Development of Novel Efficient Palladium – Catalyzed Carbonylation Reactions in Combination with Copper Salts

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ABSTRACT

The development of sustainable and efficient methodologies based on catalysis and organometallic chemistry has gained considerable attention. In this regard, carbonylation reactions catalyzed by transition metal are now widely recognized as a powerful tool in advanced organic synthesis to provide efficient entries to a variety of useful homologated carbonyl compounds utilizing carbon monoxide (CO) as an inexpensive and readily available C1 unit, which also meets the principles of “atom economy”, “step economy”, and “green chemistry”. Among the different types of carbonylation reactions, palladium-catalyzed oxidative carbonylation of alkenes have attracted much attention from both academia and industry in recent years since they allow the direct functionalization of C=C double bond with CO in the presence of suitable nucleophiles and oxidation reagents to produce more valuable products such as aldehydes, esters, and carboxylic acid derivatives. The development of novel methods with high efficiency, selectivity, and larger substrate scope is of immense importance for continued progress in this field.

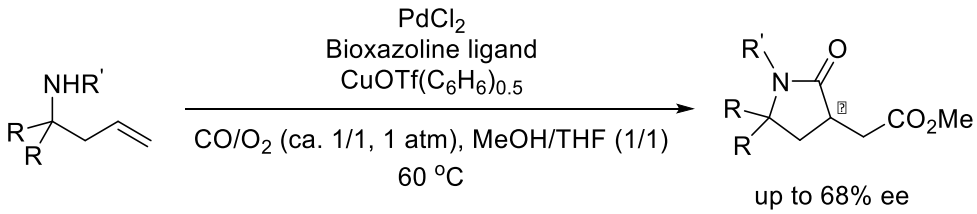
Our laboratory has studied palladium-catalyzed mono- and dicarbonylation of terminal olefins, homoallylic alcohols, homoallylic amine derivatives and already reported several asymmetric versions for dicarbonylation reactions. The combination of palladium(II) and copper(I) salt catalyzed these carbonylations under mild conditions.

Regarding to such perspectives, the aim of the study presented in this dissertation was to develop novel and efficient palladium-catalyzed oxidative carbonylation reactions in the combination with copper salts. The work involved in achieving the aim led to two main research contents as follows.

A. Asymmetric Palladium-Catalyzed Intra- and Intermolecular Dicarbonylation of Homoallylic Amine Derivatives

The γ-lactams can probably be considered as one of the most important heterocyclic

motifs used in synthetic and medicinal chemistry, which can be found in a very large number of biologically and pharmaceutically active compounds, and also serve as versatile building blocks for the synthesis of complex nitrogen-containing molecules. The development of methodologies allowing their synthesis is therefore of highly interest. Many synthetic approaches to *γ*-lactam compounds via metal-catalyzed cyclocarbonylation have been reported over the years. To the contrary, the enantioselective synthesis of *γ*-lactams has limited. Being encouraged by our previously results on asymmetric dicarbonylation reactions, an asymmetric palladium-catalyzed dicarbonylation of homoallylic amine derivatives was envisioned to produce optically active *γ*-lactams in single step. In this work, asymmetric intra- and intermolecular dicarbonylation of homoallylic amine derivatives catalyzed by palladium (II) and copper(I) salt under normal pressure of CO and O_2 has been achieved by using (*S*,*S*)-benzyl-substituted bioxazoline as a ligand. A variety of *N*-substituted homoallylic amine derivatives were applicable to the present reaction to give the corresponding optically active *γ*-lactams up to 68% ee (Scheme 1).

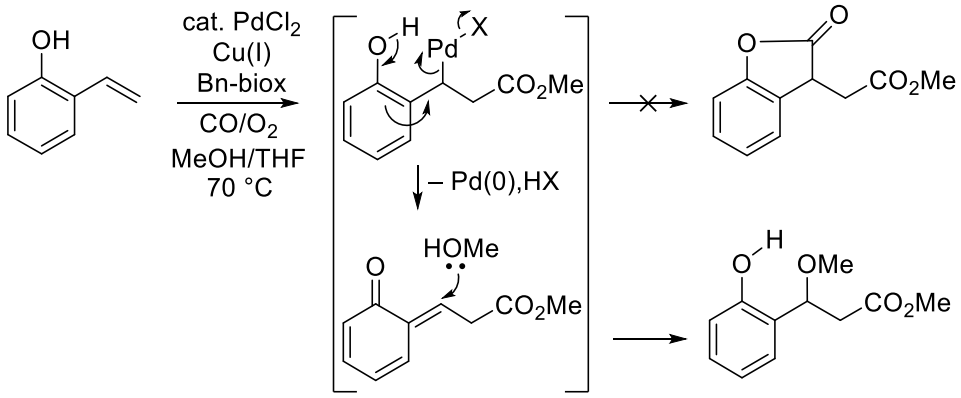


Scheme 1. Asymmetric palladium-catalyzed dicarbonylation of homoallylic amine derivatives.

B. Palladium-Catalyzed Intermolecular Alkoxy-Alkoxycarbonylation of Vinylphenols in the Presence of Copper Salt: Unexpected Cooperative Effect of Tin Salt

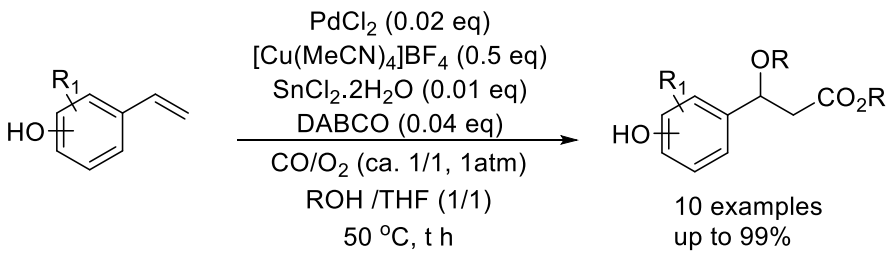
Concerning palladium-catalyzed carbonylation of unsaturated alcohols, intramolecular alkoxycarbonylation often proceeds to furnish cyclic ethers, such as tetrahydrofurans or

tetrahydropyrans. However, the intermolecular version of the alkoxy-carbonylation of alkenes is quite limited. In light of the successful development of a palladium-catalyzed intra- and intermolecular dicarbonylation protocol for homoallylic alcohols from earlier work in our laboratory, the idea of expanding the range of vinylphenols as substrates in the reaction emerged. The study was initiated with the asymmetric intra- and intermolecular bis(alkoxycarbonylation) of 2-vinylphenol. Interestingly, although the carbonylation proceeded smoothly, the expected lactone was not formed, but 3-aryl-3-methoxypropanoic acid methyl ester was obtained instead. This ester might be derived from regioselective carbopalladation followed by reductive elimination and subsequent addition of MeOH to the resulting quinonemethide before the second carbonylation (Scheme 2).



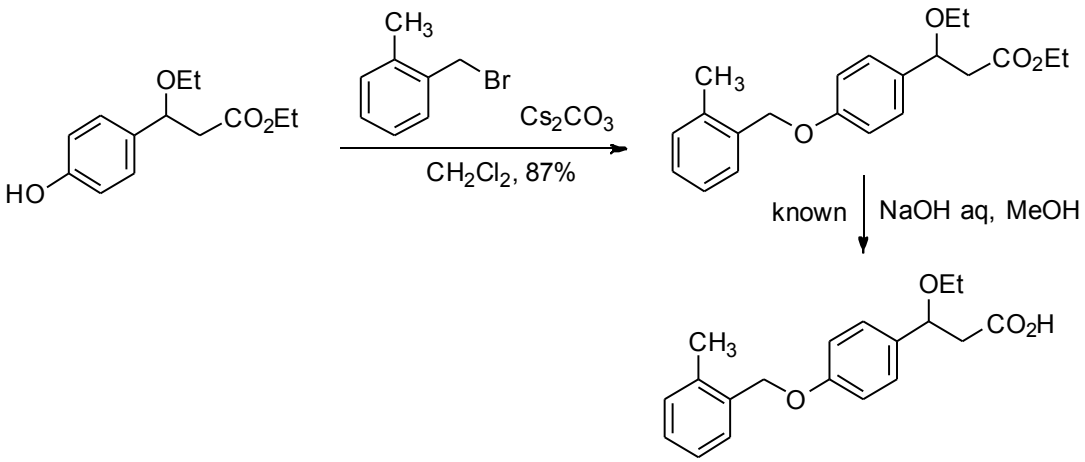
Scheme 2. Methoxy-methoxycarbonylation of 2-vinylphenol.

The unexpected result triggered the original objective to an extensive study on new intermolecular alkoxy-alkoxycarbonylation reaction. Consequently, the efficient palladium-catalyzed intermolecular alkoxy-alkoxycarbonylation of vinylphenols was developed to afford the corresponding 3-alkoxy-3-arylpropanoic acid esters in good to high yields under optimized conditions as shown in Scheme 3. Not only primary alcohols but also secondary alcohols were applicable to the present reaction. In this work, an unexpected effect of tin salt was discovered. The presence of a tin salt was crucial to realize reproducibly high yields.



Scheme 3. Alkoxy-alkoxycarbonylation of vinylphenols.

Futhermore, the 3-alkoxy-3-(4-hydroxyphenyl)propanoic acid esters obtained by the present alkoxy-alkoxycarbonylation was readily applied to the preparation of valuable chemicals and useful synthetic intermediates for biologically active compounds, such as GPR40 agonists for treatment of diabetes (Scheme 4).



GPR40 agonists for treatment of diabetes
(*Bioorg. Med. Chem*. **2015**, *23*, 5546)

Scheme 4. Transformation of 3-ethoxy-3-(4-hydroxyphenyl)propanoate.

In summary, novel and efficient palladium-catalyzed carbonylation reactions have successfully developed. The combination of palladium(II) with copper(I) salt has realized to catalyze these reactions under normal pressure of CO and O_2. Notably, the methods developed from this research could find great interest in the synthesis of highly functionalized molecules and especially in the synthesis of biologically active compounds. Thus, these results add value

to the scope of palladium-catalyzed carbonylation.

With respect to the contents, the dissertation includes following parts:

Chapter I provides general introduction, including context of the research area, relevant basic concepts, background of research and aims of the present work.

Chapter II focuses on the development of asymmetric palladium-catalyzed intra- and intermolecular dicarbonylation of homoallylic amine derivatives.

Chapter III presents the successful strategy for palladium-catalyzed intermolecular alkoxy-alkoxycarbonylation of vinylphenols.

Chapter IV provides a summary of fruitful outcomes of the present study, a proposal for extensive study, and general conclusion.

Experimental Section provides detailed experiment procedures, full spectra data for identification of new and important compounds.

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ABBREVIATIONS

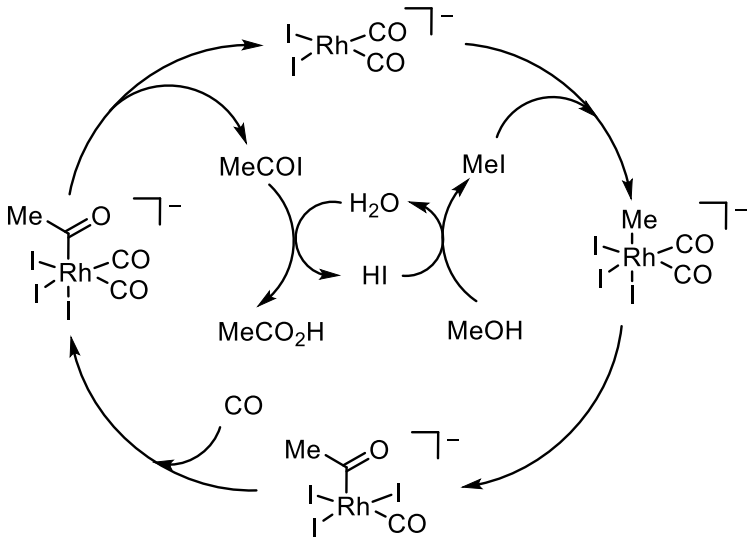
Ac	acetyl
acac	acetylacetonate
aq	aqueous
atm	atmospheric pressure
bipy	bipyridine
Bn	benzyl
BQ	1,4-benzoquinone
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DMAP	4-dimethylaminopyridine
dppf	1,1′-Bis(diphenylphosphino)ferrocene
OTf	trifluoromethanesulfonate (or triflate)
rt	room temperature
PCC	pyridinium chlorochromate
TFA	trifluoroacetate
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl
TsOH	*p*-toluenesulfonic acid

CONTENTS

CHAPTER 1: INTRODUCTION

1.1 Carbonylation Reactions: An Overview

The development of sustainable and efficient methodologies based on catalysis and organometallic chemistry has gained considerable attention. In this regard, carbonylation reactions catalyzed by transition metals are now widely recognized as a very important tool in industrial and organic chemistry to provide efficient entries to a variety of useful carbon-homologated compounds with oxygen-functional groups. The advantages of carbonylations are *(i)* it is the most potent methodology in the synthesis of carbonylcontaining chemicals, which increases the carbon number at the same time, and *(ii)* carbon monoxide (CO) can be used as an inexpensive and readily available C1 unit, which also meets the principles of "atom economy"[1b-d] "step economy"[2] and "green chemistry"[3]. Hence, it is not surprising that carbonylation has become industrial core technology for converting both bulk and fine chemicals into a diverse set of useful products of our daily life. For example, the vast majority of acetic acid is produced via carbonylation of methanol, commercialized in 1970 by Monsanto (Scheme 1.1).[4]



Scheme 1.1. Catalytic cycle for Rh-catalysed methanol carbonylation (Monsato process).

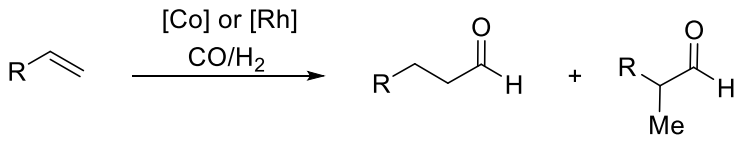
Especially, the conversion of olefins, the basic raw materials for the chemical industry, by carbonylation gives access to more valuable products such as aldehydes, alcohols, and carboxylic acid derivatives. Indeed, advancements in the field of transition-metal-catalyzed carbonylation have been proven by numerous publications. In the framework of this dissertation, a brief overview of developments as well as important works in the area of transition-metal-catalyzed carbonylation of alkenes, which is the most relevant to the present study, will be given.

A variety of transition metal catalysts are available for different types of carbonylation reactions. At the beginning of industrial homogeneous catalysis, nickel and cobalt catalysts prevailed in alkoxycarbonylations and hydroformylations. Due to the improved activities and selectivities since the 1970s, catalyst developments focused especially on rhodium (for hydroformylations) and palladium (for hydroxycarbonylations and alkoxycarbonylations) as base metals.

1.1.1 Hydroformylation

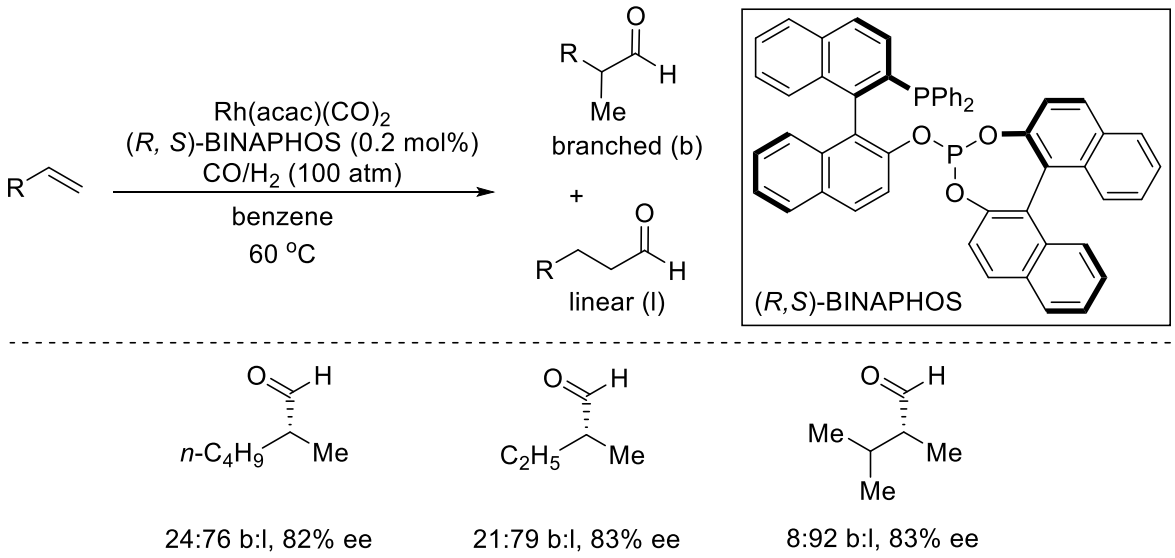
The first milestone in the history of carbonylation, discovered by Otto Roelen and patented in 1938,[5] was the reaction between alkenes and synthesis gas (syngas), an equimolar mixture of CO and H_2, to form aldehydes. Originally called "oxo-reaction", "hydroformylation" is the term used today. Given its superb atom economy, fast reaction rates, and high turnover numbers, transition-metal-catalyzed hydroformylation of alkenes has become one of the largest and most successful catalytic processes of commodity chemical manufacturing, thus producing millions of tons of oxo products per year.[6] Although earlier hydroformylations were based on cobalt; nowadays, rhodium is the preferred catalyst because it requires lower pressure and affords higher selectivity, including chemoselectivity and enantioselectivity. In recent years, extensive research aimed at producing only linear

aldehydes has provided impressive results. The application of phosphines with a wide bite angle in rhodium-catalyzed hydroformylation of terminal alkenes allows practically total control of the regioselectivity.[7] Branched selective hydroformylation, although less studied, constitutes a useful tool for organic synthesis.[8]



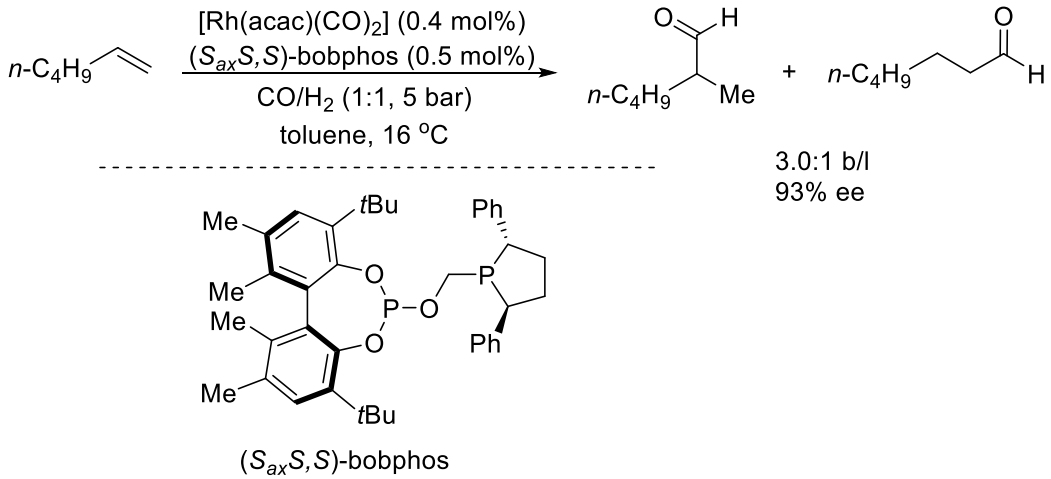
Scheme 1.2. General hydroformylation of terminal alkenes.

Furthermore, the asymmetric hydroformylation of olefins would be one of the most straightforward synthetic methods for the preparation of optically active aldehydes that are versatile intermediates for the synthesis of biologically active compounds as well as for other synthetic transformations. Developed by Takaya, Nozaki, and co-workers in 1993, the phosphine-phosphite-derived BINAPHOS was the first ligand used for a highly enantioselective hydroformylation of aliphatic terminal alkenes[9] (Scheme 1.3).



Scheme 1.3. Asymmetric rhodium-catalyzed hydroformylation of alkenes.

In 2012, Clarke and Cobley developed the first example of asymmetric hydroformylation in which electronically unbiased alkenes favored the branched isomer with high levels of enantioselectivity[10] (Scheme 1.4).



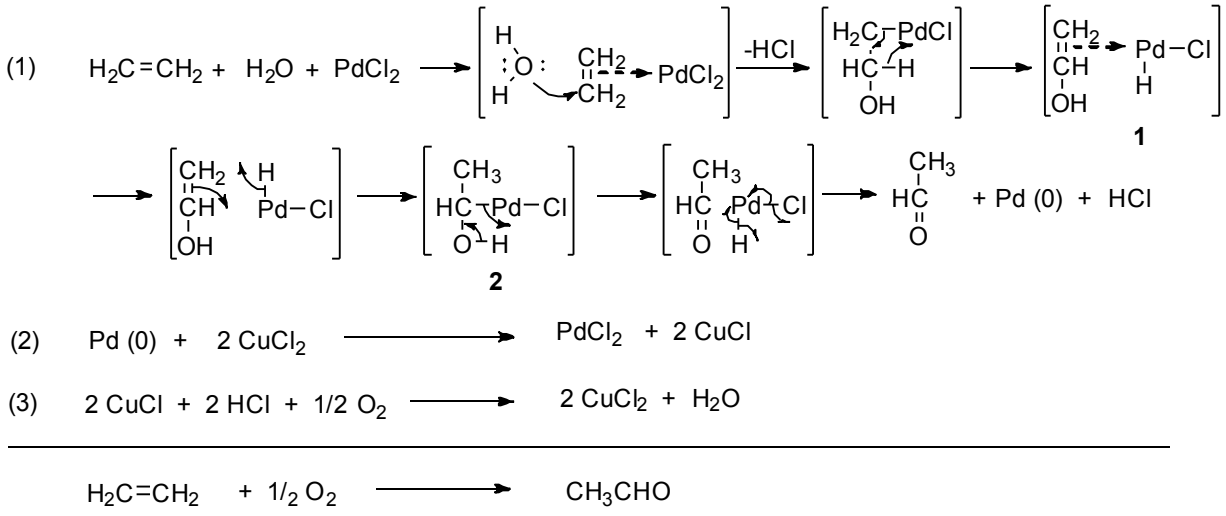
Scheme 1.4. Branched-selective rhodium-catalyzed hydroformylation of alkenes.

1.1.2 Palladium-catalyzed carbonylation

Although rhodium-catatyzed hydroformylation reactions have been well established, palladium-catalyzed carbonylation reactions also offer an interesting pathway to carbonylative derivatives. Among many transition metals used for organic synthesis, palladium forms probably the most general and versitile catalyst which are widely used for all kinds of C-C bond formation, including carbonylative processes. Thus, the importance of palladium catalysis was underlined by the 2010 Nobel Prize to R. Heck, A. Suzuki, and E. Negishi for their pioneering work in this field.[11] Palladium-catalyzed transformations are expanding rapidly, and a full description is outside the scope of this thesis. This section will therefore focus on basic concepts and fundamental processes of the Pd(II)-catalyzed oxidative transformations, especially carbonylation reactions of alkenes, which involve to the present research.

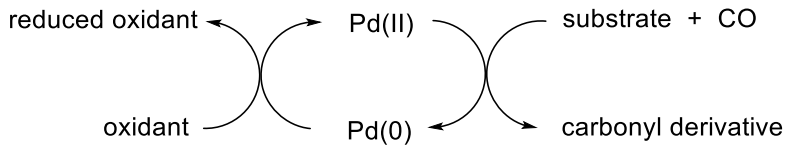
Palladium(II)-catalyzed oxidative transformations have experienced impressive improvements since the first discovery of Wacker process in the late 1950s.[12] In the Wacker process, ethylene is oxidized to acetaldehyde by using a combination of Pd(II) and Cu(II) salts. The process involves three unit reactions (Equations 1–3). The alkene coordinates to Pd(II) compounds to form π-complexes. Roughly speaking, a decrease in electron density of alkene by the coordination to electrophilic Pd(II) permits attack by nucleophiles (H_2O in particular here) to the coordinated alkene. (*The attack of nucleophiles with concomitant formation of a carbon-palladium σ-bond is called palladation of alkenes*). The sequence of hydroxypalladation followed by β-elimination give the vinyl alcohol **1**, which complexes to H-PdCl. Reinsertion of the coordinated vinyl alcohol with opposite regiochemistry gives **2**. Finally, elimination of Pd-H affords acetaldehyde, Pd(0) and hydrochloric acid (Equation 1). The essence of the Wacker process is the invention of an ingenious catalytic cycle, in which reduced Pd(0) is reoxidized *in situ* to Pd(II) with $CuCl_2$ (Equation 2). It is ingenious because the oxidation of Pd(0), a noble metal, with $CuCl_2$, a base metal salt, is expected to be very difficult. The CuCl is easily reoxidized to $CuCl_2$ with oxygen (Equation 3).[13]

Wacker reaction



Soon after the discovery of the Wacker process, a number of research groups demonstrated that Pd(II) could facilitate the addition of several different nucleophiles to alkenes, and a variety of oxidative and non-oxidative C–O, C–N, and C–C bond-forming transformations have been developed, including intra- and intermolecular reactions. Such opportunities, together with the broad functional group compatibility and air- and moisture-tolerance of the Pd(II)-catalysts, enable the preparation of important organic building blocks as well as useful hetero- and carbocyclic molecules.[14]

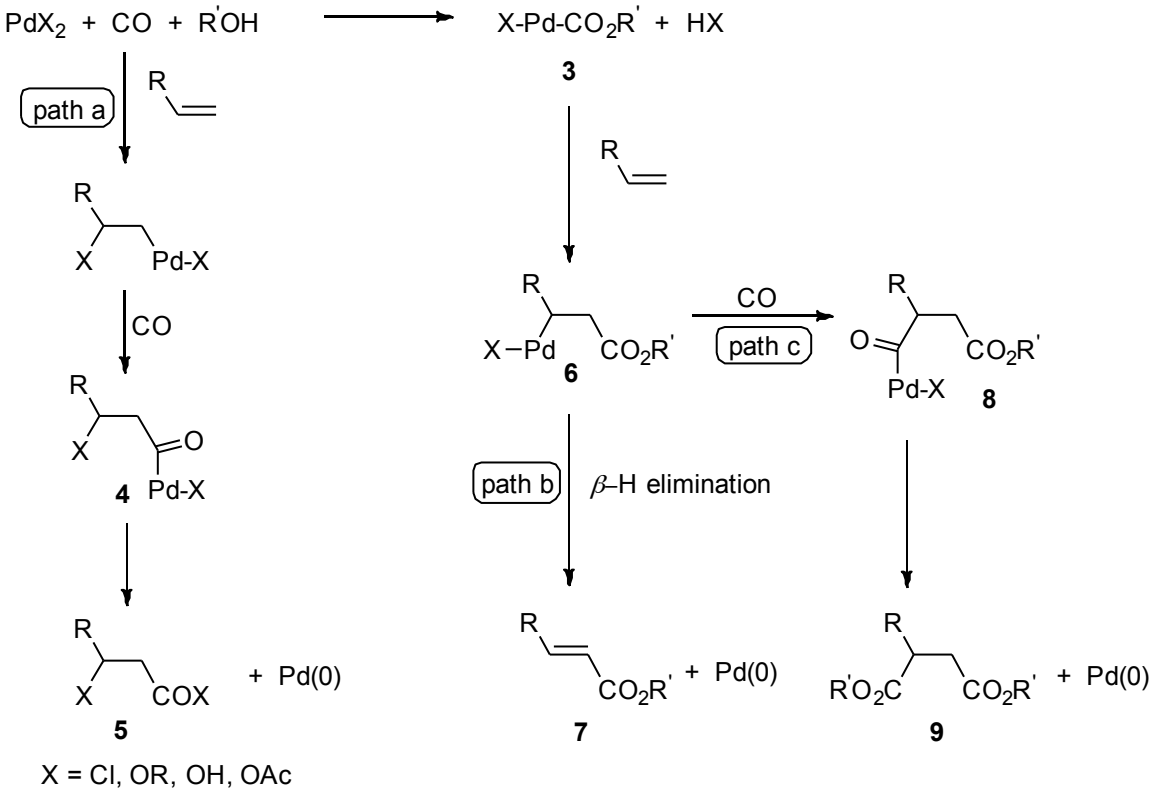
The Wacker process is the prototype for today's palladium-catalyzed oxidative carbonylations. Although no CO was used in this process, all the basic elementary steps for regenerating the catalyst under oxidative conditions are included. By definition, an oxidative carbonylation is a process in which CO is inserted into an organic substrate under the action of a metal undergoing a reduction of its oxidation state [the reduction Pd(II) → Pd(0) is the most common case] (Scheme 1.5). The external oxidants used for oxidative carbonylation reactions are either organic compounds or inorganic salts, such as benzoquinone (BQ), copper chloride, silver salts, etc. In some cases, O_2 or air can also be efficient oxidants in oxidative carbonylation process.



Scheme 1.5. General catalytic cycle for palladium-catalyzed oxidative carbonylation.

Oxidative carbonylation of alkenes is a unique reaction of Pd(II). Three types of oxidative carbonylation to give *β*-substituted carboxylic acid derivatives **5**, *α*,*β*-unsaturated esters **7** and succinate derivatives **9** are known,[13] which can be understood by the following

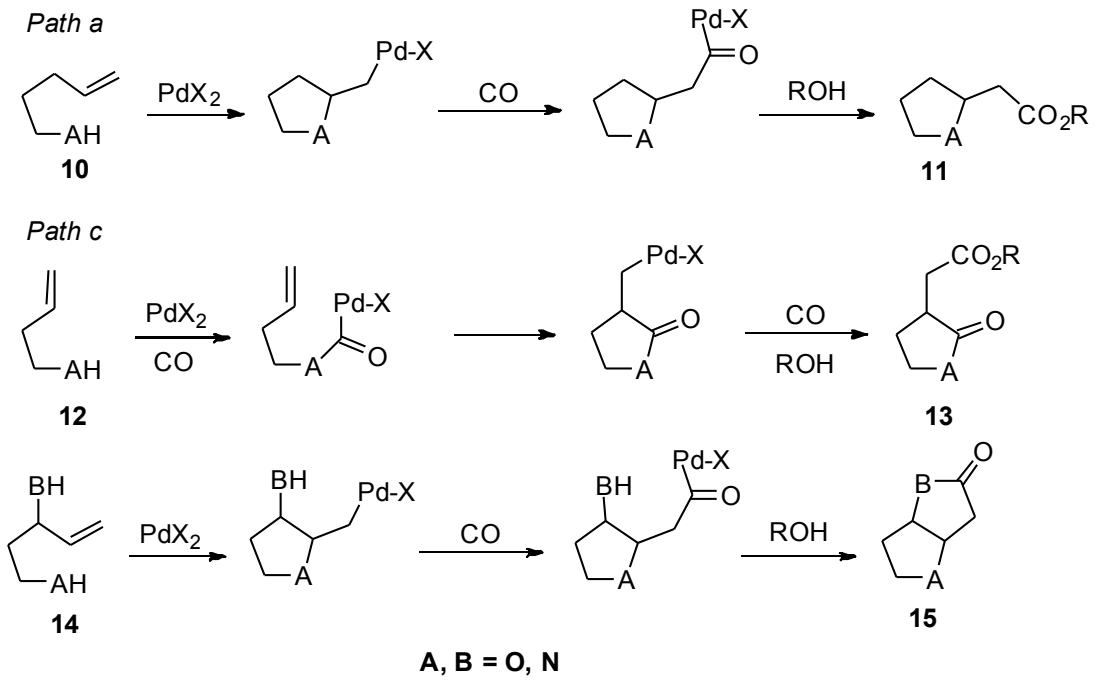
mechanism (Scheme 1.6). Palladation of alkenes with PdX_2, followed by CO insertion, generates the acylpalladium intermediate **4** whose reductive elimination affords *β*-substituted carboxylic acid derivatives **5** (path a). Reaction in alcohol in the presence of a base starts by the formation of the alkoxycarbonylpalladium **3**. Carbopalladation of alkene with **3** generates **6**. Then *β*-H elimination of the intermediate **6** yields the *α*,*β*-unsaturated esters **7** (path b). Further CO insertion to **6** gives the acylpalladium intermediates **8** and its alcoholysis yields the succinate derivatives **9** (path c). Formation of the *β*-alkoxy ester **5** (X = OR) is regarded as nucleophilic substitution of Pd-X in **6** with alcohols.



Scheme 1.6. Three types of oxidative carbonylation of alkenes.

Attack by other nucleophiles YH (such as amines, acids, carbanions) followed by alkoxycarbonylation constitutes another important type of such reactions.[15]

Ring closure with formation of heterocyclic derivatives may occur when a nucleophilic function, such as amino or hydroxy, is presented in the starting alkene and it is suitably placed for cyclization.[13, 16] It seems that, in an oversimplification, two mechanistic pathways may be suggested depending on substrates and reaction conditions (Scheme 1.7). The 4-pentenylamine or alcohol **10** is converted to **11** via amino or oxypalladation, followed by carbonylation by *path a*. The homoallylic amine or alcohol **12** is converted to lactone or lactam ester **13** by *path c*. Clearly, only in the latter case carbon monoxide is incorporated into the heterocyclic ring (cyclocarbonylation). With alkenes bearing two suitably placed nucleophilic groups **14**, the two mechanisms, palladation and carbonylation, may even occur in sequence leading to a double cyclization product **15**.



Scheme 1.7. Mechanistic pathways for carbonylation of functionalized alkenes.

The advantages of oxidative carbonylation reaction of olefins have been well-known, providing a versatile method for the functionalization of C=C double bond to produce

aldehydes, carboxylic acids, and esters. Compared with the conventially carbonylative coupling reactions of organic halides, oxidative carbonylation reactions have the potential to accommodate milder reaction conditions as it avoids the difficult oxidative addition of metal catalyst with electrophile organic halides, which is usually inhibited by the high concentration of CO in traditional carbonylation reactions.[16a, 17] Moreover, the substrates are more widely available, thus reducing the cost of the carbonylation process.

However, this process accompanies challenges which have already realized as follows:

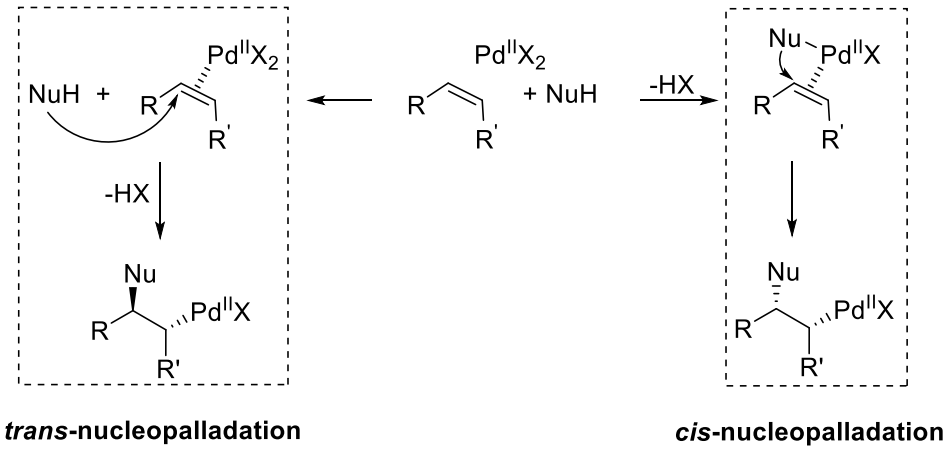
(a) To maintain a catalytic cycle, the Pd(0) formed after one catalytic cycle must be re-oxidized to Pd(II) by an oxidizing agents. These oxidants are generally required in large amounts and this excess usually interferes with phosphane- or nitrogen-based ligands;

(b) Pd(II) often catalyzes double-bond polymerization and isomerization, which can become a serious problem when the reaction is carried out under harsh conditions (e.g. high temperature or high CO pressure);[18]

(c) Oxidation of CO to carbonic acid derivatives by Pd(II) may compete with the carbonylation of olefins in the presence of water or alcohols, causing palladium aggregation.[19]

In term of asymmetric transformations, enantioselective Pd(II)-catalyzed functionalization of alkenes has experienced considerably less success than have many other classes of enantioselective transformations. Asymmetric Pd(II)-catalyzed oxidative carbonylation of alkenes was no exception, having experienced considerable difficulties in simultaneously obtaining both high regio- and enantioselectivities.[20] The former reactions face several challenges.[14] Phosphine ligands, which have been highly successful in other enantioselective processes, are often incompatible with the oxidants used in these reactions (such as O_2), and their σ-donating ability can attenuate the electrophilicity and/or oxidizing ability of the Pd(II) salts. A mechanistic basis for the difficulty in achieving effective

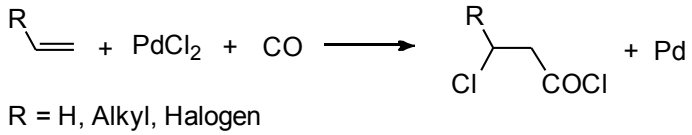
enantioselective catalysis is that nucleopalladation reactions are capable of proceeding by two stereochemically different pathways: *cis*- or *trans*-nucleopalladation (Scheme 1.8). Experimental results obtained over the past 40 years demonstrate that the energy barriers associated with these different pathways can bevery similar, in some cases similar enough that both pathways operate in parallel.[14] This mechanistic scenario can increase the difficulty of achieving high levels of enantioinduction.



Scheme 1.8. Stereochemical pathways of nucleopalladation.

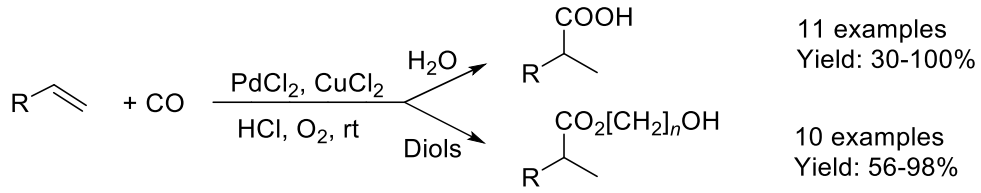
Above all, the great synthetic value of such carbonylation has been encouraging chemists to overcome its challenges. Indeed, it should be noticed that carbonylation of olefins catalyzed by palladium has far studied, and advancements in this area have been proven by numerous publications. I wish to provide a brief summary for the main achievements to realize the scientific reality of the present research area.

The first report of the oxidative carbonylation is reaction of alkenes with CO in benzene in the presence of $PdCl_2$ to afford the *β*-chloroacyl chloride (*path a*) by Tsuji and co-workers as early as in 1963 (Scheme 1.9).[21] Both internal and terminal aliphatic olefins were transformed into the corresponding chloroesters when the reaction was conducted in alcohols.



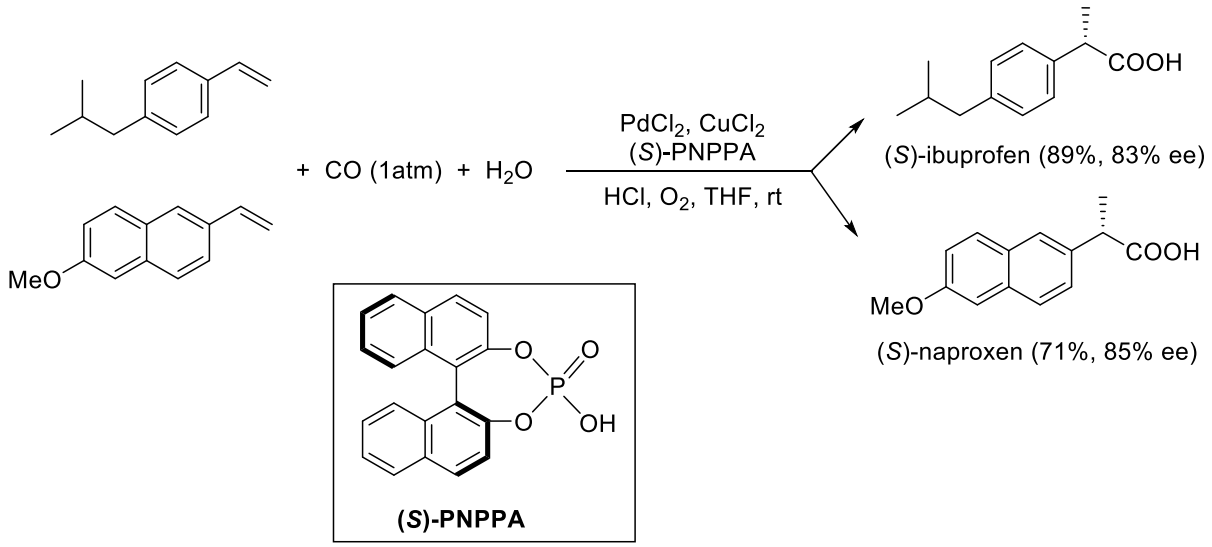
Scheme 1.9. Monocarbonylation of alkenes to β-chloroacyl chloride.

After that, extensive studies have been carried out on oxidative carbonylation. In 1983, Alper and co-workers reported a protocol for the hydrocarbonylation of alkenes.[22] Here, $PdCl_2$ and $CuCl_2$ were applied as the catalytic system. Alkenes were transformed into branched propionic acids in good yields in the presence of water, oxygen, and HCl. Later, they extended their protocol to the monohydroesterification of diols.[23] The reactions could be conducted under mild conditions (room temperature, 1 bar of CO) as shown in Scheme 1.10.



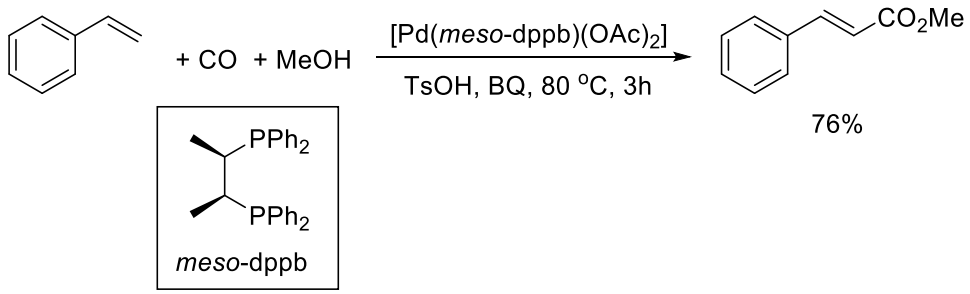
Scheme 1.10. Monohydrocarbonylation of alkenes to branched products.

By addition of the (*S*)-1,1-binaphthyl-2,2-diyl hydrogen phosphate (BNPPA) chiral ligand, it was possible to transform *p*-isobutylstyrene into (*S*)-ibuprofen and 2-vinyl-6-ethoxynaphtalene into (*S*)-naproxen, which both possess nonsteroidal anti-inflammatory properties[24] (Scheme 1.11).



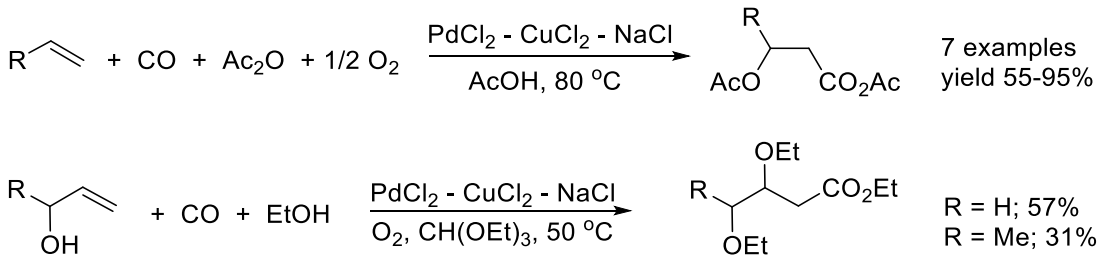
Scheme 1.11. Asymmetric hydroxycarbonylation of alkenes.

In 1979, Cometti and Chiusoli published their results on the synthesis of methyl cinnamates from styrene.[25] Using a mixture of $PdCl_2$, $CuCl_2$, $MgCl_2$, and NaOAc, the reaction was run in methanol at room temperature under atmospheric pressure of CO to produce methyl cinnamate. In 2001, Bianchini and co-workers also described new diphosphine-modified palladium systems that are able to catalyze the oxidative monocarbonylation of styrene in MeOH yielding methyl cinnamate (highest selectivity 99%)[26] (Scheme 1.12).



Scheme 1.12. Oxidative carbonylation of styrene to methyl cinnamate.

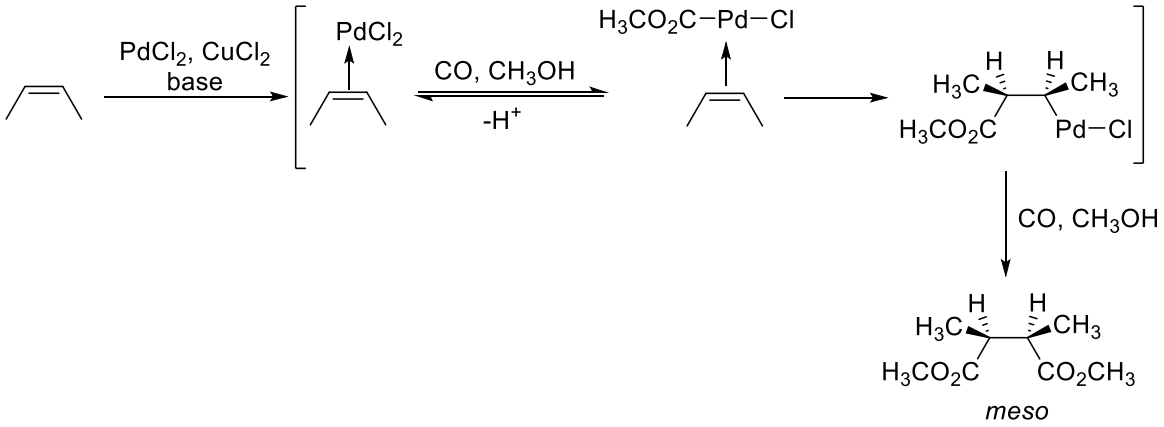
Fuchikami and co-workers[27] reported a practical preparation of *β*-hydroxyalkanoic acid derivatives by aerobic oxidative carbonylation of olefins under atmospheric pressure (Scheme 1.13). Olefins were heated in acetic acid and acetic anhydride in the presence of $PdC1_2$, $CuC1_2$, and NaCl under atmospheric pressure of CO and O_2 (ca. 2/l, v/v) to yield corresponding *β*-hydroxyalkanoic acid derivatives. *β,γ*-Diethoxybutanoates were also prepared from allylic alcohols with triethyl orthoformate.



Scheme 1.13. Oxidative-carbonylations of terminal olefins to hydroxyalkanoic acid derivatives.

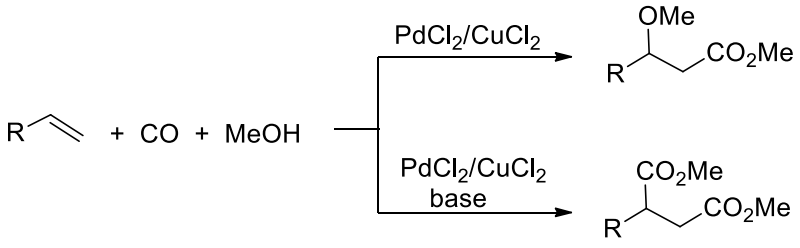
The first catalytic dialkoxycarbonylation of olefins was reported by Medema *et al*. in 1969.[28] More specifically, a catalytic amount of palladium was used together with an equivalent of $CuCl_2$, and the reactions were run at a high pressure of CO and comparatively high reaction temperature (140–150 °C). To elucidate the mechanism in more detail, Stille and co-workers[18a] carried out the stereospecific oxidative carbonylation of *cis*- and *trans*-2-butene in methanol in the presence of a catalytic amount of palladium(II) chloride and copper(II) chloride as reoxidant, yielding methyl *threo*- and *erythro*-3-methoxy-2-methylbutanoate, respectively, in the initial stages of the reactions. These results demonstrated that stereospecific *trans*-methoxypalladation is the exclusive reaction pathway. Addition of equimolar amounts of sodium acetate to the reaction mixture completely changed the course of the reaction. Carbonylation of *trans*-2-butene gave exclusively *dl*-dimethyl 2,3-

dimethylsuccinate while *cis*-2-butene afforded only the *meso* diastereomer (Scheme 1.14). Stereospecific *cis*-carbomethoxypalladation was therefore the exclusive reaction pathway. The authors also investigated the mechanism by means of ^{13}C NMR spectroscopy.[18b, 29]



Scheme 1.14. Mechanism for carbonylation of *cis*-2-butene to *meso*-diester.

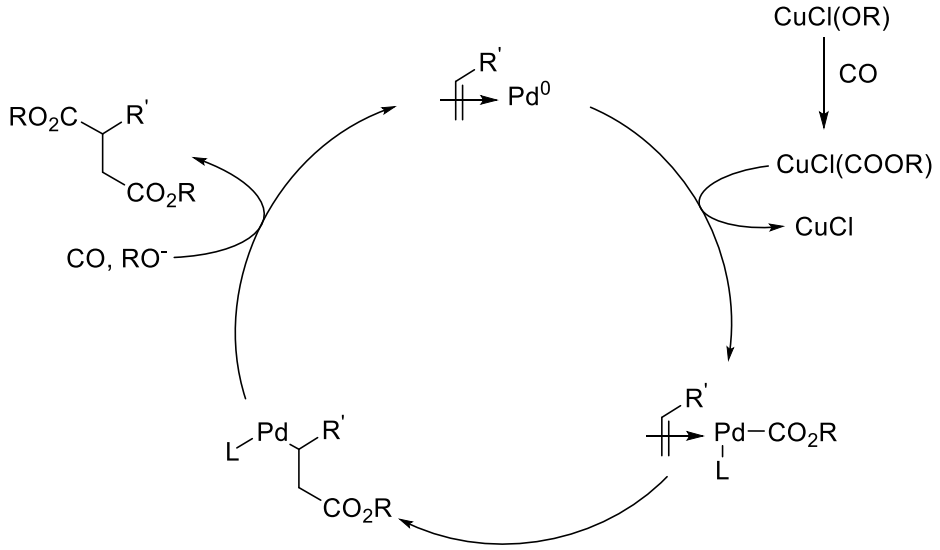
Apart from internal and terminal olefins, they extended their methodology to reactions of diolefins, vinyl ketones, unsaturated alcohols and unsaturated esters with a sodium butyrate buffer.[30] All these substrates were dicarboxylated in high yields (Scheme 1.15).



Scheme 1.15. Alkoxy-alkoxycarbonylation and bis(alkoxycarbonylation) of alkenes.

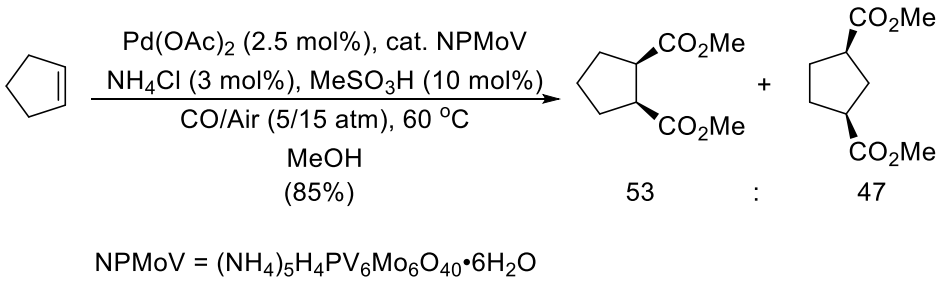
The role of copper salt used in the above mentioned reactions has merely been an oxidizing agent of Pd(0) as considered in the Wacker process. However, in 1990 Chauvin and co-workers[31] demonstrated a catalytic cycle in which the carboalkoxy groups can be

transferred to alkenes via the palladium atom by a carboalkoxycopper chloride (Scheme 1.16). Here, copper salt plays an additionally new role, as a co-catalyst, to form an active intermediate.



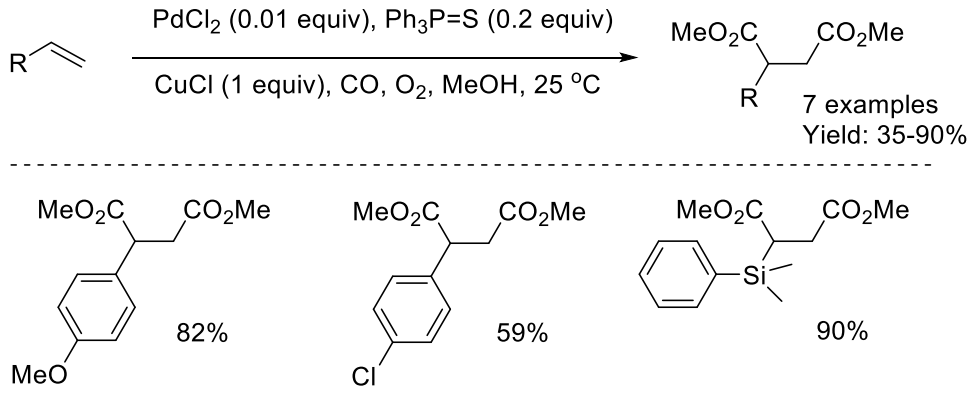
Scheme 1.16. Catalytic cycle of bis(alkoxycarbonylation) reaction.

In 2002, Y. Ishii's group reported the carbomethoxylation of cyclopentene with CO in methanol using air as the terminal oxidant by the use of a catalytic amount of $Pd(OAc)_2$ and molybdovanadophosphate (NPMoV) in the presence of a very small amount of the Cl^- ion, yielding dimethyl *cis*-1,2-cyclopentanedicarboxylate and dimethyl *cis*-1,3-cyclopentanedicarboxylate in good yields[32] (Scheme 1.17). Several alkenes were similarly converted into the corresponding dimethyl dicarboxylates.



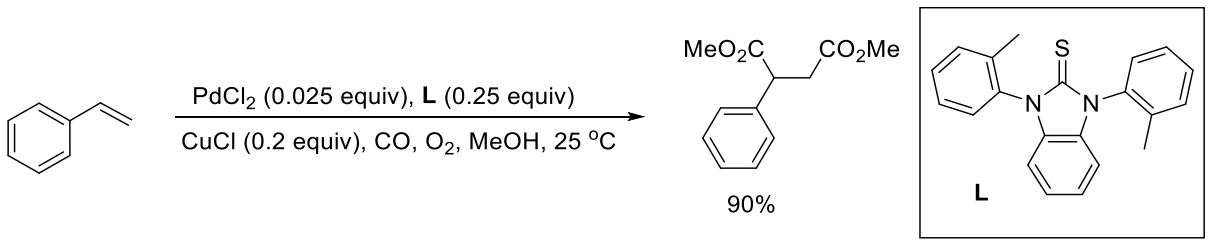
Scheme 1.17. Oxidative carbomethoxylation of cyclopentene.

Althought the ligand-accelerated Pd(II)-catalyzed carbonylation of nonfunctionalized olefins has been much less studied, some fruitful efforts to develop ligands for the oxidative carbonylation of alkenes have been given. In 1998, Saigo and co-workers reported that phosphine sulfide (Ph_3PS) is an effective ligand for the palladium(II)-catalyzed bis(alkoxycarbonylation) of olefins.[33] Aromatic olefins and vinylsilanes were converted into the corresponding succinates in high yields in the presence of Ph_3PS and CuCl at room temperature and under 1 atm of CO and O_2 (Scheme 1.18).



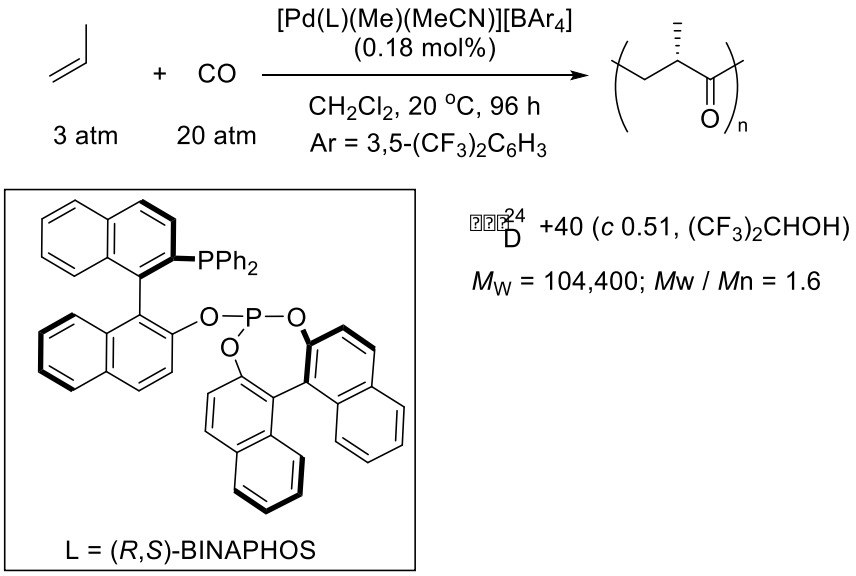
Scheme 1.18. Bis(alkoxycarbonylation) reaction of alkenes using triphenylphosphine-sulfide.

In 2003, Yang and co-workers developed procedures for the oxidative carbonylation of terminal olefins to phenylsuccinate esters by using thioureas as ligands.[34] The authors claimed that these ligands could prevent both palladium precipitation and double bond isomerization.



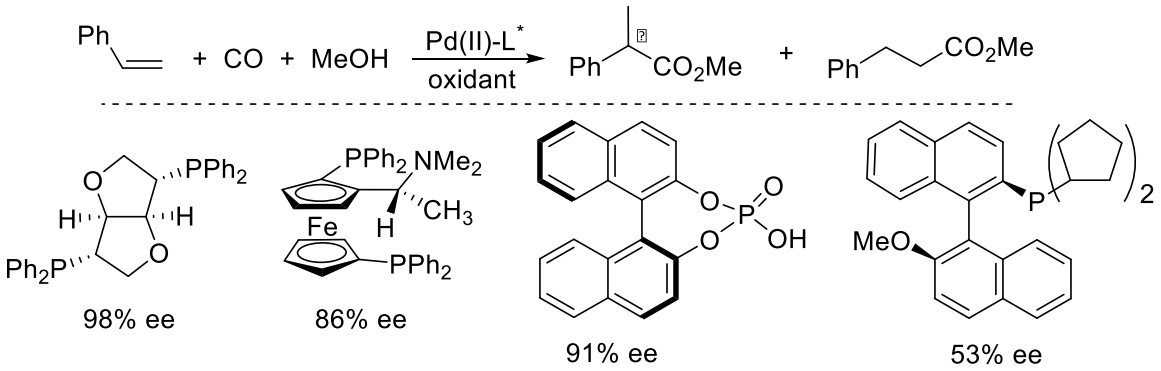
Scheme 1.19. Bis(alkoxycarbonylation) reaction of styrene using thiourea as ligand.

Asymmetric hydroxycarbonylation of olefins was first reported in 1973 using $PdCl_2$ and (-)-DIOP.[35] In 1995, K. Nozaki and coworkers reported a highly enantioselective alternating copolymerization of propene and CO catalyzed by Pd(II) complexes bearing the unsymmetrical phosphine-phosphite ligand (*R,S*)-BINAPHOS (Scheme 1.20).[36a]



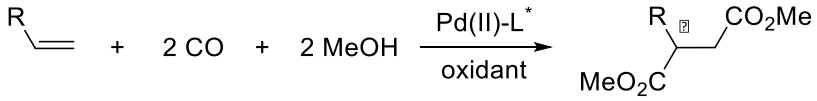
Scheme 1.20. Asymmetric alternating copolymerization of propene with CO.

Later, catalysts containing phosphine ligands had been frequently used for the asymmetric alkoxycarbonylation of alkenes, but these generally afforded low regioselectivity to the branched products.[24, 36b-c] Only few of them afforded high enantiomeric excess as shown on Scheme 1.21.



Scheme 1.21. Phosphine ligands used in asymmetric methoxycarbonylation of vinyl arenes.

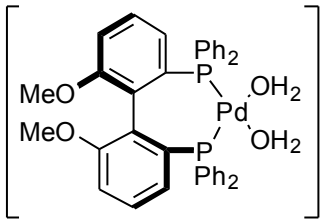
The enantioselective synthesis of optically active succinic acid derivatives is of interest as they are important intermediates of pharmaceuticals and building blocks for rennin inhibitors.[37] These products are formed by the asymmetric bis(alkoxycarbonylation) of alkenes (Scheme 1.22).



Scheme 1.22. General scheme for asymmetric bis(alkoxycarbonylation) of alkenes.

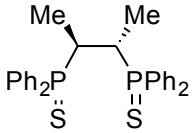
Consiglio and co-workers reported the enantioselective version of the bis-(alkoxycarbonylation) reactions of alkenes.[35,38] In 1999, they disclosed Pd-catalyzed alkoxycarbonylation of olefins using several atropoisomeric diphosphines, and high enantioselectivity (91% ee) was achieved when styrene was used as the substrate; however, the reactions were low yielding, and a pressurized autoclave was required to carry out the reactions. Later, Saigo's research group reported their efforts on asymmetric bis(alkoxycarbonylation) of styrene utilizing chiral ChiraphosS_2 under normal pressure of CO and O_2 to give diester in 68% and 33% ee.[33] In 2003, Chan *et al.* conducted the reaction using

chiral dipyridylphosphine under high pressure of CO (152 bar).[39] In 2007, Yang and co-workers developed chiral *S,N*-heterobidentate thiourea-oxazoline ligand, which were employed for asymmetric palladium-catalyzed bis(alkoxycarbonylation) of styrene under mild conditions, giving dimethyl phenylsuccinate 95% yield and 75% ee.[40]



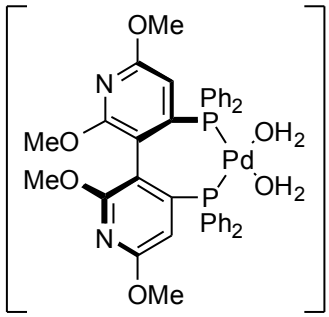
(*S*)-MeO-BIPHEP-Pd(II)

Consiglio (1993, 1999)
65%, 91% ee (*S*)
CO (50 bar), 50 °C

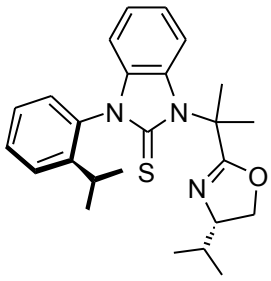


ChiraphosS$_2$

Saigo (1998)
68%, 33% ee
CO/O_2 (1/1, 1 atm), rt



Chan (2003)
56%, 84% ee (*R*)
CO (152 bar), 50 °C

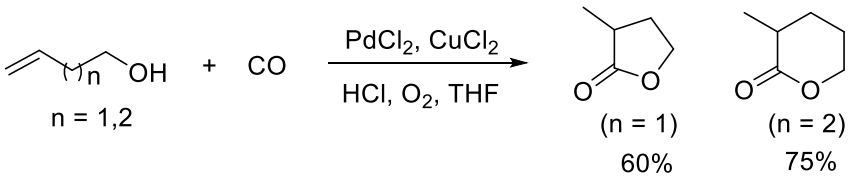


Yang (2007)
95%, 75% ee
CO/O_2 (4/1, 1 atm), rt

As early as 1996, Pd-catalyzed asymmetric bis(alkoxycarbonylation) reactions under mild conditions employing chiral bisoxazolines as ligands to furnish enantiomerically enriched diesters were already developed in our laboratory, which will be mentioned in more detail in Section 1.2.

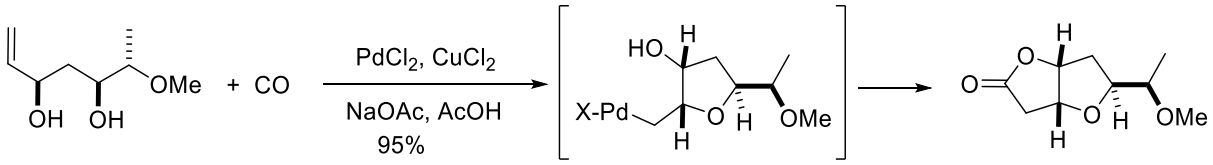
Carbonylation of alkenes having a nucleophilic function, such as an amino or hydroxy group, offers interesting synthetic methods for heterocyclic compounds.[13, 16] In 1985, Alper and Leonard reported oxidative carbonylation of alkenones to produce five-membered

lactones.[41] The reaction was conducted in THF in the presence of a $PdCl_2/CuCl_2$ catalyst system, yielding lactones in 42–80% (Scheme 1.23).



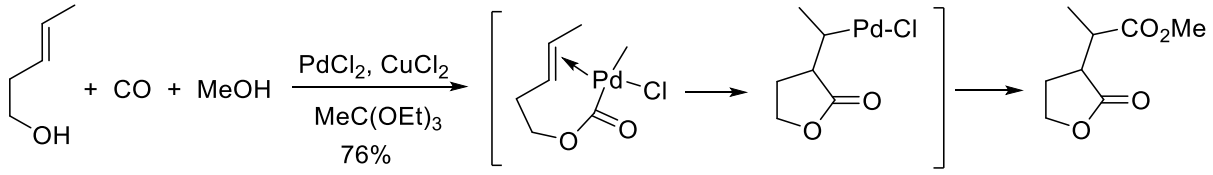
Scheme 1.23. Carbonylation reaction of alkenols.

Semmelhack and co-workers developed a methology for synthesis of *γ*-lactone by intramolecular oxycarbonylation of the alkenediol.[42] The intermediate is formed by the oxypalladation, and subsequent intramolecular carbonylation affords the lactone. The reaction was applied to the synthesis of tetronomycin (Scheme 1.24).



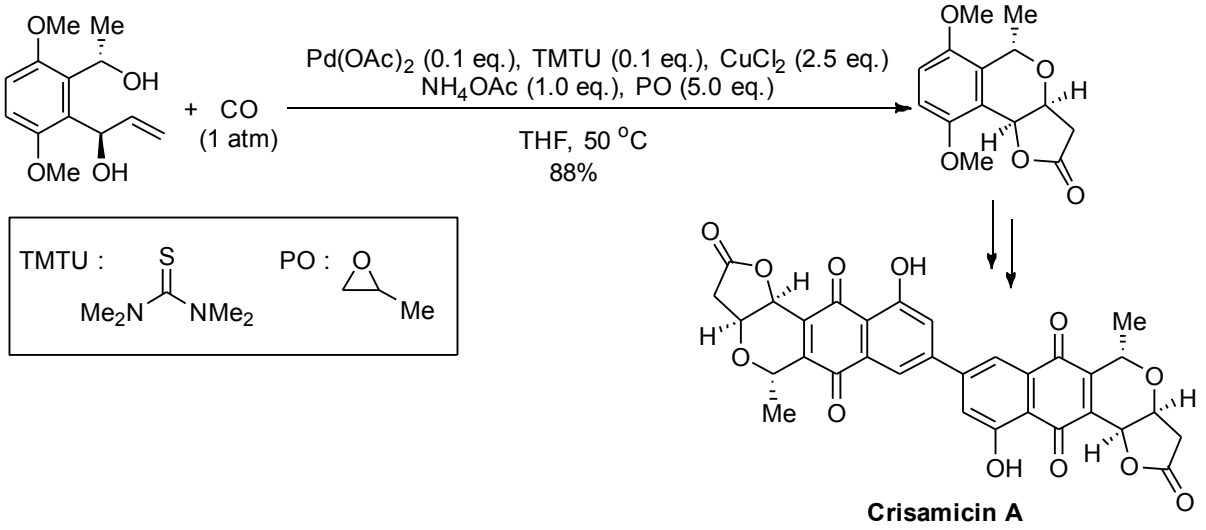
Scheme 1.24. Carbonylation of the alkenediol.

In 1991, Tamaru's group demonstrated oxidative carbonylation of 3-penten-1-ol in the presence of triethyl orthoacetate, giving the lactonic ester smoothly by dicarbonylation under mild conditions[43] (Scheme 1.25).



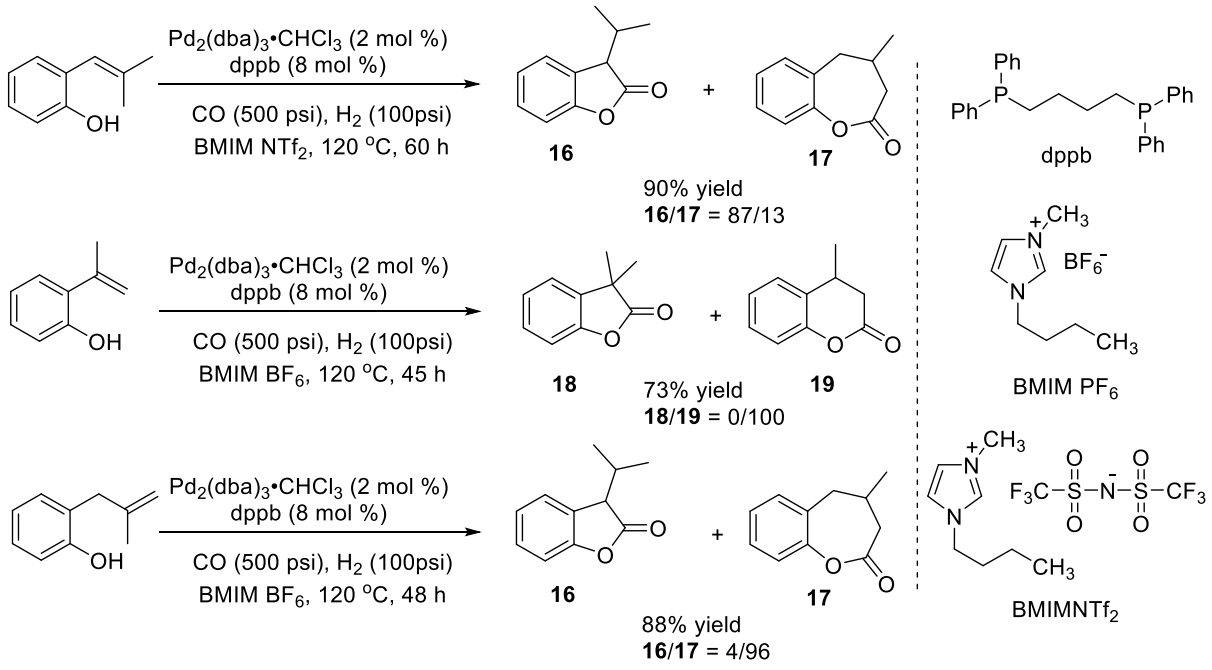
Scheme 1.25. Palladium-catalyzed dicarbonylation of 3-penten-1-ol.

In 2008, Z. Yang et *al*[44] developed Pd/TMTU-catalyzed alkoxycarbonylative annulation to generate a unique *cis*-pyran-fused lactone, which is an key intermediate for total synthesis of natural product Crisamicin A (Scheme 1.26).

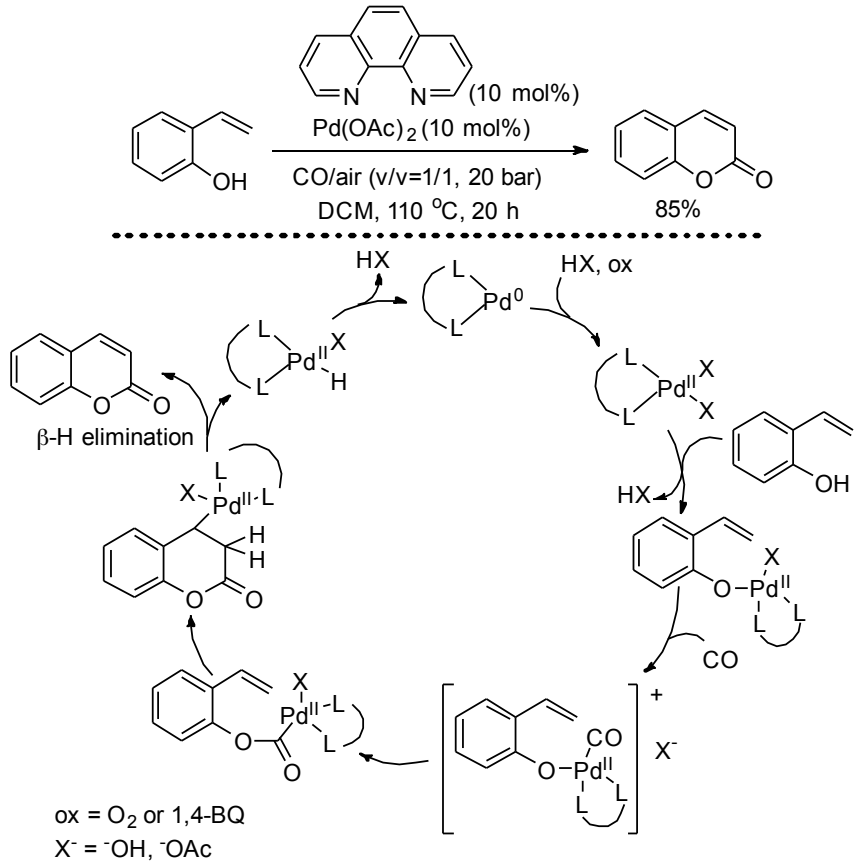


Scheme 1.26. Pd-catalyzed carbonylative cnnulation: Total synthesis of Crisamicin A.

Some studies have been reported on intramolecular palladium-catalyzed cyclocarbonylation of terminal olefins possessing phenol skeleton to form lactone derivatives. Alper and Ferguson reported the palladium-catalyzed cyclocarbonylation of 2-allylphenols and 2-vinylphenols in ionic liquids BMIM PF_6 or $BMIMNTf_2$.[45] The reaction proceeds cleanly and efficiently to afford high yields of lactones with good or excellent selectivity for one isomer (Scheme 1.27). Recently, Alper and co-workers have developed an efficient palladium-catalyzed oxidative cyclocarbonylation of 2-vinylphenols to prepare coumarins in high yields, using simple and mild conditions (CO $\leq$ 100 psi) with air or BQ as the oxidant.[46] This is the first intramolecular oxidative carbonylation in which a phenol has been coupled directly with a terminal alkene. The authors also outlined a possible mechanism pathway for the reaction as shown in Scheme 1.28.

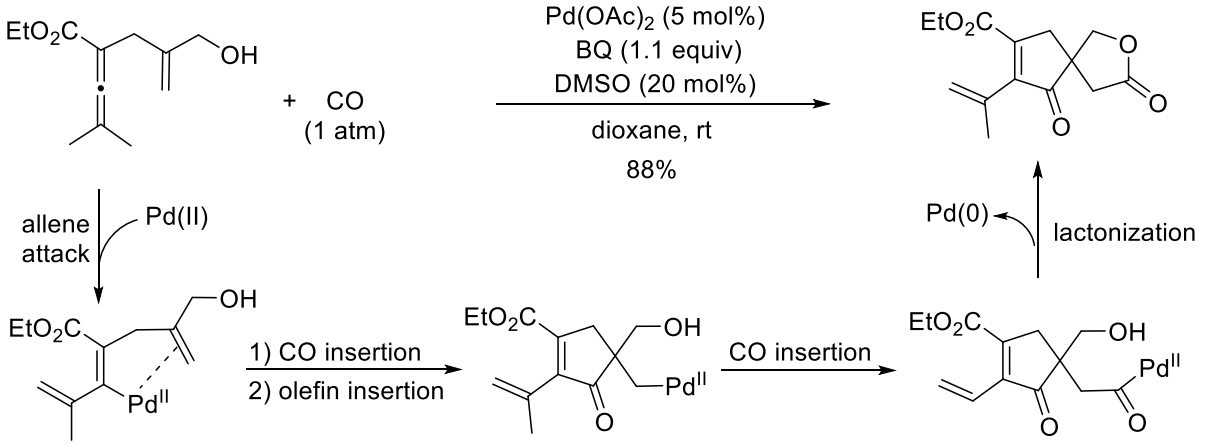


Scheme 1.27. Cyclocarbonylation reaction of vinyl- and allylphenols.



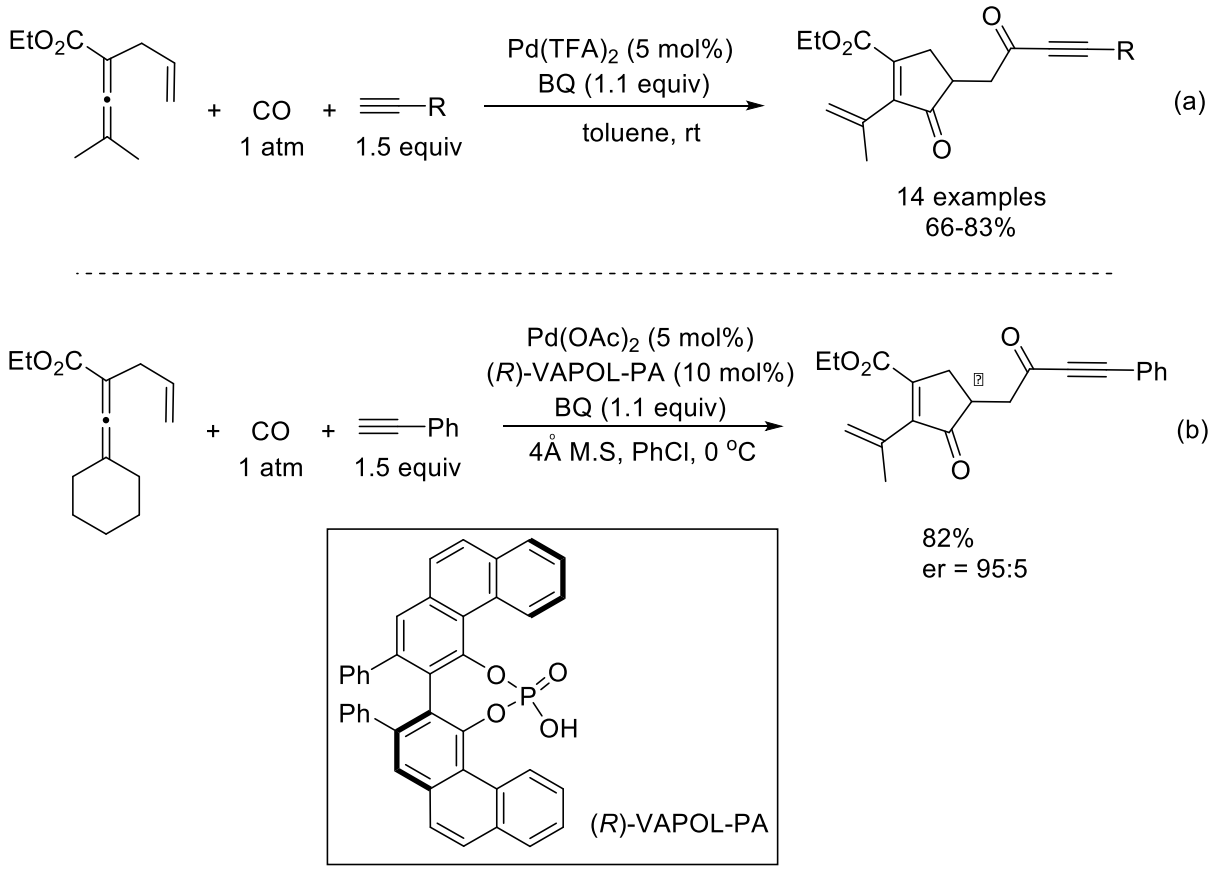
Scheme 1.28. Scheme 1.1 Cyclocarbonylation of 2-vinylphenols to coumarins.

Recently, a highly selective palladium-catalyzed oxidative carbonylation/ carbocyclization/alkoxycarbonylation of enallenols to afford spirolactones bearing an all-carbon quaternary center was developed by Bäckvall *et al*[47] (Scheme 1.29).



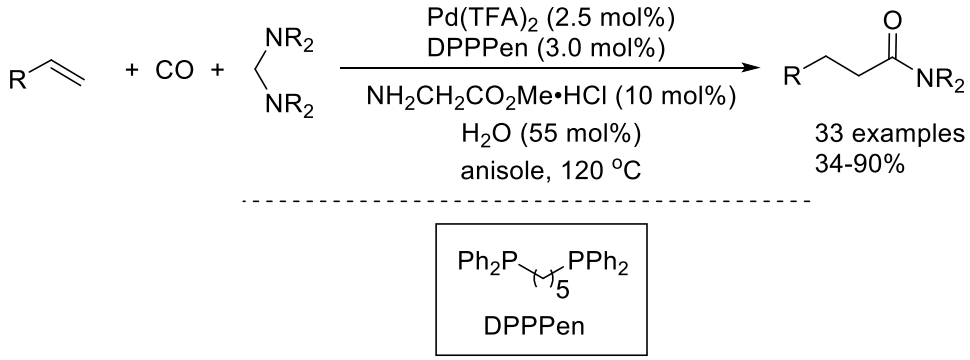
Sheme 1.29. Oxidative cascade carbonylative spirolactonization of enallenol.

The same research group reported a highly selective cascade C–C bond formation via Pd(II)-catalyzed carbonylation/carbocyclization/carbonylation/alkynylation of enallenes[48] (Scheme 1.30a). In 2017, they also developed an enantioselective Pd^{II}/VAPOL phosphoric acid-catalyzed carbonylative carbocyclization of enallenes via cross-dehydrogenative coupling with terminal alkynes for the construction of α-chiral ketones[49] (Scheme 1.30b).



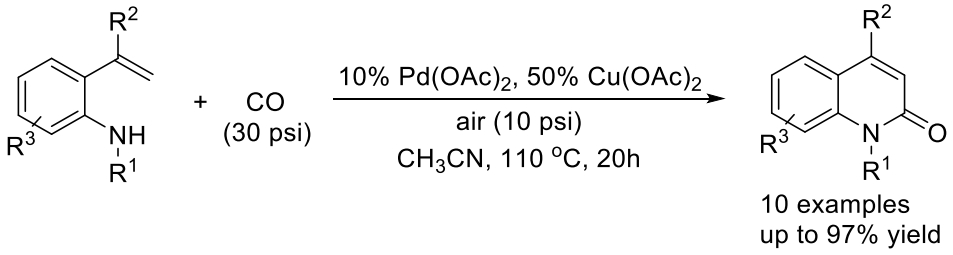
Scheme 1.30. Carbonylative carbocyclization of enallenes via cross-dehydrogenative coupling with terminal alkynes.

In 2015, Huang and co-workers[50] developed palladium-catalyzed hydro-aminocarbonylation of alkenes with amines under mild reaction conditions, and allowed the synthesis of a wide range of *N*-alkyl linear amides in good yield and high regioselectivity (Scheme 1.31).



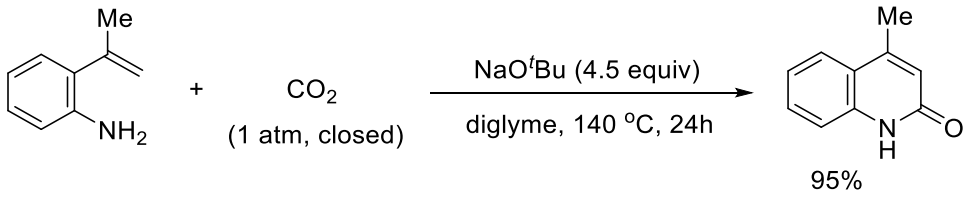
Scheme 1.31. Hydroaminocarbonylation of alkenes with amines.

Alper et *al* reported a method for the synthesis of 2(1*H*)-quinolinones via palladium-catalyzed oxidative cyclocarbonylation of 2-vinylanilines.[51] 2(1*H*)-Quinolinones with a variety of functional groups were prepared in up to 97% yield (Scheme 1.32).



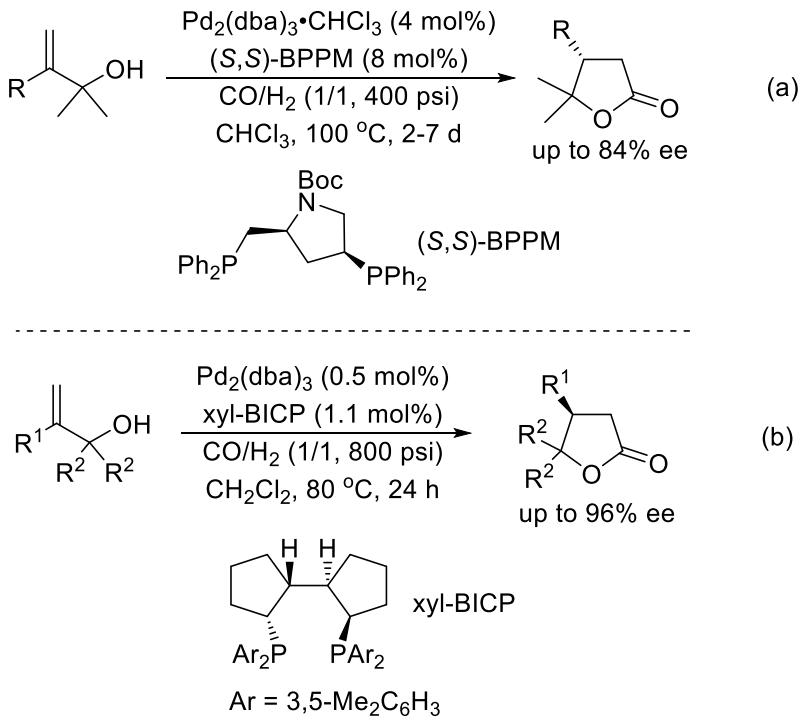
Scheme 1.32. Oxidative cyclocarbonylation of 2-vinylanilines.

In 2016, Yu and co-workers reported the first direct use of CO_2 as an ideal carbonyl source in the lactamization of alkenyl and heteroaryl C-H bonds to synthesize important 2-quinolinones and polyheterocycles in moderate to excellent yields[52] (Scheme 1.33). This transition-metal-free and redox-neutral process is efficient and eco-friendly, making it an attractive method for the pharmaceutical industry.



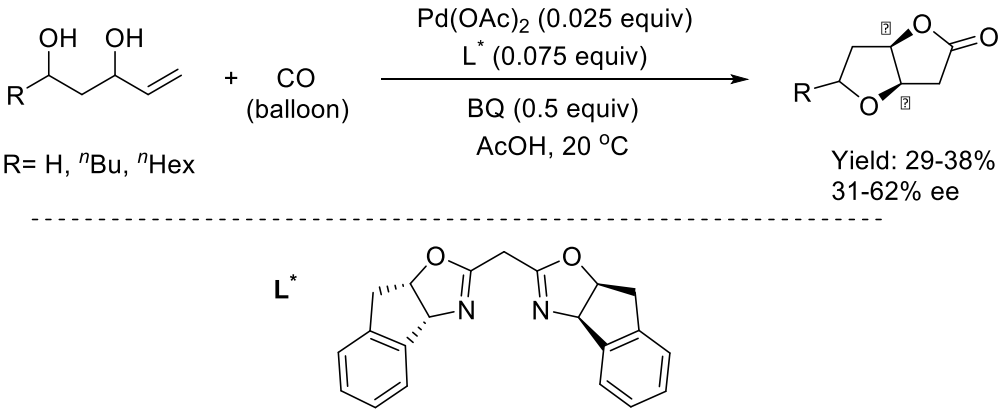
Scheme 1.33. Direct lactamization of 2-(prop-1-en-2-yl)aniline with CO_2.

Enantioselective palladium-catalyzed oxidative carbonylation of olefins bearing an amino or hydroxy group has proven particularly useful for stereoselective construction of a range of oxygen and nitrogen-containing heterocyclic compounds. Such a transformation of enantiomerically pure substrates has found numerous applications as the key step in the total syntheses of natural compounds.[53] In 1997, Alper and co-workers reported asymmetric cyclocarbonylation of allylic alcohols by using a chiral phosphine ligand derived from pyrrolidine to produce optically enriched γ-butyrolactones up to 84% ee[54] (Scheme 1.34a). In 1999, the group of Zhang also reported an asymmetric cyclocarbonylation reaction using a chiral BICP ligand and obtained the corresponding optically active lactones at a maximum of 96% ee[55] (Scheme 1.34b).



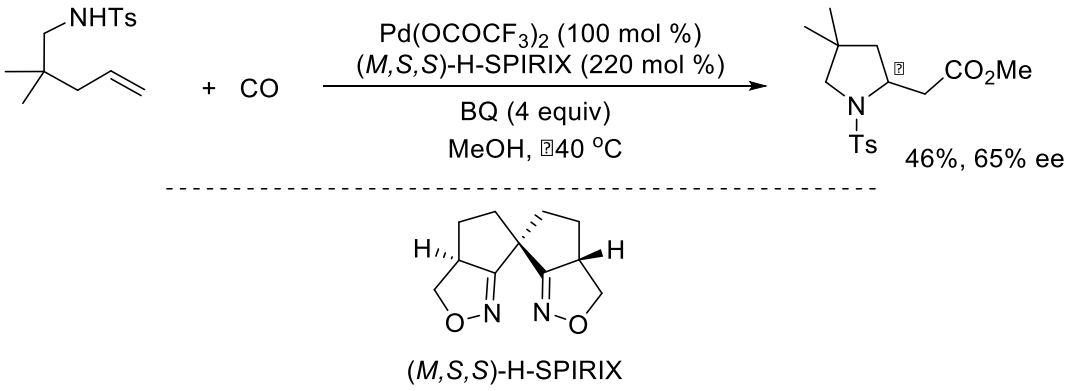
Scheme 1.34. Asymmetric cyclocarbonylation of allylic alcohols.

In 2008, Gracza and co-workers disclosed an enantioselective Pd(II)-catalyzed cyclization/carbonylation of 4-penten-1,3-diols to form bicyclic lactones.[56] Based on a ligand screening, the box-type *N*,*N*-bidentate ligand has been identified as the most suitable ligand for Pd-catalyzed oxidative lactonization of unsaturated diols (Scheme 1.35).



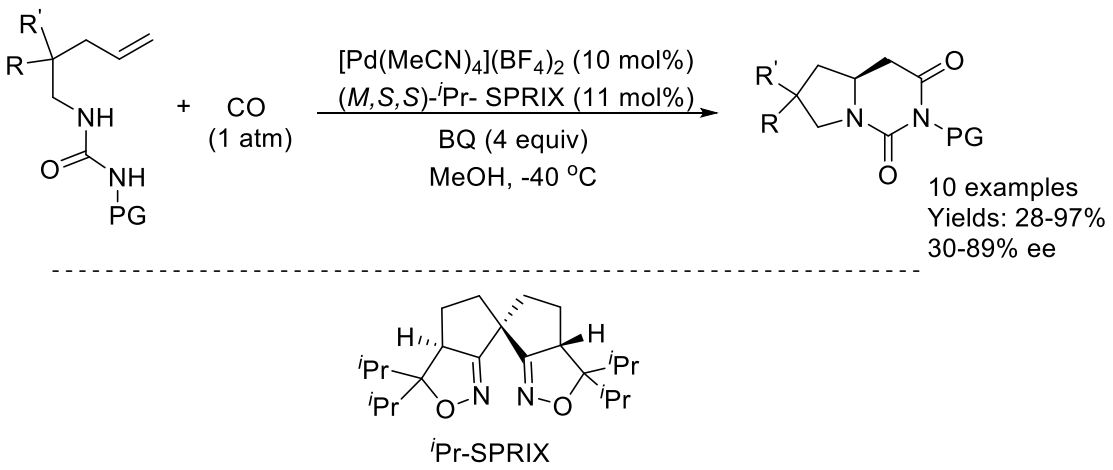
Scheme 1.35. Asymmetric intramolecular oxycarbonylation of alkene-1,3-diols.

The first enantioselective aminocarbonylation was published by Sasai and co-workers.[57] The reaction of *N*-(2,2-dimethylpent-4-enyl)-*p*-toluenesulfonamide in the presence of Pd(II)-SPRIX catalysts and BQ in methanol under a CO atmosphere afforded the corresponding pyrrolidinyl acetic acid methyl ester in moderate yield and enantioselectivity (Scheme 1.36). In comparison with the coordination ability of other known ligands, the peculiar character of SPRIX originates from two structural characteristics: low σ-donor ability of the isoxazoline coordination site and rigidity of the spiro skeleton.



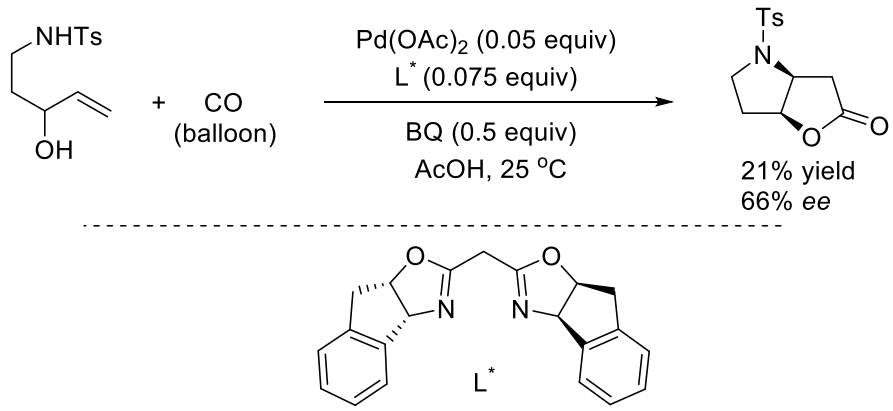
Scheme 1.36. Asymmetric aminocarbonylation using Pd(II)-[SPRIX] catalyst.

The group of Sasai also succeeded in constructing the tetrahydropyrrolo[1,2-*c*]-pyrimidine skeleton via Pd(II)-catalyzed aminocarbonylation of alkenylureas (Scheme 1.37).[58] Notably, the use of a chiral spiro bis(isoxazoline) ligand (^{i}Pr-SPRIX) was essential to obtain the desired products in optically active forms.



Scheme 1.37. Asymmetric intramolecular oxidative aminocarbonylation of alkenylureas.

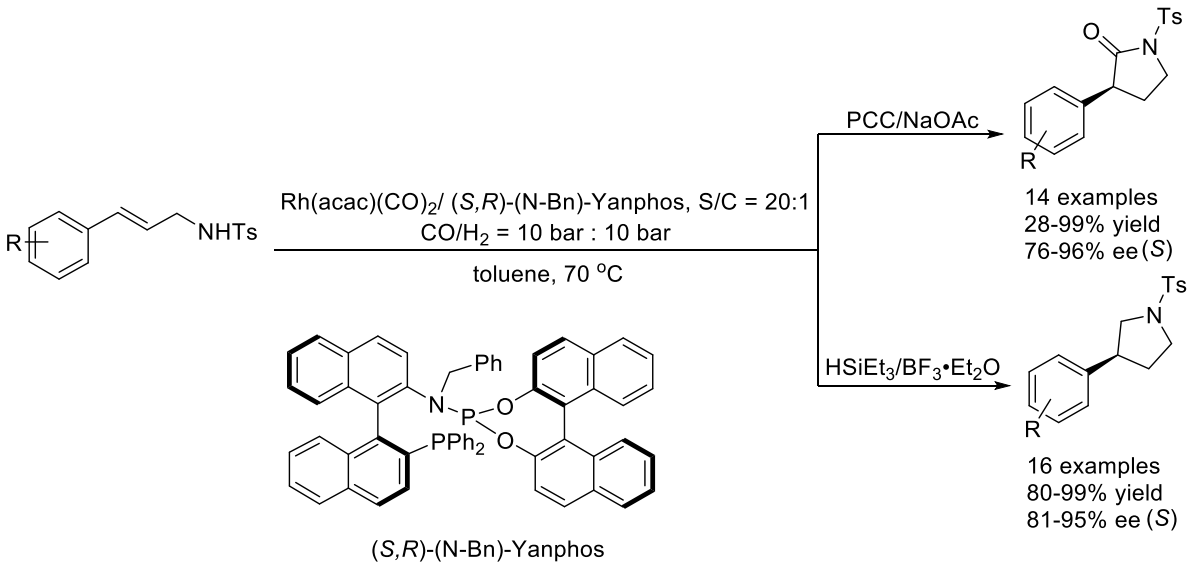
Asymmetric Pd(II)-catalyzed carbonylative bicyclization of amino alcohols has been reported by Graza's group in 2009.[59] The (*R*,*R*)-*N*-protected 2-oxa-6-azabicyclo[3.3.0]octan-3-ones (derivatives of the natural Geissman-Waiss lactone) were obtained in 20%–40% yields with 60%–73% *ee* by using chiral palladium(II)-bisoxazoline complexes (Scheme 1.38).



Scheme 1.38. Asymmetric intramolecular aminocarbonylation of unsaturated amino alcohols.

Recently, the first interrupted asymmetric intramolecular hydroaminomethylation was developed by Zhang and his co-workers.[60] The authors employed the challenging *trans*-1,2-

disubstituted alkenes as substrates, and a series of chiral pyrrolidinones and pyrrolidines was obtained in high enantioselectivity (Scheme 1.39).



Scheme 1.39. Asymmetric interrupted hydroaminomethylation of trans-1,2-disubstituted alkenes.

1.1.3 Conclusion

It is no doubt that carbonylation has attracted broad interest from both academia and industry. Especially, enormous efforts have gone into oxidative carbonylation of alkenes catalyzed by palladium. These reactions provide a novel and efficient tool for constructing a diversity of carbonylative compounds. Although considerable contributions have been made in this rapidly developing area, challenges still remain. Many of these reactions work at high pressure, limiting their application. Significant efforts should be directed towards developing a catalyst which works at atmospheric pressures, especially for the dangerous CO and O_2 gas mixture. In addition, asymmetric palladium-catalyzed carbonylations of olefins have undeveloped and still been regarded as the most challenging problem in carbonylation field.

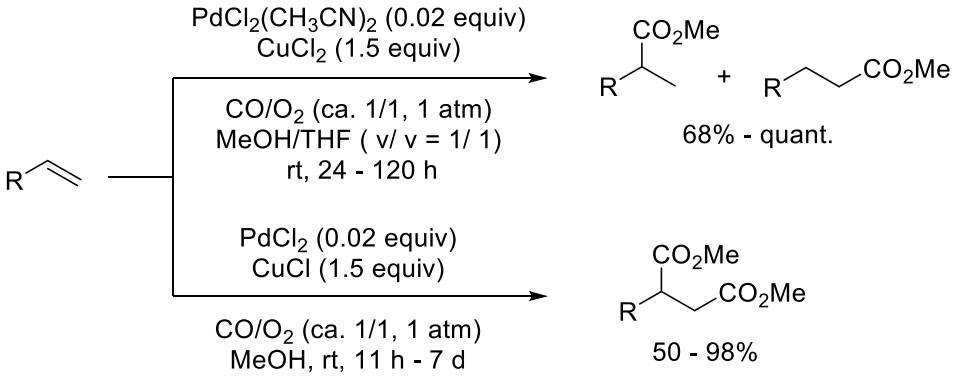
Furthermore, the intermolecular version of the alkoxy-carbonylation of alkenes is quite limited. Therefore, this area still remains space to develop in academic research. Development of catalytic system with higher efficiency, stereoselectivity, and larger substrate scope is an important issue for these transformations. Above all, the palladium-catalyzed oxidative carbonylation reaction will remain a hot research area because of both its advantages and challenges.

1.2 Research Background

1.2.1 Our previous works

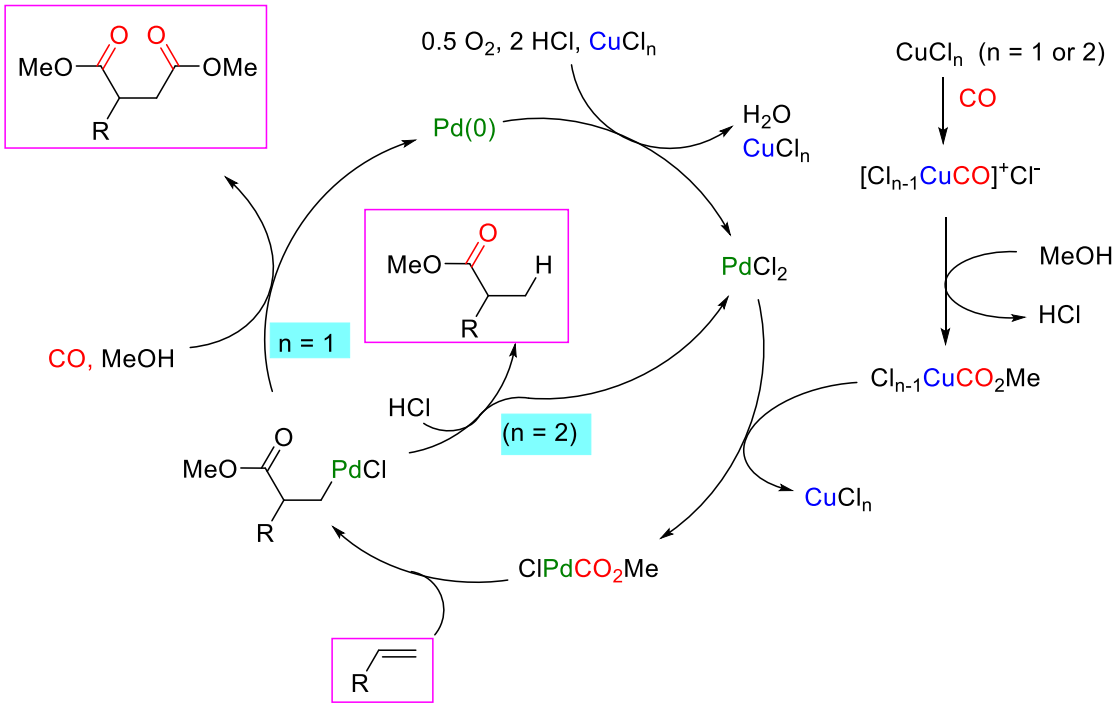
This section provides a brief summary for our previous works on palladium-catalyzed carbonylation, selecting from reported original papers of our research group. Such selected contents are presumed as a solid background for the present study. It should be noted that some contents (*i.e* our fundamental concepts, hypotheses) are presented here as a verbatim reprint under an agreement of our research group.

Considering the importance of palladium catalysis and the synthetic value of carbonylation reactions, we have had long-term interest in the palladium-catalyzed carbonylation since early as 1991. We have studied palladium-catalyzed mono- and bis(alkoxycarbonylation) of terminal olefins in the presence of Cu(II) and Cu(I) salts under normal pressure of CO and O_2.[61] Interestingly, mainly monoesters were observed if $CuCl_2$ was applied as oxidant, whereas diesters were formed in good yields by using CuCl as the oxidizing agent (Scheme 1.40).



Scheme 1.40. Selective mono- and bis(alkoxycarbonylation) reactions of terminal olefins.

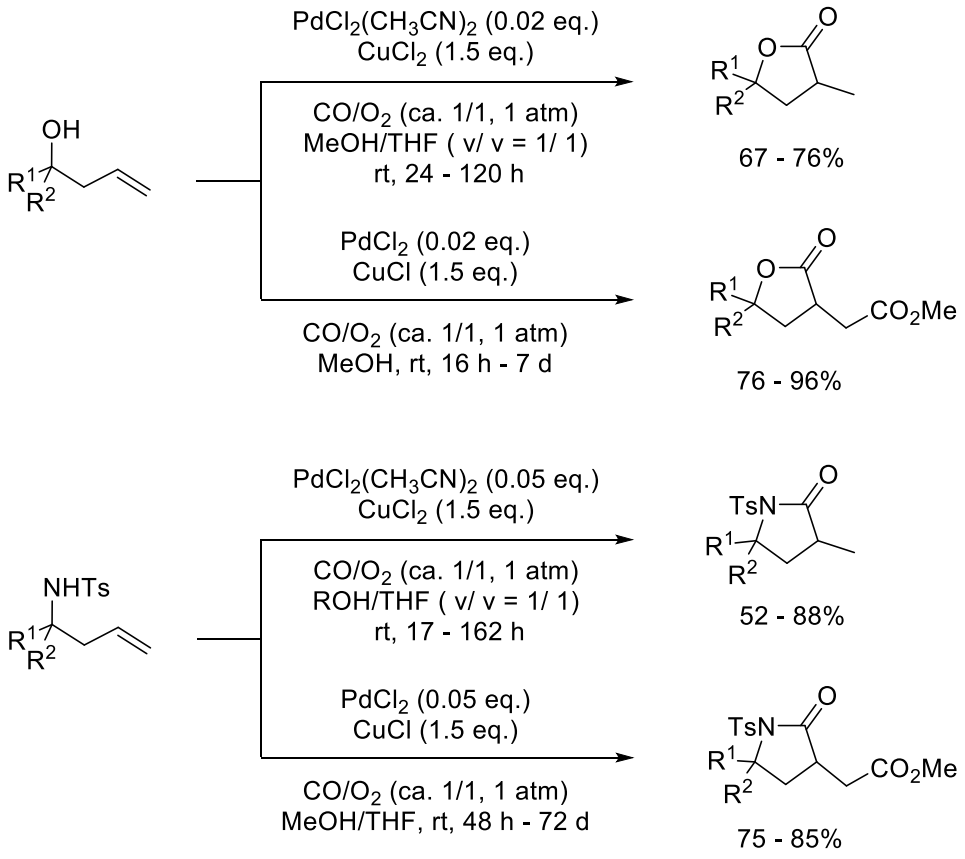
In the oxidation reaction of olefins catalyzed by palladium–copper systems, it has been proposed that copper works not as an oxidant of Pd(0) but cooperative action with palladium to generate active species.[62] Cu(I) compounds are well-known to absorb CO to generate carbonyl complexes. Carbonylation reactions of alcohols, amines, and water have been known to be catalyzed by Group 11 metals, in which alkoxycarbonyl-, carbamoyl-, and carboxyl-metal species are supposed as intermediates, respectively.[63] Thus, as shown on scheme 1.13, the $CuCO_2Me$ species might be a possible intermediate in the reaction.[31] One possible catalytic pathway for the selective mono- and bis(alkoxycarbonylation) reaction was hypothesized as shown on Scheme 1.41. That is, copper salts will react with CO to give the copper-alkoxycarbonyl complex, followed by the reaction with $PdCl_2$ to afford an active palladium-carboxyl complex. Subsequently, olefin insertion occurs to generate an intermidiate, in which olefin can coordinate to the palladium metal. In a reaction using Cu(II) salt, protonation by HCl furnished monoester. On the other hand, second carbonylation proceeds from palladium-carboxyl complex by using Cu(I), followed by reductive elimination to give diester. Pd(II) is regenerated by a reaction with O_2 and copper salt.



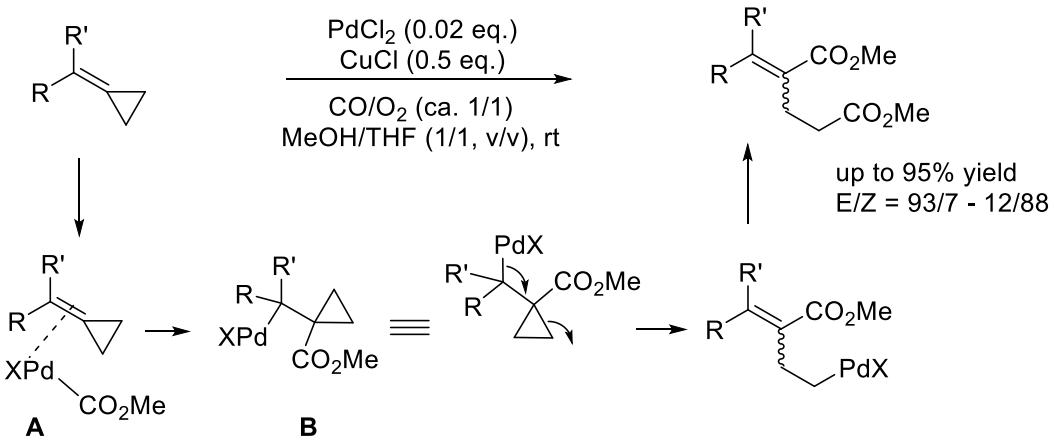
Scheme 1.41. Plausible catalytic pathway for the selective mono- and bis(alkoxycarbonylation) reactions.

Based on this hypothesis, *γ*-butyrolactones and *γ*-butyrolactams were also prepared chemoselectively from homoallylic alcohols and amine derivatives under the similar conditions, respectively (Scheme 1.42).[61b, 64]

Furthermore, the bis(alkoxycarbonylation) reaction of methylene cyclopropanes was found to proceed accompanied with ring-opening to furnish *α*-methyleneglutarates.[65] The carbopalladation of a double bond in **A** with (methoxycarbonyl)palladium intermediate, formed in the presence of CuCl, gives **B** which undergoes ring-opening *cis*- or *trans*-carbon elimination followed by the second carbonylation (Scheme 1.43).

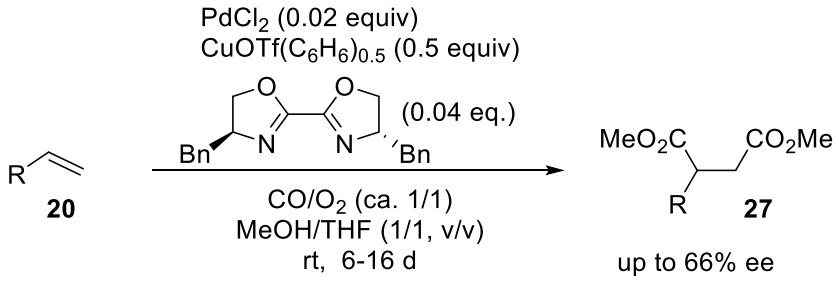


Scheme 1.42. Mono- and dicarbonylation reactions of homoallylic alcohols and homoallylic amines.

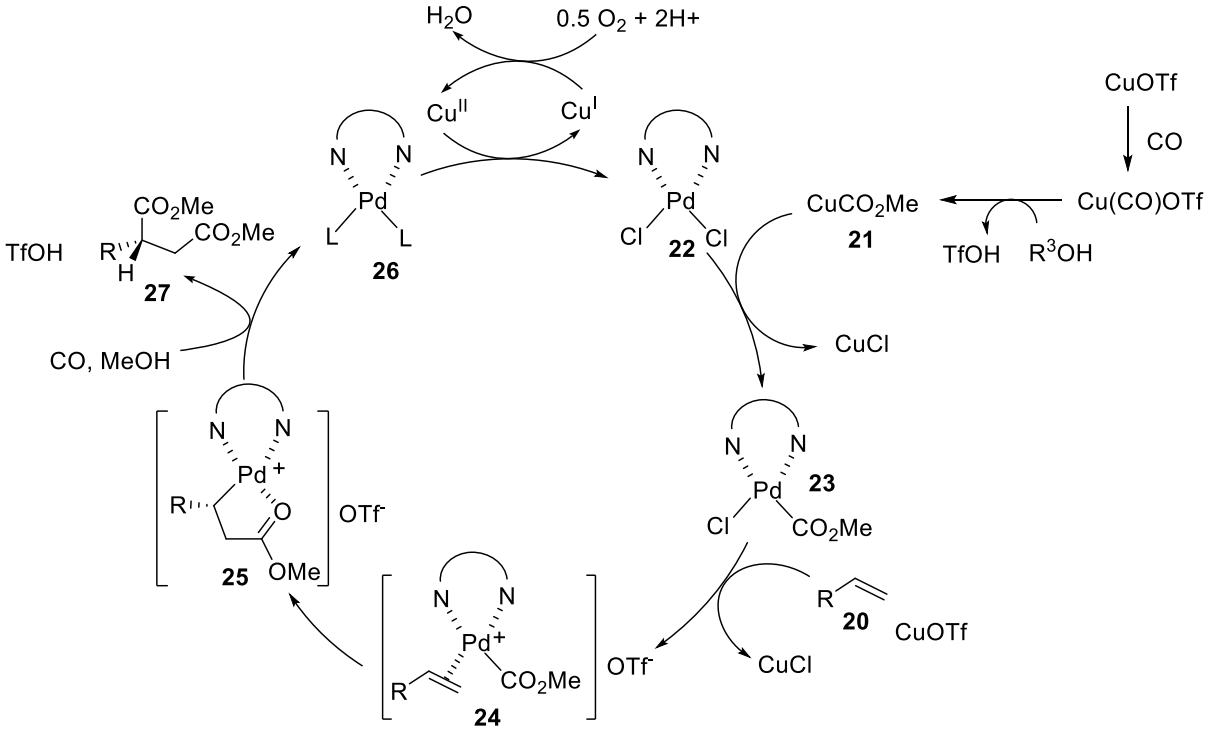


Scheme 1.43. Bis(alkoxycarbonylation) reaction of methylene cyclopropanes.

As the regio- and chemoselectivity of alkoxycarbonylations have been continuously improved and milder reaction conditions were applicable, we already developed asymmetric versions of bis(alkoxycarbonylation) reactions. A palladium-catalyzed asymmetric bis(alkoxycarbonylation) reaction of terminal olefins in the presence of copper(I) triflate was investigated to give the corresponding optically active monosubstituted succinates with enantioselectivity up to 66% ee (Scheme 1.44).[66] One possible reaction pathway is shown on Scheme 1.45.



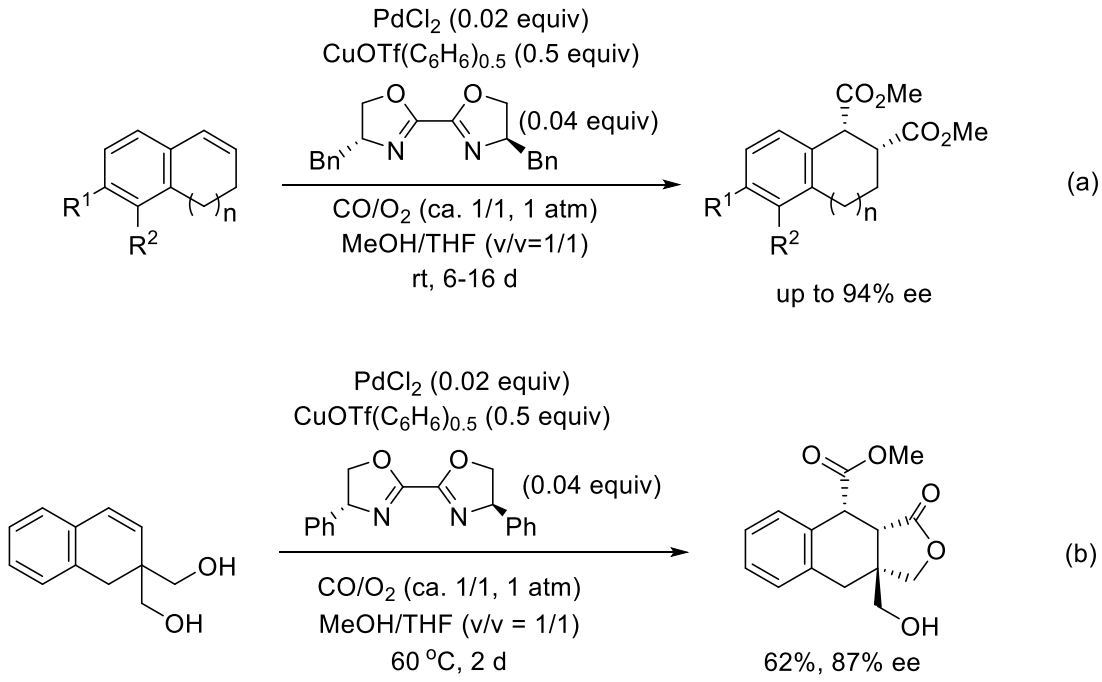
Scheme 1.44. Asymmetric bis(alkoxycarbonylation) of terminal alkenes.



Scheme 1.45. Plausible mechanism pathway.

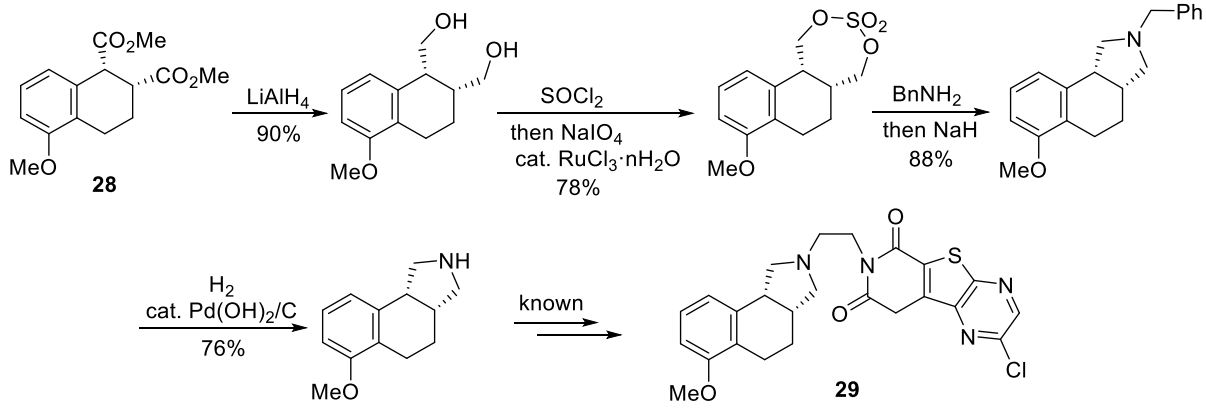
Copper(I) triflate reacts with CO and MeOH successively to give the $CuCO_2Me$ species **21** and the methoxycarbonyl group was transferred to palladium chloride complex **22** with the chiral ligand to generate complex **23**. Further, copper(I) triflate also reacts with **23** to afford a cationic palladium intermediate **24**, in which olefin can strongly coordinate to the palladium metal. An attack of palladium upon internal carbon of the olefin might be more favorable than that on terminal carbon to avoid a direct repulsion between a substituent R in olefin and the methoxycarbonyl group, producing an optically active mono-substituted succinate **27** along with palladium(0) complex **26**. The palladium(II) catalyst **22** is regenerated by the oxidation of **26** with oxygen in the presence of copper(I) salt.

Enantioselective palladium-catalyzed asymmetric bis(alkoxycarbonylation) reaction of 1,2-dihydronaphthalenes and related cyclic olefins[67] proceeded smoothly to form the optically active *cis*-diesters with excellent enantioselectivities by using benzyl-substituted bioxazoline ligand (Scheme 1.46a). Meanwhile, the intra- and intermolecular version of the bis-(alkoxycarbonylation) of a prochiral diol possessing dihydro-naphthalene skeleton[68] was also realized to give higher enantioselectivity (87% ee) with phenyl-substituted ligand (Scheme 1.46b).



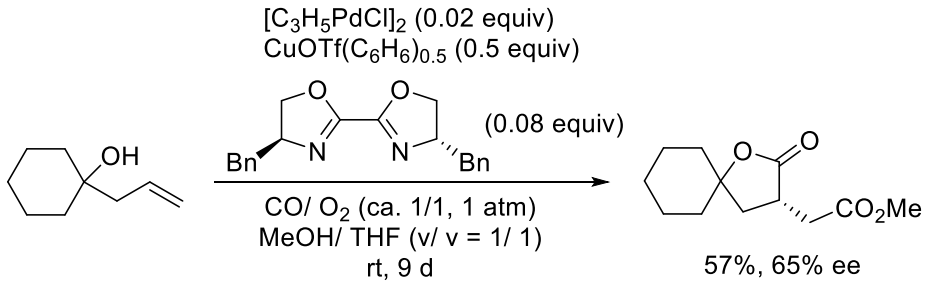
Scheme 1.46. Asymmetric bis(alkoxycarbonylation) reaction of cyclic olefins.

This carbonylation method provides a useful route to synthesize chiral polycyclic compounds. Thus, the carbonylated product **28** was well applied to the synthesis of hexahydrobenz[e]isoindoles **29** which are reported to be 1A adrenoceptor antagonists as potential agents for benign prostatic hyperplasia (Scheme 1.47).[67]



Scheme 1.47. Application for construction of a hexahydrobenz[e]isoindole skeleton.

We also developed asymmetric dicarbonylation reaction of homoallylic alcohols[69] in the presence of Cu(I) triflate using a chiral bioxazoline ligand which gave the corresponding optically active γ-butyrolactones up to 65% ee (Scheme 1.48).



Scheme 1.48. Asymmetric dicarbonylation of homoallylic alcohols.

The role of $CuOTf(C_6H_6)_{0.5}$ and stereochemical course might be explained as follows: Copper(I) triflate reacts with palladium chloride complex to afford a cationic palladium intermediate, in which the olefinic moiety could more strongly coordinate to the palladium metal, as illustrated in Figure 1.1. At this stage, a steric hindrance between the substituent R in homoallylic alcohol and the substituent at C_4 of the bioxazoline ligand would disfavor the transition state $\mathbf{T_2}$, and, thus transition state $\mathbf{T_1}$ was favored to produce (*S*)- γ-butyrolactones (Figure 1.2).

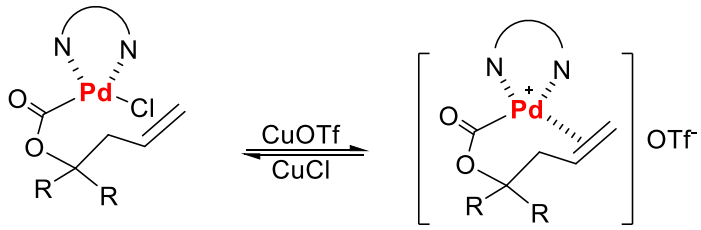


Figure 1.1

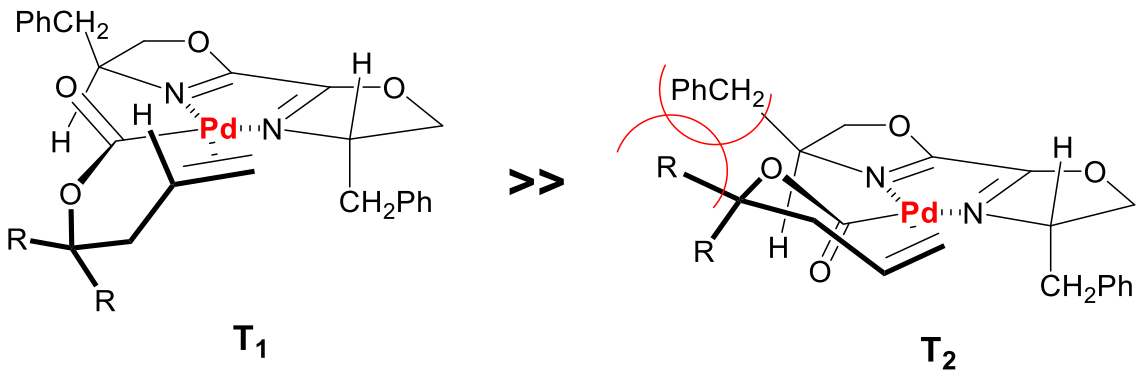
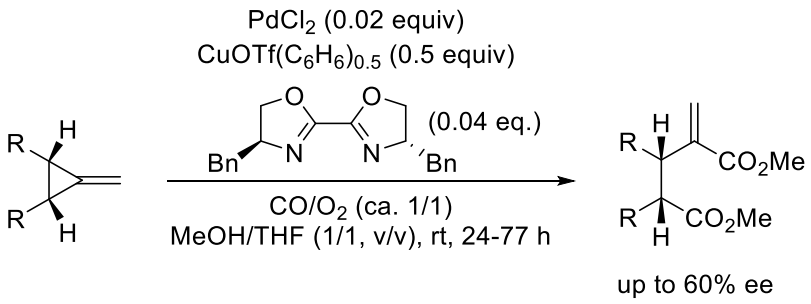


Figure 1.2

Desymmetrization of various *meso*-methylenecyclopropanes was accomplished by a palladium-catalyzed asymmetric ring-opening bis(alkoxycarbonylation) reaction employing a chiral bioxazoline ligand to give the corresponding optically active *γ*-methyleneglutarates with up to 60% ee (Scheme 1.49). Desymmetrization of protected *meso*-(3-methylene-cyclopropane-1,2-diyl)dimethanols was also carried out to give enantioenriched highly oxygen-functionalized *γ*-methyleneglutarates.[70]



Scheme 1.49. Desymmetrization of *meso*-methylenecyclopropanes by asymmetric ring-opening bis(alkoxycarbonylation) reaction.

1.2.2 Conclusion for our previous works

In overall, our laboratory has developed catalytic system with high efficiency and selectivity for mono- and dicarbonylation reactions of olefins. The combination of palladium with copper salt has realized to catalyze these or related reactions under normal pressure of CO and O_2. With respect to the synthetic value of carbonylation reactions towards preparation of intermidates for biologically and pharmaceutically active targets, various asymmetric versions of bis(alkoxycarbonylation) reaction have already studied employing chiral bioxazoline ligand to afford optically active products in moderate to good enantioselectivity, and some of those have successfully applied to the synthesis of the bioactive agents.

On the basic of our remarkably achieved results and the significant roles of the carbonylation reaction in organic synthesis, our laboratory will continue pursuing interest in this promissing research area. The developement of improved catalyst, ligands as well as extension of functionalized substrates will be key issues for further investigations in our research group.

1.3 Aims of the Present Study

With regard to enantioselective carbonylation catalyzed by palladium, only limited methods have been developed. These transformations have experienced considerable difficulties in simultaneously obtaining both high regio- and enantioselectivities. Being encouraged by our previously results on asymmetric bis(alkoxycarbonylation) reactions, an asymmetric palladium-catalyzed dicarbonylation of homoallylic amine derivatives was envisoned to produce optically active *γ*-lactams, which are valuable for medicinal applications, in single step. If this reaction could be promoted stereoselectively, it is expected to be an efficient synthetic method for preparation of enantiomerically pure *γ*-lactam derivatives.

Moreover, concerning great synthetic value of carbonylation reactions, an extensive study to new intermolecular mono(alkoxycarbonylation) reaction was desired as its products, *β*-alkoxy esters, could be useful synthetic intermediates for biologically active compounds. These aldol-type compounds were not detected as major products by our previous approaches and the fact that efficient one-pot synthesis of *β*-alkoxy esters by aldol reaction is expected to be difficult due to competitive elimination reaction of *β*-alkoxyl group.

According to above mentions, I wish to pursuit these challenges with an aspiration to be able to contribute a new synthetic methodology regard to the important and promissing research fields.

The main aims of the work presented in this thesis was to investigate novel and efficient palladium-catalyzed carbonylation reactions in the combination with copper salts. On the basic of the relevant previous studies and the context of mentioned research areas, the specific objectives of the present study were as follows:

1) Direct construction of optically active *γ*-lactams derivatives by asymmetric palladium-catalyzed intra- and intermolecular dicarbonylation reaction of homoallylic amine derivatives.

2) Development of suitable conditions for the palladium-catalyzed intermolecular alkoxy-alkoxycarbonylation of vinylphenols, and identification of effects of metal salt on the present reaction.

CHAPTER 2: ASYMMETRIC PALLADIUM-CATALYZED INTRA- AND INTERMOLECULAR DICARBONYLATION OF HOMOALLYLIC AMINE DERIVATIVES

2.1 Introduction

The γ-lactams can probably be considered as one of the most important heterocyclic motifs used in synthetic and medicinal chemistry.[71] Functionalized γ-lactams are widespread among the structures of a large number of biologically active natural and non-natural products and have therefore been used as aprivileged structural subunit for the design of several pharmaceutical agents (Figure 2.1). In addition, they also serve as important intermediates for the synthesis of some complex nitrogen containing molecules.

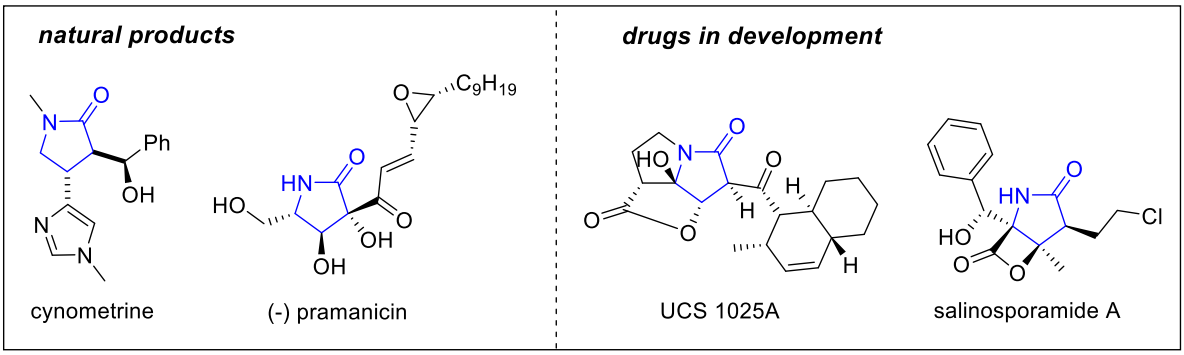


Figure 2.1. Selected examples of γ-lactam structures possessing a biological activity.

Metal-catalytic cyclocarbonylation of unsaturated amines with CO is an attractive way to access this heterocyclic motifs that are often difficult to prepare by other methods. Many synthetic approaches to γ-lactam compounds via metal-catalyzed cyclocarbonylation have been reported over the years.[72] The rhodium-catalyzed tandem cyclohydrocarbonylation/CO insertion of α-imino alkynes under CO and H_2 was reported to prepare 2-oxo-3-pyrroline-4-carbaldehyde, regarded as intra- and intermolecular dicarbonylation products.[72c] Furthermore, the cyclocarbonylation of allylaminoalcohols catalyzed by rhodium gave selectively either *N*-

(2-hydroxy-alkyl)-*γ*-lactams or oxazolidines, depending on the reaction conditions.[72e] The formation of 1,3-dihydropyrrolone derivatives was achieved via a reaction of *α,β*-unsaturated imines derived from cinnamaldehyde with CO and terminal alkenes in the presence of $Ru_3(CO)_{12}$ as a precatalyst.[72f] Recently, a nickel(0)-catalyzed carbonylative cycloaddition of ene-imines with CO was developed to afford polycyclic *γ*-lactams.[72d] Our laboratory already described selective mono- and dicarbonylation reactions of *N*-tosylhomoallylamine derivatives catalyzed by palladium in the presence of $CuCl_2$ or CuCl under remarkably mild conditions to afford 3-methyl-1-tosyl-2-pyrrolidones or methyl 2-oxo-1-tosylpyrrolidine-3-acetate, respectively.[64] Concerning the enantioselective synthesis of *γ*-lactams, a limited number of approaches via asymmetric carbonylation was reported. The asymmetric interrupted intramolecular hydroaminomethylation of *trans*-1,2-disubstituted alkenes catalyzed by rhodium complex with Yanphos ligand afforded chiral pyrrolidinones.[60] Synthesis of enantioenriched polycyclic *γ*-lactams was achieved via the nickel(0)-catalyzed asymmetric [2+2+1] carbonylative cycloaddition of en-imines by using chiral phosphoramidite ligand.[72d]

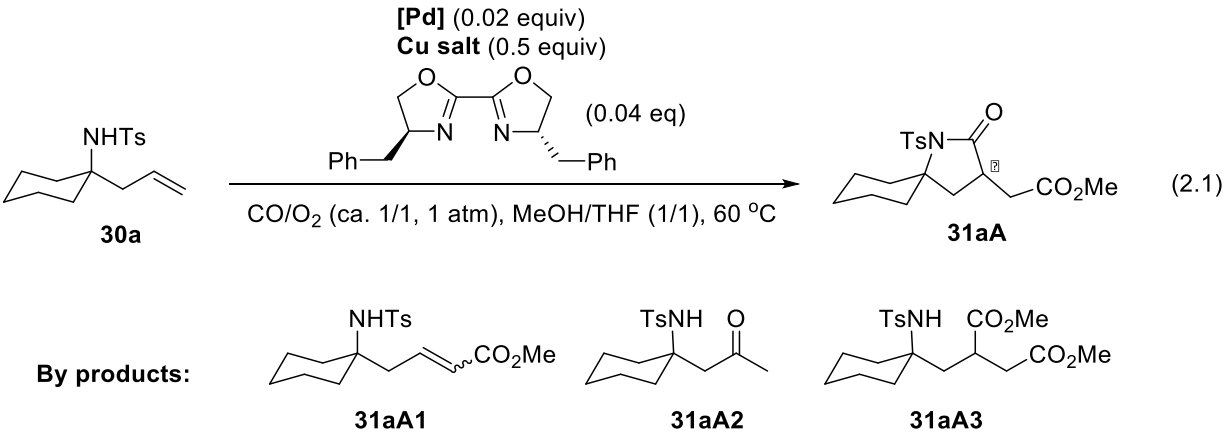
We previously developed asymmetric dicarbonylation reactions catalyzed by palladium in the presence of copper salts to prepare optically active succinates and *γ*-butyrolactones from terminal olefins and homoallylic alcohols respectively.[66,69] Moreover, desymmetrization of various *meso*-methylenecyclopropanes was accomplished by a palladium-catalyzed asymmetric ring-opening bis(alkoxycarbonylation) reaction employing a chiral bioxazoline ligand to give the corresponding optically active *γ*-methyleneglutarates.[70] Being encouraged by these results, an asymmetric intra- and intermolecular palladium-catalyzed dicarbonylation of homoallylic amine derivatives was envisoned to produce optically active *γ*-lactams.

2.2 Results and Discussion

2.2.1 Optimization of reaction conditions

Our previous study revealed that in the palladium-carbonylation reaction of *N*-benzoyl, *N*-benzyloxycarbonyl and *N*-trifluoromethylsulfonyl substituted homoallylamines, intramolecularly carbonylated products were not formed, but only intermolecularly monocarbonylated esters were obtained. To the contrary, *N*-tosyl homoallylamines afforded corresponding desired *γ*-lactams.[64] Therefore, *N*-tosyl homoallylamine **30a** was chosen as the model substrate to examine the present reaction. First, a dicarbonylation of *N*-tosyl homoallylamine **30a** was examined on a combination of palladium(II) and copper(I) salts in the presence of (4*S*,4′*S*)-4,4′-dibenzyl-4,4′,5,5′-tetrahydro-2,2′-bioxazole (**32**) under a CO and O_2 (ca.1/1, v/v, 1 atm) atmosphere in THF/MeOH (1/1,v/v) at 60 ^oC (Equation 2.1). The results were summarized in Table 2.1. A reaction using a 0.02 molar amount of of $PdCl_2$ and 0.5 molar amount of CuCl gave *γ*-lactam **31aA** in 52% yield. The optical yield of the obtained *γ*-lactam **31aA** was determined to be only 5% ee by a HPLC analysis (Entry 1, Table 2.1). It should be noted that *β*-H elimination product **31aA1** (14%), Wacker-type product **31aA2** (7%) and intermolecularly bis(alkoxycarbonylated) diesters **31aA3** (10%) formed as byproducts during the reaction. To our more disappointment, the carbonylation using CuBr gave major Wacker-type product **31aA2** (82%) along with only 6% of desired *γ*-lactam **31aA** (Entry 2); meanwhile, the reaction did not proceed when utilizing CuI salt (Entry 3). It was found that cationic copper(I) salts were quite effective to give the *γ*-lactam product in moderate chemical yield and enantioselectivity (Entry 4-5). To our delight, the combination of $PdCl_2$ and $CuOTf(C_6H_6)_{0.5}$ afforded **31aA** with enhanced stereoselectivity of 68% ee (Entry 5). As predicted, Cu(II) salt which often catalyzes selectively monocarbonylation reaction indeed afforded the desired *γ*-lactam **31aA** in low yield 24% and 16% ee (Entry 6).

Next, various Pd(II) sources were screened to investigate whether counter ions have impact on the yield and/or the enantioselectivity of **31aA** but none of the other tested Pd(II) sources instead of $PdCl_2$ furnished either better yield or enantioselectivity (Entry 7-12). Notably, the combination of a soluble palladium salt as $[PdCl(allyl)]_2$ with $CuOTf(C_6H_6)_{0.5}$, by which the best catalytic result was realized in the asymmetric dicarbonylation reaction of homoallylic alcohols,[69] was not effective to the present reaction, giving a low of 42% for both chemical yield and enantioselectivity (Entry 8). The amount of $CuOTf(C_6H_6)_{0.5}$ was realized to influence the activity and stereoselectivity of the reaction. A significant reduction in the ee was observed when using a large amount of copper (I) triflate (Entries 13,14). A plausible explanation for the decrease of asymmetric induction is that copper could displace the chiral ligand from palladium, leading to the formation of a copper-ligand complex. Interestingly, using 0.25 molar amount of $CuOTf(C_6H_6)_{0.5}$ afforded almost desired γ-lactam **31aA** in 84% yield with a trace amount of byproducts (Entry 15). Unfortunately, in this case the enantioselectivity considerably decreased to 46% ee. The scrupulous reason for the remarkable effects is yet to be known. The use of 0.1 molar amount of $CuOTf(C_6H_6)_{0.5}$ resulted in a further decline of enantioinduction (Entry 16).



(2.1)

Table 2.1. Screening of Cu salts and Pd sources.

Entry	Pd source	Cu salt	Time/ d	Yield/ %	ee/ %
1	$PdCl_2$	CuCl	3	52	8
2	$PdCl_2$	CuBr	3	6	n.d
3	$PdCl_2$	CuI	3	No reaction	-
4	$PdCl_2$	$Cu(MeCN)_4BF_4$	3	61	54
5	**$PdCl_2$**	**$CuOTf(C_6H_6)_{0.5}$**	**3**	**49**	**68**
6	$PdCl_2$	$Cu(OTf)_2$	3	24	16
7	$PdCl_2(PhCN)_2$	$CuOTf(C_6H_6)_{0.5}$	3	25	56
8[a]	$[PdCl(allyl)]_2$	$CuOTf(C_6H_6)_{0.5}$	3	42	42
9	$Pd(OAc)_2$	$CuOTf(C_6H_6)_{0.5}$	4	30	42
10	$Pd(TFA)_2$	$CuOTf(C_6H_6)_{0.5}$	3	16	56
11	$[Pd(CH_3CN)_4](OTf)_2$	$CuOTf(C_6H_6)_{0.5}$	4	35	43
12[b]	$Pd(dba)_2$	$CuOTf(C_6H_6)_{0.5}$	3	25	53
13	$PdCl_2$ (0.05 eq.)	$CuOTf(C_6H_6)_{0.5}$ (1.5 eq.)	3	51	57
14	$PdCl_2$	$CuOTf(C_6H_6)_{0.5}$ (1.0 eq.)	3	44	37
15	$PdCl_2$	$CuOTf(C_6H_6)_{0.5}$ (0.25 eq.)	3	84	46
16	$PdCl_2$	$CuOTf(C_6H_6)_{0.5}$ (0.1 eq.)	3	57	43
17[c]	$PdCl_2$	$CuOTf(C_6H_6)_{0.5}$	7	21	66
18[d]	$PdCl_2$	$CuOTf(C_6H_6)_{0.5}$	5	53	67

n.d = not determined. All the yields were isolated ones. All the ee were determined by HPLC analysis.

[a] 0.08 equiv of ligand was used. [b] 0.04 equiv of LiCl was used.

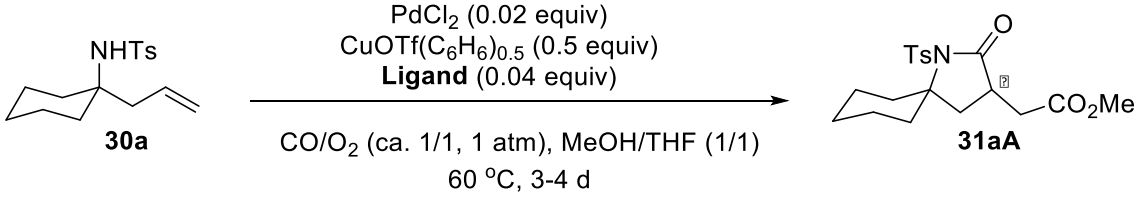
[c] The reaction was conducted at room temperature for 7 days, 32% of starting material was recorvered.

[d] After prolonged reaction time (5 days).

Then, the poor conversion was observered when the dicarbonylation conducted at room temperature. The chiral *γ*-lactam **31aA** was obtained in 21% yield with 66% ee, and 32% of starting material was recorvered after the reaction being proceeded one week (Entry 17). It can be seen that heating conditions were necessary in order to accelerate the reaction but not deprive enantioselectivity. Finally, noteworthy is that prolonged reaction period at 60 ^{o}C afforded **31aA** in better yield and 67% ee (Entry 18).

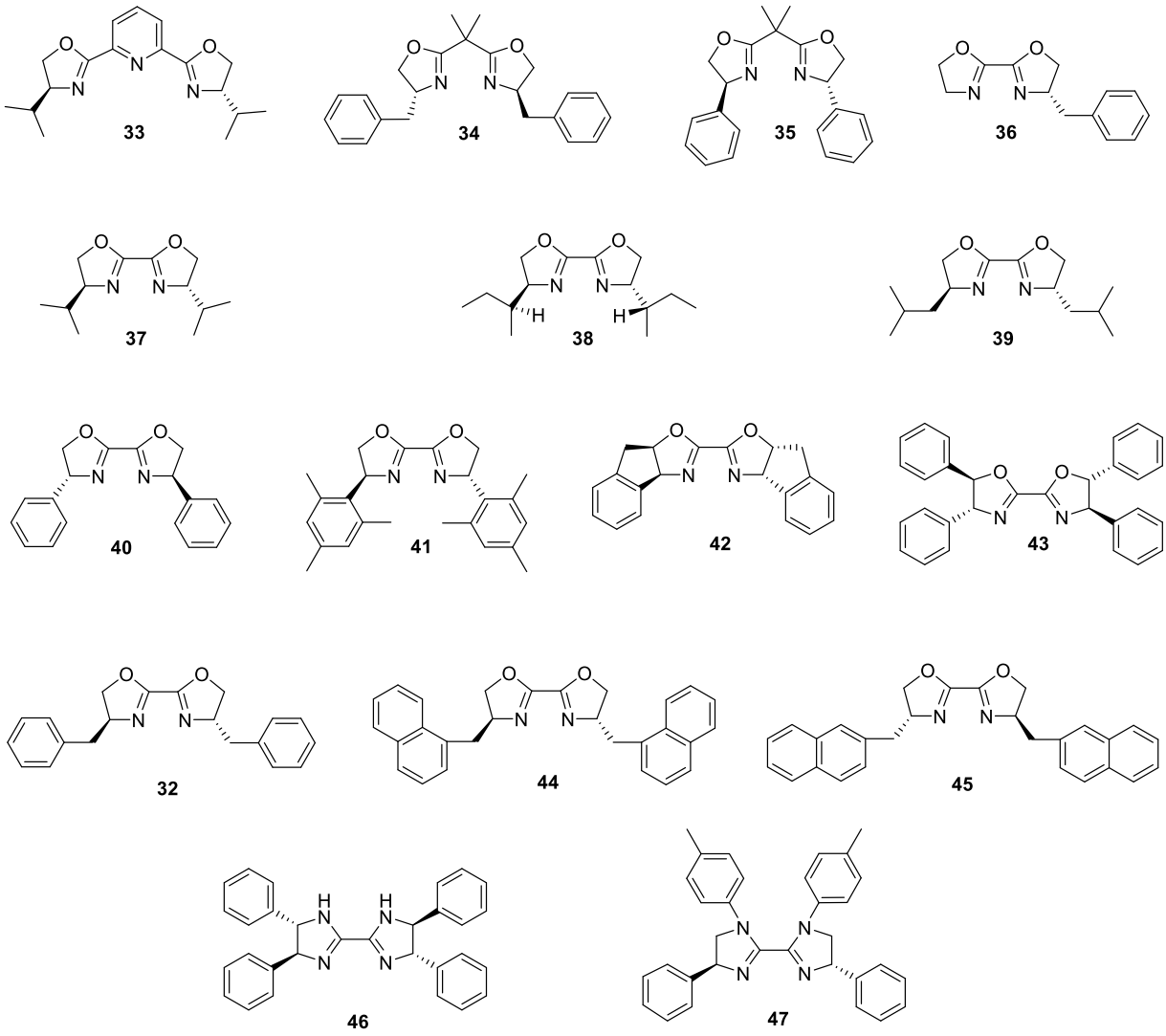
The attention was then focused towards the effect of ligand on the yield and the enantioselectivity of **31aA** (Table 2.2). The use of other C2-symmetric PyBOX **33** and BOX ligands **34**, **35** was unpromissing, giving poor conversion and/or low enantioselectivity (Entries 1-3). By employing an asymmetric bioxazolize ligand **36**, the dicarbonylation reaction proceeded smoothly with a further improved chemical yield of 61% but poor enantioselective excess (Entry 4). Next, the effects of substituents at the 4- and 4'- positions in the bioxazoline ligands was investigated. As shown in entries 5-7, the dicarbonylation of **30a** using aliphatic substituted ligands **37-39** gave disappointing results. Meanwhile, it could be seen that aromatic substituted oxazoline ligands were more effective, and thus generally giving desired *γ*-lactam **31aA** in higher yields and enantioselectivities (Entries 8-14). Notably, the ligands with (*R,R*)-substituents **40**, **42** and **45** resulted in a reverse stereodifferentiation. The use of bioxazoline ligands **42**, **43** substituted simultaneously at both 4, 4'- and 5, 5'- positions afforded promissing enantiopurity (Entries 10, 11). Moreover, the bis(imidazoline) ligands **46** and **47** did not work efficiently in asymmetric induction (Entries 15, 16). In overall, among all tested ligands, benzyl substituted bioxazoline **32** appeared to be the most effective ligand for the intra- and intermolecular dicarbonylation reaction of *N*-tosyl homoallylamine derivative **30a**.

Table 2.2. Screening of ligands.



Entry	Ligand	Yield/ %[a]	ee/ %[b]
1	**33**	19	1
2	**34**	44	-9
3	**35**	37	11
4	**36**	61	25
5	**37**	31	2
6	**38**	39	3
7	**39**	41	34
8	**40**	62	-49
9	**41**	52	50
10	**42**	30	60
11	**43**	59	-54
12	**32**	**49**	**68**
13	**44**	51	47
14	**45**	57	-53
15[c]	**46**	9	20
16	**47**	50	19

[a]All the yields were isolated ones. [b]All the eewere determined by HPLC analysis.
[c]86% of starting material were recovered.

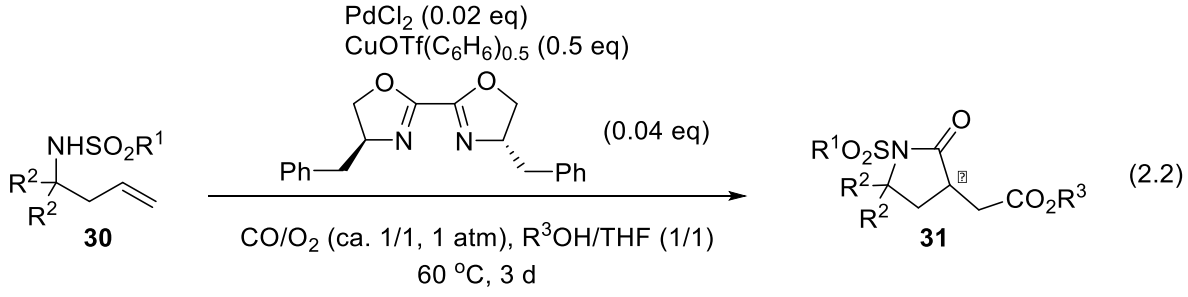


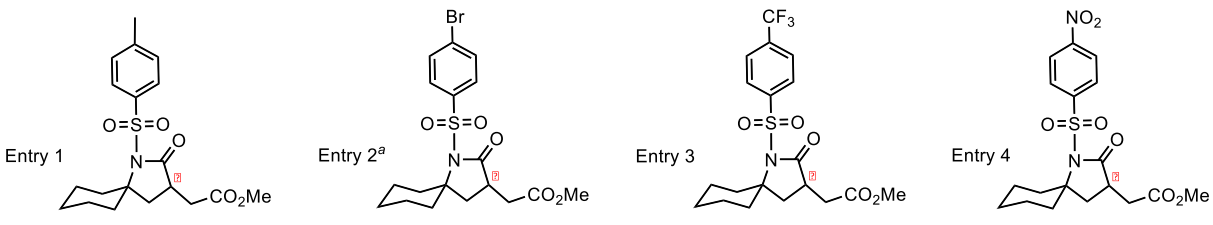
2.2.2 Scope of substrates

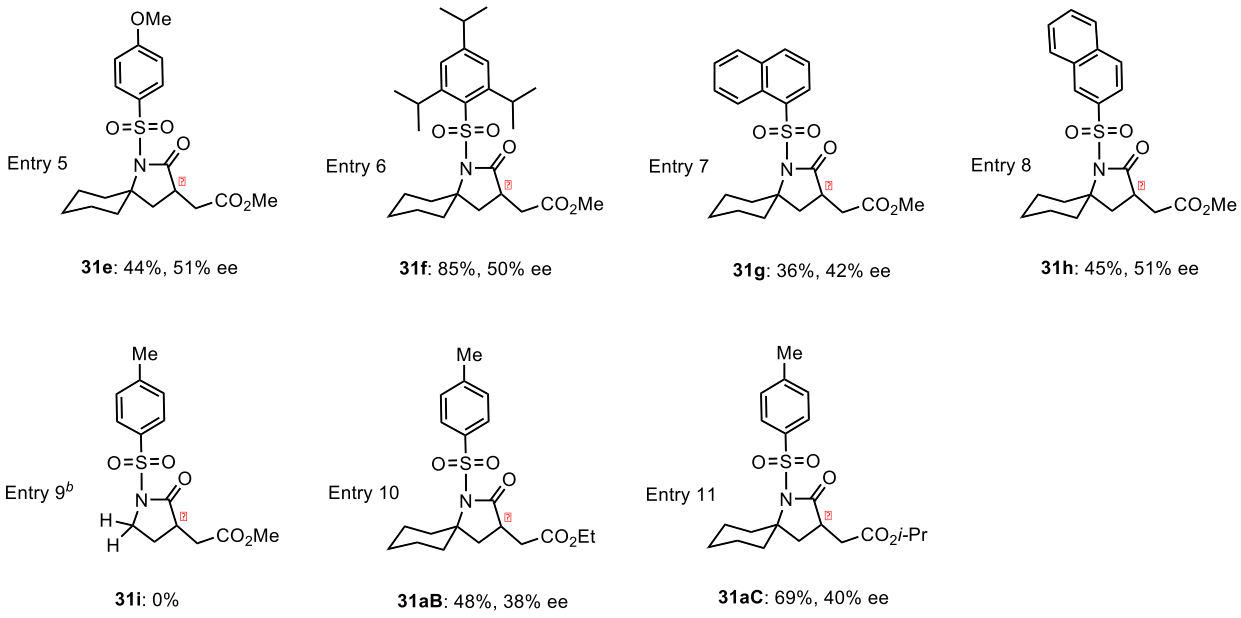
Having optimized the reaction conditions, the scope of this transformation with a variety of homoallylic amine derivative substrates **30** was explored (Equation 2.2), and the results are shown in Table 2.3. Similar to the tosyl group of **30a**, a variety of electron-donating and electron-withdrawing substituent-bearing benzenesulfonyl groups **30b-30h** was tolerated as protecting groups (PGs). Substrates with PG bearing electron-withdrawing substituent on aromatic ring **30b-30d** formed corresponding *γ*-lactams **31b-31d** in moderate

enantioselectivity (Entries 2-4). The dicarbonylation of substrate **30e**, bearing an electron-donating methoxy substituent on phenyl group, gave 44% yield of the product **31e** with higher enantioselectivity (51% ee) (Entry 5). The dicarbonylation of **30f** proceeded smoothly to form the desired product **31f** in high yield (85%) with 50% ee (Entry 6). Using 2-naphthalenesulfonyl substituted substrate **30h** gave corresponding *γ*-lactam **31h** in better chemical yield and stereoselectivity compared with that in the case of 1-naphthalenesulfonyl substituted substrate **30g** (Entries 7 and 8). When *N*-tosyl allylamine **30i** was used as substrate, desired *γ*-lactam **31i** was not obtained. Instead, the dicarbonylation gave the intermolecularly bis(alkoxycarbonyl)ated succinate (40%) as major product accompanied with the Wacker-type product (31%) (Entry 9). Primary alcohol and secondary alcohol were also tolerated affording the corresponding *γ*-lactams in moderate yields (Entries 10 and 11). In the case of EtOH, the reaction proceeded sluggishly to give a 48% yield of **31aB** with 38% ee after 5 day. To the contrary, complete consumption of **30a** was detected after 2 day in the case of the reaction in the presence of ^{i}PrOH.

Table 2.3. Scope of substrates.







All the yields were isolated ones. All the ee were determined by HPLC analysis.

[a]Ligand **43** was used instead of ligand **32**.

[b]Dimethyl 2-(2-((4-methylphenyl)-sulfonamido)ethyl)succinate was isolated in 40% yield.

2.2.3 Absolute stereochemistry of the *γ*-lactam 31aA

At this stage, the absolute configuration of **31aA** was not determined yet. Based on the result of asymmetric bis(alkoxycarbonylation) reaction of homoallylic alcohols which afforded mainly (*S*)-*γ*-butyrolactones under similar reaction conditions,[69] the stereochemical course of the present asymmetric dicarbonylation of homoallylic amine derivatives might be envisioned as follows: A steric hindrance between the substituent R in the homoallylic amine derivatives and the substituent at C4 of the bioxazoline ligand would disfavor the transition state **T2**, and transition state **T1** is expected to be favored, producing mainly (*S*)- *γ*-lactams (Figure 2.2).

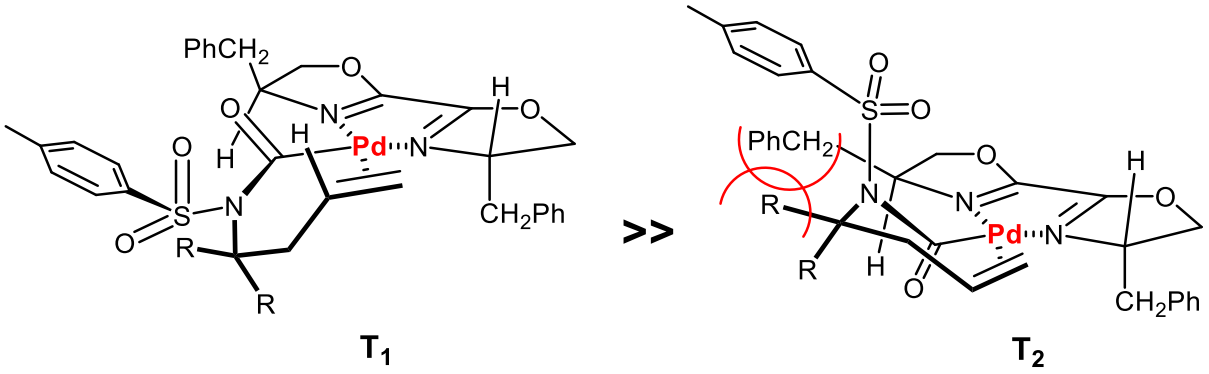
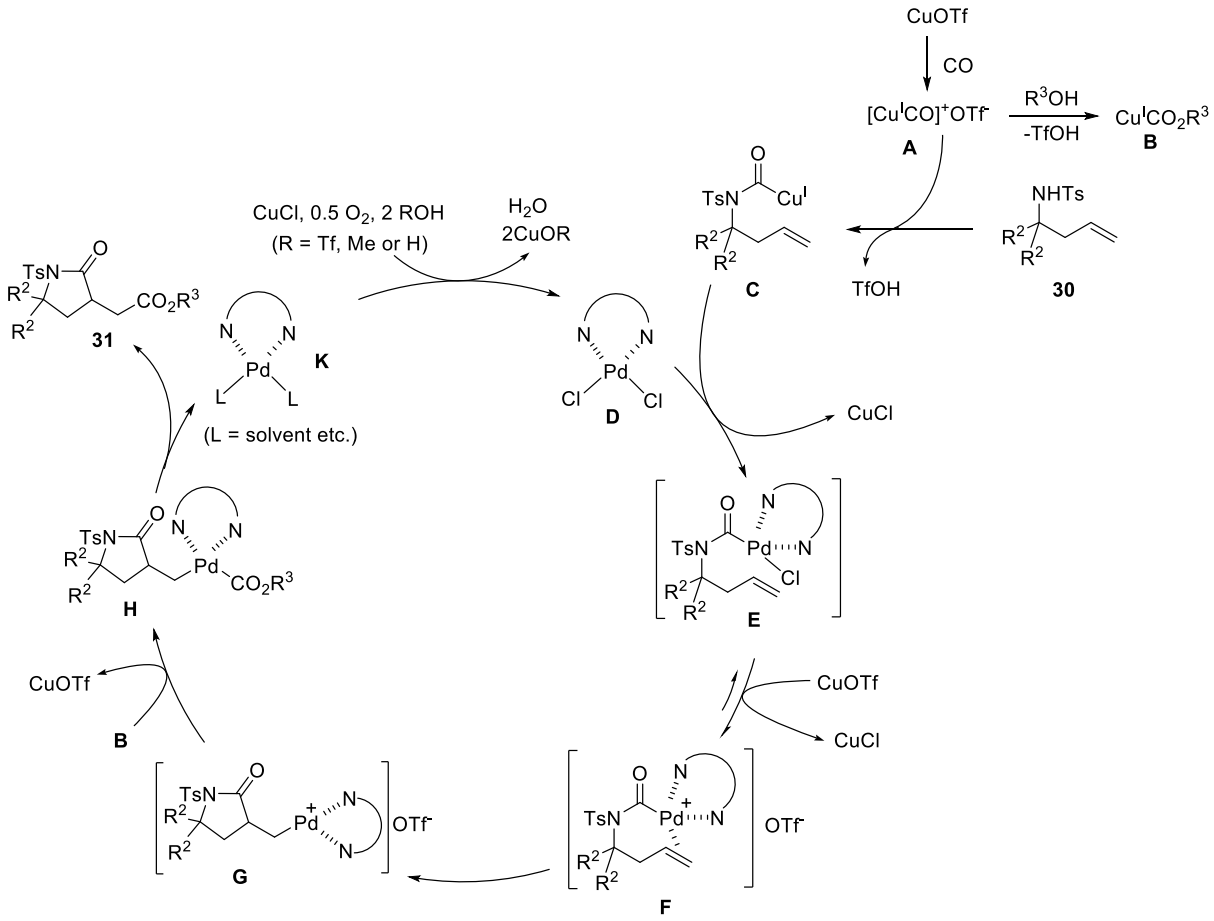


Figure 2.2

2.2.4 Proposed mechanism

The precise mechanism of the present reaction is not clear yet. One possible reaction pathway is shown in Scheme 2.1. In the present dicarbonylation, copper might work not only as an oxidant, but also as a co-catalyst to generate active species. That is, copper(I) triflate reacts with CO and MeOH successively to give the copper-carbonyl complex **A** followed by a reaction with homoallylamine derivatives **30** to afford **C**. The aminocarbonyl group was transferred to palladium chloride **D** to generate complex **E**. Further, copper(I) triflate reacts with **E** to afford a cationic palladium intermediate **F**, in which olefin can strongly coordinate to the palladium metal. Successive carbopalladation via transition state **T1** gave the optically active cyclized intermediate **G**. Second carbonylation proceeded via **H** which is generated from **G** by a carbonyl transfer from **B**, followed by reductive elimination to give optically active γ-lactam **31**. The palladium(II) catalyst **D** is regenerated by the oxidation of **K** by oxygen in the presence of copper(I) salt. During this oxidation step, copper(I) triflate might be partially produced again and recycled. By using a large amount of copper(I) triflate, liberated trifluoromethanesulfonic acid might decompose the reactive palladium intermediate to decrease the chemical yield (Table 2.1, Entry 14).



Scheme 2.1. Proposed mechanism.

2.3 Conclusion

In conclusion, a novel asymmetric intra- and intermolecular dicarbonylation reaction of homoallyl amine derivatives catalyzed by palladium(II) and copper(I) salt under normal pressure of CO and O_2 has been achieved by using a chiral bioxazoline ligand. A variety of *N*-substituted homoallylic amine derivatives was applicable to the present reaction to give the corresponding optically active *γ*-lactams with morderate enantioselectivity. Thus, this method provides a new synthetic entry for the rapid construction of optically active *γ*-lactams, which are imperative scaffolds of biologically important molecules.

CHAPTER 3: PALLADIUM-CATALYZED INTERMOLECULAR ALKOXY-ALKOXYCARBONYLATION OF VINYLPHENOLS IN THE PRESENCE OF COPPER SALT:UNEXPECTED COOPERATIVE EFFECT OF TIN SALT

3.1 Introduction

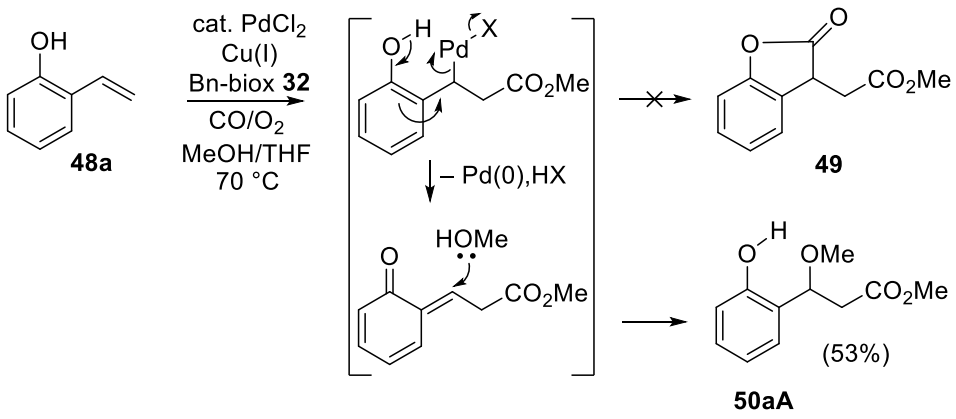
Concerning palladium-catalyzed carbonylation of unsaturated alcohols, intramolecular alkoxycarbonylation often proceeds to furnish cyclic ethers, such as tetrahydrofurans or tetrahydropyrans.[73] However, the intermolecular version of the alkoxy-carbonylation of alkenes is quite limited.[18b, 74] Carbonylation of terminal alkenes in the presence of $PdCl_2$ and $CuCl_2$ under 3 atm of CO in MeOH was reported to give predominantly *β*-methoxy esters, while the corresponding succinates were obtained under basic conditions.[18b] A palladium-catalyzed acetoxy-carbonylation of alkenes proceeded in the presence of $CuCl_2$ in acetic anhydride and acetic acid.[27, 75] In light of the successful development of a palladium-catalyzed intra- and intermolecular dicarbonylation protocol for homoallylic alcohols from earlier work in our laboratory, herein an efficient palladium-catalyzed intermolecular alkoxy-alkoxycarbonylation of vinylphenols is described to afford the corresponding 3-alkoxy-3-arylpropanoates.

3.2 Results and Discussion

3.2.1 Initial discovery leading to an unpredictable intermolecular alkoxy-alkoxycarbonylation reaction of vinylphenols

The study was initiated with the asymmetric intra- and intermolecular bis(alkoxycarbonylation) of 2-vinylphenol (**48a**) in the presence of $PdCl_2$ (0.02 equiv) and $CuOTf(C_6H_6)_{0.5}$ (0.5 equiv) under normal pressure of CO and O_2 in MeOH (**51A**)/THF using (*S*,*S*)-benzyl-substituted bioxazoline **32** as a ligand.[68-69] Although the carbonylation proceeded

smoothly, the expected lactone **49** was not formed, but instead 3-aryl-3-methoxypropanoic acid methyl ester **50aA** was obtained in 53% yield. This ester might be derived from regioselective carbopalladation followed by reductive elimination and subsequent addition of MeOH to the resulting quinonemethide before the second carbonylation (Scheme 3.1).



Scheme 3.1. Alkoxy-alkoxycarbonylation of 2-vinylphenol.

If this hypothesis is correct, 4-vinylphenol would also afford the corresponding 3-methoxypropanoate. Indeed, the alkoxycarbonylation of 4-vinylphenol (**48b**) was performed, and 3-methoxypropanoate **50bA** was obtained in good chemical yield (up to over 90% yield). In the same manner, 4-vinylphenol is considered to produce *p*-quinone methide (Figure 3.1).

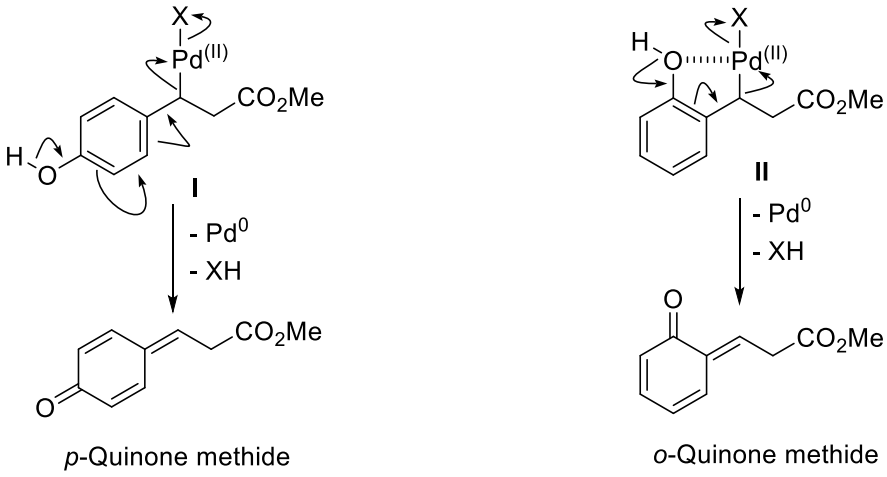


Figure 3.1

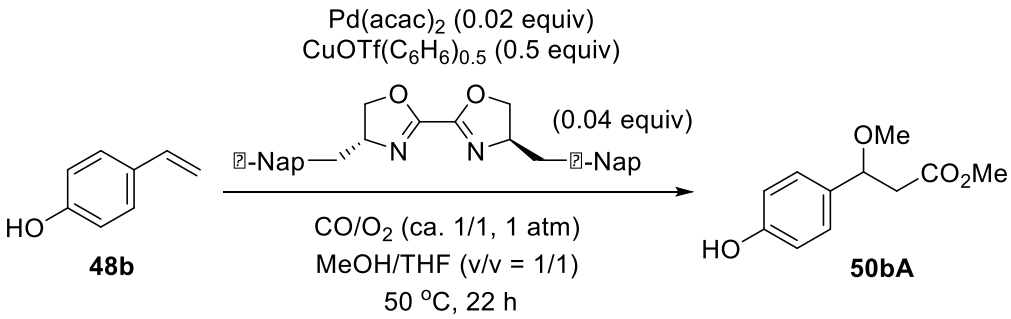
It can be seen that the electron-donating ability of the hydroxy group in the intermediate **I** is stronger in comparison with that in the intermediate **II** since the oxygen of hydroxyl group is not coordinated to the palladium species. As a result, the reaction with 4-vinylphenol proceed more smoothly to form 3-methoxypropanoate **50bA** in a higher yield.

Based on these unexpected results, the original objective was triggered to an extensive study on novel intermolecular alkoxy-alkoxycarbonylation reaction of 4-vinylphenols.

3.2.2 Effect of MeOH source

As mentioned above, the alkoxycarbonylation of 4-vinylphenol (**48b**) furnished 3-methoxypropanoate **50bA** in good chemical yield. Unfortunately, the chemical yield was not reproducible. After intensive examination, the chemical yield was found to fluctuate depending on the MeOH source used (Table 3.1).

Table 3.1. Effect of MeOH source on the intermolecular alkoxycarbonylation reaction.



Entry	MeOH	Yield (%)[a]
1	A	83
2	B	57

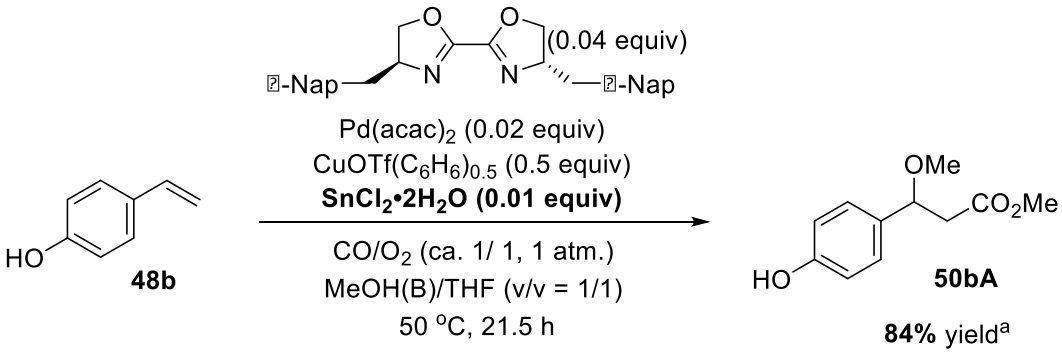
[a] Yields were determined by ^{1}H NMR of crude products using octane as an internal standard.

A : Eighteen litre drum (Cica. 1°, 25183-81)

B : Bottle (Cica. 1°, 25183-01)

When MeOH purchased in an amber glass bottle was used, **50bA** was obtained in around 30% lower yields than when using MeOH purchased in 18 L tin plates. When analyzing the components in these two methanol sources by inductively coupled plasma mass spectrometry (ICP-MS), it was found that methanol derived from a 18 L can contained 10 times higher tin amount compared with methanol derived from a bottle.[76] From these results, it is realized that tin has a beneficially unexpected effect on the present reaction.

To confirm more strongly the effect of tin, the reaction using superdehydrated methanol in glass bottle was performed by the external addition of $SnCl_2 \cdot 2H_2O$. Delightedly, the product **50bA** was obtained in reproducibly high yields (Scheme 3.2).



[a] Yield was determined by ^{1}H NMR of crude products using octane as an internal standard. and two times average .
B : Bottle (Cica 1°, 25183-01)

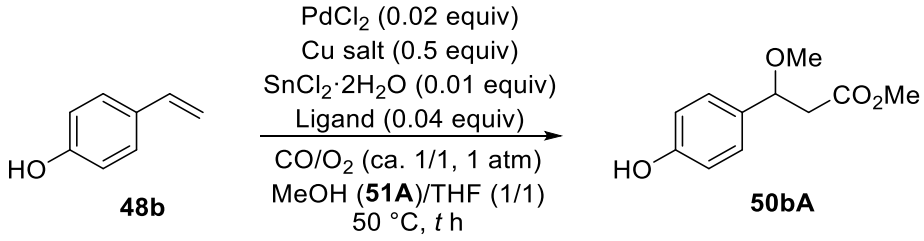
Scheme 3.2. Reproducibility of the reaction by the addition of $SnCl_2 \cdot 2H_2O$.

3.2.3 Optimization of reaction conditions

The present intermolecular methoxy-methoxycarbonylation of 4-vinylphenol (**48b**) in the presence of a bioxazoline ligand **45**[70] was examined under various conditions (Table 3.2). Among the copper salts, CuCl, CuBr, and CuI were not effective (Entries 2–4). It was confirmed that cationic copper(I) salts, especially $[Cu(MeCN)_4]BF_4$, were quite effective to

give the product quantitatively within 3 h (Entry 5). In this case, the enantiomeric excess of the obtained **50bA** was confirmed to be 0% ee. The reaction proceeded in a similar manner by the use of $[PdCl_2(PhCN)_2]$ instead of $PdCl_2$ (Entry 6). Concerning the tin salts, $SnCl_4$ and $Sn(OAc)_4$ were interchangeable (Entries 7 and 8). In the absence of the bioxazoline ligand **6**, the reaction was sluggish and a Wacker-type product, 4-hydroxyacetophenone, was formed (Entry 9). Substituents on the bioxazolines did not influence the reaction (Entry 10). Achiral ligands instead of bioxazoline compounds were examined. By the use of bidentate pyridine-type ligands, the reaction proceeded smoothly (Entries 11 and 12). DABCO was found to be comparable to bioxazoline **45** to afford 3-methoxypropanoate **50bA** in high yield (Entry 13). Oxygen was crucial to promote the present alkoxy-alkoxycarbonylation (Entry 14).

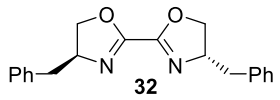
Table 3.2. Alkoxy-alkoxycarbonylation of 4-vinylphenol (**48b**).[a]



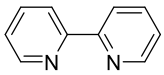
Entry	Cu salt	Ligand	*t*/h	Yield/%[a]
1	$[Cu(C_6H_6)_{0.5}]OTf$	**45**	7.5	99
2	CuCl	**45**	7.5	--
3	CuBr	**45**	7.5	--
4	CuI	**45**	7.5	--
5	$[Cu(MeCN)_4]BF_4$	**45**	3	99
6[b]	$[Cu(MeCN)_4]BF_4$	**45**	4.5	80
7[c]	$[Cu(MeCN)_4]BF_4$	**45**	3	96
8[d]	$[Cu(MeCN)_4]BF_4$	**45**	3	74
9	$[Cu(MeCN)_4]BF_4$	--	8	38[e]

10	$[Cu(MeCN)_4]BF_4$	**32**	8	91
11	$[Cu(MeCN)_4]BF_4$	bipy	6.5	91
12	$[Cu(MeCN)_4]BF_4$	phen	20	91
13	$[Cu(MeCN)_4]BF_4$	DABCO	8	99
14[f]	$[Cu(MeCN)_4]BF_4$	DABCO	8	5

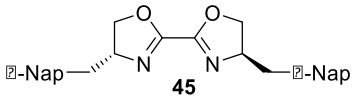
[a]Yields were determined by the analyses of ^{1}H-NMR spectra of the crude products based on octane as an internal standard. [b]$[PdCl_2(PhCN)_2]$ was used instead of $PdCl_2$. [c]$SnCl_4$ was used instead of $SnCl_2 \cdot 2H_2O$. [d]$Sn(OAc)_4$ was used instead of $SnCl_2 \cdot H_2O$. [e]4-Hydroxyacetophenone was also isolated in 33% yield. [f]Reaction was carried out without O_2.



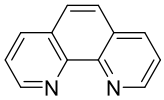
32



bipy



45



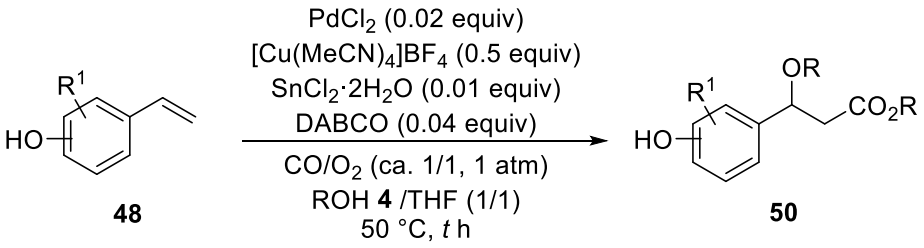
phen

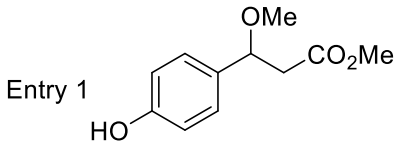
3.2.4 Scope of substrates

Under the optimized reaction conditions, the alkoxy-alkoxycarbonylation of vinylphenols **48** was performed in the presence of various alcohols (Table 3.3, Entries 1–6). By the use of not only primary alcohols but also secondary alcohols, the corresponding 3-alkoxy esters **50bA**–**50bE** were obtained in good to high yields (Entries 1–5). In the case of *t*-butyl alcohol (**51F**), the reaction was sluggish and gave the product **50bF** in poor yield (Entry 6). When H_2O was used as a nucleophile instead of alcohols for 65 h, 93% of 4-vinylphenol (**48b**) was recovered and a carbonylated 3-aryl-3-hydroxypropanoic acid was not observed in the ^{1}H-NMR spectrum of the crude products. Generally, isolated yields, as listed in parentheses, tended to decrease because the obtained 3-alkoxy-3-(hydroxylaryl)propanoates **50** were rather labile under purification by column chromatography on SiO_2 to often give the corresponding 3-(hydroxyphenyl)prop-2-enoates via *β*-elimination of the alcohols. In fact, the purification of 3-(*t*-butoxy)-

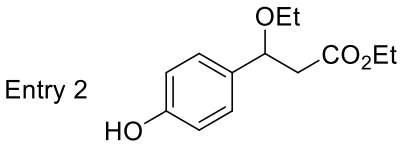
propanoate **50bF** failed. The reaction of 2-methyl-4-vinylphenol (**48c**) furnished the desired product **50cA** in high yield by the use of enhanced amounts of the catalysts (Entry 7). Unfortunately, side reactions, presumably polymerization, proceeded prior to the desired alkoxy-alkoxycarbonylation, resulting in unknown product mixtures when the 4-vinylphenol derivatives with rather electron-donating groups, such as 2-methoxy-4-vinylphenol and 2,6-dimethyl-4-vinylphenol, were used as substrates. 2-Bromo-4-vinylphenol (**48d**), bearing an electron-withdrawing bromo group, afforded the corresponding 3-alkoxyesters **50dA** in 60% yield (Entry 8). The reaction of 2-vinylphenol (**48a**) afforded **50aA** in reasonable yield (Entry 9). However, the treatment of 3-vinylphenol (**48e**) modulated the carbonylation into the bis(alkoxycarbonylation) reaction to produce a succinate derivative **52** (Entry 10).[18b, 61b, 68-69]

Table 3.3. Alkoxy-alkoxycarbonylation of vinylphenols **48**.[a,b]

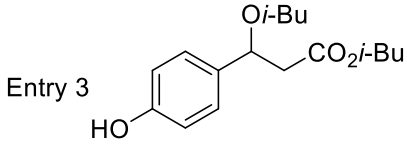




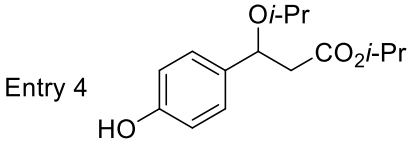
50bA: 8 h, 99% [86%]



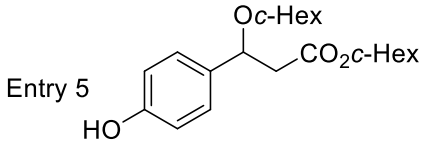
50bB: 9 h, 73% [74%]



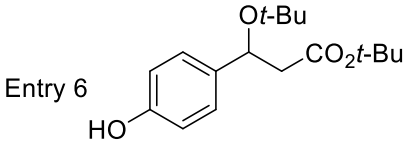
50bC: 4 h, 99%[c] [74%]



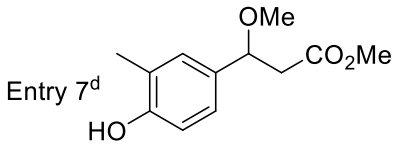
50bD: 7 h, 81%[c] [69%]



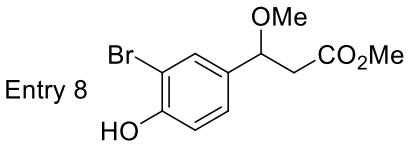
50bE: 20 h, 90% [58%]



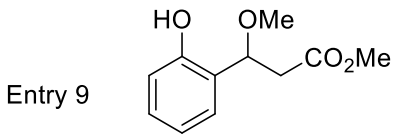
50bF: 47 h, 12%[c]



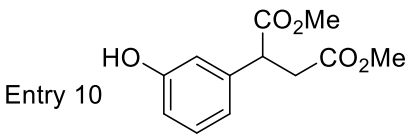
50cA: 16 h, 94% [78%]



50dA: 25 h, 60% [53%]



50aA: 7 h, 62%

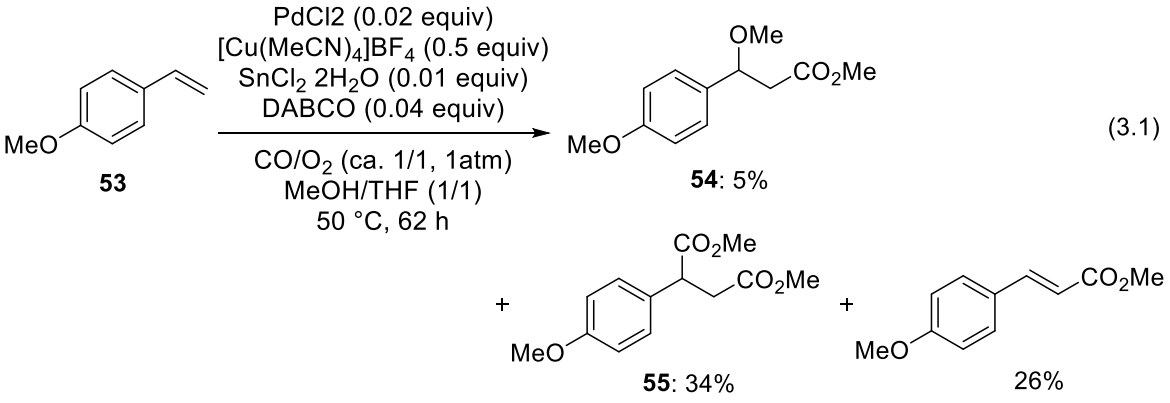


52: 31 h, [60%]

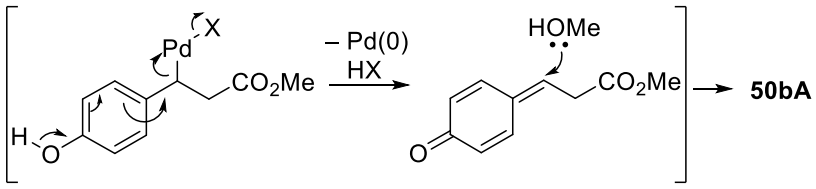
[a]Yields were determined by the analysis of ^{1}H NMR spectra of the crude products based on octane as an internal standard otherwise mentioned. [b]Yields in parentheses are isolated yields.[c]Yield was determined by the analysis of ^{1}H NMR spectrum of the crude products based on dibromomethane as an internal standard. [d]$PdCl_2$ (0.05 equiv), $[Cu(MeCN)_4]BF_4$ (0.5 equiv), $SnCl_2{\cdot}2H_2O$ (0.02 equiv), and DABCO (0.10 equiv) were used.

3.2.5 Effect of hydroxy group in vinylphenols

The effect of the hydroxy group in the vinylphenol was then examined. When 1-methoxy-4-vinylbenzene (**53**) was subjected to the present carbonylation, the reaction was sluggish to give the corresponding 3-methoxypropanoate **54** in poor yield accompanied with the succinate **55** and prop-2-enoate (Equation 3.1).



(3.1)



(3.2)

This result suggested that the electron-donating ability of the hydroxy group might be crucial in promoting reductive elimination from the Pd intermediate to produce quinone-methide (Equation 3.2). The result of Entry 10 in Table 3.2 would also support the significance of the electron-donating effect of the hydroxy group on *para*- or *ortho*-position to the vinyl group.

3.2.6 The role of tin salt

The role of the tin salt is not clear yet. In the case of palladium-catalyzed hydroformylation, $SnCl_2$ was also reported to promote the carbonylation although these reactions required high-pressure CO conditions.[77] Recently, the heterobimetallic Pd-Sn catalyst, $PdCl(COD)SnCl_3$, was reported to activate oxygen functional groups, resulting in promotion of the nucleophilic addition,[77e] Suzuki-Miyaura coupling reaction,[77f] and Michael reaction.[77g]

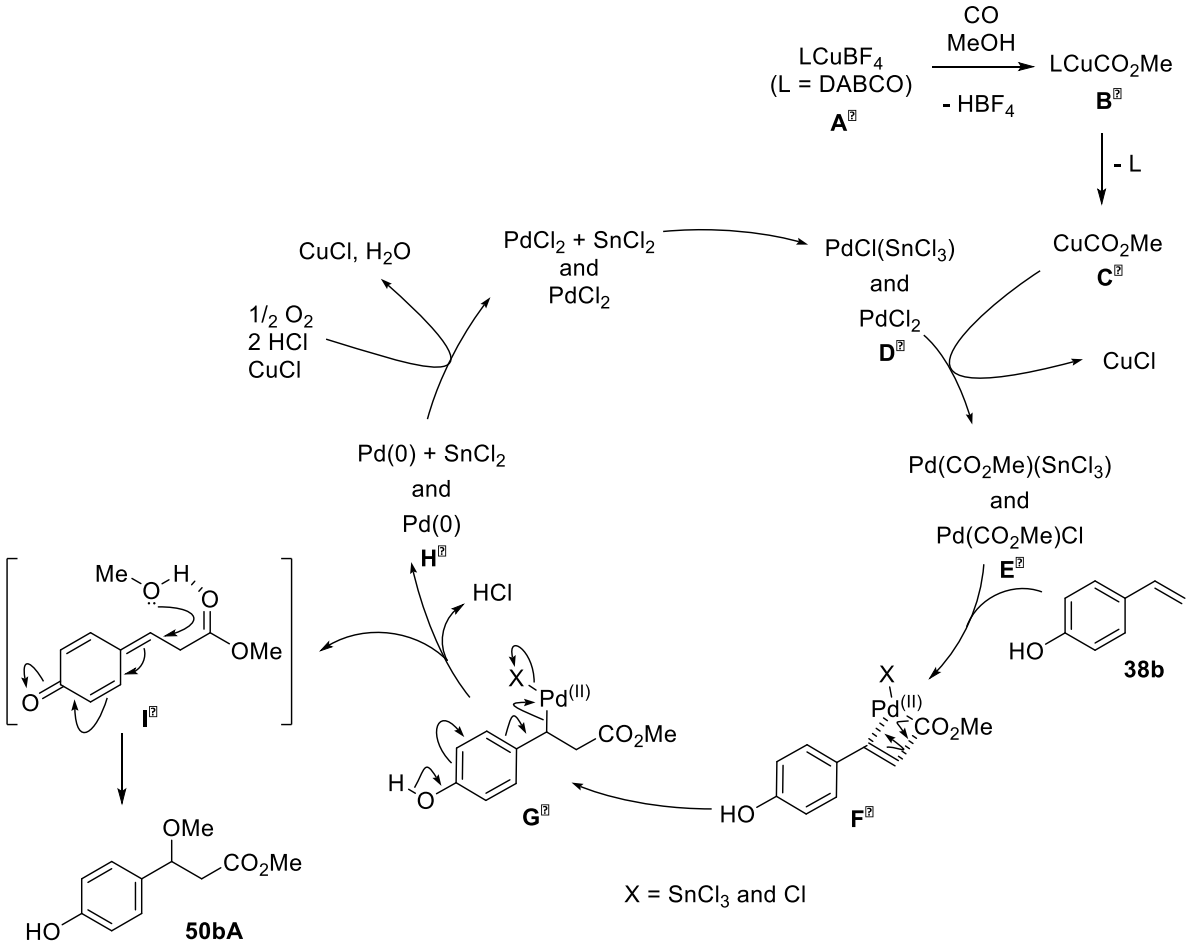
Clear, milky ***Sticky***

Picture 3.1. The reaction mixture with and without$SnCl_2$. *Reaction Conditions*: $PdCl_2$, $Cu(MeCN)_4BF_4$, DABCO, CO/O_2 (ca, 1/1, 1atm), MeOH/THF (v/v =1/1), 50 ^{0}C, 3 h.

In the present alkoxy-alkoxycarbonylation, the reaction mixture without $SnCl_2$ was heterogeneous with undissolved metallic salts. Upon the addition of $SnCl_2$, the suspension became rather milky, which suggested the formation of a new species containing a tin moiety (Picture 3.1). *One possible role of the tin salt might be in making the palladium salt soluble and/or activation of the quinonemethide or alcohol for the nucleophilic addition of alcohol to quinonemethide (Equation 3.2).*

3.2.7 Proposed mechanism for alkoxy-alkoxycarbonylation of vinylphenols

The mechanism of the reaction is still an open question. One possible catalytic cycle was proposed as shown in Scheme 3.2.



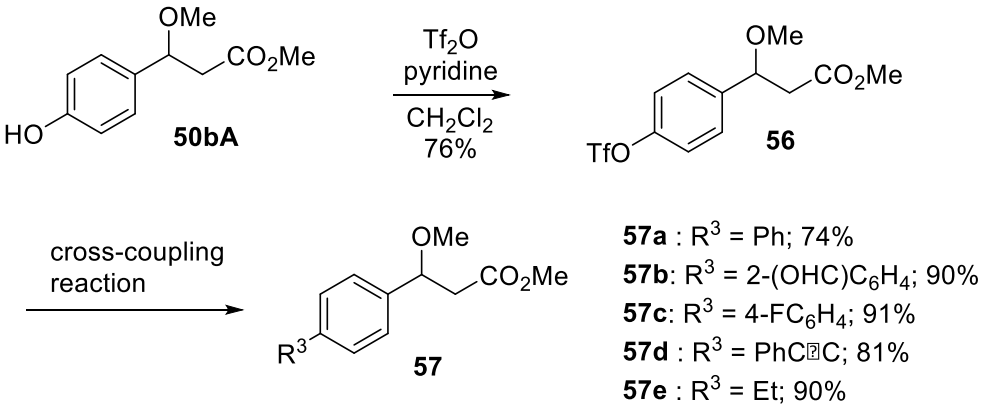
Scheme 3.2. Proposed mechanism.

Starting with the ligand coordinated Cu(I) complex **A**', the reaction of complex **A**' with CO and alcohol generates complex **B**', followed by ligand elimination to form an alkoxycarbonyl copper(I) complex **C**'. Also, the combination of palladium(II) salt and tin salt leads to the *in situ* generation of a heterobimetallic palladium-tin species **D**',[77g] which then is converted into **C**' to furnish alkoxycarbonylpalladium(II) - tin(II) intermediate **E**'. After that,

the intermediate **E**' coordinates to the olefin moiety of substrate and then undergoes a carbopalladation via intermediate **F**', resulting in intermediate **G**'. The electron-donating ability of the hydroxyl group might be crucial in promoting the reductive elimination from the palladium intermediate **G**' to produce *p*-quinone methide **I**', which then undergoes a direct addition of alcohol to generate the *β*-alkoxy ester **50bA**. Finally, palladium (0) is reoxidized by O_2 and copper(I) chloride to regenerate palladium(II).

3.2.8 Applications of the present alkoxy-alkoxycarbonylation products

The application of product **50bA** from the present reaction was demonstrated by its transformation into various 3-(4-substituted-phenyl)propanoate derivatives **57** via cross-coupling reactions, as shown in Scheme 3.3.

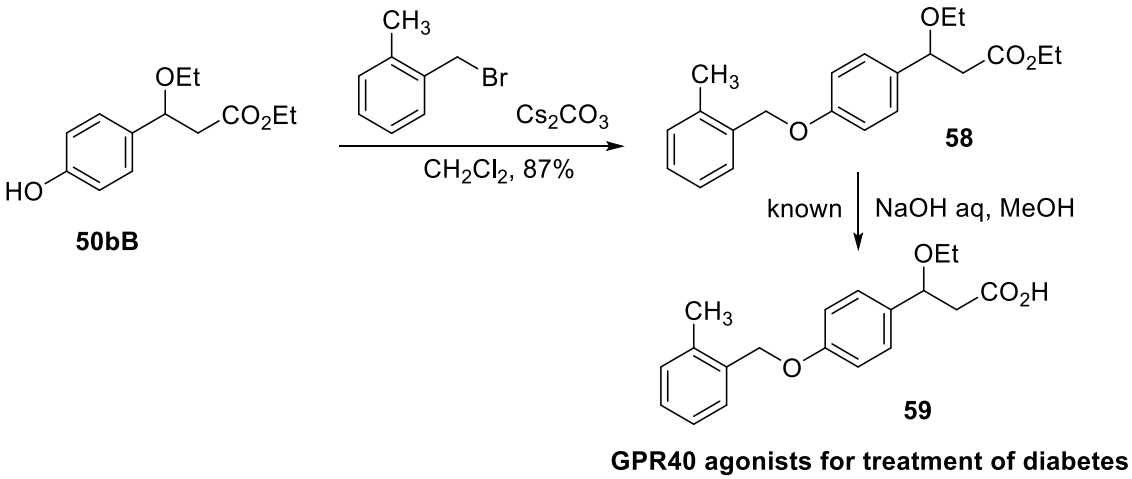


Reaction conditions for **57a-57c**: $RB(OH)_2$, cat. $[Pd(PPh_3)_4]$, K_2CO_3, toluene/DMF (10/1).
57d: PhC≡CH, cat. $[PdCl_2(PPh_3)_2]$, Et_3N, DMF. **57e**: Et_3B, cat. $[PdCl_2(dppf)_2]$, CsOAc, THF.

Scheme 3.3. Transformation of **50bA** to 3-(4-substituted-phenyl)propanoate derivatives **57**.

Furthermore, the 3-alkoxy-3-(hydroxyphenyl)propanoic acid esters obtained by the present alkoxy-alkoxycarbonylation could be useful synthetic intermediates for biologically active compounds.[78] For example, the 3-ethoxy-3-(hydroxyphenyl)propanoate **50bB** was readily applied to the preparation of **58**, which was an intermediate to **59** as a potent GPR40

agonist for treatment of diabetes (Scheme 3.4).[78b] Notably, the present method could avoid the alkylation of the hydroxyl group in 3-hydroxypropanoic acid esters, that often causes trouble.[78b, 78c]



Scheme 3.4. Transformation of **50bB**.

3.3 Conclusion

The efficient palladium-catalyzed alkoxy-alkoxycarbonylation of vinylphenols in the presence of copper and tin salts under normal pressure of CO and O_2 was developed to afford the corresponding 3-alkoxy-3-arylpropanoic acid esters in good to high yields. Not only primary alcohols but also secondary alcohols were applicable to the present reaction. The distinctive feature of the present study is that an unexpected effect of tin salt was discovered. The presence of a tin salt was crucial to realize reproducibly high yields. It is noteworthy that the 3-alkoxy-3-(hydroxyphenyl)propanoic acid esters obtained by the present alkoxy-alkoxycarbonylation could be useful synthetic intermediates for further transformations to valuable chemicals and biologically active compounds.

CHAPTER 4: CONCLUSION

4.1 Summary of Fruitful Outcomes

The work presented in this thesis describes the development of novel and efficient palladium(II)-catalyzed oxidative carbonylation reactions. The fruitful outcomes from the present research are summarized below.

- A novel asymmetric intra- and intermolecular dicarbonylation reaction of homoallylic amine dervivatives catalyzed by palladium(II) and copper(I) salt under normal pressure of CO and O_2 has been achieved by using a chiral bioxazoline ligand. A variety of *N*-substituted homoallylic amine derivatives was applicable to the present reaction to give the corresponding optically active γ-lactams up to 68% ee. Thus, this method provides a new synthetic entry for the construction of enantiomerically pure γ-lactams, which have biological activity and are versatile building blocks for nitrogen-containing chemicals.

- An efficient palladium-catalyzed intermolecular alkoxy-alkoxycarbonylation of vinylphenols in the presence of copper and tin salts was developed to afford the corresponding 3-alkoxy-3-arylpropanoic acid esters in good to high yields. In this work, an unpredictable effect of tin salt was discovered. The presence of a tin salt was crucial to realize reproducibly high yields. It is noteworthy that the application of the 3-alkoxy-3-(hydroxyphenyl)propanoic acid esters obtained by the present alkoxy-alkoxycarbonylation was demonstrated for their further transformations towards various useful chemicals and bioactive agents.

4.2 A Proposal of Further Studies

In the near future, oxidative carbonylation should be an extraordinarily powerful approach towards the synthesis of carbonylated compounds. Here, the development of

improved catalysts and ligands will be a key issue for further investigations. Particularly, our research group is developing a novel class of chiral bioxazoline ligands (Figure 4.1), which are expected to promote various asymmetric processes including palladium-catalyzed carbonylations.

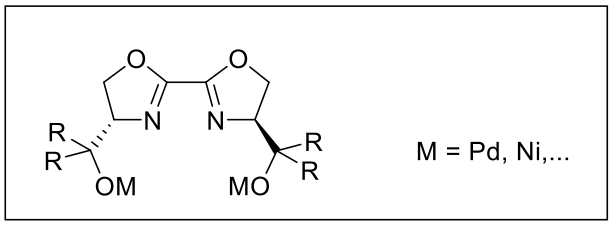
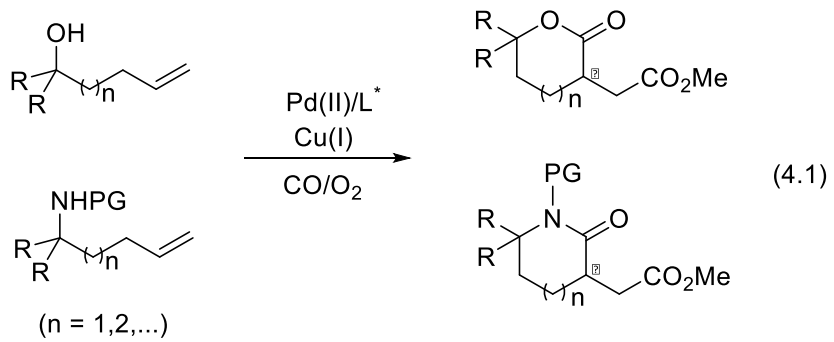


Figure 4.1. Novel class of ligands containing bioxazolines.

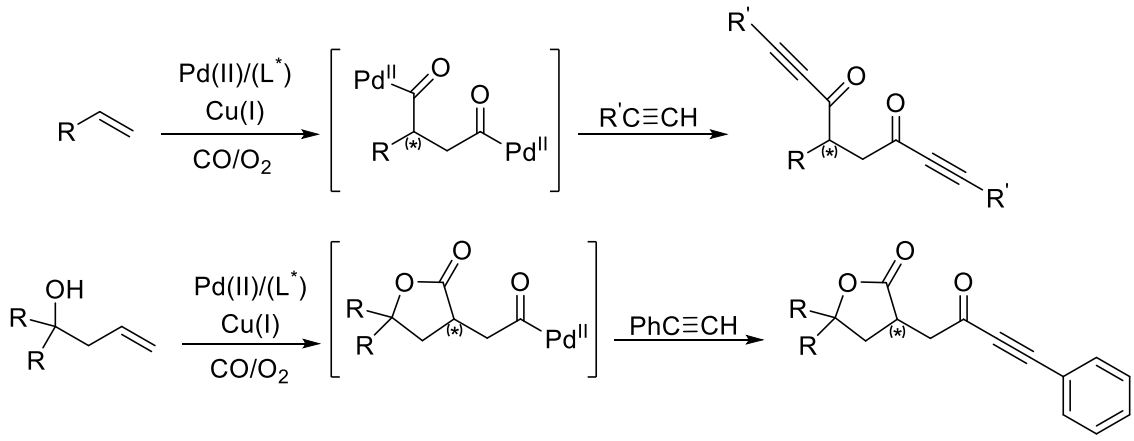
Following our long-term focus on the palladium-catalyzed carbonylative cyclization of unsaturated alcohols and amine derviatives to construct highly fuctionalized heterocyclic motifs, we are interested in extending the present study for construction of six- or more number ring lactones and lactams, which have potential applications in the area of pharmaceuticals (Equation 4.1).



(4.1)

For the more functionalized substrates interesting for organic synthesis, beside alcohols other different nucleophiles could be applicable for the palladium-catalyzed oxidative carbonylation. Such opportunities enable the preparation of important organic building blocks

as well as useful hetero- and carbocyclic molecules. For instance, carbo-carbonylation reactions of olefins with terminal alkynes would be envisoned to proceed towards atom-economical construction of complicated skeletons (Scheme 4.1).



Scheme 4.1. Proposal for carbo-carbonylation reactions.

It will be also necessary to study in more detail the mechanistic aspects of the carbonylation reaction. This aspect will require more work to gain a clearer understanding of the reaction. Further studies regarding the mechanism of such carbonylation reactions are ongoing in our laboratory.

4.3 General Conclusion

In conclusion, novel and efficient palladium-catalyzed oxidative carbonylation reactions have successfully developed. The combination of Pd(II) with Cu(I) has been realized to catalyze these reactions under mild conditions. Indeed, these results add value to the scope of palladium-catalyzed oxidative carbonylations. Notably, the methods developed from this research could find great interest in the synthesis of highly functionalized molecules and especially in the synthesis of biologically active compounds.

EXPERIMENTAL

General Method. ^{1}H NMR spectroscopy was performed in $CDCl_3$ using a JEOL ECS 400 NMR (400 MHz) spectrometer. Chemical shifts (δ) were determined relative to TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR spectroscopy was performed in $CDCl_3$ on a JEOL ECS 400 NMR (100 MHz) spectrometer and chemical shifts (*d*) were determined relative to $CDCl_3$ (δ = 77.0 ppm) as an internal standard. ^{19}F NMR spectroscopy was performed in $CDCl_3$ on a JEOL ECS 400 NMR (376 MHz) spectrometer and chemical shifts (δ) were determined relative to C_6F_6 (δ = –162.90 ppm) as an internal standard. IR spectra were acquired on a JASCO FT/IR-230 spectrometer. Melting points were determined on a micro-melting apparatus (Yanagimoto–Seisakusho) and were uncorrected. The MS spectra were recorded with JEOL SX-102A and BRUKER microTOFII massspectrometers.Merck silica gel 60 PF254 (Art. 7749), Cica silica gel 60N spherical neutral (37563-84) and JAIGL-SIL (s-043-15)were used for thin-layer chromatography (TLC), flash column chromatography andrecycle HPLC, respectively. The specific optical rotations were recorded on a polarimeter. Super dehydrated solvents were purchased for the reactions and used without futher desiccation.

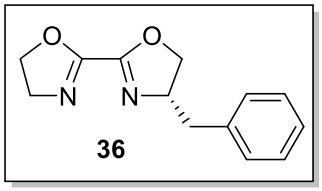
A. Asymmetric Palladium-Catalyzed Intra- and Intermolecular Dicarbonylation of Homoallylic Amine Derivatives

Chiral bioxazoline ligands **32**, **34-40**, **43**, **45**[69, 79], **46**[80] were prepared by the methods reported in the literature. Ligand **36** was prepared according to the following procedure.

2-Aminoethanol (61.1 mg, 1 mmol) and *(R)*-(+)-2-amino-3-phenyl-1-propanol (151.2 mg, 1 mmol) were added to a solution of diethyl oximidate (144.2 mg, 1 mmol, 1 equiv) in 7 ml of $ClCH_2CH_2Cl$. The reaction mixture was stirred at reflux for 1 day. After cooling to room temperature, the resulting mixture was evaporated to remove the solvent. The crude was

purified by silica gel chromatography (hexane/AcOEt = 1/1) to give desired asymmetric bioxazoline ligand (61 mg, 27%).

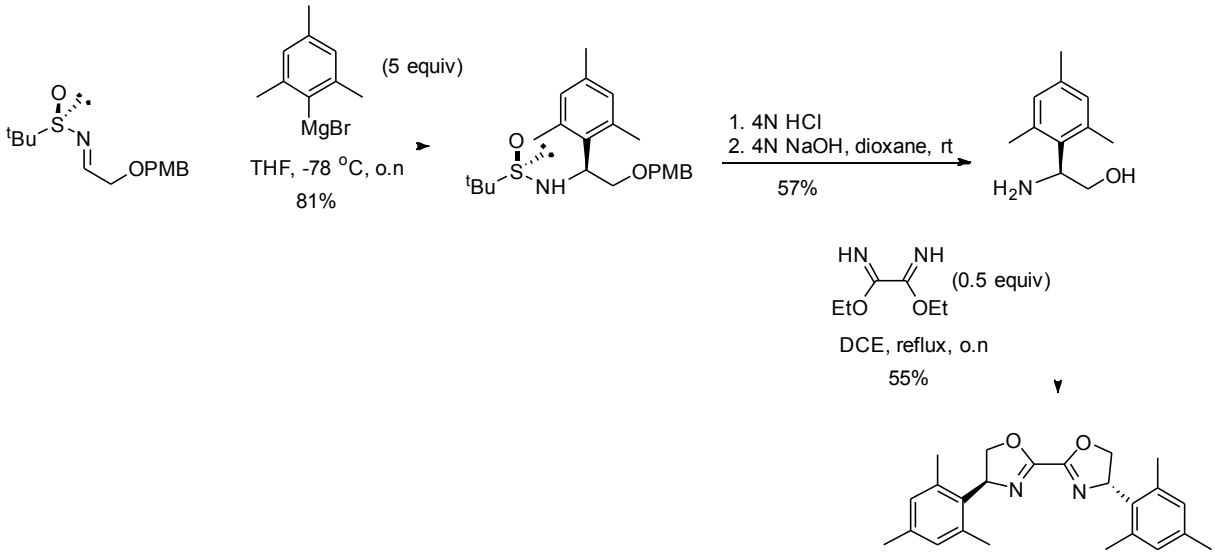
(S)-4-benzyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (36):



36

A colorless oil. R_f = 0.2 (only AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.65 (dd, 1H, J = 14.2, 9.2 Hz), 3.19 (dd, 1H, J = 14.2, 5.0 Hz), 4.08 (t,2H, J = 19.7, 9.6 Hz), 4.14 (t, 1H, J = 16.5, 8.2Hz), 4.37 (t, 1H, J = 18.3, 9.6 Hz), 4.46 (t, 2H, J = 19.3, 9.6 Hz), 4.61 (m, 1H), 7.15 – 7.28 (m, 5H); ^{13}C NMR($CDCl_3$) δ = 40.9, 55.0, 68.0, 68.3, 72.5, 126.6, 128.5, 129.0, 154.3, 155.6; IR (neat) 3283, 3028, 2932, 2359, 1651, 1620, 1520, 1496, 1455, 1386, 1346, 1255, 1127, 1072, 943, 923, 753, 702 cm^{-}1; HRMS (DART) m/z calcd for $C_{13}H_{15}N_2O_2$ [$(M+H)^+$]: 231.1134, found: 231.1139.

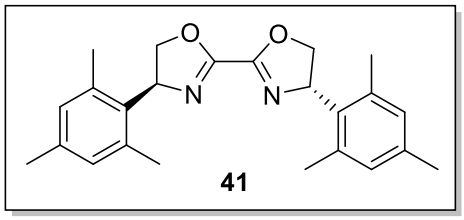
Synthesis of ligand 41:



(S)-2-amino-2-mesitylethanol was prepared according to the method reported in the literature.[81] *(S)*-2-amino-2-mesitylethanol (104.2 mg, 0.58 mmol, 2 equiv) was added to a solution of diethyl oximidate (42 mg, 0.29 mmol, 1 equiv) in 4 ml of $ClCH_2CH_2Cl$. The

reaction mixture was stirred at reflux overnight. After cooling to room temperature, the resulting mixture was evaporated to remove the solvent. The crude was purified by silica gel chromatography (hexane/AcOEt = 4/1) to give a white solid which then recrystallized from AcOEt/ hexane to afford pure ligand (59.8 mg, 55%).

(4S,4'S)-4,4'-dimesityl-4,4',5,5'-tetrahydro-2,2'-bioxazole (41):



41

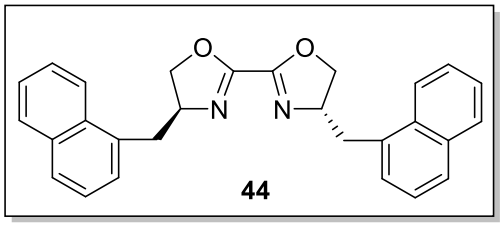
A white solid. R_f = 0.4 (hexane/AcOEt = 2/1). Mp = 196-197 ^oC (from hexane/AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ = 2.17 (s, 3H), 2.25 (s, 6H), 4.27 (t, 1H, *J*= 10.1, 1.7 Hz), 4.70 (dd, 1H, *J* = 11.4, 8.7 Hz), 5.77 (t, 1H, *J* = 11.4,10.6 Hz), 6.76 (s, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ = 20.1, 20.7, 66.5, 72.7, 130.3, 132.2, 136.8, 137.3, 155.2; IR (KBr) 3423, 3006, 2965, 2922, 2866, 1737, 1686, 1620, 1485, 1510, 1485, 1452, 1336, 1245, 1121, 1057, 930, 845, 750 cm^{-1}; HRMS (DART) *m*/*z* calcd for $C_{24}H_{29}N_2O_2$ $[(M+H)^+]$: 377.2229, found: 377.2223.

Synthesis of Ligand 44:[82]

To a solution of 3-(1-naphthyl)-*L*-alanine hydrochloride (755.1 mg, 3 mmol) in 5 ml of methanol was added 0.6 ml of thionyl chloride. The solution was heated to reflux for 2 h. After elimination of all volatile products, the remaining solid was dried and the ester was obtained in the form of an hydrochloride. To a solution of $NaBH_4$ (348 mg, 9.2 mmol) in 5 ml of a mixture water/ethanol (1/1) was added a solution of resulting aminoester and 5 ml of the same solvent mixture. The reaction mixture was heated to reflux for 4 h, then the ethanol was evaporated. The aqueous phase was saturated with NaCl and extracted with ethyl acetate. After drying and evaporation of the solvent, a pale yellow oil was obtained which soon recrystallized from ethyl acetate to form pure *(S)*-2-amino-3-(1-naphthyl) propanol (475 mg, 74%, 2 steps). *(S)*-2-amino-3-(1-naphthyl) propanol (215.3 mg, 1 mmol, 2 equiv) was added

to a solution of diethyl oximidate (72.1 mg, 0.5 mmol, 1 equiv) in 5 ml of $ClCH_2CH_2Cl$. The reaction mixture was stirred at reflux overnight. After cooling to room temperature, the resulting mixture was evaporated to remove the solvent. The crude was purified by silica gel chromatography (hexane/AcOEt = 1/1) to afford a bright yellow solid which then recrystallized from AcOEt/ hexane to afford pure ligand (200.6 mg, 95%).

(4S,4'S)-4,4'-bis(naphthalen-1-ylmethyl)-4,4',5,5'-tetrahydro-2,2'-bioxazole (44):

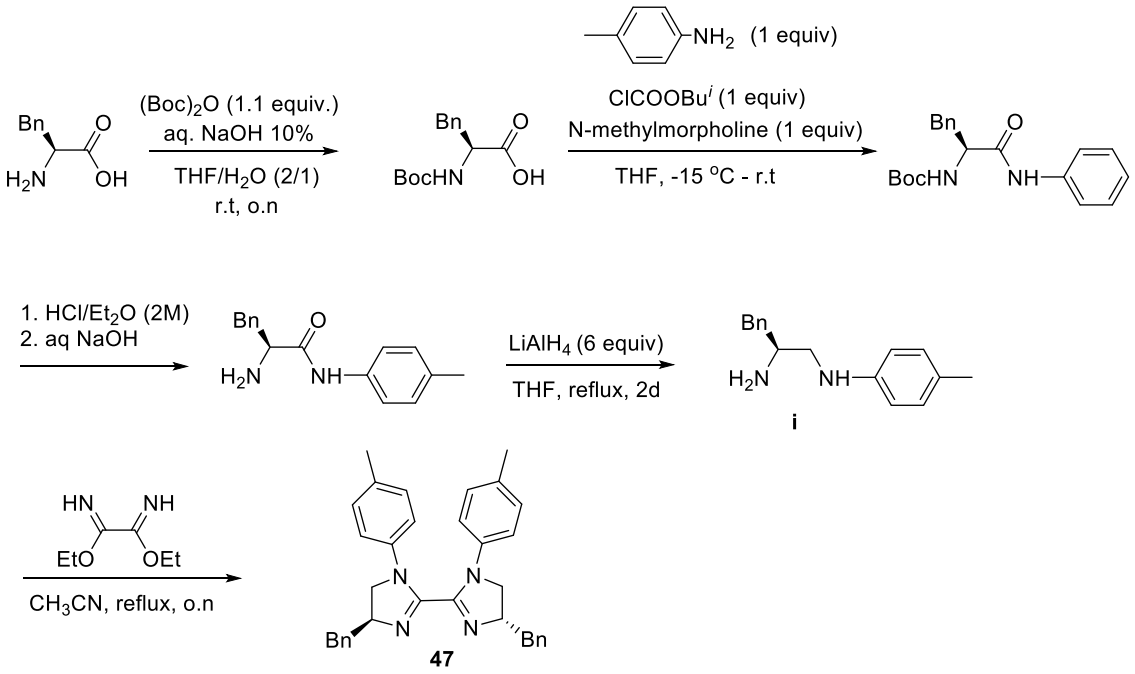


44

A yellow solid. R_f = 0.3 (hexane/AcOEt = 1/1). M.p = 150-151 ^oC (from hexane/AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ = 3.01 (dd, 1H, J = 14.2, 10.1 Hz), 4.11 (dd, 1H, J = 14.2, 6.9 Hz), 4.31 (dd, 2H, J = 8.2, 2.3 Hz), 4.82 (m, 1H), 7.34 – 7.58 (m, 4H), 7.76 (d, J = 8.2 Hz), 7.87 (d, 1H, J = 8.7 Hz), 8.10 (d, 1H, J = 8.24 Hz); ^{13}C NMR($CDCl_3$) δ = 38.7, 67.3, 73.2, 123.5, 125.6, 126.0, 126.5, 127.0, 127.9, 129.0, 155.3; IR (KBr) 3457, 3065, 2982, 2953, 2885, 1732, 1613, 1508, 1472, 1395, 1332, 1228, 1130, 1094, 953, 883, 795, 777, 741 cm^{-1}; HRMS (DART) m/z calcd for $C_{28}H_{25}N_2O_2$ $[(M+H)^+]$: 421.1916, found: 421.1905.

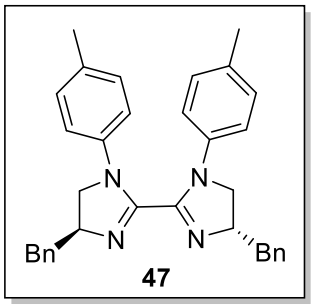
Synthesis of ligand 47:

The procedure for preaparation of ligand **47** is illustrated on the following scheme.



(*S*)-3-phenyl-1-*N*-(p-tolyl)propane-1,2-diamine (**i**) was prepared according to the method reported in the literature.[83] Diamine **i** (500 mg, 2.08 mmol) was added to a solution of diethyl oximidate (150 mg, 1.04 mmol, 0.5 equiv) in 8 ml of CH_3CN. The reaction mixture was stirred at reflux overnight. After cooling to room temperature, the resulting mixture was evaporated to remove the solvent. The residue was purified by silica gel chromatography (CH_2Cl_2/ MeOH = 10/1) to give a light yellow solid which then recrystallized from AcOEt/ hexane to afford pure ligand (257 mg, 25%).

(*4S,4'S*)-4,4'-dibenzyl-1,1'-di-p-tolyl-4,4',5,5'-tetrahydro-1H,1'H-2,2'-biimidazole (47):

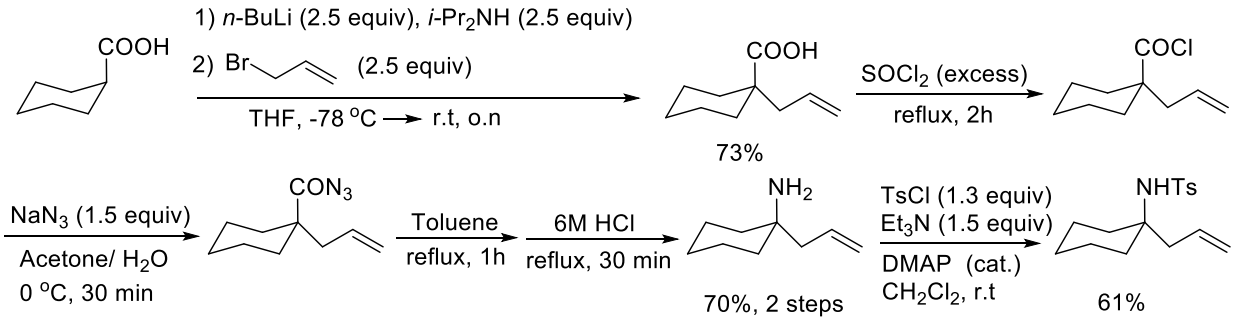


A yellow solid. R_f= 0.6 (CH_2Cl_2/ MeOH = 10/1). M.p =175-176 °C (from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.20 (s, 3H), 2.83 (dd, 1H, J = 13.8, 9.16 Hz), 3.23 (dd, 1H, J = 13.8, 5.0 Hz), 3.44 (t, 1H, J = 9.2 Hz), 3.59 (t, 1H, J = 9.2 Hz), 4.49 (m, 1H), 6.49 (d, 2H, J = 6.9 Hz), 6.79 (d, 2H, J = 7.3 Hz), 7.11 (d, 1H, J = 7.4 Hz), 7.23 (m, 5H); ^{13}C NMR($CDCl_3$) δ = 20.4, 21.1, 40.8, 54.9, 65.6, 119.1, 126.0, 127.8,

128.5, 128.6, 129.1, 132.5, 136.7, 137.9, 153.5; IR (KBr) 3067, 3063, 3027, 2974, 2919, 2853, 2363, 1944, 1897, 1800, 1626, 1611,1565, 1474, 1450, 1377, 1357, 1311, 1277, 1202, 1019, 895, 815, 705; HRMS (DART) *m/z* calcd for $C_{34}H_{35}N_4$ $[(M+H)^+]$: 499.2862; found: 499.2855.

General Procedure for Synthesis of Substrates (30a-30h):

N-(1-Allylcyclohexyl)-p-toluenesulfonamide (30a) was synthesized by adopting our method[64] as shown on following scheme.

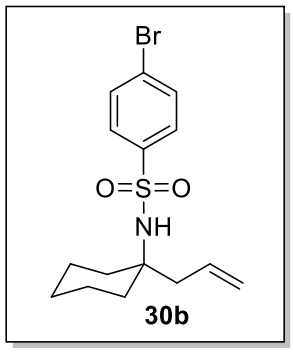


n-BuLi (1.64 M in hexane) (76.2 ml, 125 mmol, 2.5 equiv) was added dropwise to a solution of diisopropylamine (12.65 g, 125 mmol, 2.5 equiv) in THF (70 ml) at -78 °C. The mixture was allowed to warm to 0 °C and stirred at this temperature for 1 hour. A solution of cyclohexanecarboxylic acid (6.409 g, 50 mmol, 1 equiv) in THF (30 ml) was added dropwise to the resulting LDA solution still at 0 °C. The mixture was stirred at room temperature for 2 hour and then at reflux for 1 hour. It was then cooled to 0 °C, and allyl bromide (15.1 g, 125 mmol, 2.5 equiv) was added dropwise. The resulting clear solution was stirred overnight at room temperature. The reaction was quenched by adding saturated NH_4Cl solution. The aqueous layer was separated from the organic, acidified with 2M HCl (ca. 62.5 ml), and extracted with Et_2O (3 x 100 ml). The combined etheral layers were washed with K_2CO_3 (20% m/m solution, 3 x 100 ml). The combined resulting aqueous layers were acidified to pH = 3 with 6M HCl and extracted with Et_2O (3 x 100 ml). The combined organic layers were

dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, Hex/AcOEt/AcOH = 2/1/0 to 0/1/0.5) gave 1-allylcyclohexanecarboxylic acid (6.12 g, 73%) as yellowish-orange oil. 1-allylcyclohexanecarboxylic acid (6.12 g, 36.4 mmol) was treated with thionyl chloride (30 ml) and the solution was refluxed for 2 hour and condensed under reduced pressure to give corresponding acyl chloride (6.40 g). To an acetone (18 ml) solution of the crude acyl chloride was added a H_2O (9 ml) solution of sodium azide (3.34 g, 51.4 mmol, 1.5 equiv) and solution was stirred for 1.5 hour. After the addition of H_2O (45 ml), the reaction mixture was extracted with toluene several times ad the combined extracts were dried over Na_2SO_4. The filtrate was refluxed for 2 hour , followed by cooling to room temperature and evaporating the solvent in vacuo. To the residue, 6M HCl (24 ml) was added, the mixture was gradually warmed and refluxed for 1 hour. After cooling to room temperature, the mixture was washed with ether and the resulting aqueous layer was made basic by adding Na_2CO_3 and extracted with ether. The combine extracts were dried over Na_2SO_4 and then evoparated the sovent in vacuo to give almost pure 1-allyl-1-aminocyclohexane (3.23 g, 70% 2 steps). To a mixture of obtained 1-allyl-1- aminocyclohexane (1.392 g, 10 mmol), triethylamine (2.1 ml, 15 mmol, 1.5 equiv), a catalytic amount (ca. 20 mg) of 4-(dimethylamino)-pyridine in CH_2Cl_2 (20 ml) was added tosyl chloride (2.48 g, 13 mmol, 1.3 equiv) under a nitrogen atmosphere, and the reaction mixture was stirred overnight. The reaction mixture was quenched with H_2O and extracted with ethyl acetate. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, and evaporated the solvent in vacuo. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give desired product (1.80 g, 61%). Spectra data for substrate **1a** was in agreement with spectra reported in the literature.[64]

In a similar manner, allylic amines **30b-30h** were obtained from the 1-allyl-1-aminocyclohexane and corresponding sulfonyl chlorides.

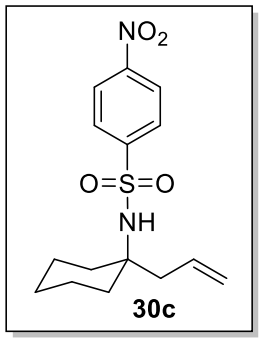
***N*-(1-allylcyclohexyl)-4-bromobenzenesulfonamide (30b):**



30b

Compound **30b** was obtained as a white solid. R_f = 0.5 (hexane/AcOEt = 4/1). Mp = 126-127 ^oC (from hexane/AcOEt); ^1H NMR (400 MHz, $CDCl_3$): δ 1.22–1.50 (m, 8H), 1.65–1.74 (m, 2H), 2.40 (d, 2H, J = 7.3 Hz), 4.53 (brs, 1H), 5.09 (d, 1H, J = 17.4 Hz), 5.13 (d, 1H, J = 10.1 Hz), 5.73 (ddt, 1H, J = 17.4, 10.1, 7.3 Hz), 7.63 (d, 2H, J = 8.7 Hz), 7.77 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 25.1, 35.4, 43.0, 59.8, 119.4, 126.9, 128.4, 132.1, 132.7, 142.7; IR (KBr) 3292, 3070, 2941, 2857, 1637, 1577, 1469, 1450, 1423, 1335, 1291, 1152, 1094, 1001, 920, 823, 739, 704, 670 cm^{-1}; HRMS (DART) *m*/*z* calcd for $C_{15}H_{21}Br_1N_1O_2S_1$ $[(M+H)^+]$: 358.0476; found: 358.0476.

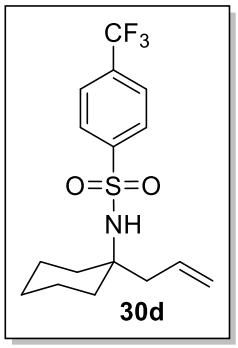
***N*-(1-allylcyclohexyl)-4-nitrobenzenesulfonamide (30c):**



30c

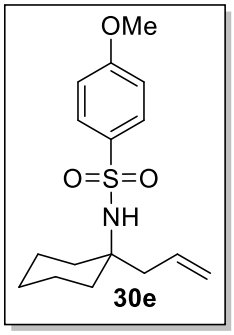
Compound **30c** was obtained as a light yellow solid. R_f = 0.8 (hexane/AcOEt = 2/1). Mp: 112-113 ^oC (from hexane/ethyl acetate); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.23–1.51 (m, 8H), 1.68–1.76 (m, 2H), 2.43 (d, 2H, J = 7.3 Hz), 4.54 (brs, 1H), 5.11 (d, 1H, J = 16.9 Hz), 5.15 (d, 1H, J = 10.5 Hz), 5.66–5.77 (m, 1H), 8.08 (d, 2H, J = 8.7 Hz), 8.35 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 25.0, 35.4, 43.0, 60.4, 119.8, 124.2, 128.1, 132.3, 149.2, 149.6; IR (KBr) 3282, 3102, 2936, 2862, 1643, 1607, 1530, 1451, 1422, 1347, 1173, 1155, 1097, 1004, 925, 857, 735, 673 cm^{-1}; HRMS (DART) *m*/*z* calcd for $C_{15}H_{21}N_2O_4S_1$ $[(M+H)^+]$: 325.1222; found: 325.1223.

***N*-(1-allylcyclohexyl)-4-(trifluoromethyl)benzenesulfonamide (30d):**



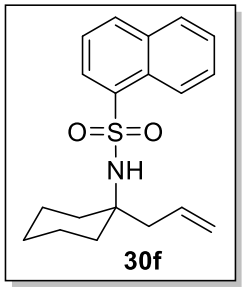
Compound **30d** was obtained as a white solid. R_f = 0.8 (hexane/AcOEt = 2/1). Mp = 118-119 ^oC (from hexane/AcOEt); ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.30-1.71 (m, 10H), 2.41 (d, 2H, J = 7.3 Hz), 4.53 (s, 1H), 5.11 (d, 1H, J = 14.2, 10.1 Hz), 5.15 (d, 1H, J = 10.1 Hz), 5.71 (ddt, 1H, J = 14.2, 10.1, 7.3 Hz), 7.76 (d, 2H, J = 8.24 Hz), 8.02 (d, 2H, J = 7.8 Hz). ^{19}F ($CDCl_3$, 376 MHz) δ = -62.9; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.5, 25.1, 35.4, 43.0, 60.1, 119.5, 126.1, 127.4, 132.5, 133.7, 134.0, 147.0; IR (KBr) 3282, 3079, 2939, 2862, 1943, 1686, 1643, 1609, 1449, 1423, 1315, 1173, 1066, 1038, 923, 823, 785, 672 cm^{-1}; HRMS (DART) *m*/*z* calcd for $C_{16}H_{21}F_3N_1O_2S_1$ [$(M+H)^+$]: 348.1245; found: 348.1248.

***N*-(1-allylcyclohexyl)-4-methoxybenzenesulfonamide (30e):**



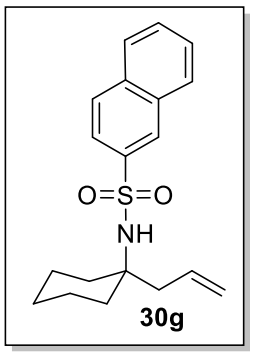
Compound **30e** was obtained as a white solid. R_f = 0.6 (hexane/AcOEt = 2/1). Mp = 156-157 ^oC (from hexane/AcOEt); ^1H NMR (400 MHz, $CDCl_3$): δ 1.22–1.52 (m, 8H), 1.68–1.78 (m, 2H), 2.39 (d, 2H, J = 7.3 Hz), 3.87 (s, 3H), 4.34 (brs, 1H), 5.08 (d, 1H, J = 18.8 Hz), 5.11 (d, 2H, J = 12.4 Hz, 1H), 5.67–5.81 (m, 1H), 6.95 (d, 2H, J = 8.7 Hz), 7.83 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 25.2, 35.5, 43.0, 55.6, 59.3, 113.9, 119.2, 129.0, 133.0, 135.3, 162.4; IR (KBr) 3295, 3077, 3010, 2944, 2853, 1639, 1597, 1499, 1453, 1418, 1313, 1258, 1188, 1141, 1096, 1000, 914, 851, 832, 766, 675 cm^{-1}; HRMS (DART) *m*/*z* calcd for $C_{16}H_{24}N_1O_3S_1$ [$(M+H)^+$]: 310.1477; found: 310.1478.

***N*-(1-allylcyclohexyl)naphthalene-1-sulfonamide (30f):**



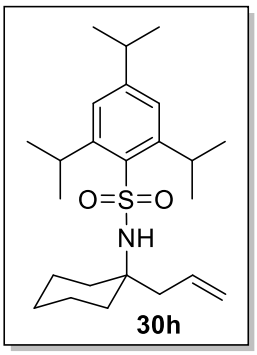
Compound **30f** was obtained as a white solid. R_f = 0.7 (hexane/AcOEt = 2/1). Mp = 138-139 °C (from hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04–1.34 (m, 8H), 1.66–1.76 (m, 2H), 2.40 (d, 2H, J = 7.3 Hz), 4.56 (s, 1H), 5.02–5.09 (m, 2H), 5.63–5.77 (m, 1H), 7.50–7.72 (m, 3H), 7.94 (d, 1H, J = 8.2 Hz), 8.04 (d, 1H, J = 8.2 Hz), 8.31 (d, 1H, J = 7.3 Hz), 8.61 (d, 1H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 25.1, 35.3, 43.5, 59.9, 119.4, 124.2, 124.6, 126.7, 128.0, 128.1, 128.9, 129.0, 132.9, 133.9, 134.1, 138.2; IR (KBr) 3308, 2926, 2862, 1640, 1593, 1508, 1448, 1416, 1310, 1199, 1127, 1005, 921, 854, 830, 805, 774, 678 cm^{-1}; HRMS (DART) *m*/*z* calcd for $C_{19}H_{24}N_1O_2S_1$ [(M+H)$^+$]: 330.1528; found: 330.1519.

***N*-(1-allylcyclohexyl)naphthalene-2-sulfonamide (30g):**



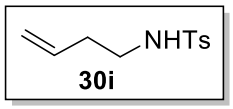
Compound **30g** was obtained as a white solid. R_f = 0.8 (hexane/AcOEt = 2/1). Mp = 160-161 °C (from hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26–1.33 (m, 6H), 1.38–1.47 (m, 2H), 1.72–1.79 (m, 2H), 2.43 (d, 2H, J = 7.3 Hz), 4.48 (s, 1H), 5.07 (d, 1H, J = 17.4 Hz), 5.11 (d, 1H, J = 10.5 Hz), 5.75 (ddt, 1H, J = 17.4, 10.5, 7.3 Hz), 7.58–7.66 (m, 2H), 7.86–7.96 (m, 4H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 25.1, 35.5, 43.1, 59.6, 119.3, 122.6, 127.4, 127.77, 127.85, 128.6, 129.19, 129.24, 132.1, 132.9, 134.5, 140.3; IR (KBr) 3282, 2939, 2858, 1641, 1591, 1504, 1452, 1419, 1314, 1128, 1073, 1036, 1002, 915, 861, 820, 749, 660 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{24}N_1O_2S_1$ [(M+H)$^+$]: 330.1528; found: 330.1528.

***N*-(1-allylcyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (30h):**



A white solid. R_f = 0.6 (hexane/AcOEt = 4/1). Mp = 71-72 ^oC (from hexane/AcOEt); ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, 6H, J = 6.9 Hz), 1.27 (d, 12H, J = 6.9 Hz), 1.35–1.53 (m, 8H), 1.77–1.84 (m, 2H), 2.50 (d, 2H, J = 7.3 Hz), 2.89 (sep, 1H, J = 6.9 Hz), 4.21 (brs, 1H), 4.25 (sep, 2H, J = 6.9 Hz), 5.11 (d, 1H, J = 17.4 Hz), 5.12 (d, 1H, J = 10.0 Hz), 5.70–5.81 (m, 1H), 7.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 23.6, 24.8, 25.3, 29.5, 34.1, 35.8, 43.2, 60.1, 119.3, 123.7, 133.1, 136.0, 149.2, 152.1; IR (KBr) 3286, 2964, 2876, 1640, 1599, 1447, 1421, 1315, 1155, 1094, 993, 915, 815, 667 cm^{-1}; HRMS (DART) *m*/*z* calcd for $C_{24}H_{40}N_1O_2S_1$ $[(M+H)^+]$: 406.2780; found: 406.2770.

N-(but-3-en-1-yl)-4-methylbenzenesulfonamide (30i):[84]

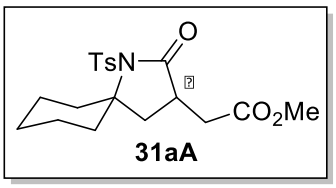


4-bromobut-1-ene (2.23 mL, 22 mmol, 1.1 eq) and K_2CO_3 (5.53 g, 40 mmol, 2.0 eq) were added to a solution of tosylamine (3.42 g, 20 mmol, 1.0 eq) in acetone (50 mL). The reaction was stirred over night at 60 °C. The reaction was quenched with sat. aq. NH_4Cl, extracted with Et_2O (50 ml x 3), washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography column on silica gel (hexane/ EtOAc = 3/1) gave desired product (2.83 g, 63 %) as a clear oil; ^1H NMR ($CDCl_3$, 400MHz) δ = 2.18 (q, 2H, J = 6.9Hz), 2.41 (3H, s), 3.00 (q, 2H, J = 6.9 Hz), 5.00 (1H, t), 5.02 (1H, s), 5.23 (1H, s), 5.63 (1H, m), 7.28 (d, 2H, J = 7.8Hz), 7.33 (d, 2H, J = 7.8Hz).

Representative Procedure for Asymmetric bis(alkoxycarbonylation) Reaction of *N*-(1-allylcyclohexyl)-4-methylbenzenesulfonamide (30a) (Table 2.4, Entry 1):

Under an Ar atmosphere, $PdCl_2$ (1.1 mg, 0.006 mmol, 0.02 equiv), $CuOTf(C_6H_6)_{0.5}$ (37.8 mg, 0.15 mmol, 0.5 equiv), benzyl-bioxazoline ligand (3.8 mg, 0.012 mmol, 0.04 equiv) were placed in a flask. Next, a solution of *N*-(1-allylcyclohexyl)-4-methylbenzenesulfonamide **30a** (92.8 mg, 0.3 mmol) in MeOH superdehydrate (2 ml) and THF (2 ml) were added via cannulation. The Ar atmosphere was replaced with CO/O_2 (v/v=1/1) and the reaction was stirred at a 60 ^oC. After reaction completion (monitored by TLC), aqueous $NaHCO_3$ solution was added. The insoluble substance was filtered off through Celite. After the filtrate was extracted three times with AcOEt, the combined organic layer was washed with water and brine, and dried over Na_2SO_4. The crude product was purified by silicagel column chromatography (Hex/AcOEt = 3/1) to obtain desired γ-lactam **31aA** as a white solid (55.8 mg, 49%) accompanied with byproducts **31aA1**(20 mg, 19%), **31aA2** (9.2 mg, 10%) and **31aA3** (20.9 mg, 17%, 54% ee).

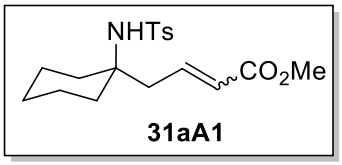
Methyl 2-(2-oxo-1-tosyl-1-azaspiro[4.5]decan-3-yl)acetate (31aA):



31aA

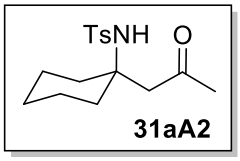
A white solid. R_f = 0.4 (hexane/AcOEt = 2/1). Mp = 141-142 ^oC (from hexane/AcOEt). $[\alpha]_D^{25}$ = -1.6 (*c* 0.4, $CHCl_3$). The ee was determined to be 68% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 10/1, 0.75 mL/min, 220 nm, major 32.2 min, minor 71.3 min). (Table 2.1, Entry 5); ^1H NMR (400 MHz, $CDCl_3$): δ 1.24−1.49 (m, 4H), 1.66−1.85 (m, 5H), 2.33 (dd, 1H, *J* = 16.9, 8.7 Hz), 2.42 (s, 3H), 2.44−2.51 (m, 1H), 2.67 (dd, 1H, *J* = 12.4, 9.2 Hz), 2.80 (dd, 1H, *J* = 16.9, 4.1 Hz), 2.85−2.91 (m, 2H), 3.65 (s, 3H), 7.30 (d, 2H, *J* = 8.2 Hz), 7.93 (dz, 2H, *J* = 8.2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 22.8, 24.1, 24.5, 33.5, 34.3, 36.6, 36.8, 37.8, 51.9, 69.7, 128.5, 129.2, 136.6, 144.6, 171.7, 174.7; IR (KBr): 2938, 2867, 1722, 1596, 1442, 1363, 1343, 1260, 1215, 1161, 1089, 1066, 998, 882, 826, 683, 657 cm^{-1}; HRMS (DART) *m*/*z* calcd for $C_{19}H_{26}N_1O_5S_1$ $[(M+H)^+]$: 380.1532; found: 380.1526.

Methyl 4-(1-((4-methylphenyl)sulfonamido)cyclohexyl)but-2-enoate (31aA1):



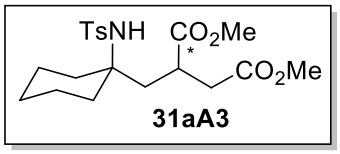
A white solid. R_f = 0.5 (hexane/AcOEt = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21-1.68 (m, 10H), 2.51 (d, 2H, J = 7.8 Hz), 3.65 (s, 3H), 4.40 (s, 1H), 5.70 (d, 1H, J = 14.2 Hz), 6.78 (m, 1H), 7.20 (d, 2H, J = 9.6 Hz), 7.71 (d, 2H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 21.5, 25.0, 35.8, 41.7, 51.4, 59.4, 124.4, 126.9, 129.5, 140.3, 143.1, 143.8, 166.5.

4-Methyl-N-(1-(2-oxopropyl)cyclohexyl)benzenesulfonamide (31aA2):



A white solid. R_f = 0.4 (hexane/AcOEt = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (m,1H), 1.21-1.36 (m, 9H), 1.83 (s, 3H), 2.30 (s, 3H), 2.6 (s, 2H), 5.29 (s, 1H), 7.19 (d, 2H, J = 1.8 Hz), 7.68 (d, 2H, J = 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 21.5, 31.1, 35.9, 50.3, 57.4, 127.2, 129.5, 139.9, 143.0, 208.0.

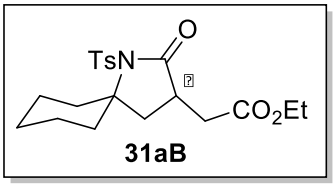
Dimethyl 2-((1-((4-methylphenyl)sulfonamido)cyclohexyl)methyl)succinate (31aA3):



A white solid. R_f = 0.3 (hexane/AcOEt = 2/1). $[\alpha]_D^{25}$ = -1.5 (c 0.53, $CHCl_3$). The ee was determined to be 54% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 7/1, 0.2 mL/min, 240 nm, major 28.2 min, minor 30.6 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25-1.86 (m, 10H), 2.12 (dd, 1H, J = 14.7, 9.2Hz), signal of C-H was not observed clearly at δ = 2.41 due to be overlapped with other peak), 2.41 (s, 3H), 2.45 (dd, 1H, J = 16.5, 5.9 Hz), 2.68 (dd, 1H, J = 16.5, 8.7Hz), 2.97 (m, 1H), 3.65 (s, 3H), 3.69 (s, 3H), 4.75 (s, 1H), 7.27 (d, 2H, J = 7.8 Hz), 7.77 (d, 2H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 21.6, 25.0, 35.5, 36.6, 37.8, 51.8 (d), 52.2, 59.5, 126.8, 129.5,

140.6, 142.8, 172.0, 176.1; IR (KBr): 3288, 2938, 2864, 2360, 1738, 1599, 1438, 1321, 1287, 1153, 1093, 1043, 995, 817, 666 cm^{-1}.

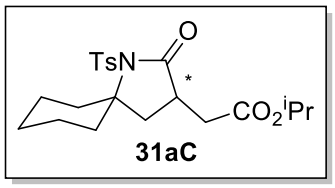
Ethyl 2-(2-oxo-1-tosyl-1-azaspiro[4.5]decan-3-yl)acetate (31aB):



31aB

Starting from **30a** (92.8 mg, 0.3 mmol), compound **31aB** was obtained as a white solid (56.7 mg, 48%). R_f = 0.4 (hexane/AcOEt = 2/1). Mp = 116-117 ^oC (from hexane/AcOEt). $[\alpha]_D^{25}$ = -1.8 (*c* 1.3, $CHCl_3$). The ee was determined to be 38% by HPLC (Daicel CHIRALPAK IB, hexane/EtOH = 20/1, 0.5 mL/min, 220 nm, major 48.7 min, minor 50.7 min); ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, 3H, *J* = 7.3 Hz), 1.23–1.52 (m, 4H), 1.23–1.52 (m, 5H), 2.32 (dd, 1H, *J* = 16.5, 8.7 Hz), 2.42 (s, 3H), 2.42–2.53 (m, 1H), 2.67 (dd, 1H, *J* = 12.9, 6.9 Hz), 2.77–2.94 (m, 3H), 4.10 (q, 2H, *J* = 7.3 Hz), 7.30 (d, 2H, *J* = 8.7 Hz), 7.93 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.6, 22.8, 24.1, 24.5, 33.5, 34.5, 36.6, 36.8, 37.8, 60.8, 69.7, 128.5, 129.2, 136.7, 144.5, 171.2, 174.7; IR (KBr): 2980, 2938, 2969, 1947, 1716, 1595, 1455, 1382, 1364, 1345, 1305, 1262, 1215, 1152, 1066, 1029, 983, 884, 825, 682, 656 cm^{-1}; HRMS (DART) *m/z* calcd for $C_{20}H_{28}N_1O_5S_1$ $[(M+H)^+]$: 394.1688; found: 394.1688.

Isopropyl 2-(2-oxo-1-tosyl-1-azaspiro[4.5]decan-3-yl)acetate (31aC):



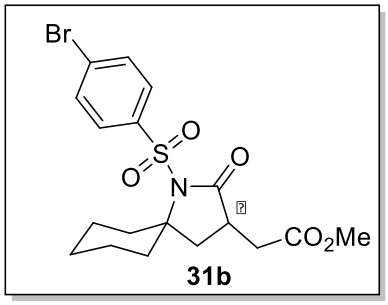
31aC

Starting from **30a** (92.8 mg, 0.3 mmol), compound **31aC** was obtained as a colorless oil (84.4 mg, 69%). R_f = 0.5 (hexane/AcOEt = 2/1). $[\alpha]_D^{25}$ = -3.5 (*c* 0.29, $CHCl_3$). The ee was determined to be 40% by HPLC (Daicel CHIRALPAK IB, hexane/EtOH = 20/1, 0.2 mL/min, 230 nm, major 94.7 min, minor 98.1 min); ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, 6H, *J* = 6.4 Hz), 1.22–1.50 (m, 4H), 1.62–1.88 (m, 5H), 2.29 (dd, 1H, *J* = 17.0, 9.2 Hz), 2.42 (s, 3H),

2.41–2.52 (m, 1H), 2.66 (dd, 1H, J = 12.4, 9.2 Hz), 2.75 (dd, 1H, J = 17.0, 3.7 Hz), 2.79–2.93 (m, 2H), 4.93–5.02 (m, 1H), 7.30 (d, 2H, J = 8.7 Hz), 7.93 (d, 2H, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 21.69, 21.73, 22.9, 24.1, 24.5, 33.5, 34.8, 36.6, 36.8, 37.9, 68.3, 69.7, 128.6, 129.2, 136.7, 144.5, 170.7, 174.7; IR (KBr): 2934, 2867, 1721, 1597, 1496, 1452, 1364, 1343, 1298, 1225, 1157, 1109, 1075, 1011, 957, 906, 812, 769, 684, 658 cm^{-1}; HRMS (DART) m/z calcd for $C_{21}H_{30}N_1O_5S_1$ [$(M+H)^+$]: 408.1845; found: 408.1851.

In a similar manner, γ-lactams **31b** – **31h** were obtained from allylic amines **30b -30h**.

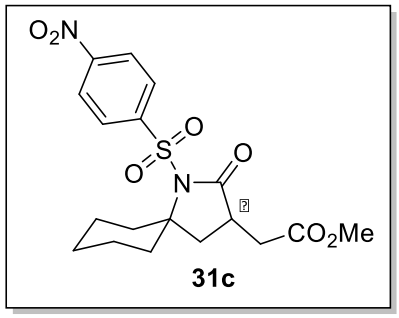
Methyl 2-(1-((4-bromophenyl)sulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (31b):



31b

Starting from **30b** (107.5 mg, 0.3 mmol), compound **31b** was obtained as a white solid (66.3 mg, 50%). R_f = 0.4 (Hex/AcOEt = 2/1). Mp = 122-123 ^{o}C (from hexane/AcOEt). $[\alpha]_D^{25}$ = -1.5 (c 0.53, $CHCl_3$). The ee was determined to be 30% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 1.0 mL/min, 230 nm, major 13.3 min, minor 24.8 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.57 (m, 4H), 1.66–1.94 (m, 5H), 2.34 (dd, 1H, J = 17.4, 8.7 Hz), 2.38–2.50 (m, 1H), 2.67 (dd, 1H, J = 12.8, 9.6 Hz), 2.78 (dd, 1H, J = 17.4, 4.1 Hz), 2.82–2.93 (m, 2H), 3.65 (s, 3H), 7.65 (d, 2H, J = 8.7 Hz), 7.92 (d, 2H, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 24.0, 24.5, 33.6, 34.1, 36.4, 36.7, 37.7, 51.9, 70.0, 128.8, 130.0, 131.9, 138.5, 171.5, 174.8; IR (KBr): 2944, 2867, 1727, 1574, 1443, 1366, 1347, 1300, 1160, 1068, 1011, 970, 823, 763, 702 cm^{-1}; HRMS (DART) m/z calcd for $C_{18}H_{23}Br_1N_1O_5S_1$ [$(M+H)^+$]: 444.0480; found: 444.0477.

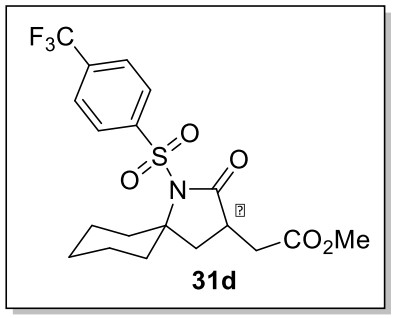
Methyl 2-(1-((4-nitrophenyl)sulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (31c):



31c

Starting from **30c** (97.3 mg, 0.3 mmol), compound **31c** was obtained as a light yellow solid (61.4 mg, 50%). R_f = 0.3 (Hex/AcOEt = 2/1). Mp = 176-179 ^oC (from hexane/ethyl acetate). $[\alpha]_D^{25}$ = -1.4 (*c* 0.38, $CHCl_3$). The ee was determined to be 46% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, 254 nm, major 85.4 min, minor 116.1 min); ^1H NMR (400 MHz, $CDCl_3$): δ 1.18–1.48 (m, 4H), 1.58–1.84 (m, 5H), 2.22–2.42 (m, 2H), 2.58–2.84 (m, 3H), 3.57 (s, 3H), 8.18 (d, 2H, *J* = 7.8 Hz), 8.28 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 24.0, 24.4, 33.8, 33.9, 36.3, 36.6, 37.6, 52.0, 70.4, 123.9, 129.9, 144.9, 150.4, 171.4, 175.1; IR (KBr): 2928, 2859, 1730, 1607, 1530, 1439, 1357, 1296, 1228, 1178, 1151, 1085, 1009, 852, 742, 687 cm^{-1}; HRMS (DART) *m/z* calcd for $C_{18}H_{23}N_2O_7S_1$ $[(M+H)^+]$: 411.1226; found: 411.1232.

Methyl 2-(2-oxo-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1-azaspiro[4.5]decan-3-yl)acetate (31d):

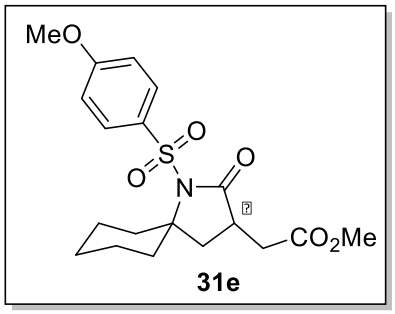


31d

Starting from **30d** (104.2 mg, 0.3 mmol), compound **31d** was obtained as a white solid (52.7 mg, 41%). R_f = 0.5 (Hex/AcOEt = 2/1). Mp = 176-179 ^oC (from hexane/AcOEt). $[\alpha]_D^{25}$ = +1.4 (*c* 0.52, EtOH). The ee was determined to be 36% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, 230 nm, major 18.9 min, minor 39.4 min); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25-1.81 (m, 10H), 2.32 (dd, 1H, *J* = 7.8, 17.4 Hz), 2.39 (dd, 1H, *J* = 11.5, 3.2 Hz), 2.61 (dd, 1H, *J* = 12.4, 9.2 Hz), 2.68 (dd, 1H, *J* = 17.4, 4.1 Hz), 2.83 (m, 1H), 3.59 (s, 3H), 7.71 (d, 2H, *J* = 8.2 Hz), 8.12 (d, 2H, *J* = 8.7 Hz); ^{19}F ($CDCl_3$, 376 MHz) δ = -63.1; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 24.0, 24.4, 33.8, 33.9, 36.4, 36.7, 37.6, 51.9, 70.2, 125.77, 125.81, 142.9, 171.5, 174.9. IR (KBr):

3449, 2941, 2871, 1727, 1442, 1407, 1370, 1323, 1173, 1133, 1062, 1017, 973, 910, 845, 764, 715, 677 cm^{-1}; HRMS (DART) *m/z* calcd for $C_{19}H_{23}F_3N_1O_5S_1$ $[(M+H)^+]$: 434.1249; found: 434.1253.

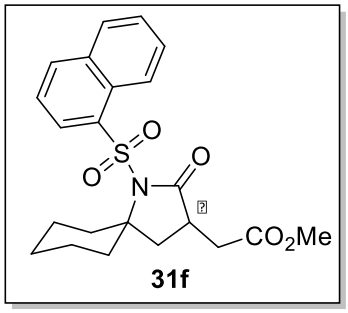
Methyl 2-(1-((4-methoxyphenyl)sulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (31e):



31e

Starting from **30e** (92.9 mg, 0.3 mmol), compound **31e** was obtained as a white solid (55.3 mg, 47%). R_f = 0.5 (Hex/AcOEt = 2/1). Mp = 151-152 °C (from hexane/AcOEt). $[\alpha]_D^{25}$ = +0.6 (*c* 0.37, EtOH). The ee was determined to be 51% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.75 mL/min, 240 nm, major 25.8 min, minor 65.7 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.48 (m, 4H), 1.66–1.84 (m, 5H), 2.33 (dd, 1H, *J* = 16.9, 8.2 Hz), 2.42–2.52 (m, 1H), 2.66 (dd, 1H, *J* = 12.4, 10.1 Hz), 2.77–2.92 (m, 3H), 3.64 (s, 3H), 3.86 (s, 3H), 6.96 (d, 2H, *J* = 8.7 Hz), 7.97 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 24.0, 24.5, 33.4, 34.3, 36.6, 36.7, 37.8, 51.9, 55.6, 69.6, 113.7, 130.8, 131.1, 163.5, 171.7, 174.6; IR (KBr): 2988, 2946, 2861, 1721, 1595, 1498, 1453, 1367, 1344, 1330, 1261, 1162, 1072, 1021, 838, 730, 662 cm^{-1}; HRMS (DART) *m/z* calcd for $C_{19}H_{26}N_1O_6S_1$ $[(M+H)^+]$: 396.1481; found: 396.1474.

Methyl 2-(1-(naphthalen-1-ylsulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (31f):

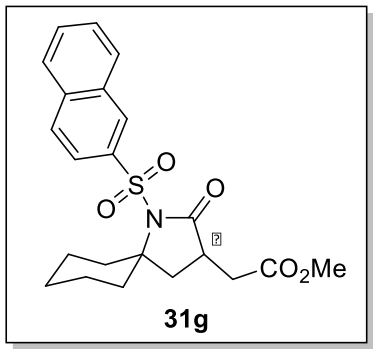


31f

Starting from **30f** (98.9 mg, 0.3 mmol), compound **31f** was obtained as a white solid (44.6 mg, 36%). R_f = 0.3 (Hex/AcOEt = 2/1). Mp = 151-152 °C (from hexane/ethyl acetate). $[\alpha]_D^{25}$ = -2.9 (*c* 0.34, $CHCl_3$). The ee was determined to be 42% by HPLC

(Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, 230 nm, minor 36.7 min, major 41.1 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–1.62 (m, 4H), 1.68–2.06 (m, 5H), 2.31 (dd, 1H, J = 17.4, 8.7 Hz), 2.60–2.74 (m, 3H), 2.83–2.92 (m, 1H), 2.96–3.05 (m, 1H), 3.58 (s, 3H), 7.54–7.68 (m, 3H), 7.93 (d, 1H, J = 8.2 Hz), 8.10 (d, 1H, J = 8.2 Hz), 8.43 (d, 1H, J = 7.8 Hz), 8.80 (d, 1H, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 24.2, 24.6, 33.9, 34.1, 36.2, 36.8, 37.9, 123.8, 124.1, 126.7, 128.1, 128.3, 128.4, 129.1, 131.8, 133.9, 135.2, 171.6, 175.0; IR (KBr): 2929, 2862, 1724, 1594, 1507, 1436, 1335, 1305, 1198, 1158, 1061, 1011, 907, 802, 769, 685 cm^{-1}; HRMS (DART) m/z calcd for $C_{22}H_{26}N_1O_5S_1$ [$(M+H)^+$]: 416.1532; found: 416.1530.

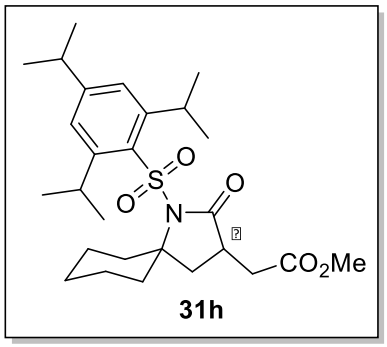
Methyl 2-(1-(naphthalen-2-ylsulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (31g):



31g

Starting from **30g** (98.9 mg, 0.3 mmol), compound **31g** was obtained as a white solid (56.7 mg, 47%). R_f = 0.3 (Hex/AcOEt = 2/1). Mp = 148-150 ^{o}C (from hexane/AcOEt). $[\alpha]_D^{25}$ = +3.0 (c 0.56, $CHCl_3$). The ee was determined to be 51% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, 230 nm, major 38.0 min, minor 45.8 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.56 (m, 4H), 1.68–1.96 (m, 5H), 2.32 (dd, 1H, J = 16.9, 8.7 Hz), 2.56–2.62 (m, 1H), 2.67–2.75 (m, 1H), 2.77 (dd, 1H, J = 16.9, 4.1 Hz), 2.85–3.02 (m, 2H), 3.61 (s, 3H), 7.62–7.68 (m, 2H), 7.93–8.06 (m, 4H), 8.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 24.1, 24.5, 33.6, 34.1, 36.5, 36.7, 37.8, 51.8, 69.8, 122.8, 127.4, 127.8, 128.8, 129.2, 129.6, 130.6, 131.7, 135.1, 136.4, 171.6, 174.7; IR (KBr): 2926, 2862, 1734, 1593, 1441, 1342, 1301, 1171, 1150, 1071, 996, 907, 816, 749, 657 cm^{-1}; HRMS (DART) m/z calcd for $C_{22}H_{26}N_1O_5S_1$ [$(M+H)^+$]: 416.1532; found: 416.1532.

Methyl 2-(2-oxo-1-((2,4,6-triisopropylphenyl)sulfonyl)-1-azaspiro[4.5]decan-3-yl)acetate (31h):



31h

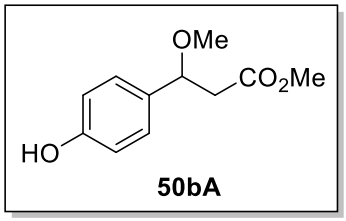
Starting from **30h** (121.7 mg, 0.3 mmol), compound **31h** was obtained as a colorless oil (125.0 mg, 85%). R_f = 0.7 (Hex/AcOEt = 2/1). $[\alpha]_D^{25}$ = -6.4 (*c* 1.25, EtOH). The ee was determined to be 50% by HPLC (Daicel CHIRALCEL OJ-H, hexane/^{i}PrOH = 50/1, 0.5 mL/min, 240 nm, major 25.2 min, minor 26.6 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12–1.48 (m, 24H), 1.54–1.88 (m, 4H), 2,14–2.24 (m, 1H), 2.40–2.50 (m, 1H), 2.58–2.90 (m, 3H), 3.57 (s, 3H), 4.10–4.20 (m, 3H), 7.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 23.3, 23.4, 24.1, 24.2, 24.4, 24.5, 24.7, 28.7, 33.3, 34.0, 34.7, 36.5, 36.8, 37.5, 51.8, 60.3, 71.0, 123.7, 128.2, 133.6, 151.2, 153.4, 171.7, 175.1; IR (KBr): 2955, 2868, 2359, 1730, 1601, 1462, 1362, 1327, 1151, 1060, 988, 881, 658 cm^{-1}; HRMS (DART) *m*/*z* calcd for $C_{27}H_{42}N_1O_5S_1$ [$(M+H)^+$]: 492.2784; found: 492.2797.

B. Palladium-Catalyzed Intermolecular Alkoxy-Alkoxycarbonylation of Vinylphenols in the Presence of Copper Salt:Unexpected Cooperative Effect of Tin Salt

Representative Procedure for Alkoxy-Alkoxycarbonylation of 4-Vinylphenol (48b) (Table 3.3, Entry 1).

Under an Ar atmosphere, $PdCl_2$ (1.8 mg, 0.010 mmol), $[Cu(MeCN)_4]BF_4$ (79 mg, 0.25 mmol), DABCO (2.2 mg, 0.020 mmol), $SnCl_2 \cdot 2H_2O$ (1.2 mg, 0.005 mmol) were placed in a flask. Next, a solution of 4-vinylphenol (**48b**) (60 mg, 0.50mmol) in MeOH (3mL) and THF (3 mL) were added. The Ar atmosphere was replaced with CO/O_2 (ca. v/v=1/1) and the reaction mixture was stirred for 8 h at 50 °C. After reaction completion (monitored by TLC), saturated aq. solution of $NaHCO_3$ was added. The insoluble substance was filtered off through Celite. After the filtrate was extracted with AcOEt, the combined extracts were washed with water and brine, dried over Na_2SO_4, and condensed in vacuo. (When the chemical yield was determined based onthe analysis of ^1H NMR spectrum of the crude products, octane [for example, 86.5 mg, 0.76 mmol] was added an internal standard to the residue.) The residue was purified by preparative TLC on $SiO_2$to give **50bA** (91 mg) in 86% yield as a solid.

Methyl 3-(4-Hydroxyphenyl)-3-methoxypropanoate (50bA):



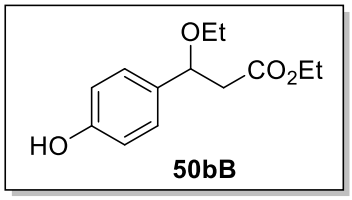
50bA

R_f = 0.45 (hexane/AcOEt = 2/1); Mp = 83 °C (from hexane/AcOEt); ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.60 (dd, 1H, J = 15.1, 5.2 Hz), 2.86 (dd, 1H, J = 15.1, 9.2 Hz), 3.20 (s, 3H), 3.69 (s, 3H), 4.60 (dd, 1H, J = 9.2, 5.2 Hz), 6.84 (d, 2H, J = 8.2 Hz), 7.18 (d, 2H, J = 8.2 Hz), signal of OH was not observed clearly; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.1, 51.9, 56.4, 79.6, 115.4, 128.0, 131.6, 156.0, 172.1; IR (KBr) 3227, 2953, 1735, 1614, 1515, 1433, 1417,

1383, 1352, 1315, 1275, 1200, 1171, 1096, 1052, 1003, 909, 823 cm^{-1}; HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{14}O_4Na$: 233.0790: $[M+Na]^+$; found: 233.0789.

In a similar manner, 3-(hydroxyphenyl)-3-methoxypropanoaic acid esters **50bB–50bF**, **50cA**, **50dA**, and **50aA** were obtained from the corresponding vinyl phenols **48a–48d** and alcohols **51A–51F**.

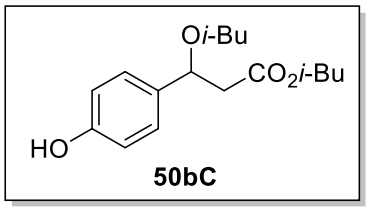
Ethyl 3-Ethoxy-3-(4-hydroxyphenyl)propanoate (50bB):[78c]



50bB

Compound **50bB** (93 mg, 74%) was obtained from **48b** (63 mg, 0.53 mmol) as an oil. R_f = 0.60 (hexane/AcOEt = 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, 3H, *J* = 6.9 Hz), 1.22 (t, 3H, *J* = 7.2 Hz), 2.58 (dd, 1H, *J* = 15.1, 5.0 Hz), 2.83 (dd, 1H, *J* = 15.1, 9.2 Hz), 3.30–3.42 (m, 2H), 4.14 (q, 2H, *J* = 7.2 Hz), 4.69 (dd, 1H, *J* = 9.2, 5.0 Hz), 6.81 (d, 2H, *J* = 8.8 Hz), 7.19 (d, 2H, *J* = 8.8 Hz), signal of OH was not observed clearly; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 15.1, 43.6, 60.7, 64.1, 77.7, 115.3, 127.9, 132.6, 155.7, 171.6; IR (neat) 3395, 2979, 2874, 2456, 1734, 1711, 1632, 1605, 1515, 1445, 1372, 1274, 1170, 1092, 1036, 835 cm^{-1}; HRMS (ESI-TOF): *m*/*z* calcd for $C_{13}H_{18}O_4Na$: 261.1103: $[M+Na]^+$; found: 261.1106.

Isobutyl 3-Isobutoxy-3-(4-hydroxyphenyl)propanoate (50bC):

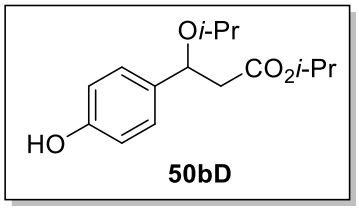


50bC

Compound **50bC** (108 mg, 74%) was obtained from **48b** (60 mg, 0.50 mmol) as an oil. R_f = 0.4 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.745 (d, 3H, *J* = 6.8 Hz), 0.753 (d, 3H, *J* = 6.4 Hz), 0.83 (d, 6H, *J* = 6.9 Hz), 1.66–1.76 (m, 1H), 1.78–1.88 (m, 1H), 2.50 (dd, 1H, *J* = 14.6, 4.6 Hz), 2.75 (dd, 1H, *J* = 14.6, 9.2 Hz), 2.91–3.01 (m, 2H), 3.80 (d, 2H, *J* = 6.4 Hz), 4.57 (dd, 1H, *J* = 9.2, 4.6 Hz), 6.45–6.80 (br, 1H), 6.74 (d, 2H, *J* = 8.7 Hz), 7.10 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.0, 19.3, 27.5, 28.3, 43.8, 70.9, 75.5, 78.2,

115.3, 127.9, 132.6, 155.8, 172.1; IR (Neat) 3393, 2959, 2974, 1738, 1713, 1605, 1516, 1470, 1396, 1379, 1309, 1272, 1201, 1169, 1095, 1057, 999, 941, 835 cm^{-1}; HRMS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{26}O_4Na$: 317.1729: $[M+Na]^+$; found: 317.1725.

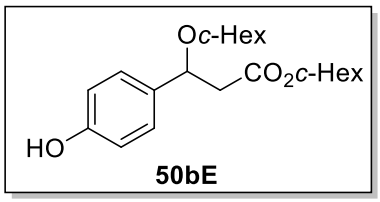
Isopropyl 3-(4-Hydroxyphenyl)-3-isopropoxypropanoate (50bD):



50bD

Compound **50bD** (92 mg, 69%) was obtained from **48b** (60 mg, 0.50 mmol) as an oil. R_f = 0.55 (hexane/AcOEt = 2/1); ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (d, 3H *J* = 6.0 Hz), 1.13 (d, 3H, *J* = 6.0 Hz), 1.19 (d, 3H, *J* = 6.4 Hz), 1.23 (d, 3H, *J* = 6.0 Hz), 2.52 (dd, 1H, *J* = 14.7, 5.0 Hz), 2.74 (dd, 1H, *J* = 14.7, 9.2 Hz), 3.44–3.53 (m, 1H), 4.79 (dd, 1H, *J* = 9.2, 5.0 Hz), 4.96–5.05 (m, 1H), 6.23 (brs, 1H), 6.81 (d, 2H, *J* = 8.3 Hz), 7.21 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.1, 21.7, 21.8, 23.3, 44.4, 68.1, 69.0, 75.3, 115.3, 127.9, 133.5, 155.6, 171.2; IR (Neat) 3400, 2977, 2933, 1731, 1707, 1614, 1516, 1453, 1375, 1305, 1271, 1204, 1169, 1107, 1045, 972, 907, 837, 758, 734 cm^{-1}; HRMS (ESI-TOF): *m*/*z* calcd for $C_{15}H_{22}O_4Na$:289.1416: $[M+Na]^+$; found: 289.1418.

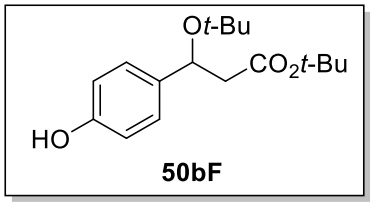
Cyclohexyl 3-Cyclohexyloxy-3-(4-hydroxyphenyl)propanoate (50bE):



50bE

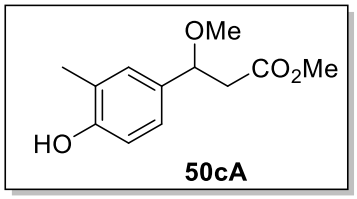
Compound **50bE** (101 mg, 58%) was obtained from **48b** (60 mg, 0.50 mmol) as an oil. R_f = 0.2 (hexane/AcOEt = 10/1); ^1H NMR ($CDCl_3$, 400 MHz): δ= 1.12–1.94 (m, 20H), 2.52 (dd, 1H, *J* = 15.1, 5.0 Hz), 2.76 (dd, 1H, *J* = 15.1, 9.2 Hz), 3.14–3.20 (m, 1H), 4.73–4.78 (m, 1H), 4.85 (dd, 1H, *J* = 9.2, 5.0 Hz), 6.65 (br, 1H), 6.81 (d, 2H, *J* = 8.2 Hz), 7.20 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7, 23.9, 24.1, 25.3, 25.6, 31.2, 31.46, 31.54, 33.3, 35.3, 44.5, 73.2, 75.0, 115.2, 127.8, 133.6, 155.6, 171.3; IR (Neat) 3395, 2934, 2857, 1731, 1706, 1613, 1515, 1450, 1360, 1301, 1271, 1169, 1084, 977, 912, 892, 835, 757, 734 cm^{-1}; HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{30}O_4Na$: 369.2042: $[M+Na]^+$; found: 369.2040.

***t*-Butyl 3-(*t*-Butoxy)-3-(4-hydroxyphenyl)propanoate(50bF):**



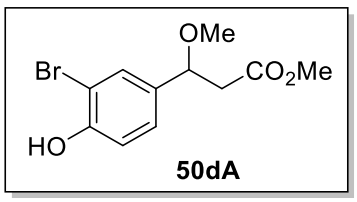
Production of compound **50bF** starting from **48b** (60 mg, 0.50 mmol) was confirmed by the analysis of ^{1}H NMR of the crude products. However **50bF** could not be purified by column chromatography or TLC on SiO_2 due to serious decomposition to the corresponding 3-arylpent-2-enoate. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.10 (s, 9H), 1.43 (s, 9H), 2.42 (dd, 1H, J = 14.2, 5.0 Hz), 2.62 (dd, 1H, J = 14.2, 8.7 Hz), 4.90 (dd, 1H, J =8.7, 5.0 Hz), 6.54 (brs, 1H), 6.83 (d, 2H, J = 8.2 Hz), 7.20 (d, 2H, J = 8.2 Hz).

Methyl 3-(4-hydroxy-3-methylphenyl)-3-methoxypropanoate (50cA):



$PdCl_2$ (4.4 mg, 0.025mmol), $[Cu(MeCN)_4]BF_4$ (79 mg, 0.25 mmol), DABCO (2.2 mg, 0.050 mmol), $SnCl_2{\cdot}2H_2O$ (2.3 mg, 0.004mmol) were used for2-methyl-4-vinylphenol (**1c**)(67 mg, 0.50 mmol) in MeOH(3mL) and THF (3 mL). Compound **50cA**(87 mg, 78 %) wasobtained as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.15 (s, 3H), 2.50 (dd, 1H, J = 15.6, 4.6 Hz), 2.74 (dd, 1H, J = 15.6, 9.2 Hz), 3.09 (s, 3H), 3.59 (s, 3H), 4.47 (dd, 1H, J = 9.2, 4.6, Hz), 5.51 (s, 1H), 6.68 (d, 1H, J = 7.8 Hz), 6.94 (d, 1H, J = 7.8 Hz), 7.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.8, 43.0, 51.8, 56.3, 79.6, 114.8, 124.4, 125.2, 129.2, 131.5 154.2, 172.1.IR (Neat) 3410, 2951, 1715, 1611, 1509, 1438, 1262, 1097, 820 cm^{-1};HRMS (ESI): m/z calcd for $C_{12}H_{17}O_4$: 225.1127: $[M+H]^+$; found: 225.1133.

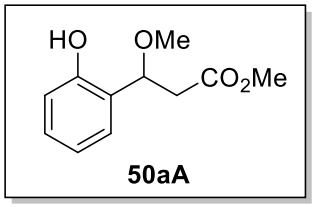
Methyl 3-(3-Bromo-4-hydroxyphenyl)-3-methoxypropanoate (50dA):



Compound **50dA** (77 mg, 53%) was obtained from **48d** (100 mg, 0.50 mmol) as an oil. R_f = 0.45 (hexane/AcOEt = 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.56 (d, 1H, J = 15.6, 5.0 Hz), 2.81 (dd,

1H, *J* = 15.5, 9.2 Hz), 3.21 (s, 3H), 3.69 (s, 3H), 4.56 (dd, 1H, *J* = 9.2, 5.0 Hz), 6.09 (br, 1H), 7.00 (d, 1H, *J* = 8.2 Hz), 7.18 (d, 1H, *J* = 8.2 Hz), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.1, 51.8, 56.7, 78.9, 110.2, 116.2, 127.4, 130.3, 133.9, 152.2, 171.4; IR (Neat) 3392, 2990, 2951, 2824, 1732, 1718,1634, 1604, 1579, 1496, 1439, 1370, 1287, 1202, 1169,1100, 1042, 1014, 988, 884, 825, 723, 667, cm^{-1}; HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{13}O_4{}^{79}BrNa$: 310.9895, $C_{11}H_{13}O_4{}^{81}BrNa$: 312.9874: $[M+Na]^+$; found: 310.9890, 312.9864.

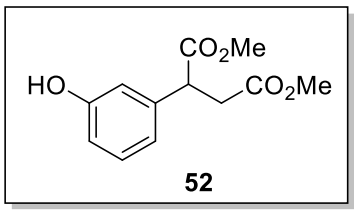
Methyl 3-(2-Hydroxyphenyl)-3-methoxypropanoate (50aA):



50aA

Compound **50aA** (62% ^{1}HNMR yield) was obtained from **48a** (60 mg, 0.50 mmol) as an oil. For the analytical sample, the careful purification by TLC on SiO_2 was performed. R_f = 0.40 (hexane/AcOEt = 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.67 (dd, 1H, *J* = 15.6, 5.0 Hz), 2.99 (dd, 1H, *J* = 15.6, 9.2 Hz), 3.40 (s, 3H), 3.71 (s, 3H), 4.83 (dd, 1H, *J* = 9.2, 5.0 Hz), 6.84–6.89 (m, 2H), 7.06 (dd, 1H, *J* = 7.3, 1.4 Hz), 7.19–7.23 (m, 1H), 7.72 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 41.0, 51.9, 57.6, 81.0, 117.1, 120.1, 123.5, 128.1, 129.6, 155.3, 171.2 ; IR (Neat) 3392, 2951, 2829, 1739, 1716, 1597, 1488, 1457, 1438, 1354, 1304, 1202, 1159, 1093, 1055, 1011, 940, 915, 835, 757 cm^{-1}; HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{14}O_4Na$:233.0790: $[M+Na]^+$; found: 233.0785.

Dimethyl 2-(3-Hydroxyphenyl)succinate (52):



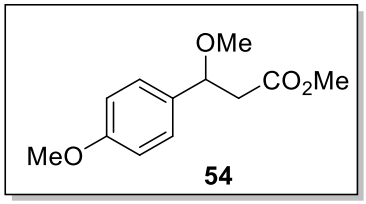
52

The alkoxycarbonylation of 3-vinylphenol (**48e**) (60 mg, 0.50 mmol) gave **52** (71 mg, 60%) as an oil. R_f = 0.50 (hexane/AcOEt = 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.68 (dd, 1H, *J* = 16.9, 5.0 Hz), 3.19 (dd, 1H, *J* = 16.9, 10.1 Hz), 3.671 (s, 3H), 3.674 (s, 3H), 4.05 (dd, 1H, J = 10.1, 5.0 Hz), 6.76– 6.81 (m, 3H), 7.17 (t, 1H, *J* = 7.3 Hz), signal of OH was not observed clearly; ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 37.4, 46.9, 52.0, 52.5, 114.5, 114.9, 119.6, 130.1, 138.7,

156.3, 172.4, 173.8; IR (Neat) 3421, 2954, 2848, 1737, 1718, 1590, 1487, 1438, 1224, 1163, 1084, 999, 898, 872, 786, 742, 693 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{15}O_5$: 239.0920: $[M+H]^+$; found: 239.0925.

The reaction starting from 1-methoxy-4-vinylbenzene (**53**) (69 mg, 0.52 mmol) gave the crude products containingmethyl 3-(4-methoxyphenyl)-3-methoxypropanoate (**54**) (5%), dimethyl 2-(4-methoxyphenyl)succinate (**55**) (34%), and methyl (*E*)-3-(4-methoxyphenyl)prop-2-enoate (26%) by ^1H NMR analysis by addition of octane (95.1 mg, 0.83 mmol) as an internal standard. From the crude product, the analytical samples of the succinate **55** was isolated by careful purification by TLC on SiO_2 (hexane/AcOEt = 4/1).

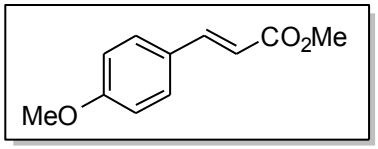
Methyl 3-(4-Methoxyphenyl)-3-methoxypropanoate (54):[85]



54

^1H NMR ($CDCl_3$, 400 MHz); selected data δ = 2.56 (dd, 1H, *J* = 15.1, 4.6 Hz), 2.82 (dd, 1H, *J* = 15.1, 9.2 Hz), 3.19 (s, 3H), 4.59 (dd, 1H, *J* = 9.2, 4.6 Hz), 6.96 (d, 2H, *J* = 8.7 Hz), 7.31 (d, 2H, *J* = 8.7 Hz).

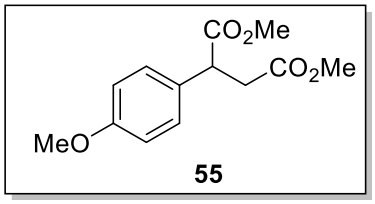
Methyl (*E*)-3-(4-Methoxyphenyl)prop-2-enoate:[86]



^1H NMR ($CDCl_3$, 400 MHz): δ = 3.79 (s, 3H), 3.84 (s, 3H), 6.32 (d, 1H, *J* = 16.0 Hz),6.91 (d, 2H, *J* = 8.7 Hz),7.48 (d, 2H, *J* = 8.7 Hz),7.66 (dd, 1H, *J* = 16.0 Hz).

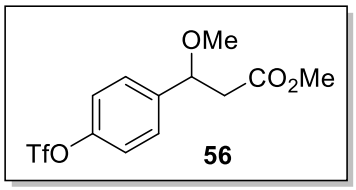
Dimethyl 2-(4-Methoxyphenyl)succinate (55):[40]

An oil. R_f = 0.60 (hexane/AcOEt = 4/1); ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.65 (dd, 1H, *J* = 17.0, 5.5 Hz), 3.18 (dd, 1H, *J* = 17.0, 10.1 Hz), 3.67 (s, 6H), 3.78 (s, 3H), 4.04 (dd, 1H, *J* = 10.1, 5.5 Hz), 6.85 (d, 2H, *J* = 8.2 Hz), 7.20 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 37.6, 46.2, 51.8, 52.3, 55.2, 114.2, 128.7, 129.6, 159.0, 172.0, 173.7; IR (Neat)



3000, 2953, 2838, 1738, 1731, 1611, 1584, 1513, 1436, 1368, 1303, 1254, 1159, 1111, 1032, 832, 795 cm^{-1}; HRMS (ESI-TOF): *m*/*z*calcd for $C_{13}H_{17}O_5$: 253.1076: $[M+H]^+$; found: 253.1075.

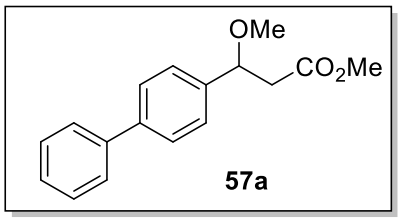
Methyl 3-Methoxy-3-(4-trifluoromethanesulfonyloxy)phenylpropanoate (56): To a solution of methyl 3-(4-hydroxyphenyl)-3-methoxypropionate (**50bA**) (1.60 g, 7.6 mmol) in CH_2Cl_2 (15mL) was added pyridine (1.80 g, 22.8mmol), followed by trifluoromethanesulfonic anhydride (3.22 g, 11.4 mmol) at 0 °C. After stirring at 0 °C overnight, the mixture was quenched by addition of saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by preparative TLC on $SiO_2$to give the corresponding triflate **56** (1.98 g) in 76% yield as an oil.



^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.56 (dd, 1H, *J* = 15.6, 5.2 Hz), 2.80 (dd, 1H, *J* = 15.6, 9.2 Hz), 3.24 (s, 3H), 3.69 (s, 3H), 4.68 (dd, 1H, *J* = 9.2, 5.2 Hz), 7.28 (d, 2H, *J* = 8.7 Hz), 7.44 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.1, 51.8, 57.1, 79.1, 118.7 (d, *J* = 320 Hz), 121.6, 128.4, 141.3, 149.1, 171.0; ^{19}F NMR ($CDCl_3$, 376 MHz, $CDCl_3$) –76.1; IR (neat) 2953, 2828, 1742, 1600, 1500, 1425, 1367, 1306, 1250, 1213, 1140, 1104, 1061, 1016, 992, 889, 844, 750, 693 cm^{-1}; HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{13}O_6F_3SNa$: 365.0283: $[M+Na]^+$; found: 365.0280.

Methyl 3-([1,1'-Biphenyl]-4-yl)-3-methoxypropanoate (57a): Under an N_2 atmosphere, $PhB(OH)_2$(122 mg, 1.0 mmol), K_2CO_3 (180 mg, 1.3 mmol) was suspended in a mixture oftoluene/DMF (10/1, total 6 mL). Triflate **56** (171 mg, 0.50 mmol) and $[Pd(PPh_3)_4]$ (58 mg, 0.05 mmol) was added to the mixture. The reaction was stirred and heated at 80 °C.[87] After reaction completion (monitored by TLC), the mixture was filtered through Celite and the

filtrate was extracted with AcOEt. The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on $SiO_2$to give **57a** (100 mg, 74% yield) as an oil.

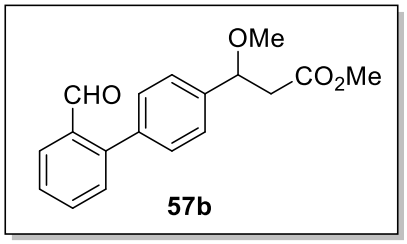


57a

R_f = 0.40 (hexane/AcOEt = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.63 (dd, 1H, J =15.6, 4.6 Hz), 2.84 (dd, 1H, J = 15.6, 9.2 Hz), 3.26 (s, 3H), 3.67 (s, 3H), 4.69 (dd, 1H, J = 9.2, 4.6 Hz), 7.34–7.45 (m, 5H), 7.58 (d, 4H,J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz):δ = 43.2, 51.7, 56.9, 79.7, 126.98, 127.01, 127.3, 128.7, 139.5, 140.6, 140.9, 171.4; IR (Neat):2949, 1737, 1599, 1565, 1487, 1437, 1407, 1364, 1199, 1160, 1103, 1009, 911, 841, 768, 698cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{19}O_3$ $[M+H]^+$:271.1334; found: 271.1324.

In a similar manner, the coupling products **57b** and **57c** were obtained from the triflate **56** and the corresponding boronicacids, respectively.

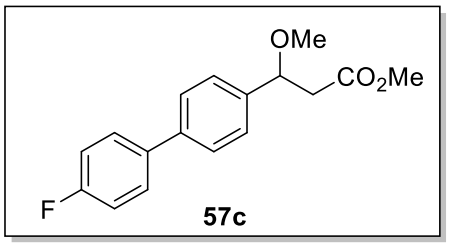
Methyl 3-(2'-Formylbiphenyl-4-yl)-3-methoxypropanoate (57b):



57b

Compound **57b** (134 mg, 90% yield) was obtained from **56** (171 mg, 0.50mmol)as a solid; R_f = 0.60 (hexane/AcOEt = 3/1); Mp. 103–104 °C (from hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.66 (dd, 1H, J = 15.1, 4.6 Hz), 2.86 (dd, 1H, J = 15.1, 9.2Hz), 3.27 (s, 3H), 3.72 (s, 3H), 4.73 (dd, 1H, J = 9.2, 4.6 Hz), 7.39 (d, 2H, J = 7.8 Hz), 7.45 (d, 3H, J = 8.2 Hz), 7.51 (t, 1H, J = 7.4 Hz), 7.65 (t, 1H, J = 7.4 Hz), 8.04 (d, 1H, J = 7.3 Hz), 9.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.2, 51.8, 57.0,79.7,126.6, 127.6, 127.8, 130.4, 130.7, 133.6, 133.7, 137.5, 140.6, 145.5,171.3, 192.3; IR (KBr): 2933, 1730, 1694, 1594, 1434, 1363, 1193, 1152, 1102, 1054, 988, 910, 847, 773, 704cm^{-1}; Elemental analysis calcd (%) for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08; found: C, 72.19; H, 5.81.

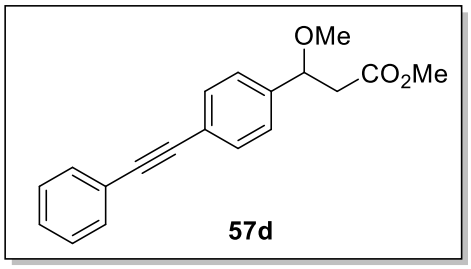
Methyl 3-(4'-Fluoro-[1,1'-biphenyl]-4-yl)-3-methoxypropanoate (57c):



57c

Compound **57c** (132 mg, 91% yield) was obtained from **56** (171 mg, 0.50mmol) as an oil. R_f = 0.30 (hexane/AcOEt = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.62 (dd, 1H, *J* = 15.6, 4.6Hz), 2.85 (dd, 1H, *J* = 15.6, 9.2 Hz), 3.26 (s, 3H), 3.71 (s, 3H), 4.69 (dd, 1H, *J* = 9.2, 4.6 Hz), 7.12 (t, 2H, *J* = 8.72 Hz), 7.39 (d, 2H, *J* = 8.2 Hz), 7.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.2, 51.8, 56.9, 79.7,115.6 (d, *J* = 21 Hz), 127.1 (d, *J* = 11 Hz), 128.5, 128.6, 136.8 (d, *J* = 3 Hz), 139.5, 140.0, 162.4 (d, *J* = 246 Hz), 171.4; ^{19}F NMR ($CDCl_3$, 376 MHz):δ = –115; IR (neat): 2931, 2824, 1740, 1603, 1497, 1437, 1366, 1224, 1159, 1103, 1007, 991, 824, 747, 671; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{18}FO_3$ $[M+H]^+$: 289.1240; found: 289.1234.

Methyl 3-Methoxy-3-(4-(phenylethynyl)phenyl)propanoate (57d):

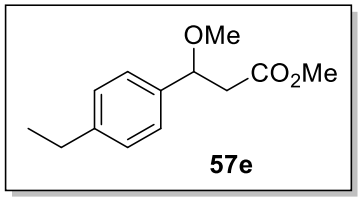


57d

Under N_2 atmosphere, amixture of the triflate **56** (171 mg, 0.50mmol), ethynylbenzene (153.2 mg, 1.50mmol) Et_3N (0.5 mL, 3.6 mmol), and $[PdCl_2(PPh_3)_2]$ (17.5 mg, 0.025 mmol) in DMF (1.5 mL) was stirred at 90 °C for 23 h.[88] The reaction mixture was then diluted with water, the resulting mixture was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on SiO_2 (hexane/AcOEt = 10/1) to give **57d** (119 mg) in 81% yield as an oil. R_f = 0.3 (hexane/AcOEt = 9/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.57 (dd, 1H, *J* = 15.6, 5.0 Hz), 2.80 (dd, 1H, *J* = 15.6, 9.2 Hz), 3.23 (s, 3H), 3.69 (s, 3H), 4.64 (dd, 1H, *J* = 9.2, 5.0 Hz), 7.34 (m, 5H), 7.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.1, 51.8, 56.9, 79.7,89.0, 89.6, 123.0, 123.1, 126.6, 128.30, 128.32, 131.6, 131.8 140.7,171.2; IR (Neat) 2930, 1740, 1597, 1509, 1437,

1366,1202, 1103, 1061, 1017, 911, 838, 757, 691cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{19}H_{19}O_3$ $[M+H]^+$: 294.1334; found:294.1339.

Methyl 3-(4-Ethylphenyl)-3-methoxypropanoate (57e):

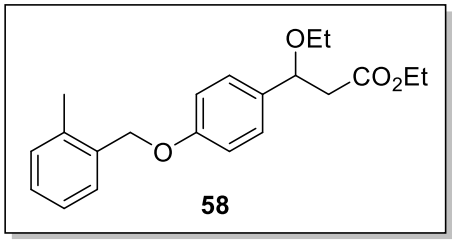


Triethylborane (1.0 M inhexane, 1.0 mL, 1.0mmol) was added to a suspension of the triflate **56** (171 mg, 0.50mmol), [Pd(dppf)Cl_2] (7.5 mg, 0.01 mmol), and CsOAc (192 mg, 1.0mmol) in THF (1.5 mL) under an Ar atmosphere, and the mixture was heated at reflux for 44h.[89] After cooling, the reaction mixture was filtered through Celite and diluted with diethyl ether. The organic layer was washed with aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2(hexane/AcOEt = 10/1) to give **57e** (101 mg) in 91% yield as an oil. R_f = 0.6 (hexane/AcOEt = 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (t, 3H, *J* = 7.8 Hz), 2.58 (dd, 1H, *J* =15.1, 4.6 Hz), 2.64 (q, 2H, *J* = 7.8 Hz), 2.79 (dd, 1H, *J* = 15.1, 9.6Hz), 3.22 (s, 3H), 3.69 (s, 3H), 4.61 (dd, 1H, *J* = 9.6, 4.6Hz), 7.21 (dd, 4H, J = 8.2, 22.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 15.4, 28.4, 43.3, 51.6, 56.7, 79.8,126.5, 128.0, 137.6, 144.0, 171.5; IR (Neat) 2927, 2360, 1744, 1512, 1437, 1364, 1272, 1198, 1159, 1105, 1018, 993, 910, 828 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{13}H_{19}O_3$ $[M+H]^+$: 223.1334; found: 223.1327.

Ethyl 3-Ethoxy-3-(4-((2-methylbenzyl)oxy)phenyl)propanoate (58):[78b]

Cesium carbonate (352mg, 1.08mmol) was added to a CH_2Cl_2 (2 mL) solution of the 3-ethoxy ester **50bB** (86mg, 0.36 mmol) and 1-(bromomethyl)-2-methylbenzene (73 mg, 0.40mmol) at 0°C. The mixture was allowed to warm to room temperature and stirred for 14 h. After water was added to the reaction mixture, the solution was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried over Na_2SO_4 and

concentrated in vacuo. The residue was purified by column chromatography on SiO_2 to give **58** (107 mg, 87% yield) as an oil.



58

R_f = 0.60 (hexane/AcOEt = 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (t, 3H, J = 7.3 Hz), 1.22 (t, 3H, J = 6.9 Hz), 2.36 (s, 3H), 2.56 (dd, 1H, J = 15.1, 5.0 Hz), 2.79 (dd, 1H, J = 15.1, 8.7 Hz), 3.33–3.38 (m, 2H), 4.12 (dd, 2H, J = 14.2, 7.3 Hz); 4.69 (dd, 1H, J = 8.7, 5.1 Hz), 5.0 (s, 2H), 6.95 (d, 2H, J = 8.3 Hz), 7.19–7.28 (m, 5H), 7.38 (d, 1H, J = 6.8 Hz).; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 14.2, 15.1, 18.8, 43.6, 60.3, 64.0, 68.5, 114.6, 115.0, 125.9, 127.7, 128.2, 128.5, 130.3, 133.5, 134.6, 158.5, 170.9; IR (neat) 2977, 2929, 2874, 2359, 1736, 1610, 1585, 1510, 1463, 1373, 1345, 1305, 1268, 1240, 1172, 1092, 1011, 941, 881, 832, 747 cm^{-1}; HRMS (FAB$^+$): m/z calcd for $C_{13}H_{18}O_4Na$: 261.1103: $[M+Na]^+$; found: 261.1106.

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APPENDIX

Appendix consits of reference theses:

Title: “Palladium-catalyzed Intermolecular Alkoxy-alkoxycarbonylation of Vinylphenols in the Presence of Copper Salt: Unexpected Cooperative Effect of Tin Salt”.

Nga Hang Thi Phan, Tomoki Furuya, Takahiro Soeta, and Yutaka Ukaji.

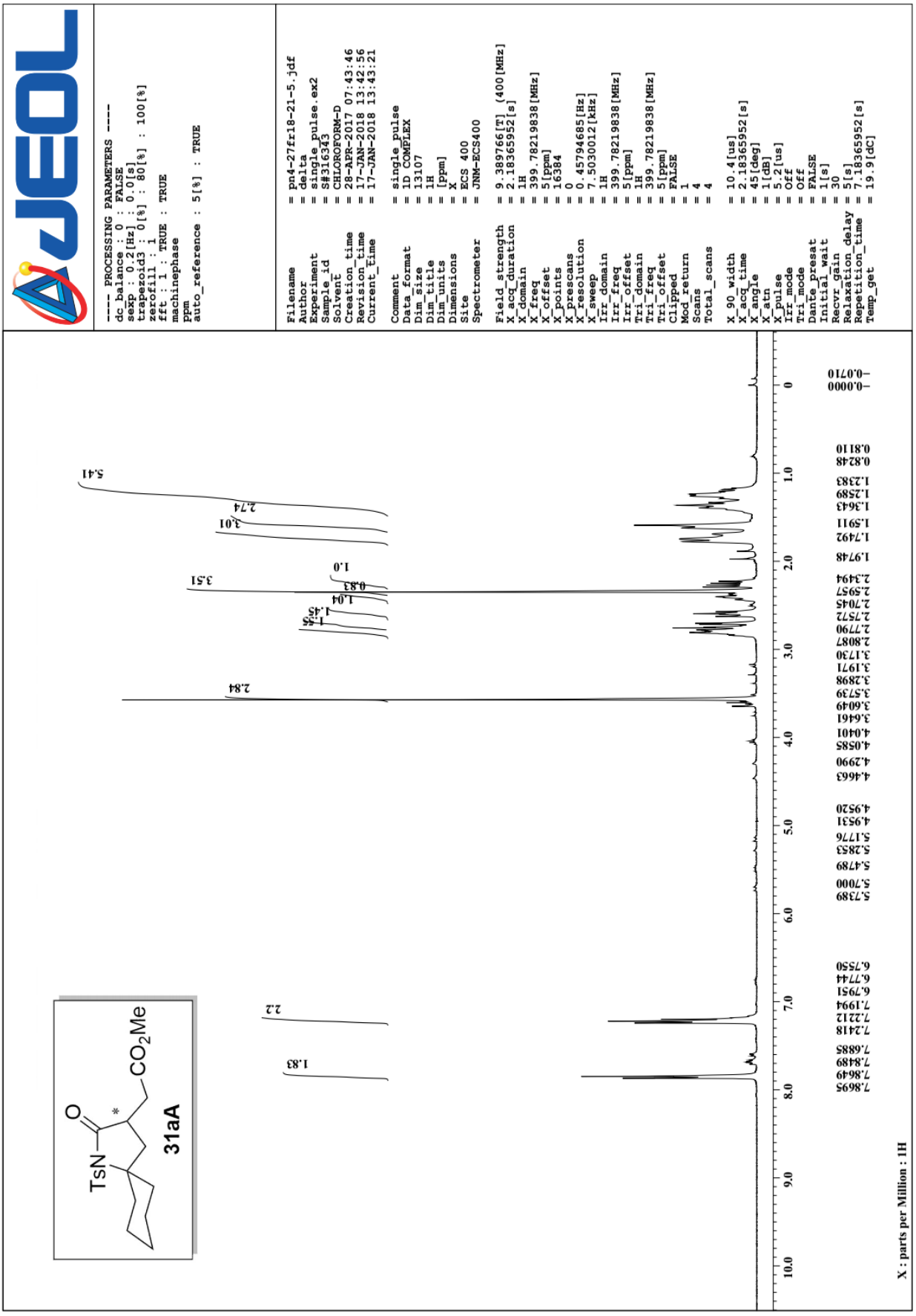
Chem. Lett. **2016**, *45*, 1431-1433.DOI: 10.1246/cl.160804

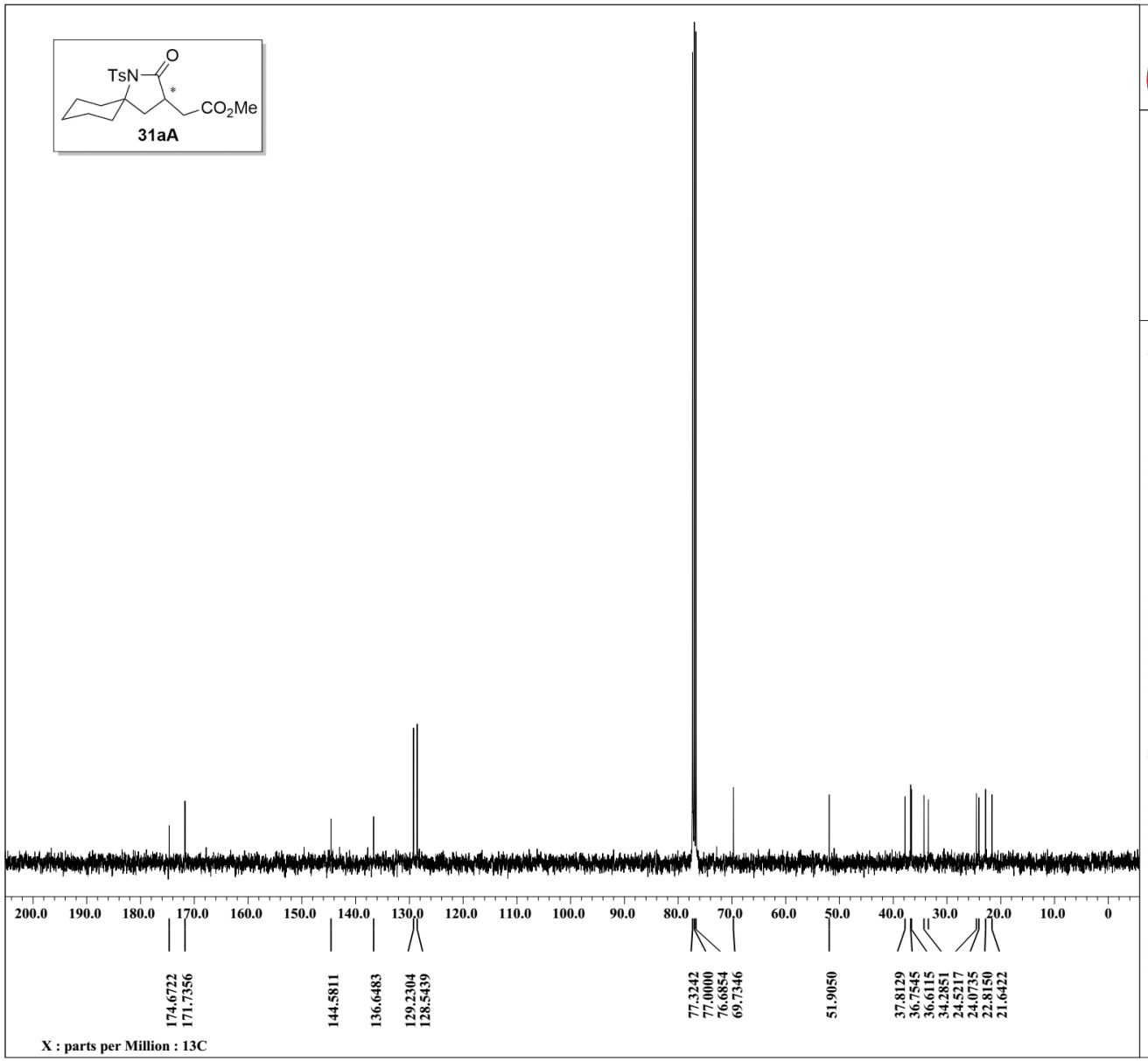
The document is attached to this rearward dissertation.

SUPPORTING INFORMATION

List of contents:

1) ^{1}H and ^{13}C NMR spectrums of the γ-lactam products **31**.



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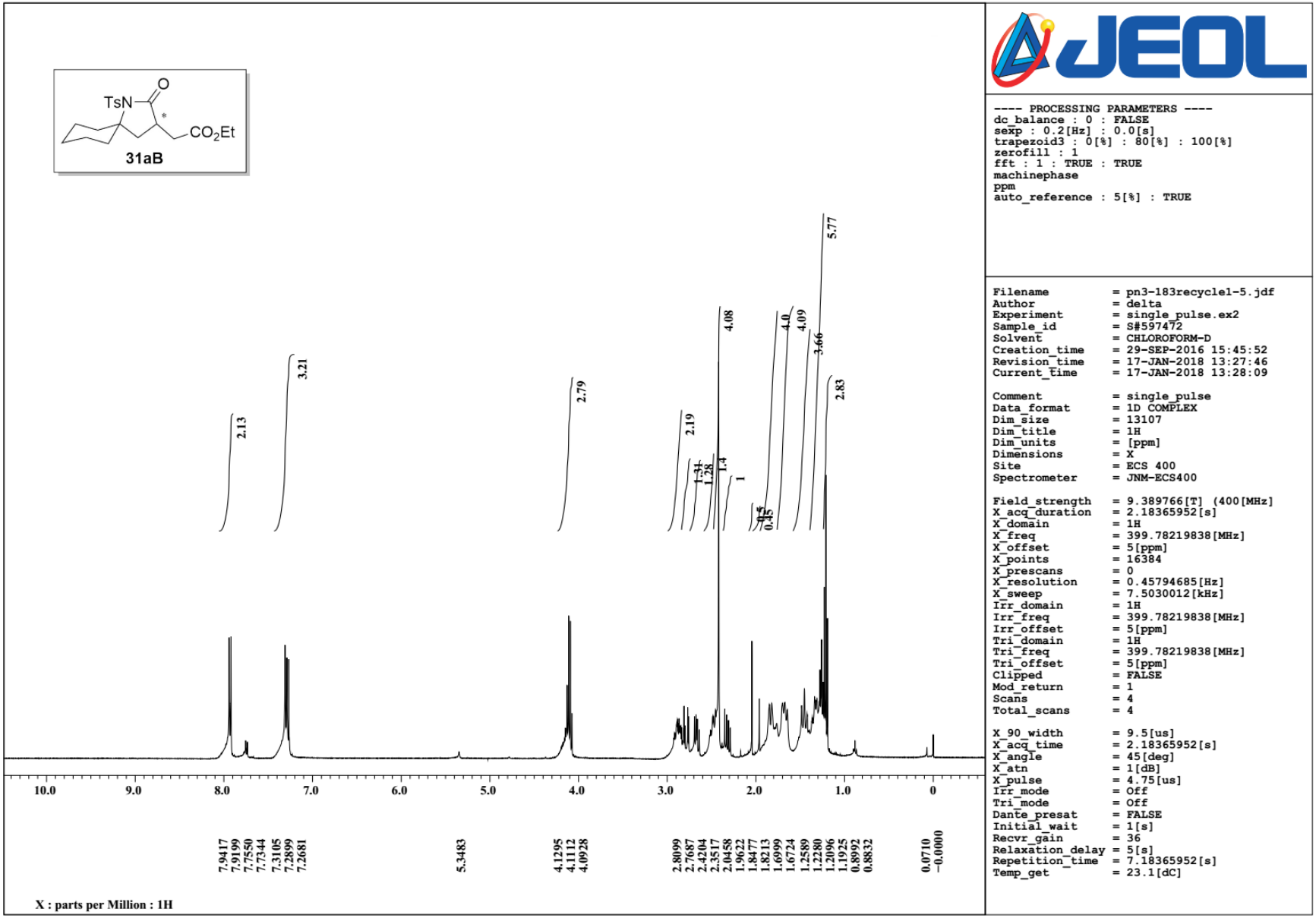
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = pn-2aA-5.jdf
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = S#702185
Solvent           = CHLOROFORM-D
Creation_time     = 20-DEC-2017 19:35:41
Revision_time     = 15-JAN-2018 14:12:45
Current_time      = 17-JAN-2018 13:10:02

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 1.04333312[s]
X_domain          = 13C
X_freq            = 100.52530333[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 0.95846665[Hz]
X_sweep           = 31.40703518[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 256
Total_scans       = 256

X_90_width        = 8.4[us]
X_acq_time        = 1.04333312[s]
X_angle           = 30[deg]
X_atn             = 6[dB]
X_pulse           = 2.8[us]
Irr_atn_dec       = 21.56853[dB]
Irr_atn_noe       = 21.56853[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 60
Relaxation_delay  = 2[s]
Repetition_time   = 3.04333312[s]
Temp_get          = 18.2[dC]
```




```
---- PROCESSING PARAMETERS ----
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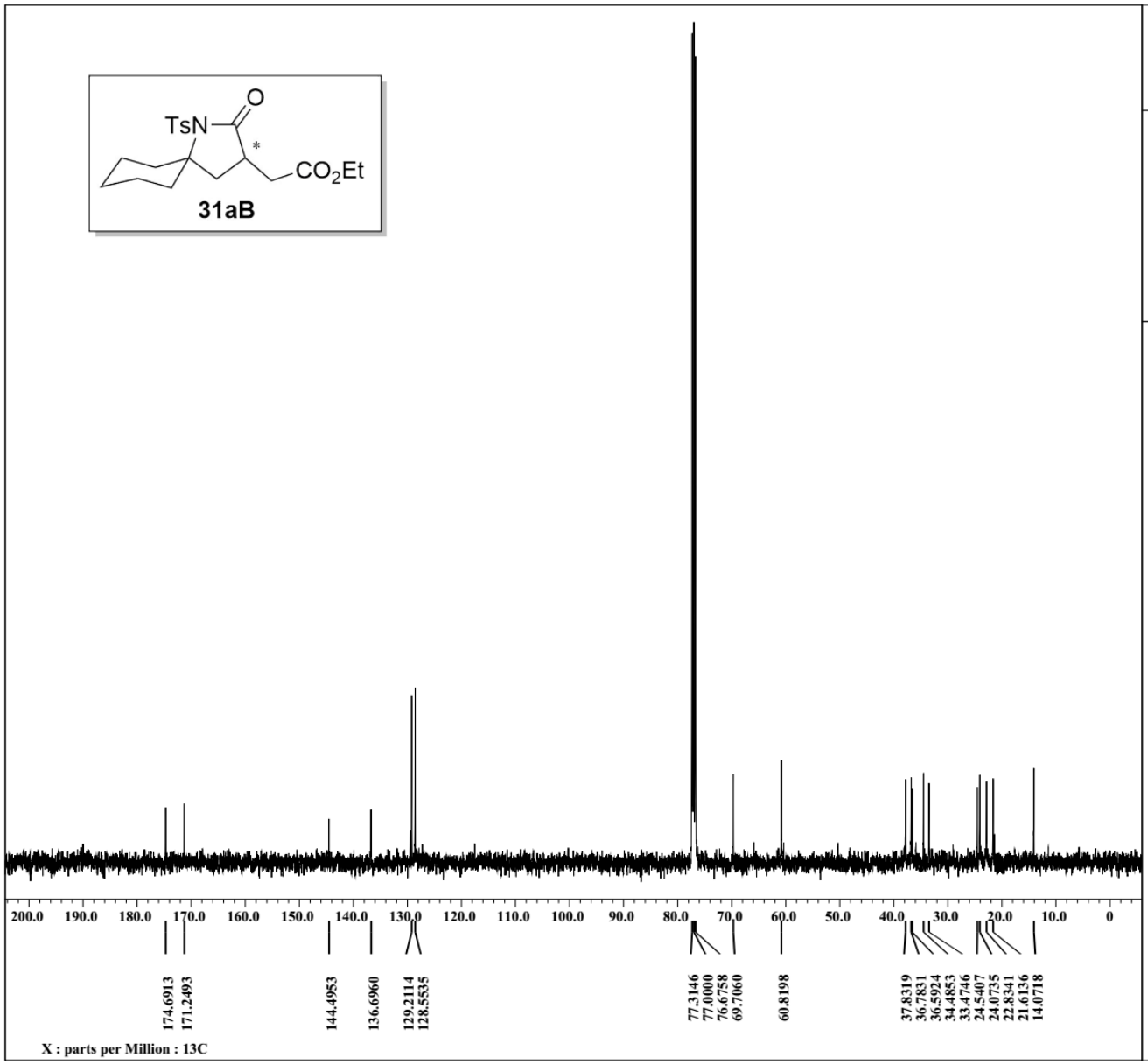
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename            = pn3-183recycle1-5.jdf
Author              = delta
Experiment          = single_pulse.ex2
Sample_id           = S#597472
Solvent             = CHLOROFORM-D
Creation_time       = 29-SEP-2016 15:45:52
Revision_time       = 17-JAN-2018 13:27:46
Current_time        = 17-JAN-2018 13:28:09

Comment             = single_pulse
Data_format         = 1D COMPLEX
Dim_size            = 13107
Dim_title           = 1H
Dim_units           = [ppm]
Dimensions          = X
Site                = ECS 400
Spectrometer        = JNM-ECS400

Field_strength      = 9.389766[T] (400[MHz]
X_acq_duration      = 2.18365952[s]
X_domain            = 1H
X_freq              = 399.78219838[MHz]
X_offset            = 5[ppm]
X_points            = 16384
X_prescans          = 0
X_resolution        = 0.45794685[Hz]
X_sweep             = 7.5030012[kHz]
Irr_domain          = 1H
Irr_freq            = 399.78219838[MHz]
Irr_offset          = 5[ppm]
Tri_domain          = 1H
Tri_freq            = 399.78219838[MHz]
Tri_offset          = 5[ppm]
Clipped             = FALSE
Mod_return          = 1
Scans               = 4
Total_scans         = 4

X_90_width          = 9.5[us]
X_acq_time          = 2.18365952[s]
X_angle             = 45[deg]
X_atn               = 1[dB]
X_pulse             = 4.75[us]
Irr_mode            = Off
Tri_mode            = Off
Dante_presat        = FALSE
Initial_wait        = 1[s]
Recvr_gain          = 36
Relaxation_delay    = 5[s]
Repetition_time     = 7.18365952[s]
Temp_get            = 23.1[dC]
```



---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
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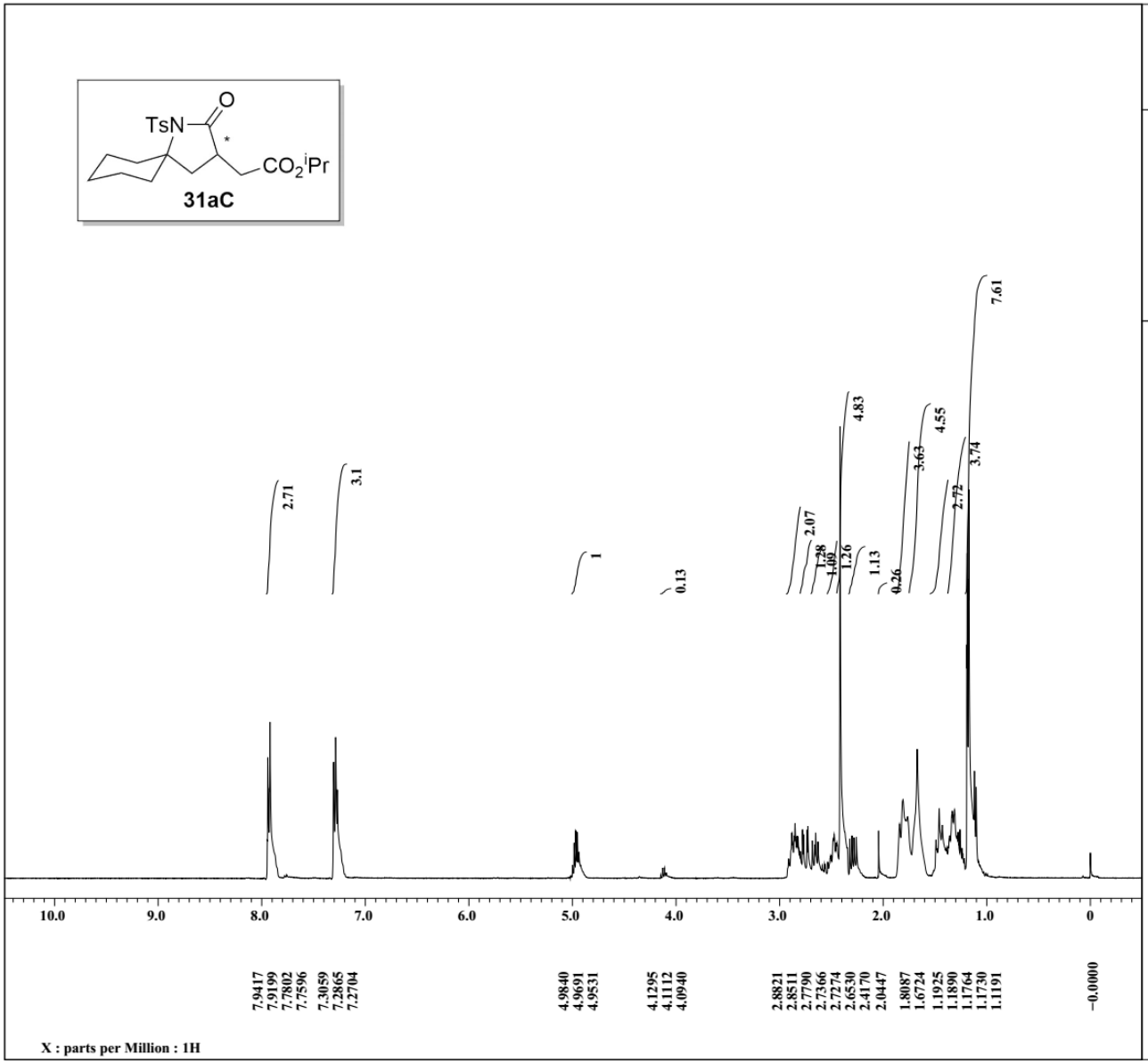
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE

Filename = pn3-183recycleC13-4.j
Author = delta
Experiment = single_pulse_dec
Sample_id = S#598625
Solvent = CHLOROFORM-D
Creation_time = 29-SEP-2016 16:00:12
Revision_time = 15-JAN-2018 13:56:04
Current_time = 17-JAN-2018 13:30:39

Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400

Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 256
Total_scans = 256

X_90_width = 8.2[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.73333333[us]
Irr_atn_dec = 22.65948[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 23.3[dC]



---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE

Filename = pn3-178recycle-5.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = S#634013
Solvent = CHLOROFORM-D
Creation_time = 9-SEP-2016 16:46:52
Revision_time = 17-JAN-2018 13:22:59
Current_time = 17-JAN-2018 13:23:20

Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400

Field_strength = 9.389766[T] (400[MHz]
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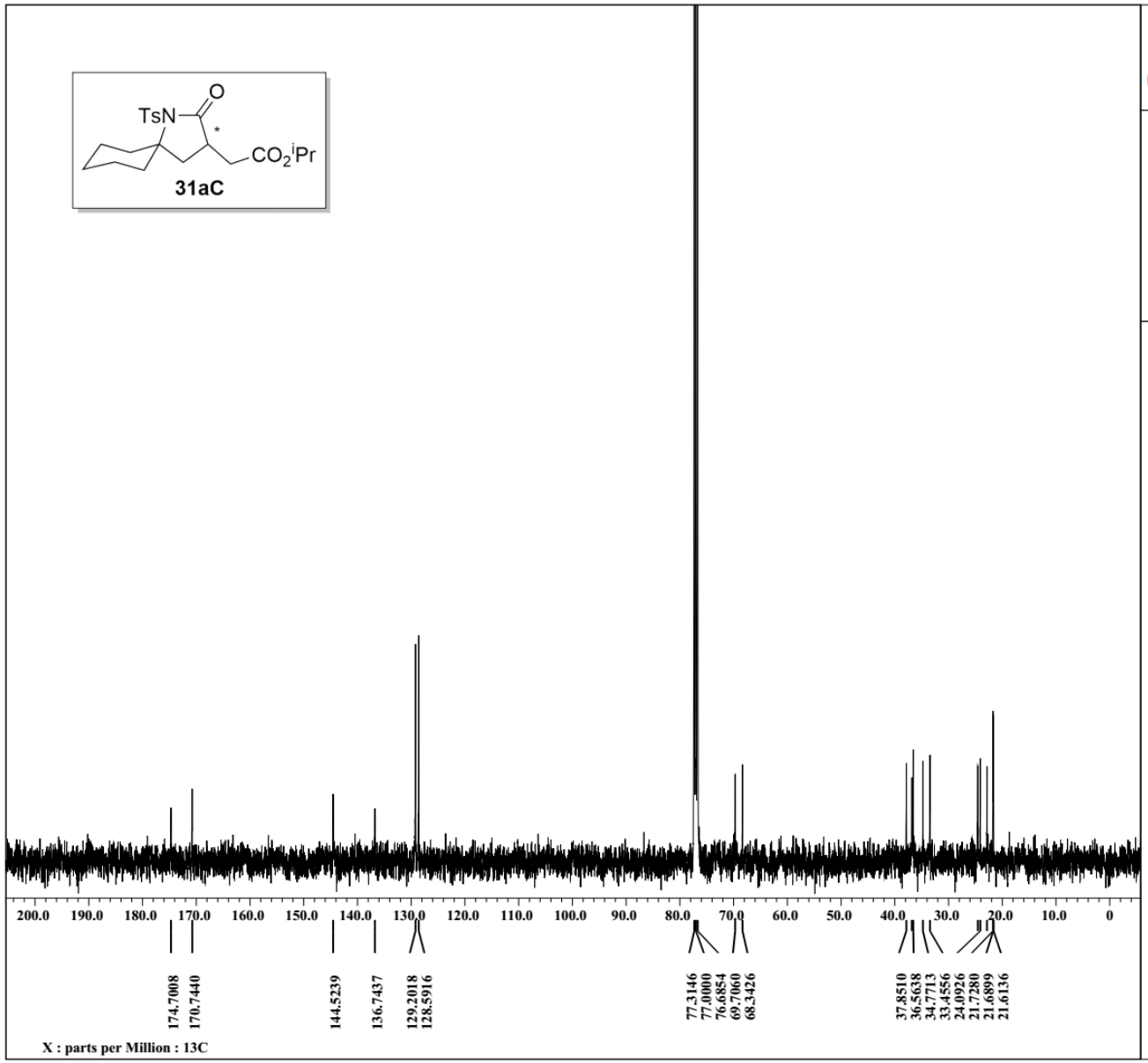
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4

X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1[dB]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 34
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 23.2[dC]




```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = PN3-178CRYSTALC13-5.j
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = S#642709
Solvent           = CHLOROFORM-D
Creation_time     = 29-SEP-2016 17:10:21
Revision_time     = 15-JAN-2018 13:59:23
Current_time      = 17-JAN-2018 13:22:09

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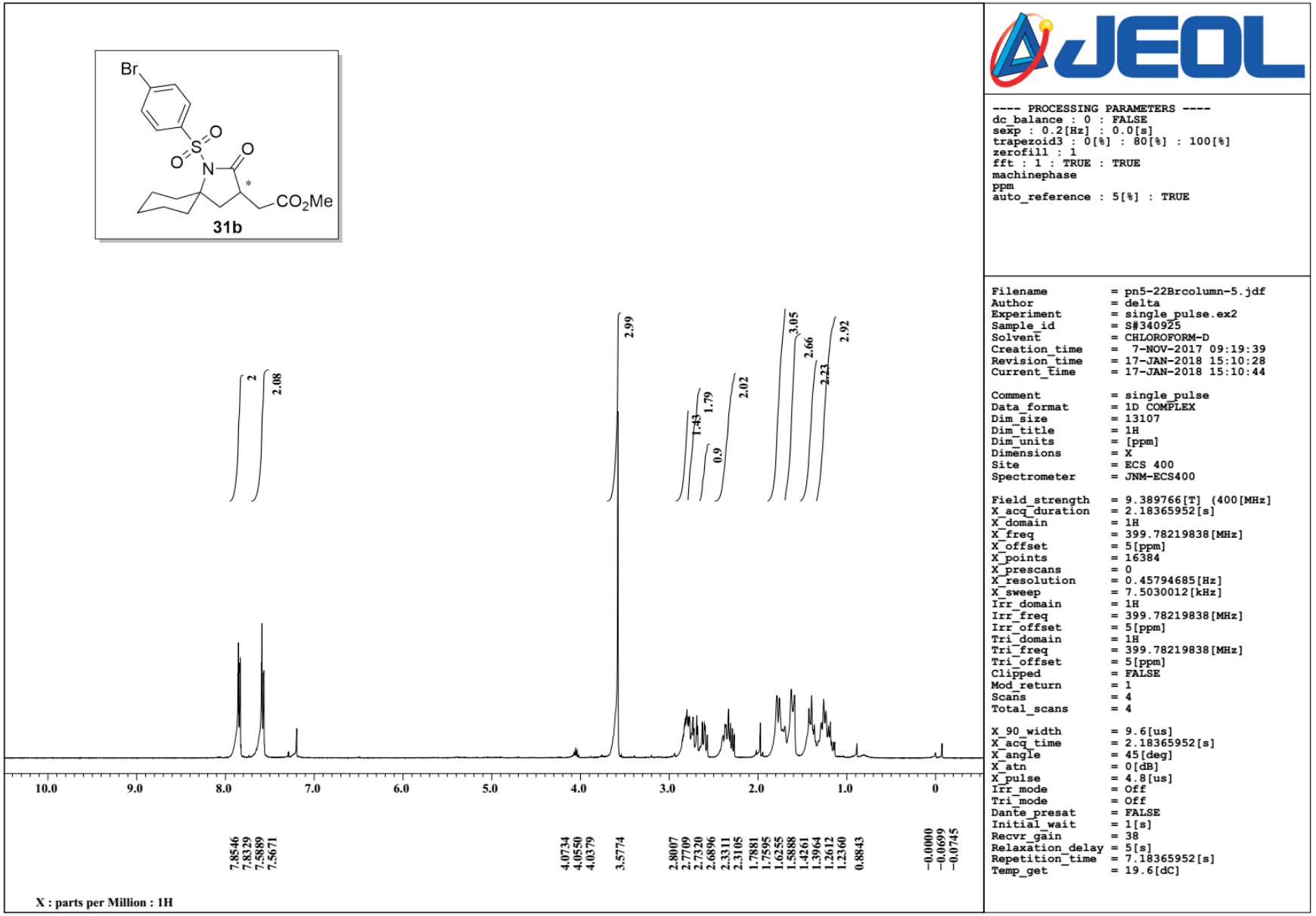
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 1.04333312[s]
X_domain          = 13C
X_freq            = 100.52530333[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 0.95846665[Hz]
X_sweep           = 31.40703518[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 190
Total_scans       = 190

X_90_width        = 8.2[us]
X_acq_time        = 1.04333312[s]
X_angle           = 30[deg]
X_atn             = 6[dB]
X_pulse           = 2.73333333[us]
Irr_atn_dec       = 22.65948[dB]
Irr_atn_noe       = 22.65948[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 60
Relaxation_delay  = 2[s]
Repetition_time   = 3.04333312[s]
Temp_get          = 23.2[dC]
```



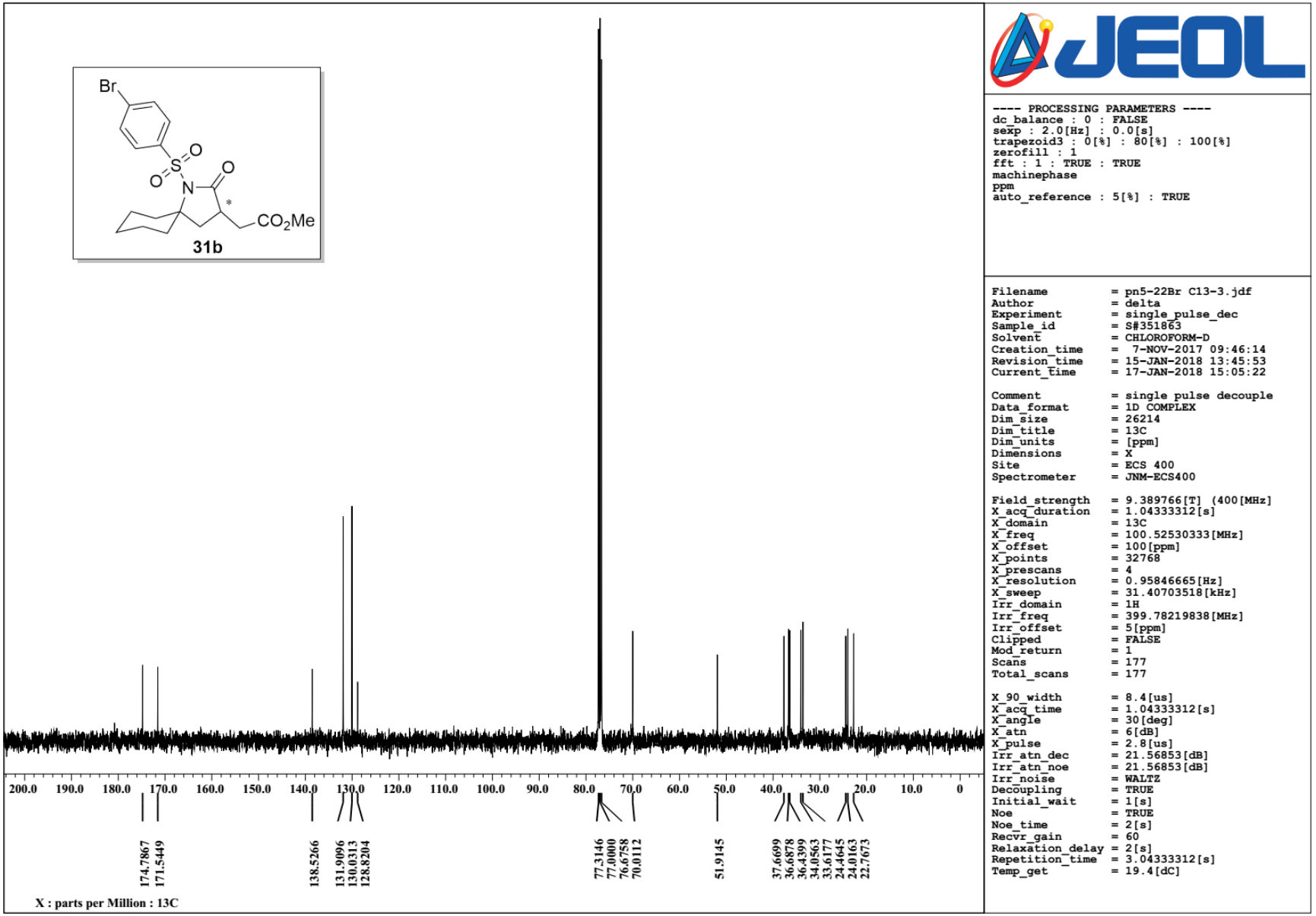

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = pn5-22Brcolumn-5.jdf
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = S#340925
Solvent           = CHLOROFORM-D
Creation_time     =  7-NOV-2017 09:19:39
Revision_time     = 17-JAN-2018 15:10:28
Current_time      = 17-JAN-2018 15:10:44

Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 2.18365952[s]
X_domain          = 1H
X_freq            = 399.78219838[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 0
X_resolution      = 0.45794685[Hz]
X_sweep           = 7.5030012[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Tri_domain        = 1H
Tri_freq          = 399.78219838[MHz]
Tri_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 4
Total_scans       = 4

X_90_width        = 9.6[us]
X_acq_time        = 2.18365952[s]
X_angle           = 45[deg]
X_atn             = 0[dB]
X_pulse           = 4.8[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 38
Relaxation_delay  = 5[s]
Repetition_time   = 7.18365952[s]
Temp_get          = 19.6[dC]
```


Br
O
O
S
N
O
*
CO2Me
31b
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
174.7867
171.5449
138.5266
131.9096
130.0313
128.8204
77.3146
77.0000
76.6758
70.0112
51.9145
37.6699
36.6878
36.4399
34.0563
33.6177
24.4645
24.0163
22.7673
X : parts per Million : 13C
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
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Author = delta
Experiment = single_pulse_dec
Sample_id = S#351863
Solvent = CHLOROFORM-D
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Revision_time = 15-JAN-2018 13:45:53
Current_time = 17-JAN-2018 15:05:22
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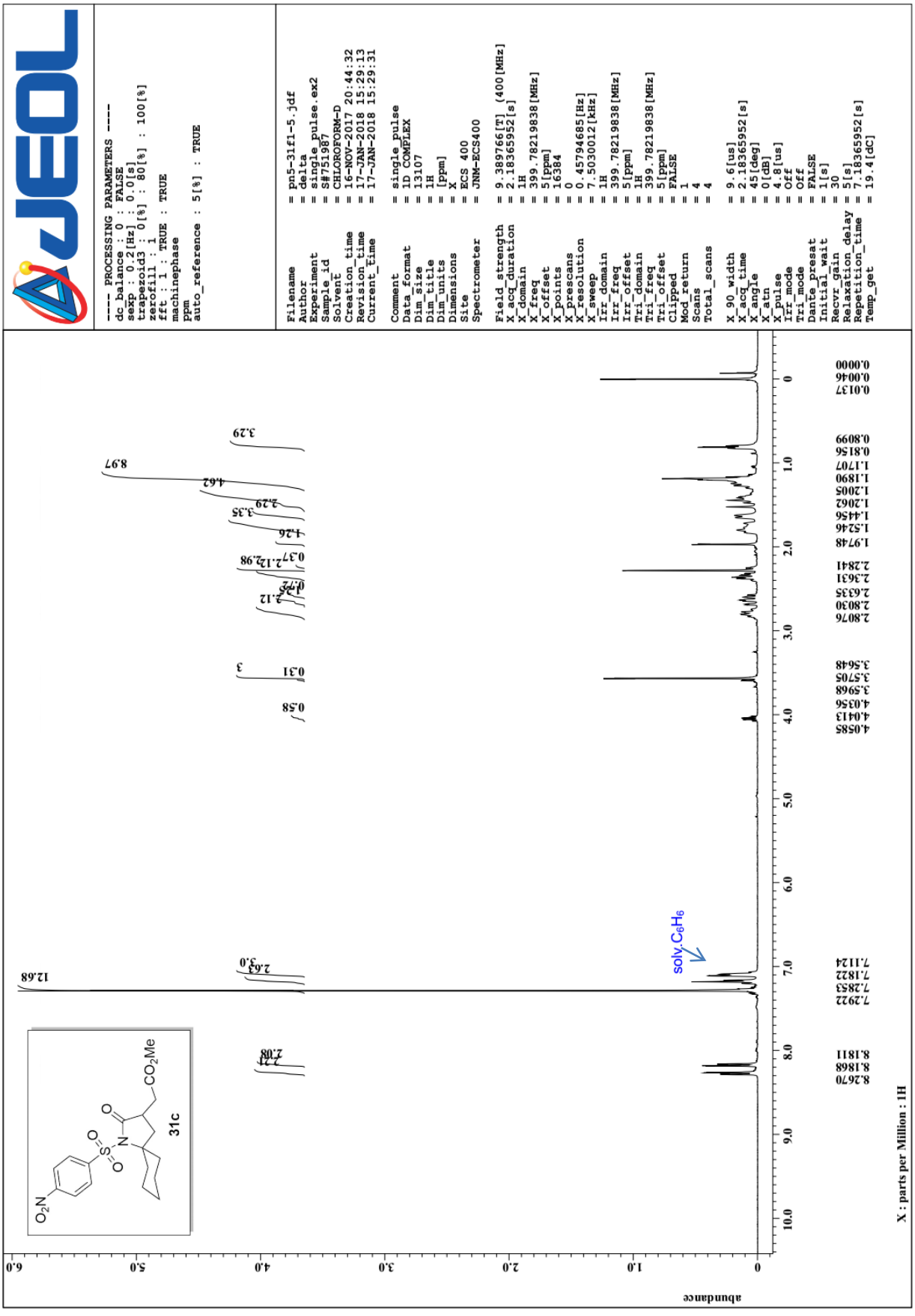
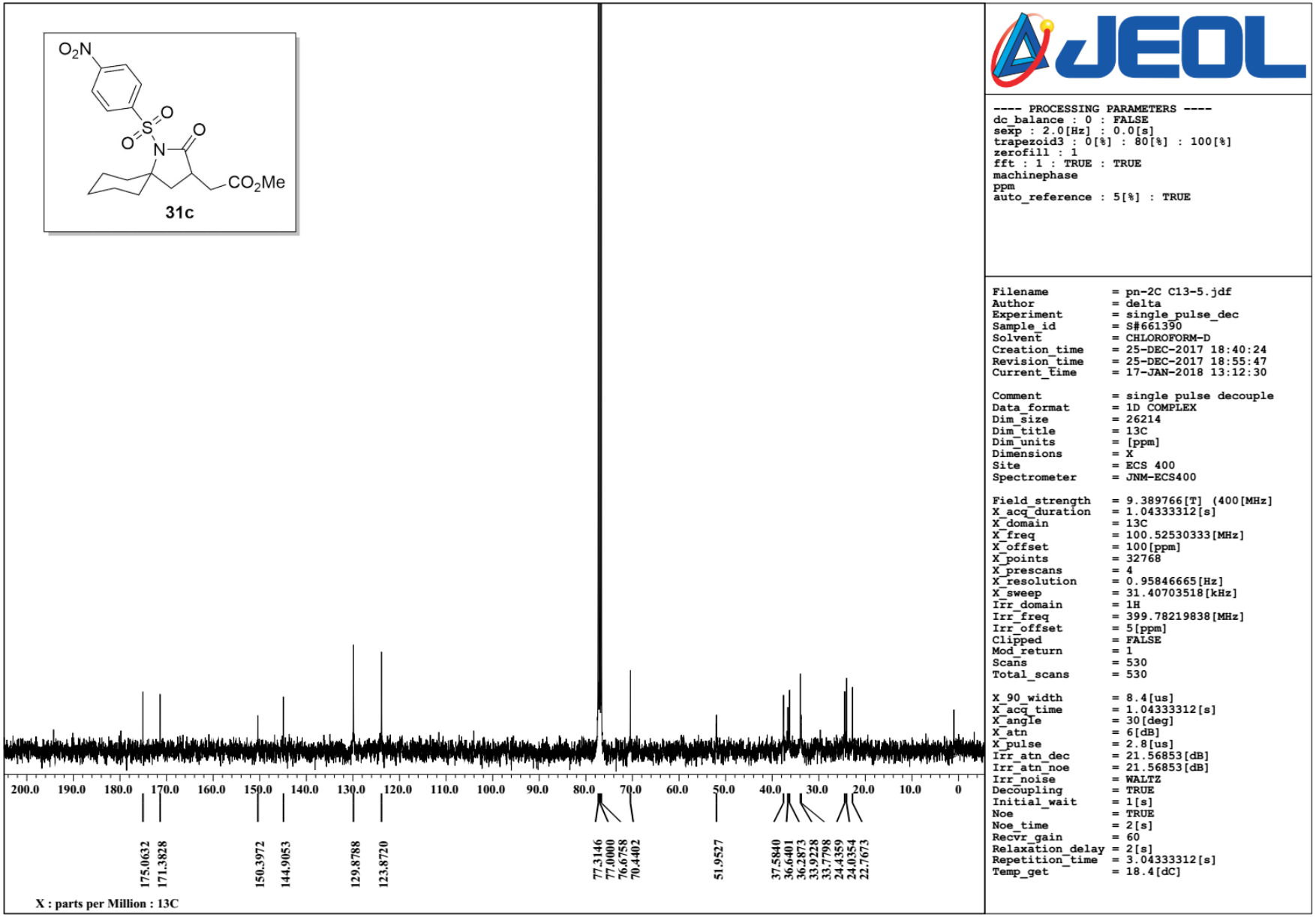
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 177
Total_scans = 177
X_90_width = 8.4[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.8[us]
Irr_atn_dec = 21.56853[dB]
Irr_atn_noe = 21.56853[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 19.4[dC]


JEOL
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn5-31f1-5.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = S#7751987
Solvent = CHLOROFORM-D
Creation_time = 16-NOV-2017 20:44:32
Revision_time = 17-JAN-2018 15:29:13
Current_Time = 17-JAN-2018 15:29:31
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.45794685[Hz]
X_sweep = 7.50300012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.6[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 0[dB]
X_pulse = 4.8[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 30
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 19.4[dC]
12.68
8.97
3.29
4.62
2.29
3.35
1.26
2.98
2.12
0.37
0.31
3
0.58
2.63
3.0
2.08
2.73
solv.C6H6
O2N
CO2Me
31c
abundance
X : parts per Million : 1H


O2N
O
O
S
N
O
CO2Me
31c
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
175.0632
171.3828
150.3972
144.9053
129.8788
123.8720
77.3146
77.0000
76.6758
70.4402
51.9527
37.5840
36.6401
36.2873
33.9228
33.7798
24.4359
24.0354
22.7673
X : parts per Million : 13C
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn-2C C13-5.jdf
Author = delta
Experiment = single_pulse_dec
Sample_id = S#661390
Solvent = CHLOROFORM-D
Creation_time = 25-DEC-2017 18:40:24
Revision_time = 25-DEC-2017 18:55:47
Current_time = 17-JAN-2018 13:12:30
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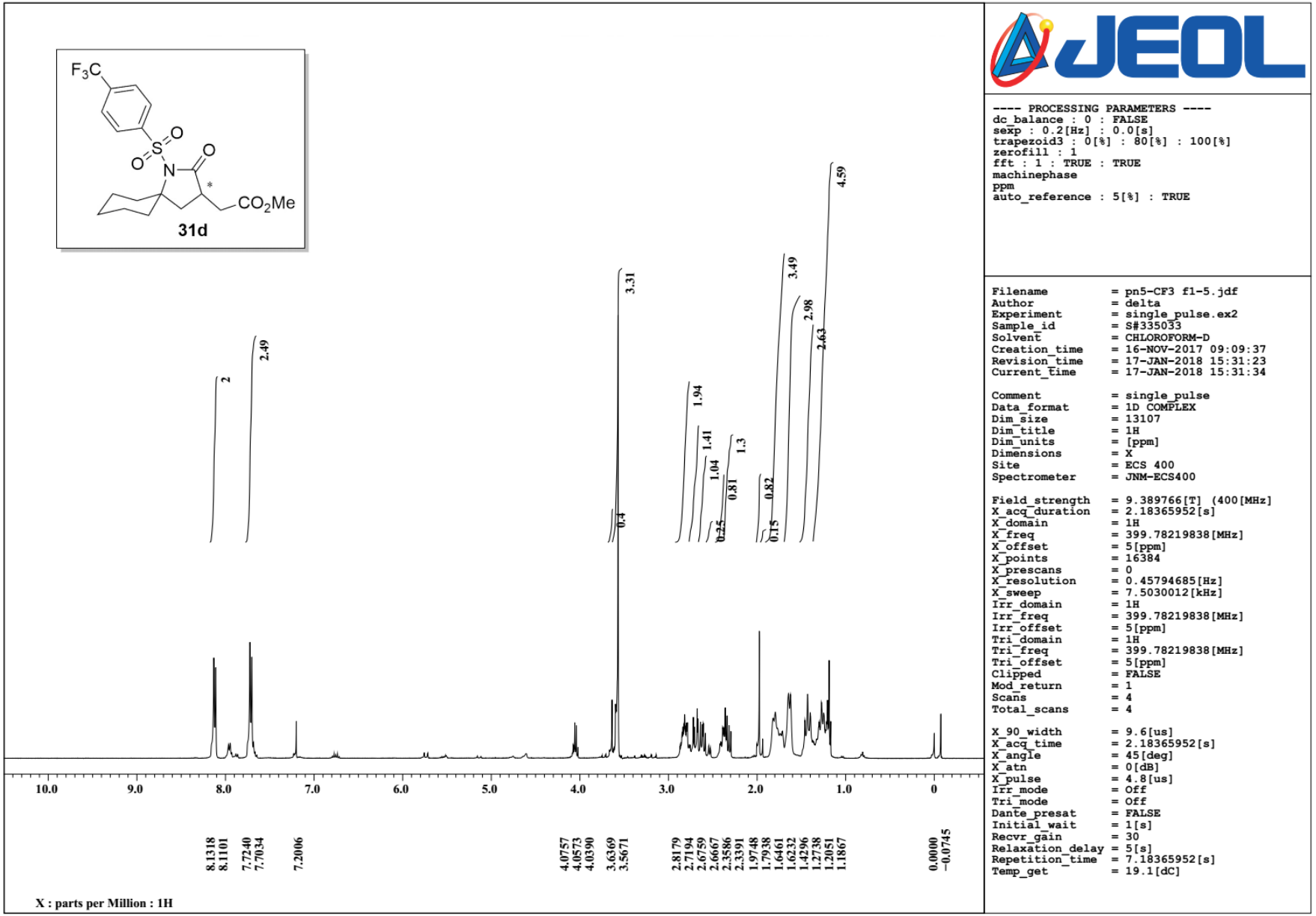
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 530
Total_scans = 530
X_90_width = 8.4[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.8[us]
Irr_atn_dec = 21.56853[dB]
Irr_atn_noe = 21.56853[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 18.4[dC]



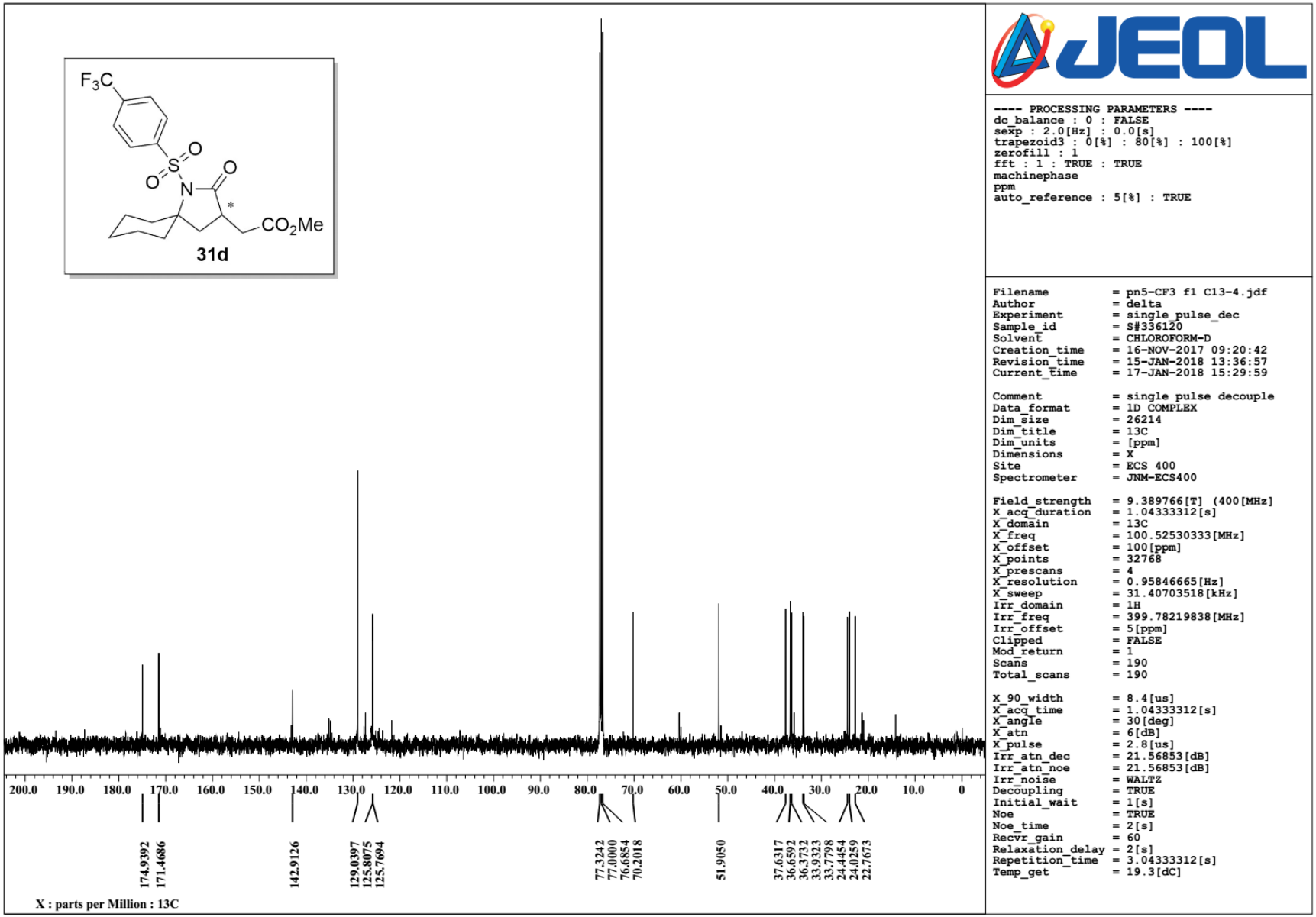

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

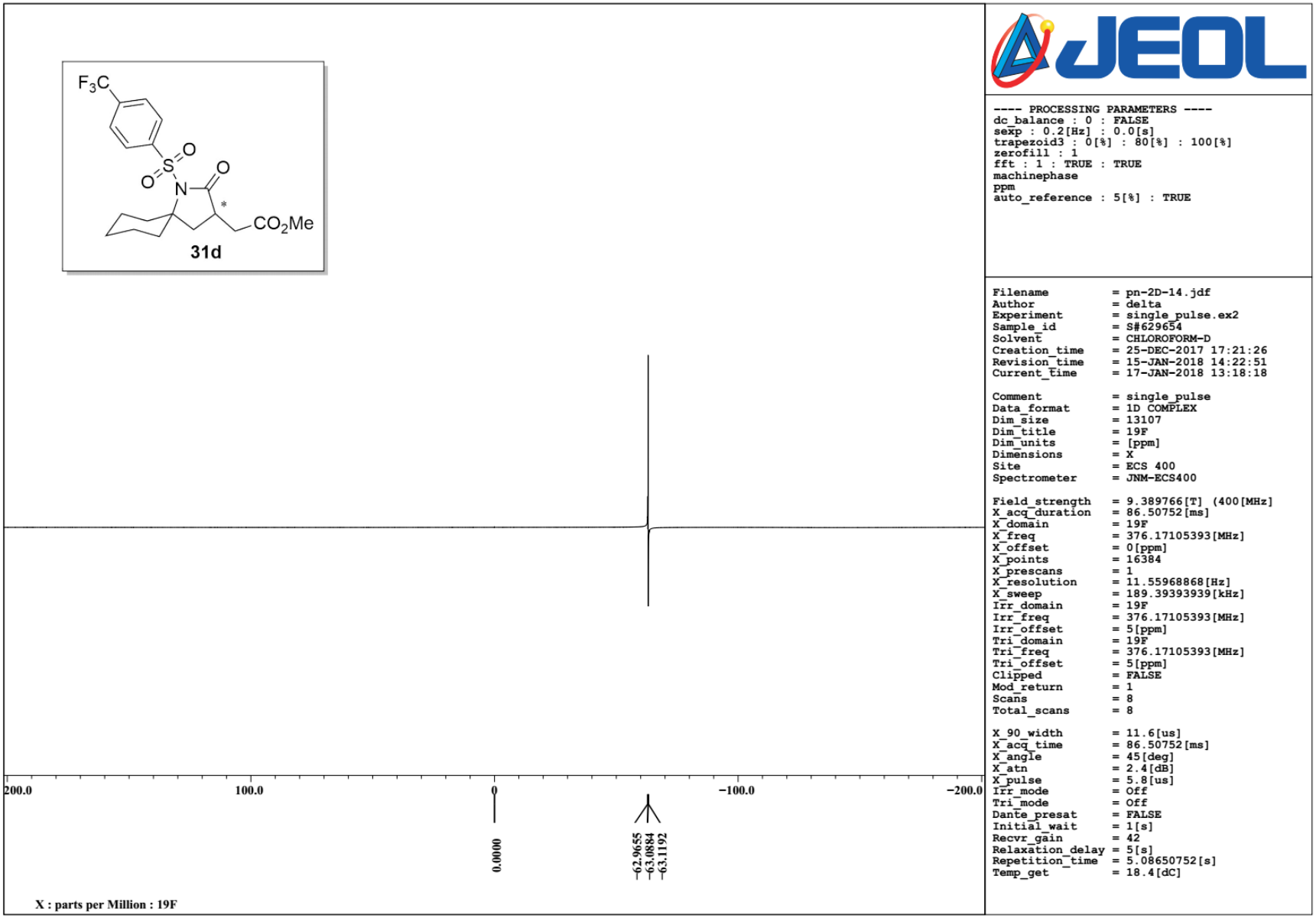
```
Filename          = pn5-CF3 f1-5.jdf
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = S#335033
Solvent           = CHLOROFORM-D
Creation_time     = 16-NOV-2017 09:09:37
Revision_time     = 17-JAN-2018 15:31:23
Current_time      = 17-JAN-2018 15:31:34

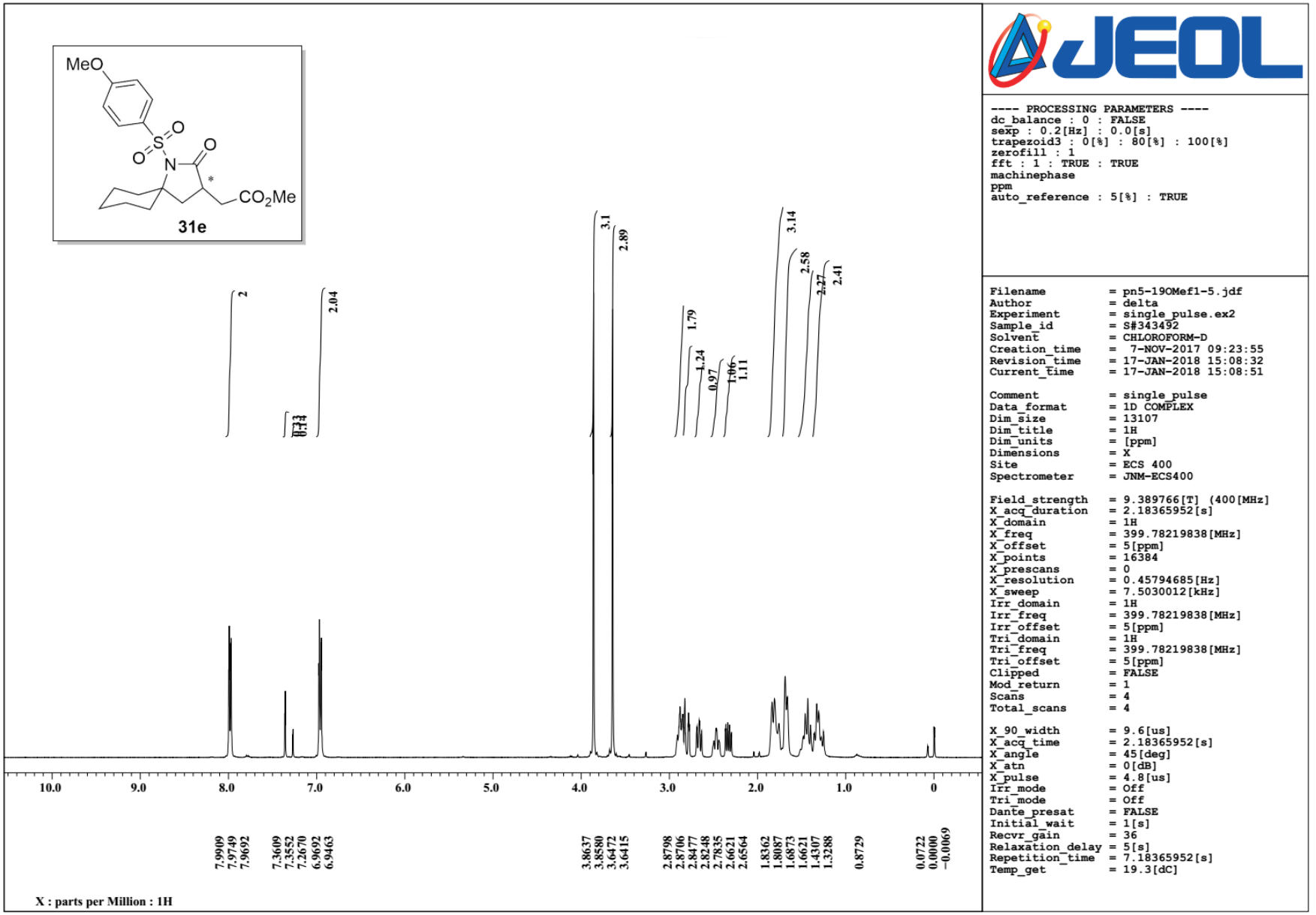
Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

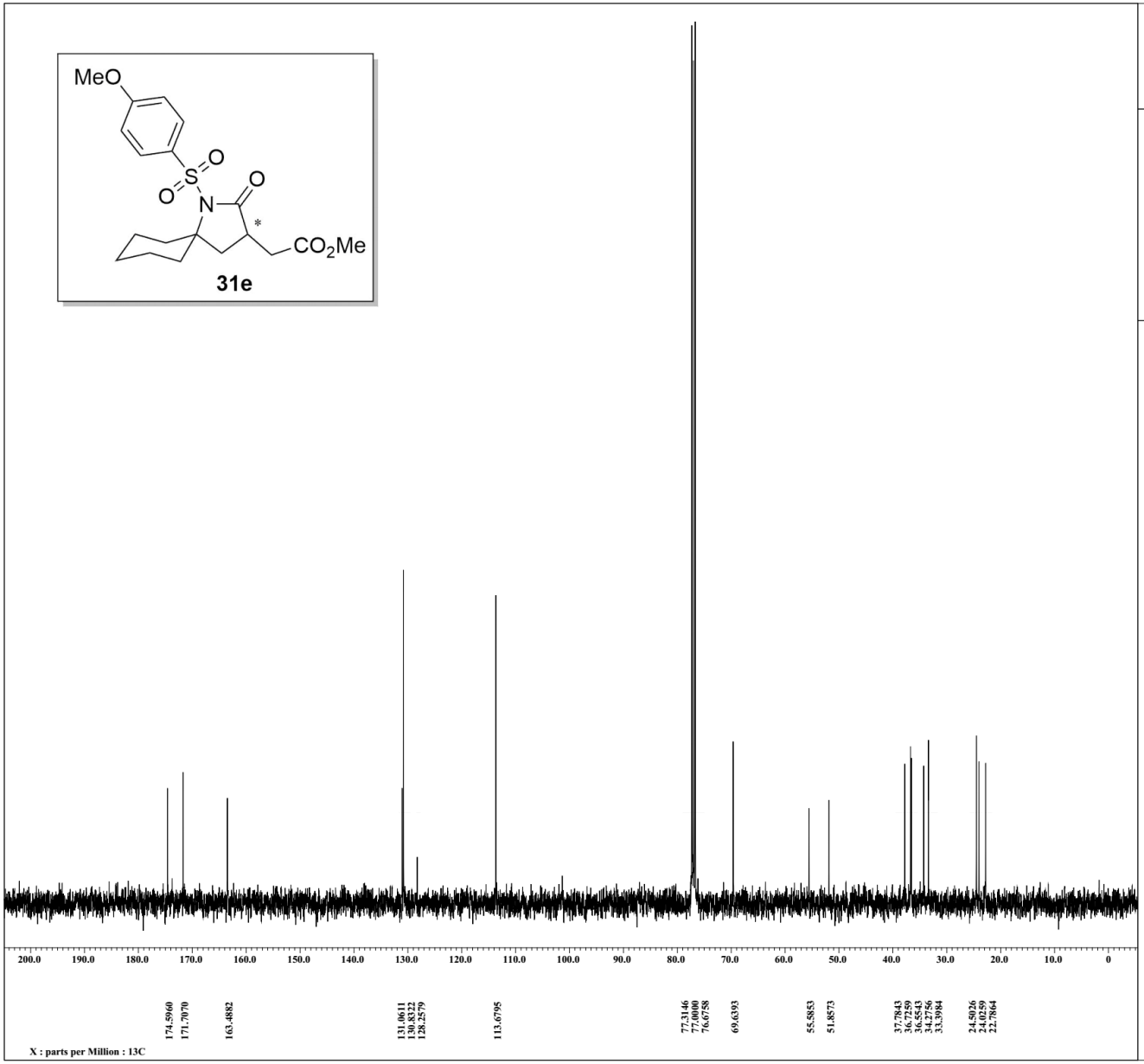
Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 2.18365952[s]
X_domain          = 1H
X_freq            = 399.78219838[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 0
X_resolution      = 0.45794685[Hz]
X_sweep           = 7.5030012[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Tri_domain        = 1H
Tri_freq          = 399.78219838[MHz]
Tri_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 4
Total_scans       = 4

X_90_width        = 9.6[us]
X_acq_time        = 2.18365952[s]
X_angle           = 45[deg]
X_atn             = 0[dB]
X_pulse           = 4.8[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 30
Relaxation_delay  = 5[s]
Repetition_time   = 7.18365952[s]
Temp_get          = 19.1[dC]
```


F3C
O
O
S
O
N
O
*
CO2Me
31d
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
174.9392
171.4686
142.9126
129.0397
125.8075
125.7694
77.3242
77.0000
76.6854
70.2018
51.9050
37.6317
36.6592
36.3732
33.9323
33.7798
24.4454
24.0259
22.7673
X : parts per Million : 13C
JEOL
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn5-CF3 f1 C13-4.jdf
Author = delta
Experiment = single_pulse_dec
Sample_id = S#336120
Solvent = CHLOROFORM-D
Creation_time = 16-NOV-2017 09:20:42
Revision_time = 15-JAN-2018 13:36:57
Current_time = 17-JAN-2018 15:29:59
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 190
Total_scans = 190
X_90_width = 8.4[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.8[us]
Irr_atn_dec = 21.56853[dB]
Irr_atn_noe = 21.56853[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 19.3[dC]


F3C
O
S
O
N
O
*
CO2Me
31d
200.0
100.0
0
−100.0
−200.0
0.0000
−62.9655
−63.0884
−63.1192
X : parts per Million : 19F
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn-2D-14.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = S#629654
Solvent = CHLOROFORM-D
Creation_time = 25-DEC-2017 17:21:26
Revision_time = 15-JAN-2018 14:22:51
Current_time = 17-JAN-2018 13:18:18
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 19F
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 86.50752[ms]
X_domain = 19F
X_freq = 376.17105393[MHz]
X_offset = 0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 11.55968868[Hz]
X_sweep = 189.39393939[kHz]
Irr_domain = 19F
Irr_freq = 376.17105393[MHz]
Irr_offset = 5[ppm]
Tri_domain = 19F
Tri_freq = 376.17105393[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 8
Total_scans = 8
X_90_width = 11.6[us]
X_acq_time = 86.50752[ms]
X_angle = 45[deg]
X_atn = 2.4[dB]
X_pulse = 5.8[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 42
Relaxation_delay = 5[s]
Repetition_time = 5.08650752[s]
Temp_get = 18.4[dC]


MeO
O
O
S
N
O
O
*
CO2Me
31e
2
2.04
3.1
2.89
1.79
1.24
0.97
1.06
1.11
3.14
2.58
2.27
2.41
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.9909
7.9749
7.9692
7.3609
7.3552
7.2670
6.9692
6.9463
3.8637
3.8580
3.6472
3.6415
2.8798
2.8706
2.8477
2.8248
2.7835
2.6621
2.6564
1.8362
1.8087
1.6873
1.6621
1.4307
1.3288
0.8729
0.0722
0.0000
−0.0069
X : parts per Million : 1H
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn5-19OMef1-5.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = S#343492
Solvent = CHLOROFORM-D
Creation_time = 7-NOV-2017 09:23:55
Revision_time = 17-JAN-2018 15:08:32
Current_time = 17-JAN-2018 15:08:51
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.6[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 0[dB]
X_pulse = 4.8[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 36
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 19.3[dC]



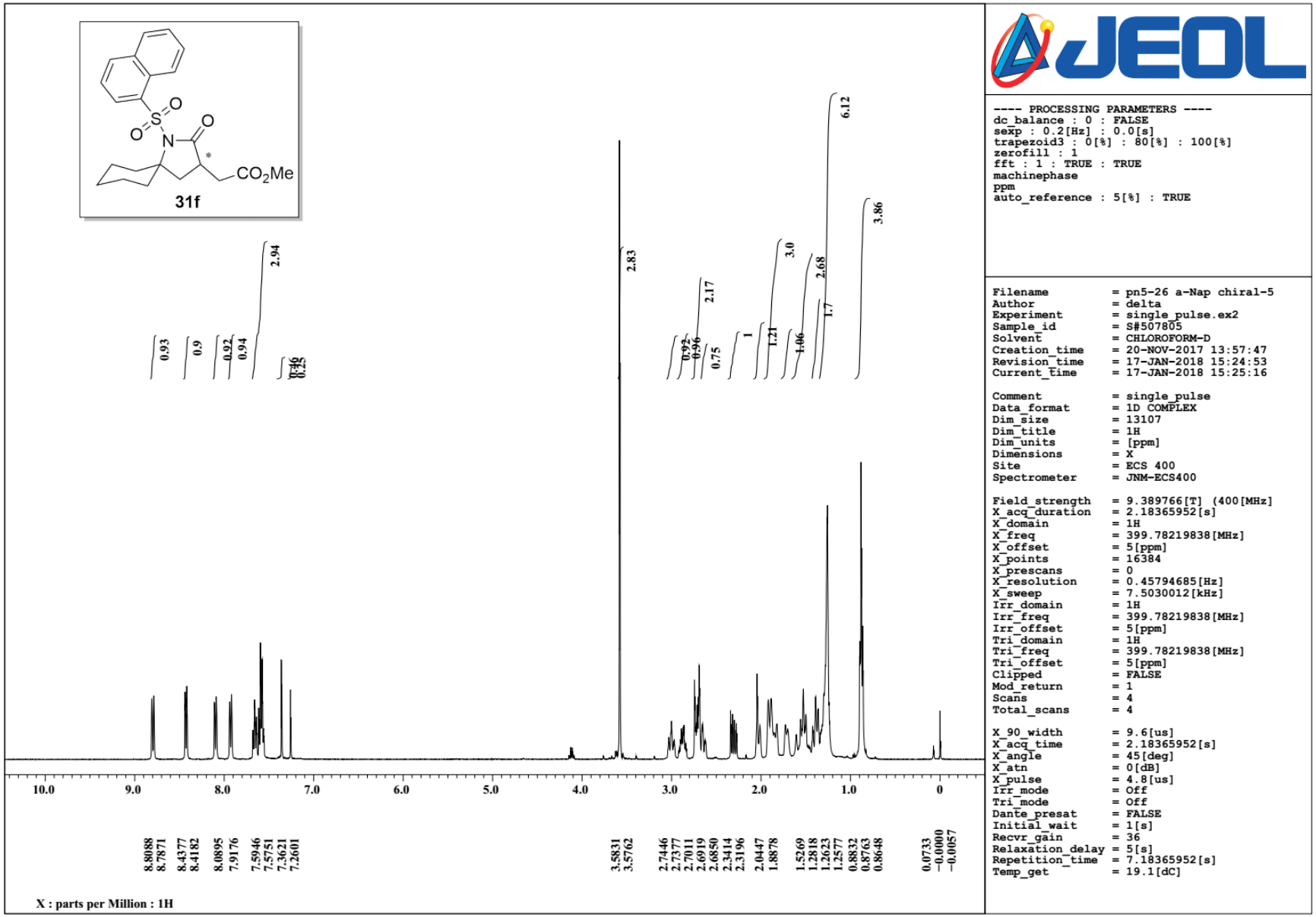
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE

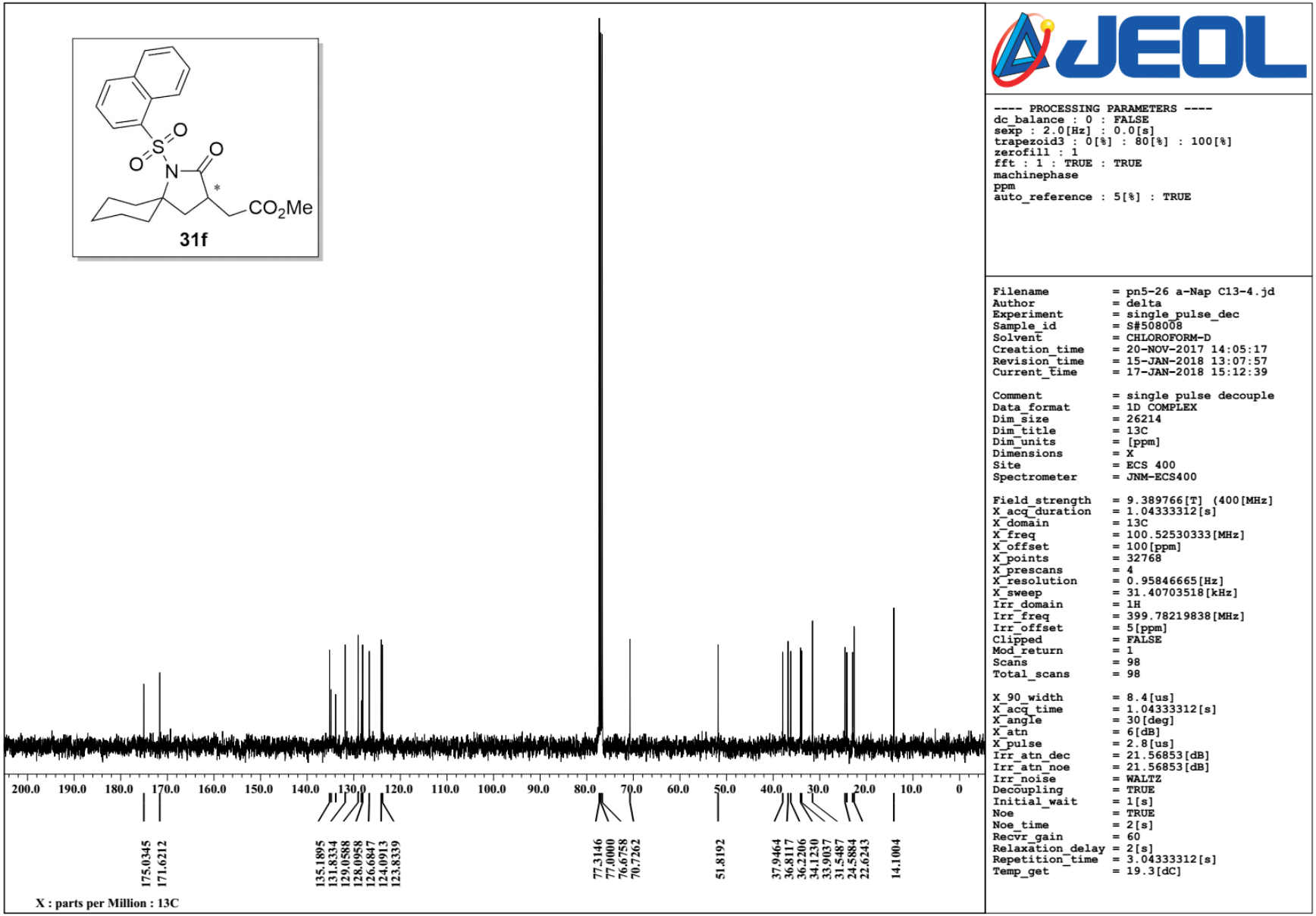
Filename = pn5-190Me C13-4.jdf
Author = delta
Experiment = single_pulse_dec
Sample_id = S#347558
Solvent = CHLOROFORM-D
Creation_time = 7-NOV-2017 09:33:47
Revision_time = 15-JAN-2018 13:20:31
Current_time = 17-JAN-2018 18:45:59

Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400

Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 73
Total_scans = 73

X_90_width = 8.4[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.8[us]
Irr_atn_dec = 21.56853[dB]
Irr_atn_noe = 21.56853[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 19.5[dC]


31f
X : parts per Million : 1H
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn5-26 a-Nap chiral-5
Author = delta
Experiment = single_pulse.ex2
Sample_id = S#507805
Solvent = CHLOROFORM-D
Creation_time = 20-NOV-2017 13:57:47
Revision_time = 17-JAN-2018 15:24:53
Current_time = 17-JAN-2018 15:25:16
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.6[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 0[dB]
X_pulse = 4.8[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 36
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 19.1[dC]



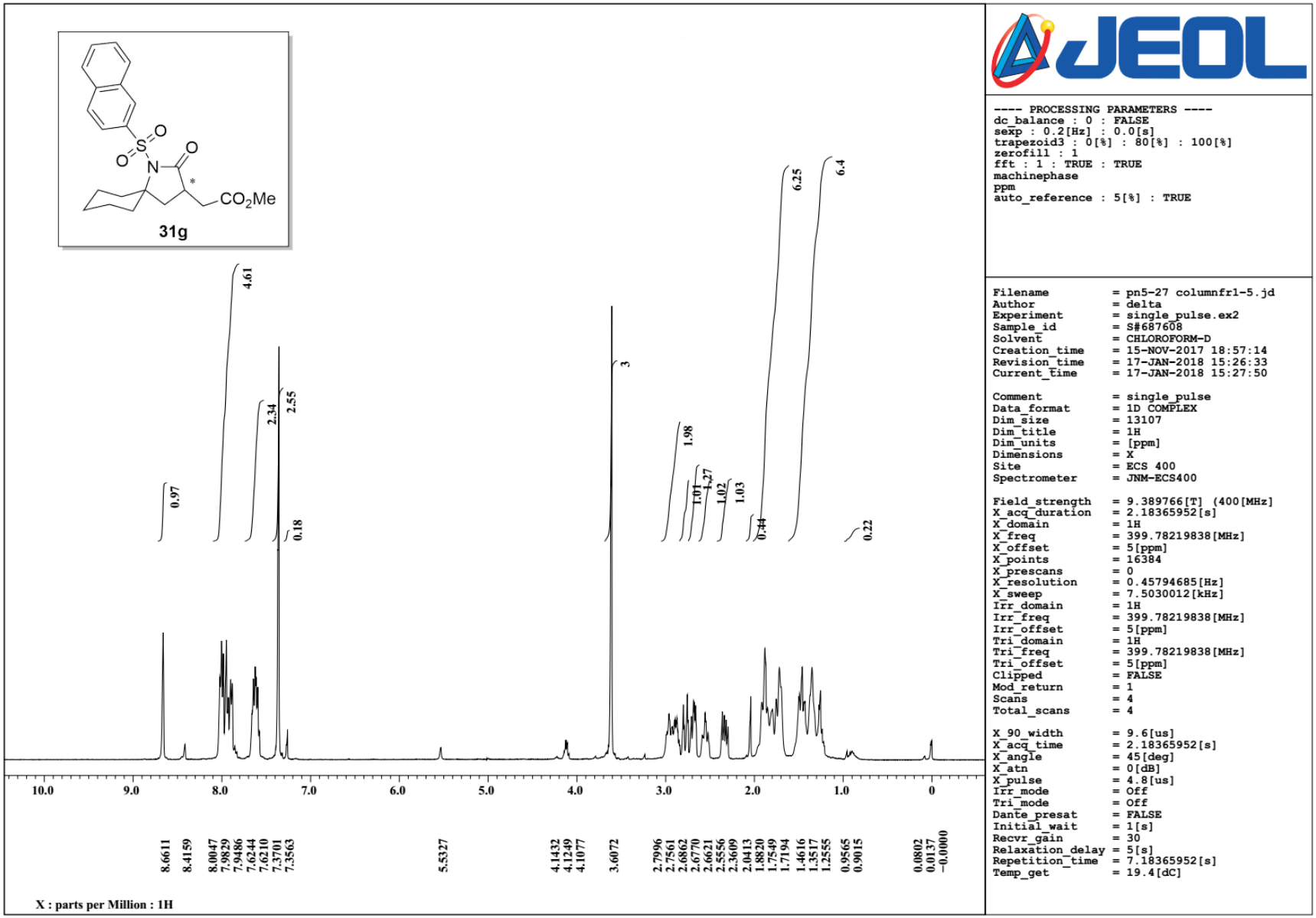

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = pn5-26 a-Nap C13-4.jd
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = S#508008
Solvent           = CHLOROFORM-D
Creation_time     = 20-NOV-2017 14:05:17
Revision_time     = 15-JAN-2018 13:07:57
Current_time      = 17-JAN-2018 15:12:39

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 1.04333312[s]
X_domain          = 13C
X_freq            = 100.52530333[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 0.95846665[Hz]
X_sweep           = 31.40703518[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 98
Total_scans       = 98

X_90_width        = 8.4[us]
X_acq_time        = 1.04333312[s]
X_angle           = 30[deg]
X_atn             = 6[dB]
X_pulse           = 2.8[us]
Irr_atn_dec       = 21.56853[dB]
Irr_atn_noe       = 21.56853[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 60
Relaxation_delay  = 2[s]
Repetition_time   = 3.04333312[s]
Temp_get          = 19.3[dC]
```



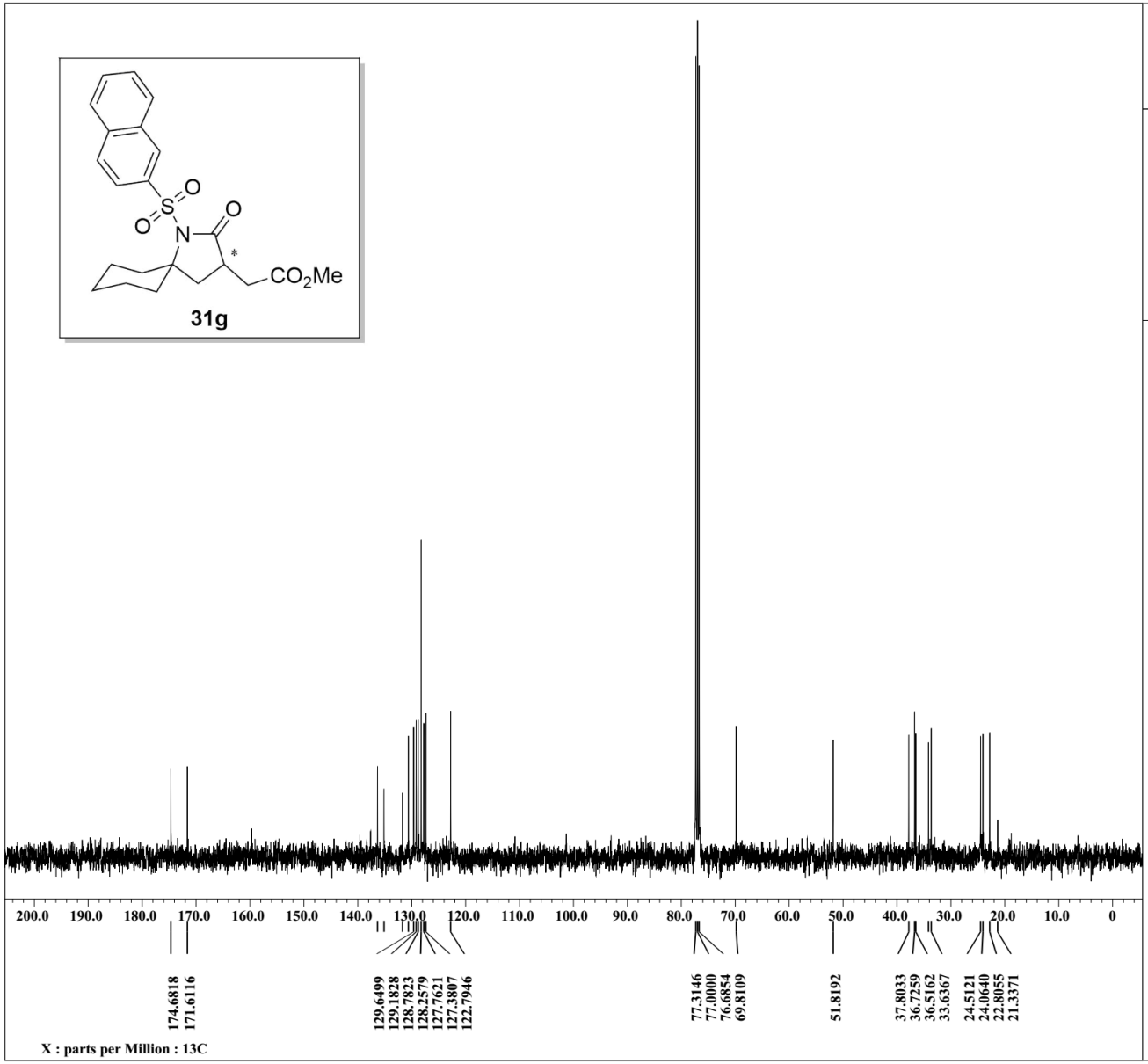

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = pn5-27 columnfr1-5.jd
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = S#687608
Solvent           = CHLOROFORM-D
Creation_time     = 15-NOV-2017 18:57:14
Revision_time     = 17-JAN-2018 15:26:33
Current_time      = 17-JAN-2018 15:27:50

Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 2.18365952[s]
X_domain          = 1H
X_freq            = 399.78219838[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 0
X_resolution      = 0.45794685[Hz]
X_sweep           = 7.5030012[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Tri_domain        = 1H
Tri_freq          = 399.78219838[MHz]
Tri_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 4
Total_scans       = 4

X_90_width        = 9.6[us]
X_acq_time        = 2.18365952[s]
X_angle           = 45[deg]
X_atn             = 0[dB]
X_pulse           = 4.8[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 30
Relaxation_delay  = 5[s]
Repetition_time   = 7.18365952[s]
Temp_get          = 19.4[dC]
```



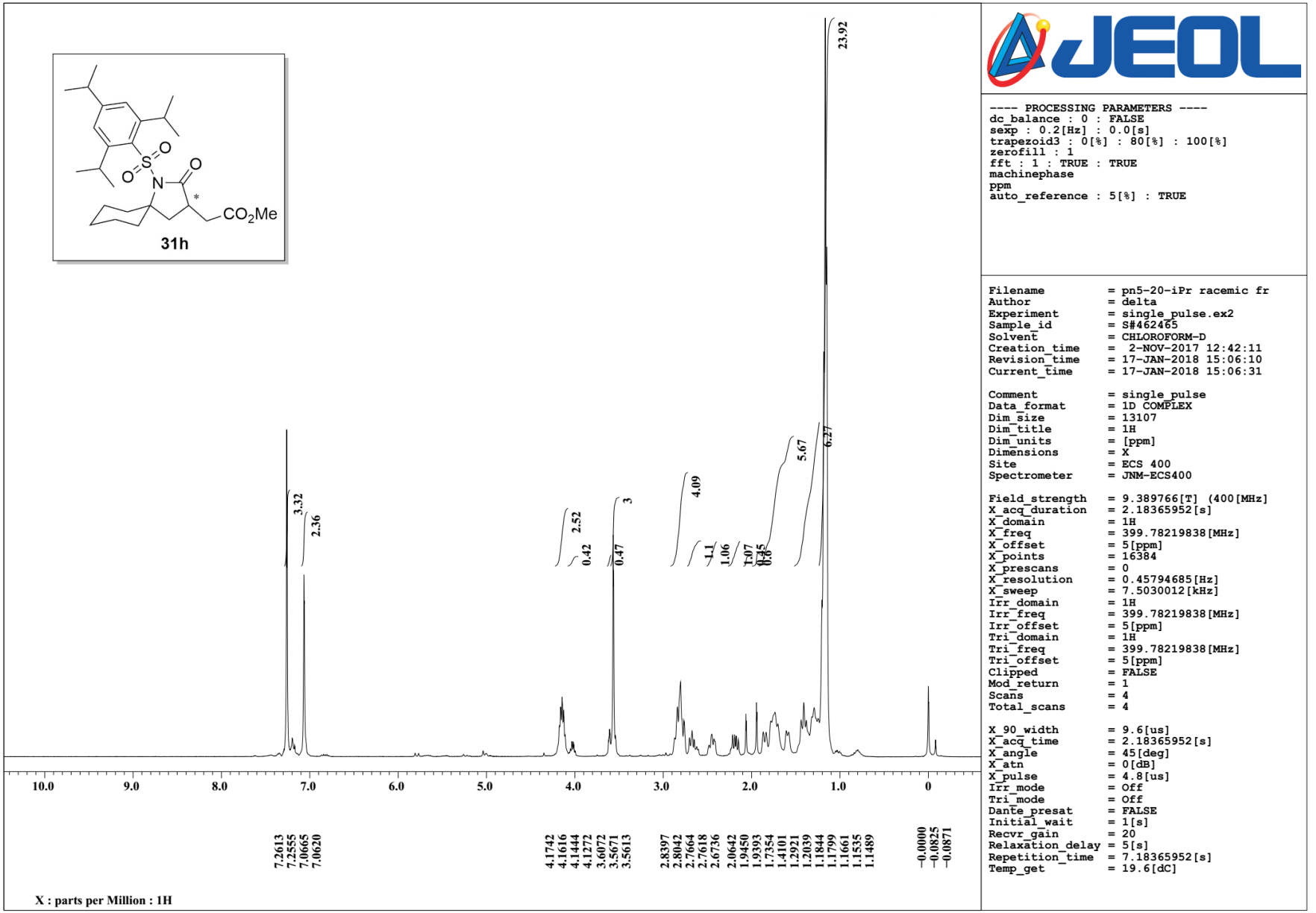
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE

Filename = pn5-27fr1C13-4.jdf
Author = delta
Experiment = single_pulse_dec
Sample_id = S#687855
Solvent = CHLOROFORM-D
Creation_time = 15-NOV-2017 19:06:19
Revision_time = 15-JAN-2018 13:13:21
Current_time = 17-JAN-2018 15:28:12

Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400

Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 165
Total_scans = 165

X_90_width = 8.4[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.8[us]
Irr_atn_dec = 21.56853[dB]
Irr_atn_noe = 21.56853[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 19.6[dC]



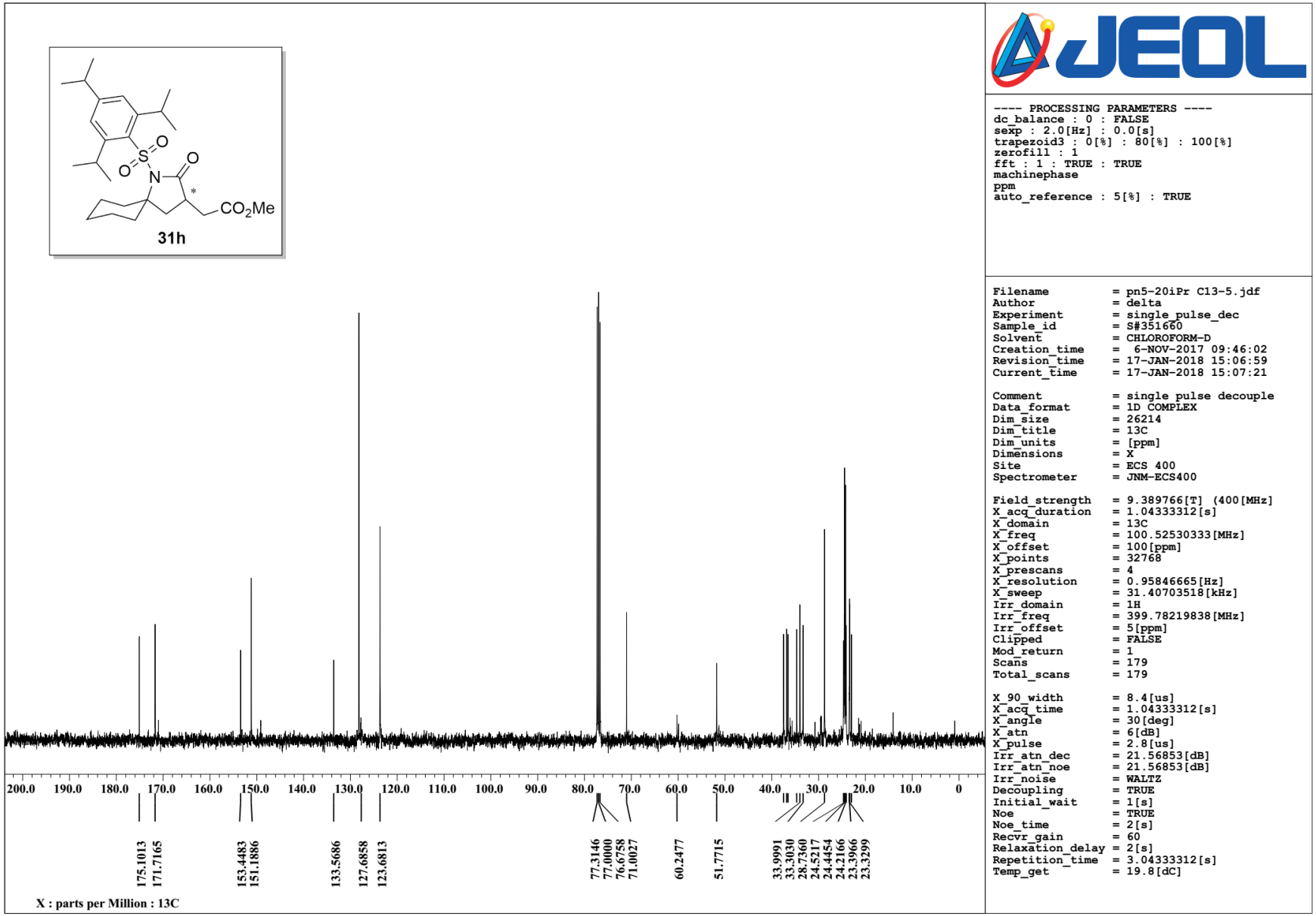

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = pn5-20-iPr racemic fr
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = S#462465
Solvent           = CHLOROFORM-D
Creation_time     =  2-NOV-2017 12:42:11
Revision_time     = 17-JAN-2018 15:06:10
Current_time      = 17-JAN-2018 15:06:31

Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 2.18365952[s]
X_domain          = 1H
X_freq            = 399.78219838[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 0
X_resolution      = 0.45794685[Hz]
X_sweep           = 7.5030012[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Tri_domain        = 1H
Tri_freq          = 399.78219838[MHz]
Tri_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 4
Total_scans       = 4

X_90_width        = 9.6[us]
X_acq_time        = 2.18365952[s]
X_angle           = 45[deg]
X_atn             = 0[dB]
X_pulse           = 4.8[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 20
Relaxation_delay  = 5[s]
Repetition_time   = 7.18365952[s]
Temp_get          = 19.6[dC]
```




```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

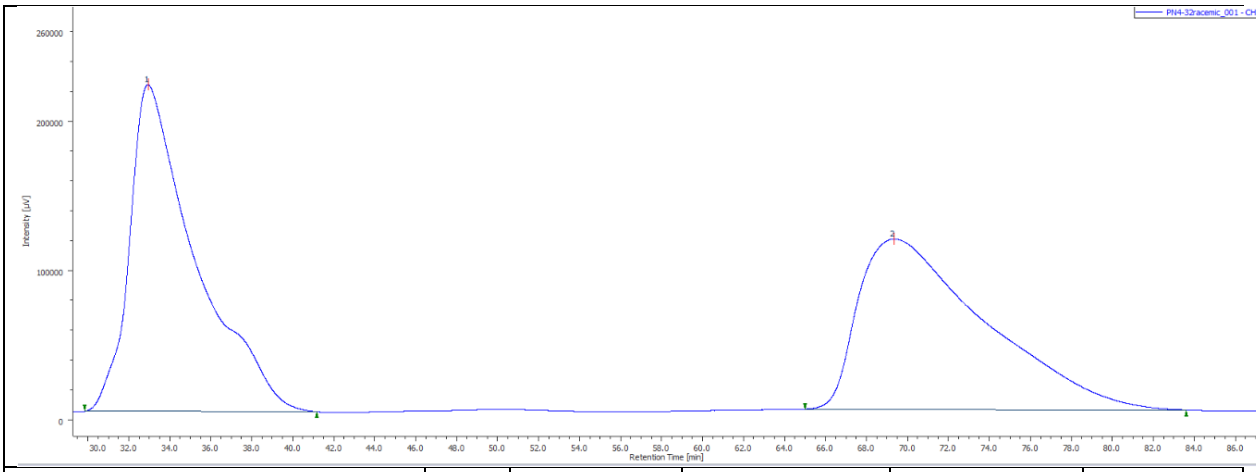
```
Filename          = pn5-20iPr C13-5.jdf
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = S#351660
Solvent           = CHLOROFORM-D
Creation_time     =  6-NOV-2017 09:46:02
Revision_time     = 17-JAN-2018 15:06:59
Current_time      = 17-JAN-2018 15:07:21

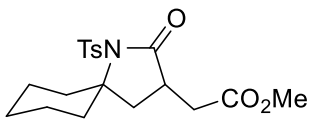
Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 1.04333312[s]
X_domain          = 13C
X_freq            = 100.52530333[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 0.95846665[Hz]
X_sweep           = 31.40703518[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 179
Total_scans       = 179

X_90_width        = 8.4[us]
X_acq_time        = 1.04333312[s]
X_angle           = 30[deg]
X_atn             = 6[dB]
X_pulse           = 2.8[us]
Irr_atn_dec       = 21.56853[dB]
Irr_atn_noe       = 21.56853[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 60
Relaxation_delay  = 2[s]
Repetition_time   = 3.04333312[s]
Temp_get          = 19.8[dC]
```

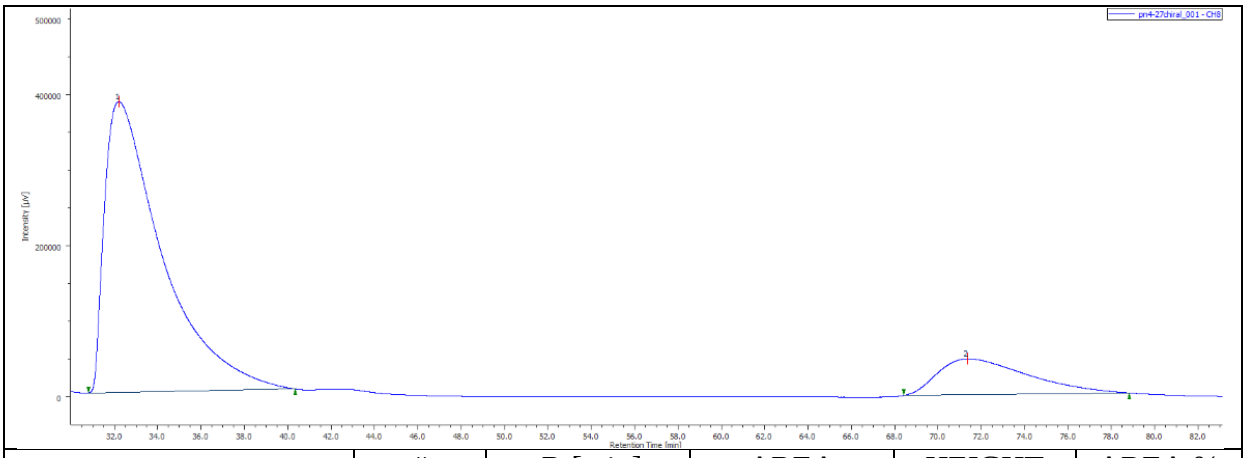
2) HPLC data for the the γ-lactam products **31** (Table 2.4)

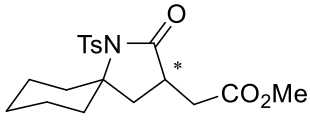




31aA racemic

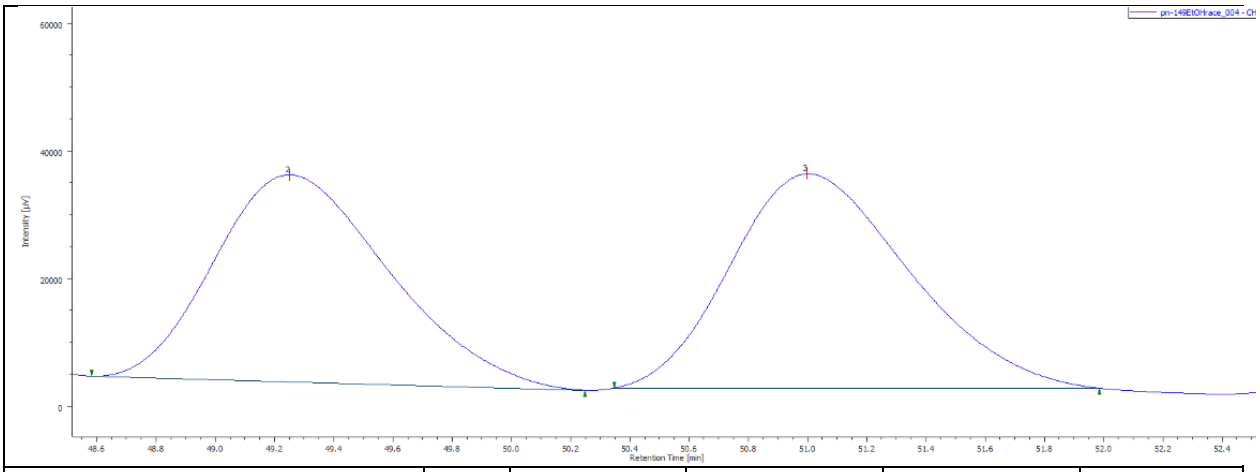
#	tR [min]	AREA	HEIGHT	AREA %
1	32.943	48860430	218608	50.008
2	69.313	48844615	113998	49.992

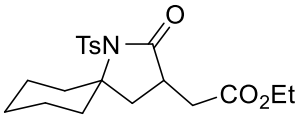


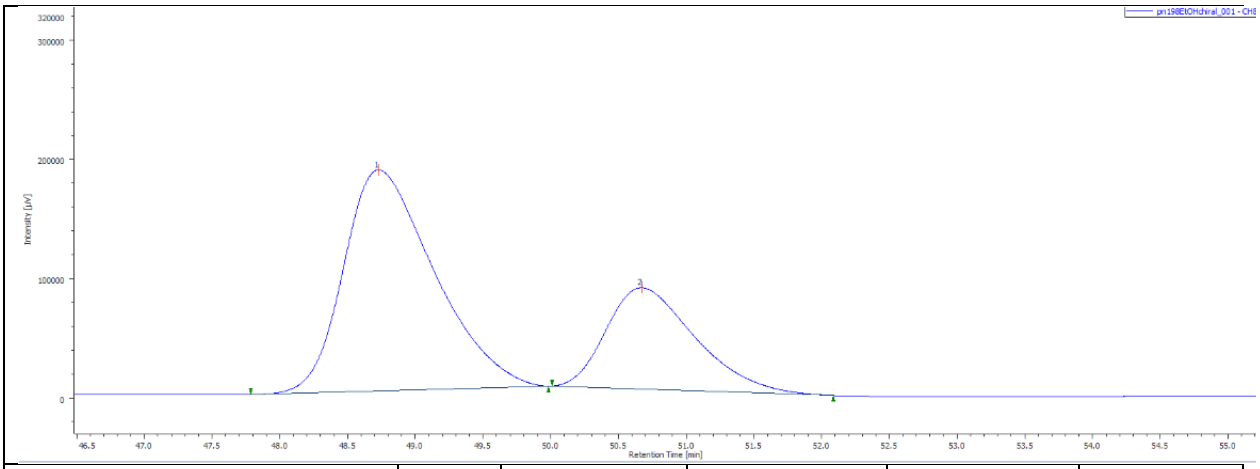


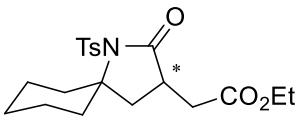
31aA, 68% ee

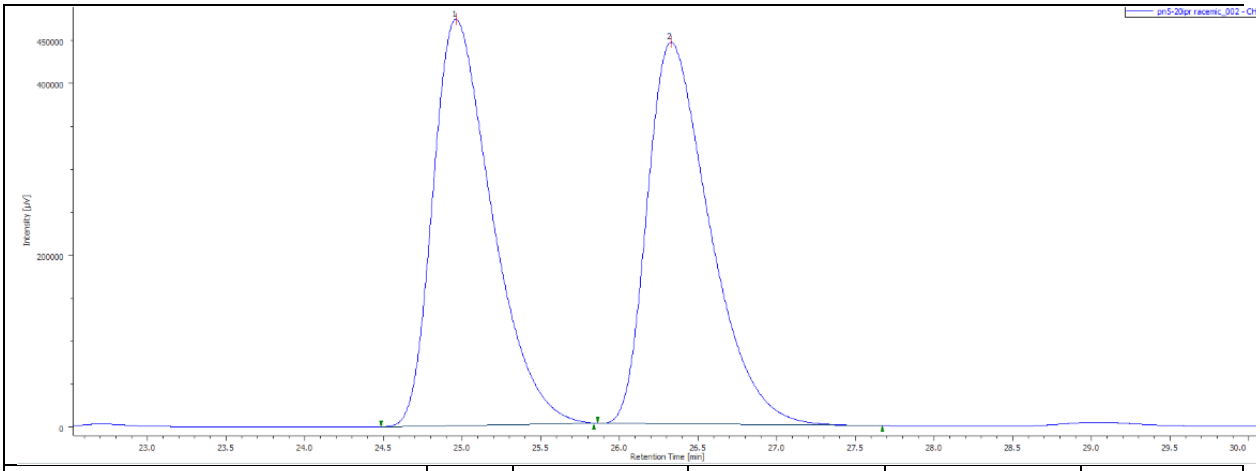
#	tR [min]	AREA	HEIGHT	AREA %
1	32.210	70767526	384293	83.788
2	71.347	13692631	47646	16.212

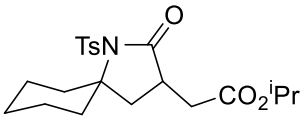


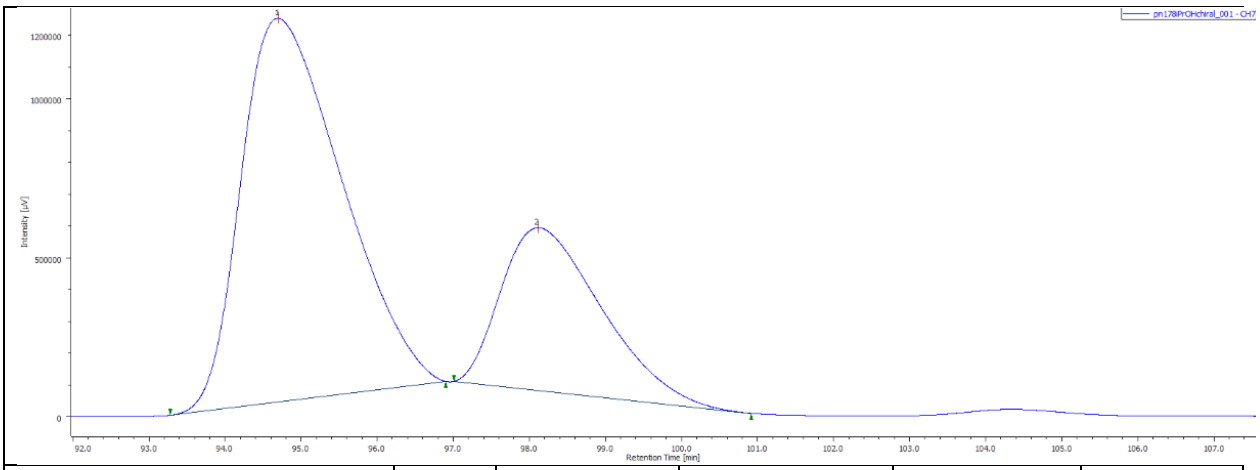
	#	tR [min]	AREA	HEIGHT	AREA %
 **31aB**	2	49.250	1322563	32361	45.957
	3	50.997	1353662	33109	47.037

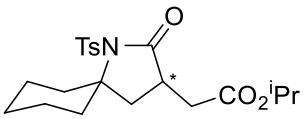


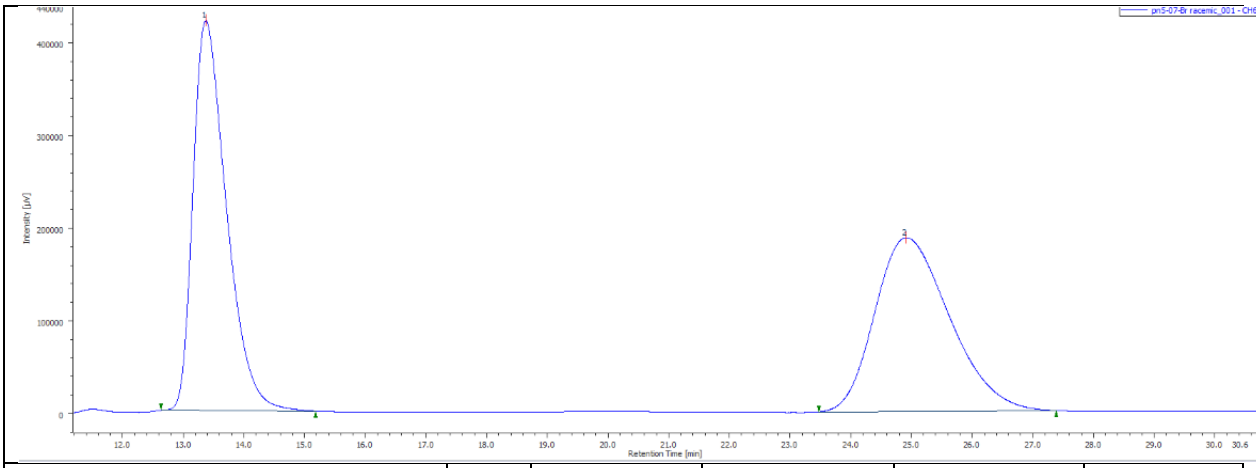
	#	tR [min]	AREA	HEIGHT	AREA %
 **31aB, 38% ee**	1	48.727	8583228	185042	68.016
	2	50.667	3853352	84756	30.984

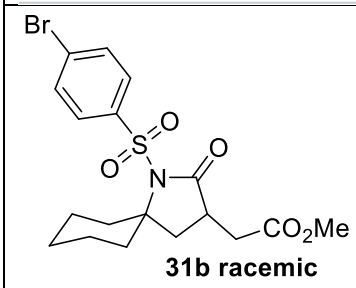


	#	tR [min]	AREA	HEIGHT	AREA %
 **31aC racemic**	1	64.403	6334994	115541	
	2	66.560	6015913	106000	



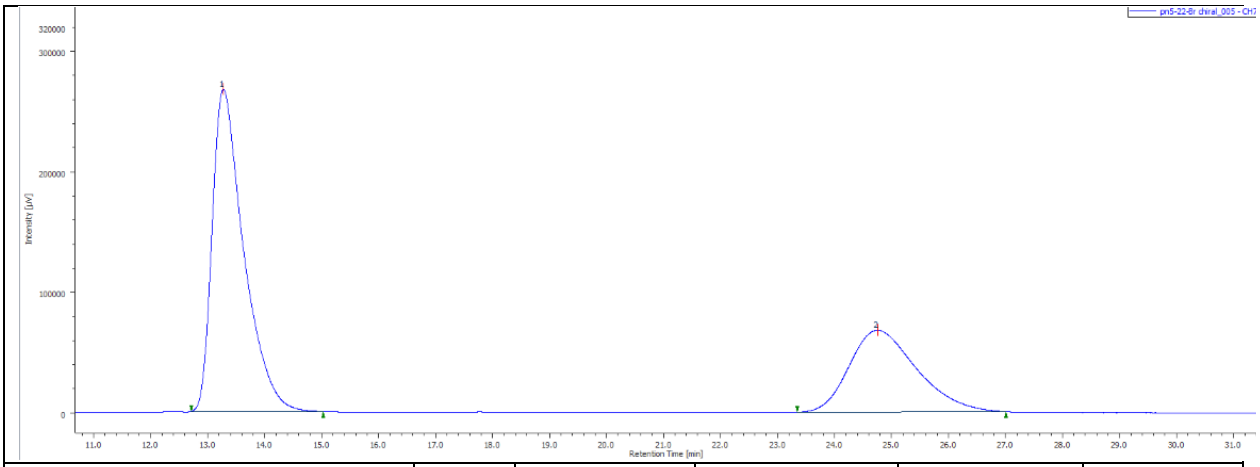
	#	tR [min]	AREA	HEIGHT	AREA %
 **31aC, 40% ee**	1	94.697	110777685	1205262	70.233
	2	98.113	46951166	511098	29.767

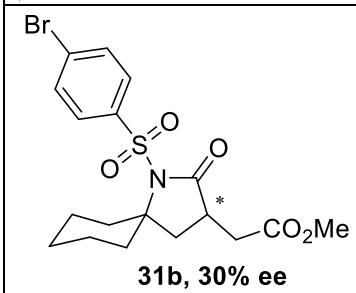




31b racemic

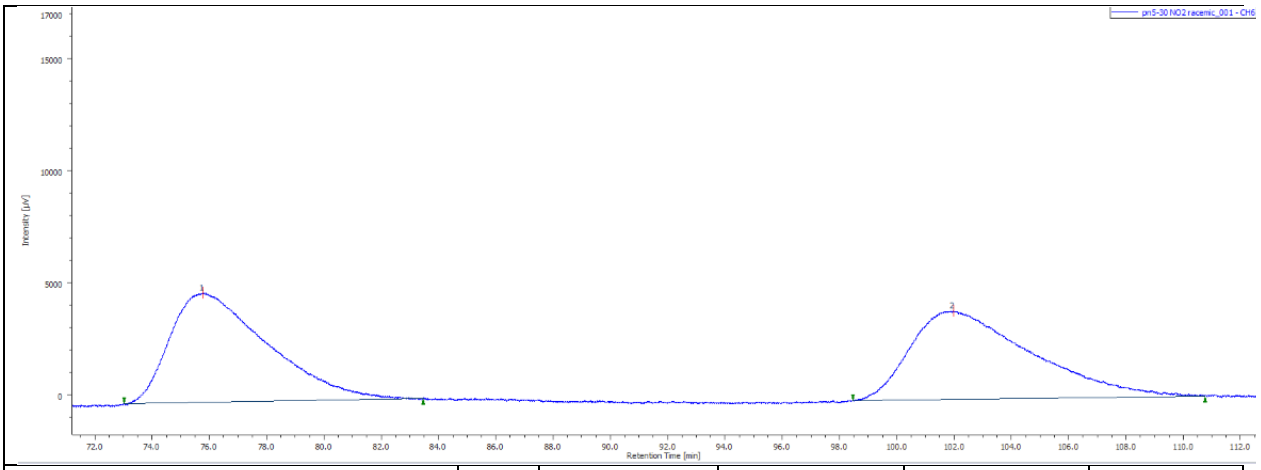
#	tR [min]	AREA	HEIGHT	AREA %
1	37.477	2776903	28943	49.708
2	44.857	2809514	24699	50.292

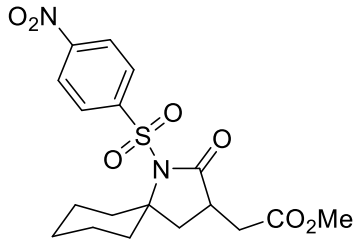




31b, 30% ee

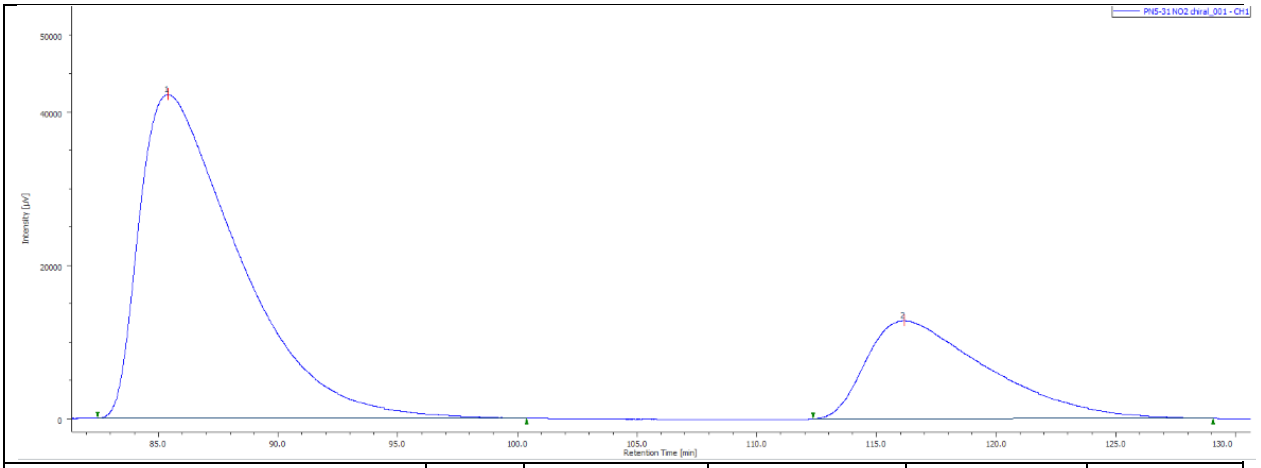
#	tR [min]	AREA	HEIGHT	AREA %
1	37.990	28828413	264777	75.463
2	45.820	9373622	71861	24.537

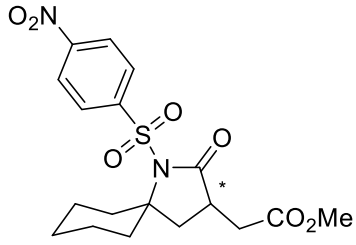




31c racemic

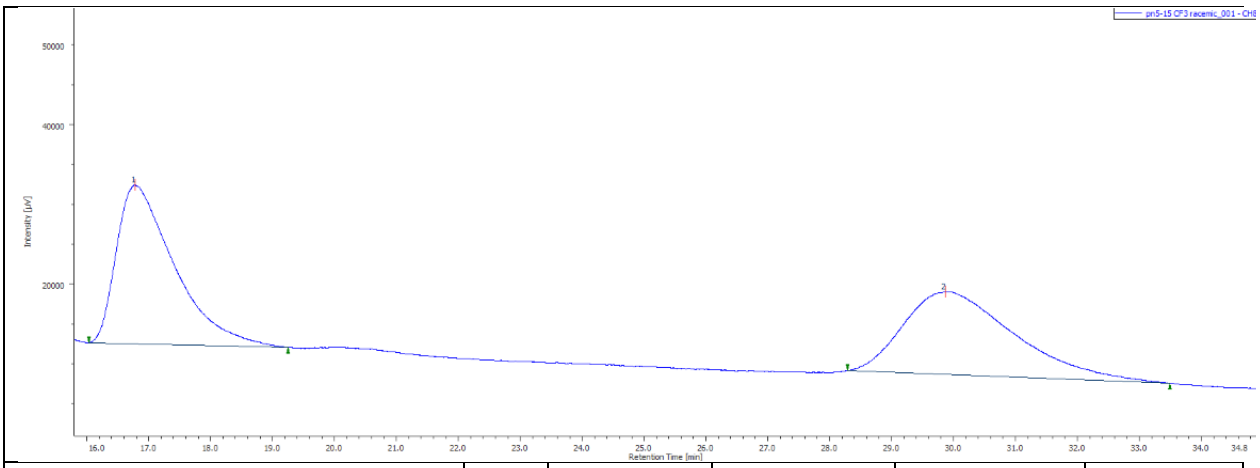
#	tR [min]	AREA	HEIGHT	AREA %
1	75.780	1146548	4885	49.882
2	101.960	1151983	1949	50.118

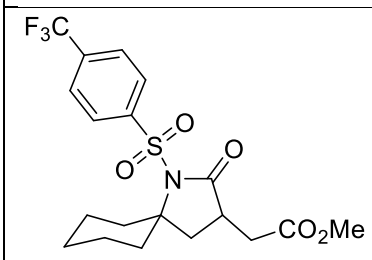




31c, 46% ee

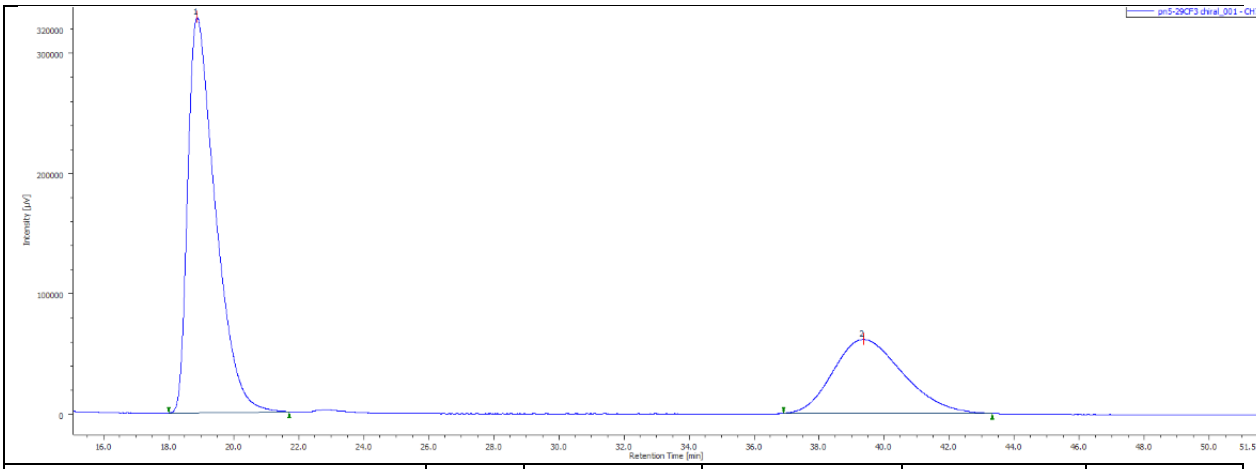
#	tR [min]	AREA	HEIGHT	AREA %
1	85.392	12162887	42111	73.024
2	116.142	4493133	12748	26.976

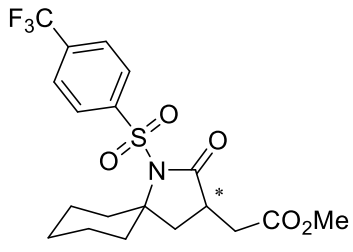




31d racemic

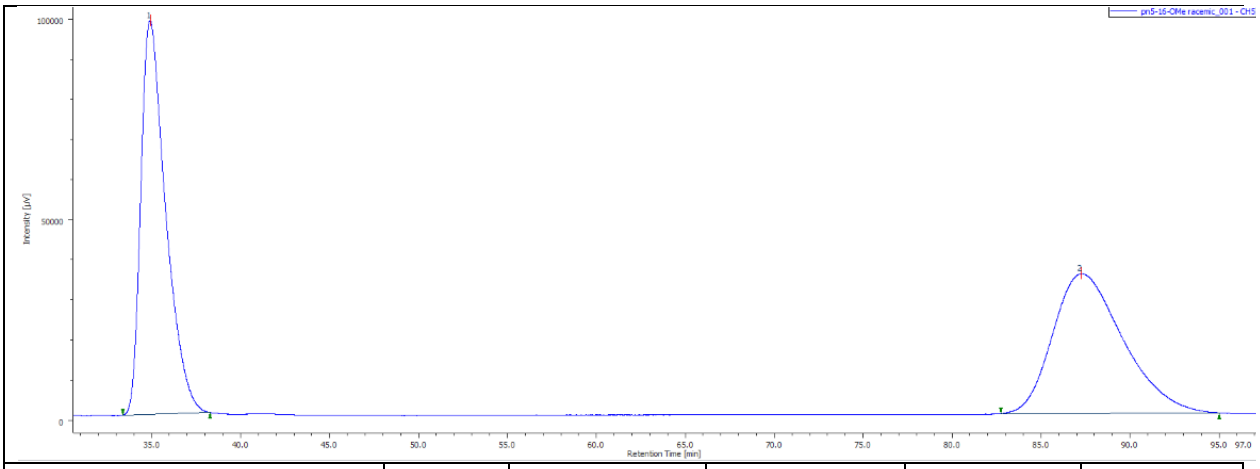
#	tR [min]	AREA	HEIGHT	AREA %
1	16.773	1285432	19842	50.045
2	29.860	1283122	10340	49.955

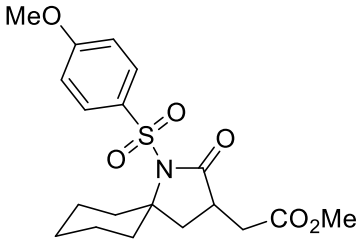


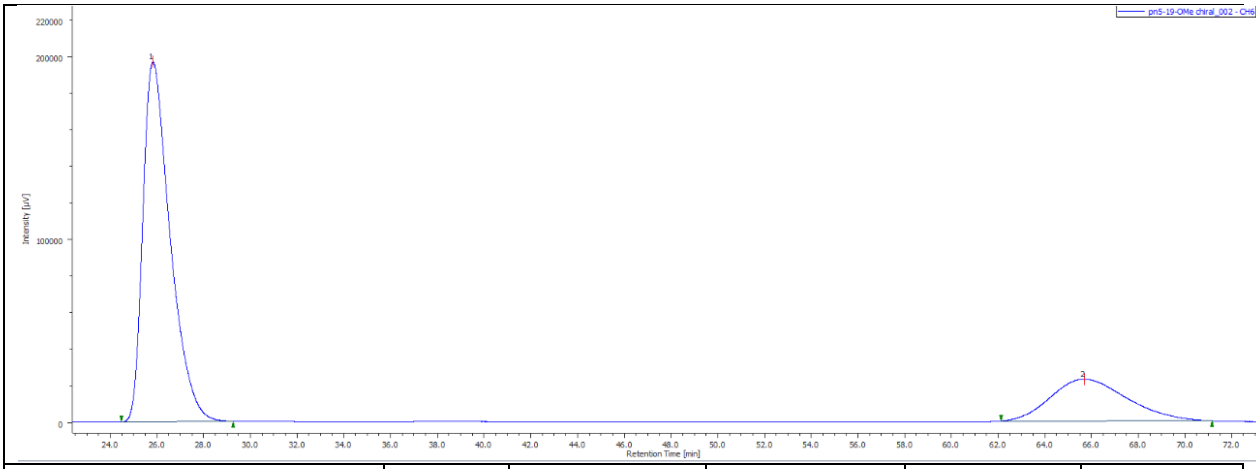


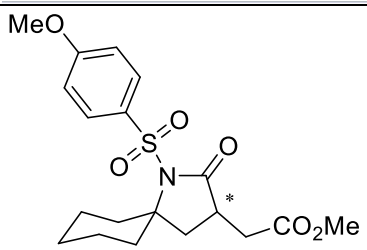
31d, 36% ee

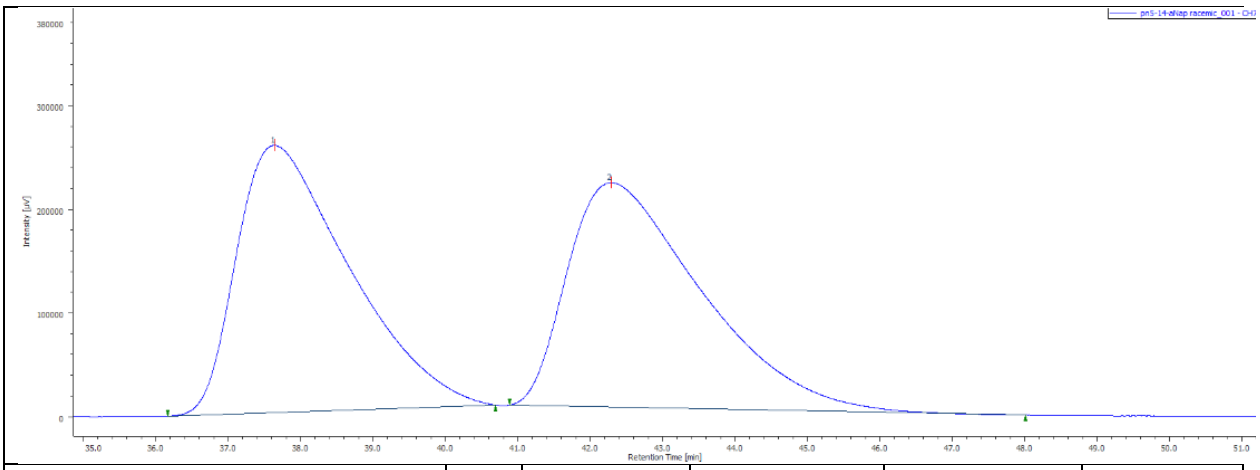
#	tR [min]	AREA	HEIGHT	AREA %
1	18.877	19376936	328091	67.892
2	39.360	9163863	61449	32.108

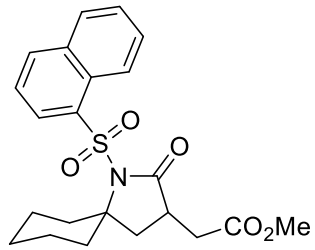


 **31e racemic**	#	tR [min]	AREA	HEIGHT	AREA %
	1	34.910	9523690	98026	50.032
	2	87.233	9511501	34732	49.968



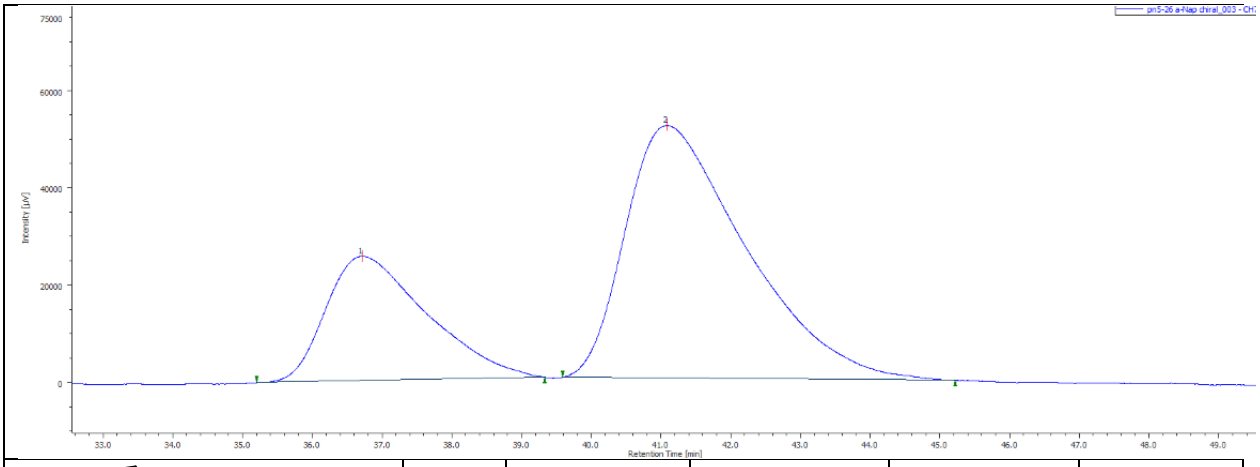
 **31e, 51% ee**	#	tR [min]	AREA	HEIGHT	AREA %
	1	25.830	15910287	196654	75.482
	2	65.677	5167828	22778	24.518

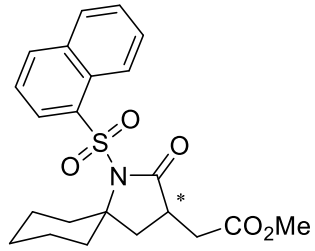




31f racemic

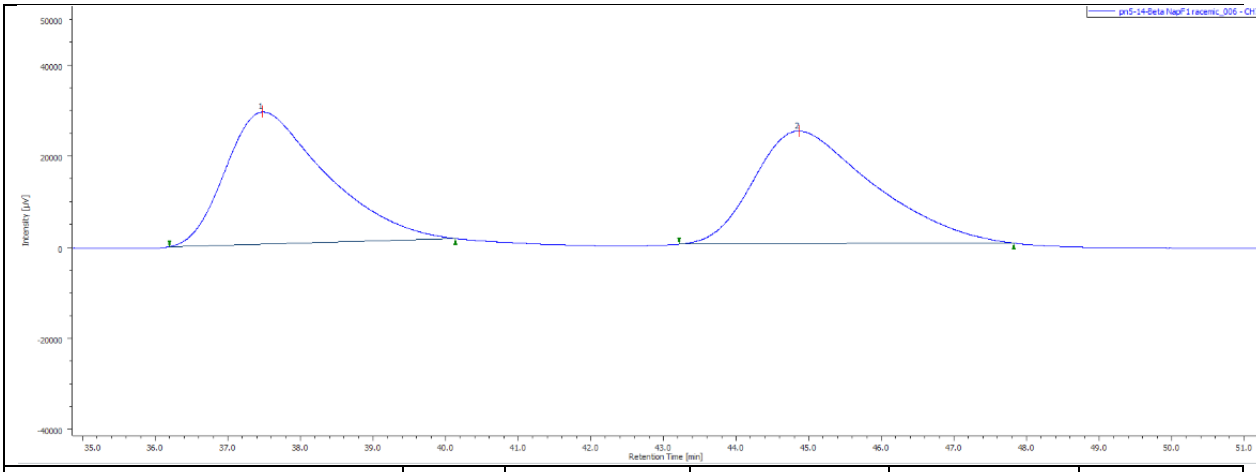
#	tR [min]	AREA	HEIGHT	AREA %
1	38.687	9163020	84778	50.095
2	43.543	9128314	71020	49.905

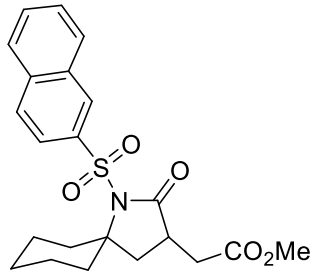




31f, 42% ee

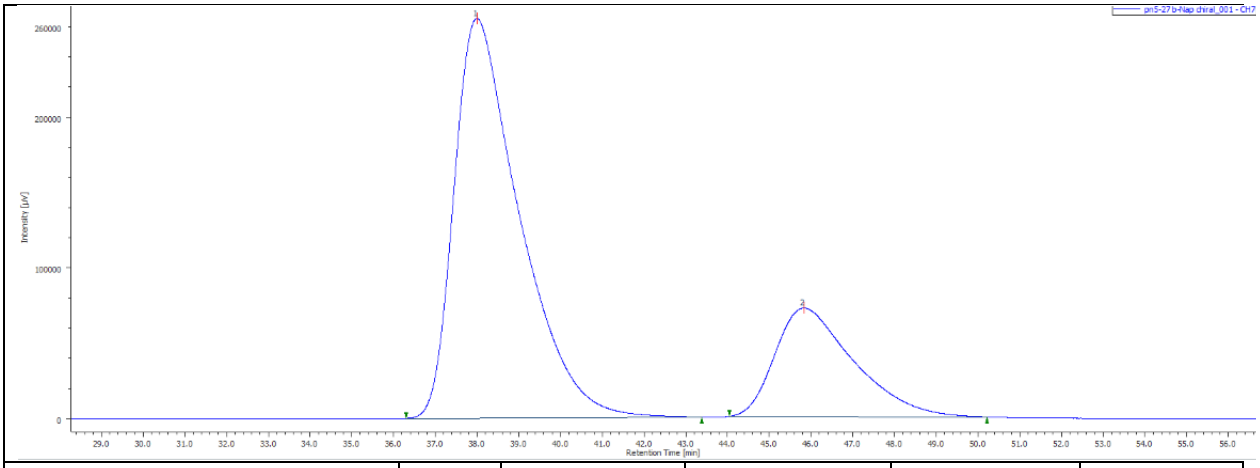
#	tR [min]	AREA	HEIGHT	AREA %
1	36.717	2555608	25515	29.159
2	41.083	6208686	51819	70.841

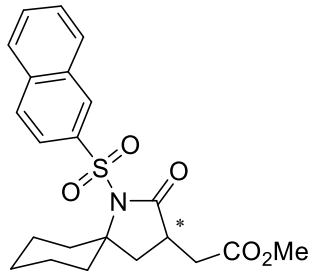




31g racemic

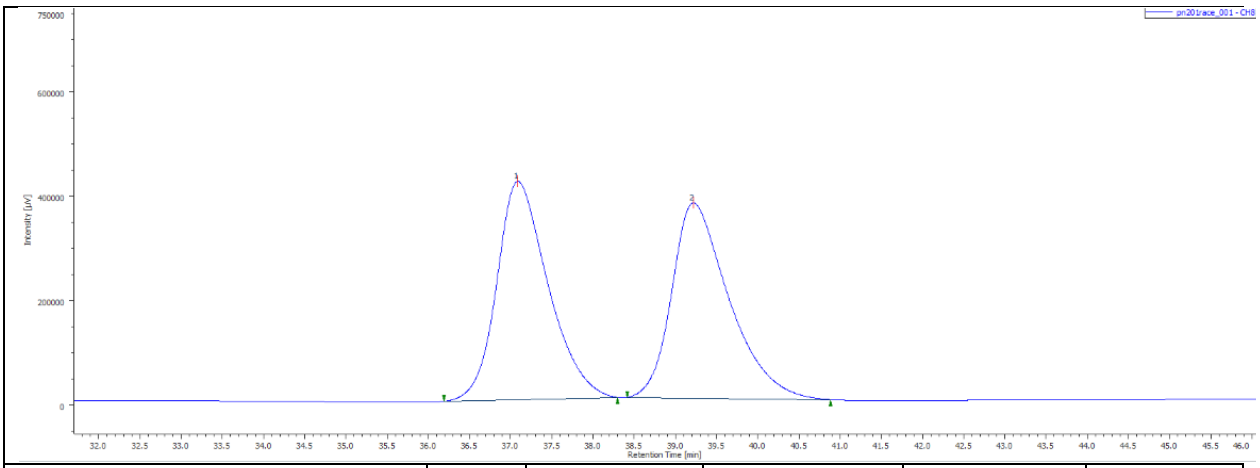
#	tR [min]	AREA	HEIGHT	AREA %
1	34.477	2776903	28943	49.708
2	44.857	2809514	24699	50.292

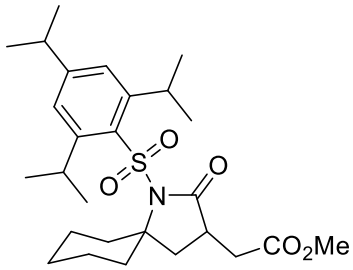




31g, 51% ee

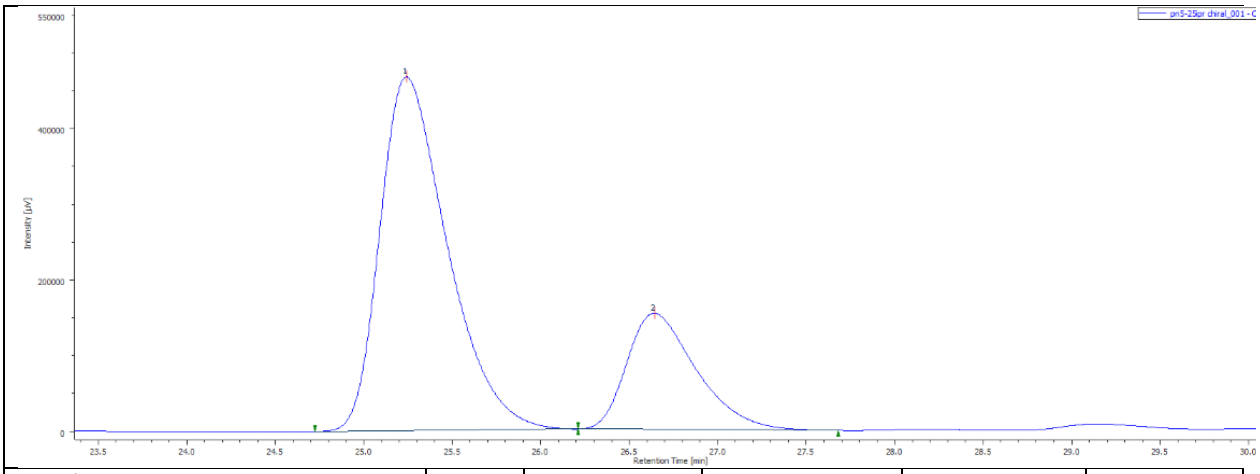
#	tR [min]	AREA	HEIGHT	AREA %
1	37.990	28828413	264777	75.463
2	45.820	9373622	71861	24.537

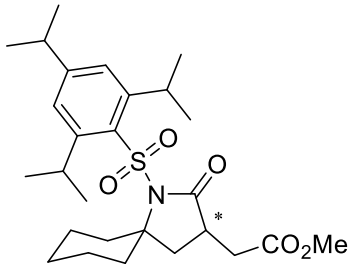




31h racemic

#	tR [min]	AREA	HEIGHT	AREA %
1	24.960	12321610	47641	50.165
2	26.327	12240675	443334	49.835

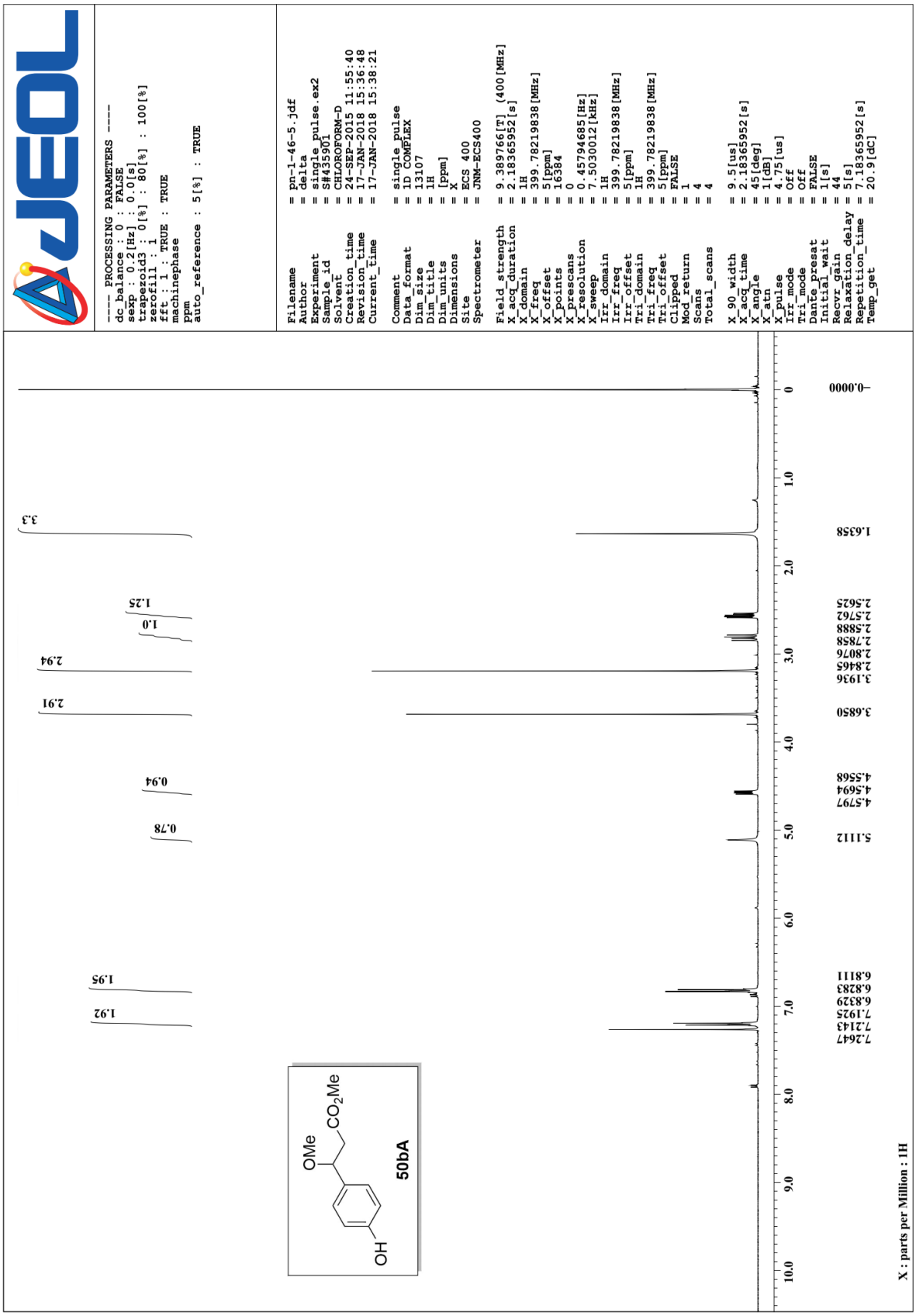


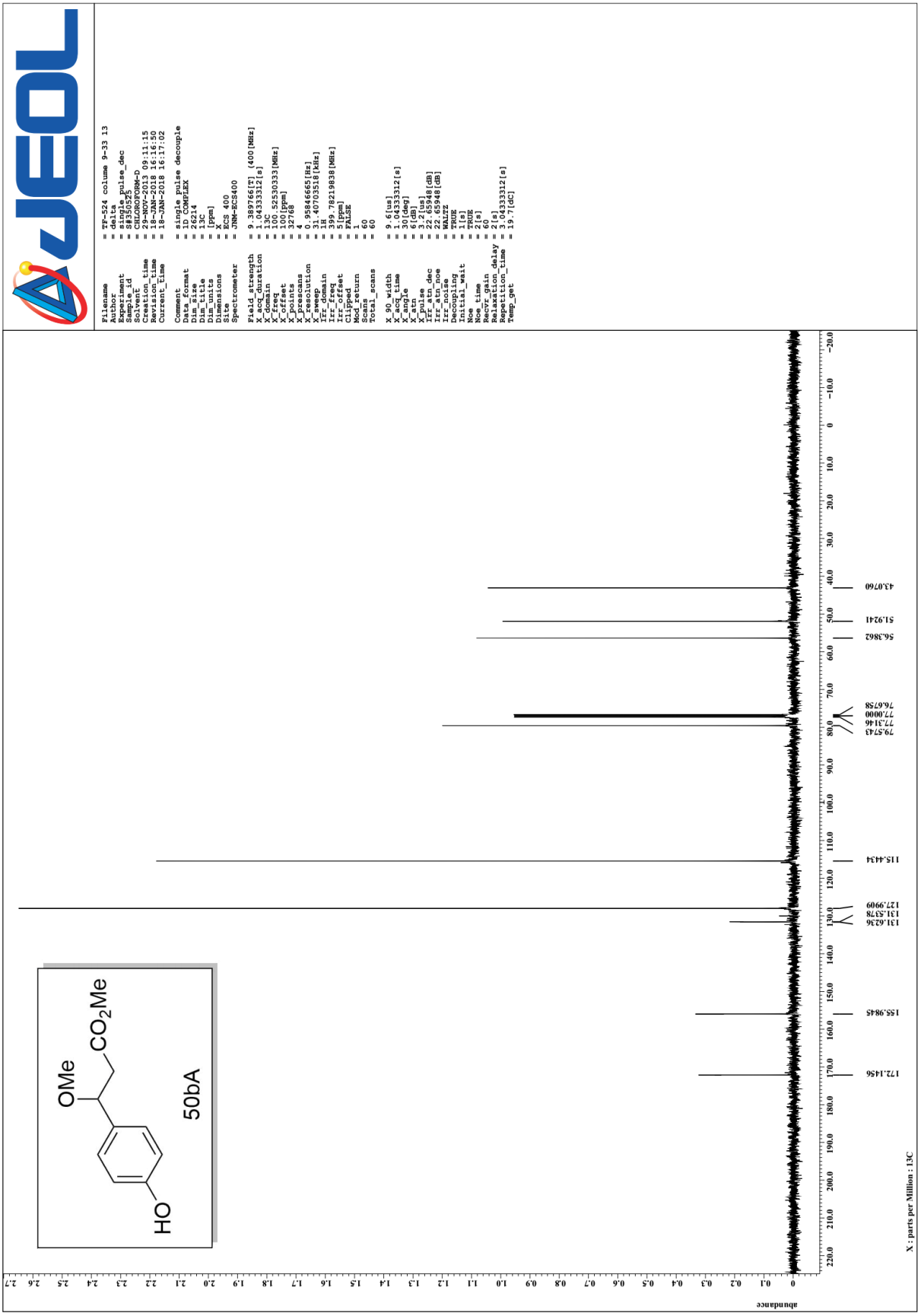


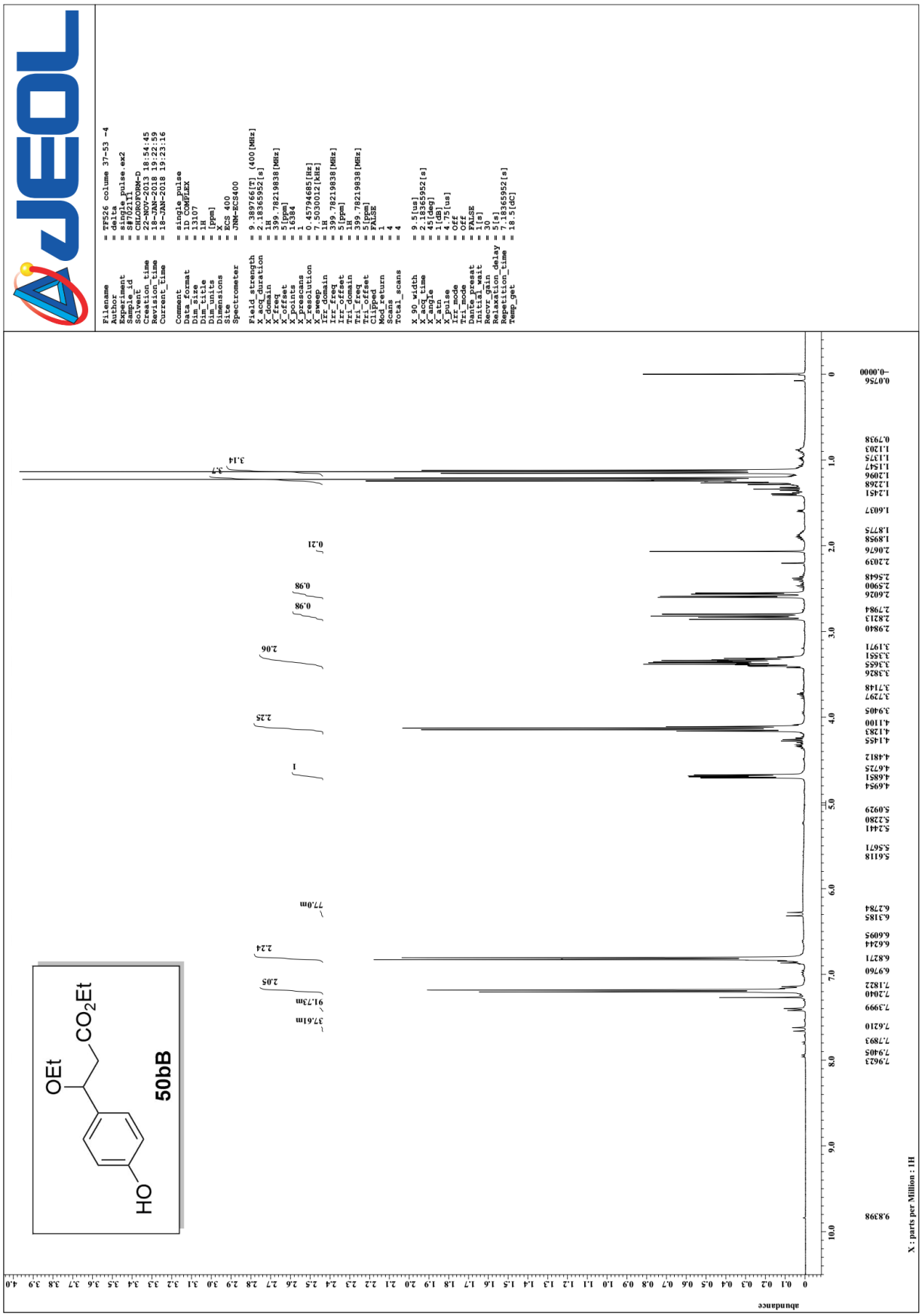
31h, 50% ee

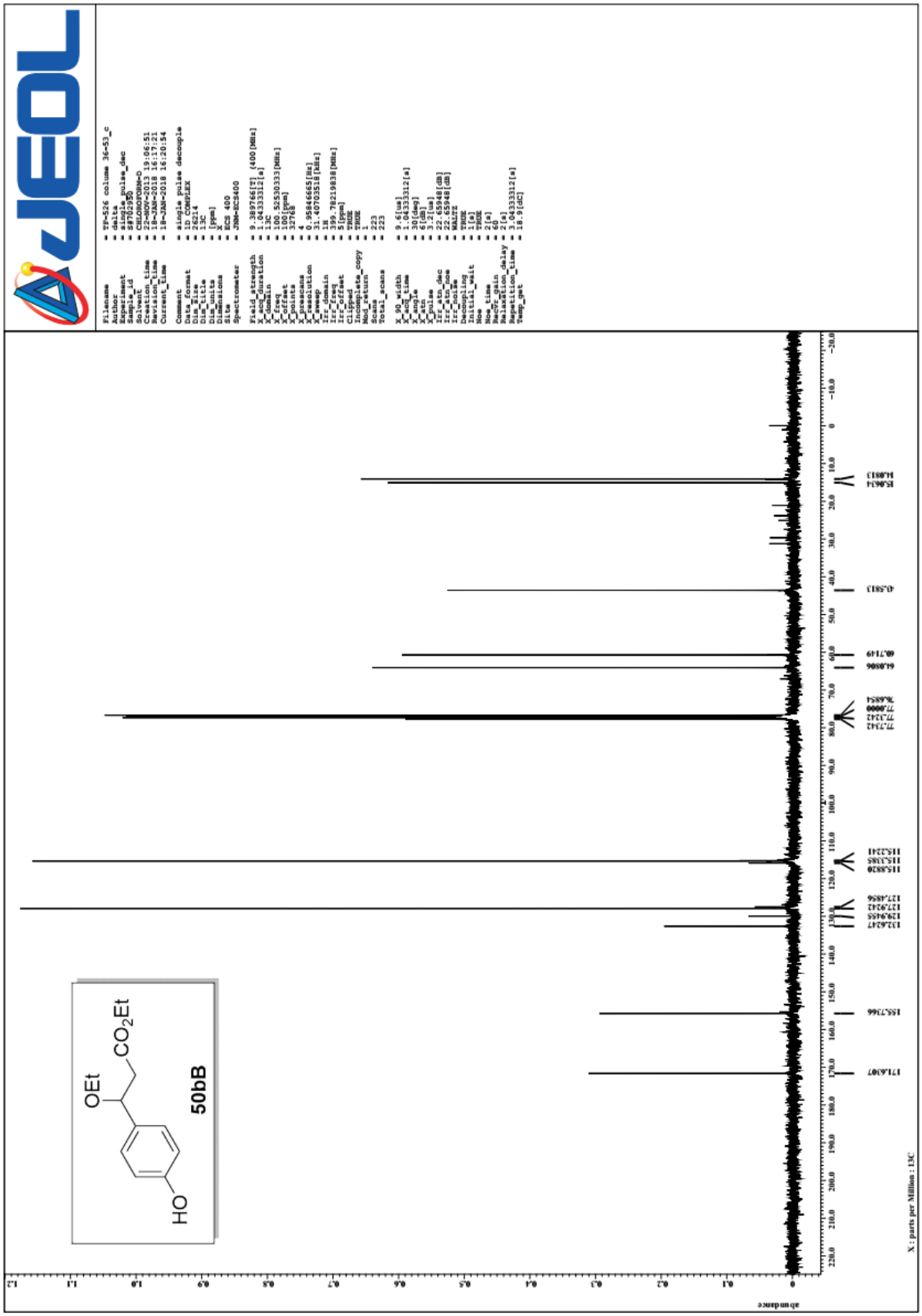
#	tR [min]	AREA	HEIGHT	AREA %
1	25.240	12355570	466839	74.268
2	26.640	4165786	153397	24.732

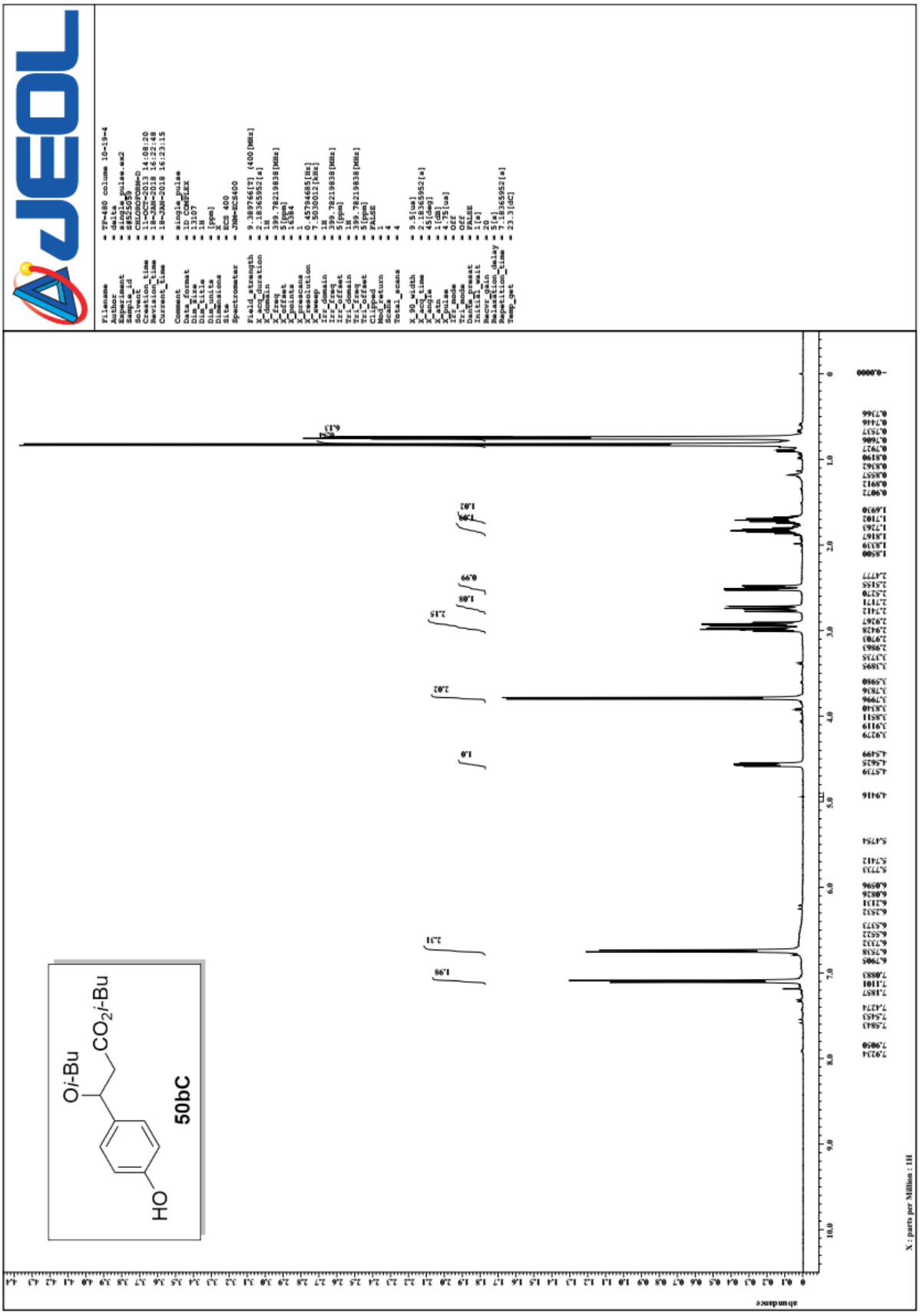
3) ^{1}H and ^{13}C NMR spectrums of the 3-(hydroxyphenyl)-3-methoxypropanoic acid esters **50bA**-**50bF**, **50cA**, **50dA**, and **50Aa**.

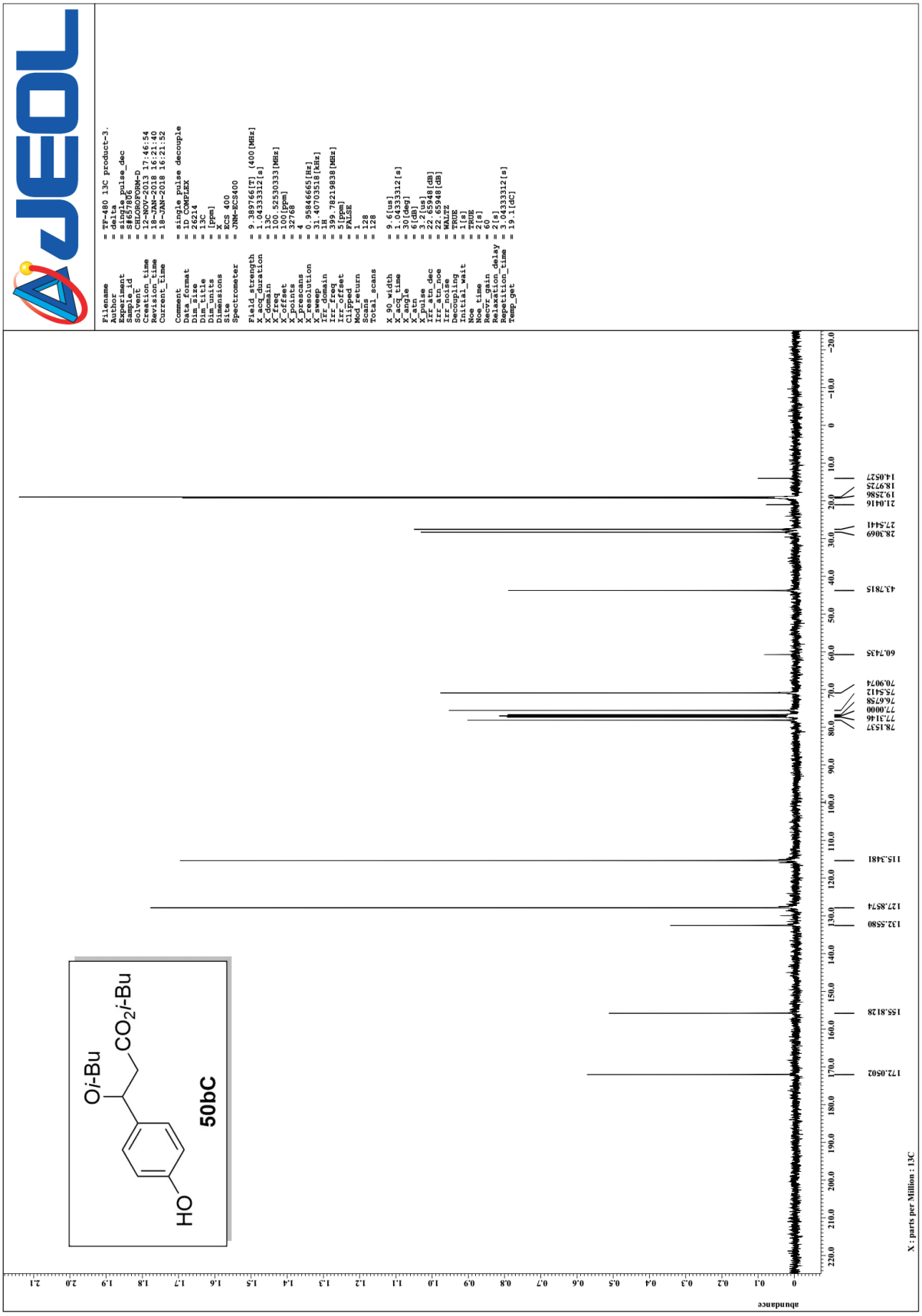


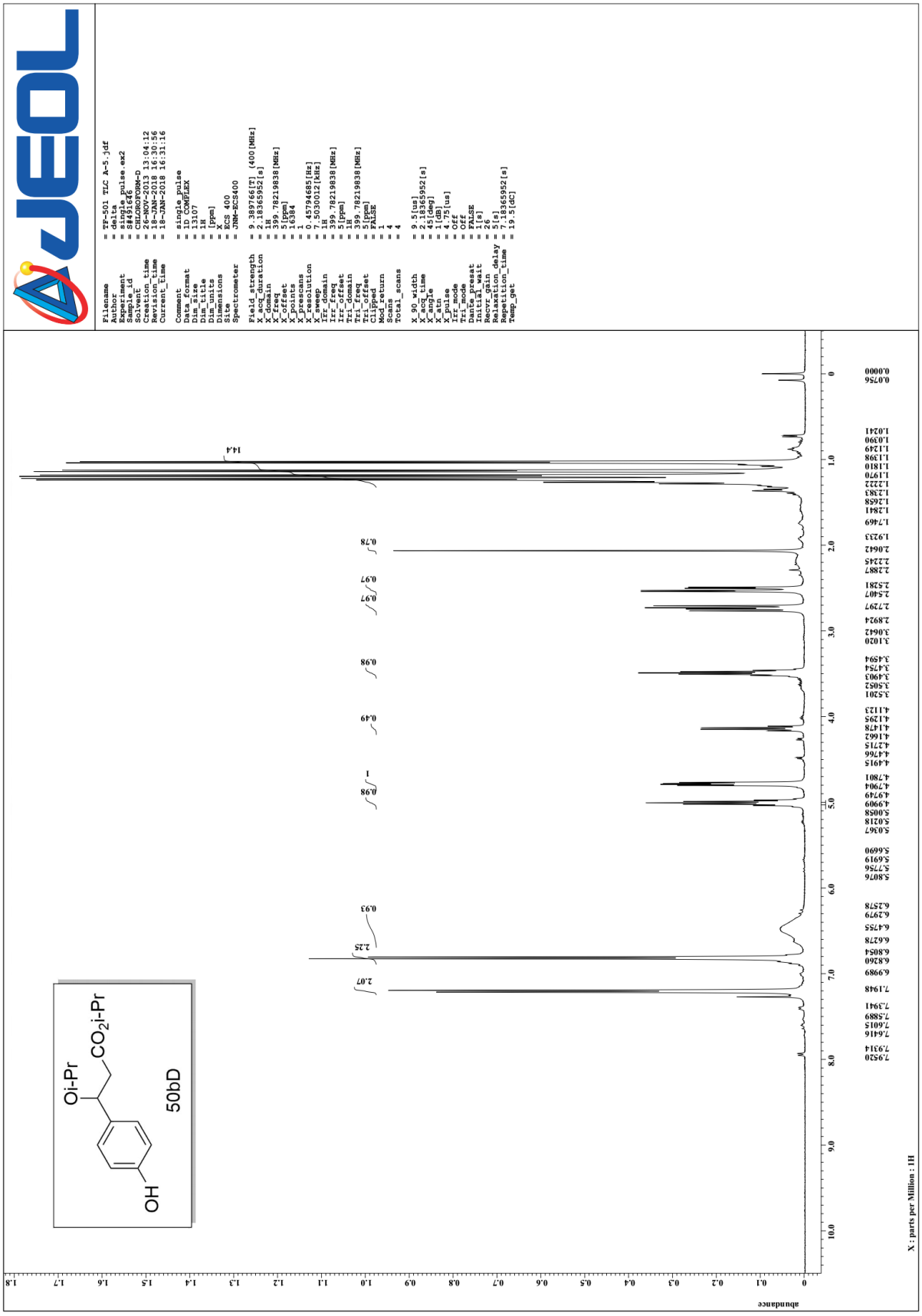

JEOL
Filename = TF-524 colume 9-33 13
Author = delta
Experiment = single_pulse_dec
Sample_id = SH350525
Solvent = CDCl3-ROOM-D
Creation_time = 29-NOV-2013 09:11:15
Revision_time = 18-JAN-2018 16:16:50
Current_time = 18-JAN-2018 16:17:02
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
IFr_domain = 1H
Ifr_freq = 399.78219838[MHz]
Ifr_offset = 4.5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 60
Total_scans = 60
X_90_width = 9.6[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 3.2[us]
Ifr_atn_dec = 22.65948[dB]
Ifr_atn_noe = 22.65948[dB]
Ifr_coupling = 400.1[MHz]
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 19.7[dC]
OMe
CO2Me
HO
50bA
172.1456
155.9845
131.6236
131.5378
127.9909
115.4434
79.5743
77.3146
77.0000
76.6758
56.3862
51.9241
43.0760
abundance
X : parts per Million : 13C

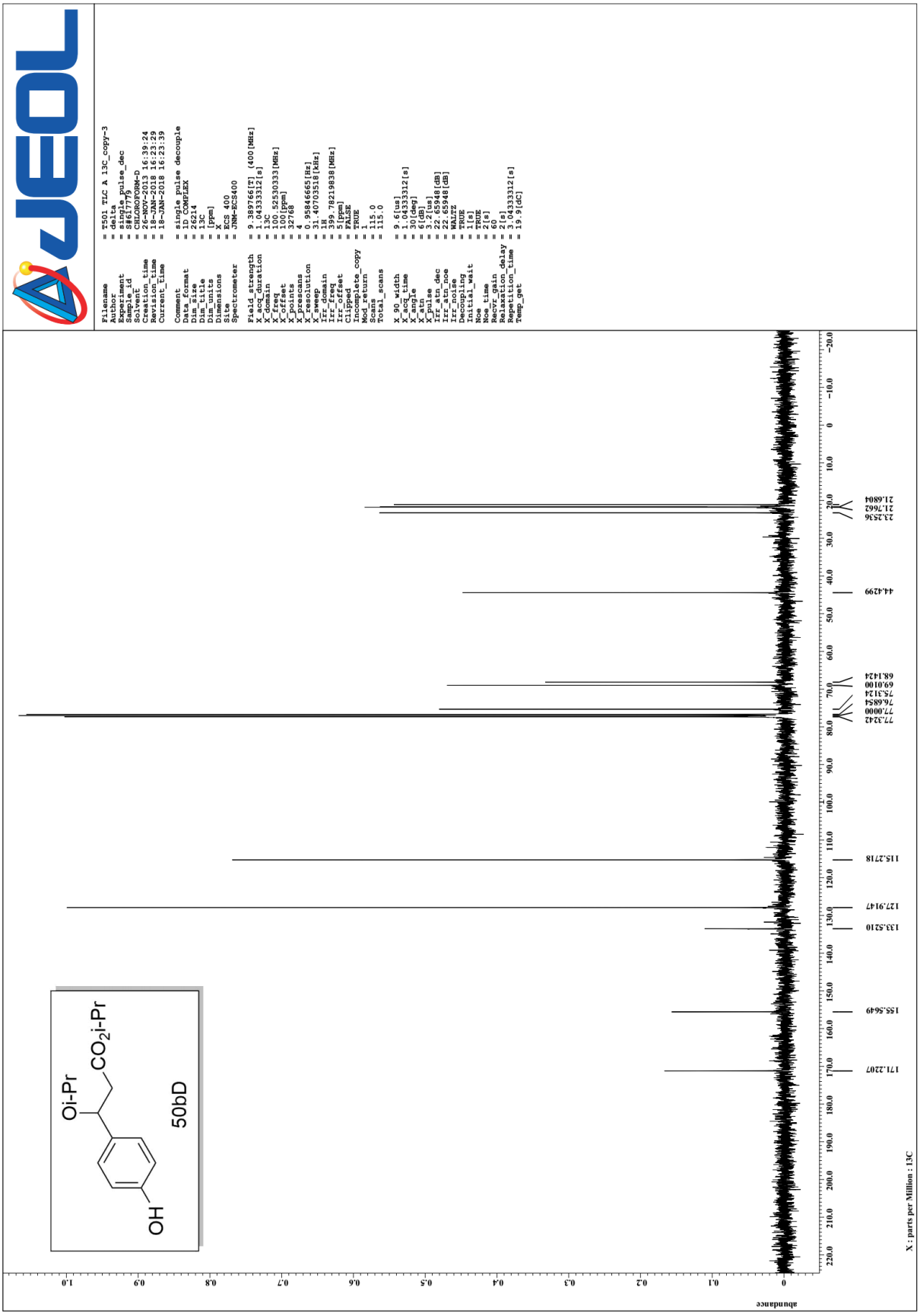

JEOL
Filename = TF526 colume 37-53 -4
Author = data
Experiment = single_pulse.ex2
Sample_id = SH702111
Solvent = CHLOROFORM-D
Creation_time = 22-NOV-2013 18:54:45
Revision_time = 18-JAN-2018 19:23:39
Current_time = 18-JAN-2018 19:23:16
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 11 077
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = RCS 400
Spectrometer = JNM-RCS400
Field_strength = 9.389766[T] (400[MHz])
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1[dB]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Decpl_preset = FALSE
Initial_wait = 30
Recvr_gain = 5[s]
Relaxation_delay = 7.18365952[s]
Repetition_time = 18.5[dC]
Temp_get = 18.5[dC]
OEt
CO2Et
HO
50bB
abundance
X : parts per Million : 1H

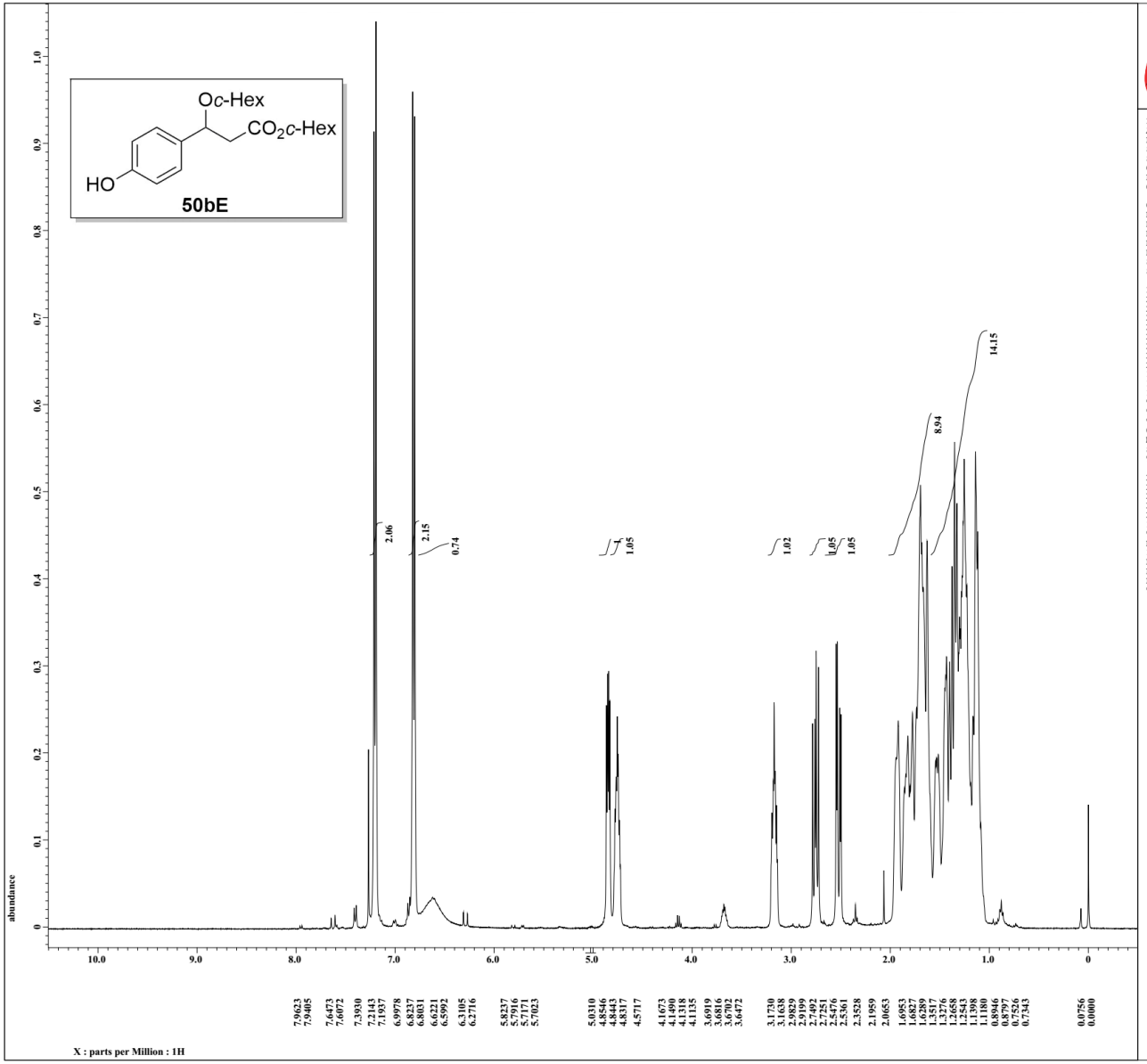

JEOL
OEt
CO2Et
HO
50bB
X : parts per Million : 13C
abundance


JEOL
Filename = TP-480 column 10-19-4
Author = dalia
Experiment = single_pulse.ex2
Sample_id = SHS2505S9
Solvent = CHLOROFORM-D
Creation_time = 11-OCT-2013 14:08:20
Revision_time = 18-JAN-2018 16:22:48
Current_time = 18-JAN-2018 16:23:15
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz])
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.45794685[Hz]
X_sweep = 7.50300012[kHz]
Ifr_domain = 1H
Ifr_freq = 399.78219838[MHz]
Ifr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Cl_pulse = PULSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_offset = 1.5[kHz]
X_pulse = 4.75[us]
Ifr_mode = Off
Tri_mode = Off
Decoupler = PULSE
Initial_wait = 1[s]
Recyc_gain = 20
Relaxation_delay = 5[s]
Repeat_time = 7.18365952[s]
Temp_get = 23.3[dC]
Oi-Bu
CO2i-Bu
HO
50bC
abundance
X : parts per Million : 1H


JEOL
Filename = TF-480 13C product-3.
Author = delta
Experiment = single_pulse_dec
Sample_id = 480 13C
Solvent = CHLOROFORM-D
Creation_time = 12-NOV-2013 17:46:54
Revision_time = 18-JAN-2018 16:21:40
Current_time = 18-JAN-2018 16:21:52
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 32214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.38976[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 128
Total_scans = 128
X_90_width = 9.6[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 3.2[us]
Irr_atn_dec = 22.65948[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 3[s]
Repetition_time = 4.04333312[s]
Temp_get = 19.1[dC]
O/-Bu
CO2/-Bu
HO
50bC
172.0502
155.8128
132.5580
127.8574
115.3481
78.1537
77.3146
77.0000
76.6758
75.5412
70.9074
60.7435
43.7815
28.3069
27.5441
21.0416
19.2586
18.9725
14.0527
abundance
X : parts per Million : 13C


JEOL
Filename = TP-501 TLC A-5.jdf
Author = delia
Experiment = single_pulse.ex2
Sample_id = S#451c46
Solvent = CHLOROFORM-D
Creation_time = 26-NOV-2013 13:04:12
Revision_time = 18-JAN-2018 16:30:56
Current_time = 18-JAN-2018 16:31:16
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_Preturn = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1.0[dB]
X_pulse = 7.5[us]
Irr_mode = Off
Tri_mode = Off
Decpl_presat = FALSE
Init_wait = 1.0[s]
Recvr_gain = 26
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 19.9[dC]
Oi-Pr
CO2i-Pr
OH
50bD
abundance
X : parts per Million : 1H


Filename = T501_TIC A 13C_copy-3
Author = delta
Experiment = single_pulse_dec
Sample_id = SH617779
Solvent = CHLOROFORM-D
Creation_time = 26-NOV-2013 16:39:24
Revision_time = 18-JAN-2018 16:23:29
Current_time = 18-JAN-2018 16:23:39
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 525530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Ifr_domain = 1H
Ifr_freq = 399.78219838[MHz]
Ifr_offset = 5[ppm]
Clipped = FALSE
Incomplete_copy = TRUE
Mod_return = 1
Scans = 115.0
Total_scans = 115.0
X_90_width = 9.6[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 3.2[us]
Ifr_atn_dec = 22.65948[dB]
Ifr_atn_one = 22.65948[dB]
Ifr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Mode = PGSE
Noe_time = 2[s]
RecVr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_set = 19.9[dC]
Oi-Pr
CO2i-Pr
OH
50bD
171.2207
155.5649
133.5210
127.9147
115.2718
77.2342
77.0000
76.6854
75.3124
69.0100
68.1424
44.4299
23.2536
21.7662
21.6804
abundance
X : parts per Million : 13C

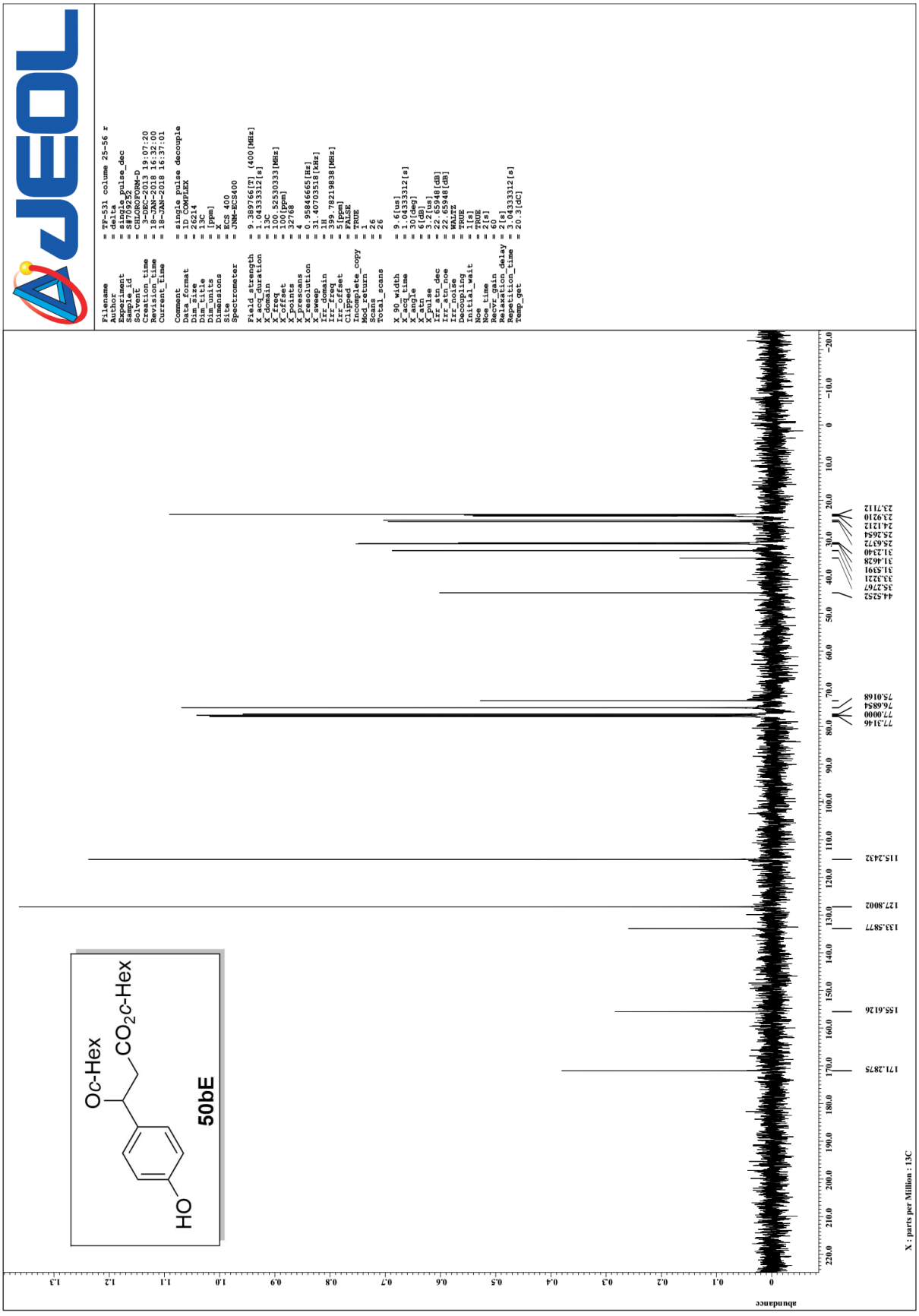


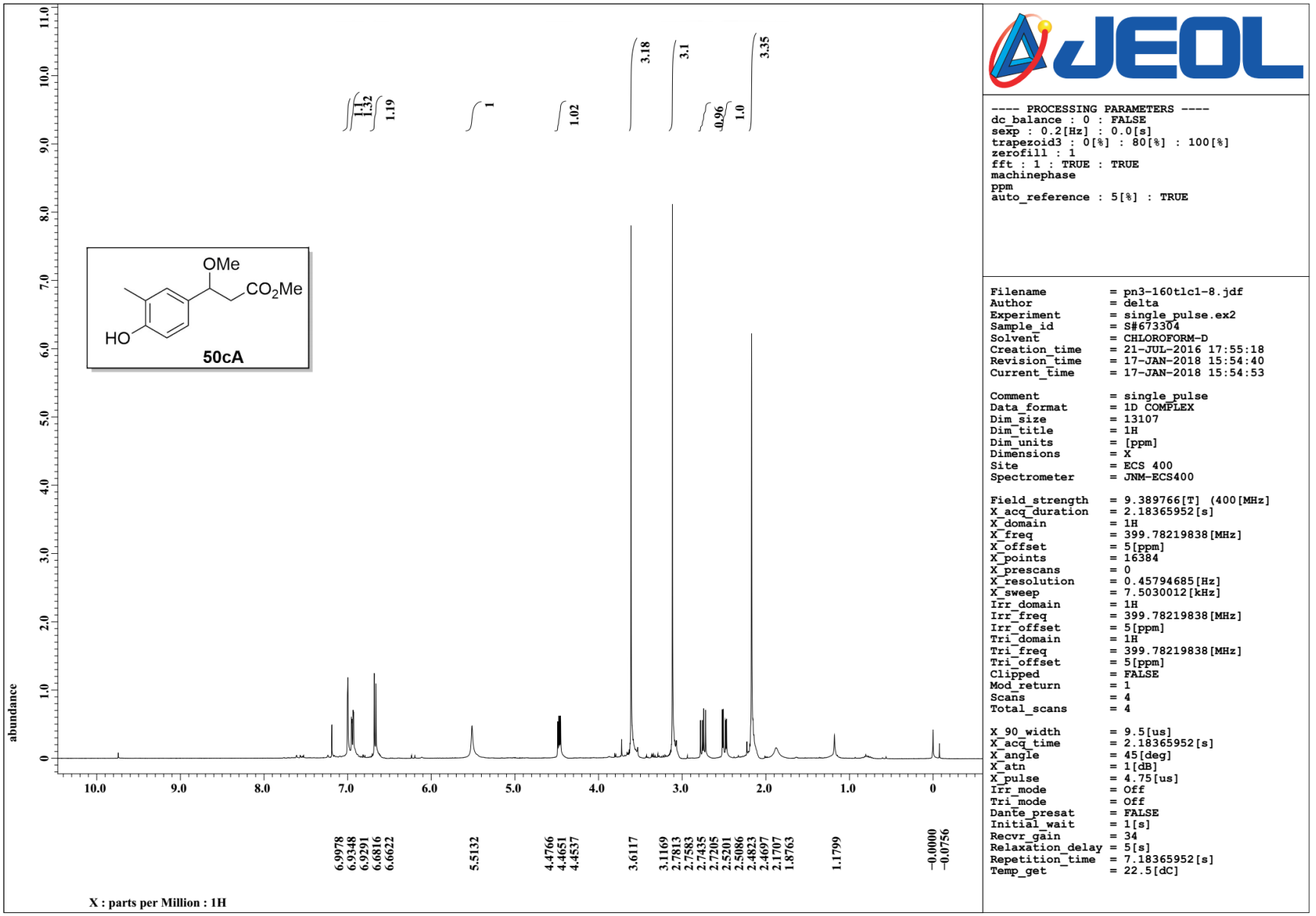
```
Filename          = TF-531 colume 25-56-4
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = S#707772
Solvent           = CHLOROFORM-D
Creation_time     =  3-DEC-2013 19:04:52
Revision_time     = 18-JAN-2018 16:38:11
Current_time      = 18-JAN-2018 16:38:31

Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 2.18365952[s]
X_domain          = 1H
X_freq            = 399.78219838[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 1
X_resolution      = 0.45794685[Hz]
X_sweep           = 7.5030012[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Tri_domain        = 1H
Tri_freq          = 399.78219838[MHz]
Tri_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 4
Total_scans       = 4

X_90_width        = 9.5[us]
X_acq_time        = 2.18365952[s]
X_angle           = 45[deg]
X_atn             = 1[dB]
X_pulse           = 4.75[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 22
Relaxation_delay  = 5[s]
Repetition_time   = 7.18365952[s]
Temp_get          = 20.2[dC]
```


JEOL
Filename = YF-531 colume 25-56 r
Author = data
Experiment = single_pulse_dec
Sample_id = S#709252
Solvent = CHLOROFORM-D
Creation_time = 3-DEC-2018 19:07:20
Revision_time = 18-JAN-2018 16:32:00
Current_time = 18-JAN-2018 16:37:01
Comment = single pulse decouple
Data_format = 1D WORDEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dim_title = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Irr_template_copy = TRUE
Mod_return = 1
Scans = 26
Total_scans = 26
X_90_width = 9.6[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 5[us]
Irr_atn_dec = 22.65948[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recycle_delay = 60[s]
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 20.3[dC]
Oc-Hex
CO2c-Hex
HO
50bE
abundance
X : parts per Million : 13C
171.2875
155.6126
133.5877
127.8002
115.2432
77.3146
77.0000
76.6854
75.0168
44.5252
35.2767
33.3221
31.5291
31.4628
31.1340
25.6372
25.2654
24.1212
23.9210
23.7112



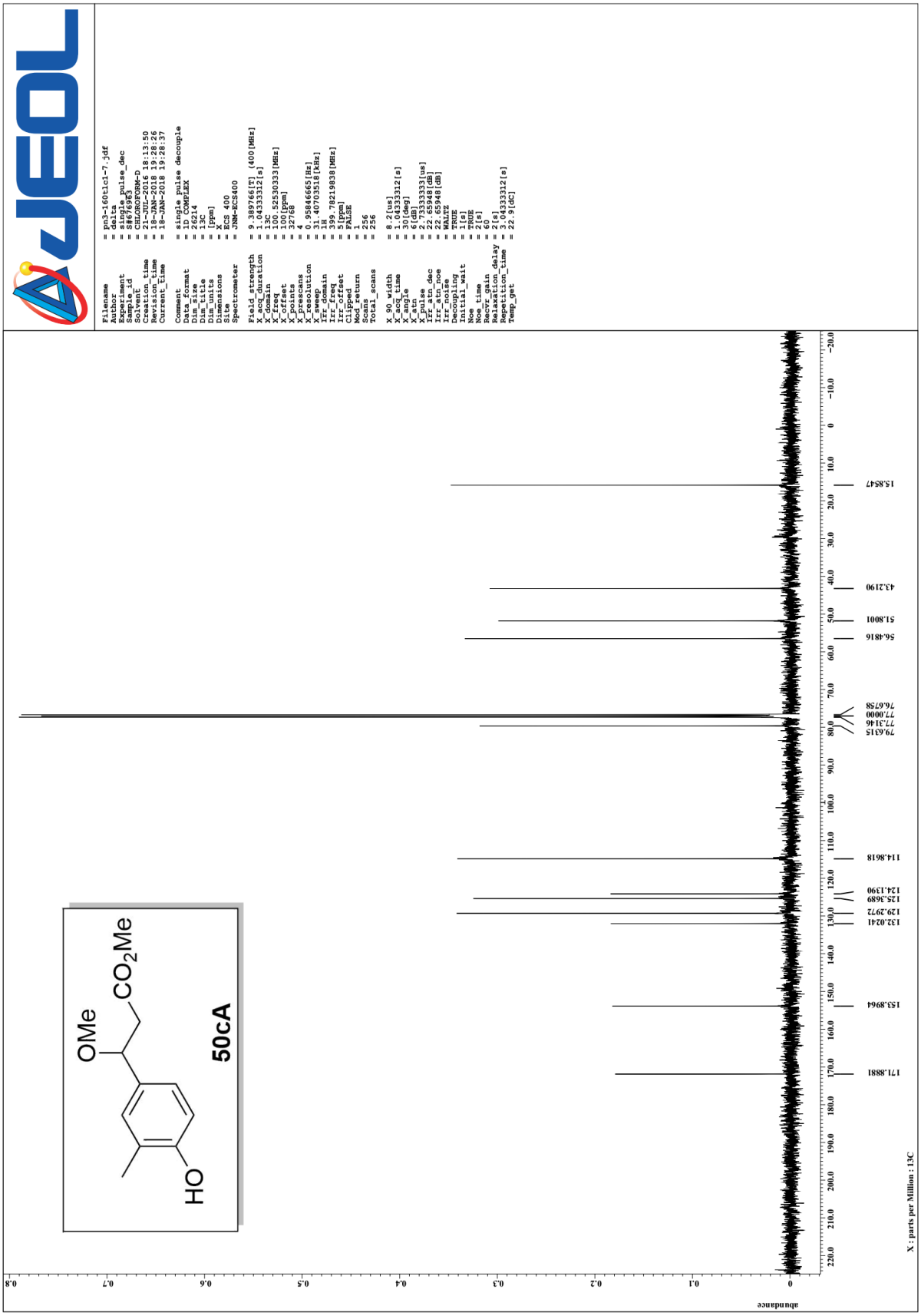

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

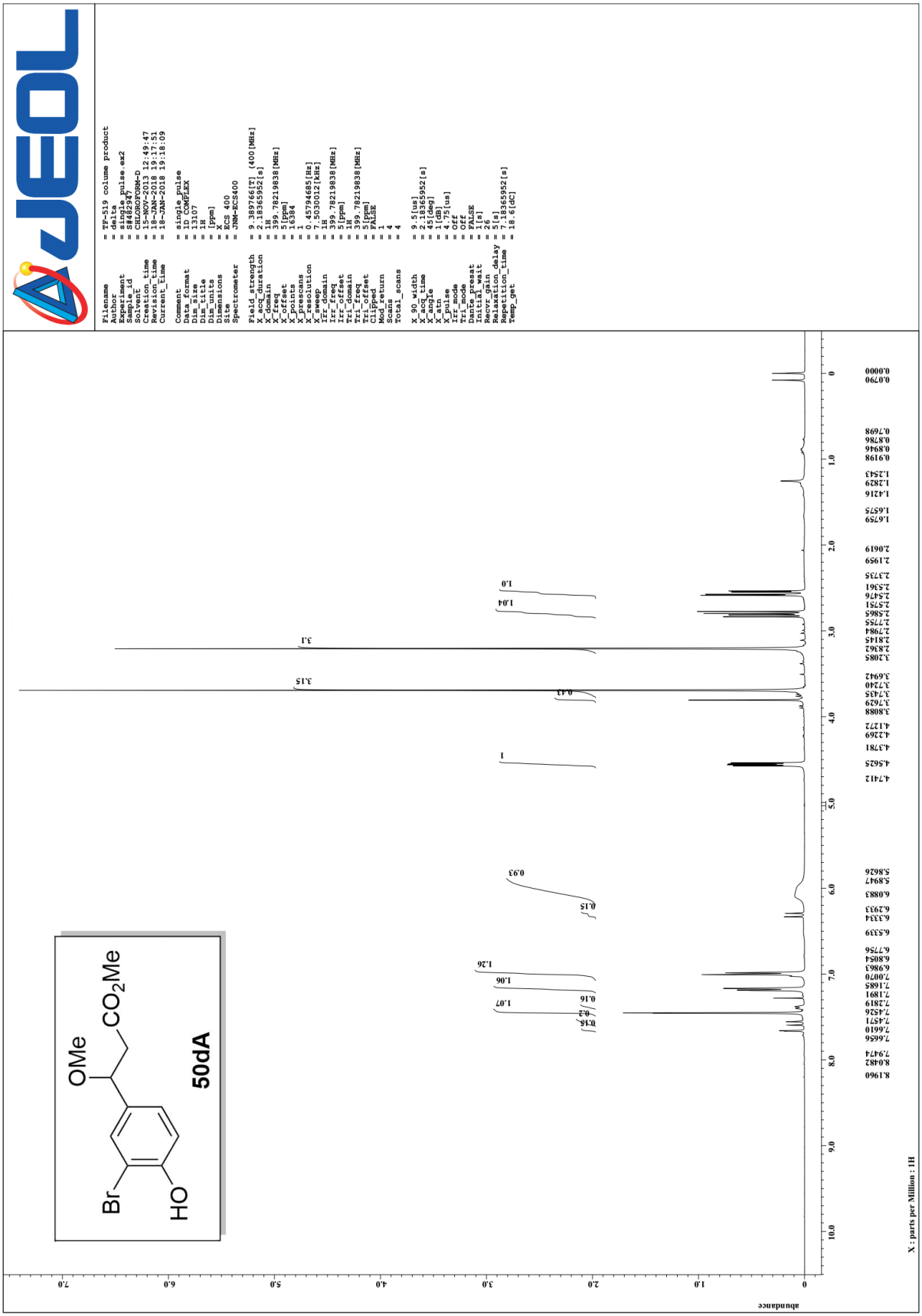
```
Filename          = pn3-160tlc1-8.jdf
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = S#673304
Solvent           = CHLOROFORM-D
Creation_time     = 21-JUL-2016 17:55:18
Revision_time     = 17-JAN-2018 15:54:40
Current_time      = 17-JAN-2018 15:54:53

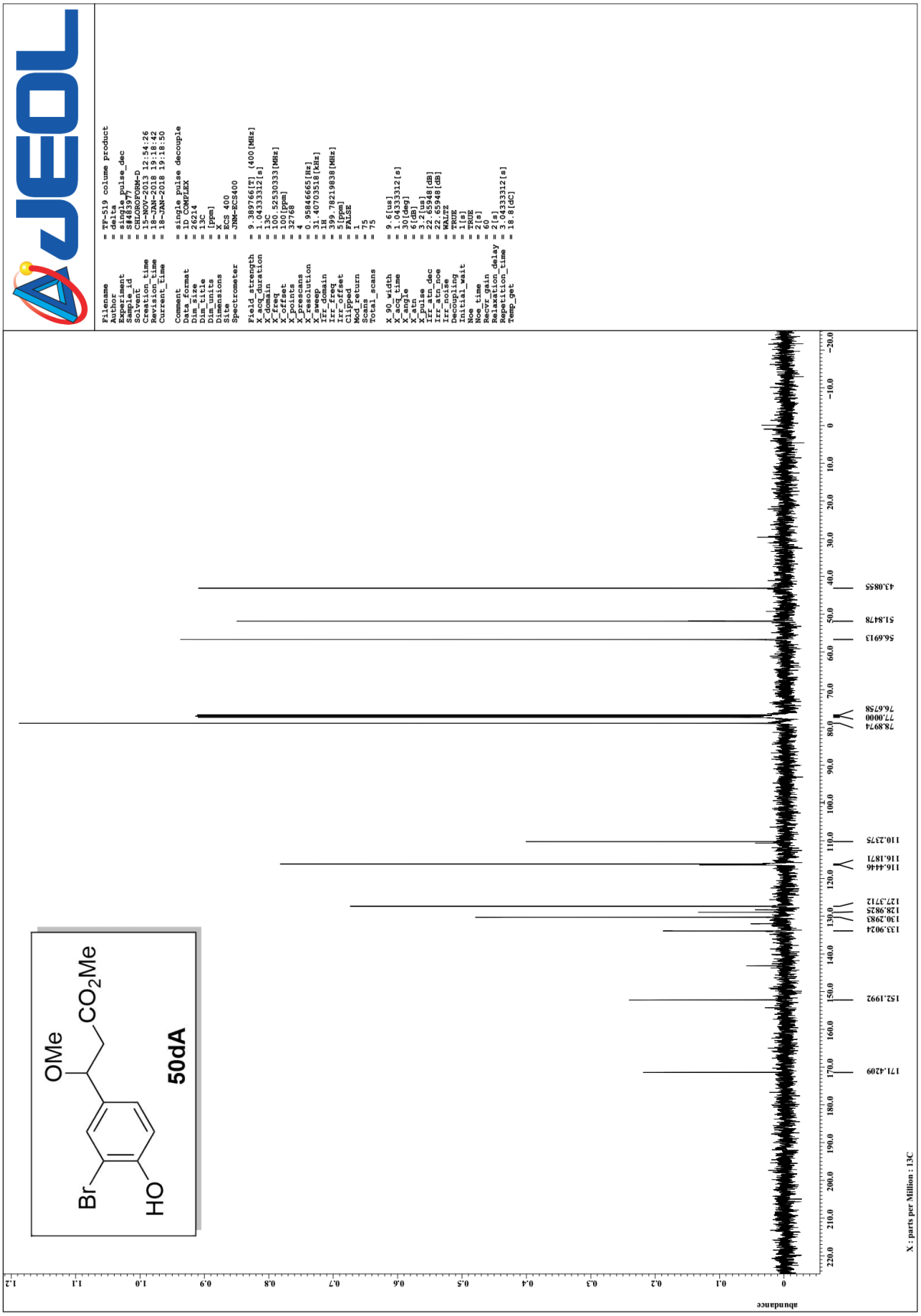
Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

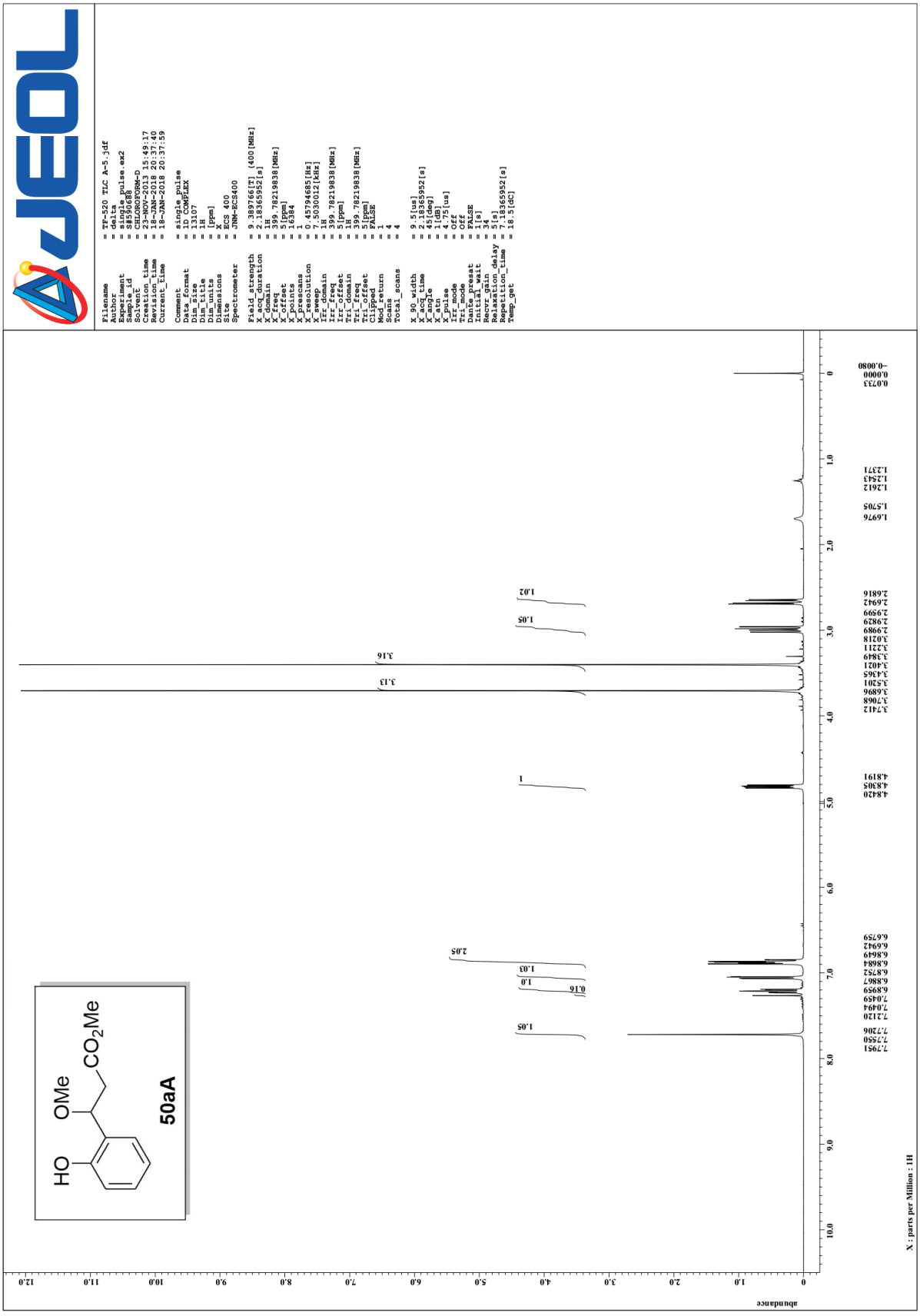
Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 2.18365952[s]
X_domain          = 1H
X_freq            = 399.78219838[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 0
X_resolution      = 0.45794685[Hz]
X_sweep           = 7.5030012[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Tri_domain        = 1H
Tri_freq          = 399.78219838[MHz]
Tri_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 4
Total_scans       = 4

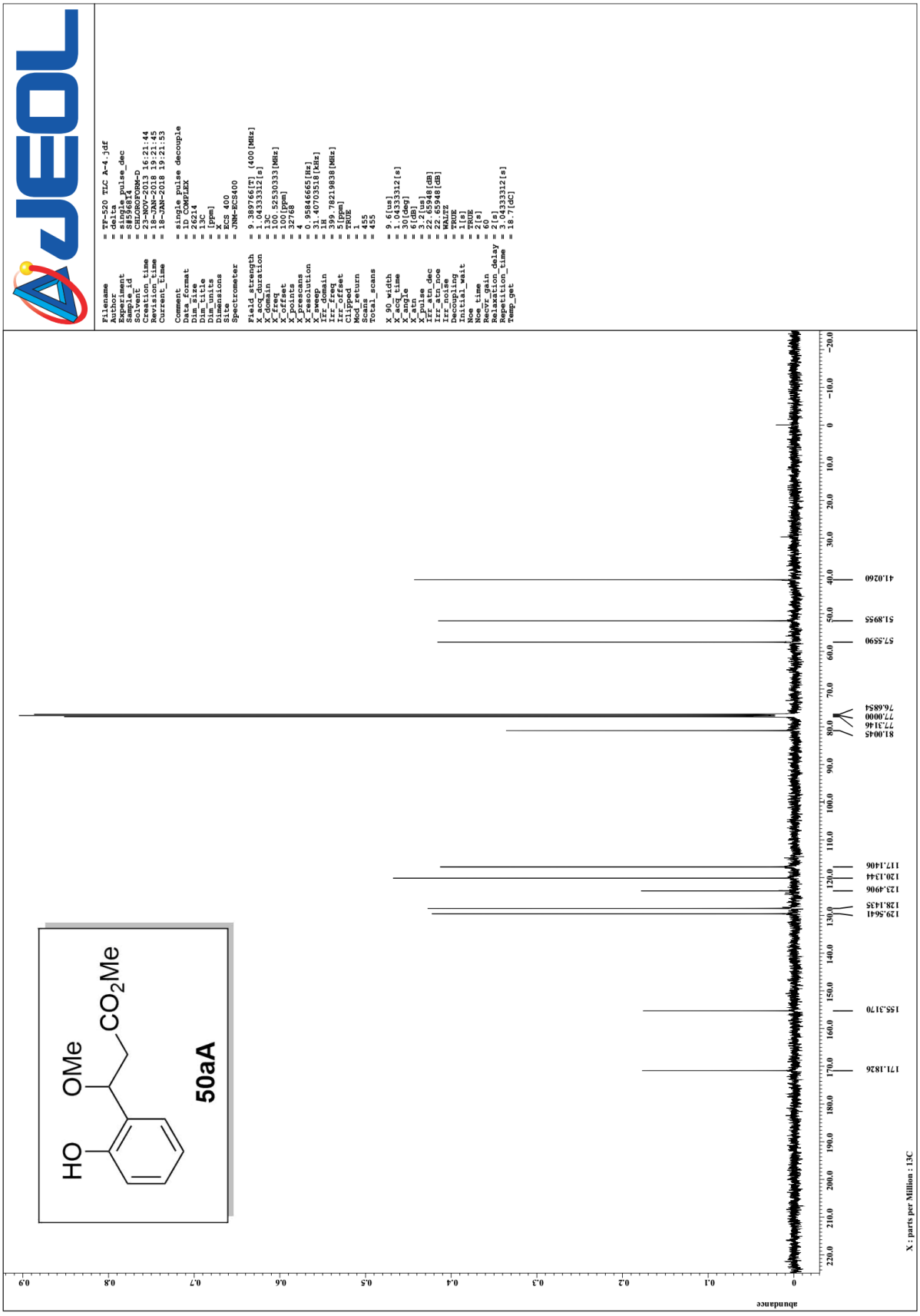
X_90_width        = 9.5[us]
X_acq_time        = 2.18365952[s]
X_angle           = 45[deg]
X_atn             = 1[dB]
X_pulse           = 4.75[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 34
Relaxation_delay  = 5[s]
Repetition_time   = 7.18365952[s]
Temp_get          = 22.5[dC]
```

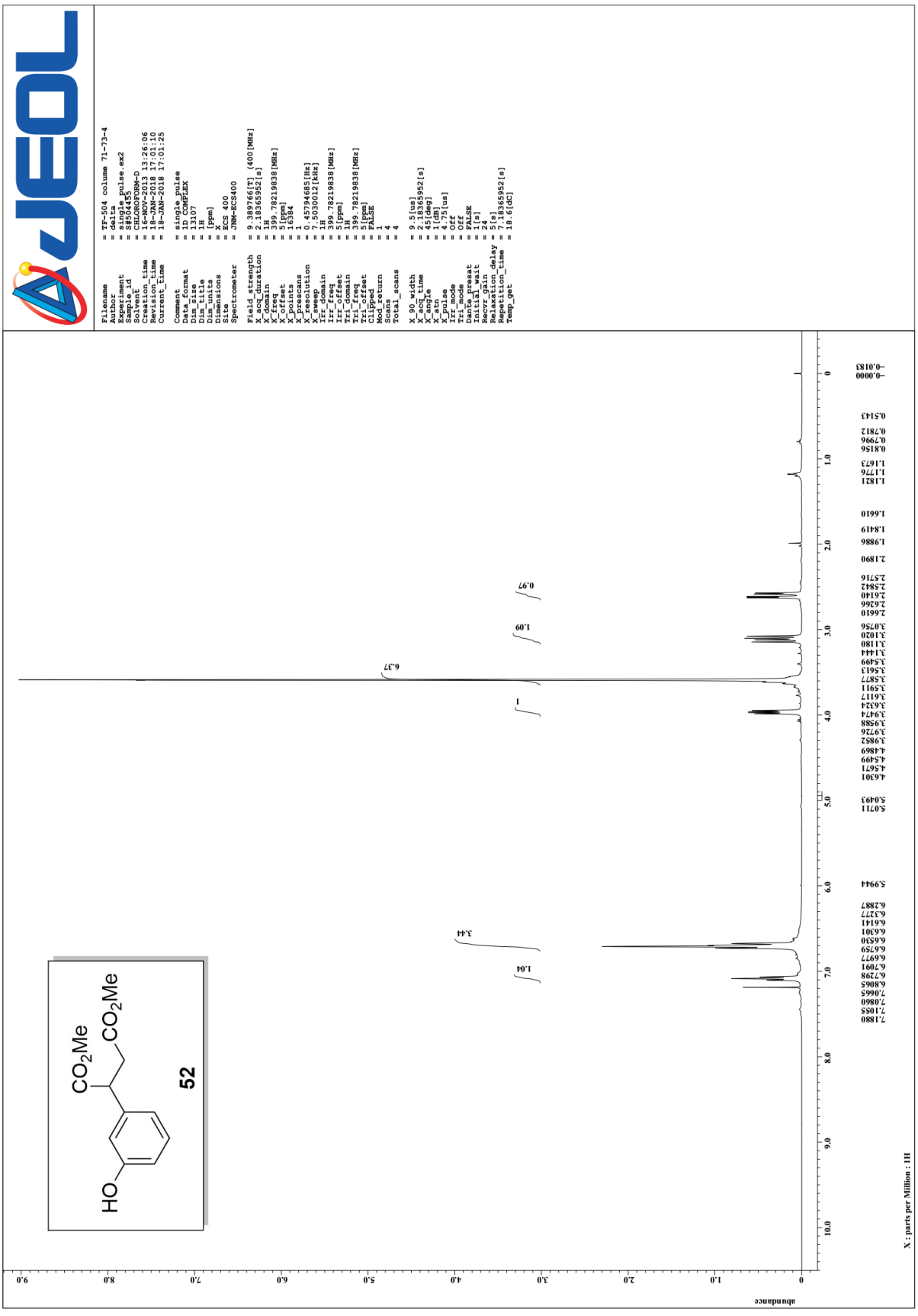

JEOL
Filename = pn3-160tlc1-7.jdf
Author = delta
Experiment = single_pulse_dec
Sample_id = HEC-6683
Solvent = CHLOROFORM-D
Creation_time = 21-JUL-2016 18:13:50
Revision_time = 18-JAN-2018 19:28:26
Current_time = 18-JAN-2018 19:28:37
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = RCS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz])
X_acq_duration = 1.043333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 2
Scans = 256
Total_scans = 256
X_90_width = 8.2[us]
X_acq_time = 1.043333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.73333333[us]
Irr_pulse_dec = 22.25648[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recyr_gain = 60
Relaxation_delay = 3.0[s]
Repetition_time = 4.043333312[s]
Temp_get = 22.9[dC]
OMe
CO2Me
HO
50cA
abundance
X : parts per Million : 13C
171.8881
153.8964
132.0241
129.2972
125.3689
124.1390
114.8618
79.6315
77.3146
77.0000
76.6758
56.4816
51.8001
43.2190
15.8547

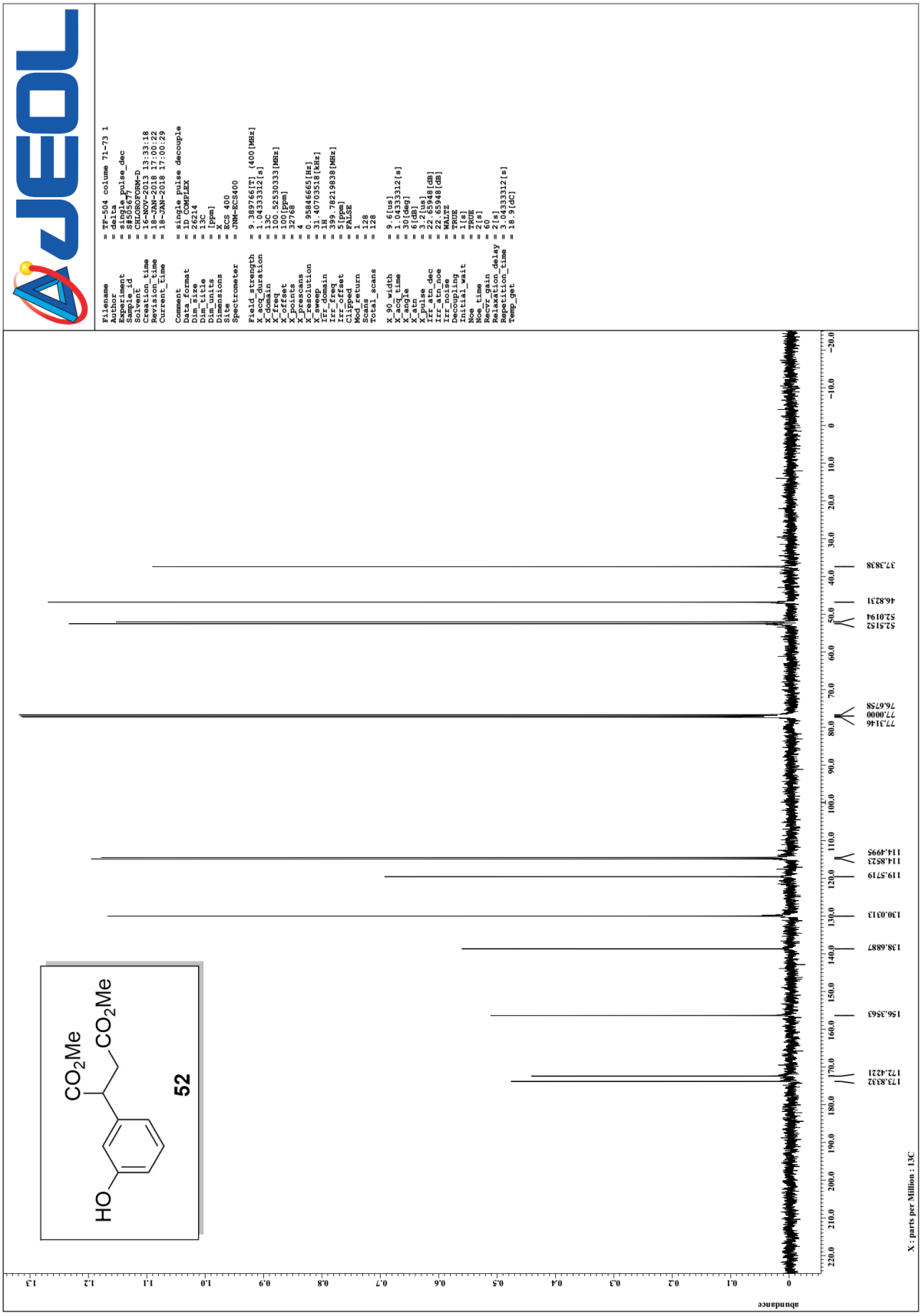

JEOL
Filename = TP-519 colume product
Author = Akira
Experiment = single_pulse.ex2
Sample_id = SH482947
Solvent = CHLOROFORM-D
Creation_time = 18-JAN-2018 12:49:47
Revision_time = 18-JAN-2018 19:17:51
Current_Time = 18-JAN-2018 19:18:09
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5.5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.45794685[Hz]
X_sweep = 7.50300012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1[dB]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 2[s]
Recvr_gain = 1
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 18.6[dC]
OMe
CO2Me
Br
HO
50dA
abundance
X : parts per Million : 1H

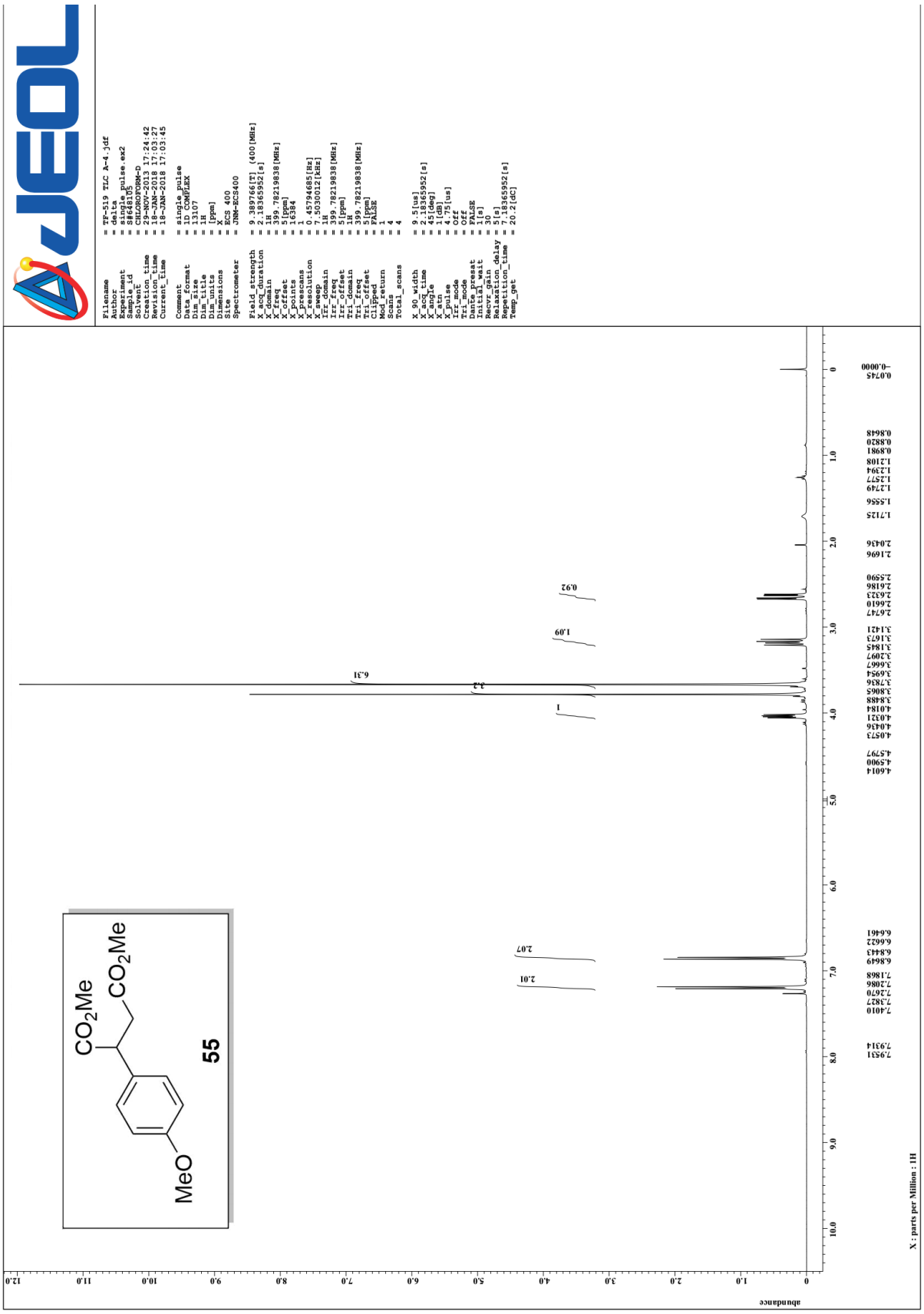

JEOL
Filename = TF-519 colume product
Author = delta
Experiment = 13C single pulse_dec
Sample_id = 8418397
Solvent = CHLOROFORM-D
Creation_time = 15-NOV-2013 12:54:26
Revision_time = 18-JAN-2018 19:18:42
Current_time = 18-JAN-2018 19:18:50
Comment = single pulse decouple
Data_format = 2D COMPLEX
Dim_size = 2014
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = RCS 400
Spectrometer = JNM-RCS400
Field_strength = 9.38976617[T] (400[MHz])
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 75
Scans = 75
Total_scans = 75
X_90_width = 9.6[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.2[us]
Irr_atn_dec = 22.65948[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 18.8[dC]
OMe
CO2Me
Br
HO
50dA
abundance
X : parts per Million : 13C
43.0855
51.8478
56.6913
76.6758
77.0000
78.8974
110.2375
116.1871
116.4446
127.3712
128.9825
130.2983
133.9024
152.1992
171.4209

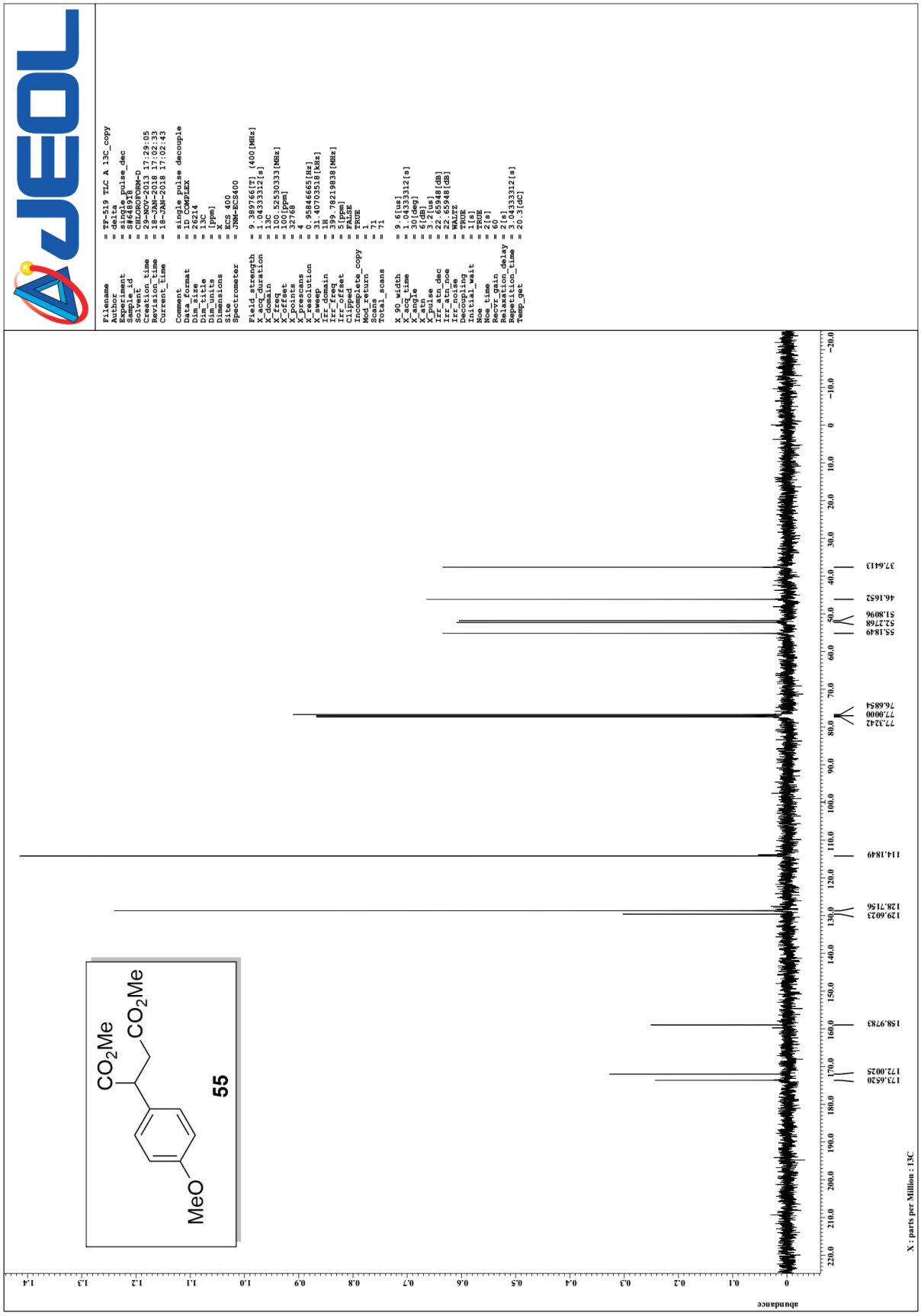

JEOL
Filename = TF-520 TLC A-5.jdf
Author = data
Experiment = single_pulse.ex2
Sample_id = S#590c88
Solvent = CHLOROFORM-D
Creation_time = 23-JAN-2018 15:49:17
Revision_time = 18-JAN-2018 20:37:40
Current_time = 18-JAN-2018 20:37:59
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_Preturn = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_delay = 1.75[s]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Data_format = FLOAT8
Data_format = 1[s]
Recvr_gain = 34
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 19.5[deg]
HO
OMe
CO2Me
50aA
3.16
3.13
1.02
1.05
1
2.05
1.03
1.0
0.16
1.05
X : parts per Million : 1H
abundance


JEOL
Filename = TF-520 TLC A-4.jdf
Author = delta
Experiment = single_pulse_dec
Sample_id = #SS6814
Solvent = CHLOROFORM-D
Creation_time = 23-NOV-2013 16:21:44
Revision_time = 18-JAN-2018 19:21:45
Current_time = 18-JAN-2018 19:21:53
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 32214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz])
X_acq_duration = 1.36333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = TRUE
Mod_return = 1
Scans = 455
total_scans = 455
X_90_width = 9.6[us]
X_acq_time = 1.0233312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 3.2[us]
Irr_atn_dec = 22.65948[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ2
Decoupling = TRUE
Initial_wait = TRUE
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 18.7[dC]
HO
OMe
CO2Me
50aA
171.1826
155.3170
129.5641
128.1435
123.4906
120.1344
117.1406
81.0045
77.3146
77.0000
76.6854
57.5590
51.8955
41.0260
abundance
X : parts per Million : 13C

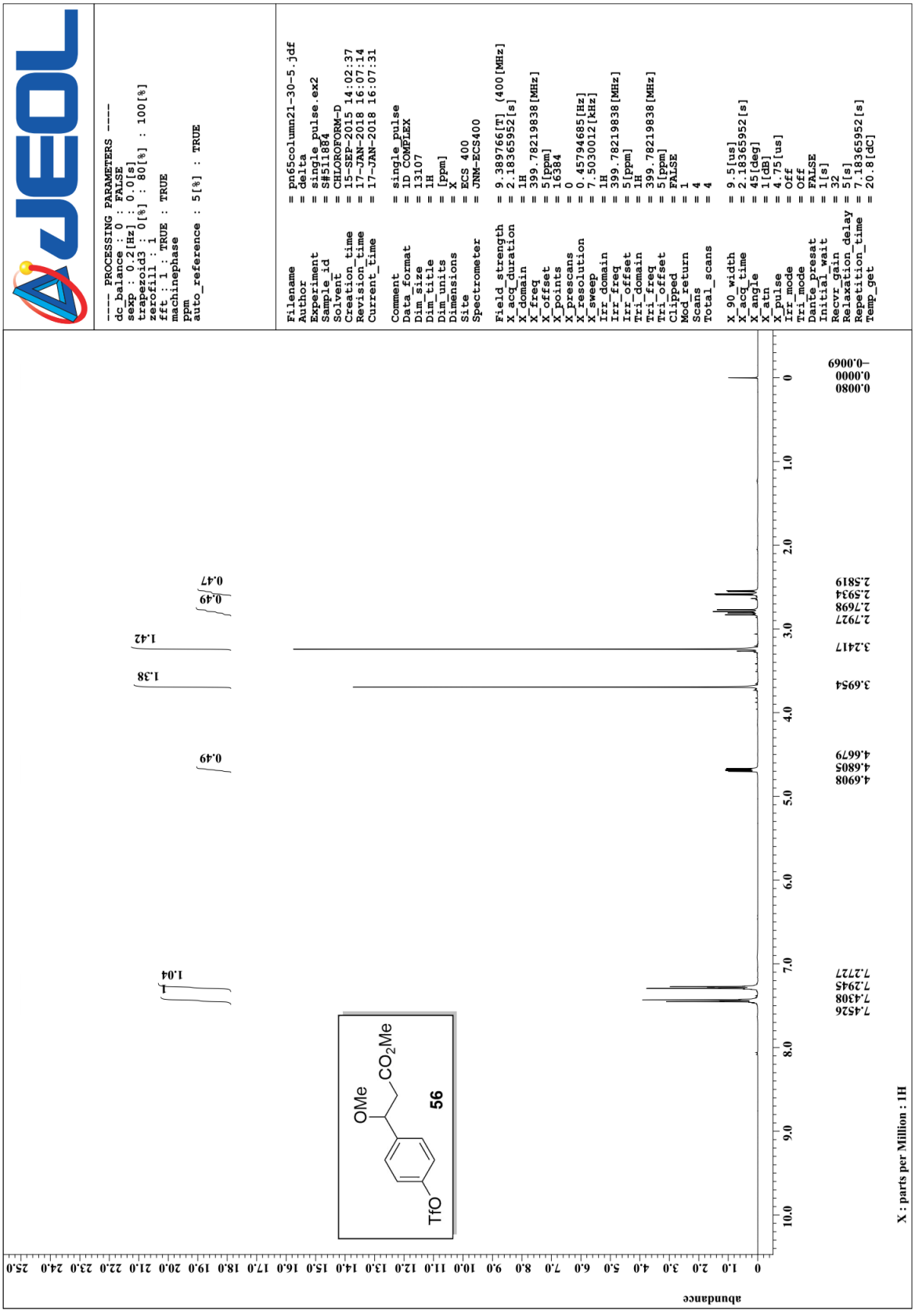

JEOL
Filename = YP-504 colume 71-73-4
Author = admin
Experiment = single_pulse.ex2
Sample_id = S#504455
Solvent = CHLOROFORM-D
Creation_time = 18-JAN-2018 13:26:06
Revision_time = 18-JAN-2018 17:01:10
Current_Time = 18-JAN-2018 17:01:25
Comment = single pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16584
X_prescans = 1
X_resolution = 0.45794685[Hz]
X_sweep = 7.50300012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1[dB]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 2[s]
Relax_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 18.6[dC]
6.37
1.09
0.97
1
3.44
1.04
CO2Me
CO2Me
HO
52
abundance
X : parts per Million : 1H

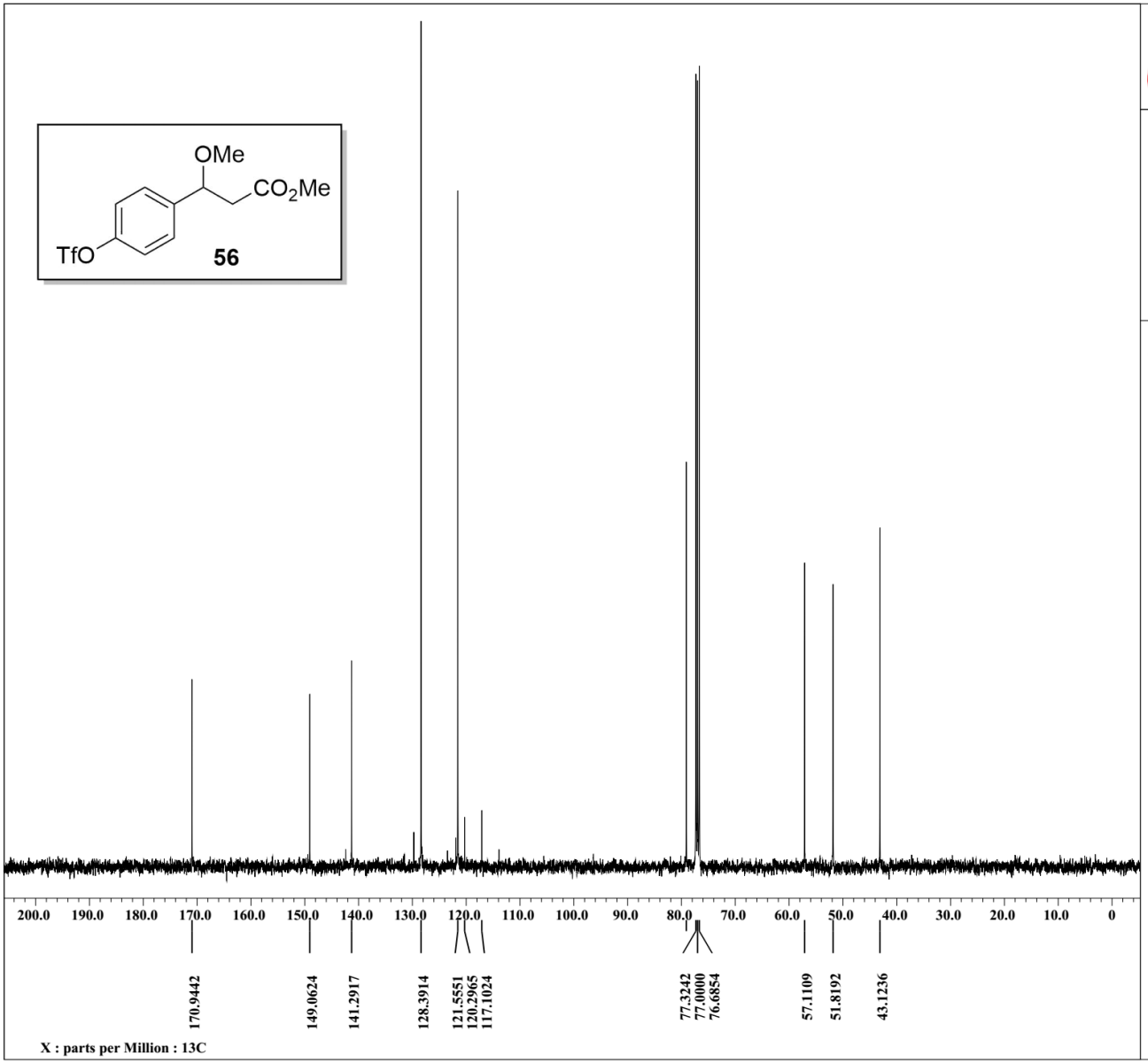

JEOL
Filename = TF-504 colume 71-73 1
Author = daita
Experiment = single_pulse_dec
Sample_id = ESI_FT_504
Solvent = CHLOROFORM-D
Creation_time = 16-NOV-2013 13:33:18
Revision_time = 18-JAN-2018 17:00:22
Current_time = 18-JAN-2018 17:00:29
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 65214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz])
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 128
Total_scans = 128
X_90_width = 9.6[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 3.2[us]
Irr_atn_dec = 27.65948[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 3[s]
Repetition_time = 4.04333312[s]
Temp_get = 18.9[dC]
CO2Me
CO2Me
HO
52
abundance
X : parts per Million : 13C
173.8332
172.4221
156.3563
138.6887
130.0313
119.5719
114.8523
114.4995
77.3146
77.0000
76.6758
52.5152
52.0194
46.8231
37.3838


JEOL
Filename = TP-519 TLC A-4.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = SH6481105
Solvent = CHLOROFORM-D
Creation_time = 29-NOV-2013 17:24:42
Revision_time = 18-JAN-2018 17:03:27
Current_Time = 18-JAN-2018 17:03:45
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = 1
Site = JCS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz])
Acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 65536
X_prescans = 1
X_resolution = 0.45794685[Hz]
X_sweep = 1.50300112[kHz]
Y_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1[dB]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Relax_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 20.2[dC]
CO2Me
CO2Me
MeO
55
6.31
3.2
1.09
0.92
1
2.07
2.01
abundance
X : parts per Million : 1H


JEOL
Filename = TF-519 TLC A 13C_copy
Author = delta
Experiment = single pulse_dec
Sample_id = MeOH-D
Solvent = CHLOROFORM-D
Creation_time = 29-NOV-2013 17:29:05
Revision_time = 18-JAN-2018 17:02:33
Current_time = 18-JAN-2018 17:02:43
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 32214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz])
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Incomplete_copy = TRUE
Model_return = 1
Scans = 71
Total_scans = 71
X_90_width = 9.6[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.4[us]
Irr_atn_dec = 22.65948[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60[%]
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 20.3[dC]
CO2Me
CO2Me
MeO
55
abundance
X : parts per Million : 13C
173.6520
172.0025
158.9783
129.6023
128.7156
114.1849
77.3243
77.0000
76.6854
55.1849
52.2768
51.8096
46.1652
37.6413

4) ^{1}H and ^{13}C NMR spectrums of the triflate **56**, coupling products **57a-57e** and compound **58**





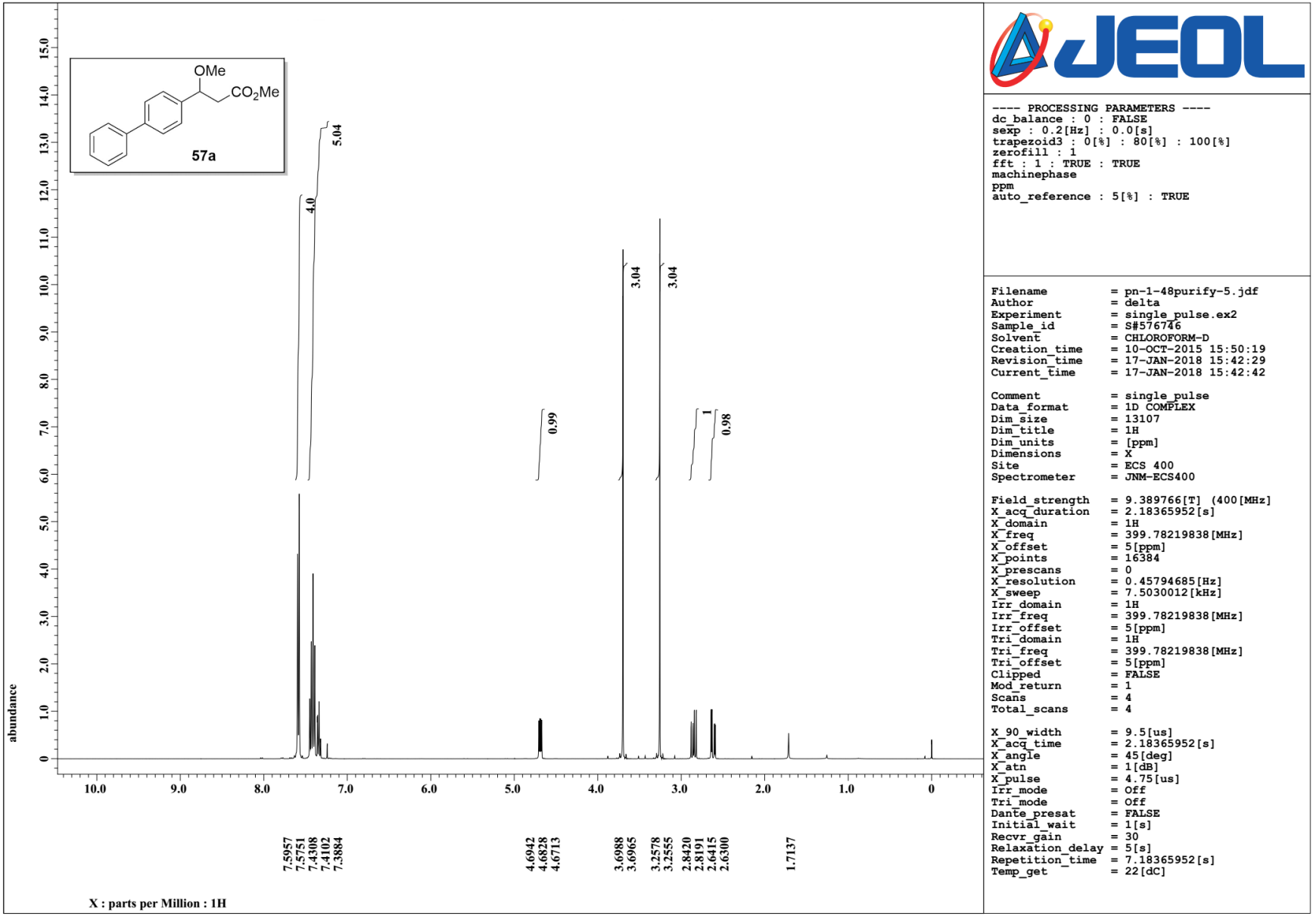

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = PN53TLC1-C-3.jdf
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = S#532886
Solvent           = CHLOROFORM-D
Creation_time     = 10-JUL-2015 14:50:14
Revision_time     = 17-JAN-2018 12:44:58
Current_time      = 17-JAN-2018 16:06:22

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 1.04333312[s]
X_domain          = 13C
X_freq            = 100.52530333[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 0.95846665[Hz]
X_sweep           = 31.40703518[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 256
Total_scans       = 256

X_90_width        = 8.2[us]
X_acq_time        = 1.04333312[s]
X_angle           = 30[deg]
X_atn             = 6[dB]
X_pulse           = 2.73333333[us]
Irr_atn_dec       = 22.65948[dB]
Irr_atn_noe       = 22.65948[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 60
Relaxation_delay  = 2[s]
Repetition_time   = 3.04333312[s]
Temp_get          = 24.1[dC]
```



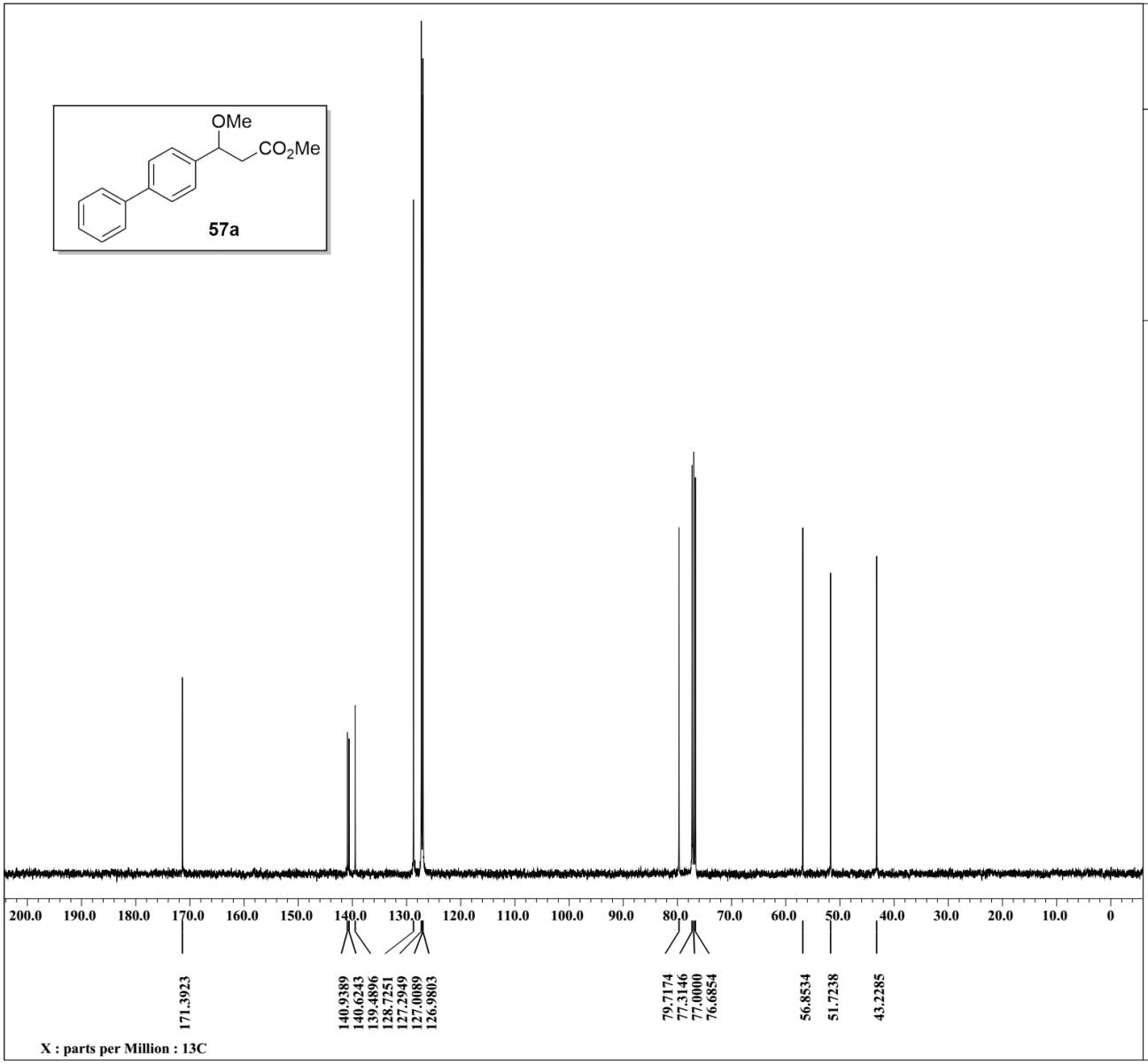

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = pn-1-48purify-5.jdf
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = S#576746
Solvent           = CHLOROFORM-D
Creation_time     = 10-OCT-2015 15:50:19
Revision_time     = 17-JAN-2018 15:42:29
Current_time      = 17-JAN-2018 15:42:42

Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 2.18365952[s]
X_domain          = 1H
X_freq            = 399.78219838[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 0
X_resolution      = 0.45794685[Hz]
X_sweep           = 7.5030012[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Tri_domain        = 1H
Tri_freq          = 399.78219838[MHz]
Tri_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 4
Total_scans       = 4

X_90_width        = 9.5[us]
X_acq_time        = 2.18365952[s]
X_angle           = 45[deg]
X_atn             = 1[dB]
X_pulse           = 4.75[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 30
Relaxation_delay  = 5[s]
Repetition_time   = 7.18365952[s]
Temp_get          = 22[dC]
```



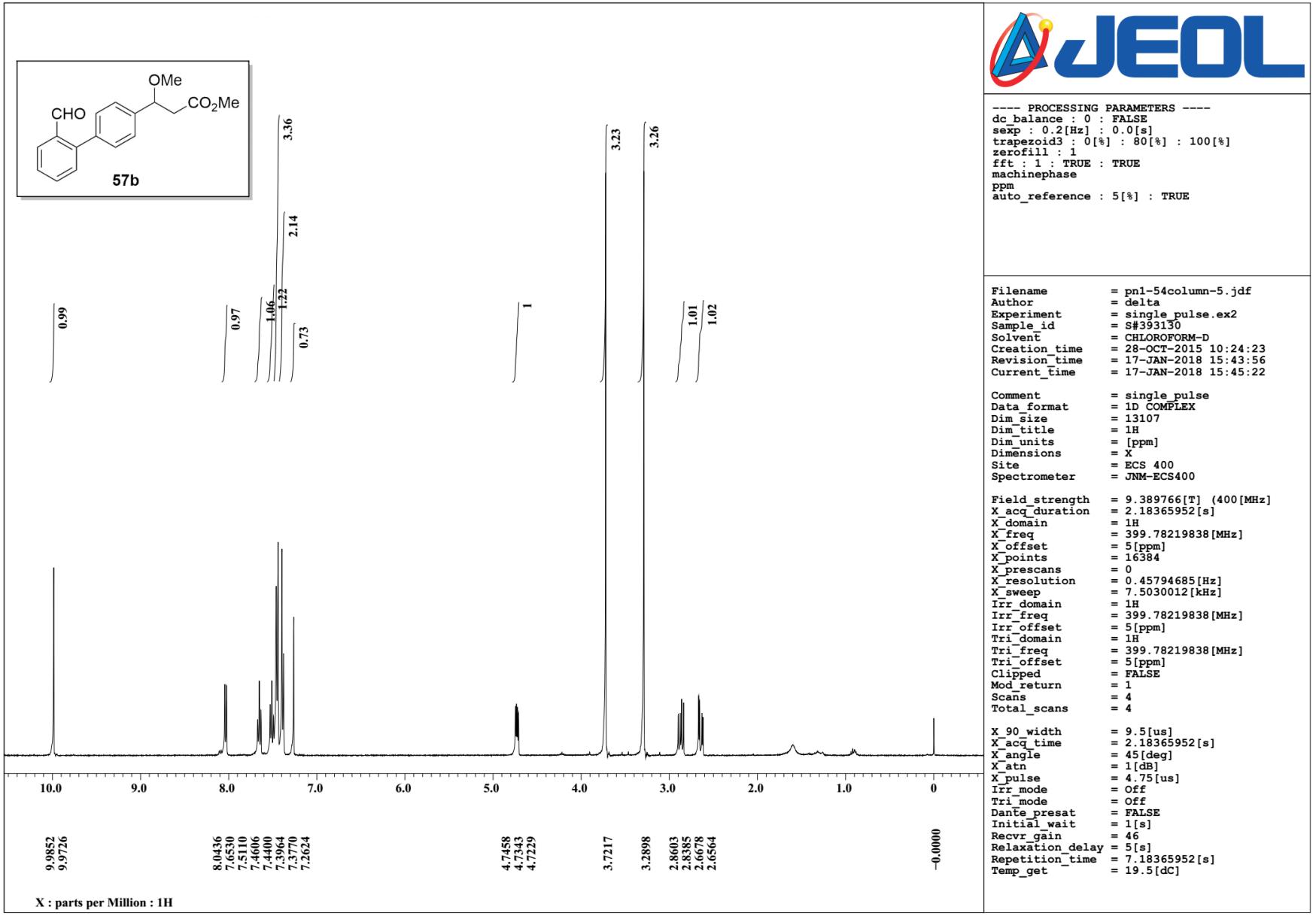

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

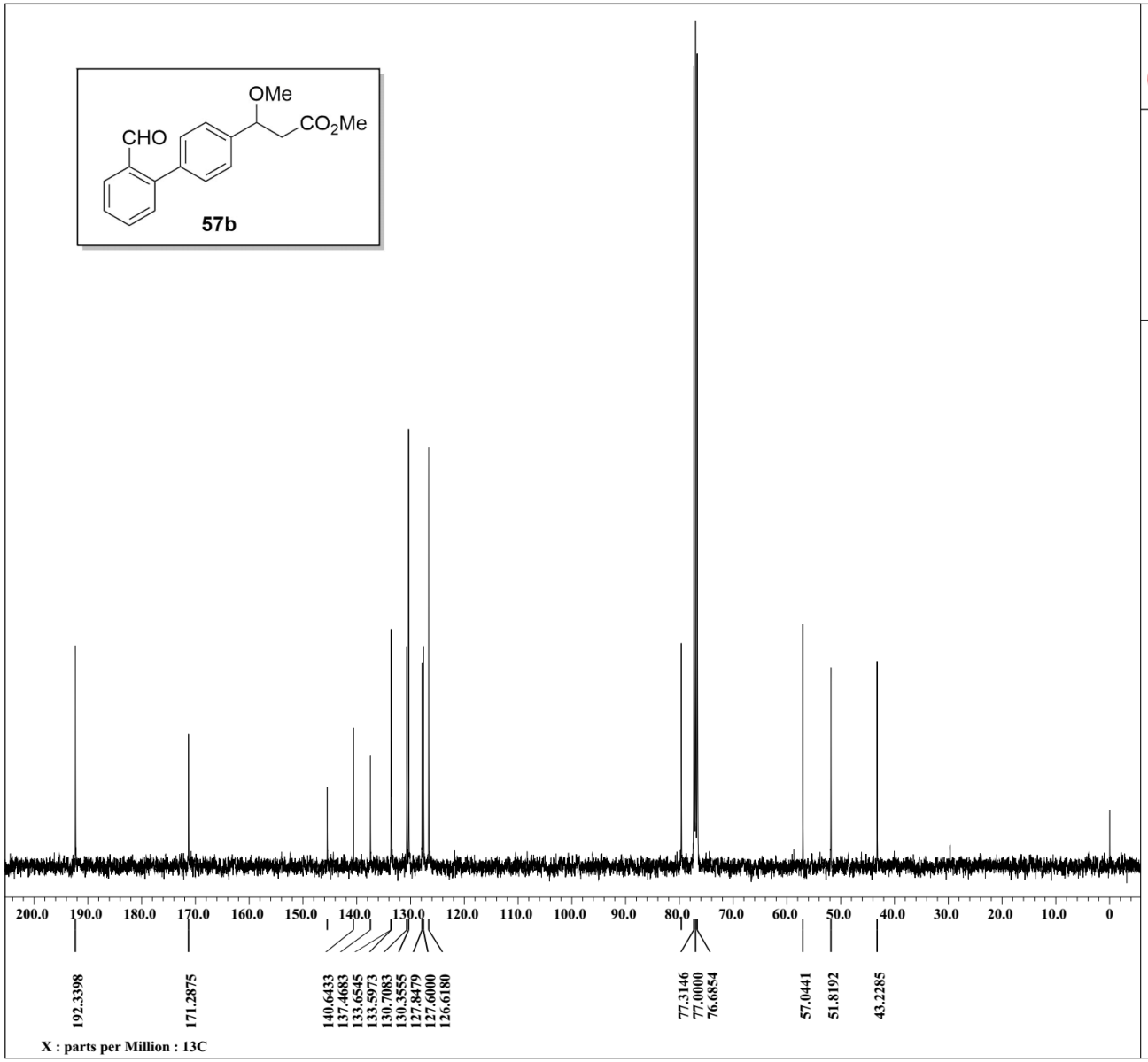
```
Filename          = pn1-48pureC-3.jdf
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = S#580161
Solvent           = CHLOROFORM-D
Creation_time     = 10-OCT-2015 16:09:02
Revision_time     = 17-JAN-2018 13:14:14
Current_time      = 17-JAN-2018 15:40:12

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 1.04333312[s]
X_domain          = 13C
X_freq            = 100.52530333[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 0.95846665[Hz]
X_sweep           = 31.40703518[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 256
Total_scans       = 256

X_90_width        = 8.2[us]
X_acq_time        = 1.04333312[s]
X_angle           = 30[deg]
X_atn             = 6[dB]
X_pulse           = 2.73333333[us]
Irr_atn_dec       = 22.65948[dB]
Irr_atn_noe       = 22.65948[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 60
Relaxation_delay  = 2[s]
Repetition_time   = 3.04333312[s]
Temp_get          = 22.3[dC]
```


OMe
CHO
CO2Me
57b
3.36
3.23
3.26
2.14
1.06
1.22
0.99
0.97
0.73
1
1.01
1.02
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.9852
9.9726
8.0436
7.6530
7.5110
7.4606
7.4400
7.3964
7.3770
7.2624
4.7458
4.7343
4.7229
3.7217
3.2898
2.8603
2.8385
2.6678
2.6564
0.0000
X : parts per Million : 1H
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn1-54column-5.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = S#393130
Solvent = CHLOROFORM-D
Creation_time = 28-OCT-2015 10:24:23
Revision_time = 17-JAN-2018 15:43:56
Current_time = 17-JAN-2018 15:45:22
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1[dB]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 46
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 19.5[dC]



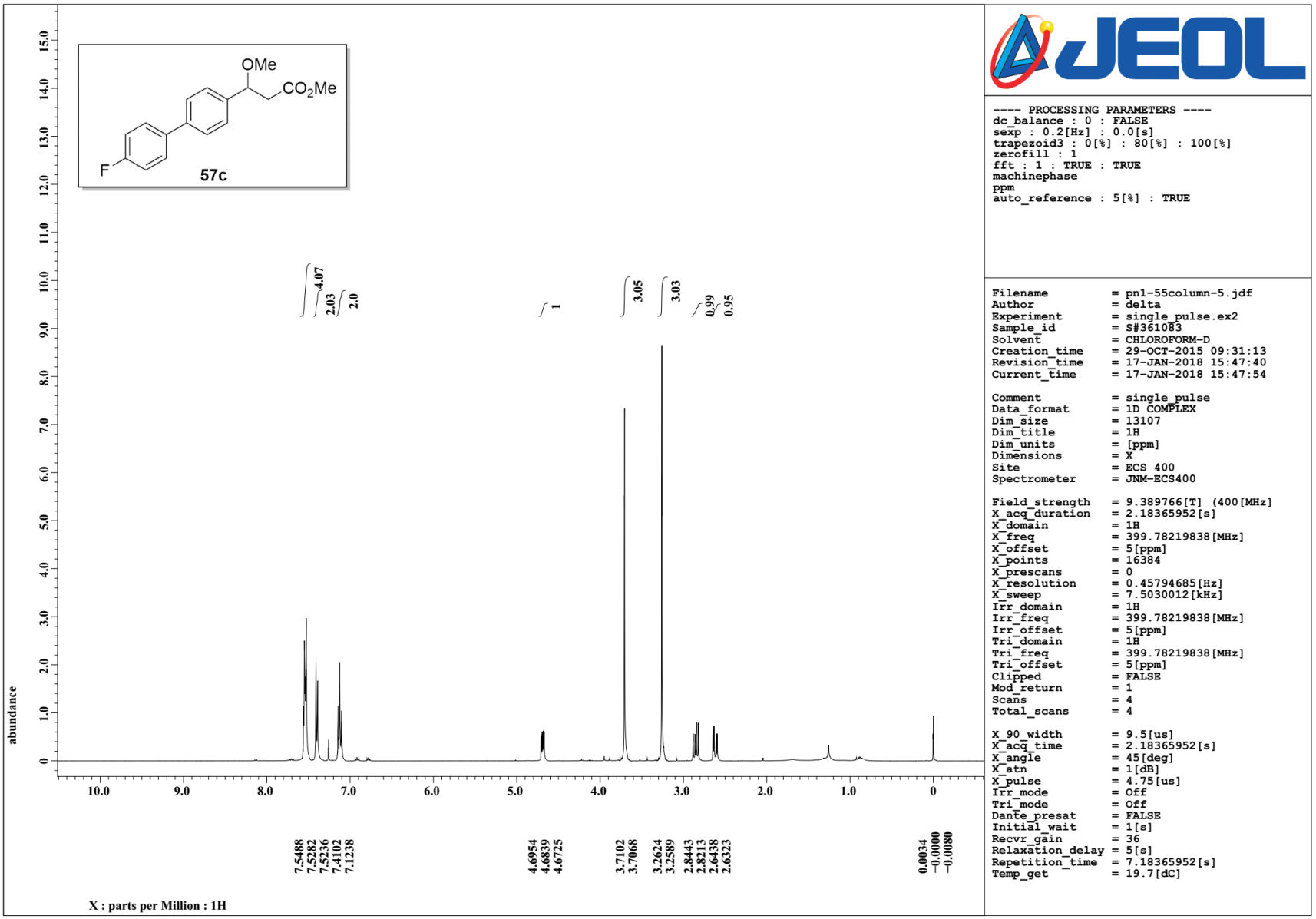

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = pn1-50colu114-27-3.jd
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = S#556914
Solvent           = CHLOROFORM-D
Creation_time     =  7-OCT-2015 15:29:52
Revision_time     = 17-JAN-2018 12:48:08
Current_time      = 17-JAN-2018 15:43:15

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 1.04333312[s]
X_domain          = 13C
X_freq            = 100.52530333[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 0.95846665[Hz]
X_sweep           = 31.40703518[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 256
Total_scans       = 256

X_90_width        = 8.2[us]
X_acq_time        = 1.04333312[s]
X_angle           = 30[deg]
X_atn             = 6[dB]
X_pulse           = 2.73333333[us]
Irr_atn_dec       = 22.65948[dB]
Irr_atn_noe       = 22.65948[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 60
Relaxation_delay  = 2[s]
Repetition_time   = 3.04333312[s]
Temp_get          = 21.8[dC]
```



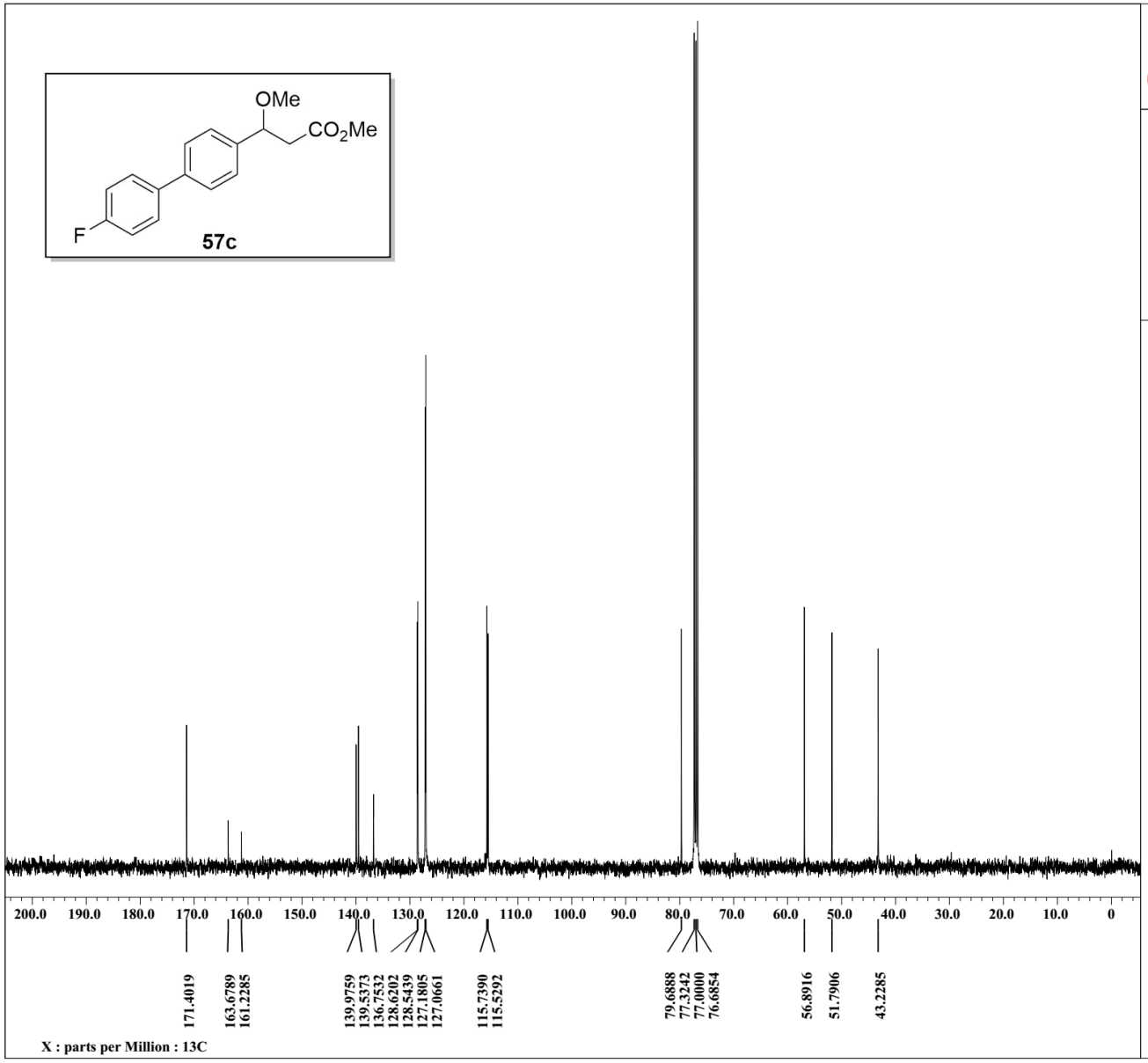

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = pn1-55column-5.jdf
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = S#361083
Solvent           = CHLOROFORM-D
Creation_time     = 29-OCT-2015 09:31:13
Revision_time     = 17-JAN-2018 15:47:40
Current_time      = 17-JAN-2018 15:47:54

Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 2.18365952[s]
X_domain          = 1H
X_freq            = 399.78219838[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 0
X_resolution      = 0.45794685[Hz]
X_sweep           = 7.5030012[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Tri_domain        = 1H
Tri_freq          = 399.78219838[MHz]
Tri_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 4
Total_scans       = 4

X_90_width        = 9.5[us]
X_acq_time        = 2.18365952[s]
X_angle           = 45[deg]
X_atn             = 1[dB]
X_pulse           = 4.75[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 36
Relaxation_delay  = 5[s]
Repetition_time   = 7.18365952[s]
Temp_get          = 19.7[dC]
```



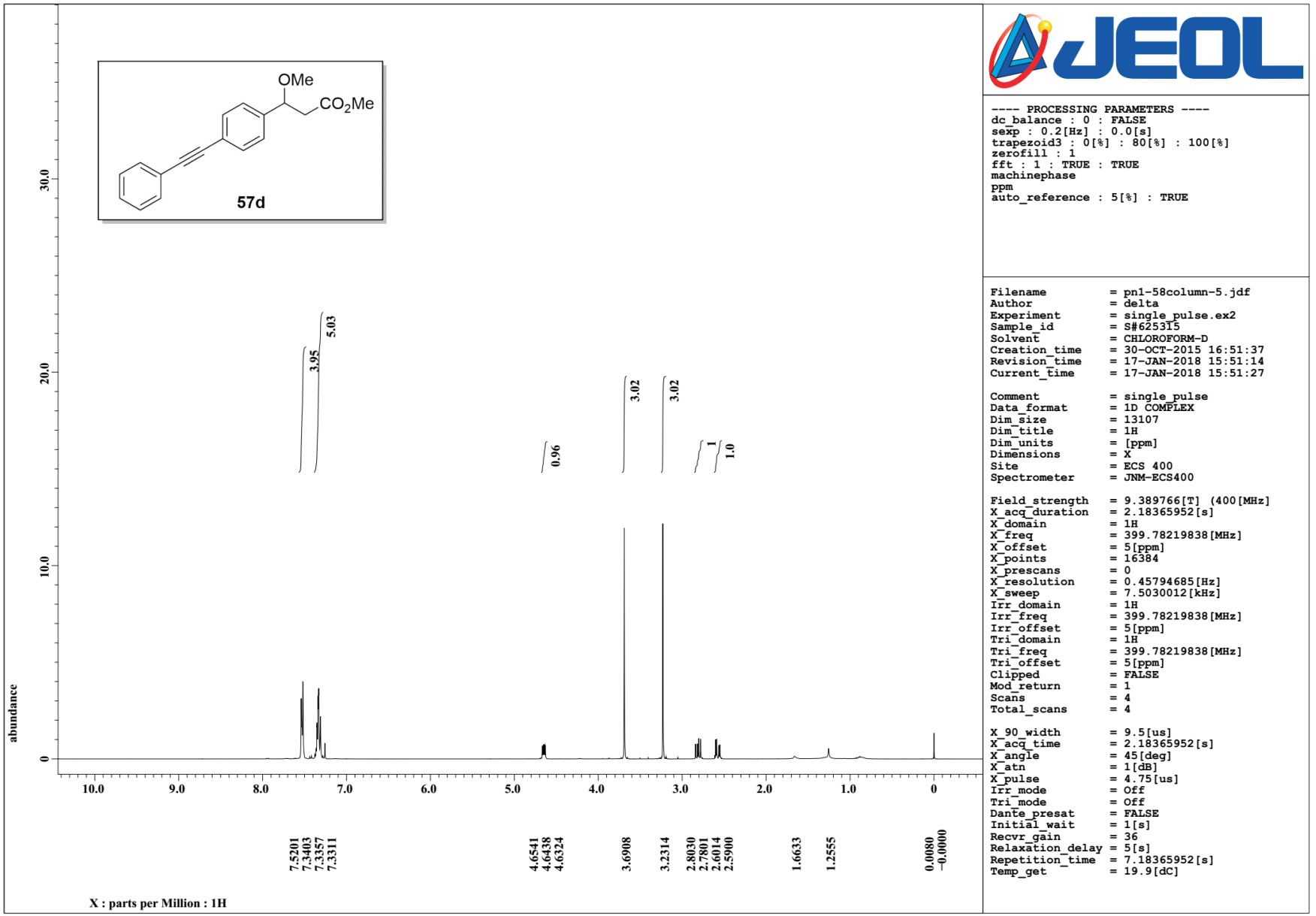
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE

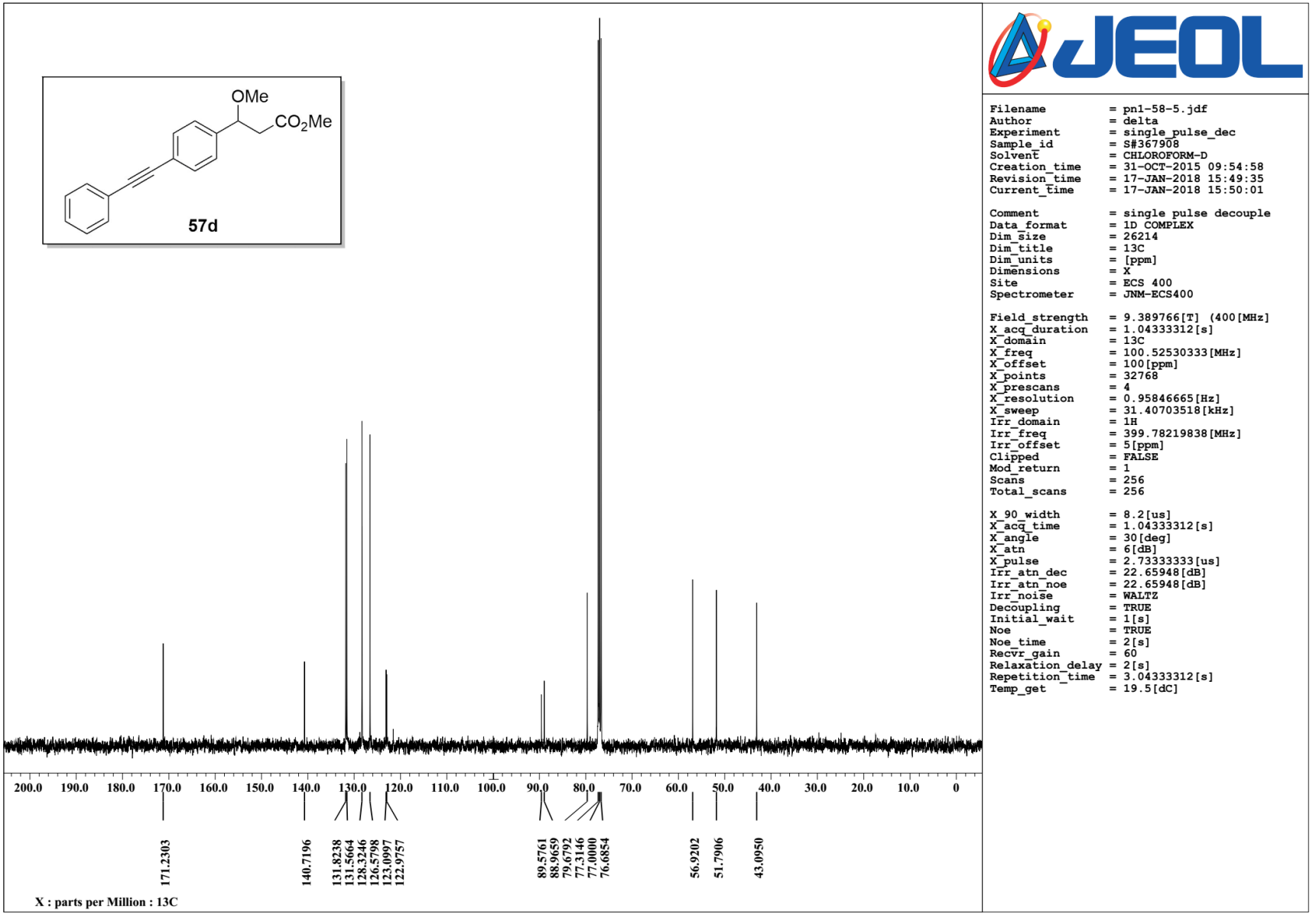
Filename = pn1-55-5.jdf
Author = delta
Experiment = single_pulse_dec
Sample_id = S#365484
Solvent = CHLOROFORM-D
Creation_time = 29-OCT-2015 09:50:55
Revision_time = 17-JAN-2018 13:09:04
Current_time = 17-JAN-2018 15:45:50

Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400

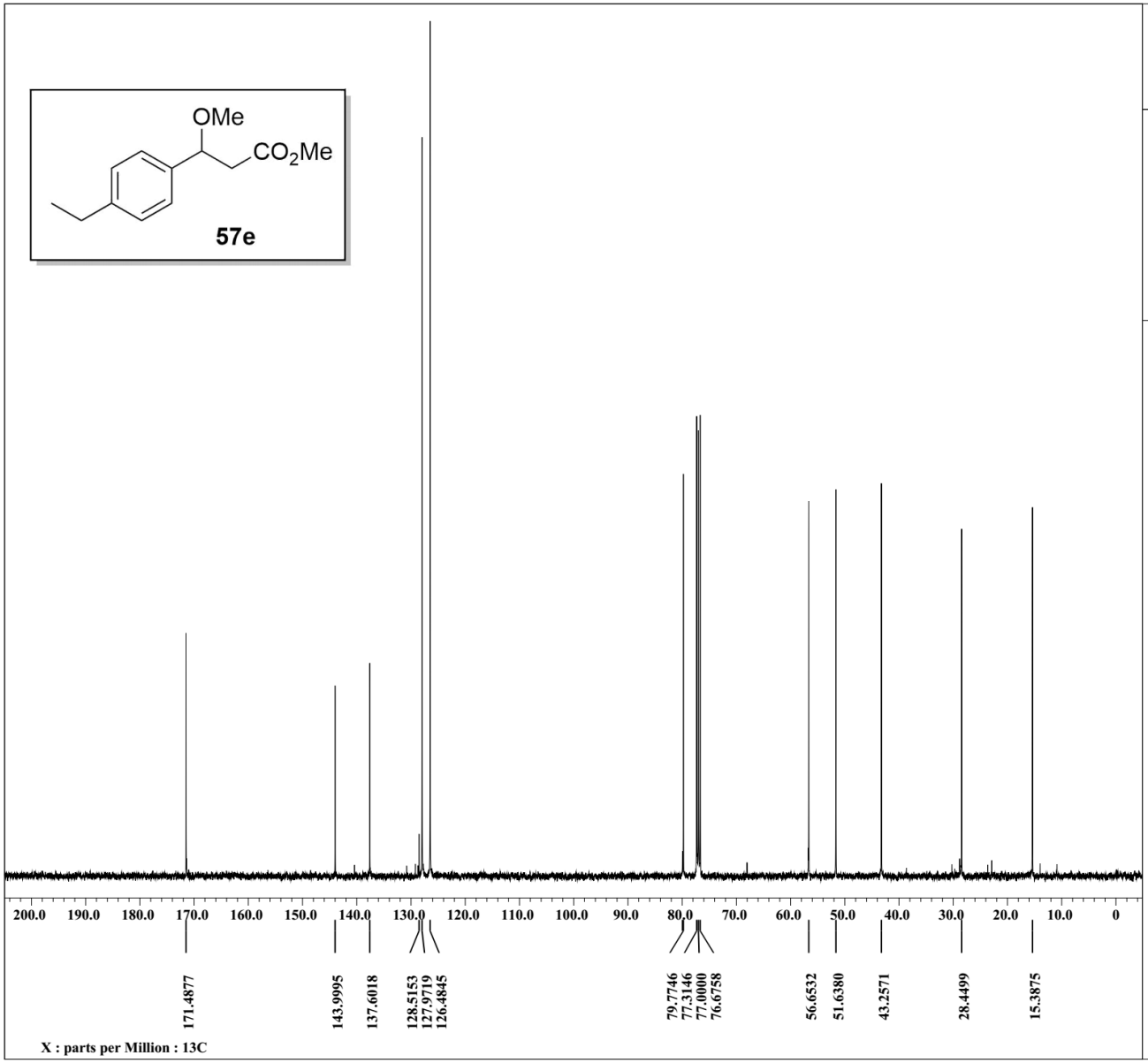
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 256
Total_scans = 256

X_90_width = 8.2[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.73333333[us]
Irr_atn_dec = 22.65948[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 19.9[dC]


OMe
CO2Me
57d
abundance
30.0
20.0
10.0
0
3.95
5.03
0.96
3.02
3.02
1
1.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.5201
7.3403
7.3357
7.3311
4.6541
4.6438
4.6324
3.6908
3.2314
2.8030
2.7801
2.6014
2.5900
1.6633
1.2555
0.0080
−0.0000
X : parts per Million : 1H
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn1-58column-5.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = S#6253I5
Solvent = CHLOROFORM-D
Creation_time = 30-OCT-2015 16:51:37
Revision_time = 17-JAN-2018 15:51:14
Current_time = 17-JAN-2018 15:51:27
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1[dB]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 36
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 19.9[dC]


OMe
CO2Me
57d
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
171.2303
140.7196
131.8238
131.5664
128.3246
126.5798
123.0997
122.9757
89.5761
88.9659
79.6792
77.3146
77.0000
76.6854
56.9202
51.7906
43.0950
X : parts per Million : 13C
Filename = pn1-58-5.jdf
Author = delta
Experiment = single_pulse_dec
Sample_id = S#367908
Solvent = CHLOROFORM-D
Creation_time = 31-OCT-2015 09:54:58
Revision_time = 17-JAN-2018 15:49:35
Current_time = 17-JAN-2018 15:50:01
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 1.04333312[s]
X_domain = 13C
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 256
Total_scans = 256
X_90_width = 8.2[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 2.73333333[us]
Irr_atn_dec = 22.65948[dB]
Irr_atn_noe = 22.65948[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 19.5[dC]

JEOL
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1 : TRUE : TRUE
ffc : 1
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn1-60column-5.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = S#603785
Solvent = CHLOROFORM-D
Creation_time = 9-NOV-2015 16:15:37
Revision_time = 17-JAN-2018 15:52:37
Current_time = 17-JAN-2018 15:52:50
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1[dB]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 24
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 20.2[dC]
OMe
CO2Me
57e
X : parts per Million : 1H
abundance
7.2555
7.2349
7.1994
4.6209
4.6083
4.5969
3.6873
3.2085
2.7755
2.6564
2.6381
2.5808
2.0470
1.8305
1.7927
1.2566
1.2371
1.2188
0.0000
0.0080
2.91
2.89
3.06
2.0
1.04
1.05
1
1.92
1.96



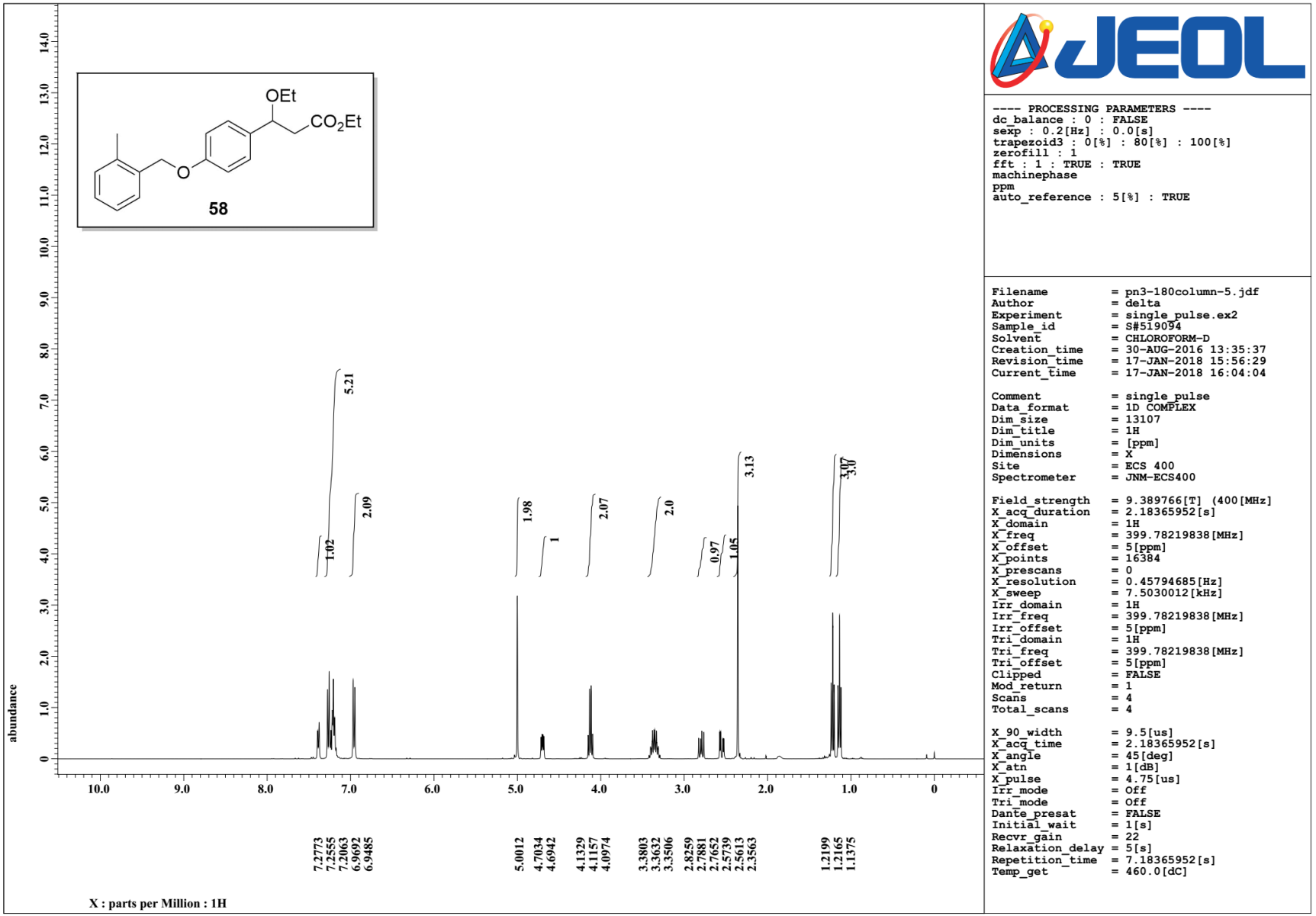

```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

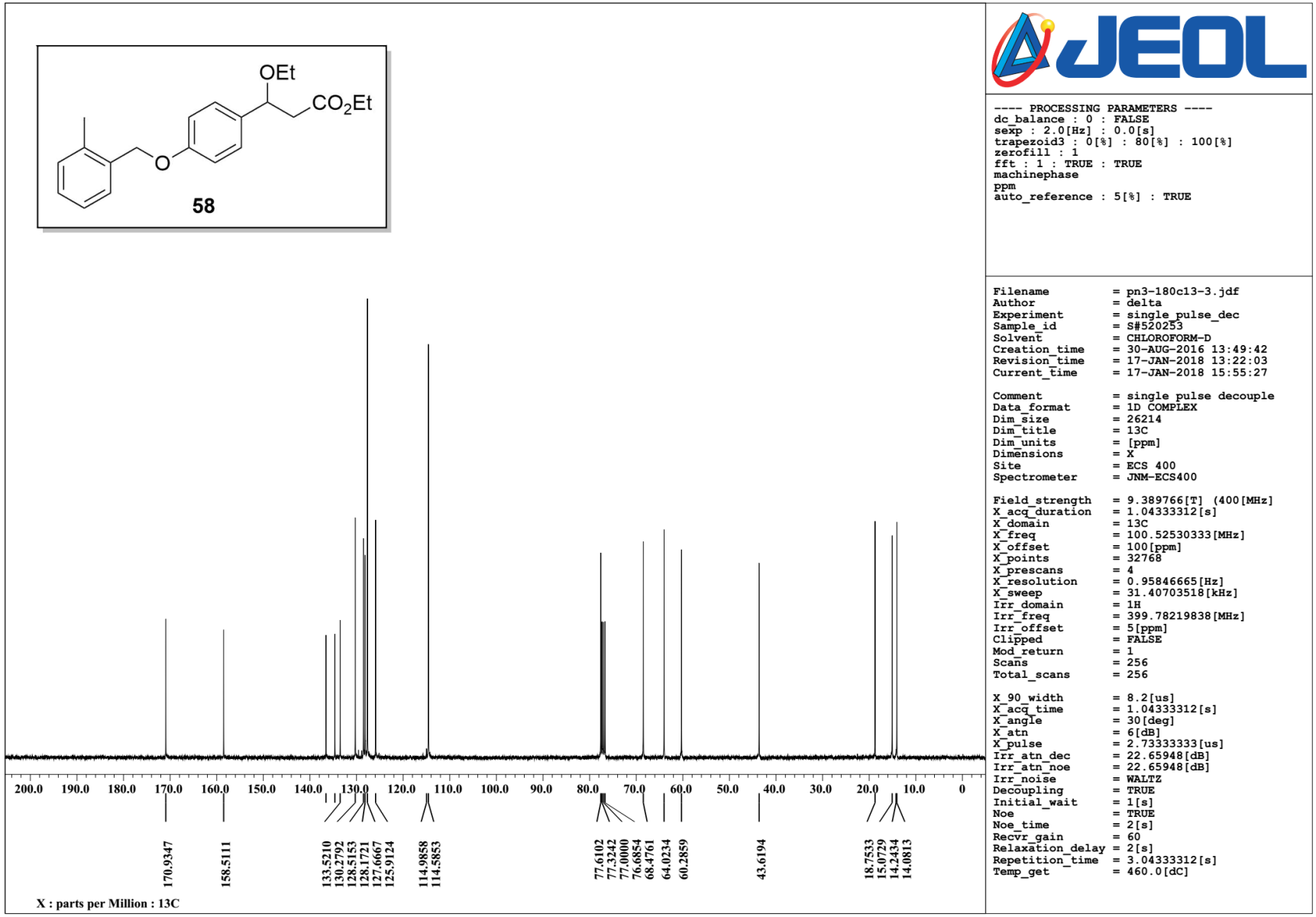
```
Filename          = pn1-60purify-3.jdf
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = S#604917
Solvent           = CHLOROFORM-D
Creation_time     =  9-NOV-2015 16:29:58
Revision_time     = 17-JAN-2018 12:56:45
Current_time      = 17-JAN-2018 15:53:32

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 1.04333312[s]
X_domain          = 13C
X_freq            = 100.52530333[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 0.95846665[Hz]
X_sweep           = 31.40703518[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 256
Total_scans       = 256

X_90_width        = 8.2[us]
X_acq_time        = 1.04333312[s]
X_angle           = 30[deg]
X_atn             = 6[dB]
X_pulse           = 2.73333333[us]
Irr_atn_dec       = 22.65948[dB]
Irr_atn_noe       = 22.65948[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 60
Relaxation_delay  = 2[s]
Repetition_time   = 3.04333312[s]
Temp_get          = 20.5[dC]
```


OEt
CO2Et
O
58
abundance
X : parts per Million : 1H
5.21
2.09
1.02
1.98
1
2.07
2.0
0.97
1.05
3.13
3.07
3.00
7.2773
7.2555
7.2063
6.9692
6.9485
5.0012
4.7034
4.6942
4.1329
4.1157
4.0974
3.3803
3.3632
3.3506
2.8259
2.7881
2.7652
2.5739
2.5613
2.3563
1.2199
1.2165
1.1375
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
Filename = pn3-180column-5.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = S#519094
Solvent = CHLOROFORM-D
Creation_time = 30-AUG-2016 13:35:37
Revision_time = 17-JAN-2018 15:56:29
Current_time = 17-JAN-2018 16:04:04
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz]
X_acq_duration = 2.18365952[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.45794685[Hz]
X_sweep = 7.5030012[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4
X_90_width = 9.5[us]
X_acq_time = 2.18365952[s]
X_angle = 45[deg]
X_atn = 1[dB]
X_pulse = 4.75[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 22
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 460.0[dC]




```
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
```

```
Filename          = pn3-180c13-3.jdf
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = S#520253
Solvent           = CHLOROFORM-D
Creation_time     = 30-AUG-2016 13:49:42
Revision_time     = 17-JAN-2018 13:22:03
Current_time      = 17-JAN-2018 15:55:27

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECS 400
Spectrometer      = JNM-ECS400

Field_strength    = 9.389766[T] (400[MHz]
X_acq_duration    = 1.04333312[s]
X_domain          = 13C
X_freq            = 100.52530333[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 0.95846665[Hz]
X_sweep           = 31.40703518[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 256
Total_scans       = 256

X_90_width        = 8.2[us]
X_acq_time        = 1.04333312[s]
X_angle           = 30[deg]
X_atn             = 6[dB]
X_pulse           = 2.73333333[us]
Irr_atn_dec       = 22.65948[dB]
Irr_atn_noe       = 22.65948[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 60
Relaxation_delay  = 2[s]
Repetition_time   = 3.04333312[s]
Temp_get          = 460.0[dC]
```