Exploring the Reactivities of Donor-Acceptor Cyclopropanes

Ph.D. Thesis

By

Braj Gopal

DEPARTMENT OF CHEMISTRY

INDIAN INSITUTE OF TECHNOLOGY ROPAR

RUPNAGAR, PUNJAB 140001, INDIA

Braj Gopal: *Exploring the Reactivities of Donor-Acceptor Cyclopropanes*

Dedicated to My Parents, My Love and My Lord Shiva

Indian Institute of Technology Ropar

Department of Chemistry

DECLARATION BY THE CANDIDATE

I, Mr. BRAJ GOPAL, hereby declare that the work presented in the thesis entitled "*Exploring the Reactivities of Donor-Acceptor Cyclopropanes*", submitted for the degree of **Doctor of Philosophy** in Chemistry to the Indian Institute of Technology Ropar, Rupnagar, India has been carried out by me under the supervision of **Dr. Avijit Goswami** in the Department of Chemistry, Indian Institute of Technology Ropar, Rupnagar, India. The work is original, based on experimental findings and has not been submitted in part or full by me elsewhere for a degree.

In keeping parity with the general practice of reporting scientific observations, due acknowledgement has been made wherever the described work is based on the findings of other investigators.

Braj Gopal

Ropar
May, 2025

Braj Gopal
(Ph.D. Student)

Indian Institute of Technology Ropar

Department of Chemistry

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Exploring the Reactivities of Donor-Acceptor Cyclopropanes***" was carried out by the candidate, Mr. Braj Gopal under my supervision in the Department of Chemistry, Indian Institute of Technology Ropar, Rupnagar, India. I am forwarding the above-mentioned thesis of him being submitted for the degree of **Doctor of Philosophy** in **Chemistry** of this Institute. To the best of my knowledge, the present work or any part thereof has not been submitted elsewhere for a degree.

Ropar

May, 2025

Dr. Avijit Goswami
Department of Chemistry
Indian Institute of Technology Ropar
Rupnagar, Punjab 140001

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Braj Gopal

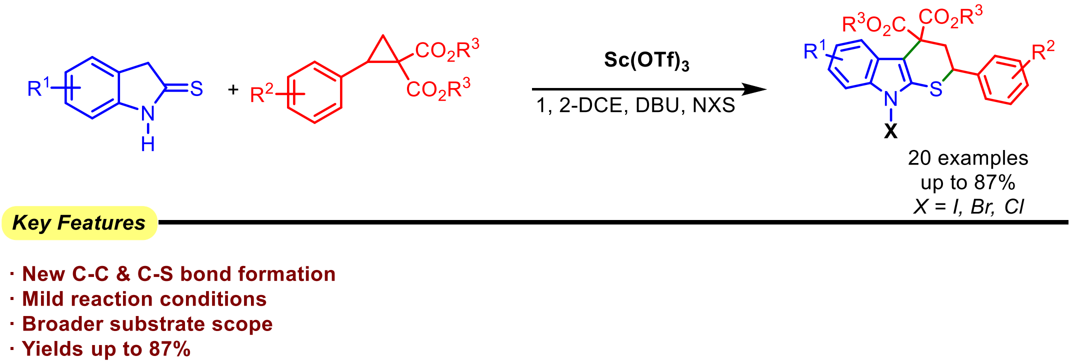
ABSTRACT

This thesis's main motive is to synthesized various functionalized heterocycles with the reactions of donor-acceptor cyclopropanes.

Chapter-1: Introduction

In modern synthetic chemistry, various small and strained molecules are harnessed as building blocks to synthesize complex compounds due to their high ring strain, easy accessibility, and diverse reactivity patterns. Cyclopropanes, the smallest three-membered carbocycles found in nature, are incredibly stable and have gained significant attention in organic chemistry, particularly as building blocks for the synthesis of cyclic and acyclic compounds. By adding donor and acceptor moieties at the vicinal position, cyclopropanes can be made reactive towards unsaturated compounds or polarophiles. The unique structural and electronic properties of cyclopropanes make them ideal and unique building blocks for a wide range of exciting transformations.

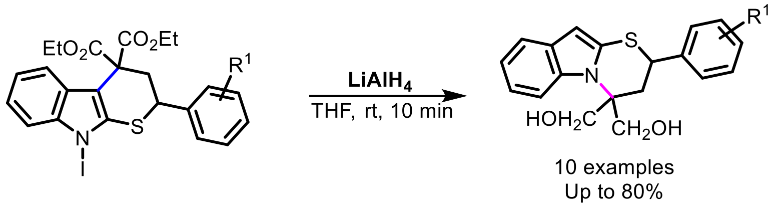
Chapter-2A In the first part of chapter 2A I have developed Synthesis of Indole-Fused Dihydrothiopyrano Scaffolds *via* (3+3)-Annulations of Donor-Acceptor Cyclopropanes with Indoline-2-Thiones.The newly developed methodology provided access to a variety of indole-fused dihydrothiopyrano molecules in good to excellent yields. In addition, the we have described transformation of the furnished product into an *N*-fused thiazino indole molecule.



- New C-C & C-S bond formation
- Mild reaction conditions
- Broader substrate scope
- Yields up to 87%

Chapter-2B

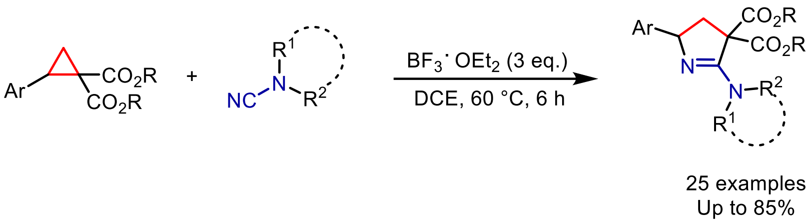
In the first part of chapter 2B I developed a straightforward and efficient $LiAlH_4$-mediated protocol has been developed for the construction of thiazino indoles. This procedure provides efficient thiazino indoles derivatives in good to satisfactory yields. DFT calculation has been done to shed light into reaction mechanism.



Key Features

- Broad Functional Group Tolorence
- Gram-Scale Synthesis
- Mild Reaction Conditions

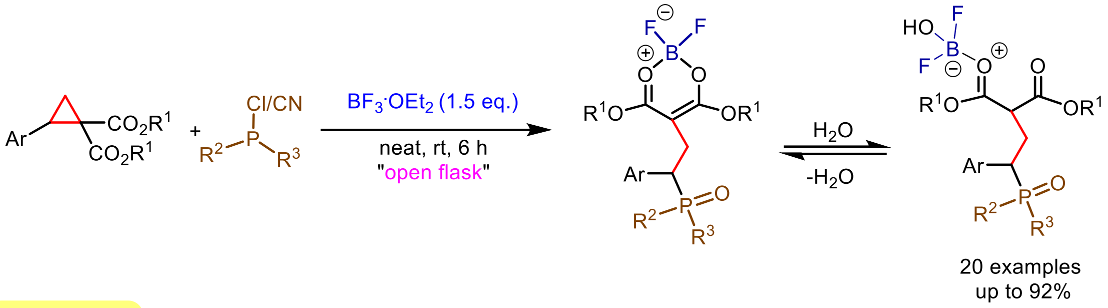
Chapter 3: In this study, I developed $BF_3\cdot OEt_2$ Mediated (3+2) Cycloaddition Reactions of DACs with Cyanamides: Access to Cyclic Amidines. A $BF_3\cdot OEt_2$ promoted facile synthesis of cyclic amidines has been developed via the (3+2)-cycloaddition of cyanamides with donor-acceptor cyclopropanes (DACs). In addition to this, the protocol has been successfully extended to construct dimerized amidine derivative and gram-scale synthesis with great efficiency.



Key Features

- Metal/Additive-Free Protocol
- Broad Functional Group Tolorence
- Gram-Scale Synthesis
- Mild Reaction Conditions

Chapter 4: Nucleophilic Ring Opening of DACs through Umpolung Reactivity of Organochlorophosphines: Phosphine Oxide Functionalized Boron Pendanted Compounds. I present a $BF_3\cdot OEt_2$ promoted protocol that offers umpolung reactivity of R^1R^2PCl/CN (R^1, R^2 = aryl, alkyl) towards donor-acceptor cyclopropanes (DACs) *via* nucleophilic ring-opening reactions to provide phosphinated O, O-chelated boron diester compounds. The newly established metal- and additive-free one-pot multicomponent reaction protocol delivers the desired products in good to excellent yields under mild reaction conditions. The compounds exist in both the forms- keto and enol, with the majority being in the keto form, according to NMR analysis. The enolic form is identified by single crystal XRD analysis and DFT calculations indicate that the keto form is more stable than the corresponding enolic form.



Key Features

- **Metal-, base- and Additive-Free**
- **Multi-Component Reaction**
- **Mild Reaction Conditions**
- **High Yields**
- **Broad substrate scope**
- **Scale-up**

Chapter 5. In this chapter, I present a comprehensive summary of the work accomplishments in the thesis entitled as “*Exploring the Reactivities of Donor-Acceptor Cyclopropanes*”.

Keywords: Donor-Acceptor cyclopropanes (DACs), Lewis-acids, Brønsted acids, Metal-free, Indoline-2-thione, Pyrrolines, chlorodiphenylphosphine, Phosphine Oxide Functionalized Boron Pendanted Compounds, amidine, indole-fused dihydrothiopyrano, thiazino indole.

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List of Abbreviations

Ac	acetyl
ACN/MeCN	acetonitrile
aq	aqueous
atm	atmospheric
α	alfa
BA	Brønsted Acid
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
brs	broad singlet
^{n}Bu	butyl
^{t}Bu	*tert*-butyl
calcd.	calculated
Cy	cyclohexyl
CuO	copper oxide
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DAC	donor-acceptor cyclopropanes

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of a doublet
DKR	dynamic kinetic resolution
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N'*-dimethyl formamide
DMSO	dimethyl sulfoxide
dq	doublet of a quartet
dr	diastereomeric ratio
dt	doublet of a triplet
DFT	density functional theory
ee	enantiomeric excess
eq.	equivalents
ESI	electron spray ionization
FT-IR	Fourier-transform infrared spectroscopy
FC	Friedel-Crafts
Gem	geminal
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HPLC	high-performance liquid chromatography

HRMS	high-resolution mass spectrum
Hz	Hertz
J	coupling constant
LDA	lithium diisopropylamide
LA	Lewis Acid
m	multiplet
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
M.P	melting point
MS	molecular sieves
m/z	mass/charge
NMR	Nuclear Magnetic Resonance
ppm	parts per million
^{n}Pr	*n*-propyl
^{i}Pr	isopropyl
p-TSA	*para*-toluenesulfonic acid
q	quartet
rt	room temperature
s	singlet

sept	septet
t	triplet
td	triplet of a doublet
tert	tertiary
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin layer chromatography

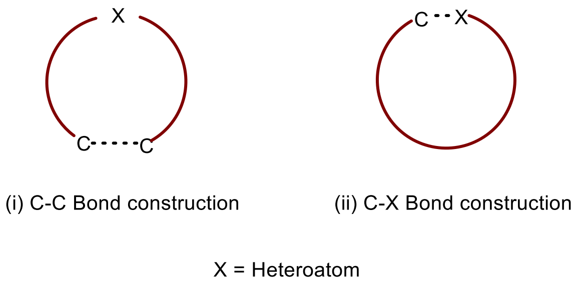
Chapter 1

Introduction

Chapter-1

1 Introduction

Heterocycles represent one of the most important categories of organic compounds that possess a ring structure containing, at least, one or more atoms in the ring that are not carbon. These compounds often include nitrogen (N), oxygen (O), sulfur (S), and occasionally phosphorus (P) as key heteroatom. These heterocyclic moieties are present in pharmaceuticals,[1] agrochemicals,[2] organic synthesis and catalysis,[3] optoelectronics,[4] flavor and fragrance industry.[5] Organic chemistry researchers have been dedicating significant efforts to the synthesis of heterocyclic molecules, recognizing their critical importance in advancing human progress. These reactions facilitate the formation of complex molecules from Accessible starting materials under moderate conditions, making them highly efficient and practical in both academic and industrial contexts. Professor Yamamoto classifies transition-metal-catalyzed reactions into two distinct categories, depending on the type of bond that is formed: the first involves the creation of C-C bonds from acyclic starting materials, while the second involves the formation of C-heteroatom bonds from acyclic precursors.[6] (Figure 1.1).



(i) C-C Bond construction

(ii) C-X Bond construction

X = Heteroatom

Figure 1.1 Key processes involved in the synthesis of heterocyclic compounds.

In modern synthetic art, various small and strained molecules are also harnessed as building blocks. Cyclopropanes, the smallest cyclic hydrocarbons, exhibit unique structural and chemical properties. In this sense, donor-acceptor cyclopropanes (DACs) as versatile intermediates in organic and medicinal chemistry, because of their high ring strain, easy accessibility and diverse reactivity patterns.

1.2 Small-Strained Molecules in organic chemistry

In 1858, *Kekule* and *Couper* both put forward the idea of carbon's tetrahedral framework, which completely transformed the way people thought about organic molecules.[7] This theory revolutionized the understanding of organic chemistry and became a fundamental concept and cornerstone in the field. Later on, in 1885, *Adolf von Baeyer* proposed the theory of strained molecules for the first time.[8] He provided an accurate explanation of the unstable nature of small ring-sized (three and four membered) molecules due to deviations in bond angles from tetrahedral values. *Pekin*, who worked in *von Baeyer's* laboratory, successfully synthesized derivatives of cyclopropanes and cyclobutanes.[9] However, due to insufficient informations at that time, the exact chemical structures were not determined until 1985. The discovery of carbine during the mid-19*th* century led to a significant advancement in the synthesis of small-ring sized molecules.

In recent decades, the construction of biologically active heterocyclic molecules utilizing small, strained ring-sized molecules has experienced noteworthy growth. In the series of small molecules, cyclopropanes are highly compact and strained three-membered carbocycles that have piqued the attention of organic chemists for their potential as fundamental components in the creation of pharmaceuticals and natural products.[10] With their small size and high strain energy, cyclopropanes offer a versatile platform for the creation of complex molecular structures. As such, they have become a significant focus of research in organic chemistry and hold great promise for the future of drug discovery.

1.2.1 Reactivity of Cyclopropanes

Cyclopropanes **1** are widely recognized for their high level of strain, which arises from their ring structure. This strain is typically measured by the conventional ring strain energy, which is found to be approximately 27.5 kcal/mol. This ring strain can be imputed to two primary factors: angular strain and torsional strain (Figure 1.2). It is well known that, ideal tetrahedral angle of sp^3-carbon is 109.5°, however, due to three membered ring system the angle between C-C-C in cyclopropanes is 60°. This indicates that the electron clouds surrounding each atom in cyclopropanes **1**, are extensively closer than anticipated, resulting in higher energy levels than in a linear alkane. Another side, the CH_2 groups of cyclopropanes **1** are observed to be in a disfavored eclipsed conformation, resulting in torsional strain. This conformational rigidity is attributed to the restricted bond angles in cyclopropanes **1**, which limit the free rotation of the CH_2 groups.

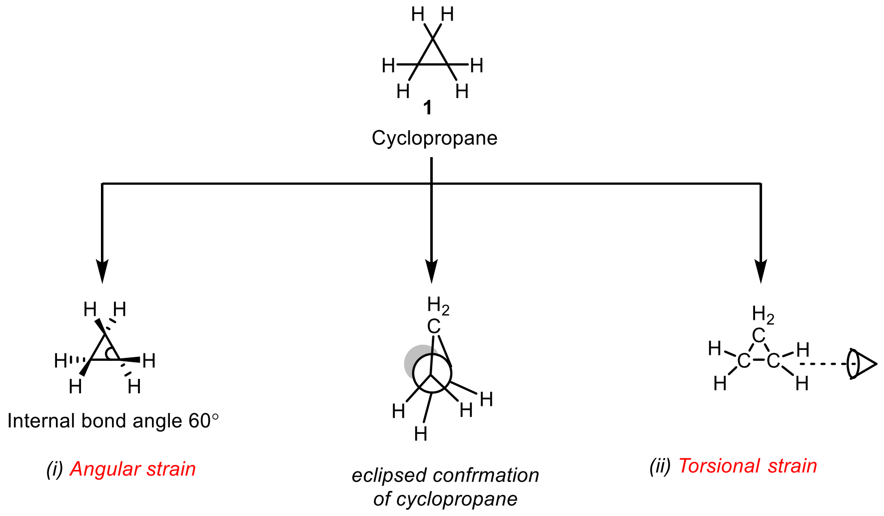


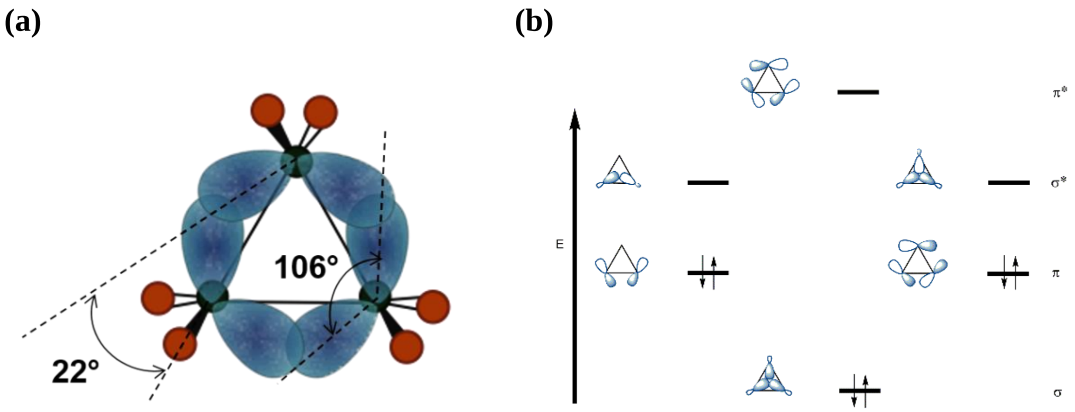
Figure 1.2 Ring Strain in cyclopropane molecule.

1.2.2 Bonding in Cyclopropane

In 1947, two main models came in to light which majorly explain the bonding in cyclopropane system: (I) The Coulson-Moffitt model and (II) The Walsh model.

(I) The Coulson-Moffitt model: *Coulson* and *Moffitt* theoretically explained the building of cyclopropane ring from three sp^3–hybridized $–CH_2–$groups.[11] These sp^3–hybridized carbon orbitals require at least two orbitals from each carbon to make a 106° angle with one another. However, these sp^3–hybrid orbitals exhibit a pointed orientation of approximately 22° away from the imaginary line linking the nuclei (Figure 1.3a). As a result, the effective overlap is reduced by approximately 20% compared to the C-C bond present in ethane. For this reason, bonds between cyclopropane molecules are commonly known as "bent bonds" or "banana bonds".

(II) The Walsh model: According to the Walsh Model, cyclopropane is composed of three sp^2-hybridized methylene carbons, where both σ and π-type orbitals of the methylene groups play a role in forming the C-C bonds within the structure.[12] This model proposes that all sp^2 orbitals in cyclopropane are directed toward the center of the ring, forming one bonding molecular orbital and two antibonding molecular orbitals. Furthermore, the interaction of p-orbitals within the plane of the ring leads to the creation of two C-C bonding interactions and one curved antibonding interaction. Due to the inadequate overlap among them, these molecular orbitals are arranged with enough angular strain (Figure 1.3b).



(i) The Coulson-Moffitt model *(ii) The Walsh model*

Figure 1.3 Explanation of bonding in cyclopropane by orbital models.

Cyclopropane motifs are known to be kinetically inert due to their high strain and weaker C-C bonds. Therefore, they require activation in order to participate in reactions. Activation can be achieved through two factors: external or internal. Although, High temperature or photochemical conditions can activate cyclopropanes externally, but these drastic conditions can result in the formation of various by-products. Alternatively, introducing a new functional group to cyclopropane internally can alter their properties in an efficien way, making them reactive towards other counter partners. Activation of cyclopropanes is generally done via the incorporation of electron-donor substituents (nucleophilic cyclopropanes), electron-withdrawing groups (electrophilic cyclopropanes), and electron-donor and withdrawing substituents at vicinal and geminal positions (donor-acceptor cyclopropanes), which stimulate diverse reactivity patterns (Figure 1.4).

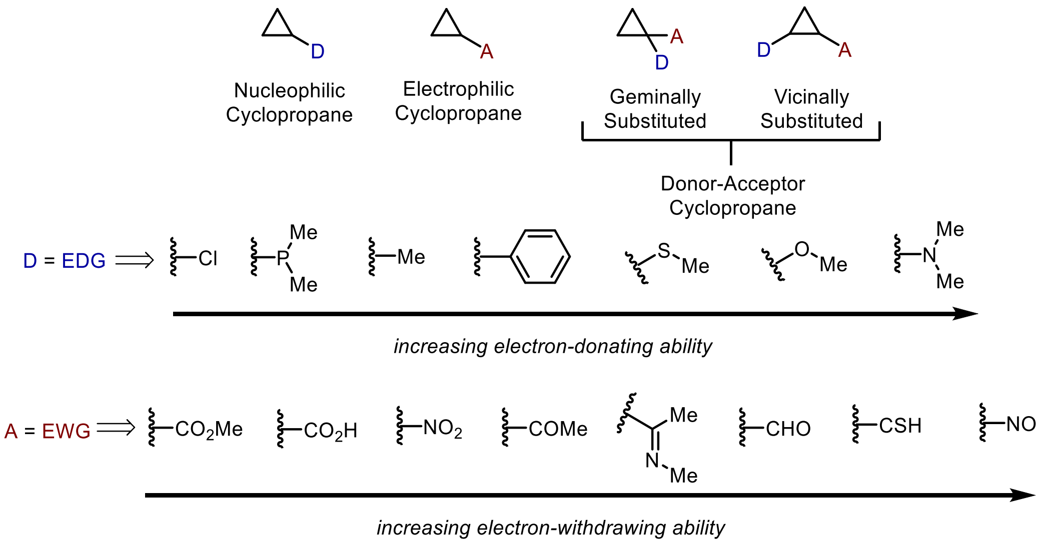


Figure 1.4 Differently categorized substituted cyclopropanes.

The incorporation of donor substituents in ring system, provide stabilization through their attached donor groups can aid in the facilitation of the electrophilic ring-opening of cyclopropane and demonstrate homo-enolate type reactivity (Figure 1.5a). On the other hand, electron-acceptor attached to the cyclopropanes facilitates ring-opening of cyclopropanes through nucleophile and offer homo Michael nucleophilic addition type products (Figure 1.5b). Although, in the existence of both electron-donor and acceptor substituents

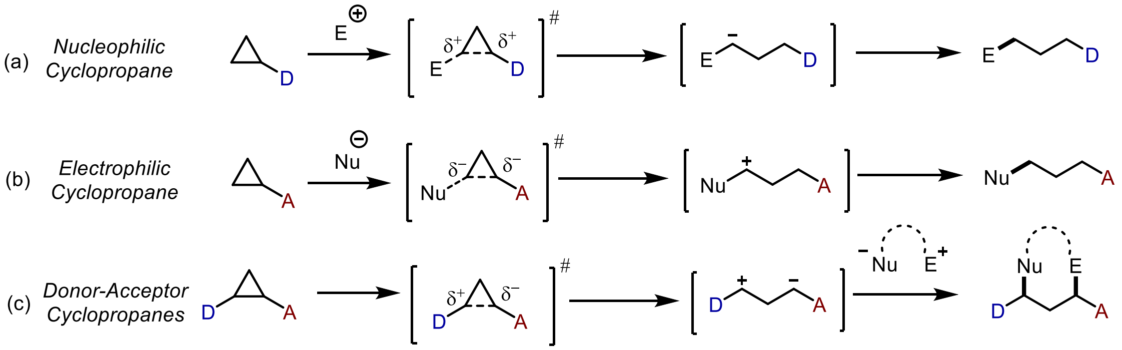


Figure 1.5 Reactivity of various activated cyclopropanes.

within the cyclopropane ring system, leads to the formation of 1,3-zwitterionic species. Through the cooperative efforts of the electron-donor and withdrawing systems in cyclopropanes, these species are stabilized and exhibit a *push-pull effect* (Figure 1.5c).

1.2.3 Donor-Acceptor Cyclopropanes

The ring-opening process of vicinally substituted donor-acceptor cyclopropanes is facilitated by the push-pull effect. When donor and acceptor groups are located in a vicinal position, they engage in a cooperative manner that is subject to *push-pull* effect. This cooperative interaction results in a pronounced segmentation of the C_1-C_3 bond bounded by the two groups, resulting in a relatively weak bond (Figure 1.6). This characteristic enables donor-acceptor cyclopropanes to function as efficient zwitterionic structural frameworks. A carbocation is stabilized by an electron-donating group, whereas a carbanion is balanced by an electron-withdrawing group. At the same time, in germinal donor-acceptor cyclopropanes the absence of synergistic action among the substituents reveals that the polarization of the C-C bond is not a crucial factor. However, vicinally substituted donor-acceptor offers number of synthetic applications because the electronic arrangement of the cyclopropane ensures for the activation of the ring. In this thesis I will discuss about vicinally substituted cyclopropanes.

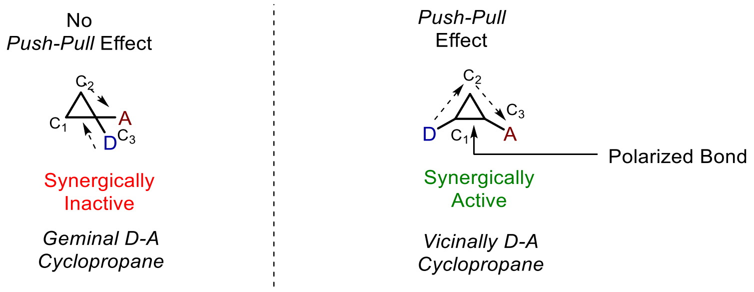


Figure 1.6 Difference between germinal and vicinal donor-acceptor cyclopropanes

1.2.4 Reactivity of Donor-Acceptor Cyclopropanes

In the late 1980s, Reissig formulated the term "donor-acceptor" for these types of molecules.[13] Since then, donor-acceptor cyclopropanes have become a major area of study. Extensive research has been conducted for the synthesis of heterocycles and carbocycles, utilizing the aforementioned small molecules.[14] The push-pull effect induces polarization of the C-C bond and produces different routeways for the ring-opening reaction of D-A cyclopropanes. When a nucleophile, electrophile, or dipolarophiles approach DACs, it undergoes a heterolytic ring-opening process, giving rise to a variety of reactions as shown in (Figure 1.7).

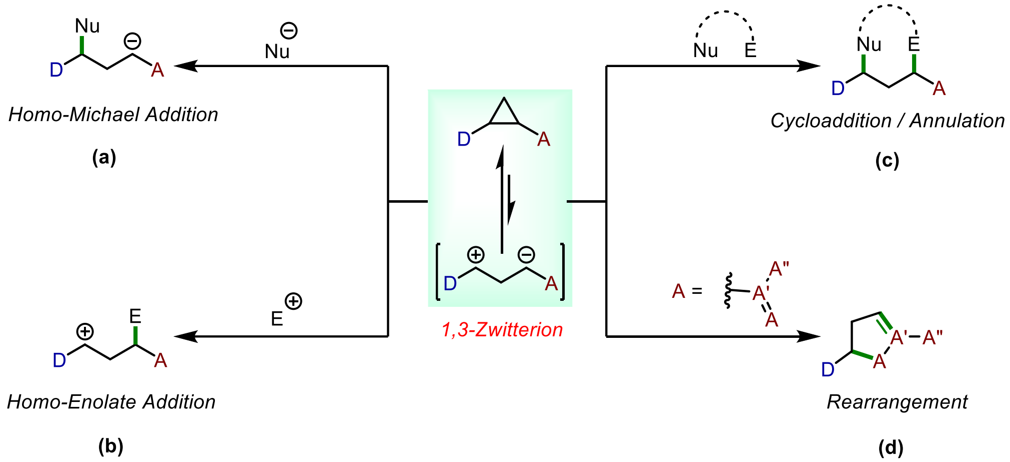
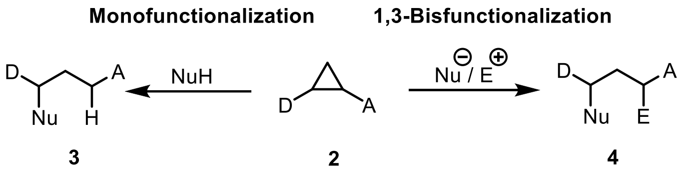


Figure 1.7 Reactivity of donor-acceptor cyclopropanes

In the subsequent lines, an in-depth analysis will be presented on distinct reactivity profiles, offering an extensive overview of the reactivity of donor-acceptor cyclopropanes.

1.2.5 Reaction of Donor-Acceptor Cyclopropanes with Nucleophiles:

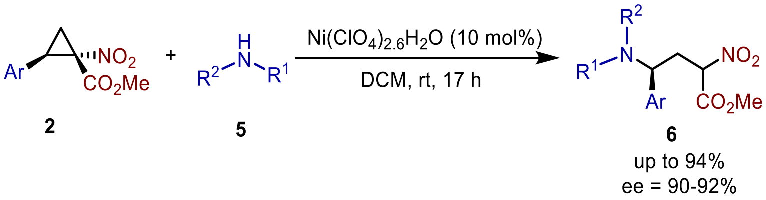
Activated donor–acceptor (D–A) cyclopropanes **2** readily undergo ring-opening reactions with nucleophiles, electrophiles, or radicals, providing an efficient method for constructing open-chain structures. In these processes, a nucleophile generally strikes the donor site of the three-membered ring, leading to the origination of a stabilized anion. This anion can either undergo protonation to produce monofunctionalized products **3** or react further with an electrophile to form 1,3-bisfunctionalized frameworks **4**, as illustrated in (Scheme 1.1).



Scheme 1.1 Ring-opening reactions of donor-acceptor (D–A) cyclopropanes leading to mono- and bis-functionalized products.

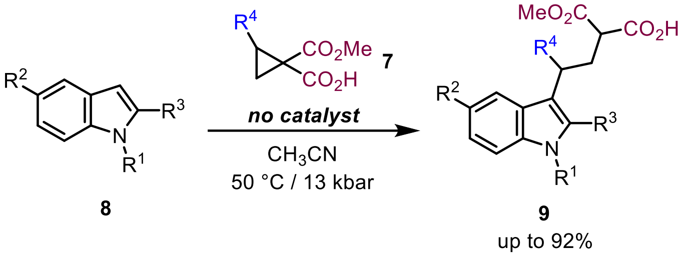
Nucleophilic ring-opening reactions of donor-acceptor cyclopropanes with diverse nucleophiles are the most fundamental transformations and straightforward approach to accessing 1,3-bifunctional acyclic compounds. In a simpler way, we can define this kind of reaction as homo conjugate addition or homo Michael addition. In this process of transformation, the open-chain system that possesses 1,3-zwitterion undergoes a reaction with a nucleophile including electron-rich arenes or heteroatom. During this reaction, the counterpart of zwitterion is balanced by a proton or other electrophilic partner. In general, amines,[15] azides, [16] alcohols, [17] thiols, [18] carboxylic acids[19] have been employed as heteroatom nucleophiles in nucleophilic ring-opening reactions of donor-acceptor cyclopropanes. The aforementioned transformations in DACs were made possible through the use of Lewis acid catalysis and occasionally Brønsted acids were employed additionally. Like nucleophiles, electrophiles also follow the same reaction mechanism for the functionalization of donor-acceptor cyclopropanes.

For instance, Charette and co-workers reported a study on the enantioselective nucleophilic ring opening of donor – acceptor cyclopropanes **2** using an amine nucleophile under nickel-based Lewis acid catalysis (Scheme 1.2).[15c] The reactions occurred with an S_N2 inversion of the absolute stereochemistry at C-1 when utilizing enantioenriched cyclopropanes as starting materials.



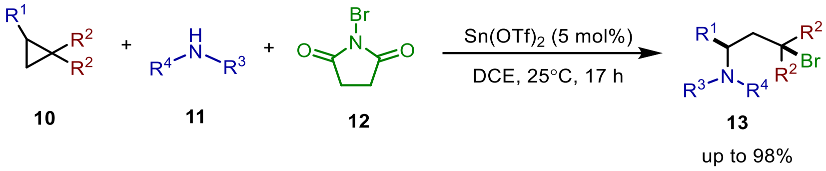
Scheme 1.2 Nucleophilic ring-opening of D-A cyclopropane with nitrogen nucleophile.

In 2011, Kerr *et al.* showed that cyclopropane hemimalonates **7** undergo nucleophilic ring-opening reactions with indoles **8** under catalyst-free conditions, resulting in 1,3-bifunctionalization of DA cyclopropanes (Scheme 1.3)[20].



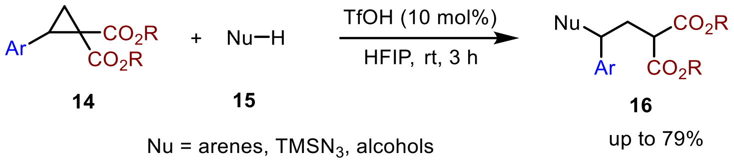
Scheme 1.3 Nucleophilic ring-opening of D-A cyclopropanes with indoles nucleophile

In 2017, Studer *et. al.* documented an article for 1,3-bifunctionalization of D-A cyclopropanes **10** for the stereospecific 1,3-aminobifunctionalization of cyclopropanes under Lewis acid catalysis.[21] A multicomponent reaction involving D-A cyclopropanes, amines, and NBS proceeds in the presence of $Sn(OTf)_2$, delivered γ-aminated α-brominated malonic diesters **13** as products (Scheme 1.4).



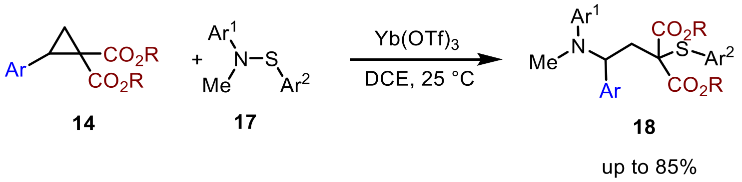
Scheme 1.4 1,3-Bifunctionalization of D-A cyclopropanes.

In 2018, Joseph Moran *et al.* published a study describing the nucleophilic ring-opening of donor–acceptor cyclopropanes **14**, mediated by Brønsted acids. This approach enabled the synthesis of 1,3-bifunctionalized products using a diverse array of nucleophiles, including arenes, indoles, azides, diketones, and alcohols (Scheme 1.5).[22]



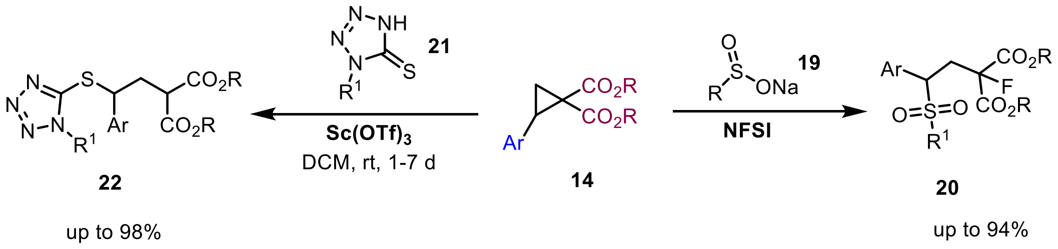
Scheme 1.5 Brønsted acid catalyzed nucleophilic ring opening of a broad range of D-A cyclopropanes.

In 2020, Biju *et al.* presented an elegant study that resulted in akin products by using sulfenamides **17** as both nucleophilic and electrophilic sources, as shown in the scheme. Under Yb(OTf)₃ catalysis, they indicated a reliable concord for the synthesis of γ-aminated α-thiolated acyclic scaffolds of type **18**, with broad group tolerance, mild reaction conditions, and yields up to 87%. Further exploration revealed that the stereospecific nucleophilic ring-opening reaction accompany an S_N2-like mechanism (Scheme 1.6).[23]



Scheme 1.6 1,3-Aminothiolation of DACs using sulfenamides.

Recently, Werz *et al.* published studies on the nucleophilic ring-opening reactions of donor-acceptor cyclopropanes with sulfinate salts **19**, electrophilic fluorination reagents, and 5-mercaptotetrazoles **21** under Lewis acid conditions, leading to the formation of γ-fluorosulfones **20** and sulfanes **22** (Scheme 1.7).[24a, 24b]



Scheme 1.7 1,3-Bifunctionalization of D-A cyclopropanes.

1.2.6 Reactions of Donor-Acceptor Cyclopropanes with Dipolarophiles

The interaction between donor-acceptor cyclopropanes and dipolar species leads to either cycloaddition or annulation reactions, resulting in the expansion of the ring. Initially, It was recognized that dipolarophiles could engage in (3+n) cycloadditions through 1,3-zwitterionic intermediates, resulting in the formation of five-, six-, seven-, and sometimes eight-membered ring structures through these cycloaddition reactions (Figure 1.8).

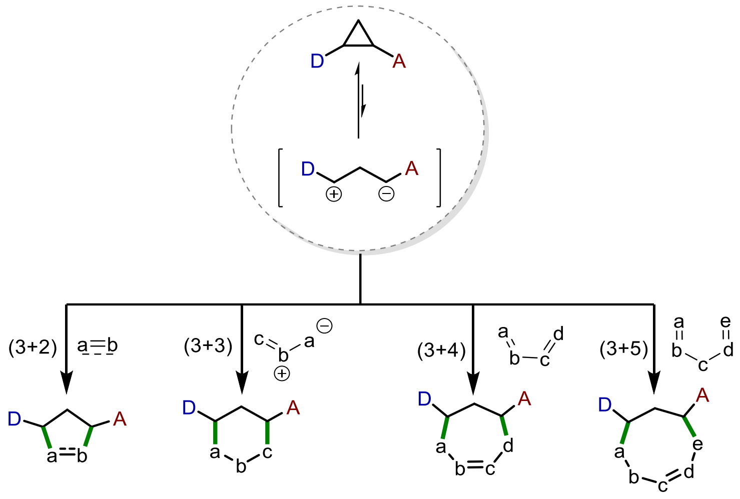


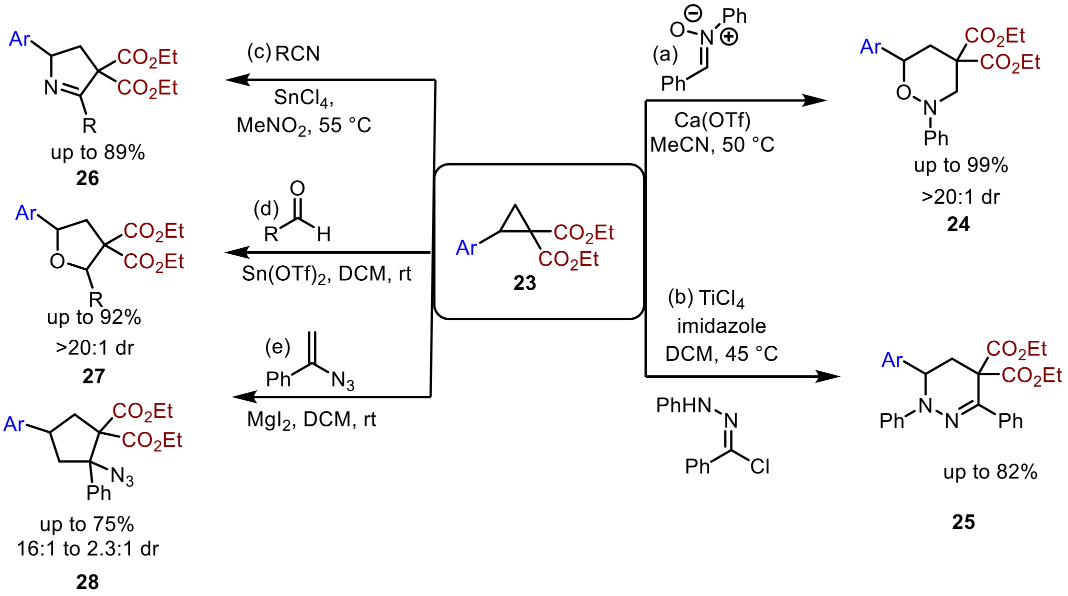
Figure 1.8 Cycloaddition type reactivity of D-A cyclopropanes.

After all, donor-acceptor (D-A) cyclopropanes can also be tuned to generate 1,4-zwitterionic species, which ultimately leads to the formation of carbo-/heterocycles with ring enlargement. This highlights the versatility of D-A cyclopropanes in forming larger ring structures through cycloaddition reactions with dipolar species.

1.2.6.1 Formal (3+2) Cycloadditions

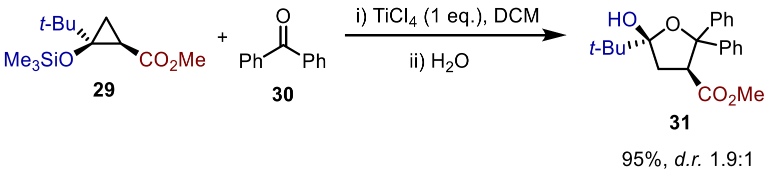
The (3+2) cycloaddition reaction involving D-A cyclopropanes and various dipolarophiles is a widely explored reactivities of D-A cyclopropanes. Dipolarophiles commonly used in this reaction includes alkenes,[25] alkynes,[26] nitriles,[27] isocyanates,[28], nitrosoarenes[29] and nitrosocarbonyl[30] for

(3+2) cycloaddition reactions. There are some few illustrations of cycloaddition reactions of donor-acceptor cyclopropanes have been reported with nitrones (Scheme 1.8a),[31] nitriles (Scheme 1.8c),[32,33] amines aldehydes (Scheme 1.8d), (Scheme 1.8b),[34,35] nitriles and with vinyl azides (Scheme 1.8e).[36] Each of these reactions are catalyzed by a Lewis acid on 1,1-dicarboxylate esters, and association with the ester carbonyl oxygens can be monodentate or bidentate, generally unspecified, with bidentate coordination offering the highest degree of stabilization for ring opening. The reaction temperature is determined by the extent of activation of the donor-acceptor cyclopropane for ring opening facilitated by the Lewis acid catalyst. Polar solvents that can stabilize charged intermediates were initially favored for cycloaddition reactions, but some of these solvents lower the rate of reaction because of their coordination with the Lewis acid catalyst. Dichloromethane is most used currently.



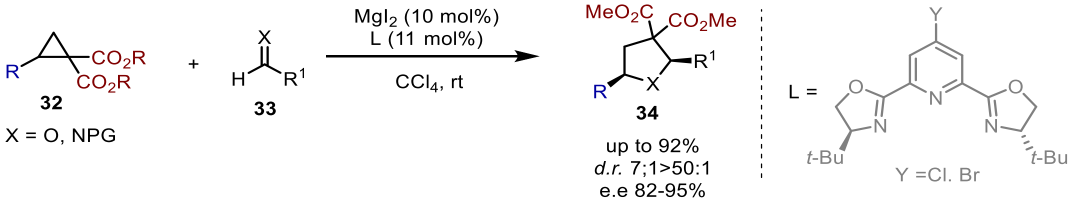
Scheme 1.8 (3+2) cycloaddition reactions of donor-acceptor cyclopropanes.

The first documented instance of (3+2) cycloaddition was presented by *Reissig*, who successfully executed the reaction between trimethylsiloxycyclopropanecarboxylate **29** and benzophenone **30** in the existence of $TiCl_4$ as a Lewis acid catalyst.[37] The reaction resulted in a diastereomeric mixture of lactol **31**, obtained in 95% yield (Scheme 1.9).



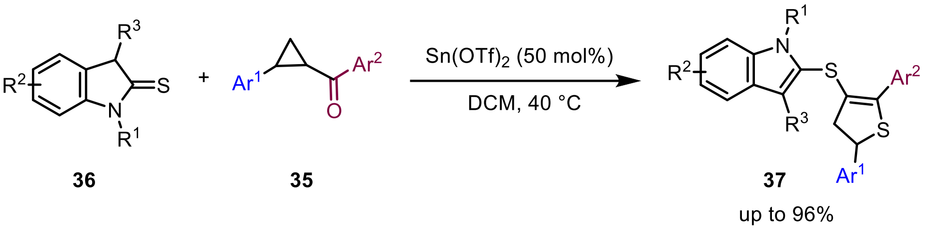
Scheme 1.9 *Reissig's* approach for furan synthesis.

After that, huge advancement has been witnessed for the methodology development in (3+2) cycloaddition of donor-acceptor cyclopropanes with dipolarophiles with high stereo and regioselectively. In the same line, Johnson and team developed enantiospecific method for affording stereoslective tetrahydrofuran derivatives **34** *via* kinetic asymmetric [3+2] cycloaddition between donor-acceptor cyclopropanes and aldehydes by using a chiral Mg(II) catalyst (Scheme 1.10).[38] In cycloaddition process, a chiral catalyst was observed to exhibit a preference for one enantiomer of cyclopropane through a diastereomeric transition state. Additionally, the catalyst was found to facilitate the interconversion of enantiomers by S_N2 mechanism.



Scheme 1.10 Enantioselective synthesis of tetrahydrofurans and pyrrolidine.

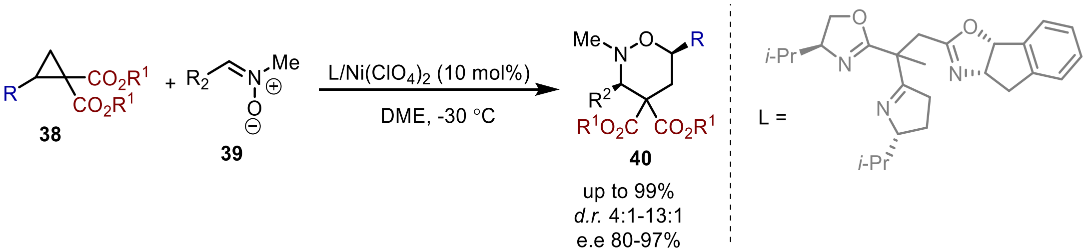
In 2024, Wang *et al*. published a study on a (3 + 2) cycloaddition/sulfur rearrangement reaction involving donor–acceptor cyclopropanes **35** with a single keto acceptor and indoline-2-thiones **36**, catalyzed by Sn(OTf)2. This reaction led to the formation of a range of functionalized 3-indolyl-4,5-dihydrothiophenes **37**. (Scheme 1.11).[39]



Scheme 1.11 Formal (3+2) cyclo-additions reactions of DACs with 3-indolyl-4,5 dihydrothiophenes.

1.2.6.2 Formal (3+3) cycloadditions

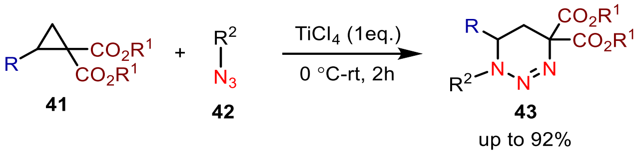
The [3+3] cycloaddition methodology is one of the highly effective means of expeditiously constructing six-membered cyclic frameworks. This approach involves the utilization of a donor-acceptor cyclopropane as a 1,3-dipole with other 1,3-dipolarophile. The majority of research in this field has engaged on Lewis acid-catalyzed reactions, where nitrones serve as the third component in the three-atom system.[40] For instance, In this line, Tang and team documented an asymmetric construction of 1,2- oxazines **40** from (3+3) cycloaddition of D-A cyclopropanes **38** with nitrones **39** under nickel catalysis (Scheme 1.12).[40a]



Scheme 1.12 Synthesis of oxazines from (3+3) cycloadditions.

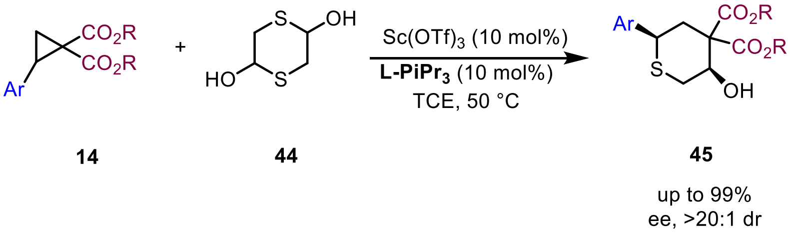
In 2014, Xu et al. presented a study on the utilization of titanium-based Lewis acids to facilitate formal [3+3] cycloaddition reactions between donor-acceptor cyclopropanes **41** and organic azides **42**. This method enabled the generation of highly functionalized triazinines **43** (Scheme 1.13)[41]

The technique was further refined to include the utilization of a catalytic amount of $TiCl_4$ (20 mol%) with the involvement of HFIP as the solvent for the reaction.



Scheme 1.13 Synthesis of triazinines *via* [3+3] cycloadditions.

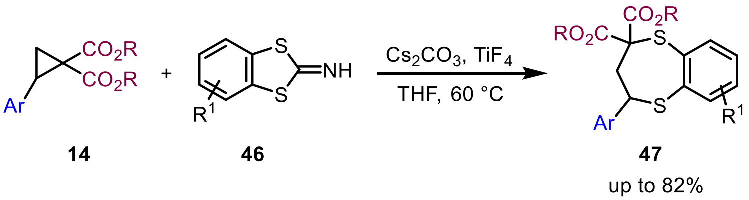
In 2016, Feng *et al*. reported a highly diastereo- and enantioselective [3+3] annulation of donor–acceptor cyclopropanes **14** with mercaptoacetaldehyde **44**. This was accomplished using a catalytic system conforming to a chiral N, N'-dioxide L-PiPr3–Sc(OTf)$_3$ complex. The reaction produced chiral tetrahydrothiopyranols **45** in moderate yields, with excellent diastereoselectivities (up to >20:1 dr) and enantioselectivities (up to 99% ee).[42]



Scheme 1.14 Synthesis of tetrahydrothiopyranols *via* [3+3] cycloadditions.

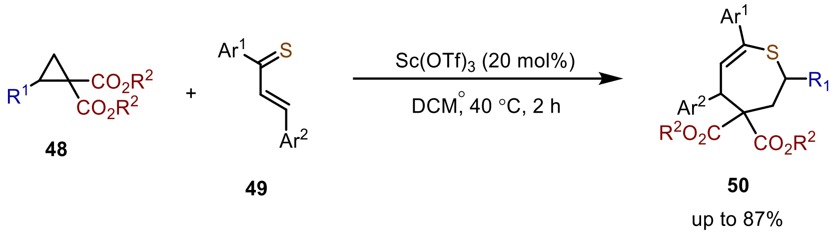
1.2.6.3 Formal (4+3) Cycloadditions

The [4+3] cycloadditions of donor-acceptor cyclopropanes with dienophiles are recognized for yielding important seven-membered ring structures. However, the extent of the exploration of these molecules through [4+3] cycloadditions remains limited. The dienophiles like, 1,3-diphenylisobenzofurans,[43] anthracenes,[44] dienes,[45] and thiochalcones,[46] containing conjugated four atoms which react with cyclopropanes to deliver cycloheptene moiety. The first hetero-(4+3) cycloaddition reaction was reported by Werz *et al.* in 2016, involving formal ortho-bisthioquinones, which act as hetero-4π components. In this study, donor–acceptor (D–A) cyclopropanes were treated with amphiphilic benzodithioloimines **46**, acting as surrogates for ortho-bisthioquinones, under TiF_4 catalysis to produce seven-membered heterocycles of type **47** (Scheme 1.15).[47]



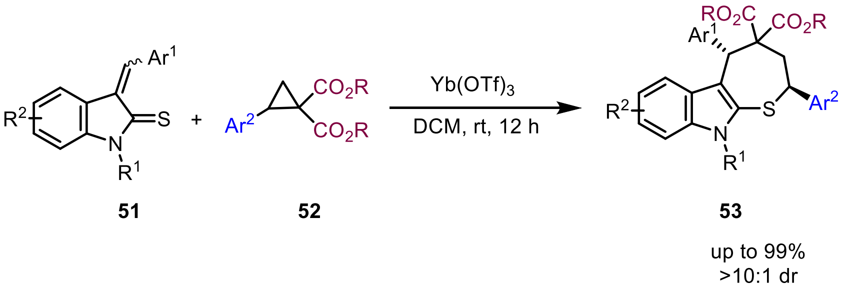
Scheme 1.15 Synthesis of Benzo- fused dithiepine *via* (4+3) annulations.

In 2019, Werz *et al.* reported on the successful (4+3) annulation reaction of diester donor-acceptor cycloproanes **48** with various thiochalcones **49** for the synthesis of tetrahydrothiepine **50** derivatives. They utilized scandium triflate as a catalyst under gentle reaction conditions (Scheme 1.16).[48] they suggested that the D-A cyclopropane follows an S_N2-type ring-opening mechanism, which occurs via the nucleophilic attack of thiochalcone form S-center. Based on the reaction mechanism and control experiments



Scheme 1.16 Formal (4+3) Cycloaddition of D-A cyclopropanes with thiochalcones.

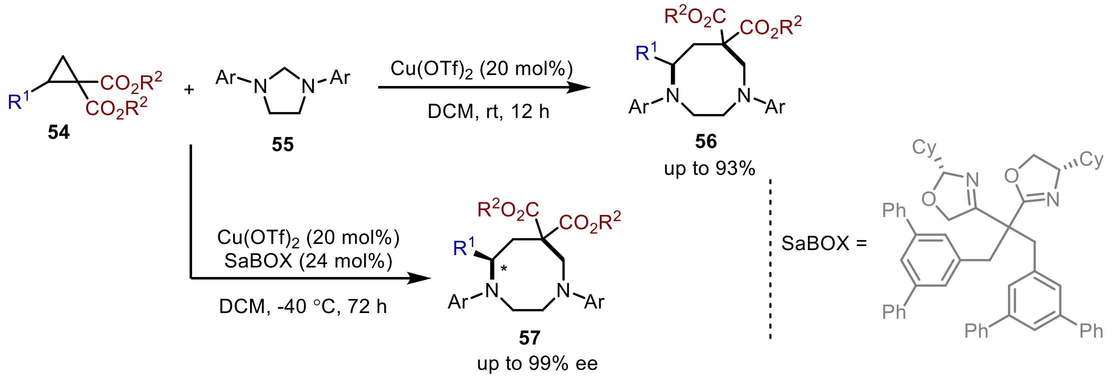
In 2023 Yang *et al.* reported an article, formal (4 + 3) cycloaddition reaction of donor–acceptor cyclopropanes **52** with 3 benzylideneindoline-2-thiones **51** under the catalysis of Yb(OTf)$_3$ for the facile synthesis of 5,10-dihydro *2H*-thiepino[2,3-*b*]indole **53** (Scheme 1.17).[49]



Scheme 1.17 Formal (4+3) Cycloaddition of D-A cyclopropanes with dihydro-*2H*-thiepino[2,3-*b*]indole.

1.2.6.4 Formal (5+3) cycloadditions

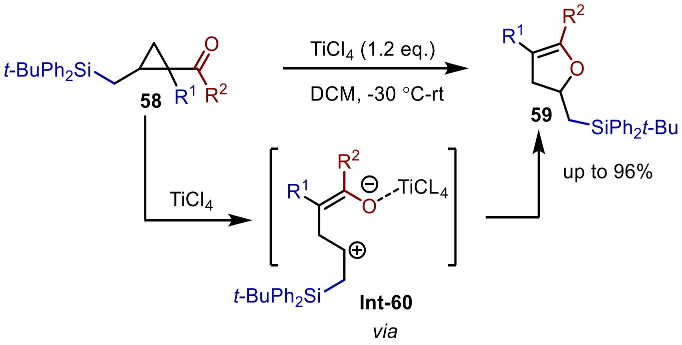
Due to the challenges of higher order cycloadditions, the formal (5+3) cycloadditions of donor-acceptor cyclopropanes with their counterpart are relatively infrequent. For the first time, Nishida and co-workers proposed a procedure for the synthesis of cycloocta[*b*]indoles *via* (5+3) cycloadditions of donor-acceptor cyclopropanes with C-2 allyl containing indoles under Lewis acids catalysis.[50] Very recently, Peng *et. al* documented the documented asymmetric formal (5+3) annulation of donor–acceptor cyclopropanes **54** with imidazolidines **55** to support the advancement of 1,4-diazocanes **56** and **57** using copper triflate as a catalyst (Scheme 1.18).[51]



Scheme 1.18 Formal (5+3) cycloaddition reactivity of D-A cyclopropanes.

1.2.7 Rearrangement reactions of D-A Cyclopropanes

In addition to cycloadditions and nucleophilic ring-opening, donor-acceptor (D-A) cyclopropanes possess a remarkable potential to undergo rearrangement processes, resulting in the formation of more stable cyclic products. These rearrangements relieve the ring strain inherent in cyclopropanes, typically leading to the formation of less strained cyclic adducts. Such rearrangement reactions are significant in organic chemistry, as they provide a strategy for synthesizing complex cyclic compounds from simpler starting materials. In this regard, Cloke-Wilson rearrangement is most popular rearrangement process for cyclopropyl ketones or carbaldehydes for the construction of multisubstituted dihydrofuran derivatives.[52] For example, Yadav *et. al* reported the Cloke-Wilson type rearrangement of (tert-butyldiphenylsilyl) methylcyclopropylketones **58** in the presence of $TiCl_4$ for the construction of dihydrofuran derivatives **60** *via* Cyclization of a titanium enolate onto a silicon-stabilized carbocation **Int-59** (Scheme 1.19).[53]



Scheme 1.19 Cloke-Wilson type rearrangement of cyclopropyl ketones.

1.4 Aim of the Thesis

In light of the current high demand for functionalized heterocycles, it has become imperative to invest in their development. The synthesis of these heterocycles has been a subject of research for several decades, and their use spans various fields such as materials science, pharmaceuticals, and agrochemicals. Therefore, I envisioned to explore the reactivities of D-A cyclopropanes. The research conducted in this thesis majorly focused on the following points:

(I) Construction of functionalized heterocycles: The central objective of this research is to leverage the reactivity of donor-acceptor cyclopropanes to synthesize functionalized heterocyclic compounds, like, functionalized like, pyrrolines, indole-fused dihydrothiopyrano, thiazino-indoles and phosphine oxide-functionalized boron-pendanted compounds which are indispensable molecules in the domains of pharmaceuticals, agrochemicals. By developing innovative methods to assemble such compounds, this thesis seeks to make a notable contribution to the creation of novel, diverse chemical structures.

(II) Methodology development: The proposed thesis endeavors to develop novel synthetic methodologies through the implementation of donor-acceptor cyclopropanes. Our research has culminated in the synthesis of functionalized heterocycles and O-O chelated boron diester containing molecules, which were achieved through the implementation of (3+2) cycloaddition, (3+3) cycloaddition, and Nucleophilic substitution reactions. These diverse synthetic routes enabled us to obtain a library of compounds that exhibit a range of structural and electronic diversity. The proposed methods will offer a streamlined approach to the synthesis of heterocyclic compounds, which bear significant promise in diverse areas of chemistry.

To sum up, this thesis provides a comprehensive study of the reactivities of donor-acceptor cyclopropanes. The study particularly focuses on their potential in constructing functionalized heterocyclic compounds. The entitled thesis as "*Exploring the Reactivities of Donor-Acceptor*

Cyclopropanes" contains the synthesis of functionalized indole-fused dihydothipyrano, and thiazinoindole in Chapter-2 (2a and 2b), synthesis of pyrrolines in Chapter-3 followed by phosphine oxide functionalized boron-pendanted cssompounds in chapter-4 is the prime focus of this thesis. This research includes mechanistic insights, method development, and practical applications. The main goal is exploring the reactivity of strained carbocyclic ring for the synthesis of various important organic molecules. the field of organic synthesis and potentially lead to the discovery of new compounds with significant applications in pharmaceutical science and industry.

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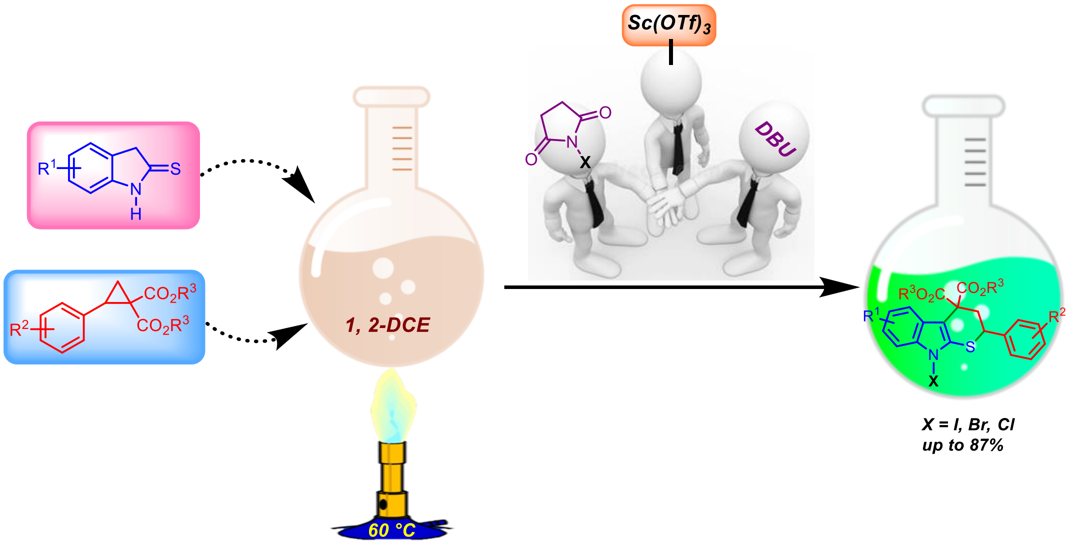
Chapter-2A

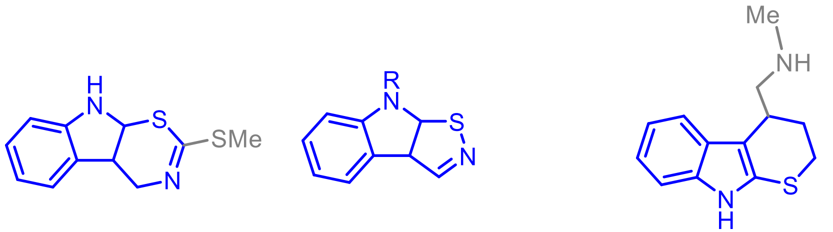
Synthesis of Indole-Fused Dihydrothiopyrano Scaffolds via (3 + 3)-Annulations of Donor–Acceptor Cyclopropanes with Indoline-2-Thiones



✓ New C-C & C-S bond formation ✓ Mild reaction conditions ✓ Broader substrate scope

2A.1 Introduction

Sulfur-containing organic frameworks have a wide range of utilities *viz*., pharmaceuticals, natural products, agro-chemicals, material industry, polymer industry and in synthetic organic chemistry.[1] Among all the known organosulfur heterocycles, thiopyran motifs are one of the most vital classes of molecules found in a variety of pharma and bioactive compounds.[2] Since the past few years, indoline-2-thione has arisen as a versatile synthon for the synthesis of indolefused/spiro organosulfur compounds. In Figure 2A, several indole-fused tricyclic heterocyclic natural products or drugs are shown, having antitumor, antifungal, antibacterial and analgesic activities.[3] To the best of our knowledge, a handful numbers of methodologies for accessing the fused-indole thiopyrano derivatives are known,[4] however, there is no strategy that involves donor-acceptor cyclopropanes (DACs). DACs received much attention in recent decades due to their outstanding strained arrangement and immense synthetic application.[5] The push-pull effect of these three-membered cyclic rings has been extensively exploited for the synthesis of acyclic, carbocyclic and heterocyclic architectures.[6] In continuation to this, there are many reports available that address the formation of organosulfur compounds from DACs in the presence of Lewis acids.[7] In 2015, Wang and co-workers reported an enantioselective protocol for the construction of spiro[thiopyranoindolebenzoisothiazole] derivatives in good to excellent yields *via* (3+3)-spiroannulation of indoline-2-thione with azadienes in the presence of chiral bifunctional tertiary amine-thiourea catalyst.[8] Later, in 2016 Ye *et al*. postulated spirocyclic reaction between cyclic dienones and indoline-2-thione using cinchona-derived primary amine catalyst.[9] Ye and Sun nicely utilized 2-indolinethiones and bromoenals as starting materials to furnish indolo[2,3-*b*]dihydrothiopyranone derivatives through *N*-heterocyclic carbene catalysis (Scheme 2A.1).[10] In 2020, Namboothiri and his team engineered and characterized the formation of tetrahydrothiopyrano[2,3-*b*]indoles from (3+3) annulation of nitro allylic acetates and indoline-2-thiones in the presence of base at mild conditions (Scheme 2A.2).[11] While preparing the present manuscript, Jiang *et. al* reported nucleophilic ring-opening reactions of D-A cyclopropanes with indoline-2-thiones in the presence of MgI_2 as a catalyst (Scheme 2A.3).[12] Keeping the potential of indole-fused thiopyrano compounds in mind, we hypothesized the reaction route in which initially DACs will be attacked by indoline-2-thione to open the ring. Once nucleophilic ring-opening is done, the C-center attached to the ester groups need to change its nucleophilic character to electrophilic character for further cyclization to furnish the indole fused sulphur containing a six-membered ring. Therefore, after ring-opening of cyclopropane good leaving group on the C-center attached to carboxylic esters need to be incorporated. Having this assumption in mind, we planned to conduct (3+3) annulation reactions of D-A cyclopropanes with indoline-2-thiones to access highly functionalized *N*-iodo-2,3-dihydrothiopyrano[2,3-*b*]indole scaffolds in the presence of Sc(OTf)$_3$ as a Lewis acid catalyst. (Scheme 2A.4).

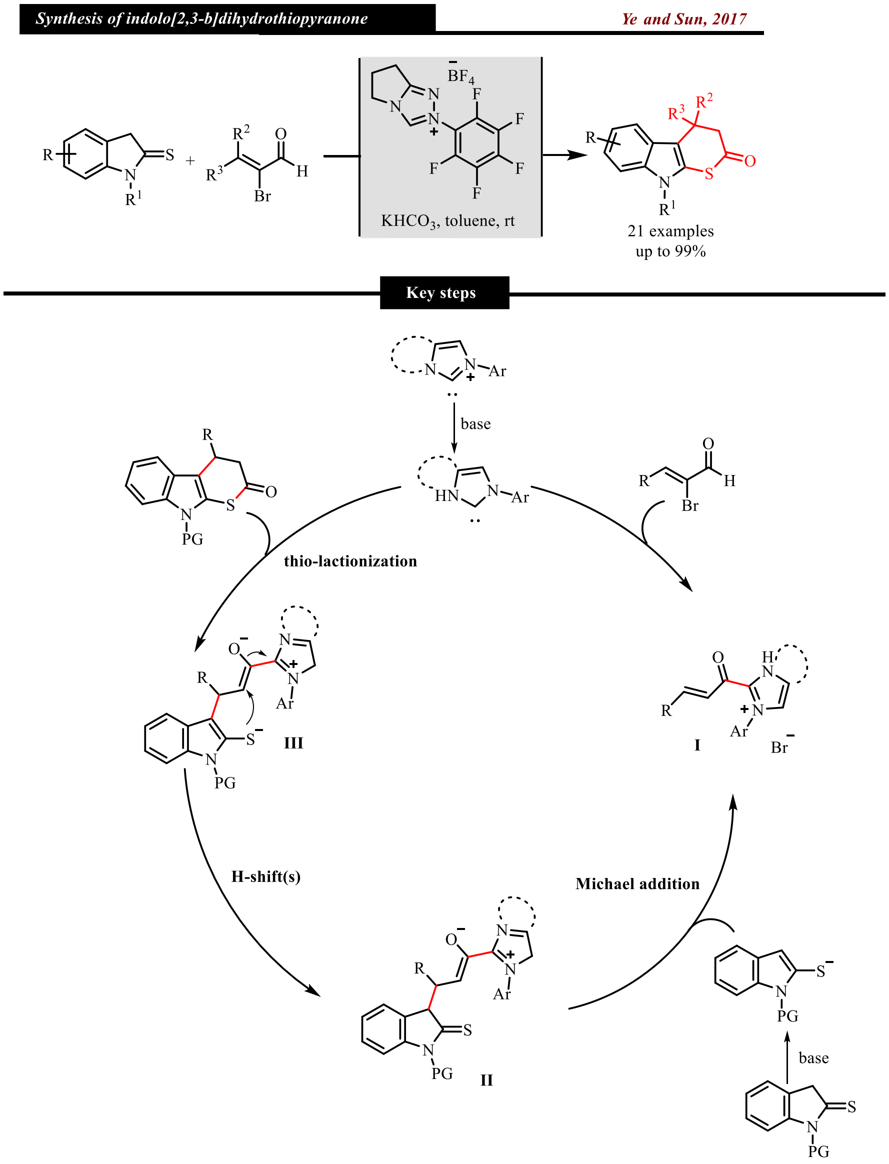


I. cyclobrassinin
(anticancer activity)

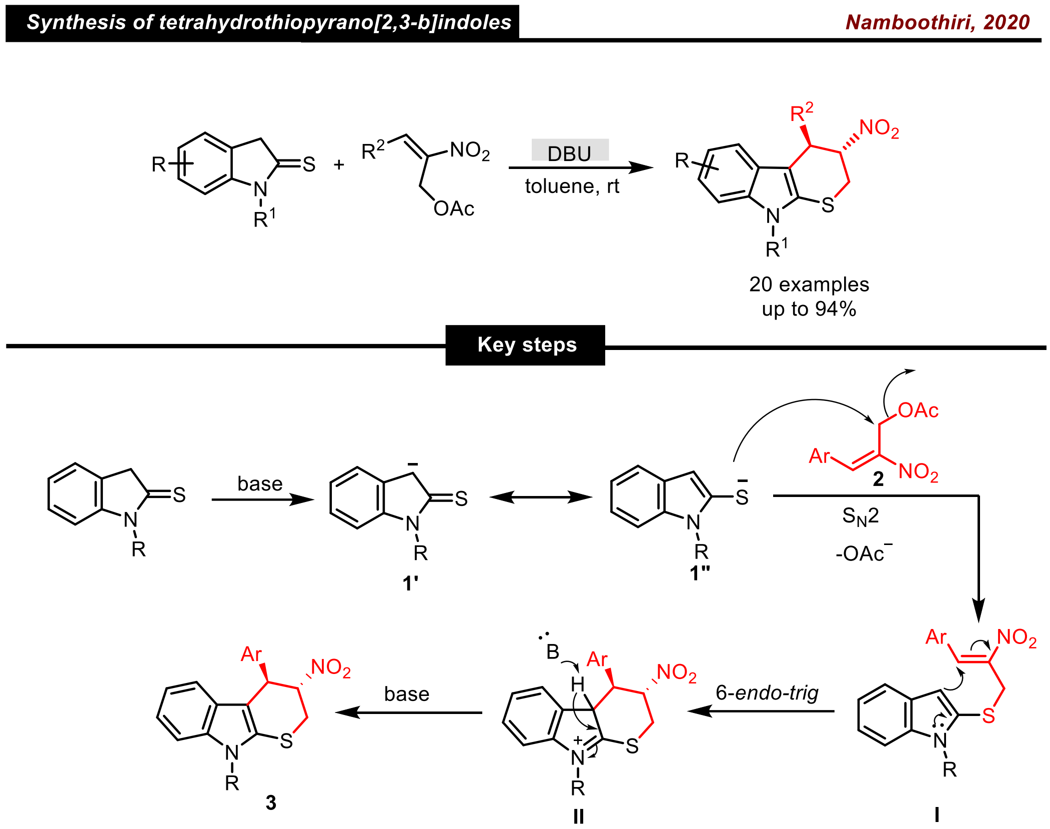
II. R = H, brassilexin
III. R = OMe, sinalexin
(antifungal activity)

IV. *N*-methyl-1-(THTP[2,3-*b*]indol-4-yl)
methanamine
(analgesic activity)

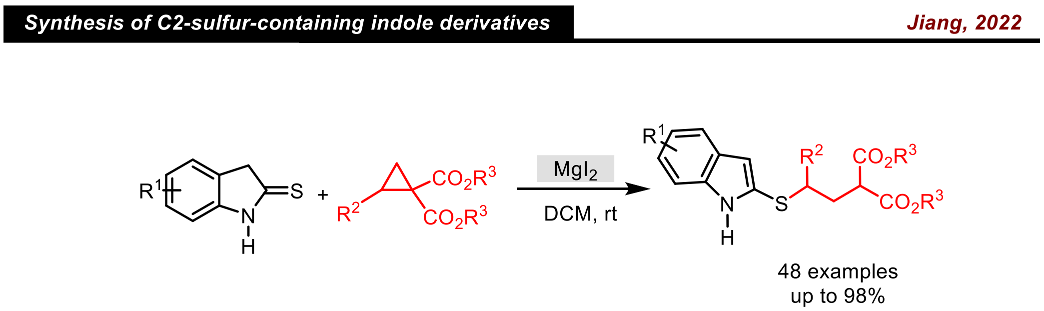
Figure 2A. Representative examples of indole-fused tricyclic bioactive agents.



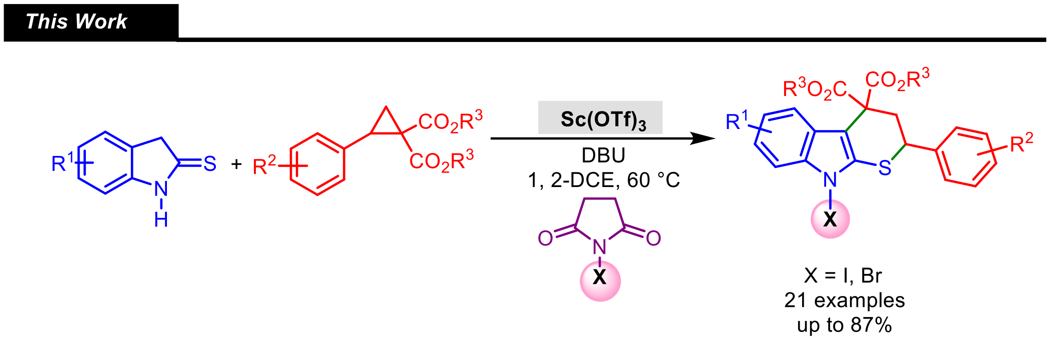
Scheme 2A.1 Ye and Sun's work on the *N*-Heterocyclic Carbene-Catalyzed (3+3) Annulation of Indoline-2-thiones with Bromoenals.



Scheme 2A.2 Namboothiri's work on the Synthesis of tetrahydrothiopyrano[2,3-*b*]indoles via (3+3) annulation of nitroallylic acetates with indoline-2-thiones.



Scheme 2A.3 Jiang's work on the MgI_2-Catalyzed Nucleophilic Ring-Opening Reactions of Donor−Acceptor Cyclopropanes with Indoline-2-thiones.

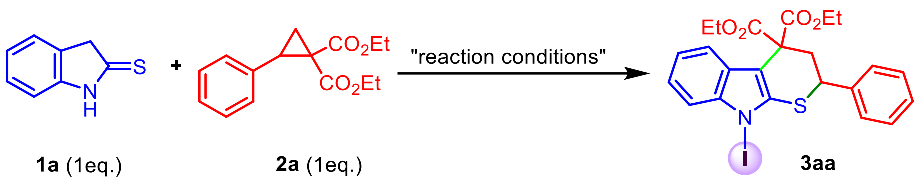


Scheme 2A.4 Synthesis of Indole-Fused Dihydrothiopyrano derivatives.

2A.2 Results and Discussions

At the onset, The present study was commenced by treating indoline-2-thione (1 eq.) **1a** with 1,1-diester cyclopropane **2a** (1 eq.) in the presence of Lewis acids like $SnCl_4$, $FeCl_3$ and $Cu(OTf)_2$ in presence of *N*-iodosuccinimide (NIS) and DBU in DCE at 60 °C (Table 2A.1, entries 1-3). These Lewis acid catalysts were unable to deliver the targeted product **3aa**. Meanwhile, we tried reaction with $InCl_3$ and MgI_2, to our delight with these Lewis acids, reaction proceeds well and compound **3aa** formed in 46% and 60% yields, respectively (Table 2A.1, entries 4, 5). Further improvement in the yield was observed when the reaction was performed with $Sc(OTf)_3$ (Table 2A.1, entry 6). Next, the reaction was optimized in terms of base, in this case, K_2CO_3 and Et_3N failed to deliver the product (Table 2A.1, entries 7, 8). Moreover, once we increase the base (DBU) loading up to 2.5 eq. the yield of 3aa was surprisingly increased to 80% in only 6 h (Table 1, entry 9). During the optimization, NIS concentration was also varied from 1 eq. – 3 eq. and found 2 eq. of NIS loading is the best choice for the transformation (Not shown in the Table 1). Increasing temperature is found reductant for the conversion of indoline-2-thione **1a** to indole fused thiopyrano derivative **3aa** (Table 2A.1, entries 11, 12). Next, we allow to react the starting materials at room temperature under the same conditions, unfortunately, we ended up with a relatively low yield of **3aa** (Table 2A.1, entry 12). Subsequently, for further improvements in the reaction yield we scanned in the presence of several solvents like DCM, chloroform, toluene, and THF, but none of the solvents used resulted in better yields when compared to DCE (Table 2A.1, entries 13-16).

Table 2A.1 Optimization of the reaction conditions[a]:

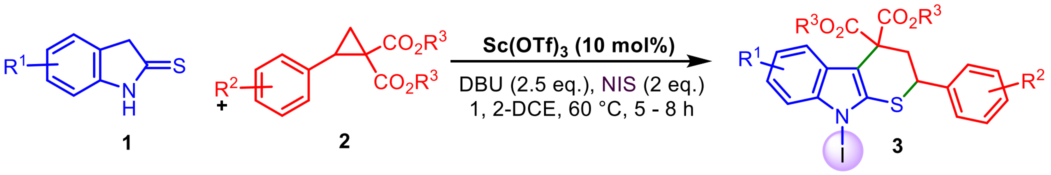


Entry	Catalyst	Base	Solvent	Time (h)	Temp.(°C)	Yield of **3aa** (%)[b]
1	$SnCl_4$	DBU	DCE	24	60	n.r.
2	$FeCl_3$	DBU	DCE	24	60	n.r.
3	$Cu(OTf)_2$	DBU	DCE	24	60	n.r.
4	$InCl_3$	DBU	DCE	24	60	46
5	MgI_2	DBU	DCE	24	60	60
6	$Sc(OTf)_3$	DBU	DCE	24	60	67
7	$Sc(OTf)_3$	K_2CO_3	DCE	24	60	n.r.
8	$Sc(OTf)_3$	Et_3N	DCE	24	60	n.r.
9[c]	$Sc(OTf)_3$	DBU	DCE	6	60	80
10[c]	$Sc(OTf)_3$	DBU	DCE	8	70	72
11[c]	$Sc(OTf)_3$	DBU	DCE	8	80	56
12[c]	$Sc(OTf)_3$	DBU	DCE	24	25	53
13[c]	$Sc(OTf)_3$	DBU	DCM	6	25	55
14[c]	$Sc(OTf)_3$	DBU	$CHCl_3$	6	60	39
15[c]	$Sc(OTf)_3$	DBU	toluene	6	60	66
16[c]	$Sc(OTf)_3$	DBU	THF	6	60	62

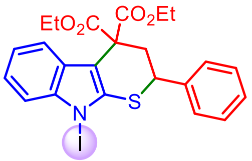
[a]Optimized reaction conditions for **3aa**: Reactions were performed with **1a** (0.6 mmol), **2a** (0.6 mmol) Lewis acid catalyst (0.06 mmol, 0.1 eq.), Base (1 eq.), NIS (2 eq.), Solvent (2 ml), N_2 atmosphere. [b]Isolated yields. [c]reaction performed with base loading 2.5 eq.

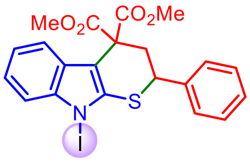
With the optimized conditions in hand (Table 2A.1, entry 9), we further examine the substrate scope of (3+3)-annulation of indoline-2-thiones **1** with D-A cyclopropanes **2** for the formation of novel *N*-iododihydrothiopyrano indole **3** scaffolds (Scheme 2A.5). A wide variety of electronically and structurally diverse D-A cyclopropanes and indoline-2-thiones provided a library of *N*-iododihydrothiopyrano indole derivatives **3** in good to excellent yields. First, we explored the scope of various D-A cyclopropanes **2** in (3+3) annulation with various indoline-2-thione **1a** (Scheme 2A.5). Having different ester functionality in D-A cyclopropanes such as ethyl and methyl worked very smoothly for the said reaction and led to the formation of **3aa** and **3ab** in 80% and 78%, respectively. Moreover, when electron-withdrawing substituents at the *para*-position of aromatic ring attached to D-A cyclopropanes were allowed to react with indoline-2-thiones, they transformed into the corresponding products in good to excellent yields **3ad**, **3ae**, **3af** and **3aj**. Electronically hindered ortho-arene decorated cyclopropane derivatives performed well under optimized conditions and furnished *N*-iododihydrothiopyrano indole skeletons **3ag** and **3ah**.

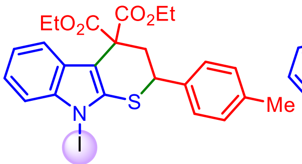
the same manner, a *meta*-substituted arene ring attached to cyclopropane provided the desired product **3ai**. Inspired by these results, we were keen to scrutinize the reaction scope of various electronically diverse thioindolenes with phenyl D-A cyclopropanes using the aforementioned methodology. Indole-2-thiones bearing electron-donating substituents at 5-position were well tolerated in reaction conditions and delivered the corresponding annulated products **3ba**, **3ca** and **3bb** in moderate yields. At the same time, C-5 and C-6 halogen (i.e., Br, Cl and F) substituted indole-2-thiones were also provided dihydrothiopyrano indoles **3da**-**3eb** in good to excellent yields.

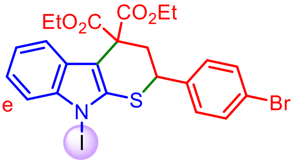


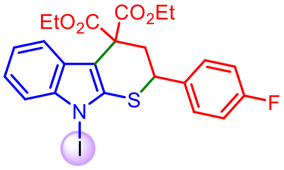
Scope of D-A Cyclopropanes

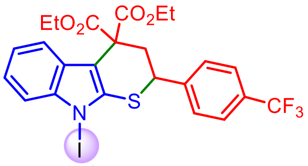

3aa, 80%, 6 h

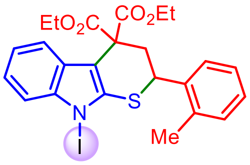

3ab, 78%, 6 h

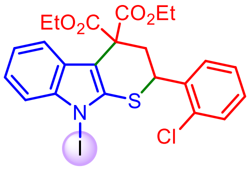

3ac, 80%, 5 h

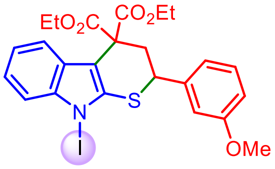

3ad, 83%, 5 h

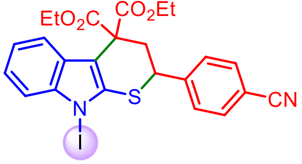

3ae, 68%, 7 h


3af, 73%, 7 h

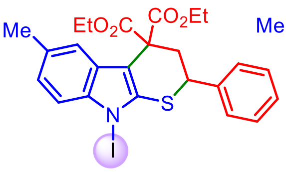

3ag, 75%, 5 h

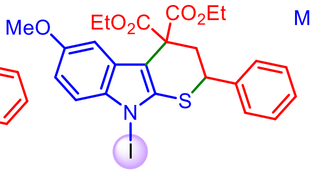

3ah, 72%, 6 h

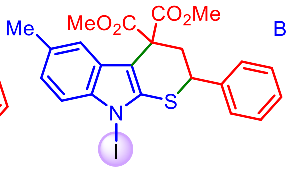

3ai, 85%, 6 h

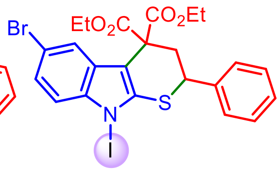

3aj, 81%, 7 h

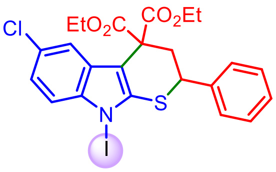
Scope of Indoline-2-thiones

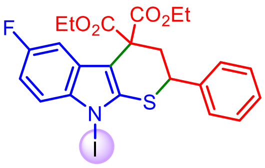

3ba, 66%, 5 h

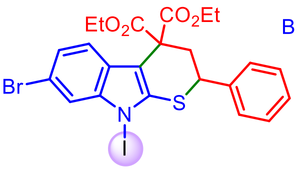

3ca, 71%, 4 h

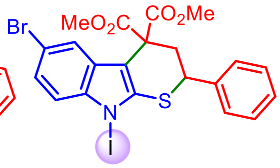

3bb, 64%, 6 h

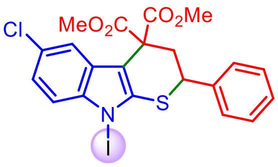

3da, 79%, 7 h


3ea, 75%, 7 h


3fa, 82%, 7 h

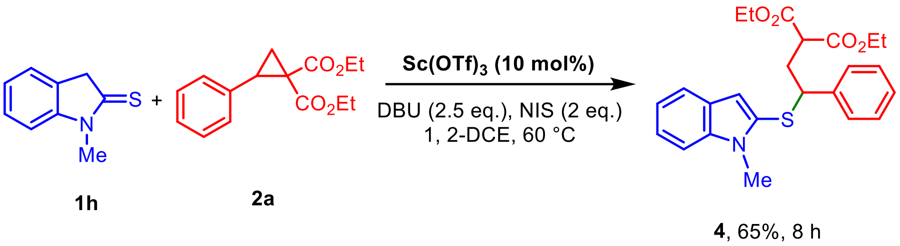

3ga, 80%, 5 h


3db, 77%, 7 h


3eb, 73%, 7 h

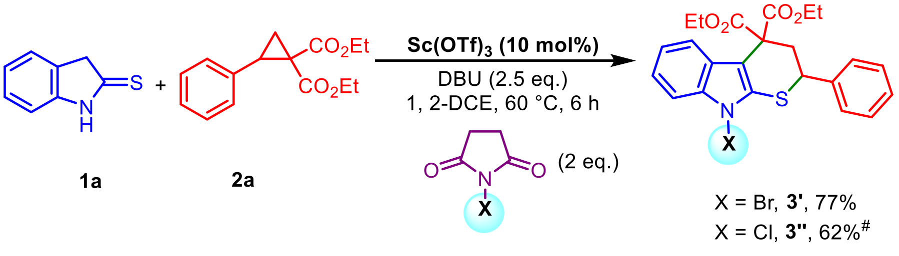
Scheme 2A.5 Substrate scope of Dihydrothiopyrano[a]. [a] Reaction Conditions: **1** (0.6 mmol, 1 eq.), **2** (0.6 mmol, 1eq.) $Sc(OTf)_3$ (0.06 mmol, 0.1 eq.), DBU (2.5 eq.), NIS (2 eq.), DCE (2 ml), 60 °C, inert conditions; [b]Isolated yield.

Additionally, when we were allowed to react N-methyl indolene-2-thione **1h** with DAC **2a** under the same optimized conditions, furnishes nucleophilic ring opening product **4** rather than cyclized one (Scheme 2A.6).



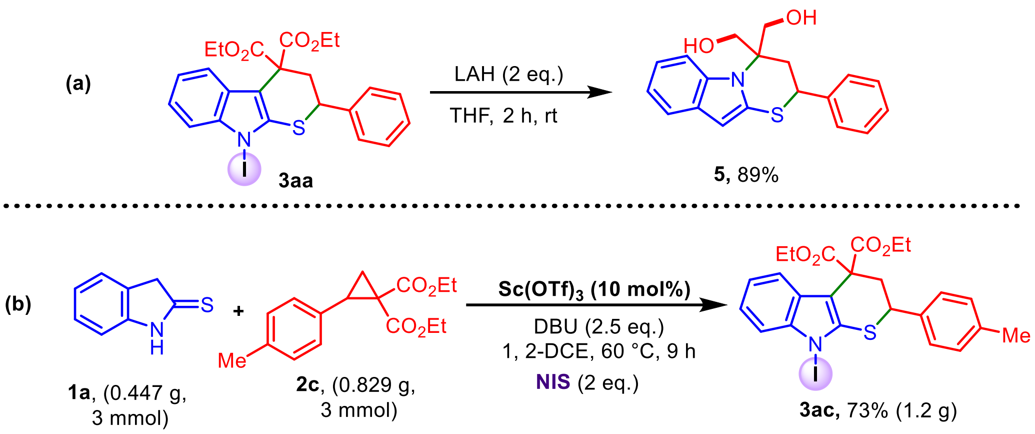
Scheme 2A.6: Nucleophilic Ring-Opening Product **4**, with reactions of Donor−Acceptor Cyclopropanes and *N*-methyl Indoline-2-thiones.

In addition, we further check the reaction scope with *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) under the standard reaction conditions, which provide corresponding *N*-haloindole fused dihydrothiopyrano derivatives in good to moderate yield (Scheme 2A.7).



Scheme 2A.7: ^{a}Reaction Conditions: **1a** (0.6 mmol, 1 eq.), **2a** (0.6 mmol, 1eq.) Sc(OTf)$_3$ (0.06 mmol, 0.1 eq.), DBU (2.5 eq.), NBS/NCS (2 eq.), DCE (2 ml), 60 °C, N_2 atmosphere; ^{b}Isolated yield. $^\#$Trace amount of unidentified compound along with **3**" was obtained.

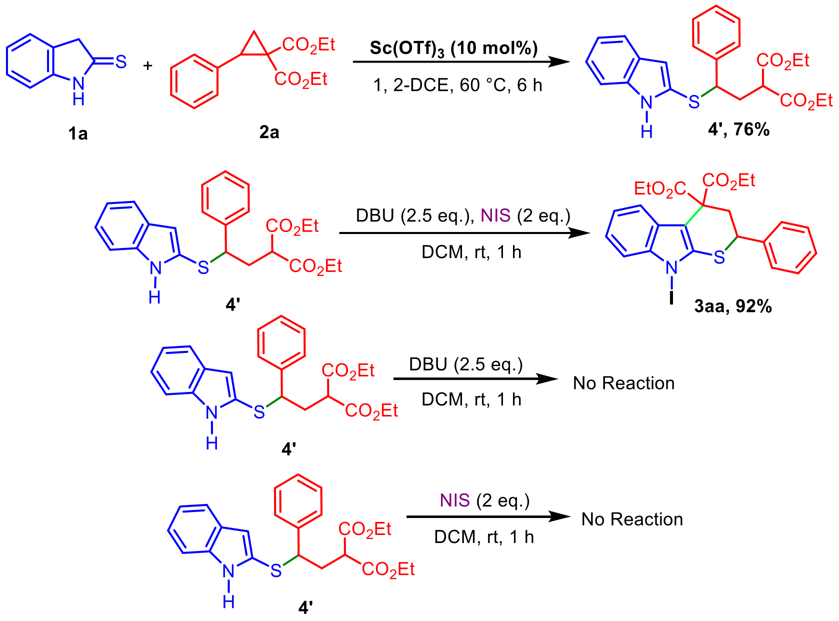
After constructing the series of indole fused thipyrano derivatives, we further check the synthetic transformation of **3aa**. The compound **3aa** was treated with lithium aluminum hydride, and to our delight *N*-fused thiazino indole derivative **5** has been formed in excellent yield (Scheme 2A.8a). To establish the credentials of this methodology, gram-scale synthesis was also carried out. The reaction was performed in the presence of 3 mmol of **1a** with 3 mmol **2c** by using the optimized reaction conditions, compound **3ac** was achieved in 73% (1.2 g) yield (Scheme 2A.8b).



Scheme 2A.8a Preparation of (2-phenyl-3,4-dihydro-2H-[1,3]thiazino[3,2-a]indole-4,4-diyl)dimethanol **5.**

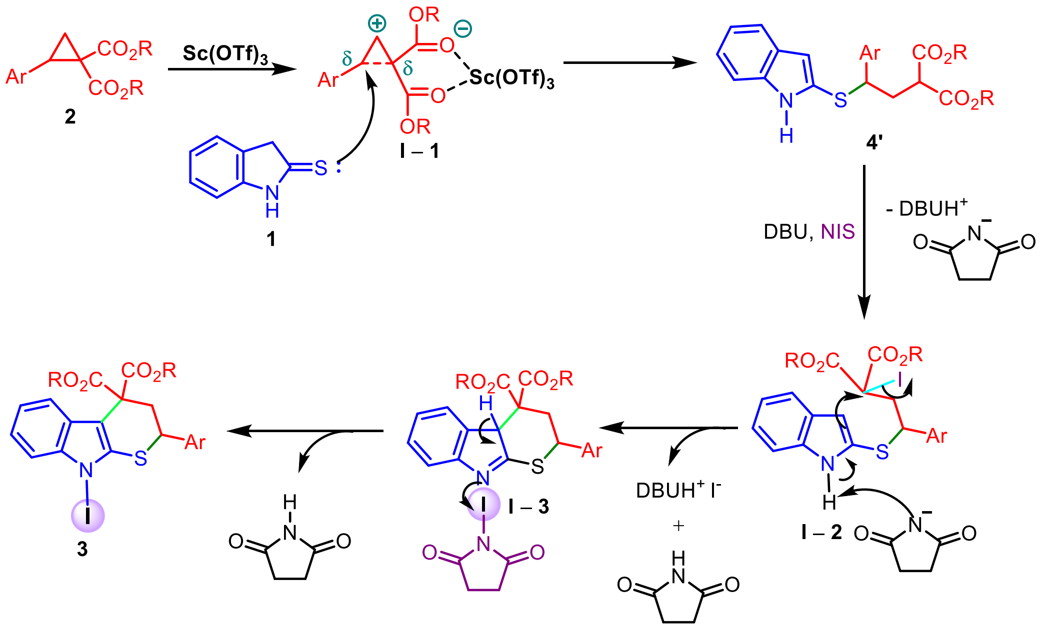
Scheme 2A.8b Gram scale synthesis of **3ac.**^{a} ^{a}Reaction conditions: **1d** (0.447 g, 3 mmol), **2a** (0.829 g, 3 mmol), Sc(OTf)$_3$ (150 mg, 30 mol%), NIS, (6 mmol, 1.35 g, 2 eq.) and DBU (7.5 mmol, 1.9 ml, 2.5 eq.), 1,2-DCE (5 mL).

To investigate the mechanistic insight of the aforementioned protocol, we performed several control experiments (Scheme 2A.9). Initially, when the reaction was screened in the presence of Sc(OTf)3, without NIS and DBU the anticipated open-chain thio-indole intermediate **4'** was observed in good yield. Next, we applied base and NIS with **4'**, which led to the formation of the desired compound **3aa** in 92% yield. Furthermore, it was observed that in the absence of either DBU or NIS compound **4'** remained unreacted.



Scheme 2A.9: control experiments to investigate the mechanistic insight.

Based on our controlled experiments attempted, following reaction mechanism is proposed (Scheme 2A.10). Initially, Lewis acid Sc(OTf)**3** coordinates with acceptor moieties in D-A cyclopropane **1** and forms activated ring intermediate **I-1**. This activated ring gets attacked by nucleophilic S-center of indoline-2-thione in S_N^2 fashion and leads to the formation of isolated intermediate **4'**. In the presence of DBU and NIS, iodination takes place on the carbon attached to ester groups, as a result, the nature of said C-center changed from nucleophilic to electrophilic center. Subsequently, nucleophilic attack from C-3 indole to emerging electrophilic C-center followed by re-aromatization and iodination of indole nitrogen leads to furnish desired product **3**.



Scheme 2A.10: Plausible Mechanism of dihydrothiopyrano.

2A.3 Conclusions

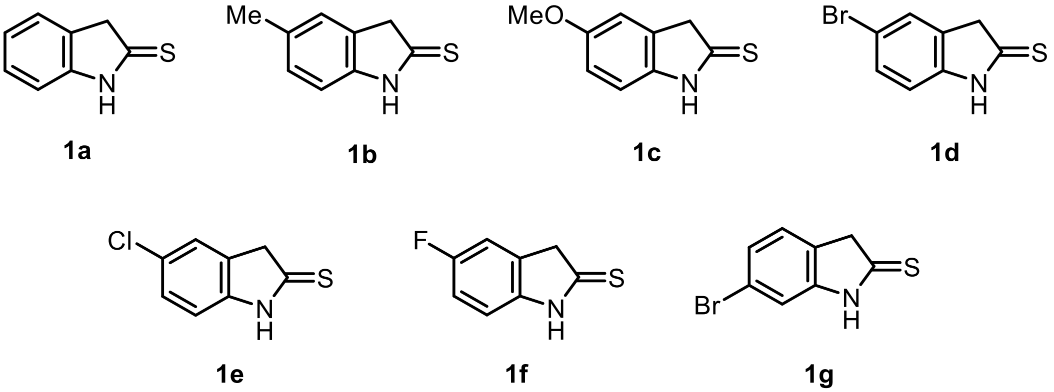
In summary, an efficient and straightforward strategy for the synthesis of *N*-haloindole fused dihydrothiopyrano derivatives has been developed via Sc(OTf)$_3$ catalyzed (3+3)-annulation reactions of DACs and indole-2-thiones under mild conditions in good to excellent yields. We are currently exploiting this protocol for synthesizing targeted biologically important molecules.

2A.4 Experimental Section

All the reactions were carried out under an inert atmosphere using the schlenk technique. All solvents were dried and stored over molecular sieves under argon atmosphere. All chemicals and reagents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using E. Merck silica gel 60 (100–200 mesh). ^{1}H, ^{13}C, and DPT-135 NMR spectra were recorded in $CDCl_3$, on JEOL JNM-ECS spectrometer at operating frequencies of 400 MHz (^{1}H) or 100 MHz (^{13}C) as indicated in the individual spectrum. Chemical shifts (δ) are given in parts per million (ppm) relative to residual solvent (chloroform, δ= 7.26 for ^{1}H and 77.16 for proton decoupled ^{13}C NMR) and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, td for triplet of doublet, q for quartet, and m for multiplet. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) methods on waters mass spectrometer (XEVO G2-XS QTOF).

2A.4.1 Preparation of starting materials

General Procedure for the synthesis of indoline-2-thiones (1a-1g)[13]: A mixture of 2-oxindole (1.63 mmol, 1.63 eq.) and $NaHCO_3$ (3.26 mmol, 3.26 eq.) in THF (25 mL) was allowed to stir for 5 min at room temperature. After that P_2S_5 (1 mmol, 1.0 eq.) was added, and the reaction mixture was stirred for 4 h at room temperature. The excess THF was removed under reduced pressure. After that ice-cold water (50 mL) was added to the residue with vigorous stirring to afford a light-yellow precipitate that was filtered and air-dried.



1a 1b 1c 1d 1e 1f 1g

Figure 2A.4.1 Used Indoline-2-thione **1**

General procedure for the preparation of cyclopropane-1,1-diester derivatives[14]: Trimethylsulfoxonium iodide (TMSOI) (1.5 eq.) was added drop-wise into the suspension of sodium hydride (NaH) (60% suspension in mineral oil, 1.5 eq.) and dry dimethyl sulfoxide (DMSO) under nitrogen atmosphere. ***Caution!*** : Reaction of trimethylsulfoxonium iodide with sodium hydride is exothermic (evolution of H_2 and heat). So, the suspension was maintained at 0 ºC before adding trimethylsulfoxonium iodide. After 15-20 min. vigorous stirring, a solution of benzylidenemalonate (1.0 eq.) in DMSO was added, mixture was allowed to warm up to room temperature. Upon completion (as determined by TLC analysis) of the reaction, crushed ice was added in the crude solution and extracted with diethyl ether. The combined organic layers were washed once with brine, dried over sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl actetate as an eluent.

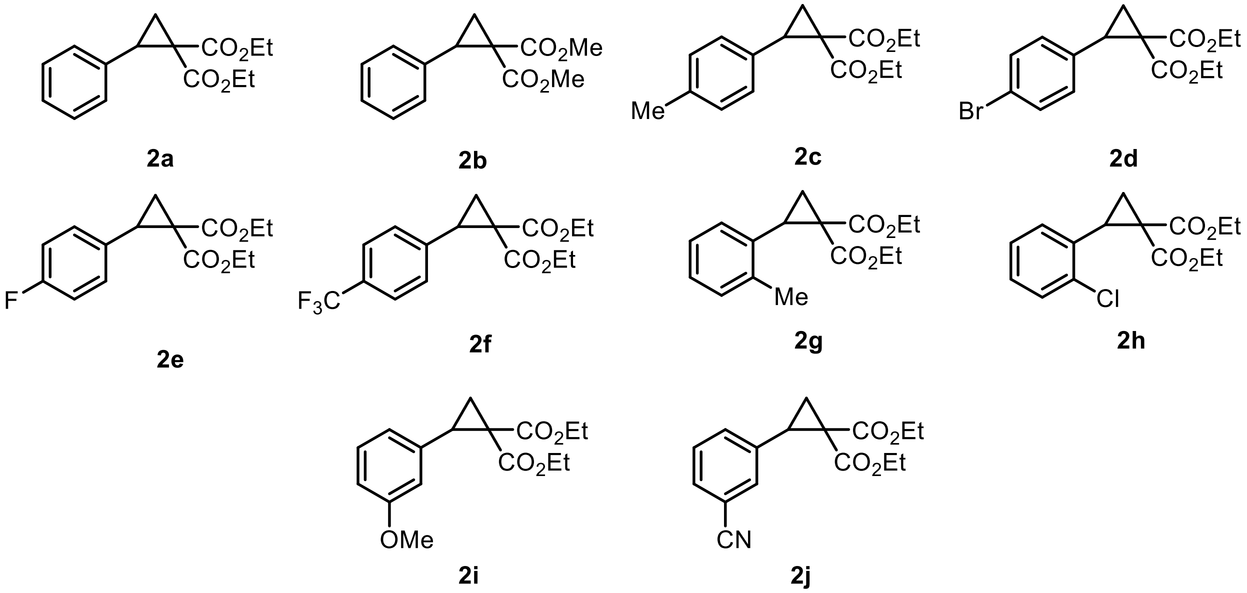


Figure 2A.4.2 Used cyclopropane-1,1-diester derivatives **2**

2A.4.2 General procedures

General Procedures for the synthesis of *N*-iodoindole fused dihydrothiopyrano derivatives (3): In a schlenk tube, indoline-2-thione **1** (0.6 mmol, 1.0 eq.), donor-acceptor cyclopropanes **2** (0.6 mmol, 1.0 eq.), and $Sc(OTf)_3$ (0.06 mmol, 30 mg, 0.1 eq.) were dissolved in anhydrous DCE (1 mL) under N_2 atmosphere. After that *N*-iodosuccinimide (NIS) (1.2 mmol, 270 mg, 2.0 eq) and DBU (1.5 mmol, 0.22 ml, 2.5 eq.) were added subsequently. The reaction mixture was allowed to stir for 5–8 h at 60 ^{0}C (oil bath). After completion (by TLC analysis) of the reaction, the crude mixture was filtered off and the filtrate was concentrated under reduced pressure. The collected crude was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents.

Gram scale synthesis of Diethyl 9-iodo-2-(*p*-tolyl)-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9H)-dicarboxylate (3ac): In a schlenk tube, indoline-2-thione **1a** (3 mmol, 0.447 g, 1 eq.), donor-acceptor cyclo-propane **2c** (3 mmol, 0.829 g, 1 eq.), and $Sc(OTf)_3$ (0.3 mmol, 0.147 g, 0.1 eq.) were dissolved in anhydrous DCE (6 mL) under N_2 atmosphere. After that NIS, (6 mmol, 1.35 g, 2 eq.) and DBU (7.5 mmol, 1.9 ml, 2.5 eq.) were added subsequently. The reaction mixture was stirred for 9 h at 60 ^{0}C (oil bath). After completion (by TLC analysis) of reaction, the crude mixture was filtered off and filtrate was concentrated under reduced pressure. The collected crude was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents**.**

General Procedures for the synthesis of *N*-haloindole fused dihydrothiopyrano derivatives (3' and 3"): In a schlenk tube, indoline-2-thione **1a** (0.1 mmol, 15 mg, 1 eq.), donor-acceptor cyclopropane **2a** (0.1 mmol, 26.2 mg, 1 eq.), and Sc(OTf)$_3$ (0.01 mmol, 5 mg, 0.1 eq.) were dissolved in anhydrous DCE (1 mL) under N_2 atmosphere. After that, NBS (for 3') or NCS (for 3") (0.2 mmol, 2 eq.) and DBU (0.25 mmol, 0.03 ml, 2.5 eq.) were added subsequently. The reaction mixture was allowed to stir for 6 h at 60 ^{0}C (oil bath). After completion of reaction, as monitored by TLC, crude mixture was filtered and concentrated under reduced pressure. The collected crude was further purified by silica gel column chromatography using hexane and ethyl acetate as an eluent.

2A.4.3 Characterization of compounds

Synthesis of Diethyl 9-bromo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3'): Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/1) 37 mg, 77 %, yield Brown solid; mp = 104 - 106 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.49 – 7.36 (m, 6H), 7.19 – 7.14 (m, 1H), 7.12 – 7.09 (m, 2H), 4.52 (dd, *J* = 12.0, 1.9 Hz, 1H), 4.41 – 4.16 (m, 4H), 3.36 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.91 (dd, *J* = 13.8, 12.0 Hz, 1H), 1.24 – 1.19 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.1, 167.3, 138.4, 137.6, 129.3, 128.9, 128.2, 127.9, 127.7, 121.8, 121.4, 117.7, 111.7, 89.6, 70.1, 63.5, 63.1, 40.9, 40.6, 14.1, 14.0; HRMS: *m/z* calculated for $C_{23}H_{23}NO_4SBr$ $[M+H]^+$ 488.0532, found 488.0531; IR (neat) ($\tilde{\upsilon}$): 2925, 2854, 1740, 1501, 1449, 1368, 1255, 1228, 1023, 739, 699 cm^{-1} .

Synthesis of Diethyl 9-Chloro-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3''): Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/1) 40 mg, 62 %, yield Brown viscous liquid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.76 (d, *J* = 7.3 Hz, 1H), 7.53

– 7.49 (m, 4H), 7.38 – 7.30 (m, 5H), 5.30 (dd, *J* = 8.1, 5.9 Hz, 1H), 4.30 – 4.14 (m, 4H), 3.77 (dd, *J* = 10.6, 7.3 Hz, 1H), 3.62 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.19 – 3.16 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H);^{13}C{^{1}H} NMR (101 MHz, DMSO-d$_6$) δ 177.4, 165.7, 164.7, 149.1, 138.4, 137.9, 132.5, 128.9, 128.6, 128.5, 128.5, 128.4, 128.1, 127.7, 127.6, 127.1, 123.2, 119.8, 81.2, 69.2, 63.3, 62.9, 45.5, 41.8, 13.6, 13.4; HRMS: *m/z* calculated for $C_{23}H_{22}NO_4SCl$ [M+H]$^+$ 444.1037, found 444.1036; IR (neat) (ṽ): 2924, 2853, 1741, 1501, 1446, 1366, 1254, 1227, 1023, 736, 698 cm^{-1} .

Diethyl 2-(2-((1-methyl-1*H*-indol-2-yl)thio)-2-phenylethyl)malonate(4): In a schlenk tube, indoline-2-thione **1a** (3 mmol, 0.447 g, 1 eq.), donor-acceptor cyclopropane **2c** (3 mmol, 0.829 g, 1 eq.), and Sc(OTf)$_3$ (0.3 mmol, 0.147 g, 0.1 eq) were dissolved in anhydrous DCE (6 mL) under N$_2$ atmosphere. The reaction mixture was stirred for 6 h at 60 ^{0}C (oil bath). After completion (by TLC analysis) of reaction, the crude mixture was filtered off and filtrate was concentrated under reduced pressure. The collected crude was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents. Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 166 mg, 65 % yield, Viscous Yellow liquid; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.24 – 7.17 (m, 5H), 7.12 – 7.08 (m, 1H), 7.04 – 7.02 (m, 2H), 6.72 (s, 1H), 4.20 – 4.08 (m, 4H), 3.97 (t, *J* = 7.8 Hz, 1H), 3.56 (t, *J*=7.3 Hz, 1H), 3.31 (s, 3H), 2.69 – 2.62 (m, 1H), 2.56 – 2.49 (m, 1H), 1.25 – 1.21 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.1, 169.0, 140.5, 138.4, 129.1, 128.7, 128.1, 127.91, 127.85, 127.6, 127.3, 122.7, 120.7, 119.8, 111.7, 109.9, 61.7, 52.8, 50.2, 33.7, 14.1; HRMS: *m/z* calculated for $C_{24}H_{28}NO_4S$ [M+H]$^+$ 426.1738, found 426.1739;IR (neat) (ṽ): 2935, 1720, 1455, 1368, 1233, 1015,750, 629 cm^{-1}.

Diethyl 2-(2-((1*H*-indol-2-yl)thio)-2-phenylethyl)malonate (4’): In a schlenk tube, 1-methylindoline-2-thione **1a** (3 mmol, 67 mg, 1 eq.), donor-acceptor cyclopropane **2c** (3 mmol, 54 mg, 1 eq.), and Sc(OTf)$_3$ (0.3 mmol, 10 mg, 0.1 eq) were dissolved in anhydrous DCE (6 ml) under N$_2$ atmosphere. The reaction mixture was stirred for 6 h at 60 ^{0}C (oil bath). After completion (by TLC analysis) of reaction, the crude mixture was filtered off and filtrate was concentrated under reduced pressure. The collected crude was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents. Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 187 mg, 75 % yield, Viscous Yellow liquid; ^{1}H NMR (400

MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.24 (m, 4H), 7.19 – 7.17 (m, 1H), 7.15 – 7.12 (m, 2H), 7.10 – 7.06 (m, 1H), 6.54 (s, 1H), 4.22 – 4.11 (m, 4H), 4.06 (t, J = 7.8 Hz, 1H), 3.58 (t, *J* = 7.2 Hz, 1H), 2.66 – 2.58 (m, 1H), 2.56 – 2.49 (m, 1H), 1.24 – 1.22 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 169.4, 169.2, 141.0, 137.4, 128.7, 128.3, 127.8, 127.7, 125.8, 122.9, 120.6, 120.0, 111.5, 110.9, 61.8, 53.6, 52.7, 50.4, 34.1, 14.1; HRMS: *m/z* calculated for $C_{23}H_{26}NO_4S$ $[M+H]^+$ 412.1581, found 412.1583; IR (neat) (ṽ): 3373, 2981,1724,1492,1370, 1340, 859, 749, 698, 649 cm^{-1}.

Synthesis of (2-Phenyl-3,4-dihydro-2*H*-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol (5): In a schlenk tube, diethyl 9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (0.15 mmol, 81 mg, 1 eq.), was dissolved in dry THF (2 ml) under N_2 atmosphere and added lithium aluminium hydride (0.30 mmol, 12 mg, 2 eq.) at 0 °C. After addition, the reaction was warmed to room temperature and stirred for 2 h. Upon completion (by TLC analysis), the reaction was quenched with ice cold-water and extracted with ethyl acetate thrice. The collected organic layers were dried over Na_2SO_4, concentrated under reduced pressure and further purified by silica gel column chromatography using hexane and ethyl acetate as eluents. Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 44 mg, 89% yield, colorless viscous liquid. ^1H NMR (400 MHz, DMSO-d_6): δ 7.68 – 7.66 (m, 1H), 7.53 – 7.51 (m, 2H), 7.45 – 7.41 (m, 2H), 7.39 – 7.31 (m, 3H), 7.04 – 6.96 (m, 2H), 6.27 (s, 1H), 5.20 (t, *J* = 5.4 Hz, 1H), 4.95 (t, *J* = 5.6 Hz, 1H), 4.88 (dd, *J* = 12.4, 1.8 Hz, 1H), 4.52 – 4.47 (m, 1H), 3.98 (d, J = 5.5 Hz, 2H), 3.76 (dd, *J* = 11.9, 5.5 Hz, 1H), 2.92 (dd, *J* = 14.1, 12.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 140.2, 136.4, 131.7, 128.9, 128.8, 128.1, 127.6, 119.6, 119.4, 118.8, 113.1, 98.8, 64.7, 62.8, 38.6. HRMS: m/z calculated for $[M+H]^+$ 326.1204, found 326.1215; IR (neat) (ṽ): 3257 (br.), 2920, 2850, 1600, 1440, 1311, 1276, 997, 773, 445, cm-1 .

Diethyl 9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3aa): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 256 mg, 80% yield, Brown solid; mp = 143-145 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.46 (m, 2H), 7.43 – 7.34 (m, 3H), 7.33 – 7.31 (m, 1H), 7.19 – 7.15 (m, 1H), 7.13 – 7.09 (m, 1H), 7.08 – 7.06 (m, 1H), 4.53 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.42 – 4.15 (m, 4H), 3.36 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.91 (dd, *J* = 13.8, 12.0

Hz, 1H), 1.24 (t, *J* = 5.3 Hz, 3H), 1.21 (t, *J* = 5.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.1, 167.3, 138.3, 138.2, 132.2, 130.7, 129.3, 128.9, 127.8, 121.8, 121.5, 119.6, 111.7, 70.3, 63.5, 63.1, 58.3, 41.3, 41.1, 14.09, 14.05; HRMS: *m/z* calculated for $C_{23}H_{22}NO_4SI$ $[M+H]^+$ 536.0391, found 536.0392; IR (neat) (ῦ): 2926, 2852, 1743, 1448, 1254, 1227, 1082, 739 cm^{-1} .

Dimethyl 9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ab): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 237 mg, 78% yield, Brown solid; mp = 134 - 136 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.45 (m, 2H), 7.43 – 7.36 (m, 3H), 7.35 – 7.32 (m, 1H), 7.21 – 7.17 (m, 1H), 7.16 – 7.11 (m, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 4.51 (dd, *J* = 12.0, 1.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.37 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.95 (dd, *J* = 13.8, 12.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.6, 167.9, 138.11, 138.07, 132.2, 130.7, 129.3, 129.0, 127.8, 122.2, 121.6, 119.7, 111.1, 70.2, 58.3, 54.1, 53.8, 41.2, 41.0; HRMS: m/z calculated for $C_{21}H_{19}NO_4SI$ $[M+H]^+$ 508.0079, found 508.0079; IR (neat) (ῦ): 2924, 2851, 1743, 1448, 1260, 1227, 1174, 1082, 738 cm-1 .

Diethyl 9-iodo-2-(*p*-tolyl)-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ac): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 165 mg, 50% yield, Brown solid; mp = 124 - 126 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.34 (m, 2H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.18 – 7.14 (m, 1H), 7.13 – 7.09 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 4.49 (dd, *J* = 12.0, 1.9 Hz, 1H), 4.41 – 4.21 (m, 4H), 3.33 (dd, *J* = 13.9, 2.0 Hz, 1H), 2.89 (dd, *J* = 13.8, 12.1 Hz, 1H), 2.37 (s, 3H), 1.22 – 1.17 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.1, 167.3, 138.8, 138.2, 135.3, 130.7, 129.9, 128.9, 127.6, 121.8, 121.5, 119.6, 111.7, 70.4, 63.5, 63.1, 58.2, 41.2, 41.0, 29.8, 14.09, 14.05; HRMS: *m/z* calculated for $C_{24}H_{25}NO_4SI$ $[M+H]^+$ 550.0549, found 550.0549; IR (neat) (ῦ): 2924, 2852, 1739, 1513, 1260, 1227, 1022, 800, 738 cm^{-1} .

Diethyl 2-(4-bromophenyl)-9-iodo-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ad): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 305 mg, 83% yield, Green solid; mp = 139 - 141 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.52 (m, 2H), 7.37 – 7.34 (m, 2H), 7.33 – 7.31 (m, 1H), 7.19 – 7.15 (m, 1H), 7.14 – 7.10 (m, 1H), 7.08 – 7.06

(m, 1H), 4.51 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.39 – 4.15 (m, 4H), 3.31 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.85 (dd, *J* = 13.7, 12.0 Hz, 1H), 1.22 – 1.18 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.9, 167.2, 138.1, 137.4, 132.4, 131.6, 130.7, 129.5, 122.9, 121.9, 121.6, 119.7, 111.8, 70.2, 63.6, 63.1, 58.5, 41.0, 40.8, 14.1, 14.0; HRMS: *m/z* calculated for $C_{23}H_{22}NO_4SBrI$ $[M+H]^+$ 613.9498, found 613.9498; IR (neat) (ῦ): 2925, 2853, 1739, 1487, 1260, 1225, 1088, 1011, 737 cm^{-1}.

Diethyl 2-(4-fluorophenyl)-9-iodo-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ae): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 226 mg, 68% yield, Brown solid; mp = 149 - 151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.43 (m, 2H), 7.33 – 7.31 (m, 1H), 7.19 – 7.06 (m, 5H), 4.53 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.42 – 4.14 (m, 4H), 3.32 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.87 (dd, *J* = 13.7, 12.1 Hz, 1H), 1.23 – 1.19 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.0, 167.3, 162.9 (d, $^{1}J_{C\text{-}F}$ = 249.44 Hz), 138.1, 134.1 (d, $^{4}J_{C\text{-}F}$ = 3.05 Hz), 131.9, 130.7, 129.5 (d, $^{3}J_{C\text{-}F}$ = 8.26 Hz), 121.9, 121.5, 119.6, 116.2 (d, $^{2}J_{C\text{-}F}$ = 21.66 Hz), 111.8, 70.2, 63.6, 63.1, 58.4, 41.2, 40.6, 14.06, 14.05; ^{19}F NMR (377 MHz, $CDCl_3$): δ -112.56; HRMS: *m/z* calculated for $C_{23}H_{22}NO_4SIF$ $[M+H]^+$ 554.0298, found 554.0298; IR (neat) (ῦ): 2925, 2852, 1740, 1603, 1509, 1257, 1226, 1022, 739 cm^{-1}.

Diethyl 9-iodo-2-(4-(trifluoromethyl) phenyl)-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3af): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 264 mg, 73% yield, Yellow solid; mp = 179 - 181 °C. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.20 – 7.16 (m, 1H), 7.15 – 7.11 (m, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 4.61 (dd, *J* = 11.9, 1.7 Hz, 1H), 4.40 – 4.16 (m, 4H), 3.34 (dd, *J* = 13.7, 1.9 Hz, 1H), 2.89 (dd, *J* = 13.7, 12.0 Hz, 1H), 1.24 – 1.19 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.9, 167.2, 142.4 (q, $^{4}J_{C\text{-}F}$ = 1.24 Hz), 138.2, 131.3, 131.2 (q, $^{2}J_{C\text{-}F}$ = 32.93 Hz), 130.6, 128.3, 126.3 (q, $^{3}J_{C\text{-}F}$ = 3.80 Hz), 123.9 (q, $^{1}J_{C\text{-}F}$ = 278.06 Hz), 122.0, 121.6, 119.7, 111.8, 70.1, 63.7, 63.2, 58.7, 40.89, 40.91, 14.1, 14.0; ^{19}F NMR (377 MHz, $CDCl_3$): δ -62.69; HRMS: *m/z* calculated for $C_{24}H_{22}NO_4SIF_3$ $[M+H]^+$ 604.0266, found 604.0266; IR (neat) (ṽ): 2990, 2856, 1740, 1445, 1323, 1227, 1169, 1017, 738 cm^{-1}.

Diethyl 9-iodo-2-(*o*-tolyl)-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ag): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 247 mg, 75% yield, Light green solid; mp = 134 - 136 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.60 – 7.58 (m, 1H), 7.33 – 7.21 (m, 4H), 7.19 – 7.07 (m, 3H), 4.79 (dd, *J* = 11.9, 1.8 Hz, 1H), 4.38 – 4.18 (m, 4H), 3.28 (dd, *J* = 13.9, 1.9 Hz, 1H), 2.92 (dd, *J* = 13.8, 11.9 Hz, 1H), 2.45 (s, 3H), 1.24 – 1.18 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.1, 167.4, 138.2, 136.4, 132.4, 131.1, 130.7, 128.6, 127.0, 121.8, 121.5, 119.5, 111.8, 70.4, 63.5, 63.1, 58.4, 40.6, 37.0, 19.4, 14.06; HRMS: *m/z* calculated for $C_{24}H_{25}NO_4SI$ [M+H]$^+$ 550.0549, found 550.0549; IR (neat) (ṽ): 2928, 2851, 1738, 1445, 1226, 1065, 1021, 737 cm^{-1} .

Diethyl 2-(2-chlorophenyl)-9-iodo-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ah): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 246 mg, 72% yield, Light green solid; mp =114 - 116 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.67 – 7.64 (m, 1H), 7.45 – 7.42 (m, 1H), 7.35 – 7.28 (m, 3H), 7.20 – 7.16 (m, 1H), 7.14 – 7.10 (m, 1H), 7.07 – 7.05 (m, 1H)., 5.11 (dd, *J* = 11.3, 2.1 Hz, 1H), 4.35 – 4.15 (m, 4H), 3.30 (dd, *J* = 13.9, 2.2 Hz, 1H), 2.99 (dd, *J* = 13.9, 11.3 Hz, 1H), 1.25 – 1.17 (m, 6H**);** ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 167.7, 167.1, 138.2, 135.9, 133.9, 131.5, 130.6, 130.1, 129.9, 129.1, 127.8, 122.0, 121.5, 119.6, 111.5, 70.0, 63.5, 63.3, 58.7, 40.0, 37.3, 14.1, 14.0; HRMS: *m/z* calculated for $C_{23}H_{22}NO_4SClI$ [M+H]$^+$ 570.0003, found 550.0003; IR (neat) (ṽ): 2923, 2850, 1739, 1445, 1225, 1021, 738 cm^{-1} .

Diethyl 9-iodo-2-(3-methoxyphenyl)-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ai): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 288 mg, 85% yield, Yellow solid; mp = 114 - 116 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34 – 7.30 (m, 2H), 7.19 – 7.15 (m, 1H), 7.13 – 7.09 (m, 1H), 7.08 – 7.04 (m, 2H), 7.01 – 7.00 (m, 1H), 6.94 – 6.86 (m, 1H), 4.51 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.40 – 4.17 (m, 4H), 3.84 (s, 3H), 3.35 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.89 (dd, *J* = 13.8, 12.0 Hz, 1H), 1.23 – 1.18 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.1, 167.3, 160.2, 139.8, 138.2, 132.1, 130.7, 130.3, 121.8, 121.5, 120.0, 119.6, 114.4, 113.4, 111.7, 70.3, 63.6, 63.1, 58.3, 55.5, 41.3, 41.1, 14.1, 14.05; HRMS: *m/z* calculated for $C_{24}H_{25}NO_5SI$ [M+H]$^+$ 566.0497, found 566.0498; IR (neat) (ṽ): 2925, 2851, 1739, 1600, 1259, 1227, 1022, 796, 739 cm^{-1} .

Diethyl 2-(4-cyanophenyl)-9-iodo-2,3-dihydrothiopyrano[2,3-b]indole-4,4(9H)-dicarboxylate(3aj): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 272 mg, 81% yield, Green solid; mp = 184 - 186 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.72 – 7.69 (m, 2H), 7.61 – 7.59 (m, 2H), 7.34 – 7.32 (m, 1H), 7.21 – 7.17 (m, 1H), 7.16 – 7.11 (m, 1H), 7.10 – 7.07 (m, 1H), 4.61 (dd, *J* = 11.9, 1.9 Hz, 1H), 4.42 – 4.13 (m, 4H), 3.32 (dd, *J* = 13.7, 2.0 Hz, 1H), 2.87 (dd, *J* = 13.7, 12.0 Hz, 1H), 1.23 – 1.19 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 167.8, 167.2, 143.7, 138.1, 133.0, 130.8, 130.6, 128.7, 122.1, 121.7, 119.8, 118.4, 112.9, 111.9, 70.0, 63.7, 63.3, 58.9, 41.0, 40.7, 14.0; HRMS: *m/z* calculated for $C_{24}H_{22}N_2O_4SI$ [M+H]$^+$ 561.0345, found 561.0345; IR (neat) (ῡ): 2981, 2852, 2228, 1737, 1607, 1225, 1113, 1020, 738 cm^{-1} .

Diethyl 9-iodo-6-methyl-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ba): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 218 mg, 66 % yield, Green solid; mp = 184 - 186 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48 – 7.46 (m, 2H), 7.43 – 7.36 (m, 3H), 7.10 – 7.09 (m, 1H), 6.97 – 6.91 (m, 2H), 4.52 (dd, *J* = 12.0, 1.9 Hz, 1H), 4.39 – 4.16 (m, 4H), 3.33 (dd, *J* = 13.9, 2.0 Hz, 1H), 2.90 (dd, *J* = 13.7, 12.1 Hz, 1H), 2.44 (s, 3H), 1.23 – 1.19 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.2, 167.4, 138.4, 136.5, 132.0, 131.0, 130.8, 129.3, 128.9, 127.8, 123.4, 119.4, 111.4, 70.3, 63.5, 63.0, 57.9, 41.3, 41.1, 21.4, 14.1, 14.07; HRMS: *m/z* calculated for $C_{24}H_{25}NO_4SI$ [M+H]$^+$ 550.0549, found 550.0549; IR (neat) (ῡ): 2960, 2860, 1740, 1455, 1254, 1226, 1084, 800, 738 cm^{-1} .

Diethyl 9-iodo-6-methoxy-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ca): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 283 mg, 71 % yield, Brown solid; mp =182 - 184 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48 – 7.45 (m, 2H), 7.43 – 7.36 (m, 3H), 6.99 – 6.96 (m, 1H), 6.77 – 6.72 (m, 2H), 4.53 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.38 – 4.18 (m, 4H), 3.88 (s, 3H), 3.33 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.89 (dd, *J* = 13.8, 12.0 Hz, 1H), 1.23 – 1.19 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.1, 167.4, 164.4, 155.4, 138.3, 133.0, 131.4, 129.3, 128.9, 127.8, 112.7, 111.6, 101.5, 70.3, 63.6, 63.1, 55.9, 41.3, 41.0, 14.1, 14.00; HRMS: *m/z* calculated for $C_{24}H_{25}NO_5SI$ [M+H]$^+$ 566.0498, found 566.0498; IR (neat) (ῡ): 2930, 2854, 1739, 1455, 1257, 1083, 739 cm^{-1} .

Diethyl 6-bromo-9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3da): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 291 mg, 79 % yield, Brown solid; mp = 158 - 160 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48 – 7.35 (m, 6H), 7.20 – 7.18 (m, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 4.52 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.40 – 4.17 (m, 4H), 3.35 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.89 (dd, *J* = 13.8, 12.0 Hz, 1H), 1.24 (t, *J* = 6.1 Hz, 3H), 1.21 (t, *J* = 6.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.8, 167.0, 138.0, 137.0, 134.1, 132.5, 129.3, 129.0, 127.7, 124.5, 122.1, 115.0, 113.2, 70.3, 63.7, 63.3, 56.8, 41.3, 40.8, 14.1, 14.07; HRMS: *m/z* calculated for $C_{23}H_{22}NO_4SBrI$ $[M+H]^+$ 613.9497, found 613.9498; IR (neat) (ῡ): 2926, 2852, 1740, 1443, 1257, 1228, 1063, 1021,791, 758 cm^{-1} .

Diethyl 6-chloro-9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ea): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 256 mg, 75 % yield, Green solid; mp =164 - 166 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.45 (m, 2H), 7.43 – 7.35 (m, 3H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.07 – 7.05 (m, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 4.53 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.40 – 4.18 (m, 4H), 3.35 (dd, *J* = 13.9, 1.9 Hz, 1H), 2.89 (dd, *J* = 13.8, 12.0 Hz, 1H), 1.24 (t, *J* = 6.2 Hz, 3H), 1.21 (t, *J* = 6.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.8, 167.0, 138.0, 136.6, 134.2, 132.0, 129.3, 129.0, 127.7, 127.4, 121.9, 119.1, 112.8, 70.3, 63.7, 63.3, 57.0, 41.3, 40.8, 14.1, 14.07; HRMS: *m/z* calculated for $C_{23}H_{22}NO_4SClI$ $[M+H]^+$ 570.0002, found 570.0003; IR (neat) (ῡ): 2931, 2855, 1742, 1601, 1440, 1257, 1230, 1021, 756 cm^{-1} .

Diethyl 6-fluoro-9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3fa): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 272 mg, 82 % yield, Brown solid; mp = 134 - 136 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.35 (m, 5H), 7.03 – 6.98 (m, 2H), 6.87 – 6.82 (m, 1H), 4.53 (dd, *J* = 12.0, 1.7 Hz, 1H), 4.42 – 4.17 (m, 4H), 3.35 (dd, *J* = 13.9, 1.8 Hz, 1H), 2.89 (dd, *J* = 13.7, 12.0 Hz, 1H), 1.26 – 1.19 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.0, 167.1, 159.0 (d, $^1J_{C\text{-}F}$ = 238.81 Hz), 138.1, 134.5 (d, $^2J_{C\text{-}F}$ = 26.07 Hz), 131.7 (d, $^3J_{C\text{-}F}$ = 10.60 Hz), 129.3, 129.0, 127.7, 112.6 (d, $^3J_{C\text{-}F}$ = 9.49 Hz), 109.8 (d, $^2J_{C\text{-}F}$ = 26.16 Hz), 105.1, 104.9, 70.3, 63.7, 63.2, 57.4, 41.2, 40.9, 14.09, 14.06; ^{19}F NMR (377 MHz, $CDCl_3$): δ -112.59; HRMS: *m/z* calculated for $C_{23}H_{22}NO_4SFI$ $[M+H]^+$ 554.0298, found 554.0298; IR (neat) (ῡ): 2990, 2860, 1740, 1615, 1450, 1253, 1227, 1021, 792 cm^{-1} .

Diethyl 7-bromo-9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3ga): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 294 mg, 80 % yield, Green solid; mp = 142 - 144 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.34 (m, 5H), 7.28 – 7.26 (m, 2H), 7.18 – 7.16 (m, 1H), 4.53 (dd, *J* = 11.9, 1.9 Hz, 1H), 4.45 – 4.39 (m, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.24 – 4.16 (m, 1H), 3.35 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.88 (dd, *J* = 13.8, 11.9 Hz, 1H), 1.28 – 1.24 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 167.7, 167.0, 138.6, 138.1, 133.4, 129.7, 129.3, 129.0, 127.7, 124.7, 120.7, 115.4, 115.0, 70.3, 63.9, 63.3, 57.9, 41.2, 40.9, 14.07; HRMS: *m/z* calculated for $C_{23}H_{22}NO_4SBrI$ [M+H]$^+$ 613.9498, found 613.9498; IR (neat) (ῦ): 2990, 2854, 1738, 1458, 1253, 1225, 1021,801, 698 cm^{-1} .

Dimethyl 9-iodo-6-methyl-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3bb): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 200 mg, 64 % yield, Brown solid; mp = 153 - 155 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48 – 7.45 (m, 2H), 7.42 – 7.36 (m, 3H), 7.11 (s, 1H), 6.96 – 6.88 (m, 2H), 4.50 (dd, *J* = 11.9, 2.0 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.35 (dd, *J* = 13.7, 1.8 Hz, 1H), 2.94 (dd, *J* = 13.9, 12.1 Hz, 1H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.7, 168.0, 138.2, 136.4, 132.0, 131.1, 130.8, 129.2, 128.9, 127.8, 123.7, 119.6, 110.8, 70.2, 57.9, 54.0, 53.8, 41.3, 41.0, 21.4; HRMS: *m/z* calculated for $C_{22}H_{21}NO_4SI$ [M+H]$^+$ 522.0236, found 522.0236; IR (neat) (ῦ): 2934, 2856, 1743, 1453, 1261, 1228, 1020,792, 737 cm^{-1} .

Dimethyl 6-bromo-9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3db): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 270 mg, 77 % yield, Green solid; mp = 199 - 201 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48 – 7.35 (m, 6H), 7.23 – 7.20 (m, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.51 (dd, *J* = 12.0, 1.8 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.37 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.93 (dd, *J* = 13.8, 12.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.2, 167.5, 137.8, 136.9, 134.0, 132.5, 129.3, 129.1, 127.7, 124.9, 122.3, 115.1, 112.5, 70.2, 56.9, 54.2, 53.9, 41.2, 40.7; HRMS: *m/z* calculated for $C_{21}H_{18}NO_4SBrI$ [M+H]$^+$ 585.9185, found 585.9185; IR (neat) (ῦ): 2952, 2854, 1743, 1443, 1253, 1225, 1021, 739 cm^{-1} .

Dimethyl 6-chloro-9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9*H*)-dicarboxylate (3eb): Isolated by chromatography on silica gel (*n*-hexane/EA = 10/1) 237 mg, 73 % yield, Brown solid; mp = 174 - 176 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.47 – 7.35 (m, 5H), 7.31 (d, *J* = 1.9 Hz, 1H), 7.09 – 7.06 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 4.50 (dd, *J* = 12.0, 1.9 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.36 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.93 (dd, *J* = 13.9, 12.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$):δ 168.3, 167.6, 137.8, 136.6, 134.1, 132.0, 129.3, 129.1, 127.7, 127.5, 122.3, 119.3, 112.1, 70.2, 57.0, 54.2, 53.9, 41.2, 40.7; HRMS: *m/z* calculated for $C_{21}H_{18}NO_4SClI$ $[M+H]^+$ 541.9691, found 541.9691; IR (neat) (ῦ): 2952, 2853, 1743, 1601, 1257, 1227, 1020, 737 cm^{-1} .

2A.5 References

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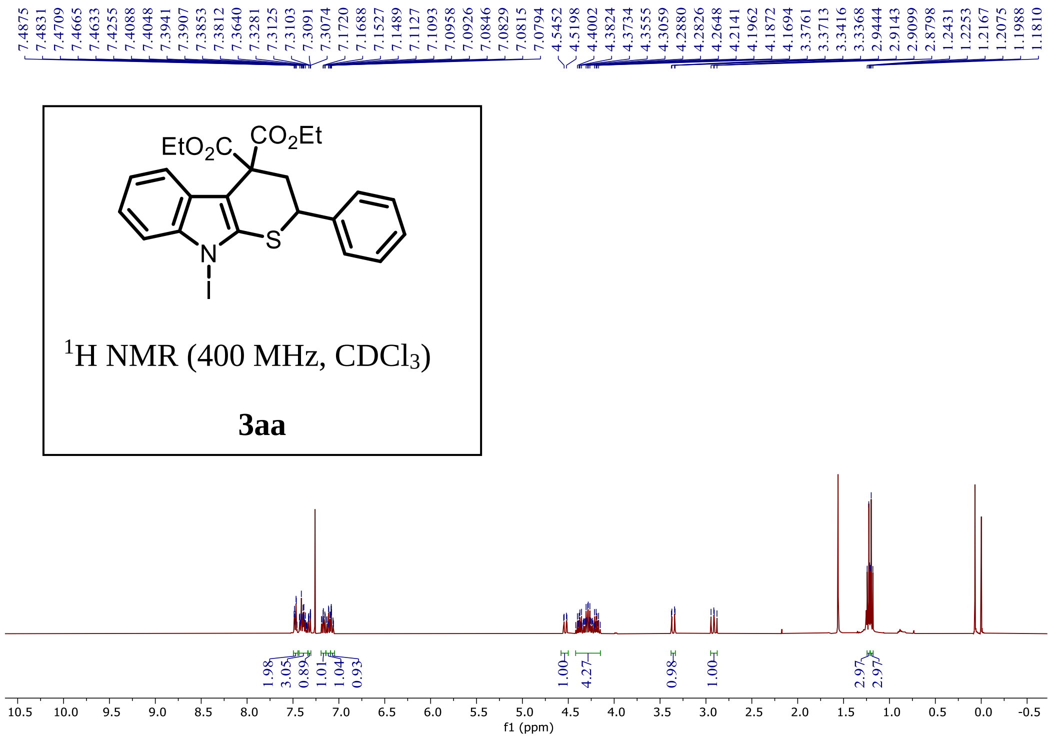
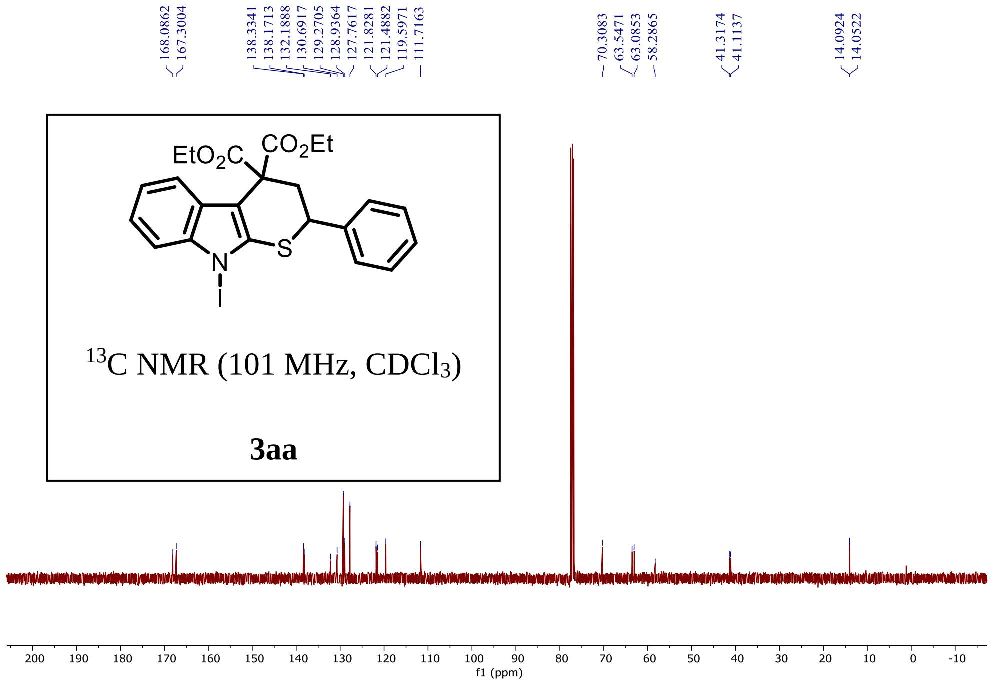
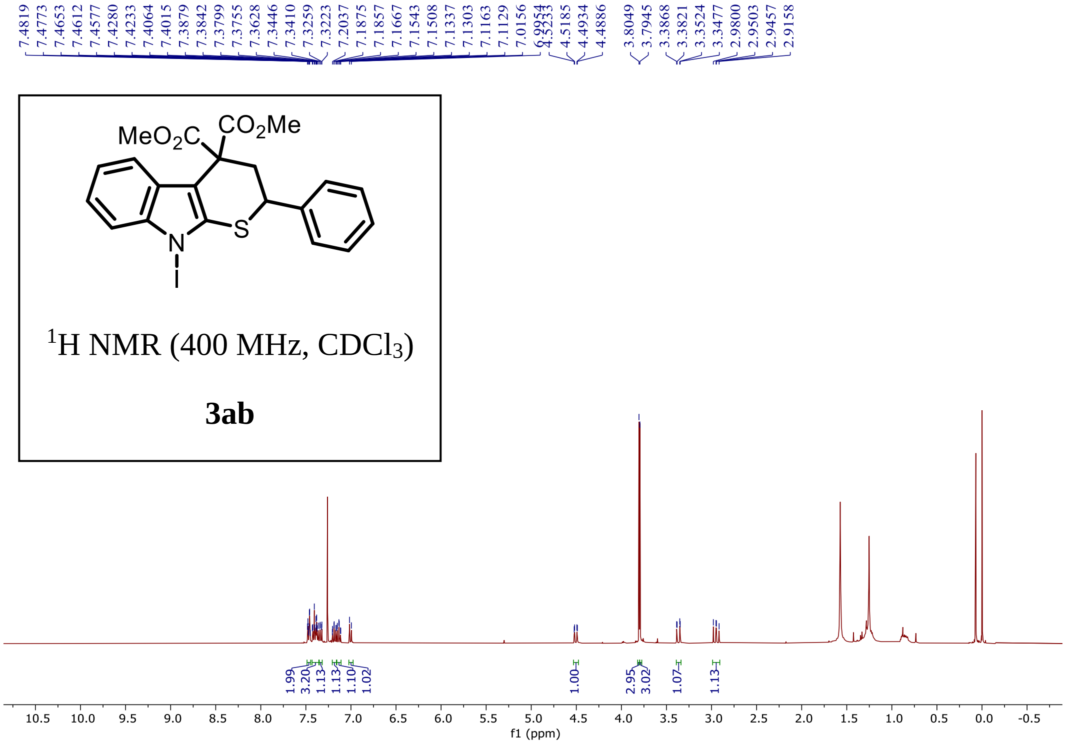
2A.6 NMR spectra of compounds

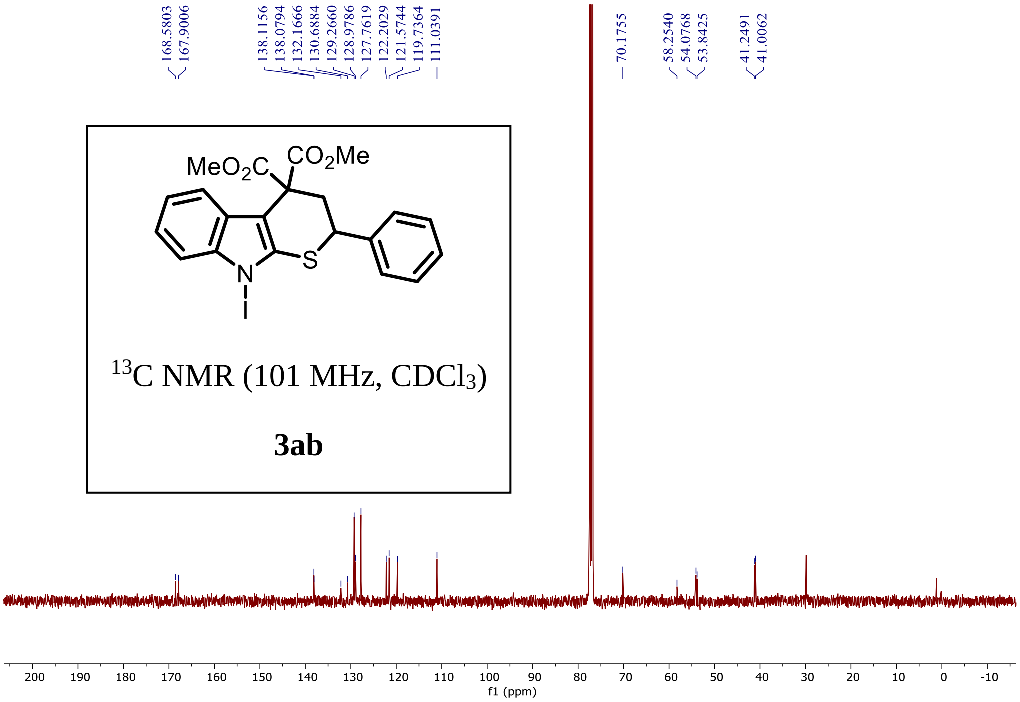






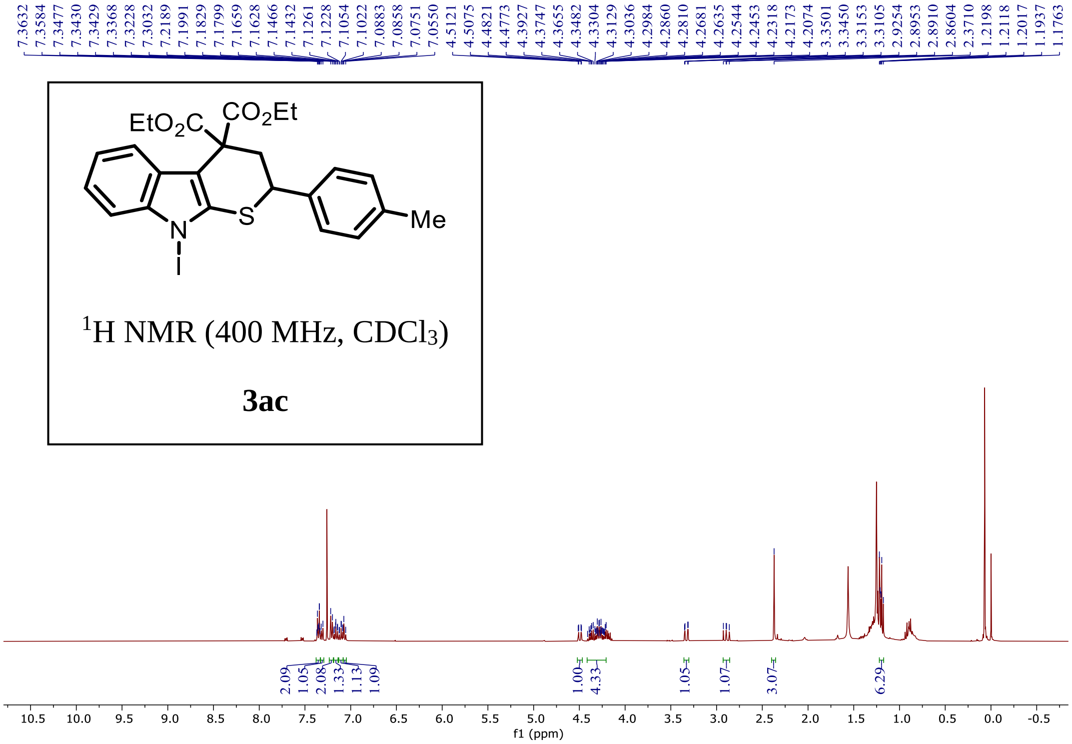
^{1}H NMR (400 MHz, CDCl$_3$)

3ab



^{13}C NMR (101 MHz, CDCl$_3$)

3ab



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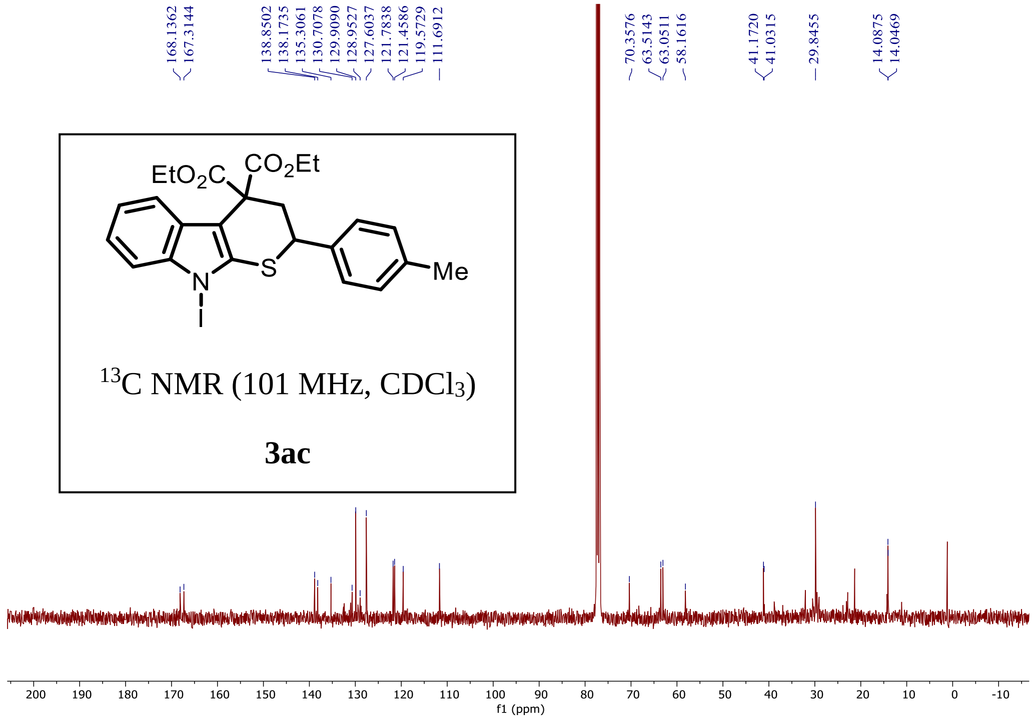
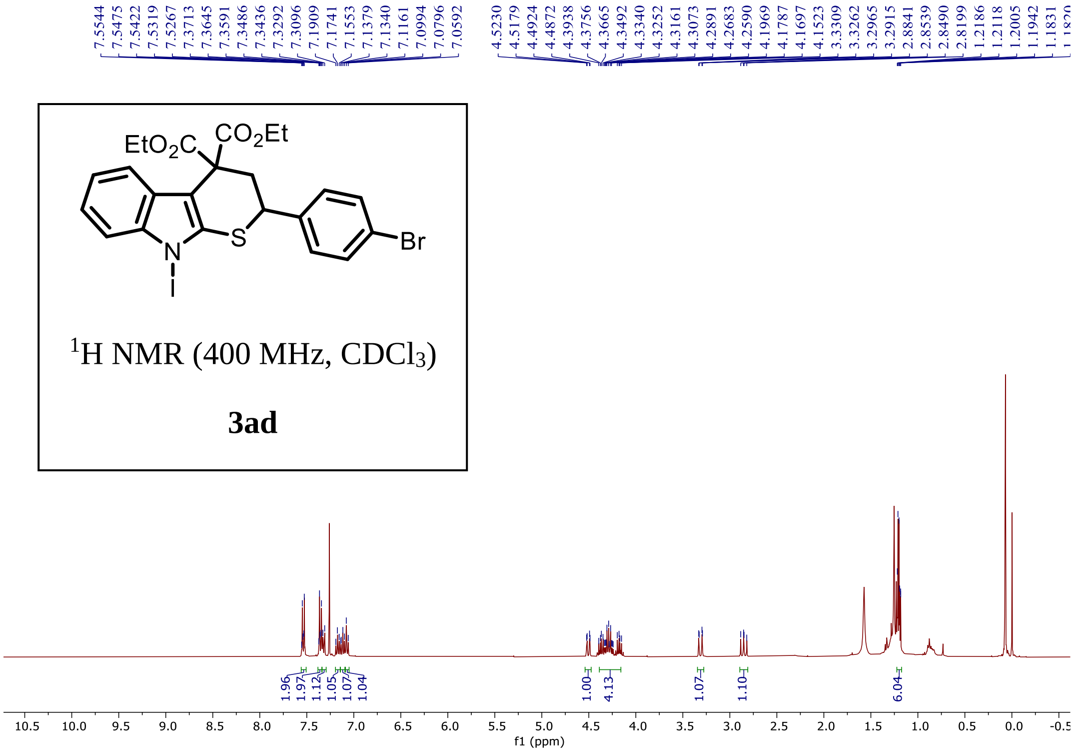
3ac



^{13}C NMR (101 MHz, $CDCl_3$)

3ac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7.5422
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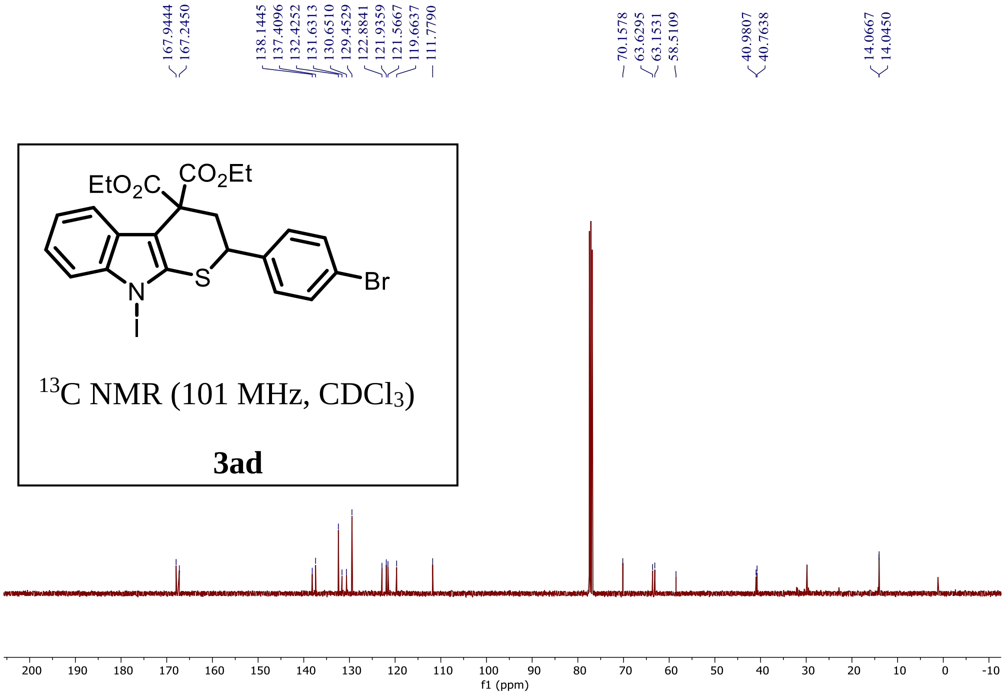
7.3096
7.1909
7.1741
7.1553
7.1379
7.1340
7.1161
7.0994
7.0796
7.0592
4.5230
4.5179
4.4924
4.4872
4.3938
4.3756
4.3665
4.3492
4.3340
4.3252
4.3161
4.3073
4.2891
4.2683
4.2590
4.1969
4.1787
4.1697
4.1523
3.3309
3.3262
3.2965
3.2915
2.8841
2.8539
2.8490
2.8199
1.2186
1.2118
1.2005
1.1942
1.1831
EtO2C
CO2Et
N
S
Br
^{1}H NMR (400 MHz, CDCl$_3$)
3ad
1.96
1.97
1.12
1.05
1.07
1.04
1.00
4.13
1.07
1.10
6.04
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
-0.5
f1 (ppm)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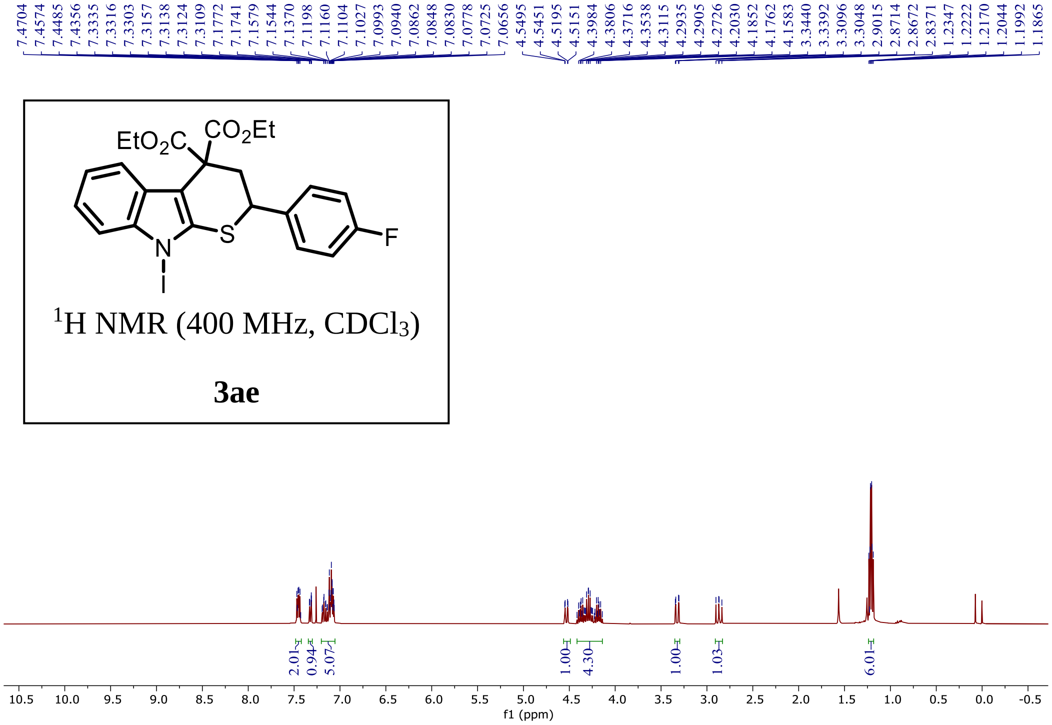
121.5667
119.6637
111.7790
70.1578
63.6295
63.1531
58.5109
40.9807
40.7638
14.0667
14.0450
EtO2C
CO2Et
N
S
Br
^{13}C NMR (101 MHz, CDCl$_3$)
3ad
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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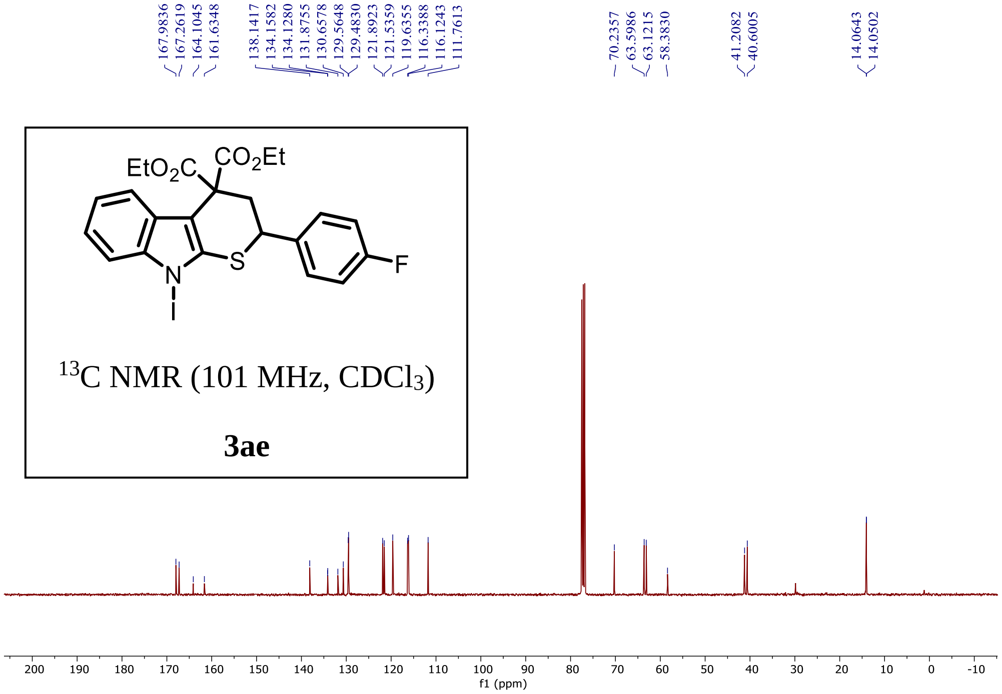
7.1772
7.1741
7.1579
7.1544
7.1370
7.1198
7.1160
7.1104
7.1027
7.0993
7.0940
7.0862
7.0848
7.0830
7.0778
7.0725
7.0656
4.5495
4.5451
4.5195
4.5151
4.3984
4.3806
4.3716
4.3538
4.3115
4.2935
4.2905
4.2726
4.2030
4.1852
4.1762
4.1583
3.3440
3.3392
3.3096
3.3048
2.9015
2.8714
2.8672
2.8371
1.2347
1.2222
1.2170
1.2044
1.1992
1.1865
EtO$_2$C
CO$_2$Et
N
S
F
^{1}H NMR (400 MHz, CDCl$_3$)
3ae
2.01
0.94
5.07
1.00
4.30
1.00
1.03
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
-0.5
f1 (ppm)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134.1280
131.8755
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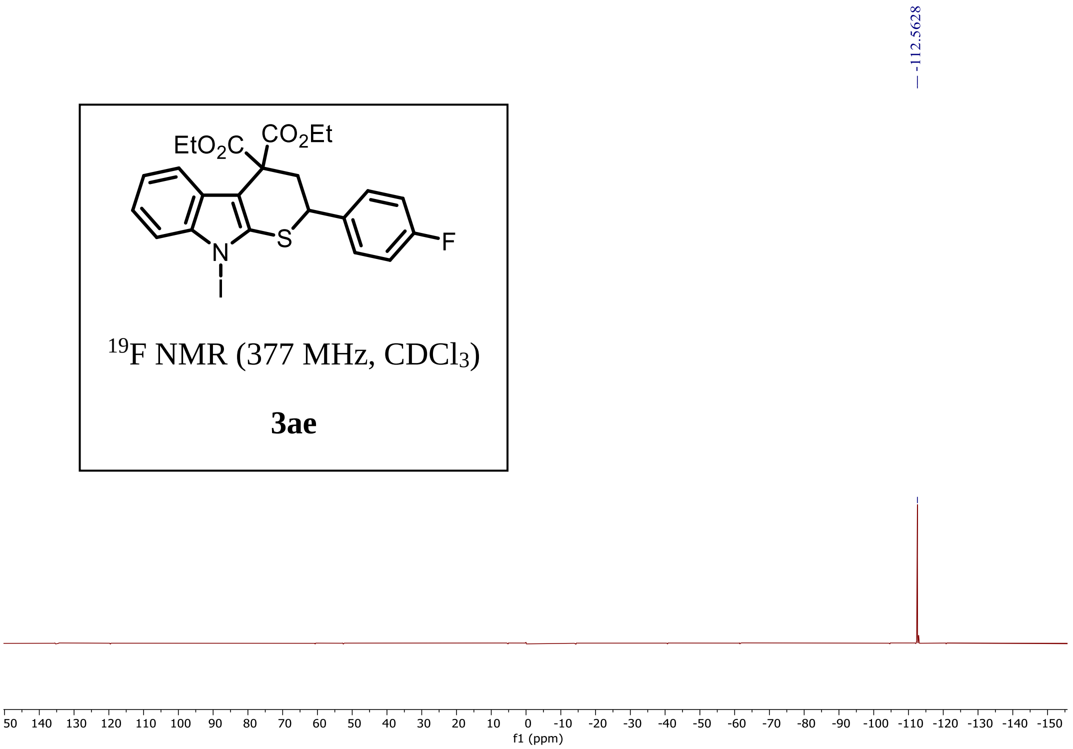
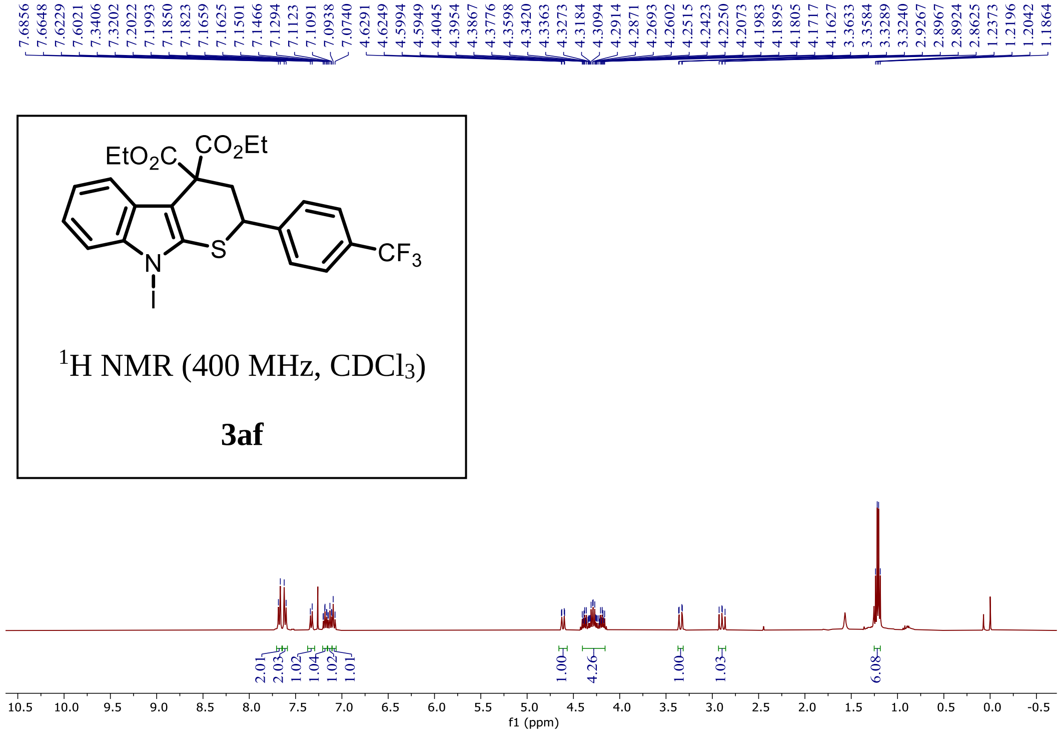
129.5648
129.4830
121.8923
121.5359
119.6355
116.3388
116.1243
111.7613
70.2357
63.5986
63.1215
58.3830
41.2082
40.6005
14.0643
14.0502
EtO$_2$C
CO$_2$Et
N
S
F
^{13}C NMR (101 MHz, CDCl$_3$)
3ae
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



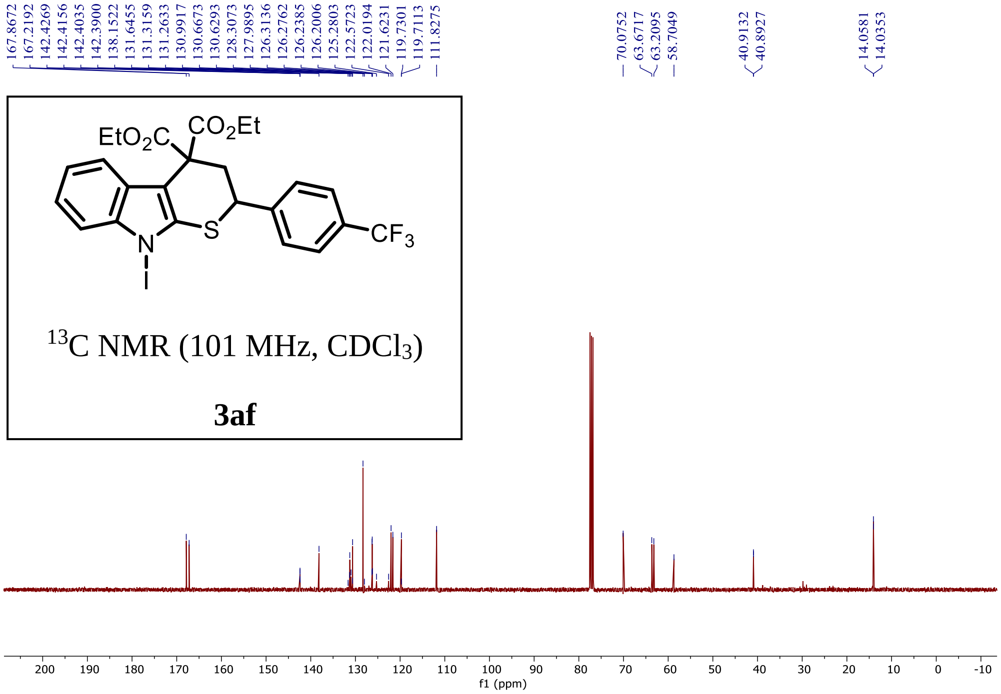
^{19}F NMR (377 MHz, $CDCl_3$)

3ae



^{1}H NMR (400 MHz, $CDCl_3$)

3af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142.4035
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138.1522
131.6455
131.3159
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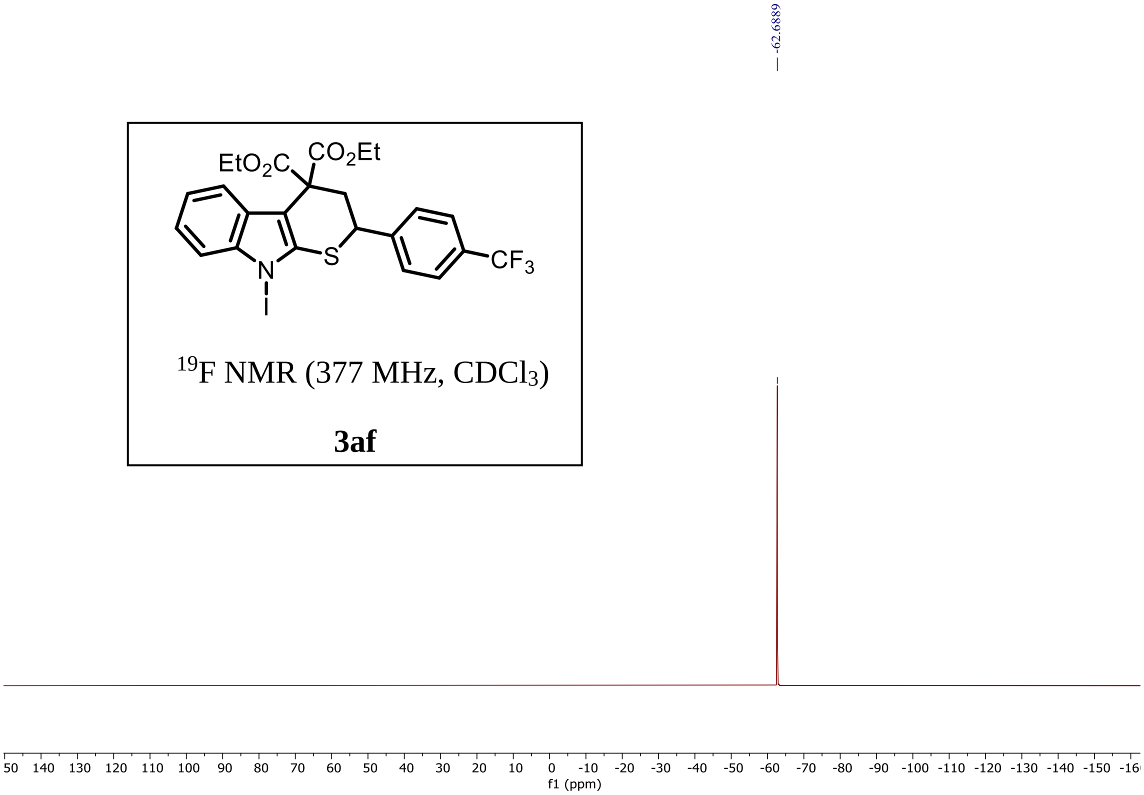
130.9917
130.6673
130.6293
128.3073
127.9895
126.3136
126.2762
126.2385
126.2006
125.2803
122.5723
122.0194
121.6231
119.7301
119.7113
111.8275
70.0752
63.6717
63.2095
58.7049
40.9132
40.8927
14.0581
14.0353
EtO2C
CO2Et
N
S
I
CF3
13C NMR (101 MHz, CDCl3)
3af
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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CO2Et
N
S
I
CF3
19F NMR (377 MHz, CDCl3)
3af
50
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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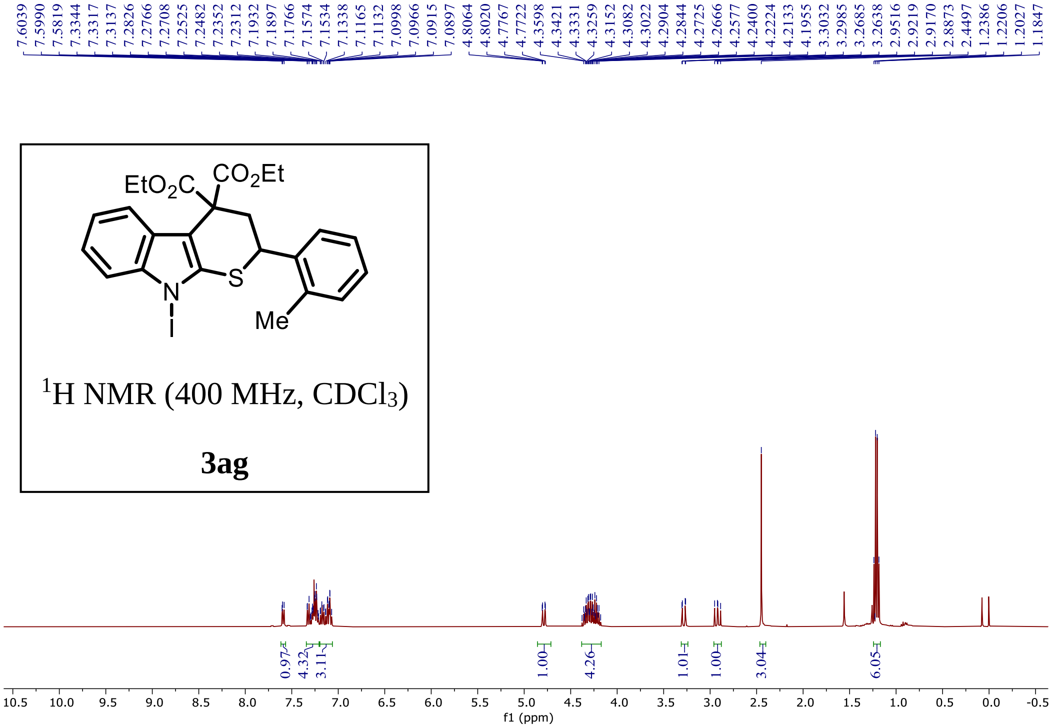
-100
-110
-120
-130
-140
-150
-16
f1 (ppm)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7.2352
7.2312
7.1932
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7.1338
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7.1132
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4.7722
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4.3331
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4.3152
4.3082
4.3022
4.2904
4.2844
4.2725
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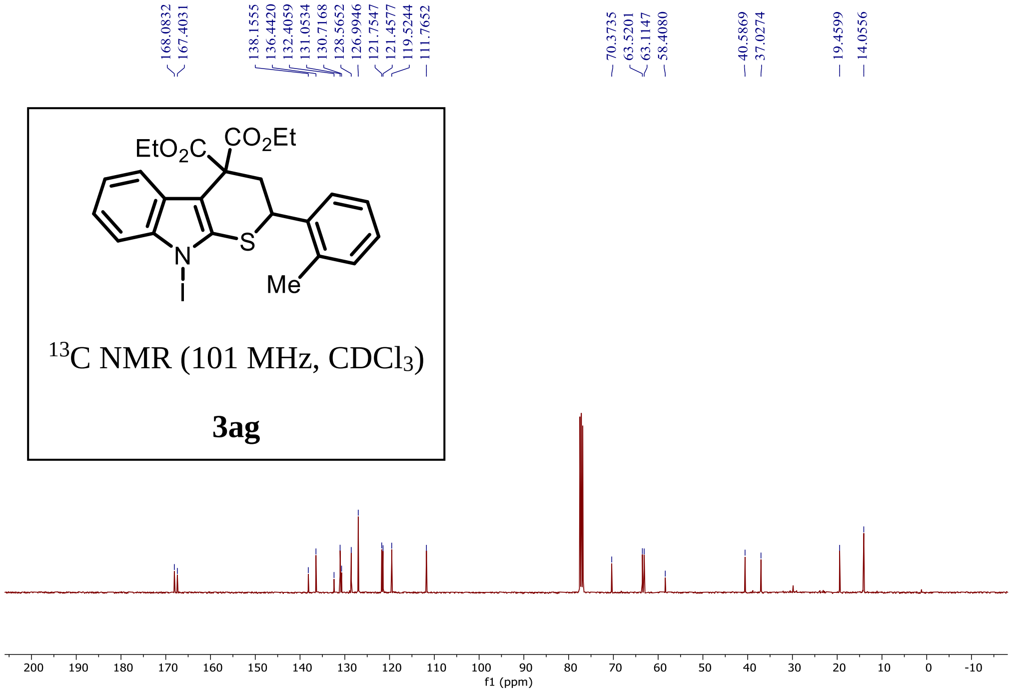
4.2577
4.2400
4.2224
4.2133
4.1955
3.3032
3.2985
3.2685
3.2638
2.9516
2.9219
2.9170
2.8873
2.4497
1.2386
1.2206
1.2027
1.1847
EtO$_2$C
CO$_2$Et
N
S
Me
^{1}H NMR (400 MHz, CDCl$_3$)
3ag
0.97
4.32
3.11
1.00
4.26
1.01
1.00
3.04
6.05
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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119.5244
111.7652
70.3735
63.5201
63.1147
58.4080
40.5869
37.0274
19.4599
14.0556
EtO$_2$C
CO$_2$Et
N
S
Me
^{13}C NMR (101 MHz, CDCl$_3$)
3ag
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
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30
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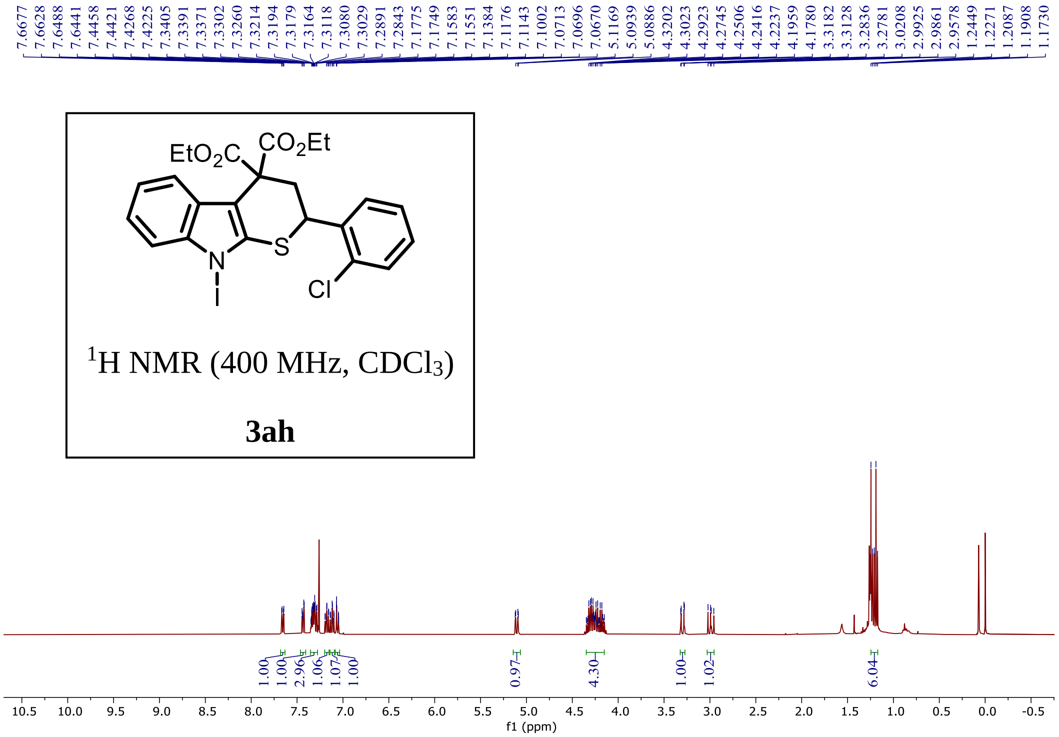
-10
f1 (ppm)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7.3302
7.3260
7.3214
7.3194
7.3179
7.3164
7.3118
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7.3029
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7.1775
7.1749
7.1583
7.1551
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7.1143
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5.0939
5.0886
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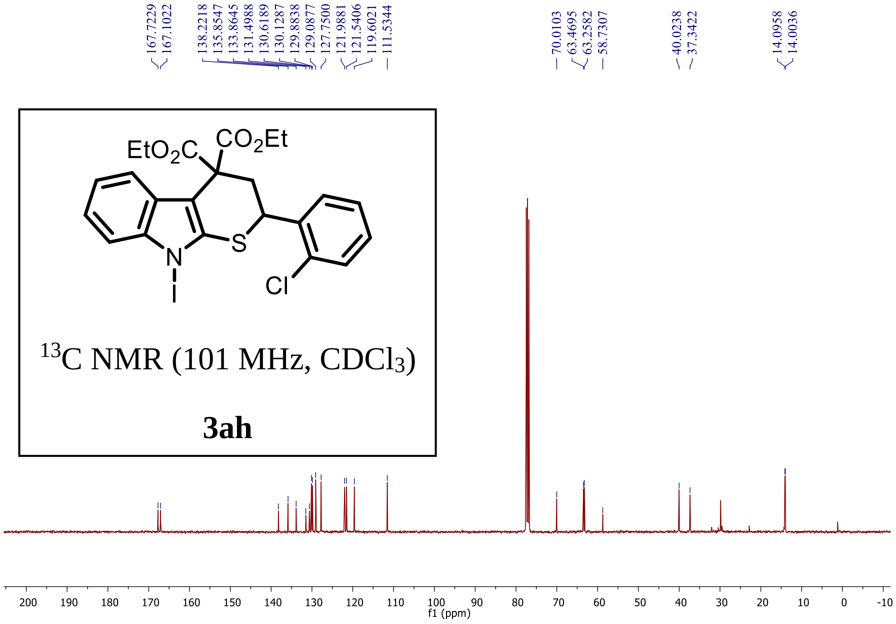
4.2237
4.1959
4.1780
3.3182
3.3128
3.2836
3.2781
3.0208
2.9925
2.9861
2.9578
1.2449
1.2271
1.2087
1.1908
1.1730
EtO2C
CO2Et
N
S
Cl
1H NMR (400 MHz, CDCl3)
3ah
1.00
1.00
2.96
1.06
1.07
1.00
0.97
4.30
1.00
1.02
6.04
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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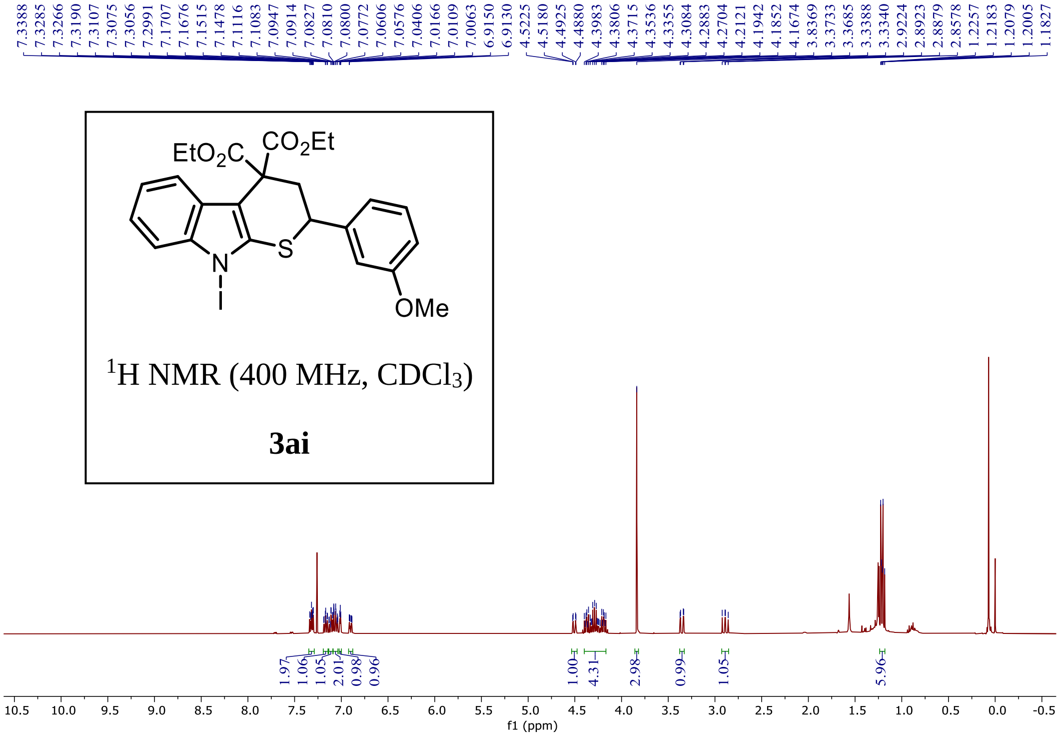
129.0877
127.7500
121.9881
121.5406
119.6021
111.5344
70.0103
63.4695
63.2582
58.7307
40.0238
37.3422
14.0958
14.0036
EtO2C
CO2Et
N
S
Cl
13C NMR (101 MHz, CDCl3)
3ah
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.1478
7.1116
7.1083
7.0947
7.0914
7.0827
7.0810
7.0800
7.0772
7.0606
7.0576
7.0406
7.0166
7.0109
7.0063
6.9150
6.9130
4.5225
4.5180
4.4925
4.4880
4.3983
4.3806
4.3715
4.3536
4.3355
4.3084
4.2883
4.2704
4.2121
4.1942
4.1852
4.1674
3.8369
3.3733
3.3685
3.3388
3.3340
2.9224
2.8923
2.8879
2.8578
1.2257
1.2183
1.2079
1.2005
1.1827
EtO$_2$C
CO$_2$Et
N
S
OMe
^{1}H NMR (400 MHz, CDCl$_3$)
3ai
1.97
1.06
1.05
2.01
0.98
0.96
1.00
4.31
2.98
0.99
1.05
5.96
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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2.0
1.5
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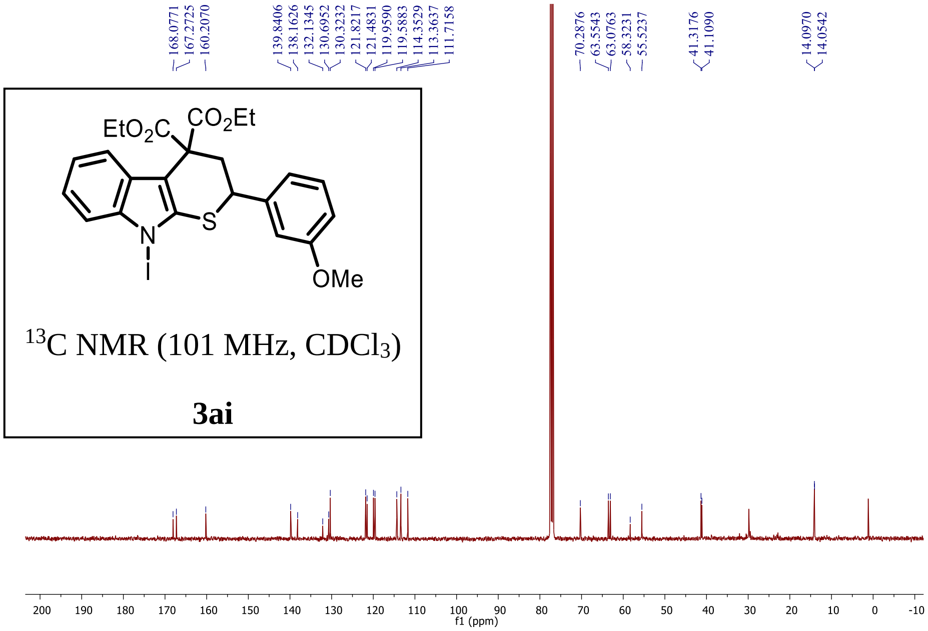
0.5
0.0
-0.5
f1 (ppm)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130.6952
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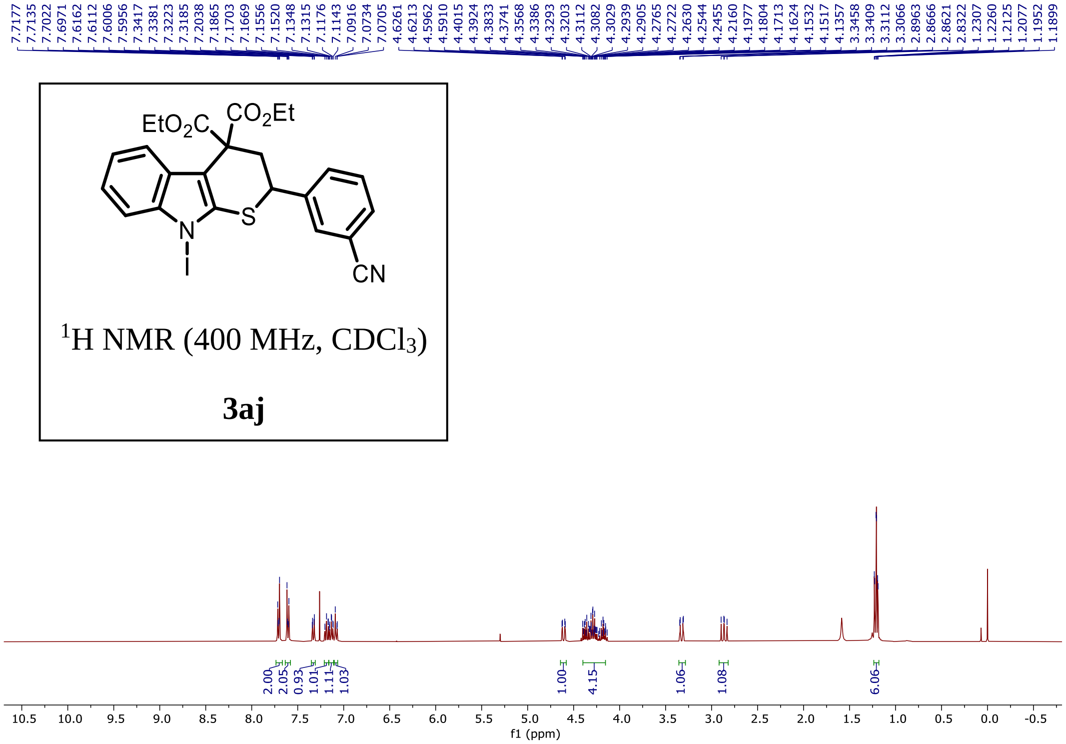
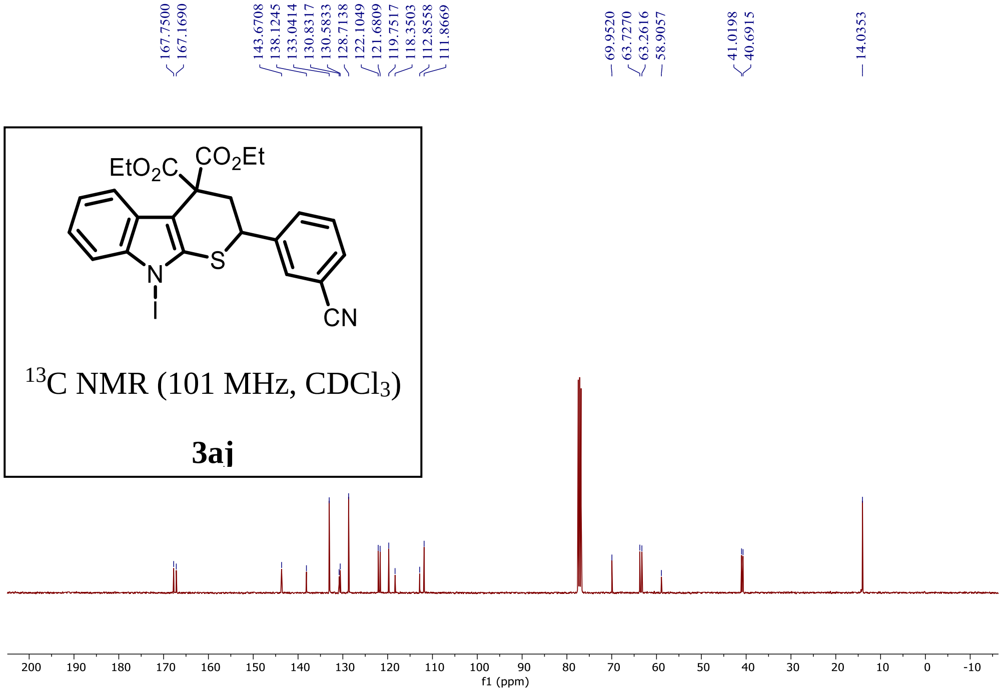
121.4831
119.9590
119.5883
114.3529
113.3637
111.7158
70.2876
63.5543
63.0763
58.3231
55.5237
41.3176
41.1090
14.0970
14.0542
EtO$_2$C
CO$_2$Et
N
S
OMe
^{13}C NMR (101 MHz, CDCl$_3$)
3ai
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



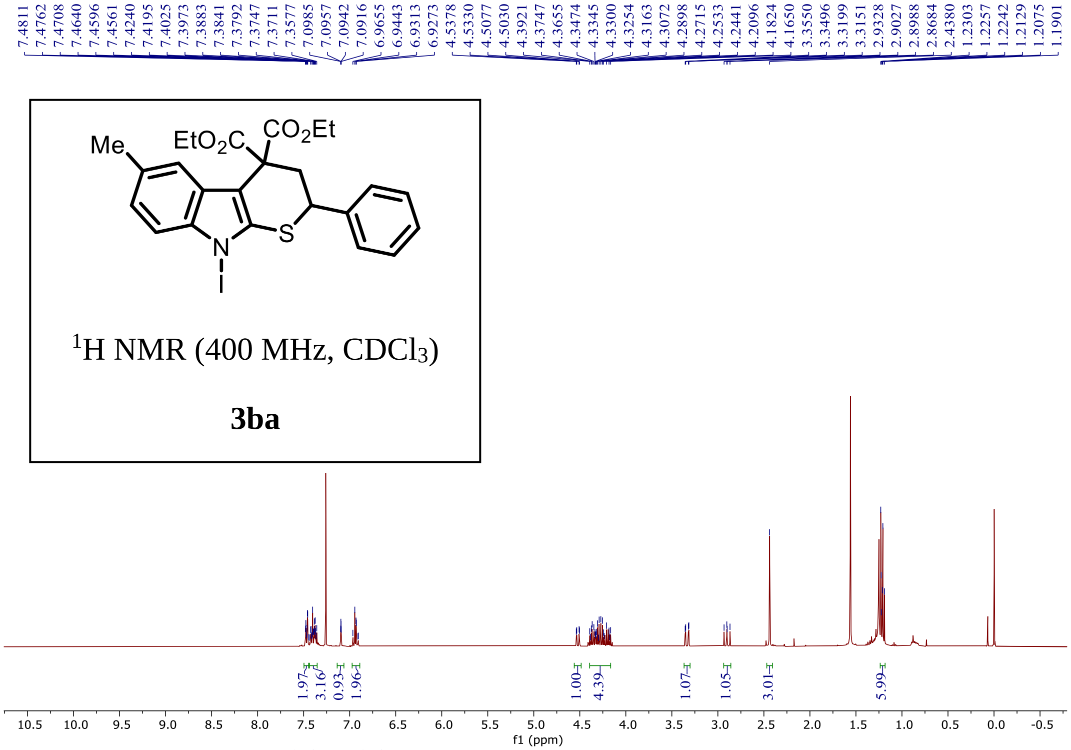
^{1}H NMR (400 MHz, $CDCl_3$)

3aj



^{13}C NMR (101 MHz, $CDCl_3$)

3aj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7.4596
7.4561
7.4240
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7.3973
7.3883
7.3841
7.3792
7.3747
7.3711
7.3577
7.0985
7.0957
7.0942
7.0916
6.9655
6.9443
6.9313
6.9273
4.5378
4.5330
4.5077
4.5030
4.3921
4.3747
4.3655
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4.3345
4.3300
4.3254
4.3163
4.3072
4.2898
4.2715
4.2533
4.2441
4.2096
4.1824
4.1650
3.3550
3.3496
3.3199
3.3151
2.9328
2.9027
2.8988
2.8684
2.4380
1.2303
1.2257
1.2242
1.2129
1.2075
1.1901
Me
EtO2C
CO2Et
N
S
1H NMR (400 MHz, CDCl3)
3ba
1.97
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0.93
1.96
1.00
4.39
1.07
1.05
3.01
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9.0
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8.0
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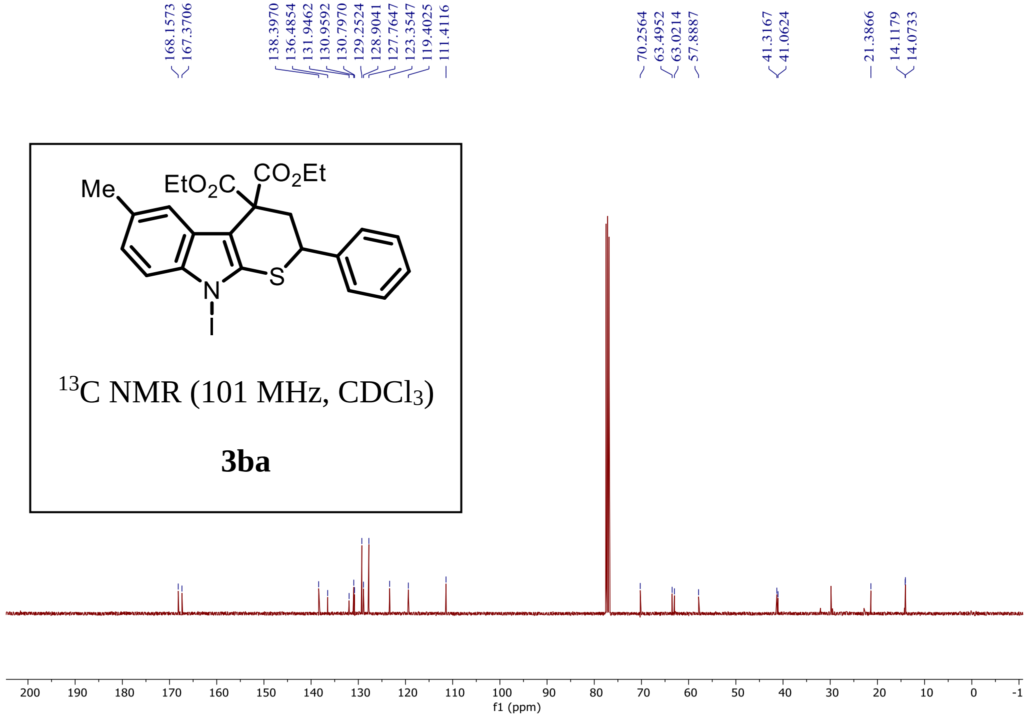
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21.3866
14.1179
14.0733
Me
EtO2C
CO2Et
N
S
13C NMR (101 MHz, CDCl3)
3ba
200
190
180
170
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110
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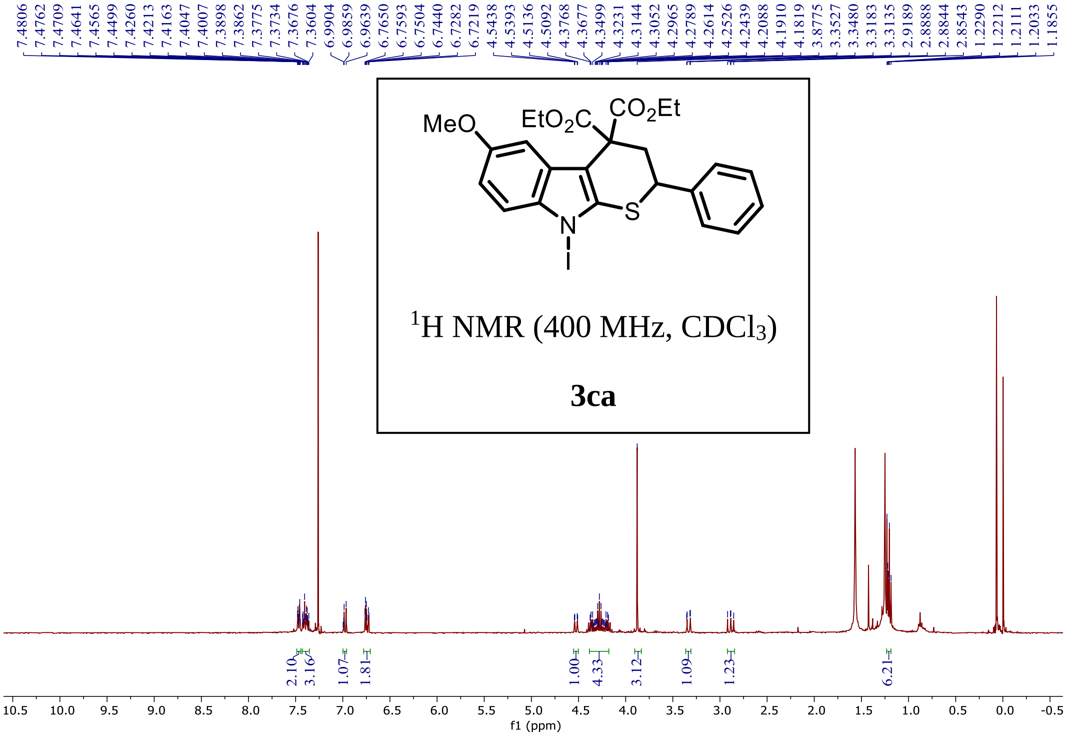
0
-1
f1 (ppm)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4.1910
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2.8844
2.8543
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1.1855
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EtO2C
CO2Et
N
S
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1.09
1.23
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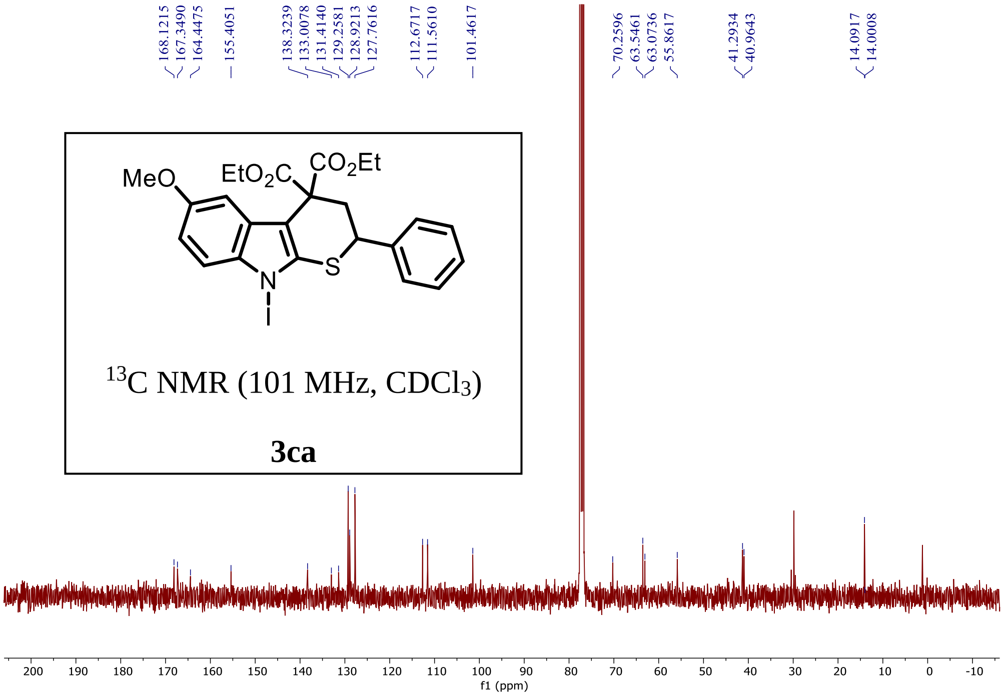
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14.0008
MeO
EtO2C
CO2Et
N
S
13C NMR (101 MHz, CDCl3)
3ca
200
190
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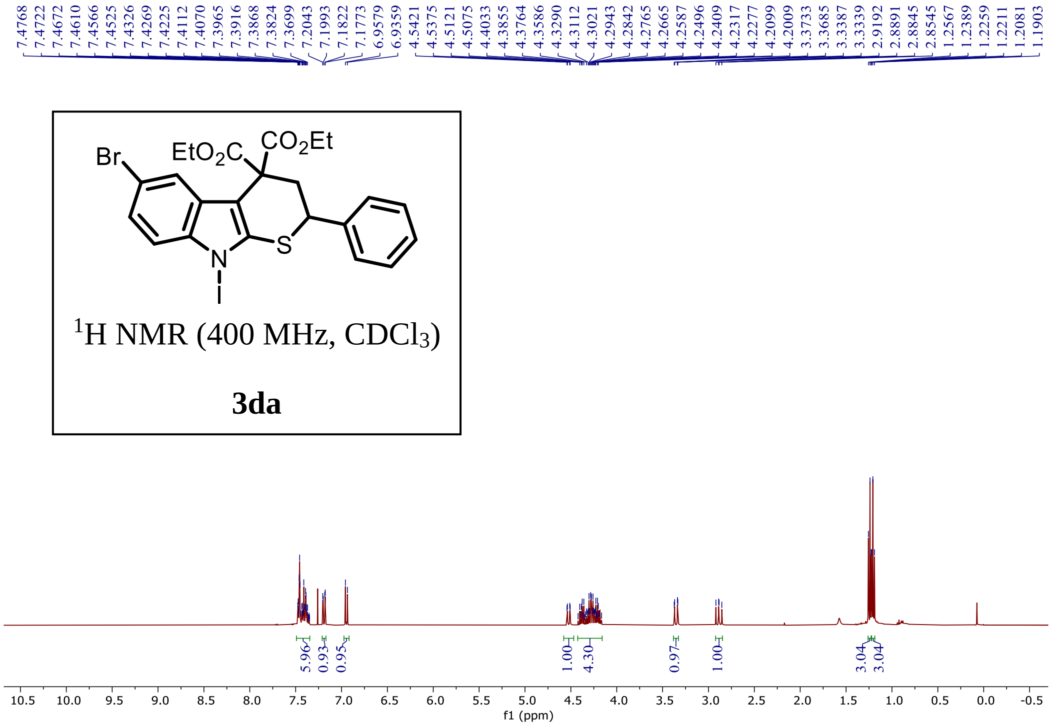
f1 (ppm)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CO2Et
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1H NMR (400 MHz, CDCl3)
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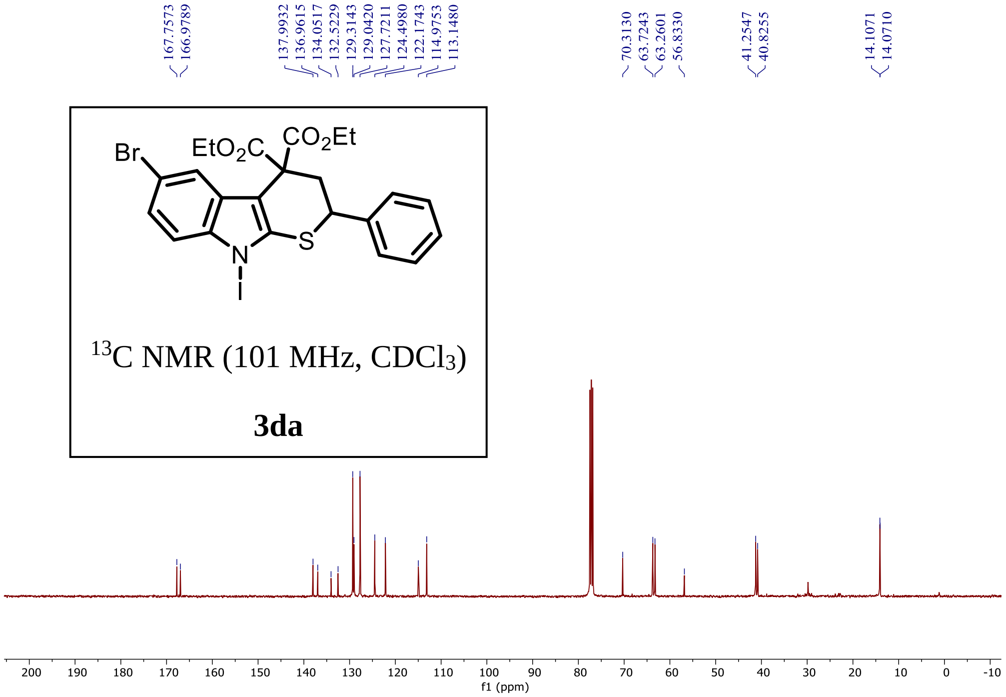
f1 (ppm)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41.2547
40.8255
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14.0710
Br
EtO2C
CO2Et
N
S
13C NMR (101 MHz, CDCl3)
3da
200
190
180
170
160
150
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120
110
100
90
80
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60
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40
30
20
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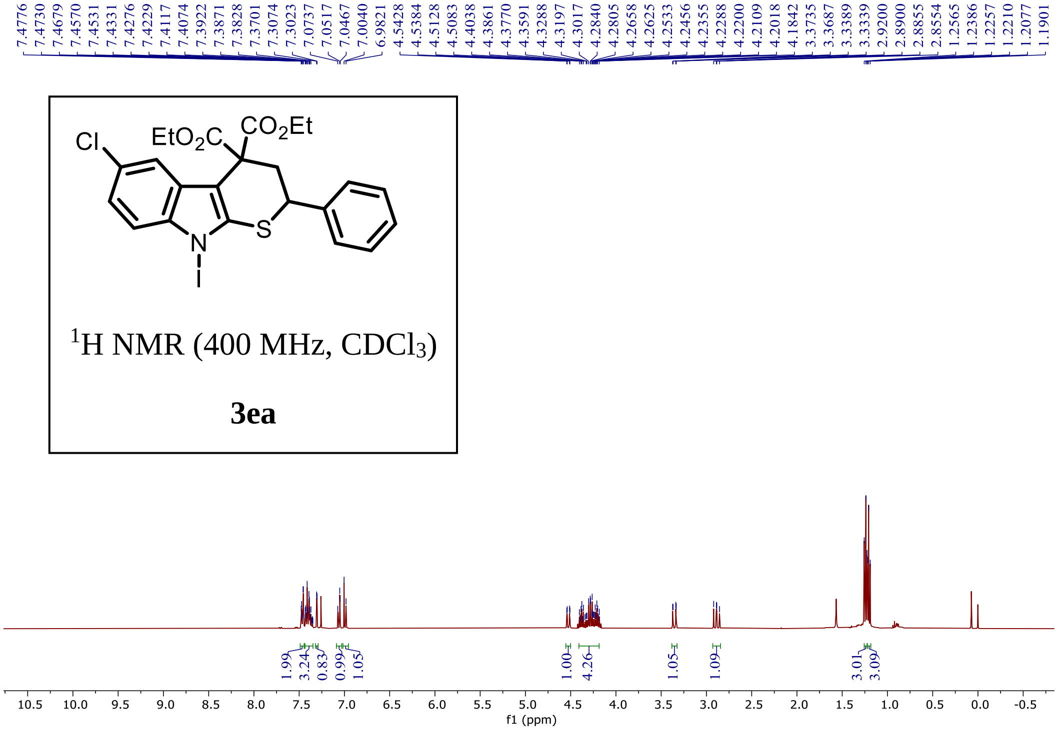
0
-10
f1 (ppm)



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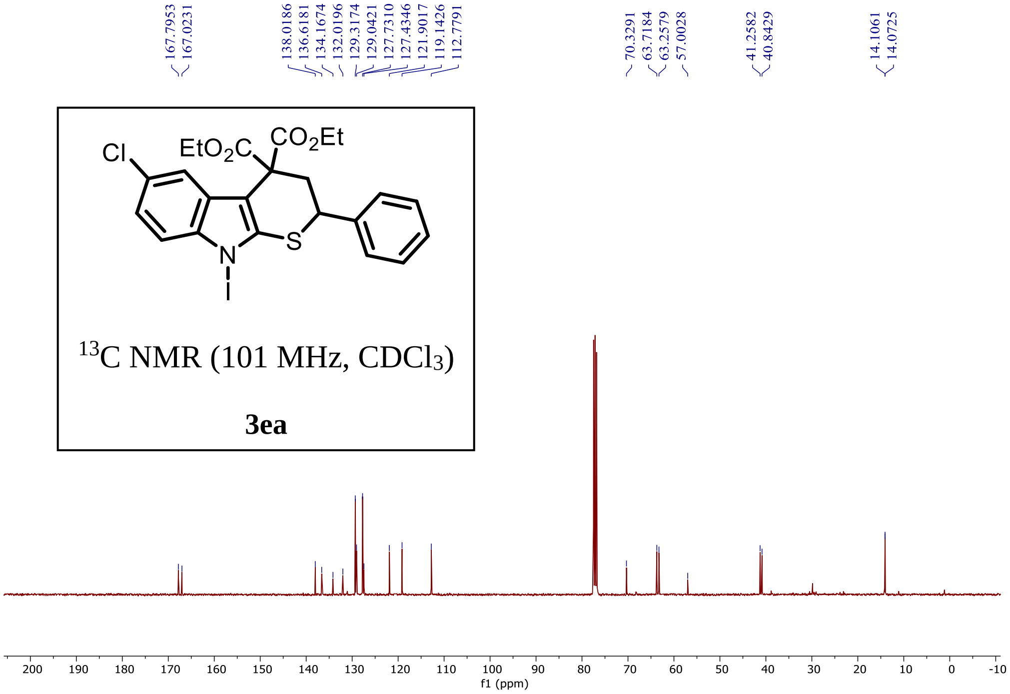

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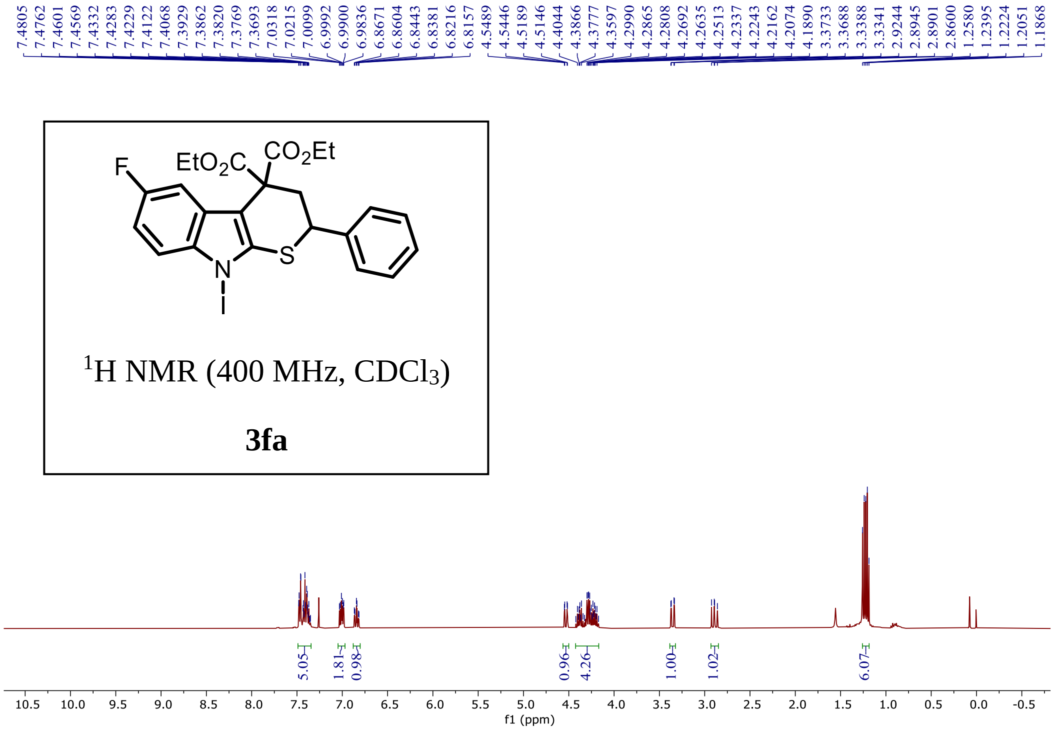

^{1}H NMR (400 MHz, CDCl$_3$)

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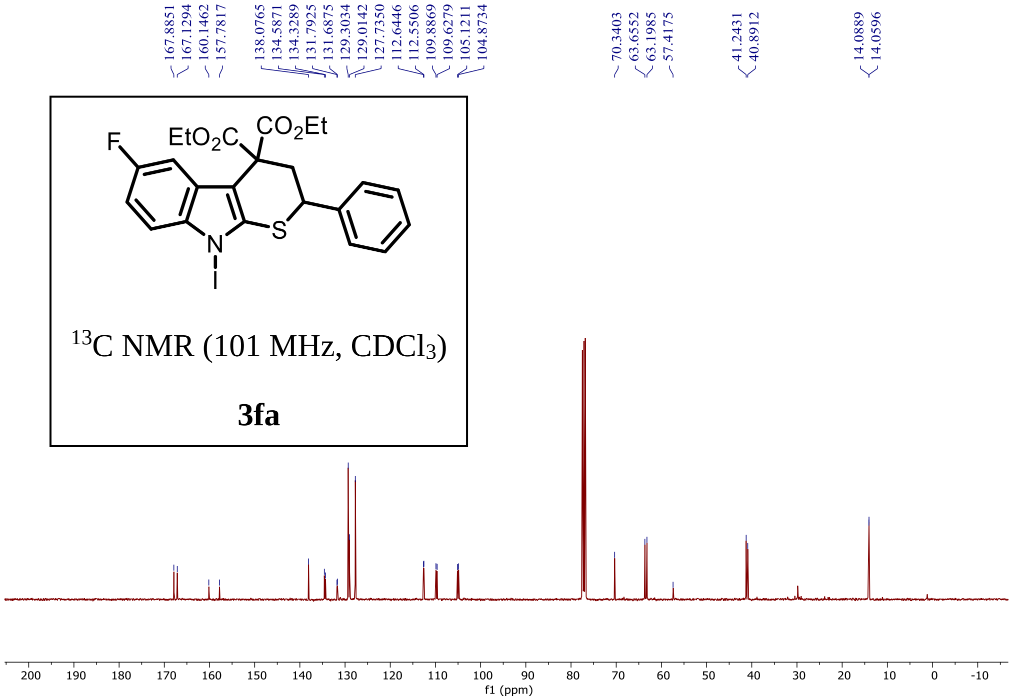

^{13}C NMR (101 MHz, CDCl$_3$)

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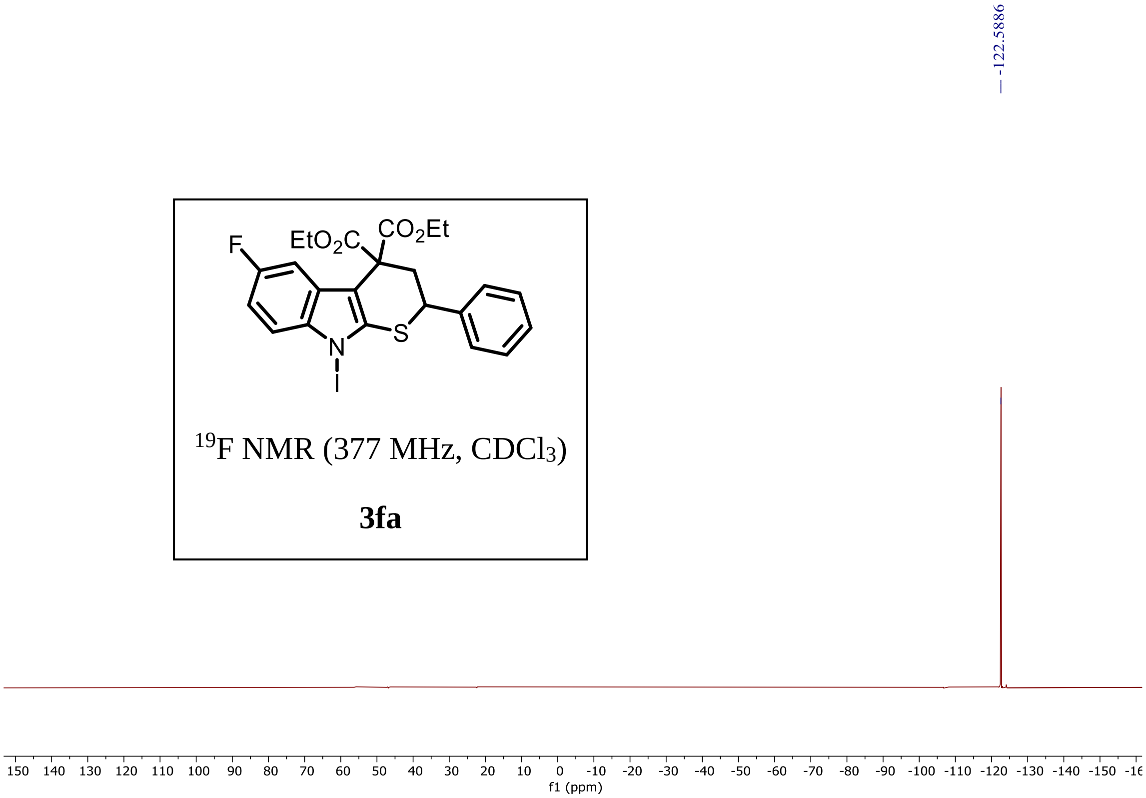

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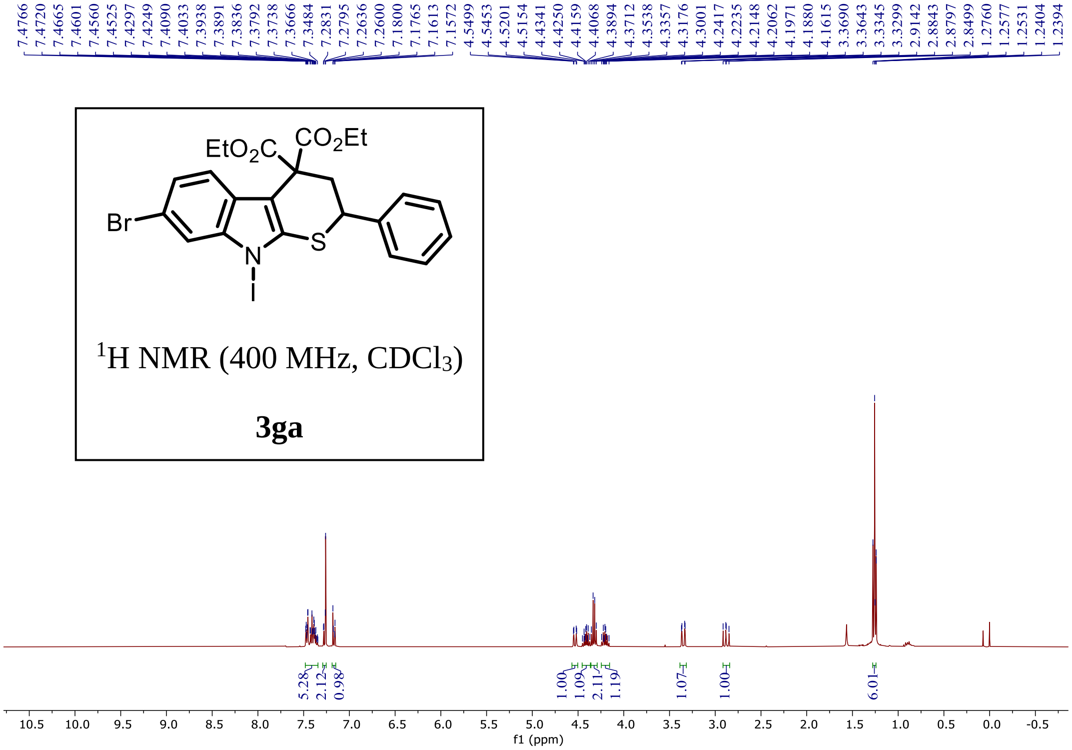

^{1}H NMR (400 MHz, CDCl$_3$)

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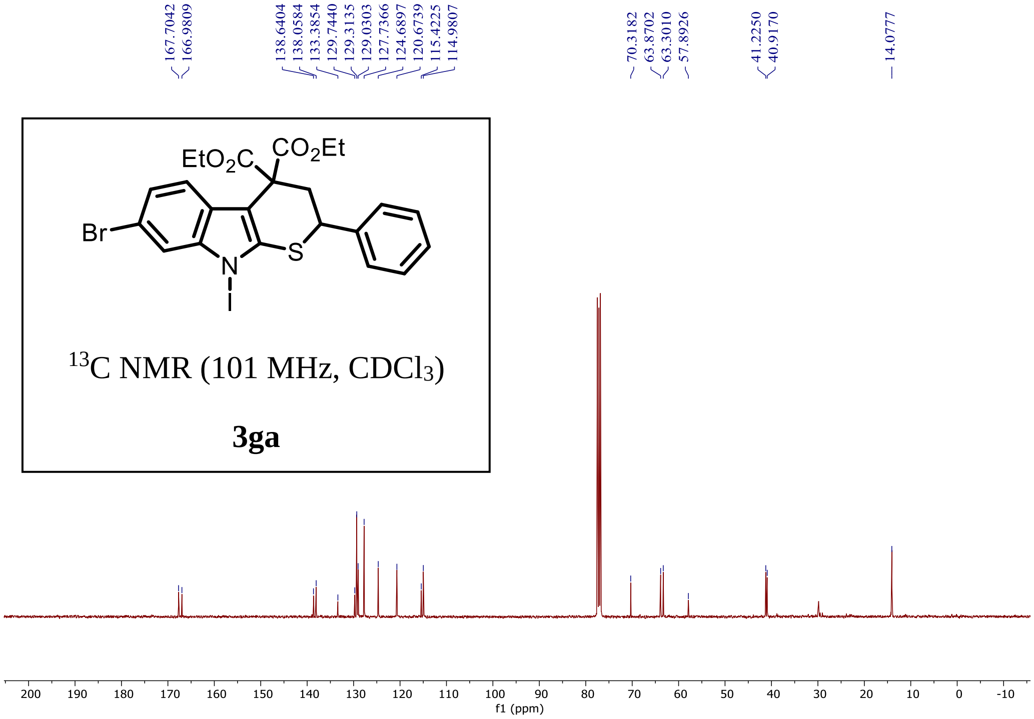

^{13}C NMR (101 MHz, CDCl$_3$)

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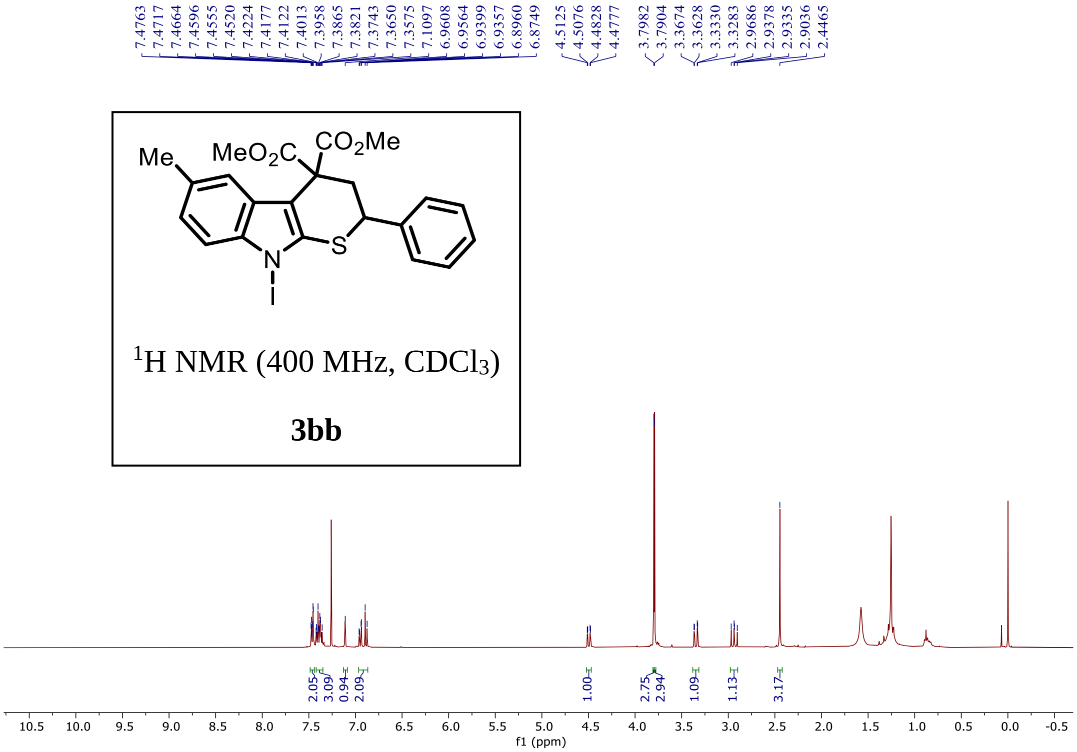
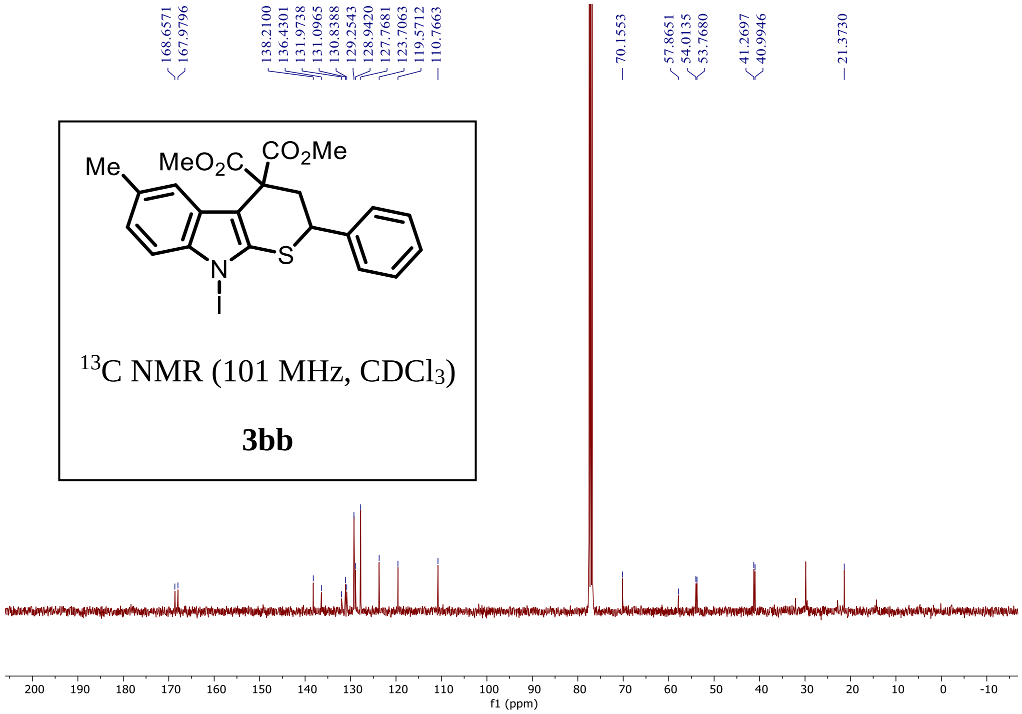


^{1}H NMR (400 MHz, CDCl$_3$)

3bb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110.7663
70.1553
57.8651
54.0135
53.7680
41.2697
40.9946
21.3730
Me
MeO_2C
CO_2Me
N
S
^{13}C NMR (101 MHz, CDCl$_3$)
3bb
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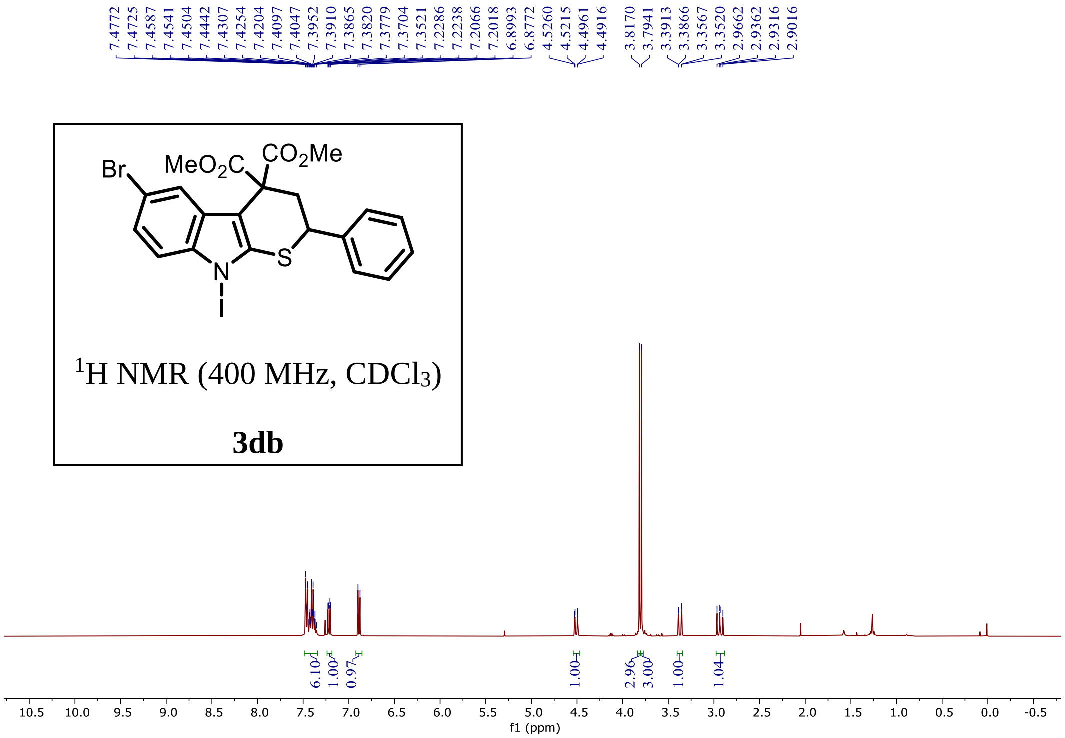
f1 (ppm)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7.3952
7.3910
7.3865
7.3820
7.3779
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7.3521
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7.2238
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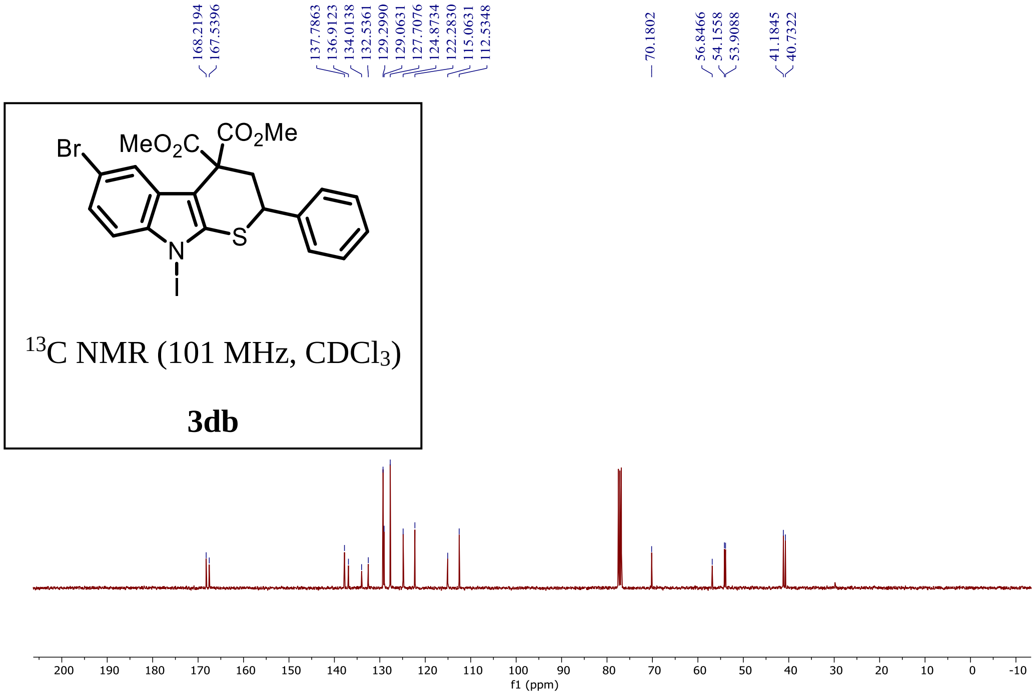
2.9362
2.9316
2.9016
Br
MeO_2C
CO_2Me
N
S
^{1}H NMR (400 MHz, CDCl$_3$)
3db
6.10
1.00
0.97
1.00
2.96
3.00
1.00
1.04
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



^{13}C NMR (101 MHz, $CDCl_3$)

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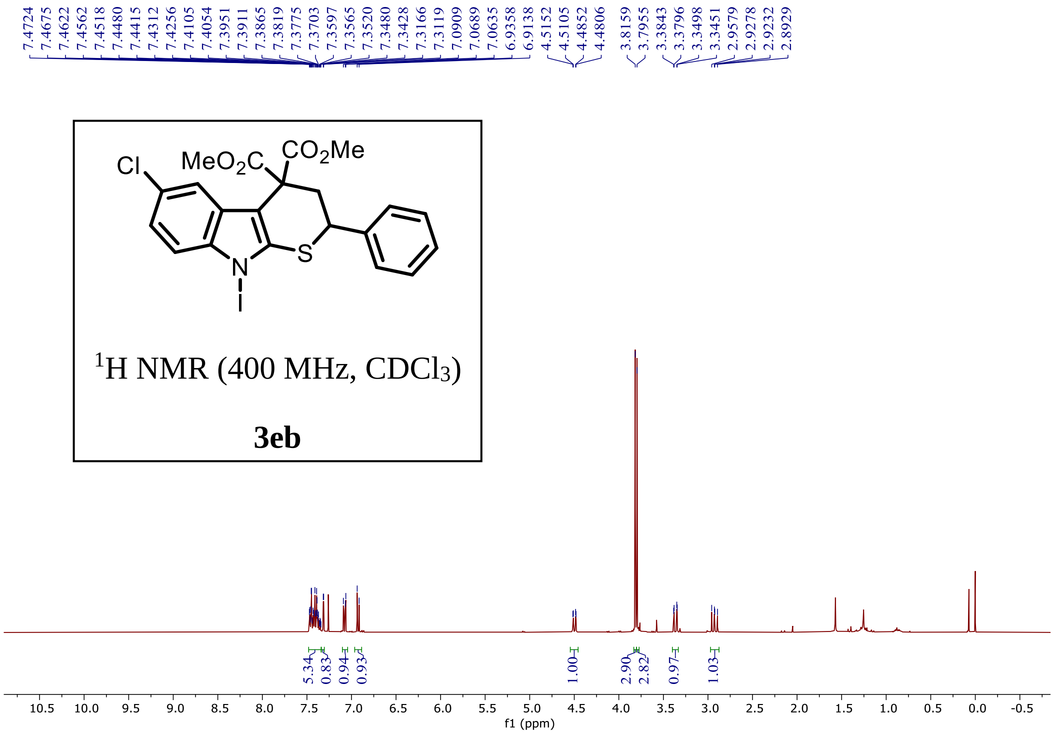

^{1}H NMR (400 MHz, $CDCl_3$)

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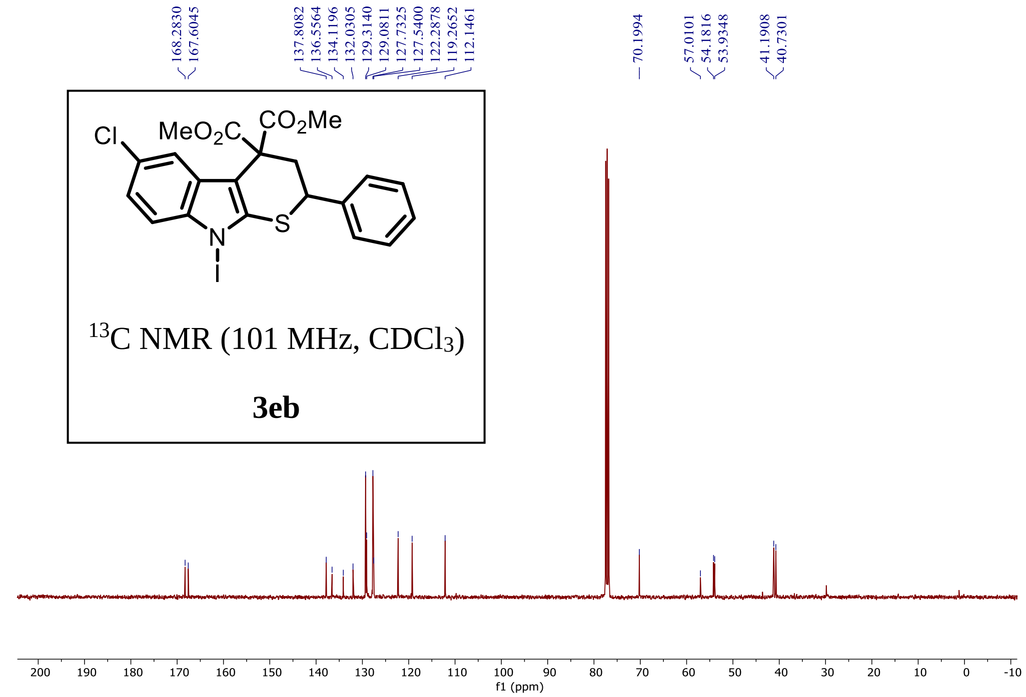
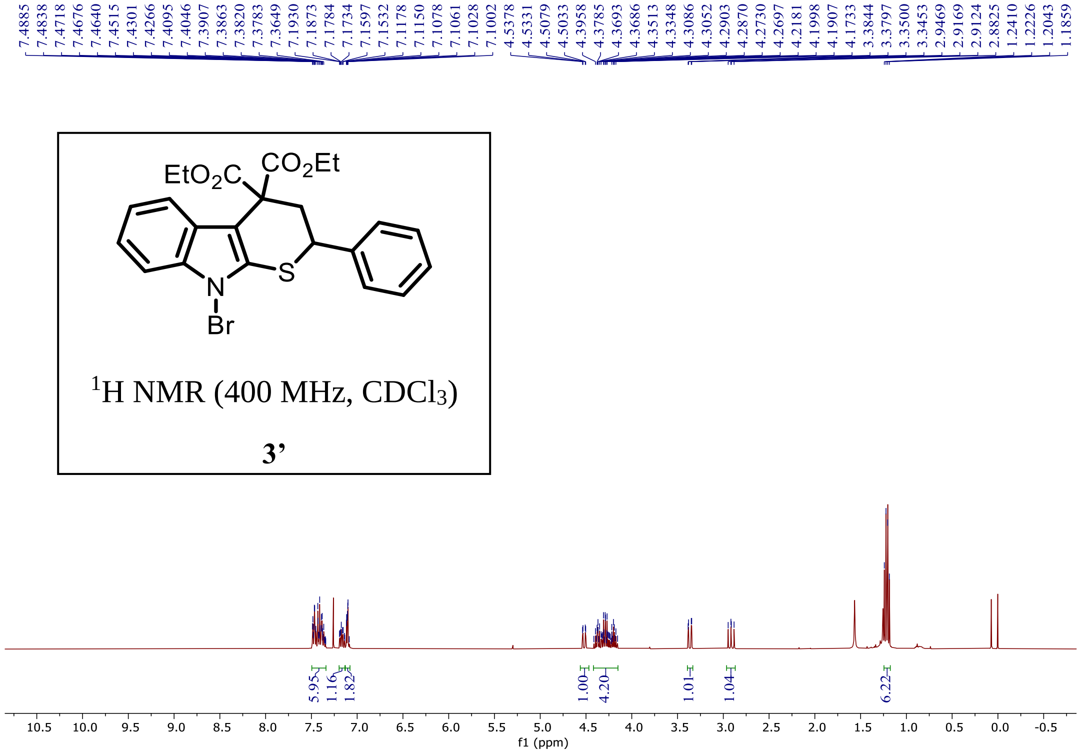


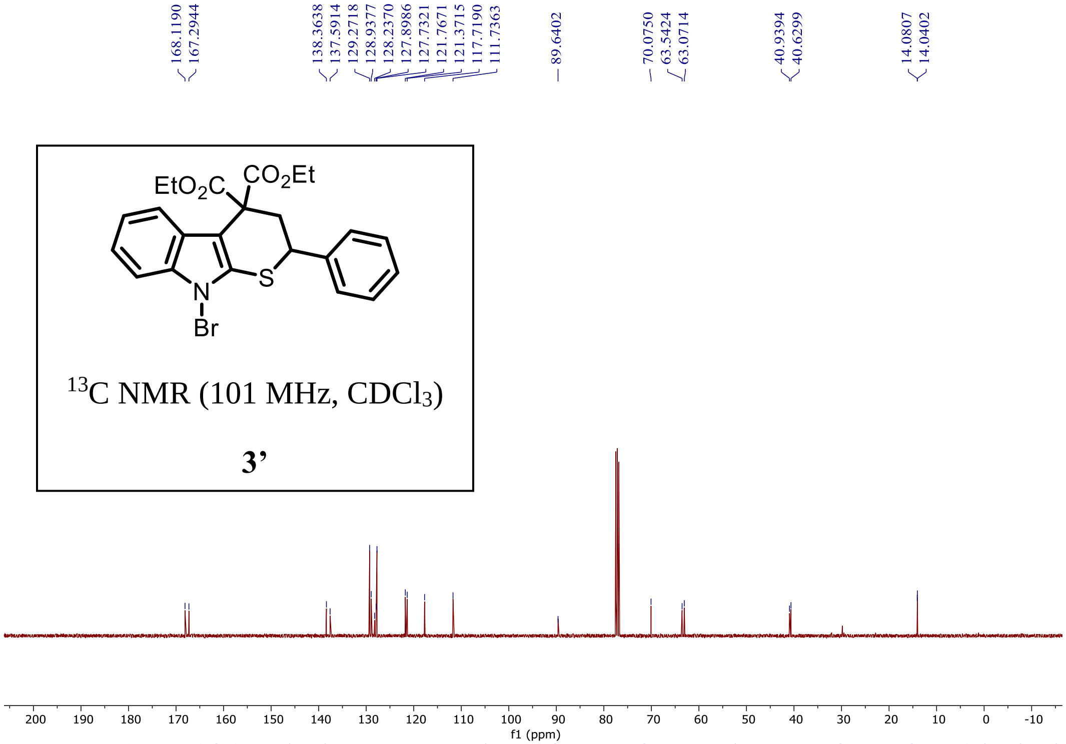
^{13}C NMR (101 MHz, CDCl$_3$)

3eb



^{1}H NMR (400 MHz, CDCl$_3$)

3’



^{13}C NMR (101 MHz, CDCl$_3$)

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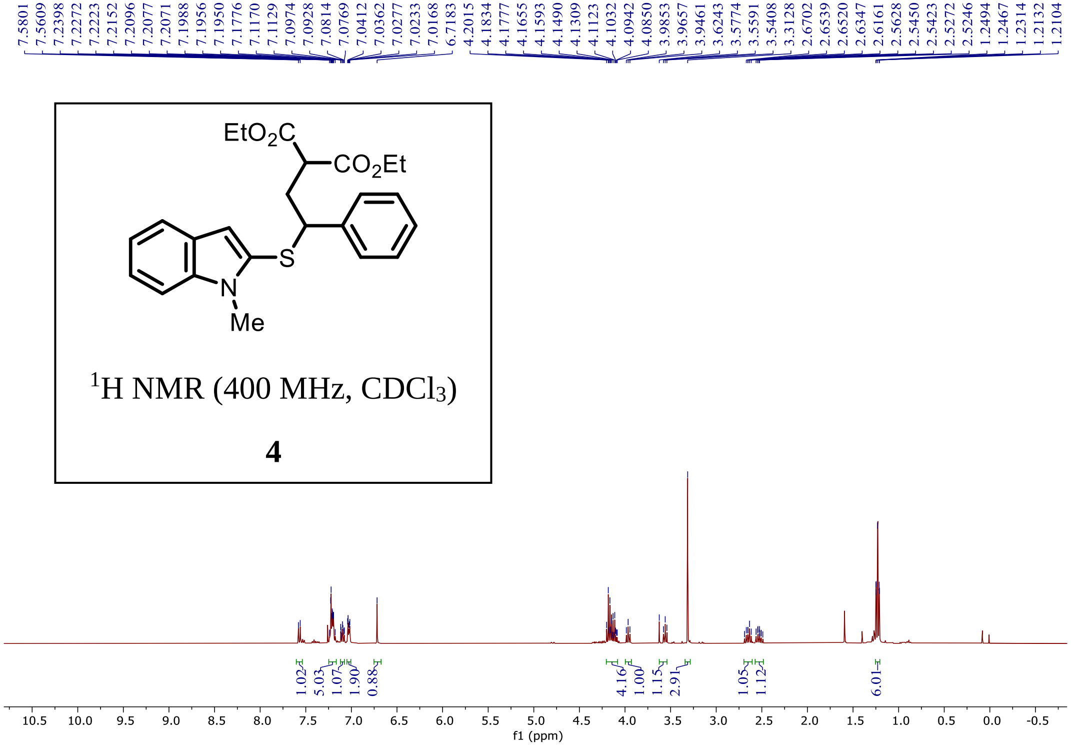
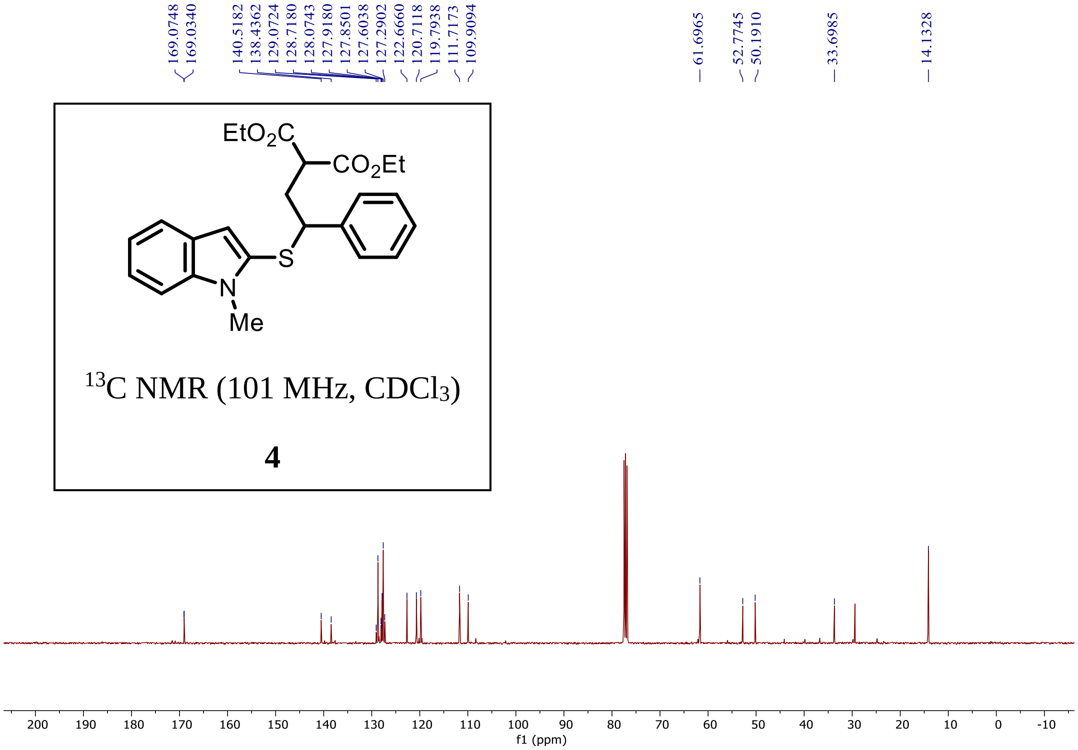


^{1}H NMR (400 MHz, CDCl$_3$)

4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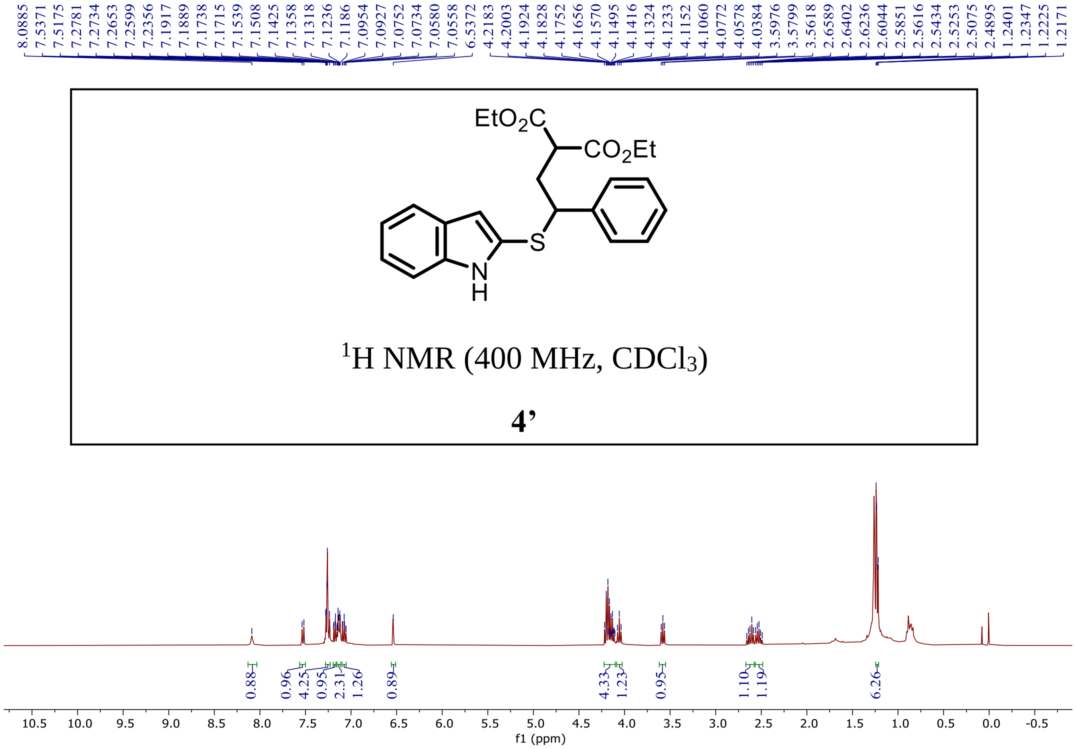
122.6660
120.7118
119.7938
111.7173
109.9094
61.6965
52.7745
50.1910
33.6985
14.1328
EtO$_2$C
CO$_2$Et
S
N
Me
^{13}C NMR (101 MHz, CDCl$_3$)
4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.1715
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7.1508
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7.1318
7.1236
7.1186
7.0954
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7.0752
7.0734
7.0580
7.0558
6.5372
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3.5976
3.5799
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2.6589
2.6402
2.6236
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2.5851
2.5616
2.5434
2.5253
2.5075
2.4895
1.2401
1.2347
1.2225
1.2171
EtO$_2$C
CO$_2$Et
S
N
H
^{1}H NMR (400 MHz, CDCl$_3$)
4’
0.88
0.96
4.25
0.95
2.31
1.26
0.89
4.33
1.23
0.95
1.10
1.19
6.26
10.5
10.0
9.5
9.0
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8.0
7.5
7.0
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6.0
5.5
5.0
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2.5
2.0
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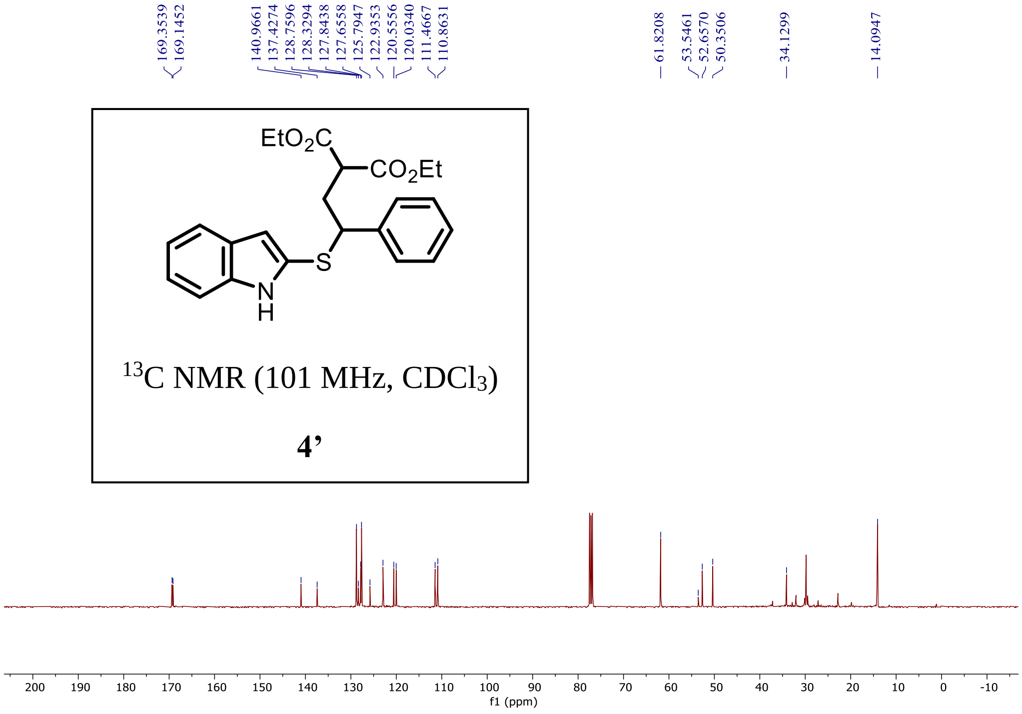
0.0
-0.5
f1 (ppm)

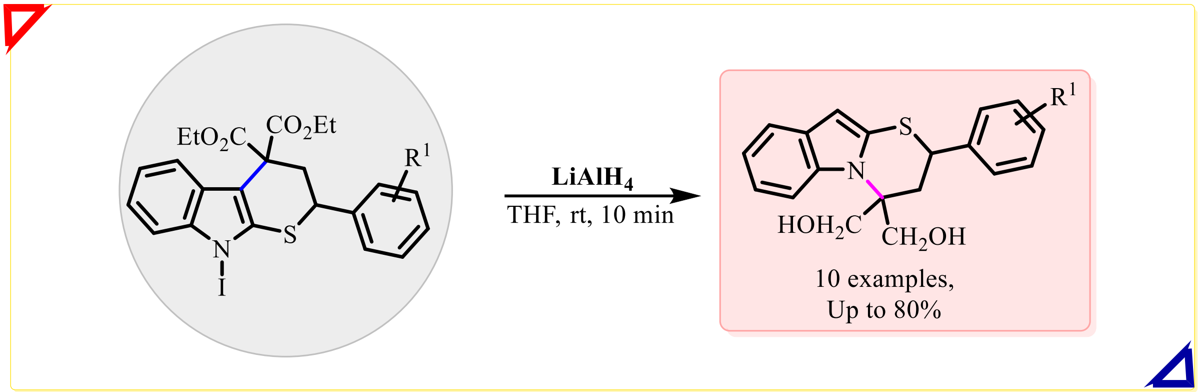


^{13}C NMR (101 MHz, CDCl$_3$)

4’

Chapter 2B

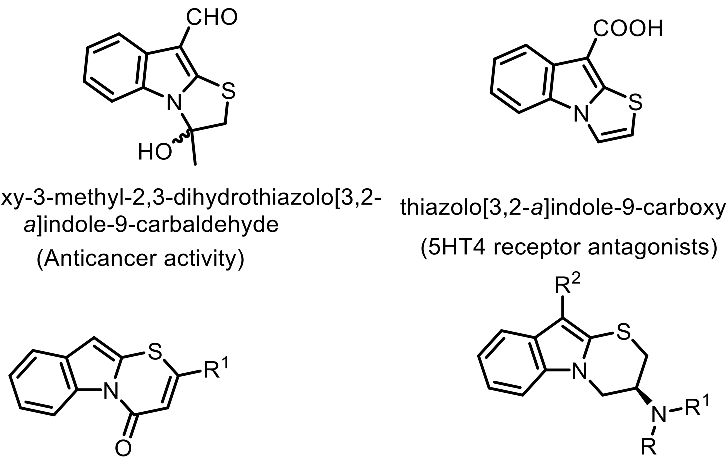
Ring-Opening and -Closing Reactions of *N*-Iodo Indole Fused Dihydro Thiopyrans



✓ Mild reaction conditions ✓ Broader substrate scope ✓ Gram scale synthesis

2B.1 Introduction

The objective of this chapter is to investigate the reactivity of dihydrothio pyrans using lithium alumium hydride, Sulfur-nitrogen-containing cyclic molecules are widely present in various fields, including pharmaceuticals, natural products, agrochemicals, materials science, polymer chemistry, and synthetic organic chemistry[1]. Among all known sulfur-nitrogen heterocycles, thiazino motifs represent a highly significant class of molecules, frequently found in various pharmaceutical and bioactive compounds[2]. Over the past few decades, fused-indole thiopyranos have served as valuable synthons for the synthesis of thiazino motifs[3]. Figure 2B.1 illustrates several fused indole derivatives, including thiazoloindoles, [1,3]thiazino[3,2-*a*]indol-4-ones, and [1,3]thiazino[3,2-*a*]indoles. These compounds, encompassing natural products and drugs, exhibit notable antiproliferative activity and function as 5-HT4 receptor antagonists,[4]. To the best of our knowledge, the synthesis of 1,2-fused indoles containing a sulfur atom has been relatively underexplored compared to 2,3-fused indole tricycles. However, a literature survey reveals several reported methods for synthesizing thiazino indoles[5]. Additionally, in 2016, Jha and their co-workers published an article detailing the construction of thiazoloindoles through a copper-catalyzed Ullmann C-N coupling reaction (Scheme 2B.1)[6]. However, no reports have been documented on the use of reducing agents for the one-step preparation of thiazoloindoles. Recently, we reported the synthesis of indole-fused dihydrothiopyrano scaffolds via (3 + 3) annulations of donor–acceptor cyclopropanes with indoline-2-thiones (Scheme 2B.2).[7] In this approach, we aim to extend our methodology to synthesize (2-phenyl-3,4-dihydro-2H-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol using reducing agents.



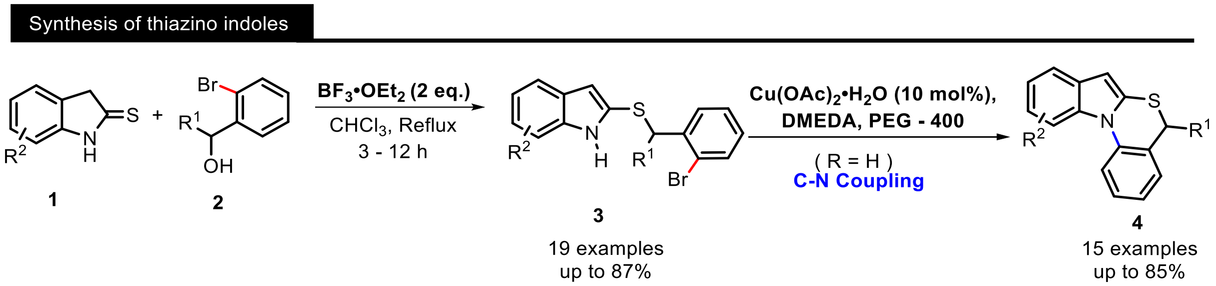
3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-*a*]indole-9-carbaldehyde
(Anticancer activity)

thiazolo[3,2-*a*]indole-9-carboxylic acid
(5HT4 receptor antagonists)

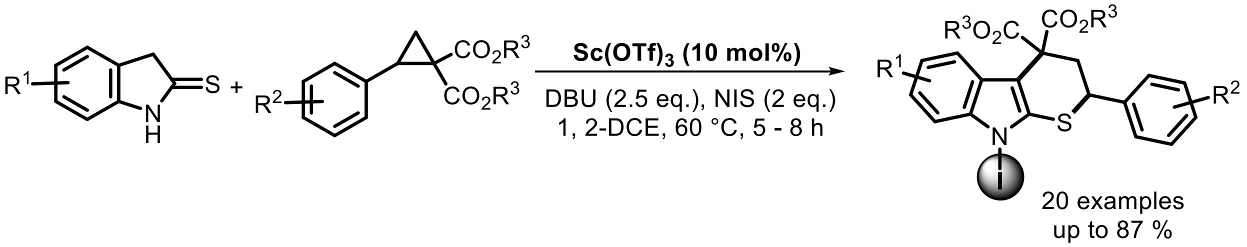
thiazino[3,2-*a*]indol-4-one
(antiproliferative activity)

thiazino[3,2-*a*]indol-3-amine
(CRTH2 and 5HT4 receptor antagonists)

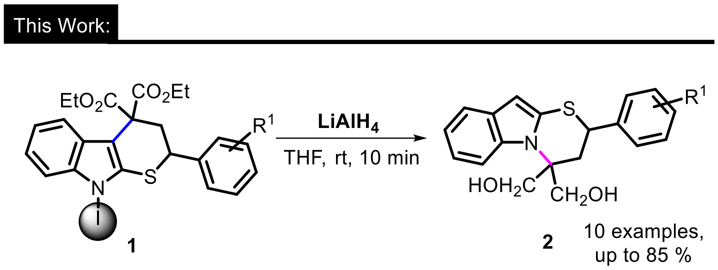
Figure 2B.1 Thiazino indoles as bio-active candidates.



Scheme 2B.1 Synthesis of thiazino indoles *via* Ullman Coupling.



Scheme 2B.2 Synthesis of *N*-iodo indole fused dihydrothio pyrans.

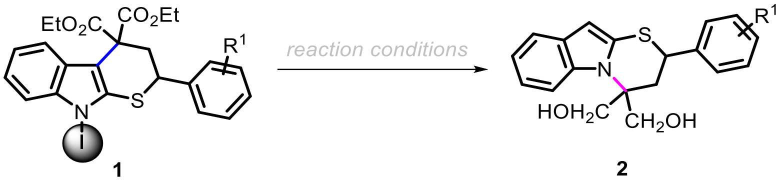


Scheme 2B.3 Proposed hypothesis for construction of thiazino indoles.

2B.2 Results and Discussions

Our study mainly commenced exploration of the efficacy of reducing agents. We begin our optimization studies by taking diethyl 9-iodo-2-phenyl-2,3-dihydrothiopyrano[2,3-*b*]indole-4,4(9H)-dicarboxylate **1** as a modal substrates scope under different reducing agents and different reactions conditions to obtain **2** and the results are discussed in (Table 2B.1). A series of reducing agents are used like $LiBH_4$, $NaBH_4$, *n*-BuLi and DIBAL-H in the presence of THF as a solvent at room temperature. In all the cases targeted product was not observed **2** (Table 2B.1, entries 1-4). Further, $LiAlH_4$ was used, the reaction was complete within 10 min. To our delight, we observed 80 % of **2** (Table 2B.1, entry 5). Other solvents like Et_2O and MeOH were not found to give a suitable yield of **2** (Table 2B.1, entries 7-8).

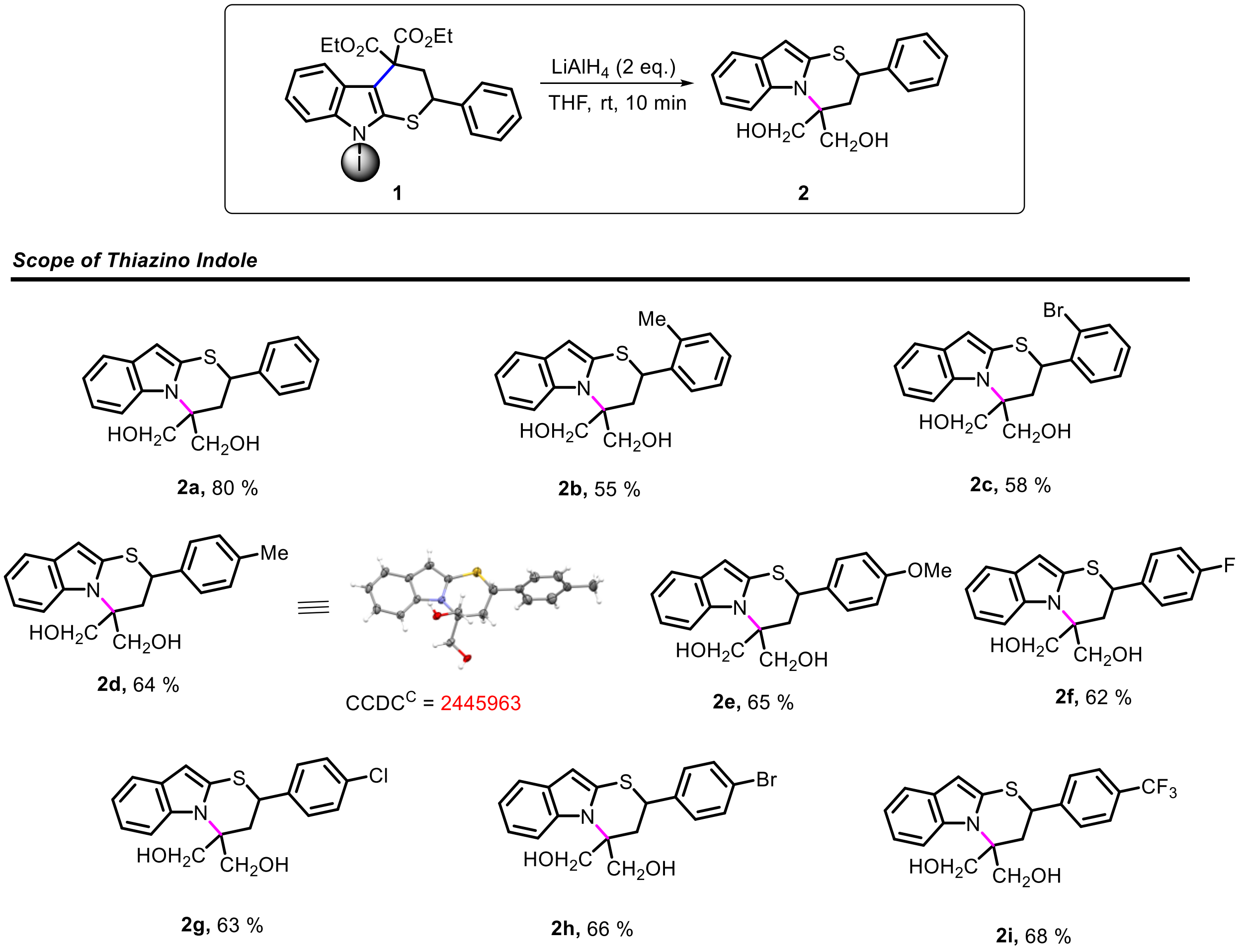
Table 2B.1 Optimization of the reaction conditions^a:



1 **2**

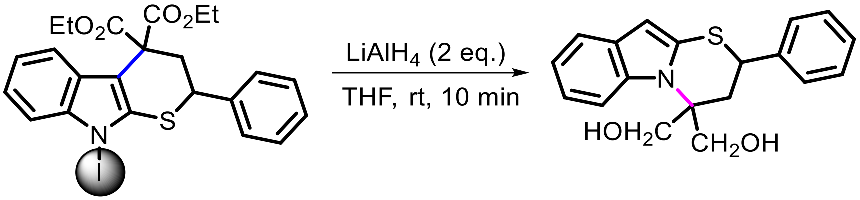
Entry no.	Reducing agent	Solvent	Temp. (0 ^{o}c)	Time	2aa (%)^b
1	LiBH$_4$	THF	rt	24 h	n. r.
2	NaBH$_4$	THF-MeOH	rt	24 h	n. r.
3	*n*-BuLi	THF	-78 - rt	24 h	n. r.
4	DiBAL-H	THF	-78 - rt	24 h	n. r.
5^c	**LiAlH$_4$**	**THF**	**0 ^{o}C - rt**	**10 min**	**80**
6^c	LiAlH$_4$	THF	0 ^{o}C - rt	5 min	78
7^c	LiAlH$_4$	Et$_2$O	0 ^{o}C - rt	10 min	72
8^c	LiAlH$_4$	MeOH	0 ^{o}C - rt	10 min	75

[a] optimized reaction conditions were performed with **1a** (0.6 mmol), Reducing Agent (0.30 mmol), room temperature, N$_2$ atmosphere. [b] Isolated yields. [c] reaction performed. n.r. = No reaction;



Scheme 2B.4 Scope of compounds **2** $^{a,\,b,\,c}$. ^{a}Reaction Conditions: **1** (0.6 mmol, 1 eq.), THF (2 ml), room temperature, N_2 atmosphere; ^{b}Isolated yield; ^{c}single crystal structure of **2d** thermal ellipsoids with 30% probability level.

At first, we started investigating the diversity of arene groups that were linked to the indole-fused dihydrothiopyrano under the optimized reaction conditions (Scheme 2B.4). Our analysis revealed that all types of arenes, including EDGs, and EWGs, and electronically hindered groups, were compatible with the above-said reaction conditions and delivered the expected compounds **2** in good to excellent yields. For example, substrates with *ortho*-substituted electron-rich functional groups viz., -Me and -Br were well tolerated under optimal reaction conditions and yielded **2b** and **2c** in 55% and 58% yields. *para*-substituted (-Me and OMe) aryl moieties on indole-fused dihydrothiopyrano were found suitable candidates for the transformation and furnished the respective products **2d** and **2e** in good yields. Moreover, at the same time, halogen (i.e., F, Cl and Br) substituted indole-fused dihydrothiopyrano were also provided thiazino indole **2f**-**3h** in good to satisfactory yields. electron-withdrawing group substituted (-CF_3) aryl moieties on indole-fused dihydrothiopyrano were found suitable candidates for the transformation and furnished the respective product **2i** in good yield.



(**1a,** 2.6 g, 5 mmol)

2a, 1.2 g, 78%

Scheme 2B.5 Gram scale synthesis of thiazino indoles.

Further, to investigate the practicality and viability of our methodology, a gram-scale synthesis of the targeted product **2** was performed as depicted in Scheme 2B.5. In this context, the reaction of **1a** was carried out at a 5 mmol scale and the product **2a** was obtained in 78% yield (1.20 g).

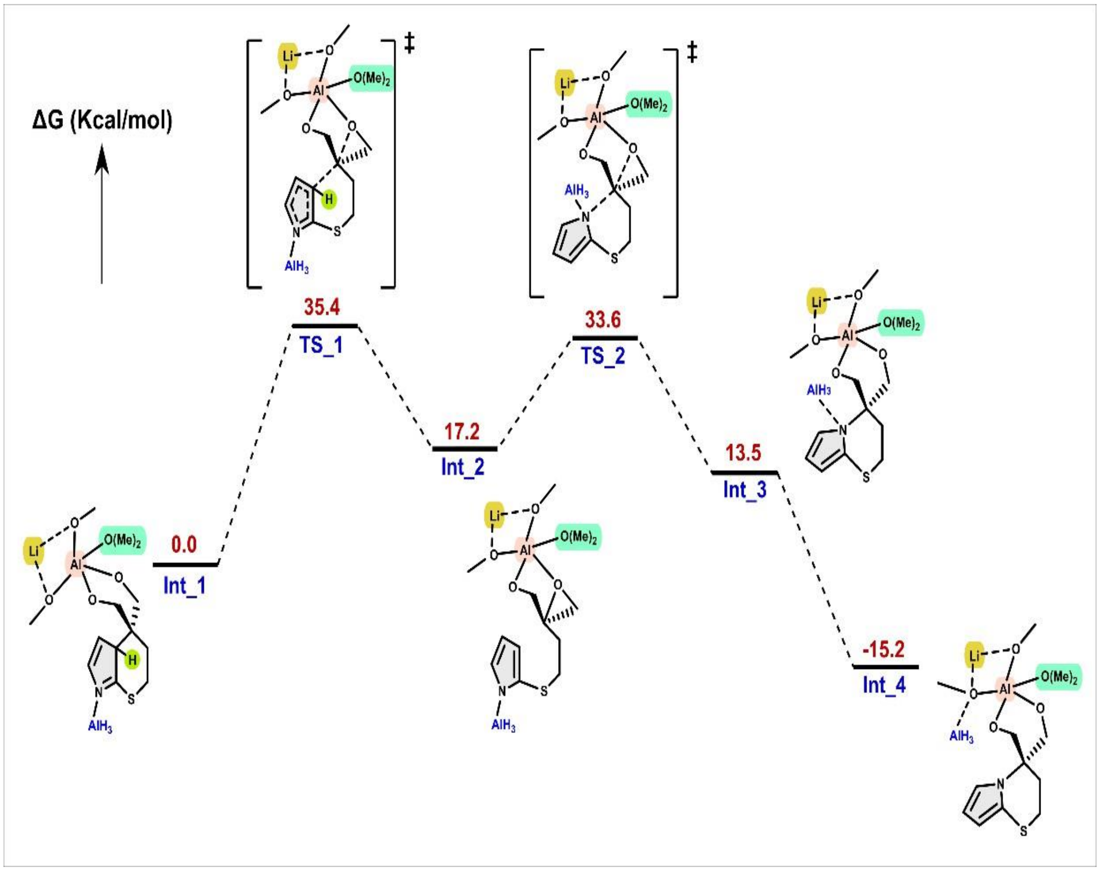


Figure 2B.2. Free energy profile showing the reaction mechanism of **2a** reaction.

To further investigate the mechanism of this reaction, (figure 2B.2). we carried out DFT calculations at M06- 2X/def2-TZVPP (SMD, solvent=THF)//M06-2X/def2-SVP level of theory. Reduction of esters in the presence of $LiAlH_4$ is very well known in the literature, hence we focused on later part of the mechanism involving ring opening and closing via epoxide intermediate. Our investigation revealed that there an involvement of solvent coordination to the aluminium during the mechanism. Hence a dimethyl ether (computationally less expensive alternative for THF) is used during all the calculations. The first step after the formation of Int_1 is the attack of oxygen atom on the carbon to form the epoxide Int_2 via TS_1. This step is accompanied with a Gibbs free energy barrier of 35.4 kcal/mol. The epoxide Int_2 is unstable by 17.2 kcal/mol compared to Int_1 due to the presence of high 3-membered ring strain. This leads to the quick attack of pyrrole's nitrogen on epoxide ring to form the Int_3 via a smaller energy barrier of TS_2. Int_3 in turn leads to the formation of a more stable Int_4. This Int_4 on hydrolysis forms the final product.

2B.3 Conclusions

In summary, a straightforward and efficient $LiAlH_4$-mediated protocol has been developed for the construction of thiazino indoles. This procedure provides efficient thiazino indoles derivatives in good to satisfactory yields. DFT calculation has been done to shed light into reaction mechanism.

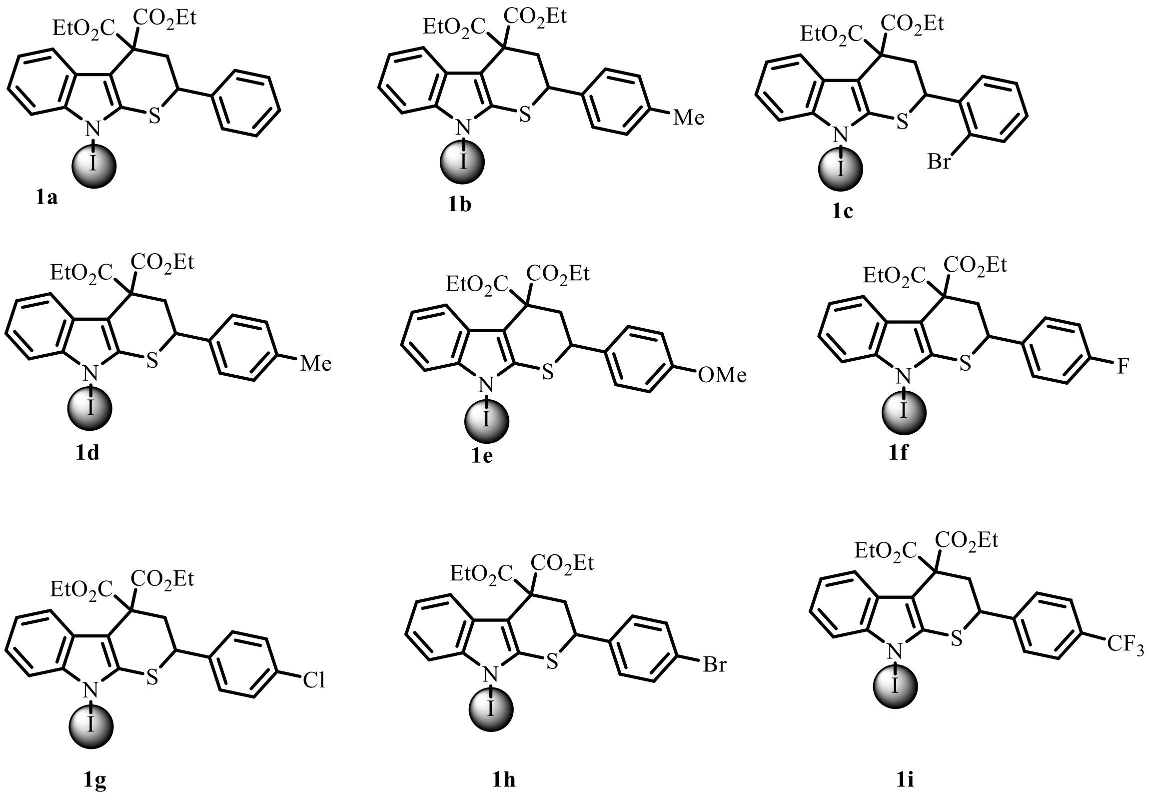
2B.4 Experimental Section

All the reactions were carried out under an inert atmosphere using the Schlenk technique. All solvents were dried and stored over molecular sieves under an argon atmosphere. All chemicals and reagents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using E. Merck silica gel 60 (100–200 mesh). ^{1}H, ^{13}C NMR spectra were recorded in $CDCl_3$, on JEOL JNM-ECS spectrometer at operating frequencies of 400 MHz (^{1}H) or 101 MHz (^{13}C) as indicated in the individual spectrum. Chemical shifts (δ) are given in parts per million (ppm) relative to residual solvent (chloroform, δ= 7.26 for ^{1}H and 77.16 for proton decoupled ^{13}C NMR) and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, q for quartet, and m for multiplet. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) methods on waters mass spectrometer (XEVO G2-XS QTOF). Melting points were taken on the Staurt digital melting point apparatus and X-ray data were recorded on a Bruker D8 venture instrument.

2B.4.1 Synthesis of starting materials

General procedure for the synthesis of N-iodo indole fused dihydrothio pyrans derivatives (GP1): In a Schlenk tube, indoline-2-thione **1** (0.6 mmol, 1.0 eq.), donor-acceptor cyclopropanes **2** (0.6 mmol, 1.0 eq.), and $Sc(OTf)_3$ (0.06 mmol, 30 mg, 0.1 eq.) were dissolved in anhydrous

1,2-DCE (1 mL) under a nitrogen atmosphere. Next, NIS (N-iodosuccinimide, 1.2 mmol, 2.0 eq.) and DBU (1.5 mmol, 0.22 mL, 2.5 eq.) were added sequentially. The reaction mixture was stirred for 6–8 hours at 60 °C (oil bath). Once the reaction was complete (monitored by TLC), the crude mixture was filtered, and the filtrate was concentrated under reduced pressure. The resulting crude was then purified by silica gel column chromatography using a hexane and ethyl acetate mixture as eluents.[1]



1a **1b** **1c**

1d **1e** **1f**

1g **1h** **1i**

Figure 2B.4.1 Used *N*-iodo indole fused dihydrothio pyrans **1**

2B.4.2 General Procedures

2B.4.2.1 Synthesis of thiazino indoles 2:

In a round-bottom flask, N-halo indole-fused dihydrothiopyrano **1** (1 mmol, 1 eq.) was dissolved in anhydrous THF under a nitrogen atmosphere at room temperature. After 2 minutes of stirring, $LiAlH_4$ (2 mmol, 2 eq.) was added, and the reaction mixture was allowed to stir for 10 minutes. Upon completion of the reaction, as monitored by TLC, the crude solution was extracted with ethyl acetate (EtOAc). The combined organic layers were washed once with brine and $NaHCO_3$, then dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting crude was purified by silica gel column chromatography using a hexane and ethyl acetate mixture as eluents.

2B.4.2.2 Gram scale synthesis of (2-phenyl-3,4-dihydro-2H-[1,3]thiazino[3,2-a]indole-4,4-diyl)dimethanol 2a:

In a round bottom flask, *N*-halo indole fused dihydrothiapyrano **1** (5 mmol, 5 eq.), dissolved in anhydrous THF solvent under N_2 atmosphere at rt. After 2 min of stirring add $LiAlH_4$ (10 mmol, 2 eq.) and allowed reaction mixture to stir for 10 min. Upon completion of the reaction, as monitored by TLC, the crude solution was extracted with EtOAc. The combined organic layers were washed once with brine and $NaHCO_3$ dried over sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents. Yield of product **2a**: 1.2 g, 78%

2B.4.3 Characterization of compounds

(2-phenyl-3,4-dihydro-*2H*-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol (2aa):

White Solid, 172 mg (85%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68−7.66 (m, 1H), 7.53−7.51 (m, 2H), 7.45−7.41(m, 2H), 7.39−7.31 (m, 3H), 7.04−6.96 (m, 2H), 6.27 (s, 1H), 5.20(t, *J* = 5.4 Hz, 1H), 4.95 (t, *J* = 5.6 Hz, 1H), 4.88 (dd, *J* = 12.4, 1.8Hz, 1H), 4.52−4.47 (m, 1H), 3.98 (d, *J* = 5.5 Hz, 2H), 3.76 (dd, *J* =11.9, 5.5 Hz, 1H), 2.92 (dd, *J* = 14.1, 12.5 Hz, 1H). ^{13}C{^{1}H} NMR(101 MHz, DMSO-d_6) δ 140.2, 136.4, 131.7, 128.9, 128.8, 128.1,127.6, 119.6, 119.4, 118.8, 113.1, 98.8, 64.7, 62.8, 38.6. HRMS:*m/z* calculated for $C_{19}H_{19}NO_2S$ $[M+H]^+$ 326.1168, found 326. 1170.

(2-(o-tolyl)-3,4-dihydro-*2H*-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol(2ab):

Brown Solid. mg (55%). ^{1}H NMR (400 MHz, DMSO-*D*$_6$) δ 7.78 – 7.70 (m, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.39 – 7.27 (m, 3H), 7.10 – 7.02 (m, 2H), 6.36 (s, 1H), 5.14 (dd, *J* = 12.3, 1.7 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.17 (d, *J* = 11.4 Hz, 2H), 4.15 – 3.99 (m, 1H), 3.84 (d, *J* = 11.8 Hz, 1H), 3.10 – 2.97 (m, 1H), 2.67 (dd, *J* = 14.1, 1.8 Hz, 1H), 2.55 (t, *J* = 1.9 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*D*$_6$) δ 138.2, 136.3, 136.2, 131.9, 130.7, 128.9, 127.8, 126.7, 126.2, 119.6, 119.4, 118.8, 113.1, 99.2, 64.8, 63.1, 62.83, 59.9, 35.6, 20.8, 18.9, 14.2. HRMS:*m/z* calculated for$C_{20}H_{21}NO_2S[M+H]^+$ 340.1326, found 340.1328.

(2-(2-bromophenyl)-3,4-dihydro-*2H*-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol (2ac)

Brown Solid. Yield: 176 mg (58%).^{1}H NMR (400 MHz, DMSO-*D*$_6$) δ 7.76 – 7.63 (m, 2H), 7.62 – 7.48 (m, 2H), 7.48 – 7.33 (m, 2H), 7.04 – 6.94 (m, 2H), 6.28 (s, 1H), 5.21 (t, *J* = 5.6 Hz, 1H), 5.01 – 4.83 (m, 2H), 4.49 (dd, *J* = 11.8, 6.2 Hz, 1H), 4.03 (q, *J* = 7.0 Hz, 1H), 3.97 (d, *J* = 5.6 Hz, 1H), 3.75 (dd, *J* = 12.0, 5.5 Hz, 1H), 2.88 (dd, *J* = 14.1, 12.4 Hz, 1H), 2.63 (dd, *J* = 14.1, 2.1 Hz, 1H).^{13}C NMR (101 MHz, DMSO-*D*$_6$) δ 142.9, 140.2, 136.4, 131.7, 131.2, 131.1, 131.0, 130.5, 128.9, 128.1, 127.7, 126.8, 122.0, 119.7, 119.6, 119.5, 119.4, 118.9, 118.8, 113.2, 113.1, 98.9, 64.7, 64.7, 62.8, 62.7, 59.9, 20.8, 14.2. HRMS:*m/z* calculated for $C_{19}H_{18}NO_2Br[M+H]^+$ 405.0220, found 405.0222.

(2-(p-tolyl)-3,4-dihydro-2H-[1,3]thiazino[3,2-a]indole-4,4-diyl)dimethanol(2ad):

White solid. 151 mg (64%). ^{1}H NMR (400 MHz, DMSO-*D*$_6$) δ 7.69 – 7.62 (m, 1H), 7.43 – 7.32 (m, 3H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.02 – 6.92 (m, 2H), 6.25 (s, 1H), 5.19 (t, *J* = 5.6 Hz, 1H), 4.99 – 4.90 (m, 1H), 4.83 (d, *J* = 11.1 Hz, 1H), 4.49 (dd, *J* = 11.7, 5.7 Hz, 1H), 3.97 (d, *J* = 5.5 Hz, 2H), 3.74 (dd, *J* = 11.9, 5.4 Hz, 1H), 2.89 (t, *J* = 13.3 Hz, 1H), 2.60 (dd, *J* = 14.2, 2.1 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*D*$_6$) δ 137.4, 137.2, 136.4, 131.9, 129.4, 128.9, 127.5, 119.5, 119.4, 118.8, 113.1, 98.7, 64.7, 62.8, 20.8. HRMS:*m/z* calculated for $C_{20}H_{21}NO_2S$ $[M+H]^+$ 340.1328, found 340.1331.

(2-(4-methoxyphenyl)-3,4-dihydro-*2H*-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol (3ea): White Solid. mg (65%). ^{1}H NMR (400 MHz, DMSO-*D*6) δ 7.71 – 7.61 (m, 1H), 7.39 – 7.32 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 2.1 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.93 (dd, *J* = 8.2, 2.7 Hz, 1H), 4.84 (dd, *J* = 12.4, 1.9 Hz, 2H), 4.49 (d, *J* = 11.8 Hz, 1H), 3.97 (s, 3H), 3.79 (s, 4H), 2.89 (dd, *J* = 14.1, 12.4 Hz, 1H), 2.62 (dd, *J* = 14.2, 2.1 Hz, 1H).^{13}C NMR (101 MHz, DMSO-*D*6) δ 159.6, 141.8, 136.4, 131.6, 130.0, 128.9, 119.7, 119.6, 119.4, 118.8, 113.5, 113.3, 113.1, 98.8, 64.7, 62.8, 55.2, 23.7, 22.2, 14.1. HRMS:*m/z* calculated for $C_{20}H_{21}NO_3S$ $[M+H]^+$ 356.1246, found 356.1248.

(2-(4-fluorophenyl)-3,4-dihydro-*2H*-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol(2af): White Solid. 137 mg (62%). ^{1}H NMR (400 MHz, DMSO-*D*6) δ 7.71 – 7.62 (m, 1H), 7.61 – 7.52 (m, 2H), 7.42 – 7.33 (m, 1H), 7.32 – 7.21 (m, 2H), 7.04 – 6.93 (m, 2H), 6.27 (s, 1H), 5.21 (t, *J* = 5.6 Hz, 1H), 4.96 (t, *J* = 5.6 Hz, 1H), 4.90 (dd, *J* = 12.4, 2.0 Hz, 1H), 4.49 (dd, *J* = 11.8, 5.7 Hz, 1H), 3.97 (d, *J* = 5.7 Hz, 1H), 3.75 (dd, *J* = 11.9, 5.5 Hz, 2H), 2.89 (dd, *J* = 14.2, 12.4 Hz, 1H), 2.62 (dd, *J* = 14.0, 2.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*D*6) δ 162.9, 160.6, 136.5, 136.4, 131.5, 129.8, 129.7, 128.6, 119.7, 119.5, 118.9, 115.9, 115.7, 113.2, 98.9, 64.7, 62.8.HRMS:*m/z* calculated for $C_{19}H_{18}NO_2F[M+H]^+$ 344.1076, found 344.1078.

(2-(4-chlorophenyl)-3,4-dihydro-*2H*-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol(2ag): White Solid. 187 mg (63%). ^{1}H NMR (400 MHz, DMSO-*D*6) δ 7.76 – 7.63 (m, 2H), 7.62 – 7.48 (m, 2H), 7.48 – 7.33 (m, 2H), 7.04 – 6.94 (m, 2H), 6.28 (s, 1H), 5.21 (t, *J* = 5.6 Hz, 1H), 5.01 – 4.83 (m, 2H), 4.49 (dd, *J* = 11.8, 6.2 Hz, 1H), 4.03 (q, *J* = 7.0 Hz, 1H), 3.97 (d, *J* = 5.6 Hz, 1H), 3.75 (dd, *J* = 12.0, 5.5 Hz, 1H), 2.88 (dd, *J* = 14.1, 12.4 Hz, 1H), 2.63 (dd, *J* = 14.1, 2.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*D*6) δ 142.9, 140.2, 136.4, 131.7, 131.2, 131.1, 131.0, 130.5, 128.9, 128.1, 127.7, 126.8, 122.0, 119.7, 119.6, 119.5, 119.4, 118.9, 118.8, 113.2, 113.1, 98.9, 64.7, 64.7, 62.8, 62.7, 59.9, 20.8, 14.2.HRMS:*m/z* calculated for $C_{19}H_{18}NO_2SCl[M+H]^+$ 361.0740, found 361.0742.

(2-(4-bromophenyl)-3,4-dihydro-*2H*-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol(2ah):
white Solid. 158 mg (66%). ^{1}H NMR (400 MHz, DMSO-*D*$_6$) δ 7.69 – 7.64 (m, 1H), 7.57 – 7.50 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.02 – 6.96 (m, 2H), 6.27 (s, 1H), 5.20 (t, *J* = 5.5 Hz, 1H), 4.95 (t, *J* = 5.5 Hz, 1H), 4.87 (dd, *J* = 12.3, 1.8 Hz, 1H), 4.50 (dd, *J* = 11.8, 5.6 Hz, 1H), 3.98 (d, *J* = 5.5 Hz, 2H), 3.75 (dd, *J* = 11.9, 5.5 Hz, 1H), 2.92 (dd, *J* = 14.1, 12.4 Hz, 1H), 2.63 (dd, *J* = 14.2, 2.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*D*$_6$) δ 140.2, 136.4, 131.7, 128.9, 128.8, 128.1, 127.7, 119.6, 119.4, 118.8, 113.1, 98.8, 64.7, 62.8. HRMS:*m/z* calculated for $C_{19}H_{18}NO_2SBr[M+H]^+$ 405.0224, found 405.0226.

(2-(4-(trifluoromethyl)phenyl)-3,4-dihydro-*2H*-[1,3]thiazino[3,2-*a*]indole-4,4-diyl)dimethanol(2ai):

White Solid. 149 mg (68%). ^{1}H NMR (400 MHz, DMSO-*D*$_6$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.72 – 7.64 (m, 1H), 7.43 – 7.34 (m, 1H), 7.04 – 6.95 (m, 2H), 6.30 (s, 1H), 5.23 (t, *J* = 5.6 Hz, 1H), 5.06 – 4.94 (m, 2H), 4.50 (dd, *J* = 11.8, 5.6 Hz, 1H), 4.06 – 3.92 (m, 2H), 3.75 (dd, *J* = 11.8, 5.4 Hz, 1H), 2.93 (dd, *J* = 14.1, 12.4 Hz, 1H), 2.66 (dd, *J* = 14.1, 2.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*D*$_6$) δ 144.9, 136.4, 130.9, 128.8, 128.7, 128.5, 125.9, 125.9, 125.6, 122.9, 119.7, 119.5, 118.9, 113.2, 99.1, 64.7, 62.8, 62.7. ^{19}F NMR (376 MHz, DMSO-*D*$_6$) δ -60.9. HRMS:*m/z* calculated for $C_{20}H_{18}F_3NO_2S[M+H]^+$ 394.1042, found 394.1044.

2B.5 References

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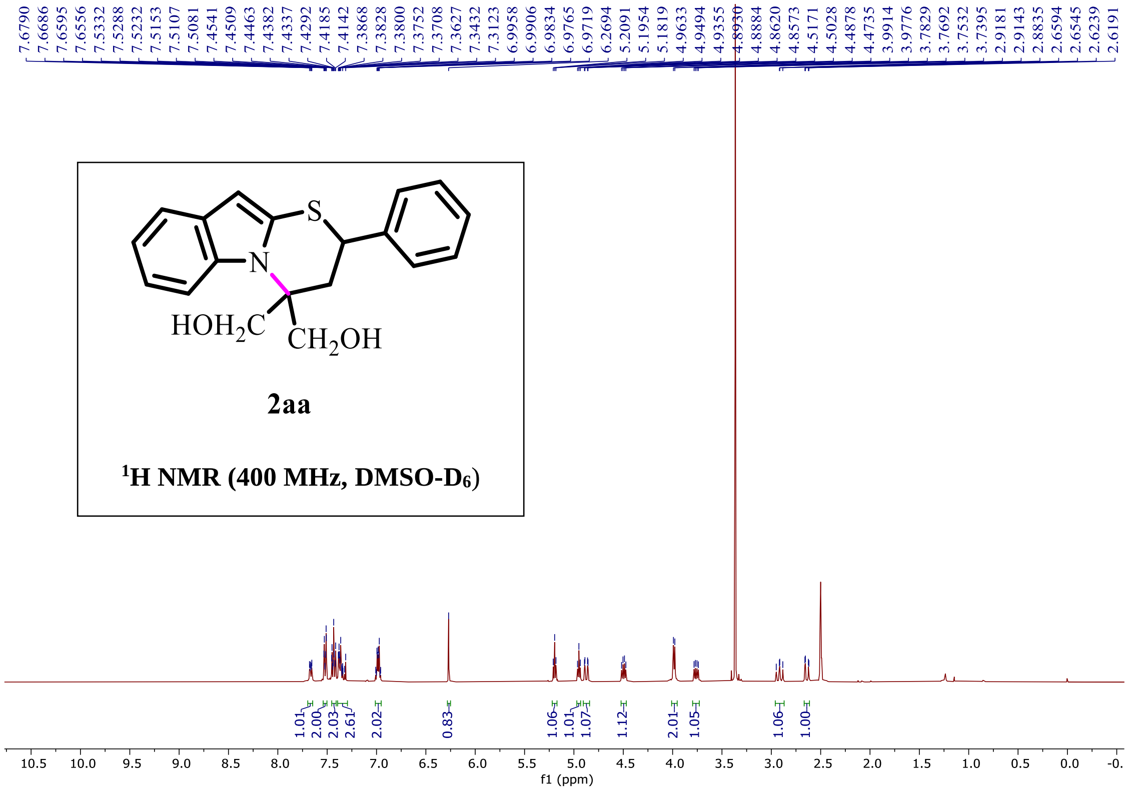
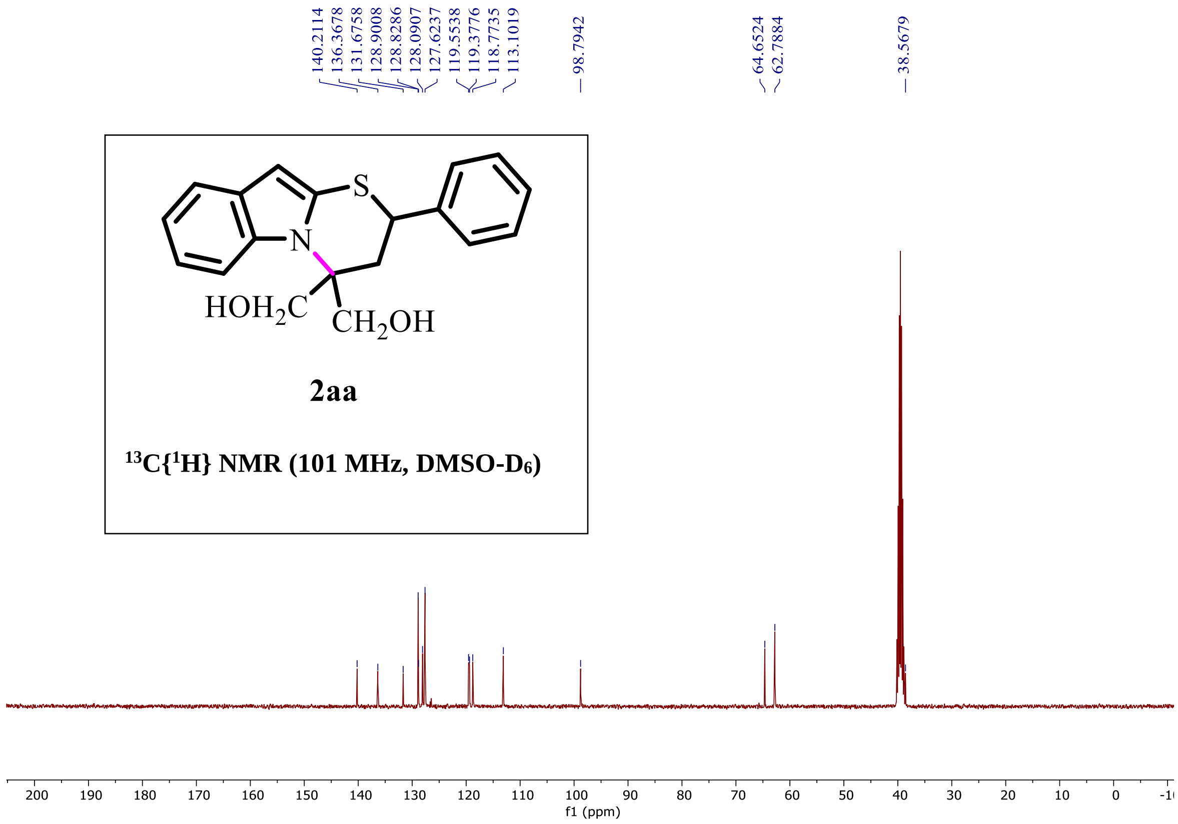
2B.6 NMR spectra of compounds

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98.7942
64.6524
62.7884
38.5679
S
N
HOH2C
CH2OH
2aa
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200
190
180
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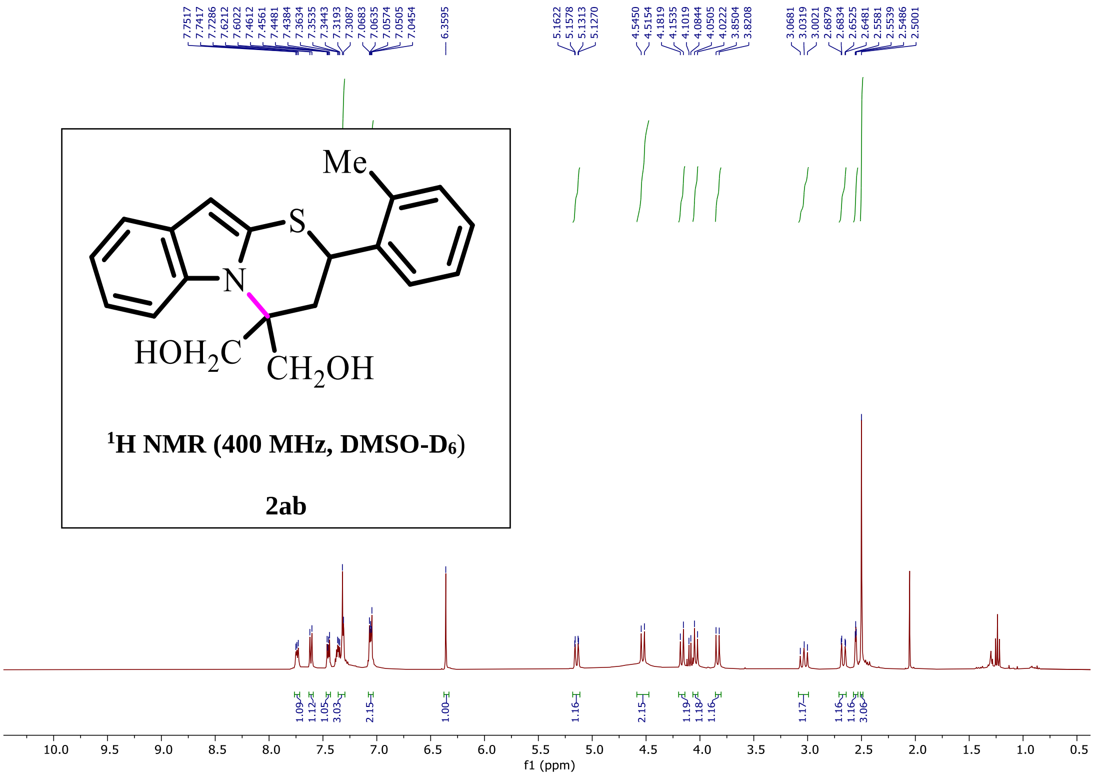
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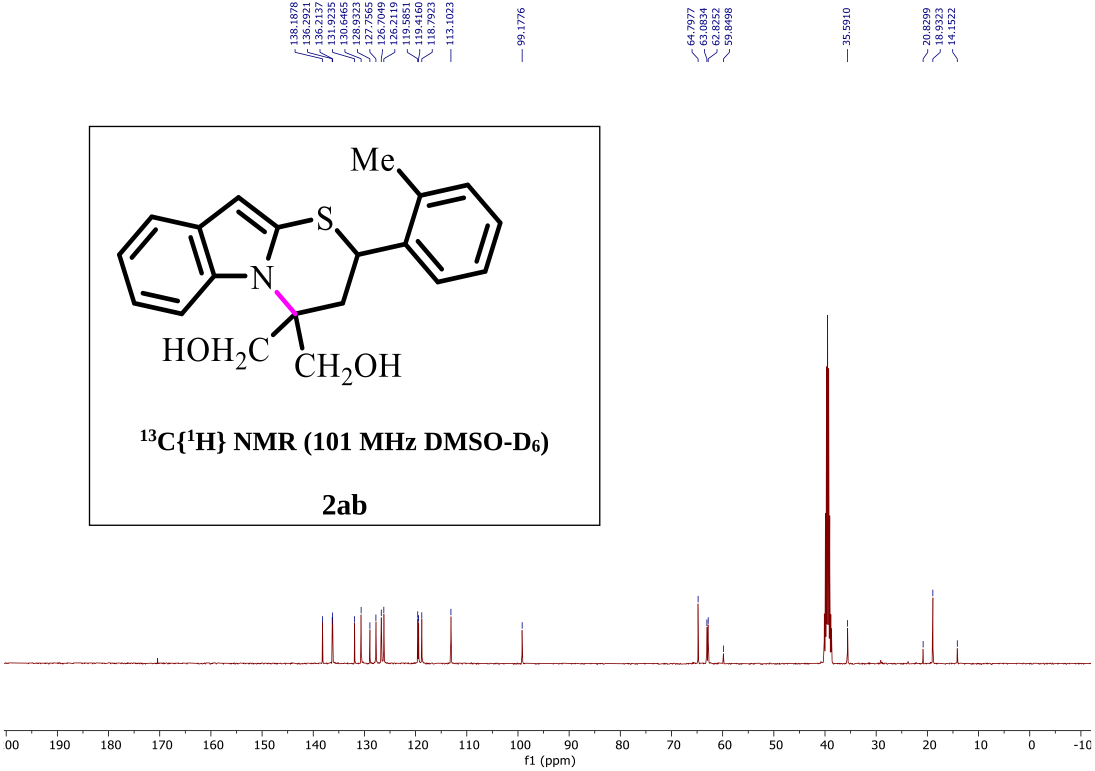
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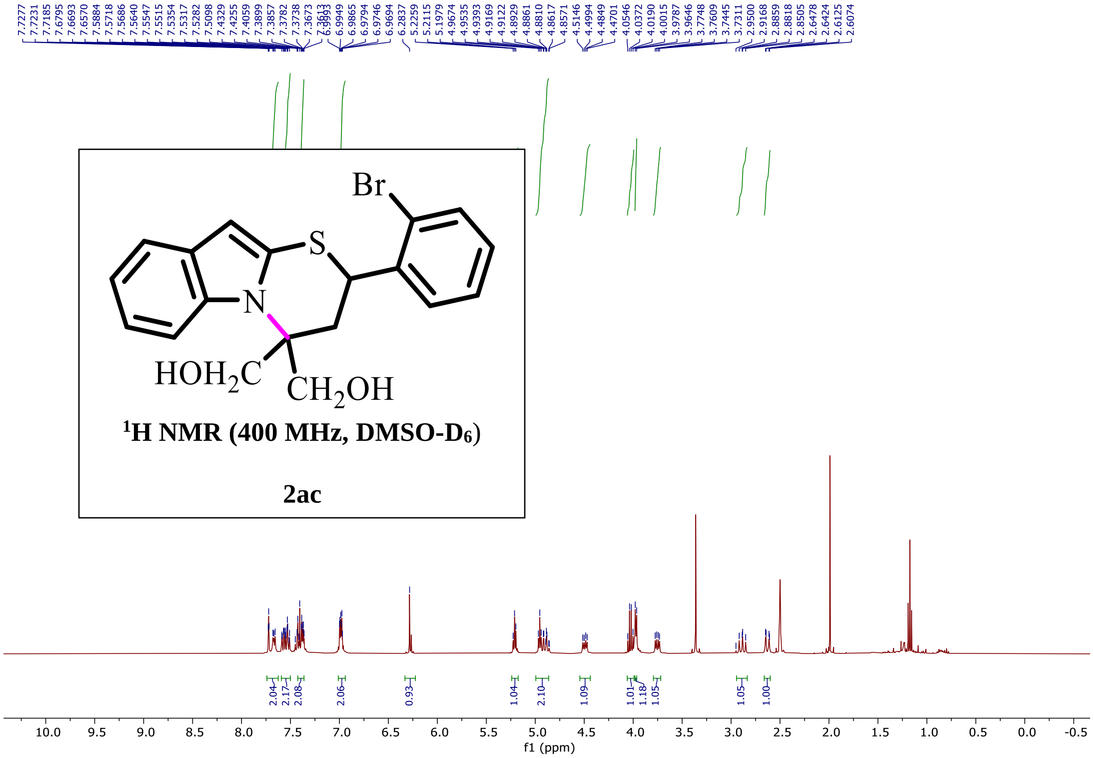
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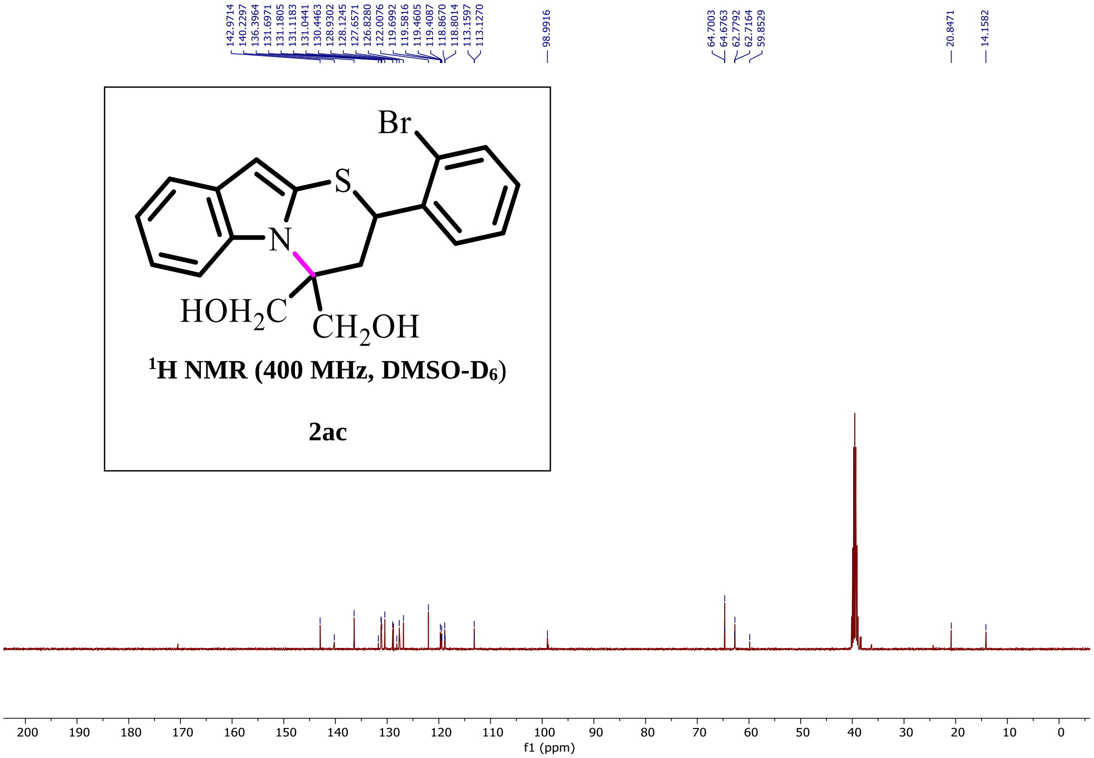
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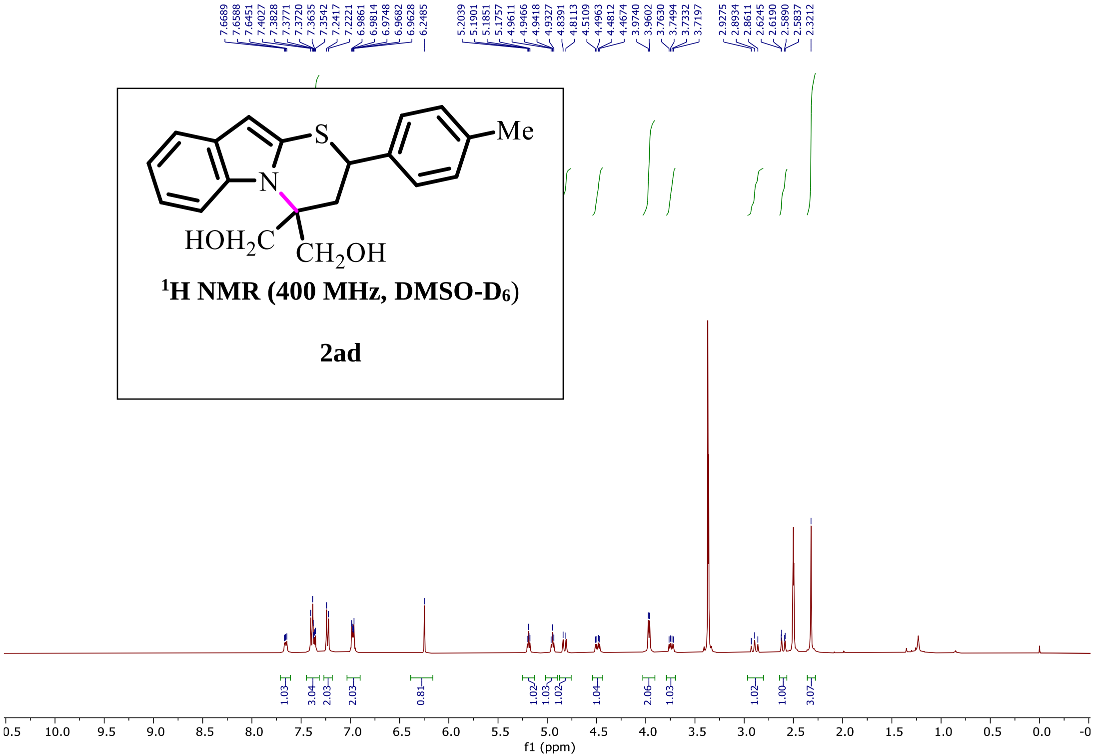
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5.1851
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1.02
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3.07
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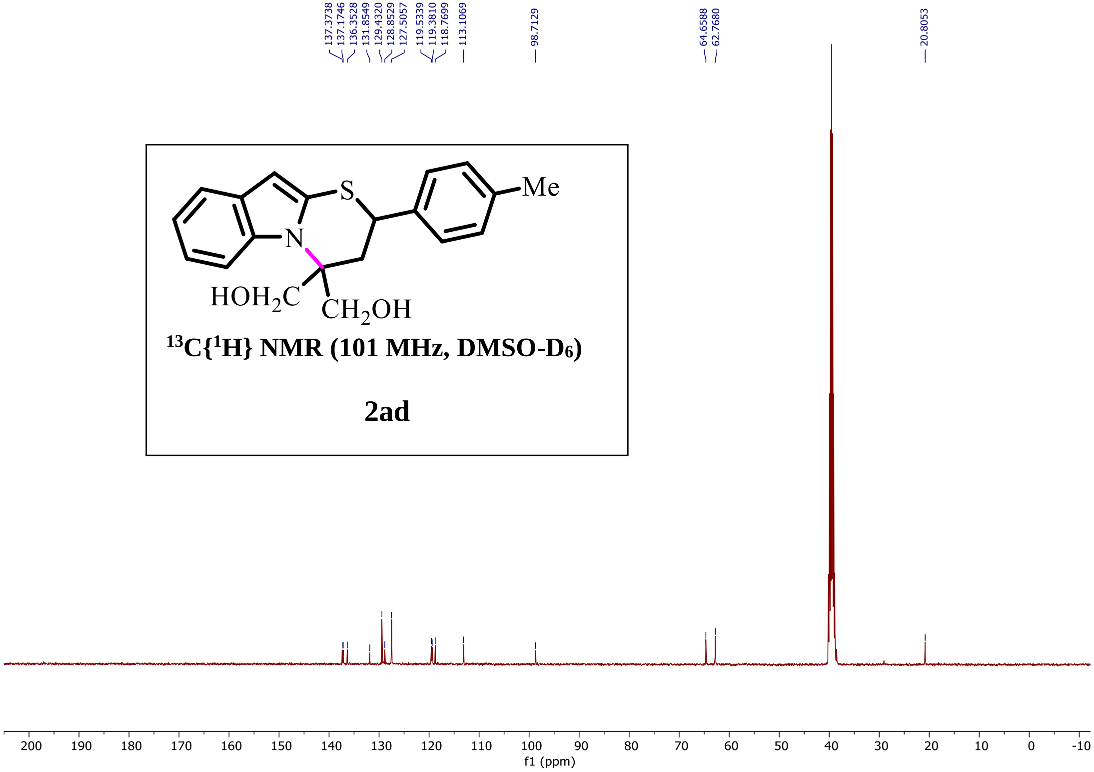
f1 (ppm)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62.7680
20.8053
S
N
Me
HOH2C
CH2OH
13C{1H} NMR (101 MHz, DMSO-D6)
2ad
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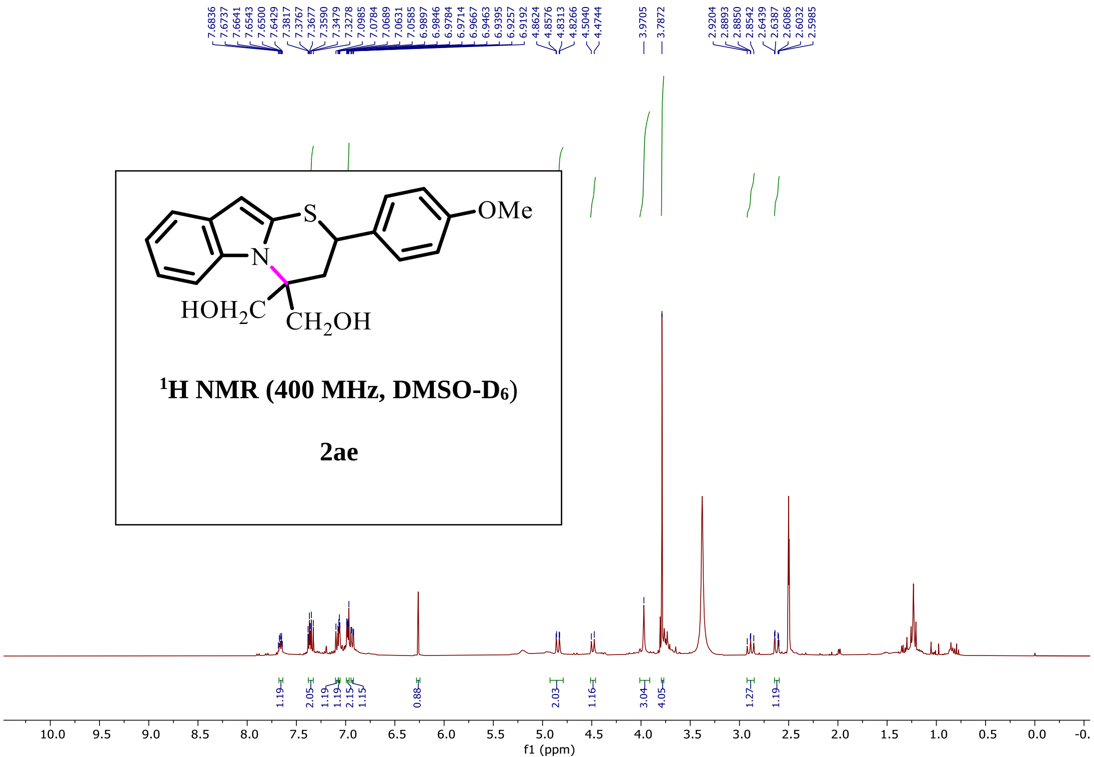
f1 (ppm)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N
HOH2C
CH2OH
1H NMR (400 MHz, DMSO-D6)
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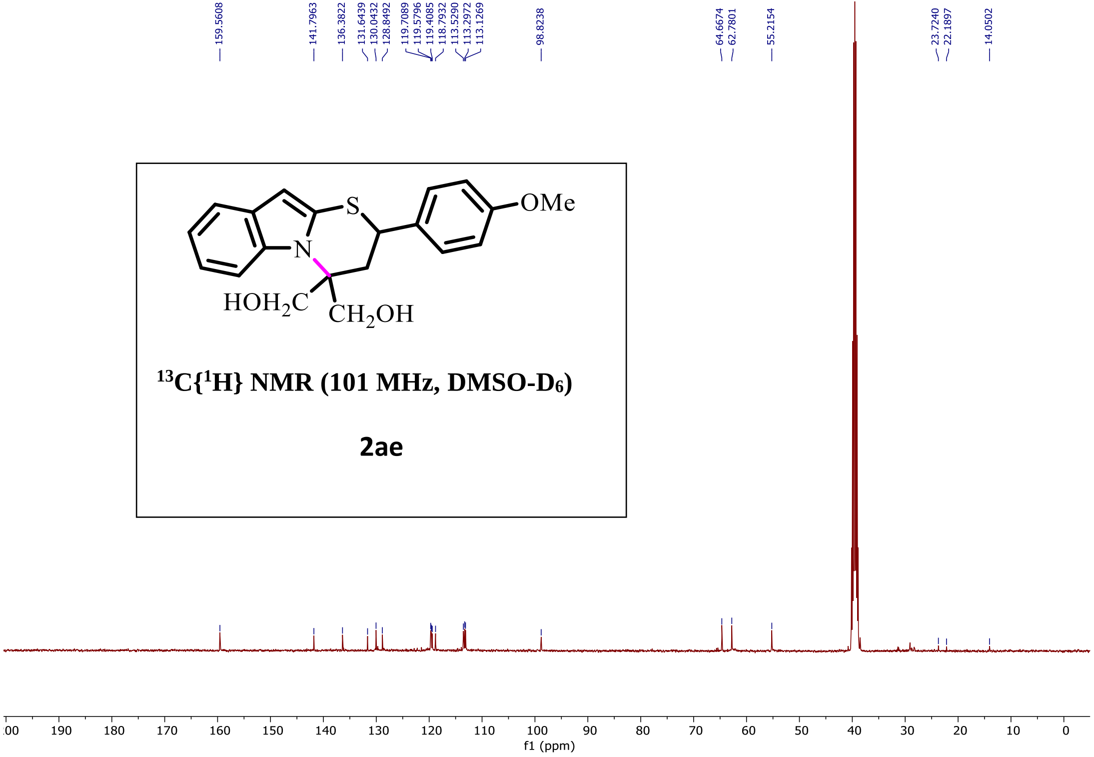
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S
OMe
N
HOH2C
CH2OH
13C{1H} NMR (101 MHz, DMSO-D6)
2ae
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180
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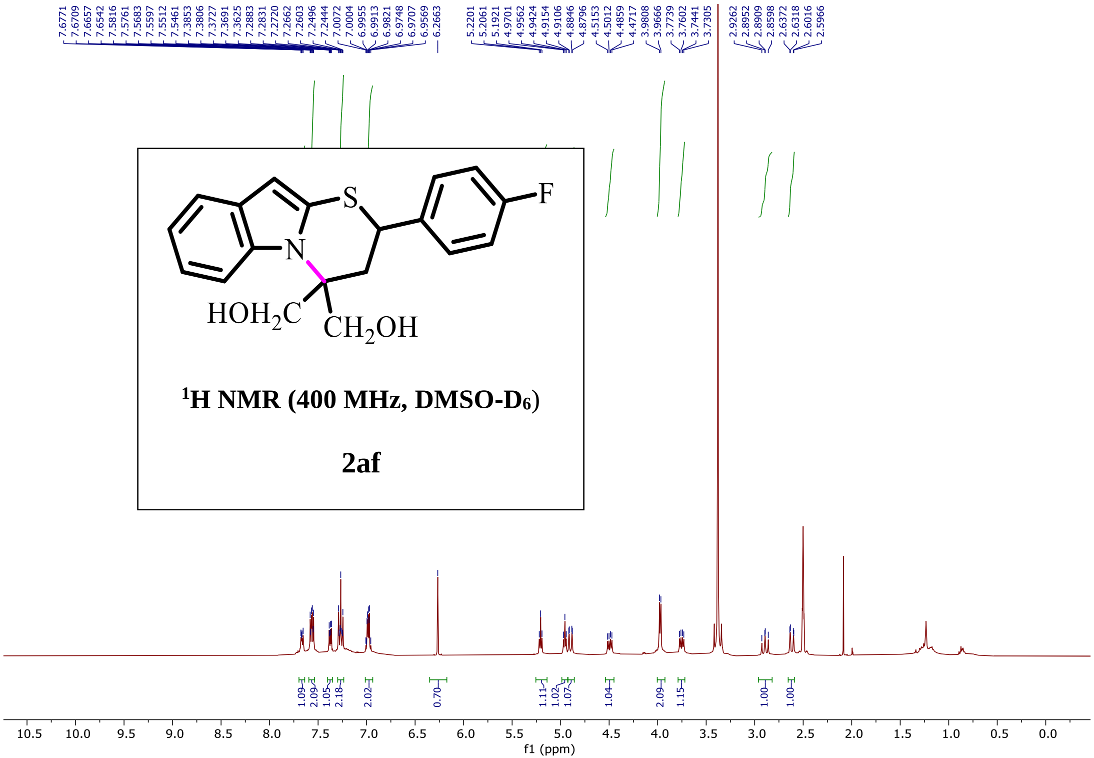
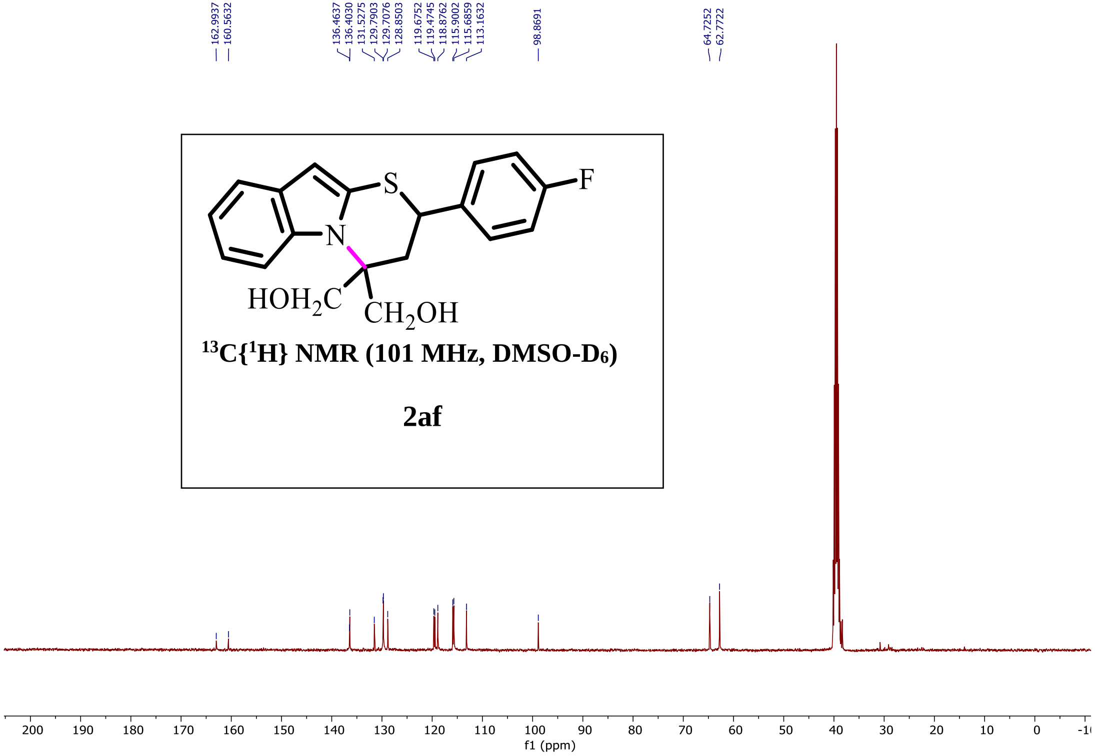


^{1}H NMR (400 MHz, DMSO-D$_6$)

2af



^{13}C{^{1}H} NMR (101 MHz, DMSO-D$_6$)

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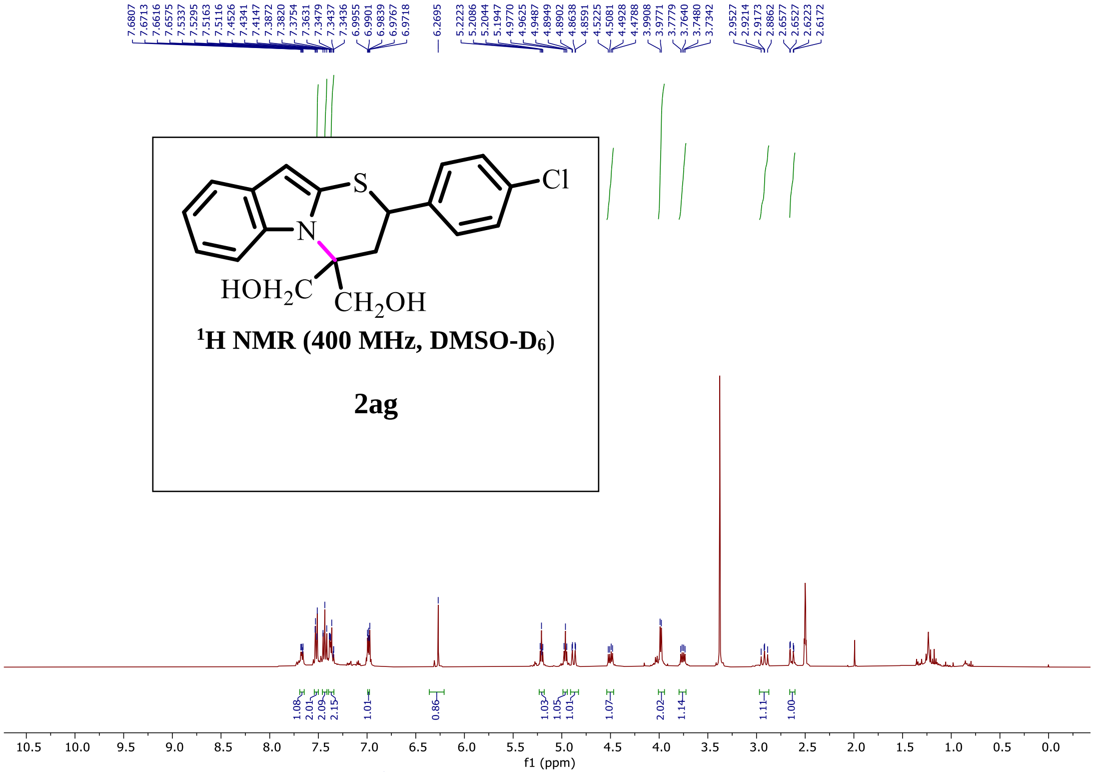

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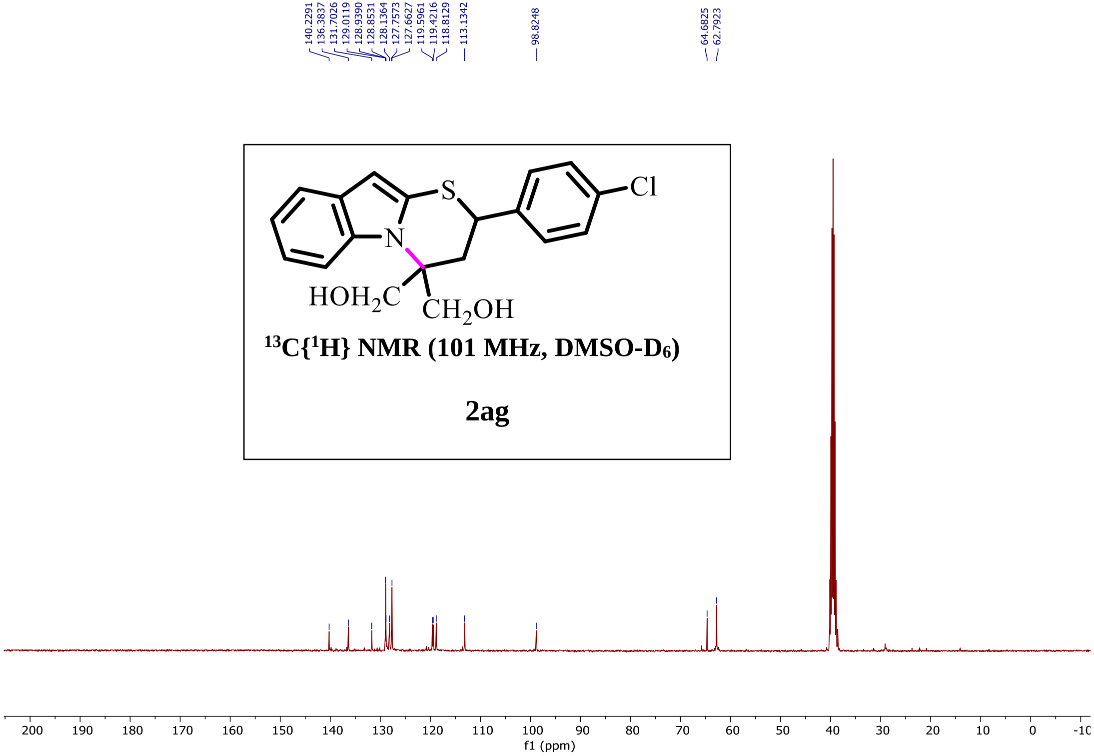

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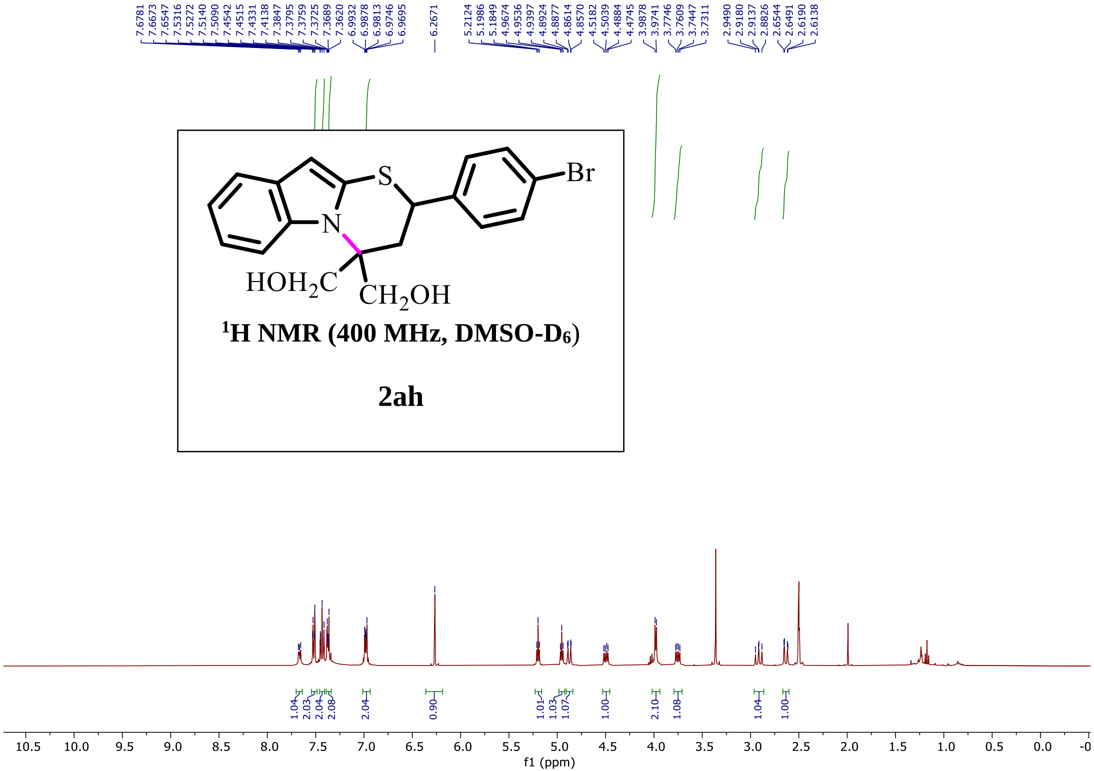

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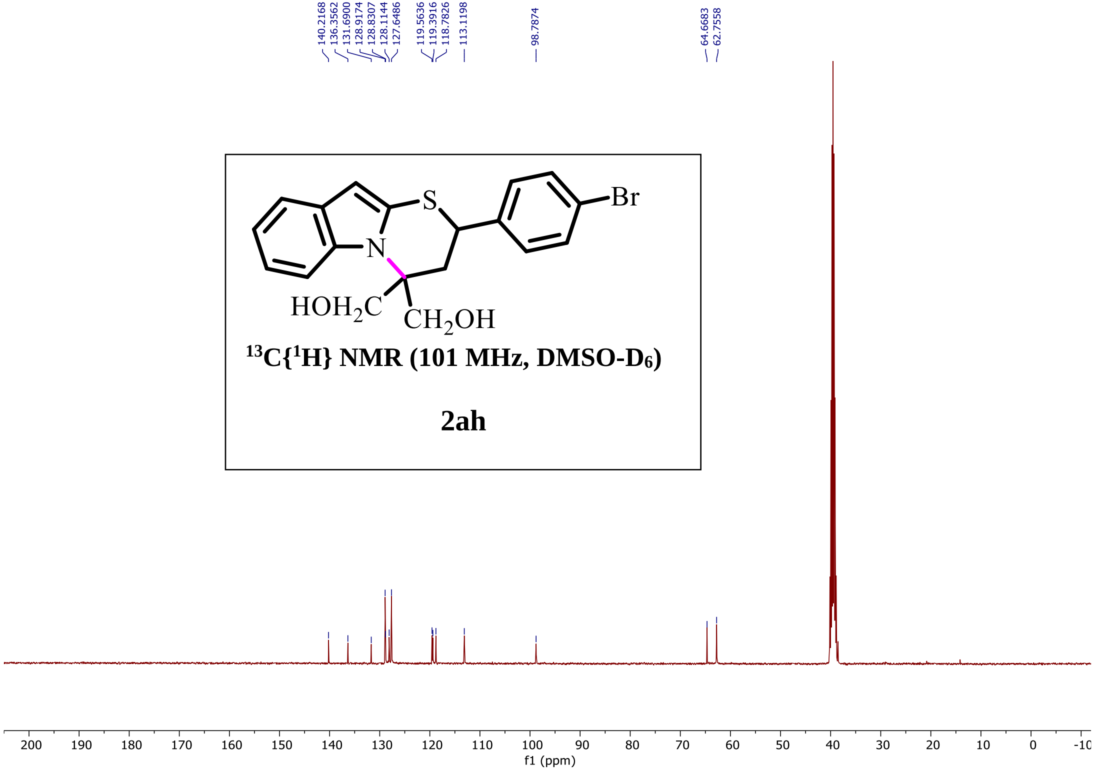

^{13}C{^{1}H} NMR (101 MHz, DMSO-D$_6$)

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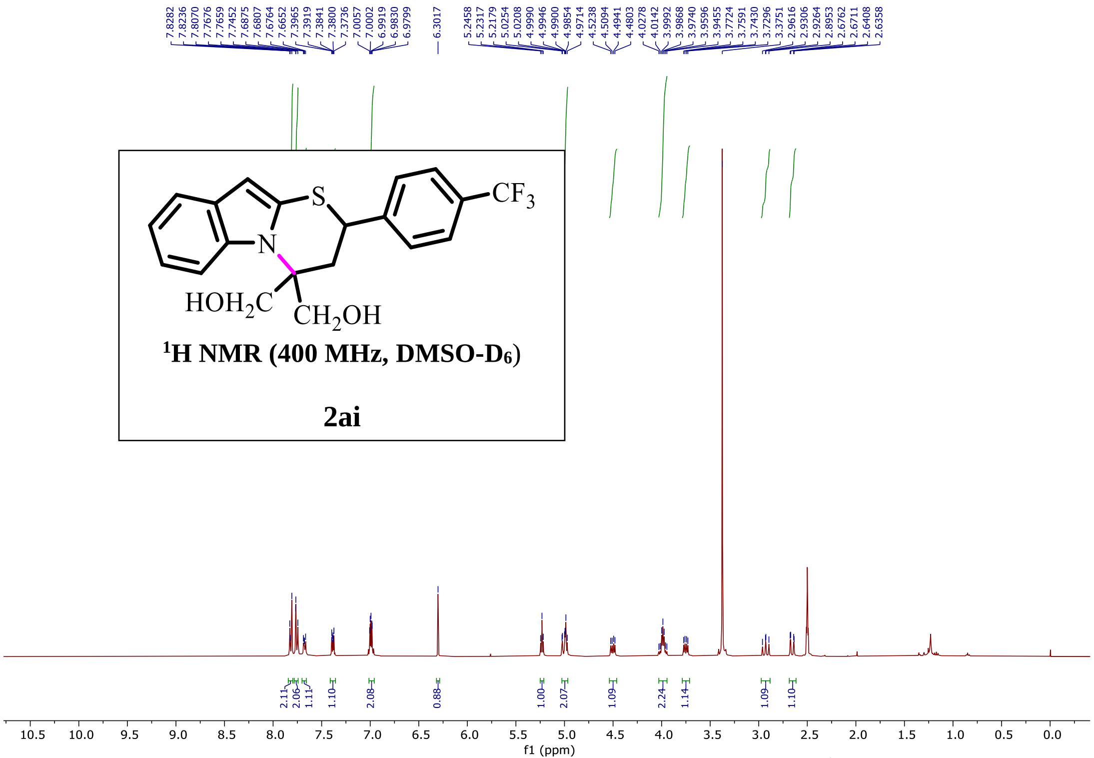
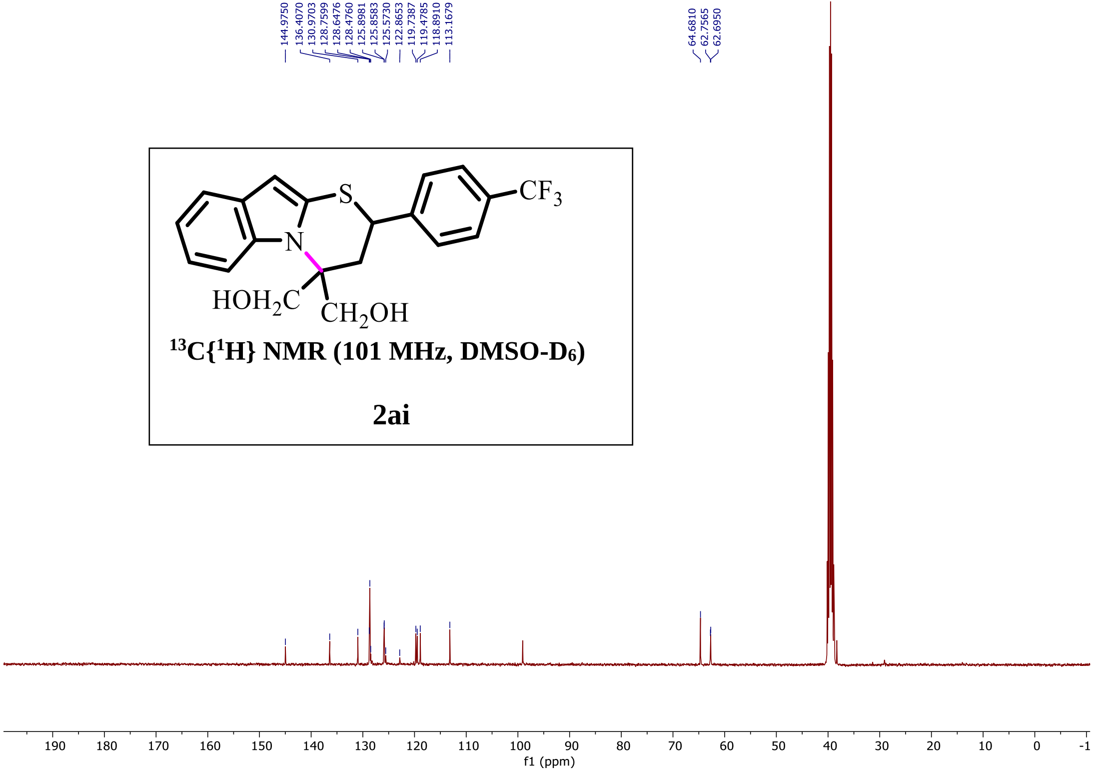


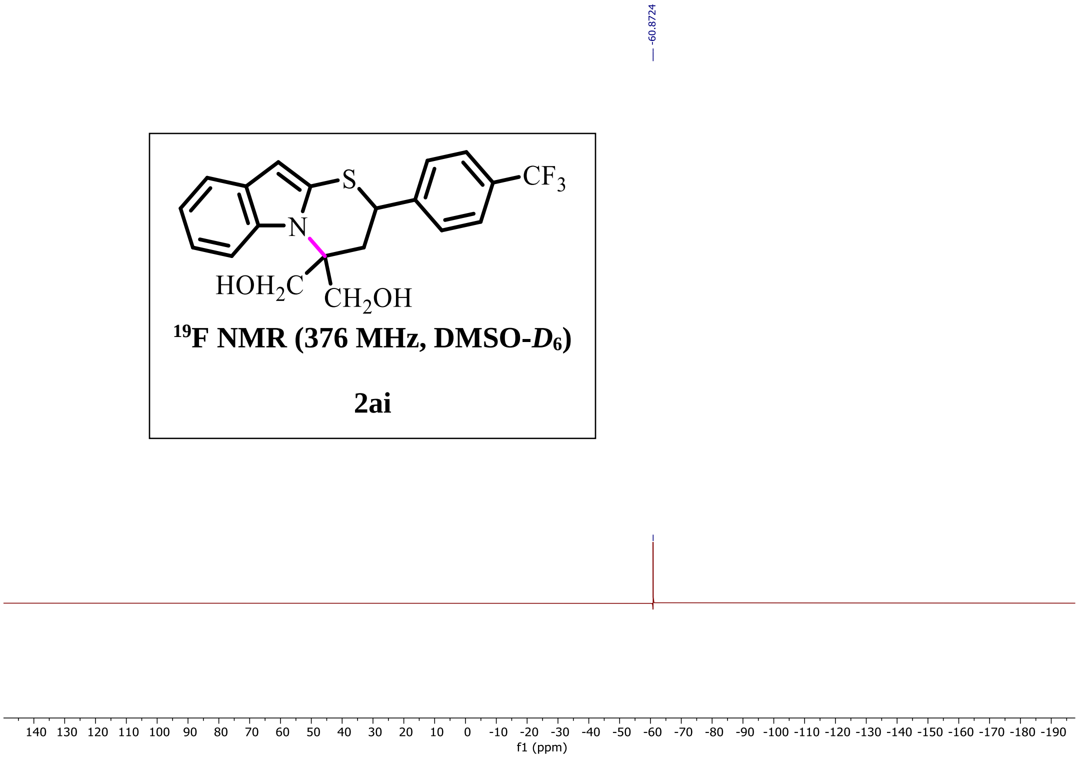
^{1}H NMR (400 MHz, DMSO-D$_6$)

2ai



^{13}C{^{1}H} NMR (101 MHz, DMSO-D$_6$)

2ai

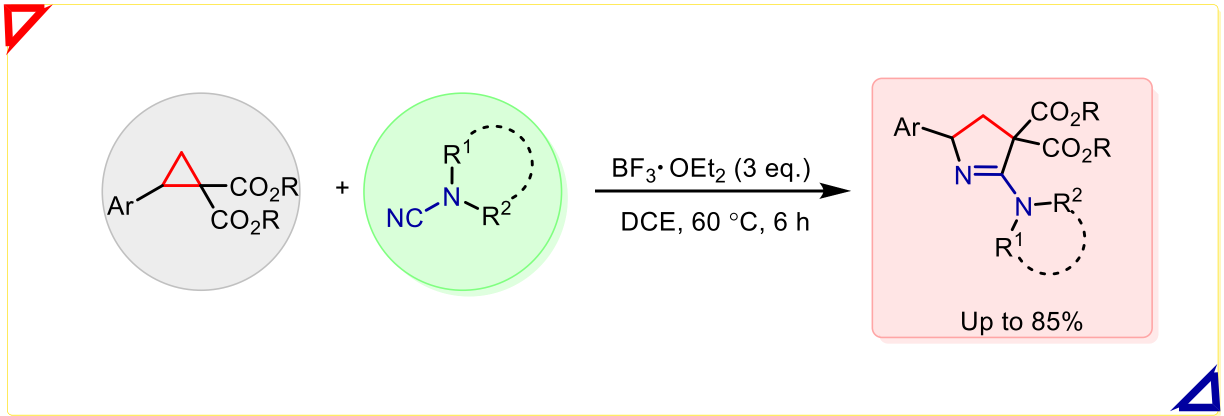


^{19}F NMR (376 MHz, DMSO-D_6)

2ai

Chapter-3

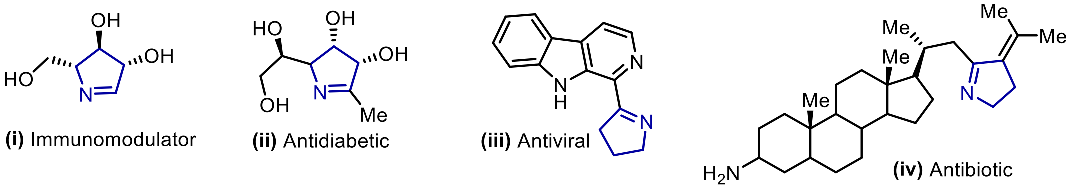
$BF_3 \cdot OEt_2$ Mediated (3+2) Cycloaddition Reactions of DACs with Cyanamides: Access to Cyclic Amidines



✓ Metal/Additive-Free Protocol ✓ Mild reaction conditions ✓ Broader substrate scope ✓ Gram-Scale Synthesis

3.1 Introduction

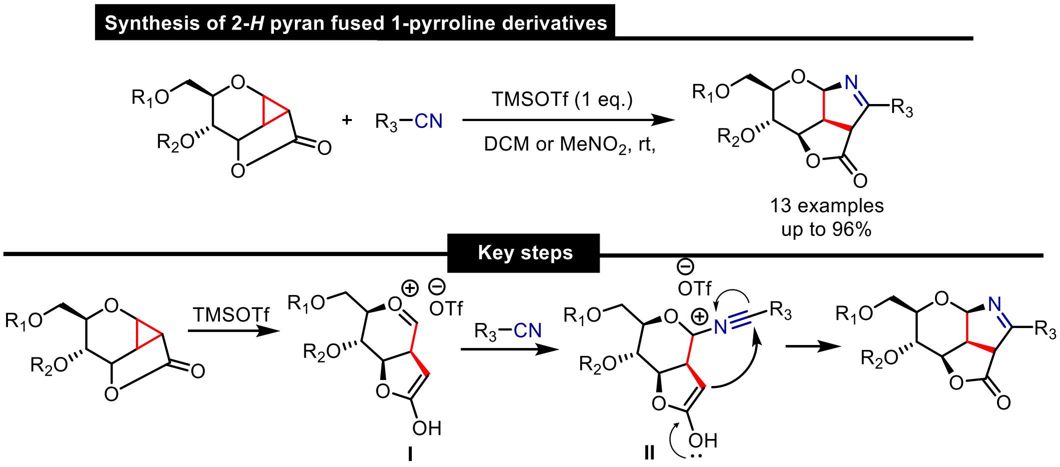
In recent years, nitrogen-containing molecules have become a significant category of heterocyclic compounds with many medicinal chemistry applications.[1] Among the known nitrogen-containing heterocycles, pyrrolines are considered as one of the most privileged class of azaheterocycles found in a variety of natural products and bioactive molecules like, hemes, chlorophyll, and alkaloids.[2] Depending on the position of double bond, there are three types of pyrrolines entities present in nature; 1-pyrrolines, 2-pyrrolines and 3-pyrrolines. These 1-pyrrolines molecules are important due to their presence in antiviral,[3] anti-inflammatory,[4] immunomodulatory,[5] cardiovascular,[6] anti-diabetic[7] and antibiotic drug agents[8] (Figure 2a.1). In addition to this, 1-pyrroline is found as a crucial intermediate for the synthesis of pyrrolidine and pyrrole containing alkaloids.[9] Several methods are reported in the literature for the development of new synthetic roots for the construction of 1-pyrrolines.[10]



(i) Immunomodulator **(ii)** Antidiabetic **(iii)** Antiviral **(iv)** Antibiotic

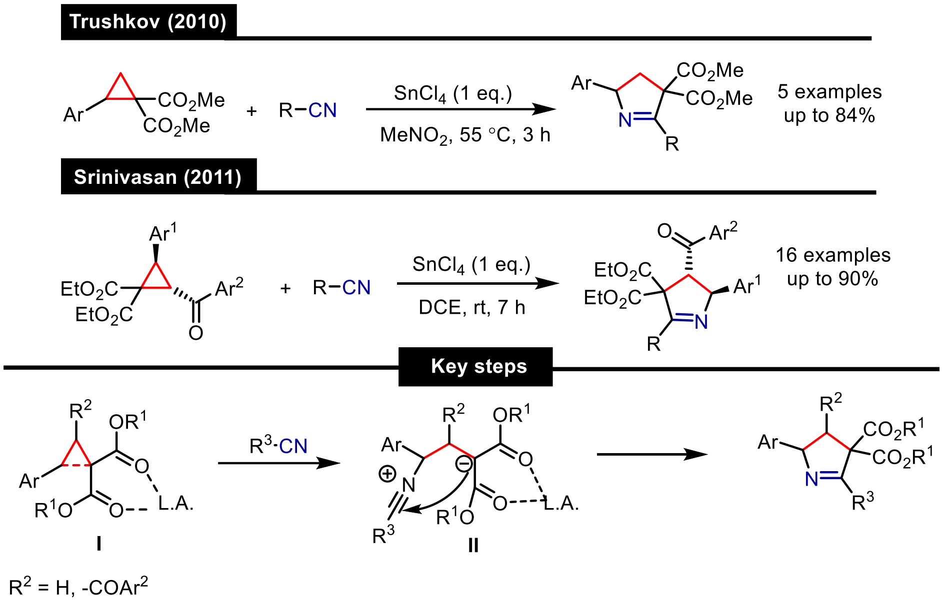
Figure 3.1 Some examples of biologically active 1-Pyrroline embedded molecules.

Over the course of the last two decades, the (3+2)-cycloaddition approach has emerged as a widely adopted and highly efficient process for the fabrication of 1-pyrroline derivatives through the combination of donor-acceptor cyclopropanes (DACs) with nitriles. The pioneering work of Pagenkopf and his team in 2003 resulted in the serendipitous discovery of this method, as they endeavored to execute a ring expansion reaction of glycolated D-A cyclopropanes with allylsilane.[11] Their efforts led them to note that when acetonitrile was employed as a solvent under TMSOTf catalysis, the acetonitrile molecule interacted with D-A cyclopropane in a (3+2) cycloaddition fashion, even in the presence of strong nucleophiles such as allyltrimethylsilane or allyltributylstannane. They proposed that the reaction followed a *Ritter-type* intermediate, in which the nitrile attacked the oxocarbenium ion instead of the allylsilane. Building on these findings, they were able to successfully leverage a variety of aromatic and aliphatic nitriles with carbohydrate-derived D-A cyclopropanes to yield fused 1-pyrroline derivatives with high efficiency (Scheme 3.1).



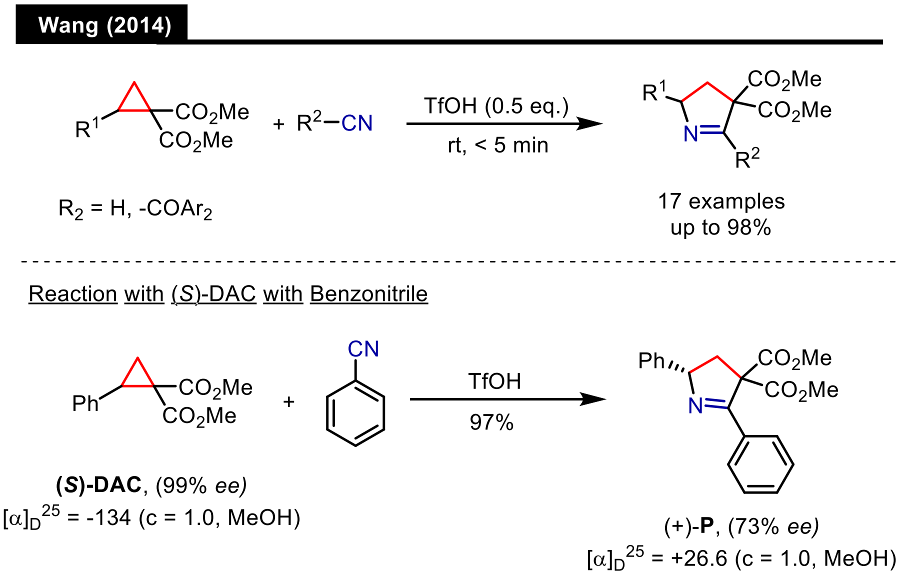
Scheme 3.1 Pagenkopf's work on the (3+2) cycloaddition of DACs with nitriles

In 2010, Trushkov and team further extended this protocol for the $SnCl_4$ mediated (3+2) cycloaddition of germinal 1, 1-diester donor-acceptor cyclopropanes with acetonitrile and propionitriles for the synthesis of 1-pyrrolines.[12] After some time Srinivasan *et al.* explored same protocol with highly activated ketone tethered D-A cyclopropanes.[13] Various D-A cyclopropanes undergo (3+2) cycloaddition with aryl and alkyl nitriles for selective synthesis of highly substituted 1-pyrroline derivatives in the presence of $SnCl_4$ (Scheme 3.2). For these protocols, initially Lewis acid interact with the acceptor moiety of D-A cyclopropanes and lead to the formation of activated intermediate **I**. Next, lone-pairs of nitrile nitrogen effectively attack to the D-A cyclopropane carbon attached to the donor part and form intermediate **II**. Further, the emerging nucleophile at malonate center attack to the nitrilium carbon and lead to the formation of desired product (Scheme 3.2).



Scheme 3.2 Construction of 1-pyrrolines.

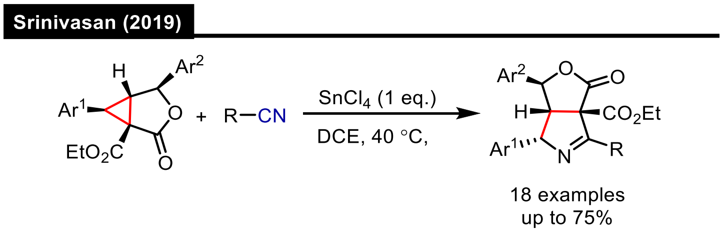
In 2014, Wang and coworkers utilized Brønsted acid (TfOH) as a promoter for (3+2) annulation of alkyl, vinyl and aryl D-A cyclopropanes with various nitriles for the synthesis of 1-pyrrolines.[14] Surprisingly, when they employed enantiopure D-A cyclopropane for the above



Scheme 3.3 TfOH mediated (3+2) cyccloaddition of DACs with nitriles

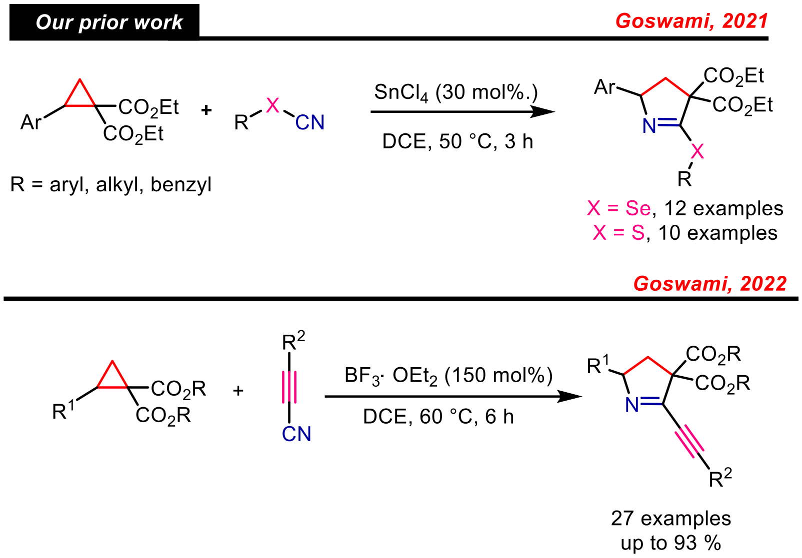
mentioned protocol, desired product was obtained with 73% *ee* (**P**). This phenomenon clearly suggests that the reaction pathway went through tight-ion-pair transition state rather than formal 1,3-zwitterioninc pathway (Scheme 3.3).

In the same line, recently, Srinivasan's group again exploited *γ*-butyrolactone-fused D-A cyclopropanes for the construction of γ-butyrolactone-fused 1-pyrrolines with aryl and alkyl nitriles in the presence of Lewis acid $SnCl_4$.[15] This methodology provides wide scope of highly diastereoselctive γ-butyrolactone-fused 1- pyrroline derivatives in moderate to good yield (Scheme 3.4).



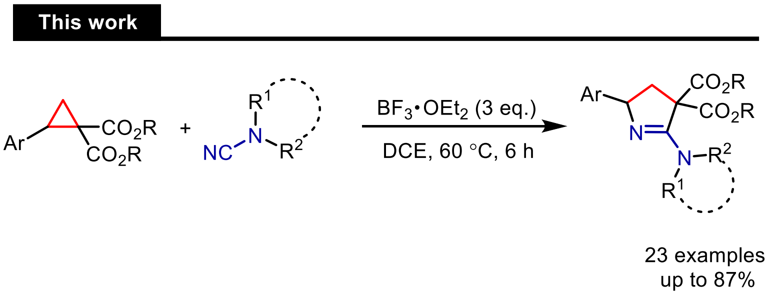
Scheme 3.4 Synthesis of γ-butyrolactone-fused 1-pyrrolines.

Previous literature reports have demonstrated that the synthesis of 1-pyrroline derivatives has largely relied on the (3+2) cycloaddition of D-A cyclopropanes with nitrile synthons in the presence of Lewis or Brønsted acid. Recently, our laboratory has also contributed to synthesized thio/-selenopyrrolines and propargylic cyclic imine derivatives via (3+2) cycloaddition of DACs with nitrile counter partners (Scheme 3.5).[16a, 16b]



Scheme 3.5 Synthesis of thio/-seleno pyrroline derivatives and propargylic cyclic imine derivatives.

As a part of our continuing research for the construction of functionalized 1-pyrroline derivatives, we are documenting a metal-free (3+2) cycloaddition protocol for synthesizing cyclic amidine derivatives from DACs and cyanamides in the presence of $BF_3 \cdot OEt_2$ under mild reaction conditions (Scheme 3.6).

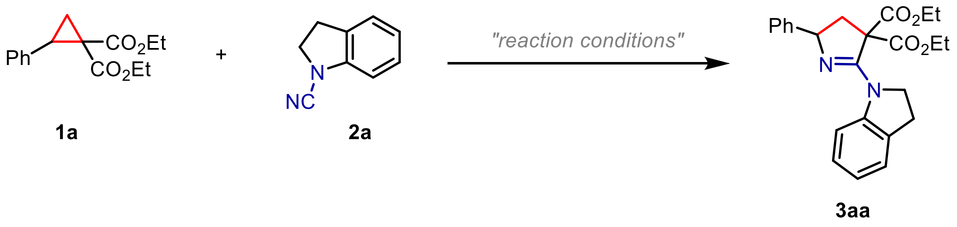


Scheme 3.6 Synthesis of cyclic amidine derivatives.

3.2 Results and Discussions

We commenced our optimization studies by taking 1,1-diester cyclopropane **1a** and indoline-1-carbonitrile **2a** as model substrates at various reaction parameters for the constructions of 3aa and the outcomes are summarized in Table 3.1. A series of reactions were carried out using several initiators like $TiCl_4$, $SnCl_4$, $AlCl_3$, TMSOTf, and $FeCl_3$ in the presence of DCE as a solvent at 60 °C temperature however, in all the cases, we did not get our targeted product **3aa** (Table 3.1, entries 1-5). Furthermore, when we utilized promoters like TfOH, $InCl_3$ and $Sc(OTf)_3$, the reaction delivered the desired product despite unsatisfactory yields (Table 3.1, entries 6-8). In order to achieve the product with a higher yield, cycloaddition reaction was further explored in the presence of $BF_3{\cdot}OEt_2$ (1 eq.); to our delight, we observed 65% of **3aa** (Table 3.1, entry 9). Next, we increased the loading of $BF_3{\cdot}OEt_2$ up to 3 eq. and significant enhancement in the formation of **3aa** was observed in the presence of DCE at 60 °C (Table 3.1, entry 11). Then, we performed the aforementioned reaction at room temperature; however, the product yield was comparatively low (Table 3.1, entry 12). Other organic solvents like DCM, chloroform, THF and toluene were found unsuitable in providing a reasonable yield of **3aa** (Table 3.1, entries 13-16).

Table 3.1 Optimization of the reaction conditions^{a}:

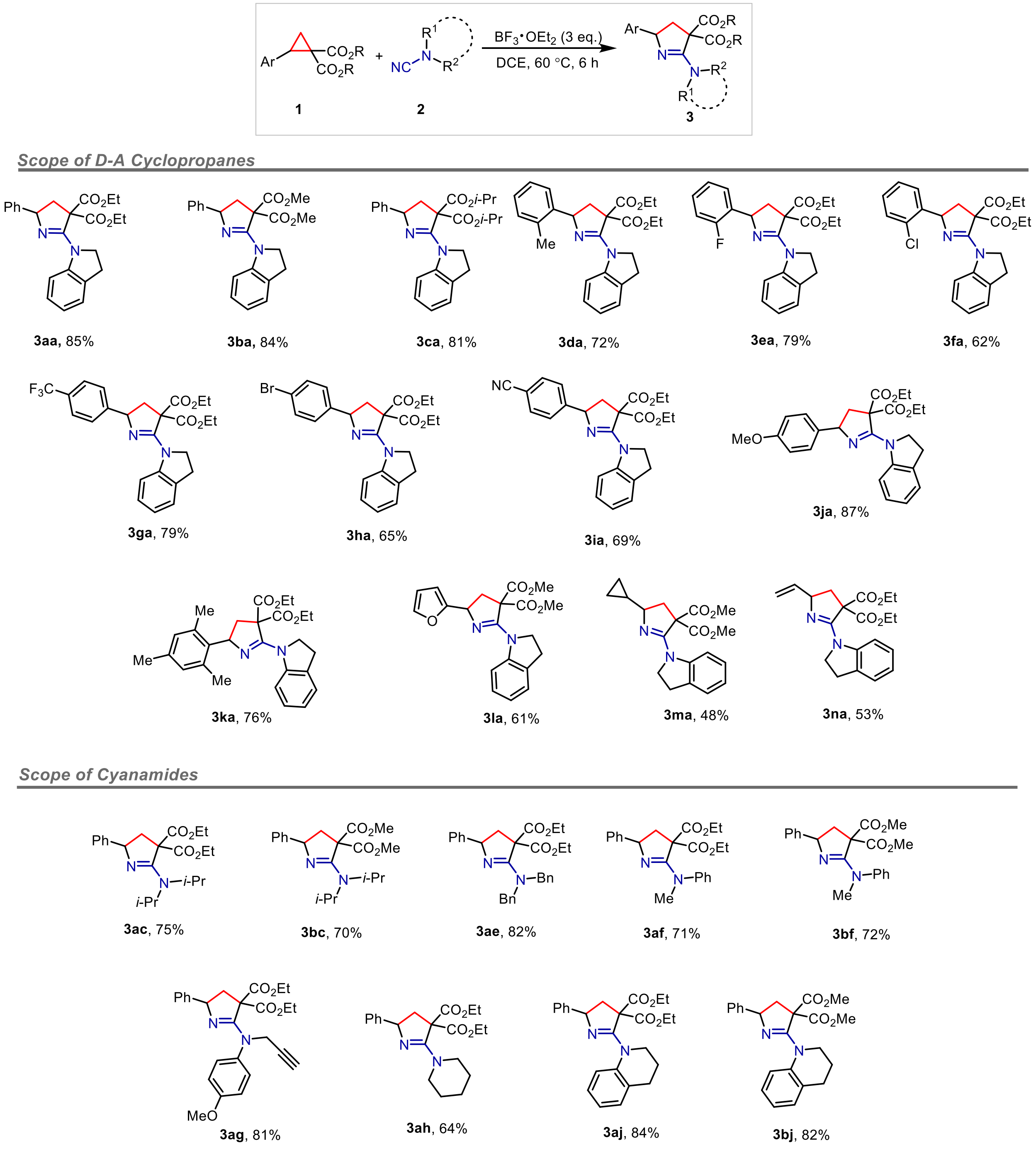


Entry no.	Promoters (x.eq.)	Solvent	Temperature (°C)	Time (h)	**3aa** (%)^{b}
1	$TiCl_4$ (1)	DCE	60	24	n.r
2	$SnCl_4$ (1)	DCE	60	24	n.r.
3	$AlCl_3$ (1)	DCE	60	24	n.r.
4	TMSOTf (1)	DCE	60	24	n.r.
5	$FeCl_3$ (1)	DCE	60	24	n.r.
6	TfOH (1)	DCE	60	24	30
7	$InCl_3$ (1)	DCE	60	24	53
8	$Sc(OTf)_3$ (1)	DCE	60	24	43
9	$BF_3{\cdot}OEt_2$ (1)	DCE	60	24	65
10	$BF_3{\cdot}OEt_2$ (2)	DCE	60	6	68
11	**$BF_3{\cdot}OEt_2$ (3)**	**DCE**	**60**	**6**	**85**
12	$BF_3{\cdot}OEt_2$ (3)	DCE	rt	6	67
13	$BF_3{\cdot}OEt_2$ (3)	DCM	rt	6	60

14	$BF_3\cdot OEt_2$ (3)	$CHCl_3$	rt	6	55
15	$BF_3\cdot OEt_2$ (3)	THF	60	6	62
16	$BF_3\cdot OEt_2$ (3)	Toulene	60	6	58

[a]Optimized reaction conditions for **3aa**: **1a** (131 mg, 0.5 mmol, 1 eq.), **2a** (86.5 mg, 0.36 mmol, 1.2 eq.), $BF_3.OEt_2$ (0.18 mL, 3 eq.), 1,2-DCE (2.0 mL), 60°C, inert atmosphere, 6 h. [b]Isolated yields.

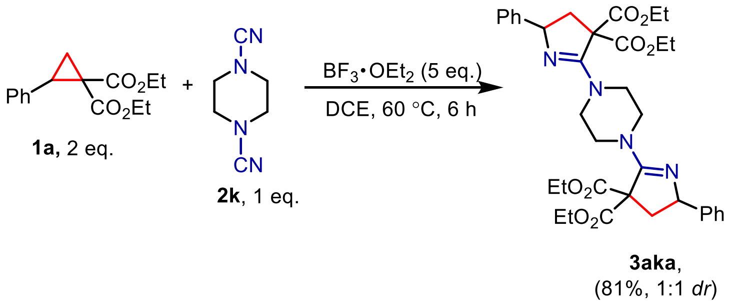
After establishing the optimal conditions, a library of five-membered cyclic amidines **3** were prepared (Scheme 3.7). First, the tolerance of electronically and structurally diverse D-A cyclopropanes **1** with indoline-1-carbonitrile **2a** was examined. D-A cyclopropanes with different ester functionality worked well under the standard conditions and deliver high yielded products **3aa**, **3ba**, and **3ca**. DACs with *o*-substituted arenes also smoothly undervent the reaction conditions and furnished desired products (**3da**, **3ea**, and **3fa**) in good yields. Furthermore, *p*-substituted arenes attached to the D-A cyclopropanes were well tolerated to give access **3ga**, **3ha**, **3ia** and **3ja** in the moderate to good yields. Highly hindered *mesityl* ring decorated D-A cyclopropane also provide the desired product **3ja** in 76% yield. Next, we have utilized heteroaryl furan substituted cyclopropane **1l** in the reaction and afforded the desired product **3la** in 61% yield. In addition to this, cyclopropyl and vinyl donor-acceptor cyclopropnes were also found compatible with the reaction protocol and furnished amidine derivatives **3ma** and **3na** respectively, in the moderate yields. Next, the reaction scope of several symmetrical and unsymmetrical cyanamides was evaluated under optimal conditions with D-A cyclopropanes. Acyclic symmetrical cyanamides having alkyl substituted (*iso – propyl, benzyl* and *propargylic* substitutents) found suitable candidates and provided good to excellent yields of cyclic amidines **3ac**, **3bc** and **3ae**, (Scheme 3.7). Furthermore, the employment of unsymmetrical cyanamides like **2f** and **2g** were also found worthy in the reported methodology and furnished targeted products (**3af**, **3bf** and **3ag**). The reaction using cyclic cyanamides also afforded **3ah**, **3aj**, and **3bj** in good to excellent yields.



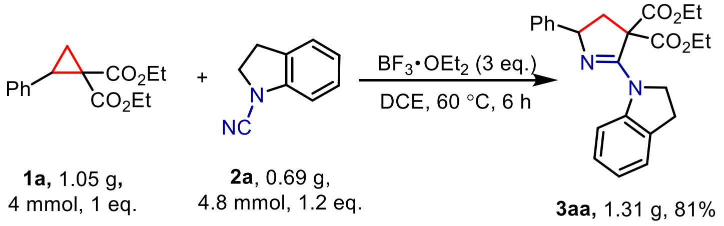
Scheme 3.7 Substrate scope of cyclic amidine derivatives.[a] [a]Reaction Conditions: **1** (0.5 mmol, 1 eq.), **2a** (0.36 mmol, 1.2 eq.), $BF_3.OEt_2$ (0.18 mL, 3 eq.), 1,2-DCE (2.0 mL), 60°C, inert atmosphere, 6 h.

In order to explore the potential of a newly developed reaction methodology, we have extended our reaction protocol. Specifically, we have reacted bisnitrile substrate piperazine-1,4-dicarbonitrile **2k** with **2** eq. of D-A cyclopropane **1a** to consecutively achieve double (3+2) cyclizations. This process has given rise to the formation of compound **3aka** in a diastereomeric mixture (1:1) (Scheme 3.8a). Additionally, we have conducted a gram-scale synthesis of **3aa** by exploiting the optimal reaction conditions, resulting in the production of 1.30 g of the product, as illustrated in (Scheme 3.8b).

(a) Extended reaction protocol:



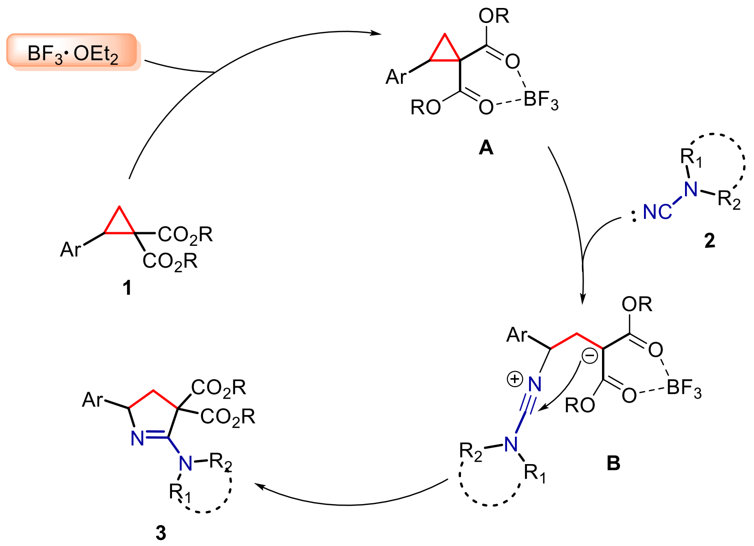
(b) Large-scale synthesis:



Scheme 3.8a Preparation of dimer of pyrazine **3aka**.

Scheme 3.8b Gram scale synthesis of **3aa.**[a] [a]Reaction conditions: **1a** (1.05 g, 4 mmol), **2a** (0.69 g, 4 mmol) $BF_3{\cdot}OEt_2$ (0.2 mL, 3 eq.), 1,2-DCE (4 mL).

In Scheme 3A.9, we would like to propose the plausible reaction pathway for the formation of amidine derivatives **3** via (3+2) cycloaddition of D-A cyclopropanes with cyanamides. At first instance, the initiator $BF_3{\cdot}OEt_2$ interacts with the acceptor moieties of D-A cyclopropane and form the activated intermediate **A**, followed by the nucleophilic attack from the cyanamide's nitrile center to the cyclopropane's C-center attached to the donor group and forms intermediate **B**. Next, the emerging nucleophile at the malonate center attacks the nitrile's carbon, leading to the transformation of desired cyclic amidine derivative **3**.



Scheme 3.9: Plausible Mechanism for cyclic amidine (**3**).

3.3 Conclusions

In summary, we have developed a straightforward metal-free $BF_3 \cdot OEt_2$ mediate protocol for the construction of cyclic amidines via (3+2) cycloadditions of DACs with cyanamides under mild conditions. This procedure provides an efficient and atom-economical way to construct cyclic amidine derivatives in good to excellent yields.

3.4 Experimental Section

All the reactions were carried out under an inert atmosphere using the schlenk technique. All solvents were dried and stored over molecular sieves under argon atmosphere. All chemicals and reagents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using E. Merck silica gel 60 (100–200 mesh). ^{1}H, ^{13}C, and DPT-135 NMR spectra were recorded in $CDCl_3$, on JEOL JNM-ECS spectrometer at operating frequencies of 400 MHz (^{1}H) or 100 MHz (^{13}C) as indicated in the individual spectrum. Chemical shifts (δ) are given in parts per million (ppm) relative to residual solvent (chloroform, δ= 7.26 for ^{1}H and 77.16 for proton decoupled ^{13}C NMR) and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, td for triplet of doublet, q for quartet, and m for multiplet. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) methods on waters mass spectrometer (XEVO G2-XS QTOF).

3.4.1 Preparation of starting materials

General procedure for the preparation of cyclopropane-1,1-diester derivatives[17]:

Using N_2 atmosphere, a solution of dry dimethyl sulfoxide (DMSO) and sodium hydride (NaH) (60% suspension in mineral oil, 7.5 mmol, 1.5 eq.) was made. Drop by drop, trimethylsulfoxonium iodide (TMSOI) (7.5 mmol, 1.5 eq.) was added to the mixture. ***Be careful!*** When sodium hydride and trimethylsulfoxonium iodide react exothermically, heat and H_2 are produced. For this reason, the suspension was maintained at 0 ºC before adding trimethylsulfoxonium iodide. After vigorously stirring for 15 to 20 minutes, the mixture was allowed to come to room temperature. In the meantime, a benzylidene-malonate solution (5 mmol, 1.0 eq.) in DMSO was added. After the reaction was completed, as determined by TLC, the crude solution was combined with crushed ice and extracted using diethyl ether. The combined organic layers were washed with brine, dried over sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate as an eluent. Dimethyl [1,1'-bi(cyclopropane)]-2,2-dicarboxylate (**1m**)[17f] and Diethyl 2-vinylcyclopropane-1,1-dicarboxylate (**1n**)[17e]. The spectral data obtained are in accordance with those described in the literature.

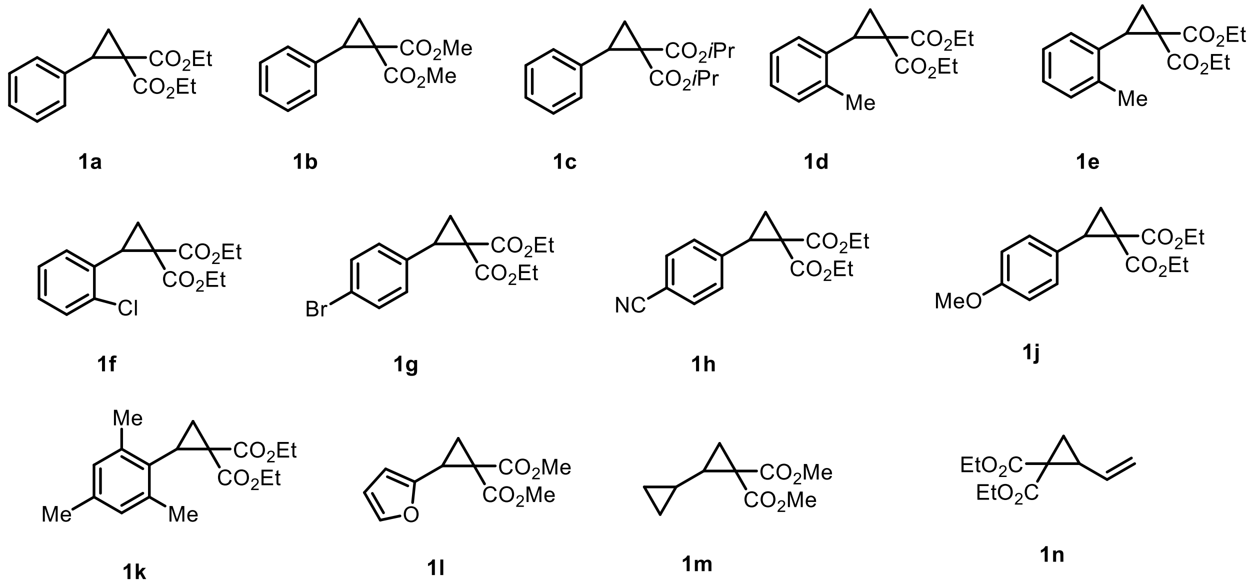


Figure 3.4.1 Used Donor-Acceptor Cyclopropanes in this study.

General procedure for the Synthesis of known cyanamides[18]: Secondary amine (2mmol, 2eq.) dissolved in THF add Cyanogen bromide (1mmol, 1eq.) at 0° C. After the reaction mixture is stirred for 6 h at room temperature. Upon completion of the reaction mixture, as monitored by TLC, the crude solution was extracted with ethyl acetate. The combined organic layers were washed once with brine, dried over sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents.

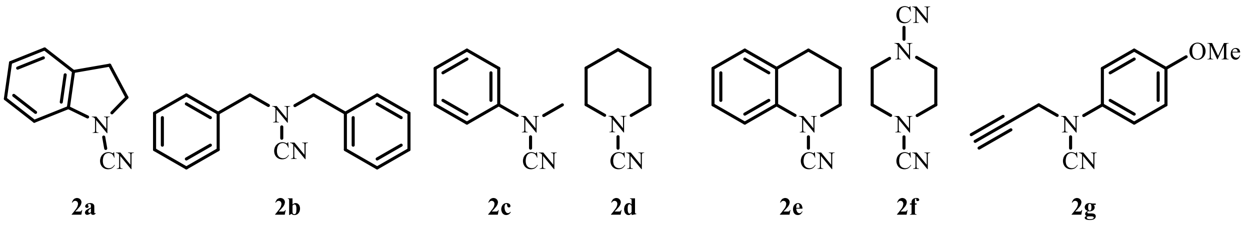


Figure 3.4.2 Used Cyanamides in this study.

3.4.2 General procedures

General procedure for the synthesis of cyclic amidine derivatives (3): In a schlenk tube, cyanamide **2** (0.6 mmol, 1.2 eq.), and donor-acceptor cyclopropanes **1** (0.5 mmol, 1 eq.) were dissolved in anhydrous DCE under inert atmosphere at 60 ^{o}C. After 2 min of stirring $BF_3{\cdot}OEt_2$ (1.5 mmol, 3 eq.) was added and reaction mixture was allowed to stir for 6 h. Upon completion of the reaction, as monitored by TLC, the crude reaction mixture was extracted with DCM. The combined organic layers were washed once with brine and $NaHCO_3$ dried over sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified by column chromatography using hexane and ethyl acetate as eluents.

Synthesis of compound 3aka: In a schlenk tube, piperazine-1,4-dicarbonitrile **2k** (0.6 mmol, 1.2 eq.), and donor-acceptor cyclopropanes **1a** (1 mmol, 2 eq.) were dissolved in anhydrous DCE under inert atmosphere at 60 ^{o}C. After 2 min of stirring $BF_3{\cdot}OEt_2$ (5 mmol, 5 eq.) was added and reaction mixture was allowed to stir for 6 h. Upon completion of the reaction, as monitored by TLC, the crude reaction mixture was extracted with DCM. The combined organic layers were washed once with brine and $NaHCO_3$ dried over sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified by column chromatography using hexane and ethyl acetate as eluents.

Gram scale synthesis of (3aa): In a schlenk tube, indoline-1-carbonitrile **2a** (691 mg, 4.8 mmol, 1.2 eq.), and DAC **1a** (1048 mg, 4 mmol, 4 eq.) were dissolved in anhydrous DCE under inert atmosphere at 60 ^{o}C. After 2 min of stirring $BF_3{\cdot}OEt_2$ (12 mmol, 12 eq.) was added and reaction mixture was allowed to stir for 6 h. Upon completion of the reaction, as monitored by TLC, the crude reaction mixture was extracted with DCM. The combined organic layers were washed once with brine and $NaHCO_3$ dried over sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified by column chromatography using hexane and ethyl acetate as eluents. Yield of product **3aa**: 1.3 g, 81%

3.4.3 Characterization of compounds

Diethyl 2-(indolin-1-yl)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3aa)

Yield: 172 mg (85%); Brown viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.46 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.39 – 7.35 (m, 2H), 7.30 – 7.26 (m, 1H), 7.22 – 7.18 (m, 2H), 6.98 – 6.95 (m, 1H), 5.21 (t, *J* = 7.2 Hz, 1H), 4.38 – 4.17 (m, 5H), 4.00 (q, *J* = 9.2 Hz, 1H), 3.34 (dd, *J* = 12.6, 6.7 Hz, 1H), 3.23 – 3.07 (m, 2H), 2.49 (dd, *J* = 12.5, 7.9 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), ^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.3, 168.0, 157.7, 145.4, 144.5, 131.4, 128.4, 127.4, 127.0, 126.4, 124.2, 122.3, 116.6, 69.6, 69.3, 62.5, 62.4, 49.5, 46.9, 28.7 14.1, 13.9, HRMS: *m/z* calculated for $C_{24}H_{27}N_2O_4[M+H]^+$ 407.1980, found 407.1971.

Dimethyl 2-(indolin-1-yl)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ba)

Yield: 159 mg (84%); Brown viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.45 (d, *J*= 7.9 Hz, 1H), 7.43 – 7.41 (m, 2H), 7.38 – 7.34 (m, 2H) , 7.28 (d, *J*= 7.3 Hz, 1H), 7.21 – 7.17 (m, 2H), 6.98 – 6.94 (m, 1H), 5.20 (t, 1H), 4.28 – 4.21 (m, 1H), 3.96– 3.91 (m, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.32 (dd, *J* = 12.5, 6.5 Hz, 1H), 3.24 – 3.12 (m, 2H), 2.47 (dd, *J* = 12.6, 8.0 Hz, 1H), ^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.8, 168.5, 157.5, 145.4, 144.4, 131.4, 128.5, 127.5, 127.1, 126.4, 124.3, 122.4, 116.6, 69.8, 69.2, 53.5, 53.3, 49.5, 47.0, 28.7, HRMS**:** *m/z* calculated for $C_{22}H_{23}N_2O_4\,[M+H]^+$ 379.1670, found 379.1658.

Diisopropyl 2-(indolin-1-yl)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ca)

Yield: 176 mg (81%); Brown viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.44 (d, *J* = 8.9 Hz, 1H), 7.43 – 7.40 (m, 2H), 7.37 – 7.33 (m, 2H), 7.28 – 7.23 (m, 1H), 7.21 – 7.16 (m, 2H), 6.97 – 6.93 (m, 1H), 5.21 – 5.13 (m, 2H), 5.05 – 4.99 (m, 1H), 4.31 – 4.25 (m, 1H), 4.05 (q, *J* = 9.2 Hz, 1H), 3.30 (dd, *J* = 12.5, 6.7 Hz, 1H), 3.21 – 3.10 (m, 2H), 2.48 (dd, *J* = 12.4, 7.5 Hz, 1H), 1.31 (dd, *J* = 11.6, 6.2 Hz, 6H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), ^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) δ 168.8, 167.6, 158.0, 145.5, 144.7, 131.4, 128.4, 127.4, 126.9, 126.5, 124.2, 122.2, 116.6, 70.3, 70.2, 69.5, 49.8, 46.8, 28.7, 21.7, 21.5, HRMS:*m/z* calculated for $C_{26}H_{31}N_2O_4[M+H]^+$ 435.2292, found 435.2284.

Diethyl 2-(indolin-1-yl)-5-(o-tolyl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3da)

Yield: 151 mg (72%); Brown viscous liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.21 – 7.16 (m, 5H), 6.98 – 6.94 (m, 1H), 5.39 (t, *J* = 7.0 Hz, 1H), 4.37 – 4.14 (m, 6H), 3.32 (dd, *J* = 12.5, 6.7 Hz, 1H), 3.18 – 3.12 (m, 2H), 2.40 (s, 3H), 2.39 – 2.33 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), $^{13}C\{^1H\}$ NMR(101 MHz, $CDCl_3$) δ 169.2, 168.2, 157.7, 145.5, 142.5, 134.7, 131.5, 130.1, 127.5, 126.9, 126.2, 125.9, 124.3, 122.3, 116.6, 69.3, 67.0, 62.6, 62.4, 49.6, 45.5, 28.7, 19.4, 14.1, 13.9, HRMS: *m/z* calculated for $C_{25}H_{29}N_2O_4$ $[M+H]^+$ 421.2131, found 421.2127.

Diethyl 5-(2-fluorophenyl)-2-(indolin-1-yl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ea)

Yield: 168 mg (79%); Brown viscous liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 7.7 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.24 – 7.19 (m, 3H), 7.13 – 7.09 (m, 1H), 7.06 – 7.01 (m, 1H), 6.99 – 6.95 (m, 1H), 5.48 (t, *J* = 6.9 Hz, 1H), 4.35 – 4.29 (m, 2H), 4.22 – 4.04 (m, 4H), 3.36 (dd, *J* = 12.7, 7.0 Hz, 1H), 3.20 – 3.11 (m, 2H), 2.53 (dd, *J* = 12.6, 6.7 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), ^{13}C $\{^1H\}$ NMR(101 MHz, $CDCl_3$) δ 169.0, 168.3, 160.2 (d, $^1J_{C-F}$ = 246.61 Hz), 158.2, 145.4 131.6, 131.5, 131.4, 128.4 (d, $^3J_{C-F}$ = 8.12 Hz), 128.0 (d, $^4J_{C-F}$ = 4.46 Hz), 127.5, 124.3, 124.2, 124.1, 122.4, 116.6, 114.95 (d, $^2J_{C-F}$ = 21.49 Hz), 69.2, 63.8, 62.6, 62.4, 49.6, 45.4, 28.7, 14.1, 13.9, ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.83, HRMS: *m/z* calculated for $C_{24}H_{26}N_2O_4F$ $[M+H]^+$ 425.1878, found 425.1877.

Diethyl 5-(2-chlorophenyl)-2-(indolin-1-yl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3fa)

Yield: 137 mg (62%); Brown viscous liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.2 Hz, 1H), 7.51 – 7.49 (m, 1H), 7.36 – 7.34 (m, 1H), 7.23 – 7.16 (m, 4H), 7.01 – 6.92 (m, 1H), 5.54 (t, *J* = 6.8 Hz, 1H), 4.34 – 4.07 (m, 6H), 3.43 (dd, *J* = 12.8, 7.3 Hz, 1H), 3.17 – 3.12 (m, 2H), 2.44 (dd, *J* = 12.8, 6.4 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), ^{13}C $\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.9, 168.4, 158.4, 145.4, 142.0, 132.5, 131.6, 129.2, 128.2, 127.8, 127.5, 127.0, 124.4, 122.5, 116.7, 69.1, 67.2, 62.6, 62.4, 49.6, 45.0, 28.7, 14.1, 13.9, HRMS: *m/z* calculated for $C_{24}H_{26}N_2O_4Cl$ $[M+H]^+$ 441.1577, found 441.1581.

Diethyl 2-(indolin-1-yl)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ga)

Yield: 187 mg (79%); Brown viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.42 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J*= 8.2 Hz, 2H), 7.22 – 7.19 (m, 2H), 6.99 – 6.95 (m, 1H), 5.23 (t, *J* = 7.3 Hz, 1H), 4.34 – 4.15 (m, 4H), 3.99 (q, *J* = 9.1 Hz, 1H), 3.35 (dd, *J* = 12.4, 6.8 Hz, 1H), 3.20 – 3.09 (m, 2H), 2.44 (dd, *J* = 12.4, 7.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), ^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.1, 167.8, 158.2, 148.7, 145.3, 131.6, 129.3 (q, ^{2}J$_{C-F}$ = 32.34 Hz), 127.5, 126.8, 125.4 (q, ^{3}J$_{C-F}$ = 3.83 Hz), 124.4 (q, ^{1}J$_{C-F}$ = 273.19 Hz), 124.4, 122.6, 116.7, 69.4, 69.2, 62.7, 62.6, 49.6, 46.6, 32.1, 28.7, 14.1, 13.9, ^{19}F NMR (376 MHz, CDCl$_3$) δ -61.95, HRMS:*m/z* calculated for $C_{25}H_{26}N_2O_4F_3$[M+H]$^+$ 475.1848, found 475.1845.

Diethyl 5-(4-bromophenyl)-2-(indolin-1-yl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ha)

Yield: 158 mg (65%); Brown viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.39 (d, *J* = 8.8 Hz, 1H), 7.47 – 7.45 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.20 – 7.17 (m, 2H), 6.99 – 6.94 (m, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 4.34 – 4.16 (m, 5H), 3.96 (q, *J* = 9.2 Hz, 1H), 3.30 (dd, *J* = 12.5, 6.6 Hz, 1H), 3.19 – 3.09 (m, 2H), 2.40 (dd, *J* = 12.4, 7.8 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), ^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.2, 167.8, 158.0, 145.3, 143.6, 131.5, 128.3, 127.5, 124.4, 122.5, 120.8, 116.6, 69.4, 69.1, 62.7, 62.6, 49.6, 46.7, 28.7, 14.1, 14.0, HRMS: *m/z* calculated for $C_{24}H_{26}N_2O_4Br$ [M+H]$^+$ 485.1062, found 485.1076.

Diethyl 5-(4-cyanophenyl)-2-(indolin-1-yl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ia)

Yield: 149 mg (69%); Brown viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.39 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.22 – 7.18 (m, 2H), 6.99 – 6.96 (m, 1H), 5.21 (t, *J* = 7.3 Hz, 1H), 4.34 – 4.15 (m, 5H), 3.96 (q, *J* = 9.2 Hz, 1H), 3.36 – 3.31 (m, 1H), 3.19 – 3.08 (m, 2H), 2.39 (dd, *J* = 12.8, 7.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.3 Hz, 3H), ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.0, 167.7, 158.4, 150.2, 145.2, 132.4, 131.6, 127.5, 127.3, 124.46, 122.8, 119.2, 116.7, 110.8, 69.4, 69.2, 62.8, 62.7, 49.7, 46.4, 28.7, 14.1, 14.0, HRMS: *m/z* calculated for $C_{25}H_{26}N_3O_4$[M+H]$^+$ 432.1923, found 432.1923.

Diethyl 2-(indolin-1-yl)-5-(4-methoxyphenyl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ja)

Yield: 189 mg (87%); colorless viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.41 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.22 – 7.12 (m, 2H), 6.97 – 6.87 (m, 3H), 5.19 – 5.08 (m, 1H), 4.38 – 4.11 (m, 5H), 3.96 (q, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 3.28 (dd, *J* = 12.4, 6.4 Hz, 1H), 3.22 – 3.01 (m, 2H), 2.43 (dd, *J* = 12.4, 7.8 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), ^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.4, 168.0, 158.7, 157.6, 145.5, 136.8, 131.4, 127.6, 127.5, 124.3, 122.3, 116.6, 113.8, 69.4, 69.2, 62.6, 62.5, 55.4, 49.6, 47.1, 28.7, 14.1, 14.0, HRMS: *m/z* calculated for $C_{25}H_{28}N_2O_5$ [M+H]$^+$ 437.2832, found 437.2838.

Diethyl 2-(indolin-1-yl)-5-mesityl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ka)

Yield: 170 mg (76%); Brown viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.42 (d, *J* = 8.2 Hz, 1H), 7.20 – 7.12 (m, 2H), 6.95 – 6.92 (m, 1H), 6.88 (s, 2H), 5.52 (dd, *J* = 10.1, 6.2 Hz, 1H), 4.47 – 4.23 (m, 5H), 3.92 (q, *J* = 9.4 Hz, 1H), 3.26 (dd, *J*= 12.7, 6.2 Hz, 1H), 3.22 – 3.03 (m, 2H), 2.59 (dd, *J* = 12.8, 10.1 Hz, 1H), 2.41 (s, 6H), 2.30 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), ^{13}C{^{1}H}NMR(101 MHz, CDCl$_3$) δ 169.9, 167.4, 155.7, 145.6, 136.9, 136.4, 135.2, 131.4, 130.3, 127.5, 124.2, 122.1, 116.4, 69.3, 67.0, 62.5, 49.6, 44.0, 28.7, 21.1, 20.9, 14.1, 14.0, HRMS: *m/z* calculated for $C_{27}H_{33}N_2O_4$[M+H]$^+$ 449.2459, found 449.2440.

Dimethyl 5-(furan-2-yl)-2-(indolin-1-yl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3la)

Yield: 112 (61%); Brown viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (d, *J* = 9.1 Hz, 1H), 7.36 (d, *J* = 1.5 Hz, 1H), 7.19 – 7.13 (m, 2H), 6.99 – 6.89 (m, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 – 6.16 (m, 1H), 5.22 (t, *J* = 6.6 Hz, 1H), 4.14 – 3.95 (m, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.18 – 3.07 (m, 3H), 2.83 (dd, *J* = 12.6, 6.2 Hz, 1H), ^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.3, 169.0, 158.1, 156.2, 145.2, 142.0, 131.4, 127.5, 124.9, 124.3, 122.5, 116.7, 110.2, 105.9, 68.6, 64.1, 53.6, 53.4, 49.4, 43.1, 28.7, HRMS: *m/z* calculated for $C_{20}H_{20}N_2O_5$ [M+H]$^+$ 369.1405 found 369.1501.

Dimethyl 5-cyclopropyl-2-(indolin-1-yl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ma)

Yield: 82 mg (48%); colorless viscous liquid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.27 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.10 (m, 2H), 6.96 – 6.86 (m, 1H), 4.18 – 4.06 (m, 1H), 3.91 – 3.80 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.70 (q, *J* = 6.6 Hz, 1H), 3.17 – 3.01 (m, 2H), 2.99 (dd, *J* = 12.7, 6.3 Hz, 1H), 2.40 (dd, *J* = 12.6, 7.6 Hz, 1H), 1.01 – 0.81 (m, 2H), 0.52 – 0.47 (m, 2H), 0.46 – 0.41 (m, 1H),

^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 170.1, 168.8, 156.6, 145.4, 131.3, 127.4, 124.2, 122.1, 116.2, 69.8, 68.8, 53.35, 49.2, 44.2, 28.7, 16.7, 2.5, 2.4, HRMS: m/z calculated for $C_{19}H_{22}N_2O_4$ $[M+H]^+$ 343.2201, found 343.2203.

Diethyl 2-(indolin-1-yl)-5-vinyl-4,5-dihydro-3H-pyrrole-3,3-dicarboxylate (3na)

Yield: 94 mg (53%); Yellow viscous liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.2 Hz, 1H), 7.23 – 7.11 (m, 2H), 6.97 – 6.88 (m, 1H), 6.04 – 5.89 (m, 1H), 5.30 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.14 – 5.06 (m, 1H), 4.63 – 4.53 (m, 1H), 4.33 – 4.17 (m, 4H), 4.13 (dd, *J* = 9.3, 6.2 Hz, 1H), 4.04 – 3.91 (m, 1H), 3.20 – 3.03 (m, 2H), 3.01 (dd, *J* = 12.5, 6.7 Hz, 2H), 2.42 (dd, *J* = 12.4, 6.8 Hz, 1H), 1.31 – 1.29 (m, 3H), 1.28 – 1.26 (m, 3H), ^{13}C {^1H} NMR (101 MHz, $CDCl_3$) 169.2, 168.3, 157.4, 145.3, 140.4, 131.3, 127.4, 124.2, 122.2, 116.4, 114.8, 68.8, 68.5, 62.5, 62.4, 49.5, 43.8, 28.6, 14.0, HRMS: *m/z* calculated for $C_{20}H_{24}N_2O_4$ $[M+H]^+$ 357.2742, found 357.2748.

Diethyl 2-(diisopropylamino)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ac)

Yield: 145 mg (75%); Yellow viscous liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 7.22 – 7.18 (m, 1H), 5.03 (t, *J* = 7.0 Hz, 1H), 4.32 – 4.05 (m, 4H), 3.63 (s, 2H), 3.15 (dd, *J* = 12.6, 6.7 Hz, 1H), 2.32 (dd, *J* = 12.4, 7.3 Hz, 1H), 1.34 – 1.26 (m, 9H), 1.18 (t, *J* = 7.1 Hz, 3H), ^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 169.9, 169.0, 159.2, 146.1, 128.2, 126.5, 126.5, 69.4, 69.4, 68.4, 62.1, 61.9, 47.8, 14.2, 13.9, HRMS: *m/z* calculated for $C_{22}H_{33}N_2O_4$ $[M+H]^+$ 389.2441, found 389.2440.

Dimethyl 2-(diisopropylamino)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3bc)

Yield: 126 mg (70%); Yellow viscous liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 4H), 7.22 – 7.18 (m, 1H), 5.03 (t, *J* = 7.2 Hz, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.16 (dd, *J* = 12.6, 6.7 Hz, 1H), 2.30 (dd, *J* = 12.6, 7.6 Hz, 1H), 1.33 – 1.30 (m, 6H), 1.26 – 1.20 (m, 2H), ^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 170.4, 169.4, 159.0, 145.9, 128.3, 126.6, 126.5, 69.3, 68.3, 53.1, 52.9, 47.7, 20.5, 20.1, HRMS: *m/z* calculated for $C_{20}H_{29}N_2O_4$ $[M+H]^+$ 361.2128, found 361.2127.

Diethyl 2-(dibenzylamino)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ae)

Yield: 199 mg (82%); Yellow viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 4H), 7.27 – 7.23 (m, 10H), 7.22 – 7.19 (m, 1H), 5.11 (t, *J* = 7.1 Hz, 1H), 4.73 (d, *J* = 16.3 Hz, 2H), 4.54 (d, *J* = 16.0 Hz, 2H), 4.14 – 3.92 (m, 4H), 3.37 (dd, *J* = 12.8, 6.8 Hz, 1H), 2.58 (dd, *J*= 12.8, 7.6 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)δ 169.4, 168.5, 162.6, 144.8, 137.4, 128.4, 128.3, 127.6, 127.1, 126.8, 126.4, 68.3, 67.6, 62.5, 62.3, 51.6, 48.5, 13.9, 13.8, HRMS: *m/z* calculated for $C_{30}H_{33}N_2O_4$ $[M+H]^+$ 485.2449, found 485.2440.

Diethyl 2-(methyl(phenyl)amino)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3af)

Yield: 140 mg (71%); Yellow viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 3H),7.34 – 7.29 (m, 5H), 7.26 – 7.20 (m, 2H), 4.97 (t, *J* = 7.1 Hz, 1H), 4.20 – 4.13 (m, 2H), 3.83 – 3.77 (m, 1H), 3.71 – 3.64 (m, 1H), 3.41 (s, 3H), 3.15 (dd, *J* = 12.6, 6.6 Hz, 1H), 2.62 (dd, *J* = 12.8, 7.8 Hz, 1H), 1.29 – 1.25 (m, 3H), 1.04 – 1.00 (m, 3H), ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.8, 168.7, 162.3, 145.2, 144.3, 129.0, 128.7, 128.4, 127.1, 127.0, 126.7, 68.1, 67.8, 62.2, 62.0, 48.8, 42.2, 14.1, 13.7, HRMS: *m/z* calculated for $C_{23}H_{27}N_2O_4$ $[M+H]^+$ 395.1985, found 395.1971.

Dimethyl 2-(methyl(phenyl)amino)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3bf)

Yield: 132 mg (72%); Brown viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 3H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.20 (m, 1H), 4.98 (dd, *J* = 7.8, 6.4 Hz, 1H), 3.71 (s, 3H), 3.42 (s, 3H), 3.30 (s, 3H), 3.13 (dd, *J* = 12.8, 6.4 Hz, 1H), 2.62 (dd, *J* = 12.7, 7.8 Hz, 1H), ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.0, 167.0, 161.6, 144.8, 143.9, 129.0, 128.7, 128.4, 127.4, 127.0, 126.6, 67.9, 67.5, 53.1, 52.8, 49.0, 42.3, 32.0, 22.8, 14.2, HRMS: *m/z* calculated for $C_{21}H_{23}N_2O_4$ $[M+H]^+$ 367.1660, found 367.1658.

Diethyl 5-phenyl-2-(piperidin-1-yl)-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ah)

Yield: 116 mg (64%); Yellow viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.33 – 7.29 (m, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 7.25 (s, 1H), 5.21 (t, *J* = 7.0 Hz, 1H), 4.39 (q, *J*= 7.2 Hz, 2H), 4.27 – 4.12 (m, 2H), 3.71 – 3.68 (m, 7H), 3.63 (s, 3H), 3.35 (dd, *J* = 13.1, 7.1 Hz, 1H), 2.71 (dd, *J* = 13.2, 6.9 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), ^{13}C {^{1}H}

NMR (101 MHz, $CDCl_3$) δ 166.0, 165.2, 164.9, 161.5, 137.7, 129.2, 128.9, 126.1, 64.6, 64.5, 64.01, 61.4, 51.3, 44.2, 43.5, 25.9, 25.2, 25.1, 22.8, 14.0, 13.8, HRMS: *m/z* calculated for $C_{21}H_{29}N_2O_4$ $[M+H]^+$ 373.2128, found 373.2127.

Diethyl 2-((4-methoxyphenyl)(prop-2-yn-1-yl)amino)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3ag)

Yield: 206 mg (92%); Brown viscous liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.35 (m, 4H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.00 (t, *J* = 7.1 Hz, 1H), 4.63 – 4.50 (m, 2H), 4.16 – 4.04 (m, 2H), 3.77 (s, 3H), 3.74 (dd, *J* = 8.5, 7.1 Hz, 1H), 3.65 – 3.57 (m, 1H), 3.16 – 3.11 (m, 1H), 2.65 – 2.59 (m, 1H), 2.25 (q, *J* = 2.2 Hz, 1H), 1.23 (t, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H), ^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 168.4, 168.3, 161.5, 159.1, 144.0, 134.8, 131.8, 128.2, 126.8, 126.5, 113.7, 80.0, 72.1, 67.9, 67.6, 62.0, 61.8, 55.4, 48.8, 43.6, 13.9, 13.4, HRMS: *m/z* calculated for $C_{26}H_{29}N_2O_5$ $[M+H]^+$ 449.2070, found 449.2076

Diethyl 2-(3,4-dihydroquinolin-1(2H)-yl)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3aj)

Yield: 177 mg (84%); Yellow viscous liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.24 (m, 5H), 7.16 – 7.10 (m, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 5.06 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.36 – 4.31 (m, 2H), 4.06 – 3.93 (m, 3H), 3.47 – 3.41 (m, 1H), 3.24 (dd, *J* = 12.6, 6.2 Hz, 1H), 2.84 (t, *J* = 6.9 Hz, 2H), 2.70 (dd, *J* = 12.7, 8.5 Hz, 1H), 2.18 – 2.08 (m, 1H), 2.04 – 1.94 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), ^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 168.7, 161.7, 144.0, 141.2, 130.2, 128.8, 128.3, 126.8, 126.4, 125.7, 124.0, 123.5, 68.5, 68.3, 62.3, 62.1, 48.4, 47.2, 26.7, 23.2, 14.0, 13.8, HRMS: *m/z* calculated for $C_{25}H_{2}$ N_2O_4 $[M+H]^+$ 421.2118, found 421.2127.

Dimethyl 2-(3,4-dihydroquinolin-1(2*H*)-yl)-5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3bj)

Yield: 181 mg (82%); Yellow viscous liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 9.4 Hz, 1H), 7.41 – 7.31 (m, 5H), 7.15 – 7.09 (m, 2H), 7.02 – 6.98 (m, 1H), 5.04 (dd, *J* = 8.5, 6.2 Hz, 1H), 4.00 – 3.94 (m, 1H), 3.86 (s, 3H), 3.54 (s, 3H), 3.46 – 3.40 (m, 1H), 3.21 (dd, *J* = 12.6, 6.2 Hz, 1H), 2.82 (t, *J*= 7.0 Hz, 2H), 2.65 (dd, *J* = 12.8, 8.7 Hz, 1H), 2.16 – 2.09 (m, 1H), 2.00 –

1.93 (m, 1H), ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.2, 161.6, 143.9, 141.1, 130.9, 128.9, 128.4, 127.0, 126.5, 125.9, 124.1, 123.9, 68.6, 68.1, 53.3, 53.0, 48.7, 47.4, 26.7, 23.3, HRMS: *m/z* calculated for $C_{23}H_{24}N_2O_4$ $[M+H]^+$ 393.1835, found 393.1830.

Tetraethyl 2,2'-(piperazine-1,4-diyl)bis(5-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate) (3aka)

Yield: 267 mg (81%); Yellow viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 4.5 Hz, 8H), 7.24 – 7.20 (m, 2H), 4.99 (t, *J* = 7.2 Hz, 2H), 4.35 – 4.25 (m, 4H), 4.22 – 4.12 (m, 4H), 3.60 – 3.54 (m, 8H), 3.30 – 3.25 (m, 2H), 2.50 – 2.43 (m, 2H), 1.35 – 1.30 (m, 6H), 1.24 – 1.19 (m, 6H), ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.2, 168.0, 161.6, 144.3, 128.3, 127.2, 126.9, 126.8, 126.4, 68.2, 67.1, 62.4, 62.3, 47.2, 46.6, 14.0, 13.9, HRMS: *m/z* calculated for $C_{36}H_{45}N_4O_8$ $[M+H]^+$ 661.3237, found 661.3237.

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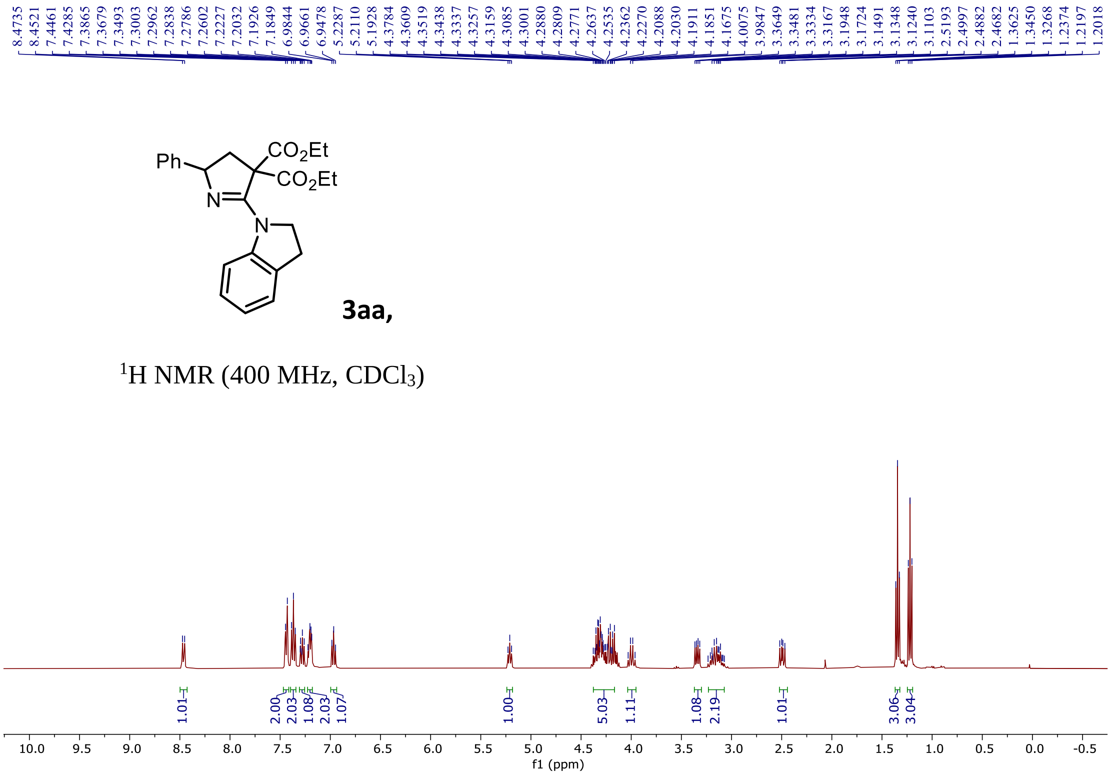
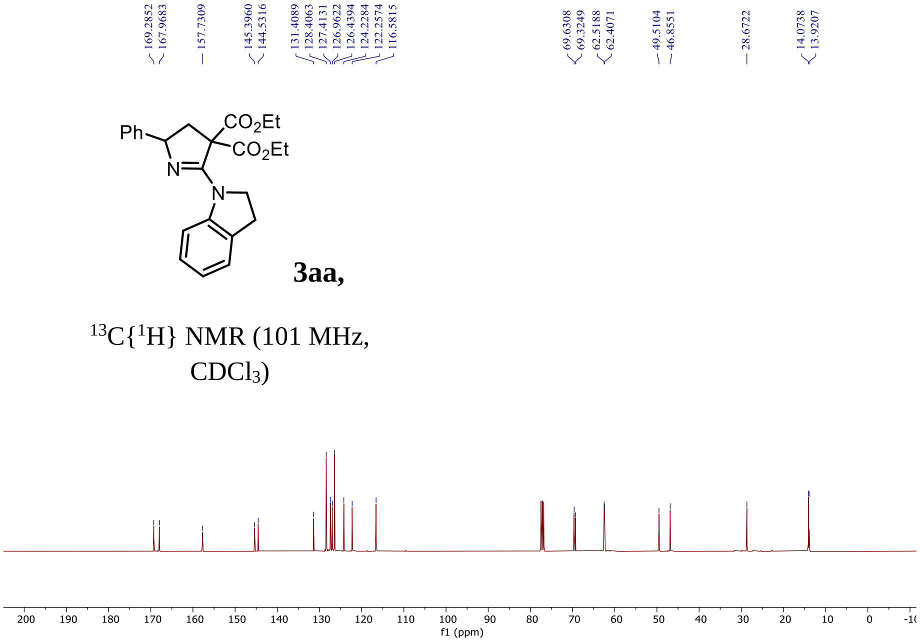
3.6 NMR spectra of compounds



3aa,

^{1}H NMR (400 MHz, CDCl$_3$)



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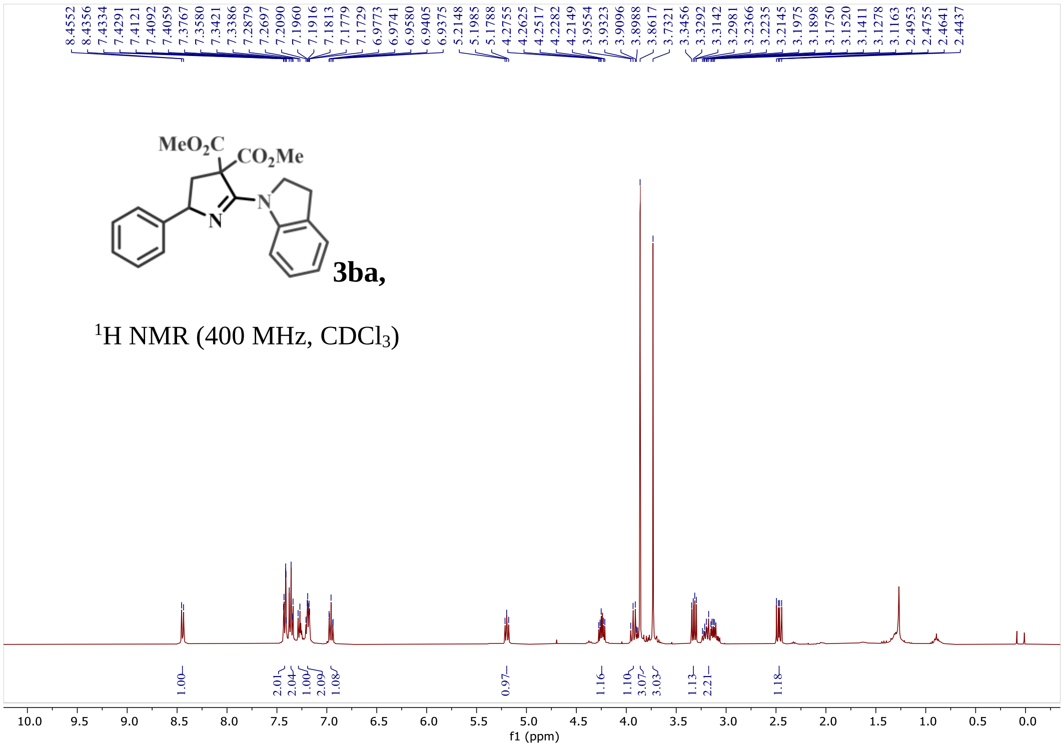

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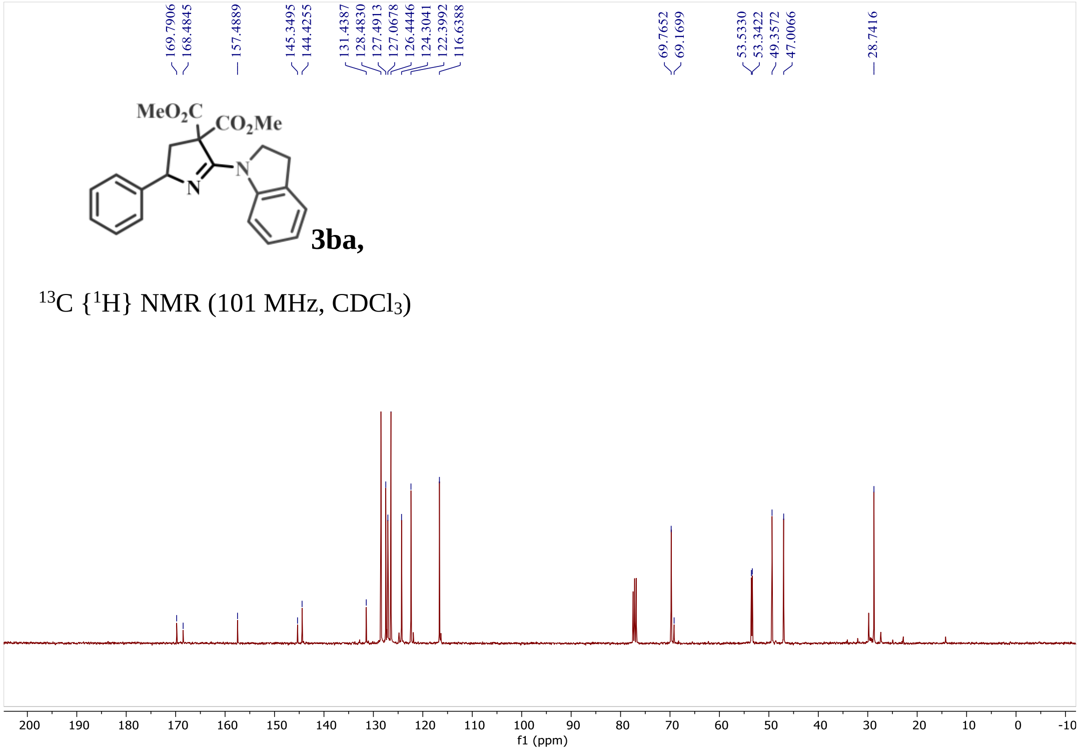

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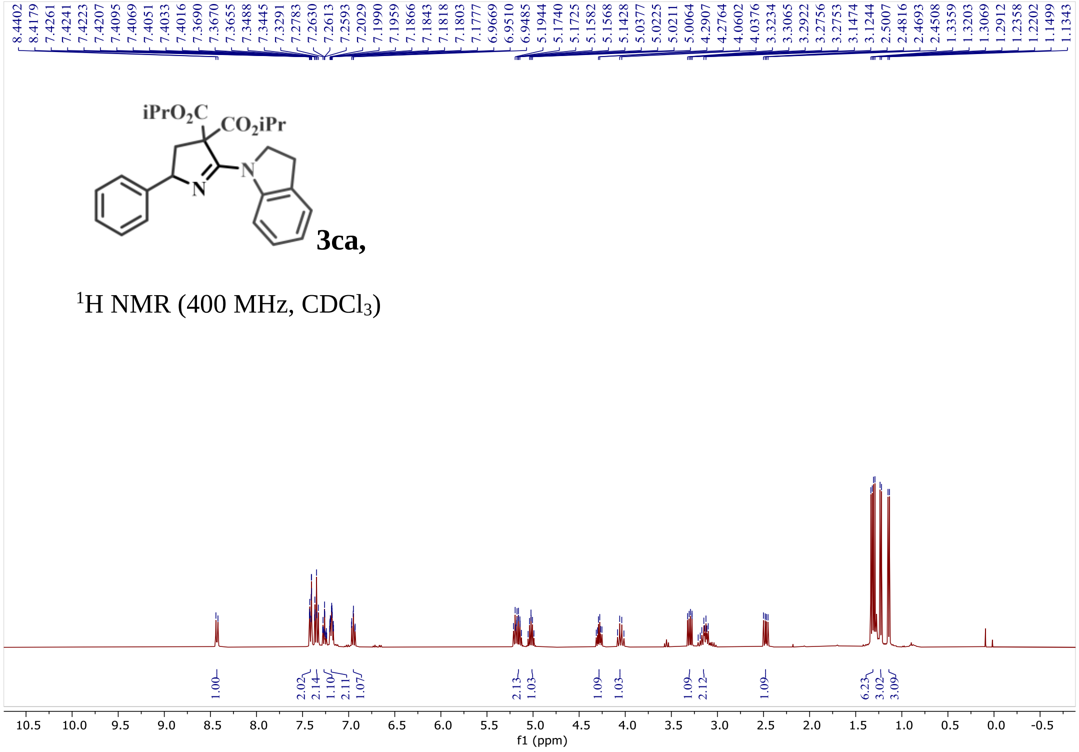

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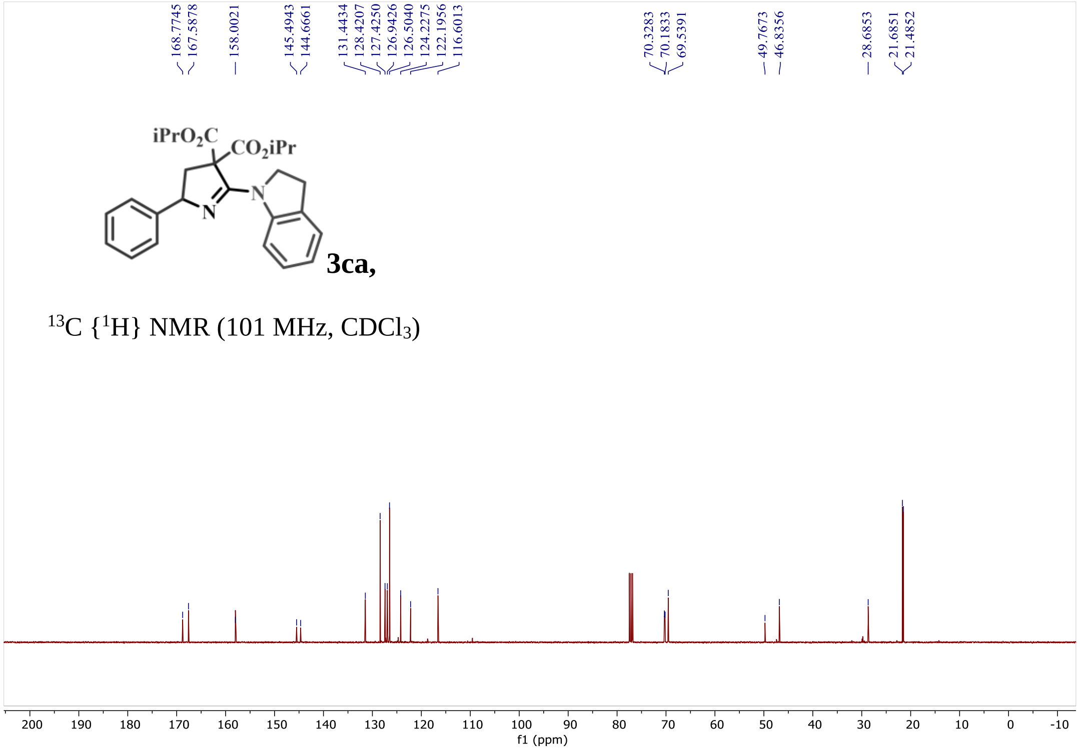

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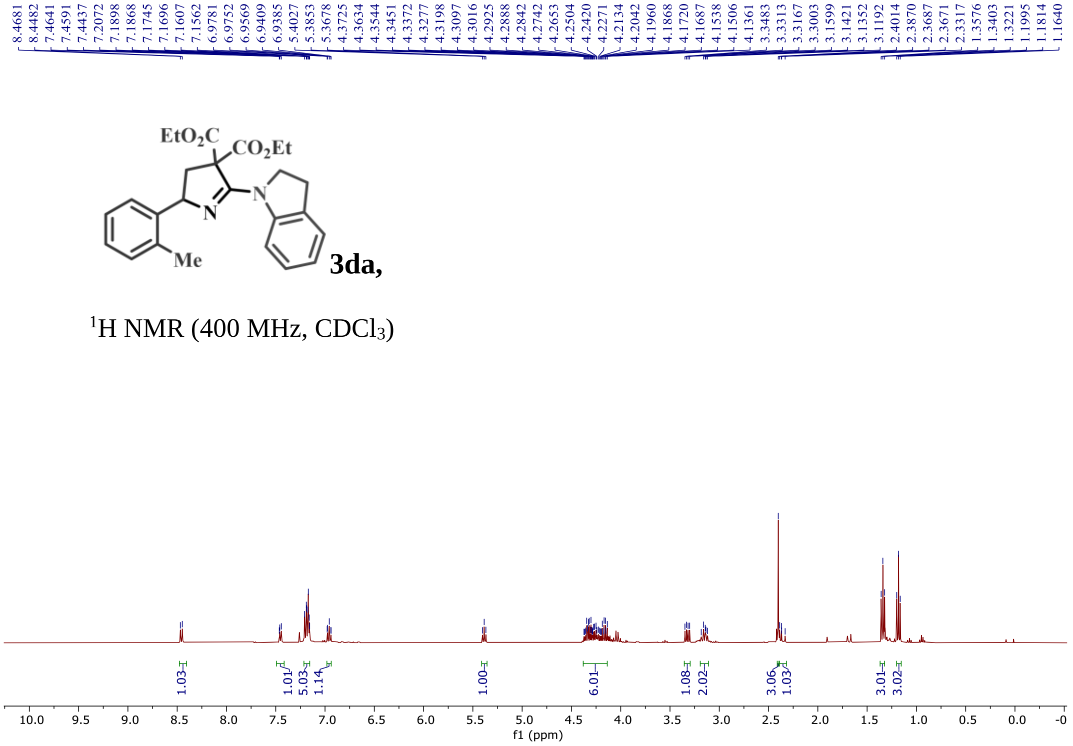

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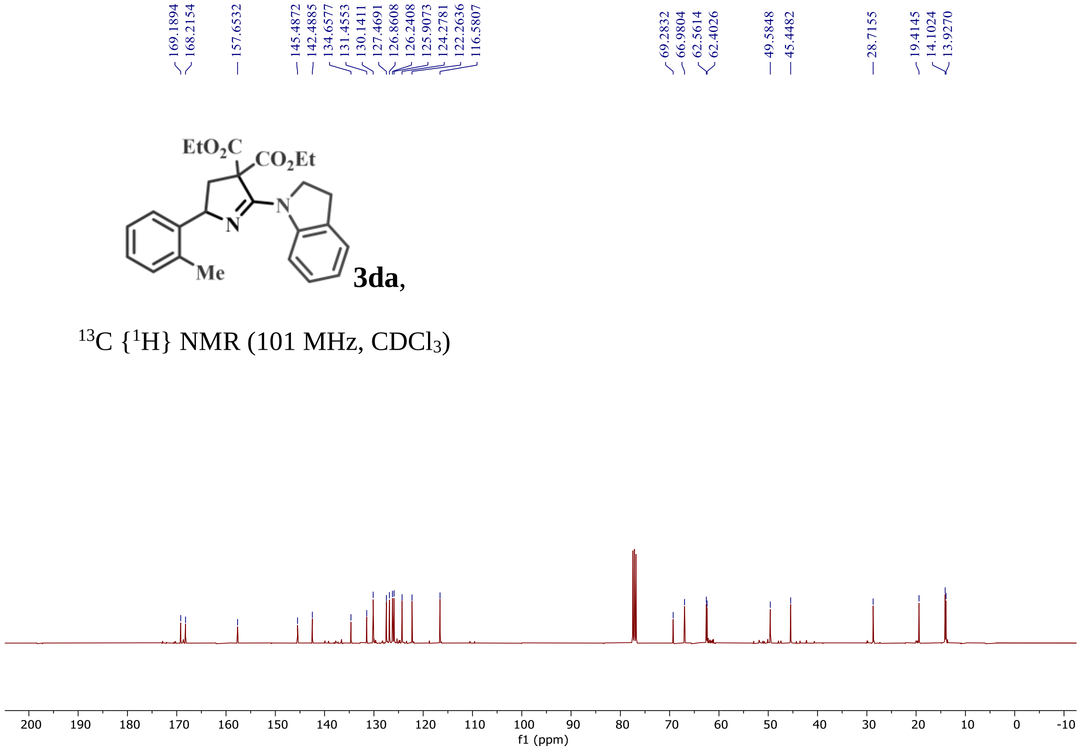

3da,

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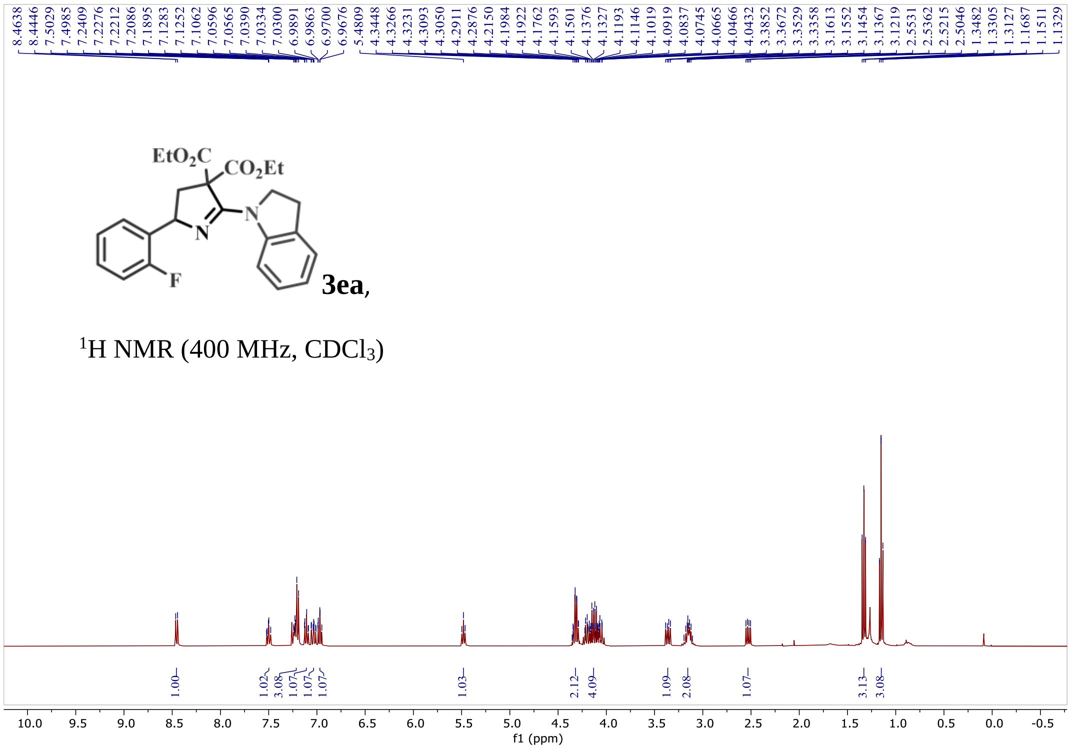
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8.4446
7.5029
7.4985
7.2409
7.2276
7.2212
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7.1252
7.1062
7.0596
7.0565
7.0390
7.0334
7.0300
6.9891
6.9863
6.9700
6.9676
5.4809
4.3448
4.3266
4.3231
4.3093
4.3050
4.2911
4.2876
4.2150
4.1984
4.1922
4.1762
4.1593
4.1501
4.1376
4.1327
4.1193
4.1146
4.1019
4.0919
4.0837
4.0745
4.0665
4.0466
4.0432
3.3852
3.3672
3.3529
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3.1613
3.1552
3.1454
3.1367
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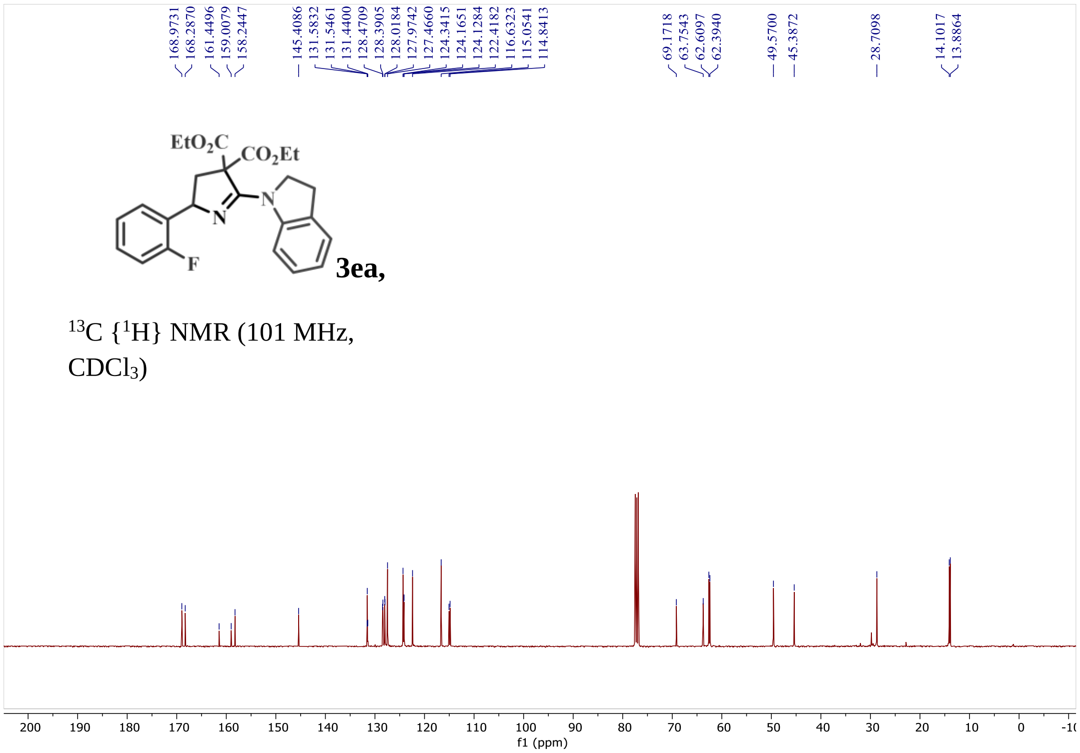
2.5215
2.5046
1.3482
1.3305
1.3127
1.1687
1.1511
1.1329
EtO2C
CO2Et
N
N
F
3ea,
1H NMR (400 MHz, CDCl3)
1.00
1.02
3.08
1.07
1.07
1.07
1.03
2.12
4.09
1.09
2.08
1.07
3.13
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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114.8413
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62.6097
62.3940
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28.7098
14.1017
13.8864
EtO2C
CO2Et
N
N
F
3ea,
13C {1H} NMR (101 MHz, CDCl3)
200
190
180
170
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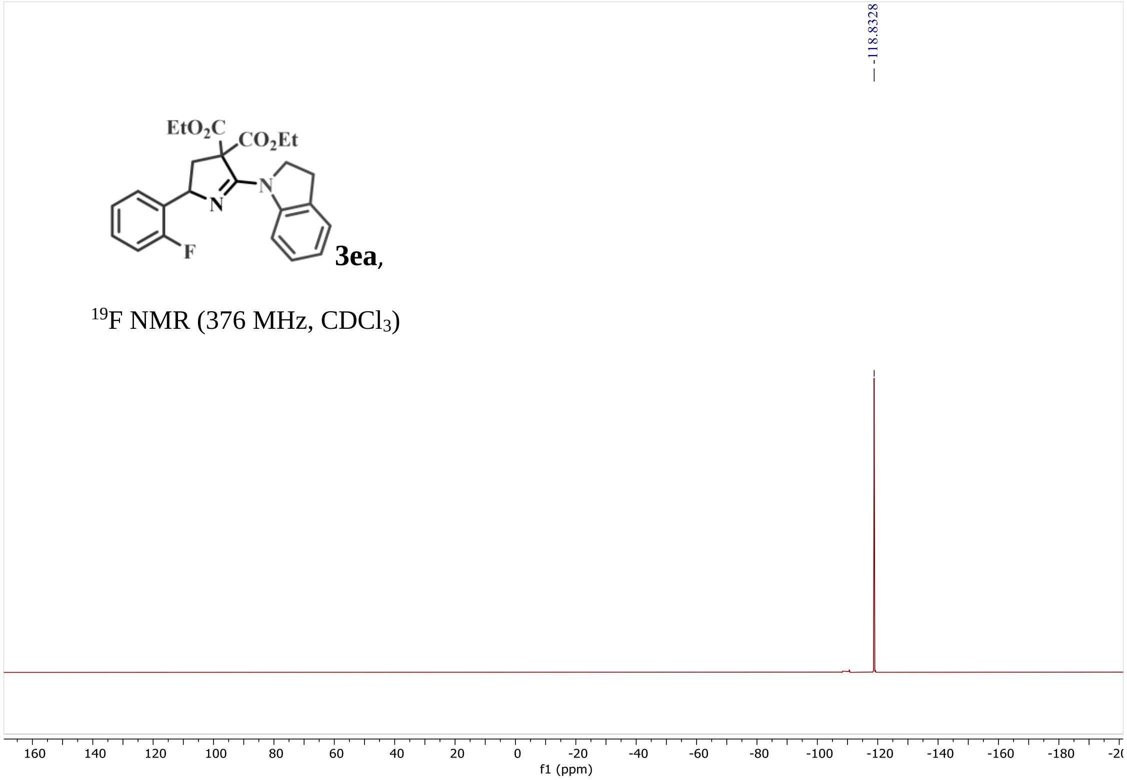
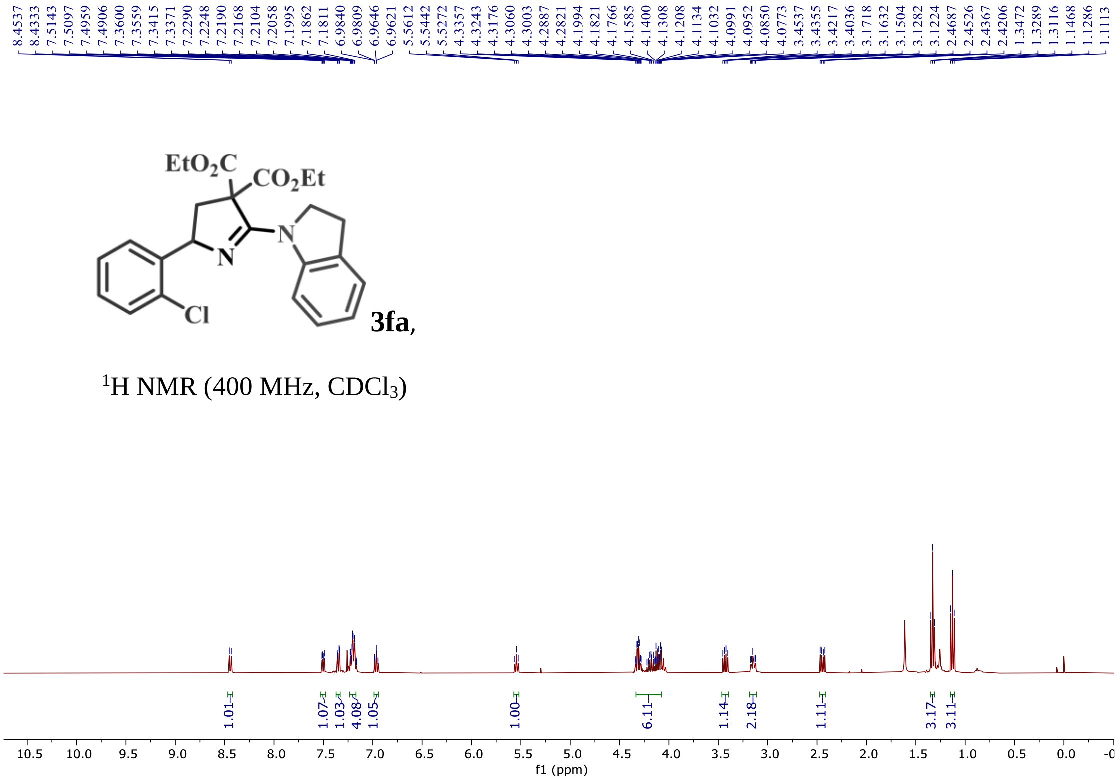
30
20
10
0
-10
f1 (ppm)



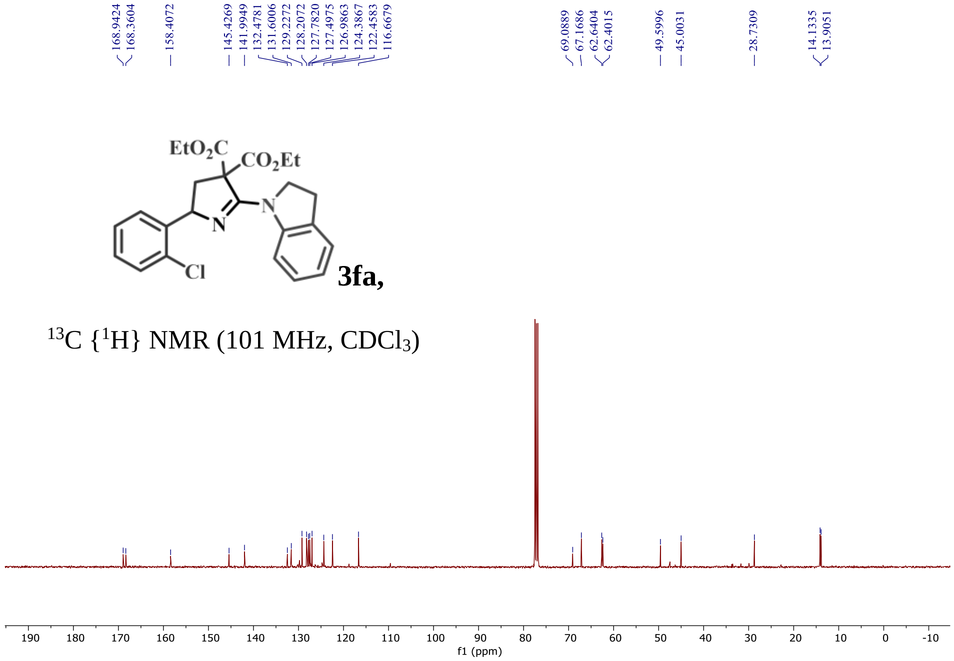
3ea,

^{19}F NMR (376 MHz, CDCl$_3$)



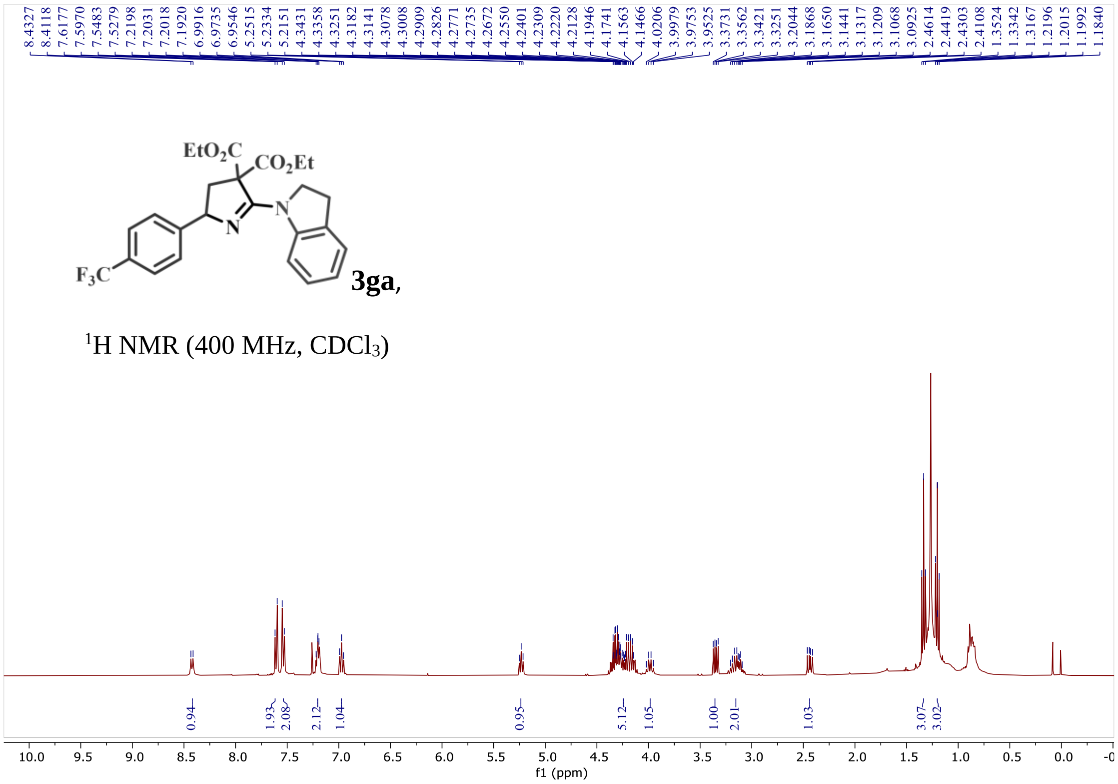
3fa,

^{1}H NMR (400 MHz, CDCl$_3$)



3fa,

$^{13}C\ \{^1H\}$ NMR (101 MHz, $CDCl_3$)



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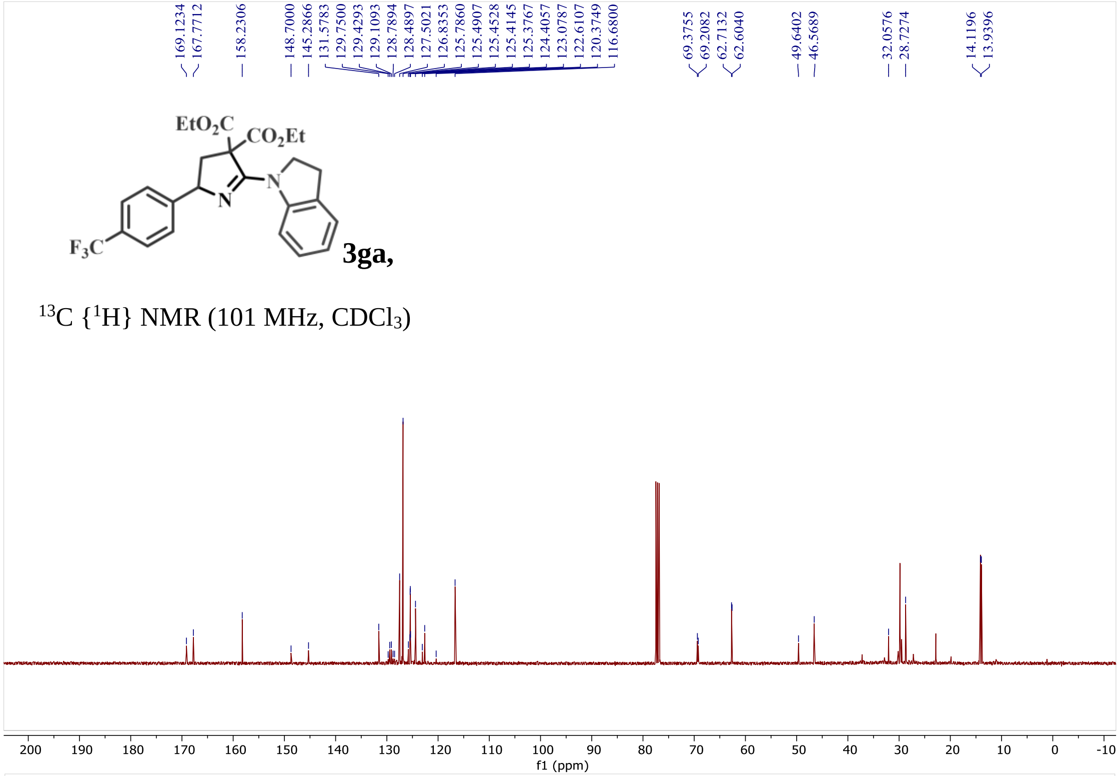
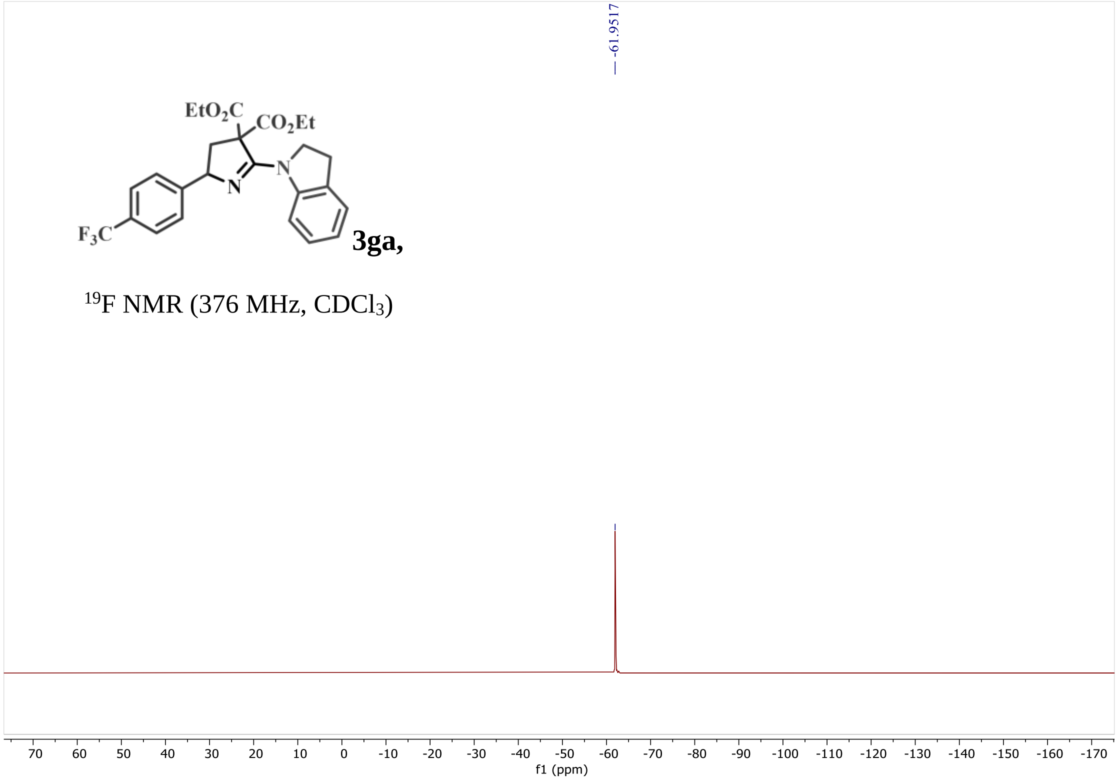
^1H NMR (400 MHz, $CDCl_3$)



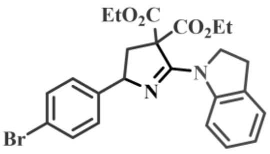
3ga,

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)



3ga,

^{19}F NMR (376 MHz, CDCl$_3$)



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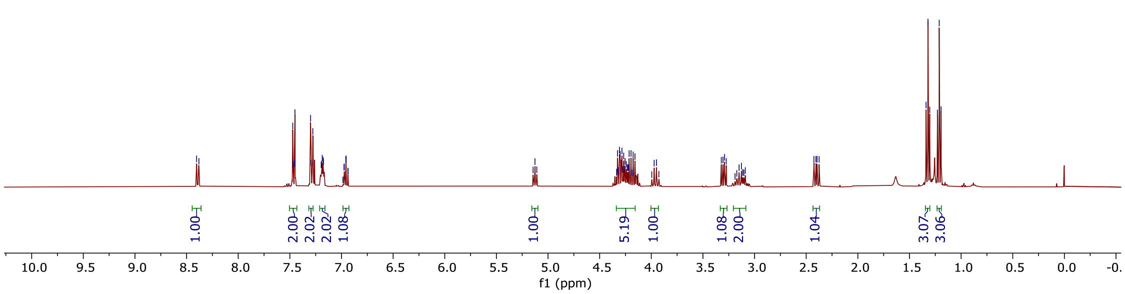
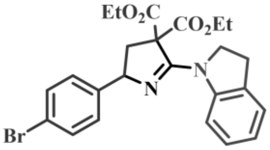
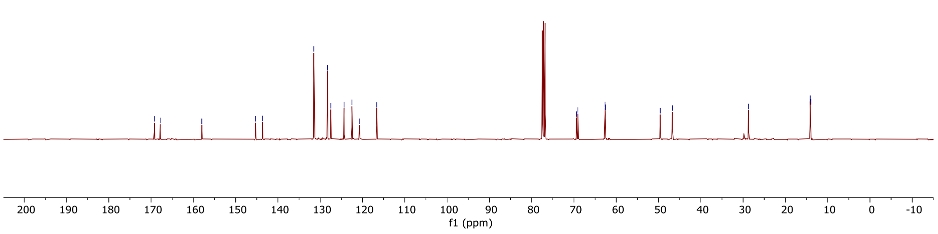
^{1}H NMR (400 MHz, CDCl$_3$)

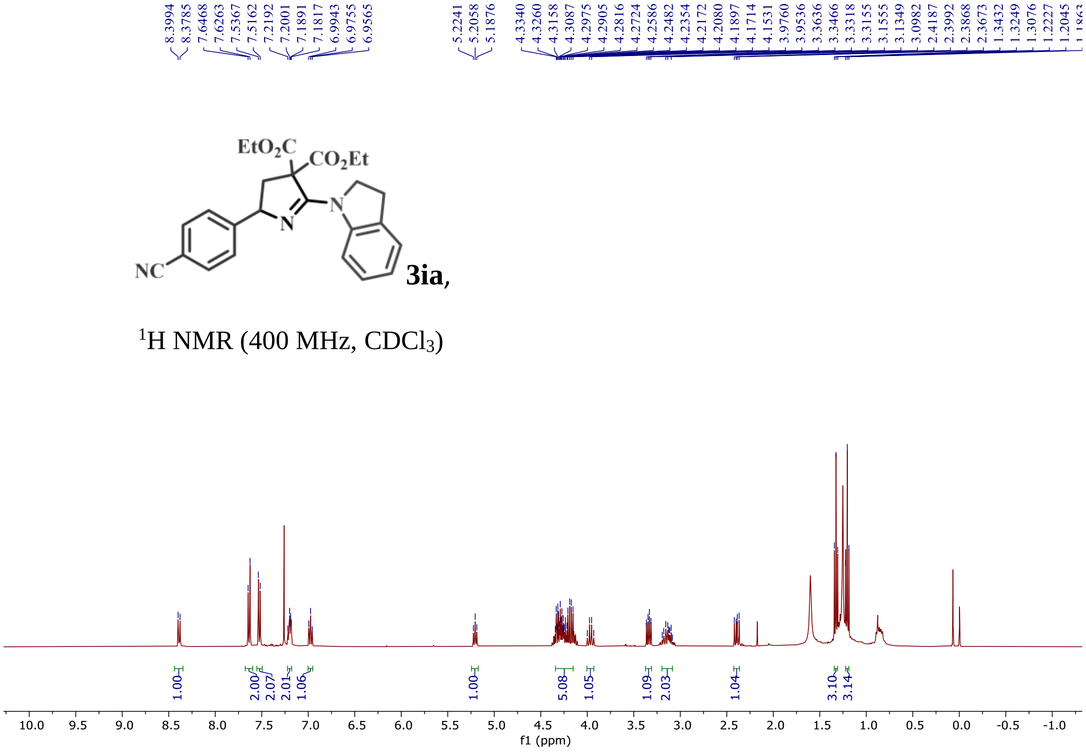




3ha,

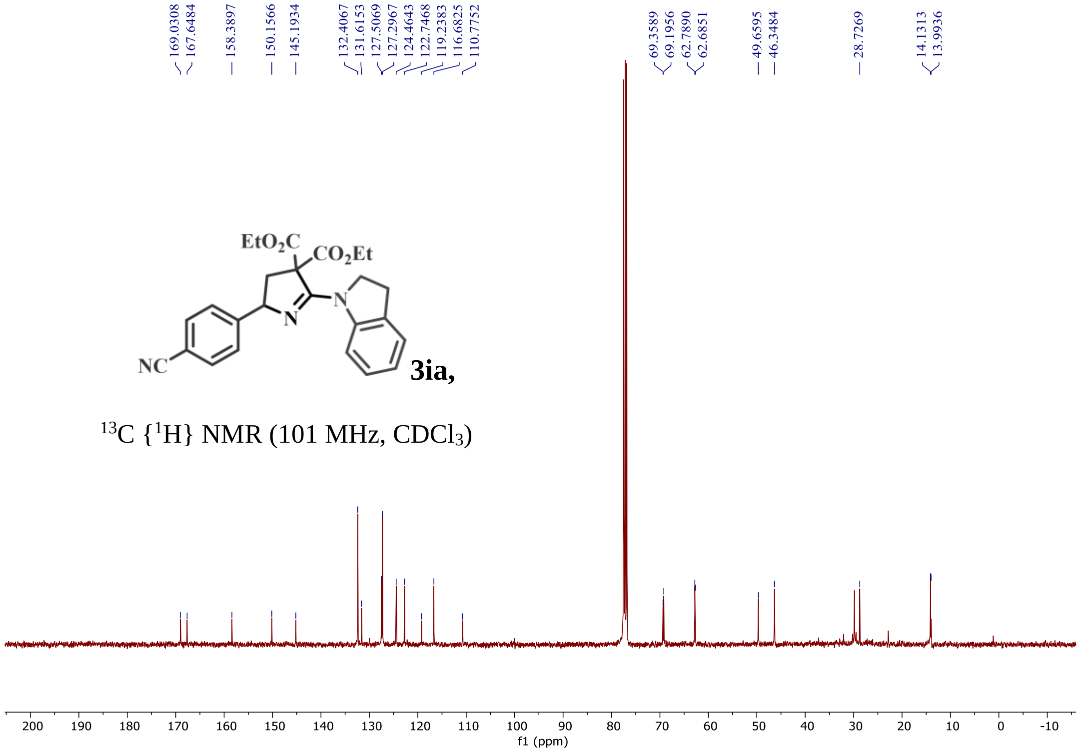
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)





3ia,

^{1}H NMR (400 MHz, CDCl$_3$)



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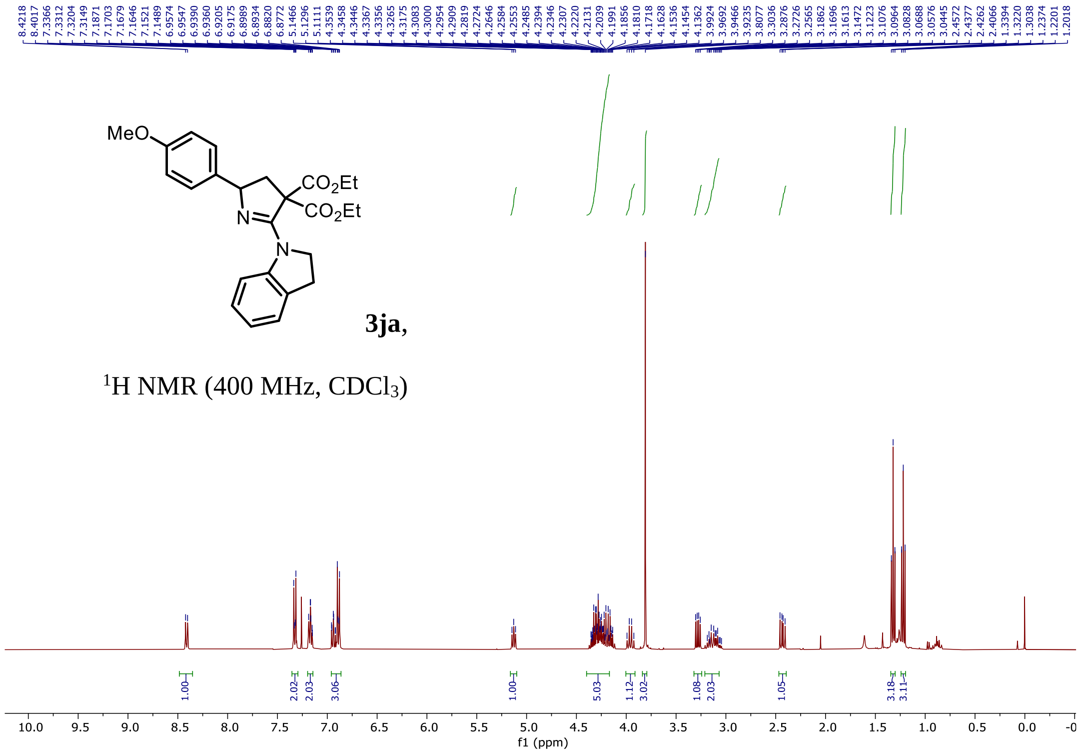

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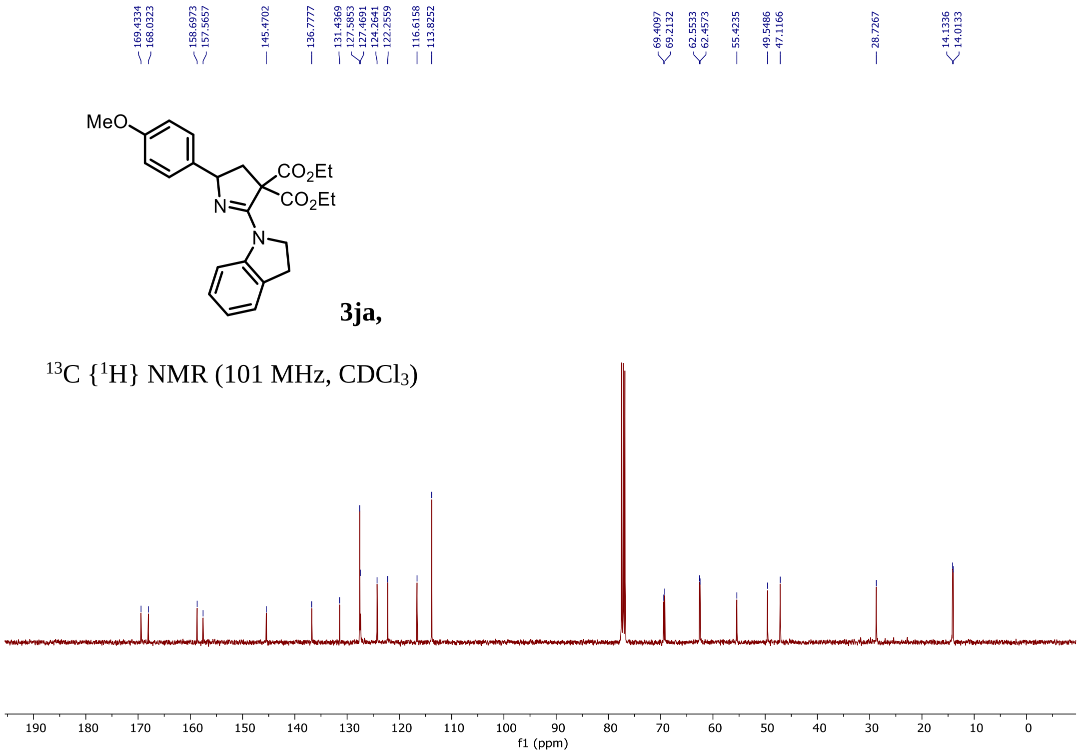

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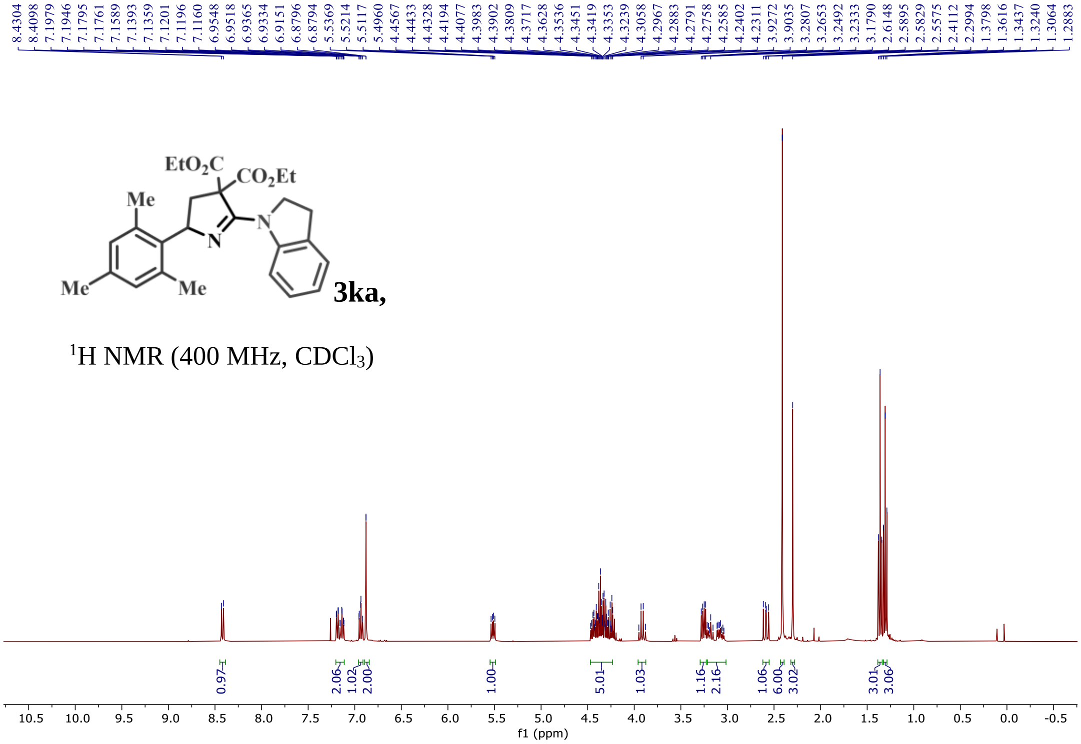

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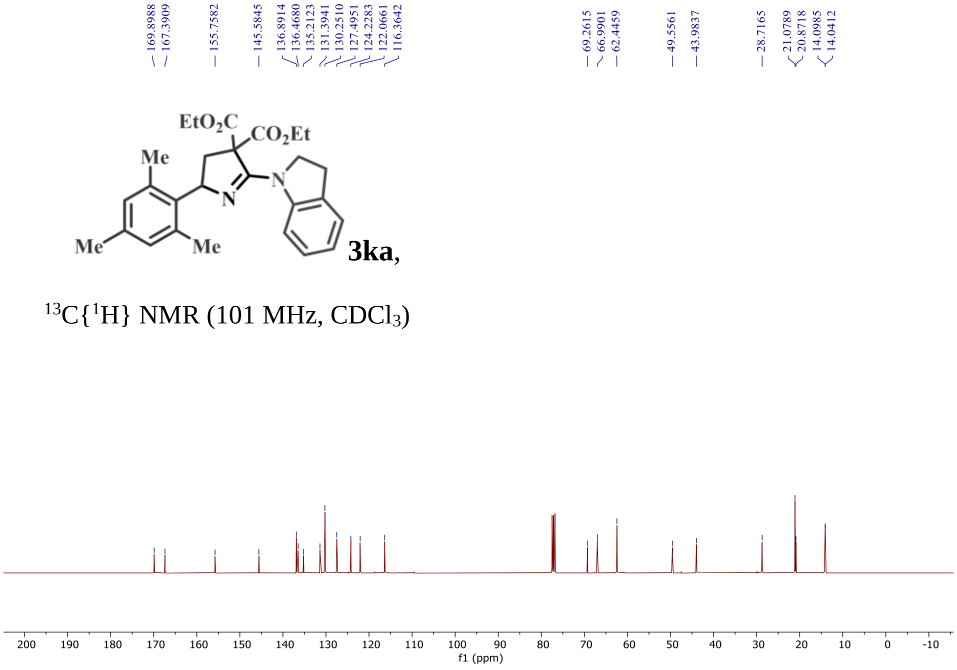

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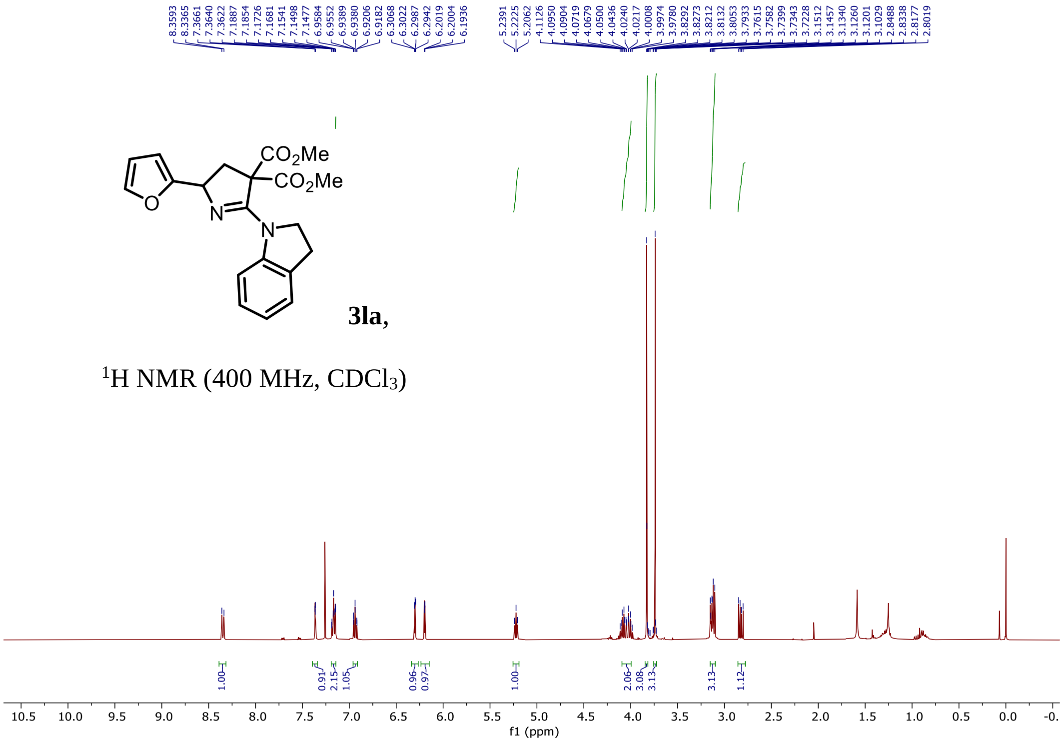

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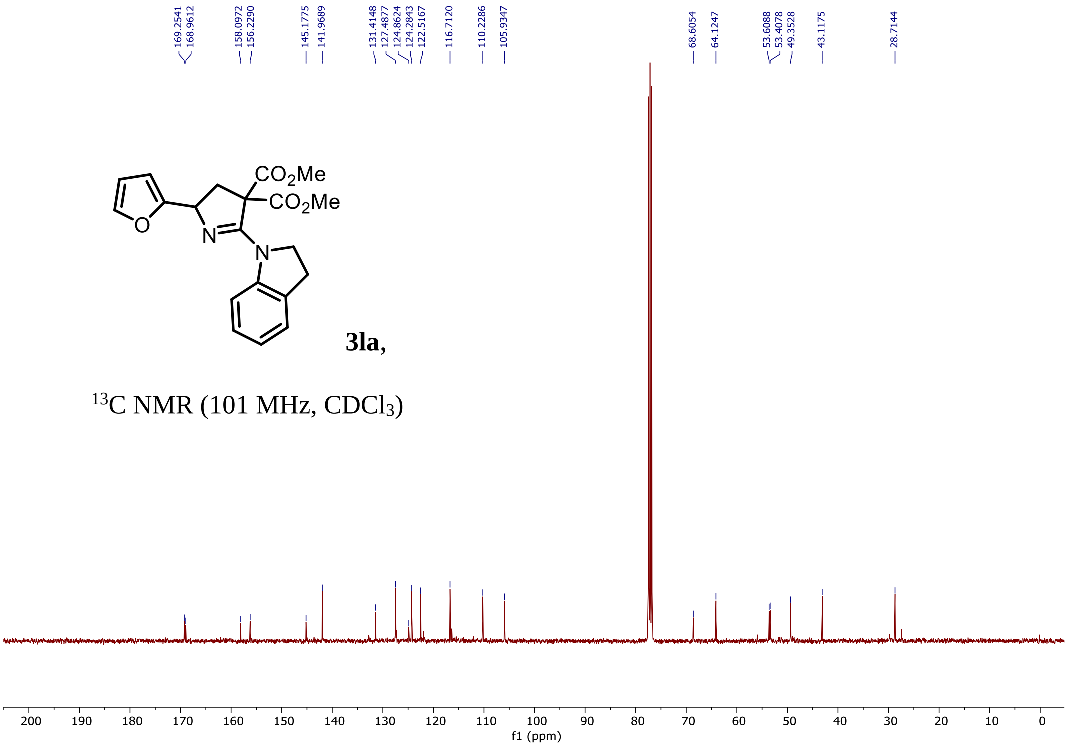

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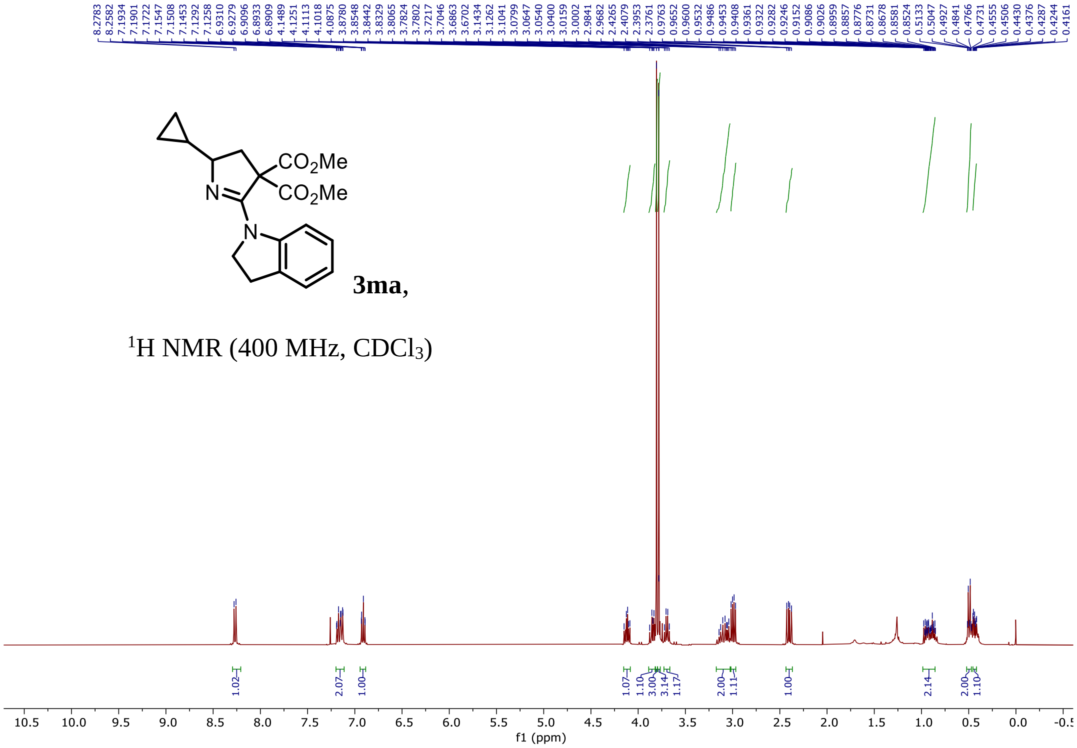

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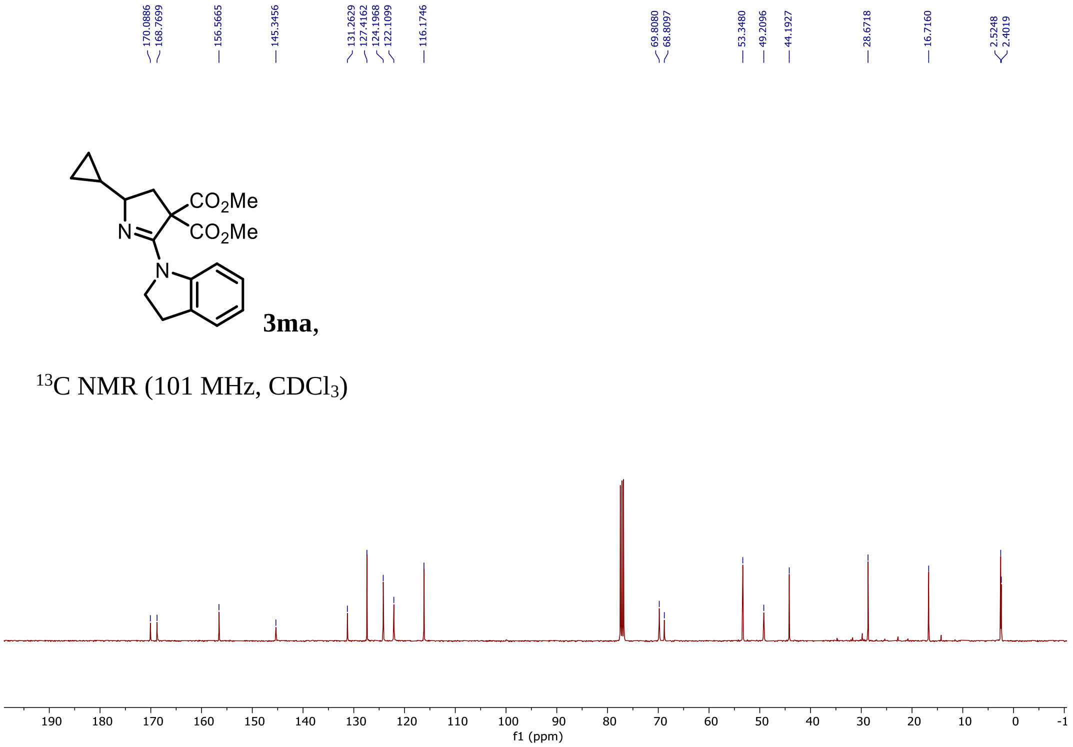

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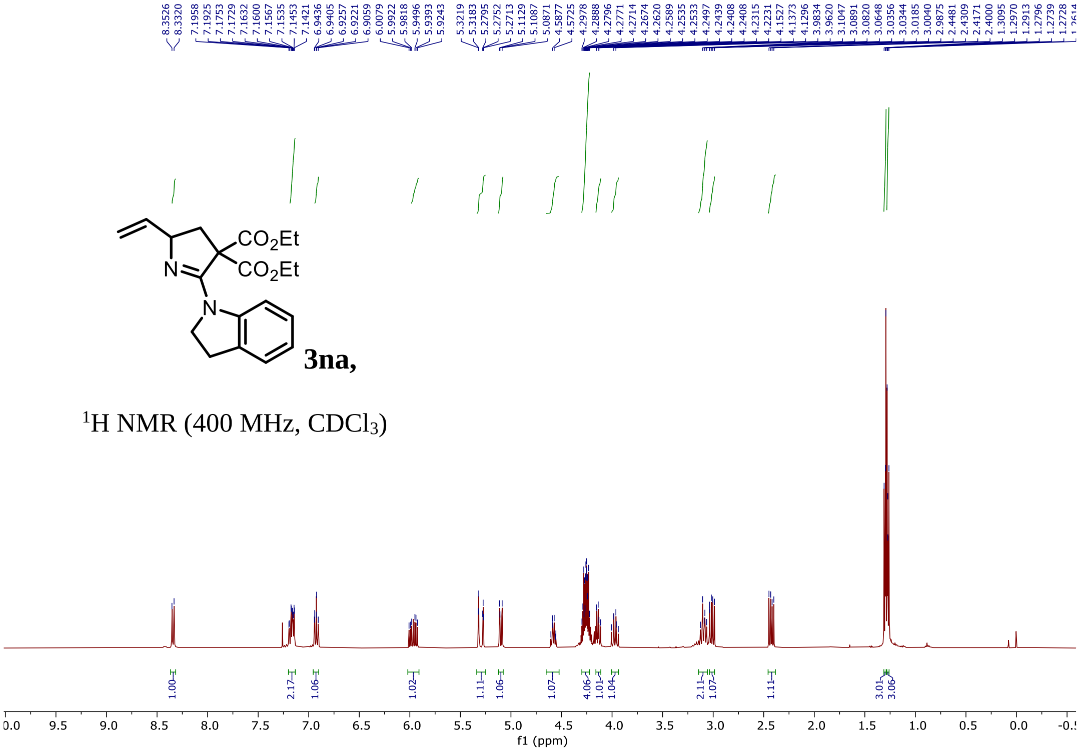

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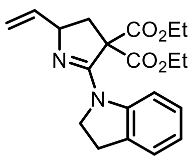

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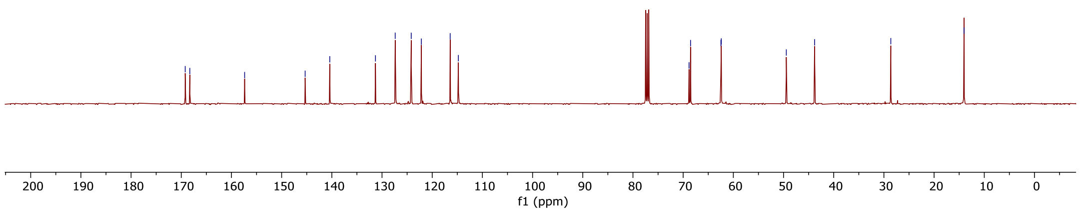

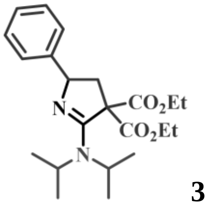

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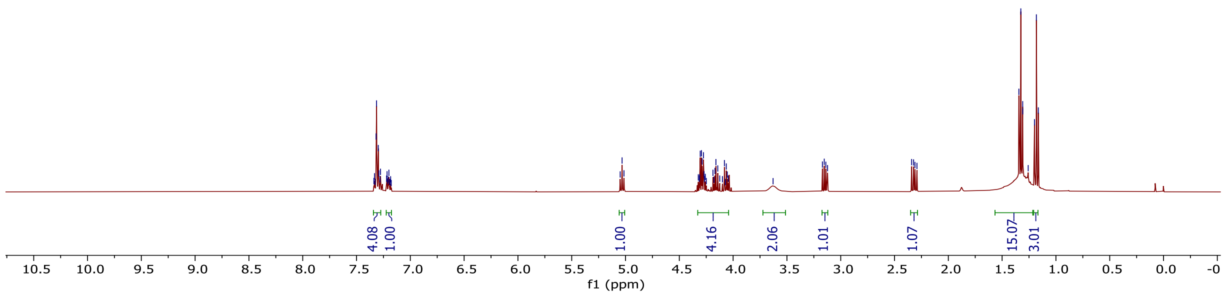

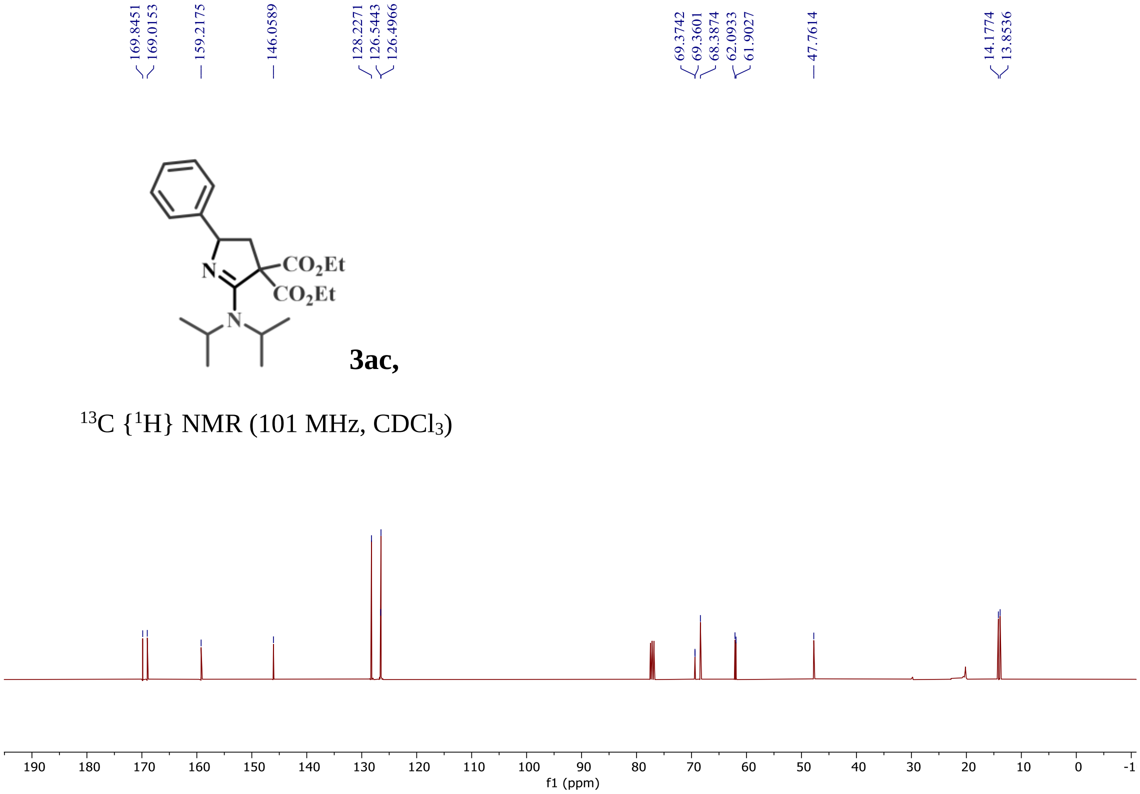

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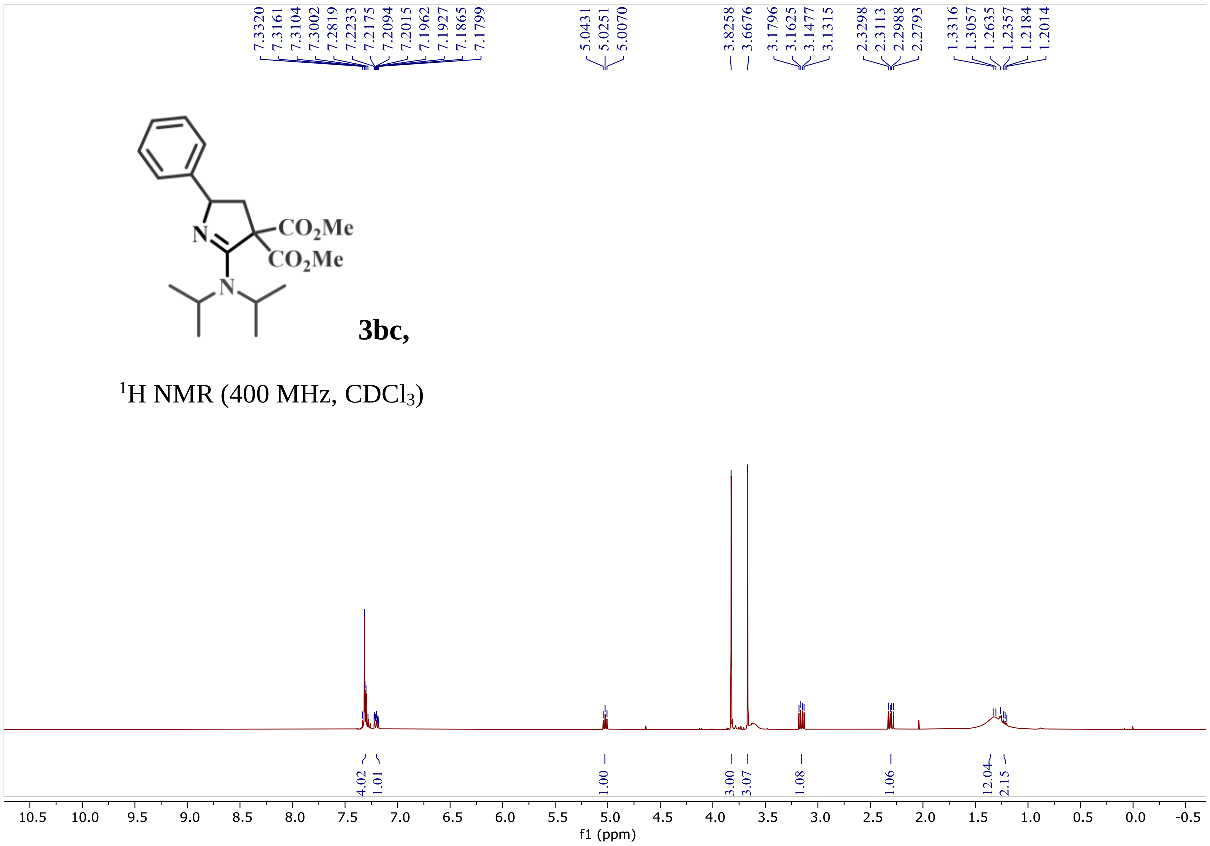

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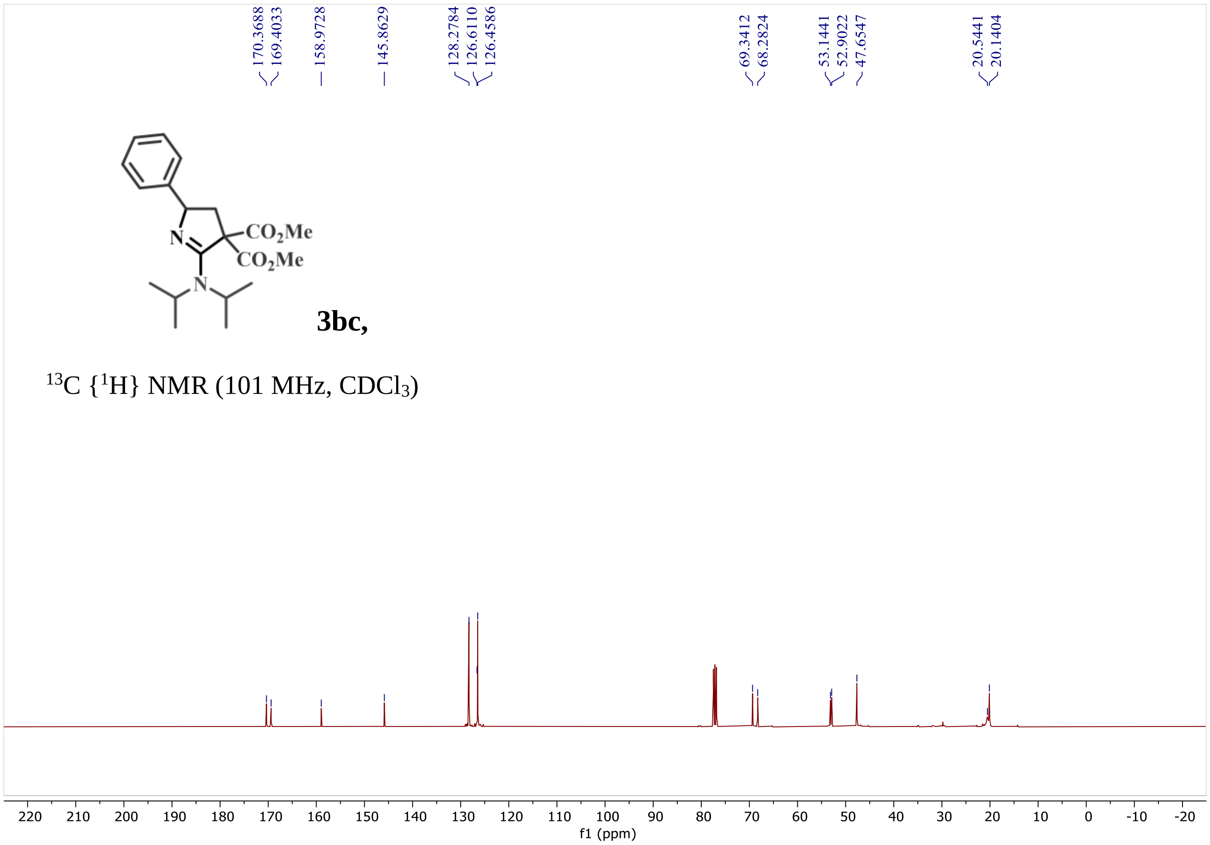

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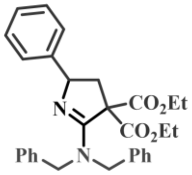

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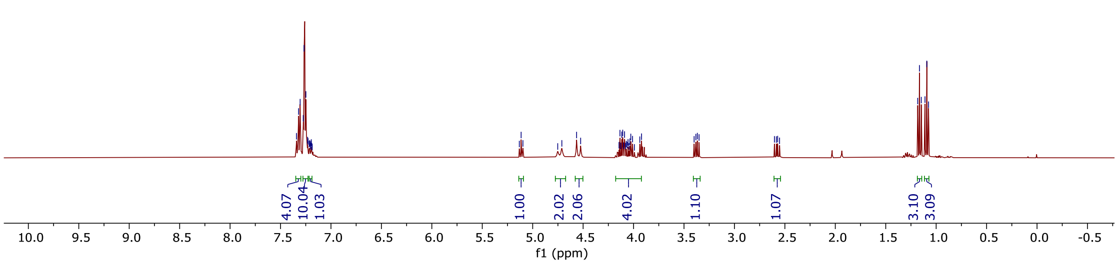

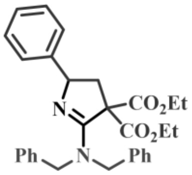

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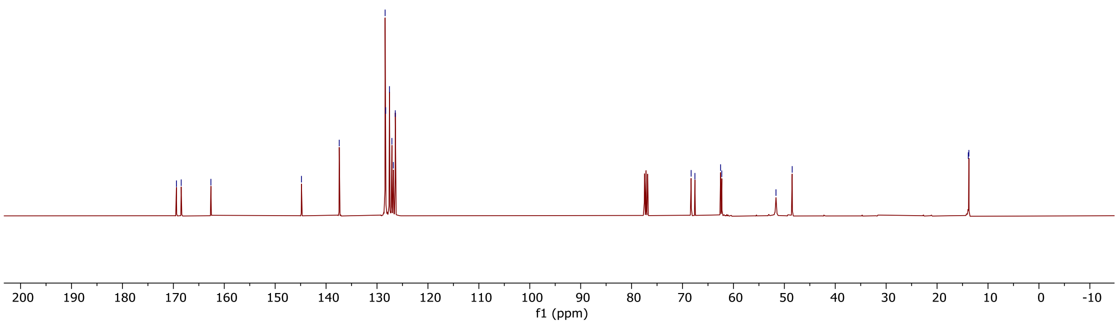

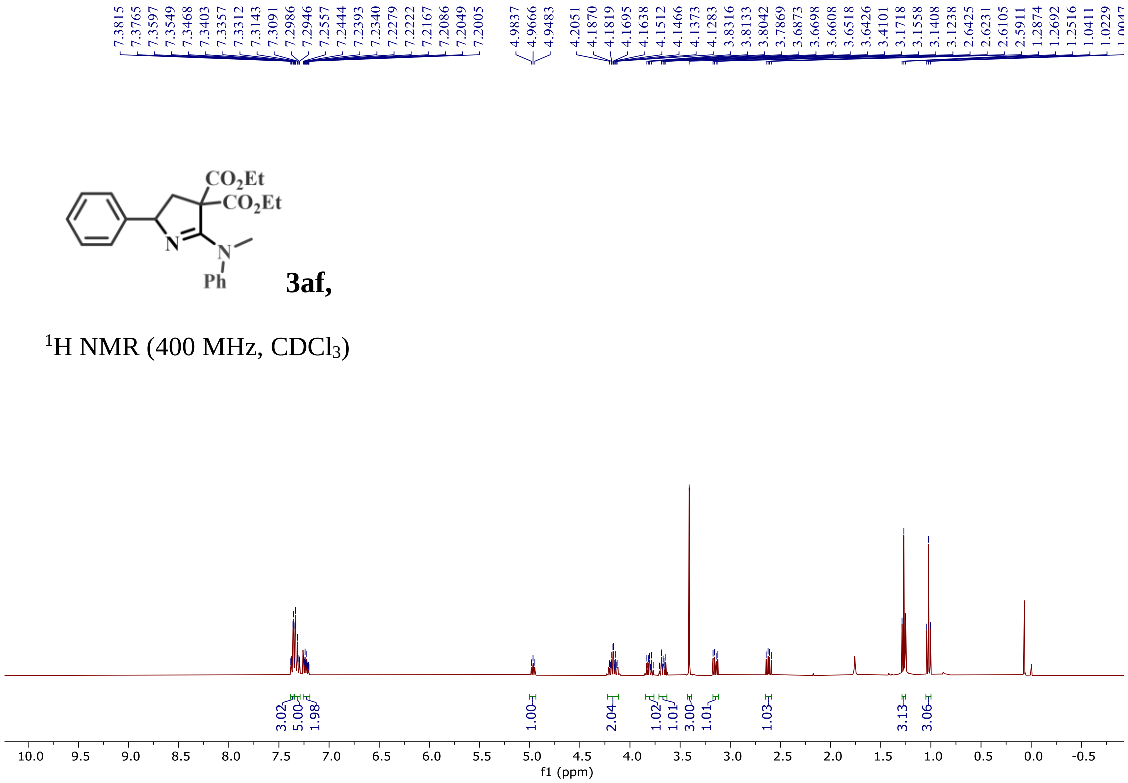

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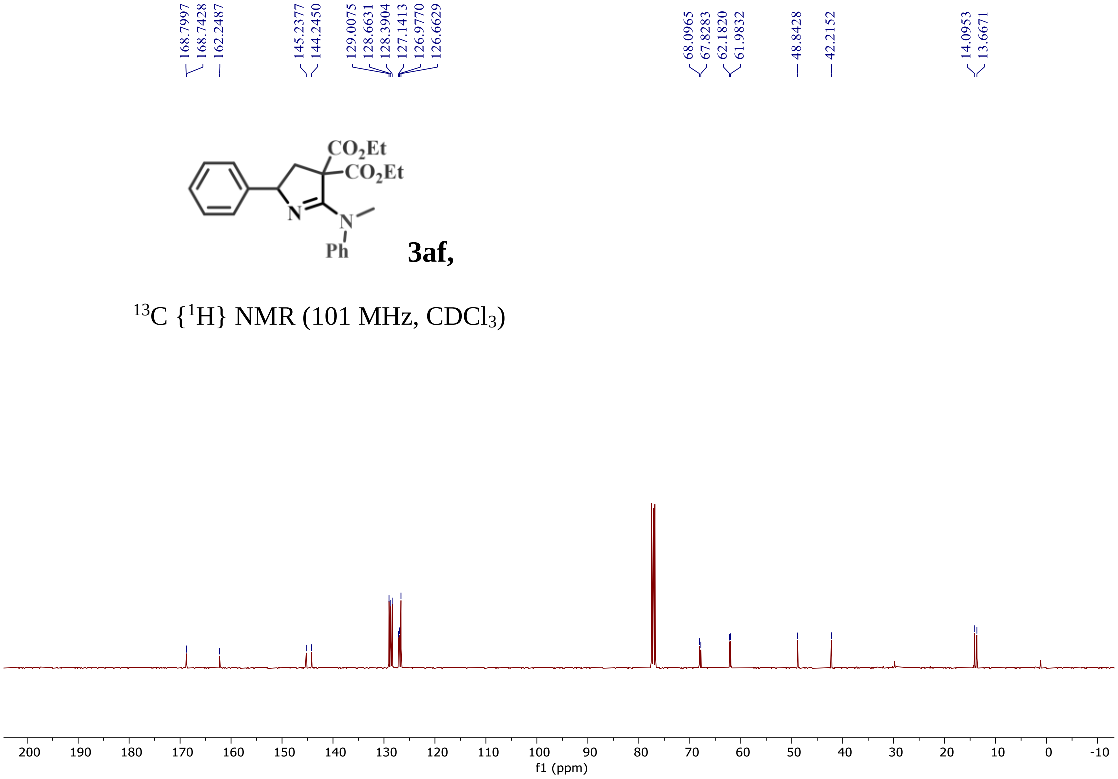

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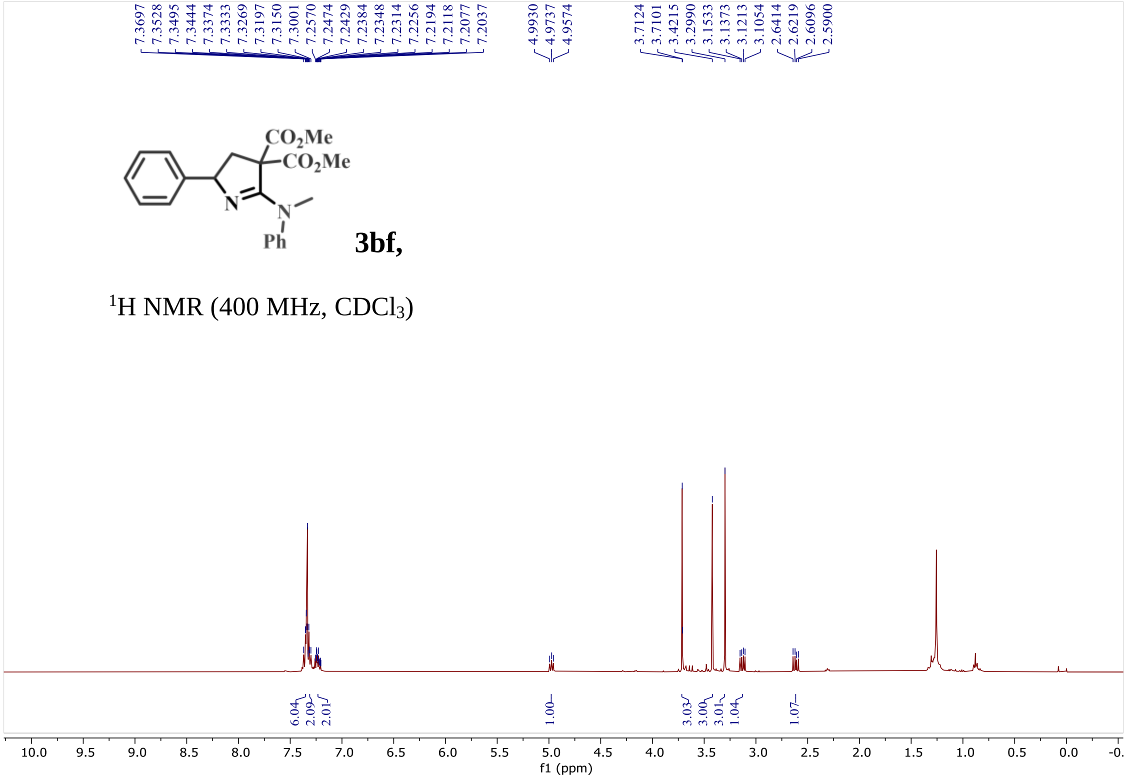

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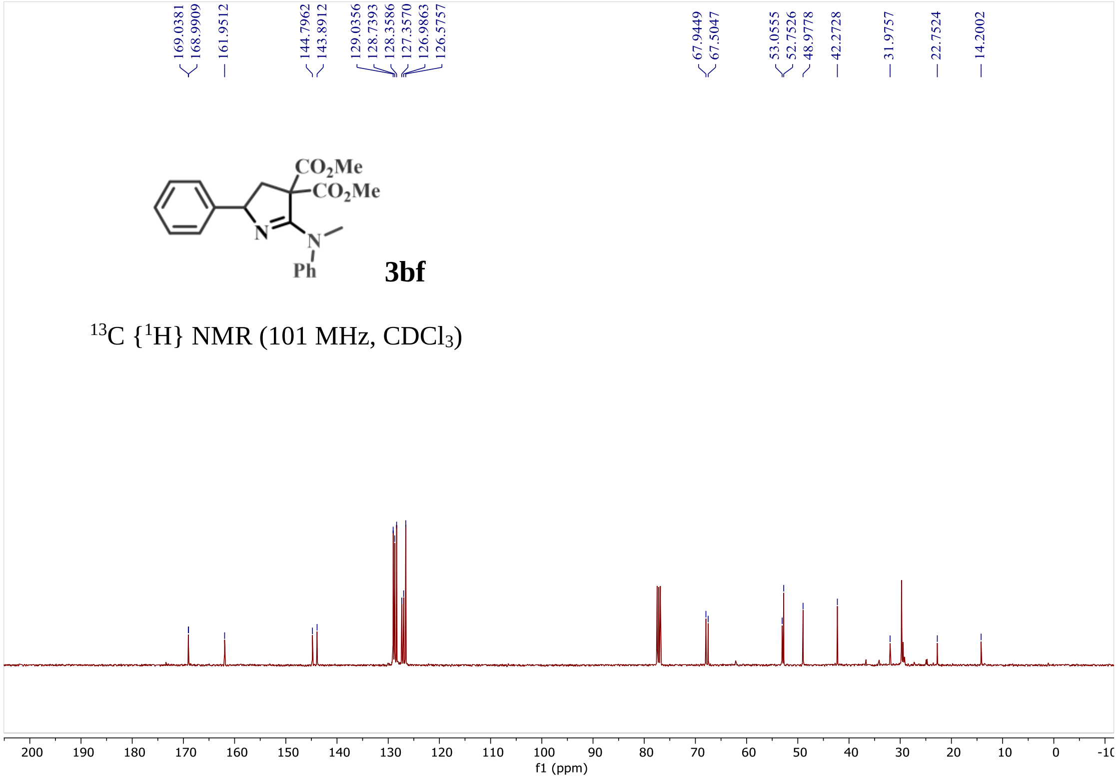

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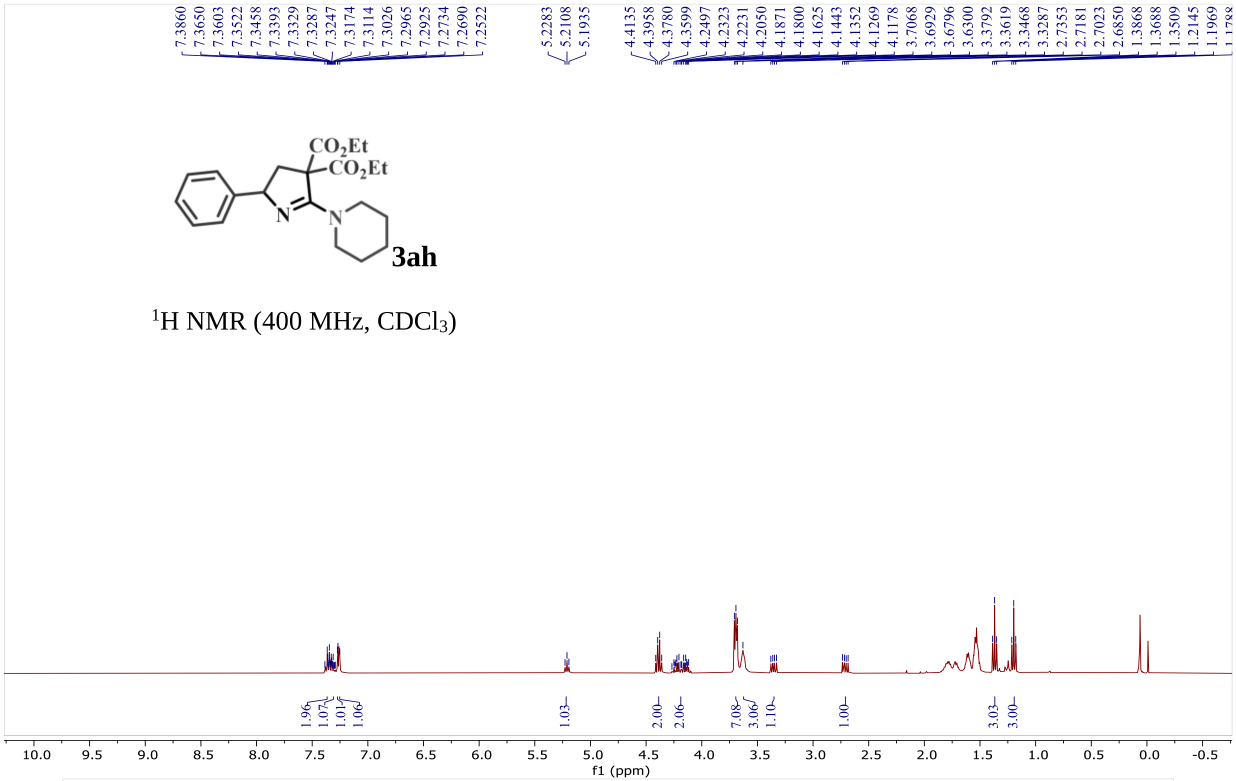

3ah

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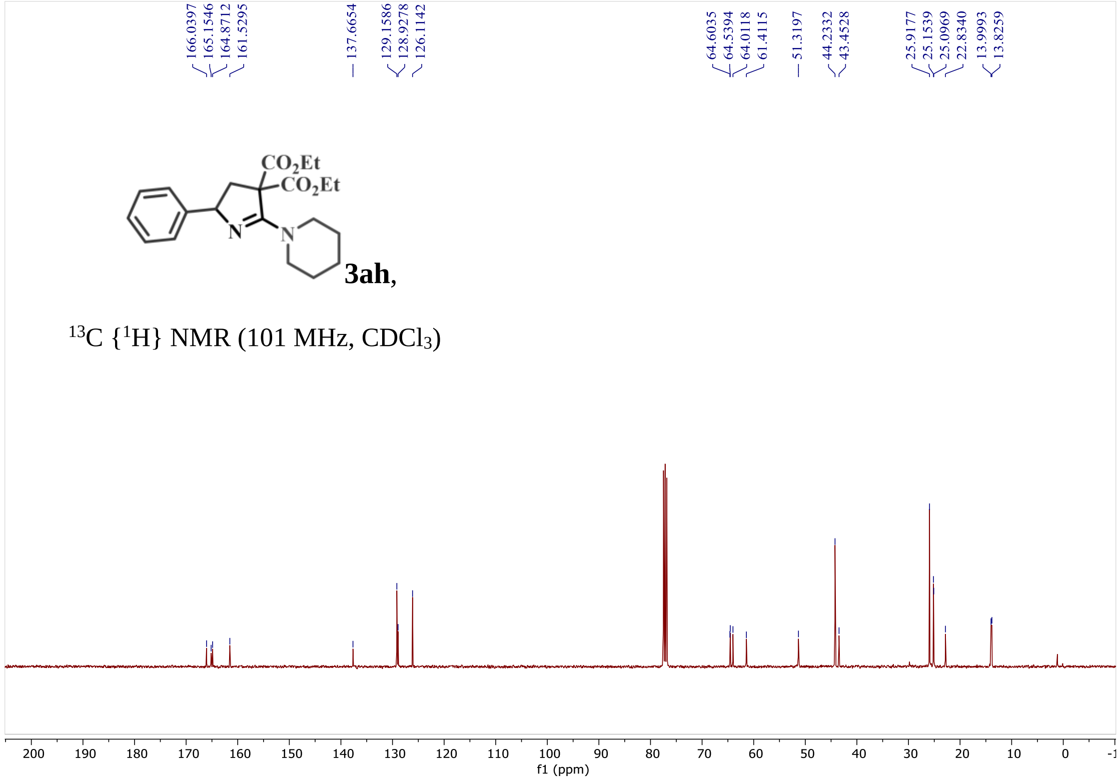
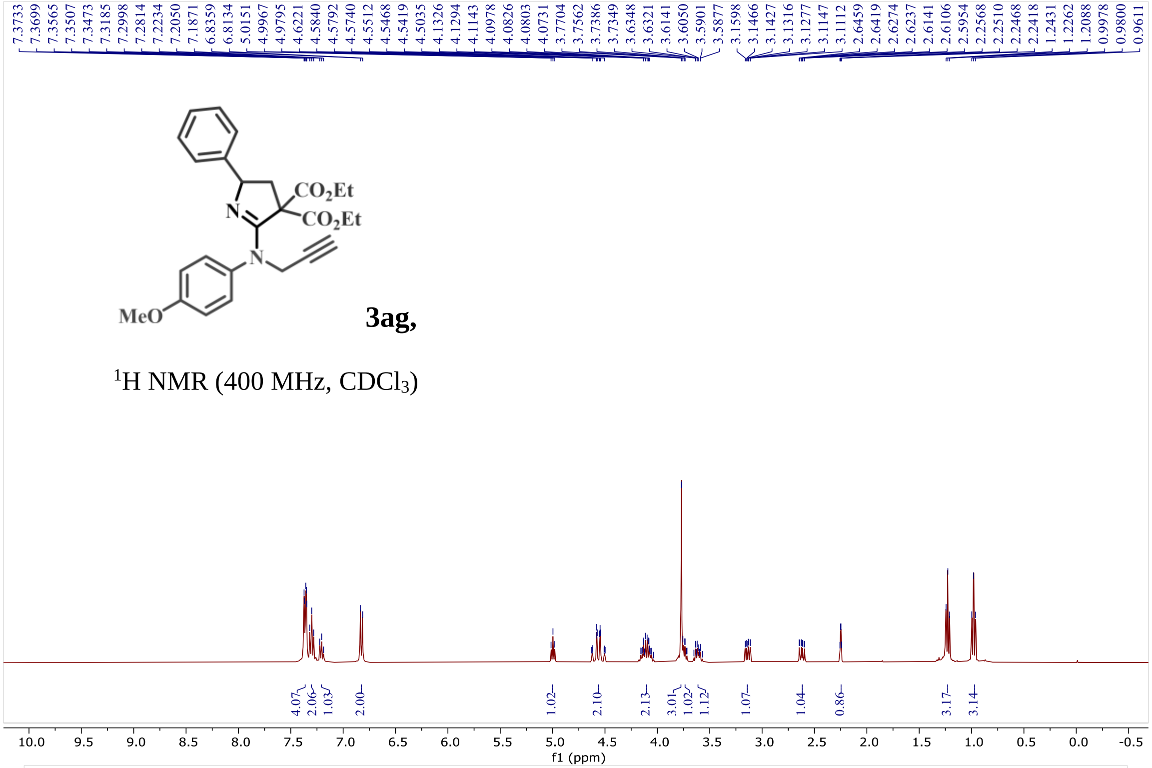


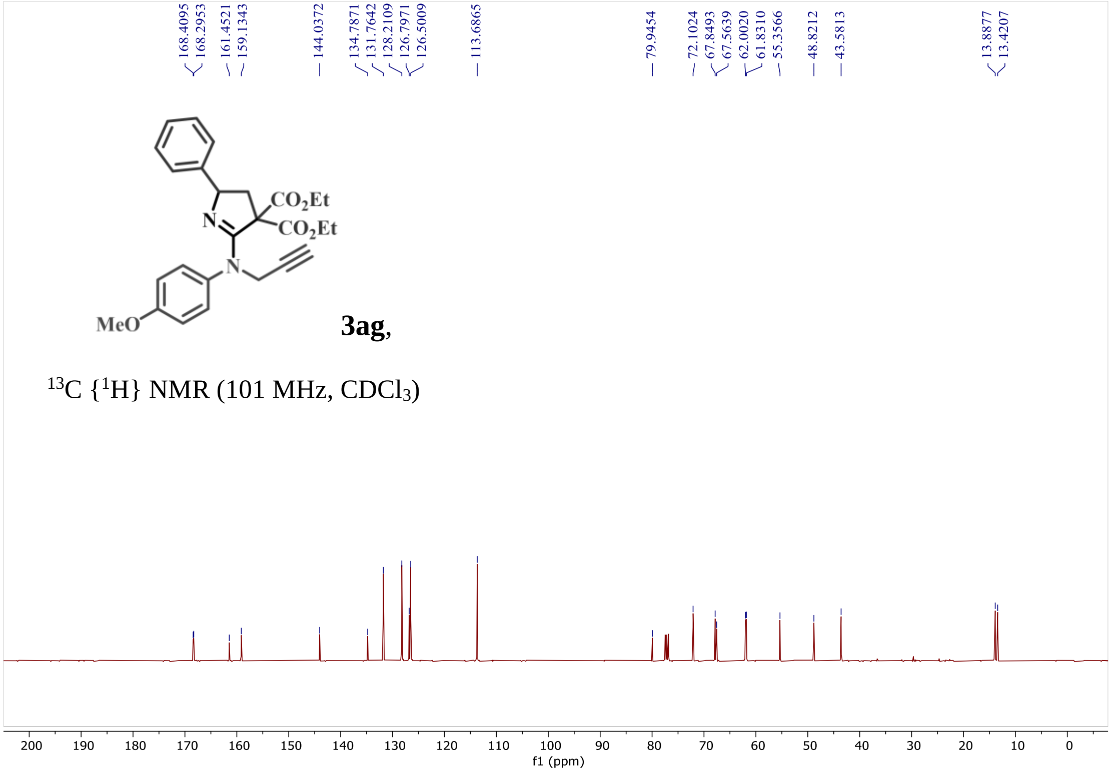
3ah,

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)



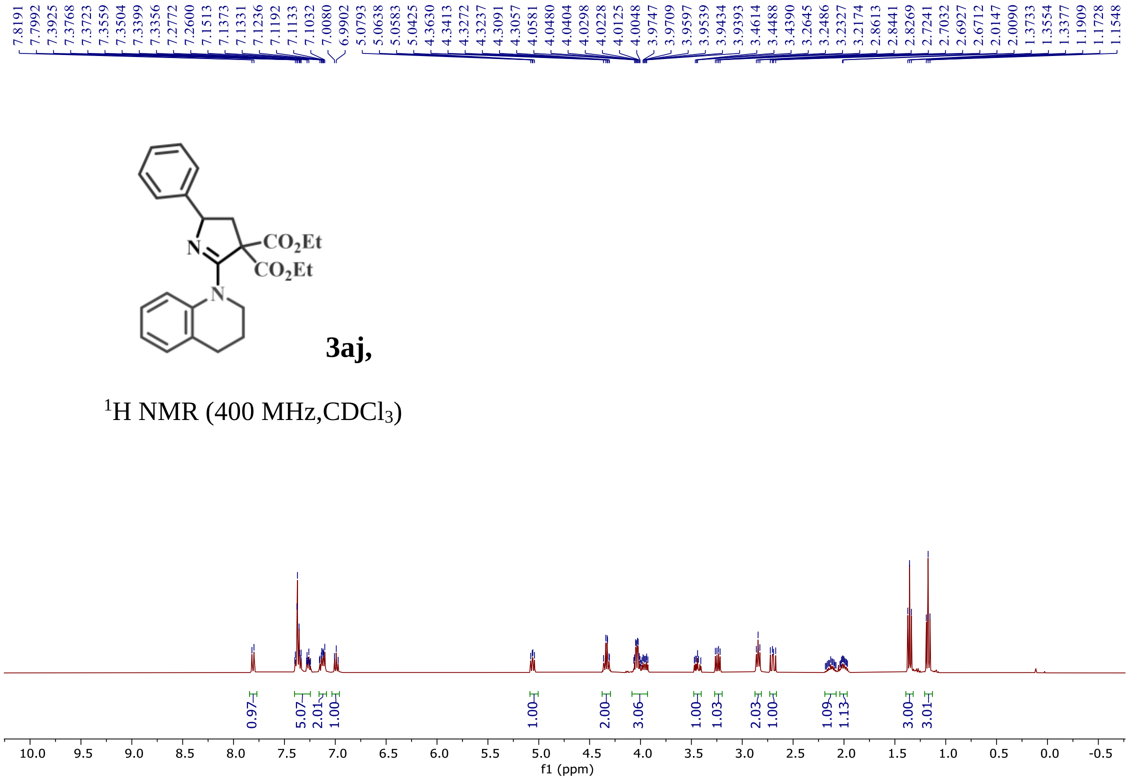
3ag,

^{1}H NMR (400 MHz, CDCl$_3$)



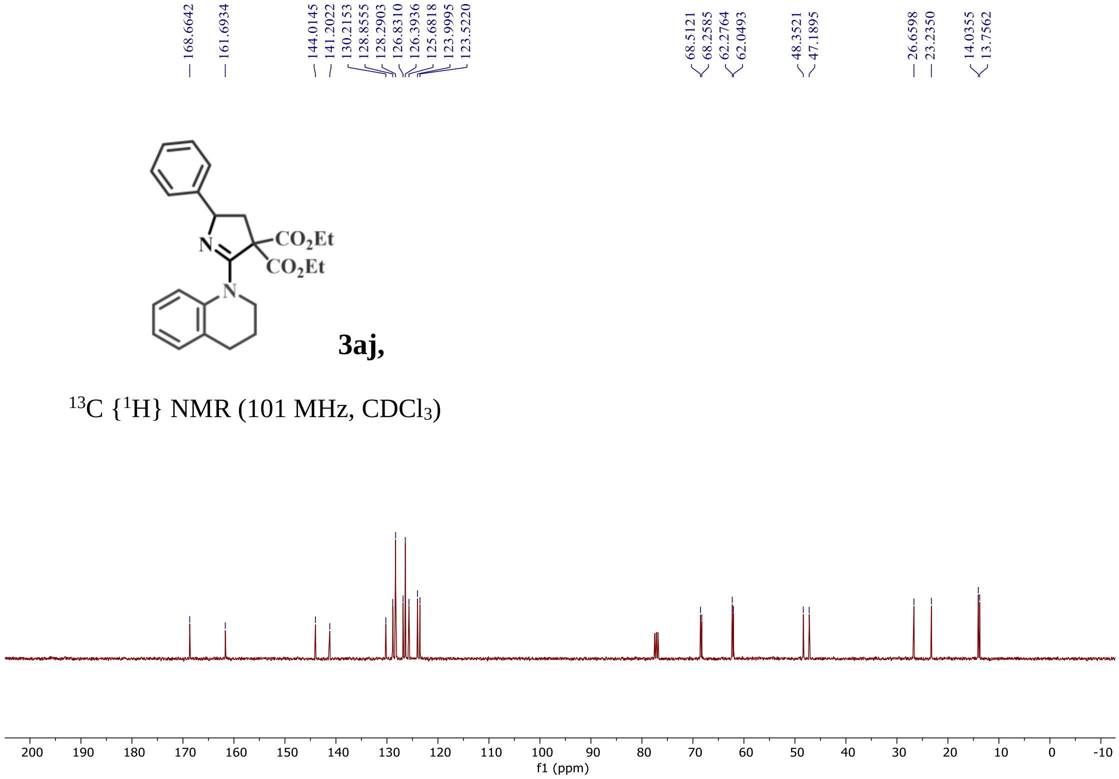
3ag,

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)



3aj,

^{1}H NMR (400 MHz,CDCl$_3$)



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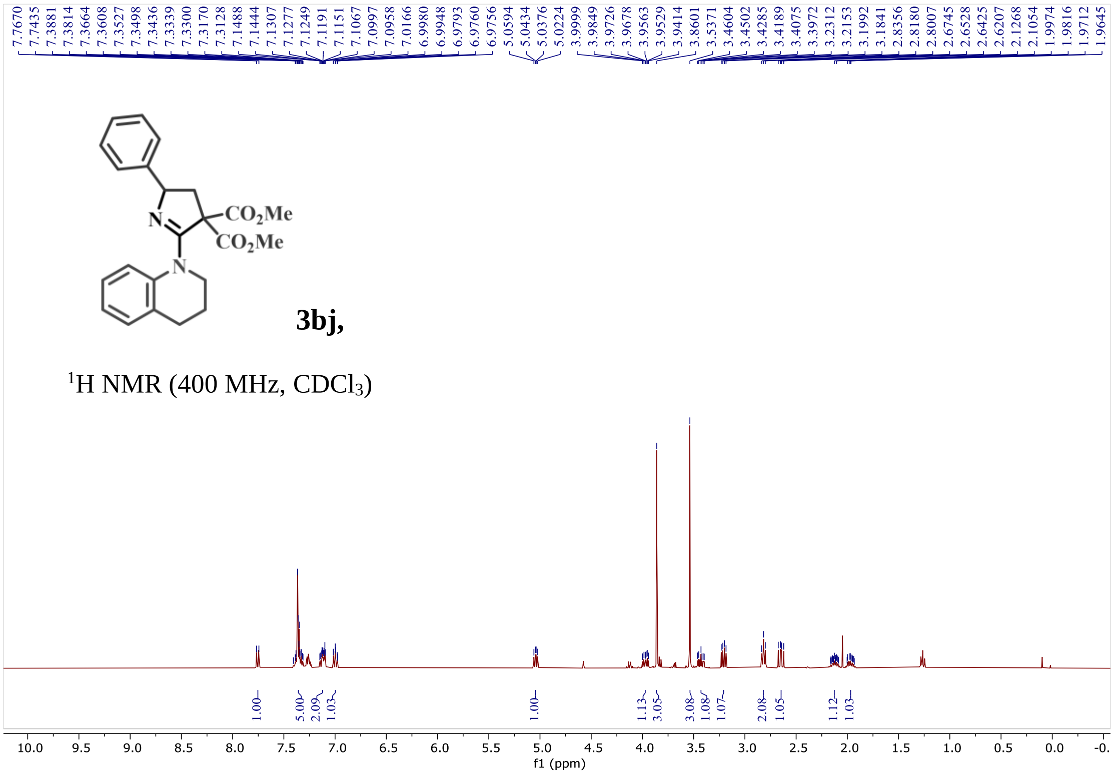
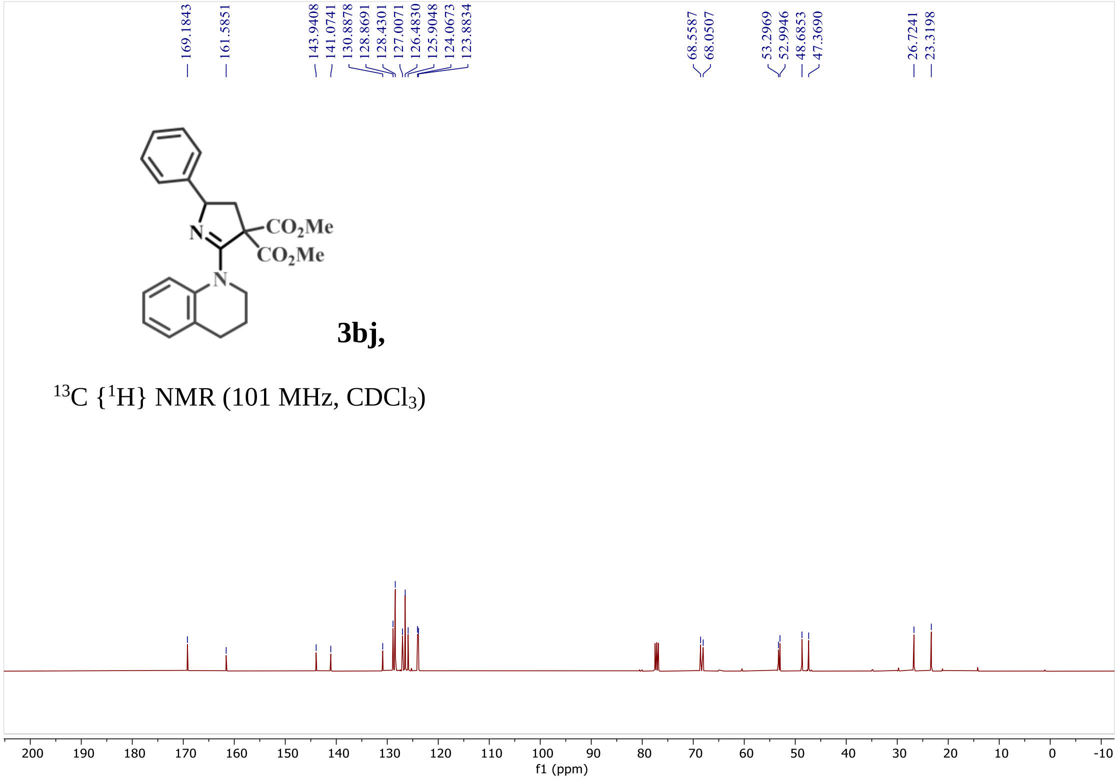
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)



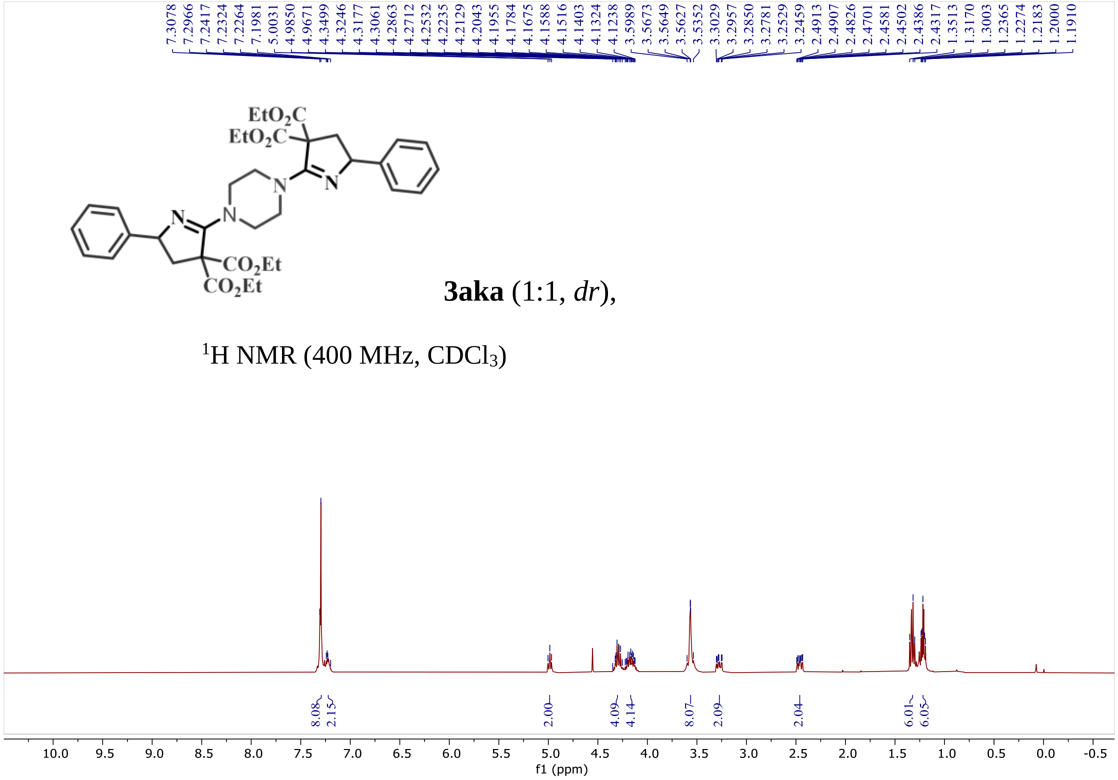
3bj,

^1H NMR (400 MHz, $CDCl_3$)



3bj,

^{13}C {^1H} NMR (101 MHz, $CDCl_3$)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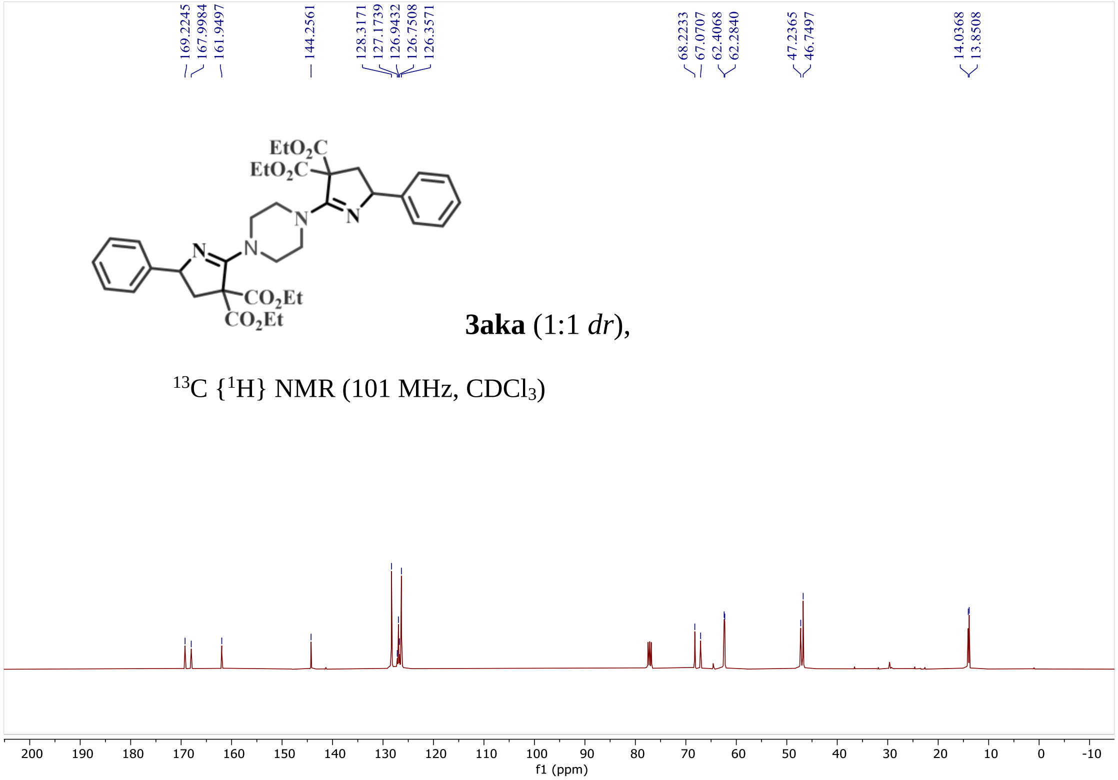
7.2966
7.2417
7.2324
7.2264
7.1981
5.0031
4.9850
4.9671
4.3499
4.3246
4.3177
4.3061
4.2863
4.2712
4.2532
4.2235
4.2129
4.2043
4.1955
4.1784
4.1675
4.1588
4.1516
4.1403
4.1324
4.1238
3.5989
3.5673
3.5649
3.5627
3.5352
3.3029
3.2957
3.2850
3.2781
3.2529
3.2459
2.4913
2.4907
2.4826
2.4701
2.4581
2.4502
2.4386
2.4317
1.3513
1.3170
1.3003
1.2365
1.2274
1.2183
1.2000
1.1910
EtO2C
EtO2C
N
N
N
N
CO2Et
CO2Et
3aka (1:1, dr),
1H NMR (400 MHz, CDCl3)
8.08
2.15
2.00
4.09
4.14
8.07
2.09
2.04
6.01
6.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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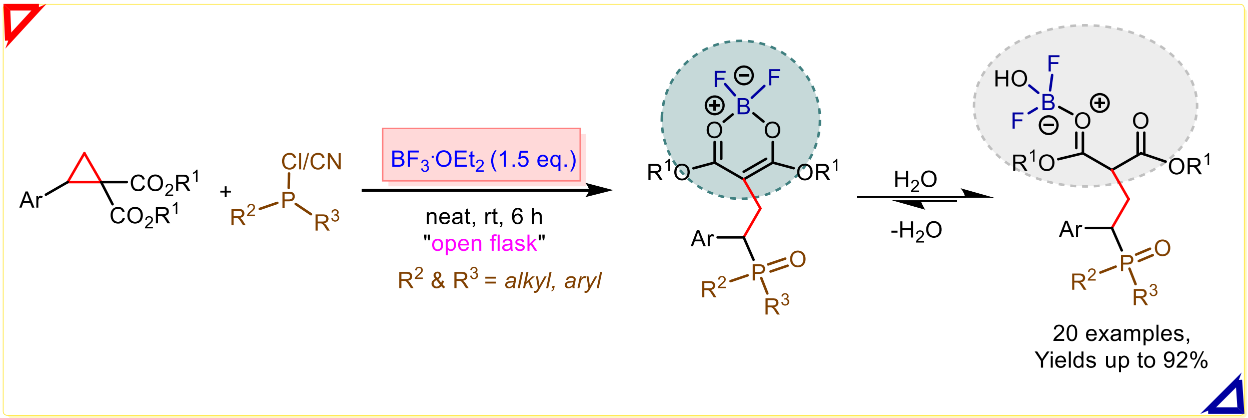
161.9497
144.2561
128.3171
127.1739
126.9432
126.7508
126.3571
68.2233
67.0707
62.4068
62.2840
47.2365
46.7497
14.0368
13.8508
EtO2C
EtO2C
N
N
N
N
CO2Et
CO2Et
3aka (1:1 dr),
13C {1H} NMR (101 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Chapter 4

Nucleophilic Ring Opening of DACs through Umpolung Reactivity of Organochlorophosphines: Phosphine Oxide Functionalized Boron Pendanted Compounds



✓ New C-P Bond Formation ✓ Metal-, Base Additive Free Approach ✓ Multi Component Reaction ✓ Detailed Mechanistic Study ✓ Mild Reaction Conditions ✓ Broad Functional Group Tolerance

4.1 Introduction

Modern chemistry demands breaking the dogma of using transition metals and promotes the usage of readily available, cheaper, and non-toxic earth-abundant elements. The p-block elements are naturally abundant and support the greener approach as they are environmentally benign and show diverse applications.[1] In particular, organic compounds possessing phosphorous functionality tend to impart various biological, pharmacological, and toxicological activities as shown in Figure (4.1)[2] Similarly, many organoboron compounds possess low-lying LUMO and exhibit a bathochromic shift in absorption and emission spectra. As a result, such organoboron compounds have very high demand in material science e.g., O, O-chelated boron diketonates are extensively used as organic luminophores in dye-sensitized solar cells (DSSCs), molecular sensing, and organic light-emitting diodes (OLEDs) (Figure 4.1)[3] Donor-acceptor cyclopropanes (DACs) are widely used as versatile strain building blocks and have gained high interest due to their easy accessibility and high reactivities. Due to high ring strain and synergically cooperative vicinally substituted donor and acceptor functionality, they react towards nucleophiles and dipolarophiles in the presence of Lewis or Brønsted acid catalysts.[4] DACs' ability to undergo nucleophilic ring-opening reactions can be considered as homo Michael-addition type reactivity resulting in one of the powerful blueprints for implanting molecular complexity and allowing these protocols to be used in the synthesis of natural products.[5] In this regard, C-, N-, O- and S- nucleophiles have been well explored,[6] however, there exists a notable dearth of approaches that demonstrate the construction of the C-P bond through the cyclopropane ring-opening process in the presence of P-nucleophile. Frustrated Lewis Pairs (FLPs) can be a reliable alternative to transition metal catalysts as they exhibit impressive chemical behaviour that allows them to activate small molecules effectively. It is important to mention that there is only one report available where FLP is used for the ring opening of cyclopropanes. in 2010, Douglas et al. illustrated the reactions of cyclopropanes with phosphine/borane-based FLP which resulted in the formation of phosphonium borate zwitterionic derivatives. However, the strategy offered a limited substrate scope (Scheme 4.1).[7] Later, a novel chemical reaction was developed that used an inorganic base to assist a domino reaction involving acyl cyclopropanes and organophosphites. This reaction has been proven to be a reliable method for producing functionalized enol phosphates (Scheme 4.2).[8] Recently, Wu and coworkers demonstrated 2-

fluoroallylation of secondary phosphine oxides with high Z selectivity by utilizing gem-difluorocyclopropanes and palladium-based catalysis (Scheme 4.3).[9] Over time, several methodologies have been developed that illustrate the electrophilic nature of chlorodiarylphosphine (Ar_2PCl),[10] its nucleophilic reactivity is unknown. As a part of our ongoing studies on the reactivities of donor-acceptor ring opening of DACs in the presence of $BF_3{\cdot}OEt_2$ to afford modular cyclopropanes,[11] we have unveiled a new set of FLP systems where the acids and bases are not strictly frustrated and exhibit the capability to facilitate the ring opening of DACs. The umpolung behavior of chlorophosphines and cyanophosphines can be elucidated by analyzing their Electron Density Surface Potential (ESP) plots and Mulliken charges. These analyses clearly indicate that phosphorous exhibits electrophilic behavior, while the chlorine and nitrogen centers display nucleophilic character (Figure 4.2). Furthermore, it is observed that the compounds are obtained in their tautomeric forms (keto and enol forms). The majority of the derivatives are found in keto form, as determined by NMR analysis, while enolic form is characterized through single crystal X-ray analysis. These findings are consistent with the results obtained by Prof. Schmidt in 2011, for barbituric acid.[12]

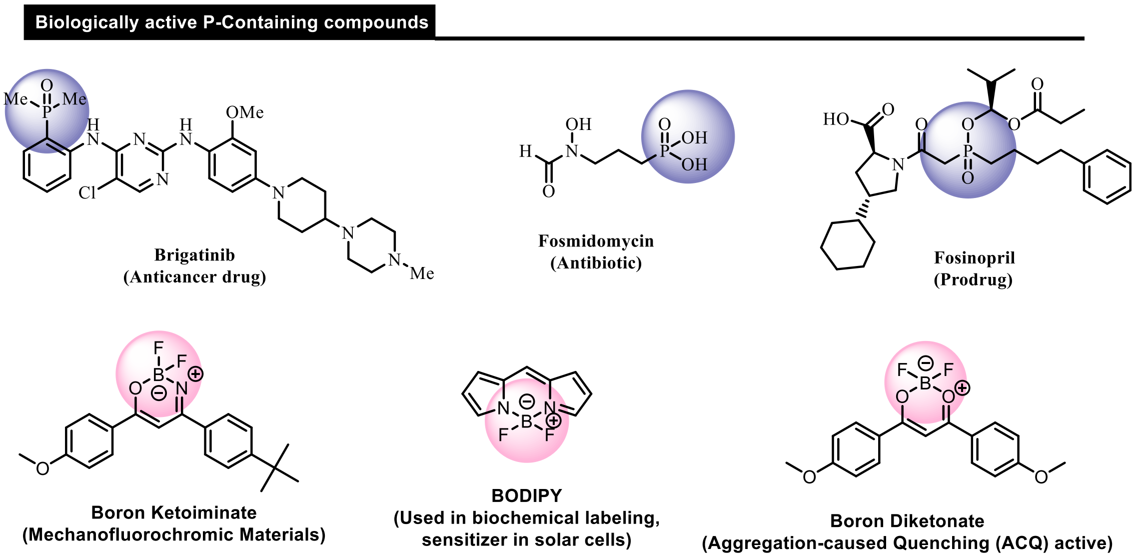
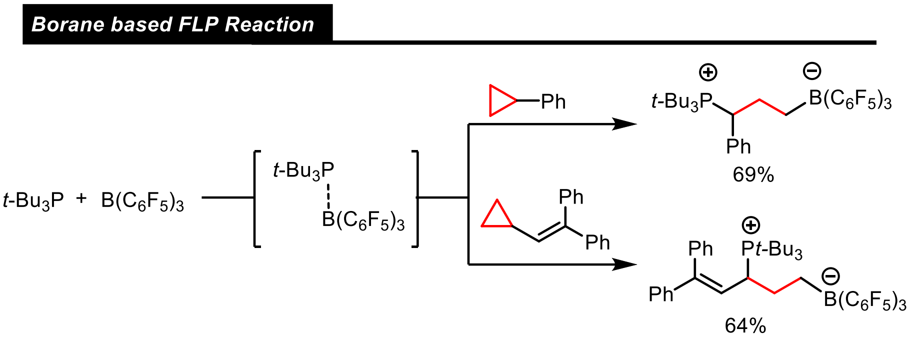
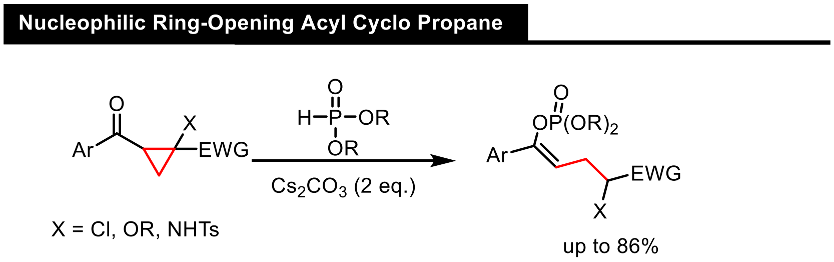


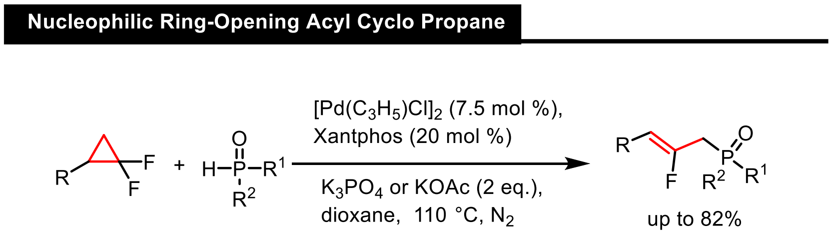
Figure 4.1 Selected examples of Biologically active *P* & B-containing drugs.



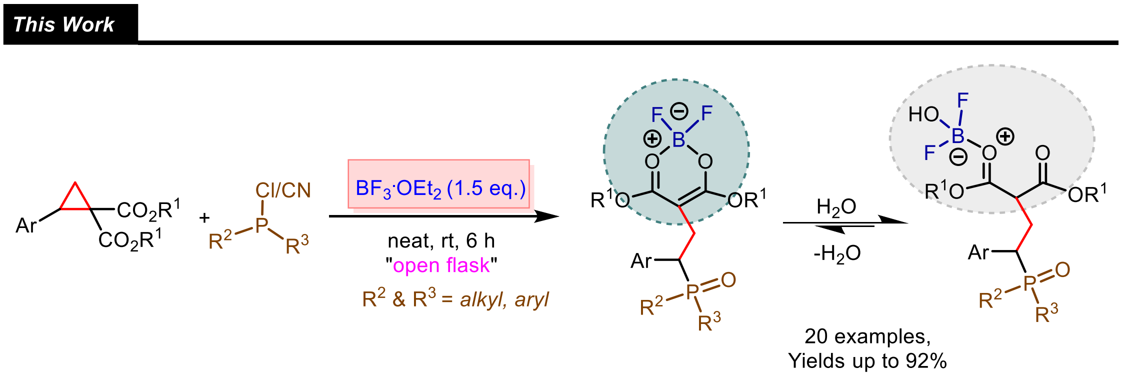
Scheme 4.1 Doulgas protocol for the reaction by using FLP.



Scheme 4.2 Wu's work on the Nucleophilic ring opening reactions.



Scheme 4.3 Yuefa Gon's protocol for the construction of enol phosphates derivatives.

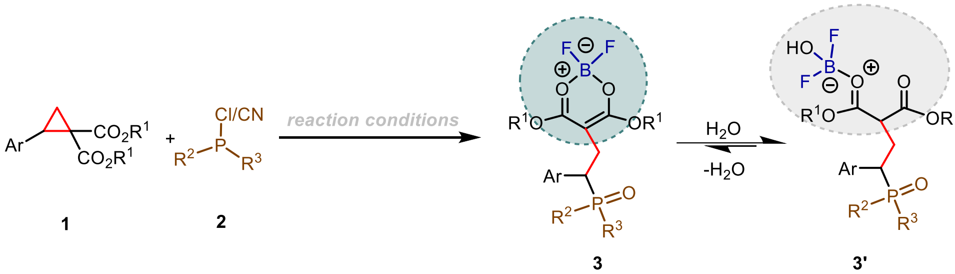


Scheme 4.4 Our Hypothesis for the construction of Phosphine Oxide Functionalized Boron-Pendanted Compounds derivatives.

4.2 Results and Discussions

At the outset of our primary investigations to optimize the reaction, we chose phenyl 1,1-diethyl cyclopropane **1a** and diphenylphosphine chloride **2a** as the model substrates (Table 4.1). Initially, reactions were carried out using post-transition metal chlorides like $SnCl_4$ and $InCl_3$ as Lewis acid catalysts in DCE at 60 ^oC. The former didn't produce any product and the starting materials were recovered while the latter resulted in the formation of **4aa** in 60% yield (Table 4.1, entries 1-2). Motivated by the initial scrutiny, strong Lewis acids like $TiCl_4$, MgI_2, and $Cu(OTf)_3$ were examined for the reaction conversion, however, no promising results could be achieved (Table 4.1, entries 3-5). On the other hand, utilization of $Sc(OTf)_3$ proved beneficial for the transformation and increased the yield of **4aa** to 72% (Table 4.1, entry 6). In the course of finding better reaction conditions to obtain the desired product in good yield and taking the lead from our previous work, we performed the above-mentioned reaction in the presence of $BF_3{\cdot}OEt_2$, (0.2 eq.) and interestingly we afforded a highly polar product **3aa** (Table 4.1, entry 7). The resulting compound was characterized by virtue of its spectral data and it was noticed that $BF_3{\cdot}OEt_2$ participated as a reactant in the reaction and resulted in the formation of O, O-chelated boron diester compound. However, the product was obtained with very low yield. Increasing the promoter loading did not lead to the complete consumption of all the starting materials (Table 4.1, entry 8). Screening the reaction in other organic solvents like toluene, THF, $CHCl_3$, DCM, DCE provided a certain increment in the product yield (Table 4.1, entries 9-13). Further tuning the reaction conditions in terms of promoter loading and solvent-free conditions substantially increased the yield of product **3aa** (Table 4.1, entry 14). Next, we attempted the reaction in the presence of the catalytic as well as stoichiometric amount of Tris(pentafluorophenyl)borane (BCF), unfortunately, both attempts failed to provide the desired product (Table 4.1, entries 15-16).

Table 4.1 Optimization of Reaction Conditions^a



Entry	Promoter (eq.)	Solvent	Temp. (^{o}C)	Time (h)	**3aa** Yield[b]	**4aa** Yield[b]
1	$SnCl_4$ (0.1 eq.)	DCE	60	24 h	-	-
2	$InCl_3$ (0.1 eq.)	DCE	60	20 h	-	60%
3	$TiCl_4$ (0.1 eq.)	DCE	60	24 h	-	-
4	MgI_2 (0.1 eq.)	DCE	60	24 h	-	-
5	$Cu(OTf)_2$ (0.1eq.)	DCE	60	24 h	-	-
6	$Sc(OTf)_3$ (0.1eq.)	DCE	60	20 h	-	72%
7	$BF_3 \cdot OEt_2$ (0.2 eq.)	DCE	60	16 h	20%	-
8	$BF_3 \cdot OEt_2$ (1 eq.)	DCE	60	24 h	51%	-
9	$BF_3 \cdot OEt_2$ (2 eq.)	Toluene	60	24 h	55%	-
10	$BF_3 \cdot OEt_2$ (2 eq.)	THF	60	20 h	67%	-
11	$BF_3 \cdot OEt_2$ (2 eq.)	$CHCl_3$	60	15 h	72%	-
12	$BF_3 \cdot OEt_2$ (2 eq.)	DCM	30	15 h	72%	-
13	$BF_3 \cdot OEt_2$ (2 eq.)	DCE	25	6 h	78%	-
14[c]	$BF_3 \cdot OEt_2$ (1.5 eq.)	-	25	6 h	92%	-

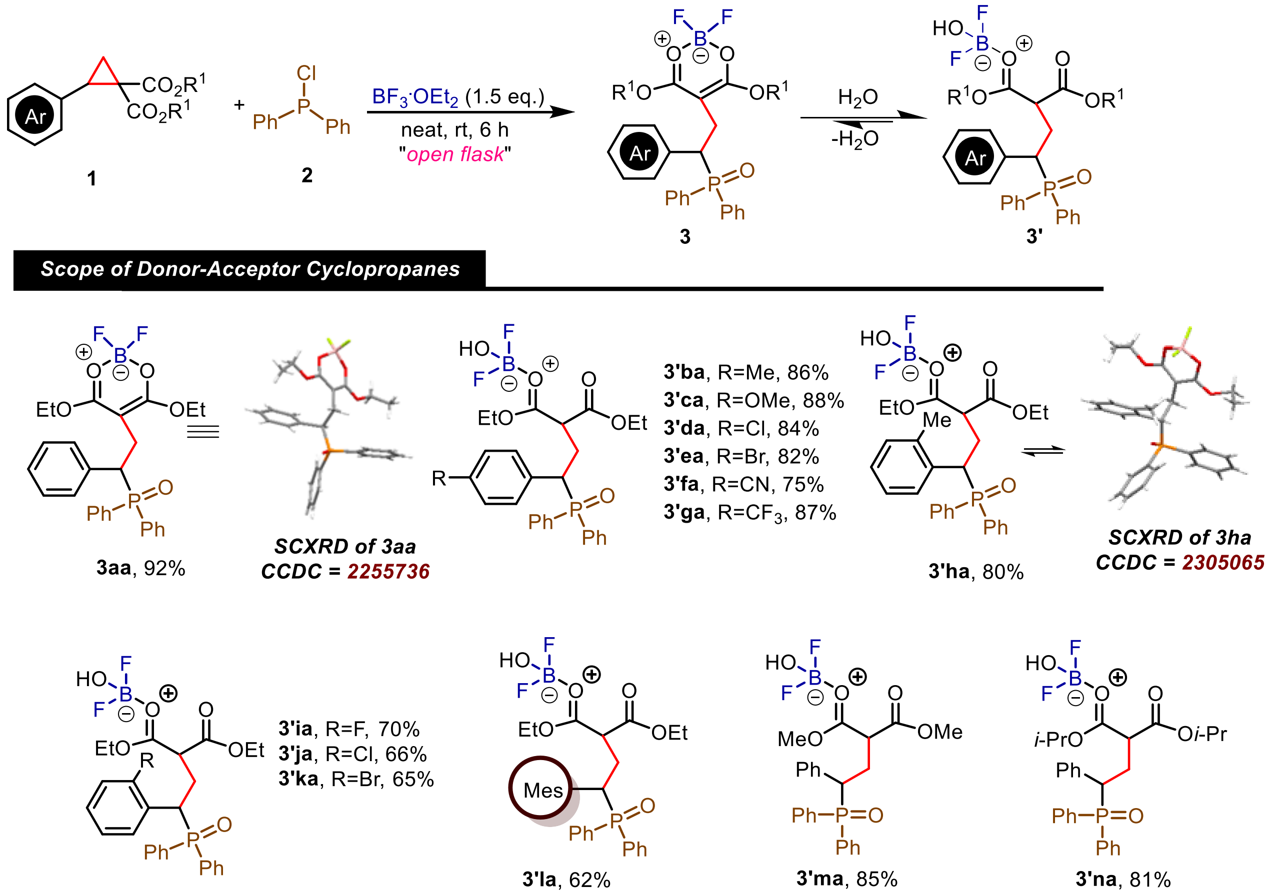
15	BCF (0.2 eq.)	DCE	60	24 h	-	-
16	BCF (2 eq.)	DCE	60	24 h	-	-

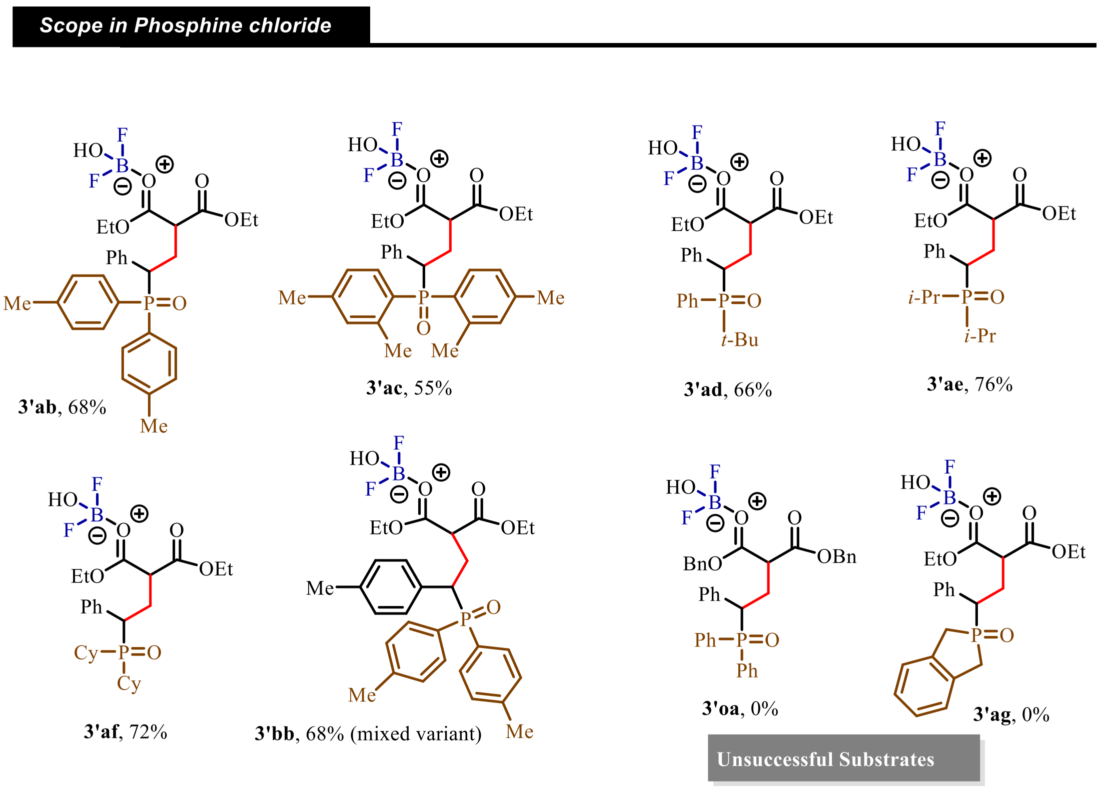
Scheme 4.5 [a]Reaction conditions: **1a** (0.11 mmol, 1 eq.), **2a** (0.132 mmol, 1.2 eq.), solvent (2 mL), N_2 atmosphere. [b]Isolated yield. [c]Reaction performed in an open flask without solvent.

After the optimized conditions were obtained for the formation of **3aa**, the scope for this transition metal-free three-component reaction was tested (Scheme 4.5). Besides, **3aa**, all other derivatives were isolated in a more stable tautomeric form, i.e. keto form as shown through the DFT calculations. At first, we started investigating the diversity of arene groups that were linked to the D-A cyclopropanes under the optimized reaction conditions. Our analysis revealed that all types of arenes, including EDGs, EWGs, and electronically hindered groups, were compatible with the above-said reaction conditions and delivered the expected compounds **3**' in good to excellent yields. For example, substrates with *para*-substituted electron-rich functional groups *viz*., -Me, -OMe were well tolerated under optimal reaction conditions and yielded **3'ba** and **3'ca** in 86% and 88% yield, respectively. Moreover, the halogen-substituted (-Cl, -Br) and electron-withdrawing group substituted (-CN, -CF_3) aryl moieties on DACs were found suitable candidates for the transformation and furnished the respective products **3'da** and **3'ga** in good yields. Further, cyclopropanes with *ortho*-decorated arenes also participated in this conversion, providing the desired products **3'ha-3'ka** in good to moderate yields. The cyclopropane-bearing mesitylene group delivered the targeted product **3'la** in 62% yield. Gratifyingly, changing the ester moieties in DACs also worked well in the reactions and furnished **3'ma** and **3'na** in 85% and 81% yield, respectively.

After surveying the variation in the DACs **1**, we turned our attention to examining the scope of various chlorophosphines **2** for the said reaction. To our pleasure, both symmetrical and unsymmetrical chlorophosphines were found suitable under the optimized reaction conditions. Initially, functionalized diarylchlorophosphines were evaluated and afforded the products **3'ab**, and **3'ac** in good yields. Mono-alkyl-substituted chlorophosphines also participated in the synthetic transformation, providing the desired product **3’ad** in 66% yield. Moreover, substrates like chlorodiisopropyl phosphine and chlorodicyclohexyl phosphine were smoothly converted to the expected products **3’ae** and **3’af** under the optimized reaction conditions. Mixed variant *viz*. **3’bb** was also successfully obtained in 68% yield. Unfortunately, **3’oa** and **3’ag** were not obtained under the optimized reaction conditions.

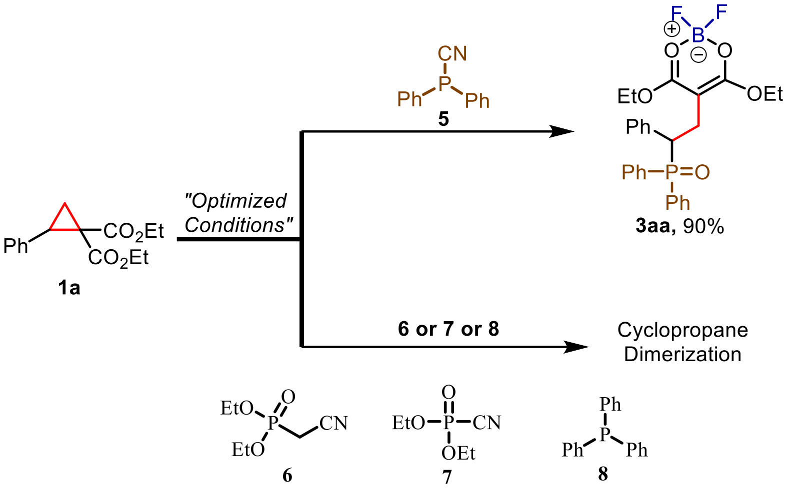
The structure of **3aa** and **3ha** was unambiguously determined using a single crystal X-ray analysis CCDC No. 2255736 and 2305065.





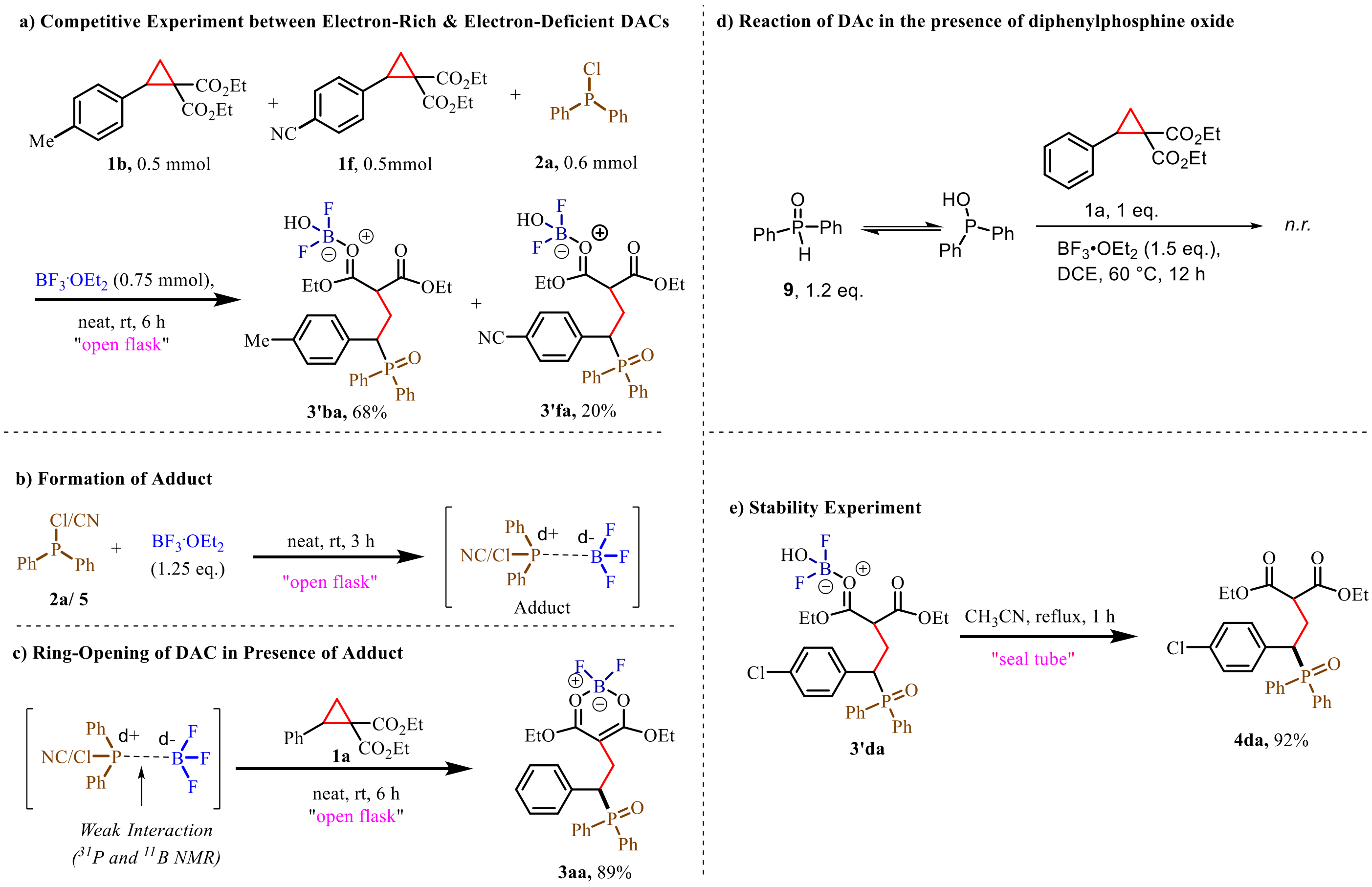
Scheme 4.5 ^{a}Reaction conditions for Substrate Scope: **1a** (0.11 mmol, 1 eq.), **2a** (0.132 mmol, 1.2 eq.), solvent (2 mL), N_2 atmosphere. ^{b}Isolated yield. ^{c}Reaction performed in an open flask without solvent.

To check the broader reaction scope, donor-acceptor cyclopropane **1a** was treated with diphenylphosphanecarbonitrile **5** (Scheme 4.6). To our surprise, it was found that the cyanide group acted as a leaving group and a nucleophilic attack occurred from the P-centre of compound **5**. This is contrary to the results obtained by our group from the reaction of aryl thio/selenocyanates with DACs in the presence of SnCl4.[14] Next, we went to explore the reaction of **1a** with diethyl(cyanomethyl)phosphonate **6**, diethyl phosphorocyanidate **7**, and triphenyl phosphine **8**, however, they were found inactive in the transformation and cyclopropane dimerization was observed.



Scheme 4.6 the reaction scope, donor-acceptor cyclopropane with phosphine-based carbonitrile.

To gain insight into the phosphorylation reaction on DACs, several mechanistic studies were carried out as illustrated in (Scheme 4.7). Firstly, substitution effects on arenes were checked by conducting a competitive experiment between **1b** and **1f** under the standard reaction conditions (Scheme 4.7a) and it was observed that electron-rich aryl substituted DAC **1b** got preference over electron-poor DAC **1f** and furnished **3'ba** as major product. Next, an attempt was initiated to react **2a** with $BF_3{\cdot}OEt_2$ (1.25 eq.), and the formation of an adduct was observed (Scheme 4.7b), which was characterized through ^{31}P and ^{11}B NMR spectroscopy as depicted in the SI file. The phosphine/boron-based Lewis acid-base pair was allowed to react with DAC 1a resulting in the formation of the O-,O-chelated boron complex, **3aa** (Scheme 4.7c). From here it can be inferred that the reaction could undergo in the presence of in situ generated as well as separately formed adduct. Next, we examined the reaction of diphenylphosphine oxide, **9** with DAC, **1a** and interestingly, no product formation was observed in the reaction mixture (Scheme 4.7d). An experiment was conducted to illustrate the stability of the newly developed compounds and it was found that -BF2 moiety was eliminated on heating at a relatively high temperature and formed **4da** (Scheme 4.7e).



Scheme 4.7a competitive experiment between electron-rich and electron-deficient DACs.

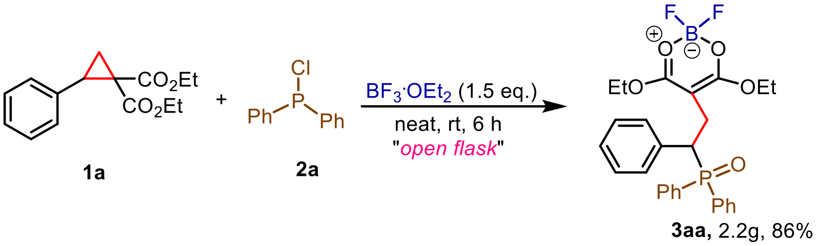
Scheme 4.7b Formation of adduct.

Scheme 4.7c Ring-Opening of DACs in presence of adduct.

Scheme 4.7d Reactions of DACs in the presence of Diphenylphosphine oxide.

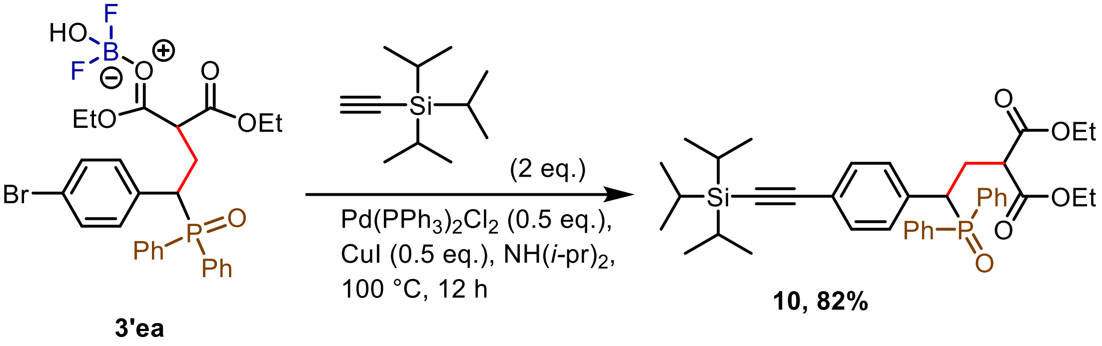
Scheme 4.7e Stability experiment.

Further, to investigate the practicality and viability of our methodology, a gram-scale synthesis of the targeted product **3aa** was performed as depicted in (Scheme 4.8). In this context, the reaction of **1a** and **2a** was carried out at a 5 mmol scale and the product **3aa** was obtained in 86% yield (2.20 g).



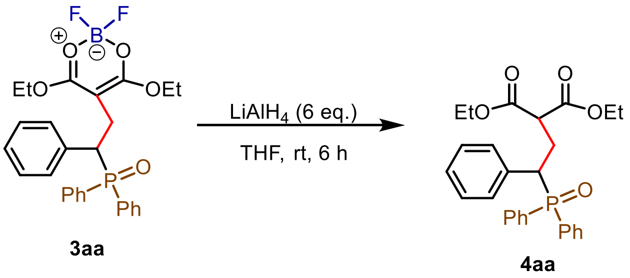
Scheme 4.8 Gram scale synthesis of **3aa.**^{a} ^{a}Reaction conditions: **1a** (5 mmol, 1 eq.), **2a** (6 mmol, 1.2 eq.) BF$_3$·OEt$_2$ (7 mmol, 1.5 eq.).

For the post-functionalization of **3'ea**, we planned a Sonagashira coupling reaction of **3'ea** with ethynyltriisopropylsilane, and compound **10** was furnished in 82% yield (Scheme 4.9).



Scheme 4.9. Synthetic transformations for compound **3'ea**.

Next, we endeavored to reduce the ester of **3aa** by employing LAH. Regrettably, this procedure only resulted in the removal of BF$_2$, leaving the ester groups intact, even in the presence of an excess amount of LAH. (Scheme 4.10).



Scheme 4.10. Synthetic transformations for **3aa**.

To gain deeper mechanistic insight, density functional theory (DFT) calculation for PR_2Cl-based nucleophilic ring-opening reaction of DACs was conducted at B3LYP/6-31G(d)[14,15] level of theory in Gaussian 16 software.[16,17] The Gibbs free energy profile for the nucleophilic reaction is shown in (figure 4.2). A zwitterionic complex (Int-A) is produced by coordinating DAC with $BF_3.PMe_2Cl$. This step has a Gibbs free energy uphill of 7.36 kcal/mol. In the resulting intermediate (Int-A), PMe_2Cl performs an SN_2 nucleophilic attack on the cyclopropane moiety, resulting in the formation of intermediate, Int-B. The activation barrier for this step is 14.03 kcal/mol. After that, a water molecule forms a hydrogen bond with the fluorine of BF_3 (Int-C). The water molecule then steadily moves towards the positively charged P-center *via* C_TS, which leads to the removal of an HCl molecule and the formation of Int-D. This step is -19.81 kcal/mol downhill of C_TS. In structure Int-D, one of the -F atoms of the BF_3 moiety forms a hydrogen bond with the OH group attached to the P-center. Finally, the bond distance between fluorine and hydrogen decreases, and HF is eliminated via D_TS forming product **3.** The final step is -14.24 kcal/mol downhill from D_TS. Its keto form (3') is found to be more stable, lying -3.28 kcal/mol below product 3. The overall reaction has the activation barrier of 18.60 kcal/mol (w.r.t. reference 1 and 2) and is found to be exothermic with products 3 and 3' lying 13.05 kcal/mol and 16.34 kcal/mol below reference. According to the Gibbs free energy profile, the SN_2 ring-opening C-C bond cleavage step is found to be the rate-determining step (RDS). DFT-computed Gibbs free energy reaction profiles (in kcal/mol at 298 K and 1 atm pressure) for $BF_3{\cdot}OEt_2$ promoted synthesis of phosphine oxide functionalized boron pendant diester compounds using dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1**) and $BF_3{\cdot}PMe_2Cl$ (**2**).

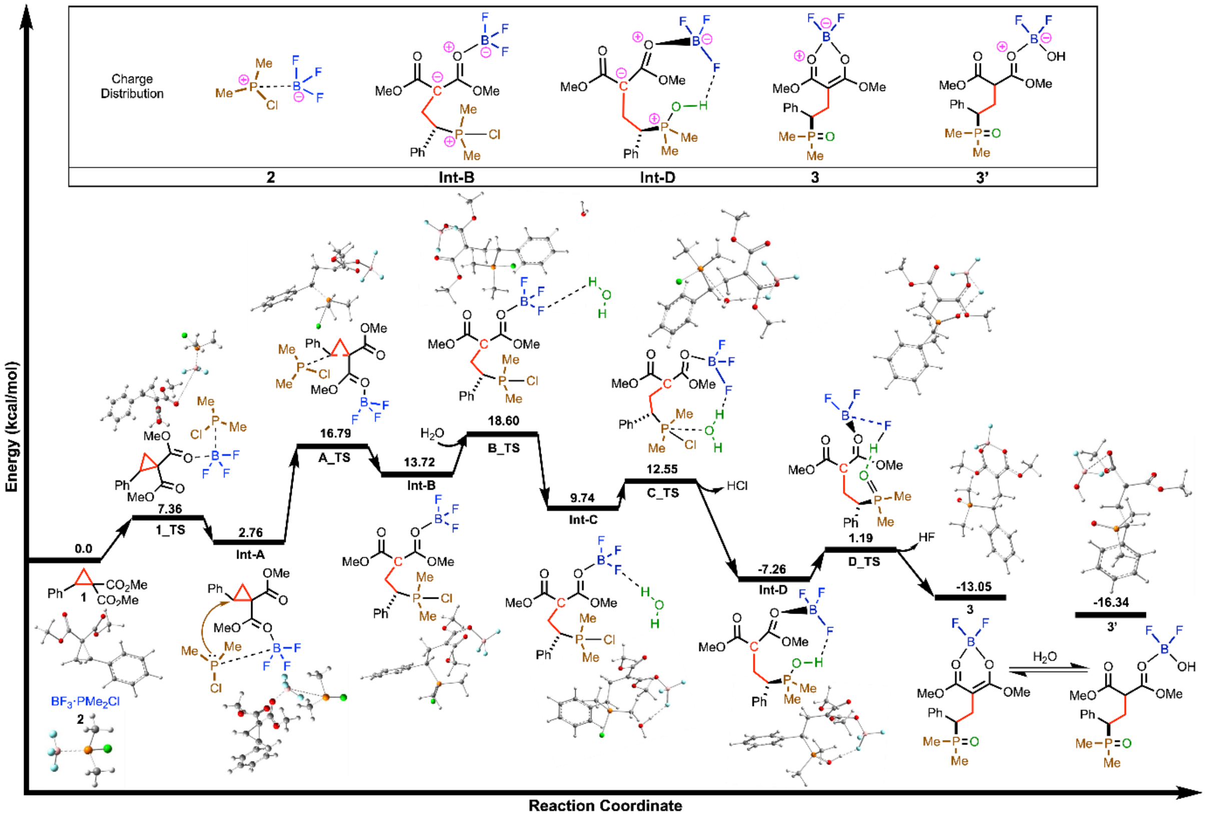


Figure 4.2 DFT Calculations.

4.3 Conclusions

In conclusion, we have disclosed a metal- and additive-free $BF_3{\cdot}OEt_2$ promoted one-pot three-component reaction involving the reactions of phosphine chlorides/cyanide with DACs. This user-friendly phosphine chloride-triggered nucleophilic ring-opening of DACs offers the formation of boron pendant diester complexes in the two tautomeric forms. Selective product formation, mild reaction conditions, and broad substrate scope are the key features of the developed protocol. The practicality of the protocol was demonstrated through the gram scale synthesis and the combined experimental and theoretical studies portray a clear mechanistic pathway.

4.4 Experimental Section

Unless otherwise noted, all reactions were performed on a Schlenk vacuum line or in a glovebox using oven-dried glassware and were stirred with teflon-coated magnetic stirring bars. All the chemicals and reagents were purchased from commercial suppliers Sigma Aldrich, GLR Innovations, BLD Pharma, Spectrochem and used without further purification. Solvents were dried and stored over molecular sieves under argon atmosphere prior to use. All work-up and purification procedures were done with reagent grade solvents in air atmosphere. Reaction temperatures above 25 °C refer to temperatures of an aluminum heating block or a silicon oil bath, which were controlled by an electronic temperature modulator from Hedolph. Thin-layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using E. Merck silica gel 60 (100–200 mesh).). ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded in $CDCl_3$ and d_6-DMSO, on JEOL JNM-ECS spectrometer at operating frequencies of 400 MHz {^{1}H} or 101 MHz {^{13}C} as indicated in the individual spectrum. Chemical shifts (δ) are given in parts per million (ppm) relative to residual solvent ($CDCl_3$, δ= 7.26 for ^{1}H NMR and 77.16 for ^{13}C NMR, d_6-DMSO: δ = 2.50 for ^{1}H NMR and δ = 39.52 for ^{13}C NMR) and coupling constants (*J*) in Hz. Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, q for quartet, dt for doublet of triplet and m for multiplet. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) methods on waters mass spectrometer (XEVO G2-XS QTOF). The data collection for single crystal X-ray was performed at a 298 K on a CMOS based Bruker D8 Venture PHOTON 100 diffractometer equipped with INCOATEC micro-focus source with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA.

4.4.1 Preparation of Starting Materials

Synthesis of cyclopropane-1,1-diester derivatives, 1[1]:

Trimethyl sulfoxonium iodide (TMSOI) (7.5 mmol, 1.5 eq.) was added drop-wise into the suspension of sodium hydride (NaH) (60% suspension in mineral oil, 7.5 mmol, 1.5 eq.) and dry dimethyl sulfoxide (DMSO) under nitrogen atmosphere. **Caution!** Reaction of trimethylsulfoxonium iodide with sodium hydride is exothermic (evolution of H_2 and heat). So, the suspension was maintained at 0 ºC before adding trimethyl sulfoxonium iodide. After 15-20 minutes of vigorous stirring, a solution of alkylidene-malonate or arylidene-malonate, **i** (5 mmol, 1.0 eq.) in DMSO was added, and the mixture was allowed to warm up to room temperature. Upon completion of the reaction, as monitored by TLC, crushed ice was added to the crude solution and extracted with diethyl ether. The combined organic layer was washed once with brine, dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents to afford product **1**

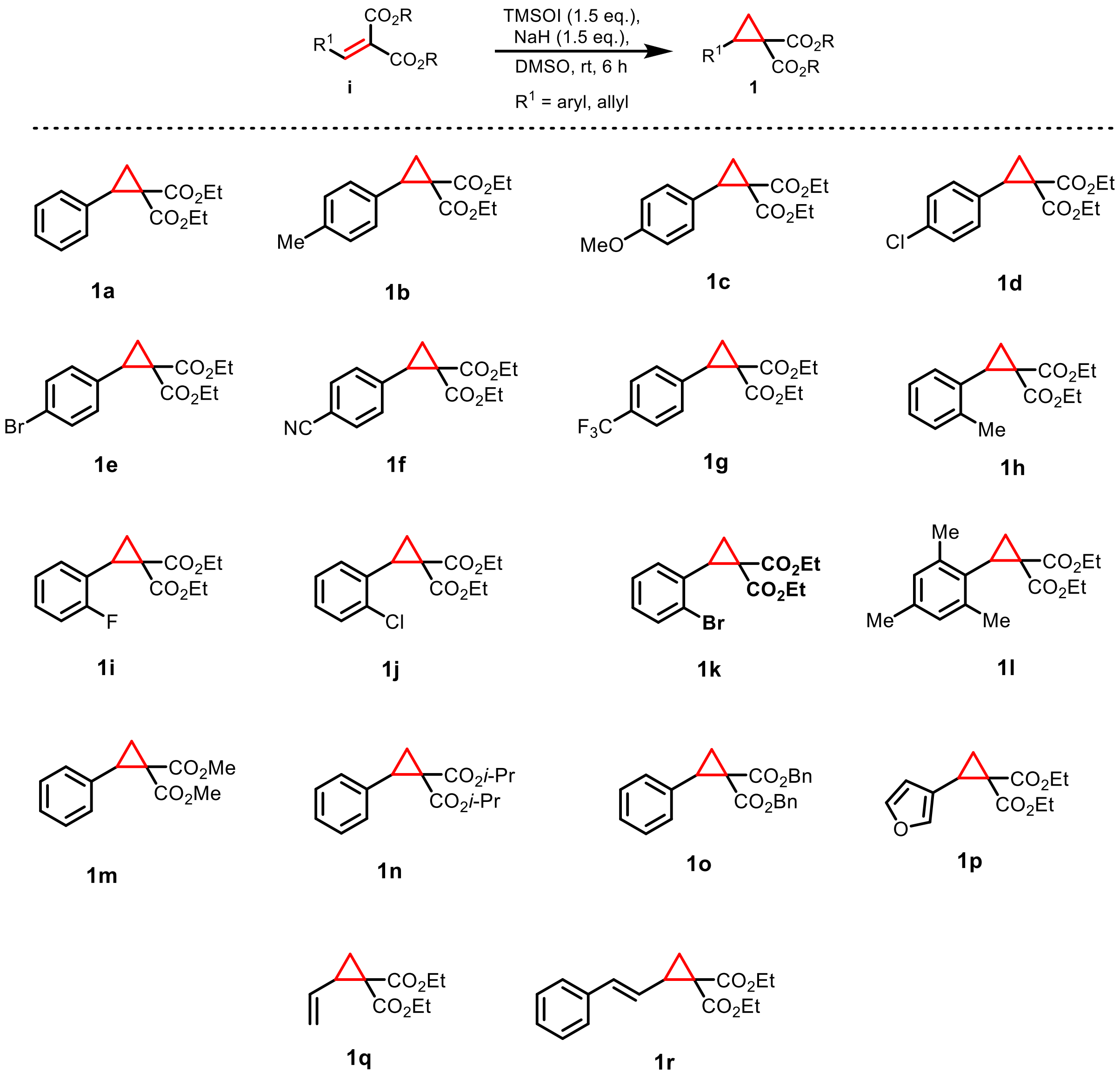


Figure 4.3 used Donor-Acceptor Cyclopropane.

Synthesis of PPh$_2$CN, 5[2]**:** Chlorodiphenylphosphine **2a** (1 mmol, 1.1eq.) was dissolved in DCM and Silver Cyanide (1 mmol, 1eq.) was added at room temperature. After that, the reaction mixture was stirred for 6 h at room temperature. Upon completion of the reaction, as monitored by TLC, the crude solution was extracted with DCM. The combined organic layer was washed once with brine, dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents to deliver the product **5**.

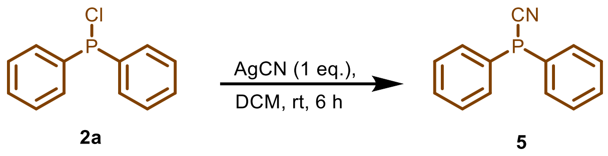


Figure 4.4 Used diphenylphosphanecarbonitrile.

Organochlorophosphines used in the transformation (commercial purchased)

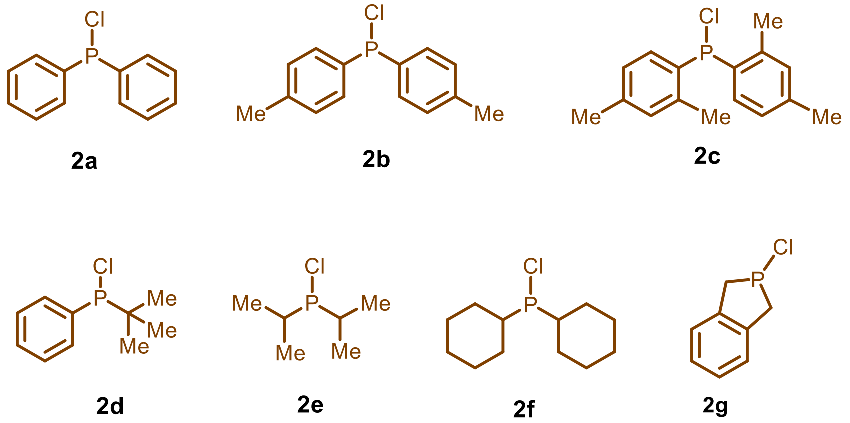


Figure 4.5 Used Organochlorophosphines.

4.4.2 General Procedures

General procedure for the synthesis of difluoro-dioxaborinin-diphenylphosphine oxide derivatives, 3 or 3' (GP-1)

An oven-dried Schlenk tube was charged with magnetic bar, organochlorophsophine **2** (0.132 mmol, 1.2 eq.), and D-A cyclopropane **1** (0.11 mmol, 1 eq.). Then, $BF_3{\cdot}OEt_2$ (0.16 mmol, 1.5 eq.) was added to the reaction mixture at room temperature and stirred the reaction for 6 h under open aerobic conditions. Upon completion of the reaction, as monitored by TLC, the reaction mixture was quenched with $NaHCO_3$ and extracted with DCM. The combined organics were dried over sodium sulfate and concentrated under reduced pressure. The crude product was further purified through silica gel chromatography using hexane and ethyl acetate as the eluent to afford the product **3** or **3'**.

Synthesis of diethyl 2-(2-(diphenylphosphoryl)-2-phenylethyl)malonate derivative, 4aa:

A schlenk tube was equipped with a magnetic bar and N_2 gas was purged. Afterward, diphenylphosphine chloride **2a** (0.132 mmol, 1.2 eq.) and 2mL anhydrous DCE solvent were added, followed by **1a** (0.11 mmol, 1 eq.). After 2 minutes of stirring, $Sc(OTf)_3$ (5 mg, 0.011 mmol, 0.1 eq.) was added and allowed to stir at 60 °C for 20 hours. Upon completion, the reaction mixture was extracted with DCM and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents to afford product **4aa** in 72% yield.

Synthesis of Diethyl 2-(2-(4-chlorophenyl)-2-(diphenylphosphoryl)ethyl)malonate, 4da

In a sealed tube, (1-(4-chlorophenyl)-2-(4,6-diethoxy-2,2-difluoro-2H-1λ^3,3,2λ^4-dioxaborinin-5-yl)ethyl) diphenylphosphine oxide **3'da** (1 mmol, 1.0 eq.) in ACN (1 mL) was added and allowed to stir at 120 ^{o}C for 1 hour. Upon completion of the reaction, as monitored by TLC, the crude solution was extracted with DCM. The combined organic layers were washed once with brine and dried over sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents to afford the product **4da** in 92% yield.

Gram scale synthesis of 3aa

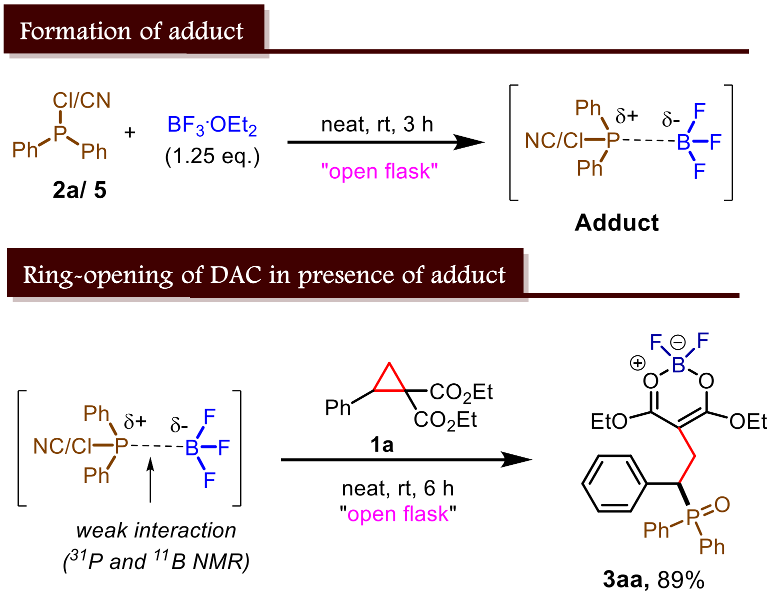
In a round bottomed flask, cyclopropane diester **1a** (5 mmol, 1 eq.) and chlorodiphenylphosphine **2a (**6 mmol, 1.2 eq.) were dissolved in DCE solvent under an open atmosphere at room temperature. After 2 minutes of stirring, $BF_3 \cdot OEt_2$ (7.5 mmol, 1.5 eq.) was added and allowed to stir for 6 h. Upon completion of the reaction, the crude solution was extracted with DCM. The combined organic layers were washed once with brine and $NaHCO_3$ dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents

Synthesis of diethyl 2-(2-(diphenylphosphoryl)-2-(4-((triisopropylsilyl) ethynyl)phenyl)ethyl) malonate, 10

To a schlenk tube, compound **3'ea** (0.11 mmol, 1 eq.), Bis(triphenylphosphine)palladium(II) dichloride (0.055 mmol, 0.5 eq.), copper iodide (0.055 mmol, 0.5 eq.) and triisopropylsilyl)acetylene (0.22 mmol, 2 eq.) were added together in diisopropylamine (1 mL) under N_2 atmosphere. Then the mixture was stirred at 100 ^{o}C for 12 h. Upon completion of the reaction, the crude solution was extracted with EtOAc. The combined organic layers were washed once with brine, dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents to afford the final product **10** in 82% yield.

4.4.3 Mechanistic Studies

$Ph_2(Cl/CN)PBF_3$ adduct studies



An attempt was made to react **2a** and **5** with $BF_3{\cdot}OEt_2$ at room temperature. Firstly, chlorodiphenylphosphine **2a** (0. 01 mL, 0.1 mmol, 1 eq.) was stirred with $BF_3{\cdot}OEt_2$ (0.002 mL, 0.0125 mmol, 1.25 eq.) in an open-to-air flask for 3 hours at room temperature. After three hours of stirring, progress of the reaction was analyzed through ^{11}B and ^{31}P NMR and it was compared with the ^{11}B NMR of $BF_3{\cdot}OEt_2$ and ^{31}P NMR of PPh_2Cl and the formation of an adduct was observed as shown below. The same experiment was repeated with diphenylphosphanecarbonitrile **5** (0.021 mL, 0.1 mmol, 1 eq.) and the formation of adduct was observed. Then this adduct was allowed to react with cyclopropane diester **1a** (0.002 mL, 0.083 mmol, 0.83 eq.) and after 6 hours of stirring at room temperature, reaction was complete as monitored by the TLC. Afterward, the reaction mixture was treated with $NaHCO_3$ solution, extracted with DCM, and dried over sodium sulfate. The crude product was further purified by silica gel column chromatography using hexane and ethyl acetate as eluents to afford the final product **3aa** in 89% yield.

4.4.5 Characterization data

(2-(4,6-diethoxy-2,2-difluoro-2*H*-1λ^3,3,2λ^4-dioxaborinin-5-yl)-1-phenylethyl)diphenyl phosphine oxide (3aa)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 53 mg, 92% white solid (m.p. = 108 - 110^{o}C), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.92 (m, 2H), 7.60 – 7.51 (m, 3H), 7.45 – 7.38 (m, 2H), 7.34 – 7.27 (m, 3H), 7.24 – 7.17 (m, 3H), 7.15 – 7.11 (m, 2H), 4.27 – 4.09 (m, 4H), 3.56 – 3.49 (m, 1H), 3.17 – 3.07 (m, 1H), 2.71 – 2.63 (m, 1H), 1.26 – 1.21 (m, 6H);^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.9, 135.3 (d, *J* = 5.0 Hz), 132.6 (d, *J* = 12.5 Hz), 131.9 (d, *J* = 10.7 Hz), 131.6 (d, *J* = 7.1 Hz), 131.3 (t, *J* = 8.6 Hz), 130.9 (d, *J* = 8.7 Hz), 130.2 (d, *J* = 6.2 Hz), 128.8 (d, *J* = 11.3 Hz), 128.4 (d, *J* = 13.1 Hz), 128.3, 128.1 (d, *J* = 3.8 Hz), 127.3, 65.3, 45.7 (d, *J* = 66.8 Hz), 22.6, 14.3;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.48;^{19}F NMR (376 MHz, $CDCl_3$): δ -143.29;^{31}P NMR (162 MHz, $CDCl_3$): δ 33.82;HRMS: m/z: $[M+H]^+$ -BF_2 calculated for $C_{27}H_{29}O_5P$ 465.1831; found 465.1840;IR Data: 3272, 3058, 1645,1438, 1370, 1031, 834, 799, 753, 503, 439.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-(*p*-tolyl)ethyl) diphenylphosphine oxide (3'ba)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 59 mg, 86% white solid (m.p. = 116 - 118 ^{o} C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 – 7.93 (m, 2H), 7.55 – 7.54 (m, 3H), 7.38 – 7.33 (m, 2H), 7.30 – 7.26 (m, 1H), 7.21 – 7.16 (m, 2H), 7.07 (d, *J* = 6.6 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.68 – 3.62 (m, 1H), 3.09 (dd, *J* = 11.5, 3.5 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.50 – 2.42 (m, 1H), 2.23 (s, 3H), 1.20 (t, *J* = 7.3 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H);^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.2, 169.1, 137.2, 132.8, 132.0, 131.8, 131.5 (d, *J* = 8.7 Hz), 131.3, 130.9 (d, *J* = 8.7 Hz), 130.8, 130.7 (d, *J* = 5.9 Hz), 129.8 (d, *J* = 5.6 Hz), 129.4, 128.9 (d, *J* = 11.4 Hz), 128.1 (d, *J* = 11.6 Hz), 61.5 (d, *J* = 19.8 Hz), 49.4(d, *J* = 13.3 Hz), 43.5 (d, *J* = 67.6 Hz), 28.3, 21.2, 14.2, 14.0;^{11}B NMR (128 MHz, $CDCl_3$): δ -1.75;^{19}F NMR (376 MHz,$CDCl_3$): δ -143.22;^{31}P NMR (162 MHz, $CDCl_3$): δ 33.32;HRMS: m/z: $[M+H]^+$-BF_2OH calculated for $C_{28}H_{32}O_5P$ 479.1987; found 479.1994; IR Data: 3273, 3061, 2981, 2937, 2378,1688,1545,1495,1025, 544, 506, 424.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-(4-methoxyphenyl) ethyl)diphenylphosphine oxide (3’ca

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 55 mg, 88% of viscous liquid;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.94 (m, 2H), 7.59 – 7.52 (m, 3H), 7.39 – 7.34 (m, 2H), 7.32 – 7.27 (m, 1H), 7.22 – 7.17 (m, 2H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.75 – 6.69 (m, 3H), 4.15 (q, *J* = 7.4 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 4H), 3.13 (dd, *J* = 11.6, 3.4 Hz, 1H), 2.68 – 2.59 (m, 1H), 2.51 – 2.40 (m, 1H), 1.24 – 1.12 (m, 6H);^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.1, 169.0, 159.6, 135.3 (d, *J* = 5.8 Hz), 132.2, 132.1, 131.5 (d, *J* = 7.8 Hz), 131.2, 130.9 (d, *J* = 9.3 Hz), 130.3, 129.6, 129.0 (d, *J* = 11.4 Hz), 128.1 (d, *J* = 11.9 Hz), 122.4 (d, *J* = 5.8 Hz), 114.3 (d, *J* = 100.7 Hz), 61.5 (d, *J* = 18.5 Hz), 55.2, 49.3 (d, *J* = 13.3 Hz), 43.9 (d, *J* = 67.3 Hz), 28.1, 14.1, 14.0;^{11}B NMR (128 MHz, $CDCl_3$): δ -1.77;^{19}F NMR (376 MHz, $CDCl_3$): δ -143.86; ^{31}P NMR (162 MHz, $CDCl_3$): δ 34.08;HRMS: m/z: [M+H]$^+$ -BF_2OH calculated for $C_{28}H_{32}O_6P$ 495.1937; found 495.1950;IR Data: 3272, 3060, 2982, 2934, 2328, 1724, 1688, 1022, 543, 506.

(1-(4-chlorophenyl)-2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)ethyl)diphe nyl phosphine oxide (3’da)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 53 mg, 84% white solid (m.p. = 111 - 113 ° C);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.94 (m, 2H), 7.57 – 7.54 (m, 3H), 7.38 – 7.28 (m, 3H), 7.21 – 7.18 (m, 2H), 7.14 (s, 4H), 4.17 – 4.11 (m, 2H), 4.06 – 4.00 (m, 2H), 3.72 – 3.66 (m, 1H), 3.04 (dd, *J* = 11.6, 3.7 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.51 – 2.42 (m, 1H), 1.23 – 1.12 (m, 6H);^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.8, 133.5 (d, *J* = 3.5 Hz), 132.4, 132.4, 132.3, 131.8, 131.7, 131.4 (d, *J* = 8.9 Hz), 131.2 (d, *J* = 5.5 Hz), 130.7 (d, *J* = 9.1 Hz), 129.8, 129. (d, *J* = 11.5 Hz), 128.8, 128.3 (d, *J* = 12.0 Hz), 61.6 (d, *J* = 17.1 Hz), 49.2 (d, *J* = 13.0 Hz), 43.2 (d, *J* = 67.1 Hz), 28.1, 14.1, 13.9;^{19}F NMR (376 MHz, $CDCl_3$): δ -143.08;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.40;^{31}P NMR (162 MHz, $CDCl_3$): δ 33.62;HRMS: m/z: [M+H]$^+$ -BF_2OH calculated for $C_{27}H_{29}O_5PCl$ 499.1441; found 499.1447;IR Data: 3287, 3060, 2981, 2937, 2335, 1729, 1474, 1029, 860, 509, 456.

(1-(4-bromophenyl)-2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl) ethyl)diphenylphosphine oxide (3’ea)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 55 mg, 82% viscous liquid;^{1}H NMR (400 MHz, CDCl$_3$): δ 7.98 – 7.89 (m, 2H), 7.57 – 7.48 (m, 3H), 7.45 – 7.43 (m, 1H), 7.41 – 7.36 (m, 1H), 7.34 – 7.28 (m, 2H), 7.25 – 7.147 (m, 4H), 7.06 (d, *J* = 8.7 Hz, 1H), 4.24 – 4.00 (m, 5H), 3.72 – 3.46 (m, 1H), 3.08 – 2.99 (m, 1H), 2.70 – 2.55 (m, 1H), 1.23 – 1.13 (m, 6H);^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.9, 168.8, 134.1 (d, *J* = 4.9 Hz), 132.7, 132.4, 132.0, 131.7, 131.6, 131.0 (d, *J* = 9.6 Hz), 130.8, 130.7 (d, *J* = 4.0 Hz), 129.8, 129.1 (d, *J* = 12.1 Hz), 128.3, 127.9 (d, *J* = 11.8 Hz), 126.7 (d, *J* = 7.7 Hz), 61.8 (d, *J* = 3.8 Hz), 49.3 (d, *J* = 13.4 Hz), 41.7 (d, *J* = 66.9 Hz), 28.9, 14.1, 14.0;^{11}B NMR (128 MHz, CDCl$_3$): δ -0.41;^{19}F NMR (376 MHz, CDCl$_3$): δ -143.29;^{31}P NMR (162 MHz, CDCl$_3$): δ 33.99; HRMS: m/z: [M+H]$^+$ -BF$_2$OH calculated for C$_{27}$H$_{29}$O$_5$PBr 543.0936; found 543.0940; IR Data: 3284, 3056, 2983, 2936, 2330, 1730, 1470, 1028, 504, 450.

4-(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-(diphenyl phosphoryl)ethyl)benzonitrile (3’fa)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 46 mg, 75% viscous liquid;^{1}H NMR (400 MHz, CDCl$_3$): δ 8.01 – 7.96 (m, 2H), 7.61 – 7.56 (m, 3H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.30 (m, 5H), 7.25 – 7.21 (m, 2H), 4.19 – 4.11 (m, 2H), 4.08 – 4.03 (m, 2H), 3.84 – 3.79 (m, 1H), 2.99 (dd, *J* = 11.5, 3.6 Hz, 1H), 2.70 – 2.60 (m, 1H), 2.54 – 2.47 (m, 1H), 1.22 – 1.15 (m, 6H);^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.8, 168.7, 140.2 (d, *J* = 5.4 Hz), 132.6, 132.3, 131.9, 131.5, 131.4, 130.8, 130.7, 129.3, 129.2, 128.5, 128.4, 118.7, 111.5, 61.8 (d, *J* = 17.1 Hz), 49.3 (d, *J* = 12.8 Hz), 44.4 (d, *J* = 65.0 Hz), 28.1, 14.2, 14.1;^{11}B NMR (128 MHz, CDCl$_3$): δ -0.43;^{19}F NMR (376 MHz, CDCl$_3$): δ -143.42;^{31}P NMR (162 MHz, CDCl$_3$): δ 33.31;HRMS: m/z: [M+H]$^+$ -BF$_2$OH calculated for C$_{28}$H$_{29}$NO$_5$P 490.1783; found 490.1786;IR Data: 3272, 3062, 2980, 2326, 2001, 1724, 1688, 1545, 1025, 507, 424.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-(4-(trifluoromethyl) phenyl) ethyl)diphenylphosphine oxide (3’ga)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 58 mg, 87% white solid (m.p. = 116 - 118 ° C);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 – 7.97 (m, 2H), 7.60 – 7.54 (m, 3H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.30 (m, 5H), 7.23 – 7.18 (m, 2H), 4.19 – 4.11 (m, 2H), 4.07 – 4.01 (m, 2H), 3.82 – 3.76 (m, 1H), 3.02 (dd, *J* = 11.4, 3.6 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.56 – 2.47 (m, 1H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H);^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 168.8, 138.5 (d, *J* = 5.9 Hz), 132.4, 132.0, 131.8, 131.5 (d, *J* = 8.6 Hz), 131.0, 130.9, 130.8 (d, *J* = 8.8 Hz), 130.3 (d, *J* = 5.3 Hz), 129.9, 129.6, 129.1 (d, *J* = 11.5 Hz), 128.3 (d, *J* = 12.1 Hz), 125.5, 61.8 (d, *J* = 17.8 Hz), 49.3 (d, *J* = 13.2 Hz), 44.0 (d, *J* = 65.6 Hz), 28.2, 14.1, 14.0;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.46;^{19}F NMR (376 MHz, $CDCl_3$): δ -62.61, -143.55;^{31}P NMR (162 MHz, $CDCl_3$): δ 32.61;HRMS: m/z: $[M+H]^+$ -BF_2OH calculated for $C_{28}H_{29}O_5PF_3$ 533.1705; found 533.1709;IR Data: 3247, 2985, 2905, 1726, 1617, 1591, 1045, 1018, 239, 432.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^{3},3,2λ^{4}-oxaborinin-5-yl)-1-(*o*-tolyl)ethyl) diphenylphosphine oxide (3’ha)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 48 mg, 80% viscous liquid;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.94 (m, 2H), 7.56 – 7.51 (m, 3H), 7.38 – 7.33 (m, 2H), 7.31 – 7.26 (m, 1H), 7.21 – 7.16 (m, 2H), 7.07 – 7.05 (m, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.68 – 3.62 (m, 1H), 3.09 (dd, *J* = 11.7, 3.4 Hz, 1H), 2.66 – 2.57 (m, 1H), 2.50 – 2.41 (m, 1H), 2.23 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H);^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.13, 169.04, 137.2, 132.6, 132.0, 131.5 (d, *J* = 8.7 Hz), 131.4, 130.98, 130.89, 130.6 (t, *J* = 6.5 Hz), 129.8 (d, *J* = 5.5 Hz), 129.4, 128.98, 128.87, 128.1, 128.0, 61.5 (d, *J* = 19.3 Hz), 49.4 (d, *J* = 13.2 Hz), 43.4 (d, *J* = 68.0 Hz), 28.3, 21.1, 14.1, 14.0;^{11}B NMR (128 MHz, $CDCl_3$): δ -1.75 (d, *J* = 40.3 Hz);^{19}F NMR (376 MHz, $CDCl_3$): δ -143.22;^{31}P NMR (162 MHz, $CDCl_3$): δ 33.63;HRMS: m/z: $[M+H]^+$ -BF_2OH calculated for $C_{28}H_{32}O_5P$ 479.1988; found 479.1993;IR Data: 3273, 3062, 2980, 2937, 2378,1698,1545,1495,1025, 546, 506, 425.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^{3},3,2λ^{4}-oxaborinin-5-yl)-1-(2-fluorophenyl) ethyl)diphenylphosphine oxide (3’ia)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 43 mg, 70% viscous liquid;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 – 7.94 (m, 2H), 7.79 – 7.70 (m, 1H), 7.56 – 7.48 (m, 4H), 7.43 –

7.36 (m, 1H), 7.25 – 6.98 (m, 5H), 6.80 – 6.72 (m, 1H), 4.29 – 4.23 (m, 1H), 4.17 – 3.99 (m, 4H), 3.07 (dd, *J* = 11.4, 3.7 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.57 – 2.45 (m, 1H), 1.24 – 1.11 (m, 6H);^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.9, 168.8, 162.2 (d, *J* = 6.2 Hz), 159.7 (d, *J* = 6.7 Hz), 132.4, 132.3, 131.6, 131.4 (d, *J* = 8.9 Hz), 130.6 (d, *J* = 9.0 Hz), 130.4, 129.2 (dd, *J* = 16.3, 9.6 Hz), 128.1 (d, *J* = 11.6 Hz), 124.9, 121.6 (dd, *J* = 14.6, 5.3 Hz), 115.0 (d, *J* = 23.2 Hz), 61.7 (d, *J* = 14.4 Hz), 49.6 (d, *J* = 13.4 Hz), 34.3 (d, *J* = 68.1 Hz), 27.9, 14.11,14.06;^{11}B NMR (128 MHz, CDCl$_3$): δ -0.43;^{19}F NMR (376 MHz, CDCl$_3$): δ -118.8 (d, *J* = 621.7 Hz), -143.3;^{31}P NMR (162 MHz, CDCl$_3$): δ 33.3 (d, *J* = 104.2 Hz);HRMS: m/z: [M+H]$^+$ -BF$_2$OH calculated for C$_{27}$H$_{29}$O$_5$PF 483.1737; found 483.1741;IR Data: 3282, 2940, 2362, 2341, 1731, 1647, 1603, 1016, 539, 419.

(1-(2-chlorophenyl)-2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl) ethyl)diphenylphosphine oxide (3’ja)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 66% viscous liquid;^{1}H NMR (400 MHz, CDCl$_3$): δ 8.11 – 8.02 (m, 2H), 7.92 – 7.89 (m, 1H), 7.61 – 7.58 (m, 3H), 7.36 – 7.26 (m, 4H), 7.17 – 7.14 (m, 2H), 7.10 – 7.09 (m, 2H), 4.52 – 4.44 (m, 1H), 4.23 – 4.13 (m, 2H), 4.07 – 3.99 (m, 2H), 3.05 (dd, *J* = 11.0, 4.1 Hz, 1H), 2.68 – 2.53 (m, 2H), 1.24 – 1.20 (m, 3H), 1.17 – 1.13 (m, 3H);^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 168.9, 168.8, 135.2 (d, *J* = 7.3 Hz), 132.4, 132.3 (d, *J* = 5.1 Hz), 131.9, 131.6, 131.5, 130.8 (d, *J* = 9.5 Hz), 130.6 (d, *J* = 4.2 Hz), 129.9, 129.3, 129.1 (d, *J* = 11.5 Hz), 128.9, 128.0 (d, *J* = 11.7 Hz), 127.7, 61.7 (d, *J* = 9.3 Hz), 49.3 (d, *J* = 13.3 Hz), 38.7 (d, *J* = 67.3 Hz), 28.7, 14.1, 14.0;^{11}B NMR (128 MHz, CDCl$_3$): δ -0.46;^{19}F NMR (376 MHz, CDCl$_3$): δ -142.99;^{31}P NMR (162 MHz, CDCl$_3$): δ 33.95;HRMS: m/z: [M+H]$^+$ -BF$_2$OH calculated for C$_{27}$H$_{29}$O$_5$PCl 499.1441; found 499.1446;IR Data: 3284, 3062, 2981, 2936, 2335, 1725, 1474, 1025, 860, 509, 456.

(1-(2-bromophenyl)-2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl) ethyl)diphenylphosphine oxide (3’ka)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 44 mg, 65% viscous liquid;^{1}H NMR (400 MHz, CDCl$_3$): δ 8.09 – 8.05 (m, 1H), 8.03 – 7.97 (m, 1H), 7.96 – 7.88 (m, 1H), 7.58 – 7.45 (m, 4H), 7.33 – 7.28 (m, 3H), 7.23 – 7.09 (m, 3H), 7.02 – 6.90 (m, 1H), 4.50 – 4.43 (m, 1H), 4.20 – 3.98 (m, 4H), 3.15 – 3.02 (m, 1H), 2.68 – 2.55 (m, 2H), 1.22 – 1.10 (m, 6H);^{13}C{^{1}H} NMR

(101 MHz, $CDCl_3$): δ 168.9, 168.8, 134.1 (d, *J* = 4.9 Hz), 132.7, 132.4, 132.0, 131.6 (d, *J* = 8.6 Hz), 131.0 (d, *J* = 9.6 Hz), 130.7 (d, *J* = 4.0 Hz), 129.8, 129.1 (d, *J* = 12.1 Hz), 128.3, 127.9 (d, *J* = 11.8 Hz), 126.7 (d, *J* = 7.7 Hz), 61.8 (d, *J* = 3.8 Hz), 49.3 (d, *J* = 13.4 Hz), 41.7 (d, *J* = 66.9 Hz), 28.9, 14.1, 14.0;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.42;^{19}F NMR (376 MHz, $CDCl_3$): δ -142.72;^{31}P NMR (162 MHz, $CDCl_3$): δ 34.04;HRMS: m/z: $[M+H]^+$ -BF_2OH calculated for $C_{27}H_{29}O_5PBr$ 543.0936; found 543.0941; IR Data: 3284, 3058, 2983, 2936, 2330, 1731, 1470, 1026, 504, 433.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-mesitylethyl) diphenylphosphine oxide (3'la)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 41 mg, 62% viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 – 8.03 (m, 2H), 7.64 – 7.63 (m, 3H), 7.28 – 7.26 (m, 1H), 7.15 – 7.08 (m, 4H), 6.87 (s, 1H), 6.51 (s, 1H), 4.25 – 4.02 (m, 5H), 3.11 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.06 – 2.99 (m, 1H), 2.82 (s, 3H), 2.53 – 2.43 (m, 1H), 2.19 (s, 3H), 1.67 (s, 3H), 1.19 – 1.14 (m, 6H);^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.5, 169.3, 139.3, 138.5 (d, *J* = 5.8 Hz), 136.8, 132.1 (d, *J* = 8.1 Hz), 131.8, 131.4, 131.1 (d, *J* = 9.3 Hz), 129.3, 129.1 (d, *J* = 11.3 Hz), 127.7 (d, *J* = 11.6 Hz), 61.6 (d, *J* = 22.5 Hz), 49.5 (d, *J* = 12.8 Hz), 40.1 (d, *J* = 67.5 Hz)., 26.2, 22.2, 21.1, 20.8, 14.1;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.45;^{19}F NMR (376 MHz, $CDCl_3$): δ -143.44;^{31}P NMR (162 MHz, $CDCl_3$): δ 35.62;HRMS: m/z: $[M+H]^+$ -BF_2OH calculated for $C_{30}H_{36}O_5P$ 507.2300; found 507.2302;IR Data: 3288, 2986, 2343, 1730, 1647, 1153, 1098, 543, 505, 420.

(2-(2,2-difluoro-2-hydroxy-4,6-dimethoxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-phenylethyl) diphenyl phosphine oxide (3'ma)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 47 mg, 85% viscous liquid;_^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.98 (m, 2H), 7.59 – 7.56 (m, 3H), 7.36 – 7.28 (m, 3H), 7.21 – 7.17 (m, 7H), 3.69 (s, 4H), 3.59 (s, 3H), 3.15 (dd, J = 11.5, 3.6 Hz, 1H), 2.72 – 2.62 (m, 1H), 2.55 – 2.46 (m, 1H);^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.5, 169.5, 133.8 (d, *J* = 6.1 Hz), 132.2, 131.6, 131.5, 131.4, 130.9 (d, *J* = 8.8 Hz), 130.5, 129.9 (d, *J* = 5.6 Hz), 129.0 (d, *J* = 11.4 Hz), 128.7, 128.1 (d, *J* = 11.6 Hz), 127.7, 52.7 (d, *J* = 11.9 Hz), 49.1 (d, *J* = 12.8 Hz), 44.0 (d, J = 67.4 Hz), 28.4;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.47;^{19}F NMR (376 MHz, $CDCl_3$): δ -143.28;^{31}P NMR (162 MHz,$CDCl_3$): δ 33.81;HRMS: m/z: $[M+H]^+$ -BF_2OH calculated for $C_{25}H_{26}O_5P$ 437.1518; found 437.1530;IR Data: 3272, 3054, 1647,1438, 1370, 1031, 834, 790, 750, 503, 439.

(2-(2,2-difluoro-2-hydroxy-4,6-diisopropoxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-phenylethyl) diphenyl phosphine oxide (3’na)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 81% of 3’na as viscous liquid;^{1}H NMR (400 MHz, $CDCl_3$):_δ 8.02 – 7.97 (m, 2H), 7.57 – 7.54 (m, 3H), 7.35 – 7.26 (m, 3H), 7.20 – 7.15 (m, 7H), 5.08 – 5.02 (m, 1H), 4.91 – 4.85 (m, 1H), 3.72 – 3.66 (m, 1H), 3.01 (dd, *J* = 11.6, 3.4 Hz, 1H), 2.69 – 2.60 (m, 1H), 2.51 – 2.42 (m, 1H), 1.19 – 1.16 (m, 6H), 1.13 – 1.10 (m, 6H);$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.6, 168.6, 133.7 (d, *J* = 6.0 Hz), 132.2, 131.6, 131.5, 131.1 (d, *J* = 8.7 Hz), 130.9 (d, *J* = 9.3 Hz), 130.2, 129.9 (d, *J* = 5.7 Hz), 129.0 (d, *J* = 11.5 Hz), 128.7, 128.1 (d, *J* = 12.2 Hz), 127.6, 69.1 (d, *J* = 27.9 Hz), 49.7 (d, *J* = 13.0 Hz), 43.9 (d, *J* = 67.7 Hz)., 27.9, 21.7, 21.6;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.98 (d, *J* = 143.9 Hz);^{19}F NMR (376 MHz, $CDCl_3$): δ -143.88;^{31}P NMR (162 MHz, $CDCl_3$): δ 33.85;HRMS: m/z: $[M+H]^+$ -BF_2OH calculated for $C_{29}H_{34}O_5P$ 493.2144; found 493.2161;IR Data: 3272, 3061, 2981, 2937, 2328, 1723, 1688, 1545, 1025, 543, 506, 423.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-phenylethyl) di-*p*-tolylphosphine oxide (3’ab)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 68% of 3’ab as white solid (m.p. = 120 - 122 ° C);^{1}H NMR (400 MHz, $CDCl_3$):_δ 7.86 – 7.81 (m, 2H), 7.36 – 7.33 (m, 2H), 7.22 – 7.14 (m, 7H), 6.98 (dd, *J* = 8.2, 2.7 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.66 – 3.60 (m, 1H), 3.08 (dd, *J* = 11.6, 3.6 Hz, 1H), 2.68 – 2.58 (m, 1H), 2.52 – 2.41 (m, 1H), 2.41 (s, 3H), 2.22 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H);$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 169.1, 169.0, 142.5, 141.7, 134.2 (d, *J* = 5.7 Hz), 131.5 (d, *J* = 8.7 Hz), 130.9 (d, *J* = 9.4 Hz), 129.9 (d, *J* = 5.3 Hz), 129.7 (d, *J* = 12.0 Hz), 128.8 (d, *J* = 12.4 Hz), 128.6, 128.2 (d, *J* = 10.0 Hz), 127.5, 127.2, 61.5 (d, *J* = 19.3 Hz), 49.5 (d, *J* = 13.3 Hz), 44.1 (d, *J* = 67.3 Hz), 28.3, 21.7, 21.5, 14.1, 14.0;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.49;^{19}F NMR (376 MHz, $CDCl_3$): δ -144.06; ^{31}P

NMR (162 MHz, CDCl$_3$):_δ 34.54;HRMS: m/z: $[M+H]^+$ -BF$_2$OH calculated for $C_{29}H_{34}O_5P$ 493.2144; found 493.2154;IR Data: 3286, 2981, 2932, 1727, 1541, 1340, 1261, 1093, 845, 512, 432.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-phenylethyl)bis(3,5-dimethyl phenyl)phosphine oxide (3'ac)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 36 mg, 55% white solid (m.p. = 121 - 123 ° C);^{1}H NMR (400 MHz, CDCl$_3$):_δ 7.57 – 7.54 (m, 2H), 7.19 – 7.17 (m, 6H), 6.89 (d, *J* = 11.2 Hz, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.02 (q, *J*= 7.2 Hz, 2H), 3.65 – 3.59 (m, 1H), 3.09 (dd, *J* = 11.3, 3.5 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.51 – 2.44 (m, 1H), 2.38 (s, 6H), 2.11 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H);^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$): δ 169.1, 168.9, 138.5 (d, *J* = 11.7 Hz), 137.5 (d, *J* = 12.4 Hz), 134.3 (d, *J* = 5.8 Hz), 133.7, 132.9, 132.2, 131.2 (d, *J* = 5.9 Hz), 130.2, 130.0, 129.9, 129.0 (d, *J* = 8.6 Hz), 128.6, 128.5, 127.4, 61.4 (d, *J* = 23.1 Hz), 49.4 (d, *J* = 13.1 Hz), 43.9 (d, *J* = 66.9 Hz)., 28.2, 21.4, 21.1, 14.1, 14.0;^{11}B NMR (128 MHz, CDCl$_3$): δ -0.52;^{19}F NMR (376 MHz, CDCl$_3$): δ -143.35;^{31}P NMR (162 MHz, CDCl$_3$): δ 34.54;HRMS: m/z: $[M+H]^+$ -BF$_2$OH calculated for $C_{31}H_{38}O_5P$ 521.2457; found 521.2462;IR Data: 3282, 2940, 2362, 2341, 1732, 1647, 1603, 1016, 539, 419.

tert-butyl(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-phenyl ethyl)(phenyl)phosphine oxide (3'ad)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 37 mg, 66% viscous liquid;^{1}H NMR (400 MHz, CDCl$_3$):_δ 7.85 – 7.81 (m, 2H), 7.51 – 7.49 (m, 2H), 7.41 – 7.36 (m, 2H), 7.20 – 7.11 (m, 2H), 7.02 – 6.94 (m, 2H), 4.20 – 3.90 (m, 4H), 3.61 – 3.57 (m, 1H), 2.98 – 2.87 (m, 1H), 2.66 – 2.37 (m, 1H), 2.15 – 2.04 (m, 1H), 1.23 – 1.13 (m, 7H), 1.05 (t, *J* = 7.1 Hz, 2H), 0.74 (d, *J* = 14.6 Hz, 6H);^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$): δ 169.1, 168.9 (d, *J* = 8.9 Hz), 136.1 (d, *J* = 5.7 Hz), 135.7 (d, *J* = 4.7 Hz), 131.8, 130.57 (d, *J* = 18.2 Hz), 128.4 (d, *J* = 10.4 Hz), 127.9, 127.4 (d, *J* = 10.7 Hz), 127.0, 61.4 (t, *J* = 14.8 Hz), 49.6 (d, *J* = 11.4 Hz), 48.6 (d, *J* = 12.0 Hz), 41.0 (d, *J* = 58.3 Hz), 39.7 (d, *J* = 59.3 Hz), 34.6 (d, *J* = 37.5 Hz), 33.9 (d, *J* = 40.7 Hz), 30.1 (d, *J* = 17.1 Hz), 25.8, 24.8, 14.1 (d, *J* = 5.3 Hz), 13.9 (d, *J* = 8.8 Hz);^{11}B NMR (128 MHz, CDCl$_3$): δ -1.02;^{19}F

NMR (376 MHz, $CDCl_3$): δ -146.00;^{31}P NMR (162 MHz, $CDCl_3$): δ 51.87;HRMS: m/z: $[M+H]^+$ -BF_2OH calculated for $C_{25}H_{34}O_5P$ 445.2144; found 445.2164;IR Data: 3273, 2968, 2838, 1732, 1647, 1542, 1339, 1028, 537, 435.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-phenylethyl) diisopropylphosphine oxide (3'ae)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 39 mg, 76% viscous liquid;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.20 (m, 5H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.01 (q, *J* = 6.9 Hz, 2H), 3.18 – 3.14 (m, 1H), 2.94 (dd, *J* = 8.6, 6.1 Hz, 1H), 2.54 – 2.48 (m, 2H), 2.32 – 2.24 (m, 1H), 1.76 – 1.69 (m, 1H), 1.31 – 1.25 (m, 6H), 1.16 – 1.10 (m, 6H), 0.97 (dd, *J* = 14.6, 7.2 Hz, 3H), 0.79 (dd, *J* = 15.3, 7.3 Hz, 3H);^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.9, 168.8, 135.1, 129.5, 128.9, 127.7, 61.5 (d, *J* = 15.0 Hz), 49.1 (d, *J* = 10.2 Hz), 39.4 (d, *J* = 56.1 Hz), 26.5, 25.9, 17.1, 16.6, 16.3, 15.8, 14.0, 13.9;^{11}B NMR (128 MHz, $CDCl_3$): δ -2.03;^{19}F NMR (376 MHz, $CDCl_3$): δ -150.27;^{31}P NMR (162 MHz, $CDCl_3$): δ 53.35;HRMS: m/z: $[M+H]^+$ -BF_2OH calculated for $C_{21}H_{34}O_5P$ 397.2144; found 397.2163;IR Data: 3272, 3061, 2981, 2328, 1723, 1686, 1025, 543, 506, 423.

Dicyclohexyl(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-oxaborinin-5-yl)-1-phenyl ethyl)phosphine oxide (3'af)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 43 mg, viscous liquid;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 5H), 4.16 (q, *J* = 7.0 Hz, 2H), 4.09 – 4.04 (m, 2H), 3.15 – 3.09 (m, 1H), 3.00 (dd, *J* = 10.6, 4.1 Hz, 1H), 2.62 – 2.50 (m, 2H), 2.11 – 2.00 (m, 3H), 1.85 – 1.81 (m, 4H), 1.66 – 1.52 (m, 5H), 1.45 – 1.39 (m, 3H), 1.24 – 1.16 (m, 6H), 1.00 – 0.94 (m, 3H), 0.87 – 0.80 (m, 2H);^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.3, 169.1, 135.6 (d, *J* = 5.6 Hz), 129.7 (d, *J* = 5.0 Hz), 129.0, 128.5, 127.7, 127.0, 61.6 (d, *J* = 23.0 Hz), 49.5 (d, *J* = 11.0 Hz), 39.6 (d, *J* = 55.6 Hz), 38.0, 37.7, 37.3, 37.1, 28.7, 27.4, 27.2, 27.1, 26.9, 26.9, 26.7, 26.6, 26.2, 26.1, 25.7, 14.2, 14.1;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.88;^{19}F NMR (376 MHz, $CDCl_3$): δ -145.28;^{31}P NMR (162 MHz,

$CDCl_3$): δ 52.30;HRMS: m/z: [M+H]$^+$-BF_2OH calculated for $C_{27}H_{42}O_5P$ 477.2770; found 477.2772;IR Data: 3273, 2968, 2878, 1731, 1648, 1370,1267, 1026, 537, 435.

(2-(4,6-diethoxy-2,2-difluoro-2-hydroxy-2*H*-1λ^3,3,2λ^4-dioxaborinin-5-yl)-1-(*p*-tolyl)ethyl)di-*p*-tolylphosphine oxide (3'bb)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 44 mg, 68% white solid (m.p. = 123 - 125 ° C);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.80 (m, 2H), 7.34 – 7.33 (m, 2H), 7.24 – 7.21 (m, 2H), 7.09 – 7.07 (m, 2H), 7.00 – 6.99 (m, 4H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.62 – 3.56 (m, 1H), 3.09 (dd, *J* = 11.6, 3.5 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.49 – 2.41 (m, 1H), 2.41 (s, 3H), 2.26 (s, 3H), 2.25 (s, 3H), 1.23– 1.20 (m, 3H), 1.17 – 1.14 (m, 3H);^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.3, 169.1, 142.4, 141.7, 137.1, 131.5 (d, *J* = 8.7 Hz), 131.0 (d, *J* = 9.7 Hz), 129.9 (d, *J* = 5.4 Hz), 129.7, 129.6, 129.4, 128.9, 128.8, 128.4, 61.5 (d, *J* = 20.2 Hz), 49.5 (d, *J* = 13.2 Hz), 43.6 (d, *J* = 68.0 Hz)., 28.4, 21.7, 21.6, 21.2, 14.2, 14.0;^{11}B NMR (128 MHz, $CDCl_3$): δ -0.45;^{19}F NMR (376 MHz, $CDCl_3$): δ -144.54;^{31}P NMR (162 MHz, $CDCl_3$): δ 34.62;HRMS: m/z: [M+H]$^+$ -BF_2OH calculated for $C_{30}H_{36}O_5P$ 507.2300; found 507.2327;IR Data: 3276, 3054, 2981, 2341, 1726, 1688, 1495, 1025, 543, 506, 423;

Diethyl 2-(2-(diphenylphosphoryl)-2-phenylethyl) malonate (4aa)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 45 mg, 87% viscous liquid;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.97 (m, 2H), 7.61 – 7.53 (m, 3H), 7.38 – 7.27 (m, 3H), 7.23 – 7.14 (m, 7H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.72 – 3.66 (m, 1H), 3.11 (dd, *J* = 11.6, 3.4 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.54 – 2.46 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H);^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.1, 133.9 (d, *J* = 6.0 Hz), 132.4, 132.1 (d, *J* = 2.6 Hz), 131.5 (d, *J* = 8.6 Hz), 131.4 (d, *J* = 2.8 Hz), 130.9 (d, *J* = 8.9 Hz), 130.4, 130.0 (d, *J* = 5.4 Hz), 129.0 (d, *J* = 11.3 Hz), 128.7 (d, *J* = 2.1 Hz), 128.1 (d, *J* = 11.9 Hz), 127.6 (d, *J* = 2.4 Hz), 61.6 (d, *J* = 19.2 Hz), 49.4 (d, *J* = 13.3 Hz), 43.9 (d, *J* = 67.4 Hz), 28.2, 14.1, 14.0;^{31}P NMR (162 MHz, $CDCl_3$): δ 34.11;HRMS: m/z: [M+H]$^+$ calculated for $C_{27}H_{30}O_5P$ 465.1831; found 465.1834;IR Data: 2986, 2937, 2342, 1730, 1647, 1153, 1098, 543, 505, 420.

Diethyl 2-(2-(4-chlorophenyl)-2-(diphenylphosphoryl)ethyl)malonate (4da)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 51 mg, 92% viscous liquid;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.94 (m, 2H), 7.72 – 7.66 (m, 1H), 7.57 – 7.54 (m, 3H), 7.51 – 7.48 (m, 1H), 7.38 – 7.30 (m, 3H), 7.24 – 7.19 (m, 2H), 7.15 (d, *J* = 4.5 Hz, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 4.09 – 4.00 (m, 2H), 3.76 – 3.65 (m, 1H), 3.05 (dd, *J* = 11.5, 3.6 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.52 – 2.43 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H);^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.9, 133.5, 132.8, 132.6 (d, *J* = 6.1 Hz), 132.3, 131.6, 131.5, 131.4, 131.2 (d, *J* = 5.9 Hz), 130.8, 130.2, 129.1 (d, *J* = 10.5 Hz), 128.9, 128.3, 128.2, 61.7 (d, *J* = 18.8 Hz), 49.3 (d, *J* = 12.9 Hz), 43.4 (d, *J* = 66.8 Hz), 28.2, 14.1, 14.0;^{31}P NMR (162 MHz, $CDCl_3$): δ 33.63;HRMS: m/z: $[M+H]^+$ calculated for $C_{27}H_{29}O_5PCl$ 499.1442; found 499.1446;IR Data: 2981, 2937, 2335, 1729, 1474, 1029, 861, 509, 456, 403.

Diethyl 2-(2-(diphenylphosphoryl)-2-(4-((triisopropylsilyl)ethynyl)phenyl)ethyl)malonate (10)

Isolated by chromatography on silica gel, (*n*-hexane/EA = 10/3) 59 mg, 82% viscous liquid;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 – 7.95 (m, 2 H), 7.60 – 7.54 (m, 3 H), 7.44 – 7.37 (m, 2 H), 7.35 – 7.29 (m, 3 H), 7.25 – 7.21 (m, 2 H), 7.16 (d, *J* = 7.7 Hz, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.08 – 4.01 (m, 2H), 3.75 – 3.67 (m, 1H), 3.03 (dd, *J* = 11.7, 3.3 Hz, 1H), 2.67 – 2.56 (m, 1H), 2.53 – 2.42 (m, 1H), 2.17 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.11 (s, 18H);^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.1, 169.0, 134.6, 134.5, 132.4, 132.2, 131.6, 131.5, 131.4, 131.0, 130.9, 130.5, 129.9, 129.8, 129.1, 129.0, 128.4, 128.3, 122.8, 106.8, 91.3, 61.69 (d, *J* = 20.2 Hz), 49.29 (d, *J* = 12.8 Hz), 43.9 (d, *J* = 66.7 Hz), 31.1, 28.4, 18.8, 14.2, 14.1, 11.4;^{31}P NMR (162 MHz, $CDCl_3$): δ 33.31;HRMS: m/z: $[M+H]^+$calculated for $C_{38}H_{50}O_5PSi$ 645.3164; found 645.3165;IR Data: 3054, 2982, 2341, 2160, 1728, 1695, 1496, 1025, 544, 508, 423.

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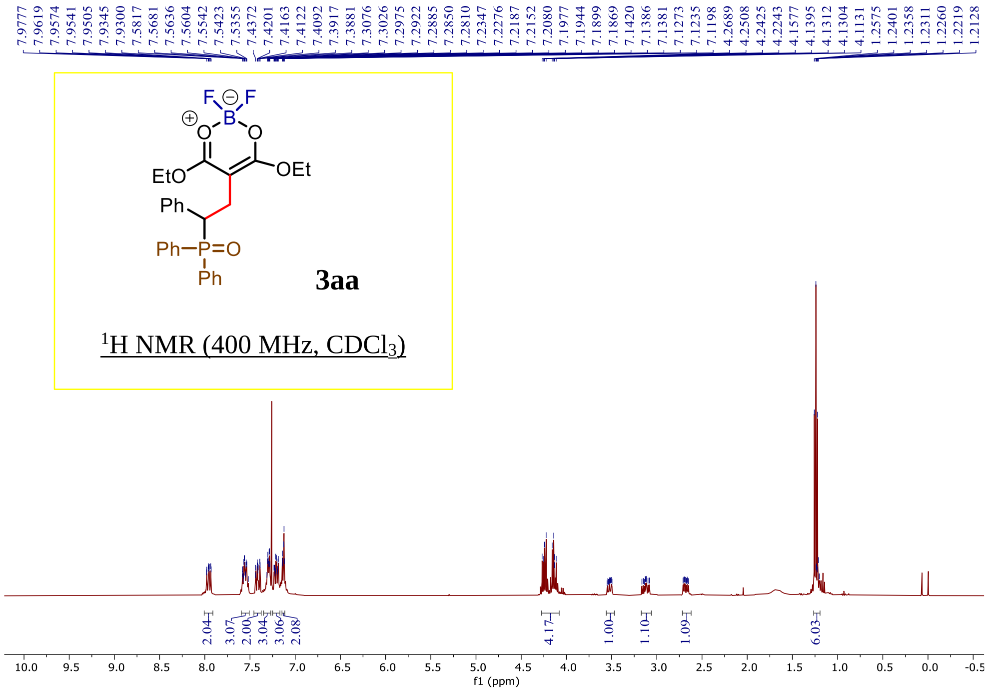
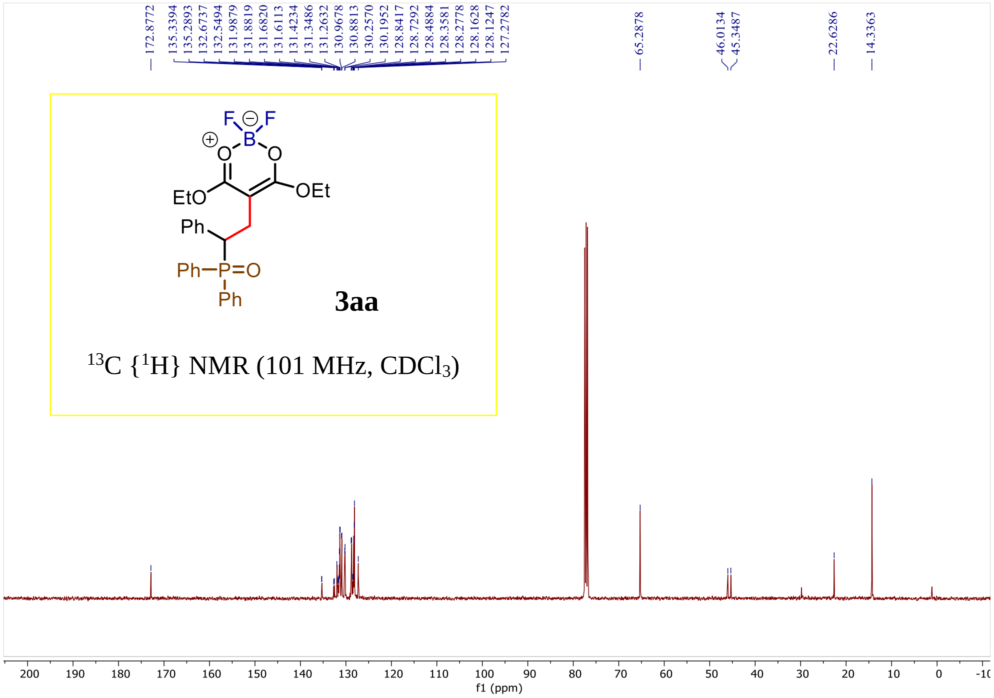
4.6 NMR spectra of compound



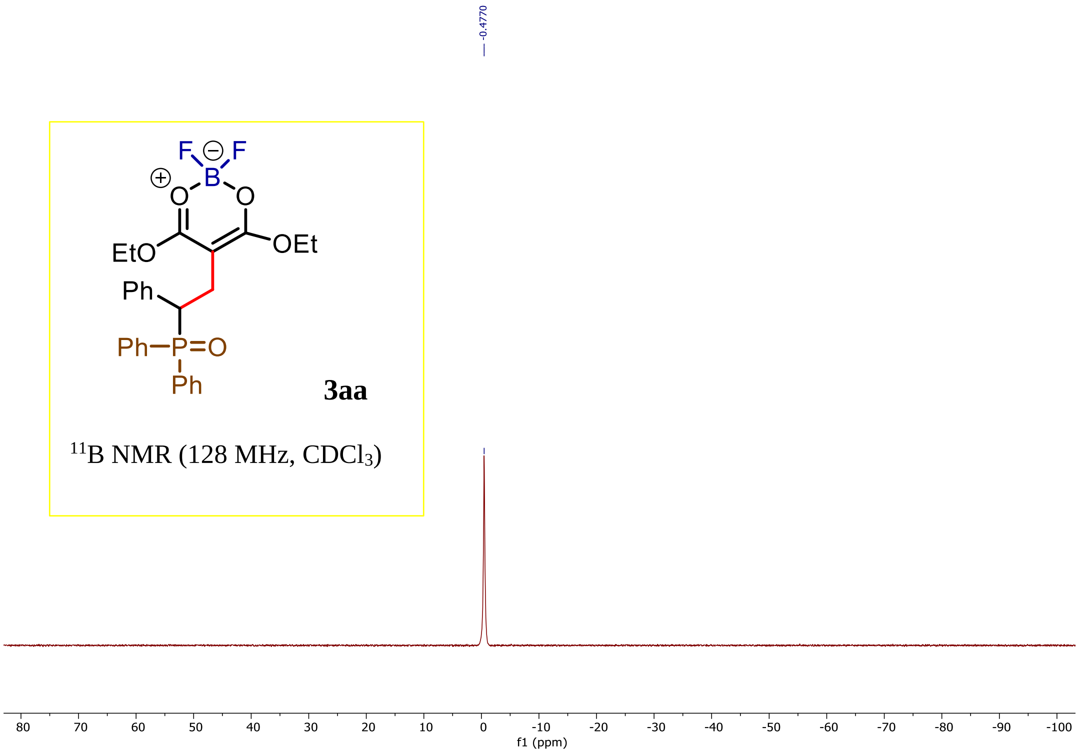
3aa

^{1}H NMR (400 MHz, $CDCl_3$)



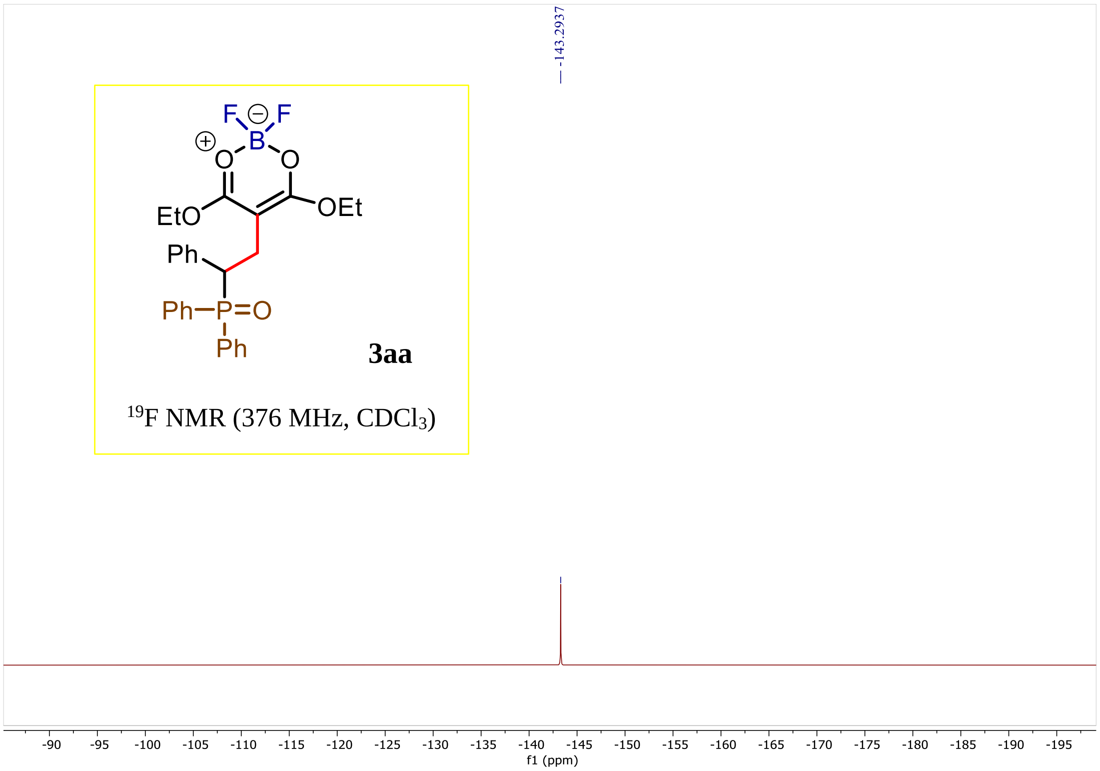
3aa

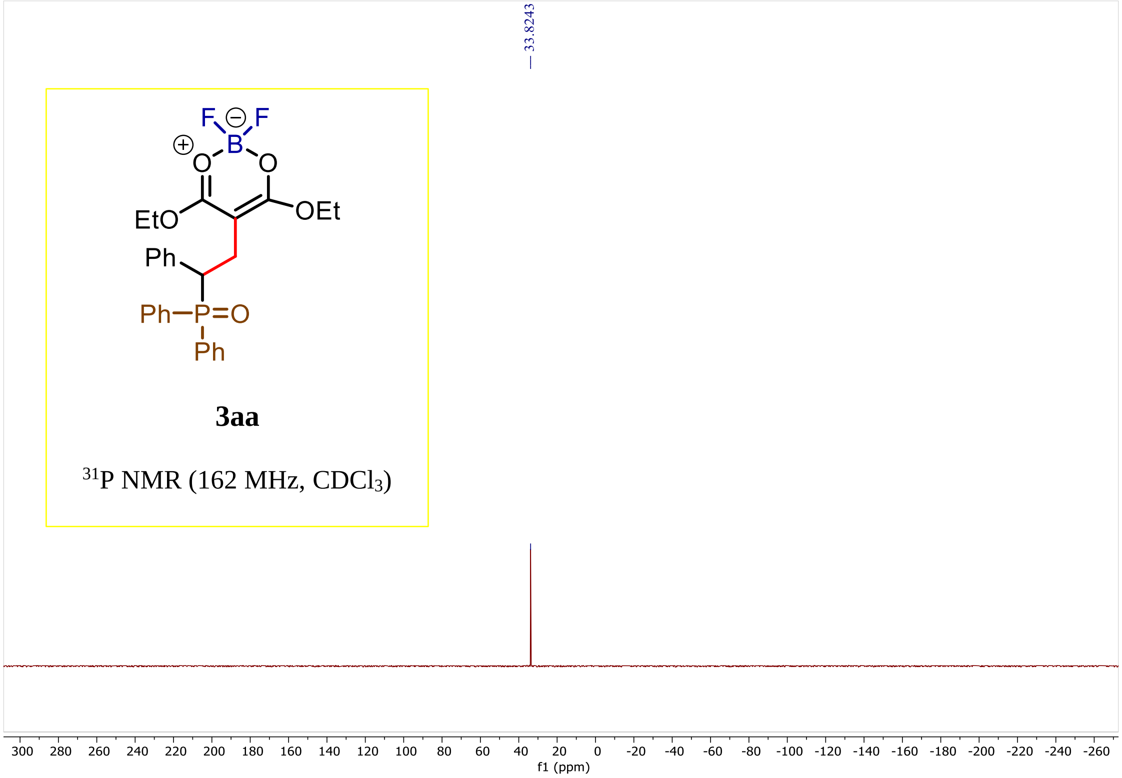
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

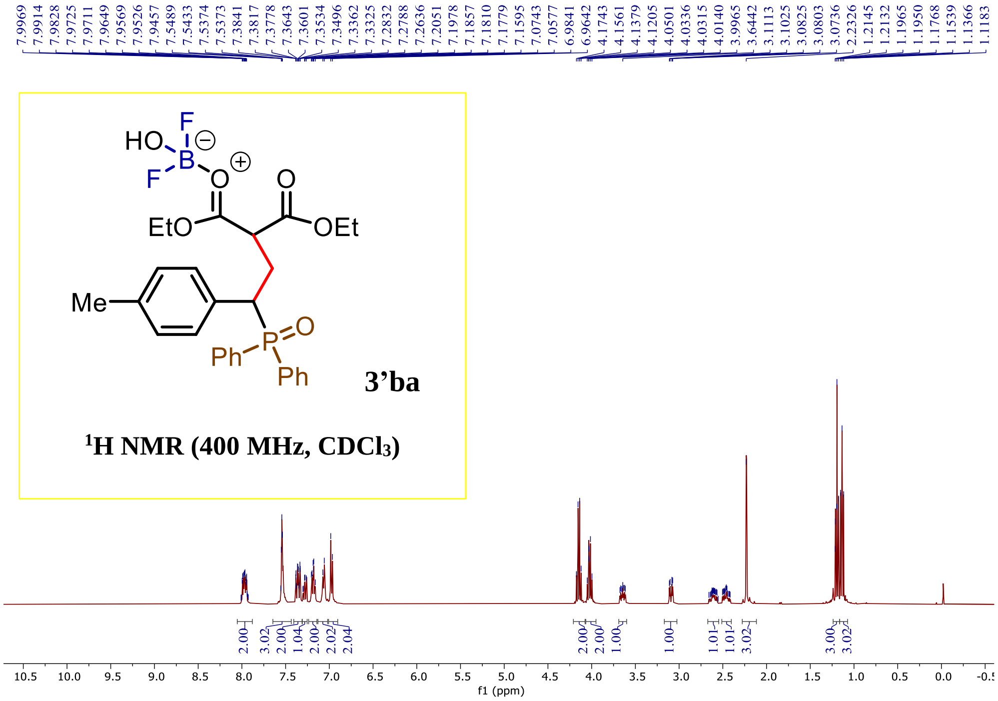


3aa

^{11}B NMR (128 MHz, CDCl$_3$)

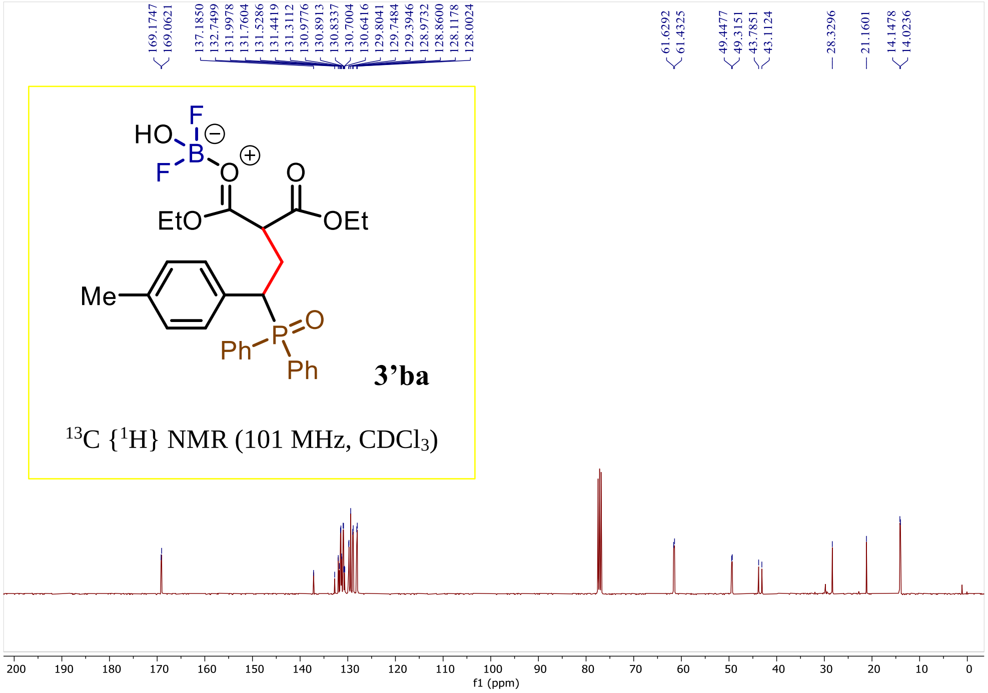

-143.2937
3aa
^{19}F NMR (376 MHz, CDCl$_3$)
-90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195
f1 (ppm)


33.8243
3aa
^{31}P NMR (162 MHz, CDCl$_3$)
300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240 -260
f1 (ppm)



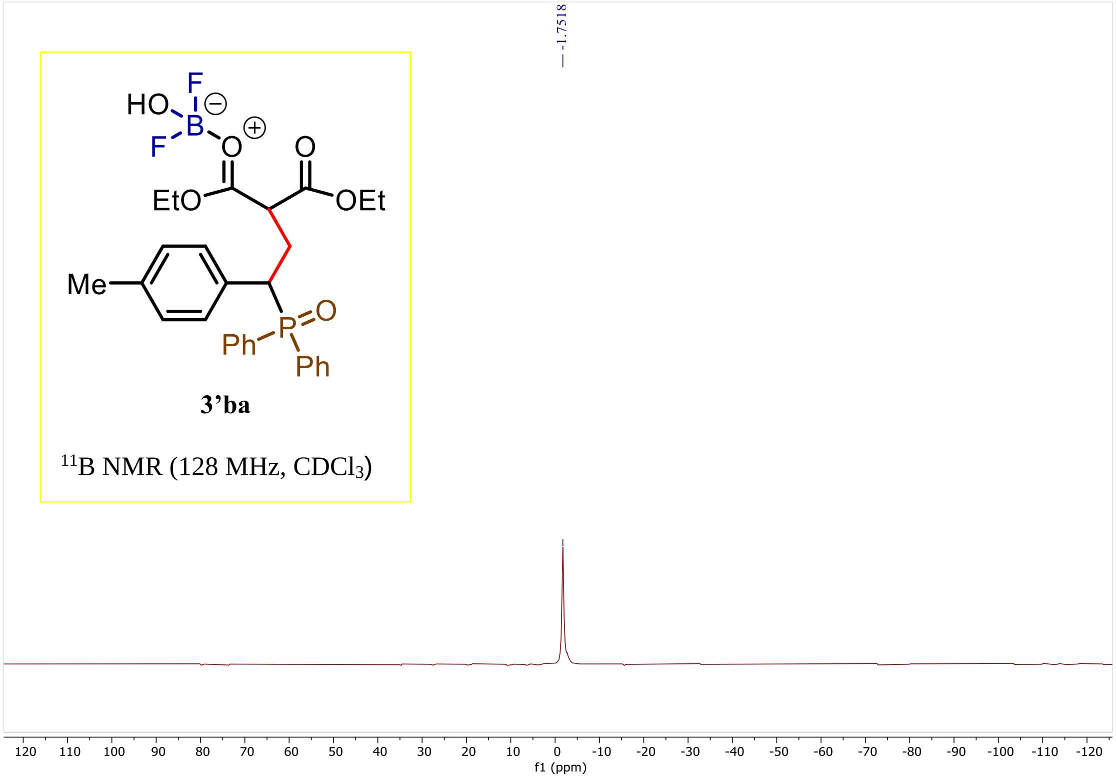
3’ba

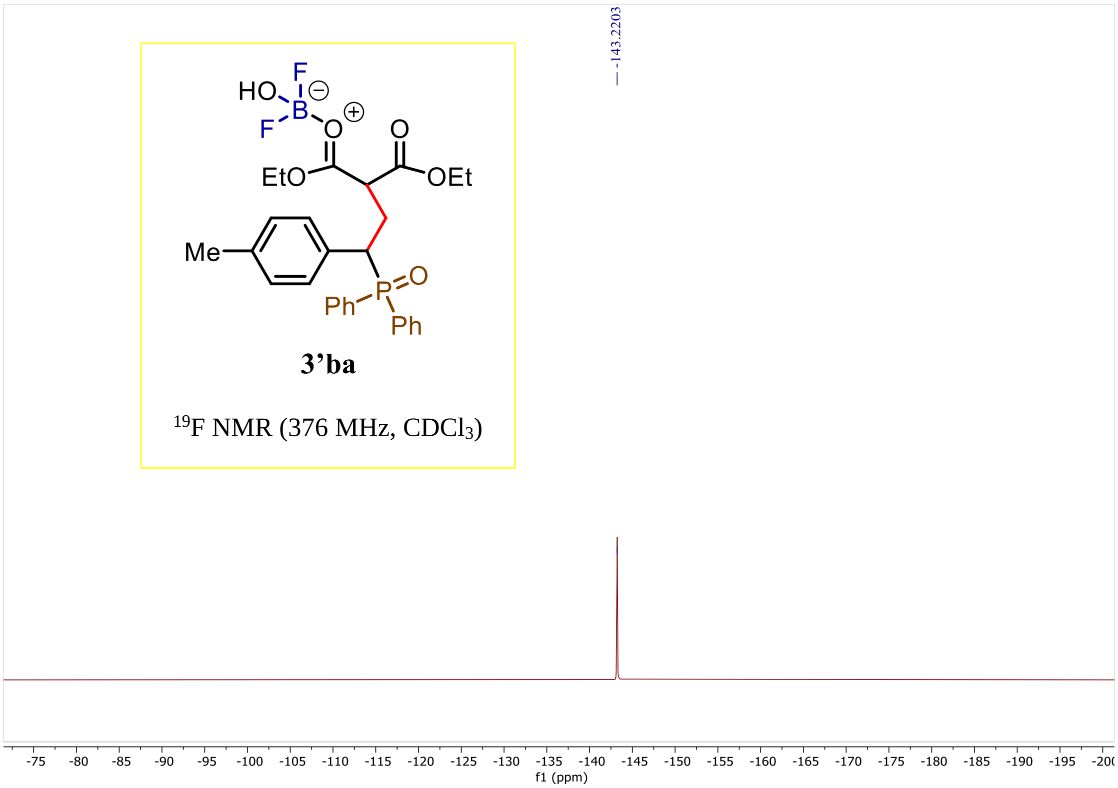
^{1}H NMR (400 MHz, CDCl$_3$)

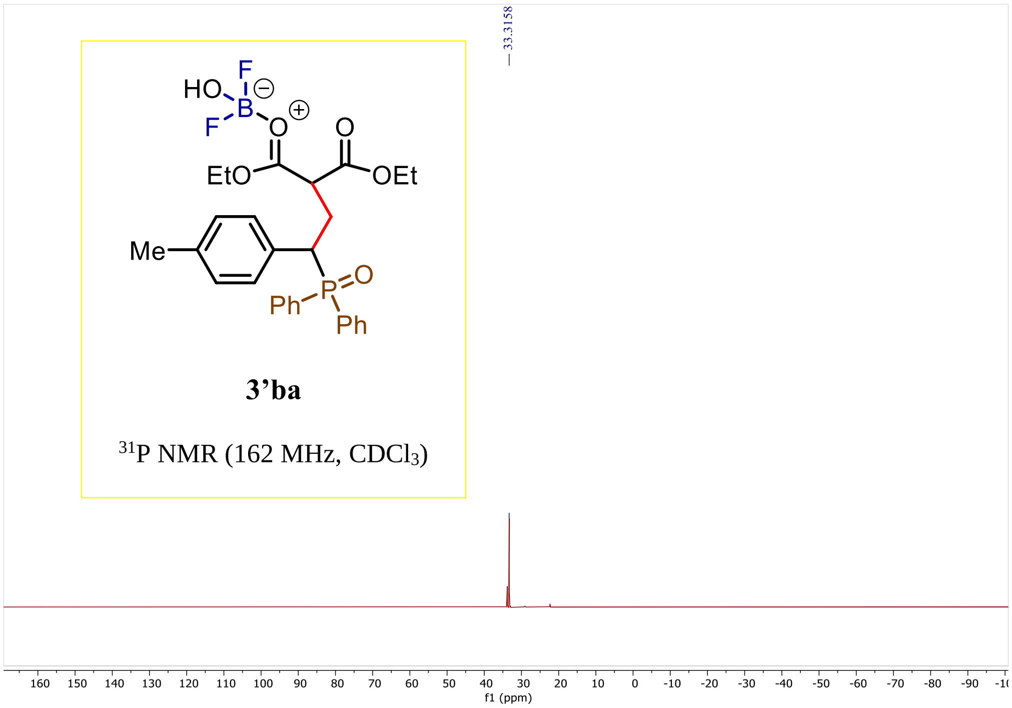


3’ba

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)

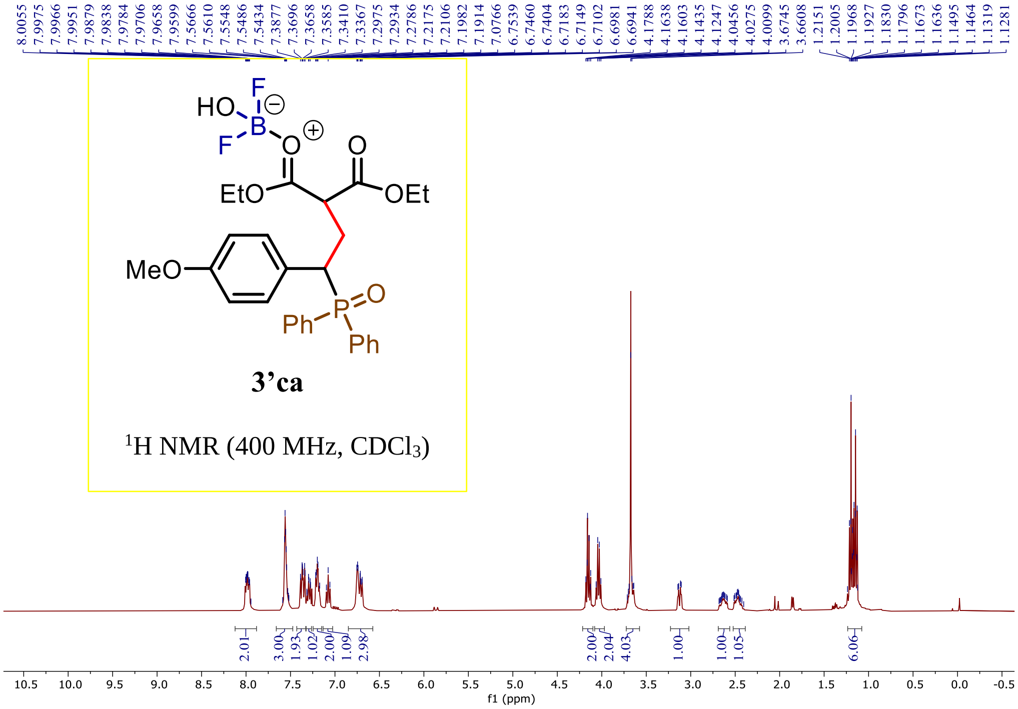

-1.7518
HO
F
B
O
F
O
EtO
OEt
Me
P=O
Ph
Ph
3'ba
^{11}B NMR (128 MHz, CDCl$_3$)
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120
f1 (ppm)


-143.2203
HO
F
B
O
F
O
EtO
OEt
Me
P=O
Ph
Ph
3'ba
^{19}F NMR (376 MHz, CDCl$_3$)
-75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195 -200
f1 (ppm)



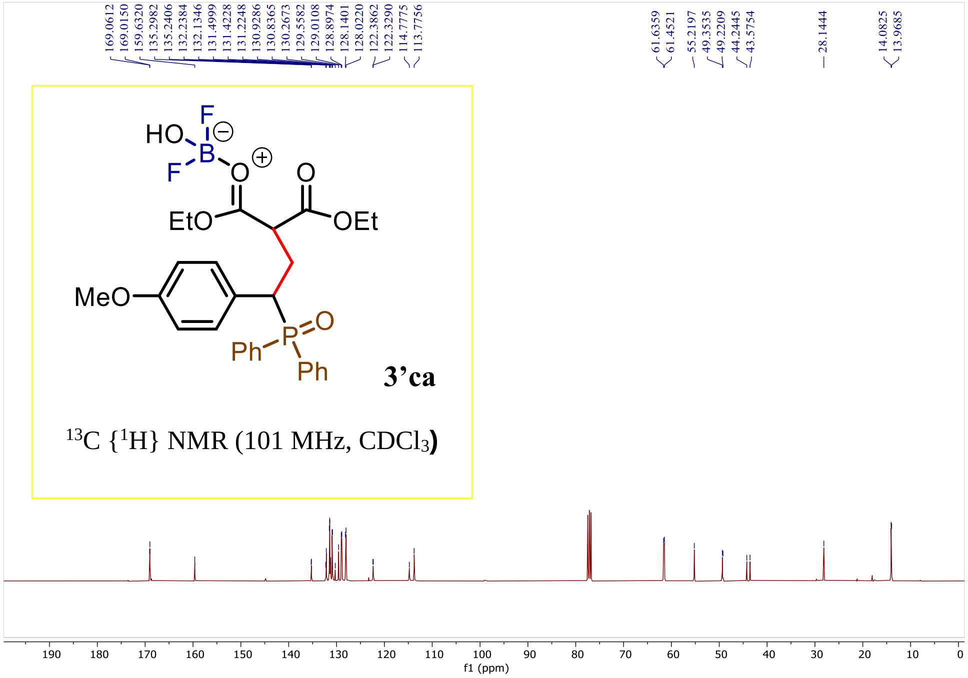
3’ba

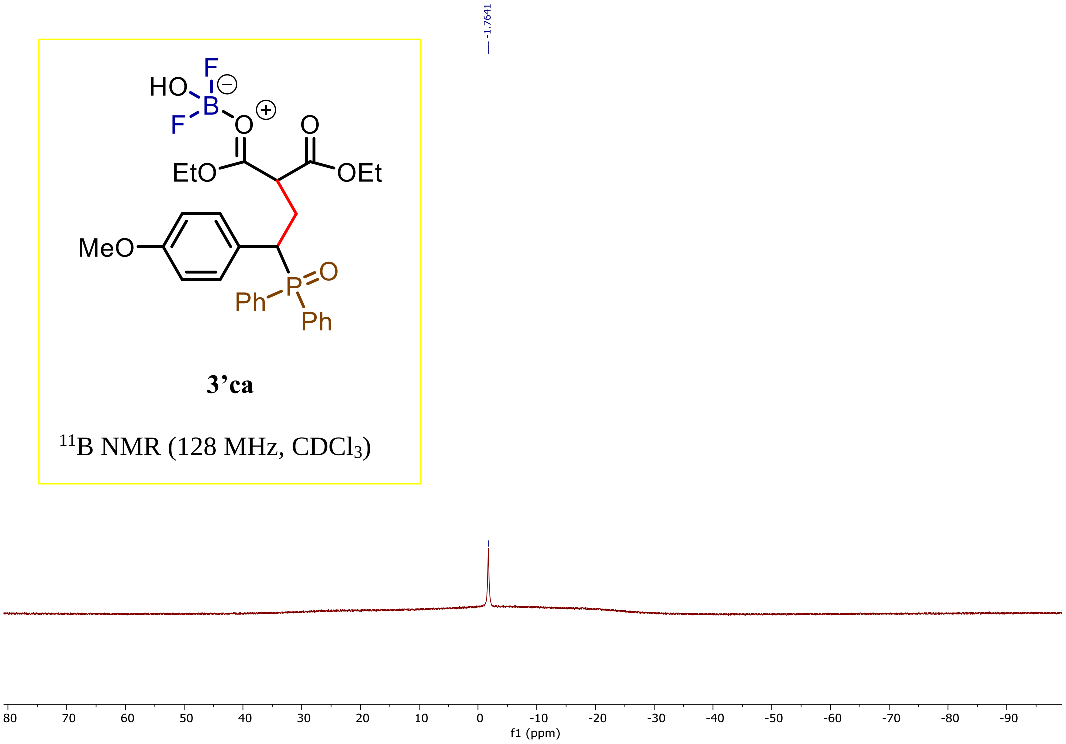
^{31}P NMR (162 MHz, CDCl$_3$)

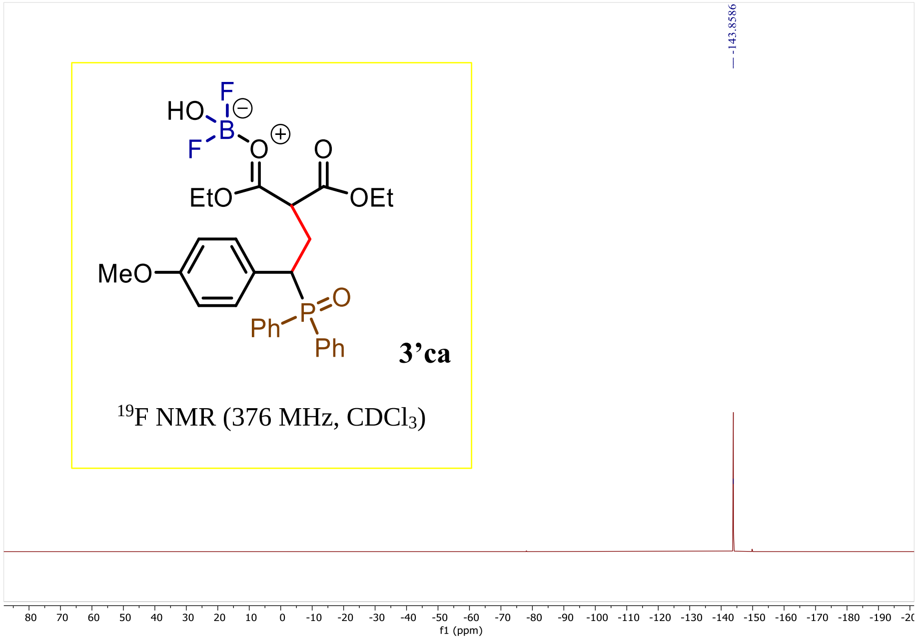


3’ca

^{1}H NMR (400 MHz, CDCl$_3$)

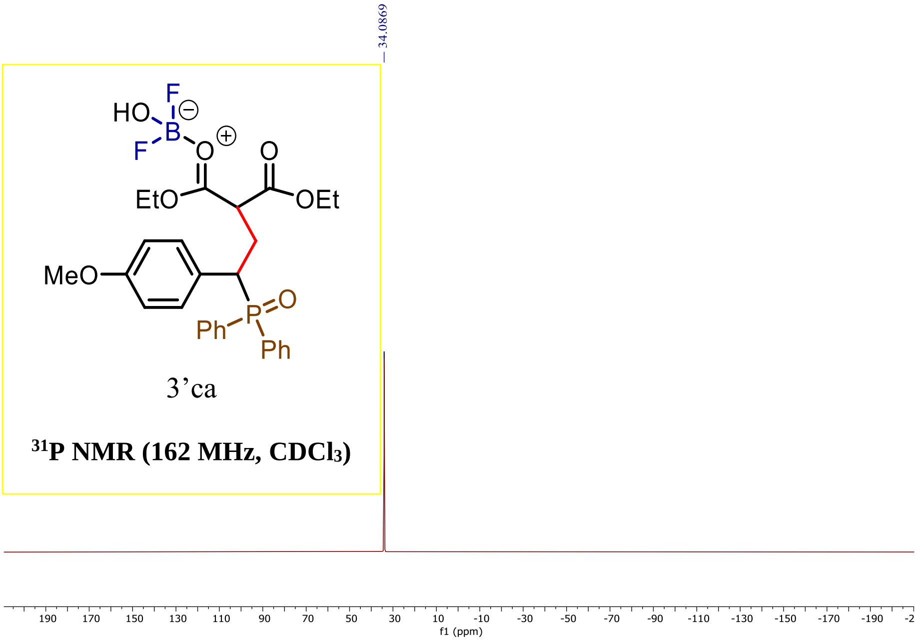

169.0612
169.0150
159.6320
135.2982
135.2406
132.2384
132.1346
131.4999
131.4228
131.2248
130.9286
130.8365
130.2673
129.5582
129.0108
128.8974
128.1401
128.0220
122.3862
122.3290
114.7775
113.7756
61.6359
61.4521
55.2197
49.3535
49.2209
44.2445
43.5754
28.1444
14.0825
13.9685
HO
F
B
F
O
O
EtO
OEt
MeO
P
O
Ph
Ph
3'ca
13C {1H} NMR (101 MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-1.7641
HO
F
B
F
O
O
EtO
OEt
MeO
P
O
Ph
Ph
3'ca
11B NMR (128 MHz, CDCl3)
80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)



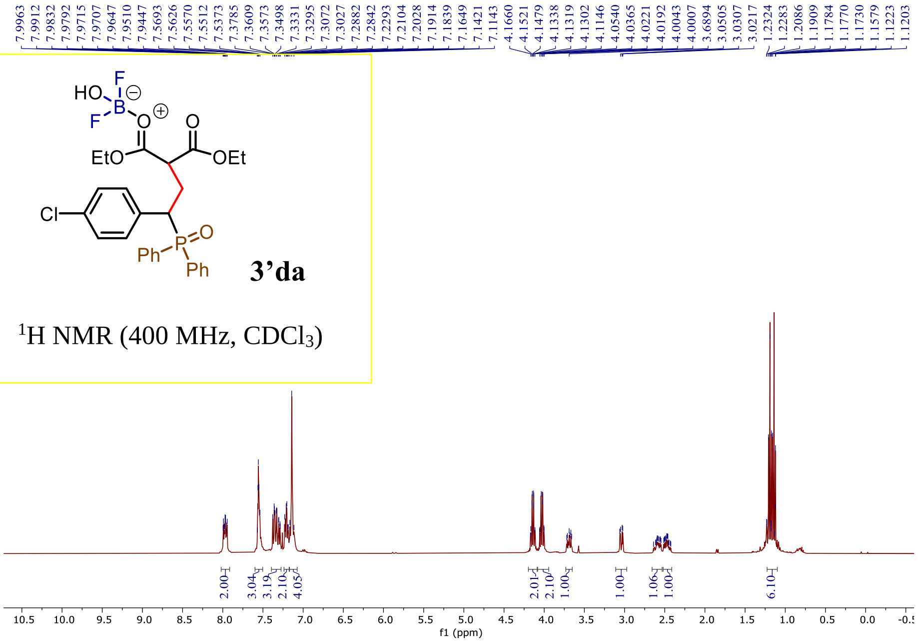
3’ca

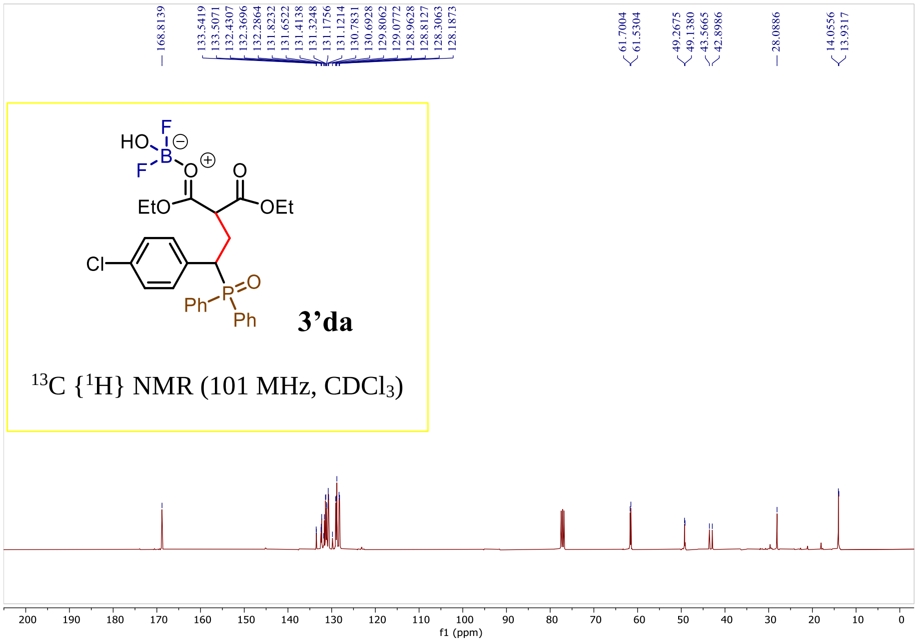
^{19}F NMR (376 MHz, $CDCl_3$)

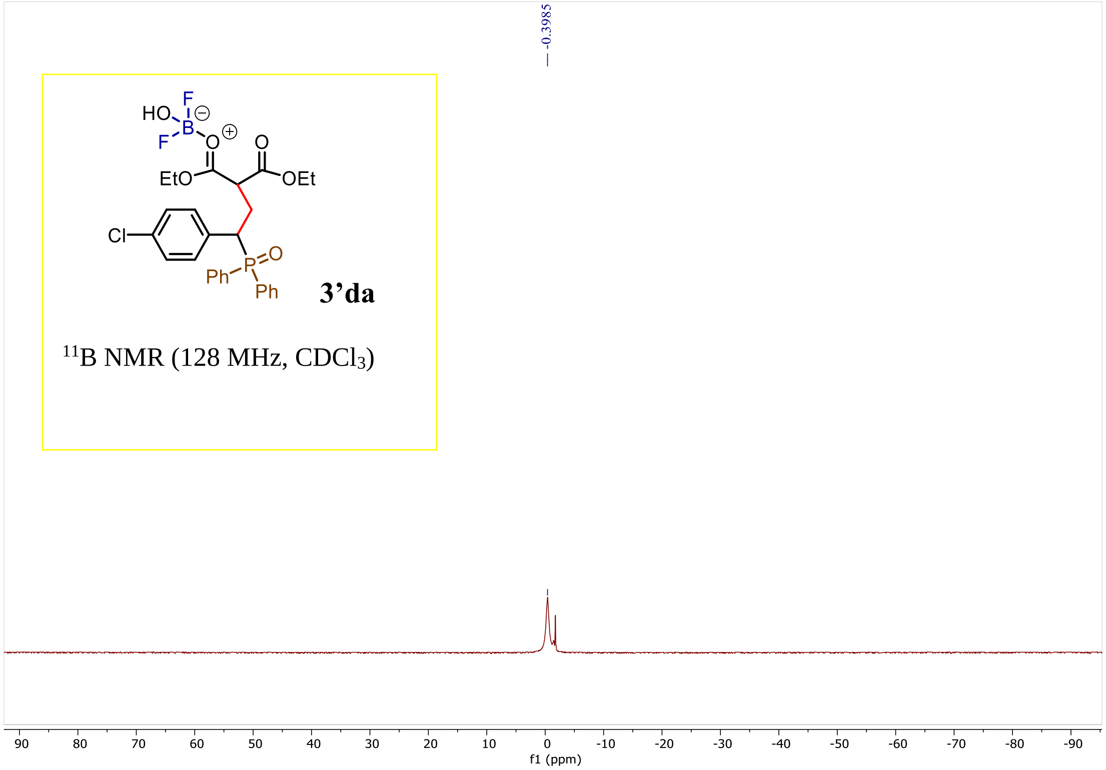


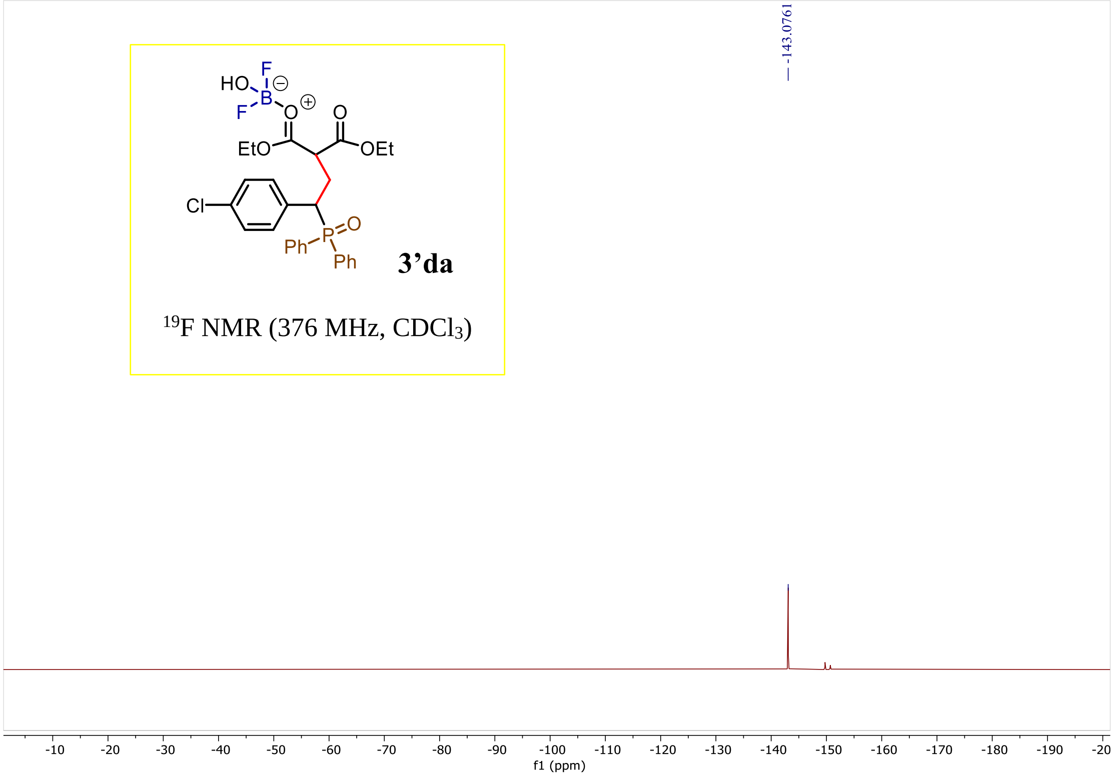
3’ca

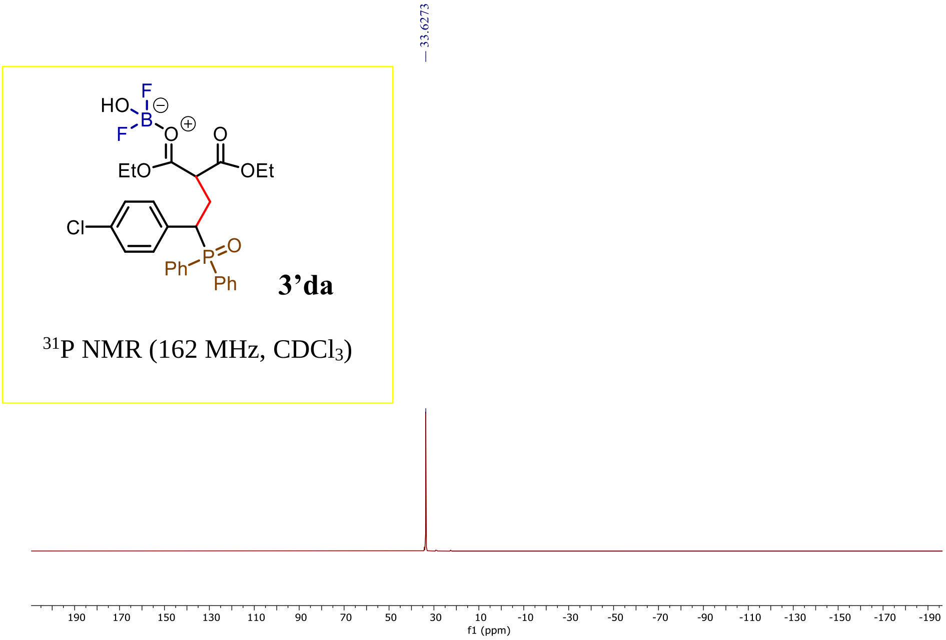
^{31}P NMR (162 MHz, $CDCl_3$)


7.9963
7.9912
7.9832
7.9792
7.9715
7.9707
7.9647
7.9510
7.9447
7.5693
7.5626
7.5570
7.5512
7.5373
7.3785
7.3609
7.3573
7.3498
7.3331
7.3295
7.3072
7.3027
7.2882
7.2842
7.2293
7.2104
7.2028
7.1914
7.1839
7.1649
7.1421
7.1143
4.1660
4.1521
4.1479
4.1338
4.1319
4.1302
4.1146
4.0540
4.0365
4.0221
4.0192
4.0043
4.0007
3.6894
3.0505
3.0307
3.0217
1.2324
1.2283
1.2086
1.1909
1.1784
1.1770
1.1730
1.1579
1.1223
1.1203
HO
F
B
F
O
O
EtO
OEt
Cl
Ph
P
O
Ph
3'da
^{1}H NMR (400 MHz, CDCl$_3$)
2.00
3.04
3.19
2.10
4.05
2.01
2.10
1.00
1.00
1.06
1.00
6.10
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


168.8139
133.5419
133.5071
132.4307
132.3696
132.2864
131.8232
131.6522
131.4138
131.3248
131.1756
131.1214
130.7831
130.6928
129.8062
129.0772
128.9628
128.8127
128.3063
128.1873
61.7004
61.5304
49.2675
49.1380
43.5665
42.8986
28.0886
14.0556
13.9317
HO
F
B
F
O
O
EtO
OEt
Cl
Ph
P
O
Ph
3'da
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

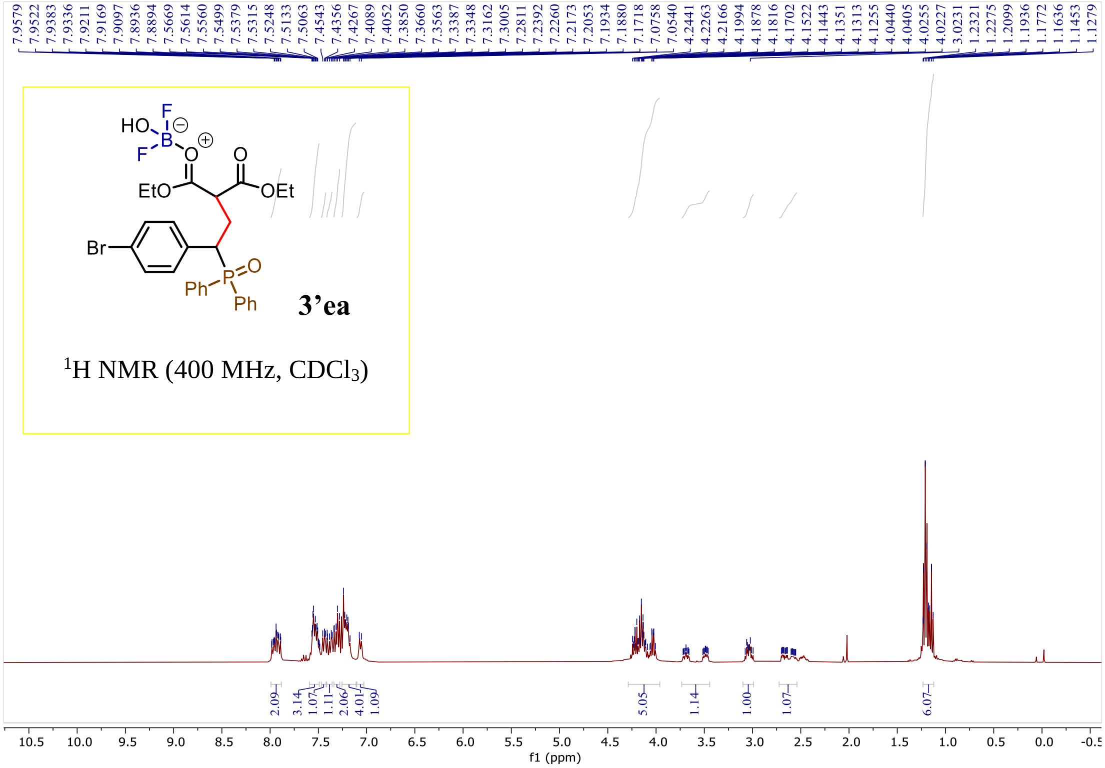

-0.3985
3'da
^{11}B NMR (128 MHz, CDCl$_3$)
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
f1 (ppm)


-143.0761
3'da
^{19}F NMR (376 MHz, CDCl$_3$)
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-20
f1 (ppm)



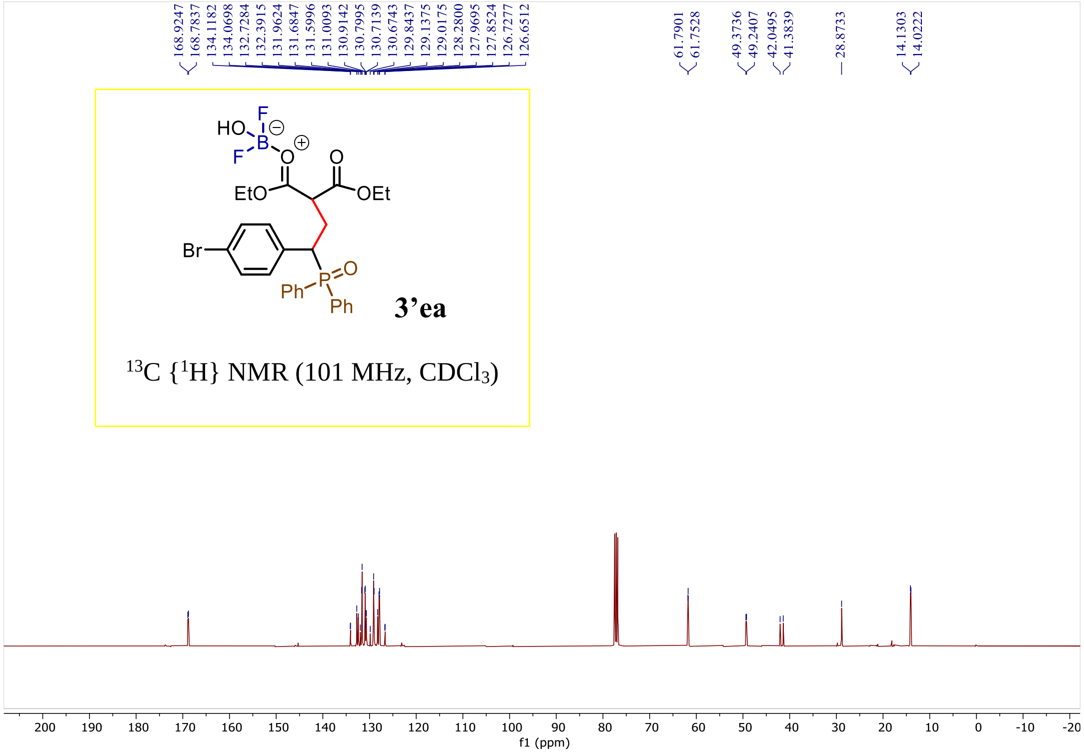
3’da

^{31}P NMR (162 MHz, $CDCl_3$)



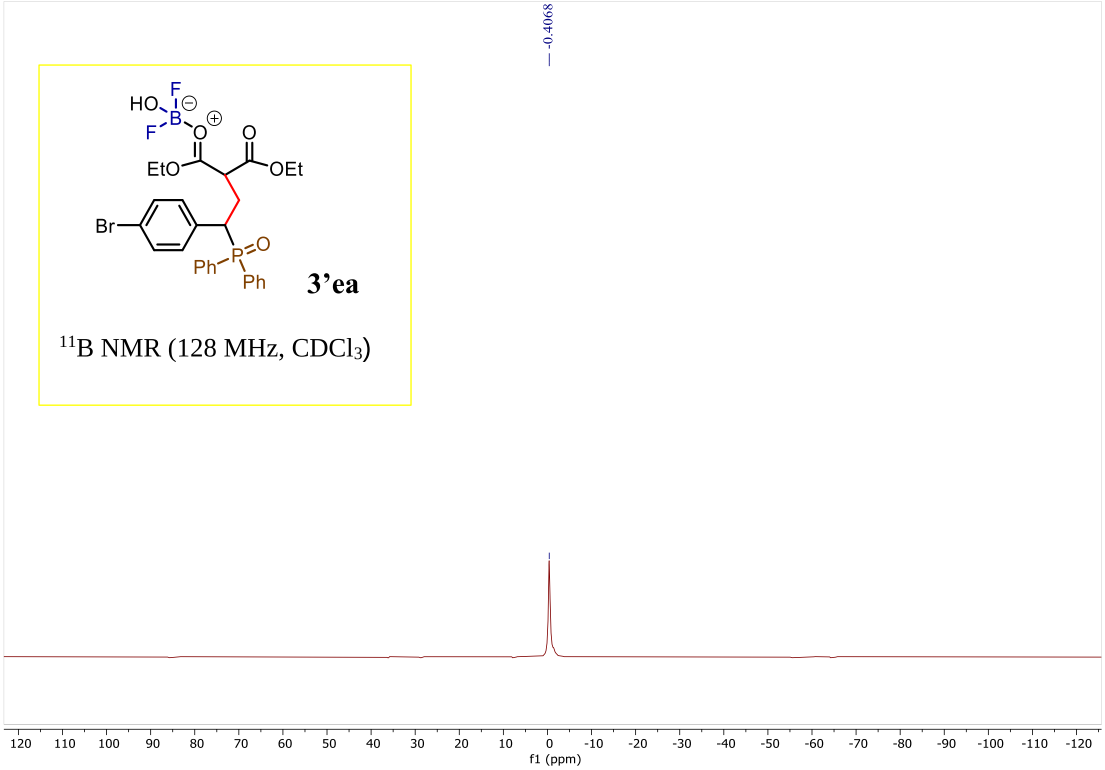
3’ea

^{1}H NMR (400 MHz, $CDCl_3$)



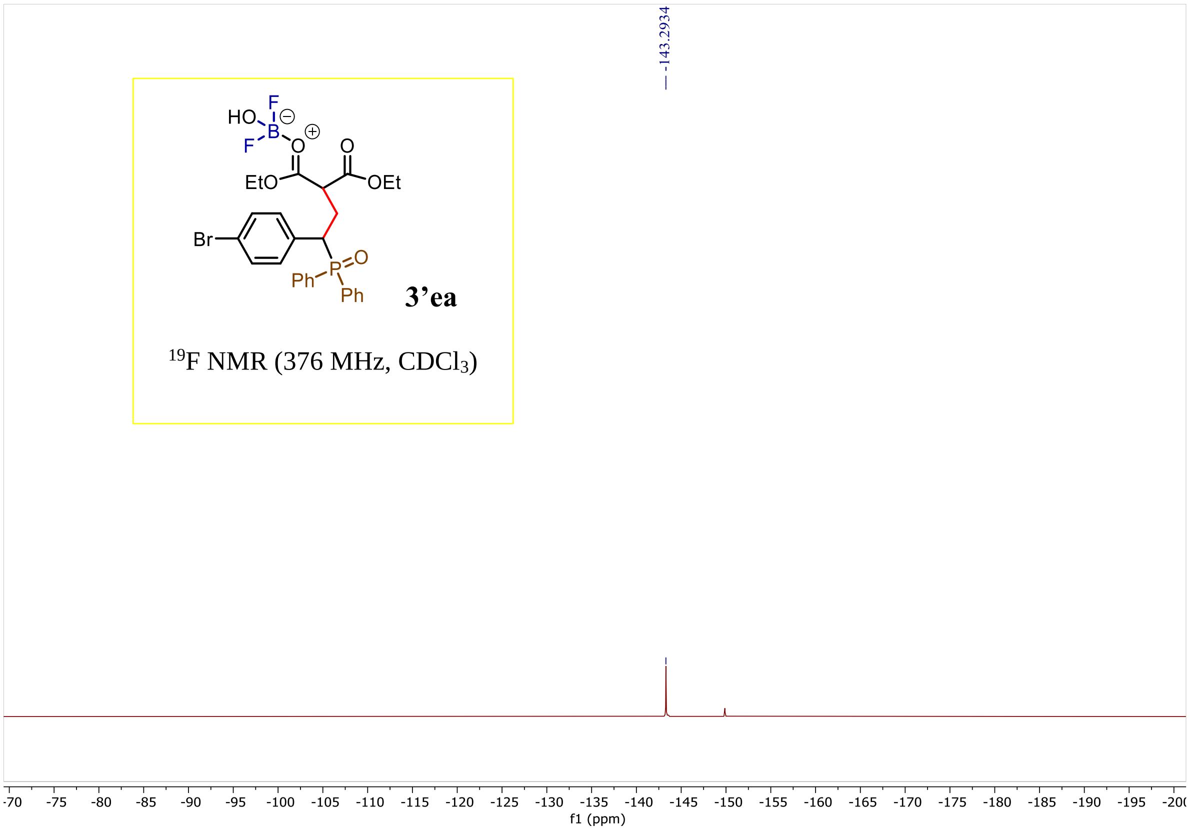
3’ea

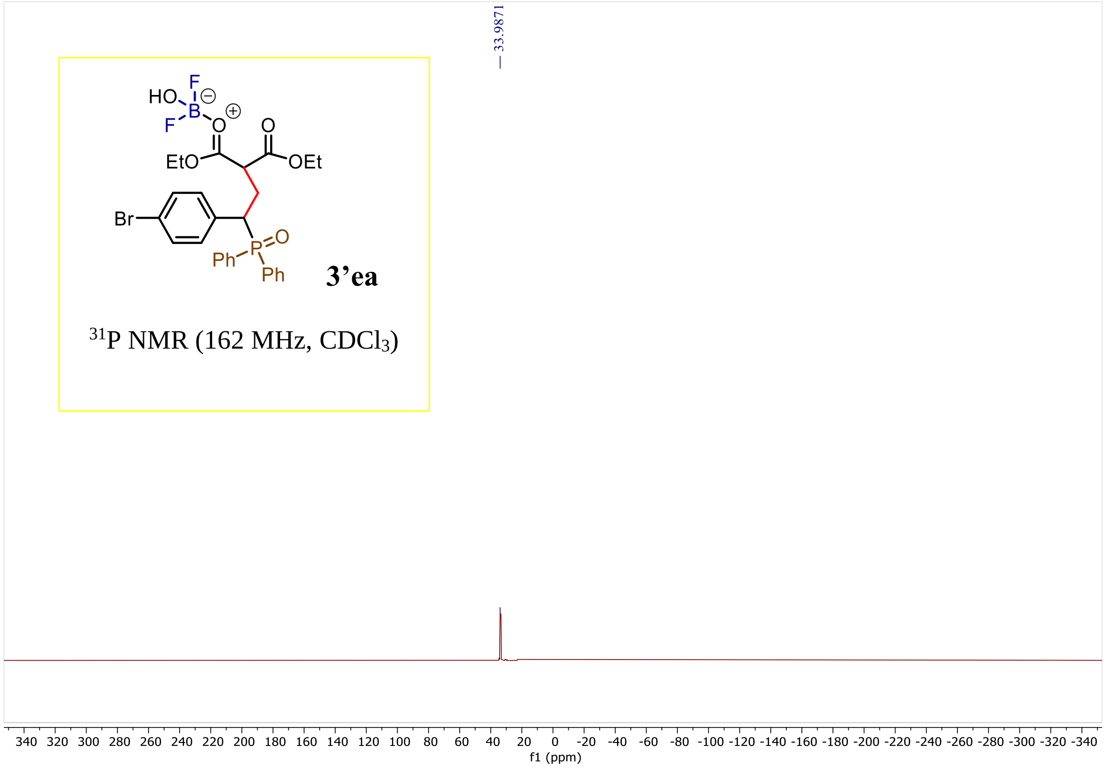
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)



3’ea

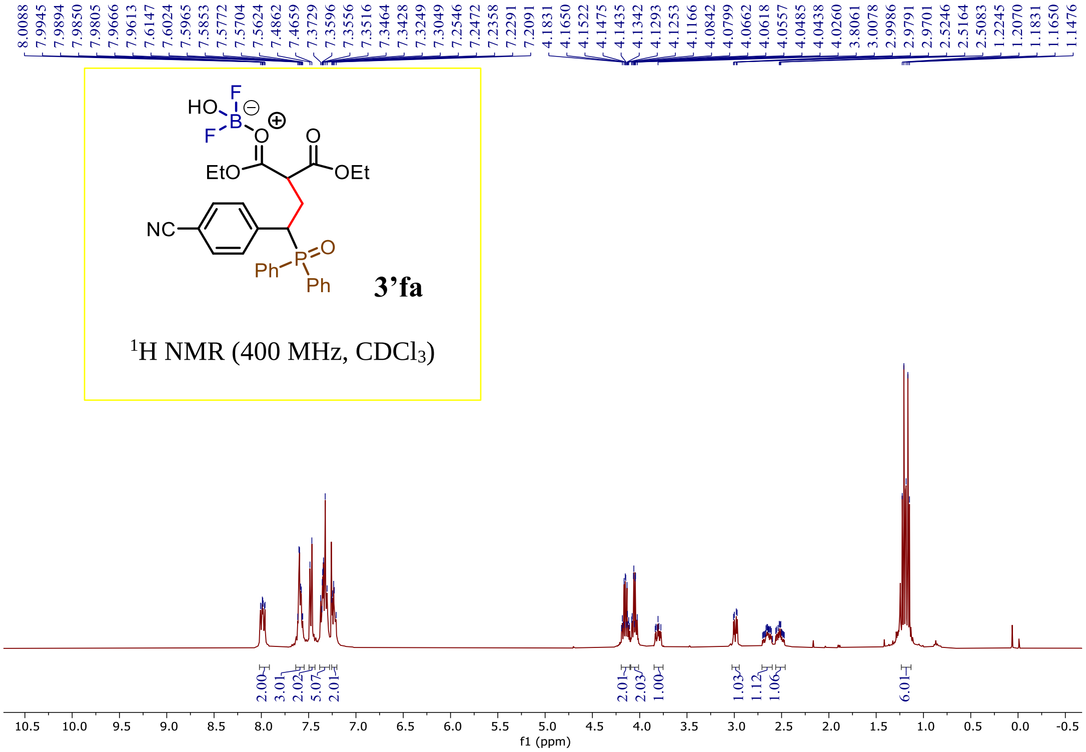
^{11}B NMR (128 MHz, CDCl$_3$)


-143.2934
HO
F
B
F
O
O
EtO
OEt
Br
P
O
Ph
Ph
3'ea
^{19}F NMR (376 MHz, CDCl$_3$)
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
-200
f1 (ppm)



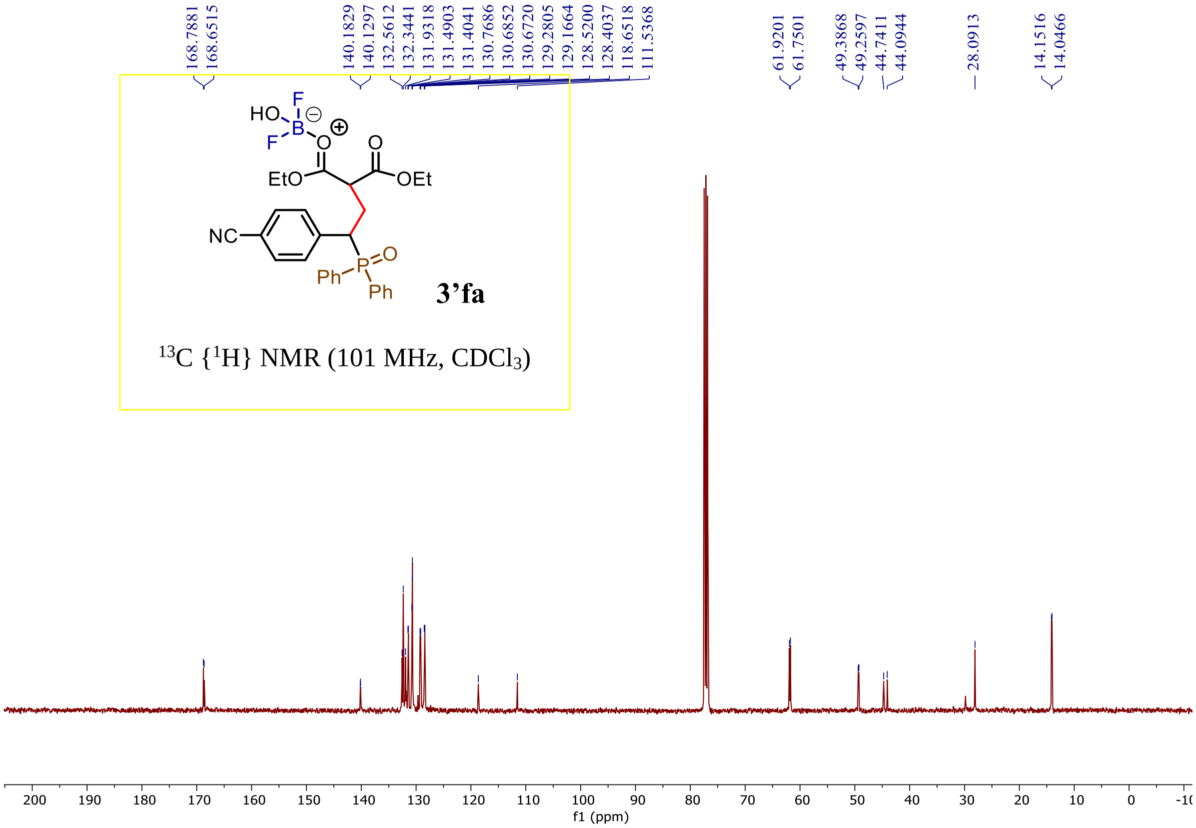
3’ea

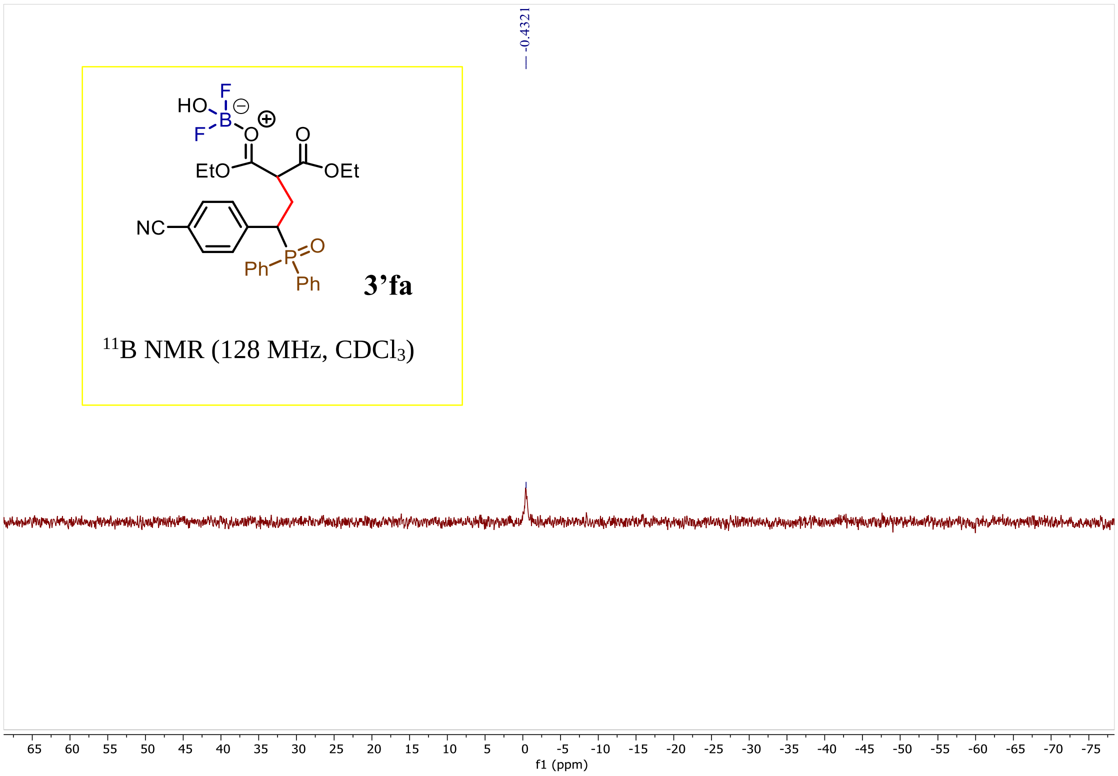
^{31}P NMR (162 MHz, CDCl$_3$)



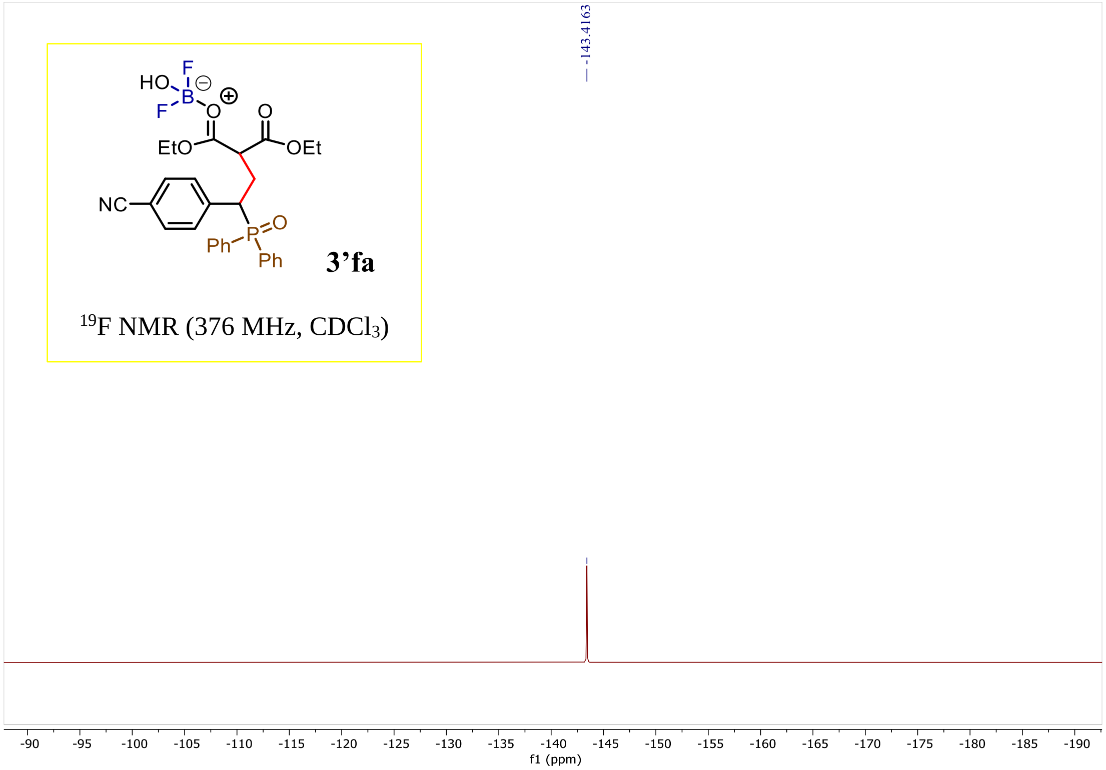
3’fa

^{1}H NMR (400 MHz, CDCl$_3$)

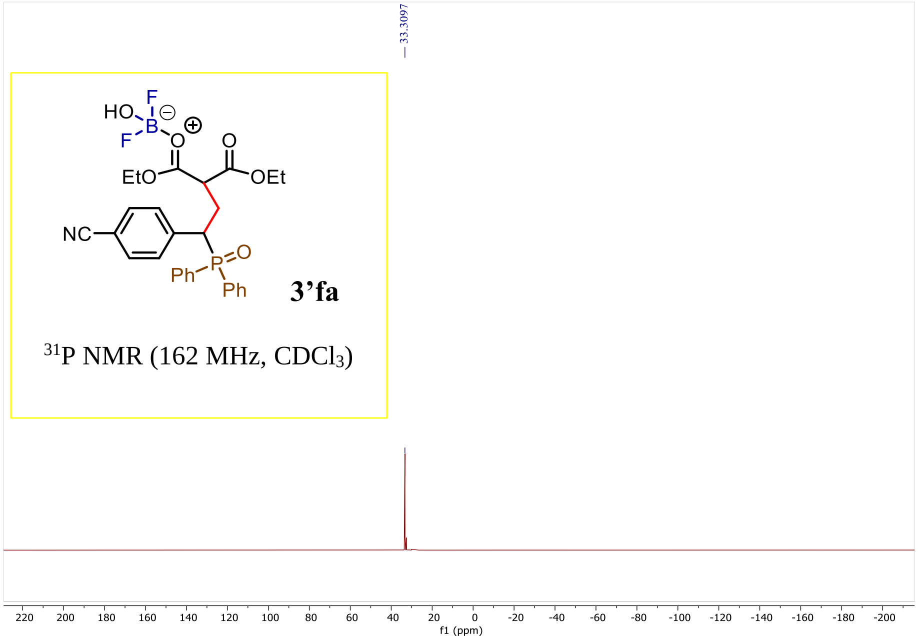

168.7881
168.6515
140.1829
140.1297
132.5612
132.3441
131.9318
131.4903
131.4041
130.7686
130.6852
130.6720
129.2805
129.1664
128.5200
128.4037
118.6518
111.5368
61.9201
61.7501
49.3868
49.2597
44.7411
44.0944
28.0913
14.1516
14.0466
HO
F
B
F
O
O
EtO
OEt
NC
P
O
Ph
Ph
3’fa
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1(
f1 (ppm)


3’fa

^{11}B NMR (128 MHz, $CDCl_3$)

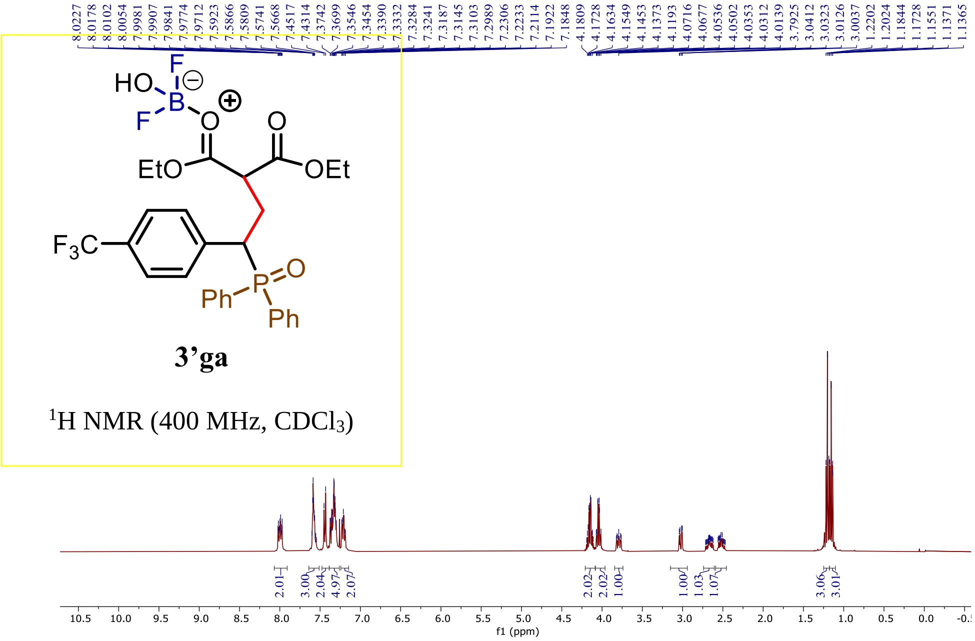

3’fa

^{19}F NMR (376 MHz, $CDCl_3$)



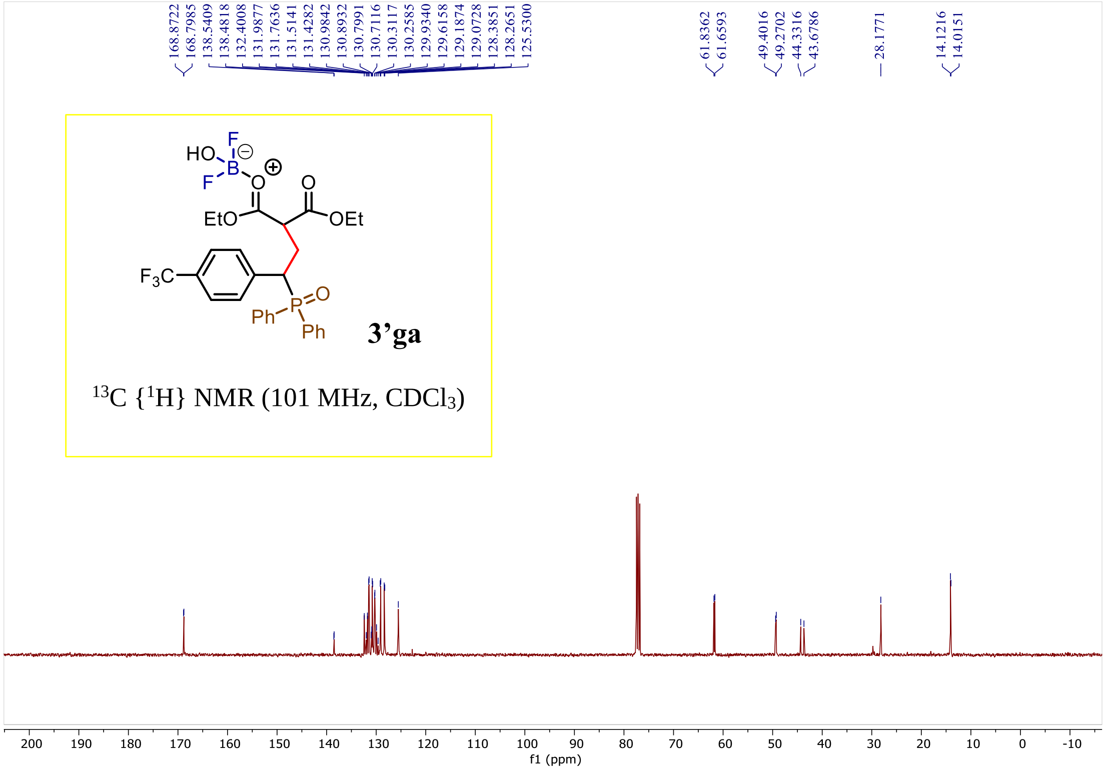
3’fa

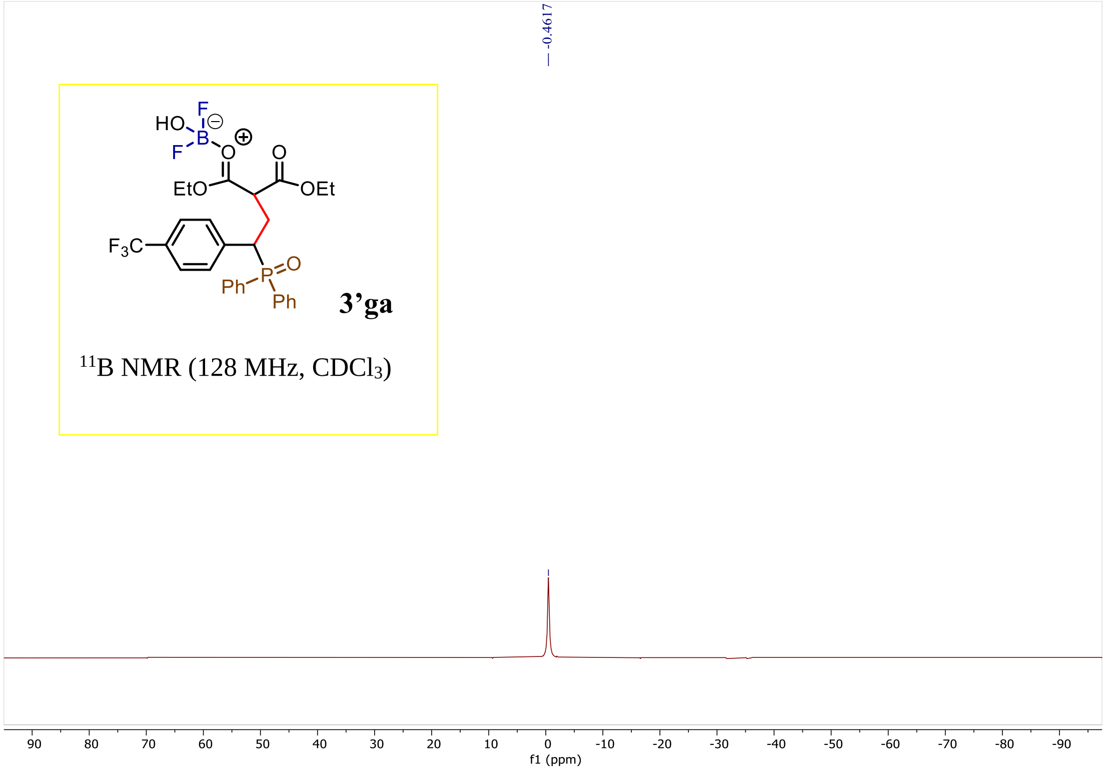
^{31}P NMR (162 MHz, CDCl$_3$)

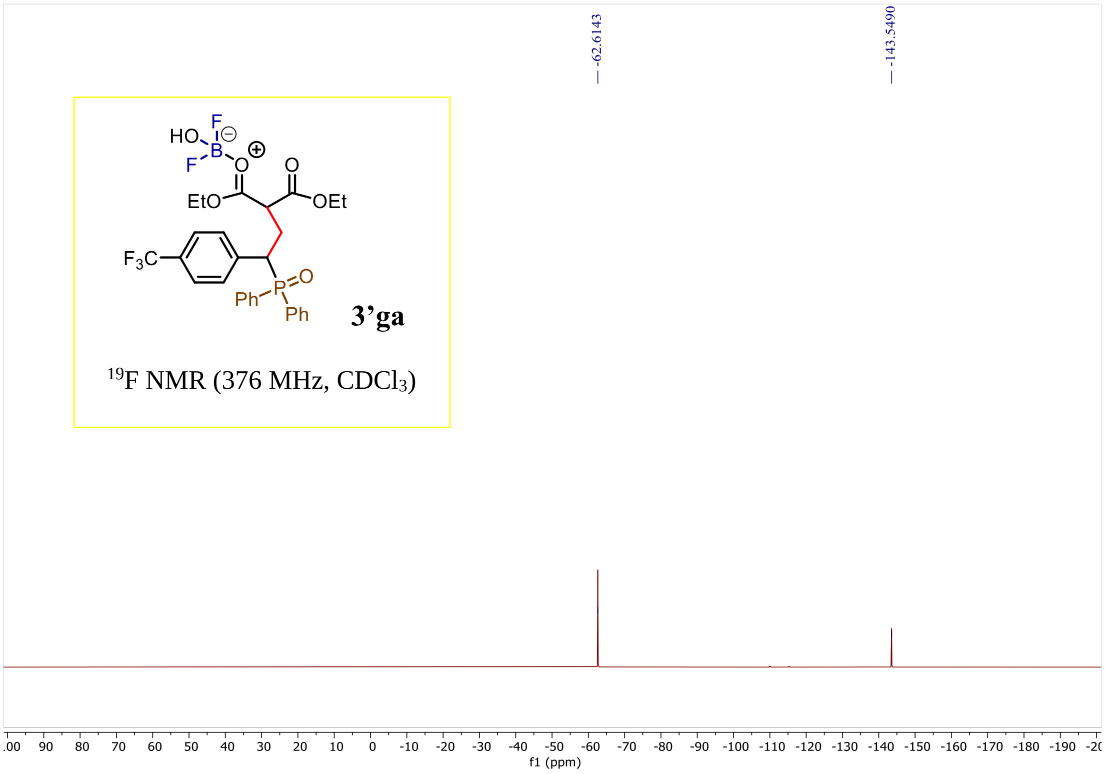


3’ga

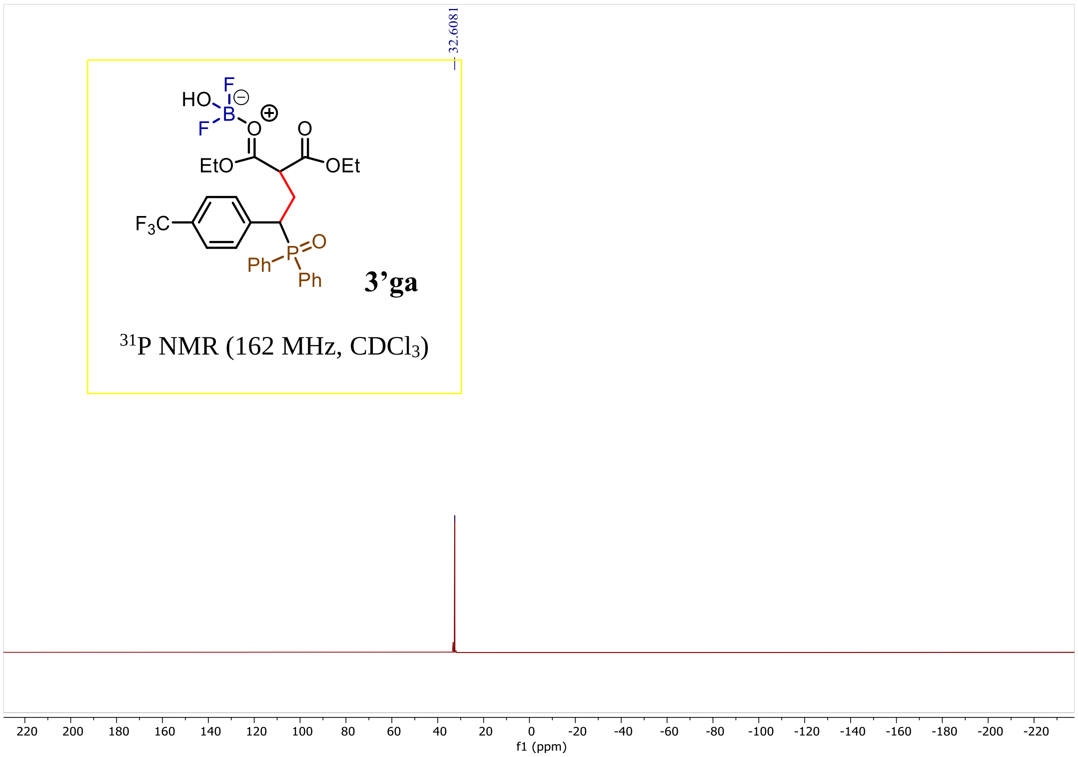
^{1}H NMR (400 MHz, CDCl$_3$)

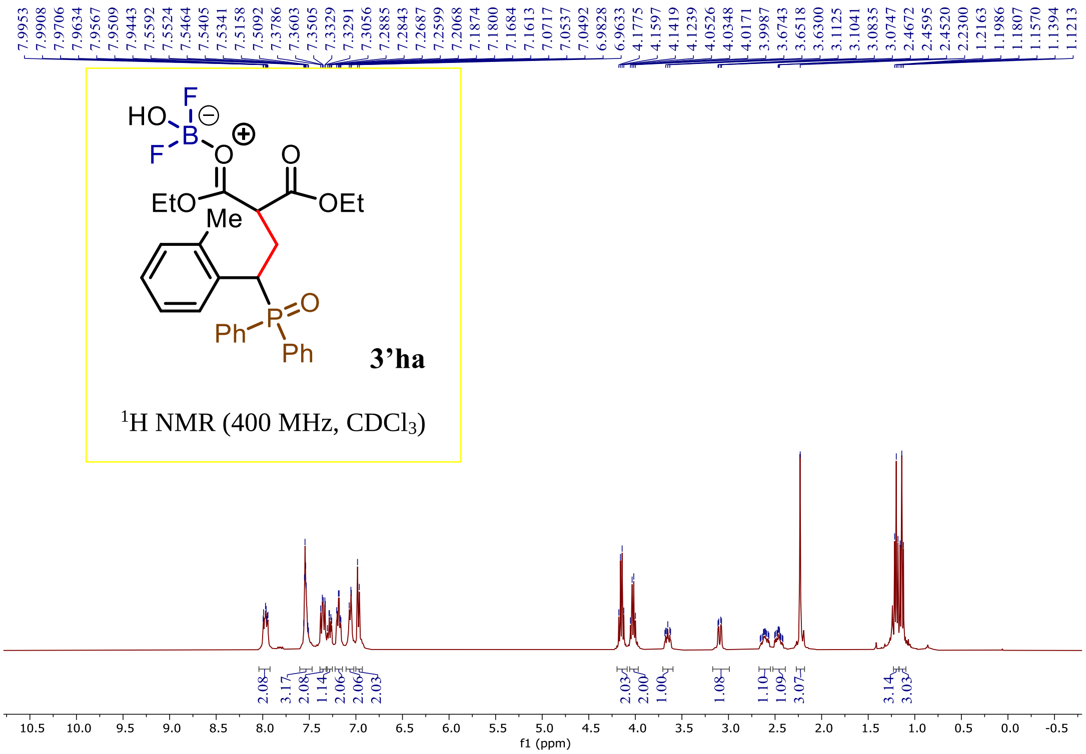

168.8722
168.7985
138.5409
138.4818
132.4008
131.9877
131.7636
131.5141
131.4282
130.9842
130.8932
130.7991
130.7116
130.3117
130.2585
129.9340
129.6158
129.1874
129.0728
128.3851
128.2651
125.5300
61.8362
61.6593
49.4016
49.2702
44.3316
43.6786
28.1771
14.1216
14.0151
HO
F
B
F
O
O
EtO
OEt
F_3C
P=O
Ph
Ph
3'ga
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

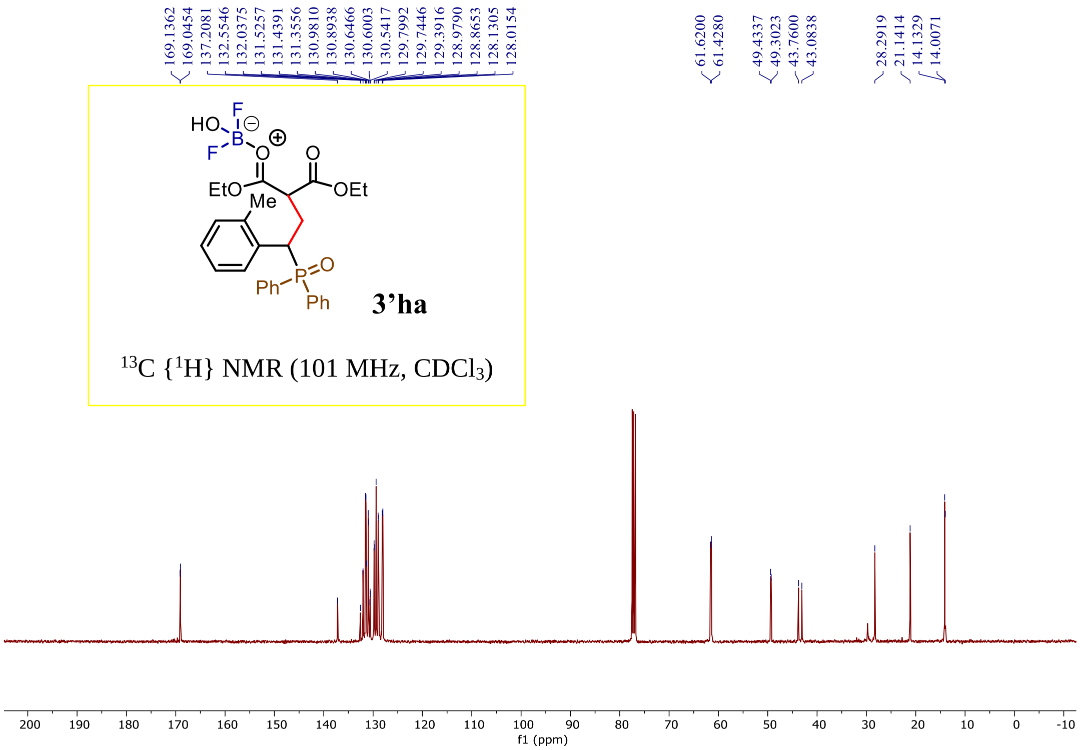

-0.4617
HO
F
B
F
O
O
EtO
OEt
F_3C
P=O
Ph
Ph
3'ga
^{11}B NMR (128 MHz, CDCl$_3$)
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)



-62.6143
-143.5490
HO
F
B
F
O
O
EtO
OEt
F3C
P=O
Ph
Ph
3'ga
19F NMR (376 MHz, CDCl3)
00
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-20
f1 (ppm)

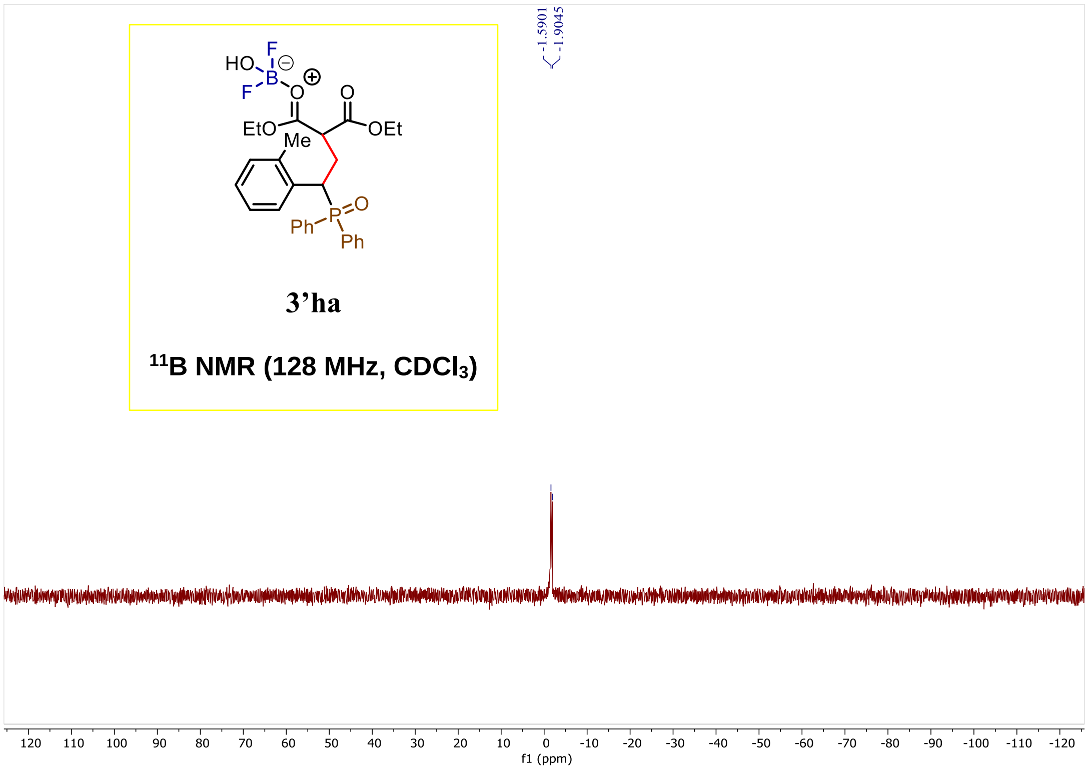

32.6081
HO
F
B
F
O
O
EtO
OEt
F3C
Ph
P=O
Ph
3'ga
31P NMR (162 MHz, CDCl3)
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
f1 (ppm)


7.9953
7.9908
7.9706
7.9634
7.9567
7.9509
7.9443
7.5592
7.5524
7.5464
7.5405
7.5341
7.5158
7.5092
7.3786
7.3603
7.3505
7.3329
7.3291
7.3056
7.2885
7.2843
7.2687
7.2599
7.2068
7.1874
7.1800
7.1684
7.1613
7.0717
7.0537
7.0492
6.9828
6.9633
4.1775
4.1597
4.1419
4.1239
4.0526
4.0348
4.0171
3.9987
3.6743
3.6518
3.6300
3.1125
3.1041
3.0835
3.0747
2.4672
2.4595
2.4520
2.2300
1.2163
1.1986
1.1807
1.1570
1.1394
1.1213
HO
F
B
F
O
O
EtO
OEt
Me
Ph
P=O
Ph
3'ha
1H NMR (400 MHz, CDCl3)
2.08
3.17
2.08
1.14
2.06
2.06
2.03
2.03
2.00
1.00
1.08
1.10
1.09
3.07
3.14
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
-0.5
f1 (ppm)



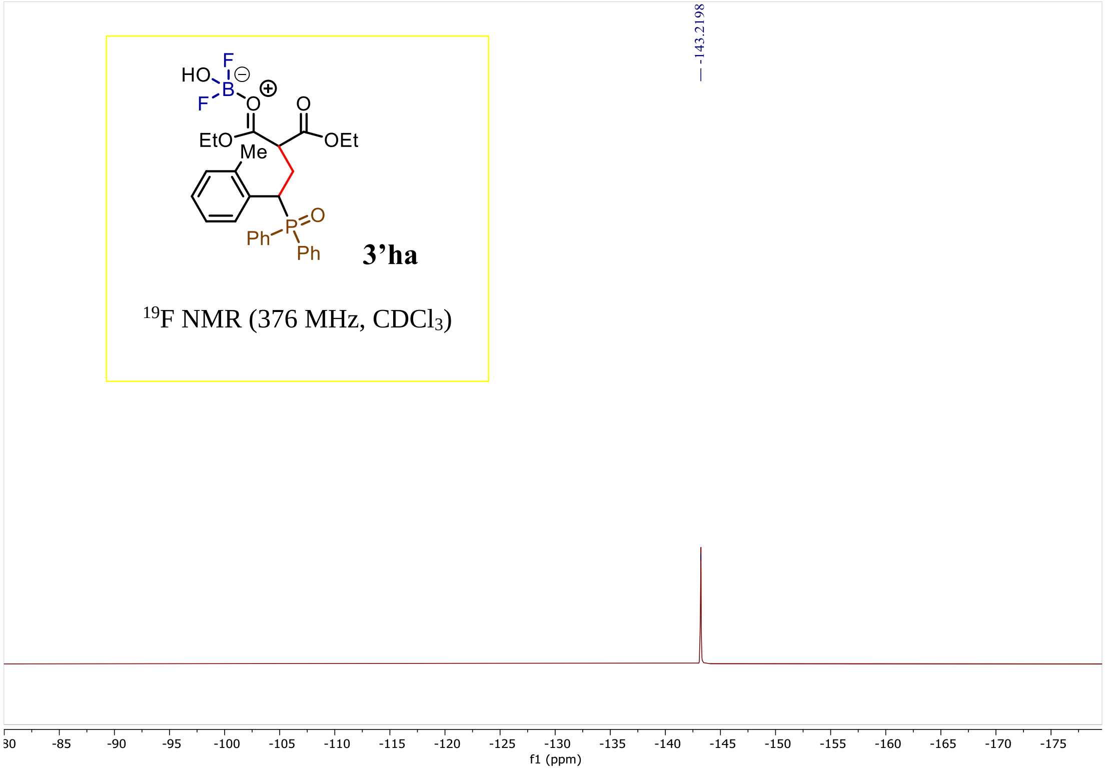
3’ha

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)



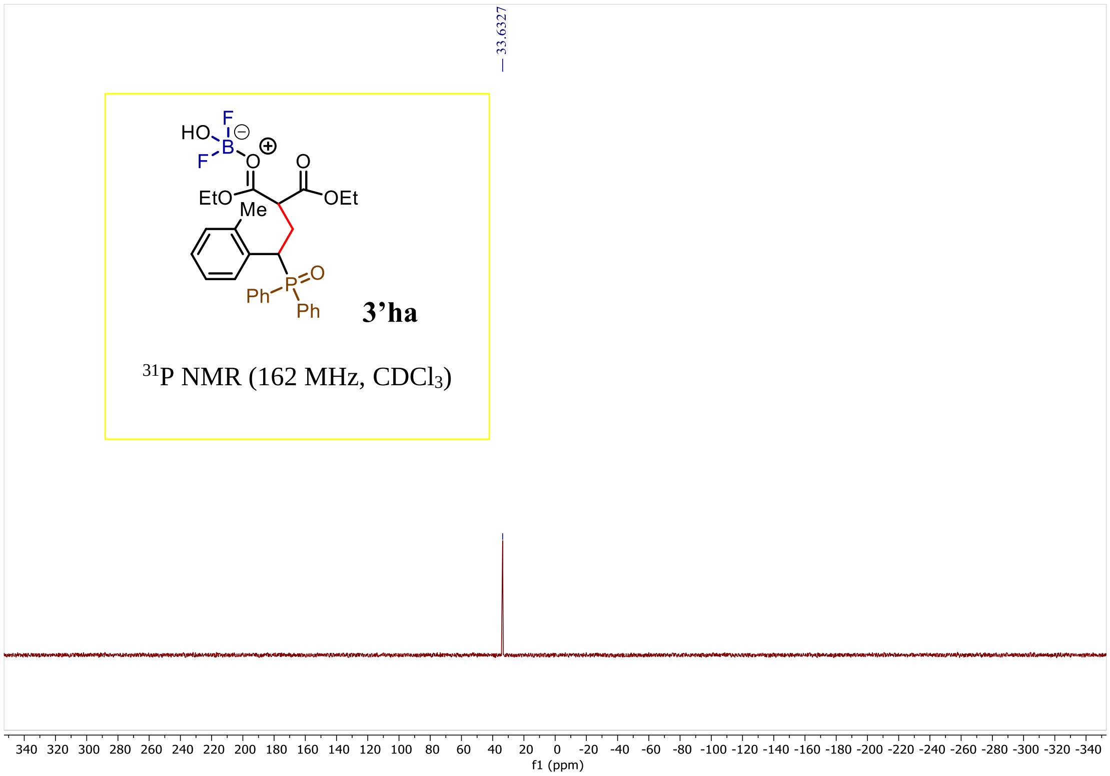
3’ha

^{11}B NMR (128 MHz, $CDCl_3$)



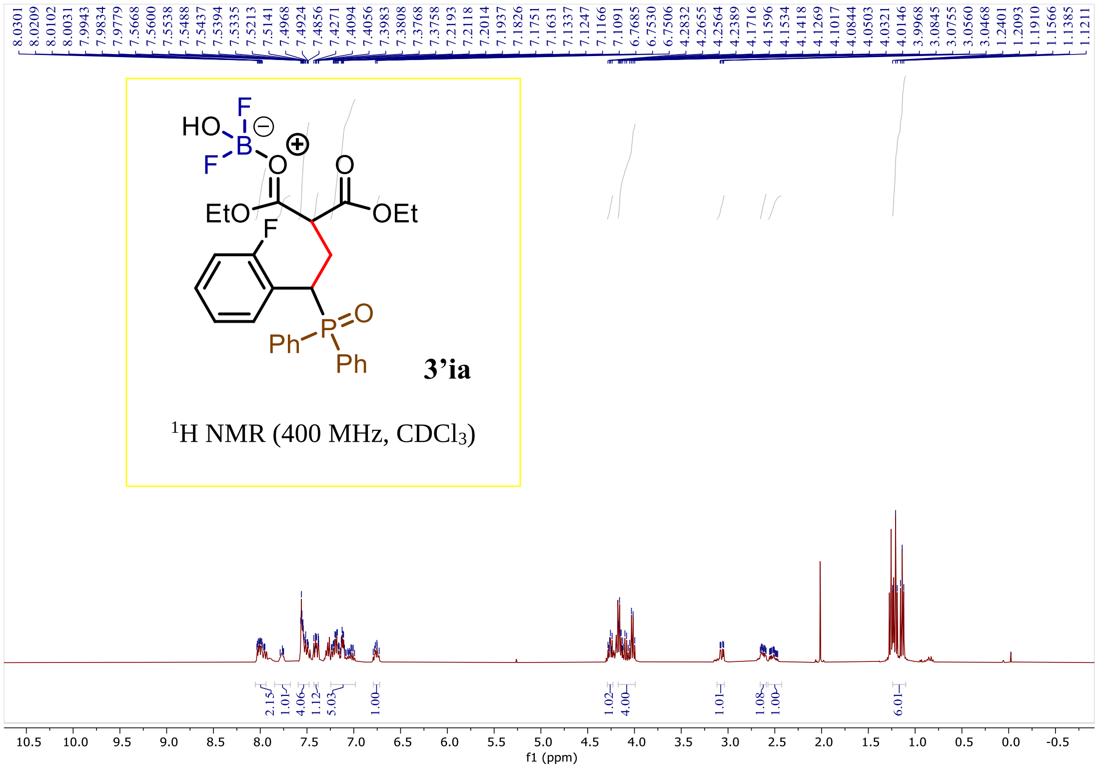
3’ha

^{19}F NMR (376 MHz, $CDCl_3$)



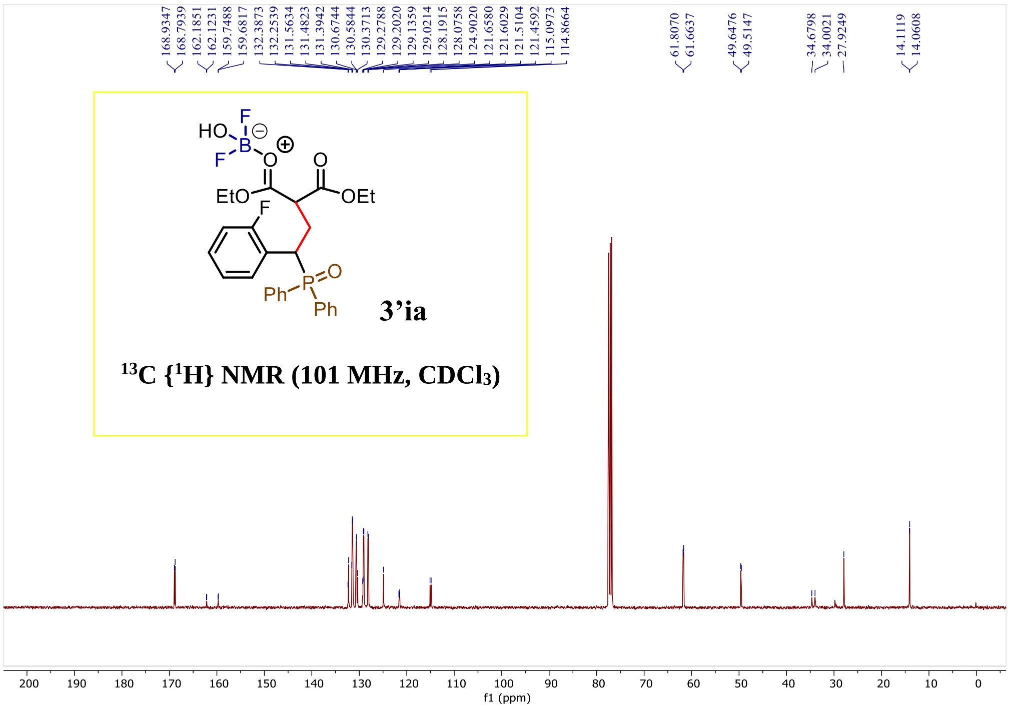
3’ha

^{31}P NMR (162 MHz, CDCl$_3$)



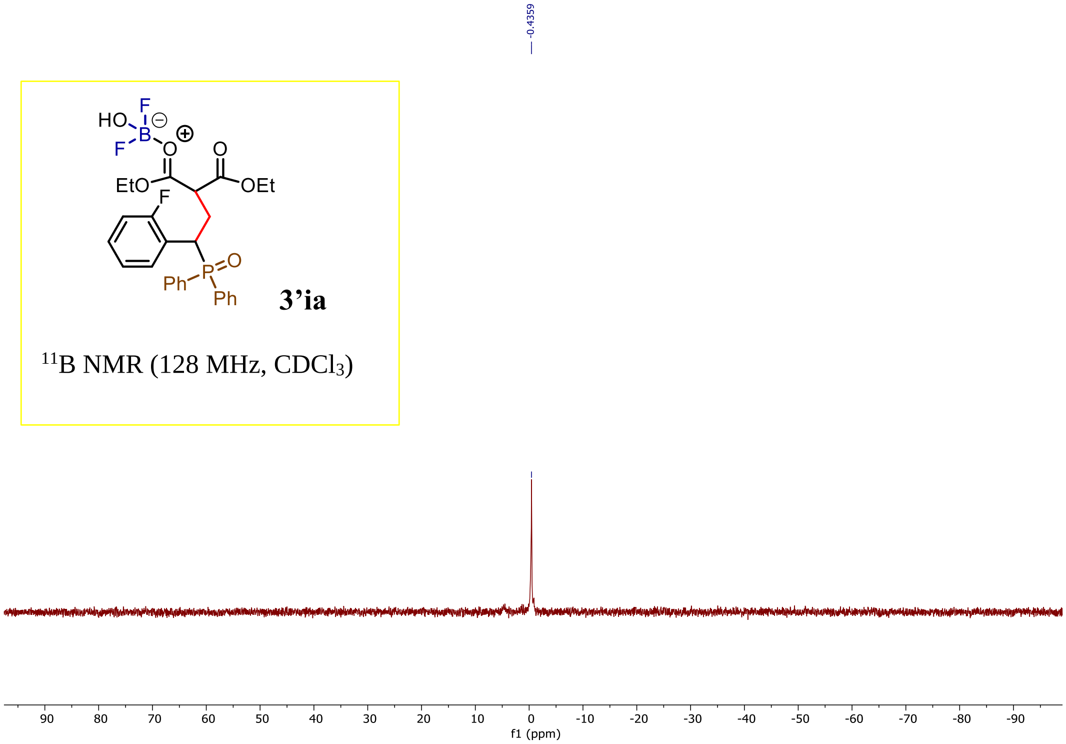
3’ia

^{1}H NMR (400 MHz, CDCl$_3$)



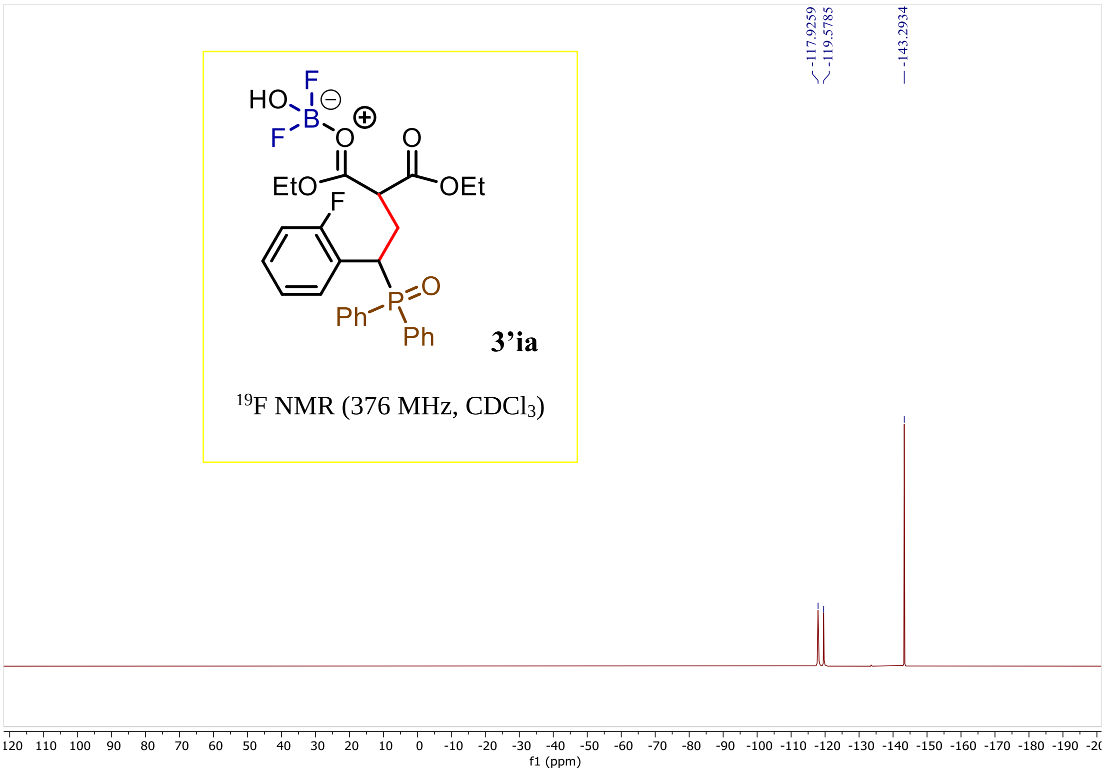
3’ia

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)



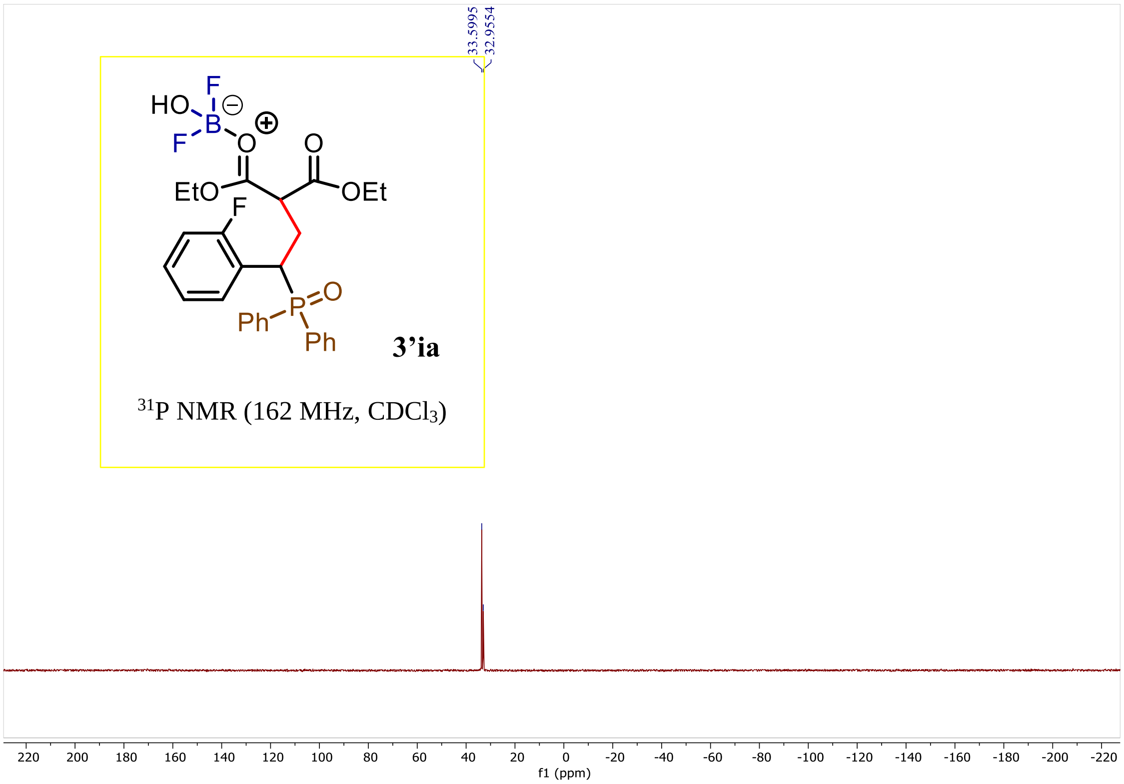
3’ia

^{11}B NMR (128 MHz, CDCl$_3$)



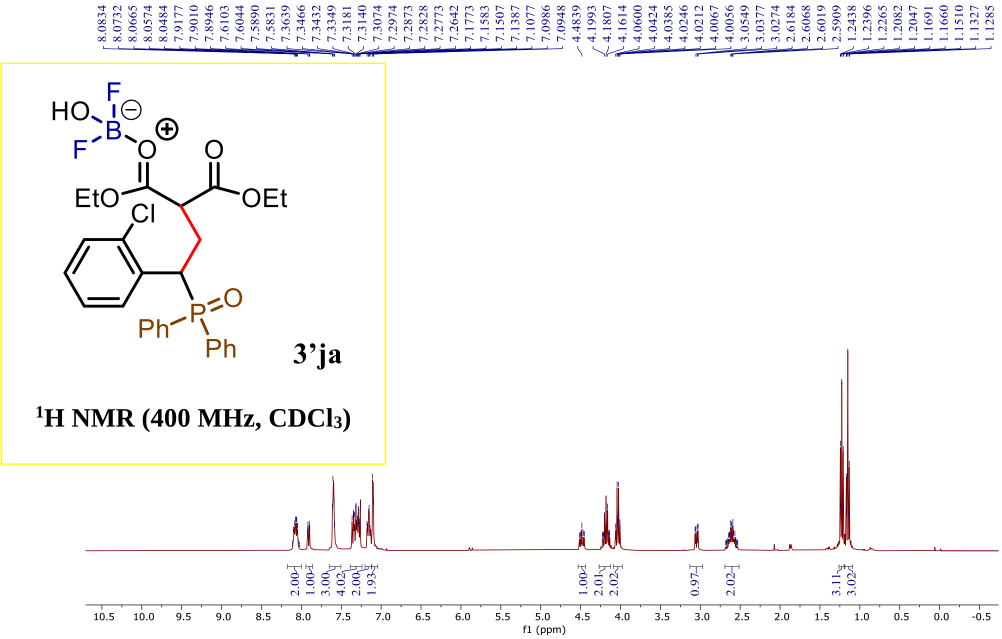
3’ia

^{19}F NMR (376 MHz, $CDCl_3$)



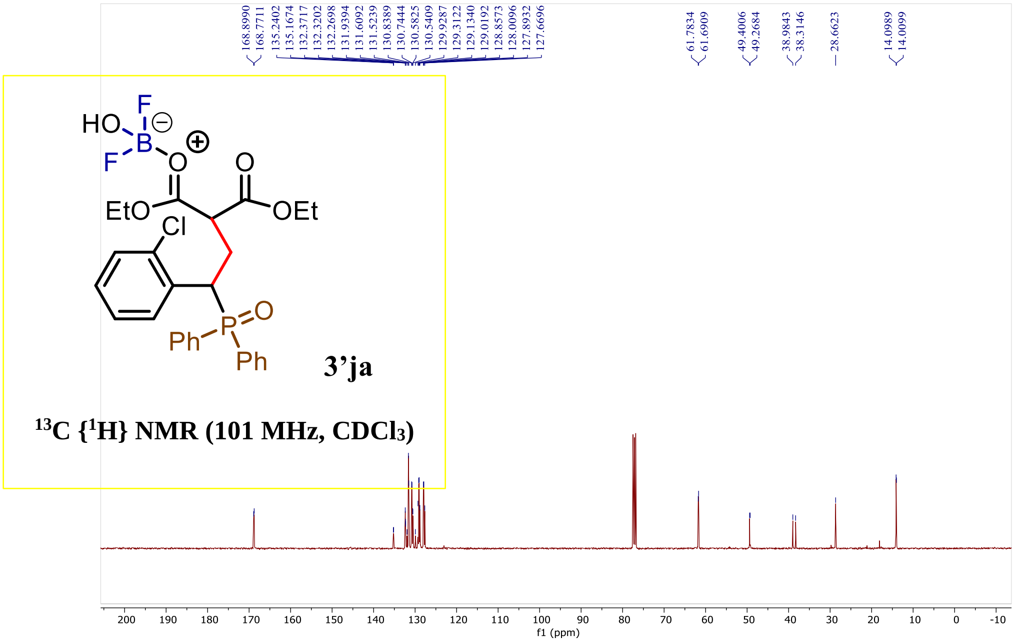
3’ia

^{31}P NMR (162 MHz, CDCl$_3$)



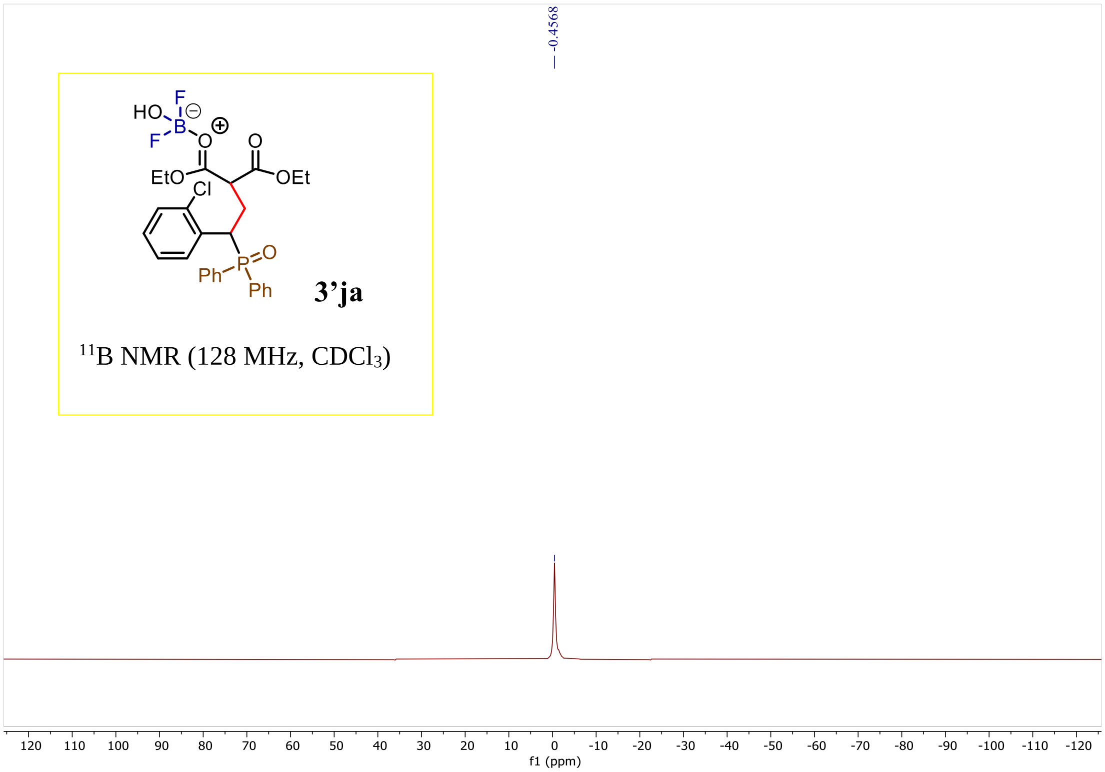
3’ja

^{1}H NMR (400 MHz, CDCl$_3$)



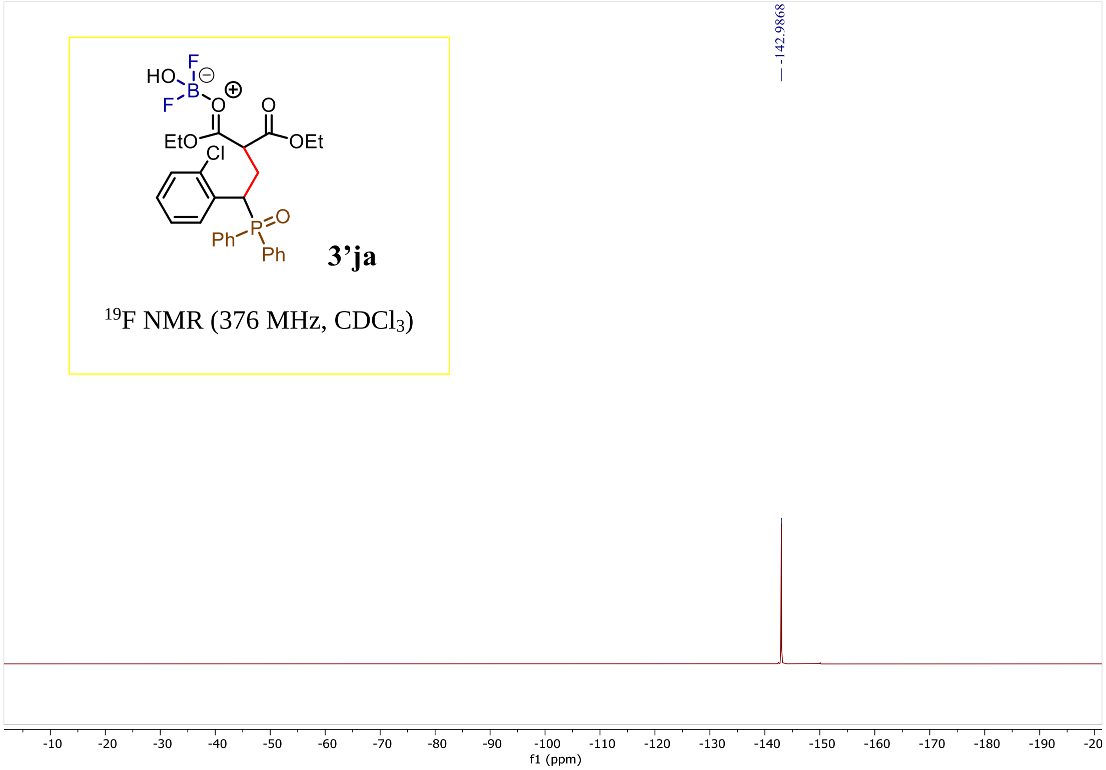
3’ja

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)



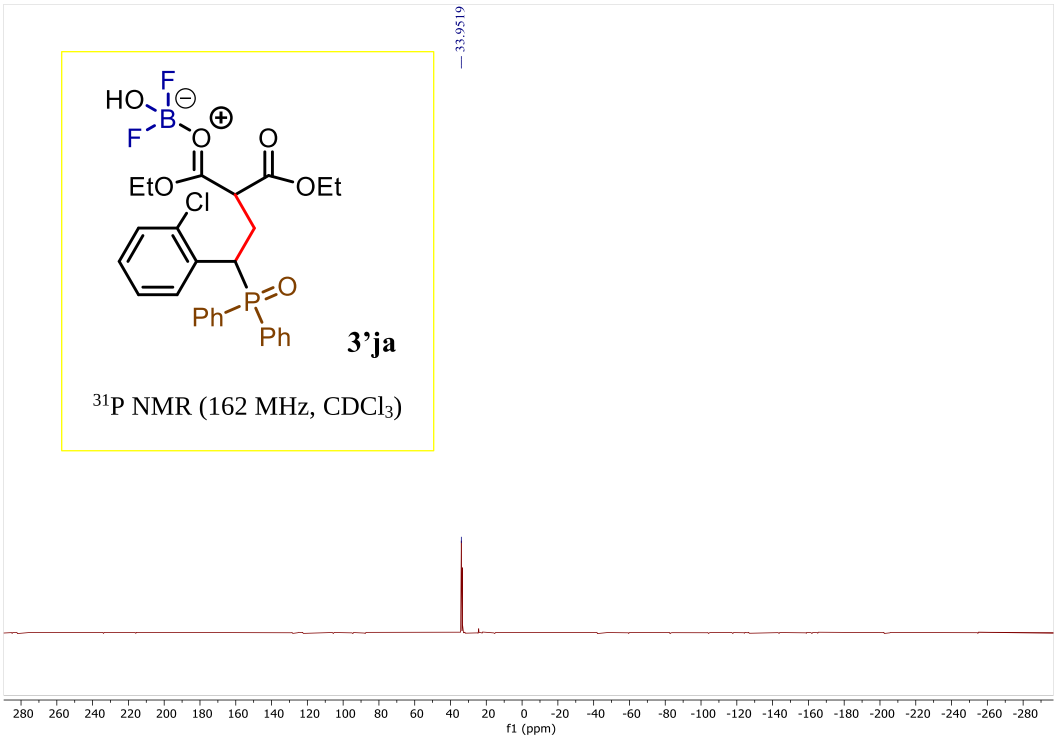
3’ja

^{11}B NMR (128 MHz, CDCl$_3$)



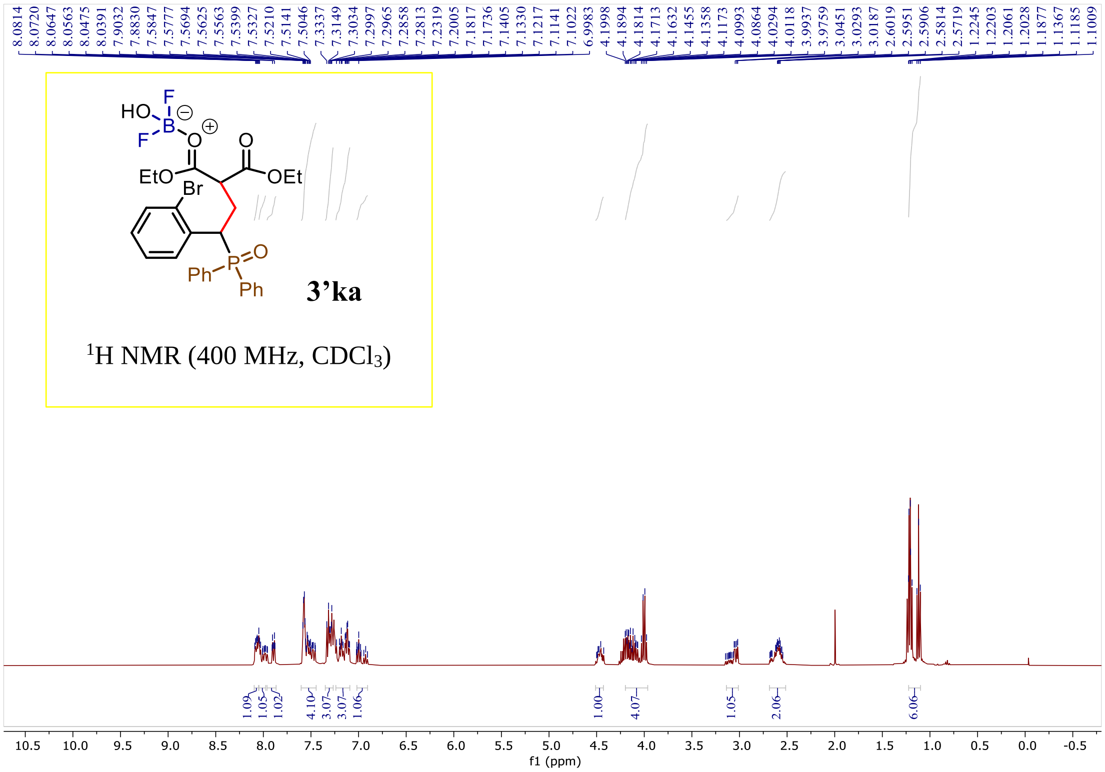
3’ja

^{19}F NMR (376 MHz, CDCl$_3$)



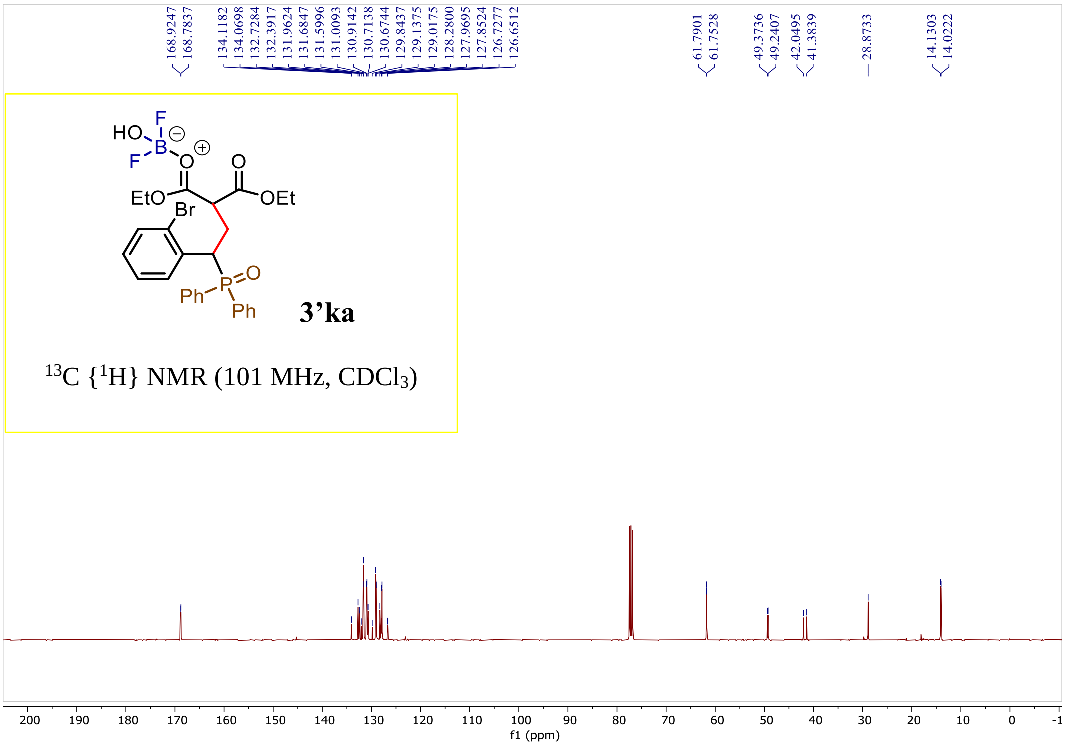
3’ja

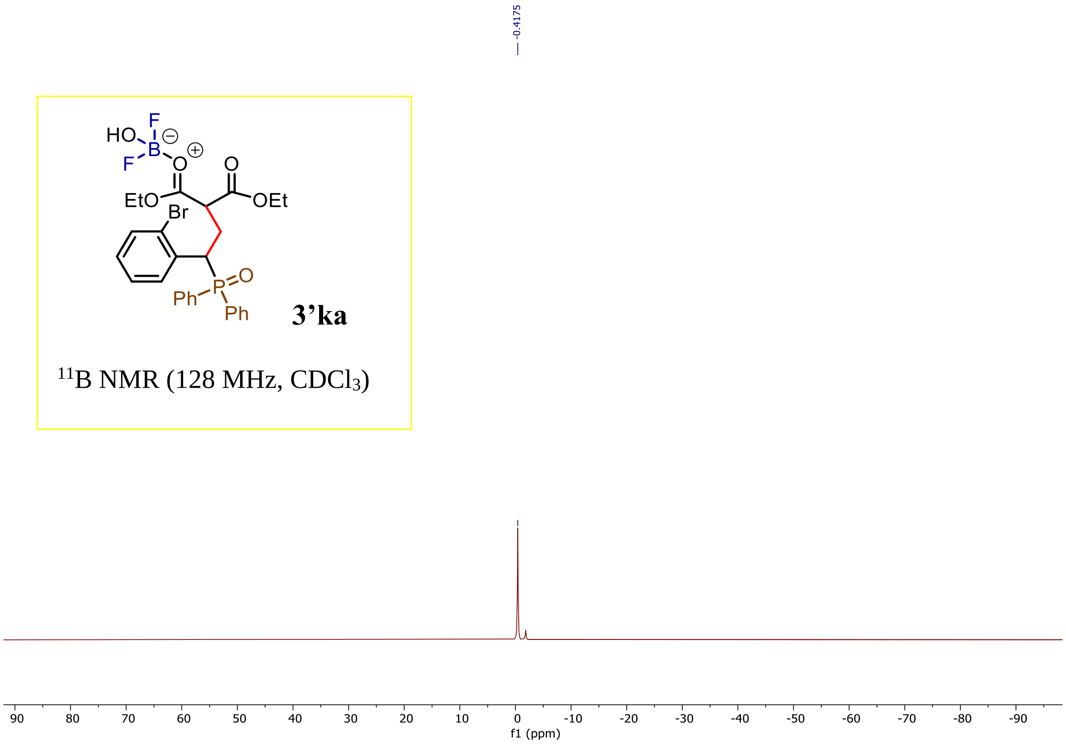
^{31}P NMR (162 MHz, CDCl$_3$)

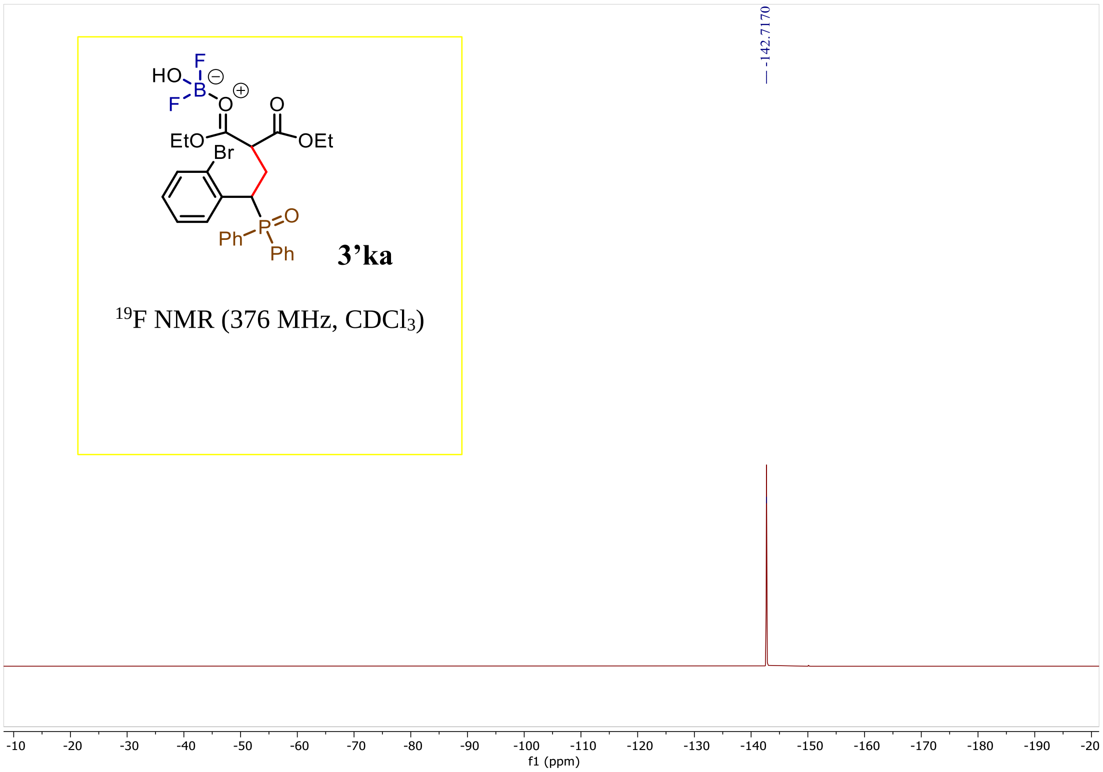


3’ka

^{1}H NMR (400 MHz, CDCl$_3$)

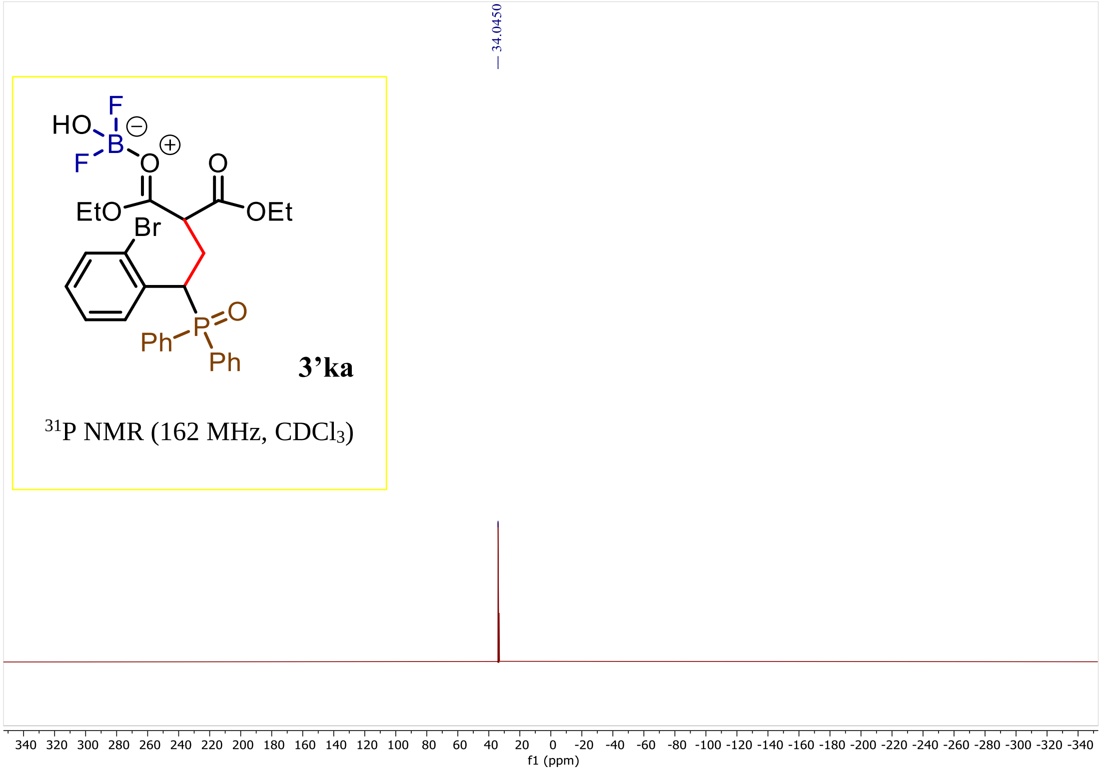

168.9247
168.7837
134.1182
134.0698
132.7284
132.3917
131.9624
131.6847
131.5996
131.0093
130.9142
130.7138
130.6744
129.8437
129.1375
129.0175
128.2800
127.9695
127.8524
126.7277
126.6512
61.7901
61.7528
49.3736
49.2407
42.0495
41.3839
28.8733
14.1303
14.0222
HO
F
B
O
F
O
EtO
OEt
Br
P
O
Ph
Ph
3'ka
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

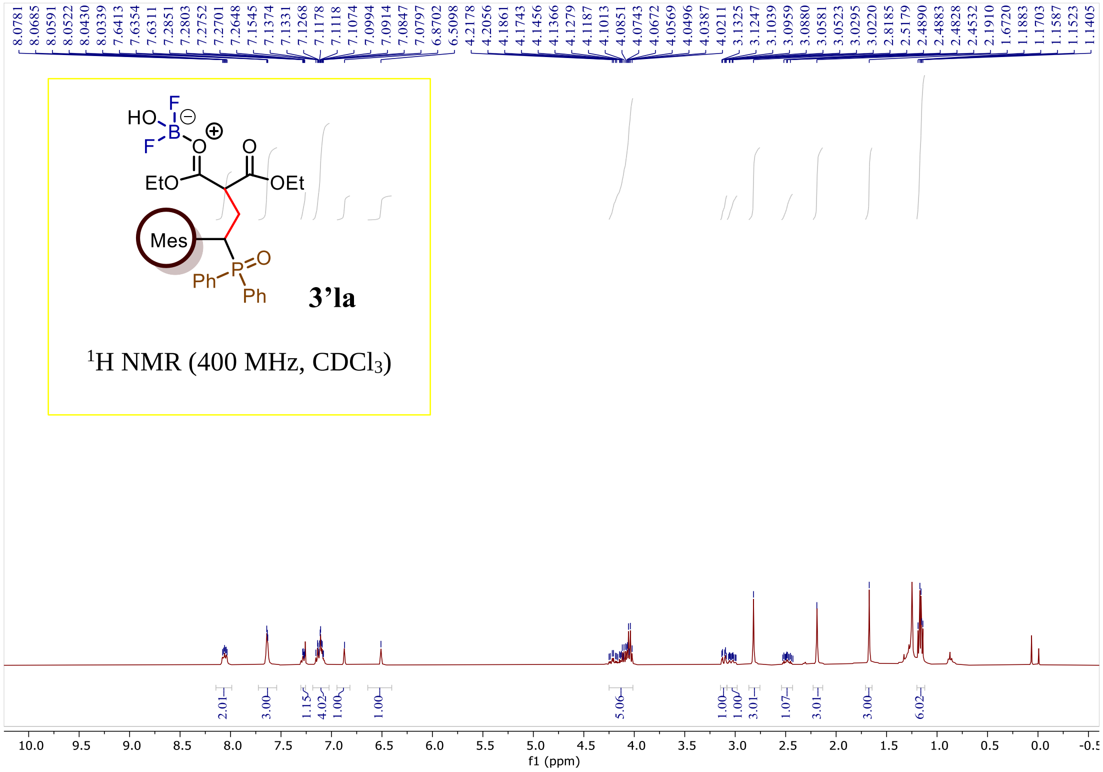

-0.4175
HO
F
B
O
F
O
EtO
OEt
Br
P
O
Ph
Ph
3'ka
^{11}B NMR (128 MHz, CDCl$_3$)
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
f1 (ppm)

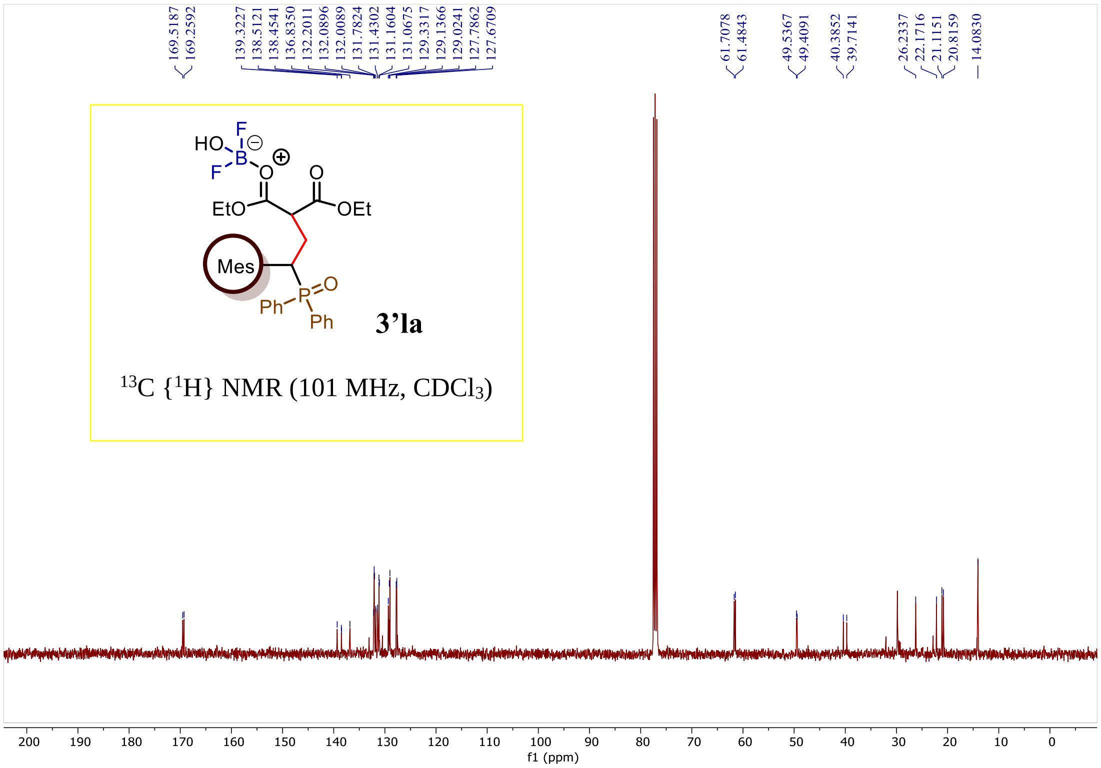


3’ka

^{19}F NMR (376 MHz, $CDCl_3$)

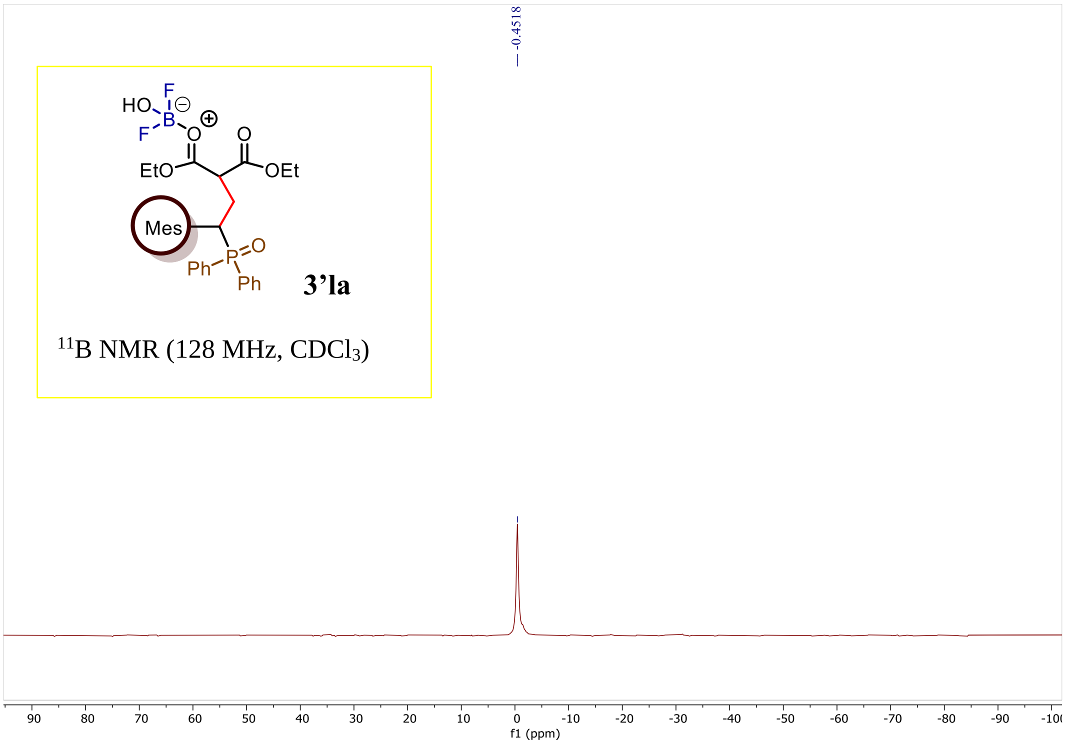

34.0450
HO
F
B
F
O
O
EtO
OEt
Br
P
O
Ph
Ph
3’ka
^{31}P NMR (162 MHz, CDCl$_3$)
340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240 -260 -280 -300 -320 -340
f1 (ppm)


8.0781
8.0685
8.0591
8.0522
8.0430
8.0339
7.6413
7.6354
7.6311
7.2851
7.2803
7.2752
7.2701
7.2648
7.1545
7.1374
7.1331
7.1268
7.1178
7.1118
7.1074
7.0994
7.0914
7.0847
7.0797
6.8702
6.5098
4.2178
4.2056
4.1861
4.1743
4.1456
4.1366
4.1279
4.1187
4.1013
4.0851
4.0743
4.0672
4.0569
4.0496
4.0387
4.0211
3.1325
3.1247
3.1039
3.0959
3.0880
3.0581
3.0523
3.0295
3.0220
2.8185
2.5179
2.4890
2.4883
2.4828
2.4532
2.1910
1.6720
1.1883
1.1703
1.1587
1.1523
1.1405
HO
F
B
F
O
O
EtO
OEt
Mes
P
O
Ph
Ph
3’la
^{1}H NMR (400 MHz, CDCl$_3$)
2.01
3.00
1.15
4.02
1.00
1.00
5.06
1.00
1.00
3.01
1.07
3.01
3.00
6.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



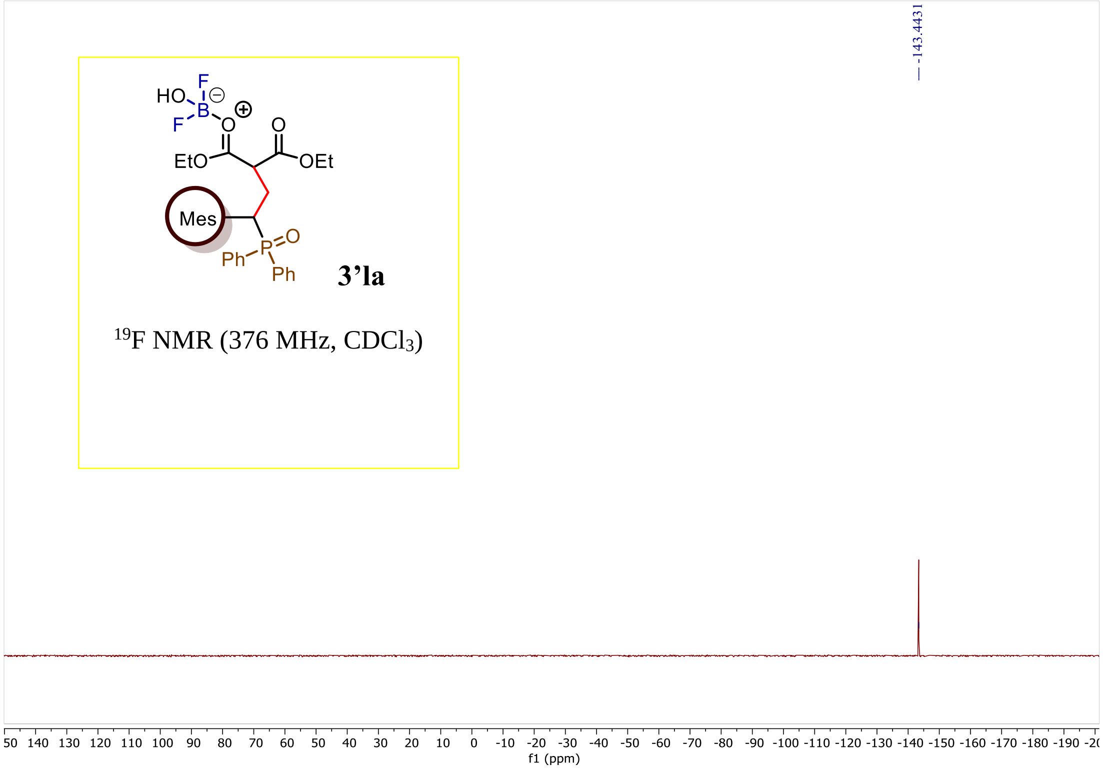
3’la

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)



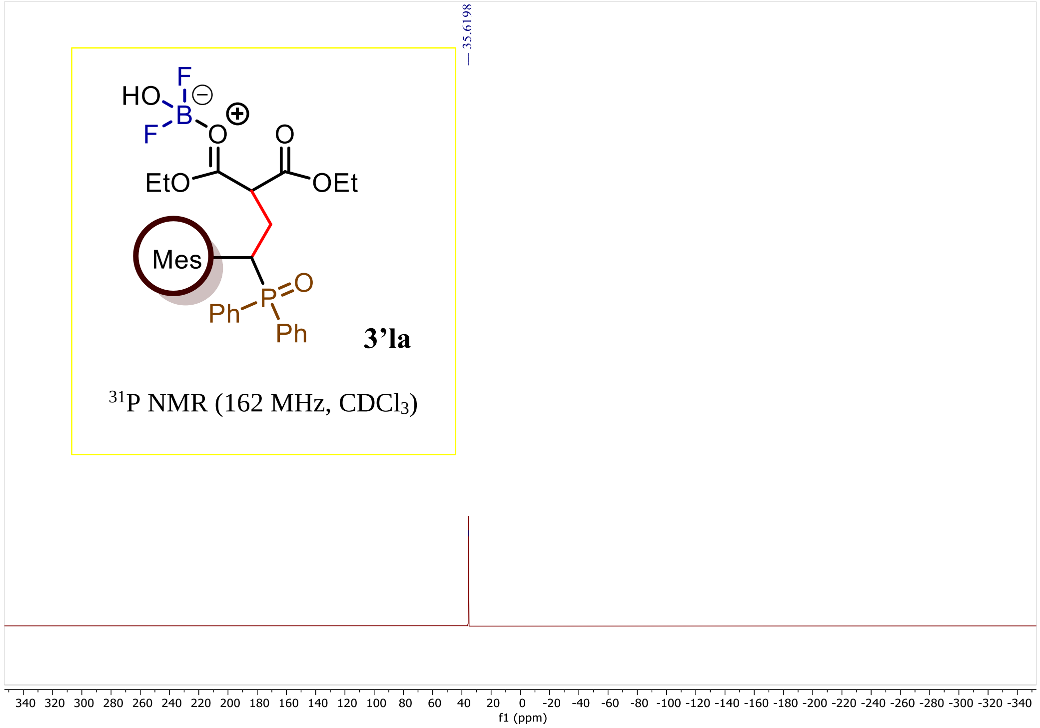
3’la

^{11}B NMR (128 MHz, $CDCl_3$)



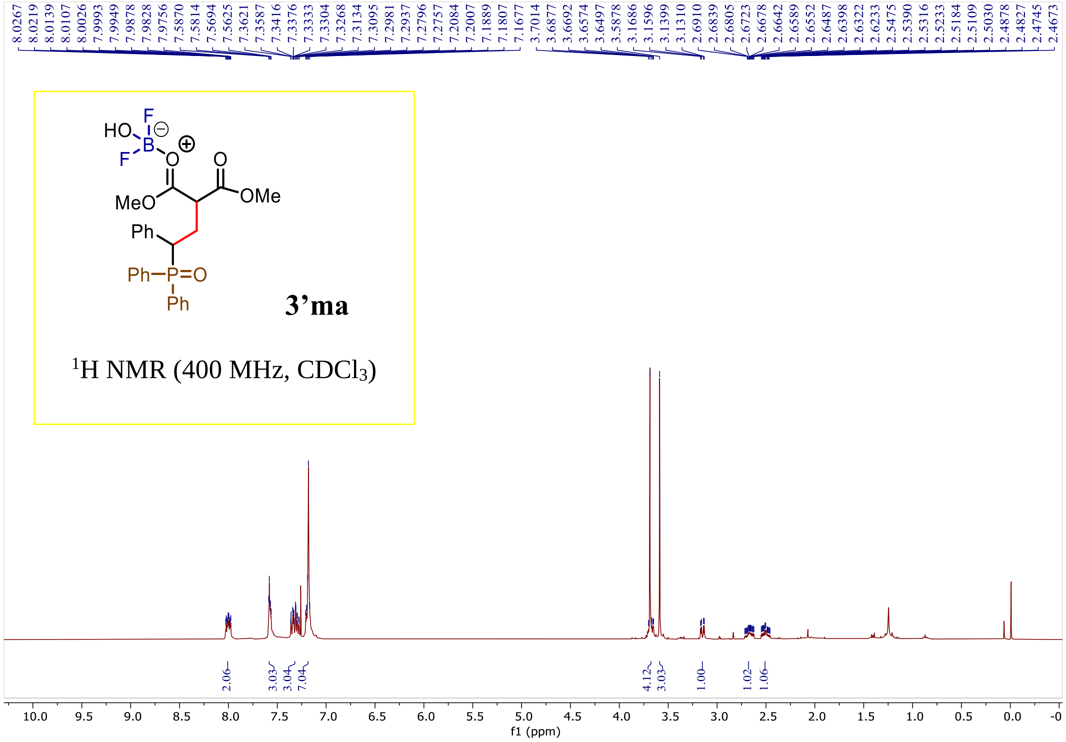
3’la

^{19}F NMR (376 MHz, $CDCl_3$)



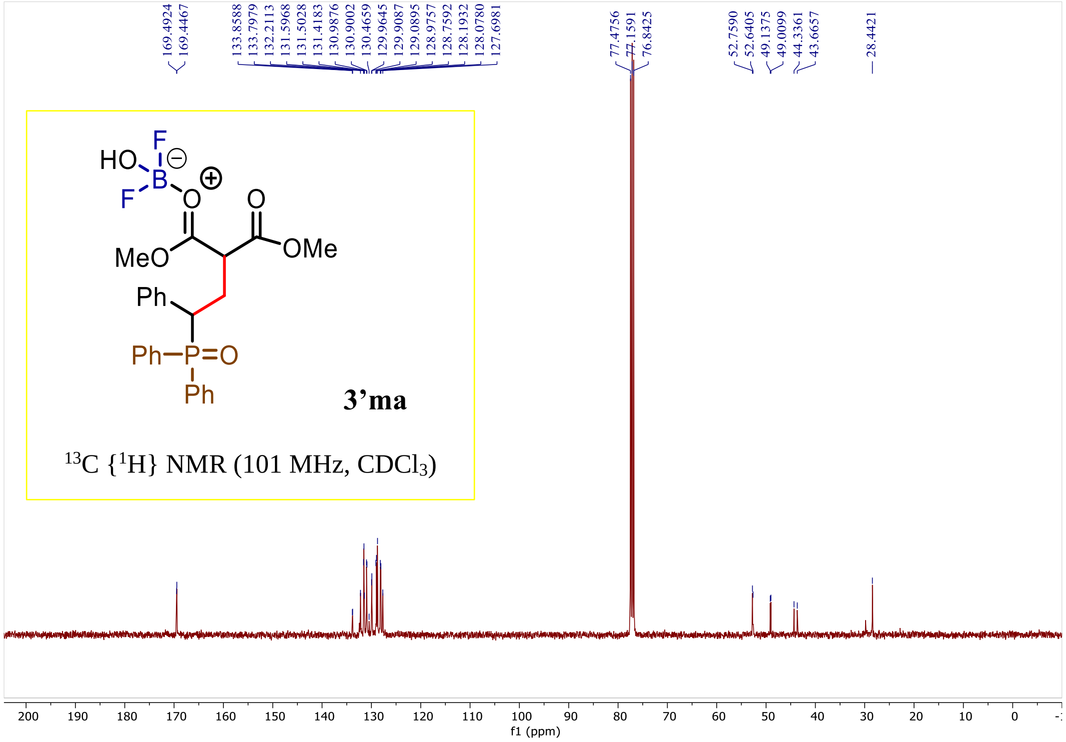
3'la

^{31}P NMR (162 MHz, $CDCl_3$)



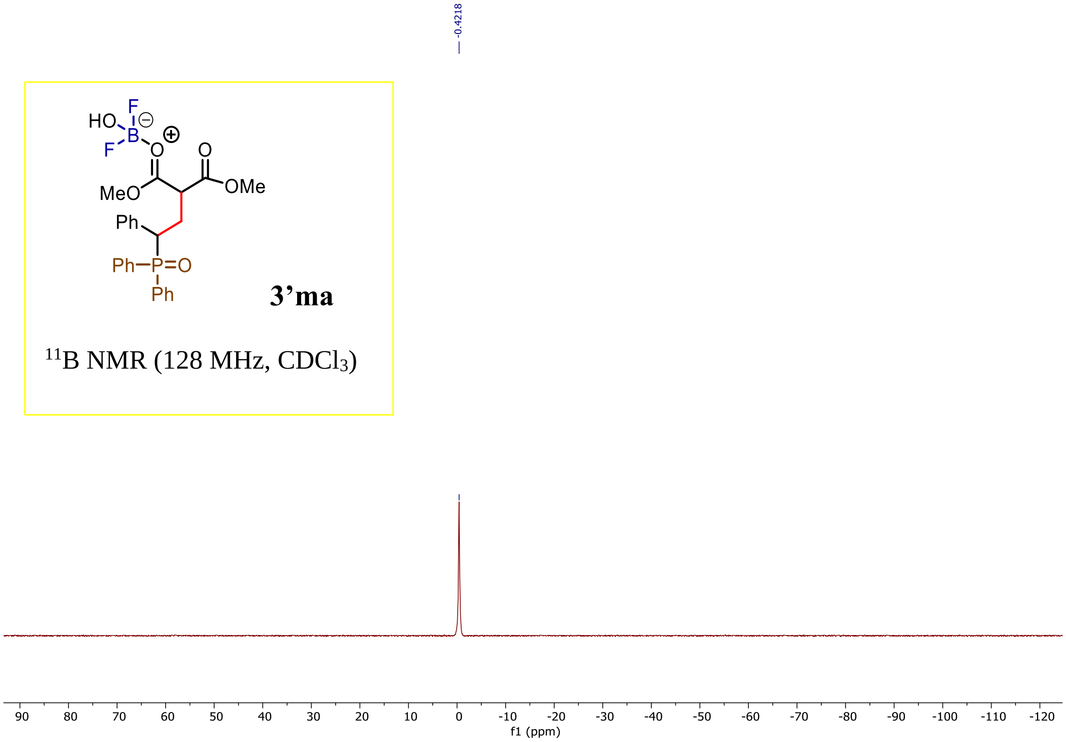
3'ma

^{1}H NMR (400 MHz, $CDCl_3$)



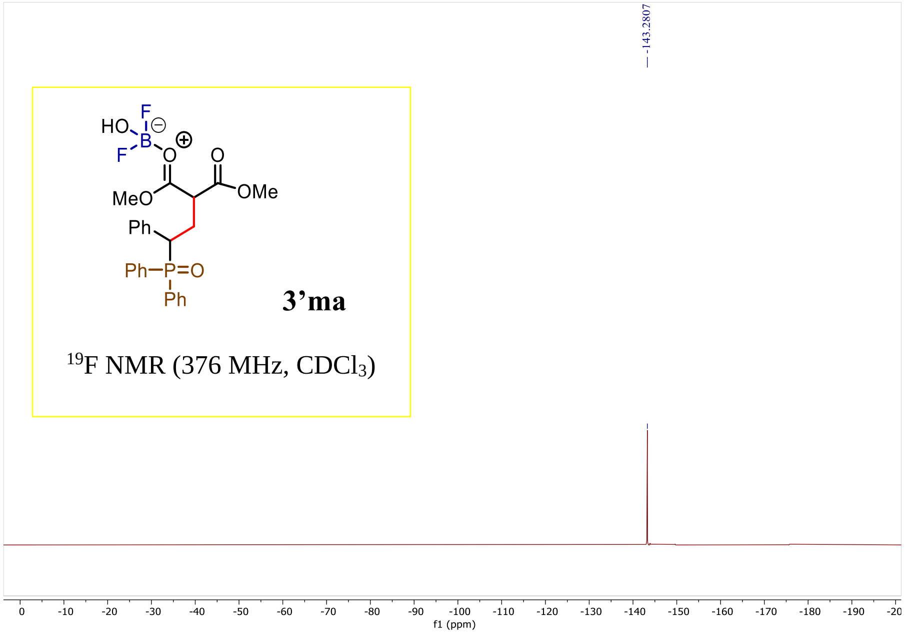
3’ma

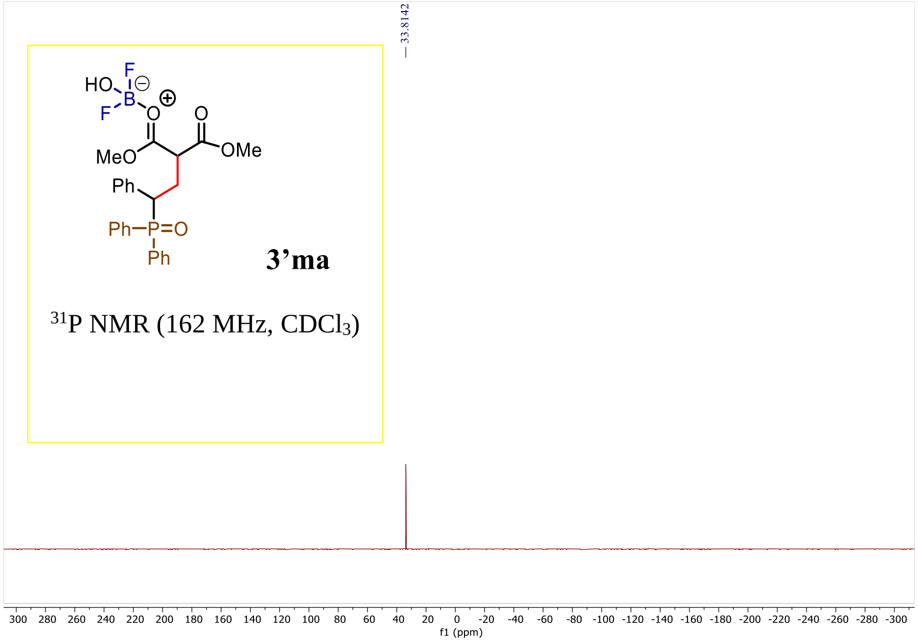
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)

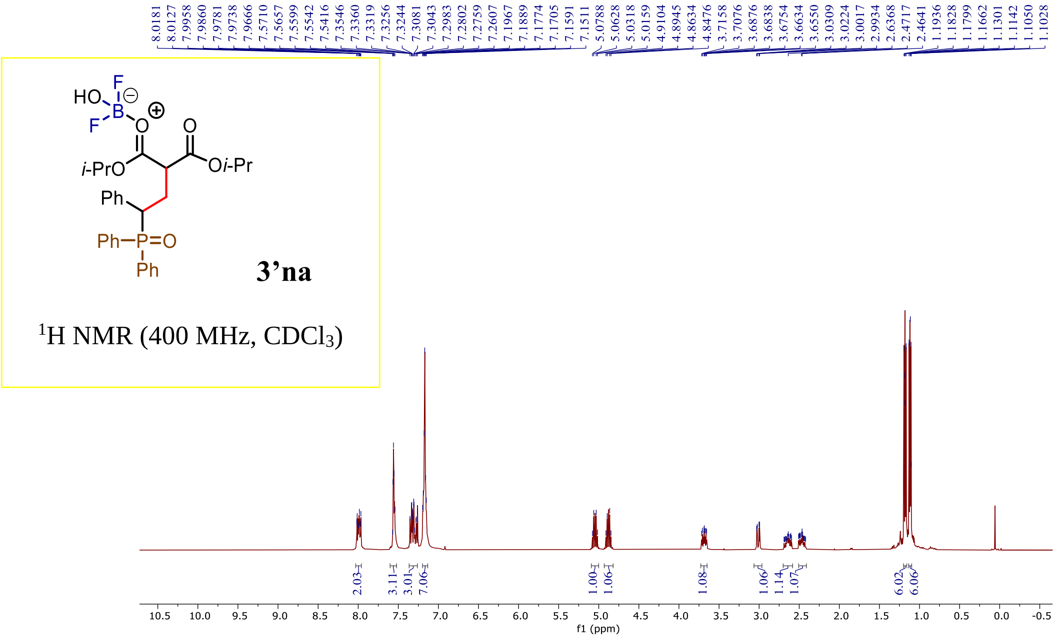


3’ma

^{11}B NMR (128 MHz, CDCl$_3$)

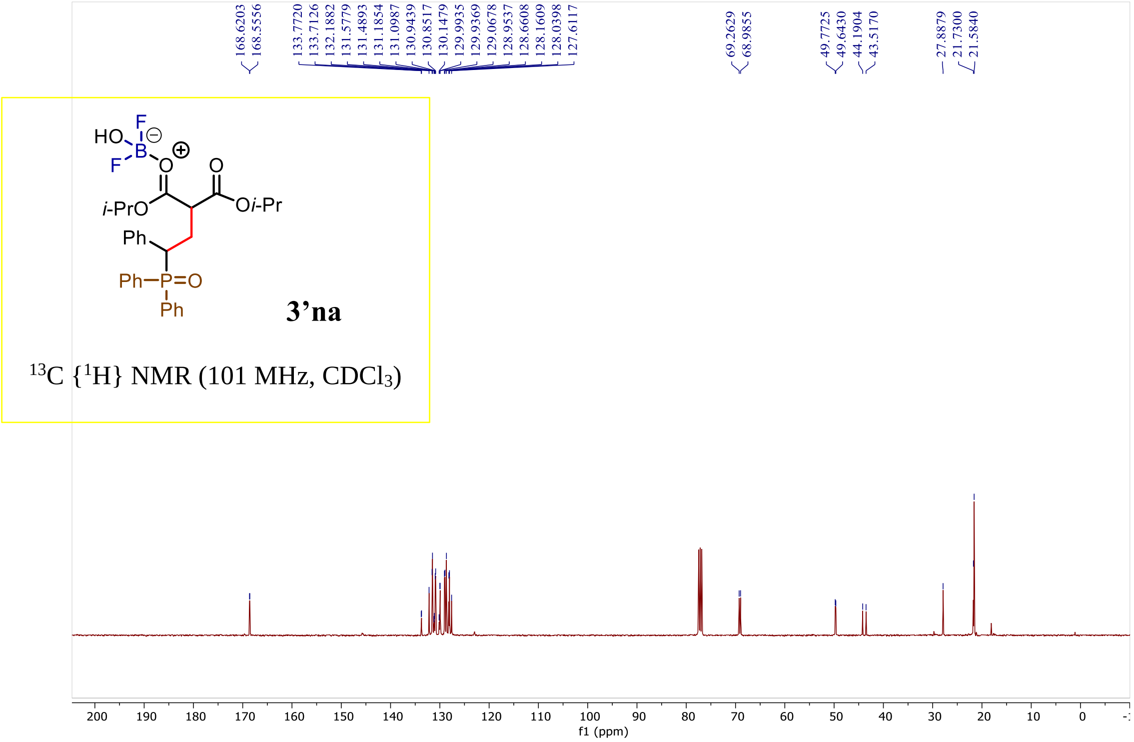

-143.2807
HO
F
B
F
O
O
MeO
OMe
Ph
Ph
P=O
Ph
3'ma
^{19}F NMR (376 MHz, CDCl$_3$)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-20
f1 (ppm)


33.8142
HO
F
B
F
O
O
MeO
OMe
Ph
Ph
P=O
Ph
3'ma
^{31}P NMR (162 MHz, CDCl$_3$)
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)



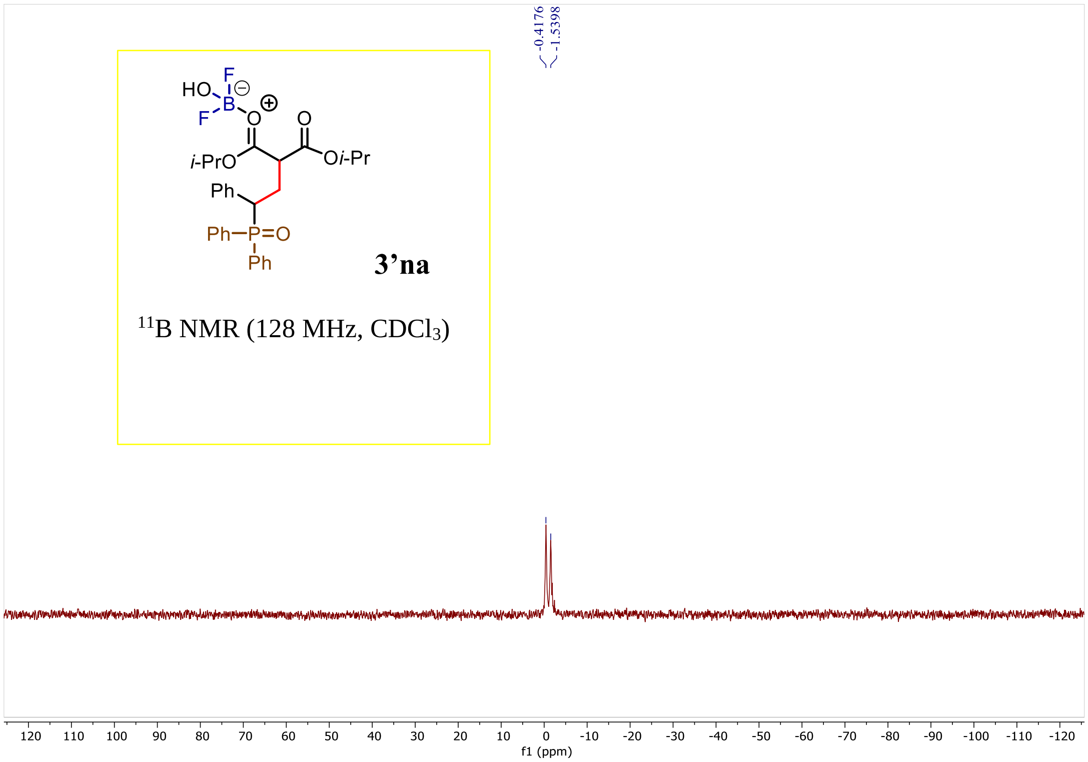
3’na

^{1}H NMR (400 MHz, CDCl$_3$)



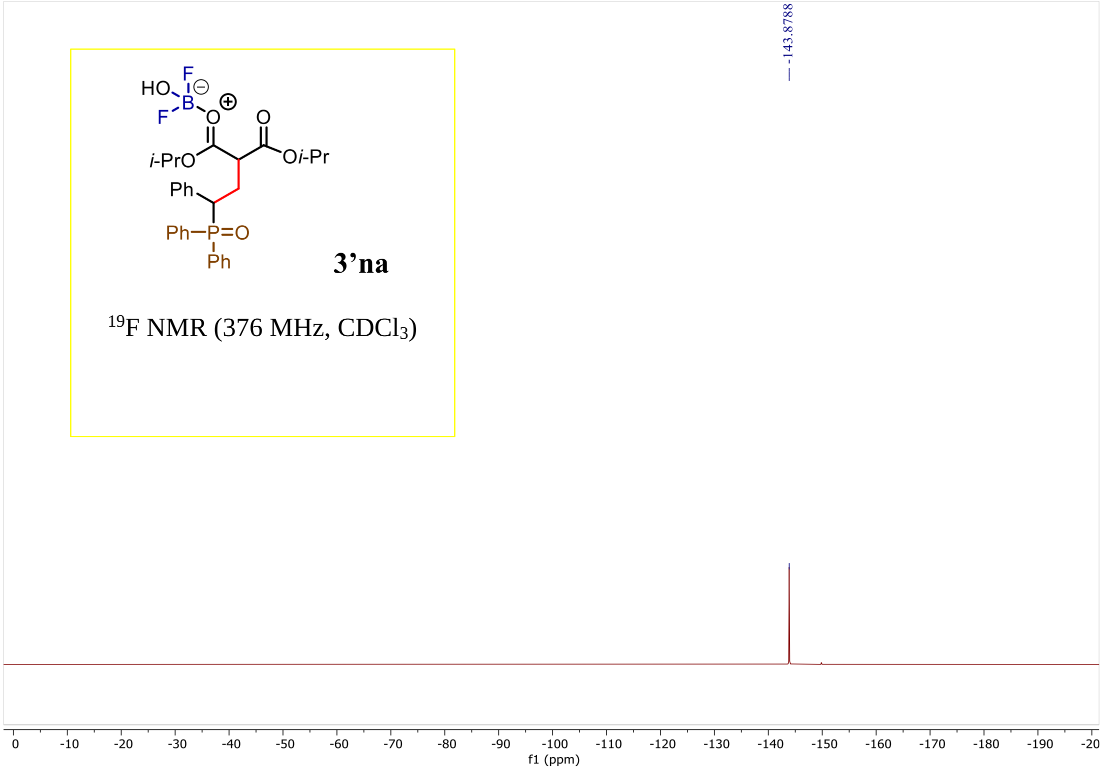
3’na

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)



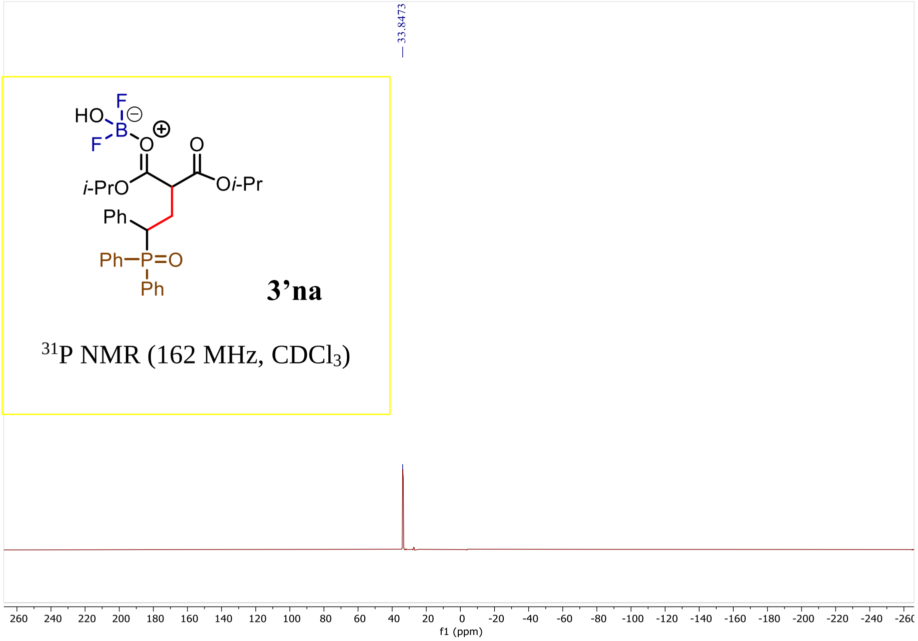
3’na

^{11}B NMR (128 MHz, CDCl$_3$)



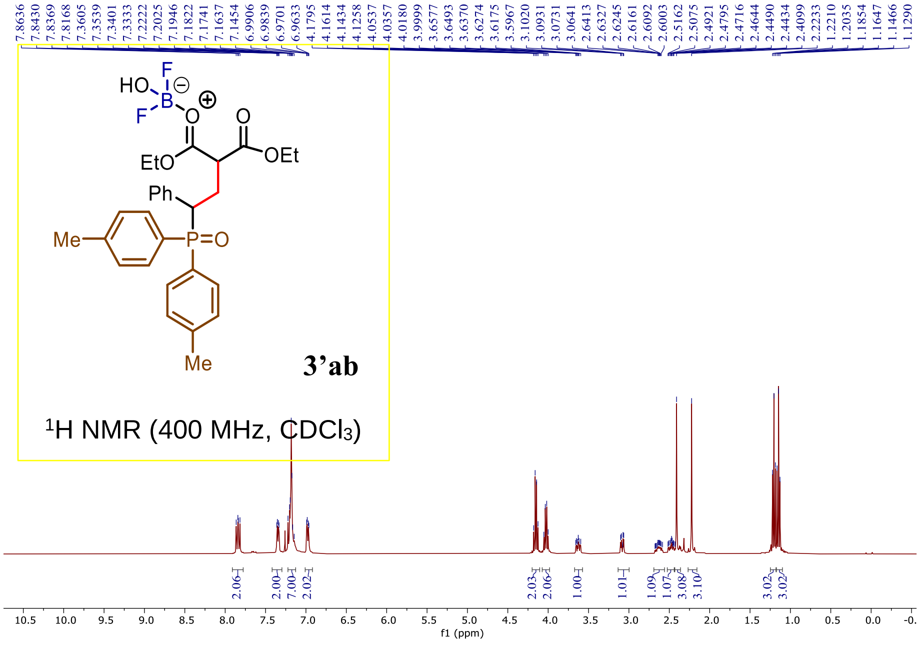
3’na

^{19}F NMR (376 MHz, CDCl$_3$)



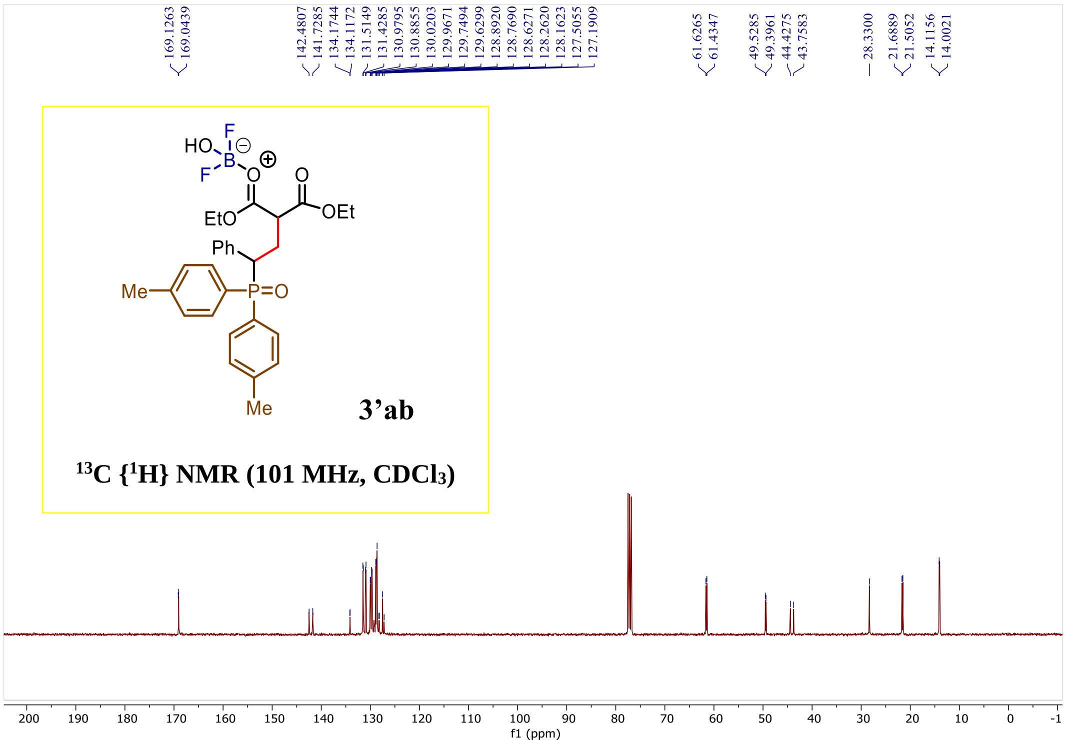
3’na

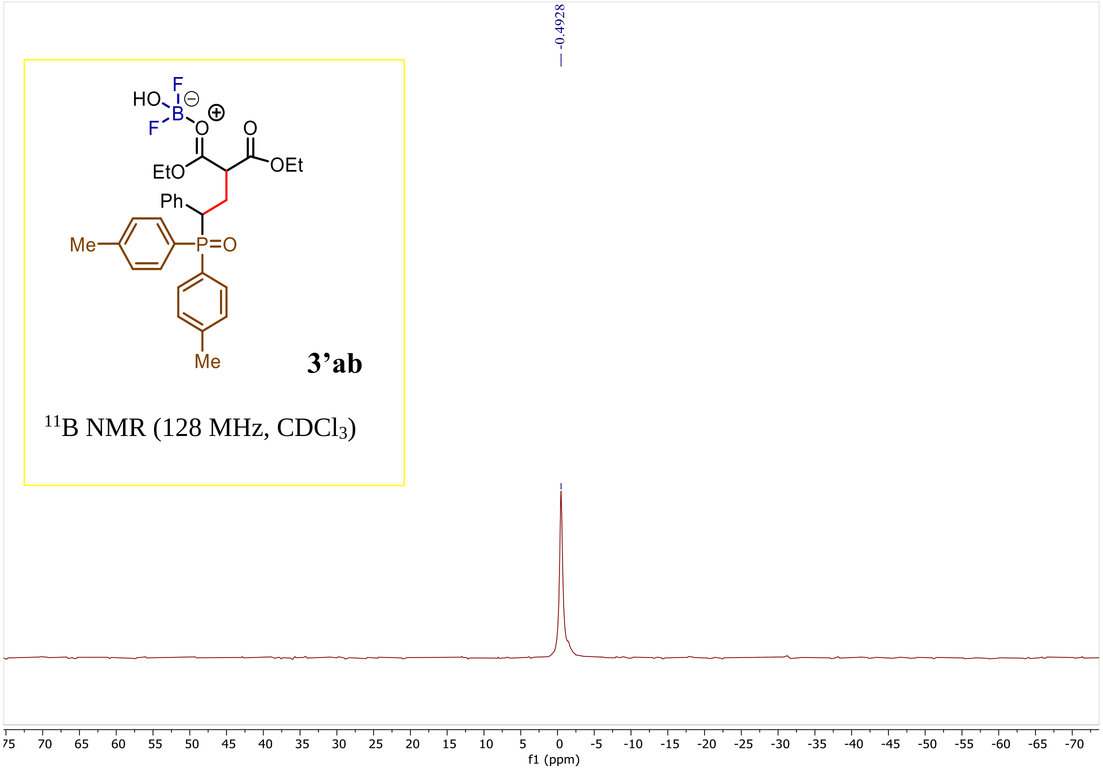
^{31}P NMR (162 MHz, CDCl$_3$)

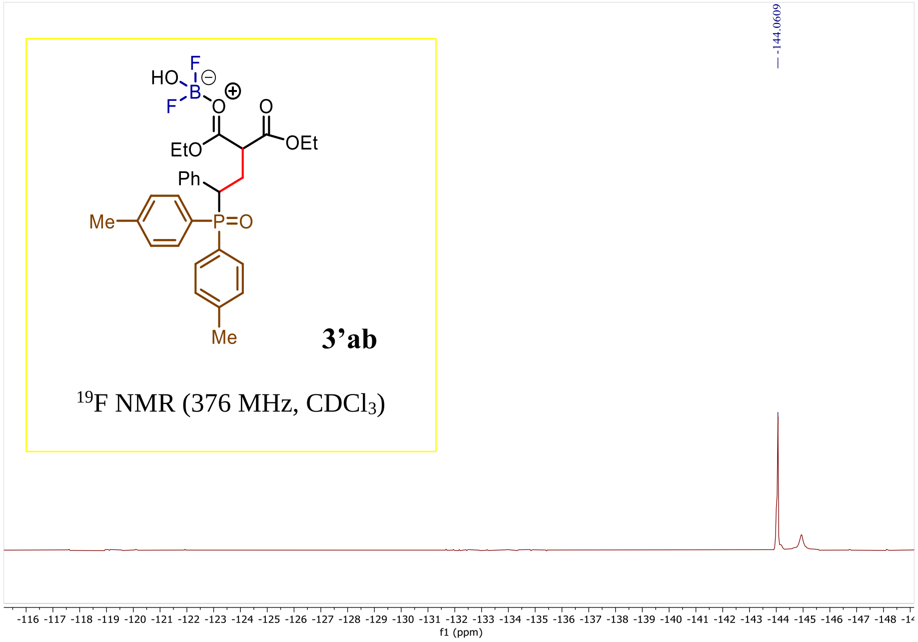


3’ab

^{1}H NMR (400 MHz, CDCl$_3$)

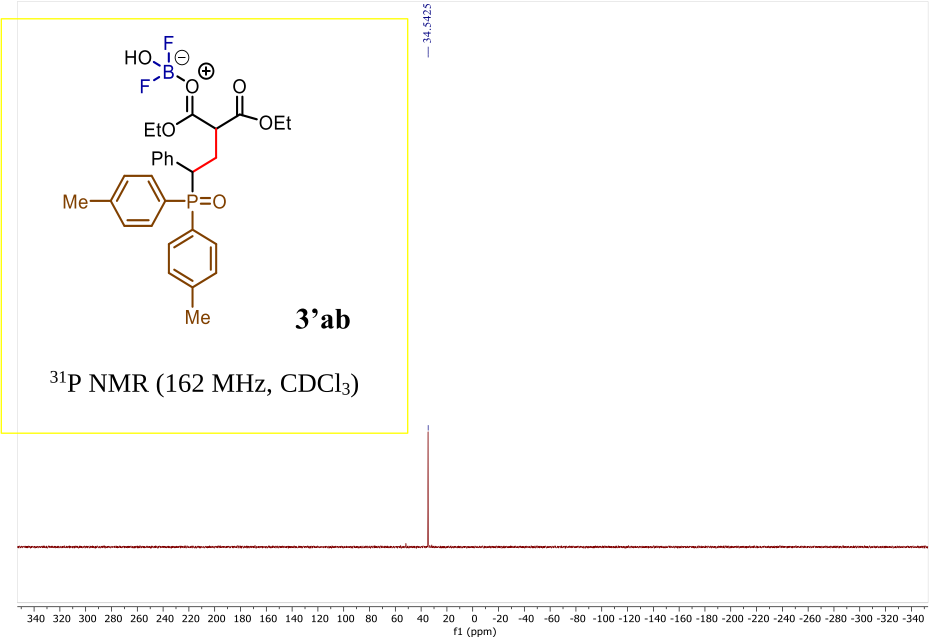

169.1263
169.0439
142.4807
141.7285
134.1744
134.1172
131.5149
131.4285
130.9795
130.8855
130.0203
129.9671
129.7494
129.6299
128.8920
128.7690
128.6271
128.2620
128.1623
127.5055
127.1909
61.6265
61.4347
49.5285
49.3961
44.4275
43.7583
28.3300
21.6889
21.5052
14.1156
14.0021
HO
F
B
F
O
O
EtO
OEt
Ph
Me
P=O
Me
3'ab
13C {1H} NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


-0.4928
HO
F
B
F
O
O
EtO
OEt
Ph
Me
P=O
Me
3'ab
11B NMR (128 MHz, CDCl3)
75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70
f1 (ppm)



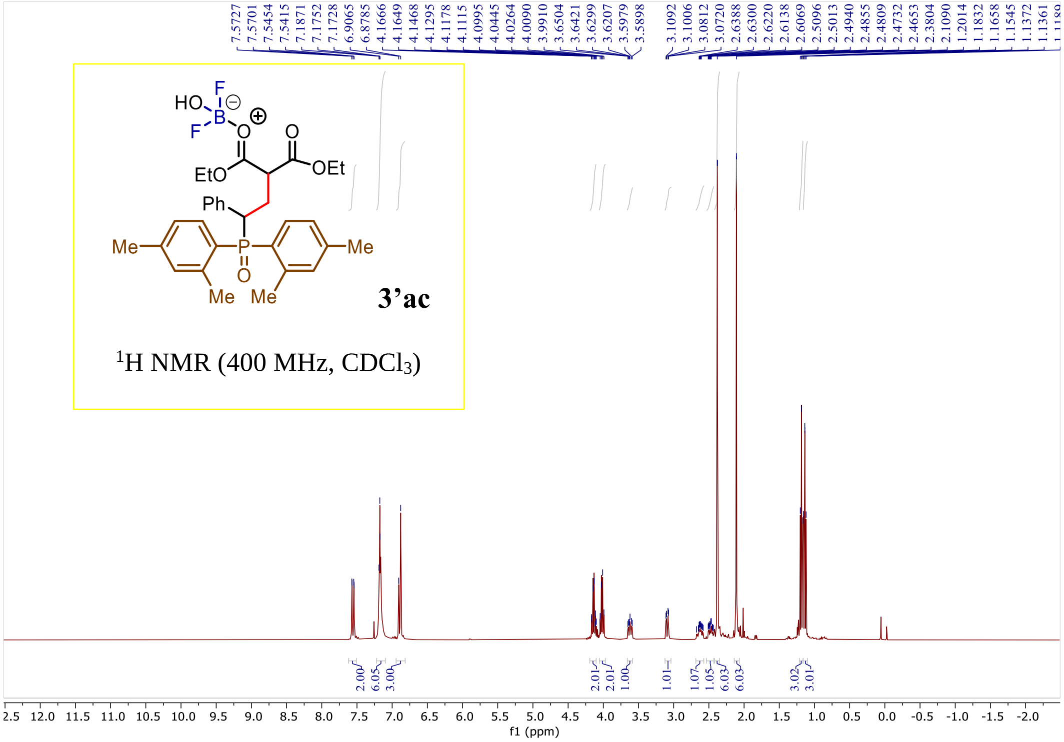
3’ab

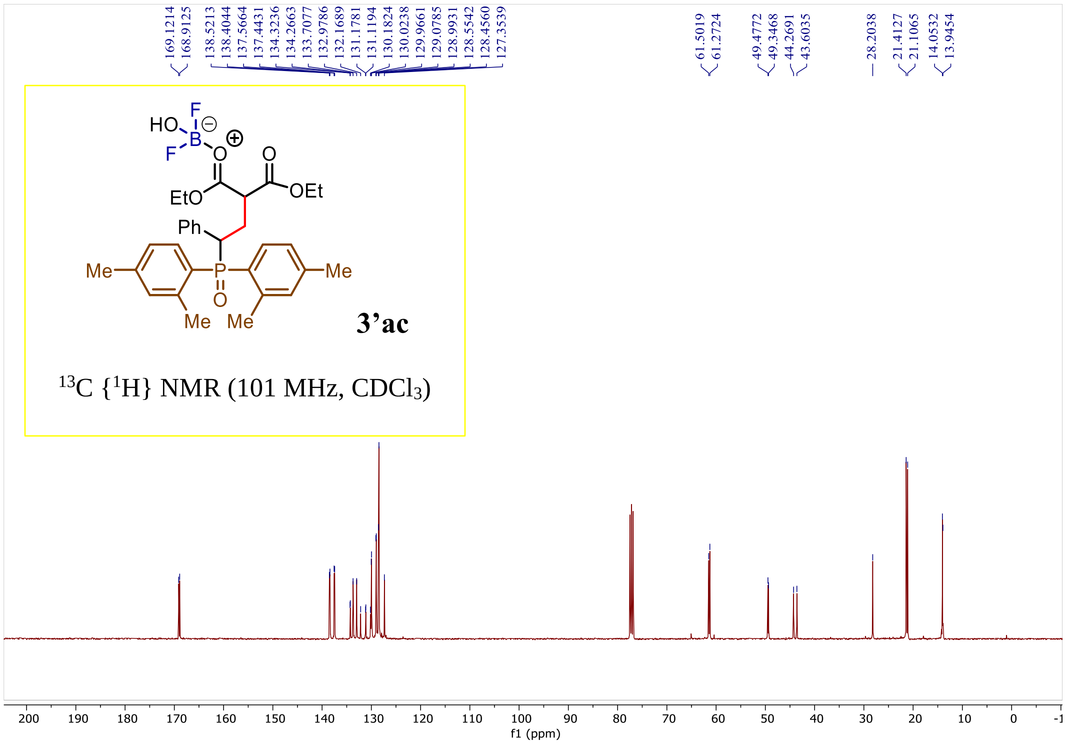
^{19}F NMR (376 MHz, $CDCl_3$)

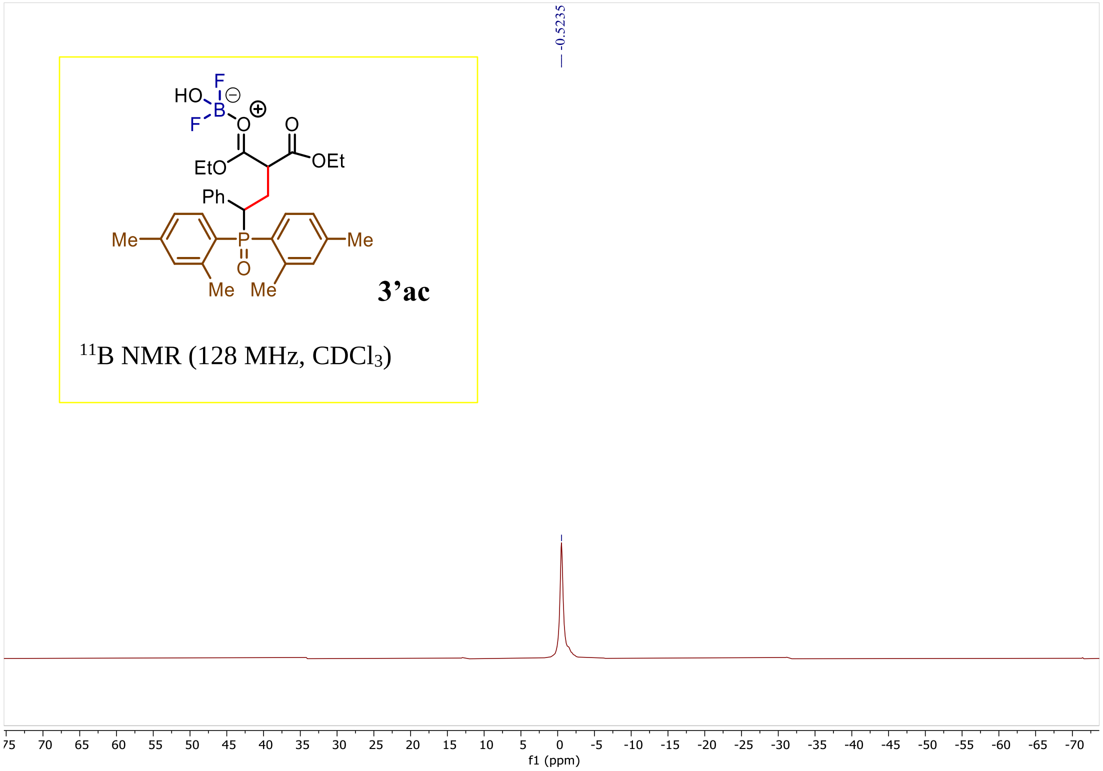


3’ab

^{31}P NMR (162 MHz, $CDCl_3$)

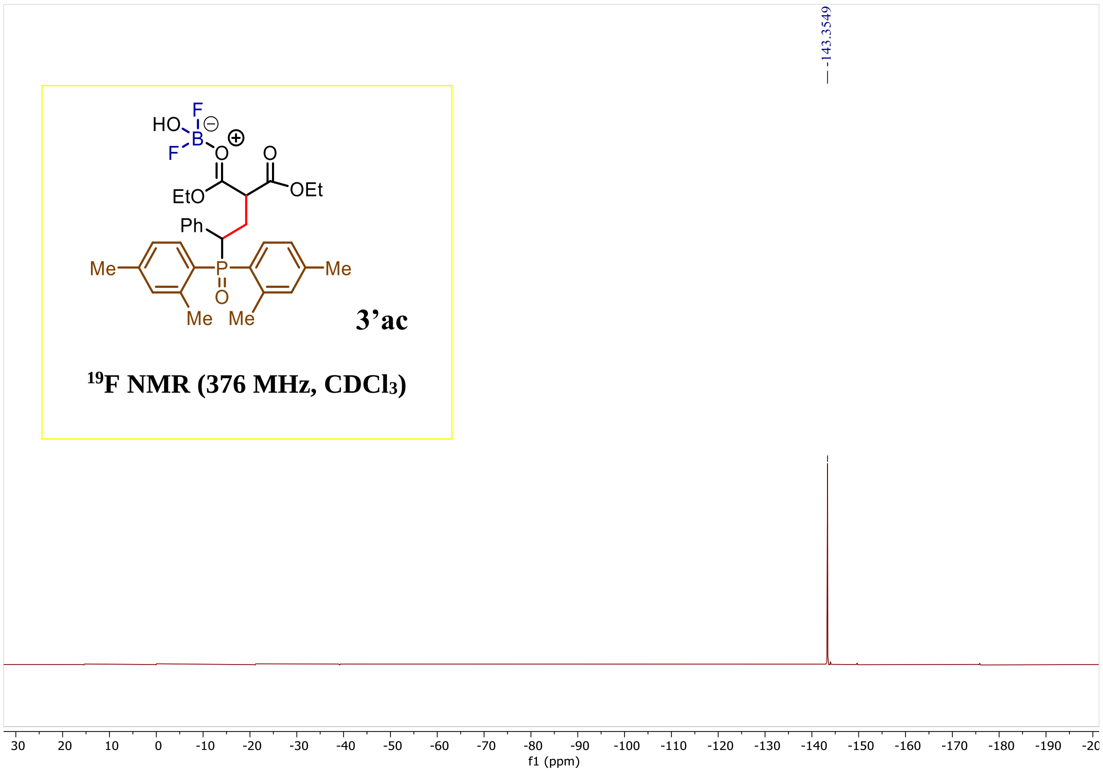

7.5727
7.5701
7.5454
7.5415
7.1871
7.1752
7.1728
6.9065
6.8785
4.1666
4.1649
4.1468
4.1295
4.1178
4.1115
4.0995
4.0445
4.0264
4.0090
3.9910
3.6504
3.6421
3.6299
3.6207
3.5979
3.5898
3.1092
3.1006
3.0812
3.0720
2.6388
2.6300
2.6220
2.6138
2.6069
2.5096
2.5013
2.4940
2.4855
2.4809
2.4732
2.4653
2.3804
2.1090
1.2014
1.1832
1.1658
1.1545
1.1372
1.1361
1.118
HO
F
B
F
O
O
EtO
OEt
Ph
Me
P
Me
O
Me
Me
3’ac
1H NMR (400 MHz, CDCl3)
2.00
6.05
3.00
2.01
2.01
1.00
1.01
1.07
1.05
6.03
6.03
3.02
3.01
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
f1 (ppm)


169.1214
168.9125
138.5213
138.4044
137.5664
137.4431
134.3236
134.2663
133.7077
132.9786
132.1689
131.1781
131.1194
130.1824
130.0238
129.9661
129.0785
128.9931
128.5542
128.4560
127.3539
61.5019
61.2724
49.4772
49.3468
44.2691
43.6035
28.2038
21.4127
21.1065
14.0532
13.9454
HO
F
B
F
O
O
EtO
OEt
Ph
Me
P
Me
O
Me
Me
3’ac
13C {1H} NMR (101 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)



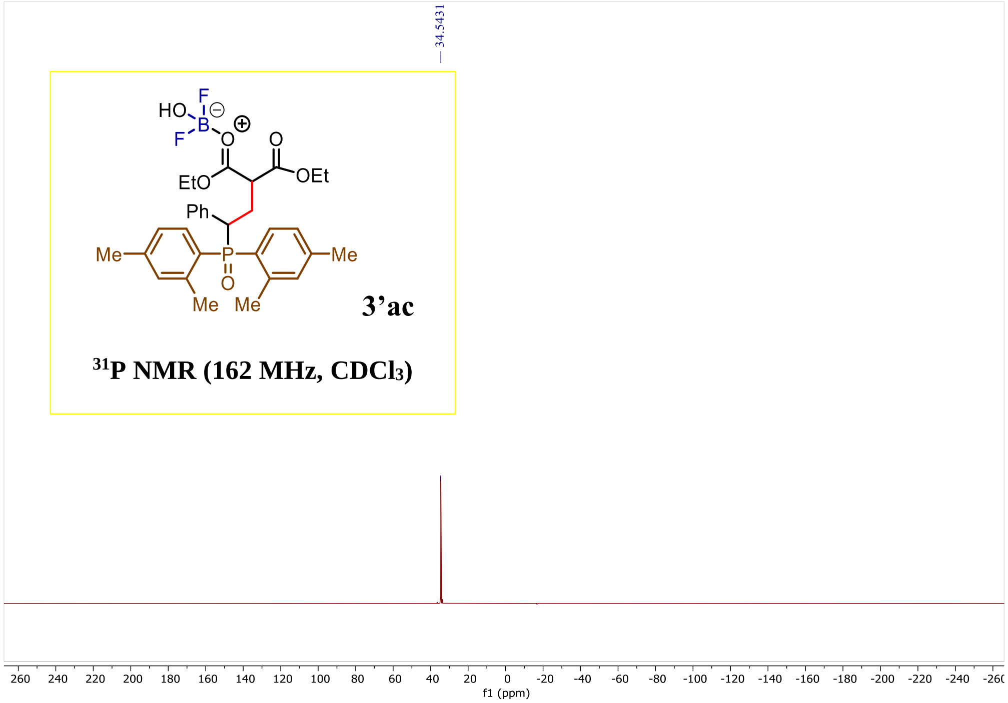
3’ac

^{11}B NMR (128 MHz, $CDCl_3$)



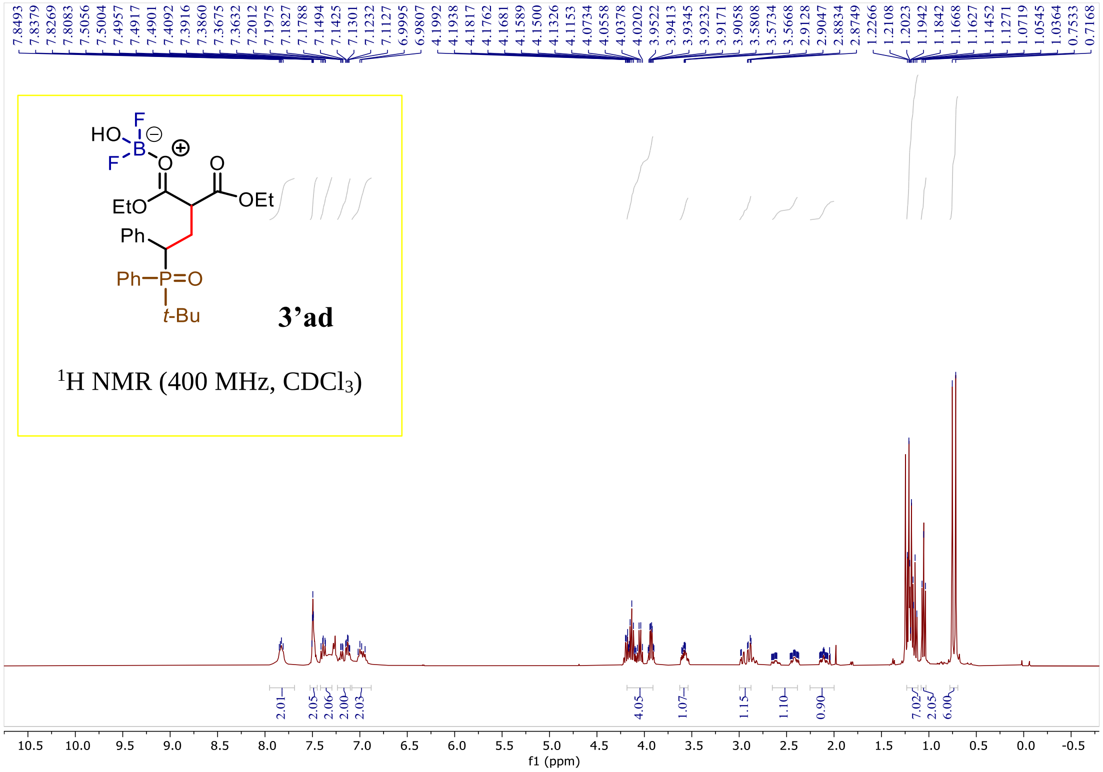
3’ac

^{19}F NMR (376 MHz, CDCl$_3$)



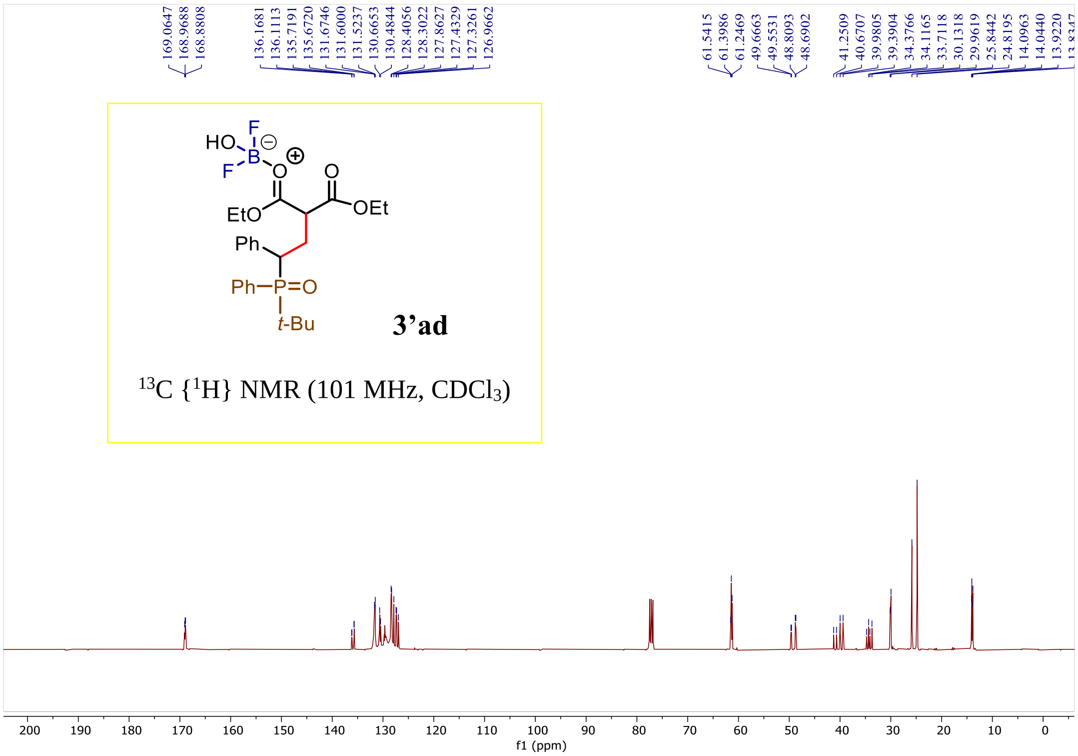
3’ac

^{31}P NMR (162 MHz, CDCl$_3$)



3’ad

^{1}H NMR (400 MHz, CDCl$_3$)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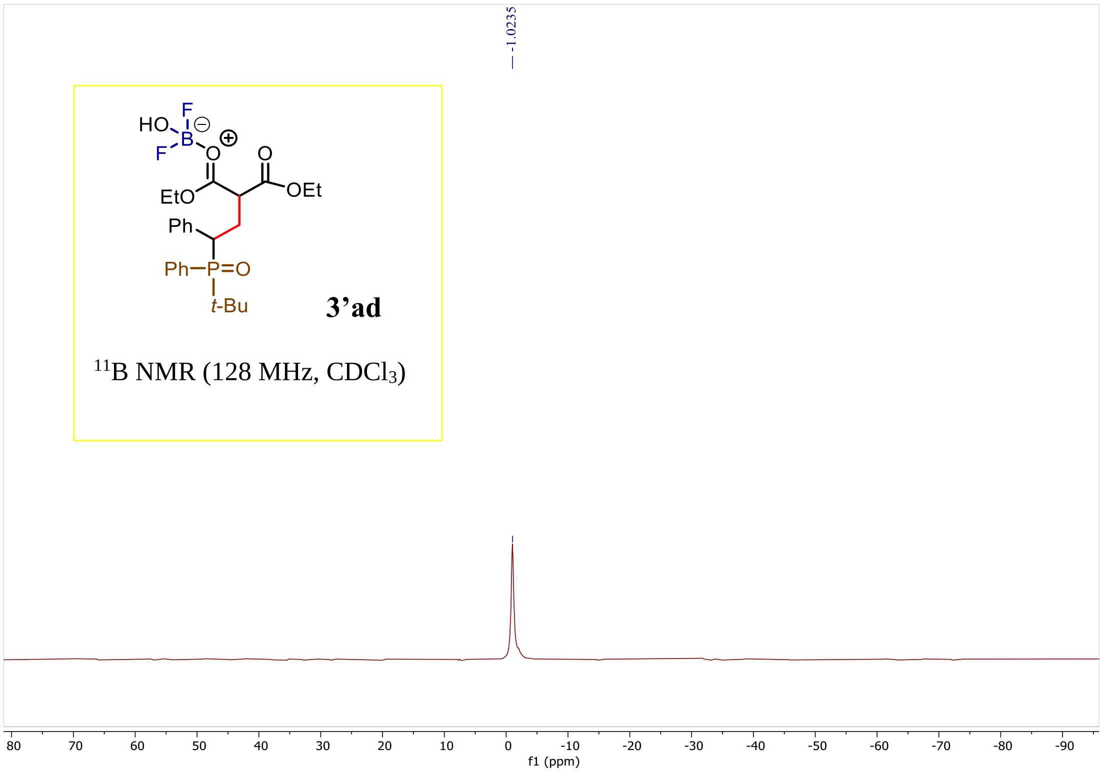
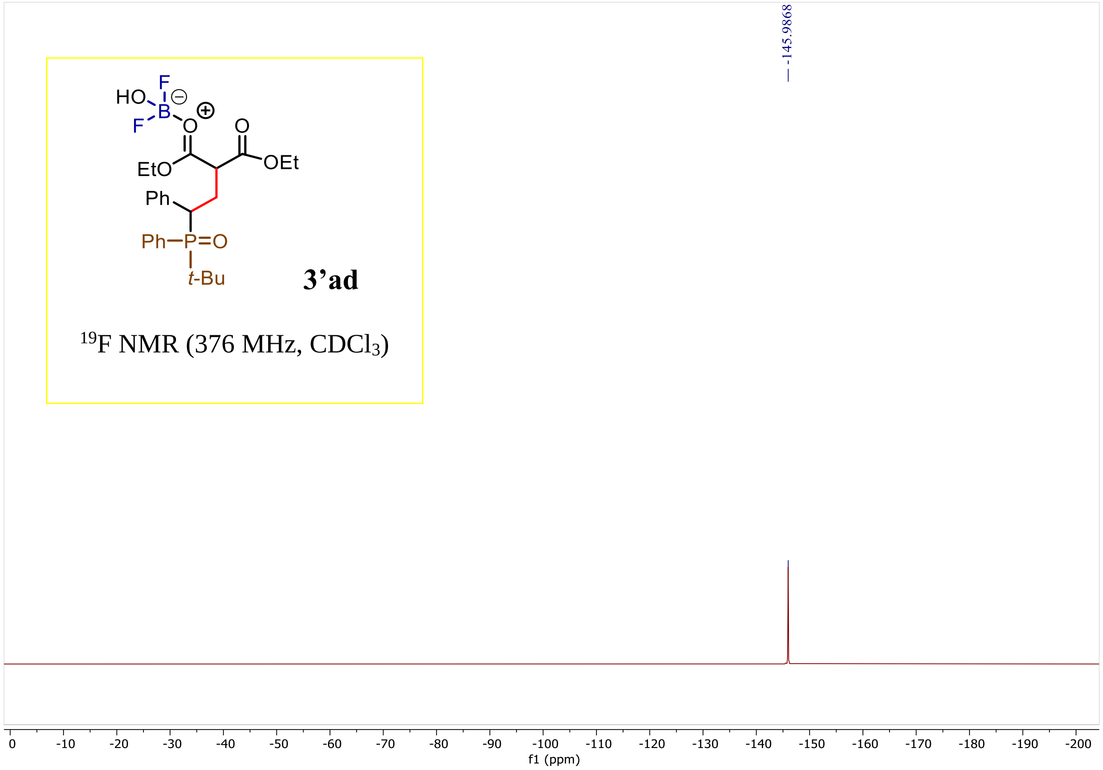
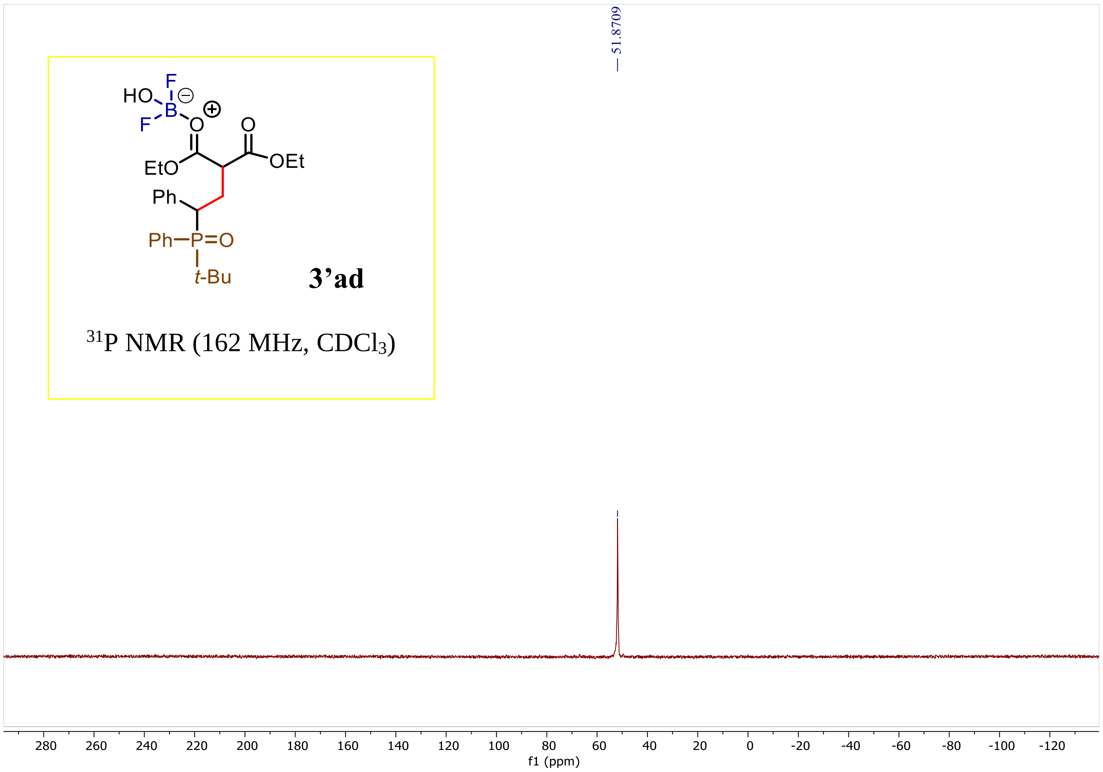
168.9688
168.8808
136.1681
136.1113
135.7191
135.6720
131.6746
131.6000
131.5237
130.6653
130.4844
128.4056
128.3022
127.8627
127.4329
127.3261
126.9662
61.5415
61.3986
61.2469
49.6663
49.5531
48.8093
48.6902
41.2509
40.6707
39.9805
39.3904
34.3766
34.1165
33.7118
30.1318
29.9619
25.8442
24.8195
14.0963
14.0440
13.9220
HO
F
B
F
O
O
EtO
OEt
Ph
Ph
P=O
t-Bu
3'ad
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-1.0235
HO
F
B
F
O
O
EtO
OEt
Ph
Ph
P=O
t-Bu
3'ad
^{11}B NMR (128 MHz, CDCl$_3$)
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
f1 (ppm)



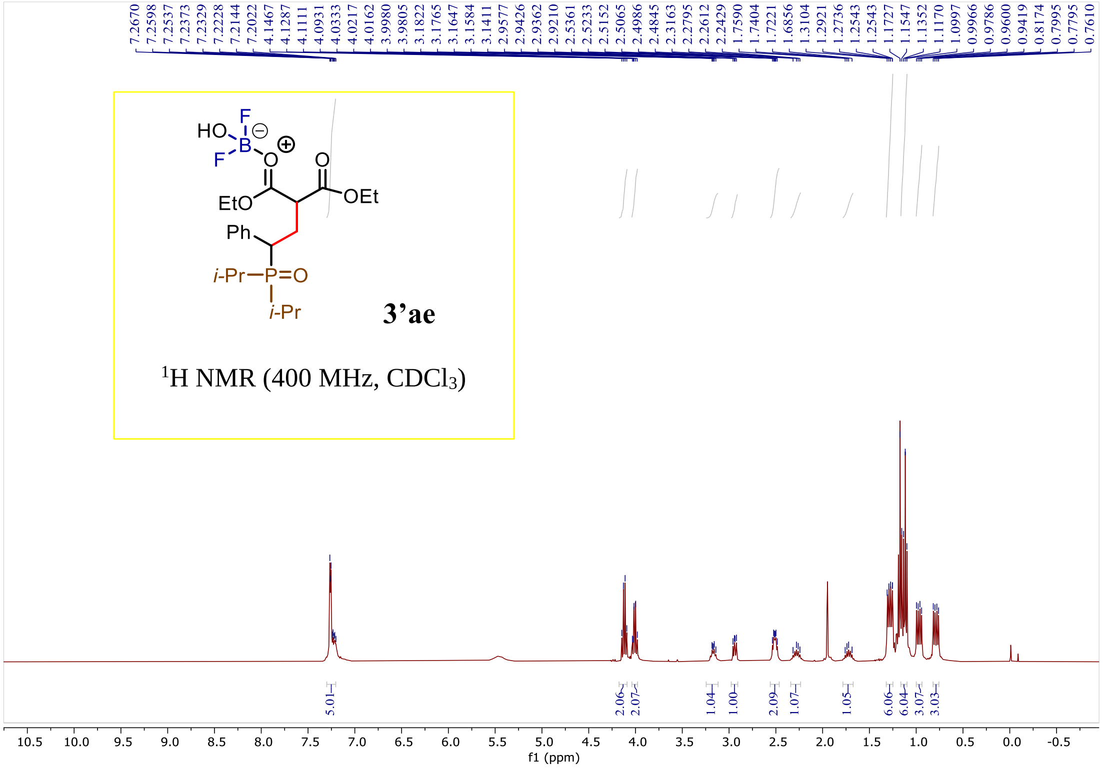
3’ad

^{19}F NMR (376 MHz, CDCl$_3$)



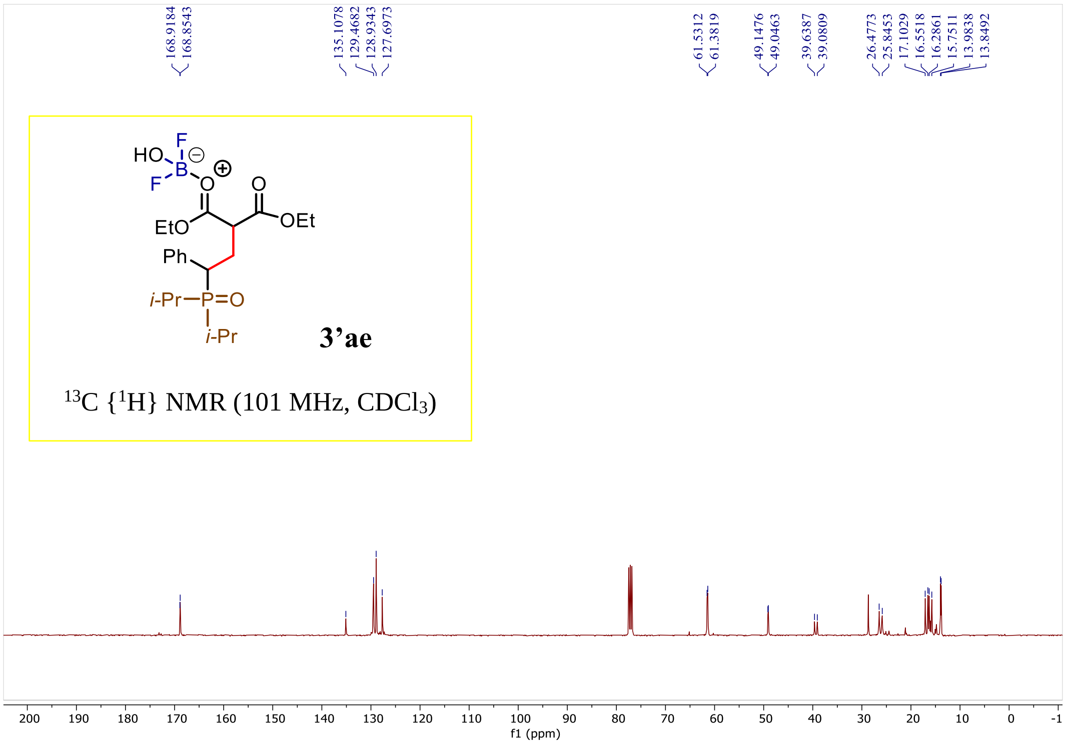
3'ad

^{31}P NMR (162 MHz, CDCl$_3$)



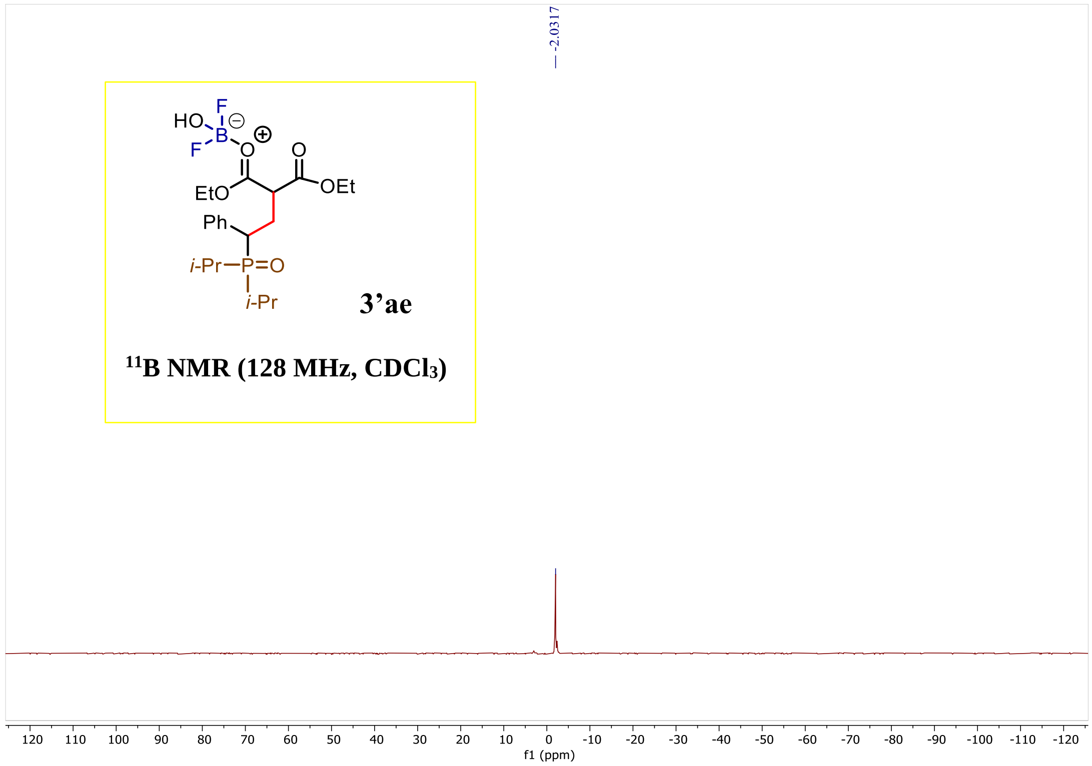
3'ae

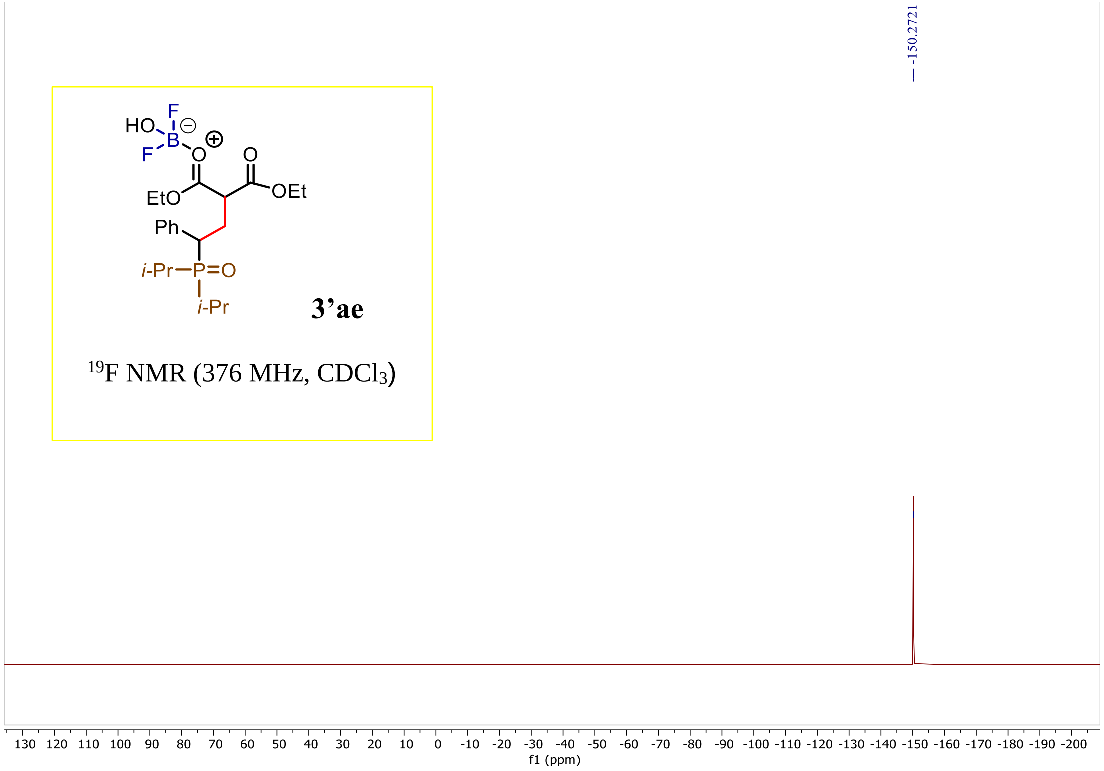
^{1}H NMR (400 MHz, CDCl$_3$)

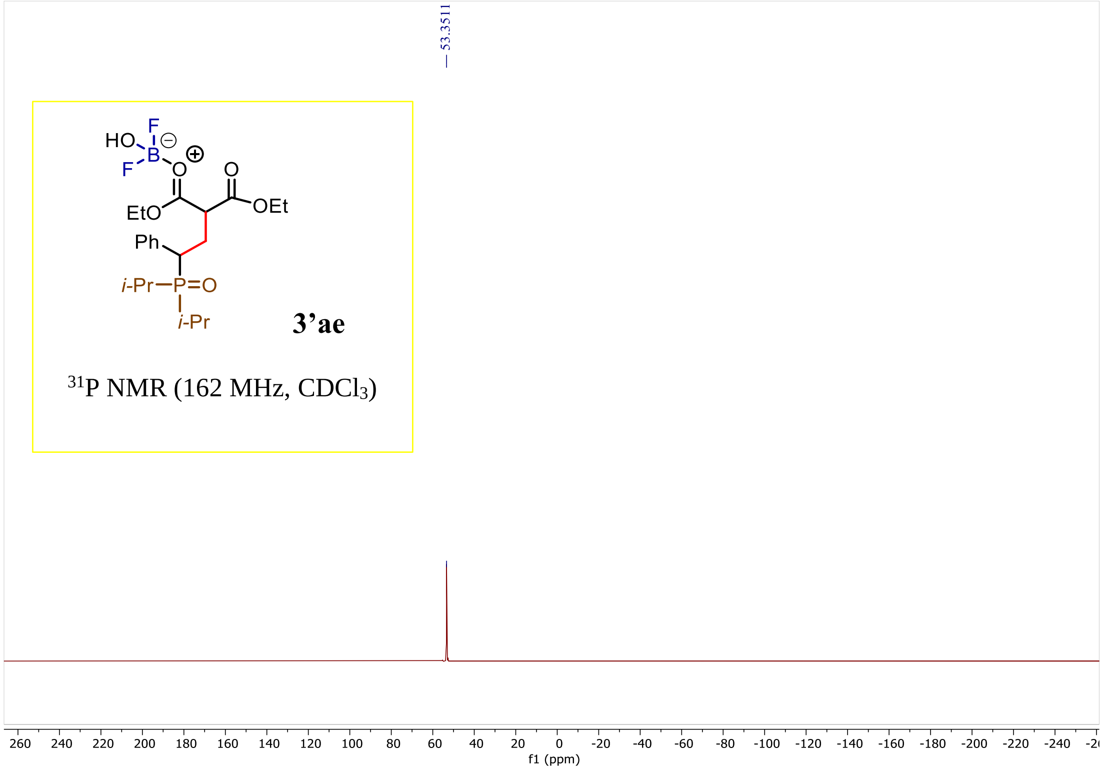


3’ae

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)

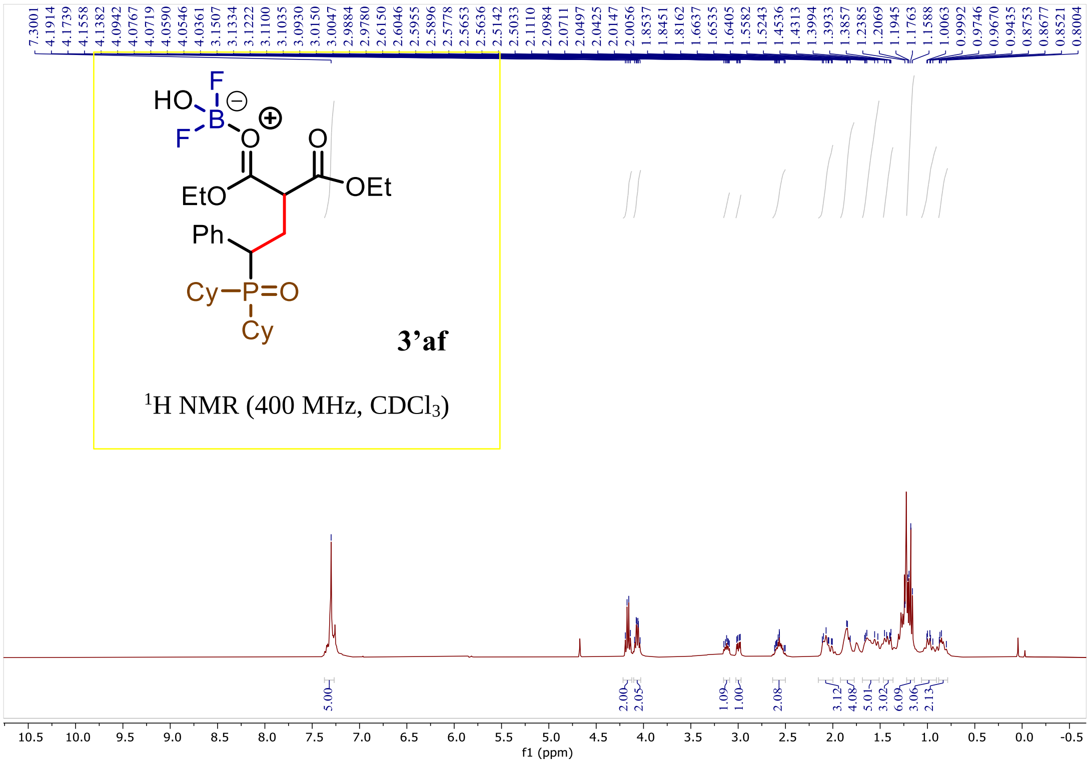

-2.0317
HO
F
B
F
O
O
EtO
OEt
Ph
i-Pr—P=O
i-Pr
3'ae
11B NMR (128 MHz, CDCl3)
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120
f1 (ppm)

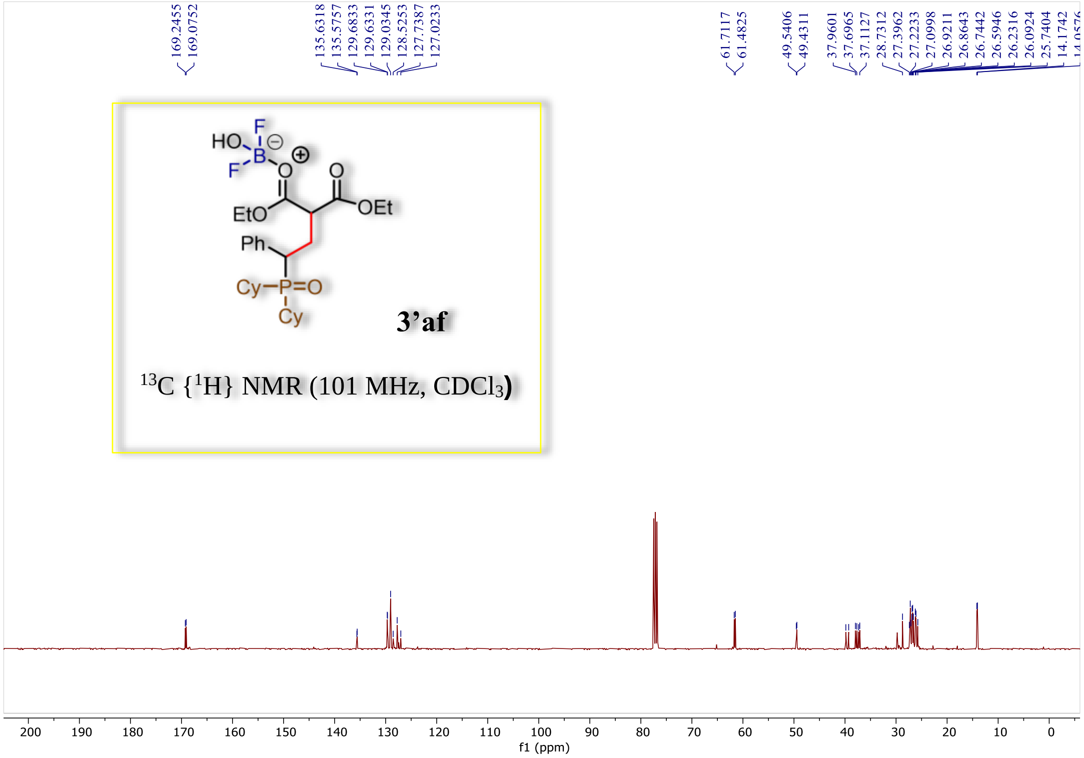

-150.2721
HO
F
B
F
O
O
EtO
OEt
Ph
i-Pr—P=O
i-Pr
3'ae
19F NMR (376 MHz, CDCl3)
130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

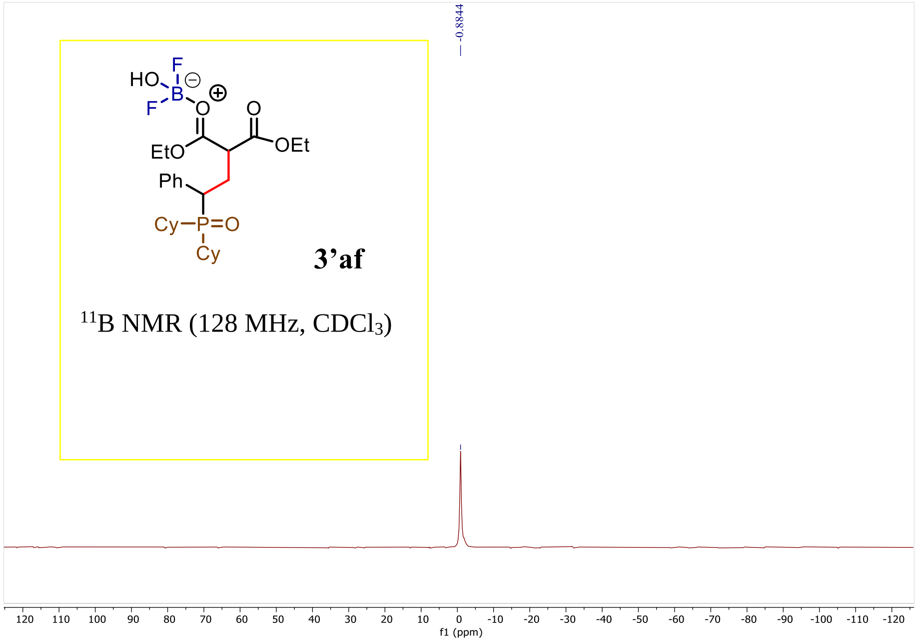


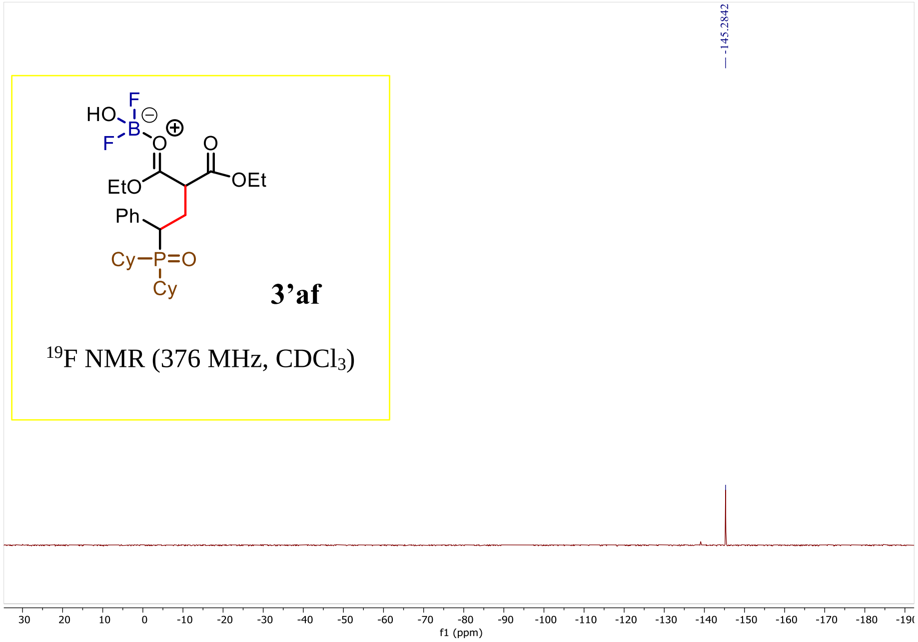
3’ae

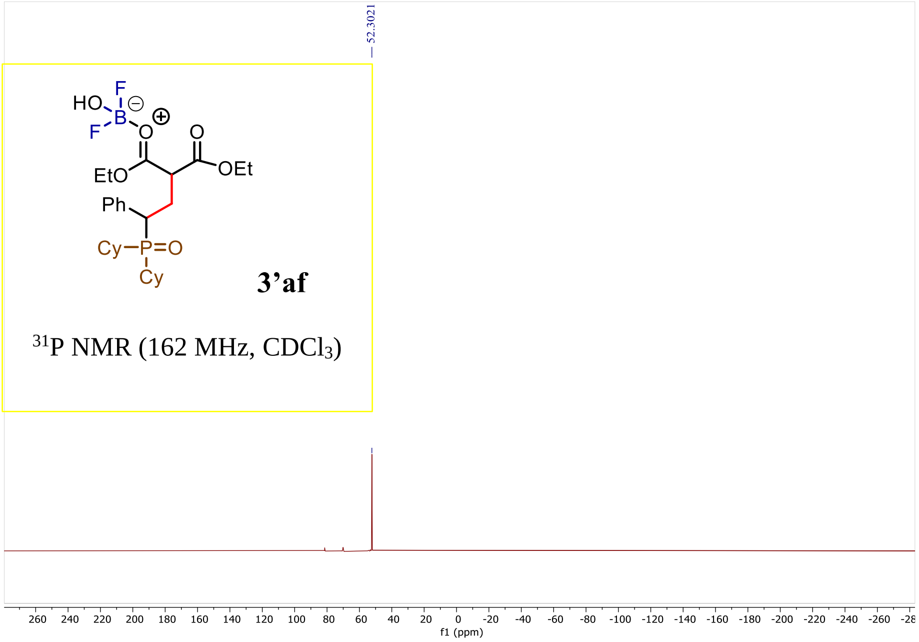
^{31}P NMR (162 MHz, CDCl$_3$)


7.3001
4.1914
4.1739
4.1558
4.1382
4.0942
4.0767
4.0719
4.0590
4.0546
4.0361
3.1507
3.1334
3.1222
3.1100
3.1035
3.0930
3.0150
3.0047
2.9884
2.9780
2.6150
2.6046
2.5955
2.5896
2.5778
2.5653
2.5636
2.5142
2.5033
2.1110
2.0984
2.0711
2.0497
2.0425
2.0147
2.0056
1.8537
1.8451
1.8162
1.6637
1.6535
1.6405
1.5582
1.5243
1.4536
1.4313
1.3994
1.3933
1.3857
1.2385
1.2069
1.1945
1.1763
1.1588
1.0063
0.9992
0.9746
0.9670
0.9435
0.8753
0.8677
0.8521
0.8004
HO
F
B
F
O
O
O
EtO
OEt
Ph
Cy
P
O
Cy
3’af
^{1}H NMR (400 MHz, CDCl$_3$)
5.00
2.00
2.05
1.09
1.00
2.08
3.12
4.08
5.01
3.02
6.09
3.06
2.13
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


169.2455
169.0752
135.6318
135.5757
129.6833
129.6331
129.0345
128.5253
127.7387
127.0233
61.7117
61.4825
49.5406
49.4311
37.9601
37.6965
37.1127
28.7312
27.3962
27.2233
27.0998
26.9211
26.8643
26.7442
26.5946
26.2316
26.0924
25.7404
14.1742
14.057
HO
F
B
F
O
O
O
EtO
OEt
Ph
Cy
P
O
Cy
3’af
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

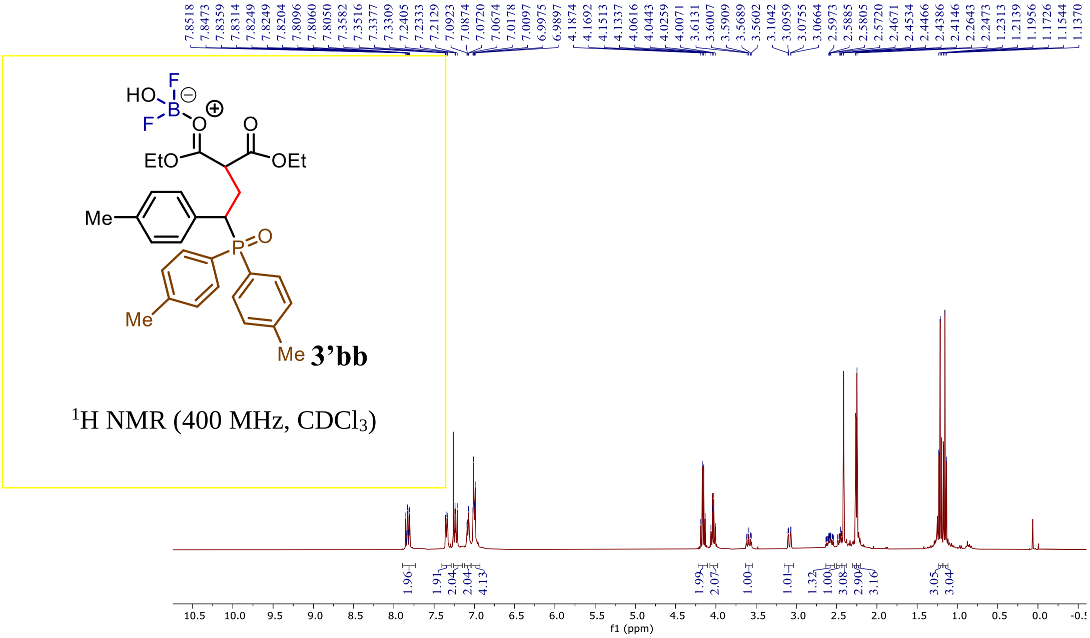

-0.8844
HO
F
B
F
O
O
EtO
OEt
Ph
Cy
P
O
Cy
3’af
^{11}B NMR (128 MHz, CDCl$_3$)
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120
f1 (ppm)


-145.2842
HO
F
B
F
O
O
EtO
OEt
Ph
Cy
P
O
Cy
3’af
^{19}F NMR (376 MHz, CDCl$_3$)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)



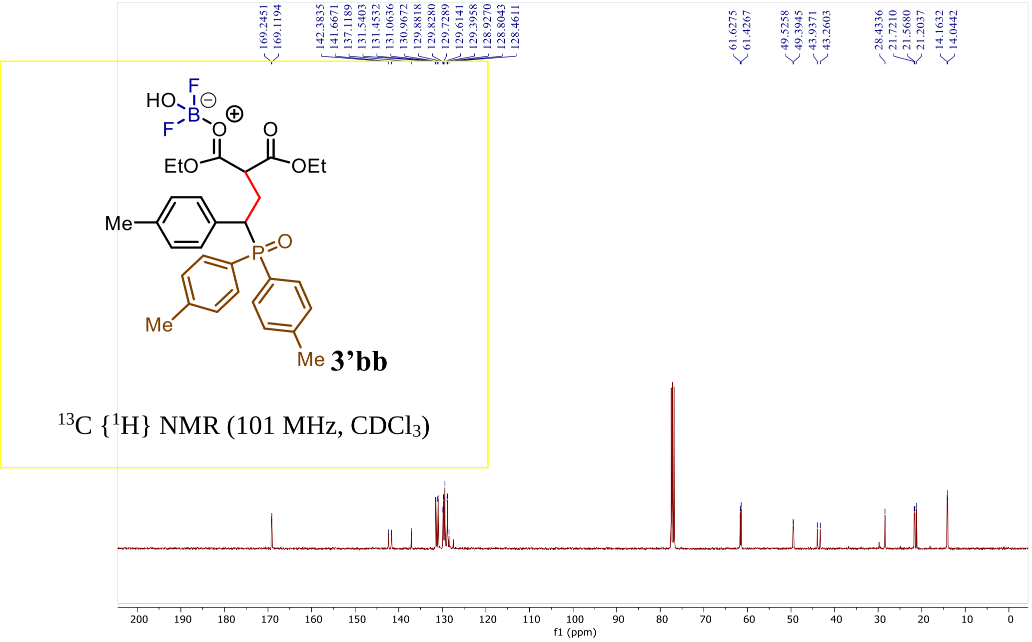
3’af

^{31}P NMR (162 MHz, CDCl$_3$)



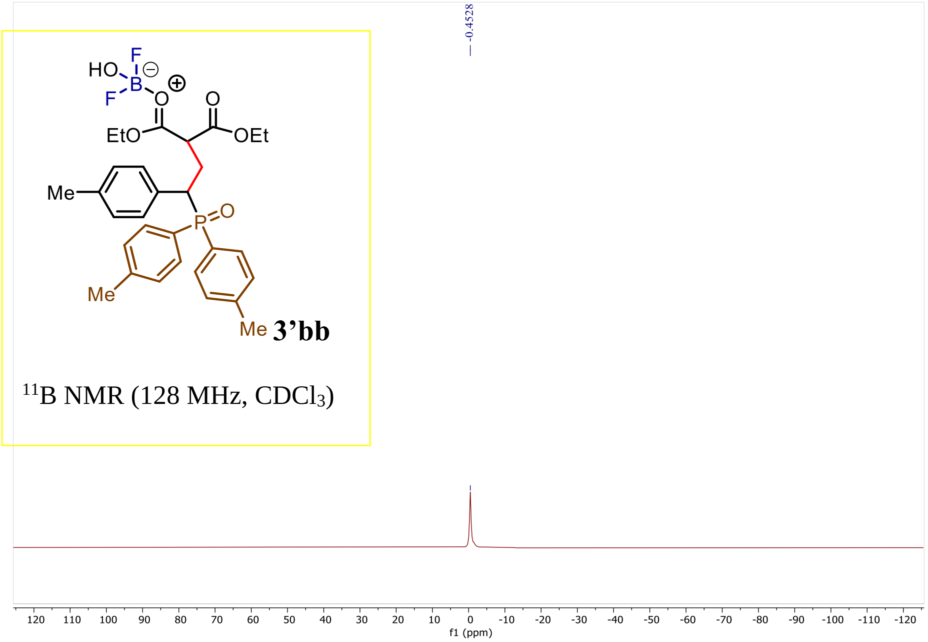
3’bb

^{1}H NMR (400 MHz, CDCl$_3$)



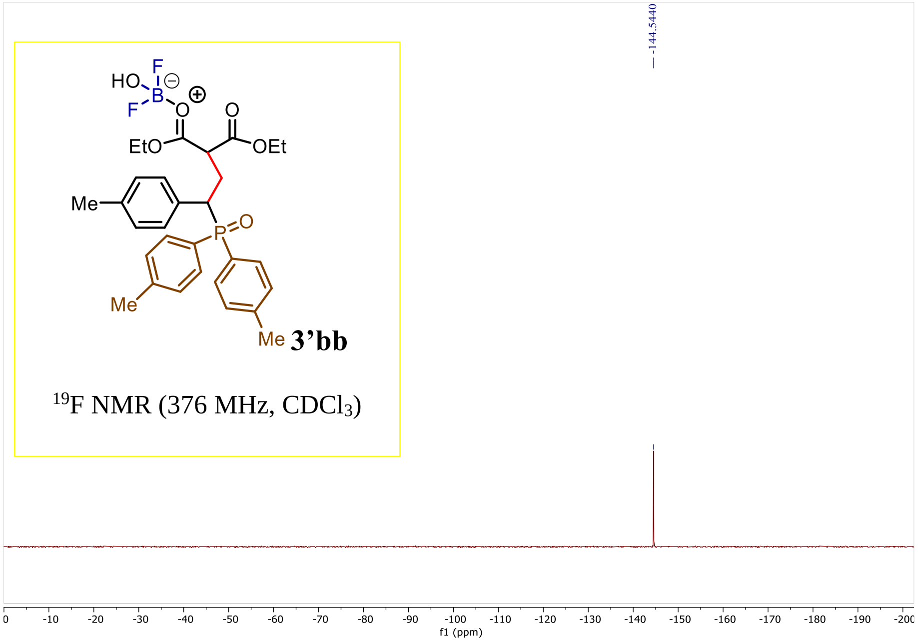
3’bb

^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)

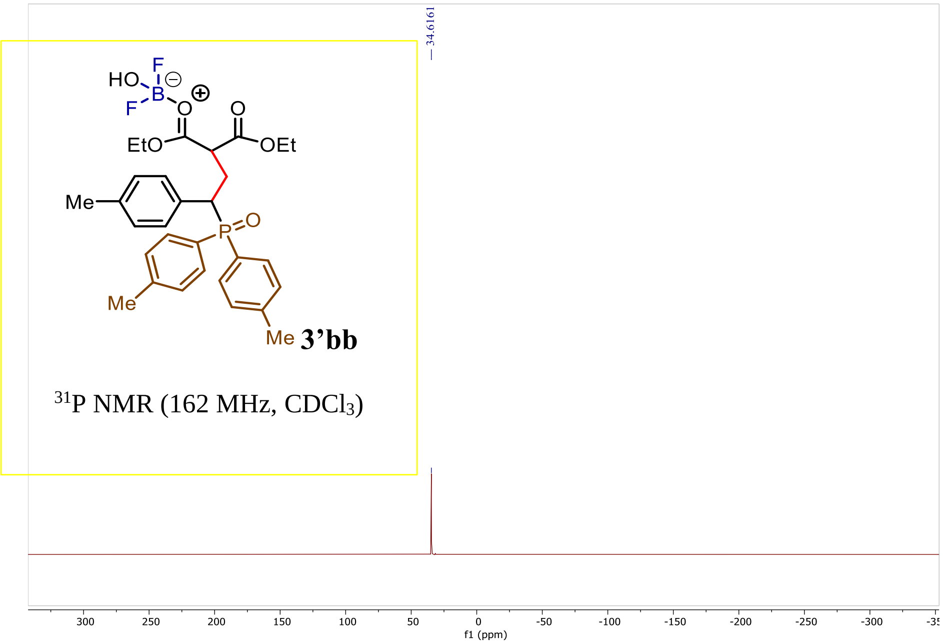


3’bb

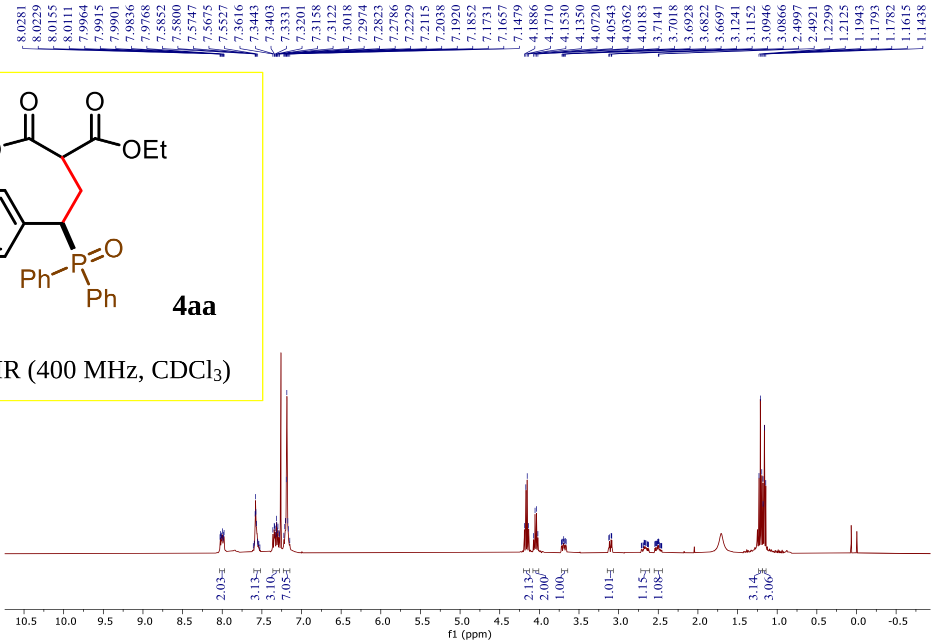
^{11}B NMR (128 MHz, CDCl$_3$)



HO
F
B
F
O
O
EtO
OEt
Me
P
O
Me
Me
3’bb
^{19}F NMR (376 MHz, CDCl$_3$)
-144.5440
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

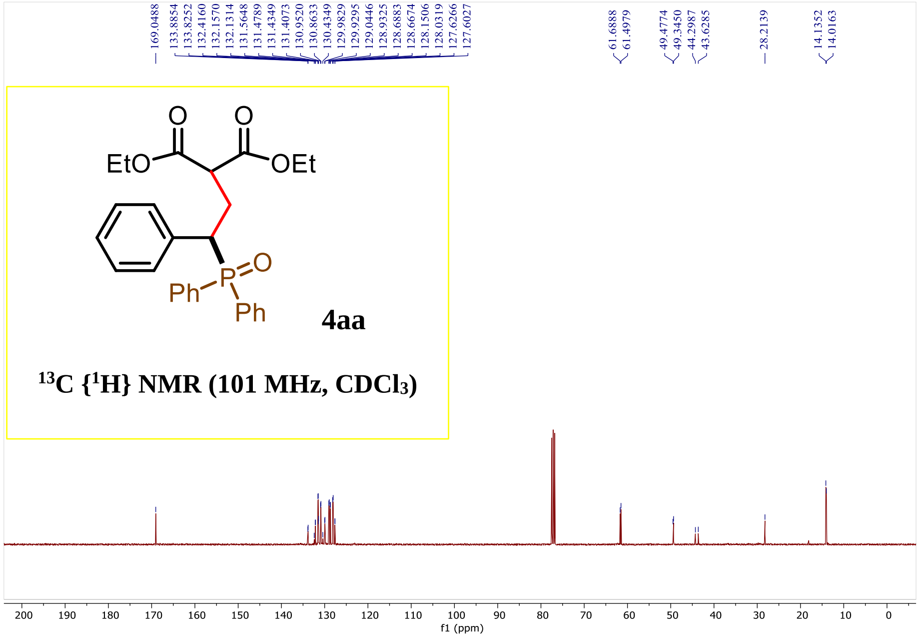


HO
F
B
F
O
O
EtO
OEt
Me
P
O
Me
Me
3’bb
^{31}P NMR (162 MHz, CDCl$_3$)
34.6161
300
250
200
150
100
50
0
-50
-100
-150
-200
-250
-300
f1 (ppm)



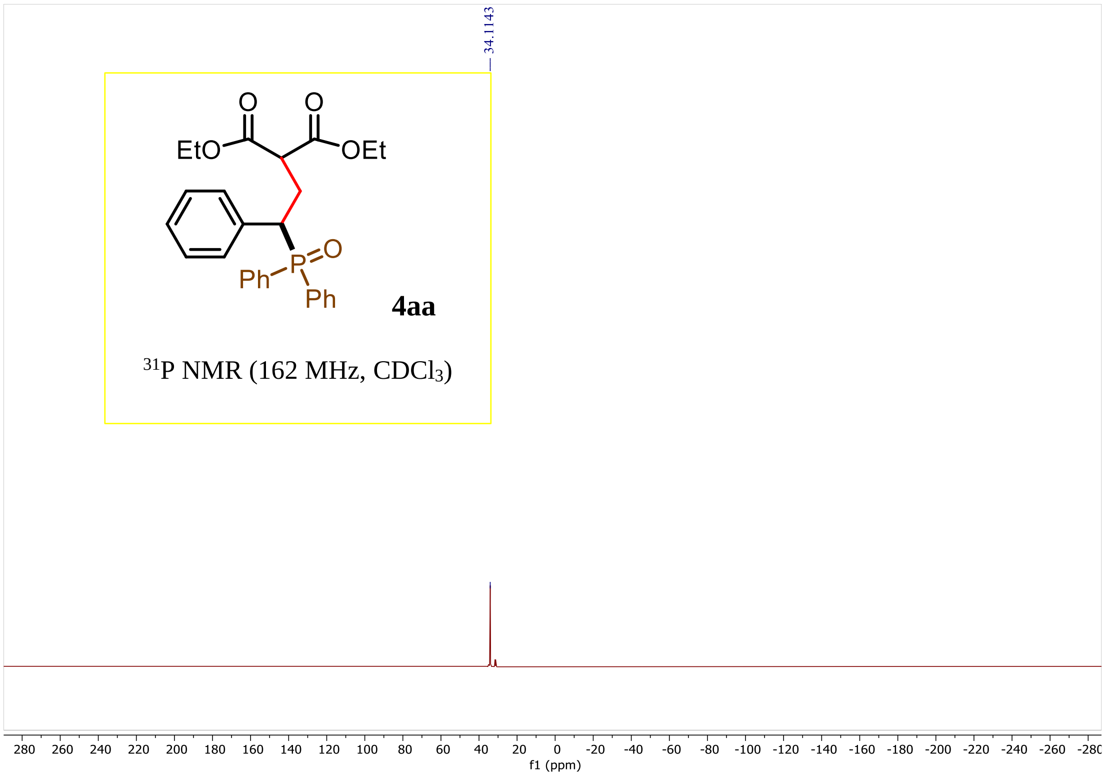
4aa

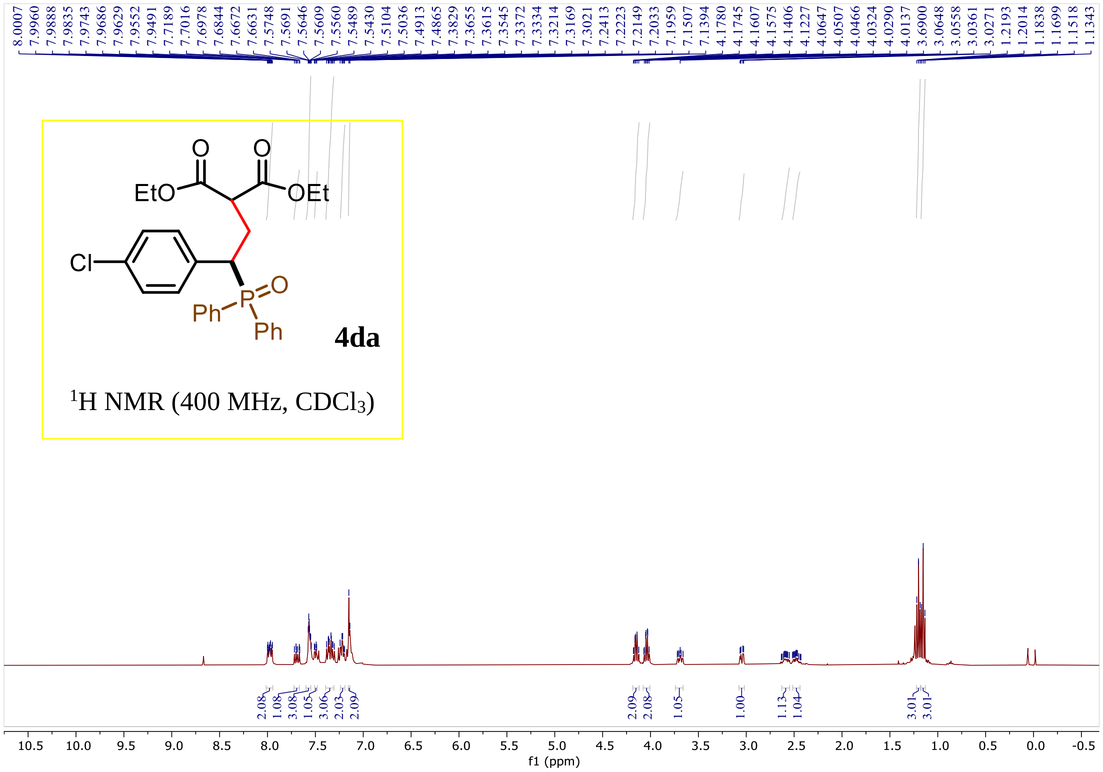
^{1}H NMR (400 MHz, $CDCl_3$)



4aa

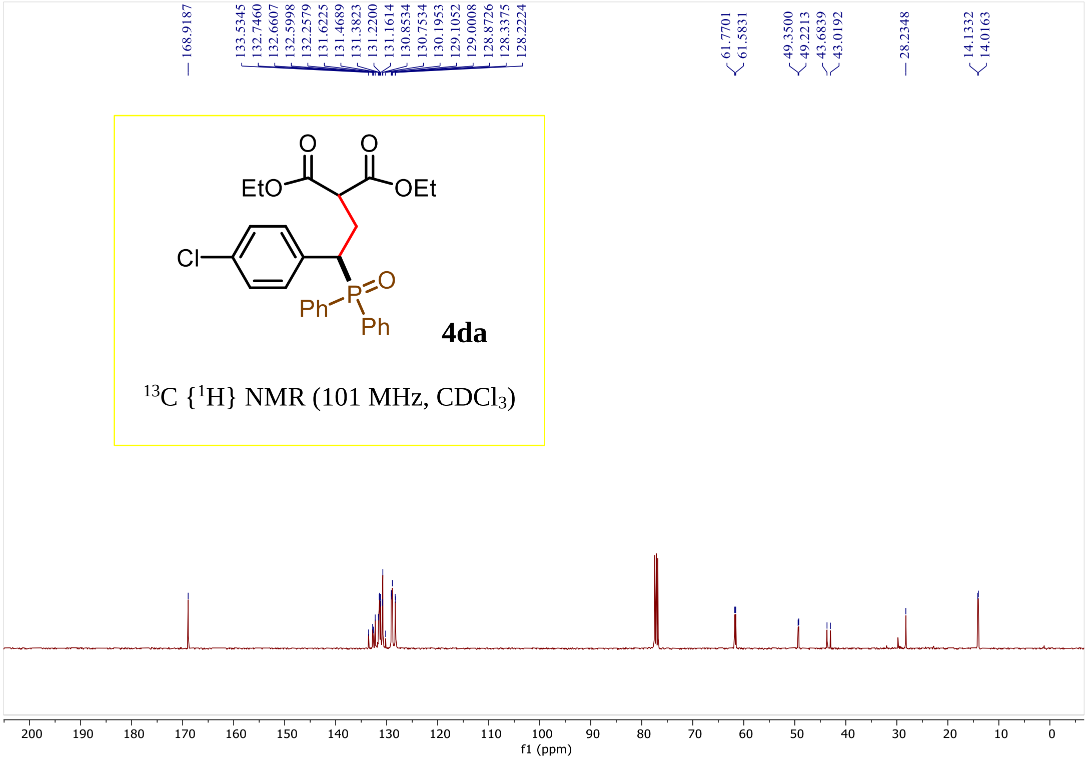
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)


34.1143
O
O
EtO
OEt
P
O
Ph
Ph
4aa
^{31}P NMR (162 MHz, CDCl$_3$)
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
f1 (ppm)



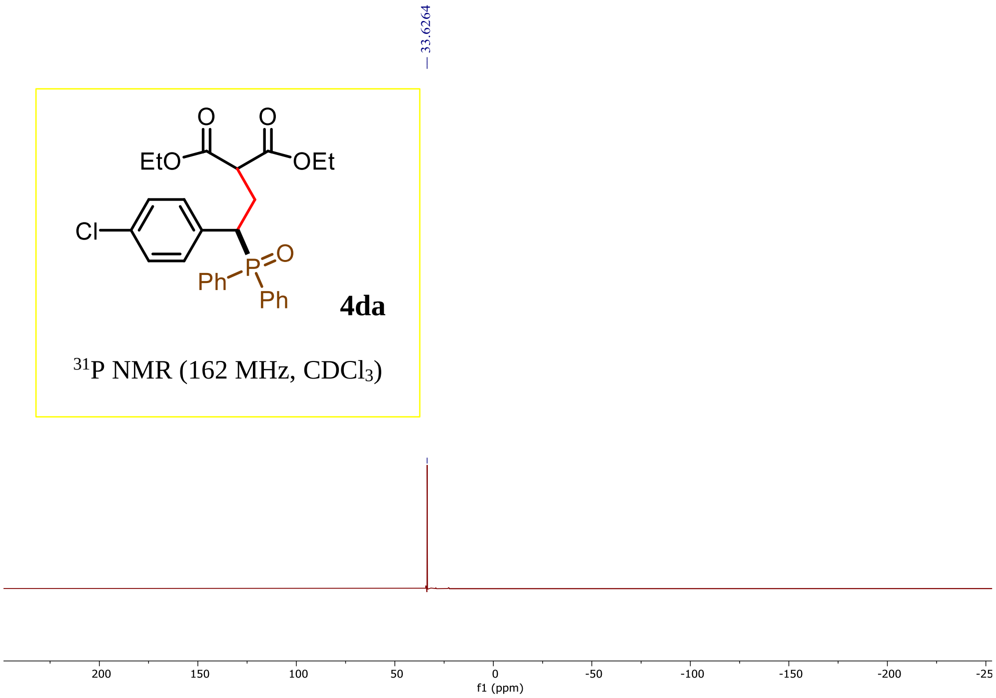
4da

^{1}H NMR (400 MHz, $CDCl_3$)



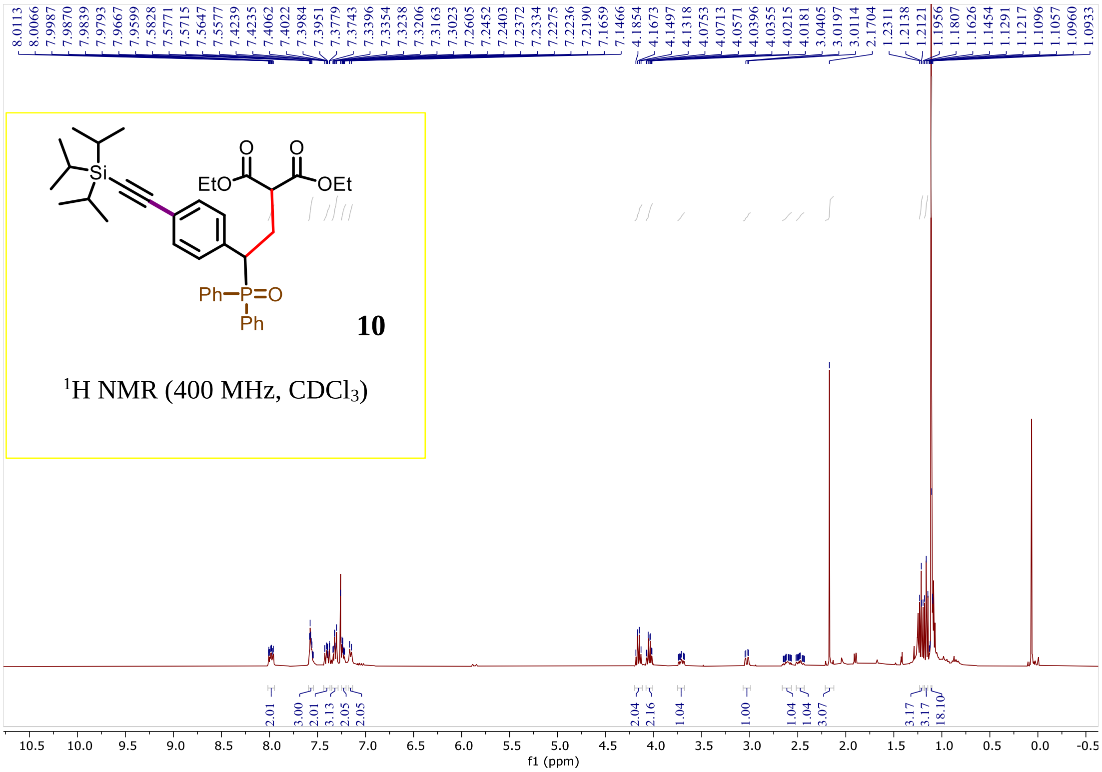
4da

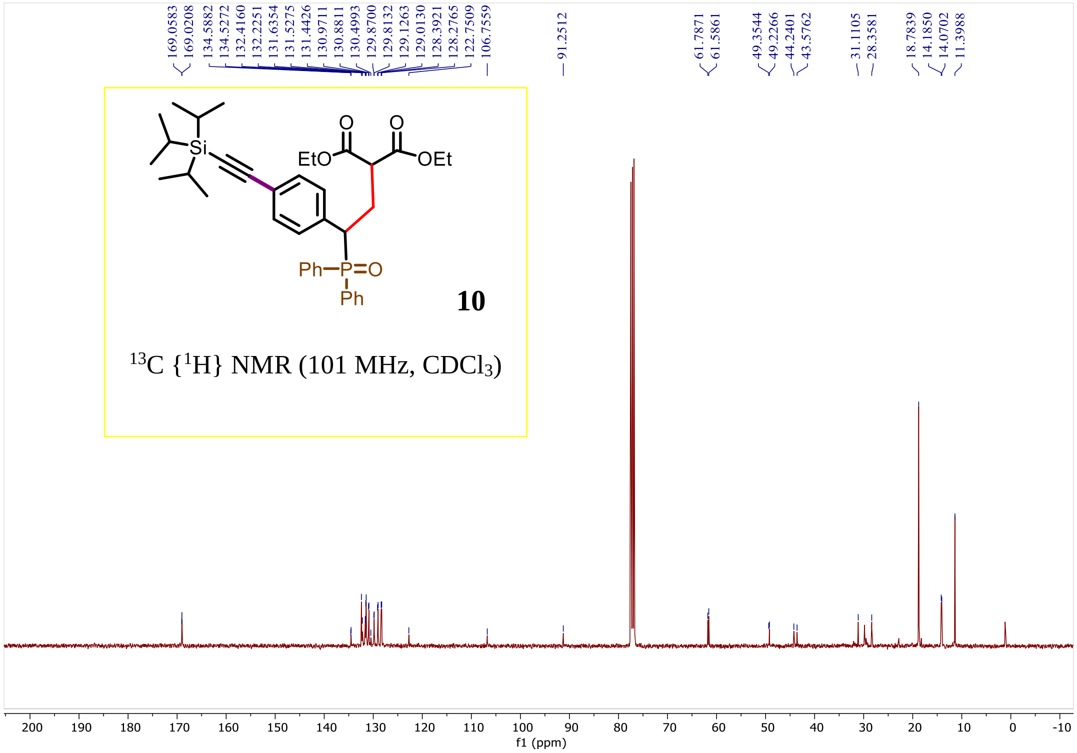
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

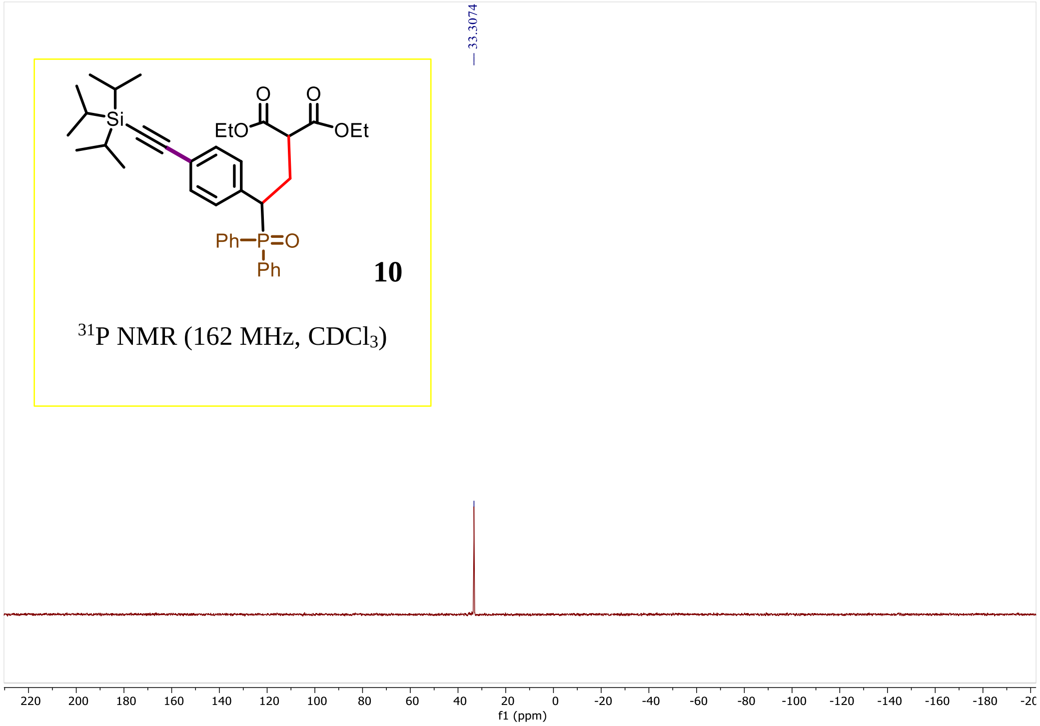


4da

^{31}P NMR (162 MHz, $CDCl_3$)


8.0113
8.0066
7.9987
7.9870
7.9839
7.9793
7.9667
7.9599
7.5828
7.5771
7.5715
7.5647
7.5577
7.4239
7.4235
7.4062
7.4022
7.3984
7.3951
7.3779
7.3743
7.3396
7.3354
7.3238
7.3206
7.3163
7.3023
7.2605
7.2452
7.2403
7.2372
7.2334
7.2275
7.2236
7.2190
7.1659
7.1466
4.1854
4.1673
4.1497
4.1318
4.0753
4.0713
4.0571
4.0396
4.0355
4.0215
4.0181
3.0405
3.0197
3.0114
2.1704
1.2311
1.2138
1.2121
1.1956
1.1807
1.1626
1.1454
1.1291
1.1217
1.1096
1.1057
1.0960
1.0933
Si
O
O
EtO
OEt
Ph
P=O
Ph
10
^{1}H NMR (400 MHz, CDCl$_3$)
2.01
3.00
2.01
3.13
2.05
2.05
2.04
2.16
1.04
1.00
1.04
1.04
3.07
3.17
3.17
18.10
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


169.0583
169.0208
134.5882
134.5272
132.4160
132.2251
131.6354
131.5275
131.4426
130.9711
130.8811
130.4993
129.8700
129.8132
129.1263
129.0130
128.3921
128.2765
122.7509
106.7559
91.2512
61.7871
61.5861
49.3544
49.2266
44.2401
43.5762
31.1105
28.3581
18.7839
14.1850
14.0702
11.3988
Si
O
O
EtO
OEt
Ph
P=O
Ph
10
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



10

^{31}P NMR (162 MHz, CDCl$_3$)

5.1 Conclusions

The title of the thesis is "*Exploring the Reactivities of Donor-Acceptor Cyclopropanes*". In this thesis, a comprehensive analysis is presented on the reactivity of donor-acceptor cyclopropanes. Through systematic experimentation and analysis, this study examines the various reactivities associated with these compounds, providing valuable insights that contribute to the broader scientific understanding of these important chemical species. By synthesizing and characterizing a range of new derivatives, this work sheds light on the underlying mechanisms that govern the reactivity of donor-acceptor cyclopropanes, highlighting the potential applications of these compounds in future research and development efforts. On the basis of these understandings, this thesis has been divided into four chapters and discussed in depth.

In Chapter 2A. I developed A straightforward and efficient $Sc(OTf)_3$-catalyzed (3+3)-annulation of donor-acceptor cyclopropanes (DACs) with indole-2-thiones has been developed, yielding *N*-halo indole-fused dihydrothiopyrano derivatives under mild conditions with excellent efficiency. This protocol is being extended toward the synthesis of biologically significant molecules.

In Chapter 2B. I developed a straightforward and efficient $LiAlH_4$-mediated protocol has been developed for the construction of thiazino indoles. This procedure provides efficient thiazino indoles derivatives in good to satisfactory yields. DFT calculation has been done to shed light into reaction mechanism.

Significant demands of the substituted amidine compounds in the pharma as well as in agrochemical or aroma sector promoted us to develop the novel amidines derivatives in chapter-3. Donor-acceptor cyclopropanes (DACs) in the presence of promoting or catalytic system react with various cyanamides systems through (3+2) cycloadditions to deliver amidines moieties. On this behalf of nitrile sources. In Chapter 3 I synthesized novel amidine derivatives *via* (3+2) cycloaddition of DACs with corresponding cyanamides under $BF_3{\cdot}OEt_2$ catalysis in good to excellent yields.

In the fourth chapter, I developed a metal- and additive-free $BF_3{\cdot}OEt_2$-promoted one-pot three-component reaction of phosphine chlorides/cyanides with DACs, enabling the nucleophilic ring-opening of DACs to form boron-pendant diester complexes in two tautomeric forms. The protocol features mild conditions, broad substrate scope, selective product formation, and gram-scale practicality. Combined experimental and theoretical studies elucidate a clear mechanistic pathway.

Throughout the preceding chapters, I have explored the distinct reactivities of DACs in chapter 2 and chapter 3, and Chapter 4.

Appendix A: Chapter 2A

Single Crystal X-Ray

For the determination of X-ray crystal structure of **3ae** single crystals were selected and mounted with paratone oil on a glass fiber using gum. The data were collected at 293K on a CMOS based Bruker D8 Venture PHOTON 100 diffractometer equipped with a INCOATEC micro-focus source with graphite monochromatic Mo Kα radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. For the integration of diffraction profiles SAINT program[1] was used. Adsorption correction was done applying SADABS program.[2] The crystal structure was solved by SIR 92[3] and refined by full matrix least square method using SHELXL-97[4] WinGX system, Ver 1.70.01.[5] All the non-hydrogen atoms in the structure were located from the Fourier map and refined anisotropically. The hydrogen atoms were fixed by HFIX in their ideal positions and refined using riding model with isotropic thermal parameters. The crystal structure has been deposited to Cambridge Crystallographic Data Centre and allotted deposition number is **2132801**.

Crystal structure of 3ae:

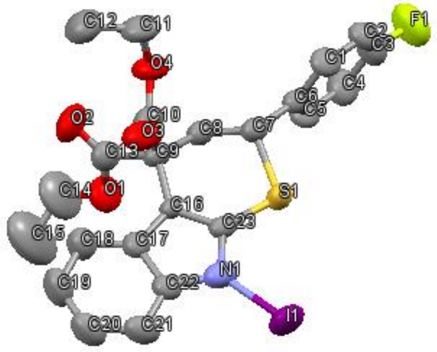


Figure S1. X-ray crystal structure of compound **3ae** with 30% probability level.

Table 1: Crystal data and structure refinement for 3ae.

CCDC No.	2132801
Empirical formula	$C_{23}H_{21}FINO_4S$
Formula weight	553.37
Temperature(K)	293.15
Crystal system	Monoclinic
Space group	P 21/n
a, b, c (Å)	9.6642 (10), 9.6880 (12), 24.773 (3)
α, β, γ (°)	90, 91.356 (4), 90
Volume ($Å^3$)	2318.7 (5)
Z	4
Calculated density (g/cm^3)	1.585
Absorption coefficient (mm^{-1})	1.508
F(000)	1104.0
Crystal size (mm^3)	0.489 × 0.346 × 0.236
Radiation	MoKα (λ = 0.71073)
Theta range for data collection	4.488 to 54.384
Index ranges	$-12 \le h \le 12, -12 \le k \le 12, -31 \le l \le 31$
Reflections collected	56218
Independent reflections	5149 [R(int) = 0.0710, R(sigma) = 0.0331]
Data/restraints/parameters	5149/0/281
Goodness-of-fit on F^2	1.092
Final R indexes [I>=2σ (I)]	$R_1 = 0.0649$, $wR_2 = 0.1526$
Final R indexes [all data]	$R_1 = 0.0838$, $wR_2 = 0.1642$
Largest diff. peak/hole (e $Å^{-3}$)	1.22/-1.05

Table 2 Bond Lengths for 3ae.

Atoms	Length [Å]	Atoms	Length [Å]
I1-N1	2.075(6)	C6-C5	1.384(8)
S1-C23	1.727(6)	C23-N1	1.366(7)
S1-C7	1.826(5)	C17-C18	1.386(9)
O4-C10	1.335(7)	O2-C13	1.207(8)
O4-C11	1.479(8)	C9-C8	1.533(8)
C16-C23	1.398(7)	C9-C10	1.545(8)
C16-C17	1.390(7)	C9-C13	1.541(8)
C16-C9	1.461(6)	C7-C8	1.507(8)

Atoms	Length [Å]	Atoms	Length [Å]
O3-C10	1.184(7)	C1-C2	1.378(9)
F1-C3	1.349(8)	C5-C4	1.383(9)
O1-C13	1.300(9)	C21-C20	1.353(10)
O1-C14	1.471(10)	C18-C19	1.392(10)
C22-N1	1.419(8)	C2-C3	1.373(10)
C22-C17	1.404(8)	C3-C4	1.359(10)
C22-C21	1.394(8)	C11-C12	1.456(11)
C6-C7	1.503(8)	C20-C19	1.377(11)
C6-C1	1.378(8)	C14-C15	1.299(16)

Table 3 Bond Angles for 3ae.

Atoms	Angle [°]	Atoms	Angle [°]
C23-S1-C7	100.4(3)	C8-C9-C13	105.6(5)
C10-O4-C11	117.2(5)	C13-C9-C10	108.6(5)
C23-C16-C9	124.0(5)	C6-C7-S1	106.6(4)
C17-C16-C23	108.3(4)	C6-C7-C8	115.2(5)
C17-C16-C9	126.3(5)	C8-C7-S1	109.6(4)
C13-O1-C14	116.6(8)	C6-C1-C2	120.9(6)
C17-C22-N1	106.2(5)	C7-C8-C9	113.6(5)
C21-C22-N1	133.8(6)	O4-C10-C9	110.4(5)
C21-C22-C17	120.1(6)	O3-C10-O4	125.1(6)
C1-C6-C7	119.6(5)	O3-C10-C9	124.4(6)
C1-C6-C5	118.4(5)	C4-C5-C6	121.7(6)
C5-C6-C7	122.0(5)	C20-C21-C22	118.8(6)
C16-C23-S1	125.9(4)	O1-C13-C9	112.0(5)
N1-C23-S1	126.0(4)	O2-C13-O1	126.4(6)
N1-C23-C16	108.0(5)	O2-C13-C9	121.6(7)
C22-N1-I1	126.3(4)	C17-C18-C19	117.3(7)
C23-N1-I1	124.5(5)	C3-C2-C1	118.6(6)
C23-N1-C22	109.2(5)	F1-C3-C2	118.7(7)
C16-C17-C22	108.2(5)	F1-C3-C4	118.5(7)
C18-C17-C16	131.0(5)	C4-C3-C2	122.7(6)
C18-C17-C22	120.8(6)	C12-C11-O4	109.6(7)
C16-C9-C8	111.2(4)	C3-C4-C5	117.7(6)
C16-C9-C10	108.5(4)	C21-C20-C19	121.5(7)

Atoms	Angle [°]	Atoms	Angle [°]
C16-C9-C13	111.0(5)	C20-C19-C18	121.5(7)
C8-C9-C10	111.9(5)	C15-C14-O1	114.8(11)

Appendix B: Chapter 2B

Crystal structure of 2d:

Single Crystal X-Ray data of 2d

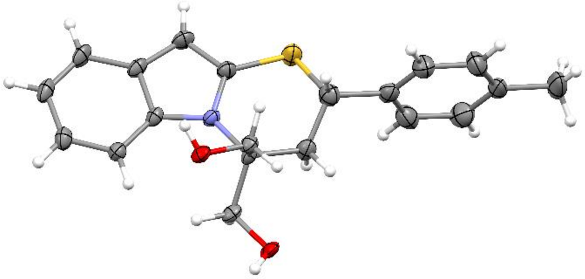


Figure S1. X-ray crystal structure of compound **2d** with 30% probability level.

The crystal structure has been deposited to Cambridge Crystallographic Data Centre and allotted deposition number is **2245963**. Suitable single – crystals of **2d** for X-ray analysis were grown up from slow crystallization in DCM at room temperature.

Table 4 Crystal data and structure refinement for 2d.	
Ccdc No.	2245963
Empirical formula	$C_{20}H_{21}NO_2S$
Formula weight	339.44
Temperature/K	298
Crystal system	monoclinic
Space group	Cc
a/Å	7.6698(17)
b/Å	37.241(10)
c/Å	6.1308(17)
α/°	90
β/°	92.114(5)
γ/°	90
Volume/Å^3	1750.0(8)
Z	4
ρ_{calc}g/cm^3	1.288
μ/mm^{-1}	0.197
F(000)	720.0
Crystal size/mm^3	0.423 × 0.029 × 0.023
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.374 to 51.522
Index ranges	$-9 \leq h \leq 9, -45 \leq k \leq 45, -7 \leq l \leq 7$
Reflections collected	9343
Independent reflections	3276 [R_{int} = 0.0457, R_{sigma} = 0.0559]
Data/restraints/parameters	3276/2/220
Goodness-of-fit on F^2	1.081
Final R indexes [I>=2σ (I)]	R_1 = 0.0595, wR_2 = 0.1302
Final R indexes [all data]	R_1 = 0.0699, wR_2 = 0.1352
Largest diff. peak/hole / e Å^{-3}	0.52/-0.20
Flack parameter	0.09(5)

Table 5 Bond Lengths for 2d.

Atom	Length/Å	Atom	Length/Å
S1-C8	1.746(6)	C18-C19	1.532(7)
S1-C9	1.801(7)	C18-C20	1.535(7)

Atom	Length/Å	Atom	Length/Å
O2-C20	1.430(6)	C18-C17	1.533(7)
O1-C19	1.394(6)	C4-C5	1.352(9)
N1-C8	1.387(7)	C16-C10	1.358(10)
N1-C1	1.423(6)	C16-C15	1.412(10)
N1-C18	1.494(6)	C17-C9	1.476(9)
C8-C7	1.355(7)	C10-C9	1.539(8)
C1-C6	1.420(7)	C10-C11	1.335(10)
C1-C2	1.383(7)	C13-C12	1.374(11)
C6-C7	1.405(8)	C13-C15	1.368(11)
C6-C5	1.420(7)	C13-C14	1.509(9)
C3-C4	1.394(9)	C12-C11	1.368(10)
C3-C2	1.382(7)		

Table 6 Bond Angles for 2d.

Atom	Angle/˚	Atom	Angle/˚
C8-S1-C9	99.5(3)	O1-C19-C18	114.6(4)
C8-N1-C1	106.7(4)	O2-C20-C18	109.6(4)
C8-N1-C18	124.7(4)	C5-C4-C3	120.0(5)
C1-N1-C18	127.0(4)	C8-C7-C6	107.5(5)
N1-C8-S1	124.9(4)	C4-C5-C6	120.2(5)
C7-C8-S1	123.5(4)	C3-C2-C1	118.8(5)
C7-C8-N1	111.2(5)	C10-C16-C15	120.6(7)
C6-C1-N1	106.6(4)	C9-C17-C18	118.0(5)
C2-C1-N1	133.2(5)	C16-C10-C9	121.8(6)
C2-C1-C6	120.2(5)	C11-C10-C16	118.7(6)
C7-C6-C1	108.1(4)	C11-C10-C9	119.5(6)
C7-C6-C5	133.1(5)	C12-C13-C14	120.7(8)
C5-C6-C1	118.9(5)	C15-C13-C12	116.4(6)
C2-C3-C4	122.0(6)	C15-C13-C14	122.9(9)
N1-C18-C19	110.3(4)	C11-C12-C13	122.5(7)
N1-C18-C20	108.7(4)	C13-C15-C16	120.5(7)

Atom	Angle/°	Atom	Angle/°
N1-C18-C17	110.6(4)	C17-C9-S1	110.4(5)
C19-C18-C20	111.0(4)	C17-C9-C10	115.0(5)
C19-C18-C17	109.6(4)	C10-C9-S1	108.0(4)
C17-C18-C20	106.5(4)	C10-C11-C12	121.2(7)

Appendix C: Chapter 4

Single Crystal X-Ray of 3aa, 3ha

The crystal structure has been deposited to Cambridge Crystallographic Data Centre and allotted deposition number are **2255736** and **2305065** for **3aa and 3ha** respectively. Suitable single – crystals of **3aa** for X-ray analysis were grown up from slow crystallization in methanol at room temperature.

Crystal structure of 3aa:

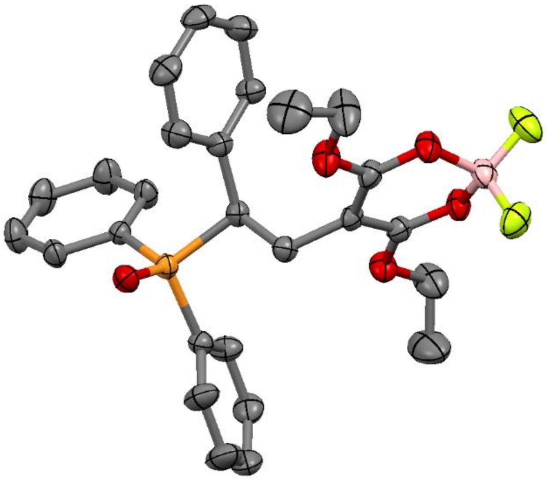


Figure S5. X-ray crystal structure of compound **3aa** with 30% probability level.

Table 7: Crystal data and structure refinement of **3aa**

Table 7 Crystal data and structure refinement for 3aa.	
CCDC NO.	**2255736**
Empirical formula	$C_{27}H_{28}BF_2O_5P$
Formula weight	512.27
Temperature/K	298
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.3298(15)
b/Å	12.2609(13)
c/Å	18.885(2)
α/°	90
β/°	92.364(5)
γ/°	90
Volume/Å^3	2621.2(5)
Z	4
ρ_{calc}g/cm^3	1.298
μ/mm^{-1}	0.154
F(000)	1072.0

Crystal size/mm^3	0.214 × 0.205 × 0.123
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.318 to 52.84
Index ranges	$-14 \leq h \leq 11$, $-13 \leq k \leq 15$, $-22 \leq l \leq 23$
Reflections collected	14750
Independent reflections	5287 [R_{int} = 0.0445, R_{sigma} = 0.0517]
Data/restraints/parameters	5287/0/327
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0754, wR_2 = 0.1808
Final R indexes [all data]	R_1 = 0.1059, wR_2 = 0.2018
Largest diff. peak/hole / e Å^{-3}	1.41/-0.44

Table 8 Bond Lengths for 3aa

Atom	Length/Å	Atom	Length/Å
P1-O5	1.490(2)	C9-C8	1.564(4)
P1-C21	1.791(3)	C15-C10	1.369(5)
P1-C9	1.817(3)	C15-C14	1.382(5)
P1-C22	1.821(4)	C22-C23	1.384(5)
O2-C4	1.295(4)	C22-C27	1.365(5)
O2-B1	1.490(5)	C10-C11	1.376(5)
O3-C4	1.303(4)	C16-C17	1.385(5)
O3-C5	1.463(5)	C23-C24	1.374(5)
F2-B1	1.338(5)	C20-C19	1.380(5)
O1-C3	1.301(4)	C14-C13	1.387(6)
O1-B1	1.486(5)	C25-C24	1.359(6)
F1-B1	1.362(5)	C25-C26	1.350(7)
O4-C3	1.312(4)	C11-C12	1.364(6)
O4-C2	1.474(5)	C12-C13	1.370(6)
C21-C16	1.381(5)	C27-C26	1.377(6)
C21-C20	1.390(4)	C17-C18	1.368(6)
C7-C4	1.382(5)	C18-C19	1.369(6)
C7-C8	1.500(4)	C5-C6	1.387(7)
C7-C3	1.378(5)	C2-C1	1.449(8)

Atom	Length/Å	Atom	Length/Å
C9-C15	1.521(5)		

Table 9 Bond Angles for 3aa

Atom	Angle/°	Atom	Angle/°
O5-P1-C21	113.61(14)	C7-C8-C9	112.8(3)
O5-P1-C9	113.75(15)	C15-C10-C11	121.0(4)
O5-P1-C22	111.42(15)	C21-C16-C17	119.9(3)
C21-P1-C9	108.31(15)	O1-C3-O4	117.2(3)
C21-P1-C22	104.20(15)	O1-C3-C7	124.0(3)
C9-P1-C22	104.74(15)	O4-C3-C7	118.8(3)
C4-O2-B1	119.8(3)	C24-C23-C22	120.5(4)
C4-O3-C5	120.9(3)	C19-C20-C21	120.7(3)
C3-O1-B1	120.0(3)	C15-C14-C13	120.8(4)
C3-O4-C2	120.3(3)	C26-C25-C24	119.9(4)
C16-C21-P1	125.0(2)	C25-C24-C23	120.0(4)
C16-C21-C20	118.7(3)	C12-C11-C10	121.1(4)
C20-C21-P1	116.0(3)	C11-C12-C13	118.8(4)
C4-C7-C8	121.5(3)	C22-C27-C26	120.2(4)
C3-C7-C4	115.6(3)	C12-C13-C14	120.3(4)
C3-C7-C8	122.9(3)	C18-C17-C16	120.8(4)
O2-C4-03	117.7(3)	C17-C18-C19	119.9(4)
O2-C4-C7	124.4(3)	C18-C19-C20	120.0(4)
O3-C4-C7	117.9(3)	C25-C26-C27	120.8(4)
C15-C9-P1	113.6(2)	C6-C5-03	111.0(4)
C15-C9-C8	111.5(3)	F2-B1-O2	109.2(4)
C8-C9-P1	108.3(2)	F2-B1-O1	110.1(4)
C10-C15-C9	119.3(3)	F2-B1-F1	110.8(3)
C10-C15-C14	118.0(3)	O1-B1-O2	109.4(3)
C14-C15-C9	122.5(3)	F1-B1-O2	109.1(3)
C23-C22-P1	123.4(3)	F1-B1-O1	108.3(4)
C27-C22-P1	118.0(3)	C1-C2-O4	107.8(5)
C27-C22-C23	118.6(4)		

Crystal structure of 3ha:

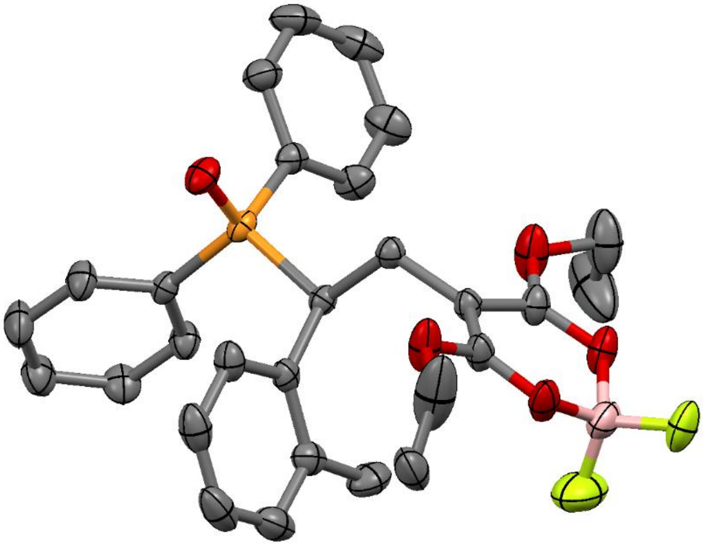


Figure S6. X-ray crystal structure of compound **3ha** with 30% probability level.

Table 10 Crystal data and structure refinement for 3ha	
Ccdc no.	**2305065**
Empirical formula	$C_{28}H_{30}BF_2O_5P$
Formula weight	526.30
Temperature/K	298.00
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.5666(13)
b/Å	14.5930(11)
c/Å	12.9789(9)
α/°	90
β/°	113.828(2)
γ/°	90

Volume/Å^3	2697.0(4)
Z	4
ρ_{calc}g/cm^3	1.296
μ/mm^{-1}	0.152
F(000)	1104.0
Crystal size/mm^3	0.321 × 0.23 × 0.105
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.996 to 52.998
Index ranges	$-19 \le h \le 19, -18 \le k \le 18, -16 \le l \le 16$
Reflections collected	34738
Independent reflections	5559 [R_{int} = 0.0627, R_{sigma} = 0.0384]
Data/restraints/parameters	5559/18/347
Goodness-of-fit on F^2	1.069
Final R indexes [I>=2σ (I)]	R_1 = 0.0713, wR_2 = 0.1657
Final R indexes [all data]	R_1 = 0.0866, wR_2 = 0.1755
Largest diff. peak/hole / e Å^{-3}	0.53/-0.42

Table 11 Bond Lengths for 3ha

Atom	Length/Å	Atom	Length/Å
P1-O5	1.488(2)	C17-C18	1.390(4)
P1-C23	1.811(3)	C17-C22	1.382(4)
P1-C9	1.826(2)	C26-C25	1.369(5)
P1-C17	1.803(3)	C26-C27	1.360(6)
O3-C4	1.290(3)	C25-C24	1.384(4)
O3-B1	1.486(5)	C7-C4	1.384(4)
F1-B1	1.370(4)	C7-C3	1.380(4)
F2-B1	1.348(5)	C5-C6	1.364(7)
O2-B1	1.484(5)	C20-C19	1.377(5)
O2-C3	1.293(3)	C20-C21	1.367(5)
O1-C3	1.311(4)	C19-C18	1.382(4)
O1-C2	1.464(5)	C22-C21	1.378(5)
C1-C2	1.256(11)	C27-C28	1.376(5)
C1A-C2	1.190(12)	C10-C11	1.395(4)

Atom	Length/Å	Atom	Length/Å
C23-C24	1.384(4)	C10-C15	1.399(4)
C23-C28	1.396(4)	C11-C12	1.388(5)
C9-C8	1.549(3)	C12-C13	1.363(6)
C9-C10	1.523(4)	C13-C14	1.367(6)
C8-C7	1.504(4)	C14-C15	1.404(5)
O4-C4	1.321(4)	C15-C16	1.511(5)
O4-C5	1.472(4)		

Table 12 Bond Angles for 3ha

Atom	Angle/°	Atom	Angle/°
O5-P1-C23	110.94(13)	C6-C5-O4	111.0(4)
O5-P1-C9	114.77(12)	C21-C20-C19	119.6(3)
O5-P1-C17	111.98(12)	C20-C19-C18	120.5(3)
C23-P1-C9	105.99(12)	C19-C18-C17	120.2(3)
C17-P1-C23	106.33(12)	C21-C22-C17	121.0(3)
C17-P1-C9	106.29(12)	C20-C21-C22	120.3(3)
C4-O3-B1	119.4(3)	C26-C27-C28	120.8(3)
C3-O2-B1	120.2(3)	C27-C28-C23	120.5(4)
C3-O1-C2	120.5(3)	C11-C10-C9	119.2(3)
C24-C23-P1	125.7(2)	C11-C10-C15	119.2(3)
C24-C23-C28	118.0(3)	C15-C10-C9	121.6(2)
C28-C23-P1	116.3(2)	C12-C11-C10	121.0(3)
C8-C9-P1	109.63(17)	C13-C12-C11	119.9(4)
C10-C9-P1	112.43(17)	C12-C13-C14	120.0(3)
C10-C9-C8	112.6(2)	C13-C14-C15	122.0(4)
C7-C8-C9	112.6(2)	C10-C15-C14	117.9(3)
C4-O4-C5	121.3(3)	C10-C15-C16	122.8(3)
C18-C17-P1	123.7(2)	C14-C15-C16	119.3(3)
C22-C17-P1	117.9(2)	F1-B1-O3	108.7(3)
C22-C17-C18	118.4(3)	F1-B1-O2	107.8(3)
C27-C26-C25	119.8(3)	F2-B1-O3	108.1(4)
C26-C25-C24	120.3(4)	F2-B1-F1	112.3(3)

Atom	Angle/°	Atom	Angle/°
C23-C24-C25	120.6(3)	F2-B1-O2	110.1(4)
C4-C7-C8	121.8(2)	O2-B1-O3	109.7(3)
C3-C7-C8	123.0(2)	O2-C3-O1	117.3(3)
C3-C7-C4	115.1(3)	O2-C3-C7	124.1(3)
O3-C4-O4	117.8(3)	O1-C3-C7	118.6(3)
O3-C4-C7	124.7(3)	C1-C2-O1	115.9(9)
O4-C4-C7	117.4(3)	C1A-C2-O1	120.8(8)

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Conferences Attended

- **CRIKC-2023:** Institute of Nano Science and Technology (INST), Mohali
- **Activity:** Attended.

- **ChemFest-2023:** Department of Chemistry, IIT Ropar, India
- **Activity:** Attended.

- **CRIKC-2024**: Punjab University, Chandigarh Punjab
- **Activity**: **Poster Presentation**: Ring-opening & Closing of Dihydrothiopyrane using Lithium aluminium hydride.

- **ChemFest-2024**: Department of Chemistry, Indian Institute of Technology (IIT)
- **Ropar Activity**: **Poster Presentation**: Ring-opening & Closing of dihydrothiopyrane using Lithium aluminium hydride

- **24th Tetrahedron Symposium-2024:** 18-21 June Le Corum Congress Center, Esplanade Charles de Gaulle BP, 2200, 34072 Montpellier Cedex 1, France.
- **Activity: Poster Presentation** entitled as “Synthesis of Indole-Fused Dihydrothiopyrano Scaffolds via (3+3)-Annulations of Donor–Acceptor Cyclopropanes with Indoline-2-Thiones”

List of Publications

Thesis Chapters

(1) **Gopal, B**.; Singh, P. R.; Kumar, M. Goswami, A. Synthesis of Indole-Fused Dihydrothiopyrano Scaffolds *via* (3 + 3)-Annulations of Donor–Acceptor Cyclopropanes with Indoline-2-Thiones. *J. Org. Chem.* **2023**, *88*, 132.

(2) **Gopal, B**.; Lamba, M.; Kushwah, A.; Singh, P. R.; Dhilip. T.J.; Goswami, A. Nucleophilic Ring Opening of DACs through Umpolung Reactivity of Organochlorophosphines: Phosphine Oxide Functionalized Boron Pendanted Compounds (*Manuscript under revision*)

(3) **Gopal, B**.; Singh, P. R.; Bhatt, S.; Goswami, A. $BF_3 \cdot OEt_2$-Mediated (3+2) Cycloaddition Reactions of Donor-Acceptor Cyclopropanes (DACs) with Cyanamides: Access to Cyclic Amidines. Synthesis **2024**, *56*, 2521–2528.

(4) **Gopal, B**.; Das. R.; Goswami, A. Ring-opening & Closing of dihydrothiopyrane using Lithium aluminium hydride (*Manuscript under preparation*)

As Co-Author

(5) Singh, P. R.; **Gopal, B**.; Kumar, M. Goswami, A. A metal-free $BF_3 \cdot OEt_2$ mediated chemoselective protocol for the synthesis of propargylic cyclic imines. *Org. Biomol. Chem.*, **2022**, *20*, 4933.

Unpublished /Submitted Manuscripts

(6) Lamba, M.; **Gopal, B**.; Das, R.; Goswami, A. Chemoselective reactions of thio-oxindoles with selectfluor under metal-free conditions: Access to dithianes “Manuscript under Preparation”.