.

Optical Rotation: $[\alpha]^{25}_D$ = 23.1 (c = 0.4, $CHCl_3$). The absolute configuration of **3.6f** was assigned by analogy to **3.6a**. 83% ee (HPLC condition: Chiralpak IB column, *n*-hexane/*i*-PrOH = 96:4, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 7.2 min for minor isomer, t_R = 8.2 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

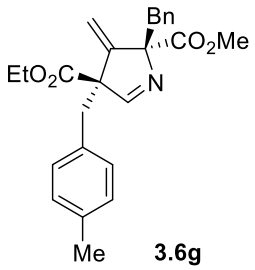
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.237	BB	0.1497	125.51192	12.76538	8.4047
2	8.154	BB	0.1773	1367.84045	116.96004	91.5953



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.160	VB	0.1471	732.23383	76.16946	49.8703
2	8.119	BB	0.1711	736.04211	65.92499	50.1297

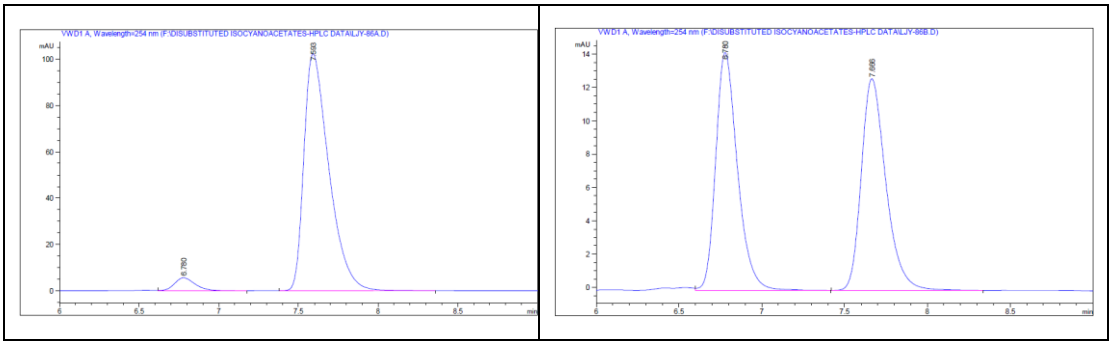
(2*R*,4*S*)-4-ethyl 2-methyl 2-benzyl-4-(4-methylbenzyl)-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (3.6g)



3.6g

7:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless wax, 58% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.19-7.05 (m, 5H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 5.73 (s, 1H), 5.70 (s, 1H), 3.99-3.89 (m, 1H), 3.77-3.66 (m, 1H), 3.51 (s, 3H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.25 (d, *J* = 13.5 Hz, 1H), 3.09 (d, *J* = 13.5 Hz, 1H), 2.88 (d, *J* = 13.5 Hz, 1H), 2.27 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.7, 170.1, 167.7, 147.6, 136.5, 135.3, 132.0, 131.2, 130.0, 128.9, 127.6, 126.4, 112.8, 85.3, 66.8, 61.6, 52.7, 45.1, 44.0, 21.0, 13.7; **HRMS** (ESI): m/z calcd. for $[C_{25}H_{28}NO_4, M+H]^+$: 406.2013; found: 406.2020.

Optical Rotation: $[\alpha]^{24}_D$ = 50.1 (c = 0.2, $CHCl_3$). The absolute configuration of **3.6g** was assigned by analogy to **3.6a**. 91% ee (HPLC condition: Chiralpak IB column, *n*-hexane/*i*-PrOH = 96:4, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 6.8 min for minor isomer, t_R = 7.6 min for major isomer).



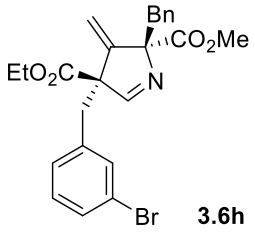
Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.780	VB	0.1378	50.58162	5.57980	4.3302
2	7.593	VV	0.1654	1117.53906	102.27230	95.6698

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.780	VB	0.1417	130.41873	14.26197	49.8791
2	7.666	BB	0.1584	131.05101	12.69028	50.1209

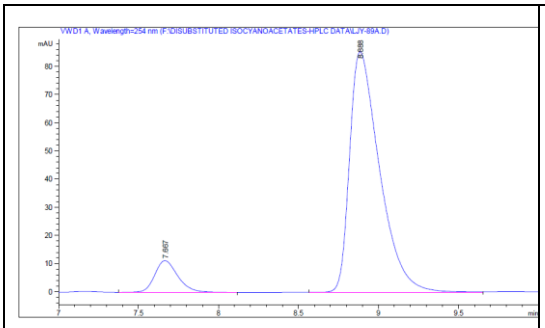
(2*R*,4*S*)-4-ethyl 2-methyl 2-benzyl-4-(3-bromobenzyl)-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (3.6h)



3.6h

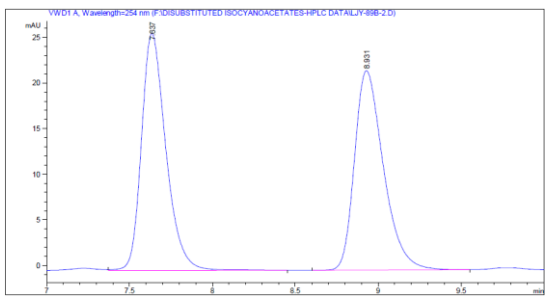
10:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 74% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.36-7.30 (m, 1H), 7.20-7.19 (m, 1H), 7.17-7.04 (m, 6H), 7.00-6.97 (m, 1H), 5.75 (s, 1H), 5.70 (s, 1H), 4.02-3.91 (m, 1H), 3.77-3.66 (m, 1H), 3.56 (s, 3H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.25 (d, *J* = 13.5 Hz, 1H), 3.10 (d, *J* = 13.5 Hz, 1H), 2.88 (d, *J* = 13.5 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.5, 169.8, 167.0, 147.3, 137.5, 135.2, 133.0, 131.2, 130.2, 129.8, 128.9, 127.6, 126.5, 122.3, 113.1, 85.4, 66.6, 61.8, 52.8, 45.0, 43.7, 13.8; **HRMS** (ESI): m/z calcd. for $[C_{24}H_{25}BrNO_4, M+H]^+$: 470.0961; found: 470.0974.

Optical Rotation: $[\alpha]^{22}_D$ = 29.8 (c = 0.4, $CHCl_3$). The absolute configuration of **3.6h** was assigned by analogy to **3.6a**. 82% ee (HPLC condition: Chiralpak IB column, *n*-hexane/*i*-PrOH = 96:4, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 7.7 min for minor isomer, t_R = 8.9 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

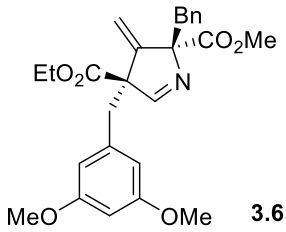
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.667	VB	0.1534	112.85846	11.25551	9.2130
2	8.888	BV	0.1957	1112.12939	85.37704	90.7870



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.637	VB	0.1559	265.85214	25.96662	50.0371
2	8.931	BV	0.1854	265.45810	21.85609	49.9629

(2*R*,4*S*)-4-ethyl 2-methyl 2-benzyl-4-(3,5-dimethoxybenzyl)-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (3.6i)

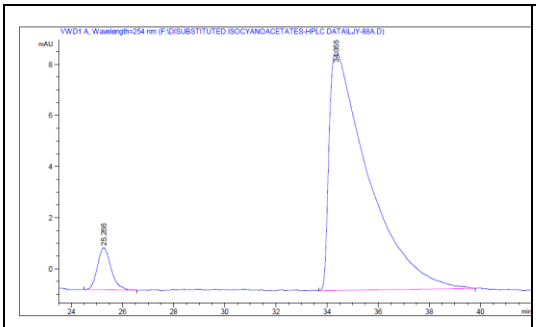


3.6i

11:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 86% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.17-7.12 (m, 3H), 7.10-7.06 (m, 2H), 6.28 (t, *J* = 2.2 Hz, 1H), 6.19 (d, *J* = 2.2 Hz, 2H), 5.74 (s, 1H), 5.72 (s, 1H), 3.98-3.92 (m, 1H), 3.73-3.69 (m, 7H), 3.58 (s, 3H), 3.44 (d, *J* = 13.6 Hz, 1H), 3.23 (d, *J* = 13.4 Hz, 1H), 3.10 (d, *J* = 13.6 Hz, 1H), 2.85 (d, *J* = 13.4 Hz, 1H), 1.05 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.8, 170.0, 167.6, 160.6, 147.8, 137.4, 135.3, 131.2, 127.6, 126.5, 112.9, 108.0, 99.2, 85.4, 66.6, 61.6, 55.2, 52.7, 45.1, 44.8, 13.8; **HRMS** (ESI): m/z calcd. for $[C_{26}H_{30}NO_6, M+H]^+$: 452.2068; found: 452.2084.

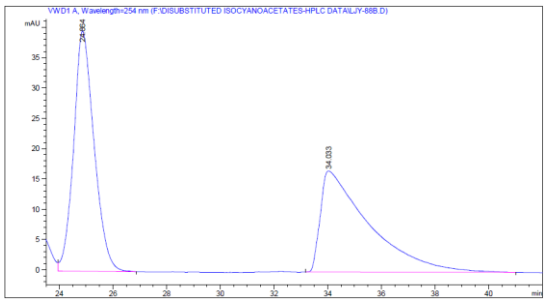
Optical Rotation: $[\alpha]^{23}_D$ = 52.5 (c = 0.2, $CHCl_3$). The absolute configuration of

3.6i was assigned by analogy to **3.6a**. 88% ee (HPLC condition: Chiralpak IE column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 25.3 min for minor isomer, t_R = 34.4 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

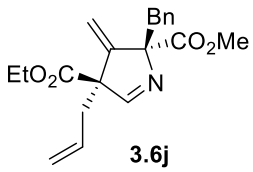
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.266	BB	0.5828	61.31674	1.64788	5.8156
2	34.355	BB	1.4259	993.03467	9.34848	94.1844



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.864	VB	0.7902	2098.56079	39.60702	50.1750
2	34.033	BB	1.6324	2083.92188	16.64777	49.8250

(2*R*,4*S*)-4-ethyl 2-methyl 4-allyl-2-benzyl-3-methylene-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (3.6j)

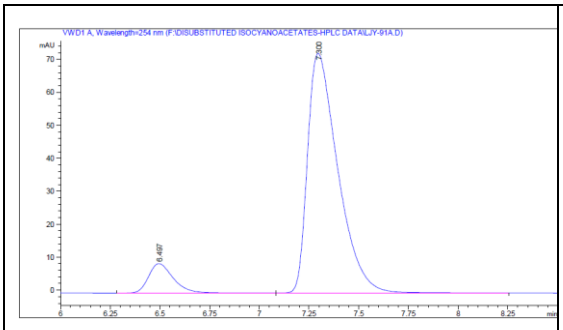


3.6j

4:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 67% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.18-7.09 (m, 5H), 5.71-5.47 (m, 3H), 5.11-5.06 (m, 1H), 5.04-4.99 (m, 1H), 4.02-3.91 (m, 1H), 3.82-3.64 (m, 4H), 3.46 (d, *J* = 13.6 Hz, 1H), 3.16 (d, *J* = 13.6 Hz, 1H), 2.66 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.37 (dd, *J* = 13.8, 7.7 Hz, 1H), 1.11 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.7, 169.8, 167.7, 147.4, 135.3, 131.7, 131.2, 127.6, 126.5, 119.5, 112.5, 85.5, 65.5, 61.6, 52.6, 44.7,

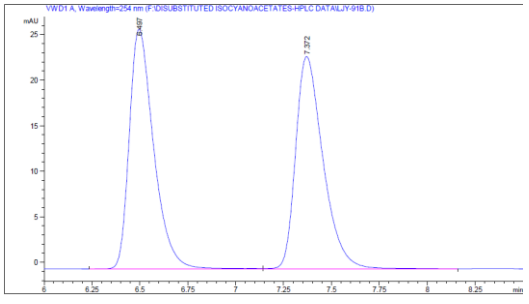
42.6, 13.8; **HRMS** (ESI): m/z calcd. for $[C_{20}H_{24}NO_4, M+H]^+$: 342.1700; found: 342.1710.

Optical Rotation: $[\alpha]^{22}_D$ = 20.3 (c = 0.2, $CHCl_3$). The absolute configuration of **3.6j** was assigned by analogy to **3.6a**. 82% ee (HPLC condition: Chiralpak IB column, *n*-hexane/*i*-PrOH = 96:4, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 6.5 min for minor isomer, t_R = 7.3 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

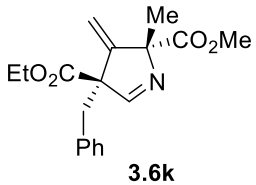
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.497	BV	0.1339	78.06826	8.94640	9.1760
2	7.300	VV	0.1621	772.71698	72.60119	90.8240



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.497	BV	0.1353	232.79108	26.31088	49.9599
2	7.372	VV	0.1516	233.16481	23.32430	50.0401

(2*R*,4*S*)-4-ethyl 2-methyl 4-benzyl-2-methyl-3-methylene-3,4-dihydro-2*H*-pyrrole -2,4-dicarboxylate (3.6k)

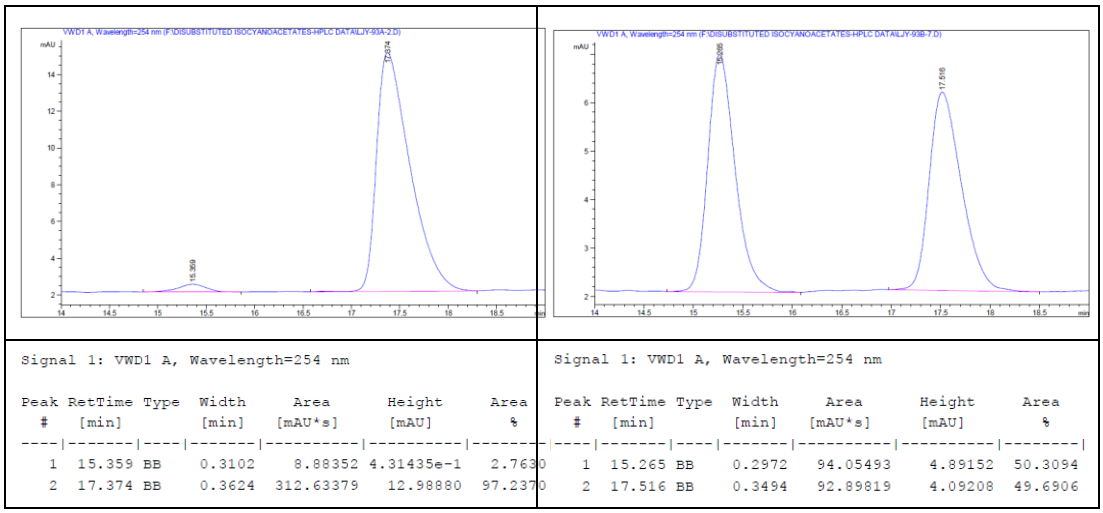


3.6k

11:1 d.r. (of crude). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 79% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.32-7.20 (m, 3H), 7.18-7.08 (m, 2H), 5.49 (s, 2H), 4.23-4.03 (m, 2H), 3.59 (s, 3H), 3.42 (d, *J* = 13.6 Hz, 1H), 2.99 (d, *J* = 13.6 Hz, 1H), 1.55 (s,

3H), 1.18 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2, 170.4, 166.8, 150.6, 135.5, 130.2, 128.3, 127.0, 111.1, 81.5, 67.0, 61.7, 52.8, 43.2, 26.2, 13.9; **HRMS** (ESI): m/z calcd. for $[C_{18}H_{22}NO_4, M+H]^+$: 316.1543; found: 316.1550.

Optical Rotation: $[\alpha]^{23}_D$ = -55.8 (c = 0.3, $CHCl_3$). The absolute configuration of **3.6k** was assigned by analogy to **3.6a**. 94% ee (HPLC condition: Chiralpak IE column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 ml/min, wavelength = 254 nm, t_R = 15.4 min for minor isomer, t_R = 17.4 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.359	BB	0.3102	8.88352	4.31435e-1	2.7630
2	17.374	BB	0.3624	312.63379	12.98880	97.2370

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.265	BB	0.2972	94.05493	4.89152	50.3094
2	17.516	BB	0.3494	92.89819	4.09208	49.6906

3.4.6 X-Ray Crystallographic Analysis and Determination of Configuration of 3.6a

The absolute configuration of **3.6a** (**2*R*,4*S***) was assigned by X-ray crystallographic analysis of a single crystal of **3.6a** (Figure 3.2), which was prepared from the solution of **3.6a** in hexanes/ethyl acetate (8:1) at ambient temperature.

Figure 3.2 X-ray Structure of **3.6a**

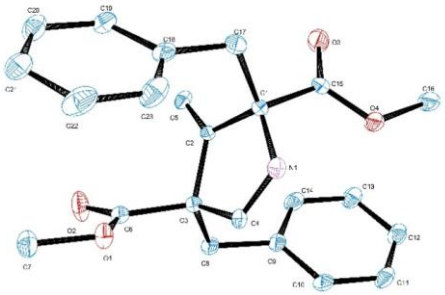
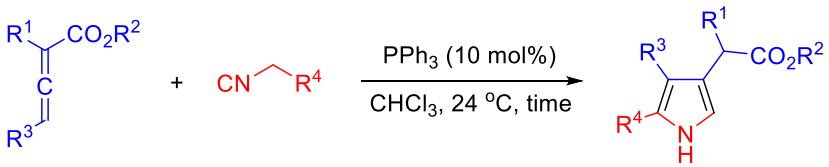


Table 3.3 Crystal Data and Structure Refinement for **3.6a**

Identification code	**3.6a**	
Empirical formula	$C_{23}H_{23}NO_4$	
Formula weight	377.42	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.2073(5) Å	α = 90°
	b = 8.4035(4) Å	β = 90.524(2)°
	c = 12.6305(7) Å	γ = 90°
Volume	977.23(9) $Å^3$	
Z	2	
Density (calculated)	1.283 Mg/m^3	
Absorption coefficient	0.711 mm^{-1}	

F(000)	400
Crystal size	0.329 x 0.025 x 0.014 mm^3
Theta range for data collection	3.499 to 72.628°
Index ranges	-9<=h<=11, -10<=k<=10, -15<=l<=15
Reflections collected	12788
Independent reflections	3778 [R(int) = 0.0558]
Completeness to theta = 67.679°	99.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3778 / 1 / 323
Goodness-of-fit on F^2	1.074
Final R indices [I>2sigma(I)]	R1 = 0.0516, wR2 = 0.1349
R indices (all data)	R1 = 0.0518, wR2 = 0.1352
Absolute structure parameter	0.32(9)
Largest diff. peak and hole	0.409 and -0.248 $e.Å^{-3}$

3.4.7 Pyrrole Synthesis by PPh_3-Catalyzed [3+2] Cyclization of 3.1 and 3.2



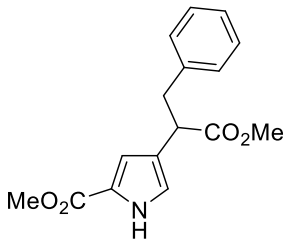
3.1 **3.2** (1.0 equiv) **3.4**

General procedure. To a 4 mL vial charged with PPh_3 (3.2 mg, 0.012 mmol) was added anhydrous $CHCl_3$ (0.5 mL). Allenoate **3.1** (0.12 mmol, 1.2 equiv) and activated isocyanide **3.2** (0.10 mmol, 1.0 equiv) were added in one portion. The reaction

mixture was allowed to stir at ambient temperature for the given time and then concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate) to afford the product **3.4**.

3.4.8 Characterization of Compounds 3.4

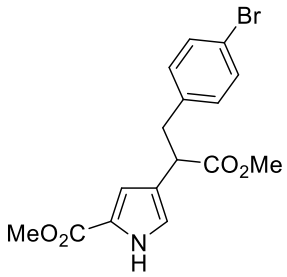
Methyl 4-(1-methoxy-1-oxo-3-phenylpropan-2-yl)-1*H*-pyrrole-2-carboxylate (3.4a)



3.4a

The general procedure outlined above was followed (using 1.0 equiv of allenoate, 24 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.42 (br s, 1H), 7.28-7.16 (m, 3H), 7.16-7.09 (m, 2H), 6.92-6.86 (m, 1H), 6.81 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.86-3.79 (m, 4H), 3.62 (s, 3H), 3.30 (dd, *J* = 13.6, 8.5 Hz, 1H), 3.01 (dd, *J* = 13.6, 7.0 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.1, 161.6, 138.9, 128.8, 128.3, 126.3, 122.9, 122.5, 121.3, 114.3, 51.9, 51.5, 46.0, 39.8; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{16}NO_4, M\text{-}H]^-$: 286.1085; found: 286.1078.

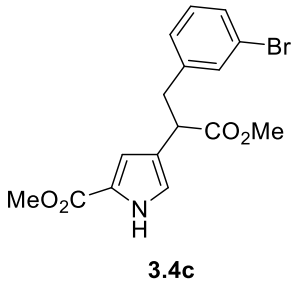
Methyl 4-(3-(4-bromophenyl)-1-methoxy-1-oxopropan-2-yl)-1*H*-pyrrole-2-carboxylate (3.4b)



3.4b

The general procedure outlined above was followed (17 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.17 (br s, 1H), 7.40-7.32 (m, 2H), 7.02-6.95 (m, 2H), 6.90-6.84 (m, 1H), 6.79 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.84 (s, 3H), 3.80-3.73 (m, 1H), 3.62 (s, 3H), 3.24 (dd, *J* = 13.7, 8.4 Hz, 1H), 2.95 (dd, *J* = 13.7, 7.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.9, 161.4, 137.9, 131.4, 130.6, 122.7, 122.6, 121.2, 120.3, 114.2, 52.0, 51.5, 45.8, 39.1; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{15}BrNO_4, M\text{-}H]^-$: 364.0190; found: 364.0188.

Methyl 4-(3-(3-bromophenyl)-1-methoxy-1-oxopropan-2-yl)-1*H*-pyrrole-2-carbox ylate (3.4c)

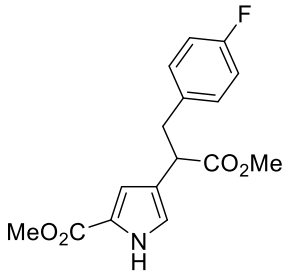


3.4c

The general procedure outlined above was followed (17 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.30 (br s, 1H), 7.35-7.25 (m, 2H), 7.13-7.00 (m, 2H), 6.87 (s, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 3.86-3.74 (m, 4H), 3.62 (s,

3H), 3.26 (dd, *J* = 13.7, 8.5 Hz, 1H), 2.96 (dd, *J* = 13.7, 7.0 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.8, 161.5, 141.3, 131.9, 129.8, 129.5, 127.6, 122.7, 122.6, 122.3, 121.2, 114.1, 52.0, 51.5, 45.7, 39.3; **HRMS** (ESI): m/z calcd. for [$C_{16}H_{15}BrNO_4$, M-H]$^-$: 364.0190; found: 364.0186.

Methyl 4-(3-(4-fluorophenyl)-1-methoxy-1-oxopropan-2-yl)-1*H*-pyrrole-2-carbox ylate (3.4d)

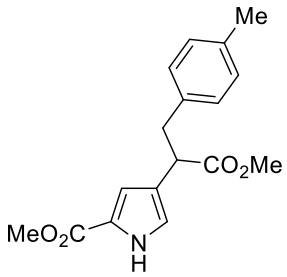


3.4d

The general procedure outlined above was followed (17 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 94% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.21 (br s, 1H), 7.10-7.02 (m, 2H), 6.97-6.89 (m, 2H), 6.88-6.84 (m, 1H), 6.82-6.78 (m, 1H), 3.84 (s, 3H), 3.80-3.73 (m, 1H), 3.62 (s, 3H), 3.25 (dd, *J* = 13.7, 8.5 Hz, 1H), 2.97 (dd, *J* = 13.7, 7.1 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.0, 161.5 (d, *J* = 242.7 Hz), 161.4, 134.6 (d, *J* = 3.2 Hz), 130.3 (d, *J* = 7.8 Hz), 122.8, 122.6, 121.2, 115.1 (d, *J* = 21.3 Hz), 114.2, 52.0, 51.5, 46.1, 39.0; **HRMS** (ESI): m/z calcd. for [$C_{16}H_{15}FNO_4$, M-H]$^-$: 304.0991; found: 304.0987.

Methyl 4-(1-methoxy-1-oxo-3-(*p*-tolyl)propan-2-yl)-1*H*-pyrrole-2-carboxylate

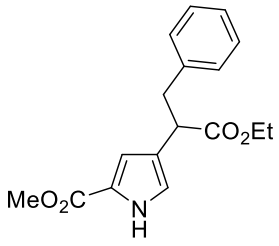
(3.4e)



3.4e

The general procedure outlined above was followed (17 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 91% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.26 (br s, 1H), 7.10-6.97 (m, 4H), 6.93-6.86 (m, 1H), 6.82 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.87-3.75 (m, 4H), 3.62 (s, 3H), 3.26 (dd, *J* = 13.7, 8.6 Hz, 1H), 2.97 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.29 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.2, 161.5, 135.8, 129.0, 128.7, 123.1, 122.5, 121.2, 114.3, 51.9, 51.5, 46.1, 39.4, 21.0; **HRMS** (ESI), m/z calcd. for $[C_{17}H_{18}NO_4, M\text{-}H]^-$: 300.1241; found: 300.1244.

Methyl 4-(1-ethoxy-1-oxo-3-phenylpropan-2-yl)-1*H*-pyrrole-2-carboxylate (3.4f)

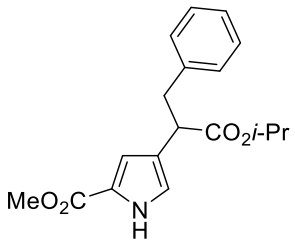


3.4f

The general procedure outlined above was followed (18 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 95% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.16 (br s, 1H), 7.28-7.17 (m, 3H), 7.17-7.10 (m, 2H), 6.93-6.85 (m, 1H), 6.82 (dd, *J* = 2.7, 1.7 Hz, 1H), 4.15-3.99 (m,

2H), 3.87-3.75 (m, 4H), 3.28 (dd, *J* = 13.6, 8.7 Hz, 1H), 3.01 (dd, *J* = 13.6, 7.0 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.7, 161.5, 139.0, 128.9, 128.2, 126.3, 123.2, 122.5, 121.2, 114.3, 60.7, 51.5, 46.1, 39.9, 14.1; **HRMS** (ESI): m/z calcd. for $[C_{17}H_{18}NO_4, M\text{-}H]^-$: 300.1241; found: 300.1233.

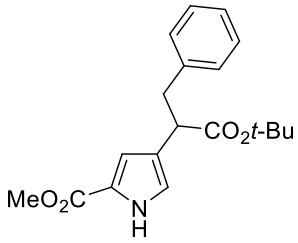
Methyl 4-(1-isopropoxy-1-oxo-3-phenylpropan-2-yl)-1*H*-pyrrole-2-carboxylate (3.4g)



3.4g

The general procedure outlined above was followed (16 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless wax, 93% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.28 (br s, 1H), 7.29-7.11 (m, 5H), 6.94-6.87 (m, 1H), 6.83 (dd, *J* = 2.5, 1.9 Hz, 1H), 5.04-4.80 (m, 1H), 3.88-3.72 (m, 4H), 3.26 (dd, *J* = 13.6, 9.0 Hz, 1H), 3.00 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.13 (d, *J* = 6.2 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.2, 161.6, 139.0, 128.9, 128.2, 126.3, 123.3, 122.4, 121.2, 114.3, 68.0, 51.4, 46.3, 40.0, 21.6, 21.6; **HRMS** (ESI): m/z calcd. for $[C_{18}H_{20}NO_4, M\text{-}H]^-$: 314.1398; found: 314.1392.

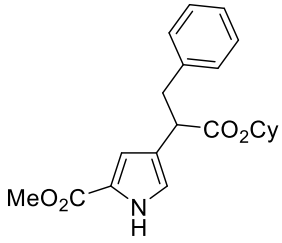
Methyl 4-(1-*tert*-butoxy-1-oxo-3-phenylpropan-2-yl)-1*H*-pyrrole-2-carboxylate (3.4h)



3.4h

The general procedure outlined above was followed (72 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless wax, 95% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.20 (br s, 1H), 7.27-7.13 (m, 5H), 6.92-6.85 (m, 1H), 6.85-6.79 (m, 1H), 3.84 (s, 3H), 3.72 (dd, *J* = 8.9, 6.8 Hz, 1H), 3.23 (dd, *J* = 13.6, 9.0 Hz, 1H), 2.97 (dd, *J* = 13.7, 6.8 Hz, 1H), 1.33 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.88, 161.6, 139.2, 129.0, 128.2, 126.2, 123.7, 122.4, 121.1, 114.3, 80.7, 51.4, 46.9, 40.0, 27.9; **HRMS** (ESI): m/z calcd. for $[C_{19}H_{22}NO_4$, M-H$]^-$: 328.1554; found: 328.1546.

Methyl 4-(1-(cyclohexyloxy)-1-oxo-3-phenylpropan-2-yl)-1*H*-pyrrole-2-carbox ylate (3.4i)

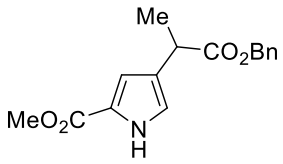


3.4i

The general procedure outlined above was followed (36 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless wax, 93% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.14 (br s, 1H), 7.27-7.12 (m, 5H), 6.93-6.87 (m, 1H), 6.83 (dd, *J* = 2.8, 1.6 Hz, 1H), 4.69 (dd, *J* = 8.2, 4.3 Hz, 1H),

3.87-3.73 (m, 4H), 3.27 (dd, *J* = 13.6, 9.0 Hz, 1H), 3.00 (dd, *J* = 13.7, 6.8 Hz, 1H), 1.85-1.55 (m, 5H), 1.36-1.18 (m, 5H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.1, 161.5, 139.1, 128.9, 128.2, 126.3, 123.5, 122.4, 121.1, 114.3, 72.9, 51.5, 46.3, 40.0, 31.3, 31.3, 25.3, 23.6; **HRMS** (ESI): m/z calcd. for [$C_{21}H_{24}NO_4$, M-H]$^-$: 354.1711; found: 354.1706.

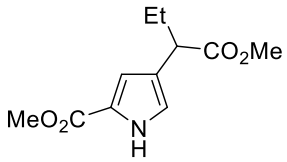
Methyl 4-(1-(benzyloxy)-1-oxopropan-2-yl)-1*H*-pyrrole-2-carboxylate (3.4j)



3.4j

The general procedure outlined above was followed (using 2.0 equiv of allenoate, 23 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless oil, 75% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.21 (br s, 1H), 7.40-7.27 (m, 5H), 6.87 (d, *J* = 2.8 Hz, 2H), 5.12 (d, *J* = 1.9 Hz, 2H), 3.84 (s, 3H), 3.73 (q, *J* = 7.2 Hz, 1H), 1.49 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.6, 161.5, 136.0, 128.5, 128.1, 128.0, 124.8, 122.4, 120.7, 114.1, 66.4, 51.4, 38.0, 18.2; **HRMS** (ESI): m/z calcd. for [$C_{16}H_{16}NO_4$, M-H]$^-$: 286.1085; found: 286.1073.

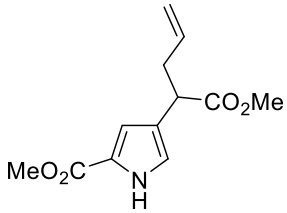
Methyl 4-(1-methoxy-1-oxobutan-2-yl)-1*H*-pyrrole-2-carboxylate (3.4k)



3.4k

The general procedure outlined above was followed (using 2.0 equiv of allenoate, 23 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless oil, 84% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.15 (br s, 1H), 6.96-6.78 (m, 2H), 3.83 (s, 3H), 3.67 (s, 3H), 3.42 (t, *J* = 7.6 Hz, 1H), 2.06-1.89 (m, 1H), 1.84-1.72 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.9, 161.5, 123.6, 122.5, 121.1, 114.4, 51.9, 51.5, 45.7, 26.8, 12.0; **HRMS** (ESI), m/z calcd. for $[C_{11}H_{14}NO_4, M\text{-}H]^-$: 224.0928; found: 224.0922.

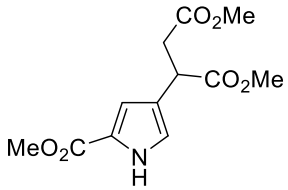
Methyl 4-(1-methoxy-1-oxopent-4-en-2-yl)-1*H*-pyrrole-2-carboxylate (3.4l)



3.4l

The general procedure outlined above was followed (16 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless oil, 81% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.31 (br s, 1H), 6.92-6.83 (m, 2H), 5.82-5.66 (m, 1H), 5.11-4.97 (m, 2H), 3.83 (s, 3H), 3.70-3.57 (m, 4H), 2.80-2.62 (m, 1H), 2.56-2.41 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.2, 161.5, 135.2, 123.0, 122.5, 121.1, 117.0, 114.3, 51.9, 51.5, 43.8, 37.6; **HRMS** (ESI), m/z calcd. for $[C_{12}H_{14}NO_4, M\text{-}H]^-$: 236.0928; found: 236.0923.

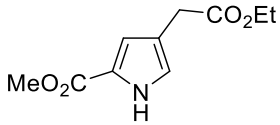
Dimethyl 2-(5-(methoxycarbonyl)-1*H*-pyrrol-3-yl)succinate (3.4m)



3.4m

The general procedure outlined above was followed (using 2.0 equiv of allenoate, 16 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 86% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.27 (br s, 1H), 6.88 (s, 1H), 6.82 (s, 1H), 4.04 (dd, *J* = 9.5, 5.8 Hz, 1H), 3.83 (s, 3H), 3.68 (d, *J* = 6.7 Hz, 6H), 3.10 (dd, *J* = 16.9, 9.6 Hz, 1H), 2.68 (dd, *J* = 16.8, 5.7 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.6, 172.0, 161.4, 122.8, 122.0, 121.0, 113.9, 52.3, 51.9, 51.5, 39.6, 37.3; **HRMS** (ESI): m/z calcd. for $[C_{12}H_{14}NO_6, M\text{-}H]^-$: 268.0827; found: 268.0827.

Methyl 4-(2-ethoxy-2-oxoethyl)-1*H*-pyrrole-2-carboxylate (3.4n)

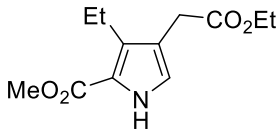


3.4n

The general procedure outlined above was followed (using 2.0 equiv of allenoate, 20 mol% PPh_3, 43 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Pale brown oil, 56% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.15 (br s, 1H), 6.91 (dd, *J* = 2.1, 1.5 Hz, 1H), 6.84 (d, *J* = 1.8 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 3.49 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.8, 161.5, 122.6, 121.9, 117.8, 115.7, 60.8, 51.4, 32.8, 14.2;

HRMS (ESI), m/z calcd. for [$C_{10}H_{12}NO_4$, M-H]$^-$: 210.0772; found: 210.0764.

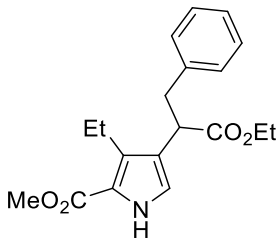
Methyl 4-(2-ethoxy-2-oxoethyl)-3-ethyl-1*H*-pyrrole-2-carboxylate (3.4o)



3.4o

The general procedure outlined above was followed (using 1.5 equiv of allenoate, 20 mol% PPh_3, 41 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 59% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.98 (br s, 1H), 6.85 (d, *J* = 3.0 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.45 (s, 2H), 2.75 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.0, 161.7, 133.1, 121.4, 118.6, 116.7, 60.8, 51.1, 30.8, 18.0, 15.2, 14.2; **HRMS** (ESI), m/z calcd. for [$C_{12}H_{16}NO_4$, M-H]$^-$: 238.1085; found: 238.1082.

Methyl 4-(1-ethoxy-1-oxo-3-phenylpropan-2-yl)-3-ethyl-1*H*-pyrrole-2-carboxylate (3.4p)

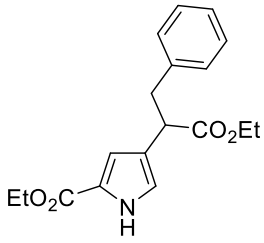


3.4p

The general procedure outlined above was followed (using 2.0 equiv of allenoate, 50 mol% PPh_3, 95 h). The crude reaction mixture was purified by flash column

chromatography (hexane/EtOAc 3:1). Colorless wax, 39% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.95 (br s, 1H), 7.28-7.11 (m, 5H), 6.95 (d, *J* = 3.1 Hz, 1H), 4.13-3.94 (m, 2H), 3.86-3.74 (m, 4H), 3.28 (dd, *J* = 13.5, 9.2 Hz, 1H), 2.97 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.83-2.57 (m, 2H), 1.16-0.98 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.1, 161.6, 139.2, 132.7, 128.9, 128.3, 126.4, 122.3, 120.2, 118.3, 60.7, 51.1, 44.1, 40.4, 17.8, 15.5, 14.0; **HRMS** (ESI), m/z calcd. for $[C_{19}H_{22}NO_4, M-H]^-$: 328.1554; found: 328.1552.

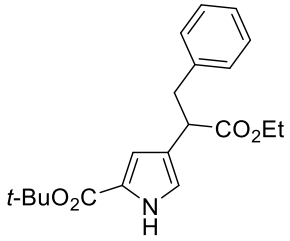
Ethyl 4-(1-ethoxy-1-oxo-3-phenylpropan-2-yl)-1*H*-pyrrole-2-carboxylate (3.4q)



3.4q

The general procedure outlined above was followed (20 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 97% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.28 (br s, 1H), 7.31-7.09 (m, 5H), 6.95-6.86 (m, 1H), 6.82 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.16-3.98 (m, 2H), 3.81 (dd, *J* = 8.7, 6.9 Hz, 1H), 3.29 (dd, *J* = 13.6, 8.8 Hz, 1H), 3.01 (dd, *J* = 13.6, 6.9 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.7, 161.2, 139.0, 128.9, 128.2, 126.3, 123.1, 122.8, 121.0, 114.1, 60.7, 60.4, 46.1, 39.9, 14.4, 14.0; **HRMS** (ESI), m/z calcd. for $[C_{18}H_{20}NO_4, M-H]^-$: 314.1398; found: 314.1392.

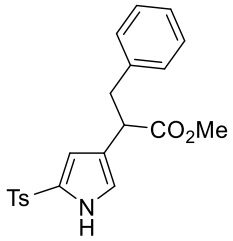
***tert*-Butyl 4-(1-ethoxy-1-oxo-3-phenylpropan-2-yl)-1*H*-pyrrole-2-carboxylate (3.4r)**



3.4r

The general procedure outlined above was followed (20 mol %PPh_3, 89 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless wax, 82% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.07 (br s, 1H), 7.33-7.09 (m, 5H), 6.92-6.71 (m, 2H), 4.18-3.98 (m, 2H), 3.80 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.28 (dd, *J* = 13.6, 9.0 Hz, 1H), 3.00 (dd, *J* = 13.6, 6.6 Hz, 1H), 1.56 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.8, 160.6, 139.1, 128.9, 128.2, 126.3, 124.3, 123.0, 120.3, 113.5, 80.9, 60.7, 46.2, 40.0, 28.3, 14.0; **HRMS** (ESI), m/z calcd. for $[C_{20}H_{24}NO_4, M\text{-}H]^-$: 342.1711; found: 342.1694.

Methyl 3-phenyl-2-(5-tosyl-1*H*-pyrrol-3-yl)propanoate (3.4s)

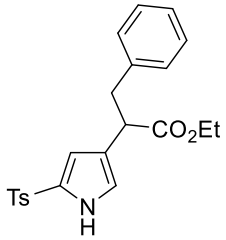


3.4s

The general procedure outlined above was followed (23 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 79% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.30 (br s, 1H), 7.76 (d, *J* = 8.2 Hz,

2H), 7.33-7.00 (m, 7H), 6.81 (d, *J* = 2.5 Hz, 1H), 6.77 (d, *J* = 1.9 Hz, 1H), 3.80-3.73 (m, 1H), 3.59 (s, 3H), 3.23 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.94 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.41 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.7, 143.9, 139.3, 138.6, 129.8, 128.8, 128.4, 128.3, 126.9, 126.5, 123.7, 121.5, 114.3, 52.0, 46.0, 40.0, 21.6; **HRMS** (ESI), m/z calcd. for $[C_{21}H_{20}NO_4S, M-H]^-$: 382.1119; found: 382.1112.

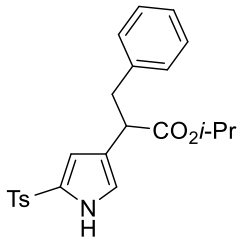
Ethyl 3-phenyl-2-(5-tosyl-1*H*-pyrrol-3-yl)propanoate (3.4t)



3.4t

The general procedure outlined above was followed (18 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Colorless wax, 83% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.58 (br s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.32-7.24 (m, 2H), 7.23-7.12 (m, 3H), 7.11-7.02 (m, 2H), 6.87-6.74 (m, 2H), 4.11-3.95 (m, 2H), 3.76 (dd, *J* = 8.7, 7.0 Hz, 1H), 3.22 (dd, *J* = 13.5, 8.8 Hz, 1H), 2.94 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.40 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.3, 143.9, 139.3, 138.6, 129.8, 128.9, 128.2, 128.1, 126.8, 126.4, 123.7, 121.7, 114.5, 60.8, 46.1, 40.0, 21.5, 14.0; **HRMS** (ESI), m/z calcd. for $[C_{22}H_{22}NO_4S, M-H]^-$: 396.1275; found: 396.1268.

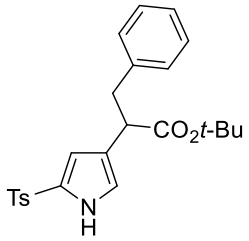
Isopropyl 3-phenyl-2-(5-tosyl-1*H*-pyrrol-3-yl)propanoate (3.4u)



3.4u

The general procedure outlined above was followed (23 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 4:1). Colorless wax, 86% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.52 (br s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.31-7.04 (m, 7H), 6.89-6.82 (m, 1H), 6.82-6.74 (m, 1H), 5.00-4.82 (m, 1H), 3.73 (dd, *J* = 9.0, 6.8 Hz, 1H), 3.21 (dd, *J* = 13.6, 9.0 Hz, 1H), 2.95 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.40 (s, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.05 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.8, 143.8, 139.4, 138.7, 129.8, 128.9, 128.2, 128.1, 126.8, 126.4, 123.9, 121.7, 114.5, 68.1, 46.2, 40.0, 21.5; **HRMS** (ESI), m/z calcd. for $[C_{23}H_{24}NO_4S, M-H]^-$: 410.1432; found: 410.1420.

***tert*-Butyl 3-phenyl-2-(5-tosyl-1*H*-pyrrol-3-yl)propanoate (3.4v)**

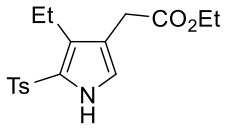


3.4v

The general procedure outlined above was followed (20 mol% PPh_3, 47 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). White solid, 71% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.46 (br s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.28-7.08 (m, 7H), 6.83 (s, 1H), 6.78 (d, *J* = 1.7 Hz, 1H), 3.68 (dd, *J* =

8.8, 7.0 Hz, 1H), 3.18 (dd, *J* = 13.6, 9.0 Hz, 1H), 2.92 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.41 (s, 3H), 1.31 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.5, 143.8, 139.5, 138.8, 129.8, 129.0, 128.1, 128.0, 126.8, 126.3, 124.3, 121.6, 114.5, 80.9, 46.9, 40.0, 27.8, 21.5; **HRMS** (ESI), m/z calcd. for $[C_{24}H_{26}NO_4S, M-H]^-$: 424.1588; found: 424.1595.

Ethyl 2-(4-ethyl-5-tosyl-1*H*-pyrrol-3-yl)acetate (3.4w)



3.4w

The general procedure outlined above was followed (using 2.0 equiv of allenoate, 30 mol% PPh_3, 95 h). The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 3:1). Pale brown wax, 58% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.20 (br s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.32-7.23 (m, 2H), 6.92 (d, *J* = 3.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.38 (s, 2H), 2.62 (q, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.5, 143.7, 139.9, 130.7, 129.7, 126.7, 123.5, 121.8, 117.5, 60.9, 30.8, 21.5, 17.3, 14.9, 14.1; **HRMS** (ESI), m/z calcd. for $[C_{17}H_{20}NO_4S, M-H]^-$: 334.1119; found: 334.1112.

3.4.9 X-Ray Crystallographic Analysis of 3.4v

The conformation of **3.4v** was determined by X-ray crystallographic analysis of a single crystal of **3.4v** (Figure 3.3). The crystal was prepared from the solution of **3.4v** in hexanes/ethyl acetate at ambient temperature.

Figure 3.3 X-ray Structure of **3.4v**

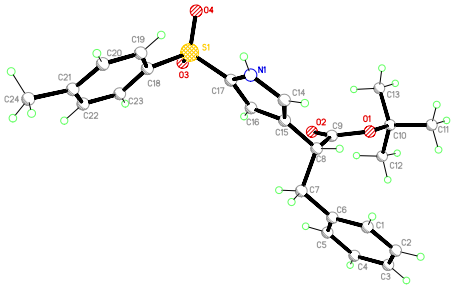


Table 3.4 Crystal Data and Structure Refinement for **3.4v**

Identification code	**3.4v**	
Empirical formula	$C_{24}H_{27}NO_4S$	
Formula weight	425.52	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 24.358(3) Å	α = 90°
	b = 8.0579(9) Å	β = 100.201(3)°
	c = 11.2629(13) Å	γ = 90°
Volume	2175.7(4) $Å^3$	
Z	4	
Density (calculated)	1.299 Mg/m^3	
Absorption coefficient	0.179 mm^{-1}	
F(000)	904	

Crystal size	0.260 x 0.200 x 0.100 mm^3
Theta range for data collection	1.699 to 27.518°
Index ranges	-31<=h<=27, -10<=k<=10, -13<=l<=14
Reflections collected	14979
Independent reflections	4999 [R(int) = 0.0578]
Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7456 and 0.6607
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4999 / 0 / 279
Goodness-of-fit on F^2	0.990
Final R indices [I>2sigma(I)]	R1 = 0.0581, wR2 = 0.1484
R indices (all data)	R1 = 0.0772, wR2 = 0.1615
Extinction coefficient	n/a
Largest diff. peak and hole	0.500 and -0.385 e.$Å^{-3}$

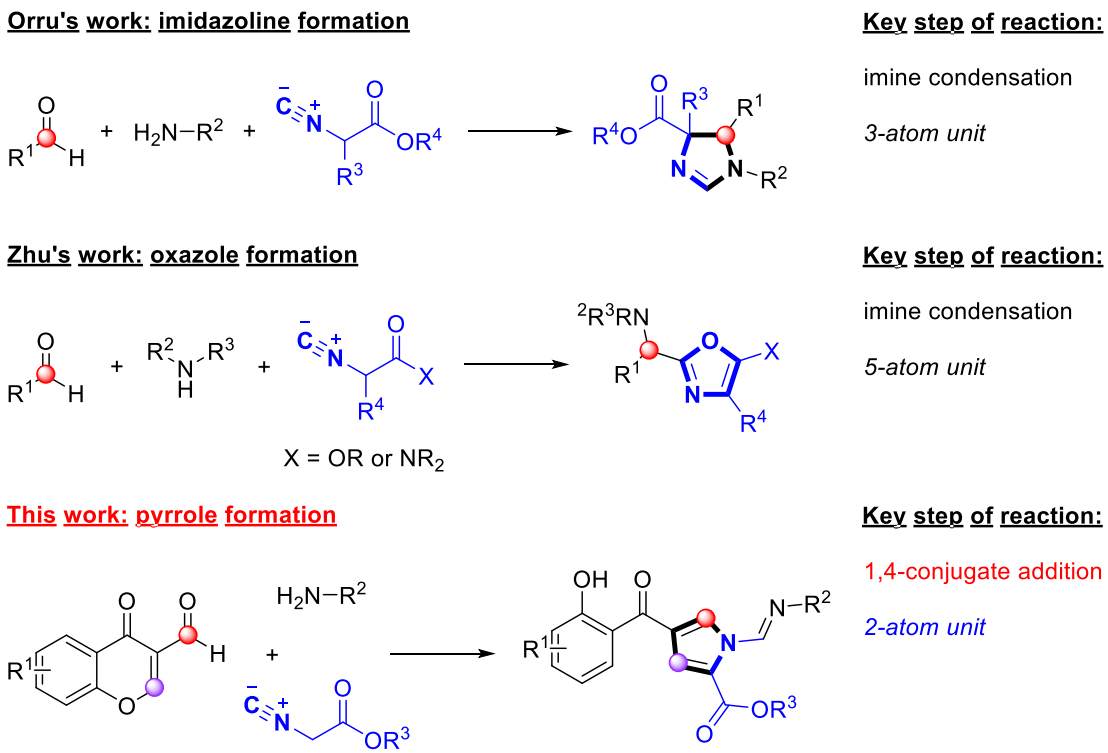
Chapter 4 Synthesis of Polysubstituted Pyrroles from Ag-Catalyzed Three-Component Reactions of Isocyanoacetates

4.1 Introduction

The development of efficient and economical methods for the construction of valuable heterocyclic compounds remains an important goal in organic synthesis and medicinal chemistry, for which multicomponent reactions (MCRs)[53] have emerged as powerful strategies due to their potential for introducing structural diversity and complexity in only one synthetic step. Along these lines, activated isocyanides (or α-acidic isocyanides)[2, 54] such as isocyanoacetates and isocyanoacetamides have found wide application in numerious MCRs due to their unique reactivities. In particular, three-component reactions of aldehydes, amines and activated isocyanides have been extensively studied to deliver a wide range of heterocycles.[55, 57a, 57c, 57d, 88] By taking advantage of the α-acidic carbon, Orru and co-workers developed an elegant synthesis of imidazolines from three-component reactions of aldehydes, amines and α-substituted isocyanoacetates (Scheme 4.1, top).[55d, 88a-e] The reaction was initiated by imine condensation, followed by nucleophilic addition of the α-carbanion to the generated imine and cyclization. In contrast, Zhu and co-workers described a completely different reactivity of activated isocyanides (both α-substituted isocyanoacetates and isocyanoacetamides) in the three-component reactions with aldehydes and amines, which was initiated by nucleophilic addition of the isocyanide carbon to the in situ generated imine/iminium, leading to the formation of oxazole scaffolds (Scheme 4.1, middle).[55a-c, 57a, 57c, 57d] Despite of these important achievements on this topic, however, the implementation of mechanistically novel catalytic transformations to achieve product structural diversity remains a significant

challenge in organic synthesis. We present here an intriguing three-component reaction of 3-formylchromones, amines and isocyanoacetates to yield highly functionalized pyrroles under silver catalysis (Scheme 4.1, bottom). Experimental studies revealed that this unusual transformation was initiated by 1,4-conjugate addition instead of imine condensation, representing a new reaction mode in isocyanide-based MCRs.

Scheme 4.1 Three-Component Reaction of Activated Isocyanides

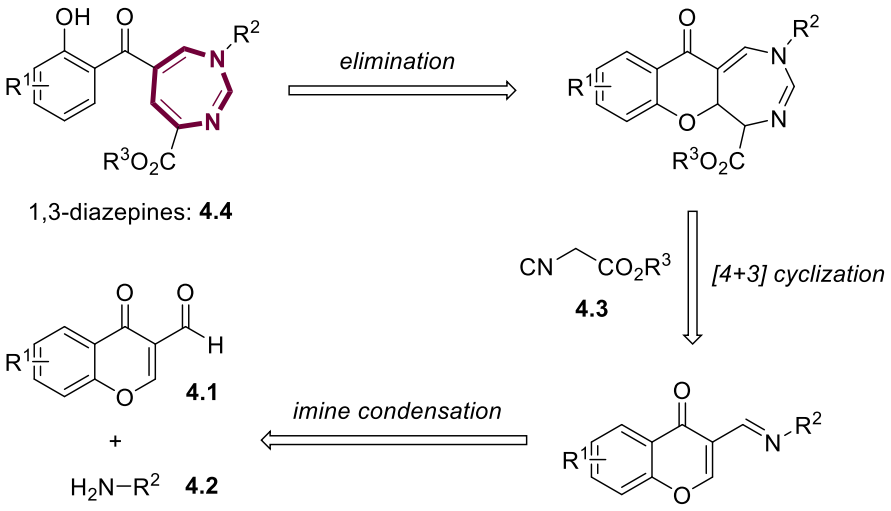


4.2 Project Design

In contrast to well-established [3+2] cycloaddition reactions, there is no evidence for the [4+3] cyclization on the basis of isocyanoacetates. Based on our group's continuous interest and efforts in isocyanoacetate chemistry,[26, 42] we became

interested in the exploration of new reaction partners of isocyanoacetates to realize the construction of seven-membered ring structures. Various α,β-unsaturated carbonyl compounds or imines were evaluated. To our disappointment, no desired product was formed; only [3+2] cyclization by-product was obtained. After many attempts, we chose 3-formylchromones[89] in which the conjugate addition pathway should be encouraged due to the presence of two electron-withdrawing groups. We envisioned that seven-membered 1,3-diazepines **4.4** could be obtained from the reaction of 3-formylchromones **4.1**, amines **4.2** and isocyanoacetates **4.3** through a sequence of imine condensation, [4+3] cyclization[90] and subsequent elimination[90b] (Scheme 4.2). This sequential approach seemed feasible and could generate complex structures from simple starting materials in a cascade fashion. The resulting products may have some interesting bioactivities as they are synthetic analogues of 1,4-benzodiazepines which are well known for their psychotropic effects.[91] Thus, we started to explore the possibility of this three-component reaction.

Scheme 4.2 Proposed Synthesis of 1,3-Diazepines

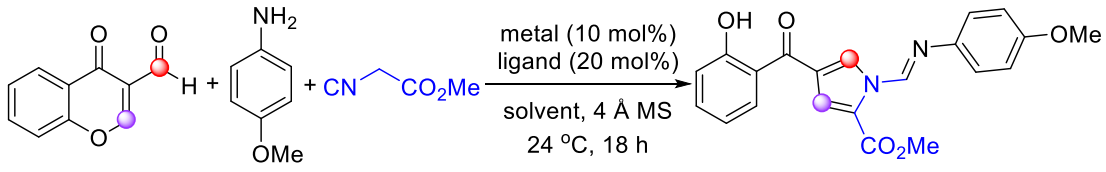


4.3 Results and Discussion

4.3.1 Observation of Unexpected Pyrrole Formation

Initial studies were performed by using the commercially available 3-formylchromone **4.1a**, *p*-anisidine **4.2a** and methyl isocyanoacetate **4.3a** as the model substrates. Based on our previous studies of isocyanoacetate chemistry,[26, 42] we first attempted the use of Ag_2O as the catalyst to promote this reaction. Intriguingly, we did not observe any formation of 1,3-diazepine **4.4a** under these conditions; instead, an unexpected five-membered ring product of polysubstituted pyrrole **4.5a** was obtained, albeit in a moderate yield of 27% (Table 4.1, entry 1). The failure of **4.4a** formation may be due to the high strain and instability of this seven-membered ring structure. In fact, the access to such architecture is still elusive in isocyanoacetate chemistry. From the viewpoint of product structure, as shown in Scheme 4.1, it is worth noting that conventional isocyanide-based MCRs led to the formation of imidazolines or oxazoles, while our method provided the access to polysubstituted pyrroles; in addition, activated isocyanide typically serves as three- or five-atom unit in the five-membered ring structure, whereas in our case, it serves as two-atom unit. Moreover, the resulted 1,2,4-trisubstituted pyrroles are important heterocycles due to their remarkable biological activities, such as synthetic histone deacetylase inhibitors,[92] while synthetic approaches toward them are quite limited.[93] Consequently, the efficient preparation of this class of molecules is undoubtedly a significant goal in organic synthesis. The novelty of the mechanism coupled with the importance of the products encouraged us for further investigation of this reaction.

Table 4.1 Optimization of Reaction Conditions[a-d]



4.1a **4.2a** **4.3a** **4.5a**

entry	metal	ligand	solvent	yield (%)[b]
1	Ag_2O	/	THF	27
2	Ag_2CO_3	/	THF	17
3	Cu_2O	/	THF	6
4	$Cu(OAc)_2$	/	THF	16
5	Ag_2O	PPh_3	THF	37
6	Ag_2O	dppf	THF	21
7	Ag_2O	dppe	THF	17
8	Ag_2O	PPh_3	1,4-dioxane	35
9	Ag_2O	PPh_3	Et_2O	14
10	Ag_2O	PPh_3	toluene	23
11	Ag_2O	PPh_3	$CHCl_3$	19
12	Ag_2O	PPh_3	CH_2Cl_2	19
13[c]	Ag_2O	PPh_3	THF	53
14[c-d]	Ag_2O	PPh_3	THF	**70**

[a] Carried out with 0.1 mmol **4.1a**, 0.12 mmol **4.2a** and 0.12 mmol **4.3a** in 1 mL solvent. [b] Isolated yields. [c] 2 mL THF was used. [d] 0.2 mmol **4.2a** was used.

4.3.2 Optimization of Reaction Conditions

With the aim of improving the efficiency of this unusual transformation, many other silver or copper salts with different levels of basicity or Lewis acidity were evaluated (Table 4.1, entries 2-4), suggesting that Ag_2O was still the optimal choice. In an effort to improve the yield further, various commercially available phosphine ligands were tested (entries 5-7), which to our delight the use of simple PPh_3 led to a higher yield of 37% (entry 5). Further optimization of reaction conditions with the use of Ag_2O-PPh_3 system was carried out. While solvent screening showed THF was still the best solvent (entries 8-12), lowering the concentration led to an obvious increase in the yield (entry 13, 53%). Finally, the use of 2.0 equiv of **4.2a** resulted in the efficient formation of **4.5a** with 70% isolated yield (entry 14).

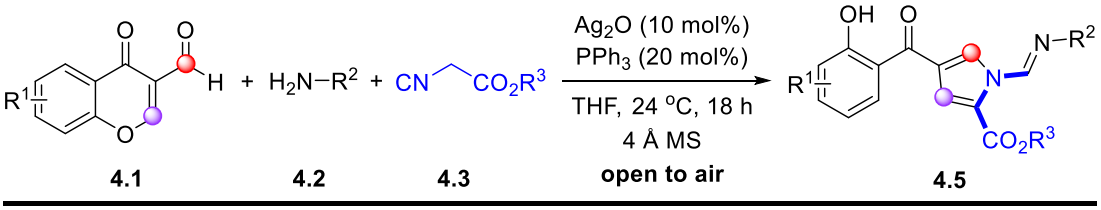
4.3.3 Substrate Scope

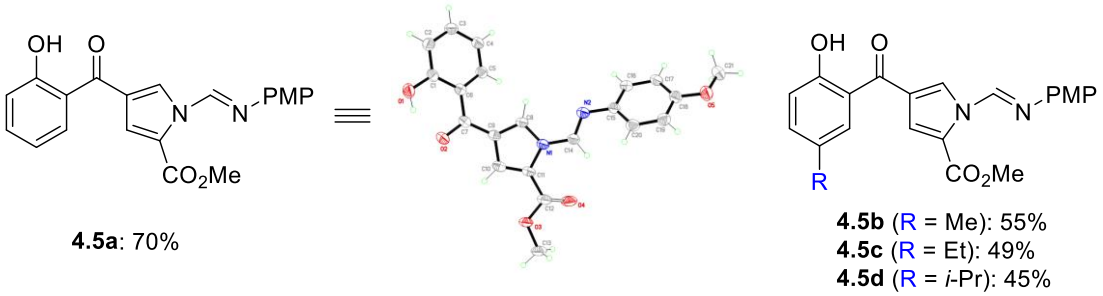
With the optimal reaction conditions in hand, we turned our attention to explore the scope of this silver-catalyzed pyrrole synthesis (Scheme 4.3). 3-Formylchromones bearing different substituents (electron-withdrawing, electron-donating and electron-neutral) with diverse substitution patterns (*para*-, *meta*-, and *ortho*-) on the aryl ring could be well-tolerated to produce highly functionalized pyrroles with different phenol units in moderate to good yields (30-70%, **4.5a**-**4.5i**). Isocyanoacetates possessing different ester groups were all suitable substrates, thus producing **4.5j** and **4.5k** in uniformly high yields. Anilines with different electron-donating groups on the *para*-position turned out to be good substrates to

generate **4.5l-4.5n** in good yields (48%-69%). To further extend the substrate scope, aliphatic amine was examined under the standard conditions. To our delight, the desired product **4.5o** was obtained, albeit with a lower yield of 23%. The structure of **4.5a** was unambiguously determined by single crystal X-ray analysis and those of other polysubstituted pyrroles were assigned by analogy.

It is noteworthy that the current catalytic system is simple to perform with a "mix and go" procedure using commercially available and cheap Ag_2O and PPh_3 as catalysts. The reactions were carried out under ambient atmosphere with no need for exclusion of air or moisture. Moreover, it is an environmentally friendly procedure as water is the only waste generated during the reaction. The combination of all these characters makes it an attractive method for polysubstituted pyrrole synthesis. The related 1,2,4-trisubstituted pyrroles such as Apricoxib[94] are important target compounds in medicinal chemistry, and this protocol provides a rapid access to the core structure of those compounds.

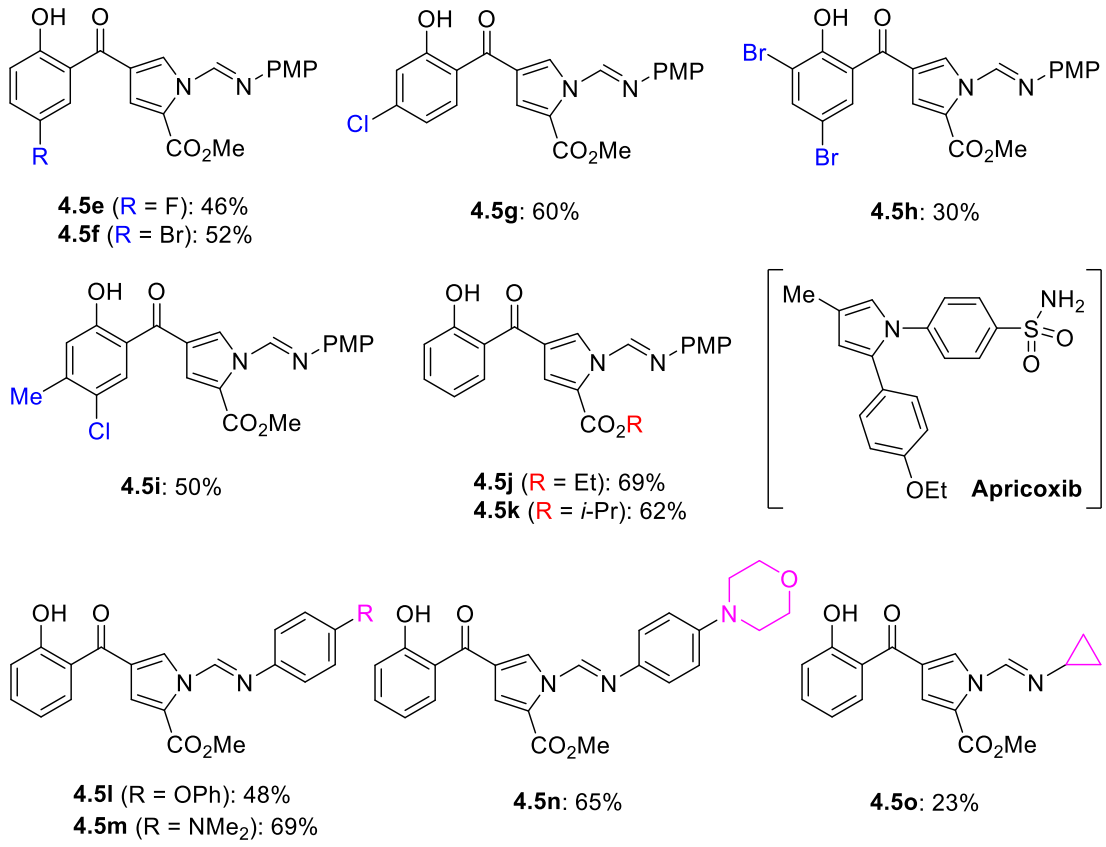
Scheme 4.3 Scope of Ag-Catalyzed Polysubstituted Pyrrole Synthesis[a-b]





4.5a: 70%

4.5b (R = Me): 55%
4.5c (R = Et): 49%
4.5d (R = *i*-Pr): 45%



4.5e (R = F): 46%
4.5f (R = Br): 52%

4.5g: 60%

4.5h: 30%

4.5i: 50%

4.5j (R = Et): 69%
4.5k (R = *i*-Pr): 62%

4.5l (R = OPh): 48%
4.5m (R = NMe_2): 69%

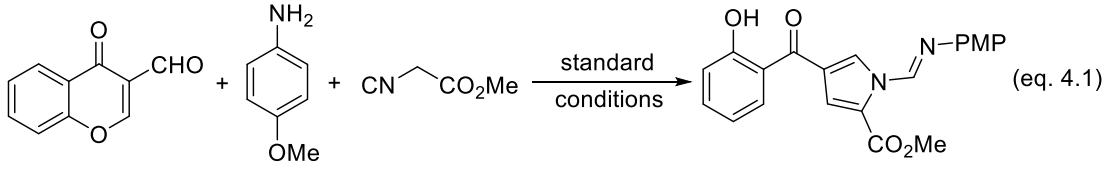
4.5n: 65%

4.5o: 23%

[a] The reactions were carried out with 0.1 mmol **4.1a**, 0.2 mmol **4.2a** and 0.12 mmol **4.3a** in 2 mL THF at ambient temperature for 18 h. [b] Isolated yields.

4.3.4 Gram-Scale Reaction

To test the robustness and efficiency of this method in preparative synthesis, a gram-scale three-component reaction of **4.1a**, **4.2a** and **4.3a** was investigated under the standard reaction conditions (eq. 4.1). To our delight, the desired product **4.5a** could be obtained with a slightly lower yield of 42%.

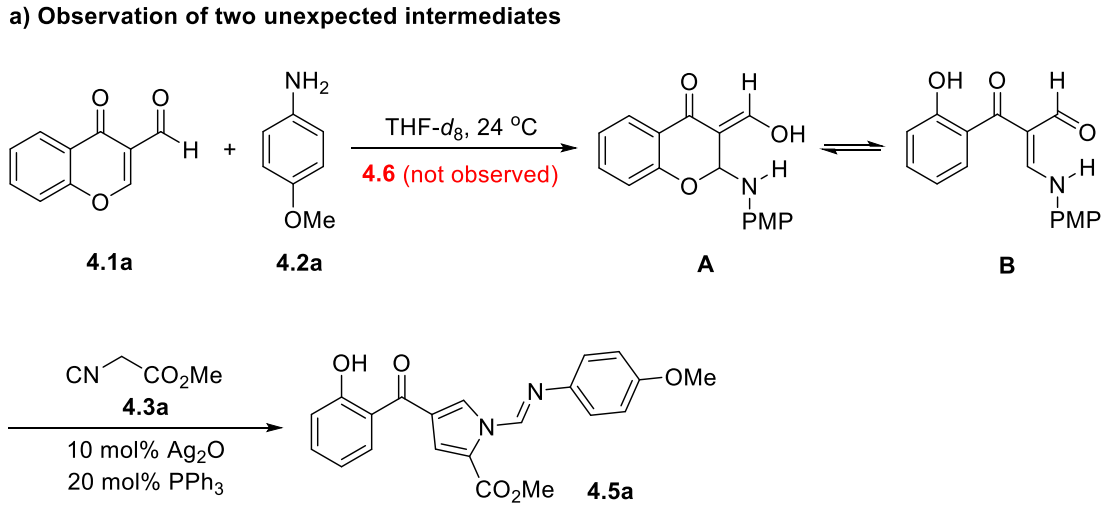


4.1a: 5 mmol **4.2a** **4.3a** **4.5a**: 802 mg, 42%

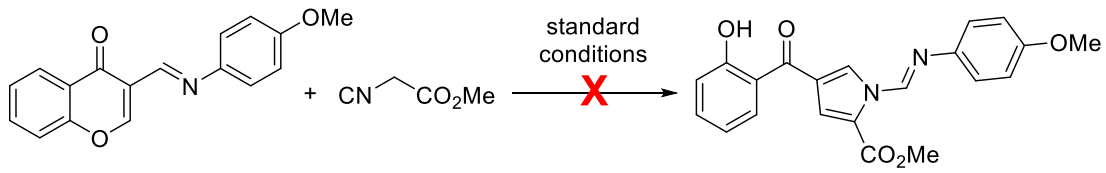
4.3.5 Mechanistic Study

In an effort to shed some light on the mechanism of this unusual transformation, the kinetics of the reaction between **4.1a**, **4.2a** and **4.3a** under silver catalysis was monitored by NMR. Intriguingly, two unexpected intermediates **A** and **B** (as a mixture, tautomers to each other) were detected once we mixed **4.1a** and **4.2a** together, which were determined by NMR analysis to be the 1,4-conjugate addition products of **4.1a** and **4.2a** and could be converted to the final product **4.5a** by the treatment with **4.3a** under silver catalysis (Scheme 4.4a). In contrast, the expected imine intermediate **4.6** (Scheme 4.4b) was not observed during the reaction, suggesting that the formation of **4.5a** does not proceed through imine condensation. To prove this, **4.6** was prepared in a pure form.[90a] When **4.6** was subjected to the standard reaction conditions with **4.3a**, as expected, we did not observe any formation of **4.5a** (Scheme 4.4b). It is worth noting that conventional isocyanide-based MCRs are all initiated by imine condensation, our method represents a new reaction mode on this topic.

Scheme 4.4 Experiments on Mechanistic Study



b) Control experiment

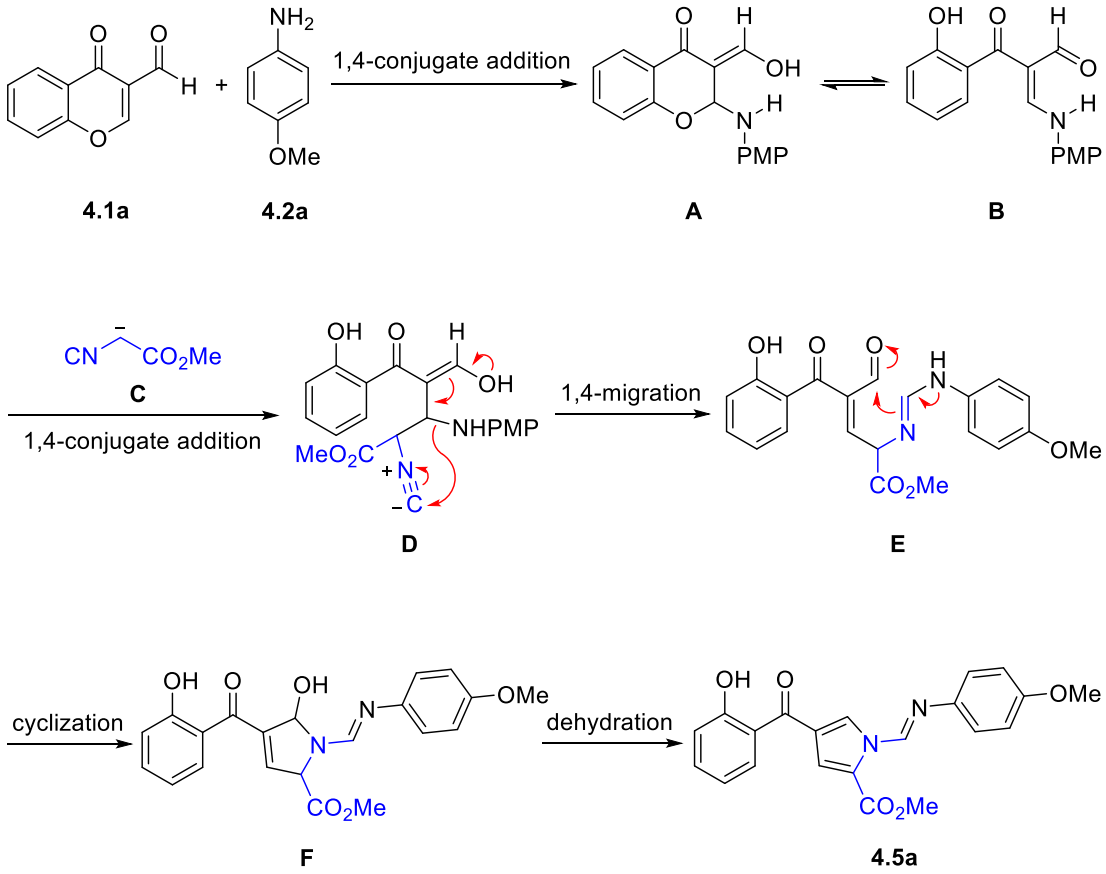


4.6 **4.3a** **4.5a**

4.3.6 Proposed Mechanism

On the basis of the above experimental results and related reports, a possible reaction pathway for the synthesis of polysubstituted pyrroles is proposed with the reaction of **4.1a**, **4.2a** and **4.3a** as an example (Scheme 4.5).

Scheme 4.5 Proposed Mechanism for the Formation of **4.5**



The reaction starts with the formation of 1,4-conjugate addition products **A** and **B** from **4.1a** and **4.2a**. It is noteworthy that for this step, there is no imine formation probably because the β-carbon in **4.1a** is more electrophilic than the carbonyl carbon in the absence of Brønsted acid[90a]. After that, 1,4-conjuagte addition of enolate **C** (derived from the deprotonation of **4.3a**) to **B** happens to give the key intermediate **D**. Subsequent intramolecular 1,4-migration[95] follwed by cyclization generates **F**, which, upon dehydration then produces **4.5a** as the final product.

4.4 Conclusion

In conclusion, we have developed, for the first time, a mechanistically intriguing three-component reaction of 3-formylchromones, amines and isocyanoacetates. Under silver catalysis, a wide range of highly functionalized pyrroles could be obtained. Current efforts in our laboratory are focused on the application of this current catalytic system to the preparation of other types of heterocycles.

4.5 Experimental Section

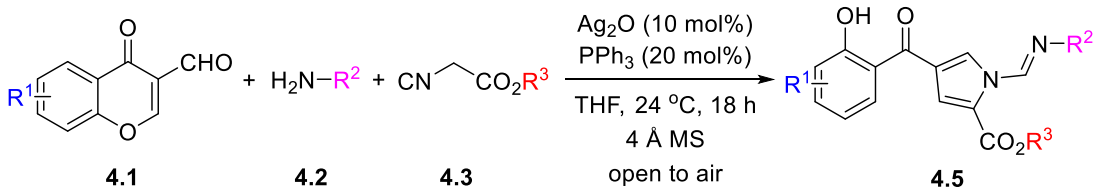
4.5.1. General Information

^{1}H and **^{13}C NMR** spectra were recorded on a Bruker AFC 300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: ^{1}H (chloroform δ 7.26; Acetone δ 2.05), ^{13}C (chloroform δ 77.0; Acetone δ 29.8, 206.3). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t =

triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets), coupling constants (Hz) and integration. For thin layer chromatography (**TLC**), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. High resolution mass spectra (**HRMS**) were obtained on a Finnigan/MAT 95XL-T spectrometer.

Unless otherwise noted, all the reactions were carried out open to air. Dichloromethane, diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were dried over a Pure Solv solvent purification system. Deuterated solvents were purchased from Cambridge Isotope Laboratories and used as received without further purification. Methyl isocyanoacetate, ethyl isocyanoacetate were purchased from Alfa Aesar company and used without further purification. Isopropyl isocyanoacetate was prepared according to literature procedure.[67] Other chemicals were purchased from commercial suppliers and used as received without further purification.

4.5.2 Ag-Catalyzed Three-Component Reaction



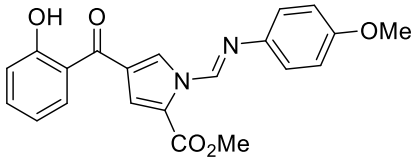
4.1 **4.2** **4.3** **4.5**

General procedure. To a 10 mL vial charged with Ag_2O (2.3 mg, 0.010 mmol), PPh_3 (5.2 mg, 0.020 mmol) and 4 Å MS (30 mg) was added anhydrous THF (2.0 mL). The mixture was allowed to stir at ambient temperature for 5 min, then amine **4.2** (0.20 mmol) was added in one portion, followed by isocyanoacetate **4.3** (0.12 mmol) and 3-formylchromone **4.1** (0.10 mmol). The reaction mixture was allowed to stirred

at ambient temperature for 18 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate) to afford the product **4.5**.

4.5.3 Characterization of Compounds 4.5

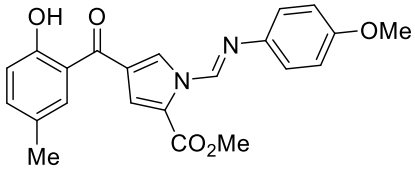
Methyl (*E*)-4-(2-hydroxybenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5a)



4.5a

Yellow wax, 70% yield. **^{1}H NMR** (500 MHz, Acetone-d_6): δ 11.88 (s, 1H), 9.52 (s, 1H), 8.50 (d, *J* = 1.8 Hz, 1H), 8.02 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.62-7.56 (m, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.34-7.24 (m, 2H), 7.07-6.96 (m, 4H), 3.91 (s, 3H), 3.83 (s, 3H). **^{13}C NMR** (126 MHz, Acetone-d_6): δ 194.0, 163.3, 161.5, 159.7, 144.0, 141.3, 137.0, 132.7, 127.7, 125.2, 125.1, 123.6, 121.7, 120.9, 120.1, 118.9 115.5, 55.8, 52.5. **HRMS (ESI):** m/z Calcd. for $[C_{21}H_{17}N_2O_5, M\text{-}H]^-$: 377.1143; Found: 377.1144.

Methyl (*E*)-4-(2-hydroxy-5-methylbenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5b)

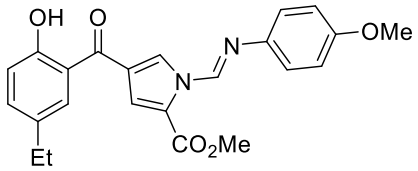


4.5b

Yellow wax, 55% yield. **^{1}H NMR** (500 MHz, Acetone-d_6): δ 11.66 (s, 1H), 9.52 (s,

1H), 8.50 (d, *J* = 1.8 Hz, 1H), 7.79 (d, *J* = 1.4 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.44-7.39 (m, 1H), 7.32-7.26 (m, 2H), 7.03-6.98 (m, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (126 MHz, Acetone-d_6): δ 194.0, 161.5, 161.2, 159.7, 144.1, 141.3, 137.9, 132.3, 129.2, 127.6, 125.3, 125.1, 123.6, 121.7, 120.7, 118.7, 115.5, 55.8, 52.5, 20.5. **HRMS (ESI):** m/z Calcd. for $[C_{22}H_{19}N_2O_5, M-H]^-$: 391.1299; Found: 391.1294.

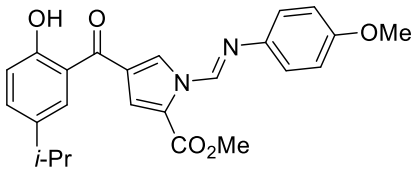
Methyl (*E*)-4-(5-ethyl-2-hydroxybenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5c)



4.5c

Yellow wax, 49% yield. **^{1}H NMR** (500 MHz, Acetone-d_6): δ 11.65 (s, 1H), 9.53 (s, 1H), 8.51 (d, *J* = 1.6 Hz, 1H), 7.82 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.46 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.32-7.27 (m, 2H), 7.04-6.99 (m, 2H), 6.97 (d, *J* = 8.5 Hz, 1H), 3.92 (s, 3H), 3.83 (s, 3H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (126 MHz, Acetone-d_6): δ 194.0, 161.5, 161.3, 159.7, 144.0, 141.3, 136.8, 135.7, 131.2, 127.7, 125.3, 125.1, 123.6, 121.6, 120.8, 118.8, 115.5, 55.8, 52.5, 28.5, 16.2. **HRMS (ESI):** m/z Calcd. for $[C_{23}H_{21}N_2O_5, M-H]^-$: 405.1456; Found: 405.1461.

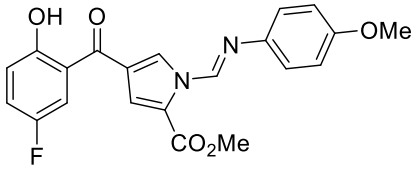
Methyl (*E*)-4-(2-hydroxy-5-isopropylbenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5d)



4.5d

Yellow wax, 45% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.73 (s, 1H), 9.56 (s, 1H), 8.56 (d, *J* = 1.8 Hz, 1H), 7.74 (d, *J* = 2.2 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.25-7.18 (m, 2H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.96-6.90 (m, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 2.92 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 193.3, 161.0, 160.7, 158.6, 142.7, 140.2, 139.3, 134.5, 129.0, 127.2, 124.6, 123.7, 122.7, 121.7, 119.6, 118.2, 114.6, 55.5, 52.1, 33.2, 24.0. **HRMS (ESI):** m/z Calcd. for $[C_{24}H_{23}N_2O_5, M\text{-}H]^-$: 419.1612; Found: 419.1623.

Methyl (*E*)-4-(5-fluoro-2-hydroxybenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5e)

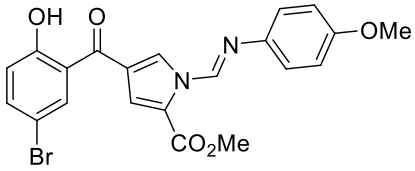


4.5e

Yellow solid, 46% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.68 (s, 1H), 9.54 (s, 1H), 8.55 (d, *J* = 1.8 Hz, 1H), 7.60 (dd, *J* = 8.9, 3.1 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.28-7.20 (m, 3H), 7.03 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.96-6.90 (m, 2H), 3.92 (s, 3H), 3.84 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.3, 160.9, 158.8 (d, *J* = 1.3 Hz), 158.7, 154.9 (d, *J* = 238.6 Hz), 142.6, 140.1, 127.0, 124.0, 123.9, 123.5 (d, *J* = 23.6 Hz), 122.7, 121.5, 119.7 (d, *J* = 7.3 Hz), 119.4 (d, *J* = 6.3 Hz), 116.6 (d, *J* = 23.7 Hz),

114.6, 55.5, 52.1; **HRMS (ESI):** m/z Calcd. for [$C_{21}H_{16}FN_2O_5$, M-H]$^-$: 395.1049; Found: 395.1049.

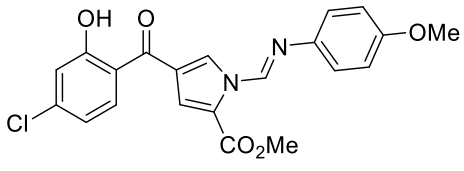
Methyl (*E*)-4-(5-bromo-2-hydroxybenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5f)



4.5f

Yellow wax, 52% yield. **^{1}H NMR** (500 MHz, Acetone-d_6): δ 11.58 (s, 1H), 9.52 (s, 1H), 8.52 (d, *J* = 1.8 Hz, 1H), 8.04 (d, *J* = 2.5 Hz, 1H), 7.70 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.33-7.24 (m, 2H), 7.06-6.98 (m, 3H), 3.92 (s, 3H), 3.83 (s, 3H). **^{13}C NMR** (126 MHz, Acetone-d_6): δ 192.8, 161.7, 161.4, 159.8, 144.0, 141.3, 139.2, 134.5, 127.9, 125.3, 124.9, 123.7, 123.1, 121.4, 121.1, 115.5, 111.2, 55.8, 52.6. **HRMS (ESI):** m/z Calcd. for [$C_{21}H_{16}BrN_2O_5$, M-H]$^-$: 455.0248; Found: 455.0252.

Methyl (*E*)-4-(4-chloro-2-hydroxybenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5g)

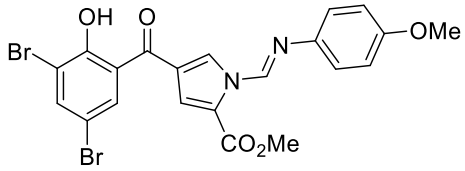


4.5g

Yellow wax, 60% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.16 (s, 1H), 9.54 (s, 1H), 8.52 (s, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.24-7.18 (m, 2H),

7.07 (s, 1H), 6.98-6.90 (m, 3H), 3.92 (s, 3H), 3.83 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.5, 163.4, 160.9, 158.7, 142.6, 141.9, 140.1, 132.6, 126.9, 124.2, 123.9, 122.7, 121.5, 119.7, 118.6, 118.4, 114.6, 55.5, 52.1.

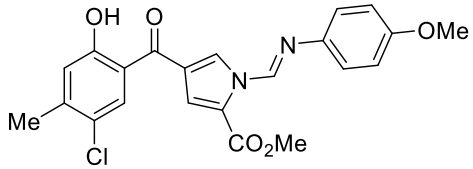
Methyl (*E*)-4-(3,5-dibromo-2-hydroxybenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole -2-carboxylate (4.5h)



4.5h

Yellow solid, 30% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.53 (s, 1H), 9.54 (s, 1H), 8.55 (s, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 7.90 (s, 1H), 7.50 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 3.93 (s, 3H), 3.84 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 191.8, 160.8, 158.8, 158.3, 142.4, 141.0, 139.9, 132.9, 127.4, 124.2, 123.4, 122.8, 121.5, 121.3, 114.6, 113.3, 110.5, 55.5, 52.2. **HRMS (ESI):** m/z Calcd. for $[C_{21}H_{15}Br_2N_2O_5, M-H]^-$: 532.9353; Found: 532.9337.

Methyl (*E*)-4-(5-chloro-2-hydroxy-4-methylbenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5i)

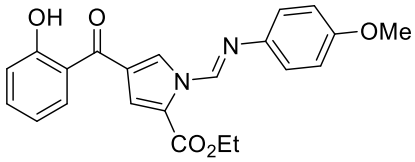


4.5i

Yellow solid, 50% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.88 (s, 1H), 9.54 (s, 1H),

8.54 (d, *J* = 1.7 Hz, 1H), 7.86 (s, 1H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.25-7.19 (m, 2H), 6.97-6.90 (m, 3H), 3.92 (s, 3H), 3.84 (s, 3H), 2.41 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.0, 161.2, 160.9, 158.7, 145.3, 142.6, 140.2, 131.1, 126.9, 124.3, 124.1, 123.9, 122.8, 121.4, 120.5, 118.8, 114.6, 55.5, 52.1, 20.8. **HRMS (ESI):** m/z Calcd. for $[C_{22}H_{18}ClN_2O_5, M-H]^-$: 425.0910; Found: 425.0912.

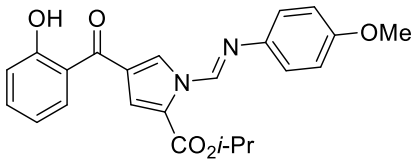
Ethyl (*E*)-4-(2-hydroxybenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5j)



4.5j

Yellow wax, 69% yield. **^{1}H NMR** (500 MHz, Acetone-d_6): δ 11.87 (s, 1H), 9.53 (s, 1H), 8.50 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.59 (dd, *J* = 11.2, 4.3 Hz, 1H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.32-7.22 (m, 2H), 7.08-6.96 (m, 4H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Acetone-d_6): δ 194.1, 163.3, 161.0, 159.7, 144.1, 141.3, 136.9, 132.7, 127.6, 125.5, 125.1, 123.6, 121.6, 121.0, 120.1, 118.9, 115.5, 61.9, 55.8, 14.5. **HRMS (ESI):** m/z Calcd. for $[C_{22}H_{21}N_2O_5, M+H]^+$: 393.1445; Found: 393.1450.

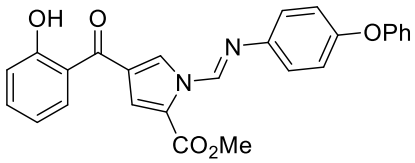
Isopropyl (*E*)-4-(2-hydroxybenzoyl)-1-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5k)



4.5k

Yellow wax, 62% yield. **^{1}H NMR** (500 MHz, Acetone-d_6): δ 11.87 (s, 1H), 9.55 (s, 1H), 8.50 (d, *J* = 1.6 Hz, 1H), 8.02 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.67-7.57 (m, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.32-7.24 (m, 2H), 7.12-6.93 (m, 4H), 5.23 (dt, *J* = 12.5, 6.2 Hz, 1H), 3.83 (s, 3H), 1.38 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (126 MHz, Acetone-d_6): δ 194.1, 163.3, 160.6, 159.7, 144.2, 141.4, 136.9, 132.7, 127.6, 125.8, 125.1, 123.6, 121.5, 121.0, 120.1, 118.9, 115.5, 69.8, 55.8, 22.1. **HRMS (ESI):** m/z Calcd. for $[C_{23}H_{23}N_2O_5, M+H]^+$: 407.1601; Found: 407.1607.

Methyl (*E*)-4-(2-hydroxybenzoyl)-1-(((4-phenoxyphenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5l)

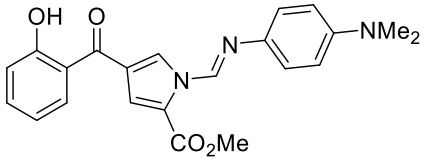


4.5l

Yellow wax, 48% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.96 (s, 1H), 9.56 (s, 1H), 8.55 (d, *J* = 1.5 Hz, 1H), 8.00-7.84 (m, 1H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.55-7.49 (m, 1H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.09-7.00 (m, 5H), 6.98 (t, *J* = 7.6 Hz, 1H), 3.92 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 193.3, 162.7, 161.0, 157.2, 156.1, 143.7, 142.6, 136.1, 131.7, 129.8, 127.0, 124.6, 123.8, 123.4, 122.8, 121.9, 119.9, 119.7, 119.0, 118.8, 118.5, 52.1. **HRMS**

(ESI): m/z Calcd. for $[C_{26}H_{21}N_2O_5, M+H]^+$: 441.1445; Found: 441.1448.

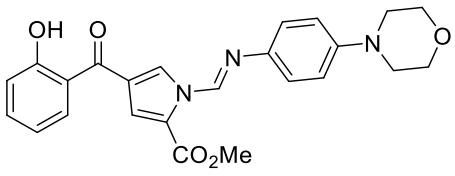
Methyl (*E*)-1-(((4-(dimethylamino)phenyl)imino)methyl)-4-(2-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylate (4.5m)



4.5m

Brown solid, 69% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.00 (s, 1H), 9.56 (s, 1H), 8.56 (d, *J* = 1.8 Hz, 1H), 7.95 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.53-7.49 (m, 1H), 7.26-7.20 (m, 2H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.98 (q, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 3.92 (s, 3H), 2.99 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 193.4, 162.7, 161.0, 140.9, 135.9, 131.7, 127.0, 124.2, 123.6, 122.8, 121.6, 120.0, 119.0, 118.4, 113.0, 52.0, 40.7. **HRMS (ESI):** m/z Calcd. for $[C_{22}H_{22}N_3O_4, M+H]^+$: 392.1605; Found: 392.1610.

Methyl (*E*)-4-(2-hydroxybenzoyl)-1-(((4-morpholinophenyl)imino)methyl)-1*H*-pyrrole-2-carboxylate (4.5n)

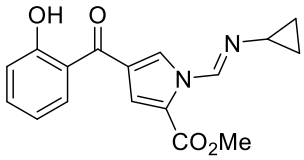


4.5n

Yellow wax, 65% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.98 (s, 1H), 9.56 (s, 1H), 8.55 (d, *J* = 1.7 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.51

(dd, *J* = 11.3, 4.2 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.01-6.90 (m, 3H), 3.92 (s, 3H), 3.90-3.82 (m, 4H), 3.24-3.12 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 193.3, 162.7, 161.0, 142.3, 136.0, 131.7, 127.0, 124.4, 123.7, 122.6, 121.7, 119.9, 119.0, 118.4, 116.2, 66.8, 52.0, 49.3. **HRMS (ESI):** m/z Calcd. for $[C_{24}H_{22}N_3O_5, M-H]^-$: 432.1565; Found: 432.1569.

Methyl (*E*)-1-((cyclopropylimino)methyl)-4-(2-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylate (4.5o)



4.5o

Pale yellow wax, 23% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.97 (s, 1H), 9.41 (s, 1H), 8.27 (d, *J* = 1.9 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.60-7.39 (m, 2H), 7.04 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.99-6.88 (m, 1H), 3.90 (s, 3H), 3.21-2.98 (m, 1H), 0.96-0.80 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 193.4, 162.6, 161.0, 143.3, 135.9, 131.7, 127.1, 123.9, 123.0, 121.1, 119.9, 118.9, 118.4, 52.0, 37.1, 8.5.

4.5.4 X-Ray Crystallographic Analysis of 4.5a

The conformation of **4.5a** was determined by X-ray crystallographic analysis of a single crystal of **4.5a** (Figure 4.1). The crystal was prepared from the solution of **4.5a** in hexanes/ethyl acetate at 0 ^{o}C.

Figure 4.1 X-ray Structure of **4.5a**

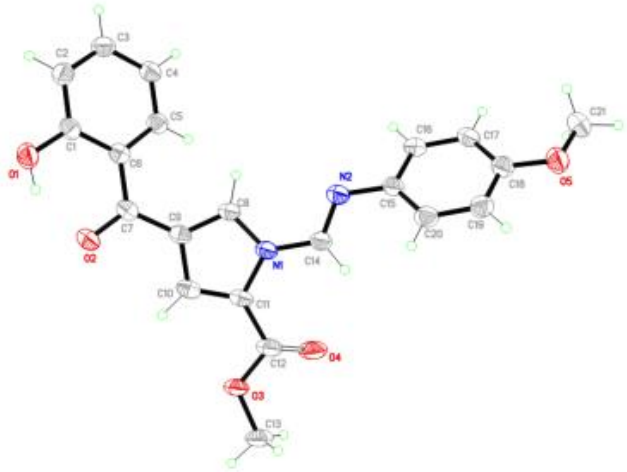
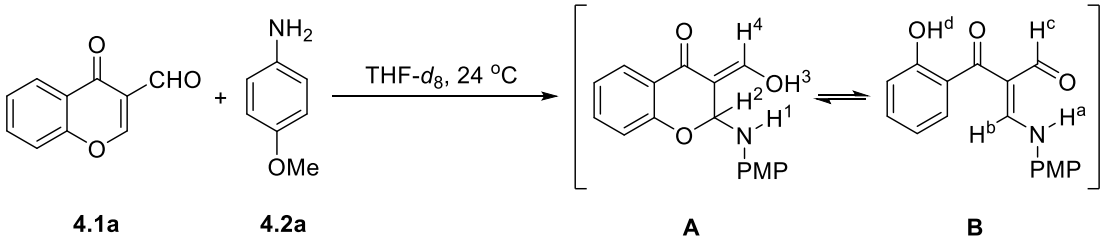


Table 4.2 Crystal Data and Structure Refinement for **4.5a**

Identification code	**4.5a**	
Empirical formula	$C_{25}H_{27}N_2O_{5.25}$	
Formula weight	439.48	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 3.8268(2) Å	α = 90°
	b = 31.4297(12) Å	β = 92.2510(10)°
	c = 17.1304(7) Å	γ = 90°
Volume	2058.77(16) $Å^3$	
Z	4	
Density (calculated)	1.418 Mg/m^3	

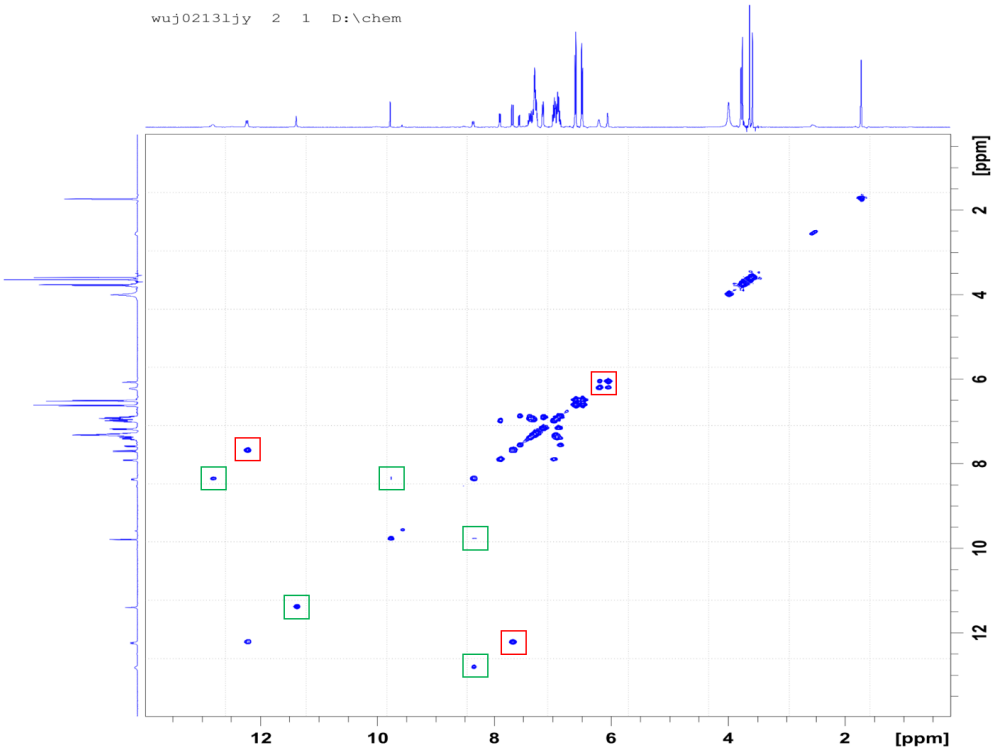
Absorption coefficient	0.817 mm^{-1}
F(000)	932
Crystal size	0.360 x 0.260 x 0.160 mm^3
Theta range for data collection	2.812 to 68.231°
Index ranges	-4<=h<=4, -37<=k<=37, -20<=l<=20
Reflections collected	31351
Independent reflections	3774 [R(int) = 0.0382]
Completeness to theta = 67.679°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7533 and 0.6531
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3774 / 9 / 288
Goodness-of-fit on F^2	1.086
Final R indices [I>2sigma(I)]	R1 = 0.0819, wR2 = 0.2745
R indices (all data)	R1 = 0.0870, wR2 = 0.2815
Extinction coefficient	n/a
Largest diff. peak and hole	1.013 and -0.653 e.$Å^{-3}$

4.5.5 Observation of Intermediates A and B



4.1a **4.2a** **A** **B**

Figure 4.2 NOESY Spectrum of Intermediates **A** and **B**



The intermediates **A** and **B** were formed immediately when we mixed **4.1a** and **4.2a** together. The structure of **A** was determined by the NOE correlation between H^1 and H^2, H^3 and H^4 (Figure 4.2, in red), while the structure of **B** was determined by the NOE correlation between H^a and H^b, H^b and H^c (Figure 4.2, in green).

Chapter 5 Divergent Synthesis of Tricyclic Ketals and Triarylmethanes from Catalytic Cascade Reactions of Activated Isocyanides

5.1 Introduction

The efficient access to structurally complex compounds and especially those with scaffold diversity is a crucial requirement for biological screening in drug discovery, which calls for the development of versatile and effective complexity-generating transformations in synthetic chemistry.[96] Diversity-oriented synthesis, in particular, has been practised successfully to generate skeletally diverse molecule libraries through stepwise, divergent chemical transformations of central core intermediates.[51, 97] In the field of natural product synthesis, the strategy of collective synthesis has also proven to be highly powerful in accessing natural products of different families from a common advanced intermediate.[98] In catalytic method development, the realization of catalyst-enabled divergent reactivities has attracted much attention in recent years as well.[82] The adoption of different catalytic conditions could lead to chemo-,[99] regio-[56a, 100] or stereoselective transformations[101] of the starting materials leading to isomeric products that are structurally related. More importantly, elegant reports on "product-selective catalysis"[82] were also documented in the literature, in which processes skeletally unrelated products could be accessed using different catalysts or reaction conditions.[102] Despite of these important advancements on this topic, however, the implementation of a general strategy of catalytic transformations to achieve scaffold diversity remains a significant challenge in organic synthesis.

5.2 Project Design

We were attracted to an intriguing and general strategy of generating a common

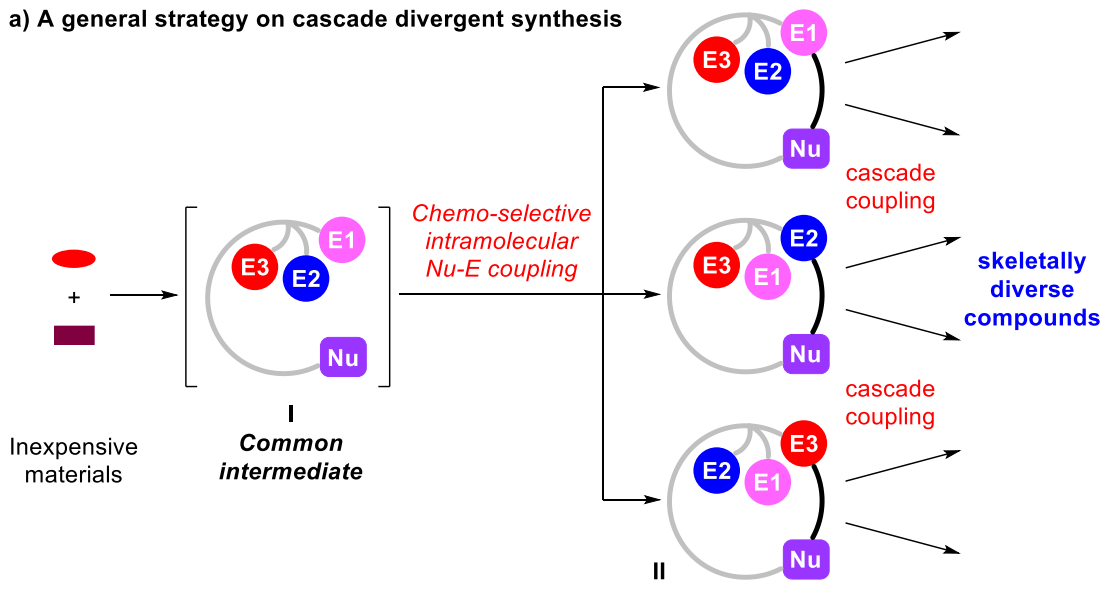
intermediate bearing multiple functionalities (depicted as **I**, Scheme **5.1a**) that may undergo chemo-divergent intramolecular couplings to produce different structures **II**, for which further coupling can in principle take place to generate complex and diverse molecular structures in a cascade catalysis fashion.[52] Such a seemingly simple strategy possesses formidable challenges in the efficient formation of **I** from readily available building blocks as well as the chemo-selective transformation of **I** afterwards. We report herein our initial progress made towards such a goal in catalytic method development.

Activated isocyanides such as isocyanoacetates (**5.4** in Scheme **5.1b**) are intriguing molecules bearing multiple reactive sites, which have found wide application in multicomponent reactions (MCRs) as well as heterocycle synthesis.[2, 53a, 54] The combination of these reactions with further functionalization of the products in a tandem fashion has also been extensively studied, in particular by the Zhu Group to produce more complex structures.[57] Based on our group's continuous interest and efforts in isocyanoacetate chemistry,[26, 42] we reasoned that isocyanoacetate **5.4** could serve as a perfect building block to introduce multiple functionalities (isocyanide and the ester as electrophiles for divergent reactions) if conjugate addition of isocyanoacetate **5.4** to *para*-quinone methide-aryl ester **5.3** could be realized.

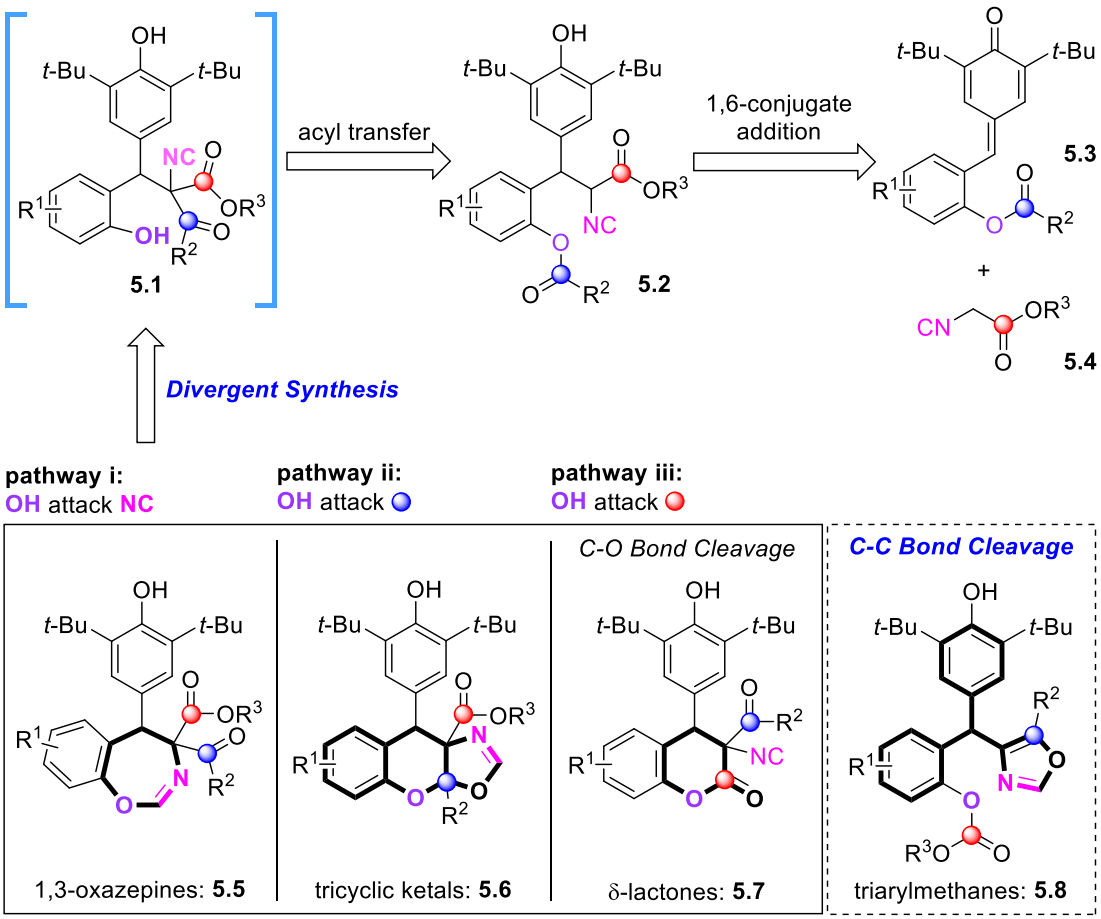
para-Quinone methides (*p*-QMs) have proven to be a powerful Michael acceptor for 1,6-conjuagte addition reactions with a wide range of carbon-,[103] sulfur-,[104] boron-[105] or silane-based[106] nucleophiles. In all of these reactions, aromatization of

the substrate served as the strong driving force. We therefore proposed that the addition of the enolate derived from isocyanoacetate **5.4** to *p*-QM-containing ester **5.3** should proceed efficiently to yield the phenol intermediate **5.2**, in which step the *p*-QM moiety in **5.3** should serve only as the Michael acceptor while undesired [3+2] cyclization reaction with isocyanoacetate **5.4** should not take place. Based on our previous discovery of oxazole formation from aryl esters and isocyanoacetates,[26] we expected that further deprotonation of the isocyanoacetate moiety in **5.2** followed by addition to the aryl ester should result in an acyl transfer to yield the key intermediate **5.1**, in which three different electrophiles (isocyanide, ketone and ester) are attached on the same carbon, while the phenol unit may serve as the nucleophile to undergo reaction with any one of the three. If chemo-selectivity could be achieved under different reaction conditions, this initial step would be followed by further cascade intramolecular couplings leading to the formation of diverse skeletons (Scheme 5.1b).

Scheme 5.1 Cascade Divergent Synthesis of Structurally Diverse Heterocycles



b) Cascade divergent synthesis of structurally diverse heterocycles from 5.3 and 5.4



As possible product structures, we envisioned that the addition of phenol to the isocyanide may lead to the formation of 1,3-oxazepines **5.5** (pathway **i**), although the construction of seven-membered ring structures still remains elusive in this field. Alternatively, if the phenol attacks the ketone moiety, the resultant hemiacetal may undergo further addition to the isocyanide to produce tricyclic ketals **5.6** bearing three continuous stereogenic centres (pathway **ii**); this should take place in preference over the addition to the ester moiety to form a more strained β-lactone. Another possibility is the generation of δ-lactones **5.7** through the addition of phenol to the ester group (pathway **iii**). The focus of this study was whether efficient catalytic methods could be

developed to realize such divergent transformations leading to skeletally diverse products, ideally in a cascade fashion. We report herein the realization of this strategy to deliver two classes of highly complex and valuable compounds in the forms of tricyclic ketals **5.6** and triarylmethanes **5.8**.

5.3 Results and Discussion

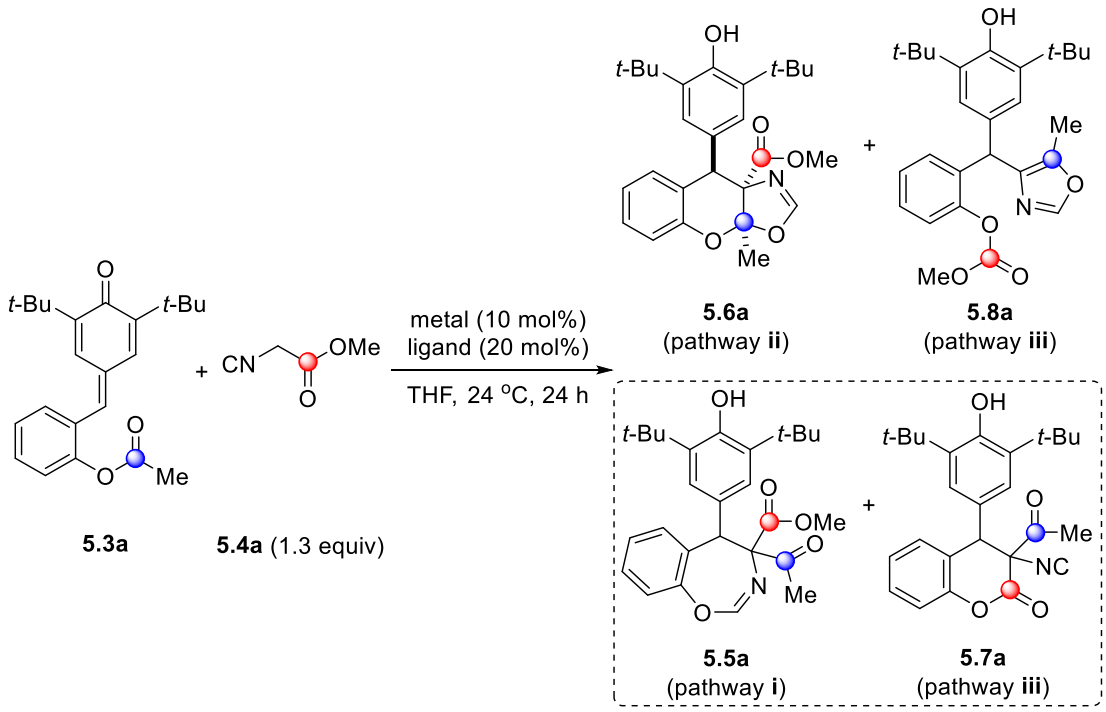
5.3.1 Investigation on Cascade Divergent Synthesis

We initiated our investigation using **5.3a** and **5.4a** as the model substrates. Various metal salts possessing different basicity or Lewis acidity were systematically screened for this reaction. The selected key results of extensive studies are summarized in Table 5.1. Based on our previous studies of isocyanoacetate chemistry,[26, 42] we first attempted the use of Ag_2O in combination with PPh_3 as the catalyst. To our excitement, an exclusive conversion to the complex tricyclic ketal **5.6a** could be achieved under these conditions, with excellent efficiency as well as exquisite stereoselectivity (entry 1, 95% yield, >20:1 d.r.). While no intermediate was observed, the formation of **5.6a** clearly suggested the formation of **5.1** and the feasibility of pathway **ii** initiated by phenol addition to the ketone moiety. The catalyst loading could be further reduced to 5 mol% without any loss of selectivity and efficiency (entry 2, 94% yield, >20:1 d.r.).

When the catalyst was switched to $Cu(OAc)_2$, intriguingly, an unexpected rearrangement product triarylmethane **5.8a** was observed, albeit in a mixture with **5.6a** (entry 3, **5.6a**:**5.8a** = 1.3:1). From the viewpoint of molecular structure, this type

of compound is clearly formed through pathway **iii**. However, instead of the expected C-O bond cleavage to produce δ-lactone **5.7** (Scheme 5.1b), an unexpected C-C bond cleavage occurred exclusively to generate the carbonate moiety followed by cyclization to give the triarylmethane scaffold. We argued that aromatization in oxazole formation served as the driven force for such an unusual transformation. This observation of switching of chemo-selectivity with Ag- or Cu-catalysis proved that the proposed divergent synthesis using this system could be realized, which also represents an interesting example of catalyst-controlled chemo-divergent reactions[82]. Recognizing that this unexpected reactivity catalyzed by copper provides a new entry to the difficult-to-access oxazole-containing triarylmethanes,[107] we screened various readily available bisphosphine ligands in order to improve the efficiency of **5.8a** formation. Although many ligands including dppm led to similarly low selectivity (entry 4, **5.6a**:**5.8a** = 1.4:1), the use of dppp resulted in exclusive formation of **5.8a** with >98% isolated yield (entry 5). With the efficient formation of **5.6a** or **5.8a** in hand, we further screened many other metal salts in an attempt to achieve the formation of pathway **i** product **5.5a**. Unfortunately, no reactivity was obtained for the use of Co, Zn, Fe, Ni or Au salts (entries 6-10). The failure of **5.5a** formation may be due to the high strain and instability of this seven-membered ring structure. In fact, the access to such architecture is still elusive in isocyanoacetate chemistry.

Table 5.1 Reaction Condition Screening for Cascade Divergent Heterocycle Synthesis[a-c]



entry	metal	ligand	conv. (%)	**5.6a**:**5.8a**	**5.6a** yield (%)[b]	**5.8a** yield (%)[b]
1	Ag_2O	PPh_3	>98	>20:1	95	/
2[c]	Ag_2O	PPh_3	>98	>20:1	**94**	/
3	$Cu(OAc)_2$	PPh_3	>98	1.3:1	n.d.	n.d.
4	$Cu(OAc)_2$	dppm	>98	1.4:1	n.d.	n.d.
5	$Cu(OAc)_2$	dppp	>98	1:>20	/	**>98**
6	$Co(OAc)_2$	PPh_3	<2	/	/	/
7	$Zn(OAc)_2$	PPh_3	<2	/	/	/
8	$Fe(OAc)_2$	PPh_3	<2	/	/	/
9	$NiCl_2$	PPh_3	<2	/	/	/
10	$AuCl_3$	PPh_3	<2	/	/	/

[a] The reactions were carried out under ambient atmosphere for 24 h. We did not

observe any formation of **5.5a** or **5.7a** in all reactions. The d.r. of **5.6a** and ratio of **5.6a**:**5.8a** were determined by crude ^{1}H NMR analysis. In all cases **5.6a** was obtained with >20:1 d.r. [b] Isolated yields. [c] 5 mol% Ag_2O and 10 mol% PPh_3 were used.

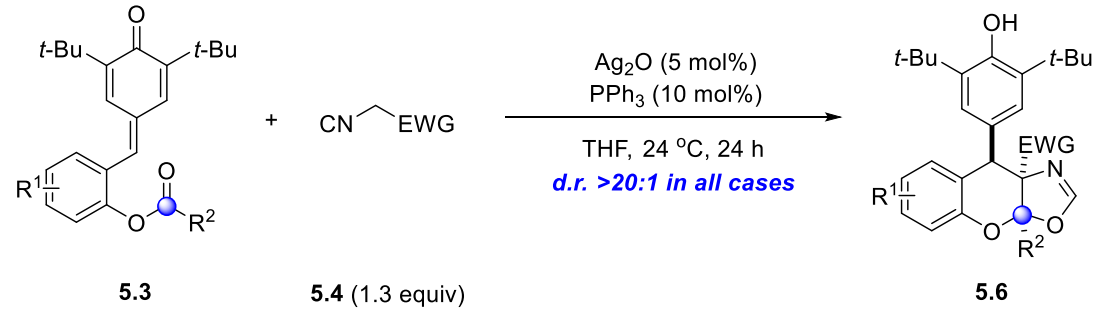
5.3.2 Tricyclic Ketal Synthesis

With the optimal conditions in hand, we moved on to explore the scope of this silver-catalyzed cascade reaction for tricyclic ketal synthesis first (Scheme 5.2). It is noteworthy that the current catalytic system is simple to perform with a "mix and go" procedure using commercially available and cheap Ag_2O and PPh_3 as catalysts. The reactions were set up open to air with no need for exclusion of air or moisture. In addition, this process is entirely atom-economical as the product incorporates all portions from the starting materials.

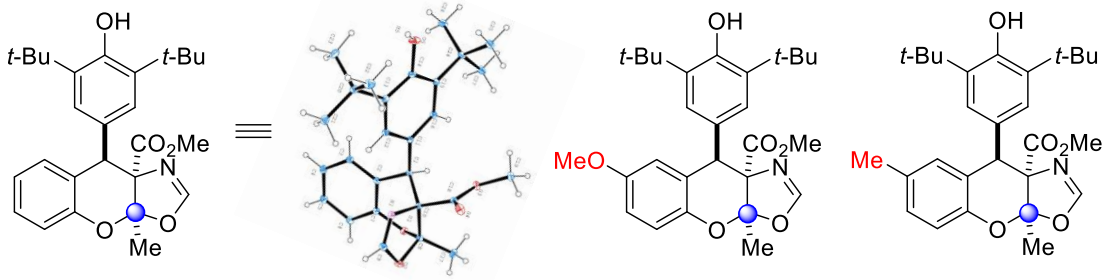
As shown, in all cases perfect diastereoselectivity (>20:1 d.r.) was obtained for product **5.6**. Different substitution patterns on the aryl ring (*para*-, *meta*- and *ortho*-) could be well adopted to form **5.6a**-**5.6h** in excellent selectivities and yields (87% to >98%). The variation on the ester moiety in **5.3** (bearing both alkyl and aryl substituents) was also tolerated to produce **5.6i**-**5.6l** in uniformly excellent yields with excellent selectivities. Different isocyanoacetates could also be used to produce **5.6m** and **5.6n** in excellent yields and selectivities. The relative configuration of **5.6a** was unambiguously assigned by single crystal X-ray analysis and those of other tricyclic ketals were assigned by analogy. To further extend the substrate scope, isocyanoacetamide was examined under the standard conditions. To our delight, the

desired product **5.6o** was obtained in 75% yield, although a small amount of the corresponding triarylmethane was formed in this case. The relative configuration of **5.6o** proved to be the same as assigned by single crystal X-ray analysis.

Scheme 5.2 Diastereoselective Synthesis of Tricyclic Ketals[a-d]

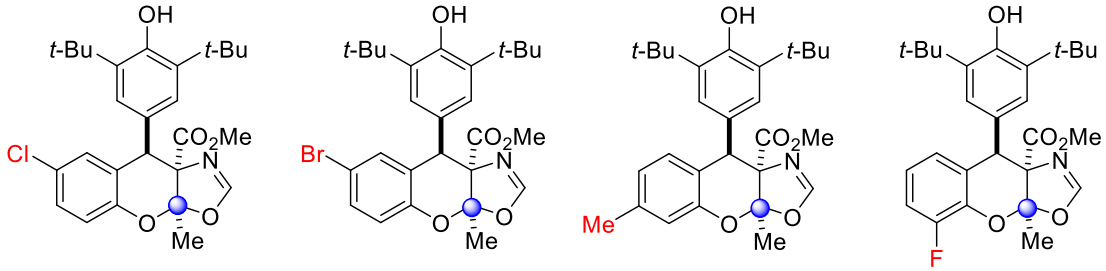


5.3 **5.4** (1.3 equiv) **5.6**

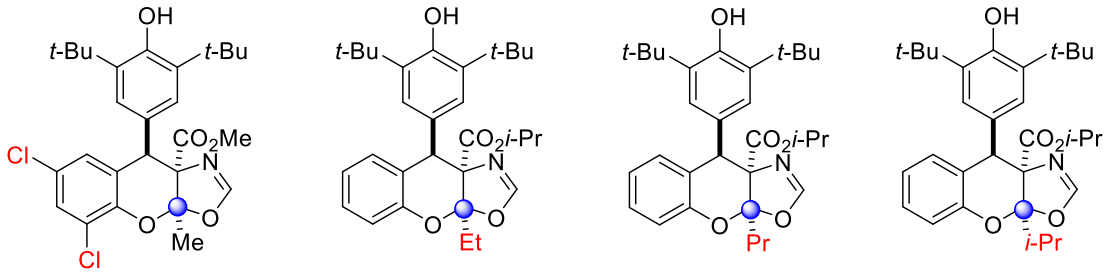


5.6a: 94%

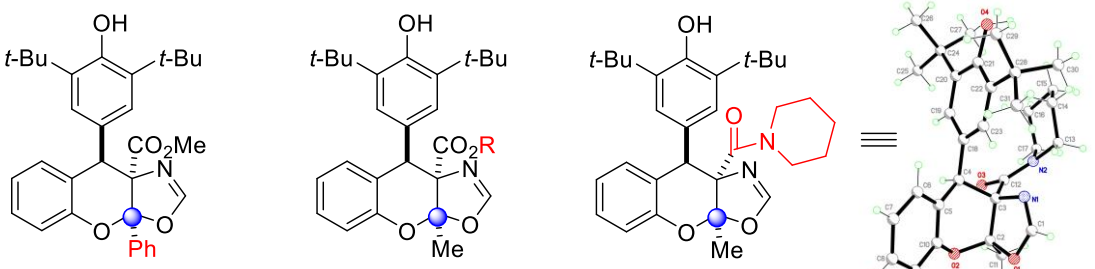
5.6b: >98% **5.6c**: >98%



5.6d: >98% **5.6e**: >98% **5.6f**: >98% **5.6g**: 98%

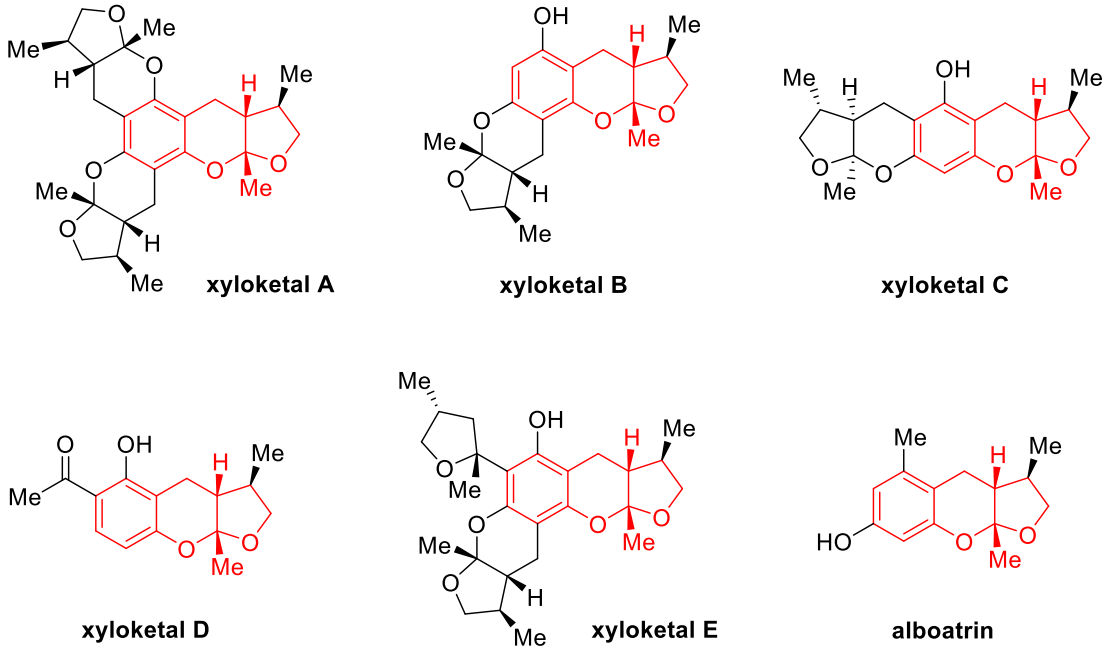


5.6h: 87% **5.6i**: >98%[c] **5.6j**: >98%[c] **5.6k**: >98%[c]



[a] The d.r. of **5.6** and ratio of **5.6**:**5.8** were determined by crude ^{1}H NMR analysis. [b] Isolated yields. [c] The reaction was carried out for 48 h. [d] In this case **5.6o** and the corresponding triarylmenthane were obtained as a mixture in a ratio of 9:1.

Figure 5.1 Natural Products Containing Tricyclic Ketal Moiety



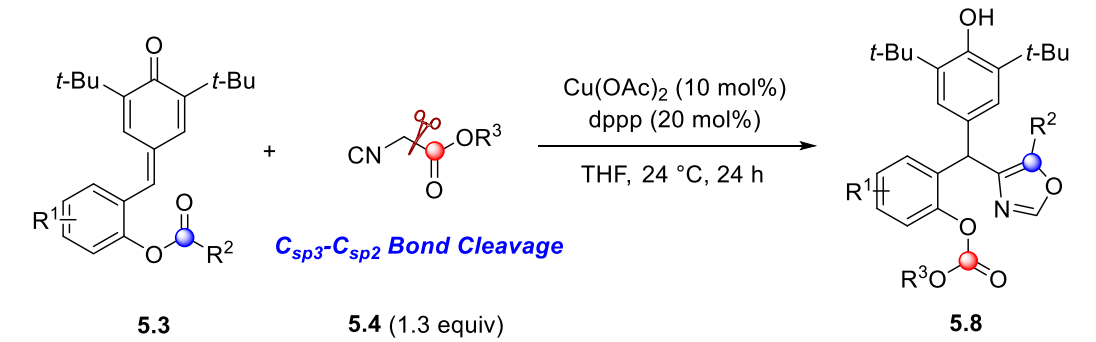
It is important to note that tricyclic ketals are important structural motif in medicinal chemistry. Related compounds such as xyloketal A and D (Figure 5.1) are known to inhibit acetylcholinesterase (AChE)[108] and are considered as potential lead compounds for the treatment of neurological disorders such as Alzheimer's disease.

The simple catalytic system developed in our studies delivers such highly functionalized tricyclic ketals for the first time. Further biological screening of these compounds is ongoing.

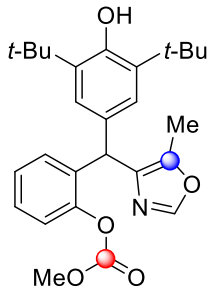
5.3.3 Triarylmethane Synthesis

The scope of the copper-catalyzed synthesis of triarylmethanes was examined next (Scheme 5.3). In almost all cases excellent chemo-selectivity and yield were obtained for product **5.8**. Different substituents (electron-donating, electron-neutral, and electron-withdrawing) with diverse substitution patterns (*para*-, *meta*- and *ortho*-) on the aryl ring could be well tolerated to give triarylmethanes in uniformly excellent chemo-selectivity and efficiency (>98% yield for **5.8a**-**5.8h**). Different ester substituents on **5.3** were all suitable to produce **5.8i** and **5.8j** in excellent yields with excellent selectivities. Isocyanoacetates possessing different ester groups could also be used to produce **5.8k** and **5.8l** in good to excellent yields and selectivities. The high efficiency of this process, coupled with the operational simplicity (use of cheap $Cu(OAc)_2$ and dppp as catalysts and running reactions open to air), makes it an attractive method for triarylmethane synthesis. The related heteroaryl-substituted triarylmethanes such as Letrozole has proven to be an effective commercial drug for the treatment of cancer and the current approach provides a rapid access to the analogues of those compounds.

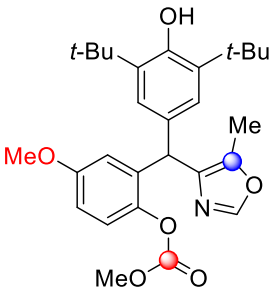
Scheme 5.3 Triarylmethane Synthesis by Copper Catalysis[a-d]



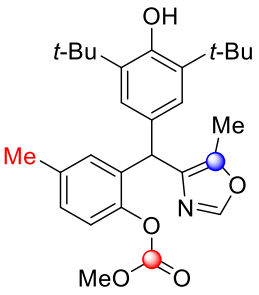
5.3 **5.4** (1.3 equiv) **5.8**



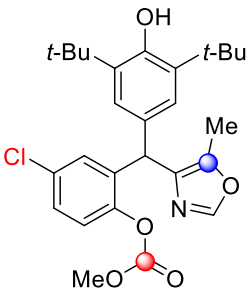
5.8a: >98%



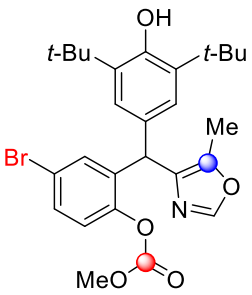
5.8b: >98%[c]



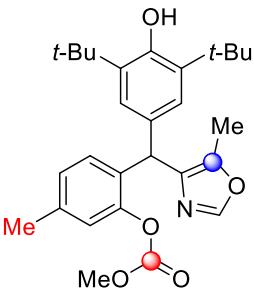
5.8c: >98%



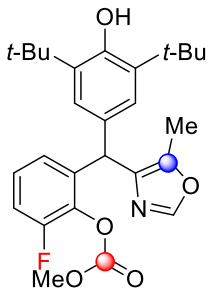
5.8d: >98%



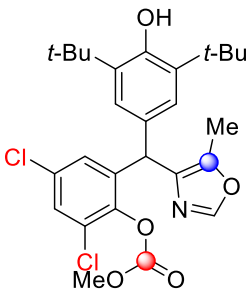
5.8e: >98%



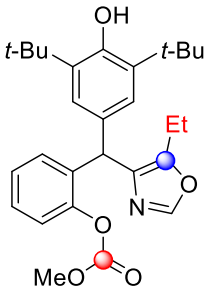
5.8f: >98%



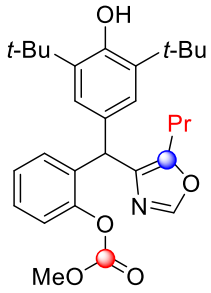
5.8g: >98%



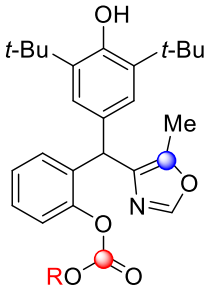
5.8h: >98%



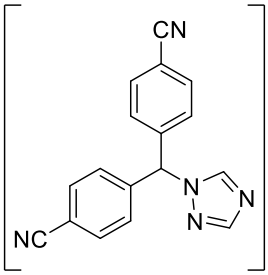
5.8i: >98%



5.8j: >98%[c]



5.8k (R = Et): >98%
5.8l (R = *i*-Pr): 90%[c-d]



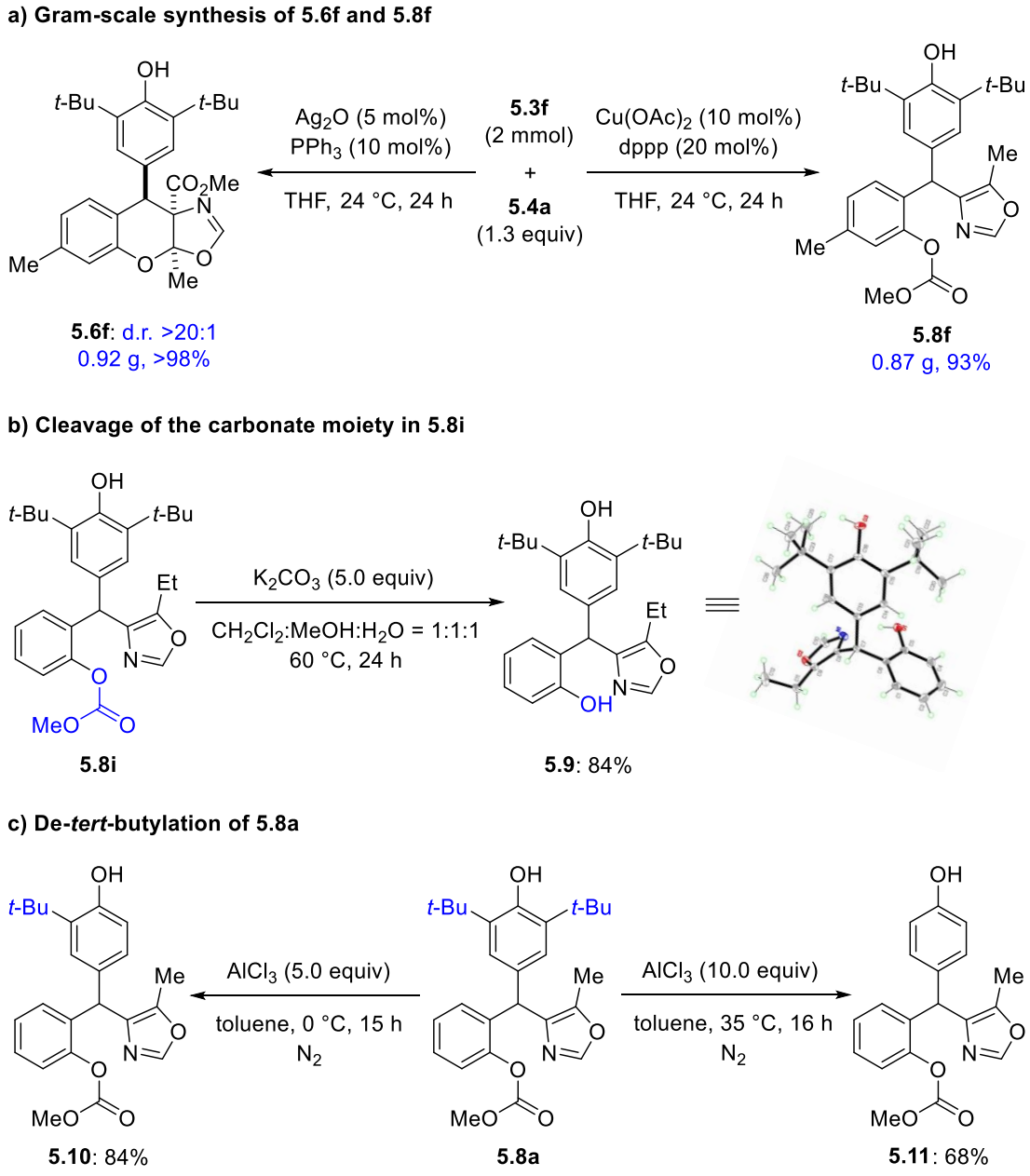
Letrozole

[a] The ratio of **5.8**:**5.6** were determined by crude ^{1}H NMR analysis. [b] Isolated yields. [c] The reaction was carried out for 48 h. [d] In this case **5.8l** and the corresponding tricyclic ketal were obtained as a mixture in a ratio of 14:1.

5.3.4 Large-Scale Preparation and Derivatization

To test the robustness and efficiency of our method in preparative synthesis, gram-scale reactions of **5.3f** and **5.4a** were investigated under the standard reaction conditions (Scheme 5.4a). To our delight, the desired products **5.6f** and **5.8f** were obtained with no loss of efficiency or selectivity.

Scheme 5.4 Gram-Scale Synthesis and Derivatization



Moreover, cleavage of the carbonate moiety in triarylmethane **5.8i** took place smoothly by the treatment with potassium carbonate to generate bisphenol **5.9** in 84% yield (Scheme 5.4b). The structure of **5.9** was unambiguously determined by single crystal X-ray analysis, and the structures of triarylmethanes **5.8** were assigned by analogy.

It is worth mentioning that the bulky *tert*-butyl substituents in the substrates were necessary for the reactions to proceed with high efficiency and chemo-selectivity, although such groups may be redundant in the product structure. Gratifyingly, the *tert*-butyl groups on **5.8** could be efficiently removed partially or completely to yield **5.10** or **5.11** by following the previously established procedure (Scheme 5.4c).[104]

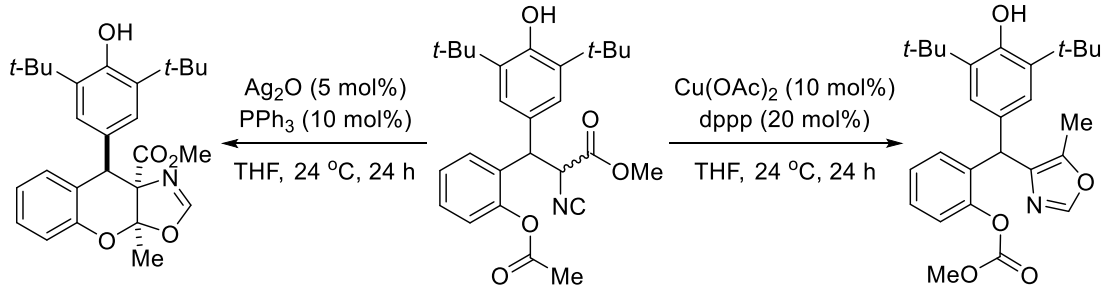
5.3.5 Mechanistic Studies

The kinetics of the reaction between **5.3a** and **5.4a** under silver or copper catalysis was monitored by NMR respectively to shed some light on the mechanism of this chemo-divergent cascade reaction. A common intermediate **5.2a** (Scheme 5.5a) was detected in both cases, which was determined by NMR analysis to be the 1,6-conjugate addition product of **5.4a** and **5.3a**. In either case, however, the key intermediate **5.1a** was not observed, which is believed to be highly reactive and undergo the following steps spontaneously. We envisioned that the chemo-selectivity between the formation of tricyclic ketal and triarylmethane is independent of the 1,6-conjugate addition step, as the stereoselectivity of **5.2a** will be lost upon deprotonation in the following steps. To probe this, **5.2a** was isolated in a pure form

as a mixture of diastereomers (1.4:1 d.r.). When **5.2a** was subjected to the standard silver or copper catalysis conditions, as expected, the desired products **5.6a** or **5.8a** were obtained with the same level of chemo- and stereoselectivity, respectively (Scheme 5.5a).

Scheme 5.5 Experiments on Mechanistic Study

a) Subjection of reaction intermediate to Ag or Cu catalysis

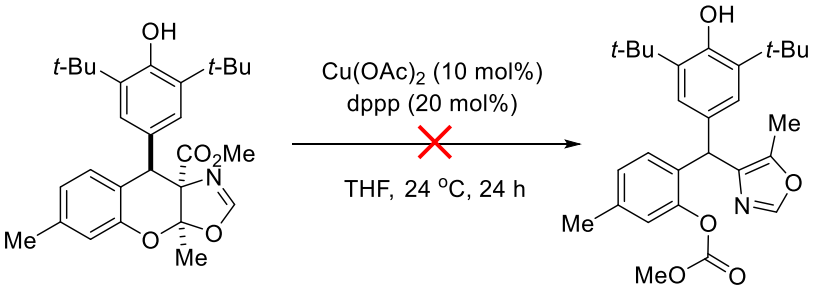


5.6a
83%, d.r. >20:1
5.6a:**5.8a** = >20:1

5.2a
d.r. = 1.4:1

5.8a
91%
5.6a:**5.8a** = 1:>20

b) Test of the possibility of product interconversion



5.6f

5.8f

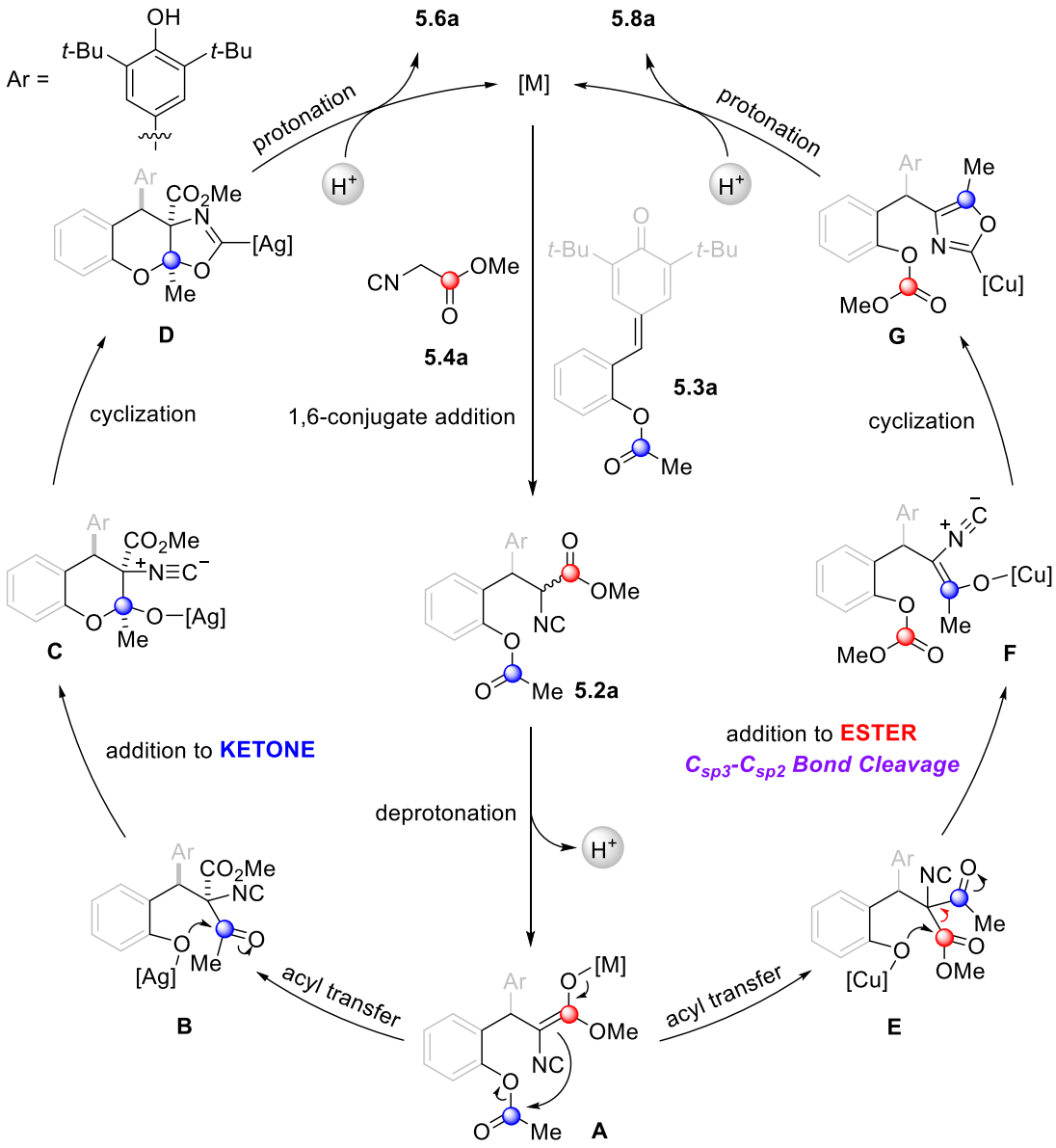
Moreover, as cyclic ketals are known to undergo fragmentation-rearrangement reactions, a control reaction of the interconversion of **5.6f** to **5.8f** was also carried out. Under the copper catalysis conditions, **5.6f** was stable and did not undergo conversion to **5.8f** at all (Scheme 5.5b), suggesting that **5.6** and **5.8** are formed through different

reaction pathways.

5.3.6 Proposed Mechanism

On the basis of the above experimental results and related reports, a possible reaction pathway for the divergent synthesis of tricyclic ketals and triarylmethanes is proposed with the reaction of **5.3a** and **5.4a** as an example (Scheme 5.6). The reaction starts with the formation of 1,6-conjugate addition adduct **5.2a**. After that, the deprotonation of **5.2a** takes place to give enolate **A**, from which Ag and Cu catalysis lead to the generation of different scaffolds. As shown in the left part, under Ag catalysis, enolate **A** will undergo an acyl transfer process to afford complex **B**. Based on the nearly perfect yield and diastereoselectivity for **5.6a** formation, intermediate **B** is believed to be formed as a single diastereomer (ester *trans* to the 2,6-di-*tert*-butyl phenol). Then, nucleophilic addition of the silver phenoxide to the ketone generates intermediate **C**, which will cyclize to form the oxazolyl-silver intermediate **D**. Subsequent protonation affords **5.6a** as the final product with the regeneration of the catalyst to complete this catalytic cycle. Similar to Ag catalysis, phenoxide **E** is generated through an acyl transfer process under Cu catalysis (right part of the proposed reaction pathway). The relative configuration of **E** is inconsequential in the following step. In contrast to the Ag system, the nucleophilic addition of phenoxide to the ester takes place next followed by the exclusive C-C bond cleavage to yield a new enolate **F**. Cyclization of **F** generates the oxazolyl-copper intermediate **G**, which, upon protonation produces triarylmethane **5.8a**.

Scheme 5.6 Proposed Mechanism for the Formation of **5.6** and **5.8**



5.4 Conclusion

We have developed, for the first time, an interesting and effective divergent cascade reaction using para-quinone methide-aryl esters and activated isocyanides as the starting materials. By the judicious choice of substrate structure, a common intermediate bearing multiple reactive sites could be accessed, which undergo different reaction pathways to realize divergent synthesis of either tricyclic ketals or

triarylmethanes under silver or copper catalysis. Current efforts in our laboratory are focused on the understanding of the origin of the divergent reactivity as well as the application of this concept to the preparation of other types of valuable heterocyclic structures.

5.5 Experimental Section

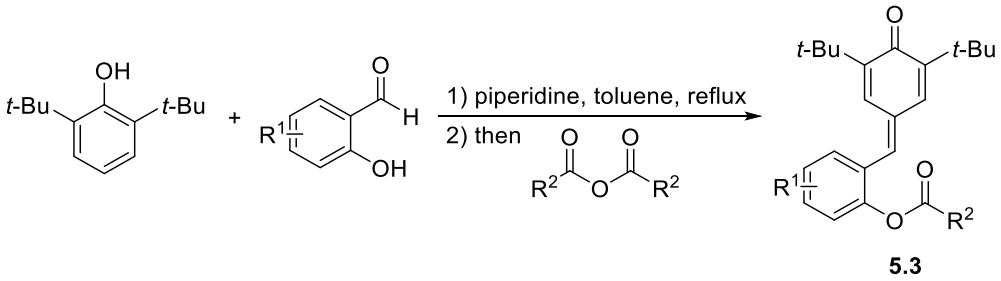
5.5.1. General Information

^{1}H and **^{13}C NMR** spectra were recorded on a Bruker AV 300 or AV 500 or DPX 400 spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: ^{1}H (chloroform δ 7.26; Acetone δ 2.05), ^{13}C (chloroform δ 77.0; Acetone δ 29.8, 206.3). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, td = triplet of doublets), coupling constants (Hz) and integration. Melting point (**MP**) was obtained on Büchi B-540. For thin layer chromatography (**TLC**), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. High resolution mass spectra (**HRMS**) were obtained on a Finnigan/MAT 95XL-T spectrometer. Diastereomeric ratio (**d.r.**) of **5.6**, and the ratio of **5.6** to **5.8** were determined by crude ^{1}H NMR analysis.

Unless otherwise noted, all the reactions were carried out open to air. Dichloromethane (DCM), tetrahydrofuran (THF), and toluene were dried over a Pure Solv solvent purification system. Deuterated solvents were purchased from

Cambridge Isotope Laboratories and used as received without further purification. Methyl isocyanoacetate (**5.4a**) and ethyl isocyanoacetate (**5.4b**) were purchased from Alfa Aesar company. Isopropyl isocyanoacetate (**5.4c**)[109] and 2-isocyano-1-(piperidin -1-yl)ethan-1-one (**5.4d**)[110] were prepared according to literature procedures. Other chemicals were purchased from commercial suppliers and used as received without further purification.

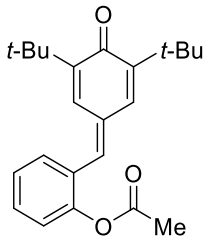
5.5.2 Synthesis of *para*-Quinone Methide-Aryl Esters 5.3[111]



5.3

General procedure. In a Dean-Stark apparatus, a solution of 2,6-di-*tert*-butylphenol (10 mmol, 2.06 g) and the corresponding salicylaldehyde (10 mmol) in toluene (40 mL) was heated to reflux. Piperidine (20 mmol, 1.97 mL) was dropwise added within 1 h. The reaction mixture was continued to reflux for overnight. After cooling just below the boiling point of the reaction mixture, the corresponding anhydride (30 mmol) was added and stirring was continued for 15 min. Then the reaction mixture was poured on ice-water (200 mL) and extracted with CH_2Cl_2 (4×80 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent of the filtrate was removed under reduced pressure. The crude products were purified by flash column chromatography to afford **5.3**.

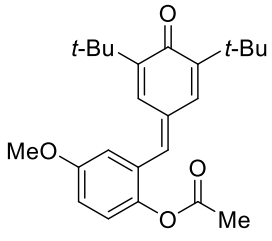
2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)phenyl acetate (5.3a)



5.3a

Yellow solid, 34% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.49-7.39 (m, 2H), 7.33-7.31 (m, 2H), 7.24-7.14 (m, 1H), 7.06 (s, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 2.30 (s, 3H), 1.33 (s, 9H), 1.28 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.6, 168.9, 149.6, 149.3, 148.2, 136.0, 134.5, 133.2, 131.8, 130.2, 128.8, 127.9, 126.0, 122.9, 35.4, 35.1, 29.5, 20.9; **MP**: 111-112 °C; **HRMS** (ESI): m/z calcd. for $[C_{23}H_{28}NaO_3, M+Na]^+$: 375.1931; found: 375.1925.

2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)-4-methoxyphenyl acetate (5.3b)

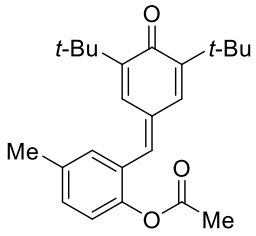


5.3b

Yellow solid, 19% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 2.3 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 7.04-6.88 (m, 4H), 3.82 (s, 3H), 2.28 (s, 3H), 1.33 (s, 9H), 1.28 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 186.6, 169.4, 157.1, 149.6, 148.2, 142.8, 136.0, 134.5, 133.3, 129.3, 127.8, 123.6, 116.2, 116.0, 55.7, 35.5, 35.1, 29.6, 29.5,

20.9; **MP**: 170-172 °C; **HRMS** (ESI): m/z calcd. for $[C_{24}H_{30}NaO_4, M+Na]^+$: 405.2036; found: 405.2030.

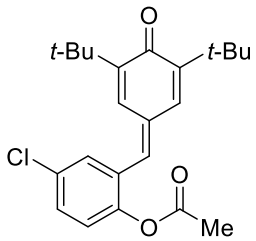
2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)-4-methylphenyl acetate (5.3c)



5.3c

Yellow solid, 42% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39-7.32 (m, 1H), 7.25-7.19 (m, 2H), 7.10-6.96 (m, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.33 (s, 9H), 1.28 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 186.6, 169.1, 149.3, 148.1, 147.1, 136.3, 135.7, 134.5, 133.1, 132.3, 130.9, 128.4, 128.1, 122.6, 35.4, 35.0, 29.5, 20.9, 20.8; **MP**: 113-115 °C; **HRMS** (ESI): m/z calcd. for $[C_{24}H_{30}NaO_3, M+Na]^+$: 389.2087; found: 389.2083.

4-Chloro-2-((3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)phenyl acetate (5.3d)

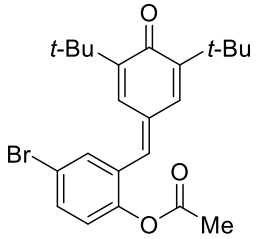


5.3d

Yellow solid, 16% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.41-7.36 (m, 2H), 7.26 (d, *J* = 2.1 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.00-6.90 (m, 2H), 2.28 (s, 3H), 1.33 (s, 9H),

1.28 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 186.5, 168.7, 150.0, 148.6, 147.6, 134.1, 134.0, 133.9, 131.5, 131.3, 130.3, 129.9, 127.3, 124.2, 35.5, 35.1, 29.5, 20.9; **MP**: 158-160 °C; **HRMS** (ESI): m/z calcd. for $[C_{23}H_{27}ClNaO_3, M+Na]^+$: 409.1541; found: 409.1538.

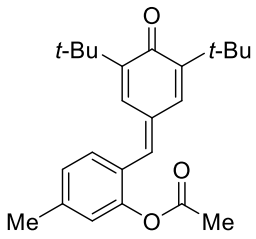
4-Bromo-2-((3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)phenyl acetate (5.3e)



5.3e

Yellow solid, 11% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.72-7.46 (m, 2H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 7.01-6.89 (m, 2H), 2.29 (s, 3H), 1.32 (s, 9H), 1.28 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.5, 168.6, 150.0, 148.6, 148.1, 134.3, 134.1, 134.0, 133.8, 132.8, 130.7, 127.3, 124.5, 119.0, 35.5, 35.1, 29.5, 20.9; **MP**: 165-166 °C; **HRMS** (ESI): m/z calcd. for $[C_{23}H_{27}BrNaO_3, M+Na]^+$: 453.1036; found: 453.1030.

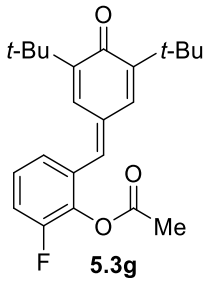
2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)-5-methylphenyl acetate (5.3f)



5.3f

Yellow solid, 48% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.32 (m, 2H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.04-6.98 (m, 3H), 2.41 (s, 3H), 2.30 (s, 3H), 1.33 (s, 9H), 1.28 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.6, 169.1, 149.3, 149.2, 147.8, 141.2, 136.3, 134.7, 132.7, 131.5, 128.0, 127.0, 125.8, 123.4, 35.4, 35.0, 29.5, 29.4, 21.3, 20.9; **MP**: 94-96 °C; **HRMS** (ESI): m/z calcd. for $[C_{24}H_{30}NaO_3, M+Na]^+$: 389.2087; found: 389.2080.

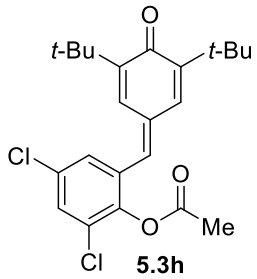
2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)-6-fluorophenyl acetate (5.3g)



5.3g

Yellow solid, 28% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.33-7.17 (m, 4H), 7.03-6.93 (m, 2H), 2.35 (s, 3H), 1.33 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.6, 167.7, 154.7 (d, *J* = 250.3 Hz), 149.9, 148.5, 137.0 (d, *J* = 13.6 Hz), 134.3, 134.2 (d, *J* = 3.1 Hz), 134.0, 131.3, 127.5, 126.7, 126.6 (d, *J* = 10.3 Hz), 117.1 (d, *J* = 19.1 Hz), 35.5, 35.1, 29.5, 20.4; **MP**: 143-145 °C; **HRMS** (ESI): m/z calcd. for $[C_{23}H_{27}FNaO_3$, $M+Na]^+$: 393.1836; found: 393.1832.

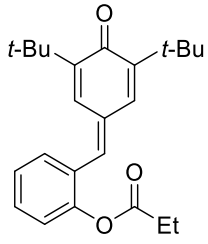
2,4-Dichloro-6-((3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)phen yl acetate (5.3h)



5.3h

Yellow solid, 12% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.85 (s, 1H), 2.35 (s, 3H), 1.32 (s, 9H), 1.28 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.5, 167.6, 150.4, 149.0, 144.4, 134.7, 133.9, 132.7, 132.2, 131.8, 130.1, 129.8, 129.1, 126.9, 35.5, 35.2, 29.5, 20.4; **MP**: 153-154 °C; **HRMS** (ESI): m/z calcd. for $[C_{23}H_{26}Cl_2NaO_3, M+Na]^+$: 443.1151; found: 443.1150.

2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)phenyl propionate (5.3i)

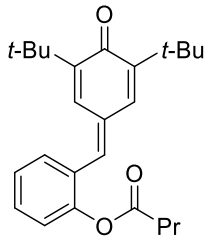


5.3i

Yellow solid, 23% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.47-7.39 (m, 2H), 7.33-7.30 (m, 2H), 7.24-7.13 (m, 1H), 7.06 (s, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.33 (s, 9H), 1.27 (s, 9H), 1.24 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.6, 172.4, 149.4, 149.3, 148.1, 136.2, 134.5, 133.1, 131.6, 130.2, 128.7, 128.0,

125.9, 122.9, 35.4, 35.0, 29.5, 27.7, 9.1; **MP**: 108-110 °C; **HRMS** (ESI): m/z calcd. for $[C_{24}H_{30}NaO_3, M+Na]^+$: 389.2087; found: 389.2084.

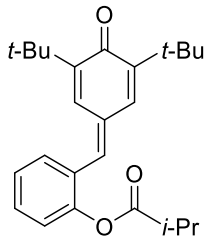
2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)phenyl butyrate (5.3j)



5.3j

Yellow solid, 34% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.47-7.38 (m, 2H), 7.35-7.29 (m, 2H), 7.23-7.11 (m, 1H), 7.05 (s, 1H), 6.97 (d, *J* = 2.3 Hz, 1H), 2.54 (t, *J* = 7.6 Hz, 2H), 1.80-1.72 (m, 2H), 1.32 (s, 9H), 1.27 (s, 9H), 1.01 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.6, 171.6, 149.4, 149.3, 148.1, 136.3, 134.5, 133.1, 131.6, 130.2, 128.8, 128.0, 126.0, 122.9, 36.1, 35.4, 35.0, 29.5, 18.4, 13.6; **MP**: 95-97 °C; **HRMS** (ESI): m/z calcd. for $[C_{25}H_{32}NaO_3, M+Na]^+$: 403.2244; found: 403.2236.

2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)phenyl isobutylrate (5.3k)

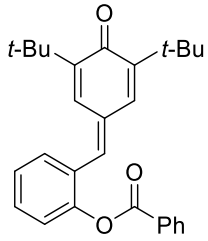


5.3k

Yellow solid, 29% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48-7.36 (m, 2H), 7.35-7.27

(m, 2H), 7.17-7.14 (m, 1H), 7.04 (s, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 2.89-2.71 (m, 1H), 1.34-1.24 (m, 24H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 186.6, 175.0, 149.5, 149.3, 148.2, 136.2, 134.4, 133.2, 131.5, 130.2, 128.9, 128.0, 125.9, 122.8, 35.4, 35.0, 34.2, 29.5, 18.9; **MP**: 99-101 °C; **HRMS** (ESI): m/z calcd. for $[C_{25}H_{32}NaO_3, M+Na]^+$: 403.2244; found: 403.2237.

2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)phenyl benzoate (5.3l)



5.3l

Yellow solid, 28% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.70-7.61 (m, 1H), 7.59-7.45 (m, 4H), 7.41-7.29 (m, 3H), 7.13 (s, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 1.28 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 186.6, 164.7, 149.5, 149.4, 148.0, 136.1, 134.6, 133.9, 133.3, 131.8, 130.3, 130.2, 129.0, 128.7, 128.0, 126.1, 123.0, 35.4, 35.0, 29.5, 29.4; **MP**: 142-144 °C; **HRMS** (ESI): m/z calcd. for $[C_{28}H_{30}NaO_3, M+Na]^+$: 437.2087; found: 437.2080.

5.5.3 X-Ray Crystallographic Analysis of 5.3a

The conformation of **5.3a** was determined by X-ray crystallographic analysis of a single crystal of **5.3a** (Figure 5.2). The crystal was prepared from the solution of **5.3a** in hexane at 0 ^oC.

Figure 5.2 X-Ray Structure of **5.3a**

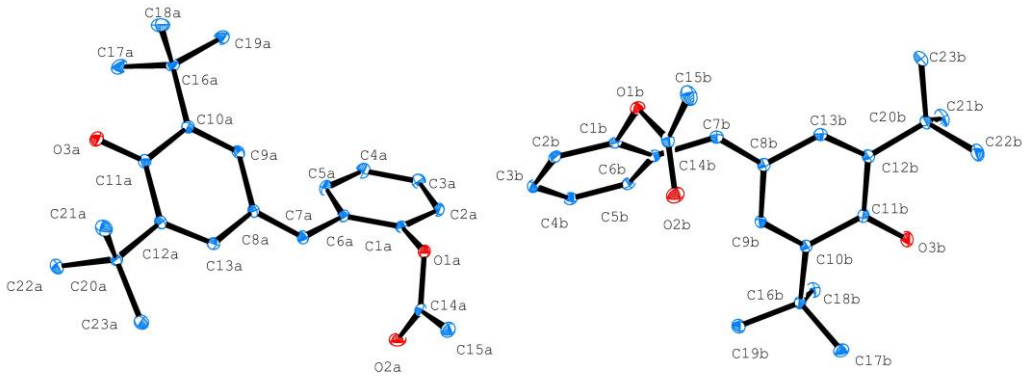
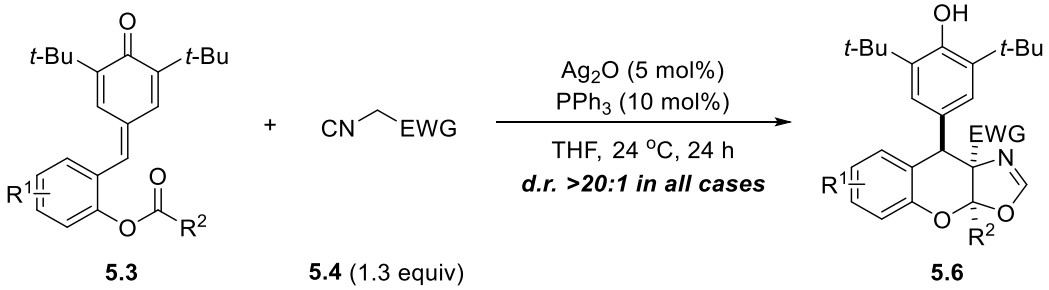


Table 5.2 Crystal Data and Structure Refinement for **5.3a**

Identification code	**5.3a**	
Empirical formula	$C_{46}H_{56}O_6$	
Formula weight	704.90	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.8989(4) Å	α = 97.562(2)°
	b = 13.6819(4) Å	β = 112.950(2)°
	c = 14.7054(5) Å	γ = 93.820(2)°
Volume	2167.04(13) $Å^3$	
Z	2	
Density (calculated)	1.080 Mg/m^3	
Absorption coefficient	0.553 mm^{-1}	

F(000)	760
Crystal size	0.204 x 0.157 x 0.106 mm^3
Theta range for data collection	3.286 to 68.235°
Index ranges	-14<=h<=14, -16<=k<=15, -17<=l<=17
Reflections collected	23256
Independent reflections	7717 [R(int) = 0.0538]
Completeness to theta = 67.679°	97.2 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7717 / 0 / 483
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0480, wR2 = 0.1060
R indices (all data)	R1 = 0.0745, wR2 = 0.1145
Largest diff. peak and hole	1.013 and -0.653 e.$Å^{-3}$

5.5.4 Diastereoselective Synthesis of Tricyclic Ketals



5.3 **5.4** (1.3 equiv) **5.6**

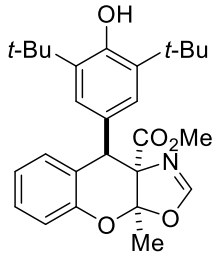
General procedure. To a 10 mL vial charged with PPh_3 (2.6 mg, 0.010 mmol) and Ag_2O (1.2 mg, 0.005 mmol) was added anhydrous THF (1.0 mL). The mixture was allowed to stir at ambient temperature for 5 min, then *para*-quinone methide-aryl

ester **5.3** (0.10 mmol) and activated isocyanide **5.4** (0.13 mmol) were added in one portion. The reaction mixture was allowed to stir at ambient temperature for 24 h, concentrated and purified by flash chromatography (silica gel or neutral Al_2O_3, hexanes/ethyl acetate) to afford the product **5.6**.

In all cases, the d.r. of **5.6** is >20:1. Unless otherwise noted, the ratio of **5.6** and the corresponding triarylmethane is >20:1.

5.5.5 Characterization of Compounds 5.6

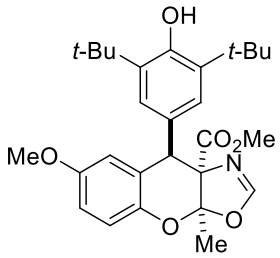
Methyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-methyl-9*H*-chromeno[3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6a)



5.6a

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 5:1). Pale yellow solid, 94% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.79-7.08 (m, 3H), 7.04-6.94 (m, 2H), 6.88 (s, 1H), 6.78 (d, J = 7.6 Hz, 1H), 5.18 (s, 1H), 4.68 (s, 1H), 3.64 (s, 3H), 1.83 (s, 3H), 1.44 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.0, 155.0, 153.1, 151.9, 135.3, 129.9, 127.9, 127.5, 125.3, 123.8, 118.1, 111.6, 85.0, 77.2, 52.4, 47.1, 34.4, 30.5, 22.7; **MP**: 193-195 °C; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{33}NNaO_5, M+Na]^+$: 474.2251; found: 474.2256.

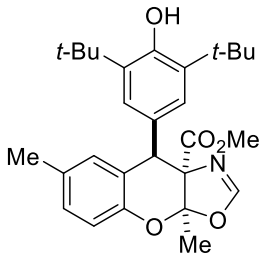
Methy-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-7-methoxy-3a-methyl-9*H*-chromeno [3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6b)



5.6b

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 5:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.74-7.07 (m, 2H), 6.97-6.84 (m, 2H), 6.69 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.34 (dd, *J* = 2.9, 1.0 Hz, 1H), 5.17 (s, 1H), 4.66 (s, 1H), 3.63 (s, 6H), 1.81 (s, 3H), 1.44 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.0, 156.0, 155.0, 153.1, 145.3, 135.4, 131.1, 125.2, 118.7, 113.9, 112.2, 111.7, 84.8, 77.2, 55.3, 52.4, 47.4, 34.4, 30.5, 22.6; **HRMS** (ESI): m/z calcd. for $[C_{28}H_{35}NNaO_6$, M+Na$]^+$: 504.2357; found: 504.2360.

Methyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a,7-dimethyl-9*H*-chromeno[3,2-*d*] oxazole-9a(3a*H*)-carboxylate (5.6c)

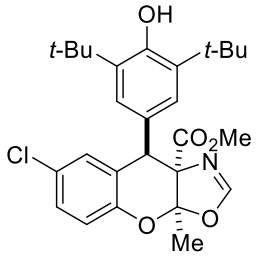


5.6c

The general procedure outlined above was followed. The crude reaction mixture was

purified by flash column chromatography (hexanes/EtOAc 5:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.72-7.08 (m, 2H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 2H), 6.60 (s, 1H), 5.18 (s, 1H), 4.66 (s, 1H), 3.63 (s, 3H), 2.20 (s, 3H), 1.82 (s, 3H), 1.46 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.0, 155.0, 153.1, 149.6, 135.3, 133.2, 129.4, 128.5, 127.9, 125.3, 117.8, 111.6, 84.9, 77.2, 52.4, 47.1, 34.4, 30.5, 22.7, 21.1; **HRMS** (ESI): m/z calcd. for $[C_{28}H_{35}NNaO_5, M+Na]^+$: 488.2407; found: 488.2413.

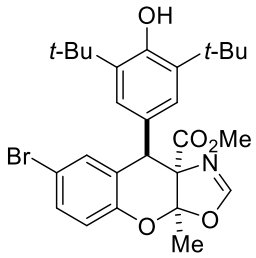
Methyl-7-chloro-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-methyl-9*H*-chromeno[3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6d)



5.6d

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 5:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78-7.04 (m, 3H), 6.98-6.86 (m, 2H), 6.77 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.21 (s, 1H), 4.63 (s, 1H), 3.63 (s, 3H), 1.82 (s, 3H), 1.45 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.6, 155.1, 153.3, 150.4, 135.5, 131.8, 129.2, 128.1, 127.5, 124.5, 119.4, 111.6, 84.7, 77.2, 52.5, 47.1, 34.4, 30.4, 22.5; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{32}ClNNaO_5, M+Na]^+$: 508.1861; found: 508.1867.

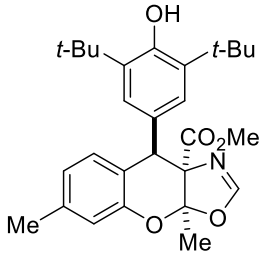
Methyl-7-bromo-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-methyl-9*H*-chromeno[3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6e)



5.6e

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 7:1). Colorless wax, >98% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.84-6.78 (m, 6H), 5.21 (s, 1H), 4.64 (s, 1H), 3.63 (s, 3H), 1.82 (s, 3H), 1.45 (s, 18H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.6, 155.1, 153.3, 150.9, 135.5, 132.2, 131.0, 130.5, 124.4, 119.9, 116.8, 111.6, 84.8, 77.2, 52.52, 47.0, 34.4, 30.4, 22.5; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{32}BrNNaO_5, M+Na]^+$: 552.1356; found: 552.1362.

Methyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a,6-dimethyl-9*H*-chromeno[3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6f)

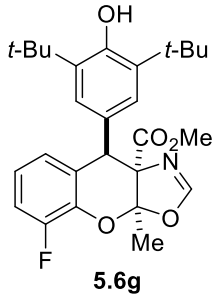


5.6f

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 7:1). Pale yellow

solid, >98% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.72-6.99 (m, 2H), 6.90 (s, 1H), 6.84 (s, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 5.17 (s, 1H), 4.64 (s, 1H), 3.63 (s, 3H), 2.30 (s, 3H), 1.82 (s, 3H), 1.44 (s, 18H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.0, 154.9, 153.0, 151.7, 137.6, 135.2, 127.6, 126.5, 125.4, 124.4, 118.8, 111.5, 84.9, 77.2, 52.4, 46.9, 34.3, 30.5, 22.7, 21.0; **MP**: 164-166 °C; **HRMS** (ESI): m/z calcd. for $[C_{28}H_{35}NNaO_5, M+Na]^+$: 488.2407; found: 488.2410.

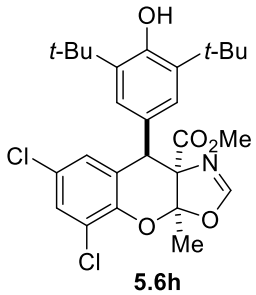
Methyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-fluoro-3a-methyl-9*H*-chromeno[3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6g)



5.6g

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc 5:1). Pale yellow wax, 98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.77-6.82 (m, 5H), 6.55 (d, *J* = 7.5 Hz, 1H), 5.19 (s, 1H), 4.67 (s, 1H), 3.64 (s, 3H), 1.88 (s, 3H), 1.44 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.6, 155.1, 153.2, 152.3 (d, *J* = 248.8 Hz), 139.1 (d, *J* = 11.5 Hz), 135.4, 132.9, 125.0, 123.6 (d, *J* = 7.0 Hz), 123.1 (d, *J* = 3.3 Hz), 114.7 (d, *J* = 18.1 Hz), 111.8, 85.1, 77.2, 52.5, 47.1 (d, *J* = 2.5 Hz), 34.4, 30.5, 22.4; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{32}FNNaO_5, M+Na]^+$: 492.2157; found: 492.2161.

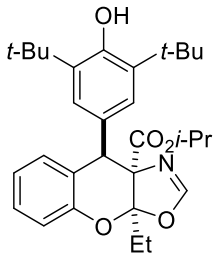
Methyl-5,7-dichloro-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-methyl-9*H*-chrome no[3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6h)



5.6h

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc 6:1). Pale yellow wax, 87% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.66-6.98 (m, 3H), 6.91 (s, 1H), 6.74-6.60 (m, 1H), 5.22 (s, 1H), 4.61 (s, 1H), 3.63 (s, 3H), 1.87 (s, 3H), 1.44 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.3, 155.2, 153.5, 146.4, 135.7, 133.5, 129.1, 127.9, 126.7, 124.3, 124.1, 112.1, 84.8, 77.2, 52.6, 47.5, 34.4, 30.4, 22.3; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{31}Cl_2NNaO_5, M+Na]^+$: 542.1471; found: 542.1479.

Isopropyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-ethyl-9*H*-chromeno[3,2-*d*]oxa zole-9a(3a*H*)-carboxylate (5.6i)

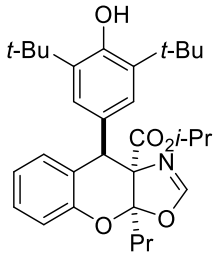


5.6i

The general procedure outlined above was followed (48 h). The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc

10:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.91-7.10 (m, 3H), 6.98 (dd, *J* = 16.1, 7.9 Hz, 2H), 6.89 (s, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 5.15 (s, 1H), 4.90 (dt, *J* = 12.5, 6.2 Hz, 1H), 4.62 (s, 1H), 2.37 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.94 (td, *J* = 14.4, 7.2 Hz, 1H), 1.44 (s, 18H), 1.22 (t, *J* = 7.3 Hz, 3H), 1.05 (d, *J* = 6.3 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.9, 154.7, 153.0, 151.8, 135.4, 130.9, 127.7, 127.4, 125.9, 123.7, 118.0, 113.4, 84.7, 77.2, 69.4, 47.7, 34.3, 30.4, 28.9, 21.4, 21.1, 7.5; **HRMS** (ESI): m/z calcd. for $[C_{30}H_{39}NNaO_5, M+Na]^+$: 516.2720; found: 516.2723.

Isopropyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-propyl-9*H*-chromeno[3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6j)

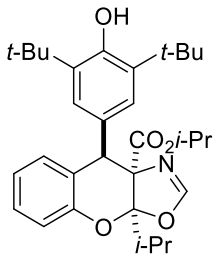


5.6j

The general procedure outlined above was followed (48 h). The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc 10:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.76-6.93 (m, 5H), 6.89 (s, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 5.16 (s, 1H), 4.92 (dt, *J* = 12.5, 6.3 Hz, 1H), 4.63 (s, 1H), 2.41-2.22 (m, 1H), 2.01-1.76 (m, 2H), 1.70-1.58 (m, 1H), 1.44 (s, 18H), 1.06 (d, *J* = 6.3 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.9, 154.7, 153.0, 151.8, 135.4, 130.9, 127.7, 127.3,

125.9, 123.7, 118.0, 113.1, 84.8, 77.2, 69.3, 47.6, 37.8, 34.3, 30.4, 21.4, 21.1, 16.4, 14.2; **HRMS** (ESI): m/z calcd. for $[C_{31}H_{41}NNaO_5, M+Na]^+$: 530.2877; found: 530.2882.

Isopropyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-isopropyl-9*H*-chromeno[3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6k)

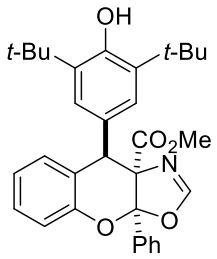


5.6k

The general procedure outlined above was followed (48 h). The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc 10:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.20-6.80 (m, 5H), 6.68 (d, *J* = 7.4 Hz, 1H), 5.15 (s, 1H), 4.87 (dt, *J* = 12.5, 6.2 Hz, 1H), 4.58 (s, 1H), 2.54 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.44 (s, 18H), 1.32 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.90 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.2, 154.7, 153.0, 151.9, 135.4, 130.7, 127.7, 127.4, 126.1, 123.6, 118.0, 115.4, 84.6, 77.2, 69.3, 48.8, 34.3, 33.4, 30.4, 21.2, 20.9, 17.6, 17.3; **HRMS** (ESI): m/z calcd. for $[C_{31}H_{41}NNaO_5, M+Na]^+$: 530.2877; found: 530.2875.

Methyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-phenyl-9*H*-chromeno[3,2-*d*]oxa

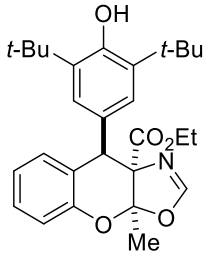
zole-9a(3a*H*)-carboxylate (5.6l)



5.6l

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 5:1). Pale yellow solid, 97% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.70-7.55 (m, 3H), 7.48-7.36 (m, 3H), 7.30-7.00 (m, 5H), 6.84 (d, *J* = 7.5 Hz, 1H), 5.17 (s, 1H), 4.87 (s, 1H), 2.99 (s, 3H), 1.44 (s, 9H), 1.43 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.9, 155.3, 153.1, 151.8, 136.4, 135.3, 135.2, 129.8, 129.4, 128.7, 128.0, 127.9, 127.7, 127.3, 126.2, 125.2, 124.1, 118.5, 112.7, 88.4, 77.2, 51.8, 46.6, 34.4, 34.3, 30.5; **MP**: 244-246 °C; **HRMS** (ESI): m/z calcd. for $[C_{32}H_{35}NNaO_5, M+Na]^+$: 536.2407; found: 536.2414.

Ethyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-methyl-9*H*-chromeno[3,2-*d*]oxazo le-9a(3a*H*)-carboxylate (5.6m)

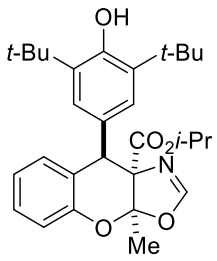


5.6m

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 7:1). Pale yellow

wax, >98% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.82-7.05 (m, 3H), 7.04-6.94 (m, 2H), 6.89 (s, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 5.17 (s, 1H), 4.67 (s, 1H), 4.23-3.92 (m, 2H), 1.86 (s, 3H), 1.44 (s, 18H), 1.04 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.4, 154.8, 153.1, 151.9, 135.3, 130.2, 127.8, 127.5, 125.4, 123.8, 118.0, 111.6, 84.7, 77.2, 61.6, 47.3, 34.3, 30.4, 22.6, 13.9; **HRMS** (ESI): m/z calcd. for $[C_{28}H_{35}NNaO_5, M+Na]^+$: 488.2407; found: 488.2414.

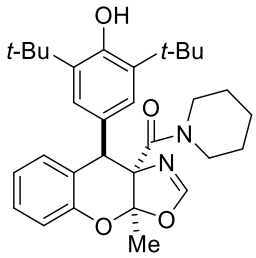
Isopropyl-9-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3a-methyl-9*H*-chromeno[3,2-*d*]oxazole-9a(3a*H*)-carboxylate (5.6n)



5.6n

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 9:1). Pale yellow wax, >98% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.90-7.04 (m, 3H), 7.02-6.94 (m, 2H), 6.88 (s, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 5.16 (s, 1H), 4.93 (dt, *J* = 12.5, 6.2 Hz, 1H), 4.65 (s, 1H), 1.87 (s, 3H), 1.44 (s, 18H), 1.09 (d, *J* = 6.3 Hz, 3H), 0.94 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.9, 154.8, 153.0, 151.8, 135.4, 130.7, 127.7, 127.4, 125.9, 123.8, 117.9, 111.7, 84.4, 77.2, 69.4, 47.1, 34.3, 30.4, 22.5, 21.5, 21.2; **HRMS** (ESI): m/z calcd. for $[C_{29}H_{37}NNaO_5, M+Na]^+$: 502.2564; found: 502.2567.

9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3a-methyl-9*H*-chromeno[3,2-*d*]oxazol-9a(3a*H*)-yl)(piperidin-1-yl)methanone (5.6o)



5.6o

The general procedure outlined above was followed (48 h). In this case, the ratio of **5o** and the corresponding triarylmethane is 9:1 (of crude). The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc 10:1). Pale yellow solid, 75% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.35-6.85 (m, 5H), 6.72 (s, 1H), 5.16 (s, 1H), 4.86 (s, 1H), 4.25-4.00 (m, 1H), 3.95-3.70 (m, 1H), 3.22-2.93 (m, 1H), 2.90-2.60 (m, 1H), 1.85 (s, 3H), 1.75-1.55 (m, 1H), 1.50-1.25 (m, 21H), 1.15-1.00 (m, 1H), 0.42-0.10 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.8, 153.2, 152.6, 152.2, 135.1, 129.9, 127.8, 127.2, 125.3, 123.4, 118.4, 113.5, 87.9, 77.2, 50.7, 46.9, 46.2, 30.5, 29.7, 26.6, 25.7, 24.5, 24.3; **MP**: 182-184 °C; **HRMS** (ESI): m/z calcd. for $[C_{31}H_{40}N_2NaO_4, M+Na]^+$: 527.2880; found: 527.2882.

5.5.6 X-Ray Crystallographic Analysis of 5.6a

The conformation of **5.6a** was determined by X-ray crystallographic analysis of a single crystal of **5.6a** (Figure 5.3). The crystal was prepared from the solution of **5.6a** in hexanes/CH_2Cl_2 at ambient temperature.

Figure 5.3 X-Ray Structure of **5.6a**

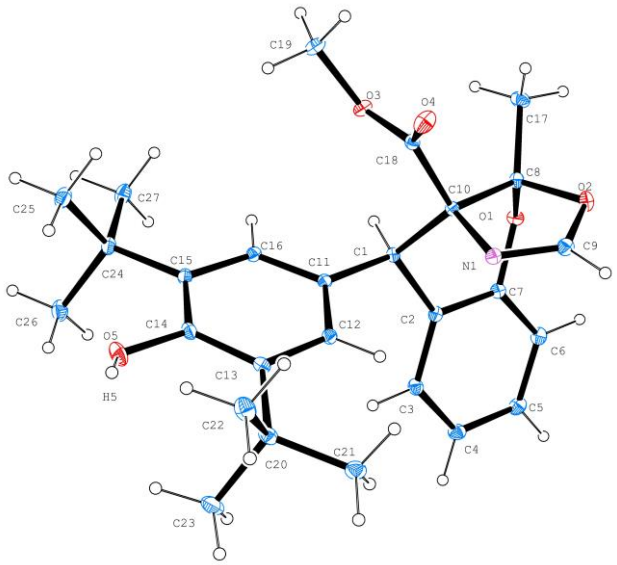


Table 5.3 Crystal Data and Structure Refinement for **5.6a**

Identification code	**5.6a**	
Empirical formula	$C_{27}H_{33}NO_5$	
Formula weight	451.54	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 25.0398(15) Å	α = 90°
	b = 10.8136(5) Å	β = 104.572(2)°
	c = 18.7266(12) Å	γ = 90°
Volume	4907.5(5) $Å^3$	
Z	8	

Density (calculated)	1.222 Mg/m^3
Absorption coefficient	0.084 mm^{-1}
F(000)	1936
Crystal size	0.307 x 0.107 x 0.024 mm^3
Theta range for data collection	2.245 to 29.173°
Index ranges	-34<=h<=33, -13<=k<=14, -25<=l<=25
Reflections collected	20967
Independent reflections	6578 [R(int) = 0.0552]
Completeness to theta = 25.242°	99.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6578 / 0 / 307
Goodness-of-fit on F^2	1.017
Final R indices [I>2sigma(I)]	R1 = 0.0539, wR2 = 0.1255
R indices (all data)	R1 = 0.0821, wR2 = 0.1431
Largest diff. peak and hole	0.450 and -0.359 $e.Å^{-3}$

5.5.7 X-Ray Crystallographic Analysis of 5.6o

The conformation of **5.6o** was determined by X-ray crystallographic analysis of a single crystal of **5.6o** (Figure 5.4). The crystal was prepared from the solution of **5.6o** in hexanes/CH_2Cl_2 at ambient temperature.

Figure 5.4 X-Ray Structure of **5.6o**

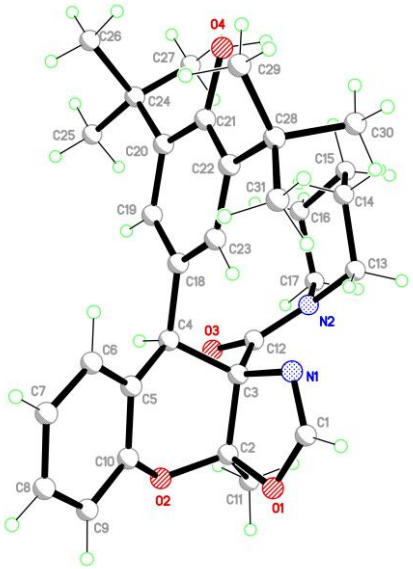


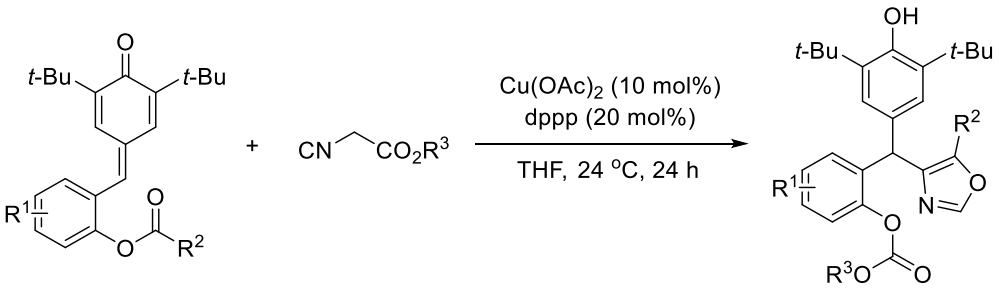
Table 5.4 Crystal Data and Structure Refinement for **5.6o**

Identification code	**5.6o**	
Chemical formula	$C_{31}H_{40}N_2O_4$	
Formula weight	504.65 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.300 x 0.400 x 0.600 mm^3	
Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 10.640(3) Å	α = 90°
	b = 14.112(4) Å	β = 95.021(4)°
	c = 18.010(5) Å	γ = 90°

Volume	2693.9(14) $Å^3$
Z	4
Density (calculated)	1.244 Mg/m^3
Absorption coefficient	0.082 mm^{-1}
F(000)	1088
Theta range for data collection	1.84 to 28.36°
Index ranges	-14<=h<=14, -18<=k<=18, -24<=l<=23
Reflections collected	37277
Independent reflections	6736 [R(int) = 0.0358]
Coverage of independent reflections	99.9%
Absorption correction	Multi-Scan
Max. and min. transmission	0.7457 and 0.6711
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick 2008)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	6736 / 0 / 345
Goodness-of-fit on F^2	1.028
Δ/σmax	0.001
Final R indices [6124 data; I>2σ(I)]	R1 = 0.0421, wR2 = 0.1052
R indices (all data)	R1 = 0.0459, wR2 = 0.1082

Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0547P)^2+1.2264P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.442 and -0.239 eÅ^{-3}
R.M.S. deviation from mean	0.052 eÅ^{-3}

5.5.8 Triarylmethane Synthesis by Copper Catalysis



5.3 **5.4** (1.3 equiv) **5.8**

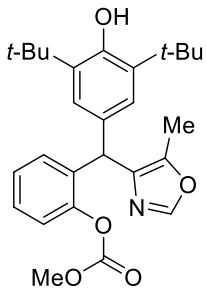
General procedure. To a 10 mL vial charged with dppp (8.2 mg, 0.020 mmol) and $Cu(OAc)_2$ (1.8 mg, 0.010 mmol) was added anhydrous THF (1.0 mL). The mixture was allowed to stir at ambient temperature for 5 min, then *para*-quinone methide-aryl ester **5.3** (0.10 mmol) and isocyanoacetate **5.4** (0.13 mmol) were added in one portion. The reaction mixture was allowed to stir at ambient temperature for 24 h, concentrated and purified by flash chromatography (silica gel or neutral Al_2O_3, hexanes/ethyl acetate) to afford the product **5.8**.

Unless otherwise noted, the ratio of **5.8** and the corresponding tricyclic ketal is >20:1.

5.5.9 Characterization of Compounds 5.8

2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)phenyl meth

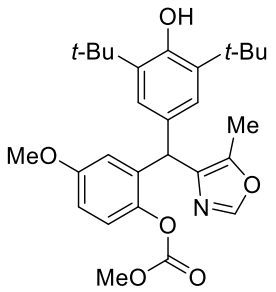
yl carbonate (5.8a)



5.8a

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 5:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.33-7.10 (m, 4H), 7.05 (s, 2H), 5.49 (s, 1H), 5.11 (s, 1H), 3.74 (s, 3H), 2.12 (s, 3H), 1.38 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 153.7, 152.4, 148.8, 144.8, 135.6, 135.0, 134.9, 131.2, 130.3, 127.5, 126.1, 125.6, 121.9, 55.2, 41.3, 34.3, 30.2, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{33}NNaO_5, M+Na]^+$: 474.2251; found: 474.2247.

2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)-4-methoxyphenyl methyl carbonate (5.8b)

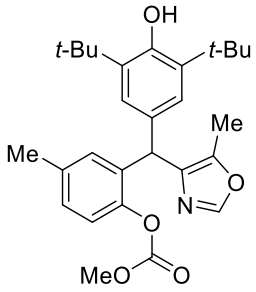


5.8b

The general procedure outlined above was followed (48 h). The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc

4:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.07 (s, 2H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.82 (d, *J* = 3.0 Hz, 1H), 6.76 (dd, *J* = 8.8, 3.1 Hz, 1H), 5.42 (s, 1H), 5.10 (s, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.12 (s, 3H), 1.39 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 157.2, 154.1, 152.4, 148.8, 144.8, 142.6, 136.0, 135.6, 134.8, 131.0, 125.6, 122.6, 115.7, 112.3, 55.4, 55.1, 41.6, 34.3, 30.2, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{28}H_{35}NNaO_6, M+Na]^+$: 504.2357; found: 504.2357.

2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)-4-methylphenyl methyl carbonate (5.8c)

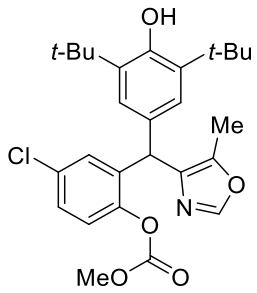


5.8c

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 5:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.14-6.96 (m, 5H), 5.44 (s, 1H), 5.09 (s, 1H), 3.73 (s, 3H), 2.28 (s, 3H), 2.13 (s, 3H), 1.39 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 153.9, 152.3, 148.8, 146.8, 144.7, 135.7, 135.5, 135.0, 134.4, 131.3, 130.7, 128.1, 125.6, 121.6, 55.1, 41.2, 34.3, 30.2, 21.1, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{28}H_{35}NNaO_5, M+Na]^+$: 488.2407; found: 488.2410.

4-Chloro-2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)phe

nyl methyl carbonate (5.8d)

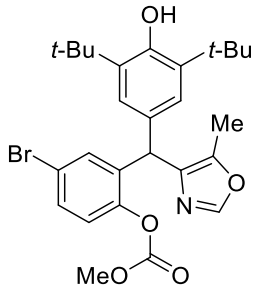


5.8d

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 5:1). Pale yellow wax, >98% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 7.04 (s, 2H), 5.42 (s, 1H), 5.14 (s, 1H), 3.73 (s, 3H), 2.12 (s, 3H), 1.39 (s, 18H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 153.5, 152.6, 149.0, 147.3, 144.9, 136.9, 135.8, 134.3, 131.5, 130.5, 130.2, 127.6, 125.5, 123.3, 55.4, 41.4, 34.3, 30.2, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{32}ClNNaO_5, M+Na]^+$: 508.1861; found: 508.1868.

4-Bromo-2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)phe

nyl methyl carbonate (5.8e)

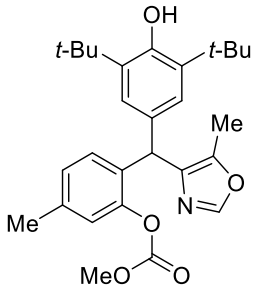


5.8e

The general procedure outlined above was followed. The crude reaction mixture was

purified by flash column chromatography (hexanes/EtOAc 7:1). Pale yellow wax, >98% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.37 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.06-6.98 (m, 3H), 5.42 (s, 1H), 5.13 (s, 1H), 3.73 (s, 3H), 2.12 (s, 3H), 1.39 (s, 18H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 153.4, 152.6, 149.0, 147.9, 145.0, 137.2, 135.8, 134.3, 133.2, 130.6, 130.5, 125.5, 123.7, 119.4, 55.4, 41.4, 34.3, 30.2, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{32}BrNNaO_5, M+Na]^+$: 552.1356; found: 552.1358.

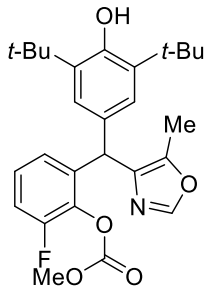
2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)-5-methylphenyl methyl carbonate (5.8f)



5.8f

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 7:1). Pale yellow wax, >98% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.06 (s, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.94 (s, 1H), 5.43 (s, 1H), 5.10 (s, 1H), 3.75 (s, 3H), 2.32 (s, 3H), 2.12 (s, 3H), 1.39 (s, 18H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 153.9, 152.3, 148.8, 148.6, 144.6, 137.6, 135.5, 135.0, 131.9, 131.4, 130.0, 127.0, 125.6, 122.4, 55.2, 41.0, 34.3, 30.2, 20.9, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{28}H_{35}NNaO_5, M+Na]^+$: 488.2407; found: 488.2416.

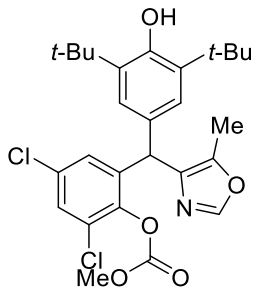
2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)-6-fluorophen yl methyl carbonate (5.8g)



5.8g

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc 5:1). Yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.19-7.11 (m, 1H), 7.10-6.98 (m, 4H), 5.47 (s, 1H), 5.13 (s, 1H), 3.75 (s, 3H), 2.13 (s, 3H), 1.39 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 154.4 (d, *J* = 249.3 Hz), 152.53, 152.48, 148.9, 144.9, 137.8, 136.8 (d, *J* = 13.1 Hz), 135.7, 134.5, 130.7, 126.5 (d, *J* = 7.8 Hz), 125.6, 125.2 (d, *J* = 3.3 Hz), 114.7 (d, *J* = 18.6 Hz), 55.6, 41.3 (d, *J* = 2.2 Hz), 34.3, 30.2, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{32}FNNaO_5, M+Na]^+$: 492.2157; found: 492.2167.

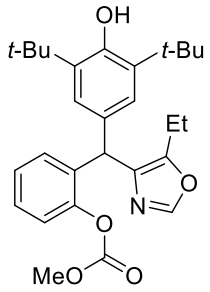
2,4-Dichloro-6-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl) phenyl methyl carbonate (5.8h)



5.8h

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc 6:1). Yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 2.5 Hz, 1H), 7.06 (s, 2H), 5.39 (s, 1H), 5.16 (s, 1H), 3.75 (s, 3H), 2.16 (s, 3H), 1.40 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.8, 151.9, 149.1, 145.0, 143.9, 139.1, 135.9, 133.9, 131.9, 130.0, 129.0, 128.2, 125.6, 55.8, 41.6, 34.3, 30.2, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{31}Cl_2NNaO_5, M+Na]^+$: 542.1471; found: 542.1478.

2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(5-ethyloxazol-4-yl)methyl)phenyl methyl carbonate (5.8i)

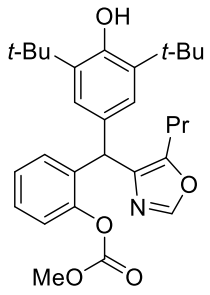


5.8i

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 5:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.33 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.27-7.10 (m, 3H), 7.00 (s, 2H), 5.52 (s, 1H), 5.08 (s, 1H), 3.72 (s, 3H), 2.52-2.39 (m, 2H), 1.37 (s, 18H), 1.10 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 153.7, 152.3, 149.8, 148.9, 148.9, 135.5, 135.0, 134.1, 131.5, 130.3, 127.5, 126.1, 125.5, 121.9, 55.2, 41.3, 34.3, 30.2, 18.1, 12.6; **HRMS** (ESI): m/z calcd. for

[$C_{28}H_{35}NNaO_5$, M+Na]$^+$: 488.2407; found: 488.2403.

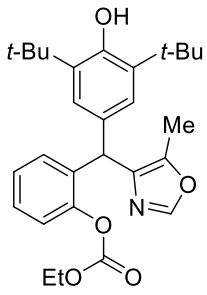
2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(5-propyloxazol-4-yl)methyl)phenyl meth yl carbonate (5.8j)



5.8j

The general procedure outlined above was followed (48 h). The crude reaction mixture was purified by flash column chromatography (neutral Al_2O_3, hexanes/EtOAc 6:1). Pale yellow wax, >98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.37-7.10 (m, 4H), 6.98 (s, 2H), 5.52 (s, 1H), 5.08 (s, 1H), 3.71 (s, 3H), 2.55-2.26 (m, 2H), 1.60-1.45 (m, 2H), 1.37 (s, 18H), 0.82 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 153.7, 152.3, 149.0, 148.9, 148.8, 135.4, 135.0, 134.8, 131.6, 130.3, 127.5, 126.0, 125.5, 121.9, 55.2, 41.3, 34.3, 30.2, 26.5, 21.5, 13.6; **HRMS** (ESI): m/z calcd. for [$C_{29}H_{37}NNaO_5$, M+Na]$^+$: 502.2564; found: 502.2571.

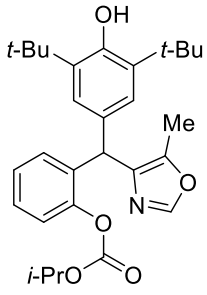
2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)phenyl ethyl carbonate (5.8k)



5.8k

The general procedure outlined above was followed. The crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc 8:1). Pale yellow wax, >98% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.28-7.23 (m, 2H), 7.21-7.11 (m, 2H), 7.05 (s, 2H), 5.50 (s, 1H), 5.10 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.11 (s, 3H), 1.38 (s, 18H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 153.2, 152.4, 148.8, 144.8, 135.6, 135.0, 134.9, 131.3, 130.3, 127.5, 126.0, 125.6, 121.9, 64.6, 41.2, 34.3, 30.2, 14.1, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{28}H_{35}NNaO_5$, M+Na$]^+$: 488.2407; found: 488.2406.

2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)phenyl isopropyl carbonate (5.8l)

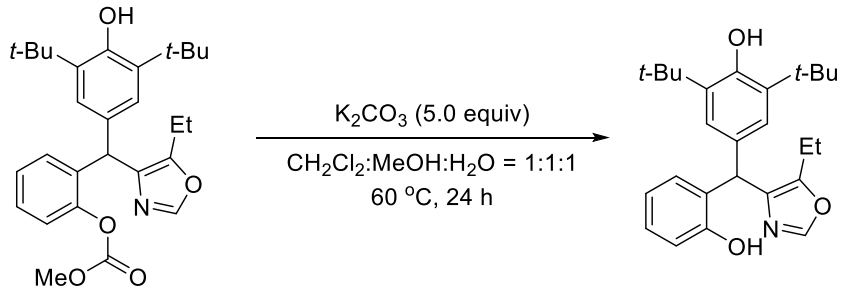


5.8l

The general procedure outlined above was followed (48 h). In this case, the ratio of **7l** and the corresponding tricyclic ketal is 14:1 (of crude). The crude reaction mixture

was purified by flash column chromatography (hexanes/EtOAc 8:1). Pale yellow wax, 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.28-7.10 (m, 4H), 7.04 (s, 2H), 5.51 (s, 1H), 5.09 (s, 1H), 4.85 (dt, *J* = 12.4, 6.2 Hz, 1H), 2.10 (s, 3H), 1.38 (s, 18H), 1.30 (d, *J* = 6.3 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.8, 152.4, 148.83, 148.77, 144.8, 135.6, 135.1, 134.9, 131.3, 130.3, 127.4, 126.0, 125.6, 122.0, 72.8, 41.2, 34.3, 30.2, 21.64, 21.61, 10.1; **HRMS** (ESI): m/z calcd. for $[C_{29}H_{37}NNaO_5, M+Na]^+$: 502.2564; found: 502.2557.

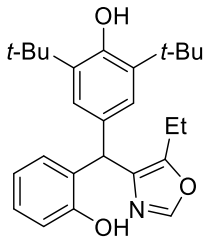
5.5.10 Cleavage of the Carbonate Moiety in 5.8i[112]



5.8i **5.9**

Potassium carbonate (69 mg, 0.5 mmol) was added to the mixture of **5.8i** (46.5 mg, 0.1 mmol), CH_2Cl_2 (0.5 mL), MeOH (0.5 mL) and H_2O (0.5 mL). The reaction mixture was allowed to stir at 60 °C for 24 h, concentrated and purified by flash chromatography (hexanes/EtOAc 5:1) to yield 34 mg of **5.9**.

2,6-Di-*tert*-butyl-4-((5-ethyloxazol-4-yl)(2-hydroxyphenyl)methyl)phenol (5.9)



5.9

Yellow solid, 84% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.84 (s, 1H), 7.24-7.13 (m, 2H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.93-6.81 (m, 3H), 5.15 (s, 1H), 5.09 (s, 1H), 2.88-2.68 (m, 2H), 1.34 (s, 18H), 1.29 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.6, 152.4, 149.7, 148.7, 135.5, 134.6, 131.5, 130.8, 129.0, 127.9, 124.3, 120.1, 119.2, 46.4, 34.3, 30.2, 18.0, 13.0; **MP**: 156-157 ^{o}C; **HRMS** (ESI): m/z calcd. for $[C_{26}H_{33}NNaO_3, M+Na]^+$: 430.2353; found: 430.2344.

5.5.11 X-Ray Crystallographic Analysis of 5.9

The conformation of **5.9** was determined by X-ray crystallographic analysis of a single crystal of **5.9** (Figure 5.5). The crystal was prepared from the solution of **5.9** in hexanes/CH_2Cl_2 at ambient temperature.

Figure 5.5 X-Ray Structure of **5.9**

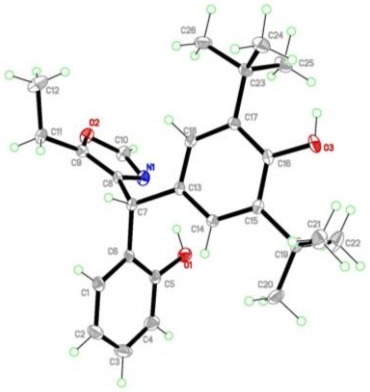
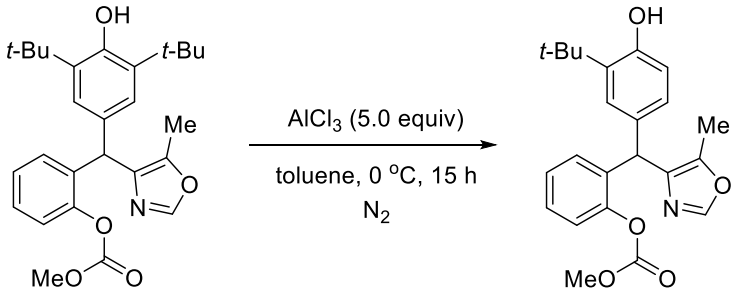


Table 5.5 Crystal Data and Structure Refinement for **5.9**

Identification code	**5.9**	
Chemical formula	$C_{26}H_{33}NO_3$	
Formula weight	407.53 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.300 x 0.360 x 0.560 mm^3	
Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 13.873(2) Å	α = 90°
	b = 10.0086(16) Å	β = 95.084(2)°
	c = 16.516(3) Å	γ = 90°
Volume	2284.2(6) $Å^3$	
Z	4	
Density (calculated)	1.185 g/cm^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	880	
Theta range for data collection	1.84 to 28.28°	
Index ranges	-18<=h<=18, -13<=k<=13, -22<=l<=22	
Reflections collected	30529	
Independent reflections	5670 [R(int) = 0.0406]	
Coverage of independent reflections	100.0%	

Absorption correction	Multi-Scan
Max. and min. transmission	0.7459 and 0.6423
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick 2008)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5670 / 0 / 308
Goodness-of-fit on F^2	1.044
Final R indices [4888 data; I>2σ(I)]	R1 = 0.0443, wR2 = 0.1105
R indices (all data)	R1 = 0.0521, wR2 = 0.1155
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0595P)^2+0.7248P]$
	where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.414 and -0.233 eÅ^{-3}
R.M.S. deviation from mean	0.049 e.Å^{-3}

5.5.12 De-*tert*-butylation of 5.8a[104]

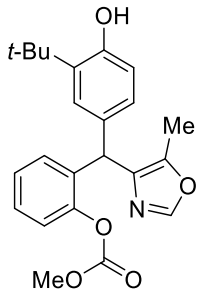


5.8a **5.10**

Under nitrogen atmosphere, the compound **5.8a** (43.3 mg, 0.096 mmol) was

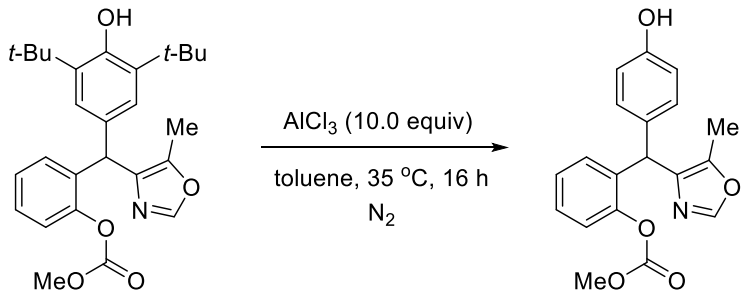
dissolved in 4 mL dry toluene. The resulting mixture was cooled to 0 °C, then $AlCl_3$ (63.8 mg, 0.48 mmol) was added. The reaction was stirred for 15 h at 0 °C and 4 mL H_2O was added and extracted with ethyl acetate for three times. The combined extracts were dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel eluting with hexanes/ethyl acetate (3:1) to afford 31.7 mg of **5.10**.

2-((3-(*tert*-Butyl)-4-hydroxyphenyl)(5-methyloxazol-4-yl)methyl)phenyl methyl carbonate (5.10)



5.10

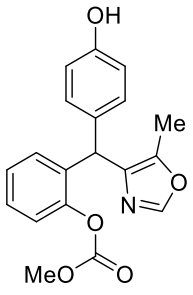
Pale yellow wax, 84% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.29-7.21 (m, 2H), 7.20-7.10 (m, 2H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.80 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.48-6.28 (m, 1H), 5.97 (s, 1H), 5.49 (s, 1H), 3.74 (s, 3H), 2.11 (s, 3H), 1.33 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.8, 153.3, 149.1, 148.8, 144.9, 135.9, 134.8, 131.9, 130.2, 127.7, 127.5, 127.2, 126.2, 121.9, 116.5, 55.3, 41.0, 34.5, 29.5, 10.0; **HRMS** (ESI): m/z calcd. for $[C_{23}H_{26}NO_5, M+H]^+$: 396.1805; found: 396.1805.



5.8a **5.11**

Under nitrogen atmosphere, the compound **5.8a** (45.1 mg, 0.1 mmol) was dissolved in 4 mL dry toluene and $AlCl_3$ (133 mg, 1.0 mmol) was added. The resulting mixture was warmed to 35 °C and stirred for 16 h. Then the reaction was cooled to room temperature and 4 mL H_2O was added and extracted with ethyl acetate for three times. The combined extracts were dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel eluting with hexanes/ethyl acetate (2:1) to afford 23 mg of **5.11**.

2-((4-Hydroxyphenyl) (5-methyloxazol-4-yl)methyl)phenyl methyl carbonate (5.11)

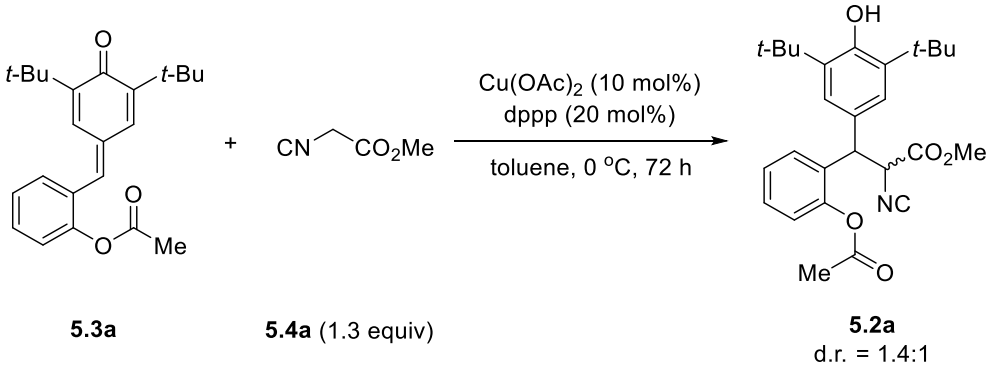


5.11

Pale yellow wax, 68% yield. **^{1}H NMR** (400 MHz, Acetone-d_6): δ 8.21 (s, 1H), 7.91 (s, 1H), 7.37 (dd, J = 7.7, 1.8 Hz, 1H), 7.30-7.24 (m, 1H), 7.24-7.13 (m, 2H), 7.13-7.06

(m, 2H), 6.80-6.66 (m, 2H), 5.49 (s, 1H), 3.78 (s, 3H), 2.16 (s, 3H); **^{13}C NMR** (101 MHz, Acetone-d_6): δ 157.0, 154.6, 150.2, 150.0, 145.4, 136.3, 135.7, 133.2, 131.3, 130.8, 128.3, 126.8, 123.0, 115.9, 55.7, 41.1, 10.0; **HRMS** (ESI): m/z calcd. for $[C_{19}H_{18}NO_5, M+H]^+$: 340.1179; found: 340.1175.

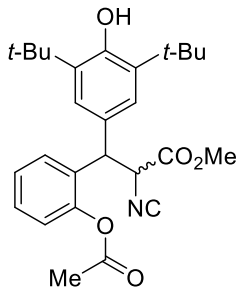
5.5.13 Synthesis of Intermediate 5.2a and Subjection to Ag or Cu Catalysis



5.3a **5.4a** (1.3 equiv) **5.2a** d.r. = 1.4:1

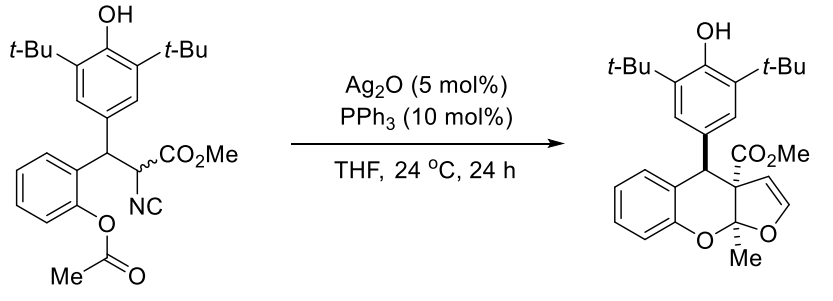
To a 10 mL vial charged with dppp (8.2 mg, 0.020 mmol) and $Cu(OAc)_2$ (1.8 mg, 0.010 mmol) was added anhydrous toluene (1.0 mL). The mixture was allowed to stir at ambient temperature for 5 min, then *para*-quinone methide-aryl ester **5.3a** (0.10 mmol) and methyl isocyanoacetate **5.4a** (0.13 mmol) were added in one portion. The reaction mixture was allowed to stir at 0 °C for 72 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate 5:1) to afford the product **5.2a**.

Methyl-3-(2-acetoxyphenyl)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-isocyanopropanoate (5.2a)



5.2a

Intermediate **5.2a** was obtained in a pure form as a mixture of two diastereomers (d.r. = 1.4:1). Pale yellow wax, 78% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.6 Hz, 0.7H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.35-7.20 (m, 3.4H), 7.10-7.05 (m, 1.7H), 7.03 (s, 2H), 6.98 (s, 1.4H), 5.18 (s, 1.7H), 4.94-4.86 (m, 1.7H), 4.83-4.73 (m, 1.7H), 3.70 (s, 3H), 3.65 (s, 2.1H), 2.17 (s, 3H), 2.14 (s, 2.1H), 1.39 (s, 18H), 1.38 (s, 12.6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.62, 168.37, 166.25, 166.21, 162.63, 162.57, 153.15, 153.10, 148.71, 148.25, 136.03, 135.82, 131.51, 130.37, 128.74, 128.43, 128.40, 128.36, 127.17, 126.11, 125.94, 125.13, 124.65, 123.09, 123.02, 60.34, 60.21, 53.32, 53.26, 46.43, 46.36, 34.31, 34.30, 30.16, 30.11, 20.73, 20.68; **HRMS** (ESI): m/z calcd. for $[C_{27}H_{33}NNaO_5, M+Na]^+$: 474.2251; found: 474.2255.

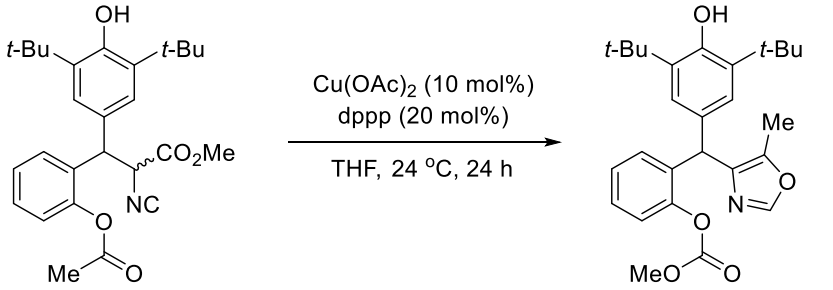


5.2a
d.r. = 1.4:1

5.6a
d.r. >20:1
5.6a:**5.8a** = >20:1, 83%

To a 10 mL vial charged with PPh_3 (2.1 mg, 0.0078 mmol) and Ag_2O (0.9 mg, 0.0039 mmol) was added anhydrous THF (0.8 mL). The mixture was allowed to stir at

ambient temperature for 5 min, then intermediate **5.2a** (35 mg, 0.078 mmol) was added in one portion. The reaction mixture was allowed to stir at ambient temperature for 24 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate 5:1) to afford 29 mg of **5.6a**.

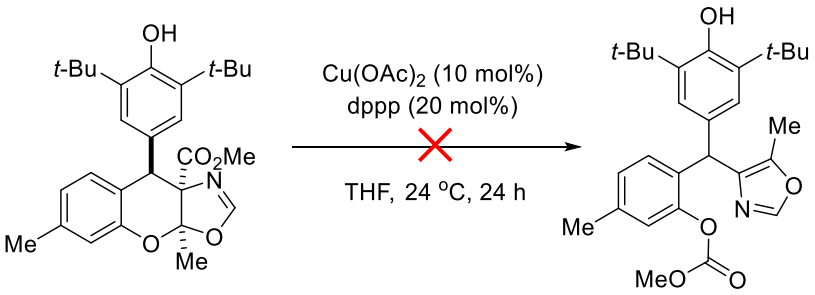


5.2a
d.r. = 1.4:1

5.8a
5.6a:**5.8a** = 1:>20, 91%

To a 10 mL vial charged with dppp (6.4 mg, 0.0156 mmol) and $Cu(OAc)_2$ (1.4 mg, 0.0078 mmol) was added anhydrous THF (0.8 mL). The mixture was allowed to stir at ambient temperature for 5 min, then intermediate **5.2a** (35 mg, 0.078 mmol) was added in one portion. The reaction mixture was allowed to stir at ambient temperature for 24 h, concentrated and purified by flash chromatography (hexanes/ethyl acetate 5:1) to afford 32 mg of **5.8a**.

5.5.14 Test of the Possibility of Product Interconversion



5.6f **5.8f**

To a 10 mL vial charged with dppp (8.2 mg, 0.020 mmol) and $Cu(OAc)_2$ (1.8 mg, 0.010 mmol) was added anhydrous toluene (1.0 mL). The mixture was allowed to stir at ambient temperature for 5 min, then tricyclic ketal **5.6f** (46.5 mg, 0.10 mmol) was added in one portion. The reaction mixture was allowed to stir at ambient temperature for 24 h.

Under the copper catalysis conditions, **5.6f** was stable and didn't undergo conversion to **5.8f** at all.

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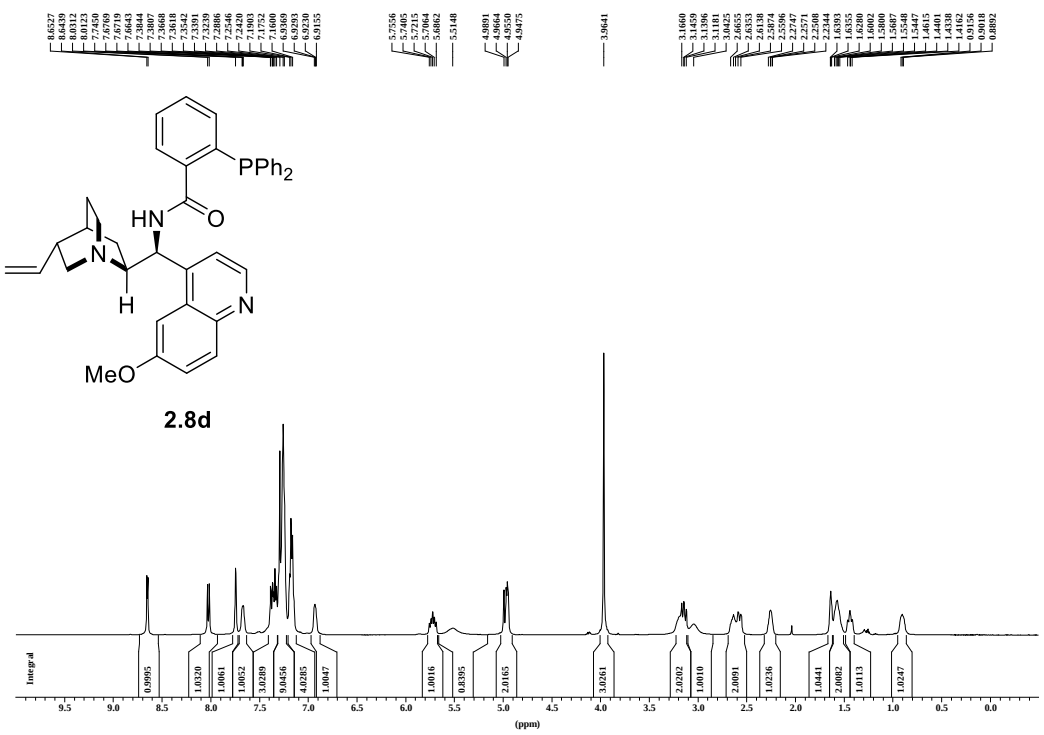
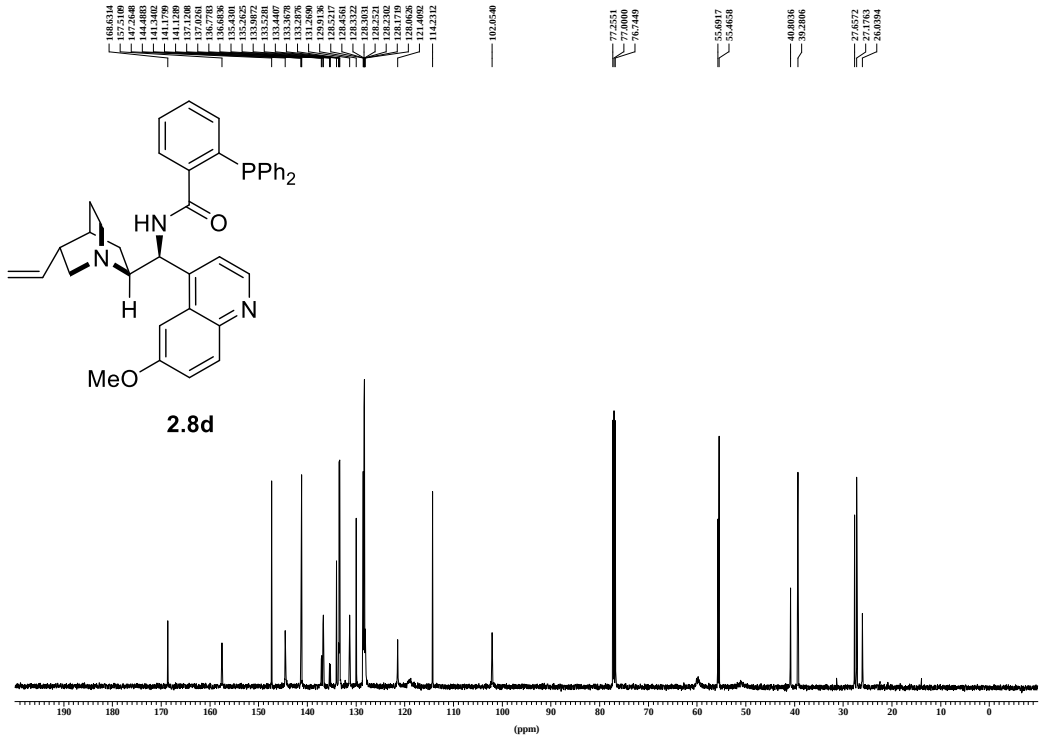
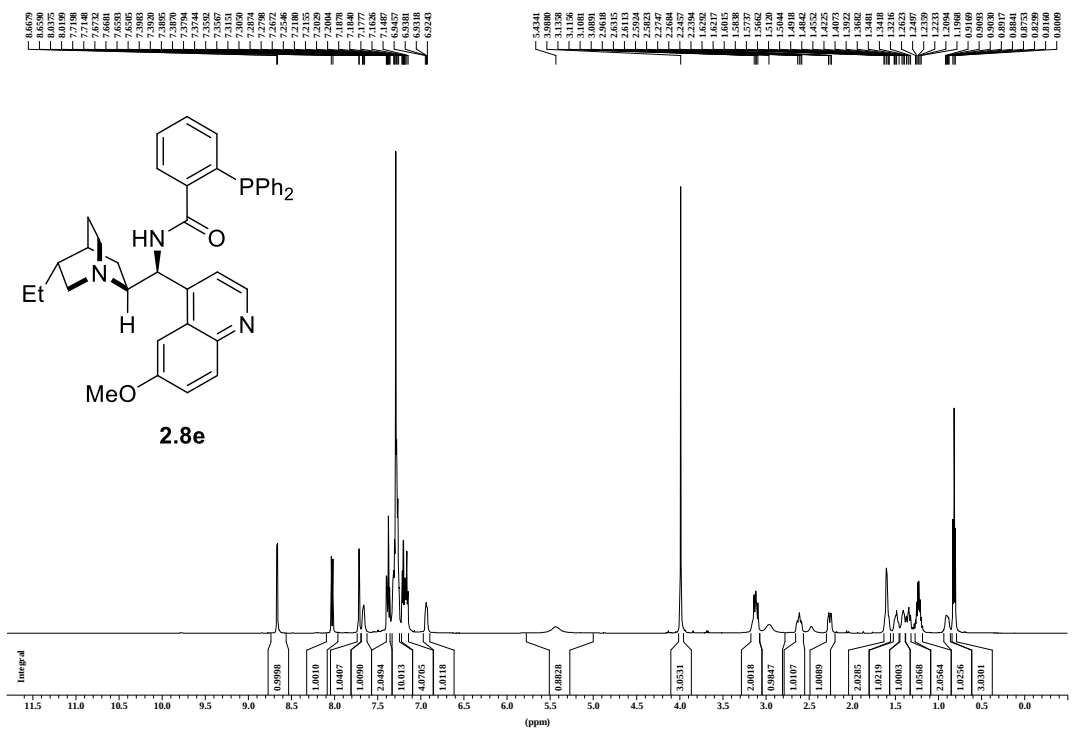
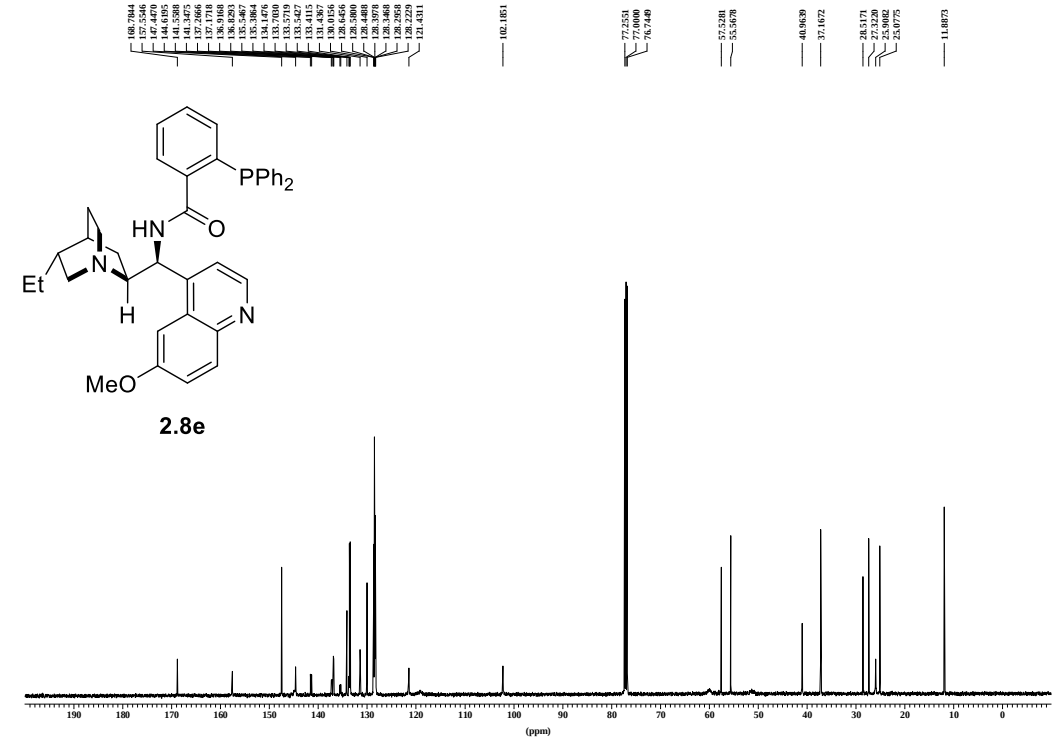
NMR Spectra of the Compounds







2.8e



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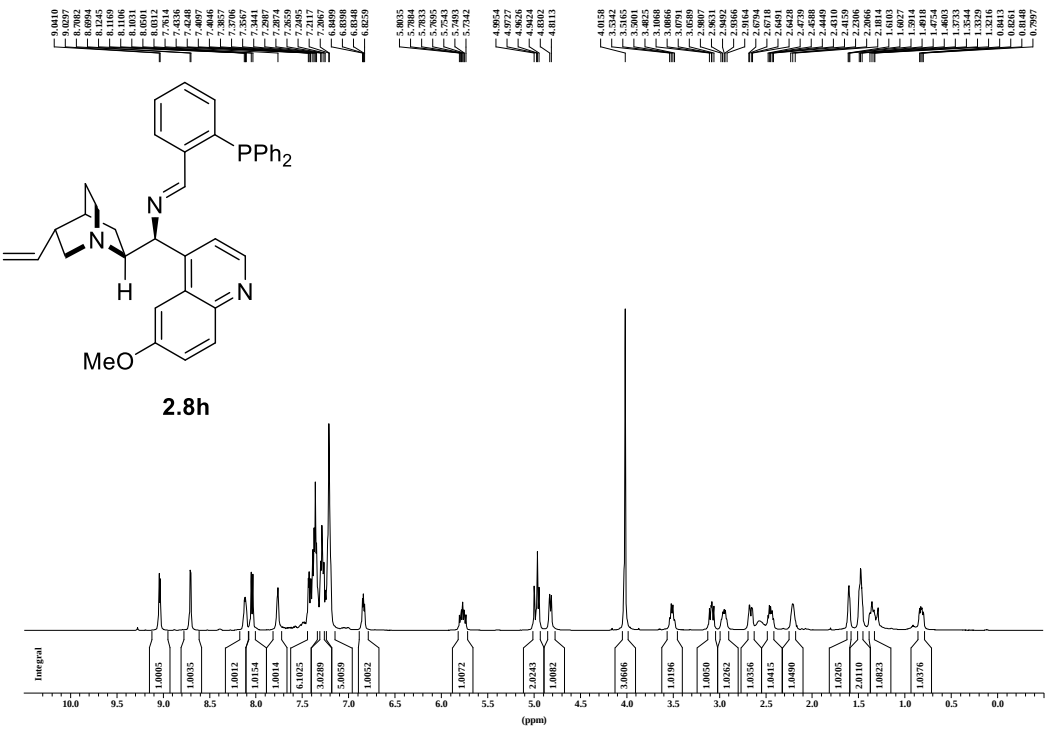
PPh2
N
N
H
N
MeO
Integral
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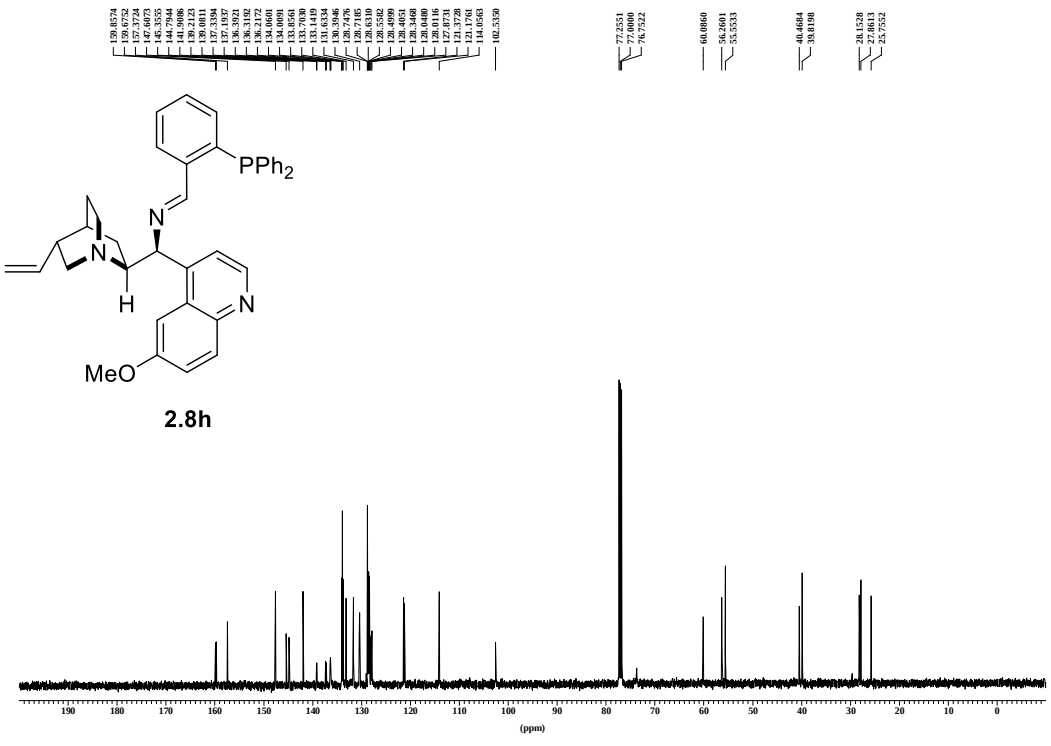
1.0035
1.0012
1.0154
1.0014
6.1025
3.0289
5.0059
1.0052
1.0072
2.0243
1.0082
3.0606
1.0196
1.0050
1.0262
1.0356
1.0415
1.0490
1.0205
2.0110
1.0823
1.0376
(ppm)

2.8h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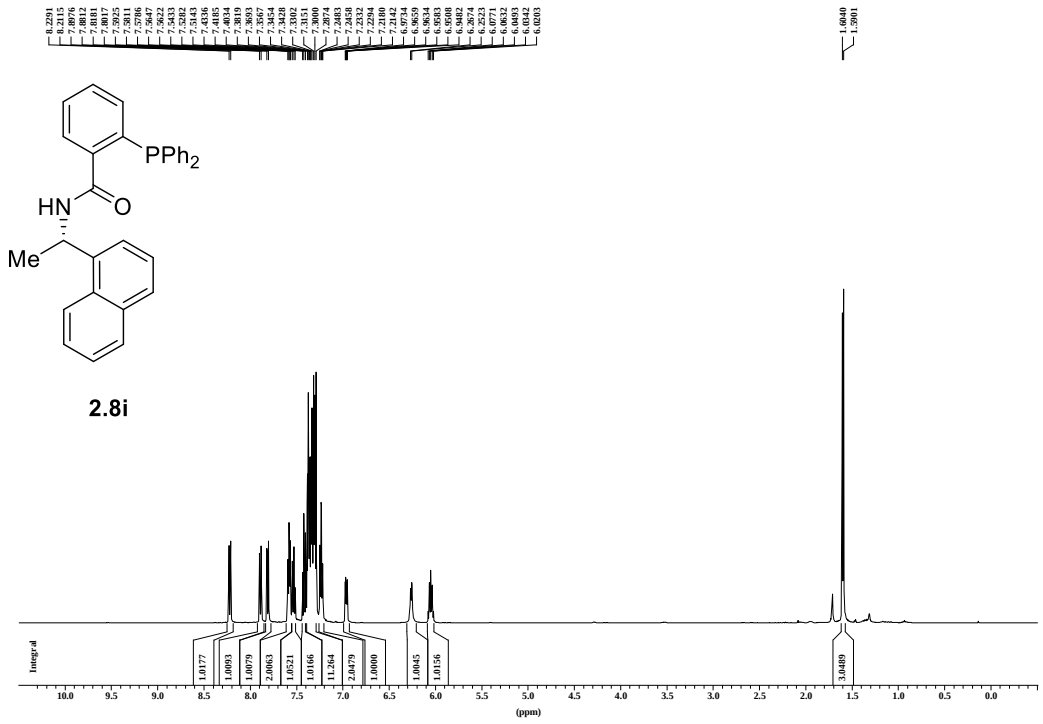
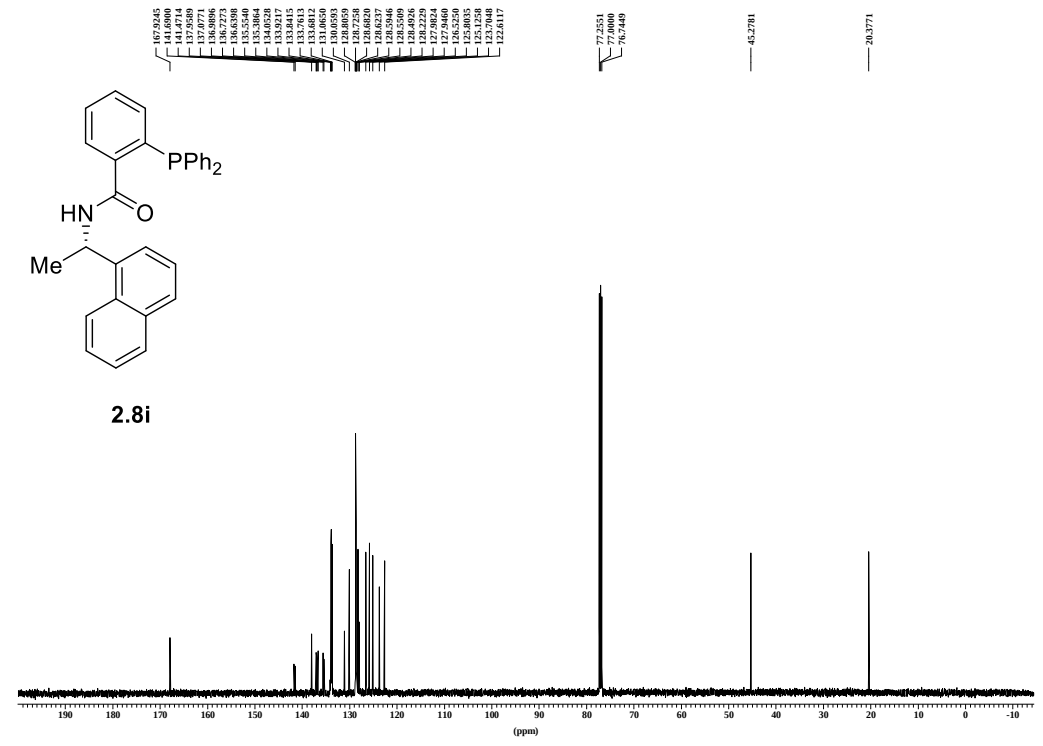
N
N
H
N
MeO
77.2551
77.0000
76.7522
60.0860
56.2601
55.5533
40.4684
39.8198
28.1528
27.2613
25.7552
(ppm)

2.8h


PPh2
HN
O
Me
2.8i
Integral
(ppm)


PPh2
HN
O
Me
2.8i
(ppm)

CN
CO2i-Pr

2.2c

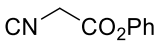
7.5600
5.1331
5.1205
5.1079
5.0953
5.0827
5.0701
5.0575
4.1725
1.2829
1.2703
Integral
1.0000
2.0712
6.0324
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

CN
CO2i-Pr

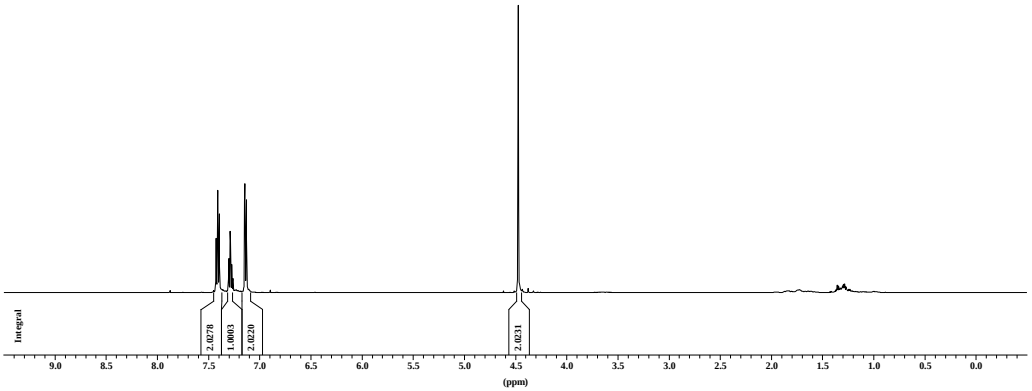
2.2c

163.3408
160.8995
77.2478
77.0000
76.7449
70.8713
43.6530
21.4994
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

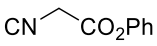

7.4252
7.4100
7.3924
7.3803
7.3695
7.2713
7.2600
7.1465
7.1440
7.1402
7.1289
4.4725


CN
CO2Ph

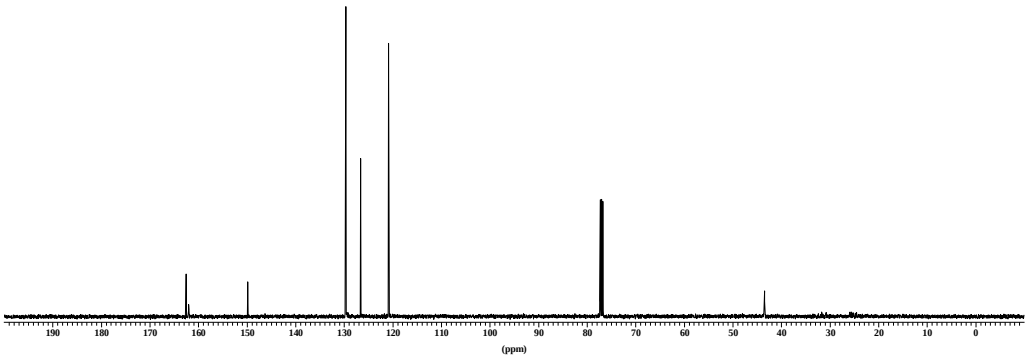
2.2e

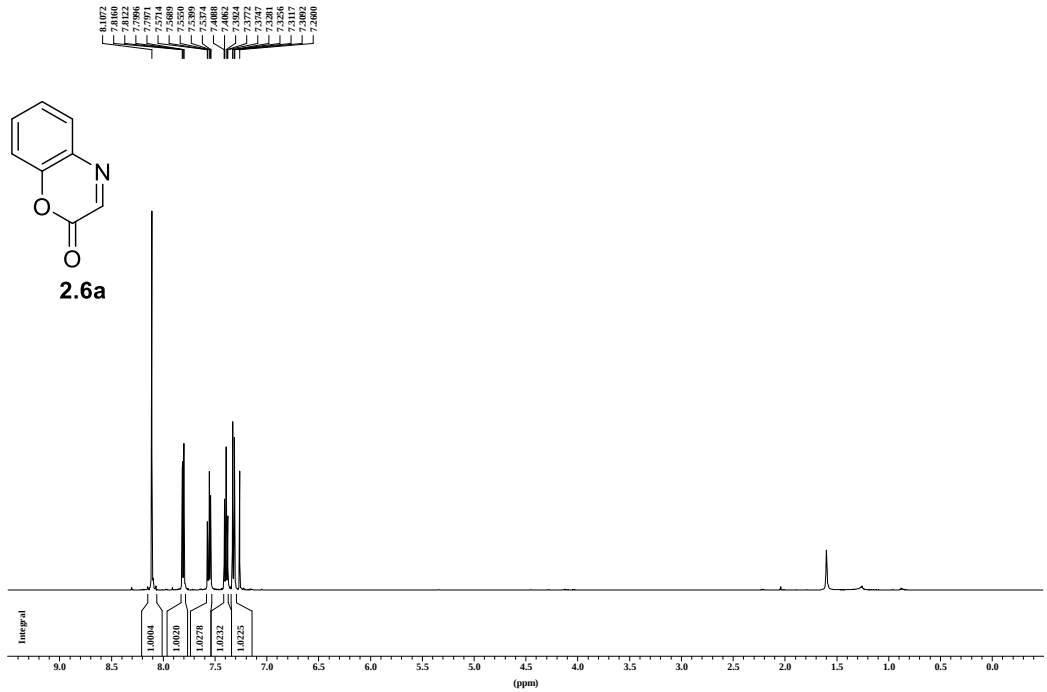

Integral
2.0278
1.0003
2.0220
2.0231
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


162.5246
162.0363
149.8518
129.6148
126.6124
120.8700
77.2551
77.0000
76.7449
43.5000


CN
CO2Ph

2.2e


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)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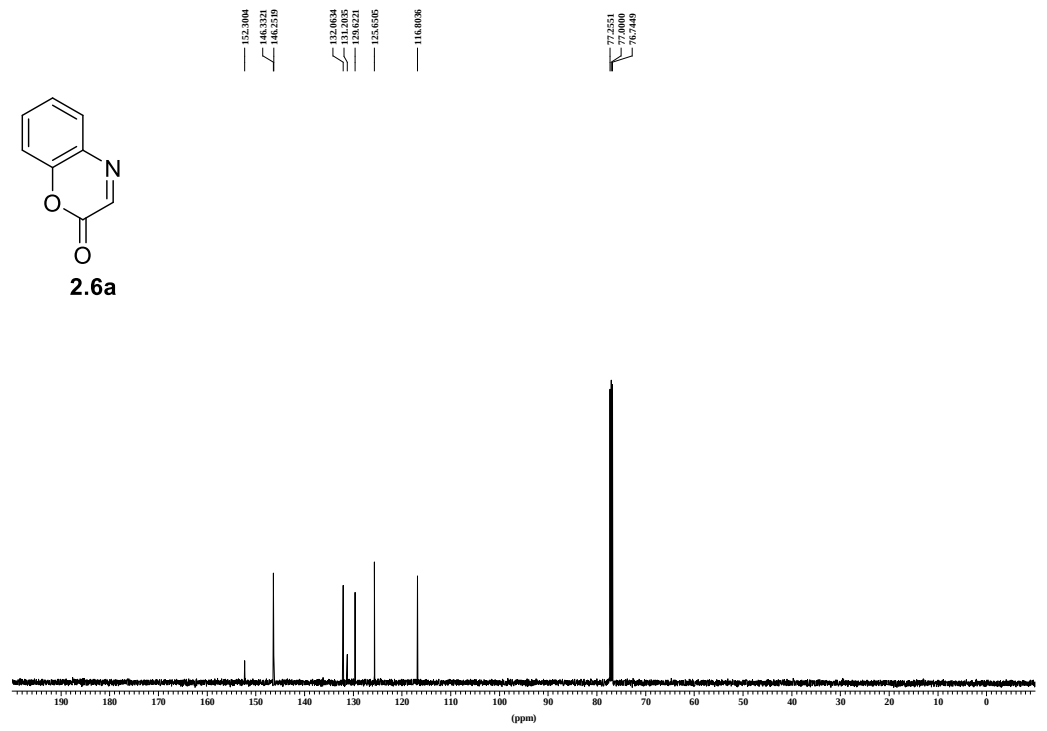
7.8160
7.8122
7.7996
7.7971
7.5714
7.5689
7.5550
7.5369
7.5374
7.4088
7.4062
7.3924
7.3772
7.3747
7.3281
7.3256
7.3117
7.3092
7.2600
2.6a
Integral
1.0004
1.0020
1.0278
1.0232
1.0225
(ppm)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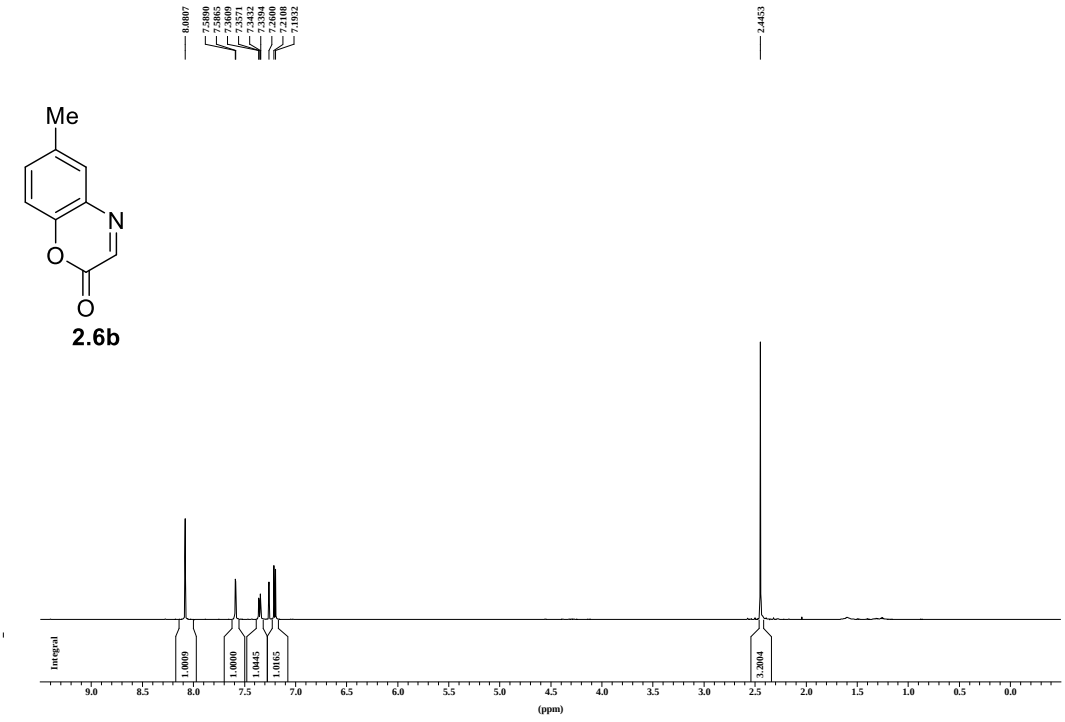
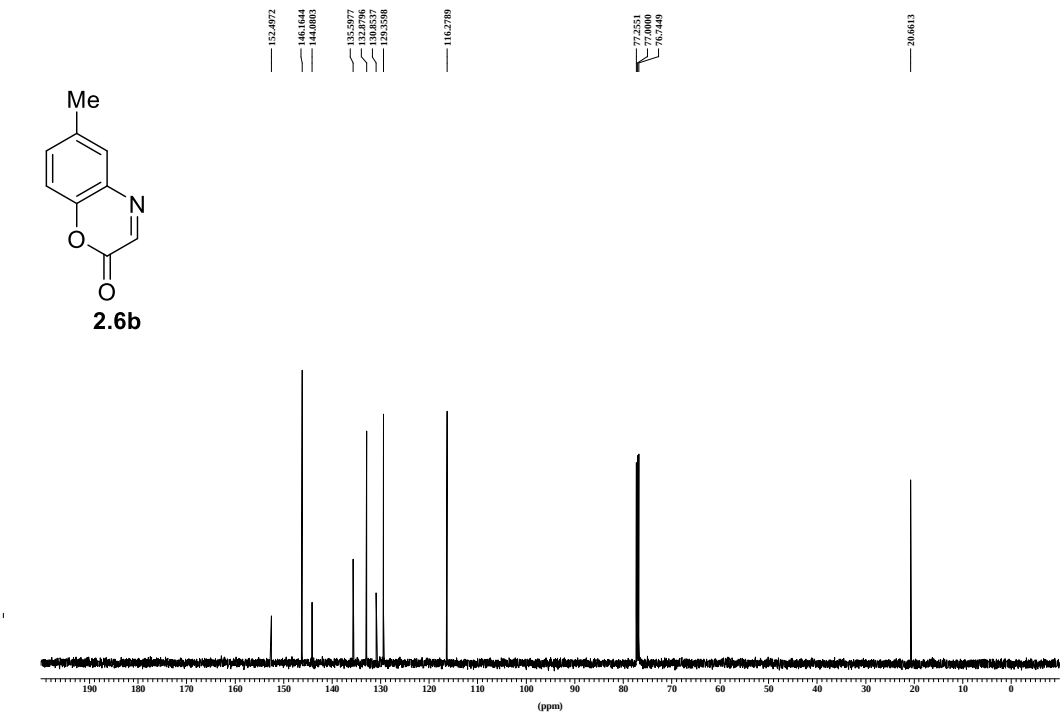
146.3321
146.2519
132.0634
131.2035
129.6221
125.6505
116.8036
77.2551
77.0000
76.7449
2.6a
(ppm)


8.0807
7.5890
7.5865
7.3609
7.3571
7.3432
7.3394
7.2600
7.2108
7.1932
2.4453
Me
N
O
O
2.6b
Integral
1.0009
1.0000
1.0445
1.0165
3.2004
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
(ppm)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146.1644
144.0803
135.5977
132.8796
130.8537
129.3598
116.2789
77.2551
77.0000
76.7449
20.6613
Me
N
O
O
2.6b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


8.1513
8.0177
8.0127
7.7895
7.7857
7.7731
7.7681
7.6269
7.6244
7.6105
7.6080
7.5046
7.4895
7.4743
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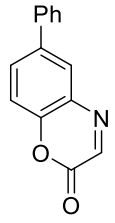
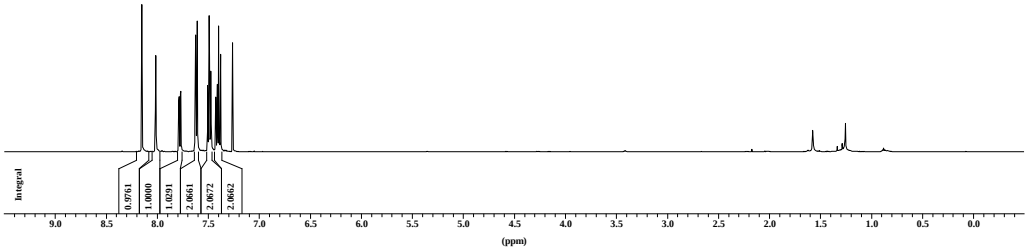
7.4239
7.4113
7.3974
7.3798
7.2600


Ph
N
O
O

2.6c


Integral
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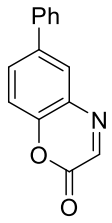
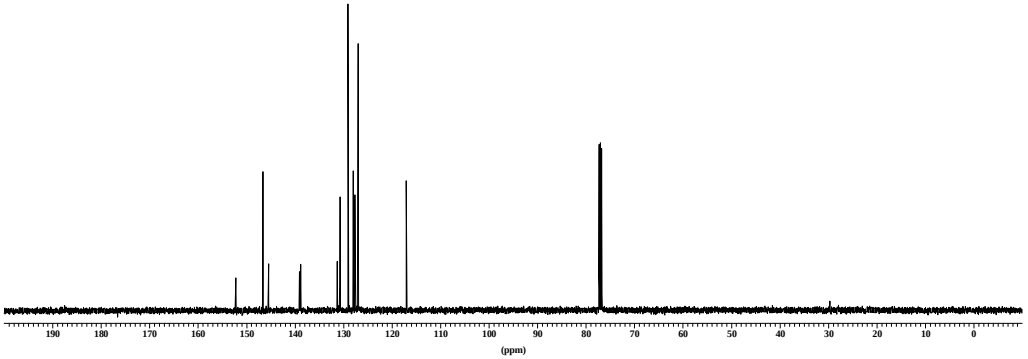
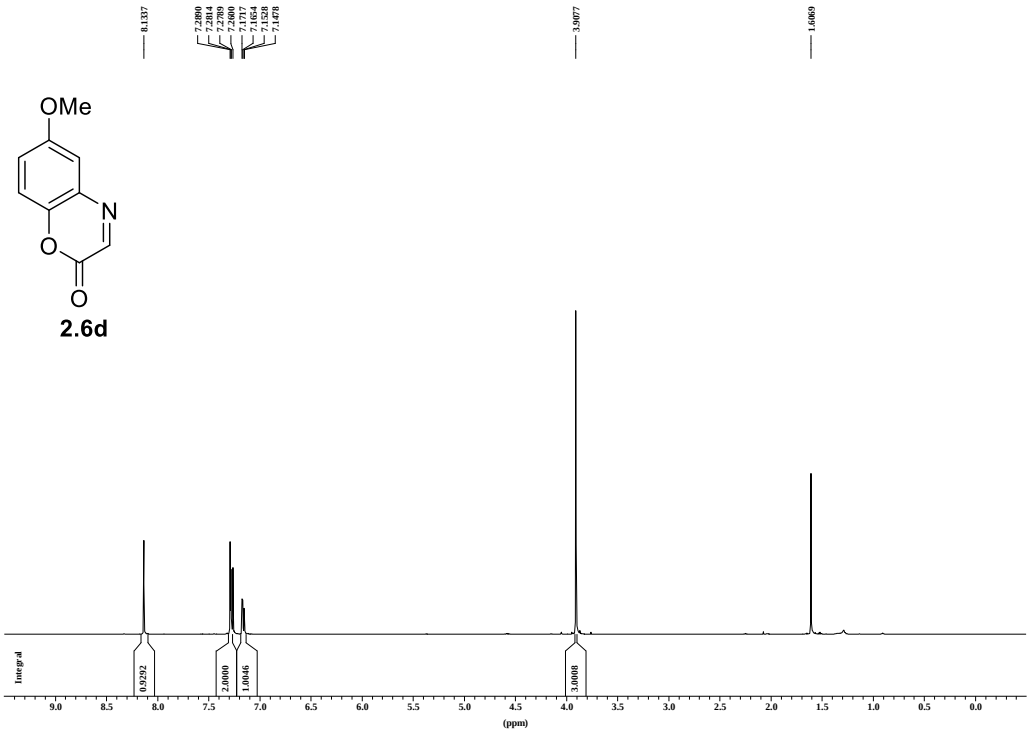
1.0291
2.0661
2.0672
2.0662
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

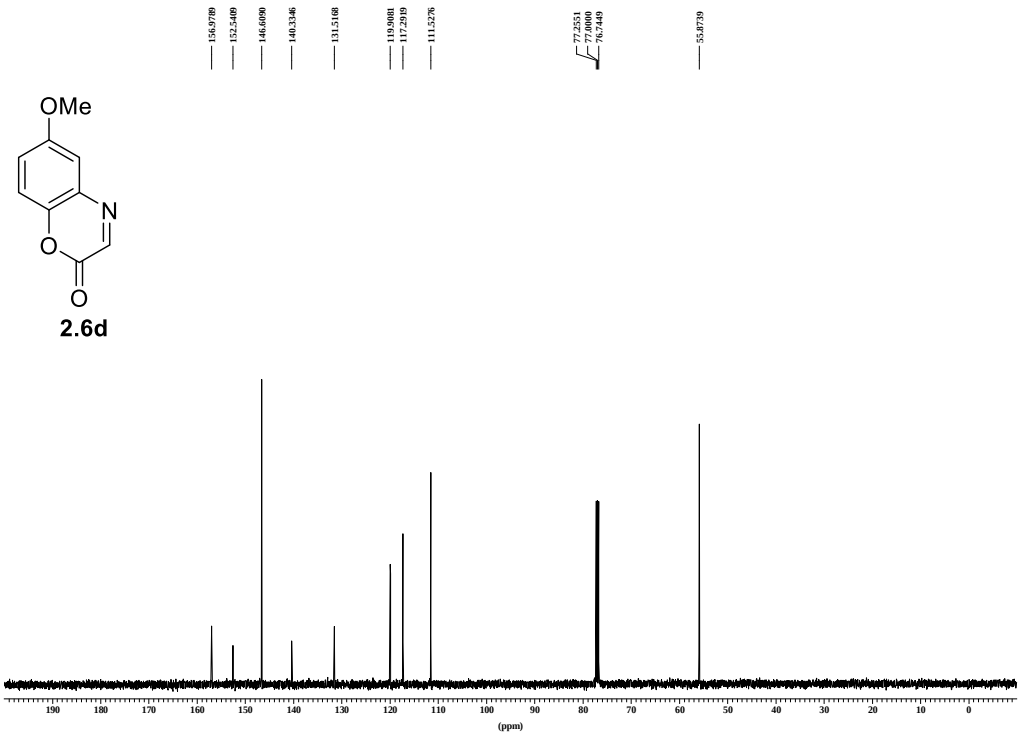

152.2203
146.6454
145.4503
139.0884
138.8115
131.2982
130.7371
129.0610
128.9189
127.6857
127.0132
117.0295
77.2551
77.0000
76.7449

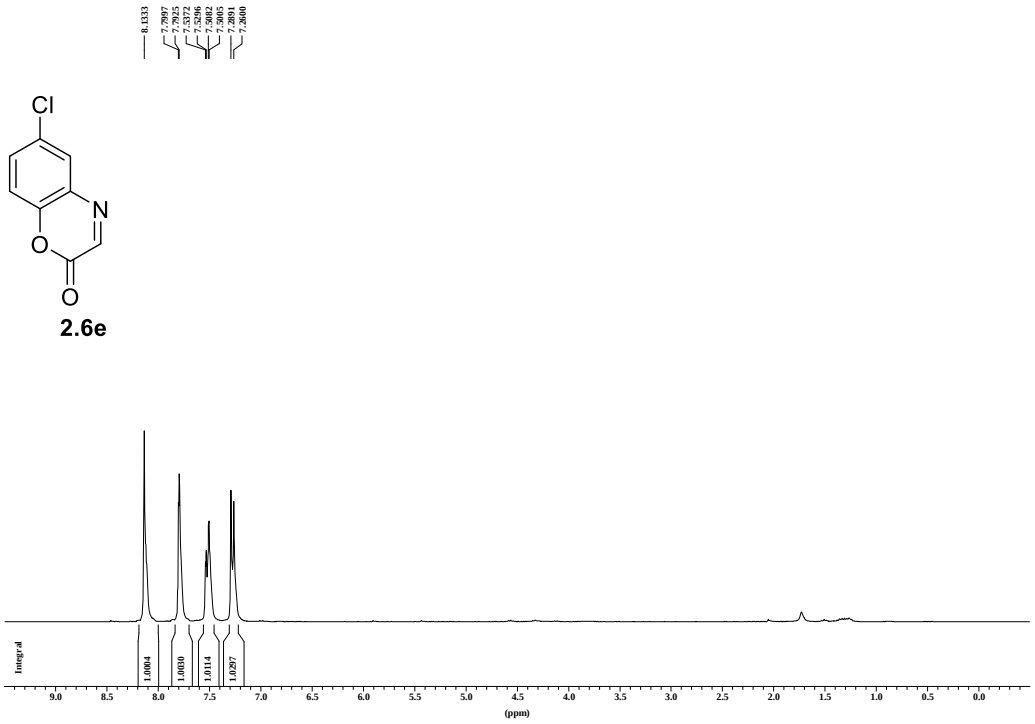

Ph
N
O
O

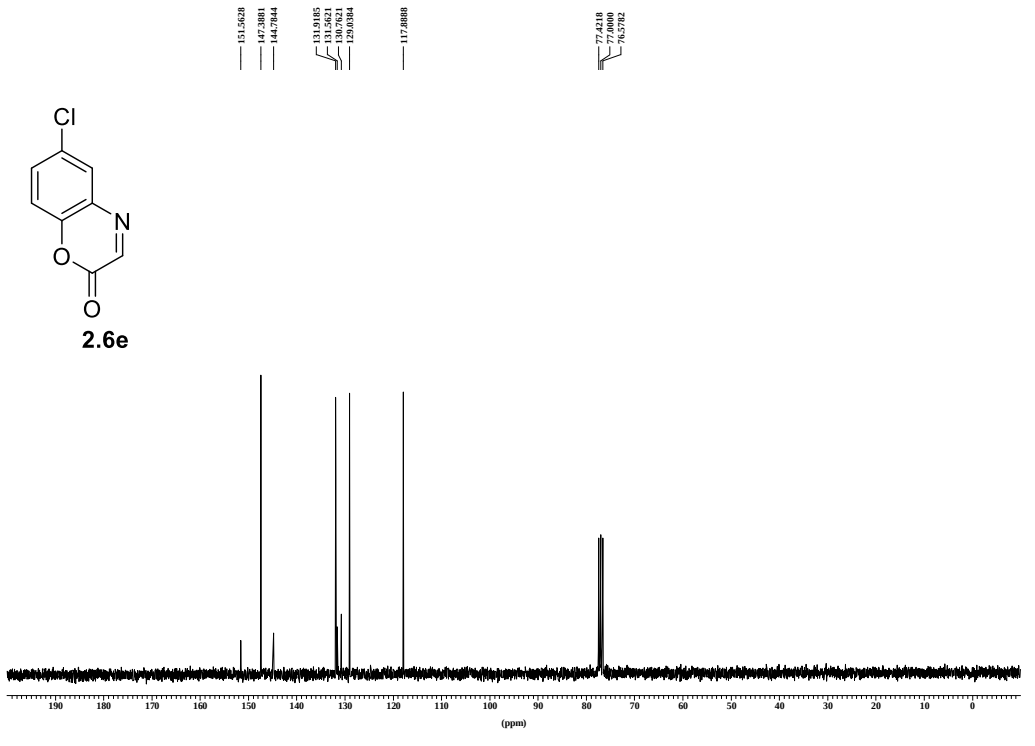
2.6c

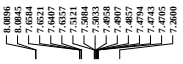

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


8.1337
7.2800
7.2814
7.2789
7.2600
7.1737
7.1564
7.1528
7.1478
3.9077
1.6069
OMe
N
O
O
2.6d
Integral
0.9292
2.0000
1.0046
3.0008
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
(ppm)


156.9780
152.5409
146.6090
140.3346
131.5168
119.9081
117.2919
111.5276
77.2551
77.0000
76.7449
55.8739
OMe
N
O
O
2.6d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


8.1333
7.7997
7.7925
7.5372
7.5296
7.5082
7.5005
7.2691
7.2600
Cl
N
O
O
2.6e
Integral
1.0004
1.0000
1.0114
1.0297
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
(ppm)


151.5628
147.3081
144.7844
131.9185
131.5621
130.7931
129.0384
117.8888
77.4218
77.0000
76.5782
Cl
N
O
O
2.6e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


8.0896
8.0845
8.0654
7.6621
7.6407
7.6357
7.5131
7.5084
7.5033
7.4958
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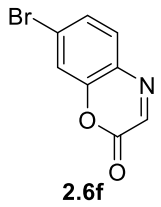
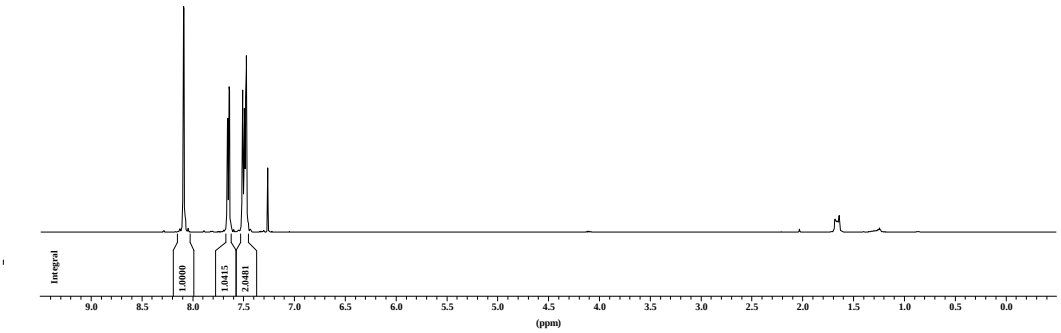
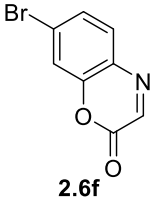
7.4857
7.4754
7.4743
7.4705
7.2600


Br
N
O
O

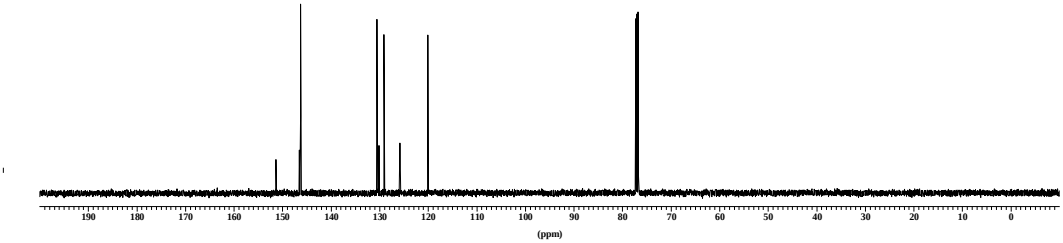
2.6f

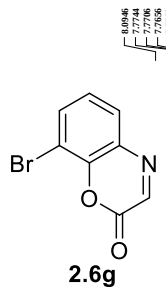

Integral
1.0000
1.0415
2.0481
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


151.3676
146.5361
146.3102
130.5330
130.3340
129.0829
125.8108
120.0465
77.2478
77.0000
76.7449


Br
N
O
O

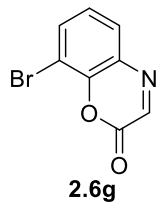
2.6f


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


Br
N
O
O

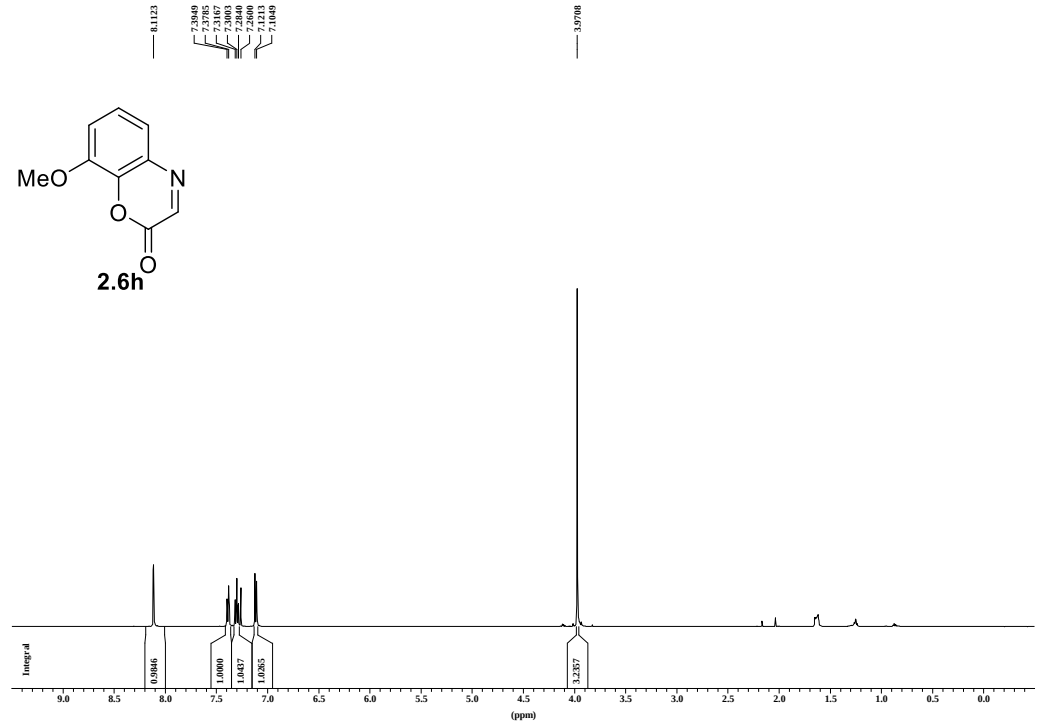
2.6g

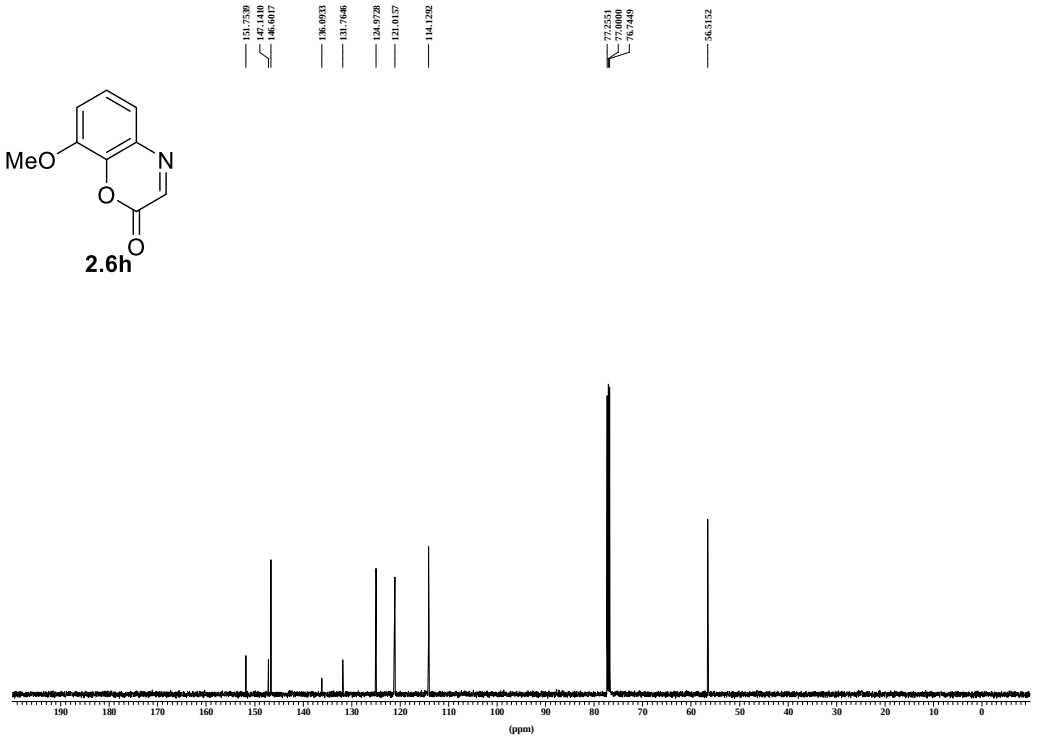
8.0946
7.7744
7.7706
7.7636
7.7580
7.7535
7.7482
7.2940
7.2789
7.2625
Integral
1.0000
2.0433
1.1054
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

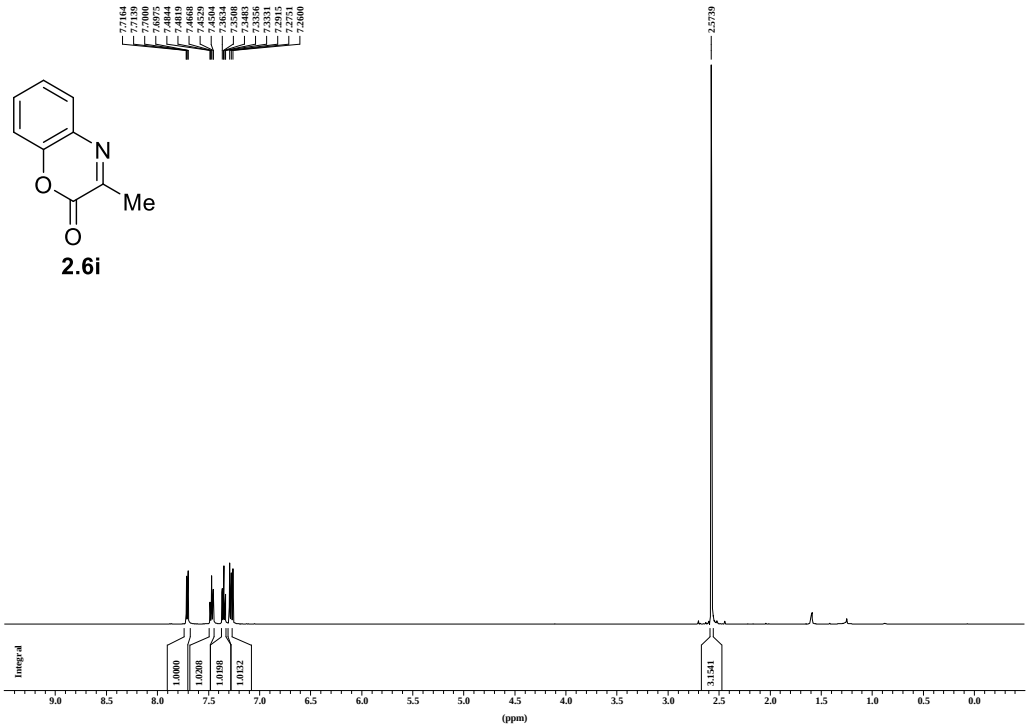

Br
N
O
O

2.6g

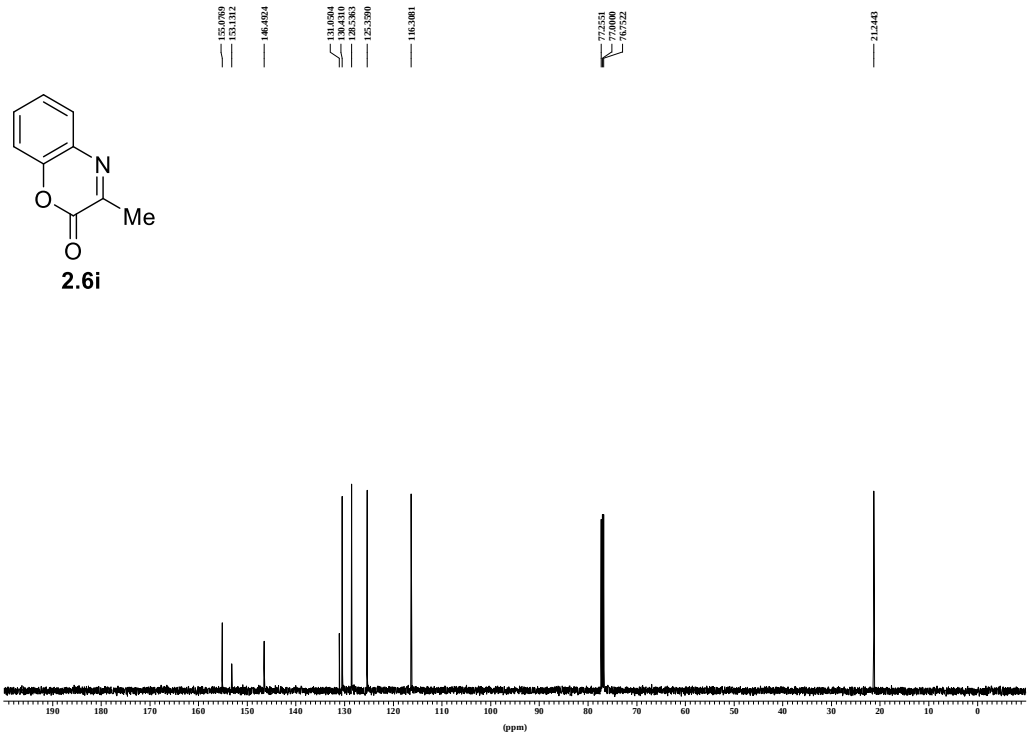
151.3749
146.7329
143.6576
135.4739
132.0998
128.8788
126.0950
109.9535
77.2551
77.0000
76.7449
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


8.1123
7.3948
7.3785
7.3167
7.3003
7.2840
7.2680
7.1215
7.1049
3.9708
MeO
N
O
O
2.6h
Integral
0.9846
1.0000
1.0437
1.0265
3.2357
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
(ppm)


151.7539
147.1410
146.6017
136.0933
131.7646
124.9728
121.0157
114.1292
77.2551
77.0000
76.7449
56.5152
MeO
N
O
O
2.6h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

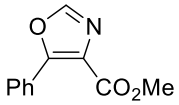

7.7164
7.7139
7.7000
7.6975
7.4844
7.4819
7.4668
7.4629
7.4484
7.3634
7.3508
7.3483
7.3336
7.3311
7.2915
7.2751
7.2600
2.5739
N
O
O
Me
Integral
1.0000
1.0208
1.0198
1.0132
3.1541
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

2.6i

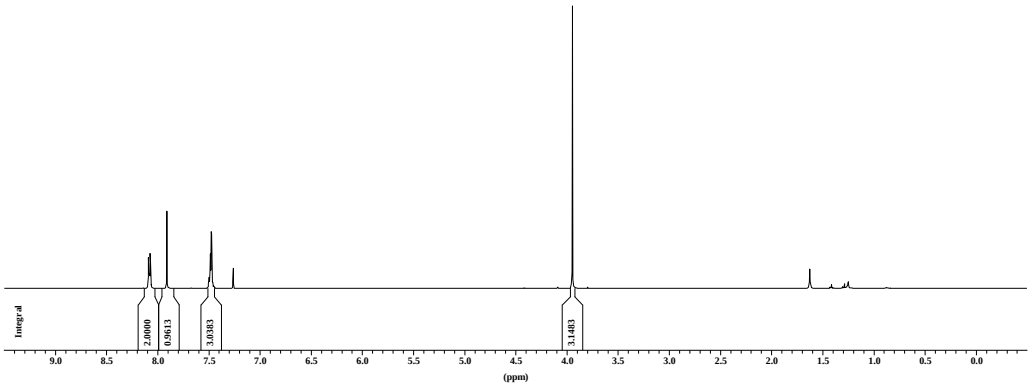

155.0769
153.1312
146.4024
131.0504
130.4310
126.5363
125.5390
116.3081
77.2551
77.0000
76.7522
21.2443
N
O
O
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

2.6i

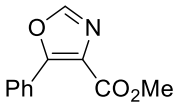

8.0883
8.0833
8.0775
8.0719
8.0681
7.9000
7.4958
7.4932
7.4857
7.4794
7.4743
7.4705
7.4655
7.2600
3.9455


O
N
Ph
CO2Me

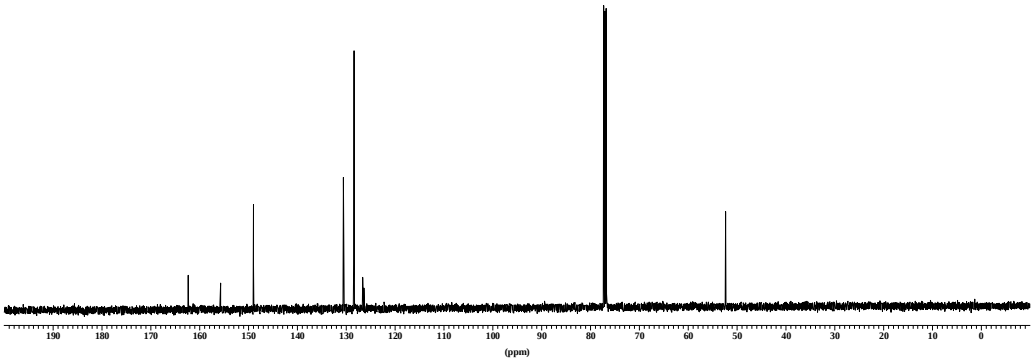
2.3a

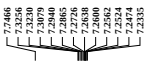

Integral
2.0000
0.9613
3.0383
3.1483
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

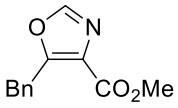

162.3570
155.6818
148.9409
130.5476
128.4707
128.4051
126.6031
126.3428
77.2551
77.0000
76.7522
52.2812


O
N
Ph
CO2Me

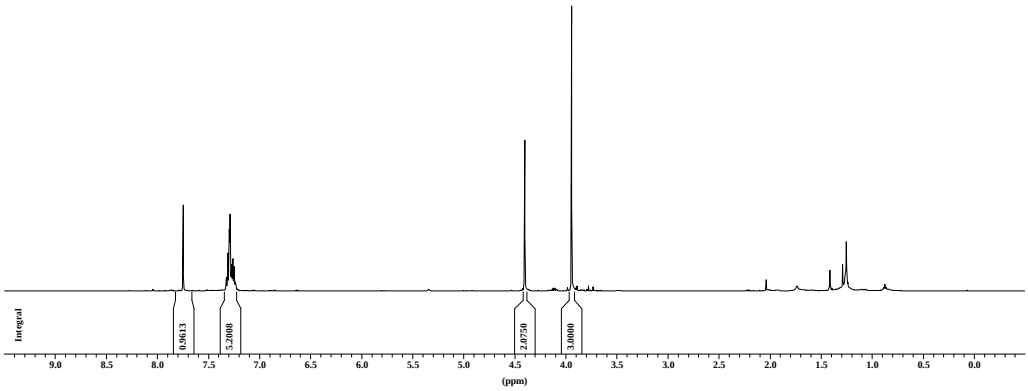
2.3a


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

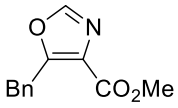

7.7466
7.3256
7.3230
7.3079
7.2940
7.2865
7.2726
7.2638
7.2600
7.2552
7.2524
7.2474
7.2335
4.4019
3.3418


O
N
Bn
CO2Me

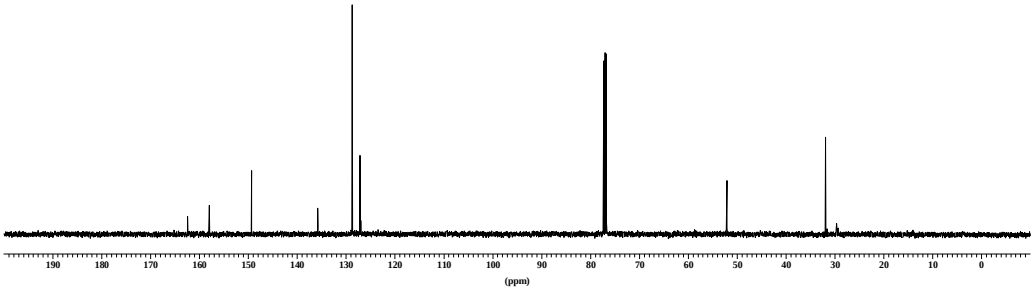
2.3b

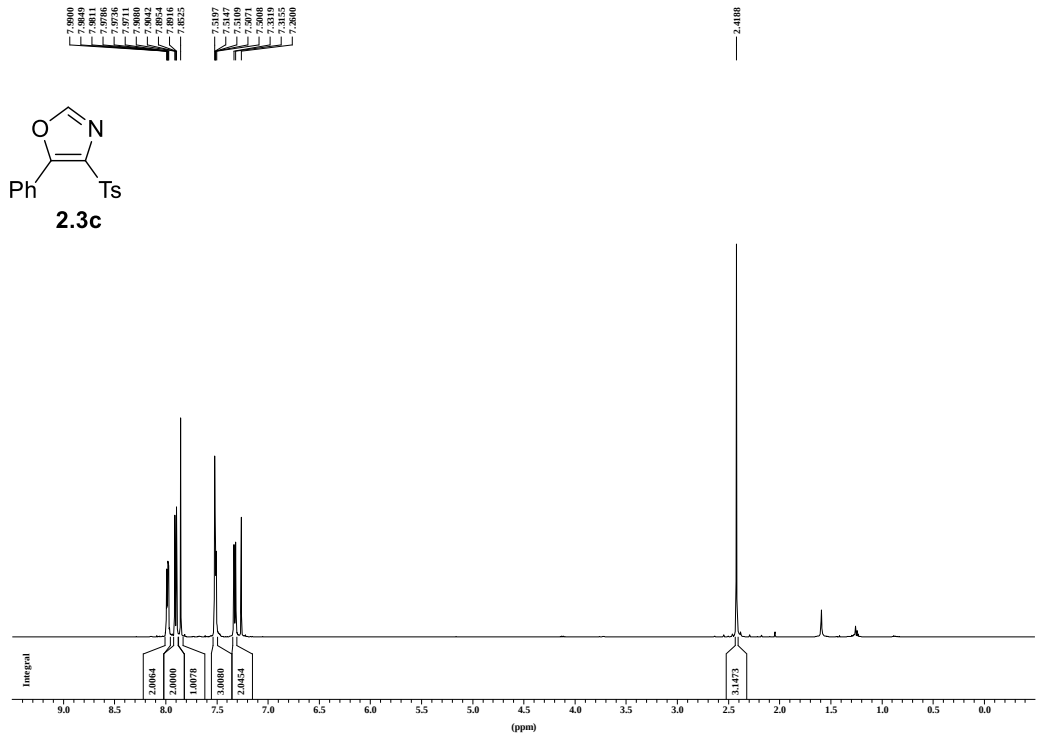

Integral
0.9613
5.2008
2.0750
3.0000
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

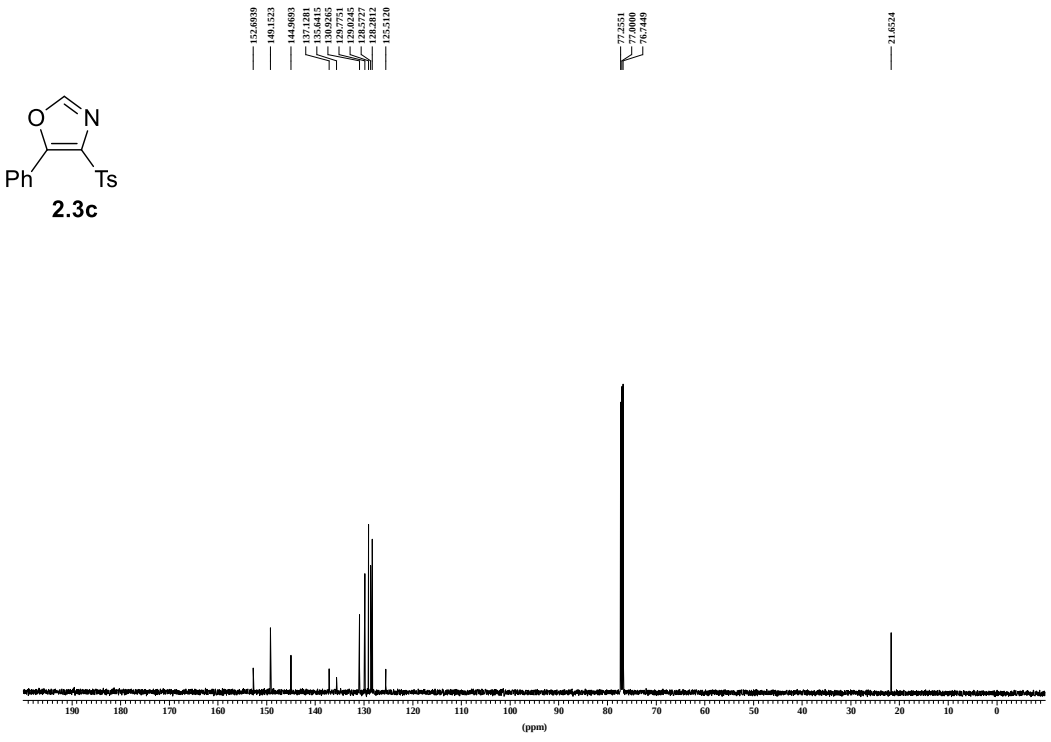

162.3934
157.9918
149.3490
135.8164
128.7330
127.1225
126.9914
77.2551
77.0000
76.7449
52.0626
31.8620

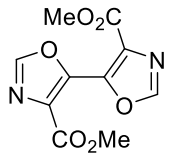

O
N
Bn
CO2Me

2.3b


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

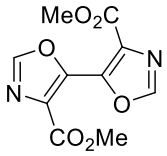

7.8900
7.8849
7.8811
7.8786
7.8736
7.8711
7.8690
7.8642
7.8054
7.8016
7.8525
7.5197
7.5147
7.5109
7.5071
7.5008
7.3319
7.3155
7.2600
2.4188
Ph
Ts
2.3c
Integral
2.0064
2.0000
1.0078
3.0080
2.0454
3.1473
(ppm)


152.6939
140.1523
144.9693
137.1281
135.6415
130.1956
129.7751
129.0245
128.5727
128.2012
125.5120
77.2551
77.0000
76.7449
21.6524
Ph
Ts
2.3c
(ppm)


MeO2C
O
N
N
O
CO2Me

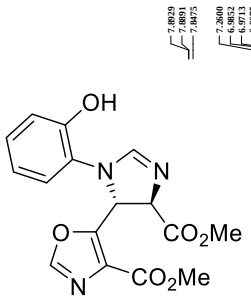
2.5

8.0770
7.3600
3.8749
Integral
2.0000
6.2746
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
(ppm)


MeO2C
O
N
N
O
CO2Me

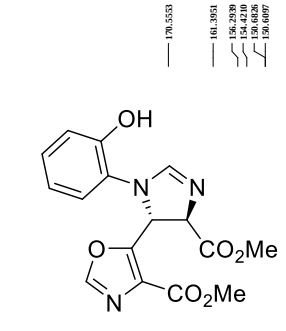
2.5

160.5643
151.6664
141.4131
132.9524
77.2551
77.0000
76.7522
52.5581
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


OH
N
N
O
CO2Me
N
CO2Me

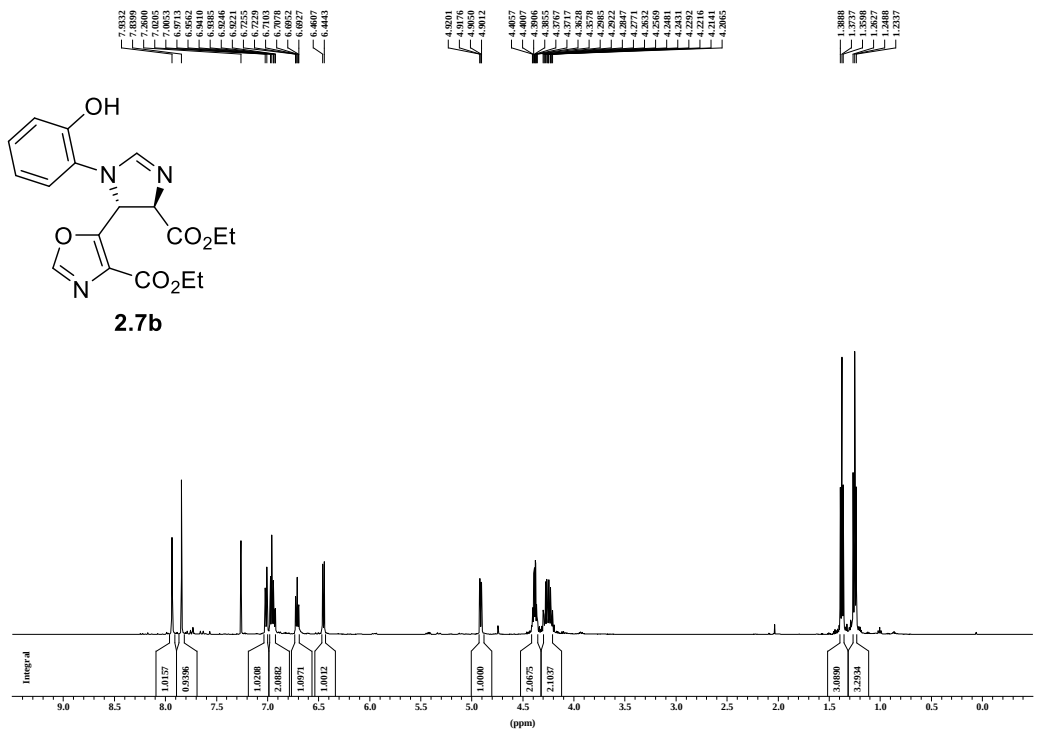
2.7a

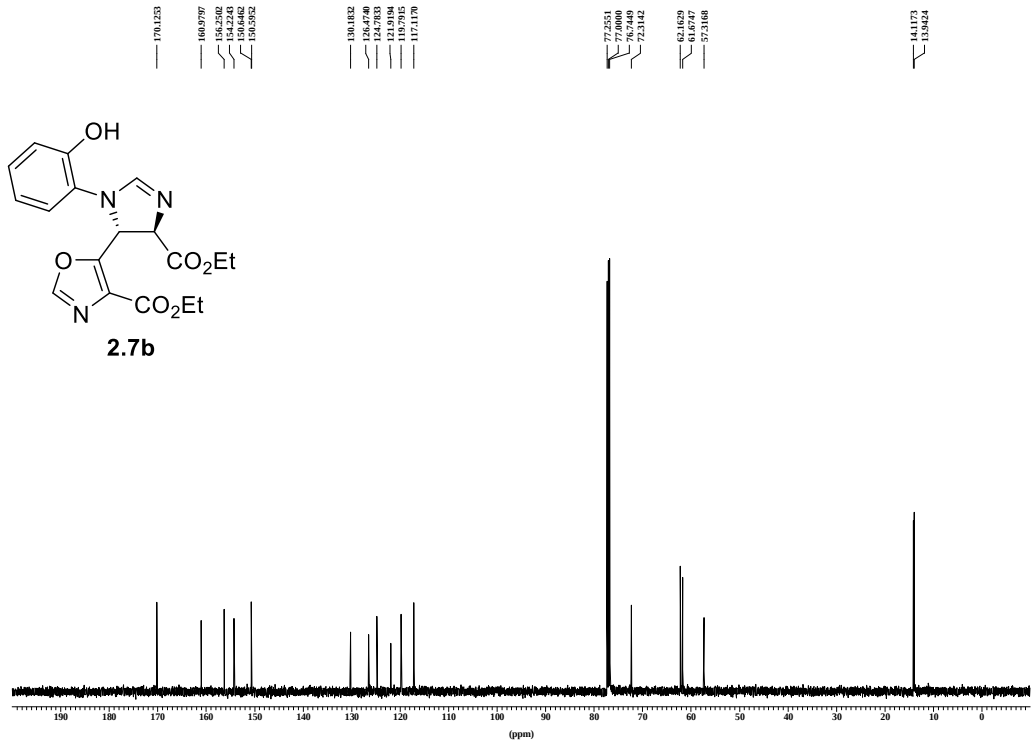
7.8929
7.8891
7.8475
7.3600
6.9832
6.9713
6.9675
6.9574
6.9433
6.9049
6.7292
6.7255
6.7116
6.6890
6.6852
6.4544
6.4393
4.9440
4.9403
4.9399
4.9251
3.8951
3.7791
integral
1.0042
0.9879
3.1455
1.0621
0.9999
1.0000
3.1151
3.1206
(ppm)

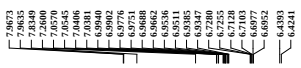

OH
N
N
O
CO2Me
N
CO2Me

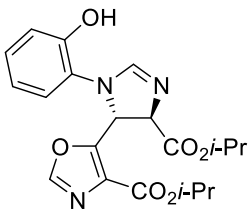
2.7a

170.5553
161.3951
156.2939
154.4210
150.6826
150.6097
129.8917
126.6343
124.7541
122.1744
119.9643
117.6507
77.2551
77.0000
76.7449
72.2413
57.3460
52.9225
52.4051
(ppm)

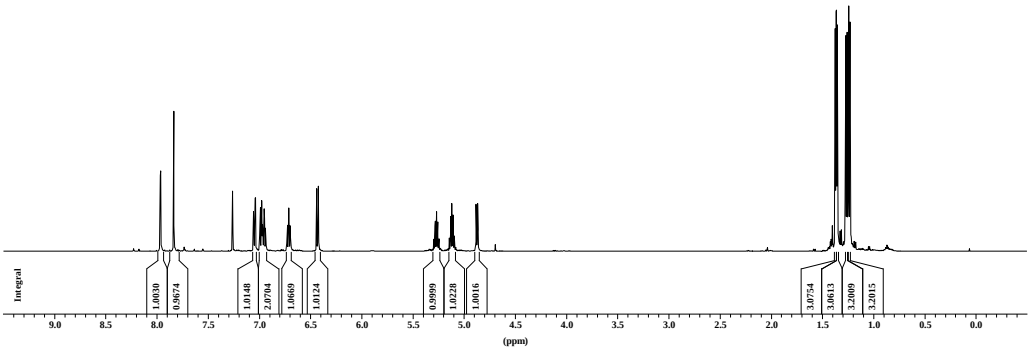

7.8332
7.8399
7.3600
7.0205
7.0053
6.9751
6.8562
6.8410
6.8385
6.8246
6.8241
6.7255
6.7229
6.7103
6.6978
6.6852
6.6927
6.4607
6.4443
4.8201
4.8076
4.8050
4.8012
4.4057
4.4007
4.3906
4.3855
4.3707
4.3717
4.3628
4.3578
4.2985
4.2932
4.2847
4.2771
4.2632
4.2589
4.2481
4.2431
4.2292
4.2216
4.2141
4.2065
1.3888
1.3737
1.3588
1.2627
1.2488
1.2337
OH
N
N
O
CO2Et
N
CO2Et
2.7b
Integral
1.0157
0.9396
1.0208
2.0082
1.0971
1.0012
1.0000
2.0675
2.1037
3.0890
3.2934
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
(ppm)

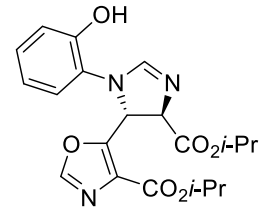

170.1253
160.9797
156.2502
154.2243
150.6462
150.5952
130.1832
126.4740
124.7833
121.5934
118.3795
117.1170
77.2551
77.0000
76.7449
72.3142
62.1629
61.6747
57.3168
14.1173
13.9424
OH
N
N
O
CO2Et
N
CO2Et
2.7b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)



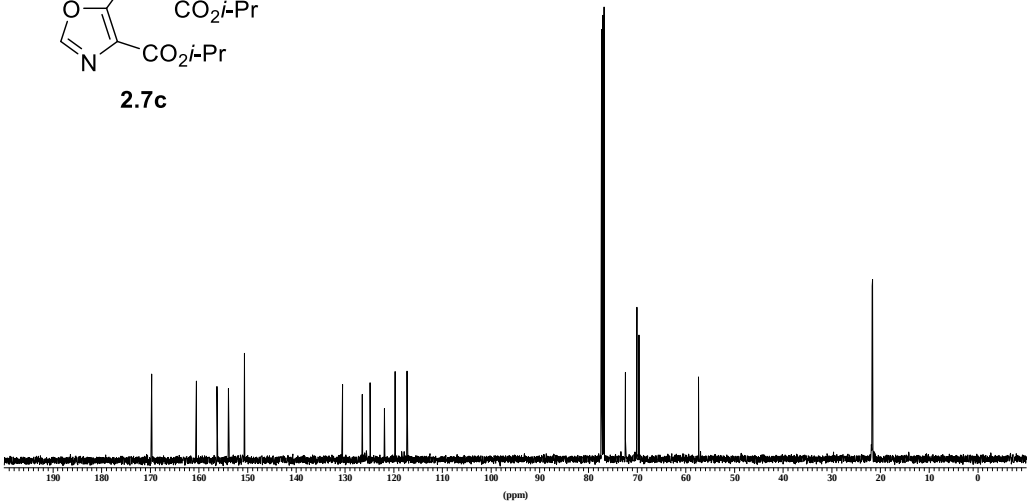


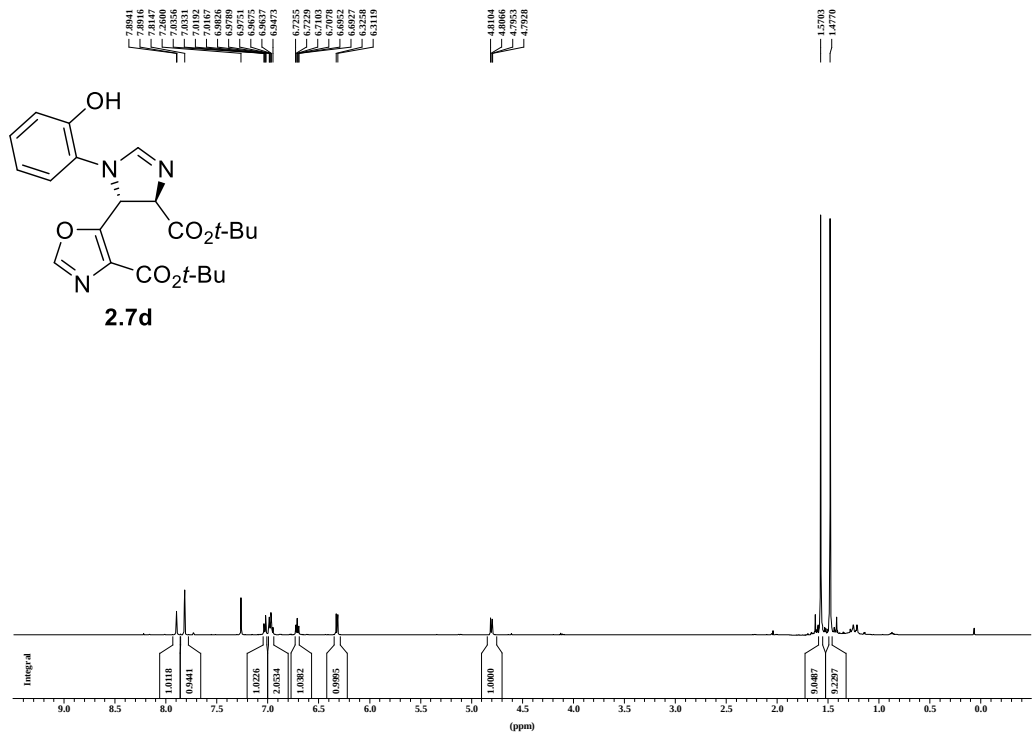
2.7c


Integral
1.0030
0.9674
1.0148
2.0704
1.0669
1.0124
0.9999
1.0228
1.0016
3.0754
3.0613
3.2009
3.2015
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
(ppm)



2.7c


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)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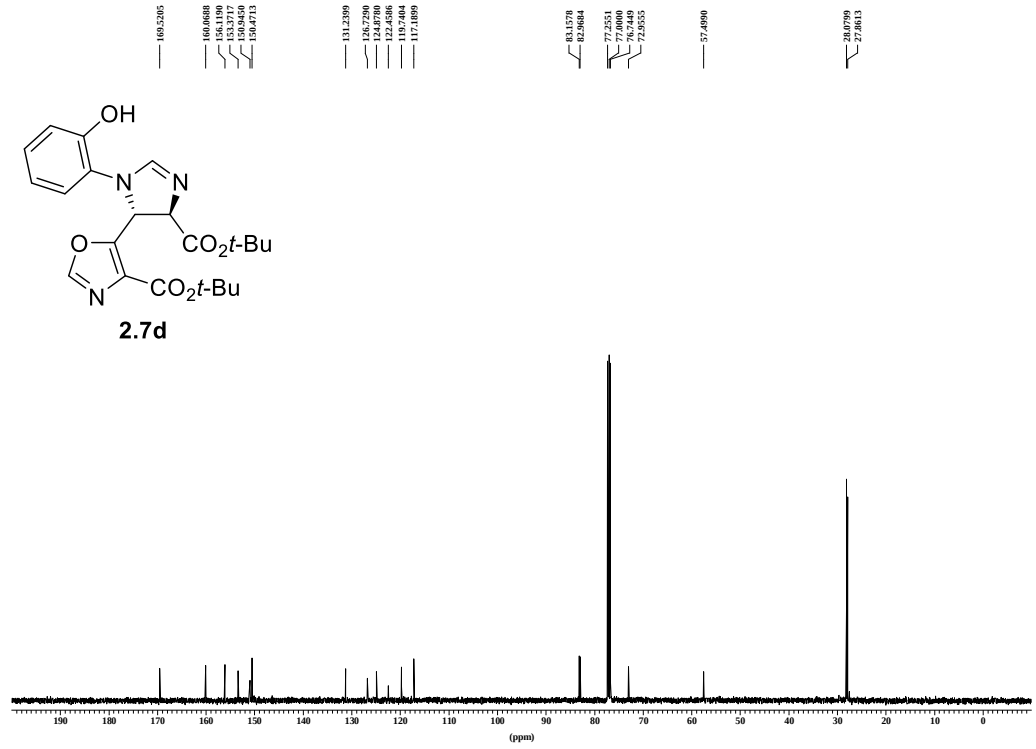
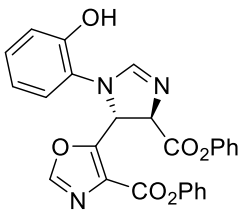
7.8916
7.8147
7.2600
7.0356
7.0331
7.0192
7.0165
6.9826
6.9780
6.9751
6.8675
6.8657
6.8473
6.7255
6.7229
6.7101
6.7078
6.6952
6.6927
6.3258
6.3119
4.8104
4.8066
4.7955
4.7928
1.5703
1.4770
OH
N
N
O
N
CO2t-Bu
CO2t-Bu
Integral
1.0118
0.9441
1.0226
2.0834
1.0382
0.9995
1.0000
9.0487
9.2297
9.0
8.5
8.0
7.5
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
(ppm)

2.7d


169.5205
160.0688
156.1190
153.3717
150.9450
150.4713
131.2399
126.7290
124.8780
123.4586
119.7404
117.1899
83.1578
82.3684
77.2551
77.0000
76.7449
72.5555
57.4990
28.0799
27.8613
OH
N
N
O
N
CO2t-Bu
CO2t-Bu
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

2.7d



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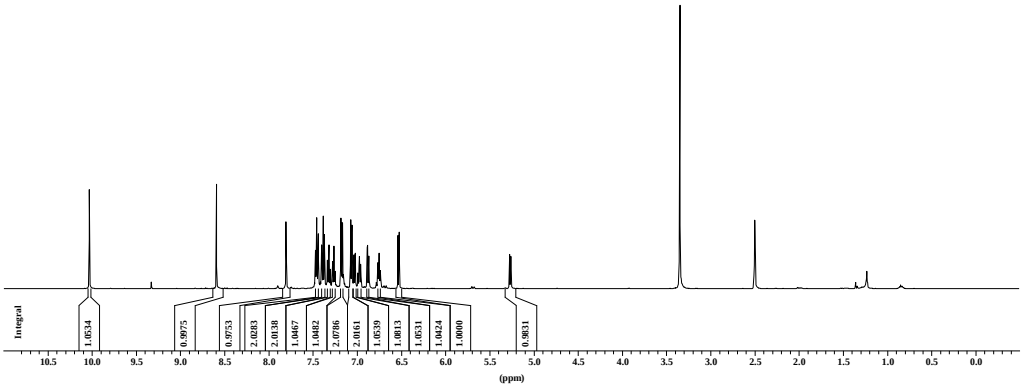
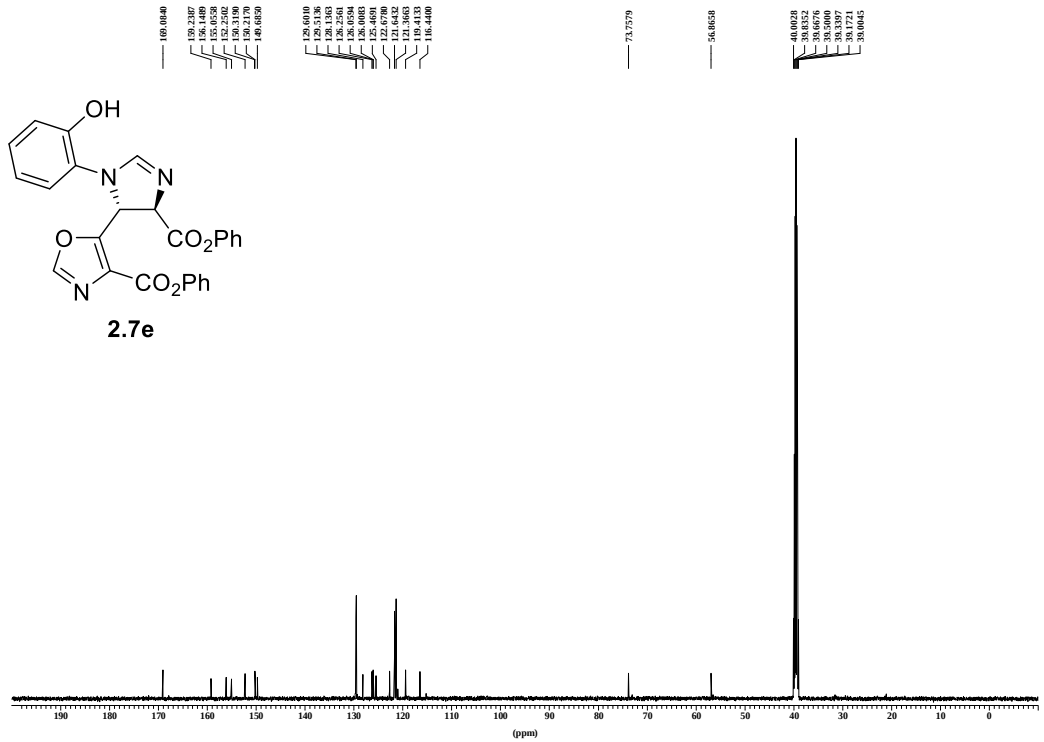
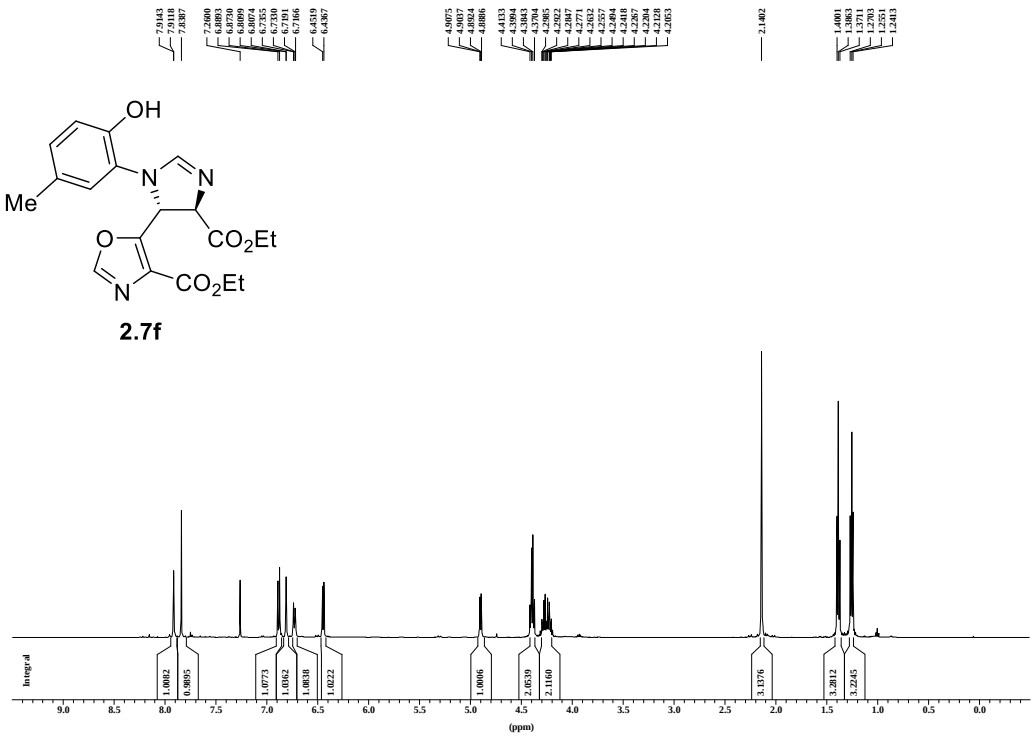
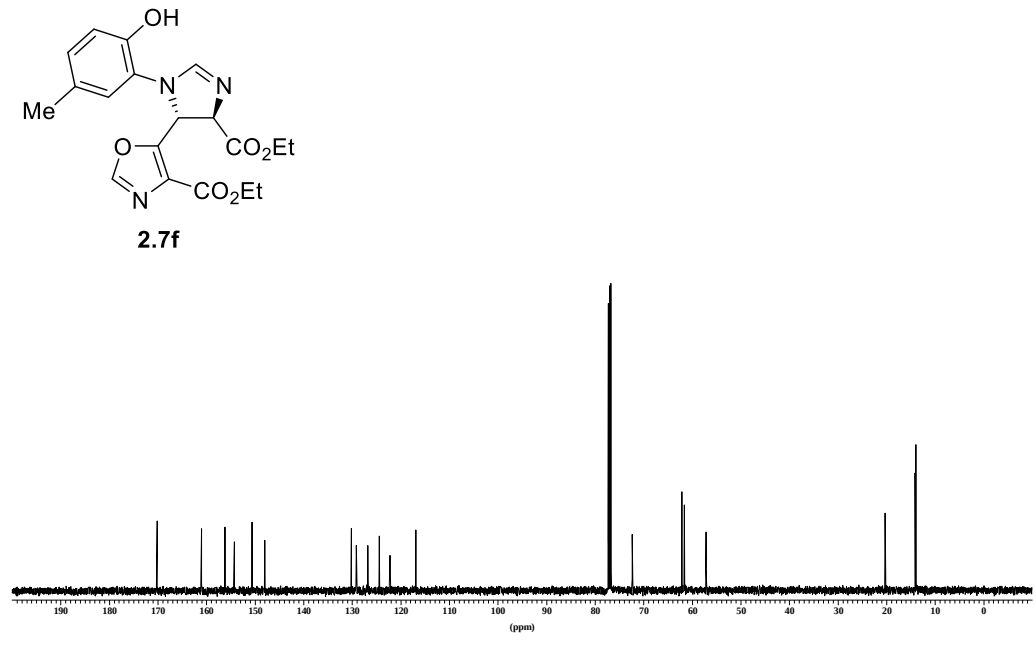
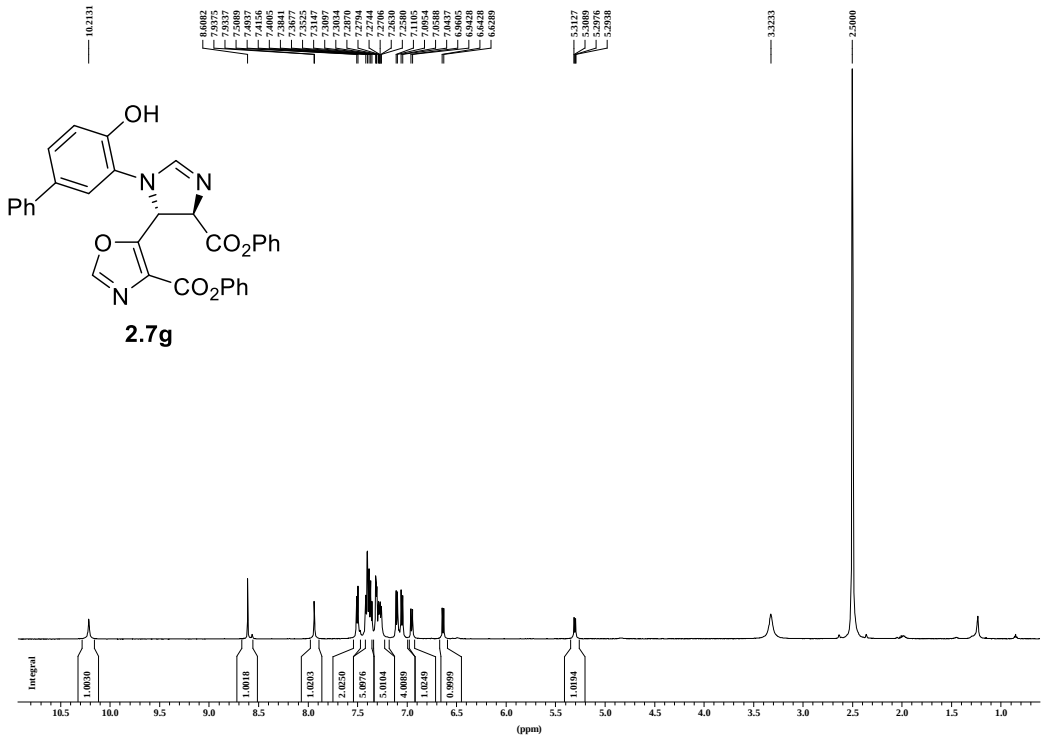


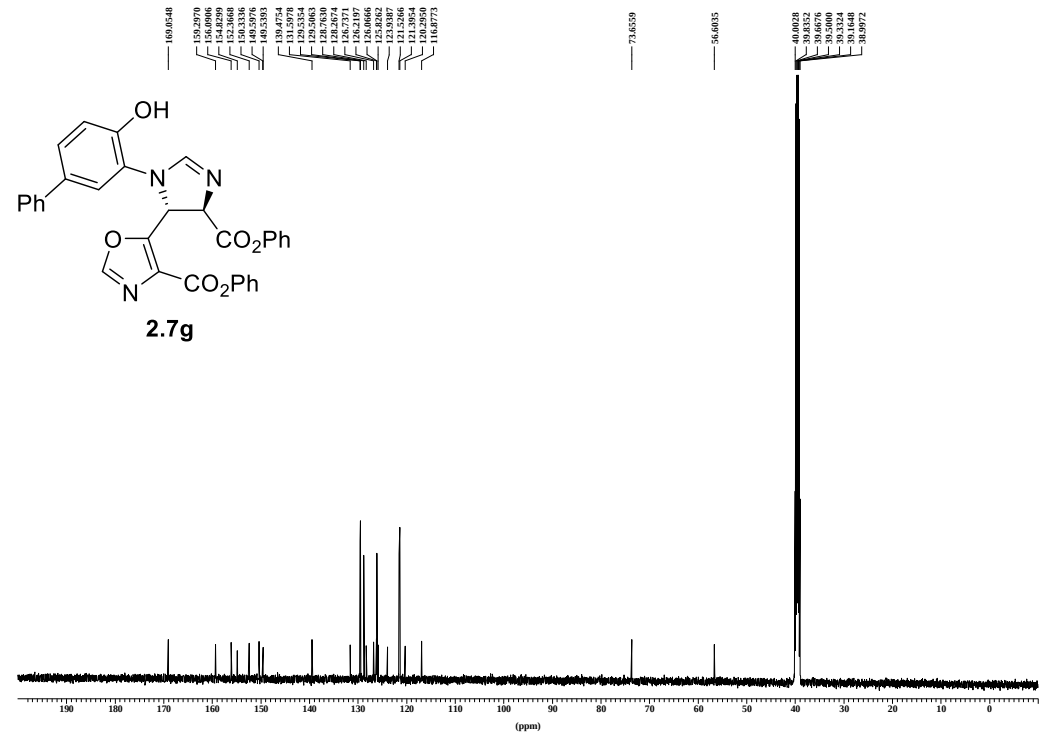


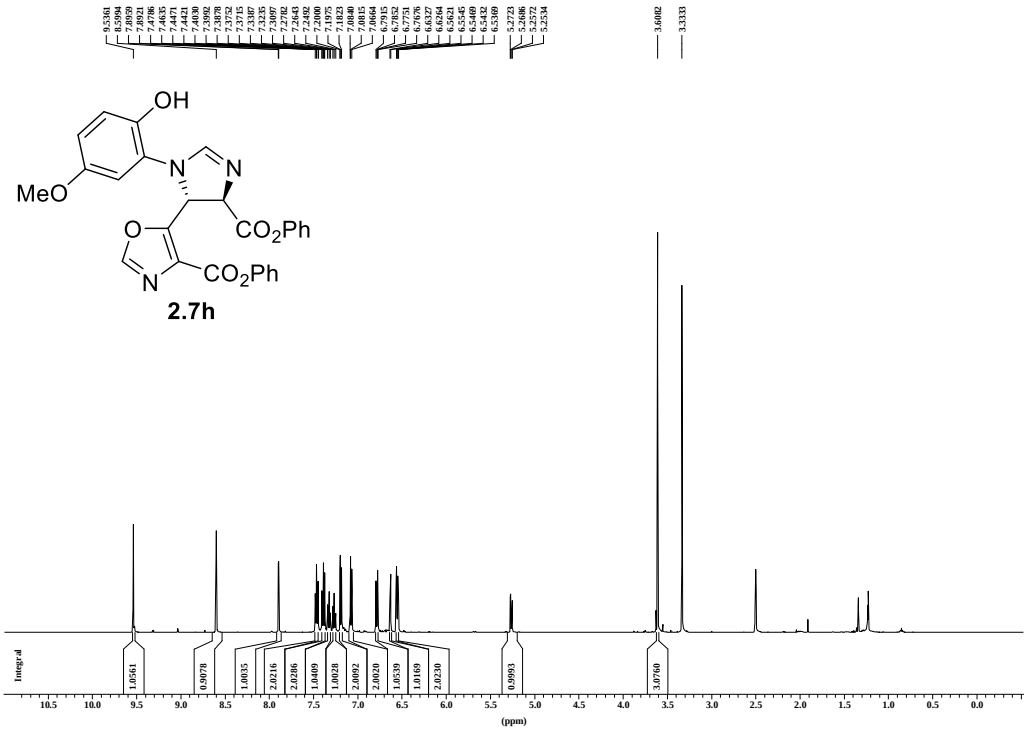
2.7e

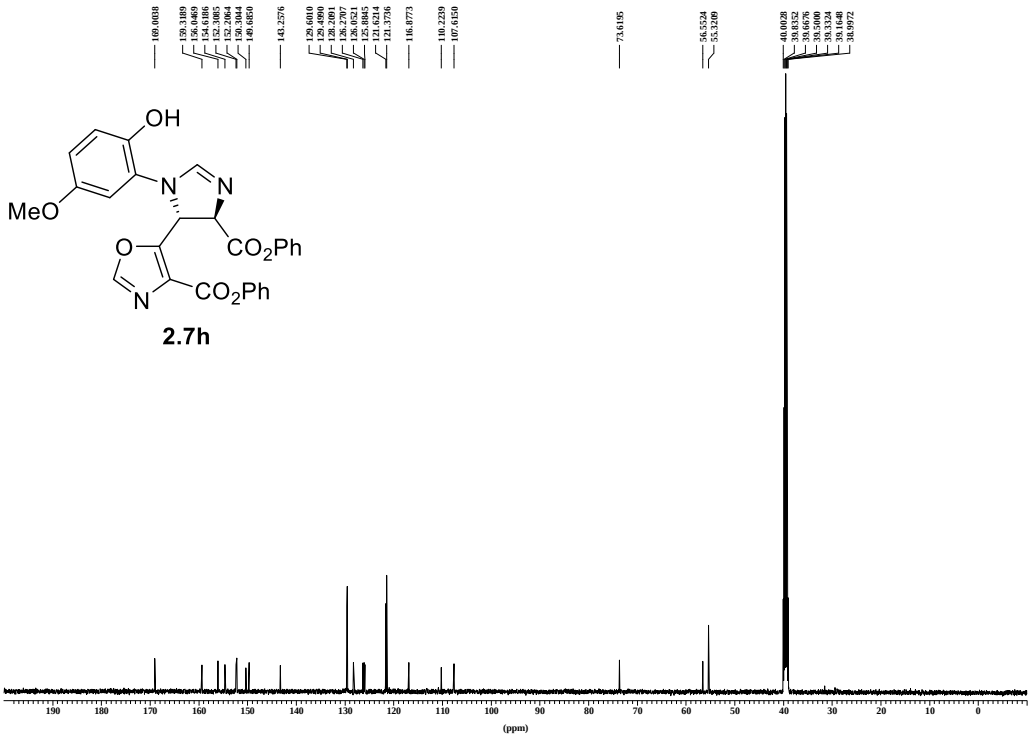

OH
Me
N
N
O
N
CO2Et
CO2Et
2.7f
Integral
1.0082
0.9895
1.0773
1.0362
1.0838
1.0322
1.0006
2.0539
2.1160
3.1376
3.2812
3.2245
(ppm)

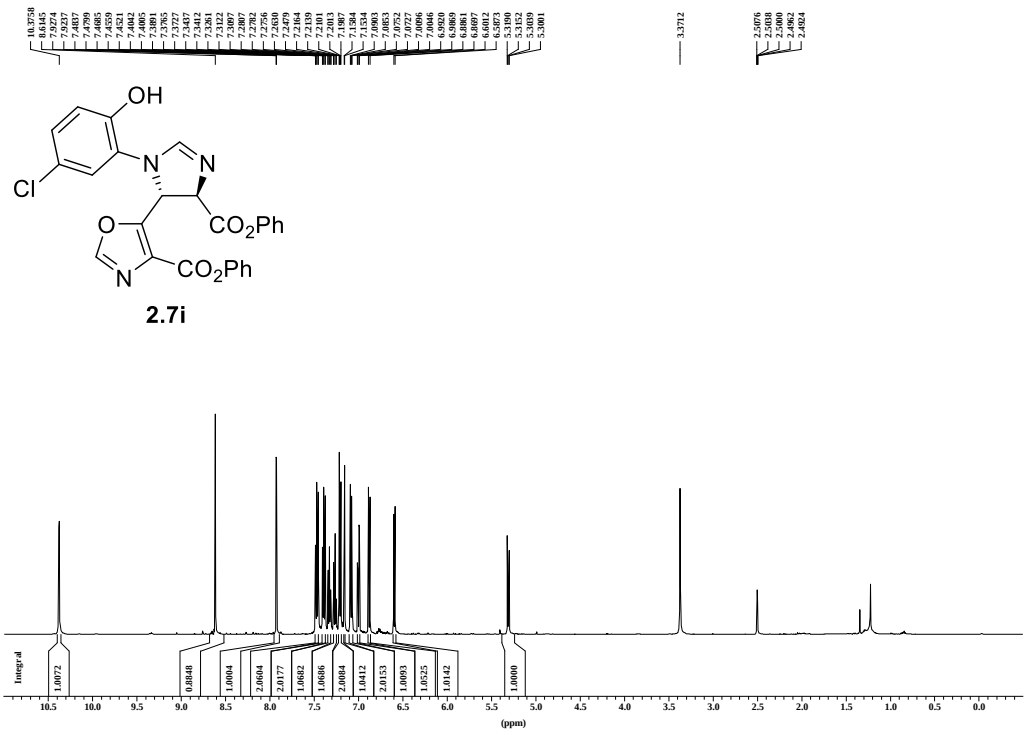

OH
Me
N
N
O
N
CO2Et
CO2Et
2.7f
(ppm)


10.2131
8.6082
8.0375
7.9337
7.5089
7.4937
7.4156
7.4001
7.3841
7.3677
7.3525
7.3147
7.3000
7.2870
7.2794
7.2744
7.2706
7.2630
7.2580
7.1105
7.0954
7.0850
7.0437
6.9605
6.9428
6.4218
6.4209
5.3127
5.3089
5.2976
5.2938
3.3233
2.5000
OH
Ph
N
N
O
N
CO2Ph
CO2Ph
2.7g
Integral
1.0030
1.0018
1.0003
2.0250
5.0976
5.0104
4.0089
1.0249
0.9999
1.0394
(ppm)

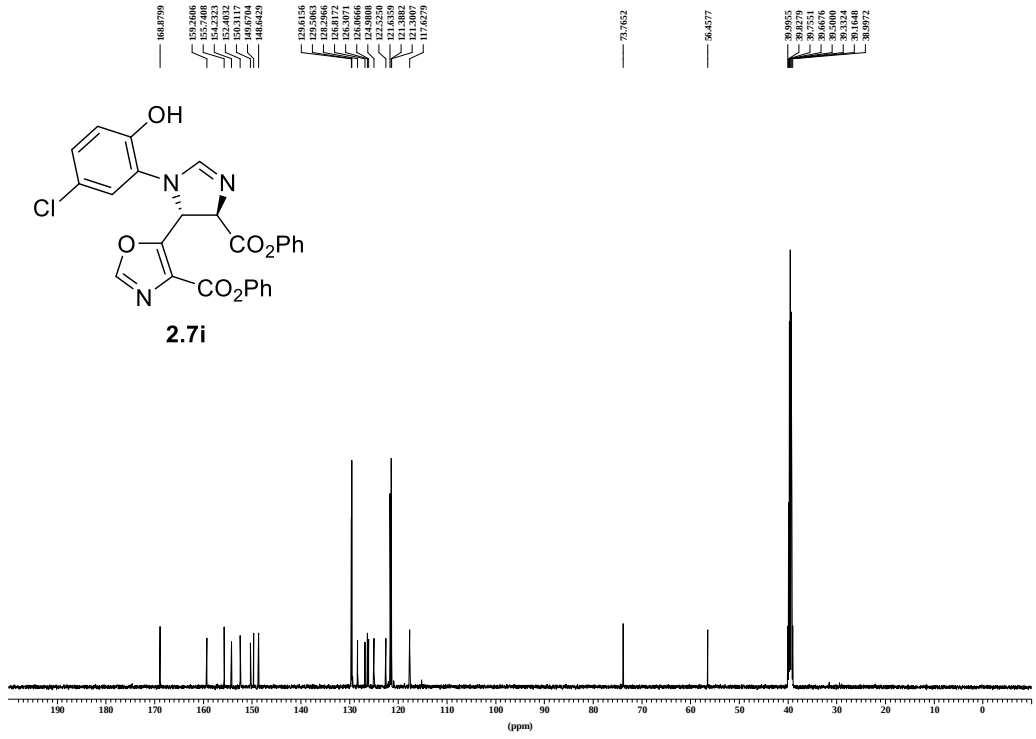

169.0548
159.2970
156.0906
154.8299
152.3668
150.1636
149.5976
149.5393
139.4754
131.5978
129.5354
128.9565
128.7630
128.2674
126.7371
126.2197
125.8466
125.8262
123.9387
121.5266
121.3954
120.9993
116.8773
73.6559
56.6035
40.0028
39.8352
39.6676
39.5000
39.3324
39.1648
38.9972
OH
Ph
N
N
O
N
CO2Ph
CO2Ph
2.7g
(ppm)


OH
MeO
N
N
O
N
CO2Ph
CO2Ph
2.7h
Integral
(ppm)

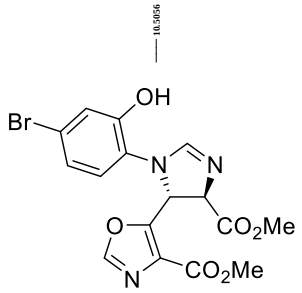

OH
MeO
N
N
O
N
CO2Ph
CO2Ph
2.7h
(ppm)


10.3758
8.6145
7.9274
7.9237
7.4457
7.4399
7.4085
7.4059
7.4021
7.4042
7.4006
7.3891
7.3765
7.3727
7.3437
7.3412
7.3261
7.3122
7.3097
7.2907
7.2702
7.2756
7.2630
7.2479
7.2364
7.2139
7.2101
7.1987
7.1784
7.1534
7.0903
7.0853
7.0752
7.0727
7.0096
7.0046
6.9920
6.9869
6.9804
6.8697
6.6012
6.5873
5.3159
5.3152
5.3039
5.3001
3.3712
2.5076
2.5038
2.5000
2.4962
2.4824
OH
Cl
N
N
O
N
CO2Ph
CO2Ph
Integral
1.0072
0.8848
1.0004
2.0604
2.0177
1.0682
1.0686
2.0084
1.0412
2.0153
1.0093
1.0525
1.0142
1.0000
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
(ppm)

2.7i

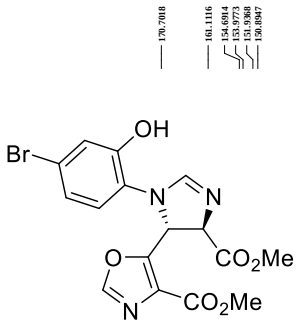

168.8799
159.2606
155.7408
154.2323
152.4032
150.3117
149.7704
148.6429
129.6156
129.5063
128.2966
126.8172
126.5471
126.0666
124.9808
122.5250
121.6359
121.3682
121.3007
117.6279
73.7652
56.4577
39.9955
39.8279
39.7551
39.6876
39.5000
39.3324
39.1648
38.9972
OH
Cl
N
N
O
N
CO2Ph
CO2Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

2.7i


OH
Br
N
N
O
N
CO2Me
CO2Me

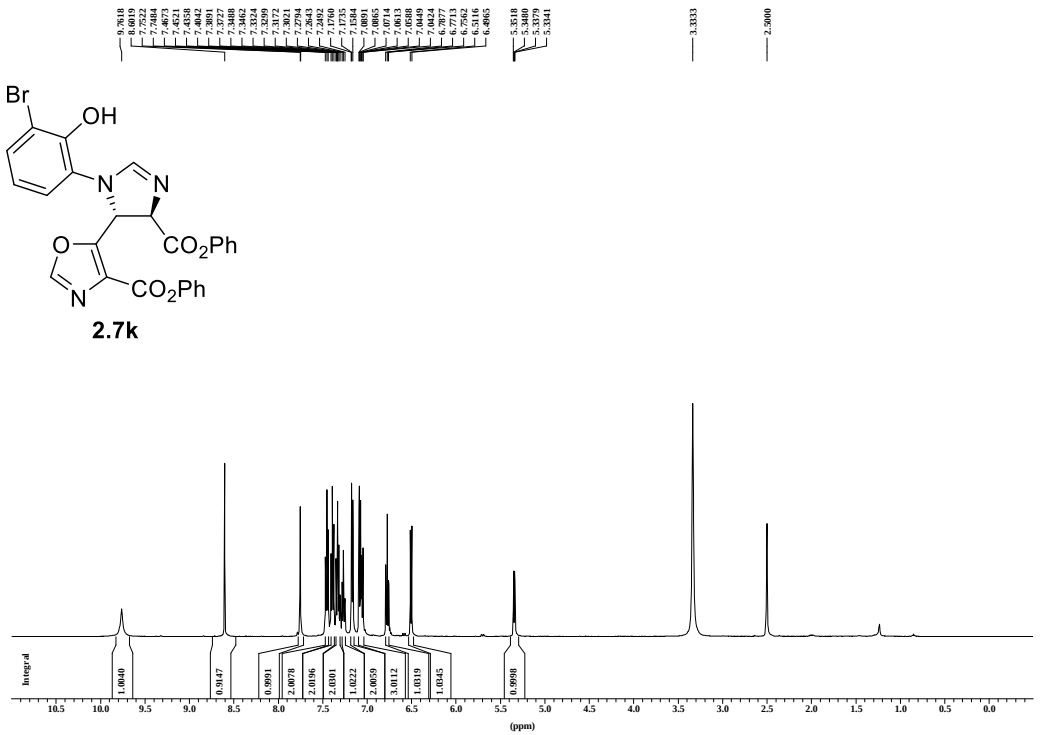
2.7j

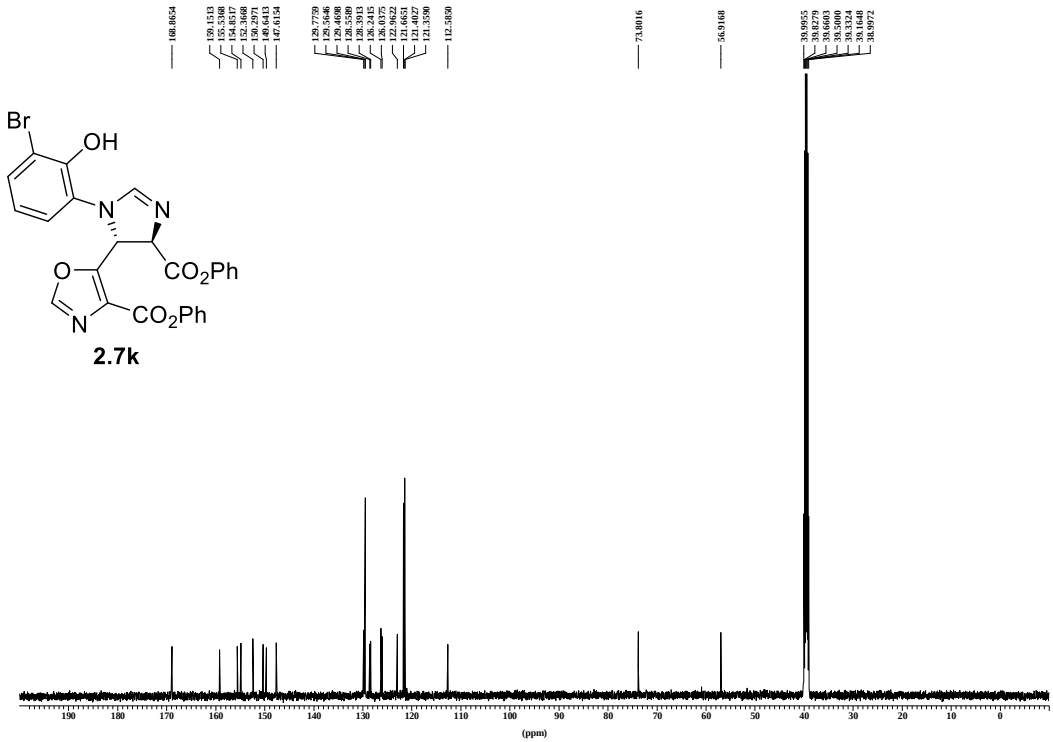
10.5056
8.4330
7.7371
6.9731
6.8798
6.2608
6.2456
4.8676
4.8525
3.7098
3.7179
3.5510
2.5000
Integral
1.0196
0.9375
1.0125
1.0225
2.0396
1.0205
1.0000
3.0611
3.0603
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

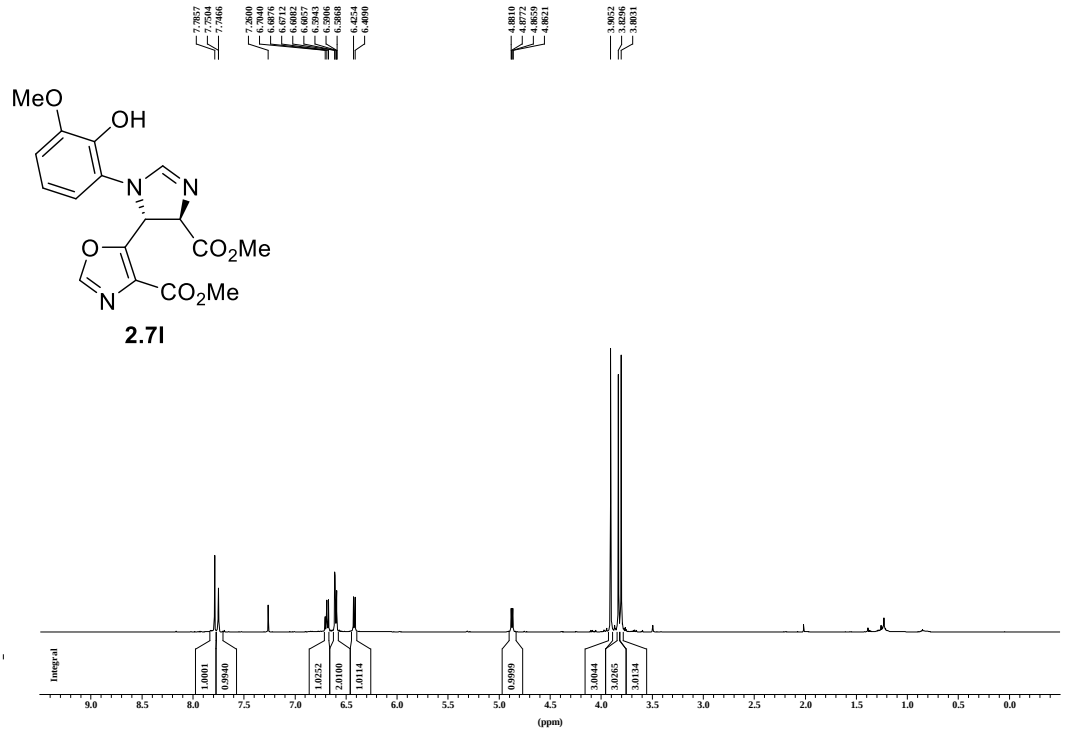

OH
Br
N
N
O
N
CO2Me
CO2Me

2.7j

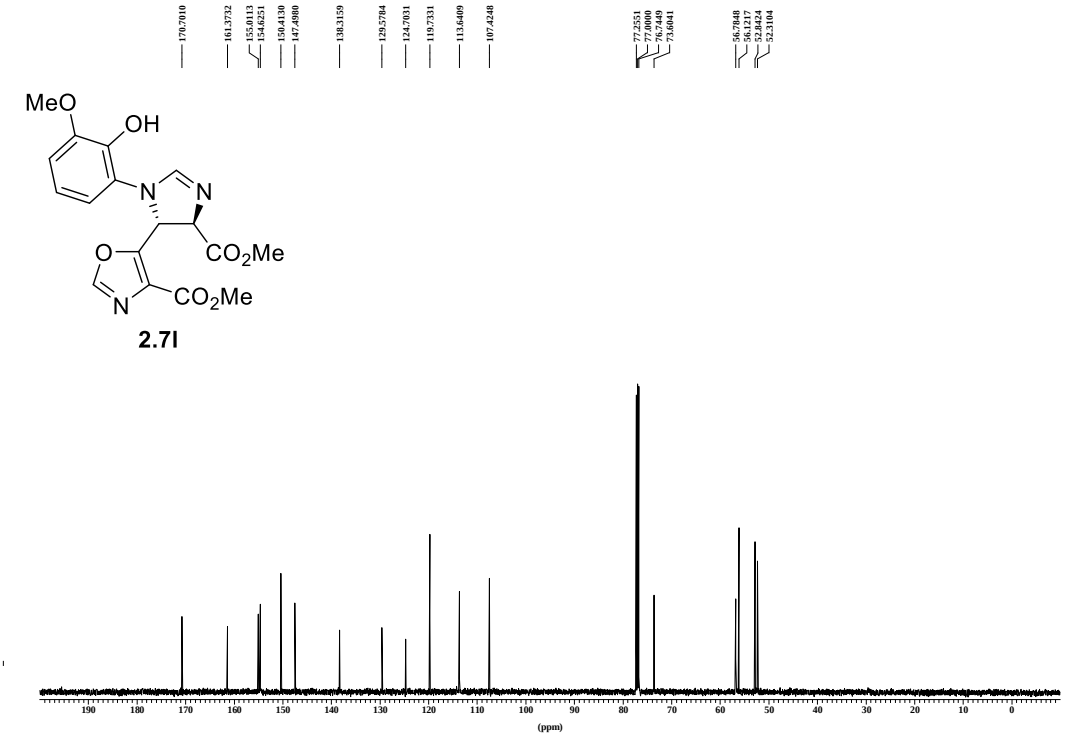
170.7018
161.1116
154.6914
153.9773
151.9368
130.8947
128.5371
125.3452
123.3339
122.0149
118.7866
116.6659
73.4664
56.4869
52.3622
51.9541
40.0028
39.8352
39.6676
39.5000
39.3324
39.1648
38.9972
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


9.7618
8.6019
7.7522
7.7484
7.4655
7.4521
7.4458
7.4042
7.3891
7.3727
7.3488
7.3462
7.3324
7.3199
7.3172
7.3021
7.2794
7.2643
7.2193
7.1760
7.1735
7.1594
7.0891
7.0866
7.0714
7.0613
7.0588
7.0449
7.0341
6.7877
6.7713
6.7562
6.5416
6.4865
5.3518
5.3480
5.3379
5.3341
3.3333
2.5000
Br
OH
N
N
O
CO2Ph
N
CO2Ph
2.7k
Integral
1.0040
0.9147
0.9991
2.0078
2.0196
2.0001
1.0222
2.0059
3.0112
1.0019
1.0345
0.9998
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
(ppm)


168.8654
139.1513
155.5368
134.8517
132.3698
130.2971
149.6413
147.6154
129.7739
129.5446
129.4698
128.5589
128.3913
126.2415
126.1115
122.9622
121.6651
121.4027
121.3390
112.5850
73.8016
56.9168
39.9955
39.8279
39.6603
39.5000
39.3324
39.1648
38.9972
Br
OH
N
N
O
CO2Ph
N
CO2Ph
2.7k
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


7.7857
7.7594
7.7046
7.3600
6.7040
6.6876
6.6712
6.6082
6.6077
6.5943
6.5906
6.5868
6.4254
6.4090
4.8810
4.8772
4.8659
4.8621
3.9052
3.8296
3.8031
MeO
OH
N
N
O
CO2Me
N
CO2Me
Integral
1.0001
0.9940
1.0252
2.0100
1.0114
0.9999
3.0044
3.0265
3.0134
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
(ppm)

2.7l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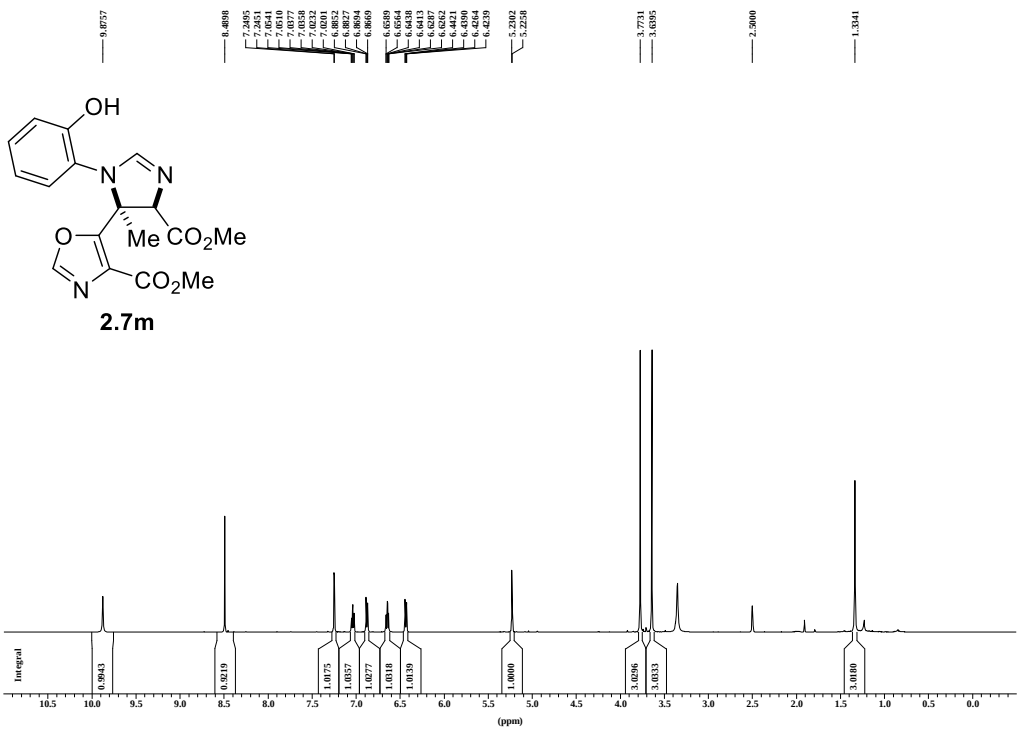
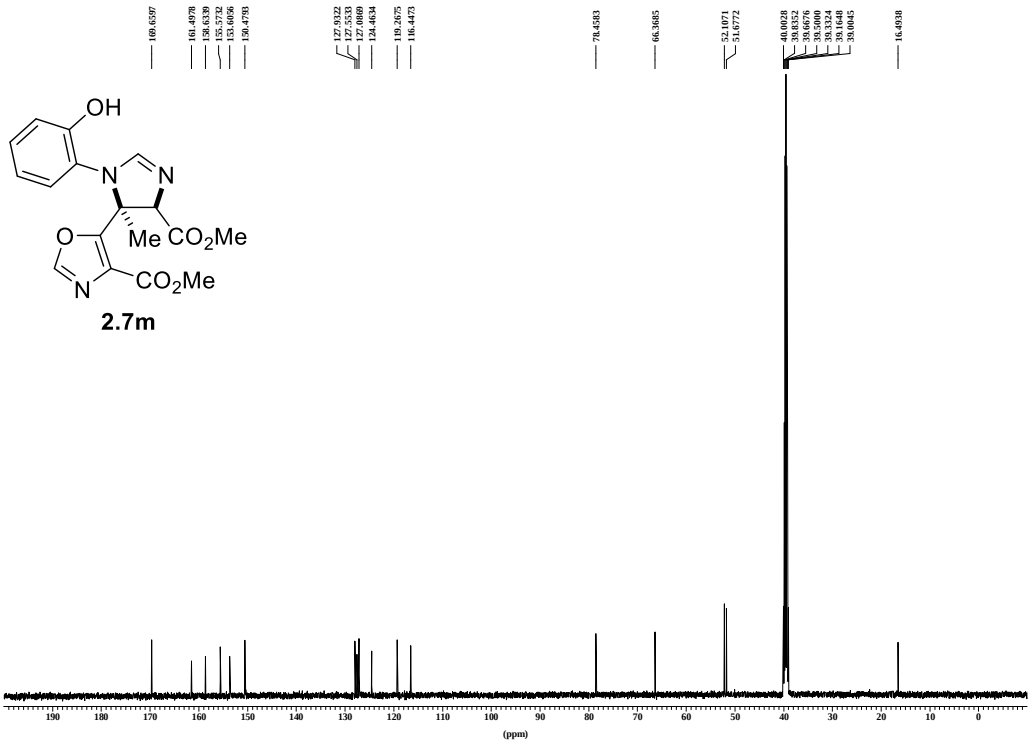
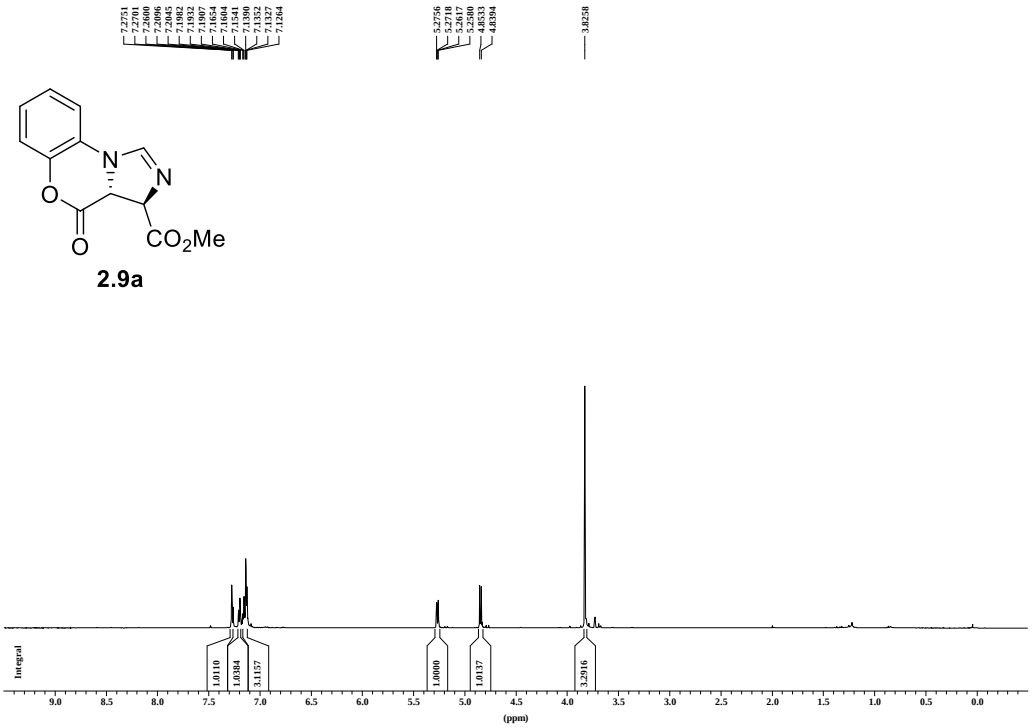
161.3732
155.0113
154.6251
150.4130
147.4980
138.3159
129.5784
124.7031
119.7331
113.6409
107.4248
77.2551
77.0000
76.7449
73.6041
56.7848
56.1217
52.8424
52.3104
MeO
OH
N
N
O
CO2Me
N
CO2Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

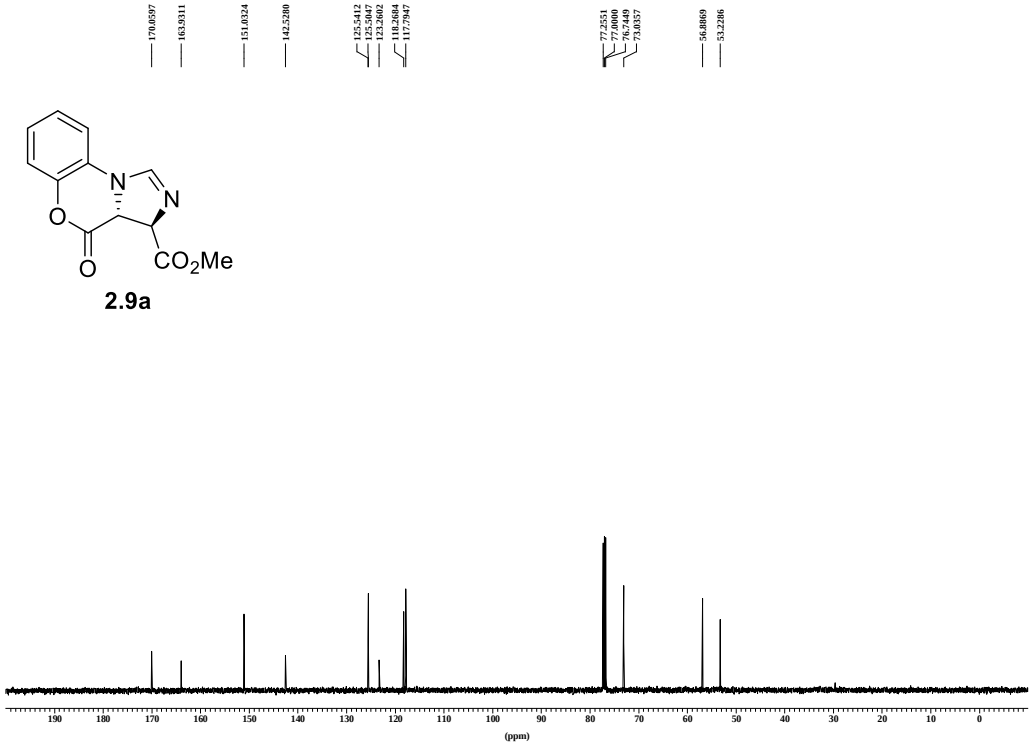
2.7l


9.0757
8.4898
7.2495
7.2451
7.0641
7.0610
7.0377
7.0358
7.0232
7.0091
6.8852
6.8827
6.8694
6.8669
6.6589
6.6564
6.6438
6.6413
6.6287
6.6262
6.4421
6.4399
6.4264
6.4239
5.2302
5.2258
3.7731
3.6895
2.9000
1.3341
OH
N
N
O
Me
CO2Me
N
CO2Me
2.7m
Integral
0.9843
0.9219
1.0175
1.0357
1.0277
1.0318
1.0139
1.0000
3.0296
3.0333
3.0100
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
(ppm)

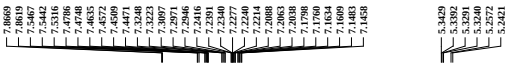

169.6597
161.4978
158.6339
155.5732
153.6096
150.4793
127.9322
127.5533
127.0869
124.4634
119.2675
116.4473
78.4583
66.3685
52.1071
51.6772
40.0028
39.8352
39.6676
39.5000
39.3324
39.1648
39.0045
16.4938
OH
N
N
O
Me
CO2Me
N
CO2Me
2.7m
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

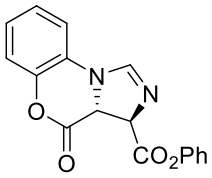

7.2751
7.2701
7.2600
7.2506
7.2045
7.1932
7.1907
7.1764
7.1684
7.1541
7.1390
7.1352
7.1327
7.1264
5.2756
5.2718
5.2617
5.2580
4.8533
4.8394
3.8258
N
N
O
O
CO2Me
Integral
1.0110
1.0384
3.1157
1.0000
1.0137
3.2916
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

2.9a

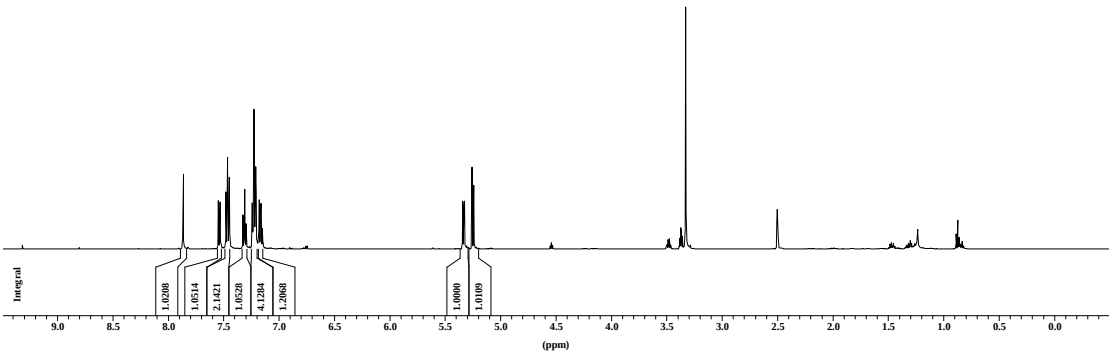

170.0597
163.9311
151.0324
142.5280
125.5412
125.5047
121.2600
119.2684
117.7947
77.2551
77.0000
76.7449
73.0357
56.8869
53.2286
N
N
O
O
CO2Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

2.9a

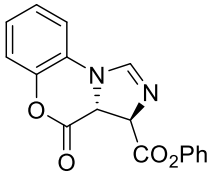

7.8660
7.8619
7.5467
7.5442
7.5316
7.4786
7.4748
7.4655
7.4572
7.4509
7.4471
7.3248
7.3223
7.3097
7.2971
7.2946
7.2416
7.2391
7.2340
7.2277
7.2240
7.2214
7.2088
7.2063
7.2038
7.1798
7.1760
7.1654
7.1609
7.1483
7.1458
5.3420
5.3392
5.3291
5.3240
5.2572
5.2421


N
N
O
O
CO2Ph

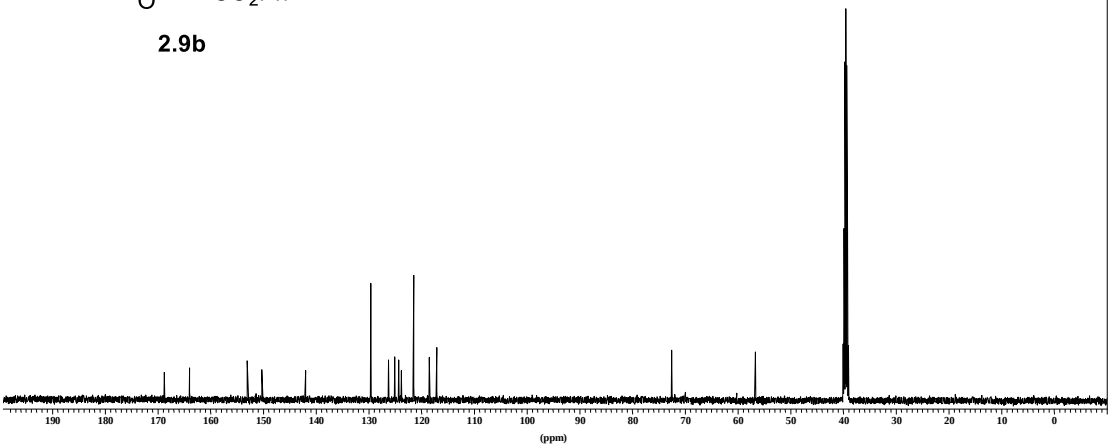
2.9b

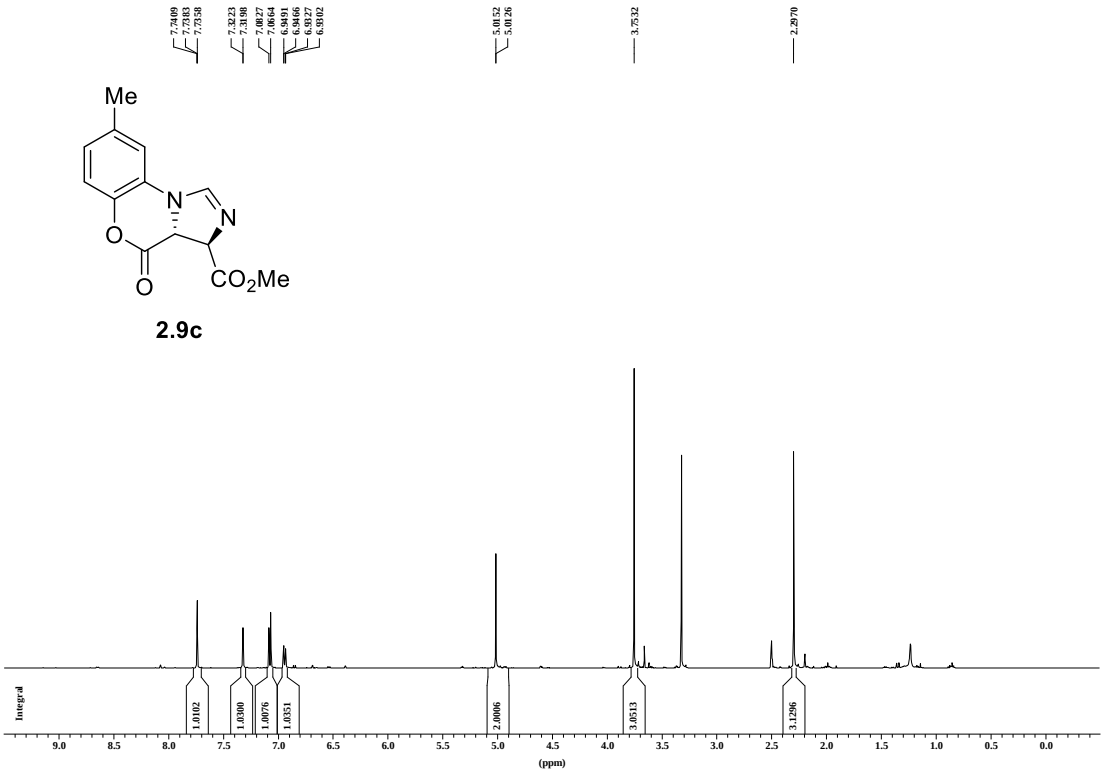

Integral
1.0208
1.0514
2.1421
1.0528
4.1284
1.2068
1.0000
1.0109
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


168.7998
163.9755
153.0226
150.2607
142.0114
129.6447
126.2488
125.1031
124.3541
123.8586
121.4829
118.4951
117.1105
72.5191
56.6909

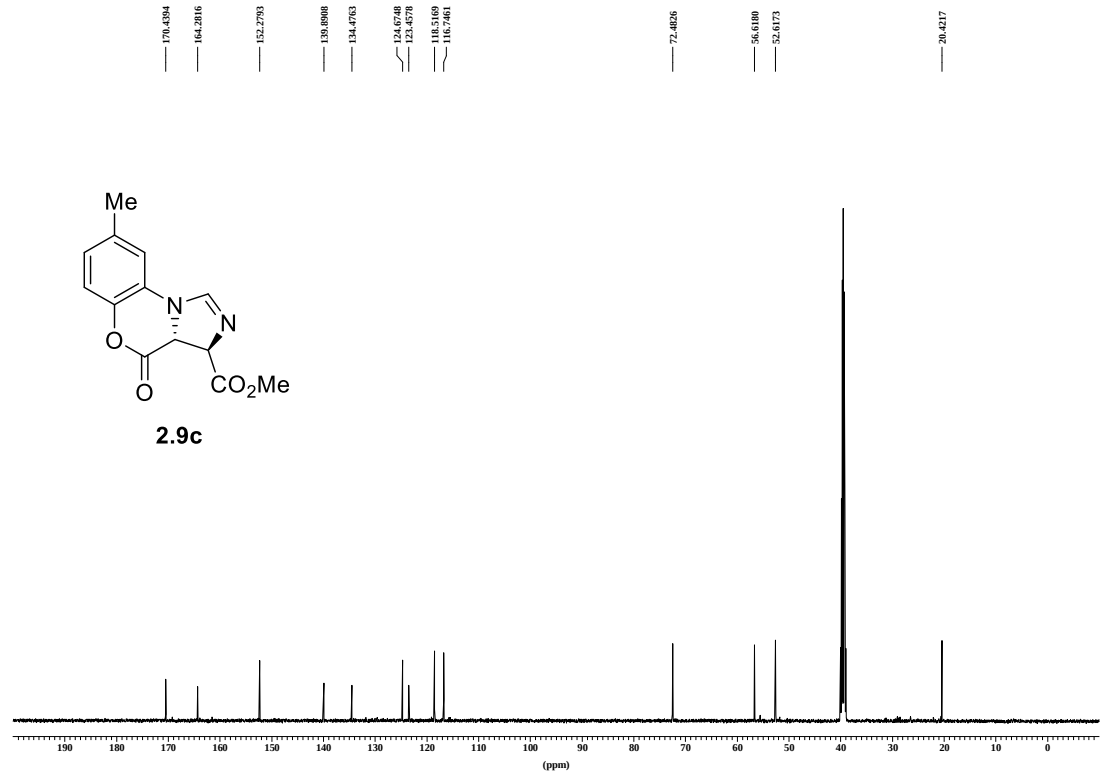

N
N
O
O
CO2Ph

2.9b


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

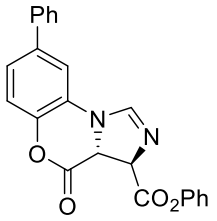

7.7409
7.7383
7.7358
7.3223
7.3198
7.0827
7.0664
6.9491
6.9466
6.9127
6.9102
5.0152
5.0126
3.7532
2.2970
Me
N
N
O
O
O
CO2Me
Integral
1.0102
1.0300
1.0076
1.0351
2.0006
3.0513
3.1296
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

2.9c

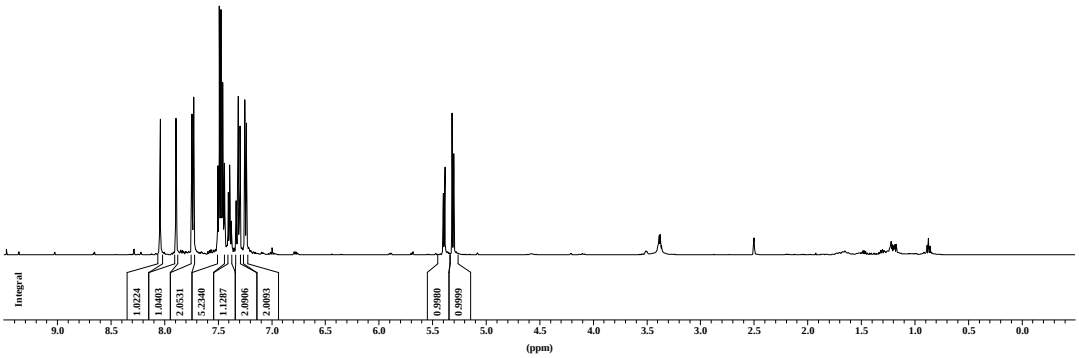

170.4394
164.2816
152.2793
139.8908
134.4763
124.6748
123.4578
118.5169
116.7461
72.4826
56.6180
52.6173
20.4217
Me
N
N
O
O
O
CO2Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

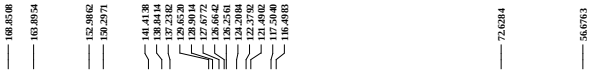
2.9c

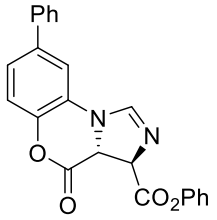

8.0422
8.0184
8.0034
7.9884
7.7421
7.7270
7.5026
7.4874
7.4711
7.4584
7.4547
7.4421
7.4283
7.4055
7.3904
7.3765
7.3311
7.3160
7.3122
7.3089
7.2946
7.2504
7.2353
5.4022
5.3884
5.3871
5.3833
5.3152
5.3001


Ph
N
N
O
O
CO2Ph

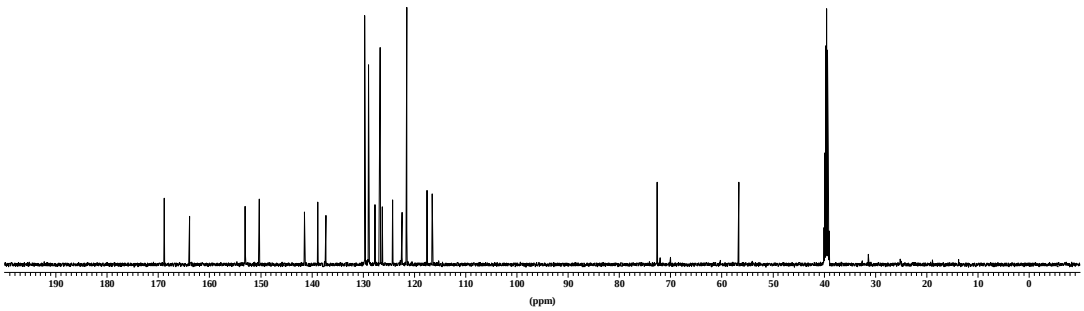
2.9d

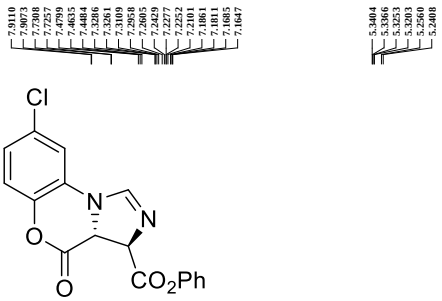

Integral
1.0224
1.0403
2.0531
5.2340
1.1287
2.0906
2.0093
0.9980
0.9999
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


168.8508
163.8954
152.9862
150.2971
141.4138
138.8414
137.2302
135.1539
128.9014
127.6772
126.6642
126.2561
124.3084
122.3756
121.4902
117.5040
116.4983
72.6284
56.6763

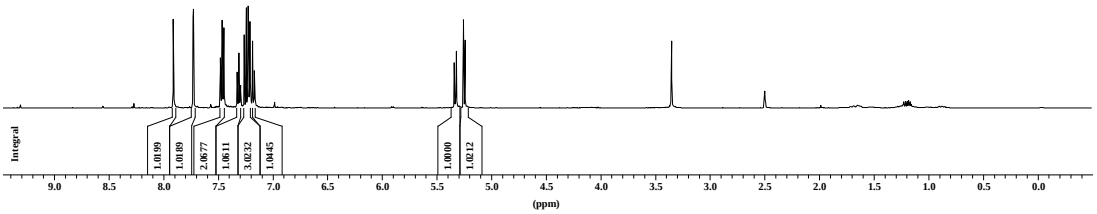

Ph
N
N
O
O
CO2Ph

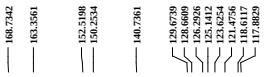
2.9d

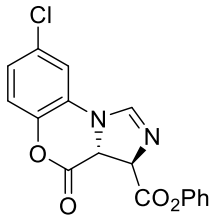

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


7.9110
7.9073
7.7998
7.7257
7.4799
7.4635
7.4484
7.3286
7.3261
7.3109
7.2958
7.2605
7.2429
7.2277
7.2252
7.2101
7.1861
7.1811
7.1685
7.1647
5.3404
5.3366
5.3253
5.3203
5.2560
5.2408
Cl
N
N
O
O
CO2Ph

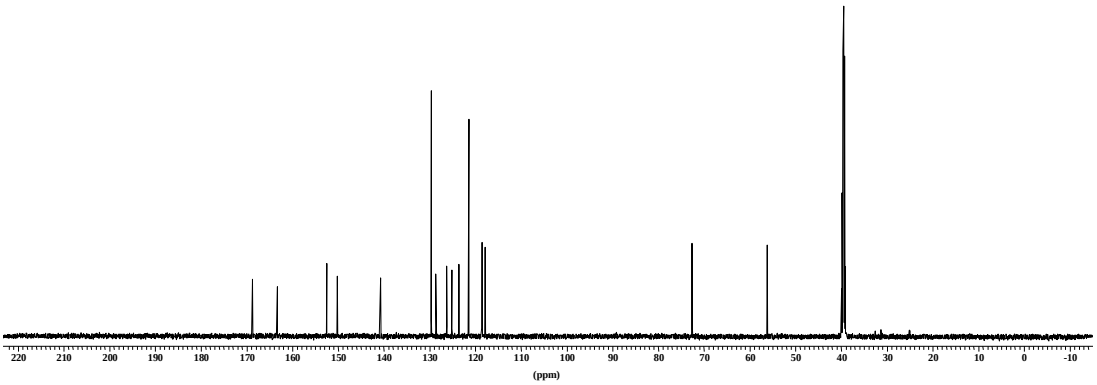
2.9e

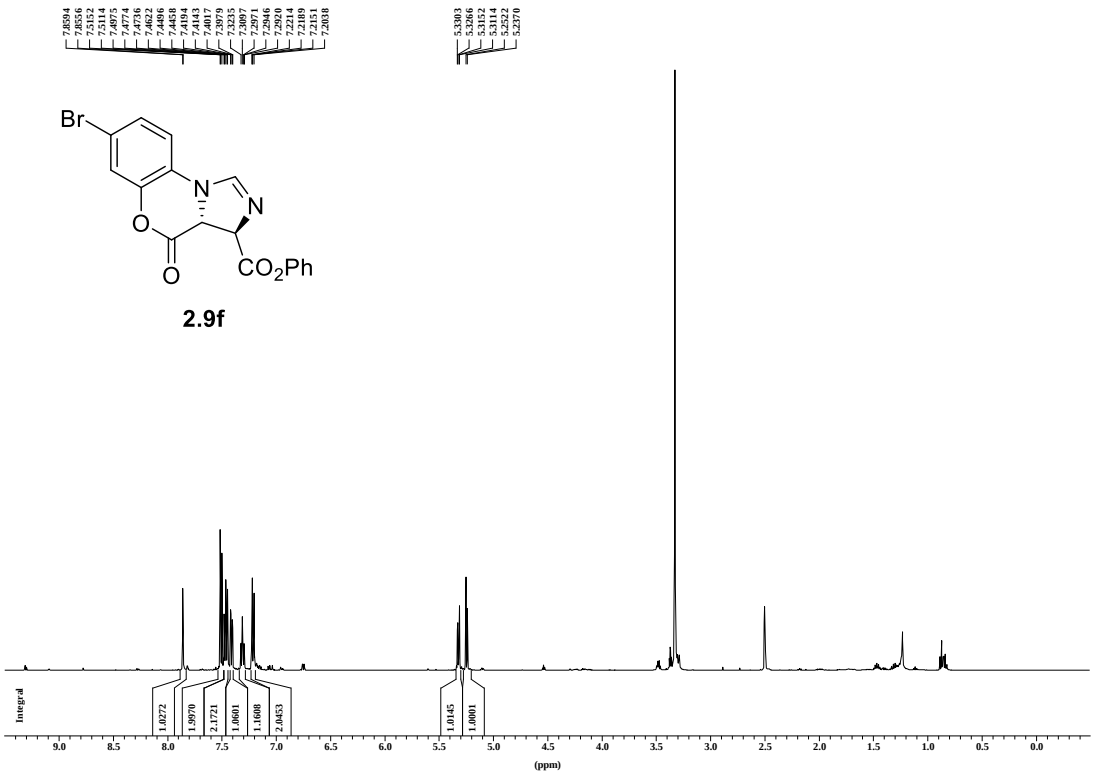

Integral
1.0199
1.0189
2.0677
1.0611
3.0232
1.0445
1.0000
1.0212
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


168.7342
163.3561
152.5198
150.2534
140.7361
129.6739
128.6609
126.2926
124.7412
123.6254
121.4756
118.6117
117.8829
72.6211
56.2245

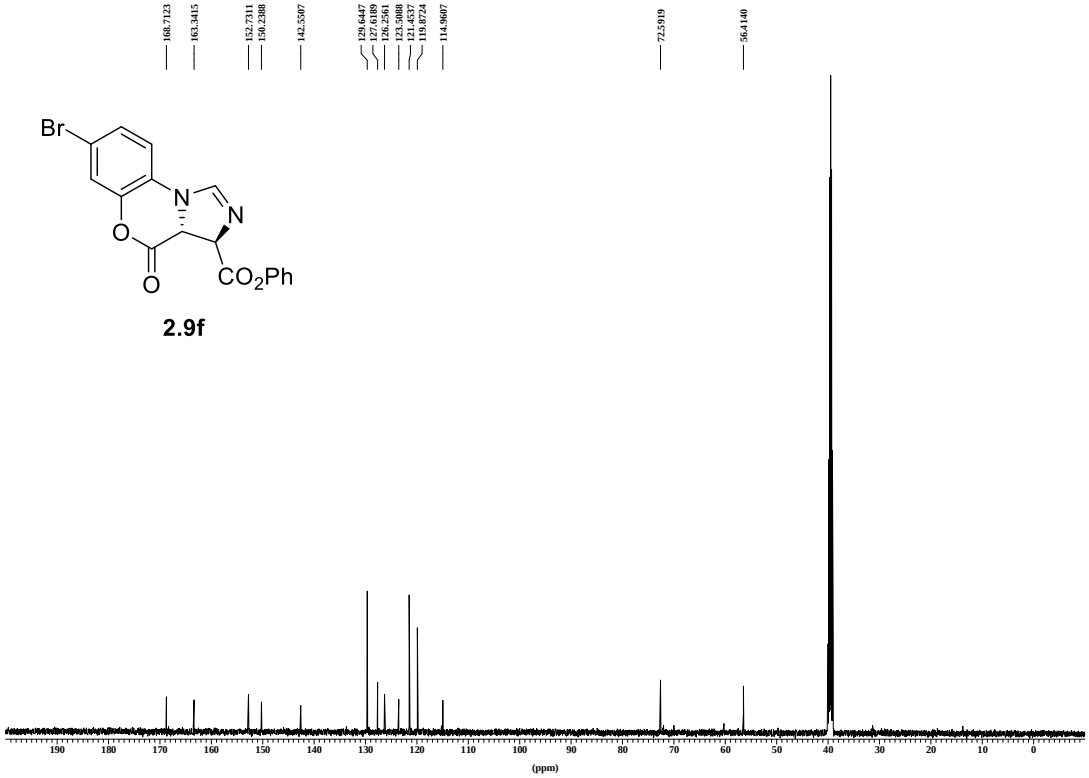

Cl
N
N
O
O
CO2Ph

2.9e


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

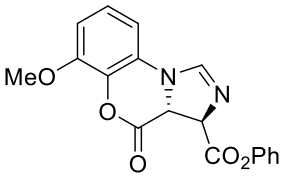

7.8594
7.8556
7.5152
7.5114
7.4975
7.4774
7.4736
7.4622
7.4486
7.4456
7.4194
7.4143
7.4017
7.3979
7.3235
7.3097
7.2971
7.2946
7.2920
7.2214
7.2189
7.2151
7.2038
5.3303
5.3266
5.3152
5.3114
5.2522
5.2370
Br
N
N
O
O
CO2Ph
Integral
1.0272
1.9970
2.1721
1.0601
1.1608
2.0453
1.0145
1.0001
9.0
8.5
8.0
7.5
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
(ppm)

2.9f

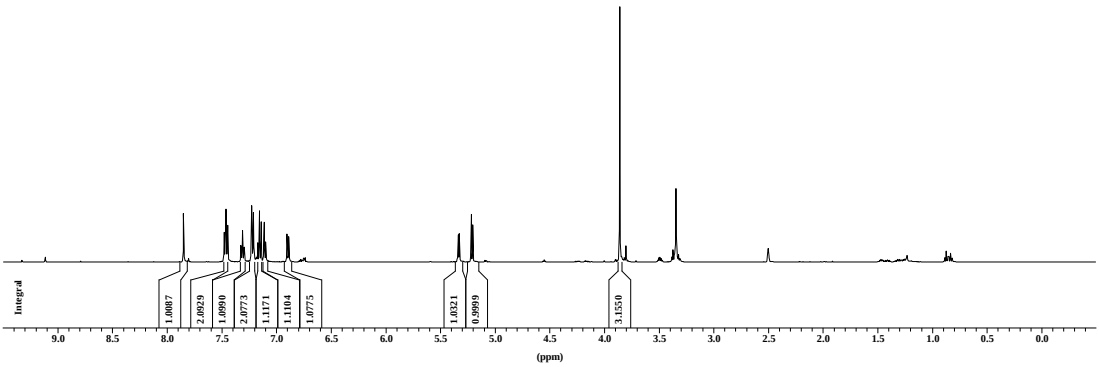

168.7123
163.3415
152.7311
150.2388
142.5507
129.6447
127.6189
126.2561
123.5088
121.4577
119.8724
114.9607
72.5919
56.4140
Br
N
N
O
O
CO2Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

2.9f

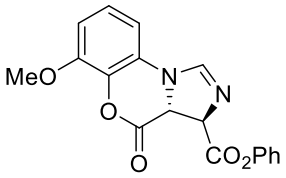

7.8493
7.8455
7.4774
7.4622
7.4446
7.3355
7.3084
7.2933
7.2277
7.2252
7.2101
7.1710
7.1546
7.1382
7.1130
7.1105
7.0979
7.0841
6.9025
6.8999
6.8861
6.8836
5.3404
5.3366
5.3266
5.3215
5.2169
5.2030
3.8570


MeO
N
N
O
O
CO2Ph

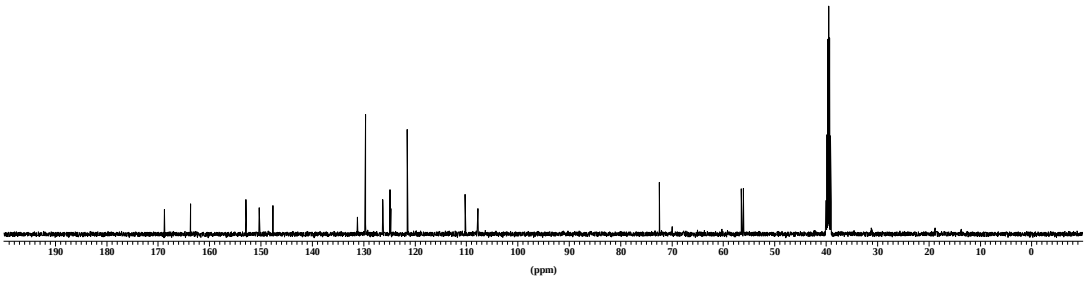
2.9g

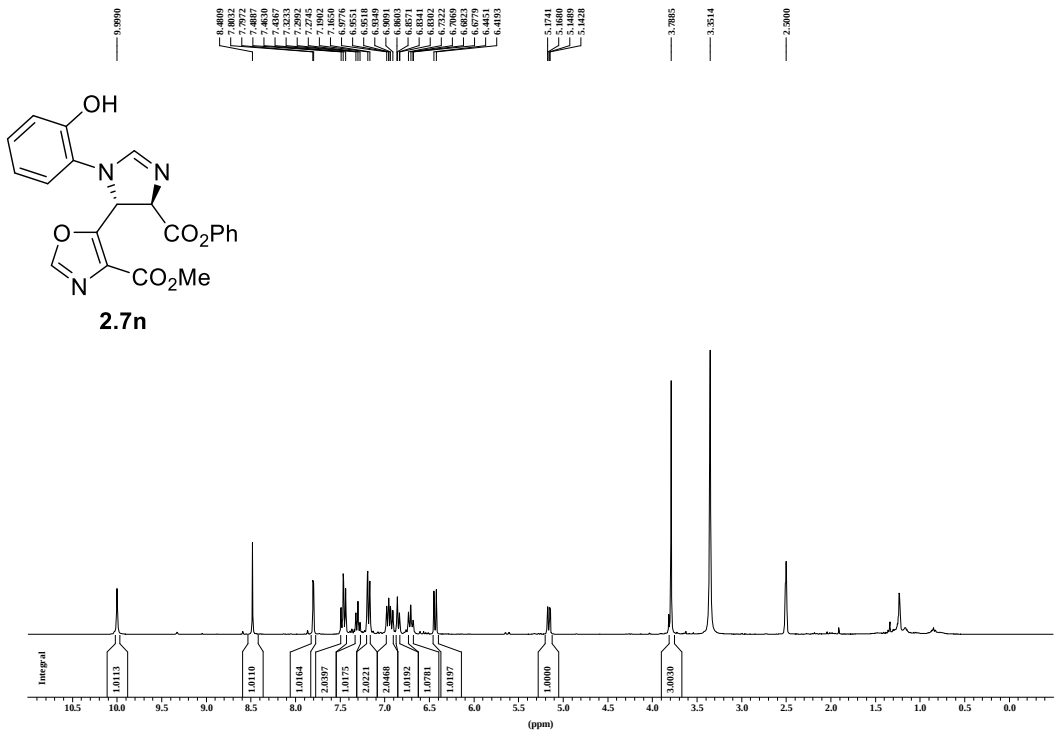

Integral
1.0087
2.0929
1.0990
2.0773
1.1171
1.1104
1.0775
1.0321
0.9999
3.1550
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

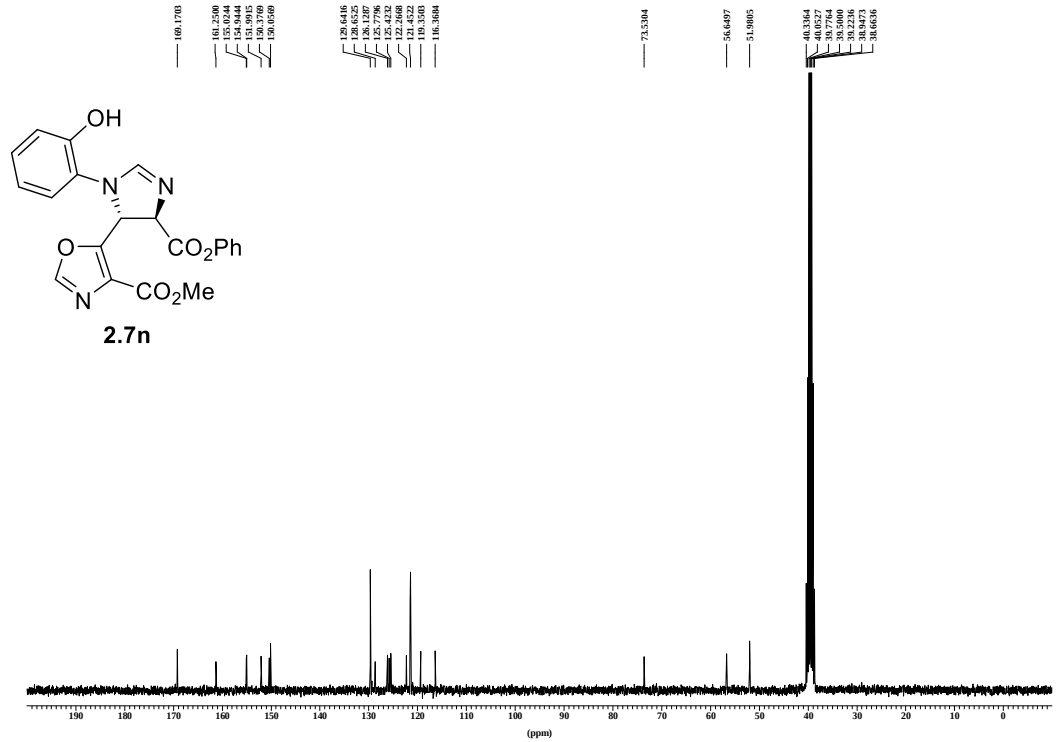

168.7779
163.6476
132.8987
130.2607
147.6008
131.1751
129.6447
126.2561
124.8265
124.7039
121.4902
110.2166
107.7608
72.4389
56.4594
56.0569

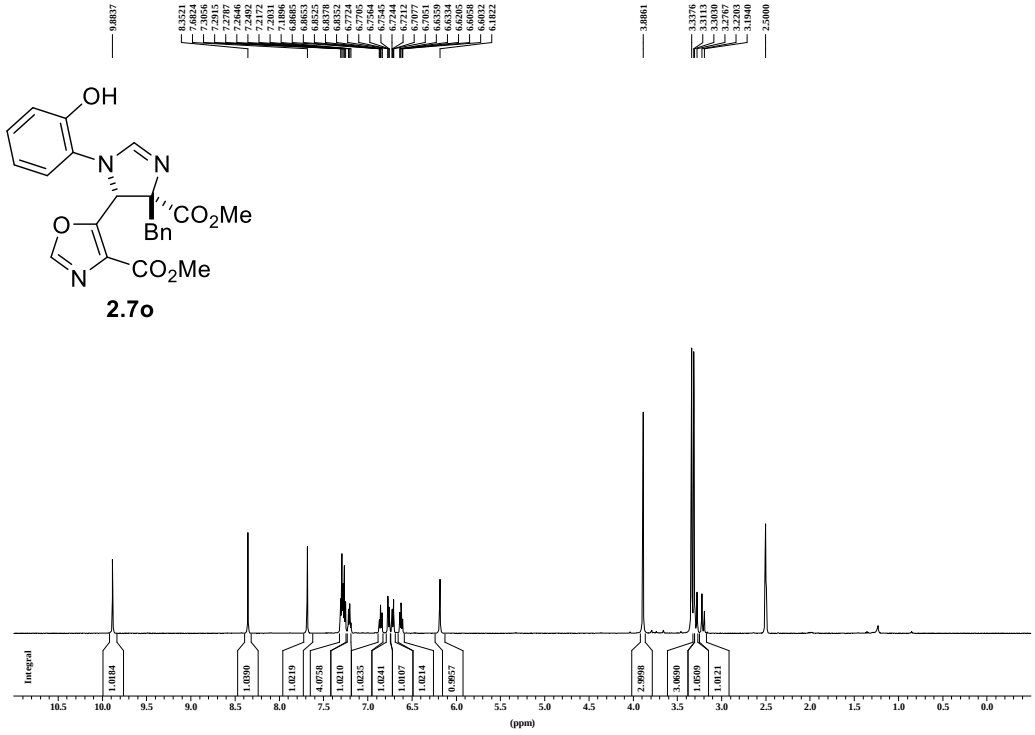

MeO
N
N
O
O
CO2Ph

2.9g


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


9.9990
8.4099
7.8032
7.7972
7.4887
7.4830
7.4657
7.3233
7.2992
7.2745
7.1892
7.1650
6.8976
6.8551
6.8518
6.8349
6.8091
6.8003
6.8571
6.8341
6.8102
6.7322
6.7069
6.6823
6.6779
6.6451
6.4193
5.1741
5.1680
5.1499
5.1428
3.7885
3.3514
2.5000
OH
N
N
O
CO2Ph
N
CO2Me
2.7n
Integral
1.0113
1.0110
1.0164
2.0397
1.0175
2.0221
2.0468
1.0192
1.0781
1.0197
1.0000
3.0030
(ppm)


169.1703
161.2500
155.0244
154.9444
153.9965
150.3769
150.0569
129.6416
128.6525
126.1287
125.7796
125.4232
122.2668
121.4522
119.3503
116.3684
73.5304
56.6497
51.9805
40.3364
40.0527
39.7764
39.5000
39.2236
38.9473
38.6636
OH
N
N
O
CO2Ph
N
CO2Me
2.7n
(ppm)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8.3521
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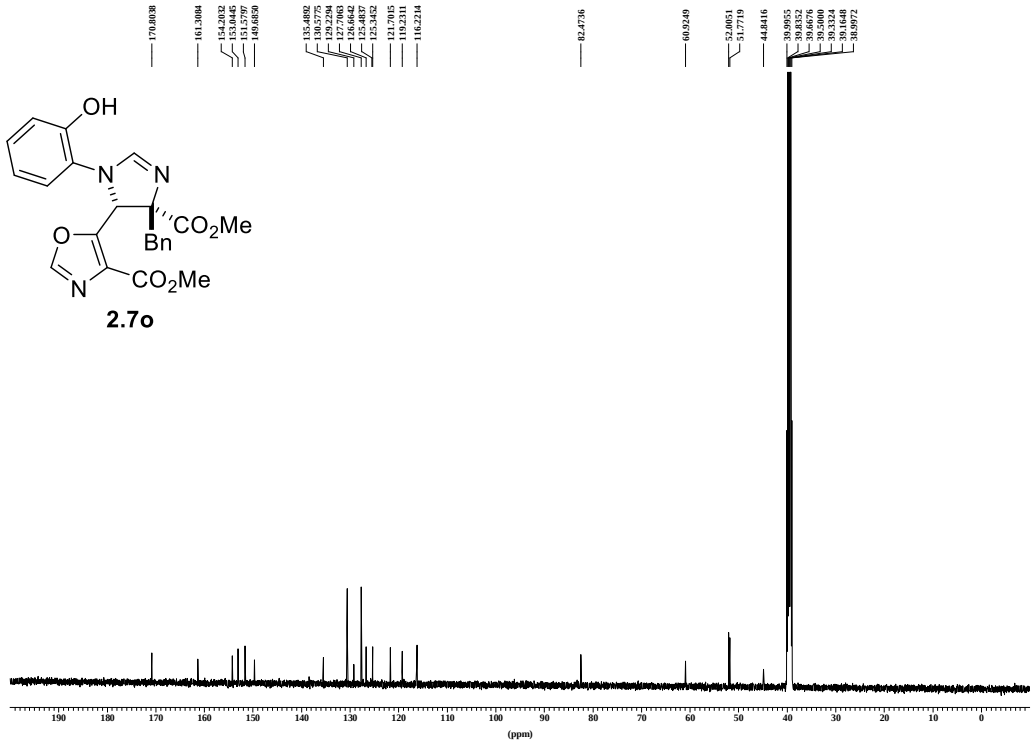
7.2915
7.2787
7.2646
7.2172
7.2031
7.1896
6.8525
6.8378
6.8352
6.7724
6.7564
6.7545
6.7244
6.7077
6.7051
6.6359
6.6334
6.6058
6.6032
6.1822
3.8861
3.3376
3.3113
3.3030
3.2797
3.2203
3.1940
2.5000
OH
N
N
O
N
CO2Me
Bn
CO2Me
Integral
1.0184
1.0390
1.0219
4.0758
1.0210
1.0235
1.0241
1.0107
1.0214
0.9957
2.8998
3.0690
1.0609
1.0221
(ppm)

2.7o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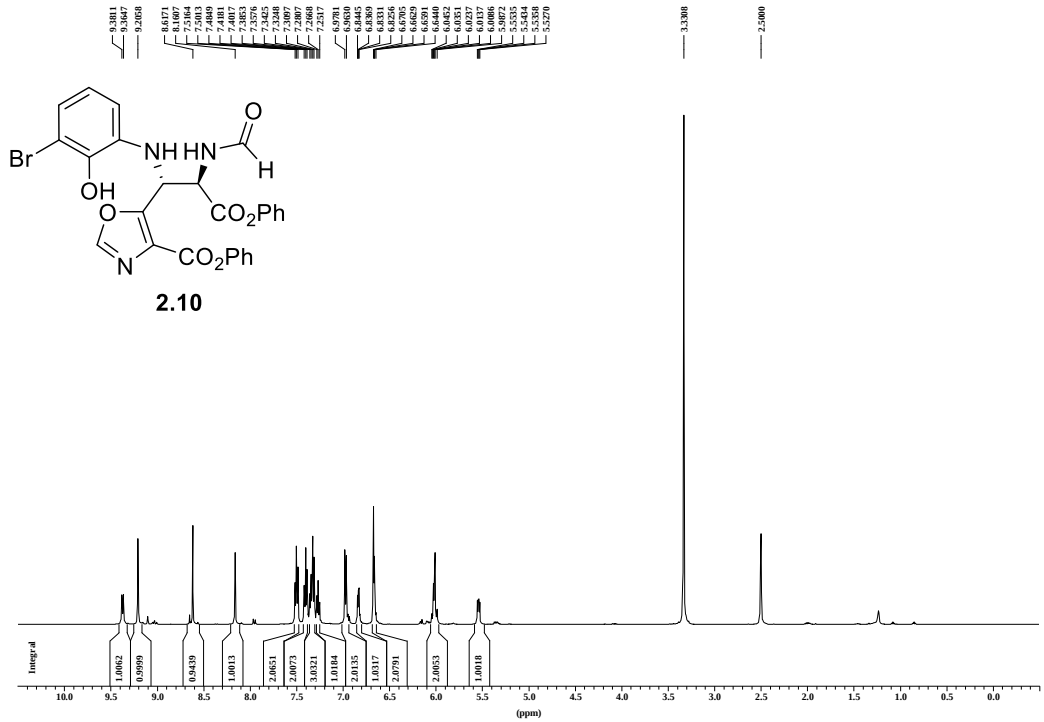
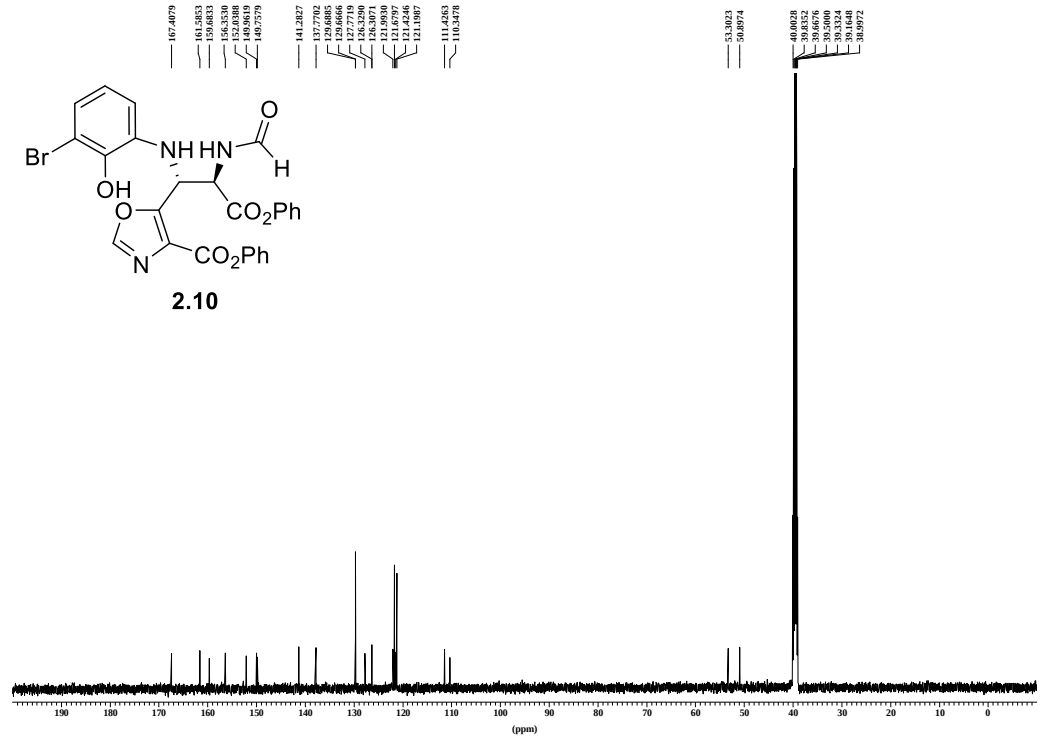
154.2032
153.0445
151.5797
149.6850
135.4892
130.3575
129.2294
127.7063
126.6642
125.4837
125.3452
121.7015
119.2311
116.2234
82.4736
60.9249
52.4051
51.7719
44.8416
39.9955
39.8352
39.6676
39.5000
39.3324
39.1648
38.8972
OH
N
N
O
N
CO2Me
Bn
CO2Me
(ppm)

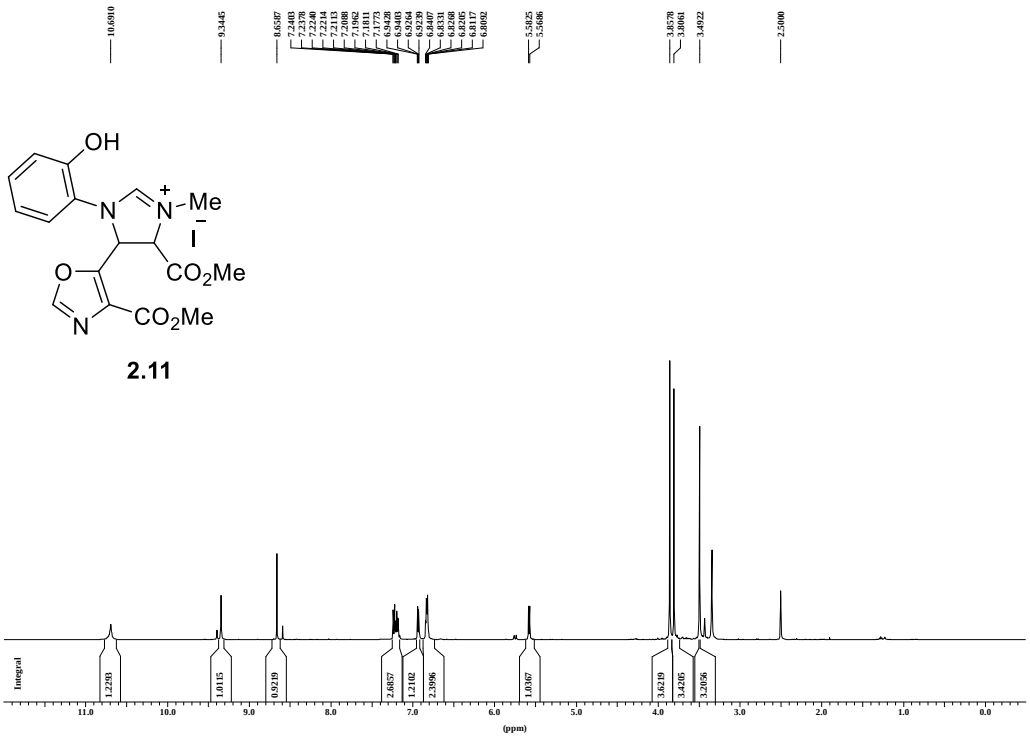
2.7o

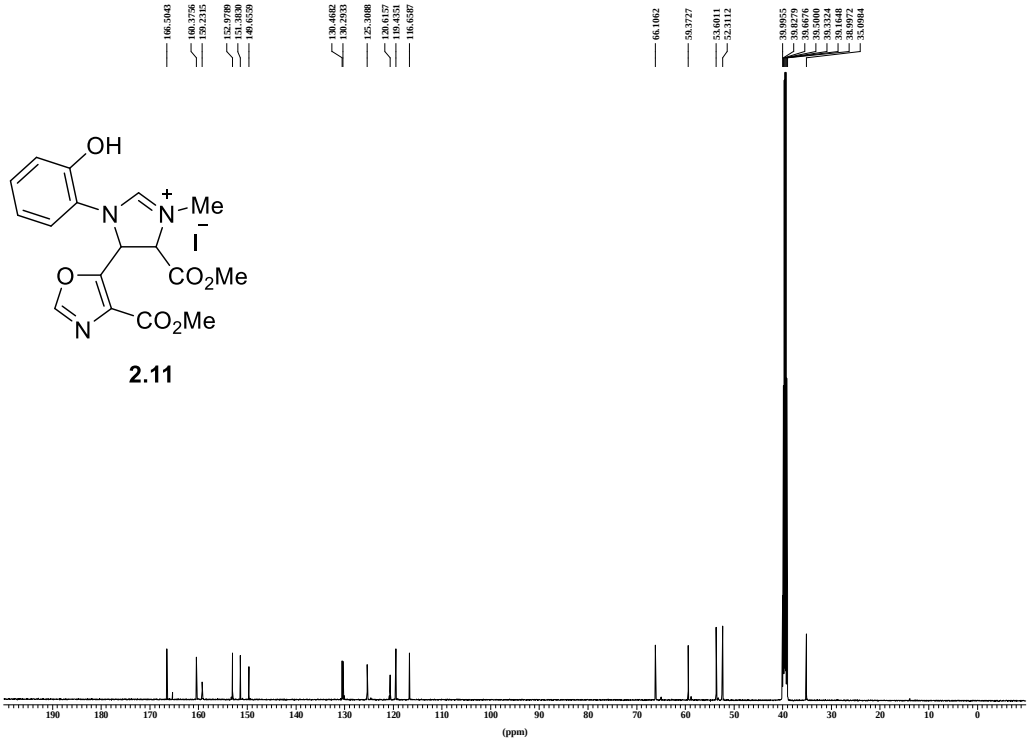

Br
NH HN
O
H
OH
O
CO2Ph
N
CO2Ph
Integral
(ppm)

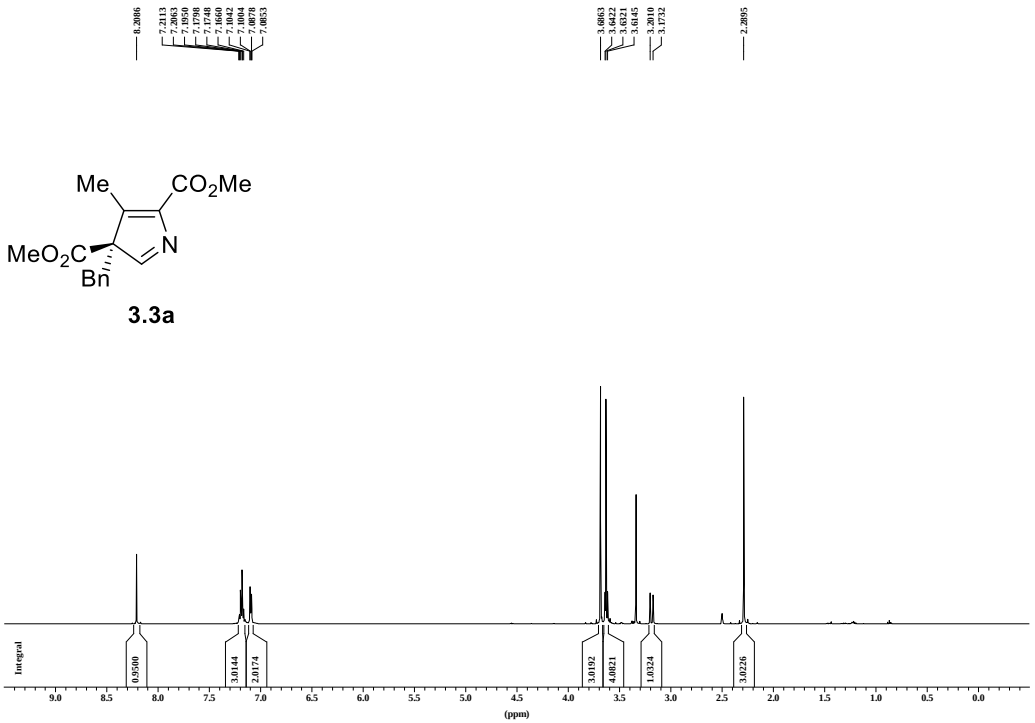
2.10


Br
NH HN
O
H
OH
O
CO2Ph
N
CO2Ph
(ppm)

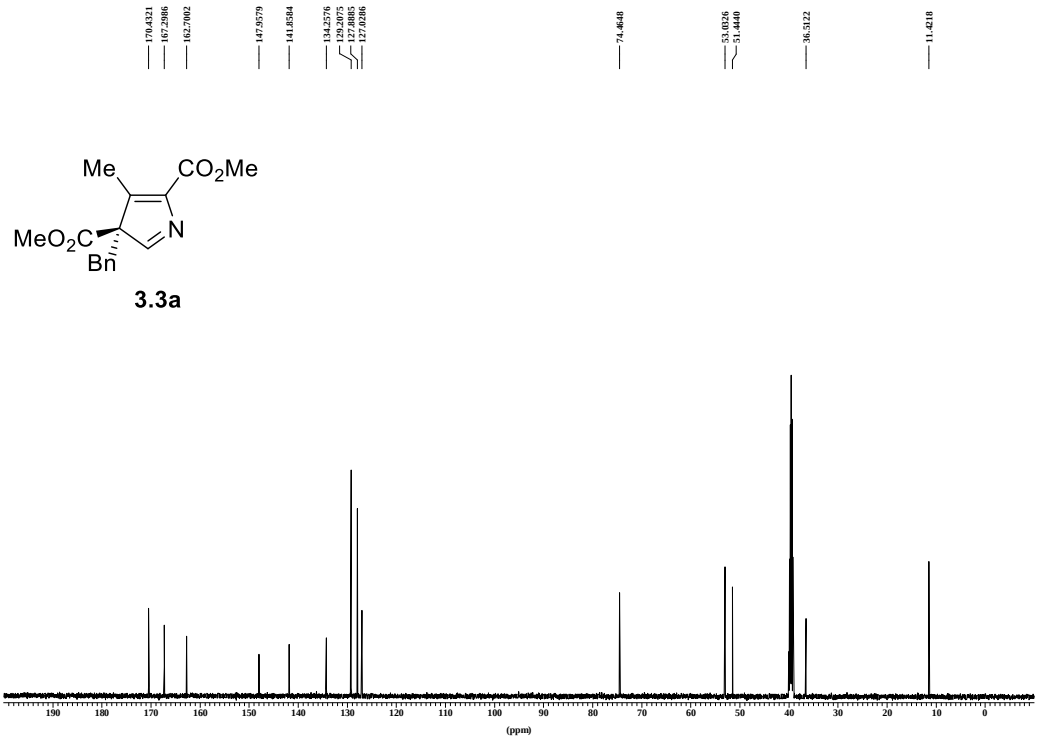
2.10


10.6910
9.3445
8.6587
7.2403
7.2378
7.2240
7.2214
7.2115
7.2088
7.1962
7.1931
7.1777
6.9428
6.9403
6.9264
6.9239
6.8407
6.8331
6.8208
6.8095
6.8117
6.8092
5.5825
5.5686
3.8578
3.8061
3.4922
2.5000
OH
N
N
Me
O
CO2Me
N
CO2Me
2.11
Integral
1.2293
1.0115
0.9219
2.6857
1.2102
2.3906
1.0367
3.6219
3.4205
3.2056
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

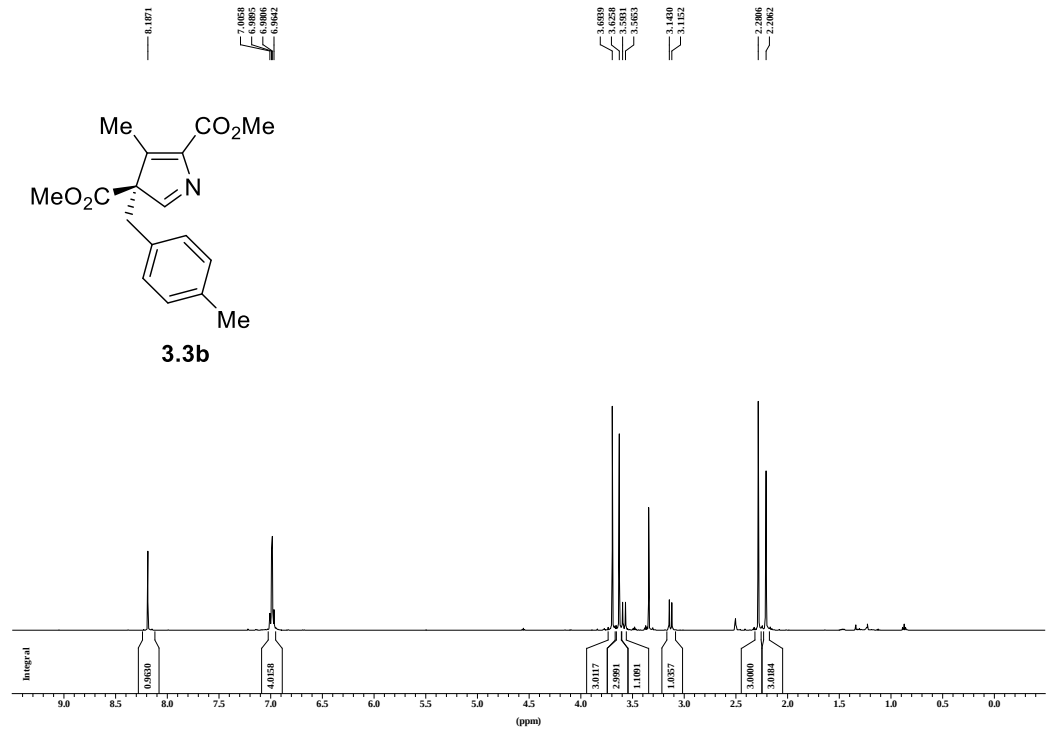

166.5043
160.3756
159.2315
152.9789
151.3830
149.6559
130.4682
130.2933
125.3088
120.6157
119.4351
116.6587
66.1062
59.3727
53.6011
52.3112
39.9955
39.8279
39.6676
39.5000
39.3324
39.1648
38.8972
35.0984
OH
N
N
Me
O
CO2Me
N
CO2Me
2.11
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


8.3086
7.2113
7.2063
7.1950
7.1798
7.1748
7.1660
7.1042
7.1004
7.0878
7.0853
3.6863
3.6422
3.6321
3.6145
3.2010
3.1732
2.2895
Me
CO2Me
MeO2C
N
Bn
Integral
0.9500
3.0144
2.0174
3.0192
4.0821
1.0324
3.0226
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
(ppm)

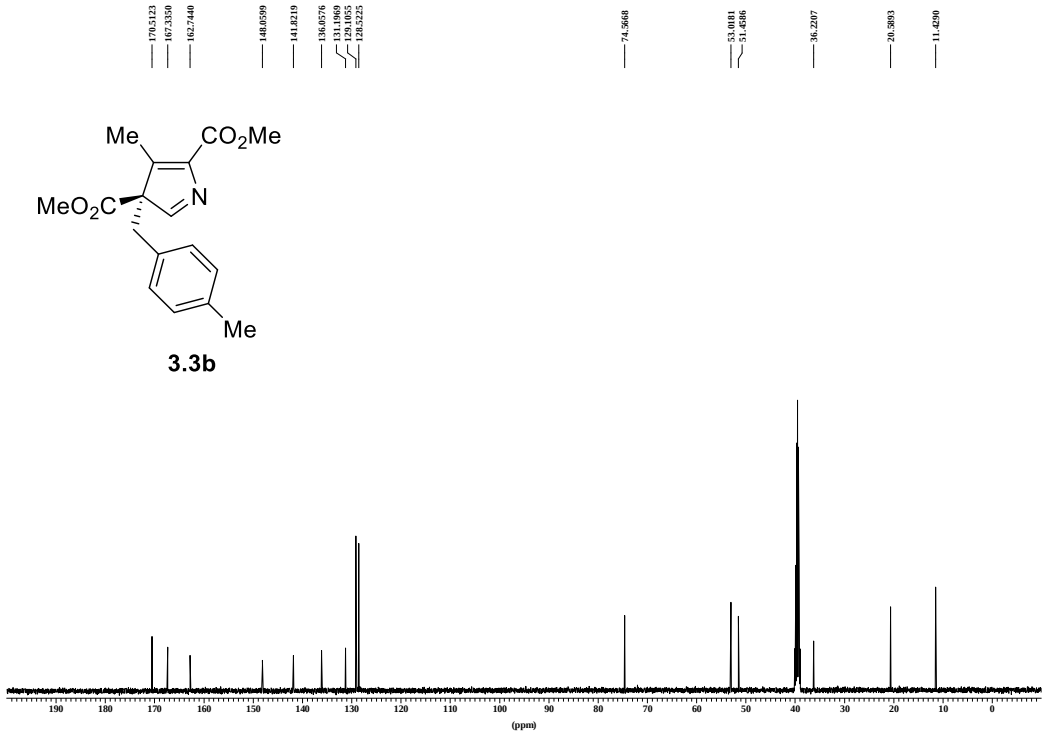
3.3a


170.4321
167.2986
162.7002
147.9579
141.8584
134.2576
129.3075
127.4085
127.0286
74.4648
53.0326
51.4440
36.5122
11.4218
Me
CO2Me
MeO2C
N
Bn
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

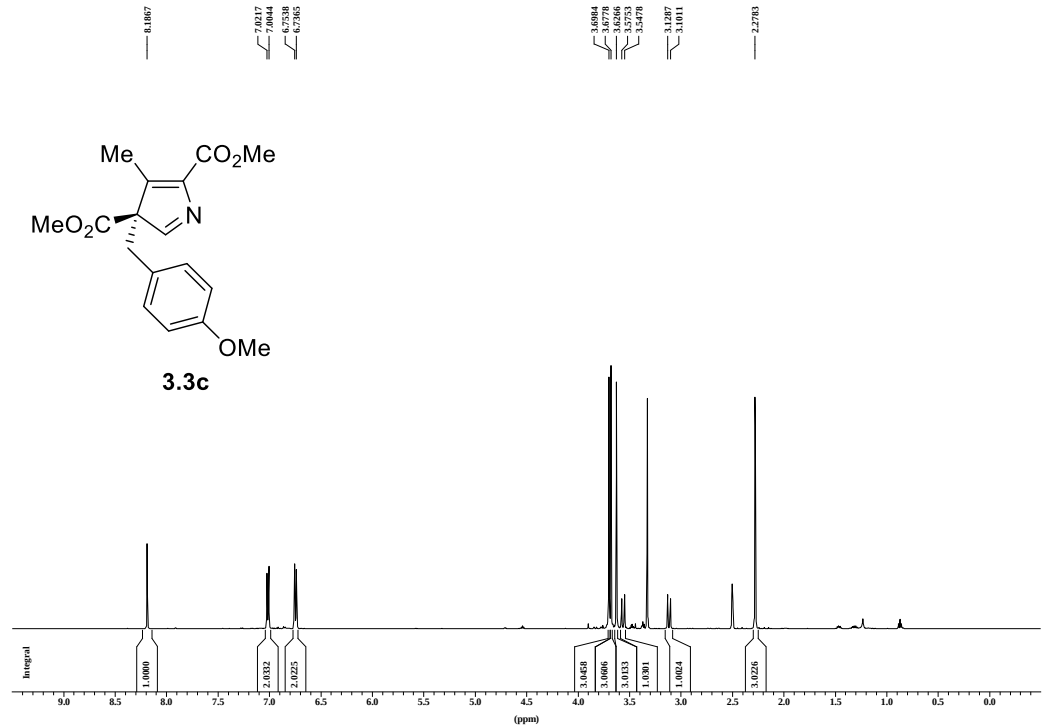
3.3a

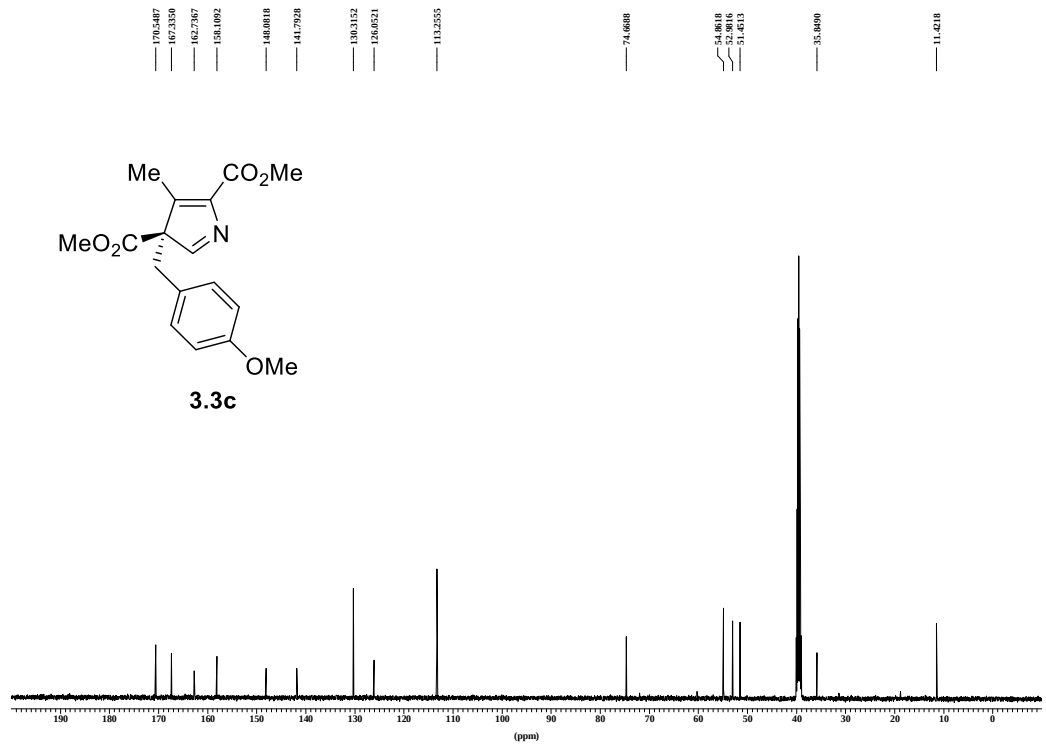

8.1871
7.0058
6.9895
6.9806
6.9642
3.6839
3.6758
3.5931
3.5653
3.1430
3.1152
2.2806
2.2062
Me
CO2Me
MeO2C
N
Me
Integral
0.9620
4.0158
3.0117
2.9991
1.1091
1.0357
3.0000
3.0184
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

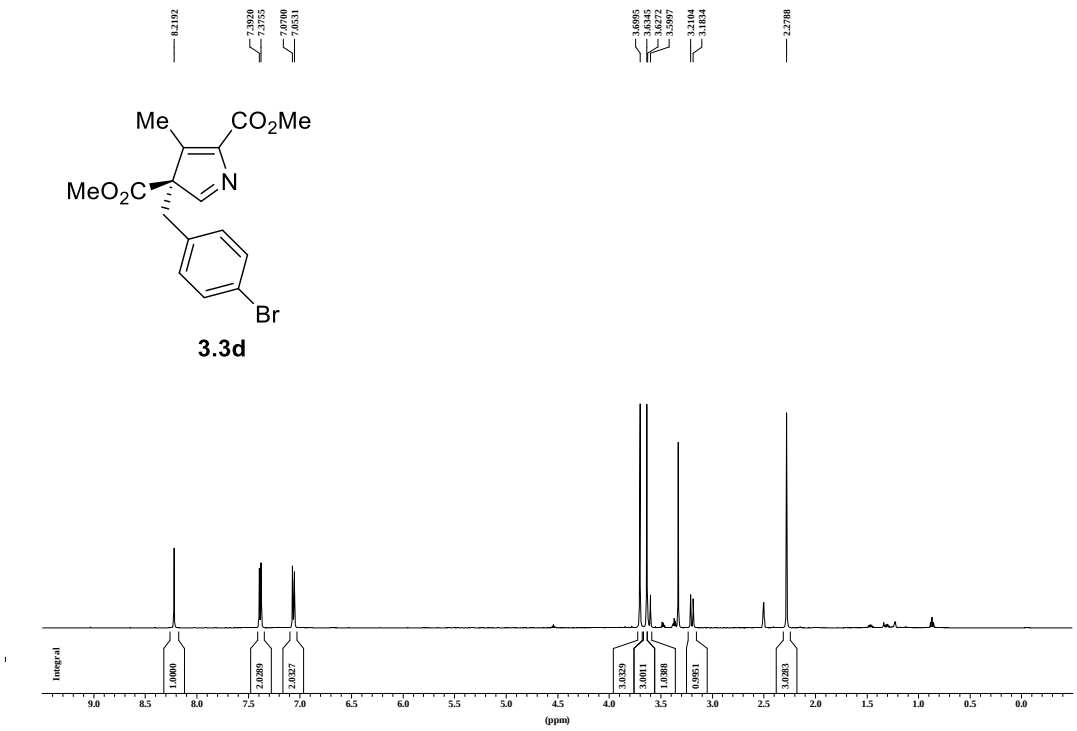
3.3b

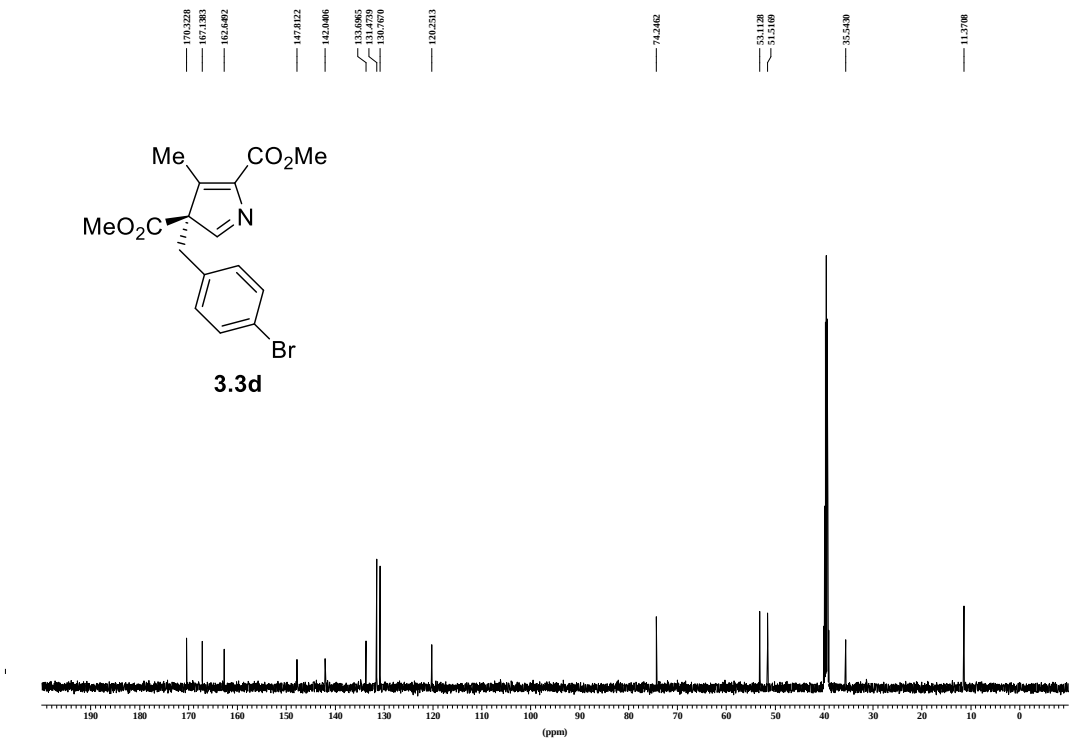

170.5123
167.3350
162.7440
148.6599
141.8219
136.6576
131.1969
129.1655
128.8225
74.5668
53.0181
51.4586
36.2207
20.5893
11.4290
Me
CO2Me
MeO2C
N
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

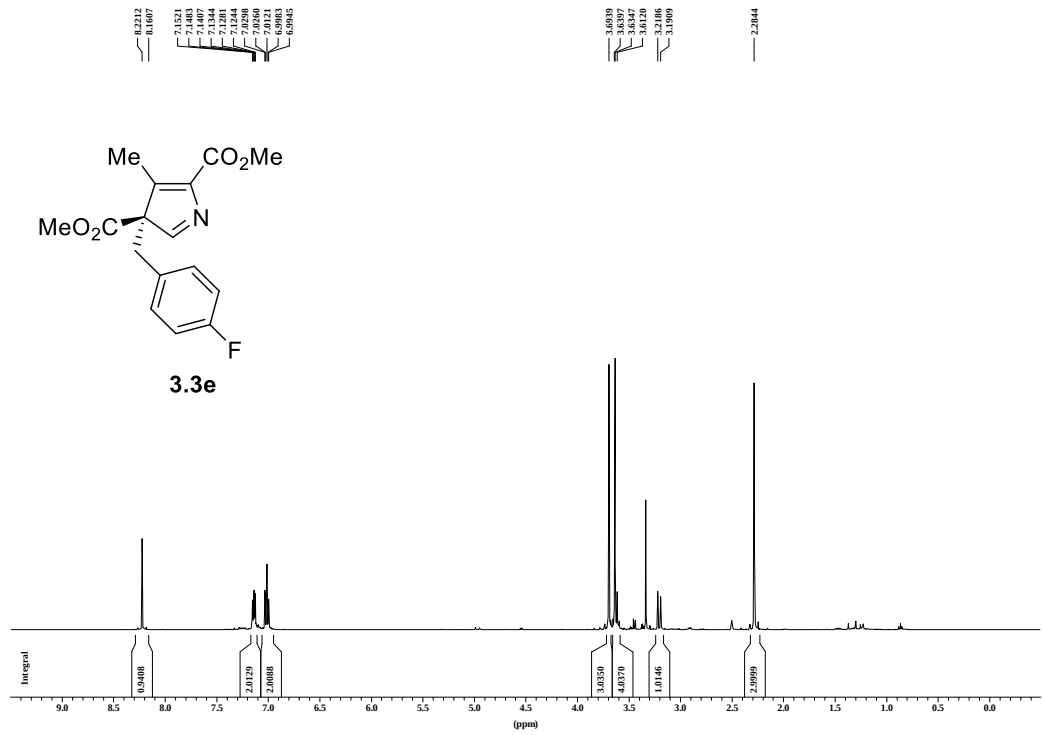
3.3b

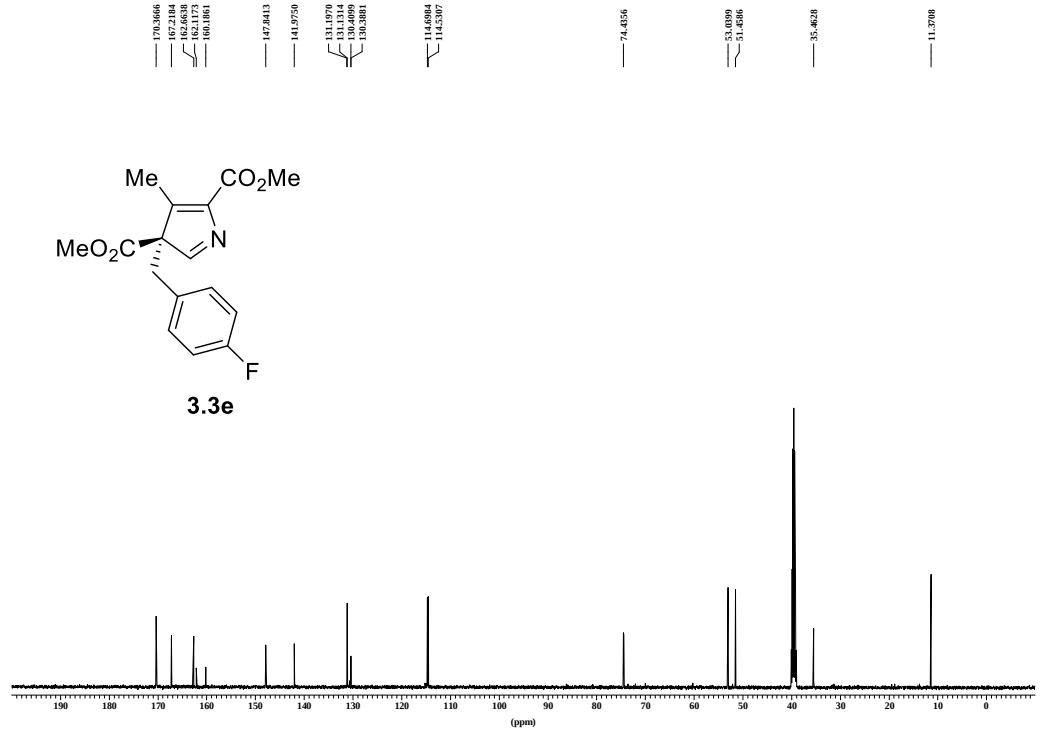

8.1867
7.0217
7.0044
6.7538
6.7365
3.6984
3.6778
3.6266
3.5753
3.5476
3.1287
3.1011
2.2783
Me
CO2Me
MeO2C
N
OMe
3.3c
Integral
1.0000
2.0332
2.0225
3.0458
3.0606
3.0133
1.0301
1.0024
3.0226
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


170.5487
167.3350
162.7367
158.1092
148.0818
141.7920
130.3152
126.0521
113.2555
74.6688
54.8618
52.9816
51.4513
35.8490
11.4218
Me
CO2Me
MeO2C
N
OMe
3.3c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


8.2192
7.3920
7.3755
7.0700
7.0531
3.6995
3.6345
3.6272
3.5997
3.2104
3.1834
2.2788
Me
CO2Me
MeO2C
N
Br
3.3d
Integral
1.0000
2.0289
2.0327
3.0329
3.0011
1.0388
0.9951
3.0283
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
(ppm)


170.3228
167.1383
162.6492
147.8122
142.0406
133.6965
131.4739
130.7670
120.2513
74.2462
53.1128
51.5169
35.5430
11.3700
Me
CO2Me
MeO2C
N
Br
3.3d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


8.2212
8.1607
7.1521
7.1483
7.1407
7.1344
7.1281
7.1244
7.0298
7.0260
7.0121
6.9983
6.9945
3.6939
3.6397
3.6347
3.6120
3.2186
3.1909
2.2844
Me
CO2Me
MeO2C
N
F
3.3e
Integral
0.9408
2.0129
2.0088
3.0330
4.0370
1.0146
2.9999
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
(ppm)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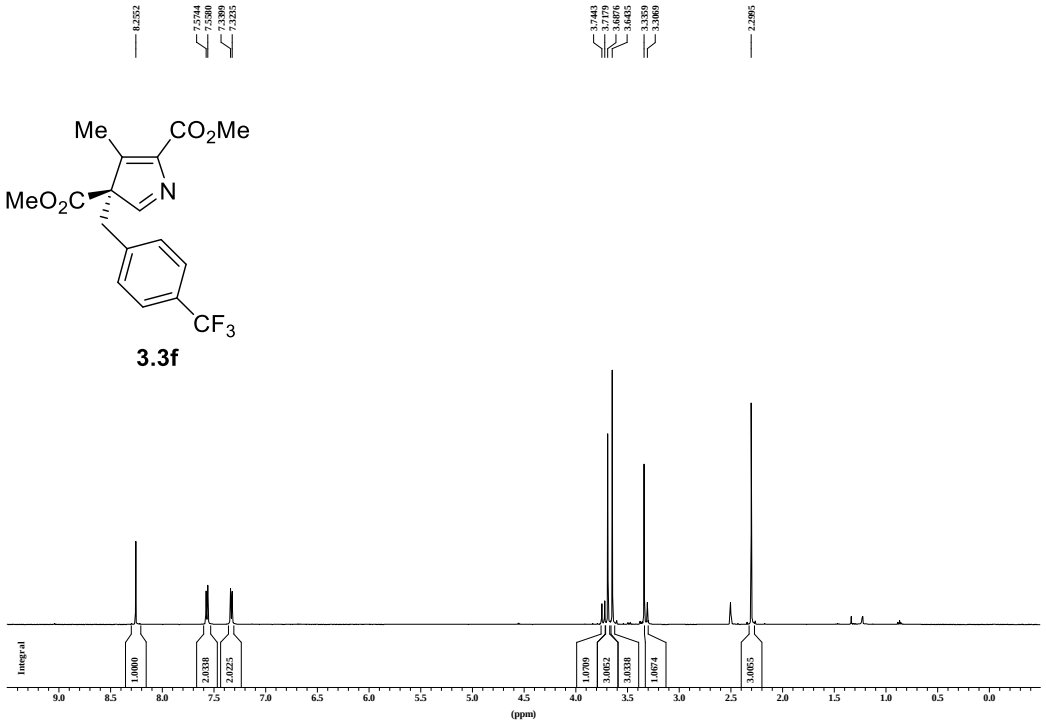
167.2184
162.6638
162.1173
160.1061
147.8413
141.9750
131.1970
131.1314
130.4099
130.3881
114.6984
114.5307
74.4356
53.0399
51.4586
35.4628
11.3708
Me
CO2Me
MeO2C
N
F
3.3e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


8.2552
7.5744
7.5580
7.3399
7.3235
3.7443
3.7179
3.6876
3.6435
3.3359
3.3069
2.2995
Me
CO2Me
MeO2C
N
CF3
Integral
1.0000
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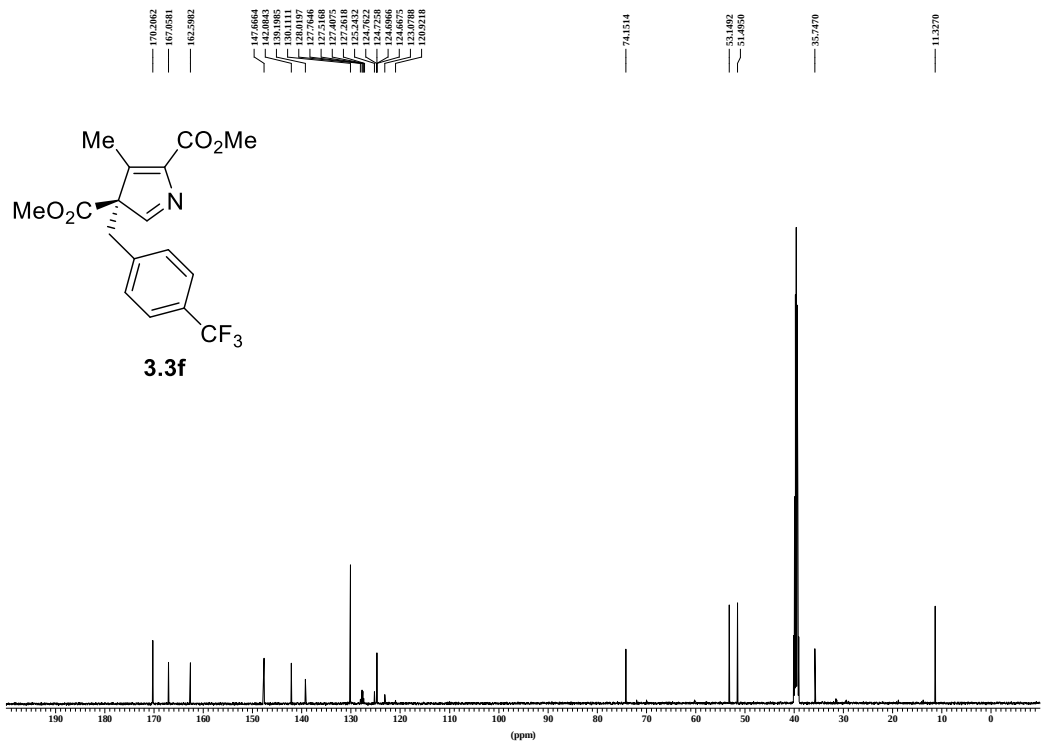
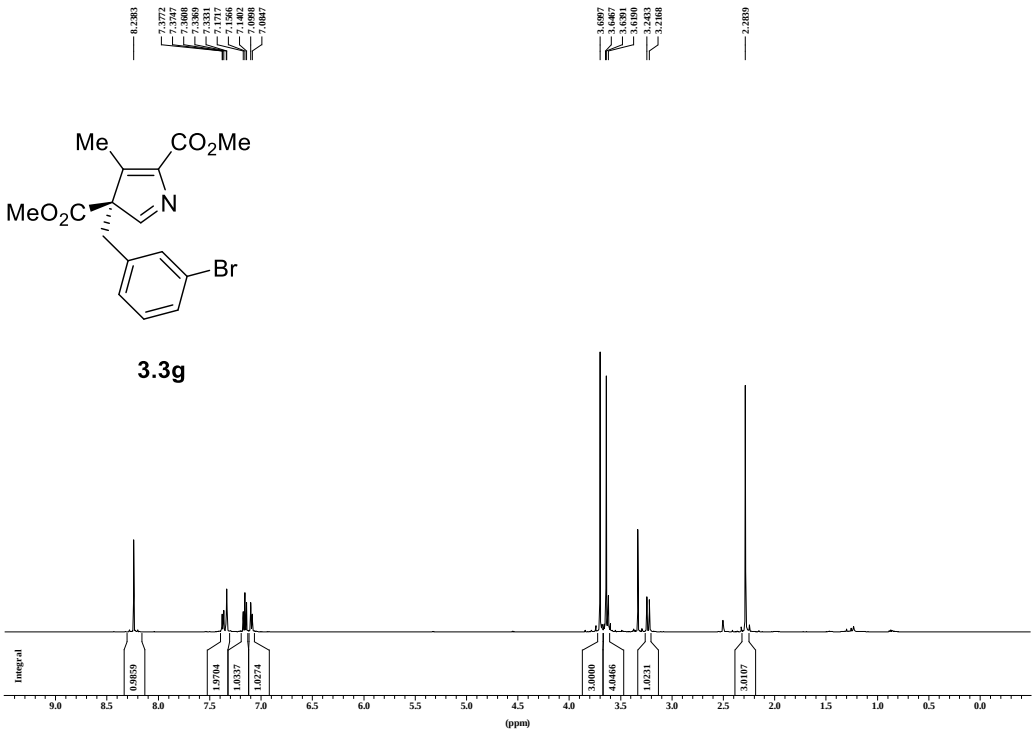
2.0225
1.0709
3.0052
3.0338
1.0674
3.0055
(ppm)

3.3f


170.2062
167.0581
162.5982
147.6664
142.0843
139.1985
130.1111
129.6697
127.7646
127.5168
127.4075
127.2618
125.2432
124.7622
124.7258
124.6966
124.6675
124.6098
120.9218
74.1514
53.1492
51.4950
35.7470
11.3270
Me
CO2Me
MeO2C
N
CF3
(ppm)

3.3f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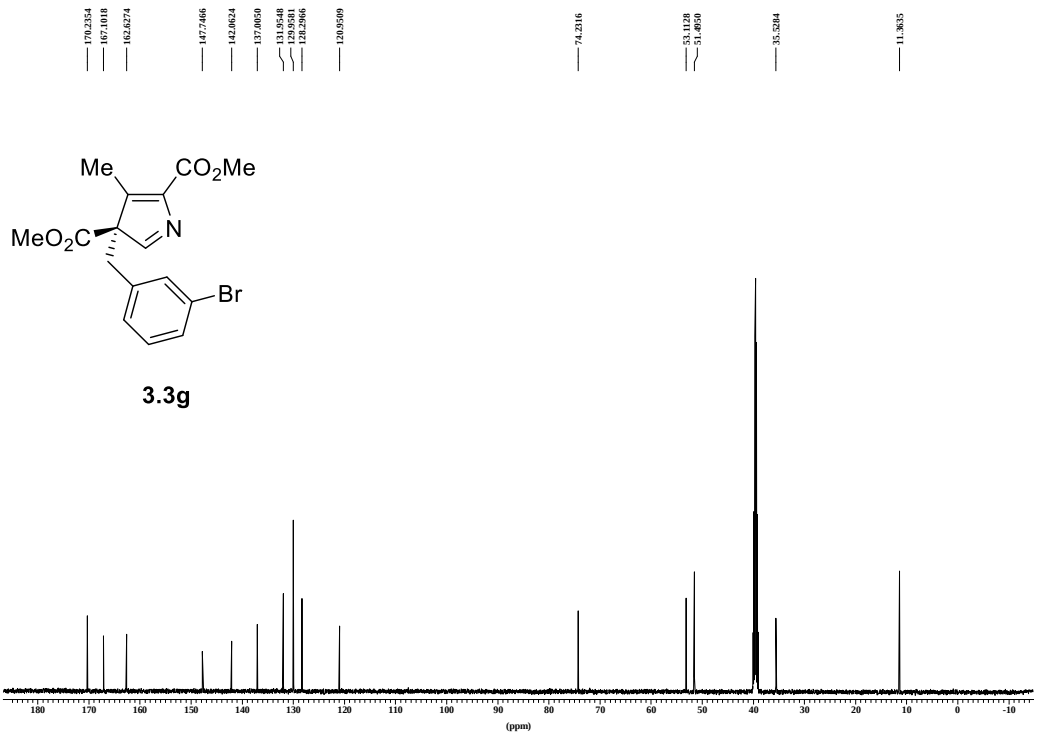
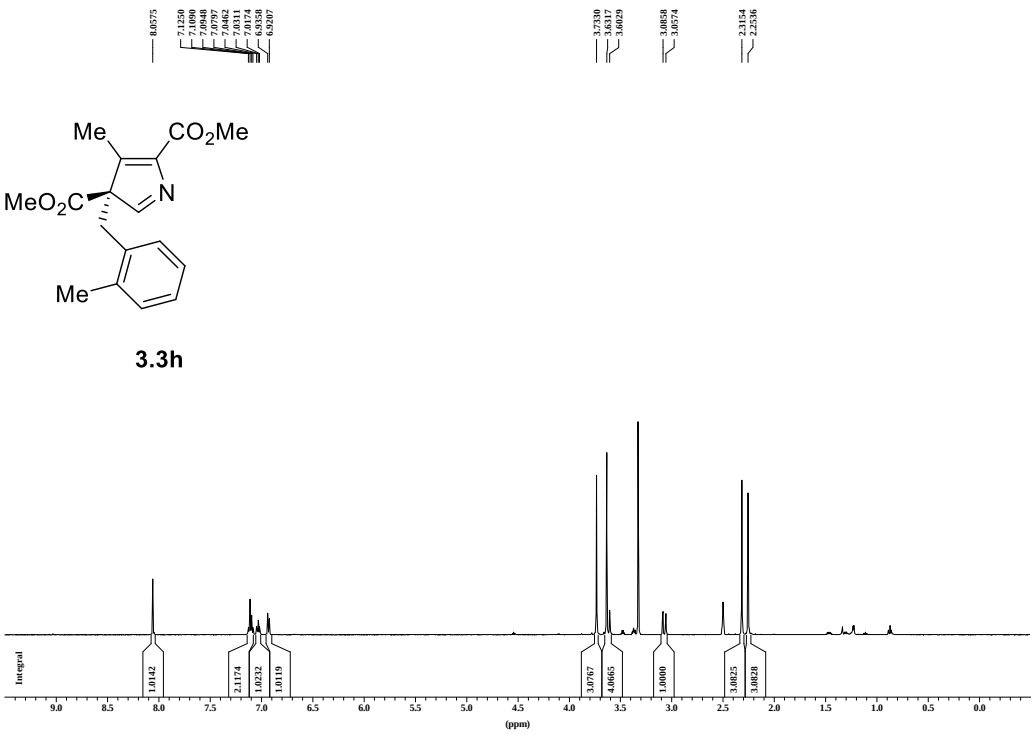
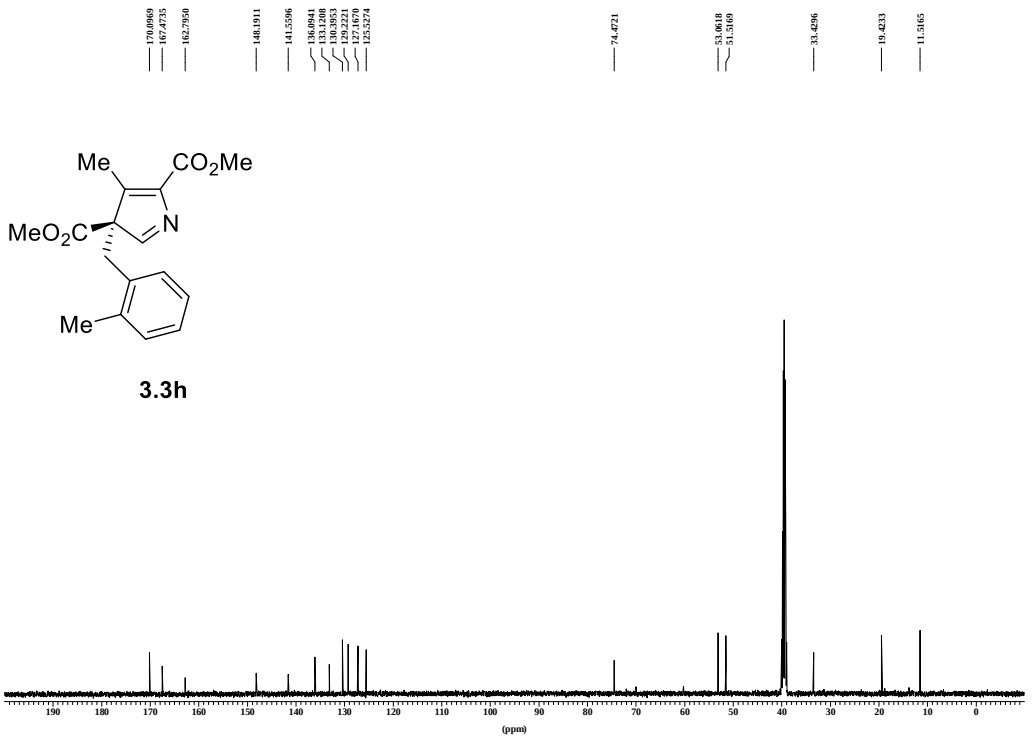
7.3772
7.3747
7.3690
7.3369
7.3331
7.1717
7.1366
7.1012
7.0998
7.0847
3.6997
3.6487
3.6391
3.6190
3.2153
3.2168
2.2839
Me
CO2Me
MeO2C
N
Br
Integral
0.9859
1.9704
1.0337
1.0274
3.0000
4.0466
1.0231
3.0107
(ppm)

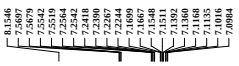
3.3g

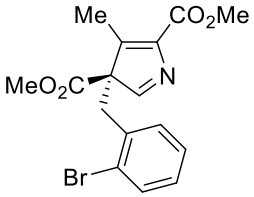

170.2354
167.1018
162.8274
147.7466
142.0624
137.0050
131.9548
129.9581
128.2966
120.9509
74.2316
53.1128
51.4950
35.5284
11.3635
Me
CO2Me
MeO2C
N
Br
(ppm)

3.3g

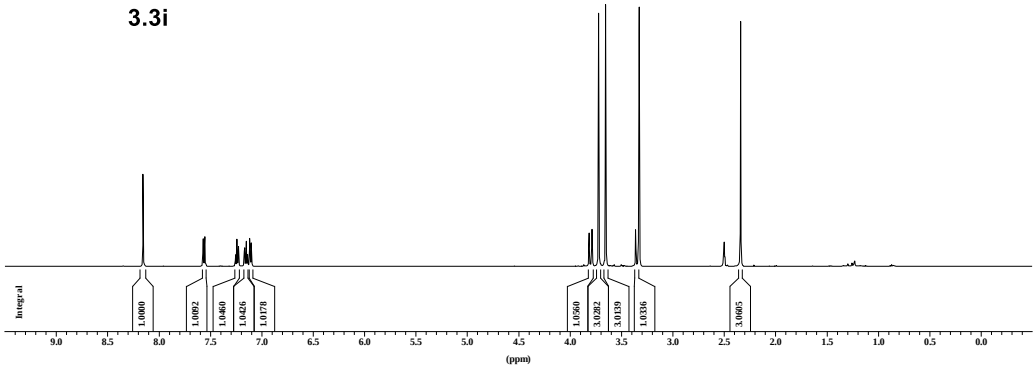

8.0575
7.1250
7.1090
7.0948
7.0797
7.0462
7.0311
7.0174
6.9358
6.9207
3.7330
3.6317
3.6029
3.0858
3.0574
2.3154
2.2536
Me
CO2Me
MeO2C
N
Me
3.3h
Integral
1.0142
2.1174
1.0232
1.0119
3.0767
4.0665
1.0000
3.0825
3.0828
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


170.0969
167.4735
162.7950
148.1911
141.5596
136.0941
133.1208
130.3953
129.2221
127.1670
125.5274
74.4721
53.0618
51.5169
33.4296
19.4233
11.5165
Me
CO2Me
MeO2C
N
Me
3.3h
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

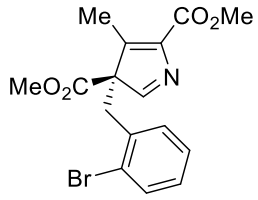

8.1546
7.5697
7.5679
7.5542
7.5519
7.2564
7.2543
7.2418
7.2390
7.2267
7.2244
7.1669
7.1667
7.1548
7.1511
7.1392
7.1366
7.1168
7.1135
7.1016
7.0984
3.8136
3.7856
3.7215
3.6537
3.3601
3.3522
2.3406


Me
CO2Me
MeO2C
N
Br

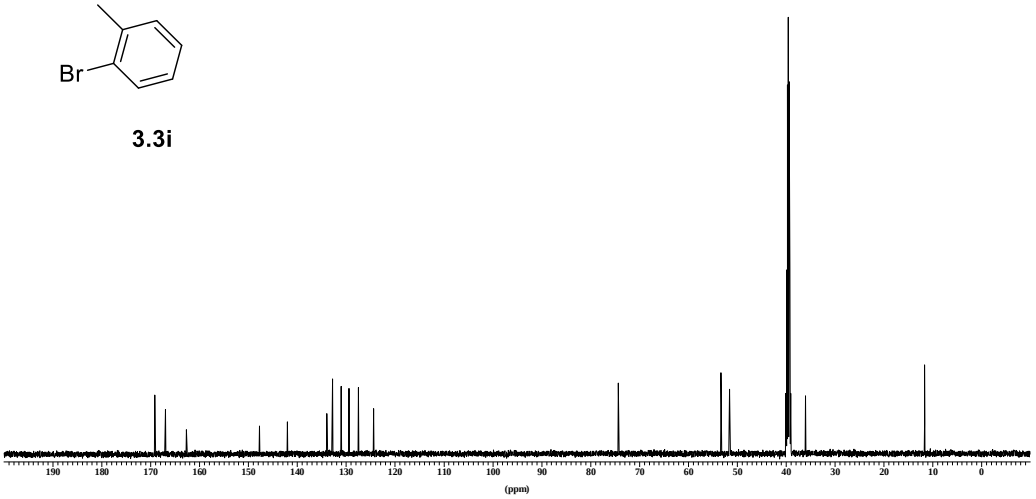
3.3i

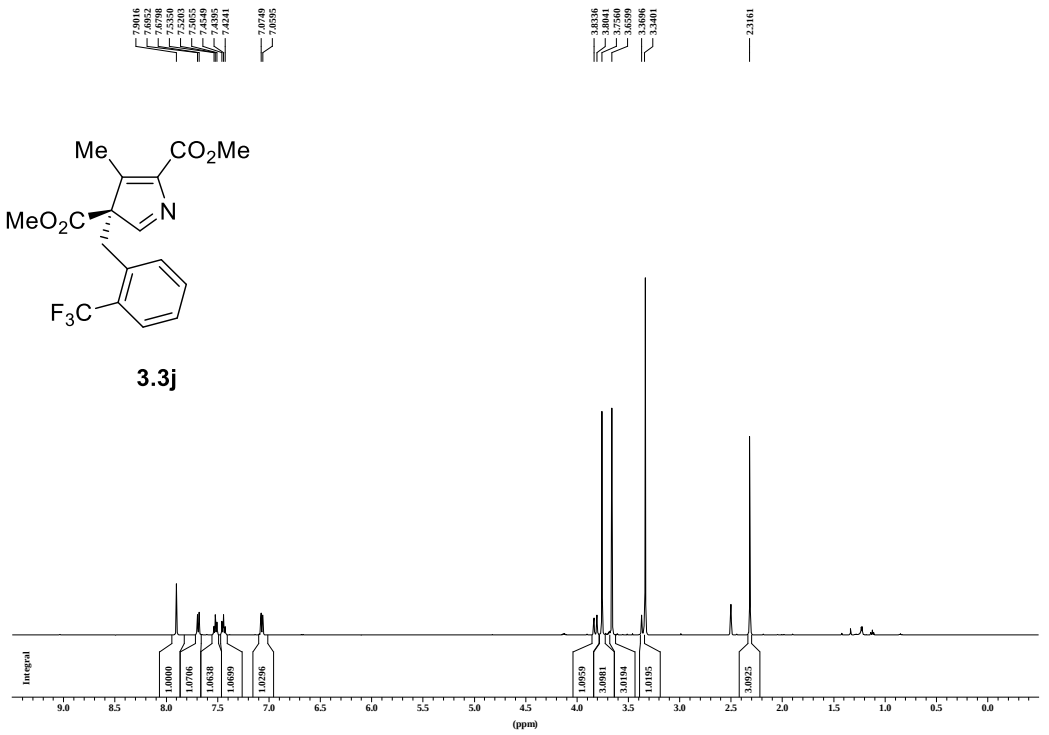

Integral
1.0000
1.0092
1.0460
1.0426
1.0078
1.0360
3.0202
3.0139
1.0336
3.0605
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


169.1423
166.9925
162.6565
147.6883
142.0187
133.9516
132.7710
130.9656
129.4497
127.4658
124.3614
74.3263
53.2658
51.5606
35.9802
11.6404

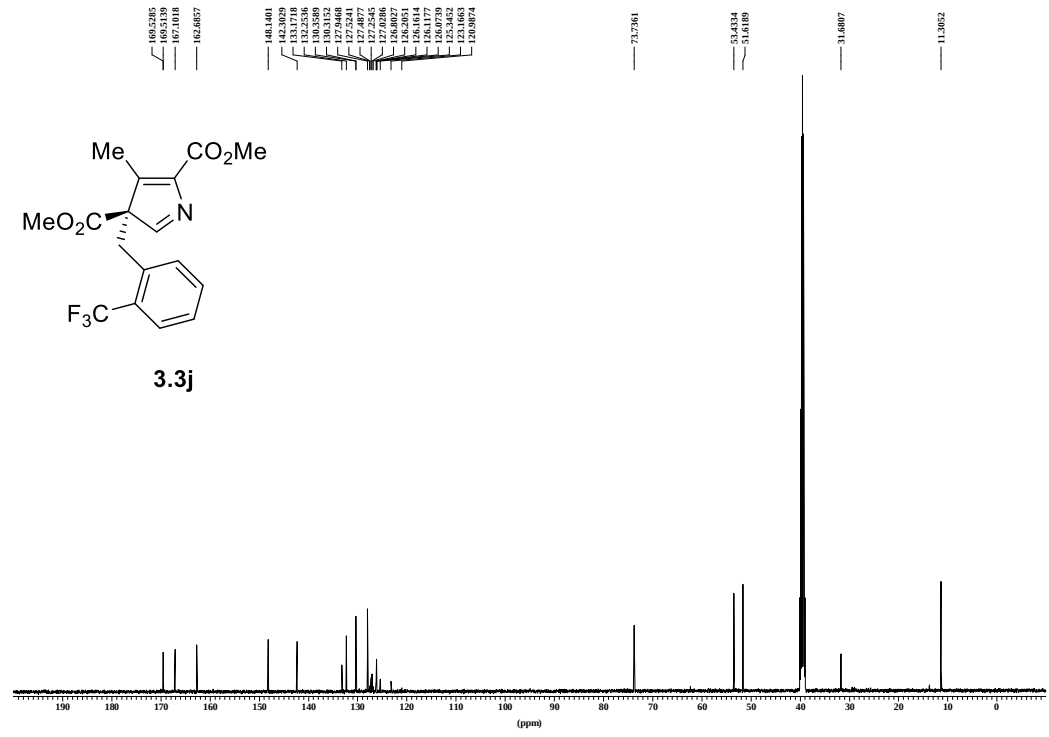

Me
CO2Me
MeO2C
N
Br

3.3i

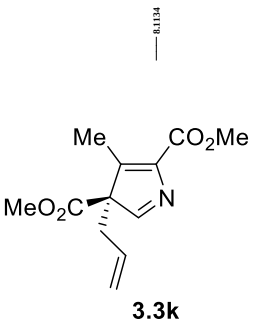

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


7.9016
7.8952
7.8798
7.5350
7.5203
7.5055
7.4540
7.4395
7.4241
7.0749
7.0595
3.8336
3.8041
3.7560
3.6599
3.3696
3.3401
2.3161
Me
CO2Me
MeO2C
N
F3C
Integral
1.0000
1.0706
1.0638
1.0699
1.0296
1.0959
3.0981
3.0194
1.0195
3.0925
(ppm)

3.3j

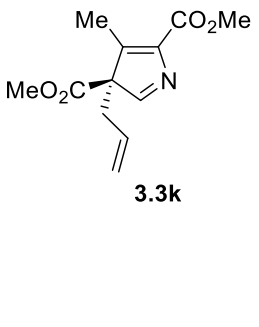

169.5205
169.1539
167.1018
162.6857
148.1401
142.3029
133.1718
132.2536
130.3589
130.3152
127.9468
127.5241
127.4477
127.2545
127.0286
126.8027
126.2051
126.1414
126.1177
126.0739
125.3452
123.1663
120.9074
73.7361
53.4334
51.6189
31.6807
11.3052
Me
CO2Me
MeO2C
N
F3C
(ppm)

3.3j


Me
CO2Me
MeO2C
N

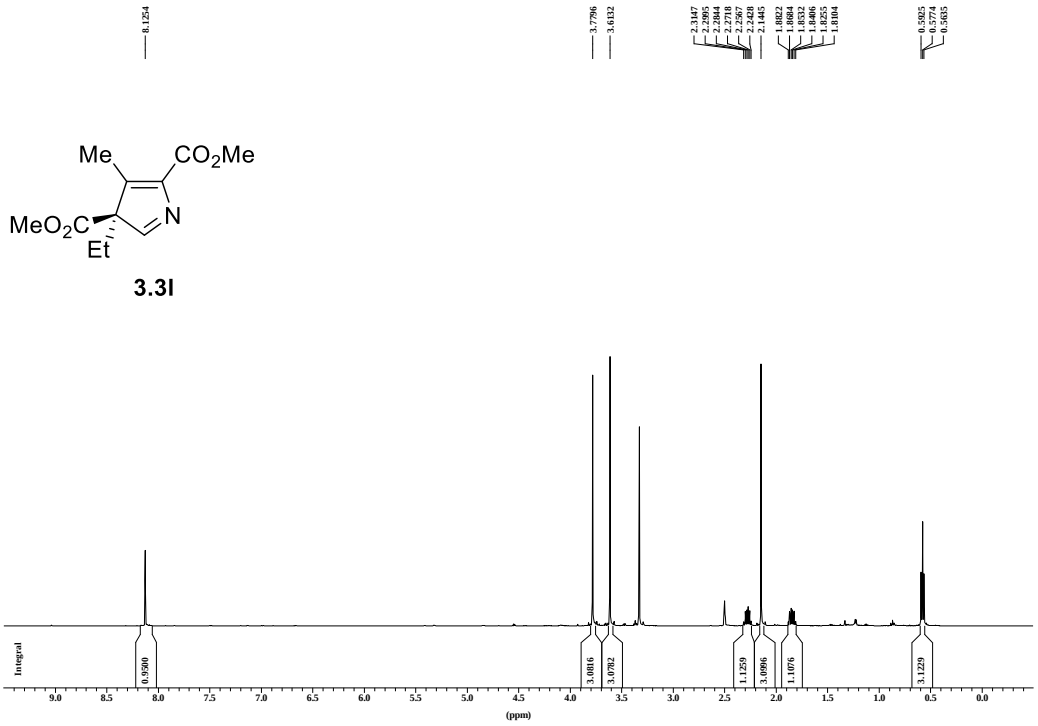
3.3k

8.1134
5.3016
5.2879
5.2820
5.2728
5.2602
5.2540
5.2481
5.2394
5.2343
5.2192
5.1395
5.1372
5.1056
5.1033
4.9864
4.9806
4.9788
4.9627
4.9604
4.9564
4.6591
3.7577
3.6065
3.0084
2.9951
2.9809
2.9672
2.6292
2.6140
2.6017
2.5866
2.1583
Integral
0.9750
1.0594
1.0607
0.9564
3.1500
3.1252
1.0460
1.0569
3.1774
(ppm)

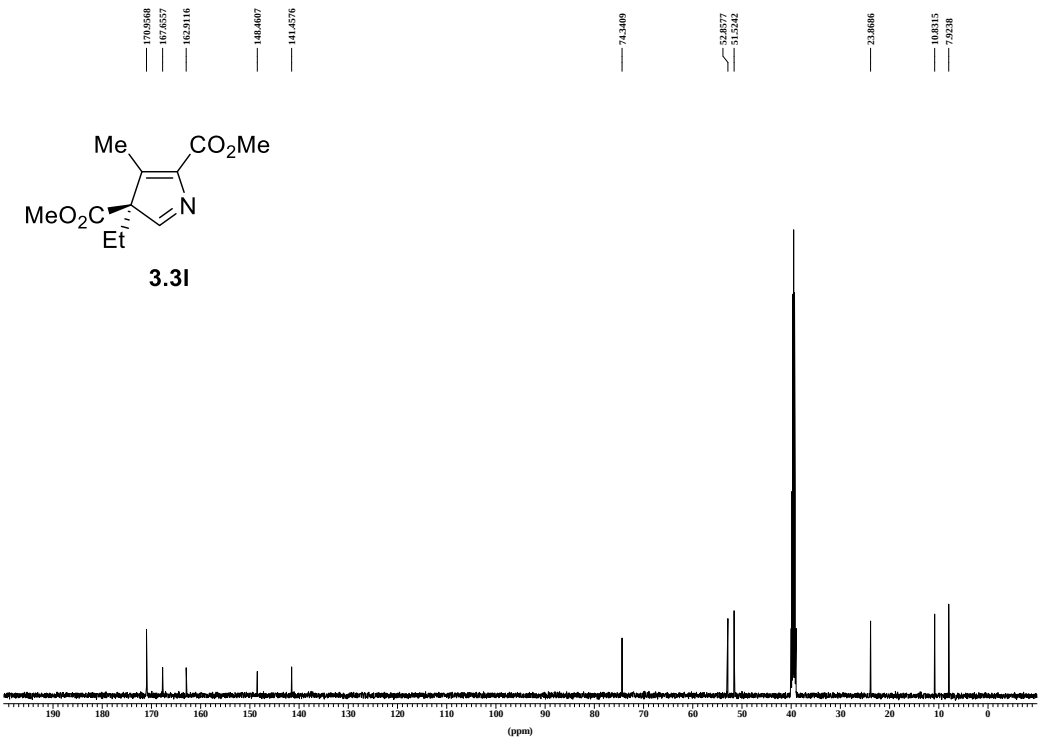

Me
CO2Me
MeO2C
N

3.3k

170.3811
167.1237
162.8824
140.3733
141.6325
130.5047
119.5153
73.2915
52.9816
51.5460
34.4061
10.9700
(ppm)

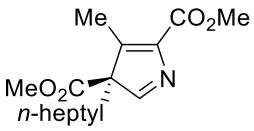

8.1254
3.7796
3.6132
2.3147
2.2895
2.2644
2.2718
2.2367
2.2428
2.1445
1.8822
1.8684
1.8572
1.8406
1.8255
1.8104
0.5925
0.5774
0.5635
Me
CO2Me
MeO2C
Et
N
Integral
0.9500
3.0816
3.0782
1.1259
3.0996
1.1076
3.1229
(ppm)

3.3l

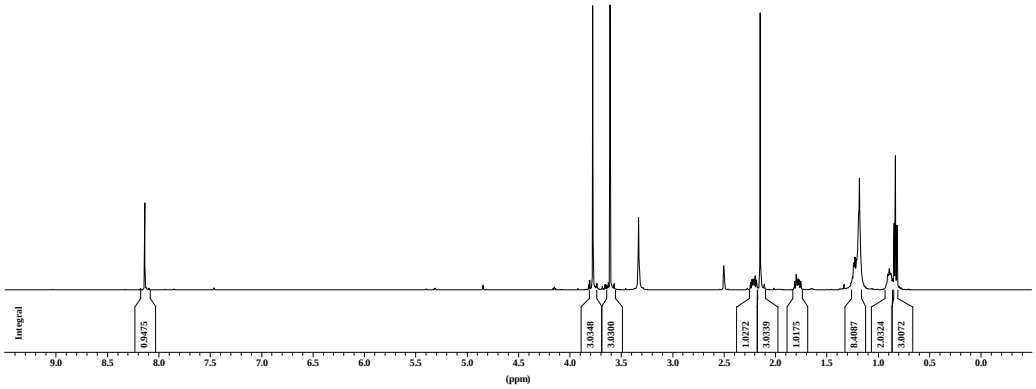

170.9568
167.6557
162.9116
148.4607
141.4576
74.3409
52.8577
51.5242
23.8686
10.8315
7.9238
Me
CO2Me
MeO2C
Et
N
(ppm)

3.3l

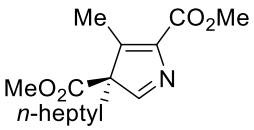

8.1355
3.7739
3.6069
2.2445
2.2277
2.2226
2.2151
2.2088
2.1974
2.1861
2.1823
2.1457
2.1429
1.7965
1.7864
1.7739
1.7713
1.7566
1.7524
1.2539
1.2367
1.2254
1.2090
1.1938
0.8926
0.8749
0.8573
0.8447
0.8368
0.8169


Me
CO2Me
MeO2C
N
n-heptyl

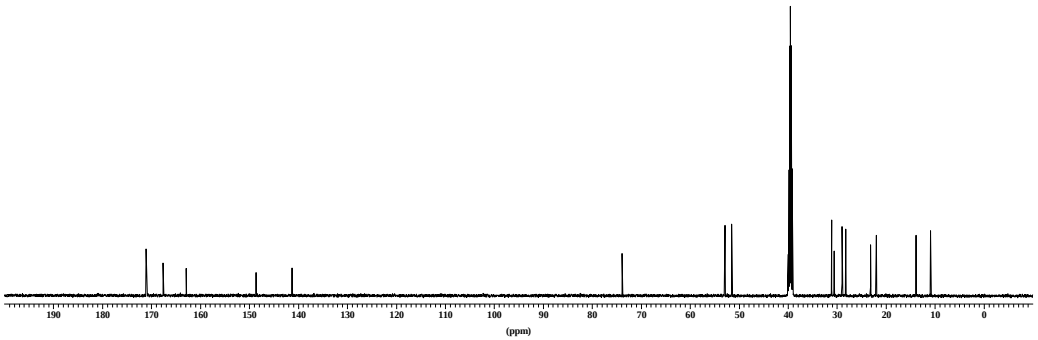
3.3m

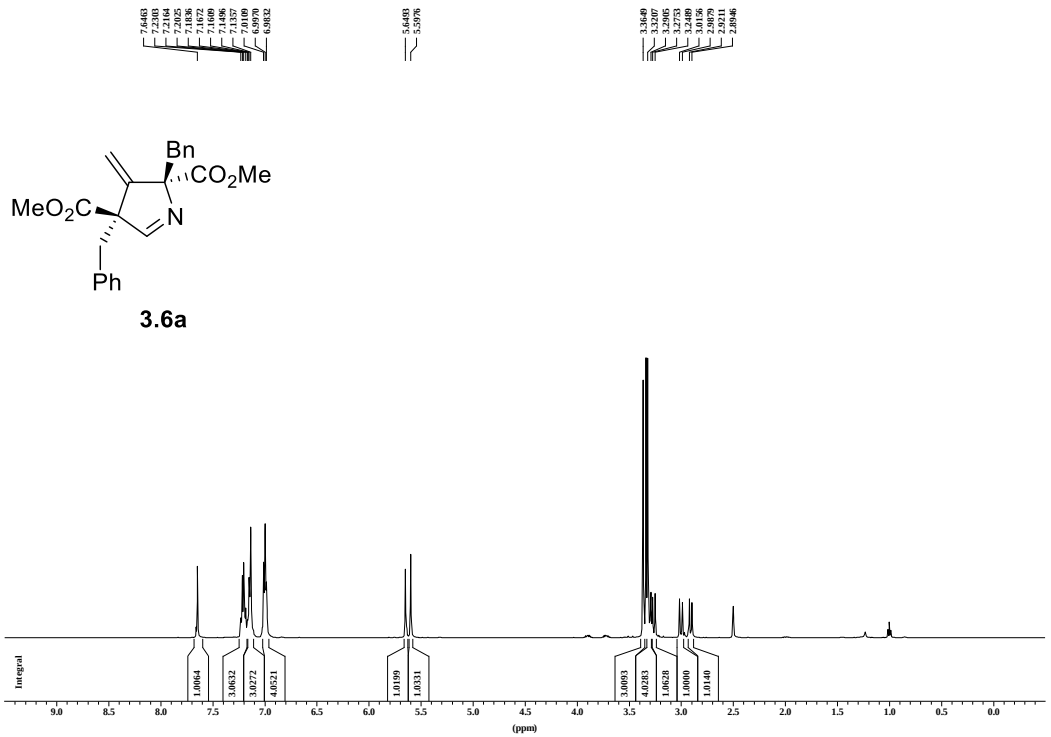

Integral
0.9475
3.0348
3.0300
1.0272
3.0339
1.0175
0.4087
2.0324
3.0072
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


171.1026
167.6192
162.9189
148.6429
141.2972
73.8891
52.4677
51.4850
31.0758
30.5739
30.1979
28.2237
23.1763
21.9593
13.8485
10.8679

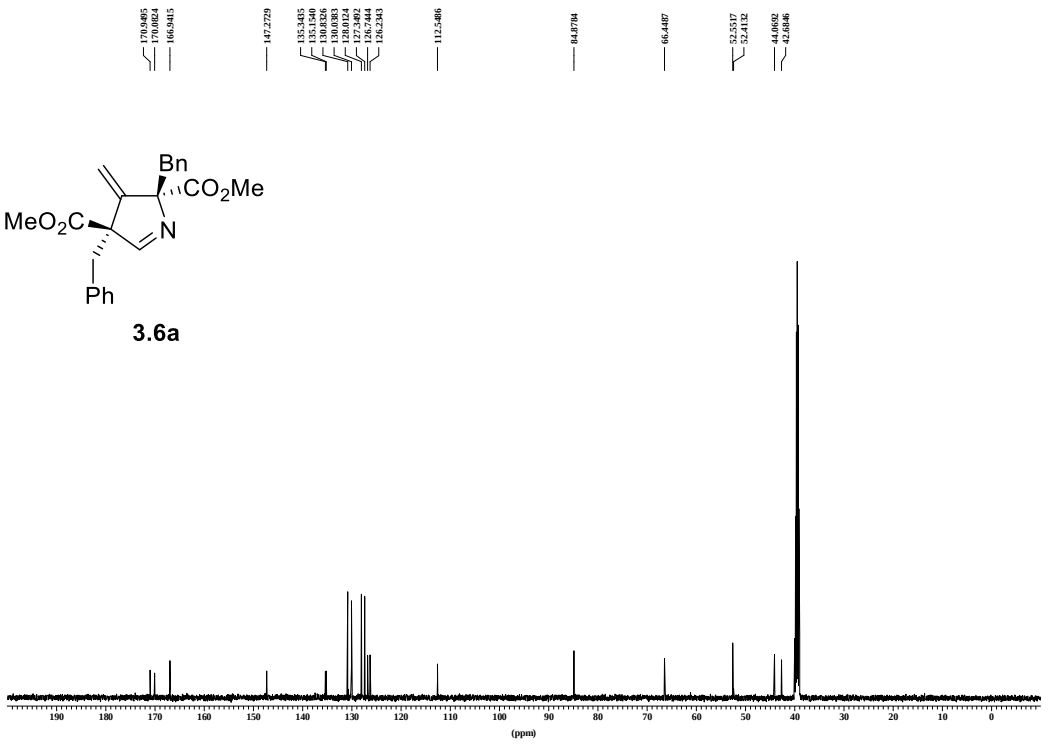

Me
CO2Me
MeO2C
N
n-heptyl

3.3m

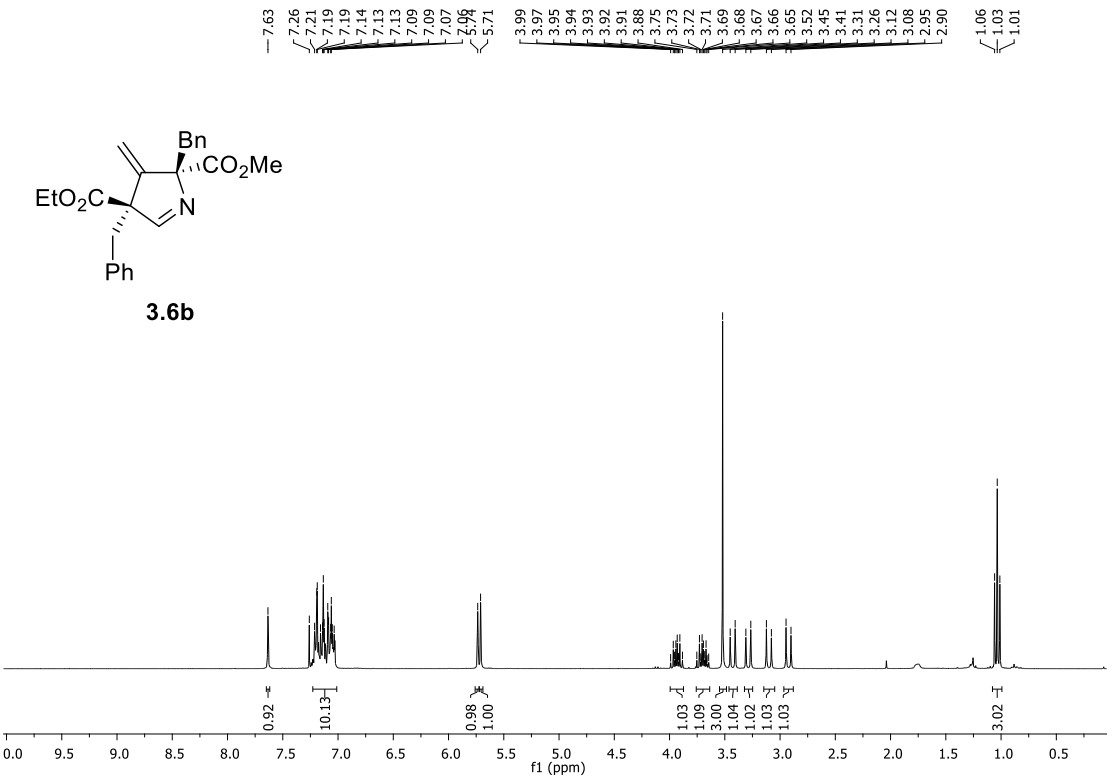

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


7.6463
7.2340
7.2164
7.2025
7.1836
7.1672
7.1600
7.1496
7.1357
7.0109
6.9979
6.9852
5.6493
5.5976
3.3649
3.3207
3.2965
3.2753
3.2498
3.0156
2.9879
2.9211
2.8946
Bn
CO2Me
MeO2C
N
Ph
Integral
1.0064
3.0632
3.0272
4.0521
1.0199
1.0331
3.0093
4.0283
1.0628
1.0000
1.0140
(ppm)

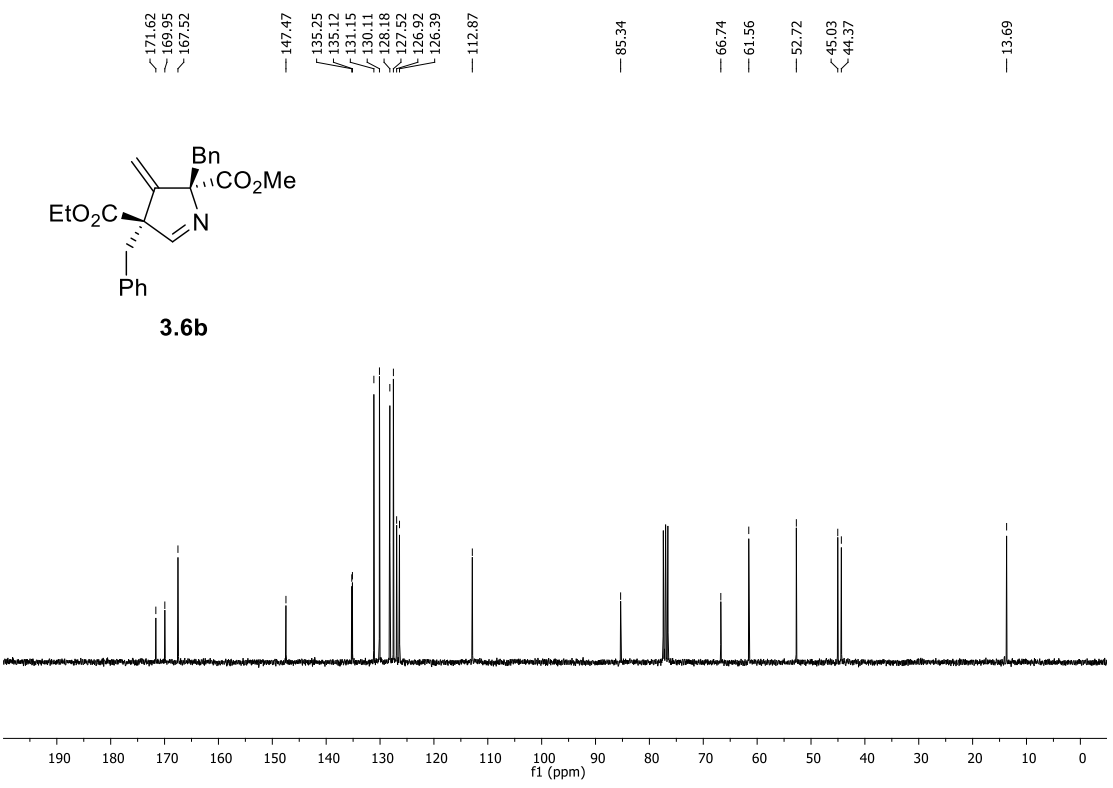
3.6a


170.9495
170.0824
166.9415
147.2729
135.3455
135.1540
130.8326
130.0383
128.0124
127.9693
126.7444
126.2343
112.5486
84.8784
66.4487
52.5517
52.4132
44.0692
42.6846
Bn
CO2Me
MeO2C
N
Ph
(ppm)

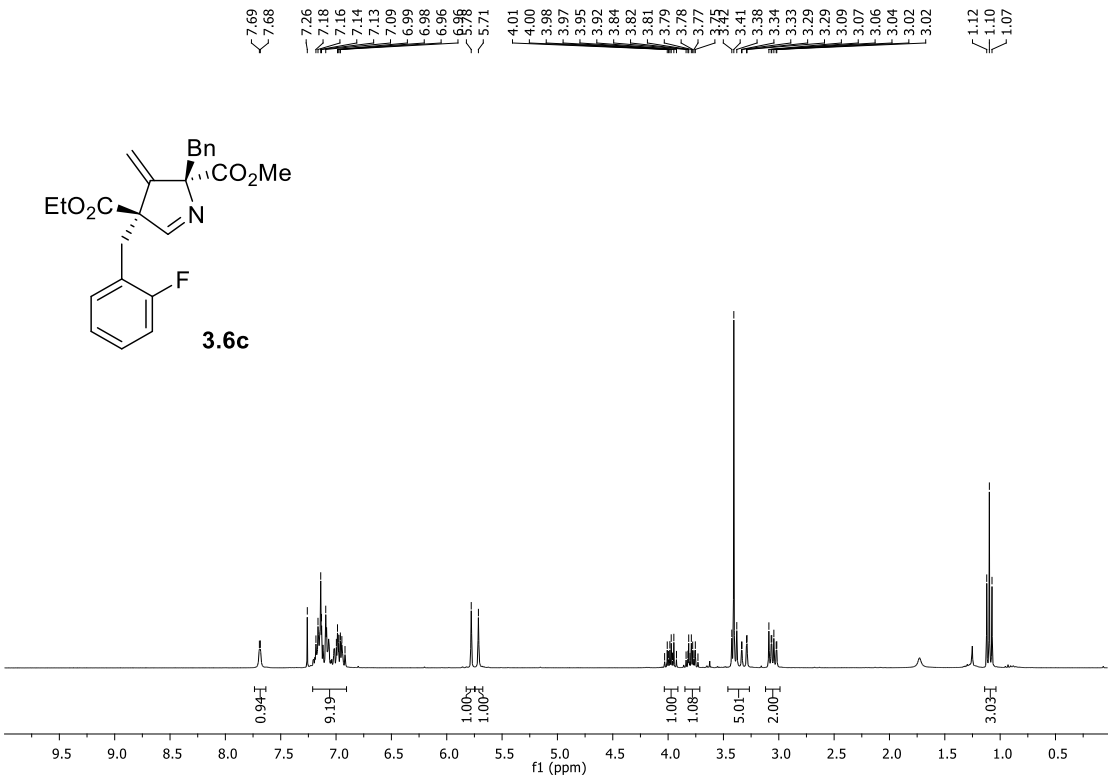
3.6a

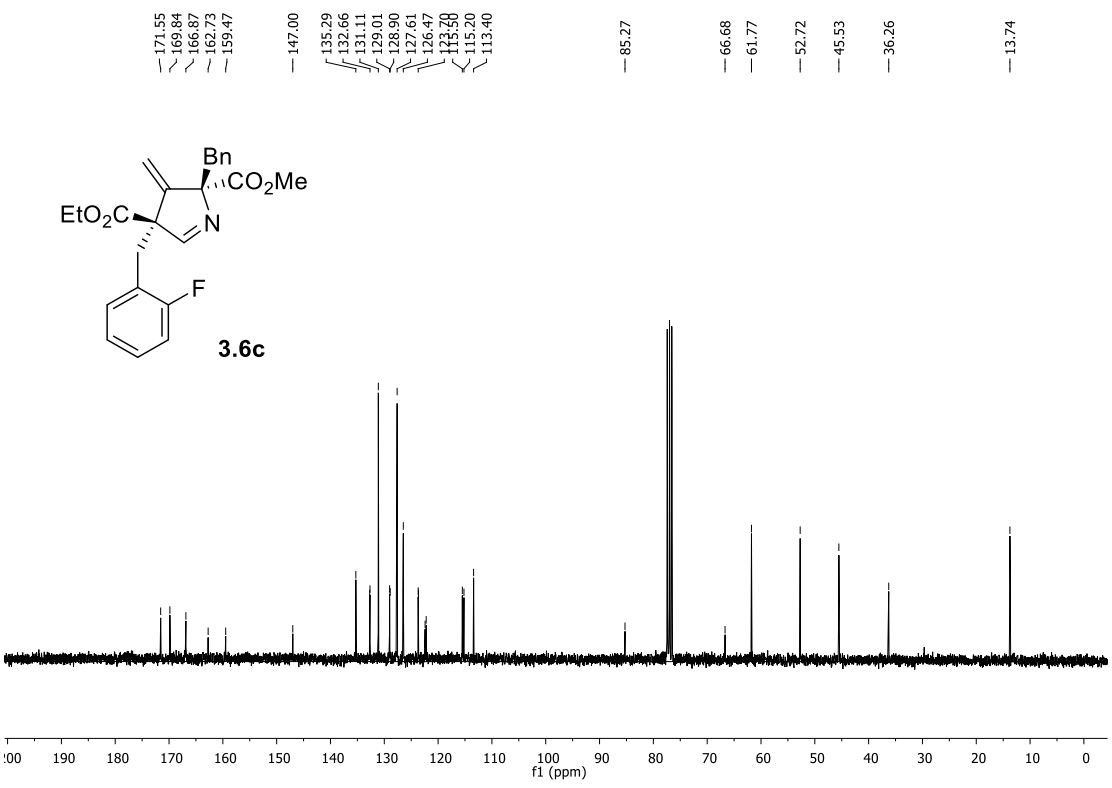

7.63
7.26
7.21
7.19
7.19
7.14
7.13
7.13
7.09
7.09
7.07
7.06
5.74
5.71
3.99
3.97
3.95
3.94
3.93
3.92
3.91
3.88
3.75
3.73
3.72
3.71
3.69
3.68
3.67
3.66
3.65
3.52
3.45
3.41
3.31
3.26
3.12
3.08
2.95
2.90
1.06
1.03
1.01
Bn
CO2Me
EtO2C
N
Ph
0.92
10.13
0.98
1.00
1.03
1.09
3.00
1.04
1.02
1.03
1.03
3.02
f1 (ppm)

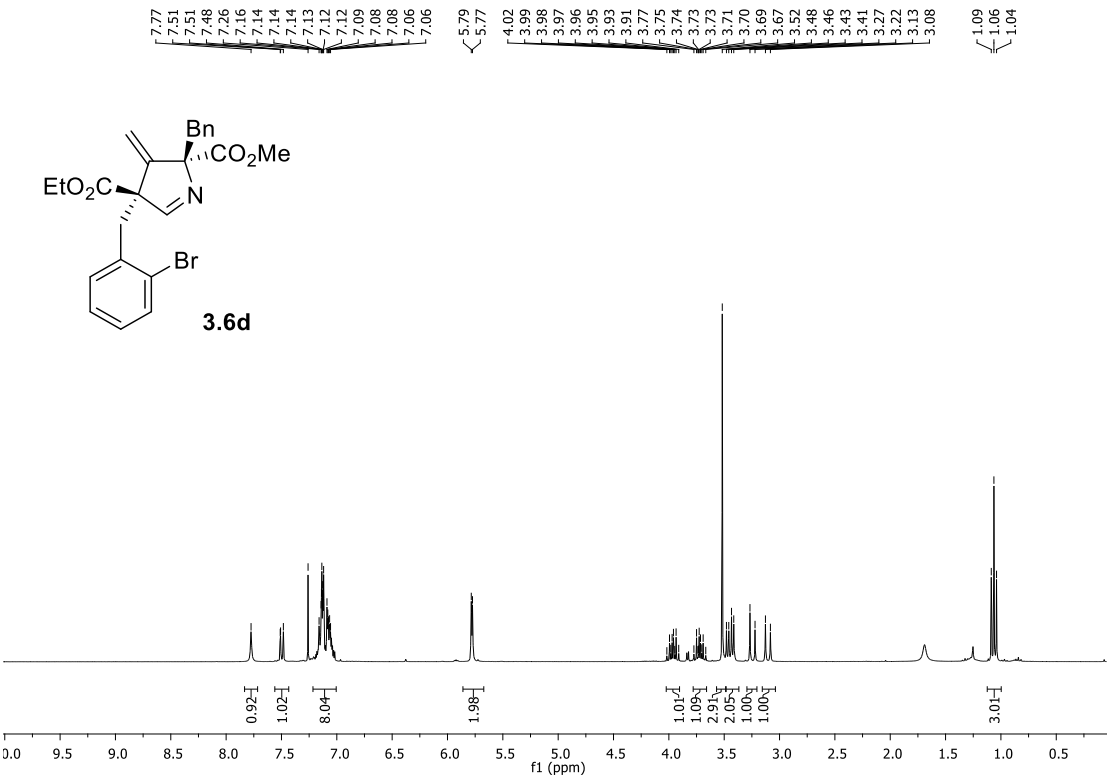
3.6b

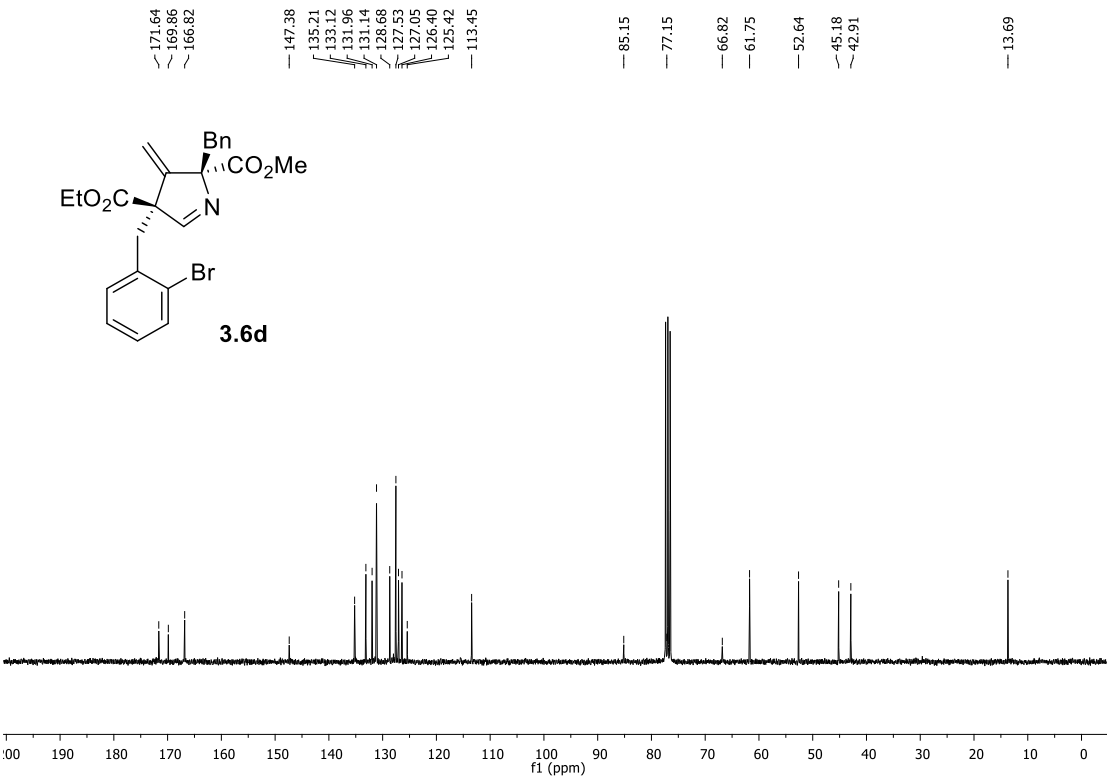

171.62
169.95
167.52
147.47
135.25
135.12
131.15
130.11
128.18
127.52
126.92
126.39
112.87
85.34
66.74
61.56
52.72
45.03
44.37
13.69
Bn
CO2Me
EtO2C
N
Ph
f1 (ppm)

3.6b


7.69
7.68
7.26
7.18
7.16
7.14
7.13
7.09
6.99
6.98
6.96
6.96
5.78
5.71
4.01
4.00
3.98
3.97
3.95
3.92
3.84
3.82
3.81
3.79
3.78
3.77
3.75
3.42
3.41
3.38
3.34
3.33
3.29
3.29
3.09
3.07
3.06
3.04
3.02
3.02
1.12
1.10
1.07
Bn
CO2Me
EtO2C
N
F
3.6c
0.94
9.19
1.00
1.00
1.00
1.08
5.01
2.00
3.03
f1 (ppm)


171.55
169.84
166.87
162.73
159.47
147.00
135.29
132.66
131.11
129.01
128.90
127.61
126.47
115.50
115.20
113.40
85.27
66.68
61.77
52.72
45.53
36.26
13.74
Bn
CO2Me
EtO2C
N
F
3.6c
f1 (ppm)


7.77
7.51
7.51
7.48
7.26
7.16
7.14
7.14
7.14
7.13
7.12
7.12
7.09
7.08
7.08
7.06
7.06
5.79
5.77
4.02
3.99
3.98
3.97
3.96
3.95
3.93
3.91
3.77
3.75
3.74
3.73
3.73
3.71
3.70
3.69
3.67
3.52
3.48
3.46
3.43
3.41
3.27
3.22
3.13
3.08
1.09
1.06
1.04
Bn
CO2Me
EtO2C
N
Br
3.6d
0.92
1.02
8.04
1.98
1.01
1.09
2.91
2.05
1.00
1.00
3.01
f1 (ppm)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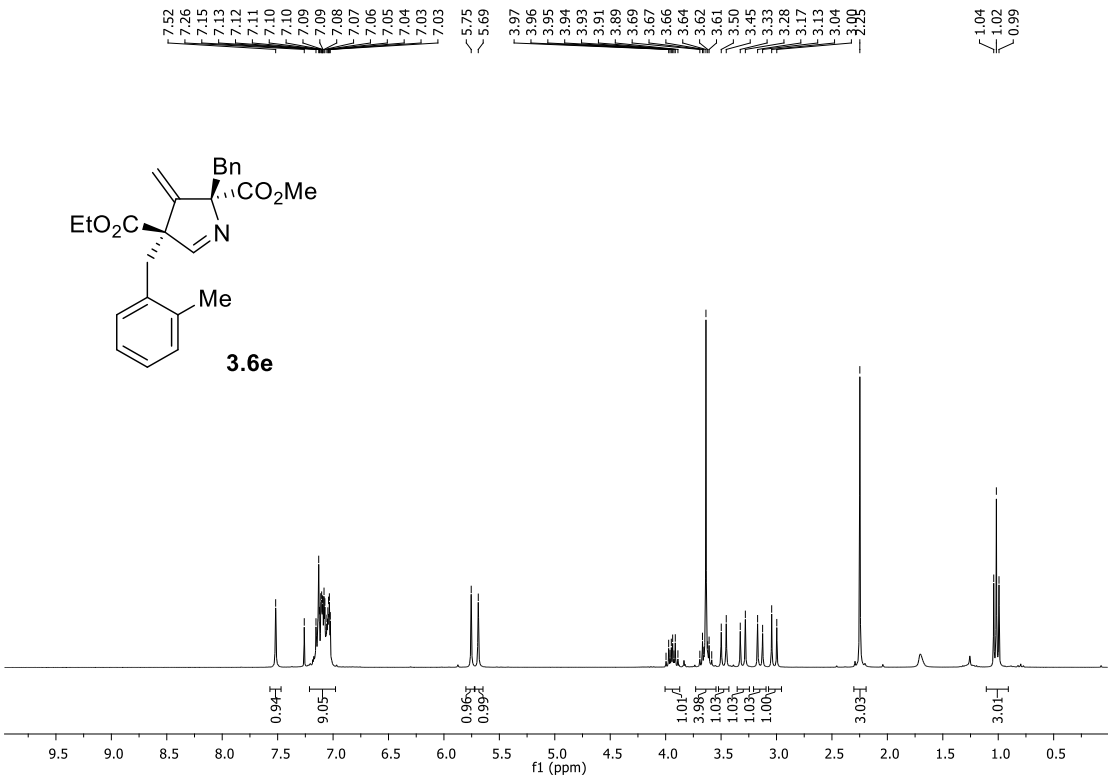
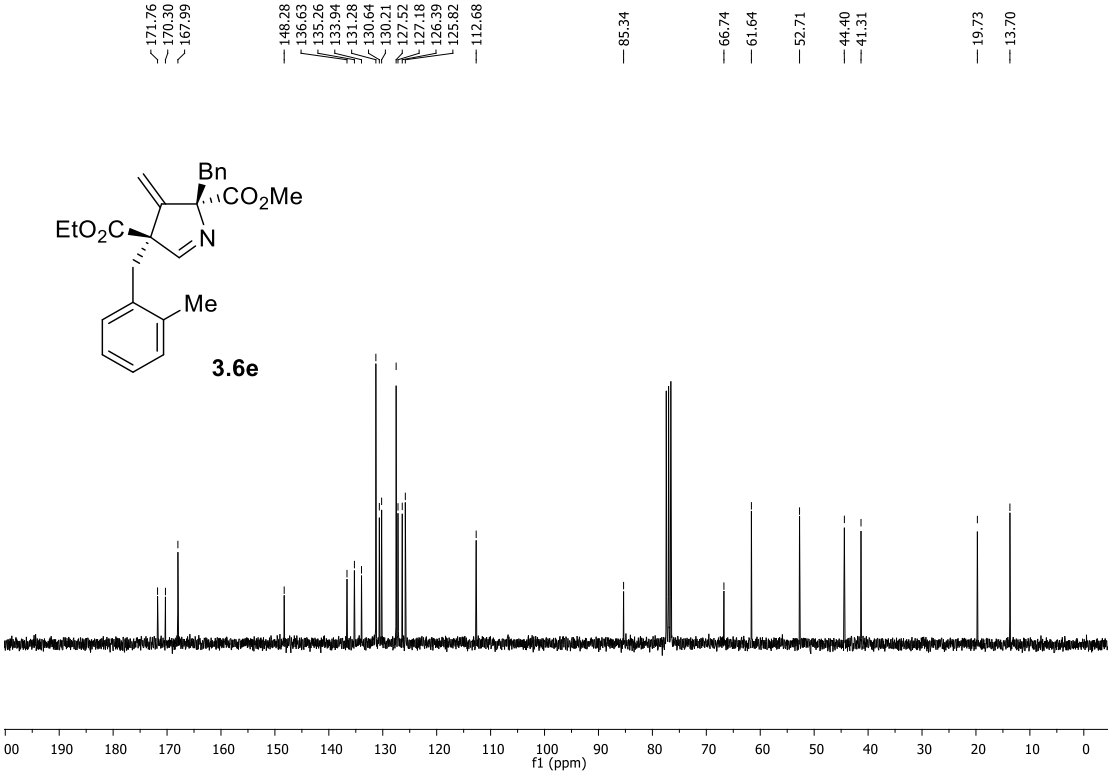
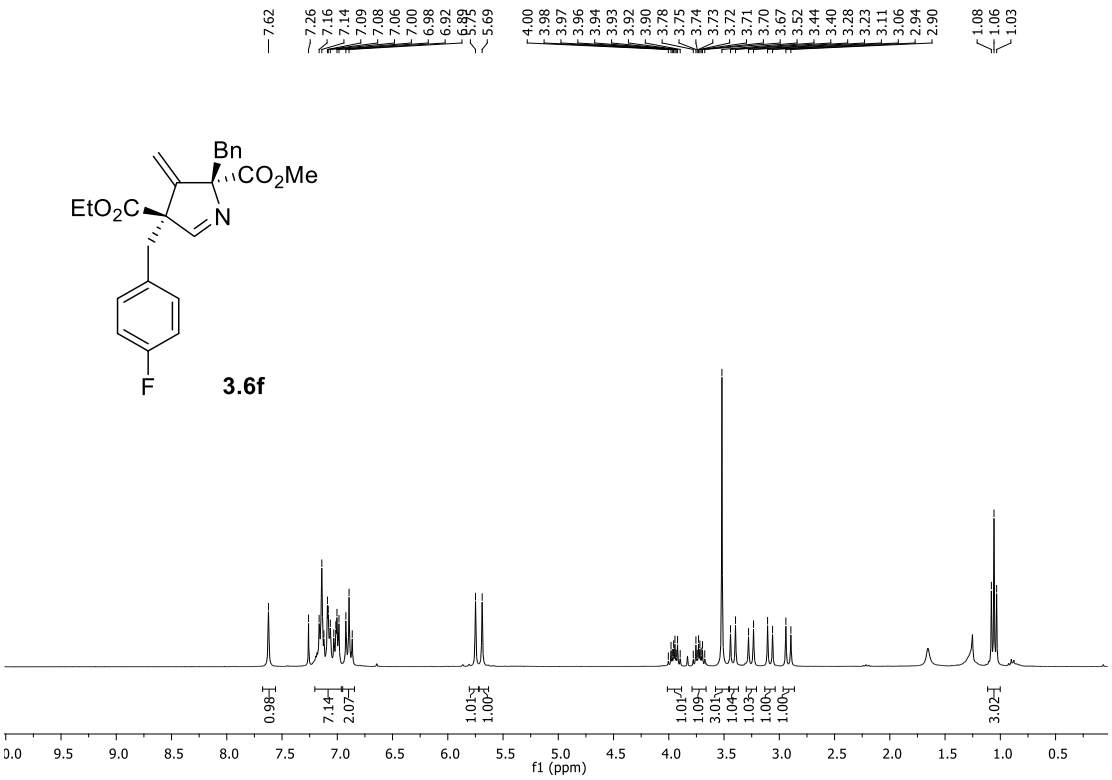
166.82
147.38
135.21
133.12
131.96
131.14
128.68
127.53
127.05
126.40
125.42
113.45
85.15
77.15
66.82
61.75
52.64
45.18
42.91
13.69
Bn
CO2Me
EtO2C
N
Br
3.6d
f1 (ppm)


7.52
7.26
7.15
7.13
7.12
7.11
7.10
7.10
7.09
7.09
7.08
7.07
7.06
7.05
7.04
7.03
7.03
5.75
5.69
3.97
3.96
3.95
3.94
3.93
3.91
3.89
3.69
3.67
3.66
3.64
3.62
3.61
3.50
3.45
3.33
3.28
3.17
3.13
3.04
3.00
2.25
1.04
1.02
0.99
Bn
CO2Me
EtO2C
N
Me
3.6e
0.94
9.05
0.96
0.99
1.01
3.98
1.03
1.03
1.03
1.00
3.03
3.01
f1 (ppm)


171.76
170.30
167.99
148.28
136.63
135.26
133.94
131.28
130.64
130.21
127.52
127.18
126.39
125.82
112.68
85.34
66.74
61.64
52.71
44.40
41.31
19.73
13.70
Bn
CO2Me
EtO2C
N
Me
3.6e
f1 (ppm)


7.62
7.26
7.16
7.14
7.09
7.08
7.06
7.00
6.98
6.92
6.88
5.72
5.69
4.00
3.98
3.97
3.96
3.94
3.93
3.92
3.90
3.78
3.75
3.74
3.73
3.72
3.71
3.70
3.67
3.52
3.44
3.40
3.28
3.23
3.11
3.06
2.94
2.90
1.08
1.06
1.03
Bn
CO2Me
EtO2C
N
F
3.6f
0.98
7.14
2.07
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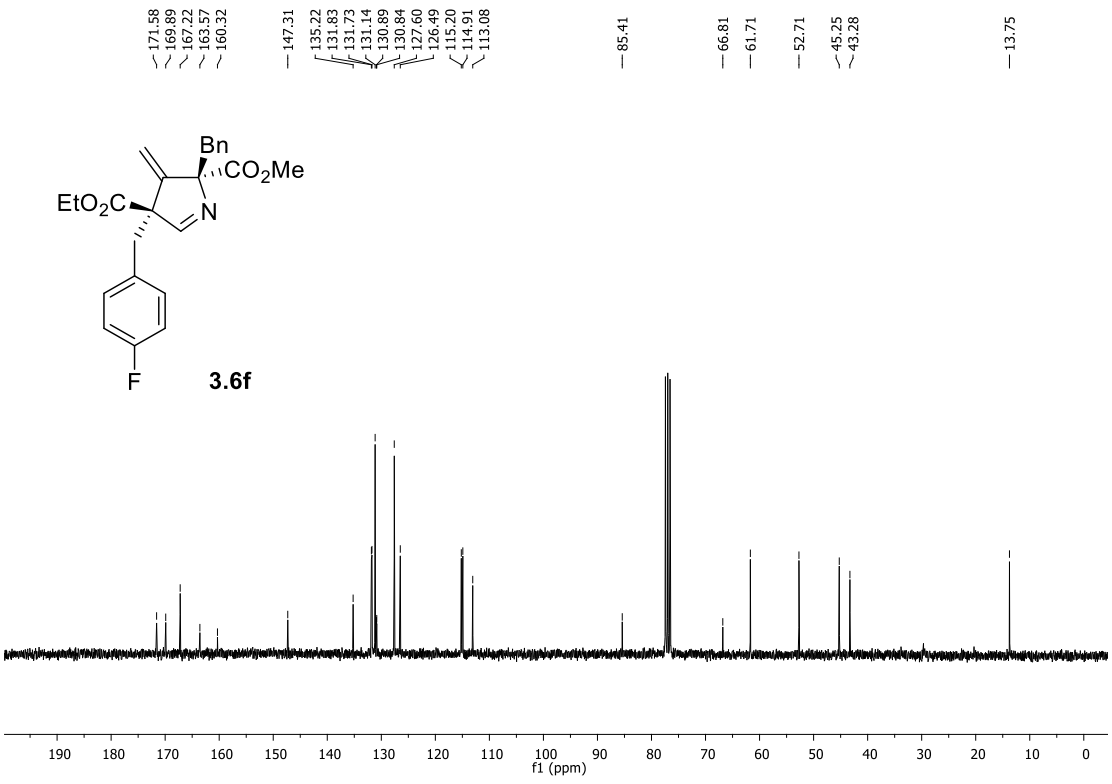
1.00
1.01
1.09
3.01
1.04
1.03
1.00
1.00
3.02
f1 (ppm)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131.83
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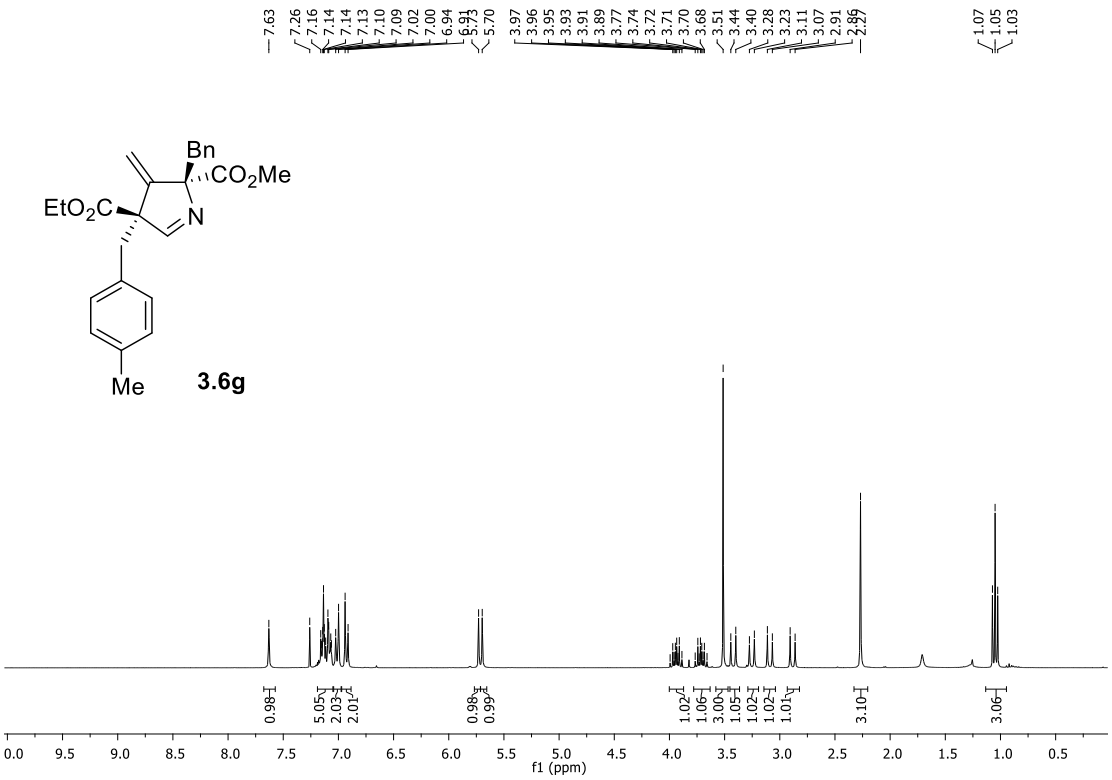
131.14
130.89
130.84
127.60
126.49
115.20
114.91
113.08
85.41
66.81
61.71
52.71
45.25
43.28
13.75
Bn
CO2Me
EtO2C
N
F
3.6f
f1 (ppm)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7.09
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7.00
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6.91
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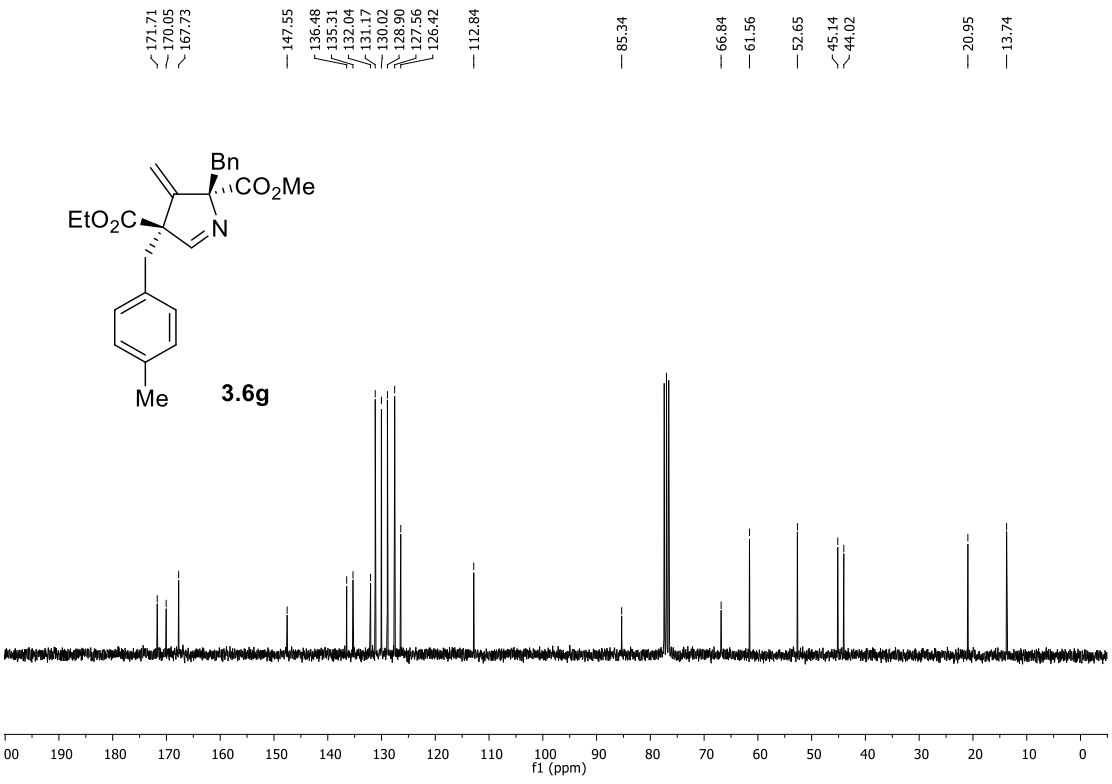
3.97
3.96
3.95
3.93
3.91
3.89
3.77
3.74
3.72
3.71
3.70
3.68
3.51
3.44
3.40
3.28
3.23
3.11
3.07
2.91
2.86
2.29
1.07
1.05
1.03
Bn
CO2Me
EtO2C
N
Me
3.6g
0.98
5.05
2.03
2.01
0.98
0.99
1.02
1.06
3.00
1.05
1.02
1.02
1.01
3.10
3.06
f1 (ppm)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131.17
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128.90
127.56
126.42
112.84
85.34
66.84
61.56
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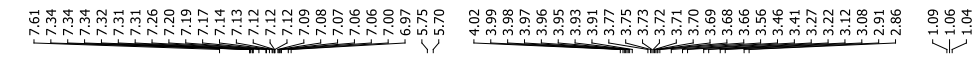
44.02
20.95
13.74
Bn
CO2Me
EtO2C
N
Me
3.6g
f1 (ppm)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7.34
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7.19
7.17
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7.12
7.12
7.12
7.09
7.08
7.07
7.06
7.06
7.00
6.97
5.75
5.70
4.02
3.99
3.98
3.97
3.96
3.95
3.93
3.91
3.77
3.75
3.73
3.72
3.71
3.70
3.69
3.68
3.66
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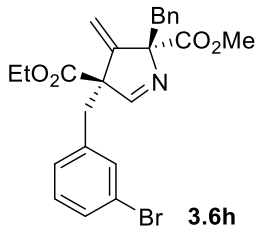
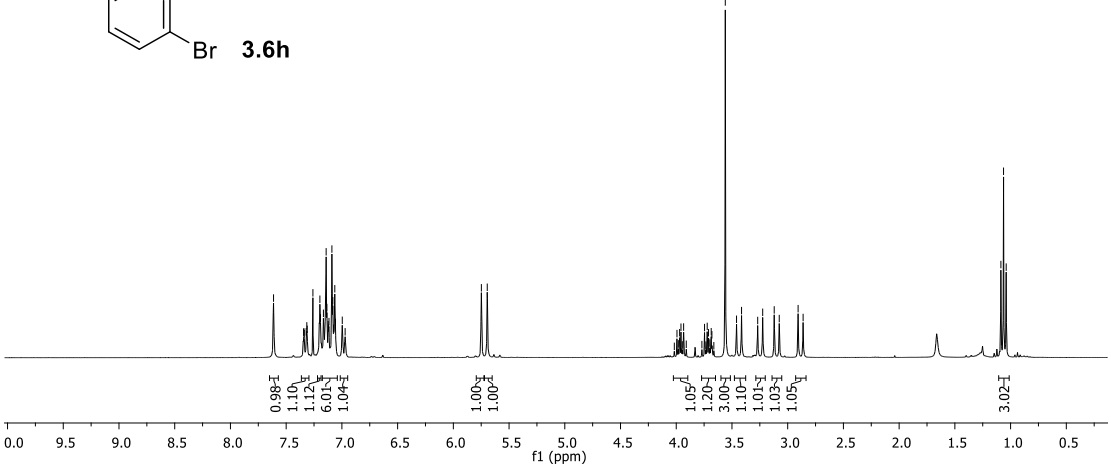
3.08
2.91
2.86
1.09
1.06
1.04


Bn
CO2Me
EtO2C
N
Br

3.6h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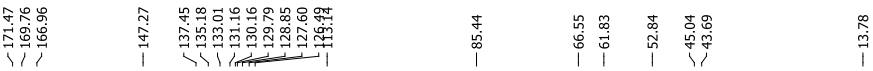
1.10
1.12
6.01
1.04
1.00
1.00
1.05
1.20
3.00
1.10
1.01
1.03
1.05
3.02
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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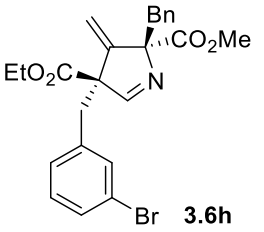
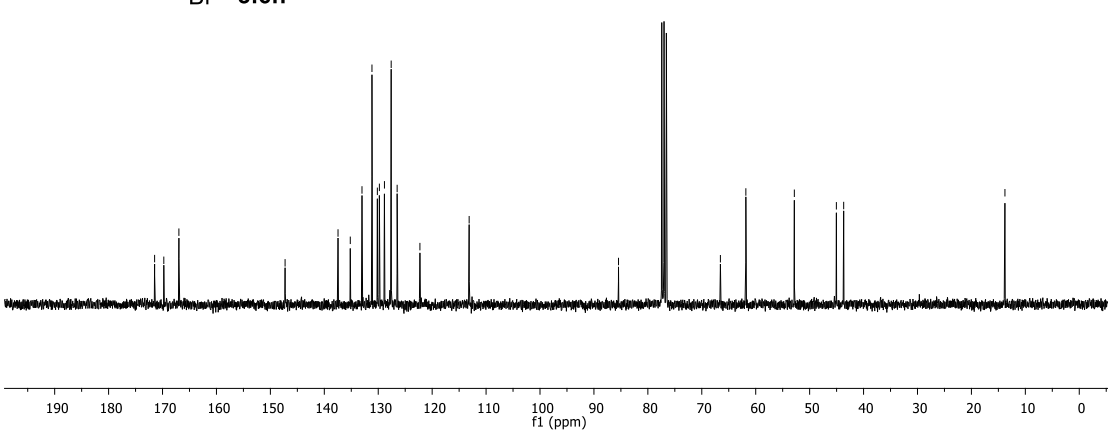
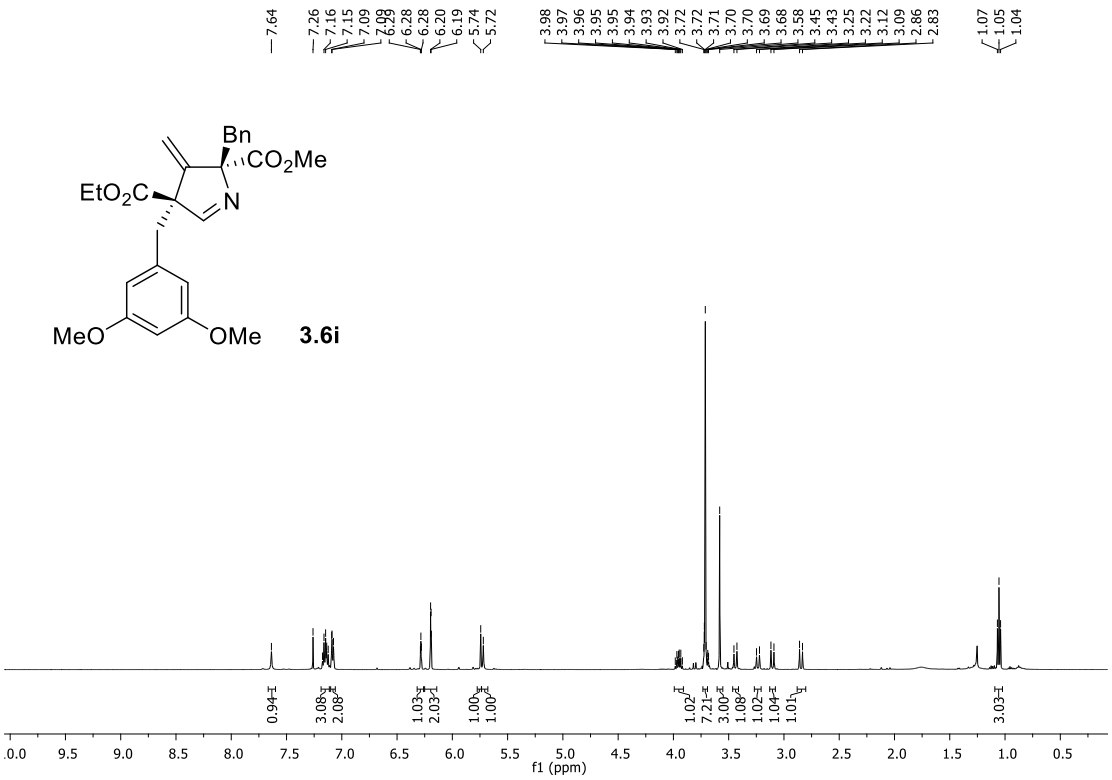
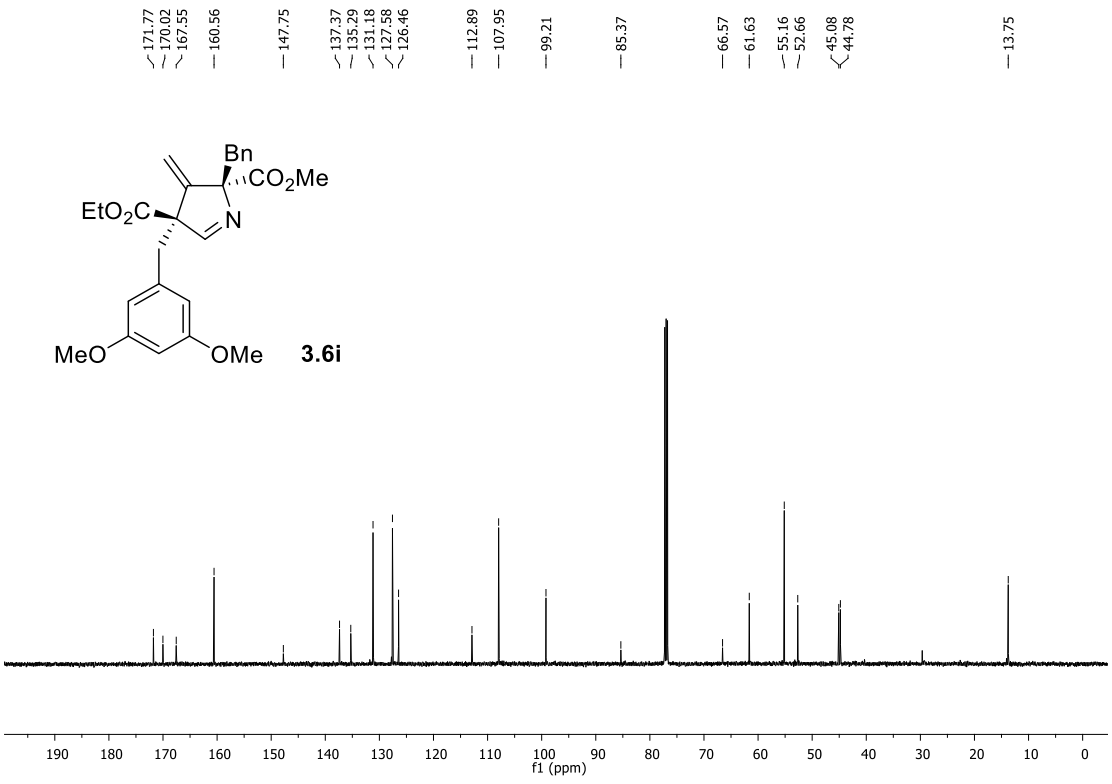
66.55
61.83
52.84
45.04
43.69
13.78

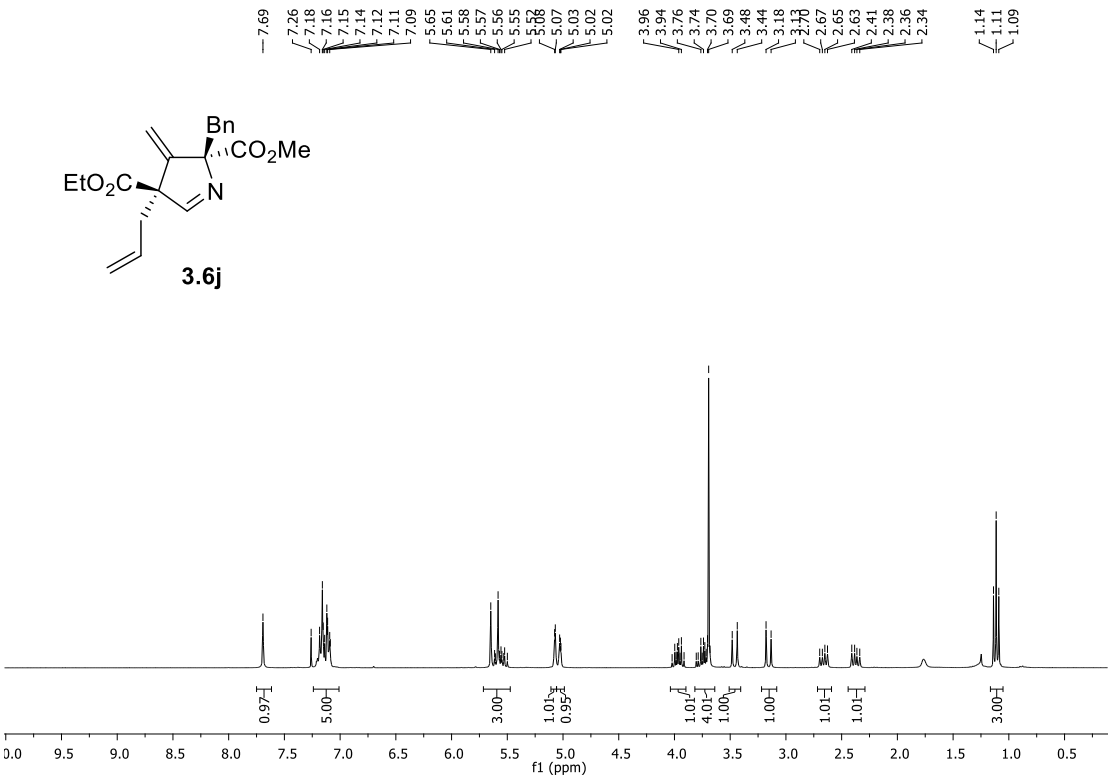

Bn
CO2Me
EtO2C
N
Br

3.6h


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


Bn
CO2Me
EtO2C
N
MeO
OMe
3.6i
f1 (ppm)


Bn
CO2Me
EtO2C
N
MeO
OMe
3.6i
f1 (ppm)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7.12
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5.61
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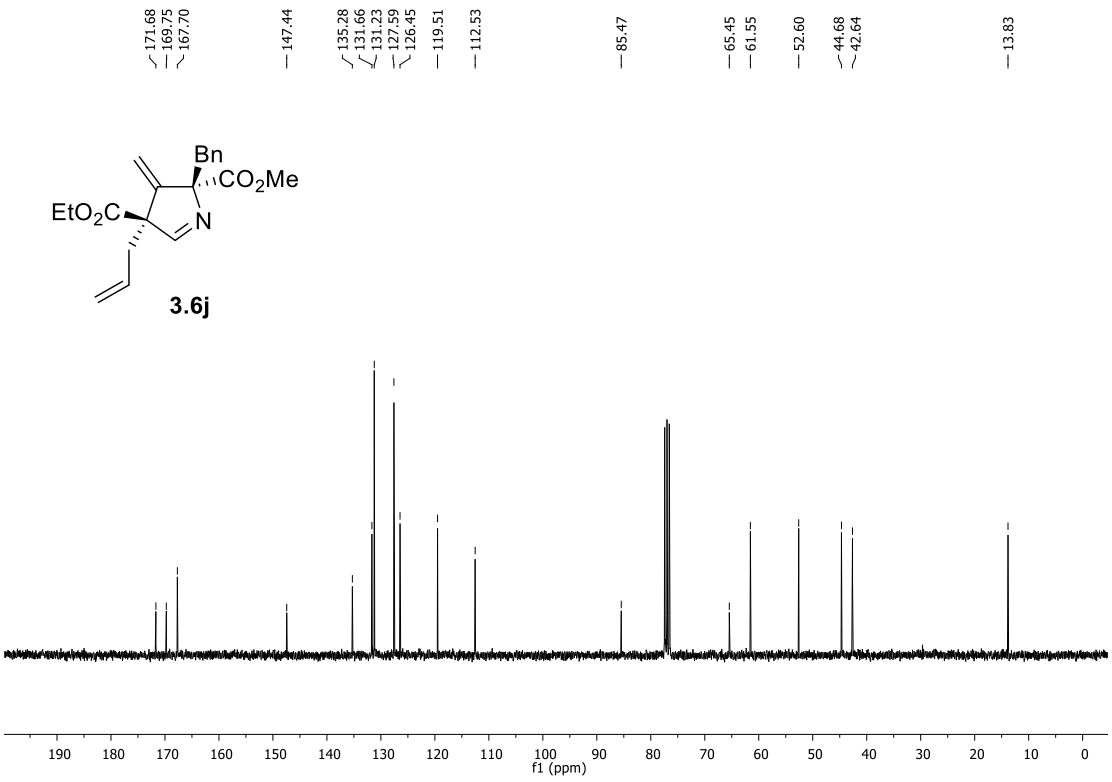
5.56
5.55
5.08
5.07
5.03
5.02
5.02
3.96
3.94
3.76
3.74
3.70
3.69
3.48
3.44
3.18
3.13
2.70
2.67
2.65
2.63
2.41
2.38
2.36
2.34
1.14
1.11
1.09
Bn
CO2Me
EtO2C
N
3.6j
0.97
5.00
3.00
1.01
0.95
1.01
4.01
1.00
1.00
1.01
1.01
3.00
f1 (ppm)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167.70
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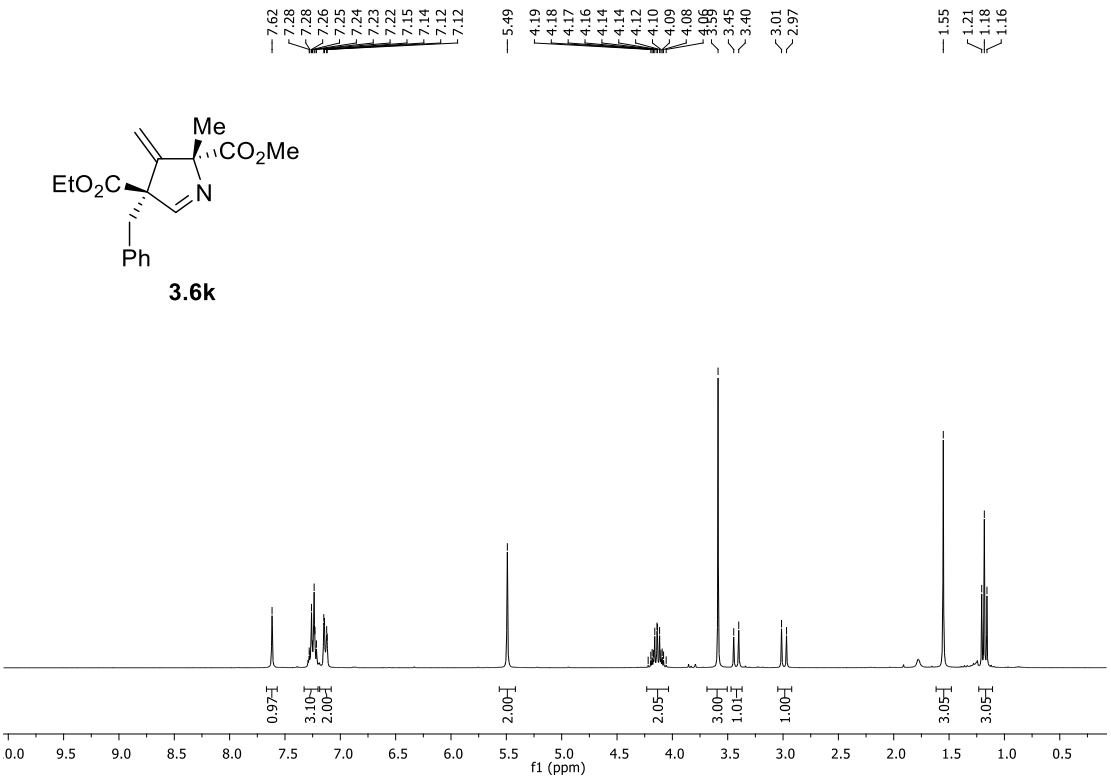
135.28
131.66
131.23
127.59
126.45
119.51
112.53
85.47
65.45
61.55
52.60
44.68
42.64
13.83
Bn
CO2Me
EtO2C
N
3.6j
f1 (ppm)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7.28
7.28
7.26
7.25
7.24
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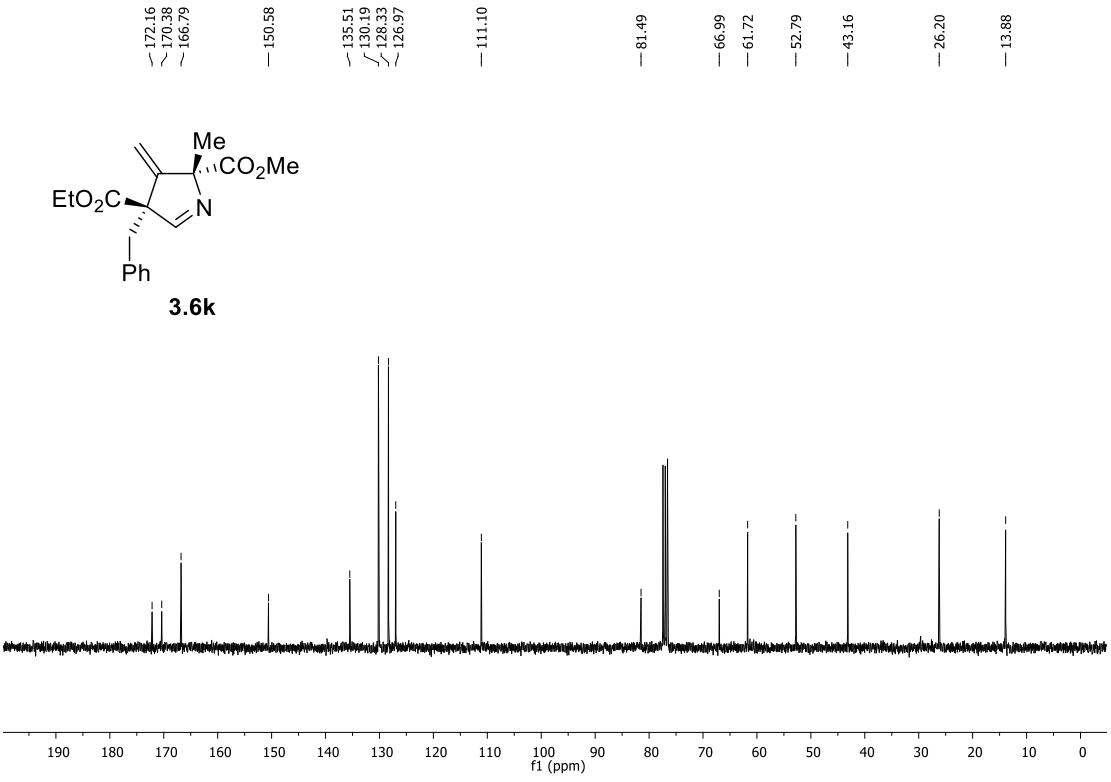
7.22
7.15
7.14
7.12
7.12
5.49
4.19
4.18
4.17
4.16
4.14
4.14
4.12
4.10
4.09
4.08
3.45
3.40
3.01
2.97
1.55
1.21
1.18
1.16
Me
CO2Me
EtO2C
N
Ph
3.6k
0.97
3.10
2.00
2.00
2.05
3.00
1.01
1.00
3.05
3.05
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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170.38
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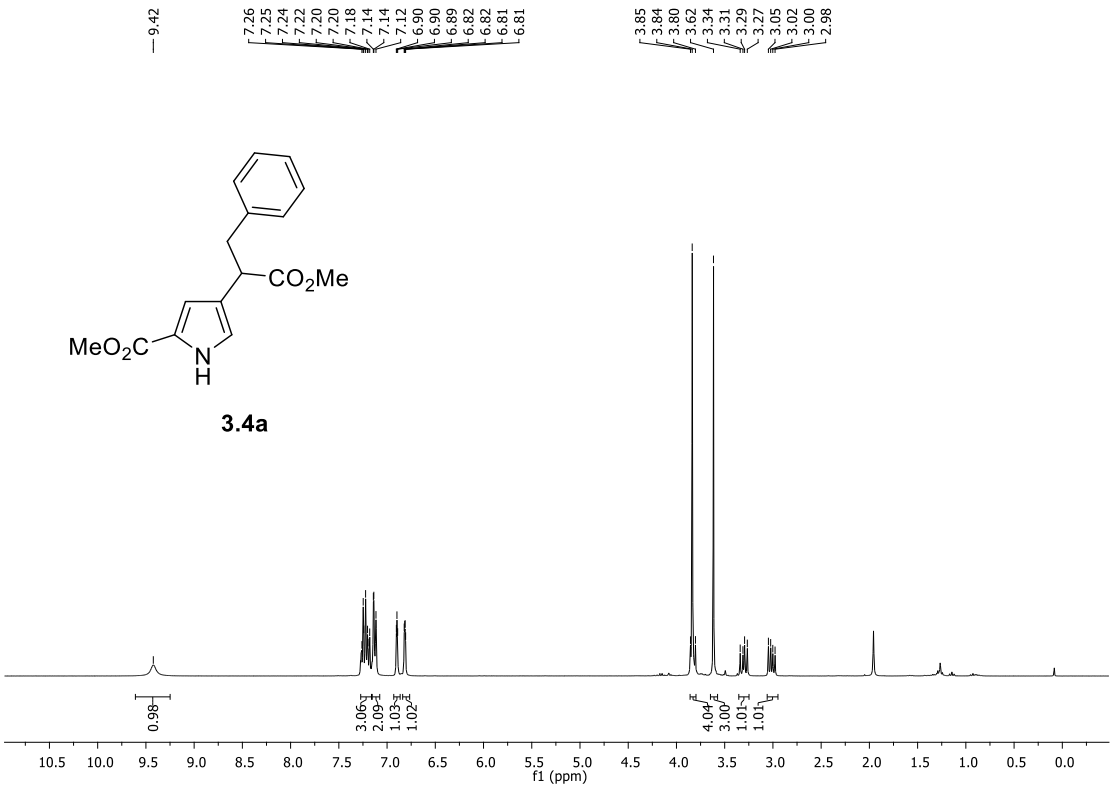
150.58
135.51
130.19
128.33
126.97
111.10
81.49
66.99
61.72
52.79
43.16
26.20
13.88
Me
CO2Me
EtO2C
N
Ph
3.6k
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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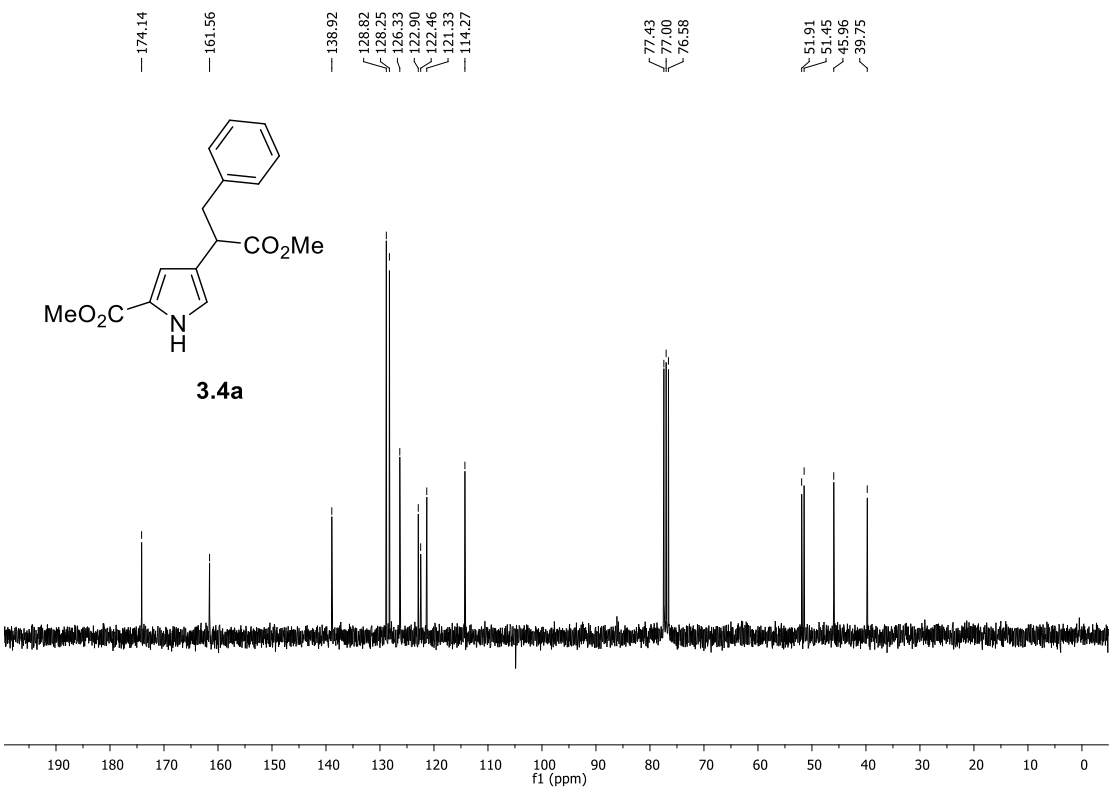
7.25
7.24
7.22
7.20
7.20
7.18
7.14
7.14
7.12
6.90
6.90
6.89
6.82
6.82
6.81
6.81
3.85
3.84
3.80
3.62
3.34
3.31
3.29
3.27
3.05
3.02
3.00
2.98
CO2Me
MeO2C
N
H
0.98
3.06
2.09
1.03
1.02
4.04
3.00
1.01
1.01
f1 (ppm)

3.4a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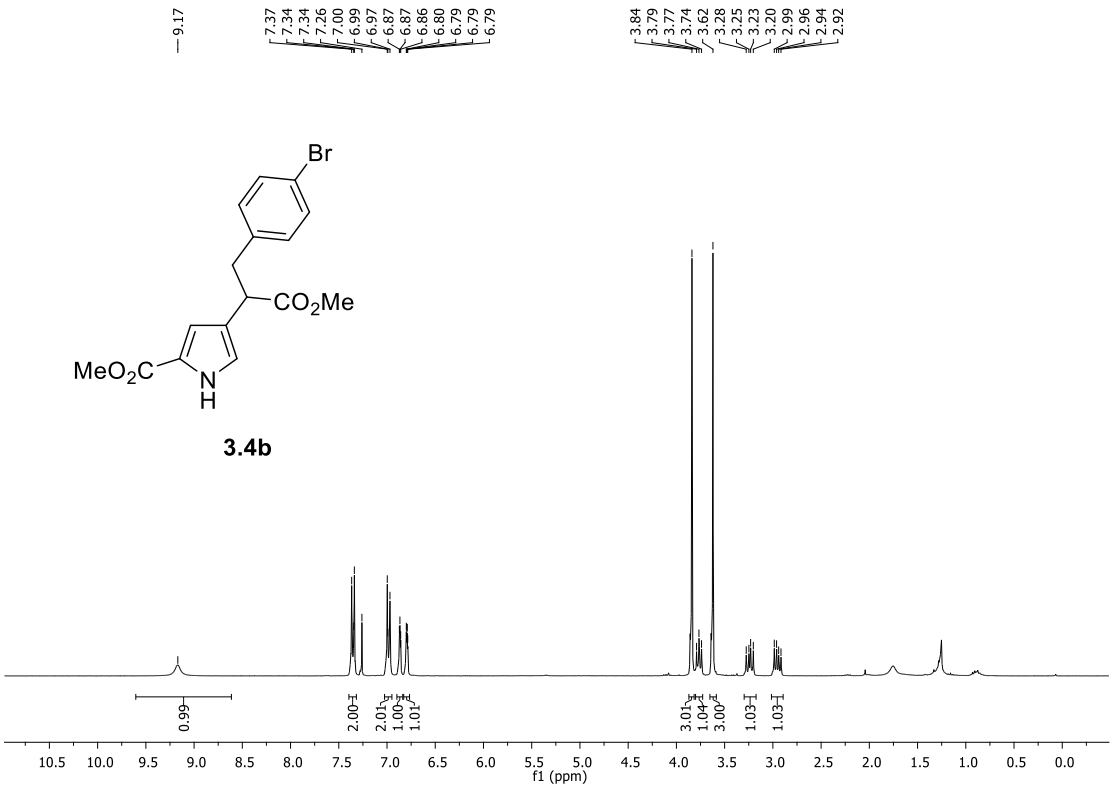
128.82
128.25
126.33
122.90
122.46
121.33
114.27
77.43
77.00
76.58
51.91
51.45
45.96
39.75
CO2Me
MeO2C
N
H
f1 (ppm)

3.4a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7.34
7.34
7.26
7.00
6.99
6.97
6.87
6.87
6.86
6.80
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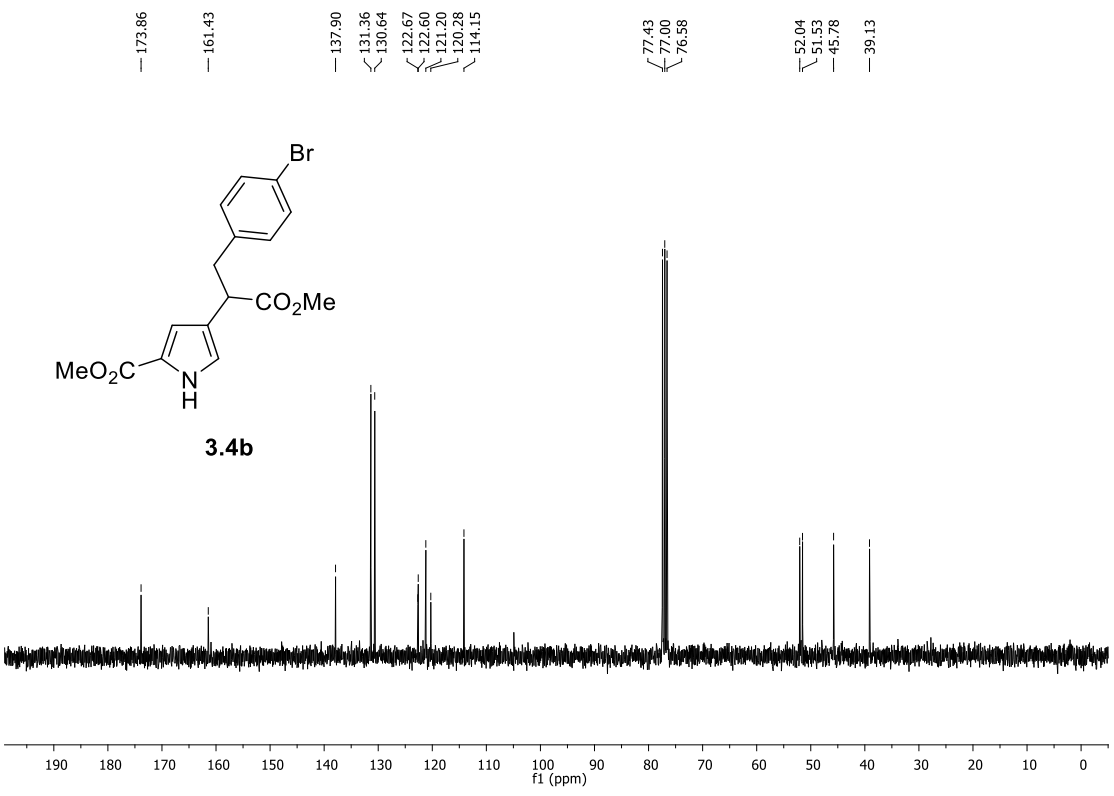
6.79
6.79
3.84
3.79
3.77
3.74
3.62
3.28
3.25
3.23
3.20
2.99
2.96
2.94
2.92
Br
CO2Me
MeO2C
N
H
3.4b
0.99
2.00
2.01
1.00
1.01
3.01
1.04
3.00
1.03
1.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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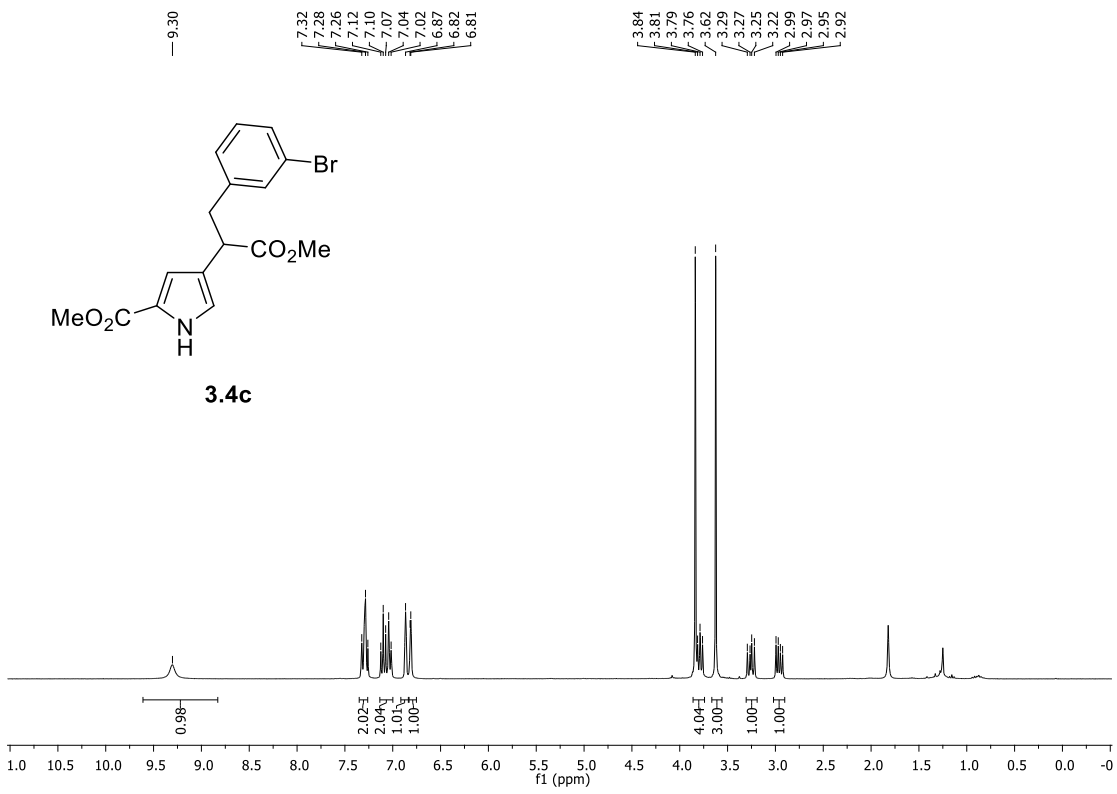
122.67
122.60
121.20
120.28
114.15
77.43
77.00
76.58
52.04
51.53
45.78
39.13
Br
CO2Me
MeO2C
N
H
3.4b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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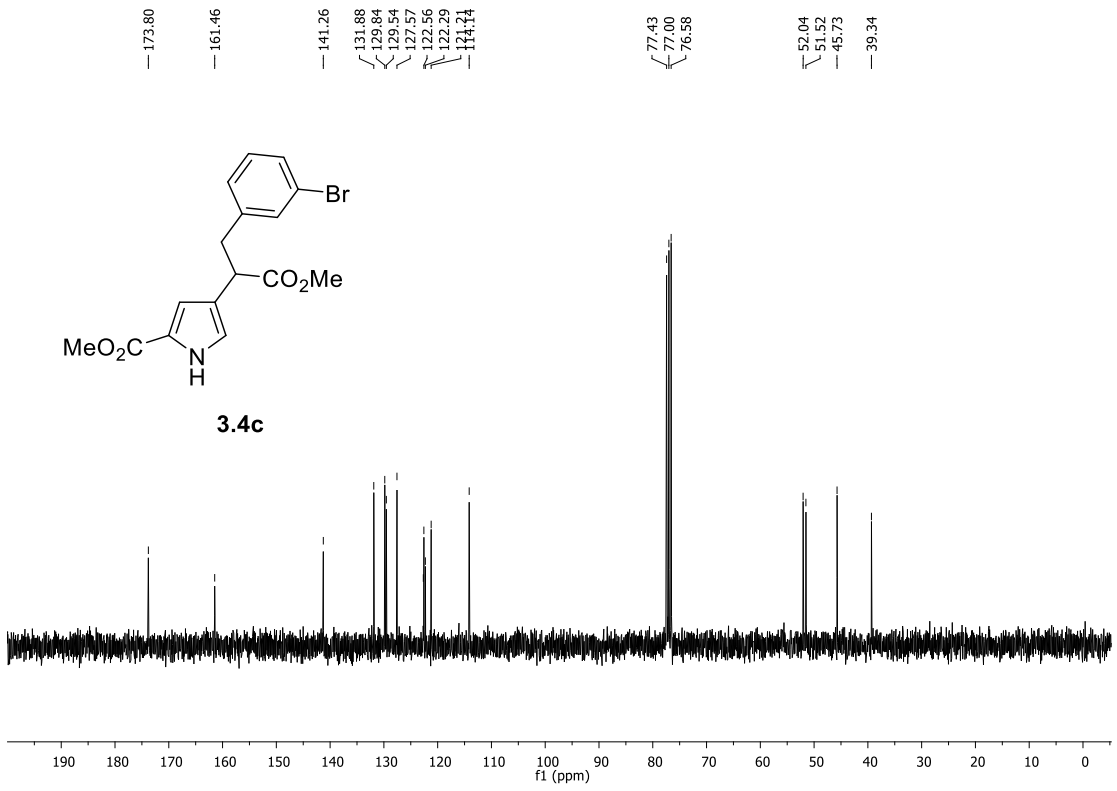
7.28
7.26
7.12
7.10
7.07
7.04
7.02
6.87
6.82
6.81
3.84
3.81
3.79
3.76
3.62
3.29
3.27
3.25
3.22
2.99
2.97
2.95
2.92
Br
CO2Me
MeO2C
N
H
0.98
2.02
2.04
1.01
1.00
4.04
3.00
1.00
1.00
f1 (ppm)

3.4c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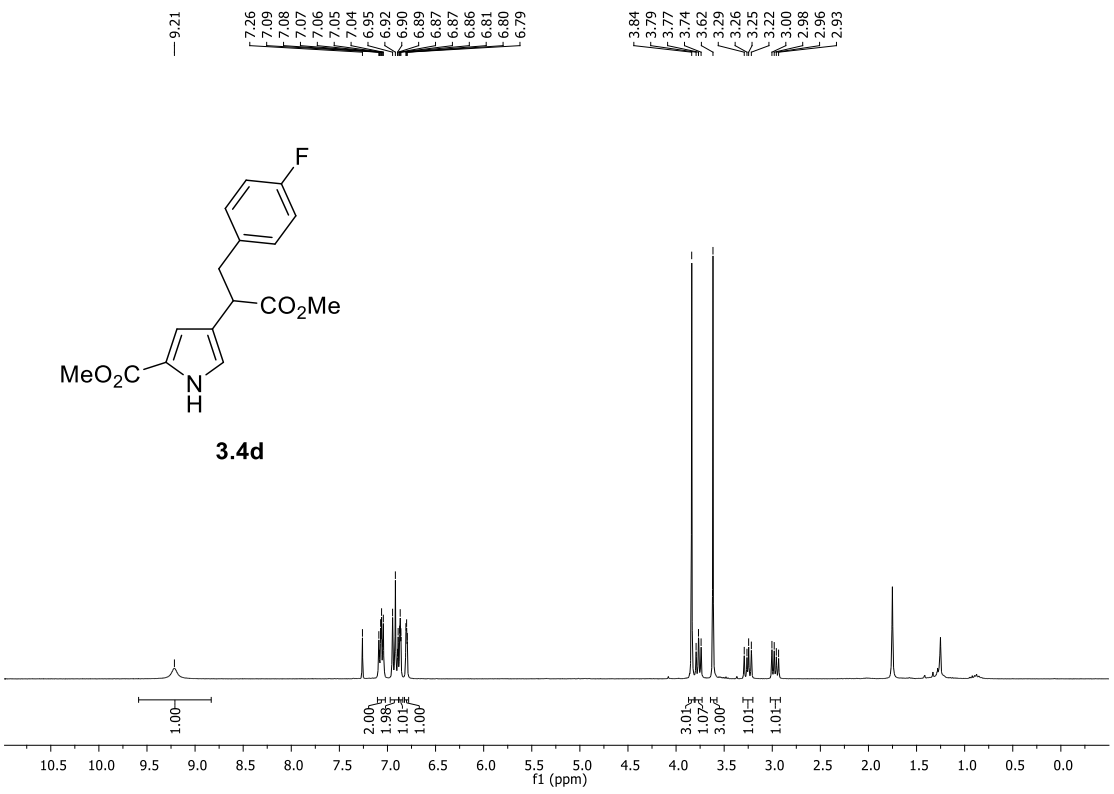
129.54
127.57
122.56
122.29
77.43
77.00
76.58
52.04
51.52
45.73
39.34
Br
CO2Me
MeO2C
N
H
f1 (ppm)

3.4c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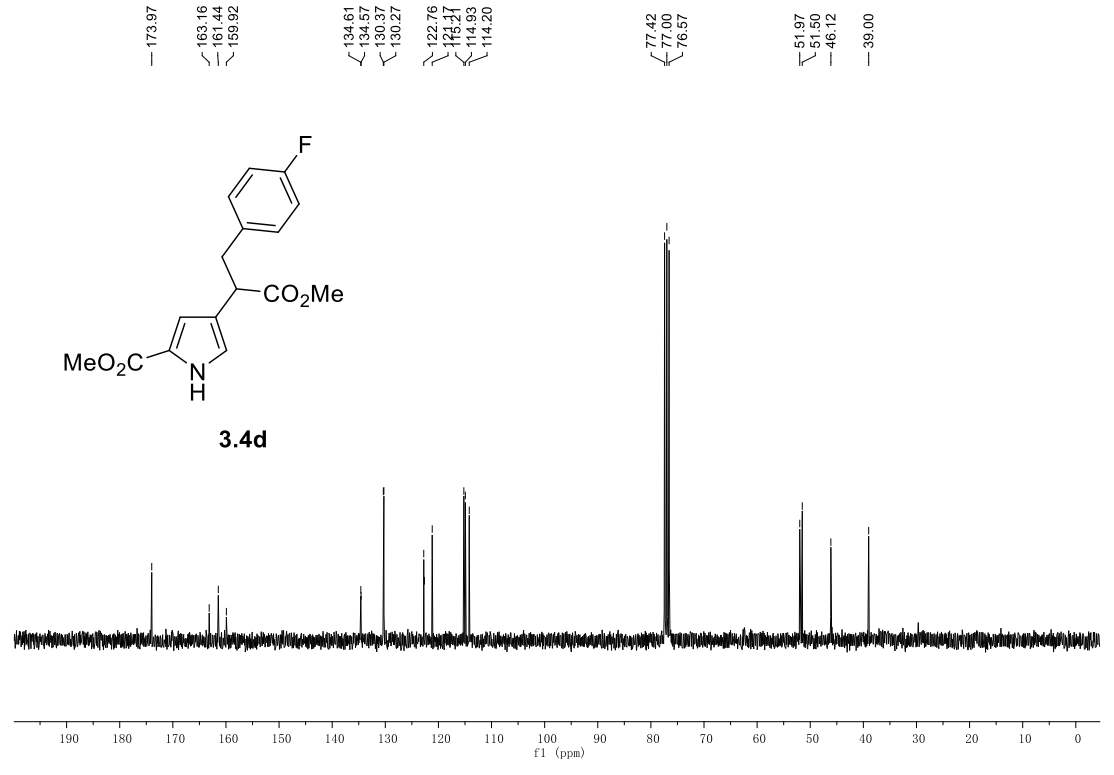
7.09
7.08
7.07
7.06
7.05
7.04
6.95
6.92
6.90
6.89
6.87
6.87
6.86
6.81
6.80
6.79
3.84
3.79
3.77
3.74
3.62
3.29
3.26
3.25
3.22
3.00
2.98
2.96
2.93
F
CO2Me
MeO2C
N
H
3.4d
1.00
2.00
1.98
1.01
1.00
3.01
1.07
3.00
1.01
1.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


173.97
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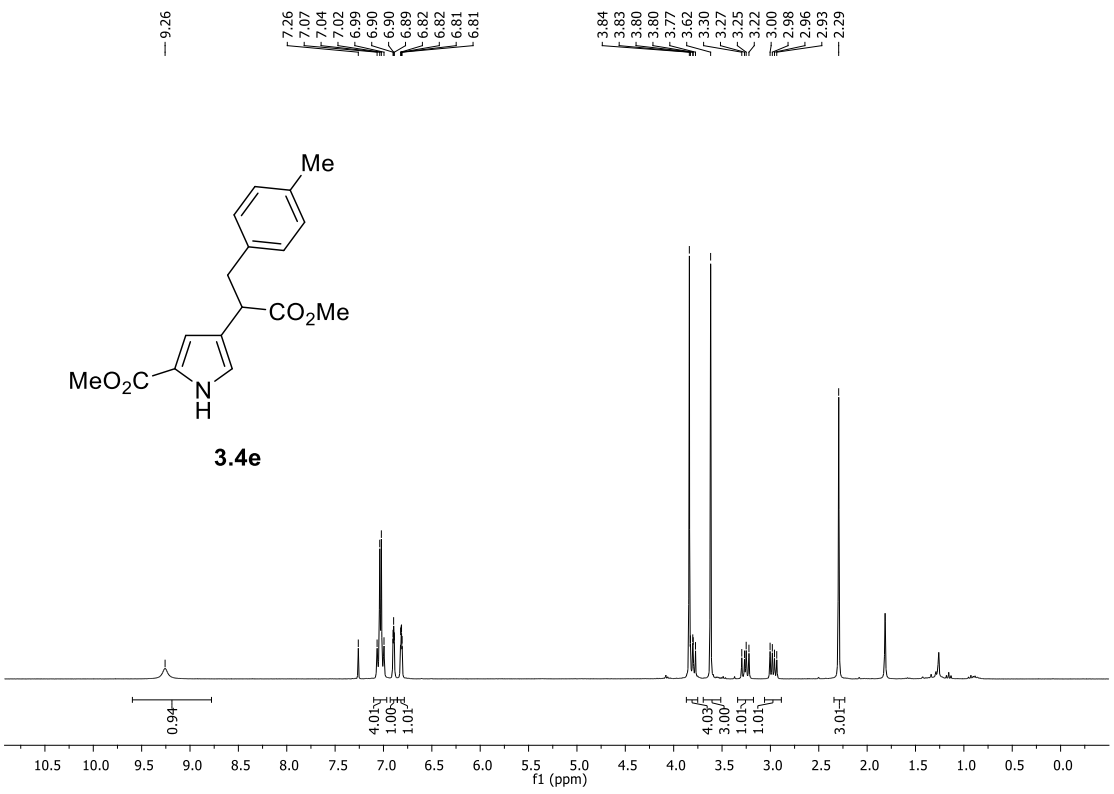
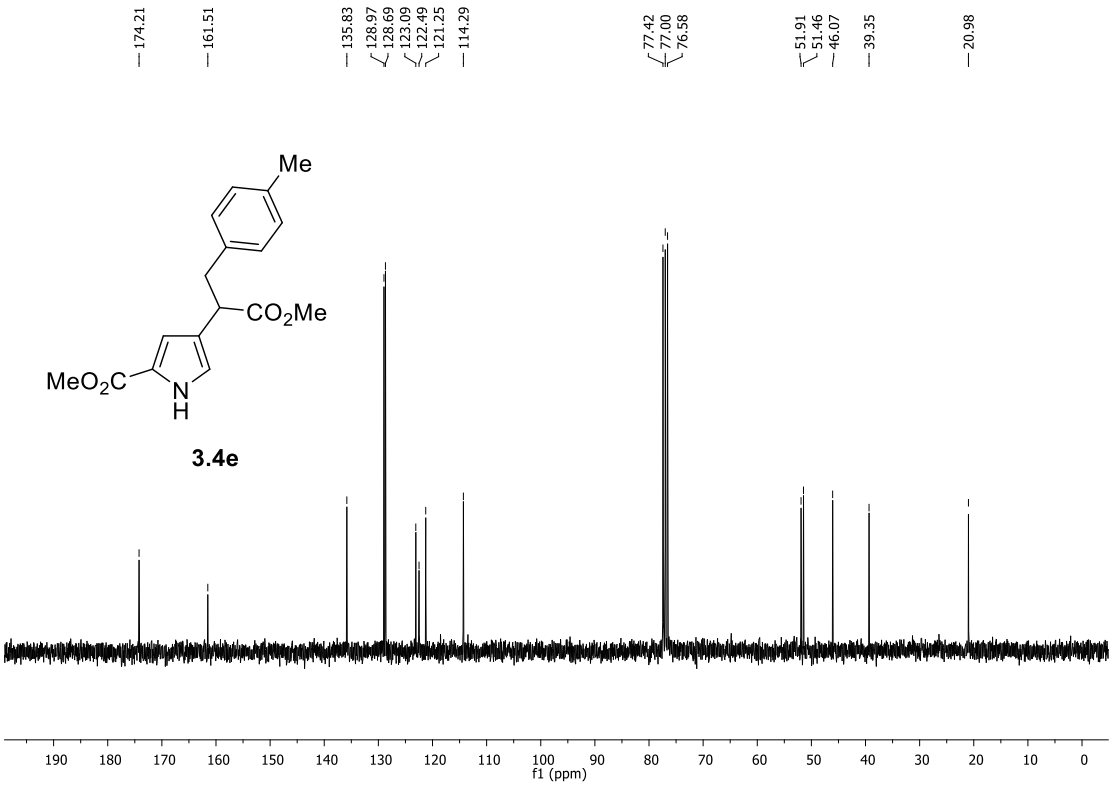
161.44
159.92
134.61
134.57
130.37
130.27
122.76
121.17
115.21
114.93
114.20
77.42
77.00
76.57
51.97
51.50
46.12
39.00
F
CO2Me
MeO2C
N
H
3.4d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


9.26
7.26
7.07
7.04
7.02
6.99
6.90
6.90
6.89
6.82
6.82
6.81
6.81
3.84
3.83
3.80
3.80
3.77
3.62
3.30
3.27
3.25
3.22
3.00
2.98
2.96
2.93
2.29
Me
CO2Me
MeO2C
N
H
3.4e
0.94
4.01
1.00
1.01
4.03
3.00
1.01
1.01
3.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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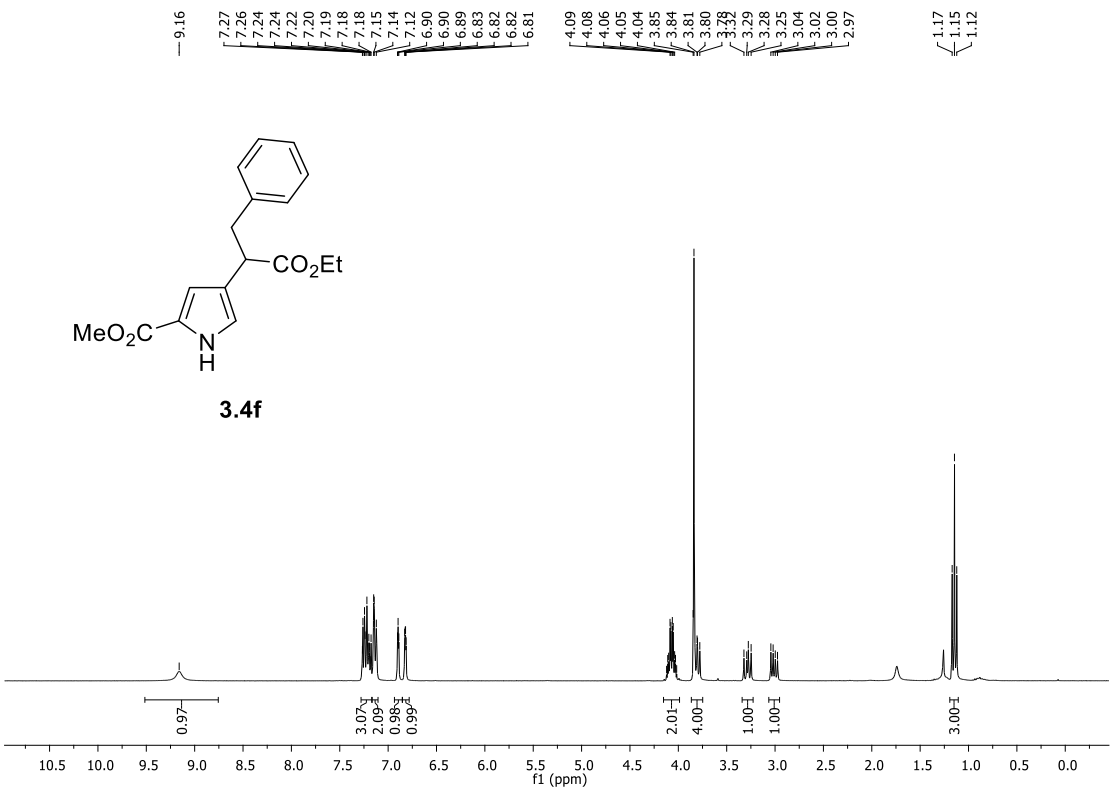
135.83
128.97
128.69
123.09
122.49
121.25
114.29
77.42
77.00
76.58
51.91
51.46
46.07
39.35
20.98
Me
CO2Me
MeO2C
N
H
3.4e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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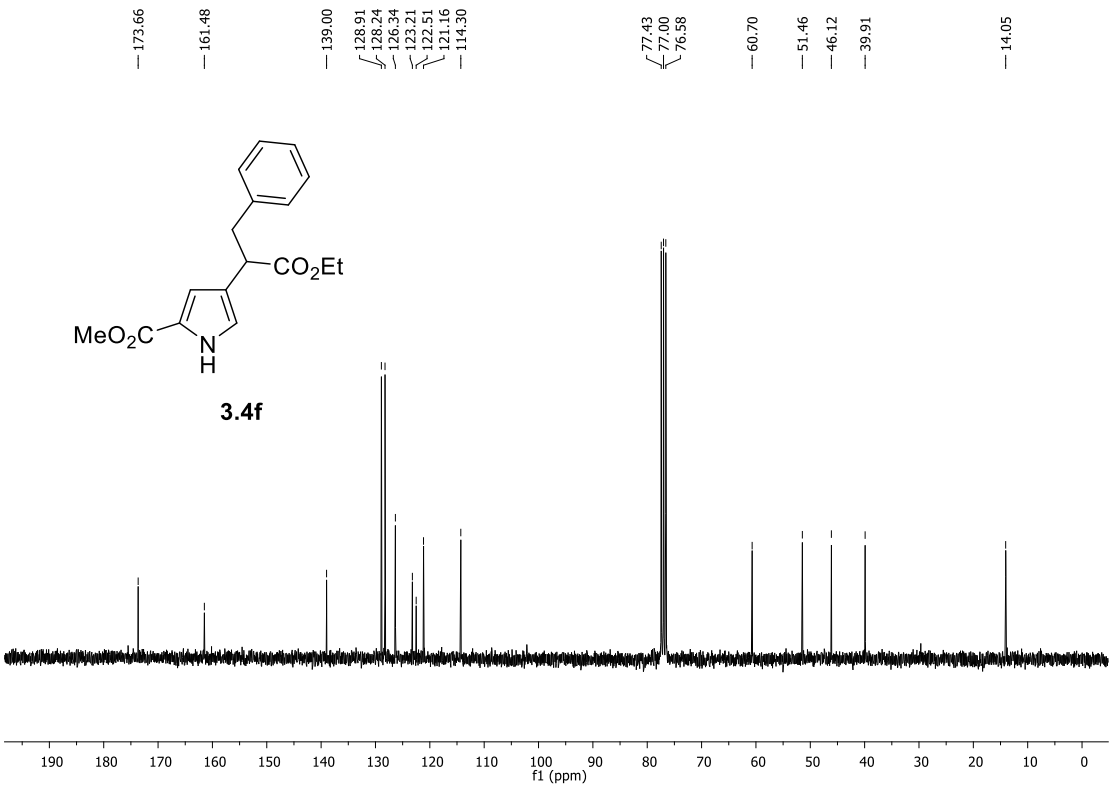
7.27
7.26
7.24
7.24
7.22
7.20
7.19
7.18
7.18
7.15
7.14
7.12
6.90
6.90
6.89
6.83
6.82
6.82
6.81
4.09
4.08
4.06
4.05
4.04
3.85
3.84
3.81
3.80
3.32
3.29
3.28
3.25
3.04
3.02
3.00
2.97
1.17
1.15
1.12
CO2Et
MeO2C
N
H
3.4f
0.97
3.07
2.09
0.98
0.99
2.01
4.00
1.00
1.00
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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122.51
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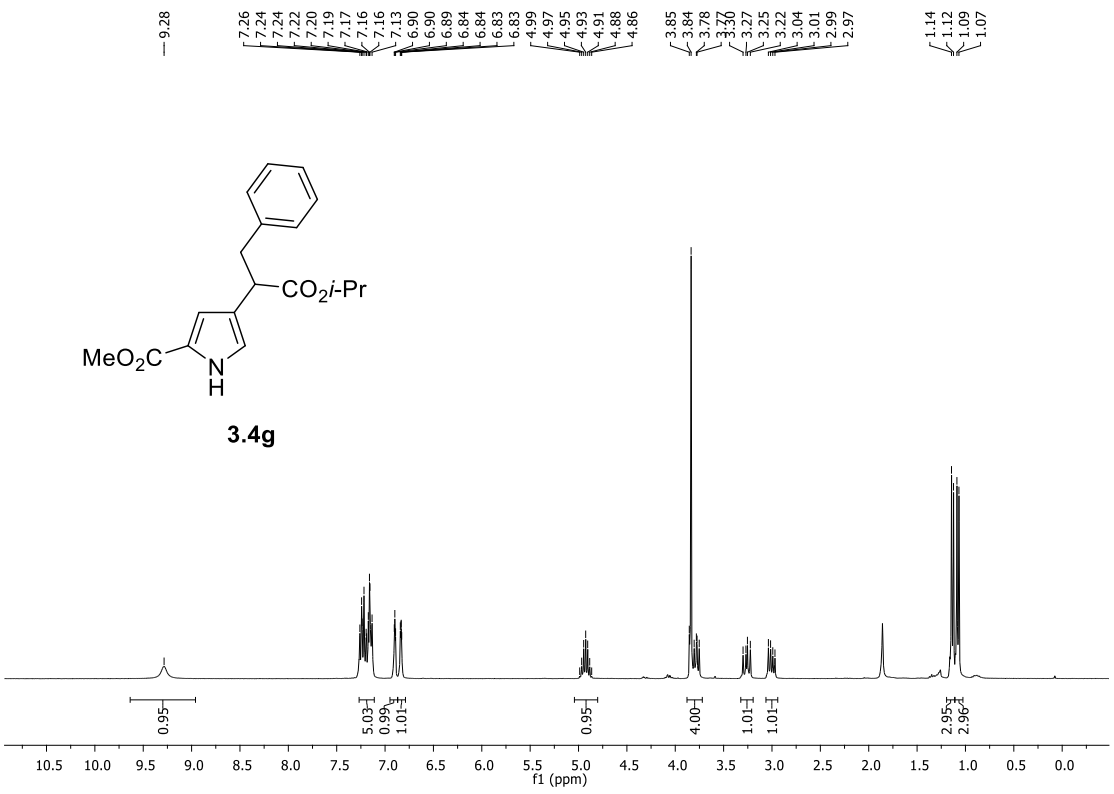
114.30
77.43
77.00
76.58
60.70
51.46
46.12
39.91
14.05
CO2Et
MeO2C
N
H
3.4f
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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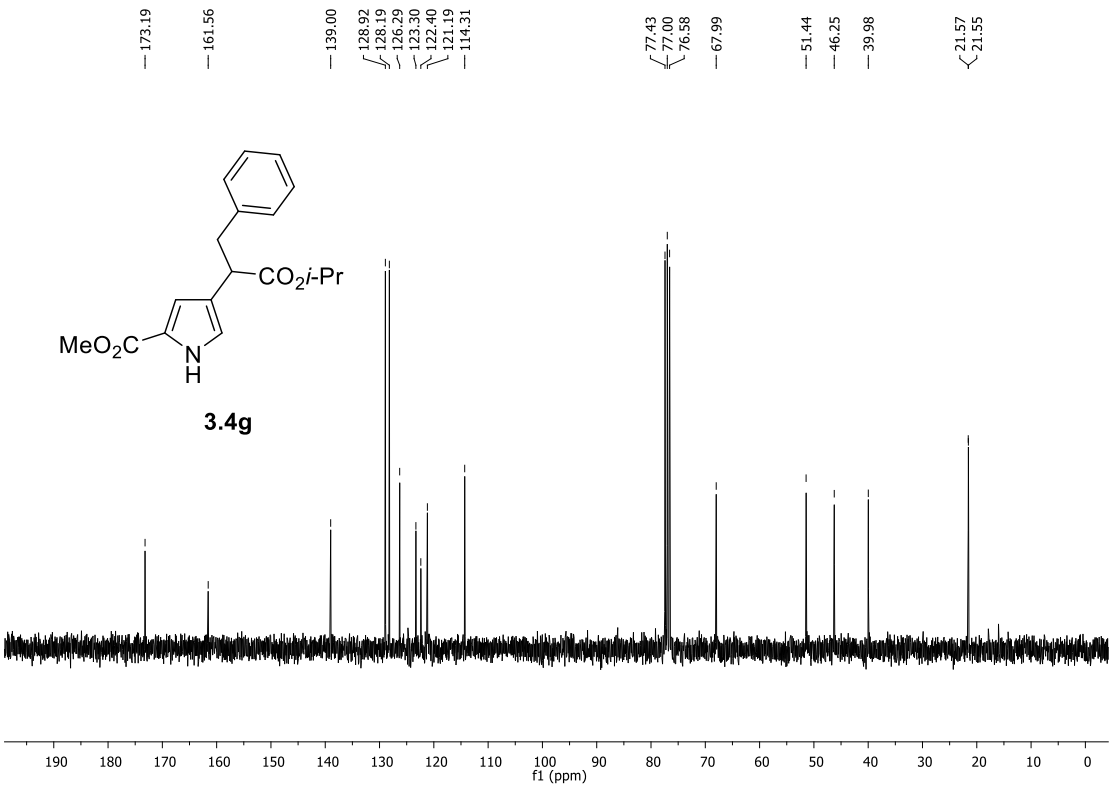
7.26
7.24
7.24
7.22
7.20
7.19
7.17
7.16
7.16
7.13
6.90
6.90
6.89
6.84
6.84
6.83
6.83
4.99
4.97
4.95
4.93
4.91
4.88
4.86
3.85
3.84
3.78
3.77
3.30
3.27
3.25
3.22
3.04
3.01
2.99
2.97
1.14
1.12
1.09
1.07
CO2i-Pr
MeO2C
N
H
3.4g
0.95
5.03
0.99
1.01
0.95
4.00
1.01
1.01
2.95
2.96
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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161.56
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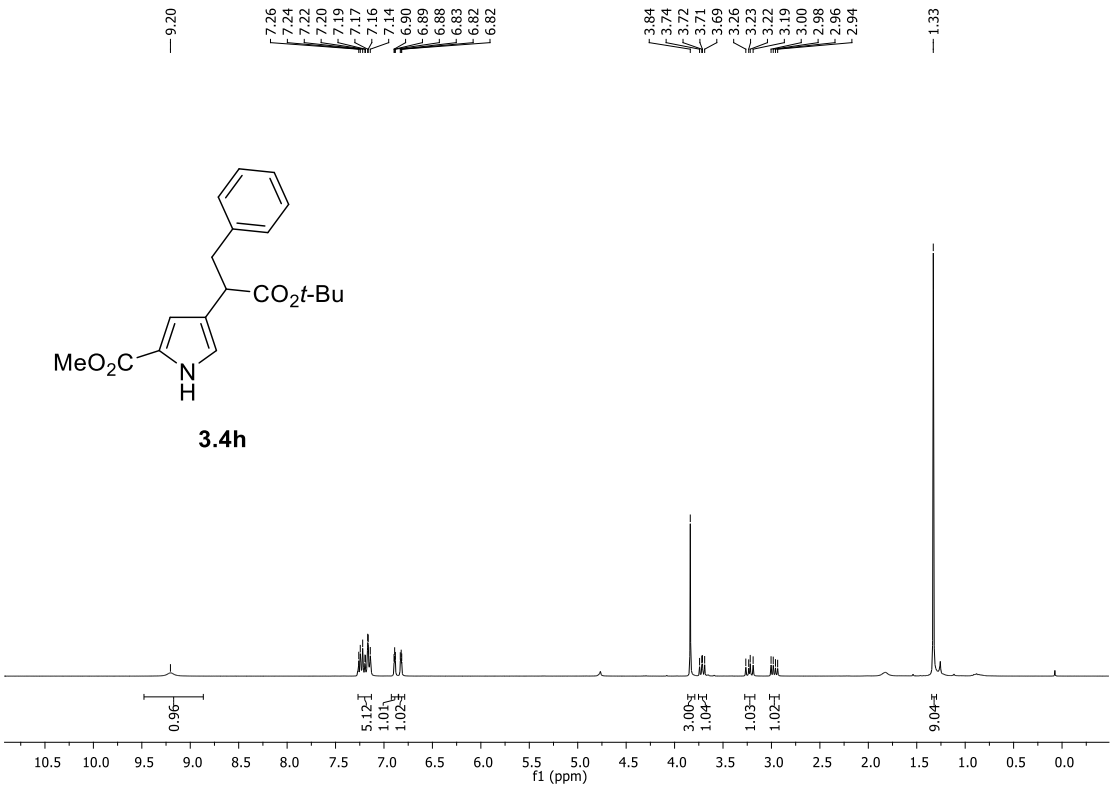
128.19
126.29
123.30
122.40
121.19
114.31
77.43
77.00
76.58
67.99
51.44
46.25
39.98
21.57
21.55
CO2i-Pr
MeO2C
N
H
3.4g
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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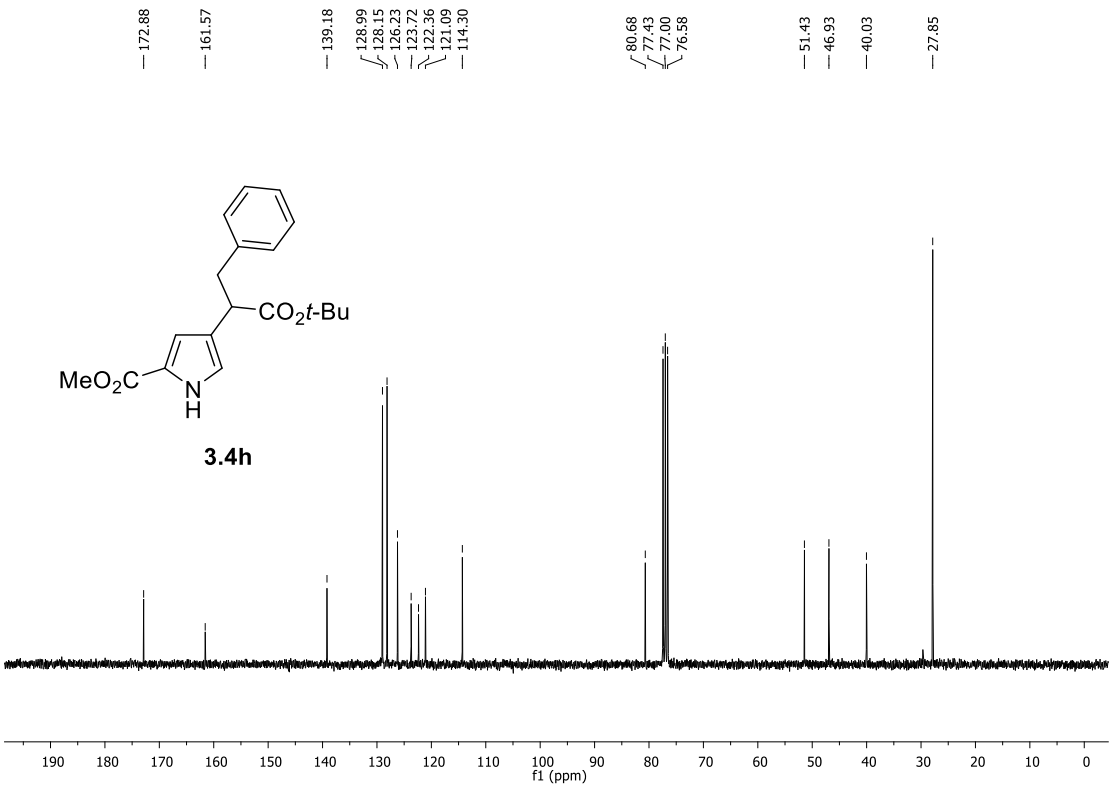
7.26
7.24
7.22
7.20
7.19
7.17
7.16
7.14
6.90
6.89
6.88
6.83
6.82
6.82
3.84
3.74
3.72
3.71
3.69
3.26
3.23
3.22
3.19
3.00
2.98
2.96
2.94
1.33
CO2t-Bu
MeO2C
N
H
3.4h
0.96
5.12
1.01
1.02
3.00
1.04
1.03
1.02
9.04
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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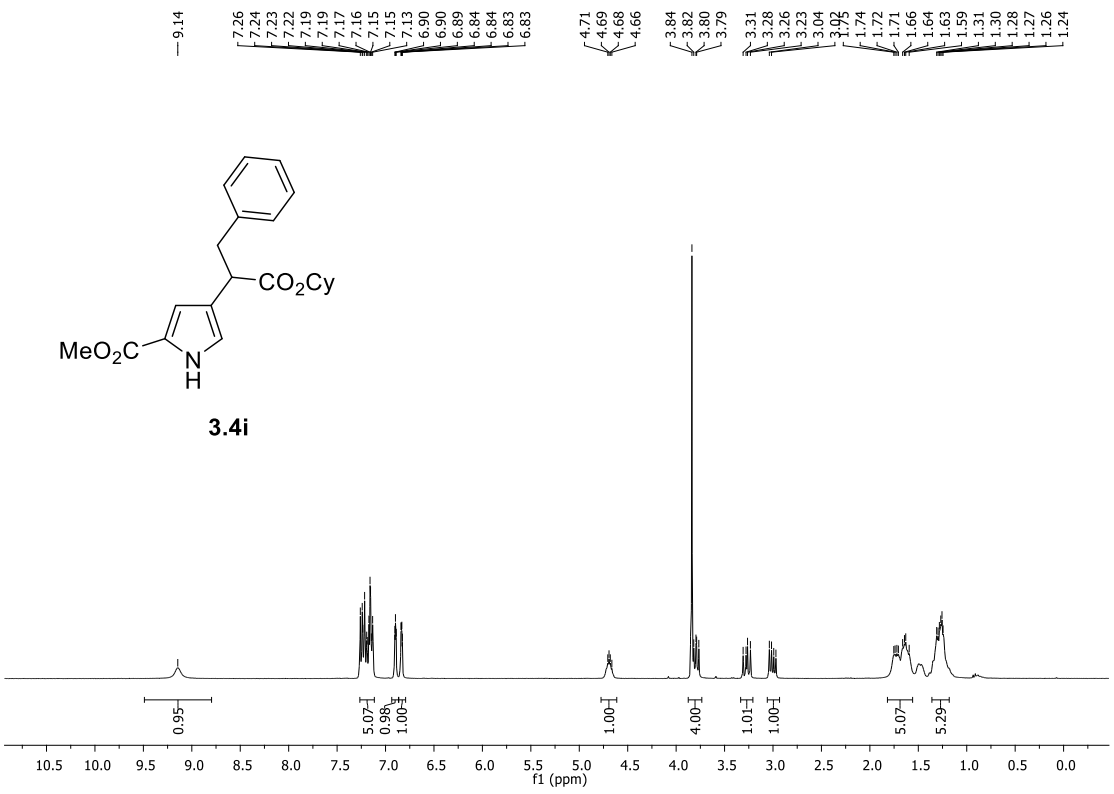
161.57
139.18
128.99
128.15
126.23
123.72
122.36
121.09
114.30
80.68
77.43
77.00
76.58
51.43
46.93
40.03
27.85
CO2t-Bu
MeO2C
N
H
3.4h
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.26
7.24
7.23
7.22
7.19
7.19
7.17
7.16
7.15
7.15
7.13
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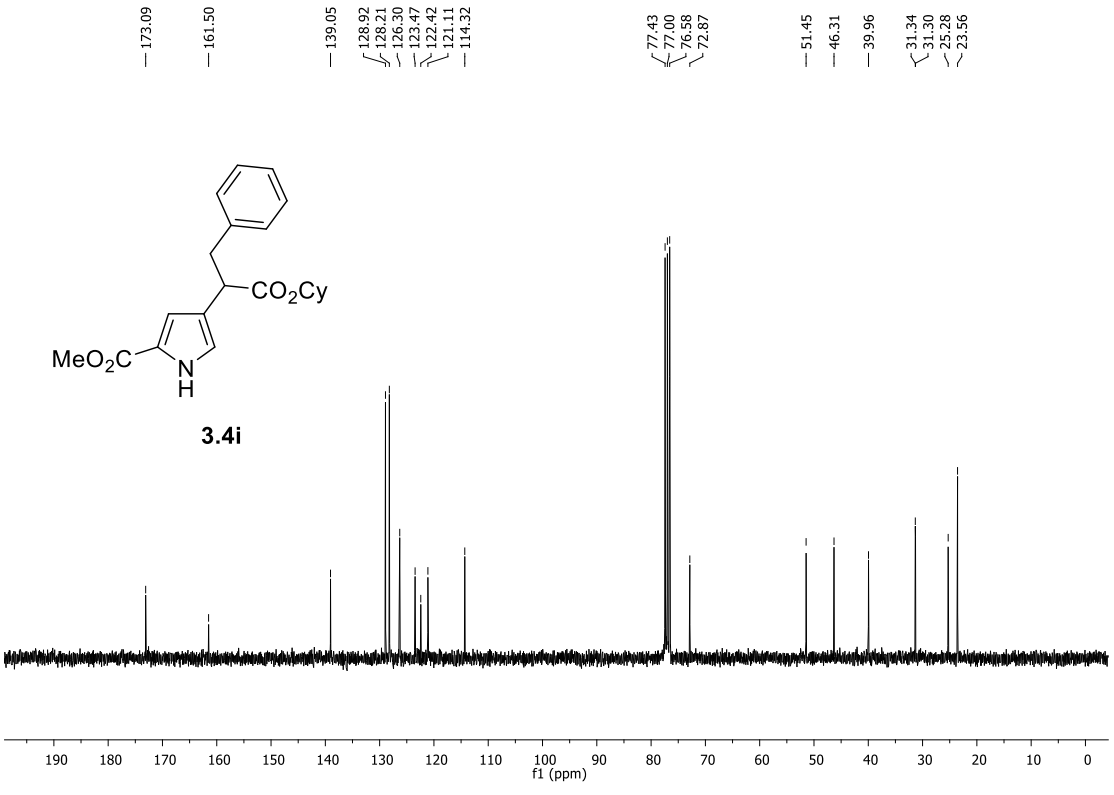
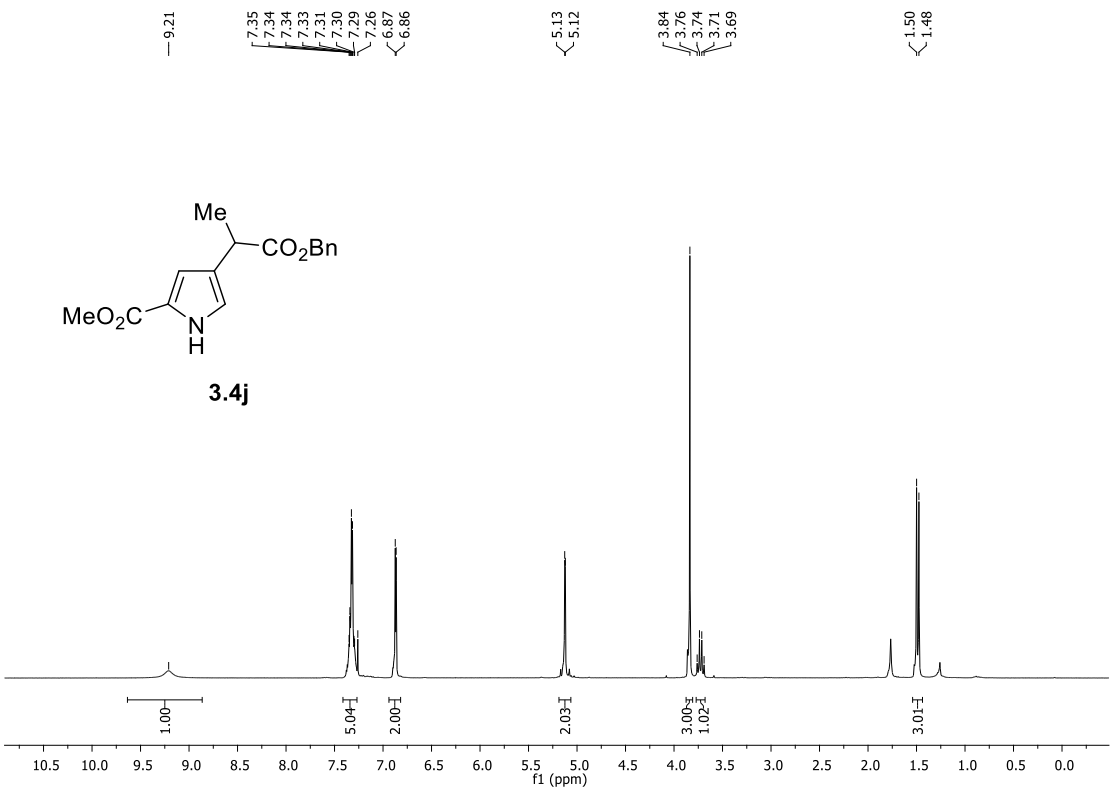
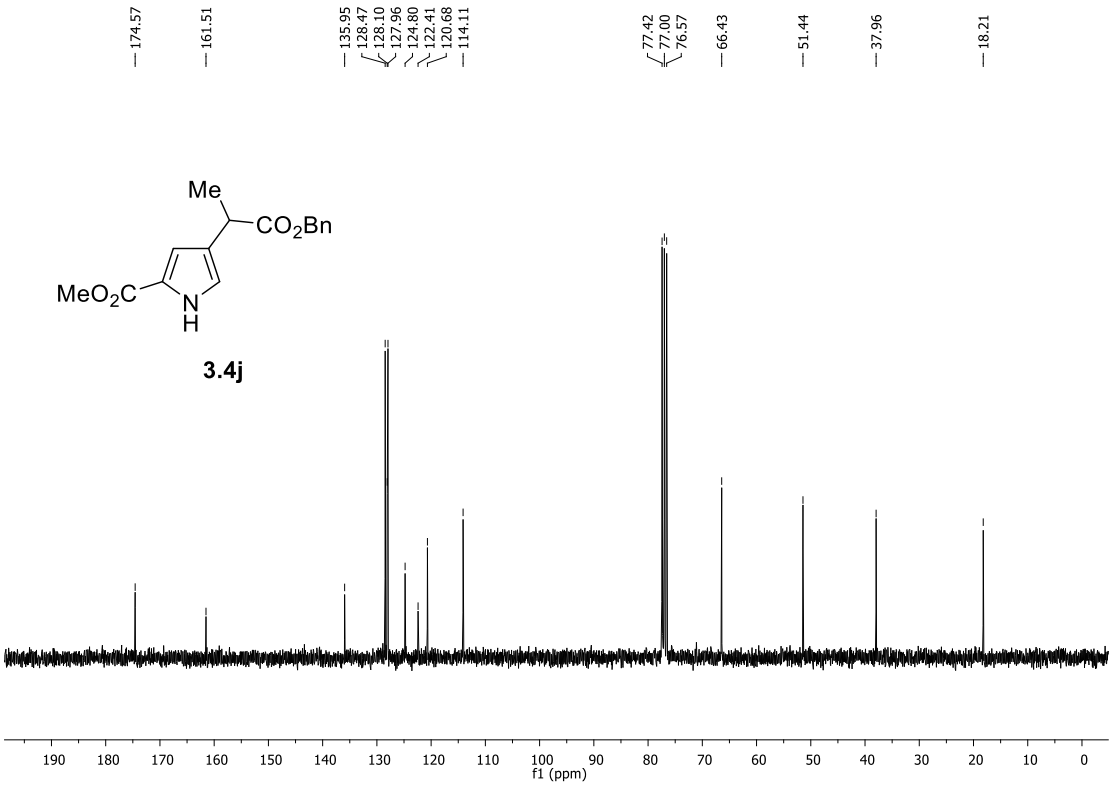
6.90
6.89
6.84
6.84
6.83
6.83
4.71
4.69
4.68
4.66
3.84
3.82
3.80
3.79
3.31
3.28
3.26
3.23
3.04
3.02
1.75
1.74
1.72
1.71
1.66
1.64
1.63
1.59
1.31
1.30
1.28
1.27
1.26
1.24
CO2Cy
MeO2C
N
H
0.95
5.07
0.98
1.00
1.00
4.00
1.01
1.00
5.07
5.29
f1 (ppm)

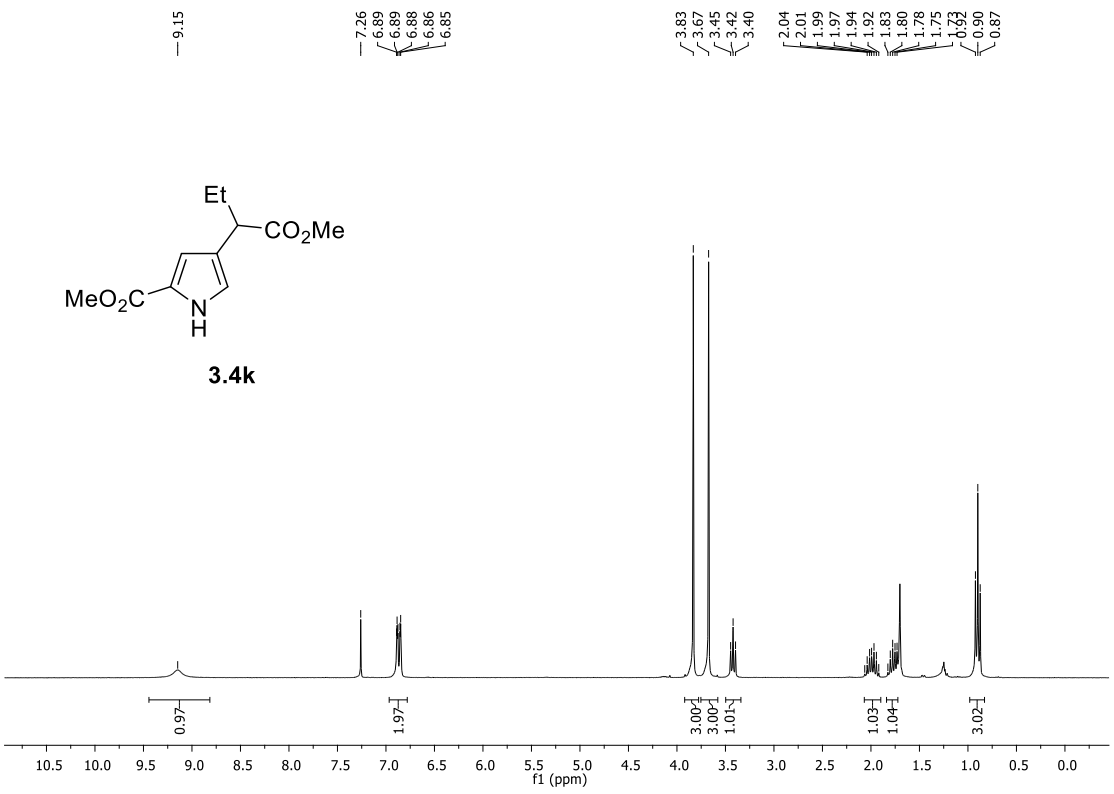
3.4i

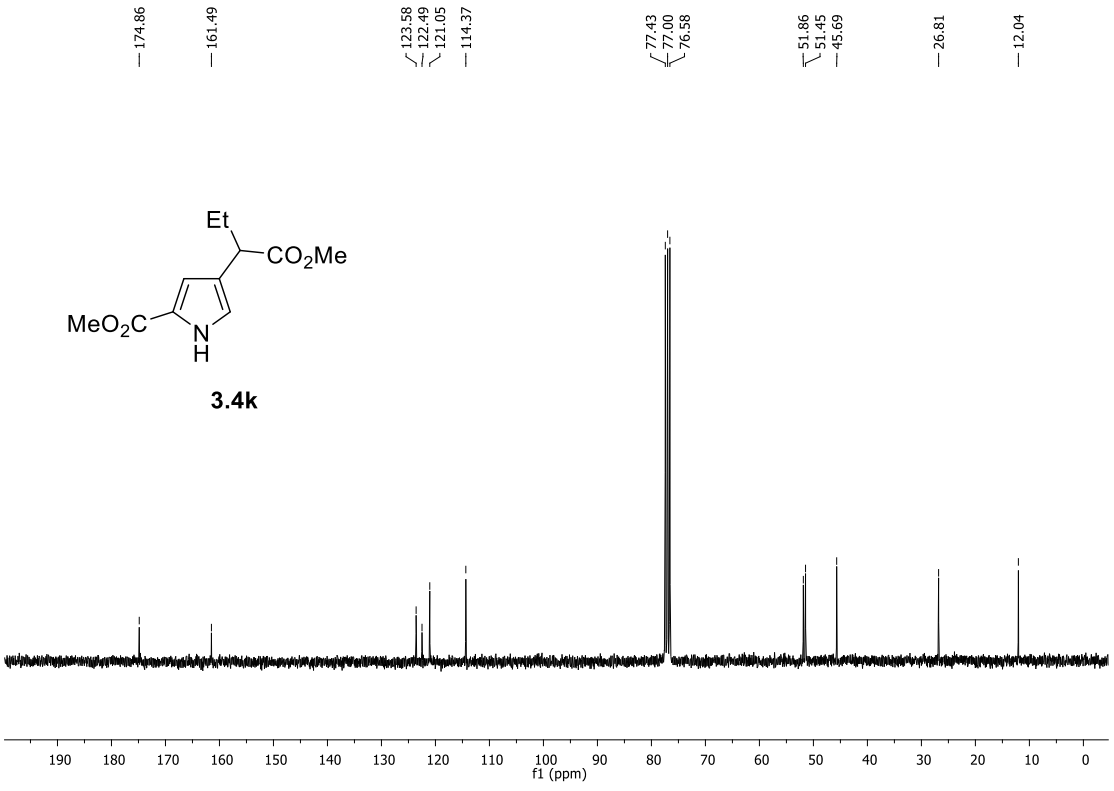

173.09
161.50
139.05
128.92
128.21
126.30
123.47
122.42
121.11
114.32
77.43
77.00
76.58
72.87
51.45
46.31
39.96
31.34
31.30
25.28
23.56
CO2Cy
MeO2C
N
H
f1 (ppm)

3.4i


9.21
7.35
7.34
7.34
7.33
7.31
7.30
7.29
7.26
6.87
6.86
5.13
5.12
3.84
3.76
3.74
3.71
3.69
1.50
1.48
Me
CO2Bn
MeO2C
N
H
3.4j
1.00
5.04
2.00
2.03
3.00
1.02
3.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


174.57
161.51
135.95
128.47
128.10
127.96
124.80
122.41
120.68
114.11
77.42
77.00
76.57
66.43
51.44
37.96
18.21
Me
CO2Bn
MeO2C
N
H
3.4j
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


9.15
7.26
6.89
6.89
6.88
6.86
6.85
3.83
3.67
3.45
3.42
3.40
2.04
2.01
1.99
1.97
1.94
1.92
1.83
1.80
1.78
1.75
1.73
0.92
0.90
0.87
Et
CO2Me
MeO2C
N
H
3.4k
0.97
1.97
3.00
3.00
1.01
1.03
1.04
3.02
f1 (ppm)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161.49
123.58
122.49
121.05
114.37
77.43
77.00
76.58
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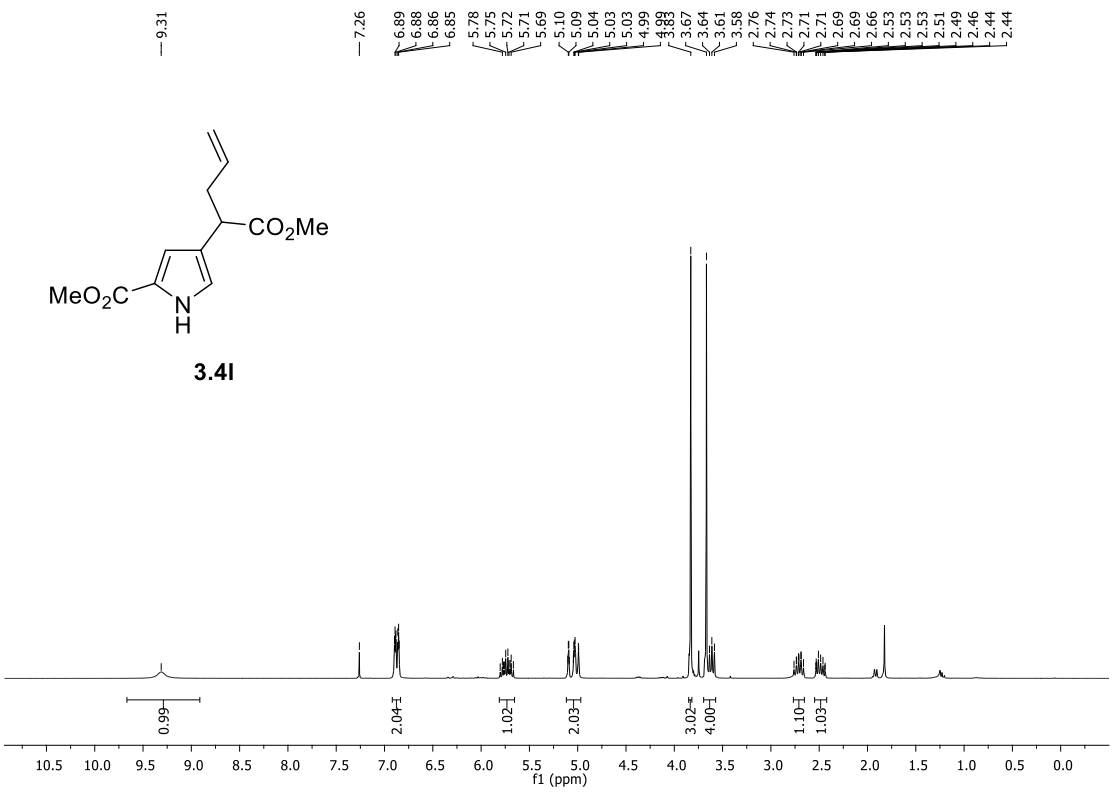
51.45
45.69
26.81
12.04
Et
CO2Me
MeO2C
N
H
3.4k
f1 (ppm)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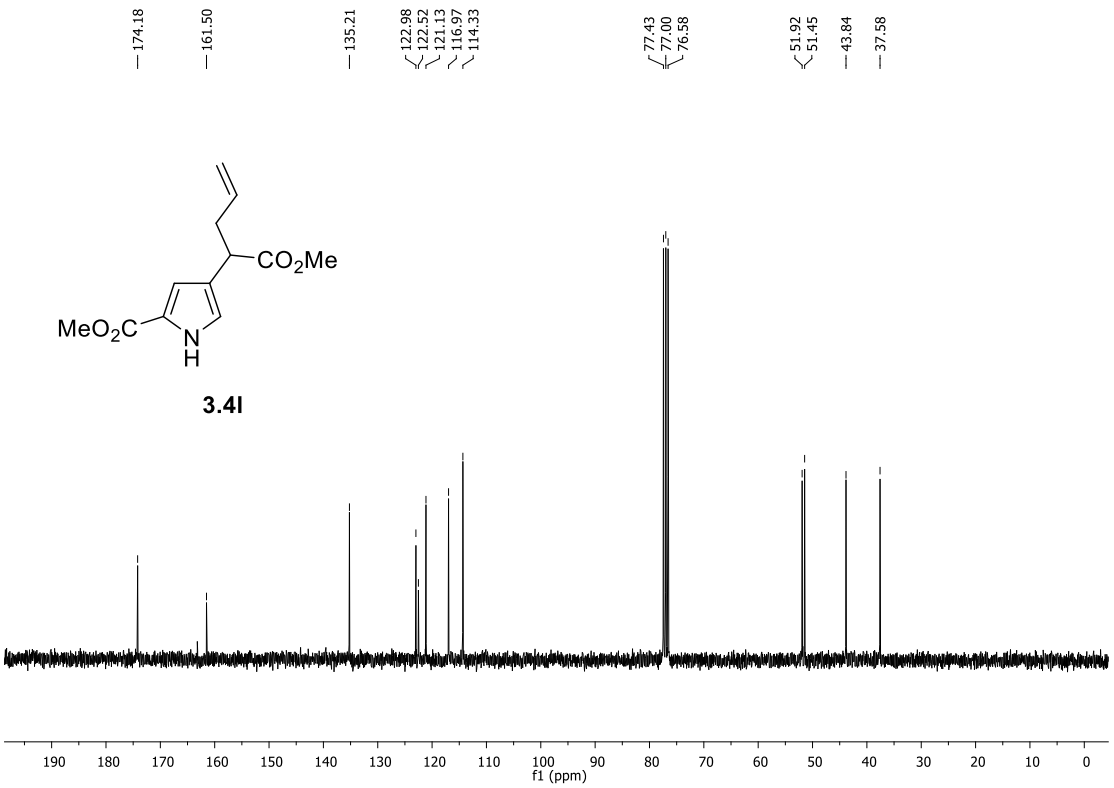
7.26
6.89
6.88
6.86
6.85
5.78
5.75
5.72
5.71
5.69
5.10
5.09
5.04
5.03
5.03
4.99
3.67
3.64
3.61
3.58
2.76
2.74
2.73
2.71
2.71
2.69
2.69
2.66
2.53
2.53
2.53
2.51
2.49
2.46
2.44
2.44
CO2Me
MeO2C
N
H
0.99
2.04
1.02
2.03
3.02
4.00
1.10
1.03
f1 (ppm)

3.4l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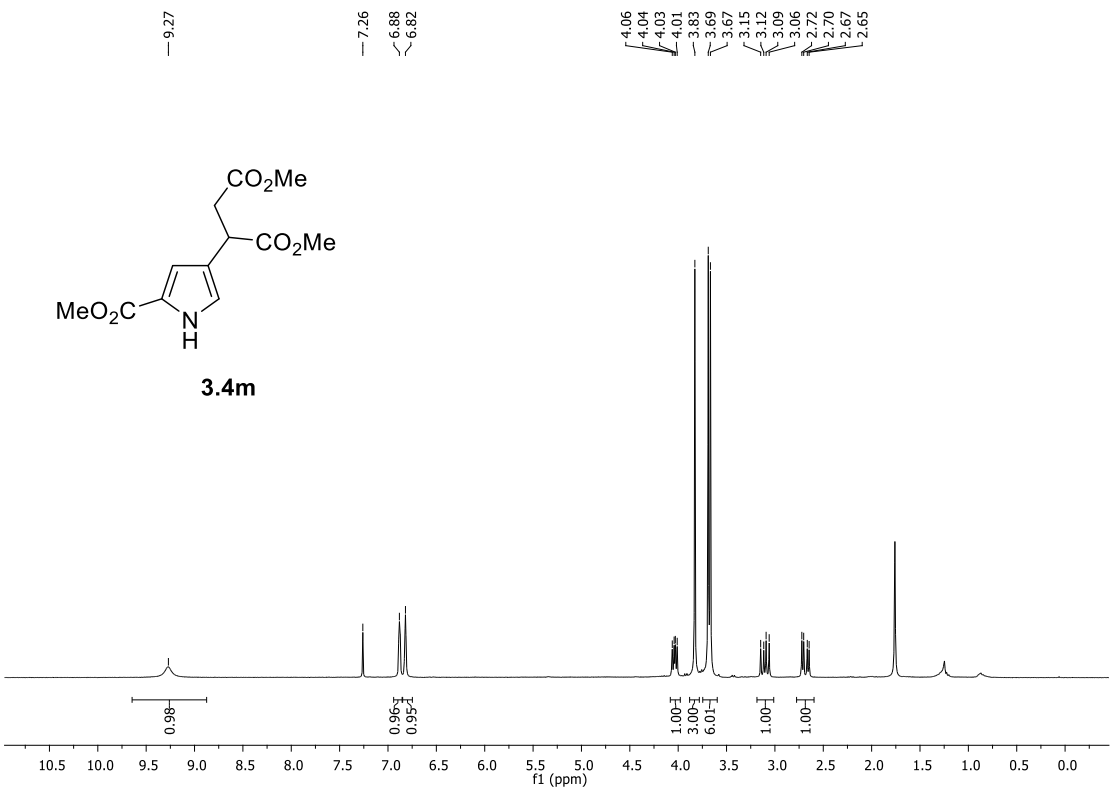
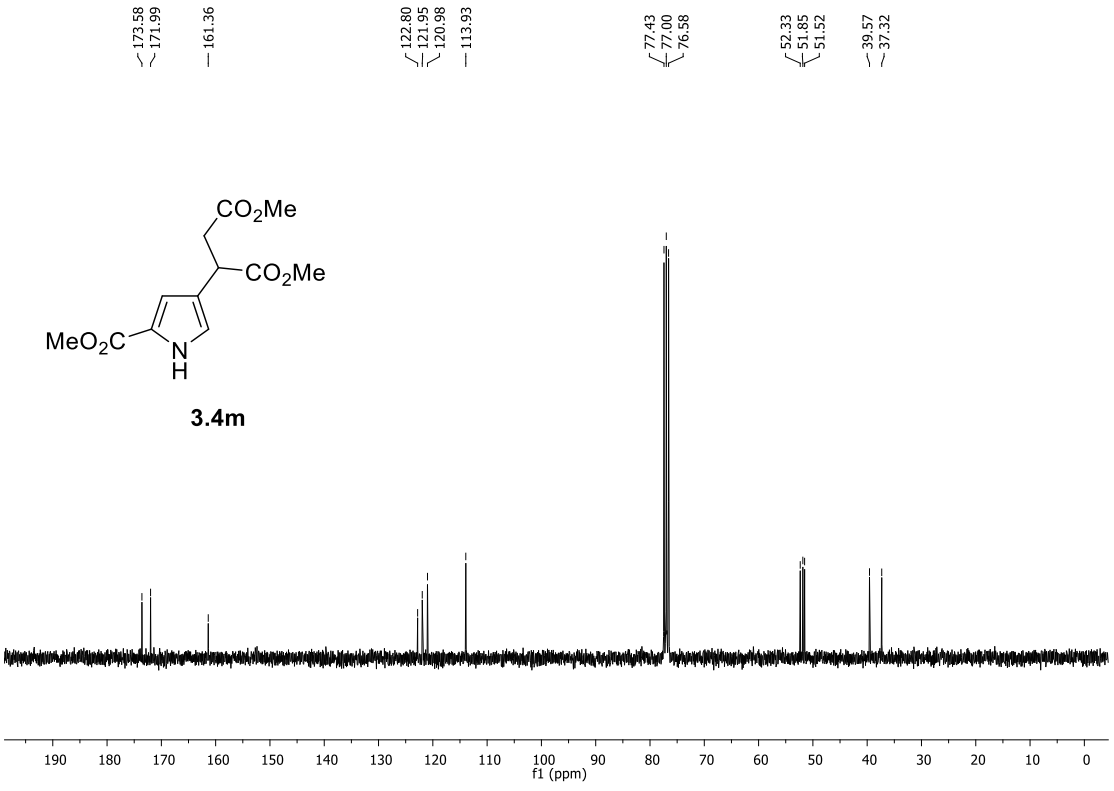
161.50
135.21
122.98
122.52
121.13
116.97
114.33
77.43
77.00
76.58
51.92
51.45
43.84
37.58
CO2Me
MeO2C
N
H
f1 (ppm)

3.4l


9.27
7.26
6.88
6.82
4.06
4.04
4.03
4.01
3.83
3.69
3.67
3.15
3.12
3.09
3.06
2.72
2.70
2.67
2.65
CO2Me
CO2Me
MeO2C
N
H
0.98
0.96
0.95
1.00
3.00
6.01
1.00
1.00
f1 (ppm)

3.4m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171.99
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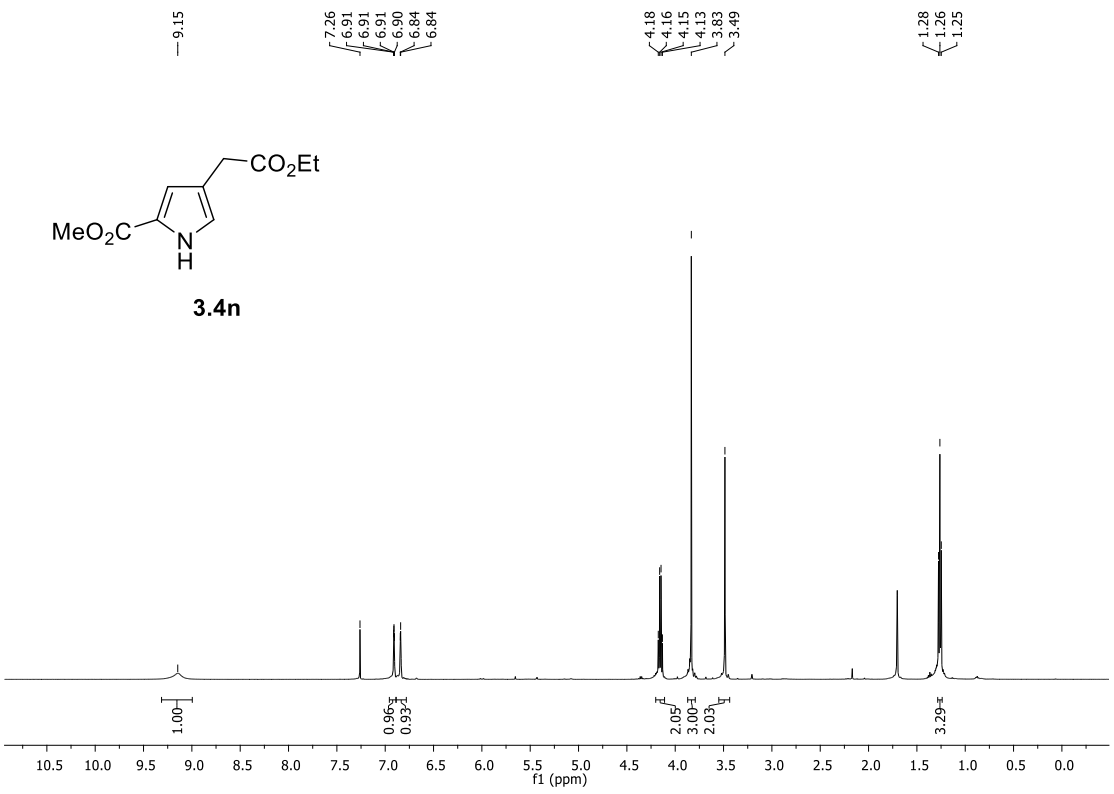
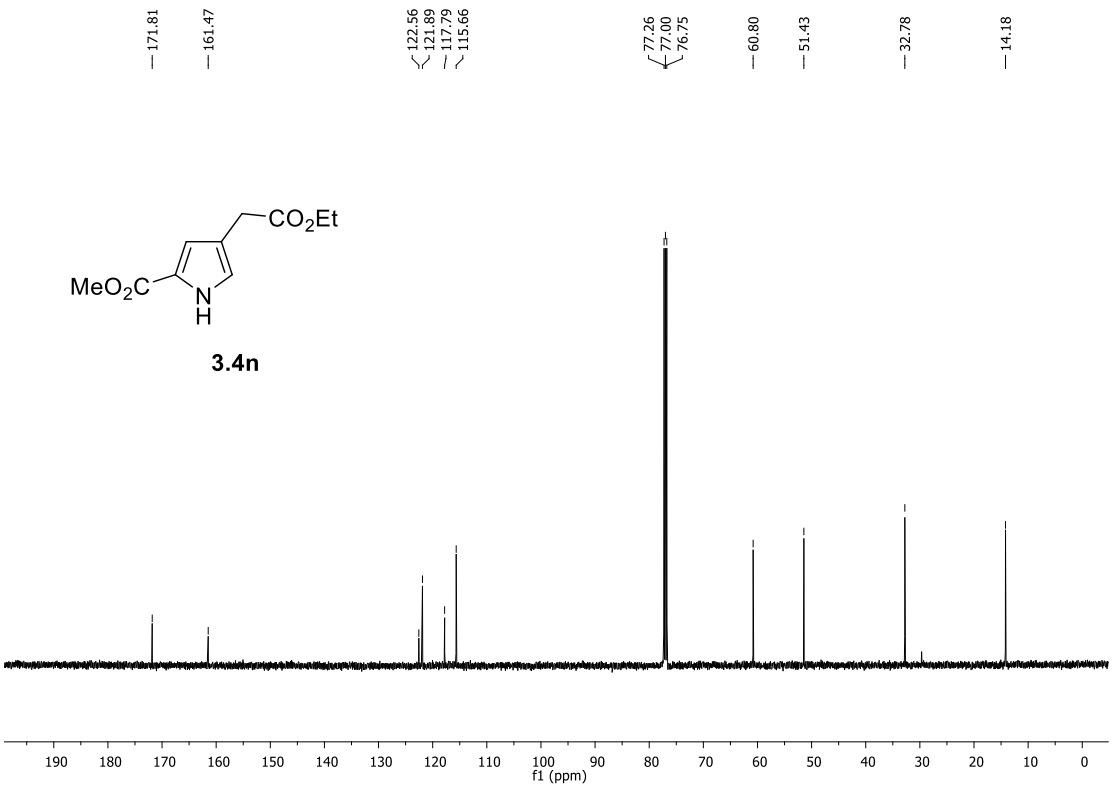
122.80
121.95
120.98
113.93
77.43
77.00
76.58
52.33
51.85
51.52
39.57
37.32
CO2Me
CO2Me
MeO2C
N
H
f1 (ppm)

3.4m


9.15
7.26
6.91
6.91
6.91
6.90
6.84
6.84
4.18
4.16
4.15
4.13
3.83
3.49
1.28
1.26
1.25
CO2Et
MeO2C
N
H
1.00
0.96
0.93
2.05
3.00
2.03
3.29
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

3.4n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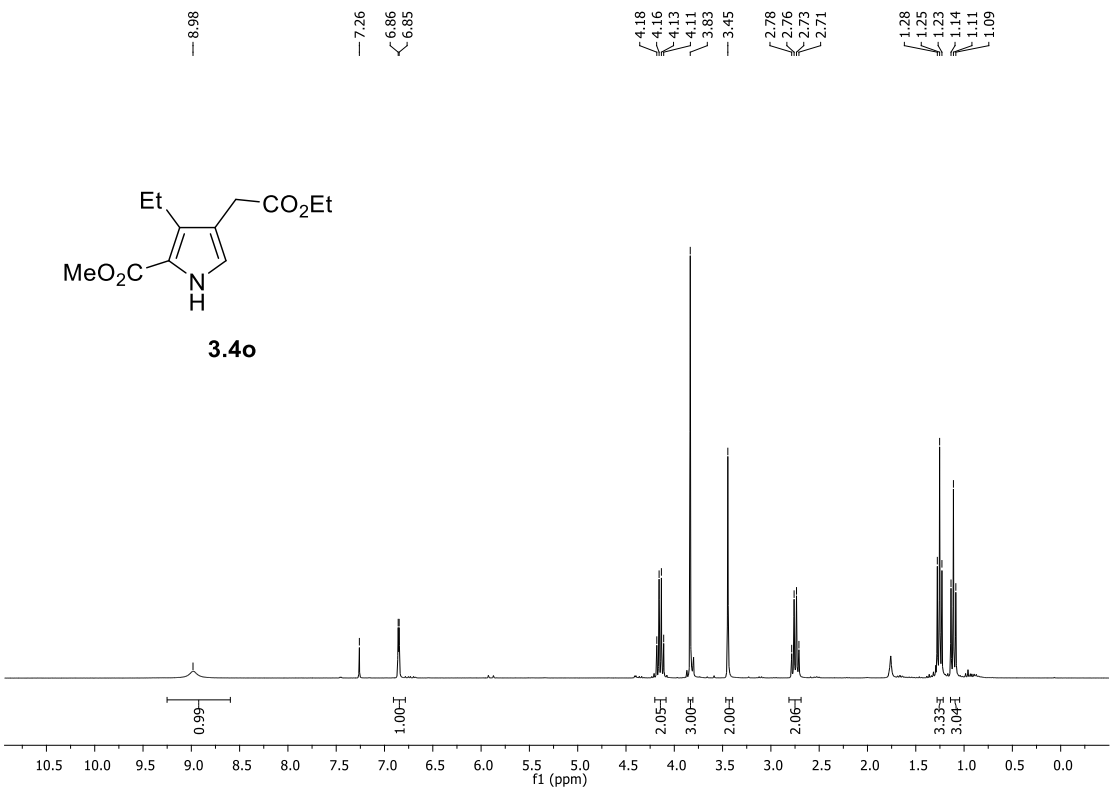
161.47
122.56
121.89
117.79
115.66
77.26
77.00
76.75
60.80
51.43
32.78
14.18
CO2Et
MeO2C
N
H
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3.4n


8.98
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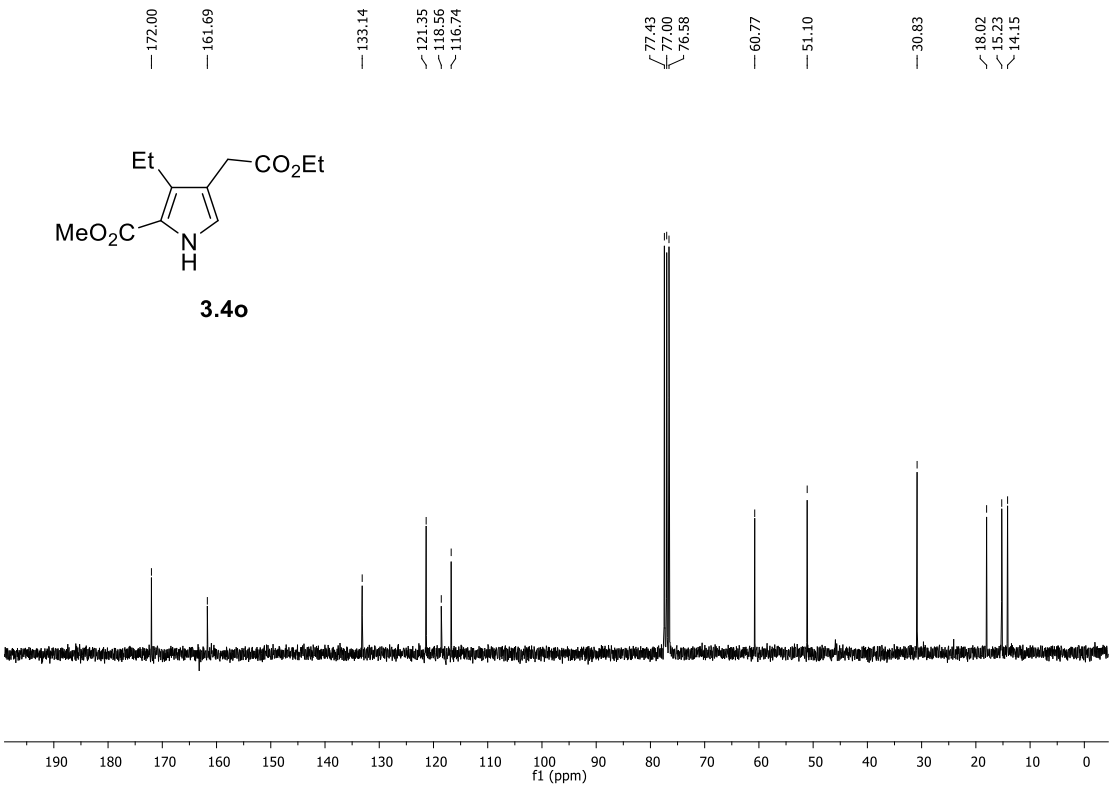
6.86
6.85
4.18
4.16
4.13
4.11
3.83
3.45
2.78
2.76
2.73
2.71
1.28
1.25
1.23
1.14
1.11
1.09
Et
CO2Et
MeO2C
N
H
0.99
1.00
2.05
3.00
2.00
2.06
3.33
3.04
f1 (ppm)

3.4o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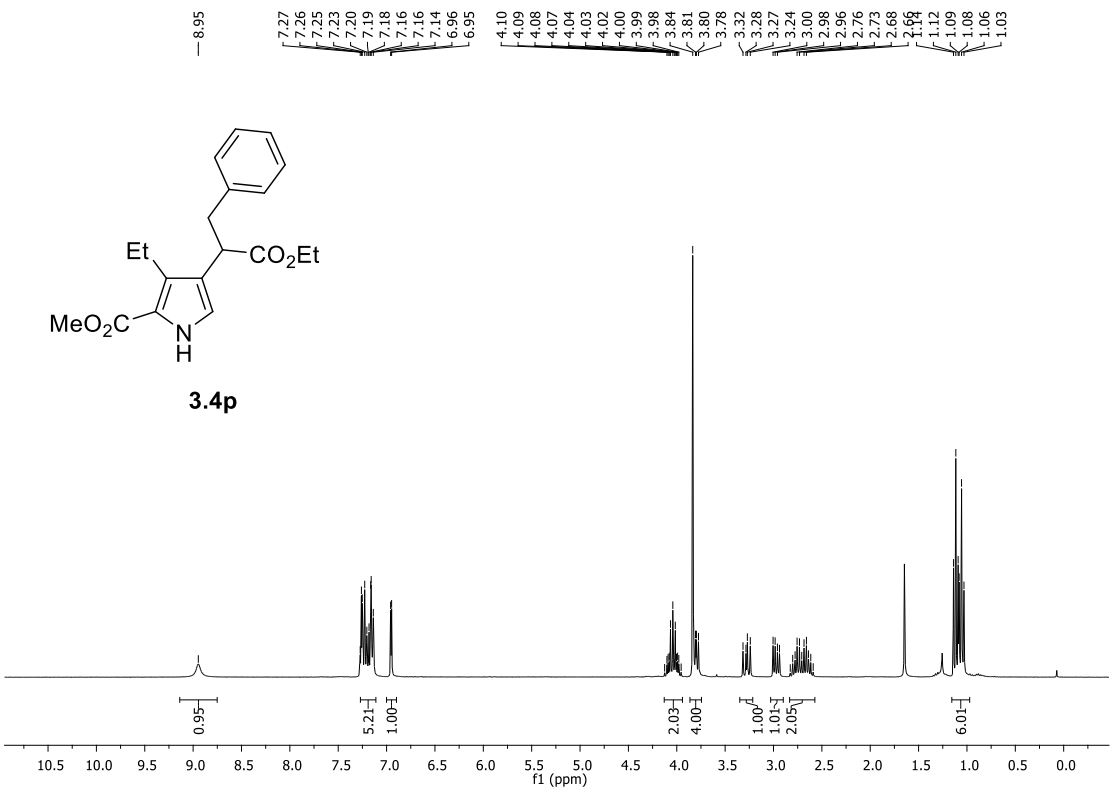
161.69
133.14
121.35
118.56
116.74
77.43
77.00
76.58
60.77
51.10
30.83
18.02
15.23
14.15
Et
CO2Et
MeO2C
N
H
f1 (ppm)

3.4o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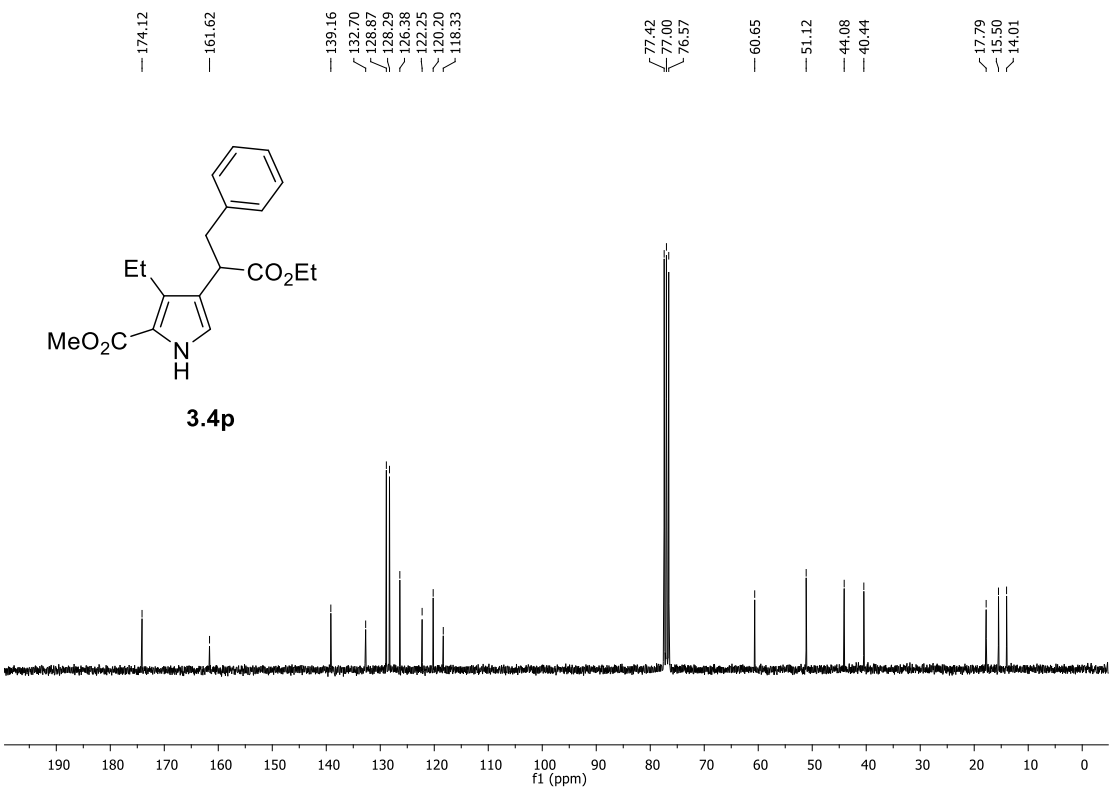
7.27
7.26
7.25
7.23
7.20
7.19
7.18
7.16
7.16
7.14
6.96
6.95
4.10
4.09
4.08
4.07
4.04
4.03
4.02
4.00
3.99
3.98
3.84
3.81
3.80
3.78
3.32
3.28
3.27
3.24
3.00
2.98
2.96
2.76
2.73
2.68
2.66
1.14
1.12
1.09
1.08
1.06
1.03
Et
CO2Et
MeO2C
N
H
0.95
5.21
1.00
2.03
4.00
1.00
1.01
2.05
6.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

3.4p


174.12
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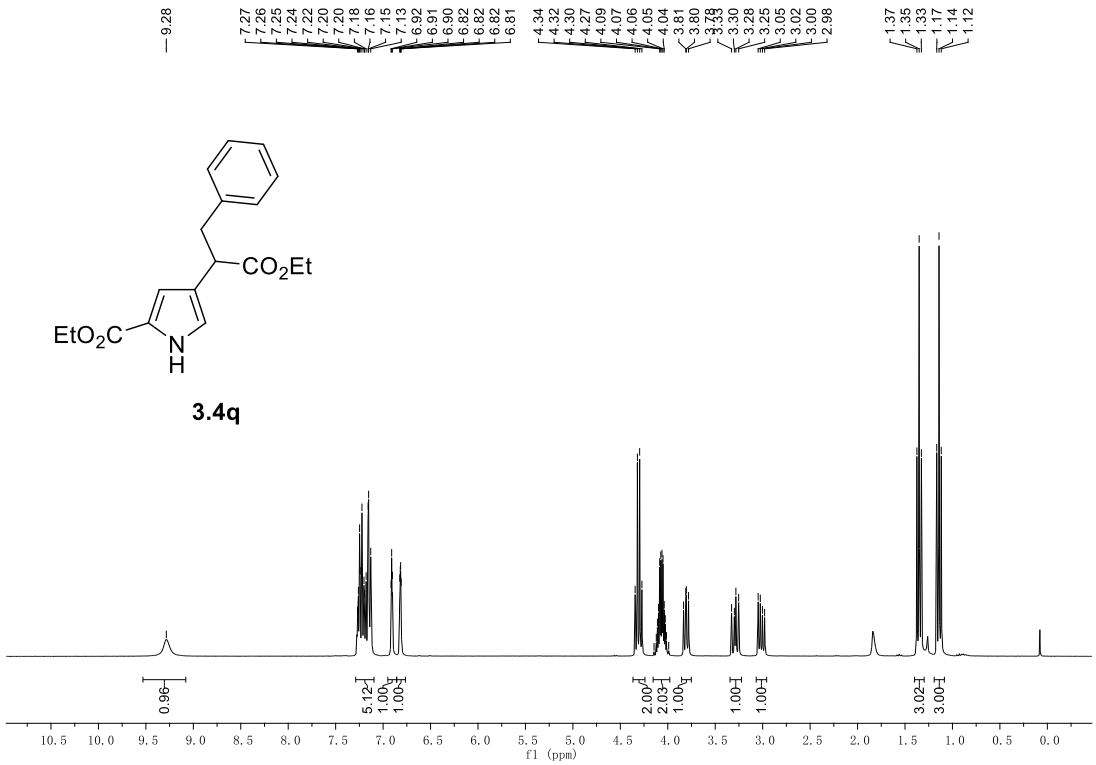
132.70
128.87
128.29
126.38
122.25
120.20
118.33
77.42
77.00
76.57
60.65
51.12
44.08
40.44
17.79
15.50
14.01
Et
CO2Et
MeO2C
N
H
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3.4p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7.27
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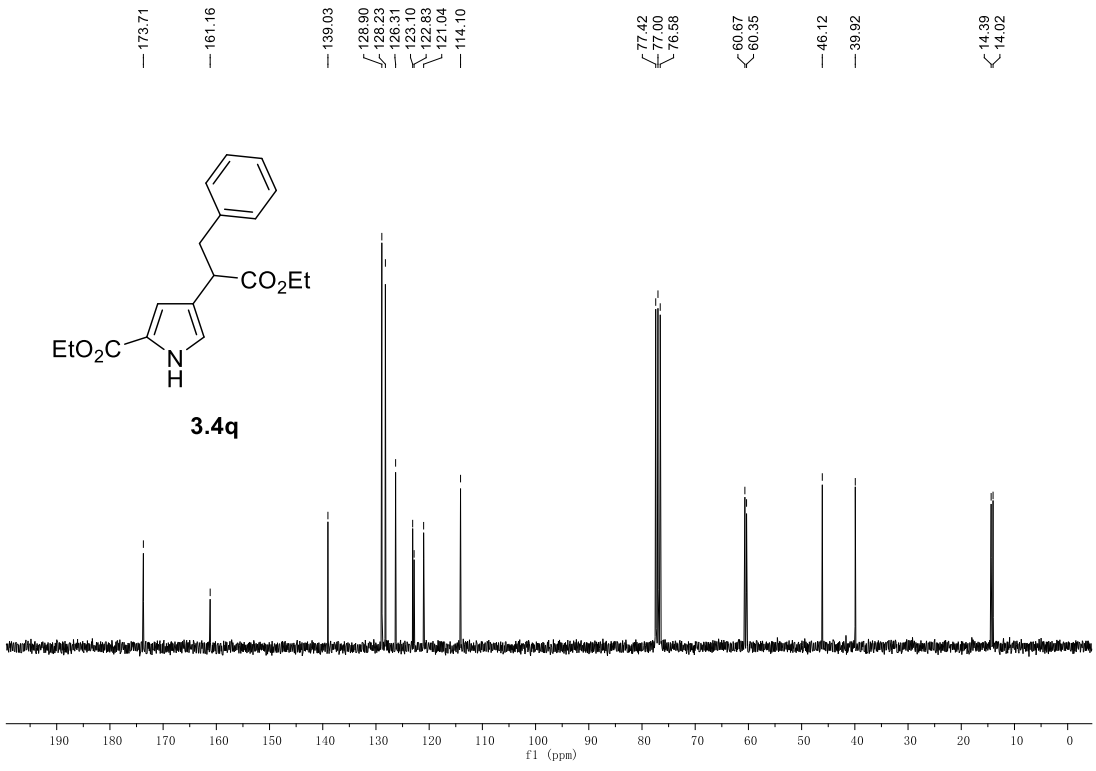
7.15
7.13
6.92
6.91
6.90
6.82
6.82
6.82
6.81
4.34
4.32
4.30
4.27
4.09
4.07
4.06
4.05
4.04
3.81
3.80
3.33
3.30
3.28
3.25
3.05
3.02
3.00
2.98
1.37
1.35
1.33
1.17
1.14
1.12
CO2Et
EtO2C
N
H
3.4q
0.96
5.12
1.00
1.00
2.00
2.03
1.00
1.00
1.00
3.02
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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123.10
122.83
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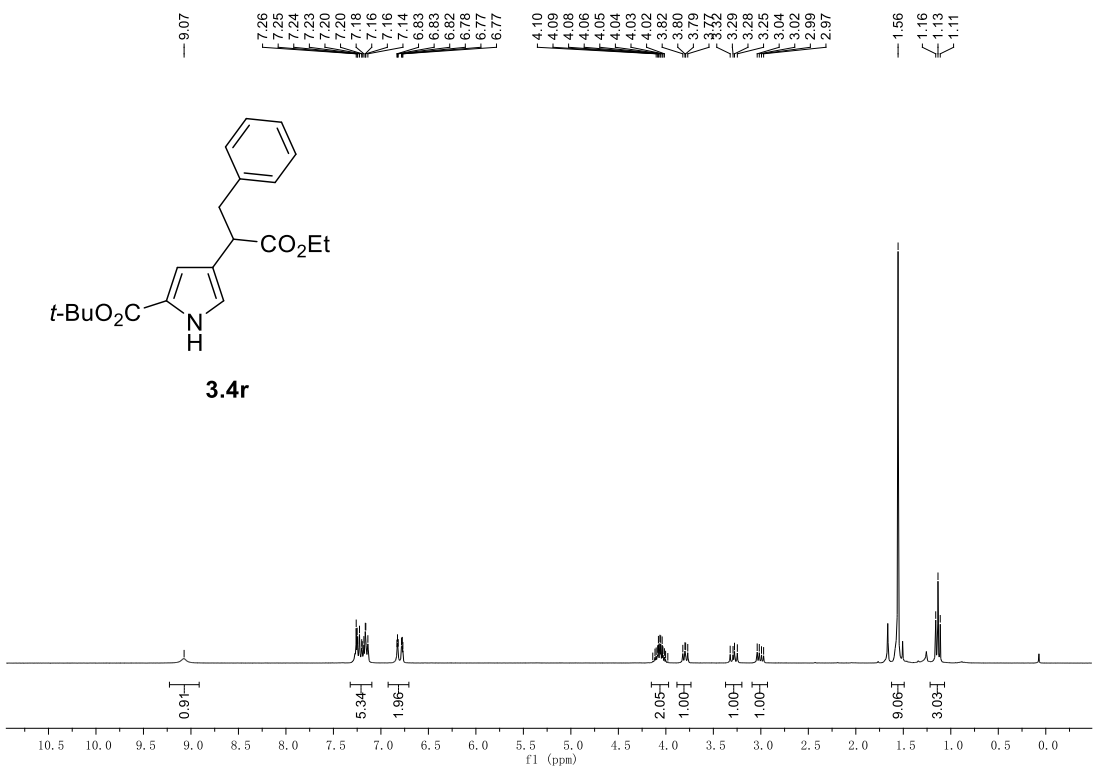
114.10
77.42
77.00
76.58
60.67
60.35
46.12
39.92
14.39
14.02
CO2Et
EtO2C
N
H
3.4q
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.18
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7.14
6.83
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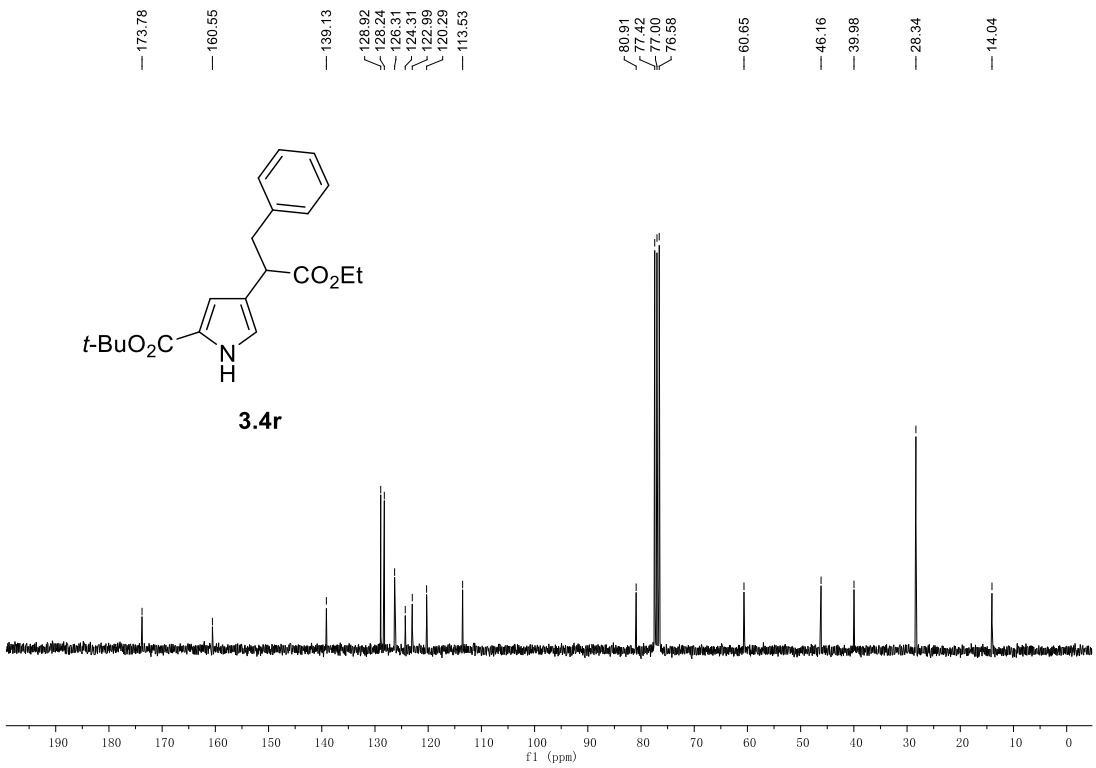
6.82
6.78
6.77
6.77
4.10
4.09
4.08
4.06
4.05
4.04
4.03
4.02
3.82
3.80
3.79
3.32
3.29
3.28
3.25
3.04
3.02
2.99
2.97
1.56
1.16
1.13
1.11
CO2Et
t-BuO2C
N
H
0.91
5.34
1.96
2.05
1.00
1.00
1.00
9.06
3.03
f1 (ppm)

3.4r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126.31
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122.99
120.29
113.53
80.91
77.42
77.00
76.58
60.65
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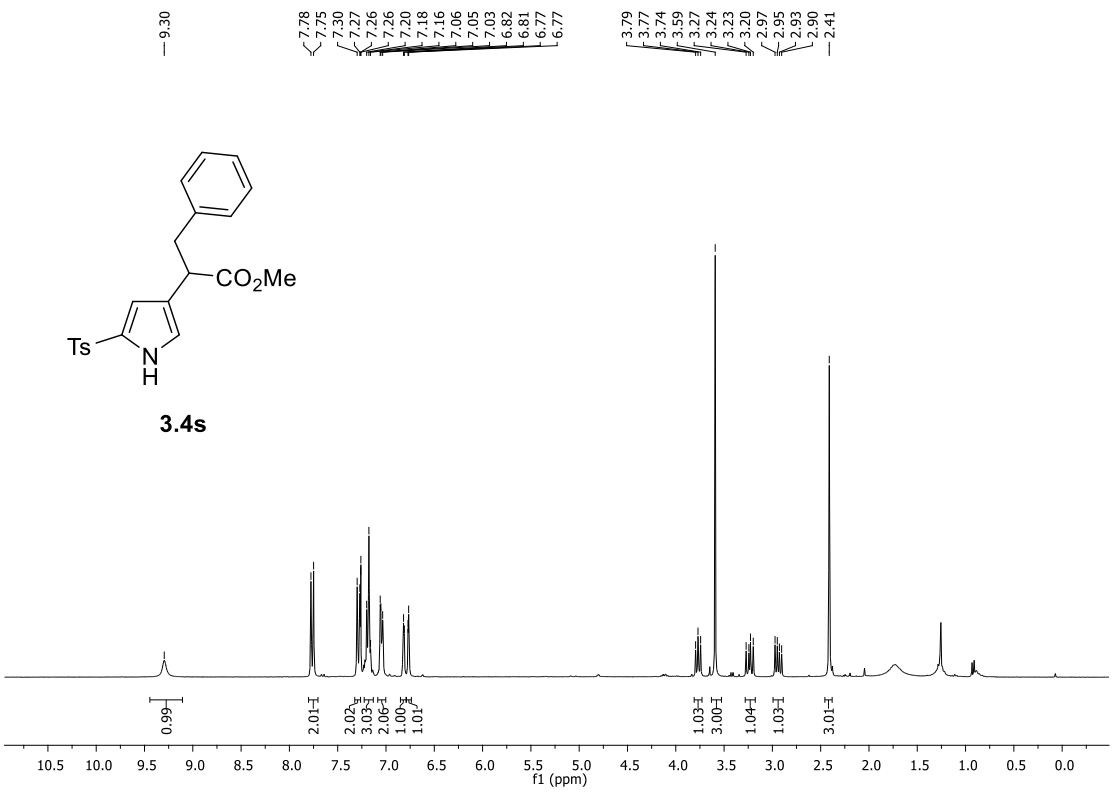
39.98
28.34
14.04
CO2Et
t-BuO2C
N
H
f1 (ppm)

3.4r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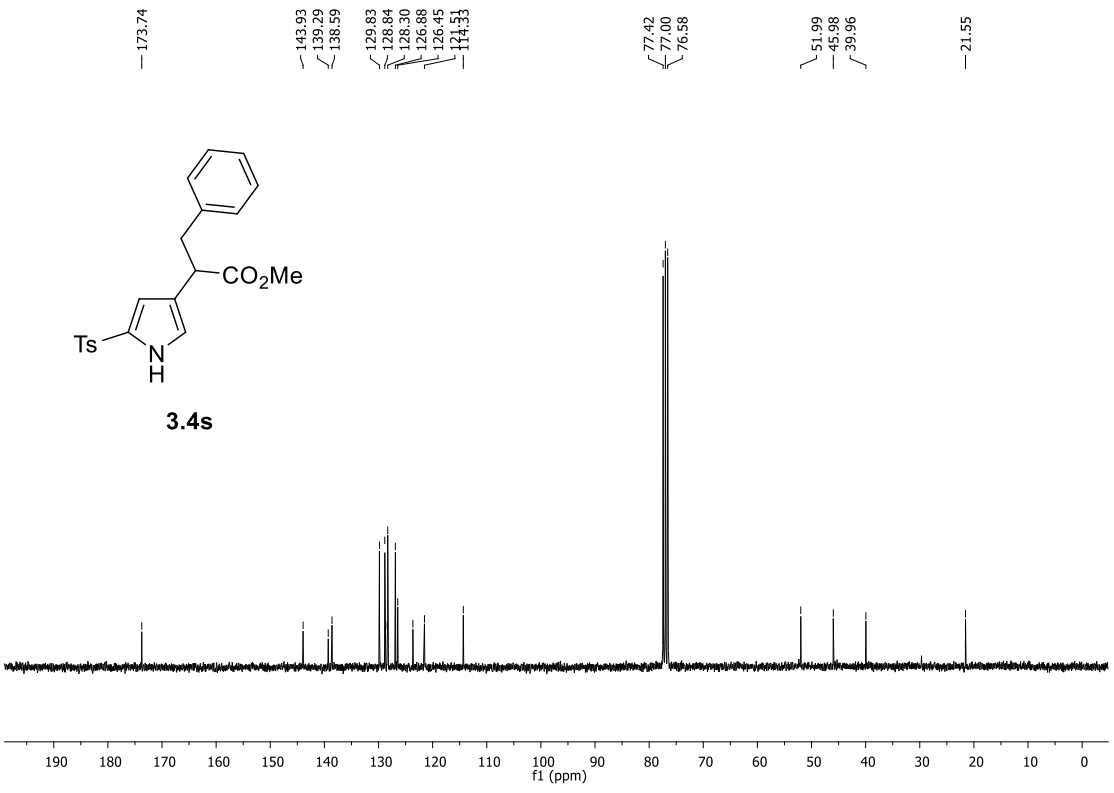
7.26
7.26
7.20
7.18
7.16
7.06
7.05
7.03
6.82
6.81
6.77
6.77
3.79
3.77
3.74
3.59
3.27
3.24
3.23
3.20
2.97
2.95
2.93
2.90
2.41
CO2Me
Ts
N
H
3.4s
0.99
2.01
2.02
3.03
2.06
1.00
1.01
1.03
3.00
1.04
1.03
3.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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126.88
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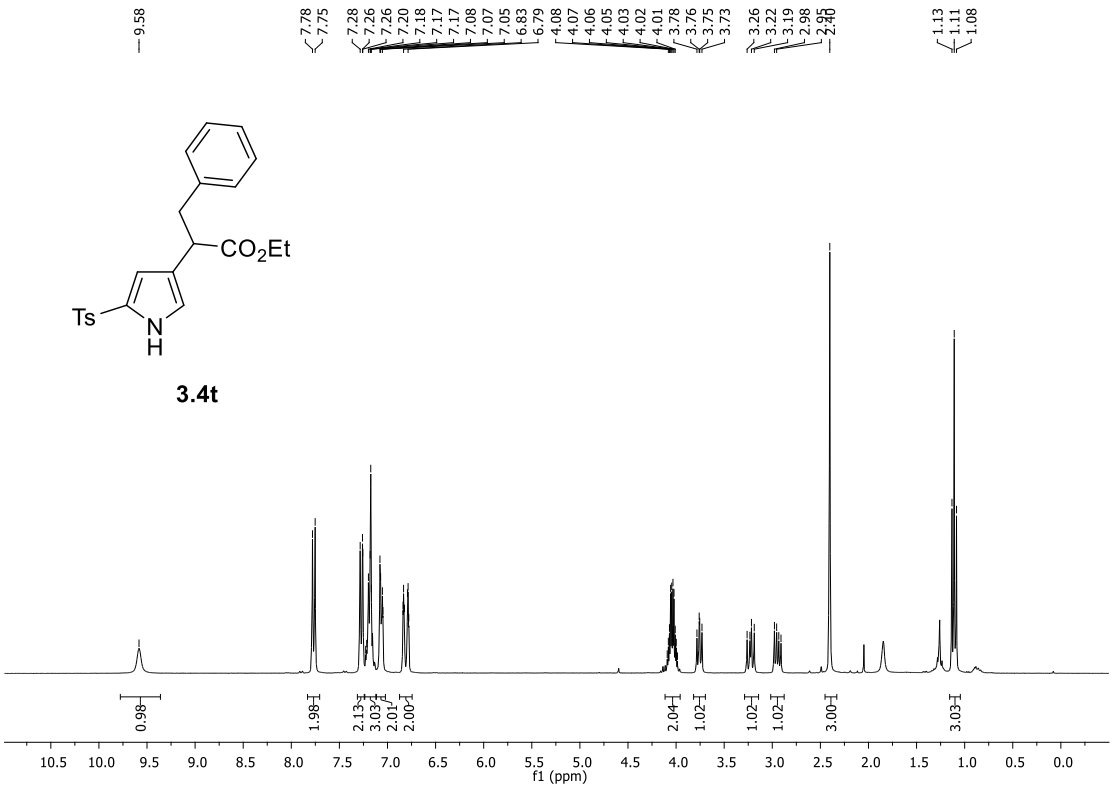
77.42
77.00
76.58
51.99
45.98
39.96
21.55
CO2Me
Ts
N
H
3.4s
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.26
7.20
7.18
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7.17
7.08
7.07
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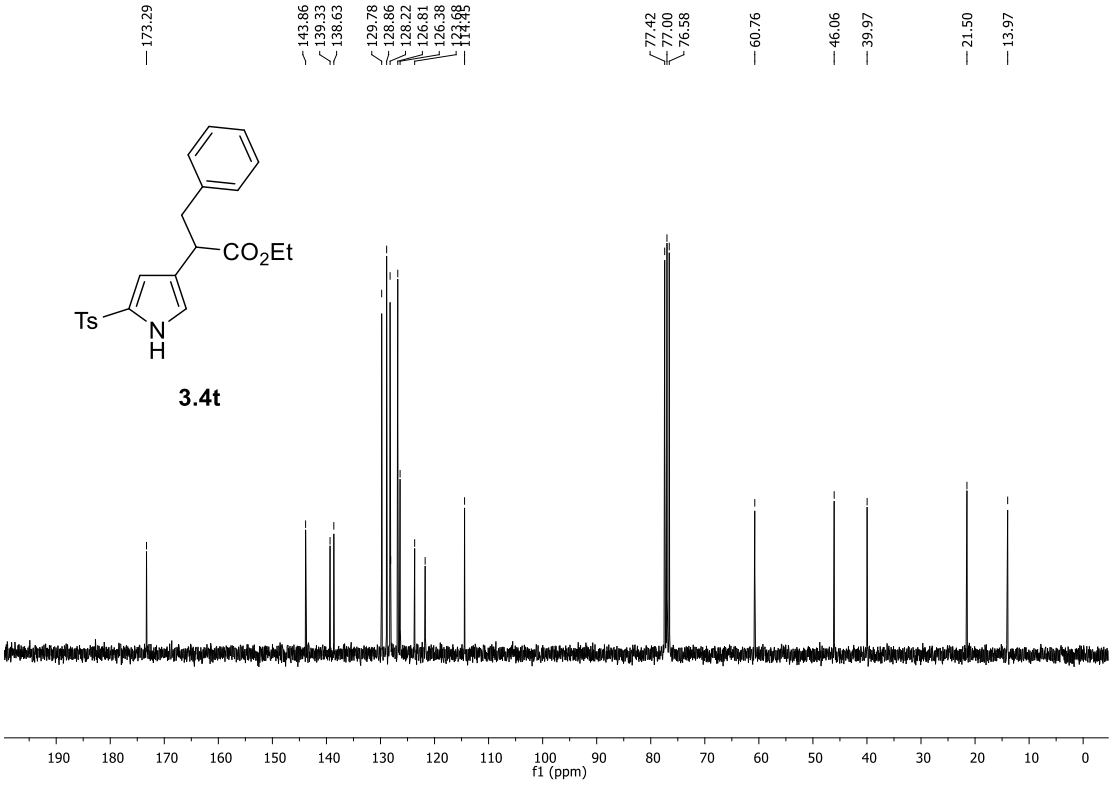
6.79
4.08
4.07
4.06
4.05
4.03
4.02
4.01
3.78
3.76
3.75
3.73
3.26
3.22
3.19
2.98
2.95
2.40
1.13
1.11
1.08
CO2Et
Ts
N
H
3.4t
0.98
1.98
2.13
3.03
2.01
2.00
2.04
1.02
1.02
1.02
3.00
3.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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128.22
126.81
126.38
77.42
77.00
76.58
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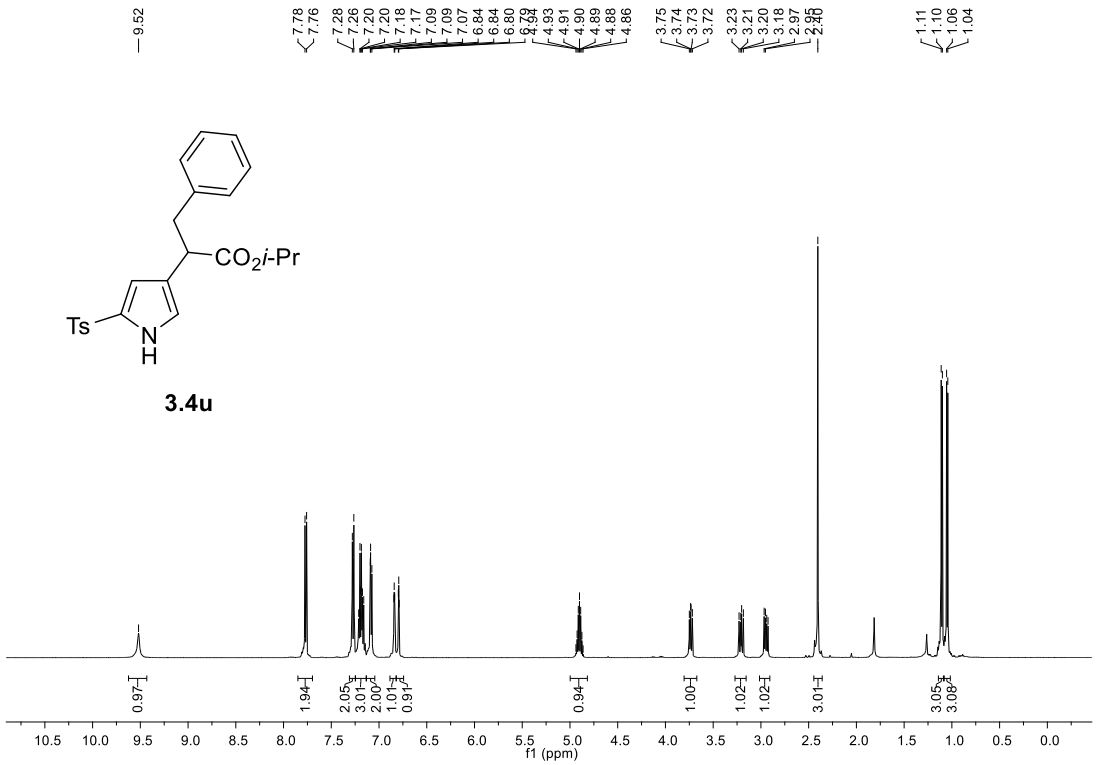
46.06
39.97
21.50
13.97
CO2Et
Ts
N
H
3.4t
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.20
7.20
7.18
7.17
7.09
7.09
7.07
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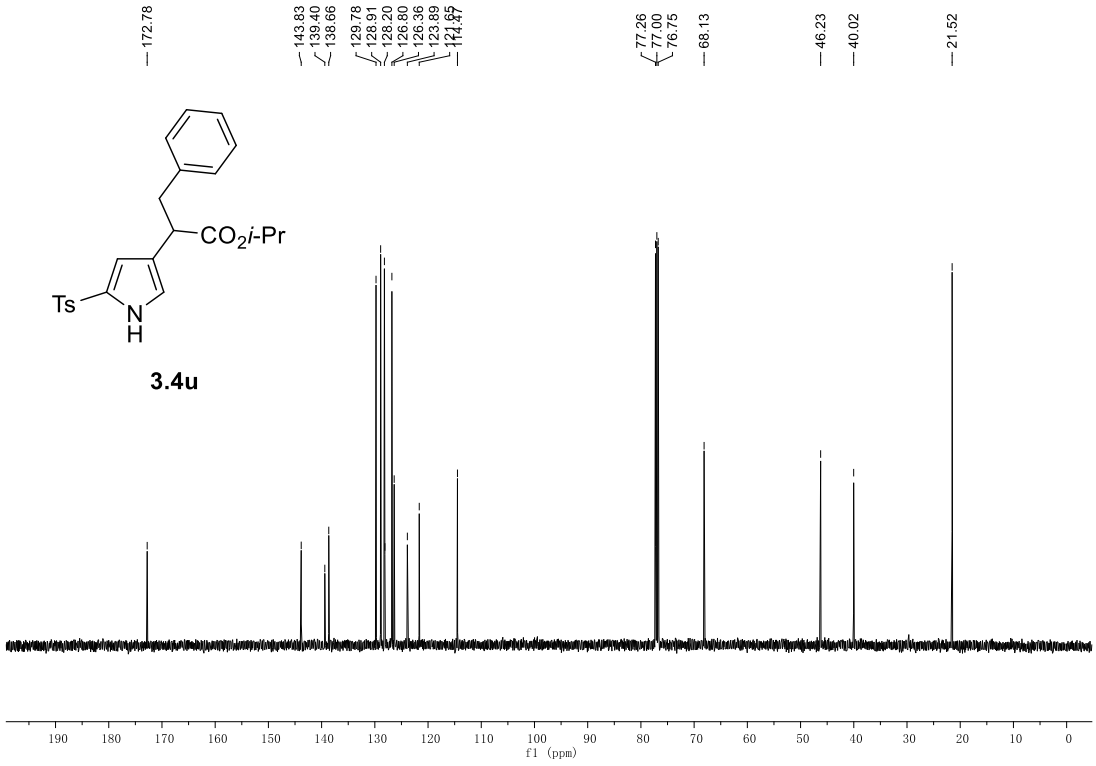
6.84
6.80
6.79
4.94
4.93
4.91
4.90
4.89
4.88
4.86
3.75
3.74
3.73
3.72
3.23
3.21
3.20
3.18
2.97
2.95
2.90
1.11
1.10
1.06
1.04
CO2i-Pr
Ts
N
H
3.4u
0.97
1.94
2.05
3.01
2.00
1.01
0.91
0.94
1.00
1.02
1.02
3.01
3.05
3.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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139.40
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129.78
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128.20
126.80
126.36
123.89
77.26
77.00
76.75
68.13
46.23
40.02
21.52
CO2i-Pr
Ts
N
H
3.4u
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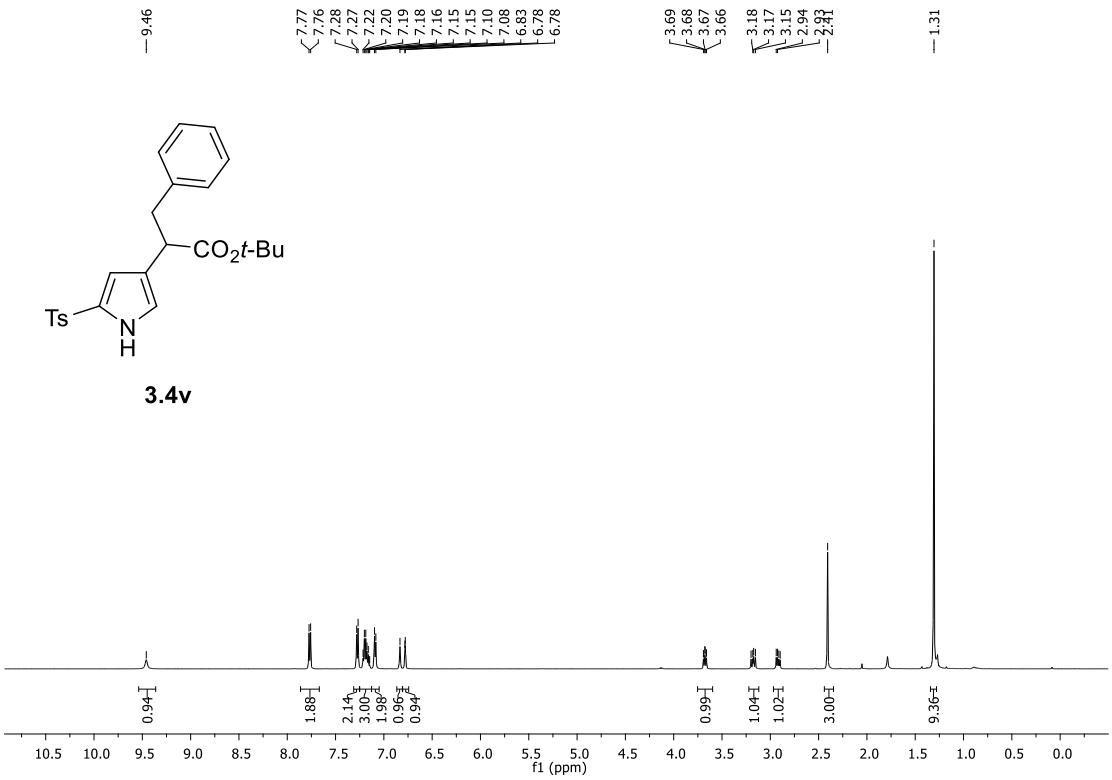
f1 (ppm)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7.19
7.18
7.16
7.15
7.15
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7.08
6.83
6.78
6.78
3.69
3.68
3.67
3.66
3.18
3.17
3.15
2.94
2.93
2.41
1.31
CO2t-Bu
Ts
N
H
0.94
1.88
2.14
3.00
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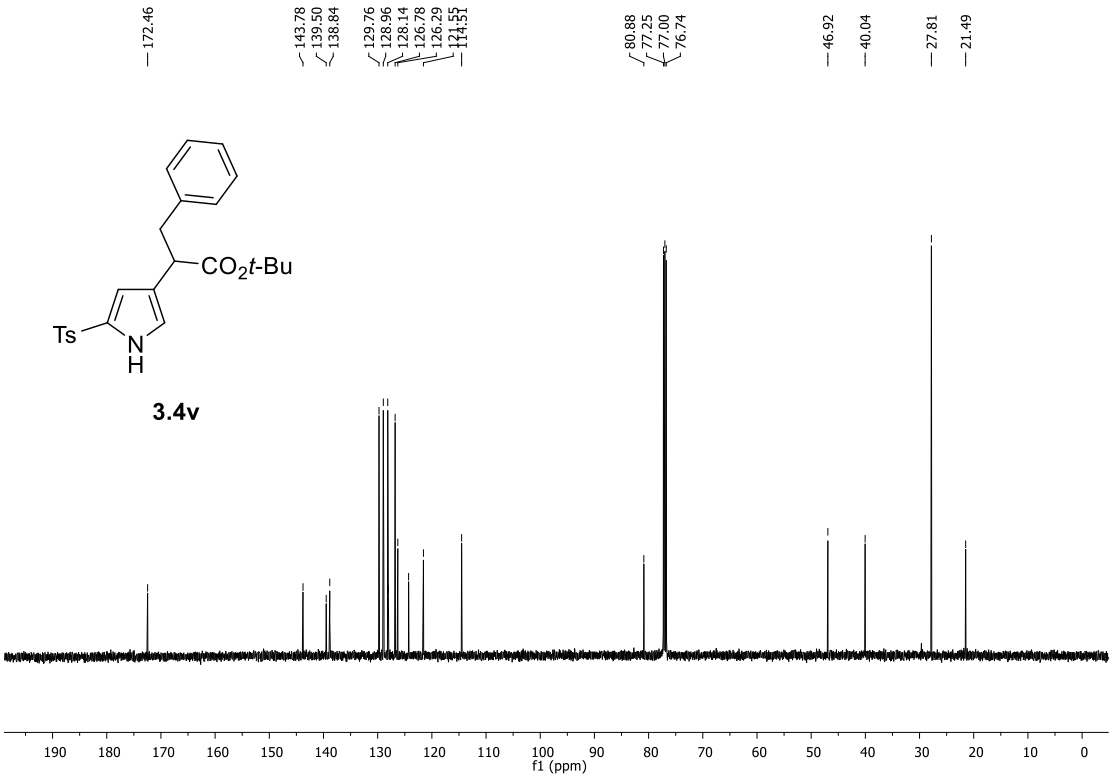
0.96
0.94
0.99
1.04
1.02
3.00
9.36
f1 (ppm)

3.4v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139.50
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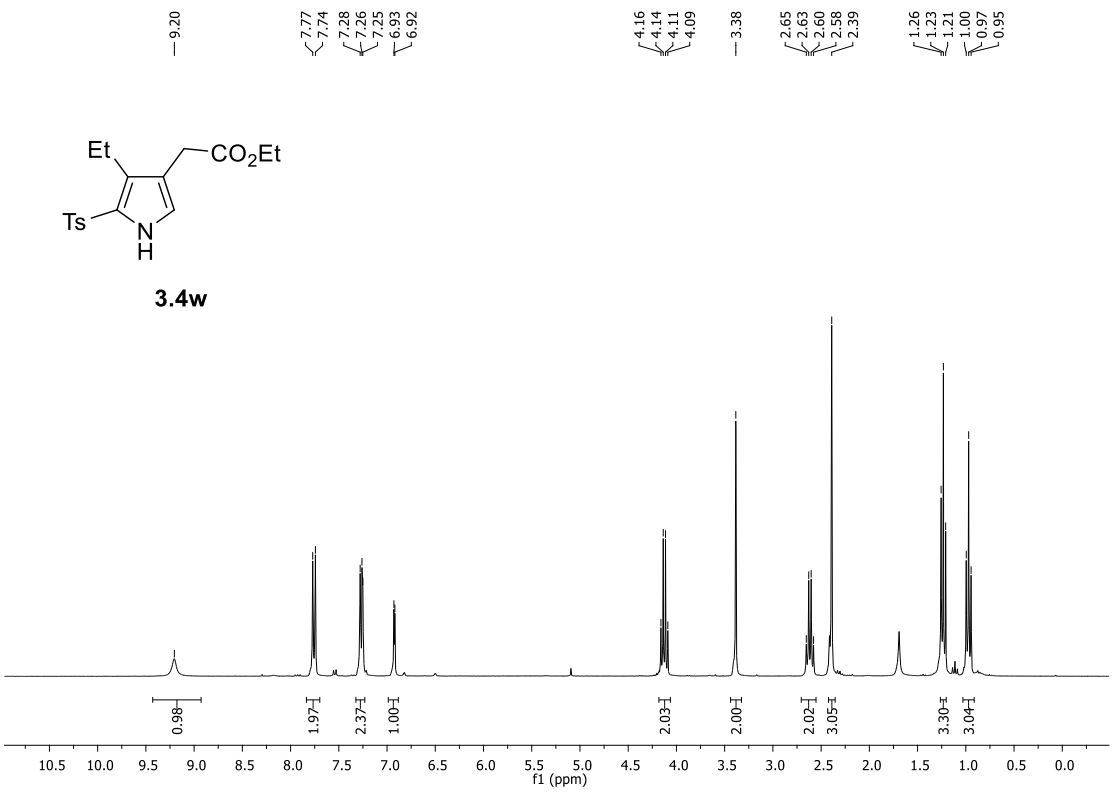
129.76
128.96
128.14
126.78
126.29
80.88
77.25
77.00
76.74
46.92
40.04
27.81
21.49
CO2t-Bu
Ts
N
H
f1 (ppm)

3.4v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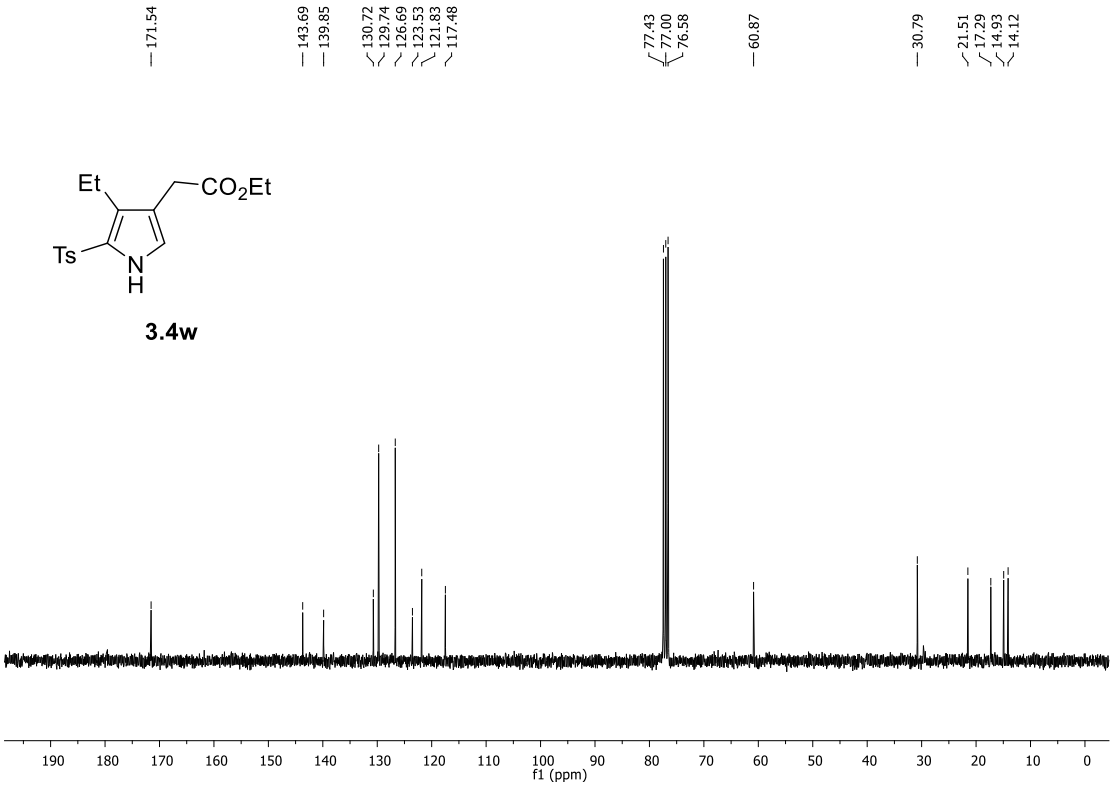
7.77
7.74
7.28
7.26
7.25
6.93
6.92
4.16
4.14
4.11
4.09
3.38
2.65
2.63
2.60
2.58
2.39
1.26
1.23
1.21
1.00
0.97
0.95
Et
CO2Et
Ts
N
H
3.4w
0.98
1.97
2.37
1.00
2.03
2.00
2.02
3.05
3.30
3.04
f1 (ppm)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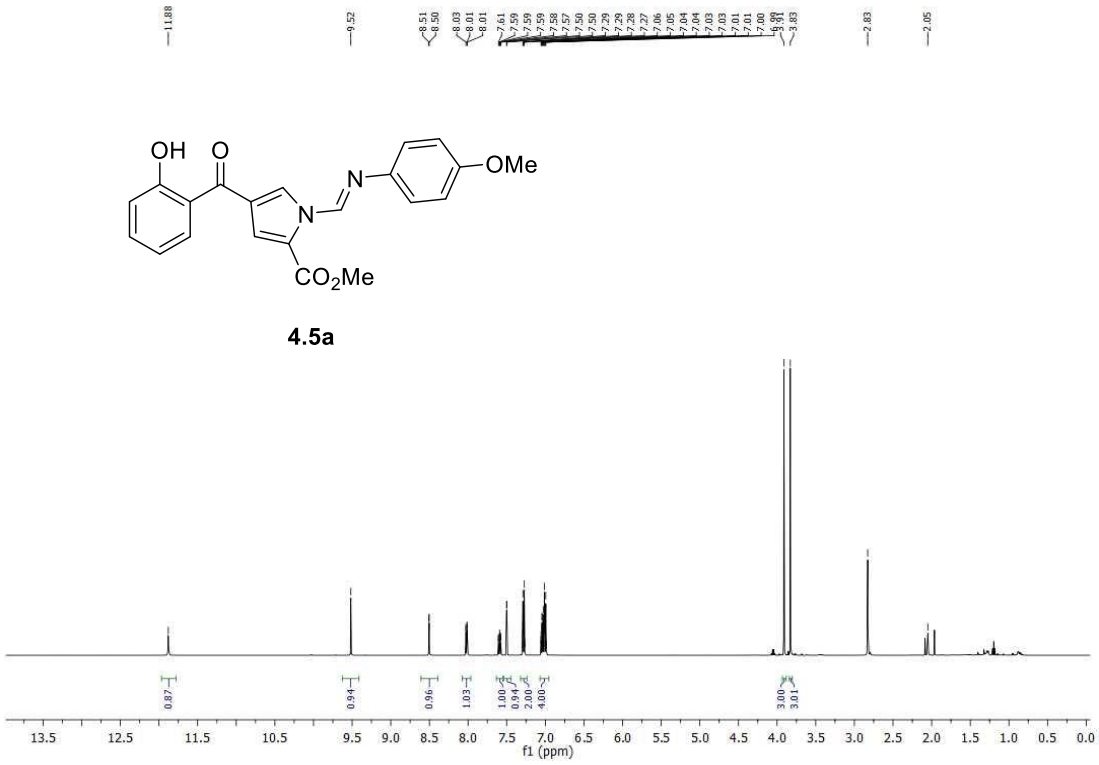
126.69
123.53
121.83
117.48
77.43
77.00
76.58
60.87
30.79
21.51
17.29
14.93
14.12
Et
CO2Et
Ts
N
H
3.4w
f1 (ppm)



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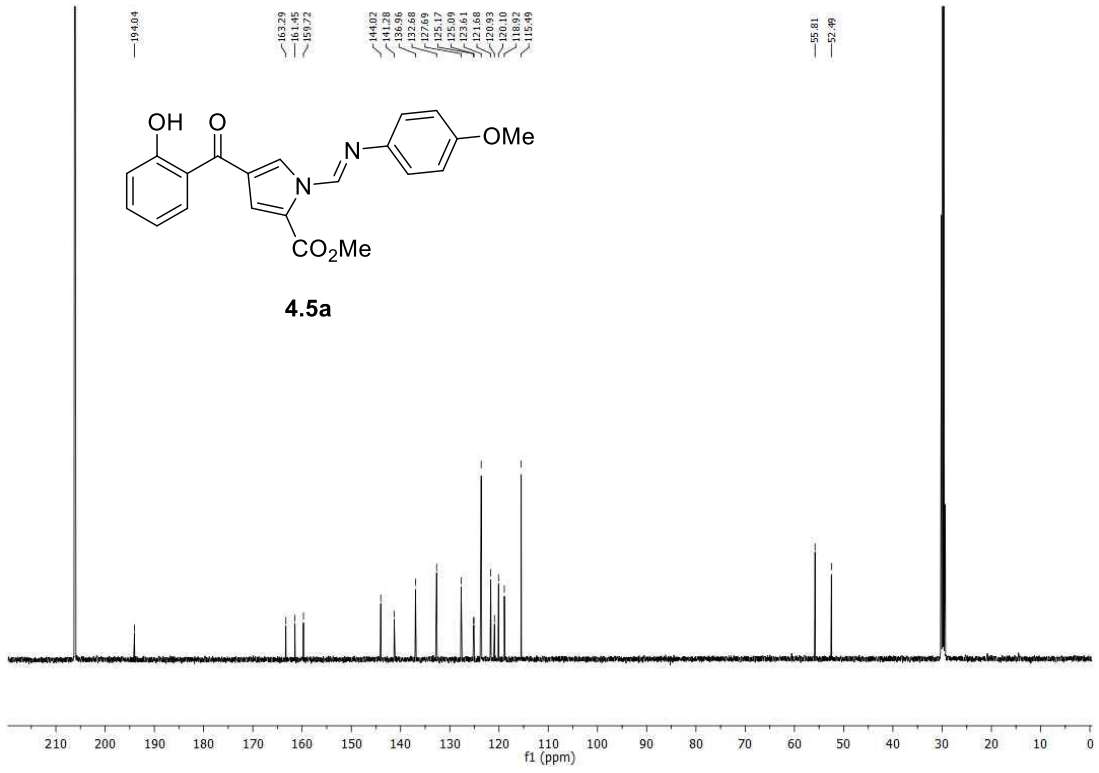

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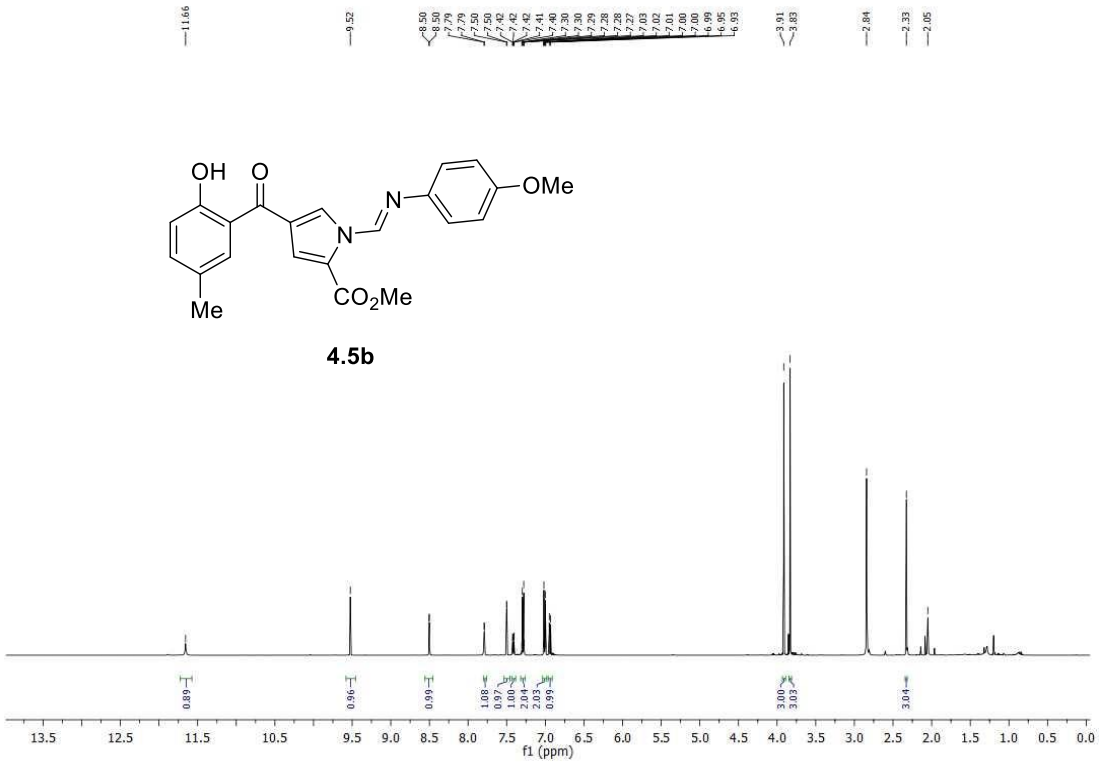
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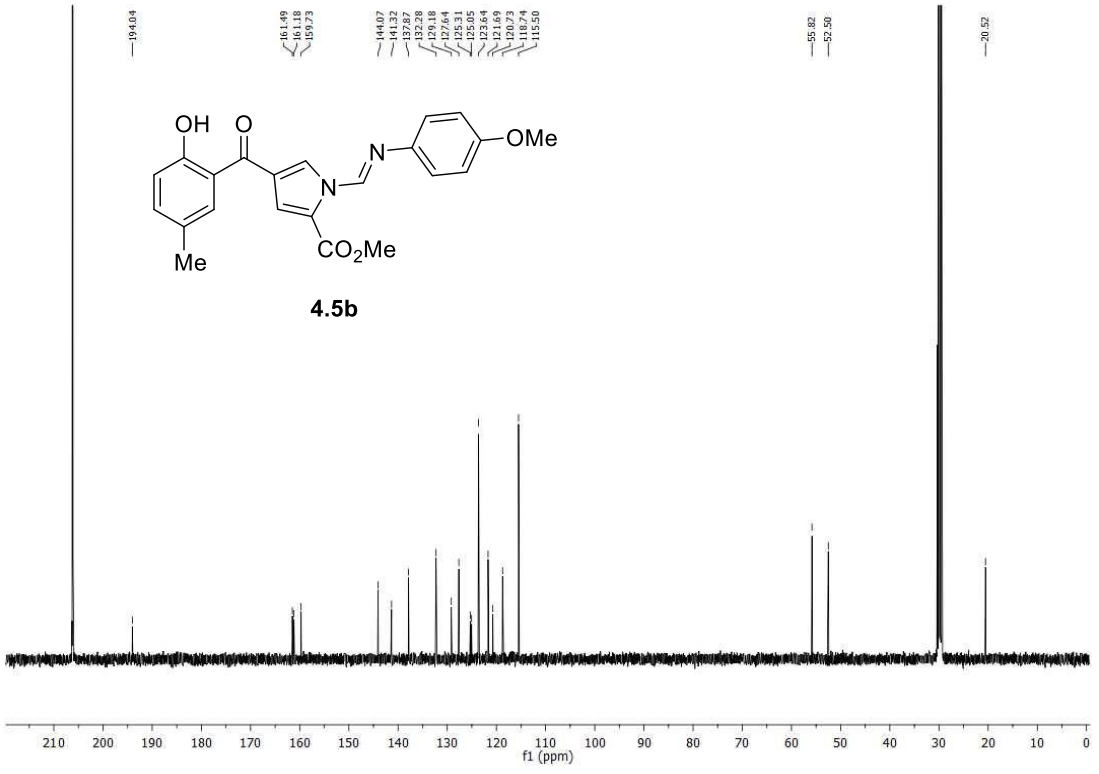
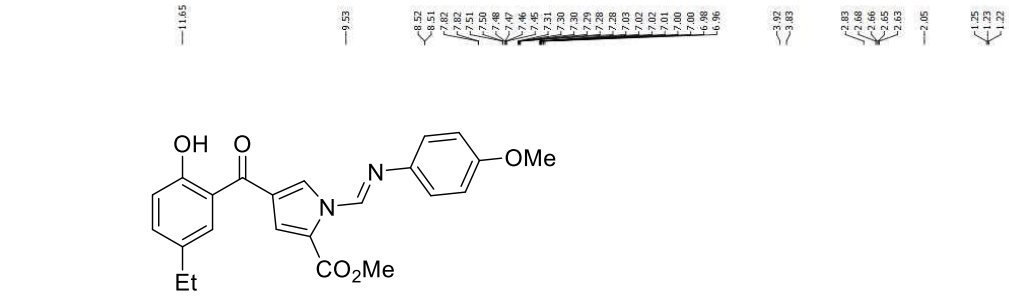
O
N
OMe
N
CO2Me
Me
4.5b
f1 (ppm)


OH
O
N
OMe
N
CO2Me
Me
4.5b
f1 (ppm)



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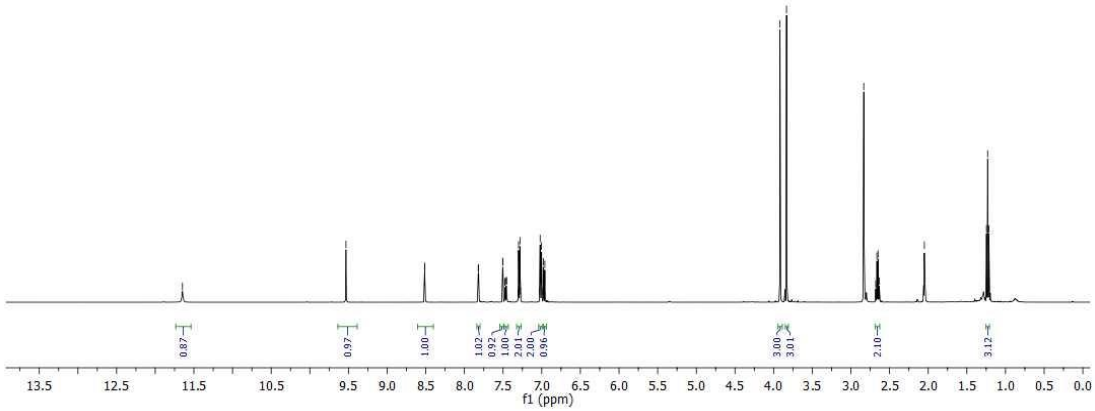

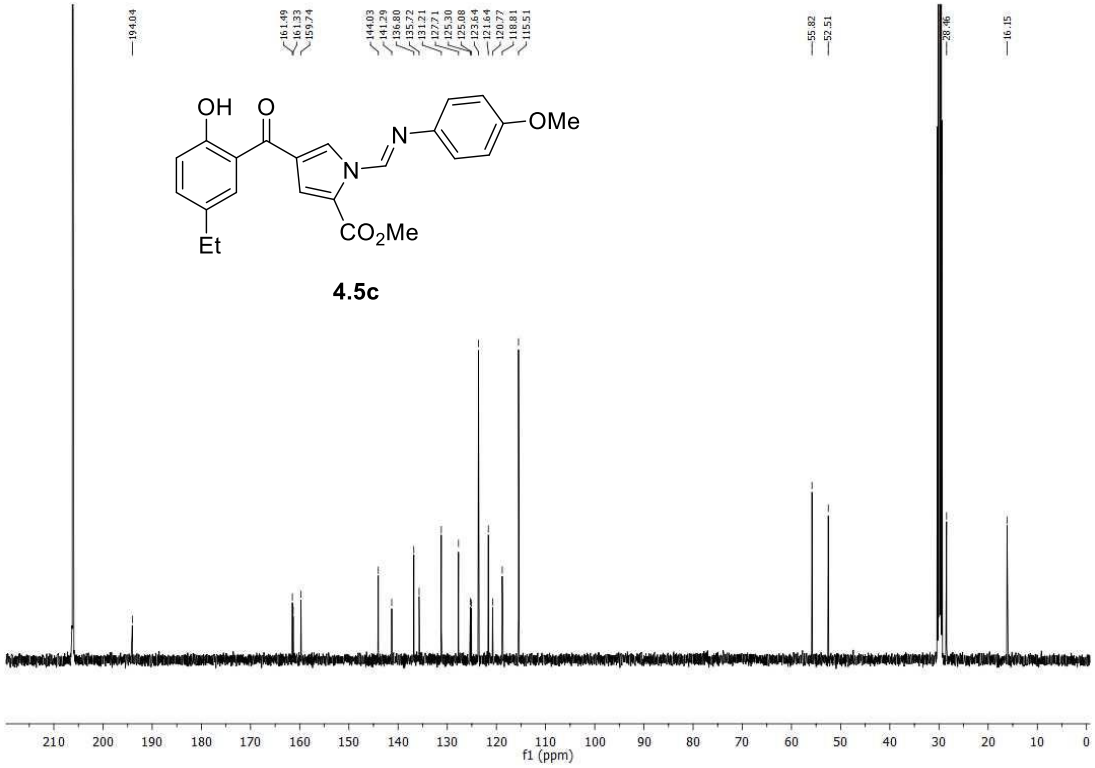

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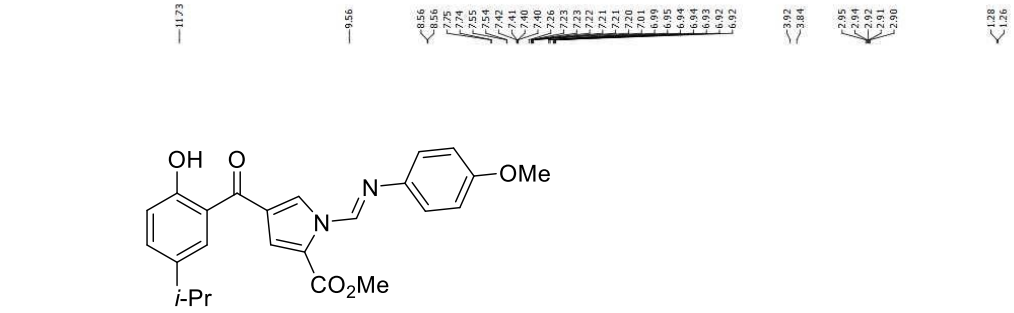

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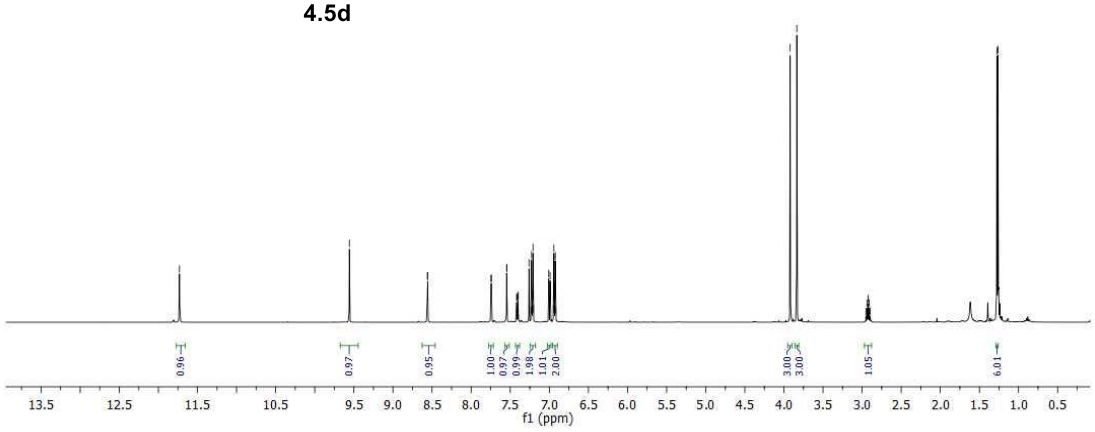
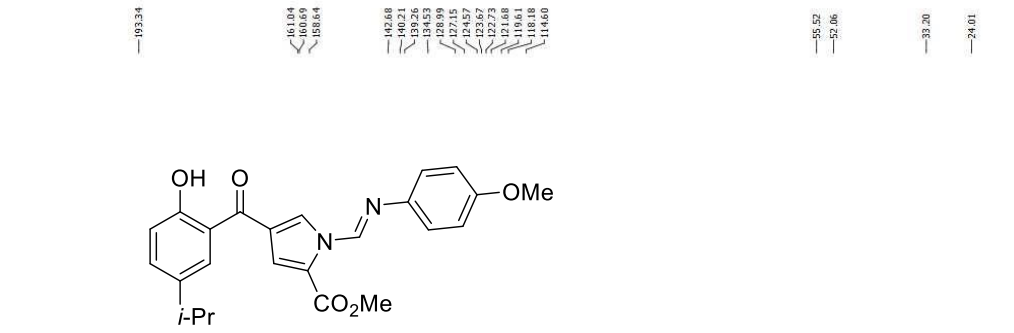
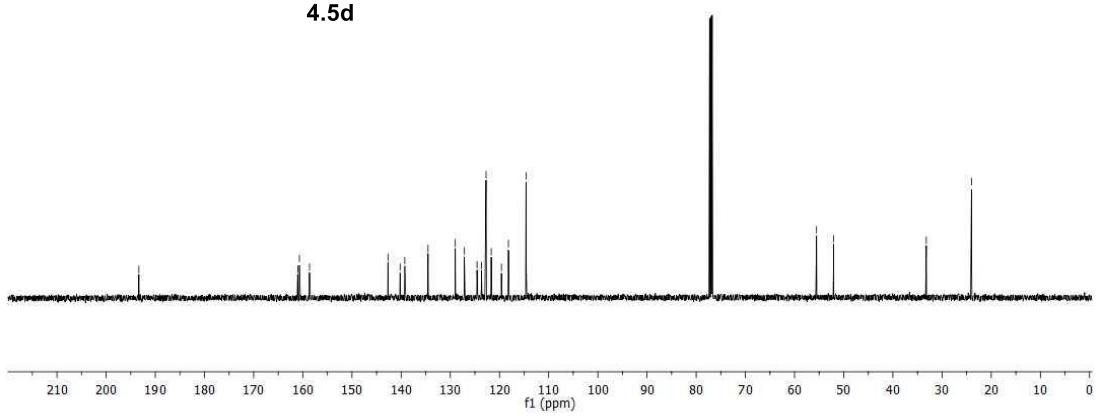
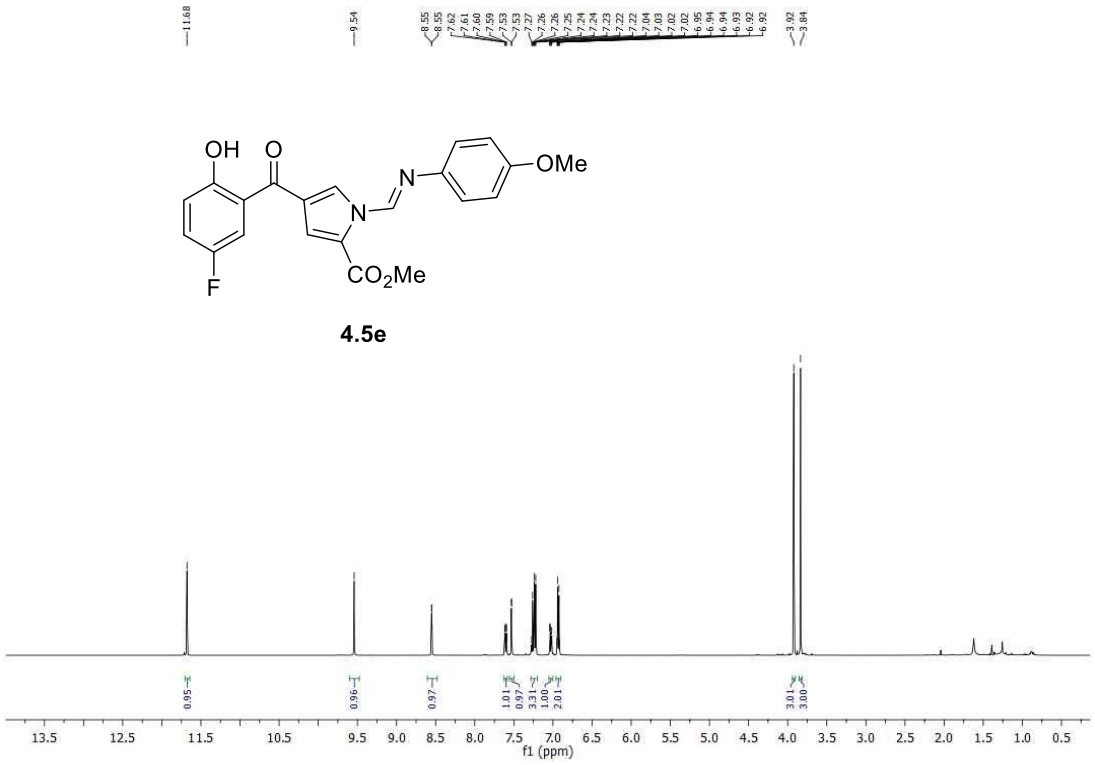




4.5d





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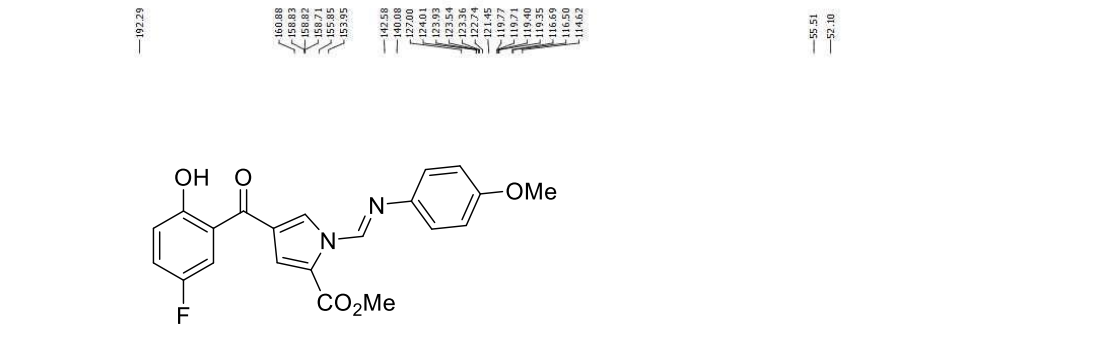

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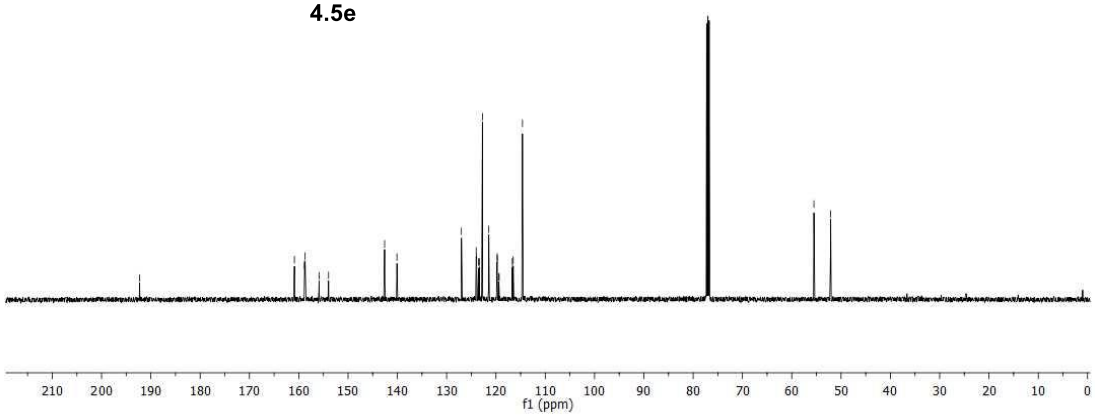
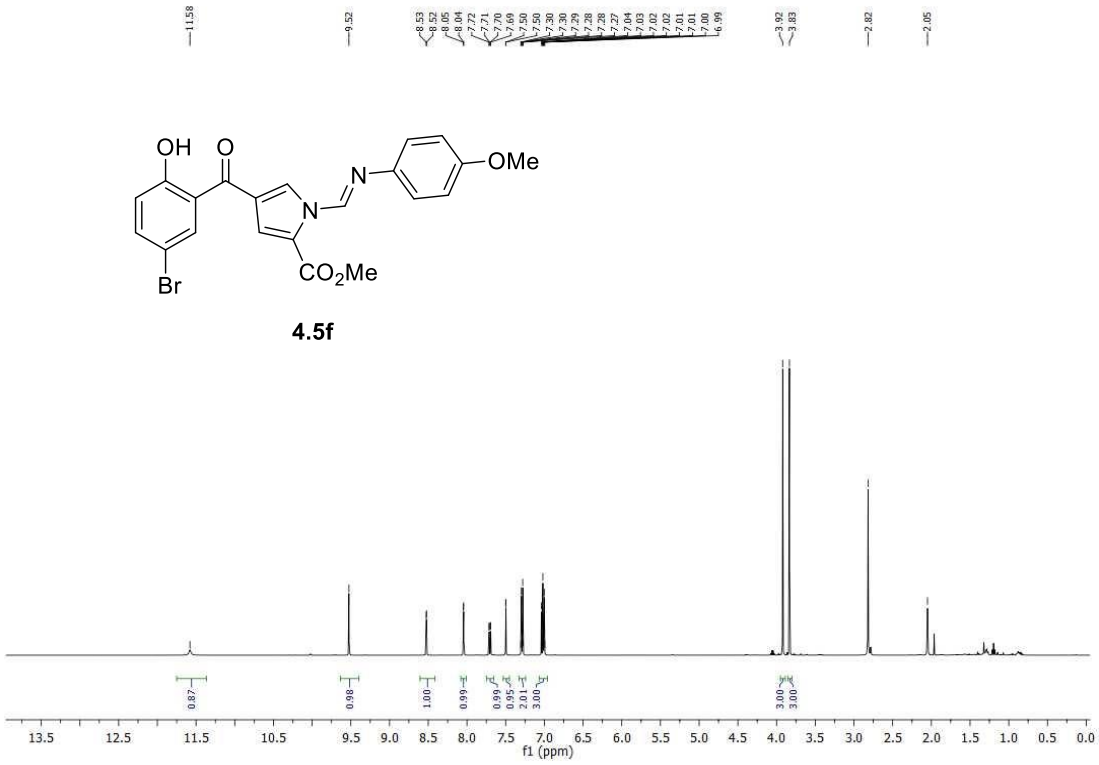
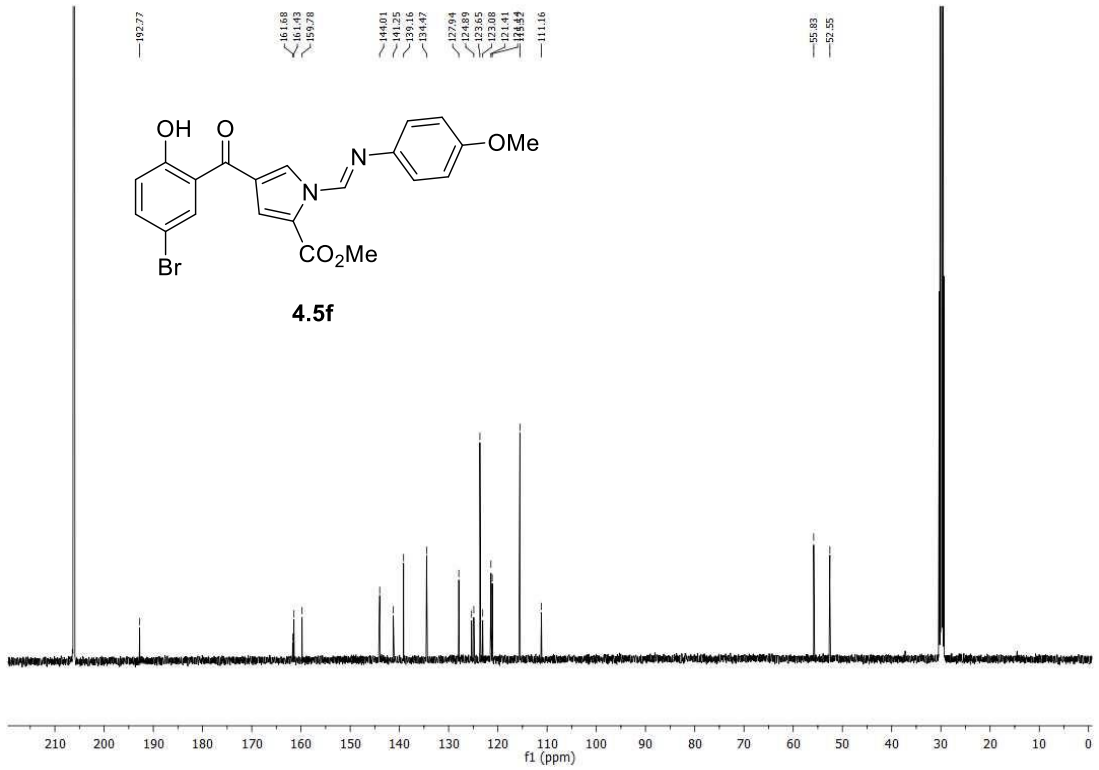
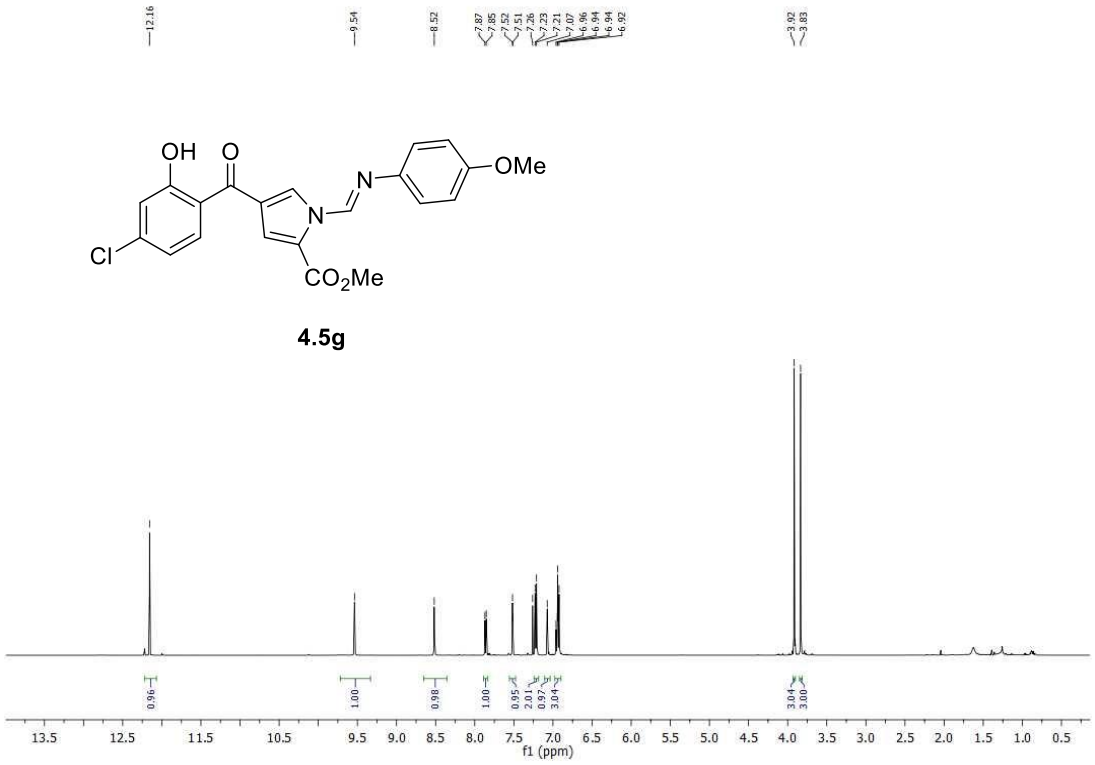




4.5f



4.5f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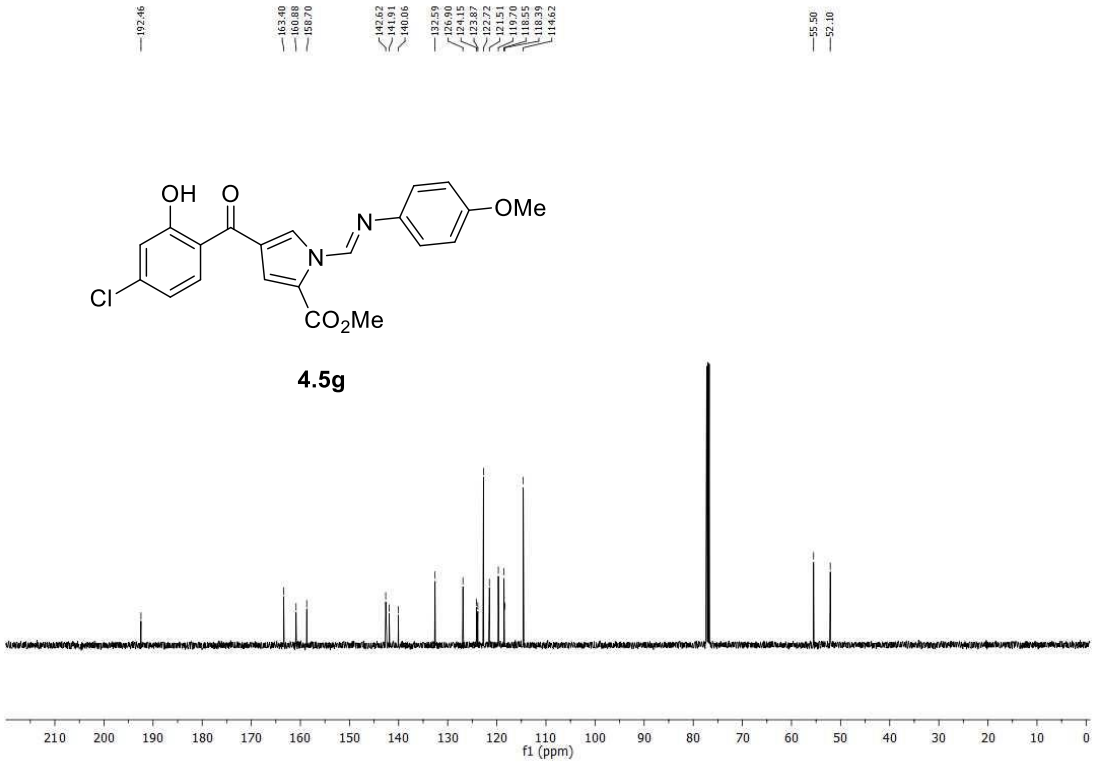
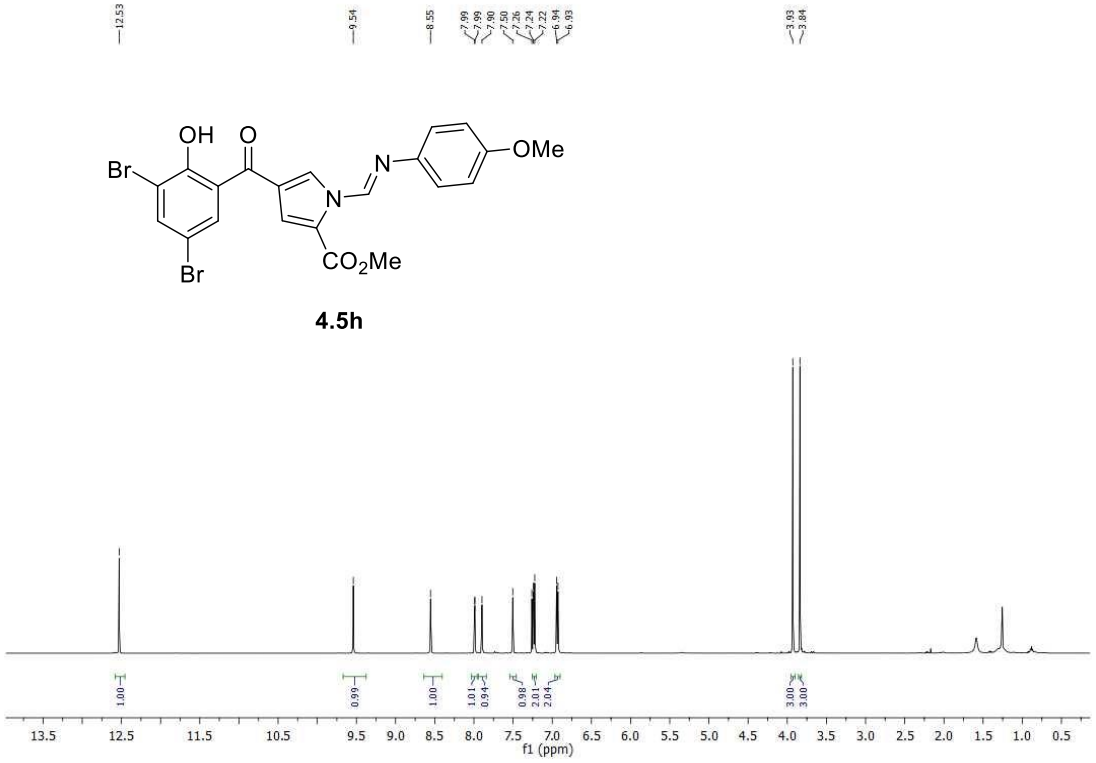
7.85
7.52
7.51
7.26
7.23
7.21
7.07
6.96
6.94
6.92
3.92
3.83
OH
O
N
OMe
N
Cl
CO2Me
0.96
1.00
0.98
1.00
0.95
2.01
0.97
3.04
3.04
3.00
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

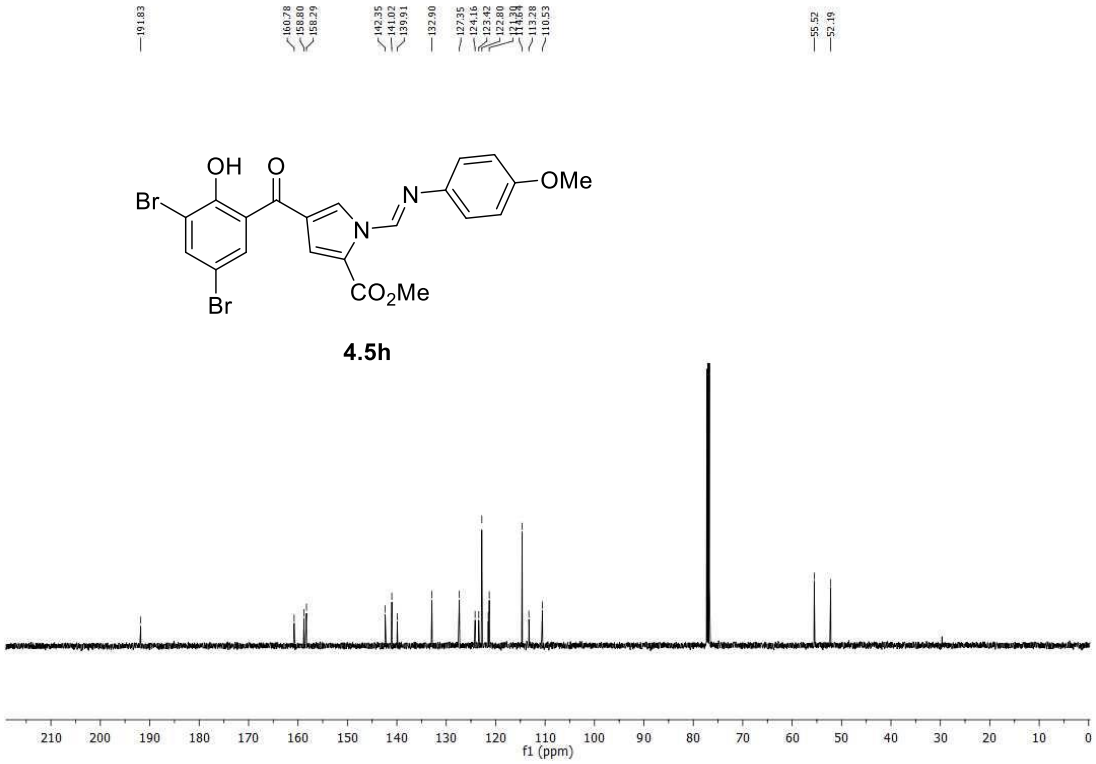
4.5g


192.46
163.40
160.88
158.70
142.62
141.91
140.06
132.59
126.90
124.15
123.87
122.72
121.51
119.70
118.55
118.39
114.62
55.50
52.10
OH
O
N
OMe
N
Cl
CO2Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

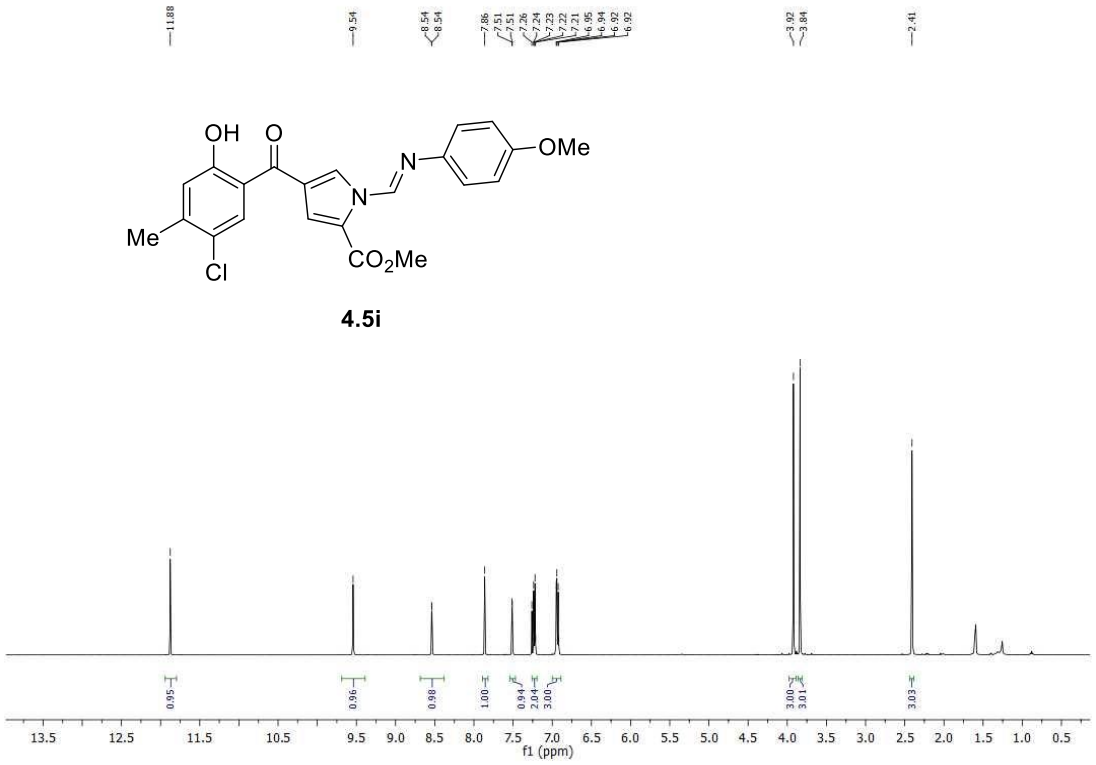
4.5g


12.53
9.54
8.55
7.99
7.99
7.90
7.50
7.26
7.24
7.22
6.94
6.93
3.93
3.84
OH
O
Br
N
OMe
N
CO2Me
Br
1.00
0.99
1.00
1.01
0.94
0.98
2.01
2.04
3.00
3.00
13.5
12.5
11.5
10.5
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)

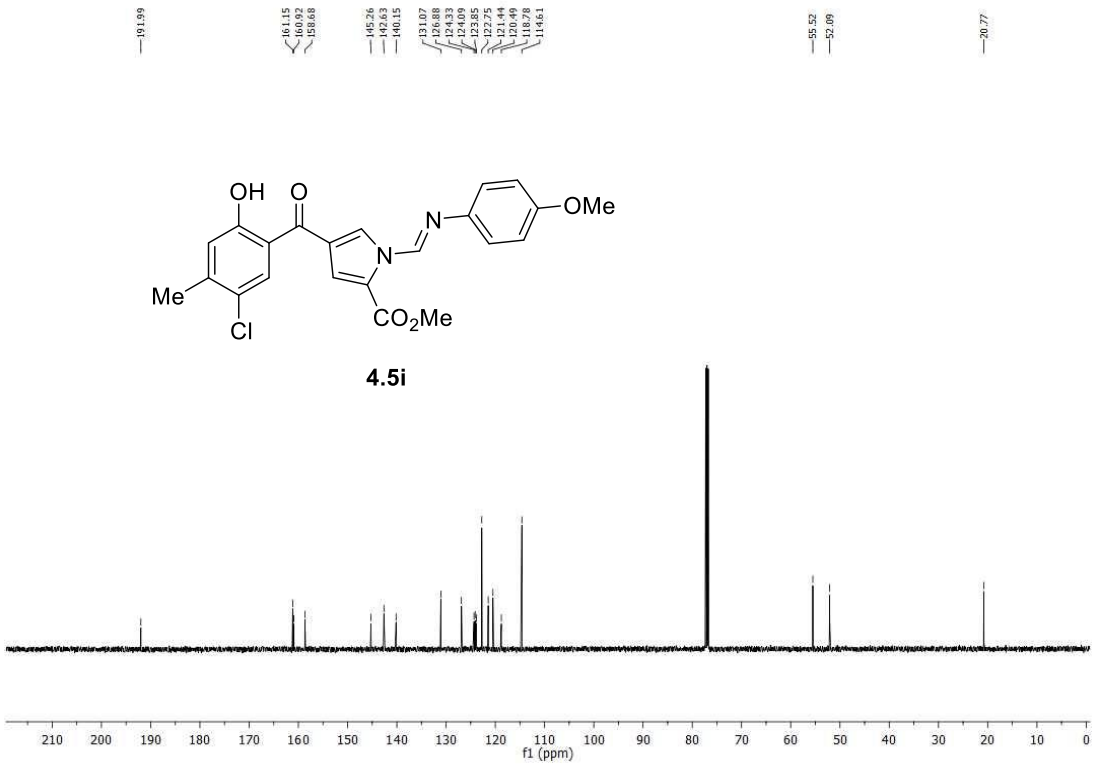
4.5h


191.83
160.78
158.80
158.29
142.35
141.02
139.91
132.90
127.35
124.16
123.42
122.80
113.28
110.53
55.52
52.19
OH
O
Br
N
OMe
N
CO2Me
Br
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

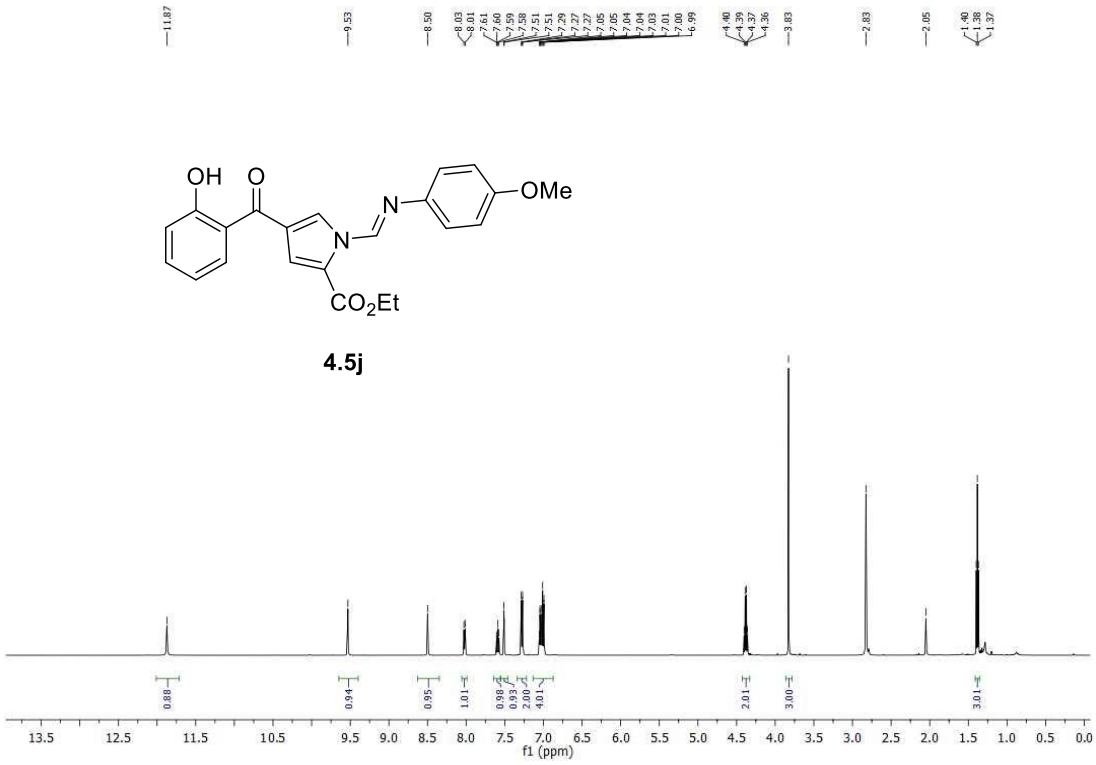
4.5h


11.88
9.54
8.54
8.54
7.86
7.51
7.51
7.26
7.24
7.23
7.22
7.21
6.95
6.94
6.92
6.92
3.92
3.84
2.41
OH
O
N
OMe
N
Me
Cl
CO2Me
0.95
0.96
0.98
1.00
0.94
2.04
3.00
3.00
3.01
3.03
13.5
12.5
11.5
10.5
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)

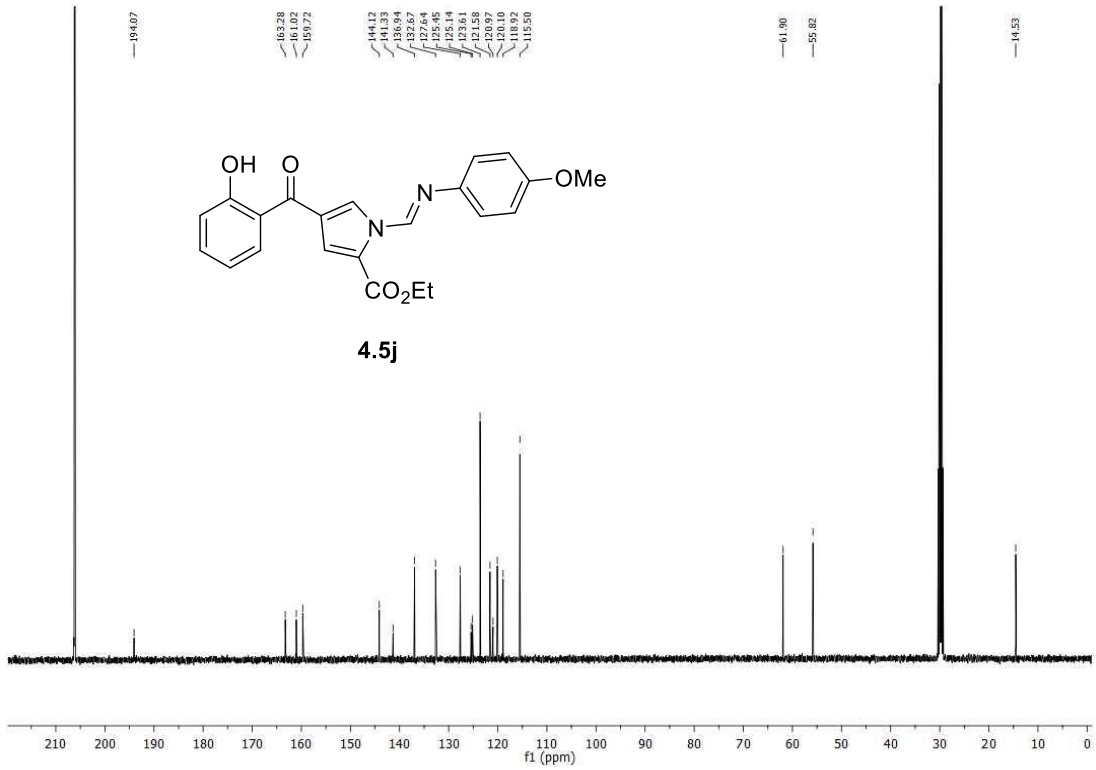
4.5i


191.99
161.15
160.92
158.68
145.26
142.63
140.15
131.07
126.88
124.33
124.09
123.85
122.75
121.44
120.49
118.78
114.61
55.52
52.09
20.77
OH
O
N
OMe
N
Me
Cl
CO2Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

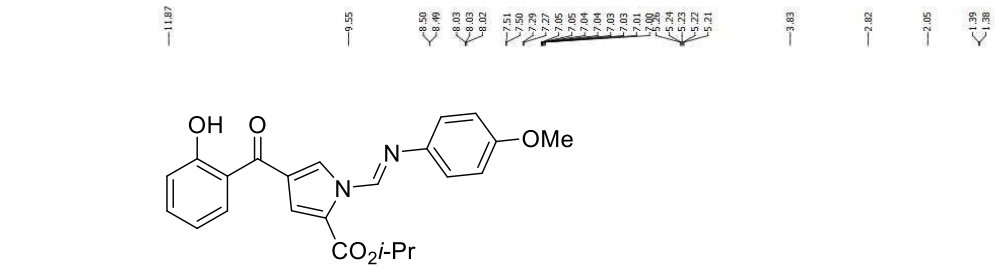
4.5i


OH
O
N
OMe
N
CO2Et
11.87
9.53
8.50
8.03
8.01
7.61
7.60
7.59
7.58
7.51
7.51
7.29
7.27
7.27
7.05
7.05
7.04
7.04
7.03
7.01
7.00
6.99
4.40
4.39
4.37
4.36
3.83
2.83
2.05
1.40
1.38
1.37
0.88
0.94
0.95
1.01
0.98
0.93
2.00
4.01
2.01
3.00
3.01
f1 (ppm)

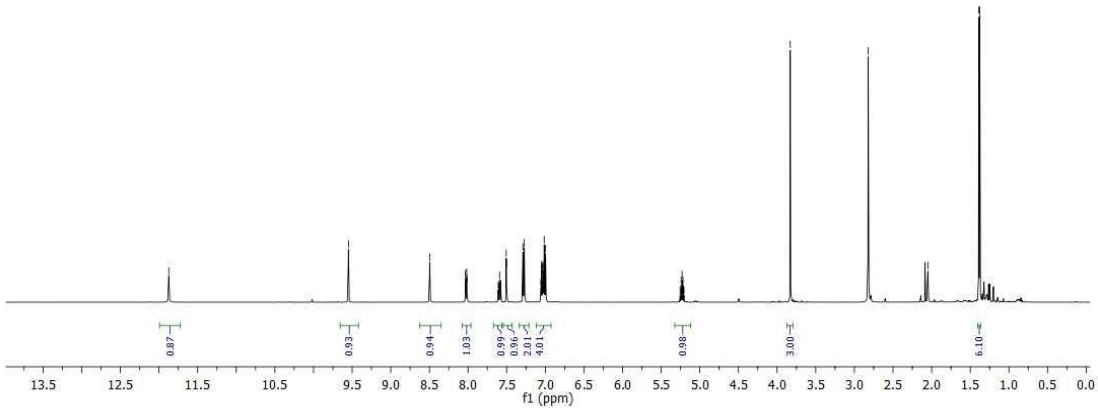
4.5j

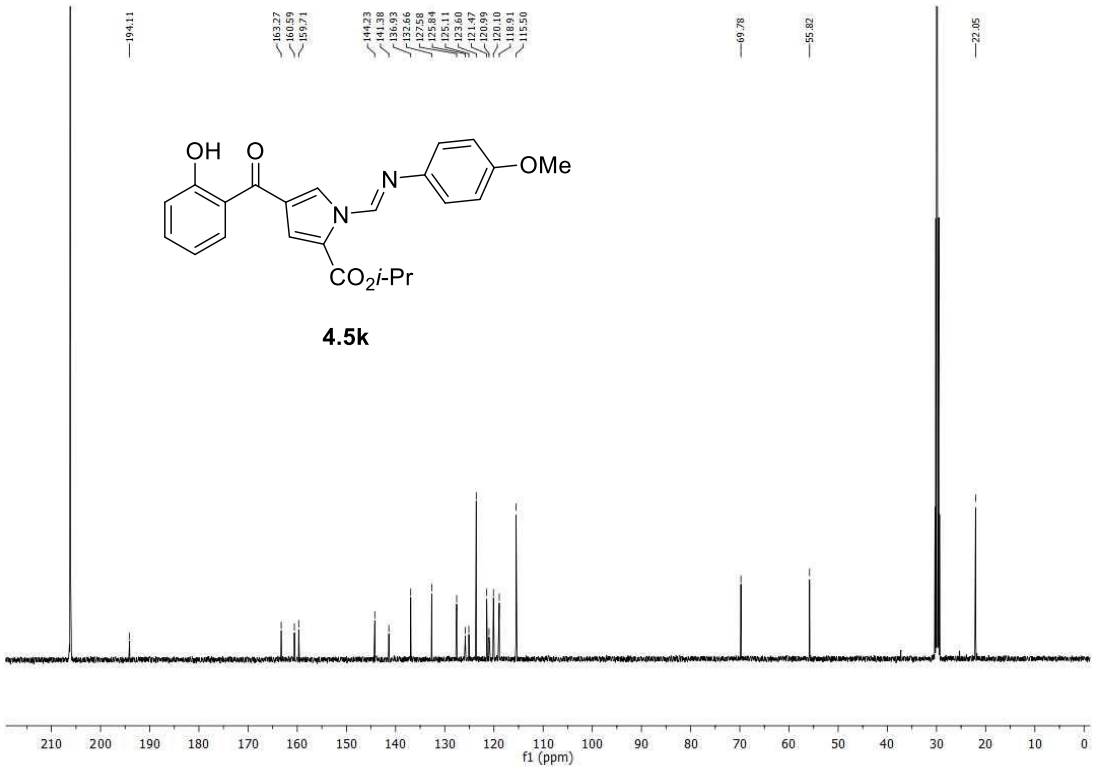

OH
O
N
OMe
N
CO2Et
194.07
163.28
161.02
159.72
144.12
141.33
136.94
132.67
127.64
125.45
125.14
123.61
121.58
120.97
120.10
118.92
115.50
61.90
55.82
14.53
f1 (ppm)

4.5j

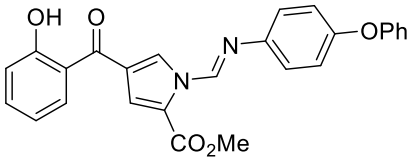


4.5k

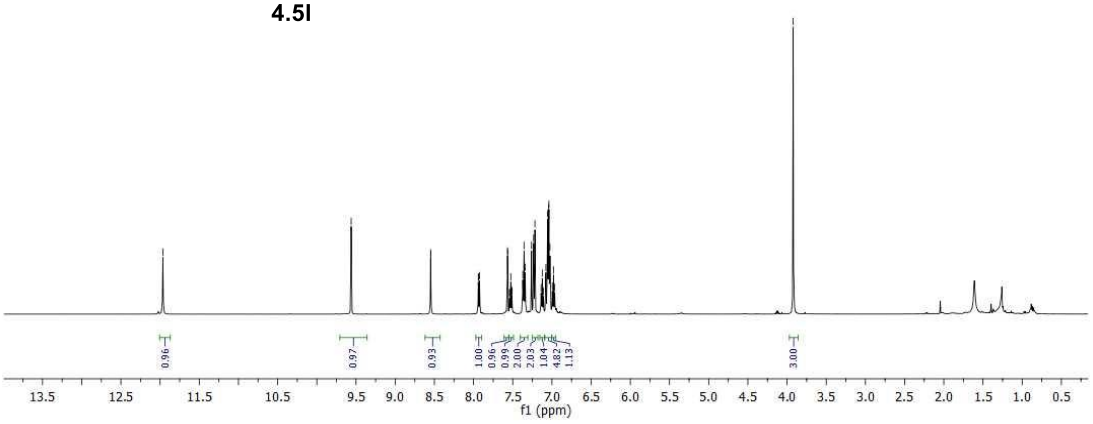


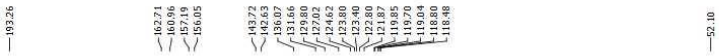


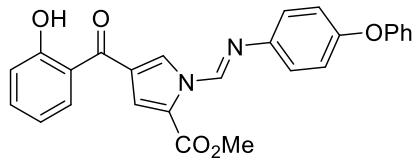
4.5k


OH
O
N
N
OPh
CO2Me

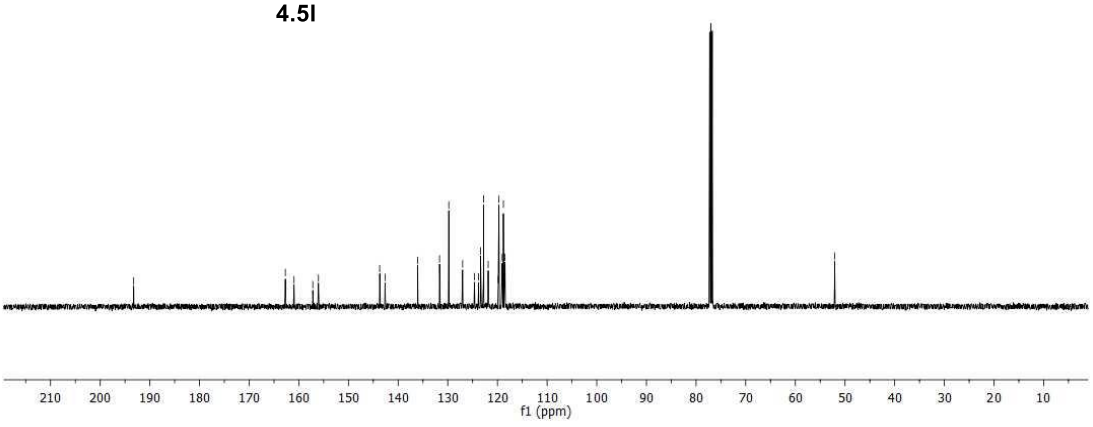
4.5l

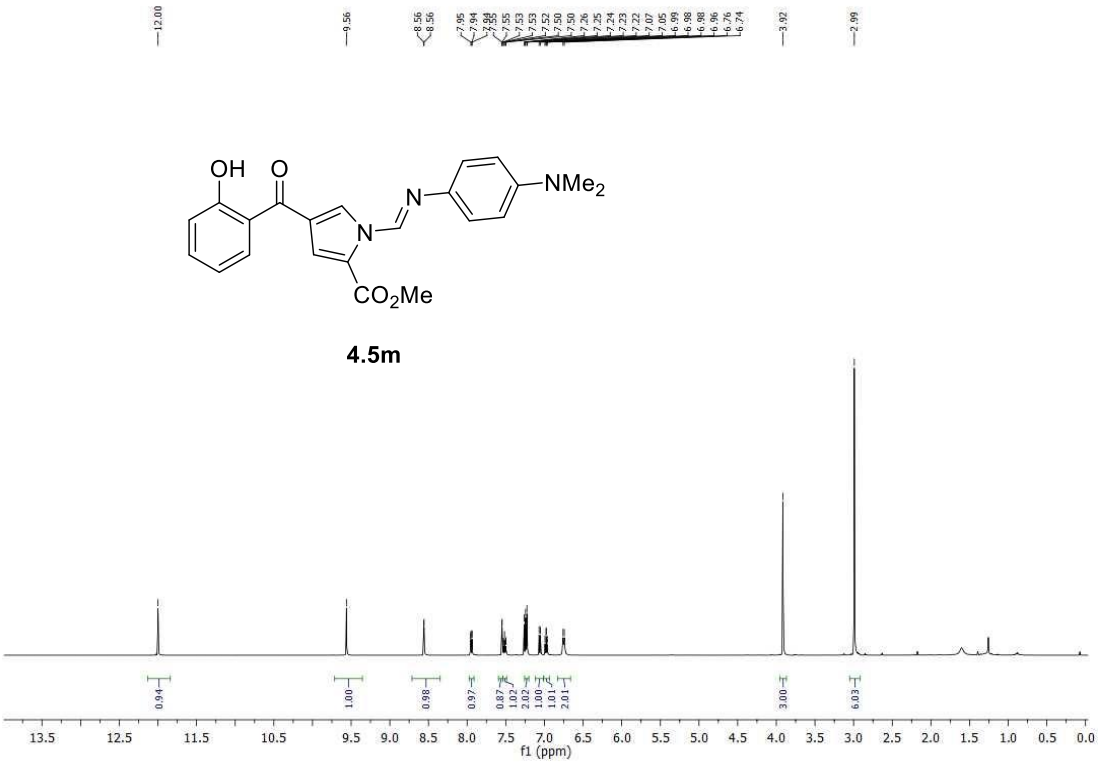

0.96
0.97
0.93
1.00
0.96
0.99
2.00
2.03
1.04
4.82
1.13
3.00
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



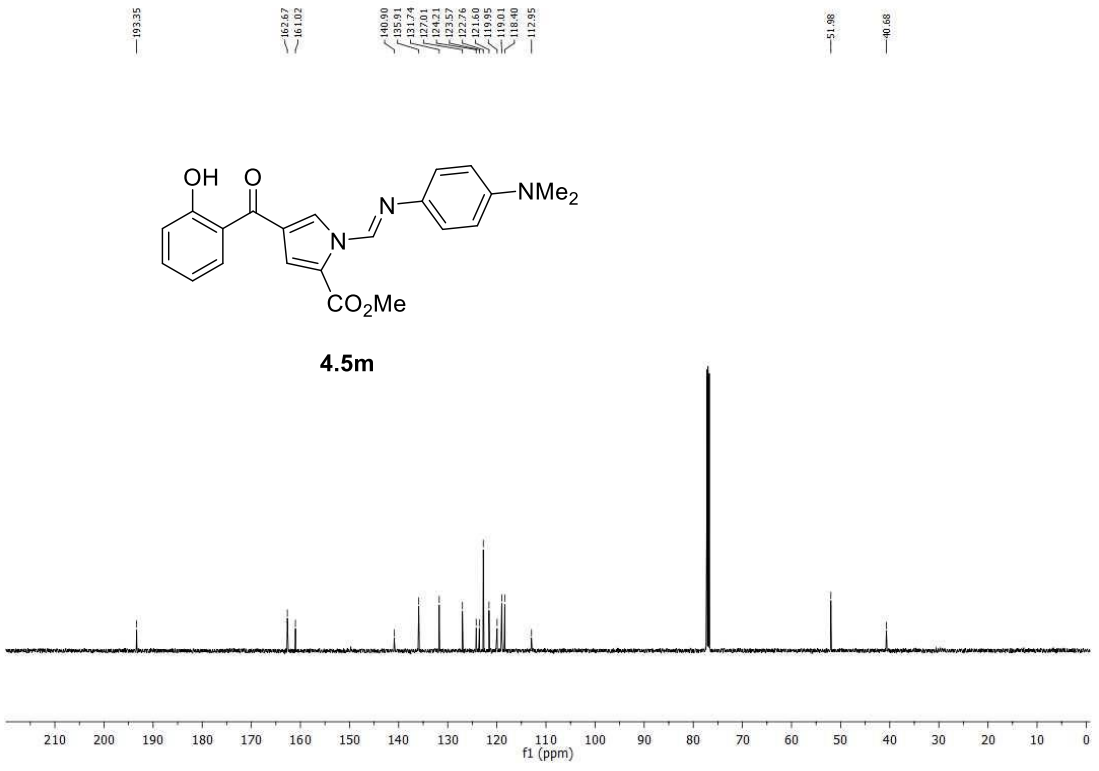

OH
O
N
N
OPh
CO2Me

4.5l

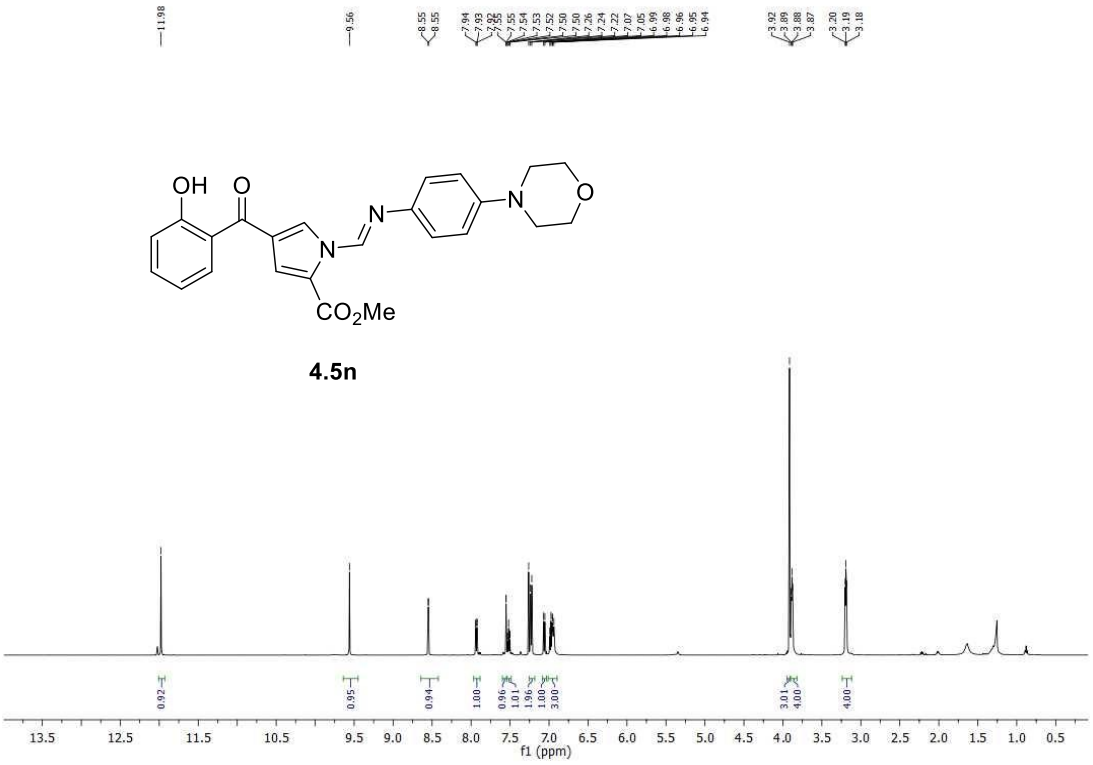

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


12.00
9.56
8.56
8.56
7.95
7.94
7.55
7.55
7.53
7.53
7.52
7.50
7.50
7.26
7.25
7.24
7.23
7.22
7.07
7.05
6.99
6.98
6.98
6.96
6.76
6.74
3.92
2.99
OH
O
N
N
NMe2
CO2Me
0.94
1.00
0.98
0.97
0.87
1.02
2.02
1.00
1.01
2.01
3.00
6.03
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

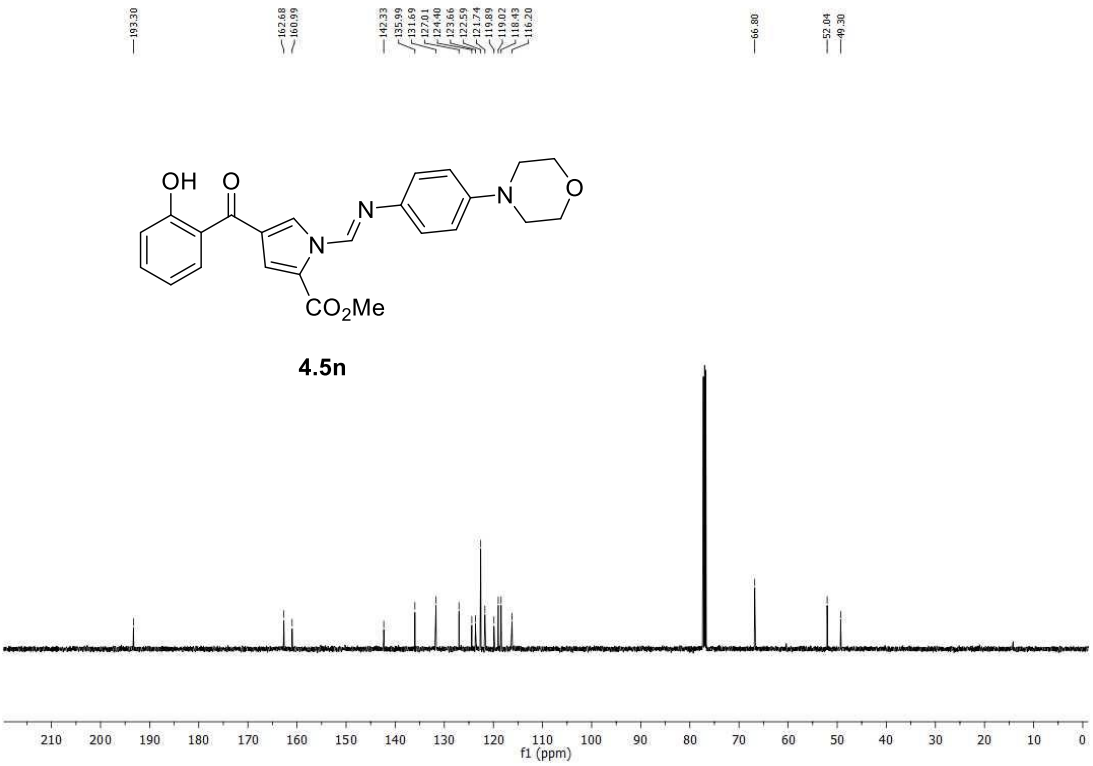
4.5m


193.35
162.67
161.02
140.90
135.91
131.74
127.01
124.21
123.57
122.76
121.60
119.95
119.01
118.40
112.95
51.98
40.68
OH
O
N
N
NMe2
CO2Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

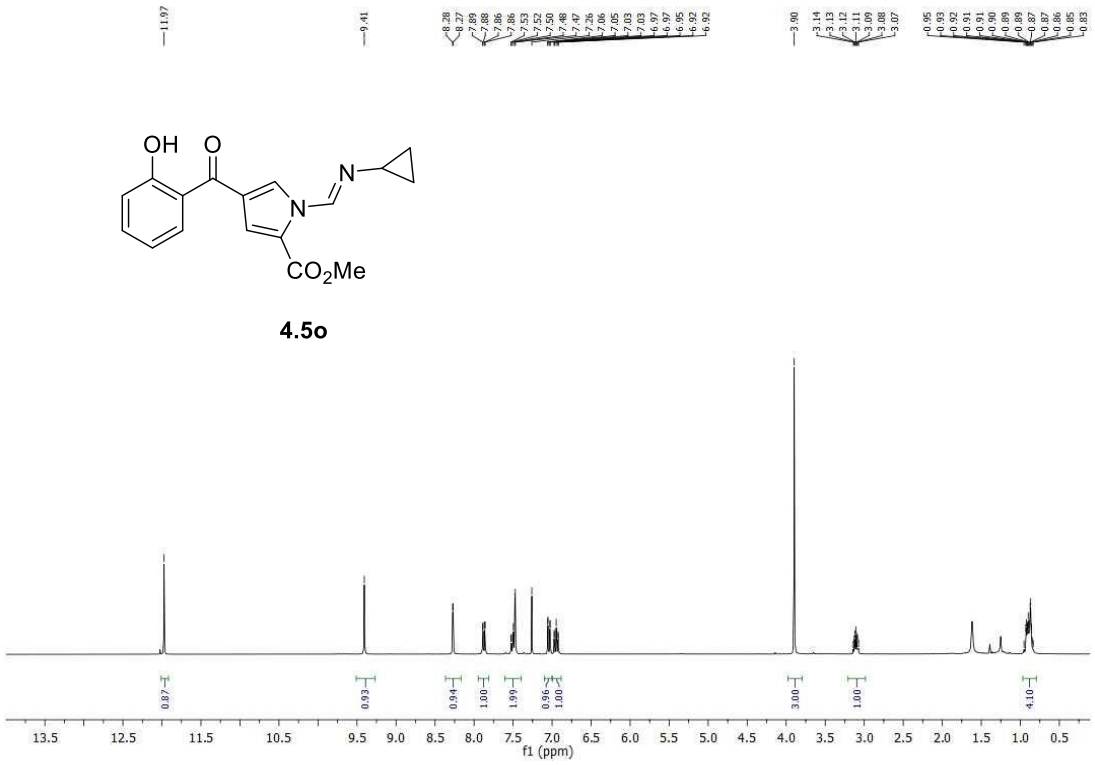
4.5m


11.98
9.56
8.55
8.55
7.94
7.93
7.92
7.55
7.55
7.54
7.53
7.52
7.50
7.50
7.26
7.24
7.22
7.07
7.05
6.99
6.98
6.96
6.95
6.94
3.92
3.89
3.88
3.87
3.20
3.19
3.18
OH
O
N
N
O
N
CO2Me
0.92
0.95
0.94
1.00
0.96
1.01
1.96
1.80
3.00
3.01
4.00
4.00
13.5
12.5
11.5
10.5
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)

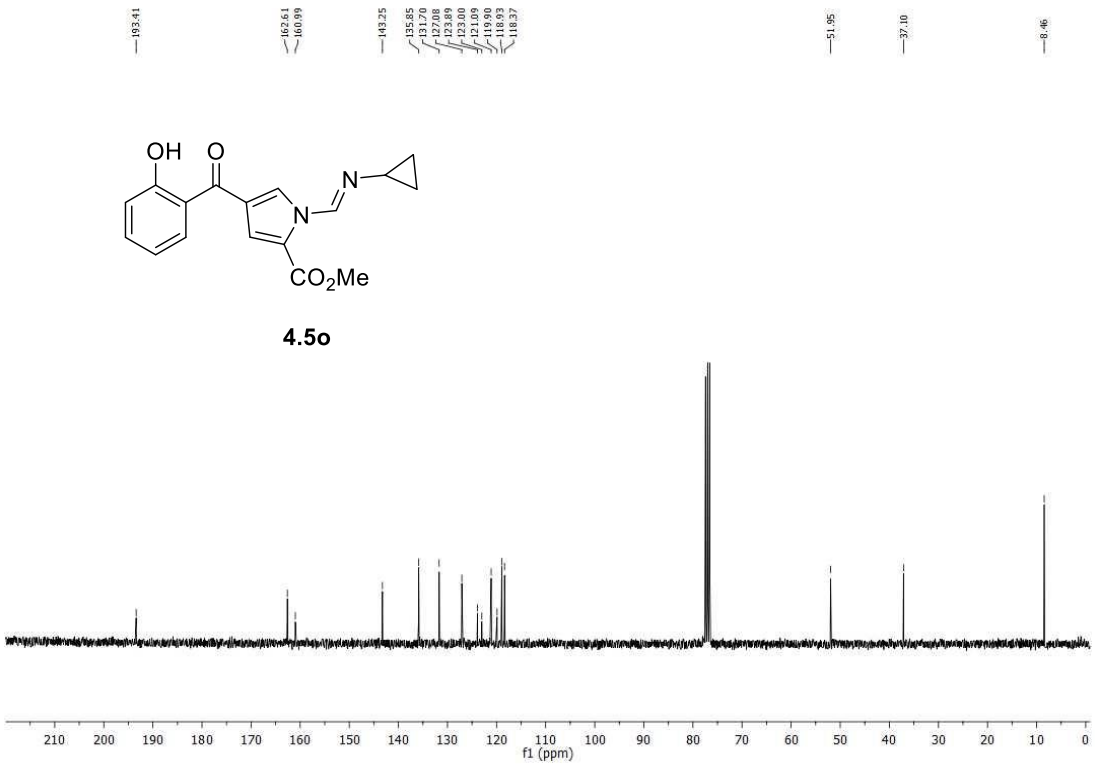
4.5n


193.30
162.68
160.99
142.33
135.99
131.69
127.01
124.40
123.66
122.59
121.74
119.89
119.02
118.43
116.20
66.80
52.04
49.30
OH
O
N
N
O
N
CO2Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

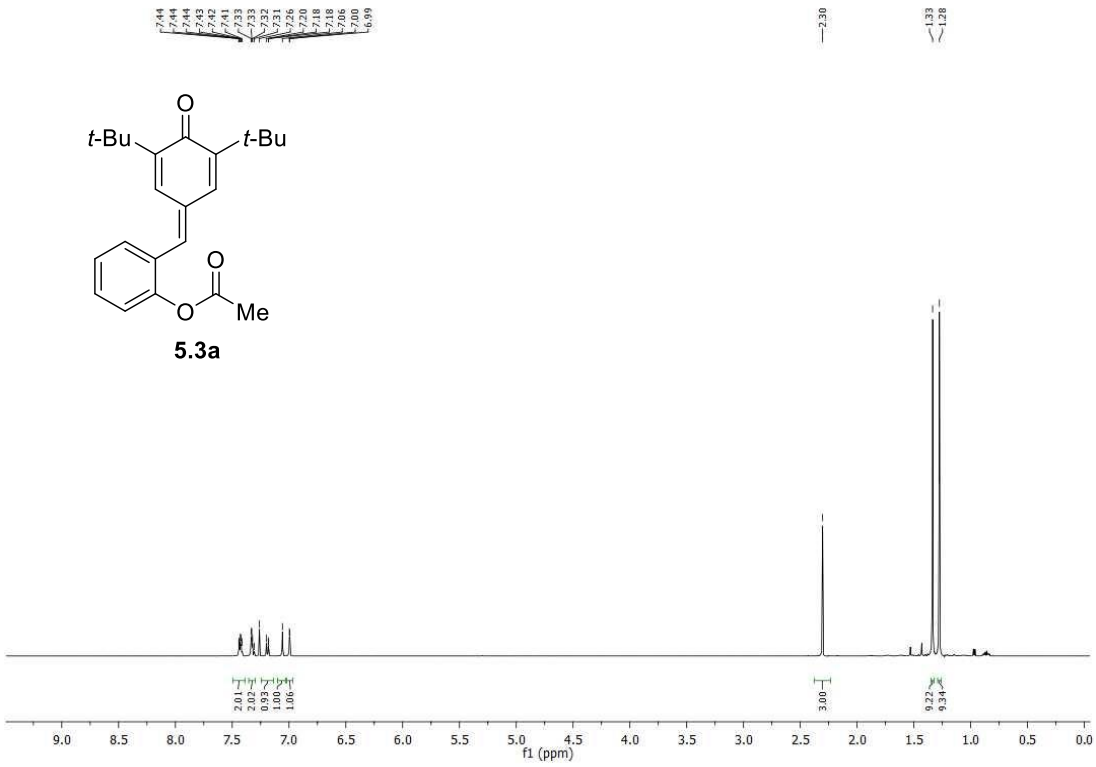
4.5n

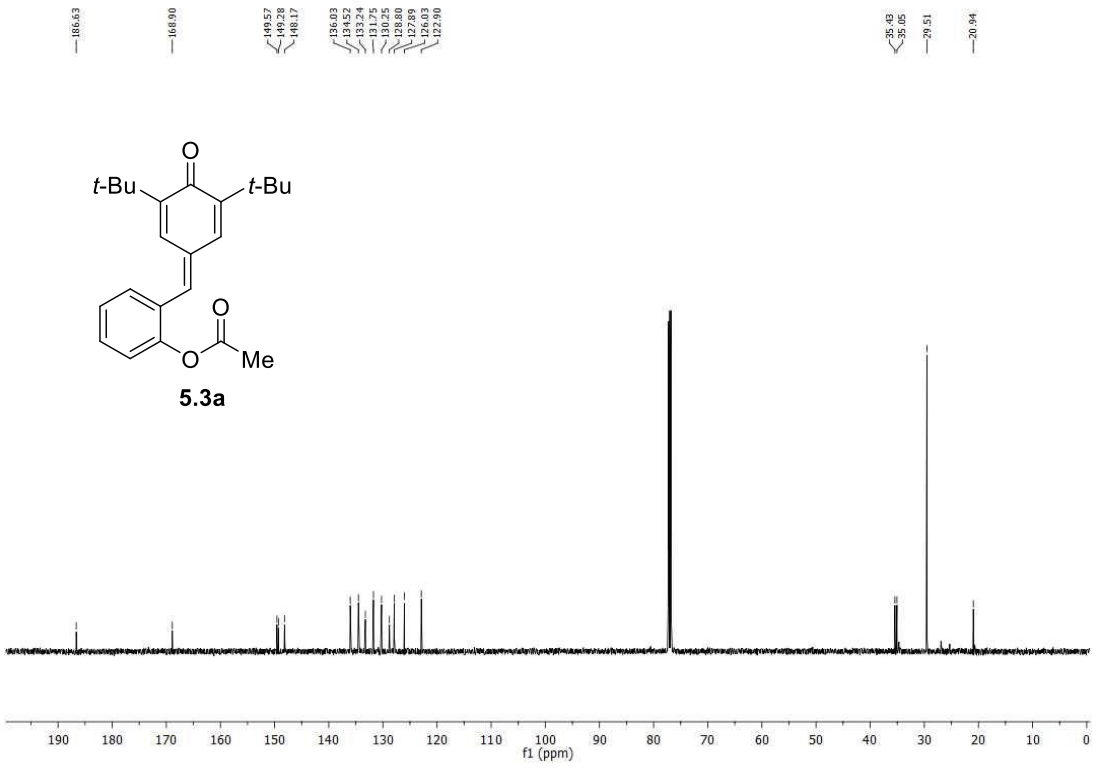

11.97
9.41
8.28
8.27
7.89
7.88
7.86
7.86
7.53
7.52
7.50
7.48
7.47
7.26
7.06
7.05
7.03
7.03
6.97
6.95
6.92
6.92
3.90
3.14
3.13
3.12
3.11
3.09
3.08
3.07
0.95
0.93
0.92
0.91
0.91
0.90
0.89
0.89
0.87
0.87
0.86
0.85
0.83
OH
O
N
N
CO2Me
0.87
0.93
0.94
1.00
1.99
0.96
1.00
3.00
1.00
4.10
13.5
12.5
11.5
10.5
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)

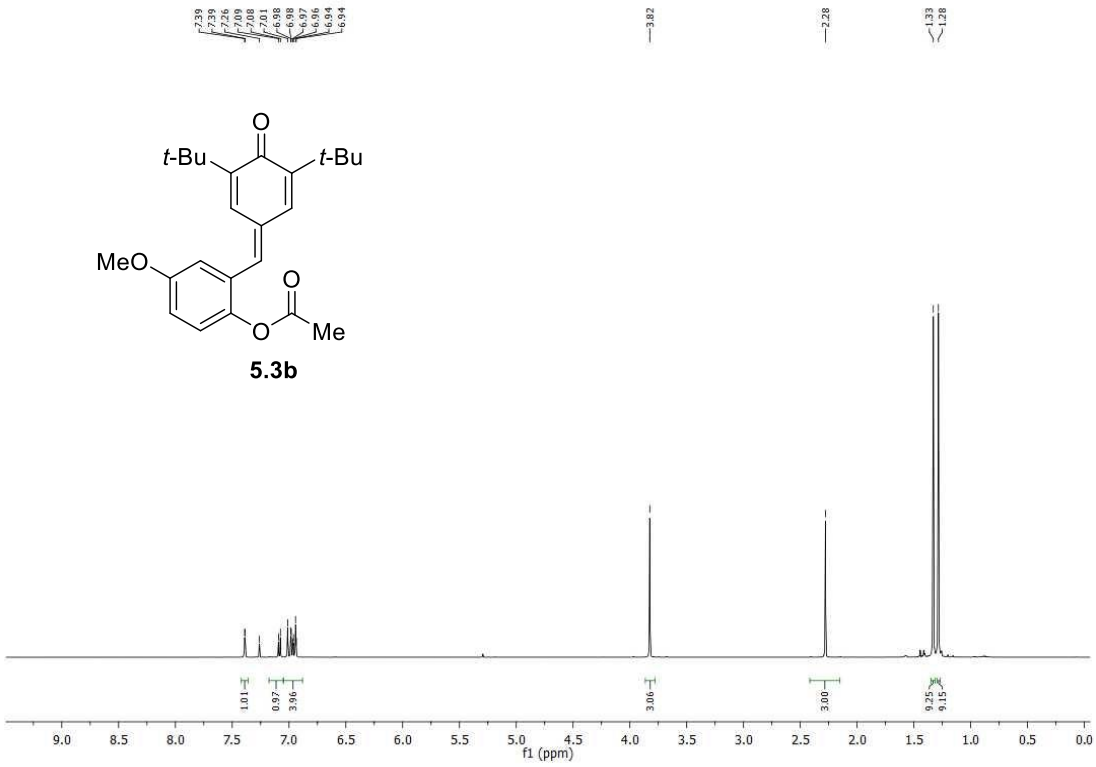
4.5o

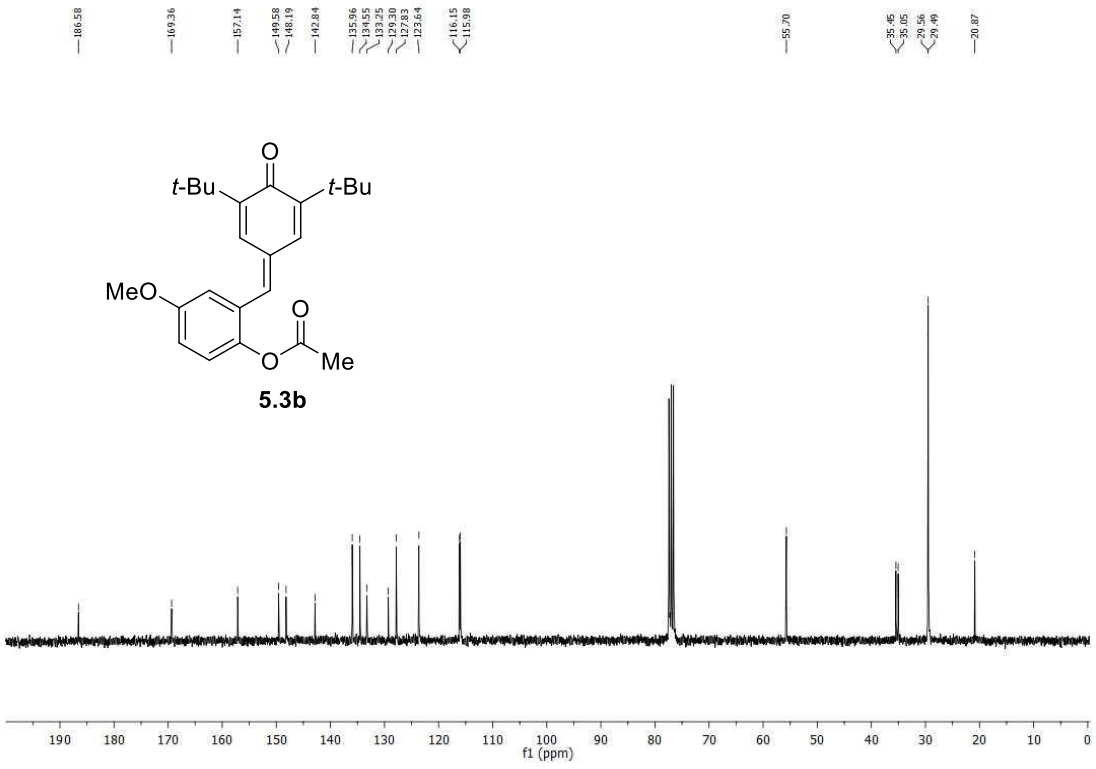

193.41
162.61
160.99
143.25
135.85
131.70
127.08
123.89
123.00
121.09
119.90
118.93
118.37
51.95
37.10
8.46
OH
O
N
N
CO2Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

4.5o


7.44
7.44
7.44
7.43
7.42
7.41
7.33
7.33
7.32
7.31
7.26
7.20
7.18
7.18
7.06
7.00
6.99
2.30
1.33
1.28
O
t-Bu
t-Bu
O
O
Me
5.3a
2.01
2.02
0.93
1.00
1.06
3.00
9.22
9.34
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


186.63
168.90
149.57
149.28
148.17
136.03
134.52
133.24
131.75
131.25
128.80
127.89
126.03
122.90
35.43
35.05
29.51
20.94
O
t-Bu
t-Bu
O
O
Me
5.3a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.39
7.39
7.26
7.09
7.08
7.01
6.98
6.98
6.97
6.96
6.94
6.94
3.82
2.28
1.33
1.28
O
t-Bu
t-Bu
MeO
O
O
Me
5.3b
1.01
0.97
3.96
3.06
3.00
9.25
9.15
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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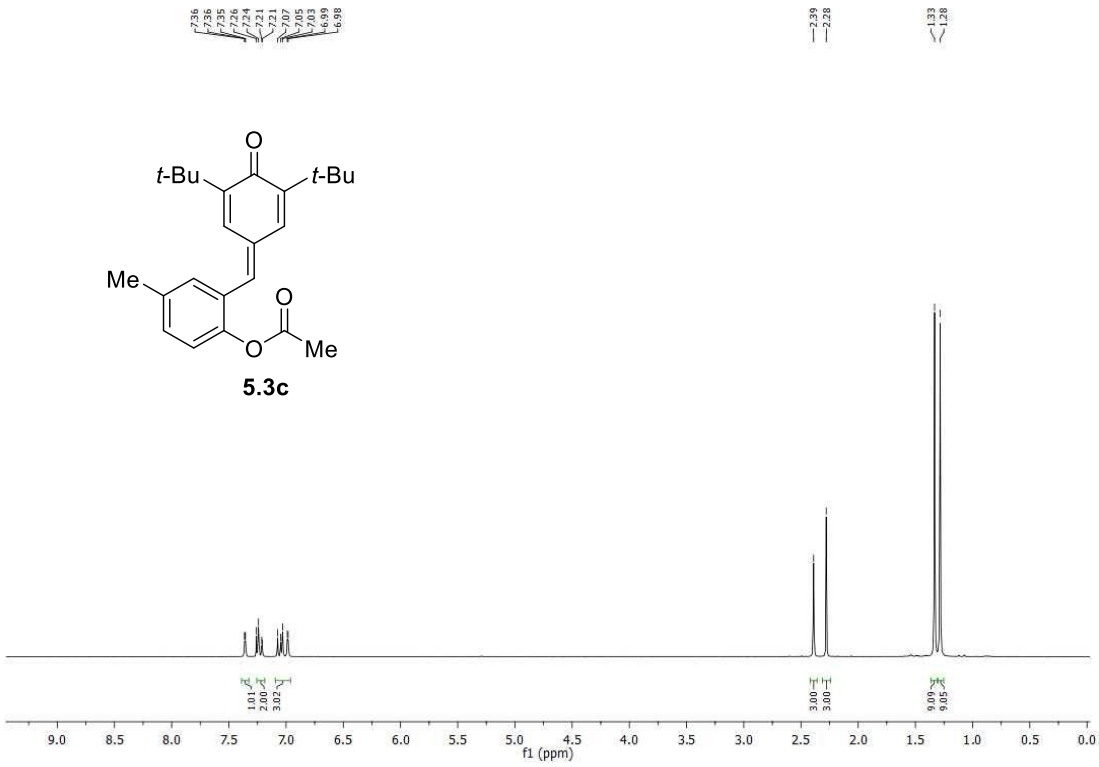
169.36
157.14
149.58
148.19
142.84
135.96
134.55
133.25
129.30
127.83
123.64
116.15
115.98
55.70
35.45
35.05
29.56
29.49
20.87
O
t-Bu
t-Bu
MeO
O
O
Me
5.3b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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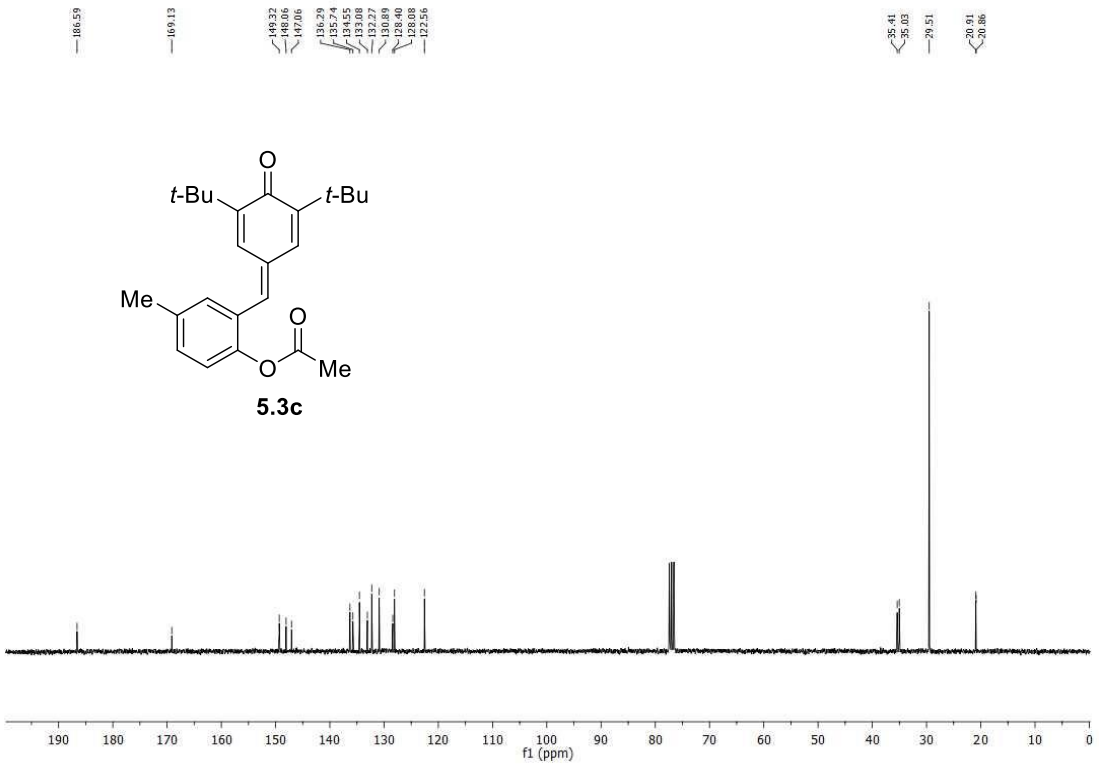
7.21
7.07
7.05
7.03
6.99
6.98
2.39
2.28
1.33
1.28
O
t-Bu
t-Bu
Me
O
O
Me
1.01
2.00
3.02
3.00
3.00
9.09
9.05
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

5.3c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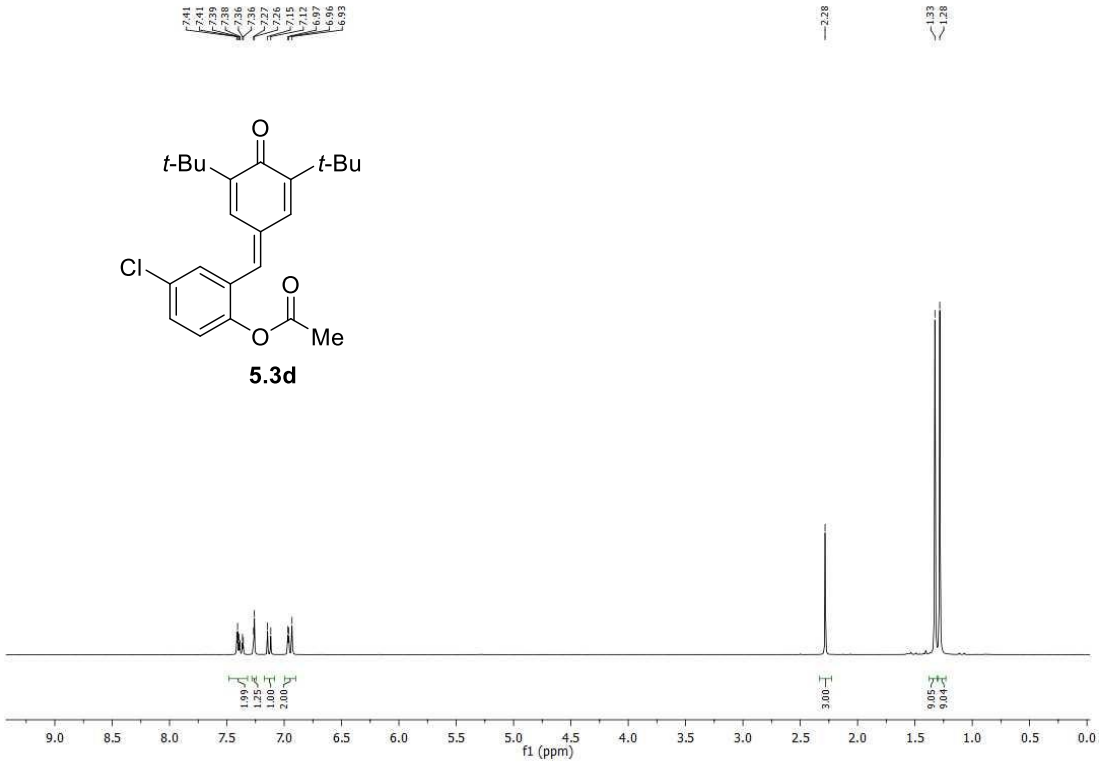
147.06
136.29
135.74
134.55
133.08
131.27
130.69
128.40
128.08
122.56
35.41
35.03
29.51
20.91
20.86
O
t-Bu
t-Bu
Me
O
O
Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

5.3c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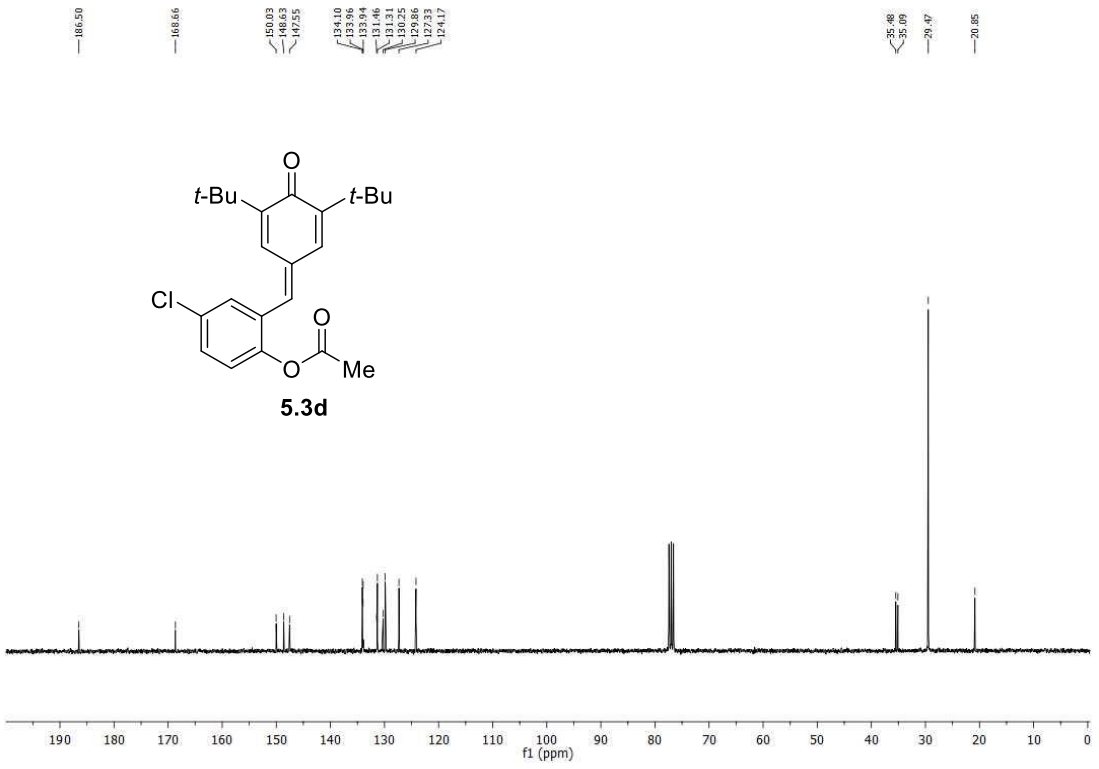
7.36
7.36
7.27
7.26
7.15
7.12
6.97
6.96
6.93
2.28
1.33
1.28
O
t-Bu
t-Bu
Cl
O
O
Me
1.99
1.25
1.00
2.00
3.00
9.05
9.04
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

5.3d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160.66
150.03
148.63
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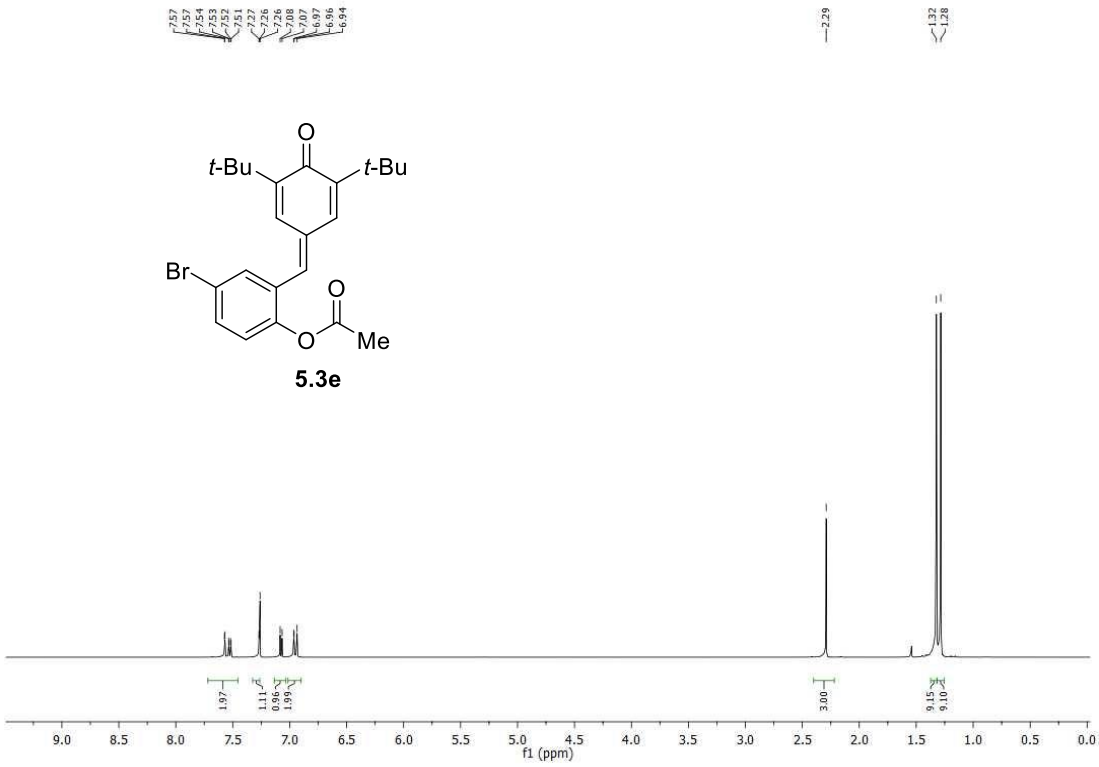
134.10
133.96
133.94
131.46
131.31
130.25
129.86
127.33
124.17
35.48
35.09
29.47
20.85
O
t-Bu
t-Bu
Cl
O
O
Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

5.3d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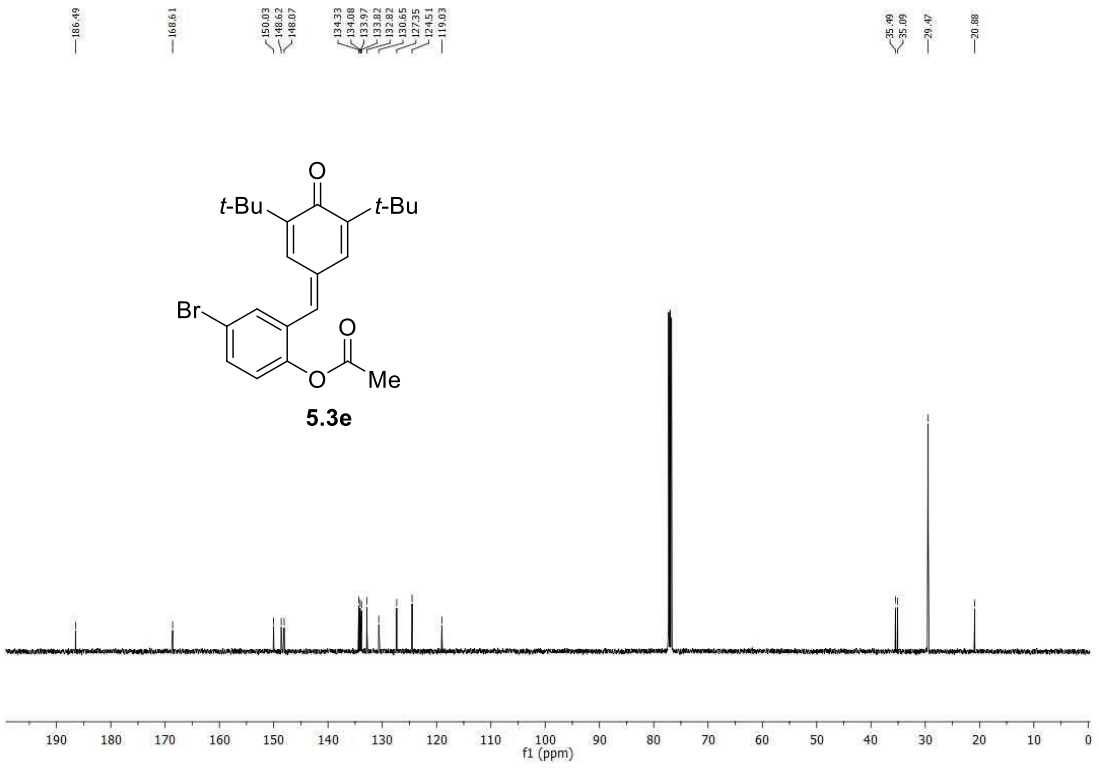
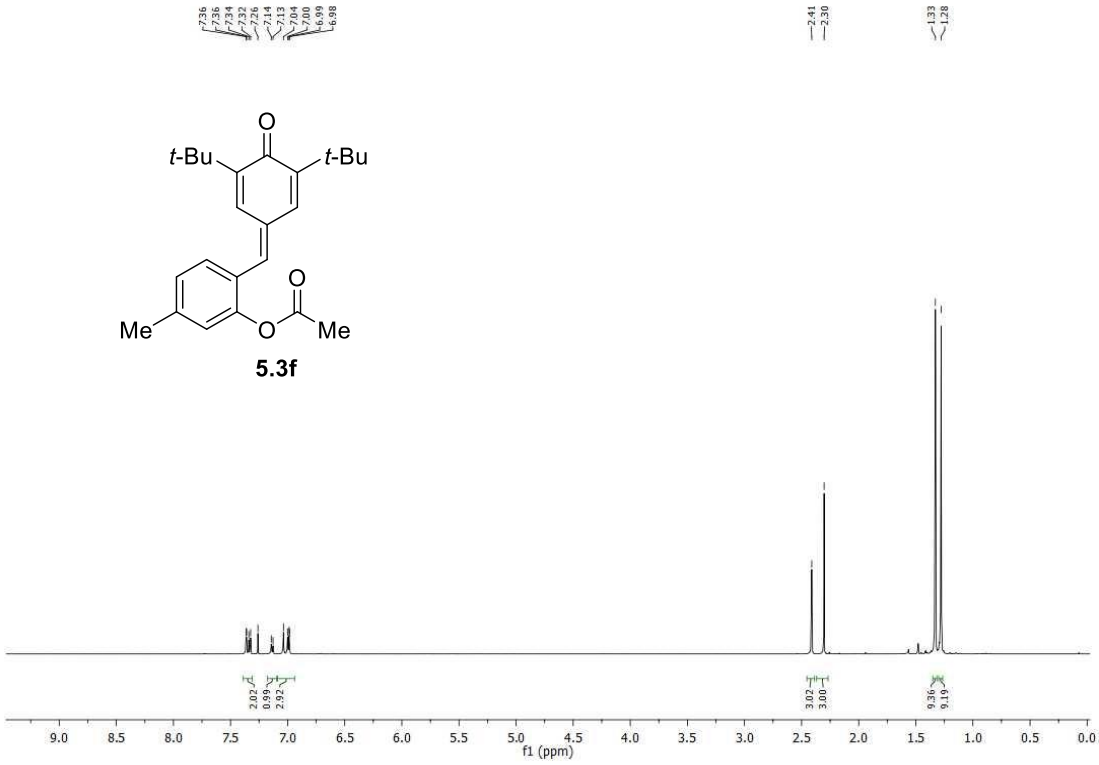
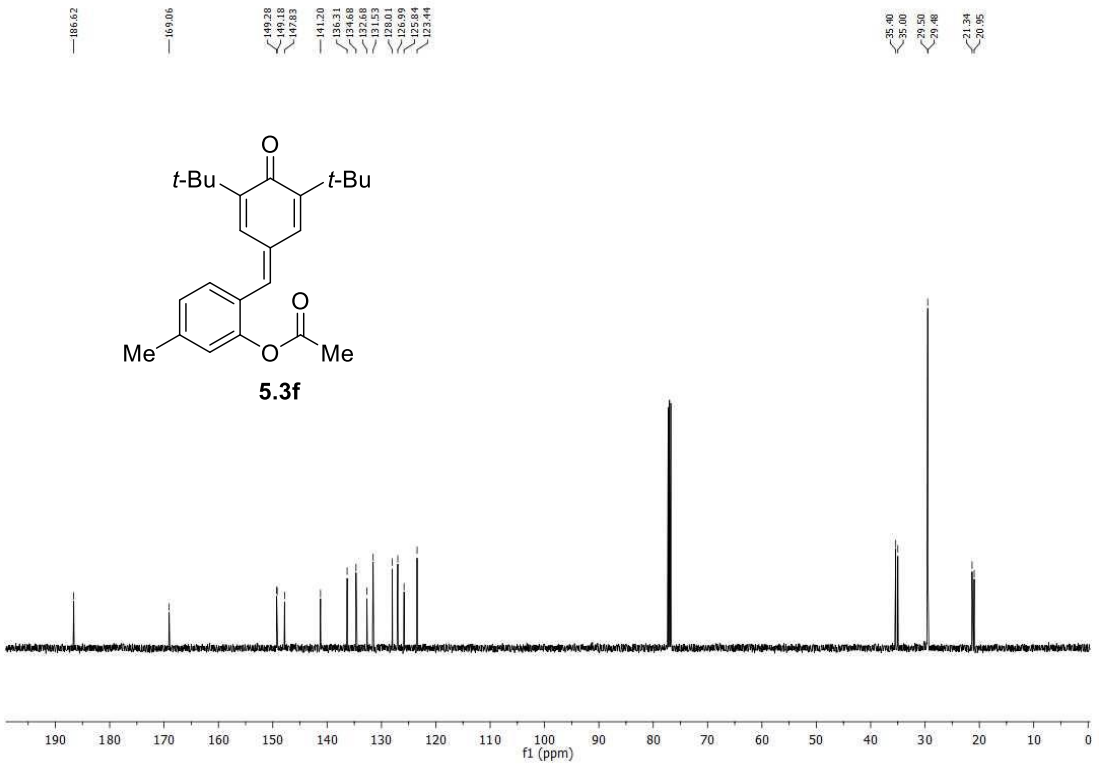
7.57
7.54
7.53
7.52
7.51
7.27
7.26
7.26
7.08
7.07
6.97
6.96
6.94
2.29
1.32
1.28
O
t-Bu
t-Bu
Br
O
O
Me
5.3e
1.97
1.11
0.96
1.99
3.00
9.15
9.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


186.49
168.61
150.03
148.62
148.07
134.33
134.08
133.97
133.82
132.82
130.65
127.35
124.51
119.03
35.49
35.09
29.47
20.88
O
t-Bu
t-Bu
Br
O
O
Me
5.3e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.36
7.36
7.34
7.32
7.26
7.14
7.13
7.04
7.00
6.99
6.98
2.41
2.30
1.33
1.28
O
t-Bu
t-Bu
O
Me
O
Me
5.3f
2.02
0.99
2.92
3.02
3.00
9.36
9.19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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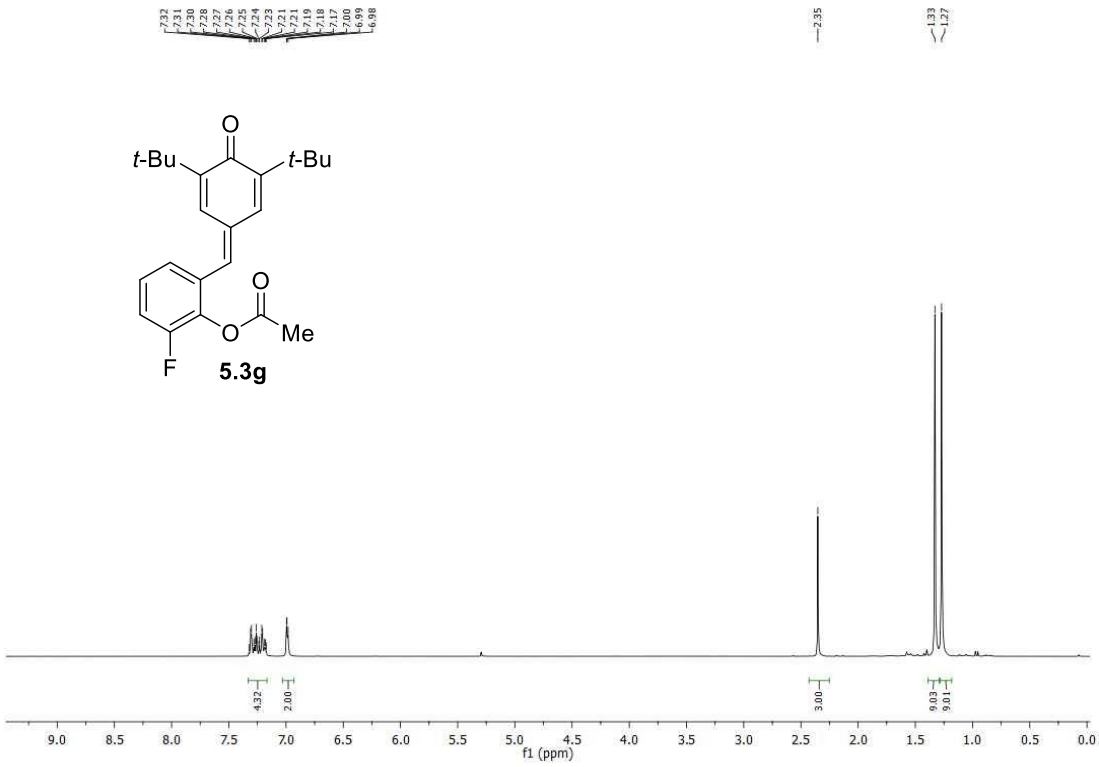
169.06
149.28
149.18
147.83
141.20
136.31
134.68
132.68
131.53
128.01
126.99
125.84
123.44
35.40
35.00
29.50
29.48
21.34
20.95
O
t-Bu
t-Bu
O
Me
O
Me
5.3f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.32
7.31
7.30
7.28
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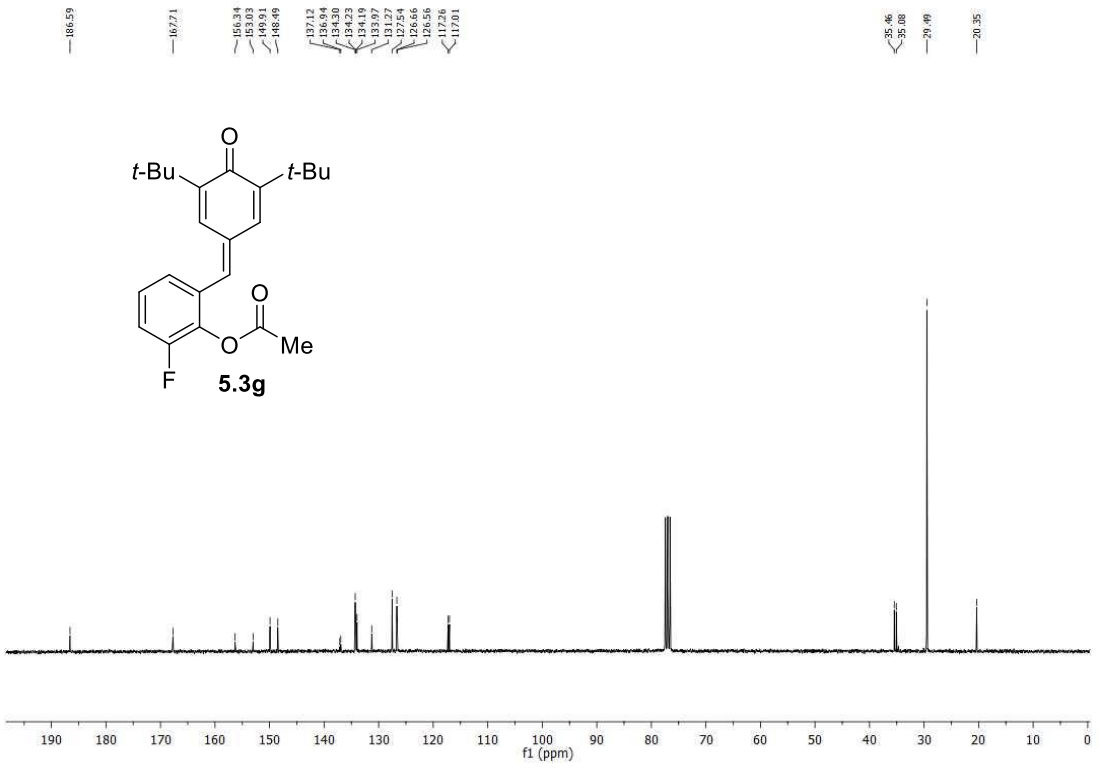
7.26
7.25
7.24
7.23
7.21
7.21
7.19
7.18
7.17
7.00
6.99
6.98
2.35
1.33
1.27
O
t-Bu
t-Bu
O
O
Me
F
5.3g
4.32
2.00
3.00
9.03
9.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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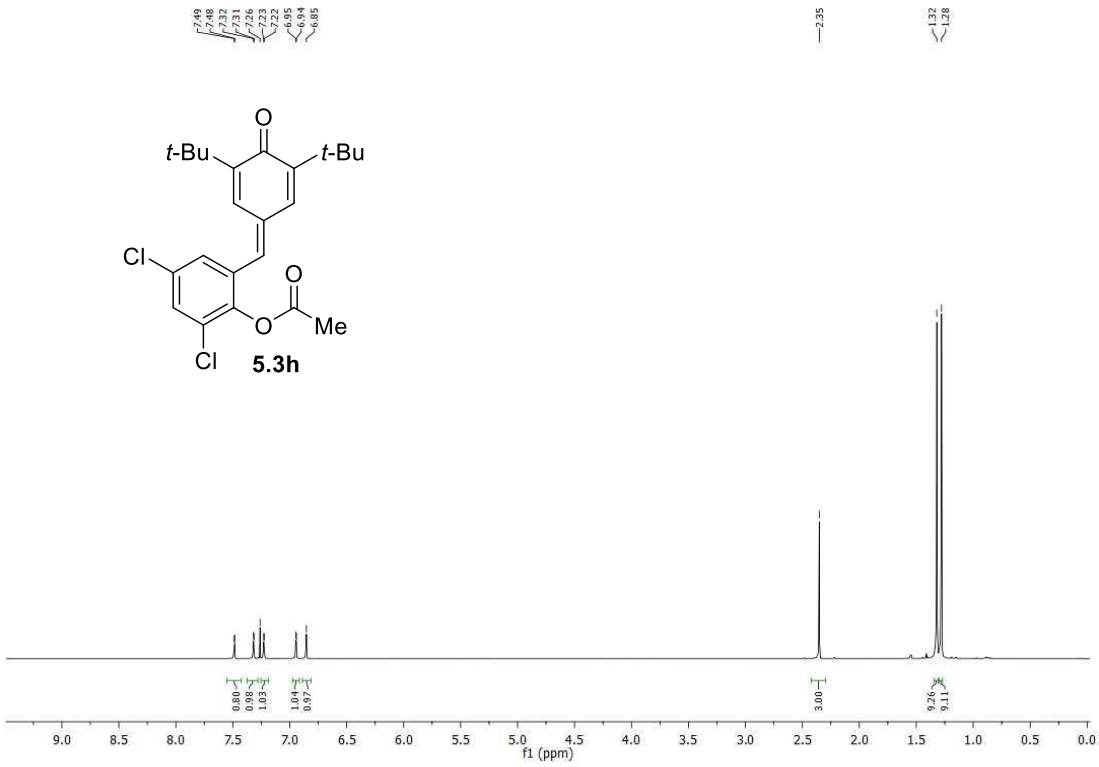
167.71
156.34
153.03
149.91
148.49
137.12
136.94
134.30
134.23
134.19
133.97
131.27
127.54
126.66
126.56
117.26
117.01
35.46
35.08
29.49
20.35
O
t-Bu
t-Bu
O
O
Me
F
5.3g
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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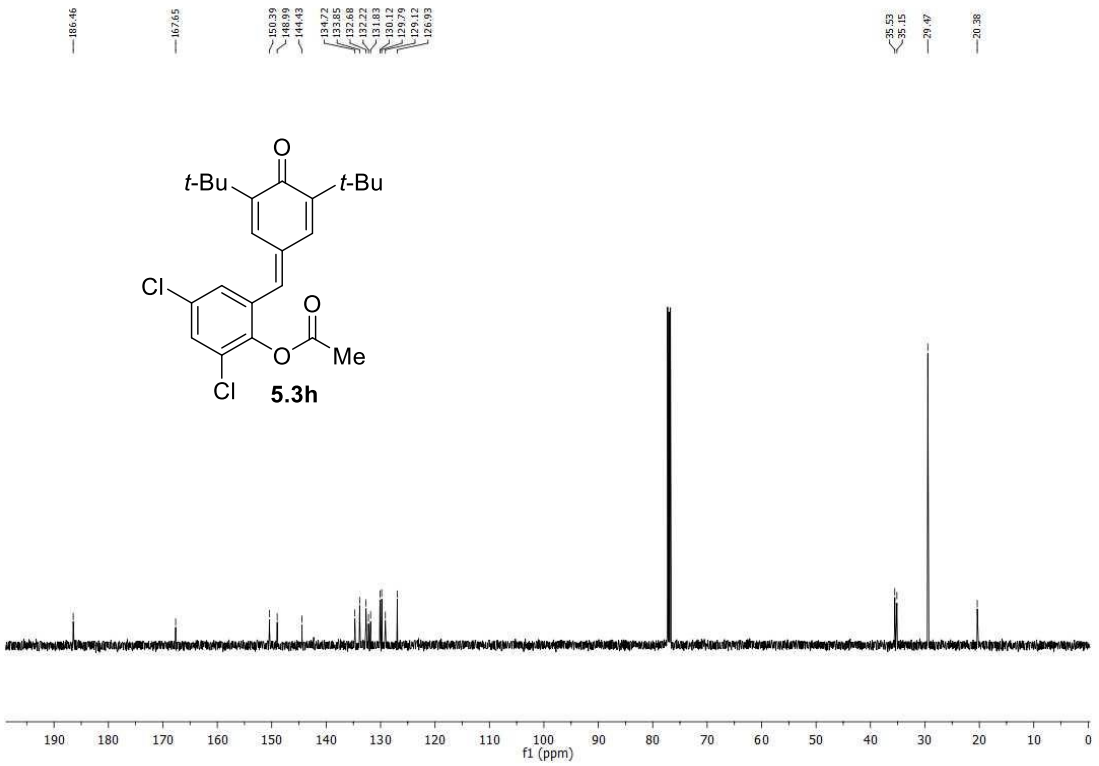
7.48
7.32
7.31
7.26
7.23
7.22
6.95
6.94
6.85
2.35
1.32
1.28
O
t-Bu
t-Bu
Cl
O
O
Me
Cl
5.3h
0.80
0.98
1.03
1.04
0.97
3.00
9.26
9.11
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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150.39
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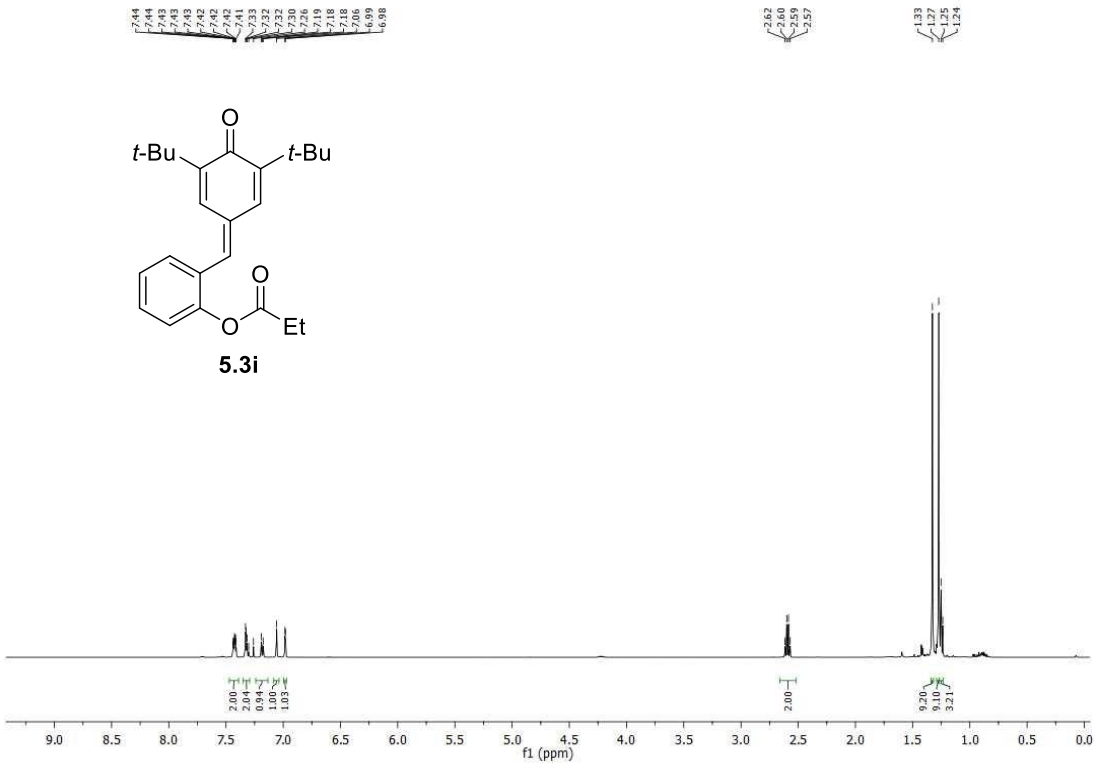
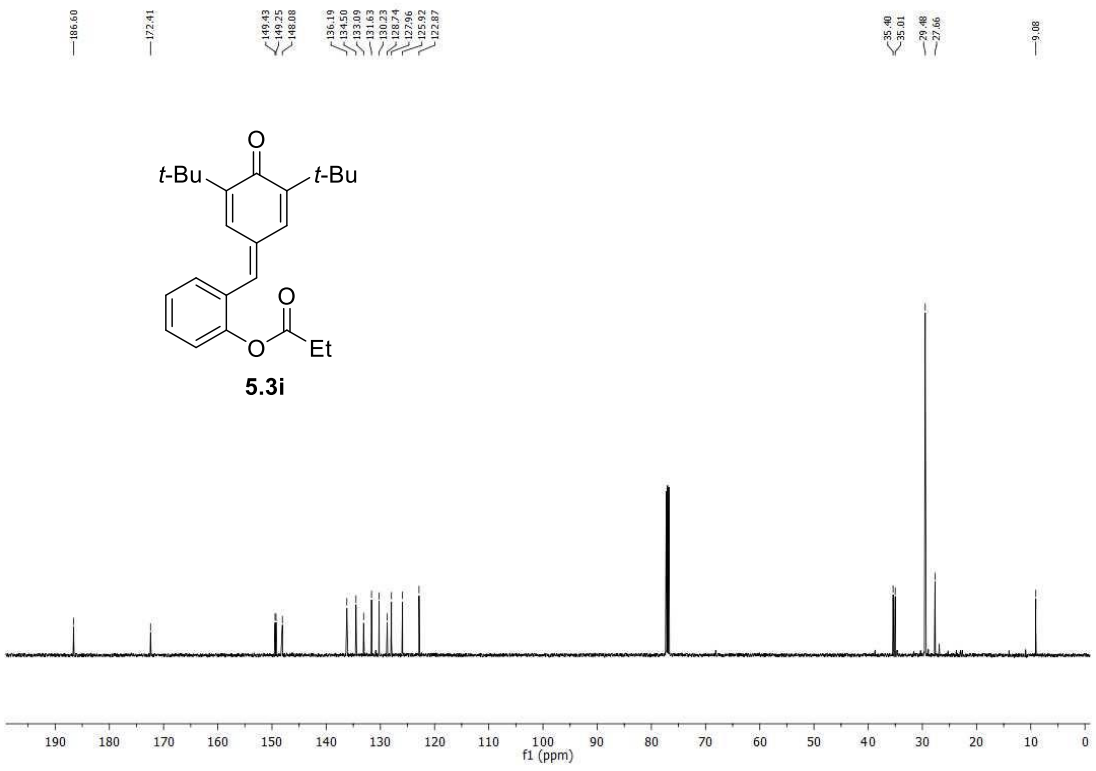
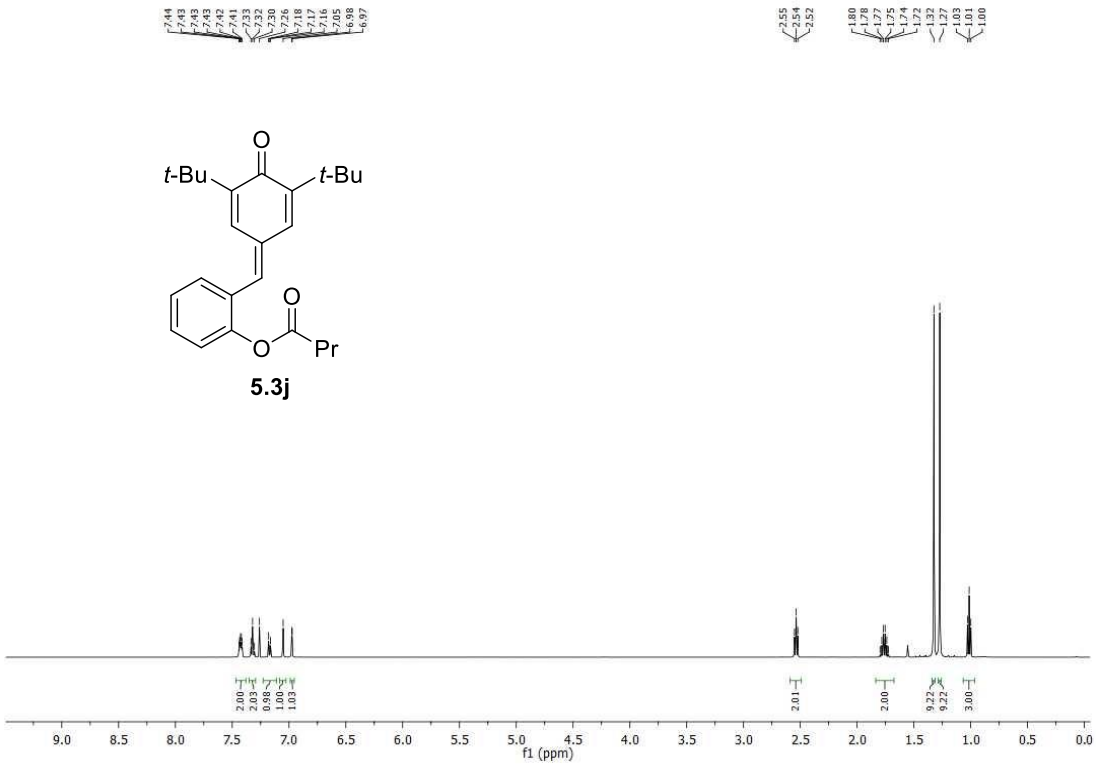
144.43
134.72
133.85
132.68
132.22
131.83
130.12
129.79
129.12
126.93
35.53
35.15
29.47
20.38
O
t-Bu
t-Bu
Cl
O
O
Me
Cl
5.3h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


t-Bu
t-Bu
O
O
O
Et
5.3i
f1 (ppm)


t-Bu
t-Bu
O
O
O
Et
5.3i
f1 (ppm)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7.18
7.17
7.16
7.05
6.98
6.97
2.55
2.54
2.52
1.80
1.78
1.77
1.75
1.74
1.72
1.32
1.27
1.03
1.01
1.00
O
t-Bu
t-Bu
O
O
Pr
2.00
2.03
0.98
1.00
1.03
2.01
2.00
9.22
9.22
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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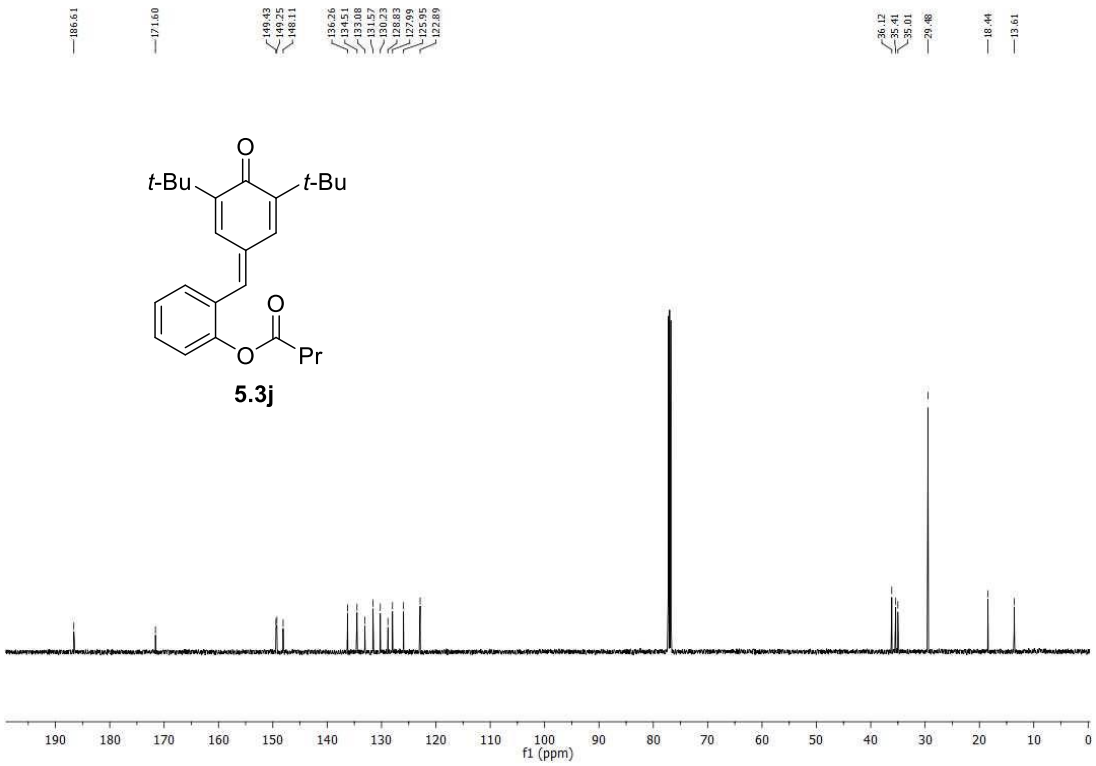
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

5.3j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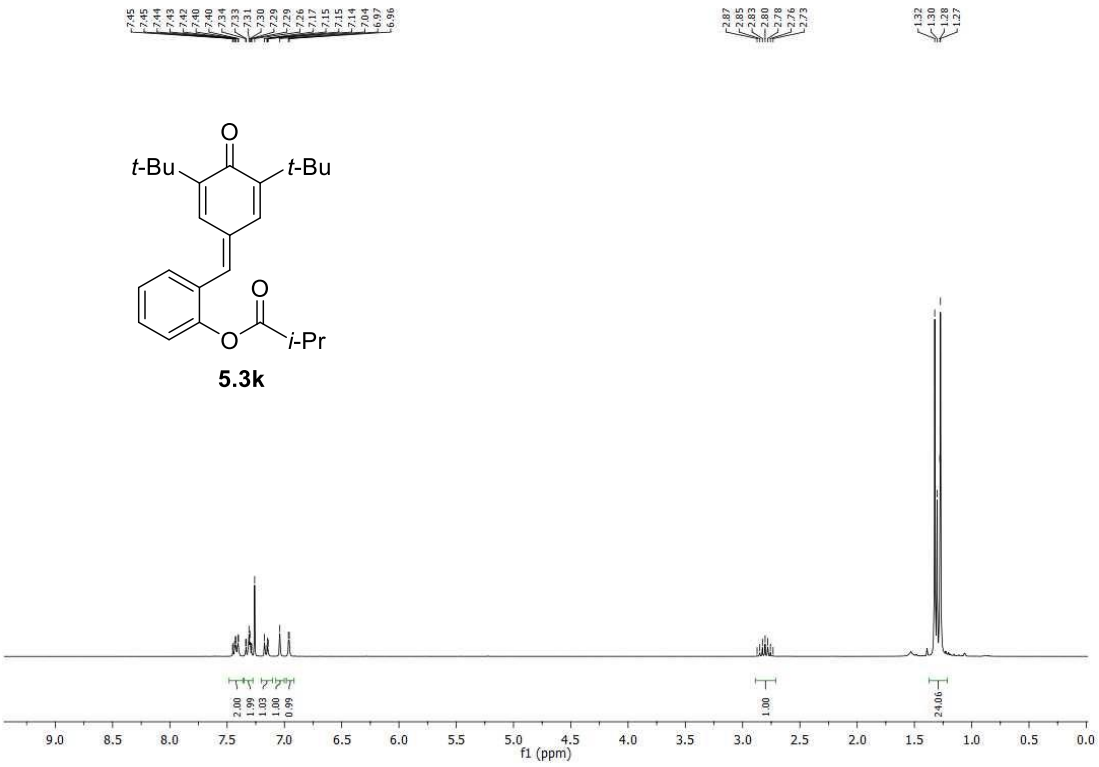
149.25
148.11
136.26
134.51
131.08
131.57
130.23
128.83
127.99
125.95
122.89
36.12
35.41
35.01
29.48
18.44
13.61
O
t-Bu
t-Bu
O
O
Pr
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

5.3j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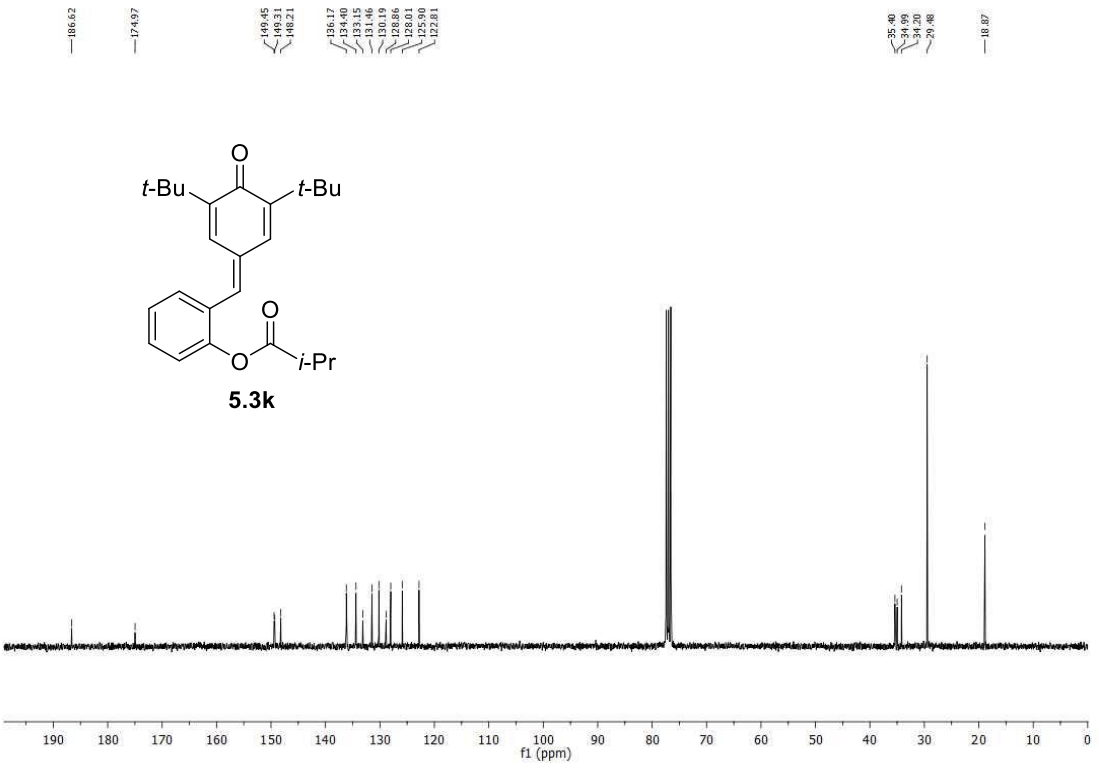
7.34
7.33
7.31
7.30
7.29
7.29
7.16
7.17
7.15
7.15
7.14
7.04
6.97
6.96
2.87
2.85
2.83
2.80
2.78
2.76
2.73
1.32
1.30
1.28
1.27
t-Bu
t-Bu
O
O
O
i-Pr
2.00
1.99
1.03
1.00
0.99
1.00
24.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

5.3k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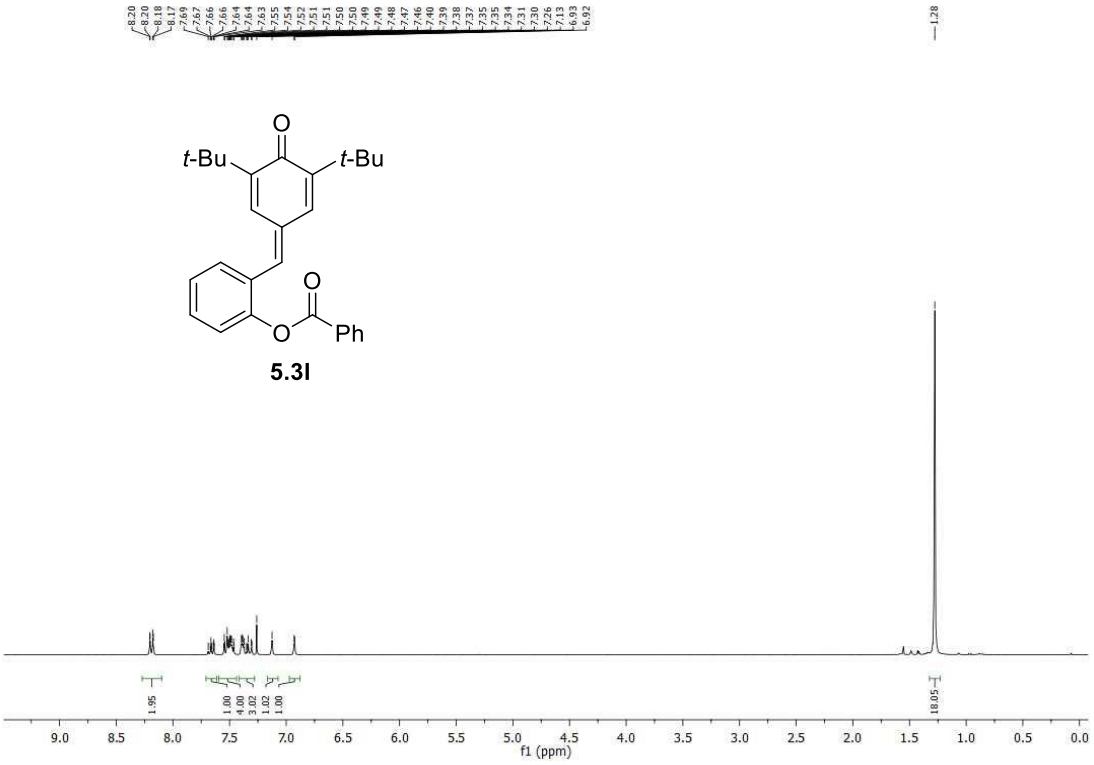
149.31
148.21
136.17
134.40
133.15
131.46
130.19
128.86
128.01
125.90
122.81
35.40
34.99
34.20
29.48
18.87
t-Bu
t-Bu
O
O
O
i-Pr
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

5.3k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7.64
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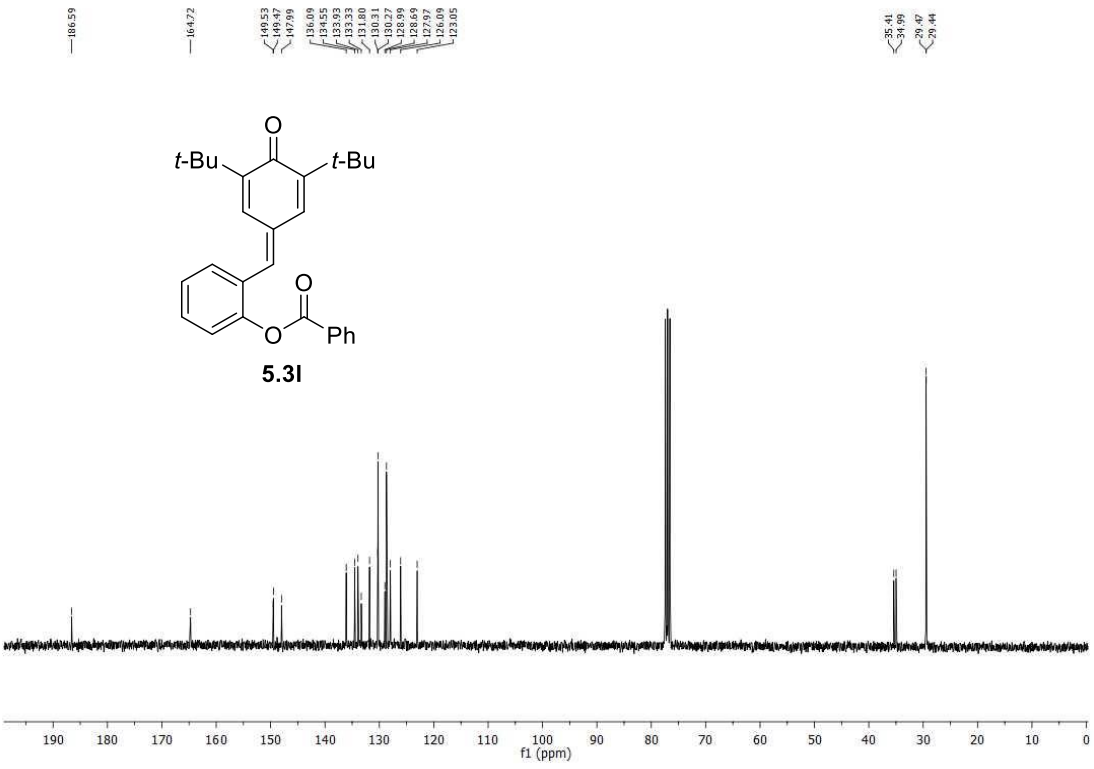
7.63
7.55
7.54
7.52
7.51
7.51
7.50
7.50
7.49
7.49
7.48
7.47
7.46
7.40
7.39
7.38
7.37
7.35
7.35
7.34
7.31
7.30
7.26
7.13
6.93
6.92
1.28
O
t-Bu
t-Bu
O
O
Ph
1.95
1.00
4.00
3.02
1.02
1.00
18.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

5.3l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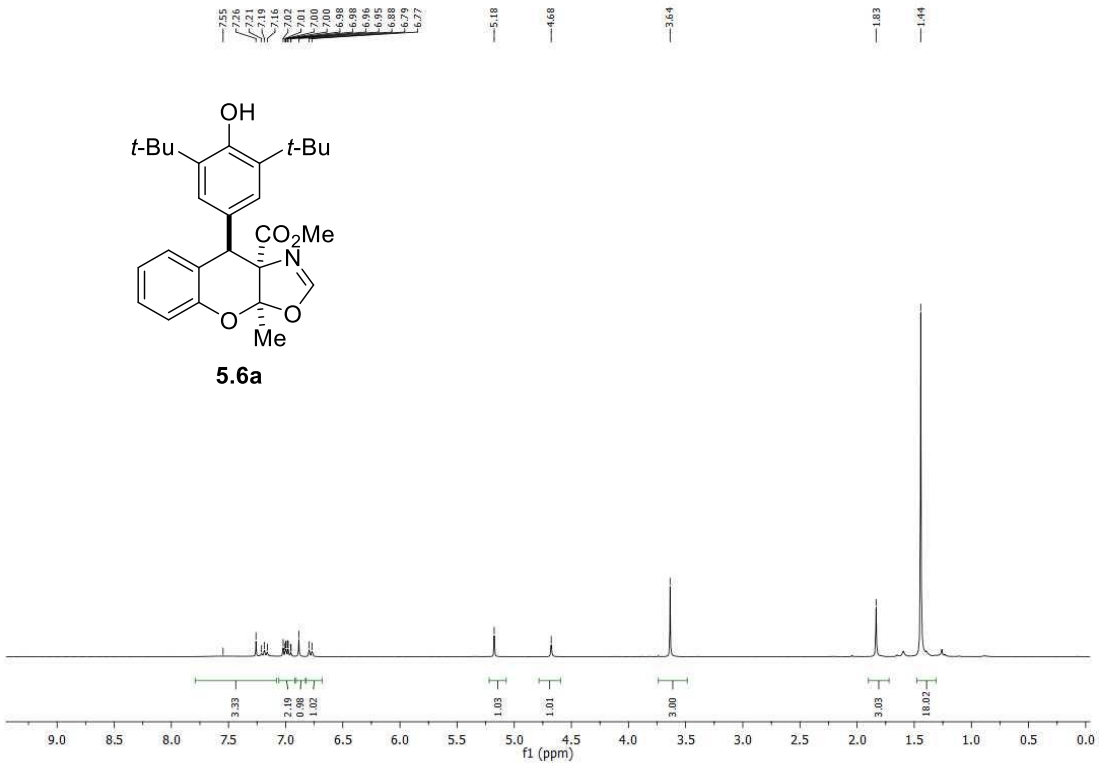
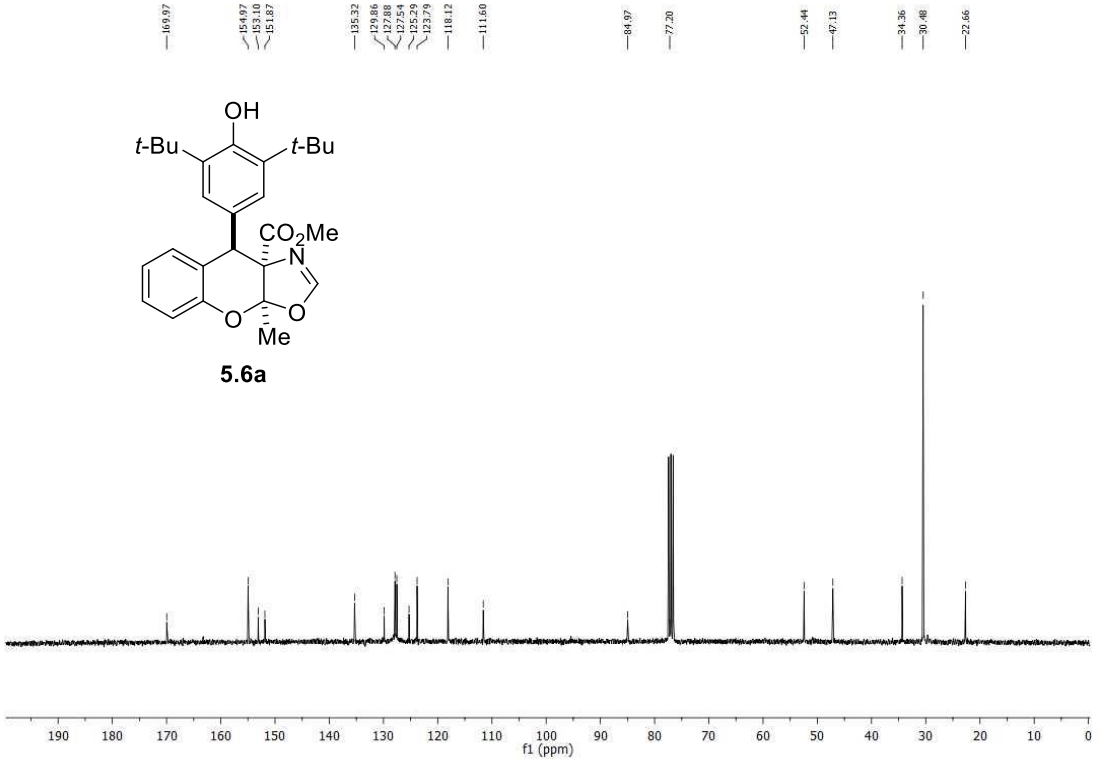
149.47
147.99
136.09
134.55
133.93
133.33
131.80
130.31
130.27
128.99
128.69
127.97
126.68
123.05
35.41
34.99
29.47
29.44
O
t-Bu
t-Bu
O
O
Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

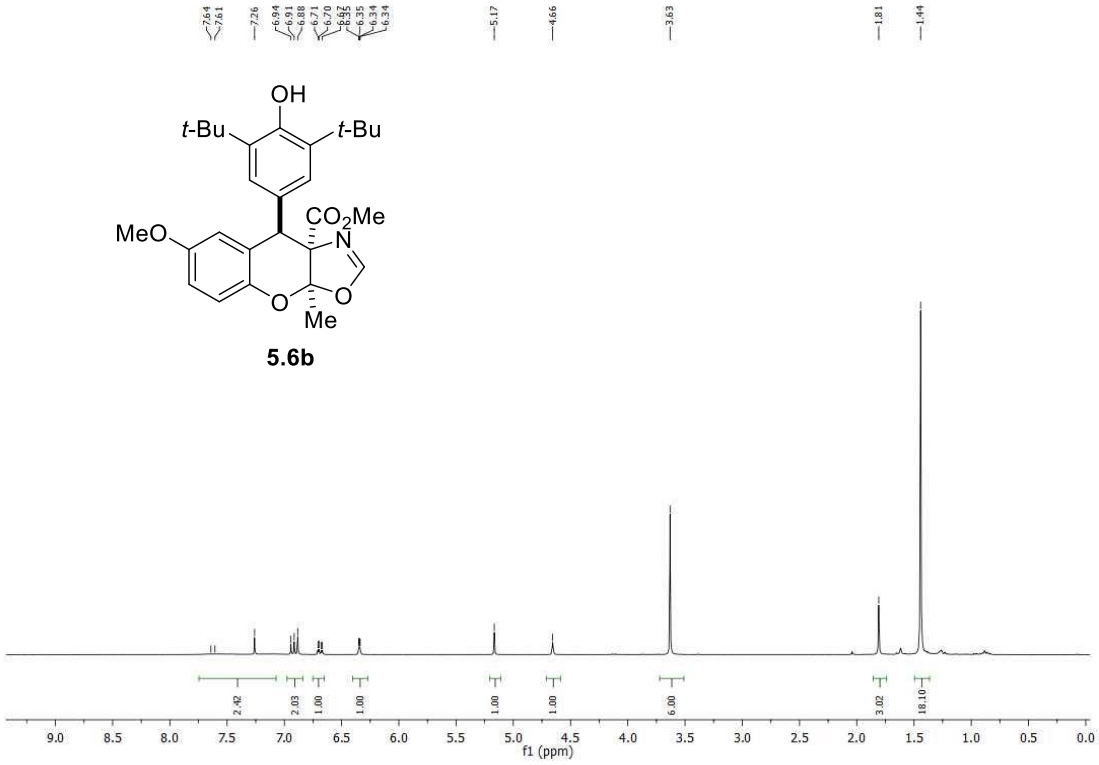
5.3l



5.6a



5.6a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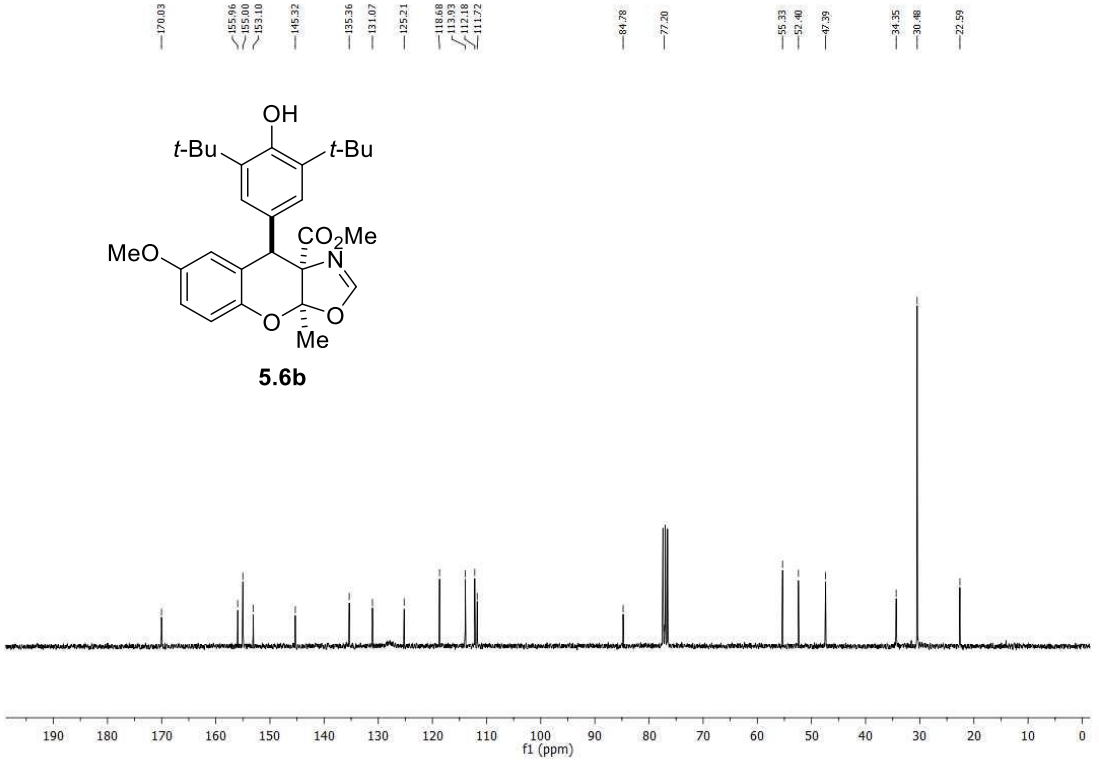
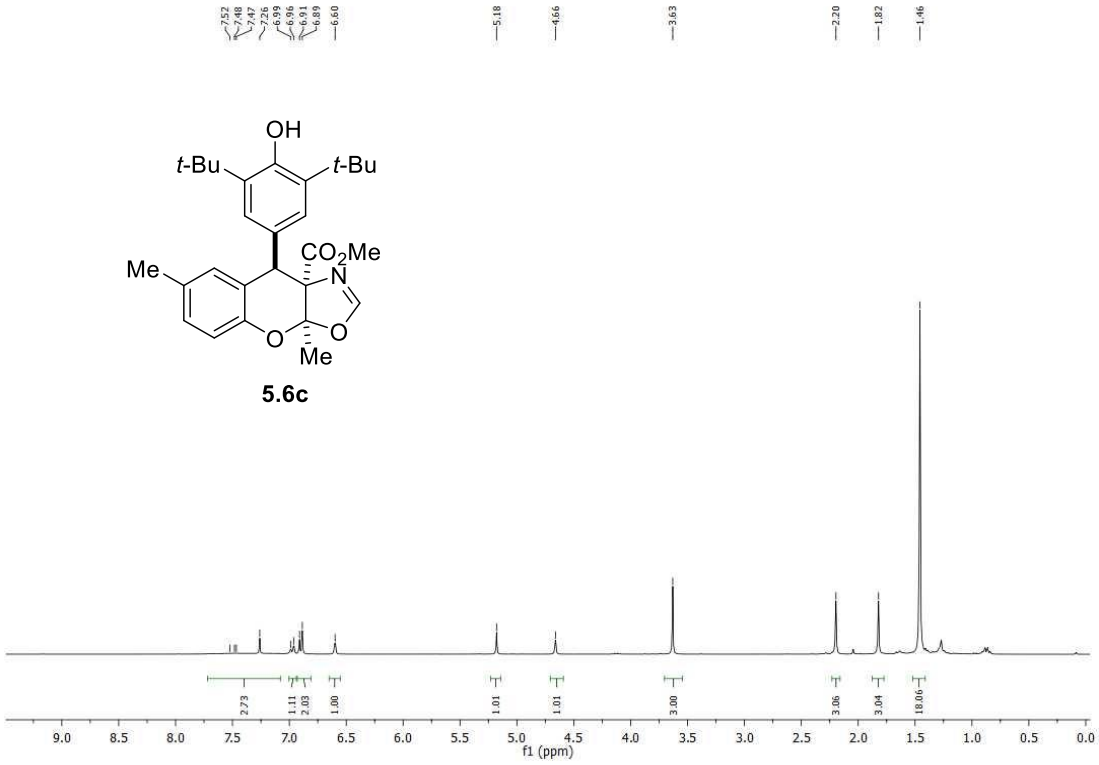
7.26
6.94
6.91
6.88
6.71
6.70
6.67
6.35
6.34
6.34
5.17
4.66
3.63
1.81
1.44
OH
t-Bu
t-Bu
CO2Me
N
MeO
O
O
Me
2.42
2.03
1.00
1.00
1.00
1.00
6.00
3.02
18.10
f1 (ppm)

5.6b


170.03
155.96
155.00
153.10
145.32
135.36
131.07
125.21
118.68
113.93
112.18
111.72
84.78
77.20
55.33
52.40
47.39
34.35
30.48
22.59
OH
t-Bu
t-Bu
CO2Me
N
MeO
O
O
Me
f1 (ppm)

5.6b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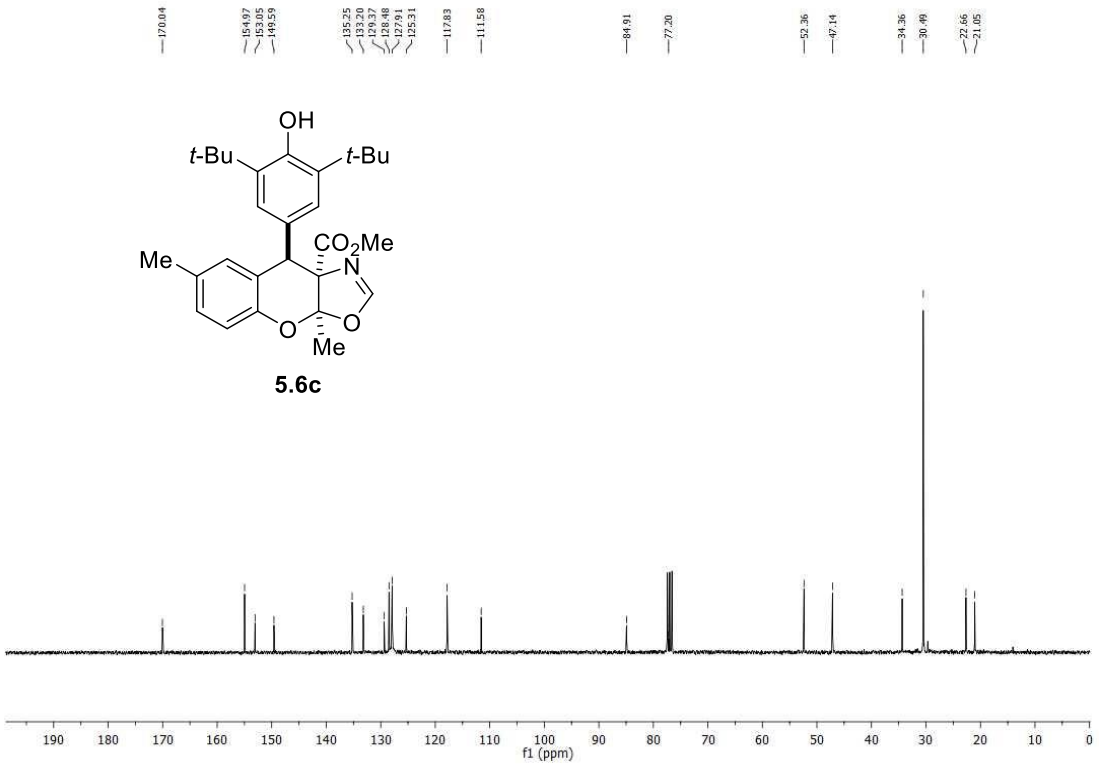
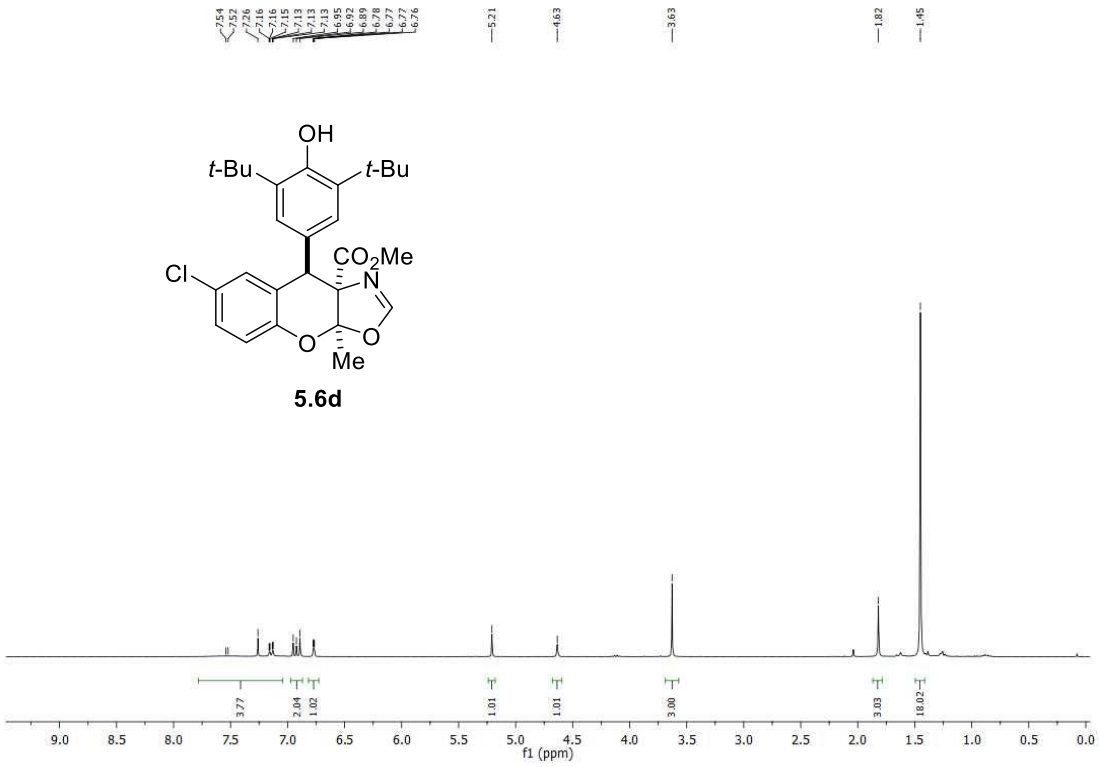
7.48
7.47
7.26
6.99
6.96
6.91
6.89
6.60
5.18
4.66
3.63
2.20
1.82
1.46
OH
t-Bu
t-Bu
CO2Me
N
Me
O
O
Me
2.73
1.11
2.03
1.00
1.01
1.01
3.00
3.06
3.04
18.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

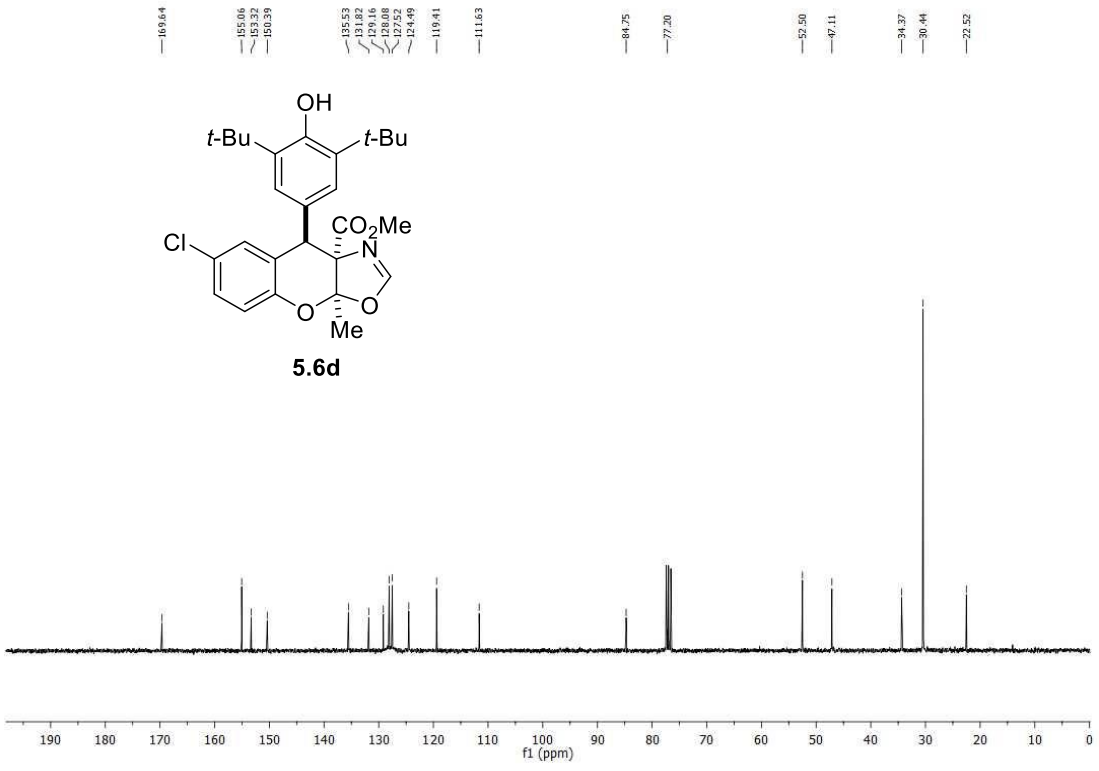
5.6c


170.04
154.97
153.05
149.59
135.25
133.20
129.27
128.48
127.91
125.31
117.83
111.58
84.91
77.20
52.36
47.14
34.36
30.49
22.66
21.05
OH
t-Bu
t-Bu
CO2Me
N
Me
O
O
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

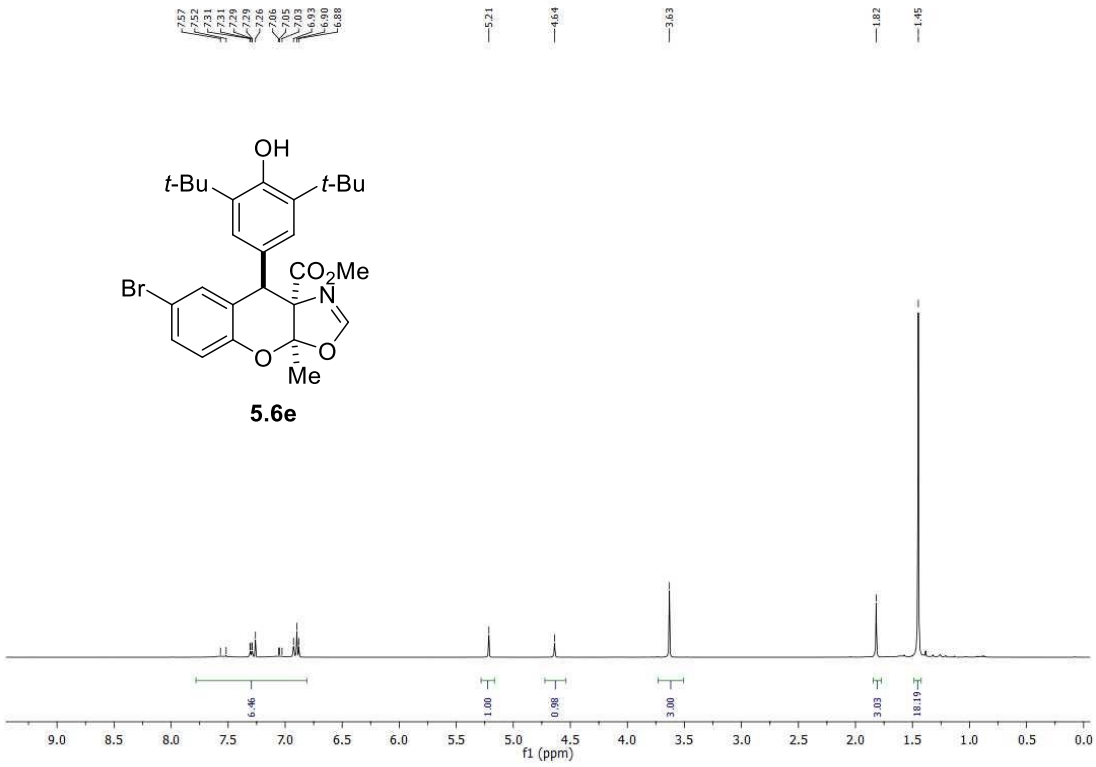
5.6c


7.54
7.52
7.26
7.16
7.15
7.13
7.13
6.95
6.92
6.89
6.78
6.77
6.77
6.76
5.21
4.63
3.63
1.82
1.45
OH
t-Bu
t-Bu
CO2Me
Cl
N
O
O
Me
3.77
2.04
1.02
1.01
1.01
3.00
3.03
18.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

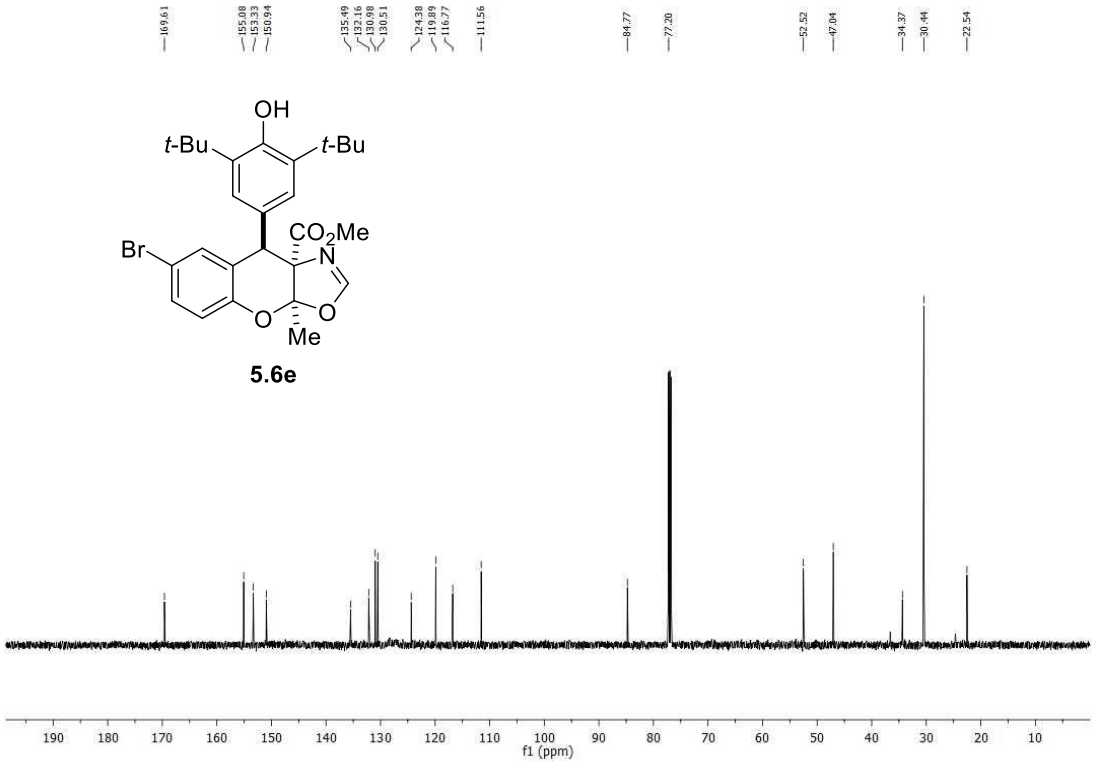
5.6d


169.64
155.06
153.32
150.39
135.53
131.82
129.16
128.68
127.52
124.49
119.41
111.63
84.75
77.20
52.50
47.11
34.37
30.44
22.52
OH
t-Bu
t-Bu
CO2Me
Cl
N
O
O
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

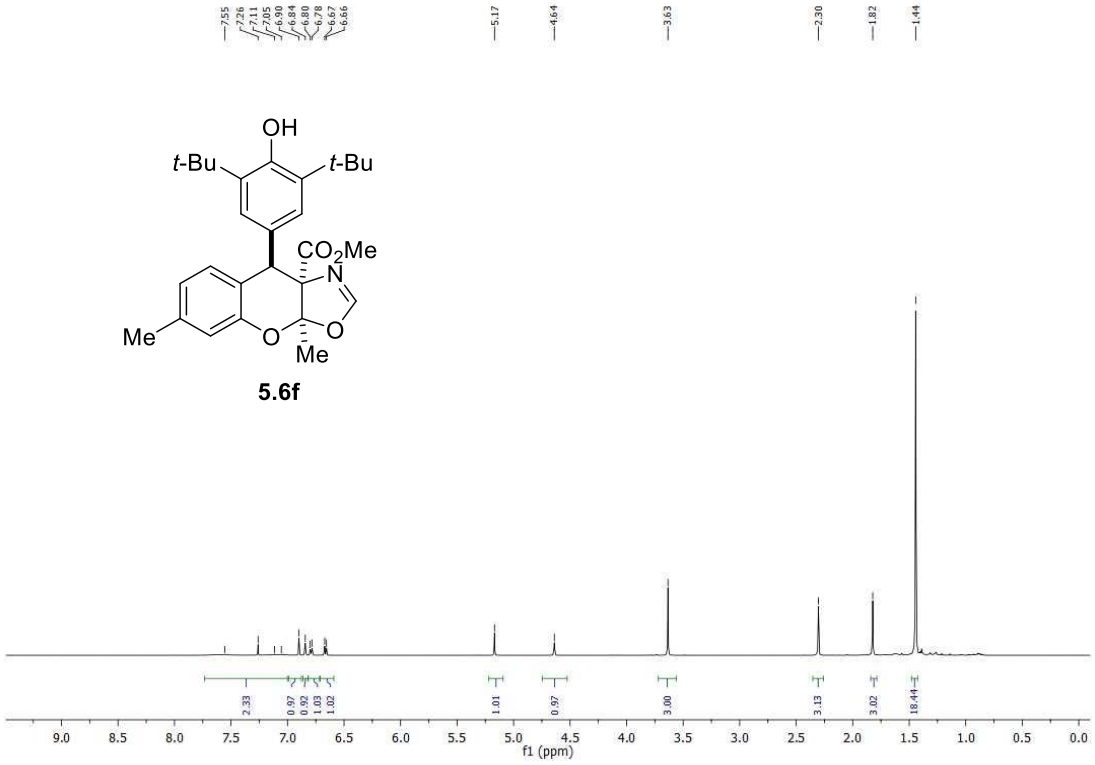
5.6d


7.57
7.52
7.31
7.31
7.29
7.29
7.26
7.06
7.05
7.03
6.93
6.90
6.88
5.21
4.64
3.63
1.82
1.45
OH
t-Bu
t-Bu
CO2Me
N
Br
O
O
Me
6.46
1.00
0.98
3.00
3.03
18.19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

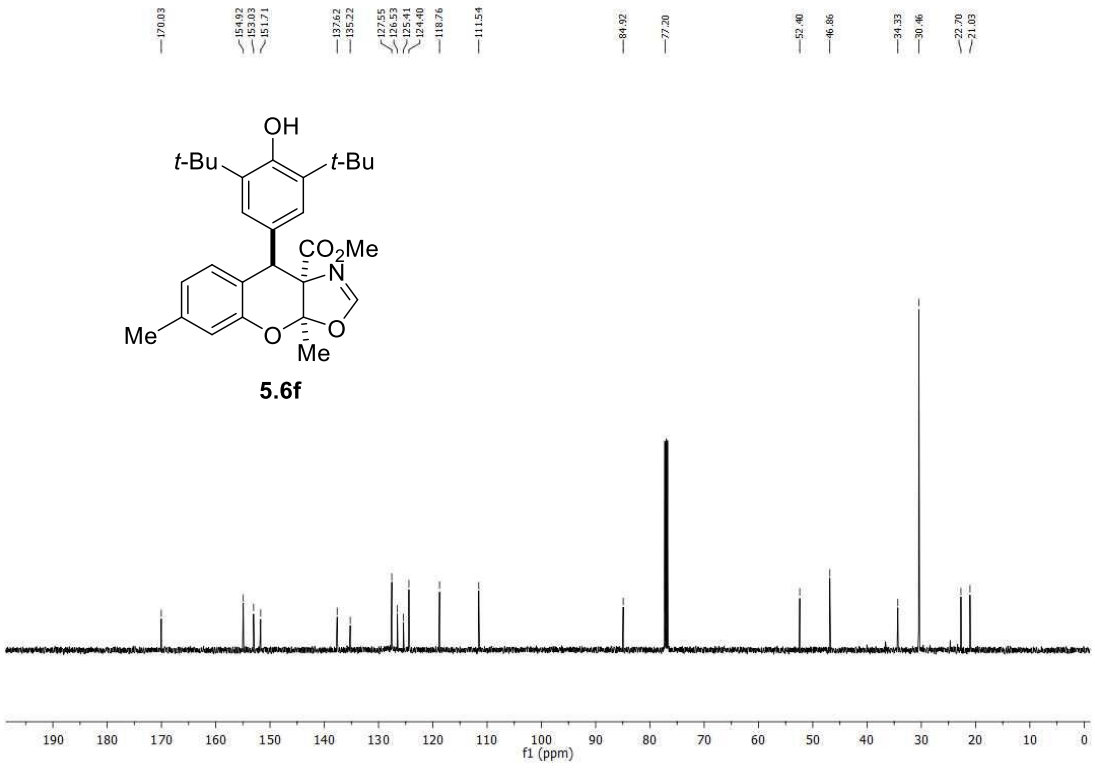
5.6e


169.61
155.08
153.33
150.94
135.49
131.16
130.98
130.51
124.38
119.89
116.77
111.56
84.77
77.20
52.52
47.04
34.37
30.44
22.54
OH
t-Bu
t-Bu
CO2Me
N
Br
O
O
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

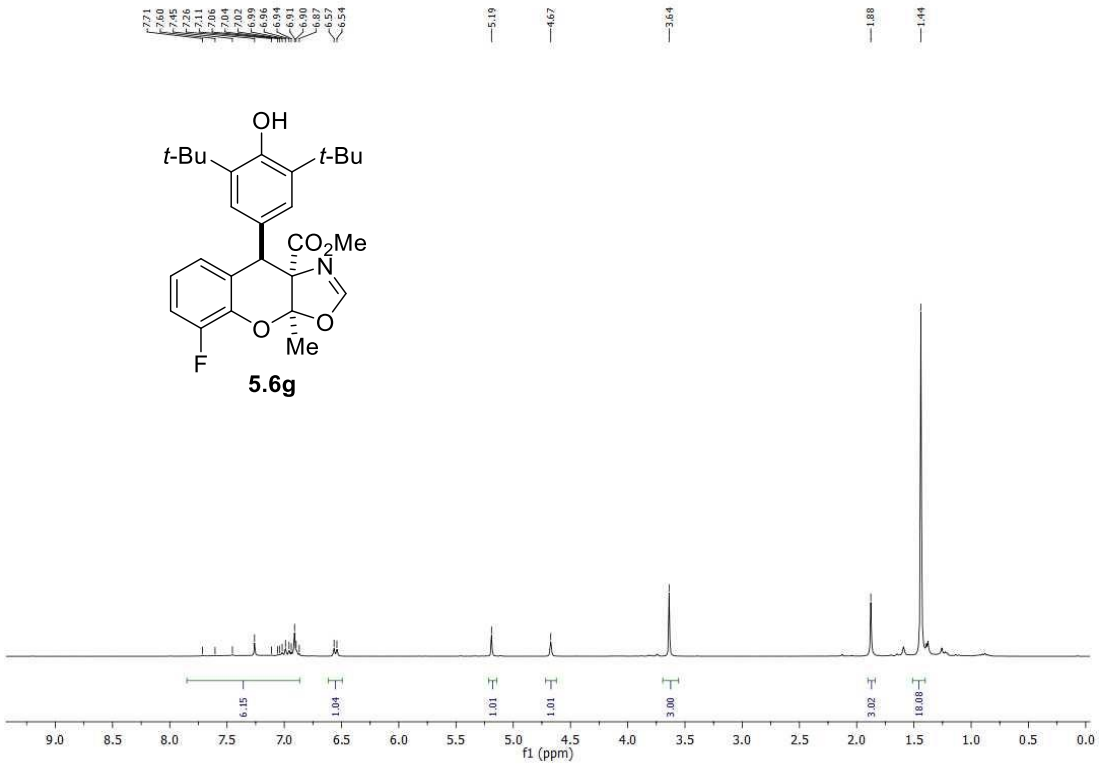
5.6e


7.55
7.26
7.11
7.05
6.90
6.84
6.80
6.78
6.67
6.66
5.17
4.64
3.63
2.30
1.82
1.44
OH
t-Bu
t-Bu
CO2Me
N
Me
O
O
Me
2.33
0.97
0.92
1.03
1.02
1.01
0.97
3.00
3.13
3.02
18.44
f1 (ppm)

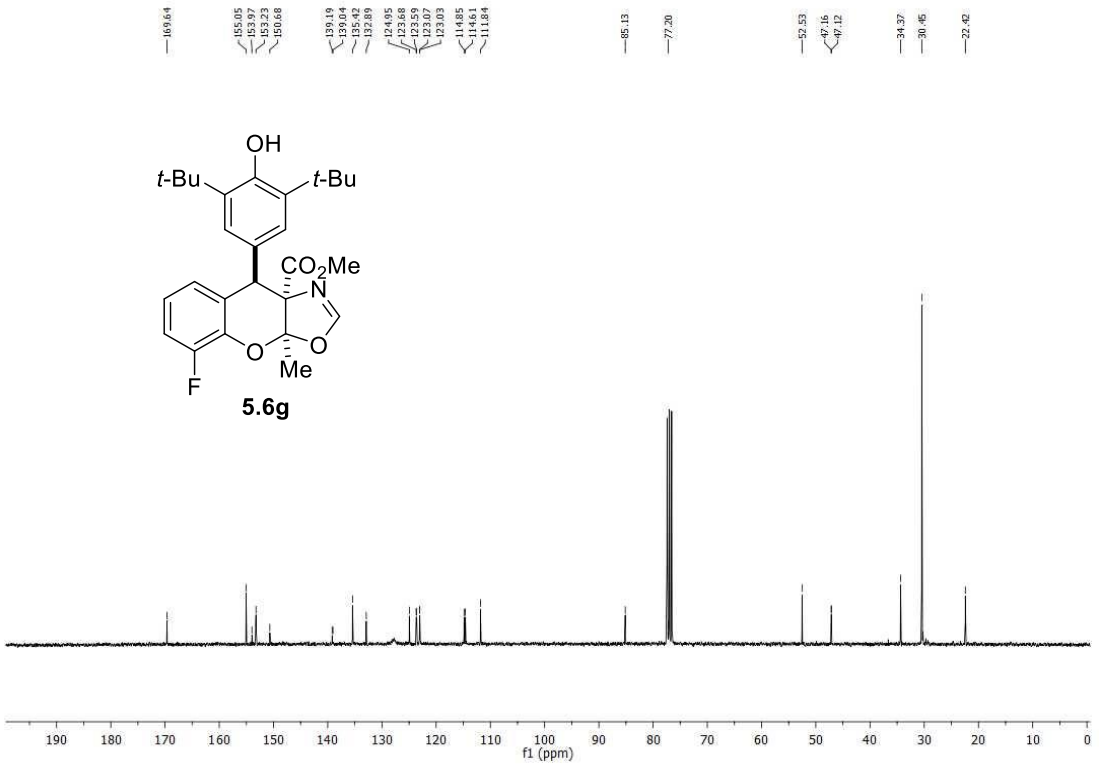
5.6f


170.03
154.92
153.03
151.71
137.62
135.22
127.55
126.53
125.41
124.40
118.76
111.54
84.92
77.20
52.40
46.86
34.33
30.46
22.70
21.03
OH
t-Bu
t-Bu
CO2Me
N
Me
O
O
Me
f1 (ppm)

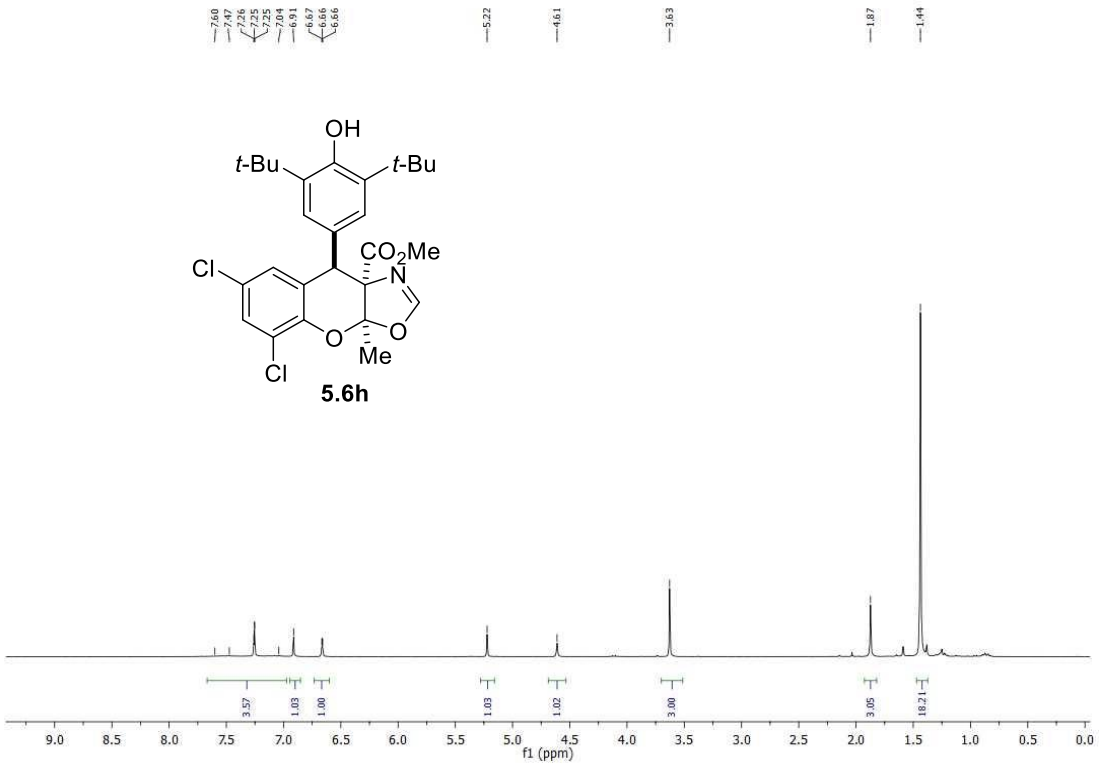
5.6f

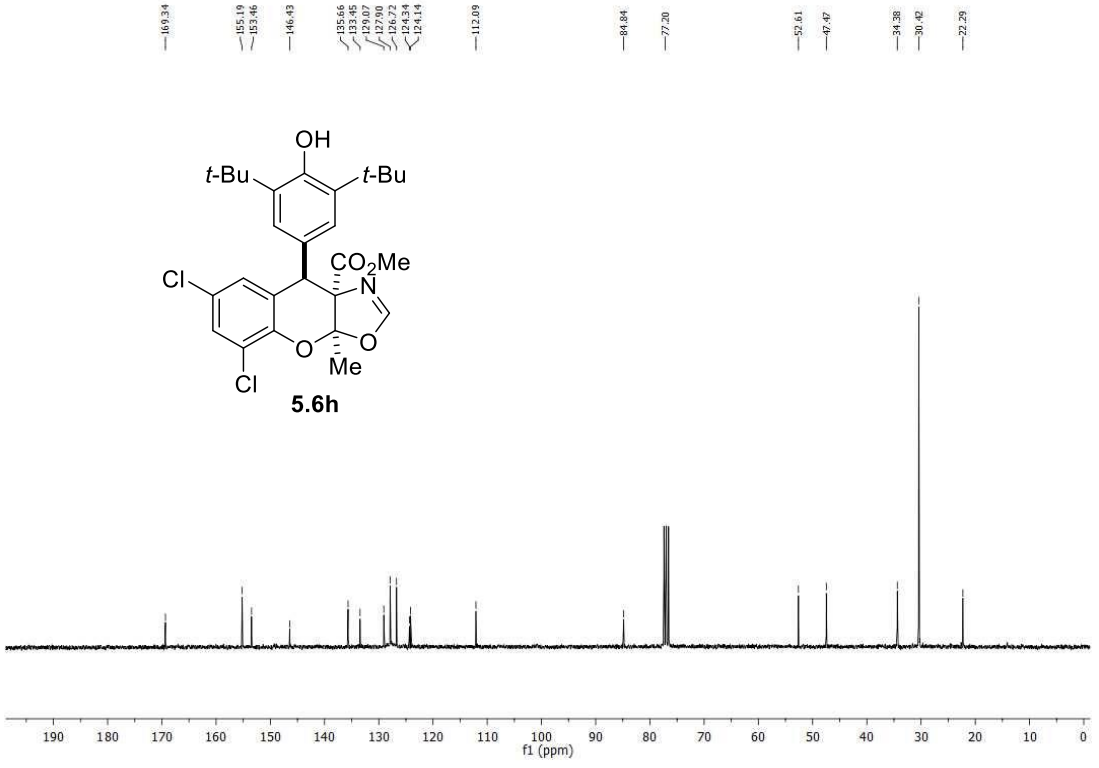

7.71
7.60
7.45
7.26
7.11
7.06
7.04
7.02
6.99
6.96
6.94
6.91
6.90
6.87
6.54
5.19
4.67
3.64
1.88
1.44
OH
t-Bu
t-Bu
CO2Me
N
O
O
Me
F
6.15
1.04
1.01
1.01
3.00
3.02
10.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

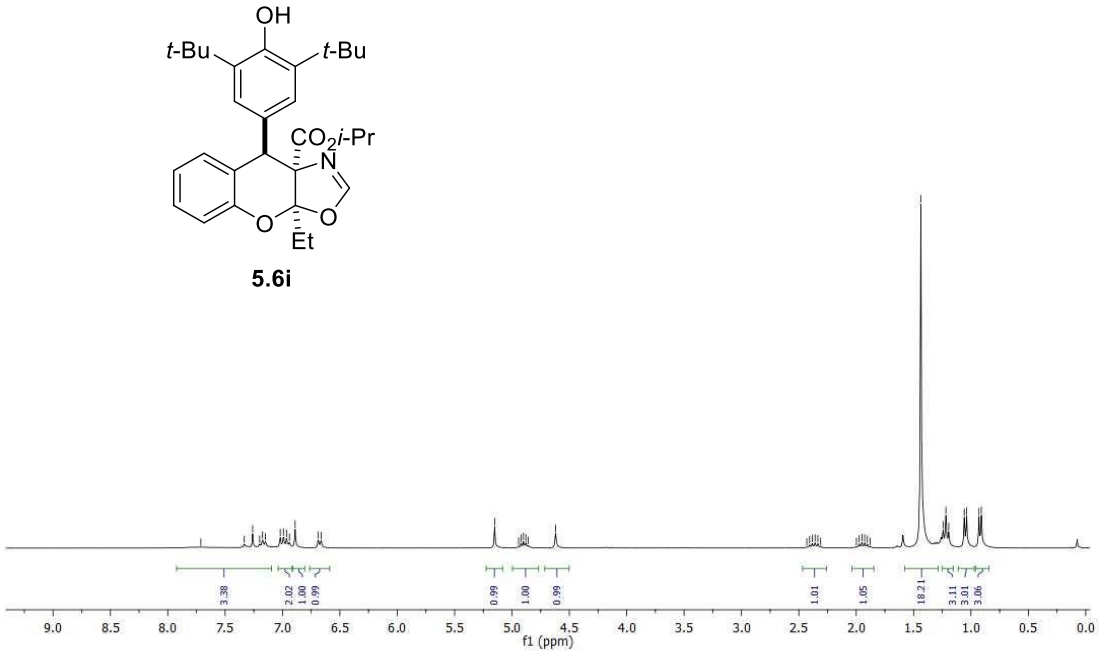
5.6g


169.64
155.05
153.97
153.23
150.68
139.19
139.04
135.42
132.89
124.95
123.68
123.59
123.07
123.03
114.85
114.61
111.84
85.13
77.20
52.53
47.16
47.12
34.37
30.45
22.42
OH
t-Bu
t-Bu
CO2Me
N
O
O
Me
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

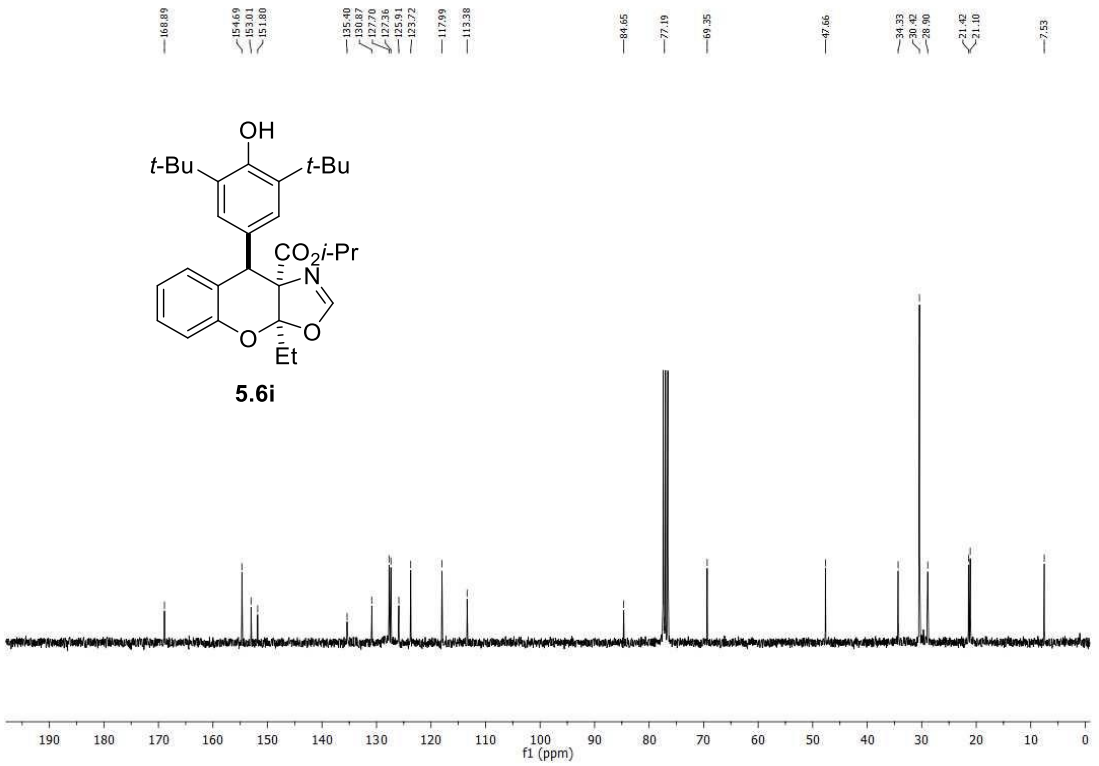
5.6g


7.60
7.47
7.26
7.25
7.25
7.04
6.91
6.67
6.66
6.66
5.22
4.61
3.63
1.87
1.44
OH
t-Bu
t-Bu
CO2Me
N
Cl
O
O
Me
Cl
5.6h
3.57
1.03
1.00
1.03
1.02
3.00
3.05
18.21
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

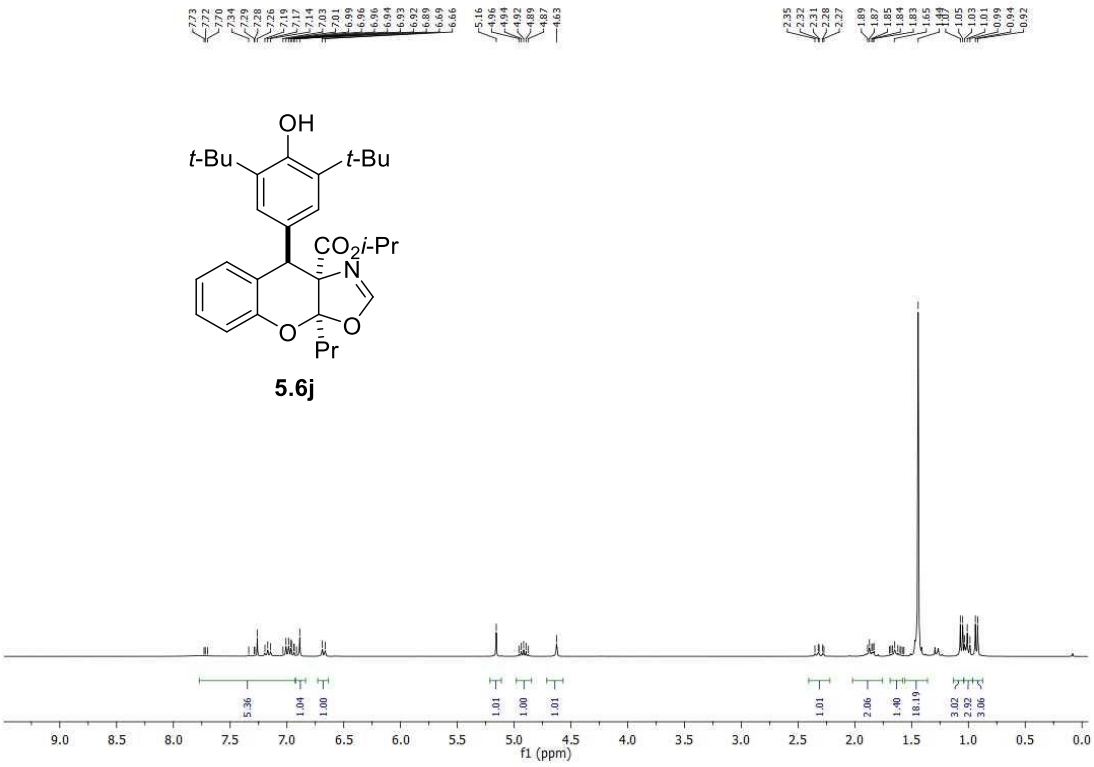

169.34
155.19
153.46
146.43
135.66
133.45
129.07
127.90
126.72
124.34
124.14
112.09
84.84
77.20
52.61
47.47
34.38
30.42
22.29
OH
t-Bu
t-Bu
CO2Me
N
Cl
O
O
Me
Cl
5.6h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



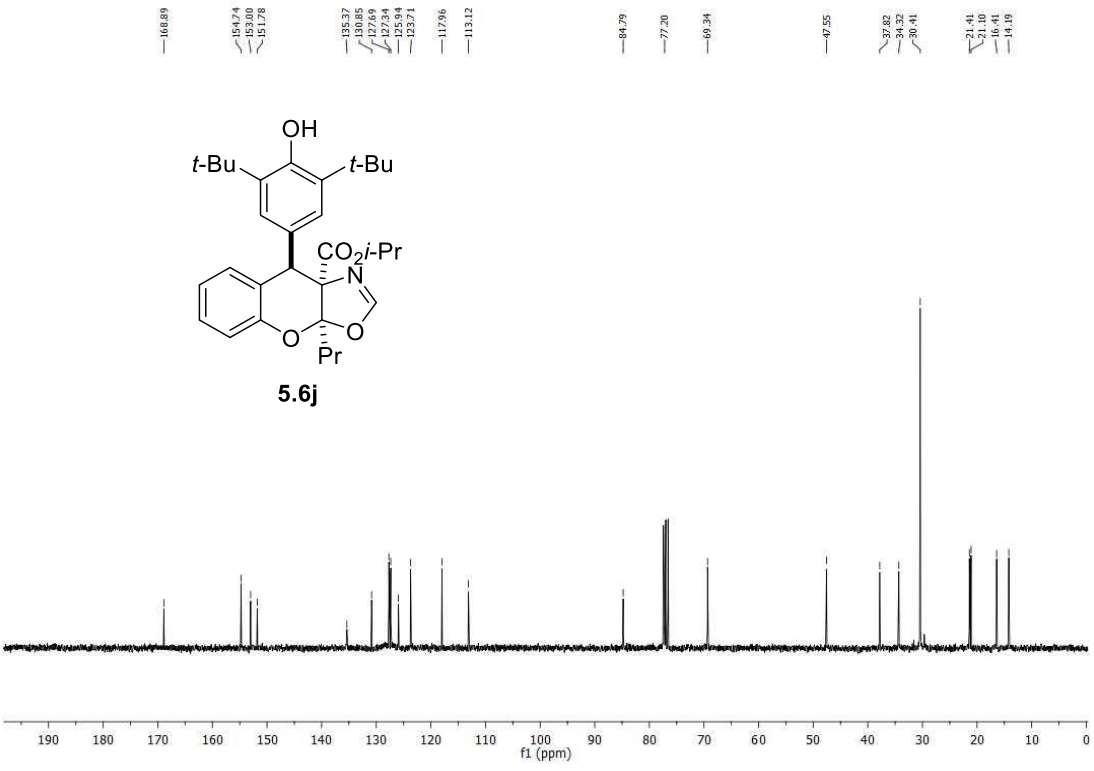
5.6i



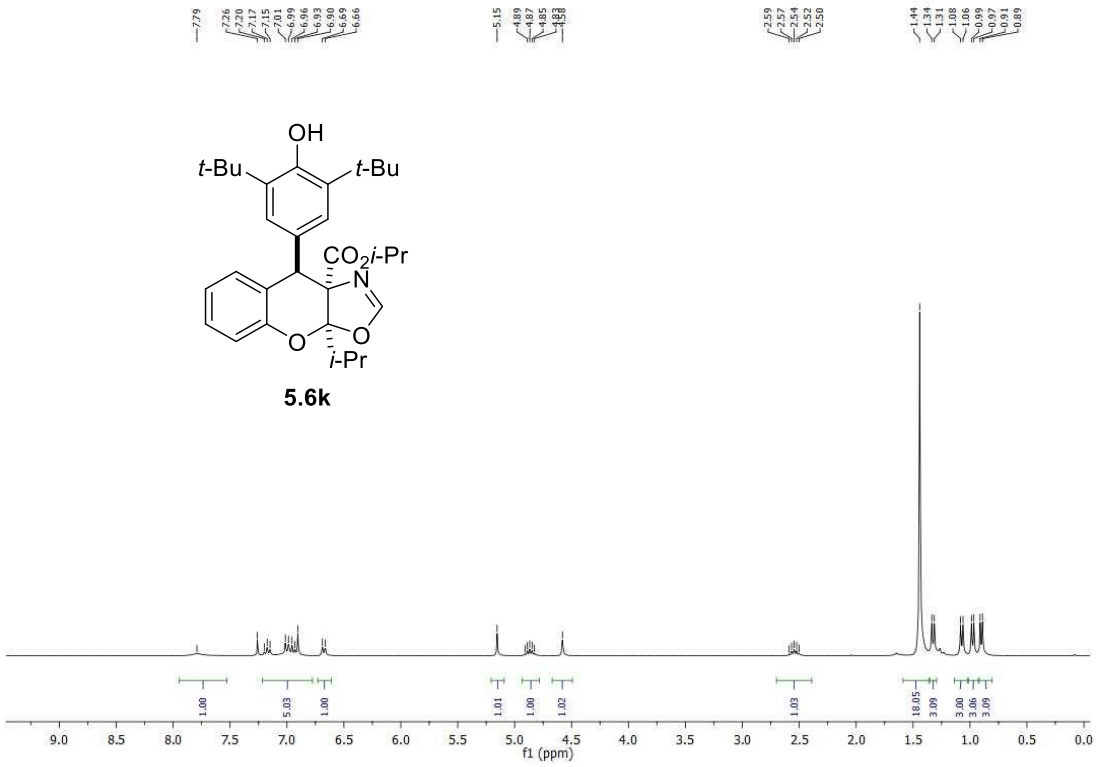
5.6i



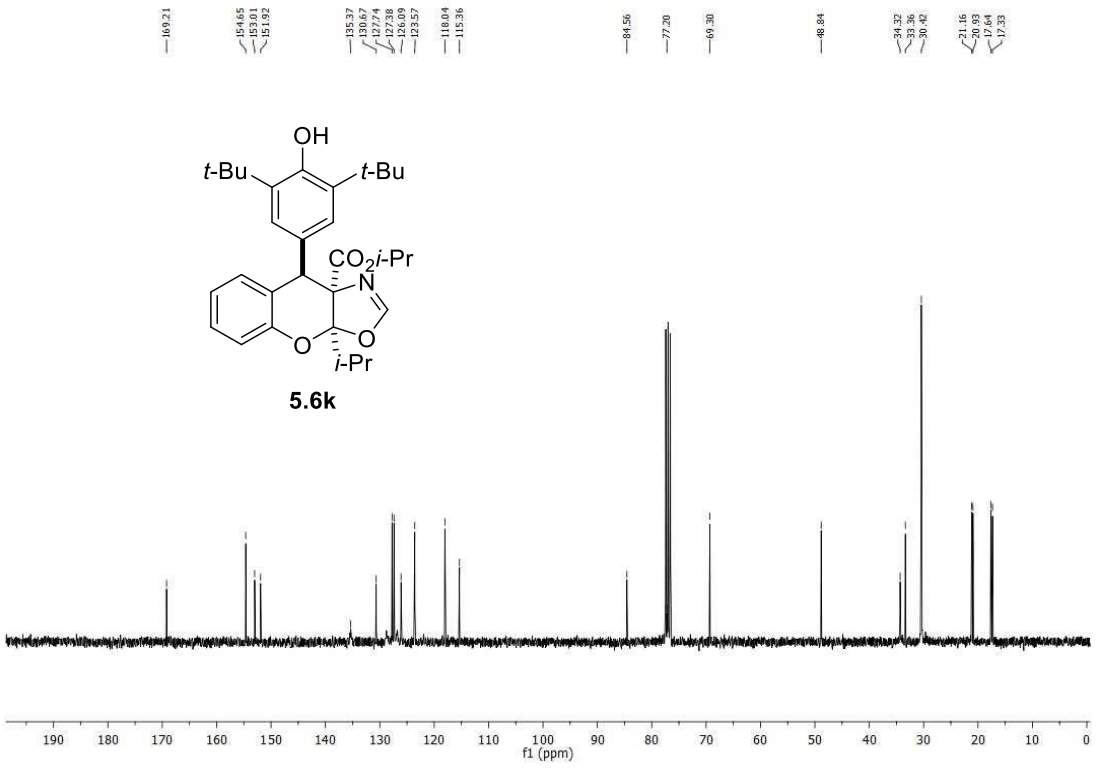
5.6j



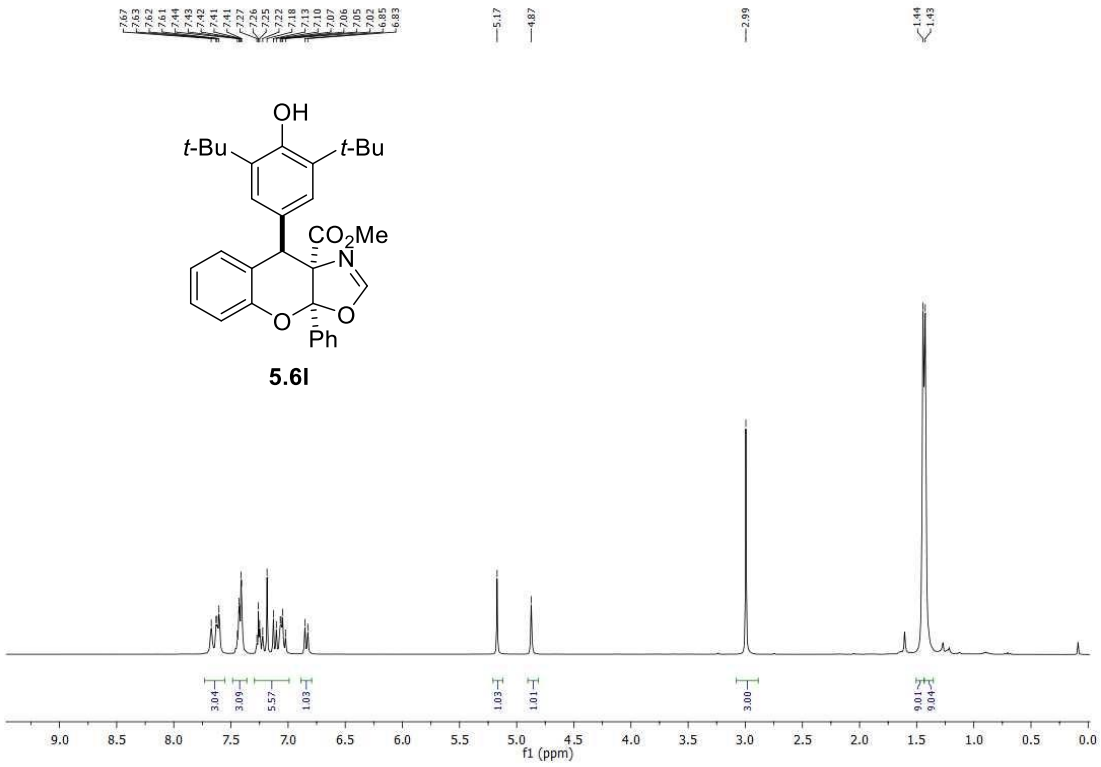
5.6j

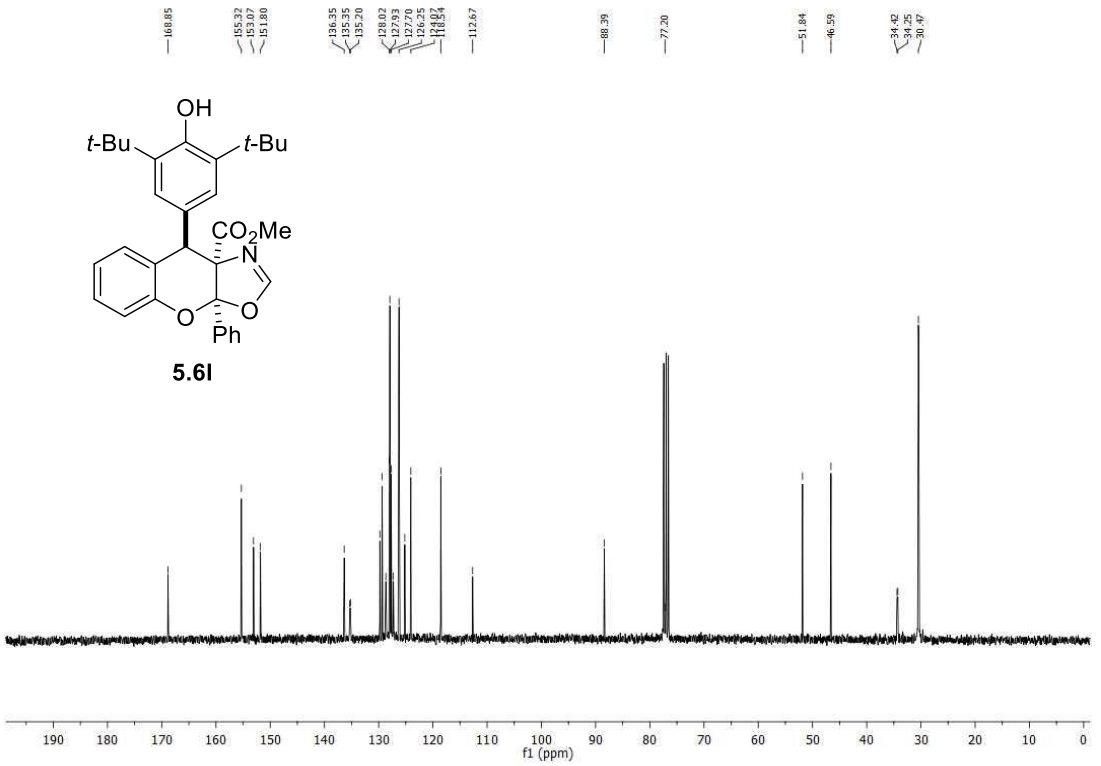

OH
t-Bu
t-Bu
CO2i-Pr
N
O
O
i-Pr
f1 (ppm)

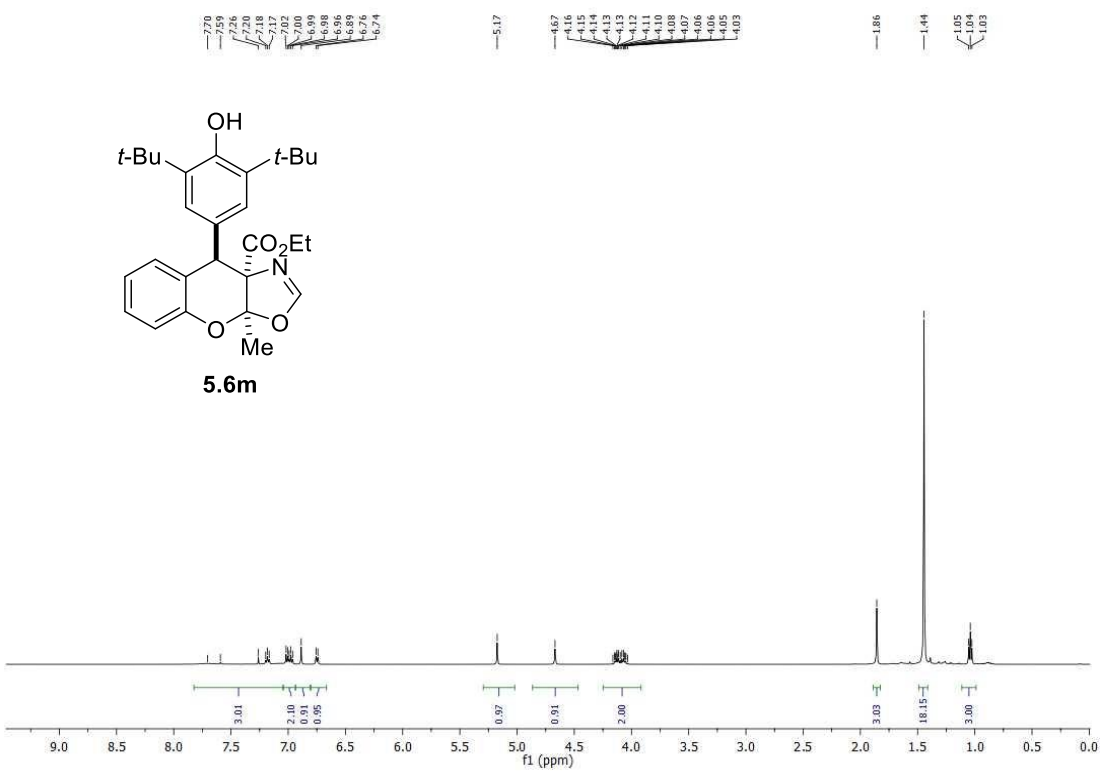
5.6k


OH
t-Bu
t-Bu
CO2i-Pr
N
O
O
i-Pr
f1 (ppm)

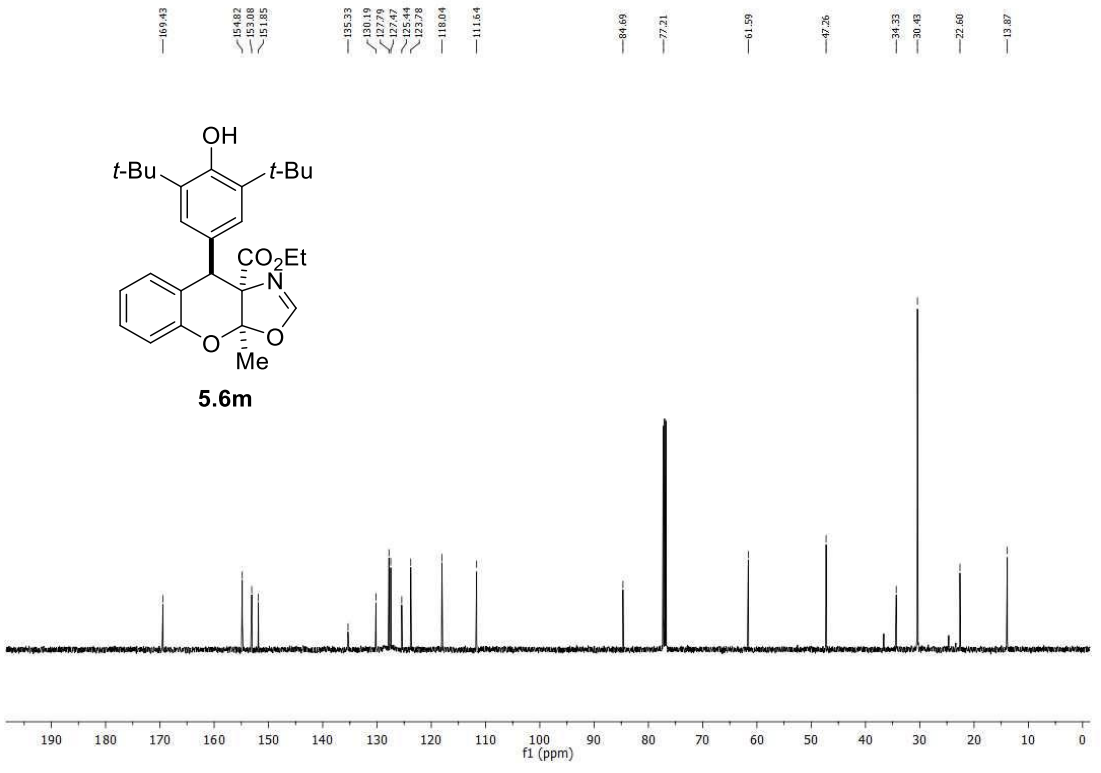
5.6k


OH
t-Bu
t-Bu
CO2Me
N
O
O
Ph
5.6l
f1 (ppm)

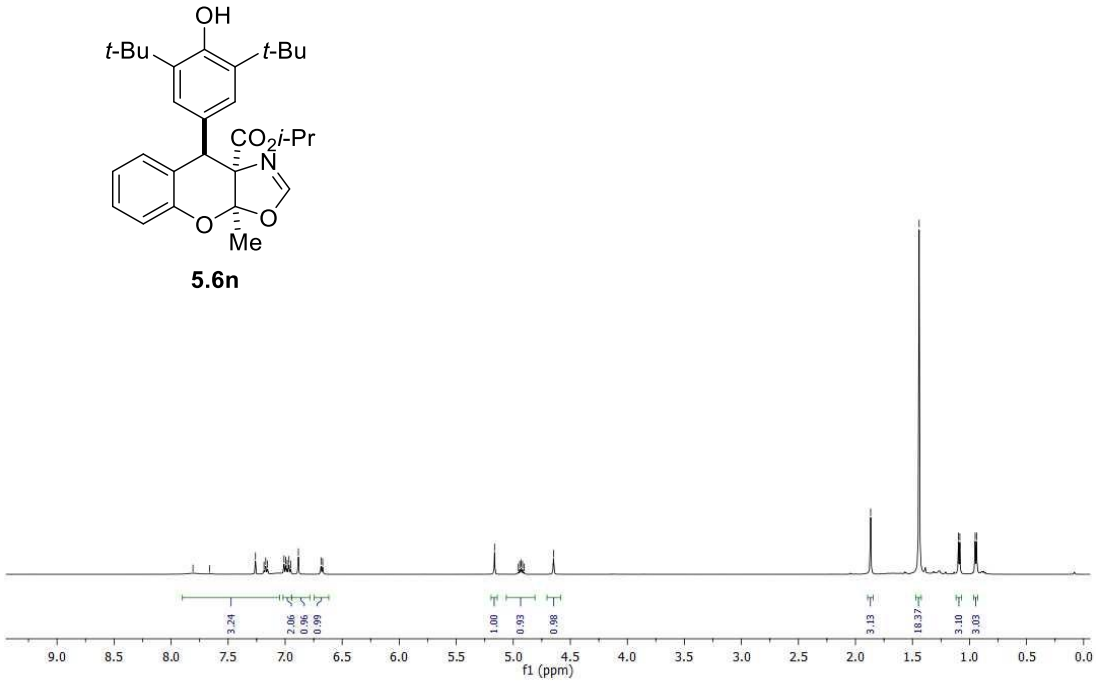

OH
t-Bu
t-Bu
CO2Me
N
O
O
Ph
5.6l
f1 (ppm)



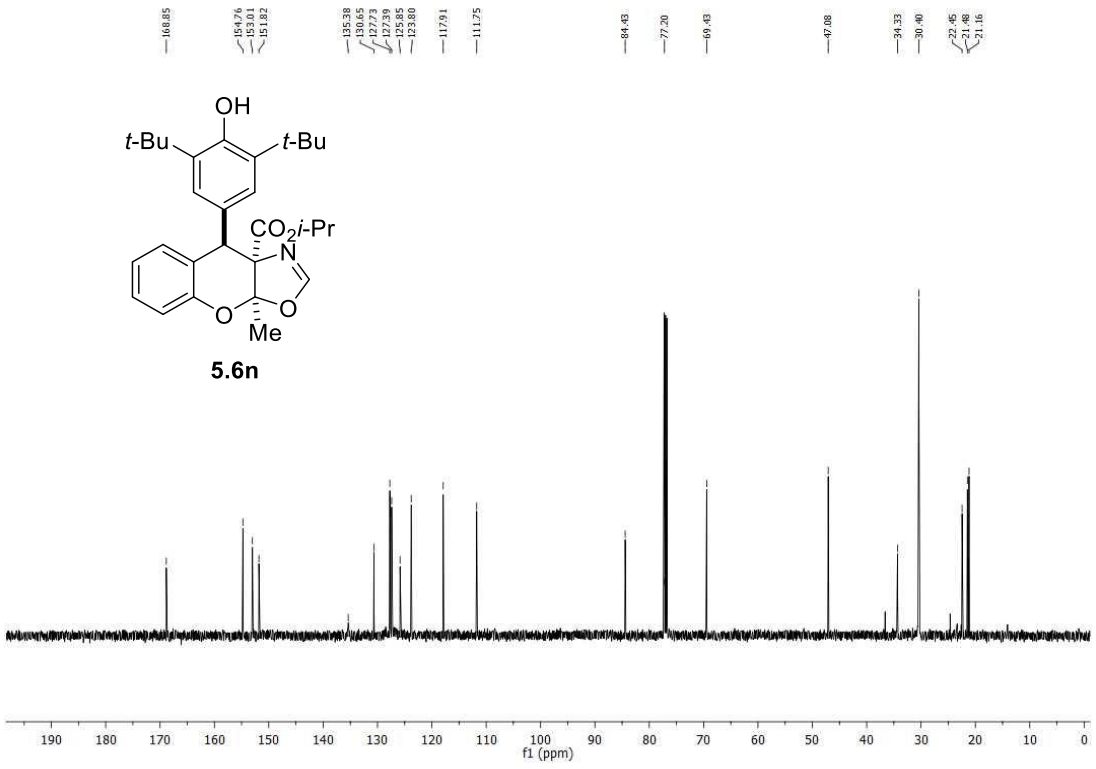
5.6m



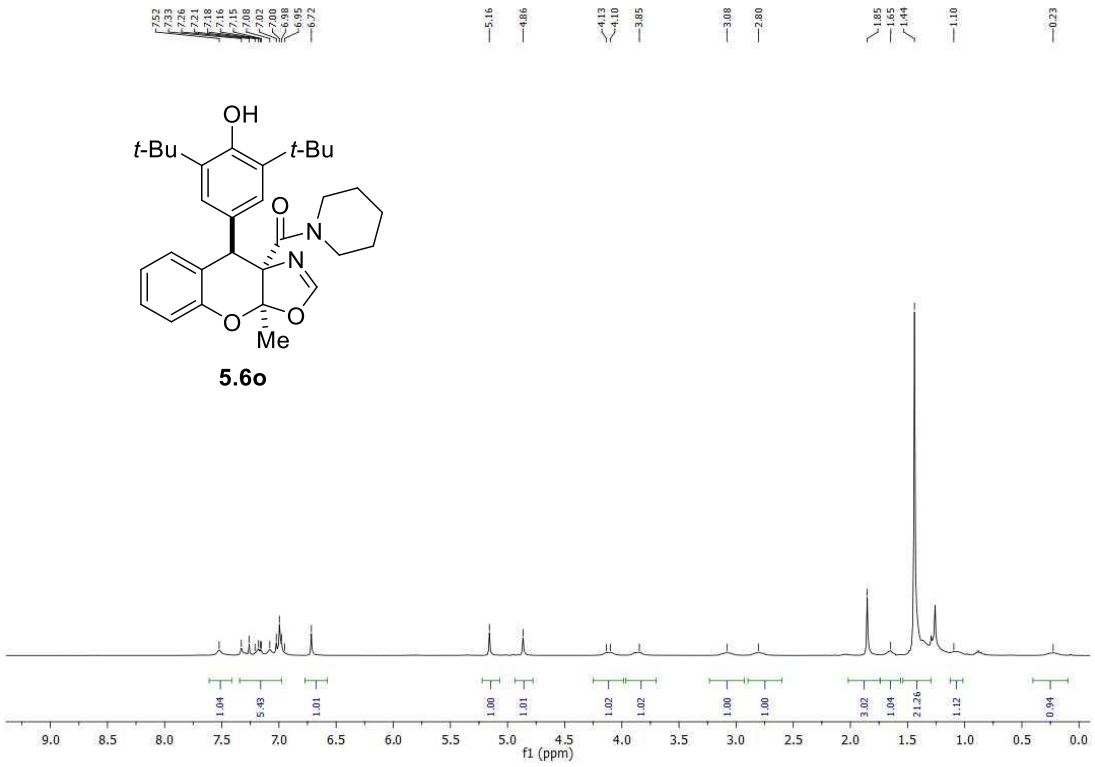
5.6m



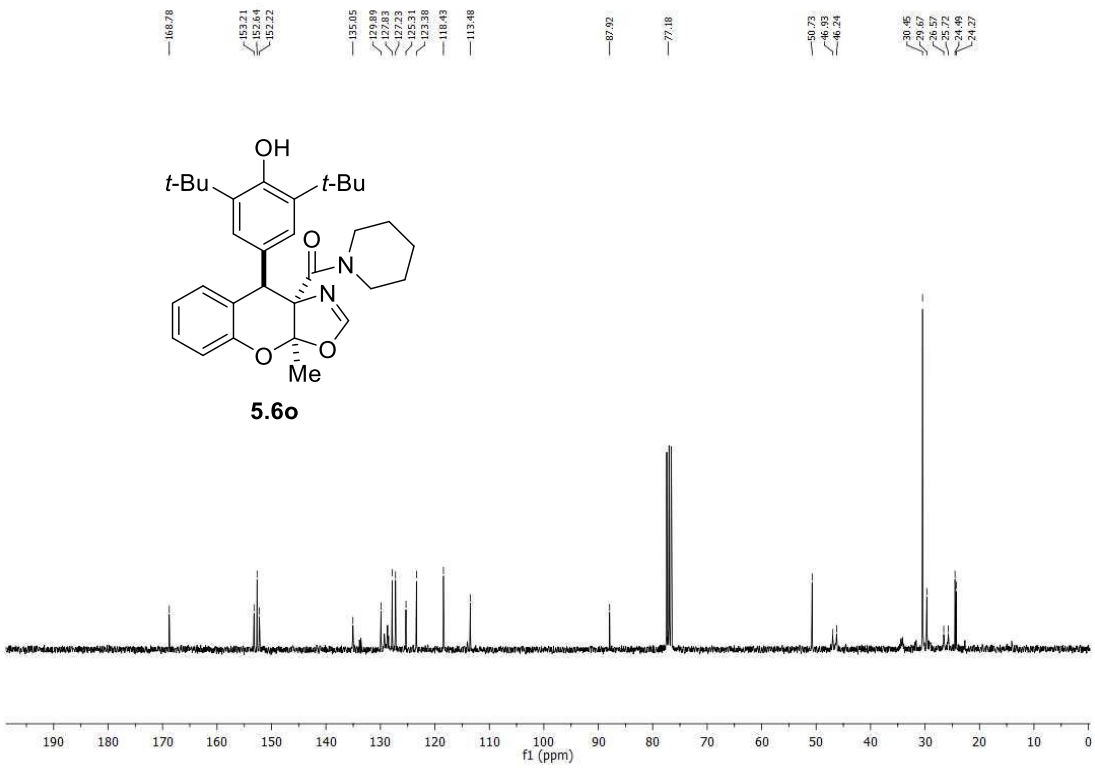
5.6n



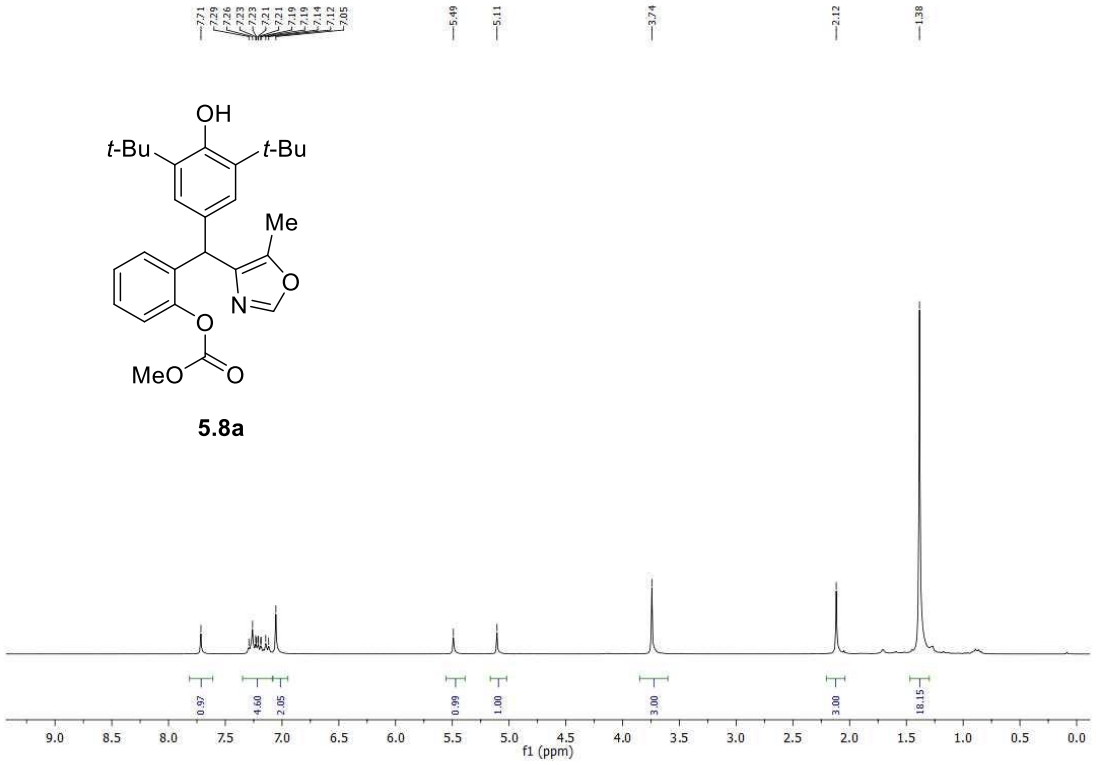
5.6n


7.52
7.33
7.26
7.21
7.18
7.16
7.15
7.08
7.03
7.00
6.98
6.95
6.72
5.16
4.86
4.13
4.10
3.85
3.08
2.80
1.85
1.65
1.44
1.10
0.23
OH
t-Bu
t-Bu
O
N
N
O
O
Me
1.04
5.43
1.01
1.00
1.01
1.02
1.02
1.00
1.00
3.02
1.04
21.26
1.12
0.94
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

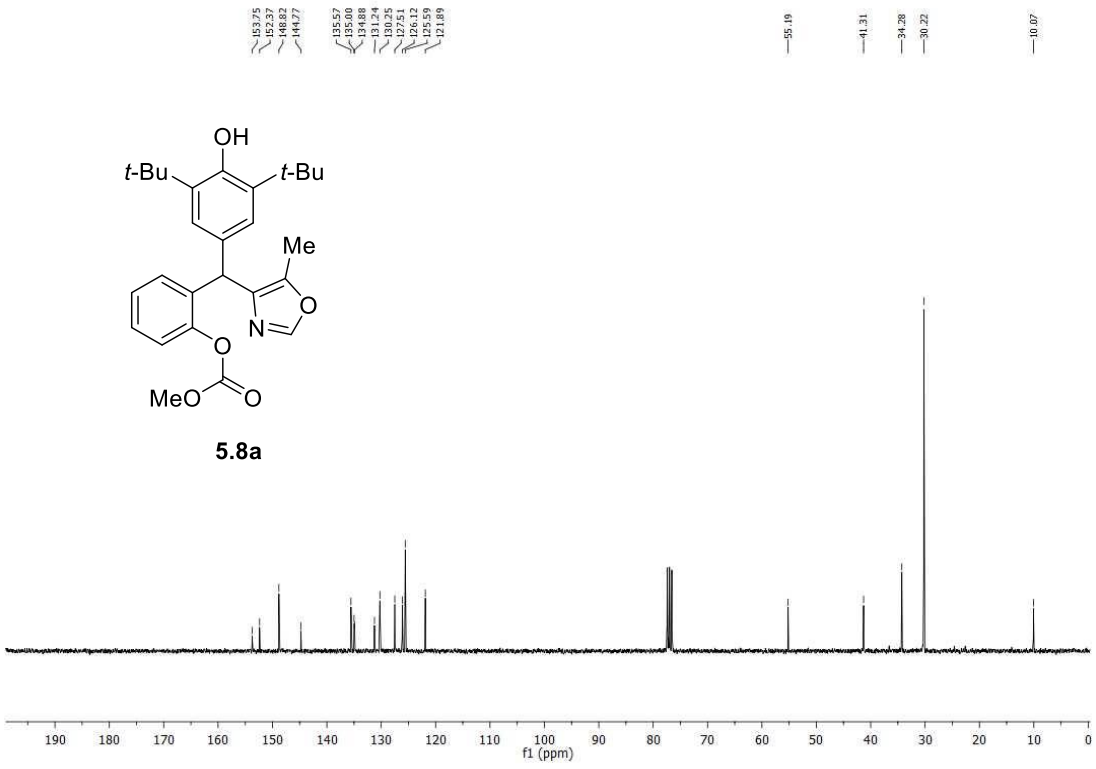
5.6o


168.78
153.21
152.64
152.22
135.05
129.89
127.83
127.23
125.31
123.38
118.43
113.48
87.92
77.18
50.73
46.93
46.24
30.45
29.67
26.57
25.72
24.49
24.27
OH
t-Bu
t-Bu
O
N
N
O
O
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

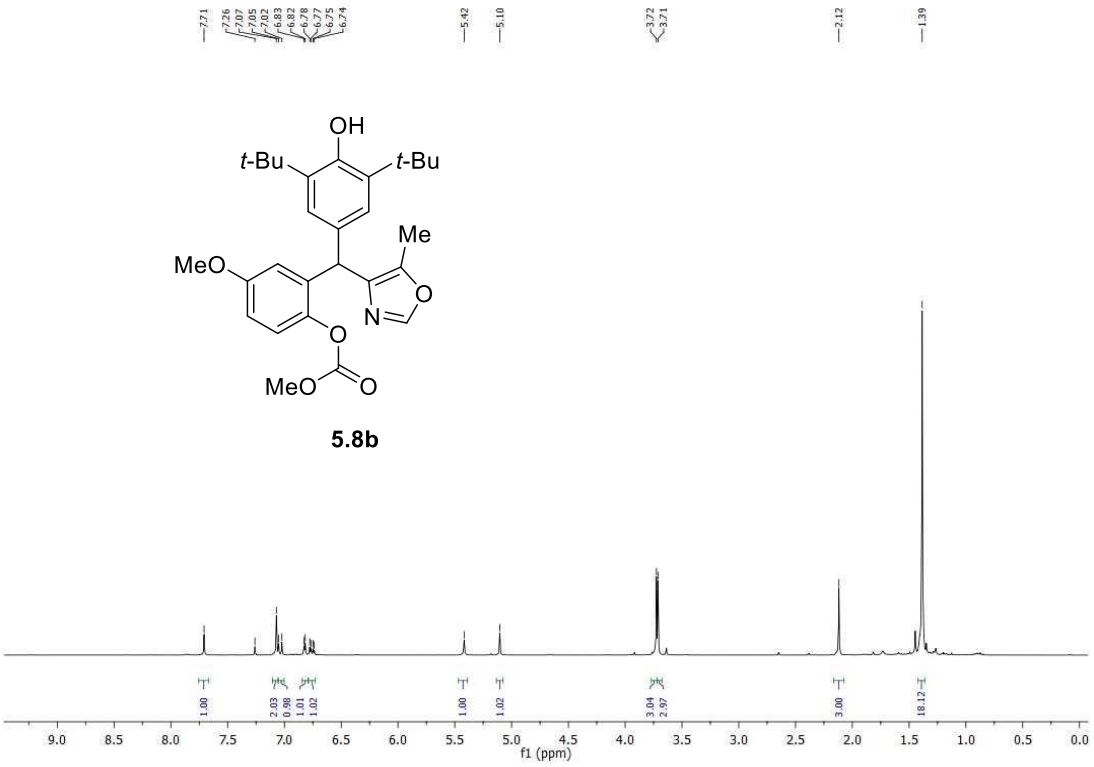
5.6o


7.71
7.29
7.26
7.23
7.23
7.21
7.21
7.19
7.19
7.14
7.12
7.05
5.49
5.11
3.74
2.12
1.38
OH
t-Bu
t-Bu
Me
O
N
O
MeO
O
0.97
4.60
2.05
0.99
1.00
3.00
3.00
18.15
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

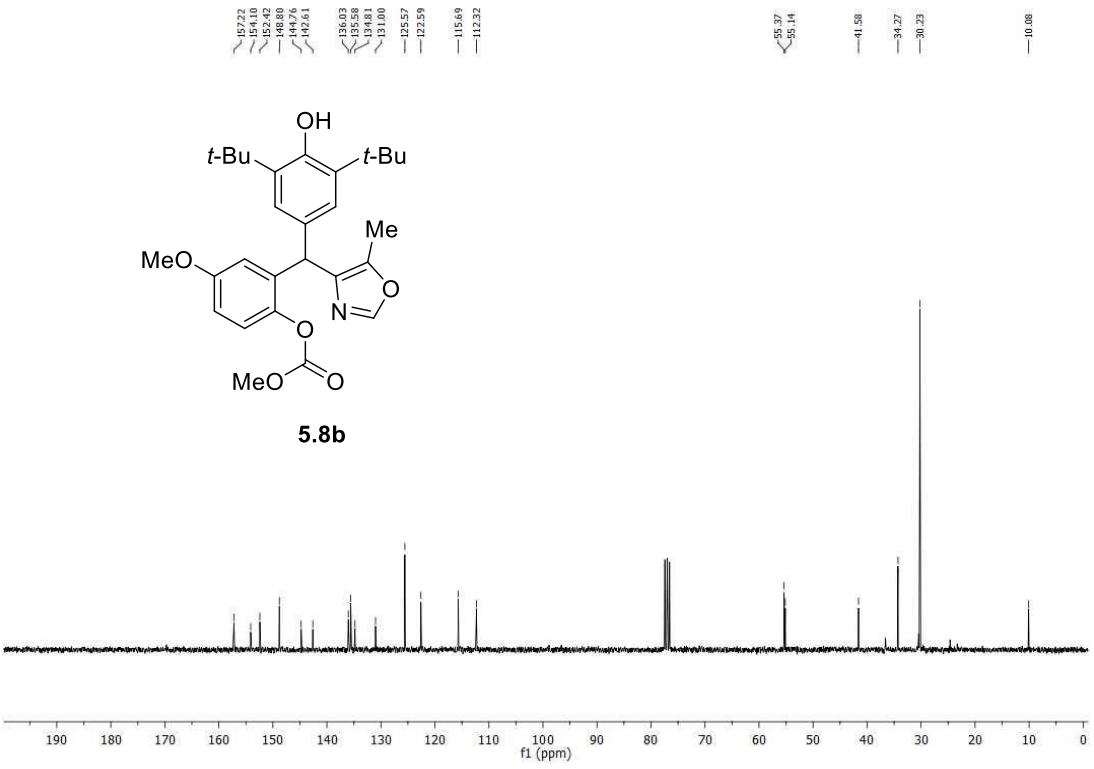
5.8a


153.75
152.37
148.82
144.77
135.57
135.00
134.88
131.24
130.25
127.51
126.13
125.59
121.89
55.19
41.31
34.28
30.22
10.07
OH
t-Bu
t-Bu
Me
O
N
O
MeO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

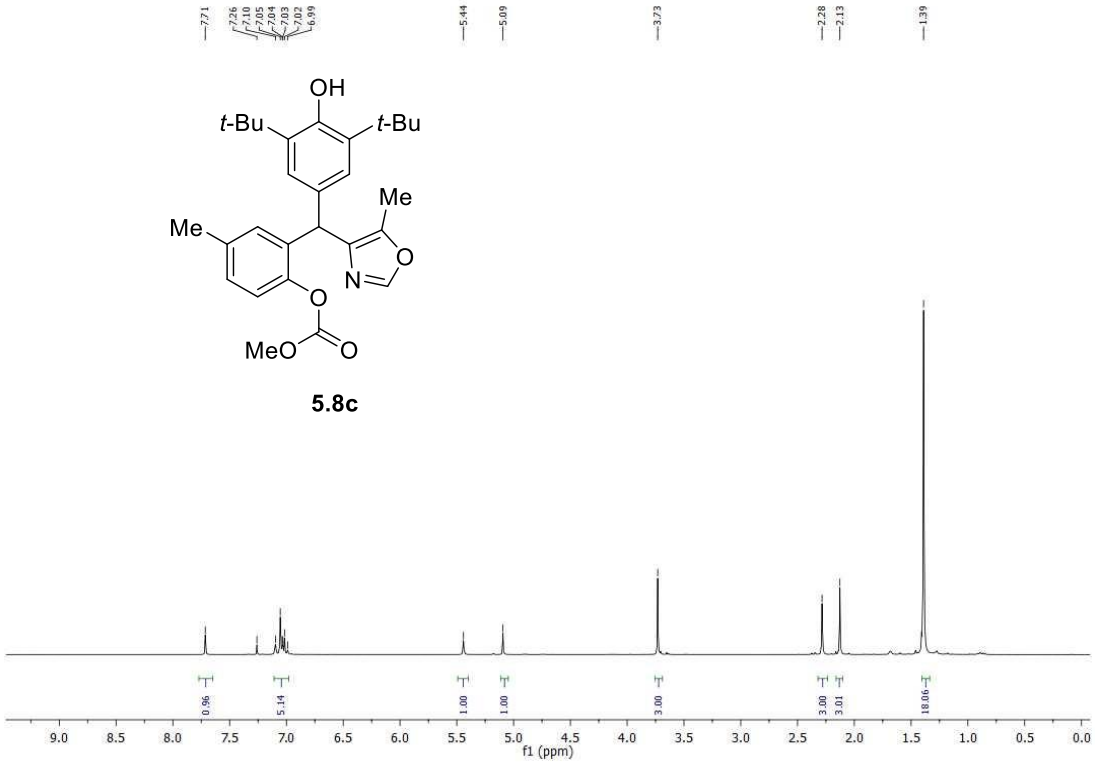
5.8a


OH
t-Bu
t-Bu
Me
MeO
O
N
O
MeO
O
f1 (ppm)

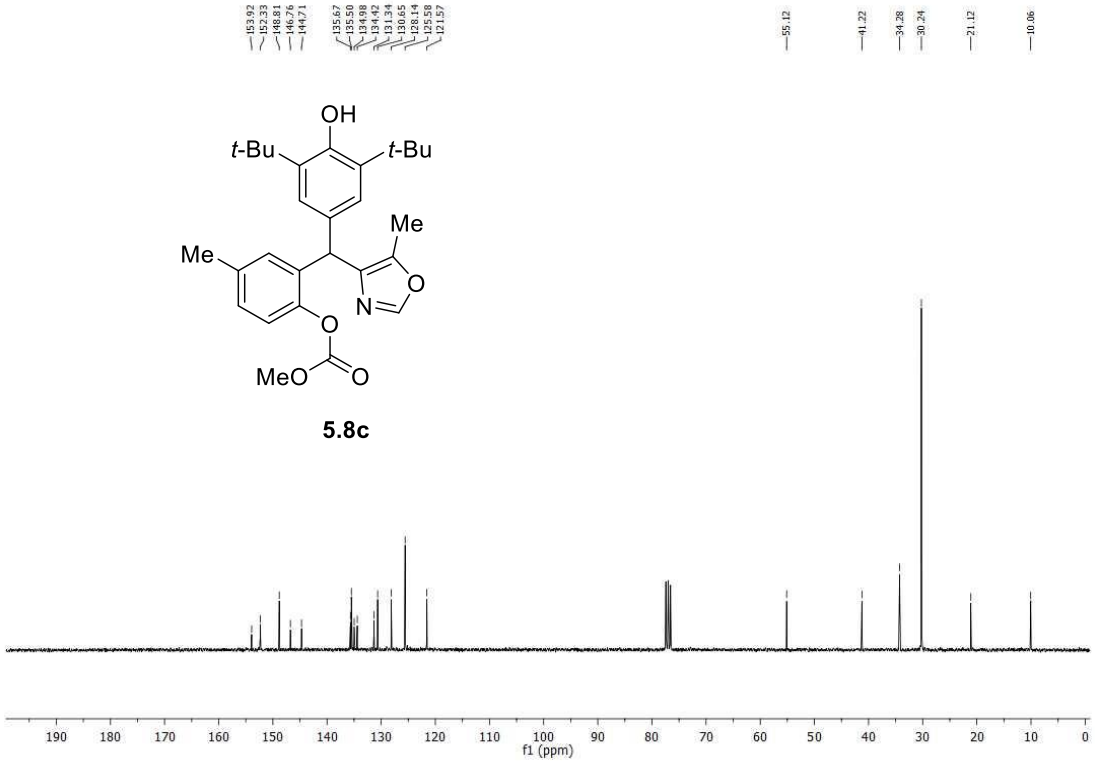
5.8b


OH
t-Bu
t-Bu
Me
MeO
O
N
O
MeO
O
f1 (ppm)

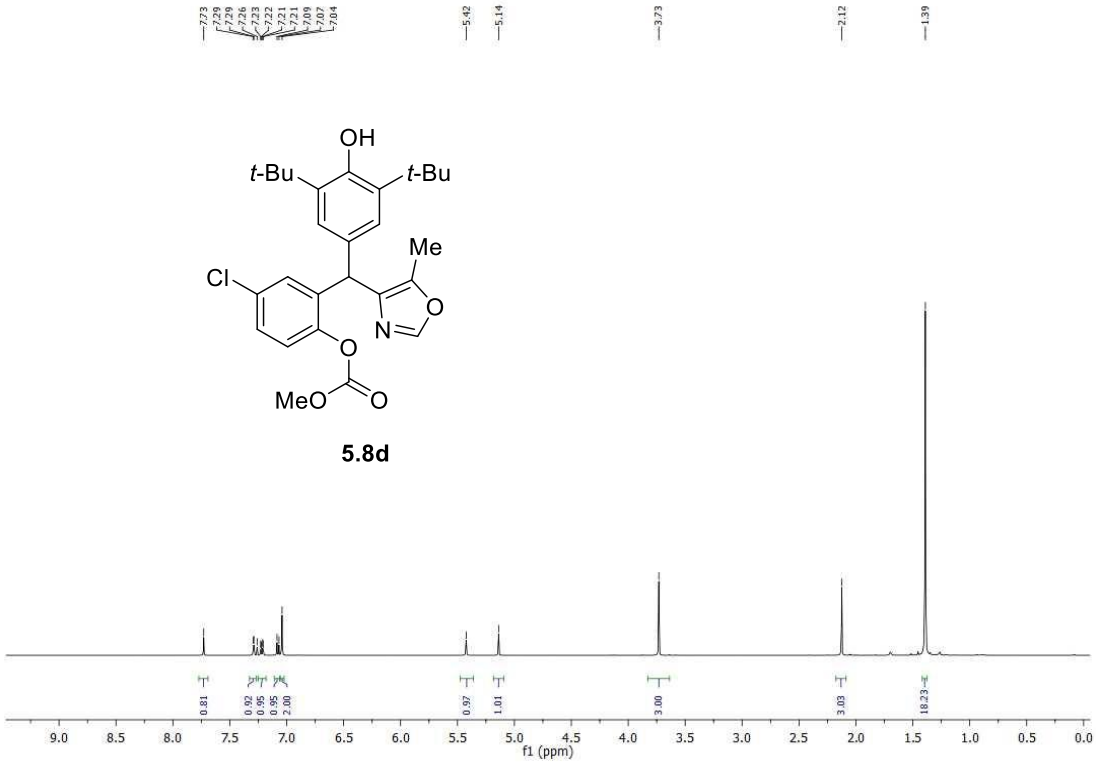
5.8b


7.71
7.26
7.10
7.05
7.04
7.03
7.02
6.99
5.44
5.09
3.73
2.28
2.13
1.39
OH
t-Bu
t-Bu
Me
Me
O
N
O
MeO
O
0.96
5.14
1.00
1.00
3.00
3.00
3.01
18.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

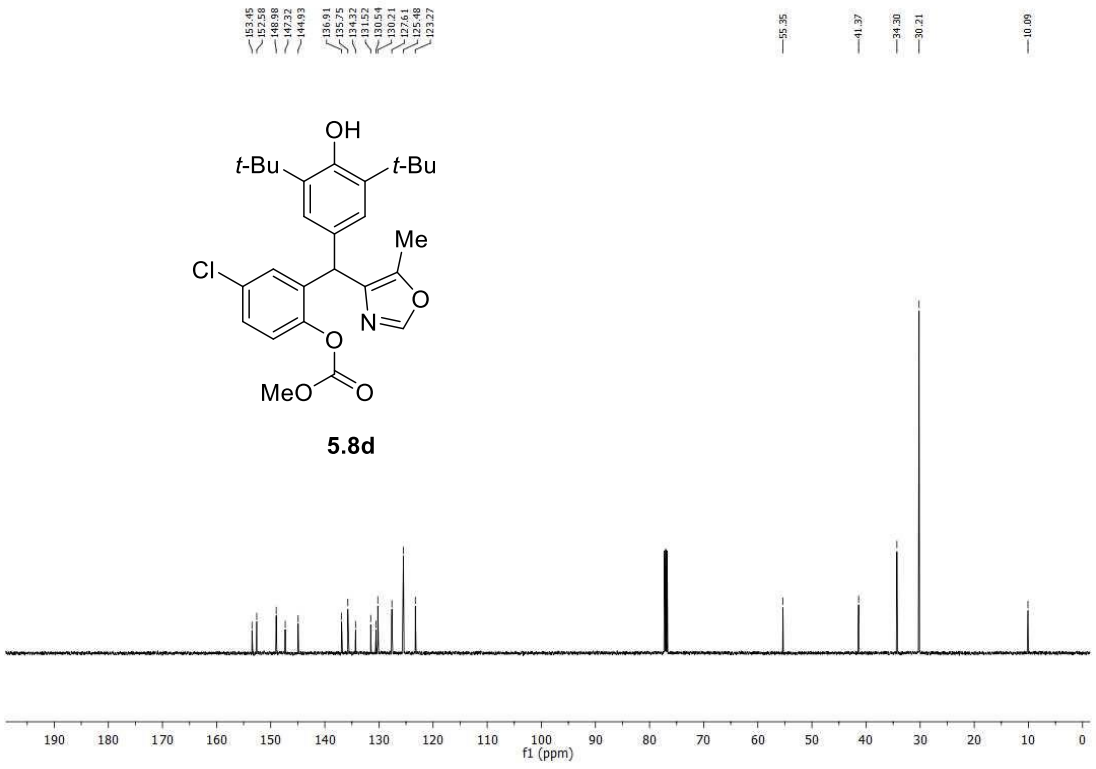
5.8c


153.92
152.33
148.81
146.76
144.71
135.67
135.50
134.98
134.42
131.34
130.65
128.14
125.58
121.57
55.12
41.22
34.28
30.24
21.12
10.06
OH
t-Bu
t-Bu
Me
Me
O
N
O
MeO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

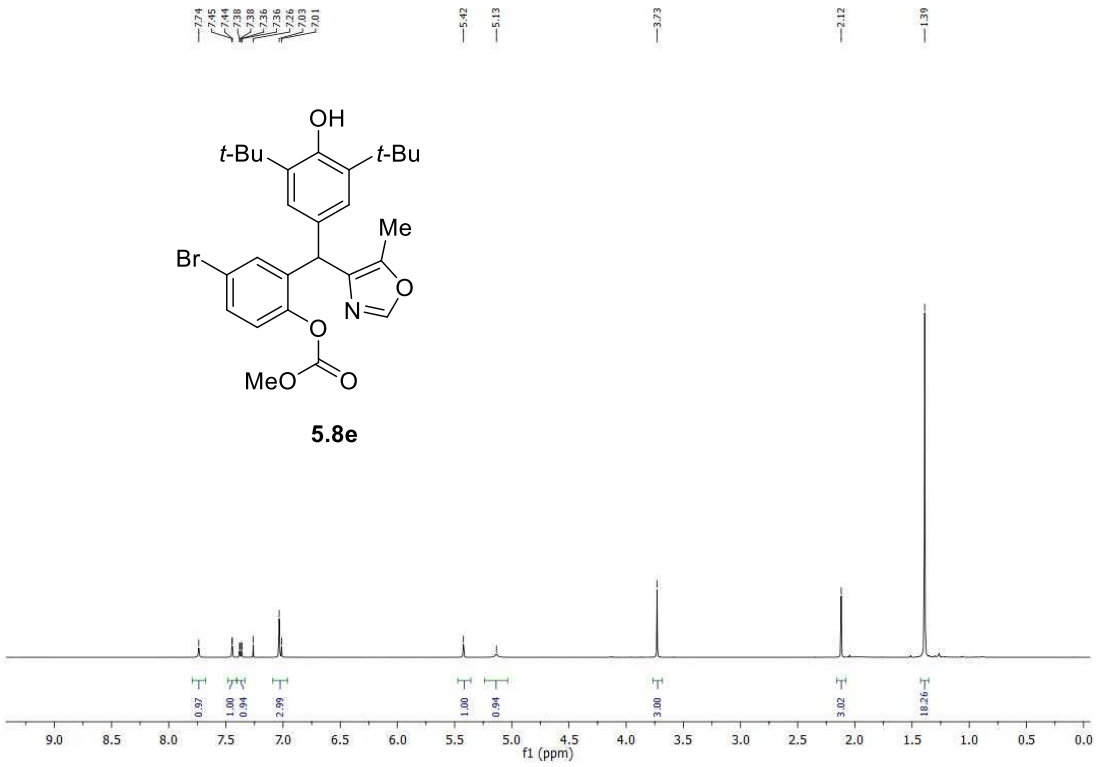
5.8c


7.73
7.29
7.29
7.26
7.23
7.22
7.21
7.21
7.09
7.07
7.04
5.42
5.14
3.73
2.12
1.39
OH
t-Bu
t-Bu
Me
Cl
O
N
O
MeO
O
0.81
0.92
0.95
0.95
2.00
0.97
1.01
3.00
3.03
18.23
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

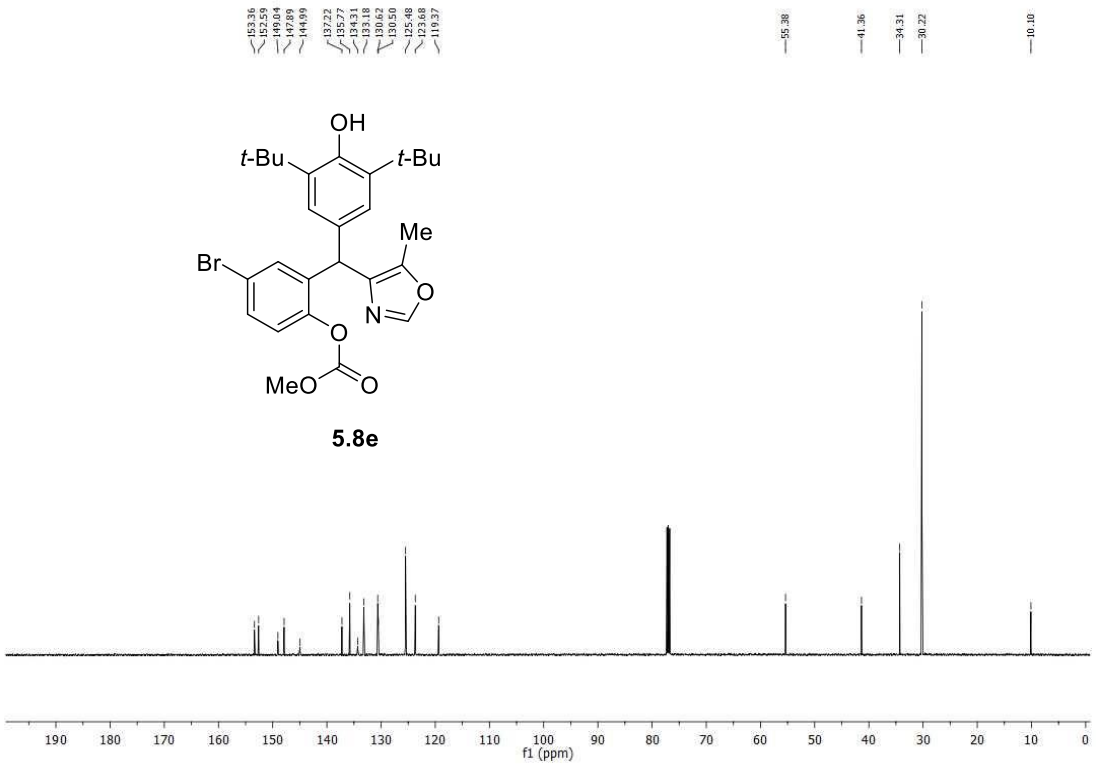
5.8d


153.45
152.58
148.98
147.22
144.93
136.91
135.75
134.32
131.52
130.54
130.21
127.61
125.48
123.27
55.35
41.37
34.30
30.21
10.09
OH
t-Bu
t-Bu
Me
Cl
O
N
O
MeO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

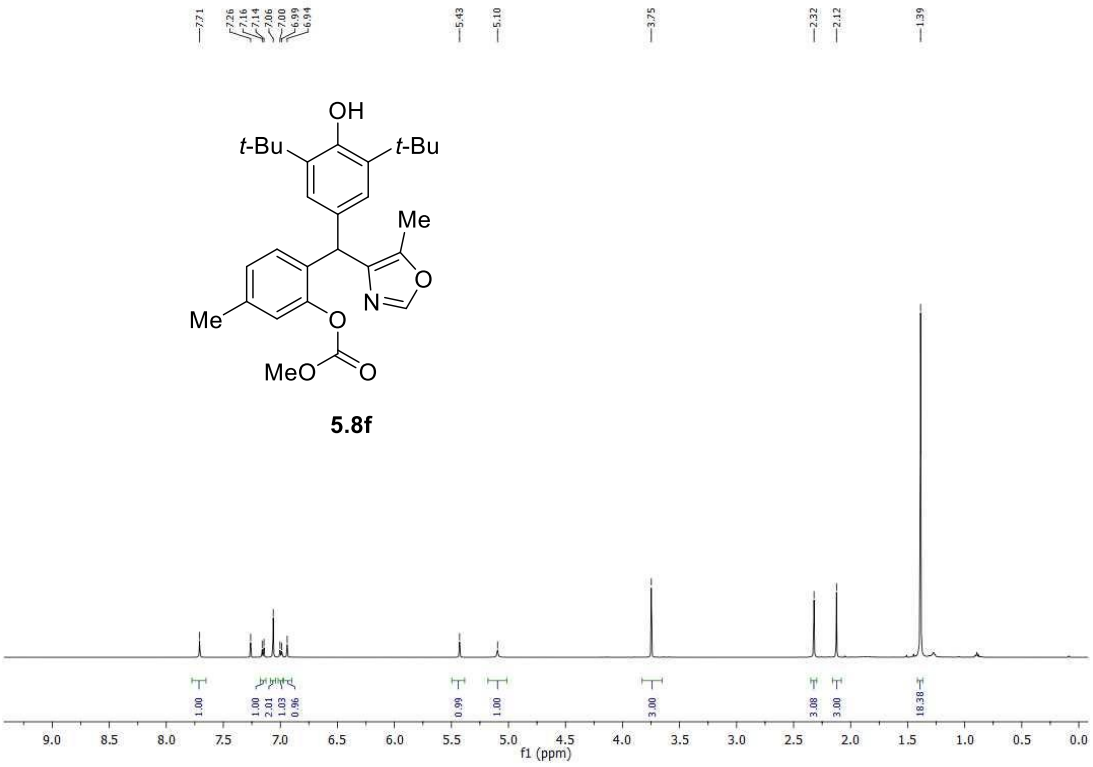
5.8d


7.74
7.45
7.44
7.38
7.38
7.36
7.36
7.26
7.03
7.01
5.42
5.13
3.73
2.12
1.39
OH
t-Bu
t-Bu
Me
Br
O
N
O
MeO
O
0.97
1.00
0.94
2.99
1.00
0.94
3.00
3.02
18.26
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

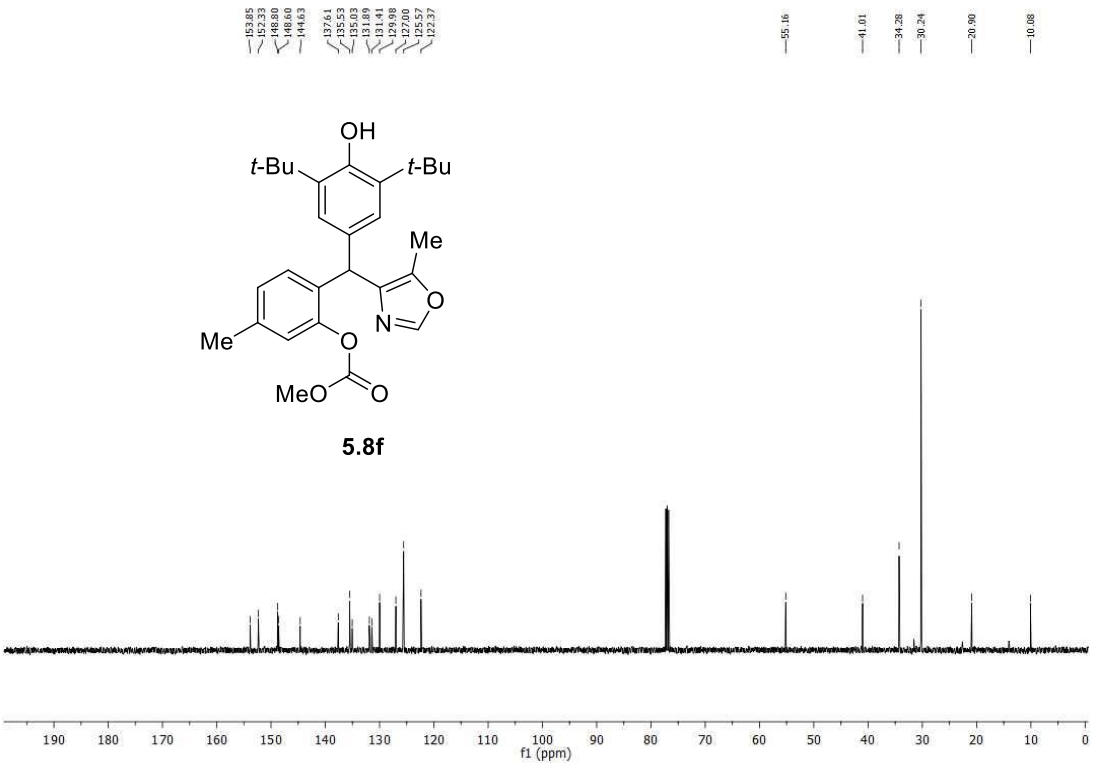
5.8e


153.36
152.59
149.04
147.89
144.99
137.22
135.77
134.31
133.18
130.62
130.50
125.48
123.68
119.37
55.38
41.36
34.31
30.22
10.10
OH
t-Bu
t-Bu
Me
Br
O
N
O
MeO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

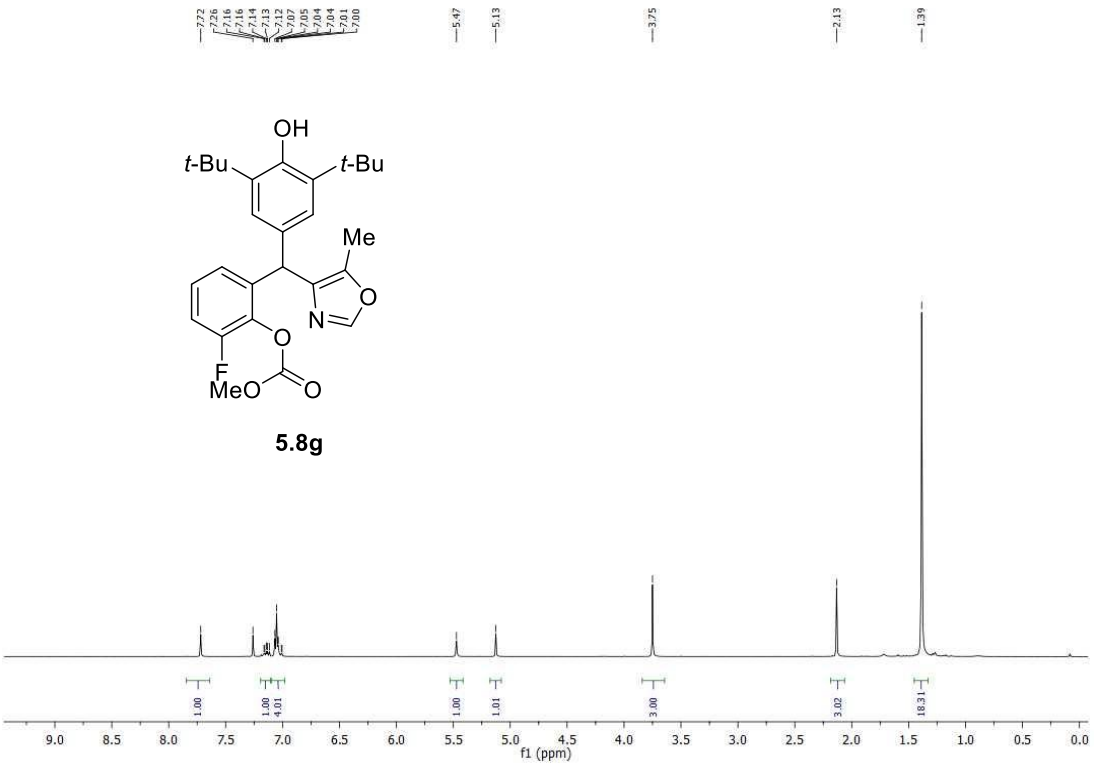
5.8e


7.71
7.26
7.16
7.14
7.06
7.00
6.99
6.94
5.43
5.10
3.75
2.32
2.12
1.39
OH
t-Bu
t-Bu
Me
O
N
Me
O
MeO
O
1.00
1.00
2.01
1.03
0.96
0.99
1.00
3.00
3.08
3.00
18.38
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

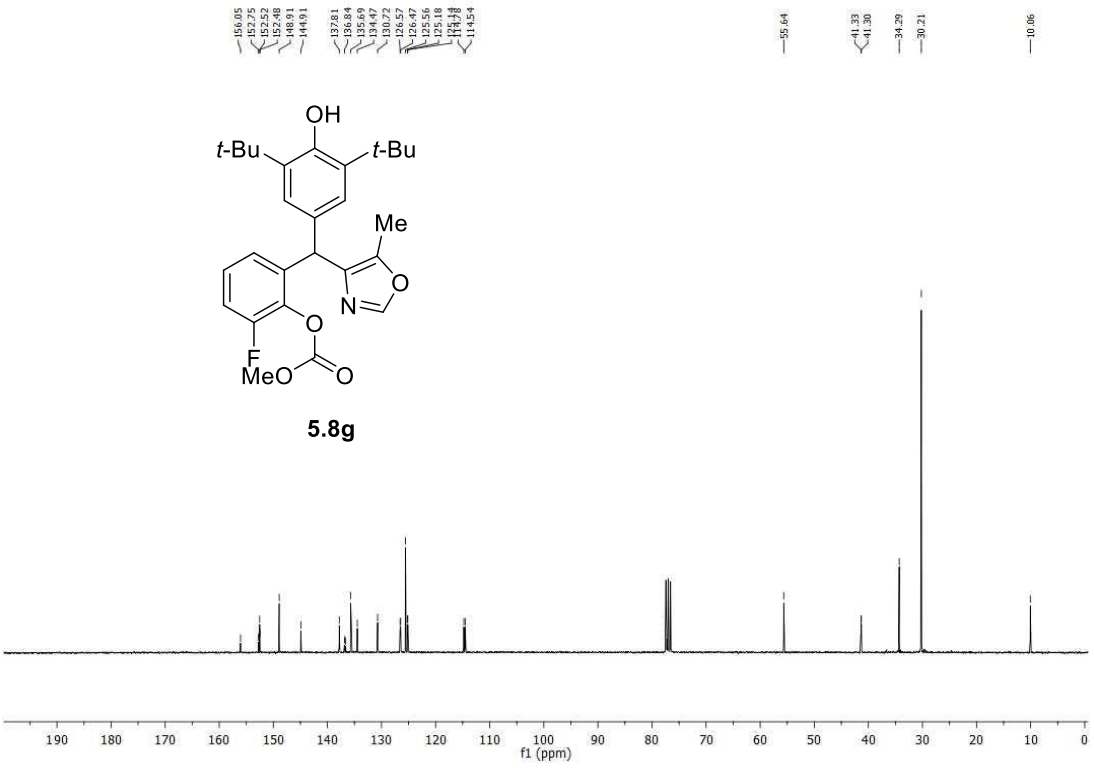
5.8f


153.85
152.33
148.80
148.60
144.63
137.61
135.53
135.03
131.89
131.41
129.98
127.00
125.57
122.37
55.16
41.01
34.28
30.24
20.90
10.08
OH
t-Bu
t-Bu
Me
O
N
Me
O
MeO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

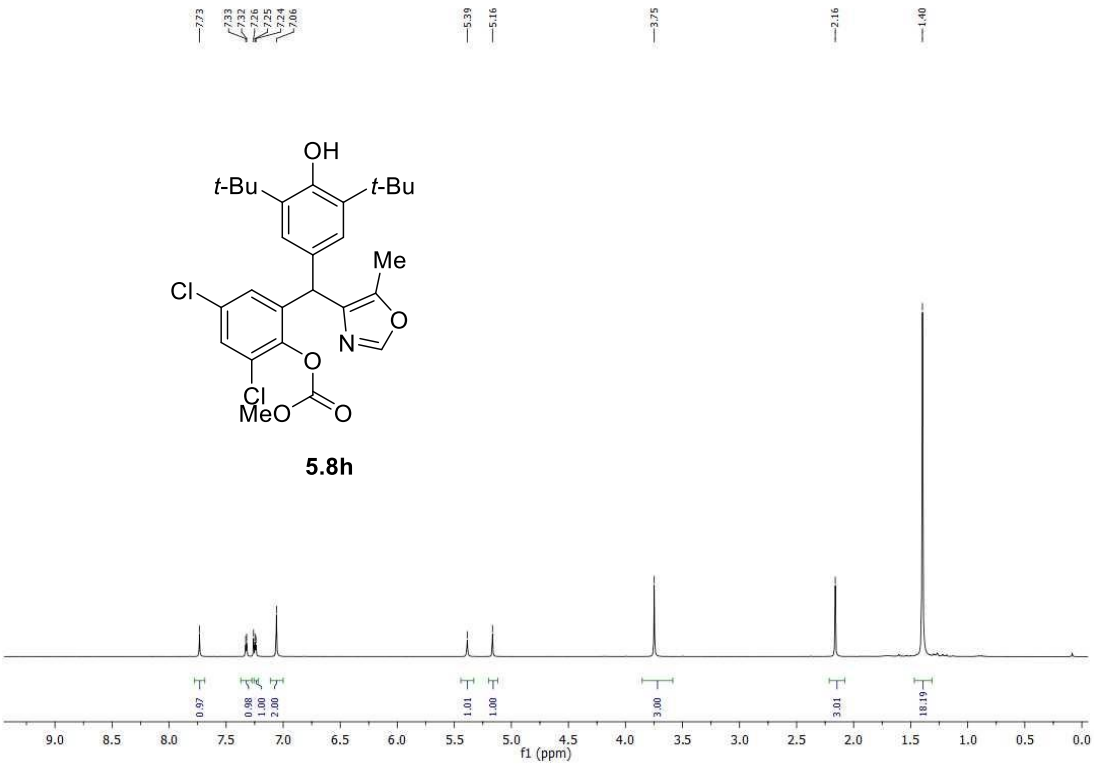
5.8f


OH
t-Bu
t-Bu
Me
O
N
O
F
MeO
O
7.22
7.26
7.16
7.14
7.13
7.12
7.07
7.05
7.04
7.04
7.01
7.00
5.47
5.13
3.75
2.13
1.39
1.00
1.00
4.01
1.00
1.01
3.00
3.02
18.31
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

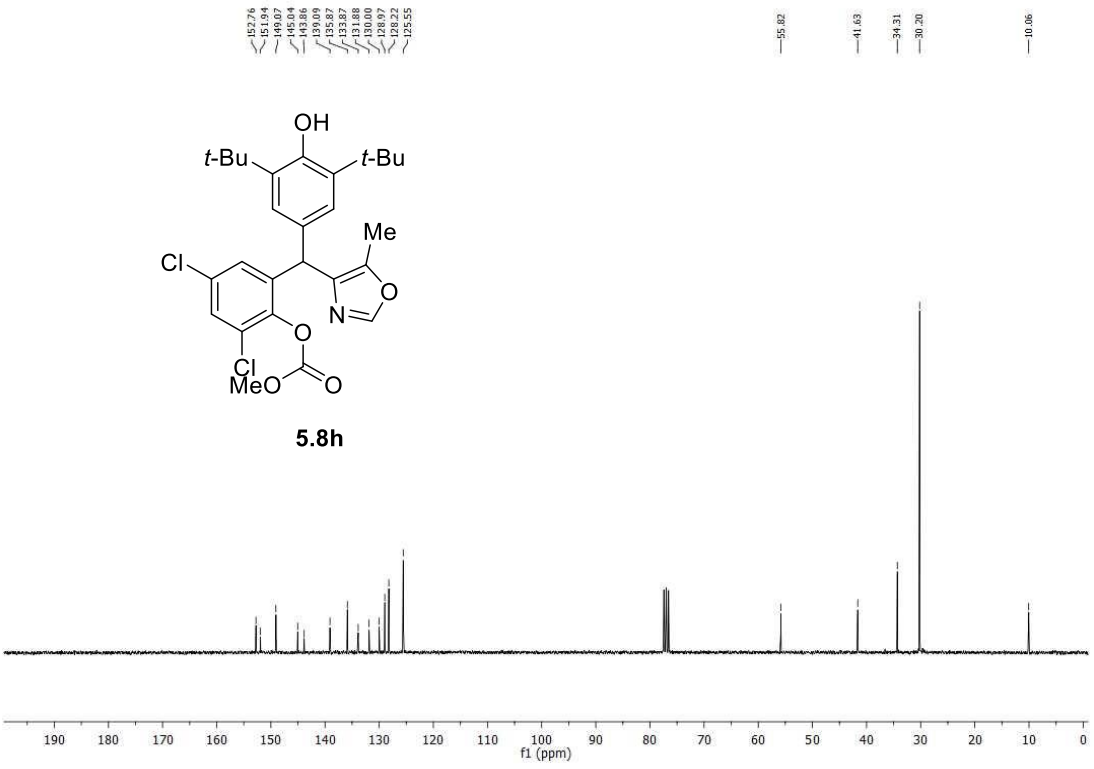
5.8g


156.05
152.75
152.52
152.48
148.91
144.91
137.81
136.84
135.69
134.47
130.72
126.57
126.47
125.56
125.18
124.78
114.54
55.64
41.33
41.30
34.29
30.21
10.06
OH
t-Bu
t-Bu
Me
O
N
O
F
MeO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

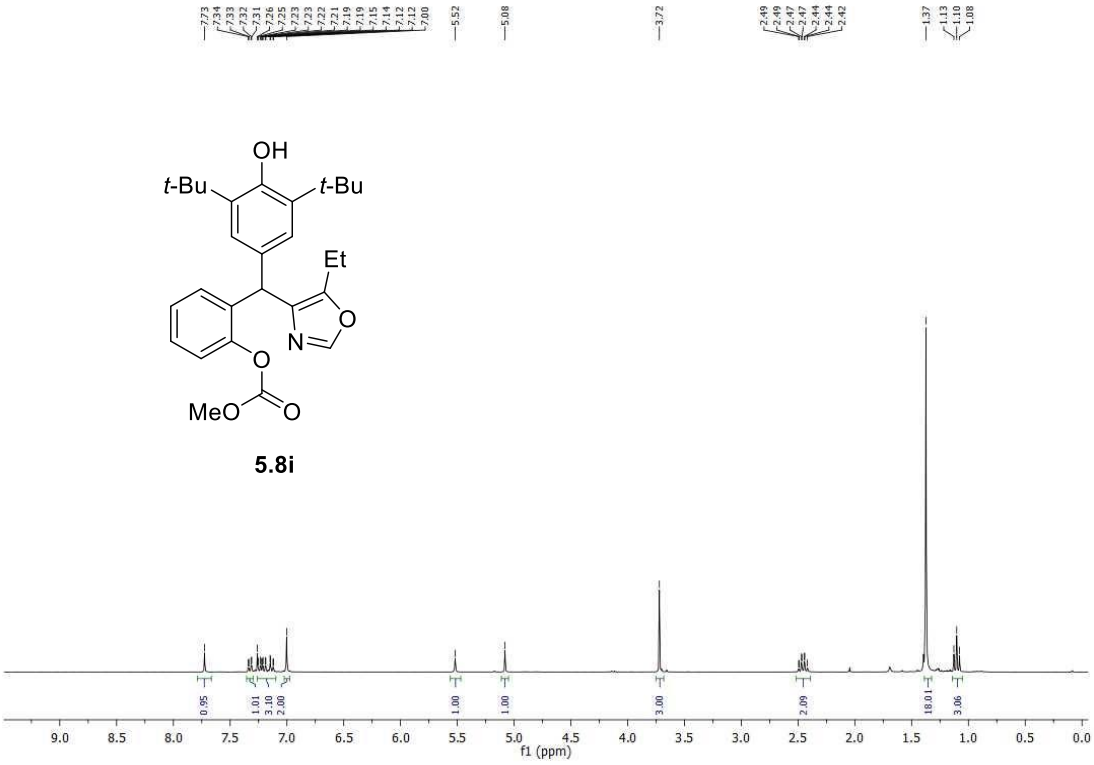
5.8g

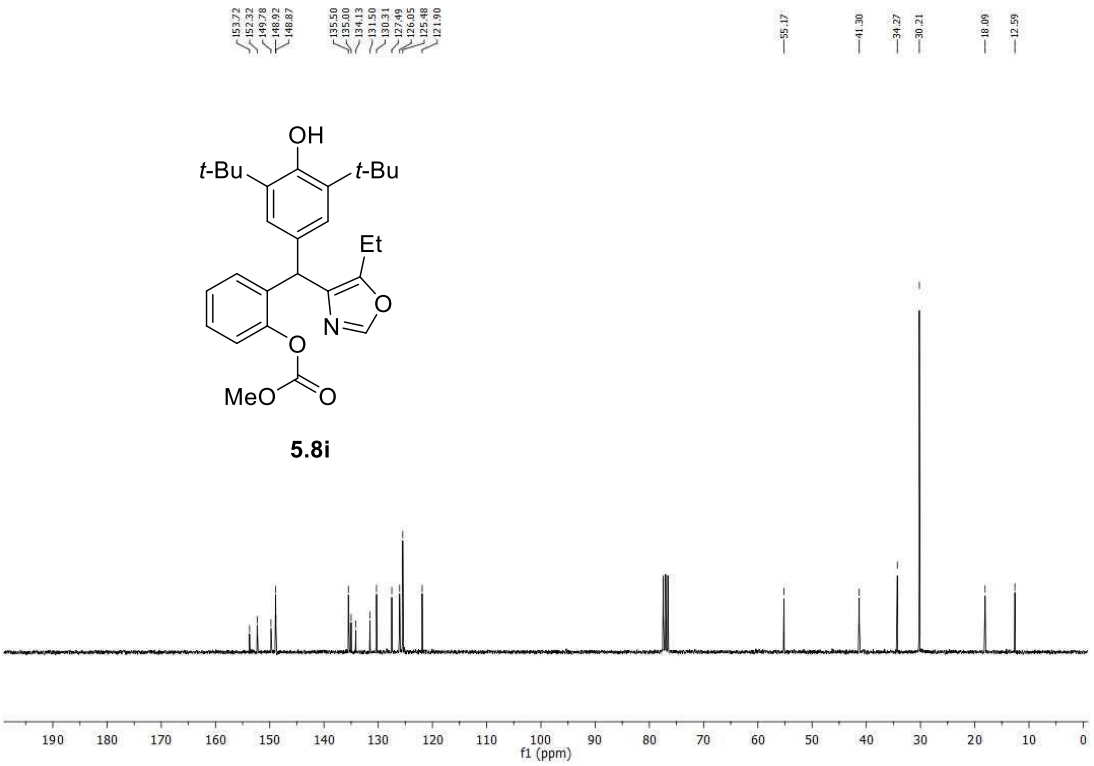

7.73
7.33
7.32
7.26
7.25
7.24
7.06
5.39
5.16
3.75
2.16
1.40
OH
t-Bu
t-Bu
Me
Cl
O
N
O
Cl
MeO
O
0.97
0.98
1.00
2.00
1.01
1.00
3.00
3.01
18.19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

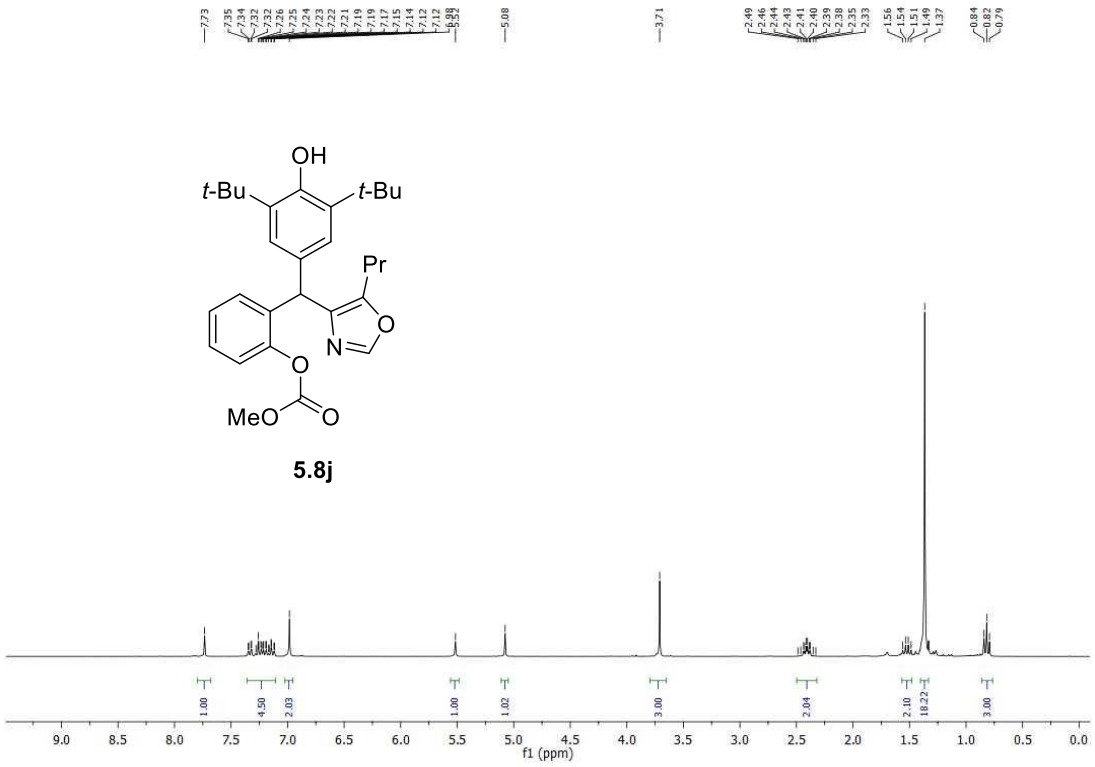
5.8h


152.76
151.94
149.07
145.04
143.86
139.09
135.87
133.87
131.68
130.00
128.97
128.22
125.55
55.82
41.63
34.31
30.20
10.06
OH
t-Bu
t-Bu
Me
Cl
O
N
O
Cl
MeO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

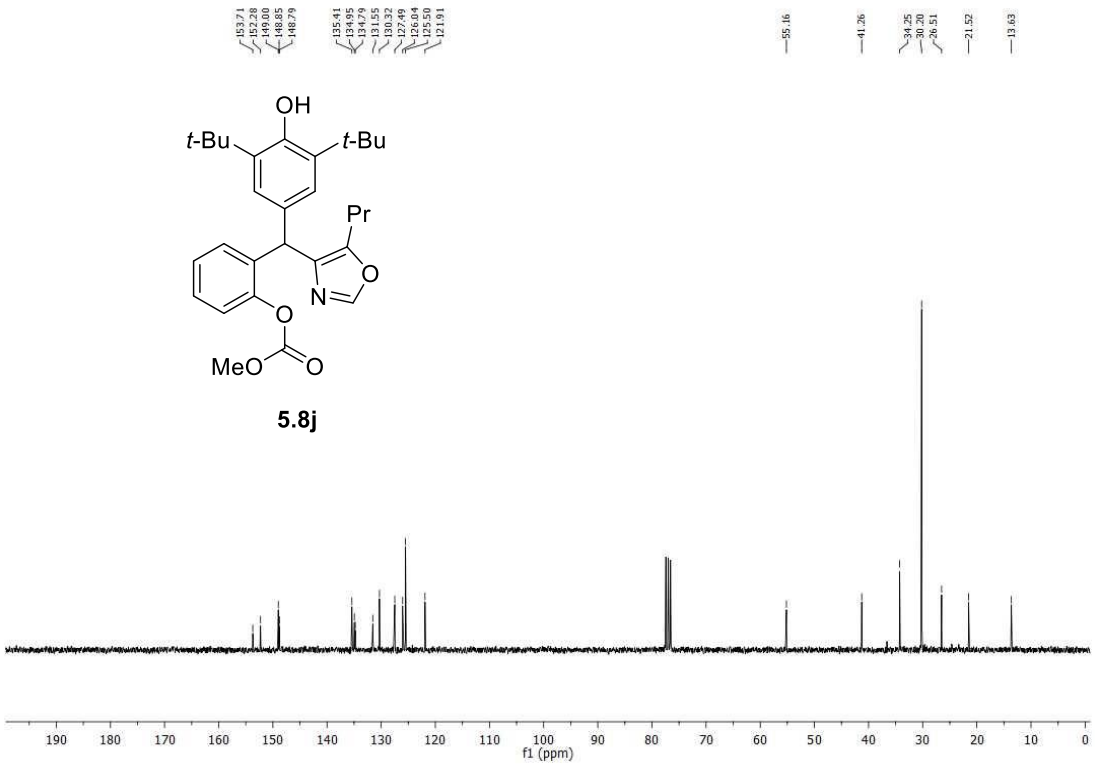
5.8h


OH
t-Bu
t-Bu
Et
O
N
O
MeO
O
5.8i
f1 (ppm)

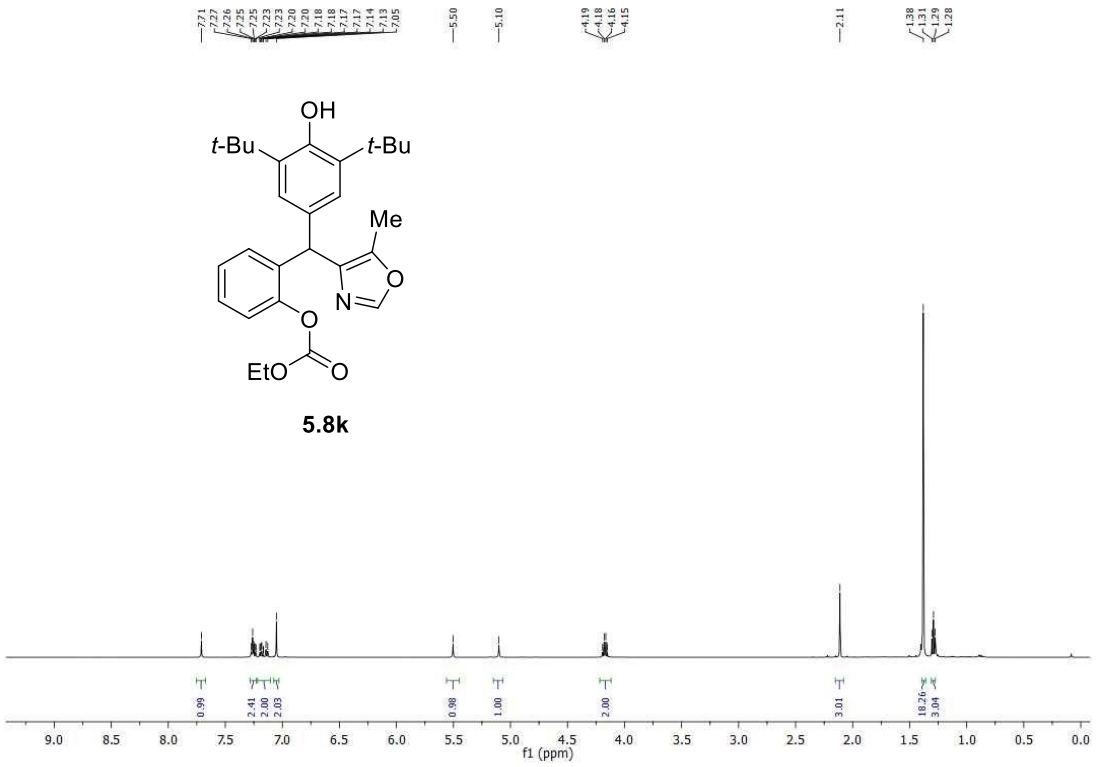

OH
t-Bu
t-Bu
Et
O
N
O
MeO
O
5.8i
f1 (ppm)



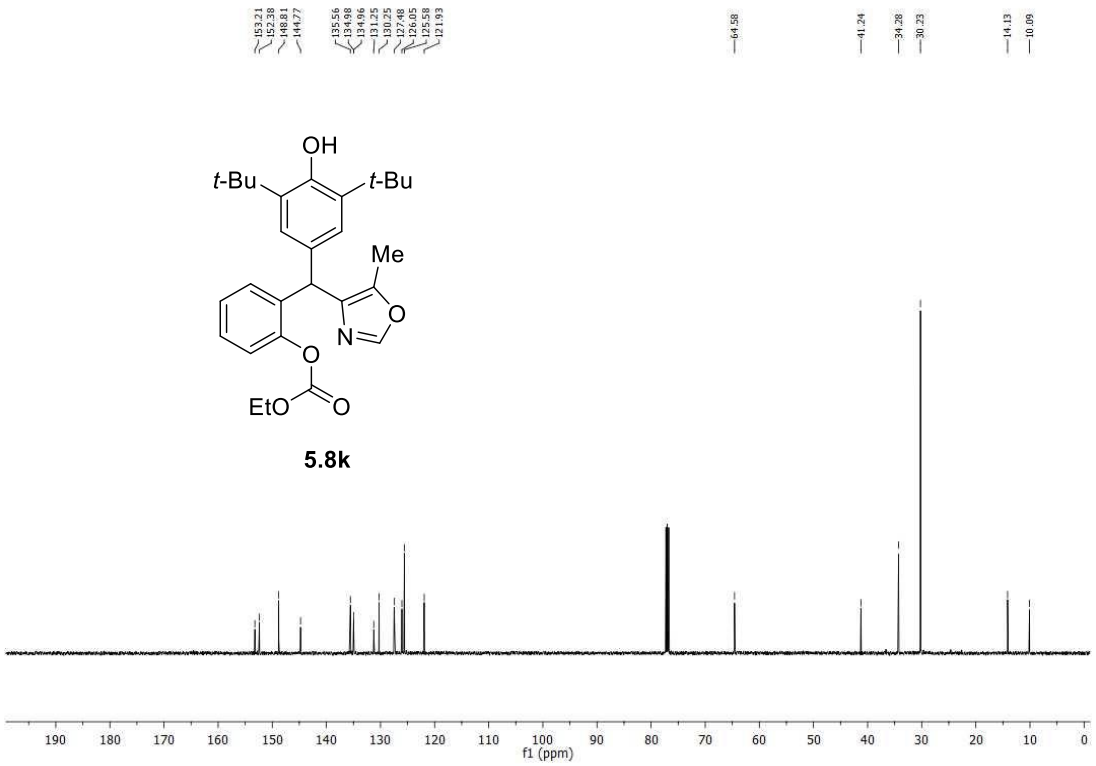
5.8j



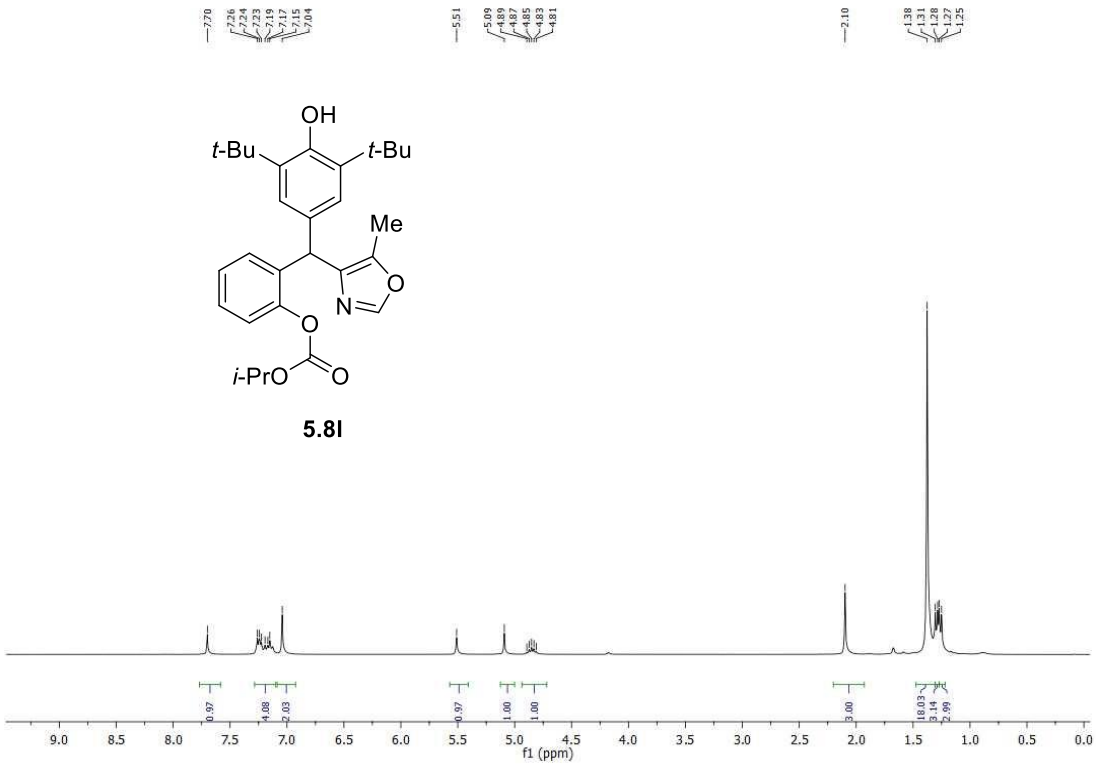
5.8j



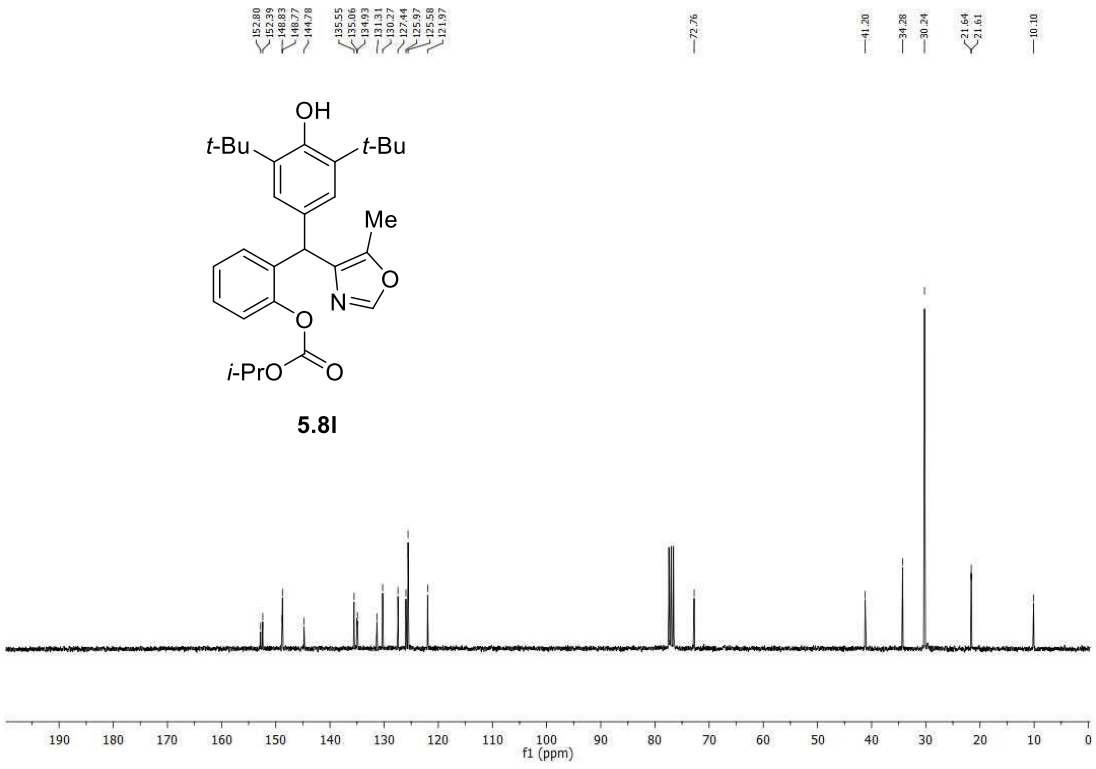
5.8k



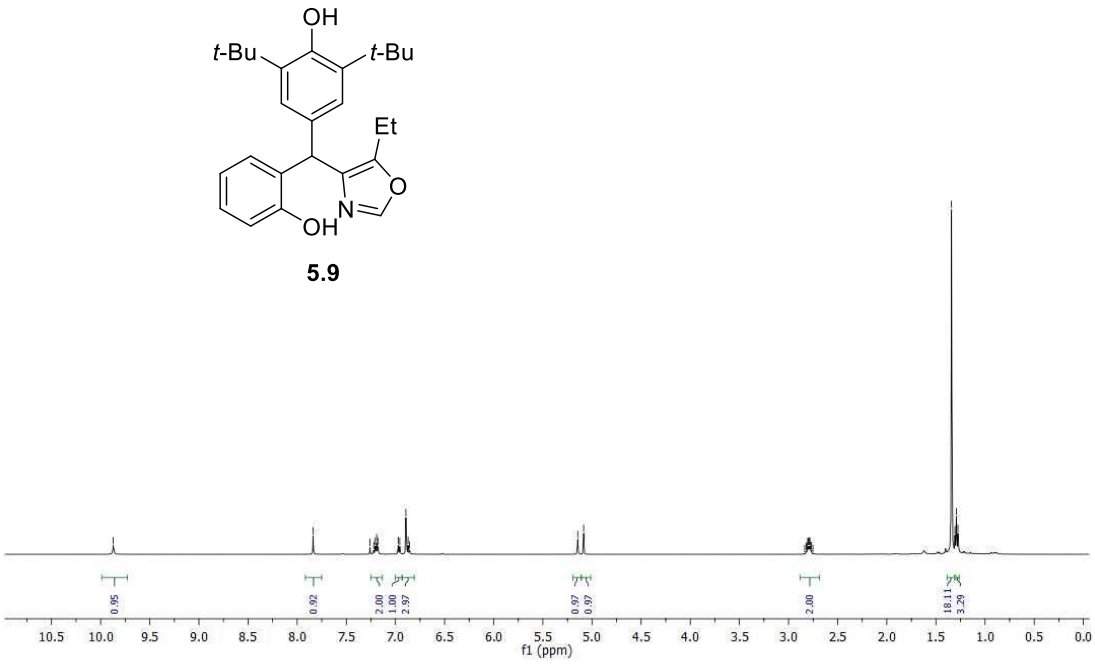
5.8k


7.70
7.26
7.24
7.23
7.19
7.17
7.15
7.04
5.51
5.09
4.89
4.87
4.85
4.83
4.81
2.10
1.38
1.31
1.28
1.27
1.25
OH
t-Bu
t-Bu
Me
O
N
O
i-PrO
O
0.97
4.08
2.03
0.97
1.00
1.00
3.00
18.03
3.14
2.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

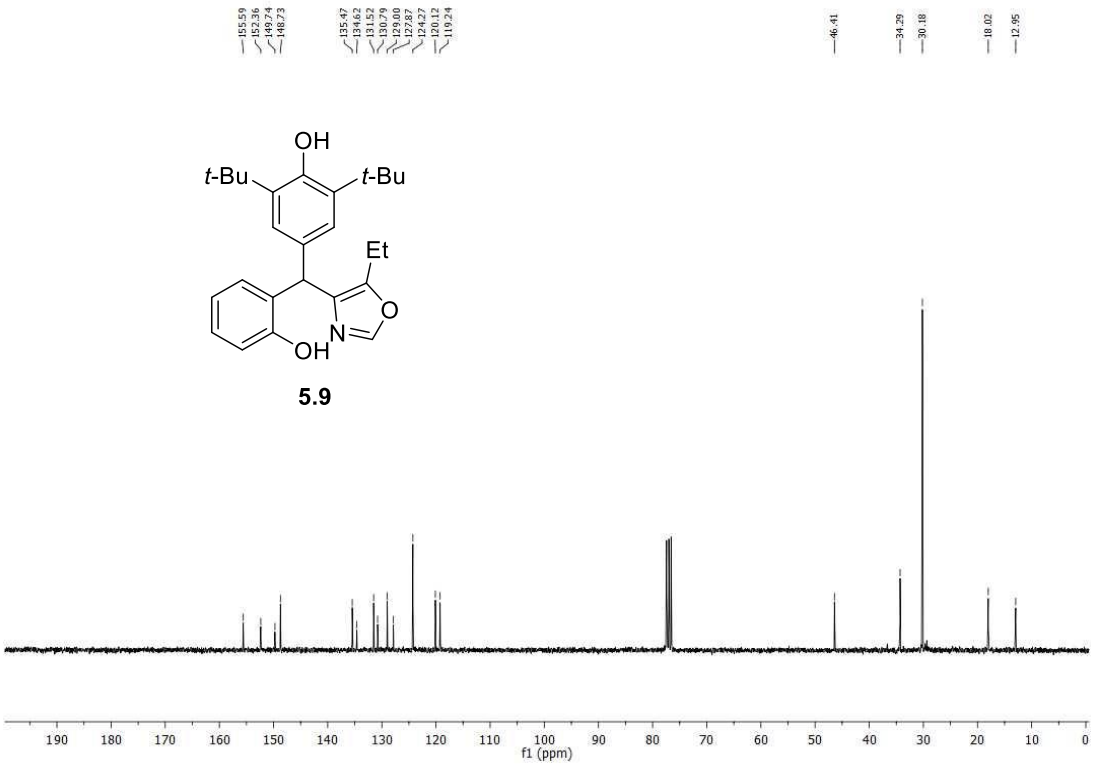
5.8l


152.80
152.39
148.83
148.77
144.78
135.55
135.06
134.93
131.31
130.27
127.44
125.97
125.58
121.97
72.76
41.20
34.28
30.24
21.64
21.61
10.10
OH
t-Bu
t-Bu
Me
O
N
O
i-PrO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

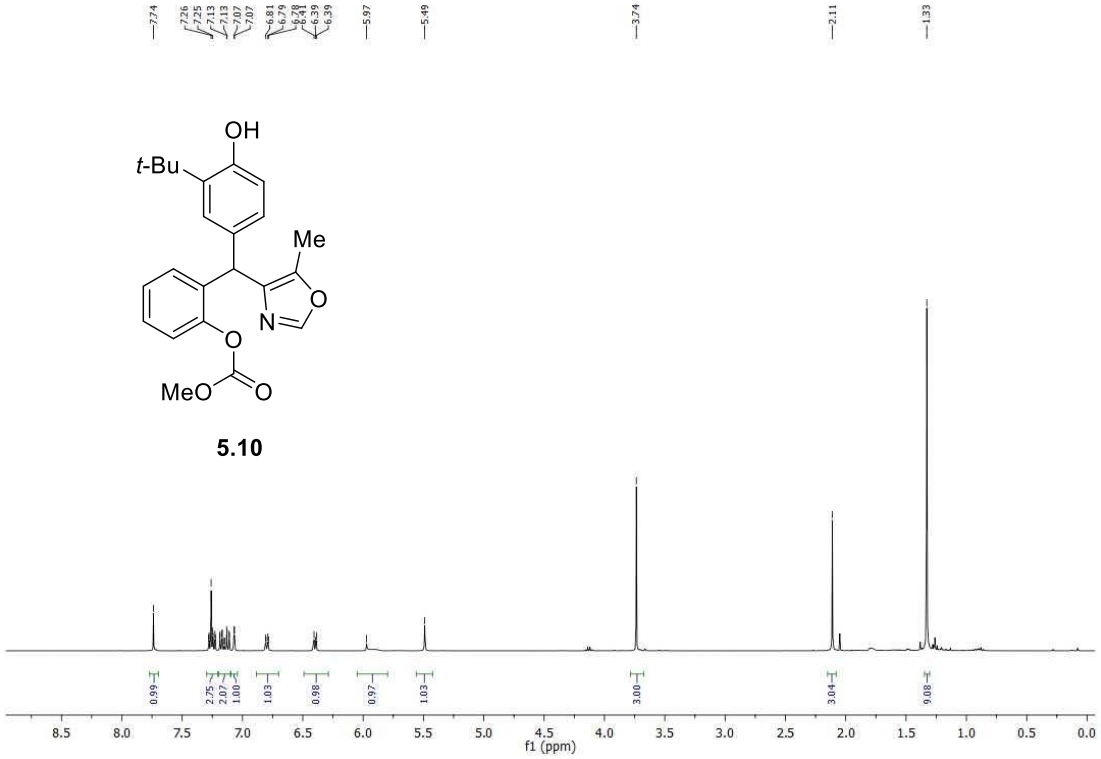
5.8l


9.87
7.84
7.26
7.22
7.21
7.19
7.18
6.97
6.96
6.89
6.87
6.86
5.15
5.09
2.84
2.82
2.81
2.80
2.80
2.79
2.78
2.78
2.77
2.75
1.34
1.31
1.29
1.28
OH
t-Bu
t-Bu
Et
O
N
OH
0.95
0.92
2.00
1.00
2.97
0.97
0.97
2.00
18.11
3.29
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

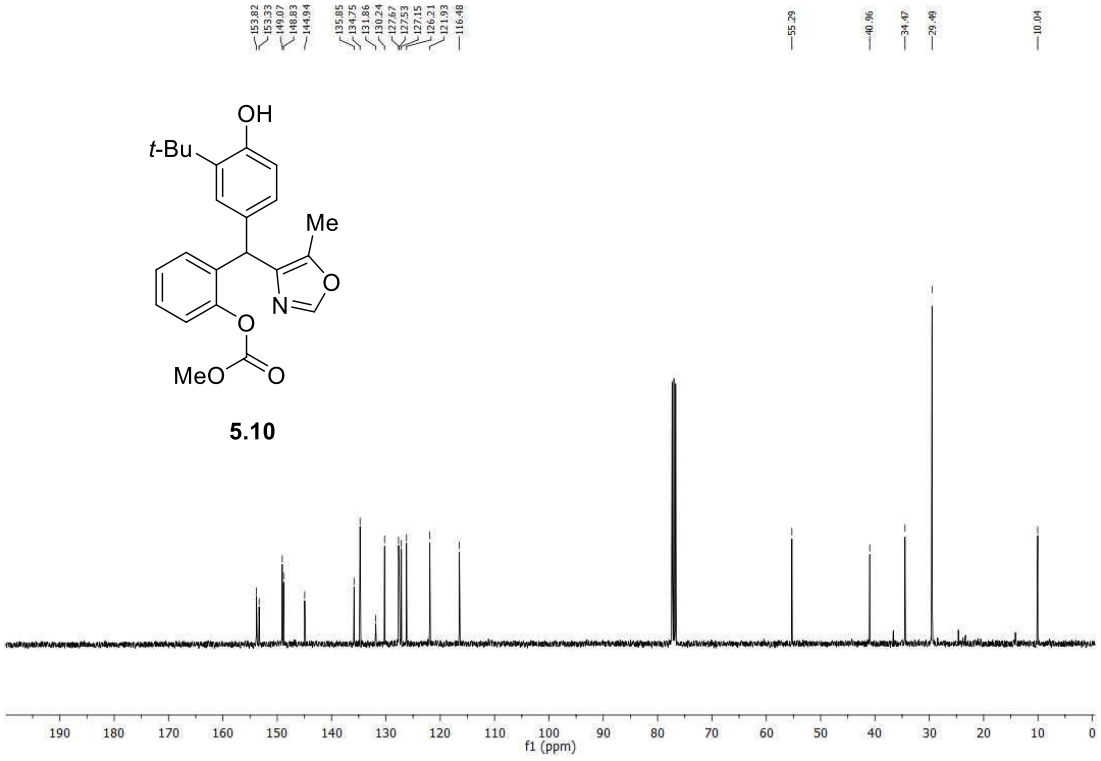
5.9


155.59
153.36
149.74
148.73
135.47
134.62
131.52
130.79
130.00
127.87
124.27
120.12
119.24
46.41
34.29
30.18
18.02
12.95
OH
t-Bu
t-Bu
Et
O
N
OH
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

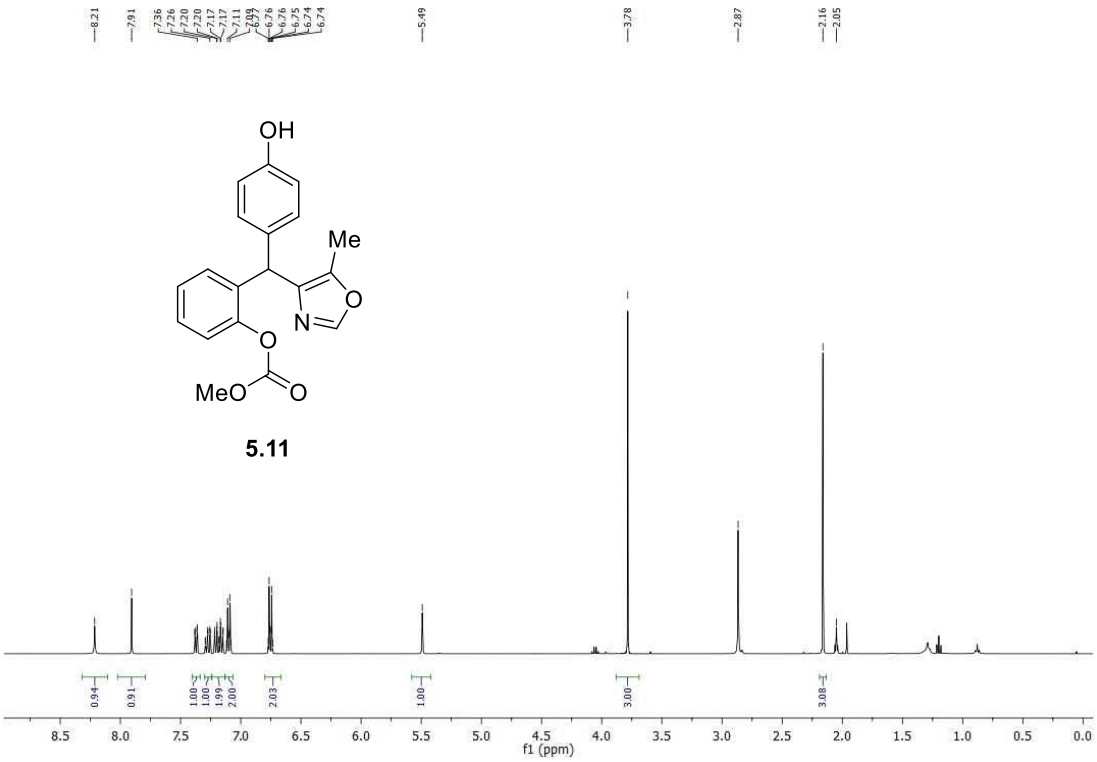
5.9


7.74
7.26
7.25
7.13
7.13
7.07
7.07
6.81
6.79
6.28
6.28
6.39
6.39
5.97
5.49
3.74
2.11
1.33
OH
t-Bu
Me
O
N
O
MeO
O
0.99
2.75
2.07
1.00
1.03
0.98
0.97
1.03
3.00
3.04
9.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

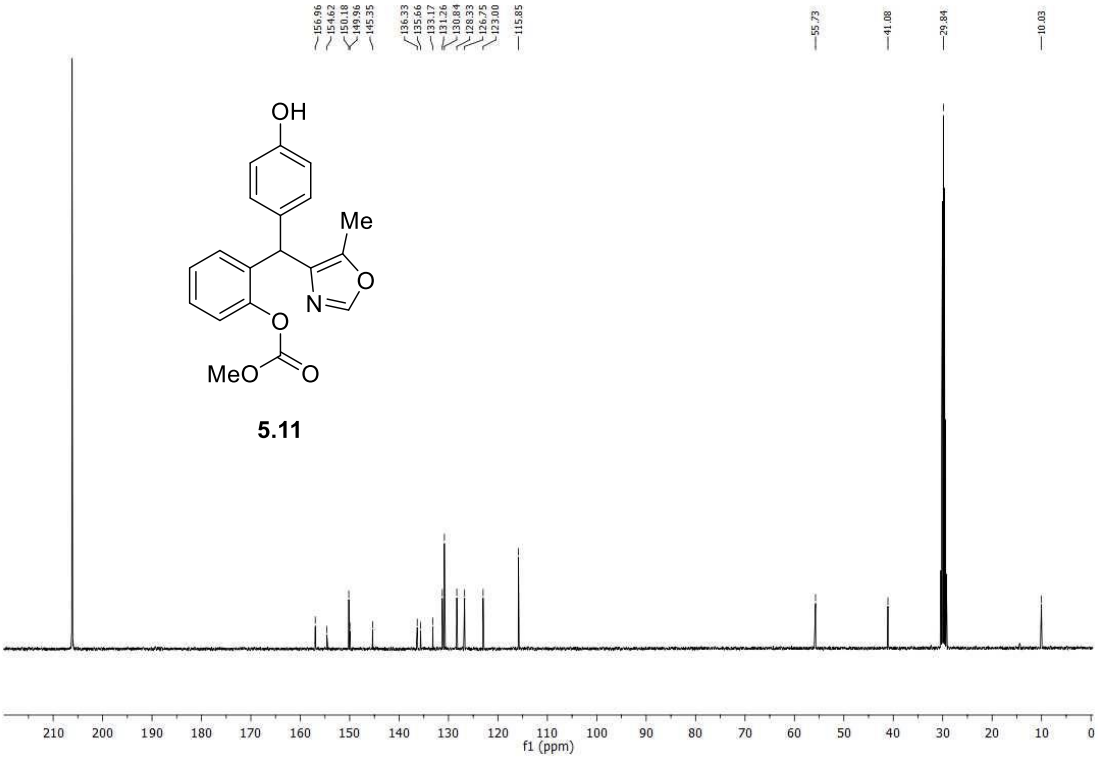
5.10


153.82
153.33
149.07
148.83
144.94
135.85
134.75
131.86
130.24
127.67
127.53
127.15
126.21
121.93
116.48
55.29
40.96
34.47
29.49
10.04
OH
t-Bu
Me
O
N
O
MeO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

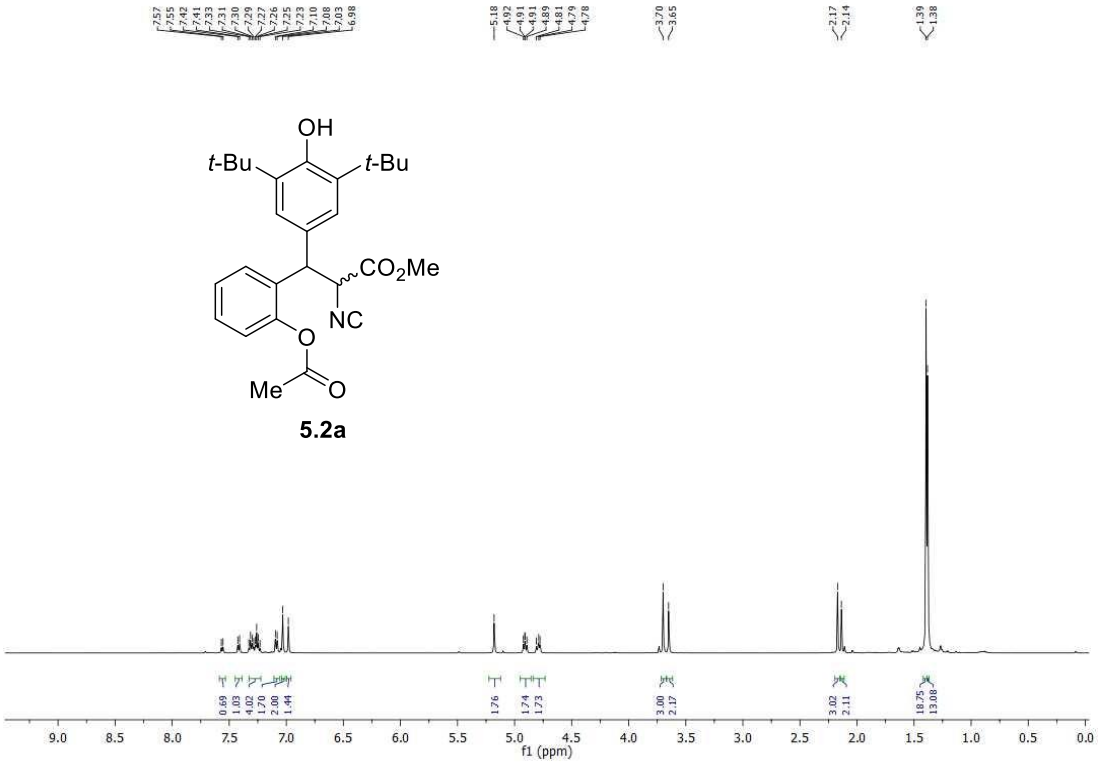
5.10


8.21
7.91
7.36
7.26
7.20
7.20
7.17
7.17
7.11
6.76
6.76
6.76
6.75
6.74
6.74
5.49
3.78
2.87
2.16
2.05
OH
Me
O
N
O
MeO
O
0.94
0.91
1.00
1.00
1.99
2.00
2.03
1.00
3.00
3.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

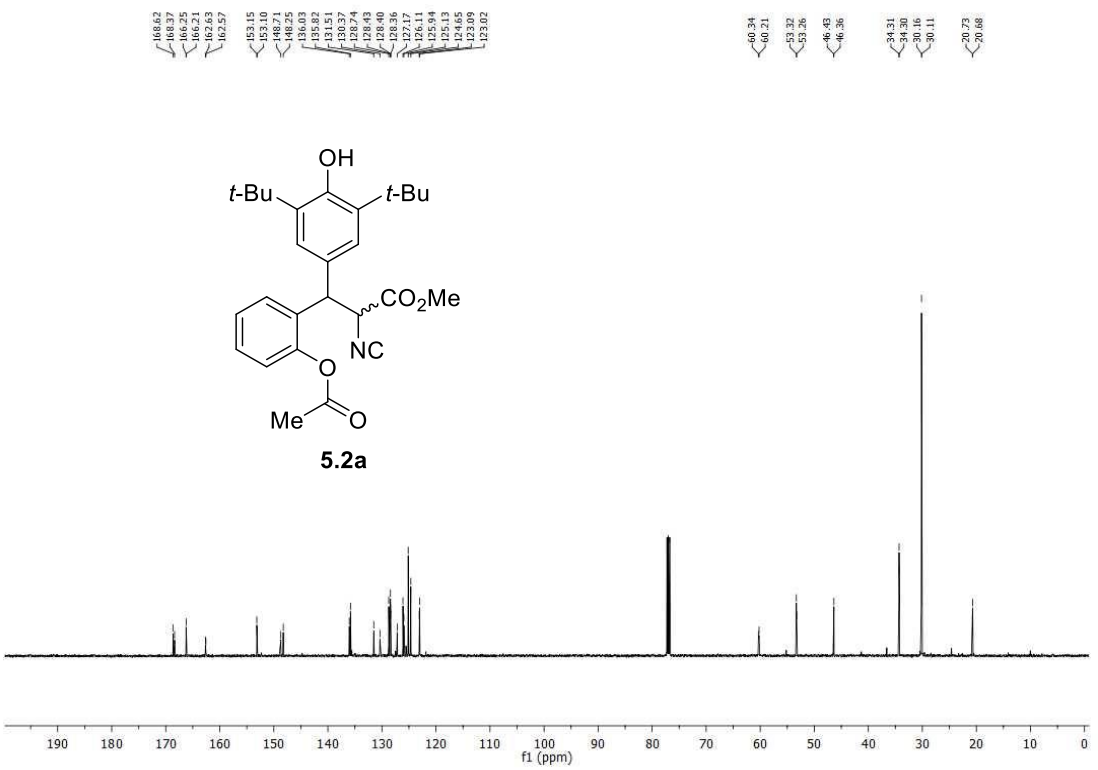
5.11


156.96
154.62
150.18
149.96
145.35
136.33
135.66
133.17
131.26
130.84
128.33
126.75
123.00
115.85
55.73
41.08
29.84
10.03
OH
Me
O
N
O
MeO
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

5.11



5.2a



5.2a