Catalytic Asymmetric Cyclopropanations of Diazo Phosphonates and Designed Diazo Ketones

（ジアゾリン酸エステルとデザインジアゾケトンの触媒的不斉シクロプロパン化反応）

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Abstract（Doctor）

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Approx. 800 words

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Although Ruthenium complex is newcomer in the field of catalytic cyclopropanation, it has emerged as the third important catalyst metal for the carbenoid chemistry of diazo compounds, besides copper and rhodium. Therefore, future developments should try to find catalysts that give ruthenium carbene intermediates electrophilic enough to react with a wide range of olefinic substrates and that at the same time give high levels of dia- and enantioselectivity. This prompted us to explore the asymmetric cyclopropanation of various diazo compounds which are potentially building blocks and expectant to be applied in pharmaceutical and medicinal fields.

Chapter 1. Describes the history of the carbene transfer reactions. A brief review of the most successful metal carbene intermediates in asymmetric cyclopropanations over the past ten years are provided. Furthermore, the application of metal carbene complexes in the synthesis of biologically-active

or natural product-like compounds are also mentioned.

Chapter 2. Recently, our research group reported that the complex, Ru(II)-pheox, has been completely efficient in carbene transfer reactions, particularly the cyclopropanation of diethyl diazomethylphosphonates with various electron-deficient olefins such as α,β-unsaturated carbonyl compounds or vinyl carbamates in excellent yields and with high enantioselectivity. Thus, here in, novel catalysis involving phosphonomethylation of N-methylaniline and asymmetric cyclopropylphosphonation reactions of *N,N*-diethylaniline derivatives with diazomethylphosphonates are reported. Optically active cyclopropylphosphonate derivatives were directly synthesized from diazomethylphosphonates and *N,N*-diethylaniline derivatives catalyzed by a *3,4,5* methoxy-Ru(II)-pheox complex in one step in good yields and high diastereoselectivities (up to trans/cis = > 99:1<) and enantioselectivities (up to 99% ee). D labeling mechanistic studies of phosphonomethylation and cyclopropylphosphonation suggested that an enamine or iminium intermediate was generated in the reaction process.

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Chapter 4. Furthermore, finding catalysts which can cyclopropanate with various diazo compounds to enrich stereoselectivity also have been developed during the last decades. In our previous researches, Ru(II)-pheox-catalyzed asymmetric cyclopropanation of succinimidyl diazoacetate with olefins and allenes resulted in high yields and excellent enantioselectivities and of α,β-unsaturated carbonyl compounds with acetonyl diazoacetate in much higher stereoselectivities (diastereoselectivity >99:1 and enantioselectivity up to 99%). Consequently, herein, The diazo derivative of acetonyl acetate is a useful basic skeleton for the synthesis of cyclopropyl ketones. The intermolecular cyclopropanations of diazo acetoxy acetone with olefins are accomplished by using a novel *p*-nitro-Ru(II)-diphenyl-Pheox catalyst to give the corresponding optically active cyclopropane derivatives in good yields (up to 95%) with excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to 98% ee).

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List of publications and experimental supporting information are included in the appendices.

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always happy and healthy. His smiling is all. We always go forward together, the happiness will be there.
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ABSTRACT

Keywords: asymmetric synthesis, intermolecular cyclopropanation, Ru(II)-Pheox catalyst.

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Catalytic Asymmetric Cyclopropanations of Diazo Phosphonates and Designed Diazo Ketones

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LIST OF ABBREVIATIONS

Ar	aryl
atm	atmosphere
Bn	Benzoyl
Bu	butyl
Calcd	calculated
Conc.	concentrated
d	doublet
dd	doublet of doublet
DFT	density functional theory
dr	diastereomeric ratio
dt	doublet of triplet
EDA	ethyl diazo acetate
ee	enantiomeric excess
EDG	electron-donating group
EPR	Electron paramagnetic resonance technique
equiv.	equivalent
ESI-MS	electrospray ionization – mass spectrometry technique
Et	ethyl
Et_3N	triethyl amine
EtOAc	ethyl acetate
EWG	electron-withdrawing group
g	gram
h	hour

HPLC	high performance liquid chromatography
Hz	hertz
*i*Pr	isopropyl
IR	infrared
m	multilplet
M	molar
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliter
mmol	millimole
Mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
q	quartet
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet
t	triplet
*t*Bu	tertiary butyl
td	triplet of douplet
temp.	temperature

tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
tR	retention time
U.V	ultra violet

NOTATIONS

α	alpha
$[\alpha]_D$	Specific rotation
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C NMR	Carbon nuclear magnetic resonance spectroscopy
^{19}F NMR	Flourine nuclear magnetic resonance spectroscopy
^{31}P NMR	Phosphorus nuclear magnetic resonance spectroscopy
Å	Ångström (10−10 m)
β	beta
%	percentage
J	coupling constant
$[M + H]^+$	Protonated molecular ion (mass spectrometry)
δ	chemical shift
^{o}C	degree Celsius

CHAPTER 1

Introduction

1.1 Carbenes

Carbenes are highly reactive species in which the central carbon only has 6 electrons. The electrons are distributed around the carbon so that 4 electrons are in bonds and the remaining 2 are in a non-bonding orbital. The general formula is R-(C:)-R' or R=C: where the R represents substituents or hydrogen atoms. The term "carbene" may also refer to the specific compound H_2C:, also called methylene, the parent hydride from which all other carbene compounds are formally derived. Carbenes are classified as either singlets or triplets, depending upon their electronic structure.

Singlet carbenes are spin-paired. In the language of valence bond theory, the molecule adopts an sp^2 hybrid structure. Triplet carbenes have two unpaired electrons. Most carbenes have a nonlinear triplet ground state, except for those with nitrogen, oxygen, or sulfur atoms, and halides directly bonded to the divalent carbon.

Carbenes are called singlet or triplet depending on the electronic spins they possess. Triplet carbenes are paramagnetic and may be observed by electron spin resonance spectroscopy if they persist long enough. The total spin of singlet carbenes is zero while that of triplet carbenes is one. Bond angles are 125–140° for triplet methylene and 102° for singlet methylene. Triplet carbenes are generally stable in the gaseous state, while singlet carbenes occur more often in aqueous media (Figure 1).

For simple hydrocarbons, triplet carbenes usually have energies 8 kcal/mol (33 kJ/mol) lower than singlet carbenes, thus, in general, triplet is the more stable state (the ground state) and singlet is the excited state species. Substituents that can donate electron pairs may stabilize the singlet state by delocalizing the pair into an empty p orbital. If the energy of the singlet state is sufficiently reduced it will actually become the ground state. No viable strategies exist for triplet stabilization.

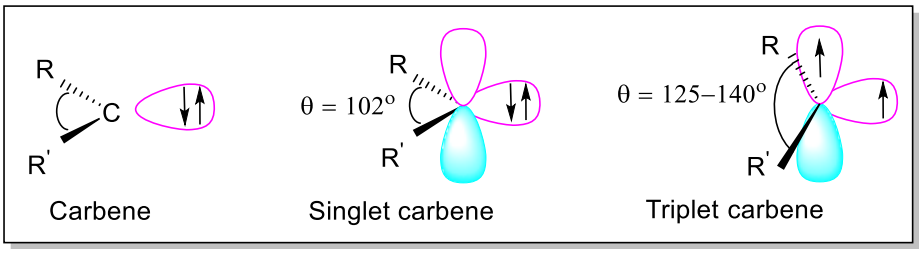


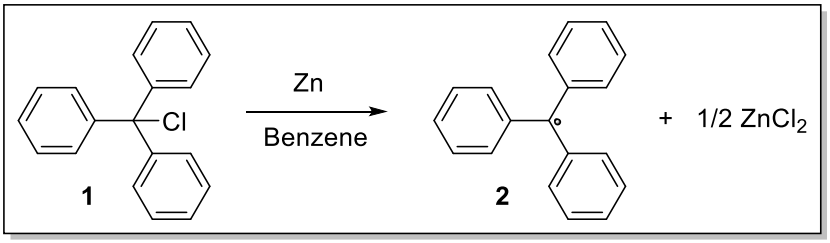
Figure 1. The electronic structure of carbene.

1.1.1 History of carbene intermediates

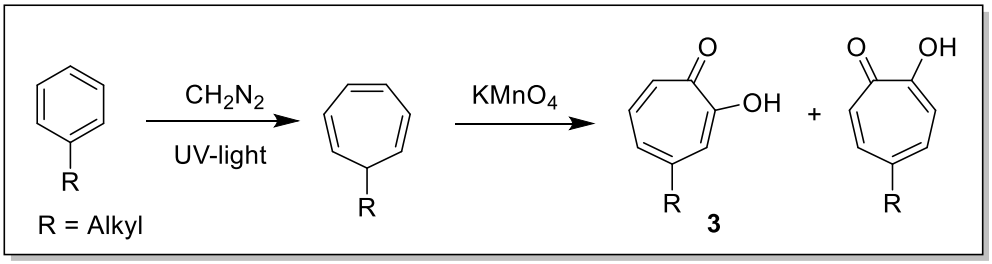
Geuther and Hermann[1] reported the first assumption of a carbene species in 1855. They suggested that the alkaline hydrolysis of chloroform proceeds though the formation of a reaction

intermediate with a divalent carbon called dichlorocarbene. In 1897, Nef proposed the same reaction intermediate for the Reimer–Tiemann reaction and the transformation of pyrrol to -chloropyridine in chloroform[2]. They both showed a lot of intuition and courage for their postulations considering that most chemists did not even believe in the existence of free radicals at that time. Indeed, it was only 3 years later that Gomberg characterized the first example of a free radical, triphenylchloromethylene **2** (Scheme 1), through elemental analysis and chemical reactivity[3]. Its discovery was freshly welcomed by the scientific community[4]. Prior to the Great War, Staudinger and Kupfer contributed to the recognition of carbenic reaction intermediates by studying the formation of methylene derivatives[5] and diazomethane[6].

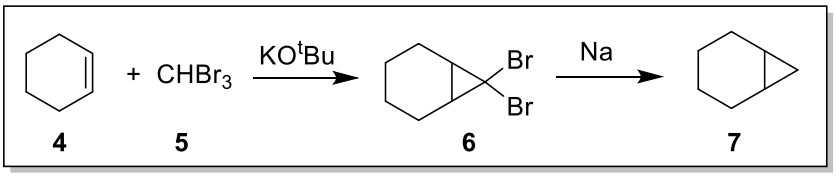
Throughout the 1920s and 1930s, the existence of free radicals was finally well recognized, and their use in organic chemistry as reaction intermediates was growing extremely rapidly[4]. In this context, carbene moieties were regarded as diradicals[7]. The methylene carbene was seen as a linear species, with two degenerate p-orbitals inevitably leading to a triplet state[8]. At the beginning of the 1950s, there was a resurgence of interest in the organic chemical reactions of carbenes[9]. In 1953, Doering and Knox disclosed an elegant synthesis of tropolones **3** via an addition of methylene to substituted benzene (Scheme 2)[10].



Scheme 1. Generation of the first stable radical



Scheme 2. Synthesis of tropolone-derivatives via the insertion of a methylene intermediate.



Scheme 3. Alkene cyclopropanation via methylene intermediate.

The most important contribution of Doering and his collaborators came a year later when

they proved the existence of a dibromomethylene intermediate **6**, in the first cyclopropanation product **7** operating via the addition of bromoform **5** to an alkene **4** (Scheme 3)[11].

Then more organic synthesis involving the use of methylene were reported[12], prompting chemists and physicists to have a closer look at this carbenic intermediate.

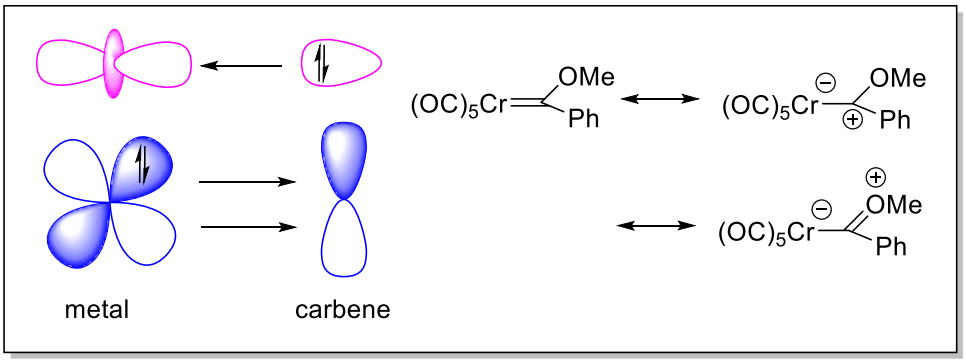
1.1.2 Transition metal carbene intermediates

A transition metal carbene complex (or another name is carbenoid) is an organometallic compound featuring a divalent organic ligand. The divalent organic ligand coordinated to the metal center is called a carbene. Carbene complexes for almost all transition metals have been reported. The term carbene ligand is formalism since many are not derived from carbenes and almost none exhibit the reactivity characteristic of carbenes. Described often as $M{=}CR_2$, they represent a class of organic ligands intermediate between alkyls ($-CR_3$) and carbynes ($\equiv CR$). They feature in some catalytic reactions, especially alkene metathesis, and are of value in the preparation of some fine chemicals.

1.1.2.1 Classification of carbene intermediates

Metal carbene complexes are often classified into two types. The **Fischer carbenes** named after Ernst Otto Fischer feature strong π-acceptors at the metal and being electrophilic at the carbene carbon atom. **Schrock carbenes**, named after Richard R. Schrock, are characterized by more nucleophilic carbene carbon centers; these species typically feature higher valent metals. *N*-Heterocyclic carbenes (NHCs) were popularized following Arduengo's isolation of a stable free carbene in 1991. Reflecting the growth of the area, carbene complexes are now known with a broad range of different reactivities and diverse substituents. Often it is not possible to classify a carbene complex with regards to its electrophilicity or nucleophilicity.

1.1.2.1.1 Fisher carbenes



Scheme 4. Metal-carbon bonding in Fisher carbene complexes

In the early 1960s, free carbenes were found to be stabilized by coordination to transition metals *via* formal metal–to–carbon double bond, and some of them could even be isolated as metal–carbene complexes. The donation of d–orbital electrons on the metal to the electron–deficient carbene carbon makes the carbene more stable and easier to work with. When this d–

electron donation is moderate, as in the low oxidation state of middle and late d–series metals, the carbenoids still behave electrophonically, and are known as Fischer carbenes.

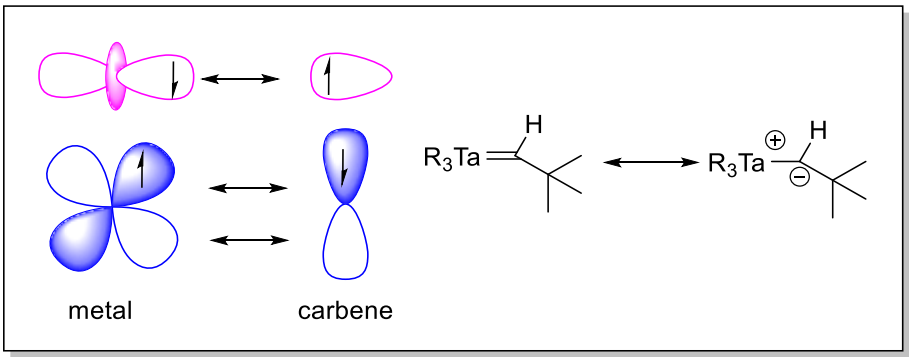
Well-stabilized heteroatom containing singlet carbenes, such aminocarbenes and alkoxycarbenes have a significant gap between their singlet and triplet ground states[13]. They form a metal–carbon bond constituted by mutual donor–acceptor interaction of two closed-shell (singlet) fragments. The dominant bonding arises from carbene–metal σ–donation and simultaneously from metal–carbene π–back donation (Scheme 4)[14].

The π–electrons are usually polarized toward the metal and the carbon–metal bond has a partial double bond character, which diminishes with the stabilization of the carbene by its groups[14,15]. For instance, in diaminocarbenes, including NHCs, the metal–carbon bond is seen as a simple bond; the π–back donation is usually weak because the carbenic carbon is already well stabilized by π–donation from its amino-groups[16,17]. Fischer carbene complexes are electrophilic at the carbon–metal bond and are prone to nucleophilic attack at the carbene center (OMe/NMe_2 exchange for instance)[14,16,18]. They are associated with low oxidation state metals[14,16,17].

1.1.2.1.2 Schrock carbenes

When the electron donation from the metal to the carbene carbon is extreme, as in the early transition metals, the carbenes become nucleophilic in their reactivity and are known as Schrock carbenes.

Poorly stabilized carbenes such as dialkylcarbenes or alkylidenes have a small gap between their singlet and triplet ground state. They form a covalent metal–carbon bond in nature created by the coupling of two triplet fragments (Scheme 5)[18b,19]. The π–electrons are nearly equally distributed between the carbon and the metal, and the metal–carbon bond is seen as a true double bond[14,19]. Schrock carbene complexes are nucleophilic at the carbon–metal bond and are susceptible to react at the carbene center with electrophiles as in a Wittig reaction involving an ylide instead of a carbene[16]. They are found exclusively among early transition metals with the highest oxidation state (d^0)[14].



Scheme 5. Metal-carbon bonding in Fisher carbene complexes

1.1.2.1.3 carbene radicals

Carbene radicals[20] are long-lived reaction intermediates found with:[21,22,23]

- Low oxidation state metal center
- Middle and late transition metal, e.g. Co(II)
- σ-donor and π-acceptor ligand
- π-acceptor substituents on the ligand such as carbonyl or sulfonyl groups. The chemical bond present in carbene radicals is described as aspects of both Fischer and Schrock carbenes (Figure 2).

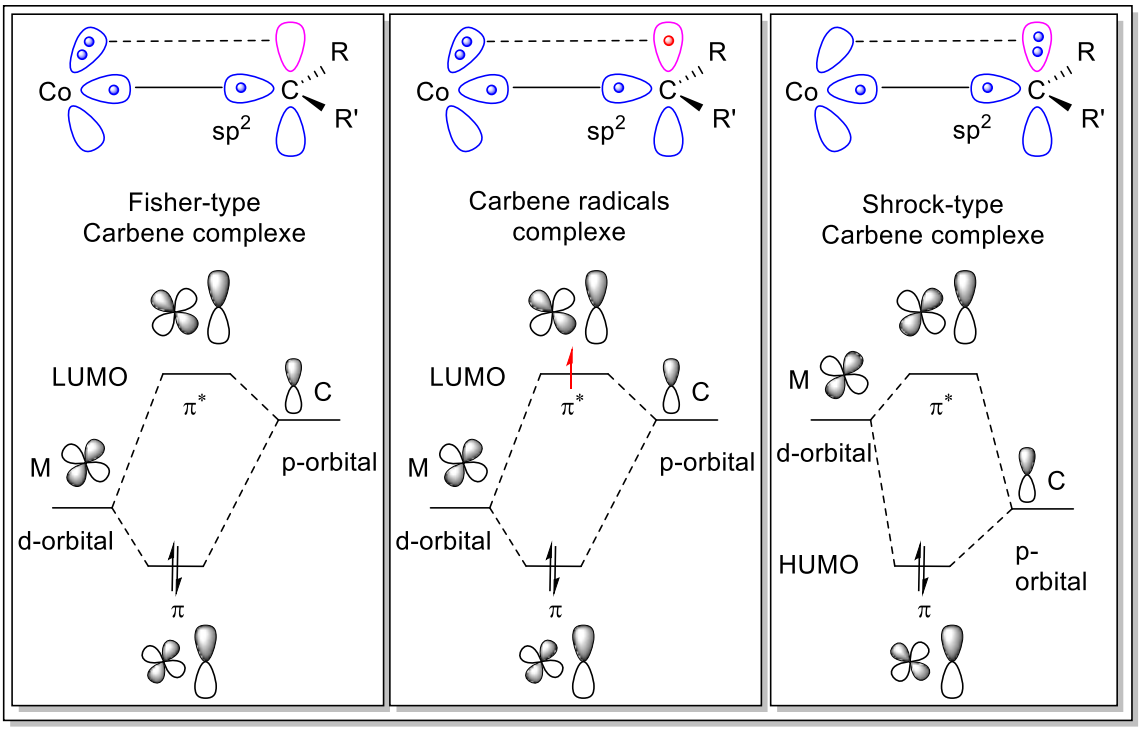


Figure 2. Bonding Scheme of Carbene Radical Complexes as compared to Schrock and Fischer-type carbene complexes.

1.1.2.2 Classification of carbenoid precursors

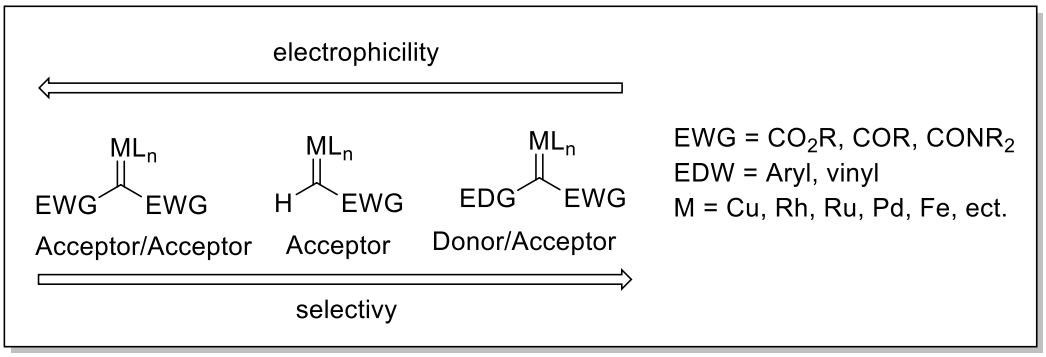


Figure 3. Classification of carbenoid precursors.

The reactivity of transitory metal carbenoids is greatly influenced by the nature of the substituents on the carbenoid. Consequently, reviews of metal carbenoids often classify the carbenoids into three distinct groups, the acceptor carbenoids, the acceptor/acceptor carbenoids and the donor/acceptor carbenoids.[24] The terms "acceptor" and "donor" refer, respectively, to the withdrawal and donation of electron density by the functional groups flanking the carbenoid (Figure 3).

Generally, an acceptor substituent makes the carbenoid species more electrophilic and more reactive, whereas a donor group makes the carbenoid more stable and thus more selective in the reaction.[25] It should be noted that the transition metal catalyzed diazo decomposition is dependent not only on the Lewis acidity of the transition metal but also on the basicity of the diazo compounds. Among the diazocarbonyl precursors, those with more withdrawing groups tend to be more stable than those with fewer withdrawing groups since the formal negative charge on diazo carbon can be further delocalized into the additional groups (Figure 4).[26]

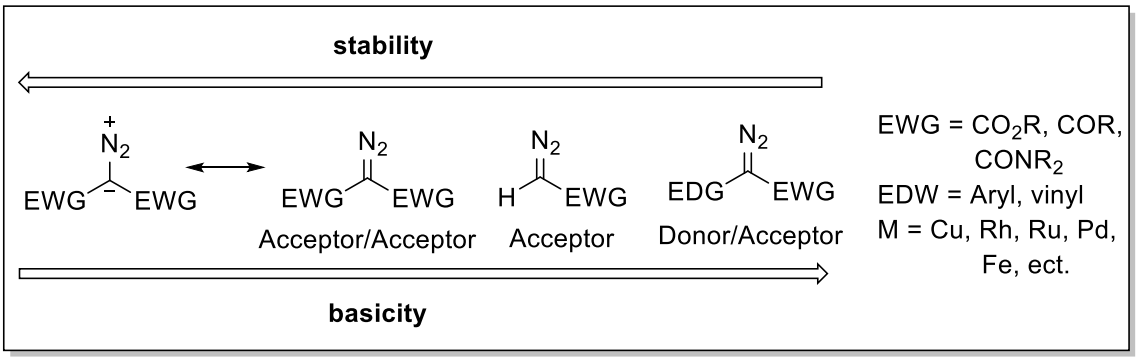


Figure 4. Stability and reactivity of carbenoid precursors in catalytic decomposition.

Thus, a larger amount of energy is required for its decomposition to generate a metal carbene. In general, higher temperatures are required for the decomposition of an acceptor/acceptor diazocarbonyl than for acceptor/donor. Catalyst design remains a central issue in transition metal catalyzed reactions of diazo compounds. The reactivity profile of these transient metal-stabilized carbenoids is highly dependent on the structure of the carbenoid and the type of the metal. Professor Padwa noted this problem succinctly: 'A survey of the literature dealing with the topic of catalytic diazo decomposition can be both enlightening and frustrating'.[25a]

1.2 Metal carbene intermediates in asymmetric cyclopropanation

Organic chemists have always been fascinated by the cyclopropane subunit.[27] Its strained structure, and interesting bonding characteristics have attracted the attention of the physical organic community.[28] The strain energy is the difference between the observed heat of formation of a strained molecule and that expected for a strain-free molecule with the same number of atoms. Due to the limited degrees of freedom, these conformationally constrained molecules have very pronounced steric, stereoelectronic, and directing effects, which make

them versatile probes for the study of regio-, diastereo-, and enantioselectivity.[29] On the other hand, the cyclopropane subunit is present in many biologically important compounds including terpenes, pheromones, fatty acid metabolites and unusual amino acids,[30] and it shows a large spectrum of biological properties, including enzyme inhibition and insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor, and antiviral activities[31] (Figure 5). Thus, the community of synthetic organic chemists is also interested in this structure, and thousands of cyclopropane compounds have been prepared.

Nearly all biological compounds are chiral and cyclopropanes are not exempt from this rule, thus synthetic methods to obtain them in enantiopure form have become a key goal and organic chemists have been challenged in this research in recent years. In 2003, the first review on enantioselective cyclopropanation reactions appeared.[32] Pellissier updated the research in this field in 2008.[33] However, new and more efficient methods for the preparation of these entities in enantiomerically pure form are still evolving. Indeed, the last four years have provided an impressive number of developments of asymmetric cyclopropanation, thus a further update is necessary, and this review will focus on the methods that have appeared in the literature from 2008 to mid-2013. Accounts on some aspects of these reactions have also appeared in the literature during recent years.[34]

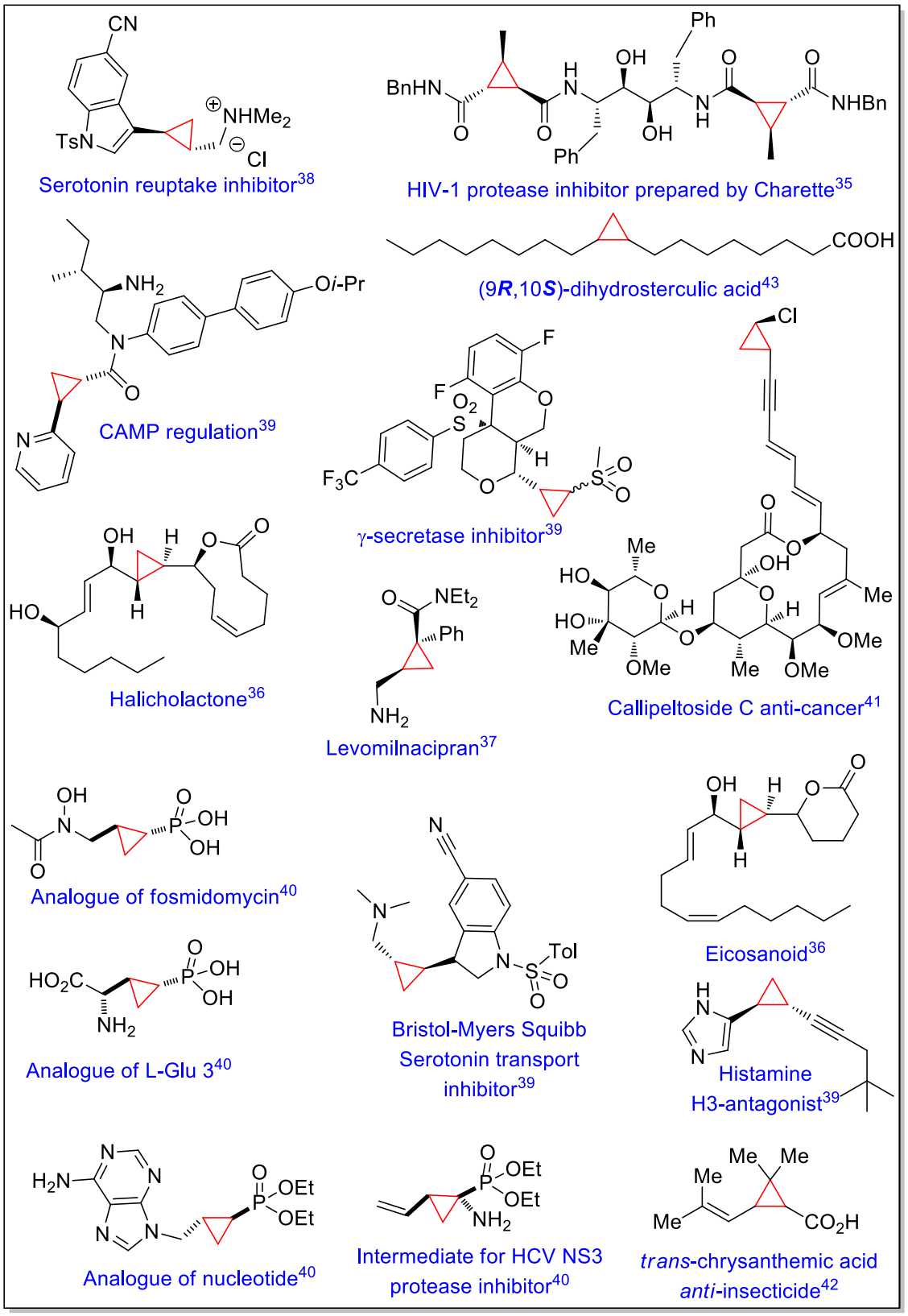
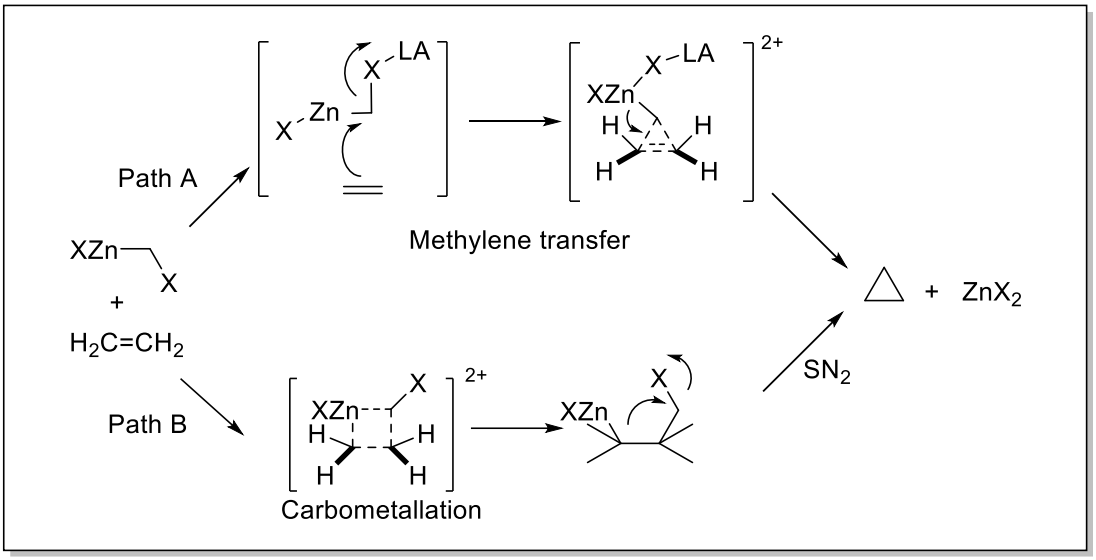

CN
TsN
NHMe2
Cl
Serotonin reuptake inhibitor38
Ph
BnHN
H
N
OH
O
O
NHBn
Ph
OH
N
H
HIV-1 protease inhibitor prepared by Charette35
COOH
(9R,10S)-dihydrosterculic acid43
NH2
O
N
O
Oi-Pr
N
CAMP regulation39
F
F
O2
S
O
H
F3C
O
S
O
O
γ-secretase inhibitor39
Cl
O
OH
Me
HO
O
H
HO
O
H
Me
Me
OMe
Me
OMe
Callipeltoside C anti-cancer41
OH
H
O
O
HO
H
Halicholactone36
O
NEt2
Ph
NH2
Levomilnacipran37
OH
N
O
P
OH
OH
O
Analogue of fosmidomycin40
N
N
N
S
Tol
O
O
Bristol-Myers Squibb
Serotonin transport
inhibitor39
OH
H
O
O
H
Eicosanoid36
HO2C
O
P
OH
OH
NH2
Analogue of L-Glu 340
H
N
N
Histamine
H3-antagonist39
H2N
N
N
N
N
O
P
OEt
OEt
Analogue of nucleotide40
O
P
OEt
OEt
NH2
Intermediate for HCV NS3
protease inhibitor40
Me
Me
Me
Me
CO2H
trans-chrysanthemic acid
anti-insecticide42

Figure 5. Selected cyclopropane-containing natural products and pharmaceutical compounds.

1.2.1 Simmons–Smith cyclopropanation



Scheme 6. Possible mechanisms for the Simmons-Smith reaction.

In the late 1950s, Simmons and Smith discovered that the reaction of alkenes with diiodomethane in the presence of activated zinc afforded cyclopropanes in high yields[44]. The reactive intermediate is an organozinc species, and the preparation of such species, including $RZnCH_2I$ or $IZnCH_2I$ compounds and samarium derivatives, was developed in the following years[45]. The popularity of the Simmons–Smith reaction arose from the broad substrate generality, the tolerance of a variety of functional groups, the stereospecificity with respect to the alkene geometry, and the *syn*–directing and rate–enhancing effect observed with proximal oxygen atoms[46].

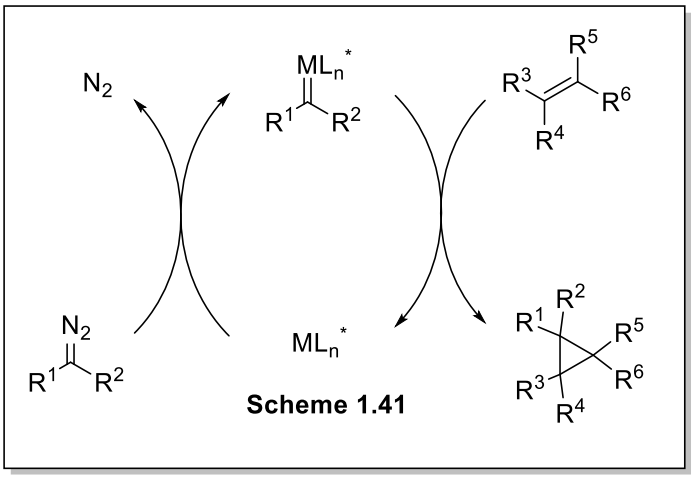
In spite of the practical importance of the asymmetric Simmons–Smith cyclopropanation, the reaction pathway is not completely clear yet[47]. Theoretically, the Simmons–Smith cyclopropanation can proceed via a concerted [2+1] methylene transfer (Scheme 6, path A), in which the pseudo–trigonal methylene group of a halomethylzinc halide adds to an alkene π–bond and forms two new carbon–carbon bonds simultaneously, accompanying a 1,2–migration of the halide anion from the carbon to the zinc atom. Alternatively, a [2+2] carbometallation mechanism, in which the halomethyl group and the zinc halide add to both termini of the alkene π-bond followed by intramolecular nucleophilic substitution of the pseudo-carbanion, can be supposed (Scheme 6, path B). Experimental studies show that, using a zinc carbenoid, the cyclopropanation very likely proceeds by the [2+1] pathway, primarily because the carbon–zinc bond is covalent and unpolarized. In 2003, Nakamura *et al.* studied the reaction pathways of cyclopropanation using the Simmons–Smith reagent by means of the B3LYP hybrid density functional method, confirming that the methylene-transfer pathway was the favored reaction course[47]. It took place through two stages, an S_N2–like displacement of the leaving

group by the olefin, followed by a cleavage of the C–Zn bond to give the cyclopropane ring. However, the alternative carbometallation and cyclization pathway was found to be preferred when the carbon–metal bond is more polarized, such as in lithium carbenoids, and this hypothesis has received experimental support[48].

Kinetic studies on the cyclopropanation of dihydropyrroles show an induction period that is consistent with a change in the structure of the carbenoid reagent during the course of the reaction. This mechanistic transition is associated with an underlying Schlenk equilibrium that favors the formation of monoalkylzinc carbenoid $IZnCH_2I$ relative to dialkylzinc carbenoid $Zn(CH_2I)_2$, which is responsible for the initiation of the cyclopropanation. Density functional theory (DFT) computational studies were also conducted to study the factors influencing reaction rates and diastereoselectivities[49].

1.2.2 Transition–Metal–Catalyzed cyclopropanation

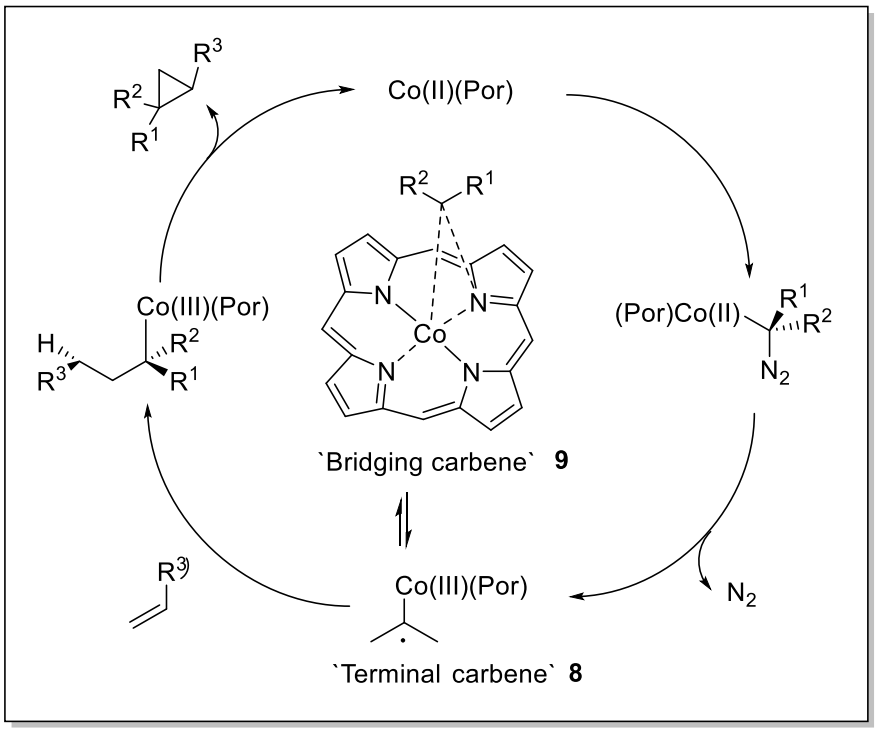
Since the pioneering work of Nozaki *et al*. in 1966[50], the transition–metal catalyzed cyclopropanation of alkenes with diazo compounds has emerged as one of the most highly effective and stereocontrolled routes to functionalized cyclopropanes. The diastereocontrol in the cyclopropanation is often governed by the particular substituents on both the alkene and the diazo compounds, and thus, the catalyst must be cleverly designed in order to enhance selective formation of *cis* versus *trans* or *syn* versus *anti*–cyclopropanes. As already seen in the previous section, the most ancient attempts to achieve enantioenriched cyclopropanes used chiral auxiliaries. Since the 1990s, many chiral ligands surrounding the metal center of the catalyst have been introduced for obtaining the enantiocontrol. The accepted catalytic cycle of the carbenoid cyclopropanation reaction involves interaction of the catalyst with the diazo precursor to afford a metallo–carbene complex followed by transfer of the carbene species to the alkene (Scheme 7).



Scheme 7. Accepted catalytic cycle for the carbenoid cyclopropanation reaction.

The type of the reaction to be carried out (inter– vs intramolecular) plays a key role in the appropriate selection of the most efficient catalyst for a given transformation. In light of this, this section is divided into inter– and intramolecular cyclopropanation reactions, and in each subsection, chiral auxiliaries are described before and then chiral ligands are listed according to the involved metal ion.

1.2.2.1 Chiral Catalysts: Cobalt

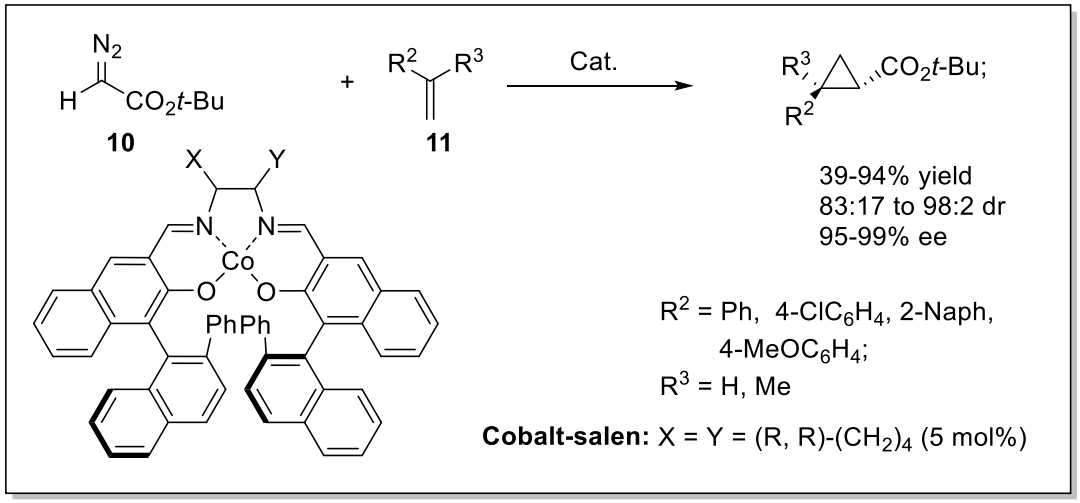


Scheme 8. Mechanism of cobalt-porphyrin catalysts

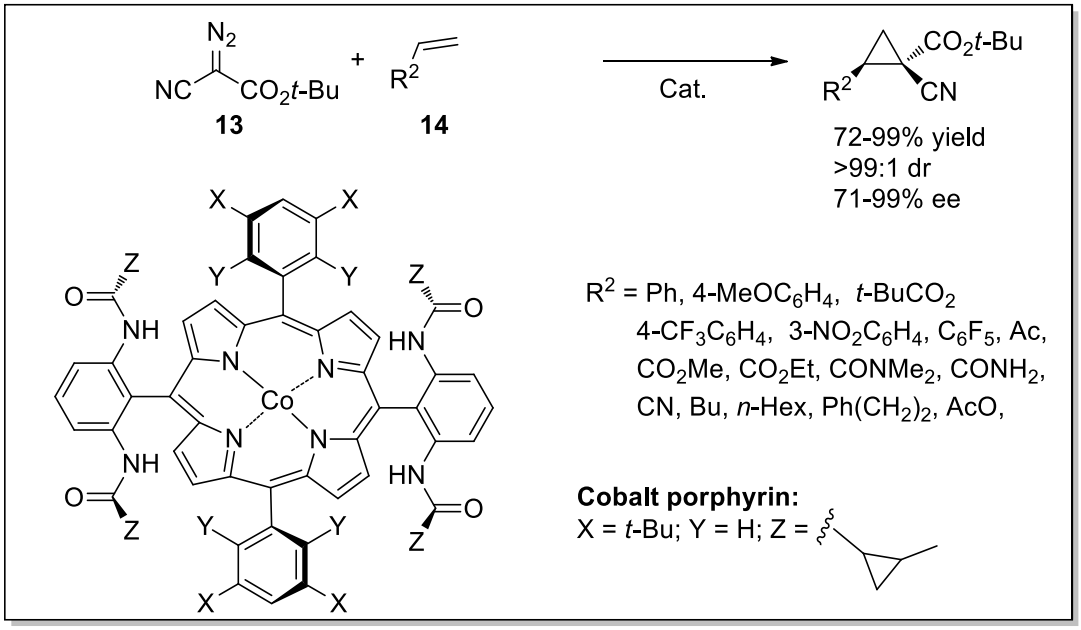
Cobalt complexes have been shown to be reactive catalysts for the α-diazoester decomposition, leading to a metal carbene that could convert alkenes to cyclopropanes. In 2009, Doyle published a highlight article collecting what was known on this topic[51]. The mechanism of this reaction was examined by EPR and electrospray ionization–mass spectrometry (ESI-MS) techniques, especially when cobalt–porphyrin catalysts were used, and evidence for a two-step mechanism was uncovered (Scheme 8)[52].

The first step is an adduct formation that could exist as two isomers: the "terminal carbene" **8** and the "bridging carbene" **9**. In the former, the "carbene" behaves as a redox noninnocent ligand having a d^6 cobalt center and the unpaired electron resides on the "carbene" carbon atom. In the latter, the "carbene" is bound to the metal and one of the pyrrolic nitrogen atoms of the porphyrin. DFT calculations suggested that the formation of the carbene is the rate–limiting step and that the cyclopropane ring formation proceeds by way of a stepwise radical process. Conclusive evidence for the existence of cobalt(III) carbene radicals has been

obtained[53]. In fact, in the absence of the alkene substrate, the "terminal carbene" arising from diazoacetate dimerizes to afford binuclear cobalt(III)–porphyrin complex, characterized by X-ray structural analysis. Calculation methods confirmed that the "terminal carbene" complex has a single bond from the metal to the carbon atom and radical character with localized spin density on the carbon. In addition, the carbon is nucleophilic in character and "tunable" through the introduction of different R substituents in order to achieve the desired reactivity. Based on these findings, rational design strategies to enhance catalytic activity can be proposed [54], highly increasing the low level of diastereo- and enantiocontrol of the early work in this area [55].



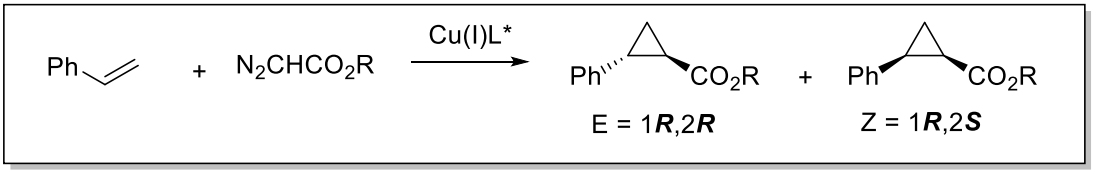
Scheme 9. Cobalt-salen in enantioselective cyclopropanation reactions.



Scheme 10. Cobalt porphyrins in enantioselective cyclopropanation reactions.

Colbalt-salens are the potential efficient catalysts for asymmetric cyclopropantions of tert-butyl diazoacetate **10** with olefins **11** in excellent yield and enantioselectivity (Scheme 9). Other hands, their analogs, cobalt-porphyrins have been also found to be efficient catalysts for cyclopropanation of α–cyanodiazoacetates with alkenes as atypical dominant Z–isomers (Scheme 10)[56]. Conversely, rhodium-based chiral catalysts provided predominantly the E–isomers (see Section 2.2.3)[57].

1.2.2.2 Chiral Catalysts: Copper



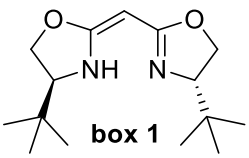
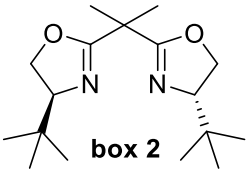
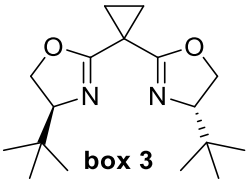
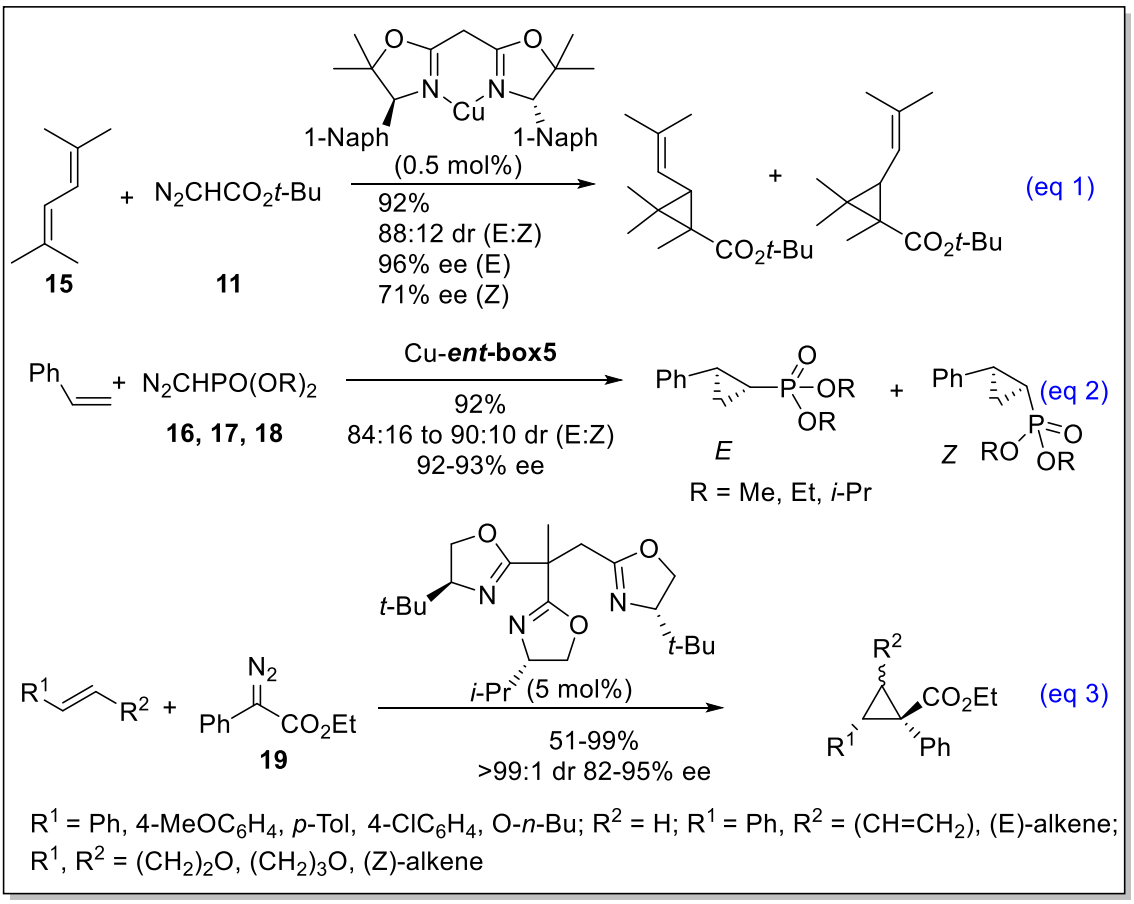
Ligand	R	E/Z	ee (%)	References
 box 1	D-Menthyl	86:14	98 (*E*) 96 (*Z*)	[165, 166]
 box 2	BHT	94:6	99 (*E*)	[167]
	Et	77:23	99 (*E*)	[168]
	Et	72:28	98 (*E*)	[169]
 box 3	Et	84:16	100 (*E*) 100 (*Z*)	[177]

Table 1. Copper(I)-box catalysts employed in enantioselective cyclopropanation reactions.

Chiral copper-based catalysts are the most effective catalysts for the preparation of the *trans*-isomer of cyclopropanes with the widest reaction scope. Among them, nonracemic C_2-symmetric bidentate bisoxazoline (box) ligands have been used in cyclopropanation reactions with copper for more than 30 years[58]. Many investigations have shown that the ligand structure has a strong influence on the stereoselectivity of the cyclopropanation. Even very small structural changes often have drastic and sometimes unpredictable effects on the enantioselectivity, and the phenomenon comprehension is complicated by very low enthalpic barrier for the transition states leading to the ***R***- and ***S***-products. However, since 2001, using DFT calculations, Salvatella and coworkers rationalized the stereochemical prediction of the cyclopropanation. The calculated relative energies are in good agreement

with the experimental enantiomeric excesses as well as with the *Z/E* ratio[59]. In 2004, Mend *et al.* studied again this reaction by means of DFT, showing that it was exothermic and that the turnover-limiting step was the formation of metal catalyst–cyclopropyl carboxylate complexes[60]. Then, Maseras and coworkers found a barrier, which arises from the entropic term, in the Gibbs free-energy surface compatible with the experimentally observed enantioselectivity[61]. The data set included 30 chiral ligands belonging to four different oxazoline-based ligand families.

Some examples of chiral ligands for the copper-catalyzed cyclopropanation in excellent yield as well as stereoselectivity are listed in Table 1.



Scheme 11. Copper-bisoxazoline-catalyzed cyclopropanation of some diazoalkanes

Some of these copper(I)-box catalyzed reaction were then employed in multistep synthesis of natural products[62]. For instance, cyclopropanation of furans was applied to the total syntheses of some key intermediates of natural products and drugs[63].

Alkenes that were more complex were also involved in copper–bisoxazolinecatalyzed cyclopropanation with diazoalkanes. The cyclopropanation of 2,5-dimethyl-2,4-hexadiene **15** with *t*-butyl diazoacetate **10** (Scheme 11, eq 1)[64]. Diazoalkanes other than alkyl diazoacetates have also been employed in copper–bisoxazoline-catalyzed cyclopropanations. For instance,

α-diazophosphonate diazomethanes **16-18** was used to obtain cyclopropylphosphonate derivatives under ***Cu-ent*-box2** catalysis (Scheme 11, eq 2). However, Nishiyama's ruthenium catalyst (see Section 1.2.2.4) gave better results and can be used with a wider range of substrates (88 : 12 to >98 : 2 *E/Z* ratio, 90–96% ee also with substituted styrenes, α-methylstyrene, and 1-phenylbuta-1,3-diene)[65]. Another example is the cyclopropanation of alkenes with ethyl phenyldiazoacetate **19** (Scheme 11, eq 3)[66].

1.2.2.3 Chiral Catalysts: Rhodium

Although many transition metal chiral complexes have been developed, dirhodium(II) complexes are among the most attractive catalysts, because of their activity and efficiency. Dirhodium(II) catalysts with very high turnover numbers have been reported, and consequently, the cost and toxicity of rhodium can be greatly overshadowed by the ability to use tiny amounts of the catalyst to generate large quantities of value added products. The use of dirhodium(II) catalysts in inter- and intramolecular asymmetric cyclopropanation has been recently reviewed [67], and readers are invited to read this review for other information.

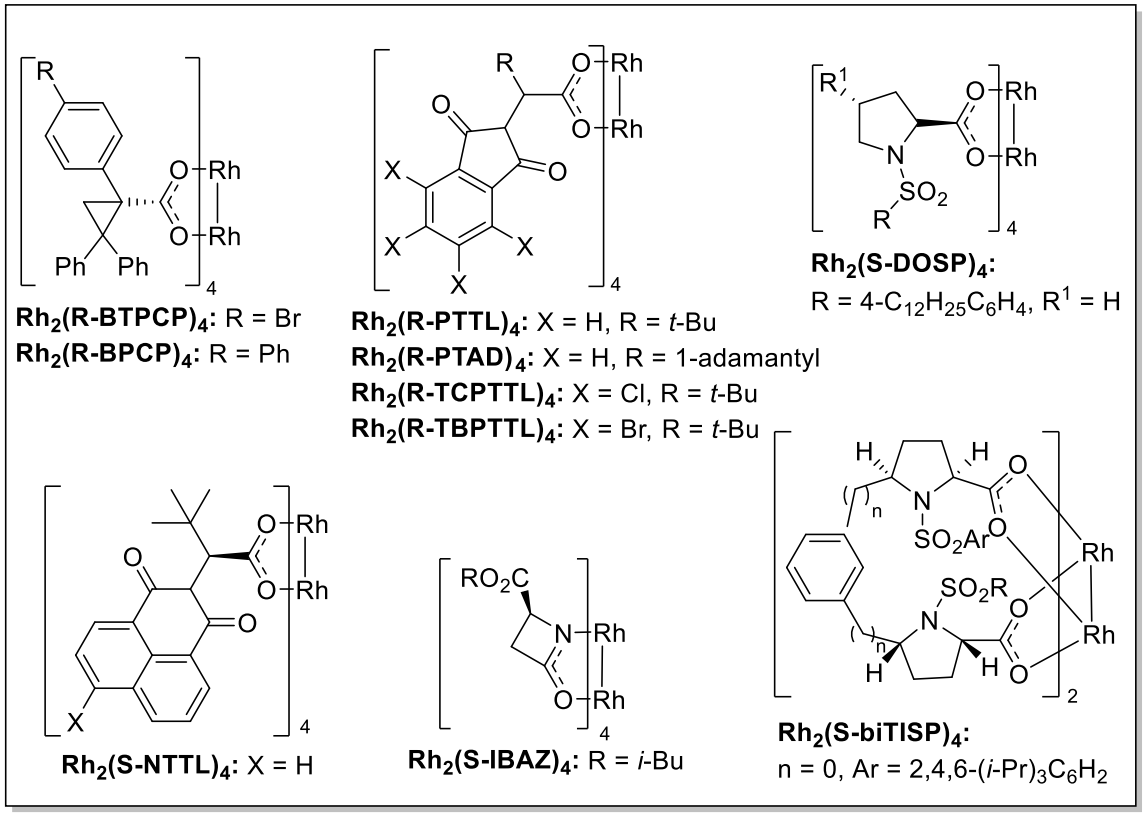
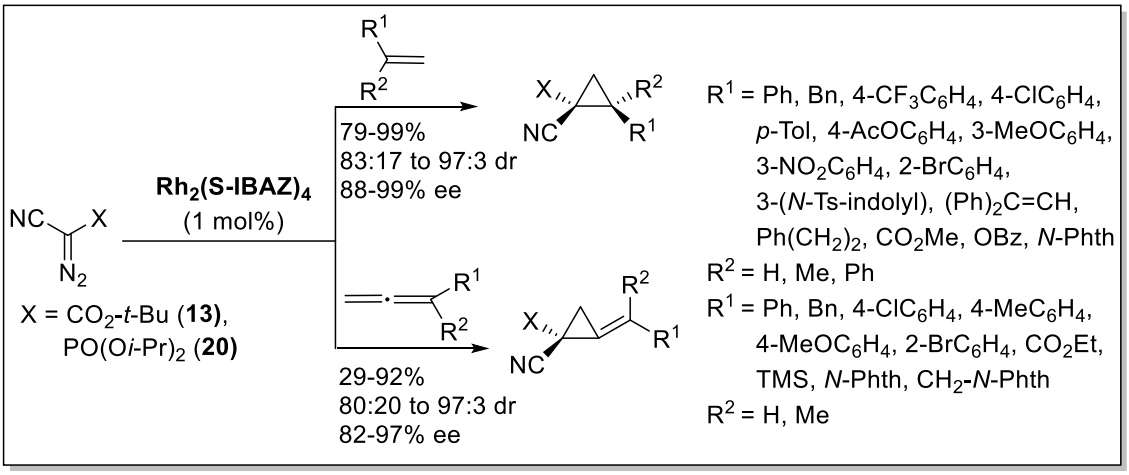


Figure 6. Chiral dirhodium catalysts for asymmetric cyclopropanation.

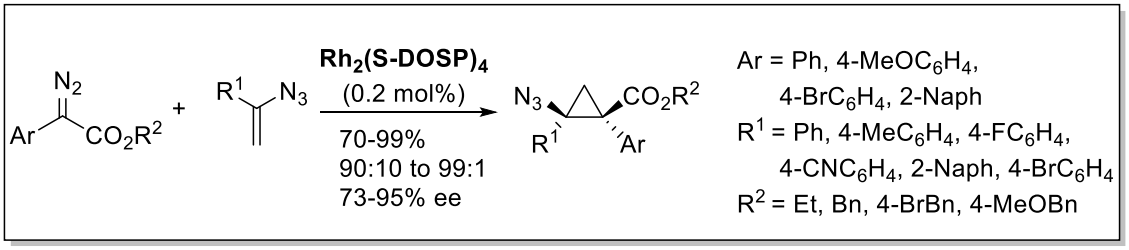
Rhodium-based chiral complexes were synthesized and tested in both inter- and intramolecular cyclopropanations. In particular, the development of dirhodium(II) carboxylate and carboxamidate catalysts (Figure 6) has resulted in many highly chemo-, regio-, and

stereoselective reactions of α-diazocarbonyl compounds[68]. As a general guideline, the level of diasterocontrol with rhodium carbenes does not match that observed with copper, ruthenium, or cobalt carbenes, even when sterically hindered α-diazoesters are used. This drawback has minimized the use of rhodium catalysts in intermolecular processes involving simple α-diazoesters in the most ancient period of asymmetric synthesis.

Charette's research group found Rh_2(*S*-IBAZ)$_4$ as an efficient catalyst for cyclopropanation of α-cyanodiazophosphonate **20** and α-cyanodiazoacetate **13** (Scheme 12)[69]. The particular electrophilicity of cyanocarbene intermediates permitted the use of allenes as substrates, affording the first catalytic asymmetric alkylidene cyclopropanation reaction using diazo compounds. In fact, α-cyanocarbenes are forced to stay in-plane, conversely from other electron-withdrawing groups, which adopt an out-of-plane conformation (see below). The in-plane conformation is highly energetic, thus leading to a more electron-deficient reactive carbene, allowing less nucleophilic π-systems such as allenes to react.



Scheme 12. Asymmetric cyclopropanation of α-cyanodiazophosphonate and α-cyanodiazoacetate.

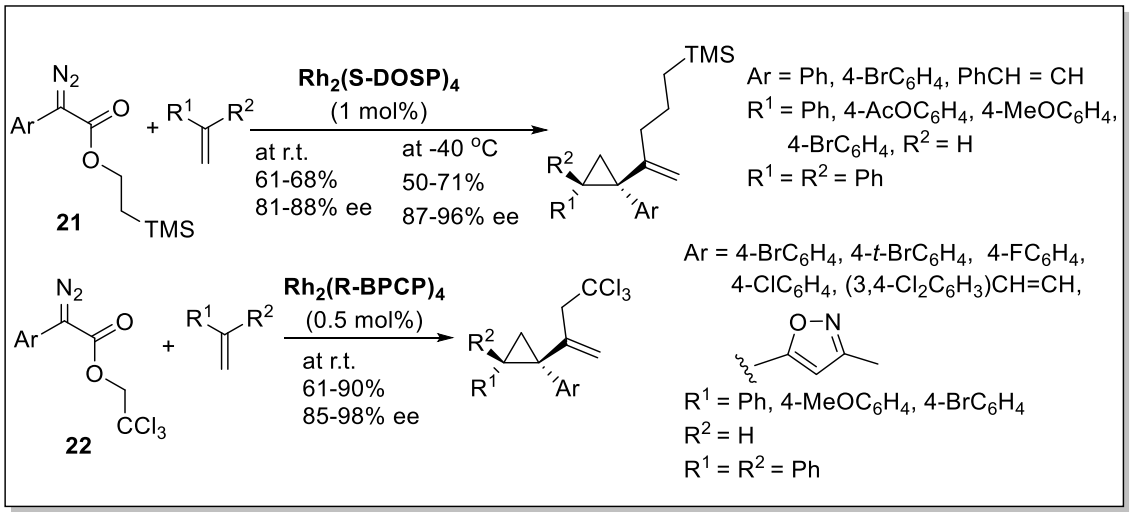


Scheme 13. Enantioselective preparation of *cis*-β-azidocyclopropane esters.

β-Aminocyclopropane carboxylic acids are widely used in peptide syntheses, but they cannot be efficiently prepared from asymmetric cyclopropanation of *N*-protected enamines[70]. However, azidoalkenes could be regarded as alternative precursors of *cis*-β-aminocyclopropane carboxylic acids, and Rh_2(*S*DOSP)$_4$ was found to be an efficient catalyst for the preparation of

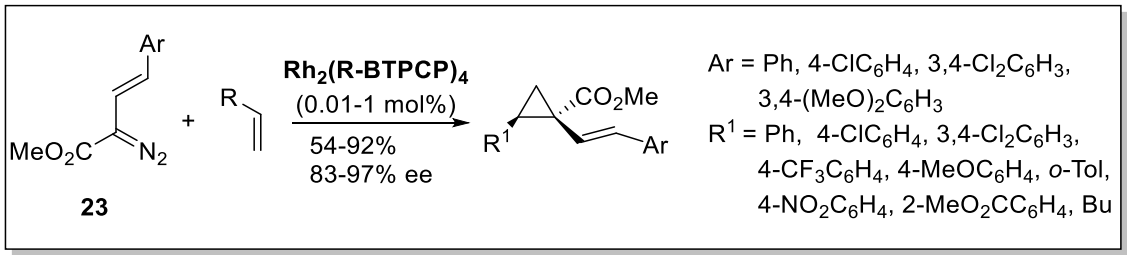
(1*R*,2*S*)-isomers (Scheme 13)[71]. The reaction can be carried out on gram scale with the same yield but with slightly lower enantioselectivity and longer reaction time.

Finally, intermolecular asymmetric cyclopropanations of aryldiazoacetates with labile protecting groups on the ester and styrene derivatives can be catalyzed by chiral dirhodium(II) complexes Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-BPCP)$_4$. In particular, the trimethylsilylethyl aryldiazoacetates **21** gave the best results with Rh_2(*S*-DOSP)$_4$, while trichloroethyl aryldiazoacetates **22** with Rh_2(*R*-BPCP)$_4$ (Scheme 14)[72].



Scheme 14. Enantioselective synthesis of cyclopropanecarboxylates with labile protecting groups on the ester.

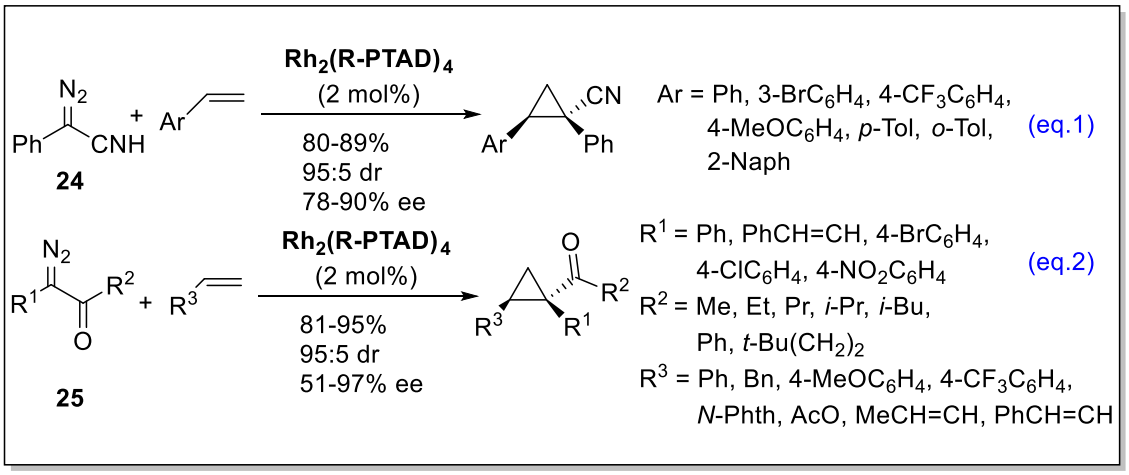
Similar dirhodium complex Rh_2(*R*-BTPCP)$_4$ was found to be an effective chiral catalyst for the enantioselective cyclopropanation of styryldiazoacetates (Scheme 15)[73]. DFT computational studies at the B3LYP and UFF levels suggested that when the carbenoid binds to the catalyst, two of the 4-bromophenyl groups rotate outward to make room for the carbenoid. Then, the ester group aligns perpendicular to the carbene plane and blocks attack on its side. Thus, the substrate approaches over the donor group, but it finds the *Re*-face blocked by the aryl ring of the ligand and only the *Si*-face open for the attack, in agreement with the observed absolute configuration of the product.



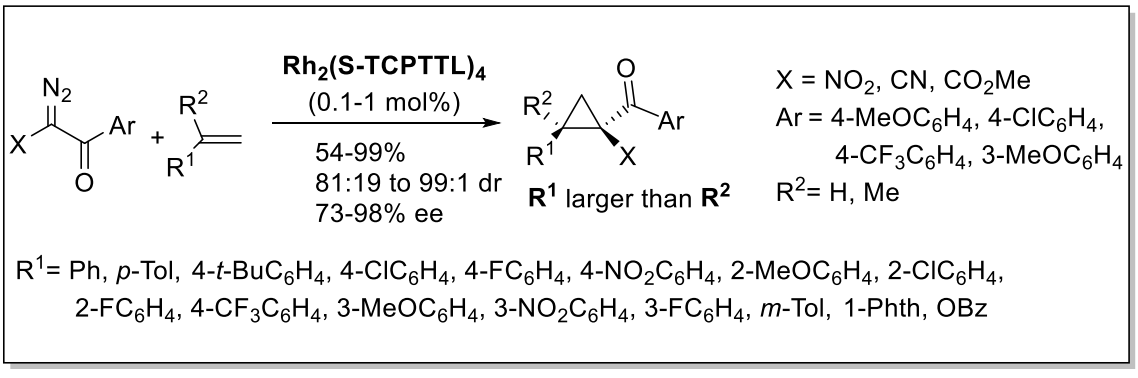
Scheme 15. Cyclopropanation of styryldiazoacetates.

The enantiomer Rh_2(*S*-PTAD)$_4$ catalyzed the stereocontrolled synthesis of nitrile-substituted

cyclopropanes from 2-diazo-2-phenylacetonitrile **24** and aryl alkenes (Scheme 16, eq 1)[74]. It is worth noting that the small cyano acceptor group would be unable to influence the selectivity. In fact, as reported earlier, studies on the mechanism asserted that the bulkiness of the electron-withdrawing group drives the selectivity. This is true for alkylethenes (formed as 61 : 39 to 46 : 54 mixtures of diastereomers), but high diastereoselectivity was observed with styrenes. Therefore, the authors claimed an attractive π-stacking interaction between the aryl rings of styrene and phthalimide during the cyclopropanation that is absent in alkyl-substituted alkenes. Catalyst Rh_2(*S*-PTAD)$_4$ also catalyzed the reaction of aryl-α-diazo ketones **25** with activated alkenes (Scheme 16, eq 2)[75]. The enantioselectivity dropped when either the aryl group in R1 was substituted with a styryl group or bulky groups were close to the carbonyl and increased when the alkyl chain of the ketone group was lengthened. Vinyl acetate, dihydrofuran, and dienes were less enantioselective, while vinyl ether and inactivated alkenes were not effective substrates.



Scheme 16. Asymmetric synthesis of some cyclopropanes catalyzed by Rh_2(S-PTAD)$_4$.

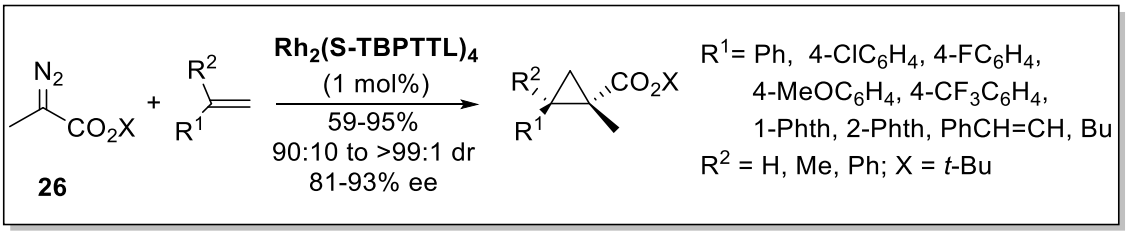


Scheme 17. Enantioselectivity synthesis of *cis*-cyclopropane α-amino acid precursors.

Similar results were obtained in the cyclopropanation of alkenes with diazoacetophenones under Rh_2(*S*-TCPTTL)$_4$ catalysis (Scheme 17)[76]. The reaction could be carried out on a multigram scale. Different substituted diazoacetophenones showed similar efficiency, except for

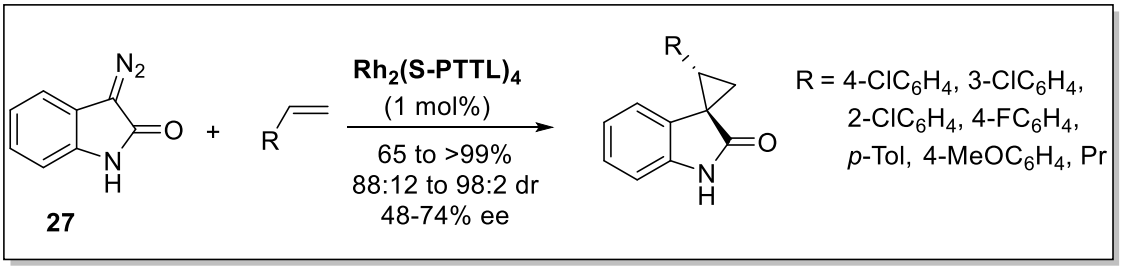
the 4-dimethylamino derivative that achieved only 38% yield. Unfortunately, alkyl-substituted alkenes did not provide the corresponding cyclopropanes in useful yields, and dienes afforded only Cope-rearranged achiral products.

Hashimoto described that the reaction of 1-aryl-substituted and related conjugated alkenes with *tert*-butyl α-diazopropionate **26** by catalysis with Rh_2(*S*-TBPTTL)$_4$ led to the corresponding (1*R*,2*S*)-cyclopropanes containing a quaternary stereogenic center (Scheme 18)[77].



Scheme 18. Enantioselective cyclopropanation with α-diazopropionate.

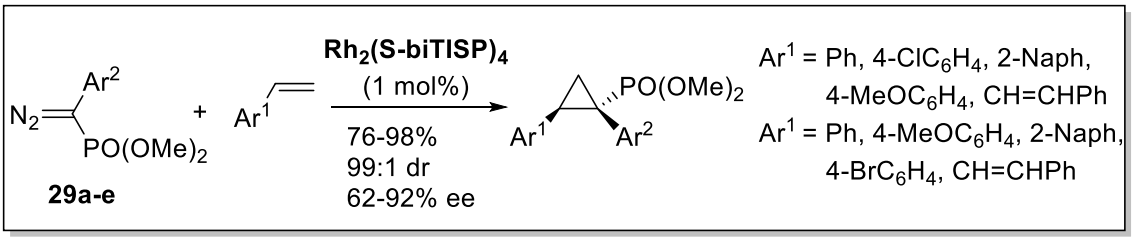
Awata and Arai achieved the asymmetric cyclopropanation of diazooxindoles **27** with Rh_2(*S*-PTTL)$_4$ as the catalyst. Spirocyclopropyloxindoles, which constitute biologically important compounds, were obtained in good yield and diastereoselectivity (Scheme 19)[78]. Then the mechanism of this reaction was detailed by DFT calculations, which demonstrated that the origin of the *trans*-diastereoselectivity lies in the π–π interactions between the *syn*-indole ring in carbenoid ligand and the phenyl group in styrene. The enantioselectivity could be ascribed both to steric interaction between the phenyl ring in styrene and the phthalimide ligand and to stabilization of π–π and CH–π interactions in the transition states[79].



Scheme 19. Enantioselective synthesis of spirocyopropyloxindoles.

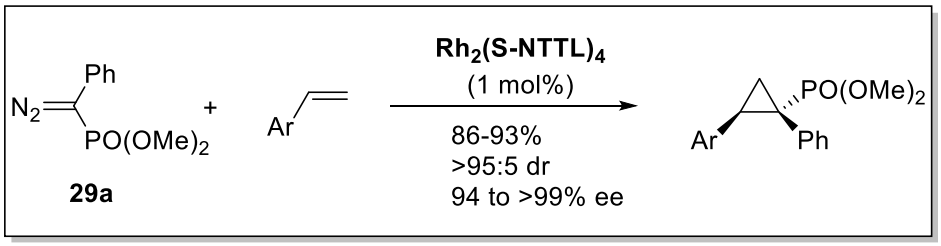
Rh_2(*S*-biTISP)$_2$ was able to catalyze the cyclopropanation of styrene with methyl phenyldiazoacetate with high turnover number (92 000) and turnover frequency (4000 h−1). This is one of the rare examples of a large-scale reaction with rhodium catalysts; in fact, with a substrate/catalyst ratio of 100 000, 92% yield and 85% ee were obtained on a crude of 46 g. In addition, this catalyst, immobilized on highly cross-linked polystyrene resins with a pyridine attachment, provided up to 88% ee for this reaction[80]. Finally, the same catalyst was applied to the stereoselective synthesis of cyclopropylphosphonates containing quaternary stereocenters by

the reaction of dimethyl aryldiazomethylphosphonates **29** (Scheme 20)[81].



Scheme 20. Asymmetric synthesis of cyclopropylphosphonates catalyzed by Rh_2(*S*-biTISP)$_2$.

The Rh_2(NTTL)$_4$ catalyst was the best-performing catalyst in the synthesis of cyclopropylphosphonate derivatives (Schemes 21)[82]. The selectivity is independent of the size of the phosphonate group and can be predicted by Hashimoto's model. The use of Meldrum's acid, methyl diazostyrylacetate **29e** and methyl diazophenylacetate **29a** instead of the phosphonate ester group dramatically deteriorated the asymmetric induction.



Scheme 21. Asymmetric cyclopropanation with Rh_2(NTTL)$_4$.

1.2.2.4 Chiral Catalysts: Ruthenium

The success of the rhodium complexes in catalyzing carbene-transfer reactions is tempered by the high price of this metal. Therefore, ruthenium, a direct neighbor of rhodium in the periodic table, has been more recently introduced in the field of catalytic cyclopropanation, because it costs roughly one-tenth the price of rhodium. Another reason for focusing attention on ruthenium catalysts is the greater diversity of complexes to be evaluated, due to the richer coordination chemistry, as compared to rhodium[83].

Thus, many highly active and selective homogeneous catalysts have been introduced for the asymmetric cyclopropanation of alkenes (Figure 7)[84].

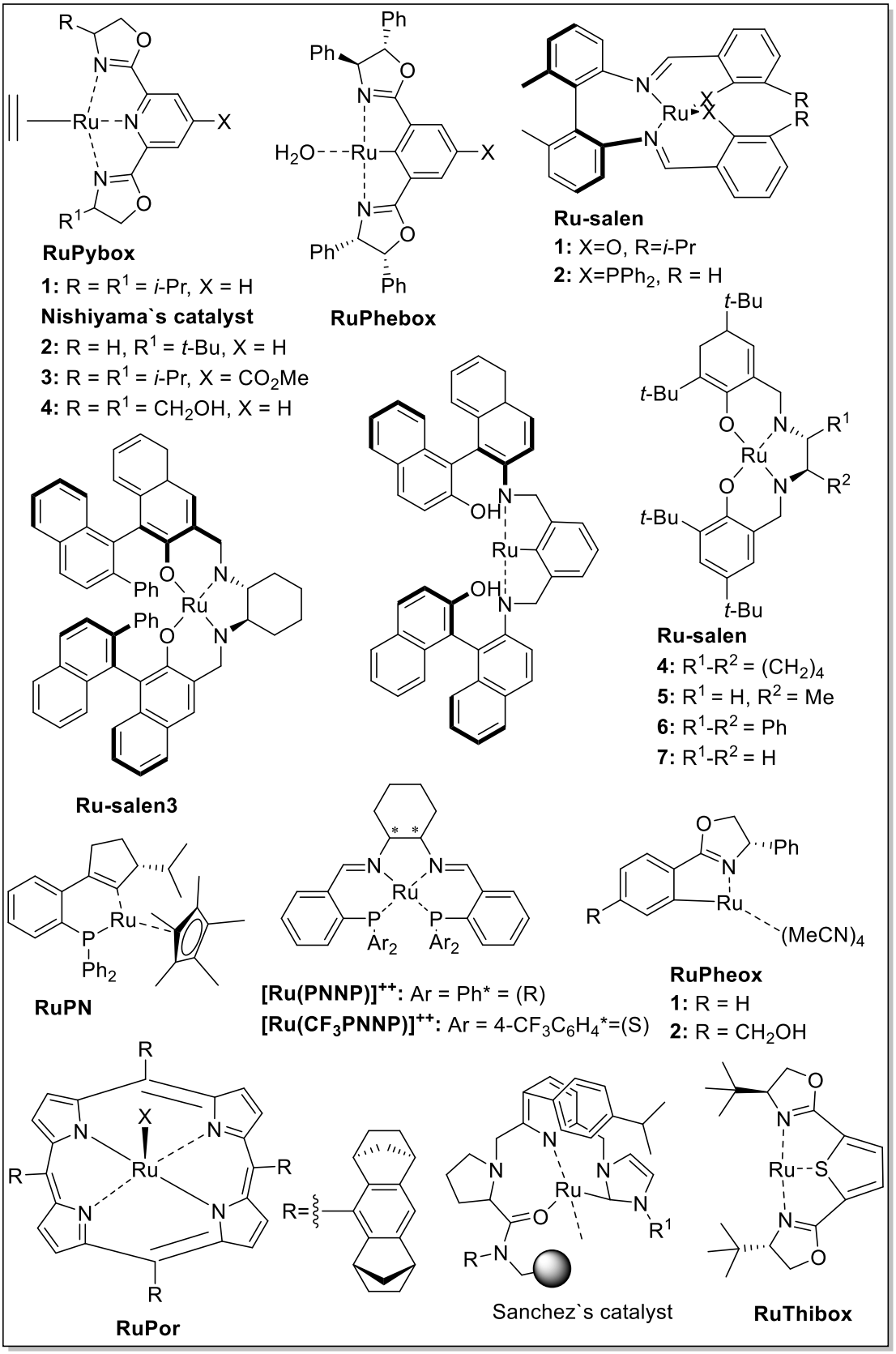


Figure 7. Chiral ruthenium catalysts for asymmetric cyclopropanations.

Indeed, in a short time, ruthenium has emerged as the third important catalyst metal for the carbenoid chemistry of diazo compounds, besides copper and rhodium. However, a significant drawback of Ru catalysts is the rather low electrophilic character of the presumed ruthenium–carbene intermediates, which often restricts the application to terminal activated alkenes and double bonds with a higher degree of alkyl substitution. Another limitation of some ruthenium complexes is the ability to catalyze other alkene reactions as well as cyclopropanation leading to many by-products. However, if ruthenium catalysts work successfully, they often rival rhodium catalysts in terms of effectiveness and relative, as well as absolute, stereochemistry.

Some methods of heterogenization of ruthenium catalysts, for instance, supporting them on polymer or porous silica supports, have been investigated. Their activity, selectivity, and recyclability have all been compared to those of the analogous homogeneous catalysts.

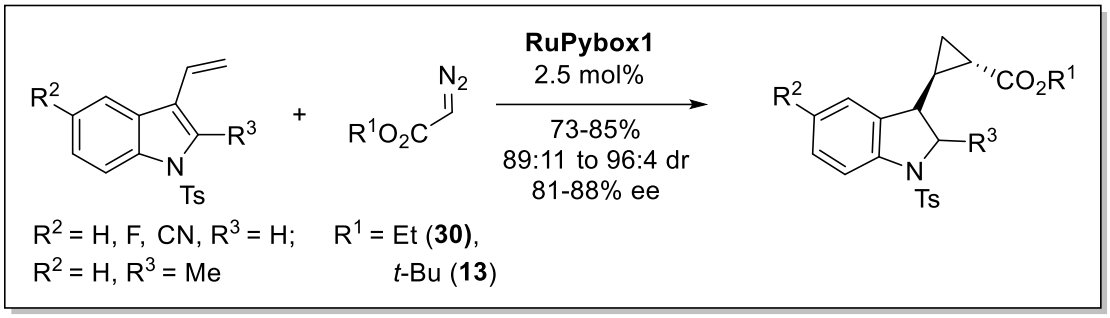
Nishiyama's catalyst[85] has already been proven as better catalyst compared to Cu-ent-box5 catalyst in the synthesis of cyclopropylphosphonate derivatives[65]. In the reactions with pybox ligands, the geometry of the recovered products is consistent with a model, in which the phenyl group of styrene approaches the carbenoid species away from the ester and isopropyl groups. Two interesting observations have been made.

i) A remote stereoelectronic effect exerted by the substituent in the 4-position of the pyridine ring has been reported[86]. Electron-donating substituents decrease (84% ee for the cyclopropanation of styrene if X = NMe_2), and electronwithdrawing groups increase the enantiomeric excess significantly (X = CO_2Me, 97% ee). The E/Z ratios were instead not affected by the substituents.

ii) Non-C_2-symmetric ligands are also quite effective in this reaction. For example, Ru-Pybox4 afforded the cyclopropane not only with high enantioselectivity but also with an improved diastereoselectivity, very likely because the removal of one of the oxazoline substituents created more space for the ester group in the chiral pocket[87].

Later, Deshpande et al. used Nishiyama's catalyst to catalyze the cyclopropanation of styrene with EDA, providing the corresponding trans-cyclopropane in 98% yield, with 96 : 4 dr, and 86% ee (trans)[88]. Moreover, 1-tosyl-3-vinylindoles were excellently cyclopropanated by Nishiyama's catalyst with ethyl and t-butyl diazoacetate (**30**, **13**) (Scheme 22)[89]. It should be noted that the *E/Z* diastereoselectivity was notably improved when using *t*-butyl diazoacetate. Moreover, the utility of this method was demonstrated by the conversion of one of the resulting chiral cycloadducts into BMS-505130, a selective serotonin reuptake inhibitor.

Nishiyama also developed the water-soluble hydroxymethyl derivative (Ru-**Pybox4**). The reaction of styrene with different diazoacetates in aqueous media provided the corresponding cyclopropanes in 24–75% yields, with 92 : 8 to 97 : 3 *E/Z* ratio, 57–94% ee (1*S*,2*S*), and 26–76% ee (1*R*,2*S*)[90].



Scheme 22. Asymmetric cyclopropanation of 1-tosyl-3-vinylindoles.

Simmoneaux *et al.* examined chiral 2,6-bis(thiazolinyl)pyridines as ligands for the Ru-catalyzed cyclopropanation of olefins. The comparison of the enantiocontrol for the cyclopropanation of styrene with chiral ruthenium bisoxazoline and bisthiazoline allowed the evaluation of the different situation with regard to the diastereoselectivity and enantioselectivity when an oxygen atom was substituted by sulfur. They found many similarities with, in some cases, good enantiomeric excesses (up to 84% ee for *trans*-cyclopropylphosphonate were observed)[91].

Nishiyama's catalyst was immobilized in different manners:

i) By grafting on a Merrifield-type resin and on supports prepared by the polymerization of 4-vinyl-substituted ligands, providing yields of over 60% with up to 91% ee in four successive reactions. The enantioselectivity and the recyclability were strongly dependent upon the catalyst preparation method and the total exclusion of oxygen and moisture in the filtration process[92].

ii) By preparing Ru-Pybox monolithic mini flow reactors on styrene–divinylbenzene polymeric backbones having different compositions and pybox chiral moieties. Under conventional conditions and in supercritical carbon dioxide, the continuous flow cyclopropanation reaction between styrene and EDA led to good enantioselectivity (up to 83% ee) demonstrating these highly efficient and robust heterogeneous chiral catalyst and allowing the development of environmentally friendly reaction conditions[93].

iii) By microencapsulation into linear polystyrene (60–68% yields, 75–85% ee in up to four successive reactions were achieved in the benchmark cyclopropanation reaction between styrene and EDA)[94].

iv) On modified starch, providing the cyclopropanation of styrene with EDA in 67% yield, 89 : 11 dr and 77% ee for the trans-isomer[95].

Zingaro and coworkers tested a modified Nishiyama's catalyst (Ru-**Thibox**) and obtained 70–82% yields with 79 : 21 to 82 : 18 *E/Z* ratio and 87% to >99% ee (1*R*,2*R*), 82% to >99%ee (1*S*,2*R*) for the cyclopropanation of styrenes and 1,1-diphenylethene with EDA[96].

Bis(oxazolinyl)phenyl ruthenium complex (Ru-**Phebox**) was efficient for the

cyclopropanation reactions of various styrene derivatives with *tert*-butyl diazoacetate (85–92% yields with 82 : 18 to 96 : 4 *E/Z* ratio and 98–99% ee (1*R*,2*R*))[97]. Only α-methylstyrene afforded the *cis*-isomer (80% overall yield, 67 : 33 dr, 98% ee (*cis*), and 93% ee (*trans*)). The cyclopropanation of aliphatic alkenes proceeded in lower yield but with good diastereo- and enantioselectivities, whereas cyclopropanation of 1,2-disubstituted alkenes, such as 1-phenylpropene or indene, did not occur. The ruthenium carbene intermediate should be obtained by replacement of the equatorial H_2O ligand with the diazoacetate group, and then the alkene approached the *Re*-face to minimize the steric repulsion between the *tert*-butyl group of the diazo compounds and the R group of the alkene.

Ru-**salen1–3** systems displayed *cis*-selectivity in the cyclopropanation reaction (83 : 17 to 93 : 7 *Z/E* ratios, >97% ee)[98]. In particular, catalyst Ru-**salen2** was effective for the cyclopropanation of 2,5-dimethyl-2,4-hexadiene, producing the *cis*-isomer in 75% ee (94 : 6 dr) but only in 18% recovered yield[98a–c]. Ru-**salen4–6**, with the two free coordinating sites occupied by pyridine ligands, gave excellent enantiomeric excesses in the cyclopropanation of mono or 1,1-disubstituted alkenes (30–97% yields, 66 : 34 to >99 : 1 *E/Z* ratios, 69–99% ee (*trans*))[99]. The heterogeneous catalysts generated the desired cyclopropanes, by reaction with EDA and styrenes, in good *trans*-selectivity but with moderate enantioselectivities. Aliphatic alkenes also reacted but in very low yields. The highest selectivities and yield were obtained with longer linker between the Ru-**salen** active site and the polymer support, probably for a lessened steric hindrance around the catalytic site. The silica support resulted in important background reactions on the silica surface, thus lowering enantioselectivity. The addition of pyridine during the washing steps between catalytic cycles stabilized the complex, preventing both leaching of this ligand and losses in activity and selectivities upon recycling.

Recently, Ru-**pheox** was found to be an efficient catalyst for the cyclopropanation reaction of monosubstituted alkenes with succinimidyldiazoacetate[100]. The desired cyclopropanes were obtained in 94–98% yield with >99 : 1 *E/Z* ratio. The enantiomeric excess was calculated after reduction without epimerization of succinimidyl cyclopropanecarboxylates to cyclopropylmethanols and found in the range of 91–99% (1*R*,2*R*). The preferred face for the attack of the ruthenium carbene by the terminal alkene was determined by the steric crowding around the seven-membered ring resulting after the coordination between the succinimidyl carbonyl group and the ruthenium metal center. Then, the same research group applied the Ru-**Pheox1** catalyzed cyclopropanation:

1) To vinylcarbamates with diazoesters (77–99% yields, up to 96 : 4, with N,Ndisubstituted vinylcarbamates and up to 99% ee). However, the reaction of carbobenzyloxyvinylamine and tert-butyldiazoacetate or succinimidyl diazoacetate led to about equimolecular amounts of cis- and trans-isomers, the latter with low enantiomeric

excess[101].

2) To diazomethylphosphonate with alkenes (72–93% yields, 62 : 38 to 99 : 1 E/Z ratio, 94–99% ee (R,R)) and α,β-unsaturated carbonyl compounds (33–87% yields, 98 : 2 to 99 : 1 E/Z ratio, 78–98% ee (R,R)). These compounds were used as key intermediates in the synthesis of the analogs of nucleotide and l-Glu (Scheme 1.89)[102].

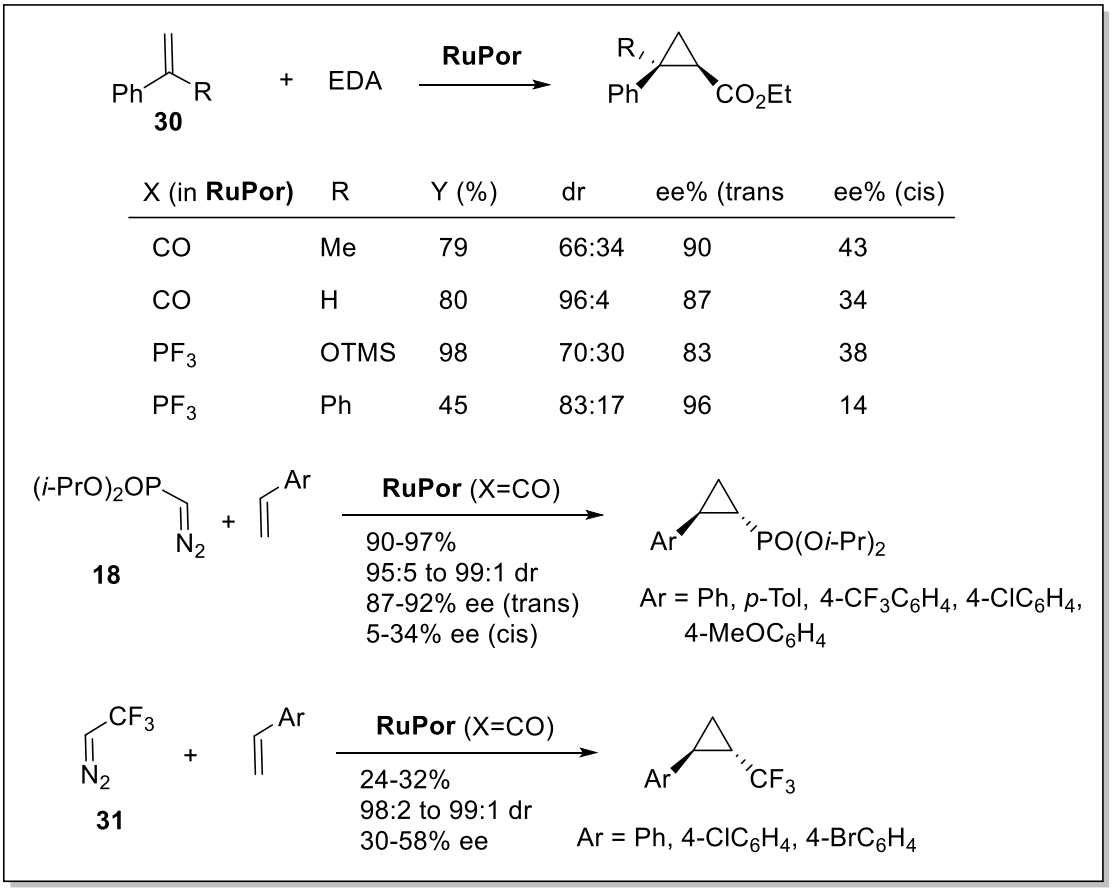
3) To allenes with succinimidyl diazoacetate (60–92% yields, 90 : 10 to 99 : 1 E/Z ratio, 84–99% ee (R,R)). It should be noted that only the less sterically hindered double bond was attacked and that the reduction of the exocyclic double bond was performed with high stereoselectivity, affording enantioenriched cis-cyclopropanes[103].

4) To diazosulfones with alkenes (43-96% yields, 99:1 E/Z ratio, 76-99% ee (R,R) and vinyl ethers together with vinyl amines (71-99% yield, 99:10 to 99:1 E/Z ratio, 95-98% ee (R,R))[104].

5) To trifluorodiazoethane with alkenes (48-99% yields, 93:7 to 99:1 E/Z ratio, 92-97% ee (R,R) and vinyl ethers together with vinyl amines (74-96% yield, 80:20 to 99:1 E/Z ratio, 91-97% ee (R,R))[105].

On the other hand, the cyclopropanation of styrene with diazoacetate catalyzed by Ru-**Pheox2** was attempted, but despite the high *trans*-enantioselectivity (97% ee), the cyclopropanation product was isolated in only 30% yield[106]. Better results are obtained with Ru-**Pheox2** supported on a macroporous polymer; in fact, the corresponding (*R*,*R*)-cyclopropanecarboxylates were obtained in 80–99% yield and with 91–99% ee[107]. The most relevant features of this catalyst were the best results achieved among the heterogeneous catalysts and its reusability, because it was recycled more than 10 times, even after 3 months of storage of the used catalyst, without any loss in its catalytic activity or selectivity.

Cobalt porphyrins have provided robust catalysts for asymmetric cyclopropanations as described in Scheme 9 but ruthenium–porphyrin catalysts were also often employed in this reaction. In 2003, a comparison between rhodium and ruthenium–porphyrin complexes for similar reactions showed that better *E/Z* ratios and higher ee values for the *trans*-isomer were obtained with ruthenium complexes than with the corresponding rhodium complexes[108]. Moreover, Ru-**Por** (Figure 7 for the structure) afforded cyclopropanation of alkenes with EDA **30**[109] and of substituted styrenes with diisopropyl diazomethylphosphonate **18**[110] or with 2,2,2-trifluorodiazoethane **31**[111] (Scheme 23). The reactions of EDA[112] and 2,2,2-trifluorodiazoethane[111] were also investigated, giving similar results, under heterogeneous conditions with the corresponding metalloporphyrin polymers, obtained from a chiral ruthenium–porphyrin complex, functionalized with four vinyl groups and copolymerized with divinylbenzene.

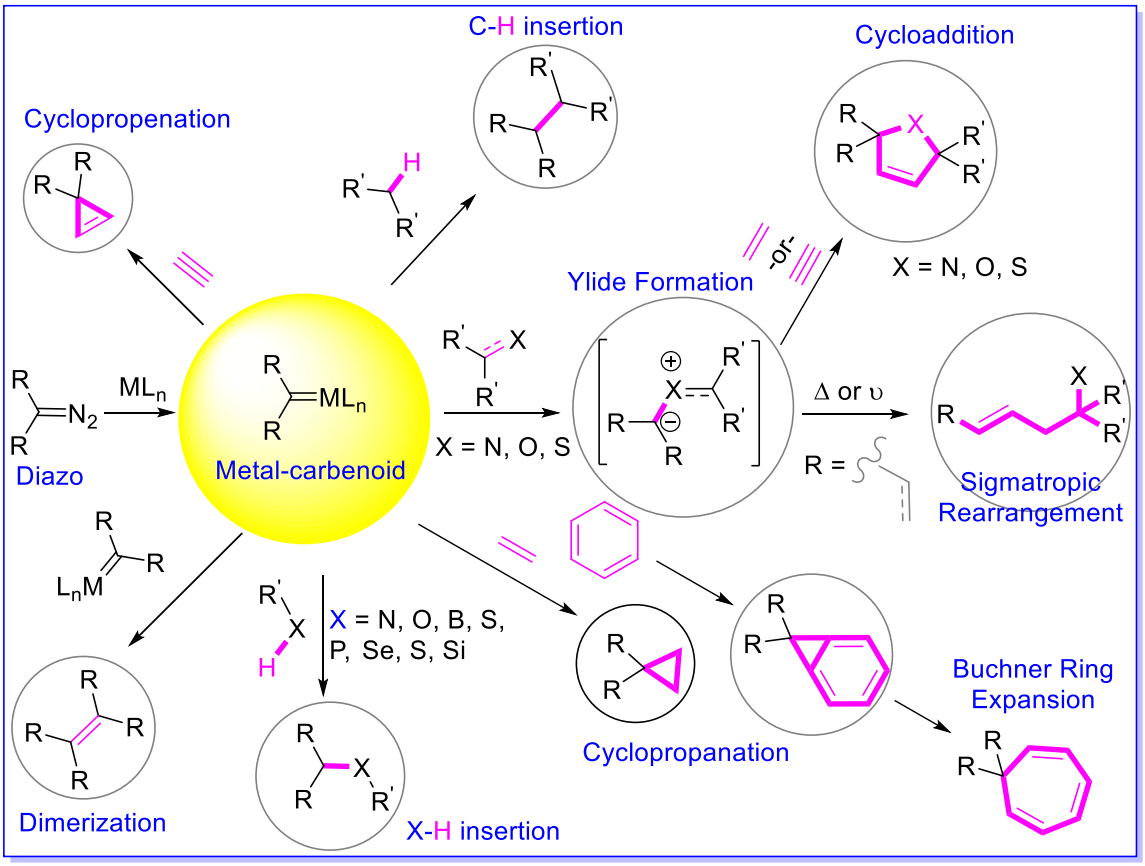


Scheme 23. Asymmetric cyclopropanation catalyzed by ruthenium porphyrin.

3. Application of metal carbene complexes (metal-carbenoids) for bioactive organic compounds

Carbene and metal carbenoid species, originally viewed as too reactive to be useful for complex molecule synthesis, have now emerged as attractive intermediates for the construction of highly functionalized heterocyclic compounds. A popular route to metal carbenoids involves the decomposition of diazo starting materials, using various transition metals. In the last two decades several groups have demonstrated that other transition metals, such as Cu, Fe, Ag, Au, Pd and Hg, can also generate carbenoids that are selective and that when appropriately utilized, carbenoids could be powerful intermediates that can be successfully and selectively trapped to yield "value-added" intermediates,[113] which can be further elaborated into complex alkaloids, for example. Other utilities of metal carbenoids in the synthesis of biologically-active or natural product-like compounds via asymmetric reactions such as C-H insertion, cyclopropanation, cycloaddition, etc. are showed (Scheme 24).

Some researchers anticipate that diazo intermediates will continue to be used to construct complex natural products and drug-like chemical libraries.



Scheme 24. Reaction classes of metal-carbenoids.

1.4 Objectives

Since the pioneering work of Nozaki et al.,[58b] significant effort has been devoted to developing the highly stereoselective cyclopropanation of olefins via carbene transfer catalyzed by copper, rhodium, ruthenium, cobalt complexes…Electron-rich styrene derivatives are usually employed as the olefinic substrate due to their high reactivity toward the electrophilic metal−carbene intermediate. In contrast to the excellent results achieved with styrene derivatives, which have been described in more than 300 reports over the last two decades. Thus, the development of new powerful catalysts with broad substrate scope is the next challenge in this field.

Therefore, in this thesis, the study objectives include:

- To develop the broad substrate scopes in the catalytic asymmetric carbene transfer cyclopropanations of diazo ketones and diazo phosphonates.
- To improve the enantioselectivity in the cyclopropanations of transition Ruthenium carbene complexes.
- To clarify the mechanisms of the catalytic asymmetric cyclopropanation reactions.

CHAPTER 2

Direct Catalytic Asymmetric Cyclopropylphosphonation Reactions of *N,N*-Dialkyl Groups of Aniline Derivatives by Ru(II)-Pheox Complex

2.1. Introduction

Phosphonates are an important group of compounds in pharmaceutical and biological fields because these functional groups are commonly found in biological systems. Furthermore, the cyclopropane ring is an important structure in biologically active compounds[114] and a versatile unit that can be transferred to an array of other bioactive compounds.[115] Therefore, cyclopropylphosphonate derivatives have numerous applications in a wide range of natural and artificial compounds in the pharmaceutical industry[116] and in recent studies, the synthesis of cyclopropylphosphonates has been extended to improve pharmaceutical properties.

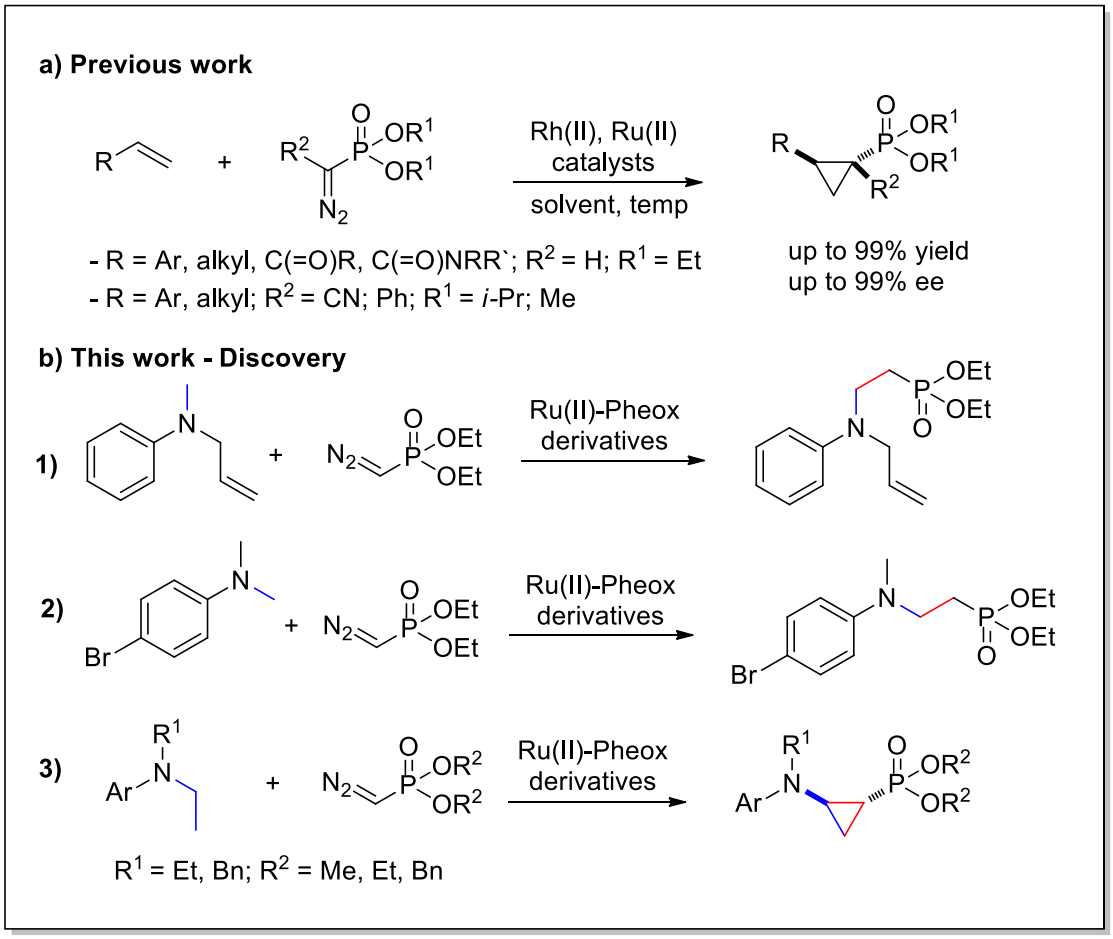


Figure 8. Research background

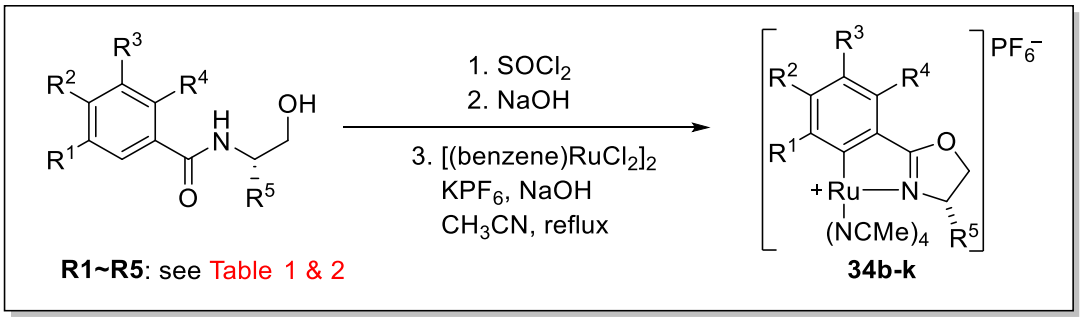
After the pioneering work by Seyferth *et al.*,[117] transition-metal-catalyzed asymmetric cyclopropylphosphonation of alkenes with diazomethylphosphonate derivatives was quickly developed, and several excellent results have been reported.[118] Highly effective and stereo-controlled syntheses of phosphonate functionalized cyclopropanes have been reported

using chiral transition metal complexes such as Rh(II) and Ru(II) catalysts. In 2013, Lindsay *et al.*,[119] described the catalytic asymmetric synthesis of diacceptor cyclopropylphosphonate derivatives from α-cyano-diazomethyl phosphonates in the presence of Rh_2(S-IBAZ)$_4$ as a chiral catalyst under mild conditions and reported excellent yield and enantioselectivity with electron-rich alkenes. Recently, we reported highly stereoselective cyclopropanation of olefins with diethyl diazomethylphosphonate using a Ru(II)-Pheox catalyst (Figure 8, a)). Importantly, the cyclopropanation of electron-deficient olefins such as α,β-unsaturated esters, ketones, and amides were also performed under mild conditions to afford the corresponding cyclopropylphosphonates in high yields (up to 93%) and with excellent diastereo- and enantioselectivity (up to 99:1 dr and 99% ee)[120].

Herein, we examined *N*-methyl and *N*-allylaniline with diethyl diazomethylphosphonate using a Ru(II)-Pheox catalyst to synthesize β-amino cyclopropylphosphonate and observed no cyclopropanation product. However, we isolated an interesting phosphonomethylation reaction product on the -CH_3 group[121] of the aniline, along with trace amounts of phosphonation on the aromatic ring as a minor product (Figure 8, b.1)). Thus, here, we describe a novel phosphonomethylation of *N*-methylaniline and asymmetric cyclopropylphosphonation reactions of *N,N*-diethylaniline derivatives with diazomethyl phosphonates using Ru(II)-pheox derivatives as chiral catalysts (Figure 8, b.2,3)).

2.2 Results and discussions

2.2.1 Catalyst screening for the phosphonomethylation reaction of *N*-methylaniline with diazomethyl phosphonates.

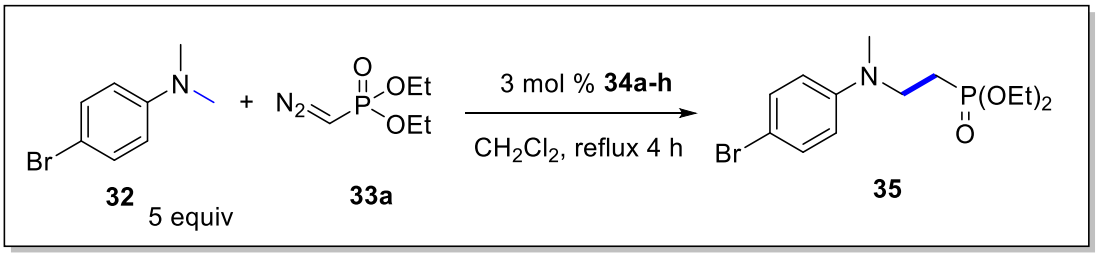


Scheme 25. Procedure for the synthesis of a series of Ru(II)-Pheox catalysts

After the novel reaction of *N*-methyl aniline with diazomethylphosphonate catalyzed by Ru(II)-Pheox was observed, we were encouraged to develop a novel catalytic process using *N,N*-dimethylaniline as a substrate to further examine the reaction. A brief optimization of the phosphonomethylation reaction of *N,N*-dimethylaniline catalyzed by Ru(II)-Pheox (Table 1) and the synthesis of a series of Ru(II)-Pheox catalysts (Scheme 25) were performed. $Rh_2(OAc)_4$ and other transition metals such as Fe(II), Cu(I), and Cu(II) are well-known carbene transfer catalysts, but had almost no effect on the C-H insertion reaction (Table 2, entry 1).

Phosphonomethylation product **4** was obtained in the highest yield (72%) in the presence of electron-rich functional group-substituted Ru(II)-Pheox **3f** (Table 2, entry 6). Furthermore, the electron-rich substituents on the phenyl group bonding with Ru(II) were more effective than the electron-withdrawing groups (Table 2, entries 3–7).

Table 2. Catalyst screening for the phosphonomethylation of *N,N*-dimethylaniline with diazomethylphosphonate



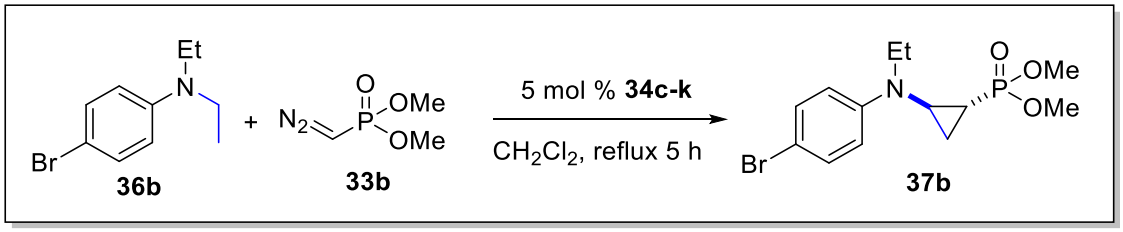
entry	catalyst	yield[b] (%)
1	**34a**: $Rh_2(OAc)_4$	trace
2	**34b**: $R^1 \sim R^5 = H$	52
3	**34c**: $R^1 \sim R^4 = H$, $R^5 = Ph$	53
4	**34d**: $R^1 \sim R^4 = F$, $R^5 = Ph$	27
5	**34e**: $R^2 = NO_2$, $R^1 = R^3 = R^4 = H$, $R^5 = Ph$	41
6	**34f**: $R^3 = OMe$, $R^1 = R^2 = R^4 = H$, $R^5 = Ph$	**72**
7	**34g**: $R^1 = OMe$, $R^2 = R^3 = R^4 = H$, $R^5 = Ph$	71
8	**34h**: $R^1 = R^3 = OMe$, $R^2 = R^4 = H$, $R^5 = Ph$	15

[a]Reaction conditions: to Ru(II)-Pheox **3**(3%) in CH_2Cl_2 (2.0 mL) a solution of diazomethylphosphonate **2a** (0.2 mmol) in CH_2Cl_2 (2.0 mL) was added under Ar. [b] Isolated yield.

2.2.2 Catalyst screening for asymmetric cyclopropylphosphonation reactions of *N,N*-diethylaniline derivatives with diazomethyl phosphonates.

The optimized reaction conditions from Table 2 were then applied to *N*,*N*-diethylaniline to further understand the reaction process. First, the reaction of *N*,*N*-diethyl-*p*-bromoaniline **36b** with dimethyl diazomethylphosphonate **33b** was performed using a series of Ru(II)-Pheox catalysts, and the results are summarized in Table 3.

Table 3. Ru(II)-Pheox catalyst screening of cyclopropanation



entry	catalyst	yield[b] (%)	ee[c] (%)
1	**34c**	26	96
2	**34d**	37	87
3	**34e**	20	94
4	**34f**	19	94
5	**34g**	19	94
6	**34h**	41	94
7	**34i**: $R^1 \sim R^3$ = OMe, R^4 = H, R^5 = *t*Bu	30	82
8	**34j**: $R^1 \sim R^3$ = OMe, R^4 = H, R^5 = *i*Pr	34	51
9	**34k**: $R^1 \sim R^3$ = OMe, R^4 = H, R^5 = Ph	**49**	**96**

[a] Reaction conditions: to Ru(II)-Pheox (3%) in CH_2Cl_2 (2.0 mL), a solution of diazomethylphosphonate **2a** (0.2 mmol) in CH_2Cl_2 (2.0 mL) was added under Ar. [b] Isolated yield. [c]Determined by chiral HPLC analysis.

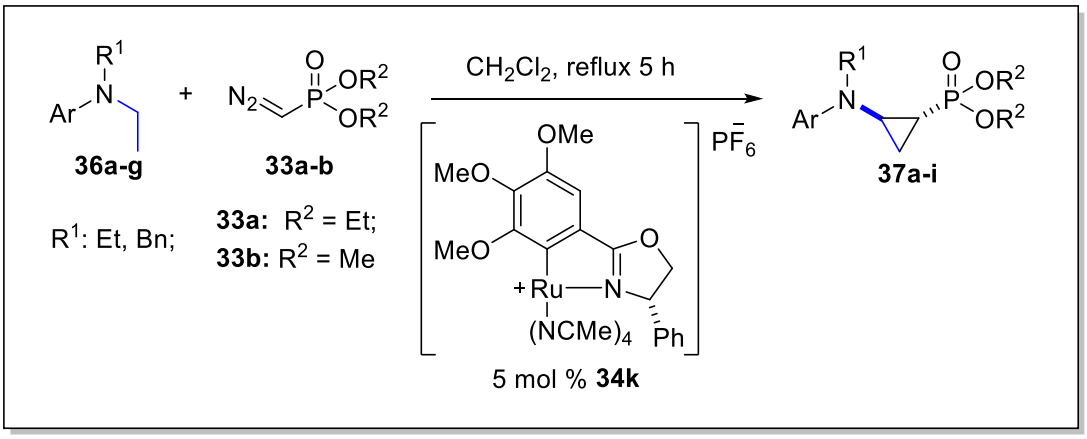
Surprisingly, the cyclopropanation product was obtained via a C-H insertion reaction with high enantioselectivity without the formation of a methylphosphonation product in the case of *N*,*N*-diethyl-*p*-bromoaniline **36b**. As can be seen from Table 3 (entry 1), 96% ee as a sole *trans* diastereomer in a 26% yield was obtained with the dimer as a minor product. Various electronic effects on the aromatic ring bonding with Ru(II) and chiral environment on the oxazoline ring were examined for the cyclopropylphosphonation reaction (Table 3, entries 2–6). The Ru(II)-Pheox catalyst bearing an electron-donating group on the benzene ring bonding with Ru(II) and a phenyl group providing a chiral environment was found to be the most efficient catalyst for this reaction in terms of yield and stereoselectivity (Table 3, entry 9). For all of the reaction conditions listed in Table 2, only the *trans*-isomers were observed.

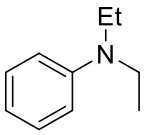
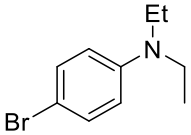
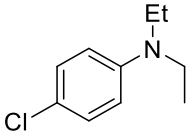
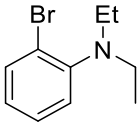
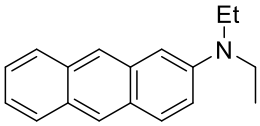
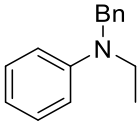
2.2.3 Intermolecular asymmetric cyclopropylphosphonation reactions of diazomethyl phosphonates with various *N*,*N*-diethylaniline derivatives.

Based on the optimized conditions, we next explored the scope and generality of the direct

catalytic asymmetric cyclophosphonation reaction of diazomethylphosphonate and *N*, *N*-diethyl aniline derivatives, and the results are summarized in Table 4.

Table 4. Substrate scope of cyclopropanation



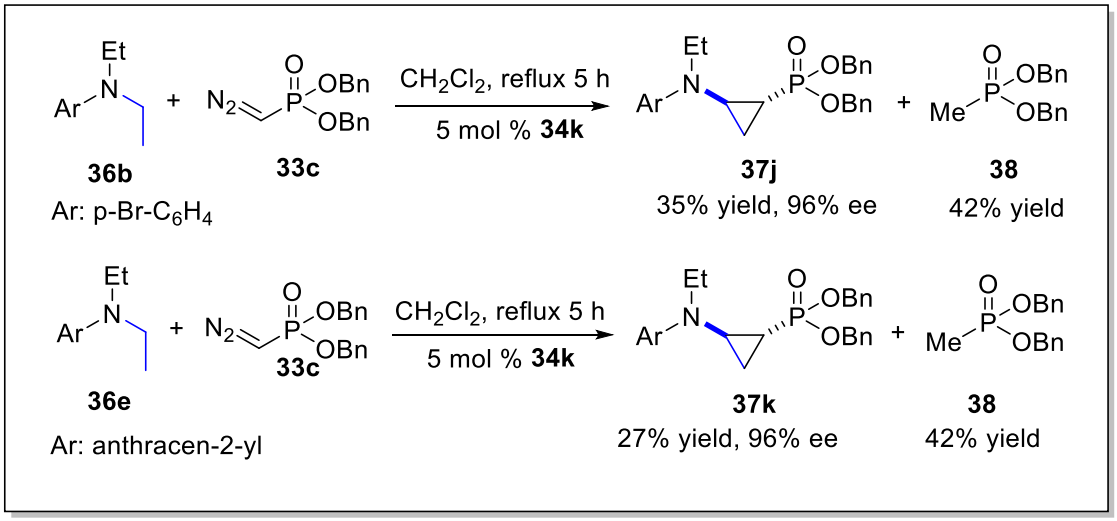
entry	**36**		**33**	**37**	yield[a] (%)	ee[b] (%)
1[c]		**36a**	**33b**	**37a**	46	93
2[c]		**36a**	**33a**	**37g**	28	93
3		**36b**	**33b**	**37b**	49	96
4		**36b**	**33a**	**37h**	35	97
5		**36c**	**33b**	**37c**	36	94
6		**36d**	**33b**	**37d**	30	93
7		**36e**	**33b**	**37e**	40	94
8		**36g**	**33b**	**37i**	28	99

N,*N*-Diethyl aniline as well as *p*-bromo- and chloroaniline were reacted with diazomethylphosphonate in the presence of the Ru(II)-Pheox catalyst **34k** to afford their corresponding cyclopropane products in high enantioselectivities up to a 49% yield and 97% ee (Table 4, entries 1, 3, 5, and 6). *N*-benzyl-*N*-ethylaniline gave a slightly lower enantioselectivity and yield (Table 4, entry 8) than the other substrates. In addition, we examined *N*,*N*-diethyl-*p*-OMe substituted aniline and the product was found to be unstable during the work up and purification process, which might be due to cyclopropane ring opening. Furthermore, the methyl ester substituent of the diazophosphonate showed 10 to 20% higher yields compared to the ethyl ester (Table 4, entries 1, 3 and entries 2, 4). The minor products in these reactions were difficult to isolate.

2.2.4 Mechanistic studies for intermolecular asymmetric cyclopropylphosphonation reactions of diazomethyl phosphonates with *N*,*N*-diethylaniline derivatives.

2.2.4.1 Determination of by-product

We used dibenzyl diazomethylphosphonate for cyclopropane reactions in the presence of catalyst **34k** (Scheme 26). Notably, the cyclopropanation products (**37j** and **37k**) gave the same high enantioselectivity, 96% ee. Meanwhile, the minor product **7** in both reactions was isolated in a 42% yield.



Scheme 26. By-product of cyclopropanation

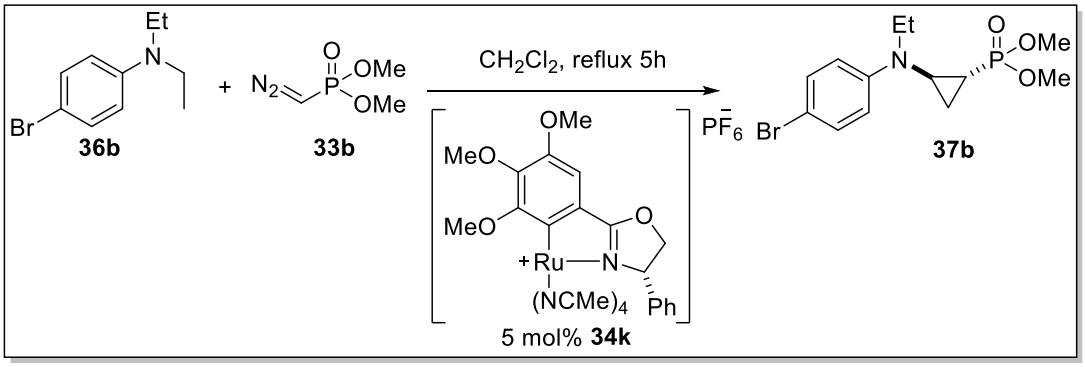
2.2.4.2 Cyclopropylphosphonation reaction with hydrogen acceptors

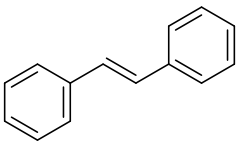
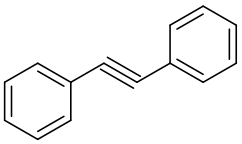
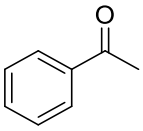
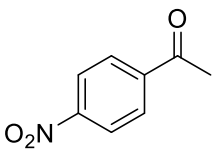
The results reported above, such as the direct methylphosphonation of *N*-methyl aniline, direct catalytic asymmetric cyclopropylphosphonation of *N*-ethyl aniline derivatives, and the formation of benzyl methylphosphonate as a side product encouraged us to further explore the mechanisms of these reactions.

First, mixtures of the Ru(II)-Pheox catalyst and aniline derivative and the Ru(II)-Pheox catalyst, aniline derivative, and olefin without diazophosphonate were tested, but afforded no

reaction under the identical reaction conditions listed above. Second, the cyclopropylphosphonation reaction was conducted with hydrogen acceptors such as norbornene, stilbene, 1,2-diphenylethyne, acetophenone, and *p*-nitroacetophenone, but no reducing product was observed (Table 5).

Table 5. Cyclopropylphosphonation reaction with hydrogen acceptors



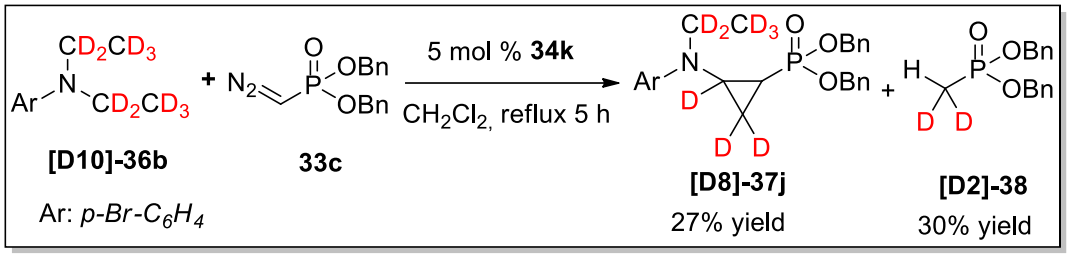
entry	hydrogen aceptors (2 equiv.)	yield [%]	ee [%]
1	None	**49**	**96**
2	 Norbornene	32	94
3	 Stilbene	41	95
4	 1,2-diphenylethyne	34	93
5	 Acetophenone	36	95
6	 *p*-nitroacetophenone	34	94

These results suggest that a transition metal hydride[122] was not formed during the reaction.

Remarkably, the other diazo compounds, such as diazoesters, also showed no reaction for *N*, *N*-diethylaniline.

2.2.4.3 Catalytic asymmetric cyclopropanation of *N,N'*-deuterated diethylaniline with diazophosphonate

A D-labeled *N*,*N*-diethylaniline derivative was applied to determine the mechanism for this reaction. The deuterated aniline **[D10]-36b** was synthesized and reacted with dibenzyl diazomethylphosphonate **33c** in the presence of catalyst **34k** to afford the corresponding partially deuterated cyclopropyl product **[D8]-37j** in a 27% yield with the minor product **[D2]-8** in a 30% yield. This indicated that two protons from *N*-ethyl group of N-ethylaniline were transformed into the by-product (Scheme 27) and suggested the formation of an imine or enamine intermediate[121a] for the cyclopropylphosphonation via olefin insertion reaction of the Ru-carbene complex.



Scheme 27. Preliminary mechanistic studies

2.2.4.4 Plausible mechanism

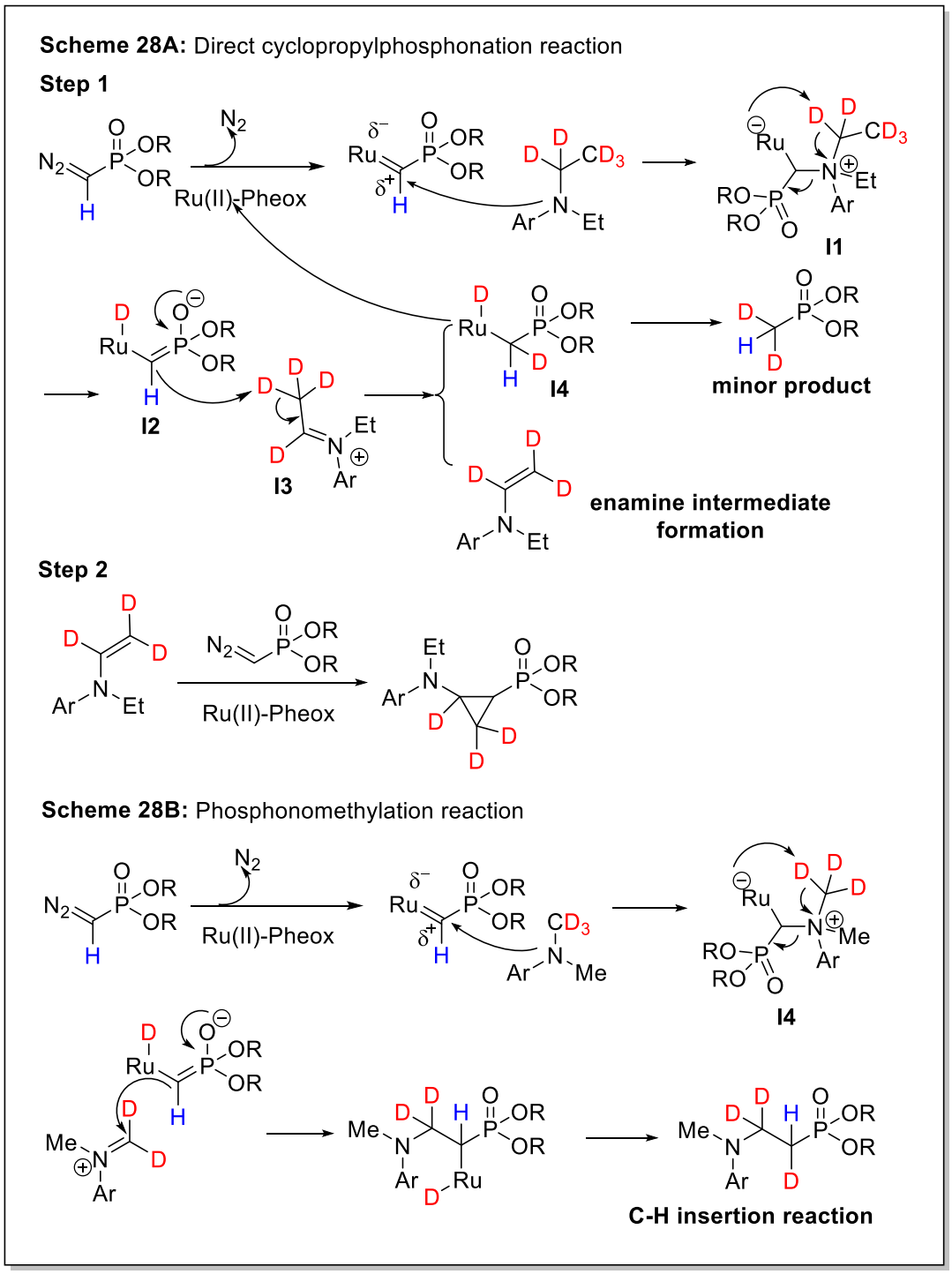
From all information above, a plausible mechanism was summarized (Scheme 28). First, the reaction of Ru(II)-pheox catalyst and diazophosphonate generates a metal-carbene complex, which coordinates with the nitrogen of aniline immediately to activate intermediate **I1**. Then, the Ru phosphonate intermediate **I2** and iminium intermediate **I3** are formed. The iminium intermediate **I3** is easily converted to the enamine and reacted with the Ru-carbene intermediate to afford the corresponding cyclopropylphosphonation product. Simultaneously, the intermediate **I2** attracts hydrogen to form intermediate **I4**, then reductive elimination occurs to generate the corresponding benzyl methyl phosphonate and end of the catalytic cycle (Scheme 28A). The process involved a C-H activation reaction when the substrates were aniline derivatives with a $-CH_3$ group (Scheme 28B).

The highly stereoselective cyclopropanation of ethylaniline derivatives with diazomethylphosphonates catalyzed by Ru(II)-Pheox complex was determined to occur without the formation of cis-isomer products. Although the cyclopropanation yields are moderate because of multi-step reaction, excellent enantioselectivities are noteworthy.

Obviously, our previous report regarding the cyclopropanation of vinyl-amine derivatives with diazomethylphosphonate in the presence of a Ru(II)-Pheox complex also achieved high

yields.[123a] However, the synthetic procedure for the vinyl-amine derivatives involved many steps with low yield and required long cyclopropanation times.[123] Here, we demonstrated direct cyclopropylphosphonate derivatives simultaneously from an *N*-ethylaniline derivative.

Scheme 28. Plausible mechanism based on D-labeling experiment



2.3 Conclusion

In summary, we developed a novel catalytic phosphonomethylation of *N*-methylaniline and characterized the asymmetric cyclopropylphosphonation reactions of *N,N*-diethylaniline derivatives with diazomethylphosphonates. The catalytic asymmetric cyclopropanation reaction of diazophosphonates and *N*-ethylaniline derivatives by Ru(II)-pheox complexes represent a novel methodology for the synthesis of optically active cyclopropylphosphonate analogues. Furthermore, we showed that the Ru(II)-Pheox complex catalyzes the intermolecular C−H insertion reactions of diethyl diazomethylphosphonate to form an inactivated methyl group in the dimethylaniline derivatives in moderate yields to afford corresponding β-aminophosphonates. These structures represent important skeletons found in biologically active compounds. This procedure is an efficient strategy for the introduction of phosphonate groups. To the best of our knowledge, no reports regarding the direct catalytic asymmetric synthesis of cyclopropylphosphonate analogues have been published to date.

CHAPTER 3

Asymmetric Synthesis of Diaceptor Cyclopropylphosphonates Catalyzed by Chiral Ruthenium(II)-Pheox Derivatives

3.1 Introduction

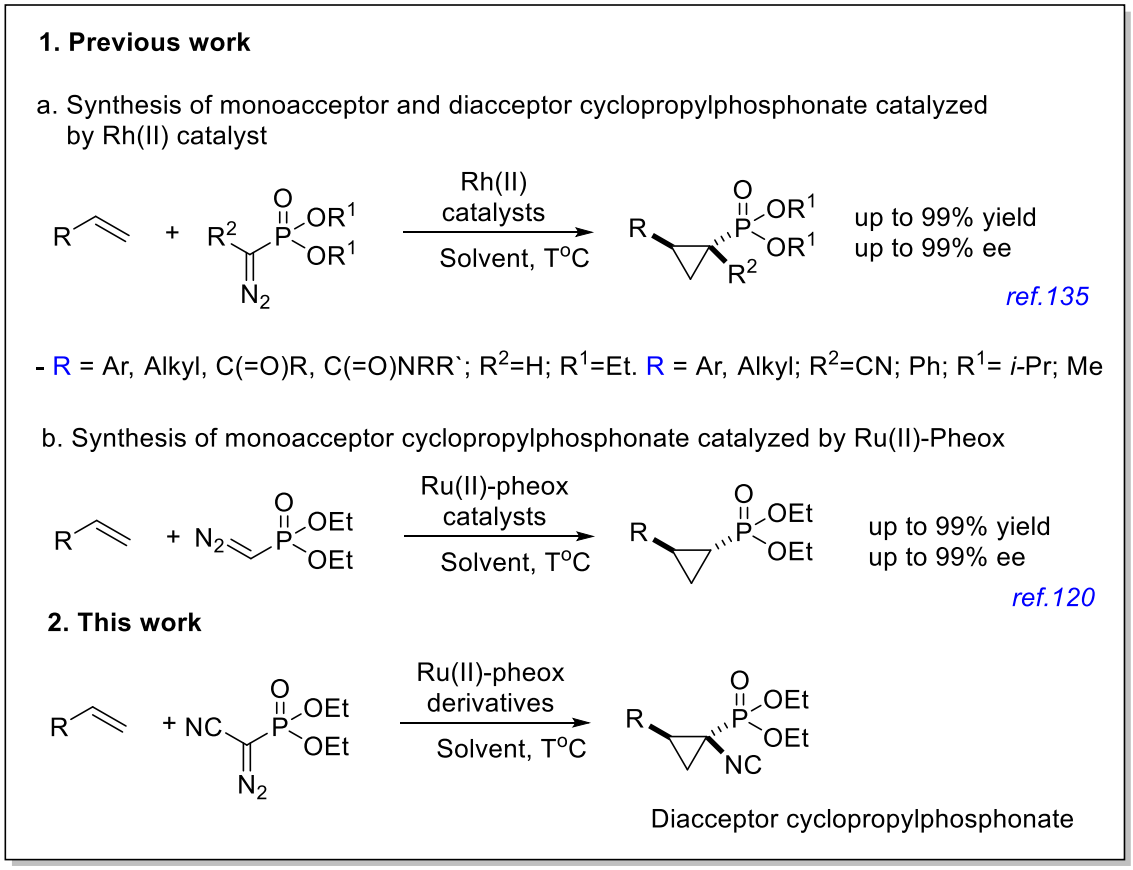


Figure 9. Research background

The Chiral cyclopropyl moiety has participated an important role in organic chemistry for decades[124]. Of particular interest, cyclopropylphosphonate derivatives have been widely studied during the last decade as they are found in immense natural or artificial compounds of pharmaceutical field due to their biological activities[125]. While the phosphorus–oxygen bond in phosphates is weak, the carbon–phosphorus bond is stable, which their characteristics increase the resistance to *enzymatic hydrolysis*[126,127]**.** On the other hand, the addition of a cyclopropyl ring into chemical frame can extend the significant for biological activities[128]. Whereby, desirable pharmacological properties can gain from the apposition of both cyclopropyl and phosphonate groups in the same compound. For example, cyclopropylphosphonates play as selective anti-HBV agents[129], N-methyl-D-aspartate (NMDA) receptor antagonists[130].

Moreover, they possess anti-proliferation properties[131a], are virostatics[131b], and display antiviral activity[131c]. In addition, some other cyclopropylphosphonates are served as mimicry models for their phosphorus analogues, which have expressed important biological properties[132]. They are employed as imitation of 1-aminocyclopropane carboxylic acid (ACC) with a high inhibitory activity for the ACC-deaminase and alanine racemase[133a], as structural moieties of nucleotides[133b], as phosphonic analogues of the antidepressant milnacipran[133c], as a constrained analogue of the GABA antagonist phaclophen[133d].

Among the methods for the stereoselective synthesis of highly functionalized cyclopropyl-phosphonation have been extensively developed[134], transition-metal- catalyzed cyclopropanation of olefins with diazo phosphonates is the most efficient method. In the recent years, chiral rhodium(II) complex has been known as an efficient catalyst in the asymmetric cyclopropanation of a monoacceptor or a *diacceptor* diazophosphonate species with an alkene in high yields and excellent diastereo- and enantioselectivity[135]. However, the cost of rhodium maybe becomes an issue when a catalytic reaction is carried out in an industrial process unit because of its expensiveness[136]. Therefore, many researchers usually chose Ruthenium, a next neighbor of rhodium in the periodic table, currently costs nearly one tenth the price of rhodium. Furthermore, ruthenium is considered by the greater diversity of complexes, due to the larger number of oxidation states and the richer coordinate chemistry when compared to rhodium.

Recently, our research group reported that the complex, Ru(II)-pheox, has been completely efficient in carbine transfer reactions, particularly the cyclopropanation of diethyl diazomethylphosphonates with various electron-deficient olefins such as α,β-unsaturated carbonyl compounds or vinyl carbamates in excellent yields and with high enantioselectivity[120]. Herein, we report the initial step of the research about the first asymmetric cyclopropanation of diacceptor diazophosphonate with olefin catalyzed by Ru(II)-pheox derivatives in high yield and good enantioselectivity (Figure 9). This research is still in improving the enantioselectivity stage to get the optimization conditions, so in this paper we still not describe about substrate scope.

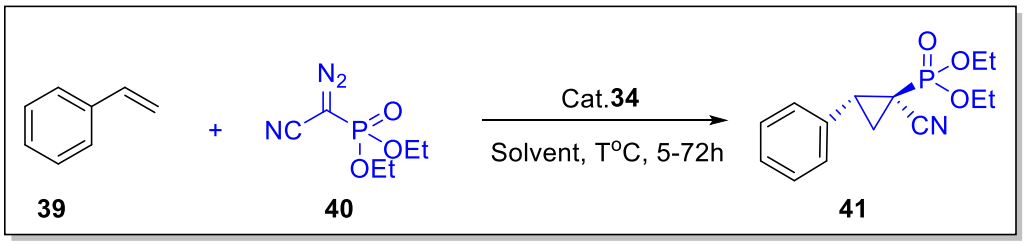
3.2 Results and discussions

3.2.1 Catalyst screenings

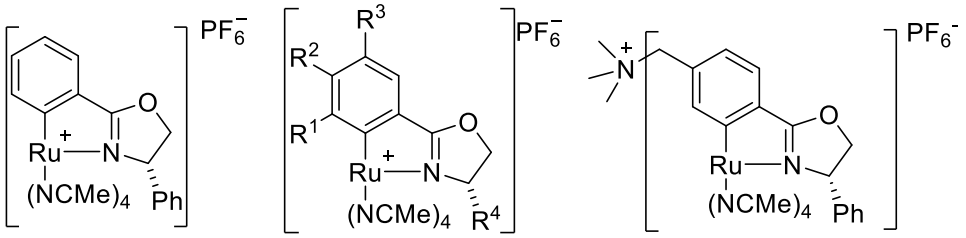
The cyclopropanation of (Diethyl cyano(diazo)methyl)Phosphonate (**2**) with styrene using series of Ru(II)-Pheox complexes and the influence of various solvents were preliminarily described in Table 6. Firstly, as the results, the cyclopropyl reactions catalyzed by Ru-Pheox catalysts always obtained in excellent yields together with excellent diastereoselectivity (99:1). To describe the screening catalysts, the series of Ru-Pheox complexes which bear different substituents at the phenyl backbone and the oxazoline moiety were carried out to cyclopropanate the reaction above. It was observed that the cyclopropyl reactions catalyzed by

Ru(II)-Pheox compound carrying electron donating groups at phenyl backbone in dichloromethane, at room temperature were more effective in both yield and enantioselectivity than eletron withdrawing groups at the same position (entries 2,3).

Table 6: Catalyst screenings



39 40 41



34c 34e,f,h,i,j,k 34l

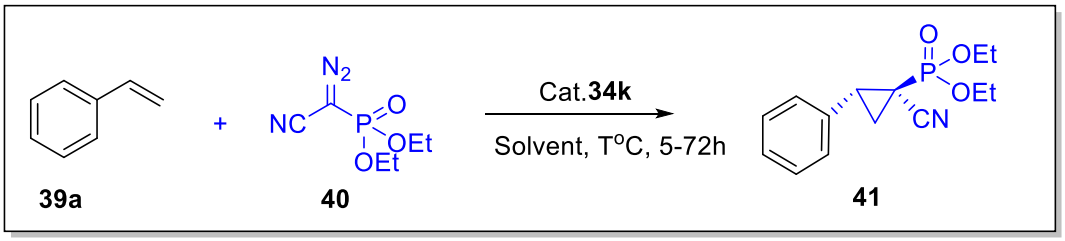
Entry	Catalyst	Solvent	Tem [°C]	yield [%][b]	-ee [%][c]
1	**34c**	CH_2Cl_2	RT	99	55
2	**34e**: $R^1 = R^2 = H$, $R^2 = NO_2$, $R^4 = Ph$	CH_2Cl_2	RT	92	21
3	**34f**: $R^1 = R^2 = H$, $R^3 = OMe$, $R^4 = Ph$	CH_2Cl_2	RT	99	48
4	**34h**: $R^1 = R^3 = OMe$, $R^2 = H$, $R^4 = Ph$	CH_2Cl_2	RT	99	50
5	***34k**: $R^1 = R^2 = R^3 = OMe$, $R^4 = Ph$*	*CH_2Cl_2*	*RT*	*99*	*63*
6	**34j**: $R^1 = R^2 = R^3 = OMe$, $R^4 = i$Pr	CH_2Cl_2	RT	80	32
7	**34i**: $R^1 = R^2 = R^3 = OMe$, $R^4 = t$Bu	CH_2Cl_2	RT	86	35
8	**34l**	CH_2Cl_2	RT	0	-

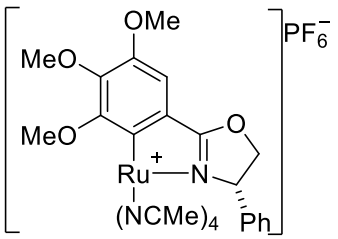
Therein, the highest enantioselectivity and yield could be received in 63% ee and 99% yield by using Ru-Pheox catalyst, which holds three OMe electron-donations group at phenyl backbone (entry 6). After that, the cyclopropyl reaction also was considered by the effective of *3,4,5 methoxy Ru(II)-Pheox* derivatives bearing the substituents at the C4 position of oxazoline

ring. The result was found these kinds of catalyst derivative could not improve the enantioselectivity (entries 6,7). In contrast, we also examined the cyclopropanation by using chiral Ru(II)-Amm-Pheox complexe; however, no cyclopropane products were observed.

3.2.2 Optimization conditions

Table 7. Optimization of Reaction Conditions





34k

Entry	Solvent	Tem [°C]	yield [%][b]	-ee [%][c]
1	Et_2O	RT	90	58
2	1,4 Dioxan	RT	89	63
3	THF	RT	93	51
4	Toluene	RT	95	57
5	CH_2Cl_2	5	99	68

Besides, due to improve the reactive cyclopropanation of this type diazo compounds, we tried to express the influence of various solvents on the cyclopropyl reaction to improve the enantioselectivity (Table 7). However, both the yields and the enantioselectivity had significantly decreases, from 99% to 89% in yield and from 63% to 51% in enantioselectivity (entries 1-4). Moreover, as we can see, *1,4 Dioxan* also had same effect with dichloromethane, however we still chose dichloromethane as the best solvent in this case because of its low boiling point.

In entry 5, the cyclopropyl reaction was carried out by using catalyst **7e**, in dichloromethane at 5 °C and the enantioselectivity could be obtained in 68%. This means that the temperature has

effected on the enantioselectivity of this reaction. Thereby, the cyclopropylphosphonate reactions will be conducted more with various conditions to improve the enantioselectivity.

3.3 Conclusion

In conclusion, we presented the first catalytic asymmetric synthesis of diacceptor cyclopropylphosphonate reaction, using an α-cyano diazophosphonate reagent and Ru(II)-Pheox derivatives as chiral catalyst in excellent yields and good enantioselectivity. The development of catalytic asymmetric cyclopropanation of olefin using diacceptor diazo compounds plays an important role in synthetic intermediates in a vast array of transformations. Based on the results above, we are completely believed that Ru(II)-Pheox derivatives are potential to this reactions, hence, conducting more experiments to improve the enantioselectivity is necessary.

CHAPTER 4

Catalytic Asymmetric Intermolecular Cyclopropanation of Diazoketones with Olefins by using Novel Ru(II)-Pheox Complex

4.1 Introduction

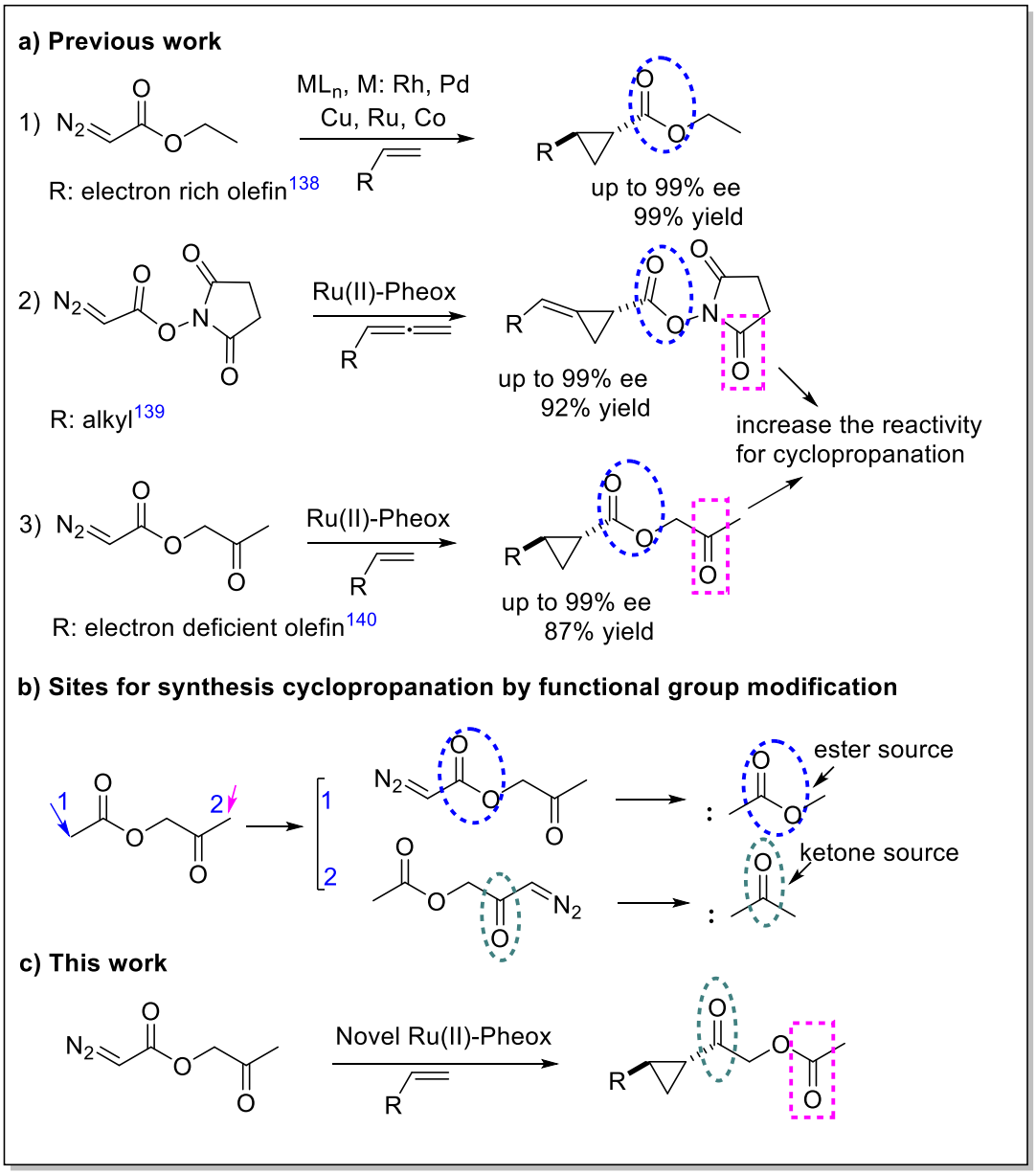


Figure 10. Research background

Optically active cyclopropane derivatives have received considerable attention in the fields of organic and pharmaceutical chemistry owing to the biological activities of cyclopropanes.[137] The transition metal-catalyzed asymmetric cyclopropanations of diazoacetates with olefins using chiral Cu,[138a-d] Rh,[138e-g], Ru,[138h-j] Co,[138k-l] and Ir[138m] catalysts have been reported with excellent stereoselectivities. In most cases, steric hindrance plays an important role in

obtaining high stereoselectivities. For example, for a carbene transfer reaction of diazoacetate to olefins, sterically hindered ester substituents such as *i*-Pr and *t*-Bu gave generally higher stereoselectivities than that from the less hindered Et substituent. Carbene transfer reactions have also thus far been generally limited to the use of a diazoester (Figure 10, reaction 1).

Recently, we reported on the modification of diazoacetates to improve catalytic asymmetric cyclopropanations not only for electron-rich olefins, but also for allenes and electron-deficient olefins. Thus, Ru(II)-pheox-catalyzed asymmetric cyclopropanation of succinimidyl diazoacetate with olefins and allenes resulted in cyclopropanes with high yields and excellent enantioselectivities (up to 99%) (Figure 10, reaction 2).[139] Continuing this line of research, an asymmetric cyclopropanation of α,β−unsaturated carbonyl compounds with acetonyl diazoacetate by using Ru(II)-pheox was reported (Figure 10, reaction 3).[140] Succinimidyl diazoacetate and acetonyl diazoacetate gave much higher stereoselectivities (diastereoselectivity >99:1 and enantioselectivity up to 99%) in the cyclopropanation reactions compared with sterically hindered esters.[140] Consequently, we proposed that the carbonyl groups of succinimidyl diazoacetate and acetonyl diazoacetate played an important role, in which the carbonyl group might be coordinated to Ru after the formation of a carbene-metal complex, resulting in enhanced stereoselectivity.

Since the reaction of acetonyl diazoacetate with olefins gave the corresponding cyclopropyl esters in high yields and high stereoselectivities, we thought to introduce the diazo group onto the acetonyl group. This could give the corresponding cyclopropyl ketone moiety with high stereoselectivity, since the carbonyl group is the same distance from another carbonyl group of the acetyl group and therefore we would expect the same effect on the stereoselectivity.[141] Furthermore, cyclopropyl ketone moieties are found in natural products having important physiological properties,[142] but only α-diazoacetophenone has been developed as a ketone source, having been obtained in 67% yield with 86% ee.[143] Thus, we report herein the first catalytic asymmetric synthesis of a ketone carbene precursor based on an acetonyl acetate skeleton by using novel Ru(II)-Pheox complexes as chiral catalysts (Figure 10).

4.2 Results and discussions

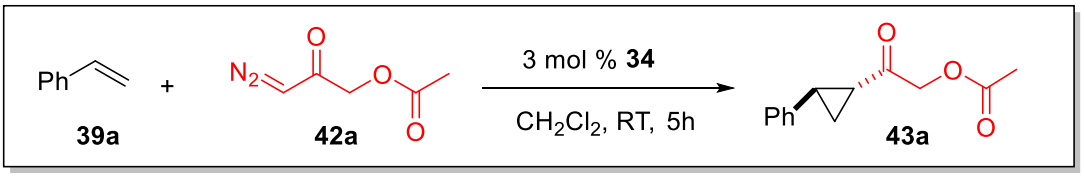
4.2.1 Catalyst screenings

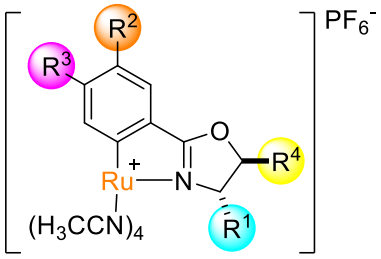
Diazo acetoxy acetone[144] was prepared by modification of the diazo acetonyl acetate synthesis, and examined in the carbene transfer reaction by using a series of Ru(II)-Pheox complexes, which had been found to be efficient catalysts for the inter- and intramolecular cyclopropanation of various diazo compounds.[123]

As part of our ongoing interest in cyclopropanation reactions with alternative diazo esters, we first examined the reaction of styrene **39a** with diazo acetoxy acetone **42a** using $Rh_2(OAc)_4$ and the series of Ru(II)-Pheox derivatives **34** as catalysts. The results are summarized in Table

8.

Table 8. Initial catalyst screenings.[a]





Cat. 34

34b: R^1 = Ph, R^2 = R^3 = R^4 = H

34m: R^1 = *i*Pr, R^2 = R^3 = R^4 = H

34n: R^1 = *t*Bu, R^2 = R^3 = R^4 = H

34o: R^1 = Bn, R^2 = R^3 = R^4 = H

34p: R^1 = Ph, R^2 = NO_2, R^3 = R^4 = H

34f: R^1 = Ph, R^2 = OMe, R^3 = R^4 = H

34e: R^1 = Ph, R^2 = R^4 = H, R^3 = NO_2

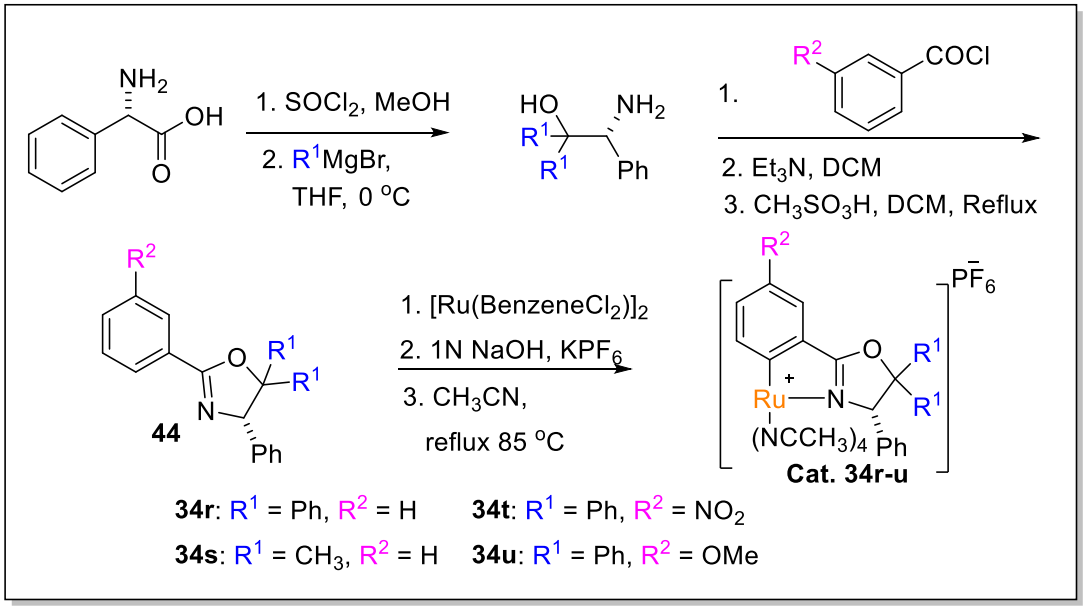
34q: R^1 = Ph, R^2 = R^3 = H, R^4 = Ph

Entry	Cat **3**	Yield[%][b]	d.r [c]	-ee [%][d]
1	**34b**	70	92:8	68
2	**34m**	54	85:15	50
3	**34n**	60	90:10	65
4	**34o**	68	75:25	46
5	**34p**	50	95:5	74
6	**34f**	53	90:10	55
7	**34e**	60	90:10	43
8	**34q**	**73**	**95:5**	**75**

[a] Reaction conditions: To Ru(II)-Pheox **3**(3%) in CH_2Cl_2 (2.0 mL), a solution of diazoketone **2a** (0.2 mmol) in CH_2Cl_2 (2.0 mL) was added under Ar. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by chiral HPLC analysis.

$RhOAc_2$ and other transition metals such as $FeSO_4$, CuOAc, and $CuOAc_2$ are well-known carbene transfer catalysts, yet had almost no effect on the cyclopropanation reaction at room temperature. In contrast, using Ru(II)-Pheox derivatives **34** as catalysts gave moderate to high reactivities and moderate to good stereoselectivities. Having a phenyl group on the oxazoline

ring of the catalyst improved the enantioselectivity to 70% ee (Table 8, entries 1–4). The influence of the electron donating or withdrawing ability of the R^2 and R^3 groups on the Ru(II)-pheox complexes were then examined. Changing the R^2 or R^3 group improved the enantioselectivity to up to 74% ee (Table 8, entries 5–7). A Ru(II)-pheox skeleton bearing an R^4 substituent at the C5 position of the oxazoline ring was also examined (R^4=Ph, catalyst **3h**). This was the most efficient catalyst for both stereoselectivity and yield (73% yield and 75% ee) (Table 8, entry 8).

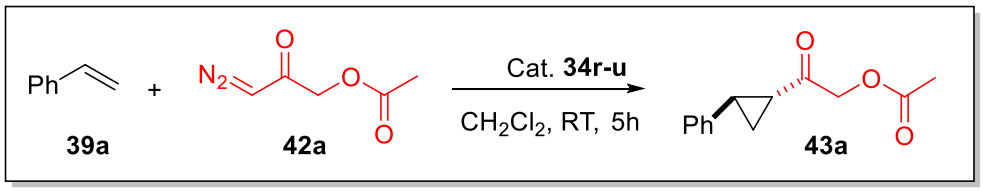


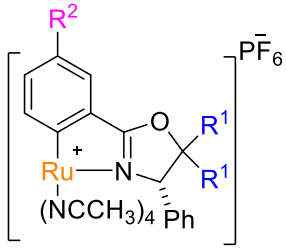
Scheme 29. Synthesis of Ru(II)-*dialkyl*-Pheox complexes.

The enantioselectivity and yield were further improved when Ru(II)-Pheox **34q** was modified with bulky dialkyl substituents at the C5 position of the oxazoline ring (catalysts **34r-u**). Based on the previous method for synthesizing Ru(II)-Pheox derivatives,[123] catalysts **34r-u** were prepared as shown in Scheme 29. First we synthesized dialkyl-phenylglycinol[145] from the corresponding Grignard reagent, alkyl magnesium bromide, and (***S***)-2-amino-2-phenylacetic acid, and then treated it with benzoyl chloride and methanesulfonic acid[146] to give ligand **44**. Ru(II)-*diphenyl*-Pheox derivatives were synthesized from ligand **44** in high yields for each step, for an overall yield from the amino acid up to 60% in yield.

The screening of Ru(II)-*diphenyl*-Pheox catalysts **34r-u** for the carbene transfer reaction is summarized in Table 9. We found that the bulky *p*-nitro-Ru(II)-*diphenyl*-Pheox complex **34t** had higher activity and enantioselectivity compared with Ru(II)-*phenyl*-Pheox **34q**, giving the corresponding product in high yield (78% yield) and good enantioselectivity (83% ee) (Table 9, entry 3). Ru(II)-*dimethyl*-Pheox catalyst **34s** was also tested for use in the cyclopropanation reaction, however, the enantioselectivity and yield decreased in comparison with **34t**.

Table 9. Screening of various Ru(II)-pheox type catalysts[a].





Cat. 34r-u

34r: R^1 = Ph, R^2 = H
34s: R^1 = CH_3, R^2 = H
34t: R_1 = Ph, R_2 = NO_2
34u: R_1 = Ph, R_2 = OMe

Entry	Cat **3**	Yield[%][a)]	d.r[b)]	-ee [%][c)]
1	**34r**	75	95:5	79
2	**34s**	72	92:8	75
3	**34t**	**78**	**90:10**	**83**
4	**34u**	70	90:10	62

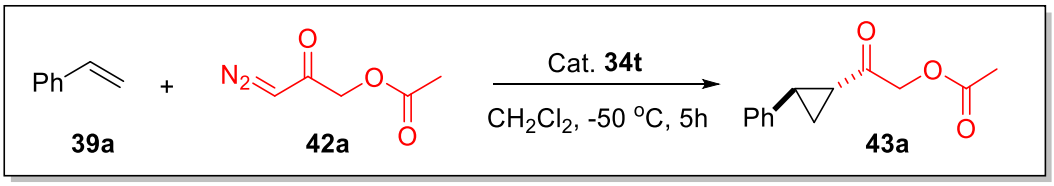
[a)] Isolated yield. [b)] Determined by ^{1}H NMR analysis.

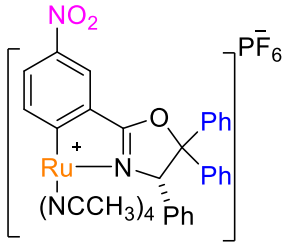
[c)] Determined by chiral HPLC analysis.

4.2.2 Optimization conditions

Next, we optimized the reaction using *p*-nitro-Ru(II)-*diphenyl*-Pheox **34t** as the catalyst in various solvents and temperatures as shown in Table 10. Dichloromethane was the best solvent among those examined, and the catalytic cyclopropanation proceeded at –50 °C to give the highest yield (85%) with excellent enantioselectivity (95% ee) (Table 10, entry 12). Although diethyl ether (Et_2O) was a more efficient solvent for diastereoselectivity, its use resulted in a very low yield (Table 10, entry 1).

Table 10. Optimization of the reaction conditions.





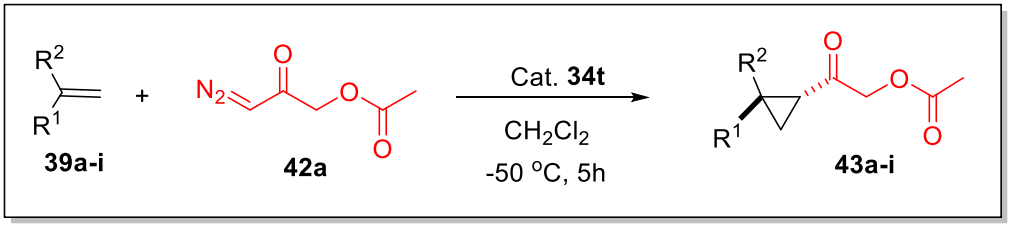
Cat. 34t

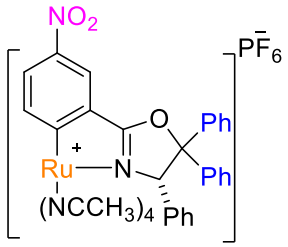
Entry	Solvent	Temp. [°C]	Yield [%][a)]	d.r[b)]	-ee [%][c)]
1	Et_2O	RT	23	99:1	90
2	CH_2Cl_2/ Et_2O	RT	60	95:5	77
3	Acetone	RT	60	99:1	80
4	EDC[d)]	RT	75	90:10	60
5	1,4 Dioxane	RT	70	95:5	82
6	Diglyme	RT	65	86:14	68
7	Diisopropyl ether	RT	62	90:10	80
8	CH_2Cl_2	RT	78	90:10	83
9	CH_2Cl_2	0	80	95:1	84
10	CH_2Cl_2	-10	80	99:1	88
11	CH_2Cl_2	-30	82	99:1	90
12	**CH_2Cl_2**	**-50**	**85**	**99:1**	**95**
13	CH_2Cl_2	-70	85	99:1	92

a) Isolated yield. b) Determined by ^1H NMR analysis, the enantioselectivty for trans product only. c) Determined by chiral HPLC analysis. d) 1,2-Dichloroethane.

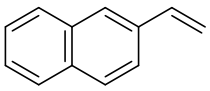
4.2.3 Asymmetric cyclopropanation of various olefins

Table 11. Asymmetric cyclopropanation of various olefins.





Cat. 34t

Entry	**43a-i**	Yield[%][b]	d.r[c]	-ee [%][d]
1*	**39a**: R^1 = Ph, R^2 = H	85	99:1	95
2*	**39b**: R^1 = 4-CH_3-C_6H_4, R^2 = H	79	98:2	96
3*	**39c**: R^1 = 4-OMe-C_6H_4, R^2 = H	62	97:3	83
4*	**39d**: R^1 = 4-*t*Bu- C_6H_4, R^2 = H	72	98:2	91
5*	**39e**: R^1 = 4-Cl-C_6H_4, R^2 = H	95	97:3	98
6*	**39f**: R^1 = 3- CH_3-C_6H_4, R^2 = H	85	91:9	92
7*	**39g**: R^1 = 2-Cl-C_6H_4, R^2 = H	92	99:1	97
8	**39h**: 	90	90:10	97
9	**39i**: R^1 = Ph, R^2 = CH_3	55	98:2	85

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis, the enantioselectivity for trans product only.
[c] Determined by chiral HPLC analysis.

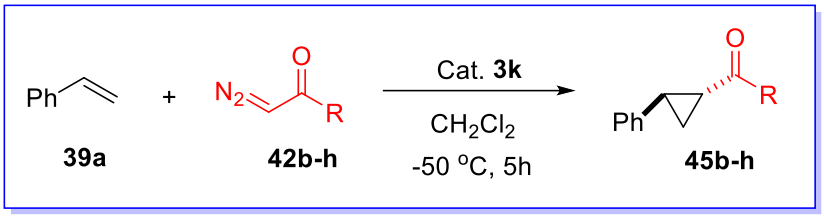
Encouraged by the above results, we investigated the cyclopropanation of diazo acetoxy acetone **42a** with olefins **39a–j** using *p*-nitro-Ru(II)-*diphenyl*-Pheox **34t** under the optimized conditions. The results are summarized in Table 4. Styrene derivatives having ortho, meta, or para substituents were all tolerated under the reaction conditions (Table 11, entries 2–7). It is

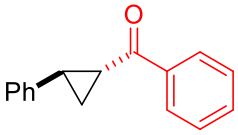
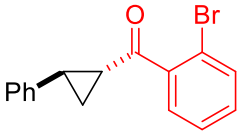
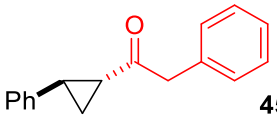
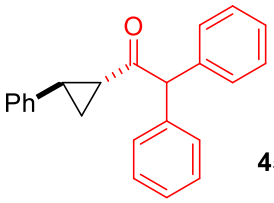
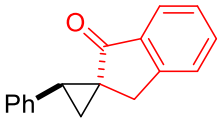
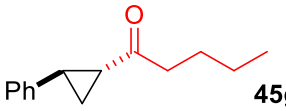
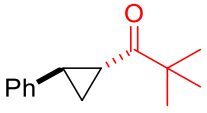
noteworthy that styrenes bearing an electron-withdrawing group at the para position were more effective than those with an electron-rich substituent at that position, due to the strong electrophilic nature (Table 11, entries 2–5). The highest enantioselectivity (98% ee) and yield (95%) were obtained for the styrene bearing a para-Cl substituent (Table 11, entry 5). In contrast, the cyclopropanation of α-methyl substituted styrene afforded the desired product with good enantioselectivity (85% ee) but in only moderate yield (55%) (Table 11, entry 9).

4.2.4 Asymmetric cyclopropanation of various diazo ketones

To consider other functional groups on diazoketone in asymmetric cyclopropanation reaction, various diazo ketones **42b-h** were examined under the optimization conditions above and the results were shown in Table 12. Besides the catalytic asymmetric cyclopropanation of α−diazoacetophenone **45b**[143] and 4**5f**[146] reported before, other various diazo ketones **45c-h** as carbene precursors are first investigated to cyclopropanate and give the coresponding several cyclopropane products in high diastereoselectivity with good enantioselectivity and yield. The optimization conditions are suitable for simple diazoketon in stereoselectivity than bulky diazoketon subtituted aromatic ring (entry 6 compare with entries 1-5).

Table 12. Asymmetric cyclopropanation of various diazo ketones.



Entry	5b-h	Yield [%][a]	d.r[b]	-ee [%][c]
1	 45b	80	96:4	80/75 Trans/Cis
2	 45c	87	99:1	86
3	 45d	70	90:10	89/88 Trans/Cis
4	 45e	85	97:3	65
5	 45f	62	99:1	65
6	 45g	45	95:5	90
7	 45h	60	92:8	41

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis, the enantioselectivty for trans product only.

[c] Determined by chiral HPLC analysis.

4.3. Conclusion

In summary, on the basis of our experimental evidence concerning the stereoinduction mechanism in Ru(II)-*dialkyl*-Pheox complexes catalyzed cyclopropanation, we have designed and developed a highly stereoselective cyclopropanation of alkenes with simple diazo ketone without aromatic substituent **42a** excellent yield (up to 87% yield) with diastereoselectivity (up to 99:1) and enantioselectivity (up to 98% ee). This work contributes to access a variety of new and useful enantioenriched cyclopropyl ketones, variously functionalized cyclopropyl ketones were synthesized in good yields (up to 87% yield) with high trans selectivity and enantioselectivity (up to 90% ee).

CHAPTER 5

Conclusion

Firstly, we developed a novel catalytic phosphonomethylation of *N*-methylaniline and characterized the asymmetric cyclopropylphosphonation reactions of *N,N*-diethylaniline derivatives with diazomethylphosphonates. The catalytic asymmetric cyclopropanation reaction of diazophosphonates and *N*-ethylaniline derivatives by 2,3,4 methoxy-Ru(II)-pheox complexes represent a novel methodology for the synthesis of optically active cyclopropylphosphonate analogues. Furthermore, we showed that the Ru(II)-Pheox complex catalyzes the intermolecular C−H insertion reactions of diethyl diazomethylphosphonate to form an inactivated methyl group in the dimethylaniline derivatives in moderate yields to afford corresponding β-aminophosphonates.

Next, we presented the first catalytic asymmetric synthesis of diacceptor cyclopropylphosphonate reaction, using an α-cyano diazophosphonate reagent and Ru(II)-Pheox derivatives as chiral catalyst in excellent yields (up to 99% yield) and good enantioselectivity. Although the stereoselectivity just got 68%, we are completely believed that Ru(II)-Pheox derivatives are potential to this reactions, hence, conducting more experiments to improve the enantioselectivity is necessary.

Thirdly, on the basis of our experimental evidence concerning the stereoinduction mechanism in Ru(II)-*dialkyl*-Pheox complexes catalyzed cyclopropanation, we have designed and developed a highly stereoselective cyclopropanation of alkenes with simple diazo ketone without aromatic substituent excellent yield (up to 87% yield) with diastereoselectivity (up to 99:1) and enantioselectivity (up to 98% ee). This work contributes to access a variety of new and useful enantioenriched cyclopropyl ketones, variously functionalized cyclopropyl ketones were synthesized in good yields (up to 87% yield) with high trans selectivity and enantioselectivity (up to 90% ee).

In summary, the Ru(II)−Pheox catalyzed asymmetric cyclopropanation reaction proved to be an efficient and straightforward method for the preparation of chiral cyclopropylphosphonation, diaceptor cyclopropylphosphonates, ketone cyclopropanes, which are important intermediates in the synthesis of many biologically active compounds. We believe that Ru(II)−Pheox derivatives will contribute to the progress of not only asymmetric cyclopropanation but also other asymmetric carbene transfer reactions.

CHAPTER 6

Experimental and Analytical Data

6.1 General considerations

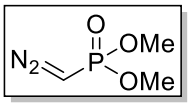
All reactions were performed under an argon atmosphere unless otherwise noted. Dichloromethane (CH_2Cl_2) was purchased from Kanto Chemical Co., Inc. Acetonitrile was purchased from Wako Pure Chemical Industries, Ltd.. All reactions were monitored by thin layer chromatography (TLC), glass plates pre-coated with silica gel Merck KGaA 60 F254, layer thickness 0.2 mm. All the staring materials are commercially available and were used without further purification unless otherwise noted. The products were visualized by irradiation with UV light or by treatment with a solution of phosphomolybdic acid, a solution of a $KMnO_4$ or a solution of *p*-anisaldehyde. Column chromatography was performed using silica gel (Merck, Art. No.7734). ^{1}H NMR (500 MHz, 400 MHz), ^{13}C NMR (126, 100 MHz) and ^{31}P NMR (202, 161 MHz) spectra were recorded on JEOL JNM-ECX500, JEOL JM-ECS400 spectrometer. Chemical shifts are reported in ppm (δ) relative internal tetramethylsilane (0.00 ppm) in $CDCl_3$. Phosphorous chemical shifts are reported in ppm (δ) relative to 85% H_3PO_4 as an external standard (0.00 ppm). Optical rotations were performed with a JASCO P-1030 polarimeter at the sodium D line (1.0 ml sample cell). DART mass (positive mode) analyses were performed on a LC-TOF JMS-T100LP.

6.2 Experimental and analytical data for chapter 2

6.2.1 Synthesis of dialkyl diazomethylphosphonates 33a–c

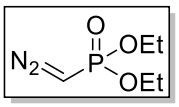
Dialkyl diazomethylphosphonates **33a–b**[120], and **33c**[147] were prepared according to literature procedures.

Dimethyl (diazomethyl)phosphonate



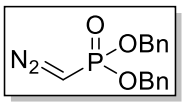
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (d, J = 11.9 Hz, 6H, 2 × OCH_3), 3.77 (d, $^2J_{HP}$ = 10.4 Hz, 1H, CH=N_2). ^{31}P NMR (202 MHz, $CDCl_3$): δ 22.5

Diethyl (diazomethyl)phosphonate



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15-4.05 (m, 4H) ppm, 3.76 (d, 1H, J = 11.3 Hz), 1.29 (t, 6H, J = 14.3 Hz)

Dibenzyl (diazomethyl)phosphonate

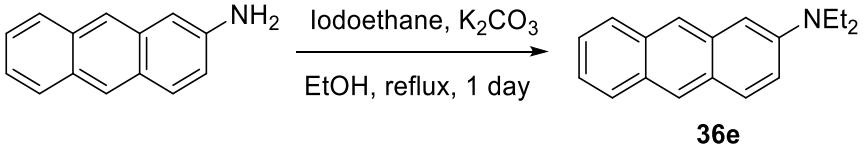


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.31 (m, 10 H), 5.06 (d, J = 8.6 Hz, 4 H), 3.74 (d, J = 11.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 135.8, 128.7, 128.6, 128.0, 68.2, 68.1, 30.2 (^1J(^{13}C, ^{31}P) = 232.2 Hz).

6.2.2 Synthesis of *N,N*-diethylaniline derivatives 36a–g

N,N-Diethylaniline derivatives **36a** and **36b** used in the cyclopropanation reactions were commercially available. **36c**[148], **36d**[149], and **36g**[150] were prepared according to literature procedures. **36e** was modified from procedure[148].

Synthesis of *N,N*-diethylanthracen-2-amine 36e



36e

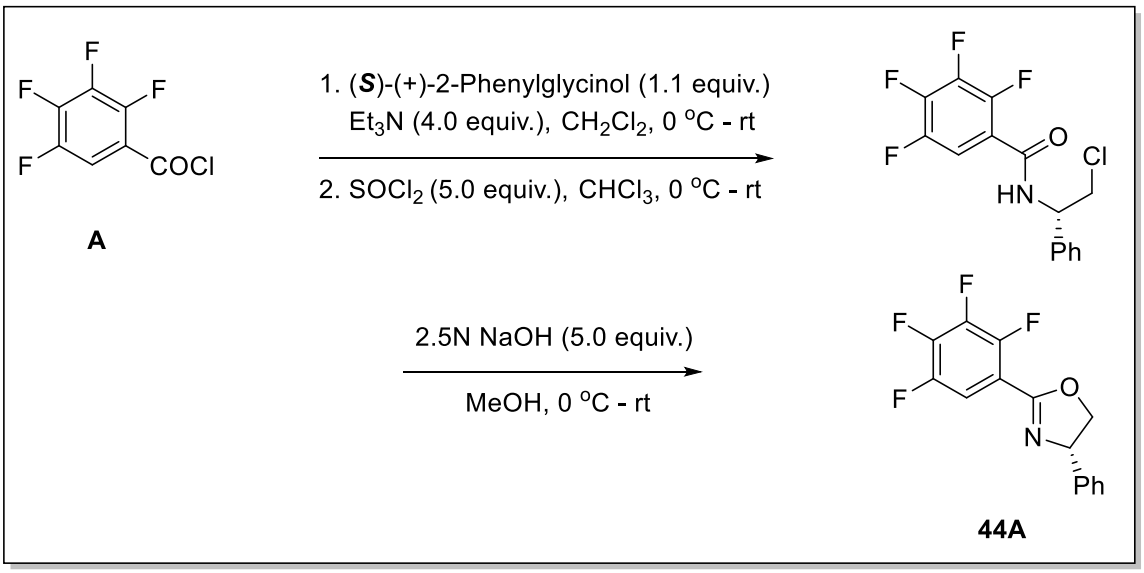
To a mixture of K_2CO_3 (553.0 mg, 4.0 mmol) and anthracen-2-amine (387.0 mg, 2.0 mmol) in EtOH (15 mL) was added iodoethane (0.75 mL, 9.4 mmol). The mixture was refluxed for 1 day. Once the starting material was consumed (monitored by TLC), the reaction mixture was added to distilled water, and the organic product was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated and purified by silica gel column chromatography with Hexane/Ether (30/1 (v/v)) as an eluent to give the desired product **36e**.

***N,N*-diethylanthracen-2-amine 36e** (244.4 mg, 49% yield): Yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 8.11 (s, 1H), 7.90-7.85 (m, 3H), 7.36 (t, J = 7.1 Hz, 1H), 7.29 (t, J = 7.1 Hz, 1H) 7.22 (dd, J = 2.3, J = 9.4 Hz, 1H), 6.94 (d, J = 2.3 Hz, 1H), 3.50 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.31, 133.92, 132.68, 129.59, 129.40, 128.43, 127.62, 127.56, 126.30, 125.40, 123.66, 122.64, 120.50, 101.42, 38.5, 14.77 ppm. IR (neat) 2971, 2927, 1628, 1494,1463, 1351, 876 cm^{-1}. HRMS (DART) calcd for $C_{18}H_{20}N$ $[M+H]^+$: 250.1596 found: 250.1590.

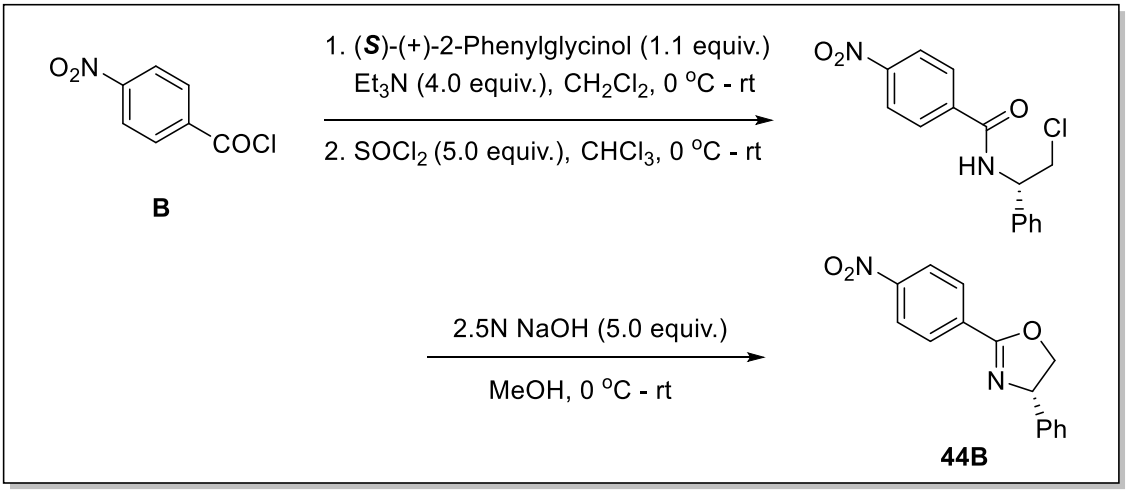
6.2.3 Synthesis of Ru(II)-Pheox ligands

6.2.3.1 (*S*)-4-phenyl-2-(2,3,4,5-tetrafluorophenyl)-4,5-dihydrooxazole



A solution of 2,3,4,5-tetrafluorobenzoyl chloride **A** (638.0 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) was added dropwise in a mixture of (***S***)-(+)-2-phenylglycinol (452.7 mg, 3.3 mmol, 1.1 equiv.) and triethylamine (1.70 mL, 12.0 mmol, 4.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. After the stirring for 2h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and treated with $SOCl_2$ (1.10 mL, 15.0 mmol, 5.0 equiv.) at 0 °C . After stirring for 12 h at room temperature, the solvent and excess $SOCl_2$ were removed under reduced pressure. Sat. $NaHCO_3$ (aq.) (40 mL) was added to the residue with stirring for 10 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. By using a sonicator, the solid residue was dissolved in CH_3OH (12 mL) and 2.5N NaOH (aq.) (600.0 mg, 15.0 mmol, 5.0 equiv.) was added slowly at 0 °C. Then the reaction mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum, followed by addition of water (25 mL) and CH_2Cl_2 (3 x 25 mL) for extraction. The solvent was evaporated under vacuum to afford (***S***)-4-phenyl-2-(2,3,4,5-tetrafluorophenyl)-4,5-dihydrooxazole **44A** (820.6 mg, 94% yield). $[\alpha]_D^{29.4}$ = –36.5 (c 1.01, $CHCl_3$). ^{1}H NMR (125 MHz, $CDCl_3$) δ 4.30 (t, *J* = 8.41 Hz, 1H), 4.82 (dd, *J* = 8.41 Hz, *J* = 10.13 Hz, 1H), 5.43 (dd, *J* = 8.41 Hz, *J* = 10.13 Hz, 1H), 7.26–7.40 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.26, 75.03, 76.86, 77.11, 77.37, 112.27, 112.36, 126.73, 128.00, 128.98, 141.50, 159.52 ppm. ^{19}F ($CDCl_3$)**δ** –153.73, –149.61, –138.17, –133.92 ppm. IR (neat) 3085, 2907, 1610, 1482 cm^{-1}, HRMS (DART) calcd for $C_{16}H_{15}NO_2$ $[M+H]^+$: 296.0693 found: 296.0704.

6.2.3.2 (*S*)-2-(4-nitrophenyl)-4-phenyl-4,5-dihydrooxazole

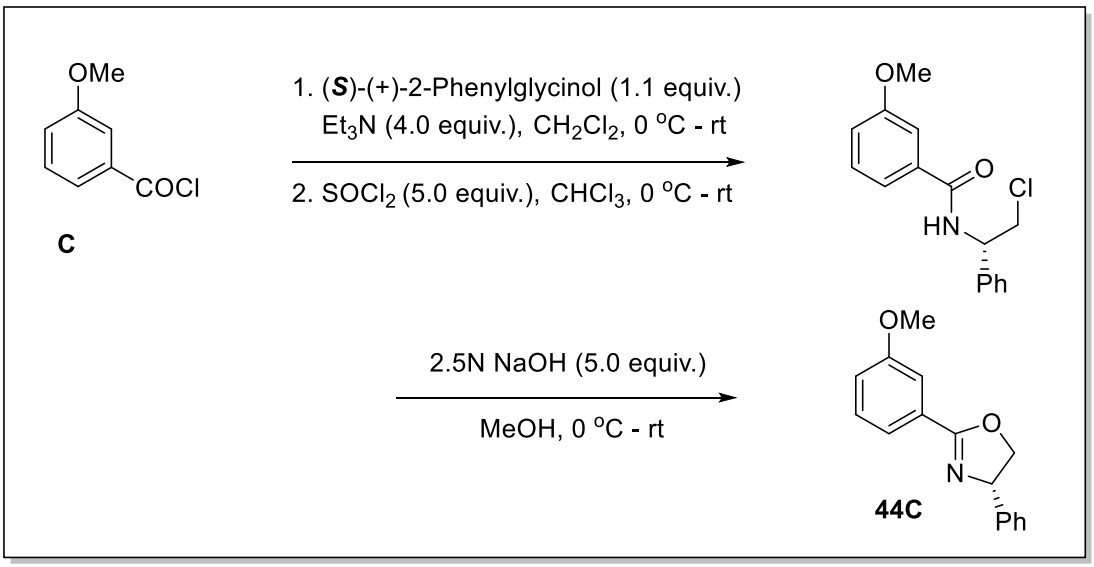


A solution of *4*-nitrobenzoyl chloride **B** (556.7 mg, 1.6 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) was added dropwise in a mixture of (***S***)-(+)-2-phenylglycinol (452.7 mg, 3.3 mmol, 1.1 equiv.) and Et_3N (1.62 mL, 4.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. After the stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and treated with $SOCl_2$ (1.10 mL, 15 mmol, 5.0 equiv.) at 0 °C. After stirring for 24 h at room temperature, the solvent and excess $SOCl_2$ were removed under reduced pressure. Sat. $NaHCO_3$ (aq.) (30 mL) was added to the residue with stirring for 5 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. By using a sonicator, the solid residue was dissolved in MeOH (12 mL) and 2.5N NaOH (aq.) (600.0 mg, 15.0 mmol, 5.0 equiv.) was added slowly at 0 °C , then the reaction mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum, followed by addition of water (25 mL) and CH_2Cl_2 (3 x 25 mL) for extraction. The solvent was evaporated under vacuum to afford (***S***)-2-(4-nitrophenyl)-4-phenyl-4,5- dihydrooxazole **44B** (804.8 mg, 100% yield). $[\alpha]_D^{31.3}$ = –24.8 (c 1.12, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (t, *J* = 8.41 Hz, 1H), 4.88 (dd, *J* = 8.41 Hz, *J* = 10.32 Hz, 1H) 5.45 (dd, *J* = 8.41 Hz, *J* = 10.32 Hz, 1H), 7.28–7.38 (m, 5H), 8.23 (d, *J* = 8.68 Hz, 2H), 8.30 (d, *J* = 8.68 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.50, 75.40, 123.67, 126.80, 128.01, 129.00, 129.60, 133.46, 141.68, 149.72, 162.98 ppm. IR (neat) 3069, 2902, 1646, 1521 cm^{-1}, HRMS (DART) calcd for $C_{15}H_{12}N_2O_3$ $[M+H]^+$: 269.0926 found: 269.0902.

6.2.3.3 (*S*)-2-(3-methoxyphenyl)-4-phenyl-4,5-dihydrooxazole

A solution of 3-methoxybenzoyl chloride **C** (512.0 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) was added dropwise in a mixture of (***S***)-(+)-2-phenylglycinol (452.7 mg, 3.3 mmol, 1.1 equiv.) and triethylamine (1.70 mL, 12.0 mmol, 4.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. After the stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The

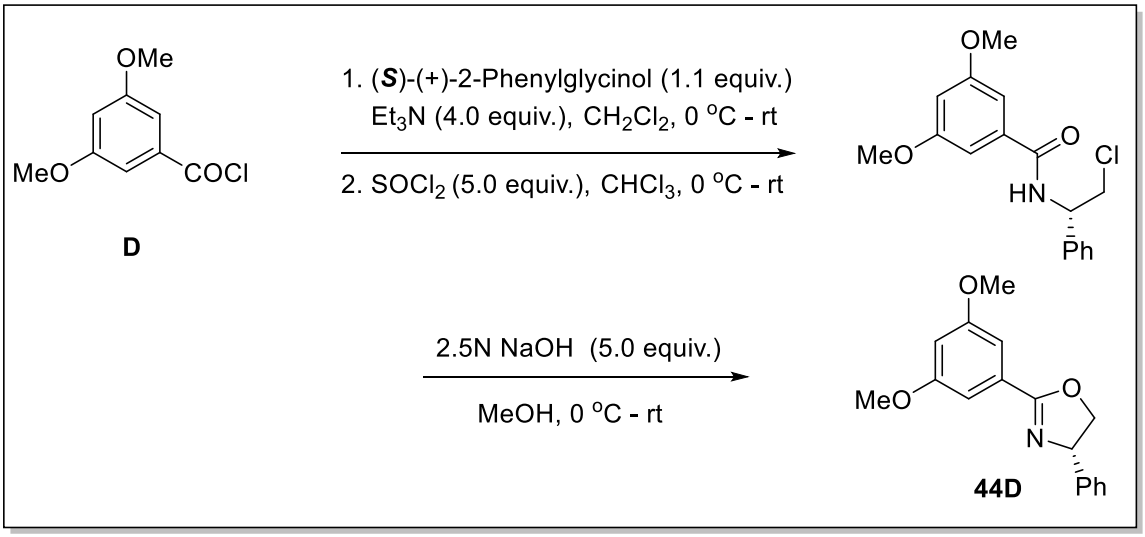
residue was dissolved in $CHCl_3$ (20 mL) and treated with $SOCl_2$ (1.10 mL, 15 mmol, 5.0 equiv.) at 0 °C. After stirring for 12 h at room temperature, the solvent and excess $SOCl_2$ were removed under reduced pressure. Sat. $NaHCO_3$ (aq.) (40 mL) was added to the residue with stirring for 10 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. By using a sonicator, the solid residue was dissolved in MeOH (12 mL) and 2.5N NaOH (aq.) (600.0 mg, 15 mmol, 5.0 equiv.) was added slowly at 0 °C, then the reaction mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum, followed by addition of water (25 mL) and CH_2Cl_2 (3 x 25 mL) for extraction. The solvent was evaporated under vacuum to afford (***S***)-2-(3-methoxyphenyl)-4-phenyl-4,5-dihydrooxazole **44C** (740.0 mg, 97% yield).
$[\alpha]_D^{32.3}$ = –9.8 (c 0.91, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.27(t, *J* = 8.41 Hz, 1H), 4.79 (dd, *J* = 8.41 Hz, *J* = 10.13Hz, 1H), 5.38 (dd, *J* = 8.03 Hz, *J* = 9.94Hz, 1H), 7.06 (dd, *J* = 2.68 Hz, *J* = 8.22Hz, 1H), 7.25–7.37 (m, 6H), 7.58 (s, 1H), 7.62 (d, *J* = 7.64 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.52, 70.24, 75.03, 112.93, 118.44, 121.05, 126.90, 127.77, 128.89, 129.59, 142.47, 159.66, 164.78 ppm.
IR (neat) 3049, 2969, 1606, 1495 cm^{-1}, HRMS (DART) calcd. for $C_{16}H_{15}NO_2$ $[M+H]^+$: 254.1176 found: 254.1171.



6.2.3.4 (*S*)-2-(3,5-dimethoxyphenyl)-4-phenyl-4,5-dihydrooxazole

A solution of *3,5*-dimethoxybenzoyl chloride **D** (602.0 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) was added dropwise in a mixture of (***S***)-(+)-2-phenylglycinol (452.7 mg, 3.3 mmol, 1.1 equiv.) and triethylamine (1.70 mL, 12.0 mmol, 4.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. After the stirring for 4 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and treated with $SOCl_2$ (1.10 mL, 15 mmol, 5.0 equiv.) at 0 °C. After stirring for 12 h at room temperature, the solvent and excess

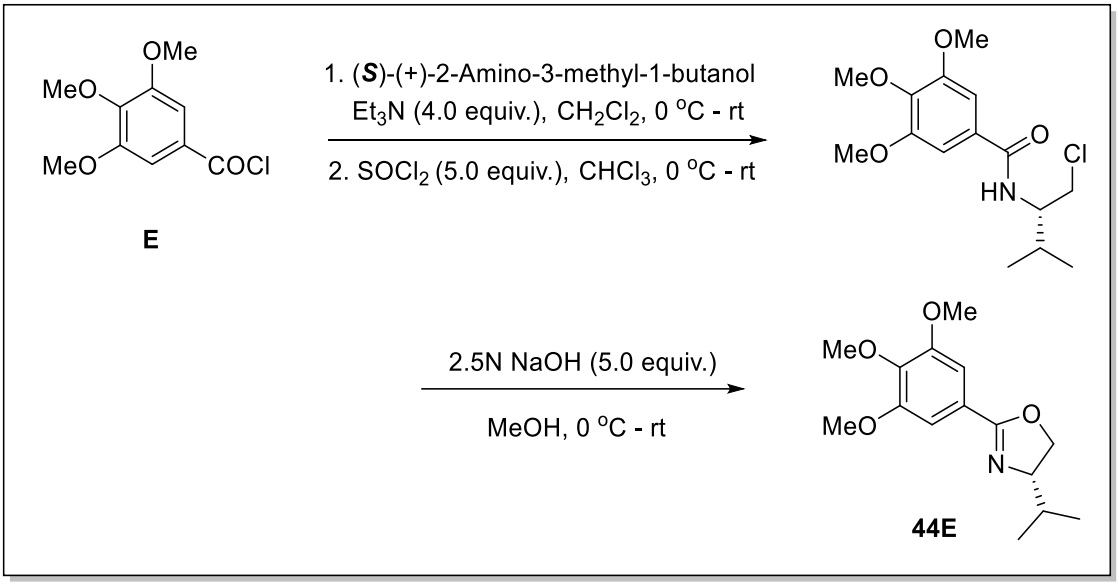
$SOCl_2$ were removed under reduced pressure. Sat. $NaHCO_3$ (aq.) (40 mL) was added to the residue with stirring for 10 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. By using a sonicator, the solid residue was dissolved in MeOH (12 mL) and 2.5 N NaOH (aq.) (600.0 mg, 15.0 mmol, 5.0 equiv.) was added slowly at 0 °C, then the reaction mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum, followed by addition of water (25 mL) and CH_2Cl_2 (3 x 25 mL) for extraction. The solvent was evaporated under vacuum to afford (***S***)-2-(3,5-dimethoxyphenyl)-4-phenyl-4,5-dihydrooxazole **44D** (940 mg, 98% yield). $[\alpha]_D^{32.4}$ = –13.3 (c 1.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 6H), 4.27 (dd, *J* = 8.24, 1H), 4.79 (dd, *J* = 8.24, *J* = 10.22, 1H), 5.38 (dd, *J* = 8.24, *J* = 10.07, 1H), 6.61 (t, *J* = 2.35, 1H), 7.20 (d, *J* = 2.44, 2H), 7.28–7.41 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.70, 70.29, 75.07, 104.79, 106.12, 126.89, 127.79, 128.88, 129.41, 142.37, 160.74, 164.77 ppm. IR (neat) 3395, 2959, 1963, 1648 cm^{-1}, HRMS (DART) caldc for $C_{16}H_{15}NO_2$ $[M+H]^+$: 284.1281 found: 284.1283.



6.2.3.5 (*S*)-4-(tert-butyl)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole

A solution of *3,4,5*-trimethoxybenzoyl chloride **E** (692.0 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) was added dropwise in a mixture of (***S***)-(+)-2-amino-3,3-dimethylbutanol (386.2 mg, 3.3 mmol, 1.1 equiv.) and triethylamine (1.70 mL, 12.0 mmol, 4.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. After the stirring for 12 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and treated with $SOCl_2$ (1.50 mL, 20.0 mmol, 5.0 equiv.) at 0 °C. After stirring for 2h at room temperature, the solvent and excess $SOCl_2$ were removed under reduced pressure. Sat. $NaHCO_3$ (aq.) (40 mL) was added to the residue with stirring for 10 min. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. By using a sonicator,

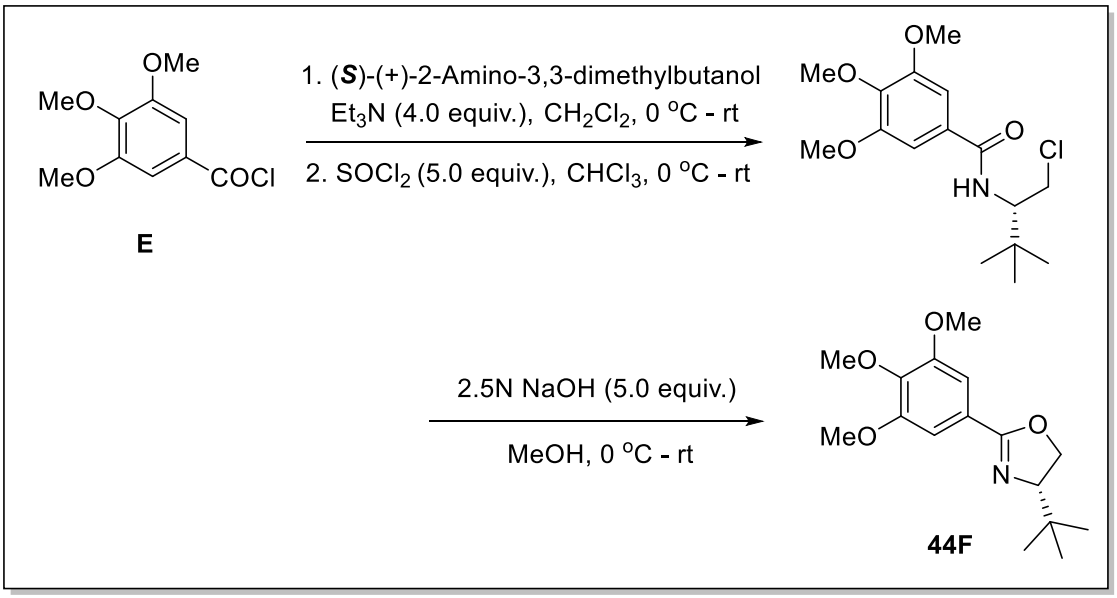
the solid residue was dissolved in methanol (12 mL) and 2.5 N NaOH (aq.) (600.0 mg, 15.0 mmol, 5.0 equiv.) was added slowly at 0 °C, then the reaction mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum followed by addition of water (25 mL) and CH_2Cl_2 (3 x 25 mL) for extraction. The solvent was evaporated under vacuum to afford (***S***)-4-(tert-butyl)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole **44E** (774 mg, 88% yield). $[\alpha]_D^{29.5}$ = –48.7 (c 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 9H), 3.87 (s, 3H), 3.90 (s, 6H), 4.02 (dd, *J* = 7.26 Hz, *J* = 10.13 Hz, 1H), 4.23 (dd, *J* = 7.64 Hz, *J* = 8.41 Hz, 1H), 4.32 (dd, *J* = 8.41 Hz, *J* = 9.94 Hz, 1H), 7.20 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.92, 27.19, 34.15, 53.51, 56.26, 60.93, 68.85, 76.30, 105.46, 123.31, 140.66, 153.03, 162.97 ppm. IR (neat) 3395, 2957, 1963, 1650 cm^{-1}, HRMS (DART) calcd. for $C_{16}H_{15}NO_2$ $[M+H]^+$: 294.1700 found: 294.1698.



6.2.3.6 (*S*)-4-(tert-butyl)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole

A solution of *3,4,5*-trimethoxybenzoyl chloride **F** (692.0 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) was added dropwise in a mixture of (***S***)-(+)-2-amino-3,3-dimethylbutanol (386.2 mg, 3.3 mmol, 1.1 equiv.) and triethylamine (1.70 mL, 12.0 mmol, 4.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. After the stirring for 12 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and treated with $SOCl_2$ (1.50 mL, 20.0 mmol, 5.0 equiv.) at 0 °C. After stirring for 2h at room temperature, the solvent and excess $SOCl_2$ were removed under reduced pressure. Sat. $NaHCO_3$ (aq.) (40 mL) was added to the residue with stirring for 10 min. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. By using a sonicator, the solid residue was dissolved in methanol (12 mL) and 2.5 N NaOH (aq.) (600.0 mg, 15.0 mmol, 5.0 equiv.) was added slowly at 0 °C, then the reaction mixture was stirred for 12 h at

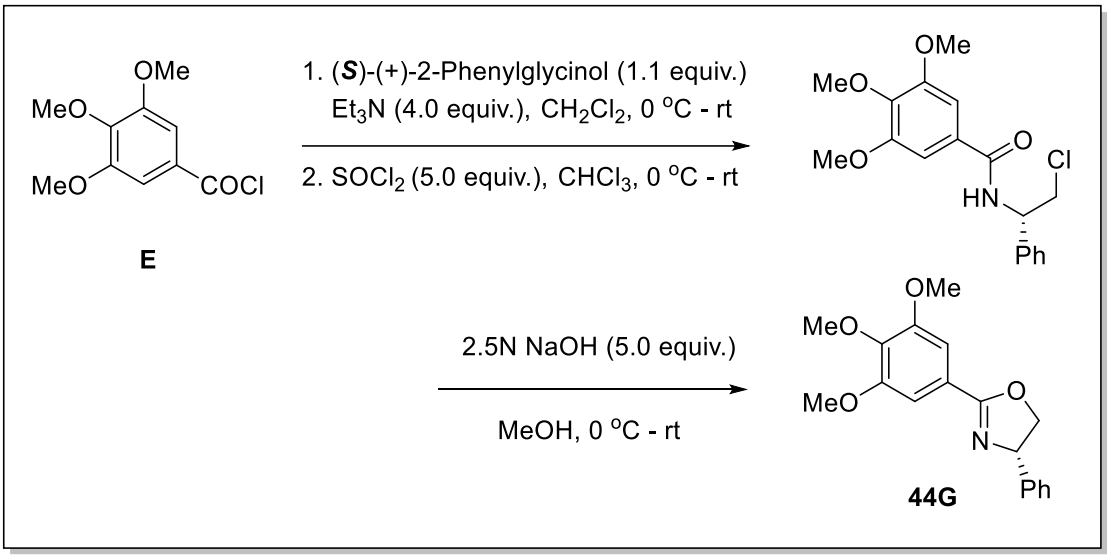
room temperature. The solvent was removed under vacuum followed by addition of water (25 mL) and CH_2Cl_2 (3 x 25 mL) for extraction. The solvent was evaporated under vacuum to afford (***S***)-4-(tert-butyl)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole **44F** (774 mg, 88% yield). $[\alpha]_D^{29.5}$ = –48.7 (c 1.02, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 9H), 3.87 (s, 3H), 3.90 (s, 6H), 4.02 (dd, *J* = 7.26 Hz, *J* = 10.13 Hz, 1H), 4.23 (dd, *J* = 7.64 Hz, *J* = 8.41 Hz, 1H), 4.32 (dd, *J* = 8.41 Hz, *J* = 9.94 Hz, 1H), 7.20 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.92, 27.19, 34.15, 53.51, 56.26, 60.93, 68.85, 76.30, 105.46, 123.31, 140.66, 153.03, 162.97 ppm. IR (neat) 3395, 2957, 1963, 1650 cm^{-1}, HRMS (DART) calcd. for $C_{16}H_{15}NO_2$ $[M+H]^+$: 294.1700 found: 294.1698.



6.2.3.7 (*S*)-4-isopropyl-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole

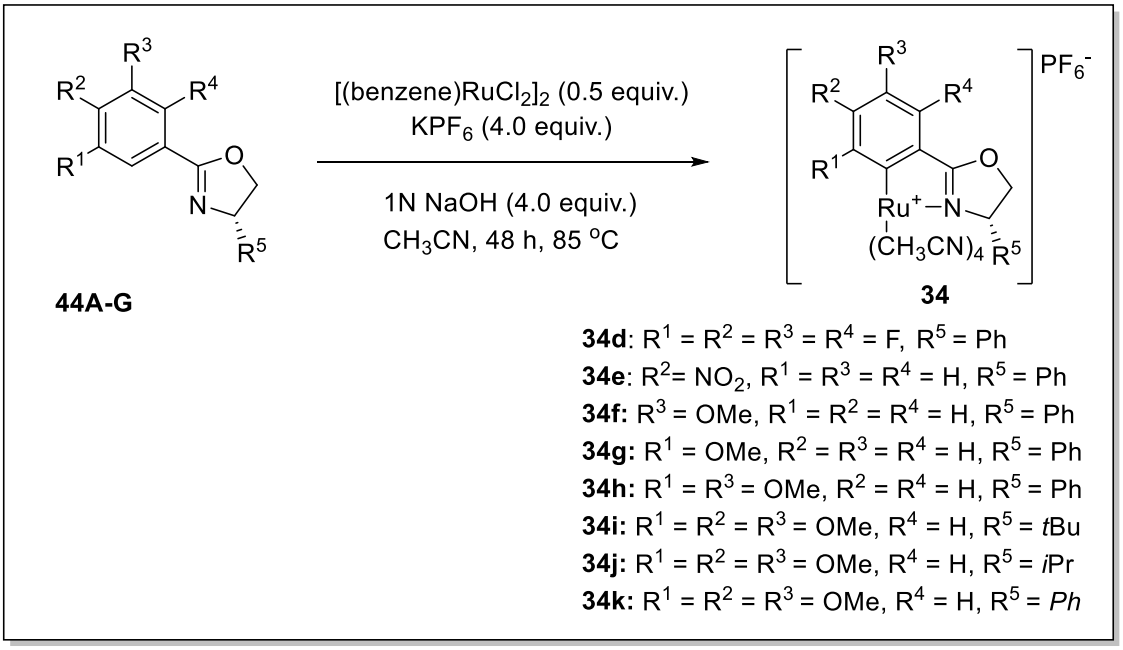
A solution of 3,4,5-trimethoxybenzoyl chloride **G** (692 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (4.0 mL) was added dropwise to a mixture of (***S***)-(+)-2-Amino-3-methyl-1-buta-nol (334.5 mg, 3.3 mmol, 1.1 equiv.) and triethylamine (1.70 mL, 12.0 mmol, 4.0 equiv.) in CH_2Cl_2 (5.0 mL) at 0 °C. After the stirring for 12h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and treated with $SOCl_2$ (1.10 mL, 15 mmol, 5.0 equiv.) at 0 °C. After stirring for 2 h at room temperature, the solvent and excess $SOCl_2$ were removed under reduced pressure. Sat. $NaHCO_3$ (aq.) (40 mL) was added to the residue with stirring for 10 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. By using a sonicator, the solid residue was dissolved in MeOH (12 mL) and 2.5N NaOH (aq.) (600.0 mg, 15 mmol, 4.0 equiv.) was added slowly at 0 °C, then the reaction mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum followed by addition of water (25 mL) and CH_2Cl_2 (3 x 25 mL) for extraction. The solvent was evaporated under vacuum to afford

(***S***)-4-isopropyl-2-(3,4,5-trimethoxyphenyl)-4,5- dihydrooxazole **44G** (770 mg, 92% yield).



$[\alpha]_D^{32.3}$ = –34.5 (c 1.31, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.71, 3H), δ 1.03 (d, *J* = 6.71, 3H), 1.88 (m, 1H), 3.88 (s, 3H), 3.91 (s, 6H), 4.13 (m, 2H), 4.40 (m, 1H), 7.21 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.99, 19.06, 32.06, 32.84, 56.28, 60.96, 70.13, 72.68, 77.16, 105.44, 125.25, 140.68, 153.04, 163.15 ppm. IR (neat) 3395, 2961, 1963, 1648 cm^{-1}, HRMS (DART) caldc for $C_{16}H_{15}NO_2$ $[M+H]^+$: 280.1543 found: 280.1548.

6.2.4 Typical procedures for the synthesis of various Ru(II)-Pheox catalysts



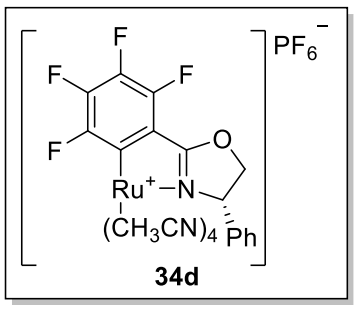
A two necked round bottom flask fitted with a magnetic stirring bar and a reflux condenser was charged with a mixture of the ligand (B, D, F, H, J, L or N) (0.4 mmol, 1.0 equiv.), $[RuCl_2(benzene)]_2$ (0.2 mmol, 0.5 equiv.) and KPF_6 (1.6 mmol, 4.0 equiv.). The reaction flask

was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aq.) (0.8 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 80 °C. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired Ru(II)-Pheox complexes (up to 96% yield).

6.2.5 Analytical data for various Ru(II)-Pheox catalysts

Catalyst **34a** used in the cyclopropanation reaction was commercially available. **34b–c**[123], were prepared according to literature procedures. **34d–k** were modified from procedures[123].

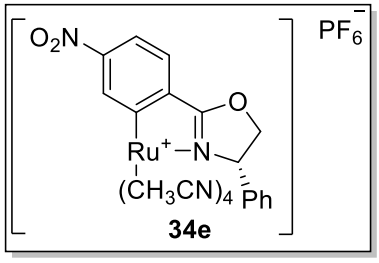
6.2.5.1 Tetrafluoro-Ru(II)-Pheox complex



34d

A two necked round bottom flask fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-4-phenyl-2-(2,3,4,5-tetrafluorophenyl)-4,5-dihydrooxazole **44A** (118.1 mg, 0.4 mmol, 1.0 equiv.), $[RuCl_2(benzene)]_2$ (100.4 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aq.) (0.8 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 85 °C. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired complex **34d** (239.5 mg, 85% yield) as a green solid. ^{1}H NMR (400 MHz, CD_3CN) δ 1.95 (s, 3H, CH_3CN), 2.04 (s, 3H, CH_3CN), 2.18 (s, 3H, CH_3CN), 2.35 (s, 3H, CH_3CN), 4.49 (dd, J = 2.75 Hz, J = 8.7, 1H), 4.89 (t, J = 9.00, 1H), 4.59 (dd, J = 7.26 Hz, J = 8.41, 1H), 5.10-5.20 (m, 3H), 7.31–7.46 (m, 5H). ^{13}C NMR (125 MHz, CD_3CN) δ 0.77, 0.98, 2.92, 3.03, 3.08, 67.60, 78.80, 117.39, 121.63, 122.52, 122.76, 123.34, 128.11, 128.41, 128.50, 140.51, 172.78 ppm. ^{19}F (376 MHz, $CDCl_3$) δ –164.81, –152.22, –139.93, –126.59, –73.67, –72.16 ppm. IR (neat) 3676, 3223, 2941, 2280, 1617, 1473, 837 cm^{-1}.

6.2.5.2 *4-Nitro*-Ru(II)-Pheox complex



34e

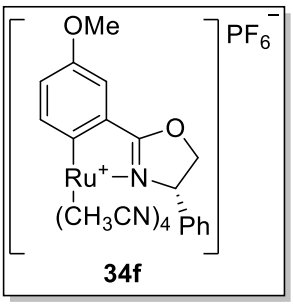
A two necked round bottom flask fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-2-(4-nitrophenyl)-4-phenyl-4,5-dihydrooxazole **44B** (107.3 mg, 0.4 mmol, 1.0 equiv.), $[RuCl_2(benzene)]_2$ (100.4 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aq.) (0.8 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 80 °C. The solvent was removed under reduced pressure and the residue was purified by silica gel column

chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired complex **34e** (271.0 mg, 94% yield) as a green solid. ^{1}H NMR (500 MHz, CD_3CN) δ 2.00 (s, 3H, CH_3CN), 2.13 (s, 3H, CH_3CN), 2.15 (s, 3H, CH_3CN) 2.48 (s, 3H, CH_3CN), 4.61 (t, *J* = 13.28 Hz, 1H), 5.19 (dd, *J* = 10.07 Hz, *J* = 13.43, 2H), 7.31–7.46 (m, 5H), 7.63 (d, *J* = 8.24 Hz, 1H), 7.73(dd, *J* = 2.14, *J* = 8.39 Hz, 1H), 8.59 (d, *J* = 2.44 Hz, 1H). ^{13}C NMR (125 MHz, CD_3CN) δ 0.73, 0.99, 3.00, 3.03, 3.42, 68.51, 78.50, 115.69, 121.88, 122.19, 123.22, 125.80, 128.21, 128.38, 128.48, 131.40, 140.73, 141.61, 147.82, 174.03, 190.57 ppm. IR (neat) ν 2934, 2276, 1621, 837 cm^{-1}.

6.2.5.3 *o-methoxy and p-methoxy* Ru(II)-Pheox 34f and 34g

A two necked round bottom flask fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-2-(3-methoxyphenyl)-4-phenyl-4,5-dihydrooxazole **44C** (202.5 mg, 0.8 mmol, 1.0 equiv.), $[RuCl_2(benzene)]_2$ (200.0 mg, 0.4 mmol, 0.5 equiv.), and KPF_6 (589.0 mg, 3.2 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aq.) (3.2 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 80 ºC. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired two complexes **34f** and **34g**.

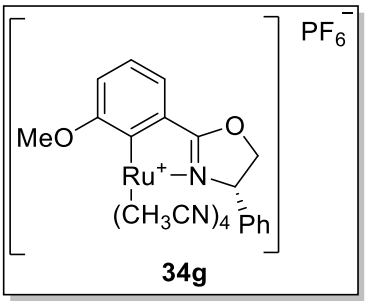
6.2.5.3.1 *o-methoxy* Ru(II)-Pheox 34f



34f

34f (353.0 mg, 77% yield) as a green solid. ^{1}H NMR (400 MHz, CD_3CN) δ 1.99 (s, 3H, CH_3CN), 2.11 (s, 3H, CH_3CN), 2.13 (s, 3H, CH_3CN), 2.40 (s, 3H, CH_3CN), 3.76 (s, 3H, OMe), 4.49 (t, *J* = 8.0 Hz, 1H), 5.09 (dd, 2H), 6.84 (d, *J* = 10.7 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 7.31–7.41 (m, 5H), 7.70 (d, *J* = 7.6, 1H). ^{13}C NMR (125 MHz, CD_3CN) δ 0.88, 3.04, 3.13, 3.38, 54.98, 68.22, 78.05, 110.42, 116.19, 121.27, 121.51, 122.49, 128.09, 128.13, 128.39, 134.44 ppm. IR (neat) 3661, 2931, 2272, 1629, 837 cm^{-1}.

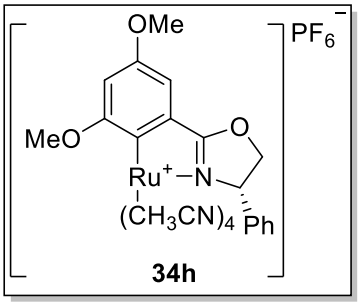
***6.2.5.3.2 p-methoxy* Ru(II)-Pheox 34g**



34g

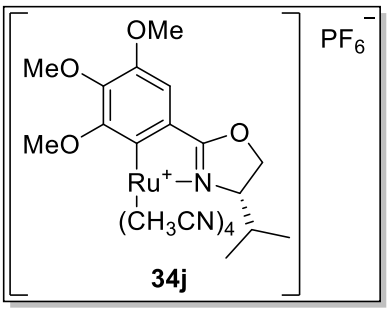
34g (67.0 mg, 13% yield) as a green solid. ^{1}H NMR (400 MHz, CD_3CN) δ 1.94 (s, 3H, CH_3CN), 2.23 (s, 6H, CH_3CN), 2.40 (s, 3H, CH_3CN), 3.9(s, 3H), 4.49 (dd, *J* = 2.75 Hz, *J* = 8.7, 1H), 4.89 (t, *J* = 9.00, 1H), 5.46 (dd, *J* = 2.75 Hz, *J* = 8.7, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 7.29–7.31 (m, 3H), 7.39–7.57 (m, 5H). ^{13}C NMR (100 MHz, CD_3CN) δ 0.78, 0.98, 3.13, 55.53, 72.44, 76.59, 116.21, 122.02, 125.28, 125.81, 128.19, 129.25, 130.01, 141.45, 159.38, 175.06 ppm. IR (neat) 3676, 3223, 2941, 1617, 1468, 837 cm^{-1}.

6.2.5.4 *3,5 - Methoxy* Ru(II)-Pheox complexe 34h



A two necked round bottom flask fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-2-(3,5-dimethoxyphenyl)-4-phenyl-4,5-dihydrooxazole **44D** (141.7 mg, 0.5 mmol, 1.0 equiv.), $[RuCl_2(benzene)]_2$ (125.0 mg, 0.25 mmol, 0.5 equiv.), and KPF_6 (368.0 mg, 2.0 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aq.) (2.0 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 80 °C. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired complex **34h** (235.0 mg, 68% yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3CN) δ 1.96 (s, 3H, CH_3CN), 2.03 (s, 3H, CH_3CN), 2.15 (s, 6H, CH_3CN), 2.38 (s, 3H, CH_3CN), 3.74 (s, 3H, OMe), 3.78 (s, 3H, OMe), 4.49 (dd, *J* = 7.01 Hz, *J* = 7.94, 1H), 5.12 (m, H), 6.40 (d, *J* = 2.44 Hz, 1H), 6.82 (dd, *J* = 2.44 Hz, 1H), 7.30–7.45 (m, 5H). ^{13}C NMR (100 MHz, CD_3CN) δ 0.78, 0.98, 3.10, 55.00, 68.26, 78.00, 102.26, 102.88, 121.67, 128.00, 128.13, 128.42, 135.62, 156.79, 159.13, 170.83, 175.27 ppm. IR (neat) 3661, 2941, 2276, 1591, 841 cm^{-1}.

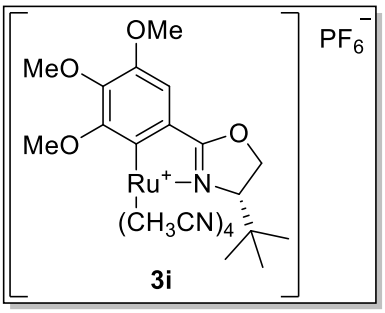
6.2.5.5 ***Iso-propyl-3,4,5 methoxy*-Ru(II)- Pheox 34j**



A two necked round bottom flask fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-4-isopropyl-2-(3,4,5-trimethoxyphenyl)-4,5-dihydroo -xazole **44E** (112.0 mg, 0.4 mmol, 1.0 equiv.), $[RuCl_2(benzene)]_2$ (100.4 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aqua) (1.6 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 80 °C. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired complex **34j** (253.0 mg, 92% yield) as a green solid. ^{1}H NMR (400 MHz, CD_3CN) δ 0.70 (d, *J* = 6.71, 3H, Me), 0.97 (d, *J* = 7.32, 3H, Me), 1.96 (s, 6H, CH_3CN), 2.15 (s, 6H, CH_3CN), 2.56 (m,1H), 3.68 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.03(m, 1H), 4.55 (t, *J* = 9.16 Hz, 1H), 4.65 (dd, *J* = 4.88 Hz, *J* = 9.16, 1H), 6.90 (s, H). ^{13}C NMR (100 MHz, CD_3CN) δ 0.78, 0.98, 3.01, 13.59, 18.48, 29.27, 60.13, 60.40, 68049, 70.04, 107.03, 121.59, 122.37, 129.58, 145.11, 149.23, 163.46, 173.43 ppm. IR (neat) 3660, 2938, 2272, 1633, 841 cm^{-1}.

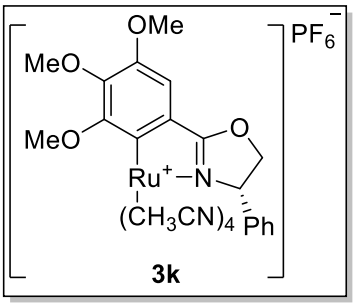
6.2.5.6 ***Tert-butyl-3,4,5 methoxy*-Ru(II)-Pheox 3i**

A two necked round bottom flask fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-4-(tert-butyl)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydro



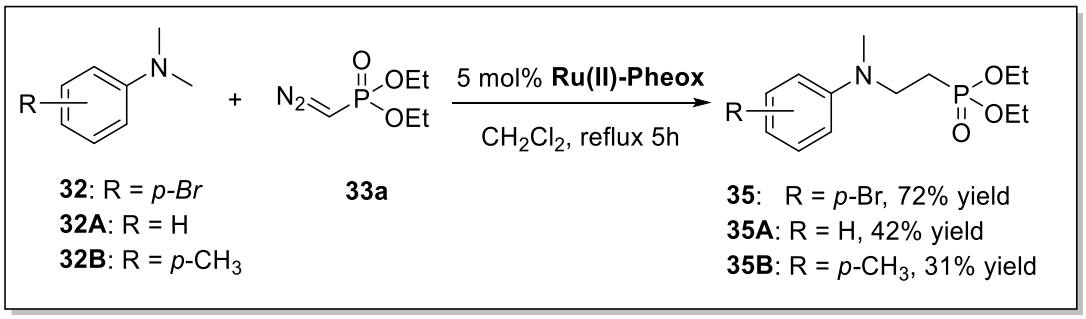
-oxazole **44F** (111.3 mg, 0.4 mmol, 1.0 equiv.), $[RuCl_2(benzene)]_2$ (100.4 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aq.) (0.8 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 90 °C. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired complex **34i** (85.0 mg, 30% yield) as a green solid. ^{1}H NMR (500 MHz, CD_3CN) δ 0.97 (s, 9H, CH_3), 1.96 (s, 6H, CH_3CN), 2.15 (s, 3H, CH_3CN), 2.20 (s, 3H, CH_3CN), 3.71 (s, 3H, OMe), 3.73(m,1H), 3.78 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.48 (t, *J* = 9.36 Hz, 1H), 4.77 (dd, *J* = 3.44 Hz, *J* = 9.17, 1H), 6.91 (s, H). ^{13}C NMR (125 MHz, CD_3CN) δ 0.72, 0.89, 3.08, 25.51, 34.65, 55.76, 60.10, 60.45, 71.99, 72.44, 107.23, 121.30, 123.00, 129.84, 145.22, 149.29, 162.89, 163.42, 174.58 ppm. IR (neat) 3660, 2938, 2268, 1618, 837 cm^{-1}.

6.2.4.7 *3,4,5 methoxy* Ru(II)-pheox complexe 34k



A two necked round bottom flask fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-4-phenyl-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazo-le **44G** (125.3 mg, 0.4 mmol, 1.0 equiv.), $[RuCl_2(benzene)]_2$ (100.4 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.60 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aq.) (1.6 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 80 °C. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired complex **34k** (251.5 mg, 87% yield) as a green solid. ^{1}H NMR (400 MHz, CD_3CN) δ 1.94 (s, 6H, CH_3CN), 2.05 (s, 3H, CH_3CN), 2.16 (s, 3H, CH_3CN), 3.66 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.49 (t, *J* = 6.87 Hz, 1H), 5.11 (m, 2H), 7.03(s, 1H), 7.33–7.44 (m, 5H). ^{13}C NMR (100 MHz, CD_3CN) δ 0.78, 0.99, 3.09, 60.15, 60.37, 68.20, 78.00, 107.40, 121.83, 127.98, 128.11, 128.41, 129.47, 141.64, 145.38, 149.35, 163.48, 164.57, 174.80 ppm. IR (neat) 3653, 3223, 2934, 2272, 1397, 837 cm^{-1}.

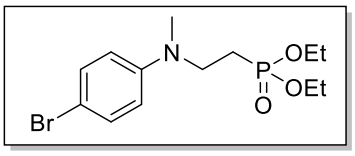
6.2.6 General procedure for catalytic asymmetric phosphonomethylation of *N,N*-dimethylaniline with diazomethylphosphonate



The solution of diazophosphonate **33a** (0.2 mmol) in CH_2Cl_2 (2.0 mL) was slowly added to a mixture of Ru(II)-Pheox catalyst **34** (6.2 mg, 0.005 mmol) and dimethylaniline derivatives **32** (1 mmol) in CH_2C1_2 (2.0 mL) for 4 h under argon atmosphere and the suspended reaction mixture was refluxed at 45 ºC. After the addition completed, the reaction mixture was continuously refluxed for 1 h. The reaction was monitored by TLC. Upon completion, solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc/n-Hexane (1/1) (1% Et_3N) to give the phosphonomethylation products.

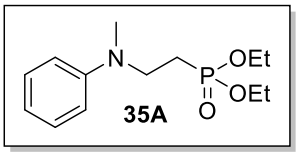
6.2.7 Analytical data for catalytic asymmetric phosphonomethylation of *N,N*-dimethylaniline with diazomethylphosphonate

Diethyl (2-((4-bromophenyl)(methyl)amino)ethyl)phosphonate 35



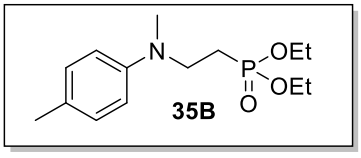
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.85 Hz, 2H), 6.58 (d, *J* = 9.16 Hz, 2H), 4.04–4.18 (m, 4H), 3.60-3.66 (m, 2H), 2.90 (s, 3H), 1.94–2.03 (m, 2 H), 1.33 (t, *J* = 7.02 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.24, 132.07, 114.26, 108.95, 61.85, 61.79, 46.66, 38.15, 21.90, 16.59, 16.53 ppm. ^{31}P NMR (200 MHz, $CDCl_3$) δ 29.98 ppm HRMS (DART) calcd for $C_{13}H_{21}BrNO_3P$ $[M+H]^+$: 350.0521, found: 350.0519.

Diethyl (2-(methyl(phenyl)amino)ethyl)phosphonate 35A[151]



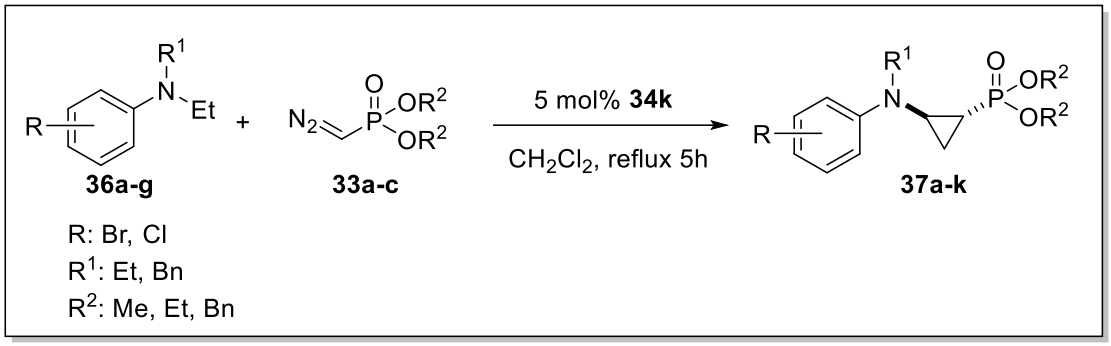
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.32 Hz, 2H), 6.72–6.75 (m, 3H), 4.06–4.16 (m, 4H), 3.64-3.69 (m, 2H), 2.93 (s, 3H), 1.97–2.06 (m, 2 H), 1.34 (t, *J* = 7.02 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.33, 129.48, 117.07, 112.78, 61.83, 61.76, 46.69, 38.12, 21.99, 16.65, 16.60 ppm

Diethyl (2-(methyl(p-tolyl)amino)ethyl)phosphonate 35B[151]



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.41 Hz, 2H), 6.65 (d, *J* = 8.79, 3H), 4.06–4.15 (m, 4H), 3.60–3.65 (m, 2H), 2.88 (s, 3H), 2.25 (s, 3H), 1.96-2.03 (m, 2 H), 1.34 (t, *J* = 7.26 Hz, 6H) ppm.

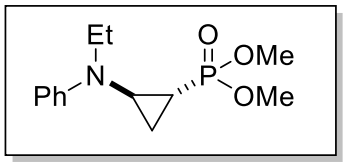
6.2.8 General procedure for catalytic asymmetric cyclopropanation of ethylaniline derivatives with dialkyl diazomethylphosphonates



A solution of diazophosphonate **33a-c** (0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) was slowly added to a mixture of Ru(II)-Pheox catalyst **34k** (3.6 mg, 0.005 mmol) and diethylaniline derivatives **36a-g** (0.5 mmol, 5.0 equiv.) in CH_2C1_2 (2.0 mL) for 4 h under argon atmosphere and the suspended reaction mixture was refluxed at 45 ºC. After the addition completed, the reaction mixture was continuously refluxed for 1 h. The reaction was monitored by TLC. Upon completion, solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc/n-Hexane (1% Et_3N) to give the cyclopropanation products. The *trans*/*cis* ratio was determined from the crude ^{1}H NMR spectra, and the enantioselectivity was determined by chiral HPLC analysis.

6.2.9 Analytical data for catalytic asymmetric cyclopropanation of ethylaniline derivatives with dialkyl diazomethylphosphonates

Dimethyl (2-(ethyl(phenyl)amino)cyclopropyl)phosphonate 37a



A solution of dimethyl diazomethylphosphonate **33b** (30.0 mg, 0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) was slowly added to a mixture of Ru(II)-Pheox catalyst **34k** (7.2 mg, 0.01 mmol) and *N,N*-diethylaniline **36a** (0.16 mL, 1.0 mmol, 5.0 equiv.) in CH_2C1_2 (2.0 mL) for 4 h under argon atmosphere and the suspended reaction mixture was refluxed at 45 ºC. After the addition completed, the reaction mixture was continuously refluxed for 1 h. The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc as an eluent to give the cyclopropanation product **37a** in (24.8 mg, 46% yield) as pale yellow oil.

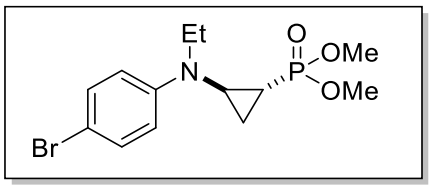
The *ee* value was determined by HPLC analysis. Column (Chiral OJ-H), UV detector 254 nm, eluent: Hexane/IPA = 20/1, Flow rate: 1 ml/min, tR = 21.8 min (major product), 23.9 min (minor product). 93% trans *ee*. $[\alpha]_D^{21}$ = −19.1 (c = 0.44, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2H, **Ph**), 6.99 (d, *J* = 9.6 Hz, 2H, **Ph**), 6.81 (dd, *J* = 7.1, 7.1 Hz, 1H, **Ph**), 3.82 (d, ^3J(P, H) = 11.1 Hz, 3H, O**Me**), 3.79 (d, ^3J(P, H) = 10.7 Hz, 3H,

O**Me**), 3.46 (m, 2H, 8 peaks, N-C**H₂**), 2.92 (dddd, *J* = 4.2, 4.2, 6.9, ^{3}J(P, H) = 10.7 Hz, 1H, N-C**H** (cyclopropane)), 1.48–1.41 (m, 1H, P-C**H** (cycloprop -ane)), 1.21–1.41 (m, 1H, C-C**H** (cyclopropane)), 1.11 (t, *J* = 6.9 Hz, 3H, C**H₃**), 1.13–1.07 (m, 1H, C-C**H** (cyclopropane)) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.60, 131.80, 116.76, 110.48, 62.17 ($^{2}J_{PC}$ = 6.0 Hz), 62.00 ($^{2}J_{PC}$ = 7.2 Hz), 46.10, 35.53 ($^{2}J_{PC}$ = 2.4 Hz), 16.66 ($^{2}J_{PC}$ = 2.4 Hz), 14.00 ($^{1}J_{PC}$ = 122.4 Hz), 11.32 ppm. ^{31}P NMR (161 MHz, $CDCl_3$) δ 27.48 ppm.

HRMS (DART) calcd for $C_{13}H_{21}NO_3P$ $[M+H]^+$: 270.1259, found: 270.1257.

Dimethyl (2-((4-bromophenyl)(ethyl)amino)cyclopropyl)phosphonate 37b

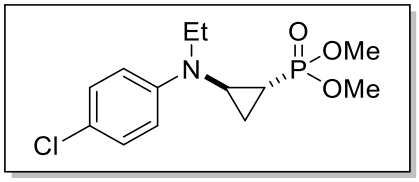


37b was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 4-bromo-*N,N*-diethylaniline **36b** (114.0 mg, 0.5 mmol) with dimethyl diazomethylphosphonate **33b** (15.0 mg, 0.1 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (1% TEA) as an eluent to give the cyclopropanation product **37b** in (17.1 mg, 49% yield) as a pale yellow oil. The *ee* value was determined by HPLC analysis. Column (Chiral OJ-H), UV detector 254 nm, eluent: Hexane/IPA = 20/1, Flow rate: 1 ml/min, tR = 20.9 min (major product), 22.7 min (minor product). 96% trans *ee*. $[\alpha]_D^{25}$ = −6.5 (c = 0.70, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 9.2 Hz, 2H, **Ph**), 6.86 (d, *J* = 9.2 Hz, 2H, **Ph**), 3.82 (d, ^{3}J(P, H) = 10.7, 3H, O**Me**), 3.79 (d, ^{3}J(P, H) = 10.7, 3H, O**Me**), 3.47-3.39 (m, 2H, N-C**H₂**), 2.89 (dddd, *J* = 4.2, 4.2, 6.9, ^{3}J(P, H) = 11.1 Hz, 1H, N-C**H** (cycloprop -ane)), 1.44 (dddd, *J* = 5.0, 6.9, 6.9, ^{2}J(P, H) = 13.38 Hz, 1H, P-C**H** (cyclopropane)), 1.15 (m, 1H, C-C**H** (cyclopropane)), 1.09 (t, *J* = 7.1 Hz, 3H, C**H₃**), 1.09–1.05 (m, 1H, C-C**H** (cyclopropane)) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.59, 131.86, 116.85, 110.65, 52.93 ($^{2}J_{PC}$ = 6.0 Hz), 52.88 ($^{2}J_{PC}$ = 6.0 Hz), 46.23, 35.45 ($^{2}J_{PC}$ = 2.4 Hz), 14.86 ($^{1}J_{PC}$ = 171.5 Hz), 14.00 ($^{2}J_{PC}$ = 4.8 Hz), 11.39 ppm. ^{31}P NMR (161 MHz, $CDCl_3$) δ 30.31 ppm.

HRMS (DART) calcd for $C_{13}H_{20}BrNO_3P$ $[M+H]^+$: 348.0364, found: 348.0365.

Dimethyl (2-((4-chlorophenyl)(ethyl)amino)cyclopropyl)phosphonate 37c



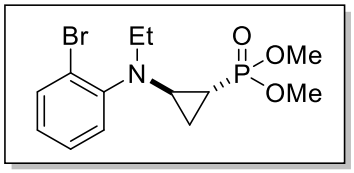
37c was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 4-chloro-*N,N*-diethylaniline **36c** (92.0 mg, 0.5 mmol) with dimethyl diazomethylphosphonate **33b** (15.0 mg, 0.1 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (1% TEA) as an eluent to give the desired product in (10.9 mg, 36% yield) as pale yellow oil. The *ee* value was determined by HPLC analysis. Column (Chiral OJ-H), UV detector 254 nm, eluent: Hexane/IPA = 30/1, Flow rate: 1.0 ml/min,

tR = 22.4 min (major product), 24.2 min (minor product). 94% trans *ee*. $[\alpha]_D^{25}$ = +12.7 (c = 0.55, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.8 Hz, 2H, **Ph**), 6.90 (d, *J* = 8.8 Hz, 2H, **Ph**), 3.82 (d, ^3J(P, H) = 10.7 Hz, 3H, O**Me**), 3.79 (d, ^3J(P, H) = 11.1 Hz, 3H, O**Me**), 3.47–3.39 (m, 2H, N-C**H$_2$**), 2.89 (dddd, *J* = 4.2, 4.2, 6.9, ^3J(P, H) = 11.1 Hz, 1H, N-C**H** (cyclopropane)), 1.44 (dddd, *J* = 4.6, 6.9, 6.9, ^2J(P, H) = 13.38 Hz, 1H, P-C**H** (cyclo -propane)), 1.19–1.13 (m, 1H, C-C**H** (cyclopropane)), 1.09 (t, *J* = 7.1 Hz, 3H, C**H$_3$**), 1.10–1.05 (m, 1H, C-C**H** (cyclopropane)) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.20, 128.98, 123.48, 116.46, 52.98 ($^2J_{PC}$ = 4.8 Hz), 52.89 ($^2J_{PC}$ = 6.0 Hz), 46.40, 35.54, 15.54 ($^1J_{PC}$ = 174.5 Hz), 14.00 ($^2J_{PC}$ = 4.80 Hz), 11.39 ppm. ^{31}P NMR (161 MHz, $CDCl_3$) δ 30.25 ppm.

HRMS (DART) calcd for $C_{13}H_{20}ClNO_3P$ $[M+H]^+$: 304.0869, found: 304.0870.

Dimethyl (2-((2-bromophenyl)(ethyl)amino)cyclopropyl)phosphonate 37d

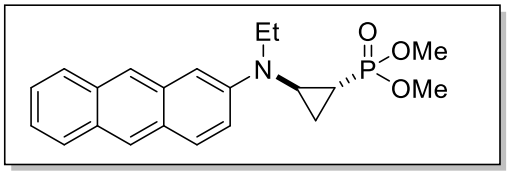


37d was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 2-bromo-*N,N*-diethylaniline **36d** (114.0 mg, 0.5 mmol) with dimethyl diazomethylphosphonate **33b** (15.0 mg, 0.1 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (1% TEA) as an eluent to give the cyclopropanation product in (10.5 mg, 30% yield) as colourless oil. The *ee* value was determined by HPLC analysis. Column (Chiral OJ), UV detector 210 nm, eluent: Hexane/IPA = 20/1, Flow rate: 1.0 ml/min, tR = 6.6 min (major product), 9.4 min (minor product). 93% trans *ee*. $[\alpha]_D^{21}$ = –8.7 (c = 0.75, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.52 (m, 1H, **Ph**), 7.28–7.27 (m, 2H, **Ph**), 6.96–6.93 (m, 1H, **Ph**), 3.72 (d, ^3J(P, H) = 10.7 Hz, 3H, O**Me**), 3.67 (d, ^3J(P, H) = 10.7 Hz, 3H, O**Me**), 3.21 (m, 2H, 8peaks, N-C**H$_2$**), 3.04 (dddd, *J* = 4.0, 4.0, 6.5, ^3J(P, H) = 10.7 Hz, 1H, N-C**H** (cyclopropane)), 1.28-1.25 (m, 1H, P-C**H** (cyclopropane)), 1.10 (t, *J* = 7.1 Hz, 3H, C**H$_3$**) , 1.04-1.00 (m, 2H, C-C**H$_2$** (cyclopropane)) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.19, 135.57, 127.93, 125.33, 125.31, 121.56, 52.69 ($^2J_{PC}$ = 6.0 Hz), 52.64 ($^2J_{PC}$ = 6.0 Hz), 49.83, 37.93 ($^2J_{PC}$ = 2.4 Hz), 14.49 ($^1J_{PC}$ = 125.96 Hz), 13.48 ($^2J_{PC}$ = 6.0 Hz), 11.86 ppm. ^{31}P NMR (161 MHz, $CDCl_3$) δ 31.25 ppm

HRMS (DART) calcd for $C_{13}H_{20}BrNO_3P$ $[M+H]^+$: 348.0364, found: 348.0364.

Dimethyl (2-(anthracen-2-yl(ethyl)amino)cyclopropyl)phosphonate 37e



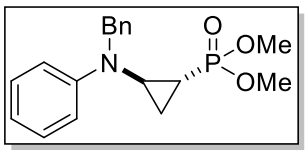
37e was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of *N,N*-diethylanthracen-2-amine **36e** (125.0 mg, 0.5 mmol) with dimethyl

diazomethylphosphonate **33b** (15.0 mg, 0.1 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (1% TEA) as an eluent to give the cyclopropanation product in (15.9 mg, 43% yield) as yellow solid. The *ee* value was determined by HPLC analysis. Column (Chiral IE), UV detector 270 nm, eluent: Hexane/IPA = 8/2, Flow rate: 1.0 ml/min, tR = 23.1 min (minor product), 26.4 min (major product). 94% trans *ee*. $[\alpha]_D^{25}$ = –14.5 (c = 0.74, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H, **Ph**), 8.20 (s, 1H, **Ph**), 7.93–7.88 (m, 3H, **Ph**), 7.42–7.32 (m, 4H, **Ph**), 3.88 (d, ^3J(P, H) = 10.7 Hz, 3H, O**Me**), 3.83 (d, ^3J(P, H) = 11.1 Hz, 3H, O**Me**), 3.61 (q, *J* = 7.1 Hz, 2H, N-C**H₂**), 3.11 (dddd, *J* = 4.2, 4.2, 6.9, ^3J(P, H) = 11.1 Hz, 1H, N-C**H** (cyclopropane)), 1.58–1.52 (m, 1H, P-C**H** (cyclopropane)), 1.30–1.23 (m, 1H, C-C**H** (cyclopropane)), 1.19–1.14 (m, 1H, , C-C**H** (cyclopropane)), 1.17 (t, *J* = 7.1 Hz, 3H, C**H₃**) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.76, 133.16, 132.45, 130.14, 129.13, 128.31, 127.70, 127.62, 125.93, 125.37, 124.03, 123.57, 119.44, 108.65, 52.95 ($^2J_{PC}$ = 6.0 Hz), 52.89 ($^2J_{PC}$ = 6.0 Hz), 46.55, 35.52, 14.85 ($^1J_{PC}$ = 157.2 Hz), 13.97 ($^2J_{PC}$ = 4.8 Hz), 11.80 ppm. ^{31}P NMR (161 MHz, $CDCl_3$) δ 30.55 ppm.

HRMS (DART) calcd for $C_{21}H_{25}NO_3P$ $[M+H]^+$: 370.1572, found: 370.1571.

Dimethyl (2-(benzyl(phenyl)amino)cyclopropyl)phosphonate 37i

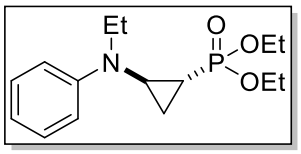


37i was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of *N*-benzyl-*N*-ethylaniline **36g** (158.0 mg, 0.75 mmol) with dimethyl diazomethylphosphonate **33b** (22.5 mg, 0.15 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (1% TEA) as an eluent to give the cyclopropanation product in (13.9 mg, 28% yield) as pale yellow oil. The *ee* value was determined by HPLC analysis. Column (Chiral IE-3), UV detector 248 nm, eluent: Hexane/IPA = 30/1, Flow rate: 1.1 ml/min, tR = 68.8 min (major product), 72.2 min (minor product). 99% trans *ee*. $[\alpha]_D^{25}$ = –11.3 (c = 0.7, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2H, **Ph**), 7.23–7.20 (m, 3H, **Ph**), 7.16–7.15 (m, 2H, **Ph**), 6.95–6.93 (m, 2H, **Ph**), 6.81–6.78 (m, 1H, **Ph**), 4.6 (s, 2H, N-C**H₂**), 3.76 (d, ^3J(P, H) = 6.9 Hz, 3H, O**Me**), 3.74 (d, ^3J(P, H) = 6.5 Hz, 3H, O**Me**), 3.09 (dddd, *J* = 4.2, 4.2, 6.9, ^3J(P, H) = 11.1 Hz, 1H, N-C**H** (cyclopropane)), 1.43 (dddd, *J* = 5.0, 6.9, 6.9, ^2J(P, H) = 13.38 Hz, 1H, P-C**H** (cyclopropane)), 1.26–1.13 (m, 2H, C-C**H₂** (cyclopropane)) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.30, 139.36, 129.14, 128.73, 127.07, 126.47, 118.65, 114.63, 56.86, 52.91 ($^2J_{PC}$ = 6.0 Hz), 52.87 ($^2J_{PC}$ = 6.0 Hz), 37.09, 14.65 ($^1J_{PC}$ = 154.75 Hz), 14.04 ($^2J_{PC}$ = 6.0 Hz) ppm. ^{31}P NMR (161 MHz, $CDCl_3$) δ 27.48 ppm

HRMS (DART) calcd for $C_{18}H_{23}NO_3P$ $[M+H]^+$: 332.1416, found: 332.1414.

Diethyl (2-((4-bromophenyl)(ethyl)amino)cyclopropyl)phosphonate 37g

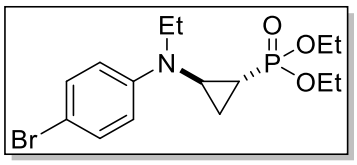


37g was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of *N,N*-diethylaniline **36a** (74.6 mg, 0.5 mmol) with diethyl diazomethylphosphonate **33a** (17.3 mg, 0.1 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (1% TEA) as an eluent to give the desired product in (10.7 mg, 36% yield) as pale yellow oil. The *ee* value was determined by HPLC analysis. Column (Chiral IC-3), UV detector 254 nm, eluent: Hexane/IPA = 20/1, Flow rate: 1.2 ml/min, tR = 23.8 min (major product), 25.5 min (minor product). 93% trans *ee*.

^{1}H NMR (500 MHz, $CDCl_3$) δ7.24 (t, *J* = 8.41 Hz, 2H, **Ph**), 7.00 (d, *J* = 8.41 Hz, 2H, **Ph**), 6.78 (t, *J* = 7.26 Hz, 1H, **Ph**), 4.08–4.18 (m, 4H, OC**H₂**), 3.42–3.48 (m, 2H, N-C**H₂**), 2.87–2.93 (dddd, *J* = 4.2, 4.2, 6.9, ^{3}J(P, H) = 11.1 Hz, 1H, N-C**H** (cyclopropane)), 1.33-1.39 (m, 7H), 1.18–1.05 (m, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.61, 129.11, 118.39, 115.20, 62.16 ($^{2}J_{PC}$ = 6.0 Hz), 62.08 ($^{2}J_{PC}$ = 7.2 Hz), 46.20, 35.66, 16.66 ($^{2}J_{PC}$ = 2.4 Hz), 16.61, 16.37, 14.18 ($^{1}J_{PC}$ = 82.77 Hz), 11.55 ppm.

HRMS (DART) calcd for $C_{15}H_{25}NO_3P$ $[M+H]^+$: 298.1572, found: 298.1570.

Diethyl (2-((4-bromophenyl)(ethyl)amino)cyclopropyl)phosphonate 37h

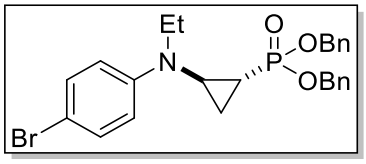


37h was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 4-bromo-*N,N*-diethylaniline **36b** (114.0 mg, 0.5 mmol) with diethyl diazomethylphosphonate **33a** (17.3 mg, 0.1 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (1% TEA) as an eluent to give the cyclopropanation product in (13.5 mg, 36% yield) as pale yellow oil. The *ee* value was determined by HPLC analysis. Column (Chiral IC-3), UV detector 254 nm, eluent: Hexane/IPA = 20/1, Flow rate: 1.2 ml/min, tR = 23.8 min (major product), 25.5 min (minor product). 97% trans *ee*. $[\alpha]_D^{25}$ = −22.7 (c = 0.65, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 9.2 Hz, 2H, **Ph**), 6.88(d, *J* = 9.2 Hz, 2H, **Ph**), 4.23-4.10 (m, 4H, OC**H₂**), 3.43 (m, 2H, 8 peaks, N-C**H₂**), 2.87 (dddd, *J* = 4.2, 4.2, 6.9, ^{3}J(P, H) = 11.1 Hz, 1H), 1.46-1.39 (m, 1H, P-C**H** (cyclopropane)), 1.37 (dt, *J* = 6.9, 14.1 Hz, 6H, ($OCH_2C\mathbf{H_3}$)$_2$), 1.18-1.05 (m, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.55, 131.54, 116.81, 110.60, 62.26 ($^{2}J_{PC}$ = 6.0 Hz), 62.05 ($^{2}J_{PC}$ = 7.2 Hz), 46.10, 35.55, 16.66 ($^{2}J_{PC}$ = 2.4 Hz), 16.61, 16.52, 14.01 ($^{1}J_{PC}$ = 88.35 Hz), 11.37 ppm. ^{31}P NMR (161 MHz, $CDCl_3$) δ 27.48 ppm

HRMS (DART) calcd for $C_{15}H_{24}BrNO_3P$ $[M+H]^+$: 376.0677, found: 376.0676.

Dibenzyl (2-((4-bromophenyl)(ethyl)amino)cyclopropyl)phosphonate 37j



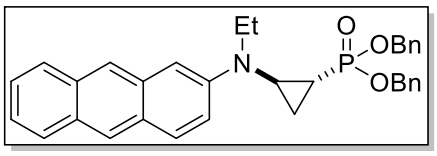
37j was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 2-bromo-*N,N*-diethylaniline **36b** (114.0 mg, 0.5 mmol) with

dibenzyl diazomethylphosphonate **33c** (30.2 mg, 0.1 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (1% TEA) as an eluent to give the cyclopropanation product in (17.5 mg, 35% yield) as a colourless oil. The *ee* value was determined by HPLC analysis. Column (Chiral IC-3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min, tR = 20.2 min (major product), 21.9 min (minor product). 96% trans *ee*. $[\alpha]_D^{17}$ = –16.5 (c = 0.55, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.35 (m, 10H, **Ph**), 7.16–7.14 (m, 2H, **Ph**), 6.82-6.80 (m, 2H, **Ph**), 5.16–4.98 (m, 4H, OC**H₂**), 3.37–3.32 (m, 2H, , N-C**H₂**), 2.86 (dddd, *J* = 4.2, 4.2, 6.9, ^3J(P, H) = 10.7 Hz, 1H), 1.39-1.32 (m, 1H, P-C**H** (cyclopropane)), 1.12–1.04 (m, 2H, C-C**H₂** (cyclopropane)), 1.01 (t, *J* = 7.3 Hz, 3H, C**H₃**) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.70, 136.46 ($^2J_{PC}$ = 4.79 Hz), 136.34 ($^2J_{PC}$ = 6.71 Hz), 131.78, 128.80, 128.77, 128.68, 128.64, 128.13, 128.07, 116.75, 110.48, 67.86 ($^2J_{PC}$ = 5.75 Hz), 67.59 ($^2J_{PC}$ = 6.71 Hz), 46.08, 35.69, 16.08 ($^1J_{PC}$ = 193.61 Hz), 14.00 ($^2J_{PC}$ = 4.79 Hz), 11.32 ppm. ^{31}P NMR (161 MHz, $CDCl_3$) δ 28.99 ppm.

HRMS (DART) calcd for $C_{25}H_{28}BrNO_3P$ $[M+H]^+$: 500.0990, found: 500.0991.

Dibenzyl (2-(anthracen-2-yl(ethyl)amino)cyclopropyl)phosphonate 37k



37k was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of *N,N*-diethylanthracen-2-amine **36e** (125.0 mg, 0.5 mmol) with dibenzyl diazomethylphosphonate **33c** (30.2 mg, 0.1 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (1% TEA) as an eluent to give the cyclopropanation product in (14.1 mg, 27% yield) as a colourless oil. The *ee* value was determined by HPLC analysis. Column (Chiral IE), UV detector 270 nm, eluent: Hexane/IPA = 8/2, Flow rate: 1.5 ml/min, tR = 22.6 min (minor product), 28.8 min (major product). 96% trans *ee*. $[\alpha]_D^{18}$ = +728 (c = 0.70, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H, **Ph**), 8.04 (s, 1H, **Ph**), 7.91 (d, *J* = 8.4 Hz, 1H, **Ph**) 7.81-7.78 (m, 2H, **Ph**), 7.42-7.30 (m, 14H, **Ph**), 5.23-5.05 (m, 4H), 3.54 (q, *J* = 7.26 Hz, 2H), 3.09 (dddd, *J* = 4.2, 4.2, 6.9, ^3J(P, H) = 11.1 Hz, 1H), 1.49 (dddd, *J* = 4.2, 6.5, 6.5, ^3J(P, H) = 13.0 Hz, 1H, P-C**H** (cyclopropane)), 1.25-1.15 (m, 2H, C-C**H₂** (cyclopropane)), 1.10 (t, *J* = 7.3 Hz, 3H, C**H₃**) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.64, 136.52, 136.47 ($^2J_{PC}$ = 6.0 Hz), 136.45 ($^2J_{PC}$ = 6.0 Hz), 136.40, 133.11, 132.36, 130.07, 129.11, 128.77, 128.74, 128.59, 128.26, 128.04, 127.76, 127.55, 125.84, 125.23, 123.96, 123.65, 119.34, 108.40, 67.88 ($^2J_{PC}$ = 6.0 Hz), 67.56 ($^2J_{PC}$ = 6.0 Hz), 46.45, 35.83, 16.05 ($^1J_{PC}$ = 193.13 Hz), 14.38 ($^2J_{PC}$ = 4.8 Hz), 11.74 ppm. ^{31}P NMR (161 MHz, $CDCl_3$) δ 29.37 ppm.

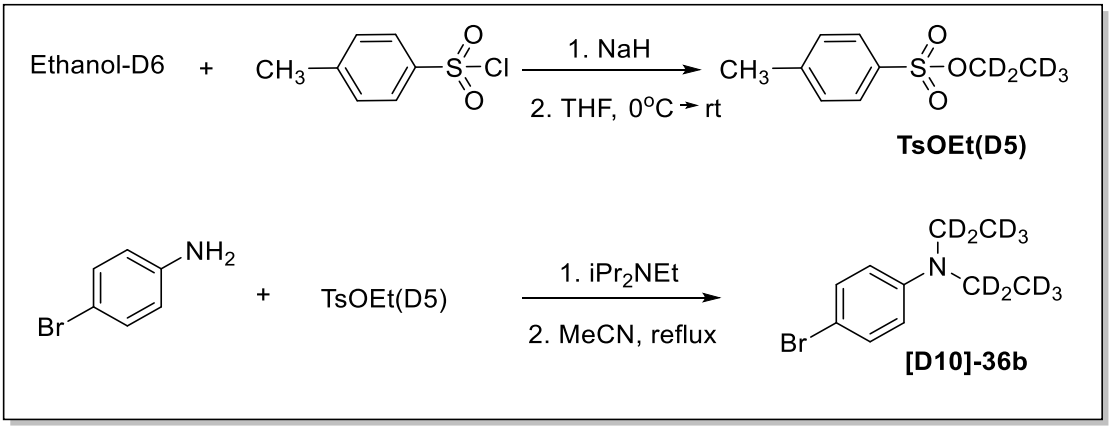
HRMS (DART) calcd for $C_{33}H_{33}NO_3P$ $[M+H]^+$: 522.2198, found: 522.2199.

6.2.10 Cyclopropylphosphonation reaction with hydrogen acceptors

A solution of diazophosphonate **33b** (0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) was slowly added to a mixture of Ru(II)-Pheox catalyst **34k** (3.6 mg, 0.005 mmol), diethylaniline derivative **33b** (0.5 mmol, 5.0 equiv.) in CH_2C1_2 (2.0 mL) and hydrogen acceptors (2.0 equiv.) for 4 h under argon atmosphere and the suspended reaction mixture was refluxed at 45 °C. After the addition completed, the reaction mixture was continuously refluxed for 1 h. The reaction was monitored by TLC. Upon completion, solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc/n-Hexane (1% Et_3N) to give the cyclopropanation products. The *trans*/*cis* ratio was determined from the crude ^{1}H NMR spectra, and the ee value was determined by chiral HPLC analysis.

6.2.11 Synthesis of *N,N'*-deuterated diethylaniline for mechanistic study

N,N'-deuterated diethylaniline **[D10]-36b**[152] was synthesized according to literature procedure from ethanol-D_6.



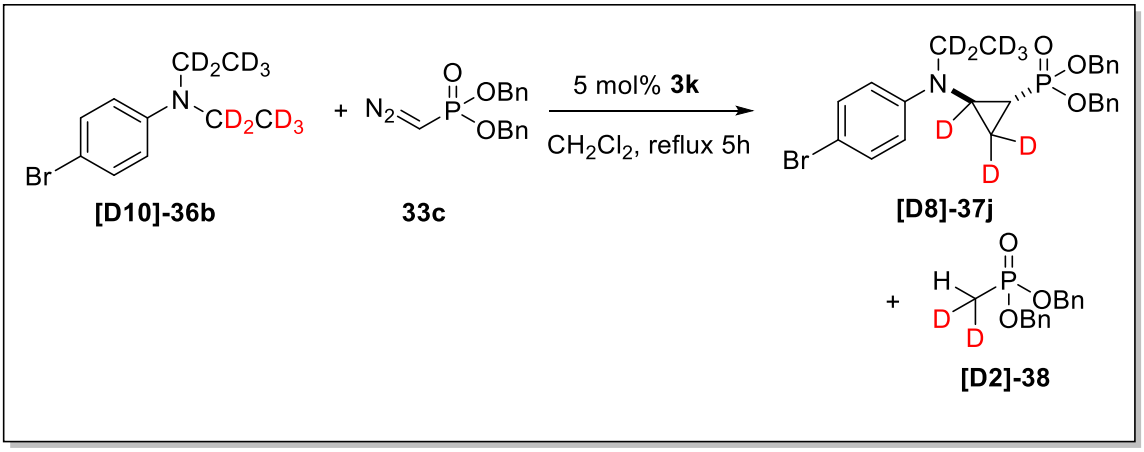
A solution of **ethanol-D_6** (390.8 mg, 7.5 mmol) was added to a solution of sodium hydride (240.0 mg, 10.0 mmol) in THF (3.0 mL) at 0 °C under argon atmosphere and the mixture was stirred at room temperature for 0.5 h. This mixture was slowly added a solution of *p*-toluenesulfonyl chloride (1906.4 mg, 10.0 mmol) in THF (2.0 mL) and was stirred for 1 h at 0 °C. The reaction was quenched with water (20 mL), and organic materials were extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography with Hexane/EtOAc (5/1(v/v)). Product **TsOEt(D5)** was obtained in 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.41 Hz, 2H), 7.34 (d, J = 8.03 Hz, 2H), 2.44 (s, 1H) ppm.

A solution of p-bromoaniline (344 mg, 2 mmol) and N-ethyl-N-isopropylpropan- 2-amine (775.5 mg, 6.0 mmol) were sequentially added to a solution of **TsOEt(D5)** (821.1 mg, 4.0 mmol) in CH_3CN (5 mL) at room temperature under argon atmosphere. The mixture was

refluxed for 4 days. At the end of this period, the solvent was removed, and the residue was purified by silica gel column chromatography with Hexane/EtOAc (10/1(v/v)) to give the desired *N,N'*-deuterated diethylaniline **[D10]-36b** in (362.1 mg 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 9.17 Hz, 2H), 6.52 (d, J = 9.17 Hz, 2H) ppm.

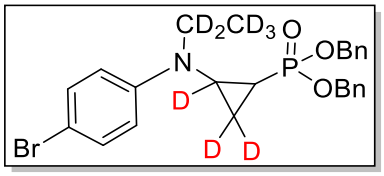
6.2.12 General procedure for catalytic asymmetric cyclopropanation of *N,N'*-deuterated diethylaniline with diazophosphonate

A solution of diazophosphonate **33c** (30.2 mg, 0.1 mmol) in CH_2Cl_2 (2.0 mL) was slowly added to a mixture of Ru(II)-Pheox catalyst (3.6 mg, 0.005 mmol) and *N,N'*-deuterated diethylaniline **[D10]-36b** (119.1 mg, 0.5 mmol) in CH_2C1_2 (2.0 mL) for 4 h under argon atmosphere and the suspended reaction mixture was refluxed at 45 °C. After the addition completed, the reaction mixture was continuously refluxed for 1 h. The progress of the reaction was monitored by TLC. Upon completion, solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc/n-Hexane (1% Et_3N) to give dibenzyl (2-((4-bromophenyl)(ethyl)amino)cyclopropyl)phosphonate **[D8]-37j** in (13.70 mg, 27% yield) as a colourless oil and dibenzyl methylphosphonate **[D2]-38** in (8.34 mg, 30% yield).



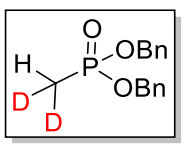
6.2.13 Analytical data for for Catalytic asymmetric cyclopropanation of *N,N'*-deuterated diethylaniline with diazophosphonate

Dibenzyl (2-((4-bromophenyl)(ethyl)amino)cyclopropyl)phosphonate [D8]-37j



^{1}H NMR (500 MHz, $CDCl_3$) δ7.39-7.35 (m, 10H), 7.16-7.14 (m, 2H), 6.82-6.80 (m, 2H), 5.16-4.98 (m, 4H), 1.12-1.04 (m, 1H) ppm.

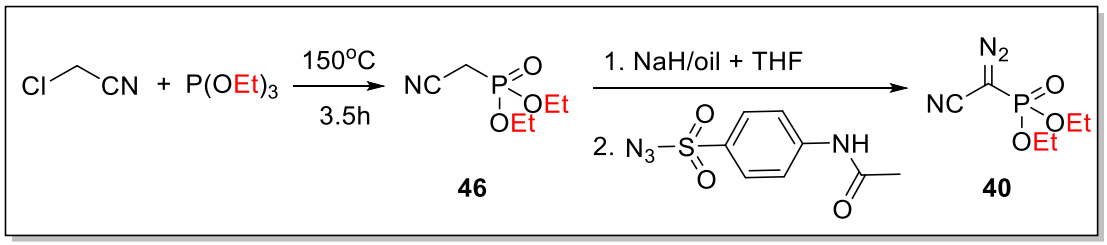
Dibenzyl methylphosphonate [D2]-38



^{1}H NMR (500 MHz, $CDCl_3$) δ7.43 - 7.29 (m, 10H), 5.00 (m, 4H), 1.52 (m, 1H) ppm.

6.3 Experimental and analytical data for chapter 3

6.3.1 Synthesis of dialkyl (cyano(diazo)methyl)phosphonates



Phosphonoacetonitrile diethyl ester **46**: 906 mg (12 mmol) triethyl phosphite were heated to 150 °C. 997 mg (6.0 mmol) chloroacetonitrile were added at 150 °C over a period of 3.5h. Yield: 75%.

(Diethyl cyano(diazo)methyl)Phosphonate **40**: Phosphonoacetonitrile diethyl ester **46** (442.8 mg, 2.5 mmol) was dissolved in 10 mL of dry toluene and NaH (150 mg, 3.75 mmol) was added portion wise, after stirred for 1 h at the 0°C, a solution of *p*-ABSA (620 mg, 2.5 mmol) in 25 mL of dry THF was added dropwise. Then, the reaction mixture was stirred at room temperature for 24 h, after the reaction was completed (monitored by TLC analysis), 50 mL petroleum ether was added, then the precipitate was filtered off, and the filter cake was washed with ether (3 x 50 mL), the filtrate was evaporated and the residue was purified by column chromatography on silica gel (Hex/EA = 2:1 to 2:1), give the **40** as yellow liquid, yield 92%. ^{1}H NMR ($CDCl_3$, 500MHz): δ 4.32–4.16 (m, 4H, OC**H**$_2$CH$_3$) , 1.41(t, 6H, OCH$_2$C**H**$_3$). ^{13}C NMR ($CDCl_3$, 125MHZ): δ 108.5, 64.6, 36.1, 16.0. ^{31}P NMR ($CDCl_3$, 202 MHz): δ 9.3. IR (neat) 2221, 2120, 1271, 1010, 984.

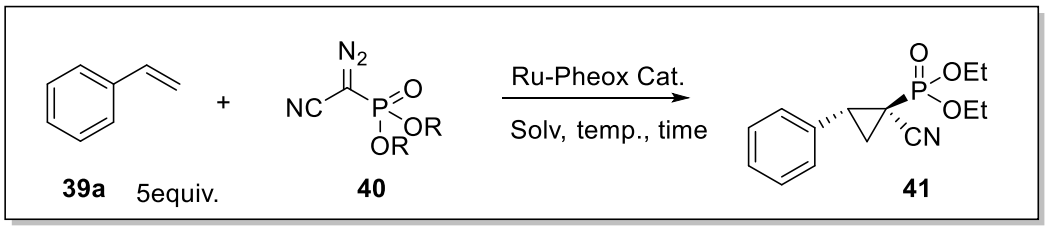
6.3.2 Analytical data for various Ru(II)-Pheox catalysts

All Catalysts **34a** used in the cyclopropanation reaction were synthesized from above (section **5.2.4**).

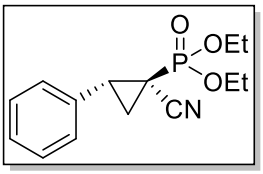
6.3.3 General procedure for catalytic asymmetric cyclopropanation of olefin with diacceptor diazomethyl phosphonates

The solution of diazophosphonate **40** (0.2 mmol) in CH_2Cl_2 (1.0 mL) was slowly added to a mixture of Ru(II)-Pheox catalyst **34** (3.8 mg, 0.006 mmol) and olefins (1.0 mmol) in CH_2C1_2 (1 ml) for 4 h under argon atmosphere at room temperature. After the addition completed, the reaction mixture was then stirred for 1 h at room temperature. The progress of the reaction was monitored by TLC. Upon completion, solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc/n-Hexane to give desired product. The trans/cis ratio was determined from the crude ^{1}H NMR spectra, and the ee value was determined by chiral HPLC analysis.

This compound **41** was prepared according to the typical procedure for asymmetric cyclopropanation reactions between styrene (104.2 mg, 1.0 mmol) and diethyl cyano diazomethylphosphonate **40** (35.6 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/n-Hexane as an eluent to give the desired product in 99% yield as yellow oil, trans/cis = >99:1.



6.3.4 Analytical data for catalytic asymmetric cyclopropanation of olefin with diacceptor diazomethyl phosphonate 41



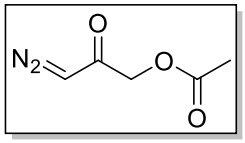
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.30 (m, 3H, ArH), 7.30-7.24 (m, 2H, ArH), 4.33-4.20 (m, 4H, OCH_2CH_3), 3.18-3.05 (m, 1H, CH cyclopropane), 2.10-1.93 (m, 2H, CH_2 cyclopropane), 1.47-1.37 (m, 6H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.1 (d, J = 1.8 Hz), 128.9 (2C), 128.7, 127.0 (2C), 115.7 (d, J = 4.1 Hz), 65.5 (d, J = 6.5 Hz, 2C), 40.8 (d, J = 1.7 Hz), 18.6 (d, J = 3.0 Hz), 17.1 (m, 2C), 15.1 (d, J = 196.2 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz): δ 16.9.

6.4 Experimental and analytical data for chapter 4

6.4.1 Synthesis of various diazo ketones

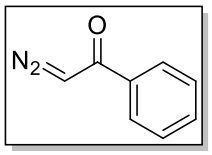
Procedure for the synthesis of diazo ketones **42a**[144], **42b**[153], **42c**[154], **42d**[155], **42e**[156], **42f**[157], **42g**[158], **42h**[159] were prepared according to literature procedures.

Diazo acetoxy acetone 42a



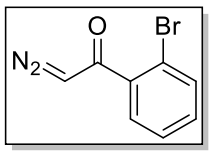
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.58 (s, 1H); 4.62 (s, 2H); 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz), δ 188.90, 169.86, 66.75, 53.25.

2-diazo-1-phenylethan-1-one 42b



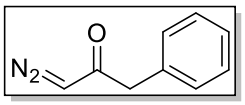
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.72 (m, 2H), 7.57- 7.50 (m, 1H), 7.43 (dd, *J* = 6.8, 4.5 Hz, 2H), 5.93 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4, 136.6, 132.7, 128.7, 126.7, 54.2.

1-(2-bromophenyl)-2-diazoethan-1-one 42c



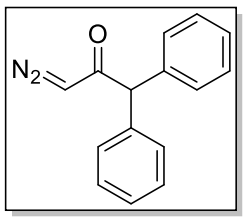
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (m, 1H), 7.45 (d, *J* = 6.9 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.30 (m, 1H), 5.72 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.82, 139.54, 133.71, 131.81, 129.00, 127.51, 119.23, 57.48.

1-diazo-3-phenylpropan-2-one 42d



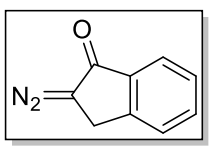
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 2H), 5.17 (s, 1H), 7.25-7.39 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.5, 55.6, 127.7, 129.3, 129.8, 135.4, 193.4

3-diazo-1,1-diphenylpropan-2-one 42e



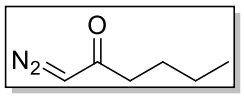
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.45 (m, 10H), 5.23 (s, 1H), 4.92 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.77, 138.95, 129.17, 128.86, 127.49, 62.35, 56.24.

2-diazo-2,3-dihydro-1H-inden-1-one 42f



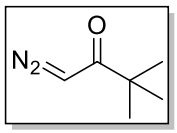
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, J=7.3, 1H); 7.54 (t, J=7.2, 1H); 7.40 (d, J=7.3, 1H); 7.39 (t, J=7.2, 1H); 4.02 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 188.4; 143.2; 137.3; 133.1; 127.8; 125.3; 122.6; 28.6.

1-diazohexan-2-one 42g



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 1H), 2.29 (t, J = 6.8, 2H), 1.10-1.18 (m, 4H), 0.92 (t, J = 4.20, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.48, 54.15, 40.78, 27.15, 22.30, 13.55.

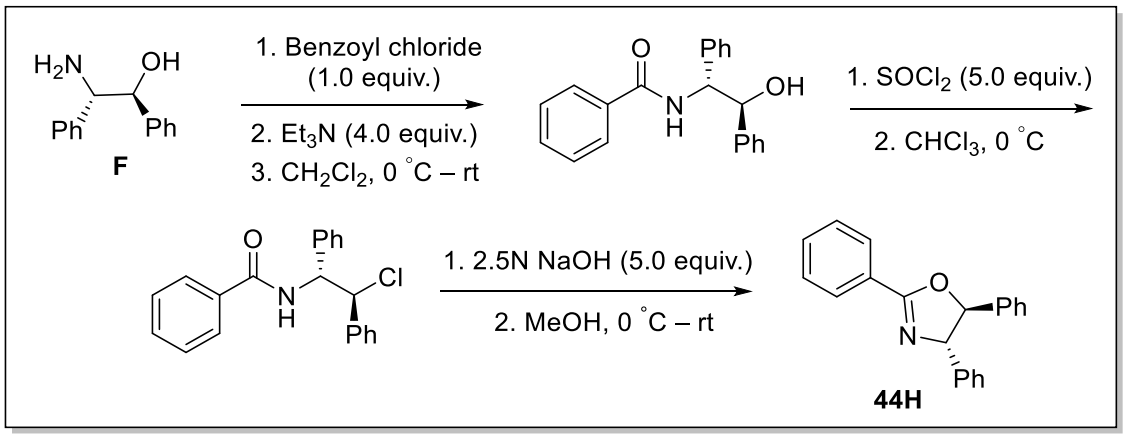
1-diazo-3,3-dimethylbutan-2-one 42h



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (s, 1H), 1.12 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.85, 52.98, 42.48, 26.99

6.4.2 Synthesis of Ru(II)-Pheox ligands

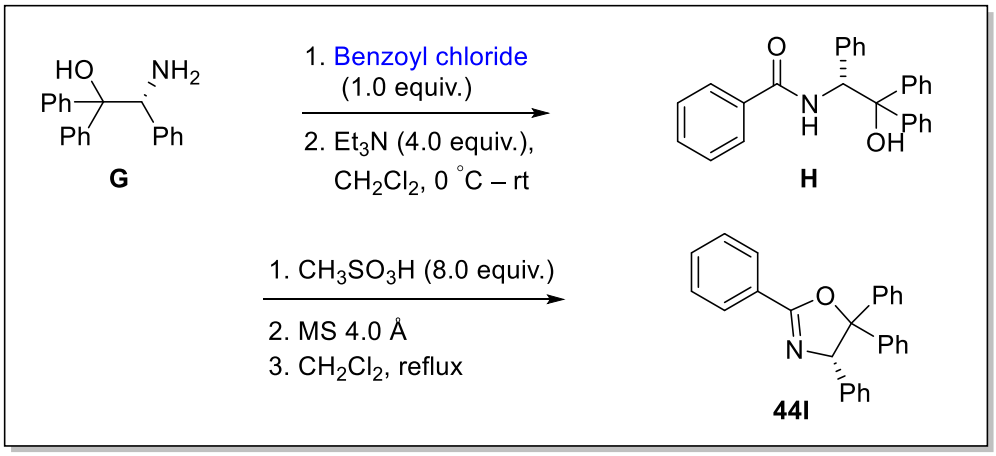
6.4.2.1 (4*S*, 5*S*)-2,4,5-triphenyl-4,5-dihydrooxazole



To a mixture of (1***S***,2***S***)2-amino-1,2-diphenylethan-1-ol **F** (639.8 mg, 3.3 mmol, 1.1 equiv.) and Et_3N (1.70 mL, 4.0 equiv.) in CH_2Cl_2 (5 mL), a solution of benzoyl chloride (421.7 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) was added dropwise with magnetic stirring at 0℃. After the stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and treated with $SOCl_2$ (1.10 mL, 15.0 mmol, 5.0 equiv.) at 0℃. After stirring for 24 h at room temperature, the solvent and excess $SOCl_2$ were removed under reduced pressure. Sat. $NaHCO_3$ (aq.) (30 mL) was added to the residue with stirring for 5 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. By using a sonicator, the solid residue was dissolved in CH_3OH (12 mL) and 2.5 N NaOH (aq.) (0.24 mL, 15.0 mmol, 5.0 equiv.) was added slowly at 0℃, then the reaction mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum, followed by addition of water (25 mL) and CH_2Cl_2 (3 x 25 mL) for extraction. The solvent was evaporated under vacuum to afford (4***S***,5***S***)-2,4,5-triphenyl-4,5-dihydrooxazole ligand **44H**[160] (898.20 mg, gummy liquid, 92% yield from **F**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, *J* = 7.2 Hz, 2H), 7.30–7.51 (m, 12H), 7.08–7.25 (m, 1H), 5.42 (d, *J* = 7.63 Hz, 1H), 5.21 (d, *J* = 7.63 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.21, 142.12, 140.62, 131.81, 129.08, 129.02, 128.79, 128.64, 128.60, 127.95, 127.64, 126.92, 125.86, 89.15, 79.18 ppm.

IR (neat) ν 3030, 2917, 1648, 1450, 1063, 695 cm^{-1}, HRMS (DART) calcd for $C_{21}H_{18}NO$ $[M+H]^+$: 300.13884 found: 300.13880.

6.4.2.2 (*S*)-2,4,5,5-tetraphenyl-4,5-dihydrooxazole



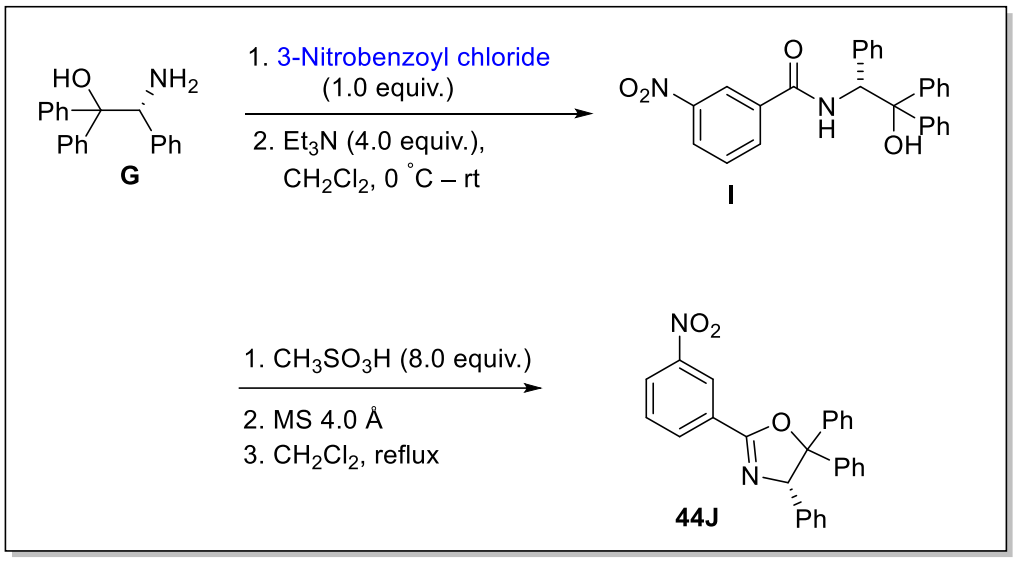
(***S***)-Diphenylphenylglycinol **G**[161] was prepared according to literature procedures.

To a mixture of (***S***)-diphenylphenylglycinol **G** (954.9 mg, 3.3 mmol, 1.1 equiv.) and a solution of benzoyl chloride (421.7 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL), Et_3N (1.70 mL, 12.0 mmol, 4.0 equiv.) was added dropwise with magnetic stirring at 0℃. After the stirring for 24 h at room temperature, the reaction mixture was concentrated under reduced pressure. Sat. $NaHCO_3$ (aq.) (30 mL) was added to the residue with stirring for 5 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the desired product. The crude **H** was purified by silica gel column chromatography with Hex/EtOAC (6/1 (v/v)) to give pure **H** (1074.3 mg, 91% yield).

To a mixture of **H** (1967.4 mg, 5.0 mmol, 1.0 equiv.) and methanesulfonic acid (40.0 mmol, 2.7 mL, 8.0 equiv.) in CH_2Cl_2 (30 mL), molecular sieve 4.0 Å (3.0 g) were added and refluxed for 20h.[146] The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aqueous $NaHCO_3$ (40 mL) and brine. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to afford pure (***S***)-2,4,5,5- tetraphenyl-4,5-dihydrooxazole **44l**[147] (1595.8 mg, 85% yield). $[\alpha]_D^{27.4}$ = –2.58 (c 0.96, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.26 Hz, 2H), 7.73 (t, *J* = 8.41 Hz, 2H), 7.53 (t, *J* = 7.26 Hz, 1H), 7.48 (t, *J* = 7.26 Hz, 2H), 7.38 (t, *J* = 8.79 Hz, 2H), 7.32 (t, *J* = 7.26 Hz, 1H), 6.90–7.04 (m, 10H), 6.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.35, 144.84, 140.54, 138.77, 131.97, 128.75, 128.68, 128.65, 128.22, 127.92, 127.77, 127.42, 126.92, 126.85, 126.65, 94.41, 80.02

IR (neat) ν 3061, 2926, 1645, 1520, 778 cm^{-1}. HRMS (DART) calcd for $C_{27}H_{22}NO$ $[M+H]^+$: 376.17014 found: 376.17010.

6.4.2.3 (*S*)-2-(3-nitrophenyl)-4,5,5-triphenyl-4,5-dihydrooxazole



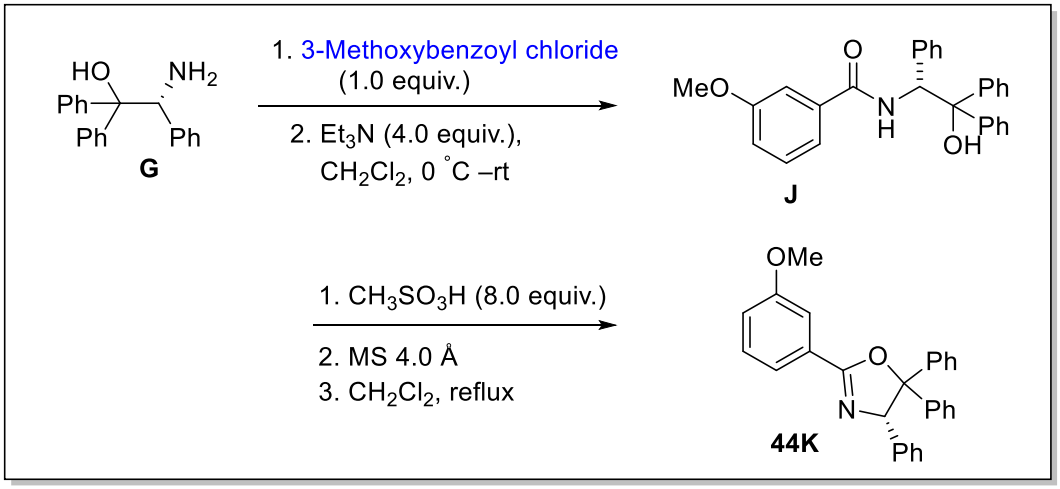
To a mixture of (***S***)-diphenylphenylglycinol **G**[161] (954.9 mg, 3.3 mmol, 1.1 equiv.) and a solution of 3-nitrobenzoyl chloride (556.7 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL), Et_3N (1.70 mL, 12.0 mmol, 4.0 equiv) was added dropwise with magnetic stirring at 0℃. After the stirring for 24 h at room temperature, the reaction mixture was concentrated under reduced pressure. Sat. $NaHCO_3$ (aq.) (30 mL) was added to the residue with stirring for 5 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the desired product **I**. The crude **I** was purified by silica gel column chromatography with Hex/EtOAC (6/1 (v/v)) to give pure **I** (929.2 mg, 89% yield).

A solution of **I** (2192.4 mg, 5.0 mmol, 1.0 equiv.), methanesulfonic acid (40 mmol, 2.7 mL, 8.0 equiv.) in CH_2Cl_2 (30 mL) and molecular sieve 4.0 Å (3.0 g) were refluxed for 20h.[146] The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aqueous $NaHCO_3$ (40 mL) and brine. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to afford pure (***S***)-2-(3-nitrophenyl)-4,5,5 -triphenyl-4,5-dihydrooxazole **44J** (1932.7 mg, 92% yield). $[\alpha]_D^{27.2}$ = –2.66 (c 1.04, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 1.91 Hz, 1H), 8.54 (d, *J* = 7.64 Hz, 1H), 8.41 (d, *J* = 8.41 Hz, 1H), 7.68–7.73 (m, 3H), 7.44 (t, *J* = 7.64 Hz, 2H), 7.36 (t, *J* = 7.64 Hz, 1H), 7.06–7.10 (m, 3H), 6.97–7.03 (m, 7H), 6.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.27, 148.53, 144.20, 139.93, 138.01, 134.39, 129.85, 129.54, 128.75, 128.50, 128.48, 127.97, 127.59, 127.46, 127.03, 126.75, 126.58, 126.37, 123.58, 95.31, 72.92 ppm.

IR (neat) ν 3087, 2926, 2316, 1951, 1659, 861 cm^{-1}, HRMS (DART) calcd for $C_{27}H_{21}N_2O_3$ $[M+H]^+$: 421.15522 found: 421.15520.

6.4.2.4 (*S*)-2-(3-methoxyphenyl)-4,5,5-triphenyl-4,5-dihydrooxazole

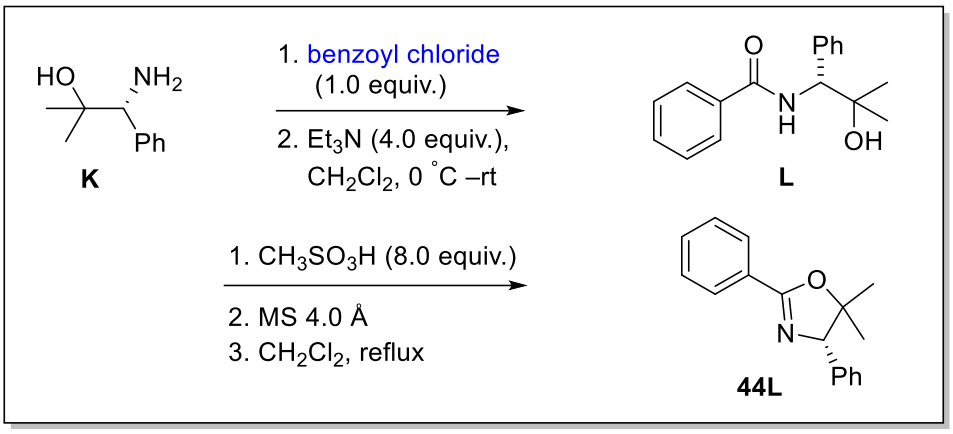
To a mixture of (*S*)-diphenylphenylglycinol **G**[161] (954.9 mg, 3.3 mmol, 1.1 equiv.) and a solution of 3-methoxybenzoyl chloride (511.8 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL), Et_3N (1.70 mL, 12.0 mmol) was added drop wise with magnetic stirring at 0℃. After the stirring for 24 h at room temperature, the reaction mixture was concentrated under reduced pressure. Sat. $NaHCO_3$ (aq.) (30 mL) was added to the residue with stirring for 5 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give desired product **J**. The crude **J** was purified by silica gel column chromatography with Hex/EtOAC (6/1 (v/v)) to give pure **J** (1129.9 mg, 89% yield).



A solution of **J** (2117.6 mg, 5.0 mmol, 1.0 equiv.), methanesulfonic acid (40 mmol, 2.7 mL, 8.0 equiv.) in CH_2Cl_2 (30 mL) and molecular sieve 4.0 Å (3.0 g) were refluxed for 20h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aqueous $NaHCO_3$ (40 mL) and brine. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to afford pure (***S***)-2-(3-methoxyphenyl)- 4,5,5-triphenyl-4,5-dihydrooxazole **44K** (1905.9 mg, 94% yield). $[\alpha]_D^{27.8} = -2.32$ (c 0.97, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 7.64 Hz, 1H), 7.72–7.75 (m, 3H), 7.48 (t, J = 8.03 Hz, 3H), 7.33 (t, J = 7.26 Hz, 1H), 6.97–7.14 (m, 11H), 6.13 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.25, 159.82, 144.82, 140.47, 138.71, 129.82, 129.04, 129.01, 128.66, 128.23, 127.93, 127.42, 126.91, 126.87, 126.62, 126.59, 121.20, 118.59, 113.18, 94.42, 80.07, 55.68 ppm. IR (neat) ν 3061, 2928, 1949, 1651, 755 cm^{-1}. HRMS (DART) calcd for $C_{28}H_{24}NO_2$ $[M+H]^+$: 406.18070 found: 406.18070.

6.4.2.5 (*S*)-5,5-dimethyl-2,4-diphenyl-4,5-dihydrooxaz-ole

(***S***)-diphenylphenylglycinol **K**[163] was prepared according to literature procedures.



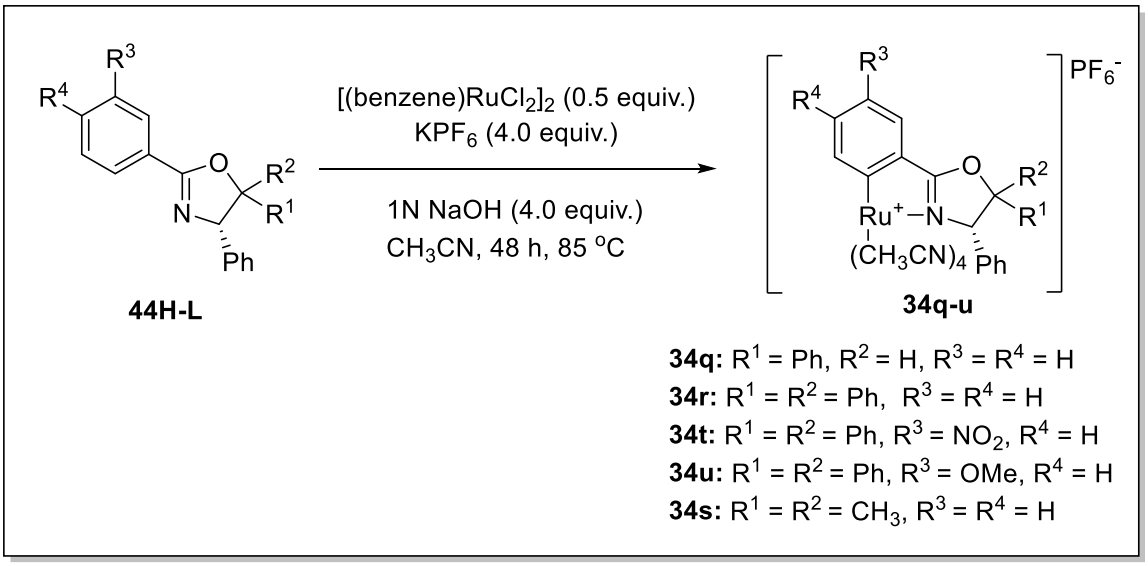
To a mixture of (***S***)-dimethylphenylglycinol **K** (545.3 mg, 3.3 mmol, 1.1 equiv.) and a solution of benzoyl chloride (421.7 mg, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL), Et_3N (1.70 mL, 12.0 mmol, 4.0 equiv.) was added drop wise with magnetic stirring at 0℃. After the stirring for 24 h at room temperature, the reaction mixture was concentrated under reduced pressure. Sat. $NaHCO_3$ (aq.) (30 mL) was added to the residue with stirring for 5 minutes. The organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude **L**.

The crude **L** was purified by silica gel column chromatography with Hex/EtOAC (6/1 (v/v)) to give pure **L** (82% yield).

A solution of **L** (1346.7 mg, 5.0 mmol, 1.0 equiv.), methanesulfonic acid (40 mmol, 2.7 mL, 8.0 equiv.) in CH_2Cl_2 (30 mL) and molecular sieve 4.0 Å (3.0 g) were refluxed for 20 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to afford pure (***S***)-5,5-dimethyl-2,4-diphenyl-4,5- dihydrooxaz-ole **44L** (95% yield). $[\alpha]_D^{24.2}$ = +0.48 (c 1.09, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.24 Hz, 2H), 7.40–7.52 (m, 3H), 7.23–7.35 (m, 5H), 5.04 (s, 1H), 1.65 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.73, 139.11, 131.46, 128.42, 128.33, 127.56, 127.35, 87.41, 78.55, 29.20, 24.01 ppm. IR (neat) ν 3061, 2975, 1645, 1339, 1066, 844 cm^{-1}. HRMS (DART) calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.13884 found: 252.13880.

6.4.3 Typical procedures for synthesis of various Ru(II)-Pheox catalysts

Catalyst **3a** used in the cyclopropanation reaction was commercially available. **3b–g**[123], were prepared according to literature procedures. **3h** were modified from procedures[9]. **3i–l**[123,146] were prepared according to literature procedures.

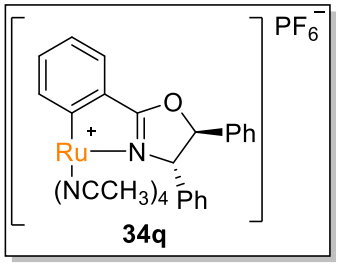


A two necked round bottom flask fitted with a magnetic stirring bar and a reflux condenser was charged with a mixture of the ligand **44H-L** (0.4 mmol, 1.0 equiv.), $[RuCl_2(benzene)]_2$ (0.2 mmol, 0.5 equiv.) and KPF_6 (1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aq.) (0.8 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 80 °C. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired Ru(II)-Pheox complexes (up to 96% yield).

6.4.4 Analytical data for Analytical data for Ru(II)-*phenyl*-Pheox catalyst and Ru(II)-*dialkyl*-Pheox catalysts

Catalysts **34b,f,e** used in the cyclopropanation reaction were aynthesize from the section **5.2.2**. **34m–p**[123,146], were prepared according to literature procedures.

6.4.4.1 Ru(II)- phenyl -Pheox complex 34q

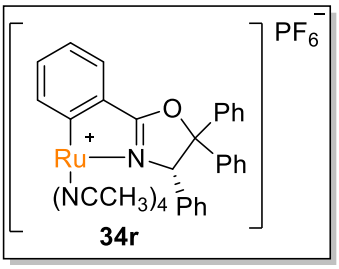


A two necked round bottom flask (100 mL) fitted with a magnetic stirring bar and a reflux condenser was charged with (4***S***,5***S***)-2,4,5-triphenyl-4,5-dihydrooxazole ligand **44H** (119.8 mg, 0.4 mmol, 1.0 equiv.), $[(benzene)RuCl_2]_2$ (100.4 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1N NaOH (aq.) (1.6 mL, 1.6 mmol, 4.0 equiv.) were injected. The suspended mixture was refluxed for 24 h at 85℃. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired complex **3h** (333.1 mg, 94% yield) as a green solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.32 Hz, 1H), 7.55(d, J

= 7.32 Hz, 1H), 7.14-7.31 (m, 11H), 6.94 (d, *J* = 7.32 Hz, 1H), 5.62 (d, *J* = 6.71 Hz, 1H), 4.83 (d, *J* = 6.71 Hz, 1H), 2.41 (s, 3H), 2.06 (s, 3H), 1.98 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.77, 174.91, 140.72, 138.95, 138.42, 134.17, 129.70, 129.20, 128.67, 128.61, 127.78, 126.41, 125.58, 121.80, 120.98, 120.71, 120.62, 120.24, 91.62, 76.80, 76.58, 29.79, 4.30, 4.07, 3.01

IR (neat) ν 3033, 2271, 1620, 839 cm^{-1}.

6.4.4.2 Ru(II)-*diphenyl*-Pheox complex 34r

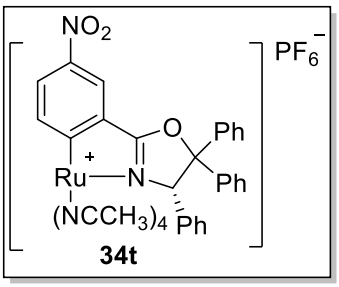


34r

A two necked round bottom flask (100 mL) fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-2,4,5,5-tetraphenyl-4,5-dihydrooxazole **44I** (150.1 mg, 0.4 mmol, 1.0 equiv.), $[(benzene)RuCl_2]_2$ (100.36 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1 N NaOH (aq.) (1.6 mL, 1.6 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 24 h at 85℃. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/15 (v/v)) to give the desired complex **34r** (271.4 mg, 94% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.63 Hz, 1H), 7.78 (t, *J* = 7.32 Hz, 3H), 7.39 (t, *J* = 7.93, 2H), 7.20–7.28 (m, 2H), 7.15 (d, *J* = 7.93 Hz, 2H), 6.94–7.11 (m, 9H), 5.84 (s, 1H), 2.43 (s, 3H), 2.22 (s, 3H), 1.89 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.84, 173.88, 144.09, 139.65, 138.39, 137.70, 134.77, 129.57, 129.41, 128.77, 128.32, 127.83, 127.63, 127.39, 127.04, 126.53, 126.34, 126.16, 121.79, 121.00, 120.67, 120.64, 120.45, 120.37, 97.36, 76.80, 4.32, 4.04, 3.46, 3.18 ppm.

IR (neat) ν 3059, 2271, 1624, 839 cm^{-1}.

6.4.4.3 *p*-Nitro Ru(II)-*diphenyl* -Pheox complex 34t



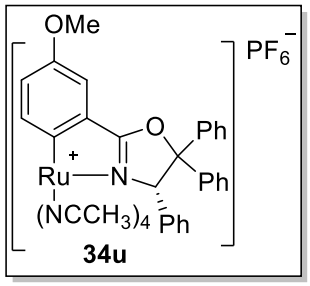
34t

A two necked round bottom flask (100 mL) fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-2-(3-nitrophenyl)-4,5,5-triphenyl-4,5-dihydrooxa -zole **44J** (168.06 mg, 0.4 mmol, 1.0 equiv.), $[(benzene)RuCl_2]_2$ (100.4 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1 N NaOH (aq.) (1.6 mL, 1.6 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 24 h at 95℃ (The high temperature was carried out to avoid the by-product). The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/15 (v/v)) to give the desired complex **34t** (156.0 mg, 94% yield) as a green solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.14 Hz, 1H), 8.07 (d, *J*

= 8.24 Hz, 1H), 7.97 (dd, *J* = 2.44, 2.44 Hz, 1H), 7.76 (d, *J* = 7.63 Hz, 2H), 7.41 (t, *J* = 7.63 Hz, 2H), 7.28 (t, *J* = 7.63 Hz, 1H), 7.15 (d, *J* = 7.02 Hz, 2H), 6.96–7.11 (m, 8H), 5.95 (s, 1H), 3.08 (s, 3H), 2.28 (s, 3H), 1.95 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.89, 143.47, 139.14, 136.99, 135.55, 129.38, 128.90, 128.59, 128.11, 127.76, 127.53, 127.25, 126.38, 126.22, 122.62, 122.01, 121.81, 121.31, 119.73, 98.39, 76.61, 4.16, 3.86, 3.33, 3.15 ppm.
IR (neat) ν 3235, 2931, 2278, 1628, 1323, 840 cm^{-1}.

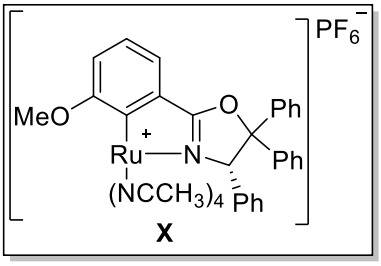
6.4.4.4 *m*-Methoxy Ru(II)-*diphenyl*-Pheox complex 34u

A two necked round bottom flask (100 mL) fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-2-(4-nitrophenyl)-4-phenyl-4,5-dihydrooxazole ligand **44J** (162.1 mg, 0.4 mmol, 1.0 equiv.), $[(benzene)RuCl_2]_2$ (100.4 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and 1 N NaOH (aq.) (1.6 mL, 1.6 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 24 h at 85℃. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the complex **X** (61.9 mg, 38% yield) as green solid and the catalyst **34u** (92.9 mg, 57% yield) as a yellow solid.



34u

34u: ^{1}H NMR (400 MHz, CD_3CN) δ 7.77 (d, *J* = 7.26 Hz, 2H), 7.54 (dd, *J* = 0.76, 1.15 Hz, 1H), 7.41 (t, *J* = 8.41 Hz, 2H), 7.25–7.3 (m, 1H), 6.96–7.14 (m, 11H), 6.77 (d, *J* = 7.64 Hz, 1H), 5.89 (s, 1H), 3.79 (s, 3H), 2.41 (s, 3H, CH_3CN), 2.25 (s, 3H, CH_3CN), 1.93 (s, 3H, CH_3CN), 1.84 (s, 3H, CH_3CN). ^{13}C NMR (100 MHz, CD_3CN) δ 174.00, 171.09, 170.59, 144.60, 139.68, 137.57, 136.24, 129.43, 128.69, 128.53, 127.86, 127.76, 127.62, 127.10, 126.43, 125.75, 122.48, 122.26, 121.49, 121.34, 119.57, 113.59, 97.12, 76.36, 56.27, 3.01, 2.46 ppm.
IR (neat) ν 3666, 3036, 2932, 1632, 1408, 843 cm^{-1}.

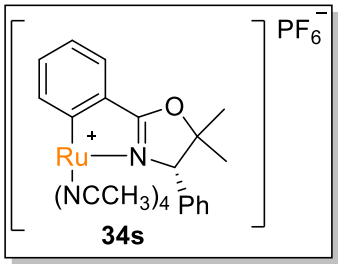


X

Complex X: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.07, 2H), 7.40 (dd, *J* = 8.41 Hz, 4H), 7.28 (d, *J* = 7.26, 1H), 7.14 (d, *J* = 7.26 Hz, 1H), 6.93–7.10 (m, 9H), 5.91 (s, 1H), 3.93 (s, 3H), 2.46 (s, 3H, CH_3CN), 2.24 (s, 3H, CH_3CN), 1.96 (s, 3H, CH_3CN), 1.89 (s, 3H, CH_3CN). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.90, 139.56, 129.40, 128.79, 128.36, 127.60, 127.34, 127.06, 126.54, 126.21, 97.40, 77.33, 55.40, 4.39, 3.08 ppm.

6.4.4.5 Ru(II)-*dimethyl*-Pheox complex 34s

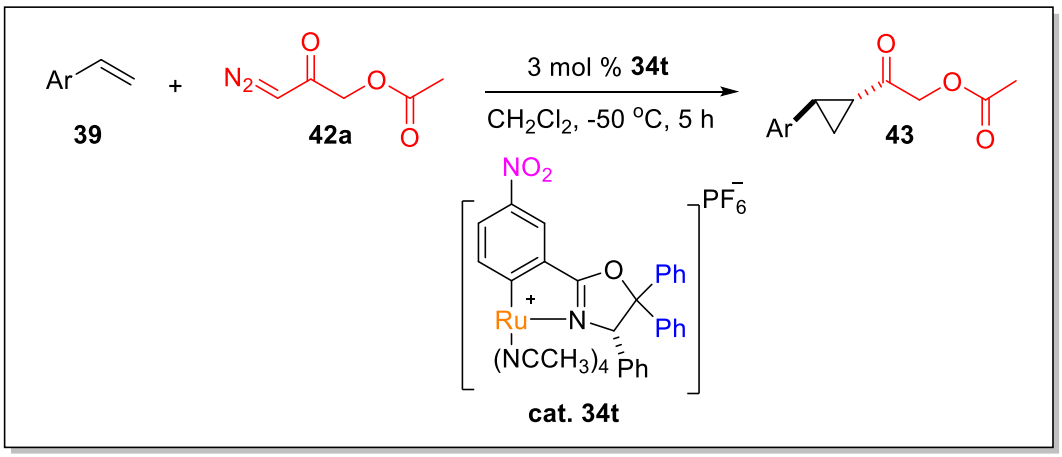
A two necked round bottom flask (100 mL) fitted with a magnetic stirring bar and a reflux condenser was charged with (***S***)-5,5-dimethyl-2,4-diphenyl-4,5-dihydrooxazole **44L** (100.4 mg, 0.4 mmol, 1 equiv.), $[(benzene)RuCl_2]_2$ (100.4 mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg,



34s

1.6 mmol, 4.0 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and NaOH (aq.) (1.6 mL, 1.6 mmol, 4.0 equiv.) were injected. The suspended reaction mixture was refluxed for 24 h at 85℃. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/15 (v/v)) to give the desired complex **3j** (124.2 mg, 92% yield) as a green solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.02, 1H), 7.51 (d, J = 7.32 Hz, 1H), 7.30 (s, 3H), 7.20 (t, J = 7.02 Hz, 1H), 6.91 (t, J = 6.71 Hz, 1H), 4.92 (s, 1H), 2.50 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H), 1.62 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.97, 138.55, 135.90, 128.58, 128.38, 128.08, 127.86, 125.77, 121.78, 120.81, 91.09, 75.87, 53.59, 29.39, 23.99, 4.34, 4.12, 3.82, 2.81 ppm. IR (neat) ν 2981, 2270, 1619, 1452, 840 cm^{-1}.

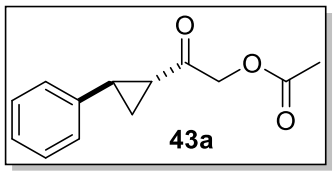
6.4.5 Typical procedure for catalytic asymmetric cyclopropanation of olefins with diazo acetoxy acetone



A solution of diazo acetoxy acetone 4**2a** (0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) was slowly added to a mixture of Ru(II)-Pheox catalyst **3** (0.01 mmol) and olefins **39a-i** (1.0 mmol, 5.0 equiv.) in CH_2C1_2 (2.0 mL) for 4 h under argon atmosphere and the suspended reaction mixture was designed at -50 °C. After the addition completed, the reaction mixture was continuously stirred for 1 h at the same temperature. The reaction was monitored by TLC. Upon completion, solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc/n-Hexane to give the cyclopropanation products. The *trans*/*cis* ratio was determined from the crude ^{1}H NMR spectra, and the enantioselectivity was determined by chiral HPLC analysis.

6.4.6 Analytical data for catalytic asymmetric cyclopropanation reaction products

6.4.6.1 2-oxo-2-(2-phenylcyclopropyl)ethyl acetate 43a



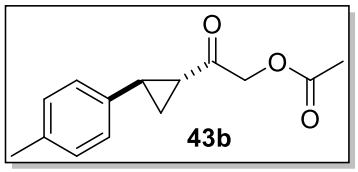
43a was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of styrene **39a** (104.2 mg, 1.0 mmol) with 3-diazo-2-oxopropyl acetate **42a** (28.4 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (10/1 (v/v)) as an eluent to give *trans*- product in (37.1 mg, 85% yield) as white solid. 95% *ee* (*trans*). The *ee* value was determined by HPLC analysis. Column (Chiral IC3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{23.6}$ = –3.66 (c 1.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.64 Hz, 2H, Ar–**H**), 7.22 (t, *J* = 7.26 Hz, 1H, Ar-**H**), 7.10 (d, *J* = 7.26 Hz, 2H, Ar–**H**), 4.86 (d, *J* = 16.82, Hz, 1H, OC**H**H), 4.81 (d, *J* = 16.82, Hz, 1H, OCH**H**), 2.59 (ddd, *J* = 4.20, 6.88, 9.56 Hz, 1H, OCC**H** (cyclopropane)), 2.18 (ddd, *J* = 4.20, 5.30, 8.41 Hz, 1H, Ar–C**H** (cyclopropane)), 2.14 (s, 3H, C**H$_3$**CO), 1.76 (ddd, *J* = 4.20, 5.30, 9.17 Hz, 1H, C**H**H (cyclopropane)), 1.49 (ddd, *J* = 4.20, 6.50, 8.03 Hz, 1H, CH**H** (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.91, 170.31, 139.72, 128.66, 126.88, 126.21, 68.64, 29.71, 29.07, 20.56, 19.09 ppm.

HRMS (DART) calcd for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.10212 found 219.10211.

IR (neat) ν 3031, 2929, 1749, 1714, 1232, 1057, 700 cm^{-1}.

6.4.6.2 2-oxo-2-(2-(*p*-tolyl)cyclopropyl)ethyl acetate 43b



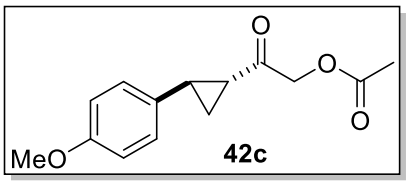
43b was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 1-methyl-4-vinylbenzene **39b** (118.2 mg, 1.0 mmol) with 3-diazo-2-oxopropyl acetate **42a** (28.4 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (5/1 (v/v)) as an eluent to give *trans*- product in (41.3 mg, 89% yield) as white solid. 96% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral IC3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{24.1}$ = –3.45 (c 0.91, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.93 Hz, 2H, Ar–**H**), 6.99 (d, *J* = 7.63 Hz, 2H, Ar–**H**), 4.85 (d, *J* = 16.78 Hz, 1H, OCH**H**), 4.79 (d, *J* = 16.78 Hz, 1H, OC**H**H), 2.56 (ddd, *J* = 4.20, 5.80, 7.02 Hz, 1H, OCC**H** (cyclopropane)), 2.32 (s, 3H, Ar–C**H$_3$**), 2.15 (s, 3H, C**H$_3$**CO), 2.13 (m, 1H, Ar–C**H** (cyclopropane)), 1.74 (ddd, *J* = 4.27, 5.65, 7.16 Hz, 1H, C**H**H (cyclopropane)), 1.45 (dt, *J* = 4.27, 5.80, 7.02 Hz, 1H, CH**H** (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.97, 170.31, 136.66, 136.58, 129.33, 126.14, 68.64, 29.60, 29.07, 21.10, 20.59, 19.10 ppm.

HRMS (DART) calcd for $C_{14}H_{17}O_3$ $[M+H]^+$: 233.11777 found 233.11782.

IR (neat) ν 3016, 2925, 1752, 1715, 1232, 1043, 810 cm^{-1}

6.4.6.3 2-(2-(4-methoxyphenyl)cyclopropyl)-2-oxoethyl acetate 43c



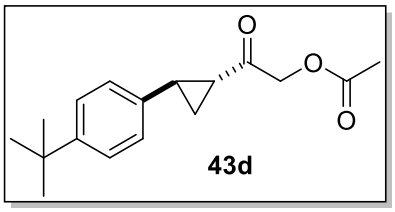
43c was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 1-methoxy-4-vinylbenzene **39c** (134.2 mg, 1.0 mmol) with 3-diazo-2-oxopropyl acetate **42a** (28.4 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (5/1 (v/v)) as an eluent to give *trans*- product in (39.7 mg, 80% yield) as yellow oil. 83% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral IC3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{24.1}$ = –6.3 (c 1.98, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.54 Hz, 2H, Ar–**H**), 6.83 (d, *J* = 8.54 Hz, 2H, Ar–**H**), 4.85 (d, *J* = 16.78 Hz, 1H, OC**H**H), 4.79 (d, *J* = 16.78 Hz, 1H, OCH**H**), 3.78 (s, 3H, O**Me**), 2.55 (ddd, *J* = 3.97, 6.71, 8.85 Hz, 1H, OCC**H** (cyclopropane)), 2.15 (s, 3H, C**H$_3$**CO), 2.12 (m, 1H, Ar–C**H** (cyclopropane)), 1.74 (ddd, *J* = 4.27, 6.71, 8.93 Hz, 1H, C**H**H (cyclopropane)), 1.43 (ddd, *J* = 4.27, 6.71, 7.93 Hz, 1H, CH**H** (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.00, 170.31, 158.63, 131.66, 127.40, 114.08, 68.64, 55.41, 29.37, 28.97, 20.56, 18.84 ppm.

HRMS (DART) calcd for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.11268 found 249.11269.

IR (neat) ν 3004, 2933, 1747, 1714, 1246, 1229, 831 cm^{-1}

6.4.6.4 2-(2-(4-(tert-butyl)phenyl)cyclopropyl)-2-oxoethyl acetate 43d



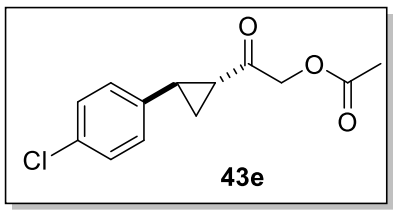
43d was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 1-(tert-butyl)-4-vinylbenzene **39d** (160.3 mg, 1.0 mmol) with 3-diazo-2-oxopropyl acetate **42a** (28.4 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (5/1 (v/v)) as an eluent to give *trans*- product in (50.5 mg, 92% yield) as white solid. 91% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral IC3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{21.6}$ = –6.68 (c 1.81, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.93 Hz , 2H, Ar–**H**), 7.05 (d, *J* = 7.93 Hz, 2H, Ar–**H**), 4.85 (d, *J* = 16.78 Hz, 1H, OC**H**H), 4.79 (d, *J* = 16.78 Hz, 1H, OCH**H**), 2.57 (ddd, *J* = 4.27, 7.63, 9.77 Hz, 1H, OCC**H** (cyclopropane)), 2.17 (m, 1H, Ar–C**H** (cyclopropane)), 2.15 (s, 3H, C**H$_3$**CO), 1.75 (ddd, *J* = 4.27, 5.30, 9.56 Hz, 1H, C**H**H (cyclopropane)), 1.47 (ddd, *J* = 4.27, 7.61, 8.85 Hz, 1H, CH**H** (cyclopropane)), 1.30 (s, 9H, Ar–C(C**H$_3$**)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.96, 170.30, 149.95, 137.60, 125.92, 125.57, 68.64, 34.55, 31.41, 29.51, 29.03, 20.59, 19.12 ppm.

HRMS (DART) calcd for $C_{17}H_{23}O_3$ $[M+H]^+$: 275.16472 found 275.16470.

IR (neat) ν 3028, 2962, 1752, 1715, 1231, 1043, 834 cm^{-1}.

6.4.6.5 2-(2-(4-chlorophenyl)cyclopropyl)-2-oxoethyl acetate 43e



43e

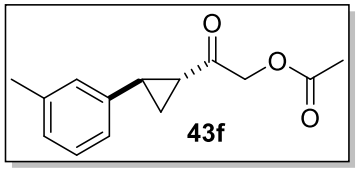
43e was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 1-chloro-4-vinylbenzene **39e** (138.6 mg, 1.0 mmol) with 3-diazo-2-oxopropyl acetate **42a** (28.4 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (5/1 (v/v)) as an eluent to give *trans*- product in (48.0 mg, 95% yield) as white solid. 98% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral IC3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{23.4}$ = –2.78 (c 0.74, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.41 Hz, 2H, Ar–**H**), 7.03 (d, *J* = 8.41 Hz, 2H, Ar–**H**), 4.83 (d, *J* = 16.82 Hz, 1H, OC**H**H), 4.79 (d, *J* = 16.82 Hz, 1H, OCH**H**), 2.57 (ddd, *J* = 3.82, 6.50, 8.79 Hz, 1H, OCC**H** (cyclopropane)), 2.15 (s, 3H, C**H**$_3$CO), 2.14 (m, 1H, Ar–C**H** (cyclopropane)), 1.76 (ddd, *J* = 4.20, 6.50, 8.85 Hz, 1H, C**H**H (cyclopropane)), 1.44 (ddd, *J* = 4.20, 6.50, 8.03 Hz, 1H, CH**H** (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.71, 170.31, 138.22, 132.59, 128.76, 127.60, 68.62, 28.89, 25.43, 20.55, 19.01 ppm.

HRMS (DART) calcd for $C_{13}H_{14}ClO_3$ $[M+H]^+$: 253.06315 found 253.06310.

IR (neat) ν 3008, 2929, 1751, 1716, 1231, 1044, 809 cm^{-1}.

6.4.6.6 2-oxo-2-(2-(m-tolyl)cyclopropyl)ethyl acetate 43f



43f

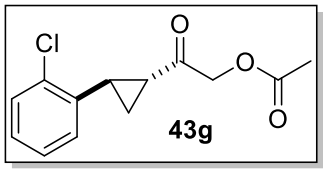
43f was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 1-methyl-3-vinylbenzene **39f** (118.2 mg, 1.0 mmol) with 3-diazo-2-oxopropyl acetate **42a** (28.4 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (5/1 (v/v)) as an eluent to give *trans*- product in (39.5 mg, 85% yield) as colourless oil. 92% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral IC3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{23.9}$ = –3.75 (c 0.98, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.63 Hz , 2H, Ar–**H**), 7.04 (s, 1H, Ar–**H**), 6.90 (dd, *J* = 6.1, 4.27 Hz, 2H, Ar–**H**), 4.86 (d, *J* = 16.78 Hz, 1H, OC**H**H), 4.80 (d, *J* = 16.78 Hz, 1H, OCH**H**), 2.56 (ddd, *J* = 3.97, 6.71, 9.46 Hz, 1H, OCC**H** (cyclopropane)), 2.33 (s, 3H, Ar–C**H**$_3$), 2.17 (m, 1H, Ar–C**H** (cyclopropane)), 2.15 (s, 3H, C**H**$_3$CO), 1.75 (ddd, *J* = 4.27, 6.50, 9.16 Hz, 1H, C**H**H (cyclopropane)), 1.47 (ddd, *J* = 4.27, 7.03, 7.93 Hz, 1H, CH**H** (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.92, 170.31, 139.66, 138.33, 128.58, 127.65, 127.04, 123.18, 68.64, 29.73, 29.04, 21.46, 20.59, 19.05 ppm.

HRMS (DART) calcd for $C_{14}H_{17}O_3$ $[M+H]^+$: 233.11777 found 233.11780.

IR (neat) ν 3019, 2925, 1754, 1748, 1230, 1059, 781 cm^{-1}

6.4.6.7 2-(2-(2-chlorophenyl)cyclopropyl)-2-oxoethyl acetate 43g



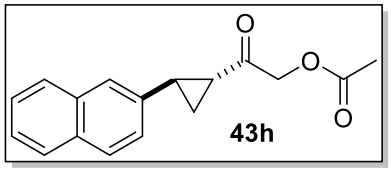
43g was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 1-methyl-3-vinylbenzene **39g** (138.6 mg, 1.0 mmol) with 3-diazo-2-oxopropyl acetate **42a** (28.4 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (5/1 (v/v)) as an eluent to give *trans*- product in (46.5 mg, 92% yield) as colourless oil. 97% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral IC3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{24.2}$ = –1.23 (c 0.60, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 1H, Ar–**H**), 7.17–7.21 (m, 2H, Ar–**H**), 7.06 (m, 1H, Ar–**H**), 4.93 (d, *J* = 16.82 Hz, 1H, OC**H**H), 4.89 (d, *J* = 16.82 Hz, 1H, OCH**H**), 2.75 (ddd, *J* = 4.20, 6.88, 8.79 Hz, 1H, OCC**H** (cyclopropane)), 2.17 (s, 3H, C**H**$_3$CO), 2.04 (ddd, *J* = 4.20, 6.35, 8.09 Hz, 1H, Ar–C**H** (cyclopropane)), 1.78 (ddd, *J* = 4.59, 6.50, 8.79 Hz, 1H, C**H**H (cyclopropane)), 1.51 (ddd, *J* = 4.20, 6.88, 8.03 Hz, 1H, CH**H** (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.71, 170.31, 138.22, 132.59, 128.76, 127.60, 68.62, 28.89, 25.43, 20.55, 19.01 ppm.

HRMS (DART) calcd for $C_{13}H_{14}ClO_3$ $[M+H]^+$: 253.06315 found 253.06312.

IR (neat) ν 3010, 2929, 1750, 1718, 1231, 1040, 771 cm^{-1}.

6.4.6.8 2-(2-(naphthalen-2-yl)cyclopropyl)-2-oxoethyl acetate 43h



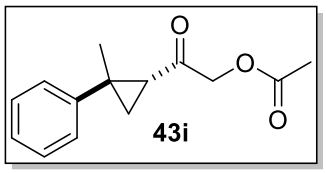
43h was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of 2-vinylnaphthalene **39h** (154.2 mg, 1.0 mmol) with 3-diazo-2-oxopropyl acetate **42a** (28.4 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (5/1 (v/v)) as an eluent to give *trans*- product in (48.3 mg, 90% yield) as white solid. 85% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral IC3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{21.4}$ = –4.11 (c 0.99, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.81 (m, 3H, Ar–**H**), 7.56 (s, 1H, Ar–**H**), 7.42–7.49 (m, 2H, Ar–**H**), 7.20 (dd, *J* = 1.91, 1.72 Hz, 1H, Ar–**H**), 4.88 (d, *J* = 16.82 Hz, 1H, OC**H**H), 4.82 (d, *J* = 16.82 Hz, 1H, OCH**H**), 2.76 (ddd, *J* = 4.20, 6.88, 9.17 Hz, 1H, OCC**H** (cyclopropane)), 2.28 (ddd, *J* = 4.20, 5.35, 8.41 Hz, 1H, Ar–C**H** (cyclopropane)), 2.15 (s, 3H, C**H**$_3$CO), 1.84 (ddd, *J* = 4.20, 5.65, 9.17 Hz, 1H, C**H**H (cyclopropane)), 1.61 (ddd, *J* = 4.20, 6.50, 8.03 Hz, 1H, CH**H** (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.91, 170.35, 137.08, 133.37, 132.49, 128.40, 127.77, 127.55, 126.48, 125.80, 124.90, 124.46, 68.66, 30.00, 29.11, 20.57, 19.02 ppm.

HRMS (DART) calcd for $C_{17}H_{17}O_3$ $[M+H]^+$: 269.11777 found 269.11780.

IR (neat) ν 3019, 2929, 1750, 1715, 1231, 1042, 819 cm^{-1}.

6.4.6.9 2-(2-methyl-2-phenylcyclopropyl)-2-oxoethyl acetate 43i



43i was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of prop-1-en-2-ylbenzene **39i** (118.2 mg, 1.0 mmol) with 3-diazo-2-oxopropyl acetate **42a** (28.4 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (5/1 (v/v)) as an eluent to give *trans*- product in (25.6 mg, 55% yield) as yellow oil. 85% *ee (trans)*. The ee was determined chiral HPLC analysis. Column (Chiral IC3), UV detector 254 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{24.1}$ = –0.37 (c 0.41, $CHCl_3$).

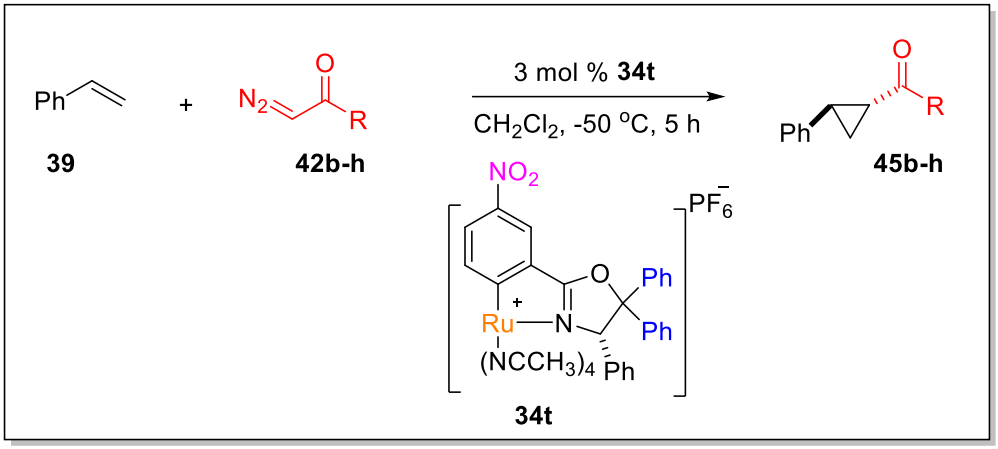
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.30 (m, 5H, Ar–**H**), 4.63 (s, 2H, OC**H₂**), 2.23 (t, *J* = 6.56 Hz, 1H, OCC**H** (cyclopropane)), 2.11 (s, 3H, C**H₃**CO), 2.00 (t, *J* = 4.58 Hz, 1H, C**H**H (cyclopropane)), 1.52 (s, 3H, C–C**H₃** (cyclopropane)), 1.28 (dd, *J* = 4.58, 7.63 Hz, 1H, CH**H** (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.54, 170.21, 140.36, 128.96, 128.45, 127.06, 68.97, 36.71, 32.97, 28.70, 21.40, 20.64 ppm.

HRMS (DART) calcd for $C_{14}H_{17}O_3$ $[M+H]^+$: 233.11777 found 233.11780.

IR (neat) ν 3025, 2926, 1752, 1719, 1232, 1071, 843 cm^{-1}.

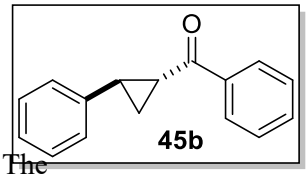
6.4.7 Typical procedure for catalytic asymmetric cyclopropanation of styrene with various diazo ketones

A solution of diazo ketones 4**2b-h** (0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) was slowly added to a mixture of Ru(II)-Pheox catalyst **34t** (0.01 mmol) and olefin (1.0 mmol, 5.0 equiv.) in CH_2C1_2 (2.0 mL) for 4 h under argon atmosphere and the suspended reaction mixture was designed at -50 °C. After the addition completed, the reaction mixture was continuously stirred for 1 h at the same temperature. The reaction was monitored by TLC. Upon completion, solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc/n-Hexane to give the cyclopropanation products. The *trans*/*cis* ratio was determined from the crude ^{1}H NMR spectra, and the enantioselectivity was determined by chiral HPLC analysis.



6.4.8 Analytical data for catalytic asymmetric cyclopropanation reaction products

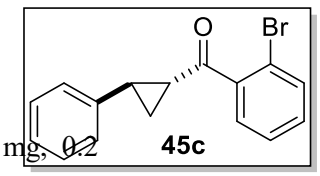
Phenyl(2-phenylcyclopropyl)methanone 45b[164]



45b was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of styrene **39a** (104.2 mg, 1.0 mmol) with α-diazoacetophenone 4**2b** (29.3 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (8/1 (v/v)) as an eluent to give the mixture of *trans*- and *cis*-diastereomers in (35.6 mg, 80% yield, dr = 96:4) as white solid. 80% *ee* (*trans*), 75% *ee* (*cis*). The ee was determined chiral HPLC analysis. Column (Chiral AD), UV detector 220 nm, eluent: Hexane/IPA = 60/1, Flow rate: 0.5 ml/min. $[\alpha]_D^{23.9}$ = –1.61 (c 0.72, $CHCl_3$).

Trans- product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.56 Hz, 2H, Ar–**H**), 7.55 (m, 1H, Ar–**H**), 7.46 (t, *J* = 7.64 Hz, 2H, Ar–**H**), 7.31 (t, *J* = 7.64 Hz, 2H, Ar–**H**), 7.17–7.25 (m, 3H, Ar–**H**), 2.90 (ddd, *J* = 4.20, 5.35, 8.03 Hz, 1H, OCC**H** (cyclopropane)), 2.66 (ddd, *J* = 4.20, 6.50, 9.17 Hz, 1H, Ar–C**H** (cyclopropane)), 1.93 (ddd, *J* = 4.20, 5.35, 9.17 Hz, 1H, CH**H** (cyclopropane)), 1.56 (ddd, *J* = 4.20, 6.88, 8.03 Hz, 1H, C**H**H (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.68, 140.58, 137.78, 133.02, 128.67, 128.63, 128.21, 128.18, 126.71, 126.67, 126.33, 126.29, 30.09, 29.42, 19.36 ppm.

(2-bromophenyl)(2-phenylcyclopropyl)methanone 45c



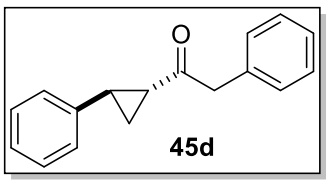
45c was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of styrene **39a** (104.2 mg, 1.0 mmol) with 1-(2-bromophenyl)-2-diazoethan-1-one **42c** (51.2 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (8/1 (v/v)) as an eluent to give *trans*- product in (44.7 mg, 87% yield) as yellow oil. 86% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral ODH), UV detector 220 nm, eluent: Hexane/IPA = 140/1, Flow rate: 0.5 ml/min. $[\alpha]_D^{23.9}$ = –2.57 (c 1.28, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.63 Hz, 1H, Ar–**H**), 7.45 (d, *J* = 7.93 Hz, 1H, Ar–**H**), 7.30 (m, 7H, Ar–**H**), 2.79 (ddd, *J* = 3.97, 7.02, 10.38 Hz, 1H, OCC**H** (cyclopropane)), 2.70 (ddd, *J* = 3.97, 5.35, 8.54 Hz, 1H, Ar–C**H** (cyclopropane)), 1.97 (ddd, *J* = 4.27, 7.02, 8.54 Hz, 1H, CH**H** (cyclopropane)), 1.59 (ddd, *J* = 4.27, 5.19, 10.38 Hz, 1H, C**H**H (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.83, 31.80, 33.64, 119.33, 126.28, 126.75, 127.52, 128.61, 129.12, 131.79, 133.68, 140.06, 142.12, 202.29.

HRMS (DART) calcd for $C_{16}H_{14}BrO$ $[M+H]^+$: 301.02280 found 301.02280.

IR (neat) ν 3061, 3029, 2923, 1681, 1213, 749 cm^{-1}.

2-phenyl-1-(2-phenylcyclopropyl)ethan-1-one 45d



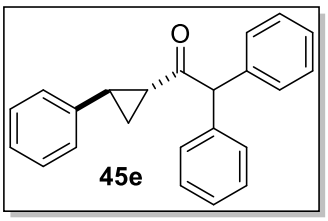
45d was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of styrene **39a** (104.2 mg, 1.0 mmol) with 1-diazo-3-phenylpropan-2-one **42d** (32.0 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (8/1 (v/v)) as an eluent to give the mixture of *trans*- and *cis*-diastereomers in (33.1 mg, 70% yield, dr = 90:10) as yellow oil. The ee was determined chiral HPLC analysis. Column (Chiral AD), UV detector 220 nm, eluent: Hexane/IPA = 100/1, Flow rate: 1.0 ml/min. 89% *ee* (*trans*), 88% *ee* (*cis*). $[\alpha]_D^{25.9}$ = –1.54 (c 0.65, $CHCl_3$).

Trans- product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.34 (m, 8H, Ar–**H**), 7.17–7.34 (m, 8H, Ar–**H**), 7.0 (d, *J* = 6.88 Hz, 2H, Ar–**H**), 2.50 (ddd, *J* = 4.20, 6.88, 9.17 Hz, 1H, OCC**H** (cyclopropane)), 3.87 (s, 2H, OCC**H$_2$**), 2.21 (ddd, *J* = 4.20, 5.35, 8.03 Hz, 1H, Ar–C**H** (cyclopropane)), 1.68 (ddd, *J* = 4.20, 5.35, 9.17 Hz, 1H, CH**H** (cyclopropane)), 1.34 (ddd, *J* = 4.20, 6.50, 8.03 Hz, 1H, C**H**H (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.48, 140.24, 134.22, 129.62, 128.84, 128.52, 127.10, 126.62, 126.34, 51.10, 31.86, 29.78, 19.18 ppm.

HRMS (DART) calcd for $C_{17}H_{17}O$ $[M+H]^+$: 237.12794 found 237.12790.

IR (neat) ν 3061, 3028, 1694, 1603, 1397, 1069, 698 cm^{-1}.

2,2-diphenyl-1-(2-phenylcyclopropyl)ethan-1-one 45e



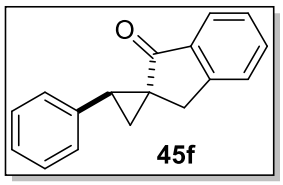
45e was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of styrene **39a** (104.2 mg, 1.0 mmol) with 3-diazo-1,1-diphenylpropan-2-one **42e** (47.3 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (8/1 (v/v)) as an eluent to give the mixture of *trans*- and *cis*-diastereomers in (55.1 mg, 85% yield, dr = 97:3) as white solid. 65% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral AD), UV detector 220 nm, eluent: Hexane/IPA = 120/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{1.56}$ = –3.2716 (c 1.56, $CHCl_3$).

Trans- product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.35 (m, 13H, Ar–**H**), 6.95 (d, *J* = 7.02 Hz, 2H, Ar–**H**), 7.21 (t, *J* = 7.26 Hz, 1H, Ar–**H**), 5.29 (s, 1H, OCC**H₂**), 2.56 (ddd, *J* = 4.27, 7.02, 9.46 Hz, 1H, OCC**H** (cyclopropane)), 2.23 (ddd, *J* = 3.97, 6.71, 7.93 Hz, 1H, Ar–C**H** (cyclopropane)), 1.75 (ddd, *J* = 3.97, 6.95, 9.16 Hz, 1H, CH**H** (cyclopropane)), 1.36 (dt, *J* = 3.97, 6.71, 9.47 Hz, 1H, C**H**H (cyclopropane)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.73, 140.13, 138.46, 138.41, 129.31, 129.26, 128.86, 128.74, 128.49, 127.35, 127.27, 126.64, 126.47, 65.55, 32.81, 30.45, 19.41 ppm.

HRMS (DART) calcd for $C_{23}H_{21}O$ $[M+H]^+$: 313.15924 found 313.15920.

IR (neat) ν 3060, 3027, 1698, 1088, 1070, 698 cm^{-1}.

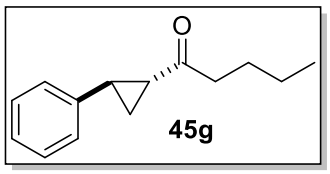
2-phenylspiro[cyclopropane-1,2'-inden]-1'(3'H)-one 45f[165]



45f was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of styrene **39a** (104.2 mg, 1.0 mmol) with 1-diazo-3-phenylpropan-2-one 4**2f** (31.6 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (8/1 (v/v)) as an eluent to give *trans*- product in (29.1 mg, 62% yield) as colourless oil. 65% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral IC3), UV detector 220 nm, eluent: Hexane/IPA = 9/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{22.7}$ = –1.00 (c 0.47, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.41 Hz, 1H), 7.53 (t, *J* = 7.26 Hz, 1H), 7.38 (t, *J* = 7.26 Hz, 2H), 7.30–7.33 (m, 3H), 7.13 (d, *J* = 6.88 Hz, 2H), 3.00 (d, *J* = 17.58 Hz, 1H,), 2.92 (t, *J* = 7.26 Hz, 1H), 2.79 (d, *J* = 17.58 Hz, 1H), 1.99 (q, *J* = 4.59 Hz, 1H), 1.69 (q, d = 4.59 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.73, 140.13, 138.46, 138.41,129.31, 129.26, 128.86, 128.74, 128.49, 127.35, 127.27, 126.64, 126.47, 65.55, 32.81, 30.45, 19.41 ppm.

1-(2-phenylcyclopropyl)pentan-1-one 45g



45g was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of styrene **39a** (104.2 mg, 1.0 mmol) with 2-diazo-2,3-dihydro-1H- inden-1-one **42g** (25.2 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (8/1 (v/v)) as an eluent to give the mixture of *trans*- and *cis*-diastereomers in (18.2 mg, 45% yield, dr = 95:5) as yellow oil. 90% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral OD), UV detector 220 nm, eluent: Hexane/IPA = 60/1, Flow rate: 0.5 ml/min. $[\alpha]_D^{23}$ = –1.3679 (c 0.53, $CHCl_3$).

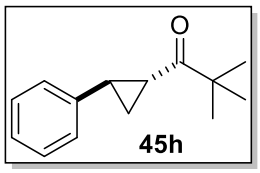
Trans– product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08–7.29 (m, 5H, Ar–**H**), 2.58 (t, *J* = 7.26 Hz, 2H, $OCCH_2$), 2.49 (ddd, *J* = 4.20, 6.50, 9.17 Hz, 1H, OCC**H** (cyclopropane)), 2.19 (ddd, *J* = 4.20, 5.35, 8.41 Hz, 1H, Ar–C**H** (cyclopropane)), 1.57–1.67 (m, 3H, C**H**H (cyclopropane),

$OCCH_2C\mathbf{H_2}$), 1.31–1.37 (m, 3H, CH**H** (cyclopropane), $C\mathbf{H_2}CH_3$), 0.903 (t, *J* = 7.26 Hz, 3H, $C\mathbf{H_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.35, 140.60, 128.57, 126.67, 126.13, 43.86, 32.27, 28.88, 26.16, 22.46, 18.92, 13.94 ppm.

HRMS (DART) calcd for $C_{14}H_{19}O$ $[M+H]^+$: 203.14359 found 203.14360.

IR (neat) ν 2957, 2931, 1697, 1399, 1065, 697 cm^{-1}.

2,2-dimethyl-1-(2-phenylcyclopropyl)propan-1-one 45h

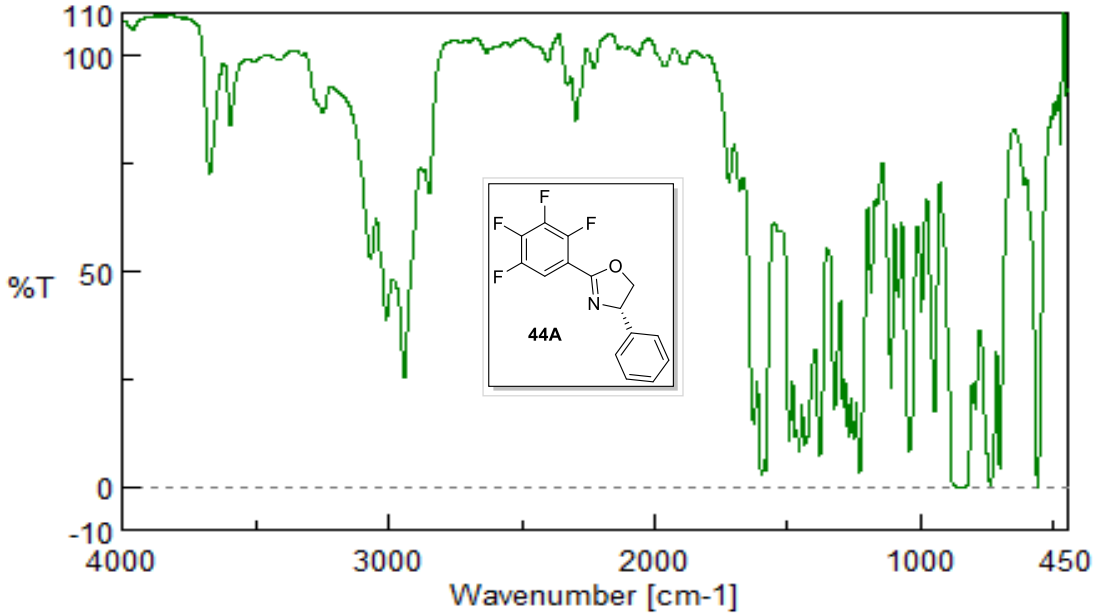


45h was obtained according to the typical procedure for the asymmetric cyclopropanation reactions of styrene **3a** (104.2 mg, 1.0 mmol) with 1-diazo-3,3-dimethylbutan-2-one **42h** (25.2 mg, 0.2 mmol). The crude mixture was purified by silica gel column chromatography with Hexane/EtOAc (8/1 (v/v)) as an eluent to give the mixture of *trans*- and *cis*-diestereomers in (24.3 mg, 60% yield, dr = 92:8) as yellow oil. 41% *ee* (*trans*). The ee was determined chiral HPLC analysis. Column (Chiral OJH), UV detector 220nm, eluent: Hexane/IPA = 50/1, Flow rate: 1.0 ml/min. $[\alpha]_D^{22.9}$ = –0.4206 (c 0.26, $CHCl_3$).

Trans– product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.26 Hz, 2H, Ar–**H**), 7.21 (t, *J* = 7.26 Hz, 1H, Ar–**H**), 7.11 (d, *J* = 7.26 Hz, 2H, Ar–**H**), 2.42 (ddd, *J* = 4.20, 6.50, 9.17 Hz, 1H, OCC**H** (cyclopropane)), 2.37 (ddd, *J* = 3.82, 5.35, 8.03 Hz, 1H, Ar–C**H** (cyclopropane)), 1.63 (ddd, *J* = 4.20, 5.35, 9.03 Hz, 1H, C**H**H (cyclopropane)), 1.35 (ddd, *J* = 4.20, 6.50, 8.03 Hz, 1H, CH**H** (cyclopropane)), 1.20 (s, 9H, C-($C\mathbf{H_3}$)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.61, 140.68, 128.57, 126.51, 126.34, 44.11, 29.79, 29.21, 27.81, 26.31, 18.57 ppm. IR (neat) ν 2965, 1690, 1365, 1068, 697 cm^{-1}.

HRMS (DART) calcd for $C_{14}H_{19}O$ $[M+H]^+$: 203.14359 found 203.14360.

IR SPECTRA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F
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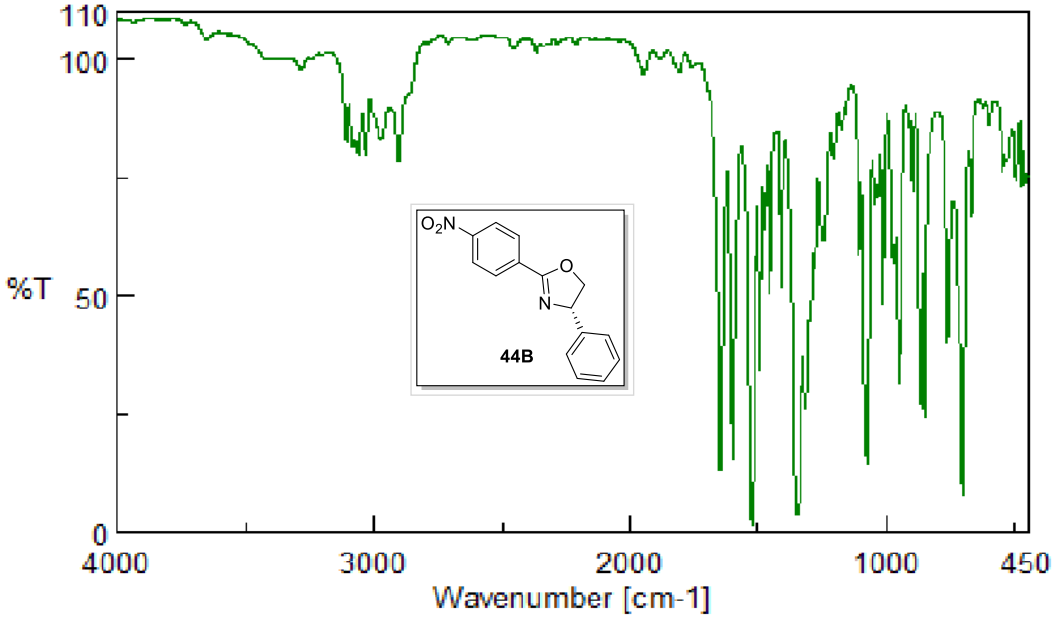
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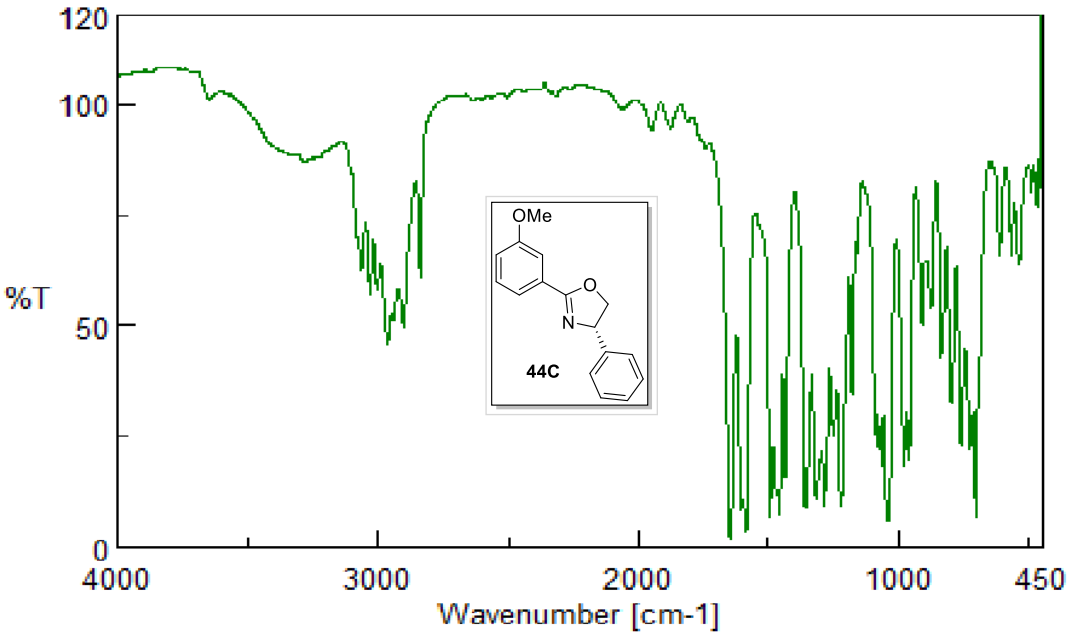
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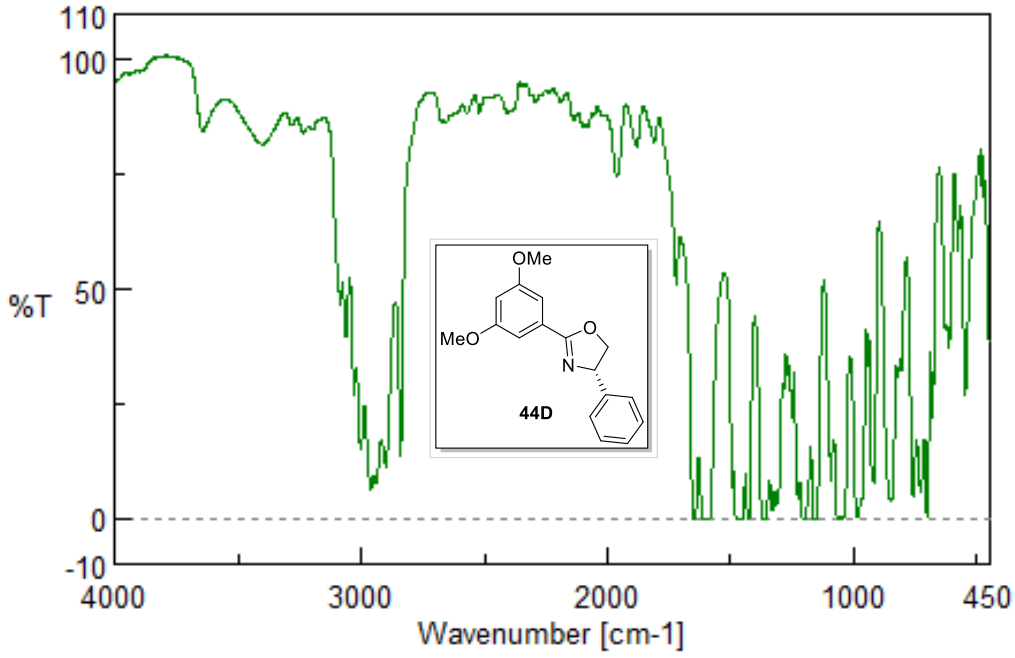
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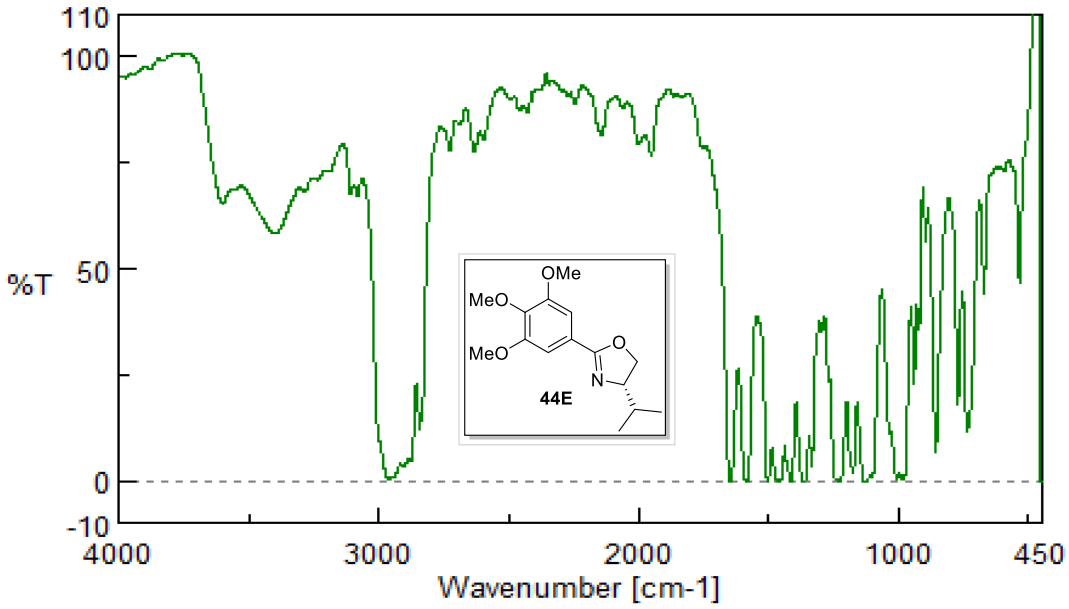
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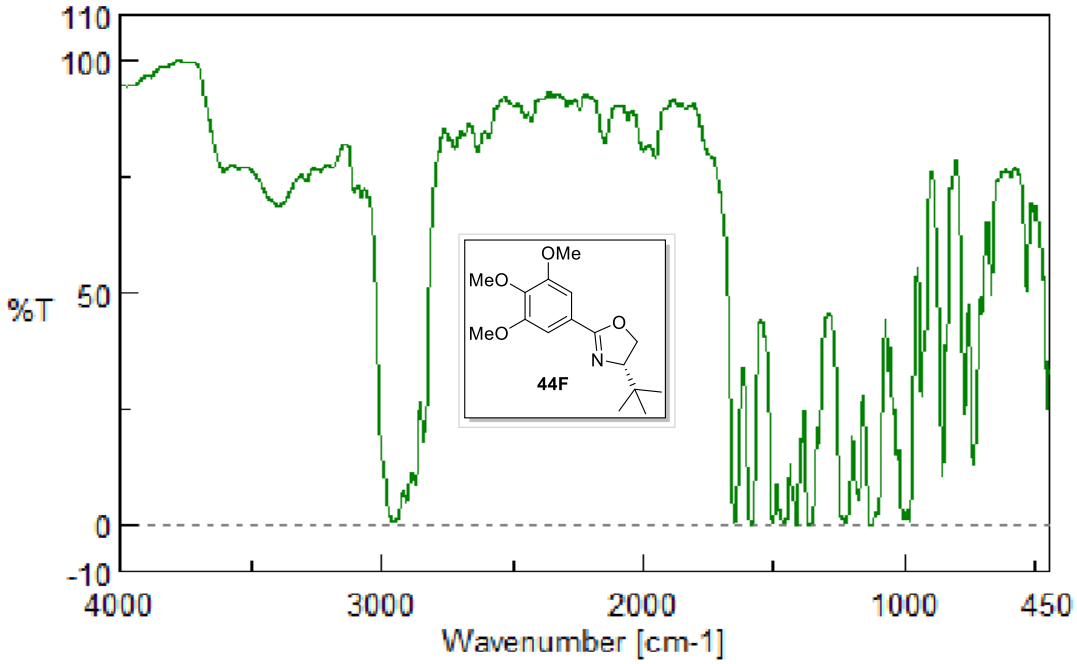
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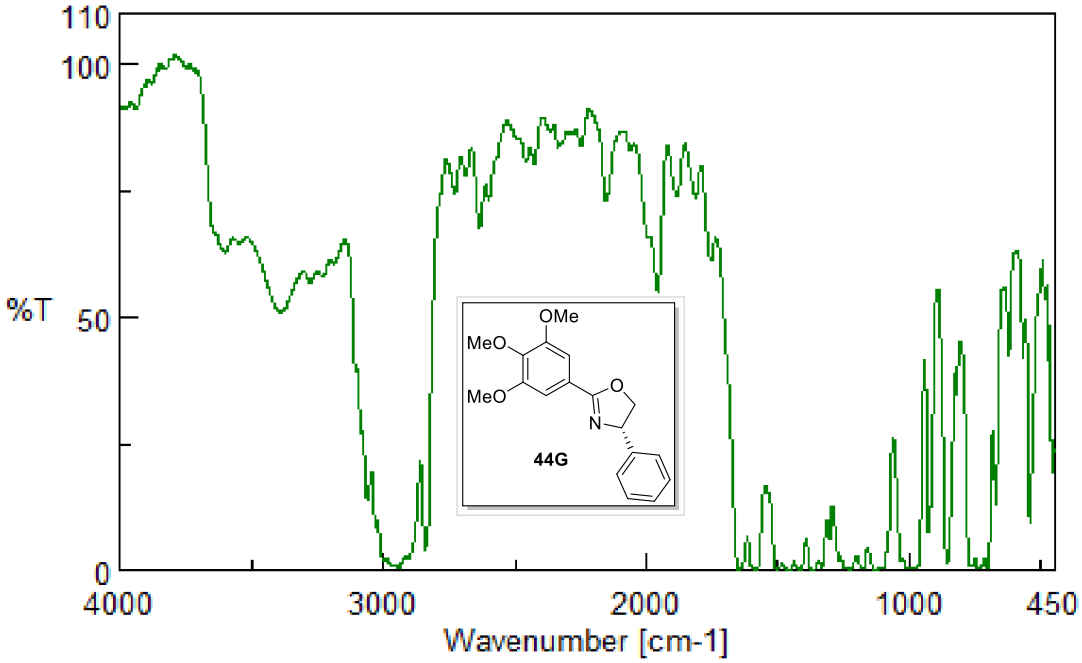
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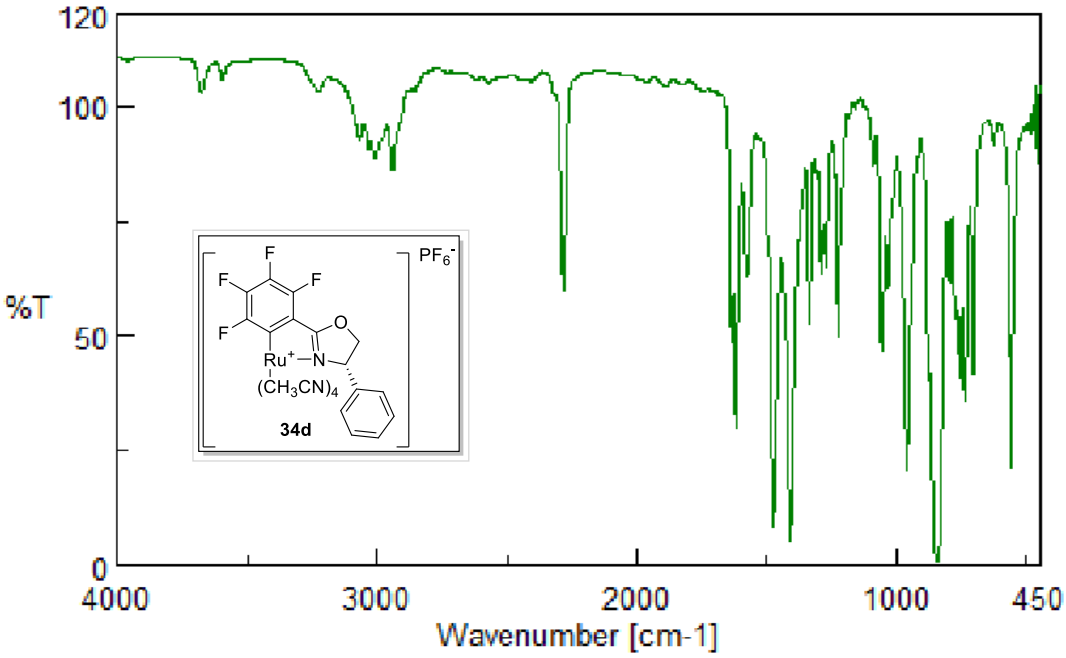
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F
F
F
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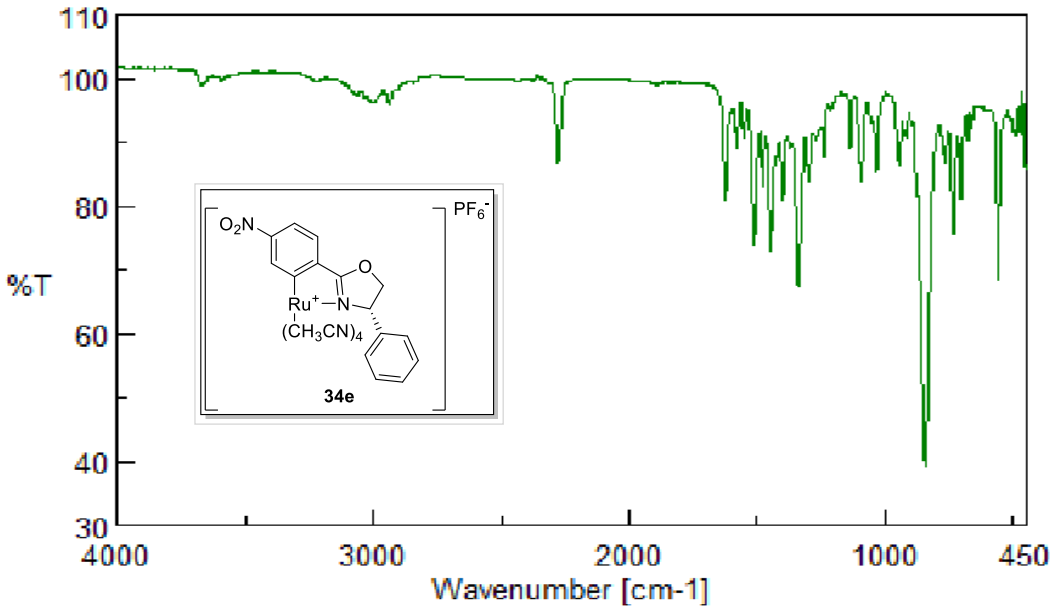
PF6-
34d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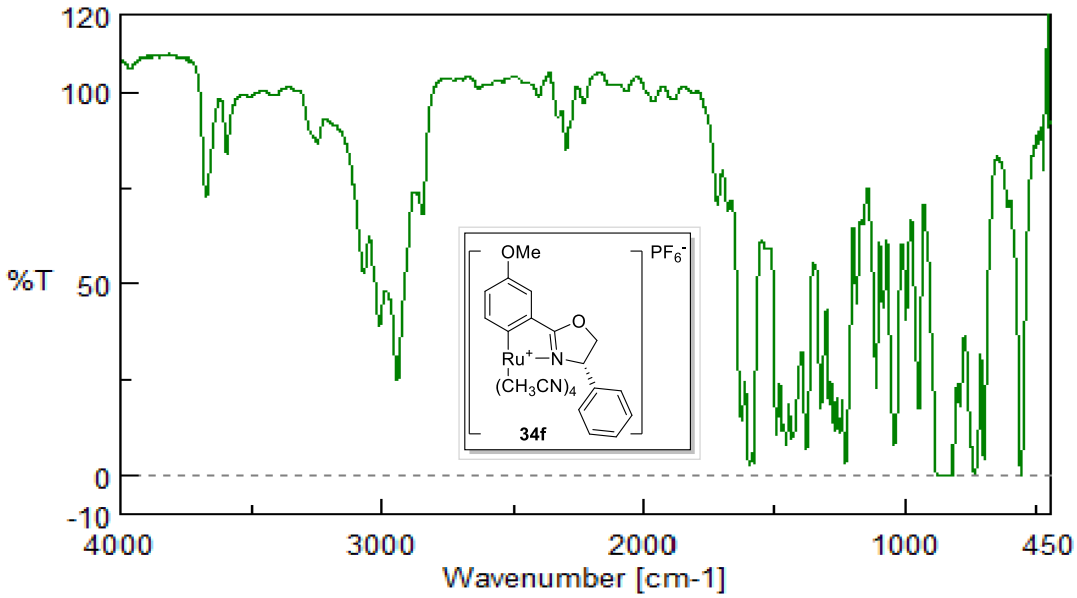
N
O
(CH3CN)4
34e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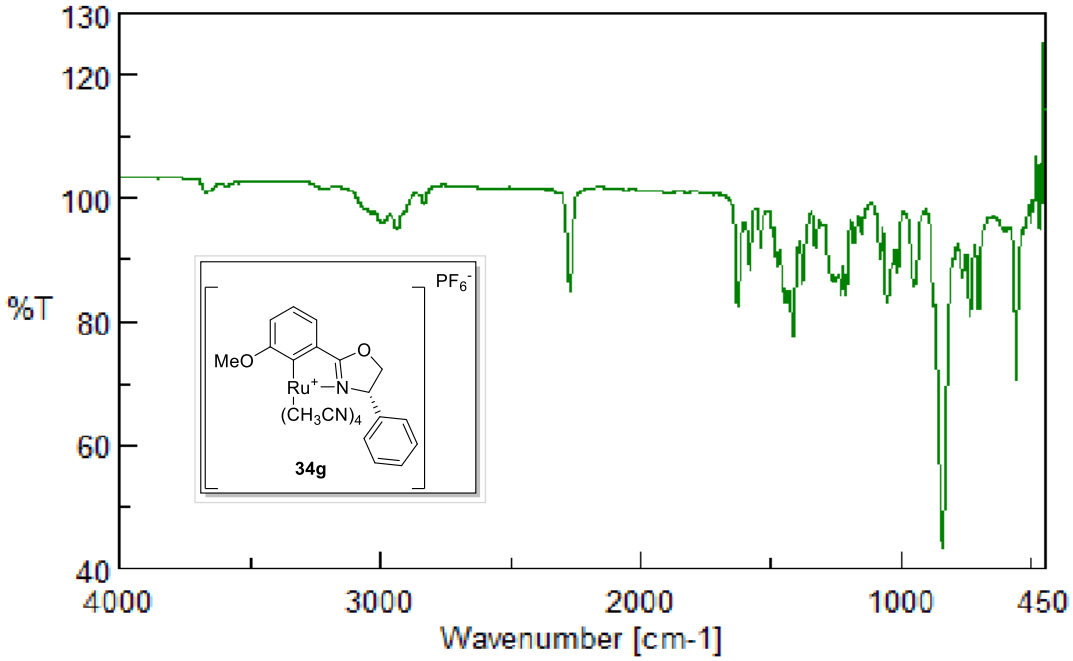
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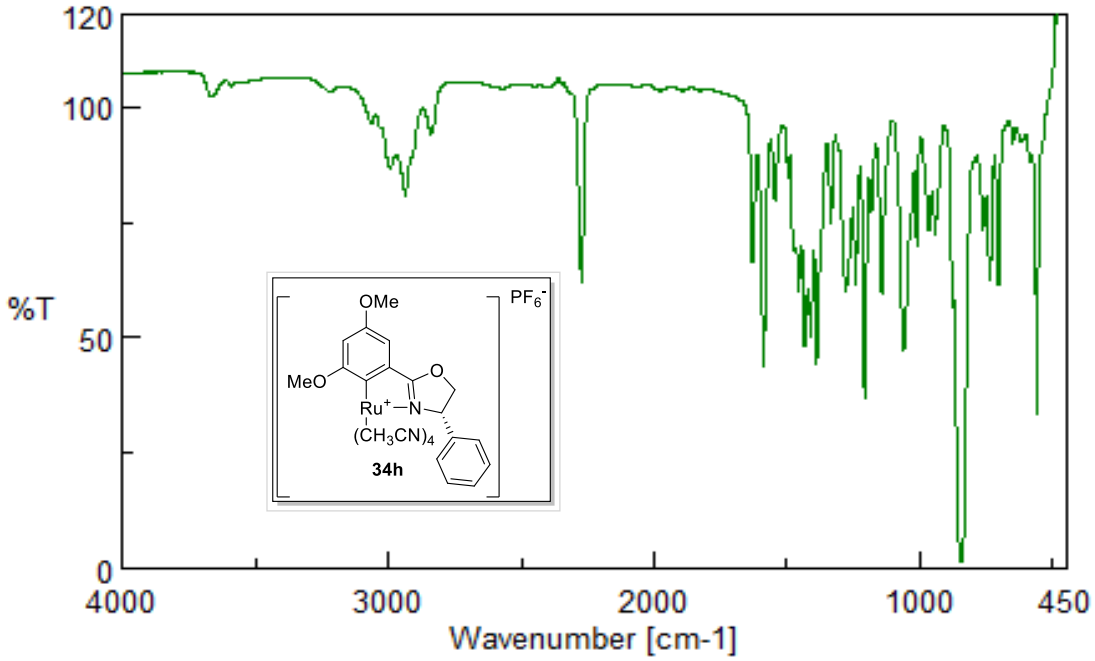
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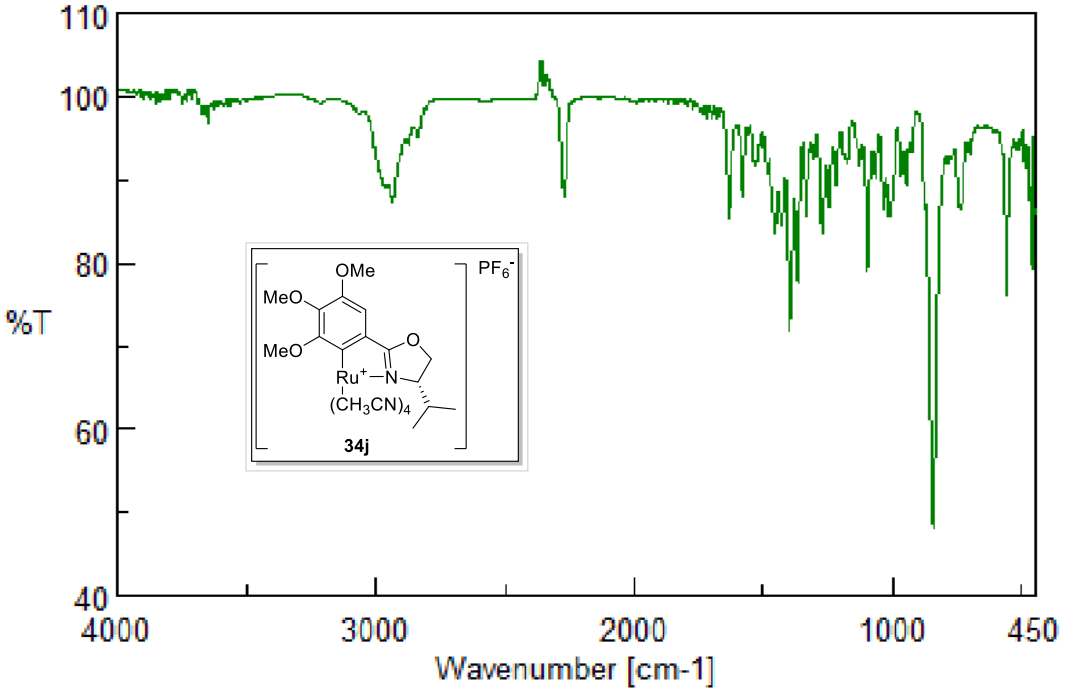
Ru+
N
O
(CH3CN)4
PF6-
34h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PF6-
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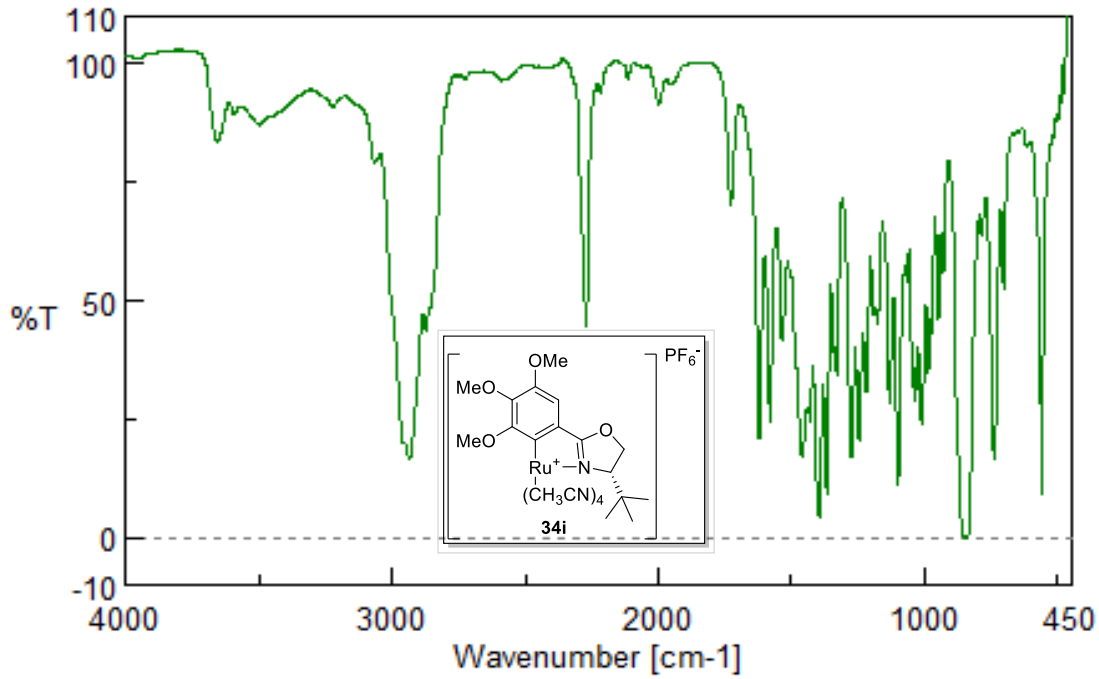
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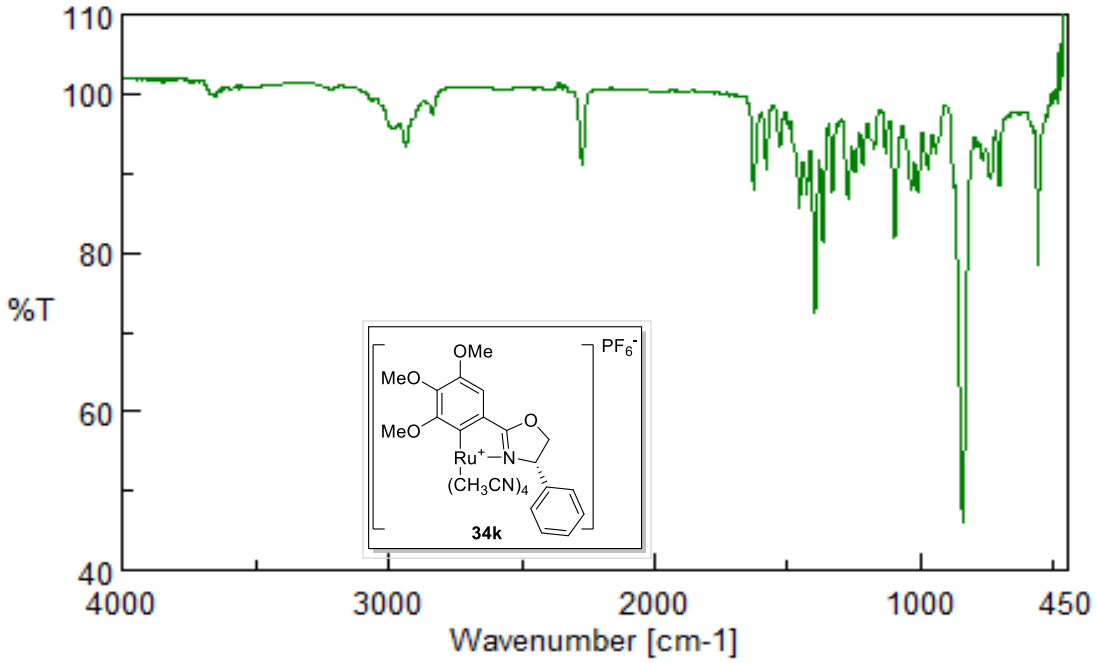
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PF6-
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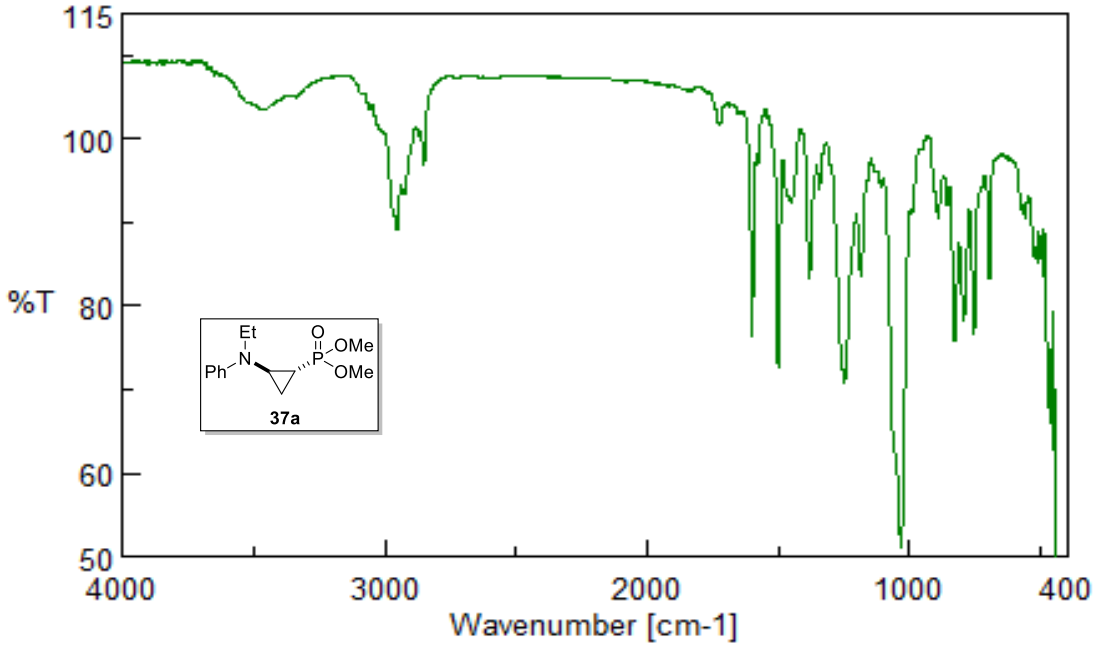
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P
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OMe
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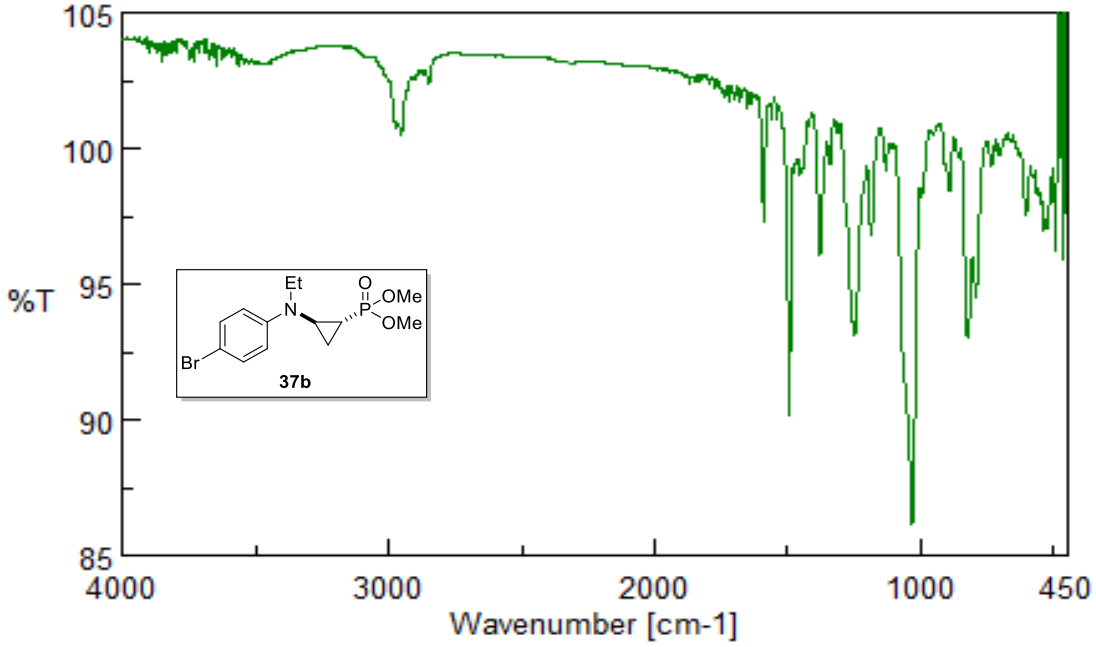
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Br
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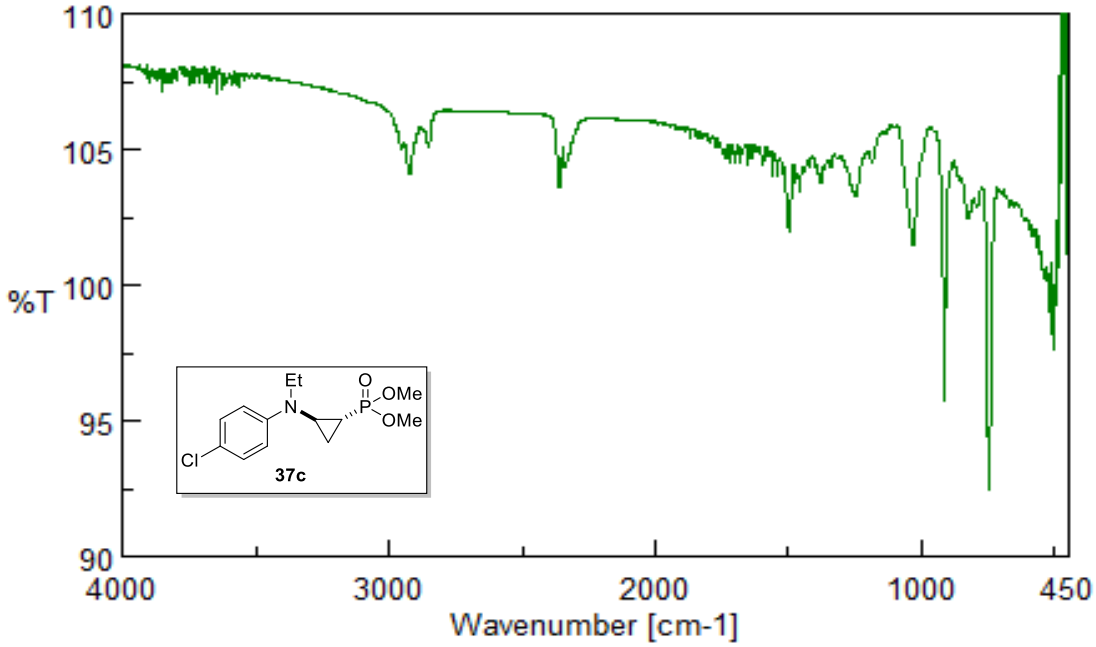
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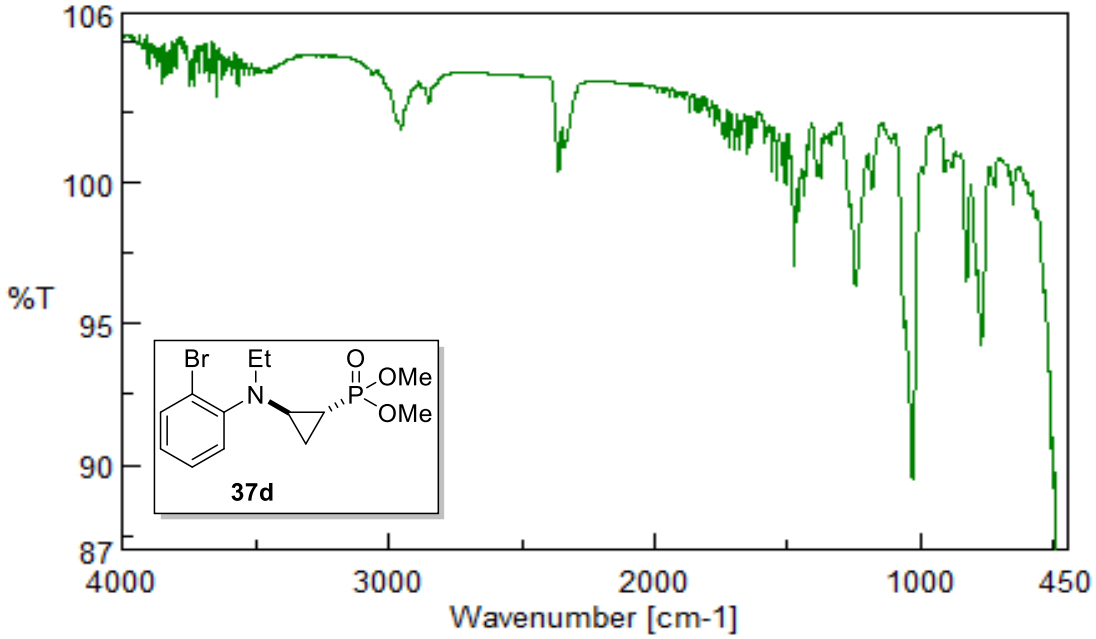
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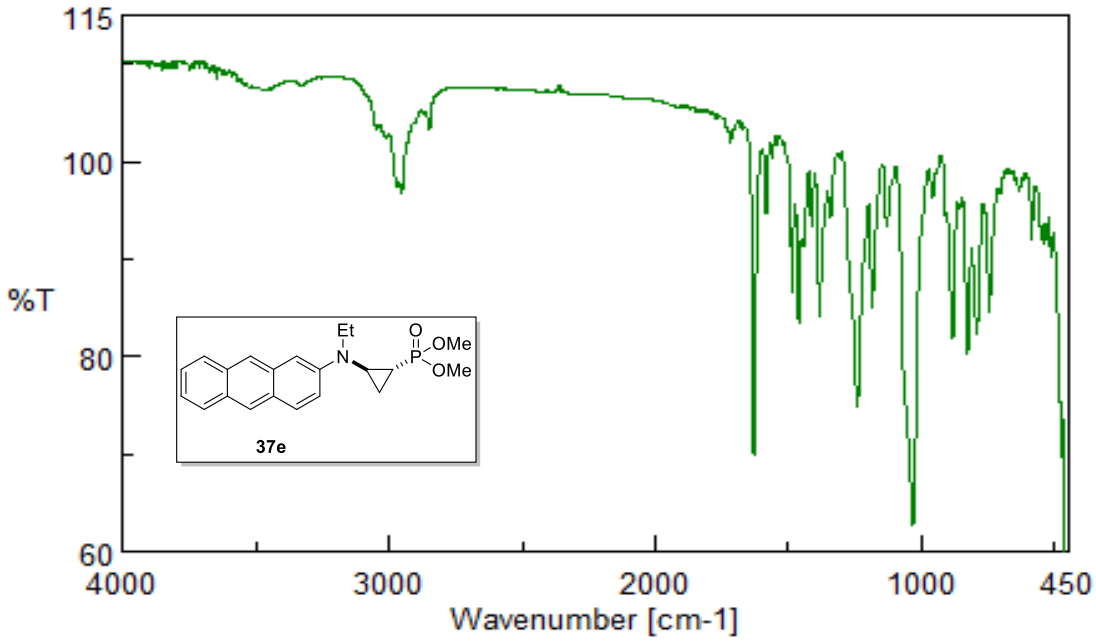
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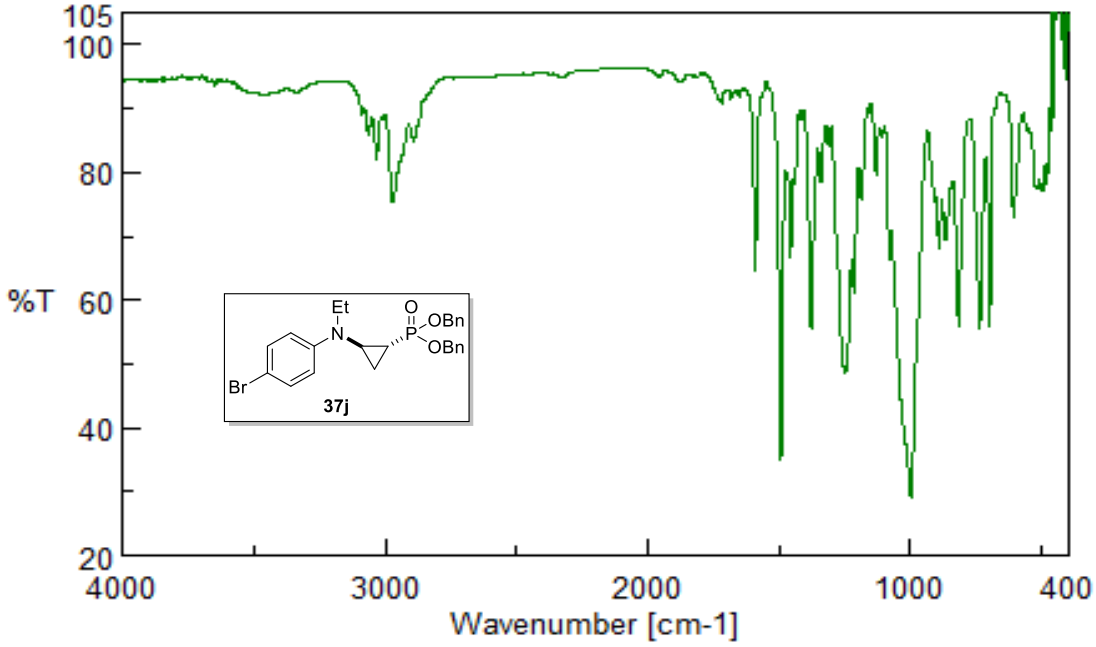
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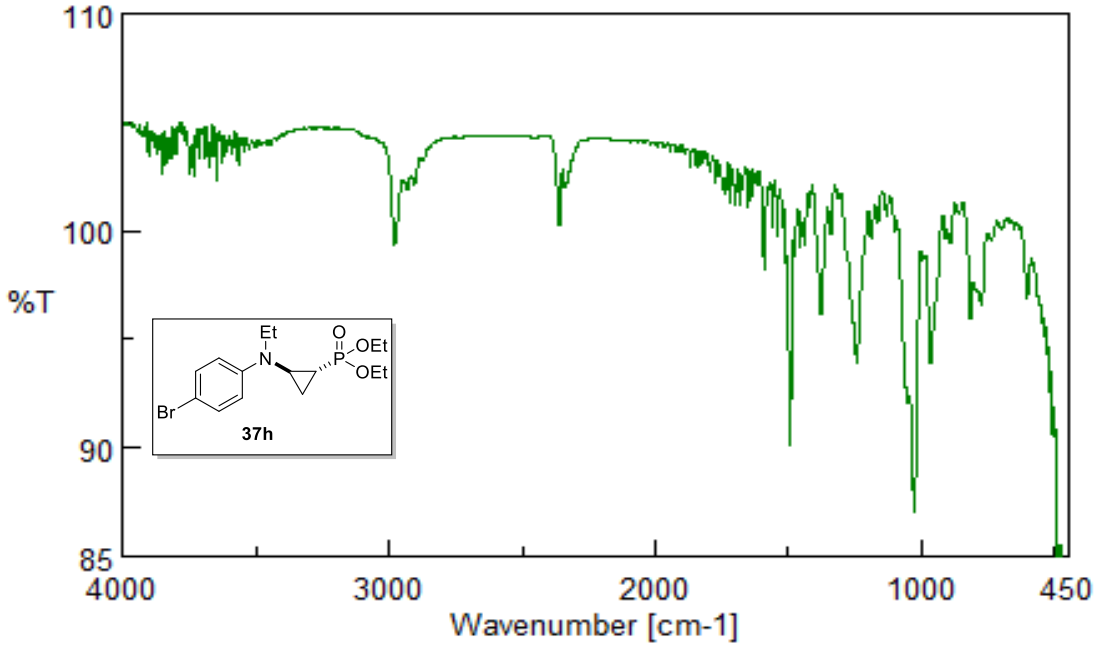
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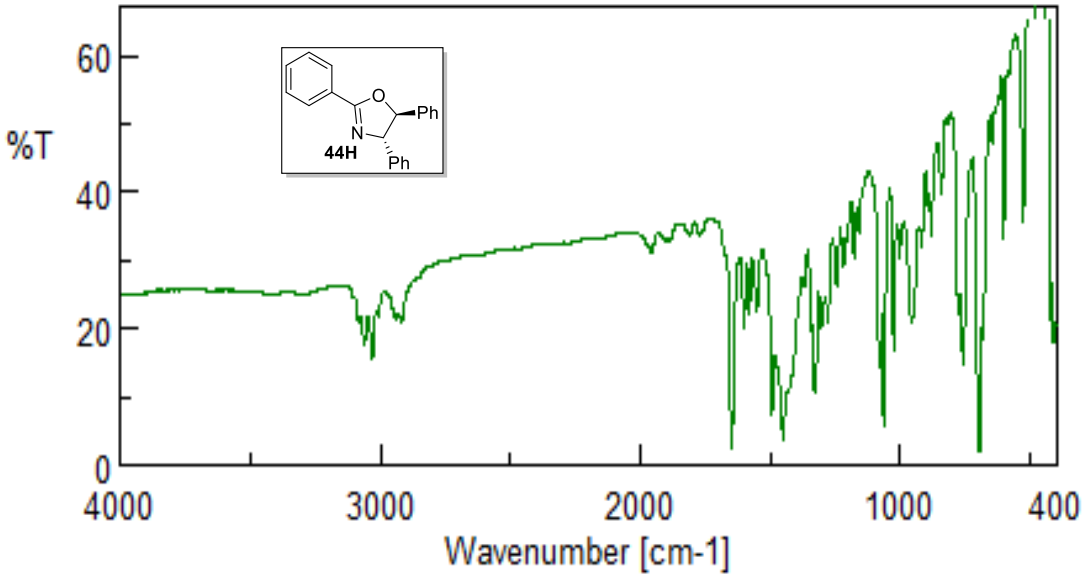
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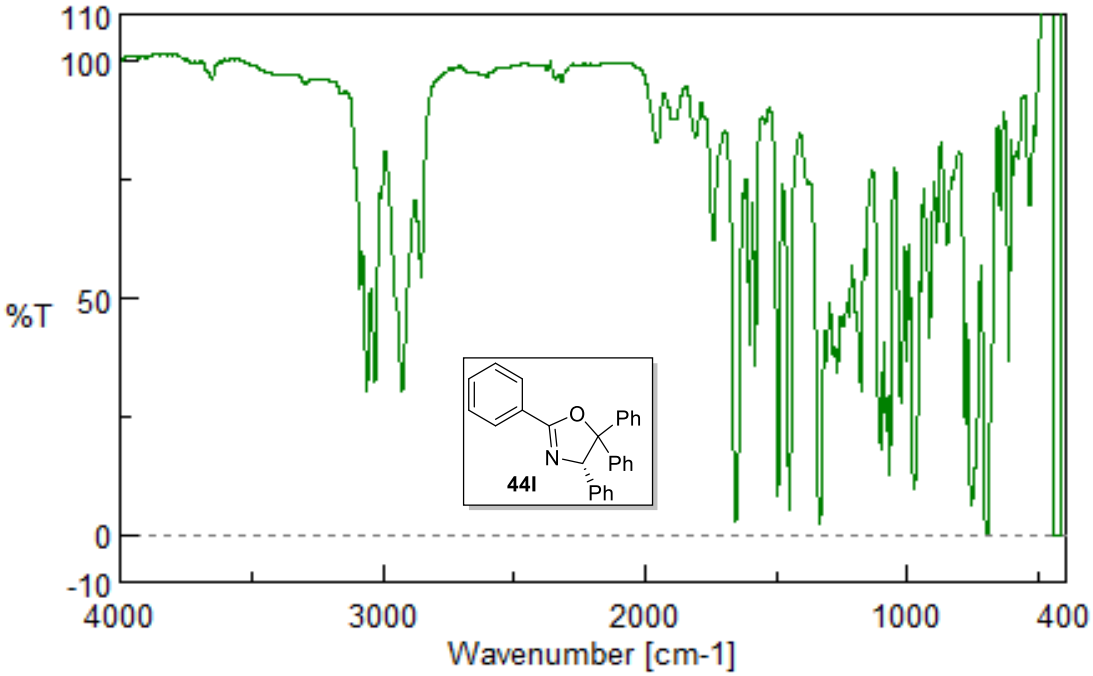
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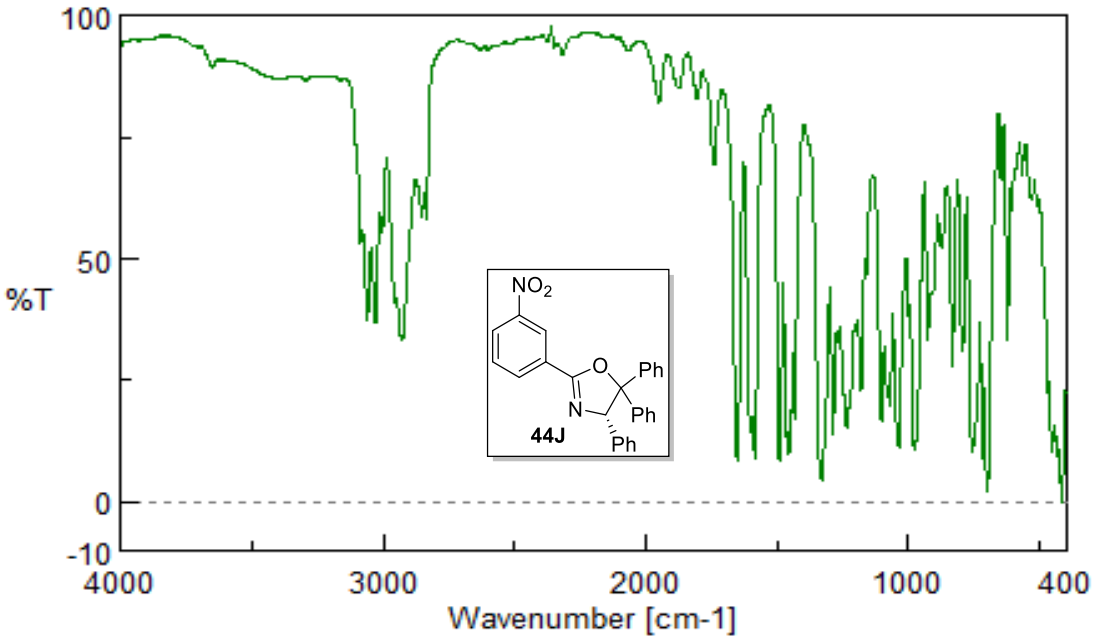
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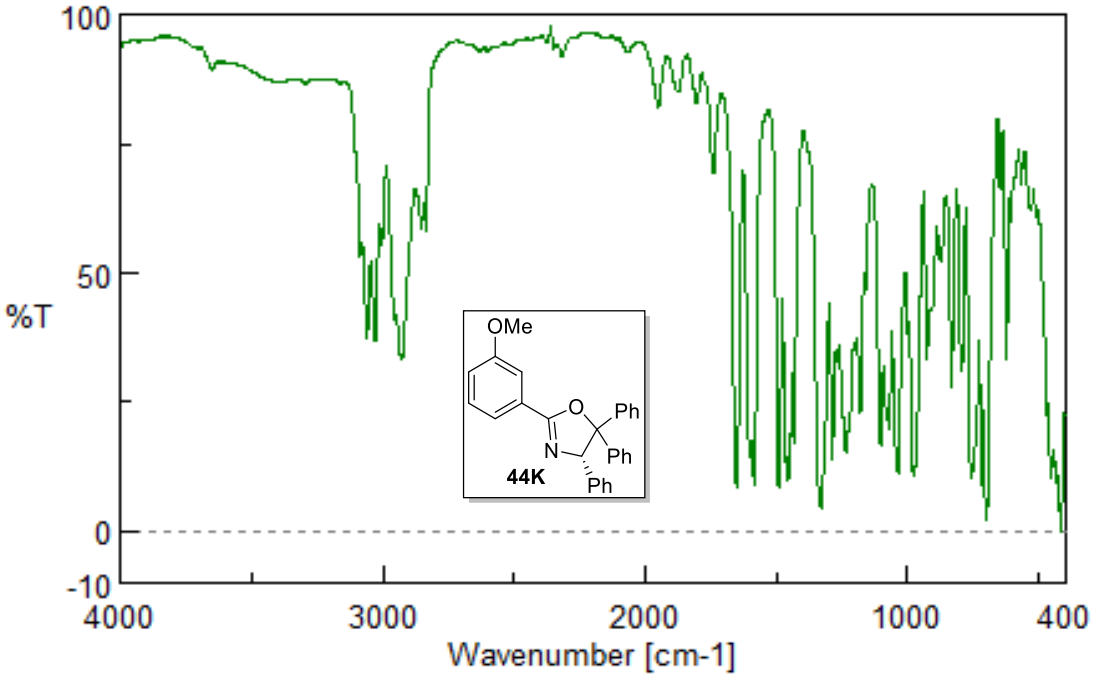
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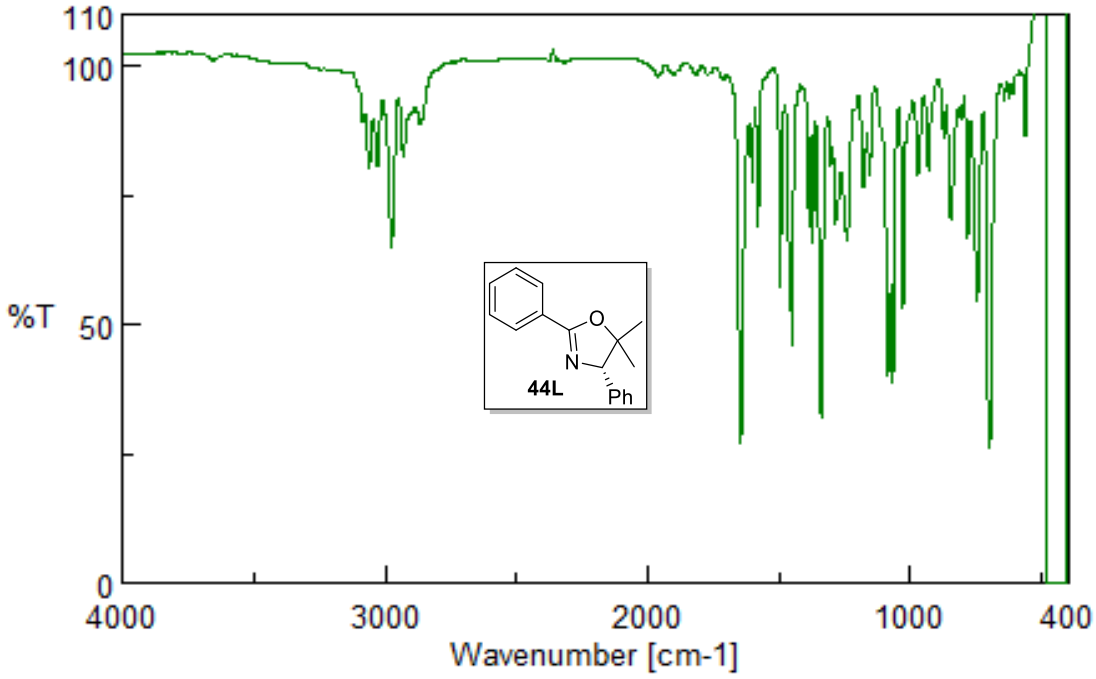
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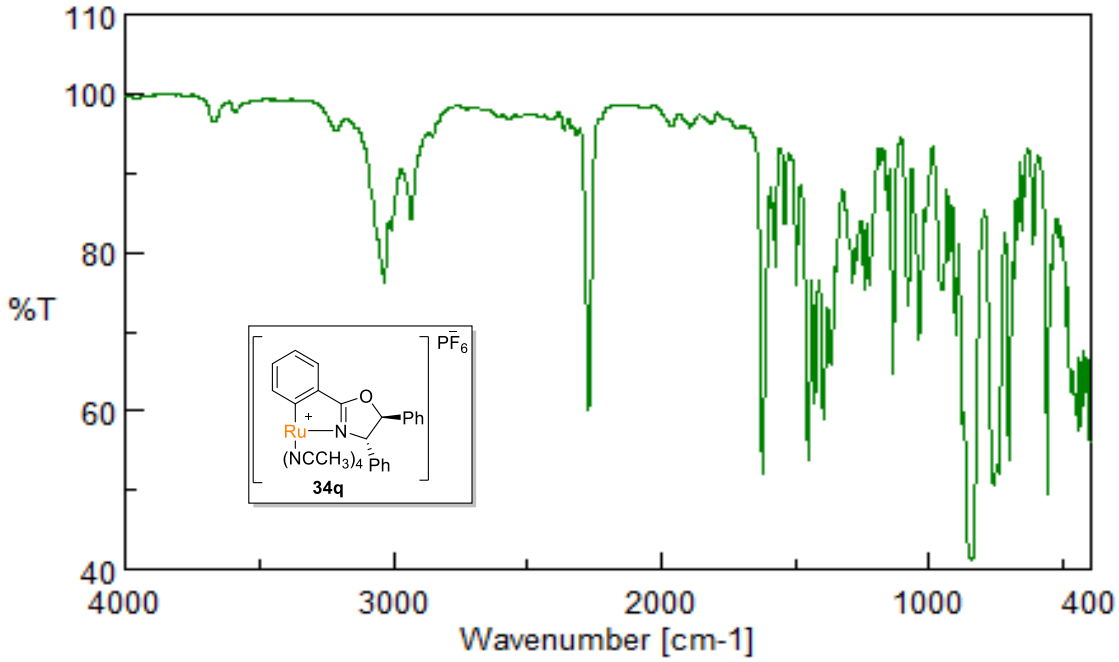
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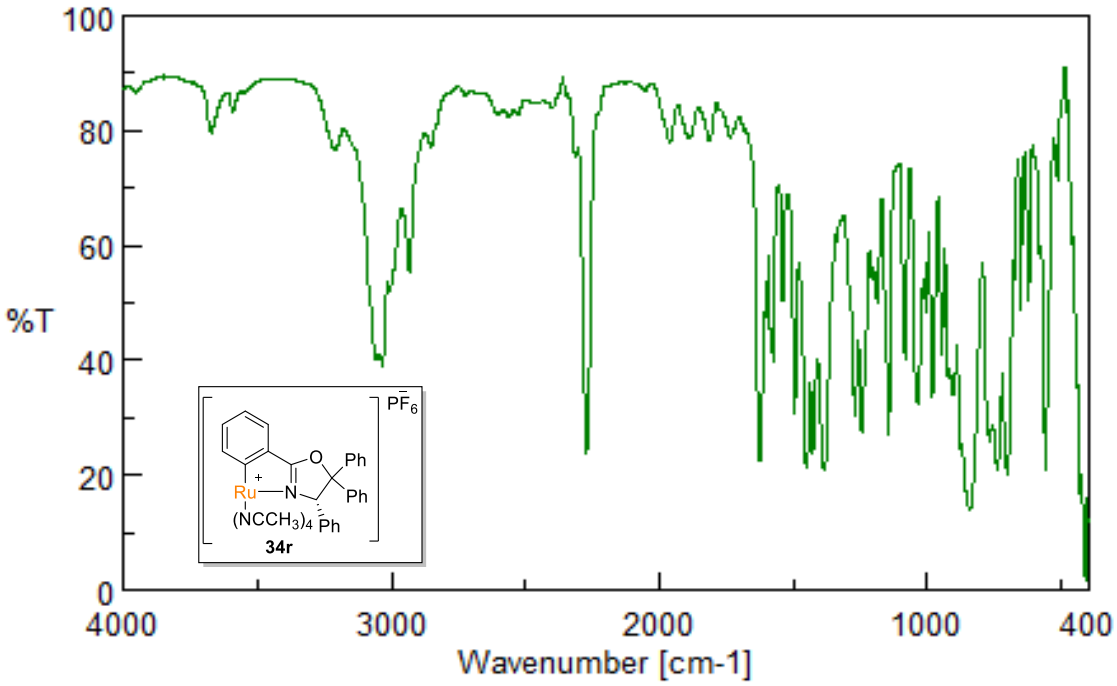
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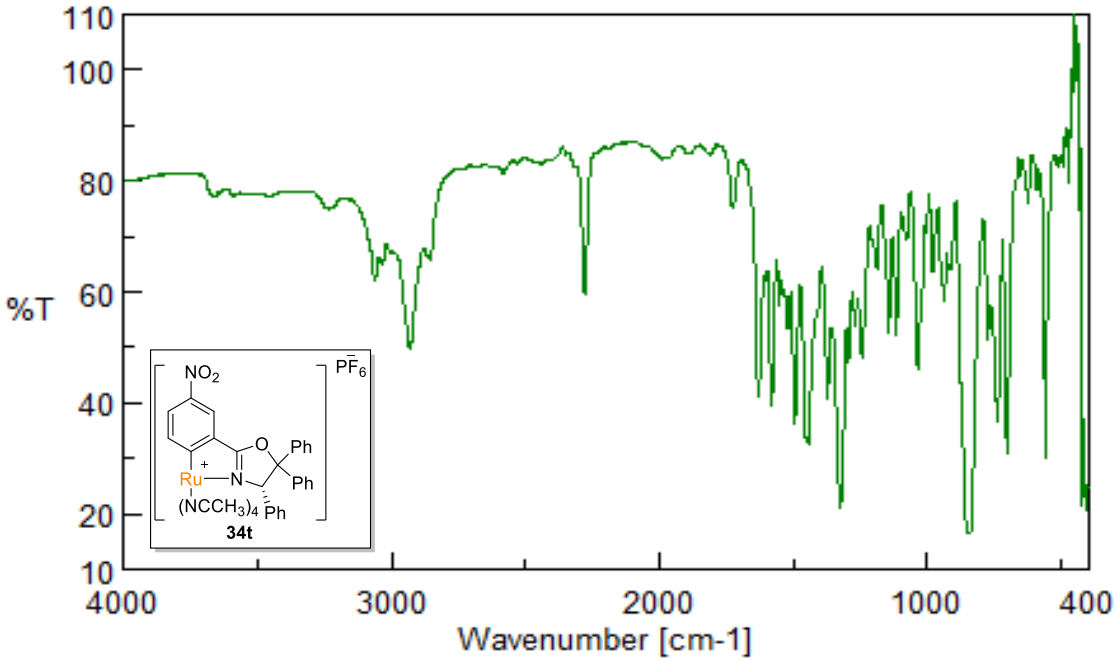
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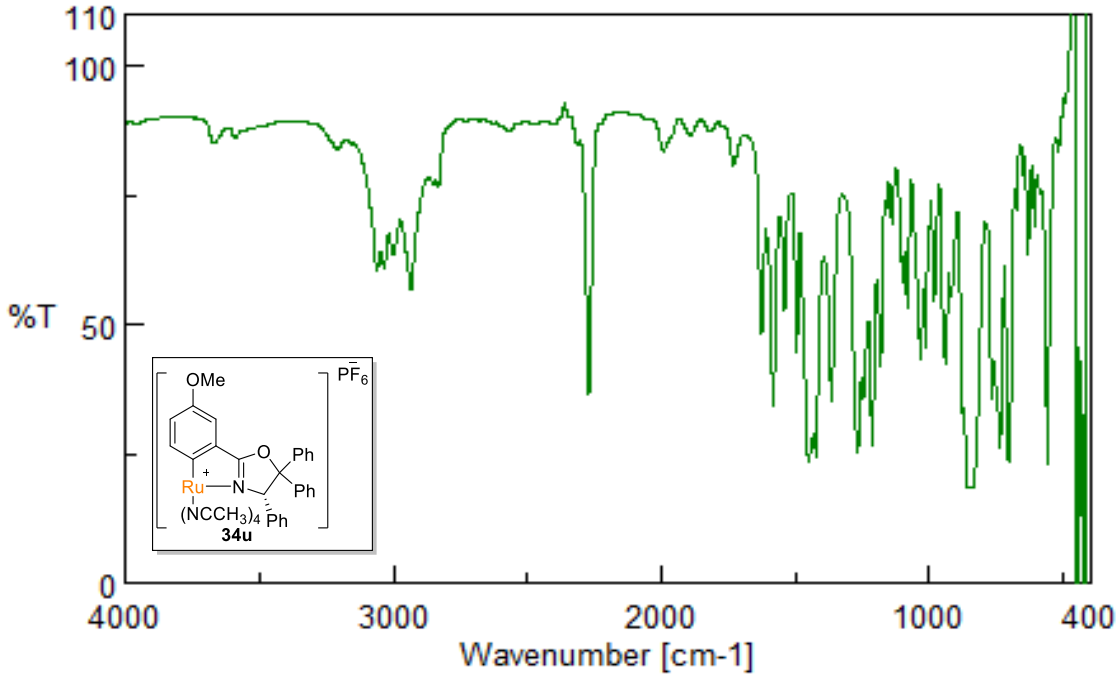
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(NCCH3)4
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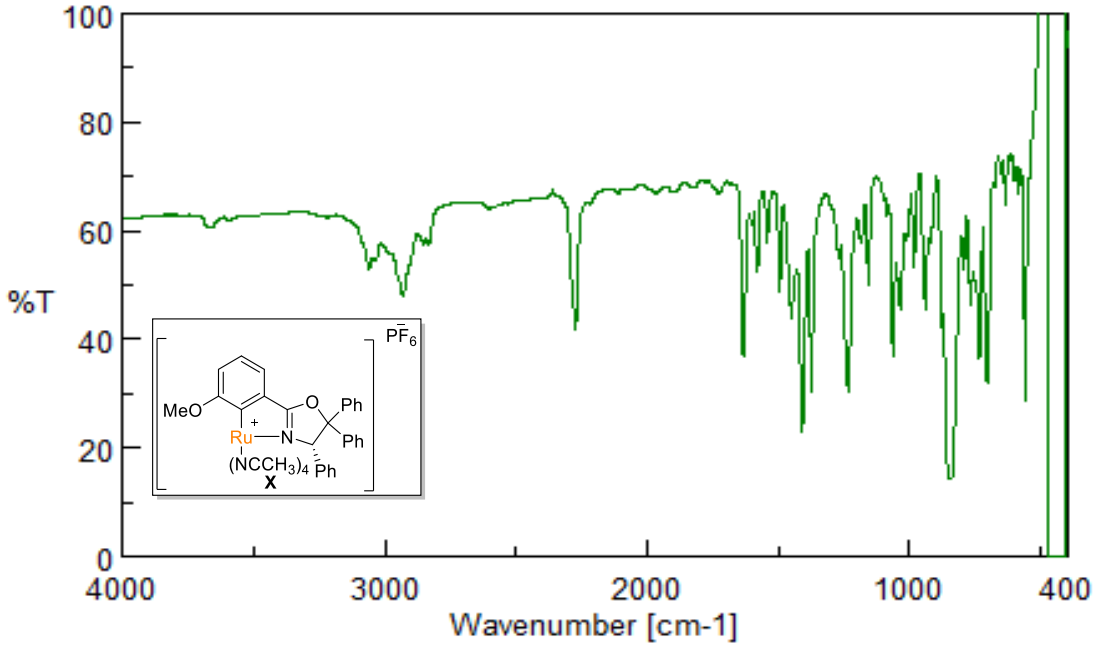
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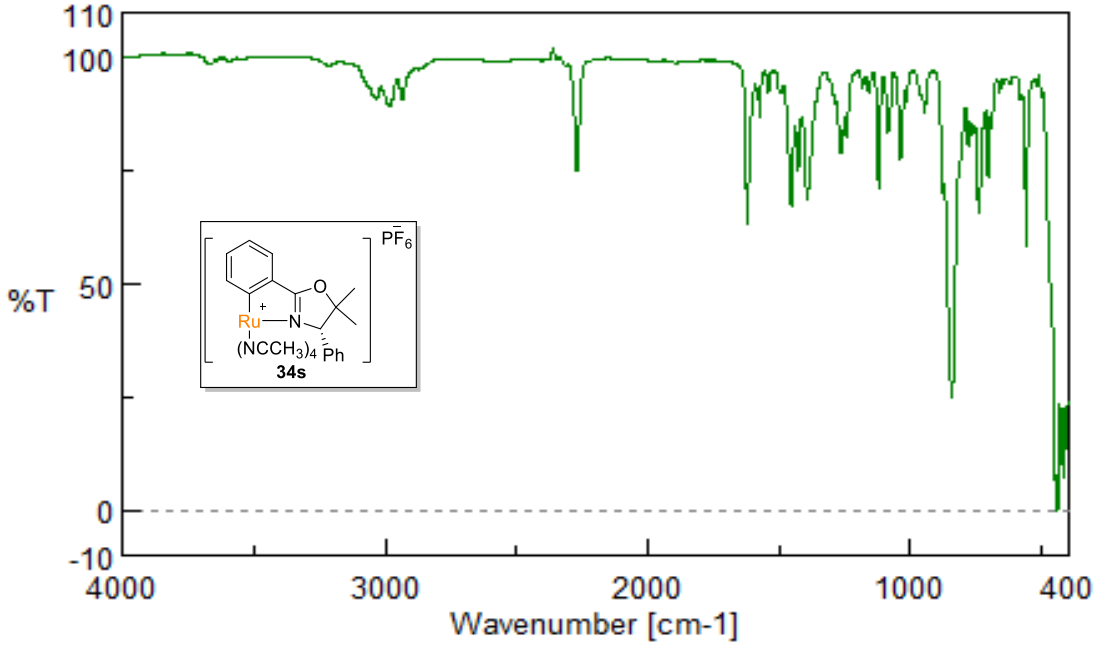
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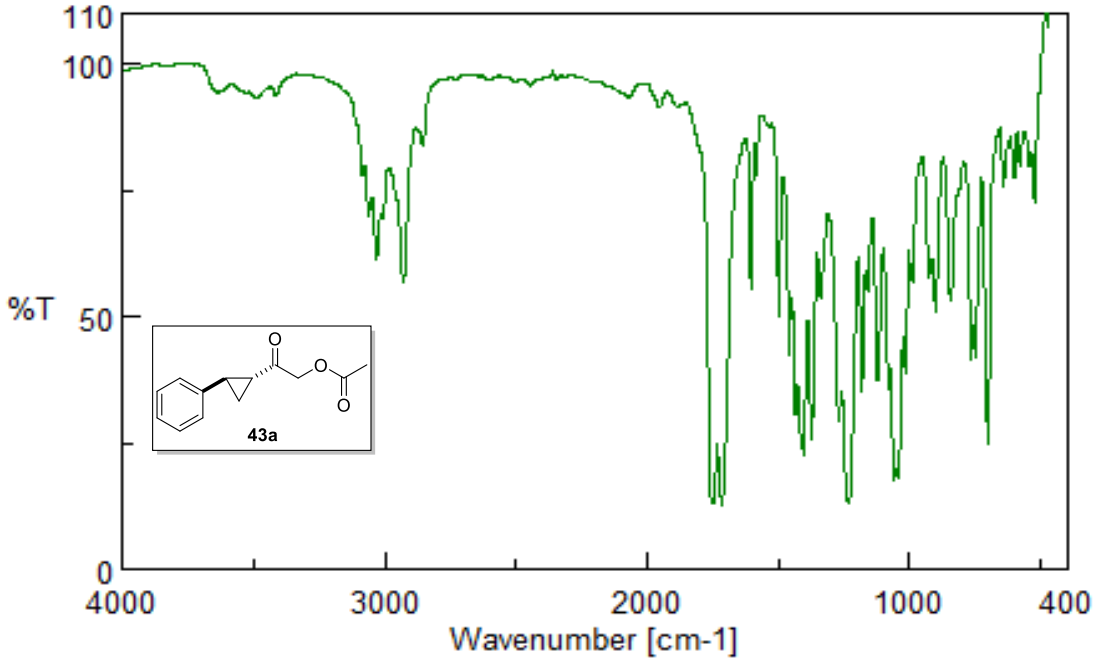
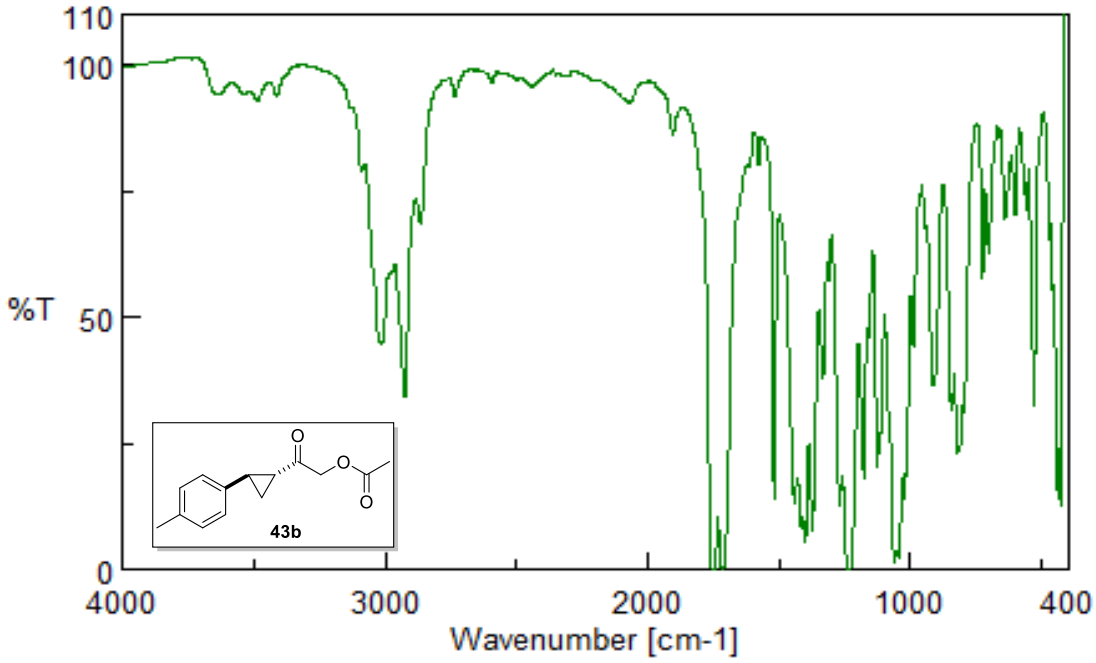
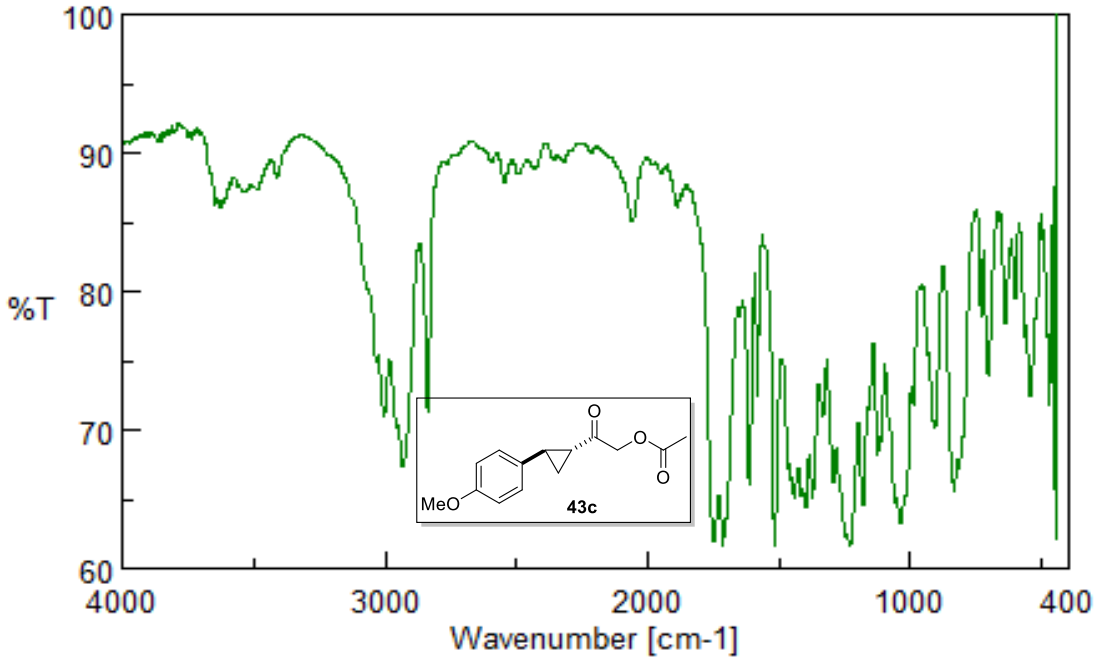
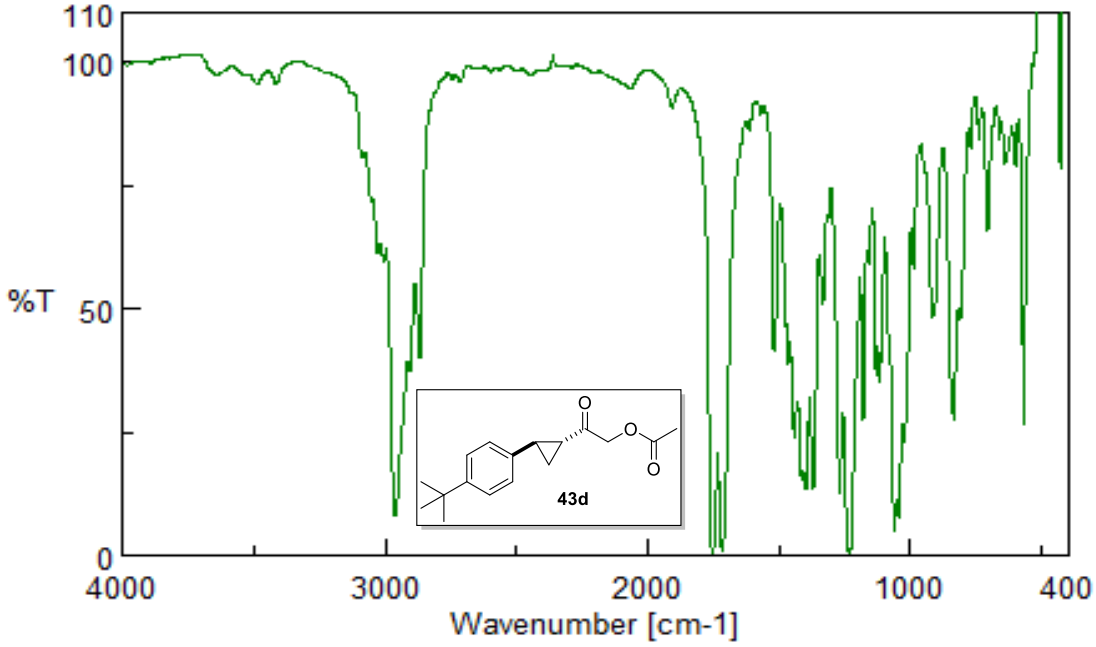
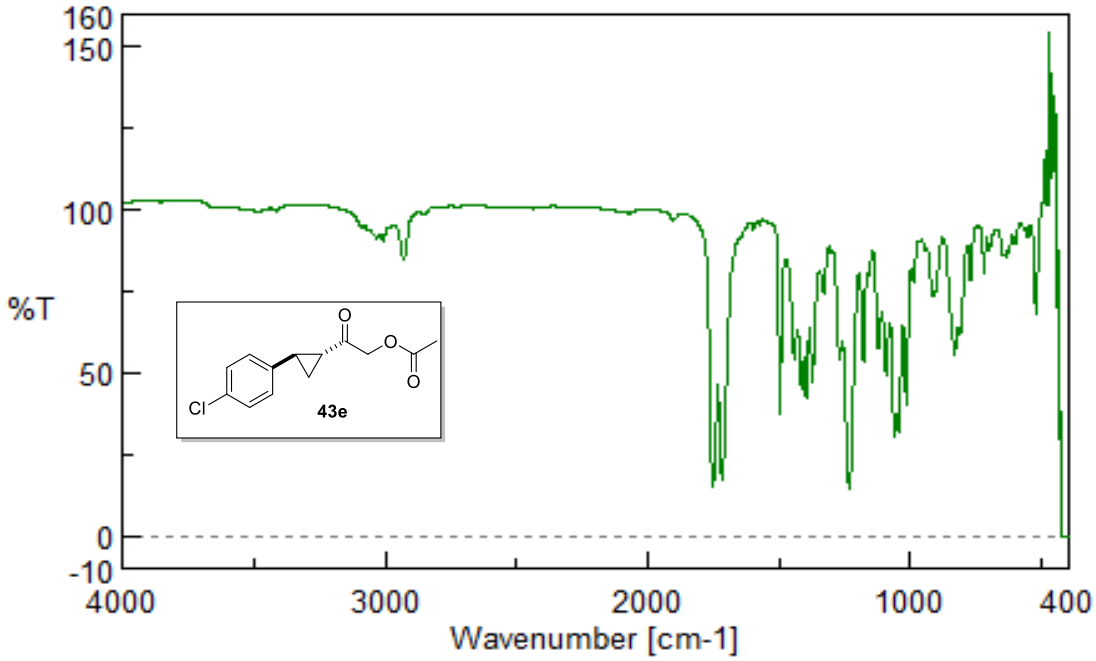
1000
400
Wavenumber [cm-1]
PF6
Ru
N
O
(NCCH3)4
Ph
34s

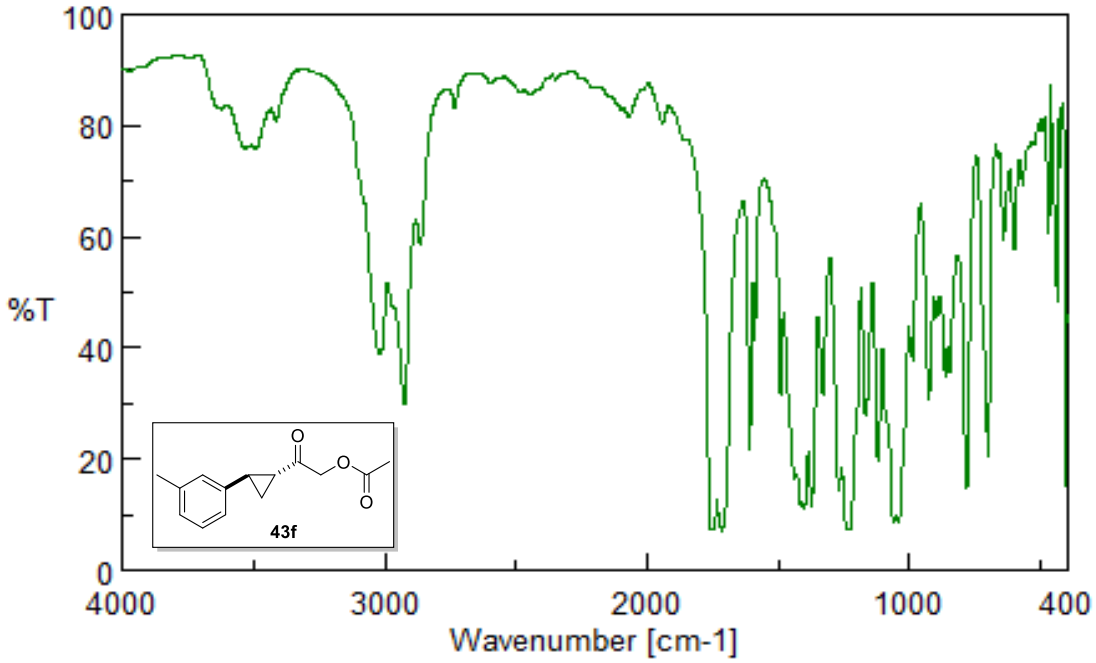

110
100
50
0
%T
4000
3000
2000
1000
400
Wavenumber [cm-1]
O
O
O
43a

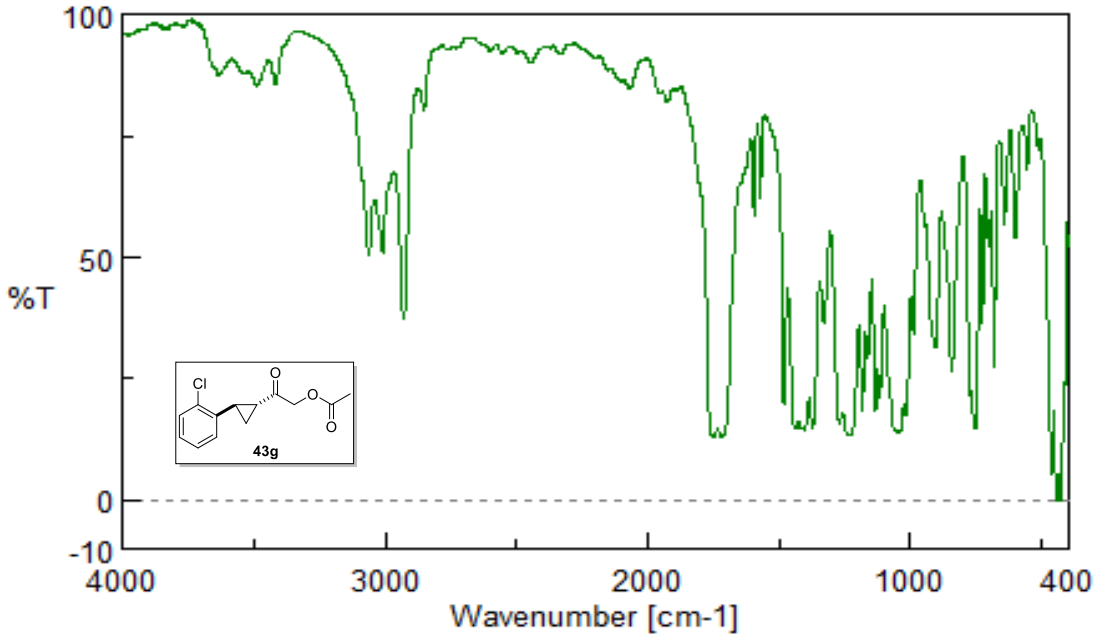

110
100
%T
50
0
4000
3000
2000
1000
400
Wavenumber [cm-1]
O
O
O
43b

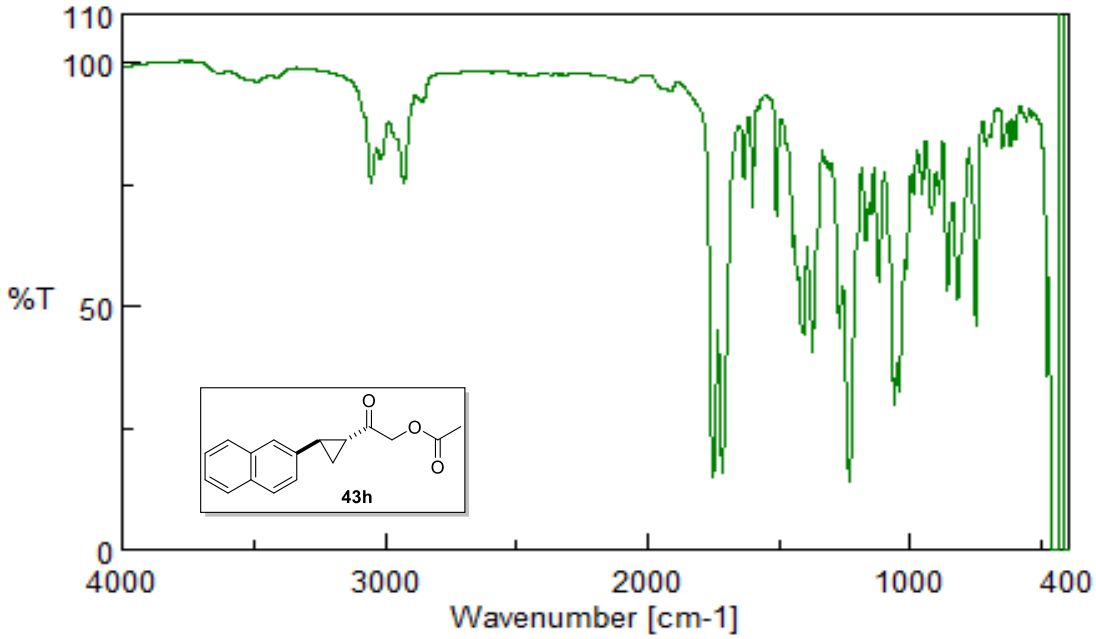

100
90
%T
80
70
60
4000
3000
2000
1000
400
Wavenumber [cm-1]
O
O
O
MeO
43c

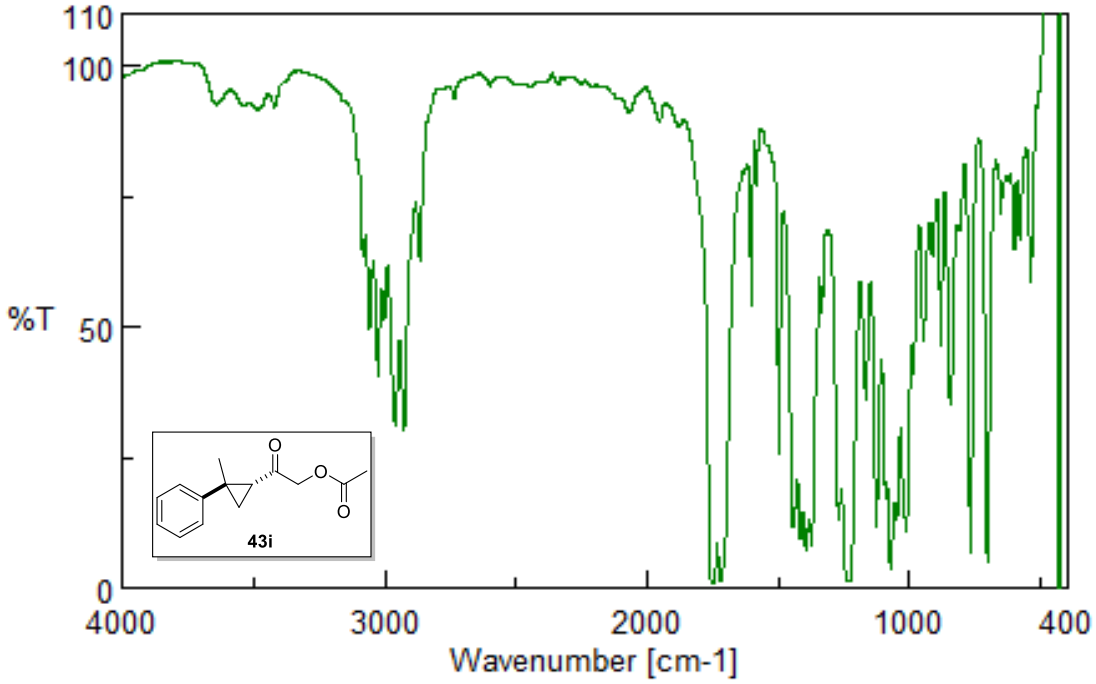

110
100
%T
50
0
4000
3000
2000
1000
400
Wavenumber [cm-1]
43d

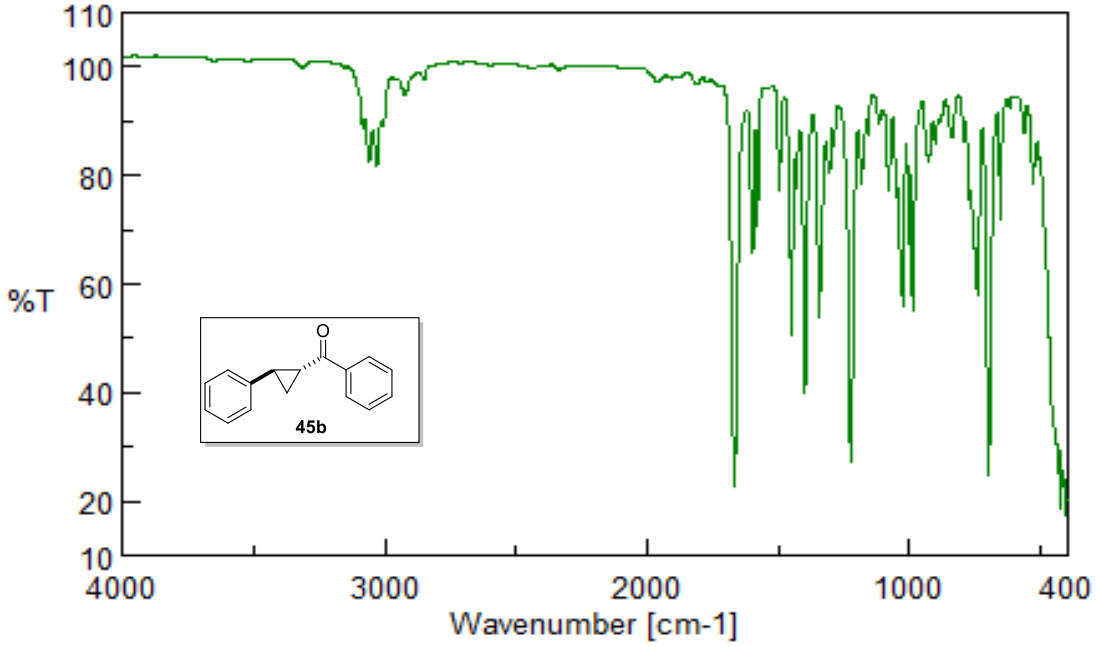

160
150
100
%T
50
0
-10
4000
3000
2000
1000
400
Wavenumber [cm-1]
Cl
43e

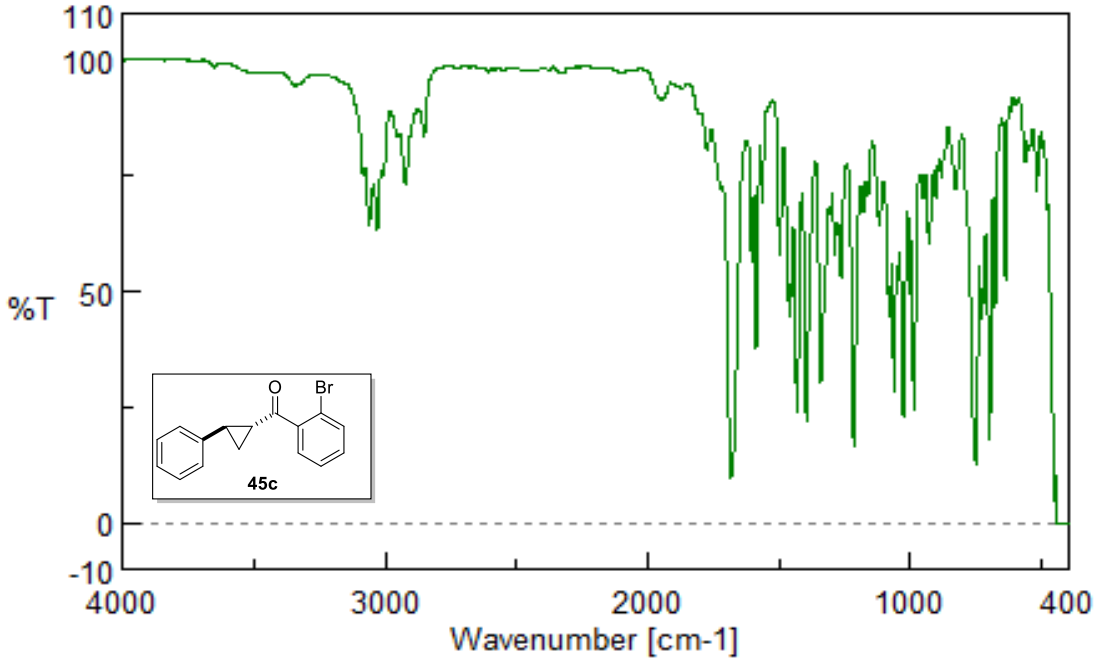

100
80
60
%T
40
20
0
4000
3000
2000
1000
400
Wavenumber [cm-1]
43f

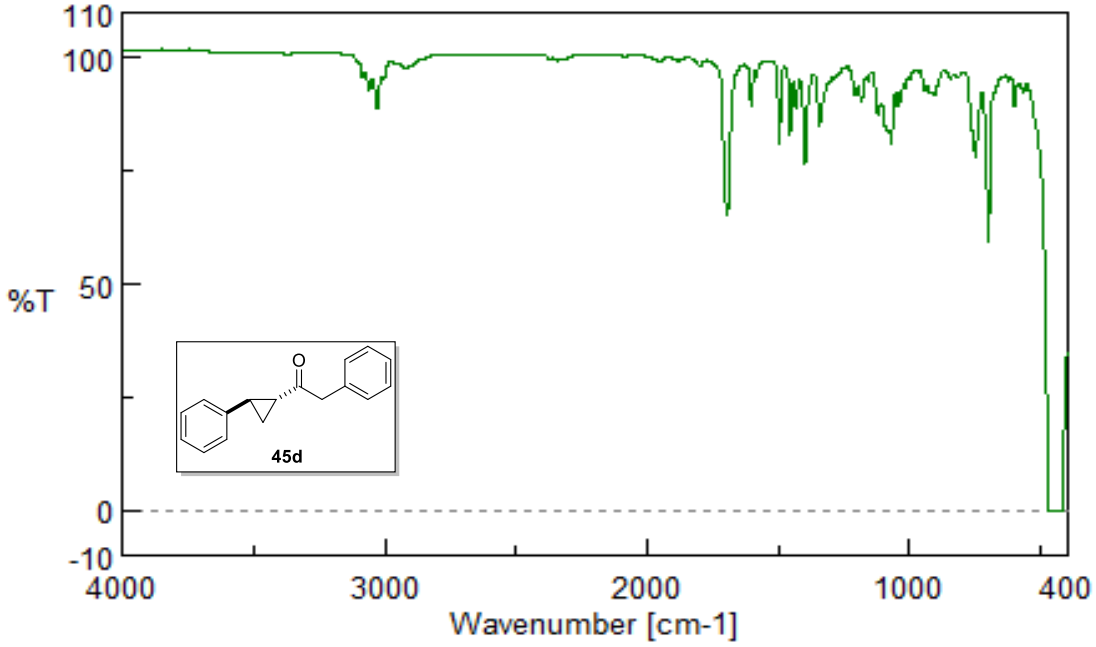

100
50
%T
0
-10
4000
3000
2000
1000
400
Wavenumber [cm-1]
Cl
43g

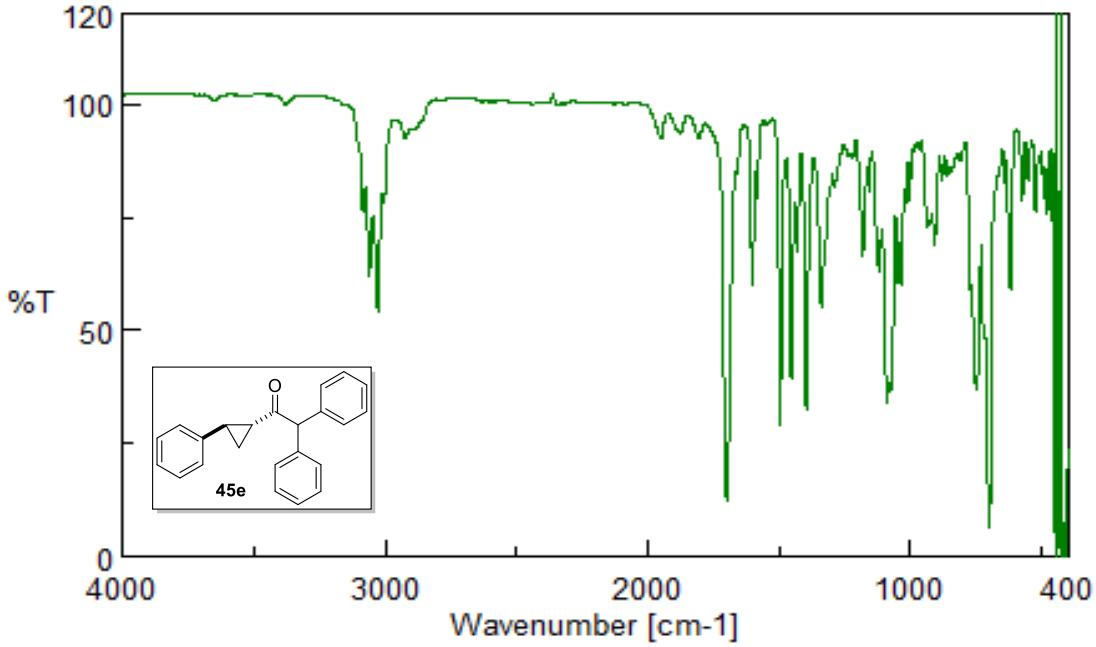

110
100
%T
50
0
4000
3000
2000
1000
400
Wavenumber [cm-1]
43h

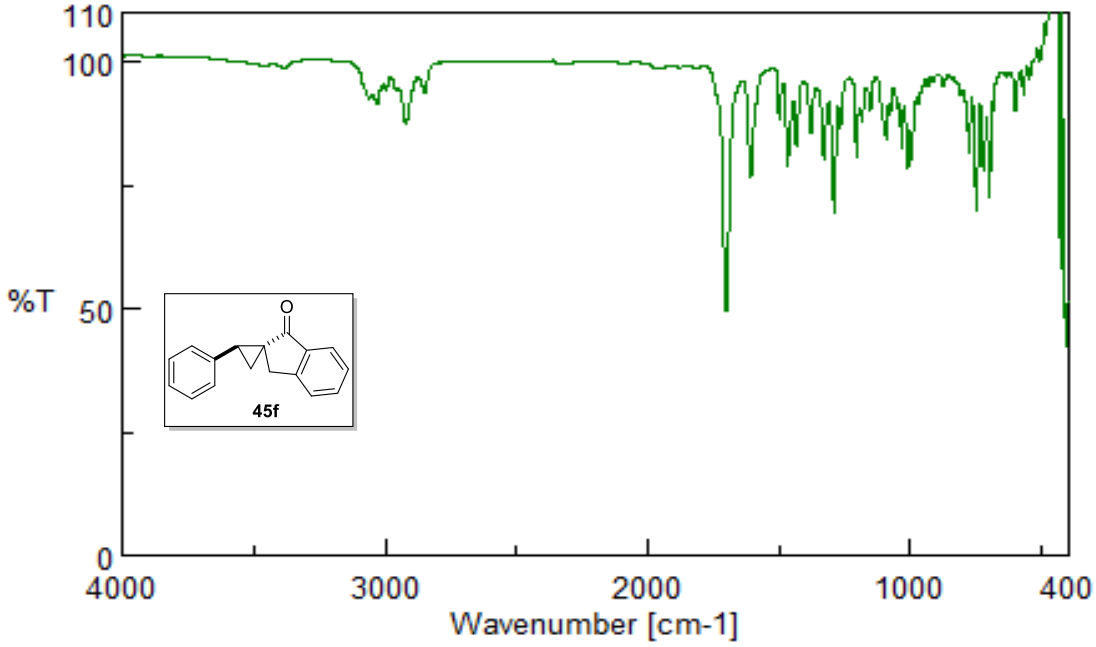

110
100
%T
50
0
4000
3000
2000
1000
400
Wavenumber [cm-1]
43i

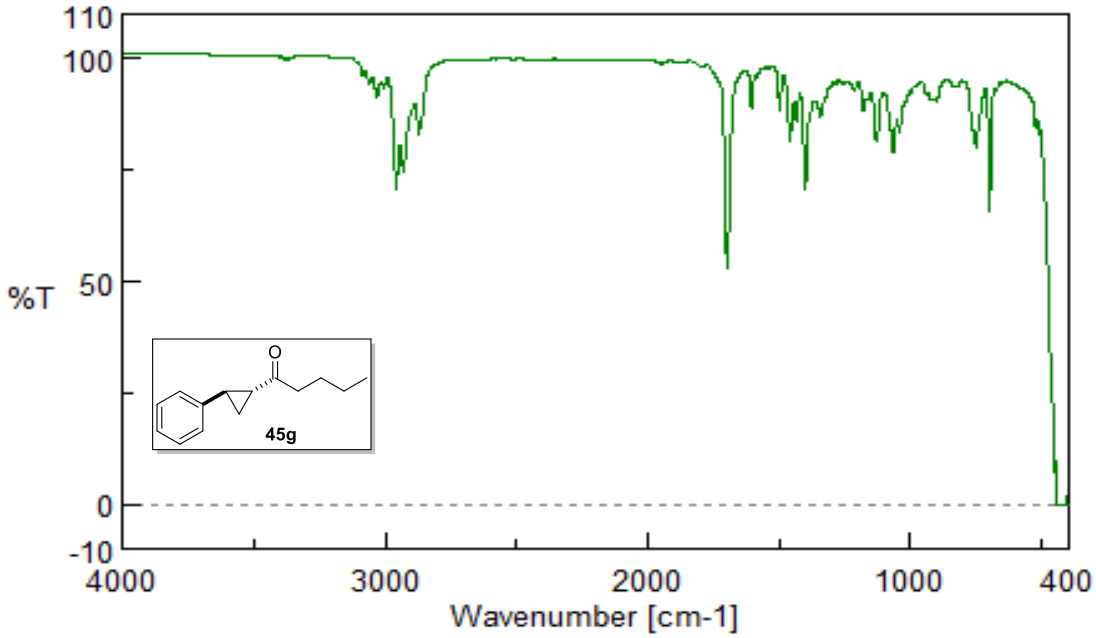

110
100
80
60
40
20
10
%T
O
45b
4000
3000
2000
1000
400
Wavenumber [cm-1]

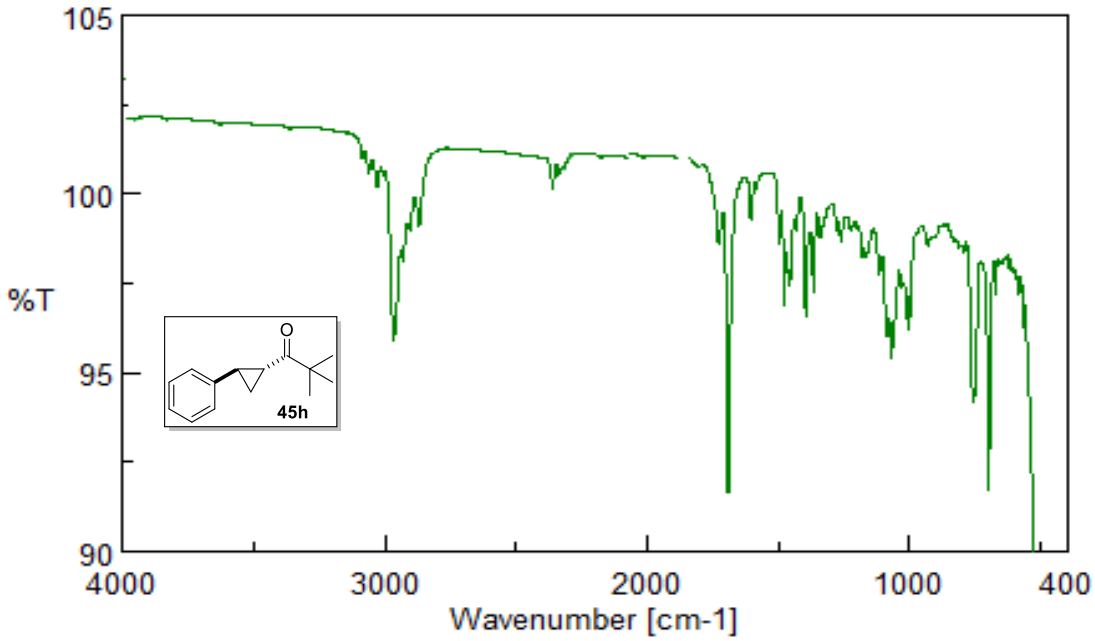

110
100
50
0
-10
%T
O
Br
45c
4000
3000
2000
1000
400
Wavenumber [cm-1]


110
100
%T
50
0
-10
4000
3000
2000
1000
400
Wavenumber [cm-1]
O
45d

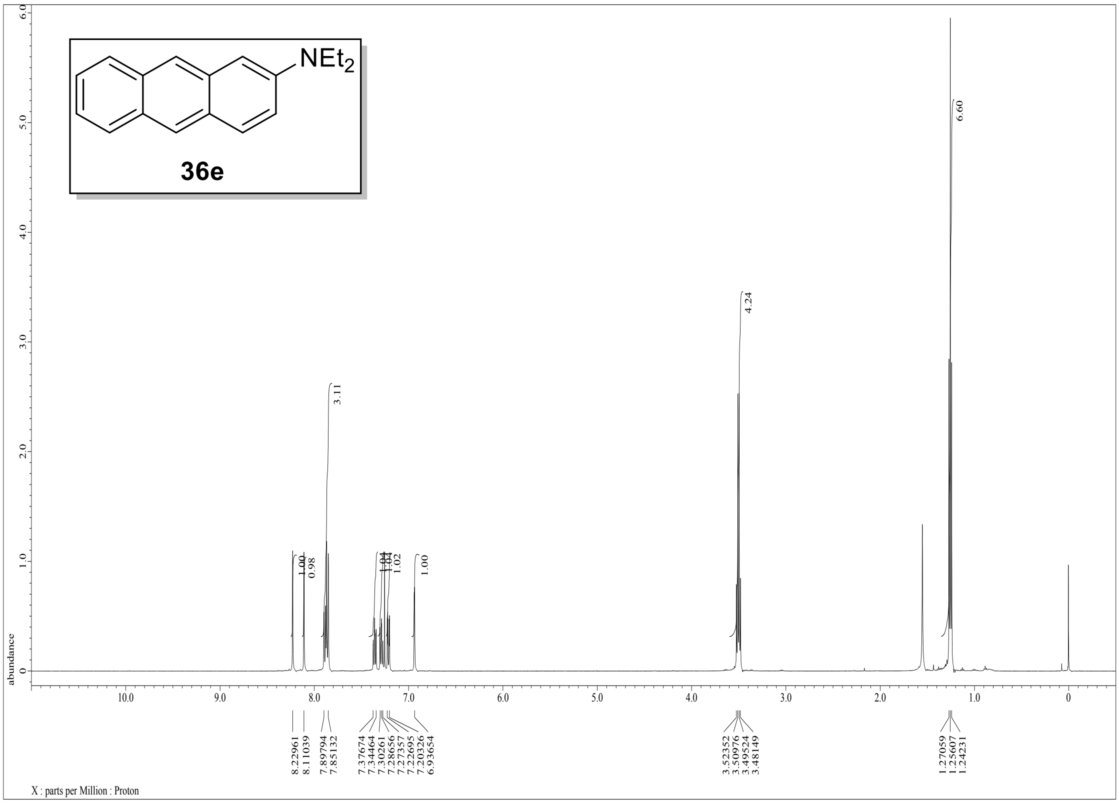

120
100
%T
50
0
4000
3000
2000
1000
400
Wavenumber [cm-1]
O
45e

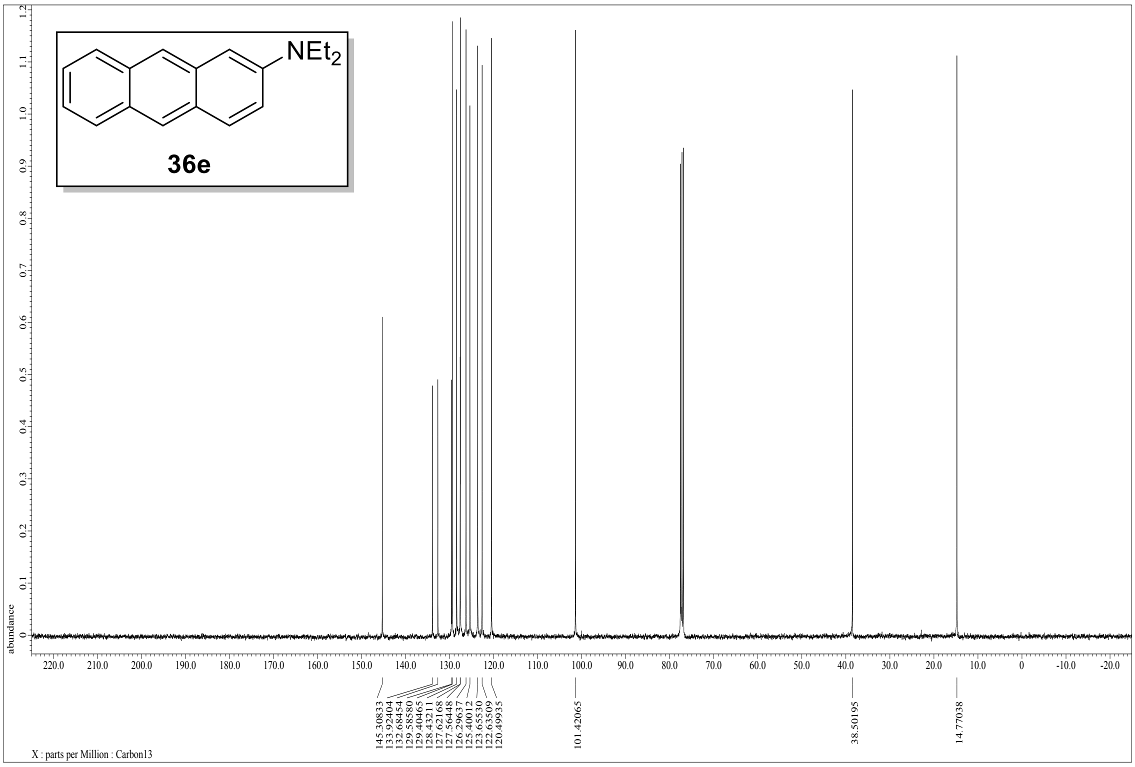

110
100
%T
50
0
4000
3000
2000
1000
400
Wavenumber [cm-1]
O
45f

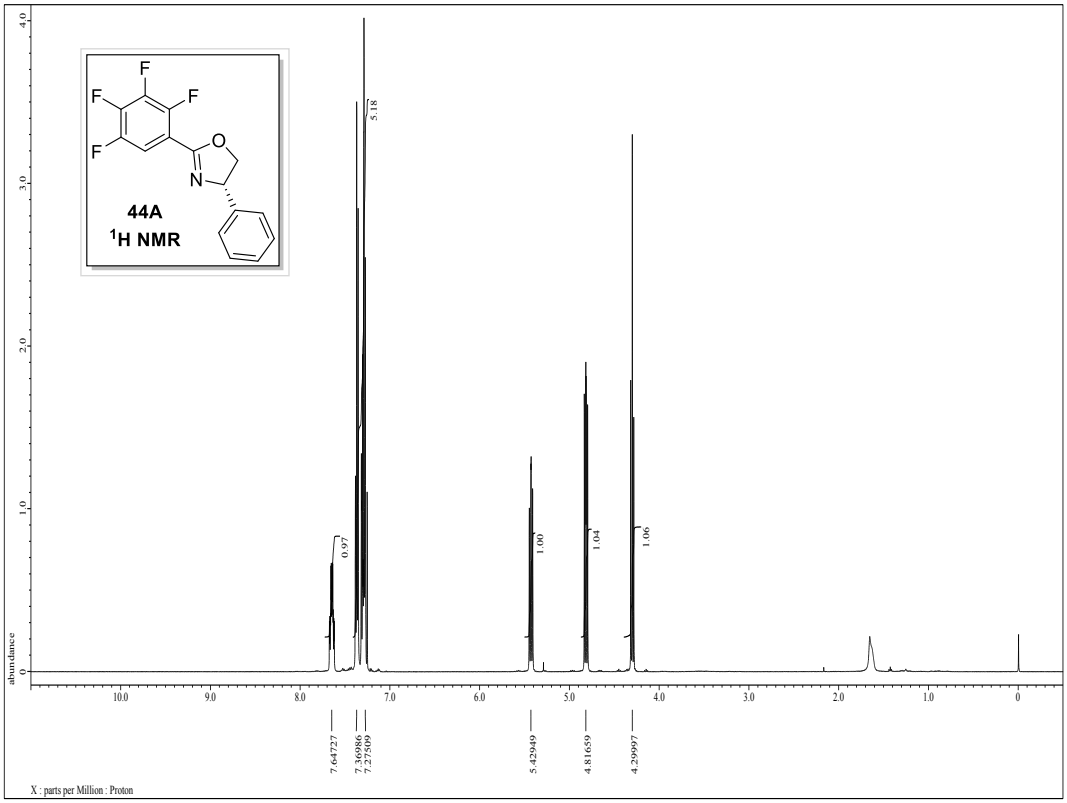

110
100
%T
50
0
-10
4000
3000
2000
1000
400
Wavenumber [cm-1]
O
45g

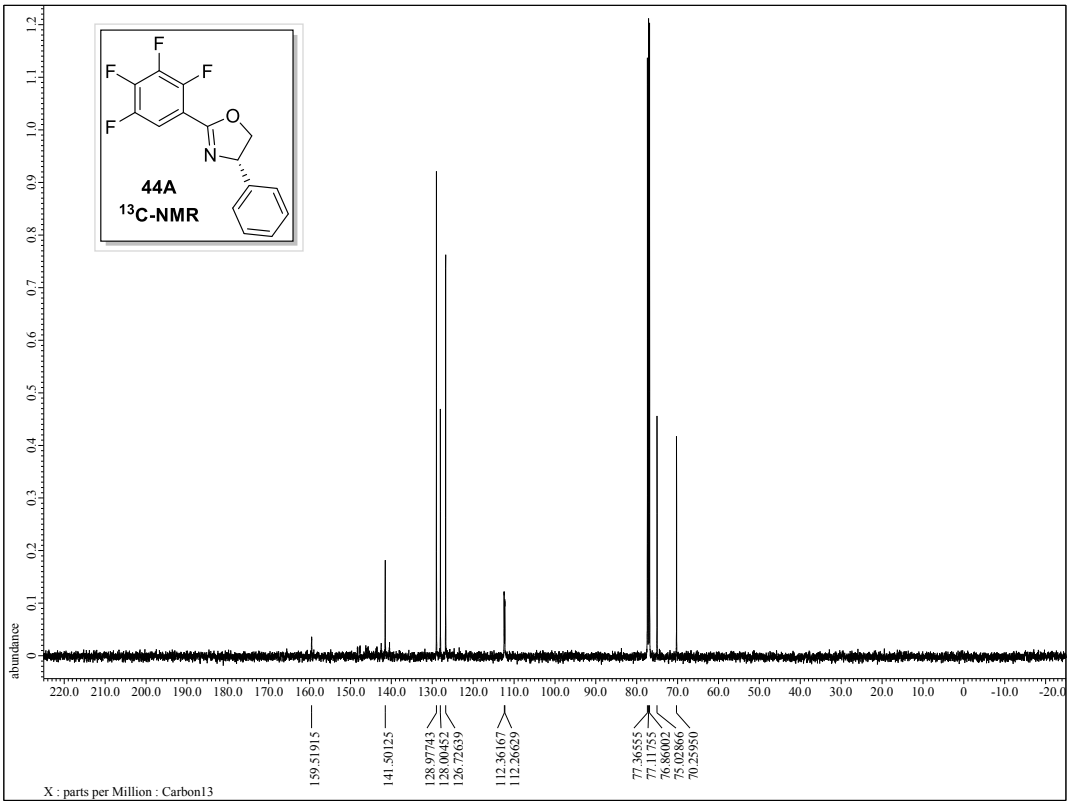

105
100
95
90
%T
4000
3000
2000
1000
400
Wavenumber [cm-1]
O
45h

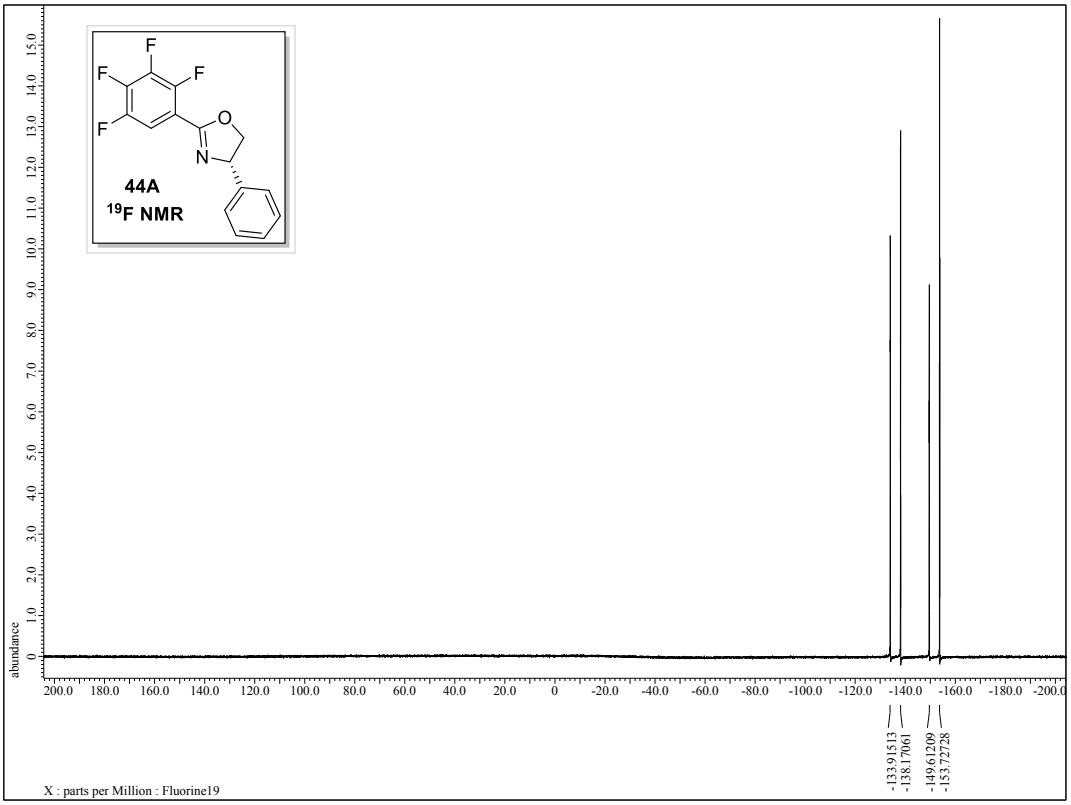
NMR SPECTRA

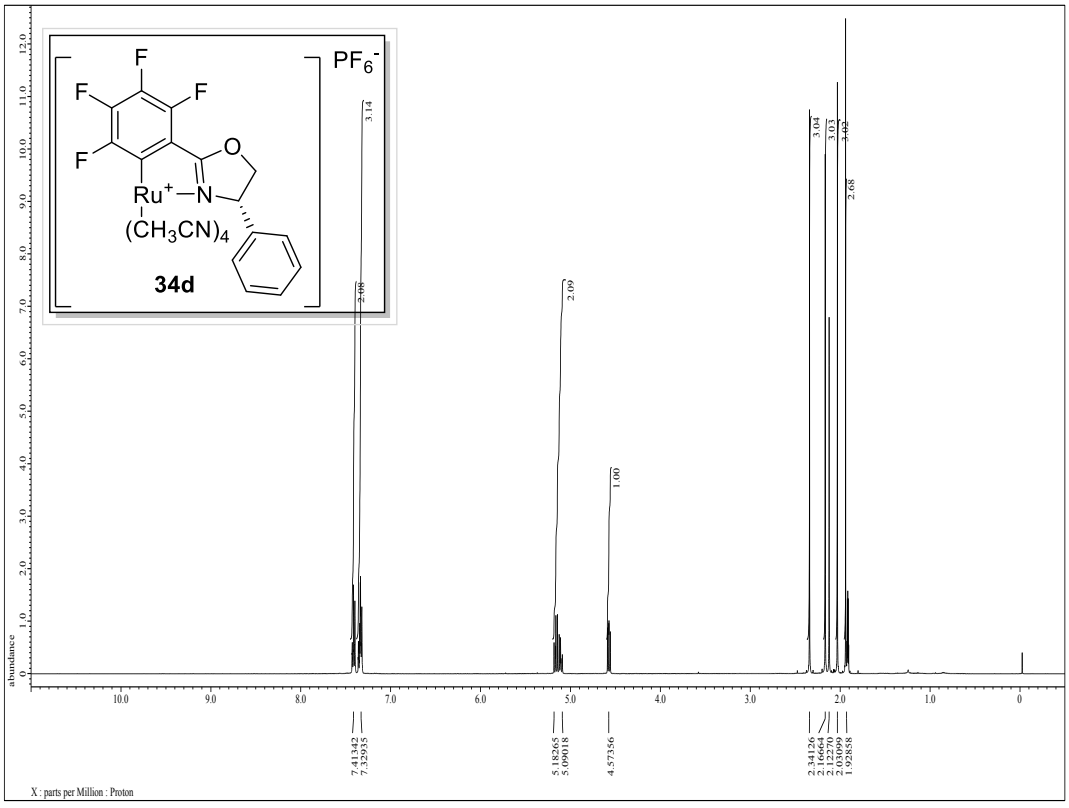

NEt2
36e
abundance
X : parts per Million : Proton
8.22961
8.11039
7.89794
7.85132
7.37674
7.34464
7.30261
7.28656
7.27357
7.22695
7.20326
6.93654
3.52352
3.50976
3.49524
3.48149
1.27059
1.25607
1.24231
1.00
0.98
3.11
1.02
1.00
4.24
6.60

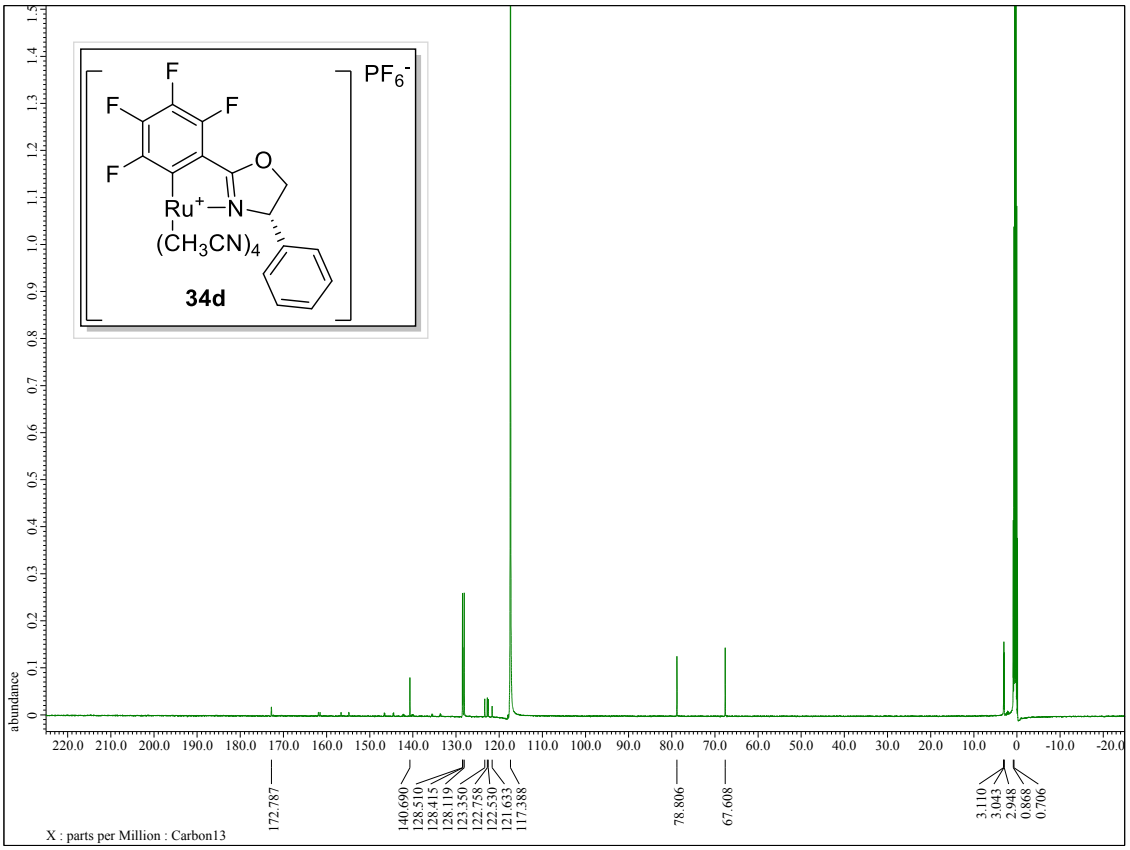

NEt2
36e
abundance
X : parts per Million : Carbon13
145.30833
133.92404
132.68454
129.58580
129.40465
128.43211
127.62168
127.56448
126.29637
125.40012
123.65530
122.63509
120.49935
101.42065
38.50195
14.77038

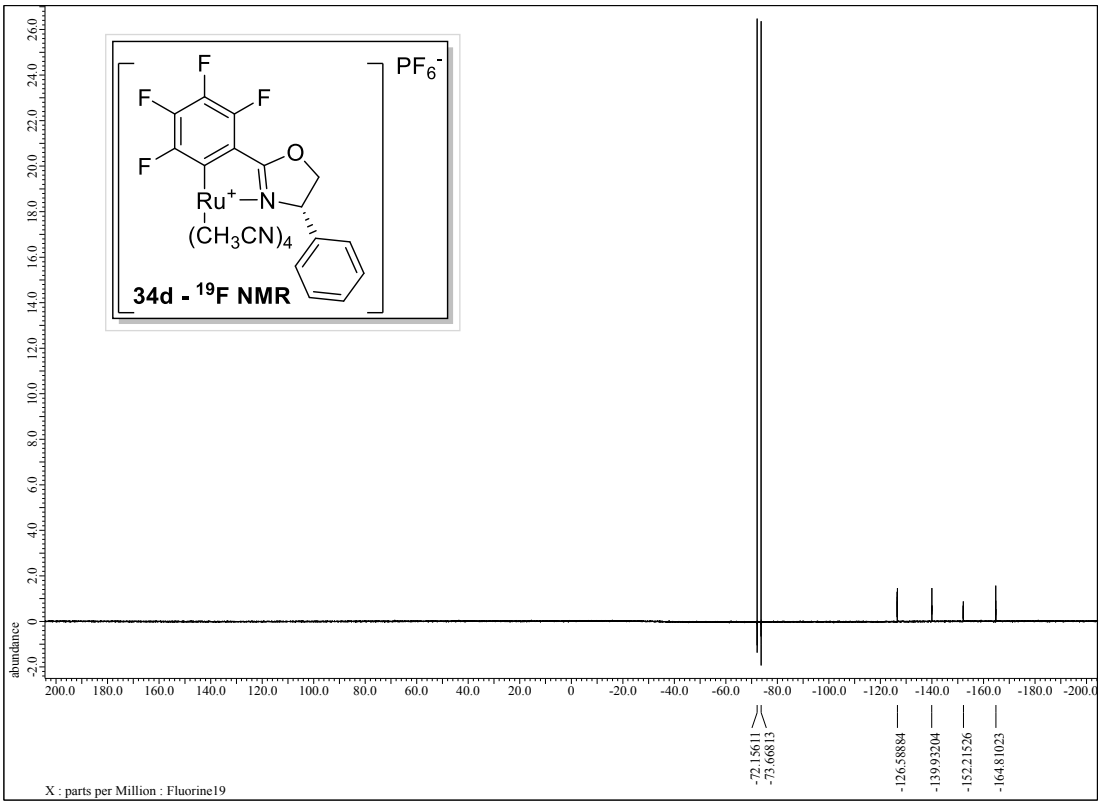

44A
1H NMR
5.18
0.97
1.00
1.04
1.06
7.64727
7.36986
7.27509
5.42949
4.81659
4.29997
abundance
X : parts per Million : Proton

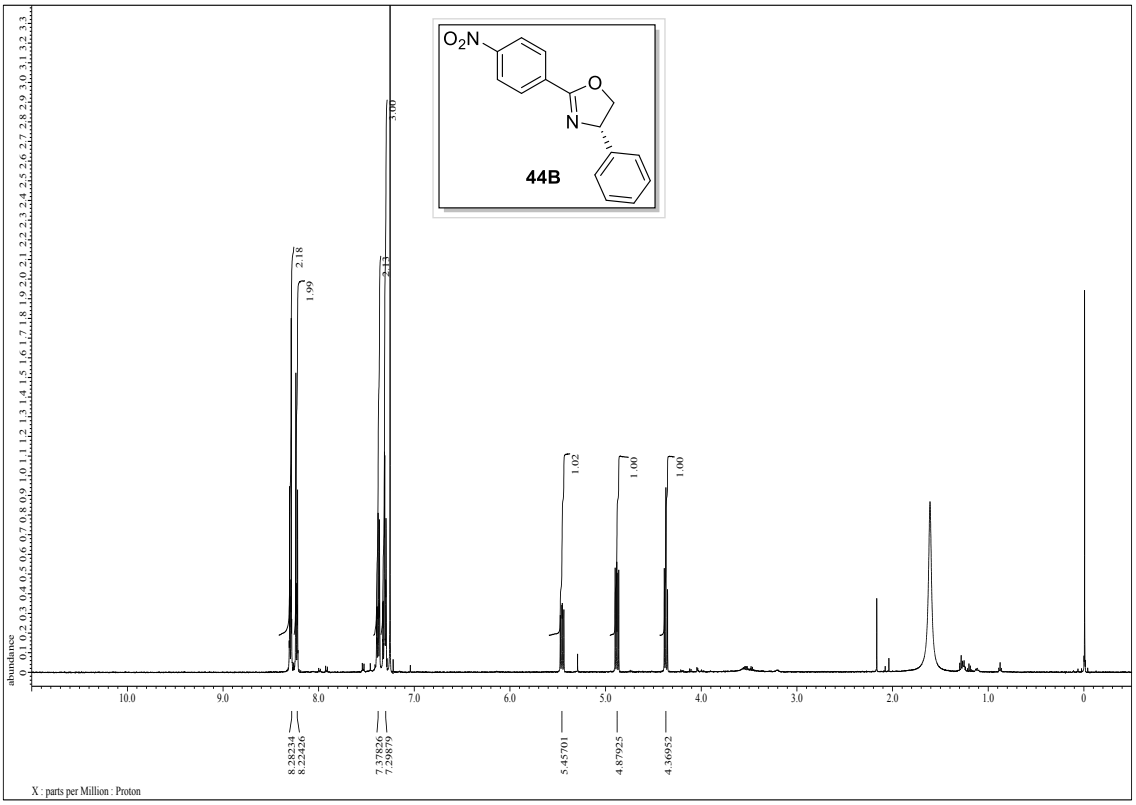

44A
13C-NMR
159.51915
141.50125
128.97743
128.00452
126.72639
112.36167
112.26629
77.36555
77.11755
76.86002
75.02866
70.25950
abundance
X : parts per Million : Carbon13

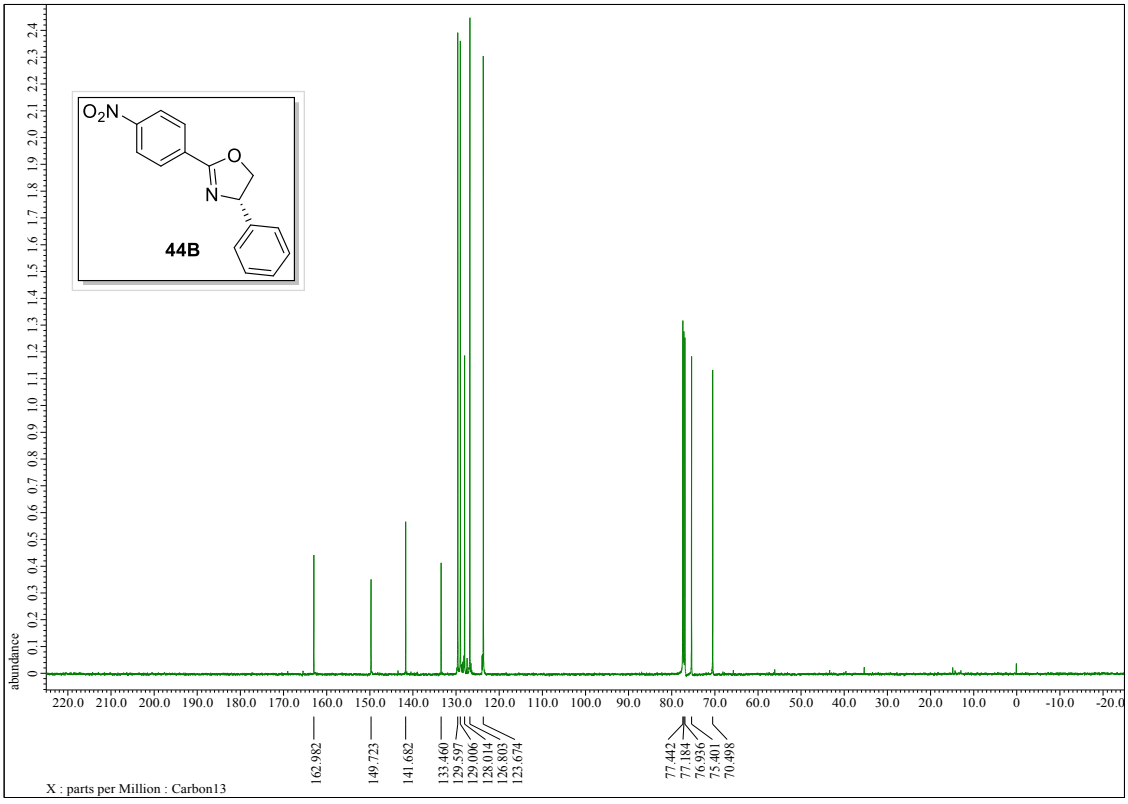

44A
19F NMR
abundance
X : parts per Million : Fluorine19
-133.91513
-138.17061
-149.61209
-153.72728

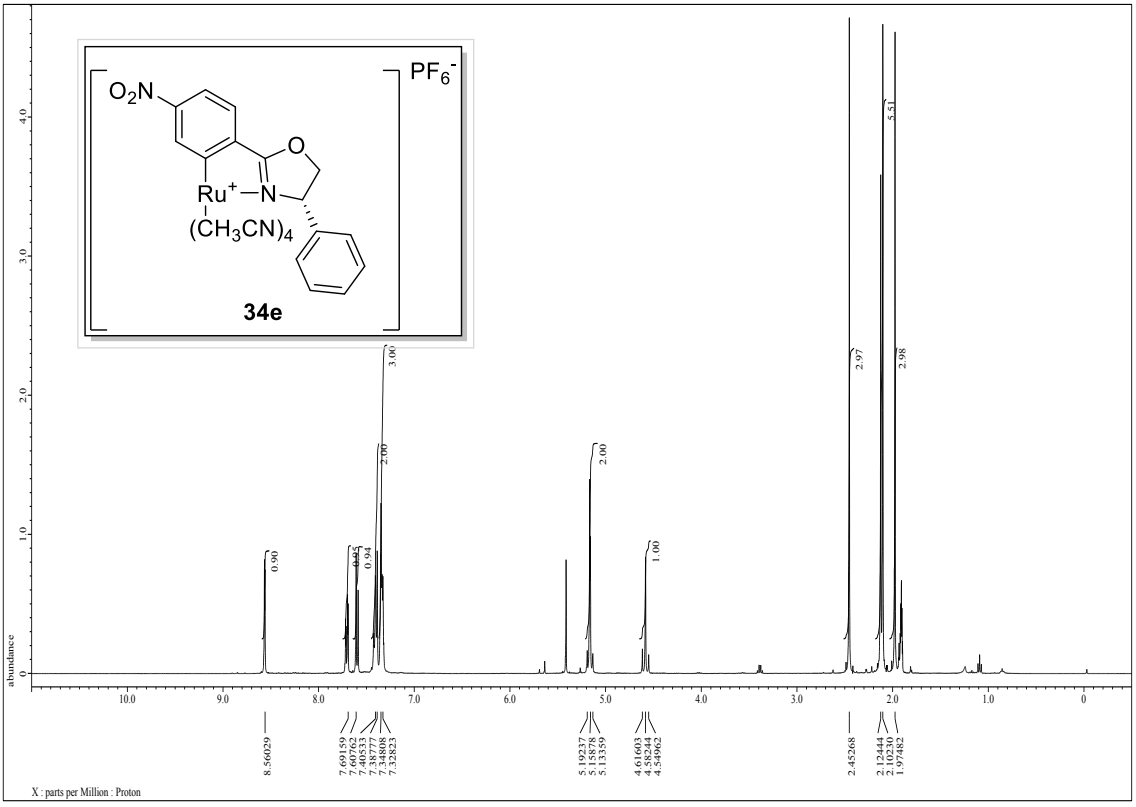

PF6-
34d
abundance
X : parts per Million : Proton
7.41342
7.32935
5.18265
5.09018
4.57356
2.34126
2.16664
2.12270
2.03969
1.92858

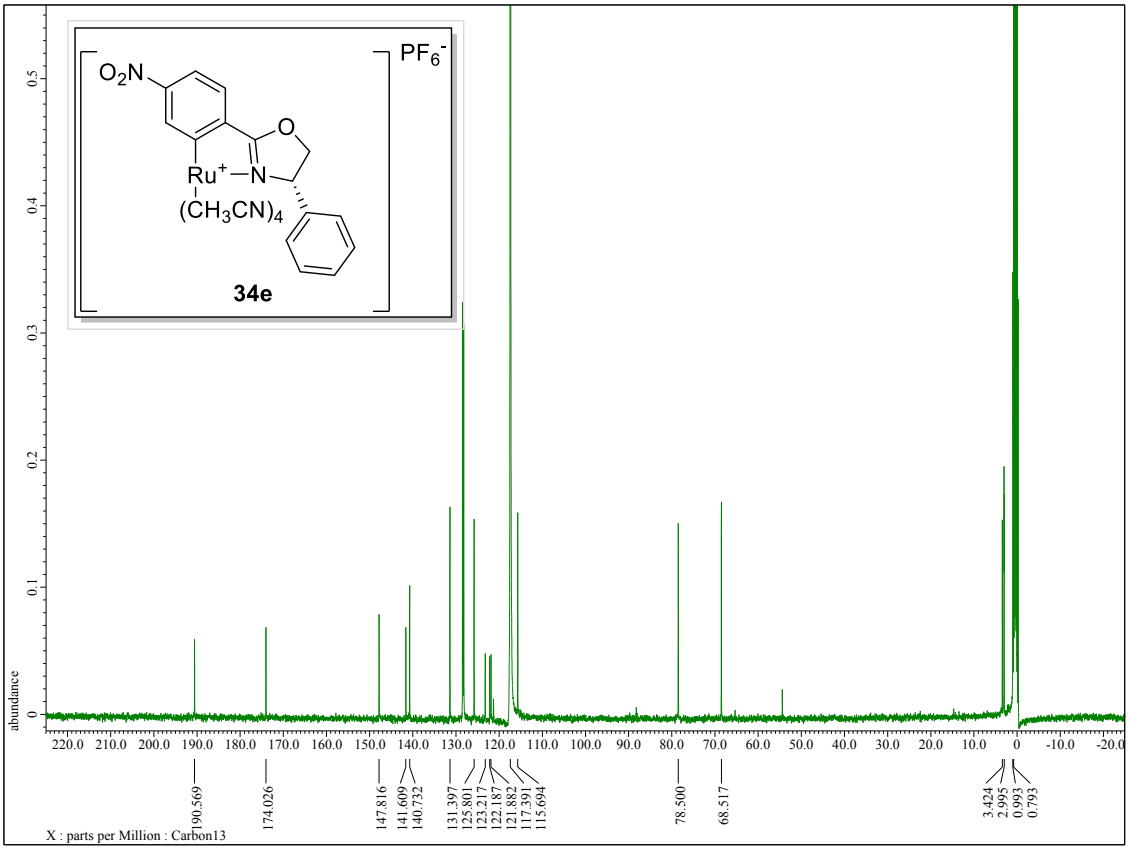

F
F
F
F
O
Ru+—N
(CH3CN)4
PF6-
34d
abundance
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
172.787
140.690
128.510
128.415
128.119
123.350
122.758
122.530
121.633
117.388
78.806
67.608
3.110
3.043
2.948
0.868
0.706
X : parts per Million : Carbon13

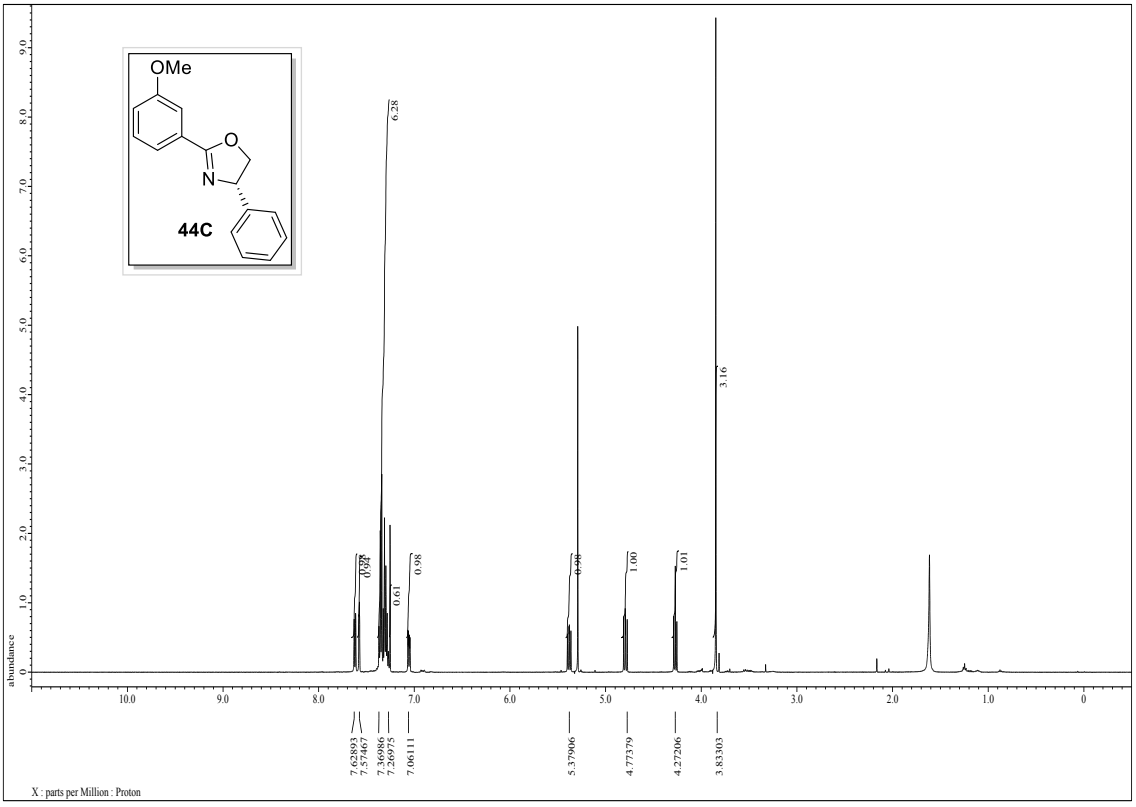

F
F
F
F
O
Ru+—N
(CH3CN)4
PF6-
34d - 19F NMR
abundance
200.0 180.0 160.0 140.0 120.0 100.0 80.0 60.0 40.0 20.0 0 -20.0 -40.0 -60.0 -80.0 -100.0 -120.0 -140.0 -160.0 -180.0 -200.0
-72.15611
-73.66813
-126.58884
-139.93204
-152.21526
-164.81023
X : parts per Million : Fluorine19

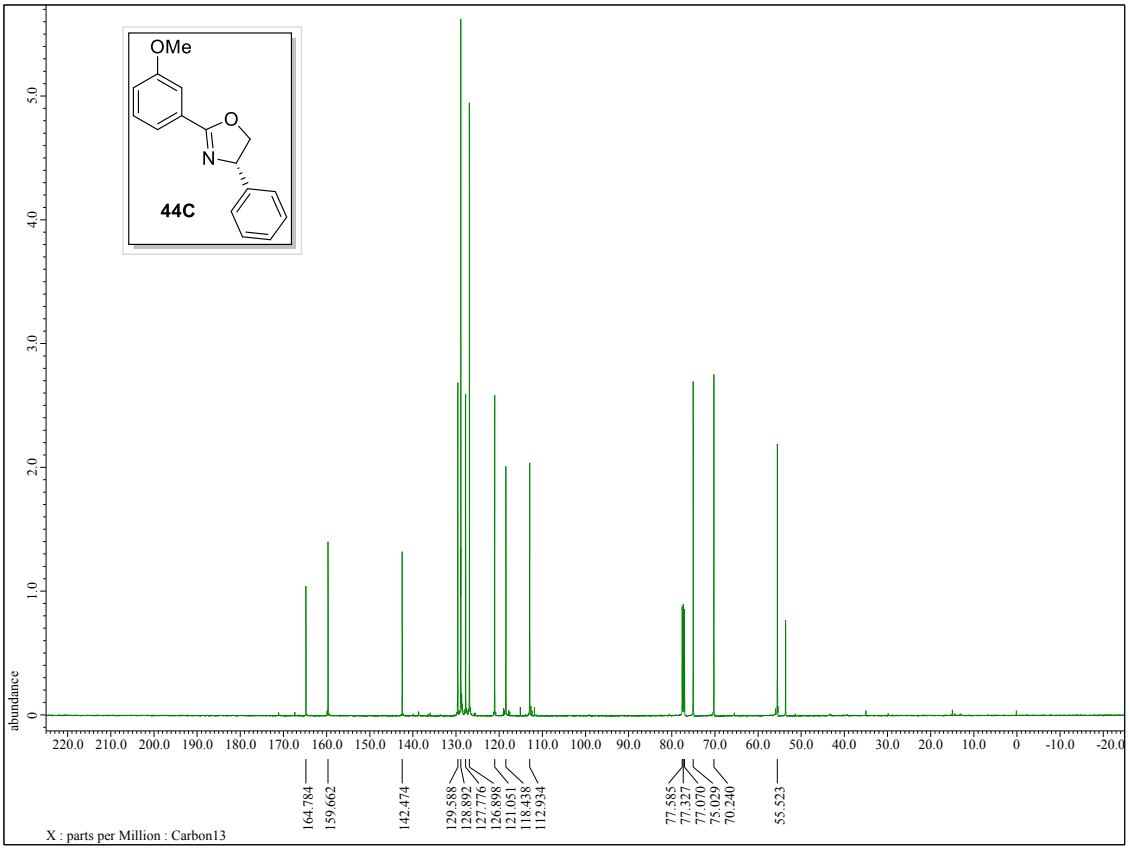

O2N
O
N
44B
2.18
1.99
3.00
2.13
1.02
1.00
1.00
8.28234
8.22426
7.37826
7.29879
5.45701
4.87925
4.36952
X : parts per Million : Proton

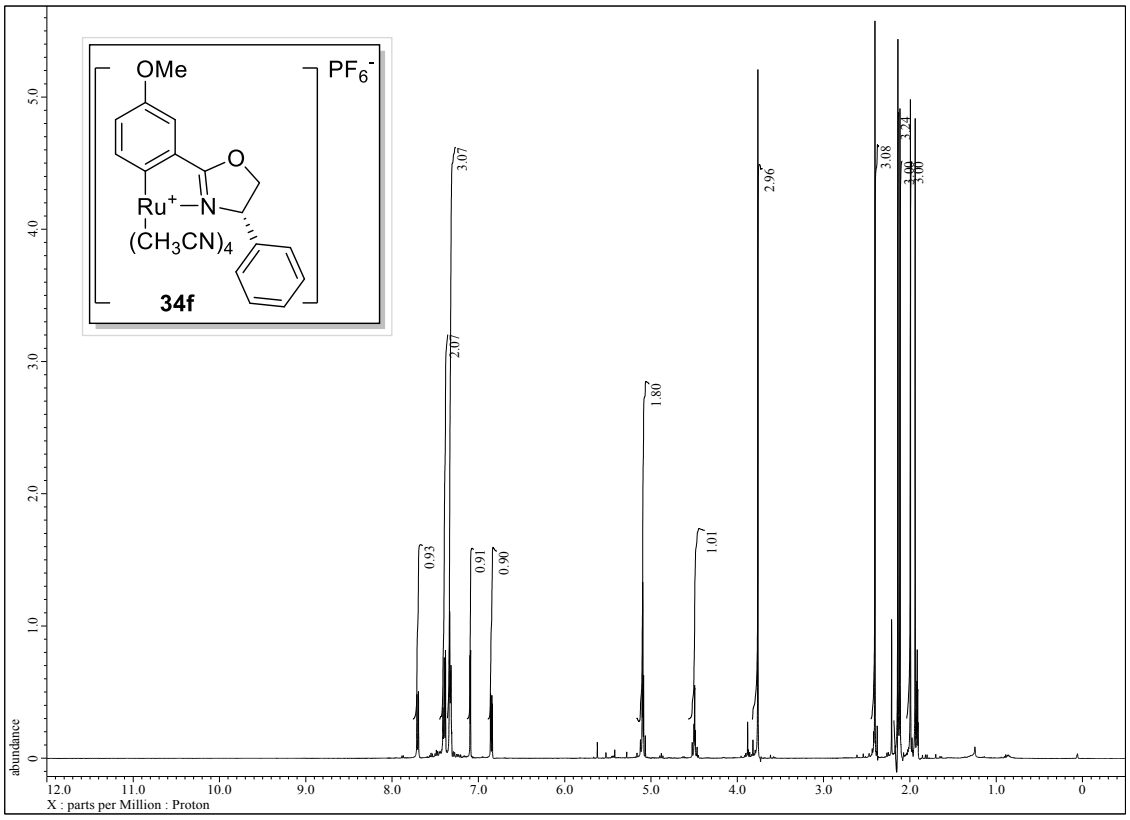

O2N
O
N
44B
162.982
149.723
141.682
133.460
129.597
129.006
128.014
126.803
123.674
77.442
77.184
76.936
75.401
70.498
X : parts per Million : Carbon13

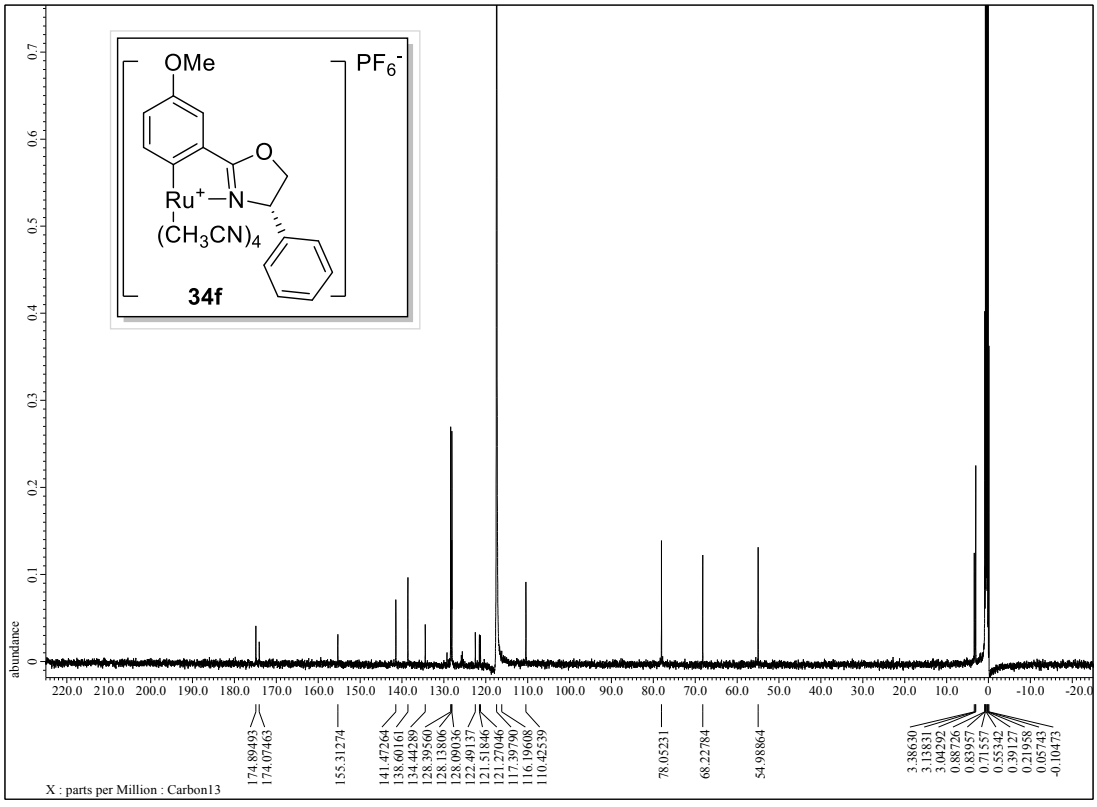

PF6-
O2N
O
Ru+—N
(CH3CN)4
34e
abundance
X : parts per Million : Proton

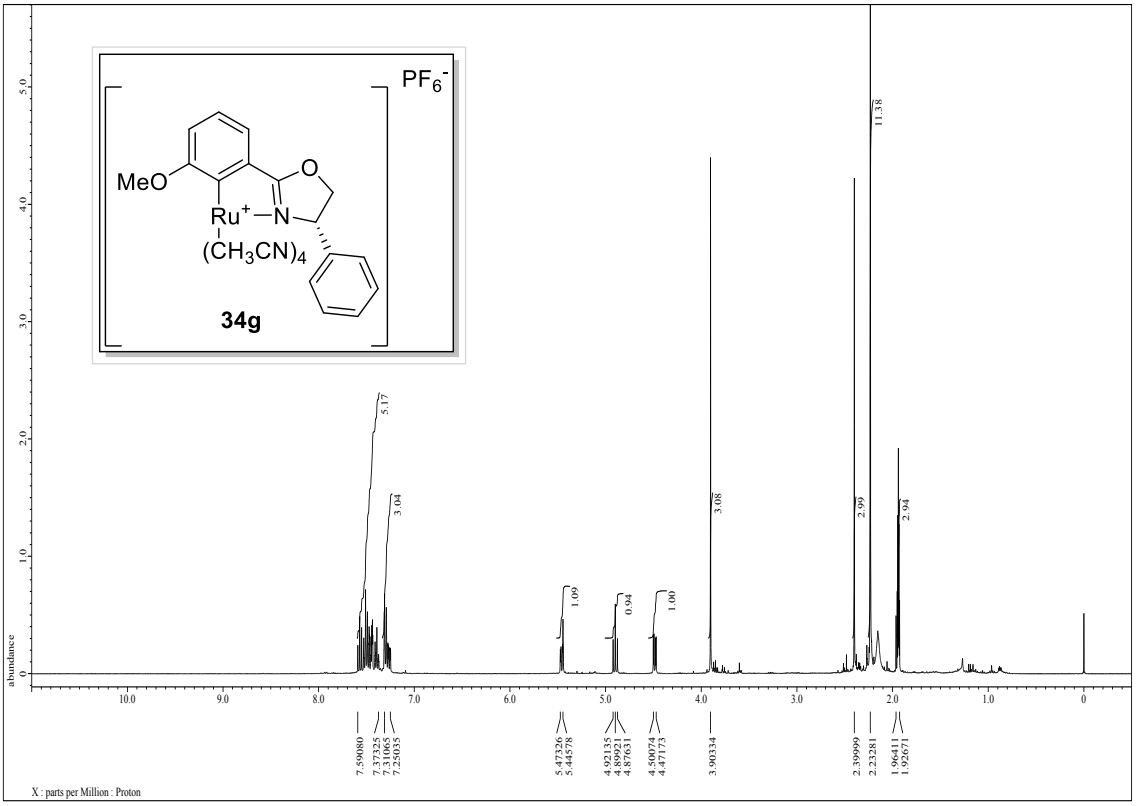

PF6-
O2N
O
Ru+—N
(CH3CN)4
34e
abundance
X : parts per Million : Carbon13

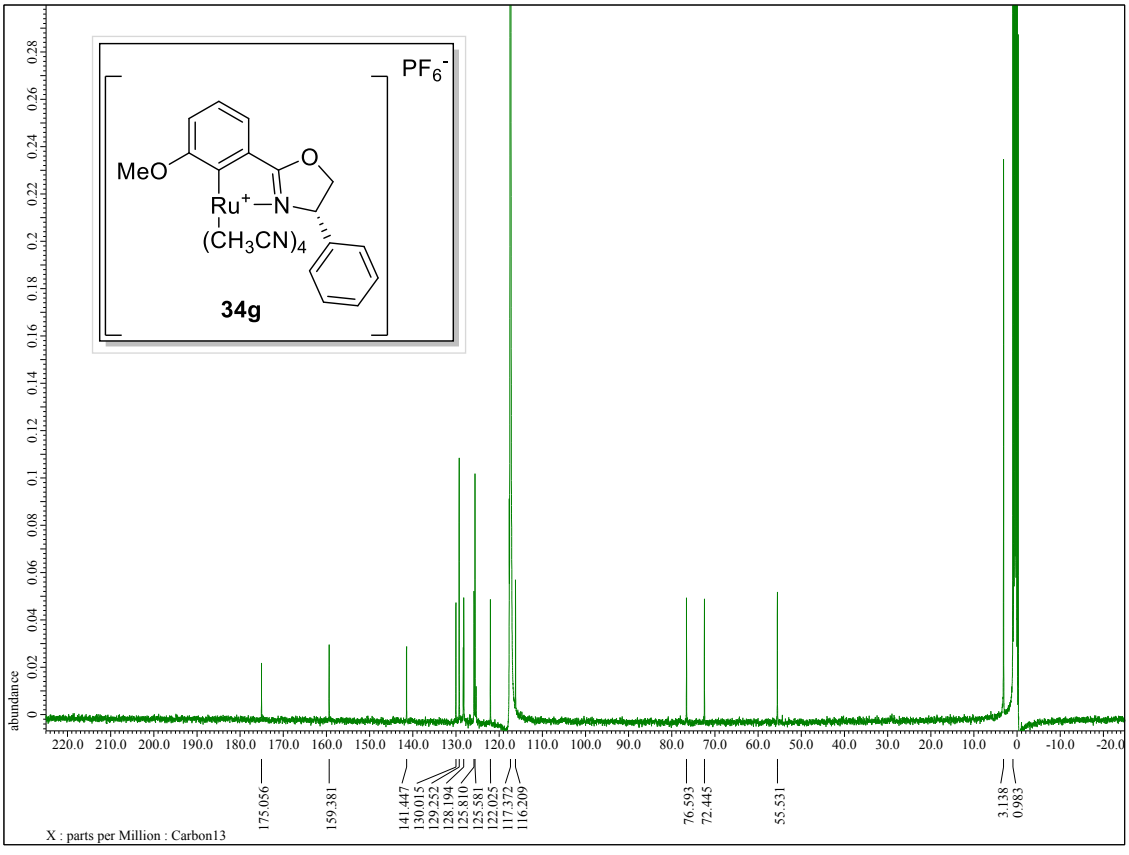

OMe
O
N
44C
6.28
3.16
0.94
0.61
0.98
1.06
1.01
abundance
7.62893
7.57467
7.36986
7.26975
7.06111
5.37906
4.77379
4.27206
3.83303
X : parts per Million : Proton

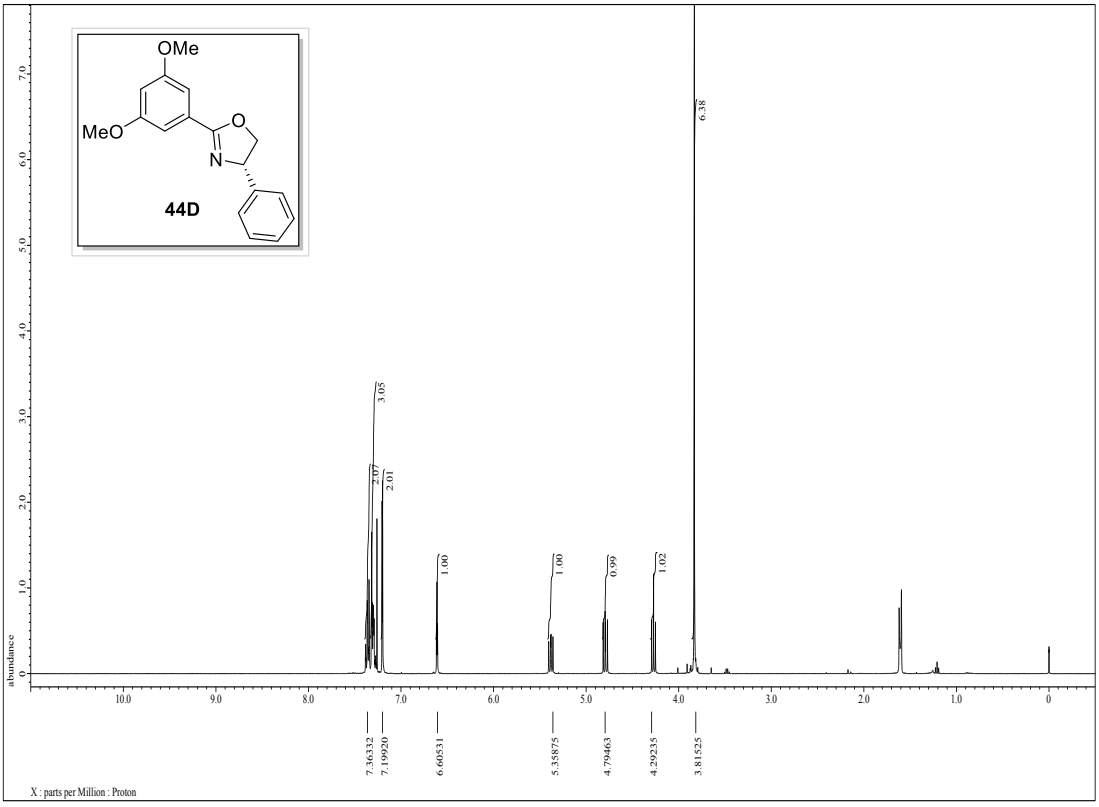

OMe
O
N
44C
abundance
164.784
159.662
142.474
129.588
128.892
127.776
126.898
121.051
118.438
112.934
77.585
77.327
77.070
75.029
70.240
55.523
X : parts per Million : Carbon13

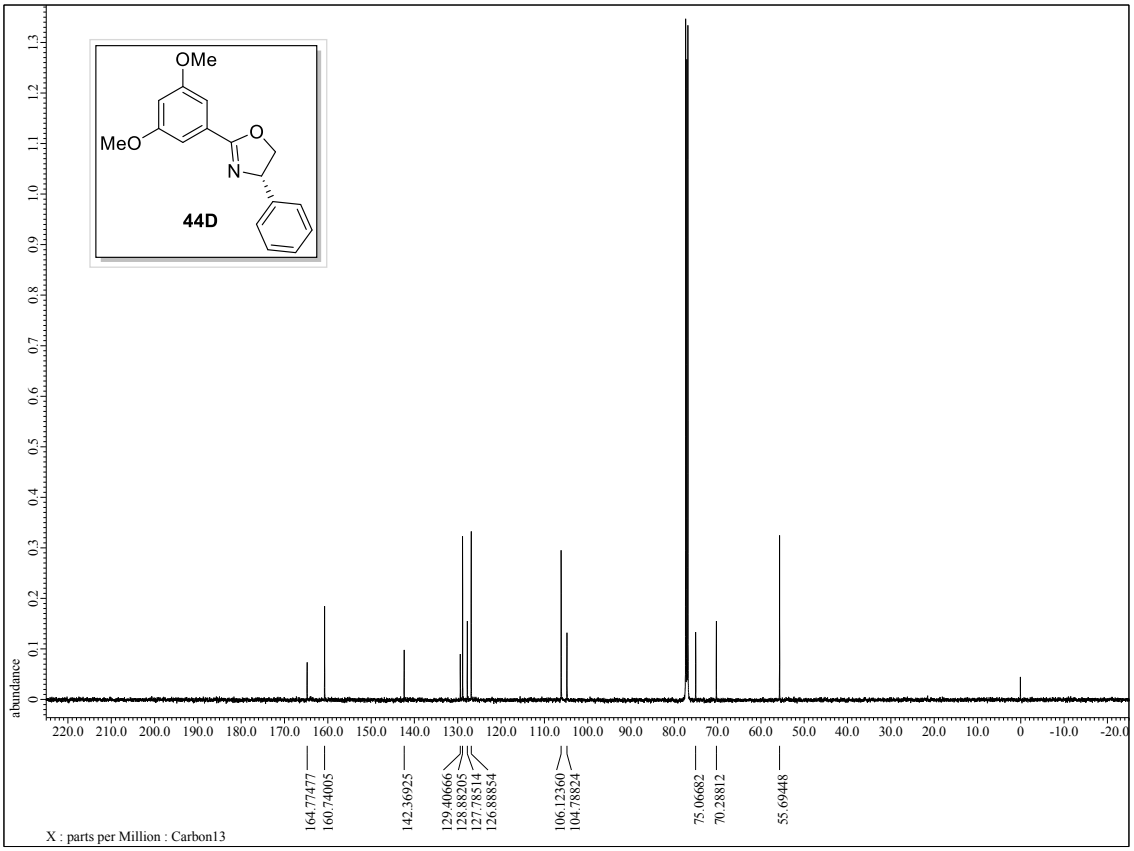

OMe
PF6-
O
Ru+—N
(CH3CN)4
34f
3.07
2.07
1.80
2.96
3.08
3.24
0.93
0.91
0.90
1.01
abundance
X : parts per Million : Proton

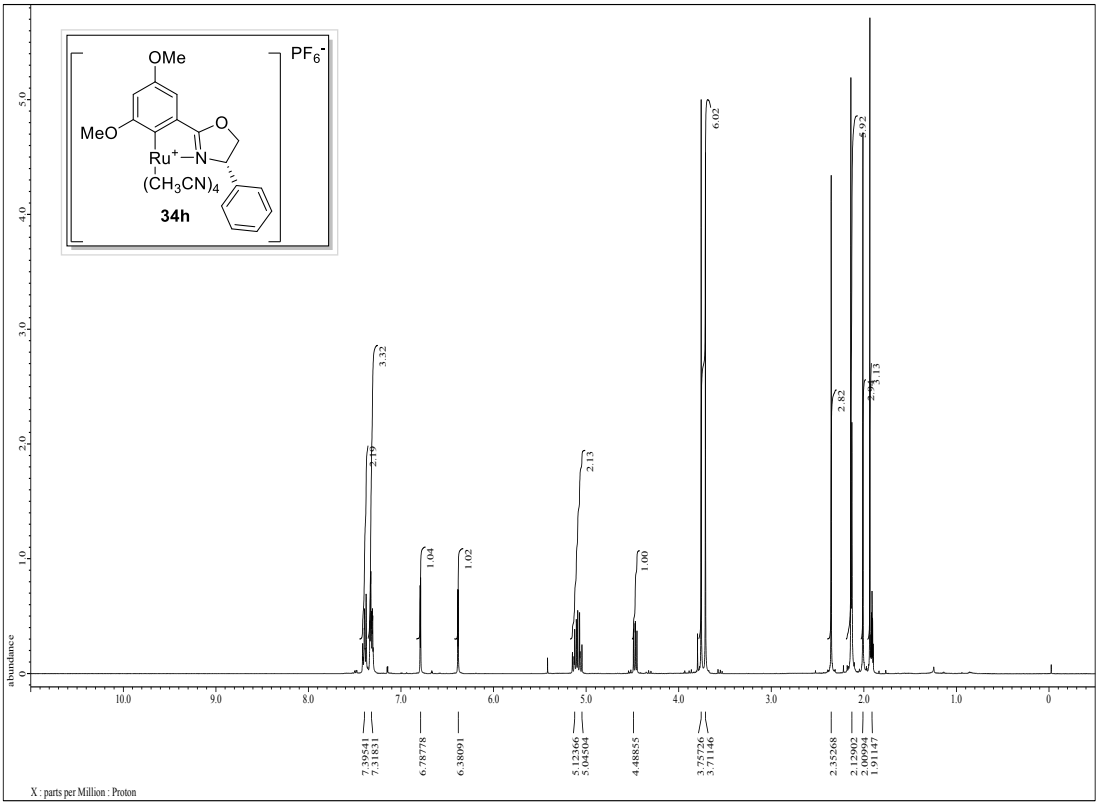

OMe
PF6-
O
Ru+—N
(CH3CN)4
34f
abundance
X : parts per Million : Carbon13
174.89493
174.07463
155.31274
141.47264
138.60161
134.44280
128.39560
128.13806
128.09036
122.49137
121.51846
121.27046
117.39790
116.19608
110.42539
78.05231
68.22784
54.98864
3.38630
3.13831
3.04292
0.88726
0.83957
0.71557
0.55342
0.39127
0.21958
0.05743
-0.10473

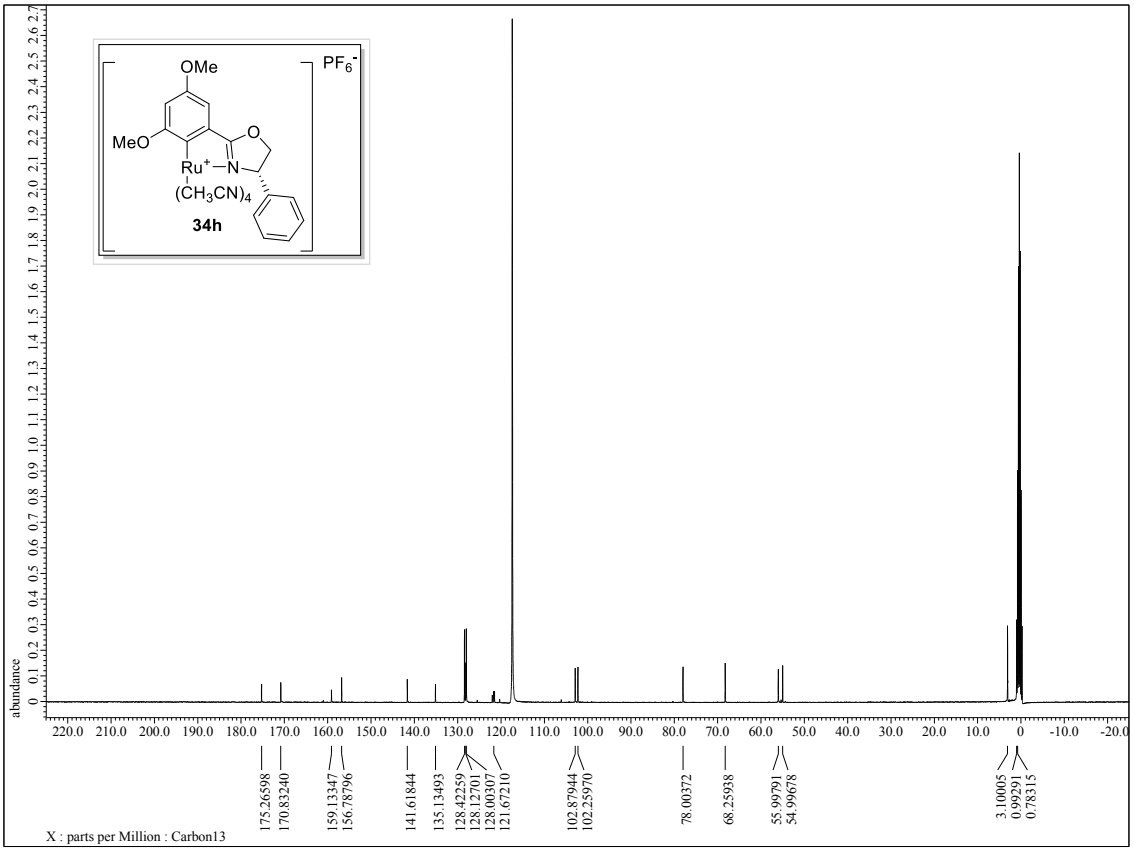

PF6-
MeO
O
Ru+—N
(CH3CN)4
34g
11.58
5.17
3.04
3.08
2.99
2.94
1.09
0.94
1.00
abundance
X : parts per Million : Proton

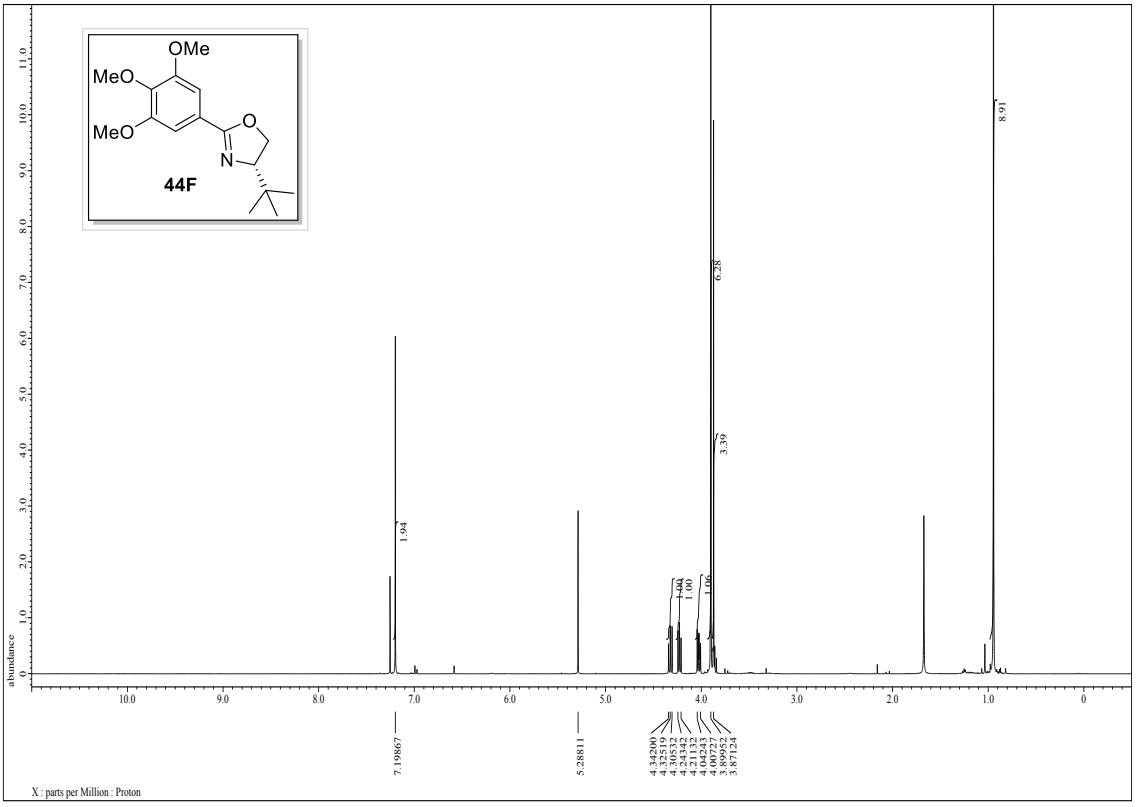

PF6-
MeO
O
Ru+—N
(CH3CN)4
34g
abundance
X : parts per Million : Carbon13

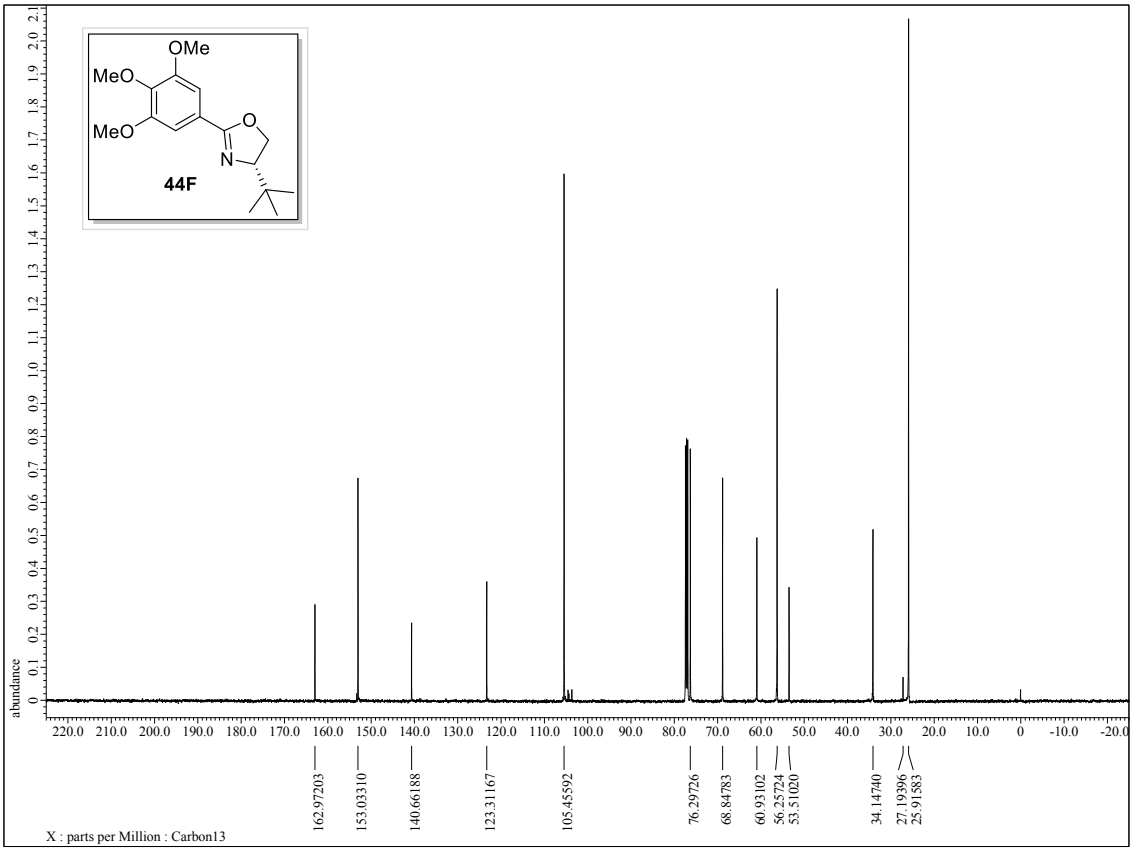

OMe
MeO
O
N
44D
6.38
3.05
2.07
2.01
1.00
1.00
0.99
1.02
abundance
7.36332
7.19920
6.60531
5.35875
4.79463
4.29235
3.81525
X : parts per Million : Proton

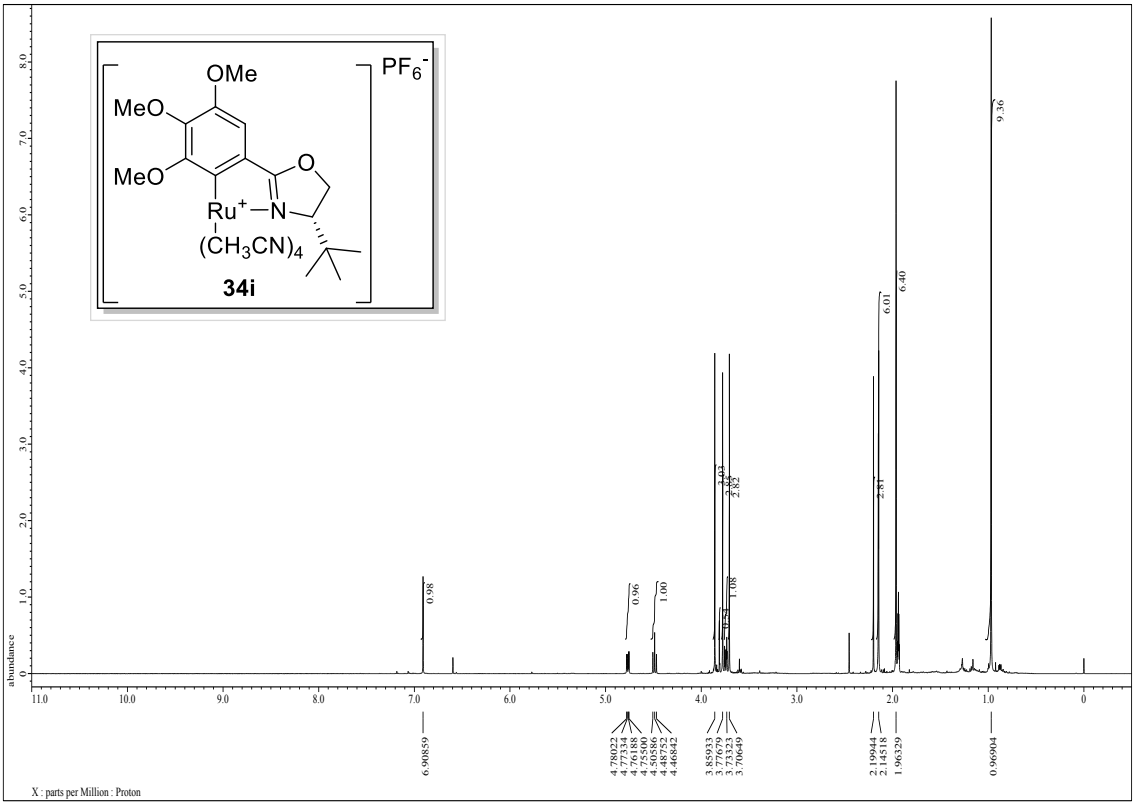

OMe
MeO
O
N
44D
abundance
164.77477
160.74005
142.36925
129.40666
128.88205
127.78514
126.88854
106.12360
104.78824
75.06682
70.28812
55.69448
X : parts per Million : Carbon13

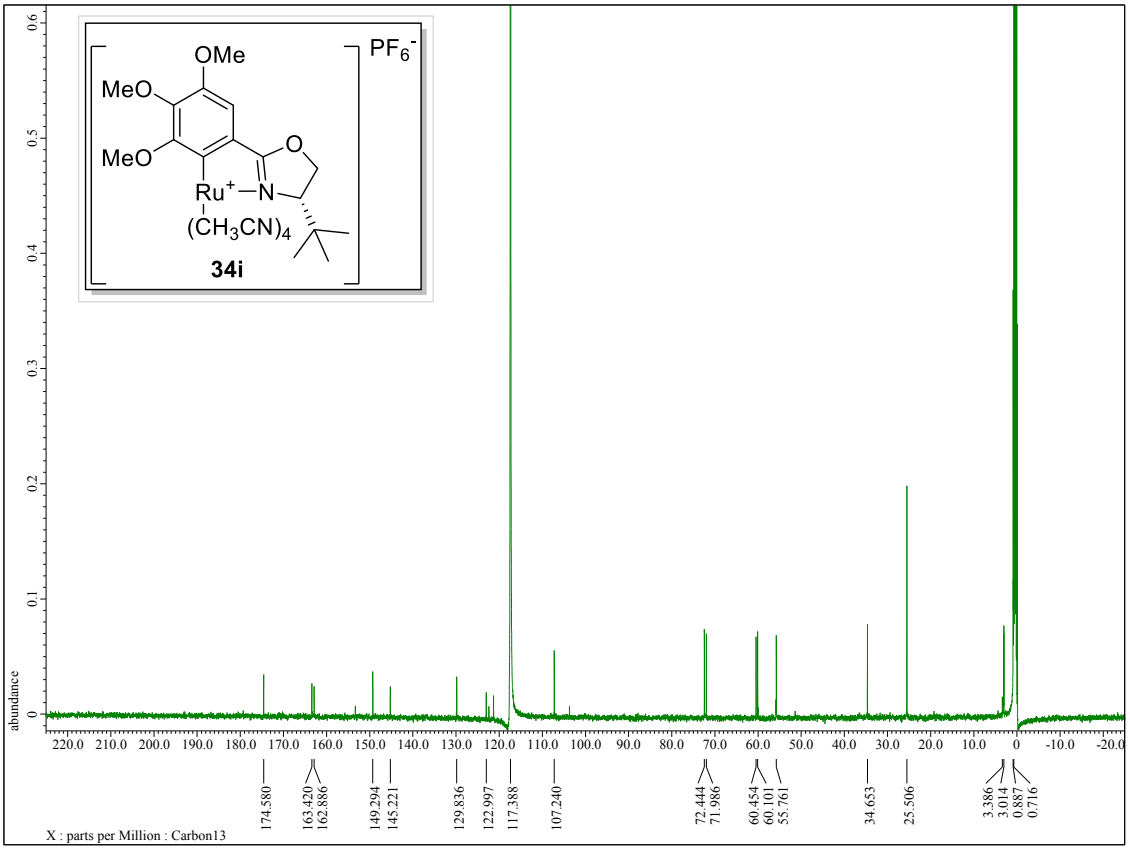

OMe
MeO
Ru+—N
(CH3CN)4
PF6-
34h
abundance
X : parts per Million : Proton

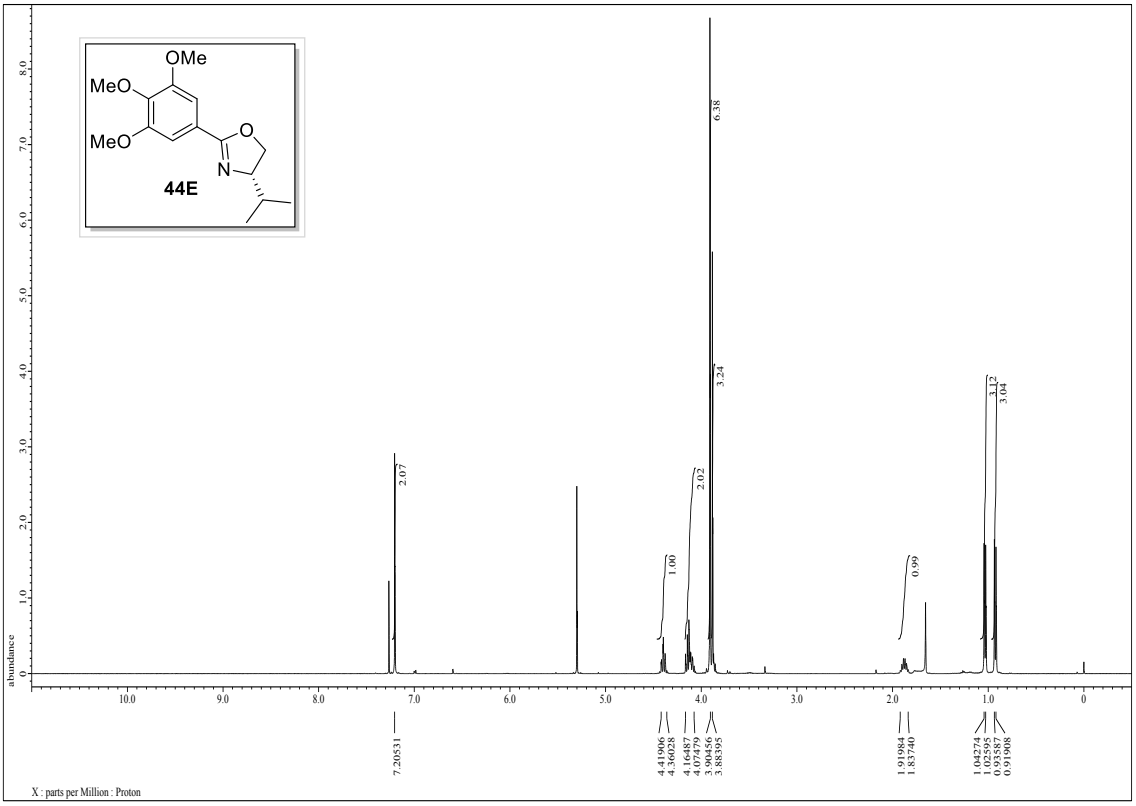

OMe
MeO
Ru+—N
(CH3CN)4
PF6-
34h
abundance
X : parts per Million : Carbon13

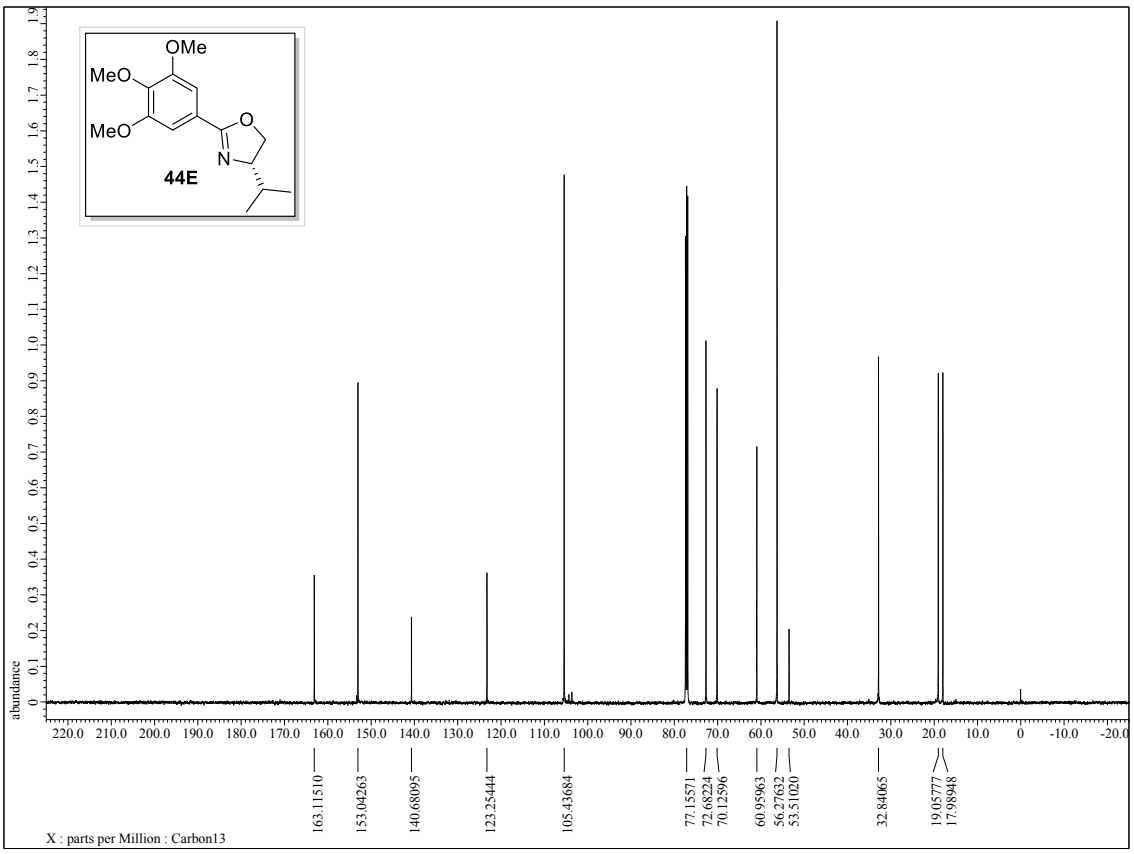

OMe
MeO
MeO
O
N
44F
8.91
6.28
3.39
1.94
1.00
1.06
abundance
7.19867
5.28811
4.34200
4.32519
4.30532
4.24348
4.21132
4.04243
4.00972
3.89952
3.87124
X : parts per Million : Proton

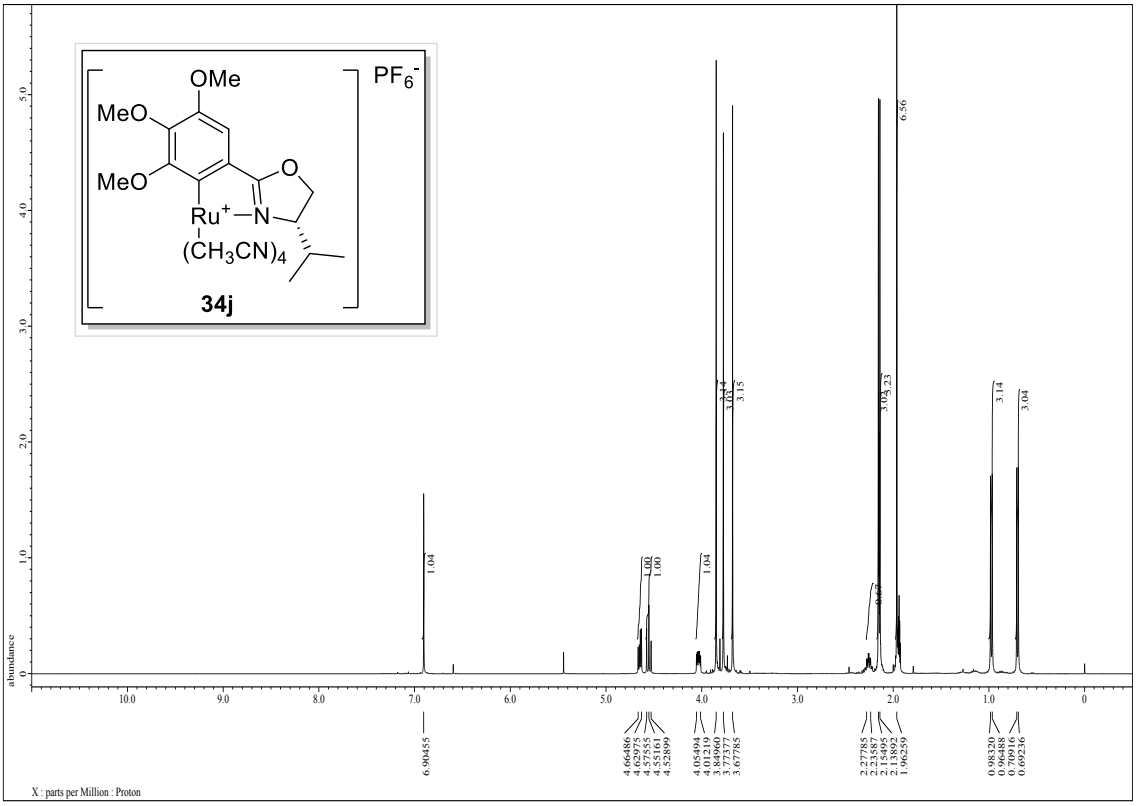

OMe
MeO
MeO
O
N
44F
abundance
162.97203
153.03310
140.66188
123.31167
105.45592
76.29726
68.84783
60.93102
56.25724
53.51020
34.14740
27.19396
25.91583
X : parts per Million : Carbon13

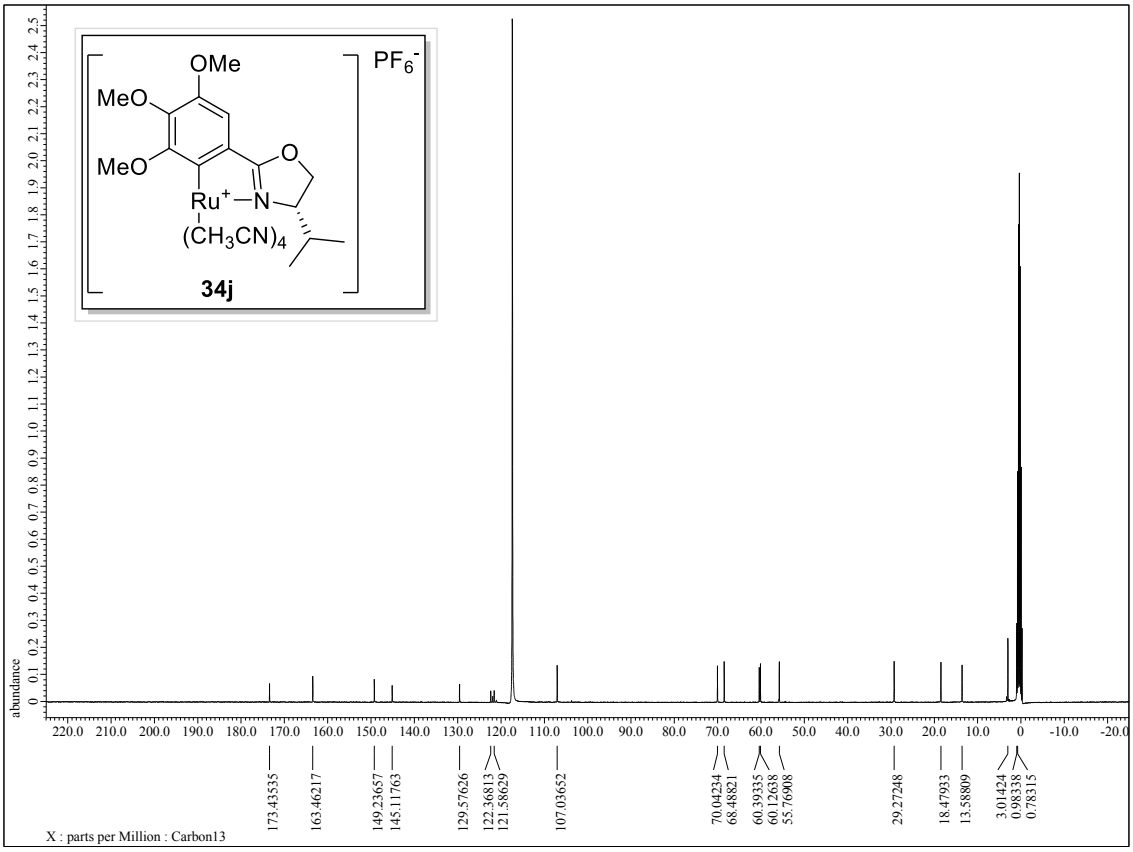

OMe
MeO
MeO
O
Ru+—N
(CH3CN)4
PF6-
34i
9.36
6.40
6.01
2.61
1.08
1.00
0.96
0.98
abundance
X : parts per Million : Proton

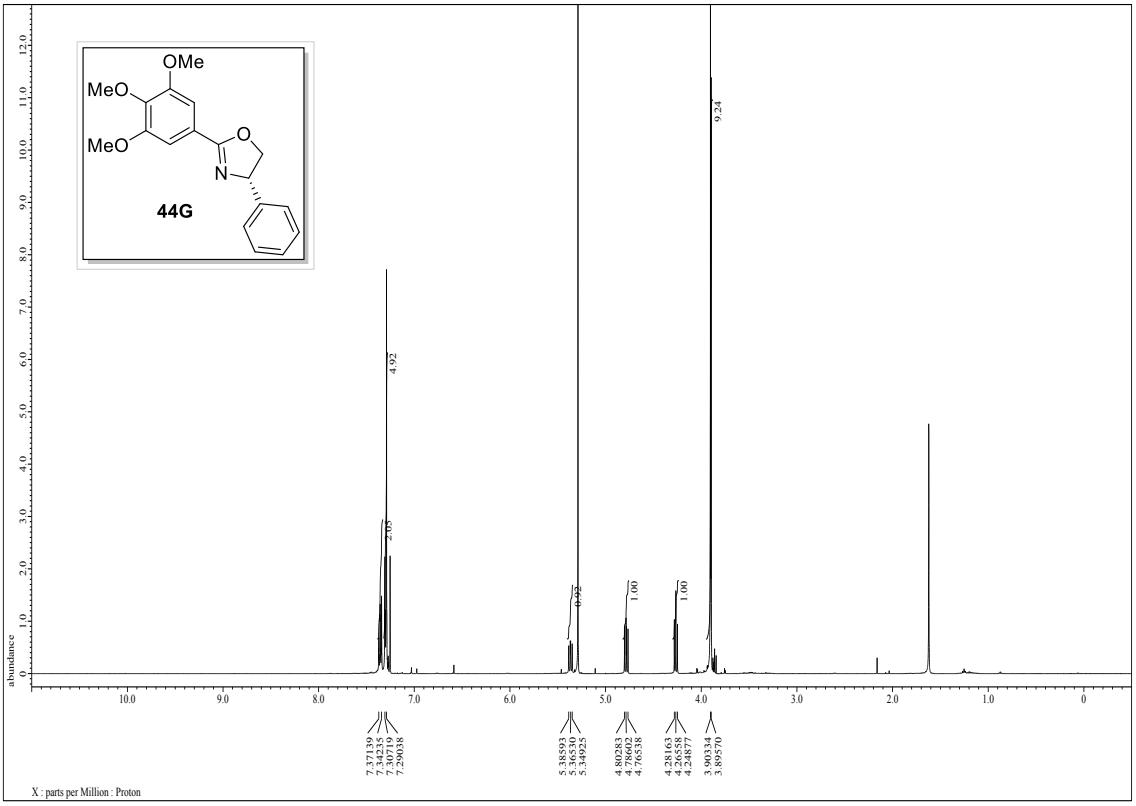

OMe
MeO
MeO
O
Ru+—N
(CH3CN)4
PF6-
34i
abundance
X : parts per Million : Carbon13

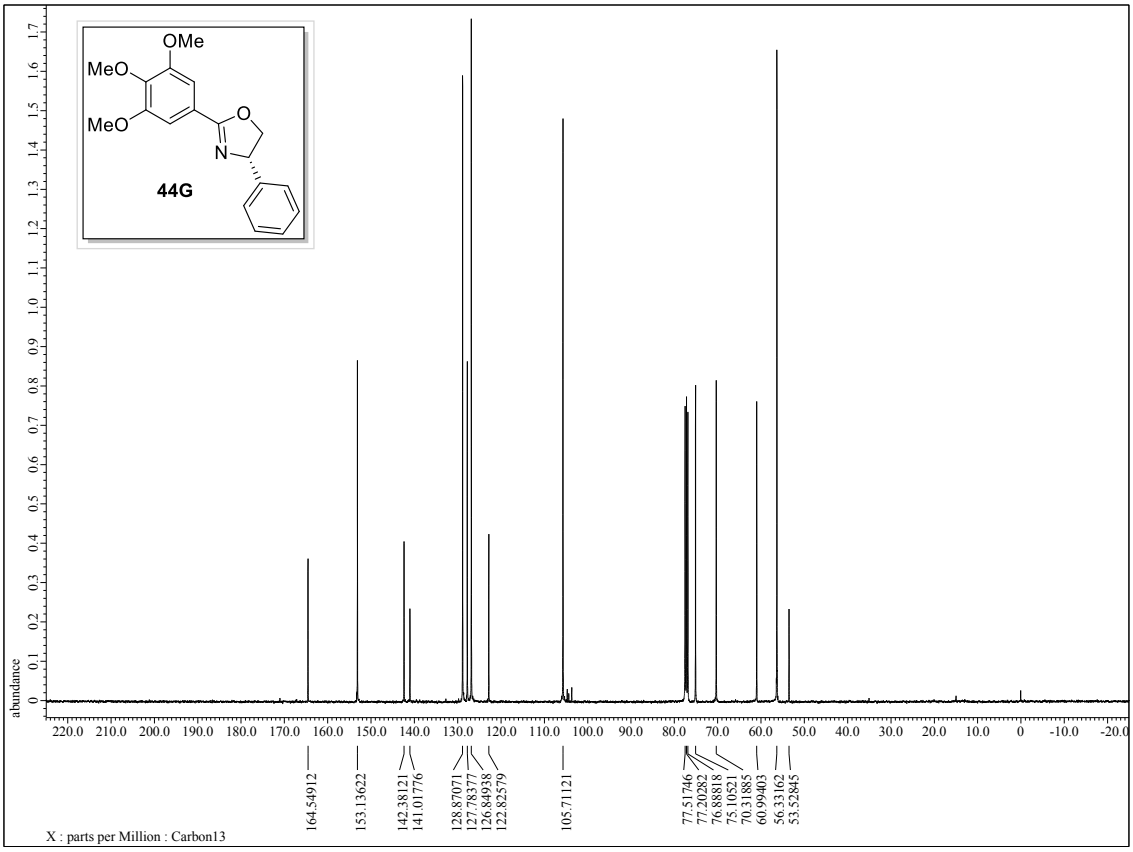

OMe
MeO
MeO
O
N
44E
abundance
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
6.38
3.24
3.12
3.04
2.07
2.02
1.00
0.99
7.20531
4.41906
4.36028
4.16487
4.07979
3.90456
3.88395
1.91984
1.83740
1.04274
1.02595
0.93587
0.91908
X : parts per Million : Proton

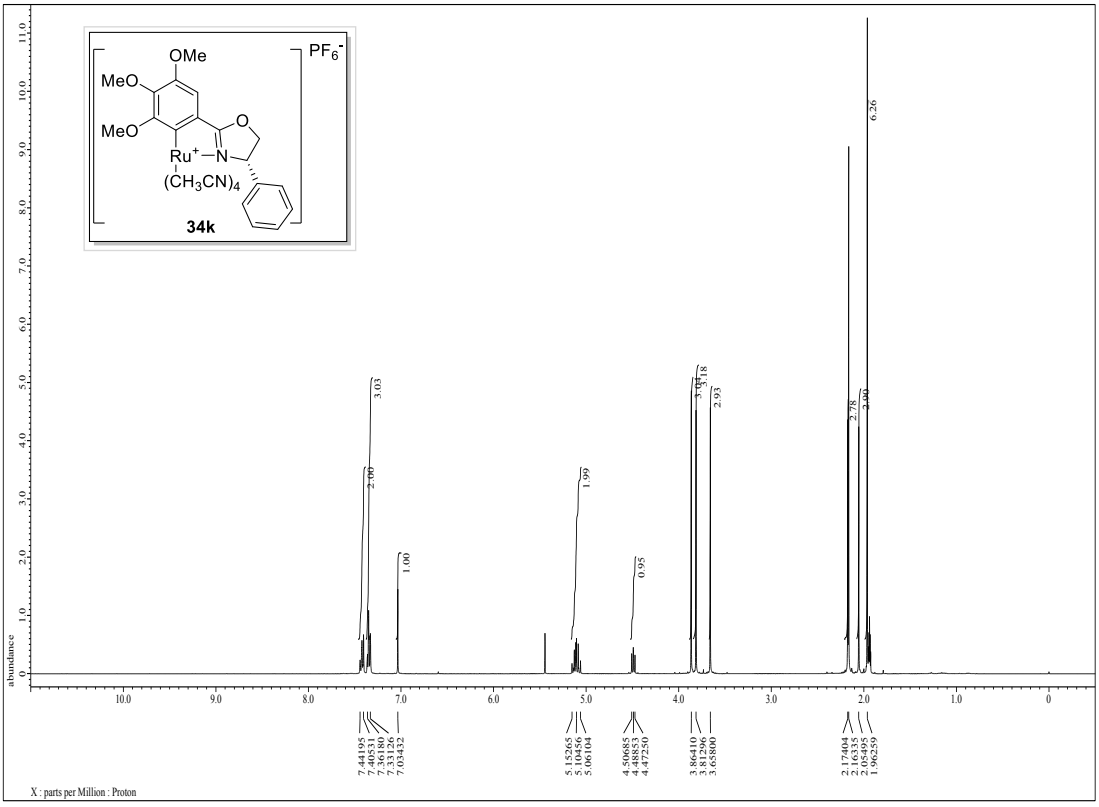

OMe
MeO
MeO
O
N
44E
abundance
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
163.11510
153.04263
140.68095
123.25444
105.43684
77.15571
72.68224
70.12596
60.95963
56.27632
53.51020
32.84065
19.05777
17.98948
X : parts per Million : Carbon13

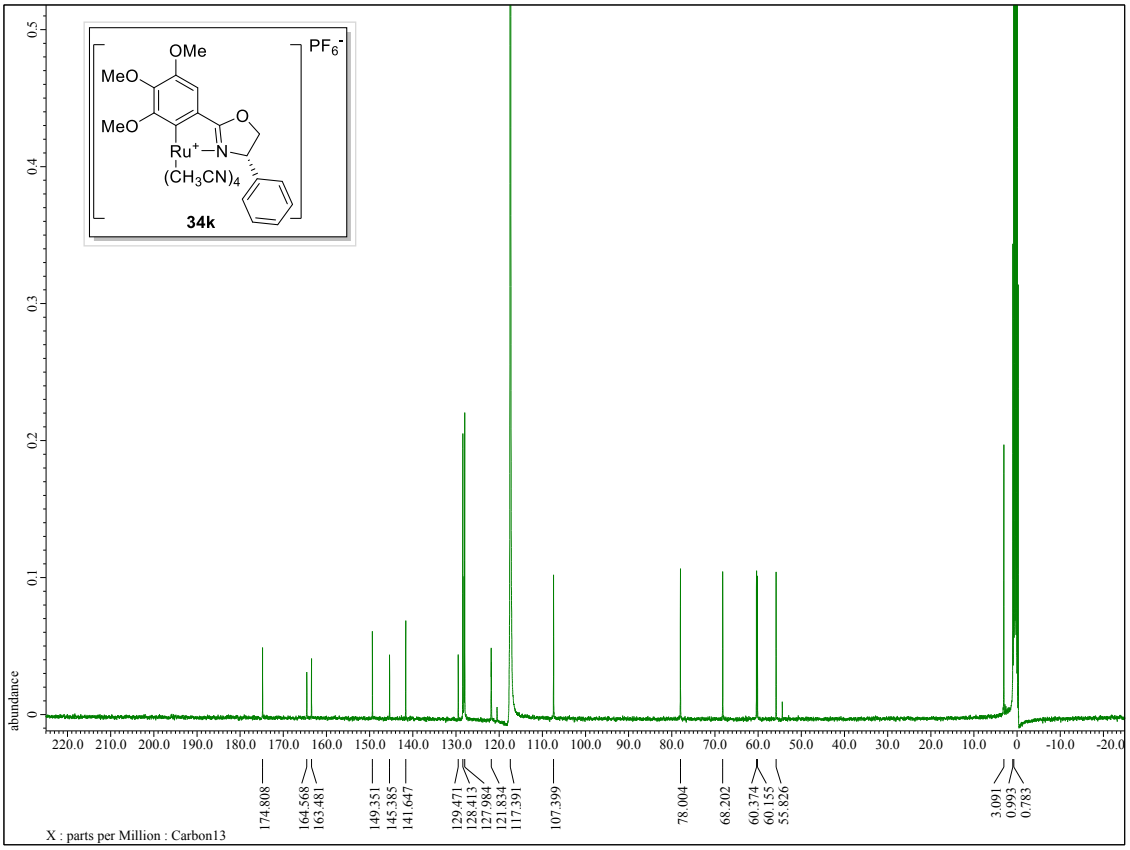

OMe
MeO
MeO
O
Ru+—N
(CH3CN)4
PF6-
34j
abundance
X : parts per Million : Proton

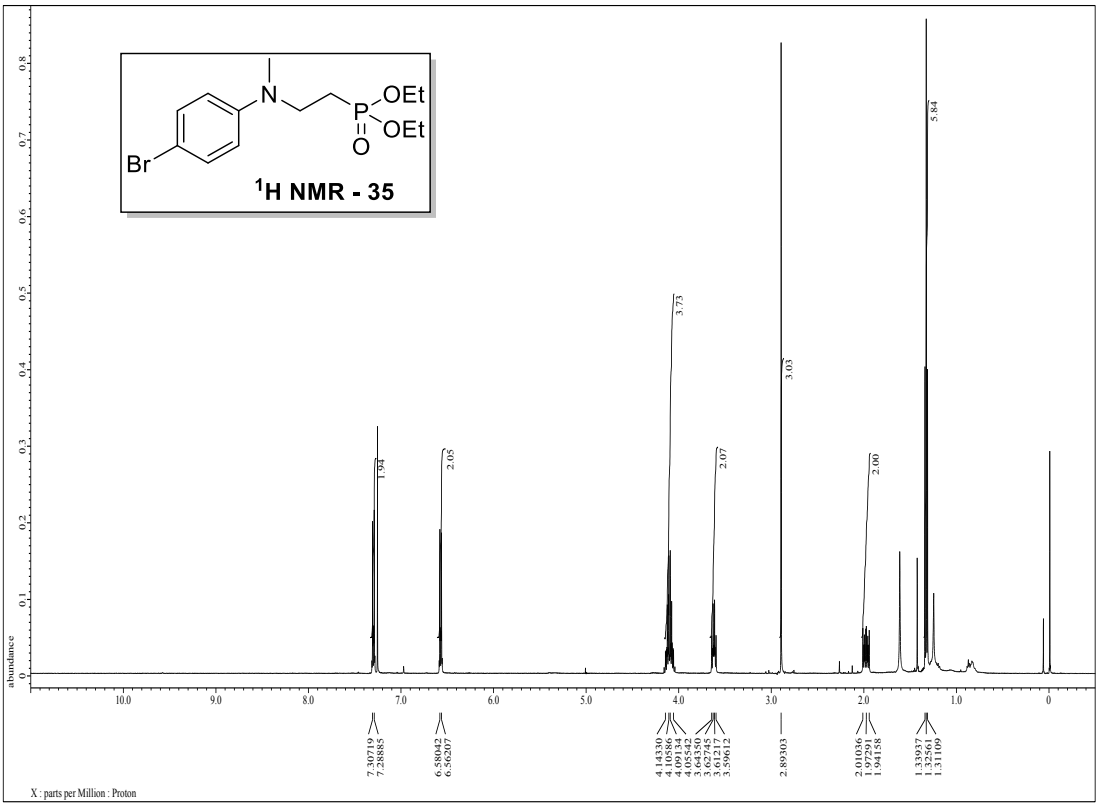

OMe
MeO
MeO
O
Ru+—N
(CH3CN)4
PF6-
34j
abundance
X : parts per Million : Carbon13

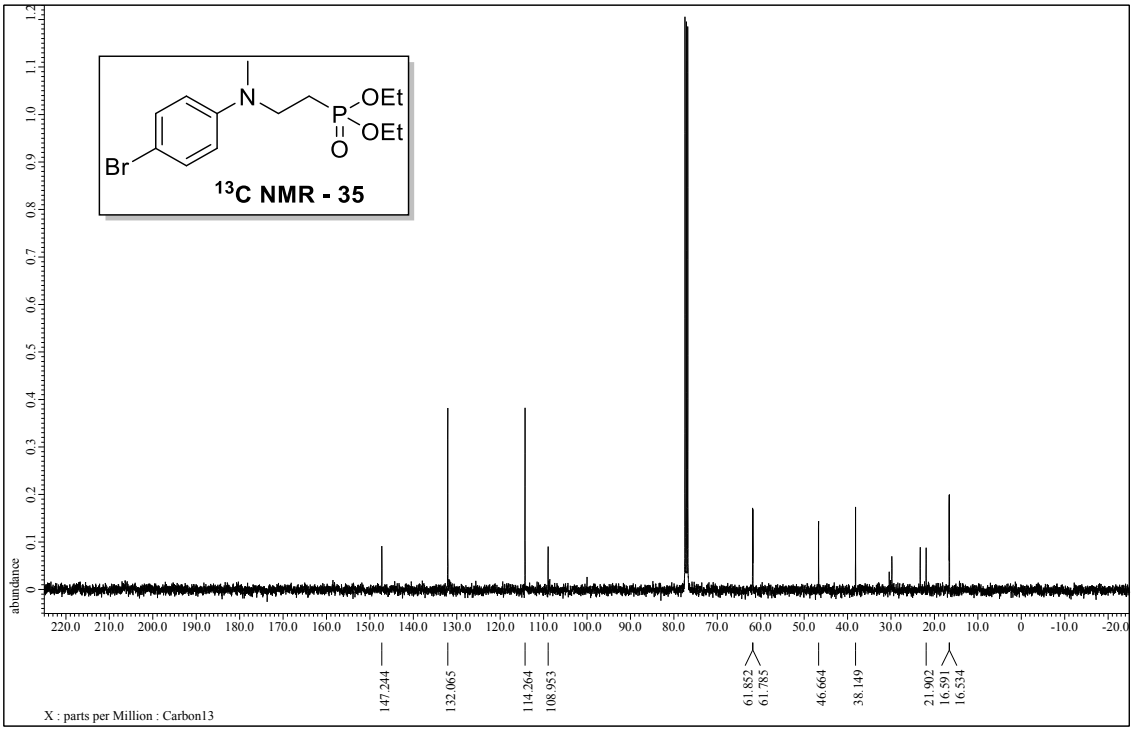

OMe
MeO
MeO
O
N
44G
4.92
2.05
0.92
1.06
1.06
9.24
abundance
X : parts per Million : Proton

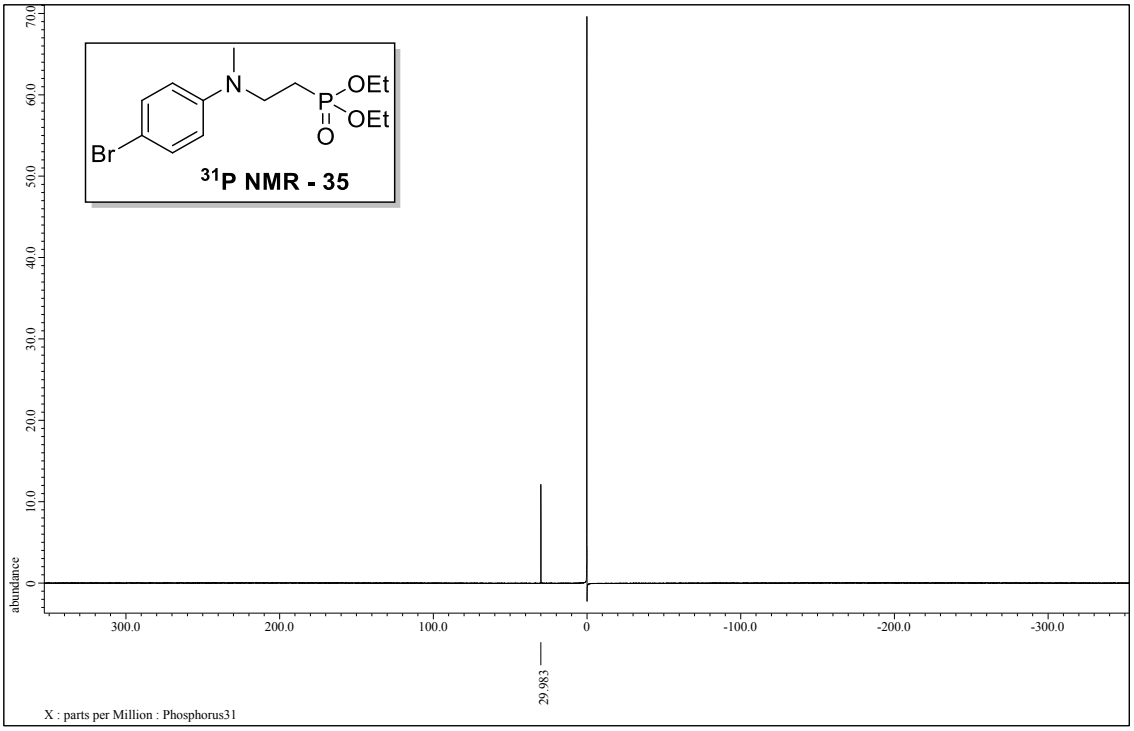

OMe
MeO
MeO
O
N
44G
abundance
X : parts per Million : Carbon13

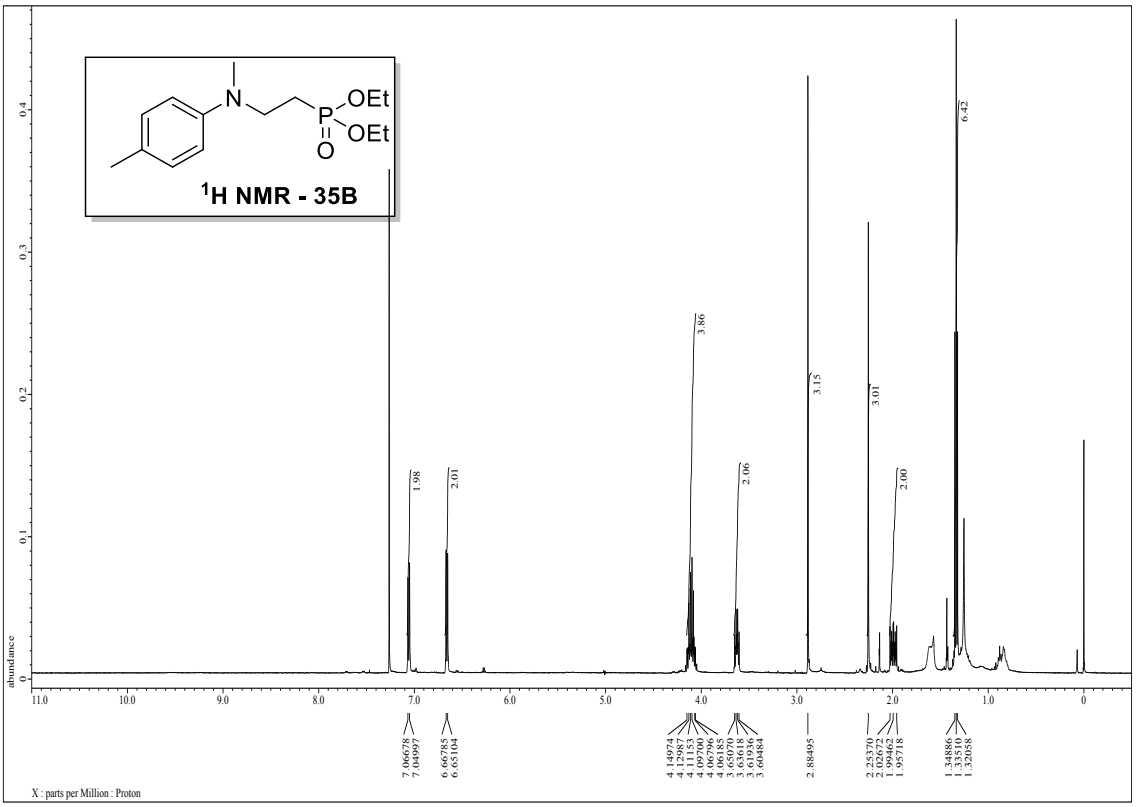

OMe
MeO
MeO
O
Ru+—N
(CH3CN)4
PF6-
34k
abundance
X : parts per Million : Proton

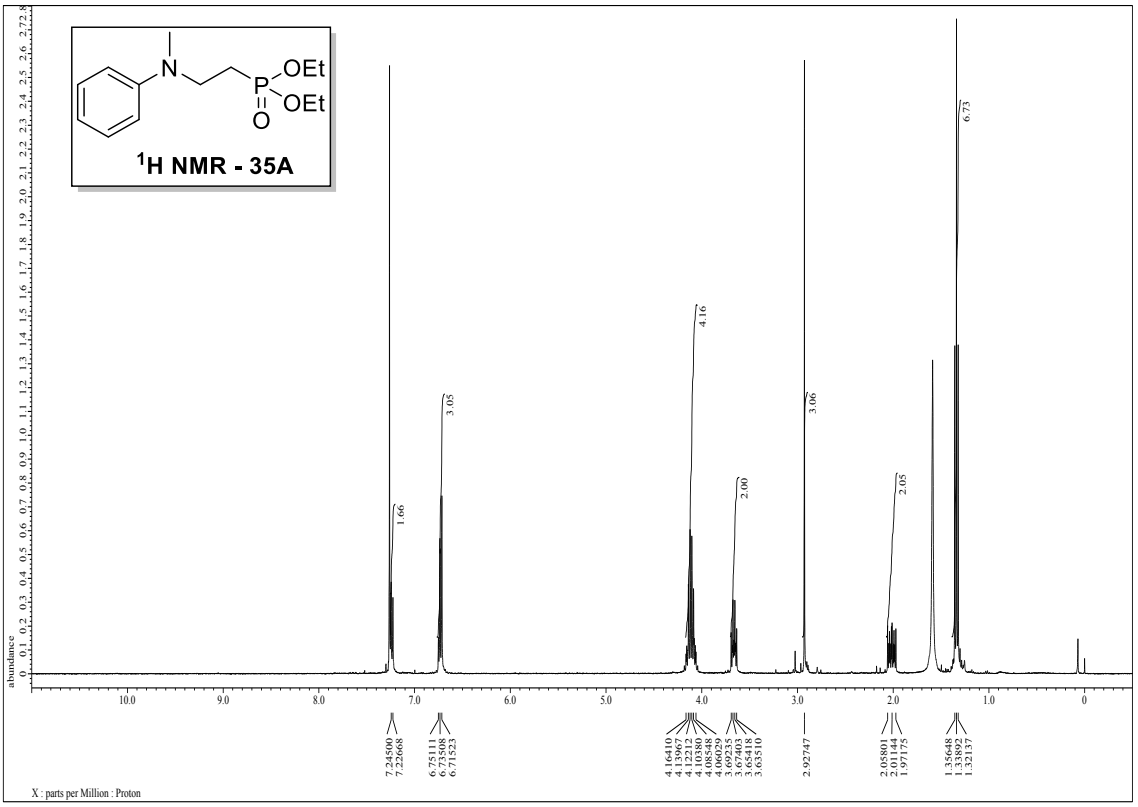

OMe
MeO
MeO
O
Ru+—N
(CH3CN)4
PF6-
34k
abundance
X : parts per Million : Carbon13

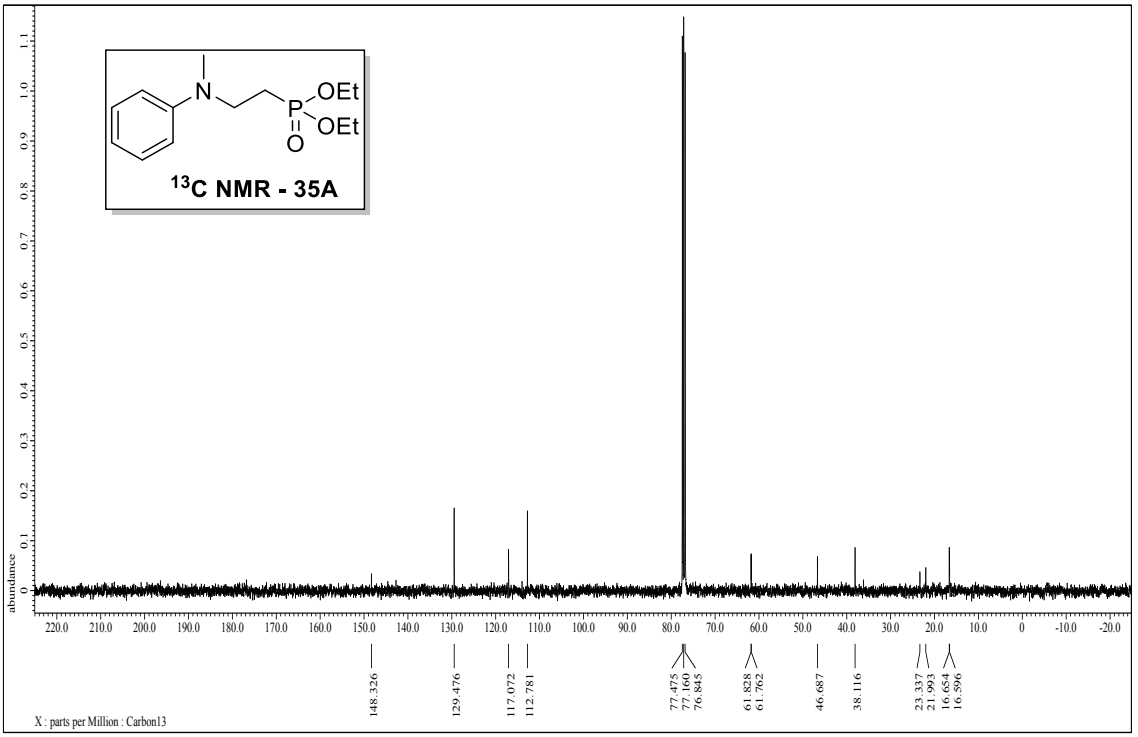

Br
N
P
OEt
OEt
O
1H NMR - 35
abundance
X : parts per Million : Proton

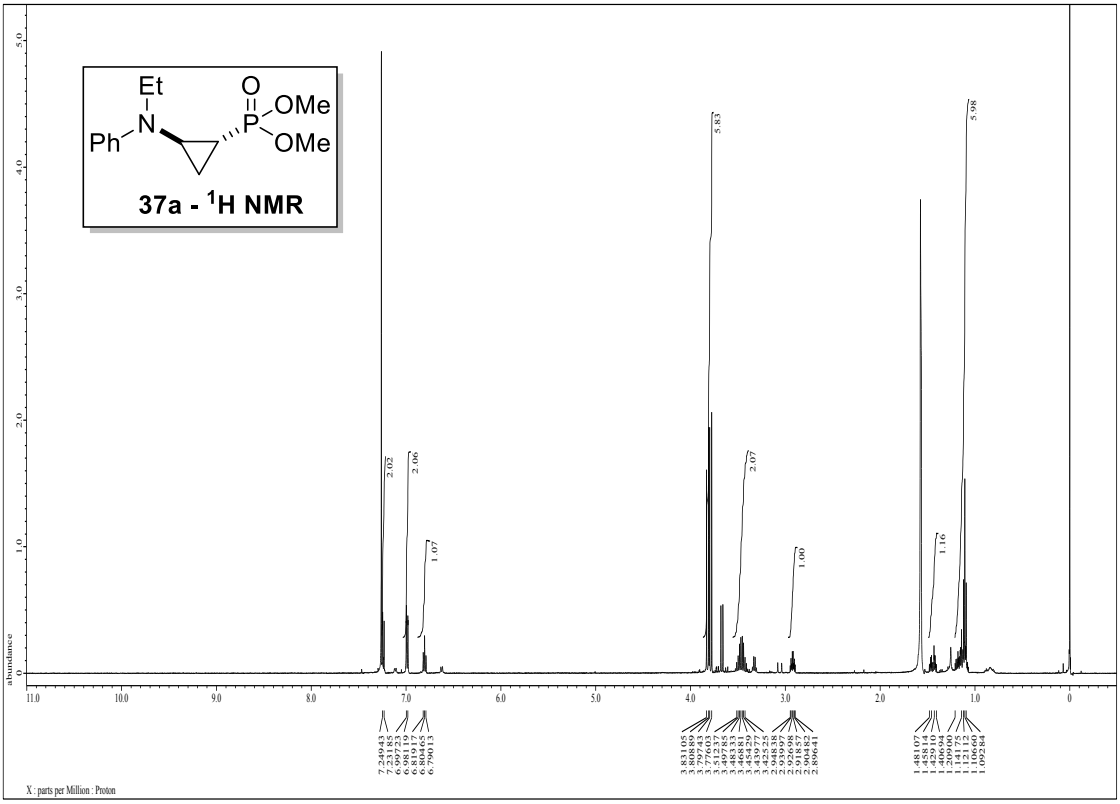

Br
N
P
OEt
OEt
O
13C NMR - 35
abundance
X : parts per Million : Carbon13

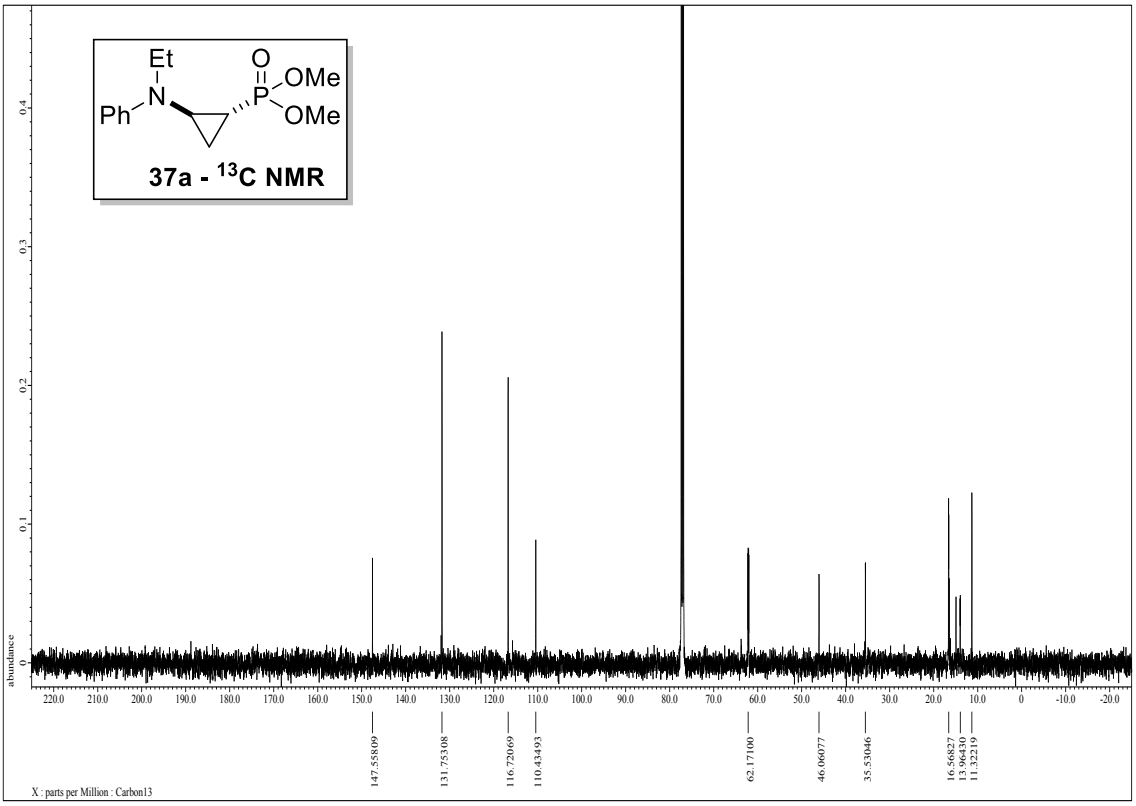

31P NMR - 35
abundance
29.983
X : parts per Million : Phosphorus31

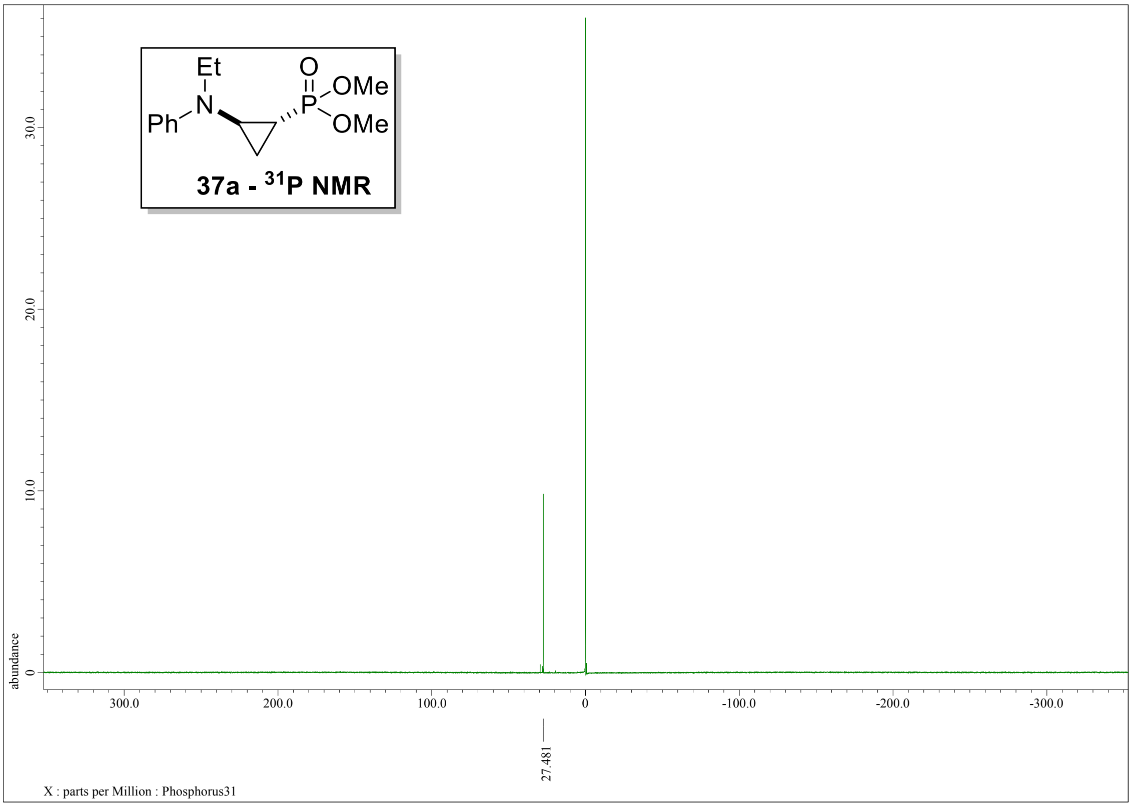

1H NMR - 35B
abundance
X : parts per Million : Proton


^{1}H NMR - 35A
abundance
X : parts per Million : Proton
1.66
3.05
4.16
2.06
3.06
2.05
6.73

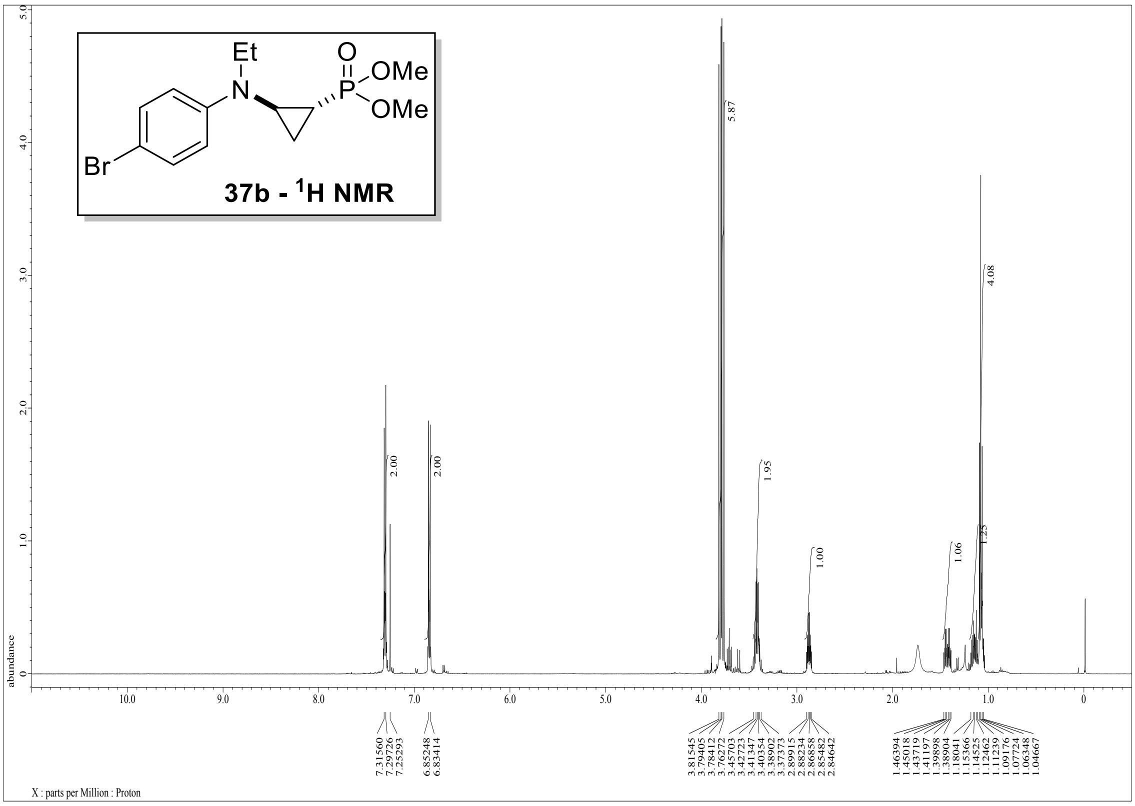

^{13}C NMR - 35A
abundance
X : parts per Million : Carbon13
148.326
129.476
117.072
112.781
77.475
77.160
76.845
61.828
61.762
46.687
38.116
23.337
21.993
16.654
16.596


Et
N
Ph
O
P
OMe
OMe
37a - 1H NMR
5.83
5.98
2.02
2.06
2.07
1.07
1.00
1.16
abundance
X : parts per Million : Proton

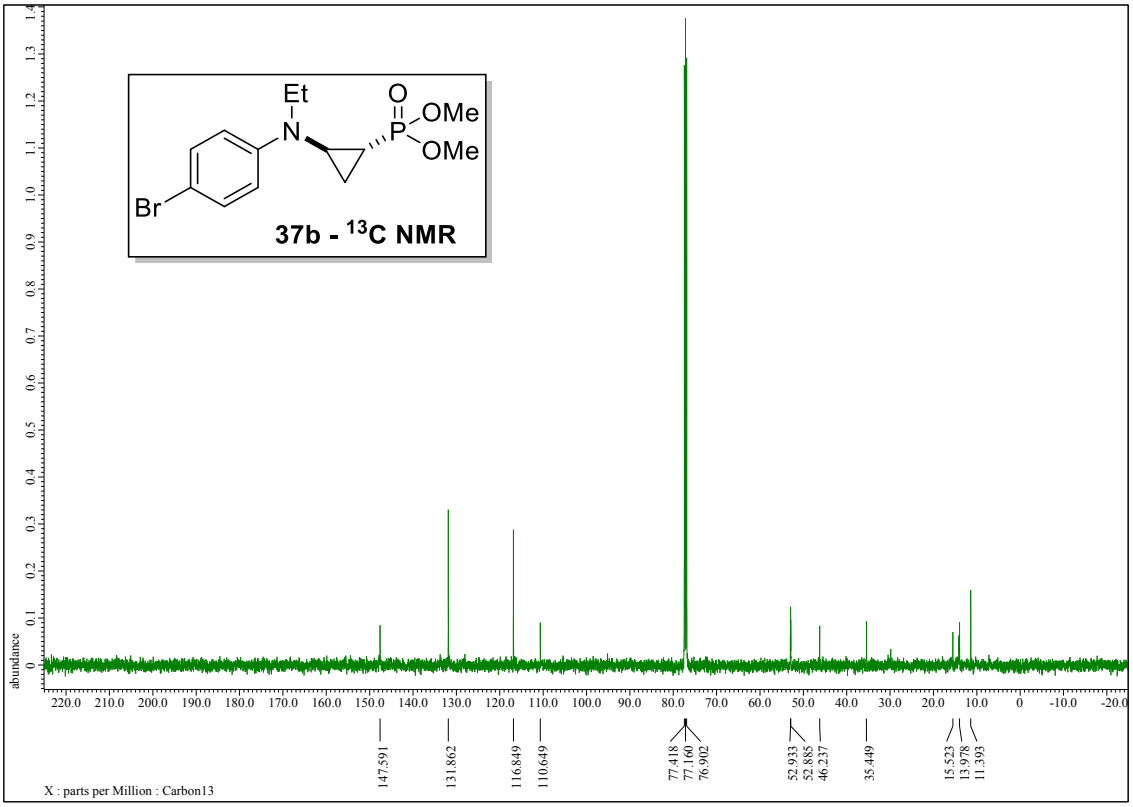

Et
N
Ph
O
P
OMe
OMe
37a - 13C NMR
147.55809
131.75308
116.72069
110.43493
62.17100
46.06077
35.53046
16.56827
13.96430
11.32219
abundance
X : parts per Million : Carbon13

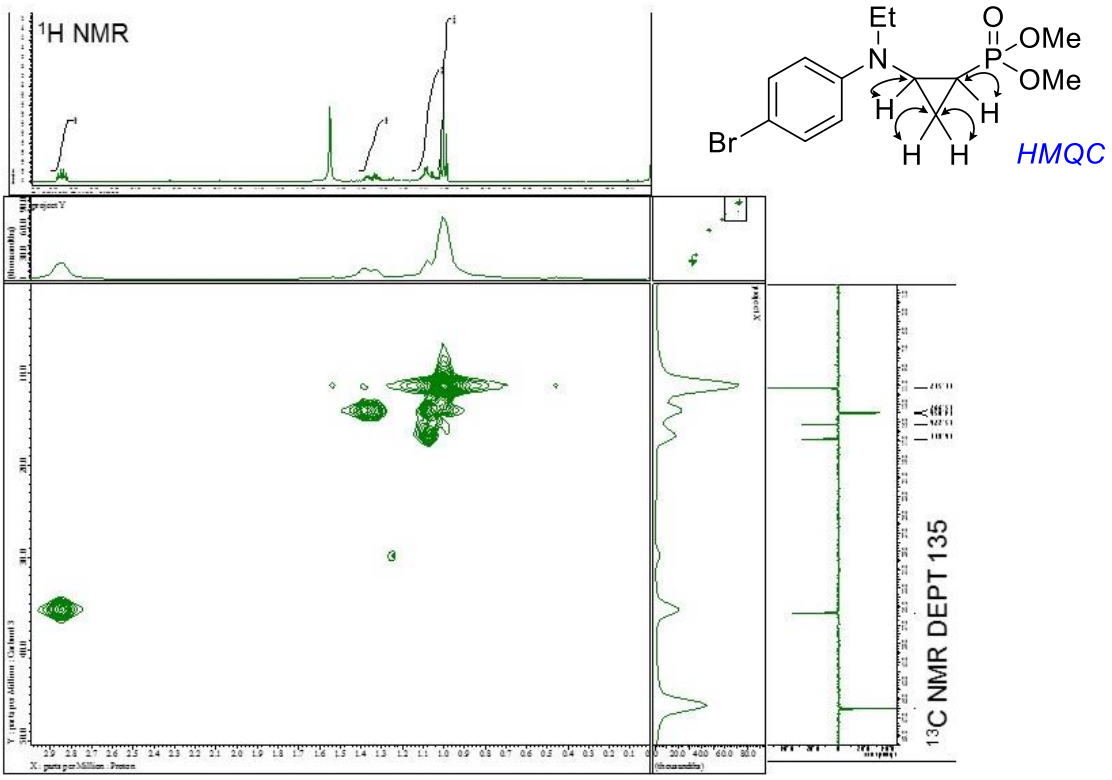


Et
N
Ph
O
P
OMe
OMe
37a - 31P NMR
27.481
abundance
X : parts per Million : Phosphorus31

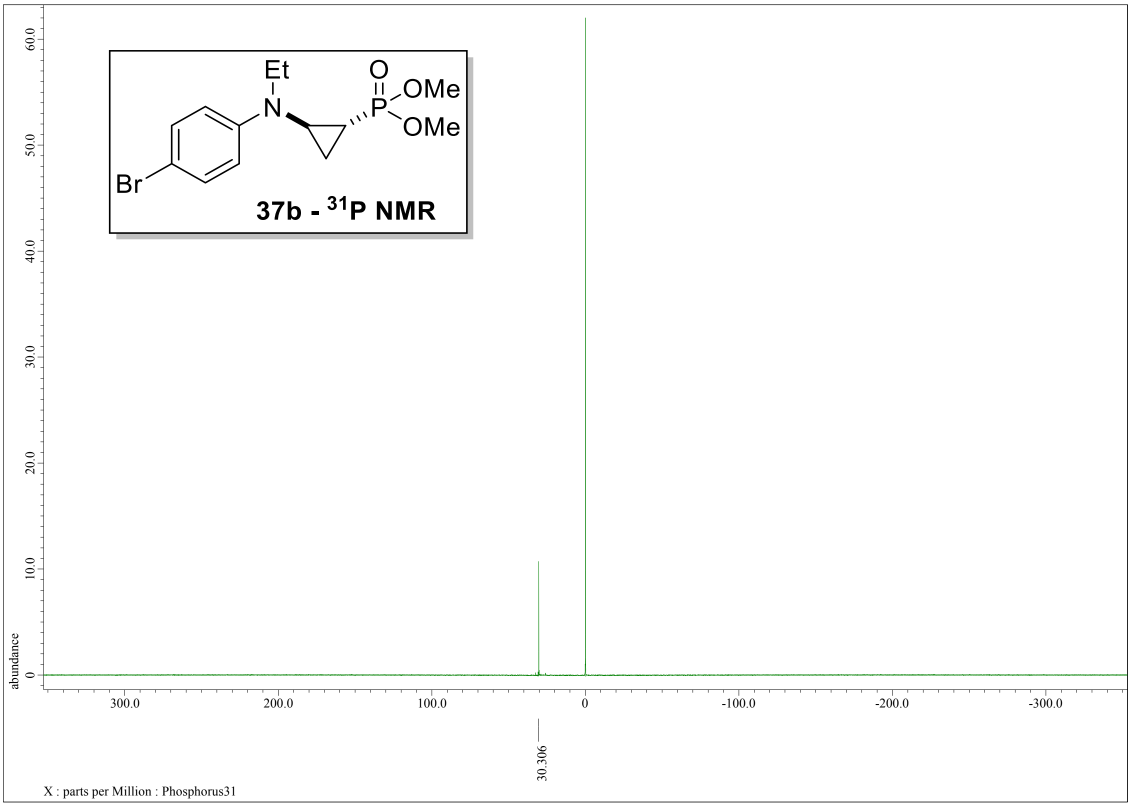


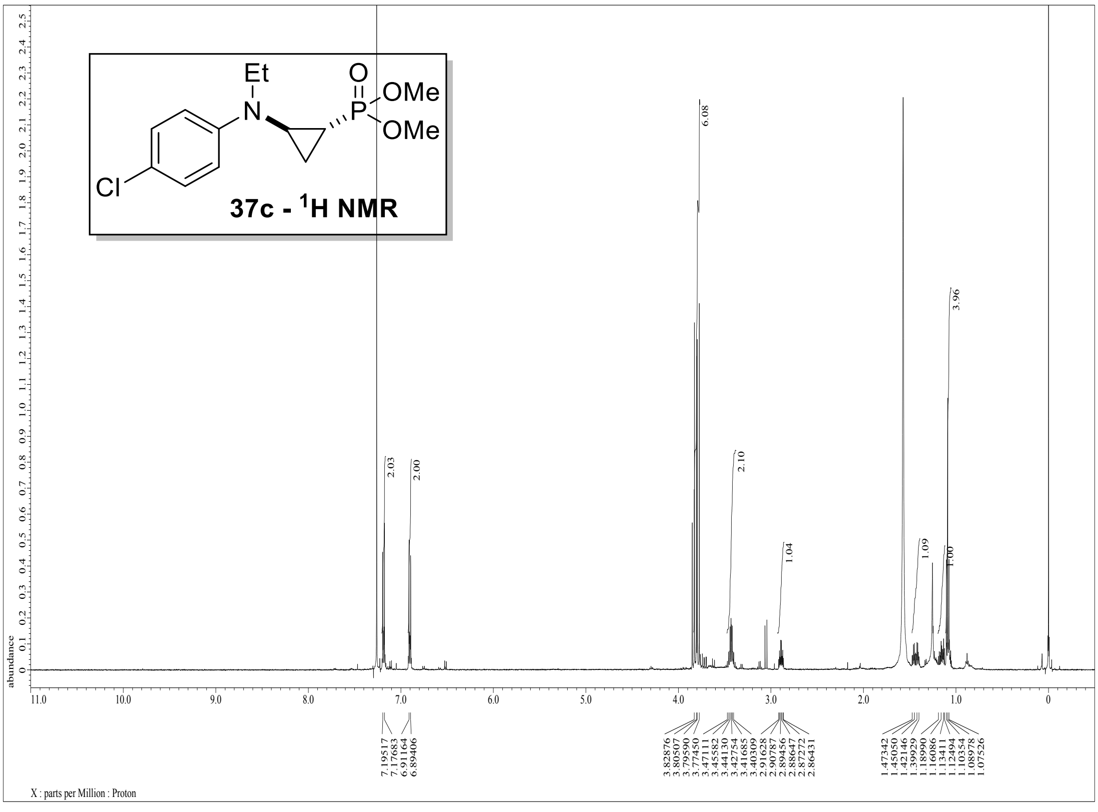
Et
N
Br
O
P
OMe
OMe
37b - 1H NMR
2.00
2.00
5.87
1.95
1.00
1.06
1.25
4.08
7.31560
7.29726
7.25293
6.85248
6.83414
3.81545
3.79405
3.78412
3.76272
3.45703
3.42723
3.41347
3.40354
3.38902
3.37373
2.89915
2.88234
2.86858
2.85482
2.84642
1.46394
1.45018
1.43719
1.41197
1.39898
1.38904
1.18041
1.15366
1.14525
1.12462
1.11239
1.09176
1.07724
1.06348
1.04667
abundance
X : parts per Million : Proton

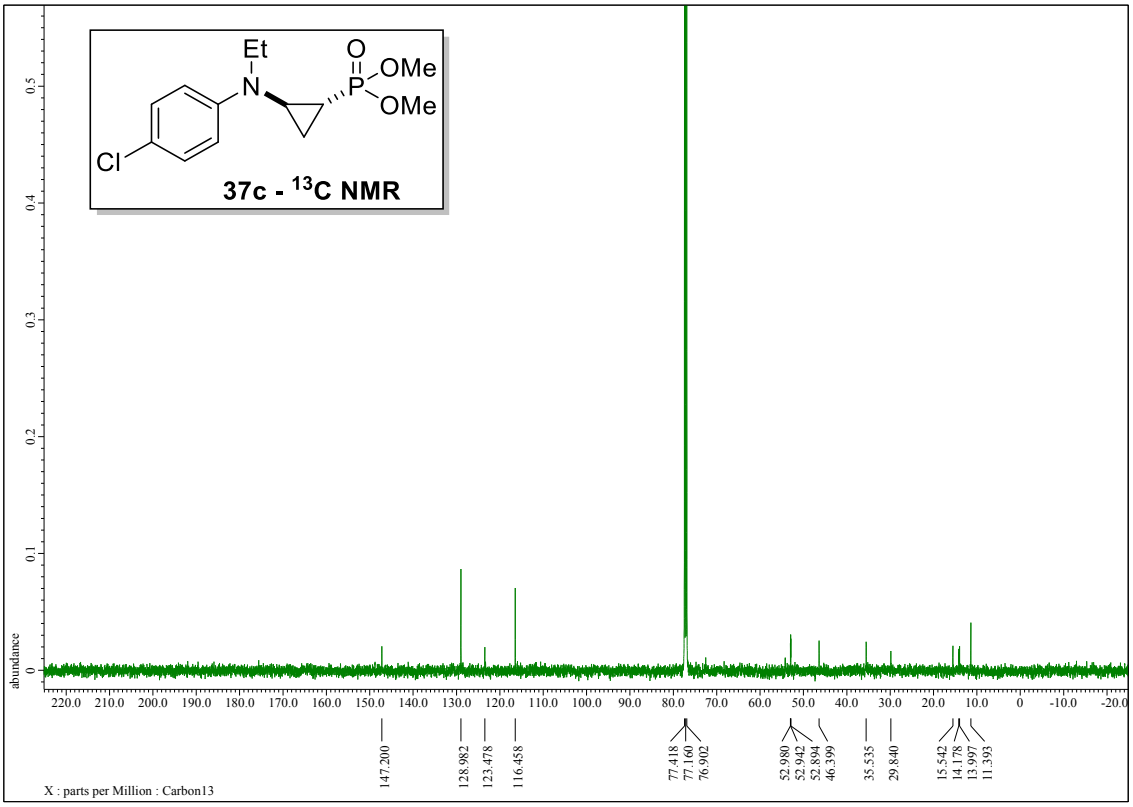


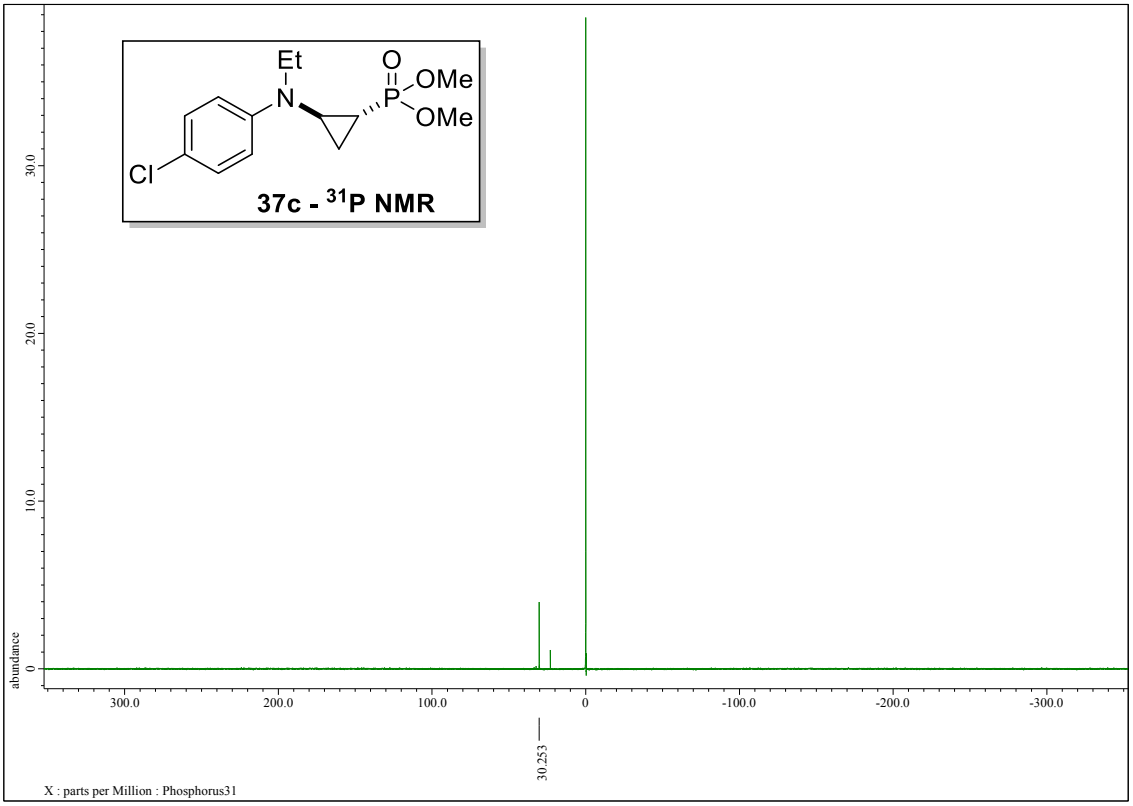


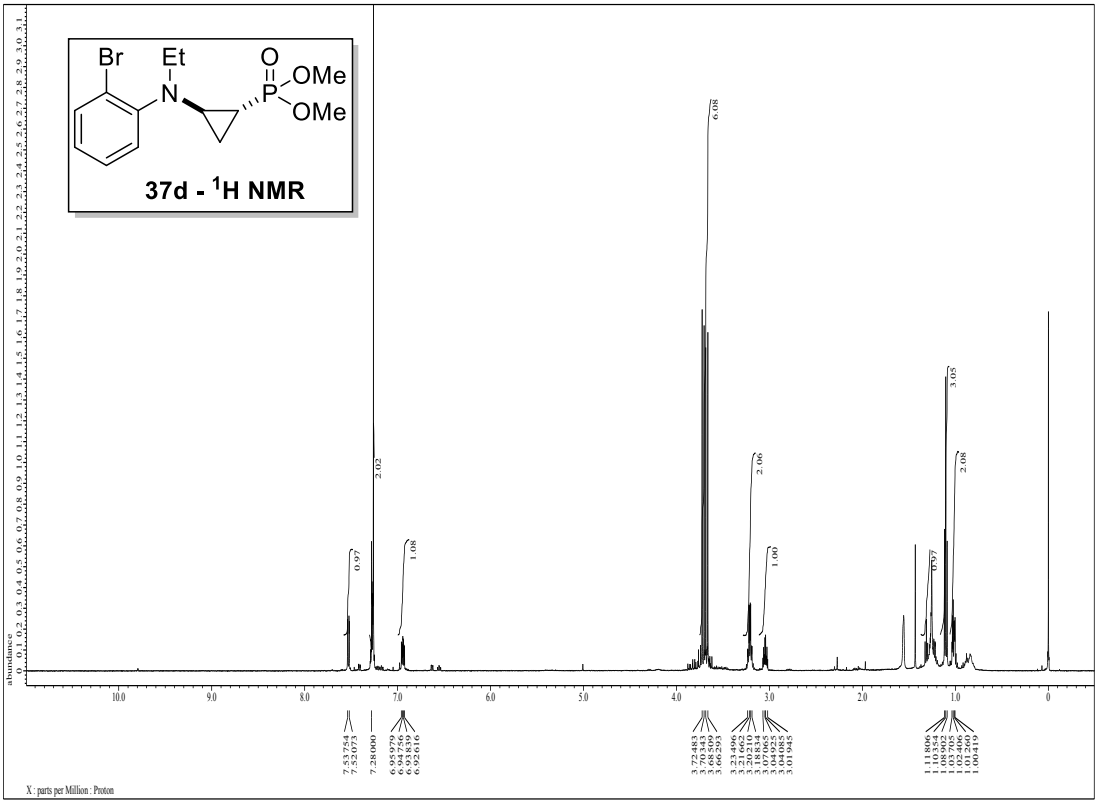
Proton identification of aminocyclopropanation by using HMQC.

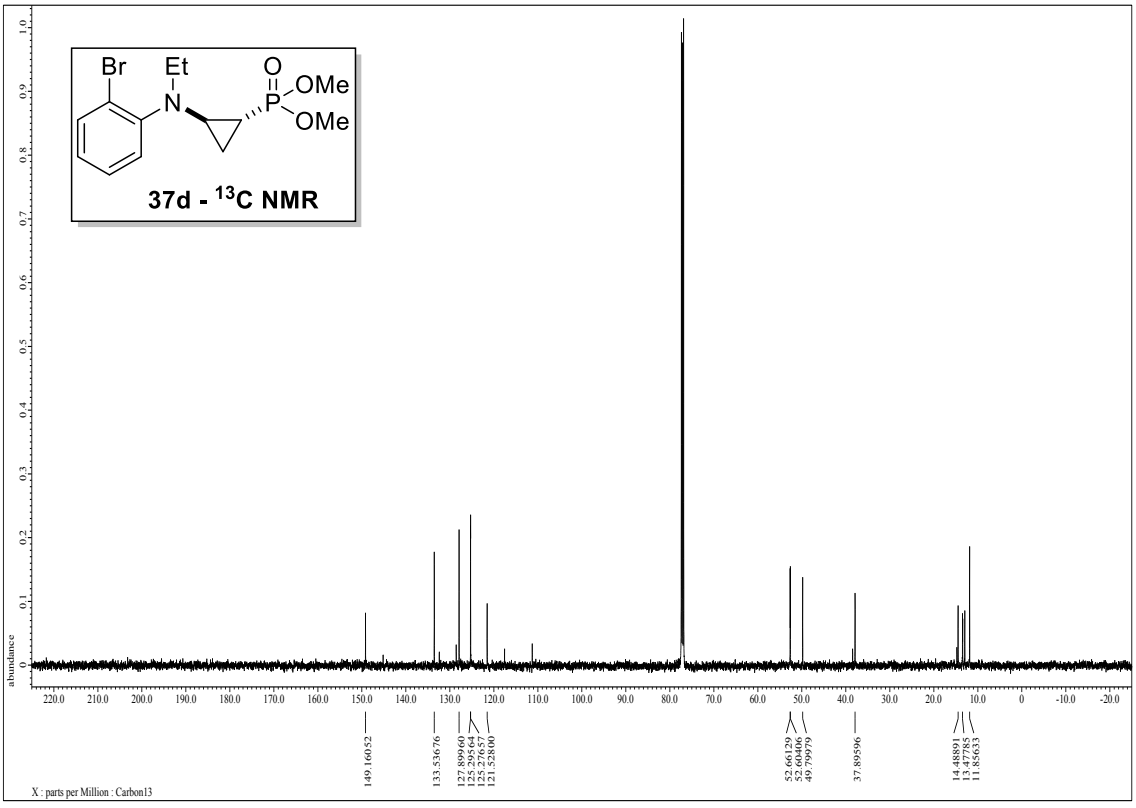

Et
N
O
P
OMe
OMe
Br
37b - ^{31}P NMR
abundance
300.0
200.0
100.0
0
-100.0
-200.0
-300.0
30.306
X : parts per Million : Phosphorus31

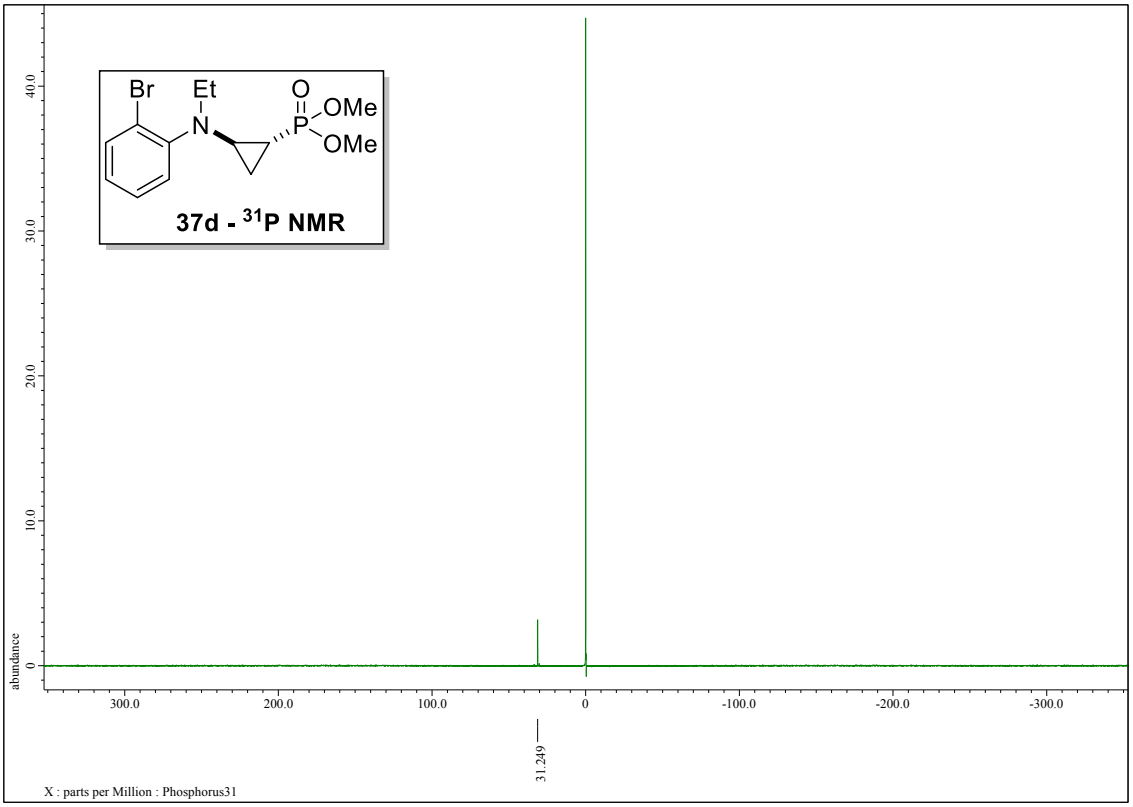

Et
N
O
P
OMe
OMe
Cl
37c - ^{1}H NMR
abundance
6.08
3.96
2.03
2.00
2.10
1.04
1.09
1.00
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.19517
7.17683
6.91164
6.89406
3.82876
3.80507
3.79590
3.77450
3.47111
3.45582
3.44130
3.42754
3.41685
3.40309
2.91628
2.90787
2.89456
2.88647
2.87272
2.86431
1.47342
1.45050
1.42146
1.39929
1.18990
1.16086
1.13411
1.12494
1.10354
1.08978
1.07526
X : parts per Million : Proton

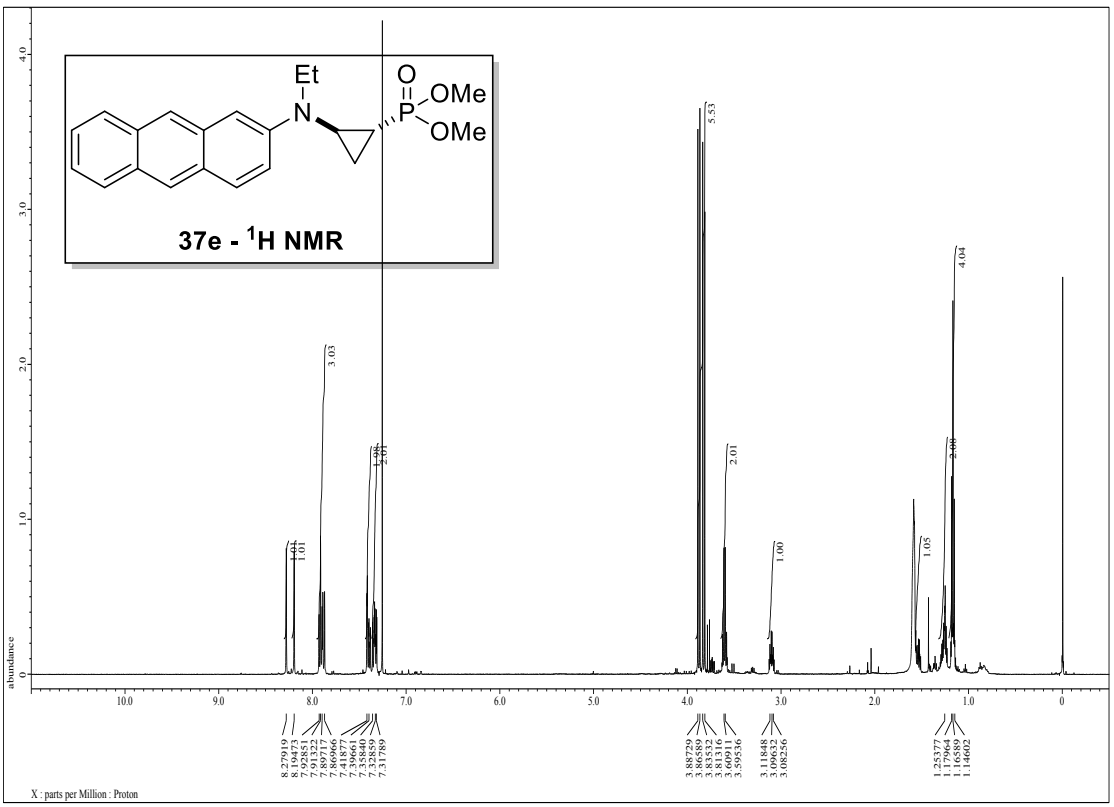

Et
N
O
P
OMe
OMe
Cl
37c - 13C NMR
abundance
X : parts per Million : Carbon13
147.200
128.982
123.478
116.458
77.418
77.160
76.902
52.980
52.942
52.894
46.399
35.535
29.840
15.542
14.178
13.997
11.393

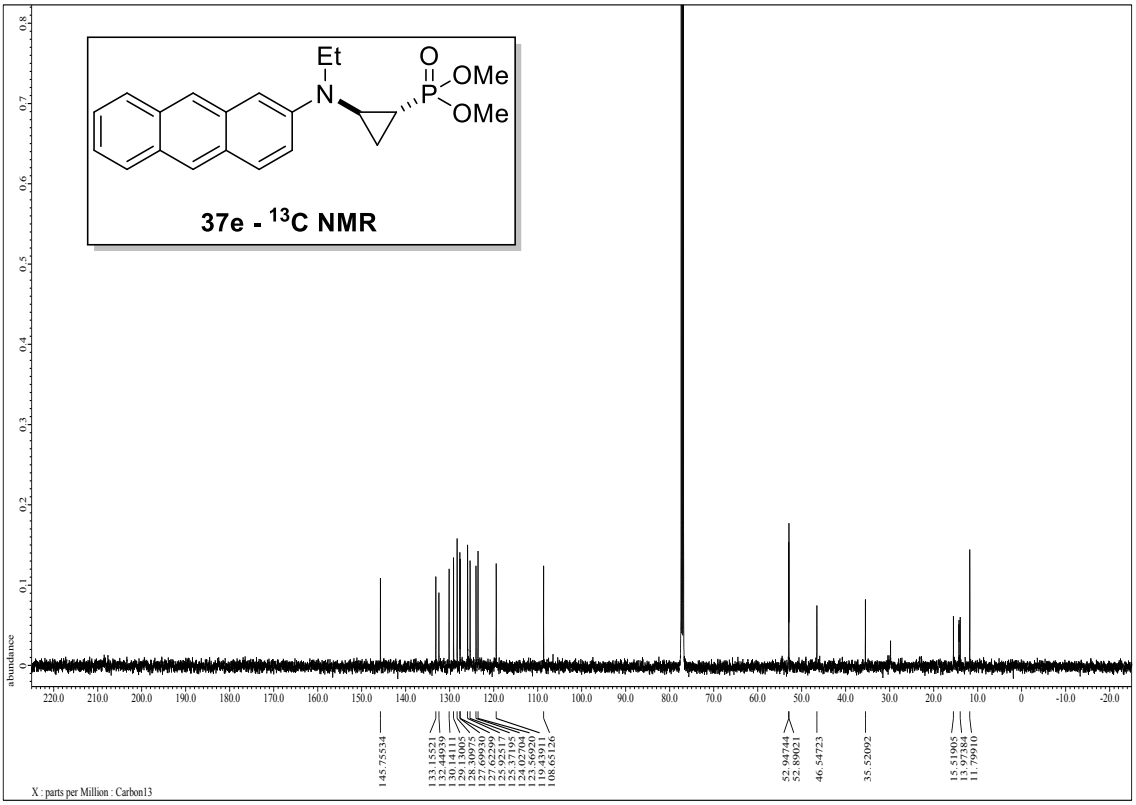

Et
N
O
P
OMe
OMe
Cl
37c - 31P NMR
abundance
X : parts per Million : Phosphorus31
30.253

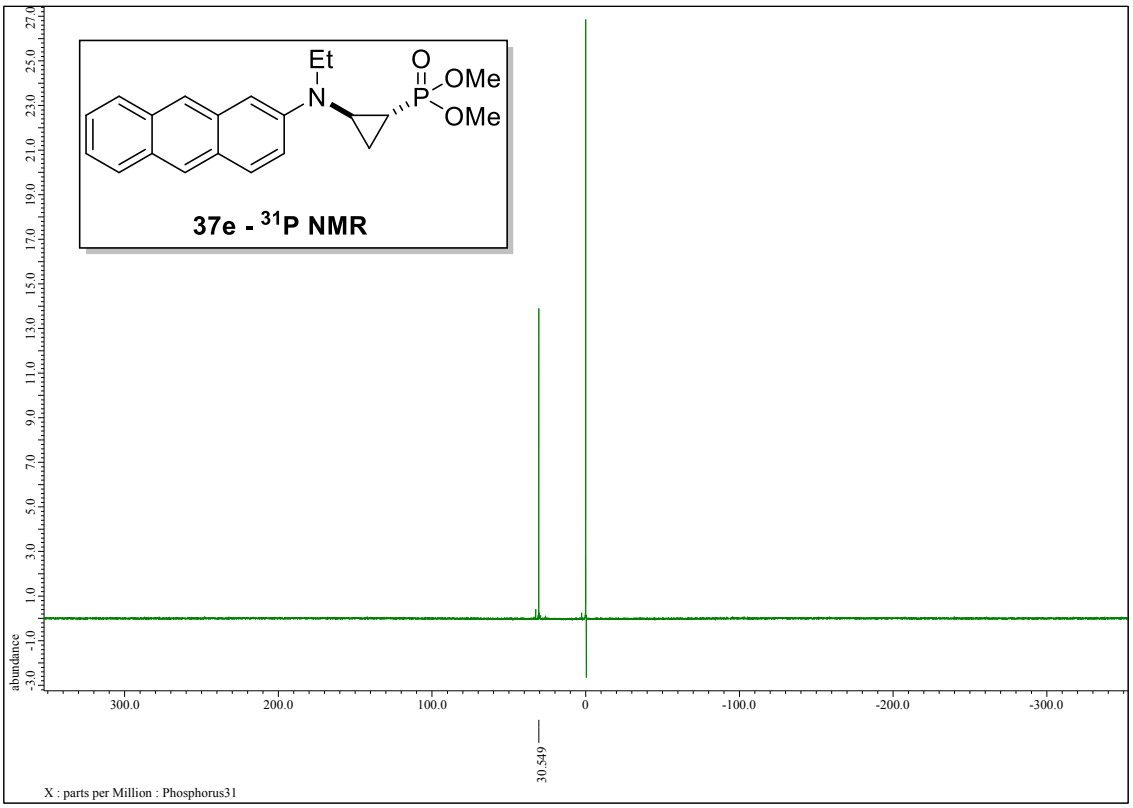

Br
Et
N
O
P
OMe
OMe
37d - 1H NMR
abundance
X : parts per Million : Proton

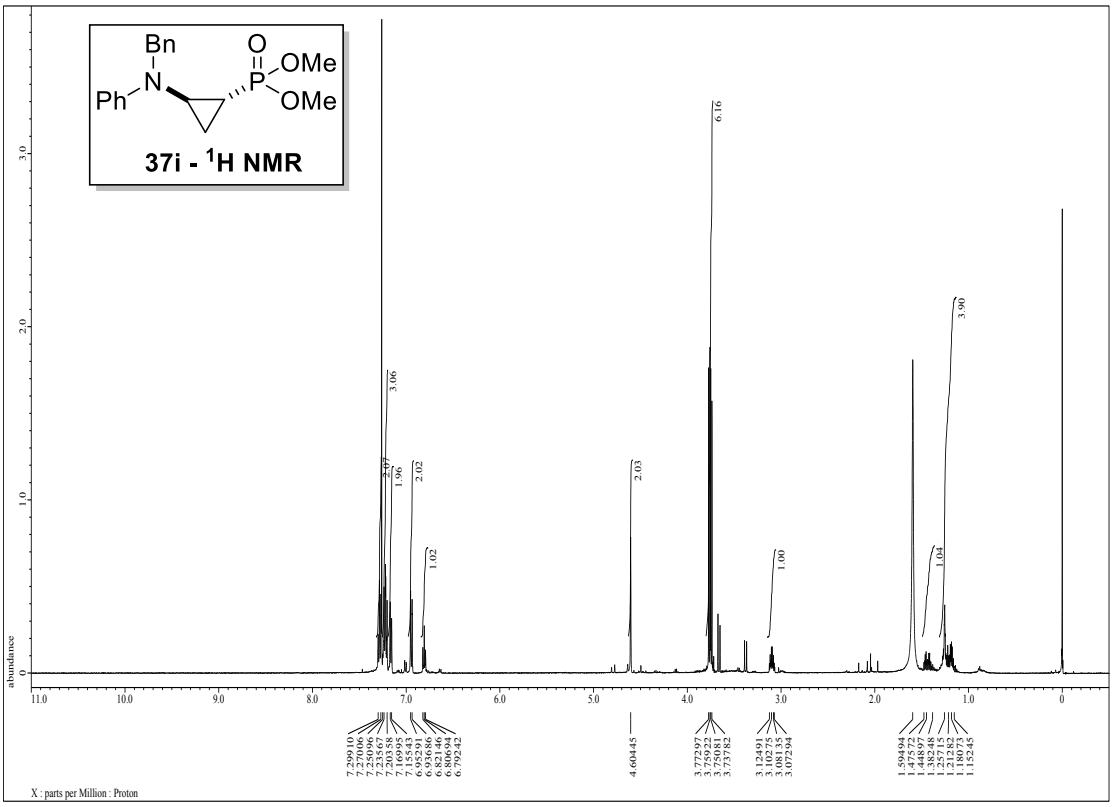

Br
Et
N
O
P
OMe
OMe
37d - 13C NMR
abundance
X : parts per Million : Carbon13

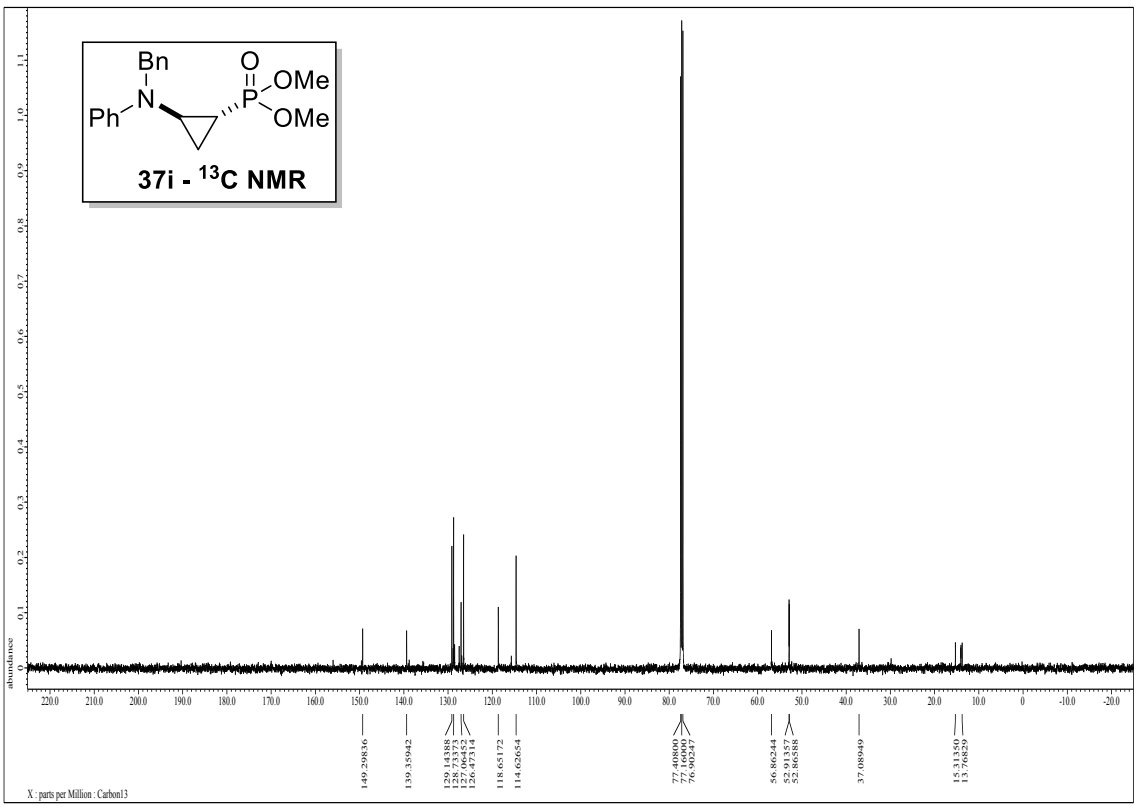

Br
Et
N
O
P
OMe
OMe
37d - 31P NMR
abundance
40.0
30.0
20.0
10.0
0
300.0
200.0
100.0
0
-100.0
-200.0
-300.0
31.249
X : parts per Million : Phosphorus31

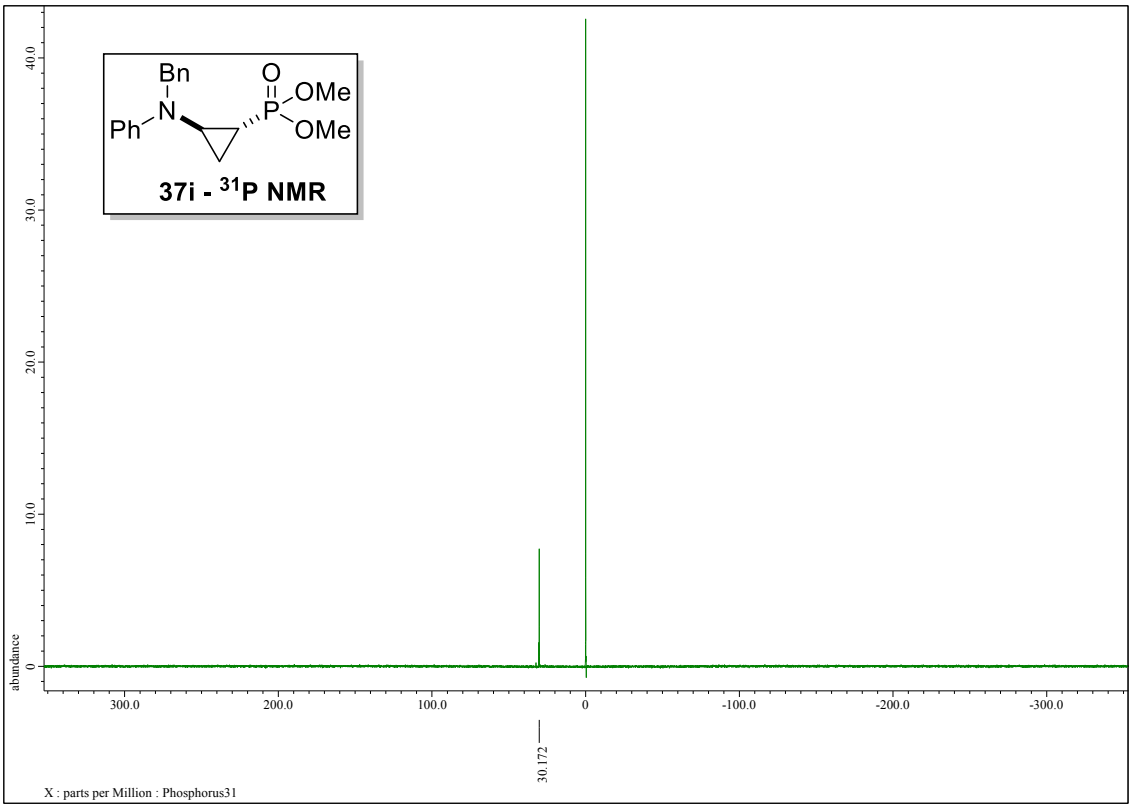

Et
N
O
P
OMe
OMe
37e - 1H NMR
abundance
4.0
3.0
2.0
1.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
5.53
4.04
3.03
2.01
1.00
1.05
X : parts per Million : Proton

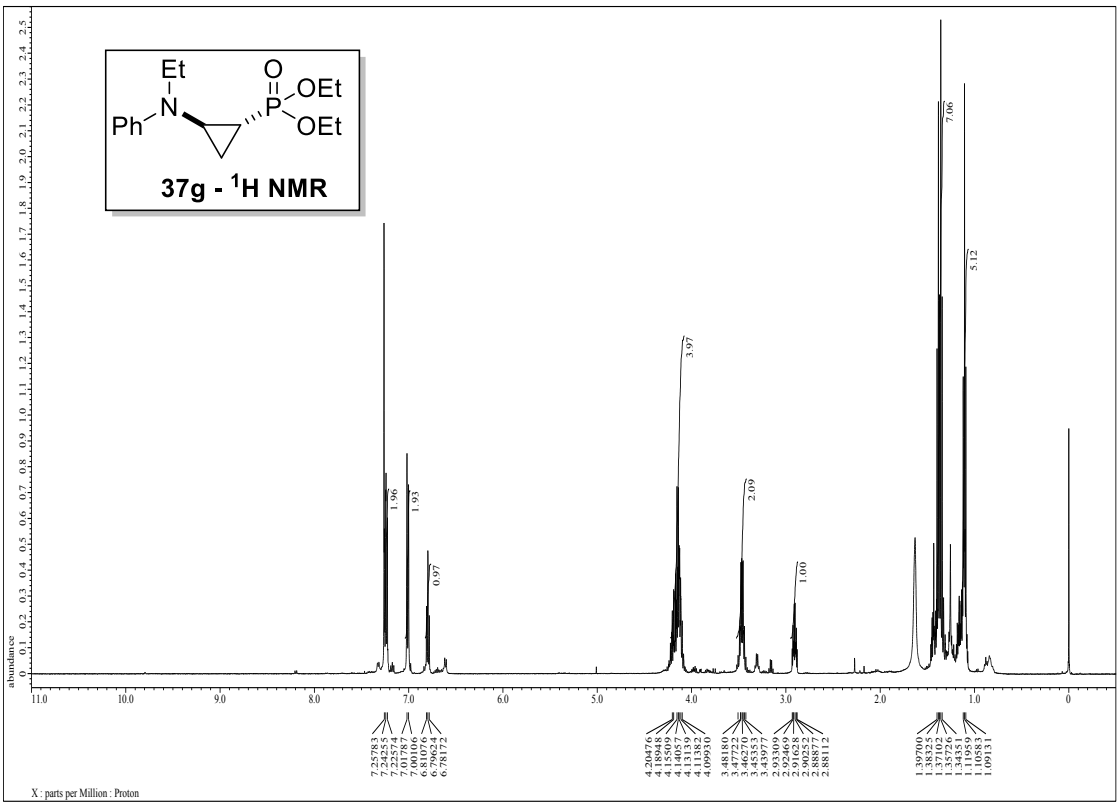

Et
N
O
P
OMe
OMe
37e - 13C NMR
abundance
X : parts per Million : Carbon13

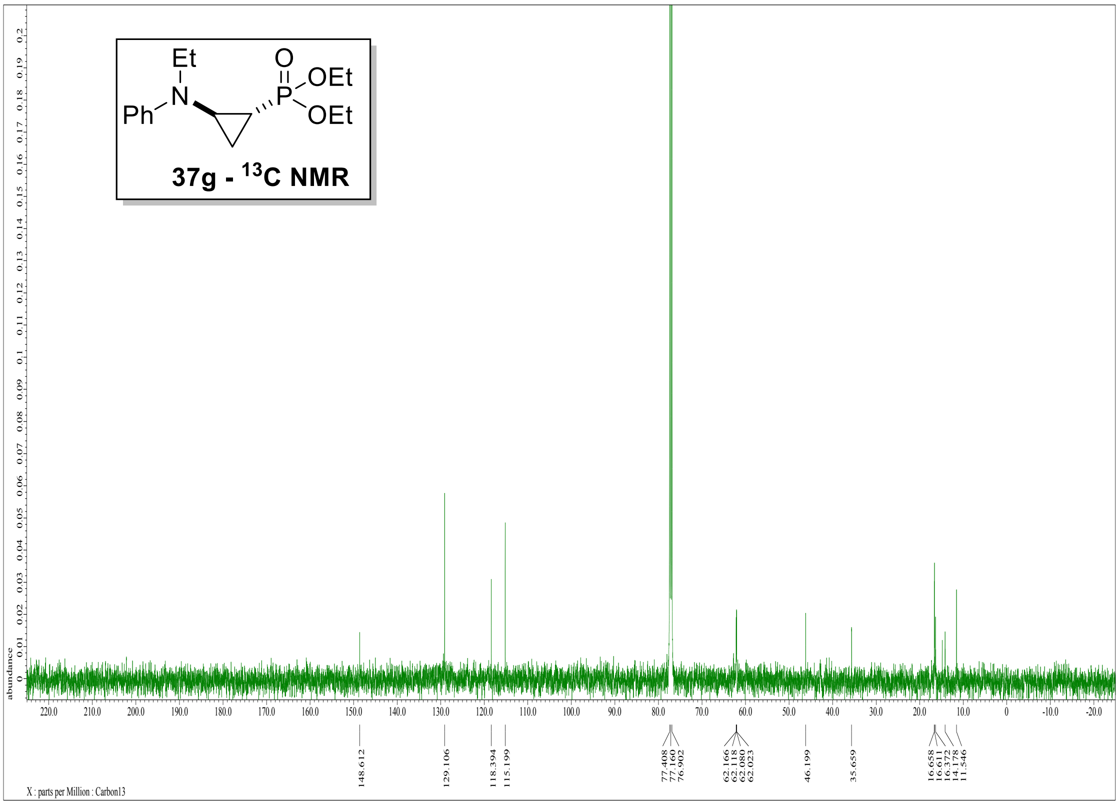

Et
N
O
P
OMe
OMe
37e - 31P NMR
abundance
X : parts per Million : Phosphorus31


Bn
N
Ph
O
P
OMe
OMe
37i - 1H NMR
abundance
X : parts per Million : Proton

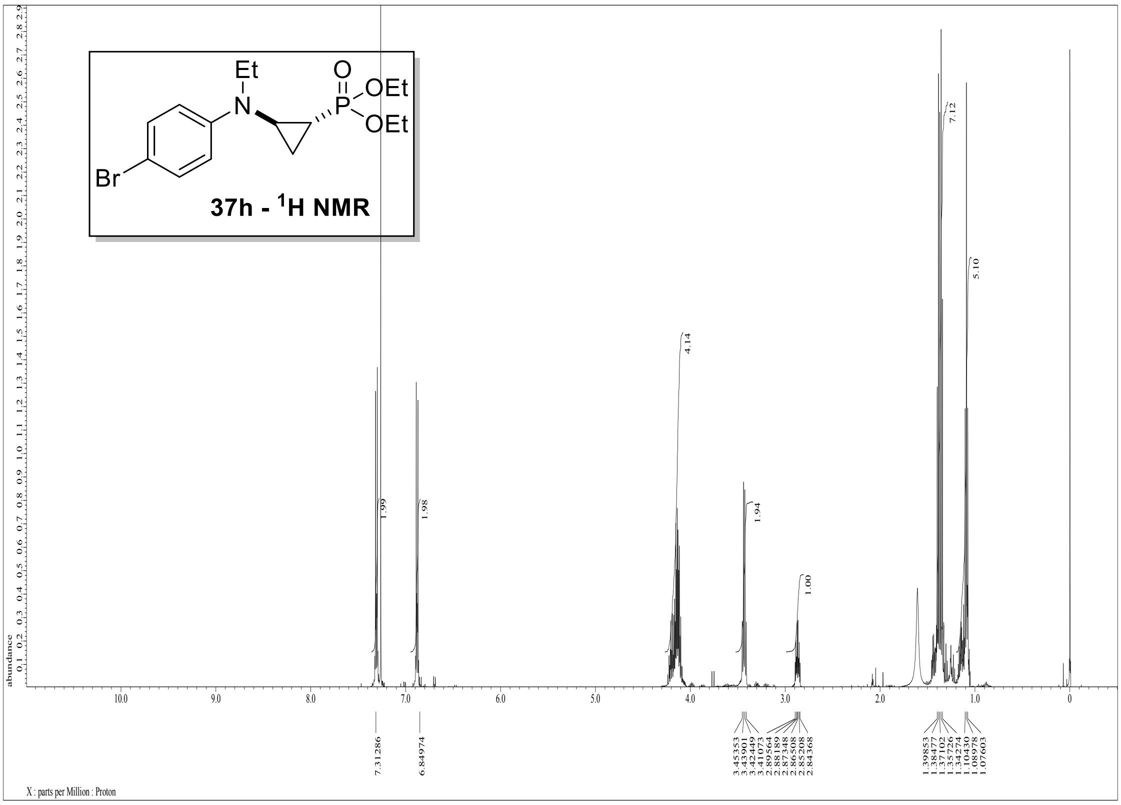

Bn
N
Ph
O
P
OMe
OMe
37i - 13C NMR
abundance
X : parts per Million : Carbon13


Bn
O
N
P
OMe
Ph
OMe
37i - 31P NMR
abundance
40.0
30.0
20.0
10.0
0
300.0
200.0
100.0
0
-100.0
-200.0
-300.0
30.172
X : parts per Million : Phosphorus31

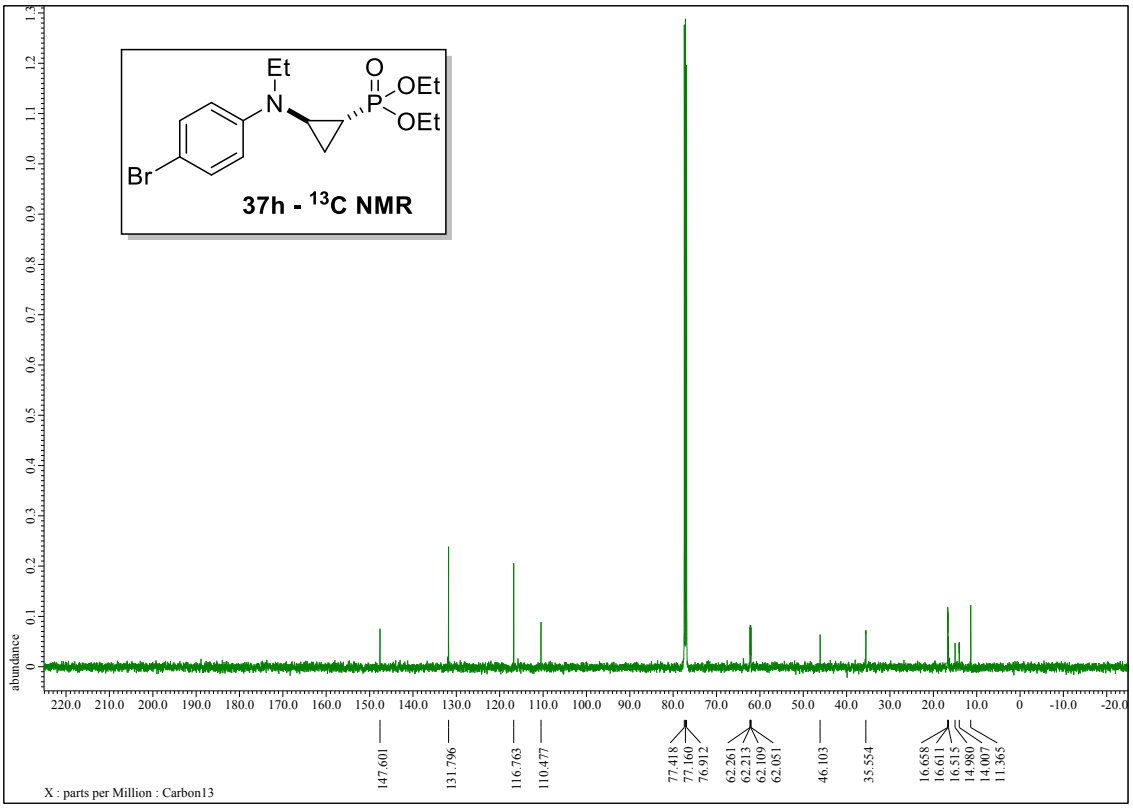

Et
O
N
P
OEt
Ph
OEt
37g - 1H NMR
abundance
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
1.96
1.93
0.97
3.97
2.09
1.00
7.06
5.12
7.25783
7.24255
7.22574
7.01785
7.00106
6.81076
6.79694
6.78172
4.20476
4.18948
4.15849
4.14057
4.13139
4.11383
4.09930
3.48180
3.47722
3.46270
3.45513
3.43977
2.93309
2.92469
2.91638
2.90252
2.88877
2.88112
1.39700
1.38325
1.37102
1.35726
1.34351
1.11959
1.10583
1.09131
X : parts per Million : Proton

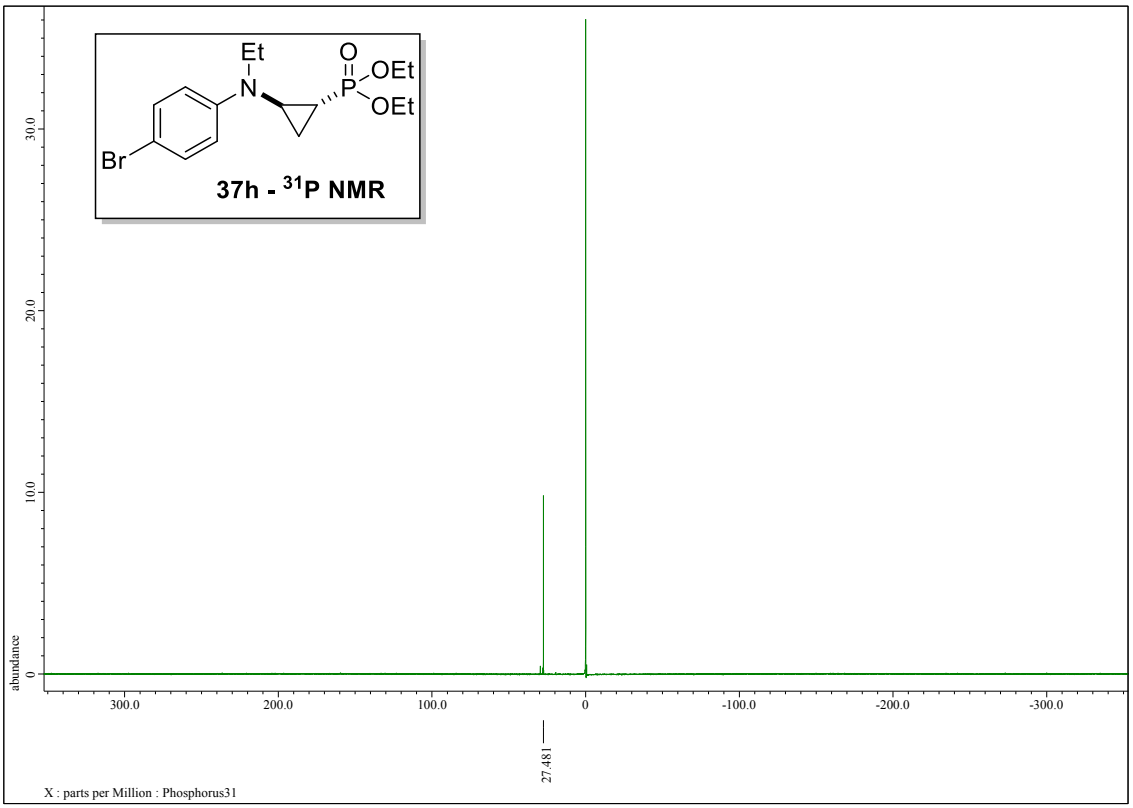


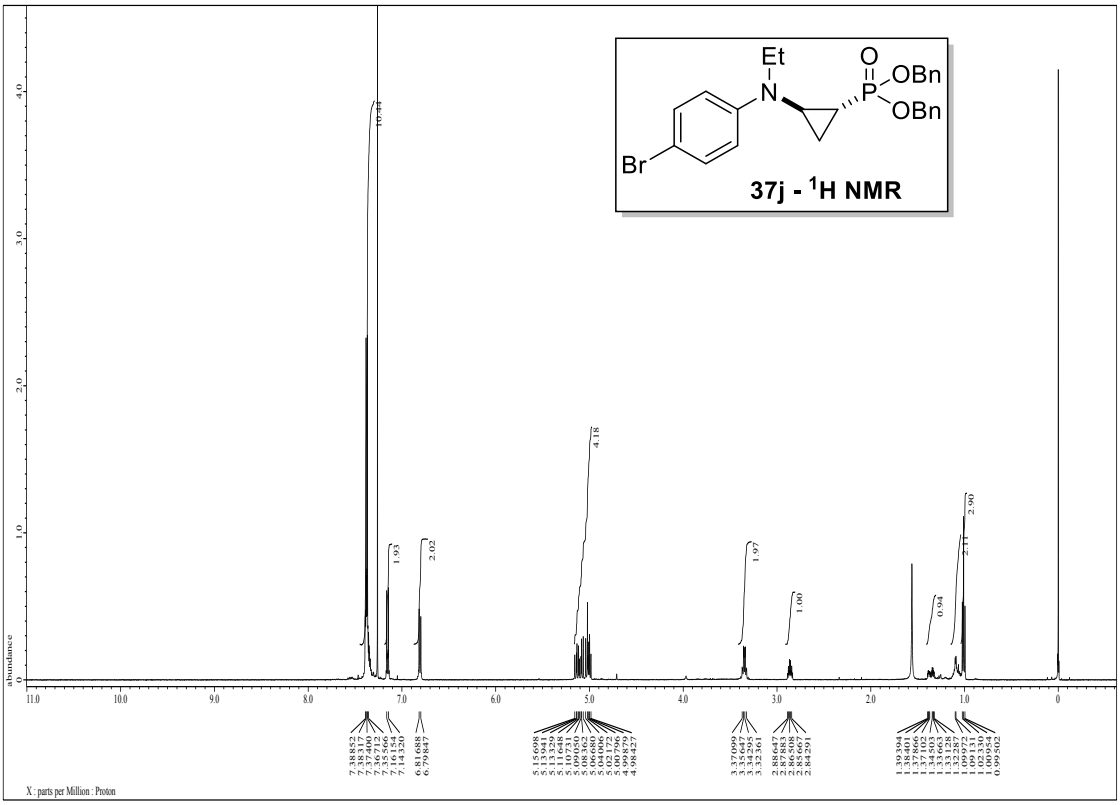
Et
N
Ph
O
P
OEt
OEt
37g - ^{13}C NMR
X : parts per Million : Carbon13
abundance
148.612
129.106
118.394
115.199
77.408
77.160
76.902
62.166
62.118
62.080
62.023
46.199
35.659
16.658
16.611
16.372
14.178
11.546

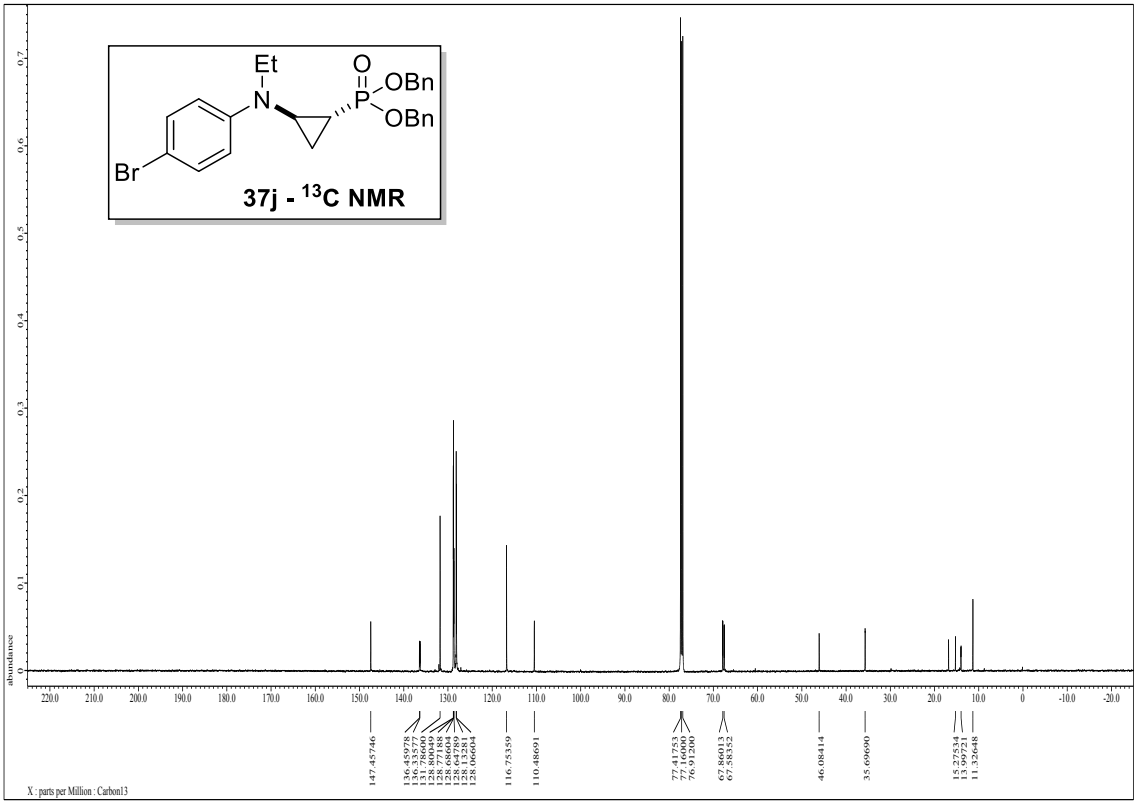


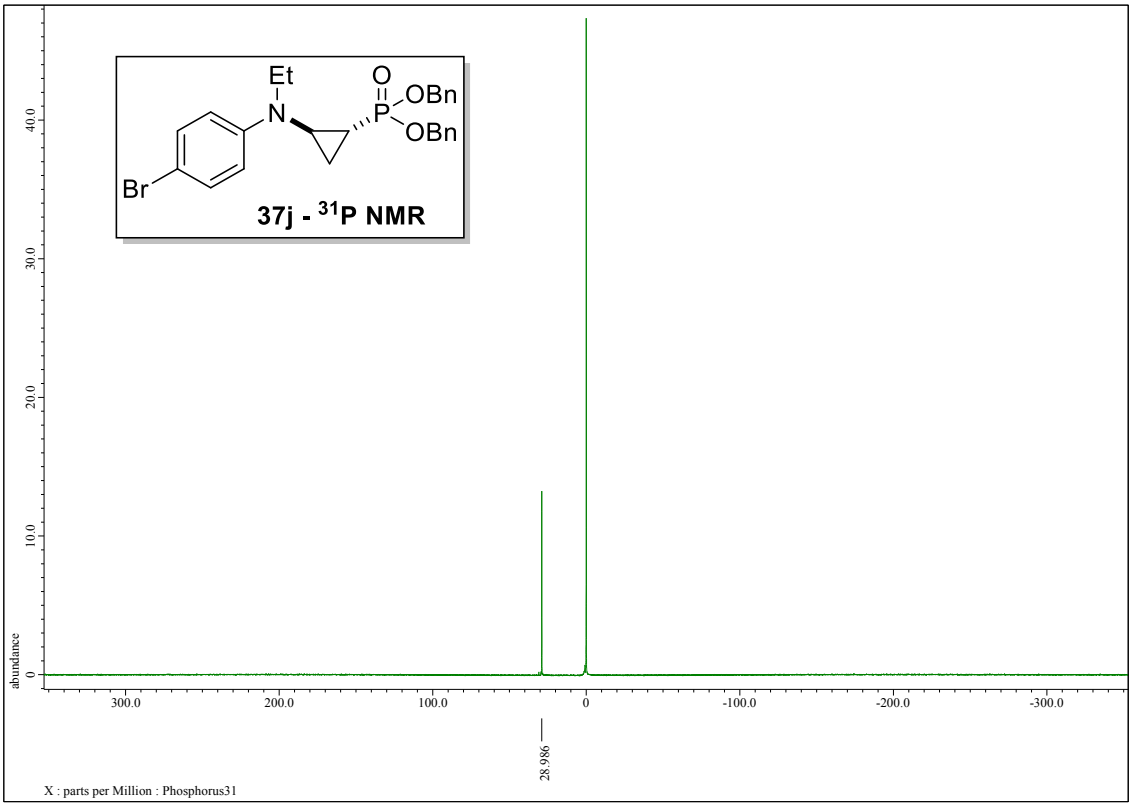
Et
N
Br
O
P
OEt
OEt
37h - ^{1}H NMR
X : parts per Million : Proton
abundance
1.99
1.98
4.14
1.94
1.00
7.12
5.10
7.31286
6.84974

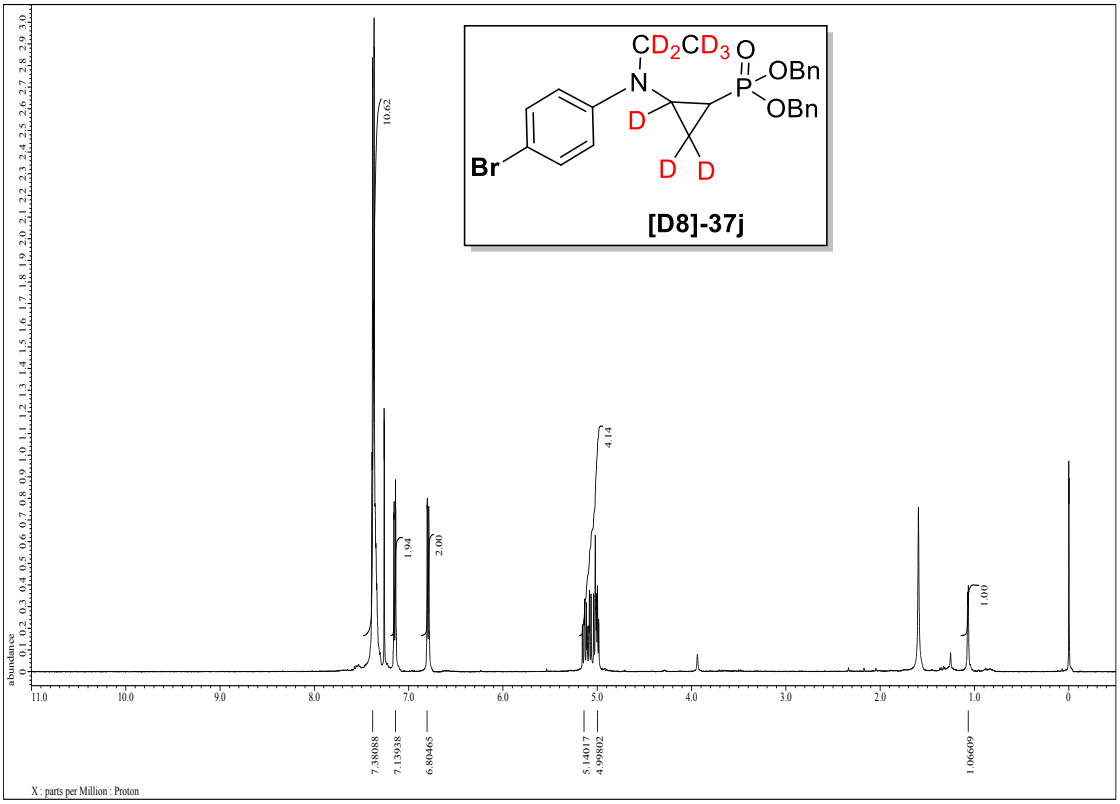

Et
O
N
P
OEt
OEt
Br
37h - 13C NMR
abundance
147.601
131.796
116.763
110.477
77.418
77.160
76.912
62.261
62.213
62.109
62.051
46.103
35.554
16.658
16.611
16.515
14.980
14.007
11.365
X : parts per Million : Carbon13

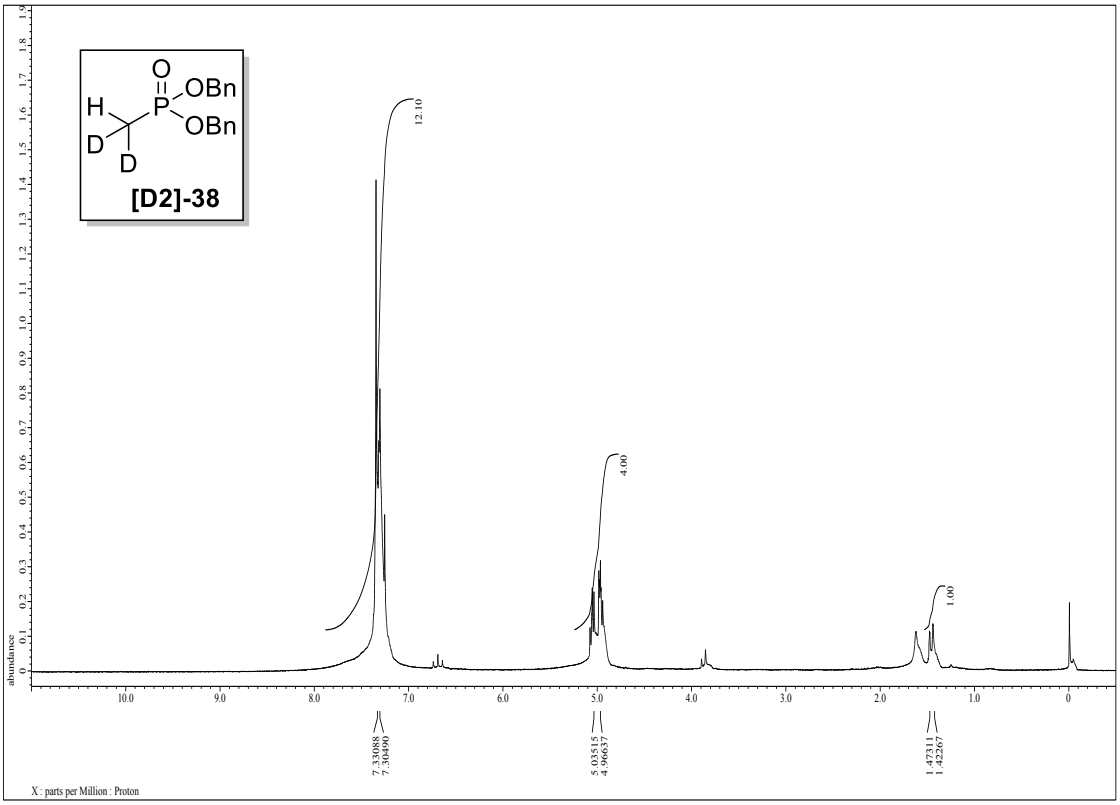

Et
O
N
P
OEt
OEt
Br
37h - 31P NMR
abundance
27.481
X : parts per Million : Phosphorus31

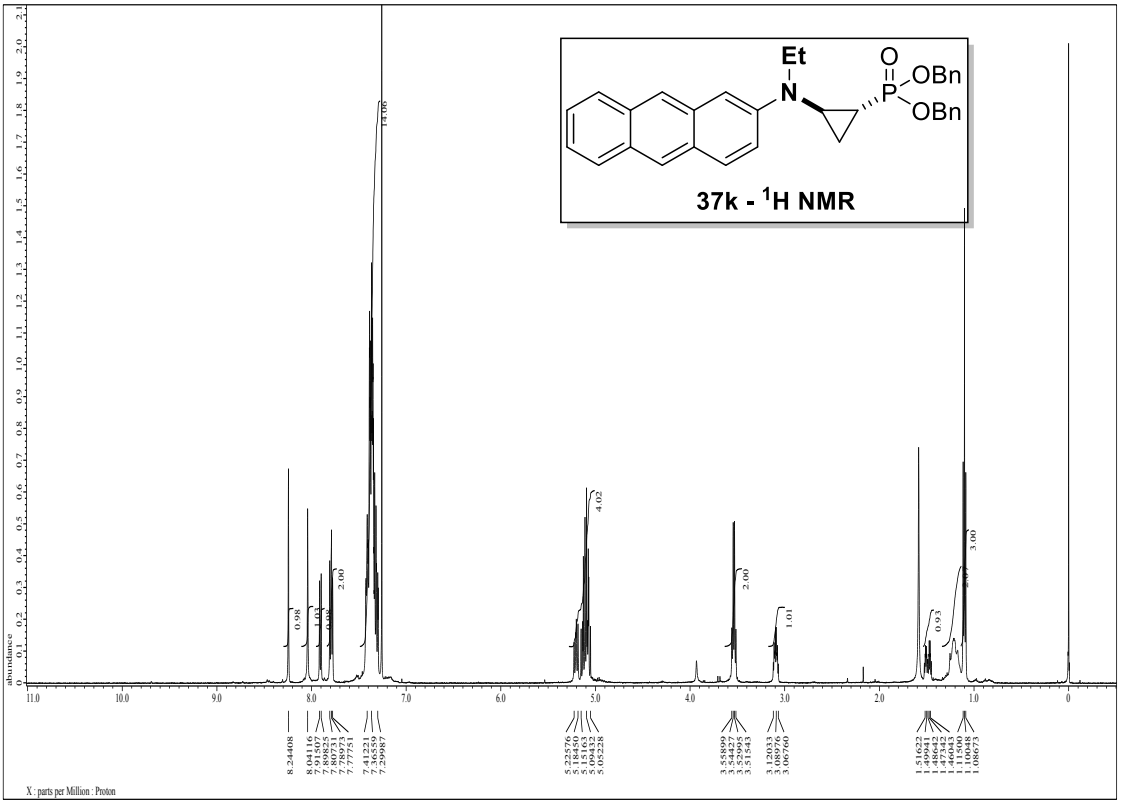

Et
N
O
P
OBn
OBn
Br
37j - 1H NMR
abundance
X : parts per Million : Proton

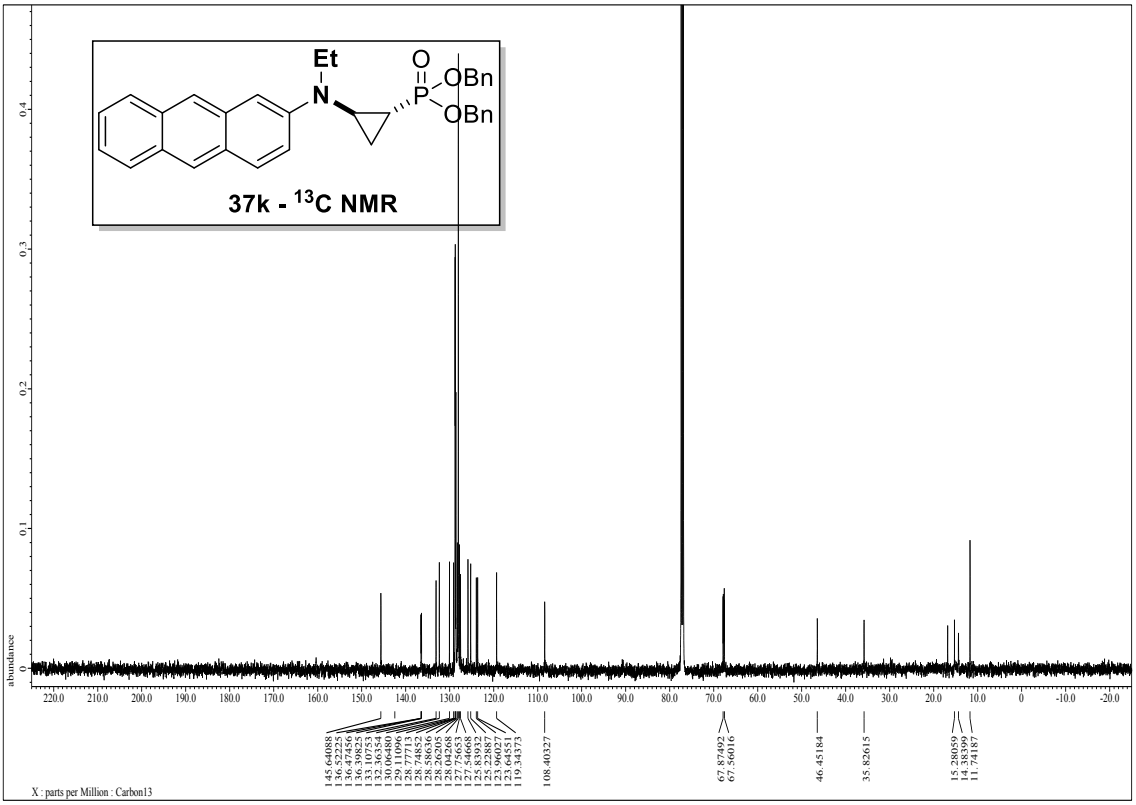

Et
N
O
P
OBn
OBn
Br
37j - 13C NMR
abundance
X : parts per Million : Carbon13

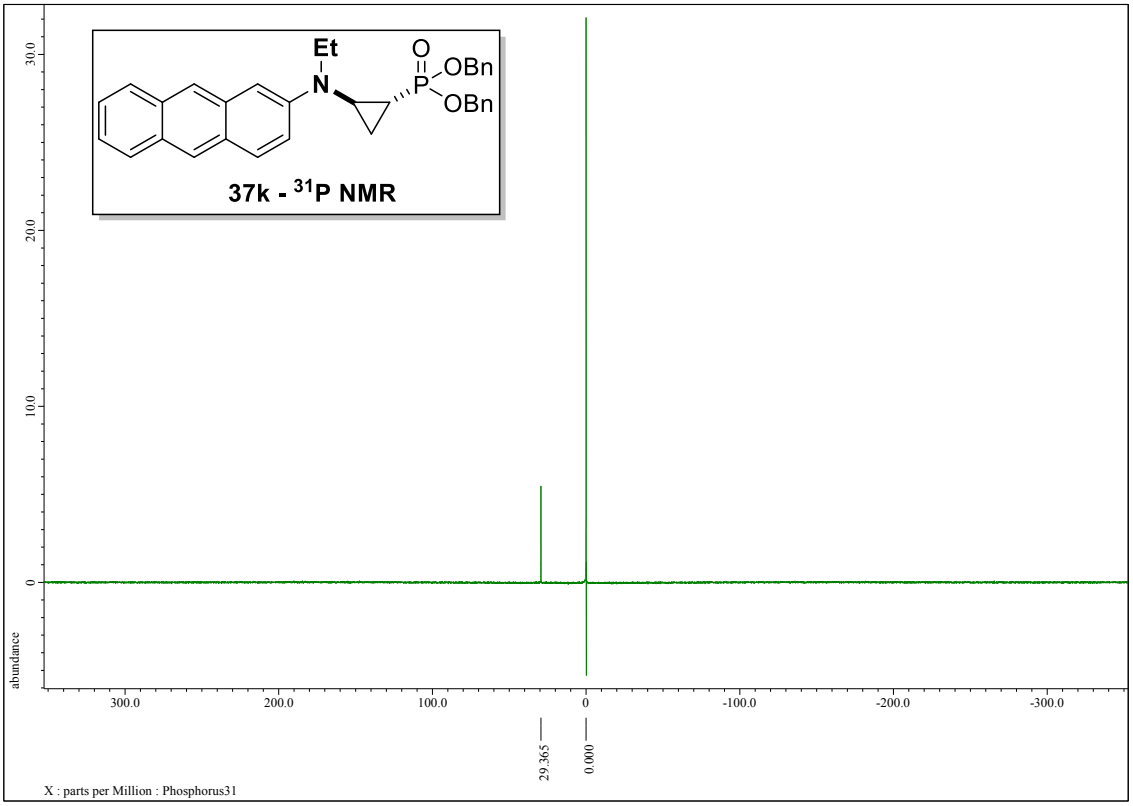

Et
N
O
P
OBn
OBn
Br
37j - 31P NMR
abundance
40.0
30.0
20.0
10.0
0
300.0
200.0
100.0
0
-100.0
-200.0
-300.0
28.986
X : parts per Million : Phosphorus31

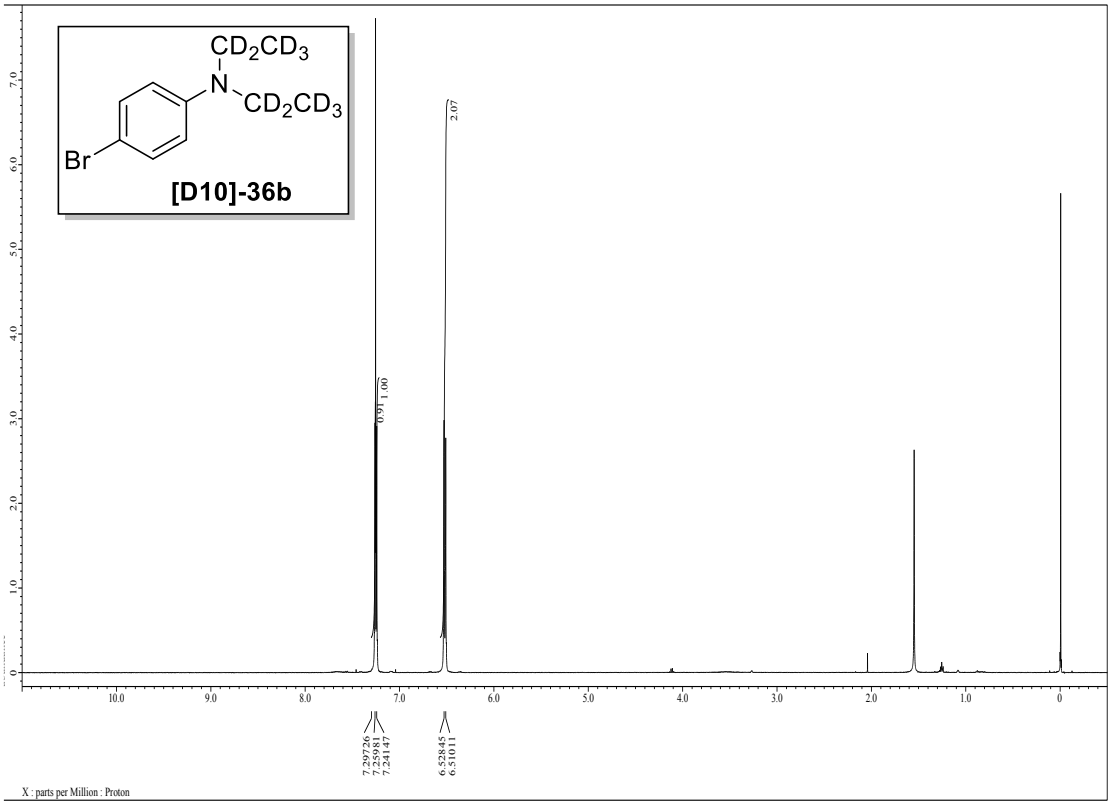

CD2CD3
O
N
P
OBn
OBn
D
D
D
Br
[D8]-37j
10.62
1.94
2.00
4.14
1.00
abundance
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.38088
7.13938
6.80465
5.14017
4.99802
1.06669
X : parts per Million : Proton

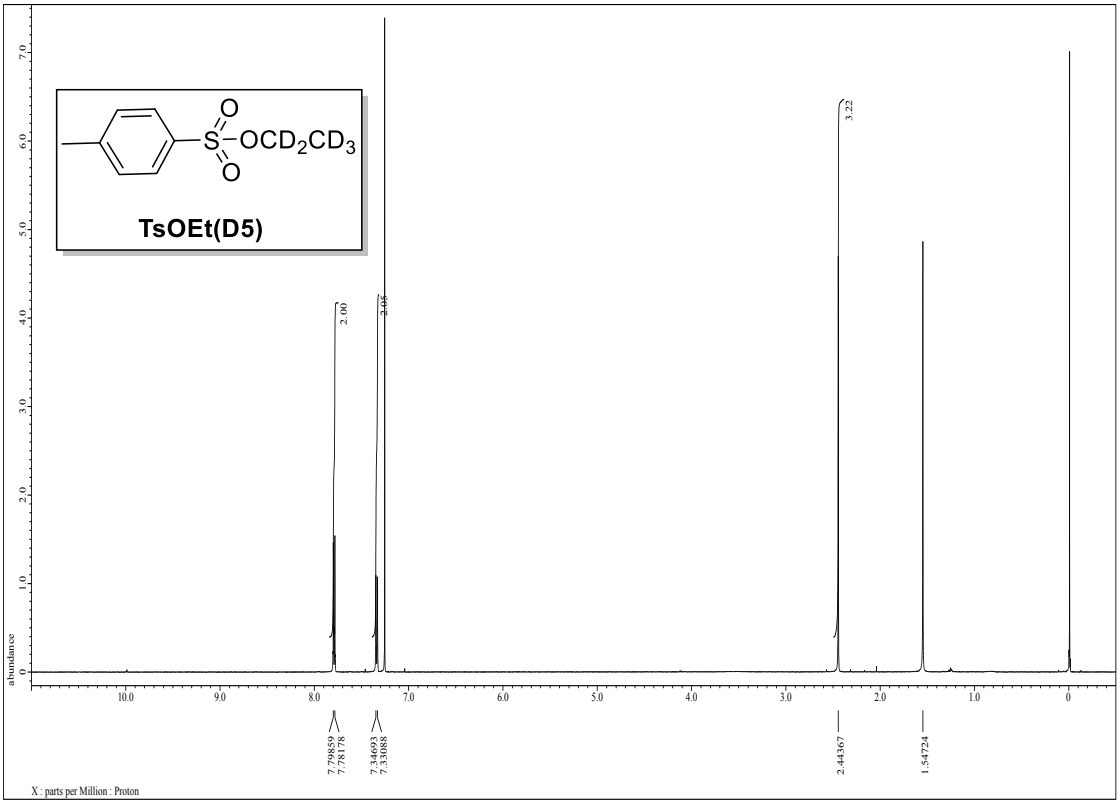

[D2]-38
12.10
4.00
1.00
7.33088
7.30490
5.03515
4.96637
1.47311
1.42267
X : parts per Million : Proton

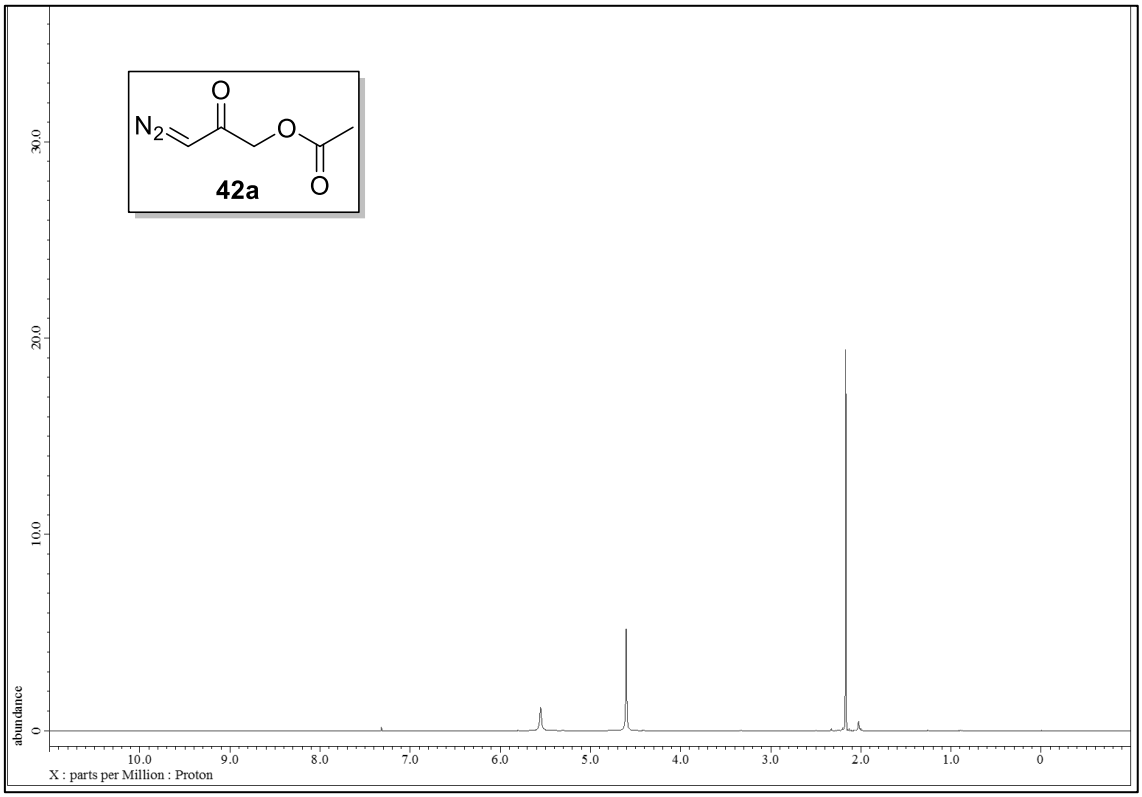

37k - 1H NMR
14.06
4.02
2.06
2.00
0.98
1.01
0.93
3.00
X : parts per Million : Proton

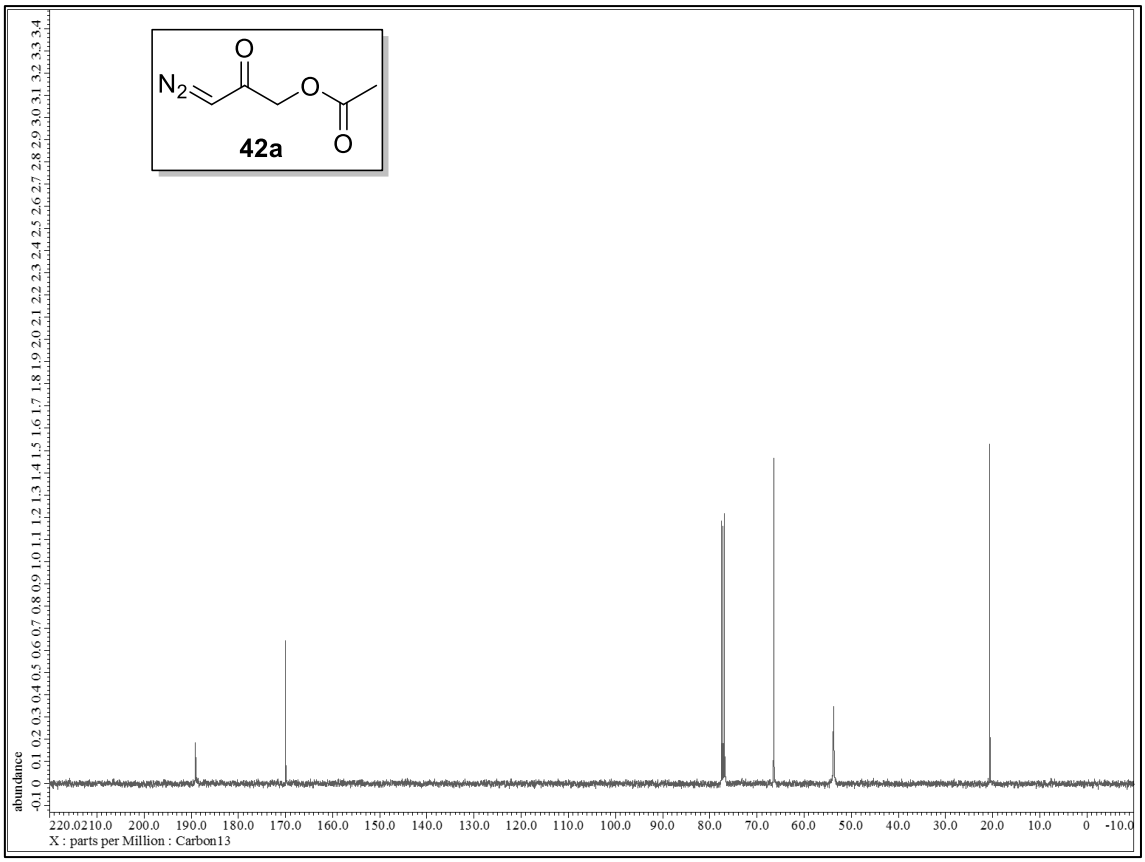

Et
N
O
P
OBn
OBn
37k - 13C NMR
abundance
X : parts per Million : Carbon13

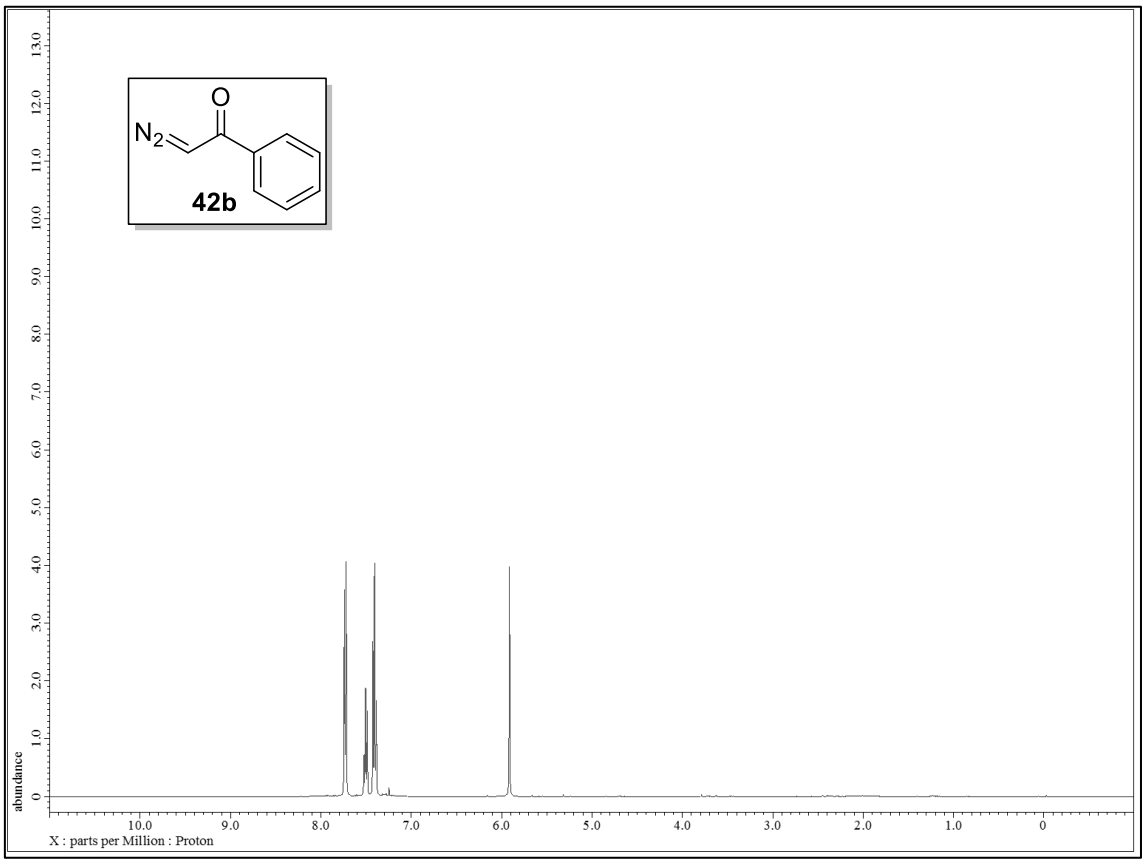

Et
N
O
P
OBn
OBn
37k - 31P NMR
abundance
29.365
0.000
X : parts per Million : Phosphorus31

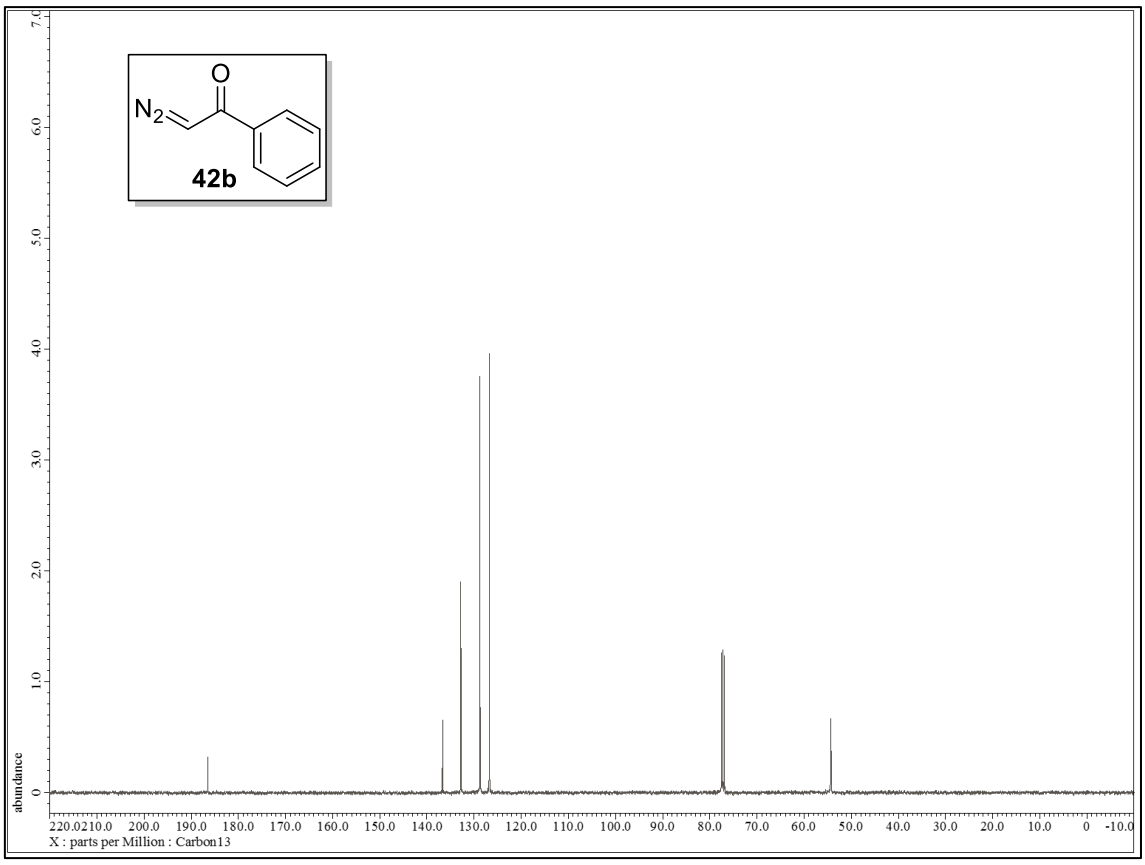

CD2CD3
N
CD2CD3
Br
[D10]-36b
2.07
0.91
1.00
7.79726
7.25981
7.24147
6.52845
6.51011
X : parts per Million : Proton

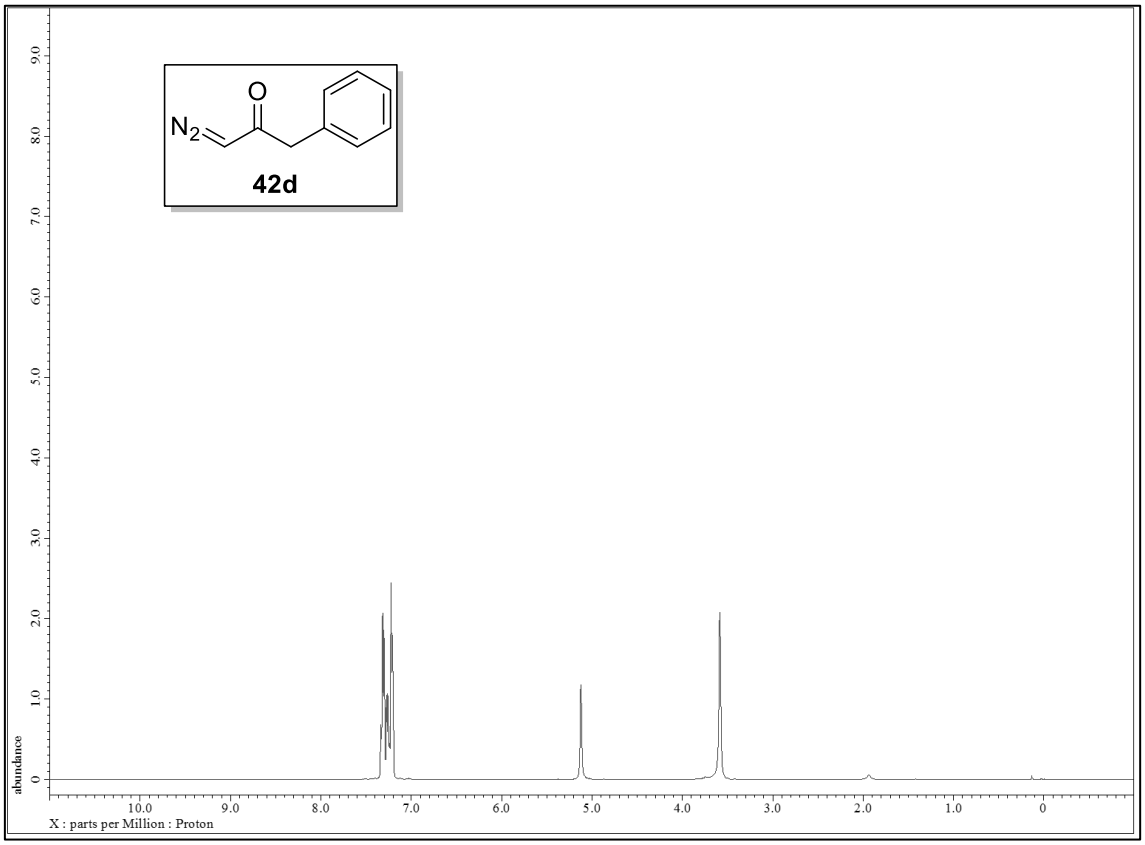

O
S
OCD2CD3
O
TsOEt(D5)
3.22
2.00
2.05
abundance
7.79859
7.78178
7.34693
7.33088
2.44367
1.54724
X : parts per Million : Proton

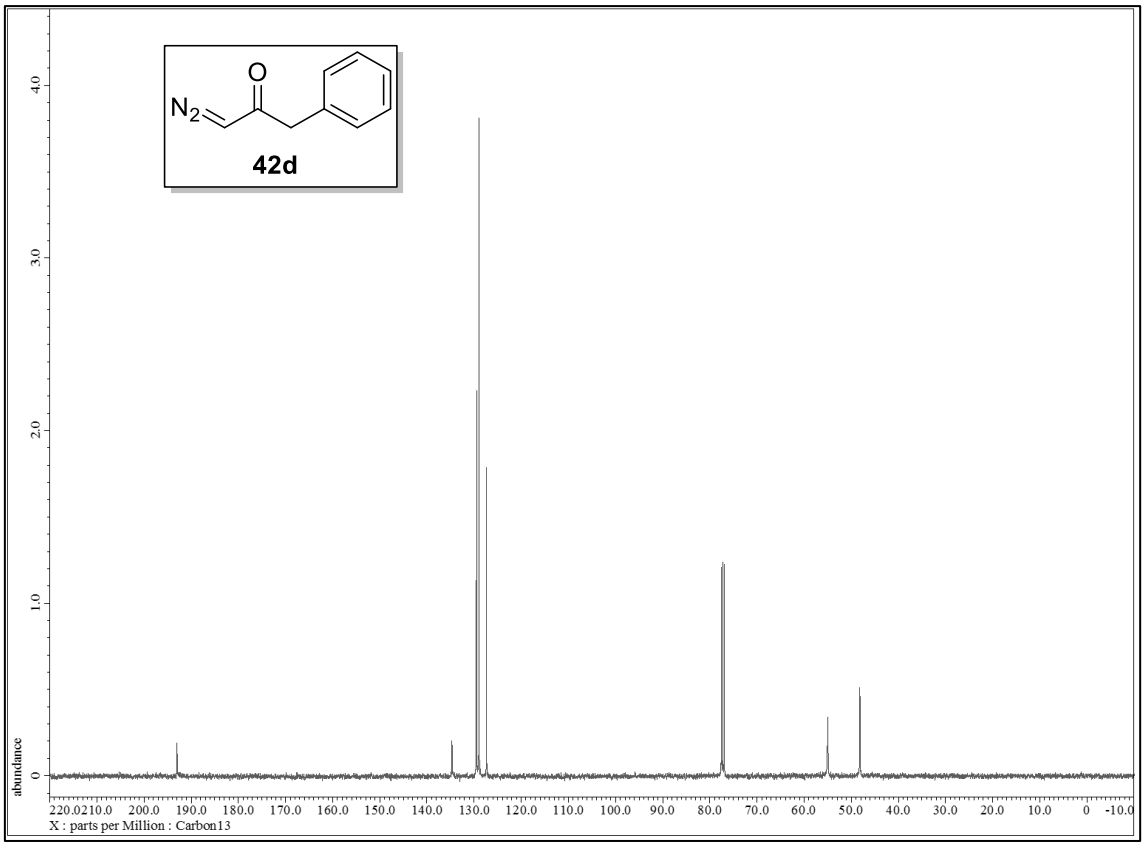

42a
abundance
X : parts per Million : Proton

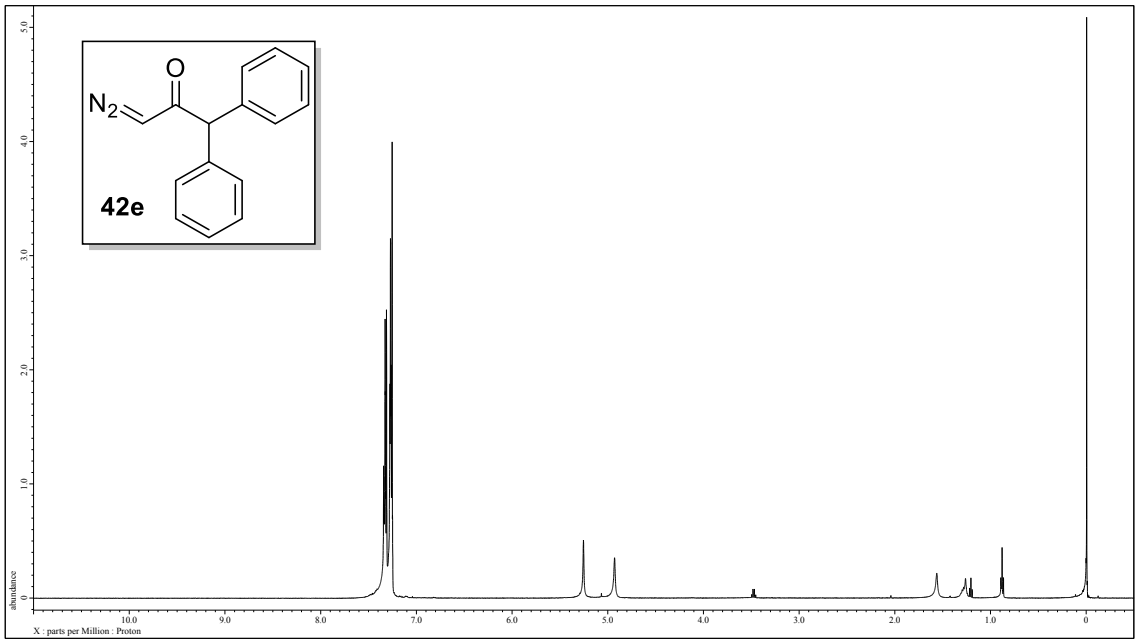

42a
abundance
X : parts per Million : Carbon13


O
N2
42b
abundance
X : parts per Million : Proton

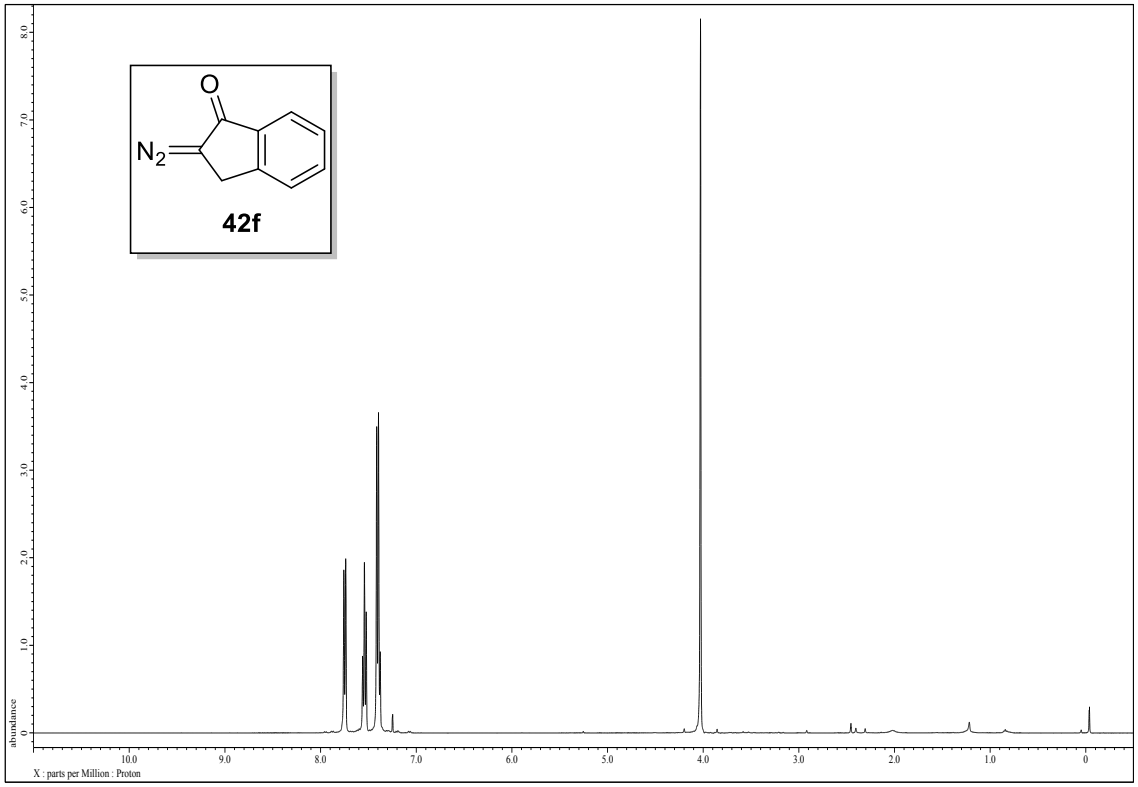

O
N2
42b
abundance
X : parts per Million : Carbon13

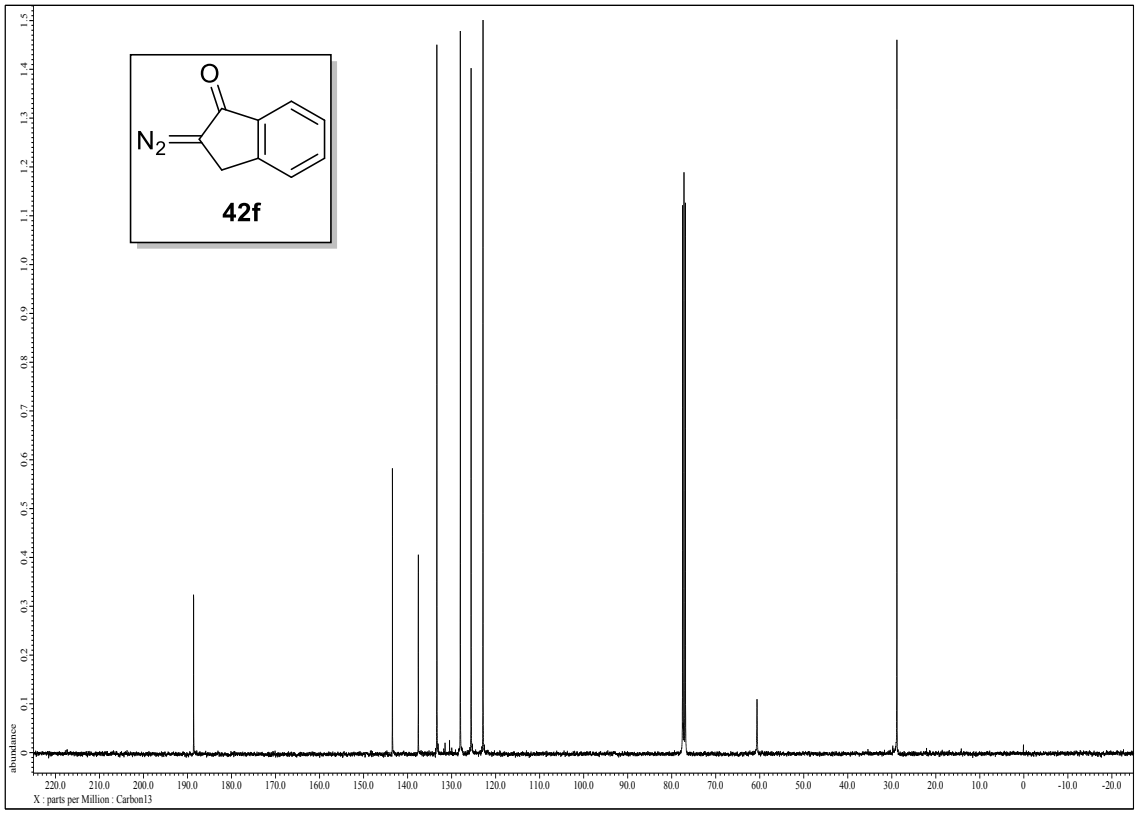

O
N2
42d
abundance
X : parts per Million : Proton

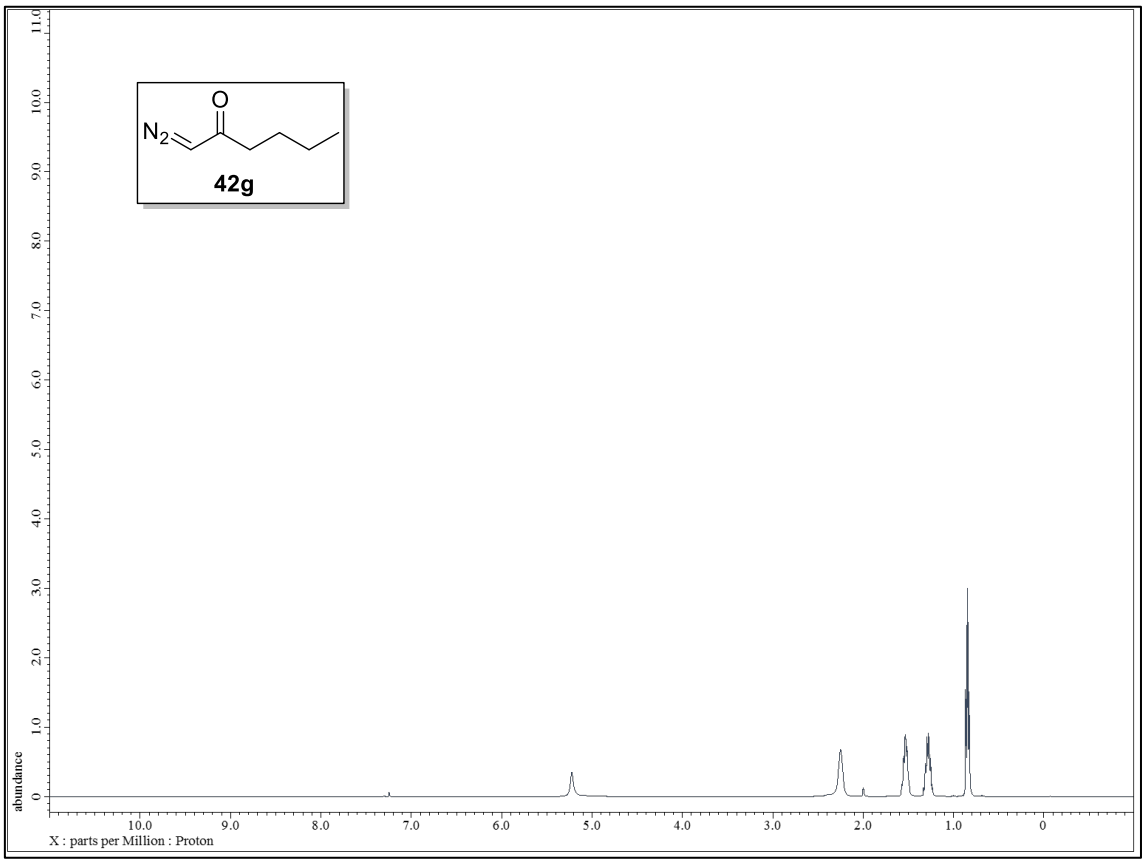

O
N2
42d
abundance
X : parts per Million : Carbon13

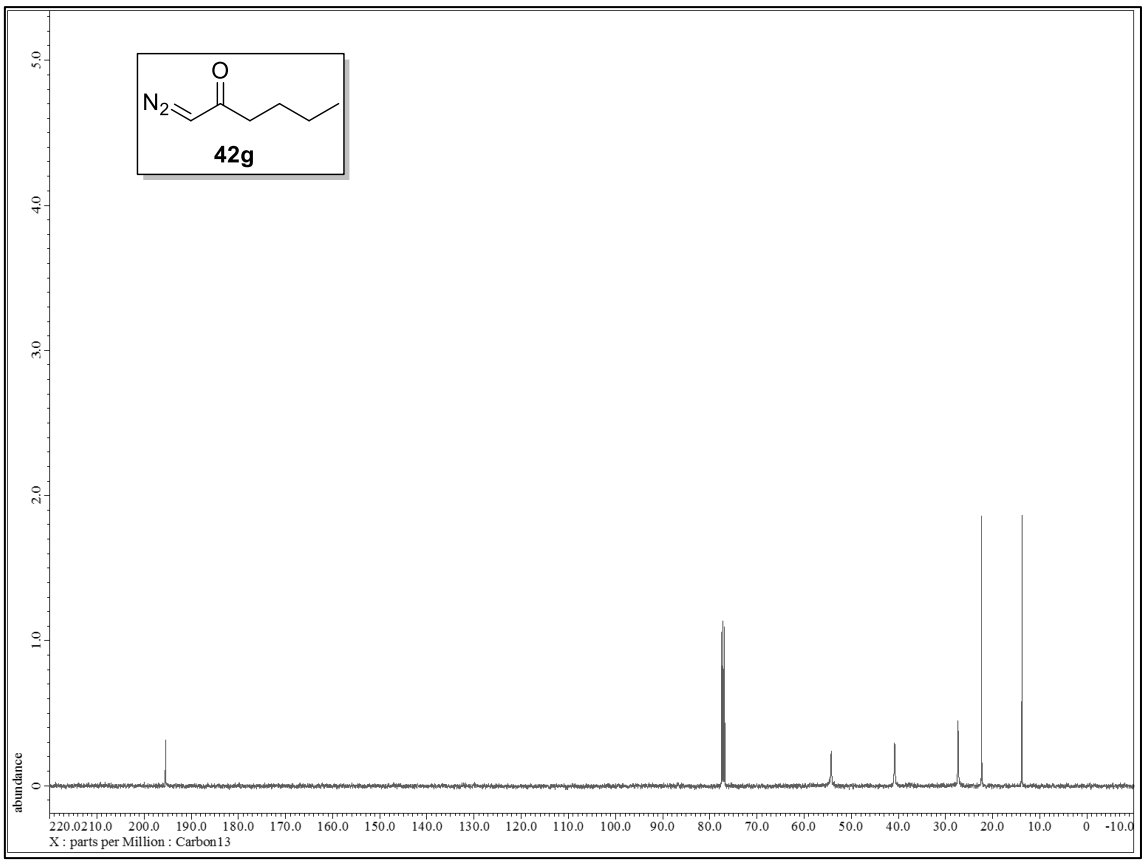

O
N2
42e
abundance
X : parts per Million : Proton


O
N2
42e
abundance
193.773
138.949
129.166
128.861
127.488
62.348
56.236
53.671
X : parts per Million : Carbon13

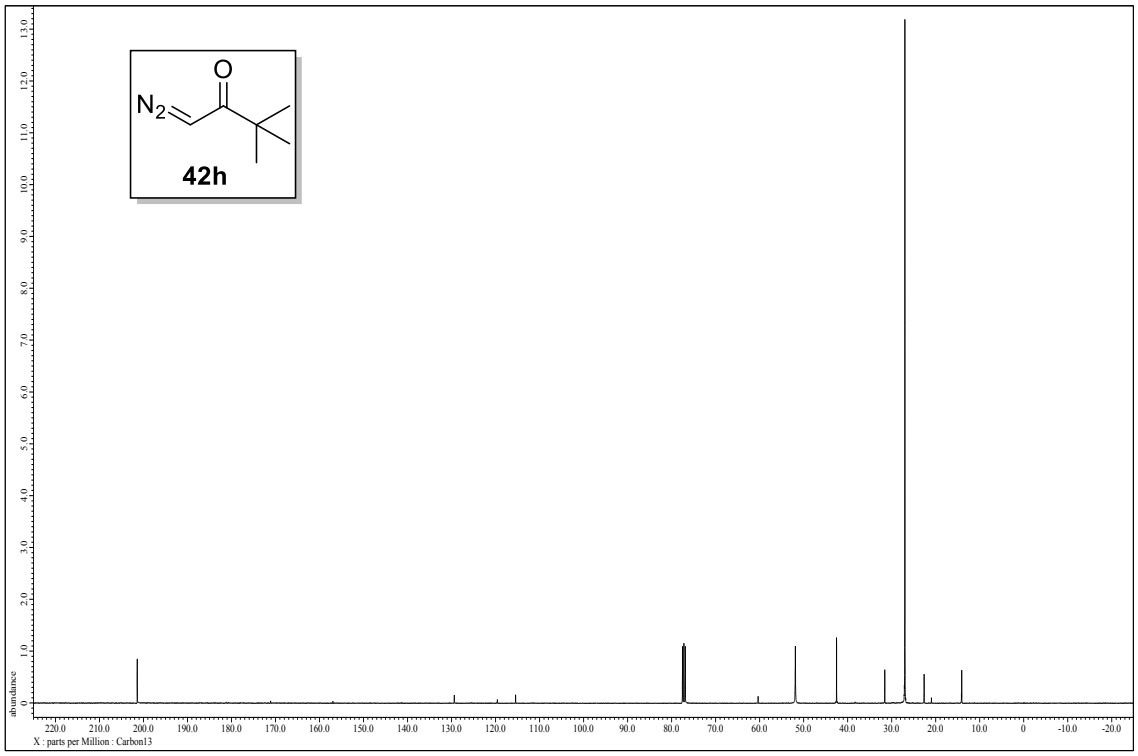

O
N2
42f
abundance
X : parts per Million : Proton

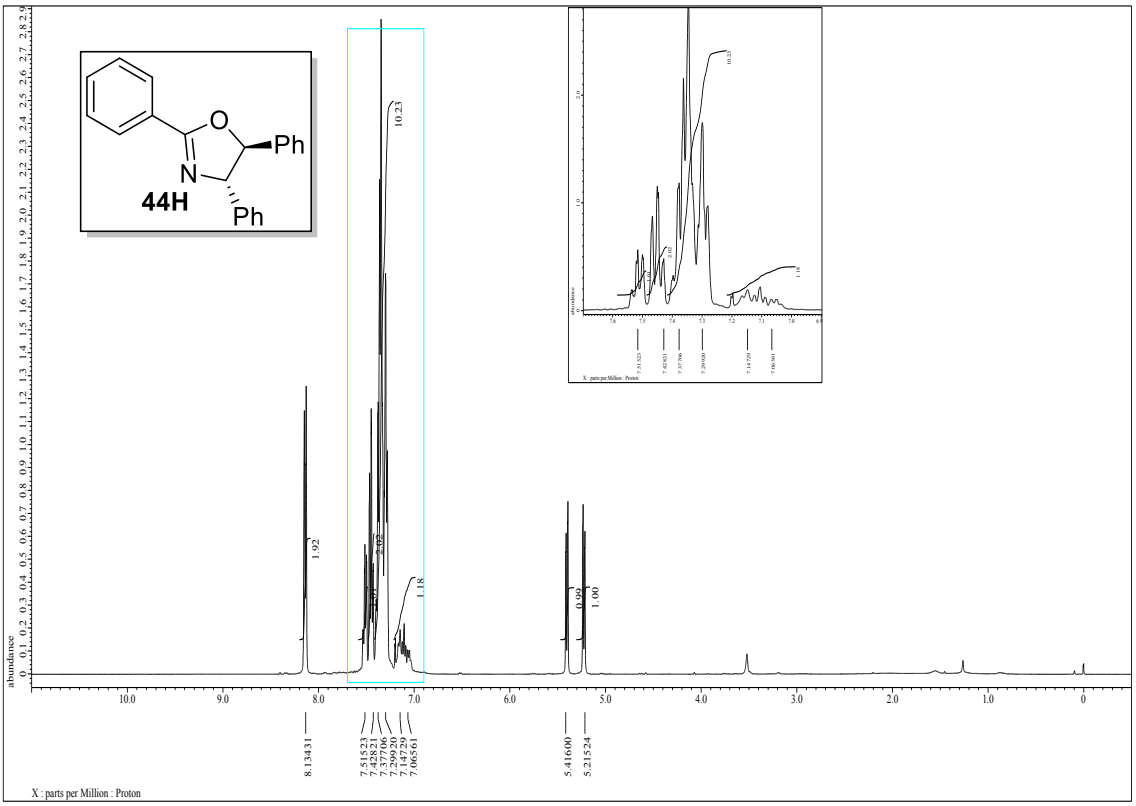

O
N2
42f
abundance
X : parts per Million : Carbon13

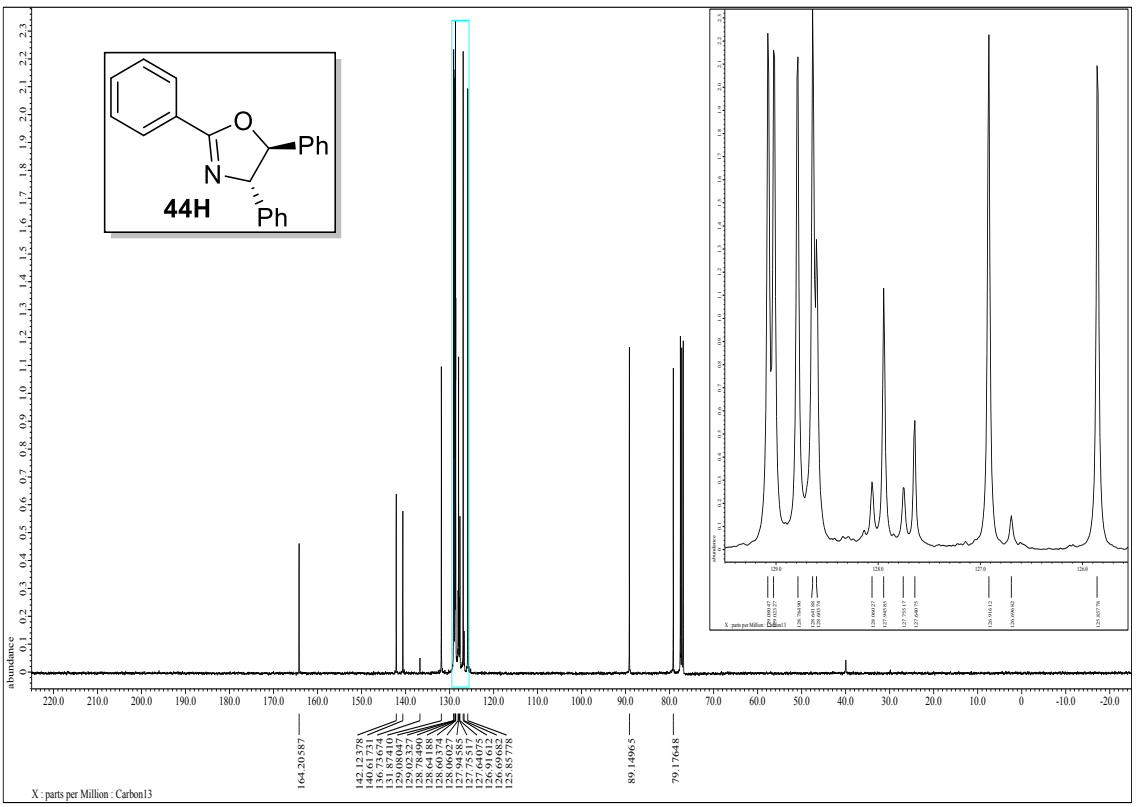

O
N2
42g
abundance
X : parts per Million : Proton

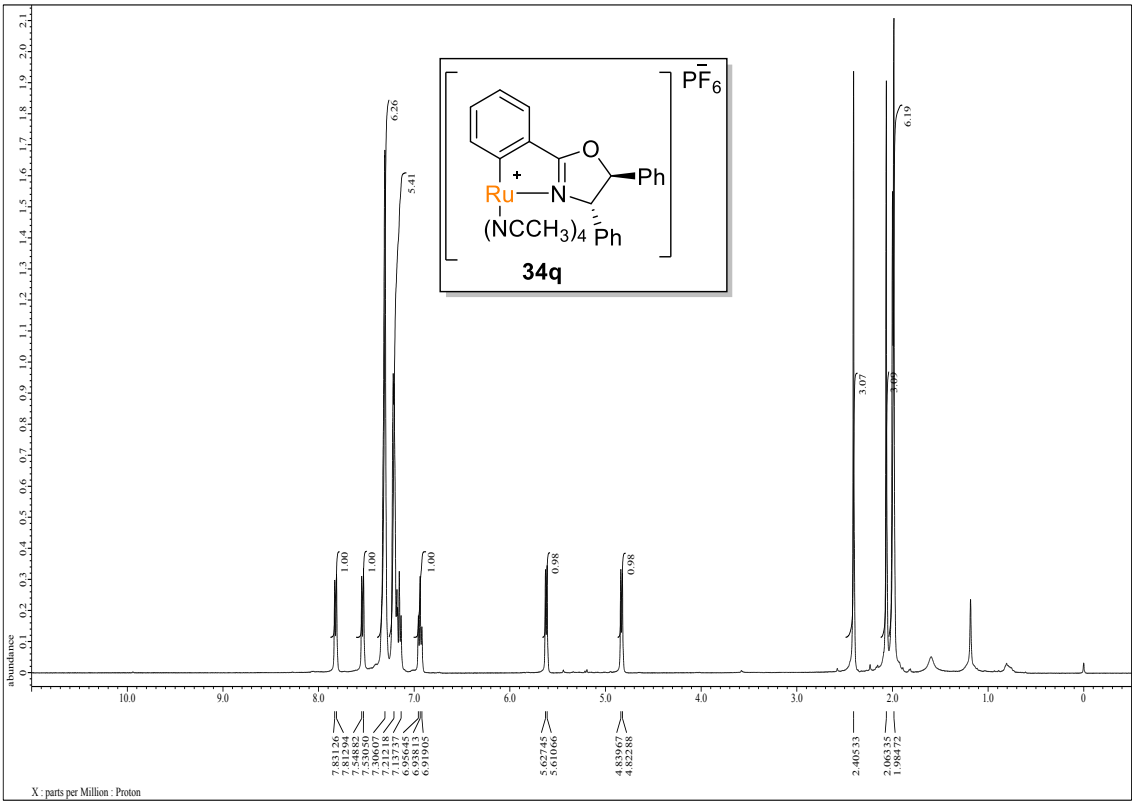

O
N2
42g
abundance
X : parts per Million : Carbon13

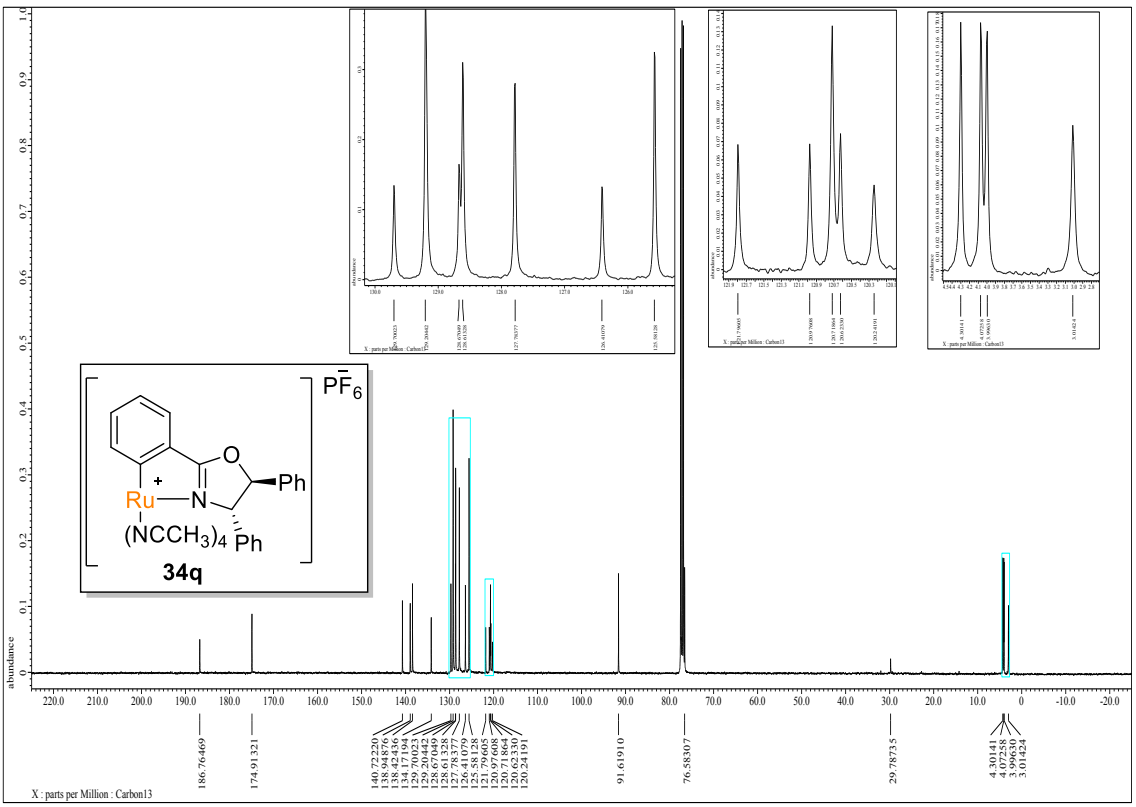

O
N2
42h
9.34
1.00
abundance
X : parts per Million : Proton

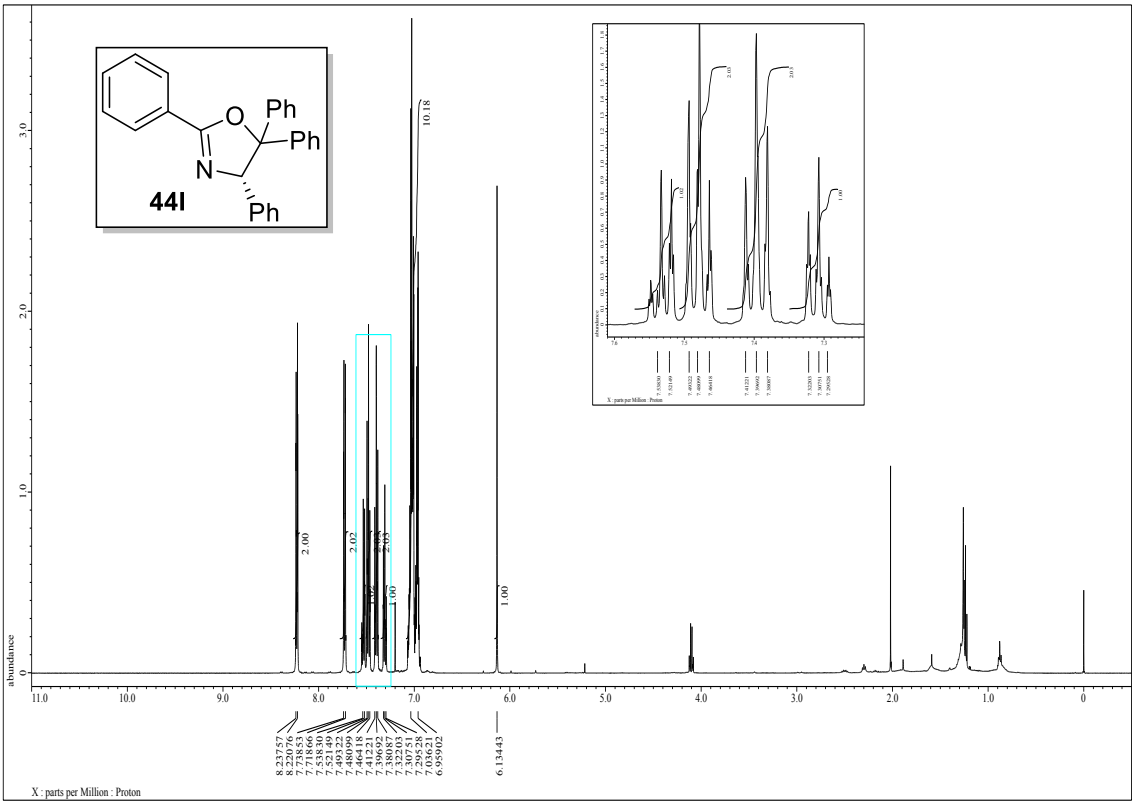

O
N2
42h
abundance
X : parts per Million : Carbon13

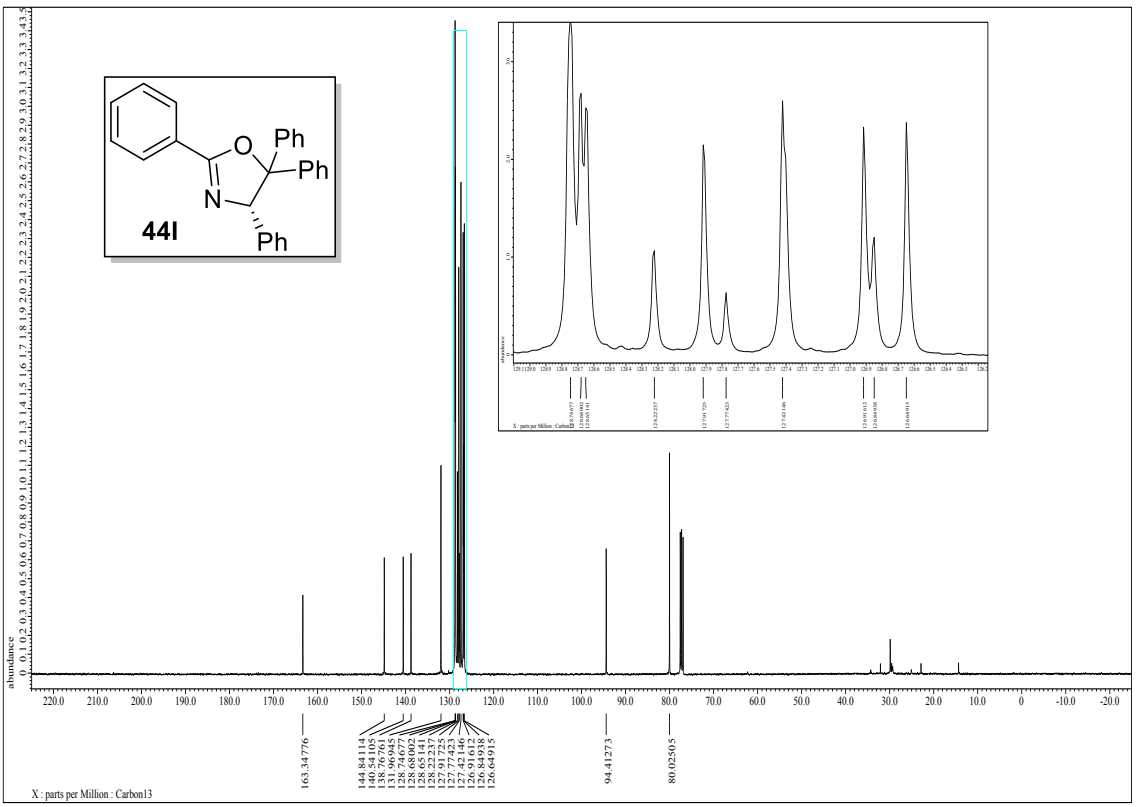

O
Ph
N
44H
Ph
10.23
1.92
2.02
2.00
1.18
0.99
1.00
abundance
8.13431
7.51523
7.42821
7.37706
7.29920
7.14729
7.06561
5.41600
5.21524
X : parts per Million : Proton

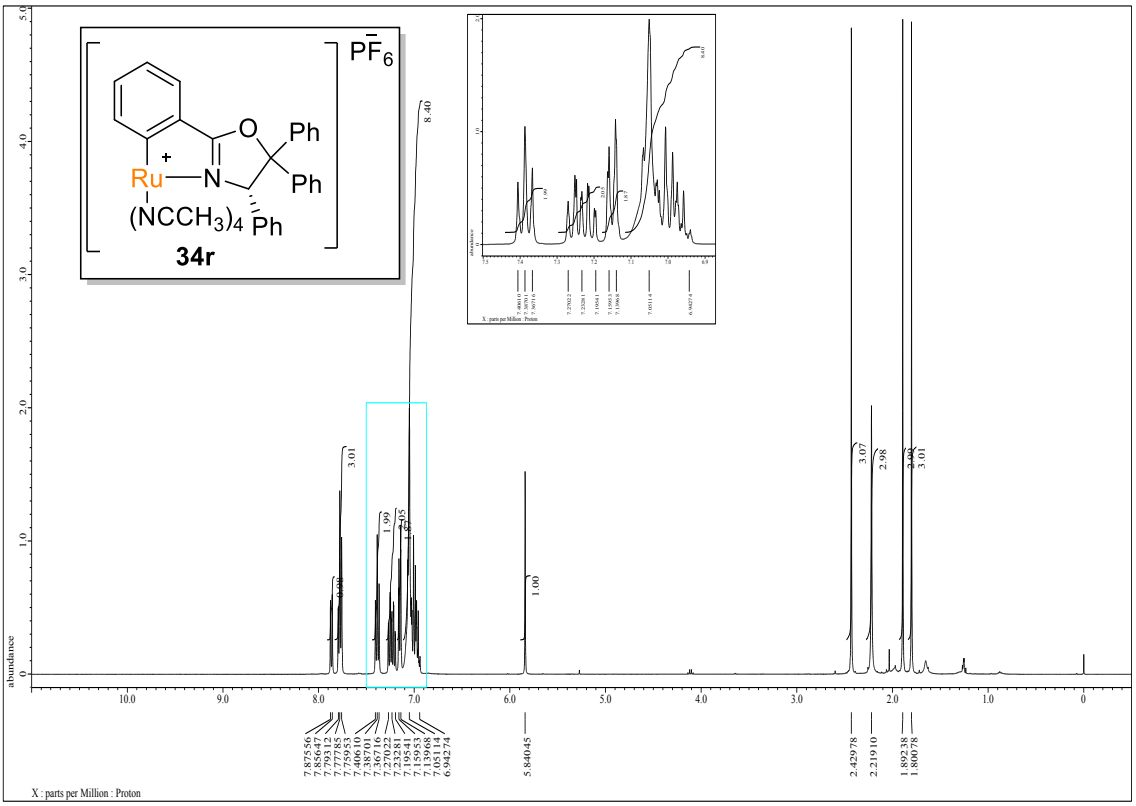

O
Ph
N
44H
Ph
abundance
164.20587
142.12378
140.61731
136.75674
131.84410
129.08047
129.02327
128.78488
128.64188
128.60374
128.06027
127.94585
127.75517
127.64075
126.91645
126.69682
125.85778
89.14965
79.17648
X : parts per Million : Carbon13

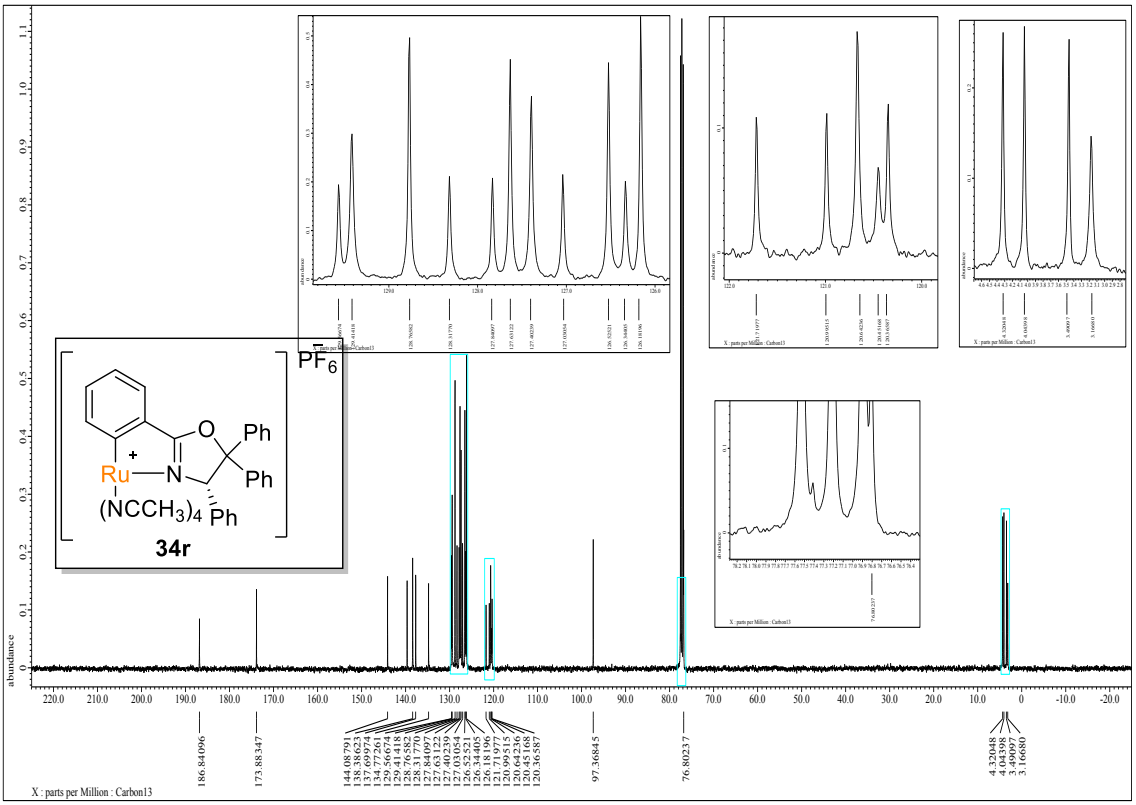

PF6
Ru
N
O
Ph
(NCCH3)4
Ph
34q
abundance
X : parts per Million : Proton

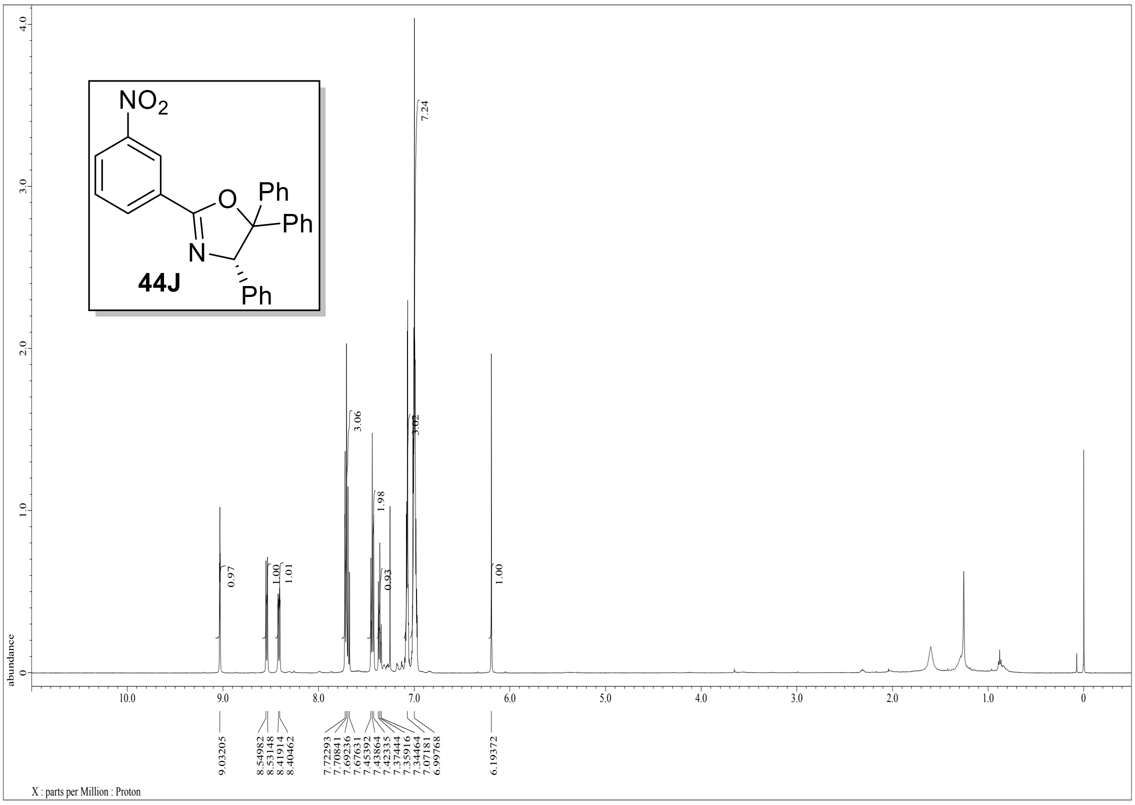

PF6
Ru
N
O
Ph
(NCCH3)4
Ph
34q
abundance
X : parts per Million : Carbon13

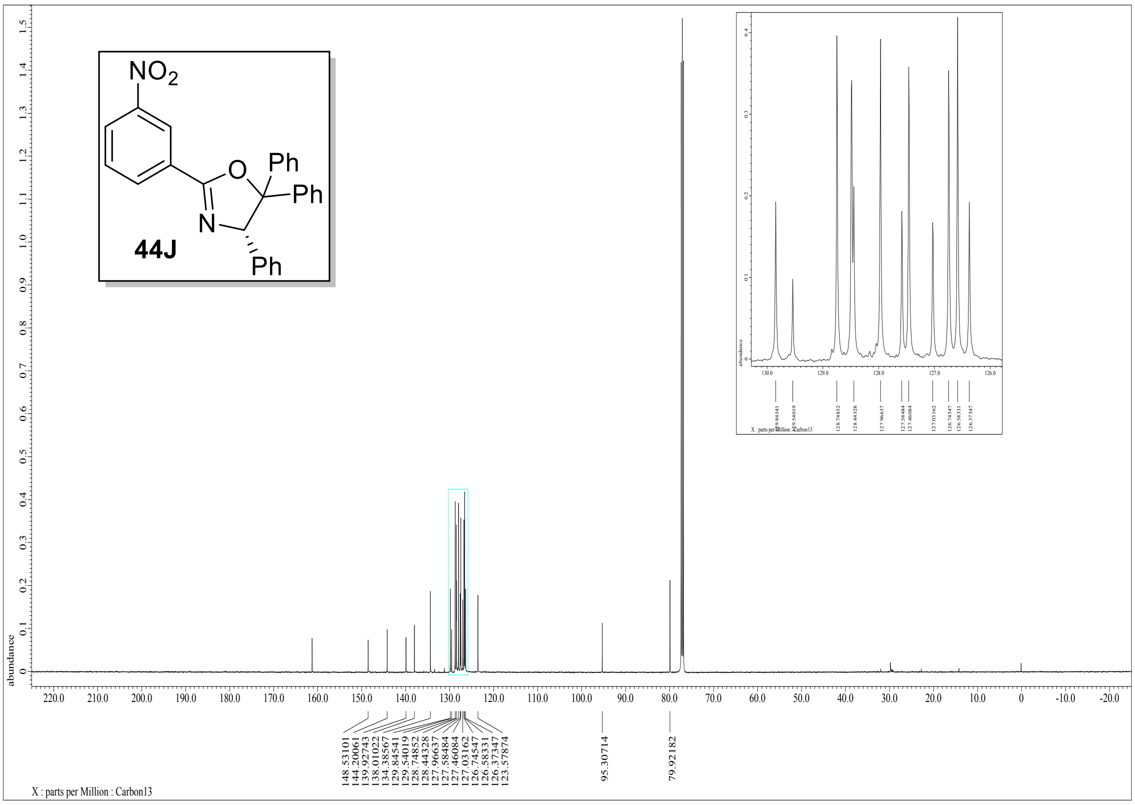

441
Ph
Ph
Ph
O
N
10.18
2.00
2.02
2.03
1.00
1.00
abundance
X : parts per Million : Proton

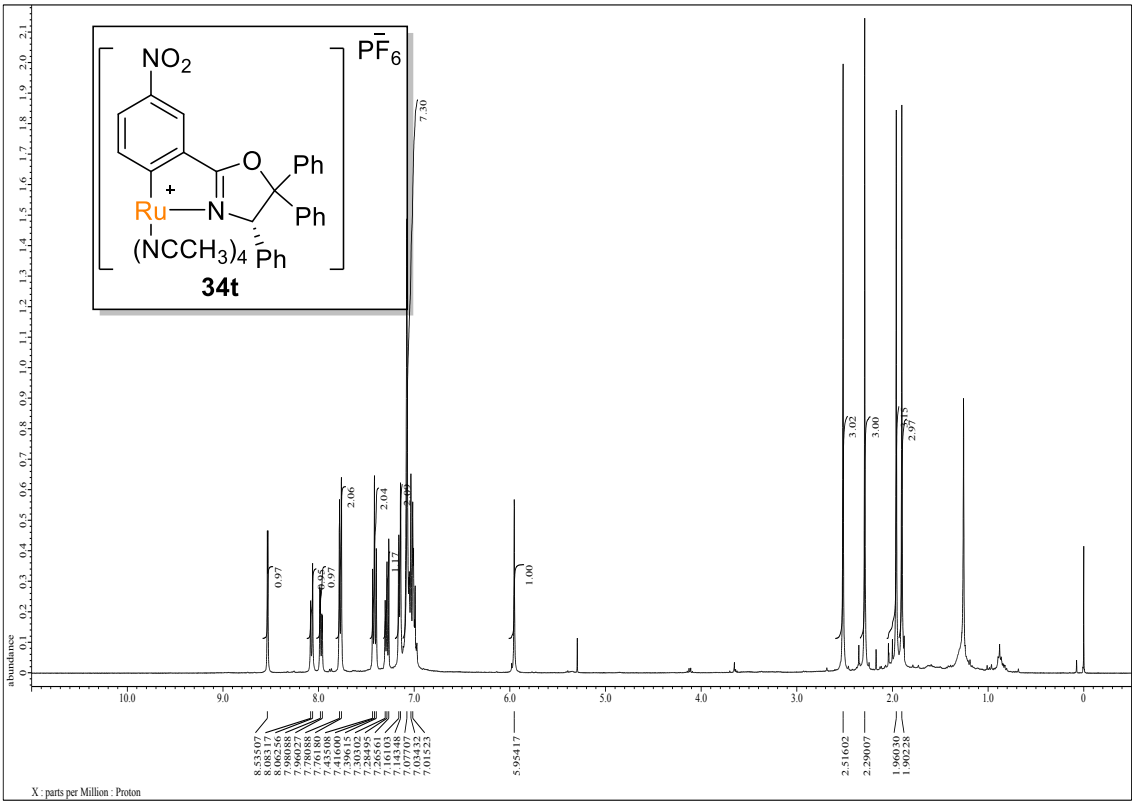

441
Ph
Ph
Ph
O
N
163.34776
144.84114
140.54105
138.76761
131.96495
128.74677
128.68002
128.65141
128.22357
127.91725
127.77423
127.47145
126.91612
126.84938
126.64915
94.41273
80.02505
abundance
X : parts per Million : Carbon13

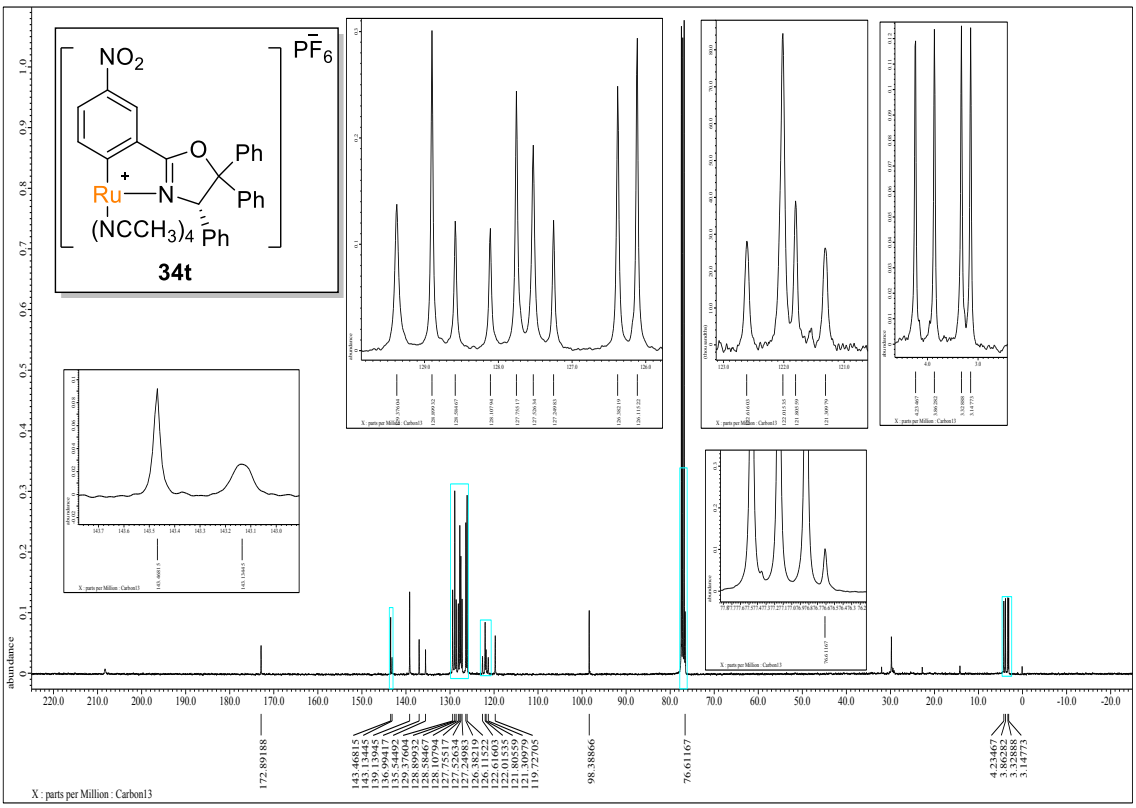

PF6
Ru
N
O
Ph
Ph
(NCCH3)4
Ph
34r
8.40
3.01
1.99
2.05
1.00
3.07
2.98
3.01
abundance
X : parts per Million : Proton

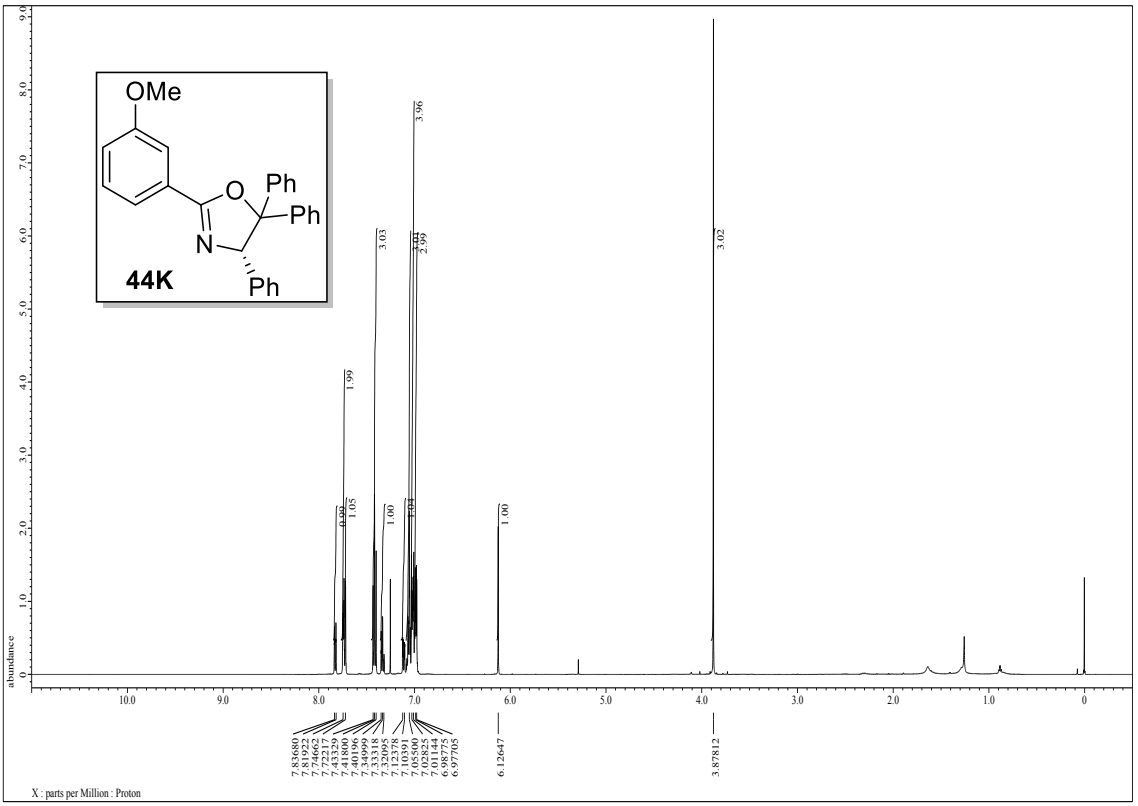

PF6
Ru
N
O
Ph
Ph
(NCCH3)4
Ph
34r
abundance
X : parts per Million : Carbon13

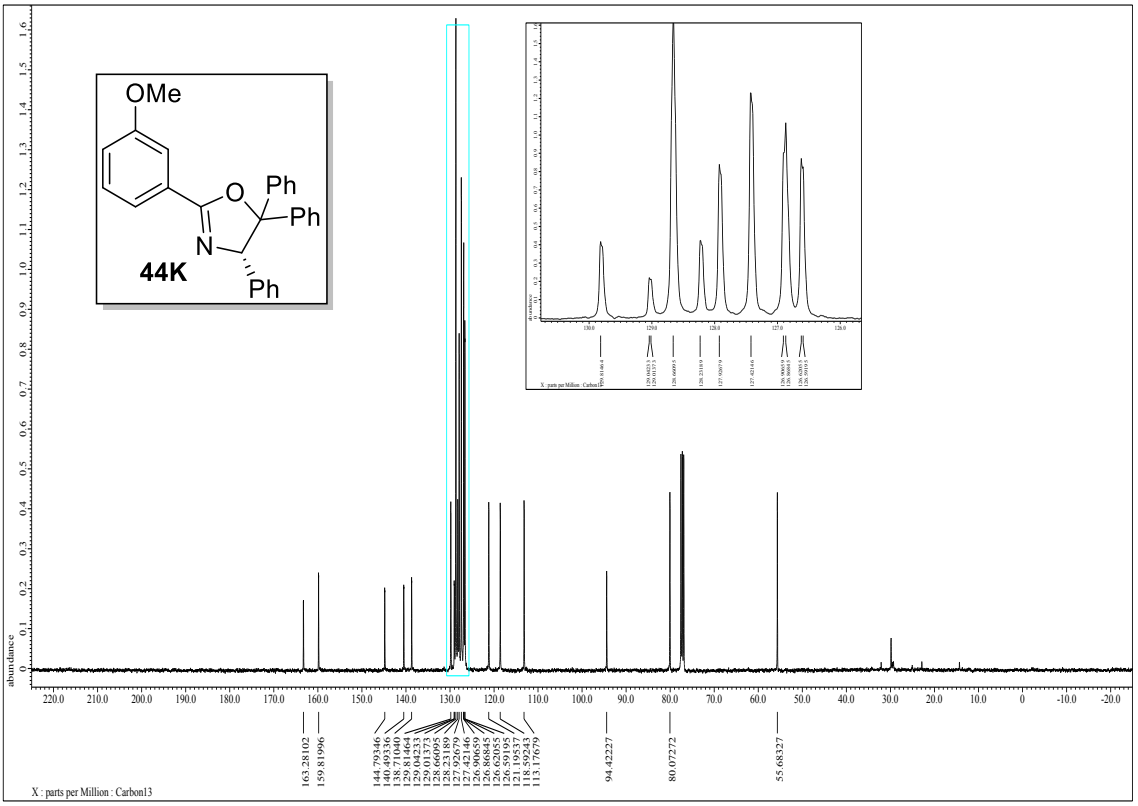

NO2
O
Ph
Ph
N
Ph
44J
abundance
X : parts per Million : Proton
9.03205
8.54982
8.53148
8.41914
8.40462
7.72293
7.70841
7.69236
7.67631
7.45392
7.43864
7.42335
7.37444
7.35916
7.34464
7.07181
6.99768
6.19372
0.97
1.00
1.01
3.06
1.98
0.93
3.02
7.24
1.00

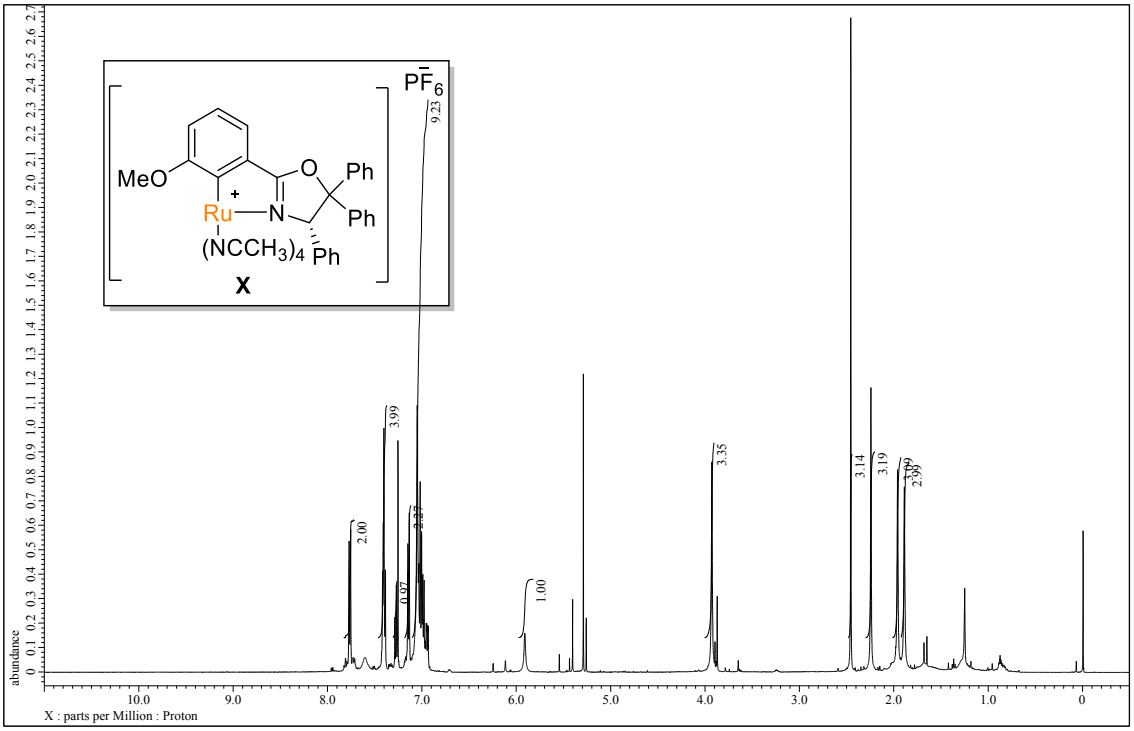

NO2
O
Ph
Ph
N
Ph
44J
abundance
X : parts per Million : Carbon13
148.53101
144.20061
139.92743
138.01022
134.38567
129.84541
129.54019
128.74852
128.44328
127.96637
127.58484
127.46084
127.03162
126.74547
126.5831
126.37347
123.57874
95.30714
79.92182

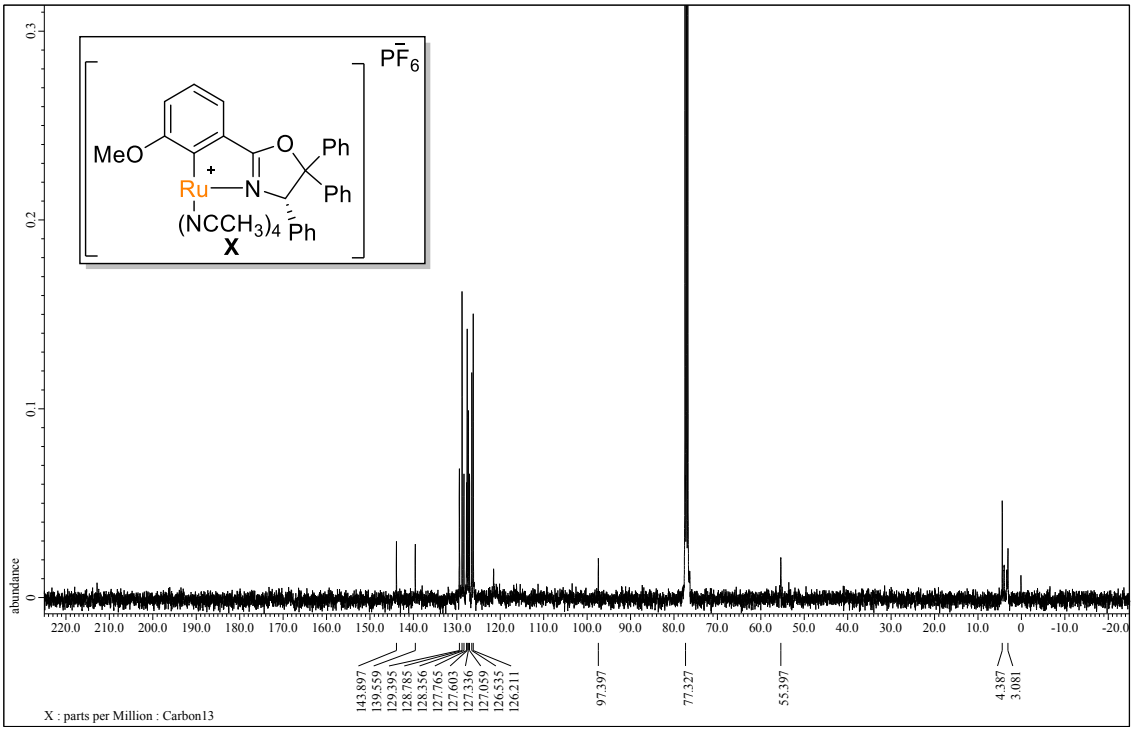

NO2
PF6
Ph
Ph
Ru
N
O
(NCCH3)4
Ph
34t
7.30
2.06
2.04
1.17
0.97
0.98
0.97
1.00
3.02
3.00
2.97
abundance
X : parts per Million : Proton

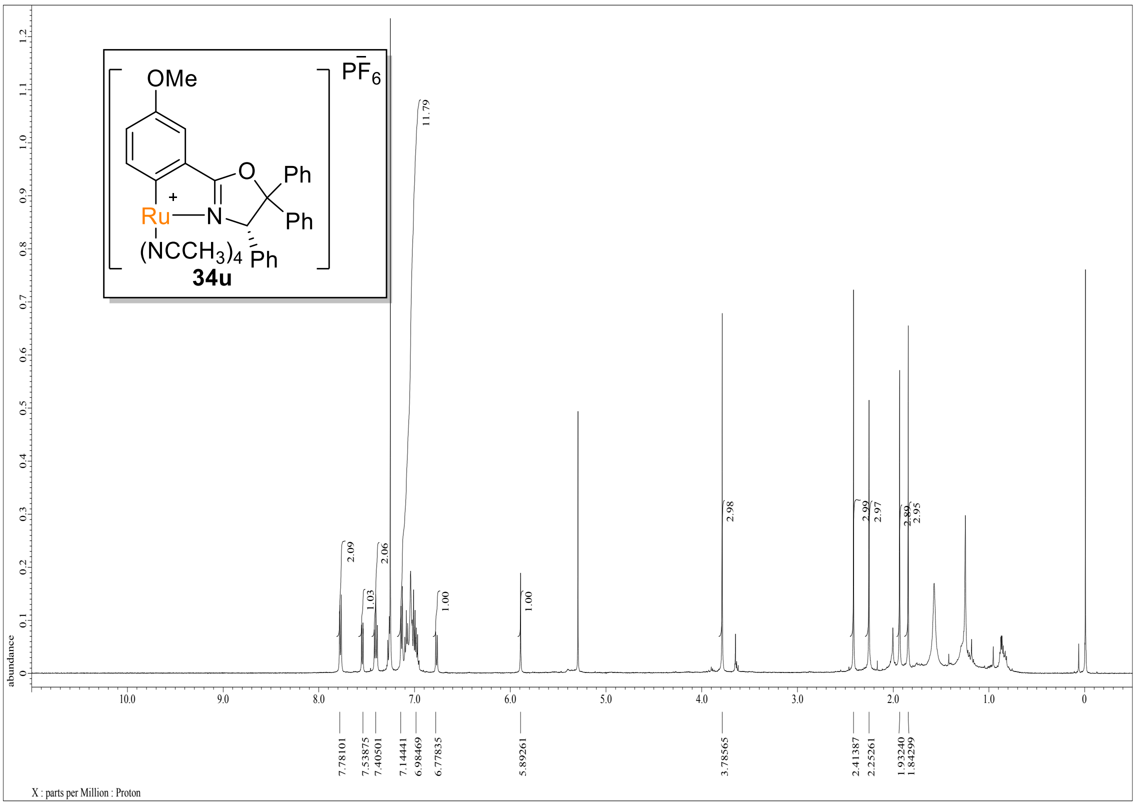

NO2
PF6
Ph
Ph
Ru
N
O
(NCCH3)4
Ph
34t
abundance
X : parts per Million : Carbon13


OMe
Ph
Ph
Ph
O
N
44K
abundance
X : parts per Million : Proton

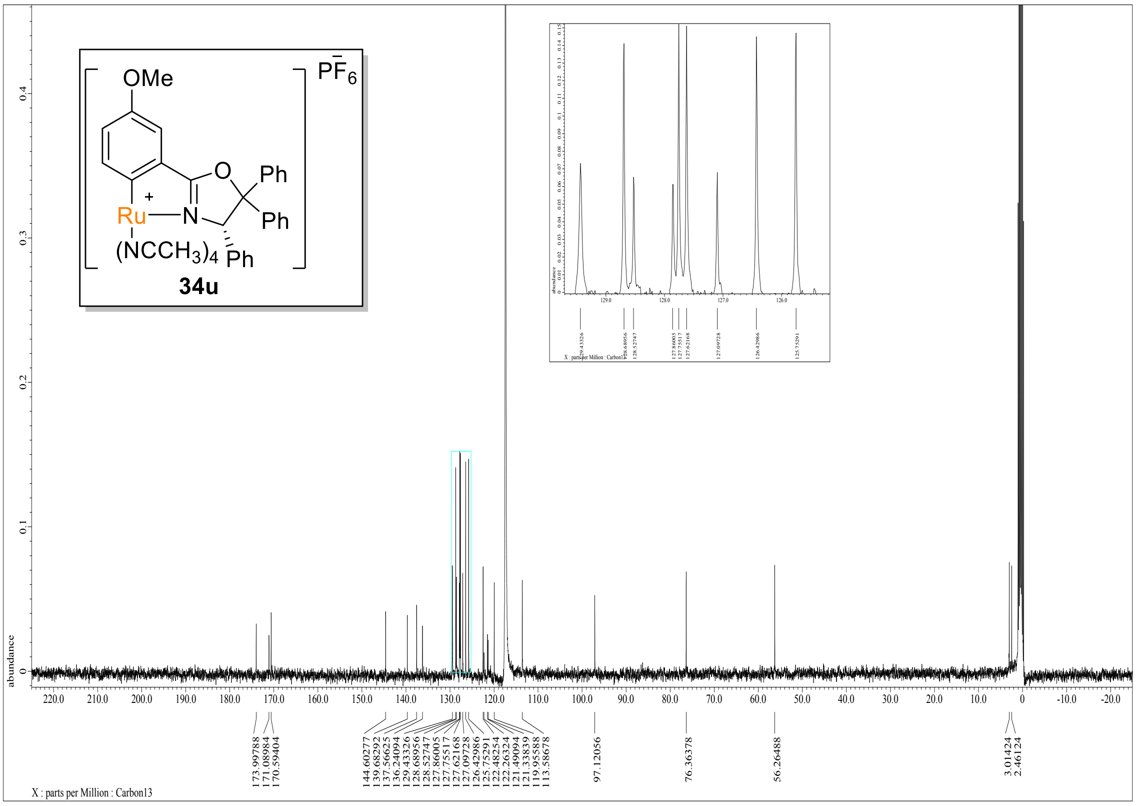

OMe
Ph
Ph
Ph
O
N
44K
abundance
X : parts per Million : Carbon13


PF6
MeO
Ru
N
O
Ph
Ph
(NCCH3)4
Ph
X
9.23
3.99
3.35
3.14
3.19
2.00
1.00
abundance
X : parts per Million : Proton

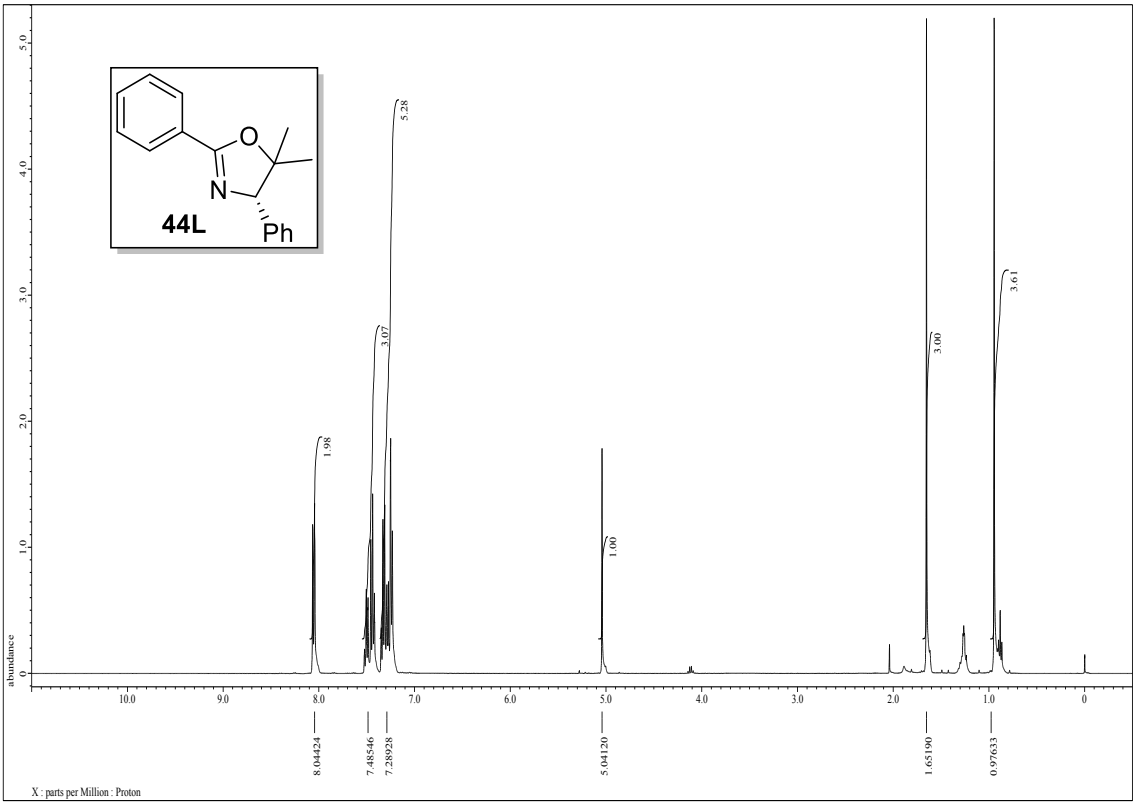

PF6
MeO
Ru
N
O
Ph
Ph
(NCCH3)4
Ph
X
143.897
139.559
129.595
128.785
128.356
127.765
127.603
127.336
127.059
126.535
126.211
97.397
77.327
55.397
4.387
3.081
abundance
X : parts per Million : Carbon13

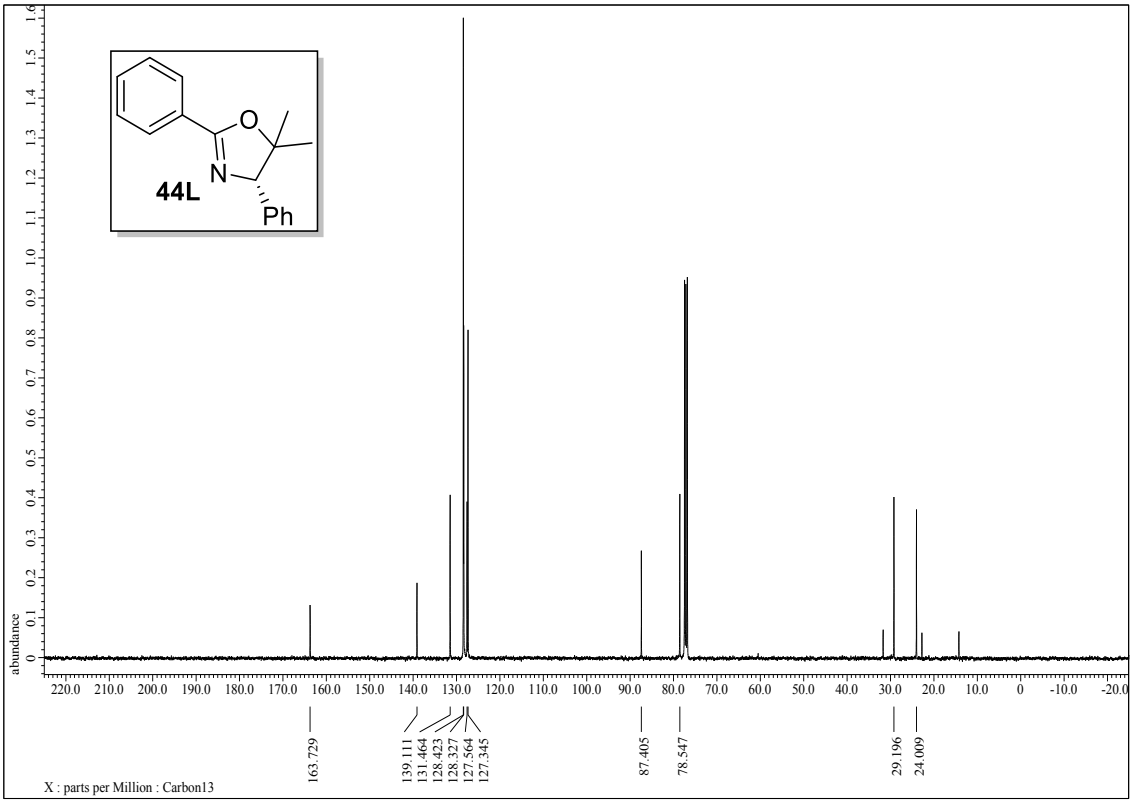


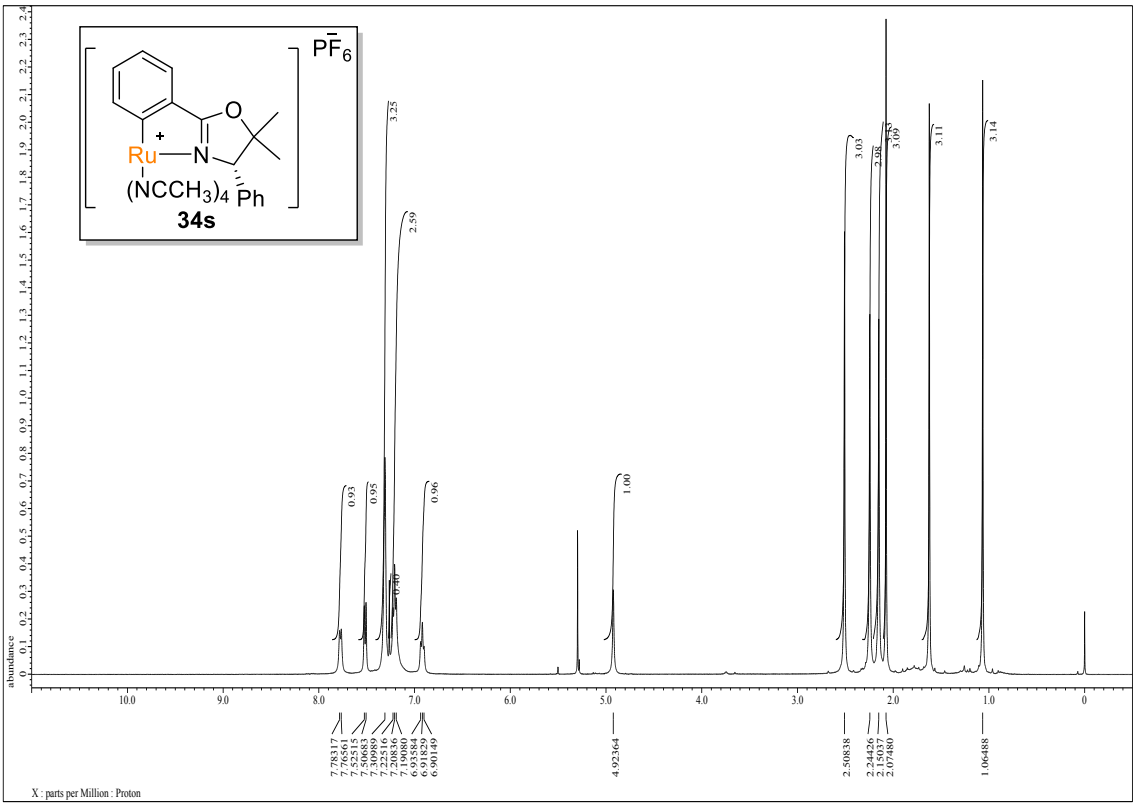
OMe
Ru
N
O
Ph
Ph
Ph
(NCCH3)4
PF6
34u
7.78101
7.53875
7.40501
7.14441
6.98469
6.77835
5.89261
3.78565
2.41387
2.25261
1.93240
1.84299
X : parts per Million : Proton

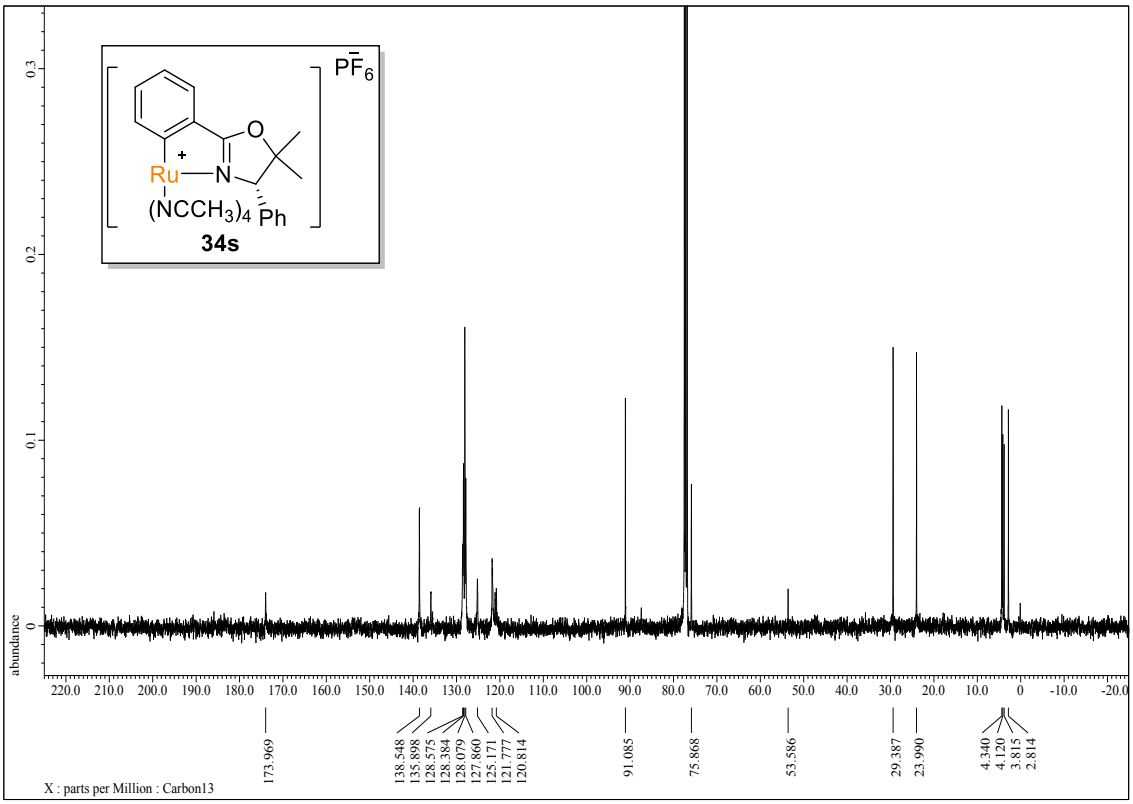


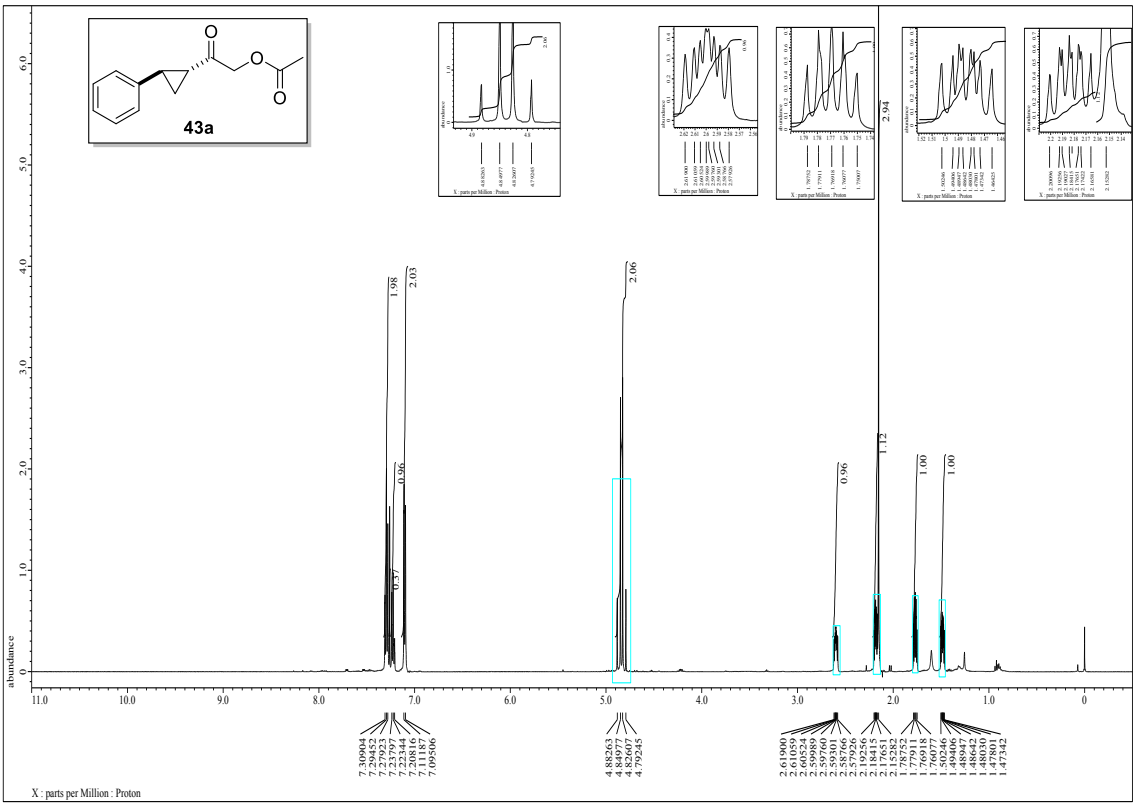
OMe
Ru
N
O
Ph
Ph
Ph
(NCCH3)4
PF6
34u
173.99788
171.08984
170.59404
144.60277
139.68292
137.56625
136.24094
129.43326
128.68956
128.52747
127.86005
127.75517
127.62168
127.09728
126.42986
125.75291
122.48254
122.26324
121.49094
121.33839
119.95588
113.58678
97.12056
76.36378
56.26488
3.01424
2.46124
X : parts per Million : Carbon13

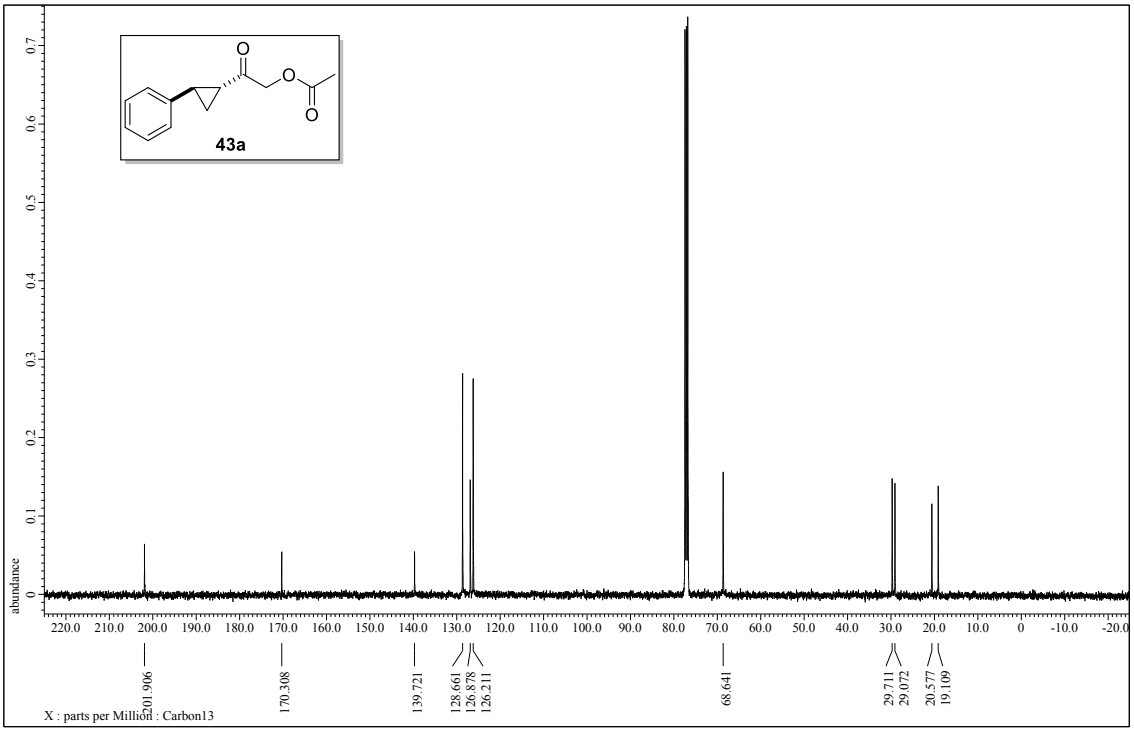

44L
Ph
abundance
1.98
3.07
5.28
1.00
3.00
3.61
8.04424
7.48546
7.28928
5.04120
1.65190
0.97633
X : parts per Million : Proton

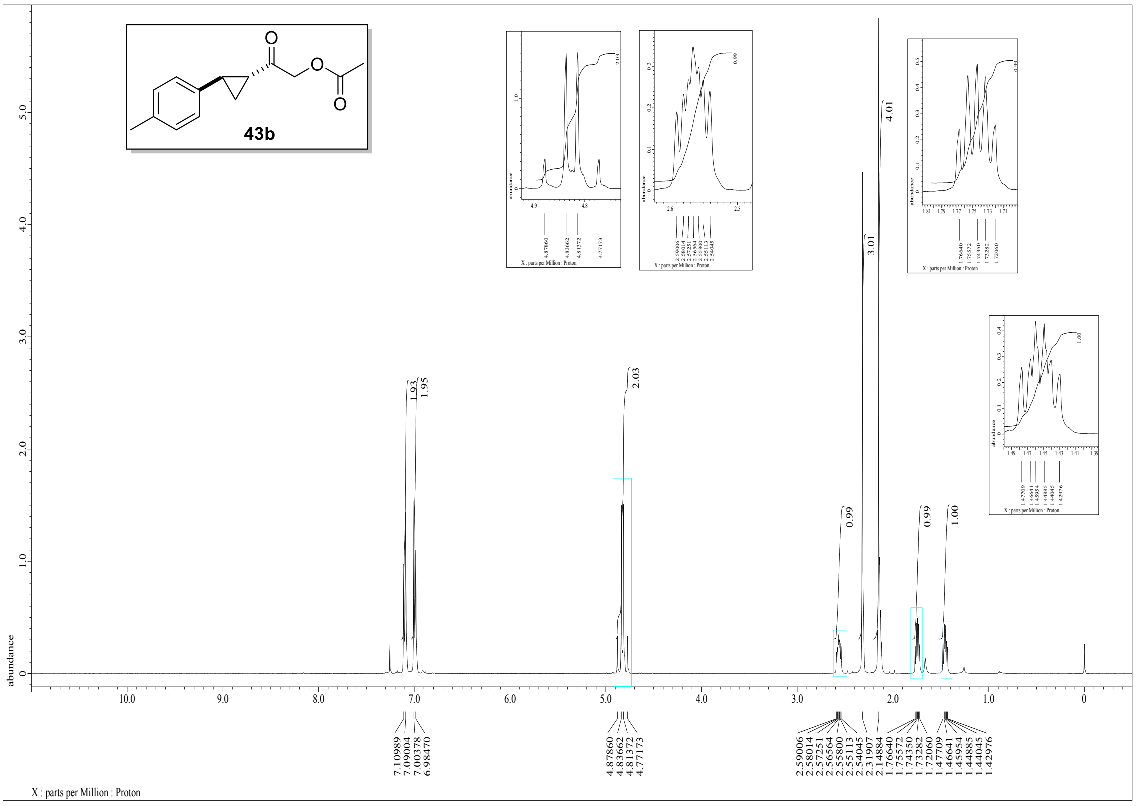

44L
Ph
abundance
163.729
139.111
131.464
128.423
128.327
127.564
127.345
87.405
78.547
29.196
24.009
X : parts per Million : Carbon13

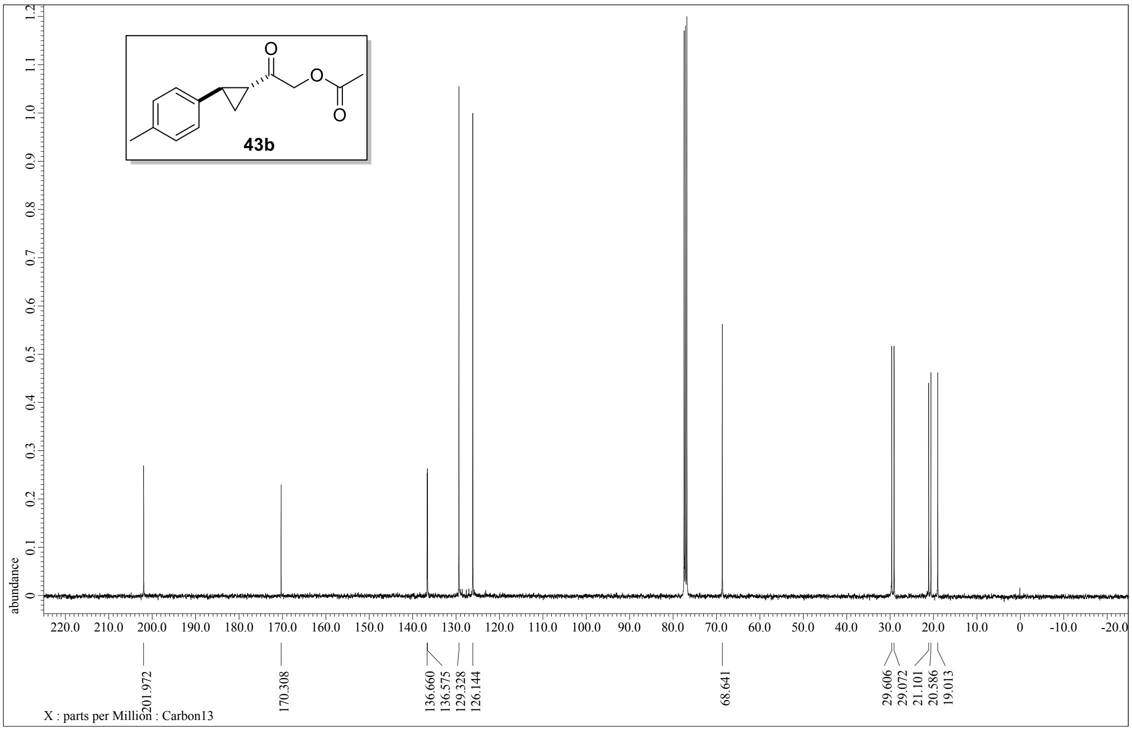

PF6
Ru
N
O
(NCCH3)4
Ph
34s
abundance
X : parts per Million : Proton

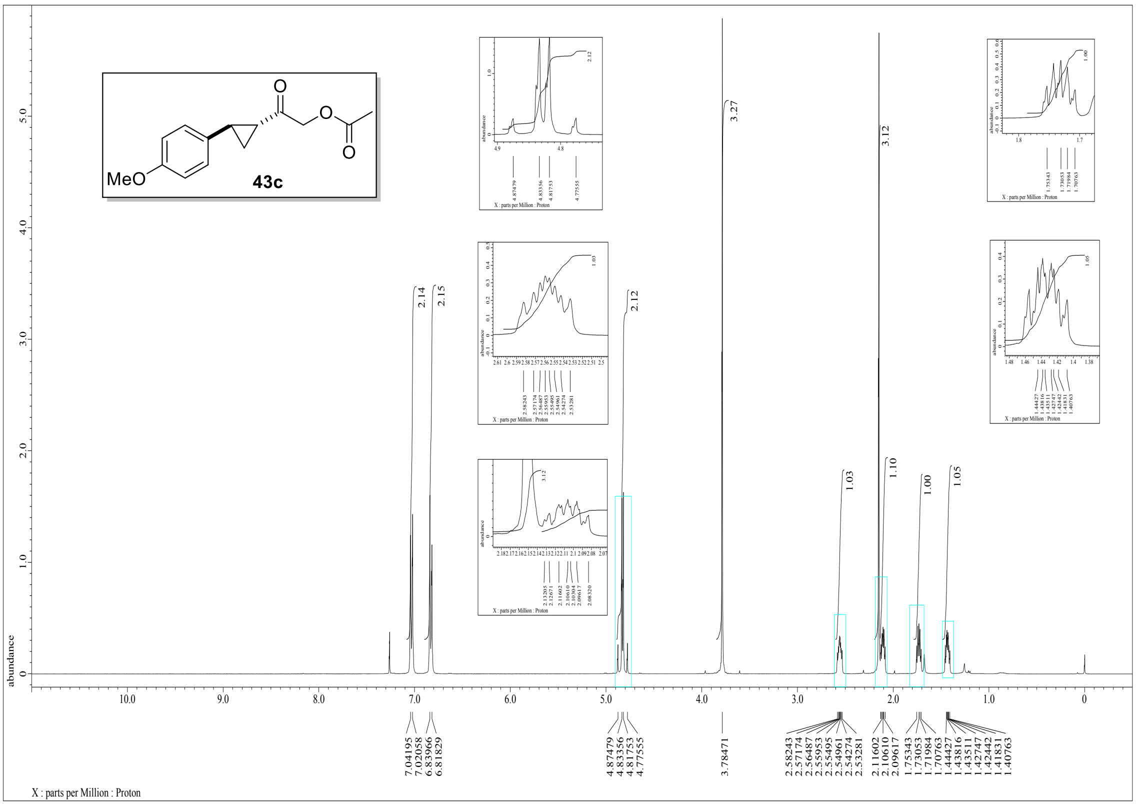

PF6
Ru
N
O
(NCCH3)4
Ph
34s
abundance
X : parts per Million : Carbon13


43a
abundance
X : parts per Million : Proton

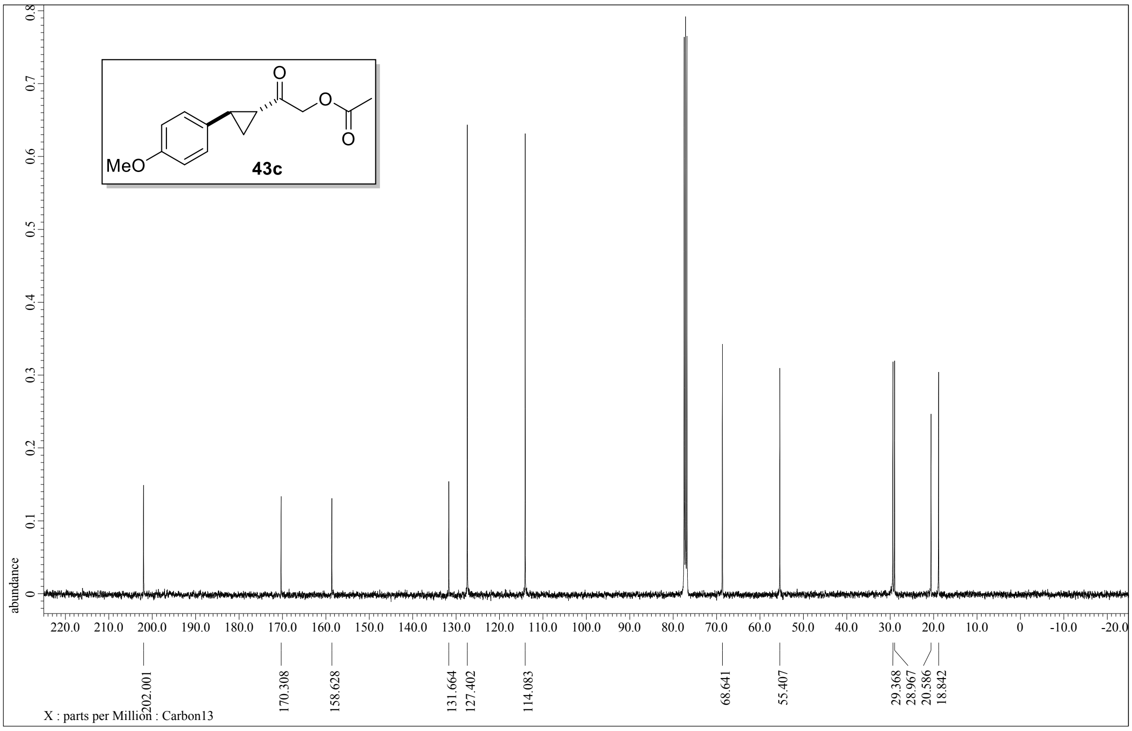

43a
abundance
X : parts per Million : Carbon13


43b
X : parts per Million : Proton
abundance
7.10989
7.09004
7.00378
6.98470
4.87860
4.83662
4.81372
4.77173
1.93
1.95
2.03
0.99
3.01
4.01
0.99
1.00

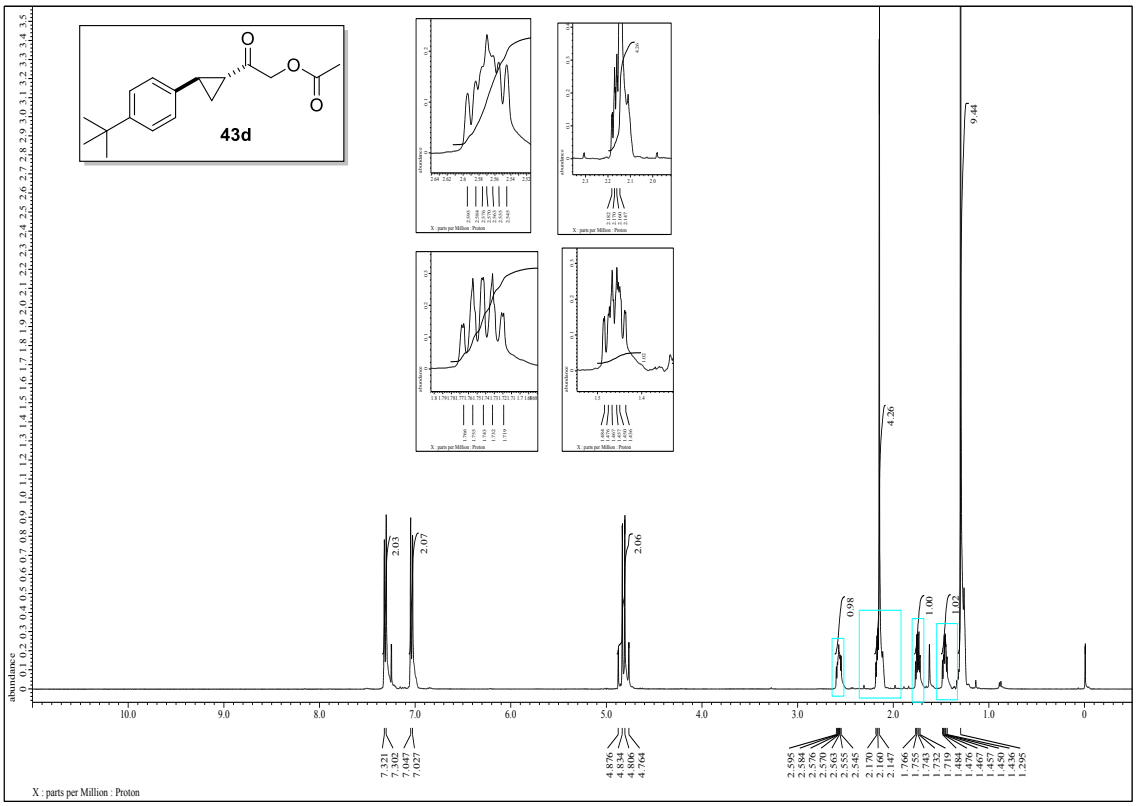

43b
X : parts per Million : Carbon13
abundance
201.972
170.308
136.660
136.575
129.328
126.144
68.641
29.606
29.072
21.101
20.586
19.013

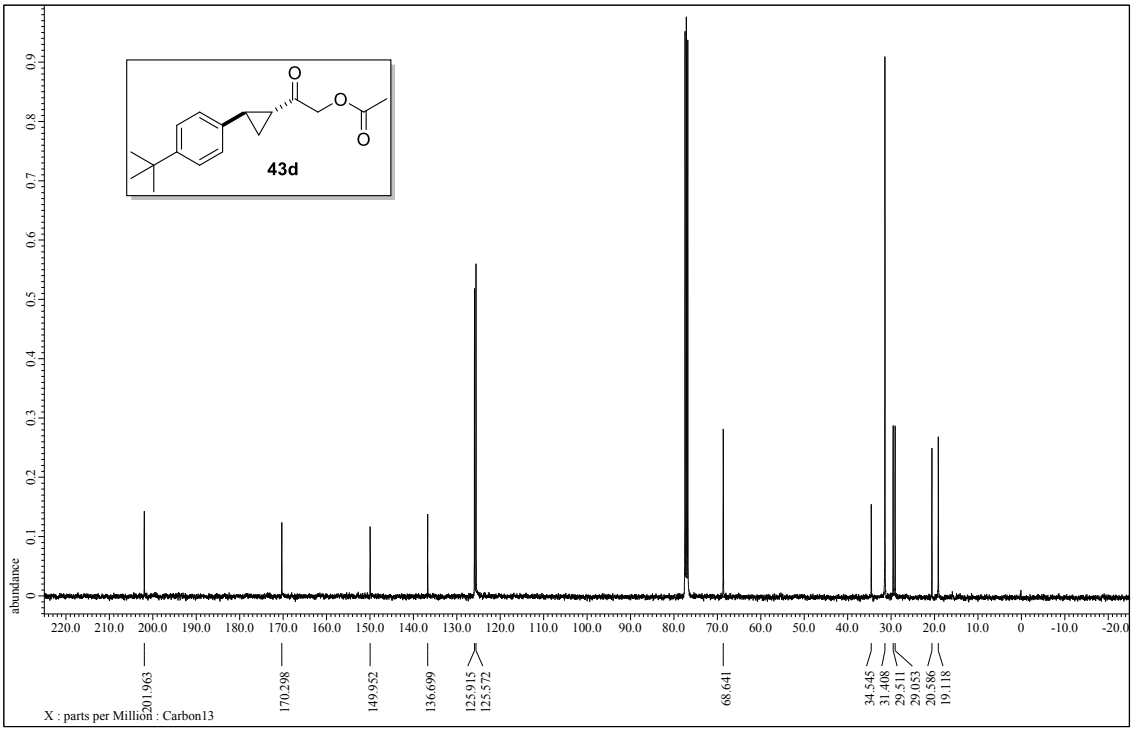


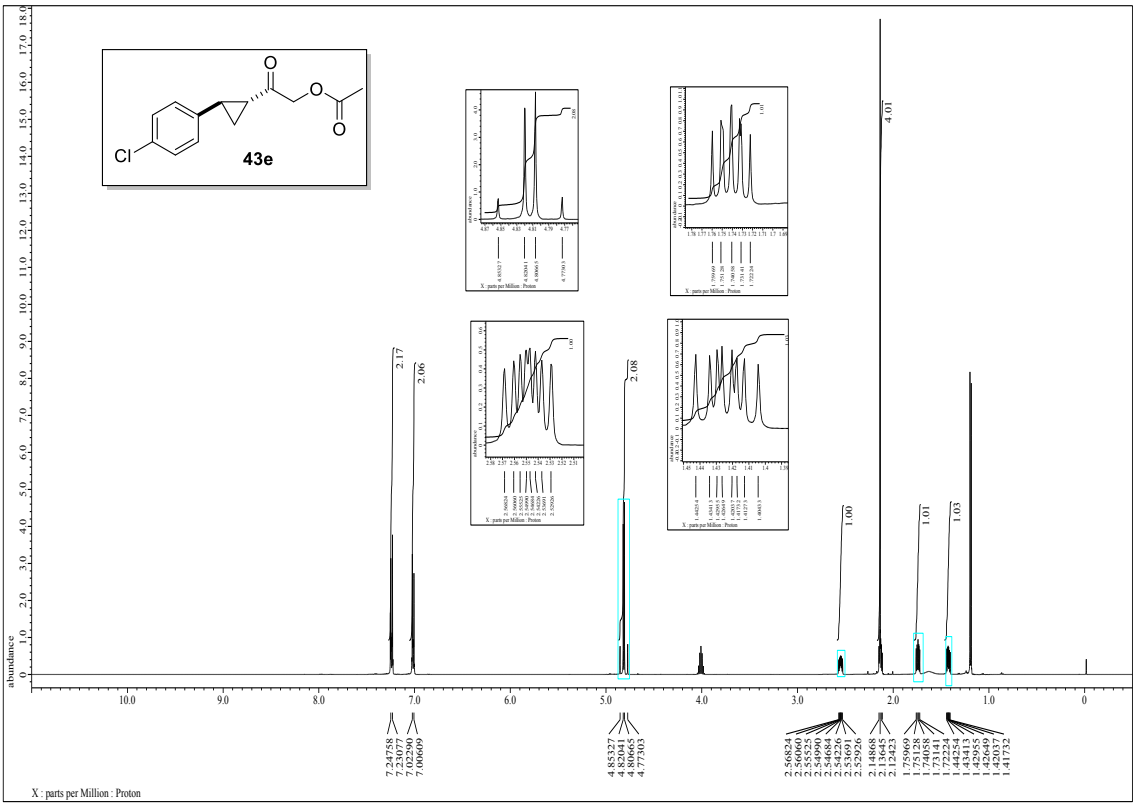
MeO
43c
X : parts per Million : Proton

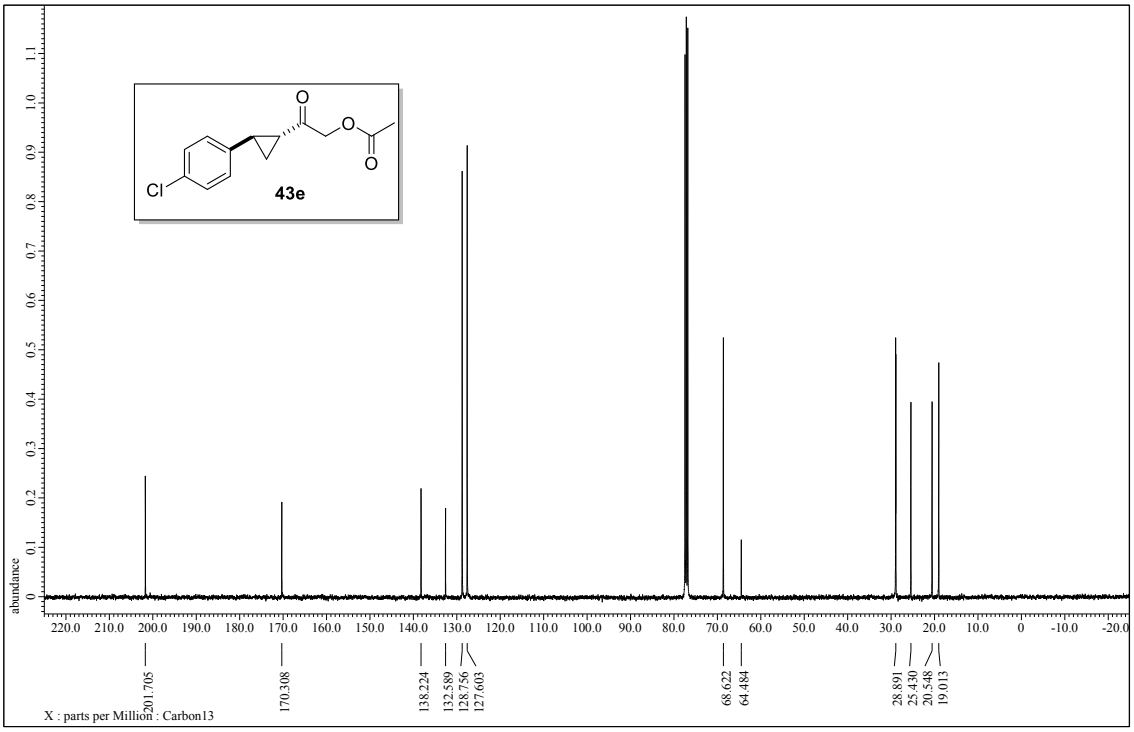


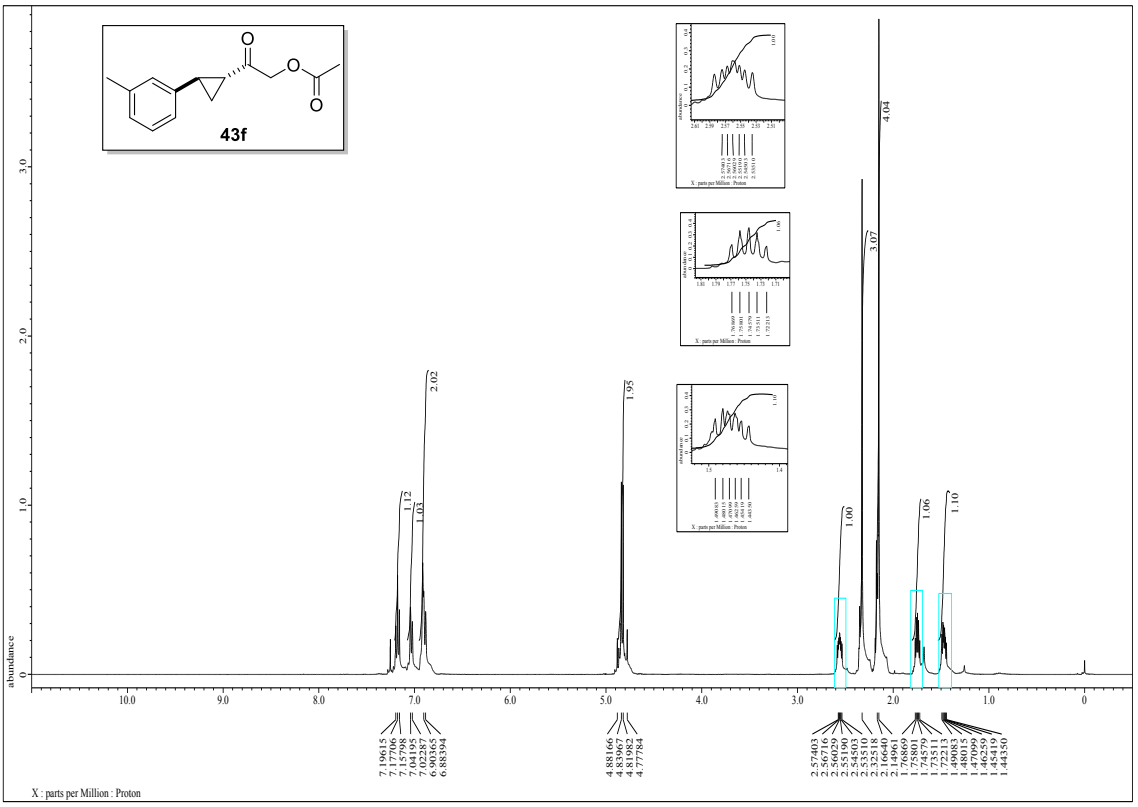
MeO
43c
202.001
170.308
158.628
131.664
127.402
114.083
68.641
55.407
29.368
28.967
20.586
18.842
X : parts per Million : Carbon13

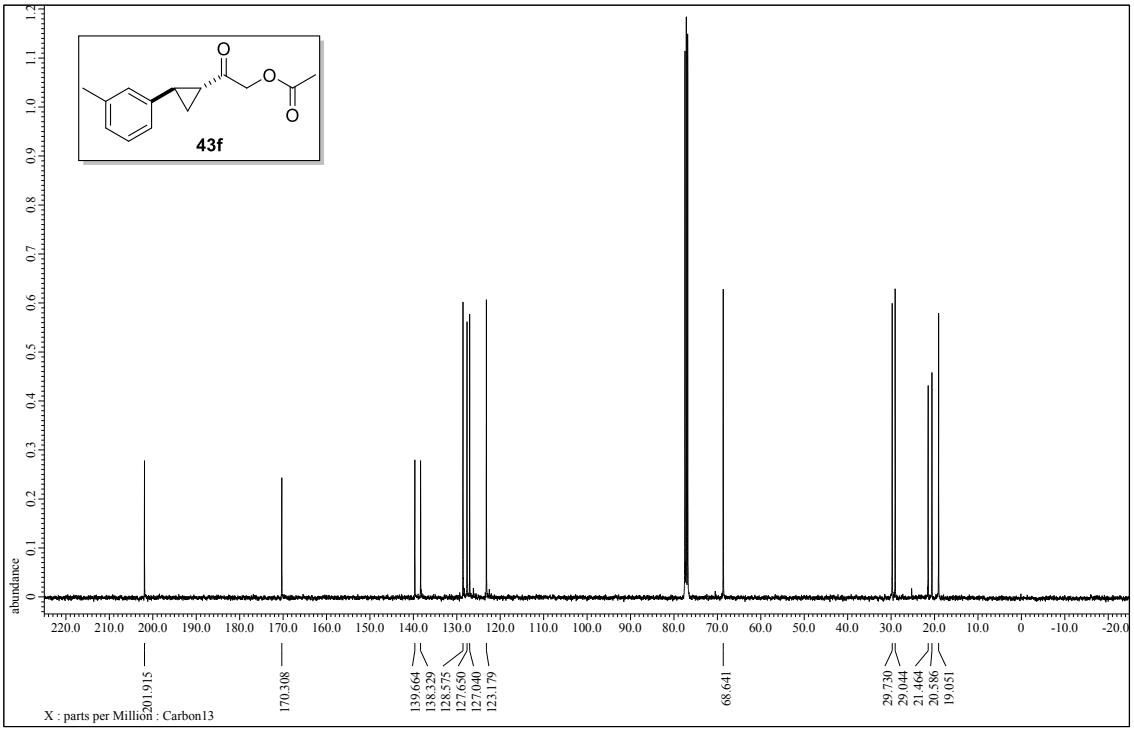

43d
abundance
X : parts per Million : Proton
7.321
7.302
7.047
7.027
4.876
4.834
4.806
4.764
2.595
2.584
2.576
2.570
2.563
2.555
2.545
2.170
2.160
2.147
1.766
1.755
1.743
1.732
1.719
1.484
1.476
1.467
1.457
1.450
1.436
1.295
2.03
2.07
2.06
4.26
9.44
0.98
1.00
1.02

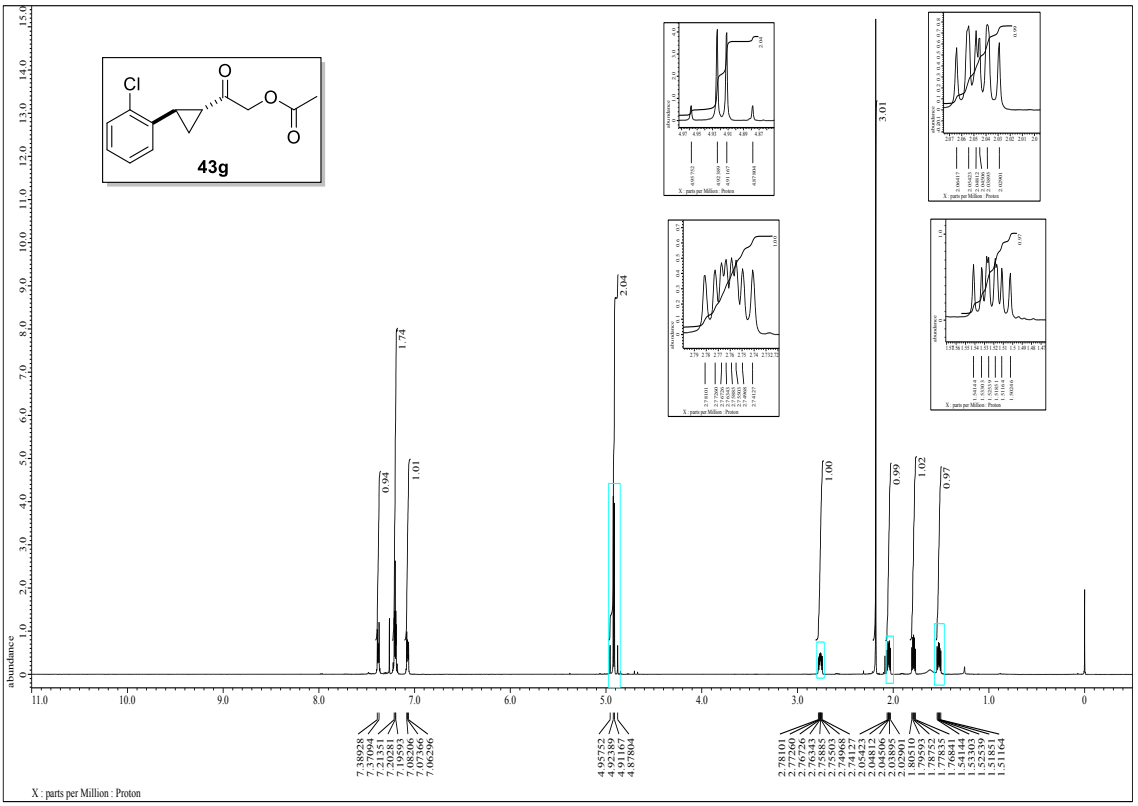

43d
abundance
X : parts per Million : Carbon13
201.963
170.298
149.952
136.699
125.915
125.572
68.641
34.545
31.408
29.511
29.053
20.586
19.118

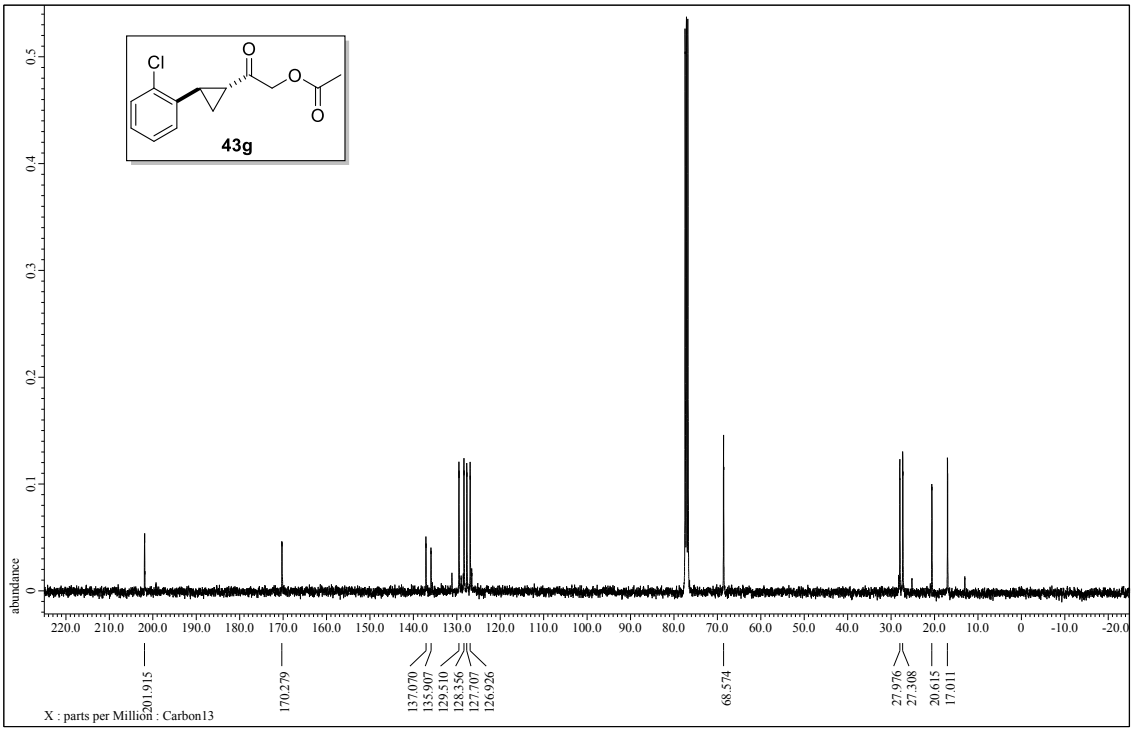

43e
abundance
X : parts per Million : Proton
2.17
2.06
2.08
4.01
1.00
1.01
1.03
7.24758
7.23077
7.02290
7.00669
4.85327
4.82041
4.80665
4.77503
2.56824
2.54990
2.53691
2.52926
2.14868
2.13425
1.75969
1.75128
1.74058
1.72224
1.44254
1.42915
1.42649
1.42037
1.41732

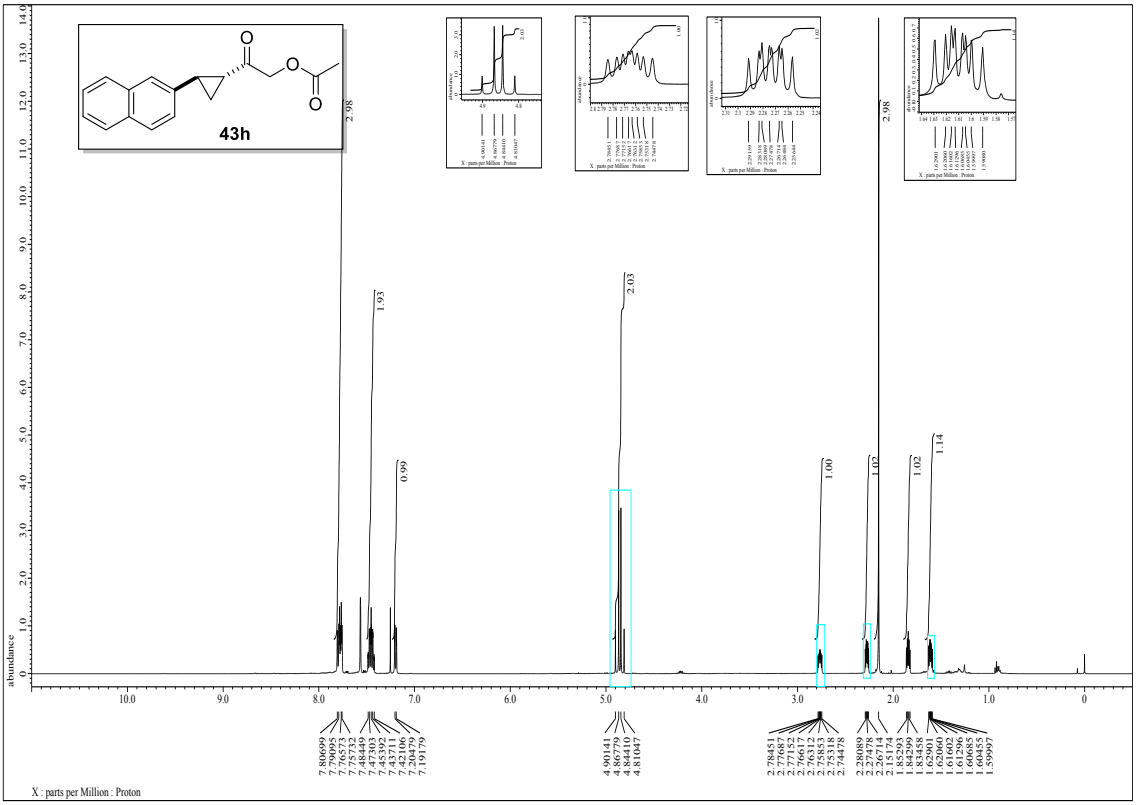

43e
abundance
X : parts per Million : Carbon13
201.705
170.308
138.224
132.589
128.756
127.603
68.622
64.484
28.891
25.430
20.548
19.013

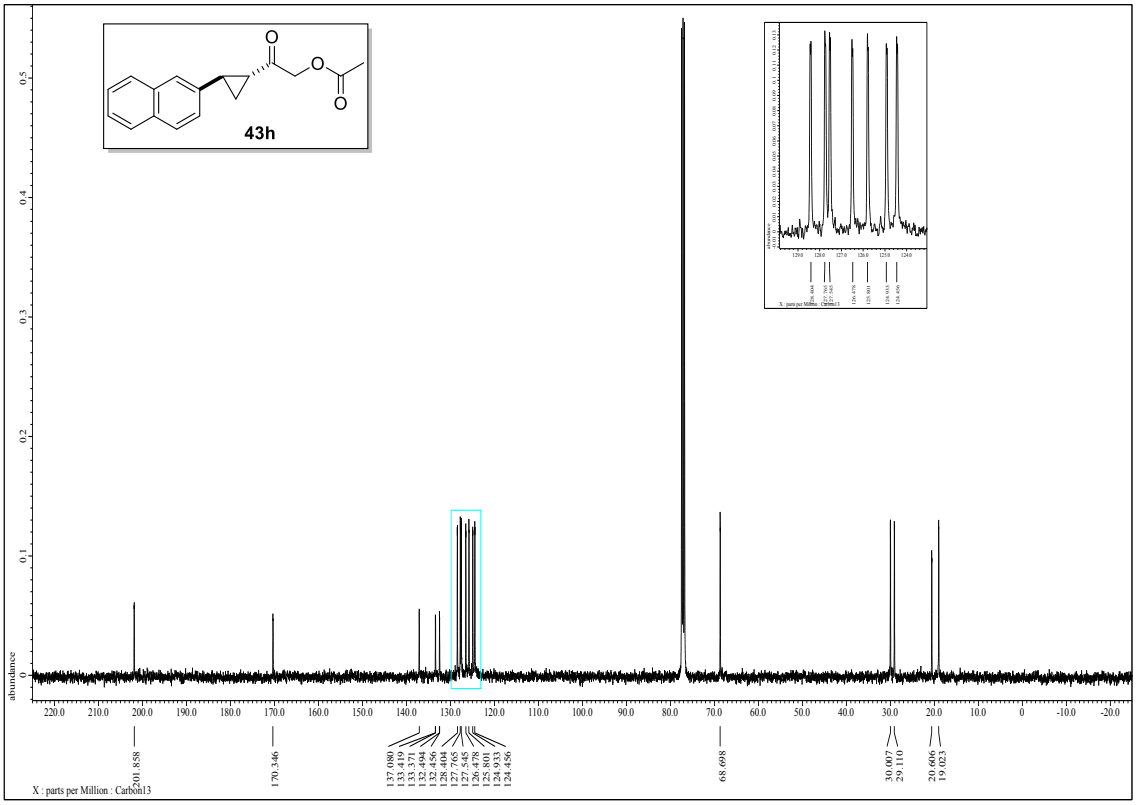

43f
abundance
X : parts per Million : Proton
7.19615
7.17706
7.17398
7.04195
7.02287
6.90565
6.88394
4.88166
4.83967
4.81092
4.77784
2.57403
2.56716
2.56029
2.55190
2.54503
2.53510
2.32518
2.16640
2.16041
1.76869
1.75801
1.75179
1.74571
1.72213
1.49083
1.48615
1.47099
1.46259
1.45419
1.44350
1.12
1.03
2.02
1.95
1.00
3.07
4.04
1.06
1.10

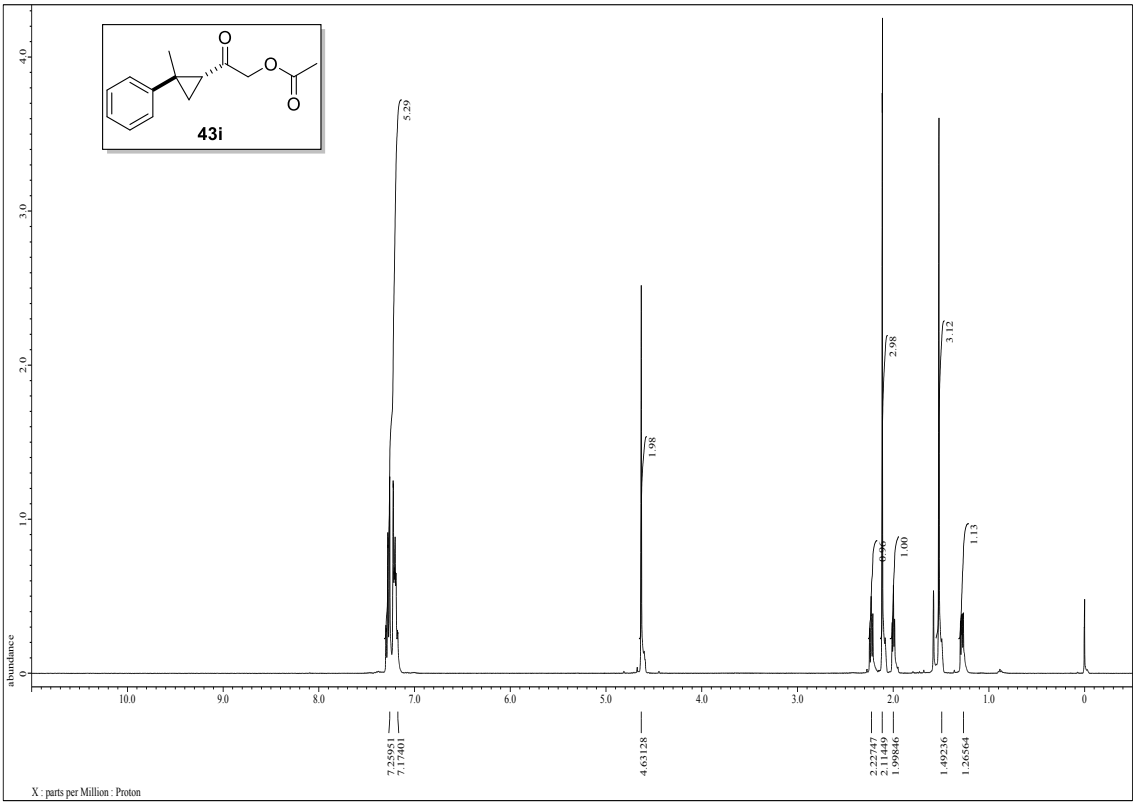

43f
abundance
X : parts per Million : Carbon13
201.915
170.308
139.664
138.329
128.575
127.650
127.040
123.179
68.641
29.730
29.044
21.464
20.586
19.051

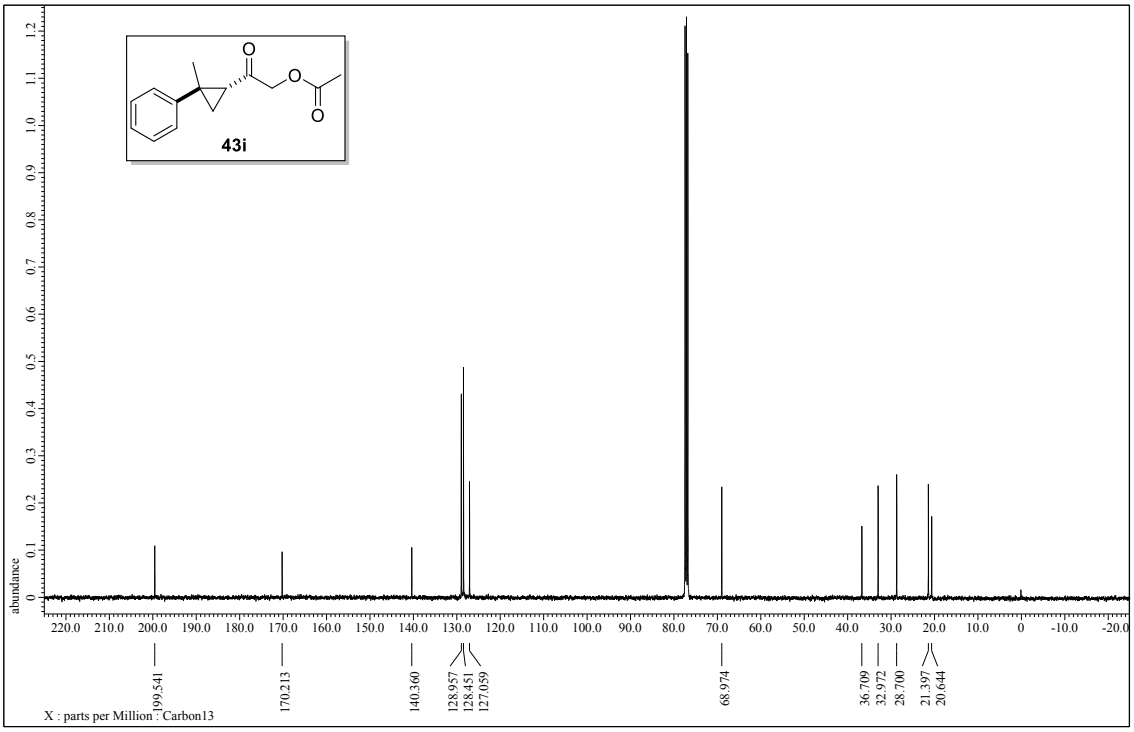

43g
abundance
X : parts per Million : Proton
7.38928
7.37094
7.21351
7.20234
7.19593
7.08206
7.07266
7.06296
4.95752
4.92389
4.91167
4.87804
2.78101
2.77260
2.76726
2.76243
2.75885
2.75503
2.74968
2.74427
2.05423
2.04812
2.04466
2.03895
2.02901
1.80510
1.79755
1.78752
1.77835
1.77684
1.54144
1.53303
1.52539
1.51853
1.51164
0.94
1.74
1.01
2.04
1.00
3.01
0.99
1.02
0.97

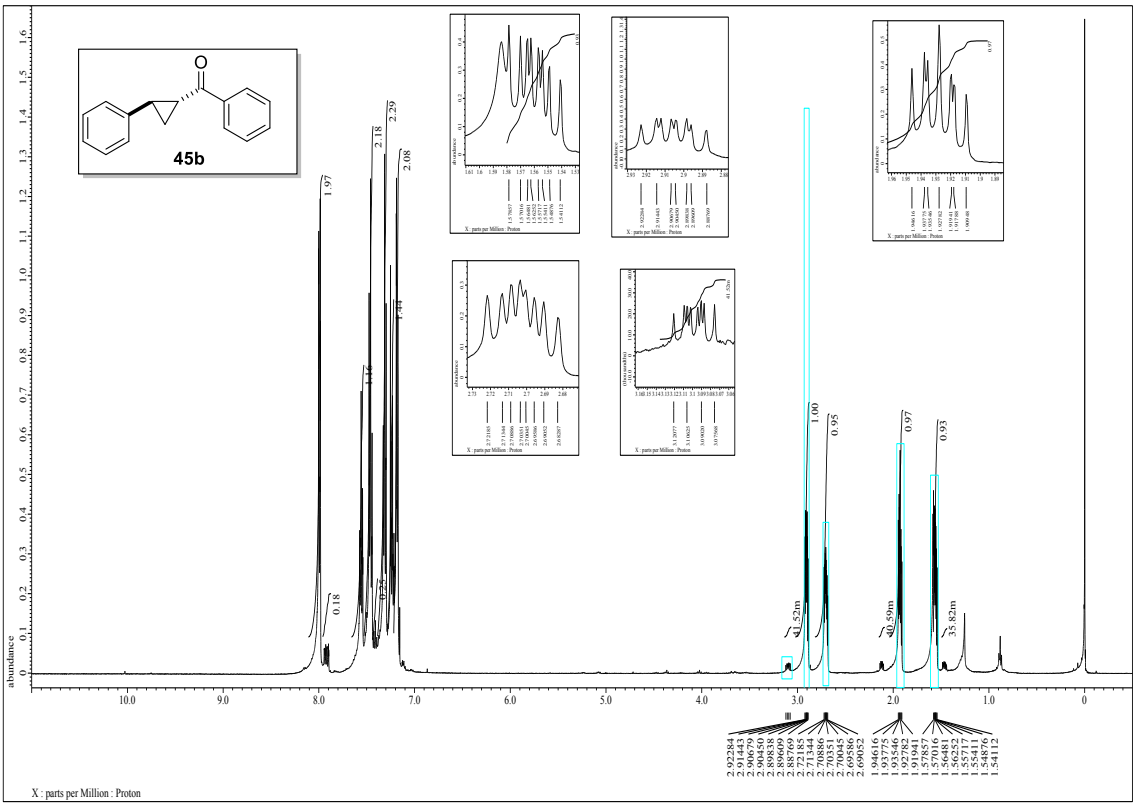

43g
abundance
X : parts per Million : Carbon13
201.915
170.279
137.070
135.907
129.510
128.356
127.707
126.926
68.574
27.976
27.308
20.615
17.011

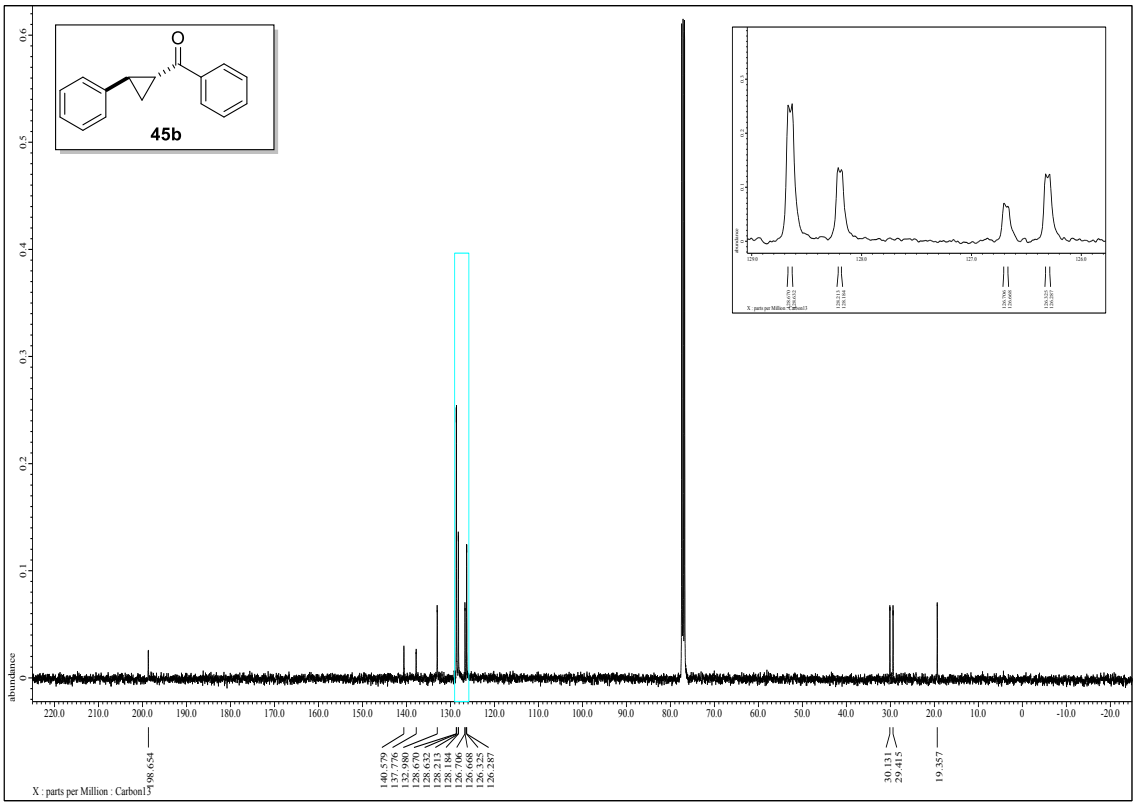

43h
abundance
X : parts per Million : Proton
2.98
1.93
2.03
0.99
1.00
1.02
1.02
1.14

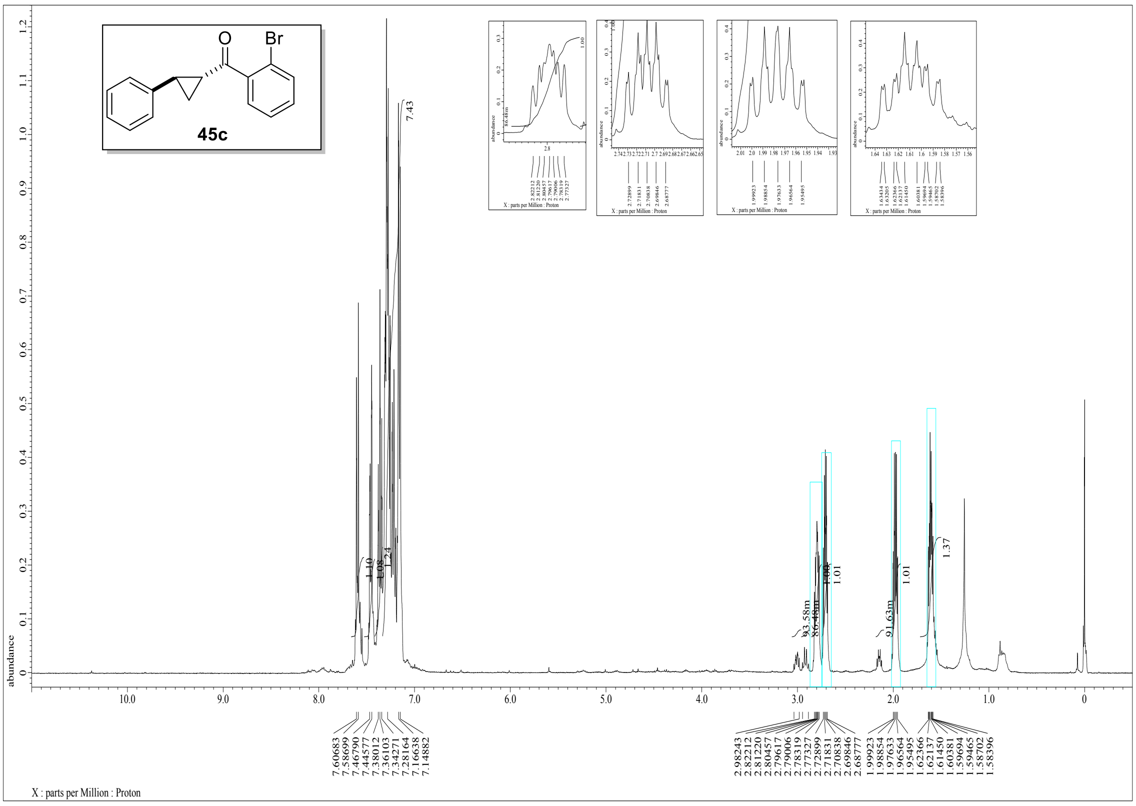

43h
abundance
X : parts per Million : Carbon13
170.346
68.698
30.007
29.110
20.606
19.023

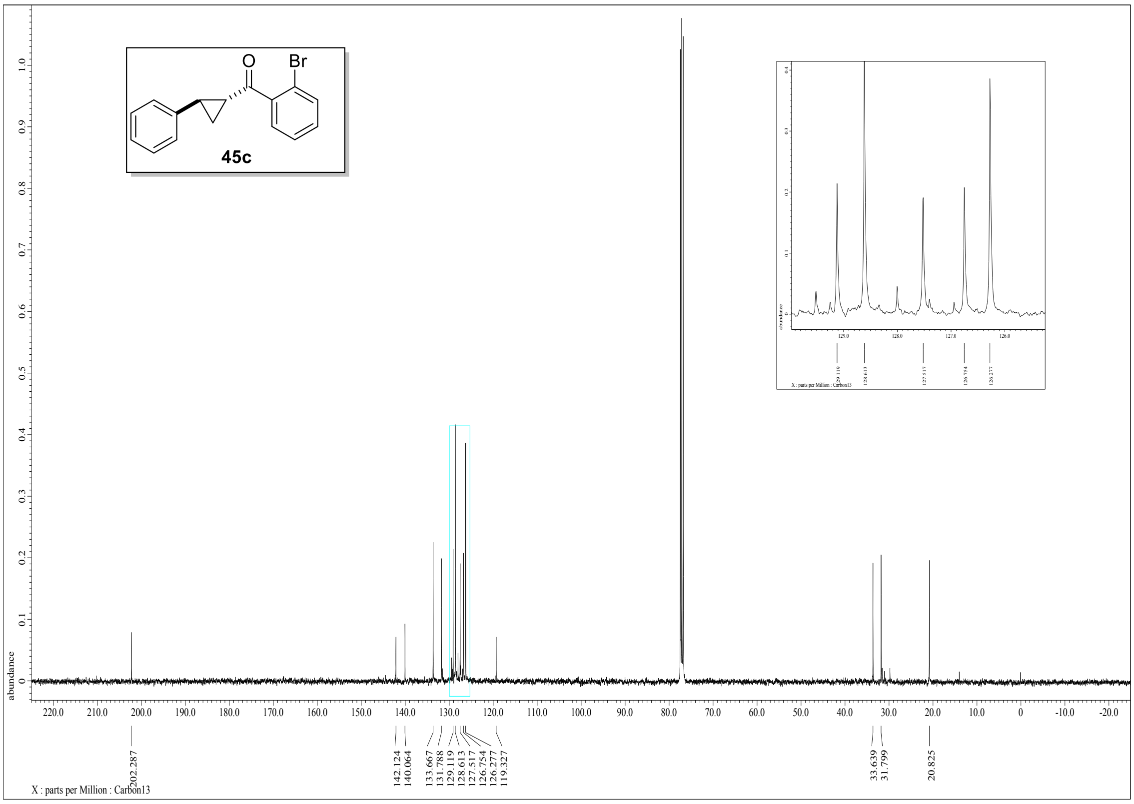

43i
5.29
1.98
2.98
3.12
0.96
1.00
1.13
abundance
7.25951
7.17401
4.63128
2.22747
2.11449
1.99846
1.49236
1.26564
X : parts per Million : Proton

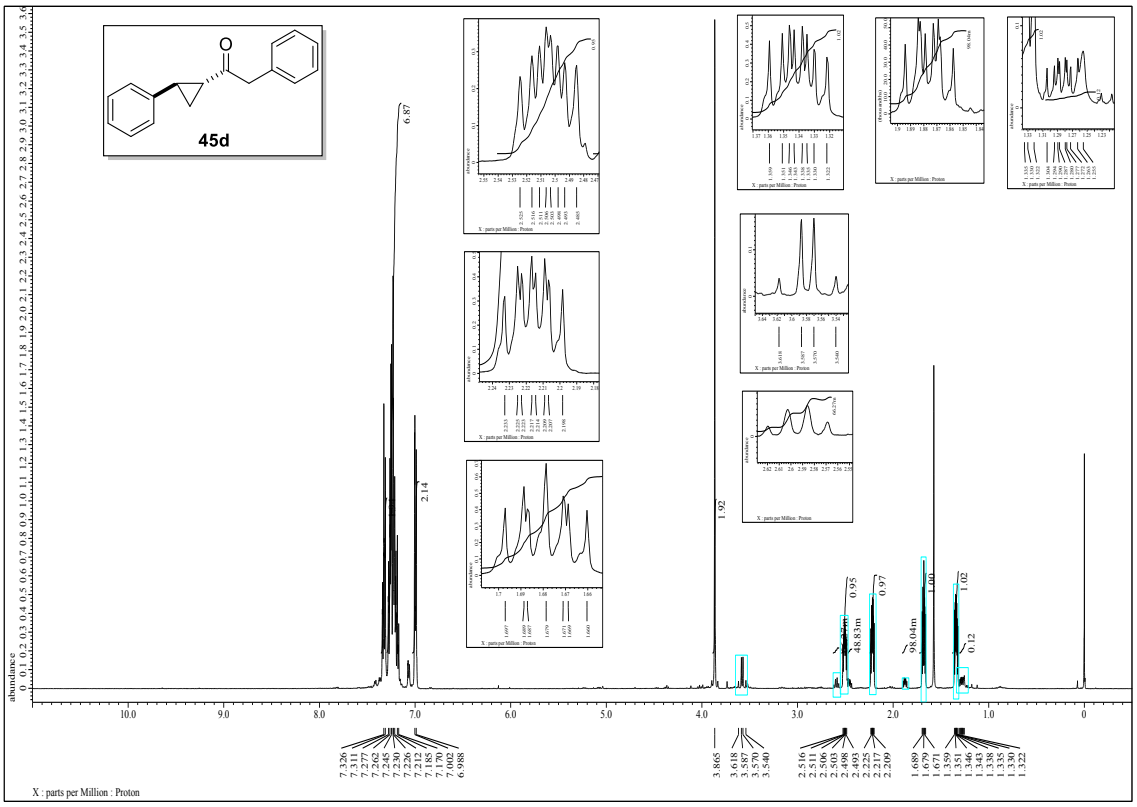

43i
abundance
199.541
170.213
140.360
128.957
128.451
127.059
68.974
36.709
32.972
28.700
21.397
20.644
X : parts per Million : Carbon13

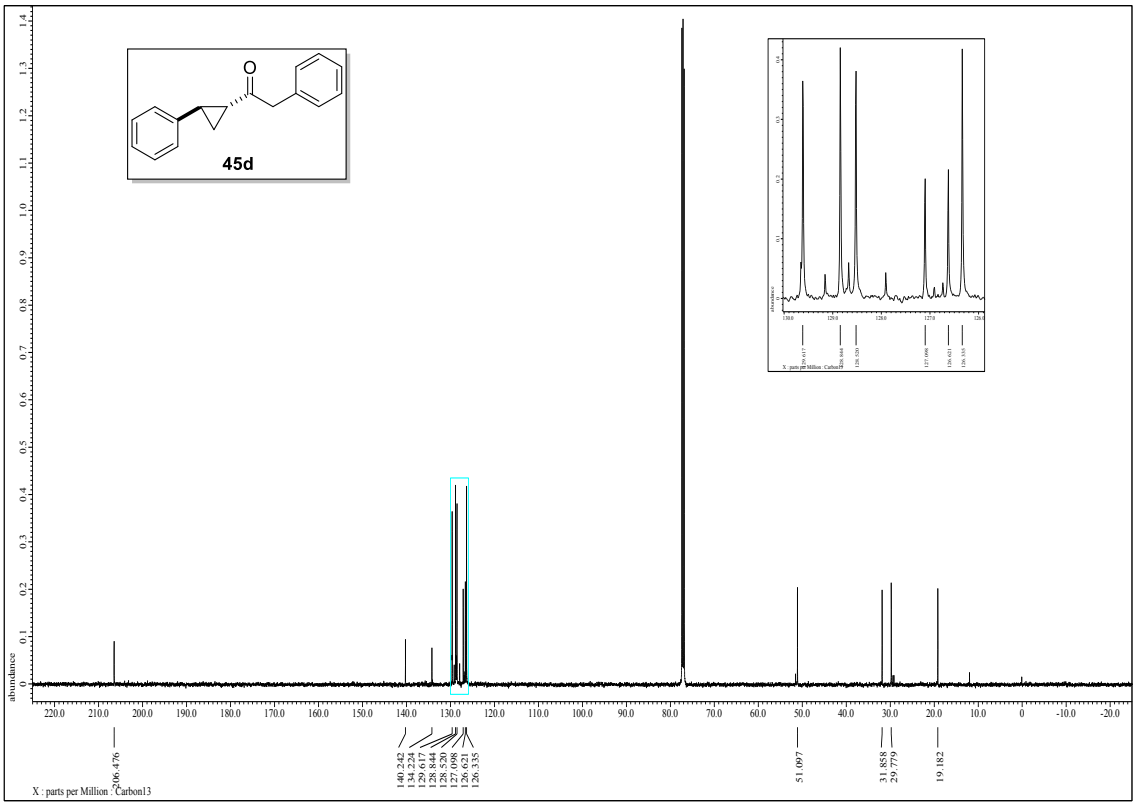

45b
abundance
X : parts per Million : Proton

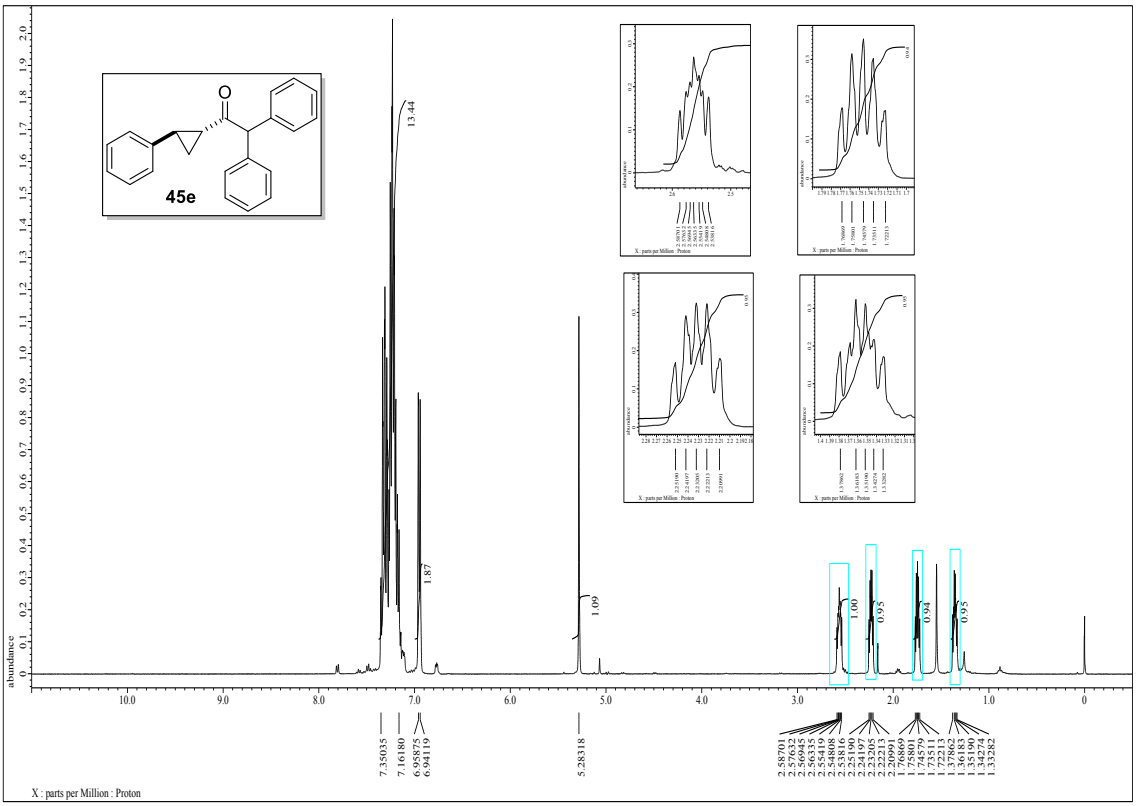

45b
abundance
X : parts per Million : Carbon13

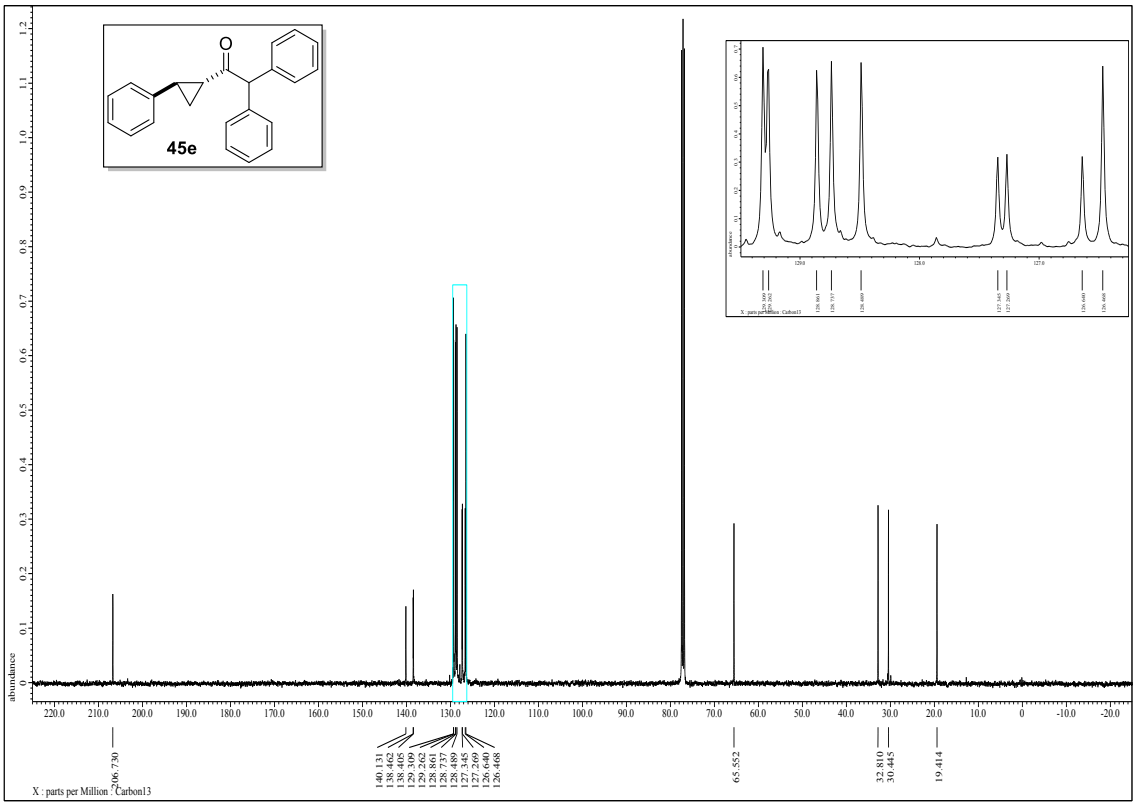

45c
Br
O
X : parts per Million : Proton
abundance

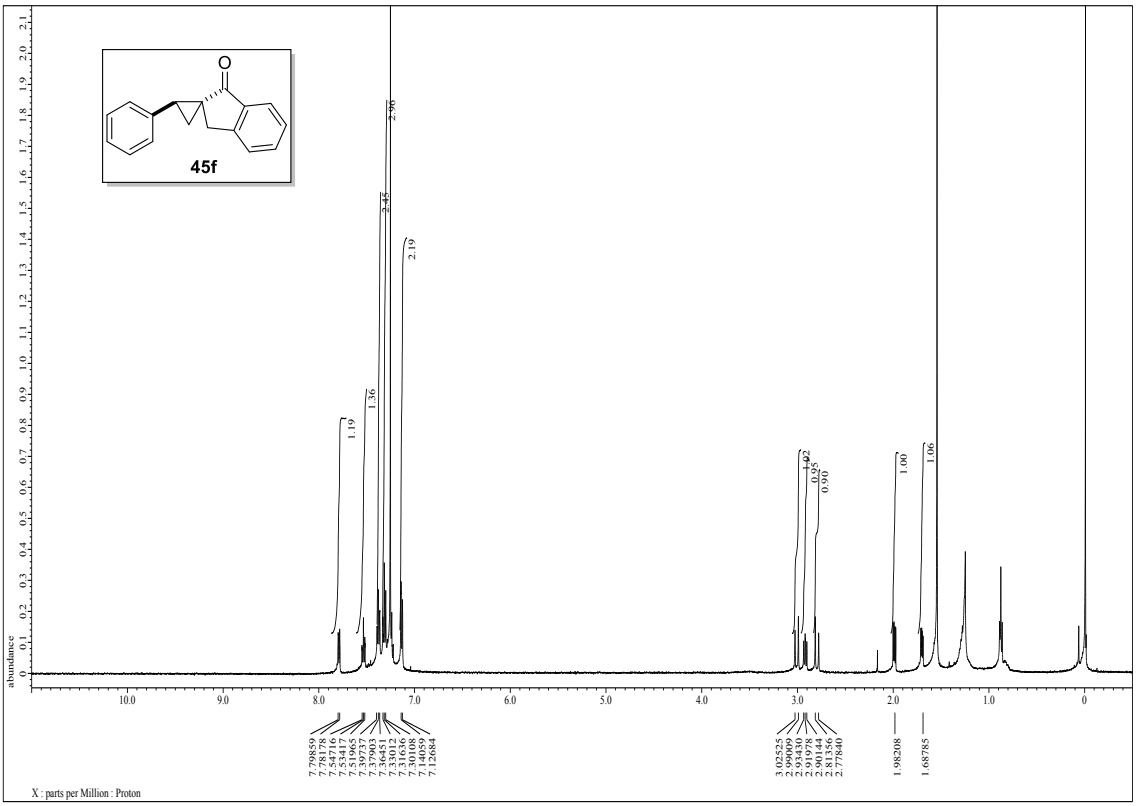

45c
Br
O
X : parts per Million : Carbon13
abundance
202.287
142.124
140.064
133.667
131.788
129.119
128.613
127.517
126.754
126.277
119.327
33.639
31.799
20.825

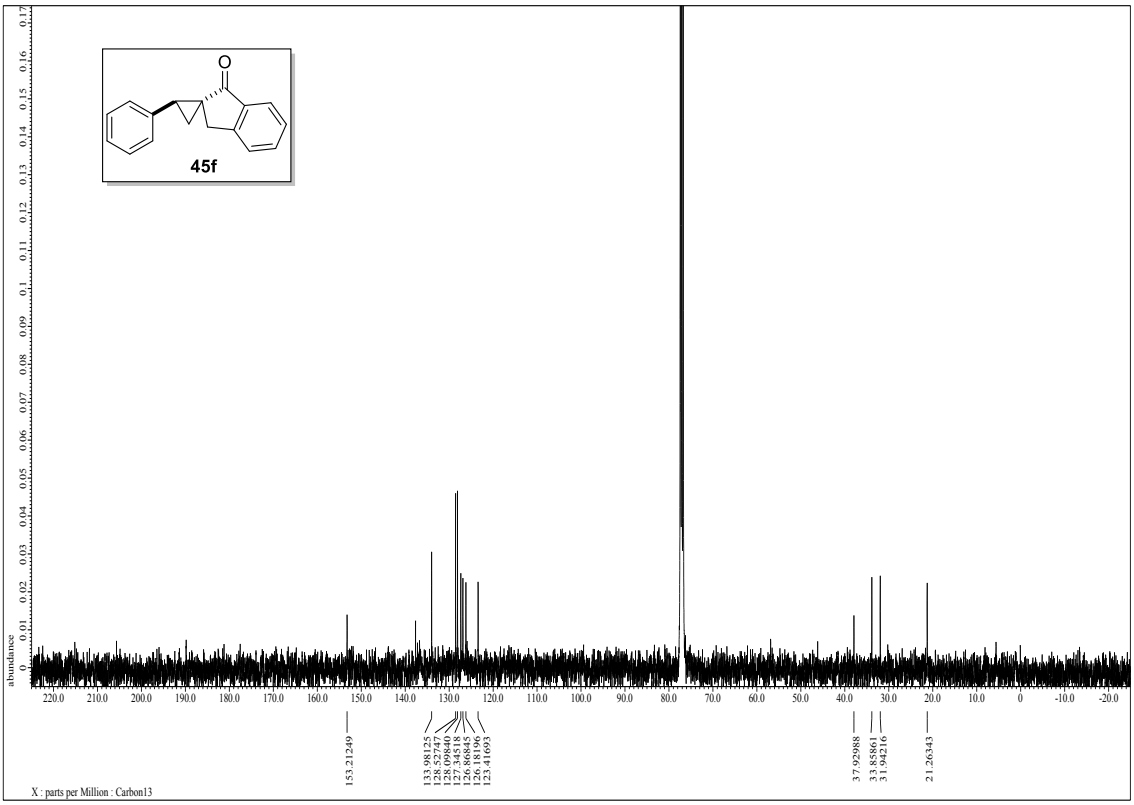

45d
6.87
2.14
1.92
0.95
0.97
1.00
1.02
48.83m
98.04m
0.12
X : parts per Million : Proton

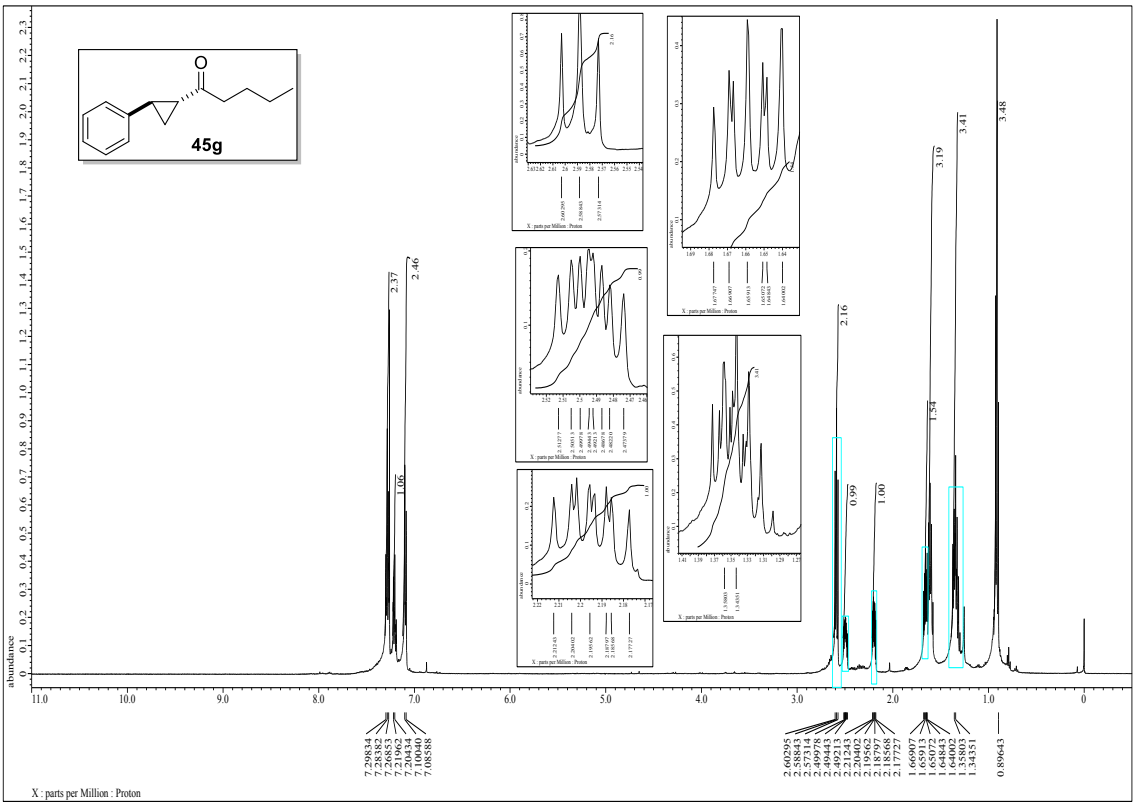

45d
206.476
140.242
134.224
129.617
128.844
128.520
127.098
126.621
126.335
51.097
31.858
29.779
19.182
X : parts per Million : Carbon13

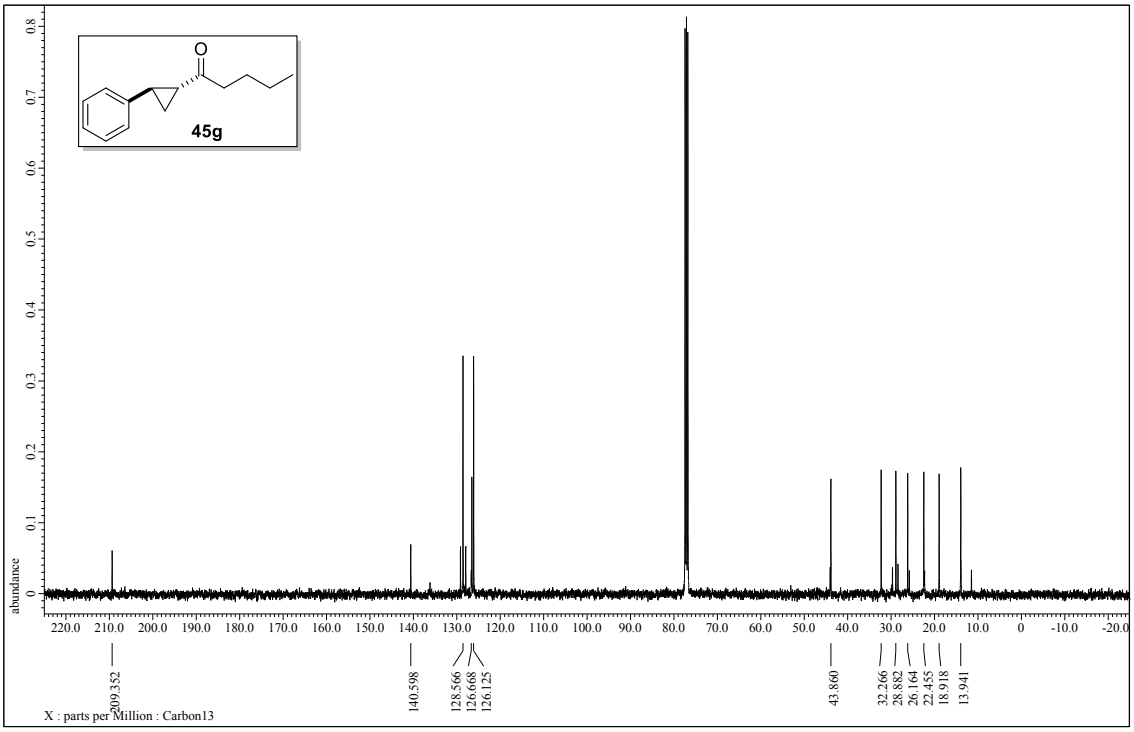

45e
13.44
1.87
1.09
1.00
0.95
0.94
0.95
abundance
X : parts per Million : Proton

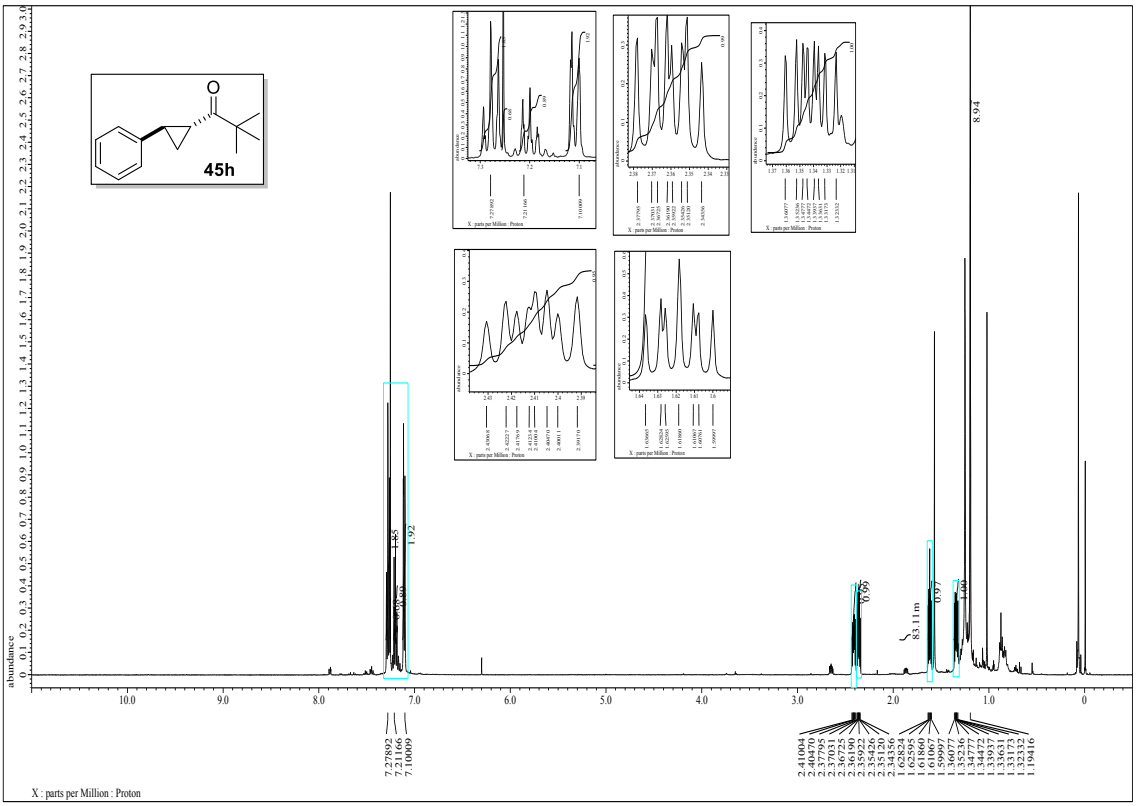

45e
abundance
X : parts per Million : Carbon13

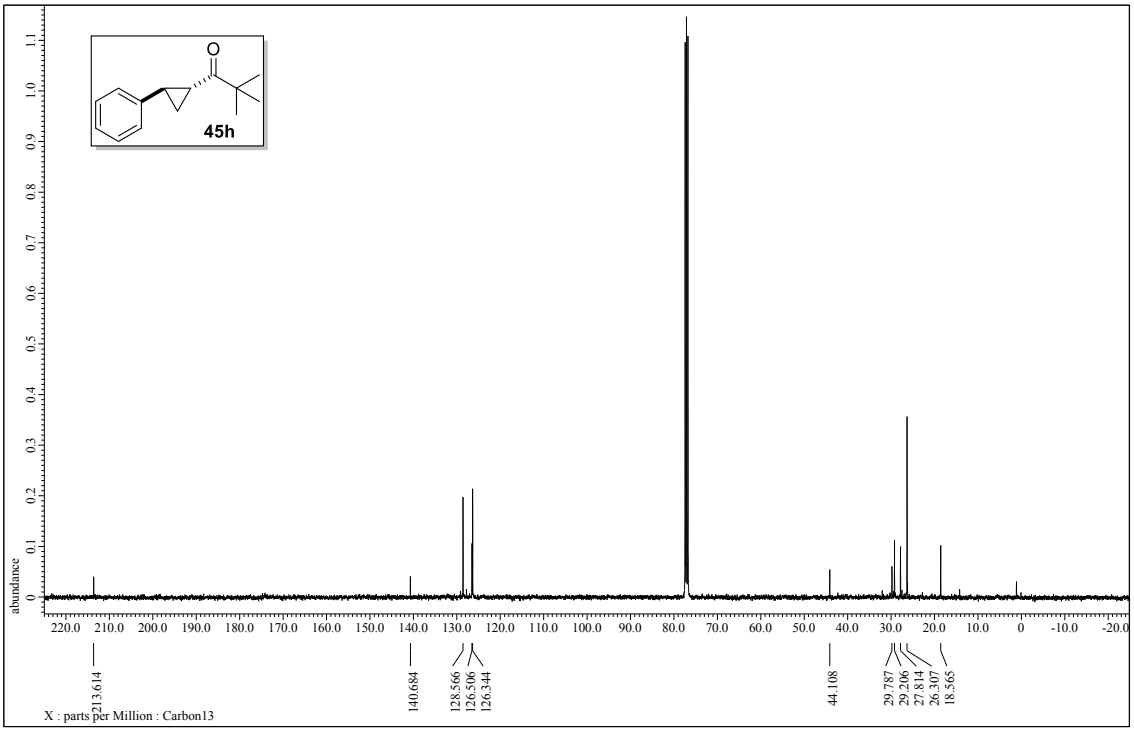

45f
abundance
X : parts per Million : Proton


45f
abundance
X : parts per Million : Carbon13

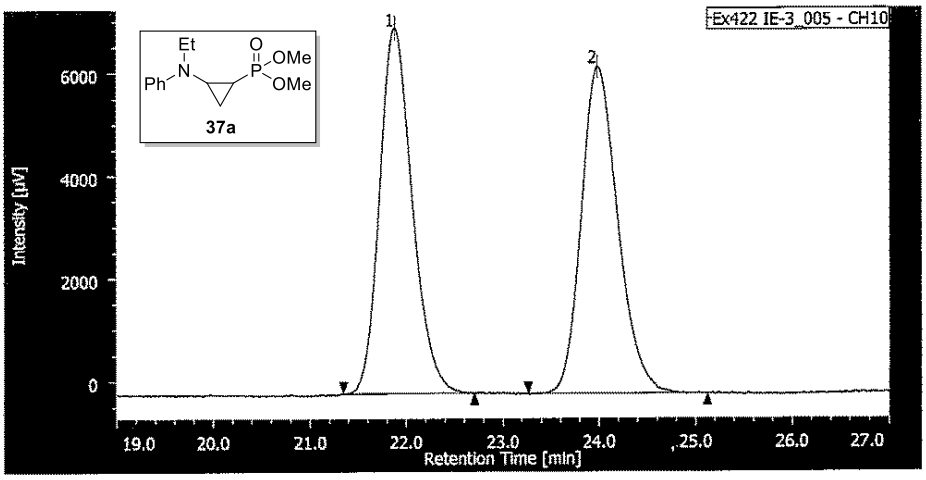

45g
abundance
X : parts per Million : Proton


45g
abundance
X : parts per Million : Carbon13


45h
abundance
X : parts per Million : Proton
7.27892
7.21166
7.10009
2.41094
2.40470
2.37795
2.37031
2.36725
2.36100
2.35922
2.35426
2.34570
2.34356
1.62824
1.62595
1.61960
1.61067
1.59997
1.59677
1.35236
1.34777
1.34472
1.34157
1.33631
1.33173
1.32733
1.19416

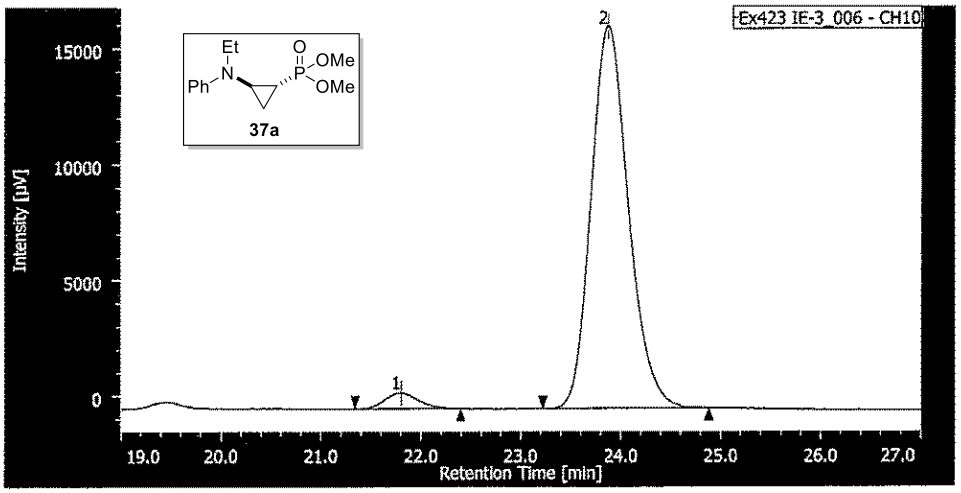

45h
abundance
X : parts per Million : Carbon13
213.614
140.684
128.566
126.506
126.344
44.108
29.787
29.206
27.814
26.307
18.565

HPLC



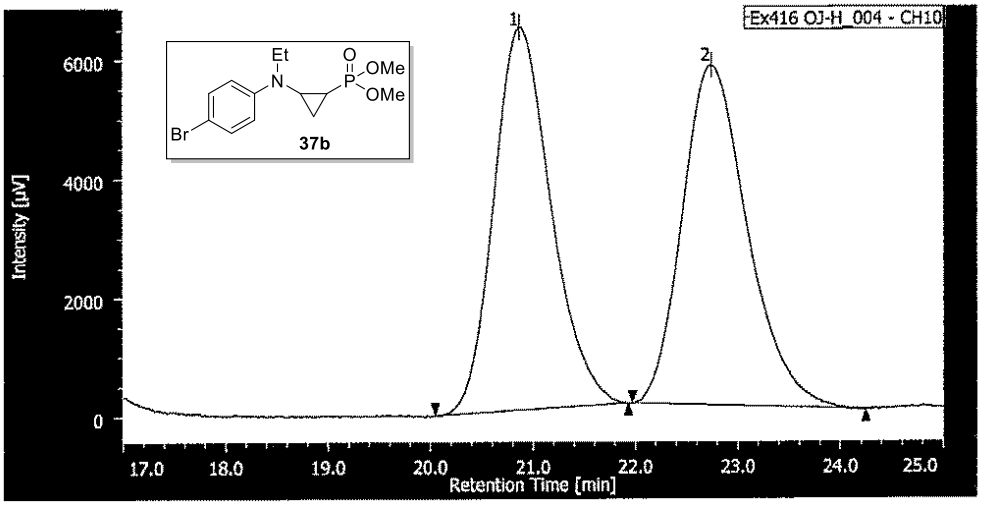
判定式

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	21.880	168162	7117	50.054	52.842	N/A	20402	3.247	1.187	
2	Unknown	10	23.982	167802	6351	49.946	47.158	N/A	19587	N/A	1.225	

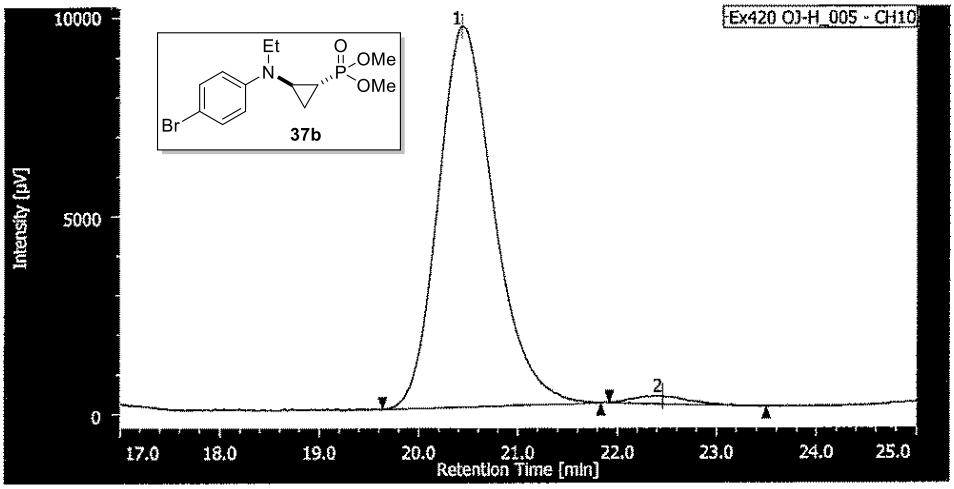


判定式

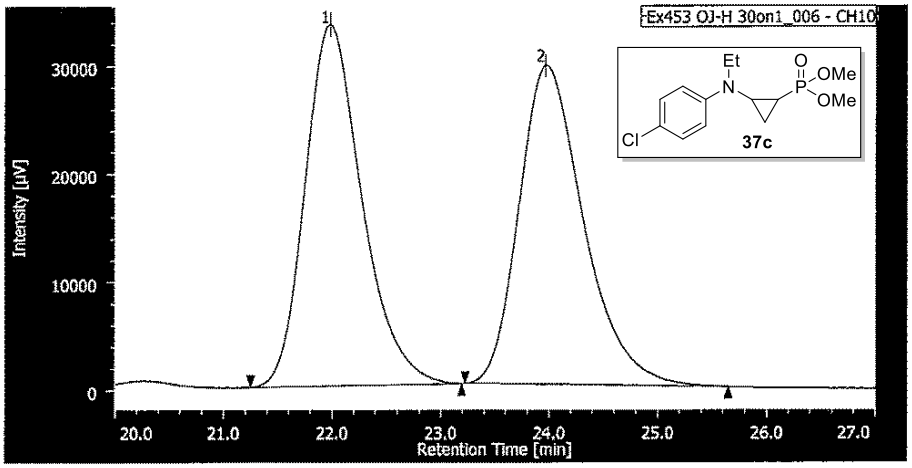
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	21.802	15748	685	3.547	3.994	N/A	20981	3.247	1.198	
2	Unknown	10	23.870	428259	16467	96.453	96.006	N/A	19998	N/A	1.207	



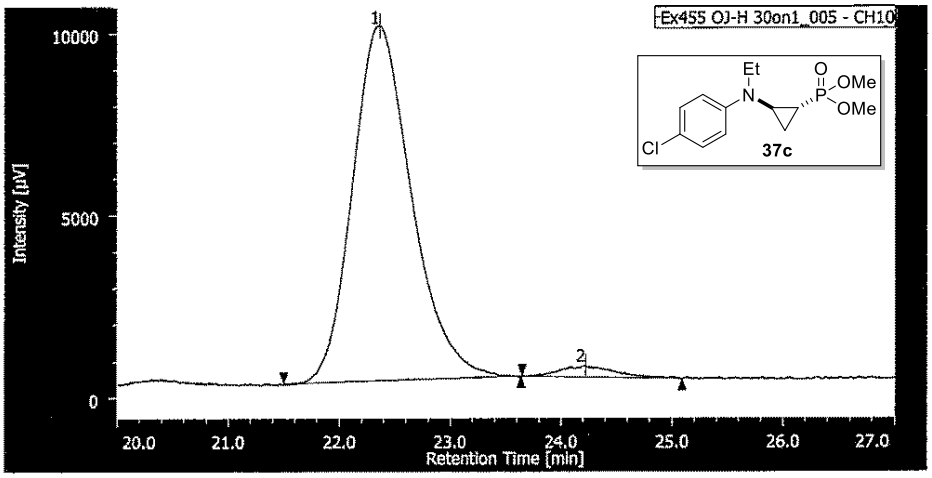
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	20.860	250341	6439	49.870	52.995	N/A	6728	1.736	1.221	
2	Unknown	10	22.738	251645	5711	50.130	47.005	N/A	6221	N/A	1.255	



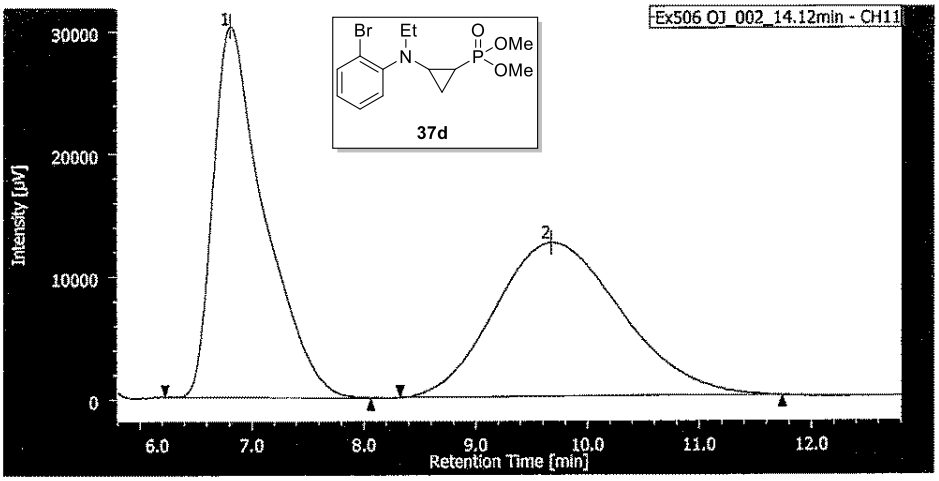
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	20.428	378034	9618	98.007	97.853	N/A	6576	2.071	1.289	
2	Unknown	10	22.455	7687	211	1.993	2.147	N/A	8849	N/A	1.457	



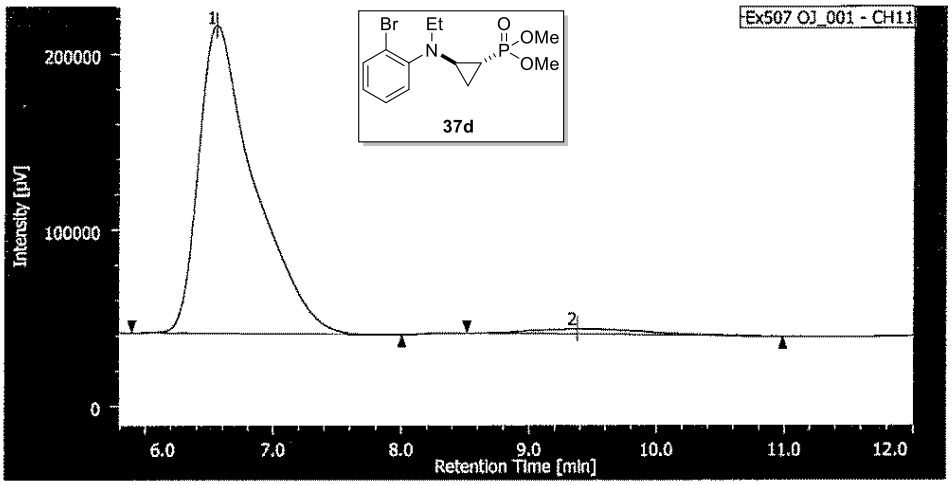
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	21.978	1220375	33463	49.968	53.114	N/A	8762	1.992	1.273	
2	Unknown	10	23.965	1221941	29540	50.032	46.886	N/A	8163	N/A	1.349	



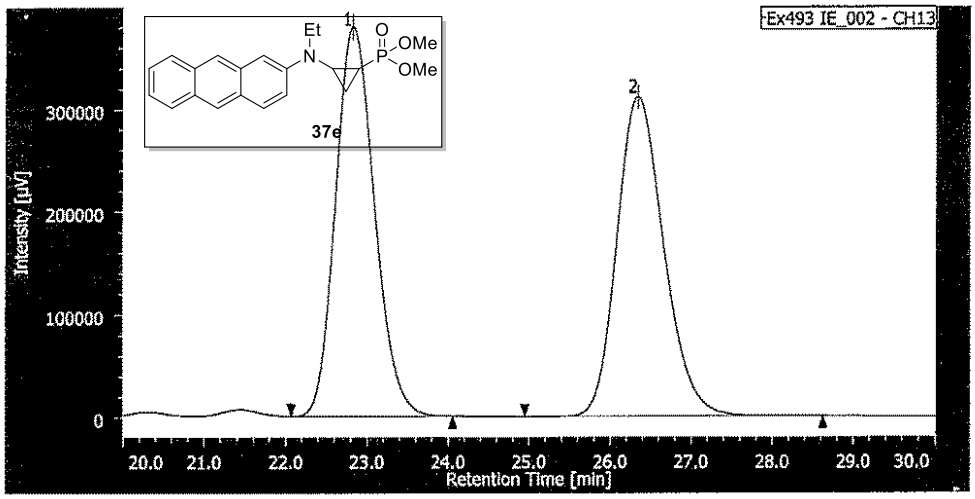
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	22.362	360472	9740	97.206	96.934	N/A	8798	2.010	1.217	
2	Unknown	10	24.222	10362	308	2.794	3.066	N/A	11529	N/A	1.306	



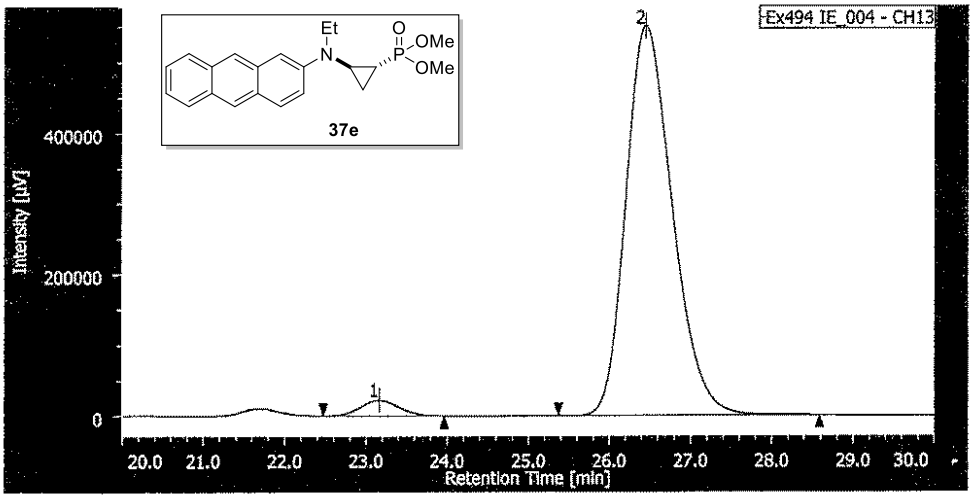
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	11	6.803	959854	30257	49.296	70.697	N/A	1190	1.992	1.791	
2	Unknown	11	9.672	987261	12541	50.704	29.303	N/A	340	N/A	1.192	



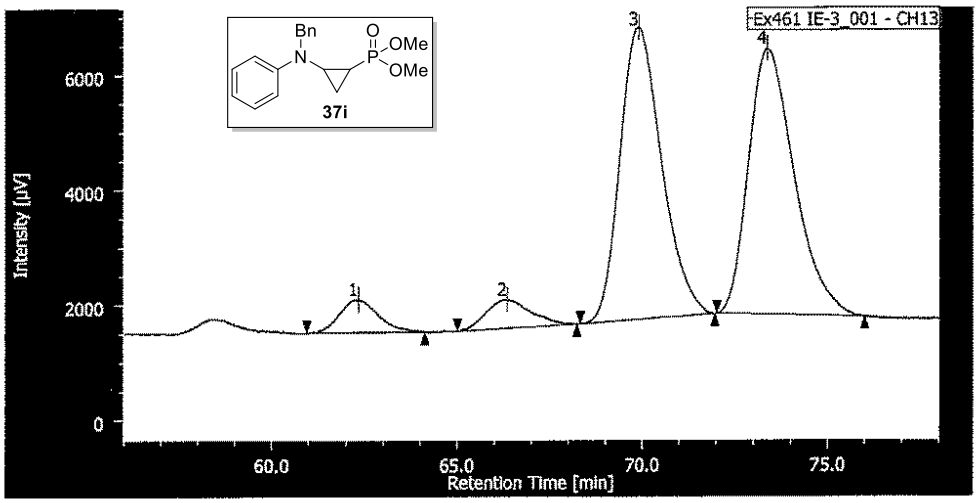
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	11	6.553	5274957	174638	96.590	98.282	N/A	1249	2.345	1.824	
2	Unknown	11	9.377	186208	3052	3.410	1.718	N/A	503	N/A	1.282	



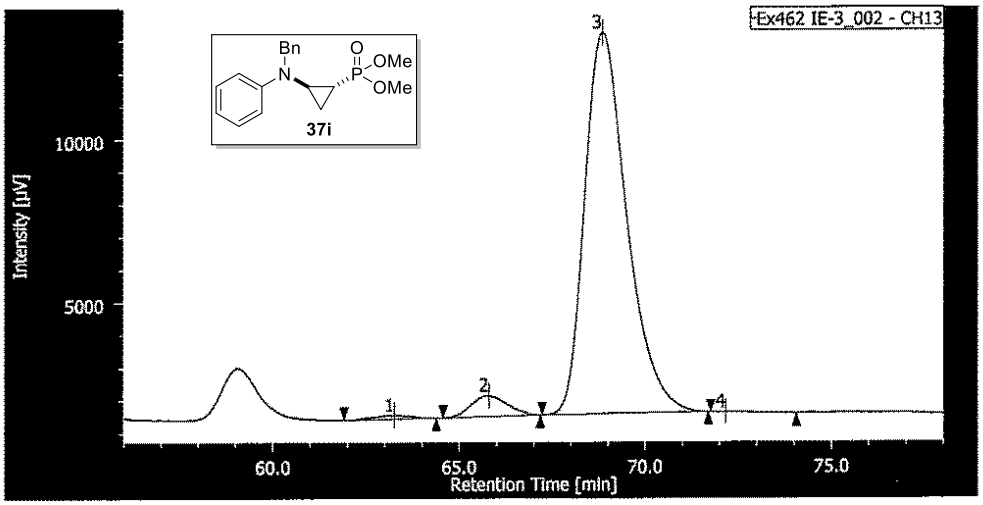
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	13	22.823	12581392	379336	50.024	54.906	N/A	10953	3.661	1.201	
2	Unknown	13	26.340	12569500	311544	49.976	45.094	N/A	9996	N/A	1.209	



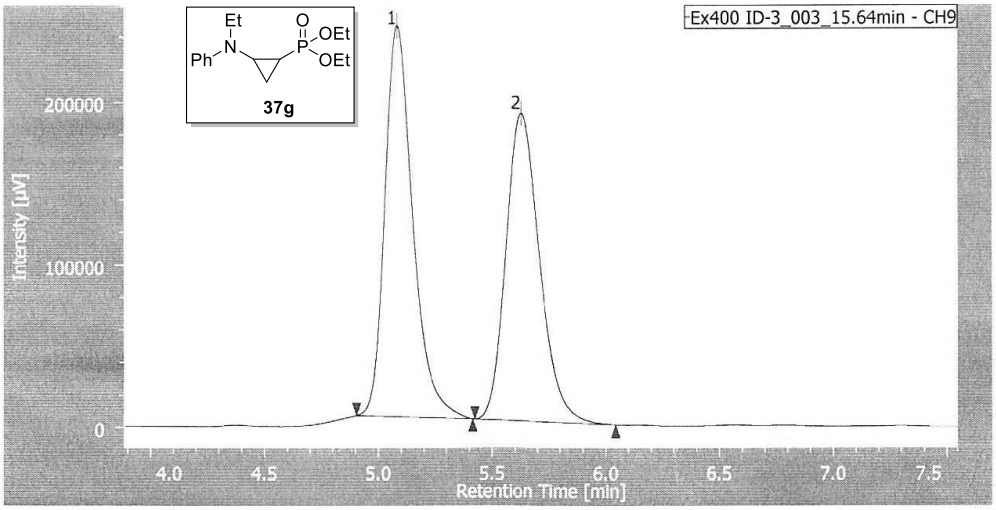
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	13	23.163	709595	21859	3.151	3.819	N/A	11614	3.477	1.082	
2	Unknown	13	26.448	21806663	550491	96.849	96.181	N/A	10455	N/A	1.265	



#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	13	62.330	41194	578	4.706	5.363	N/A	17642	1.967	1.247	
2	Unknown	13	66.348	41691	498	4.762	4.617	N/A	14286	1.660	1.219	
3	Unknown	13	69.898	398590	5078	45.532	47.126	N/A	18295	1.619	1.235	
4	Unknown	13	73.362	393935	4622	45.000	42.894	N/A	17436	N/A	1.399	

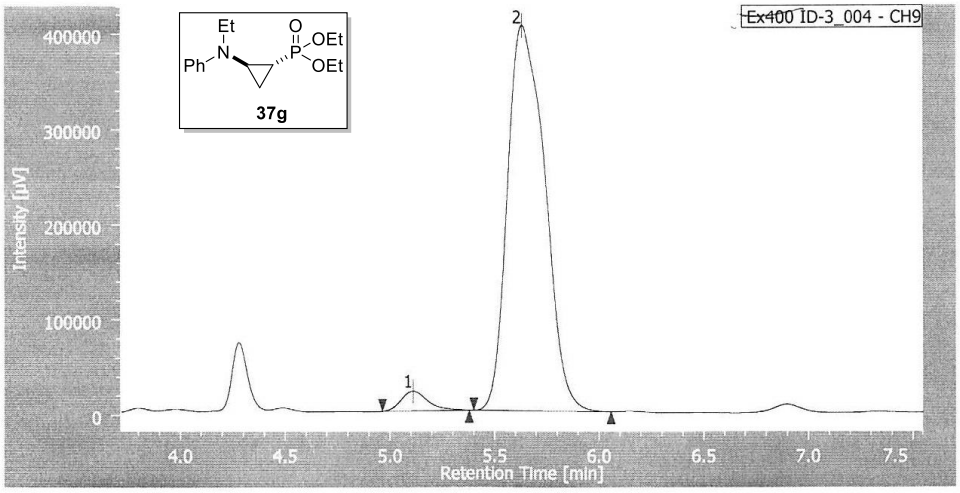


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	13	63.265	7402	123	0.764	0.988	N/A	16753	1.350	0.994	
2	Unknown	13	65.798	43615	655	4.499	5.257	N/A	21222	1.584	1.052	
3	Unknown	13	68.830	916550	11659	94.542	93.520	N/A	18373	1.238	1.405	
4	Unknown	13	72.165	1895	29	0.195	0.235	N/A	7328	N/A	2.903	



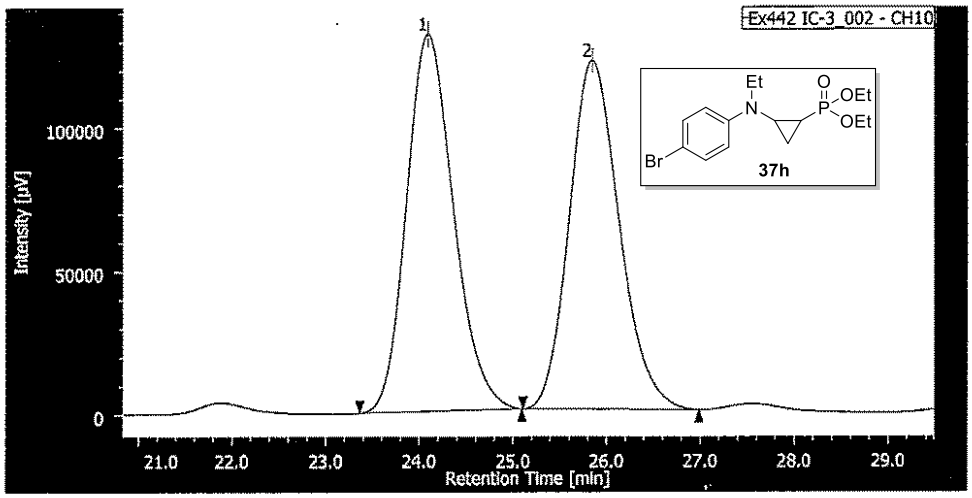
判定式

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	9	5.083	2056856	240401	51.291	55.959	N/A	8836	2.254	1.322	
2	Unknown	9	5.628	1953285	189201	48.709	44.041	N/A	7029	N/A	1.218	



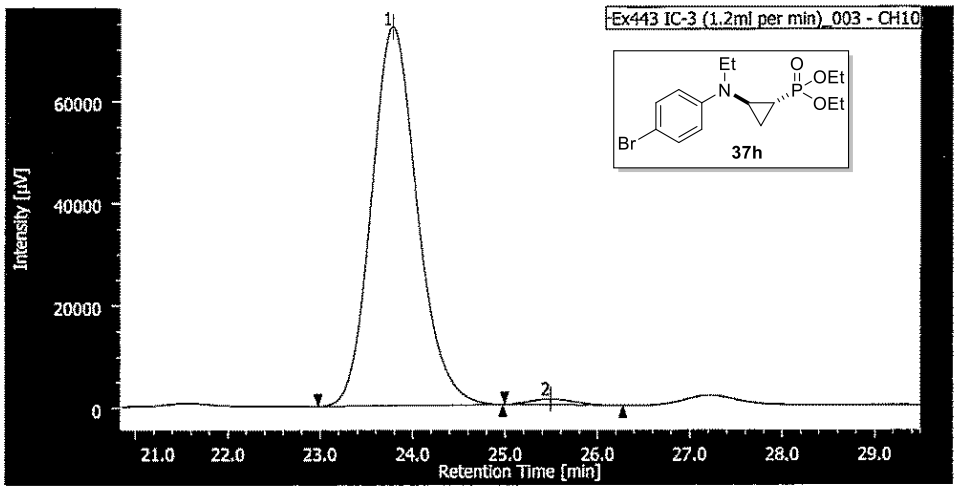
判定式

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	9	5.110	186995	20825	3.563	4.897	N/A	8042	1.815	1.411	
2	Unknown	9	5.632	5061913	404406	96.437	95.103	N/A	4179	N/A	1.274	

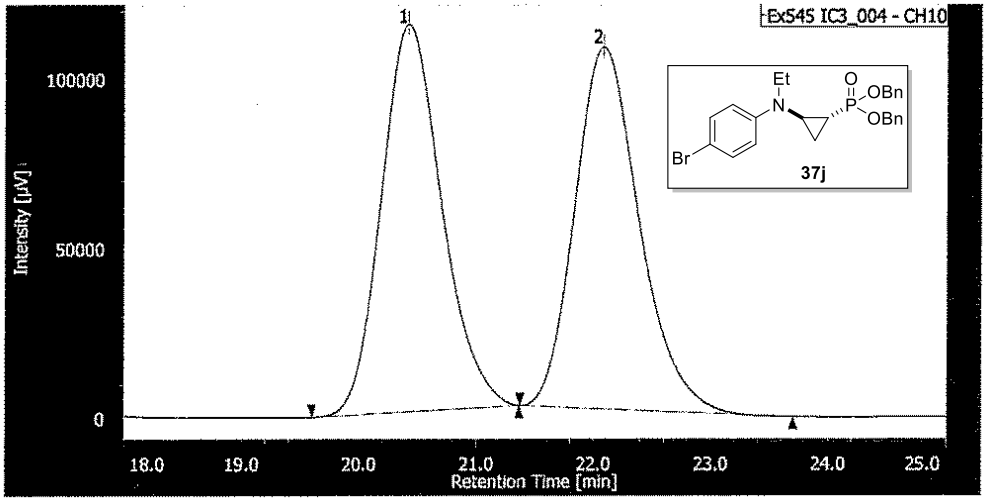


判定式

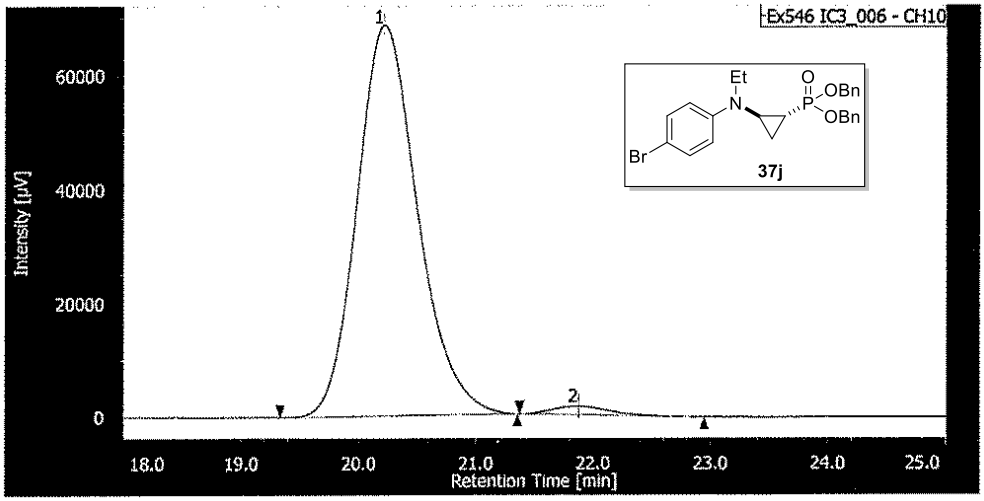
#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	24.086	4554420	131322	50.258	51.916	N/A	11329	1.880	1.195	
2	Unknown	10	25.845	4507681	121628	49.742	48.084	N/A	11389	N/A	1.193	



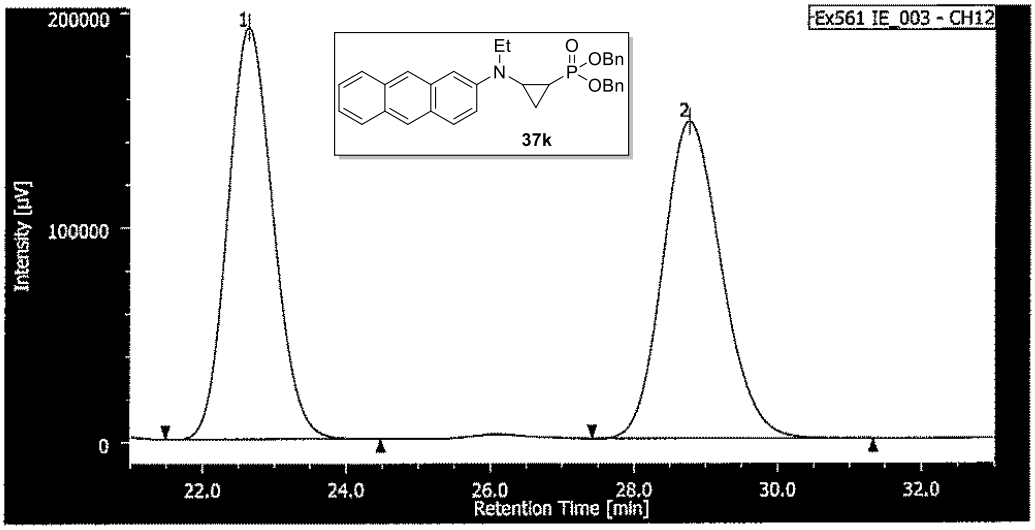
#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	23.777	2550852	73978	98.619	98.536	N/A	11327	1.933	1.185	
2	Unknown	10	25.488	35733	1099	1.381	1.464	N/A	13368	N/A	1.175	



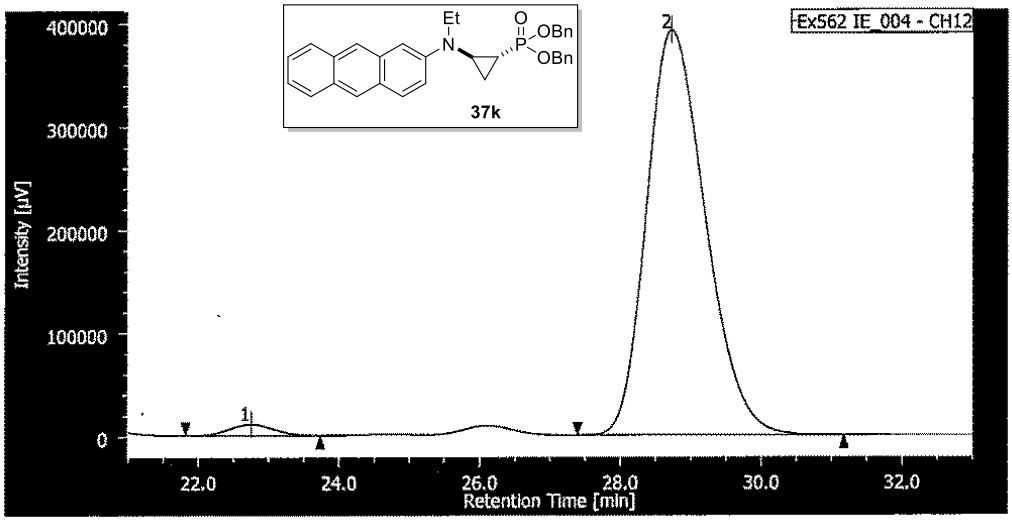
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	20.422	4085862	114309	50.083	51.703	N/A	7649	1.735	1.193	
2	Unknown	10	22.085	4072257	106779	49.917	48.297	N/A	7980	N/A	1.239	



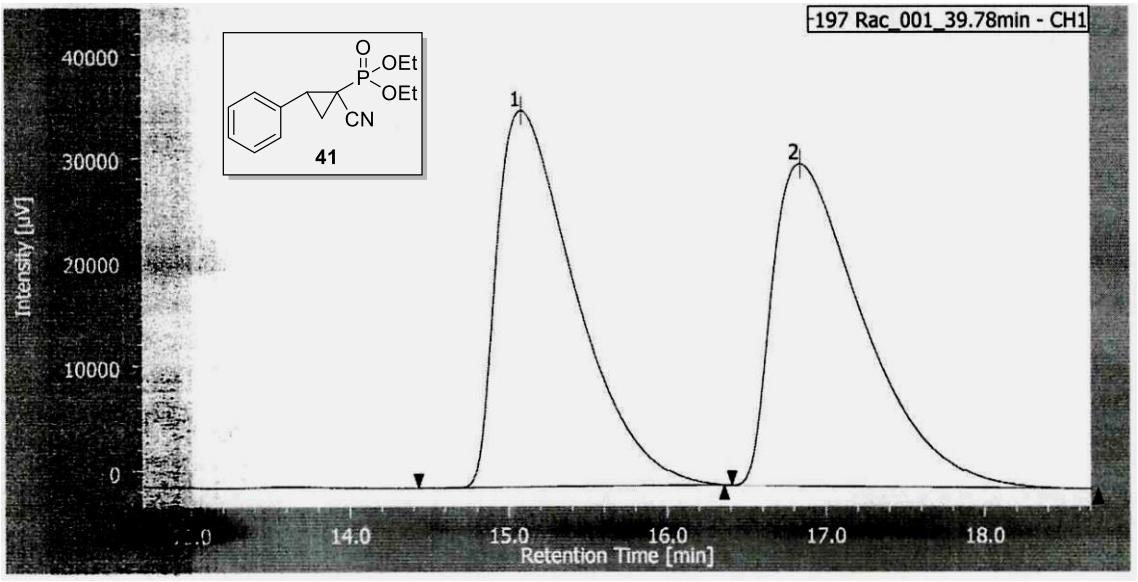
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	10	20.217	2465056	68664	98.069	97.855	N/A	7573	1.841	1.213	
2	Unknown	10	21.873	48529	1505	1.931	2.145	N/A	9989	N/A	1.157	



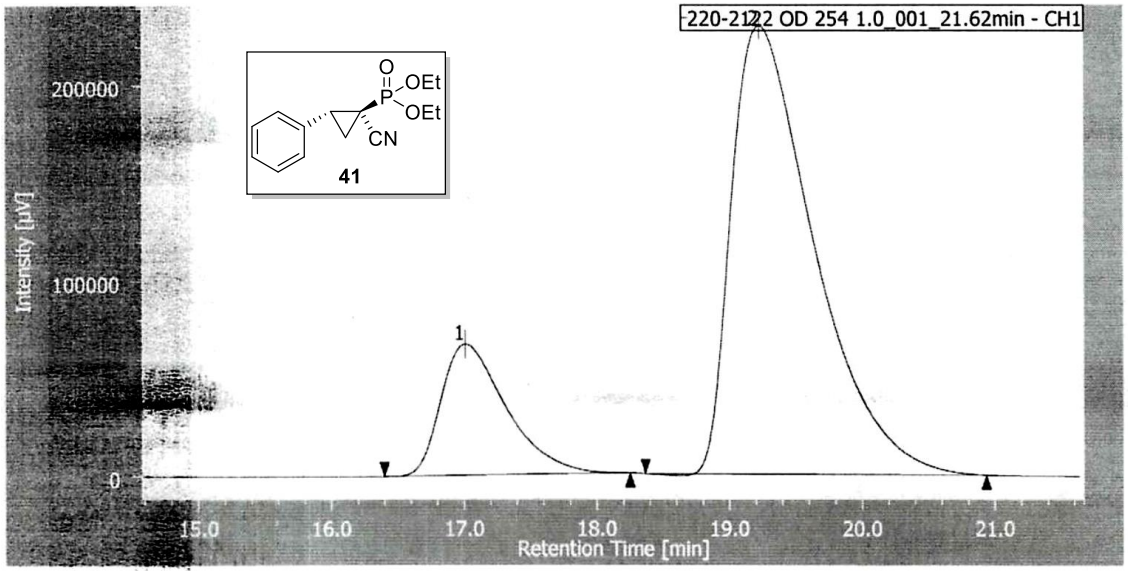
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	12	22.637	8362082	191467	49.948	56.476	N/A	6178	4.644	1.151	
2	Unknown	12	28.770	8379492	147555	50.052	43.524	N/A	5915	N/A	1.163	



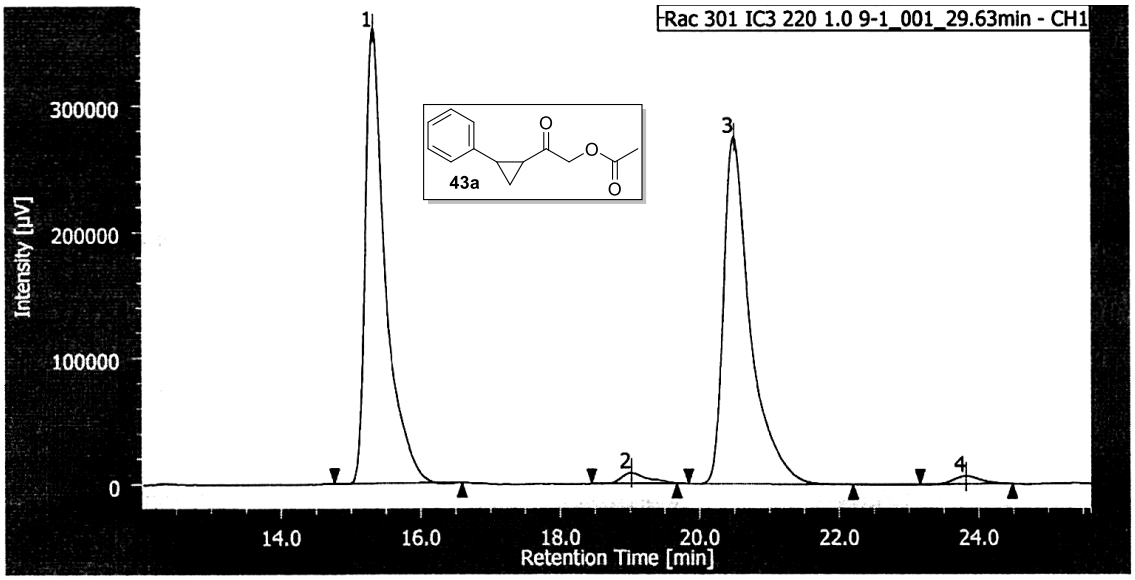
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	12	22.752	477682	10899	2.069	2.705	N/A	6059	4.456	1.062	
2	Unknown	12	28.725	22614030	392033	97.931	97.295	N/A	5721	N/A	1.269	



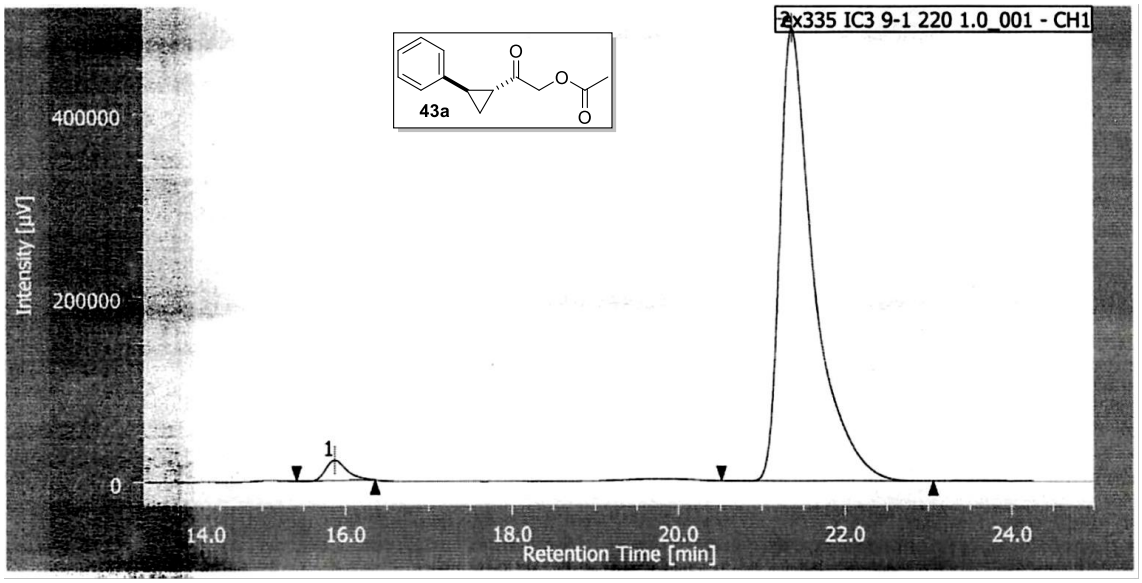
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.083	1242995	36064	50.230	53.924	N/A	4488	1.819	2.062	
2	Unknown	1	16.842	1231635	30815	49.770	46.076	N/A	4215	N/A	2.130	



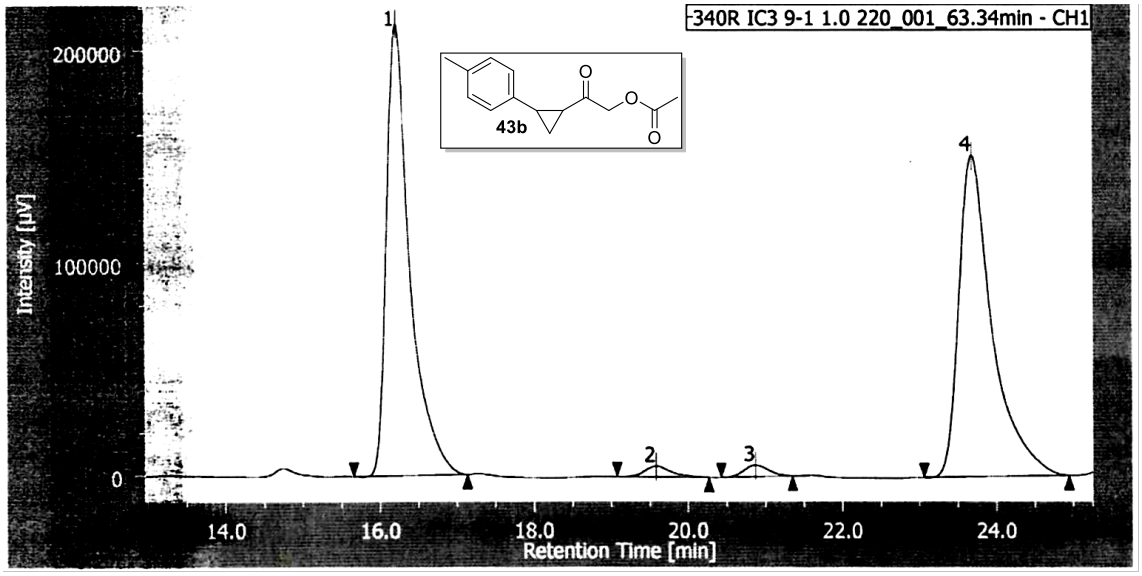
#	ピーク名	CH	tR [min]	面積 [μV sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	17.008	2281175	67175	18.675	22.638	N/A	5985	2.221	1.584	
2	Unknown	1	19.225	9934120	229556	89.325	77.362	N/A	4700	N/A	1.891	



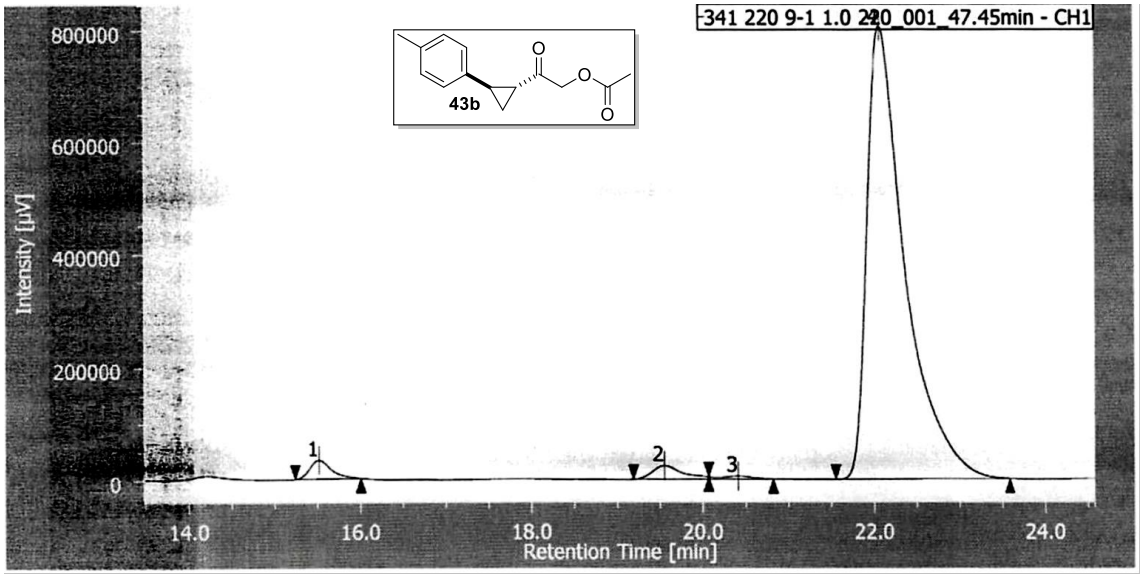
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.325	7172217	360628	48.387	55.556	N/A	17472	6.913	1.757	
2	Unknown	1	19.017	215586	8368	1.454	1.289	N/A	15699	2.418	1.494	
3	Unknown	1	20.500	7265714	273959	49.017	42.204	N/A	17324	5.021	1.697	
4	Unknown	1	23.817	169225	6170	1.142	0.950	N/A	18441	N/A	1.282	



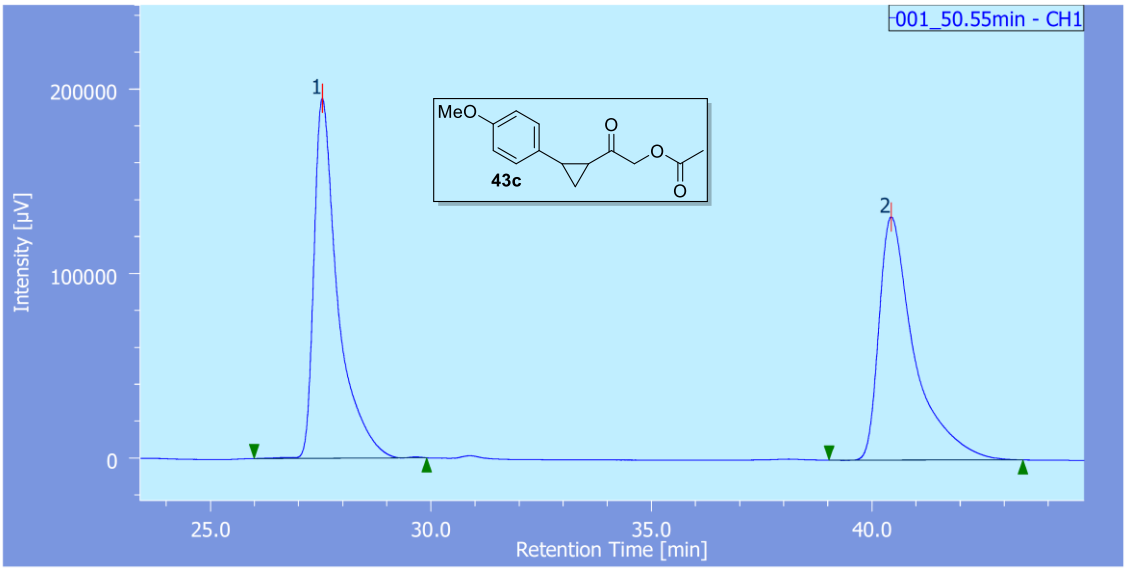
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.875	390979	22072	2.725	4.290	N/A	20071	9.878	1.358	
2	Unknown	1	21.375	13958692	492434	97.275	95.710	N/A	16368	N/A	1.797	



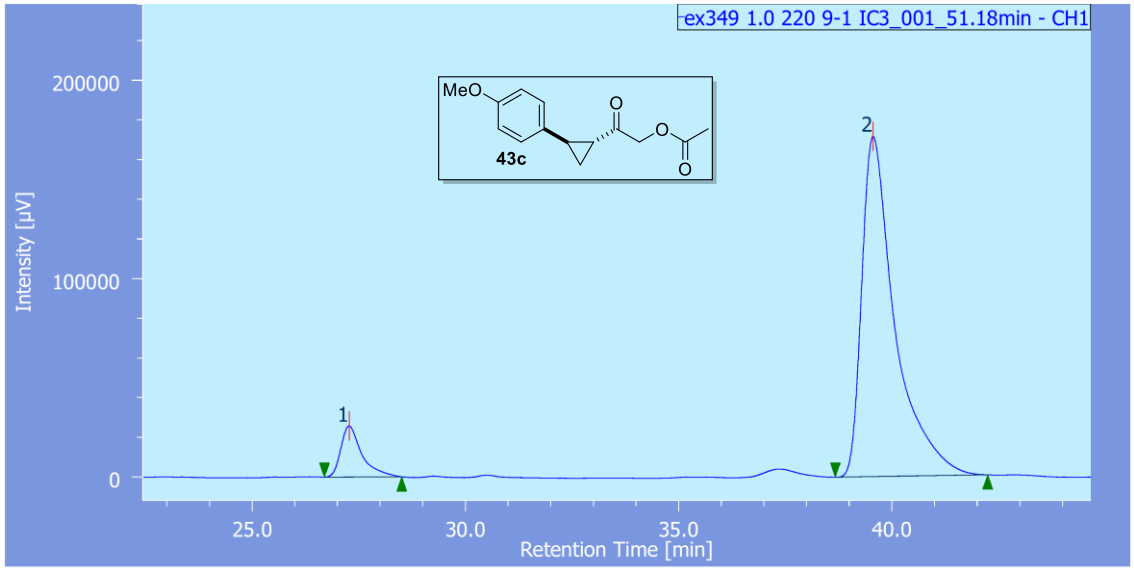
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	16.208	4483471	212432	48.455	56.869	N/A	16789	6.166	1.701	
2	Unknown	1	19.575	120567	5049	1.303	1.352	N/A	17341	2.179	1.329	
3	Unknown	1	20.867	122276	5474	1.321	1.466	N/A	19747	4.312	1.143	
4	Unknown	1	23.683	4526621	150588	48.921	40.313	N/A	17514	N/A	1.686	



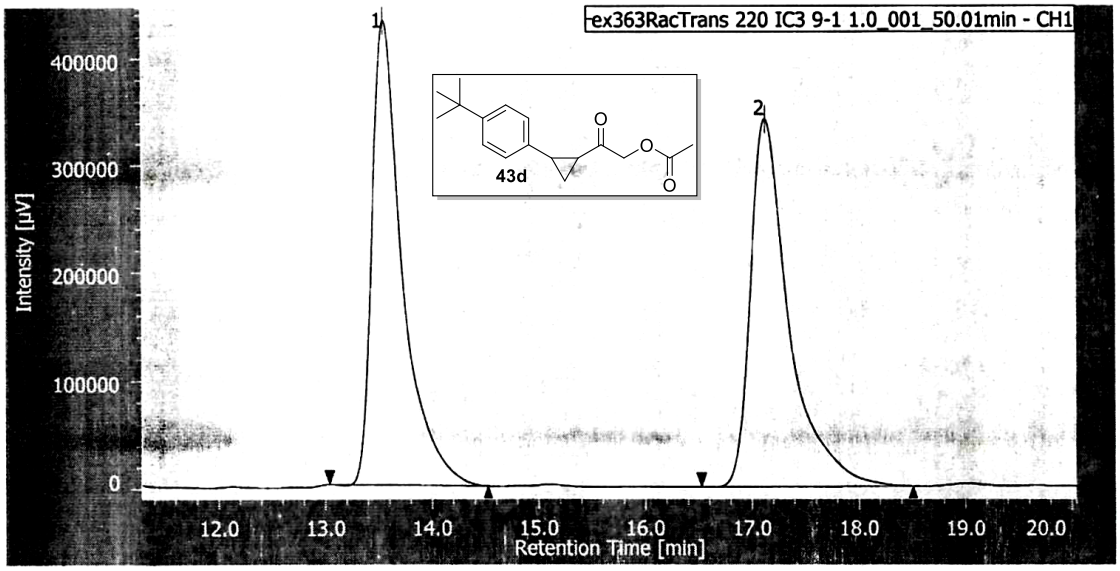
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.517	585081	33321	2.239	3.848	N/A	19786	7.938	1.408	
2	Unknown	1	19.550	581930	24167	2.227	2.791	N/A	18327	N/A	N/A	
3	Unknown	1	20.408	125758	5068	0.481	0.585	N/A	N/A	N/A	N/A	
4	Unknown	1	22.075	24835490	803376	95.052	92.776	N/A	14198	N/A	1.984	



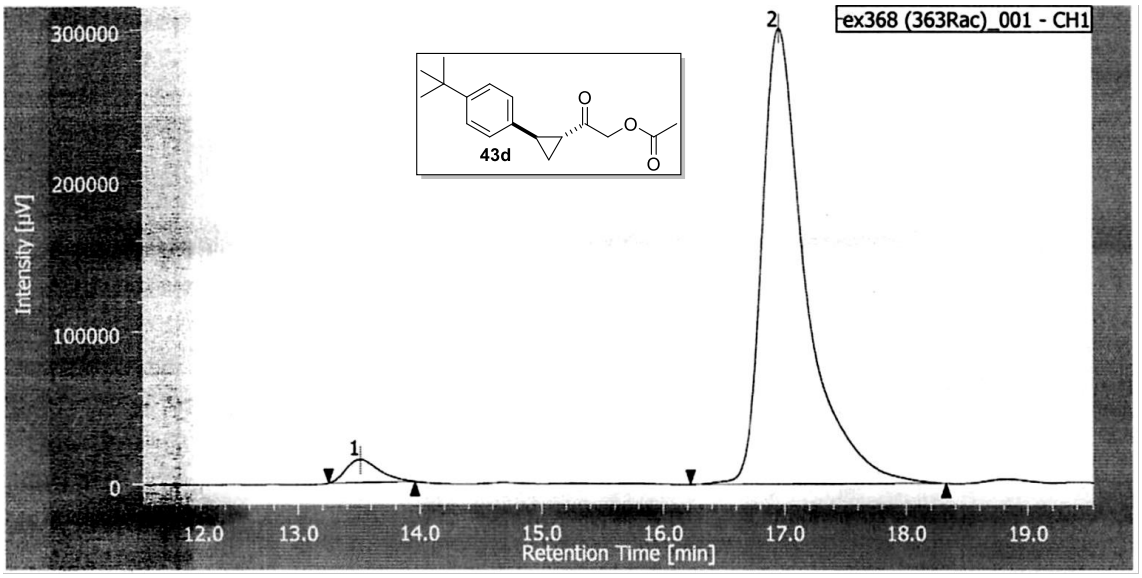
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	27.542	7327479	195048	49.946	59.683	N/A	16225	12.032	1.944	
2	Unknown	1	40.433	7343388	131758	50.054	40.317	N/A	15872	N/A	2.012	



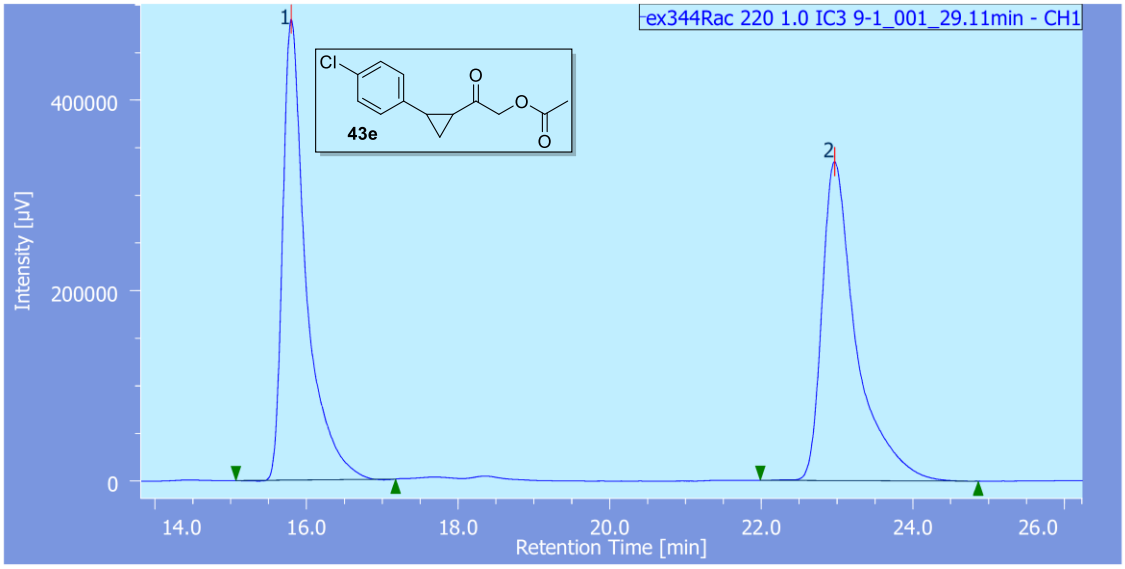
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	27.275	878271	25695	8.664	13.044	N/A	18080	11.901	1.647	
2	Unknown	1	39.550	9258798	171296	91.336	86.956	N/A	15839	N/A	2.029	



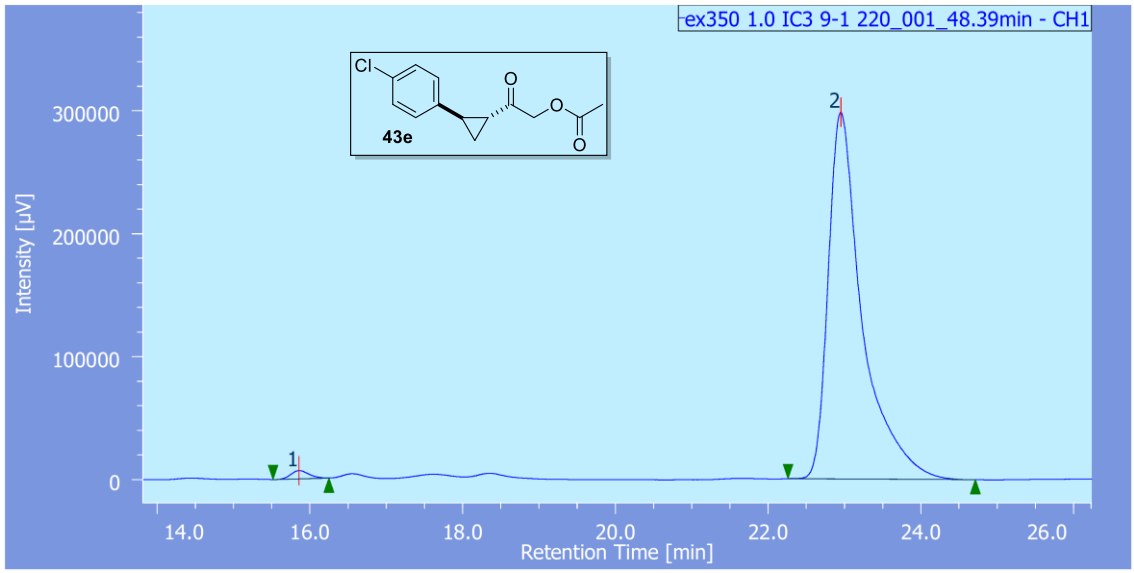
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	13.550	8495176	430230	49.898	55.837	N/A	13600	6.854	1.774	
2	Unknown	1	17.133	8529755	340281	50.102	44.163	N/A	13785	N/A	1.708	



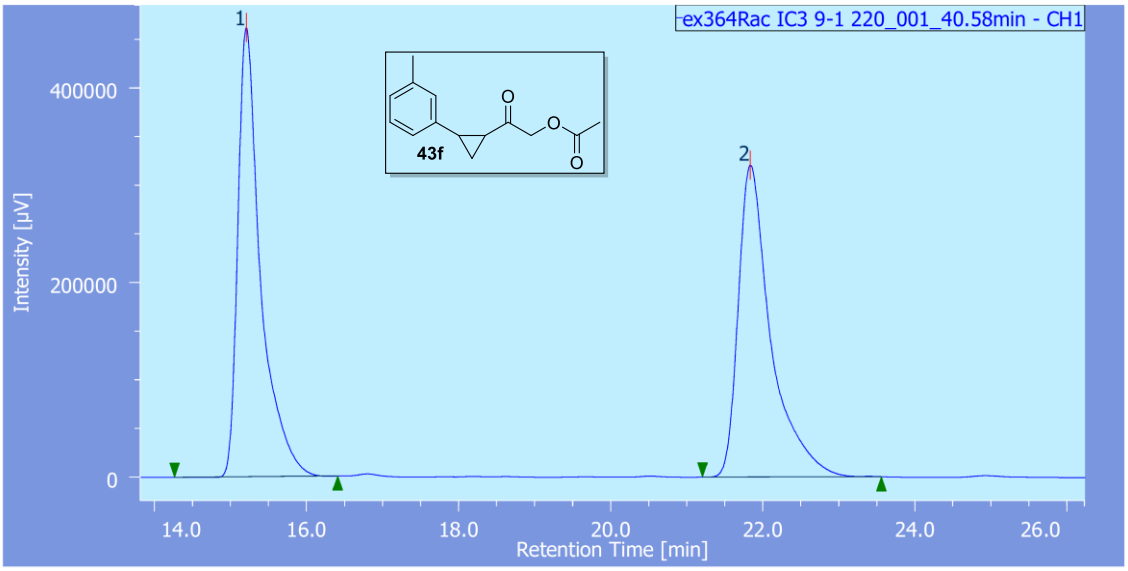
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	13.508	300918	15607	3.944	4.959	N/A	11424	6.424	1.307	
2	Unknown	1	16.958	7329062	299137	96.056	95.041	N/A	14089	N/A	1.698	



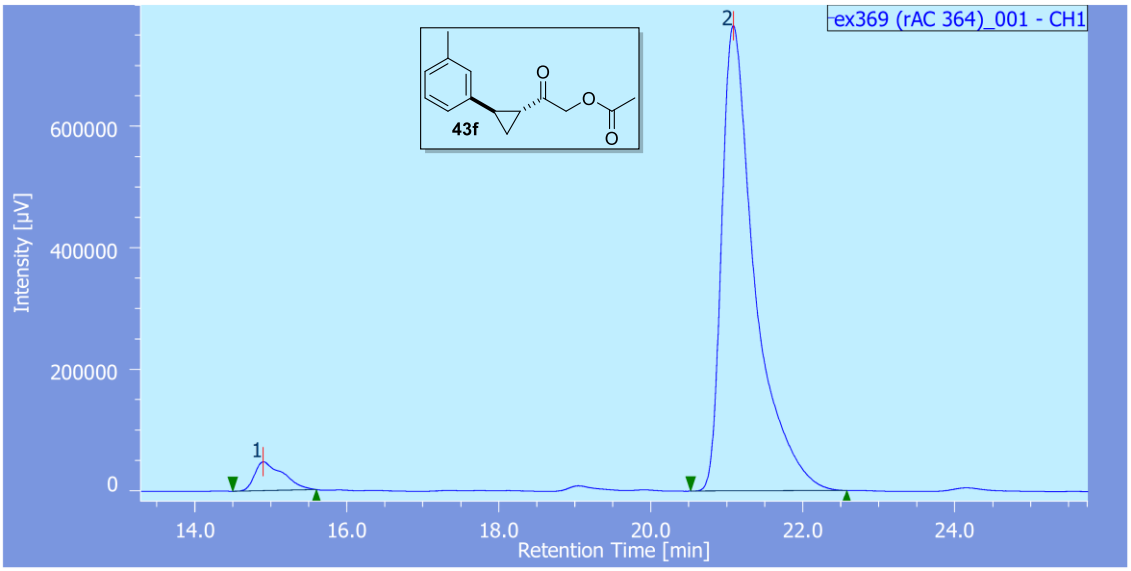
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.800	10371078	483839	49.765	59.103	N/A	16560	11.897	1.890	
2	Unknown	1	22.967	10469155	334801	50.235	40.897	N/A	16421	N/A	1.842	



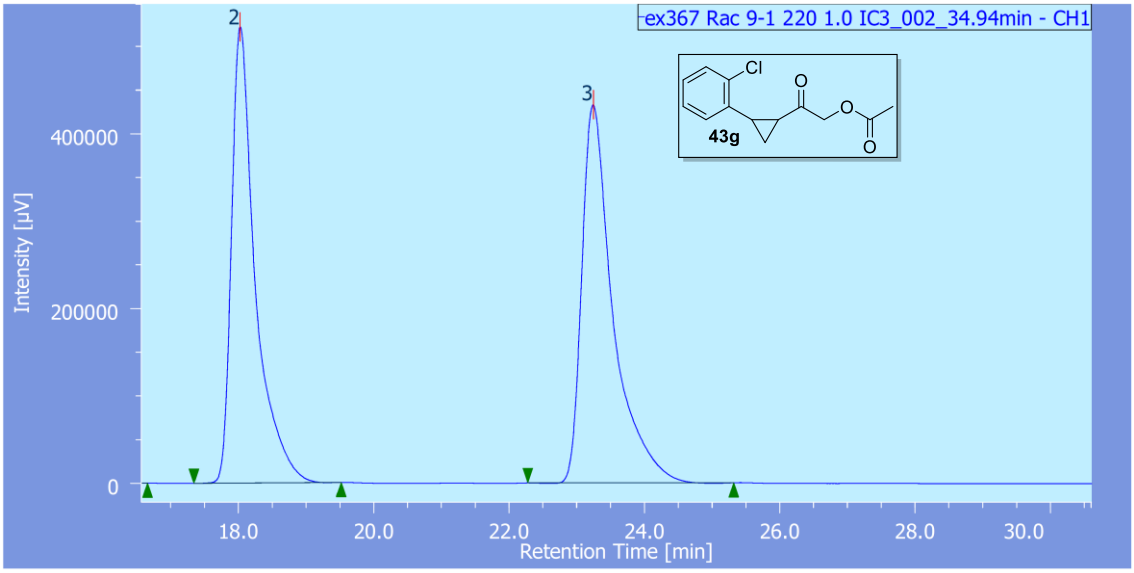
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.858	109130	6653	1.170	2.182	N/A	21304	12.435	1.195	
2	Unknown	1	22.950	9218235	298193	98.830	97.818	N/A	16762	N/A	1.826	



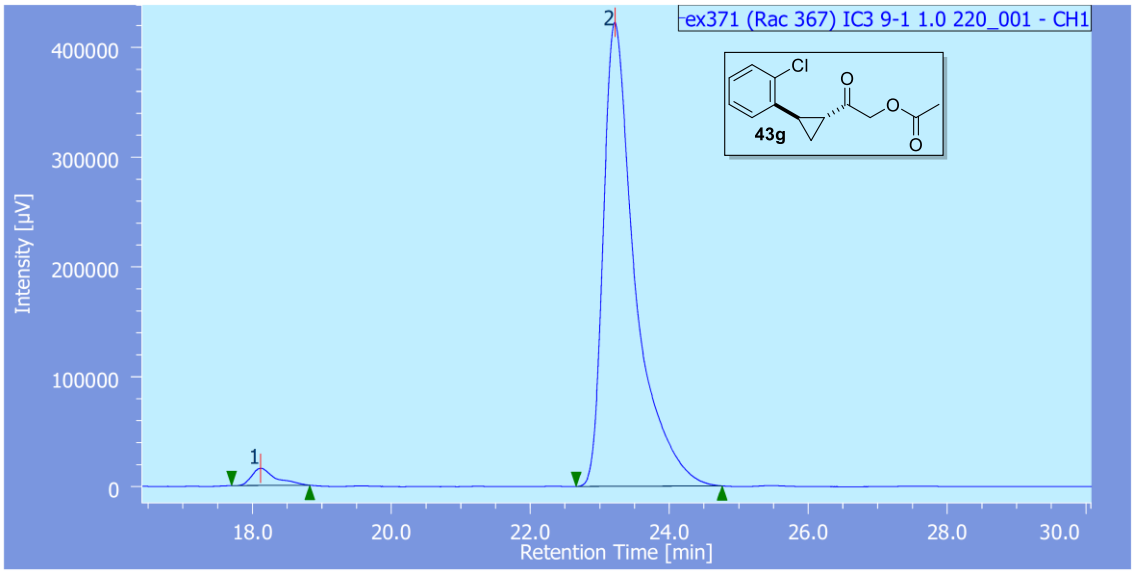
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.208	9587689	461798	50.131	59.028	N/A	16033	11.320	1.802	
2	Unknown	1	21.833	9537690	320536	49.869	40.972	N/A	15872	N/A	1.793	



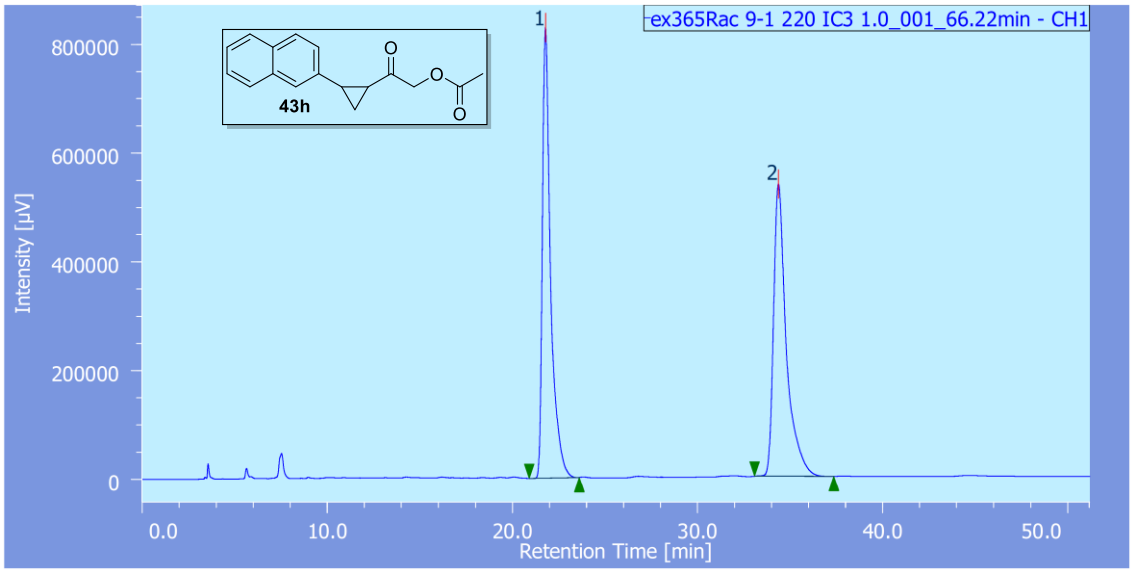
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	14.900	1216990	47456	4.994	5.840	N/A	6533	8.567	1.736	
2	Unknown	1	21.083	23151505	765185	95.006	94.160	N/A	14109	N/A	1.938	



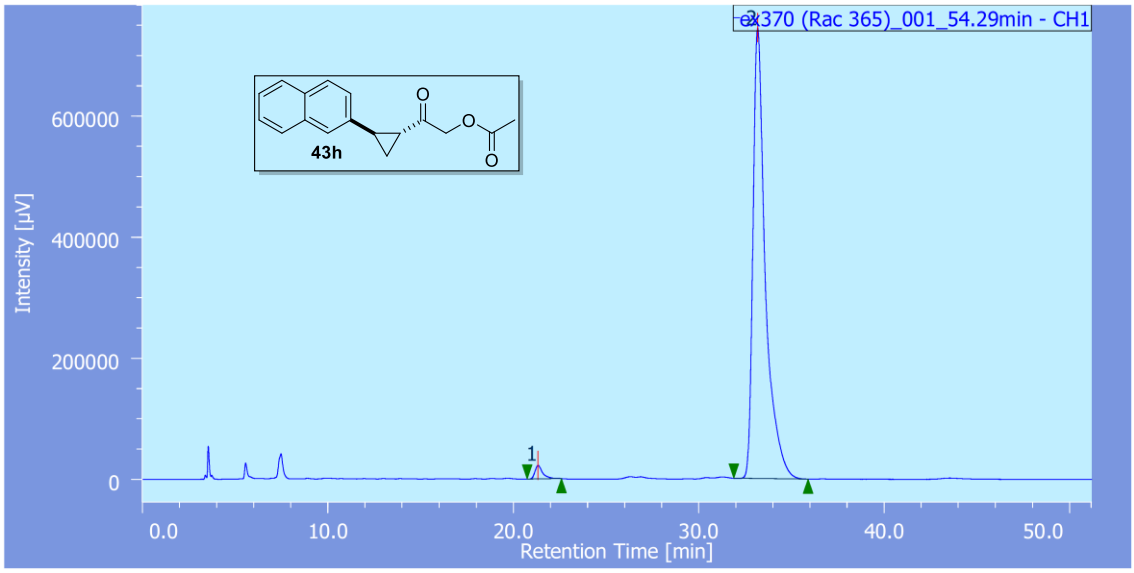
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.675	1164277	54132	4.205	5.369	N/A	15467	4.406	1.689	
2	Unknown	1	18.025	12724352	521742	45.954	51.750	N/A	16264	7.971	1.839	
3	Unknown	1	23.242	13800925	432321	49.842	42.881	N/A	15485	N/A	1.852	



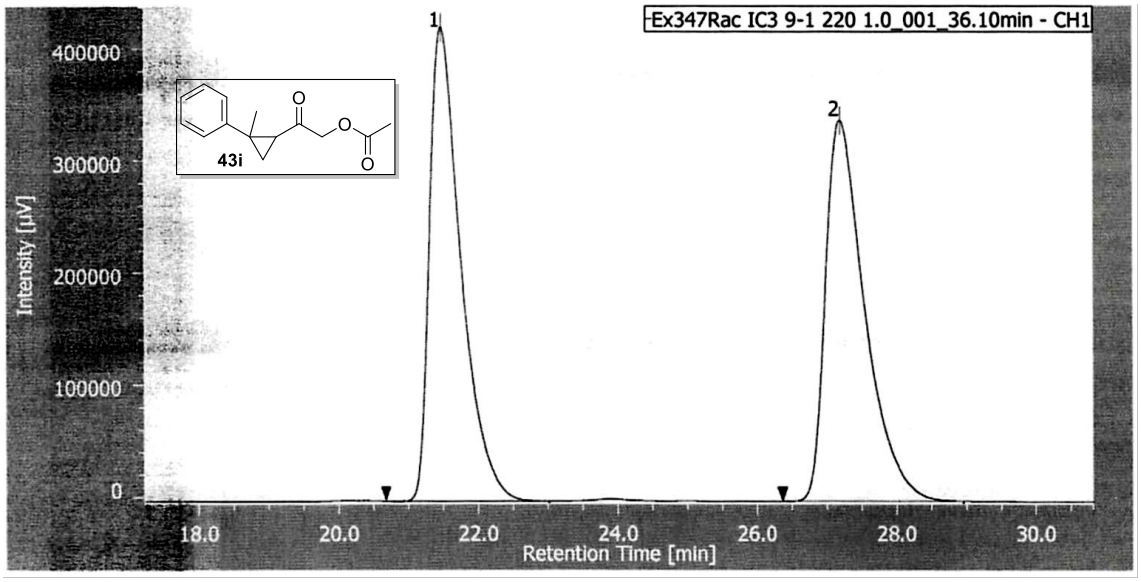
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	18.117	373391	15650	2.705	3.571	N/A	18086	7.990	1.649	
2	Unknown	1	23.217	13429662	422593	97.295	96.429	N/A	15698	N/A	1.858	



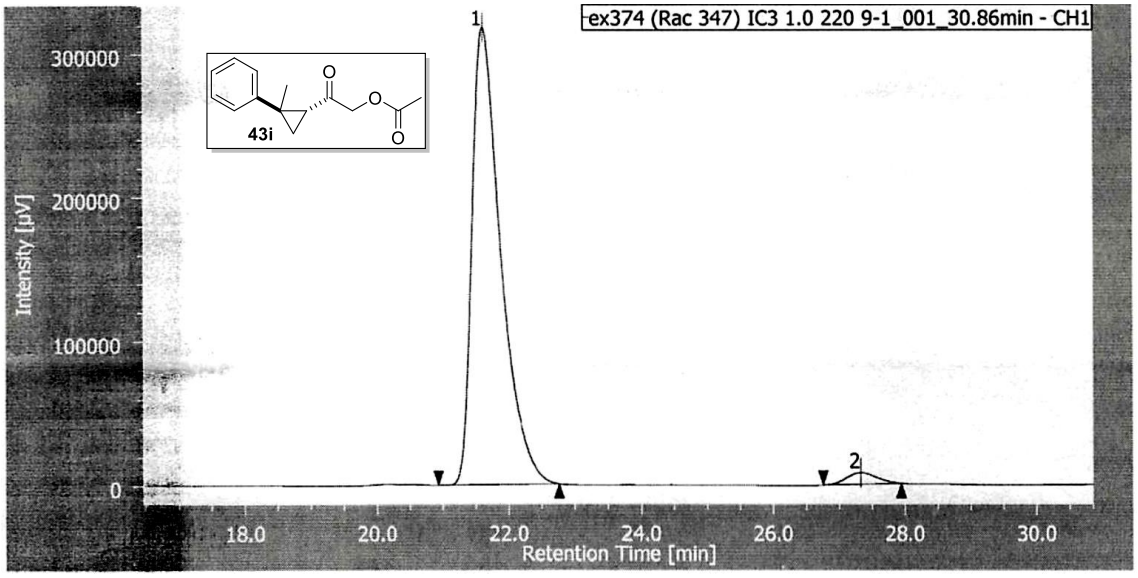
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	21.783	25572529	828137	49.795	60.662	N/A	14639	13.708	1.785	
2	Unknown	1	34.358	25783233	537038	50.205	39.338	N/A	15074	N/A	1.757	



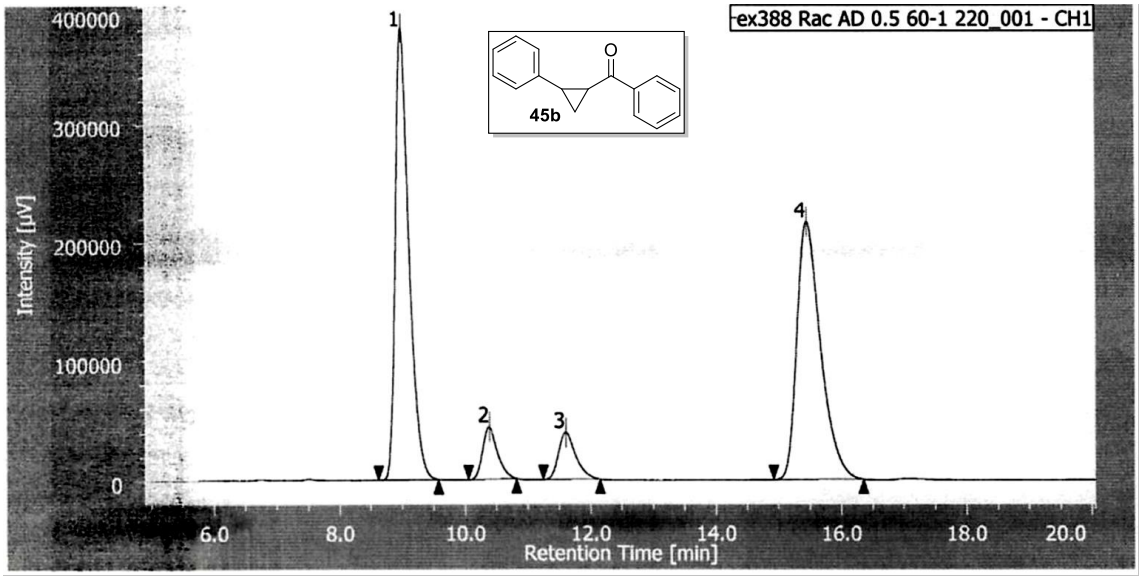
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	21.325	655718	22575	1.859	2.943	N/A	15761	13.473	1.594	
2	Unknown	1	33.167	34621129	744525	98.141	97.057	N/A	15002	N/A	1.765	



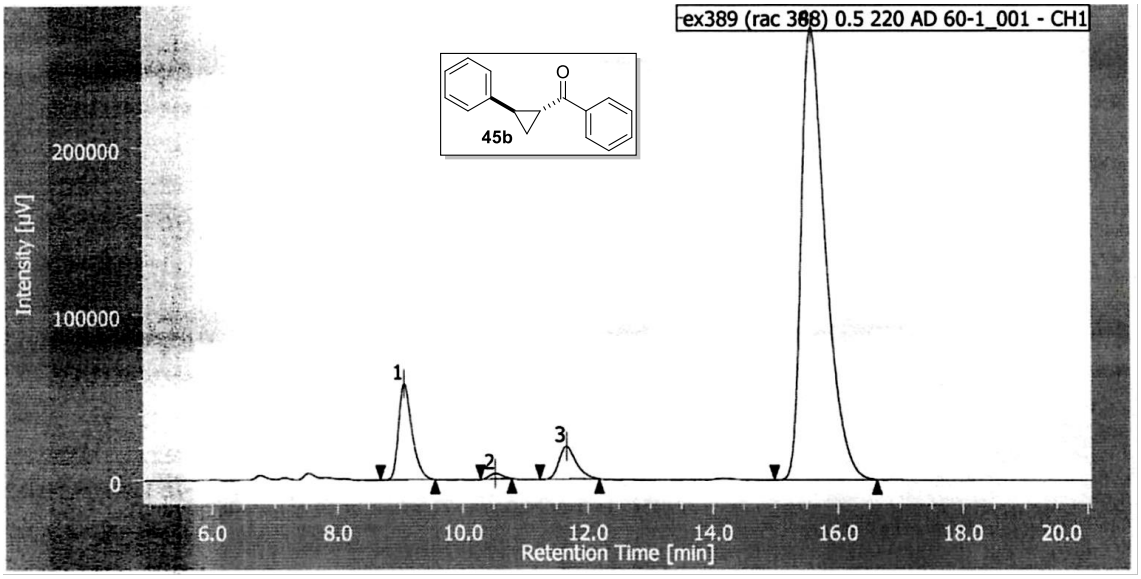
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	21.475	13184794	422568	49.934	55.490	N/A	11761	6.431	1.687	
2	Unknown	1	27.192	13219703	338958	50.066	44.510	N/A	12060	N/A	1.644	



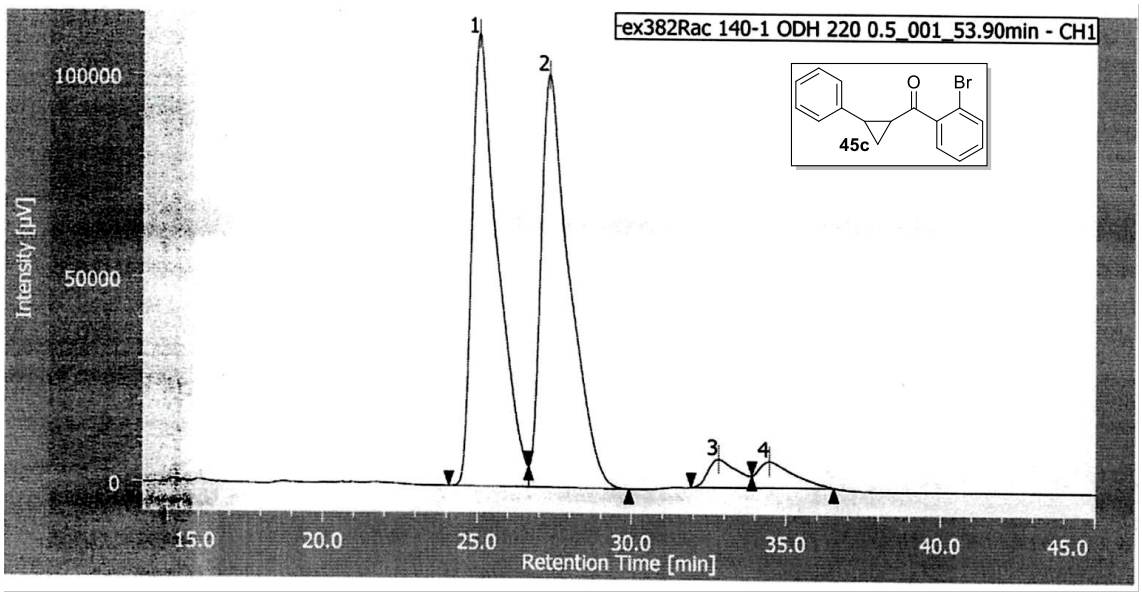
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	21.617	9605431	317631	97.429	97.543	N/A	12734	7.061	1.620	
2	Unknown	1	27.325	253484	8000	2.571	2.457	N/A	16345	N/A	1.105	



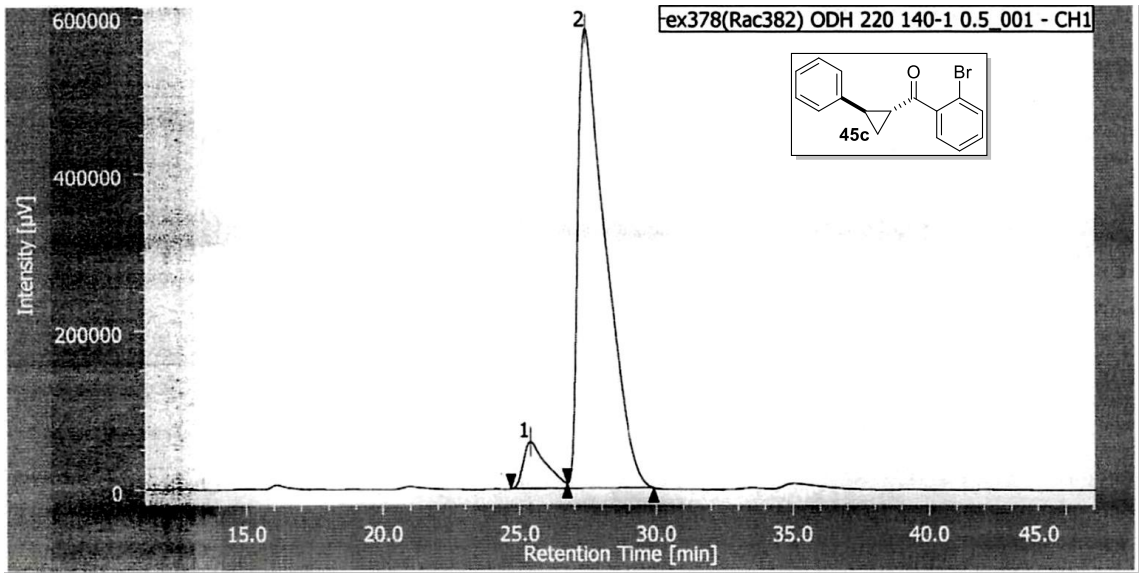
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	8.992	5706749	380758	44.196	55.941	N/A	8902	3.411	1.388	
2	Unknown	1	10.383	751181	43976	5.818	6.461	N/A	9031	2.628	1.307	
3	Unknown	1	11.600	765047	39549	5.925	5.810	N/A	8922	6.635	1.379	
4	Unknown	1	15.450	5689255	216361	44.061	31.788	N/A	8448	N/A	1.413	



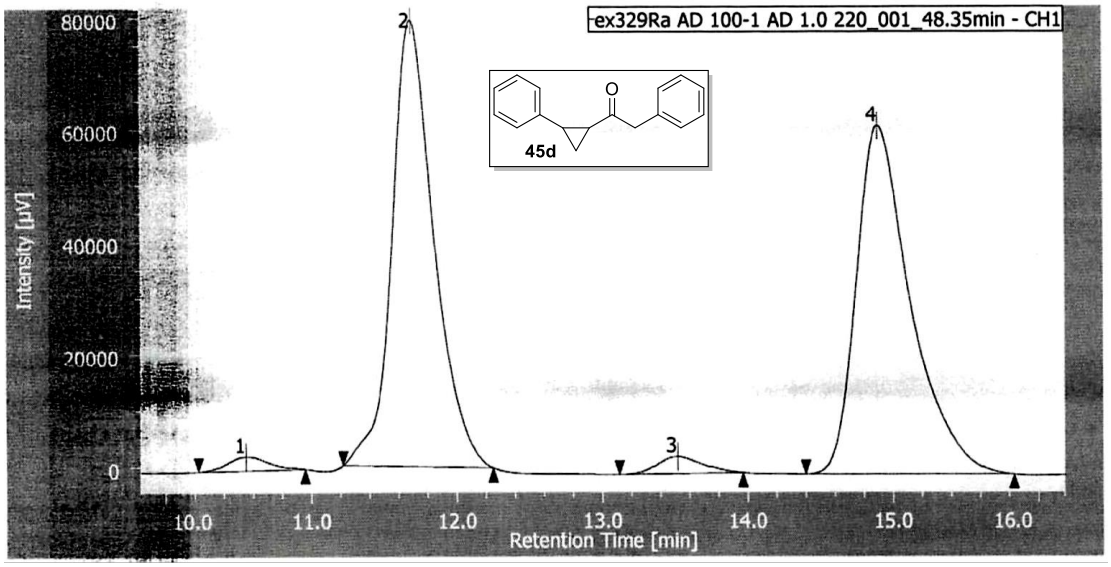
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	9.067	848260	57620	9.849	16.300	N/A	9228	3.624	1.345	
2	Unknown	1	10.525	58198	3595	0.676	1.017	N/A	9607	2.477	1.270	
3	Unknown	1	11.658	383539	19832	4.453	5.610	N/A	9132	6.692	1.370	
4	Unknown	1	15.583	7322884	272449	85.022	77.073	N/A	8205	N/A	1.465	



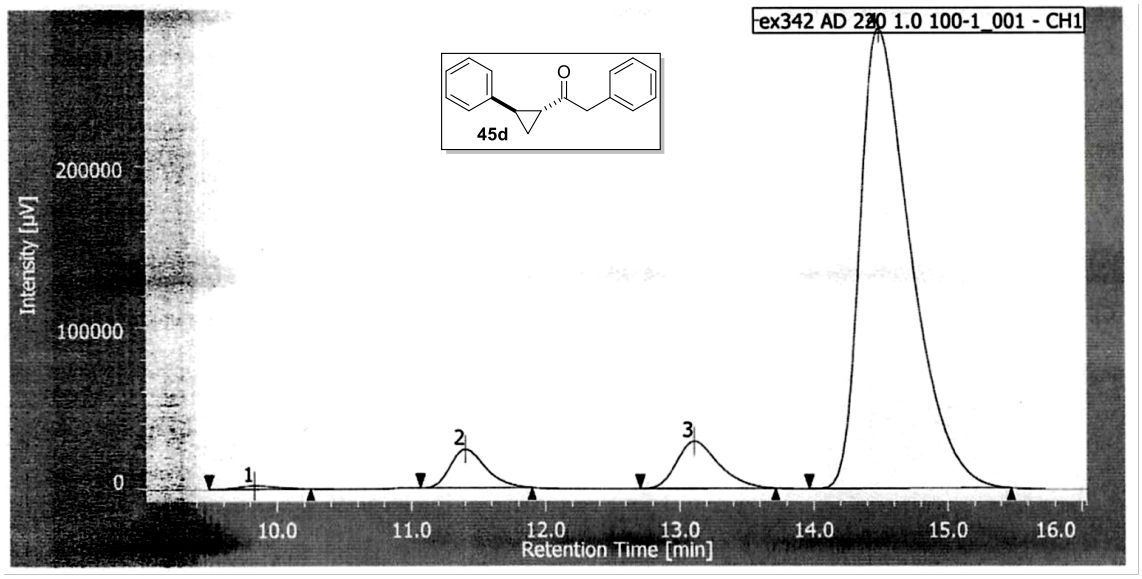
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	25.050	6483572	110974	46.469	49.207	N/A	4383	1.438	2.035	
2	Unknown	1	27.308	6484535	101096	46.476	44.827	N/A	4455	3.026	N/A	
3	Unknown	1	32.808	468254	6984	3.356	3.097	N/A	4271	0.794	N/A	
4	Unknown	1	34.475	516173	6469	3.699	2.869	N/A	3922	N/A	N/A	



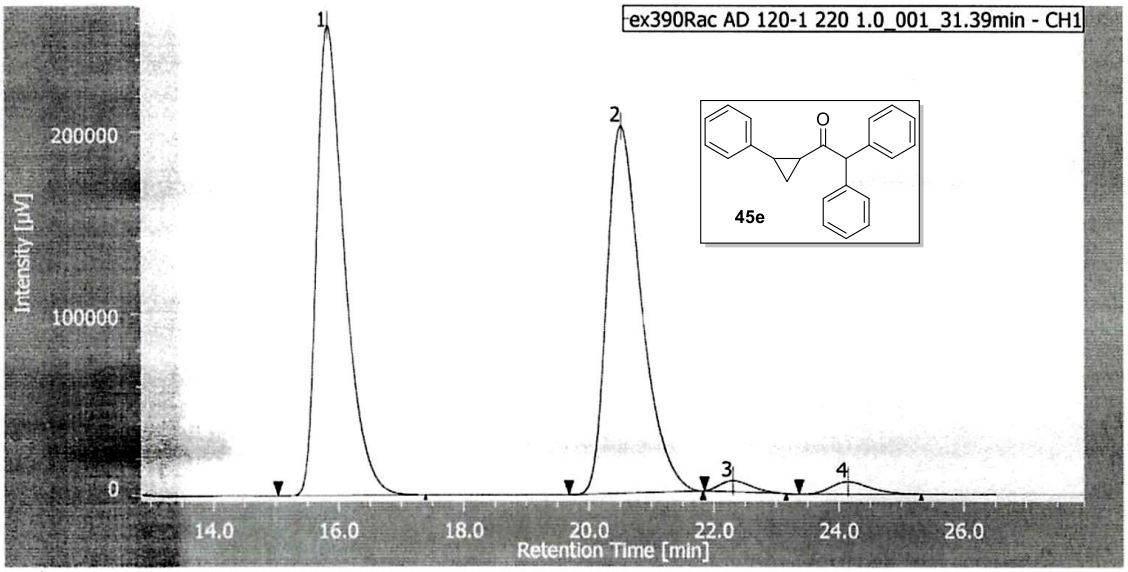
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	25.383	3440519	59576	7.697	9.273	N/A	4460	1.206	N/A	
2	Unknown	1	27.425	41256754	582891	92.303	90.727	N/A	3429	N/A	2.258	



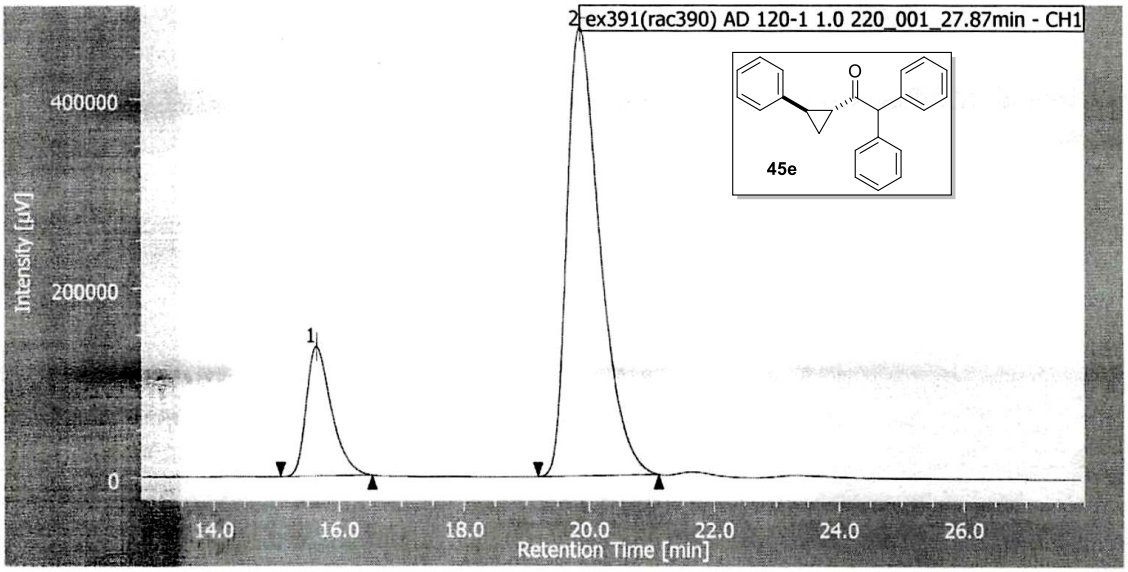
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	10.550	47703	2464	1.447	1.683	N/A	6954	2.281	1.201	
2	Unknown	1	11.692	1587155	79249	48.129	54.135	N/A	8836	3.521	1.079	
3	Unknown	1	13.517	63761	3028	1.934	2.068	N/A	9954	2.336	1.163	
4	Unknown	1	14.900	1599081	61651	48.491	42.114	N/A	8523	N/A	1.465	



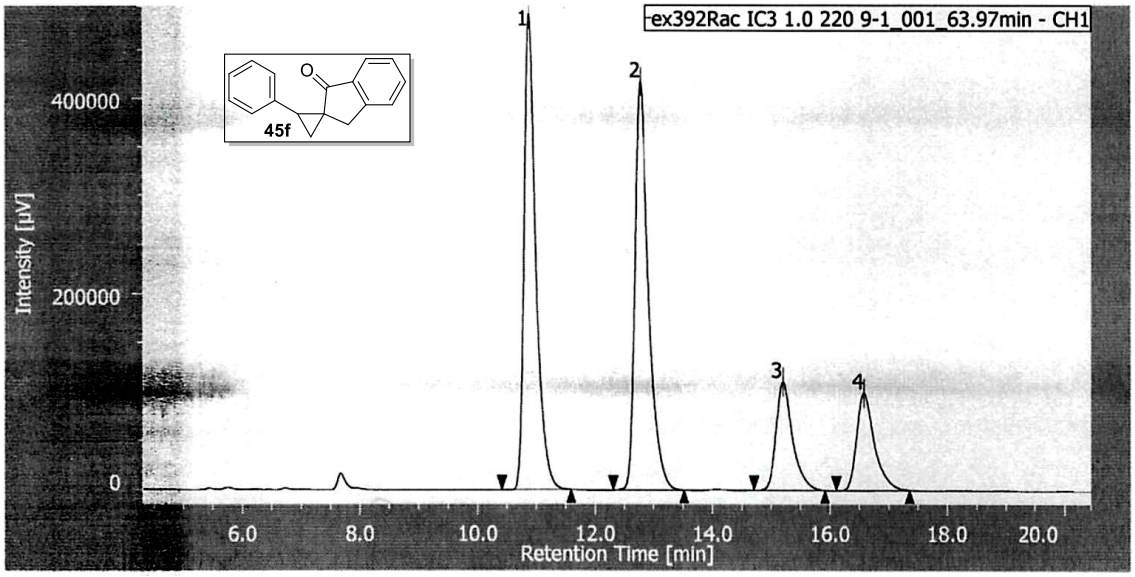
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	9.833	42105	2145	0.489	0.629	N/A	5766	3.176	1.221	
2	Unknown	1	11.400	435699	24003	5.056	7.038	N/A	9359	3.324	1.330	
3	Unknown	1	13.108	637697	29384	7.400	8.616	N/A	8793	2.258	1.325	
4	Unknown	1	14.500	7502130	285519	87.056	83.717	N/A	7339	N/A	1.507	



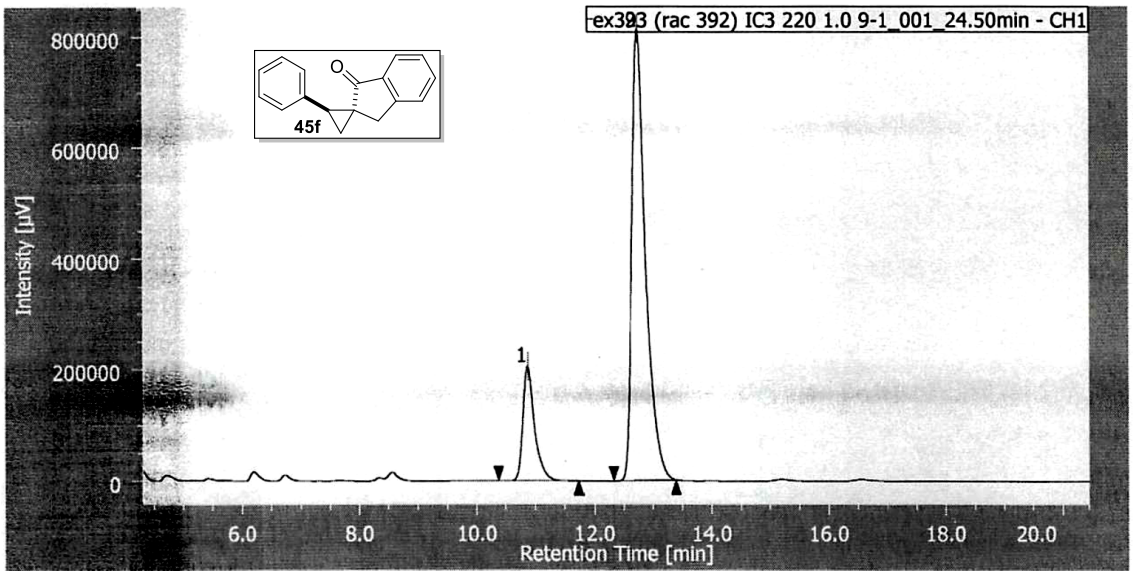
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.825	7959473	259039	48.823	54.631	N/A	6540	5.287	1.539	
2	Unknown	1	20.517	7829237	202099	48.024	42.623	N/A	6779	1.832	1.428	
3	Unknown	1	22.300	216562	6142	1.328	1.295	N/A	8726	1.775	1.374	
4	Unknown	1	24.142	297376	6878	1.824	1.451	N/A	7358	N/A	1.309	



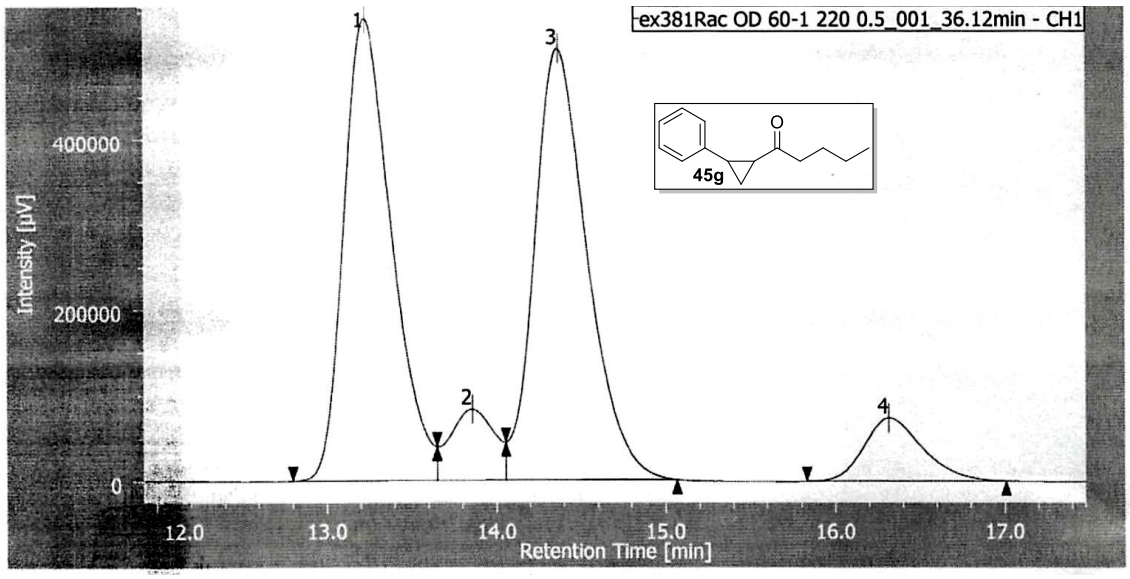
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.642	3805917	136296	17.899	22.352	N/A	7621	5.076	1.425	
2	Unknown	1	19.858	17456952	473472	82.101	77.648	N/A	7006	N/A	1.506	



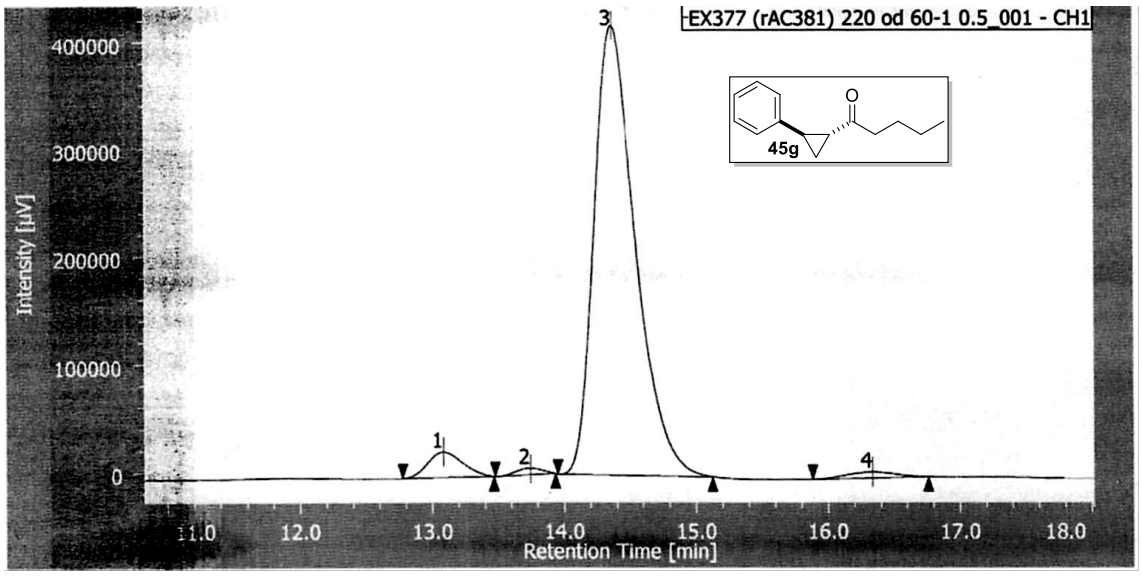
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	10.875	6693026	486693	37.973	43.675	N/A	16484	5.180	1.510	
2	Unknown	1	12.775	6715065	417561	38.098	37.471	N/A	16591	5.563	1.475	
3	Unknown	1	15.200	2133759	110523	12.106	9.918	N/A	16216	2.767	1.411	
4	Unknown	1	16.575	2083852	99581	11.823	8.936	N/A	16322	N/A	1.452	



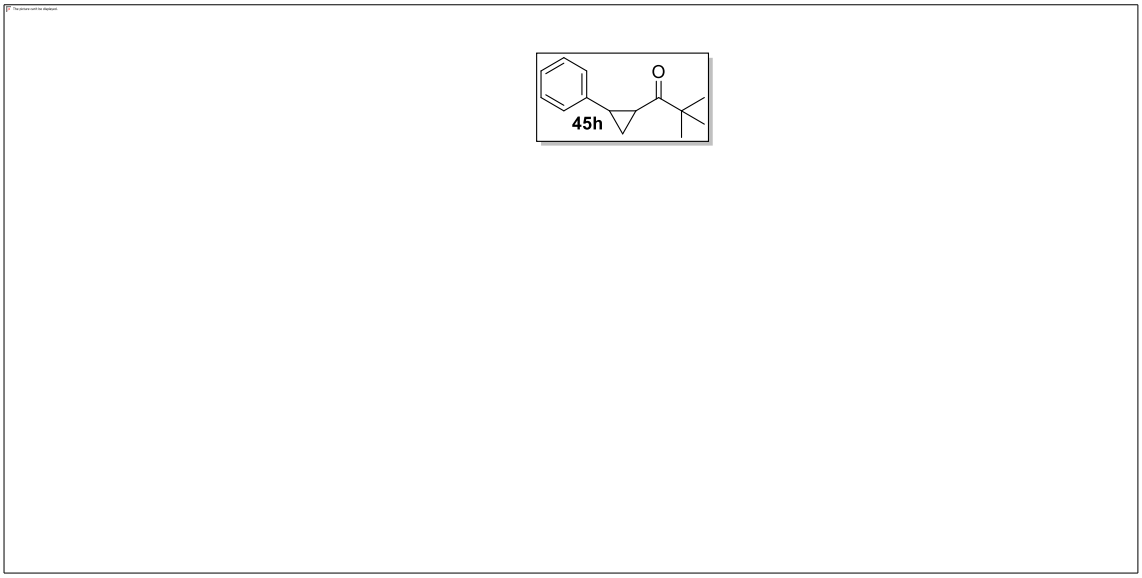
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	10.875	2786201	203860	17.405	20.060	N/A	16738	5.056	1.437	
2	Unknown	1	12.742	13222137	812390	82.595	79.940	N/A	15903	N/A	1.522	



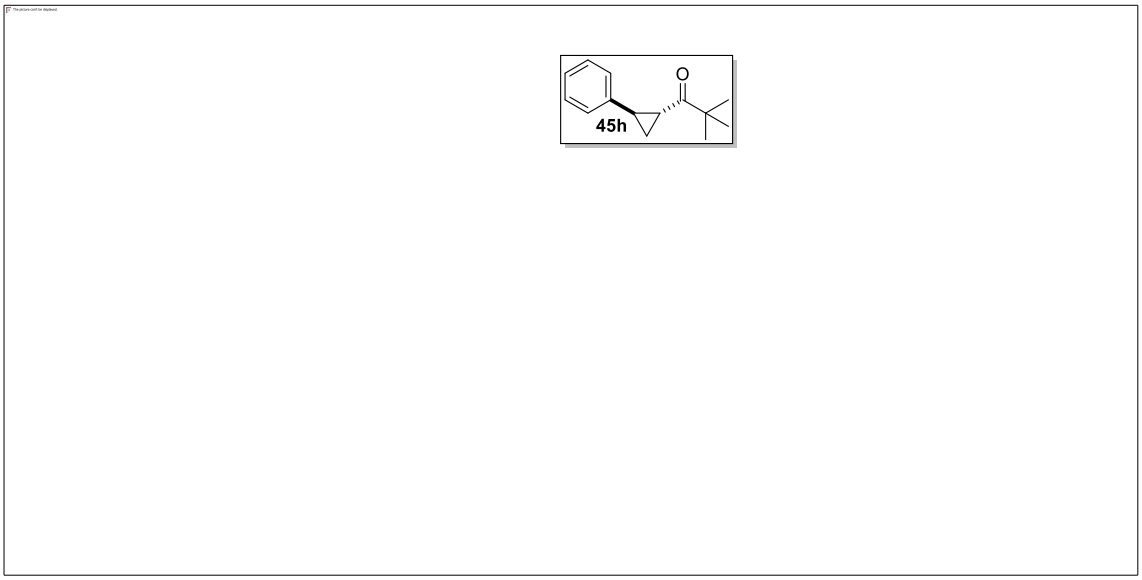
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	13.225	10638886	541408	42.864	44.978	N/A	10628	N/A	N/A	
2	Unknown	1	13.858	1534362	83432	6.182	6.931	N/A	N/A	N/A	N/A	
3	Unknown	1	14.367	10859546	504598	43.753	41.920	N/A	10845	3.327	N/A	
4	Unknown	1	16.317	1787161	74279	7.200	6.171	N/A	10962	N/A	1.258	



#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	13.083	435927	23925	4.474	5.287	N/A	11425	1.502	1.171	
2	Unknown	1	13.742	83816	6126	0.860	1.354	N/A	19943	1.315	0.955	
3	Unknown	1	14.367	9081994	416927	93.220	92.139	N/A	10387	3.110	1.356	
4	Unknown	1	16.333	140755	5521	1.445	1.220	N/A	8606	N/A	1.008	



#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	4.833	2026869	295348	34.001	38.036	N/A	12036	3.121	1.278	
2	Unknown	1	5.408	2054105	274911	34.457	35.404	N/A	12530	4.820	1.249	
3	Unknown	1	6.433	944899	105560	15.851	13.594	N/A	12176	1.419	N/A	
4	Unknown	1	6.767	935413	100682	15.691	12.966	N/A	12956	N/A	N/A	



#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	5.358	2399535	326522	27.986	29.947	N/A	12616	2.358	1.204	
2	Unknown	1	5.825	5700431	715463	66.485	65.619	N/A	12796	N/A	1.188	
3	Unknown	1	6.600	1840	44	0.021	0.004	N/A	N/A	N/A	N/A	
4	Unknown	1	6.867	472190	48300	5.507	4.430	N/A	11539	N/A	1.149	

REFERENCES

[1] Geuther, A.; Hermann, M. *Liebigs Ann. Chem.* **1855**, *95*, 211.

[2] Nef, J.U. *Liebigs Ann. Chem.,* **1897**, *298*, 202.

[3] Gomberg, M. *J. Am. Chem. Soc*. **1900**, *22*, 752.

[4] Pryor (Ed.), W.A. Organic Free Radicals, *American Chemical Society, Washington, D.C.*, **1977**.

[5] Staudinger, H.; Kupfer, O. *Berichte der Deutschen Chemischen Gesellschaft*, **1911** *44*, 2194.

[6] Staudinger, H.; Kupfer, O. *Berichte der Deutschen Chemischen Gesellschaft*, **1912**, *45*, 501.

[7] Kimse, W. *Angew*. *Chem*. *Int*. *Ed*. **1973**, *85*, 314.

[8] (a) Mulliken, R.S. *Rev. Mod. Phys*. **1932**, *4*, 1; (b) Hezberg, G. *Spectra of Diatomic Molecules*, (*D. van Nostrand Co., Princeton, NJ*), **1950**, 2nd ed., 369.

[9] (a) Hine, J. *J. Am. Chem. Soc*. **1950**, *72*, 2438; (b) Urry, W.H.; Eizner, J.R. *J. Am. Chem. Soc*. **1951**, *73*, 2977; (d) Hennion, G.F.; Maloney, D.E. *J. Am. Chem. Soc.* **1951**, *73*, 4735.

[10] Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* **1953**, *75*, 297.

[11] Doering, W. von E.; Hoffmann, A.K. *J. Am. Chem. Soc.* **1954**, 76, 6162.

[12] (a) Parham, W.E.; Reiff, H.E. *J. Am. Chem. Soc.* **1955**, *77*, 1177; (b) Parham, W.E.; Twelves, R.R. *J. Org. Chem.* **1957**, *22*, 730; (c) Skell, P.S.; Sandler, S.R. *J. Am. Chem. Soc*. **1958**, *80*, 2024.

[13] Bourissou, D.; Guerret, O.; Gabbaï, F.P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.

[14] Taylor, T.E.; Hall, M.B. *J. Am. Chem. Soc*. **1984**, *106*, 1576.

[15] Cardin, D.J.; Cetinkaya, B.; Lappert, M.F. *Chem. Rev.* **1972**, *72*, 545.

[16] Lappert, M.F. *J. Organomet. Chem.* **1988**, 358, 185.

[17] Frenking, G.; Solà, M.; Vyboishchikov, S.F. *J. Organomet. Chem.* **2005**, *690*, 6178.

[18] (a) Schoeller, W.W.; Eisner, D.; Grigoleit, S.; Rozhenko, A.B.; Alijah, A. *J. Am. Chem. Soc.* **2000**, *122*, 10115; (b) Canac, Y.; Soleilhavoup, M.; Conejero, S.; Bertrand, G. *J. Organomet. Chem*. **2004**, *689*, 3857.

[19] Vyboishchikov, S.F.; Frenking, G. *Chem. Eur. J*. **1998**, *4*, 1428.

[20] (a) Dzik, W.I.; Zhang, X.P.; de Bruin, B. *Inorganic Chemistry*. **2011**, *50, 9896.* (b) Dzik, W.I.; Xu, X.; Zhang, X.P.; Reek, J.N.H.; de Bruin, B. *J. Am. Chem. Soc*. **2010***, 132*, 10891.

[21] Bergin, Enda. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2012**, *108*, 353.

[22] Moss, Robert A.; Doyle, Michael P. *Contemporary Carbene Chemistry (1st ed.). New Jersey: John Wiley and Sons. ISBN 1118730267.* **2013**.

[23] Fischer, E. O.; Maasböl, A. *Angew. Chem. Int. Ed.* **1964***, 3, 580.*

[24] L'abbé, G, Van Stappen, P Toppet, S. *Tetrahedron.* **1985**, *41*, 4621.

[25] (a) Brown, R. F. C. *Pyrolytic Methods in Organic Chemistry*; Academic Press: New York,

1980. (b) Seybold, G. *Angew. Chem., Int. Ed.* **1977**, 16, 365. (b) Karpf, M. *Angew. Chem., Int. Ed.* **1986**, *25*, 414. (c) Wiersum, U. E. *Aldrichimica Acta.* **1984**, *17*, 31. (d) McNab, H. *Aldrichimica Acta.* **2004**, *37*, 19.

[26] (a) Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc.* **1975**, *1*, 1. (b) Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. J. *Chem. Commun.* **1971**, 1519.

[27] (a) De Meijere, A. *Top. Curr. Chem. Springer: Heidelberg*. **1986**, *133*. (b) De Meijere, A. *Top. Curr. Chem. Springer: Heidelberg*. **1987**, *135*. (c) De Meijere, A. *Top. Curr. Chem. Springer: Heidelberg*. **1988**, *144*. (d) De Meijere, A. *Top. Curr. Chem. Springer: Heidelberg*. **1990**, *155*. (e) De Meijere, A. *Top. Curr. Chem. Springer: Heidelberg*. **1996**, *178*. (f) De Meijere, A. *Top. Curr. Chem. Springer: Heidelberg*. **2000**, *207*.

[28] (a) De Meijere, A. *Angew. Chem. Int. Ed.* **1979**, *18*, 809. (b) Goudreau, S. R.; Charette, A. B. *Angew. Chem. Int. Ed*. **2010**, *49*, 486.

[29] Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7364.

[30] (a) Salaun, J.; Baird, M. S. *Curr. Med. Chem*. **1995**, *2*, 511. (b) De Meijere, A. *Top. Curr. Chem. Springer: Heidelberg*. **2000**, *207*. (c) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603. (d) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625. (e) Brackmann, F.; de Meijere, A. *Chem. Rev*. **2007**, *107*, 4493. (f) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4538. (g) Thibodeaux, C. J.; Chang, W.-c.; Liu, H.-w. *Chem. Rev*. **2012**, *112*, 1681.

[31] (a) Liu, H.-W.; Walsh, C. T. *In Cyclopropyl Group*; Vols. 1 and 2; Rappoport, Z., Ed.; John Wiley & Sons Ltd: New York, **2005**, 959. (b) Gagnon, A.; Duplessis, M.; Fader, L. Org. Prep. Proced. Int. **2010**, 42, 1

[32] Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

[33] Pellissier, H. *Tetrahedron*. **2008**, *64*, 7041.

[34] (a) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (b) Caballero, A.; Prieto, A.; Díaz-Requejo, M. M.; Pérez, P. J. *Eur. J. Inorg. Chem*. **2009**, 1137. (c) Audran, G.; Pellissier, H. *Adv. Synth. Catal.* **2010**, *352*, 575. (d) Intrieri, D.; Caselli, A.; Gallo, E. *Eur. J. Inorg. Chem.* **2011**, 5071. (e) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. (f) Zhu, S.; Cui, X.; Zhang, X. P. *Eur. J. Inorg. Chem.* **2012**, 430. (g) David, E.; Milanole, G.; Ivashkin, P.; CouveBonnaire, S.; Jubault, P.; Pannecoucke, X. *Chem. Eur. J.* **2012**, *18*, 14904. (h) Kim, H. Y.; Walsh, P. J. *Acc. Chem. Res*. **2012**, *45*, 1533. (i) Honma, M.; Takeda, H.; Takano, M.; Nakada, M. *Synlett.* **2009**, 1695.

[35] Beaulieu, L. P. B; Zimmer, L. E.; Gagnon, A.; Cherette, A. B. *Chem. Eur. J*. **2012**, *18*, 14784.

[36] Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synth. Rev.* **2014**, *46*, A.

[37] Alliot, J.; Gravel, E.; Pillon, F.; Buisson, D. A.; Nicolas, M.; Doris, E. *Chem. Commun*. **2012**, *48*, 8111.

[38] Anthes, R.; Benoit, S.; Chen, C.-K.; Corbett, E. A.; Corbett, R. M.; DelMonte, A. J.; Gingras, S.; Livingston, R. C.; Pendri, Y.; Sausker, J.; Soumeillant, M. *Org. Process Res. Dev.* **2008**, *12*, 178.

[39] Chawner, S. J; Cases-Thomas, M. J; Bull, J. A. *Eur. J. Org. Chem*. **2017**, 5015.

[40] Chanthama, S.; Ozaki, S.; Shibatomi, K.; Iwasa, S. *Org. Lett.* **2014**, *16*, 3012.

[41] Reest, J.V. D.; Gottlieb, E. *Cell Res.* **2016**, *26*, 269.

[42] Xu, H.; Lybrand, D.; Bennewitz, S.; Tissier, A.; Last, R. L.; Pichersky, E. *Metab. Eng.* **2018**, *47*, 271.

[43] Palko, J. W.; Buist, P. H.; Manthorpe, J. M. *Tetrahedron: Asymmetric*. 2013**,** *24*, 165.

[44] (a) García-Ruano, J. L.; Martin-Castro, A. M.; Rodríguez, J. H. *J. Org. Chem.* **1994**, *59*, 533; (b) Jiménez, O.; Bosch, M. P.; and Guerrero, A. *J. Org. Chem.* **1997**, *62*, 3496; (c) Bondzic, B.P., Urushima, T., Ishikawa, H., and Hayashi, Y. *Org. Lett.* **2010**, *12*, 5434.

[45] (a) Yamaguchi, J.; Hayashi, Y. *Chem. Eur. J.* **2011**, *16*, 3884; (b) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem. Int. Ed.* **1998**, *37*, 2014.

[46] (a) Bäckvall, J. E. *Modern Oxidation Methods*. **2010**, Chapters 2–4, 6, 7, 9, 11, Wiley-VCH Verlag GmbH, Weinheim; (b) Müller, C., Grover, N., Cokoja, M., and Kühn, F.E. *Advances in Inorganic Chemistry*. **2013**, *vol. 65*, Chapter 2 (eds R. van Eldik and C.D. Hubbard), Elsevier, Oxford, pp. 33–83; (c) Amini, M., Haghdoost, M. M.; Bagherzadeh, M. *Coord. Chem. Rev.* **2014**, *268*, 83; (d) Huber, S., Cokoja, M., and Kühn, F.E. *J. Organomet. Chem.* **2014**, *751*, 25; (e) Kück, J.W., Reich, R. M.; Kühn, F. E. *Chem. Rec.* **2016**, *16*, 349; (f) Saisaha, P., de Boer, J.W.; Browne, W. R. *Chem. Soc. Rev.* **2013**, *42*, 2059.

[47] Davies, S.G., Fletcher, A.M., and Thomson, J.E. *Org. Biomol. Chem.* **2014**, *12*, 4544.

[48] Gnas, Y. and Glorius, F. *Synthesis*, **2006**, *12*, 1899.

[49] For a review on chiral auxiliary controlled epoxidations, see: Adam, W. and Zhang, A. *Synlett*, **2005**, 1047.

[50] Lynch, J. E.; Choi, W. B.; Churchill, H. R. O.; Volante, R. P.; Reamer, R. A.; Ball, R. G. *J. Org. Chem*. **1997**, *62*, 9223.

[51] Gelalcha, F. G.; Bitterlich, B., Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 7293.

[52] (a) White, M. C.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 7194; (b) Mas-Ballesté, R.; Costas, M.; van der Berg, T.; Que, L. Jr. *Chem. Eur. J.* **2006**, *12*, 7489; (c) Mas-Ballést, R.; Que, L. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 15964.

[53] Wu, M.; Miao, C. X.; Wang, S.; Hu, X.; Xia, C.; Kühn, F. E.; Sun, W. *Adv. Synth. Catal.* **2011**, *353*, 3014.

[54] Cussó, O.; Ribas, X.; Lloret-Fillol, J.; and Costas, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 2729.

[55] Nishikawa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 8432.
[56] (a) Monnier, J.R. *Appl. Catal., A*. **2001**, *221*, 73; (b) Cheng, Q. F.; Xu, X.Y.; Ma, W. X.; Yang, S. J.; You, T. P. *Chin. Chem. Lett.* **2005**, *16*, 1467.
[57] Tanaka, H.; Nishikawa, H.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 12034.
[58] (a) Bian, Z.; Marvin, C. C.; Pettersson, M.; Martin, S. F. *J. Am. Chem. Soc.* **2014**, *136*, 14184; (b) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *7*, 5239.
[59] Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3087.
[60] (a) Weitz, E.; Scheffer, A. *Chem. Ber.* **1921**, *54*, 2327; For a review on the synthetic importance of epoxides derived from electron-poor alkenes, see: (b) Lauret, C. *Tetrahedron: Asymmetry.* **2001**, *12*, 2359–2383.
[61] Yu, H.-B.; Zheng, X. F.; Lin, Z. M.; Hu, Q. S.; Huang, W. S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 8149.
[62] (a) Juliá, S., Masana, J., and Vega, J.C. *Angew. Chem. Int. Ed*. **1980**, *19*, 929; (b) Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annunziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1*. **1982**, 1317; (c) Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S.; Guixer, J. *Tetrahedron*, **1984**, *40*, 5207.
[63] (a) Geller, T.; Gerlach, A.; Krüger, C. M.; Militzer, H. C. *Tetrahedron Lett*. **2004**, *45*, 5065; (b) Geller, T., Krüger, C. M.; Militzer, H. C. *Tetrahedron Lett.* **2004**, *45*, 5069; (c) Gerlach, A.; Geller, T. *Adv. Synth. Catal.* **2004**, *346*, 1247; (d) Lopez-Pedrosa, J. M.; Pitts, M. R.; Roberts, S. M.; Saminathan, S.; Whittall, J. *Tetrahedron Lett*. **2004**, *45*, 5073.
[64] Sohtome, Y.; Nagasawa, K. *Chem. Commun*. **2012**, *48*, 7777.
[65] Licini, G.; Bonchio, M.; Broxterman, Q. B.; Kaptein, B.; Moretto, A.; Toniolo, C.; Scrimin, P. *Biopolymers*. **2006**, *84*, 97.
[66] (a) Carrea, G.; Colonna, S.; Meek, A. D.; Ottolina, G.; Roberts, S.M. Tetrahedron: Asymmetry. **2004**, *15*, 2945; (b) Mathew, S. P.; Gunathilagan, S.; Roberts, S. M.; Blackmond, D. G. *Org. Lett*. **2005**, *7*, 4847; (c) Carrea, G.; Colonna, S.; Kelly, D. R.; Lazcano, A.; Ottolina, G.; Roberts, S. M. *Trends Biotechnol.* **2005**, *23*, 507.
[67] Tong, R.; Valentine, J. C.; McDonald, F. E.; Cao, R.; Fang, X.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 1050.
[68] For a review, see: Page, P. C. B.; Buckley, B. R. *Mechanisms in Homogeneous and Heterogeneous Epoxidation Catalysis*, Chapter 5 (ed. S.T. Oyama), Elsevier, Oxford, **2008,** pp. 177.
[69] Page, P. C. B.; Appleby, L. F.; Chan, Y.; Day, D.; Buckley, B. R.; Slawin, A. M. Z.; Allin, S. M.; McKenzie, M. J. *J. Org. Chem.* **2013**, *78*, 8074.
[70] (a) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; and Poss, A. J. *J. Am. Chem. Soc.* **1985**,

107, 1777; (b) Yadav, V. K.; Kapoor, K. K. Tetrahedron. **1995**, *51*, 8573.
[71] (a) MacManus, J. C.; Carey, J. S.; Taylor, R. J. K. *Synlett.* **2003**, 365; (b) MacManus, J. C.; Genski, T.; Carey, J. S.; Taylor, R. J. K. *Synlett*. **2003**, 369.
[72] Kumamoto, T.; Ebine, K.; Endo, M.; Araki, Y.; Fushimi, Y.; Miyamoto, I.; Ishikawa, T.; Isobe, T.; Fukuda, K. *Heterocycles*. **2005**, *66*, 347.
[73] Terada, M.; Nakano, M. *Heterocycles.* **2008**, *76*, 1049.
[74] Capobianco, A.; Russo, A.; Lattanzi, A.; and Peluso, A. *Adv. Synth. Catal.* **2012**, *354*, 2789.
[75] Li, Y.; Liu, X.; Yang, Y.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 288.
[76] Liu, X.; Li, Y.; Wang, G.; Chai, Z.; Wu, Y.; Zhao, G. *Tetrahedron: Asymmetry*. **2006**, *17*, 750.
[77] Cui, H.; Li, Y.; Zheng, C.; Zhao, G.; Zhu, S. *J. Fluorine Chem.* **2008**, *129*, 45.
[78] Lu, J.; Xu, Y. H.; Liu, F.; Loh, T. P. *Tetrahedron Lett.* **2008**, *49*, 6007.
[79] Zheng, C.; Li, Y.; Yang, Y.; Wang, H.; Cui, H.; Zhang, J.; Zhao, G. Adv. Synth. Catal. **2009**, *351*, 1685.
[80] Yoakim, C.; Ogilvie, W. W.; Goudreau, N.; Naud, J.; Haché, B.; O'Meara, J.A.; Cordingley, M.G.; Archambault, J.; White, P. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2539.
[81] Palumbo, C.; Mazzeo, G.; Mazziotta, A.; Gambacorta, A.; Loreto, M.A.; Migliorini, A.; Superchi, S.; Tofani, D.; Gasperi, T. *Org. Lett.* **2011**, *13*, 6248.
[82] Reisinger, C. M.; Wang, X.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 8112.
[83] Bénary, E. *Chem. Ber.* **1911**, *44*, 489.
[84] Sparr, C.; Schweizer, W. B.; Senn, H. M.; Gilmour, R. *Angew. Chem. Int. Ed.* **2009**, *48*, 3065.
[85] Sparr, C.; Tanzer, E. M.; Bachmann, J.; Gilmour, R. *Synthesis.* **2010**, 1394.
[86] Tanzer, E. M.; Zimmer, L. E.; Schweizer, W. B.; Gilmour, R. *Chem. Eur. J.* **2012**, *18*, 11334.
[87] Xu, M. H.; Tu, Y. Q.; Tian, J. M.; Zhang, F. M.; Wang, S. H.; Zhang, S. H.; Zhang, X. M. *Tetrahedron: Asymmertry*. **2016**, *27*, 294.
[88] (a) Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193; (b) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. Science. **2007**, *317*, 496.
[89] Wang, X.; List, B. *Angew. Chem. Int. Ed*. **2008**, *47*, 1119.
[90] (a) Berkessel, A; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH Verlag GmbH, Weinheim. (ed.) **2005**; (b) Dalko, P.I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley-VCH Verlag GmbH, Weinheim. (ed.) **2007**.
[91] Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227.
[92] For recent reviews, see: (a) Inokuma, T. and Takemoto, Y. *Science of Synthesis, Asymmetric*

Organocatalysis, vol. 2 (eds B. List and K. Maruoka), Thieme. **2012**, pp. 437–497; (b) Connon, S. J. *Chem. Commun.* **2008**, 2499; (c) Marcelli, T., van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed*. **2006**, *45*, 7496.

[93] Okino, T., Hoashi, Y., and Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *128*, 12672.

[94] Russo, A.; Galdi, G.; Croce, G.; Lattanzi, A. Chem. Eur. J. **2012**, *18*, 6152.

[95] Meninno, S.; Vidal-Albalat, A.; Lattanzi, A. Org. Lett. **2015**, *17*, 4348.

[96] Kobayashi, Y.; Li, S.; Takemoto, Y. *Asian J. Org. Chem.* **2014**, *3*, 403.

[97] For a recent review, see: Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613.

[98] (a) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420; (b) Lebel, H.; Jacobsen, E. N. *Tetrahedron Lett.* **1999**, *40*, 7303.

[99] For reviews, see: (a) Tokunaga, M. and Hamasaki, A. *Comprehensive Chirality,* vol. 5 (eds E. Carreira and H. Yamamoto), Elsevier, Oxford. **2012**, pp. 421–435; (b) Larrow, J. F.; Quigley, P. F. *Comprehensive Chirality*, vol. 9 (eds E. Carreira and H. Yamamoto), Elsevier, Oxford. **2012**, pp. 129–146.

[100] Kim, Y. S.; Guo, X. F.; Kim, G. J. *Catal. Today*. **2010**, 92, 91.

[101] Kim, Y. S.; Guo, X. F.; Kim, G. *J. Chem. Commun.* **2009**, 4296.

[102] Solodenko, W.; Jas, G.; Kunz, U.; Kirschning, A. *Synthesis.* **2007**, 583.

[103] Belser, T.; Jacobsen, E. N. *Adv. Synth. Catal*. **2008**, *350*, 967.

[104] Kotozaki, M.; Chanthamath, S.; Fujisawa, I.; Shibatomi, K.; Iwasa, S. *Chem*. *Commun*. **2017**, *53*, 12193.

[105] Kotozaki, M.; Chanthamath, S.; Fujii, T.; Shibatomi, K.; Iwasa, S. *Chem*. *Commun*. **2018**, *54*, 5110.

[106] (a) Haak, R. M.; Belmonte, M. M.; Escudero-Adan, E. C.; Benet-Buchholz, J.; Kleij, A. W. *Dalton Trans.* **2010**, *39*, 593; (b) Wezenberg, S. J.; Kleij, A. W. *Adv. Synth. Catal.* **2010**, *352*, 85.

[107] (a) Thakur, S. S.; Li, W. J.; Shin, C. K.; Kim, G. J. Chirality. **2006**, *18*, 37; (b) Thakur, S. S.; Chen, S. W.; Li, W.; Shin, C. K.; Kim, S. J.; Koo, Y. M.; Kim, G. J. *J. Organomet. Chem.* **2006**, *691*, 1862; (c) Patel, D.; Kurrey, G. R.; Shinde, S. S.; Kumar, P.; Kim, G. J.; Thakura, S. S. *RSC. Adv.* **2015**, 5, 82699.

[108] Bohe, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett*. **1993**, *34*, 7271.

[109] Kawthekar, R. B.; Kim, G. J. *Helv. Chim. Acta.* **2008**, *91*, 317.

[110] (a) Kim, Y.J.; Tae, J. Synlett. **2006**, 61; (b) Santhosh, R.; Chouthaiwale, P. V.; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Chem. Commun*. **2010**, *46*, 5012.

[111] Devalankar, D. A.; Karabal, P. U.; Sudalai, A. *Org. Biomol. Chem.* **2013**, *11*, 1280.

[112] Reddy, A.; Mujahid, M.; Sasikumar, M.; and Muthukrishnan, M. *Synthesis*. **2014**, *46*, 1751.

[113] (a) Davies, H.M.L.; Walji, A.M. *Modern Rhodium-Catalyzed Organic Reactions; Andrew*

Evans, P., Ed.; John Wiley & Sons. **2005**, pp. 301-340. (b) Ma, X.; Cooper, S. M.; Yang, F.; Hu, W.; Sintim, H. O. *Curr. Org. Chem.* **2016**, *20*, 82.

[114] Donaldson, W. A. *Tetrahedron*. **2001**, *57*, 8589.

[115] (a) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem*. **2014**, *53*, 5504. (b) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev*. **2009**, *38*, 3051. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, 107, 3117.

[116] (a) Duquenne, C.; Goumain, S.; Jubault, P.; Feasson, C.; Quirion, *J.-C. Org. Lett*. **2000**, *2*, 453. (b) Erion, M. D.; Walsh, C. T. *Biochemistry*. **1987**, 26, 3417. (c) Hanessian, S.; Cantin, L.-D.; Roy, S.; Andreotti, D.; Gomtsyan, *A. Tetrahedron Lett*. **1997**, *38*, 1103. (d) Orsini, F.; Sello, G.; Sisti, *M. Curr. Med. Chem*. **2010**, *17*, 264.

[117] (a) Seyferth, D.; Marmor, R. S. *Tetrahedron Lett*. **1970**, *11*, 2493. (b) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem*. **1971**, *36*, 1379.

[118] (a) Schnaars, C.; Hansen, T. *Org. Lett*. **2012**, *14*, 2794. (b) Schnaars, C.; Hennum, M.; Bonge-Hansen, T. *J. Org. Chem*. **2013**, *78*, 7488. (c) Lewis, R. T.; Motherwell, W. B. *Tetrahedron Lett.* **1988**, *29*, 5033. (d) Davies, H. M. L.; Lee, G. H. *Org. Lett*. **2004**, *6*, 2117. (e) Adly, F. G.; Maddalena, J.; Ghanem, A. *Chirality*. **2014,** *26*, 764. (f) Simonneaux, G.; De Montigny, F.; Paul-Roth, C.; Gulea, M.; Masson, S. *Tetrahedron Lett*. **2002**, *43*, 3685. (g) Ferrand, Y.; Le Maux, P.; Simonneaux, G. *Org. Lett*. **2004**, *6*, 3211. (h) Charette, A. B.; Bouchard, J.-E. *J. Chem.* **2005**, *83*, 533. (i) El-Gokha, A.; Maas, G. *Tetrahedron.* **2011**, *67,* 2849. (j) Narinozzi M., Pertusati F., Serp M. *Chem. Soc Rev.* **2016**, *116*, 13991.

[119] Lindsay, V.N.G; Fiset, D.; Gritsch, P. J.; Azzi, D; Charette. A. B. *J. Am. Chem. Soc.* **2013**, *135*, 1463.

[120] Chanthama, S.; Ozaki, S.; Shibatomi, K.; Iwasa, S. *Org. Lett.* **2014**, *16*, 3012.

[121] For carbene-mediated C-H activation reactions: (a) Davies, H M. L.; Manning, J. R. *Nature*. **2008**, 417. (b) Davies, H. M. L.; Hansen, T.; Hopper, D.W.; Panaro, S.A. *J. Am. Chem. Soc*. **1999**, *121*, 6509. (c) Bexrud, J. A.; Eisenberger, P. Leitch, D. C.; Payne, P. R.; and Schafer, L. L. *J. Am. Chem. Soc*. **2009**, *131*, 2116.

[122] (a) Zhang, X; Fried, A.; Knapp, S.; Goldman, A.S. M. *Chem. Commun*. **2003**, 2060. (b) Gupta, C. Hagen, W. C. Kaska, R. Flesher and C. M. Jensen, *Chem. Commun.* **1996**, 2083. (c) Xu, W; Rosini, G. P.; Gupta, M. C; Jensen, M.; Kaska, W. C.; Krogh-Jespersen K.; Goldman, A. S. *Chem. Commun.* **1997**, 2273. (d) Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R.; Jensen, C. M. *J. Am. Chem. Soc.* **1997**, *119*, 840. (e) Liu, F.; Pak, E. B.; Singh, B.; Jensen, C. M.; Goldman, A. S. *J. Am. Chem. Soc.* **1999**, *121*, 4086. (f) Gupta, M.; Hagen, C.; Kaska, W. C.; Jensen, C. M. *Chem. Commun.* **1997**, 461. (g) Renkema, K. B.; Kissin, Y. V.; Goldman, A. S. *J. Am. Chem. Soc.* **2003**, *125*, 7770. (h) Gu, X.-Q.; Chen, W.; Morales-Morales, D.; Jensen, C. M. *J. Mol. Catal. A*. **2002**, *189*, 119.

[123] (a) Chanthamath, S.; Nguyen, D. T; Shibatomi, K.; Iwasa, S. *Org. Lett.* **2013**, *15*, 772. (b) Abu-Elfotoh, A. M.; Phemkeona, K.; Shibatomi, K. Iwasa, S. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 8439; (c) Chanthamath, S.; Phomkeona, K.; Shibatomi, K.; Iwasa, S. *Chem*. *Commun*. **2012**, *48*, 7750; (d) Abu-Elfotoh, A. M.; Nguyen, D. P. T.; Chanthamath, S.; Phomkeona, K.; Shibatomi, K.; Iwasa, S. *Adv*. *Synth*. *Catal*. **2012**, *354*, 3435; (e) Chanthamath, S.; Nguyen, D. T.; Shibatomi, K.; Iwasa, S. *Org*. *Lett*. **2013**, *15*, 772; (f) Chanthamath, S.; Takaki, S.; Shibatomi, K.; Iwasa, S. *Angew*. *Chem*., *Int*. *Ed*. **2013**, *52*, 5818; (g) Chanthamath, S.; Chua, H. W.; Kimura, S.; Shibatomi, K.; Iwasa, S. *Org*. *Lett*. **2014**, *16*, 3408. (h) Nakagawa, Y.; Chanthamath, S.; Shibatomi, K.; Iwasa, S. *Org*. *Lett*. **2015**, *17*, 2792. (i) Chanthamath, S.; Mandour, H. S. A.; Thu, T. T. M.; Shibatomi, K.; Iwasa, S. *Chem*. *Commun*. **2016**, *52*, 7814; (j) Chanthamath, S.; Iwasa, S. *Acc*. *Chem*. *Res*. **2016**, *49*, 2080; (k) Mandour, H. S. A.; Chanthamath, S.; Shibatomi, K.; Iwasa, S. *Adv*. *Synth*. *Catal*. **2017**, *359*, 1742.

[124]. Chen, D. Y. K.; Pouwer, R. H.; Richard J. A. *Chem. Soc. Rev*. **2012**, *41*, 4631.

[125]. (a) Duquenne, C.; Goumain, S.; Jubault, P.; Feasson, C.; Quirion, *J. C. Org. Lett*. **2000**, *2*, 453. (b) Erion, M. D.; Walsh, C. T. *Biochemistry*. **1987**, *26*, 3417. (c) Hanessian, S.; Cantin, L. D.; Roy, S.; Andreotti, D.; Gomtsyan, *A. Tetrahedron Lett*. **1997**, *38*, 1103. (d) Orsini, F.; Sello, G.; Sisti, *M. Curr. Med. Chem*. **2010**, *17*, 264. (e) Clercq, E. D.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. *Nature*. **1986**, *323*, 464.

[126]. (a) Nowack Ben rd. Water Research. **2003**, 2533. (b) Magdalena, K. O.; Mucha, A.; Ewa, Z. D. *Curr Microbiol.* **2014**, *68*, 330.

[127]. (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, **1998**. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev*. **2003**, *103*, 977. (c) Davies, H. M. L. *Org. React. (Hoboken, NJ, U. S.)* **2001**, *57*, 1. (d) Roy, M.-N.; Lindsay, V. N. G.; Charette, A. B. *In Stereoselective Synthesis 1: Stereoselective Reactions of Carbon-Carbon Double Bonds*; Georg Thieme-Verlag: New York, **2011**; chapt. 1.14.

[128]. (a) Tsuji, T.; Nishida, S. *Acc. Chem. Res*. **1984,** *17*, 56. (b) Penelle, J.; Boffa, L. S.; Novak, B. M. Eds. *ACS Symposium Series.* **2000**, 59.

[129]. Choi, J. R.; Cho, D. G.; Roh, K. Y.; Hwang, J. T.; Ahn, S.; Jang, H. S.; Cho, W. Y.; Kim, K. W.; Cho, Y. G.; Kim, J.; Kim, Y. Z. *J. Med. Chem*. **2004**, *47*, 2864.

[130]. Dappen, M. S.; Pellicciari, J. R.; Natalini, B.; Monahan, J. B.; Chiorri, C.; Cordis, A. A. *J. Med. Chem*. **1991**, *34*, 161.

[131]. (a) Hatse, S.; Naesens, L.; De Clercq, E.; Balzarini, J. *Biochem. Pharmacol*. **1999**, *58*, 311. (b) Zidek, Z.; Potmesil, P.; Kmoniekova, E.; Holy, A. *Eur. J. Pharmacol. **2003**, 475, 149*. (c) Hockova, D.; Holy, A.; Masojidkova, M.; Andrei, G.; Snoeck, R. T.; De Clercq, E. *J. Med. Chern*. **2003**, *46*, 5064.

[132]. Davies, H. M. L. and Lee, G. H. *Organic Lett.* **2004**, *6*, 2117.

[133]. (a) Erion, M. D.; Walsh, C. T. *Biochemistry*. ***1987***, *26, 3417*. Groth, U.; Lehmann, L.; Richter, L.; Scho¨llkopf, U. Liebigs Ann. Chem. 1993, 427. (b) Hah, J. H.; Gil, J. M.; Oh, D. Y. *Tetrahedron Lett*. **1999**, *40, 8235*. (c) Duquenne, C.; Goumain, S.; Jubault, P.; Feasson, C.; Quirion, J. C. *Org. Lett*. **2000**, *2, 453*. (d) Hanessian, S.; Cantin, L.-D.; Roy, S.; Andretti, D.; Gomtsyan, A. *Tetrahedron Lett*. **1997**, *38, 1103*.

[134]. The method to synthesis of Cyclopropylphosphonates: (a) Jubault, P.; Goumain, S.; Feasson, C.; Collignon, N. *Tetrahedron*. **1998**, *54*, 14767. (b) Jubault, P.; Goumain, S.; Feasson, C.; Collignon, N. *Synthesis*. **1999**, 1903

[135]. (a) Davies, H. M. L.; Lee, G. H. Org. Lett. **6**, 2117 (2004). (b) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett*. **2006**, *8*, 3437. (c) Lindsay, V. N. G. Fiset, D.; Gritsch, P. J.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 1463.

[136]. Maas, G. Chem.Sov.Rev. **2003**, *33*, 183.

[137]. (a) Donalson, W. A. *Tetrahedron*. **2001**, *57*, 8589; (b) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051; (c) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625; (d) Lebal, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. J. *Chem. Rev*. **2003**, *103*, 977; (e) Reichelt, A.; Martin, S. F. *ACC. Chem. Res.* **2006**, *39*, 433. (f) Brackmann, F.; de Meijere, A. *Chem. Rev*. **2007**, *107*, 4493; (g) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631.

[138]. Asymmetric cyclopropanation of diazo compounds with olefins using chiral catalysts: **For Cu(I)**, see: (a) Bouet, A.; Heller, B.; Papamicael, C.; Dupas, G.; Oudeyer, S.; Marsais, F.; Levacher, V. *Org. Biomol. Chem*. **2007**, *9*, 1397; (b) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett*. **1990**, *42*, 6005; (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.*, **1991**, *113*, 726; (d) Itagaki, M.; Yamamoto, Y. *Tetrahedron Lett.*, **2006**, *4*, 523; **For Rh(II)**, see: (e) Rosenberg, M. L.; Krivokapic, A.; Tilset, M. *Org. Lett*. **2009**, *3*, 547; (f) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Wathins, L. M.; Eagle, C. T. *Tetrahedron Lett*. **1990**, *46*, 6613; (g). Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Muller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423; **For Ru(II)**, see: (h) Ferrand, Y.; Maux, P. L.; Simonneaux, G. *Org. Lett.* **2004**, *6*, 3211. (i) Miller, J. A.; Jin, W.; Nguyen, S. T. *Angew. Chem., Int. Ed.*, **2002**, *41*, 2953; (j) Hoang, V. D.; Reddy, P. A. N.; Kim, T. J. *Tetrahedron Lett.*, **2007**, *45*, 8014; For Co(II), see: (k) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2007**, *72*, 5931; (l) Zhu, S. F.; Xu, X.; Perman, J. A.; Zhang, X. P. *J. Am. Chem. Soc.*, **2010**, *132*, 12796; **For Ir(II)**, see: (m) Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc*. **2008**, *130*, 10327;

[139]. Chanthamath, S.; Chua, H. W.; Kimura, S.; Shibatomi, K.; Iwasa, S. *Org. Lett.* **2014**, *16*, 3408.

[140]. Chanthamath, S.; Takaki, S.; Shibatomi, K.; Iwasa, S. *Angew. Chem., Int. Ed*. **2013**, *125*, 5930.

[141]. (a) Ichiyanagi, T.; Kuniyama, S.; Shimizu, M.; Fujisawa, T. *Chem. Lett.* **1997**, 1149; (b) Enholm, E. J.; Jia, Z. J. *J. Org. Chem.* **1997**, *62*, 5248; (c) Tanko, J. M.; Phillips, J. P. *J. Am. Chem. Soc*. **1999**, *121*, 6078; (d) Hao, W.; Harenberg, J. H.; Wu, X.; Macmillan, S. N.; Lin, S. *J. Am. Soc. Chem*. **2018**, *140*, 3514; (e) Richmond, E.; Vukovic, V. D.; Moran, J. *Org. Lett.* **2018** , *20*, 574; (f) Gupta, A.; Kholiya, R.; Rawat, D. S. *Asian J. Org. Chem*. **2017**, *6*, 993.

[142]. (a) Fukuyama, Y.; Hirono, M.; Kodama, M. *Chem.Lett*. **1992**, 167; (b) Nagle, D. G.; Gerwick, W. H. *Tetrahedron Lett*. **1990**, *31*, 2995; (c) White, J. D.; Jensen, M. S.; *J. Am. Soc. Chem*. **1993**, *115*, 2970; (d) Rodrı´guez, A. D.; Shi, J.-G. *Org. Lett*. **1999**, *1*, 337.

[143]. **For diazoacetophone**: (a) Nicolas, I.; Maux, P. L.; Simonneaux, G. *Tetrahedron Lett.* **2008**, *49*, 2111; (b) Nicolas, I.; Roisnel, T.; Maux, P. L.; Simonneaux, G. *Tetrahedron Lett.* **2009**, *50*, 5149. **For diacceptor diazocompound bearing an p-methoxyphenyl ketones**: (c) Lindsay, V. N. G.; Nicolas, C.; Charette. A. B. *J. Am. Chem. Soc.* **2011**, *133*, 8972; (d) Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383. **For another diazoketone without diastereoselective report:** (e) Bauta, W.; Dodd, J.; Bullington, J.; Gauthier, D.; Leo, G.; McDonnell, P. *Tetrahedron Lett.* **2000**, *41*, 1491.

[144]. Deng, G.; Luo, J. *Tetrahedron*. **2013**, *69*, 5937.

[145]. Otsuki, T.; Kumagai, J.; Kohari, Y.; Okuyama, Y.; Kwon, E.; Seki, C.; Uwai, K.; Mawatari, Y.; Kobayashi, N.; Iwasa, T.; Tokiwa, M.; Takeshita, M.; Maeda, A.; Hashimoto, A.; Turuga, K.; Nakano, H. *Eur. J. Org. Chem.* **2015**, 7292.

[146]. (a) Sekar, G.; DattaGupta, A.; Singh. V. K. *J. Org. Chem.* **1998**, *63*, 2961;

[147] Zhang, H.; Wen, X.; Gan, L.; Peng, Y. *Org. Lett.* **2012**, *14*, 2126.

[148] Saitoh, T.; Ichikawa, J. *J. Am. Chem. Soc*. **2005**, *127*, 9696.

[149] Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc*. **2011**, *133,* 6166.

[150] Rauser, M. ; Ascheberg, C.; Niggemann, M. *Angew. Chem., Int. Ed*. **2017**, *56,* 11570.

[151] Freeman, H. S; Moser, L. S; Whaley, W. M. *Dyes & Pigments*. **1988**, *9*, 57.

[152] Saitoh, T., Ichikawa, J. *J. Am. Chem. Soc.* **2005**, *127*, 9696.

[153]. Chen, R.; Zhao, Y.; Sun, H.; Shao, Y.; Xu, Y.; Ma, M.; Ma, L.; Wan, X. *J. Org. Chem.* 2017, *82*, 9291.

[154]. Xia, Z.; Hu, J.; Gao, Y. Q; Yao, Q.; Xie, W. *Chem. Commun*. **2017**, *53*, 7485.

[155]. Pace, V. ; Verniest, G. ; Sinisterra, J. V. ; Alcántara, A. R. ; Kimpe, N. D. *J. Org. Chem.* 2010, *76*, 5760.

[156]. Stevens, C. L.; Sherr, A. E. *J. Org. Chem*. 1952, *17*, 1228.

[157]. Lngvik, O.; Saloranta, T.; Kirilin, A.; Liljeblad, A.; Mki-Arvela, P.; Kanerva, L. T.; Murzin, D. Y.; Leino, R. *ChemCatChem,* **2010**, *2*, 1615.

[158]. Ogawa, K.; Terada, T.; Muranaka, Y.; Hamakawa, T.; Hashimoto, S.; Fujii, S. *Chem. Pharm. Bull*. **1986**, *34*, 3252.
[159]. Hayashi, D.; Igura, Y.; Masui, Y.; Onaka, M. ***Catal. Sci. Technol.*** **2017**, ***7,*** 4422.
[160] Clayden, J.; Parris, S.; Cabedo, N.; Payne, A. H.; *Angew*. *Chem*. *Int*. *Ed*. **2008**, *47*, 5060.
[161] Otsuki, T.; Kumagai, J.; Kohari, Y.; Okuyama, Y.; Kwon, E.; Seki, C.; Uwai, K.; Mawatari, Y.; Kobayashi, N.; Iwasa, T.; Tokiwa, M.; akeshita, M. T.; Maeda, A.; Hashimoto, A.; Turuga, K.; Nakano, H. *Eur. J. Org. Chem*. **2015**, 7292.
[162] Ikeda, S.; Kondo, H.; Arii, T.; Odashima, K. *Chem*. *Commun*. **2002**, *0*, 2422.
[163] Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Doebler, C.; Spannenberg, A.; Maegerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* **2006**, *12*, 1855.
[164] (a) I. Nicolas, P. L. Maux, G. Simonneaux, *Tetrahedron Lett*. **2008**, 49, 2111; (b) Nicolas, I.; Roisnel, T. ; Maux, P. L. ; Simonneaux, G. *Tetrahedron Lett*. **2009**, 50, 5149.
[165] Bauta, W.; Dodd, J.; Bullington, J.; Gauthier, D.; Leo, G.; McDonnell, P. *Tetrahedron Lett*. **2000**, *41*, 1491.

LISTS OF PUBLICATIONS

1. Le, T. L.C; Ozaki, S.; Chanthamath, S.; Shibatomi, K.; Iwasa, S. *Org. Lett*, **2018**, *20*, 4490. **(DOI:** 10.1021/acs.orglett.8b01788).
2. Le, T.L.C; Chanthamath, S.; Shibatomi, K.; Iwasa, S. 2nd International Conference on Applied Science, 24-25th May **2018**, Ho Chi Minh City, Vietnam. Vol *1954*, 040002 (6 pages). (**DOI:** 10.1063/1.5033402).
3. Le, T. L.C; Agus Surhato, Chanthamath, S.; Shibatomi, K.; Iwasa, S.*, Adv. Synth. Catal*, **2018, accepted. (DOI:** 10.1002/adsc.201801077).
4. Le, T.L.C; Chanthamath, S.; Shibatomi, K.; Iwasa, S. 255th ACS National Meeting & Exposition, 18-22nd March, **2018**, New Orleans, USA. Oral Presentation.