

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

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***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.

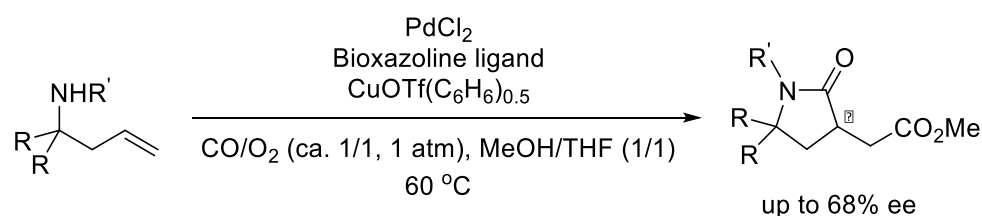
Our laboratory has studied palladium-catalyzed mono- and dicarbonylation of terminal olefins, homoallylic alcohols, homoallylic amine derivatives and already reported several asymmetric versions for dicarbonylation reactions. The combination of palladium(II) and copper(I) salt catalyzed these carbonylations 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 O₂ 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).

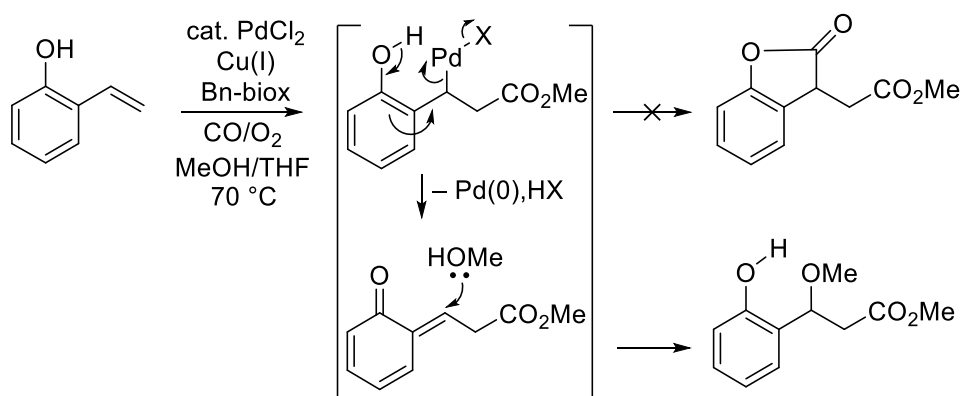


Scheme 1. Asymmetric palladium-catalyzed dicarbonylation of homoallylic amine derivatives.

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

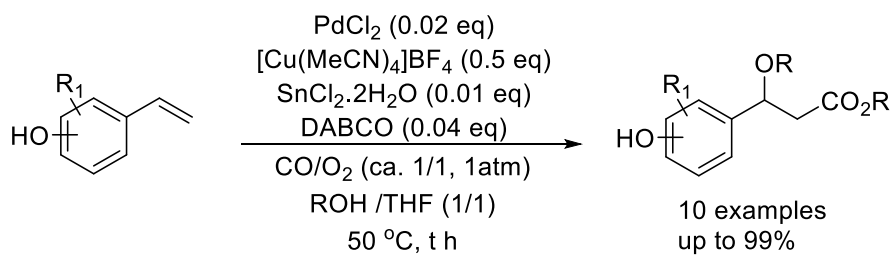
Concerning palladium-catalyzed carbonylation of unsaturated alcohols, intramolecular alkoxy carbonylation often proceeds to furnish cyclic ethers, such as tetrahydrofurans or

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).



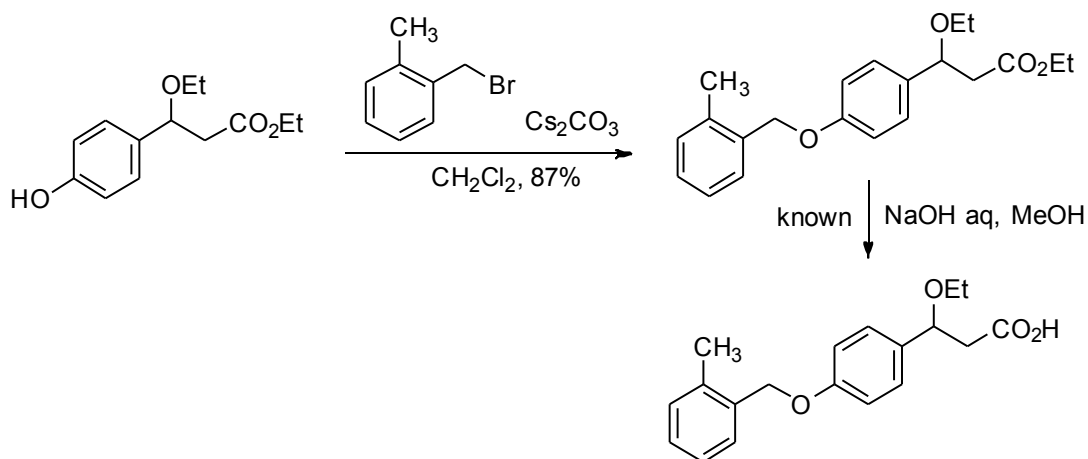
Scheme 2. Methoxy-methoxycarbonylation of 2-vinylphenol.

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.

Furthermore, 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 O₂. 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.

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	<i>p</i> -toluenesulfonic acid

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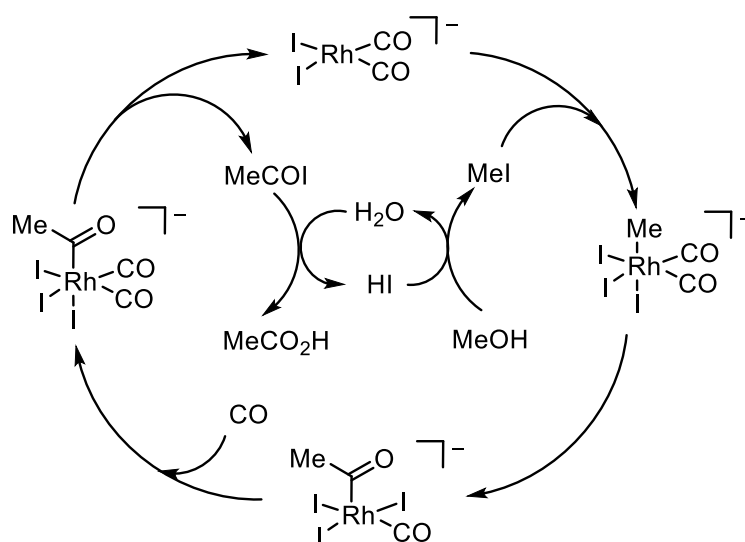
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CHAPTER 1: INTRODUCTION

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 carbonyl-containing 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 (Monsanto process).

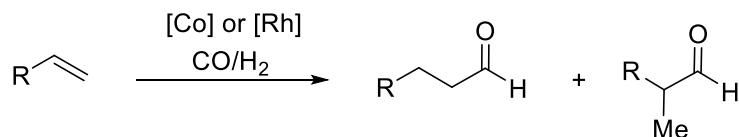
Especially, the conversion of olefins, the basic raw materials for the chemical industry, by carbonylation gives access to more valuable products such as aldehydes, alcohols, and carboxylic acid derivatives. Indeed, advancements in the field of transition-metal-catalyzed carbonylation have been proven 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 alkoxy-carbonylations 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 alkoxy-carbonylations) as base metals.

1.1.1 Hydroformylation

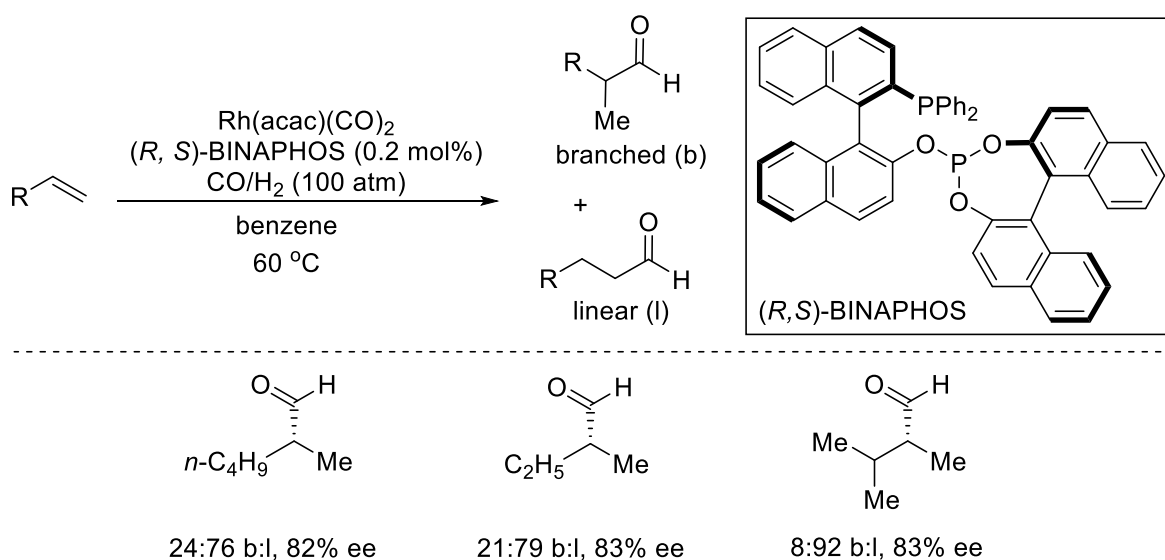
The first milestone in the history of carbonylation, discovered by Otto Roelen and patented in 1938,⁵ was the reaction between alkenes and synthesis gas (syngas), an equimolar mixture of CO and H₂, to form aldehydes. Originally called “oxo-reaction”, “hydroformylation” is the term used today. Given its 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



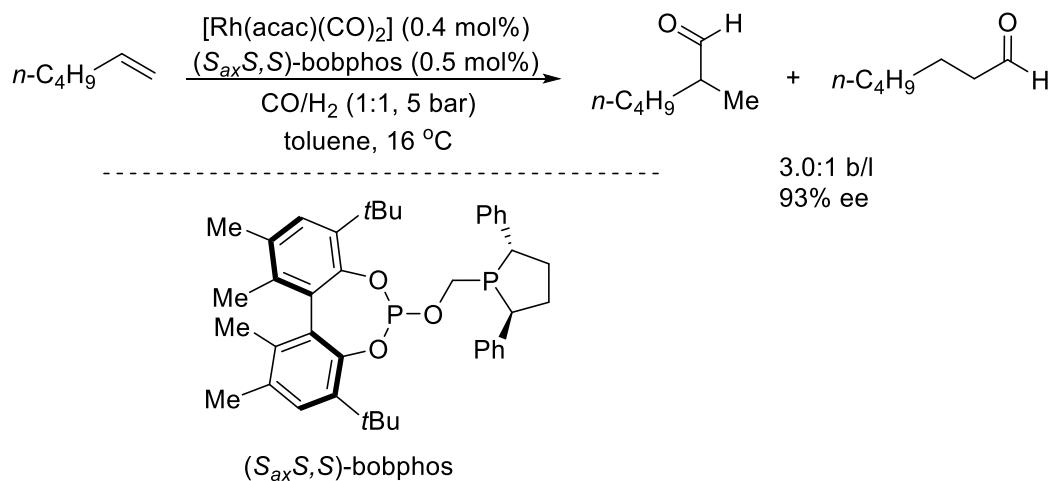
Scheme 1.2. General hydroformylation of terminal alkenes.

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 alkenes⁹ (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 enantioselectivity¹⁰ (Scheme 1.4).



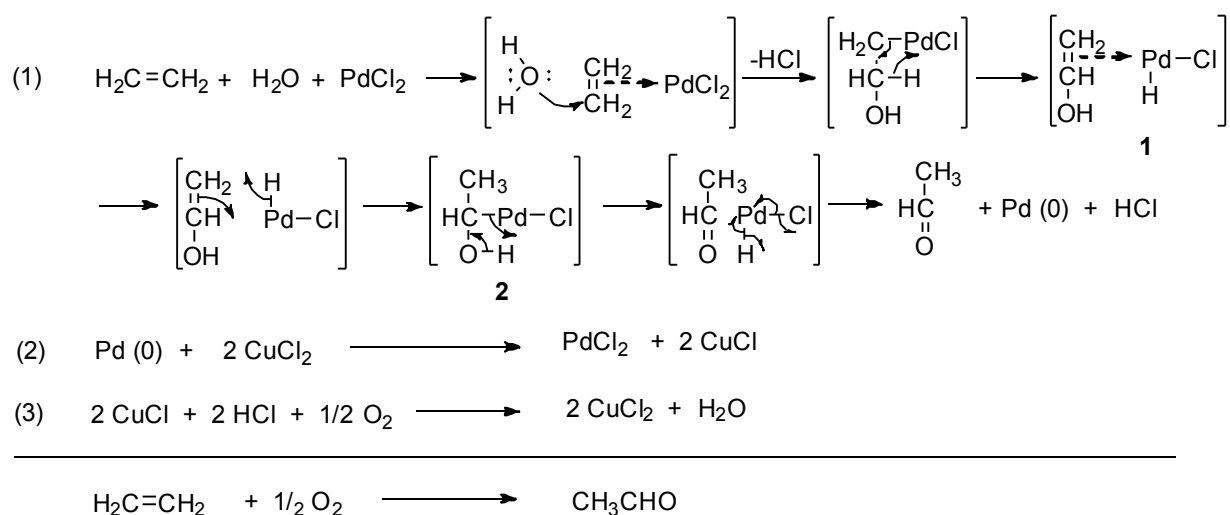
Scheme 1.4. Branched-selective rhodium-catalyzed hydroformylation of alkenes.

1.1.2 Palladium-catalyzed carbonylation

Although rhodium-catalyzed 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 versatile 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.

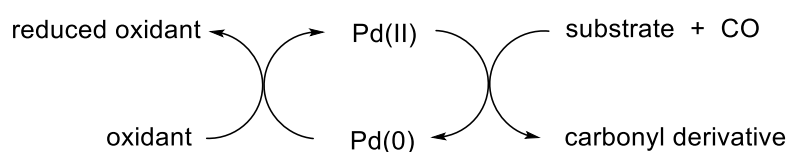
Palladium(II)-catalyzed oxidative transformations have experienced impressive improvements since the first discovery of Wacker process in the late 1950s.¹² In the Wacker process, ethylene is oxidized to acetaldehyde by using a combination of Pd(II) and Cu(II) salts. The process involves three unit reactions (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

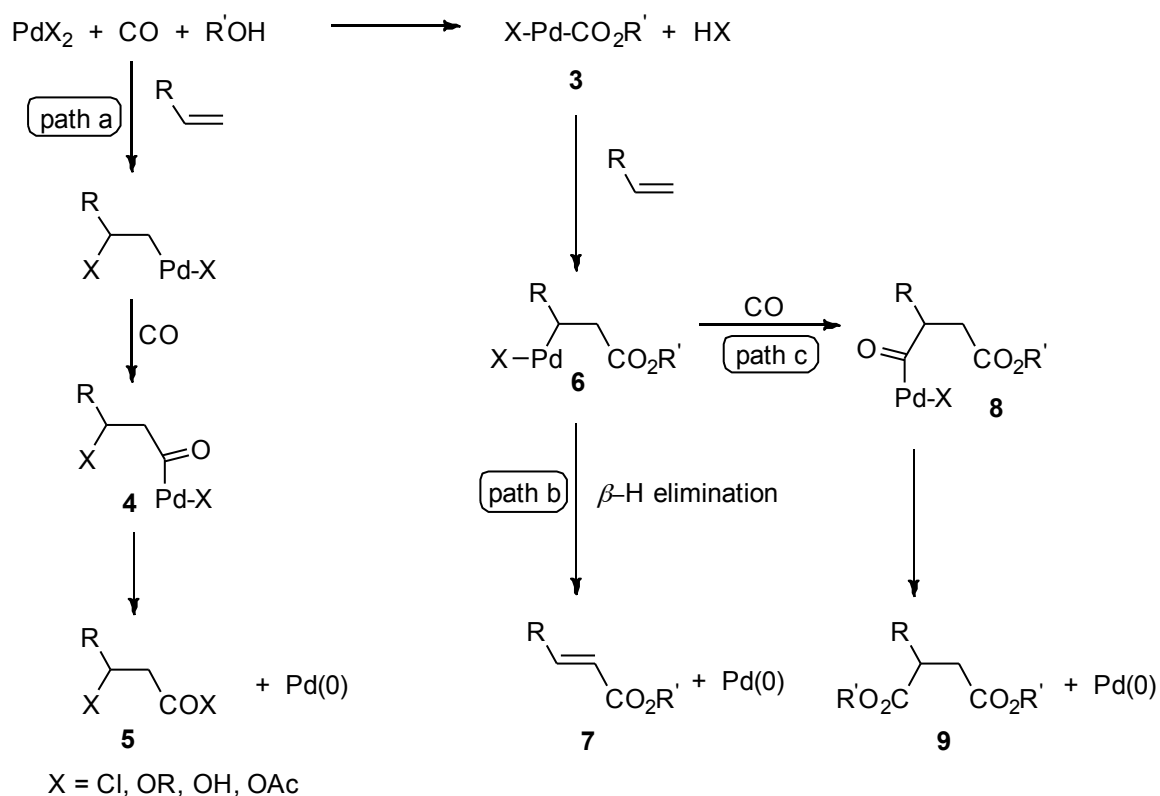
The Wacker process is the prototype for today's palladium-catalyzed oxidative carbonylations. Although no CO was used in this process, all the basic elementary steps for regenerating the catalyst under oxidative conditions are included. By definition, an oxidative carbonylation is a process in which 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, O₂ 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

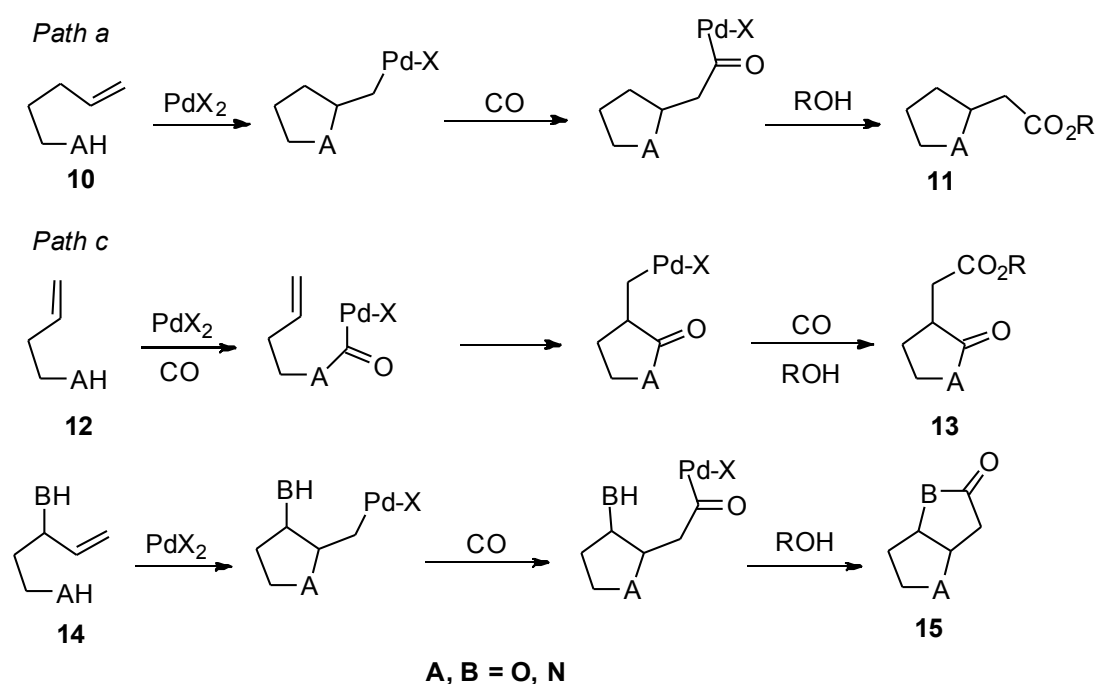
mechanism (Scheme 1.6). Palladation of alkenes with PdX_2 , followed by CO insertion, generates the acylpalladium intermediate **4** whose reductive elimination affords β -substituted carboxylic acid derivatives **5** (path a). Reaction in alcohol in the presence of a base starts by the formation of 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** ($\text{X} = \text{OR}$) 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-pentenamine 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 conventionally 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:

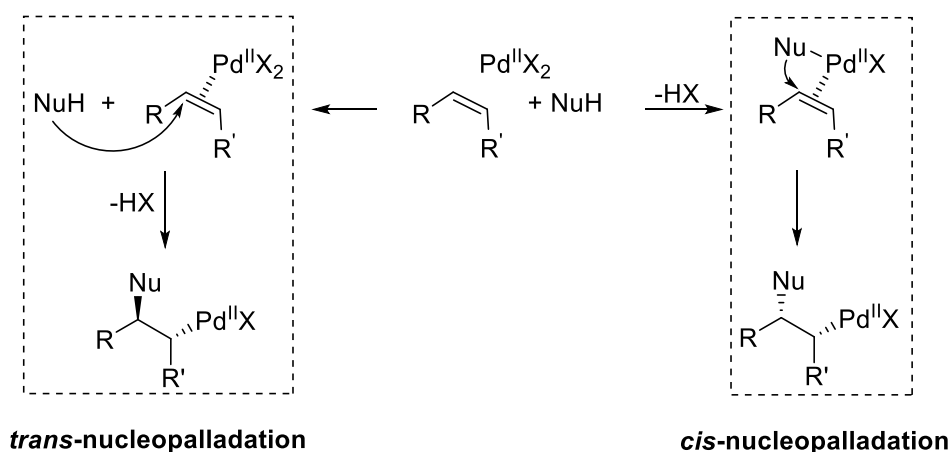
(a) To maintain a catalytic cycle, the Pd(0) formed after one catalytic cycle must be re-oxidized to Pd(II) by an oxidizing agents. These oxidants are generally required in large amounts and this excess usually interferes with phosphane- or nitrogen-based ligands;

(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 O₂), 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

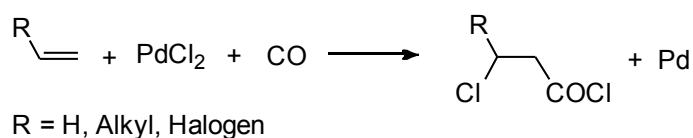
enantioselective catalysis is that nucleopalladation reactions are capable of proceeding by two stereochemically different pathways: *cis*- or *trans*-nucleopalladation (Scheme 1.8). Experimental results obtained over the past 40 years demonstrate that the energy barriers associated with these different pathways can be very 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.

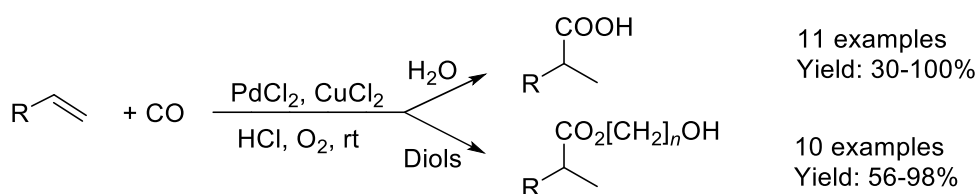
Above all, the great synthetic value of such carbonylation has been encouraging chemists to overcome its challenges. Indeed, it should be noticed that carbonylation of olefins catalyzed by palladium has far studied, and advancements in this area have been proven by numerous publications. I wish to provide 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 PdCl₂ 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.



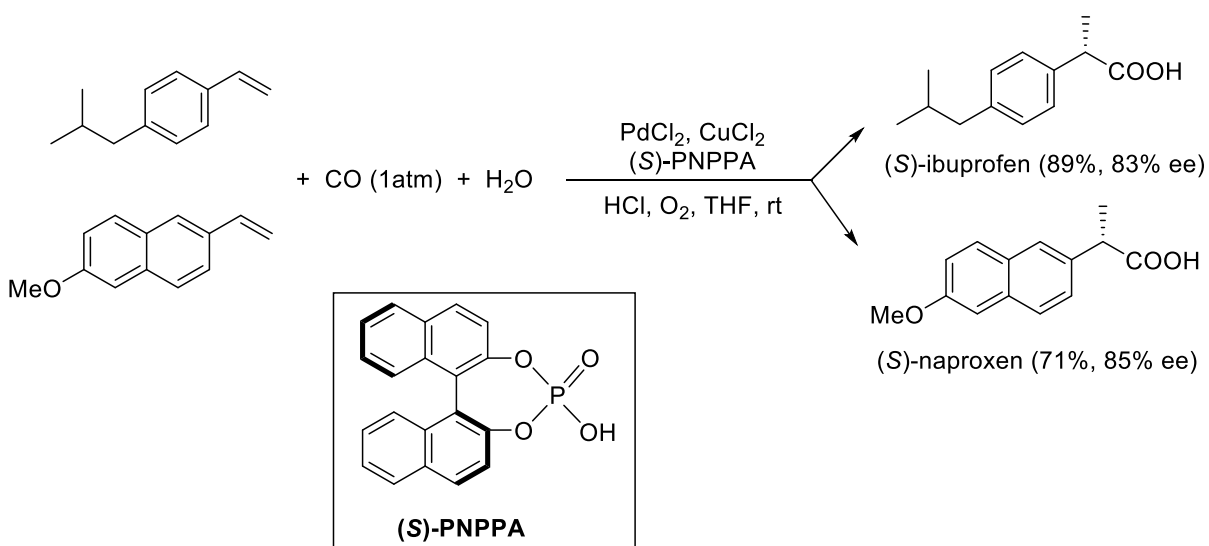
Scheme 1.9. Monocarbonylation of alkenes to β -chloroacyl chloride.

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, PdCl₂ and CuCl₂ 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.



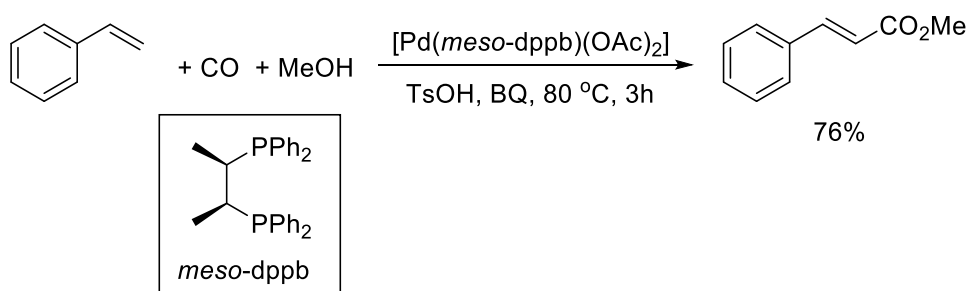
Scheme 1.10. Monohydrocarbonylation of alkenes to branched products.

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-ethoxynaphthalene into (*S*)-naproxen, which both possess nonsteroidal anti-inflammatory properties²⁴ (Scheme 1.11).



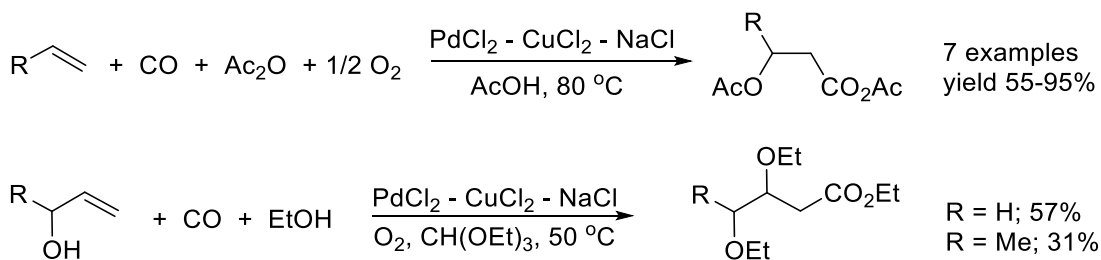
Scheme 1.11. Asymmetric hydroxycarbonylation of alkenes.

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.

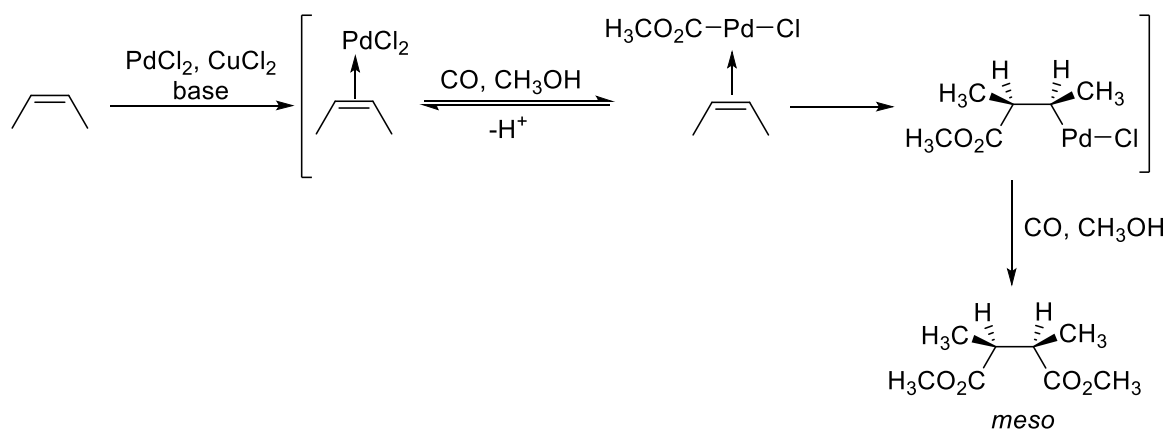
Fuchikami and co-workers²⁷ reported a practical preparation of β -hydroxyalkanoic acid derivatives by aerobic oxidative carbonylation of olefins under atmospheric pressure (Scheme 1.13). Olefins were heated in acetic acid and acetic anhydride in the presence of PdCl₂, CuCl₂, and NaCl under atmospheric pressure of CO and O₂ (ca. 2/1, 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.

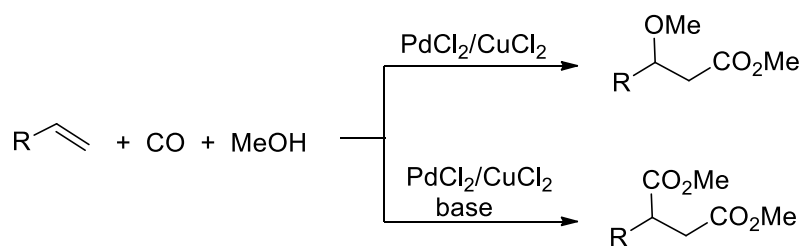
The first catalytic dialkoxycarbonylation of olefins was reported by Medema *et al.* in 1969.²⁸ More specifically, a catalytic amount of palladium was used together with an equivalent of CuCl₂, and the reactions were run at a high pressure of CO and comparatively high reaction temperature (140–150 °C). 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.

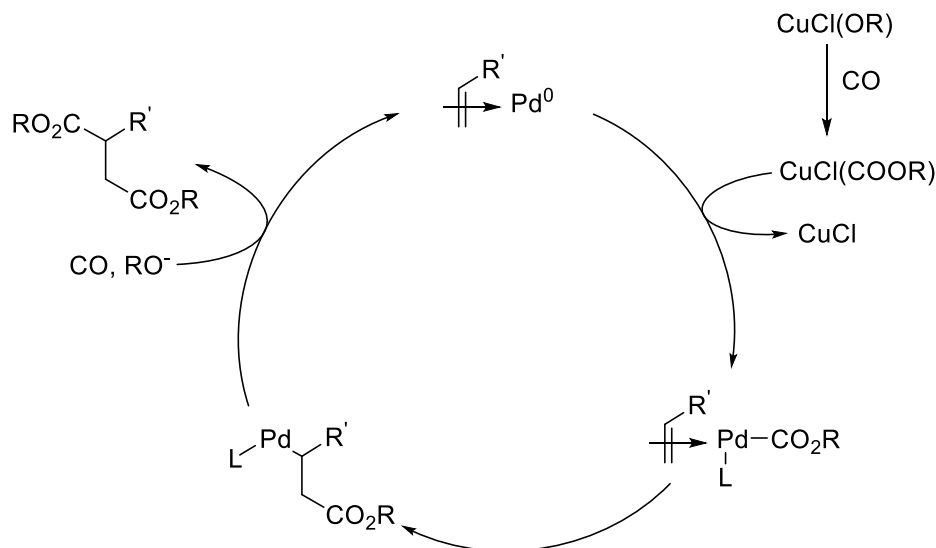
Apart from internal and terminal olefins, they extended their methodology to reactions of diolefins, vinyl ketones, unsaturated alcohols and unsaturated esters with a sodium butyrate buffer.³⁰ All these substrates were dicarboxylated in high yields (Scheme 1.15).



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

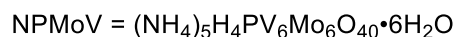
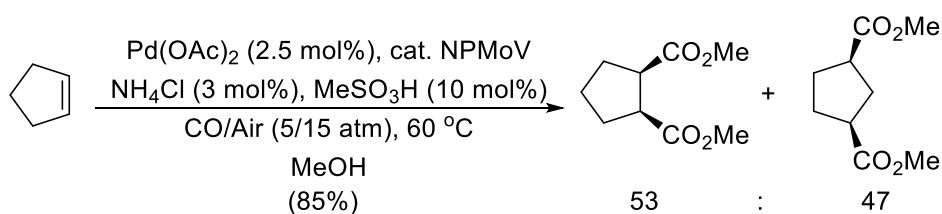
The role of copper salt used in the above mentioned reactions has merely been an oxidizing agent of $\text{Pd}(0)$ as considered in the Wacker process. However, in 1990 Chauvin and co-workers³¹ demonstrated a catalytic cycle in which the carboalkoxy groups can be

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.



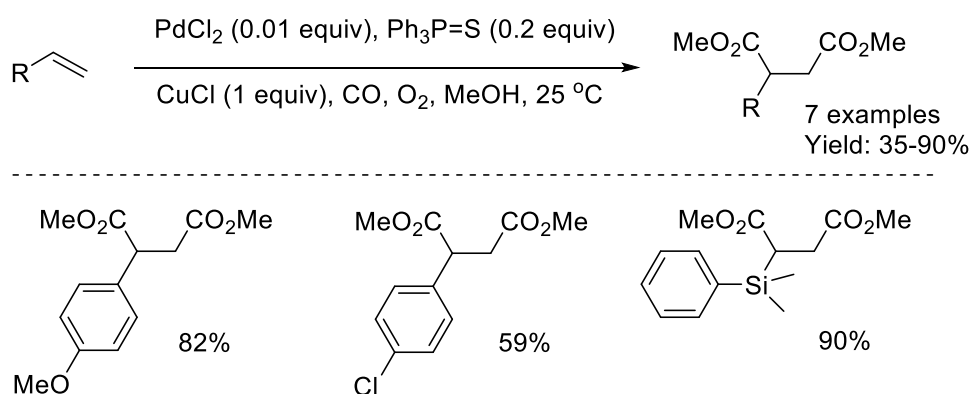
Scheme 1.16. Catalytic cycle of bis(alkoxycarbonylation) reaction.

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 yields³² (Scheme 1.17). Several alkenes were similarly converted into the corresponding dimethyl dicarboxylates.



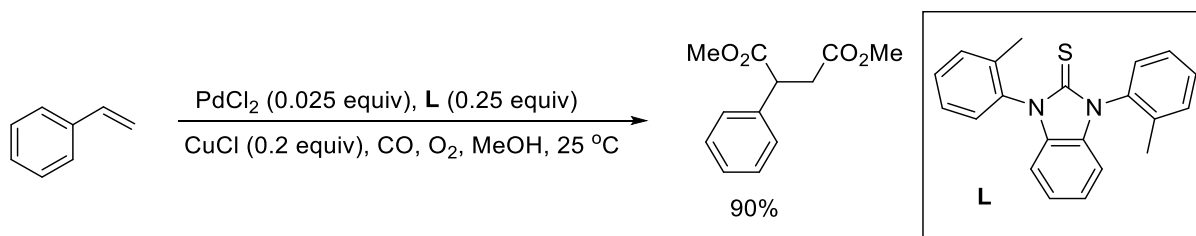
Scheme 1.17. Oxidative carbomethoxylation of cyclopentene.

Although 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 ($\text{Ph}_3\text{P=S}$) 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 $\text{Ph}_3\text{P=S}$ and CuCl at room temperature and under 1 atm of CO and O_2 (Scheme 1.18).



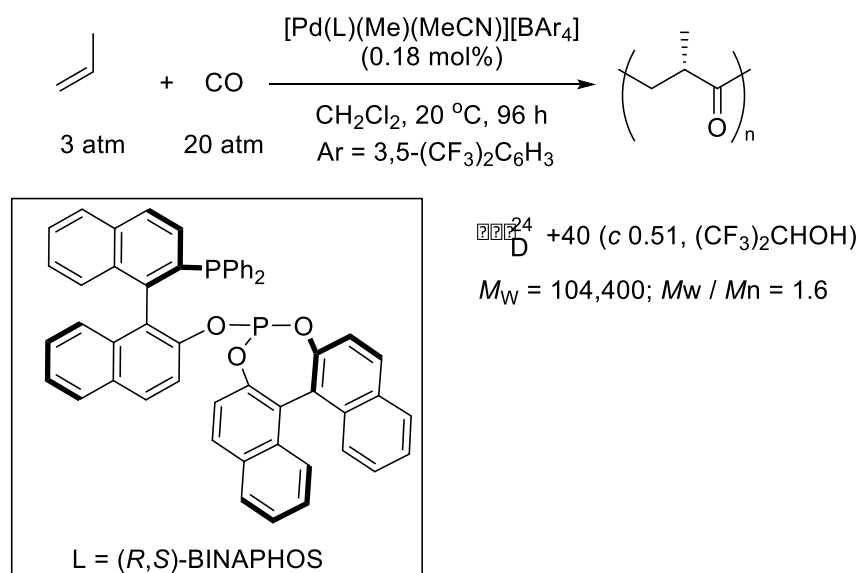
Scheme 1.18. Bis(alkoxycarbonylation) reaction of alkenes using triphenylphosphine-sulfide.

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.



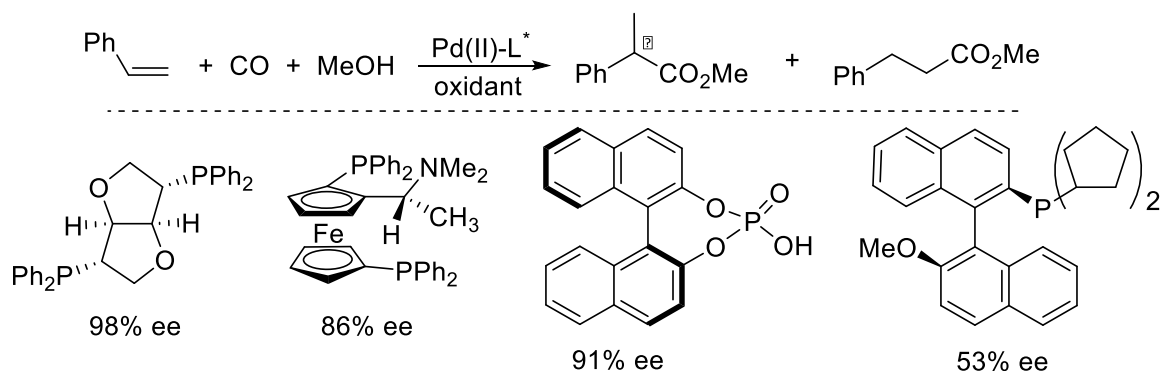
Scheme 1.19. Bis(alkoxycarbonylation) reaction of styrene using thiourea as ligand.

Asymmetric hydroxycarbonylation of olefins was first reported in 1973 using PdCl₂ 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}



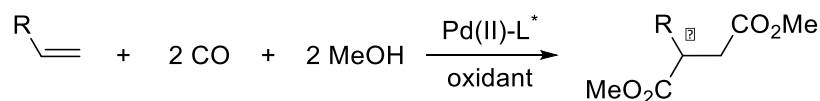
Scheme 1.20. Asymmetric alternating copolymerization of propene with CO.

Later, catalysts containing phosphine ligands had been frequently used for the asymmetric alkoxy carbonylation 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.

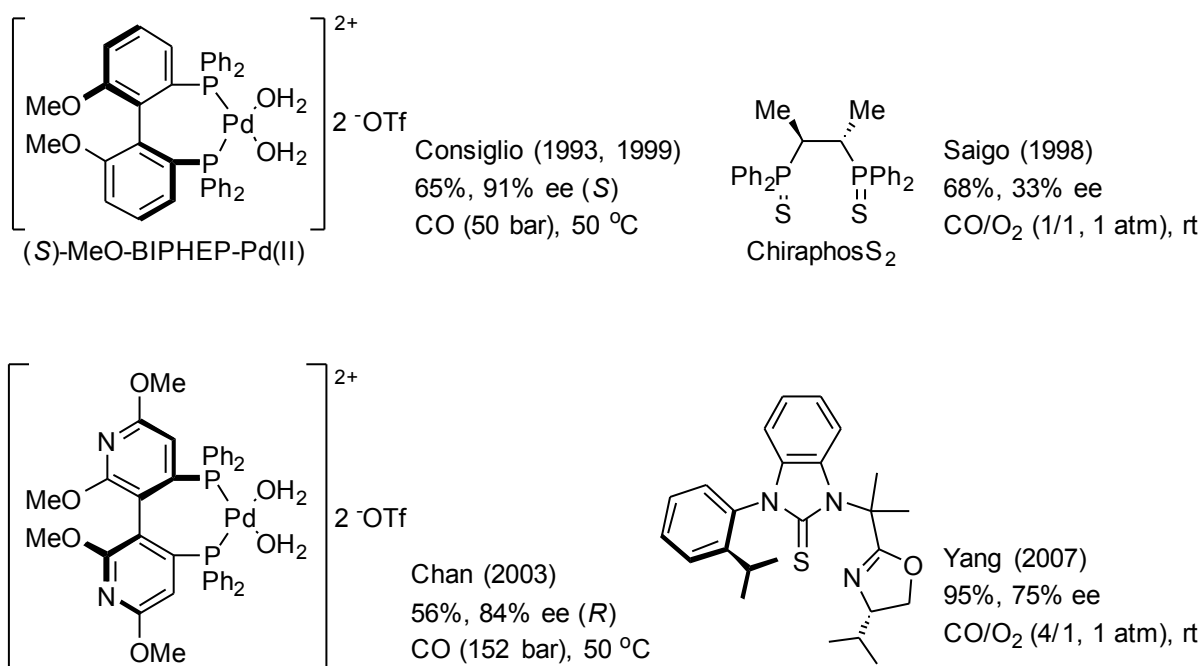
The enantioselective synthesis of optically active succinic acid derivatives is of interest as they are important intermediates of pharmaceuticals and building blocks for rennin inhibitors.³⁷ These products are formed by the asymmetric bis(alkoxycarbonylation) of alkenes (Scheme 1.22).



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 atropisomeric 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 ChiraphosS₂ under normal pressure of CO and O₂ to give diester in 68% and 33% ee.³³ In 2003, Chan *et al.* conducted the reaction using

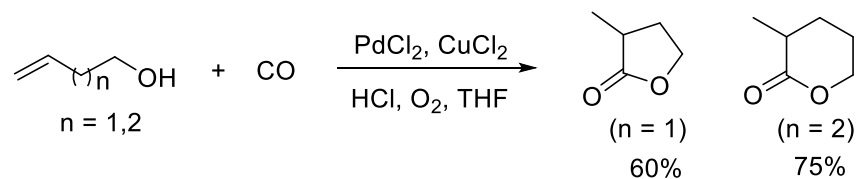
chiral dipyridylphosphine under high pressure of CO (152 bar).³⁹ In 2007, Yang and co-workers developed chiral *S,N*-heterobidentate thiourea-oxazoline ligand, which were employed for asymmetric palladium-catalyzed bis(alkoxycarbonylation) of styrene under mild conditions, giving dimethyl phenylsuccinate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



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.

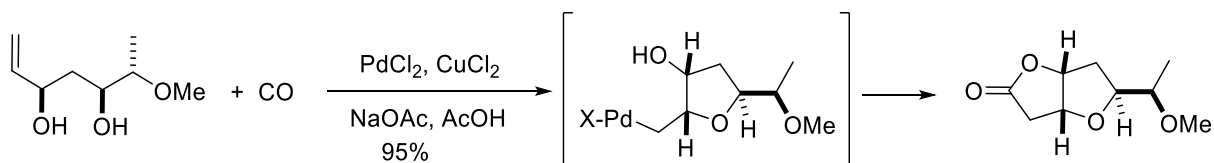
Carbonylation of alkenes having a nucleophilic function, such as an amino or hydroxy group, offers interesting synthetic methods for heterocyclic compounds.^{13, 16} In 1985, Alper and Leonard reported oxidative carbonylation of alkenones to produce five-membered

lactones.⁴¹ The reaction was conducted in THF in the presence of a PdCl₂/CuCl₂ catalyst system, yielding lactones in 42–80% (Scheme 1.23).



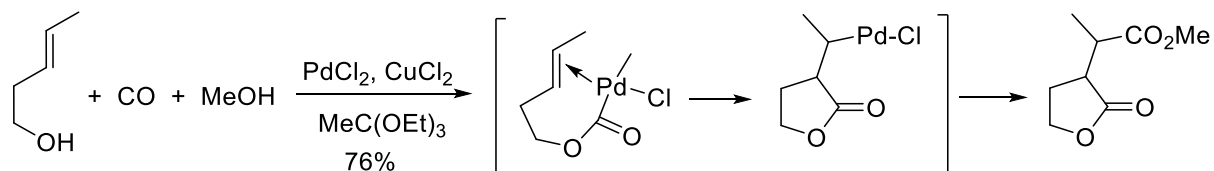
Scheme 1.23. Carbonylation reaction of alkenols.

Semmelhack and co-workers developed a methodology 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).



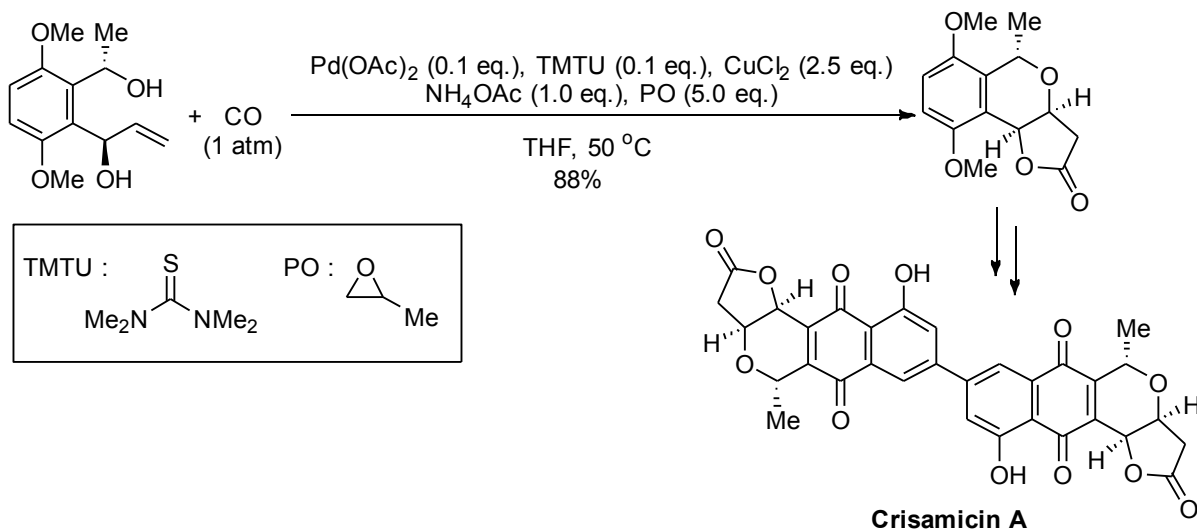
Scheme 1.24. Carbonylation of the alkenediol.

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 conditions⁴³ (Scheme 1.25).



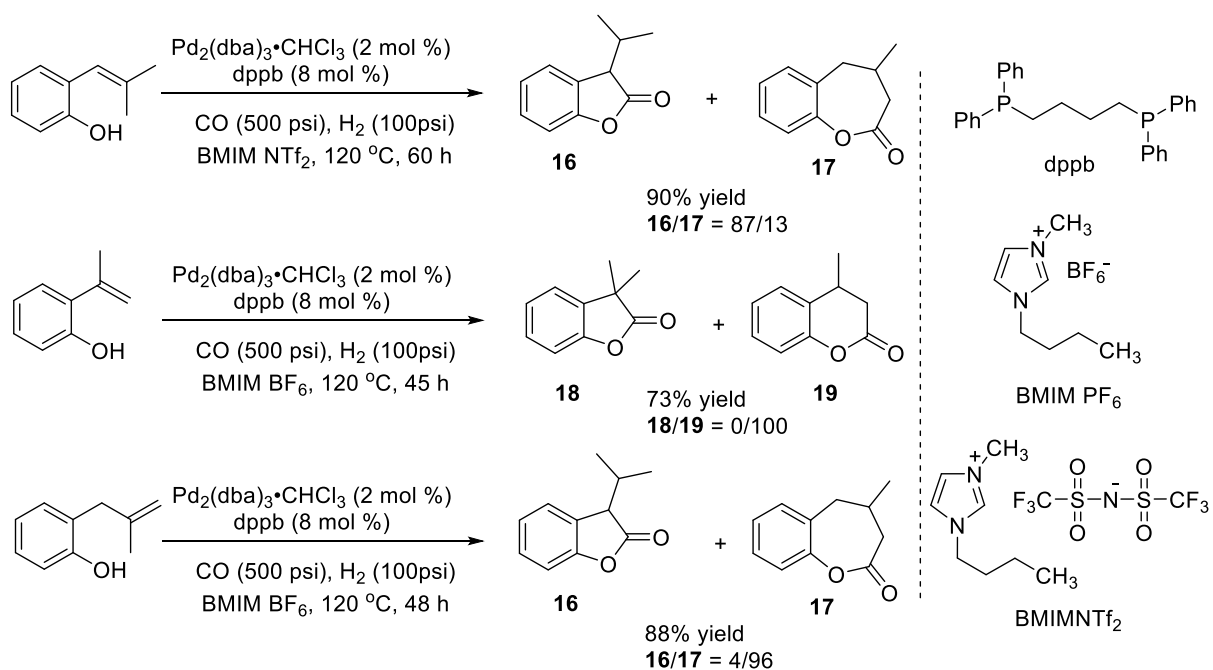
Scheme 1.25. Palladium-catalyzed dicarbonylation of 3-penten-1-ol.

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

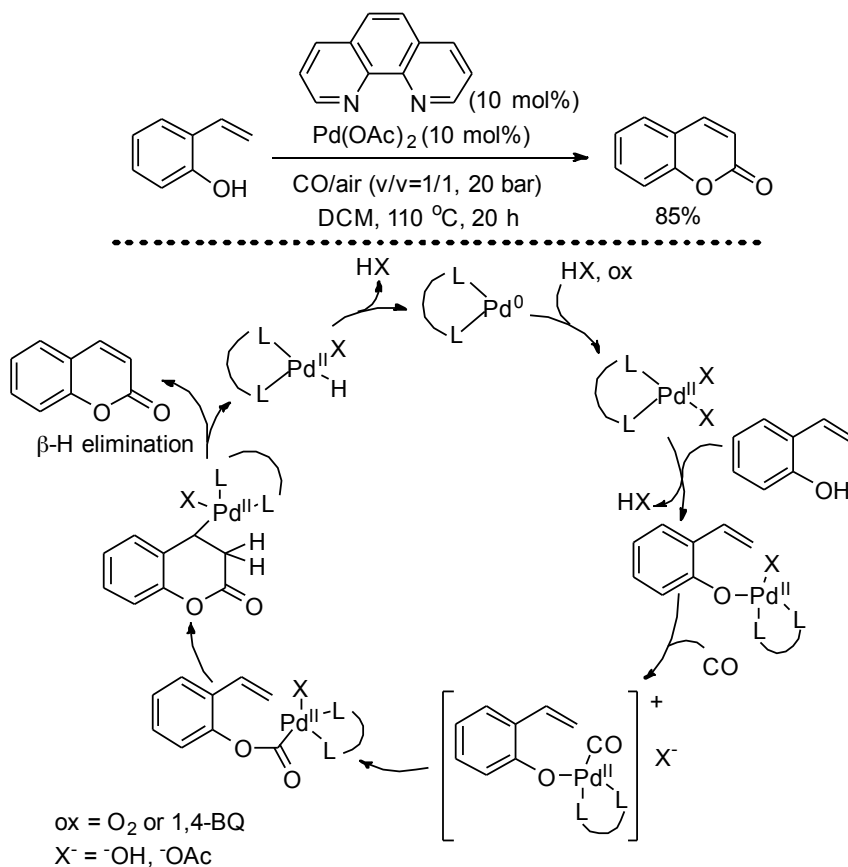


Scheme 1.26. Pd-catalyzed carbonylative annulation: Total synthesis of Crisamicin A.

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 PF₆ or BMIMNTf₂.⁴⁵ 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 ≤ 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.

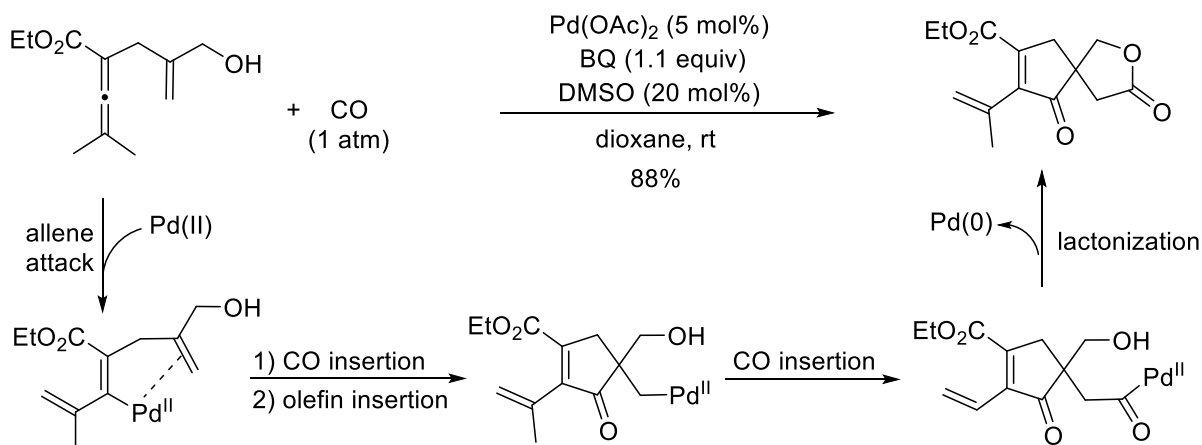


Scheme 1.27. Cyclocarbonylation reaction of vinyl- and allylphenols.



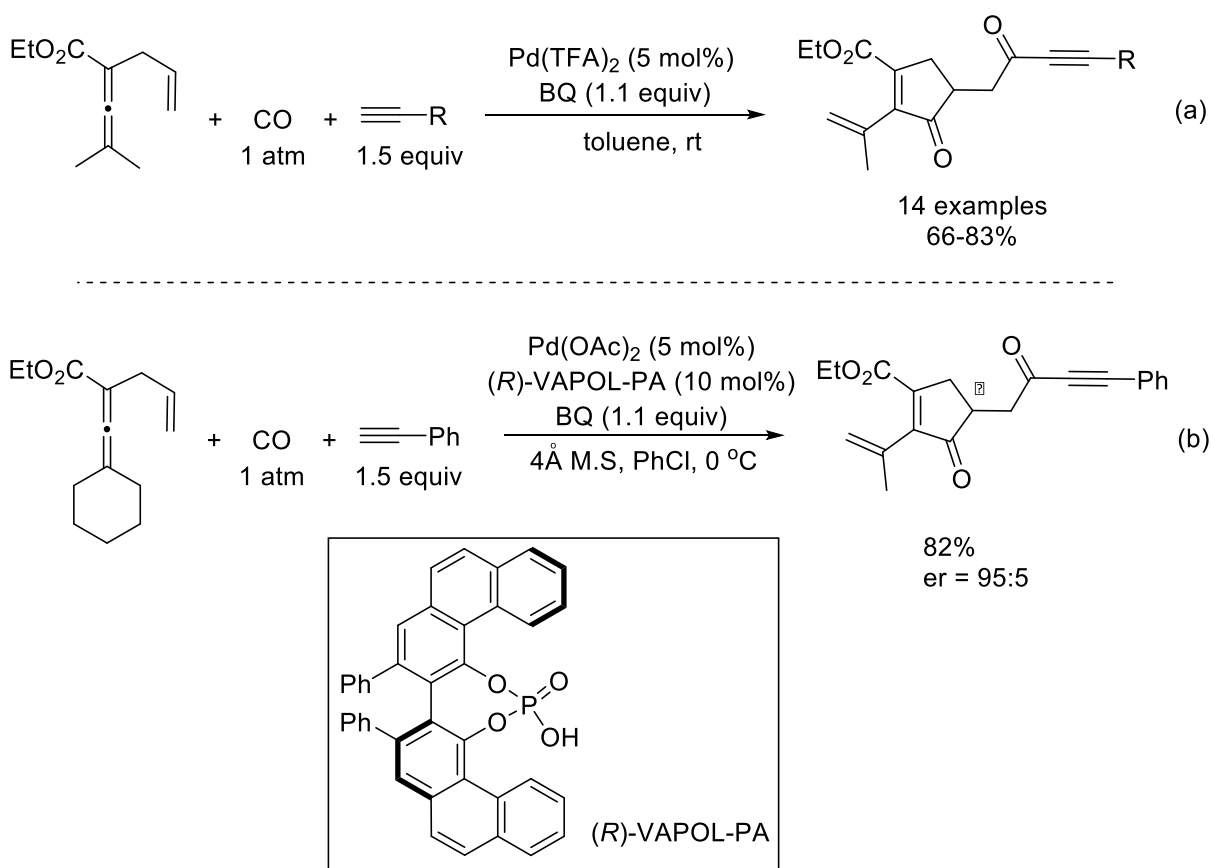
Scheme 1.28. Scheme 1.1 Cyclocarbonylation of 2-vinylphenols to coumarins.

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



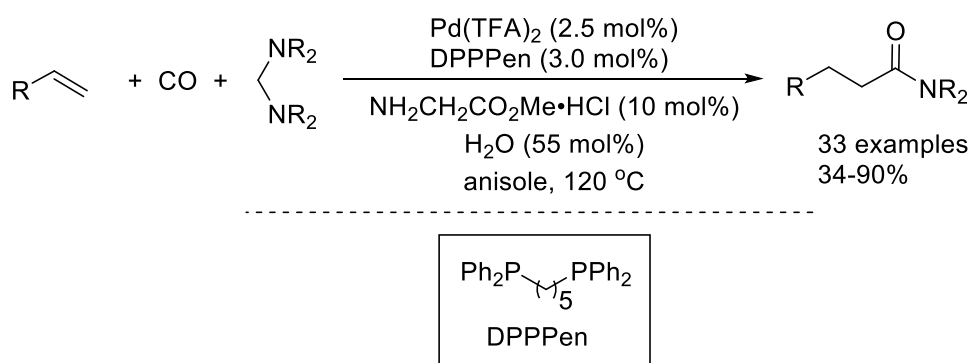
Scheme 1.29. Oxidative cascade carbonylative spiro lactonization of enallenol.

The same research group reported a highly selective cascade C–C bond formation via Pd(II)-catalyzed carbonylation/carbocyclization/carbonylation/alkynylation of enallenes⁴⁸ (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 ketones⁴⁹ (Scheme 1.30b).



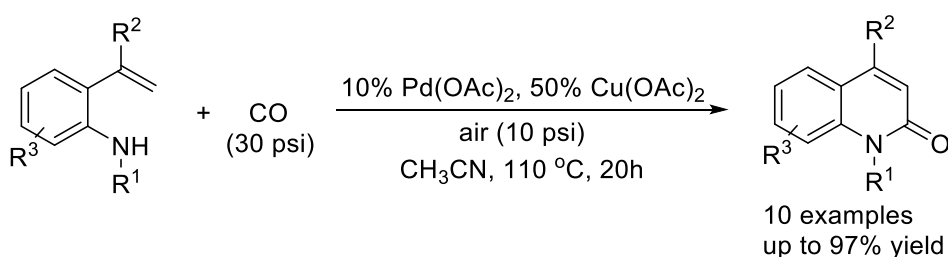
Scheme 1.30. Carbonylative carbocyclization of enallenes via cross-dehydrogenative coupling with terminal alkynes.

In 2015, Huang and co-workers⁵⁰ developed palladium-catalyzed hydroaminocarbonylation 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).



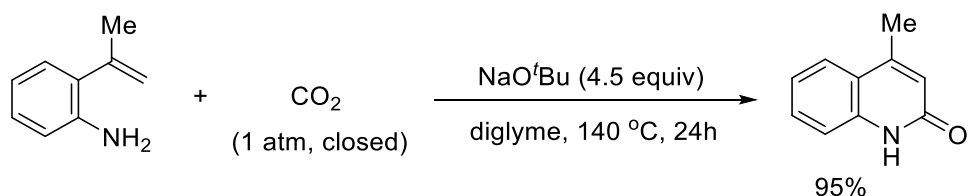
Scheme 1.31. Hydroaminocarbonylation of alkenes with amines.

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).



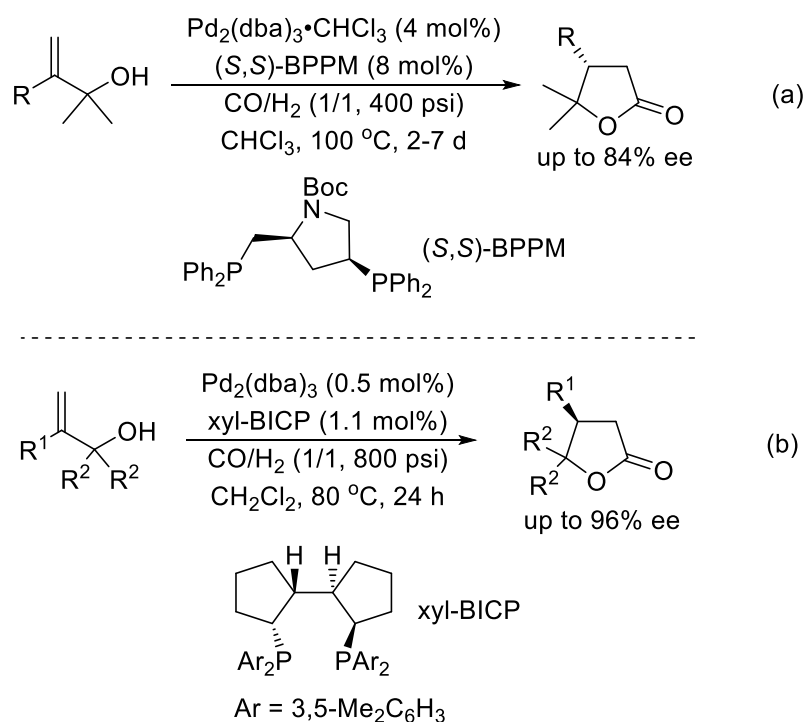
Scheme 1.32. Oxidative cyclocarbonylation of 2-vinylanilines.

In 2016, Yu and co-workers reported the first direct use of CO₂ 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 yields⁵² (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.



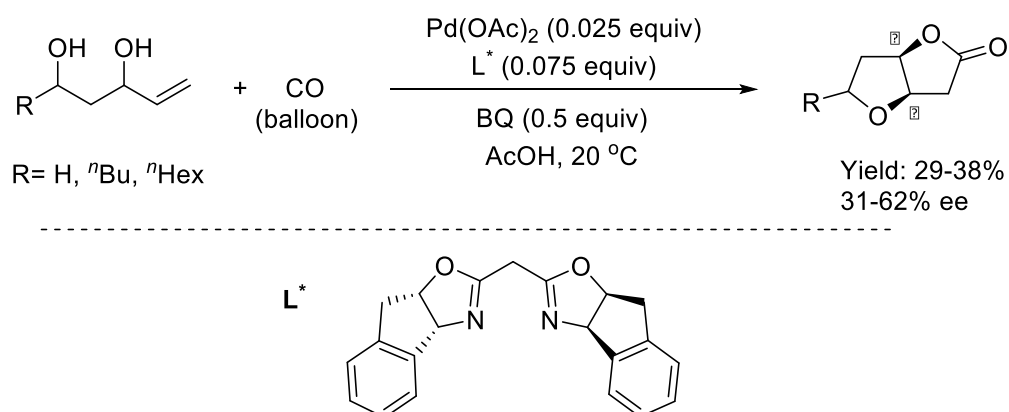
Scheme 1.33. Direct lactamization of 2-(prop-1-en-2-yl)aniline with CO₂.

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% ee⁵⁴ (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% ee⁵⁵ (Scheme 1.34b).



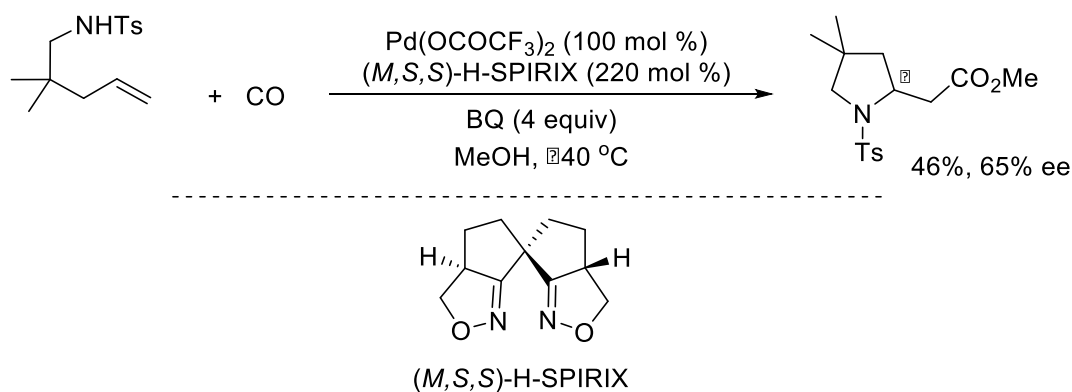
Scheme 1.34. Asymmetric cyclocarbonylation of allylic alcohols.

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).



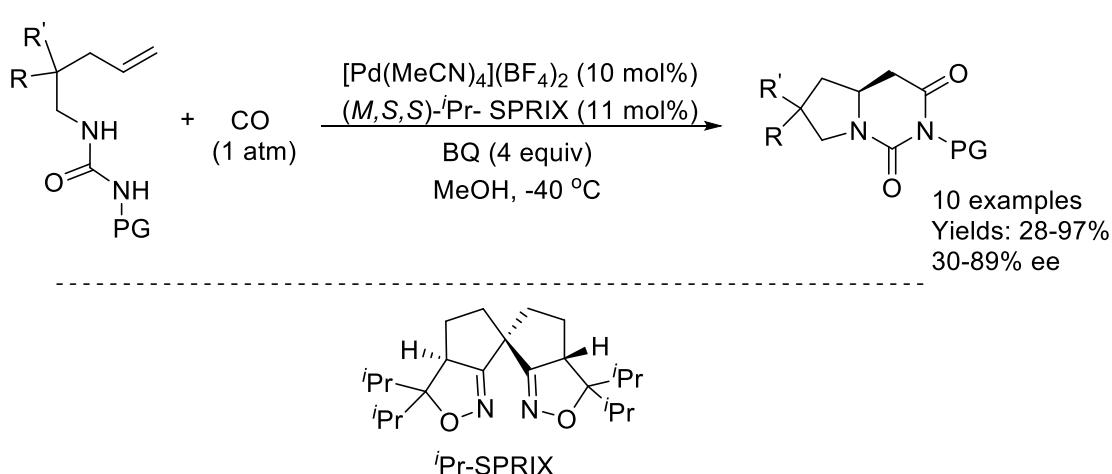
Scheme 1.35. Asymmetric intramolecular oxycarbonylation of alkene-1,3-diols.

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.



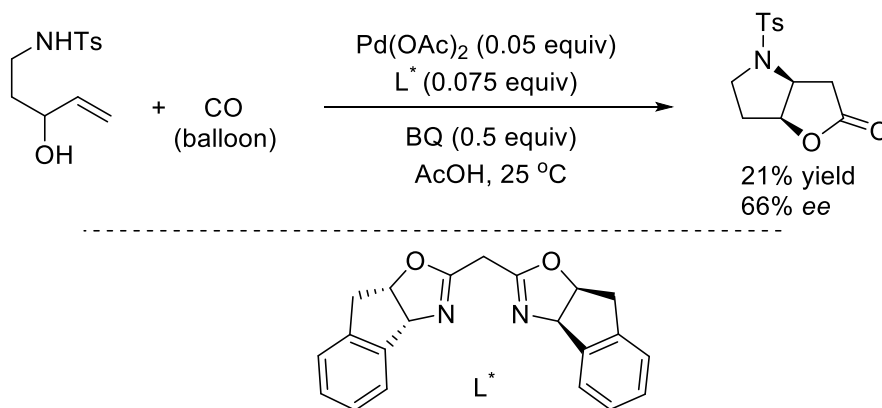
Scheme 1.36. Asymmetric aminocarbonylation using Pd(II)-[SPRIX] catalyst.

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 (^{*t*}Pr-SPRIX) was essential to obtain the desired products in optically active forms.



Scheme 1.37. Asymmetric intramolecular oxidative aminocarbonylation of alkenylureas.

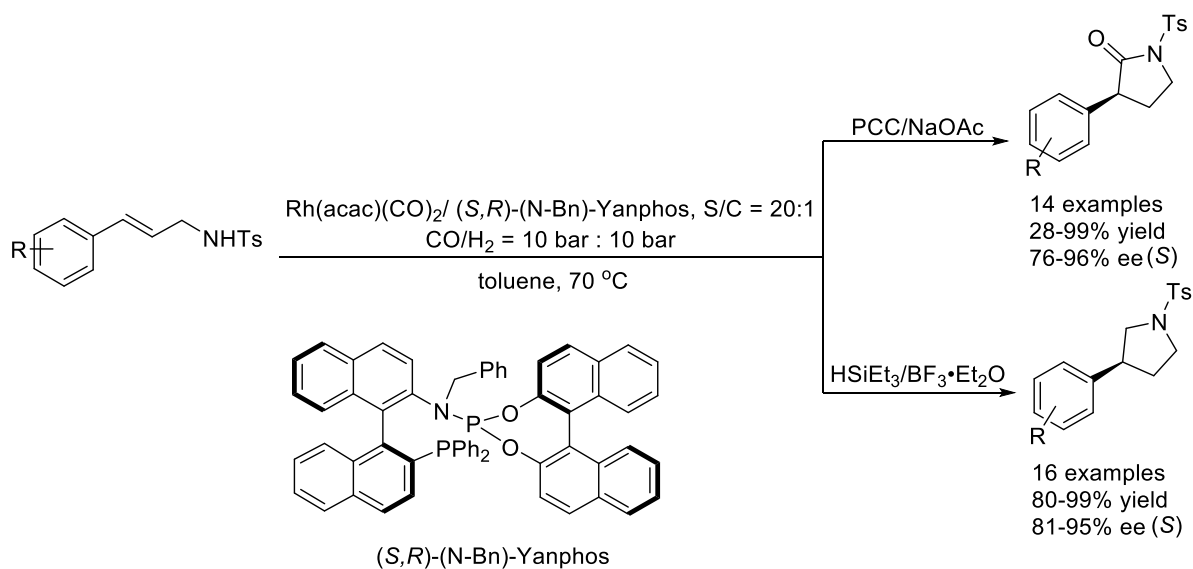
Asymmetric Pd(II)-catalyzed carbonylative bicyclization of amino alcohols has been reported by Graza's group in 2009.⁵⁹ The (*R,R*)-*N*-protected 2-oxa-6-azabicyclo[3.3.0]octan-3-ones (derivatives of the natural Geissman-Waiss lactone) were obtained in 20%–40% yields with 60%–73% *ee* by using chiral 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 O₂ gas mixture. In addition, asymmetric palladium-catalyzed carbonylations of olefins have undeveloped and still been regarded as the most challenging problem in carbonylation field.

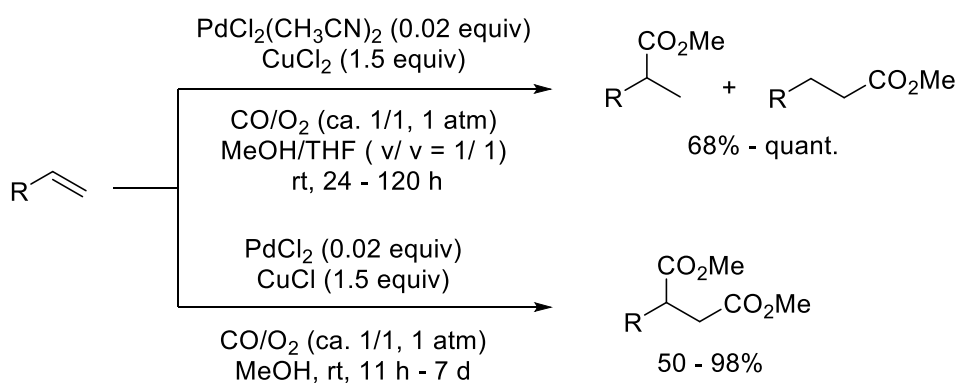
Furthermore, the intermolecular version of the alkoxy-carbonylation of alkenes is quite limited. Therefore, this area still remains space to develop in academic research. Development of catalytic system with higher efficiency, stereoselectivity, and larger substrate scope is an important issue for these 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

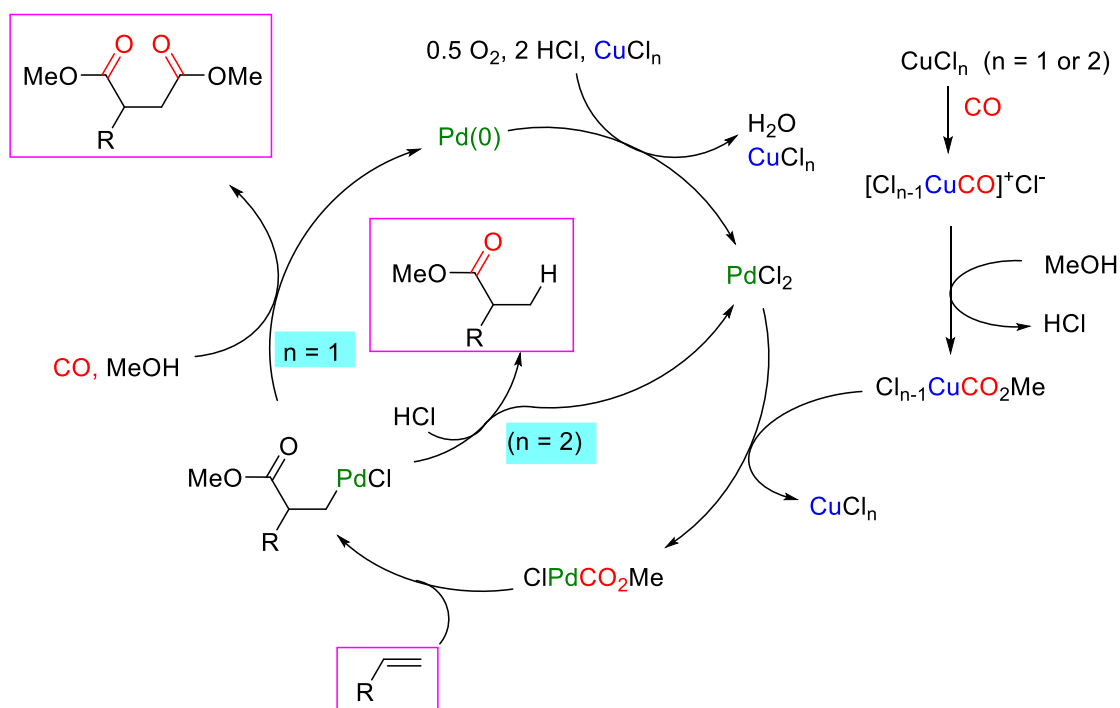
This section provides a brief summary for our previous works on palladium-catalyzed carbonylation, selecting from reported original papers of our research group. Such selected contents are presumed as a solid background for the present study. It should be noted that some contents (*i.e* our fundamental 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 O₂.⁶¹ Interestingly, mainly monoesters were observed if CuCl₂ 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.

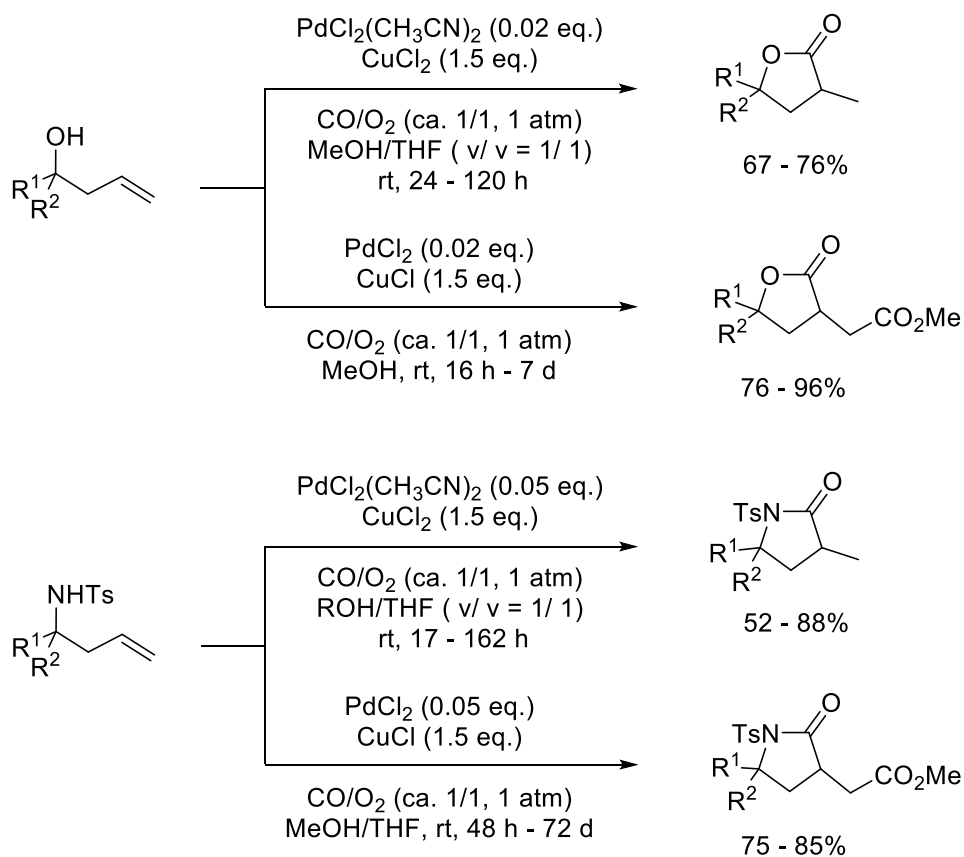
In the oxidation reaction of olefins catalyzed by palladium–copper systems, it has been proposed that copper works not as an oxidant of Pd(0) but cooperative action with palladium to generate active species.⁶² Cu(I) compounds are well-known to absorb CO to generate carbonyl complexes. Carbonylation reactions 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 intermediate, 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.



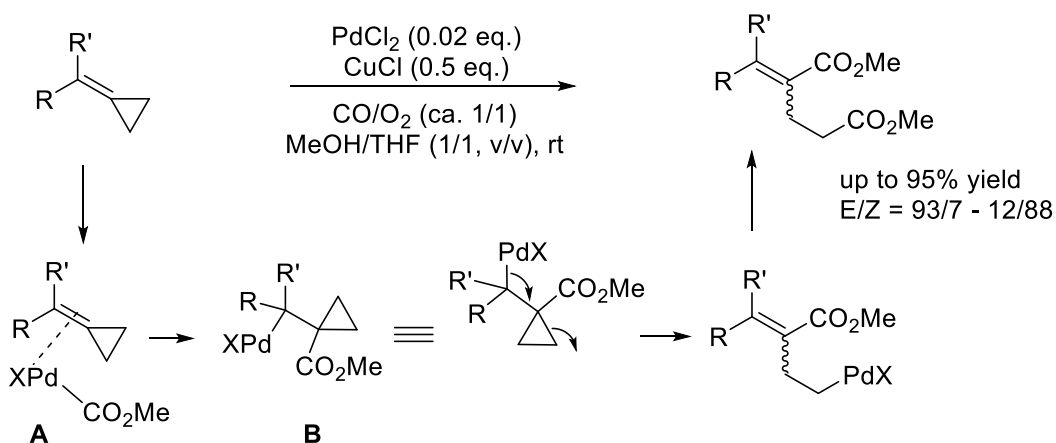
Scheme 1.41. Plausible catalytic pathway for the selective mono- and bis(alkoxycarbonylation) reactions.

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 -methylene-glutarates.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).

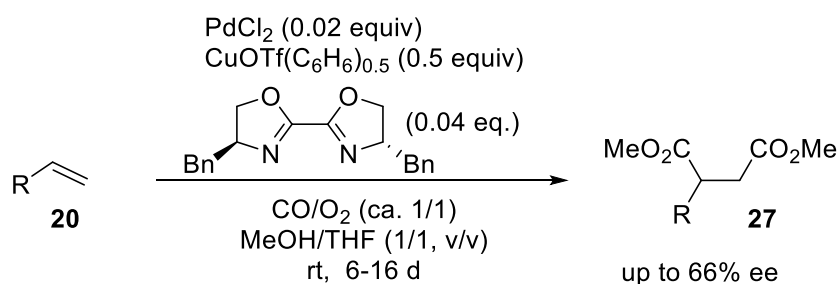


Scheme 1.42. Mono- and dicarbonylation reactions of homoallylic alcohols and homoallylic amines.

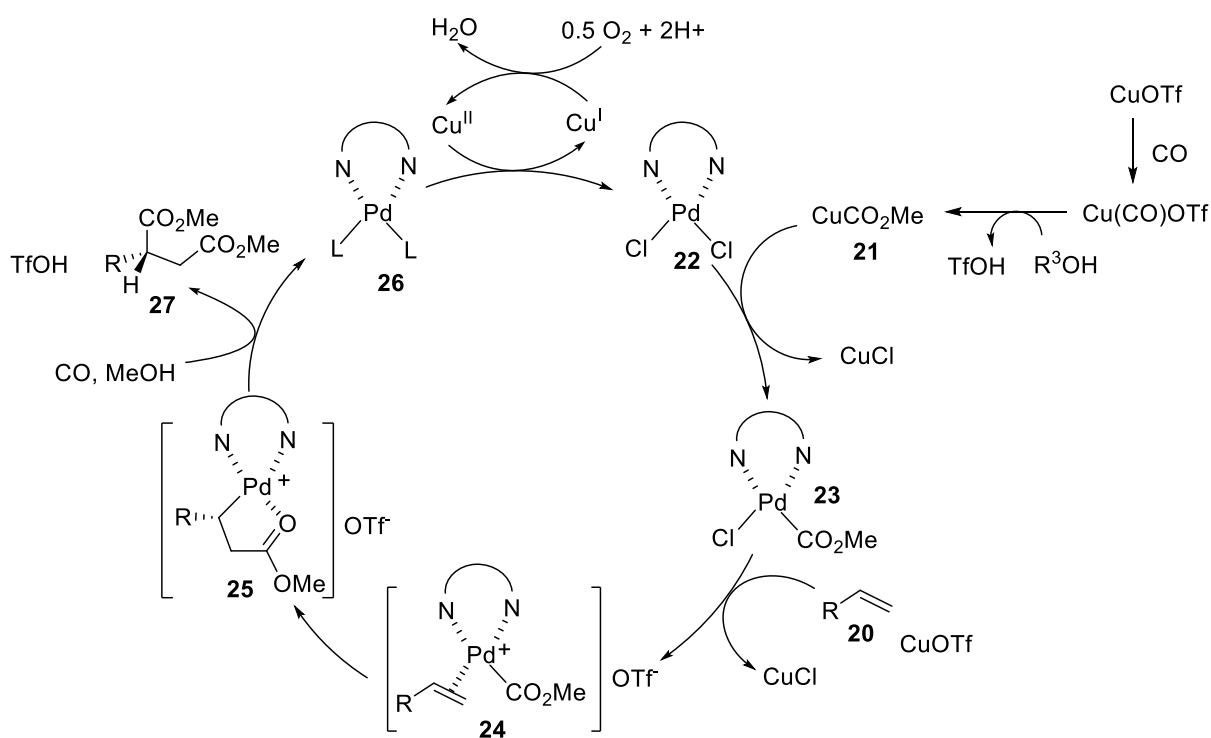


Scheme 1.43. Bis(alkoxycarbonylation) reaction of methylene cyclopropanes.

As the regio- and chemoselectivity of alkoxy-carbonylations have been continuously improved and milder reaction conditions were applicable, we already developed asymmetric versions of bis(alkoxy-carbonylation) reactions. A palladium-catalyzed asymmetric bis(alkoxy-carbonylation) 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.



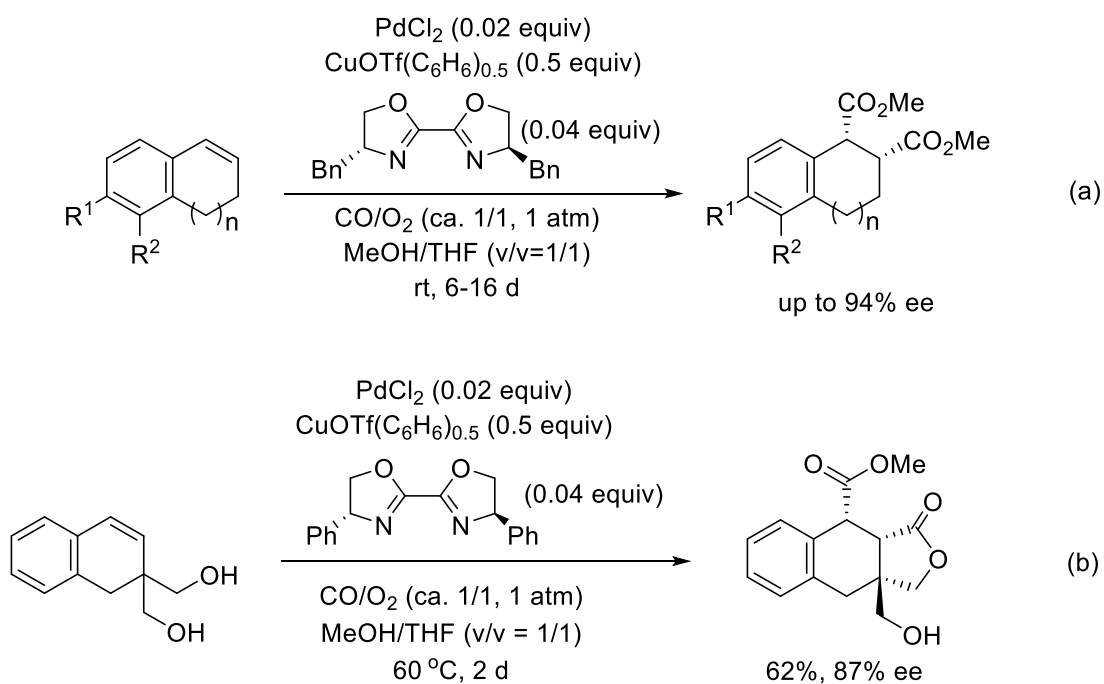
Scheme 1.44. Asymmetric bis(alkoxy-carbonylation) of terminal alkenes.



Scheme 1.45. Plausible mechanism pathway.

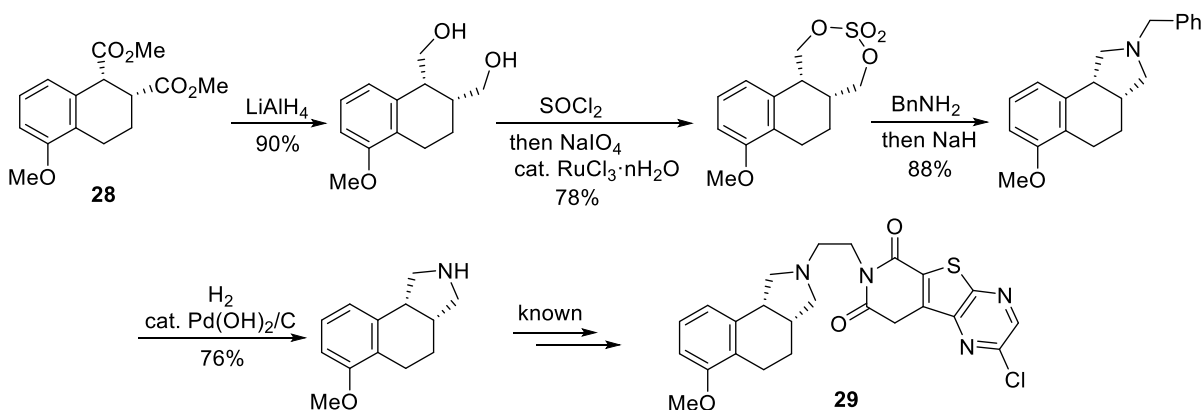
Copper(I) triflate reacts with CO and MeOH successively to give the CuCO₂Me species **21** and the methoxycarbonyl group was transferred to palladium chloride complex **22** with the chiral ligand to generate complex **23**. Further, copper(I) triflate also reacts with **23** to afford a cationic palladium 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 olefins⁶⁷ 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 skeleton⁶⁸ was also realized to give higher enantioselectivity (87% ee) with phenyl-substituted ligand (Scheme 1.46b).



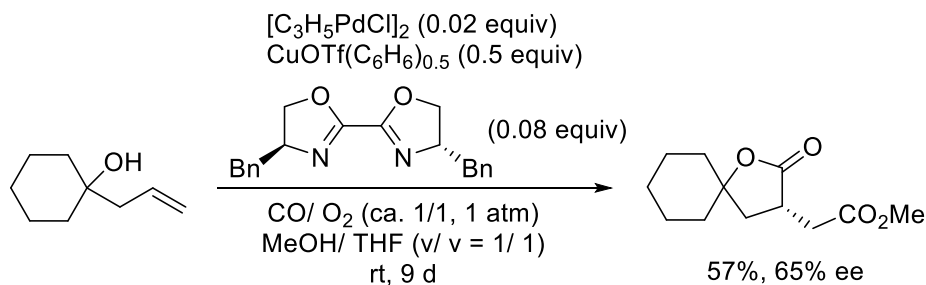
Scheme 1.46. Asymmetric bis(alkoxycarbonylation) reaction of cyclic olefins.

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 alcohols⁶⁹ 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(C₆H₆)_{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 C₄ of the bioxazoline ligand would disfavor the transition state **T**₂, and, thus transition state **T**₁ was favored to produce (*S*)- γ -butyrolactones (Figure 1.2).

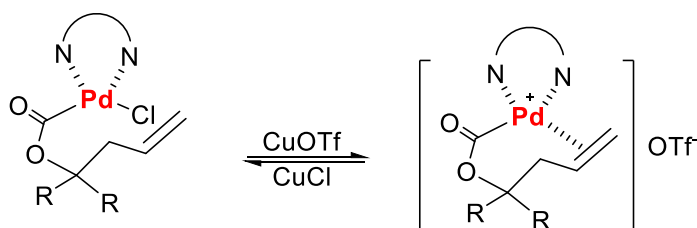


Figure 1.1

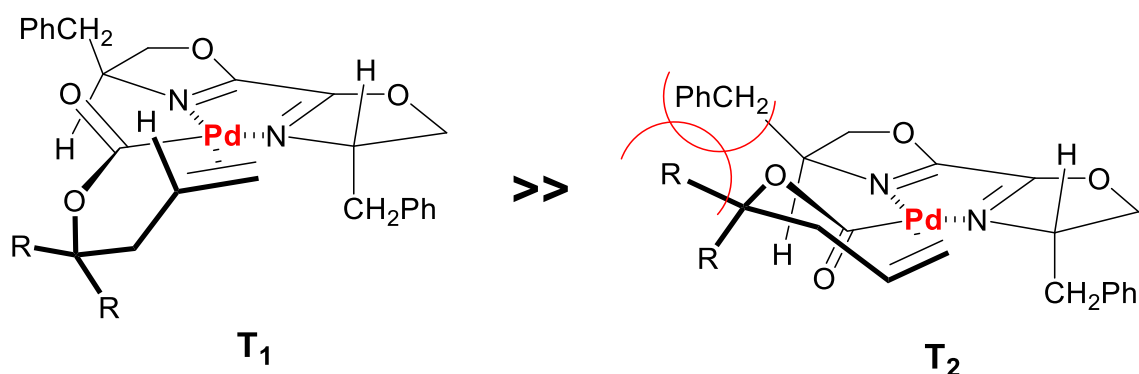
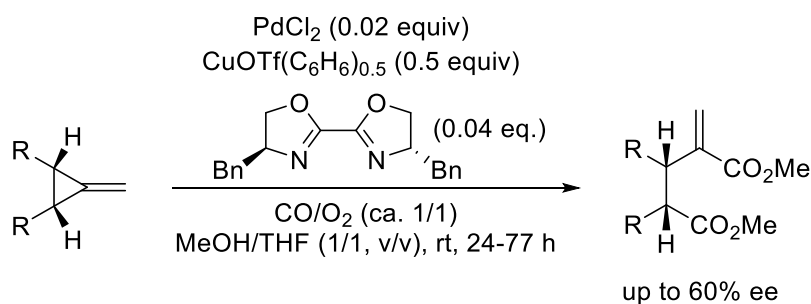


Figure 1.2

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-methylenecyclopropane-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 O₂. With respect to the synthetic value of carbonylation reactions towards preparation of intermediates 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 promising research area. The development 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 envisioned 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 promising 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 a privileged 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.

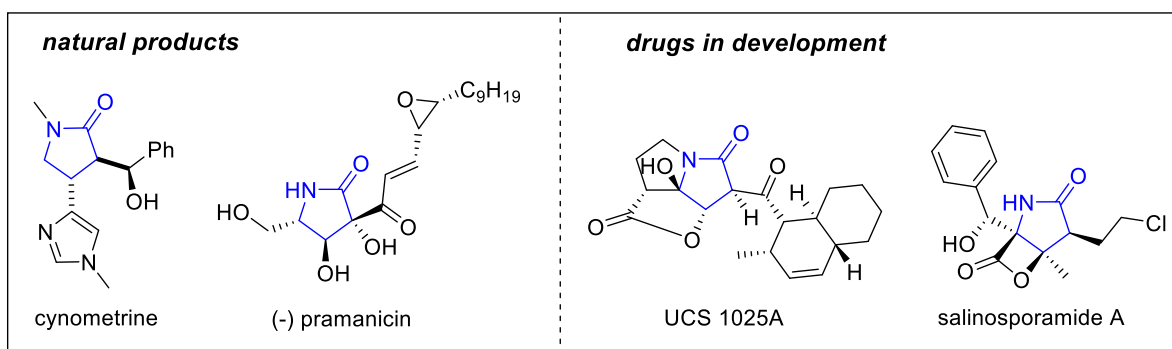


Figure 2.1. Selected examples of γ -lactam structures possessing a biological activity.

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 H₂ 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 $\text{Ru}_3(\text{CO})_{12}$ 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 envisioned 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 O₂ (ca.1/1, v/v, 1 atm) atmosphere in THF/MeOH (1/1,v/v) at 60 °C (Equation 2.1). The results were summarized in Table 2.1. A reaction using a 0.02 molar amount of PdCl₂ 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 PdCl₂ and CuOTf(C₆H₆)_{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 PdCl₂ furnished either better yield or enantioselectivity (Entry 7-12). Notably, the combination of a soluble palladium salt as [PdCl(allyl)]₂ with CuOTf(C₆H₆)_{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(C₆H₆)_{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(C₆H₆)_{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(C₆H₆)_{0.5} resulted in a further decline of enantioinduction (Entry 16).

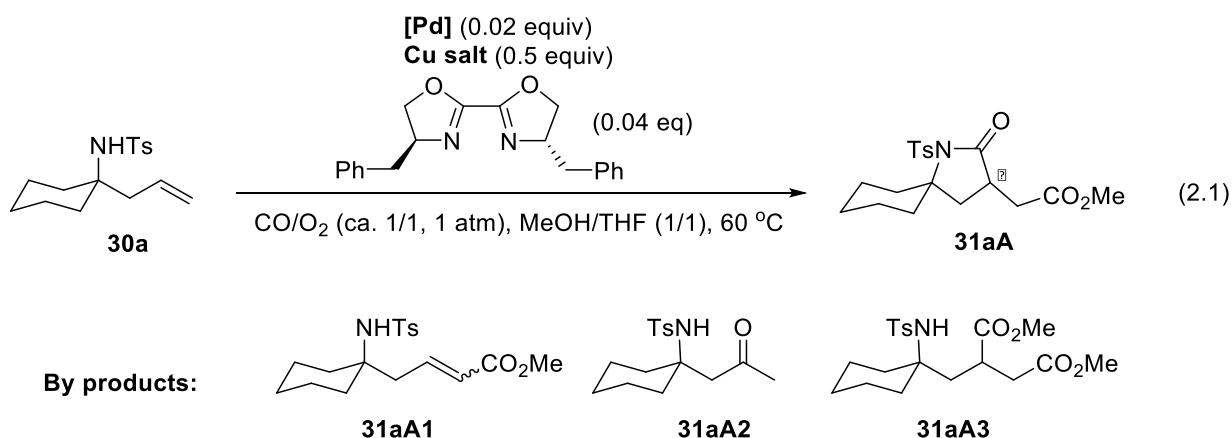


Table 2.1. Screening of Cu salts and Pd sources.

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) ₄ BF ₄	3	61	54
5	PdCl₂	CuOTf(C₆H₆)_{0.5}	3	49	68
6	PdCl ₂	Cu(OTf) ₂	3	24	16
7	PdCl ₂ (PhCN) ₂	CuOTf(C ₆ H ₆) _{0.5}	3	25	56
8 ^a	[PdCl(allyl)] ₂	CuOTf(C ₆ H ₆) _{0.5}	3	42	42
9	Pd(OAc) ₂	CuOTf(C ₆ H ₆) _{0.5}	4	30	42
10	Pd(TFA) ₂	CuOTf(C ₆ H ₆) _{0.5}	3	16	56
11	[Pd(CH ₃ CN) ₄](OTf) ₂	CuOTf(C ₆ H ₆) _{0.5}	4	35	43
12 ^b	Pd(dba) ₂	CuOTf(C ₆ H ₆) _{0.5}	3	25	53
13	PdCl ₂ (0.05 eq.)	CuOTf(C ₆ H ₆) _{0.5} (1.5 eq.)	3	51	57
14	PdCl ₂	CuOTf(C ₆ H ₆) _{0.5} (1.0 eq.)	3	44	37
15	PdCl ₂	CuOTf(C ₆ H ₆) _{0.5} (0.25 eq.)	3	84	46
16	PdCl ₂	CuOTf(C ₆ H ₆) _{0.5} (0.1 eq.)	3	57	43
17 ^c	PdCl ₂	CuOTf(C ₆ H ₆) _{0.5}	7	21	66
18 ^d	PdCl ₂	CuOTf(C ₆ H ₆) _{0.5}	5	53	67

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

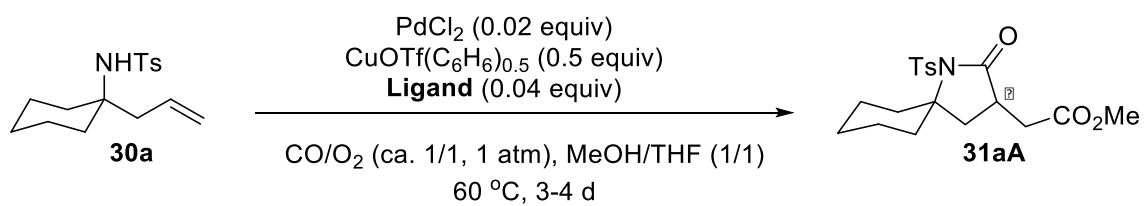
^a 0.08 equiv of ligand was used. ^b 0.04 equiv of LiCl was used.

^cThe reaction was conducted at room temperature for 7 days, 32% of starting material was recovered.

^dAfter prolonged reaction time (5 days).

Then, the poor conversion was observed 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 recovered 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 °C afforded **31aA** in better yield and 67% ee (Entry 18).

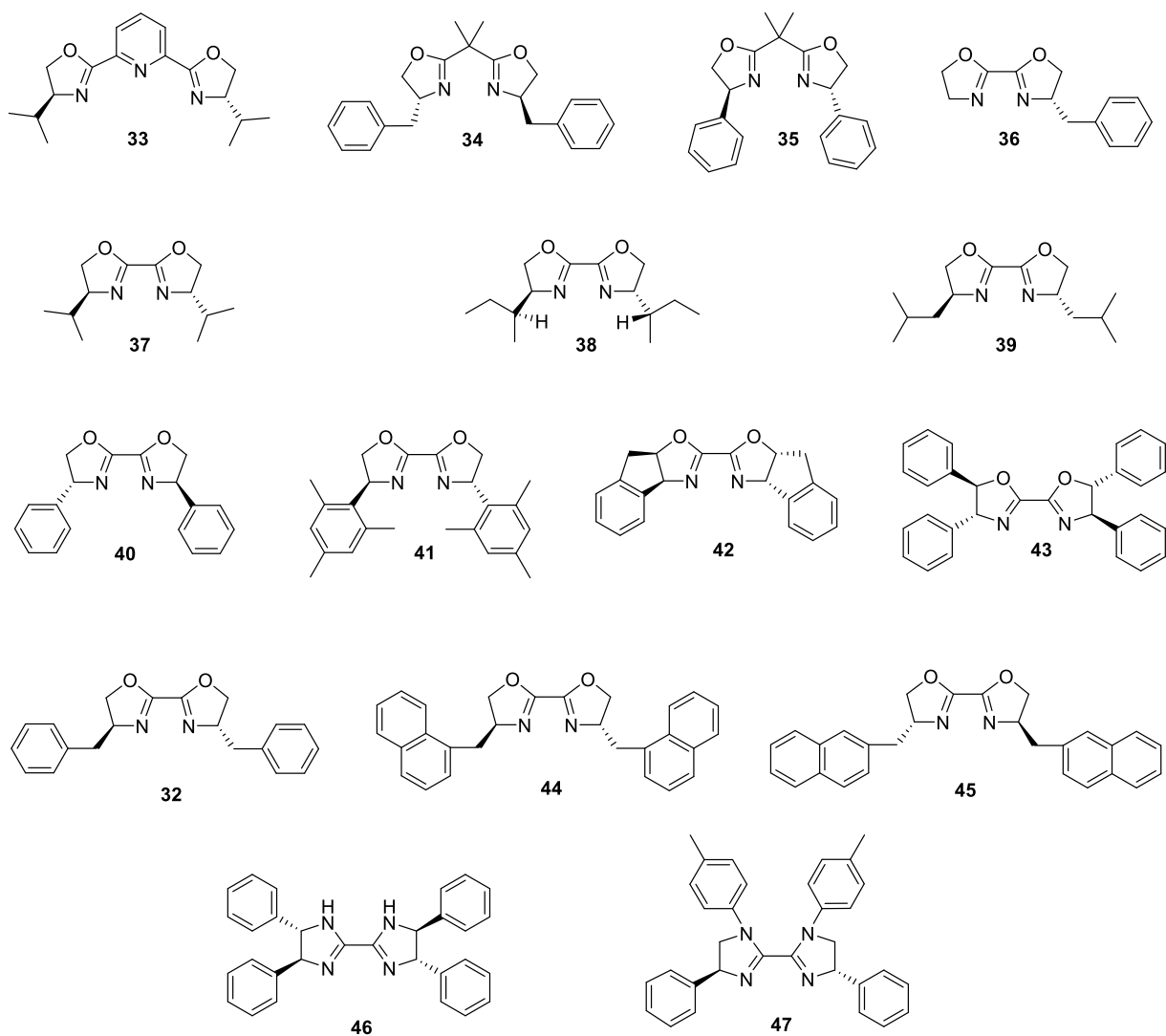
The attention was then focused towards the effect of ligand on the yield and the enantioselectivity of **31aA** (Table 2.2). The use of other C₂-symmetric PyBOX **33** and BOX ligands **34**, **35** was unpromising, giving poor conversion and/or low enantioselectivity (Entries 1-3). By employing an asymmetric bioxazoline 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 promising 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

^aAll the yields were isolated ones. ^bAll the eewere determined by HPLC analysis.

^c86% of starting material were recovered.

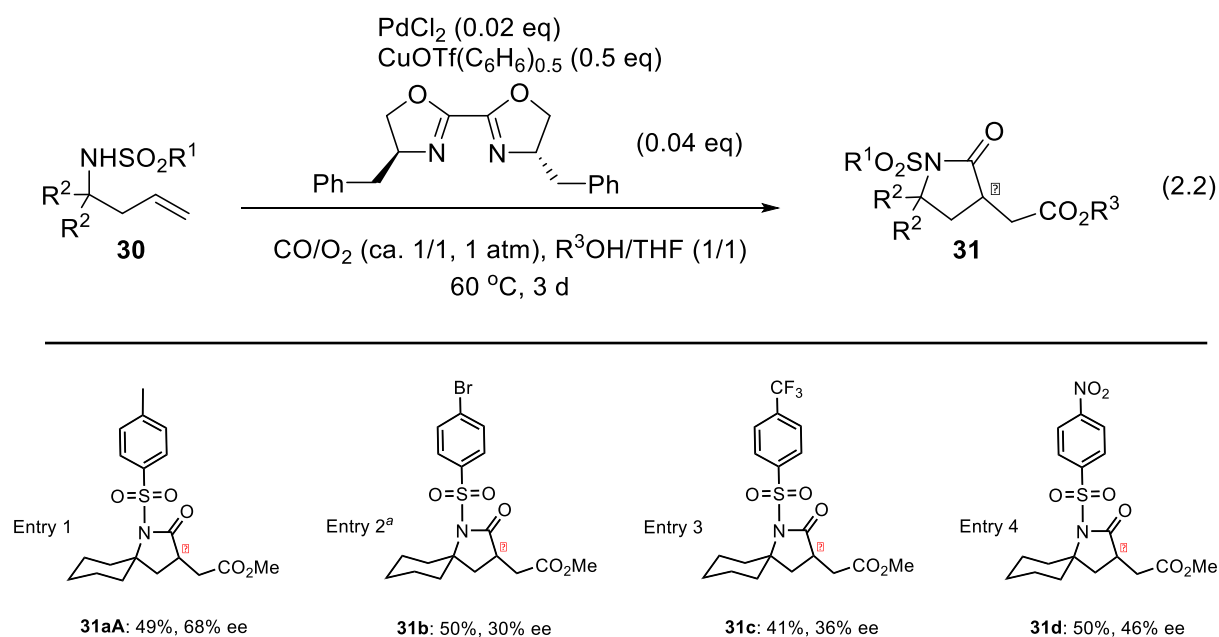


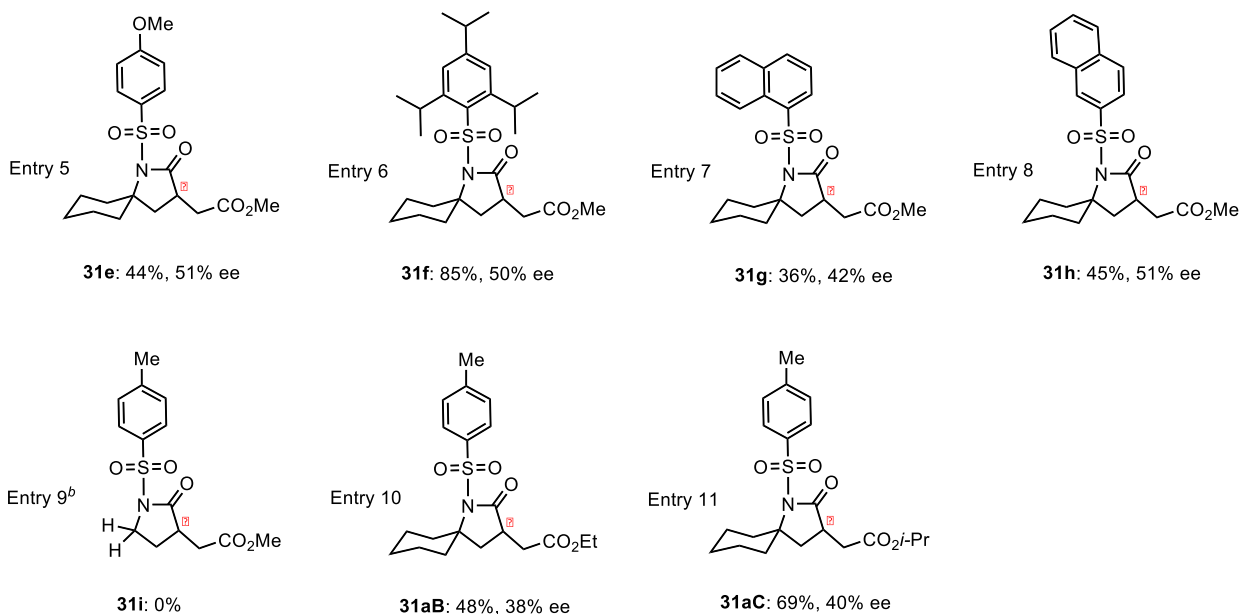
2.2.2 Scope of substrates

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.

^aLigand **43** was used instead of ligand **32**.

^bDimethyl 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).

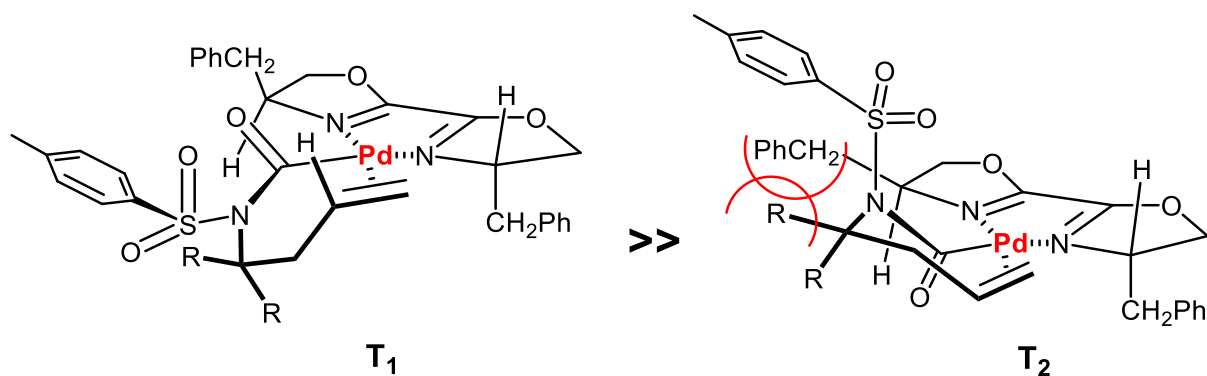
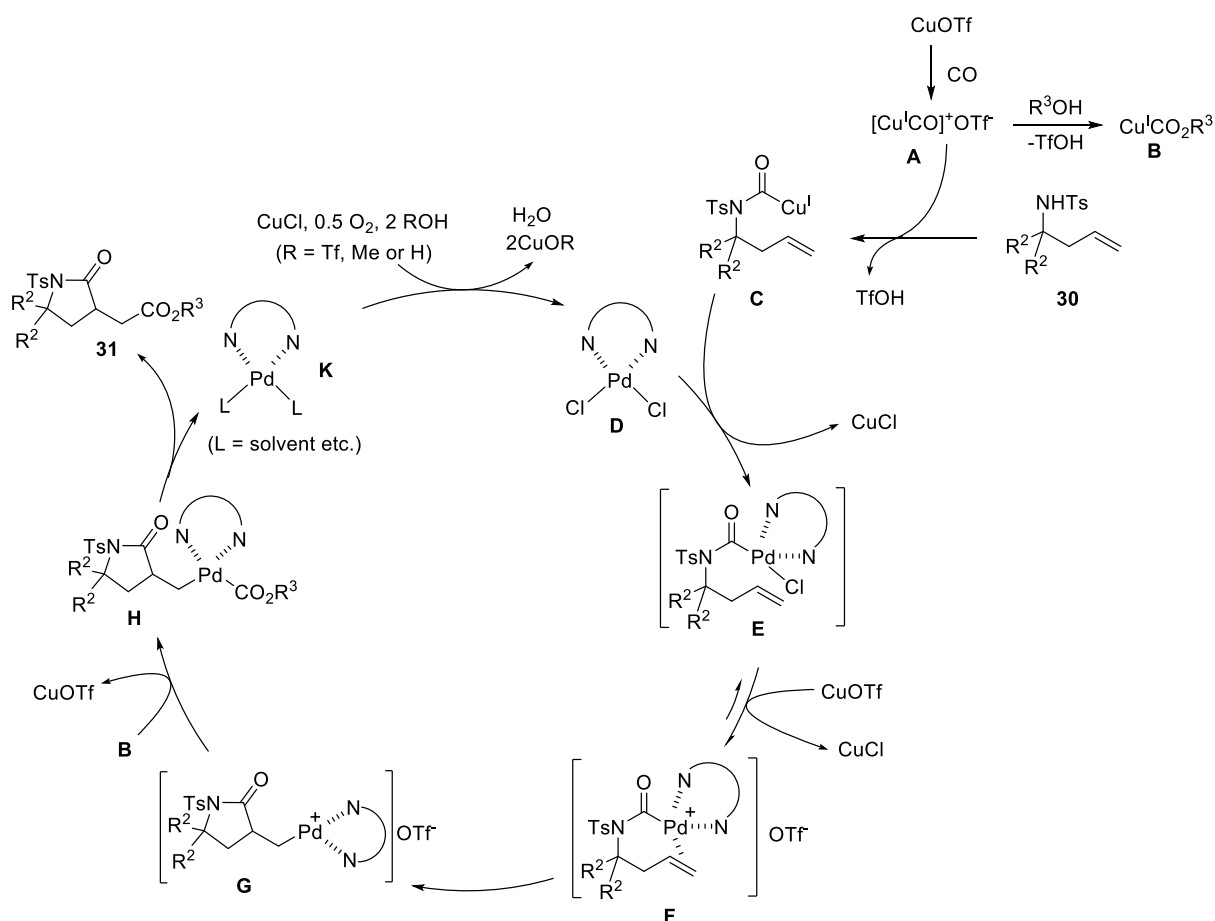


Figure 2.2

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 O₂ 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 moderate 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

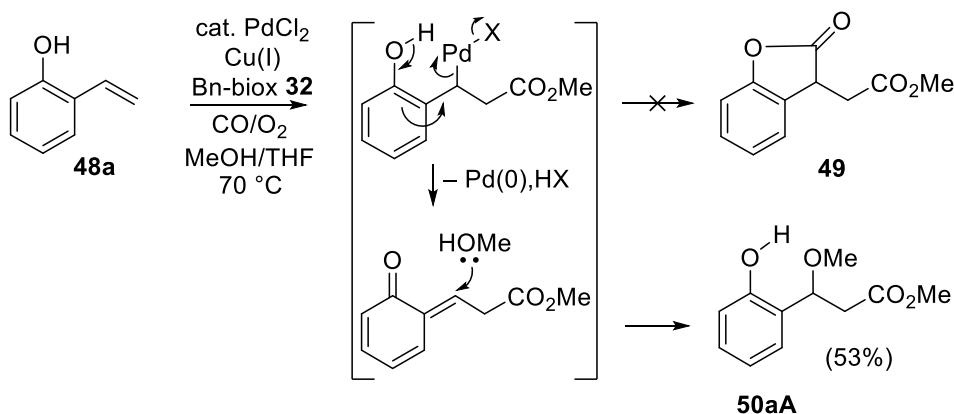
Concerning palladium-catalyzed carbonylation of unsaturated alcohols, intramolecular alkoxy-carbonylation often proceeds to furnish cyclic ethers, such as tetrahydrofurans or tetrahydropyrans.⁷³ However, the intermolecular version of the alkoxy-carbonylation of alkenes is quite limited.^{18b, 74} Carbonylation of terminal alkenes in the presence of PdCl₂ and CuCl₂ 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 CuCl₂ 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-alkoxy-carbonylation 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-alkoxy-carbonylation reaction of vinylphenols

The study was initiated with the asymmetric intra- and intermolecular bis(alkoxy-carbonylation) of 2-vinylphenol (**48a**) in the presence of PdCl₂ (0.02 equiv) and CuOTf(C₆H₆)_{0.5} (0.5 equiv) under normal pressure of CO and O₂ 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 alkoxy-carbonylation 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).

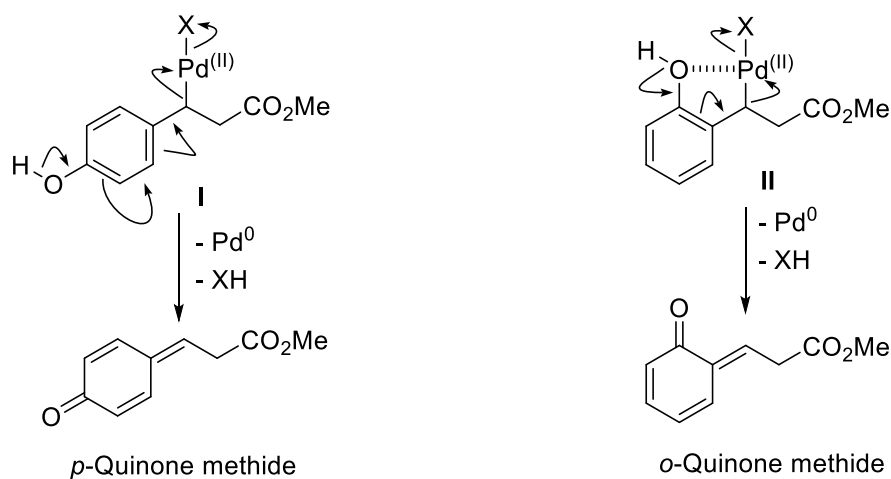


Figure 3.1

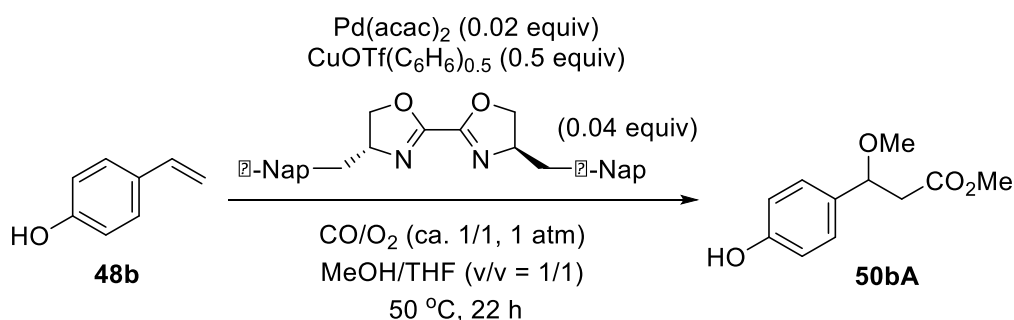
It can be seen that the electron-donating ability of the hydroxy group in the intermediate **I** is stronger in comparison with that in the intermediate **II** since the oxygen of hydroxyl group is not coordinated to the palladium species. As a result, the reaction with 4-vinylphenol proceed more smoothly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



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

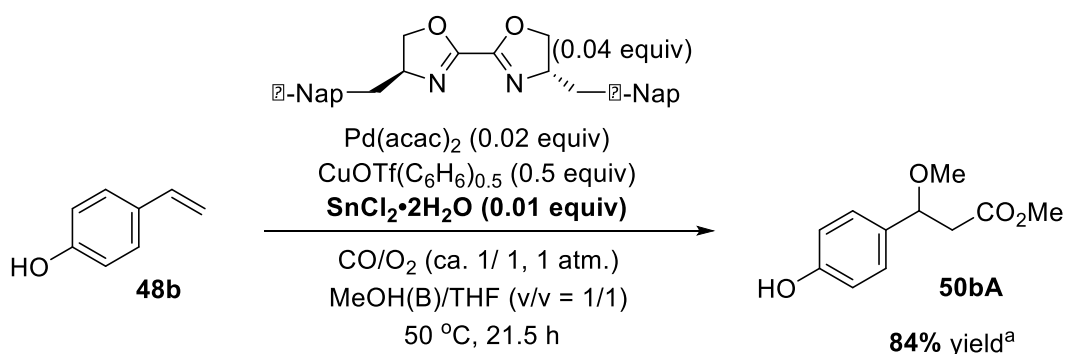
^a) Yields were determined by ¹H NMR of crude products using octane as an internal standard.

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 $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$. Delightedly, the product **50bA** was obtained in reproducibly high yields (Scheme 3.2).



^a Yield was determined by ^1H NMR of crude products using octane as an internal standard. and two times average .

B : Bottle (Cica 1°, 25183-01)

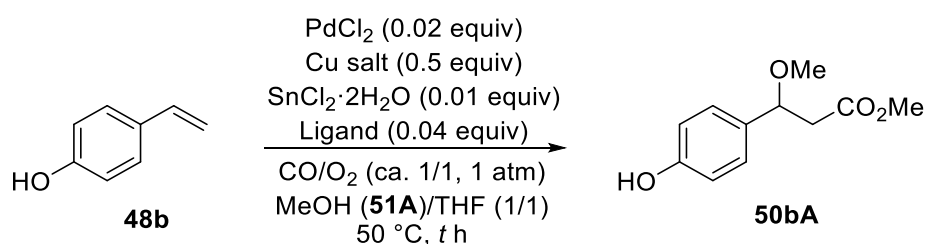
Scheme 3.2. Reproducibility of the reaction by the addition of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$.

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 $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$, 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 [PdCl₂(PhCN)₂] instead of PdCl₂ (Entry 6). Concerning the tin salts, SnCl₄ 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).

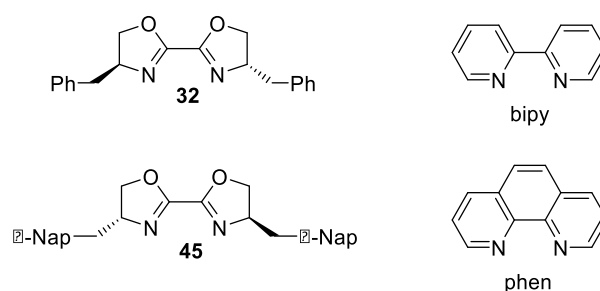
Table 3.2. Alkoxy-alkoxycarbonylation of 4-vinylphenol (**48b**).^a



Entry	Cu salt	Ligand	<i>t</i> /h	Yield/% ^a
1	[Cu(C ₆ H 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

^aYields were determined by the analyses of ¹H-NMR spectra of the crude products based on octane as an internal standard. ^b[PdCl₂(PhCN)₂] was used instead of PdCl₂. ^cSnCl₄ was used instead of SnCl₂·2H₂O. ^dSn(OAc)₄ was used instead of SnCl₂·H₂O. ^e4-Hydroxyacetophenone was also isolated in 33% yield. ^fReaction was carried out without O₂.

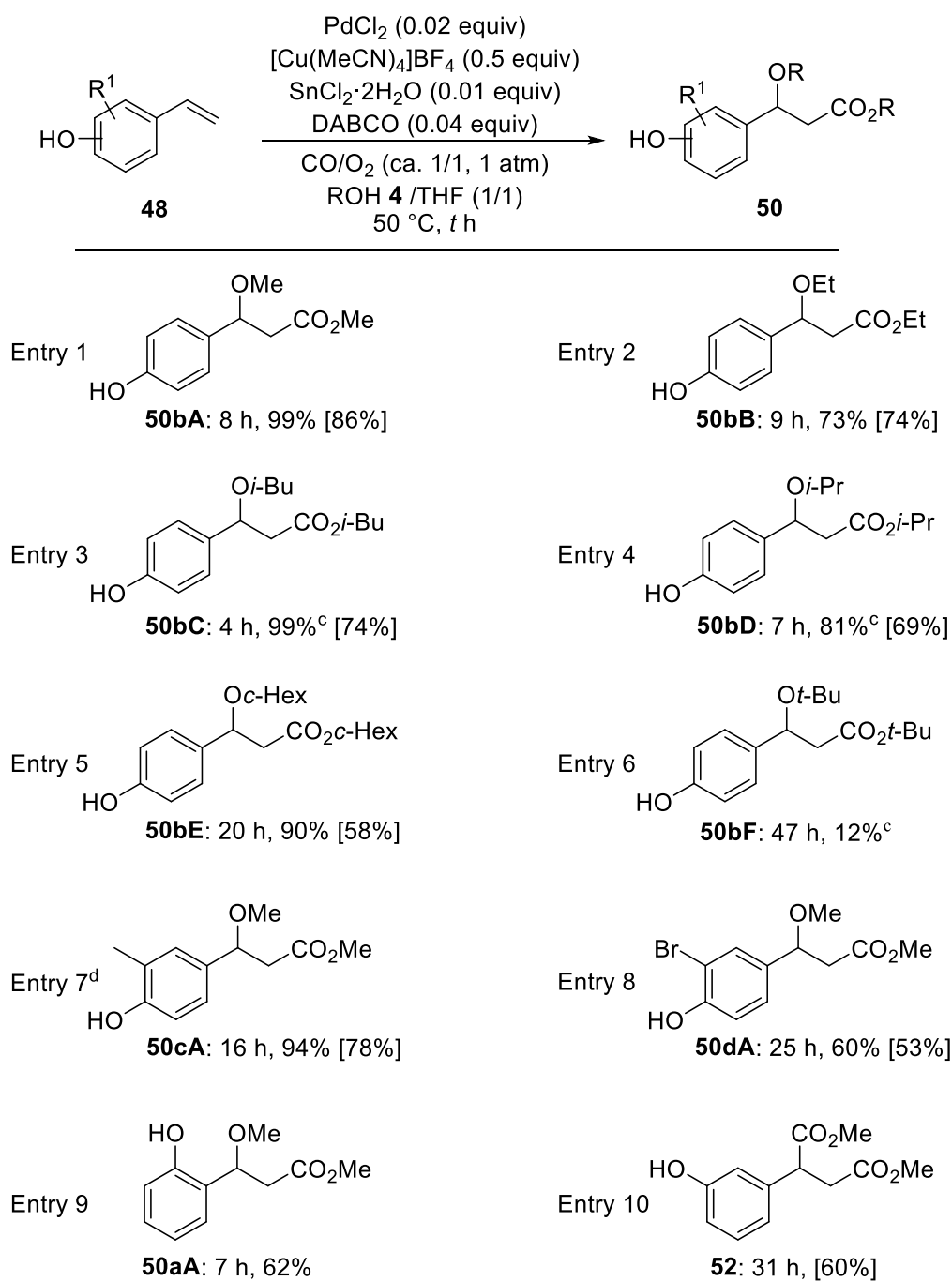


3.2.4 Scope of substrates

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 H₂O 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 ¹H-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 SiO₂ 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}

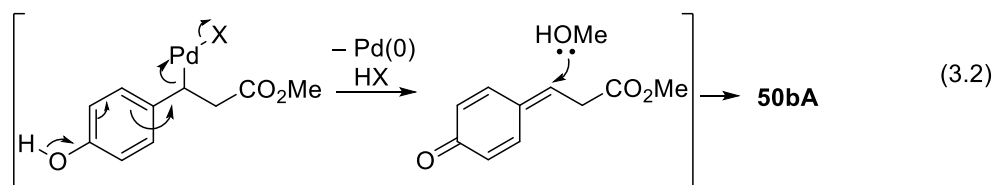
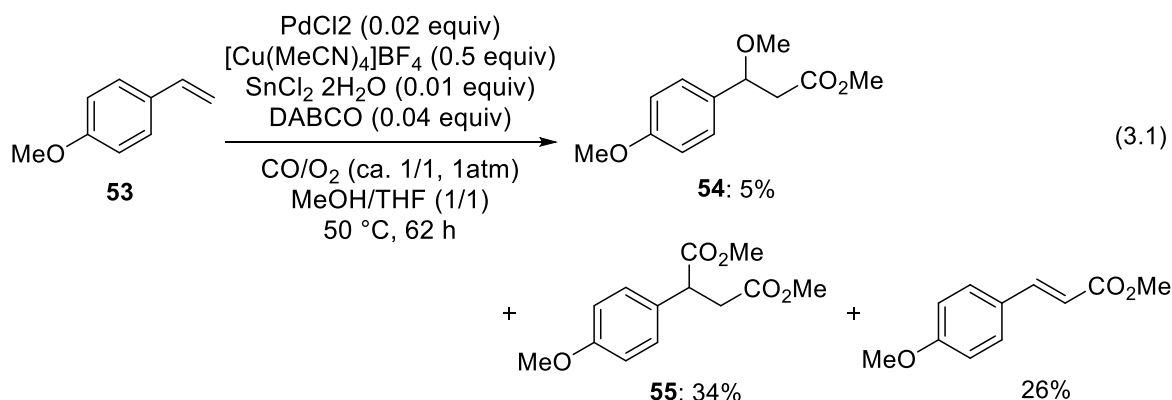
Table 3.3. Alkoxy-alkoxycarbonylation of vinylphenols **48**.^{a,b}



^aYields were determined by the analysis of ^1H NMR spectra of the crude products based on octane as an internal standard otherwise mentioned. ^bYields in parentheses are isolated yields. ^cYield was determined by the analysis of ^1H NMR spectrum of the crude products based on dibromomethane as an internal standard. ^d PdCl_2 (0.05 equiv), $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (0.5 equiv), $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (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).



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, $\text{PdCl}(\text{COD})\text{SnCl}_3$, was reported to activate oxygen functional groups, resulting in promotion of the nucleophilic addition,^{77e} Suzuki-Miyaura coupling reaction,^{77f} and Michael reaction.^{77g}

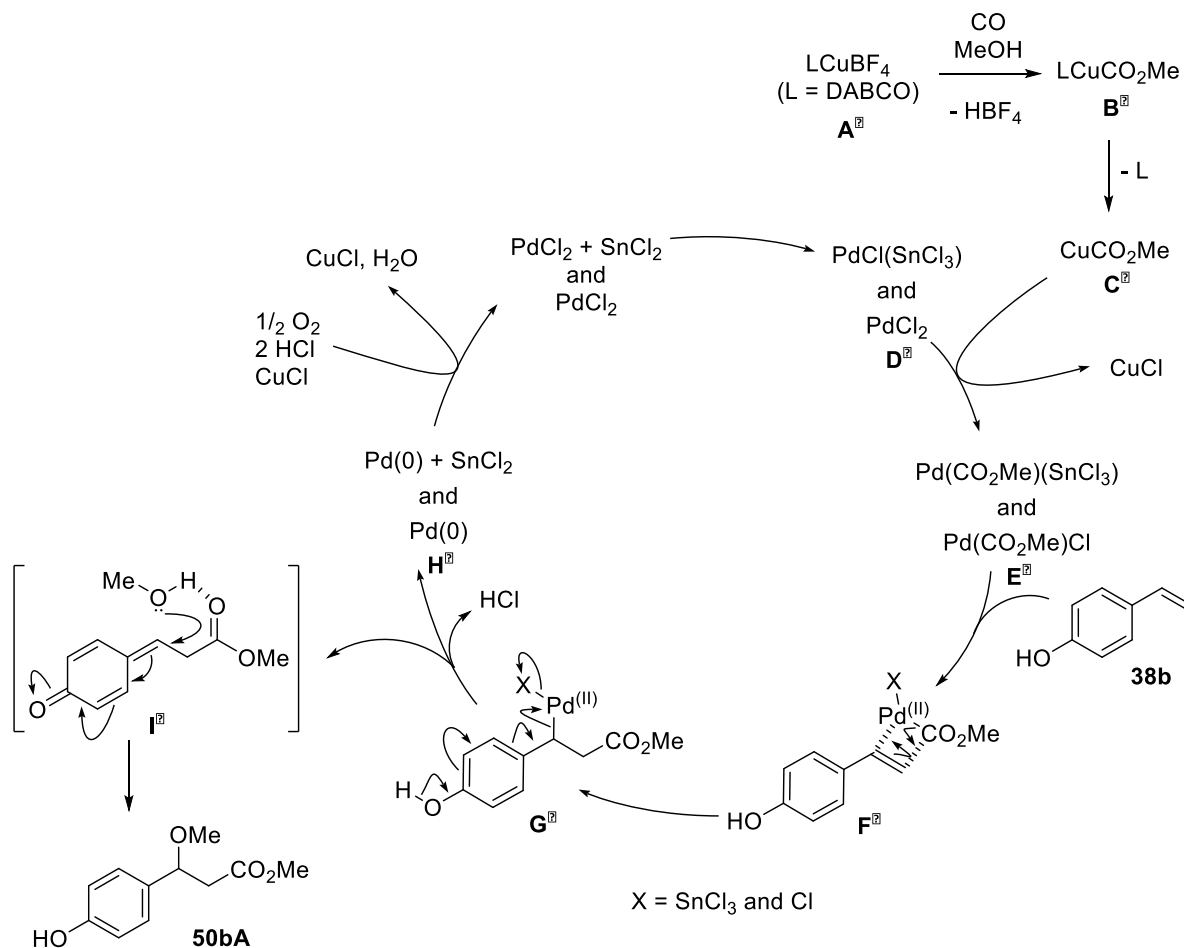


Picture 3.1. The reaction mixture with and without SnCl_2 . *Reaction Conditions:* PdCl_2 , $\text{Cu}(\text{MeCN})_4\text{BF}_4$, DABCO, CO/O_2 (ca, 1/1, 1 atm), MeOH/THF (v/v = 1/1), 50°C , 3 h.

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.



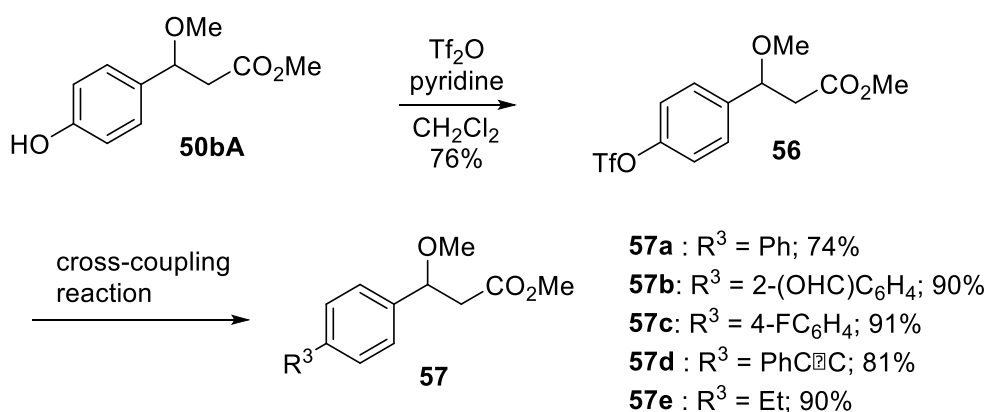
Scheme 3.2. Proposed mechanism.

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 alkoxy carbonyl 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 alkoxy carbonylpalladium(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 O₂ 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.

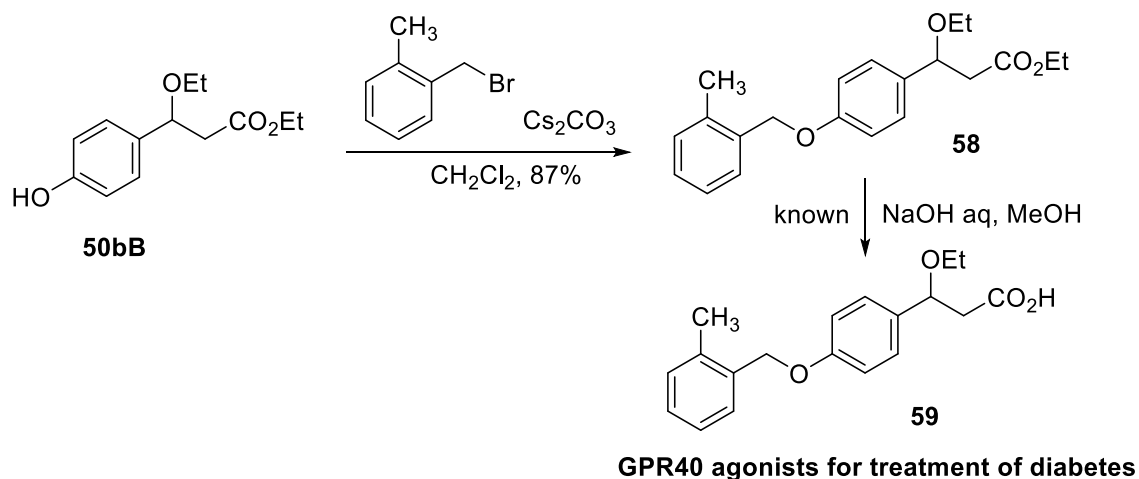


Reaction conditions for **57a-57c**: RB(OH)₂, cat. [Pd(PPh₃)₄], K₂CO₃, toluene/DMF (10/1).
57d: PhC≡CH, cat. [PdCl₂(PPh₃)₂], Et₃N, DMF. **57e**: Et₃B, cat. [PdCl₂(dppf)₂], CsOAc, THF.

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 O₂ 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 derivatives catalyzed by palladium(II) and copper(I) salt under normal pressure of CO and O₂ 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.

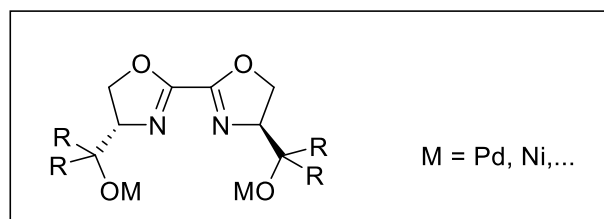
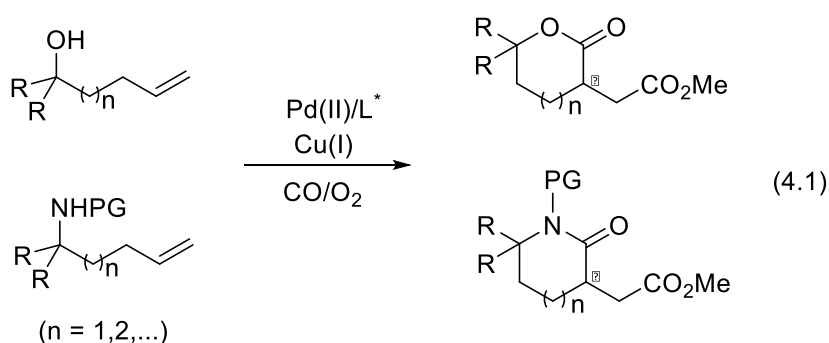


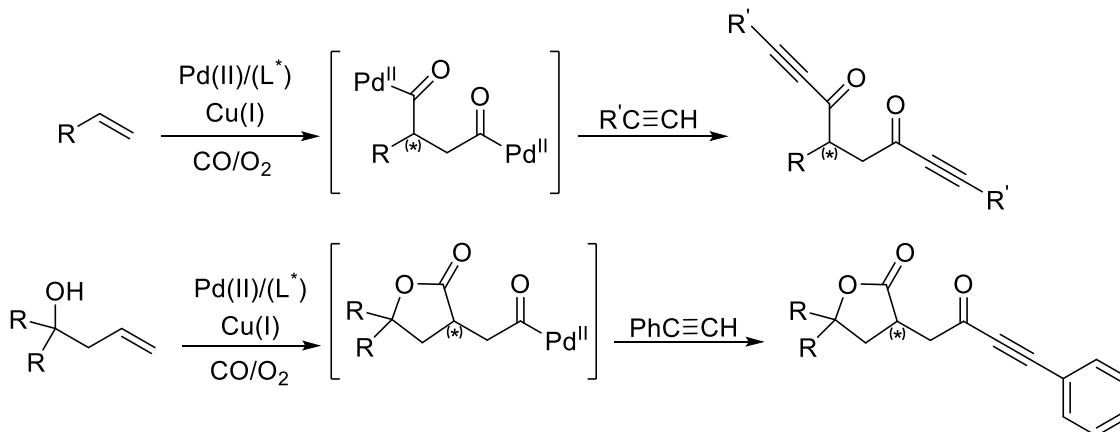
Figure 4.1. Novel class of ligands containing bioxazolines.

Following our long-term focus on the palladium-catalyzed carbonylative cyclization of unsaturated alcohols and amine derivatives to construct highly functionalized 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).



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 envisioned 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. ^1H NMR spectroscopy was performed in CDCl_3 using a JEOL ECS 400 NMR (400 MHz) spectrometer. Chemical shifts (δ) were determined relative to TMS ($\delta = 0$ 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 (δ) were determined relative to CDCl_3 ($\delta = 77.0$ 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 ($\delta = -162.90$ 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 mass spectrometers. 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 and recycle HPLC, respectively. The specific optical rotations were recorded on a polarimeter. Super dehydrated solvents were purchased for the reactions and used without further desiccation.

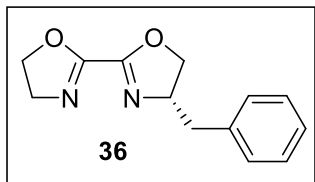
A. Asymmetric Palladium-Catalyzed Intra- and Intermolecular Dicarboxylation of Homoallylic Amine Derivatives

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 $\text{ClCH}_2\text{CH}_2\text{Cl}$. 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

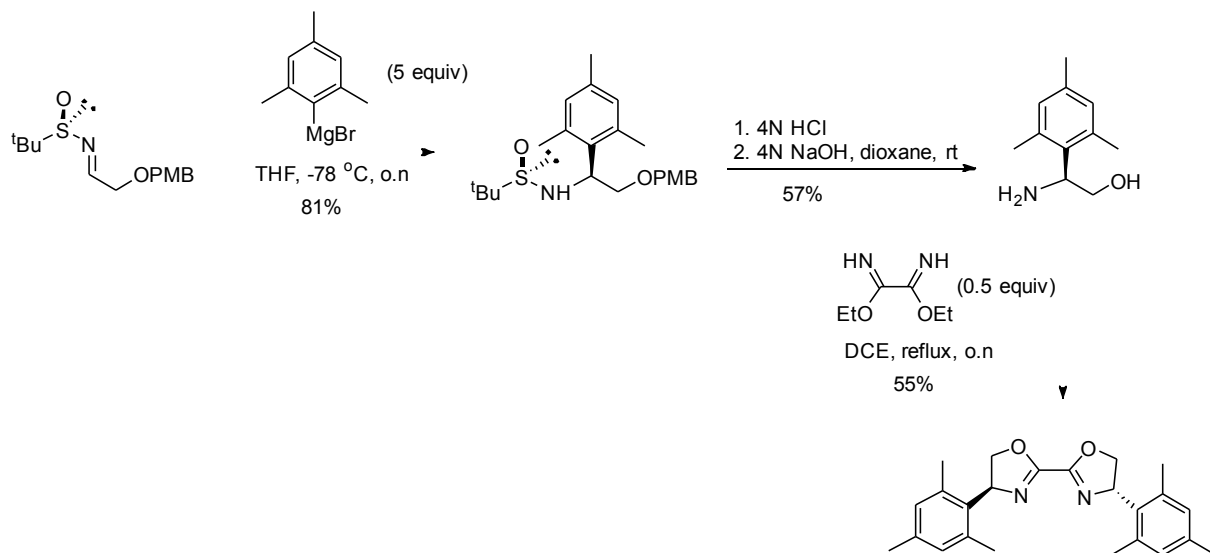
purified by silica gel chromatography (hexane/AcOEt = 1/1) to give desired asymmetric bioxazoline ligand (61 mg, 27%).

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



A colorless oil. $R_f = 0.2$ (only AcOEt); $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 2.65$ (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, $J = 16.5, 8.2$ Hz), 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); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 40.9, 55.0, 68.0, 68.3, 72.5, 126.6, 128.5, 129.0, 154.3, 155.6$; 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 $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2$ $[(\text{M}+\text{H})^+]$: 231.1134, found: 231.1139.

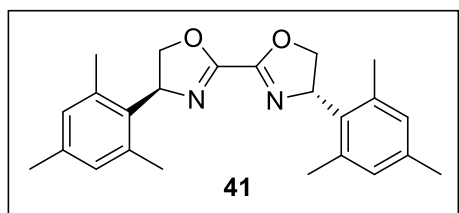
Synthesis of ligand 41:



(*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 $\text{ClCH}_2\text{CH}_2\text{Cl}$. 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%).

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



A white solid. $R_f = 0.4$ (hexane/AcOEt = 2/1). Mp = 196-197 °C (from hexane/AcOEt); ^1H NMR (400 MHz, CDCl_3) $\delta = 2.17$ (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),

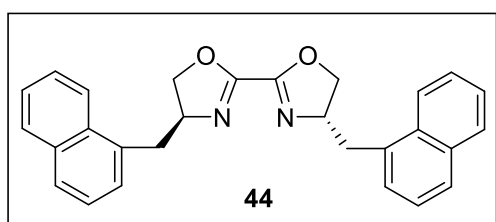
5.77 (t, 1H, $J = 11.4, 10.6$ Hz), 6.76 (s, 2H); ^{13}C NMR (100MHz, CDCl_3): $\delta = 20.1, 20.7, 66.5, 72.7, 130.3, 132.2, 136.8, 137.3, 155.2$; IR (KBr) 3423, 3006, 2965, 2922, 2866, 1737, 1686, 1620, 1485, 1510, 1485, 1452, 1336, 1245, 1121, 1057, 930, 845, 750 cm^{-1} ; HRMS (DART) m/z calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_2$ [(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 $\text{ClCH}_2\text{CH}_2\text{Cl}$. 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%).

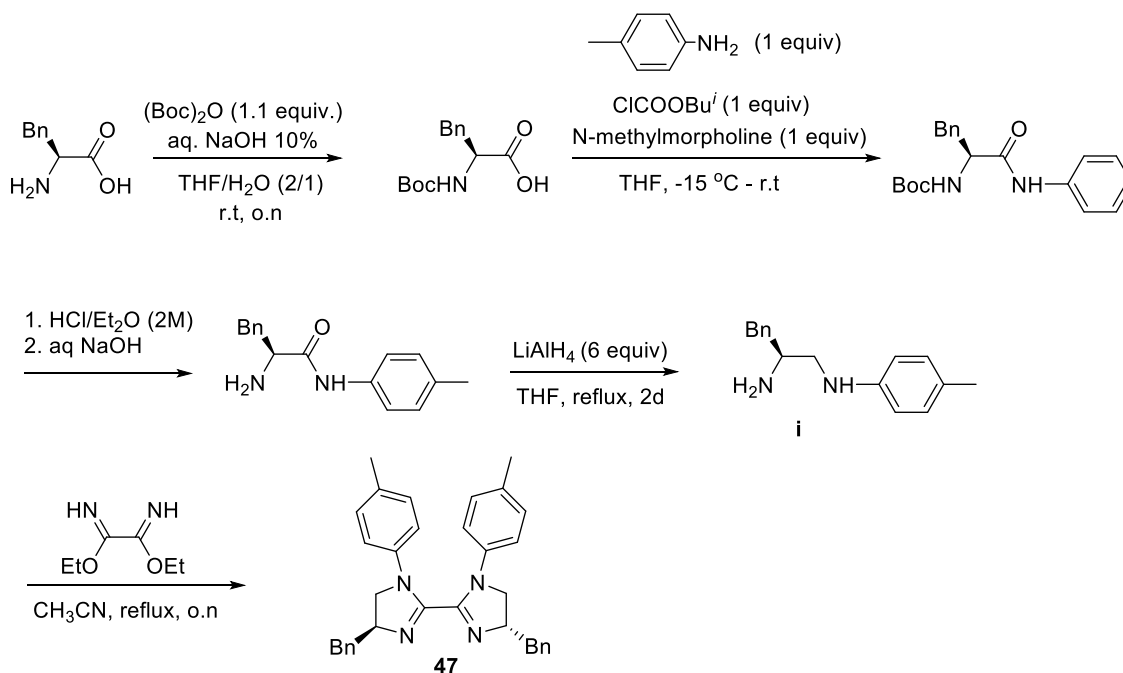
(4S,4'S)-4,4'-bis(naphthalen-1-ylmethyl)-4,4',5,5'-tetrahydro-2,2'-bioxazole (44):



A yellow solid. $R_f = 0.3$ (hexane/AcOEt = 1/1). M.p = 150-151 °C (from hexane/AcOEt); ^1H NMR (400 MHz, CDCl_3) $\delta = 3.01$ (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) $\delta = 38.7, 67.3, 73.2, 123.5, 125.6, 126.0, 126.5, 127.0, 127.9, 129.0, 155.3$; 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 $\text{C}_{28}\text{H}_{25}\text{N}_2\text{O}_2$ [(M+H) $^+$]: 421.1916, found: 421.1905.

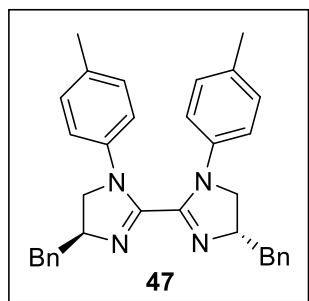
Synthesis of ligand 47:

The procedure for preparation 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 CH₃CN. 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 (CH₂Cl₂/ MeOH = 10/1) to give a light yellow solid which then recrystallized from AcOEt/ hexane to afford pure ligand (257 mg, 25%).

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

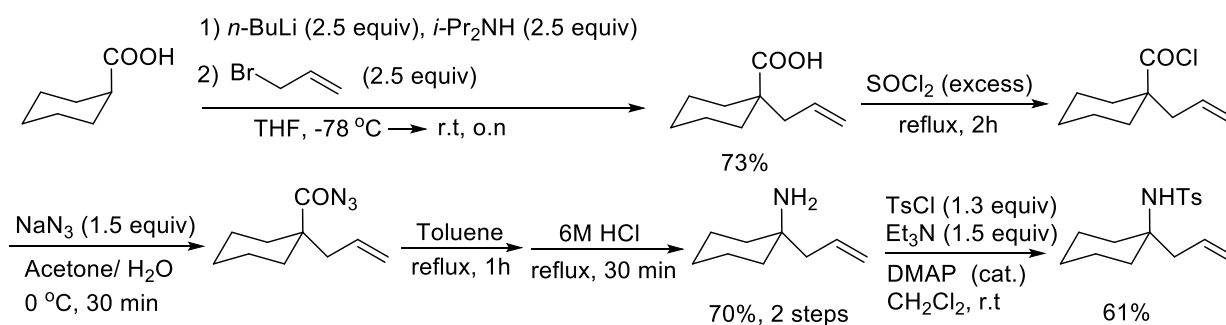


A yellow solid. $R_f = 0.6$ (CH₂Cl₂/ MeOH = 10/1). M.p = 175-176 °C (from hexane/AcOEt); ¹H NMR (400 MHz, CDCl₃) δ = 2.20 (s, 3H), 2.83 (dd, 1H, $J = 13.8, 9.16$ Hz), 3.23 (dd, 1H, $J = 13.8, 5.0$ Hz), 3.44 (t, 1H, $J = 9.2$ Hz), 3.59 (t, 1H, $J = 9.2$ Hz), 4.49 (m, 1H), 6.49 (d, 2H, $J = 6.9$ Hz), 6.79 (d, 2H, $J = 7.3$ Hz), 7.11 (d, 1H, $J = 7.4$ Hz), 7.23 (m, 5H); ¹³C NMR(CDCl₃) 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 method⁶⁴ as shown on following scheme.

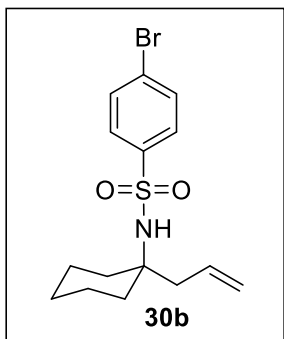


n-BuLi (1.64 M in hexane) (76.2 ml, 125 mmol, 2.5 equiv) was added dropwise to a solution of diisopropylamine (12.65 g, 125 mmol, 2.5 equiv) in THF (70 ml) at -78 °C. The mixture was allowed to warm to 0 °C and stirred at this temperature for 1 hour. A solution of cyclohexanecarboxylic acid (6.409 g, 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 NH₄Cl solution. The aqueous layer was separated from the organic, acidified with 2M HCl (ca. 62.5 ml), and extracted with Et₂O (3 x 100 ml). The combined ethereal layers were washed with K₂CO₃ (20% m/m solution, 3 x 100 ml). The combined resulting aqueous layers were acidified to pH = 3 with 6M HCl and extracted with Et₂O (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 and 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 combined extracts were dried over Na_2SO_4 and then evaporated the solvent 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

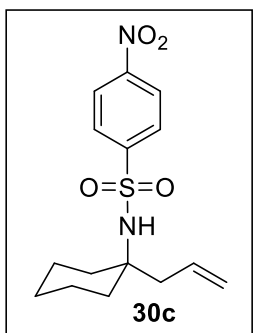
In a similar manner, allylic amines **30b-30h** were obtained from the 1-allyl-1-aminocyclohexane and corresponding sulfonyl chlorides.

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



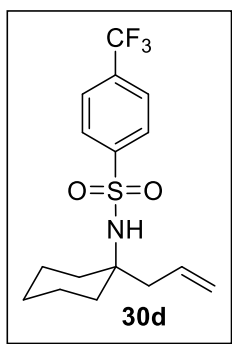
Compound **30b** was obtained as a white solid. $R_f = 0.5$ (hexane/AcOEt = 4/1). Mp = 126-127 °C (from hexane/AcOEt); ^1H NMR (400 MHz, CDCl_3): δ 1.22–1.50 (m, 8H), 1.65–1.74 (m, 2H), 2.40 (d, 2H, $J = 7.3$ Hz), 4.53 (brs, 1H), 5.09 (d, 1H, $J = 17.4$ Hz), 5.13 (d, 1H, $J = 10.1$ Hz), 5.73 (ddt, 1H, $J = 17.4, 10.1, 7.3$ 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 $\text{C}_{15}\text{H}_{21}\text{Br}_1\text{N}_1\text{O}_2\text{S}_1$ [(M+H) $^+$]: 358.0476; found: 358.0476.

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



Compound **30c** was obtained as a light yellow solid. $R_f = 0.8$ (hexane/AcOEt = 2/1). Mp: 112-113 °C (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 $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_4\text{S}_1$ [(M+H) $^+$]: 325.1222; found: 325.1223.

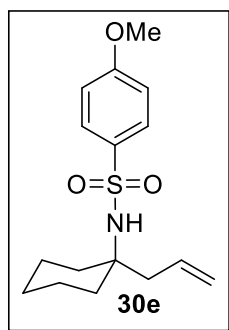
***N*-(1-allylcyclohexyl)-4-(trifluoromethyl)benzenesulfonamide (30d):**



Compound **30d** was obtained as a white solid. $R_f = 0.8$ (hexane/AcOEt = 2/1). Mp = 118-119 °C (from hexane/AcOEt); ^1H NMR (CDCl_3 , 400 MHz) $\delta = 1.30$ -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) $\delta = -62.9$; ^{13}C NMR (CDCl_3 , 100 MHz) $\delta = 21.5, 25.1, 35.4, 43.0, 60.1, 119.5, 126.1, 127.4, 132.5, 133.7, 134.0, 147.0$; 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 $\text{C}_{16}\text{H}_{21}\text{F}_3\text{N}_1\text{O}_2\text{S}_1$ [(M+H) $^+$]: 348.1245; found: 348.1248.

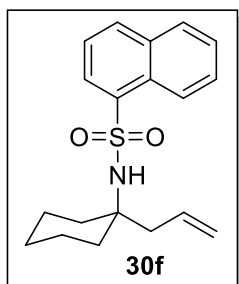
***N*-(1-allylcyclohexyl)-4-methoxybenzenesulfonamide (30e):**



Compound **30e** was obtained as a white solid. $R_f = 0.6$ (hexane/AcOEt = 2/1). Mp = 156-157 °C (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,

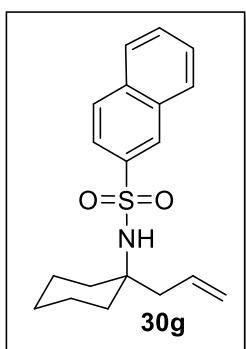
$J = 8.7$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz): δ 21.5, 25.2, 35.5, 43.0, 55.6, 59.3, 113.9, 119.2, 129.0, 133.0, 135.3, 162.4; IR (KBr) 3295, 3077, 3010, 2944, 2853, 1639, 1597, 1499, 1453, 1418, 1313, 1258, 1188, 1141, 1096, 1000, 914, 851, 832, 766, 675 cm^{-1} ; HRMS (DART) m/z calcd for $\text{C}_{16}\text{H}_{24}\text{N}_1\text{O}_3\text{S}_1$ [(M+H) $^+$]: 310.1477; found: 310.1478.

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



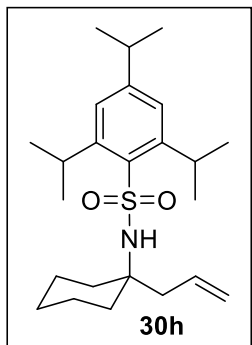
Compound **30f** was obtained as a white solid. $R_f = 0.7$ (hexane/AcOEt = 2/1). Mp = 138-139 °C (from hexane/AcOEt); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 1.04–1.34 (m, 8H), 1.66–1.76 (m, 2H), 2.40 (d, 2H, $J = 7.3$ Hz), 4.56 (s, 1H), 5.02–5.09 (m, 2H), 5.63–5.77 (m, 1H), 7.50–7.72 (m, 3H), 7.94 (d, 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); $^{13}\text{C NMR}$ (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 $\text{C}_{19}\text{H}_{24}\text{N}_1\text{O}_2\text{S}_1$ [(M+H) $^+$]: 330.1528; found: 330.1519.

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



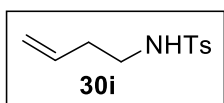
Compound **30g** was obtained as a white solid. $R_f = 0.8$ (hexane/AcOEt = 2/1). Mp = 160-161 °C (from hexane/AcOEt); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 1.26–1.33 (m, 6H), 1.38–1.47 (m, 2H), 1.72–1.79 (m, 2H), 2.43 (d, 2H, $J = 7.3$ Hz), 4.48 (s, 1H), 5.07 (d, 1H, $J = 17.4$ Hz), 5.11 (d, 1H, $J = 10.5$ 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); $^{13}\text{C NMR}$ (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 $\text{C}_{19}\text{H}_{24}\text{N}_1\text{O}_2\text{S}_1$ [(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 °C (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 $\text{C}_{24}\text{H}_{40}\text{N}_1\text{O}_2\text{S}_1$ [(M+H) $^+$]: 406.2780; found: 406.2770.

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



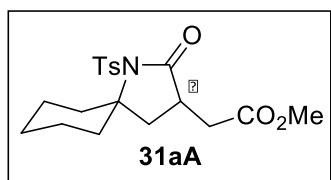
4-bromobut-1-ene (2.23 mL, 22 mmol, 1.1 eq) and K_2CO_3 (5.53 g, 40 mmol, 2.0 eq) were added to a solution of tosylamine (3.42 g, 20 mmol, 1.0 eq) in acetone (50 mL). The reaction was stirred over night at 60 °C. The reaction was quenched with sat. aq. NH_4Cl , extracted with Et_2O (50 ml x 3), washed 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, $J = 6.9\text{Hz}$), 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, $J = 7.8\text{Hz}$), 7.33 (d, 2H, $J = 7.8\text{Hz}$).

Representative Procedure for Asymmetric bis(alkoxycarbonylation) Reaction of

***N*-(1-allylcyclohexyl)-4-methylbenzenesulfonamide (30a) (Table 2.4, Entry 1):**

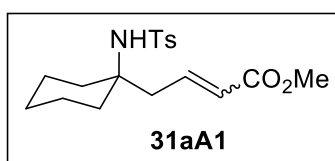
Under an Ar atmosphere, PdCl₂ (1.1 mg, 0.006 mmol, 0.02 equiv), CuOTf(C₆H₆)_{0.5} (37.8 mg, 0.15 mmol, 0.5 equiv), benzyl-bioxazoline ligand (3.8 mg, 0.012 mmol, 0.04 equiv) were placed in a flask. Next, a solution of *N*-(1-allylcyclohexyl)-4-methylbenzenesulfonamide **30a** (92.8 mg, 0.3 mmol) in MeOH superdehydrate (2 ml) and THF (2 ml) were added via cannulation. The Ar atmosphere was replaced with CO/O₂ (v/v=1/1) and the reaction was stirred at a 60 °C. After reaction completion (monitored by TLC), aqueous NaHCO₃ 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 Na₂SO₄. 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):



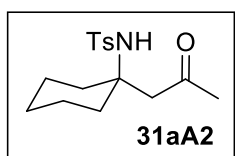
A white solid. $R_f = 0.4$ (hexane/AcOEt = 2/1). Mp = 141-142 °C (from hexane/AcOEt). $[\alpha]_D^{25} = -1.6$ (c 0.4, CHCl₃). The ee was determined to be 68% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 10/1, 0.75 mL/min, 220 nm, major 32.2 min, minor 71.3 min). (Table 2.1, Entry 5); ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₉H₂₆N₁O₅S₁ [(M+H)⁺]: 380.1532; found: 380.1526.

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



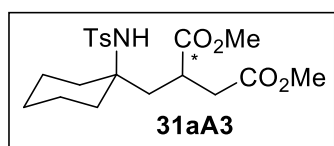
A white solid. $R_f = 0.5$ (hexane/AcOEt = 2/1); ^1H NMR (400 MHz, CDCl_3): $\delta = 1.21$ - 1.68 (m, 10H), 2.51 (d, 2H, $J = 7.8$ Hz), 3.65 (s, 3H), 4.40 (s, 1H), 5.70 (d, 1H, $J = 14.2$ Hz), 6.78 (m, 1H), 7.20 (d, 2H, $J = 9.6$ Hz), 7.71 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 21.3$, 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); ^1H NMR (400 MHz, CDCl_3): $\delta = 0.83$ (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): $\delta = 21.4$, 21.5, 31.1, 35.9, 50.3, 57.4, 127.2, 129.5, 139.9, 143.0, 208.0.

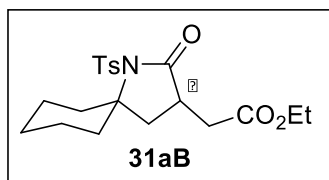
Dimethyl 2-((1-((4-methylphenyl)sulfonamido)cyclohexyl)methyl)succinate (31aA3):



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); ^1H NMR (400 MHz, CDCl_3): $\delta = 1.25$ - 1.86 (m, 10H), 2.12 (dd, 1H, $J = 14.7$, 9.2 Hz), signal of C-H was not observed clearly at $\delta = 2.41$ 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, $J = 16.5$, 8.7 Hz), 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): $\delta = 21.5$, 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} .

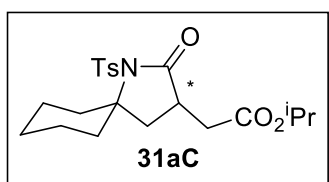
Ethyl 2-(2-oxo-1-tosyl-1-azaspiro[4.5]decan-3-yl)acetate (**31aB**):



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 °C (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 $\text{C}_{20}\text{H}_{28}\text{N}_1\text{O}_5\text{S}_1$ [(M+H) $^+$]: 394.1688; found: 394.1688.

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



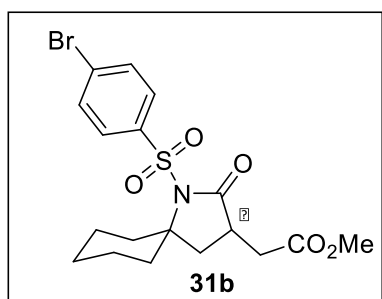
Starting from **30a** (92.8 mg, 0.3 mmol), compound **31aC** was obtained as a colorless oil (84.4 mg, 69%). $R_f = 0.5$ (hexane/AcOEt = 2/1). $[\alpha]_D^{25} = -3.5$ (c 0.29, CHCl_3). The ee was

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 $\text{C}_{21}\text{H}_{30}\text{N}_1\text{O}_5\text{S}_1$ $[(\text{M}+\text{H})^+]$: 408.1845; found: 408.1851.

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

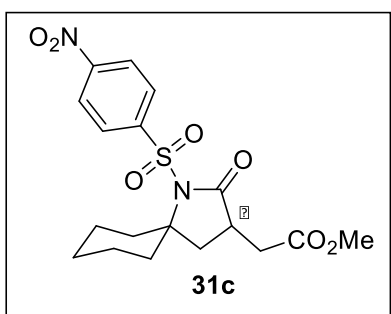
Methyl 2-(1-((4-bromophenyl)sulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (**31b**):



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 $^\circ\text{C}$ (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); ^1H 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 $\text{C}_{18}\text{H}_{23}\text{Br}_1\text{N}_1\text{O}_5\text{S}_1$ $[(\text{M}+\text{H})^+]$: 444.0480; found: 444.0477.

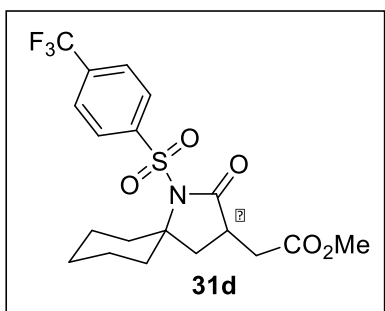
Methyl 2-(1-((4-nitrophenyl)sulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (**31c**):



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 °C (from hexane/ethyl acetate). $[\alpha]_D^{25} = -1.4$ (c 0.38, CHCl₃). 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, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₈H₂₃N₂O₇S₁ [(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):

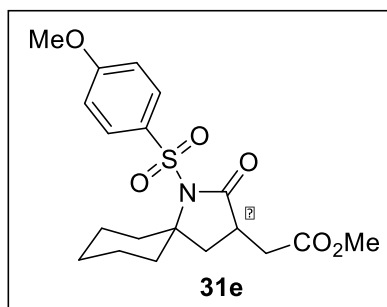


Starting from **30d** (104.2 mg, 0.3 mmol), compound **31d** was obtained as a white solid (52.7 mg, 41%). $R_f = 0.5$ (Hex/AcOEt = 2/1). Mp = 176-179 °C (from hexane/AcOEt). $[\alpha]_D^{25} = +1.4$ (c 0.52, EtOH). The ee was determined to be

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, CDCl₃): 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); ¹⁹F (CDCl₃, 376 MHz) $\delta = -63.1$; ¹³C NMR (100 MHz, CDCl₃): $\delta = 22.8, 24.0, 24.4, 33.8, 33.9, 36.4, 36.7, 37.6, 51.9, 70.2, 125.77, 125.81, 142.9, 171.5, 174.9$. 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 $\text{C}_{19}\text{H}_{23}\text{F}_3\text{N}_1\text{O}_5\text{S}_1$ $[(\text{M}+\text{H})^+]$: 434.1249; found: 434.1253.

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



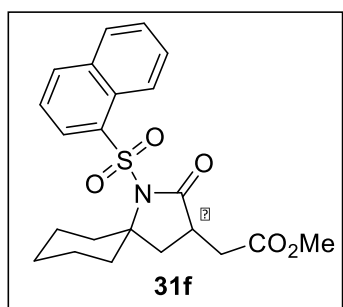
Starting from **30e** (92.9 mg, 0.3 mmol), compound **31e** was obtained as a white solid (55.3 mg, 47%). $R_f = 0.5$ (Hex/AcOEt = 2/1). Mp = 151-152 $^{\circ}\text{C}$ (from hexane/AcOEt).

$[\alpha]_D^{25} = +0.6$ (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); ^1H 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 $\text{C}_{19}\text{H}_{26}\text{N}_1\text{O}_6\text{S}_1$ $[(\text{M}+\text{H})^+]$: 396.1481; found: 396.1474.

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

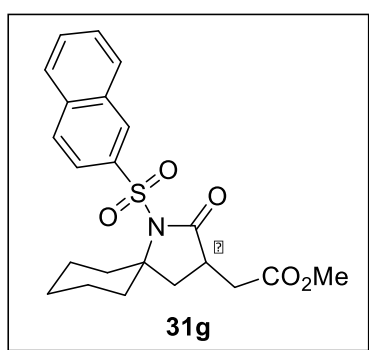


Starting from **30f** (98.9 mg, 0.3 mmol), compound **31f** was obtained as a white solid (44.6 mg, 36%). $R_f = 0.3$ (Hex/AcOEt = 2/1). Mp = 151-152 $^{\circ}\text{C}$ (from hexane/ethyl acetate). $[\alpha]_D^{25} = -2.9$ (c 0.34, CHCl_3). The ee was determined to be 42% by HPLC

(Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, 230 nm, minor 36.7 min, major 41.1 min); ^1H 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 $\text{C}_{22}\text{H}_{26}\text{N}_1\text{O}_5\text{S}_1$ $[(\text{M}+\text{H})^+]$: 416.1532; found: 416.1530.

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

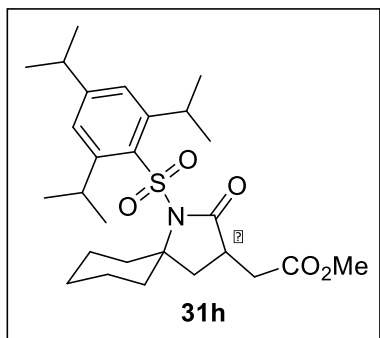
(31g):



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 °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); ^1H 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 $\text{C}_{22}\text{H}_{26}\text{N}_1\text{O}_5\text{S}_1$ $[(\text{M}+\text{H})^+]$: 416.1532; found: 416.1532.

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



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/ⁱPrOH = 50/1, 0.5 mL/min, 240 nm, major 25.2 min,

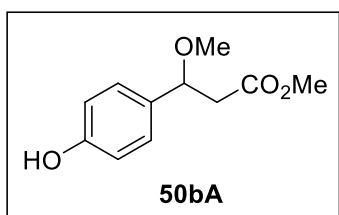
minor 26.6 min); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.12–1.48 (m, 24H), 1.54–1.88 (m, 4H), 2.14–2.24 (m, 1H), 2.40–2.50 (m, 1H), 2.58–2.90 (m, 3H), 3.57 (s, 3H), 4.10–4.20 (m, 3H), 7.07 (s, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 23.0, 23.3, 23.4, 24.1, 24.2, 24.4, 24.5, 24.7, 28.7, 33.3, 34.0, 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 $\text{C}_{27}\text{H}_{42}\text{N}_1\text{O}_5\text{S}_1$ $[(\text{M}+\text{H})^+]$: 492.2784; found: 492.2797.

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

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

Under an Ar atmosphere, PdCl₂ (1.8 mg, 0.010 mmol), [Cu(MeCN)₄]BF₄ (79 mg, 0.25 mmol), DABCO (2.2 mg, 0.020 mmol), SnCl₂·2H₂O (1.2 mg, 0.005 mmol) were placed in a flask. Next, a solution of 4-vinylphenol (**48b**) (60 mg, 0.50 mmol) in MeOH (3 mL) and THF (3 mL) were added. The Ar atmosphere was replaced with CO/O₂ (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 NaHCO₃ 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 Na₂SO₄, and condensed in vacuo. (When the chemical yield was determined based on the analysis of ¹H NMR spectrum of the crude products, octane [for example, 86.5 mg, 0.76 mmol] was added as an internal standard to the residue.) The residue was purified by preparative TLC on SiO₂ to give **50bA** (91 mg) in 86% yield as a solid.

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

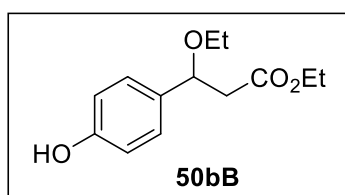


$R_f = 0.45$ (hexane/AcOEt = 2/1); Mp = 83 °C (from hexane/AcOEt); ¹H NMR (CDCl₃, 400 MHz): $\delta = 2.60$ (dd, 1H, $J = 15.1, 5.2$ Hz), 2.86 (dd, 1H, $J = 15.1, 9.2$ Hz), 3.20 (s, 3H), 3.69 (s, 3H), 4.60 (dd, 1H, $J = 9.2, 5.2$ Hz), 6.84 (d, 2H, $J = 8.2$ Hz), 7.18 (d, 2H, $J = 8.2$ Hz), signal of OH was not observed clearly; ¹³C NMR (CDCl₃, 100 MHz) $\delta = 43.1, 51.9, 56.4, 79.6, 115.4, 128.0, 131.6, 156.0, 172.1$; 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 $\text{C}_{11}\text{H}_{14}\text{O}_4\text{Na}$: 233.0790: $[\text{M}+\text{Na}]^+$; found: 233.0789.

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

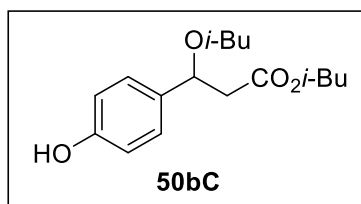
Ethyl 3-Ethoxy-3-(4-hydroxyphenyl)propanoate (**50bB**):^{78c}



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); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 1.14$ (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): $\delta = 14.1, 15.1, 43.6, 60.7, 64.1, 77.7, 115.3, 127.9, 132.6, 155.7, 171.6$; 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 $\text{C}_{13}\text{H}_{18}\text{O}_4\text{Na}$: 261.1103: $[\text{M}+\text{Na}]^+$; found: 261.1106.

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

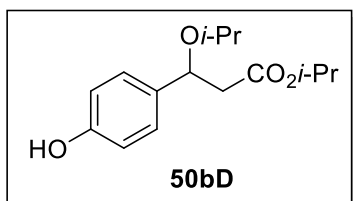


Compound **50bC** (108 mg, 74%) was obtained from **48b** (60 mg, 0.50 mmol) as an oil. $R_f = 0.4$ (hexane/AcOEt = 4/1); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 0.745$ (d, 3H, $J = 6.8$ Hz), 0.753

(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): $\delta = 19.0, 19.3, 27.5, 28.3, 43.8, 70.9, 75.5, 78.2,$

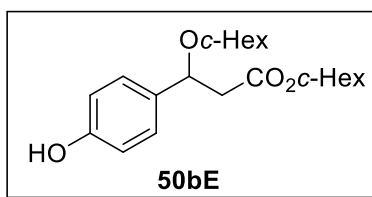
115.3, 127.9, 132.6, 155.8, 172.1; IR (Neat) 3393, 2959, 2974, 1738, 1713, 1605, 1516, 1470, 1396, 1379, 1309, 1272, 1201, 1169, 1095, 1057, 999, 941, 835 cm^{-1} ; HRMS (ESI-TOF): m/z calcd for $\text{C}_{17}\text{H}_{26}\text{O}_4\text{Na}$: 317.1729: $[\text{M}+\text{Na}]^+$; found: 317.1725.

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



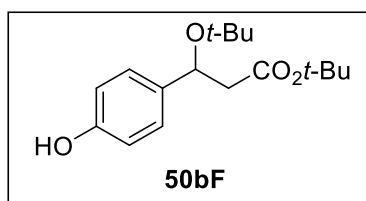
Compound **50bD** (92 mg, 69%) was obtained from **48b** (60 mg, 0.50 mmol) as an oil. $R_f = 0.55$ (hexane/AcOEt = 2/1); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 1.03$ (d, 3H $J = 6.0$ Hz), 1.13 (d, 3H, $J = 6.0$ Hz), 1.19 (d, 3H, $J = 6.4$ Hz), 1.23 (d, 3H, $J = 6.0$ Hz), 2.52 (dd, 1H, $J = 14.7, 5.0$ 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): $\delta = 21.1, 21.7, 21.8, 23.3, 44.4, 68.1, 69.0, 75.3, 115.3, 127.9, 133.5, 155.6, 171.2$; 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 $\text{C}_{15}\text{H}_{22}\text{O}_4\text{Na}$: 289.1416: $[\text{M}+\text{Na}]^+$; found: 289.1418.

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



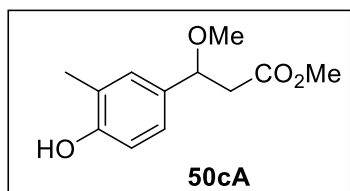
Compound **50bE** (101 mg, 58%) was obtained from **48b** (60 mg, 0.50 mmol) as an oil. $R_f = 0.2$ (hexane/AcOEt = 10/1); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 1.12$ – 1.94 (m, 20H), 2.52 (dd, 1H, $J = 15.1, 5.0$ Hz), 2.76 (dd, 1H, $J = 15.1, 9.2$ Hz), 3.14–3.20 (m, 1H), 4.73–4.78 (m, 1H), 4.85 (dd, 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): $\delta = 23.7, 23.9, 24.1, 25.3, 25.6, 31.2, 31.46, 31.54, 33.3, 35.3, 44.5, 73.2, 75.0, 115.2, 127.8, 133.6, 155.6, 171.3$; 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 $\text{C}_{21}\text{H}_{30}\text{O}_4\text{Na}$: 369.2042: $[\text{M}+\text{Na}]^+$; found: 369.2040.

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



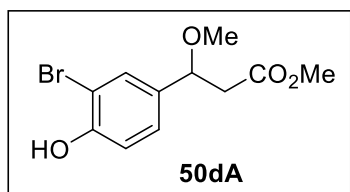
Production of compound **50bF** starting from **48b** (60 mg, 0.50 mmol) was confirmed by the analysis of ^1H NMR of the crude products. However **50bF** could not be purified by column chromatography or TLC on SiO_2 due to serious decomposition to the corresponding 3-arylpent-2-enoate. ^1H NMR (CDCl_3 , 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), $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (79 mg, 0.25 mmol), DABCO (2.2 mg, 0.050 mmol), $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.3 mg, 0.004mmol) were used for 2-methyl-4-vinylphenol (**1c**)(67 mg, 0.50 mmol) in MeOH(3mL) and THF (3 mL). Compound **50cA**(87 mg, 78 %) was obtained as an oil. ^1H 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 $\text{C}_{12}\text{H}_{17}\text{O}_4$: 225.1127; $[\text{M}+\text{H}]^+$; found: 225.1133.

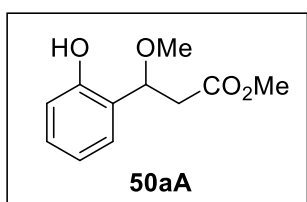
Methyl 3-(3-Bromo-4-hydroxyphenyl)-3-methoxypropanoate (50dA):



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); ^1H 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): $\delta = 43.1, 51.8, 56.7, 78.9, 110.2, 116.2, 127.4, 130.3, 133.9, 152.2, 171.4$; 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 $\text{C}_{11}\text{H}_{13}\text{O}_4^{79}\text{BrNa}$: 310.9895, $\text{C}_{11}\text{H}_{13}\text{O}_4^{81}\text{BrNa}$: 312.9874: $[\text{M}+\text{Na}]^+$; found: 310.9890, 312.9864.

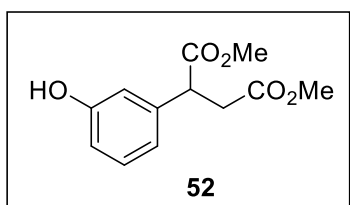
Methyl 3-(2-Hydroxyphenyl)-3-methoxypropanoate (50aA):



Compound **50aA** (62% ^1H NMR 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); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 2.67$ (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): $\delta = 41.0, 51.9, 57.6, 81.0, 117.1, 120.1, 123.5, 128.1, 129.6, 155.3, 171.2$; 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 $\text{C}_{11}\text{H}_{14}\text{O}_4\text{Na}$: 233.0790: $[\text{M}+\text{Na}]^+$; found: 233.0785.

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



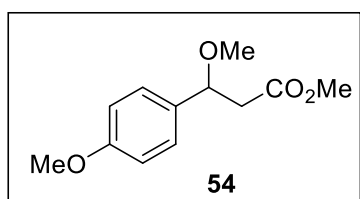
The alkoxy carbonylation of 3-vinylphenol (**48e**) (60 mg, 0.50 mmol) gave **52** (71 mg, 60%) as an oil. $R_f = 0.50$ (hexane/AcOEt = 2/1); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 2.68$ (dd, 1H, $J = 16.9,$

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): $\delta = 37.4, 46.9, 52.0, 52.5, 114.5, 114.9, 119.6, 130.1, 138.7,$

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 $\text{C}_{12}\text{H}_{15}\text{O}_5$: 239.0920: $[\text{M}+\text{H}]^+$; found: 239.0925.

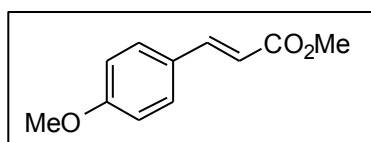
The reaction starting from 1-methoxy-4-vinylbenzene (**53**) (69 mg, 0.52 mmol) gave the crude products containing methyl 3-(4-methoxyphenyl)-3-methoxypropanoate (**54**) (5%), dimethyl 2-(4-methoxyphenyl)succinate (**55**) (34%), and methyl (*E*)-3-(4-methoxyphenyl)prop-2-enoate (26%) by ^1H NMR analysis 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



^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).

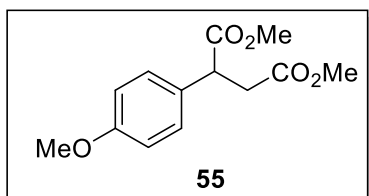
Methyl (*E*)-3-(4-Methoxyphenyl)prop-2-enoate:⁸⁶



^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

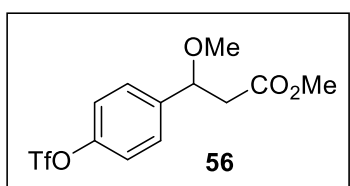
An oil. R_f = 0.60 (hexane/AcOEt = 4/1); ^1H NMR (CDCl_3 , 400 MHz): δ = 2.65 (dd, 1H, J = 17.0, 5.5 Hz), 3.18 (dd, 1H, J = 17.0, 10.1 Hz), 3.67 (s, 6H), 3.78 (s, 3H), 4.04 (dd, 1H, J = 10.1, 5.5 Hz), 6.85 (d, 2H, J = 8.2 Hz), 7.20 (d, 2H, J = 8.2 Hz); ^{13}C NMR (CDCl_3 , 100 MHz): δ = 37.6, 46.2, 51.8, 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 $\text{C}_{13}\text{H}_{17}\text{O}_5$: 253.1076: $[\text{M}+\text{H}]^+$; 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.

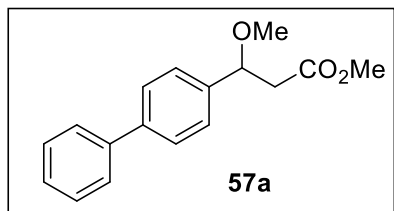


^1H NMR (CDCl_3 , 400 MHz): δ = 2.56 (dd, 1H, J = 15.6, 5.2 Hz), 2.80 (dd, 1H, J = 15.6, 9.2 Hz), 3.24 (s, 3H), 3.69 (s, 3H), 4.68 (dd, 1H, J = 9.2, 5.2 Hz), 7.28 (d, 2H, J = 8.7 Hz), 7.44 (d, 2H,

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 $\text{C}_{12}\text{H}_{13}\text{O}_6\text{F}_3\text{SNa}$: 365.0283: $[\text{M}+\text{Na}]^+$; found: 365.0280.

Methyl 3-([1,1'-Biphenyl]-4-yl)-3-methoxypropanoate (57a): Under an N_2 atmosphere, $\text{PhB}(\text{OH})_2$ (122 mg, 1.0 mmol), K_2CO_3 (180 mg, 1.3 mmol) was suspended in a mixture of toluene/DMF (10/1, total 6 mL). Triflate **56** (171 mg, 0.50 mmol) and $[\text{Pd}(\text{PPh}_3)_4]$ (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

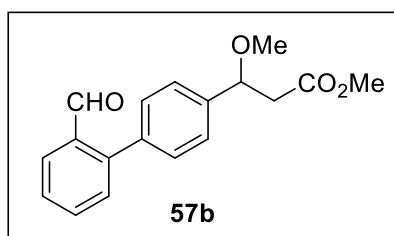
filtrate was extracted with AcOEt. The combined organic extracts were washed with water and brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ to give **57a** (100 mg, 74% yield) as an oil.



$R_f = 0.40$ (hexane/AcOEt = 6/1); ¹H NMR (CDCl₃, 400 MHz): $\delta = 2.63$ (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); ¹³C NMR (CDCl₃, 100 MHz): $\delta = 43.2, 51.7, 56.9, 79.7, 126.98, 127.01, 127.3, 128.7, 139.5, 140.6, 140.9, 171.4$; IR (Neat): $2949, 1737, 1599, 1565, 1487, 1437, 1407, 1364, 1199, 1160, 1103, 1009, 911, 841, 768, 698$ cm⁻¹; HRMS (FAB): m/z calcd for C₁₇H₁₉O₃ [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 boronic acids, respectively.

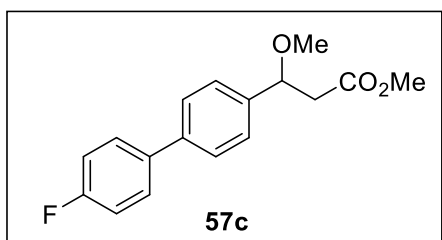
Methyl 3-(2'-Formylbiphenyl-4-yl)-3-methoxypropanoate (**57b**):



Compound **57b** (134 mg, 90% yield) was obtained from **56** (171 mg, 0.50 mmol) as a solid; $R_f = 0.60$ (hexane/AcOEt = 3/1); Mp. 103–104 °C (from hexane); ¹H NMR (CDCl₃, 400 MHz): $\delta = 2.66$ (dd, 1H, $J = 15.1, 4.6$ Hz), 2.86 (dd, 1H, $J =$

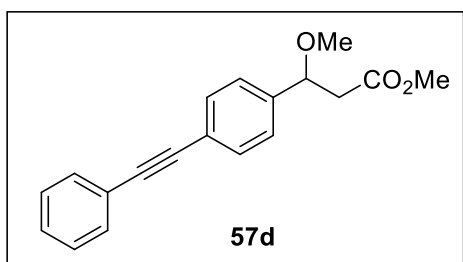
$15.1, 9.2$ Hz), 3.27 (s, 3H), 3.72 (s, 3H), 4.73 (dd, 1H, $J = 9.2, 4.6$ Hz), 7.39 (d, 2H, $J = 7.8$ Hz), 7.45 (d, 3H, $J = 8.2$ Hz), 7.51 (t, 1H, $J = 7.4$ Hz), 7.65 (t, 1H, $J = 7.4$ Hz), 8.04 (d, 1H, $J = 7.3$ Hz), 9.98 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) $\delta = 43.2, 51.8, 57.0, 79.7, 126.6, 127.6, 127.8, 130.4, 130.7, 133.6, 133.7, 137.5, 140.6, 145.5, 171.3, 192.3$; IR (KBr): $2933, 1730, 1694, 1594, 1434, 1363, 1193, 1152, 1102, 1054, 988, 910, 847, 773, 704$ cm⁻¹; Elemental analysis calcd (%) for C₁₈H₁₈O₄: 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**):



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); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): $\delta = 2.62$ (dd, 1H, $J = 15.6, 4.6\text{Hz}$), 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); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) $\delta = 43.2, 51.8, 56.9, 79.7, 115.6$ (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 ; $^{19}\text{F NMR}$ (CDCl_3 , 376 MHz): $\delta = -115$; IR (neat): 2931, 2824, 1740, 1603, 1497, 1437, 1366, 1224, 1159, 1103, 1007, 991, 824, 747, 671; HRMS (FAB): m/z calcd for $\text{C}_{17}\text{H}_{18}\text{FO}_3$ $[\text{M}+\text{H}]^+$: 289.1240; found: 289.1234.

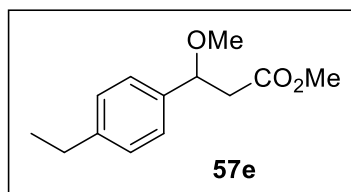
Methyl 3-Methoxy-3-(4-(phenylethynyl)phenyl)propanoate (**57d**):



Under N_2 atmosphere, a mixture of the triflate **56** (171 mg, 0.50mmol), ethynylbenzene (153.2 mg, 1.50mmol) Et_3N (0.5 mL, 3.6 mmol), and $[\text{PdCl}_2(\text{PPh}_3)_2]$ (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); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): $\delta = 2.57$ (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); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) $\delta = 43.1, 51.8, 56.9, 79.7, 89.0, 89.6, 123.0, 123.1, 126.6, 128.30, 128.32, 131.6, 131.8, 140.7, 171.2$; IR (Neat) 2930, 1740, 1597, 1509, 1437,

1366,1202, 1103, 1061, 1017, 911, 838, 757, 691 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{19}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 294.1334; found:294.1339.

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



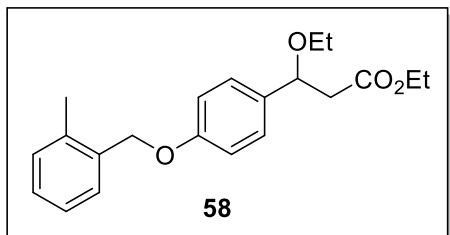
Triethylborane (1.0 M in hexane, 1.0 mL, 1.0mmol) was added to a suspension of the triflate **56** (171 mg, 0.50mmol), $[\text{Pd}(\text{dppf})\text{Cl}_2]$ (7.5 mg, 0.01 mmol), and CsOAc (192 mg,

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); ^1H 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 $\text{C}_{13}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 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 SiO₂ to give **58** (107 mg, 87% yield) as an oil.



$R_f = 0.60$ (hexane/AcOEt = 3/1); ¹H NMR (CDCl₃, 400 MHz): $\delta = 1.16$ (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).; ¹³C NMR (CDCl₃, 100 MHz): $\delta = 14.1, 14.2, 15.1, 18.8, 43.6, 60.3, 64.0, 68.5, 114.6, 115.0, 125.9, 127.7, 128.2, 128.5, 130.3, 133.5, 134.6, 158.5, 170.9$; 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 C₁₃H₁₈O₄Na: 261.1103; [M+Na]⁺; found: 261.1106.

REFERENCES

1. (a) Trost, B. M., *Science* **1991**, *254*, 1471. (b) Trost, B. M., *Angew. Chem.* **1995**, *107*, 285. (c) Trost, B. M., *Angew. Chem. Int. Ed.* **1995**, *34*, 259. (d) Trost, B. M., *Acc. Chem. Res.* **2002**, *35*, 695.
2. Wender, P. A.; Miller, B. L., *Nature* **2009**, *460*, 197.
3. (a) Anastas, P.; Eghbali, N., *Chem. Soc. Rev.* **2010**, *39*, 301. (b) Song, J. J.; Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Yee, N. K.; Senanayake, C. H., *Green Chem. Lett. Rev.* **2008**, *1*, 141.
4. Hagen, J., *Industrial catalysis: a practical approach*. John Wiley & Sons: 2015.
5. Roelen, O., *German Patent DE 849 548*, 1938.
6. Coombs, J. R.; Morken, J. P., *Angew. Chem. Int. Ed.* **2016**, *55*, 2636.
7. Van Leeuwen, P. W.; Claver, C., *Rhodium catalyzed hydroformylation*. Springer Science & Business Media: 2002; Vol. 22.
8. (a) Castellón, S.; Fernandez, E.; Van Leeuwen, P.; Claver, C., Rhodium Catalyzed Hydroformylation. *Catalysis by Metal Complexes* **2000**, *22*. (b) Breit, B.; Seiche, W., *Synthesis* **2001**, *2001*, 1.
9. (a) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H., *J. Am. Chem. Soc.* **1993**, *115*, 7033. (b) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H., *J. Am. Chem. Soc.* **1997**, *119*, 4413.
10. Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L., *Angew. Chem. Int. Ed.* **2012**, *51*, 2477.
11. (a) Wu, X. F.; Anbarasan, P.; Neumann, H.; Beller, M., *Angew. Chem. Int. Ed.* **2010**, *49*, 9047. (b) Negishi, E. i., *Angew. Chem. Int. Ed.* **2011**, *50*, 6738. (c) Suzuki, A., *Angew. Chem. Int. Ed.* **2011**, *50*, 6722.
12. Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A., *Angew. Chem. Int. Ed.* **1962**, *1*, 80.

13. Tsuji, J., *Palladium reagents and catalysts: new perspectives for the 21st century*. John Wiley & Sons: 2006.
14. McDonald, R. I.; Liu, G.; Stahl, S. S., *Chem. Rev.* **2011**, *111*, 2981.
15. (a) Henry, P., *Palladium catalyzed oxidation of hydrocarbons*. Springer Science & Business Media: 2012; Vol. 2. (b) Hemmer, H.; Rambaud, J.; Tkatchenko, I., *J. Organometal. Chem.* **1975**, *97*, C57. (c) Stille, J.; Divakaruni, R., *J. Am. Chem. Soc.* **1978**, *100*, 1303. (d) Hegedus, L. S.; Darlington, W., *J. Am. Chem. Soc.* **1980**, *102*, 4980. (e) Wieber, G. M.; Hegedus, L. S.; Akermark, B.; Michalson, E. T., *J. Org. Chem.* **1989**, *54*, 4649.
16. (a) Wu, X. F.; Neumann, H.; Beller, M., *ChemSusChem* **2013**, *6*, 229. (b) Beller, M., *Catalytic carbonylation reactions*. Springer: 2006; Vol. 18.
17. Liu, Q.; Zhang, H.; Lei, A., *Angew. Chem. Int. Ed.* **2011**, *50*, 10788.
18. (a) James, D.; Hines, L.; Stille, J., *J. Am. Chem. Soc.* **1976**, *98*, 1806. (b) James, D.; Stille, J., *J. Am. Chem. Soc.* **1976**, *98*, 1810. (c) Drent, E.; Budzelaar, P. H., *Chem. Rev.* **1996**, *96*, 663. (d) Reddy, K. R.; Chen, C.-L.; Liu, Y.-H.; Peng, S.-M.; Chen, J.-T.; Liu, S.-T., *Organometallics* **1999**, *18*, 2574.
19. (a) Fenton, D. M.; Steinwand, P. J., *J. Org. Chem.* **1974**, *39*, 701. (b) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z., *Tetrahedron Lett.* **1979**, *20*, 1401. (c) Choudary, B.; Reddy, N. P.; Kantam, M. L.; Jamil, Z., *Tetrahedron Lett.* **1985**, *26*, 6257.
20. Claver, C.; Godard, C.; Ruiz, A.; Pamies, O.; Dieguez, M., Enantioselective carbonylation reactions. *Modern Carbonylation Methods* **2008**, 65.
21. (a) Tsuji, J.; Morikawa, M.; Kiji, J., *Tetrahedron Letters* **1963**, *4*, 1061. (b) Tsuji, J., *Acc. Chem. Res.* **1969**, *2*, 144.
22. Alper, H.; Woell, J. B.; Despeyroux, B.; Smith, D. J., *J. Chem. Soc., Chem. Commun.* **1983**, *21*, 1270.
23. Fergusson, S. B.; Alper, H., *J. Chem. Soc., Chem. Commun.* **1984**, *20*, 1349.
24. Alper, H.; Hamel, N., *J. Am. Chem. Soc.* **1990**, *112*, 2803.

25. Cometti, G.; Chiusoli, G. P., *J. Organometal. Chem.* **1979**, *181*, C14.
26. Bianchini, C.; Mantovani, G.; Meli, A.; Oberhauser, W.; Brüggeller, P.; Stampfl, T., *J. Chem. Soc., Dalton Trans.* **2001**, *5*, 690.
27. Urata, H.; Fujita, A.; Fuchikami, T., *Tetrahedron Lett.* **1988**, *29*, 4435.
28. Medema, D.; Van Helden, R.; Kohll, C., *Inorg. Chim. Acta* **1969**, *3*, 255.
29. James, D.; Stille, J., *J. Org. Chem.* **1976**, *41*, 1504.
30. Stille, J.; Divakaruni, R., *J. Org. Chem.* **1979**, *44*, 3474.
31. Brechot, P.; Chauvin, Y.; Commereuc, D.; Saussine, L., *Organometallics* **1990**, *9*, 26.
32. Yokota, T.; Sakaguchi, S.; Ishii, Y., *J. Org. Chem.* **2002**, *67*, 5005.
33. Hayashi, M.; Takezaki, H.; Hashimoto, Y.; Takaoki, K.; Saigo, K., *Tetrahedron Lett.* **1998**, *39*, 7529.
34. Dai, M.; Wang, C.; Dong, G.; Xiang, J.; Luo, T.; Liang, B.; Chen, J.; Yang, Z., *Eur. J. Org. Chem.* **2003**, *2003*, 4346.
35. Nefkens, S. C.; Sperrle, M.; Consiglio, G., *Angew. Chem. Int. Ed.* **1993**, *32*, 1719.
36. (a) Nozaki, K.; Sato, N.; Tonomura, Y.; Yasutomi, M.; Takaya, H.; Hiyama, T.; Matsubara, T.; Nobuaki Koga, N., *J. Am. Chem. Soc.* **1997**, *119*, 12779. (b) Zhou, H.; Hou, J.; Cheng, J.; Lu, S.; Fu, H.; Wang, H., *J. Organometal. Chem.* **1997**, *543*, 227. (c) Kawashima, Y.; Okano, K.; Nozaki, K.; Hiyama, T., *Bull. Chem. Soc. Jpn.* **2004**, *77*, 347. (d) Oi, S.; Nomura, M.; Aiko, T.; Inoue, Y. d., *J. Mol. Catal A: Chem.* **1997**, *115*, 289.
37. (a) Yoshikawa, K.; Inoguchi, K.; Morimoto, T.; Achiwa, K., *Heterocycles* **1990**, *31*, 1413. (b) Ito, Y.; Kamijo, T.; Harada, H.; Matsuda, F.; Terashima, S., *Tetrahedron Lett.* **1990**, *31*, 2731. (c) Inoguchi, K.; Morimoto, T.; Achiwa, K., *J. Organometal. Chem.* **1989**, *370*, C9. (d) Kammermeier, B.; Beck, G.; Holla, W.; Jacobi, D.; Napierski, B.; Jendralla, H., *Chem. Eur. J.* **1996**, *2*, 307.
38. Sperrle, M.; Consiglio, G., *J. Mol. Catal. A: Chem.* **1999**, *143*, 263.

39. Wang, L.; Kwok, W.; Wu, J.; Guo, R.; Terry, T.-L.; Zhou, Z.; Chan, A. S.; Chan, K.-S., *J. Mol. Catal. A: Chem.* **2003**, *196*, 171.
40. Liang, B.; Liu, J.; Gao, Y.-X.; Wongkhan, K.; Shu, D.-X.; Lan, Y.; Li, A.; Batsanov, A.-S.; Howard, J.-A.; Marder, T.-B.; Chen, J.-H.; Yang, Z. *Organometallics* **2007**, *26*, 4756.
41. Alper, H.; Leonard, D., *Tetrahedron Lett.* **1985**, *26*, 5639.
42. (a) Semmelhack, M.; Epa, W.; Cheung, A. W.; Gu, Y.; Kim, C.; Zhang, N.; Lew, W., *J. Am. Chem. Soc.* **1994**, *116*, 7455. (b) Gracza, T.; Jäger, V. *Synthesis* **1994**, *1994*, 1359.
43. Tamaru, Y.; Hojo, M.; Yoshida, Z., *J. Org. Chem.* **1991**, *56*, 1099.
44. Li, Z.; Gao, Y.; Tang, Y.; Dai, M.; Wang, G.; Wang, Z.; Yang, Z., *Org. Lett.* **2008**, *10*, 3017.
45. Ye, F.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 1855.
46. Ferguson, J.; Zeng, F.; Alper, H. *Org. Lett.* **2012**, *14*, 5602.
47. Qiu, Y.; Yang, B.; Jiang, T.; Zhu, C.; Bäckvall, J. E., *Angew. Chem. Int. Ed.* **2017**, *129*, 3269.
48. Zhu, C.; Yang, B.; Bäckvall, J.-E., *J. Am. Chem. Soc.* **2015**, *137*, 11868.
49. Yang, B.; Qiu, Y.; Jiang, T.; Wulff, W. D.; Yin, X.; Zhu, C.; Bäckvall, J. E., *Angew. Chem. Int. Ed.* **2017**, *56*, 4535.
50. Zhang, G.; Gao, B.; Huang, H., *Angew. Chem. Int. Ed.* **2015**, *54*, 7657.
51. Ferguson, J.; Zeng, F.; Alwis, N.; Alper, H., *Org. Lett.* **2013**, *15*, 1998.
52. Zhang, Z.; Liao, L. L.; Yan, S. S.; Wang, L.; He, Y. Q.; Ye, J. H.; Li, J.; Zhi, Y. G.; Yu, D. G., *Angew. Chem. Int. Ed.* **2016**, *55*, 7068.
53. (a) Szolcsányi, P.; Gracza, T., *Chem. Commun.* **2005**, 3948. (b) Palik, M.; Karlubikova, O. g.; Lasikova, A.; Kožíšek, J.; Gracza, T., *Eur. J. Org. Chem.* **2009**, *2009*, 709. (c)

- Szolcsányi, P.; Gracza, T.; Špánik, I., *Tetrahedron Lett.* **2008**, *49*, 1357. (d) Heumann, A.; Réglie, M., *Tetrahedron* **1996**, *52*, 9289. (e) Muzart, J., *Tetrahedron* **2005**, *61*, 4179. (f) Muzart, J., *Tetrahedron* **2005**, *61*, 5955.
54. Yu, W. Y.; Bensimon, C.; Alper, H., *Chem. Eur. J.* **1997**, *3*, 417.
55. Cao, P.; Zhang, X., *J. Am. Chem. Soc.* **1999**, *121*, 7708.
56. Kapitán, P.; Gracza, T., *Arkivoc* **2008**, *8*, 8.
57. Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H., *Tetrahedron Lett.* **2003**, *44*, 711.
58. Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H., *J. Org. Chem.* **2009**, *74*, 9274.
59. Kooš, P.; Špánik, I.; Gracza, T., *Tetrahedron: Asymmetry* **2009**, *20*, 2720.
60. Chen, C.; Jin, S.; Zhang, Z.; Wei, B.; Wang, H.; Zhang, K.; Lv, H.; Dong, X.-Q.; Zhang, X., *J. Am. Chem. Soc.* **2016**, *138*, 9017.
61. (a) Inomata, K.; Toda, S.; Kinoshita, H., *Chem. Lett.* **1990**, *19*, 1567. (b) Toda, S.; Miyamoto, M.; Kinoshita, H.; Inomata, K., *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3600.
62. (a) Hosokawa, T.; Takano, M.; Murahashi, S.; Ozaki, H.; Kitagawa, Y.; Sakaguchi, K.; Katsube, Y., *J. Chem. Soc. Chem. Commun.* **1994**, 1433. (b) Hosokawa, T.; Takano, M.; Murahashi, S., *J. Am. Chem. Soc.* **1996**, *118*, 3990.
63. Bruce, M., *J. Organometal. Chem.* **1972**, *44*, 209.
64. Mizutani, T.; Ukaji, Y.; Inomata, K., *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1251.
65. Aratani, T.; Ukaji, Y.; Inomata, K., *Chem. Lett.* **2008**, *38*, 46.
66. Takeuchi, S.; Ukaji, Y.; Inomata, K., *Bull. Chem. Soc. Jpn.* **2001**, *74*, 955.
67. Aratani, T.; Tahara, K.; Takeuchi, S.; Ukaji, Y.; Inomata, K., *Chem. Lett.* **2007**, *36*, 1328.
68. Aratani, T.; Tahara, K.; Takeuchi, S.; Kitamura, S.; Murai, M.; Fujinami, S.; Inomata, K.; Ukaji, Y., *Bull. Chem. Soc. Jpn.* **2012**, *85*, 1225.

69. Ukaji, Y.; Miyamoto, M.; Mikuni, M.; Takeuchi, S.; Inomata, K., *Bull. Chem. Soc. Jpn.* **1996**, *69*, 735.
70. Yonezawa, Y.; Furuya, T.; Aratani, T.; Fijinami, S.; Inomata, K.; Ukaji, Y., *Tetrahedron: Asymmetry* **2014**, *25*, 936.
71. (a) Caruano, J.; Muccioli, G.; Robiette, R., *Org. Biomol. Chem.* **2016**, *14*, 10134. (b) Ye, L.-W.; Shu, C.; Gagosz, F., *Org. Biomol. Chem.* **2014**, *12*, 1833. (c) Jouin, P.; Castro, B.; Nisato, D., *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177. (d) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J., *J. Org. Chem.* **2002**, *67*, 5445. (e) Hanessian, S.; Bayrakdarian, M.; Luo, X., *J. Am. Chem. Soc.* **2002**, *124*, 4716. (f) Ishibashi, H.; So, T. S.; Okochi, K.; Sato, T.; Nakamura, N.; Nakatani, H.; Ikeda, M., *J. Org. Chem.* **1991**, *56*, 95.
72. (a) Ojima, I.; Korda, A.; Shay, W. R., *J. Org. Chem.* **1991**, *56*, 2024. (b) El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H., *J. Am. Chem. Soc.* **1996**, *118*, 4264. (c) Van den Hoven, B. G.; Alper, H., *J. Am. Chem. Soc.* **2001**, *123*, 10214. (d) Hoshimoto, Y.; Ashida, K.; Sasaoka, Y.; Kumar, R.; Kamikawa, K.; Verdaguer, X.; Riera, A.; Ohashi, M.; Ogoshi, S., *Angew. Chem.* **2017**. (e) Limberger, J.; Mottin, M.; Nachtigall, F.; Castellano, E. E.; da Rosa, R., *J. Mol. Catal. A: Chem.* **2008**, *294*, 82. (f) Biletzki, T.; Imhof, W., *Synthesis* **2011**, *2011*, 3979.
73. (a) Kato, K.; Matsuba, C.; Kusakabe, T.; Takayama, H.; Yamamura, S.; Mochida, T.; Akita, H.; Tat'yana, A. P.; Vologdin, N. V.; Gusev, O. V., *Tetrahedron* **2006**, *62*, 9988. (b) Tietze, L. F.; Zinngrebe, J.; Spiegl, D. A.; Stecker, F., *Heterocycles* **2007**, *74*, 473. (c) Babjak, M.; Gracza, T., *Tetrahedron* **2011**, *67*, 4980. (d) Ambrosini, L. M.; Cernak, T. A.; Lambert, T. H., *Synthesis* **2010**, *2010*, 870.
74. Bajracharya, G. B.; Koranne, P. S.; Tsujihara, T.; Takizawa, S.; Onitsuka, K.; Sasai, H., *Synlett* **2009**, *2009*, 310.
75. (a) Schmidt, E.; Wiese, W., *Tetrahedron Lett.* **1980**, *21*, 4425. (b) Taniguchi, T.; Sugiura, Y.; Zaimoku, H.; Ishibashi, H., *Angew. Chem.* **2010**, *122*, 10352. (c) Liu, W.; Li, Y.; Liu, K.; Li, Z., *J. Am. Chem. Soc.* **2011**, *133*, 10756.
76. Prof. A. Yokoyama informed that ICP-MS analysis revealed abundance of tin in MeOH stored in 18 L tin-plate.

77. (a) Knifton, J. F., *J. Org. Chem.* **1976**, *41*, 2885. (b) Naignre, R.; Chenal, T.; Ciprés, I.; Kalck, P.; Daran, J.-C.; Vaissermann, J., *J. Organometal. Chem.* **1994**, *480*, 91. (c) Lenoble, G.; Urrutigoity, M.; Kalck, P., *Tetrahedron Lett.* **2001**, *42*, 3697. (d) Noskowska, M.; Śliwińska, E.; Duczmal, W., *Trans. Metal Chem.* **2003**, *28*, 756. (e) Das, D.; Pratihar, S.; Roy, U. K.; Mal, D.; Roy, S., *Org. Biomol. Chem.* **2012**, *10*, 4537. (f) Das, D.; Pratihar, S.; Roy, S., *Organic Lett.* **2012**, *14*, 4870. (g) Das, D.; Pratihar, S.; Roy, S., *J. Org. Chem.* **2013**, *78*, 2430.
78. (a) Nakashima, R.; Yano, T.; Ogawa, J.; Tanaka, N.; Toda, N.; Yoshida, M.; Takano, R.; Inoue, M.; Honda, T.; Kume, S., *Eur. J. Pharmacol.* **2014**, *737*, 194. (b) Takano, R.; Yoshida, M.; Inoue, M.; Honda, T.; Nakashima, R.; Matsumoto, K.; Yano, T.; Ogata, T.; Watanabe, N.; Toda, N., *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2949. (c) Takano, R.; Yoshida, M.; Inoue, M.; Honda, T.; Nakashima, R.; Matsumoto, K.; Yano, T.; Ogata, T.; Watanabe, N.; Hirouchi, M., *Bioorg. Med. Chem.* **2015**, *23*, 5546.
79. (a) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A., *Helv. Chim. Acta* **1991**, *74*, 232. (b) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D., *Synlett* **1991**, *1991*, 257. (c) Levy, J.-N.; Latham, C. M.; Roisin, L.; Kandziora, N.; Di Fruscia, P.; White, A. J.; Woodward, S.; Fuchter, M. J., *Org. Biomol. Chem.* **2012**, *10*, 512. (d) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M., *J. Am. Chem. Soc.* **1991**, *113*, 726.
80. Dupont, J.; Ebeling, G.; Delgado, M. R.; Consorti, C. S.; Burrow, R.; Farrar, D. H.; Lough, A. J., *Inorg. Chem. Commun.* **2001**, *4*, 471.
81. Crimmins, M. T.; Shamszad, M., *Org. Lett.* **2007**, *9*, 149.
82. Combret, Y.; Duflos, J.; Dupas, G.; Bourguignon, J.; Quéguiner, G., *Tetrahedron: Asymmetry* **1993**, *4*, 1635.
83. Katritzky, A. R.; Suzuki, K.; He, H.-Y., *J. Org. Chem.* **2002**, *67*, 3109.
84. Belmessieri, D.; Cordes, D. B.; Slawin, A. M.; Smith, A. D., *Org. Lett.* **2013**, *15*, 3472.
85. Pardini, V. L.; Sakata, S. K.; Vargas, R. R.; Viertler, H., *J. Am. Chem. Soc.* **2001**, *12*, 223.
86. Zhang, Z.; Zha, Z.; Gan, C.; Pan, C.; Zhou, Y.; Wang, Z.; Zhou, M.-M., *J. Org. Chem.* **2006**, *71*, 4339.

87. Papst, S.; Noisier, A. F.; Brimble, M. A.; Yang, Y.; Krissansen, G. W., *Bioorg. Med. Chem.* **2012**, *20*, 5139.
88. Chen, Q.-Y.; Yang, Z.-Y., *Tetrahedron Lett.* **1986**, *27*, 1171.
89. Wang, B.; Sun, H. X.; Sun, Z. H., *Eur. J. Org. Chem.* **2009**, *2009*, 3688.

APPENDIX

Appendix consists 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:

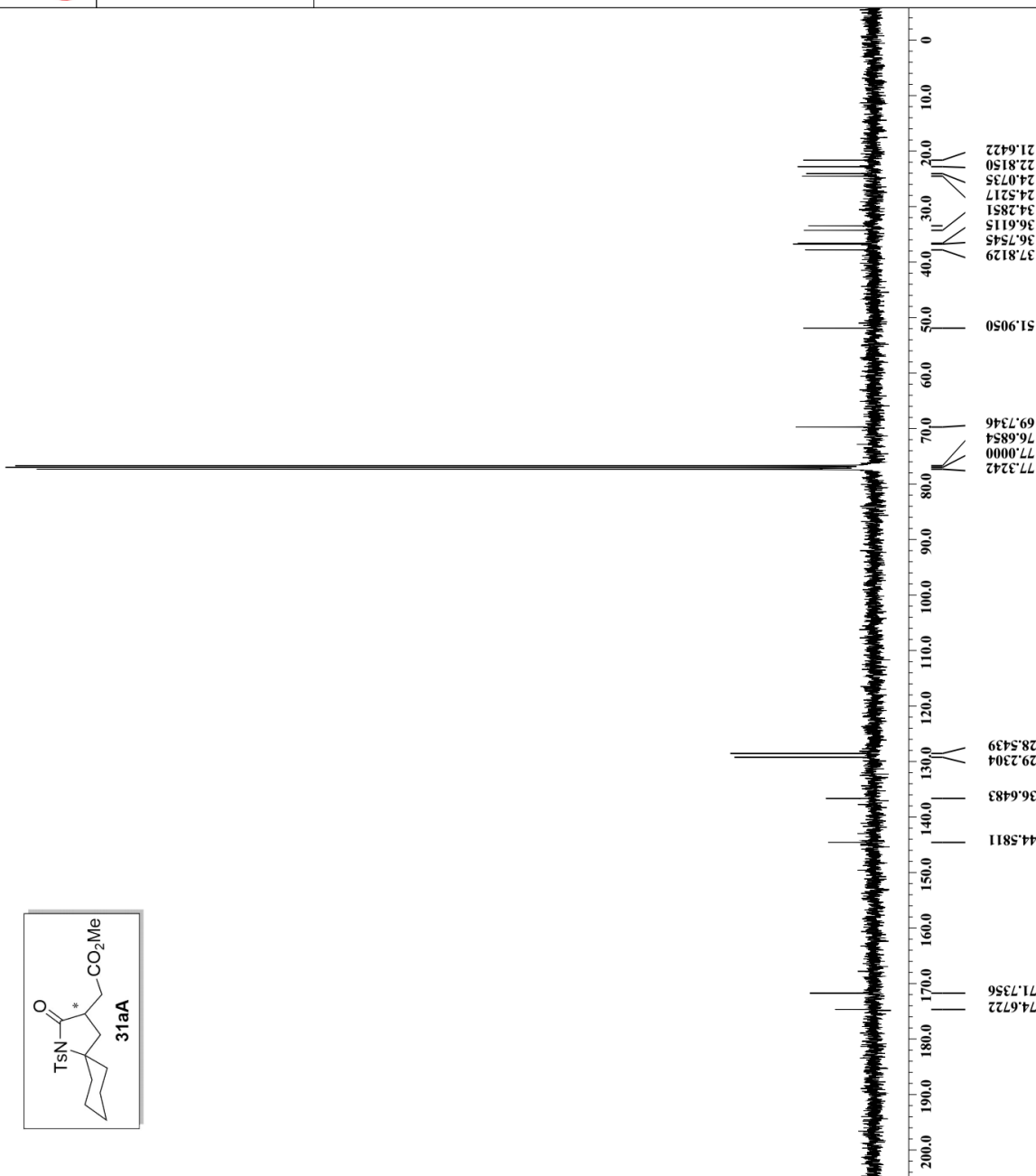
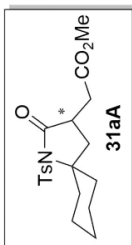
- 1) ^1H , ^{13}C , ^{19}F NMR spectrums of the γ -lactam products **31** SI2
- 2) HPLC data for the the γ -lactam products **31** (Table 2.4) SI23
- 3) ^1H and ^{13}C NMR spectrums of the 3-(hydroxyphenyl)-3-methoxypropanoic acid esters **50bA-50bF**, **50cA**, **50dA**, **50Aa** SI33
- 4) ^1H and ^{13}C NMR spectrums of the triflate **56**, coupling products **57a-57e** and compound **58** SI55



----- PROCESSING PARAMETERS -----

dc balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
FPM
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 = 4.95846665 [Hz]
X_sweep = 31.40703518 [kHz]
X_atn = 18
X_domain = 13C
X_freq = 399.78219838 [MHz]
X_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]
WALTZ
Irr_noise = TRUE
Decoupling = 1 [s]
Initial_wait = TRUE
Noe_time = 2 [s]
Recvr_gain = 60
Relaxation_delay = 2 [s]
Repetition_time = 3.04333312 [s]
Temp_get = 18.2 [dC]



X : parts per Million : 13C

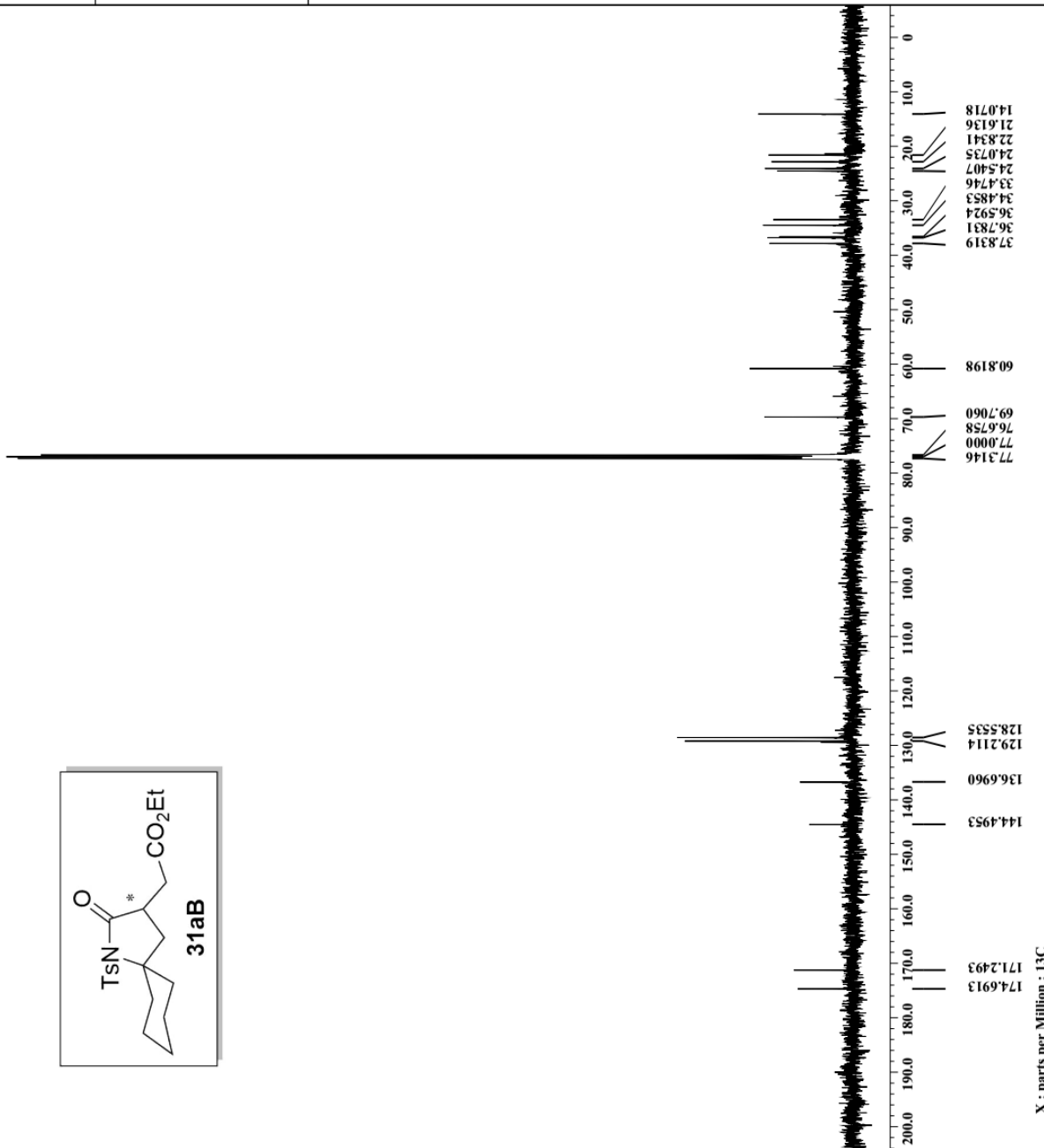
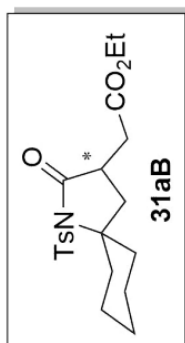


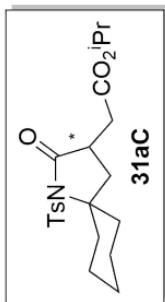
```

---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 2.0[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
fft_dir1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5[%] : TRUE
  
```

```

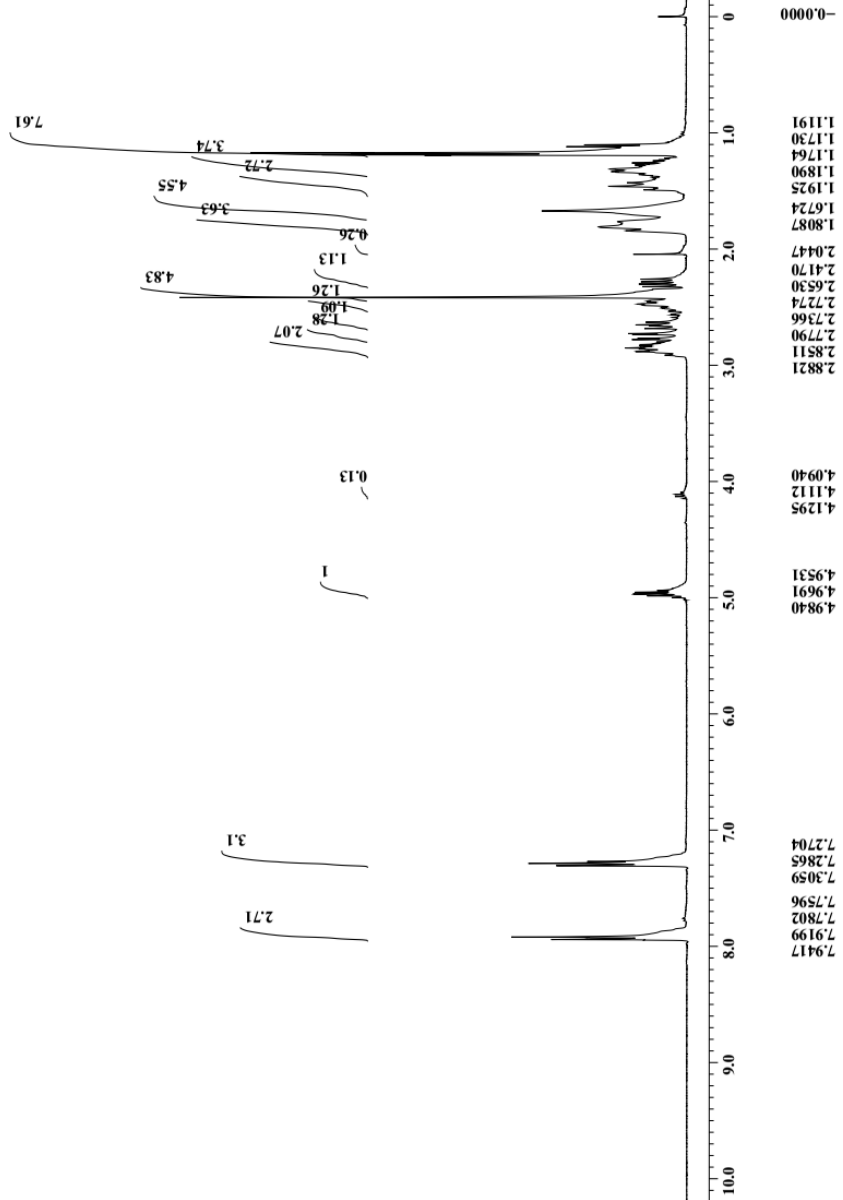
Filename = pn3-183recycleC13-4.j
Author = delta
Experiment = single_pulse_dec
Sample_id = S#598625
Solvent = CHLOROFORM-D
Creation_time = 29-SEP-2016 16:00:12
Revision_time = 15-JAN-2018 13:56:04
Current_Time = 17-JAN-2018 13:30:39
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
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 = 3[s]
Repetition_time = 1.04333312[s]
Temp_get = 23.3[dc]
  
```





----- PROCESSING PARAMETERS -----
 dc_balance : 0 : FALSE
 secp : 0.2[Hz] : 0.0[s]
 trapzoid3 : 0[%] : 80[%]
 zerofill : 1 : TRUE : TRUE
 machinephase :
 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 = ID_COMPLEX
 Dim_size = 13107
 Dim_title = HR
 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
 Scan = 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_preset = FALSE
 Initial_wait = 1[s]
 Recvr_gain = 34
 Relaxation_delay = 5[s]
 Repetition_time = 7.18365952[s]
 Temp_get = 23.2[degC]



X : parts per Million : 1H



```

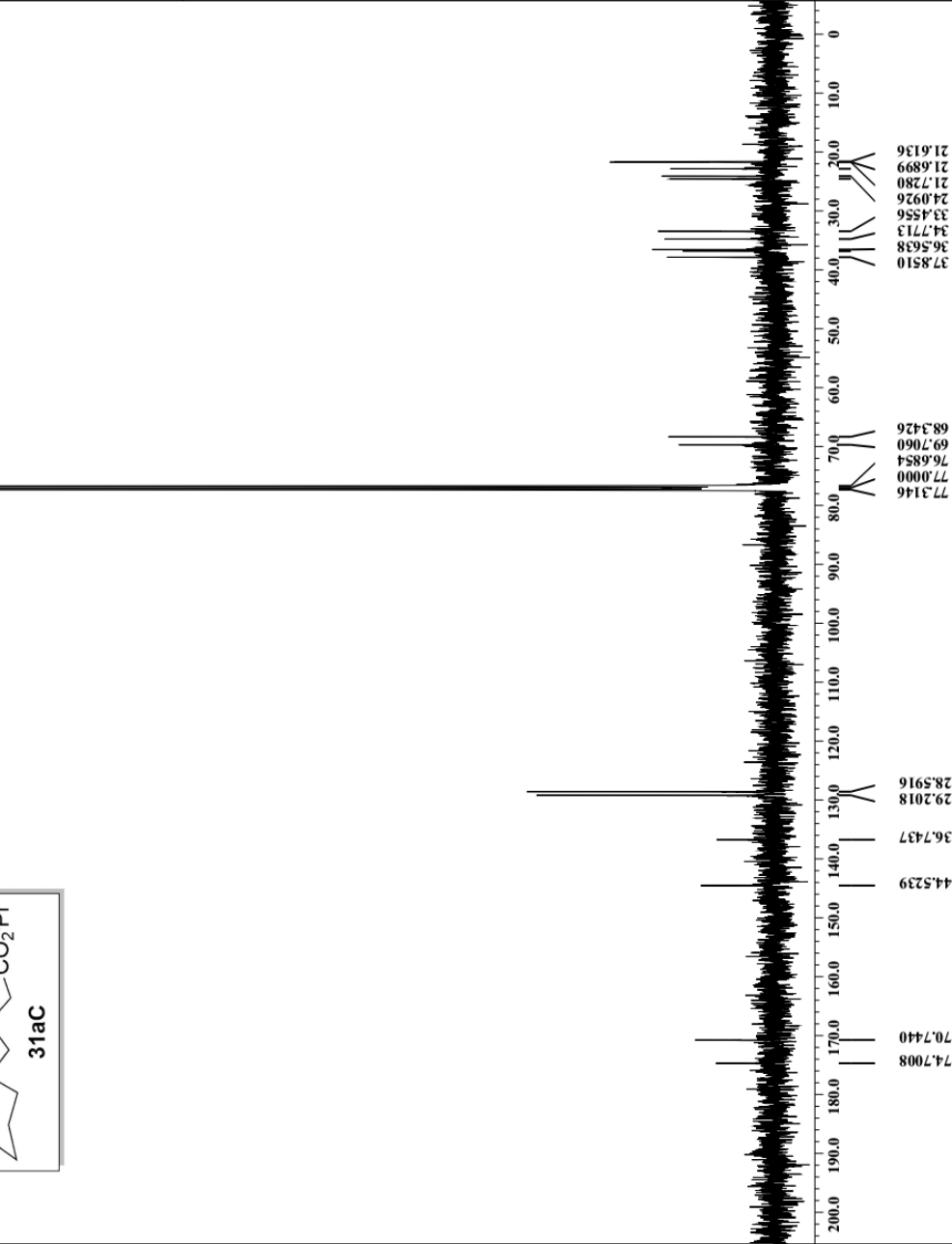
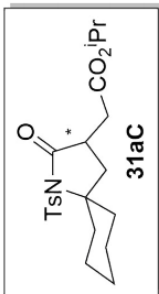
----- PROCESSING PARAMETERS -----
dc balance : 0 : FALSE
sexp : 2.0 [Hz] : 0.0 [s]
trapezoid3 : 0 [%] : 80 [%] : 100 [Hz]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
Ppm
auto_reference : 5 [%] : TRUE
  
```

```

Filename = FN3-178CRYSTALC13-5-.j
Author = delta
Experiment = S#62709
Sample_id = CHZOROPORM-D
Solvent = 29-SEP-2016 17:10:21
Creation_time = 15-JAN-2018 13:59:23
Revision_time = 17-JAN-2018 13:22:09
Current_time
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 = 9.95846665 [Hz]
X_sweep = 14.40703518 [kHz]
Irr_domain = 13C
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_time = 2 [s]
Noe_gain = 60
Relaxation_delay = 2 [s]
Repetition_time = 5.04333312 [s]
Temp_get = 23.2 [dC]
  
```



X : parts per Million : 13C

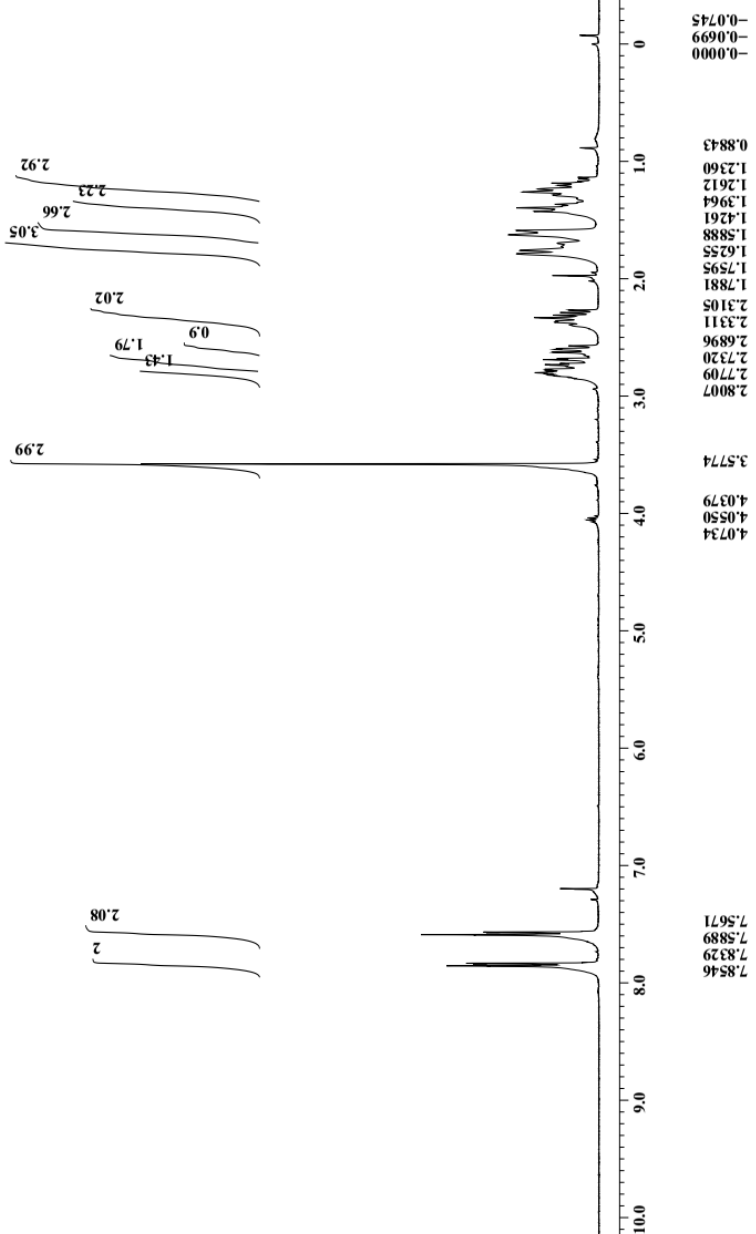
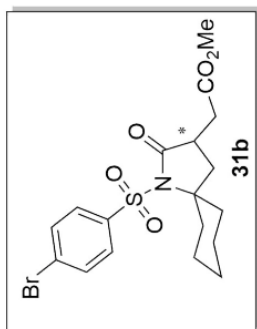


```

---- PROCESSING PARAMETERS ----
dc_balanc: 0 : FALSE
sexp: 0.2 [Hz] : 0.0 [s]
trapzoid3: 0 [%] : 80 [%] : 100 [%]
zerofill: 1
fft: 1 : TRUE : TRUE
machinephase
ppm
auto_reference: 5 [%] : TRUE
  
```

```

Filename = pn5-22Brcolumn-5.jdf
Author =
Experiment = single_pulse.ex2
Sample_id = S#34025B
Solvent = CHLOROFORM-D
Creation_time = 17-JAN-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 =
Dim units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNN-ECS400
Field strength = 9.389766 [T] (400 [MHz])
X_acq_duration = 2.18365952 [s]
X_domain = 1H
X_freq = 399.78219838 [MHz]
X_offset = 16384
X_points = 0
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_preset = FALSE
Initial_wait = 1 [s]
Recvr_gain = 38
Relaxation_delay = 5 [s]
Repetition_time = 7.18365952 [s]
Temp_get = 19.6 [dC]
  
```



X : parts per Million : 1H

```

---- 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
  
```

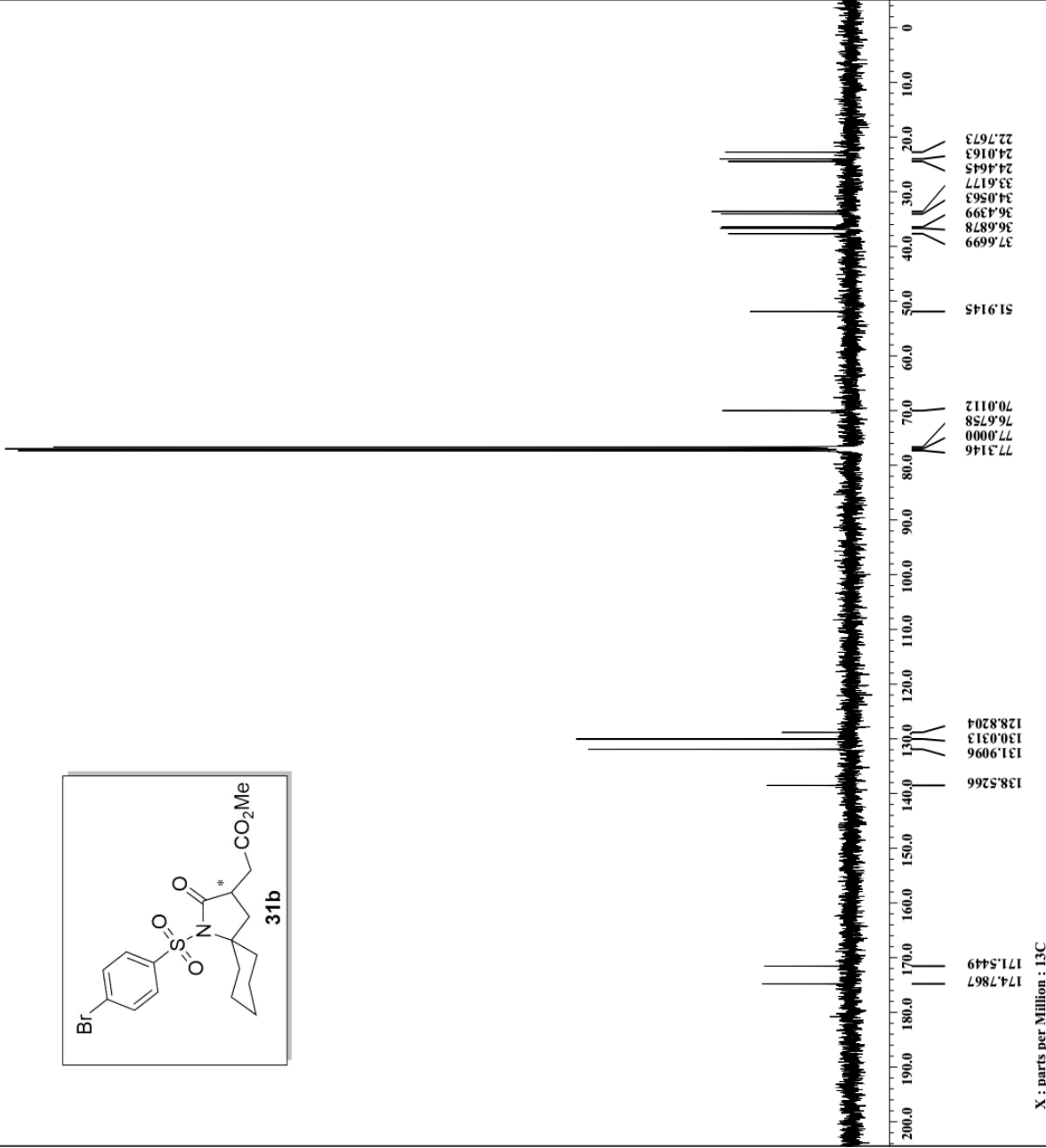
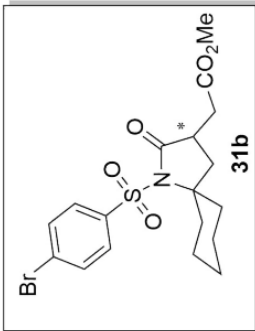
```

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Author        =
Experiment    = single_pulse_dec
Sample_id     = S#351853
Solvent       = CHLOROFORM-D
Creation_time = 7-NOV-2017 09:46:14
Revision_time = 15-JAN-2018 13:45:53
Current_Time  = 17-JAN-2018 15:05:22

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

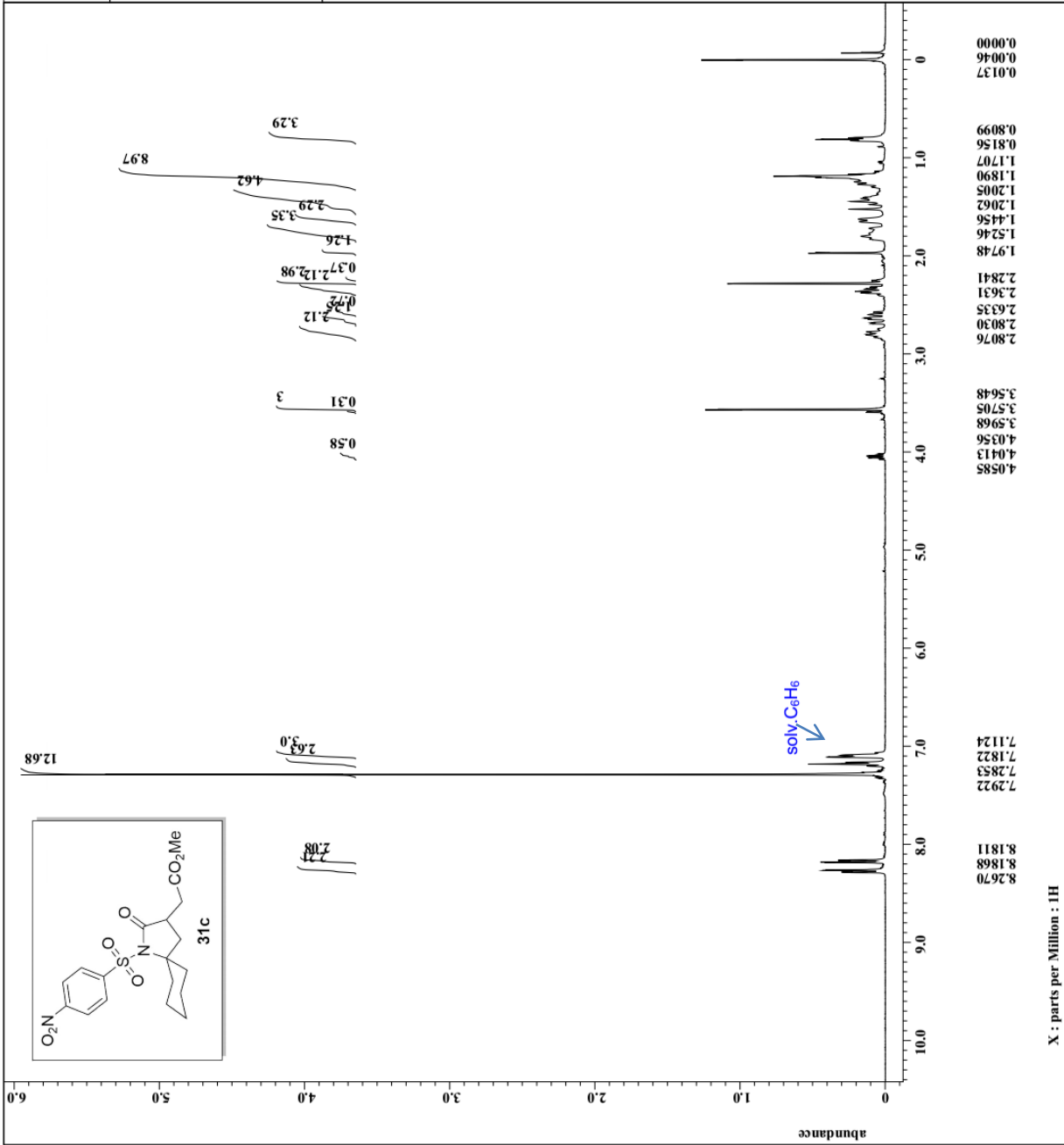
Field strength = 9.389766[T] (400[MHz])
X_acq_duration = 1.04333312[s]
X_domain       = 13C
X_freq         = 100.52530333[MHz]
X_offset      = 100[ppm]
X_points      = 32768
X_resolution  = 4
X_sweep       = 0.95846665[Hz]
X_step        = 31.40703518[kHz]
Irr_domain    = 1H
Irr_freq      = 399.78219838[MHz]
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_atn_dec     = 2.8[us]
X_pulse       = 21.56853[db]
Irr_atn_dec   = 21.56853[db]
Irr_atn_noe   = TRUE
Decoupling    = WALTZ
Initial_wait  = 1[s]
Noe           = TRUE
Noe_time      = 2[s]
Recvr_gain    = 60
Relaxation_delay = 3[s]
Repetition_time = 3.04333312[s]
Temp_get      = 19.4[dc]
  
```



----- PROCESSING PARAMETERS -----
 dc balance : FALSE
 sq : 0.2 [Hz] : 0.0 [Hz]
 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#751987
 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 =
 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_preset = FALSE
 Initial_wait = 1 [s]
 Recvr_gain = 30
 Relaxation_delay = 5 [s]
 Repetition_time = 7.18365952 [s]
 Temp_get = 19.4 [dC]

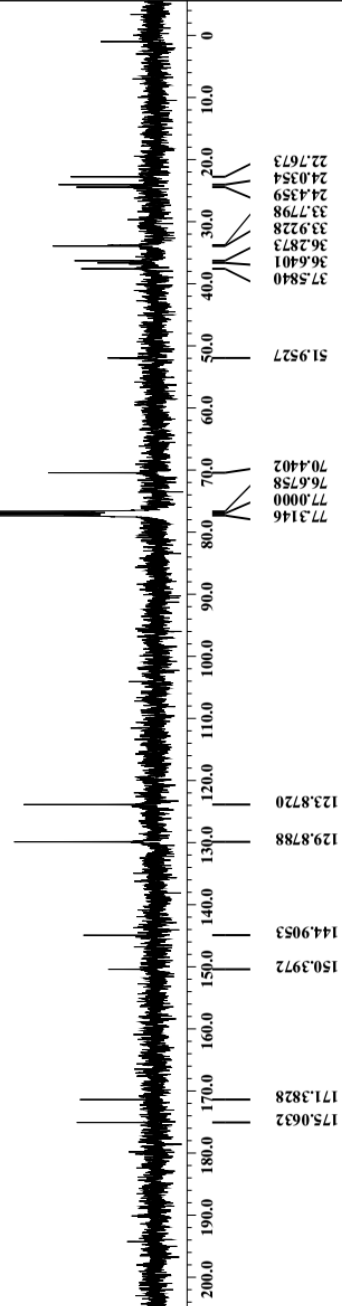
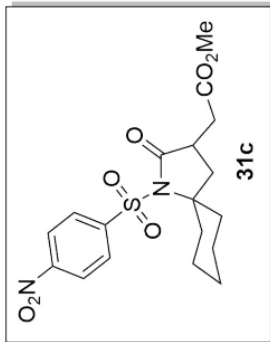




----- PROCESSING PARAMETERS -----

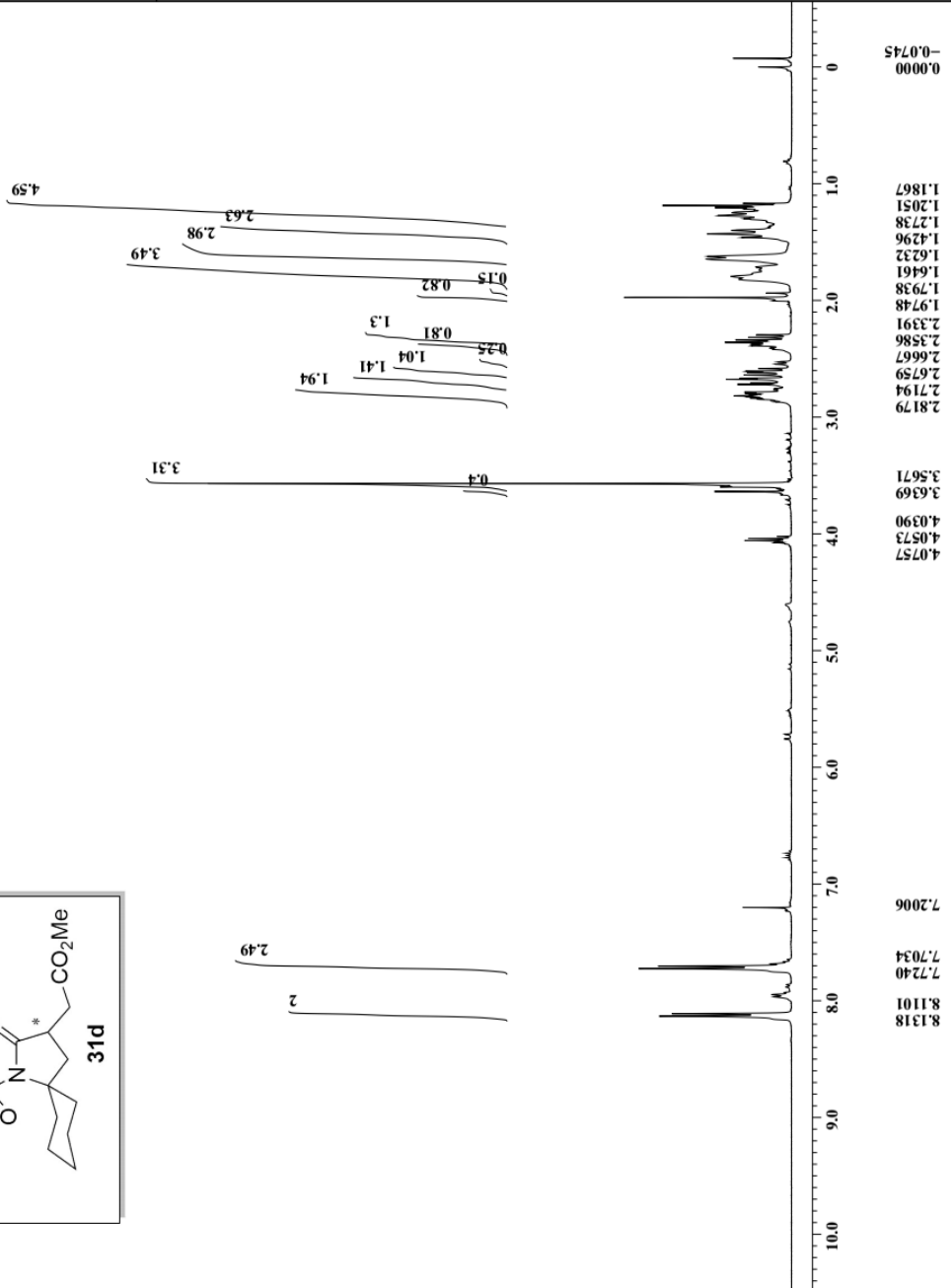
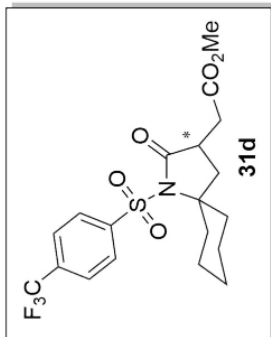
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 trapezoid3 : 0[%] : 80[%] : 100[%]
 zerofill : 1
 fft : 1 : TRUE : TRUE
 machinephase
 Ppm
 auto_reference : 5[%] : TRUE

Filename = pn-2C C13-5.jdf
 Author = delta
 Experiment = single_pulse_dec
 Sample_id = SH661390
 Solvent = CHLOROFORM-D
 Revision_time = 25-DEC-2017 18:40:24
 Revision_time = 15-DEC-2017 18:55:47
 Current_time = 17-JAN-2018 13:12:30
 Comment = single pulse decouple
 Data_format = 1D COMPLEX
 Dia_size = 26214
 Dia_title = 13C
 Dia_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 = 1
 Initial_wait = 1[s]
 Noe_time = 6[s]
 Relv_gain = 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 = pa5-CF3 fl-5.jdf
 Author = delta
 Experiment = single_pulse.ex2
 Sample_id = SF35033
 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_units = [ppm]
 Dimensions = X
 Site = EGS 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]
 Ir_domain = 1H
 Ir_freq = 399.78219838[MHz]
 Ir_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]
 Ir_mode = Off
 Dante_presat = Off
 Dante_presat = FALSE
 initial_wait = 1[s]
 Recvr_gain = 30
 Relaxation_delay = 7[s]
 Repetition_time = 7.18365952[s]
 Temp_get = 15.1[degC]



X : parts per Million : 1H

```

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

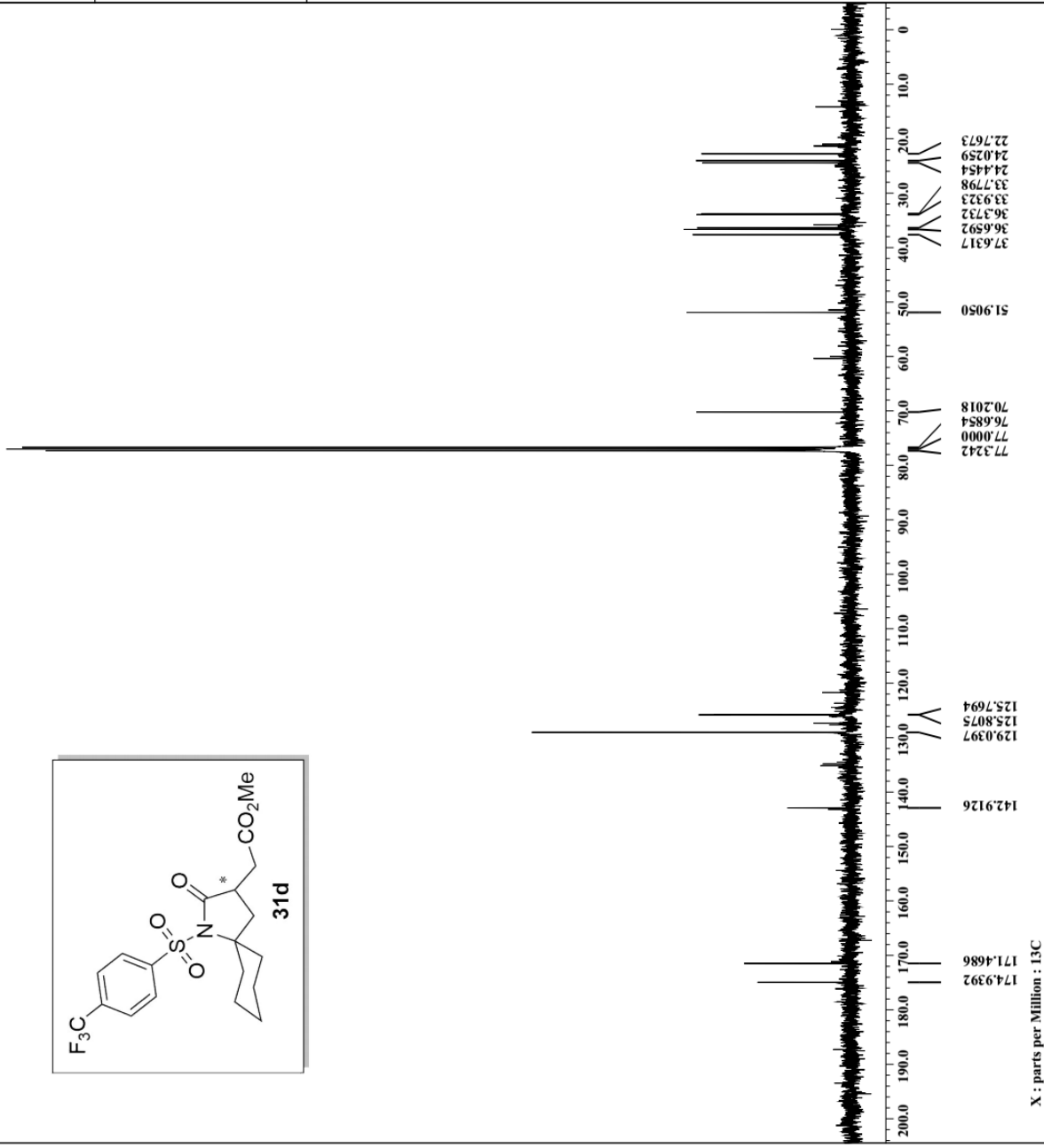
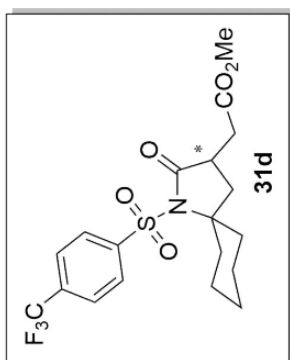
```

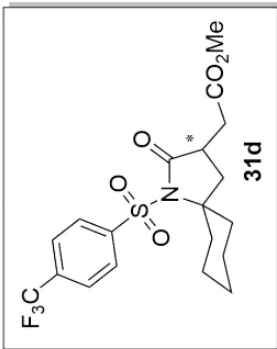
Filename = pn5-CF3 f1 C13-4.jdf
Author = delta
Experiment = single pulse_dec
Sample_id = S#336120
Solvent = CHLOROFORM-D
Creation_time = 16-NOV-2017 09:20:42
Revision_time = 15-JAN-2018 13:36:57
Current_time = 17-JAN-2018 15:29:59

Comment = single pulse decouple
Data_format = 3D COMPLEX
Dim_1 = 26214
Dim_2 = 13C
Dim_title = [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 = IH
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 190
Total_scans = 190

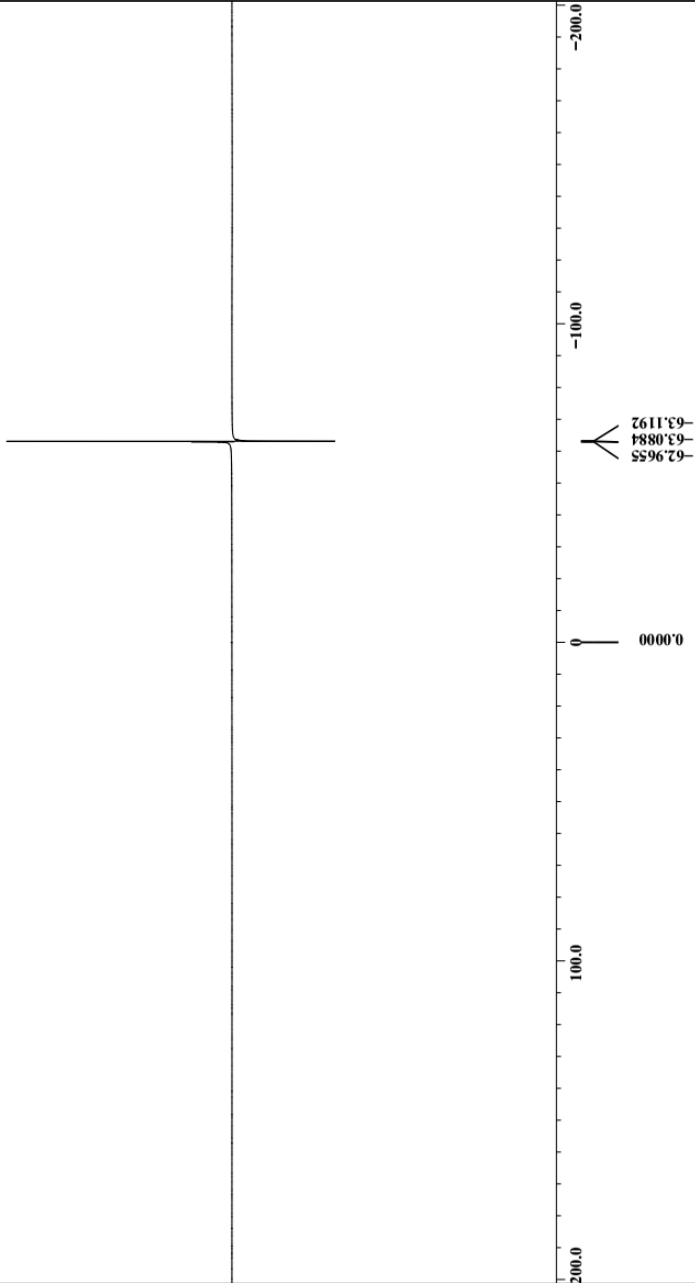
X_90_width = 8.4[us]
X_acq_time = 1.04333312[s]
X_angle = 30[deg]
X_atn = 6[db]
X_pulse = 2.8[us]
Irr_atn_dec = 21.56853[db]
Irr_atn_noe = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe_time = TRUE
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 19.3[dc]
  
```





----- 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 = 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 = ID 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 = 9[deg]
X_gain = 5.8[db]
X_offset = 0[us]
Tri_mode = Off
Dante_preset = FALSE
Initial_wait = 1[s]
Recvr_gain = 42
Relaxation_delay = 5[s]
Repetition_time = 5.08650752[s]
Temp_get_time = 18.4[dc]

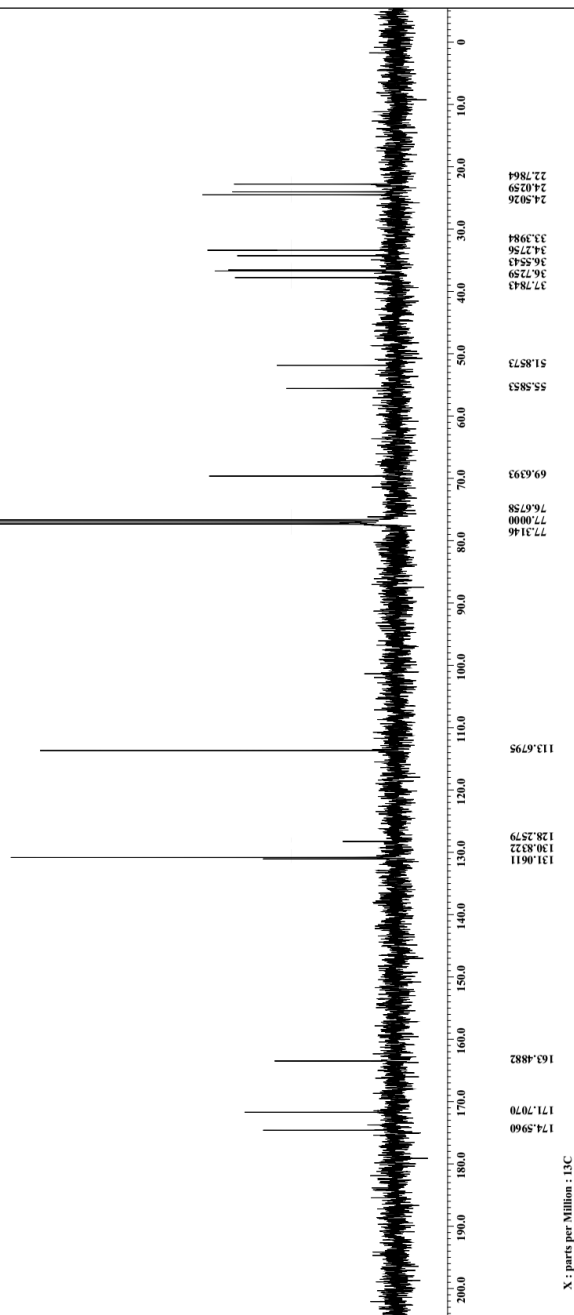
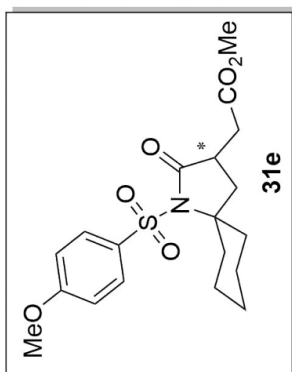



```

----- PROCESSING PARAMETERS -----
dc balance 0 : FALSE
f2presol3 : 0 [%] : 80 [%] : 100 [%]
zerofill : TRUE : TRUE
machinphase
File
Auto_reference : 5 [%] : TRUE
  
```

```

File name = 05-190Me C13-4 .jdf
Author =
Experiment = single_pulse_dec
Sample =
Solvent = CHLOROFORM-D
Date_1 = 7-NOV-2017 09:33:47
Creation time =
Revision time = 15-JAN-2018 13:20:33
Current time = 17-JAN-2018 16:55:59
Comment = single pulse decouple
Name comment =
Dim_size = 26214
Dim_title = 13C
Dimensions = X [ppm]
Site = ECS 400
Spectrometer = JNM-EC400
Field strength = 9.389766 [T] (400 [MHz])
X_nucleation = 13C 40033312 [s]
X_freq = 100.5250333 [MHz]
X_pulses = 327 [8]
X_prescans = 4
X_resolution = 31.984655 [Hz]
IR_domain = 1H 40763516 [kHz]
IR_freq = 599.78219838 [MHz]
Clipped = FALSE
Sof_return = 73
Total_scans = 73
X_90_width = 8.4 [us]
X_acq_time = 1.0433312 [s]
X_angle = 30 [deg]
X_p1 = 2.8 [us]
X_pulse = 2.8 [us]
IR_atn_dec = 21.56853 [dB]
IR_atn_noe = 21.56853 [dB]
Decoupling = TRUE
P1_delay = 2 [s]
Nox_time = 2 [s]
Socv_gain = 0
Repetition_delay = 3.0433312 [s]
Repetition_time = 19.5 [DC]
Temp_set = 19.5 [DC]
  
```



X : parts per Million : 13C



```

---- PROCESSING PARAMETERS ----
dc balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zsf : 1 : TRUE
zsf : 1 : TRUE
machinephase : TRUE
auto_reference : 5[%] : TRUE
  
```

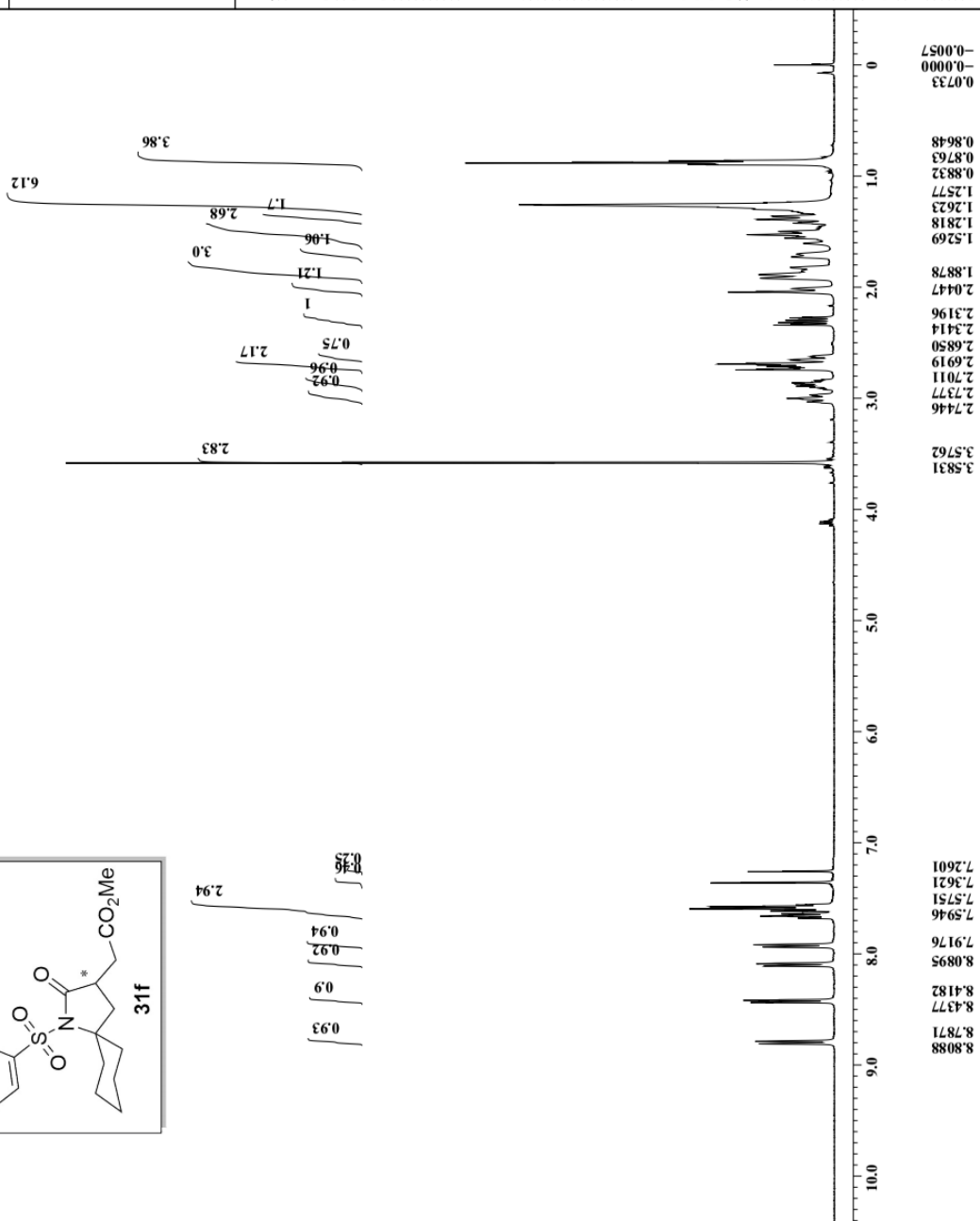
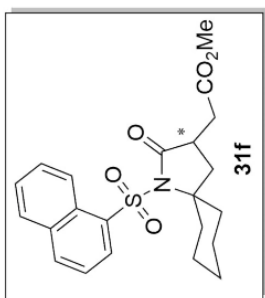
```

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[MHz]
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        = Off
X_mode         = Off
Date_acq       = FALSE
Date_presat    = FALSE
Initial_wait   = 1[s]
Recvr_gain     = 36
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get       = 19.1[dc]
  
```



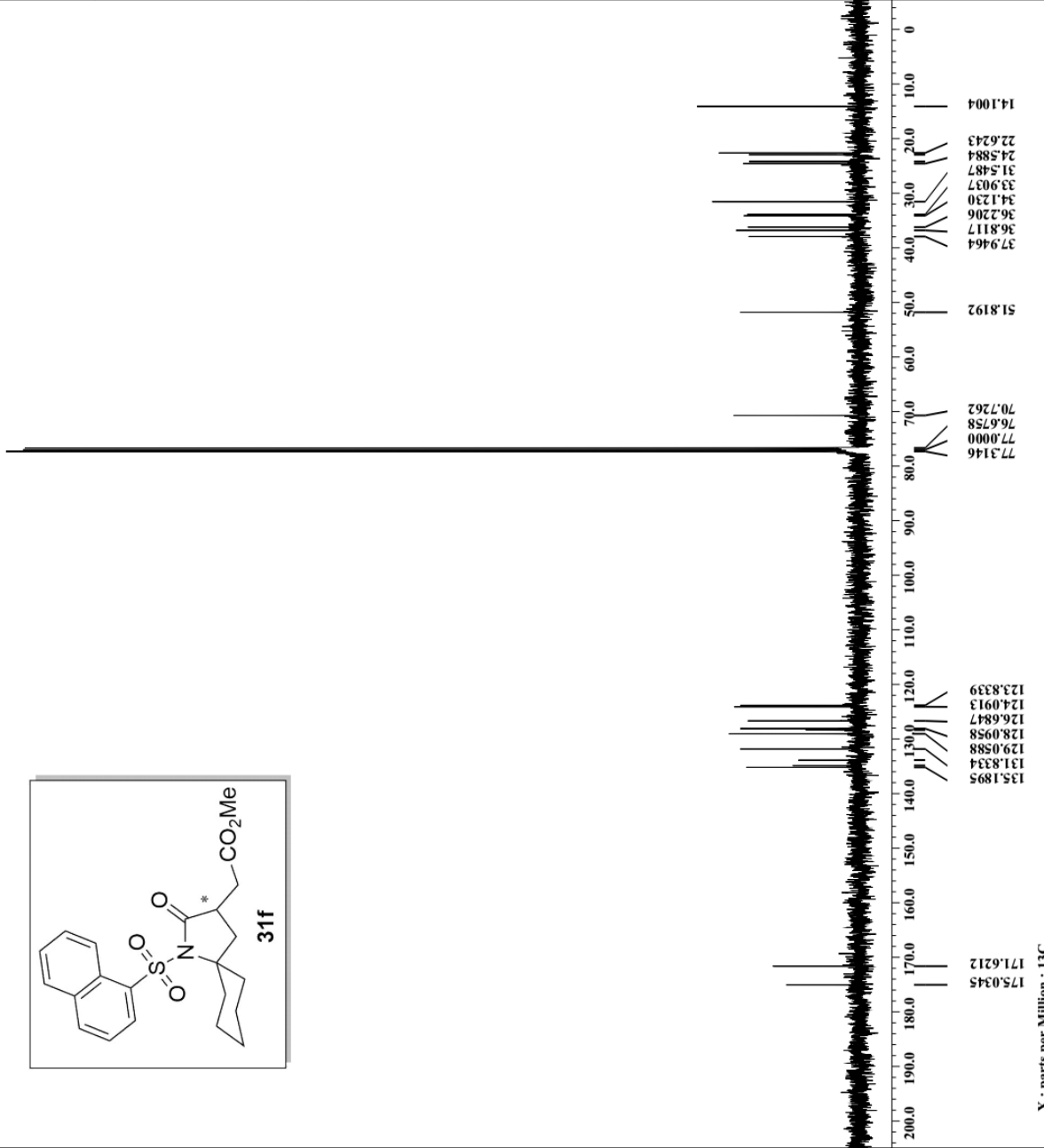
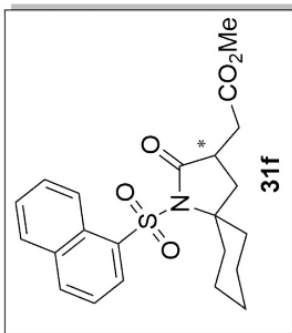
X : parts per Million : 1H

```

----- 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
  
```

```

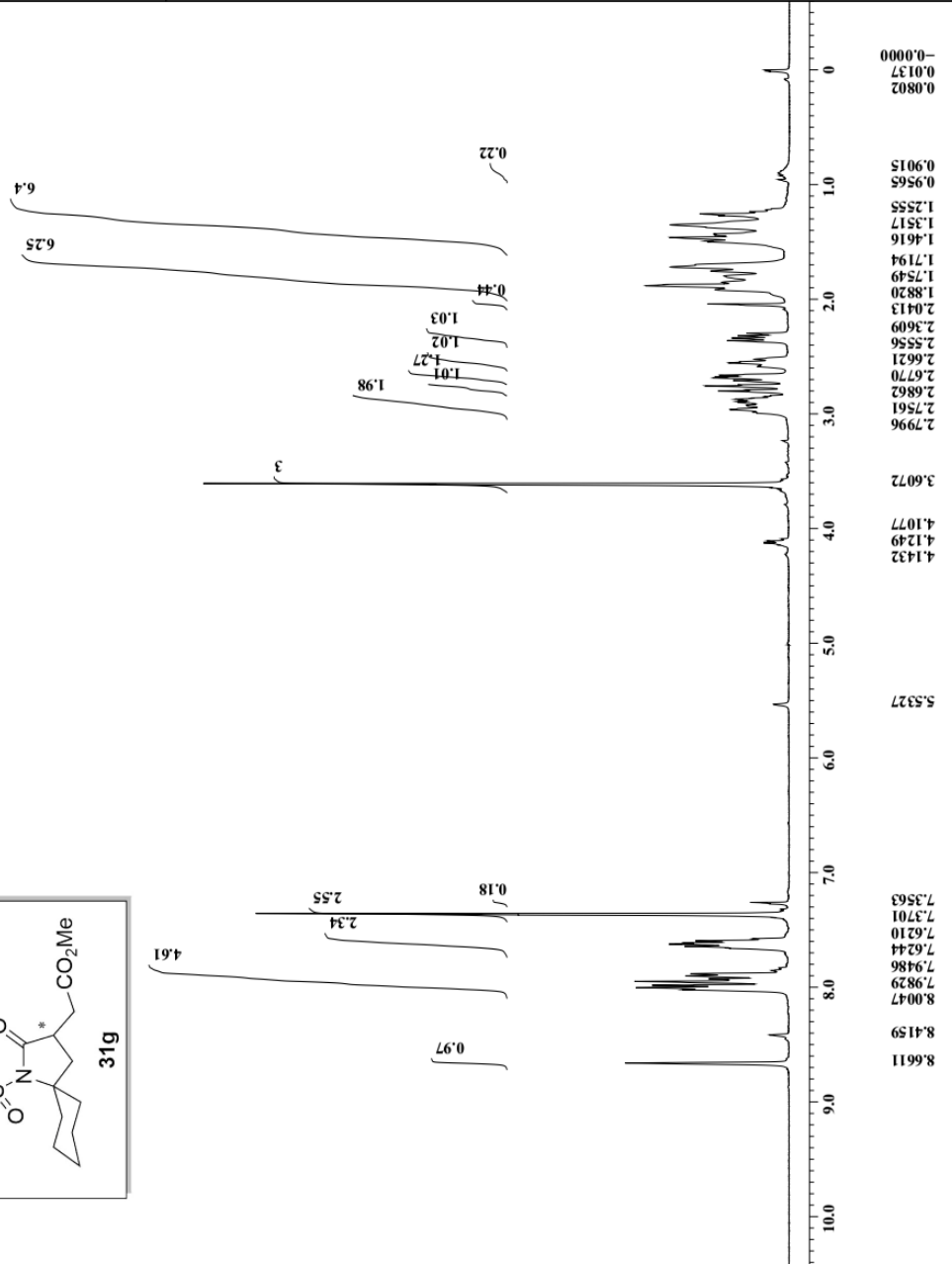
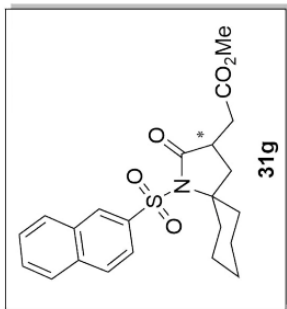
Filename = pn5-26 a-Nap C13-4 .jd
Author = delta
Experiment = single pulse_dec
Sample_id = #458008
Solvent = CHLOROFORM-D
Creation_time = 20-NOV-2017 14:05:17
Revision_time = 15-JAN-2018 13:07:57
Current_time = 17-JAN-2018 15:12:39
Comment = single pulse decouple
Data format = 1D_COMPLEX
Dim_size = 26214
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 = 299.78219838[MHz]
Irr_offset = 5[ppm]
No_mipped = FALSE
Scan_return = 58
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]
WALTZ = TRUE
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
 fit : 1 : TRUE : TRUE
 machinephase
 Ppm
 auto_reference : 5[%] : TRUE

```

Filename = pm5-27 columnfml-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 = ID COMPLEX
Data_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 = 16384
X_points = 0
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]
Irr_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]
  
```



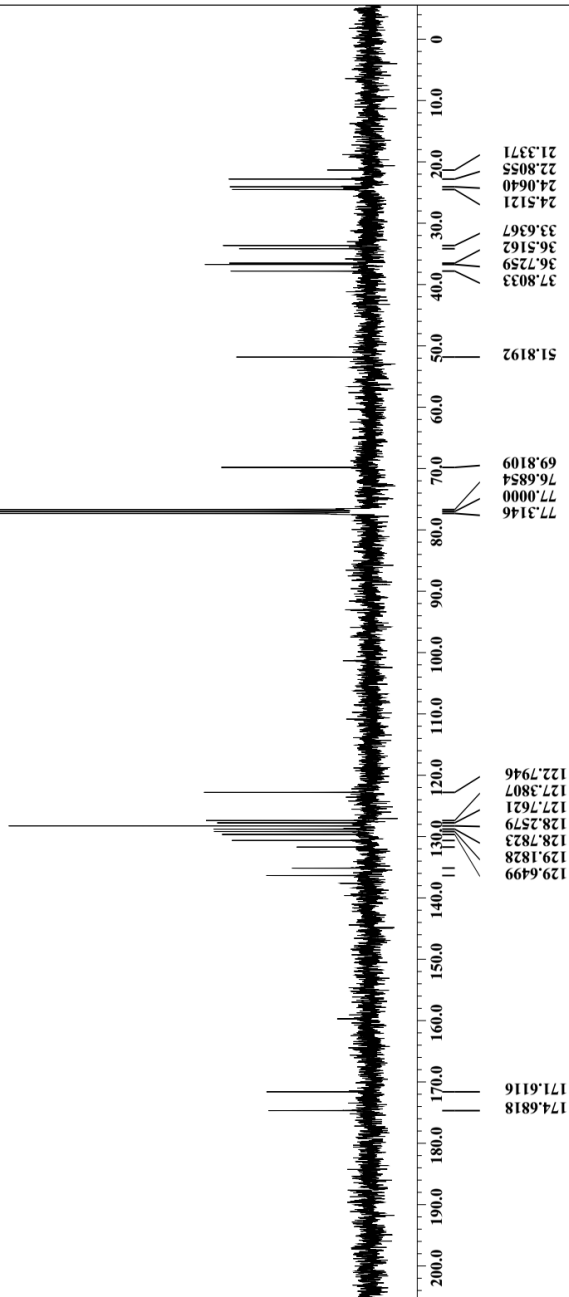
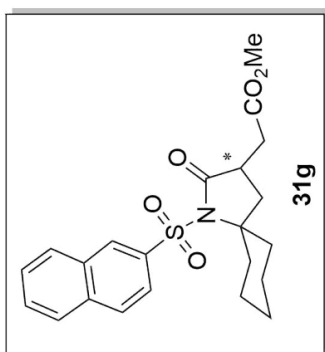
X : parts per Million : 1H


```

---- 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 = pp5-27f1c13-4.jdf
Author =
Experiment = single pulse_dec
Sample_id = #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 = ID 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 = 9.95846665[Hz]
X_sweep = 31.40703518[MHz]
Irr_domain =
Irr_freq = 399.78219838[MHz]
Irr_offset = FALSE
Cliped =
ModReturn = 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]
Decoupling = 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[degC]
  
```

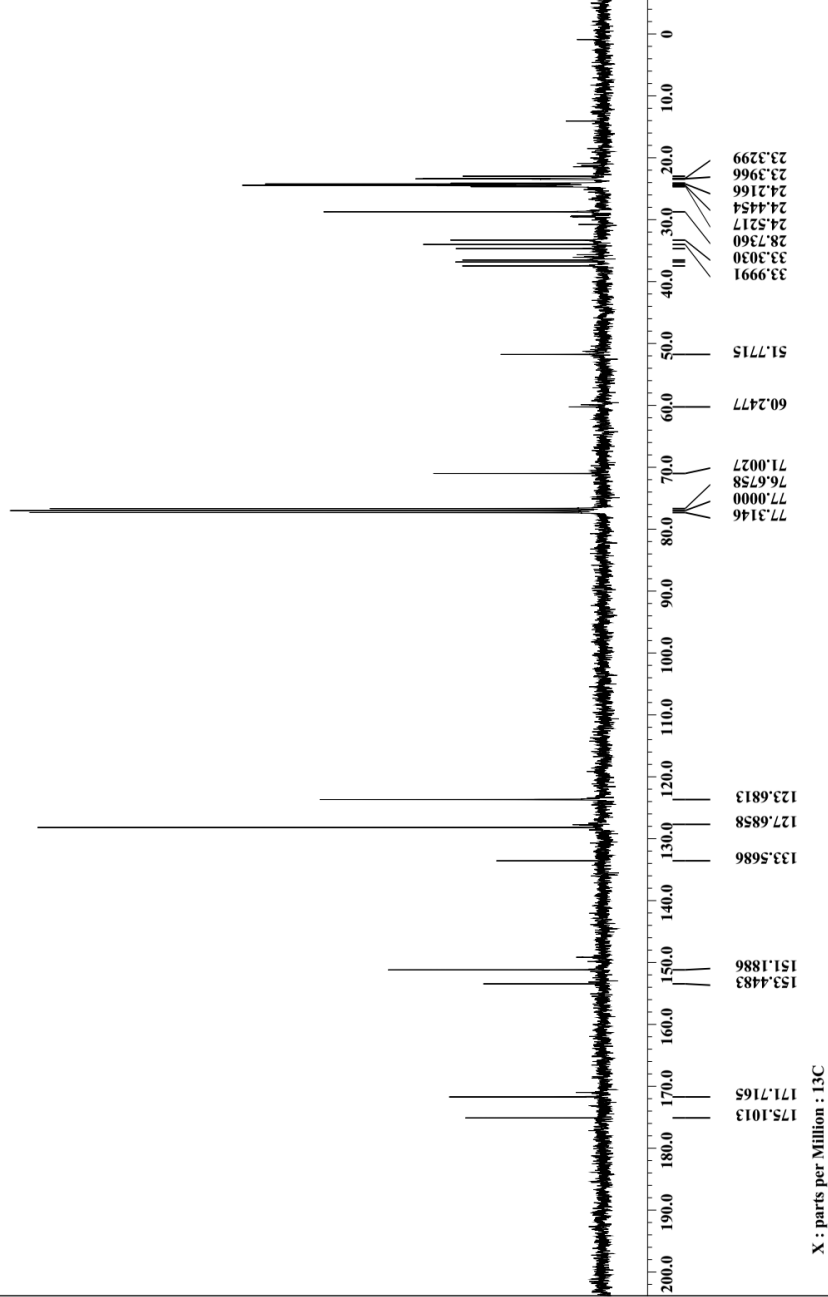
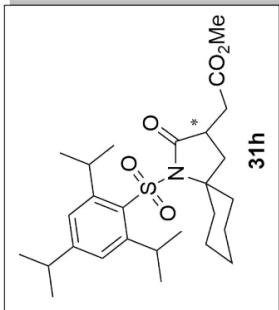


X : parts per Million : 13C



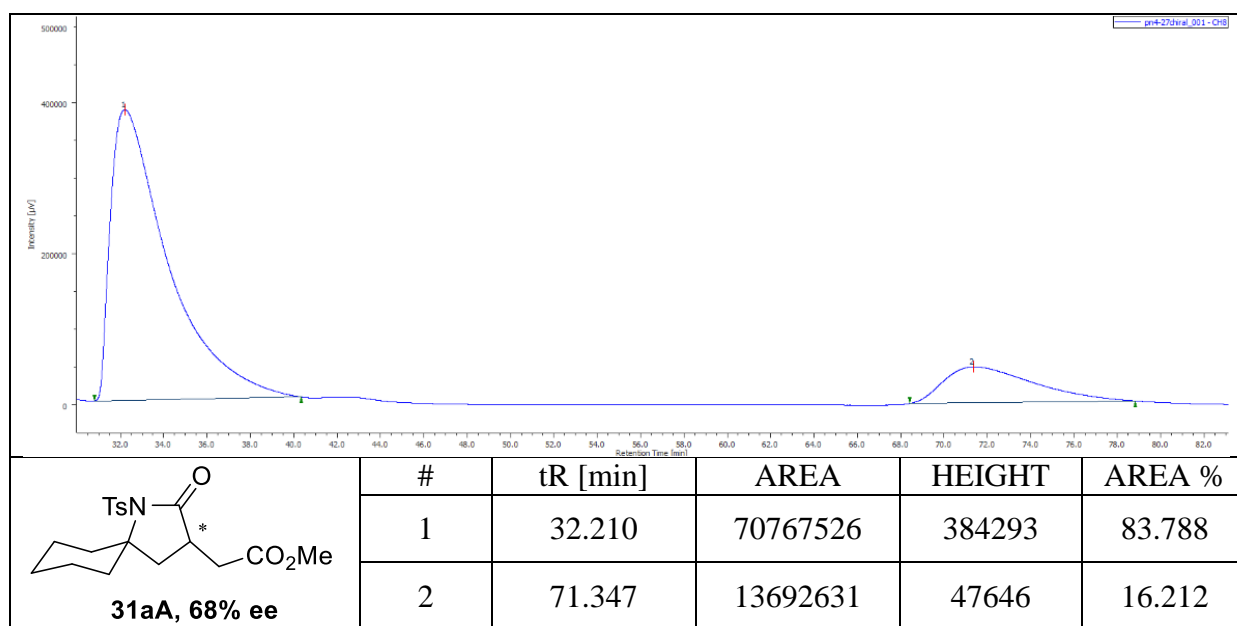
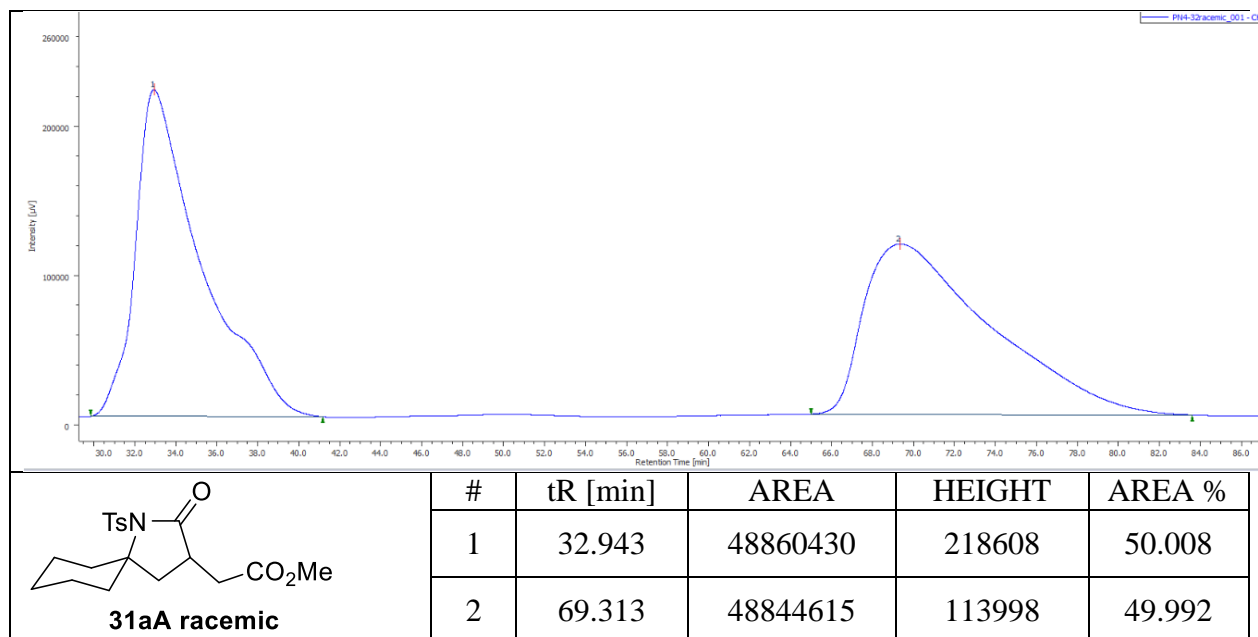
----- PROCESSING PARAMETERS -----
 dc_balance : 0 : FALSE
 sexp : 2.0[Hz] : 0.0[s]
 trezoid3 : 0[%] : 80[%] : 100[%]
 zerofill : 1
 fft : 1 : TRUE : TRUE
 machinephase
 ppm
 auto_reference : 5[%] : TRUE

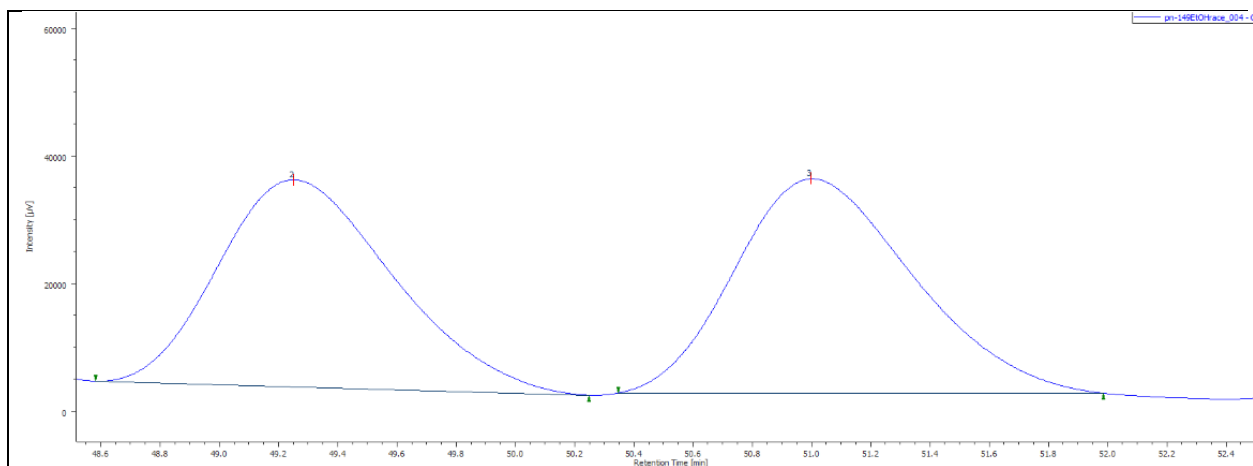
Filename = pn5-20iPr_C13-5.jdf
 Author = Delta
 Experiment = single pulse_dec
 Sample_id = S#351660
 Solvent = CHLOROFORM-D
 Creation_time = 6-NOV-2017 09:46:02
 Revision_time = 17-JAN-2018 15:06:59
 Current_time = 17-JAN-2018 15:07:21
 Comment = single pulse decouple
 Data_format = ID COMPLEX
 Dim_size = 26214
 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 = 6
 X_resolution = 95846665[Hz]
 X_resolution = 31.40703516[kHz]
 Irr_width = 1H
 Irr_delta = 1H.40703516[kHz]
 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 = TRUE
 Decoupling = WALTZ
 Initial_wait = 1[s]
 Noe_time = 2[s]
 Noe_gain = 60
 Relaxation_delay = 2[s]
 Repetition_time = 3.04333312[s]
 Temp_get = 19.8[degC]

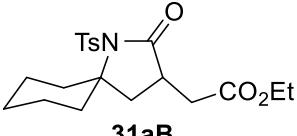


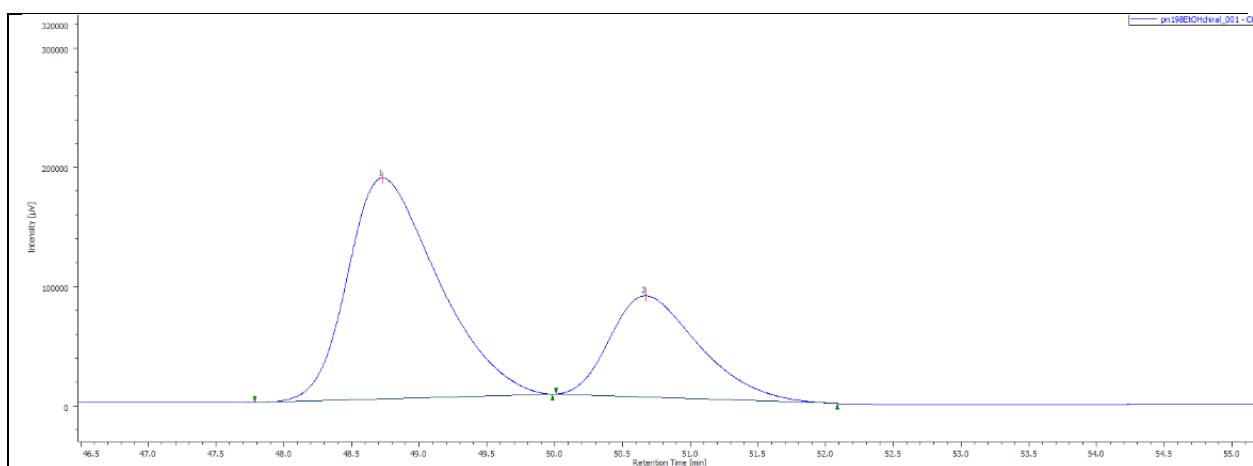
X : parts per Million : 13C

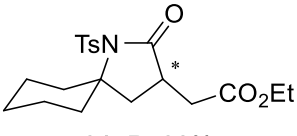
2) HPLC data for the the γ -lactam products **31** (Table 2.4)

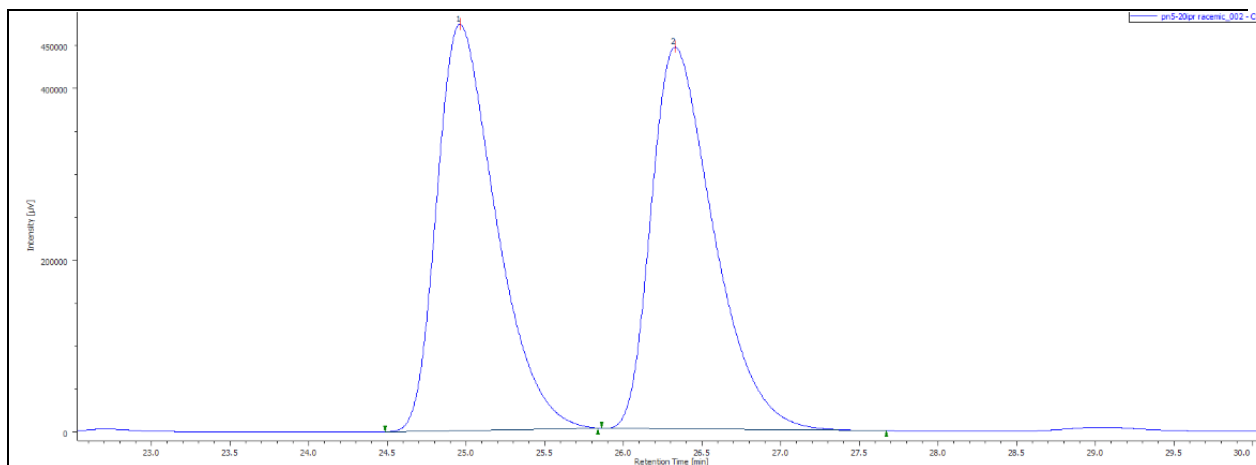


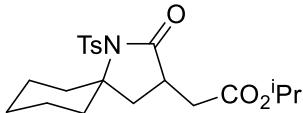


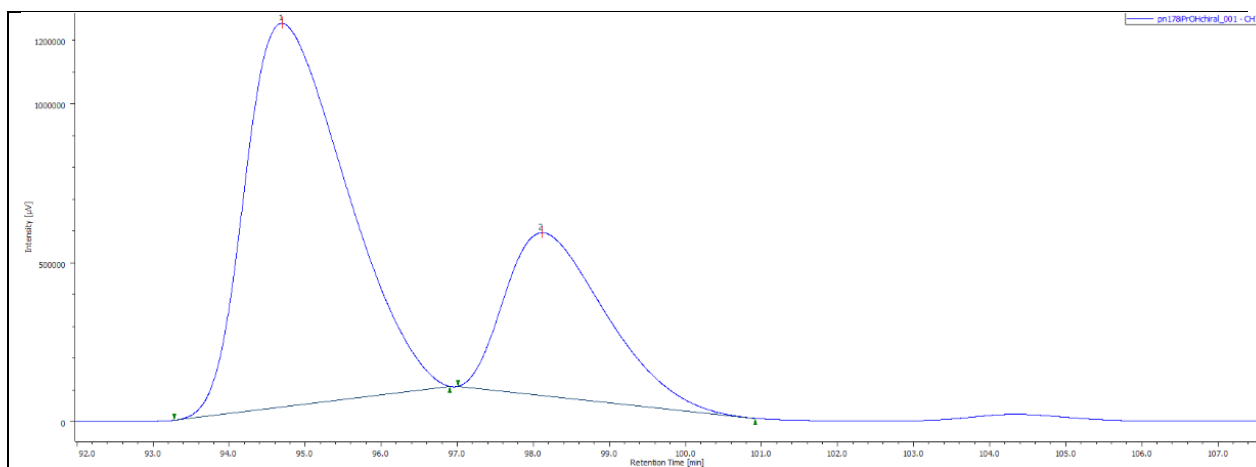
 31aB	#	tR [min]	AREA	HEIGHT	AREA %
	2	49.250	1322563	32361	45.957
3	50.997	1353662	33109	47.037	

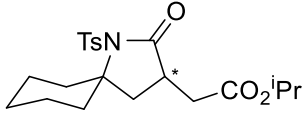


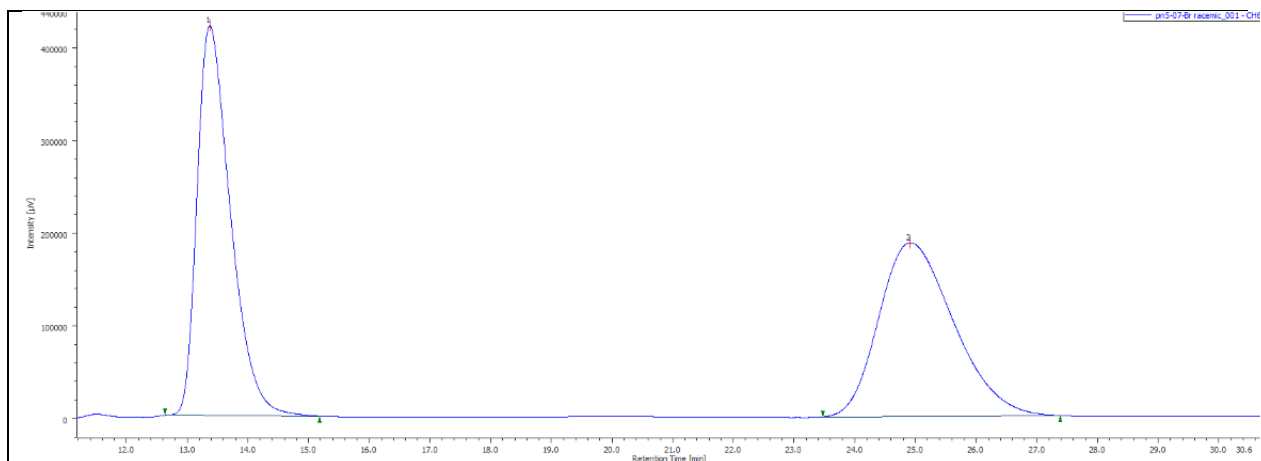
 31aB, 38% ee	#	tR [min]	AREA	HEIGHT	AREA %
	1	48.727	8583228	185042	68.016
2	50.667	3853352	84756	30.984	

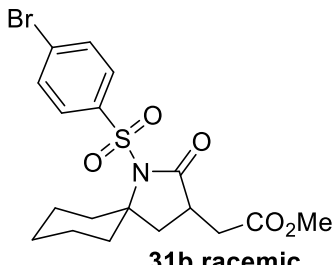


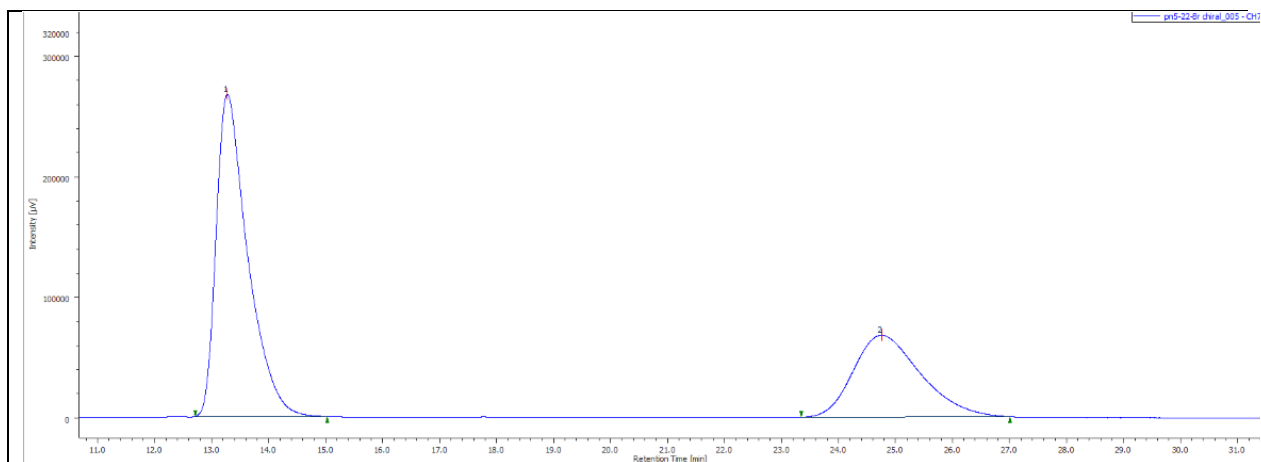
 31aC racemic	#	tR [min]	AREA	HEIGHT	AREA %
	1	64.403	6334994	115541	
2	66.560	6015913	106000		

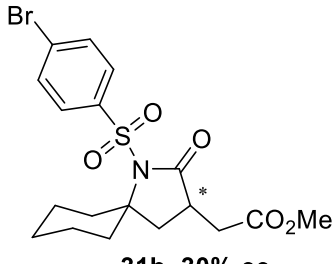


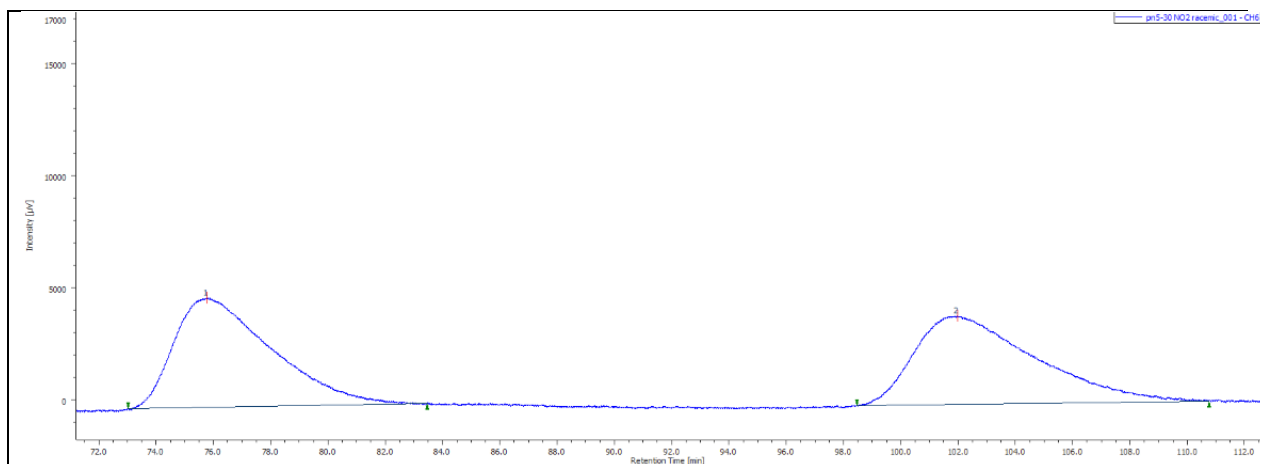
 31aC, 40% ee	#	tR [min]	AREA	HEIGHT	AREA %
	1	94.697	110777685	1205262	70.233
2	98.113	46951166	511098	29.767	

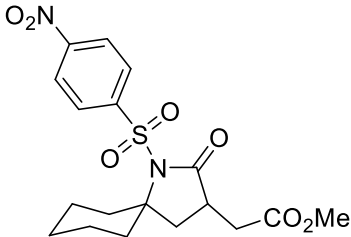


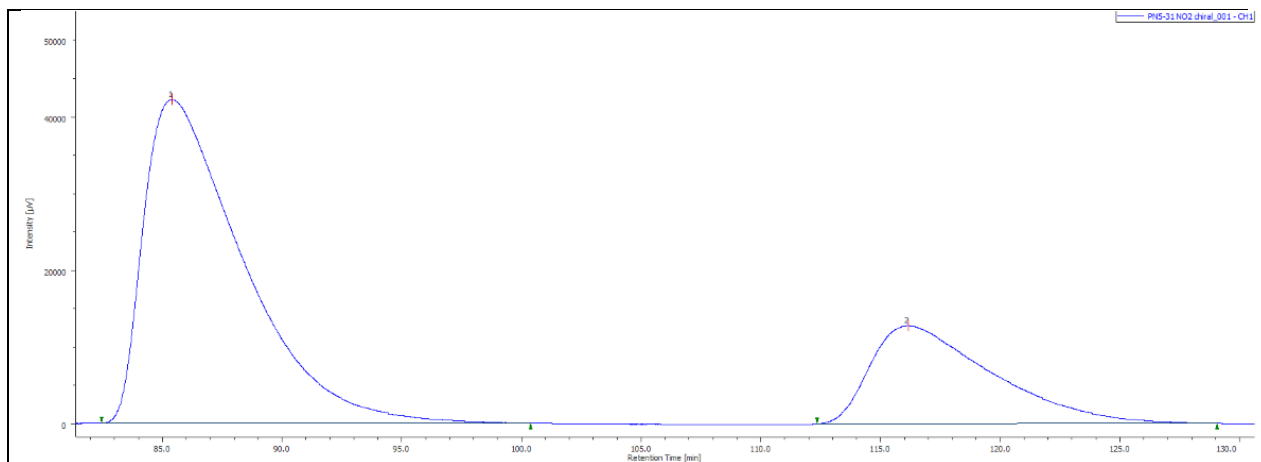
 31b racemic	#	tR [min]	AREA	HEIGHT	AREA %
	1	37.477	2776903	28943	49.708
2	44.857	2809514	24699	50.292	

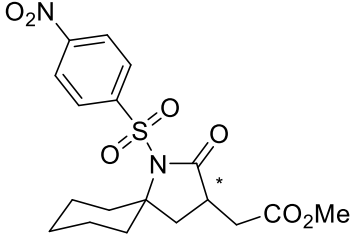


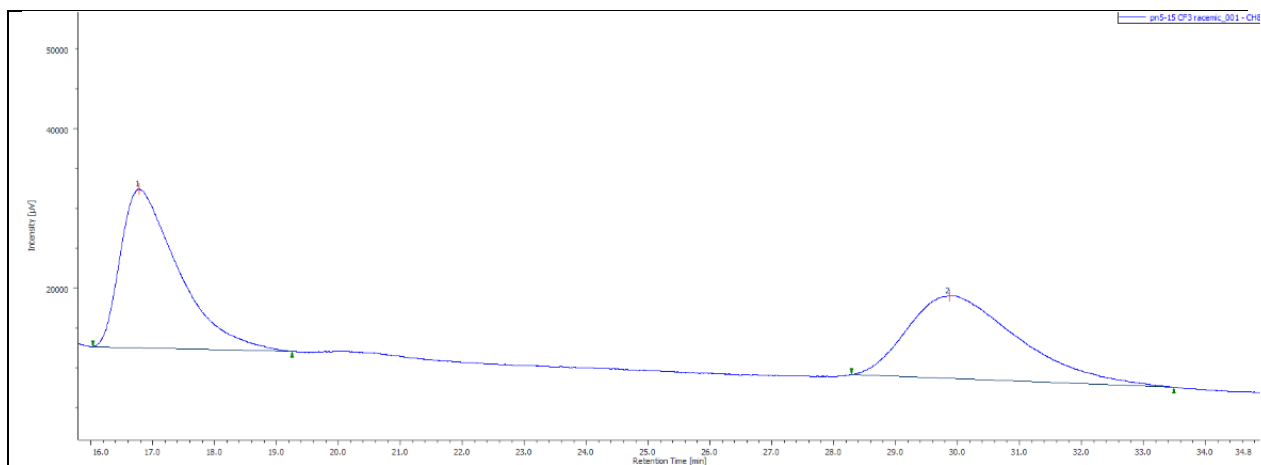
 31b, 30% ee	#	tR [min]	AREA	HEIGHT	AREA %
	1	37.990	28828413	264777	75.463
2	45.820	9373622	71861	24.537	

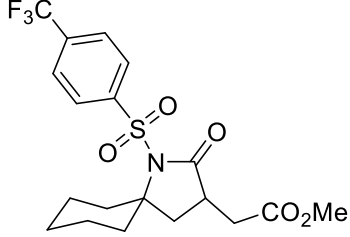


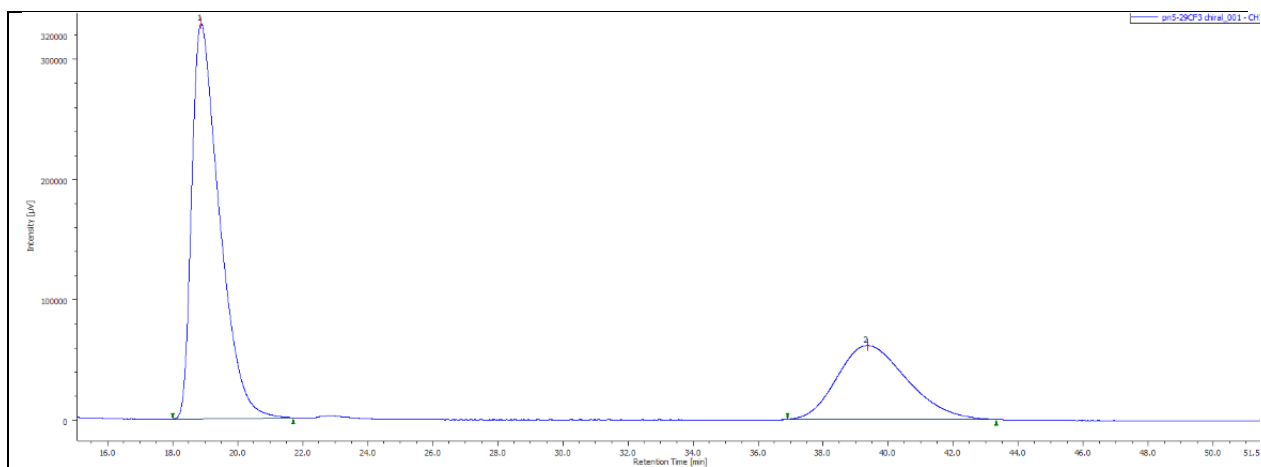
 31c racemic	#	tR [min]	AREA	HEIGHT	AREA %
	1	75.780	1146548	4885	49.882
2	101.960	1151983	1949	50.118	

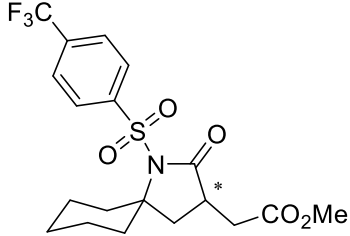


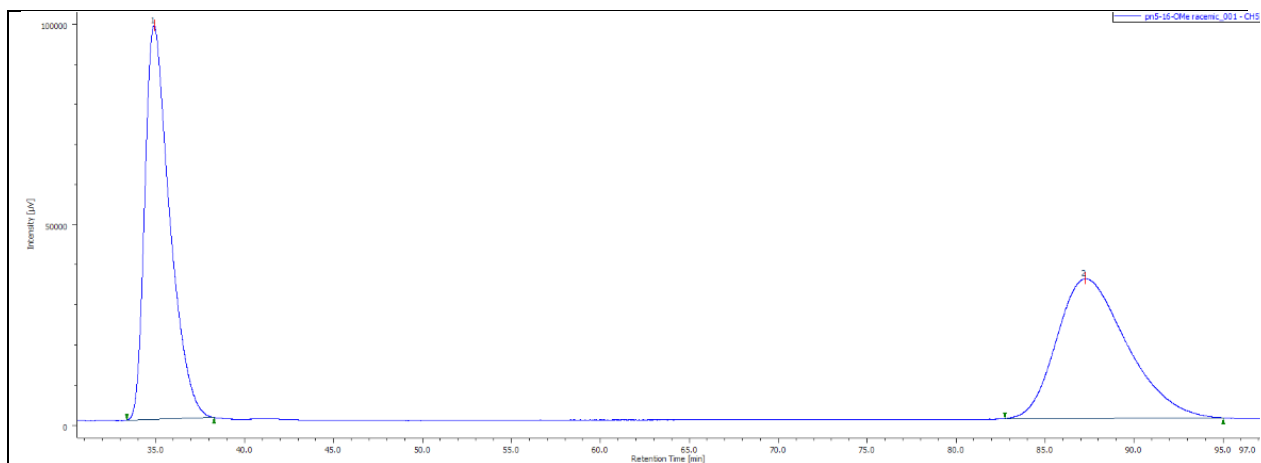
 31c, 46% ee	#	tR [min]	AREA	HEIGHT	AREA %
	1	85.392	12162887	42111	73.024
2	116.142	4493133	12748	26.976	

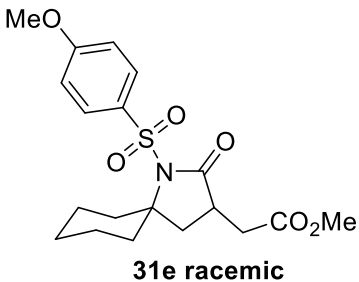


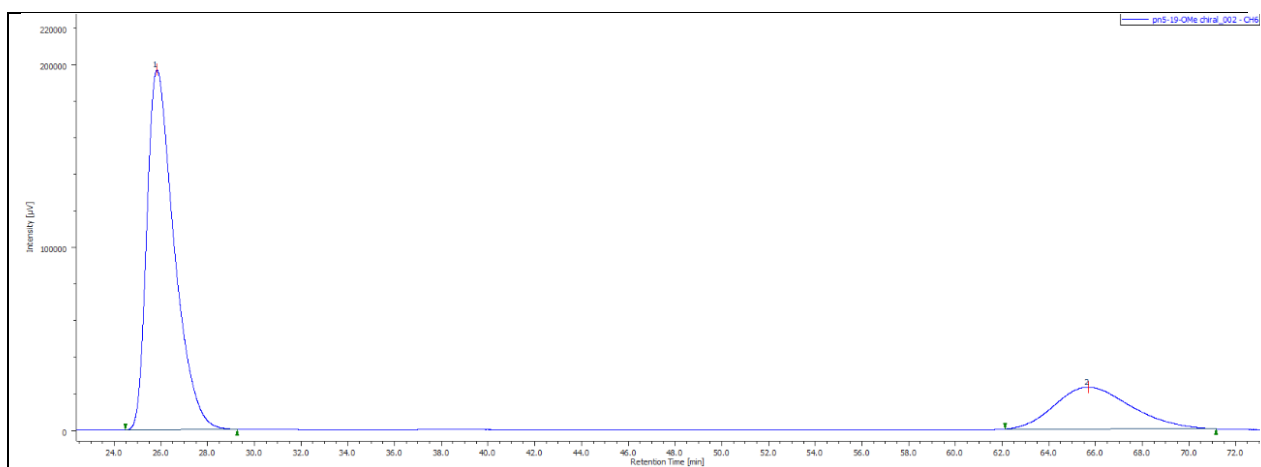
 31d racemic	#	tR [min]	AREA	HEIGHT	AREA %
	1	16.773	1285432	19842	50.045
2	29.860	1283122	10340	49.955	

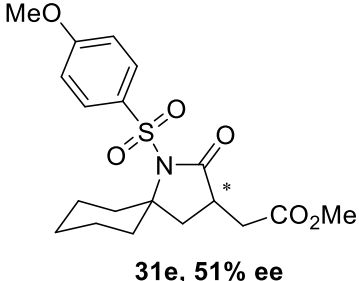


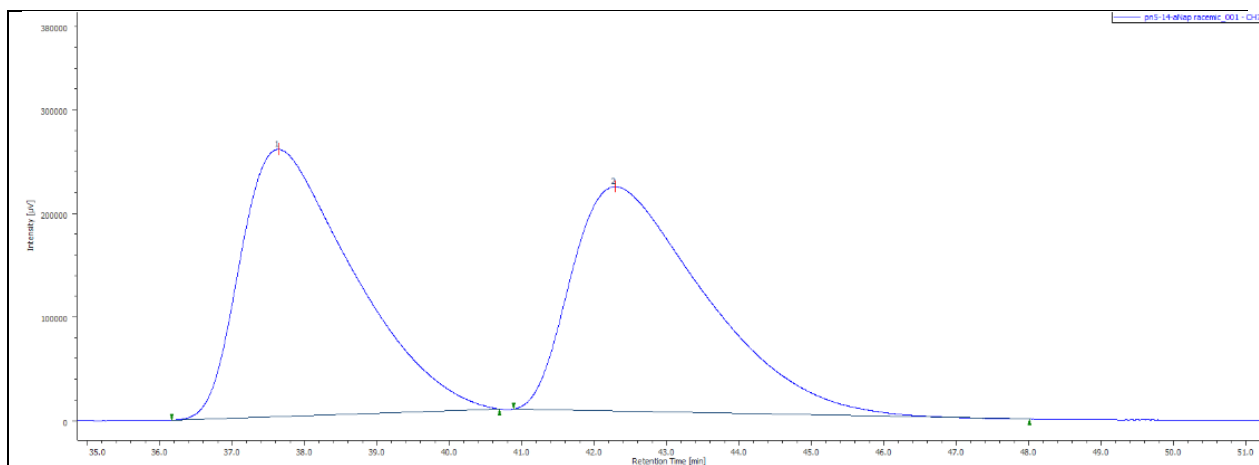
 31d, 36% ee	#	tR [min]	AREA	HEIGHT	AREA %
	1	18.877	19376936	328091	67.892
2	39.360	9163863	61449	32.108	

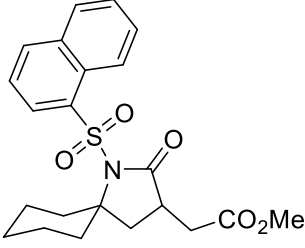


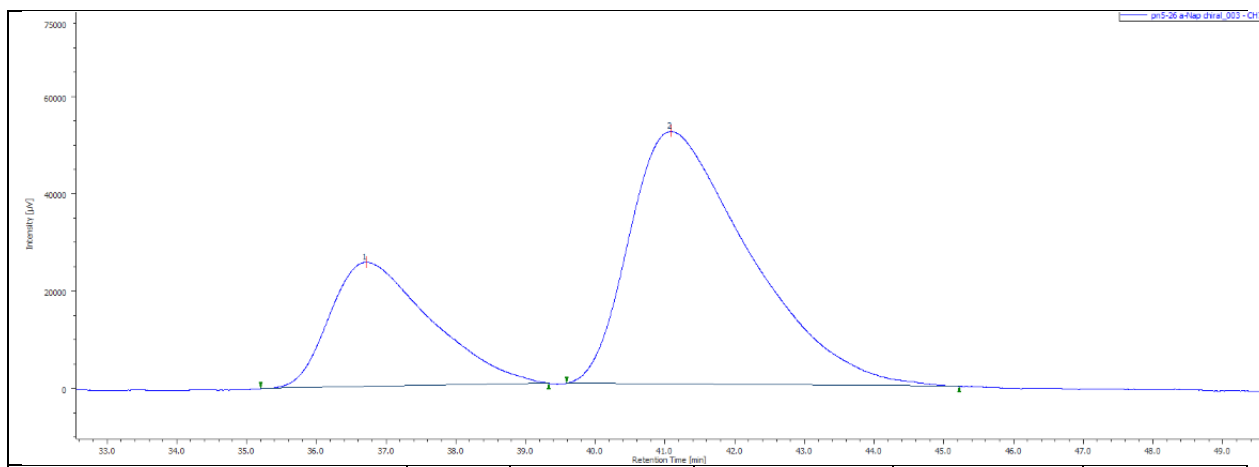
 31e racemic	#	tR [min]	AREA	HEIGHT	AREA %
	1	34.910	9523690	98026	50.032
2	87.233	9511501	34732	49.968	

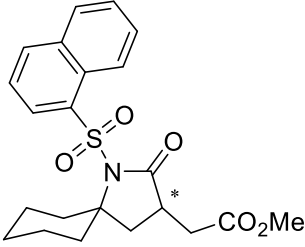


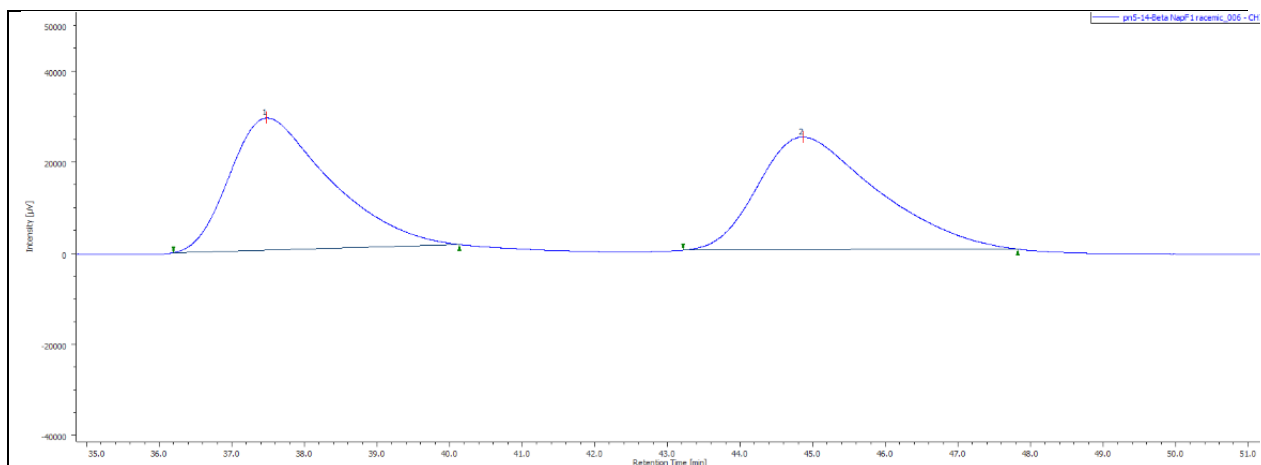
 31e, 51% ee	#	tR [min]	AREA	HEIGHT	AREA %
	1	25.830	15910287	196654	75.482
2	65.677	5167828	22778	24.518	

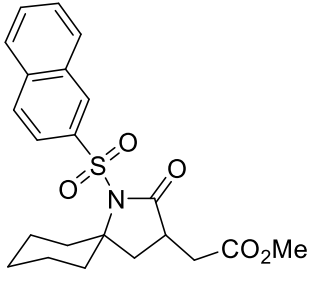


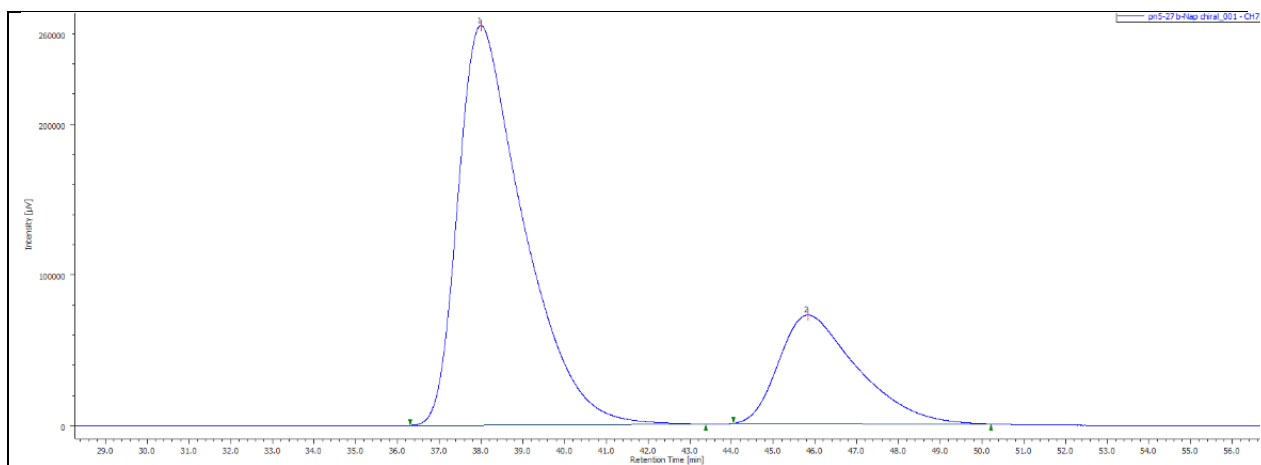
 31f racemic	#	tR [min]	AREA	HEIGHT	AREA %
	1	38.687	9163020	84778	50.095
2	43.543	9128314	71020	49.905	

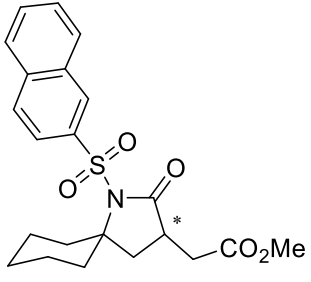


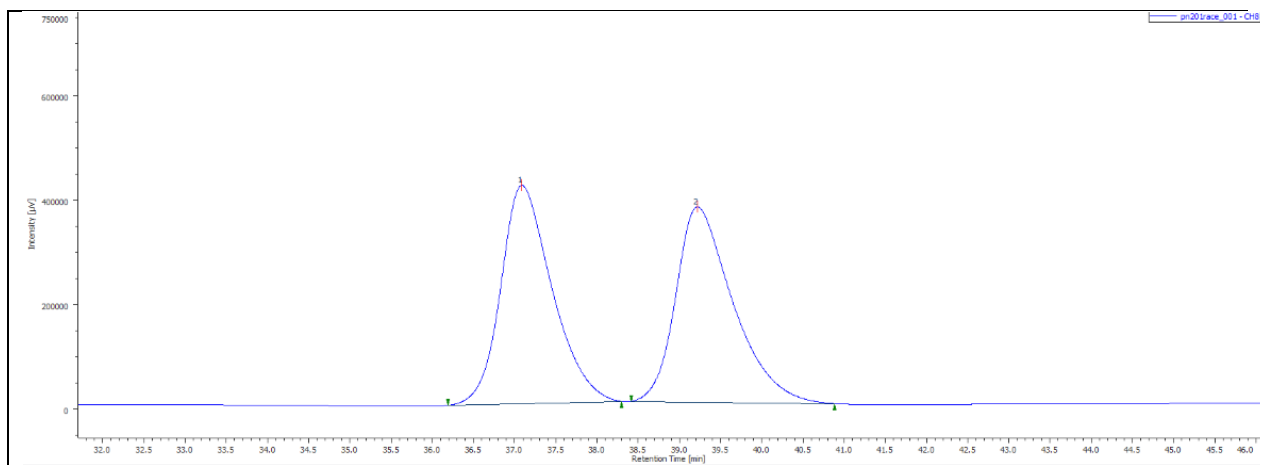
 31f, 42% ee	#	tR [min]	AREA	HEIGHT	AREA %
	1	36.717	2555608	25515	29.159
2	41.083	6208686	51819	70.841	

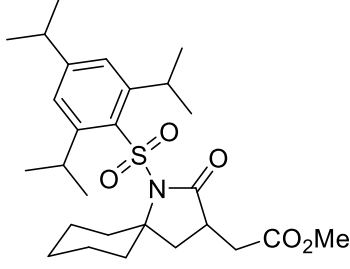


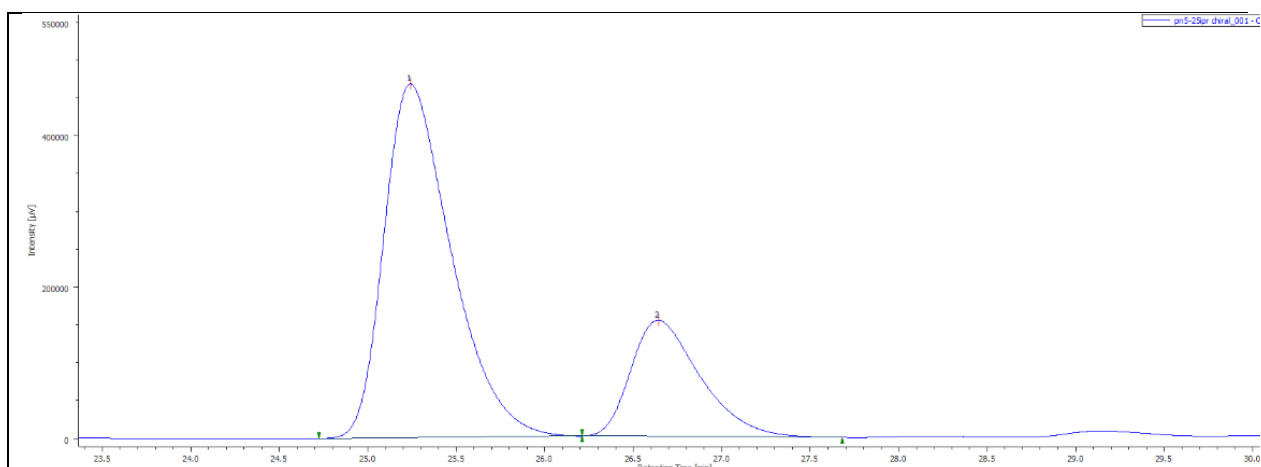
 31g racemic	#	tR [min]	AREA	HEIGHT	AREA %
	1	34.477	2776903	28943	49.708
2	44.857	2809514	24699	50.292	

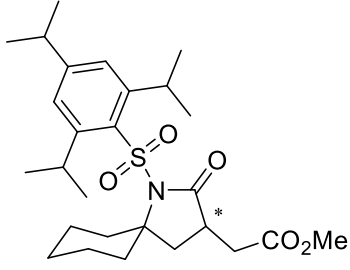


 31g, 51% ee	#	tR [min]	AREA	HEIGHT	AREA %
	1	37.990	28828413	264777	75.463
2	45.820	9373622	71861	24.537	

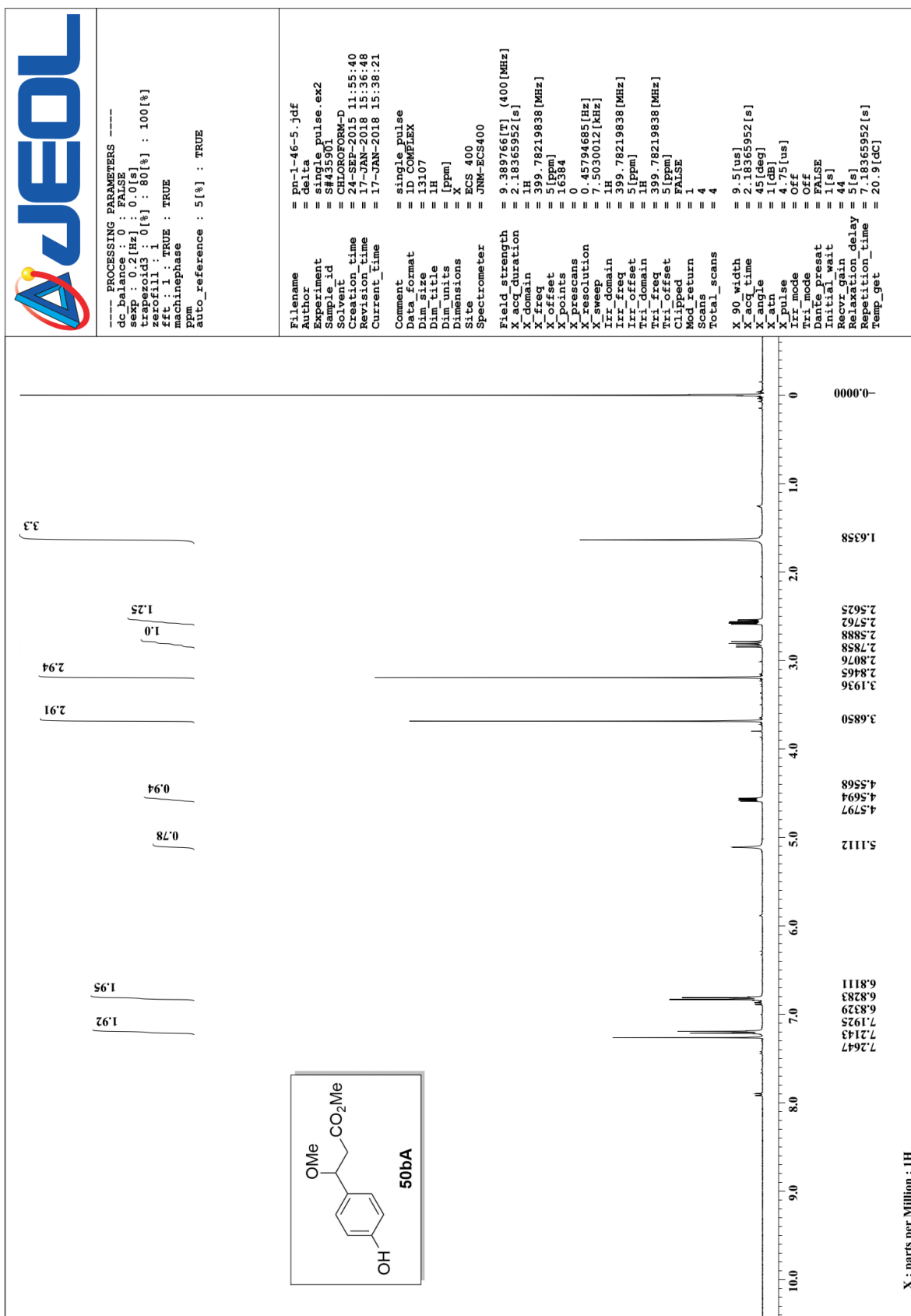


 31h racemic	#	tR [min]	AREA	HEIGHT	AREA %
	1	24.960	12321610	47641	50.165
2	26.327	12240675	443334	49.835	



 31h, 50% ee	#	tR [min]	AREA	HEIGHT	AREA %
	1	25.240	12355570	466839	74.268
2	26.640	4165786	153397	24.732	

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



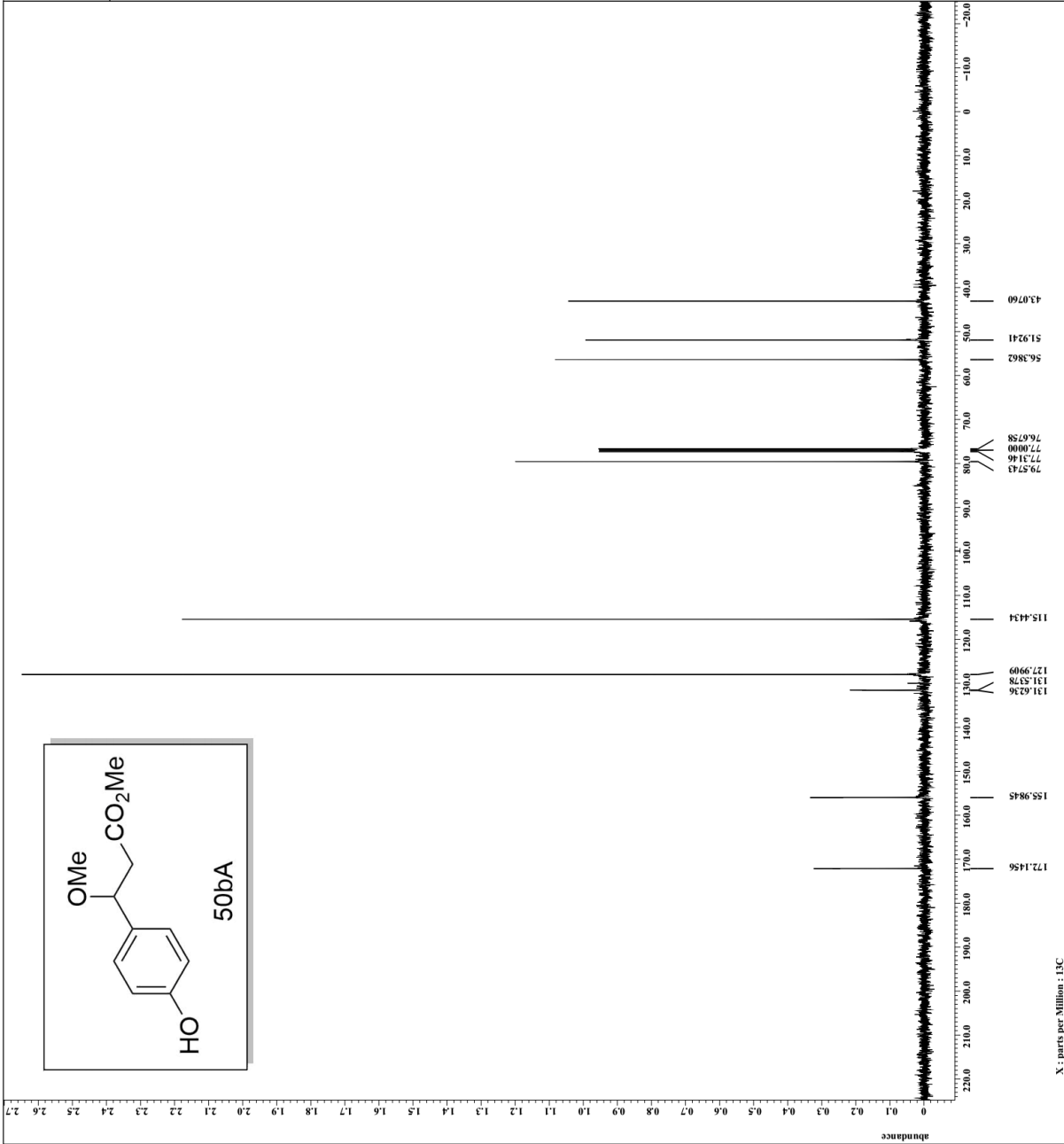
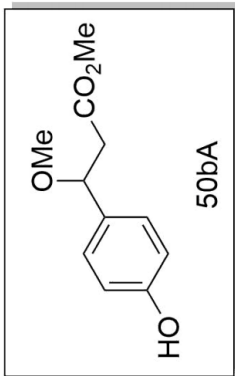
```

Filename = RF-524 column 9-33 13
Sample_id = 8835925
Experiment = single pulse_dec
Sample_name = 2018-11-15
Creation_time = 2018-NOV-20 09:11:15
Revision_time = 18-JAN-2018 16:14:50
Current_time = 18-JAN-2018 16:17:02

Comment = single pulse decouple
Name = 2018-11-15
Dir_name = 2018-11-15
Dir_title = 13C
Dir_units = ppm
Dir_site = JNM-ECX400
Spectrometer = JNM-ECX400

Field_strength = 9.389766[T] (400 MHz)
X_acq_duration = 1.0433312[s]
X_freq = 100.6253033[MHz]
X_offset = 30.748[ppm]
X_prescans = 4
X_resolution = 0.9984665[Hz]
X_sfs = 18.4078516[Hz]
IR_domain = 359.7821989[MHz]
IR_freq = FALSE
IR_offset = FALSE
Mod_return = 1
Total_scans = 60

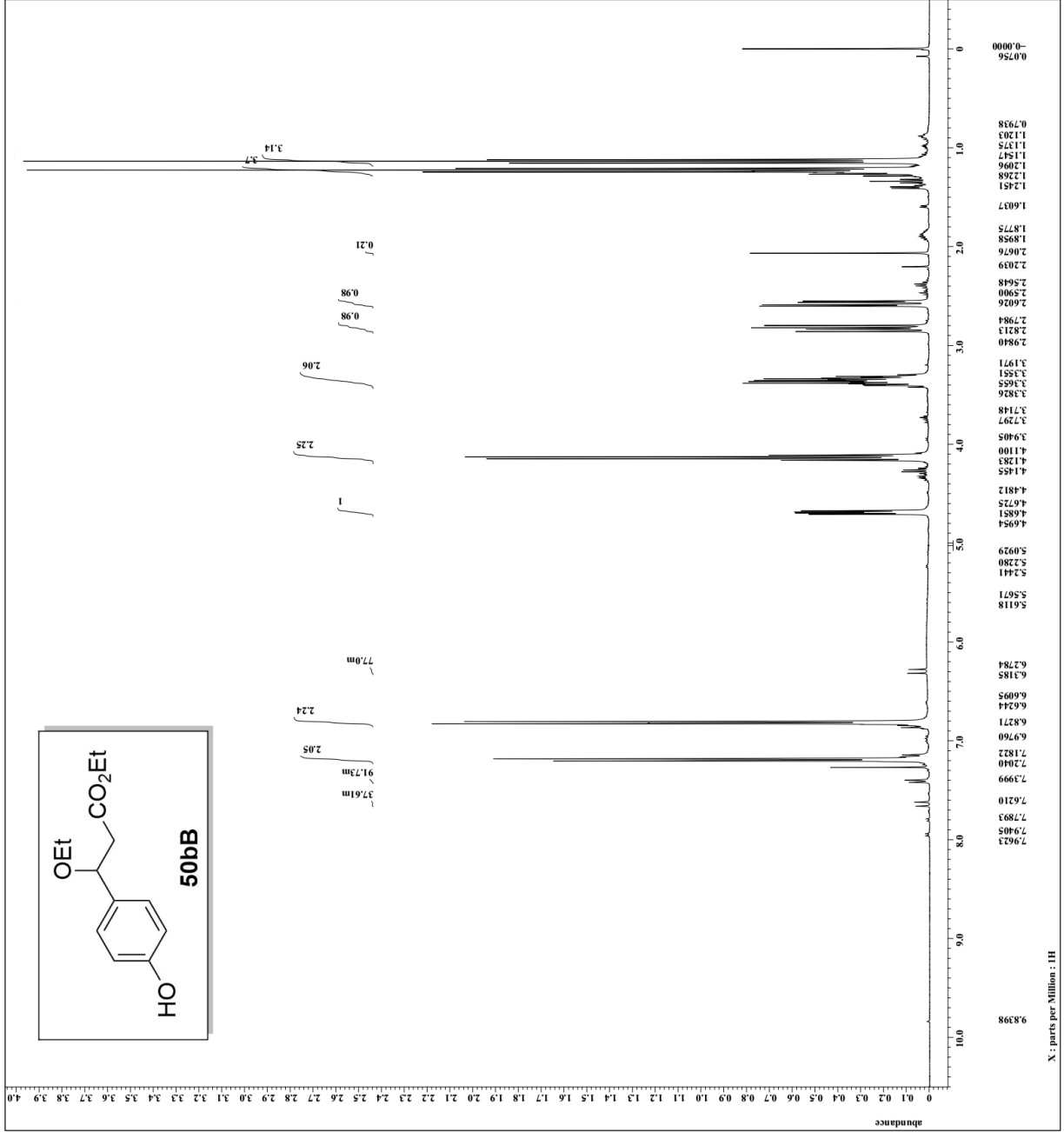
X_90_width = 9.6[us]
X_acq_time = 1.0433312[s]
X_pulse_prog = 1[us]
X_pulse = 3.2[us]
IR_atn_dec = 22.65948[dB]
IR_atn = 22.65948[dB]
IR_noise = WALTZ
Decoupling = TRUR
Noe_time_wait = TRUR
Noe_time = 2[s]
Noe_delay = 2[s]
Relaxation_delay = 2[s]
Repetition_time = 3.0433312[s]
Temp_get = 13.7[degC]
  
```



X : parts per Million : 13C



Filename = TF526 column 37-53 -4
Sample = 509B
Experiment = single_pulse.ea2
Sample_id = SF70211
Date_1 = 22-NOV-2013 18:54:45
Date_2 = 18-JAN-2018 19:22:59
Revision_time = 18-JAN-2018 19:23:16
Current_time =
Comment = single_pulse
Operator = CDFMK
Date_comment = 13/07
Date_1 = 18
Date_2 = 18
Dimensions = X [ppm]
Site = ECS 400
Spectrometer = JNM-EC5400
Field_strength = 9.389766[T] (400 [MHz])
X_acq_duration = 1.1836592[s]
X_acq_time = 1.1836592[s]
X_freq = 399.78219838 [MHz]
X_offset = 5 [ppm]
X_offset2 = 1.0584
X_prescans = 1
X_resolution = 0.45794685 [Hz]
X_resolution2 = 1H 0.50012 [kHz]
IR_domain = 1H
Irr_freq = 399.78219838 [MHz]
Irr_freq2 = 1H
Tr1_domain = 1H
Tr1_freq = 399.78219838 [MHz]
Tr1_freq2 = 1H
Tr2_domain = FALSE
Tr2_freq =
Tr2_freq2 =
Mod_return = 1
Saver = 1
Total_scans = 4
X_90_width = 9.5 [us]
X_90_time = 2.1836592[s]
X_angle = 45 [deg]
X_pulse = 4.75 [us]
X_pulse2 = 4.75 [us]
Irr_mode = Off
Irr_mode2 = Off
Tr1_mode = PULSE
Tr1_mode2 = PULSE
Initial_wait = 1[s]
Revr_gain = 0
Revr_gain_delay = 5[s]
Repetition_time = 7.1836592[s]
Temp_get = 18.5 [dC]

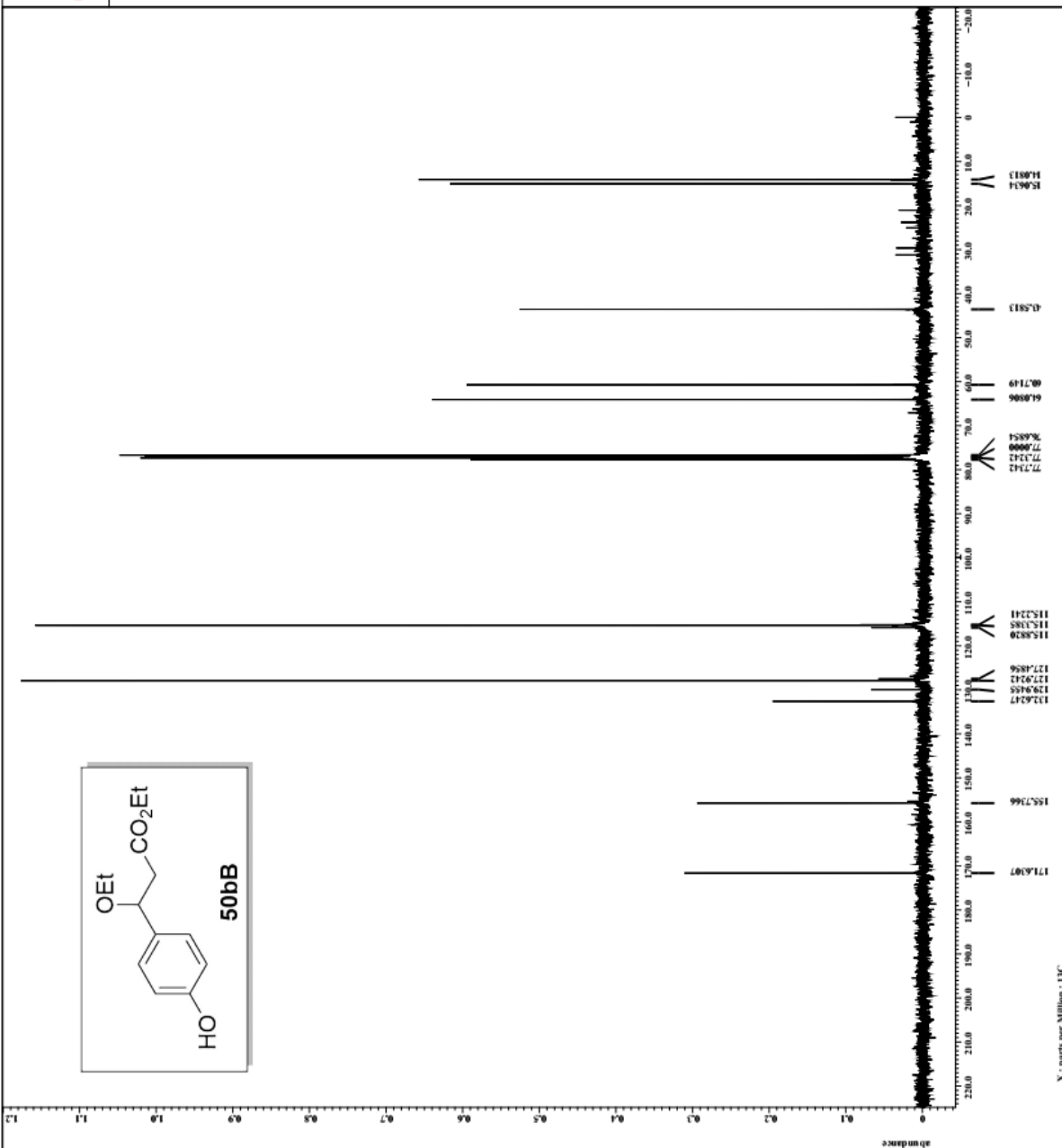
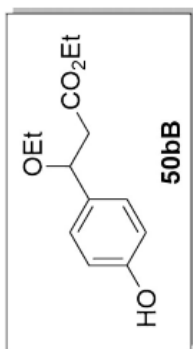



```

Filename      = TP-526 column 3c-53_e
Date_UTC     = 2018-01-18 16:17:21
Experiment    = single_pulse_dec
Sample_ID    = 58702950
Sample_Name  = 50bB
Creation_Time = 22-NOV-2013 19:06:51
Revision_Time = 18-JAN-2018 16:17:21
Current_Time = 18-JAN-2018 16:20:54

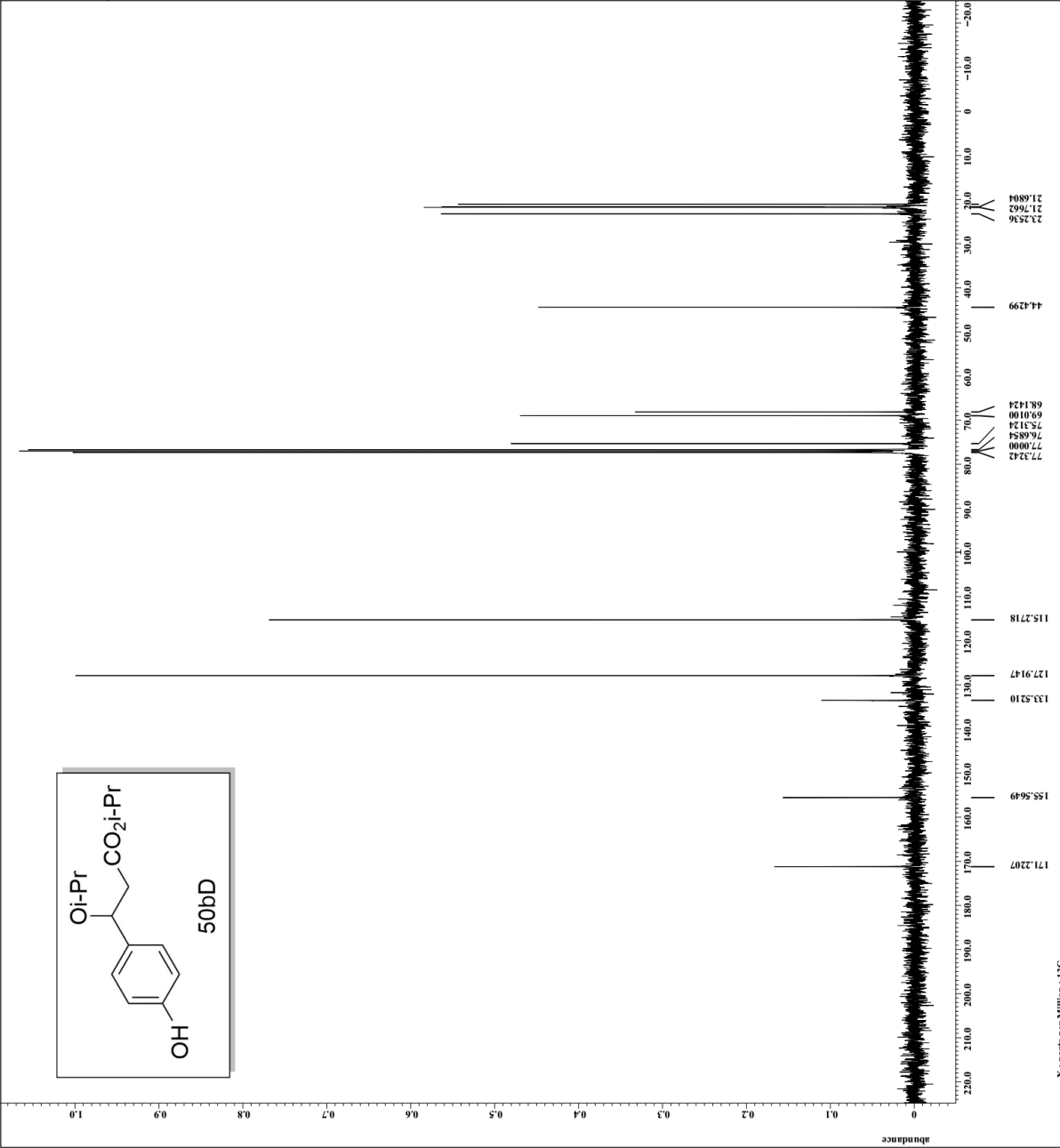
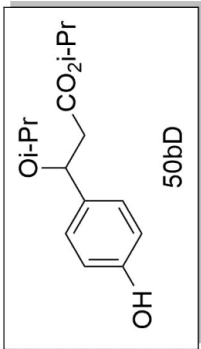
Comment      = single pulse decouple
Dir_Path     = 1: C:\MSDCHEM
Dir_File     = 26214
Dir_Title    = 13C
Dir_Unit     = X[PPM]
Dir_Units    = X[PPM]
Site         = ECS 400
Spectrometer = JNM-EC5400

Field_strength = 9.38976617 (400[MHz])
X_coordination = 1.3C 4333312[a]
X_freq         = 100.6250333[MHz]
X_resolution   = 32748[Hz]
X_processing   = 4.8646655[Hz]
X_resolution   = 31.40703518[MHz]
X_domain      = 1H 78219838[MHz]
X_sweep        = 5[PPM]
X_offset       = 5[PPM]
Clipped       = TRUE
Monitored     = 1
Monitored_copy = 1
Total_scans   = 223
X_90_width    = 9.6[us]
X_90_delay    = 300[ns]
X_pulse_prog  = 30[deg]
X_atn         = 6[db]
X_atn_dec     = 22.65948[db]
X_atn_dec     = 22.65948[db]
X_atn_dec     = TRUE
Decoupling    = WALTZ
Initial_wait  = 1[s]
Solve_time    = 2[s]
AcqGain       = 50
Repetition_delay = 5[s]
Repetition_time = 5.043333312[s]
Temp_get      = 18.3[degC]
  
```



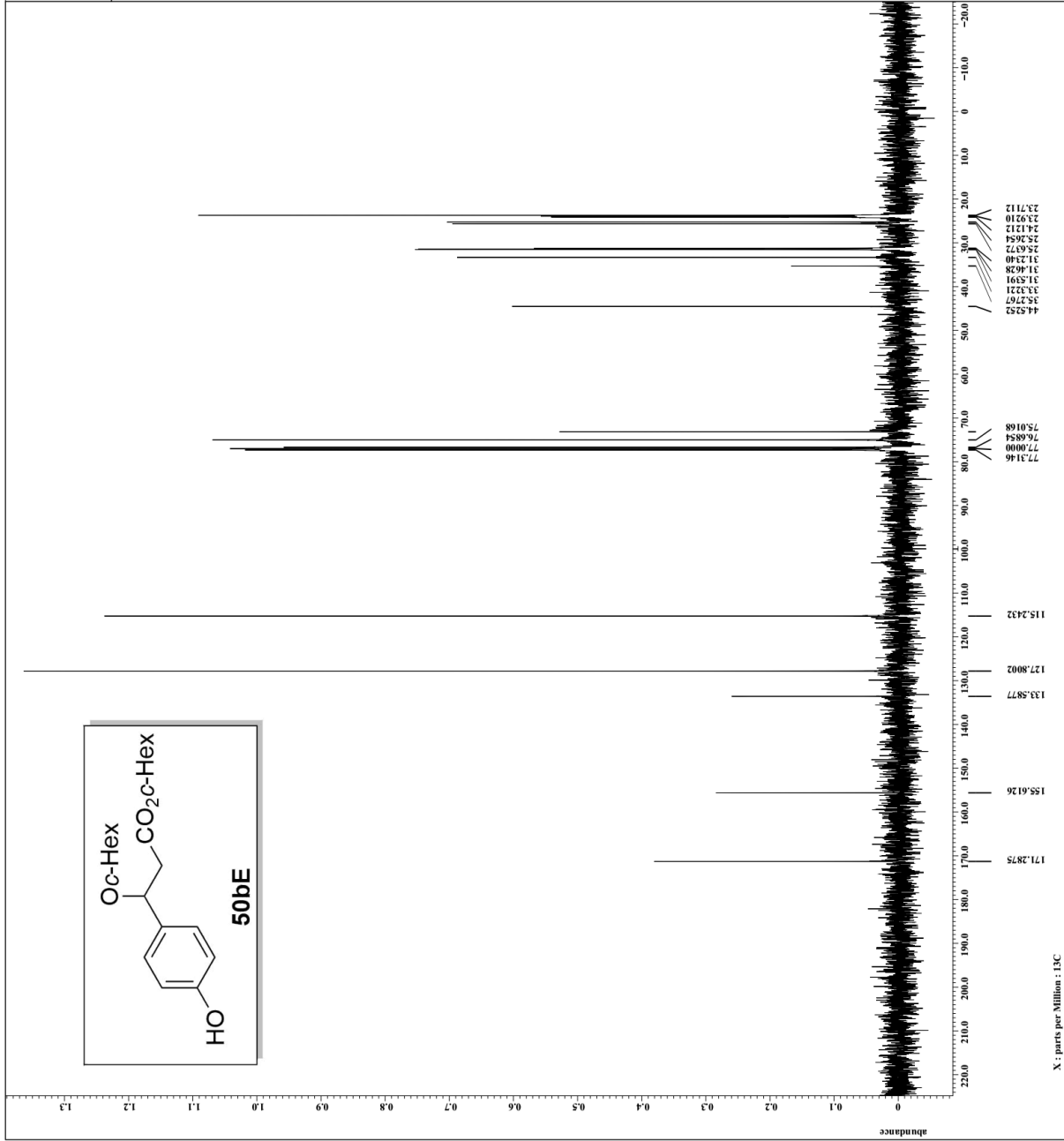
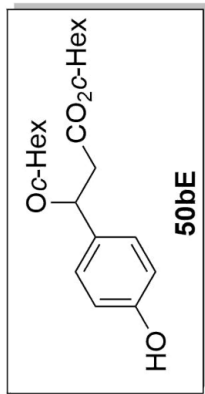

```

=====
Filename = T501 TIC A 13C_copy-3
Sample_id = 8861779
Experiment = single pulse_dec
Sample_id = 8861779
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
          = 66
          = 2021
          = 13C
          = X FPM
          = EGS 400
          = JNM-EC5400
Spectrometer = EGS 400
Field_strength = 9.389766[T] (400 [MHz])
X_acq_duration = 1.0433312[s]
X_freq = 100.62530333 [MHz]
X_offset = 32.7496 [ppm]
X_pulses = 4
X_pulsescans = 9
X_resolution = 9.9846665 [Hz]
X_sweep = 18.40785516 [Hz]
IR_domain = 18.78219895 [MHz]
IR_freq = 599.78219895 [MHz]
IR_resolution = 0.5
Clipped = FALSE
Incomplete_copy = TRUE
Retain = TRUE
Total_scans = 115.0
X_90_width = 9.6 [us]
X_acq_time = 1.0433312 [s]
X_pulses = 4
X_pulsescans = 6 (DB)
X_pulse_dec = 32 [us] (DB)
IR_resolution = 22.65948 [dB]
IR_noise = WALTZ
IR_resolution = 1 [s]
IR_noise = TRUE
Nox_time = 60 [s]
Relaxation_delay = 2 [s]
Relaxation_time = 19.9 [DC]
=====
  
```




```

Filename = TF-531 column 25-56 F
Author = delta
Experiment = SFT032
Sample_ID = CHLOROFORM-D
Solvent = CHLOROFORM-D
Acquisition_Time = 18-JUN-2018 16:32:00
Revision_Time = 18-JUN-2018 16:32:00
Current_Time = 18-JUN-2018 16:37:01
Comment = single pulse decouple
Data_format = 1D COMPLEX
Pulse_program = zgpg30
Date_acq = 18-JUN-2018
Time_acq = 16:32:00
Date_time = 18-JUN-2018 16:37:01
Dimensions = [ppm]
Spectrometer = ECS 400
Preamplifier = JNM-ECZ400
Field_strength = 9.38976671 (400 [MHz])
X_acq_duration = 1.04333312 [s]
X_domain = 130
X_f0 = 52530331 [MHz]
X_offset = 100 [ppm]
X_resolution = 32768
X_points = 0.95846665 [Hz]
X_resolution = 31.40703518 [kHz]
X_sweep = 31.40703518 [kHz]
X_freq = 525.303312 [MHz]
Irr_freq = 525.303312 [MHz]
Irr_offset = 5 [ppm]
C13_offset = 5 [ppm]
Incomplete_copy = TRUE
Mod_return = 1
Total_scans = 26
X_90_width = 9.6 [us]
X_acq_time = 1.04333312 [s]
X_angle = 30 [deg]
X_pulse = 3.2 [us]
Irr_atn_dec = 22.65948 [dB]
Irr_atn_wat = 22.65948 [dB]
Decoupling = WALTZ
Noe = TRUE
Relaxation_delay = 2 [s]
Repetition_delay = 3.04333312 [s]
Repetition_time = 3.04333312 [s]
Temp_set = 20.3 [dC]
  
```



X : parts per Million : EC



```

----- PROCESSING PARAMETERS -----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapoid3 : 0[%] : 80[%] : 100[%]
sfreq1 : TRUE : TRUE
machinephase
prm
auto_reference : 5[%] : TRUE
  
```

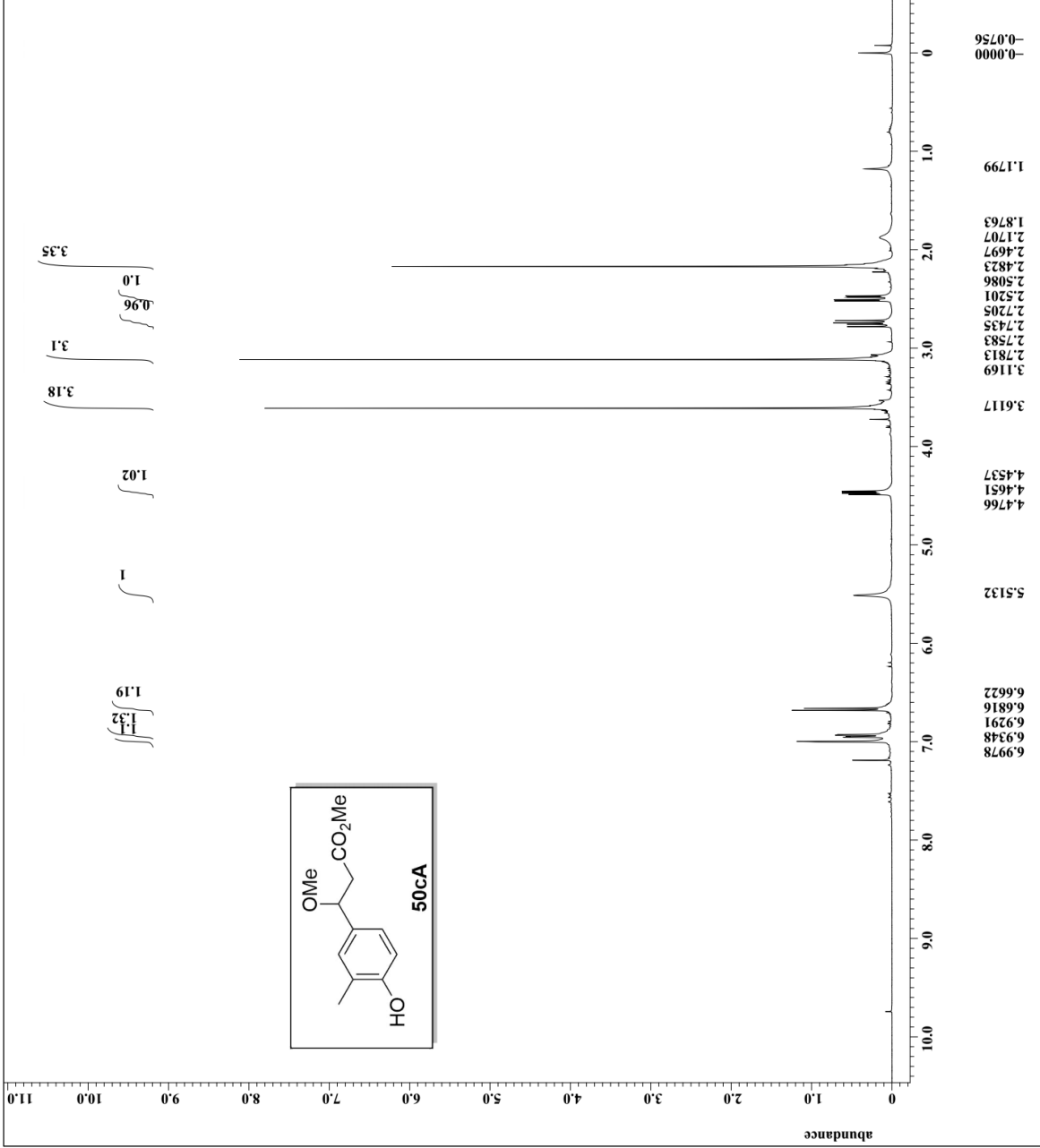
```

Filename = pn3-160tlci-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_c1 = H
Dim_c2 = Y[ppm]
Dimensions = Y
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]
Irr_domain = 1H
Irr_freq = 399.78219838 [MHz]
Irr_offset = 5 [ppm]
Clipped = FALSE
Mod_return = 1
Scans = 4
Total_scans = 4

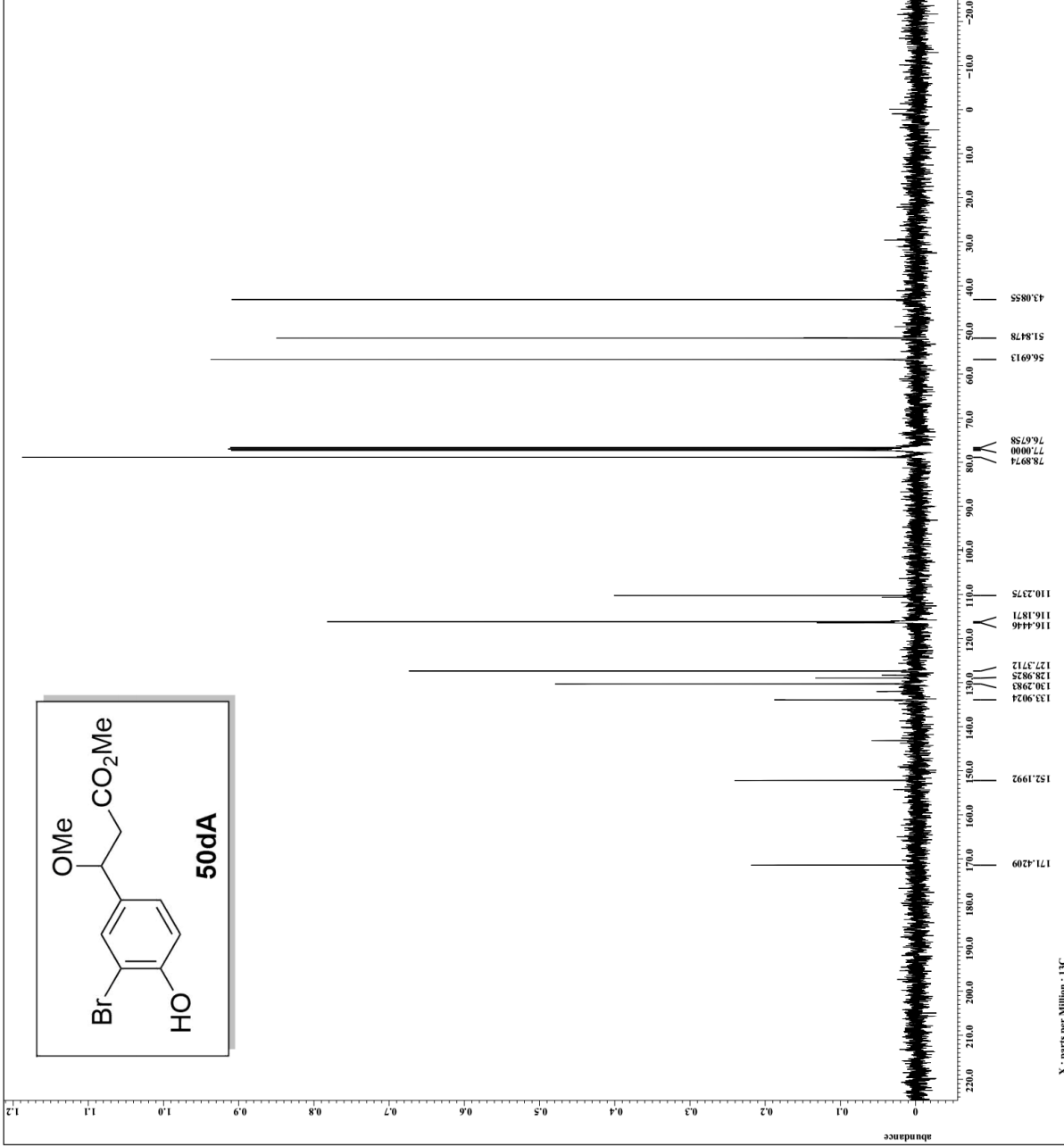
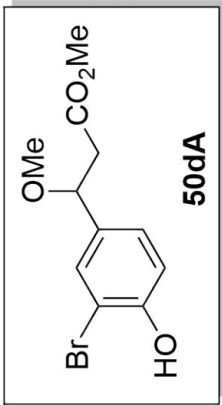
X_90_width = 9.5 [us]
X_acq_time = 2.18365952 [s]
X_angle = 45 [deg]
X_atn = 1 [dB]
X_pulse = 4.75 [us]
Irr_mode = Off
Tri_mode = Off
Dante_preset = FALSE
Initial_wait = 1 [s]
Recvr_gain = 34
Relaxation_delay = 5 [s]
Repetition_time = 7.18365952 [s]
Temp_get = 22.5 [dc]
  
```



X : parts per Million : 1H



File Name = TP-519 column product
Author = delta
Experiment = single_pulse_dec
Solve Id = CHL007098-D
Creation Time = 15-NOV-2013 12:54:26
Operator Name = JY
Current Time = 18-JUN-2018 19:18:50
Comment = 51.41, pulse decouple
Data Format = 1D COMEXX
Data Size = 26214
Data Units = [ppm]
Dimensions = X=3
Spectrometer = JNM-ECZ400
Field Strength = 9.9876181 [100 [MHz]]
X_acquisition = 1.04833312 [s]
X_domain = 13C
X_freq = 65830333 [MHz]
X_gain = 100 [ppm]
X_offset = 32768
X_points = 0
X_resolution = 0.95846665 [Hz]
X_sweep = 31.40703518 [kHz]
X_start = 399.78219838 [MHz]
X_stop = 399.78219838 [MHz]
Irr_offset = 5 [ppm]
C13ppm = 1
Modulate = 75
Total_scans = 75
X_90_width = 9.6 [us]
X_acq_time = 30.04833312 [s]
X_gain = 6 [dB]
X_offset = 22.65948 [dB]
X_pulse_dec = 22.65948 [dB]
Irr_on_pos = 22.65948 [dB]
Irr_on_neg = 22.65948 [dB]
Irr_off = 0 [dB]
Initial_wait = 1 [s]
Noe_time = 2 [min]
Recvr_gain = 60 [dB]
Relaxation_delay = 3.04833312 [s]
Temp_get_time = 18.8 [dc]

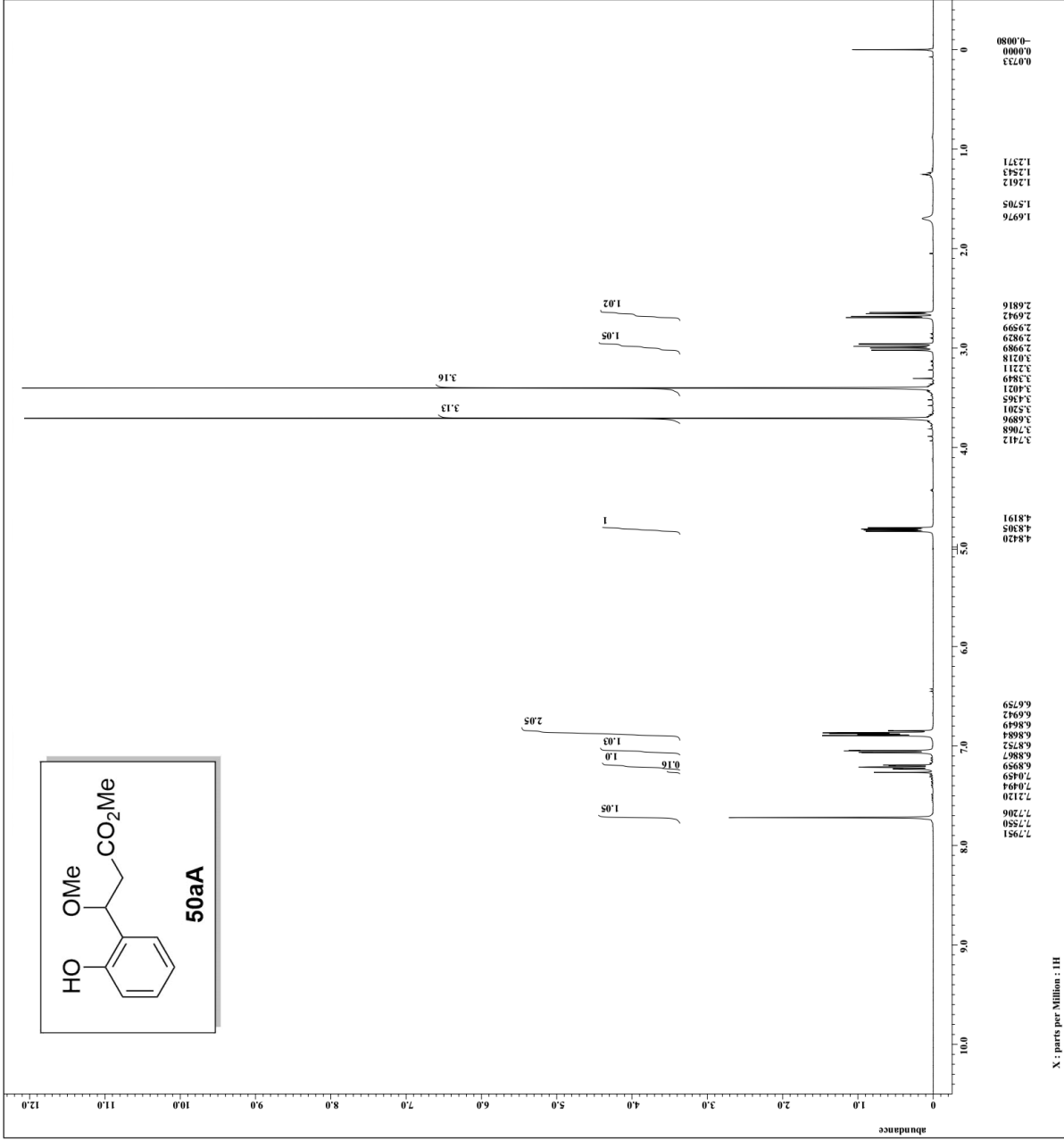
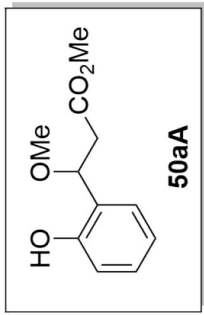




```

=====
Name      = TP-520 TIC A-5_jdf
Author    =
Experiment = single_pulse_eaz
Date      =
Solvent   = CHLOROFORM-D
Creation_time = 23-NOV-2013 15:49:17
Current_time   = 18-JAN-2018 20:37:59
Current_time   = 18-JAN-2018 20:37:59
Comment    = single_pulse
Data format = 1D COMPLEX
Dir_size   = 13107
Dir_units = [ppm]
Dimensions = Xcs 400
Spectrometer = JNM-SCC400
Field_strength = 9.38766571 (400 [MHz])
X_acq_duration = 2.18365952 [s]
X_domain      = 18.78219838 [MHz]
X_offset      = 5 [ppm]
X_points      = 16384
X_resolution  = 0.45794685 [Hz]
X_sweep       = 7.5030012 [Hz]
X_tune        = 399.78219838 [MHz]
Xir_freq      = 5 [ppm]
Xir_offset    = 399.78219838 [MHz]
Xir_freq      = 5 [ppm]
Xir_offset    = 399.78219838 [MHz]
Xir_freq      = 5 [ppm]
Xir_offset    = 399.78219838 [MHz]
Mod_return    = 1
Scans         = 4
Focal_scans   = 4
X_f0_width   = 9.5 [us]
X_f0_offset   = 8.0 [us]
X_f0_delay    = 44 [deg]
X_pulse       = 1 [db]
X_tune        = 1 [db]
Xir_pulse     = Off [us]
Xir_mode      = Off
Xir_wait      = Off
Xir_wait      = 1 [s]
Repr_gain     = 34
Repr_delay    = 34
Repetition_delay = 7.18365952 [s]
Temp_get      = 18.5 [deg]
=====

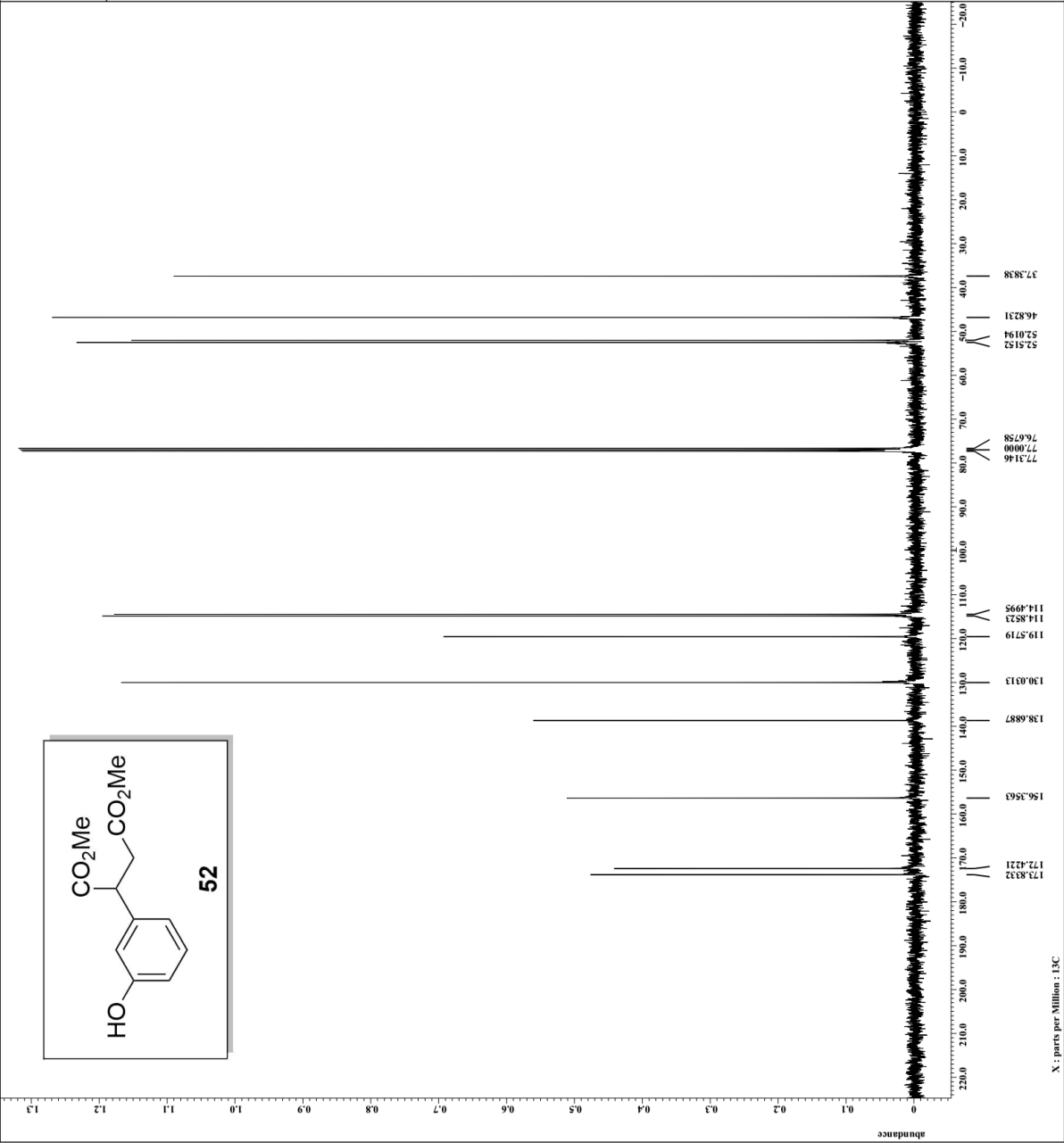
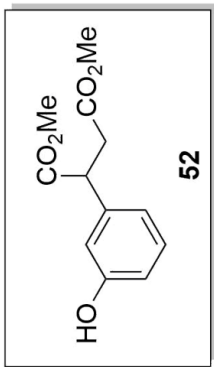
```



X : parts per Million : 1H



Filename = 1F-504 column 71-73 1
Experiment = single_pulse_dec
Sample Id = 8195677 BM-0
Revision = 16-NOV-2013
Creation Time = 16-NOV-2013 13:33:18
Revision Time = 18-JUN-2018 17:00:22
Current Time = 18-JUN-2018 17:00:22
Comment = single pulse decouple
Dim Comment = 26214
Dim Title = 13C
Dim Size = 1 ppm
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECZ400
Field_strength = 139766[1] (400 [MHz])
X_domain = 13C
X_freq = 100.6259333 [MHz]
X_points = 32788
X_prescans = 4
X_resolution = 4.9846465 [Hz]
X_sweep_rate = 31.40703518 [kHz]
IR_domain = 16
IR_freq = 16.76219838 [MHz]
IR_offset = 5 [ppm]
Clipped = FALSE
Solve = 128
Total_scans = 128
X_90_width = 9.6 [us]
X_acq_time = 1.0433312 [s]
X_delay = 6 [us]
X_gain = 6 [dB]
X_pulse_dec = 2.7 [us] (dB)
IR_gain_noe = 22.65548 [dB]
IR_noise = WALZ
IR_resolution = 1 [s]
Initial_wait = 1 [s]
Noe_time = TRUE
Noe_delay = 60 [s]
Relaxation_delay = 2 [s]
Relaxation_time = 18.9 [s] (C)
Temp_gpt = 18.9 [C]



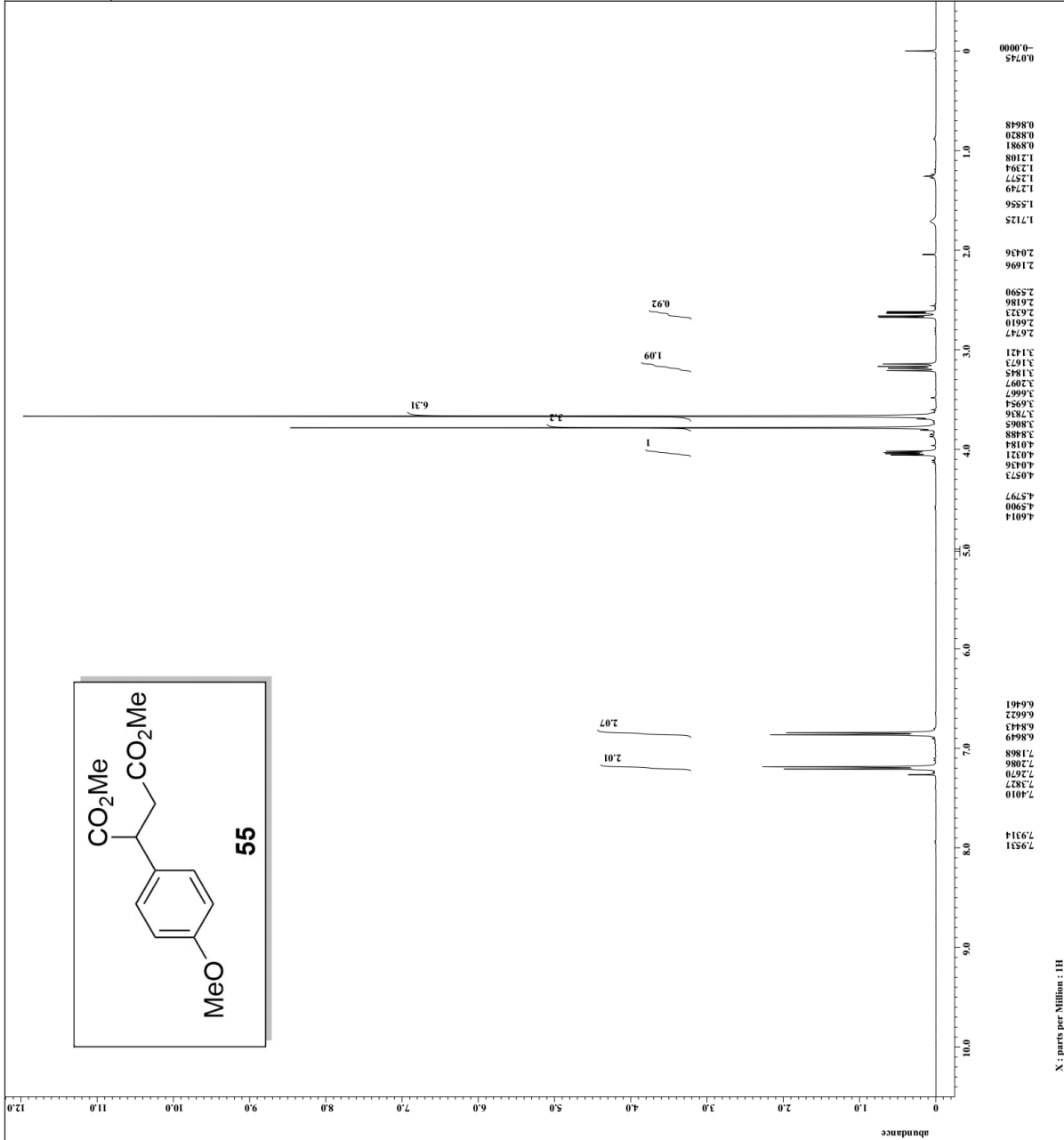
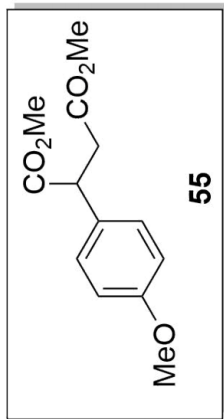
X : parts per Million : 13C

```

Filename      = TP-219 TIC A-4_1.jdf
Experiment    = single_pulse.ex2
Sample_id     = S1648105
Revision      = 29-NOV-2013 17:24:42
Creation_time = 18-JAN-2018 17:03:27
Current_time  = 18-JAN-2018 17:03:45

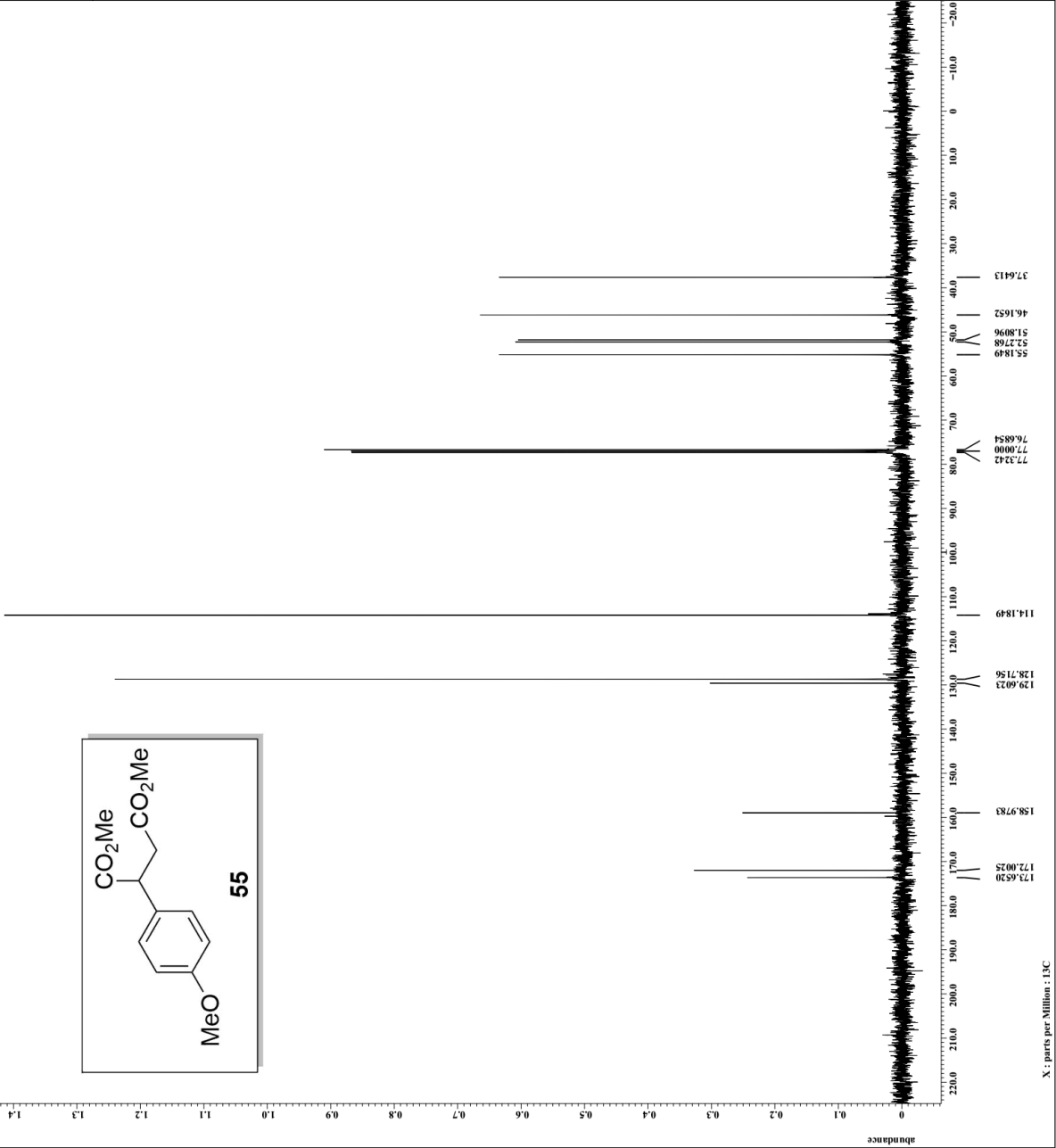
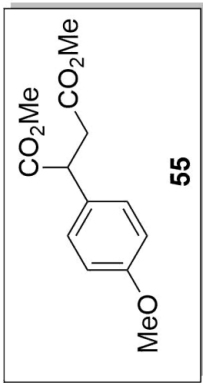
Comment       = single_pulse
              = 1648105.jdf
Dia_file      = 131107
Dia_title     = IR
Dimensions    = X [ppm]
Site          = ECS 400
Spectrometer = JNM-ECS400

Field_strength = 9.3897661 [T] (400 [MHz])
X_resolution   = 1.1852592 [s]
X_domain       = 399.78219838 [MHz]
X_freq         = 399.78219838 [MHz]
X_points       = 16384
X_prescans     = 1
X_resolution   = 1.45794685 [Hz]
X_domain       = 19.78219838 [MHz]
IR_domain     = 19.78219838 [MHz]
IR_offset     = 5 [ppm]
TR1_domain    = 19.78219838 [MHz]
TR1_offset    = 5 [ppm]
Clipped       = FALSE
Spectrum      = 1
Solve         = 4
Total_scans   = 4
X_90_width    = 9.5 [us]
X_acq_time    = 2.183592 [s]
X_delay       = 4 [us]
X_pulse       = 1 [dB]
X_pulse       = 4.72 [us]
TR1_mode      = Off
TR1_mode      = Off
Data_preset   = FALSE
Relaxation_delay = 30 [s]
Relaxation_delay = 5 [s]
Relaxation_time = 20.2 [s]
Temp_get      = 20.2 [C]
  
```



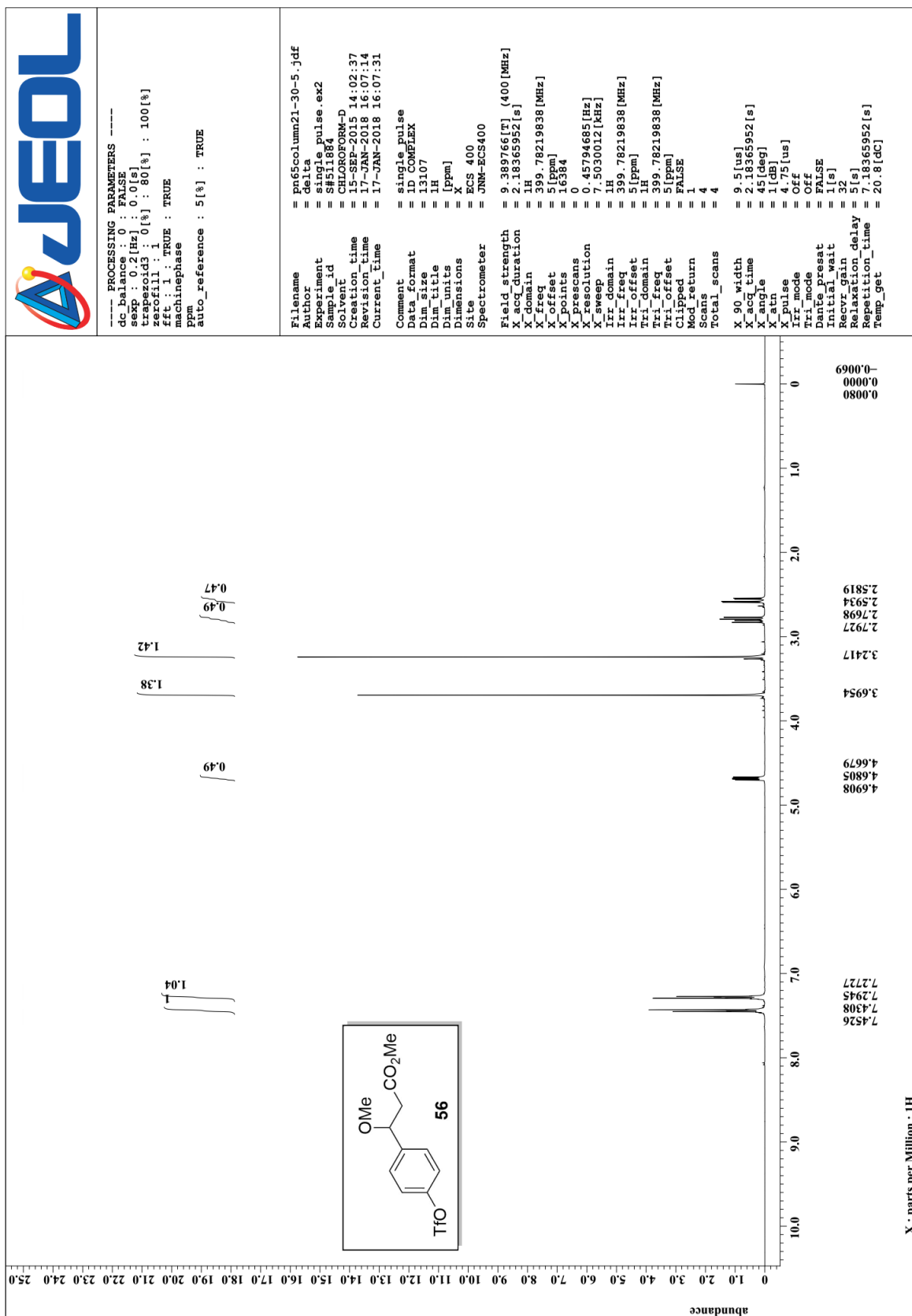


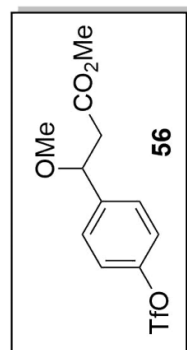
File Name = 78_519 TIC A 13C_copy
Run Date = 2013-11-18
Experiment = single_pulse_dec
Sample ID = CHLOROFORM-D
Solve Date = 2013-11-18
Creation Time = 29-NOV-2013 17:29:05
Revision Time = 18-JAN-2018 17:02:33
Current Time = 18-JAN-2018 17:02:43
Comment = 13C NMR
Injec_Pulse Decouple = 13C
Dil Size = 26214
Dil Title = 13C
Dimensions = X [ppm]
Site = 5CP 400
Spectrometer = JNM-ECZ400
Field_strength = 9.3897661 [400 MHz]
X_domain = 13C
X_resolution = 13C 40033312 [s]
X_freq = 100.5230333 [MHz]
X_points = 32748
X_prescans = 6
X_sweep = 6.9846665 [Hz]
X_resolution = 31.40703518 [kHz]
Irr_domain = 13C
Irr_freq = 39.78219838 [MHz]
Irr_offset = 5 [ppm]
Clipped = FALSE
Mod_return_copy = 1
Mod_return = 1
Scans_scans = 71
X_90_width = 9.6 [us]
X_pulse_time = 5.0433312 [s]
X_angle = 30 [deg]
X_nu1 = 6 [dB]
X_nu2 = 22.65948 [dB]
Irr_nu1_dec = 22.65948 [dB]
Irr_nu2 = 22.65948 [dB]
Decoupling = WURZ
Initial_wait = 1 [s]
Pulse_prog = zgpg30
Noe_time = 2 [s]
Recvr_gain_delay = 60
Repetition_time = 5.0433312 [s]
Temp_get = 20.3 [degC]



X : parts per Million : 13C

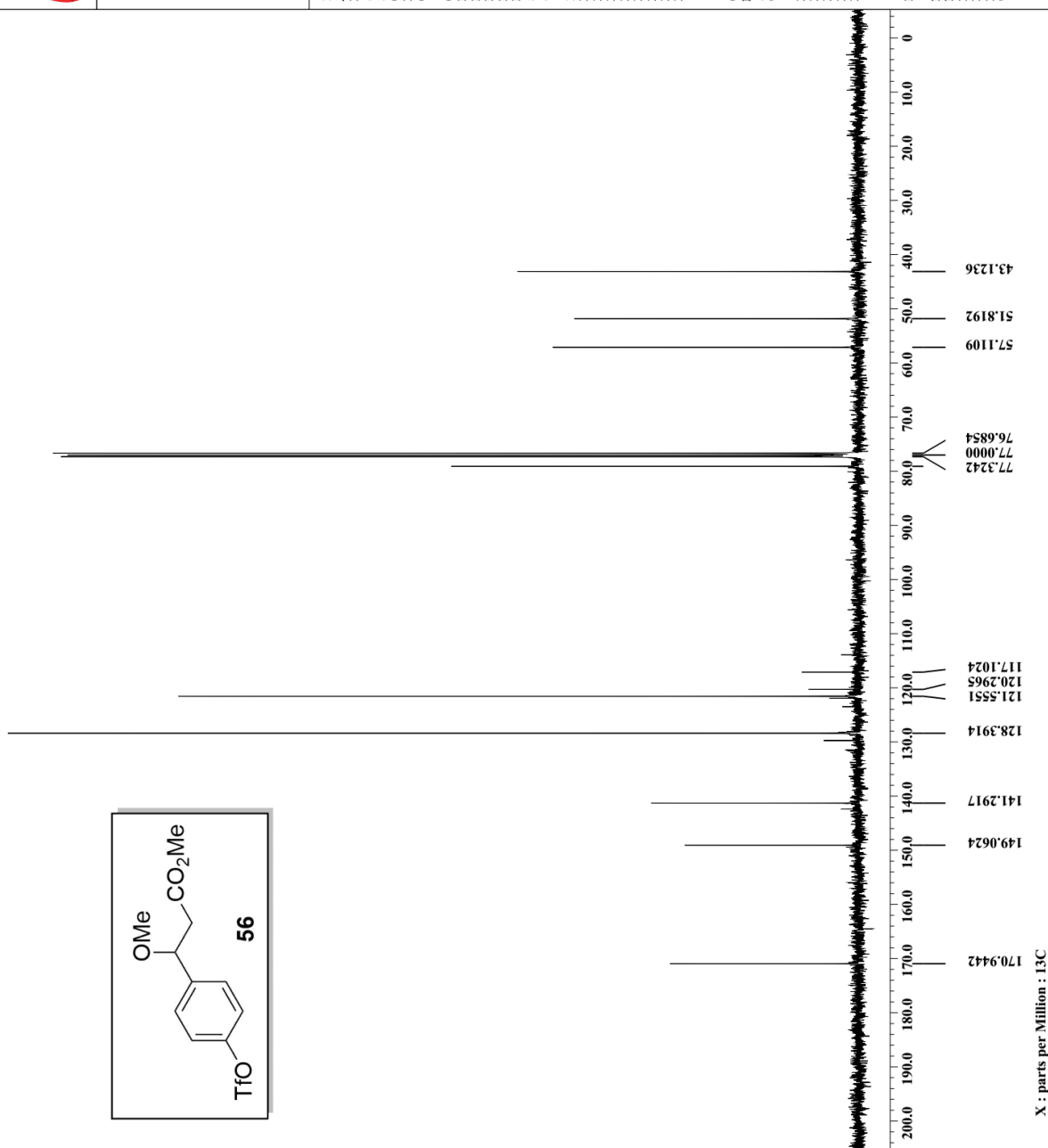
4) ^1H and ^{13}C NMR spectra of the triflate **56**, coupling products **57a-57e** and compound **58**





----- 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

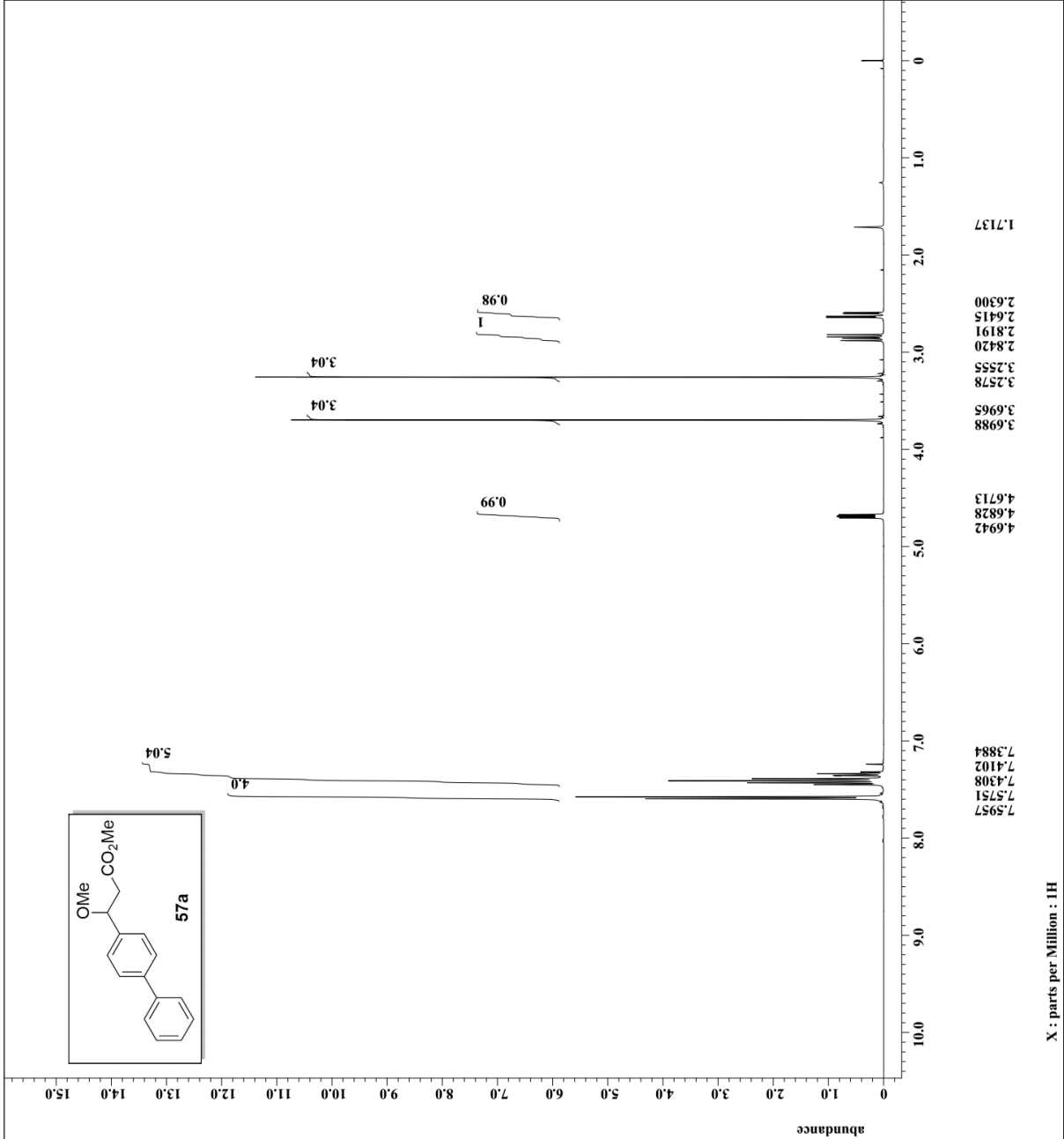
Filename = PMS3TLC1-C-3.jdf
Author = delta
Experiment = single pulse_dec
Sample id = S#532886
Solvent = CHLOROFORM-D
Creation time = 10-JUL-2015 14:50:14
Revision time = 17-JAN-2018 12:44:58
Current time = 17-JAN-2018 16:06:22
Comment = single pulse decouple
Data format = ID COMPLEX
Dim_size = 26214
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 = 13.04333312[MHz]
X_freq = 100.52530333[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.95846665[MHz]
X_sweep = 31.40703518[MHz]
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 = TRUE
Irr_noise_coupling = 4[us]
Noe_tial_wait = 1[s]
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get_time = 24.1[dc]

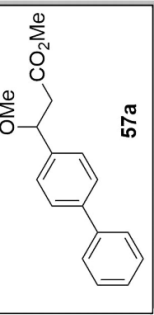




----- PROCESSING PARAMETERS -----
 dc_balance : 0 : FALSE
 sexp : 0.2[Hz] : 0.0[s]
 trapezoid3 : 0[%] : 80[%] : 100[%]
 zerofill : 1 : TRUE : TRUE
 machinephase
 Spectrometer : JNM-ECS400
 auto_reference : 5[%] : TRUE

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 = ID COMPLEX
 Dim_size = 13107
 Dim_title = 1H
 Dim_units = [ppm]
 Dimensions = X
 Site = ECS 400
 Spectrometer = JNM-ECS400
 Field_strength = 9.389766[MHz] (400[MHz])
 X_acq_duration = 2.18365952[s]
 X_domain = 1H
 X_offset = 399.78219838[MHz]
 X_phase = 5[ppm]
 X_point = 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_db = 1[dB]
 X_pulse = 4.75[us]
 Irr_mode = Off
 Irr_mode = Off
 Dante_preset = FALSE
 Initial_wait = 3[s]
 Recvr_gain = 50
 Relaxation_delay = 7.18[sec]
 Repetition_time = 22[sec]
 Temp_get = 22[degC]



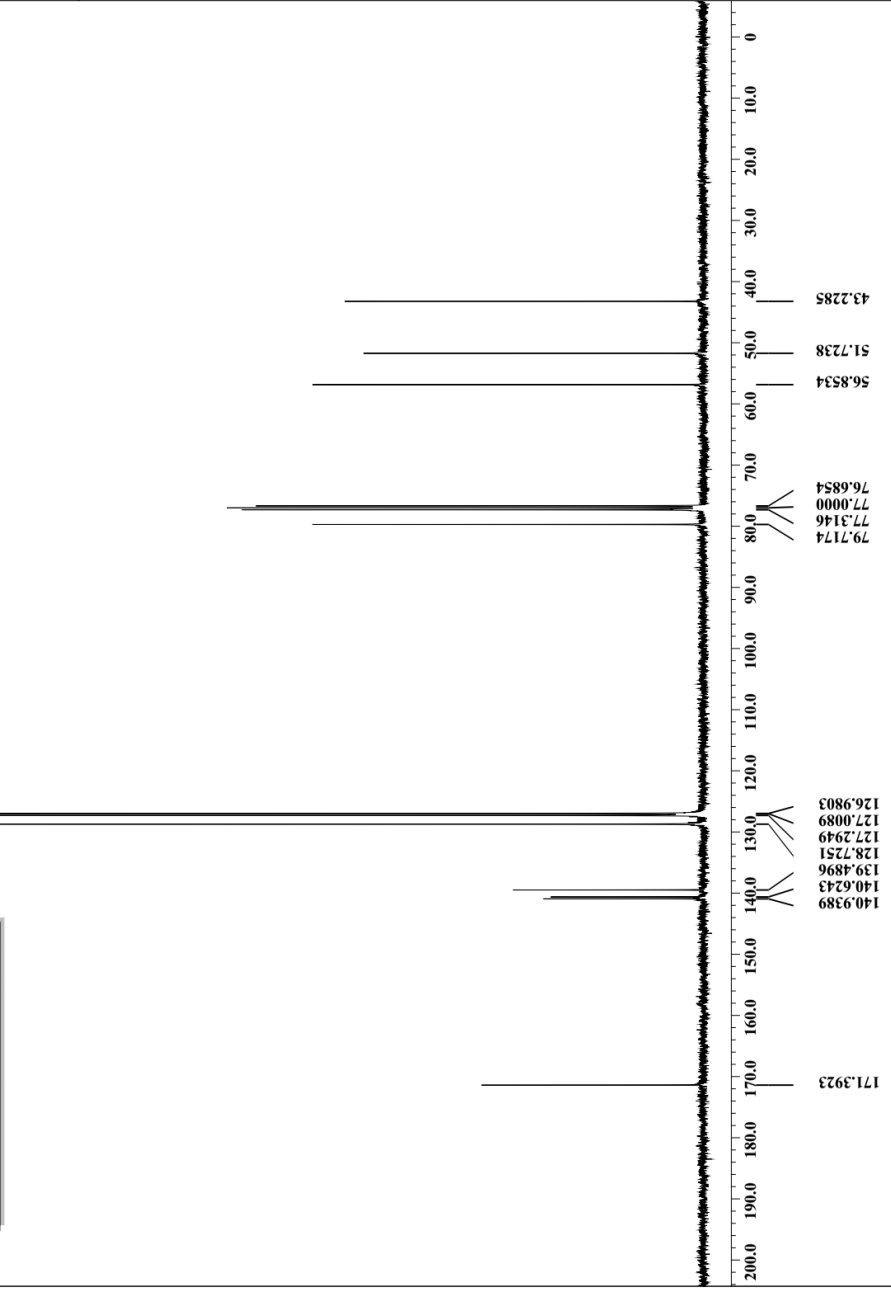


```

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

```

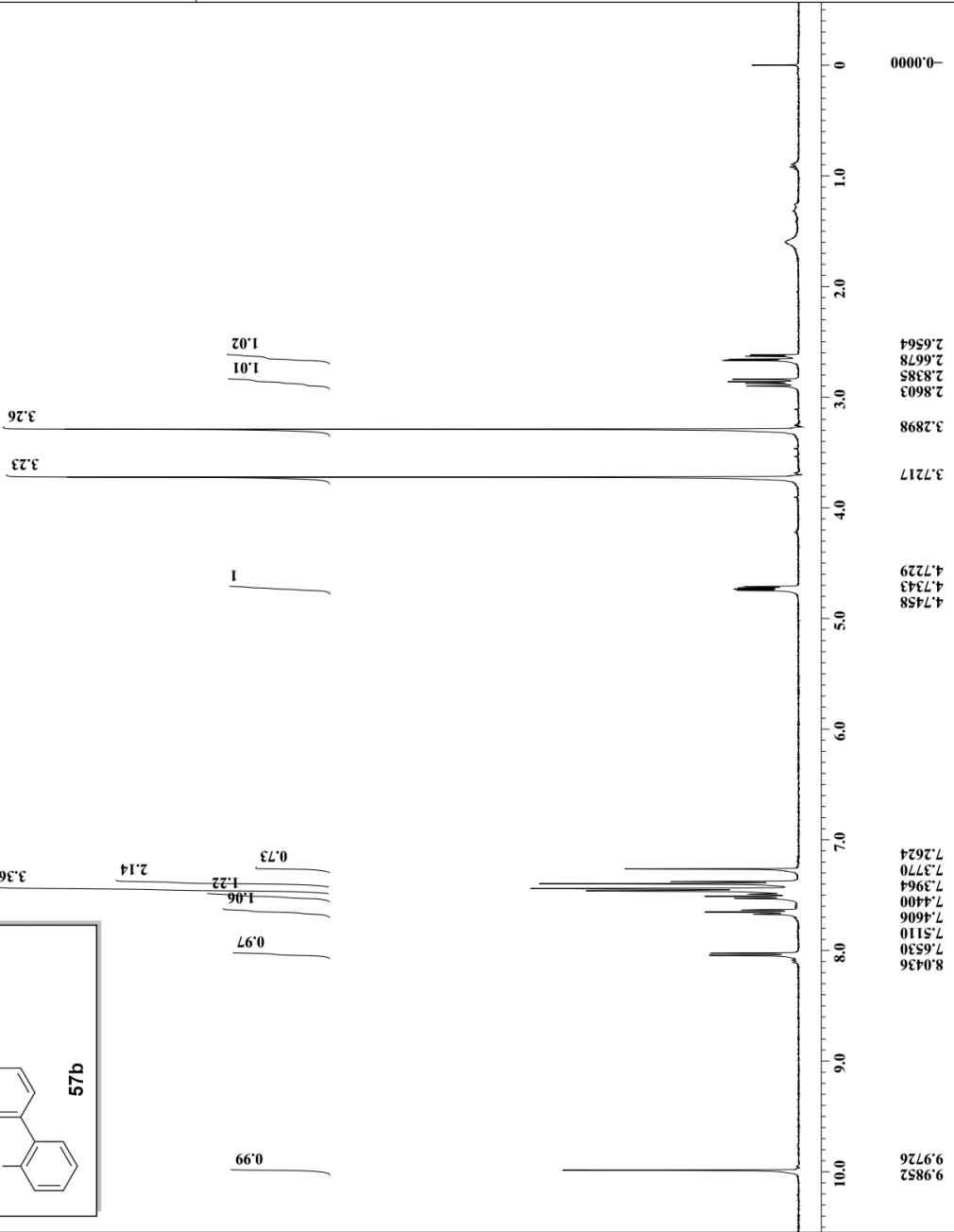
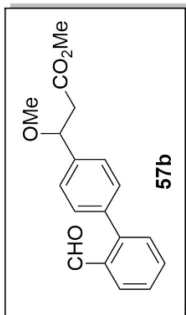
Filename = pn1-48pureC-3.jdf
Author = Delta
Experiment = single pulse_dec
Sample_id = S#580161
Solvent = CHLOROFORM-D
Creation_time = 10-OCT-2015 16:09:02
Revision_time = 17-JAN-2018 13:14:14
Current_time = 17-JAN-2018 15:40:12
Comment = single pulse decouple
Data_format = ID COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = 1
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 = 0.04333312 [s]
X_angle = 30.0 [deg]
X_pulse = 2 [us]
X_atn = 2.73333333 [dB]
X_atn_dec = 22.65948 [dB]
Irr_atn = 22.65948 [dB]
Irr_atn_noe = WALTZ
Decoupling = TRUE
Initial_wait = 1 [s]
Noe_time = 2 [s]
Recvr_gain = 60
Relaxation_delay = 2 [s]
Repetition_time = 3.04333312 [s]
Temp_get = 22.3 [dC]
  
```





----- PROCESSING PARAMETERS -----
 dc_balance : 0 : FALSE
 exp : 0.2[Hz] : 0.0[s]
 trapzoid3 : 0[%] : 80[%] : 100[%]
 zerofill : 1
 ift : 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[Ti] (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 = 4.45794685[Hz]
 X_sweep = 1.5030012[kHz]
 Irr_domain = 1H
 Irr_freq = 399.78219838[MHz]
 Irr_offset = 5[ppm]
 T1_domain = 1H
 T1_freq = 399.78219838[MHz]
 T1_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_preset = FALSE
 Initial_wait = 1[s]
 Recvr_gain = 46
 Relaxation_delay = 5[s]
 Repetition_time = 7.18365952[s]
 Temp_get = 19.5[dC]

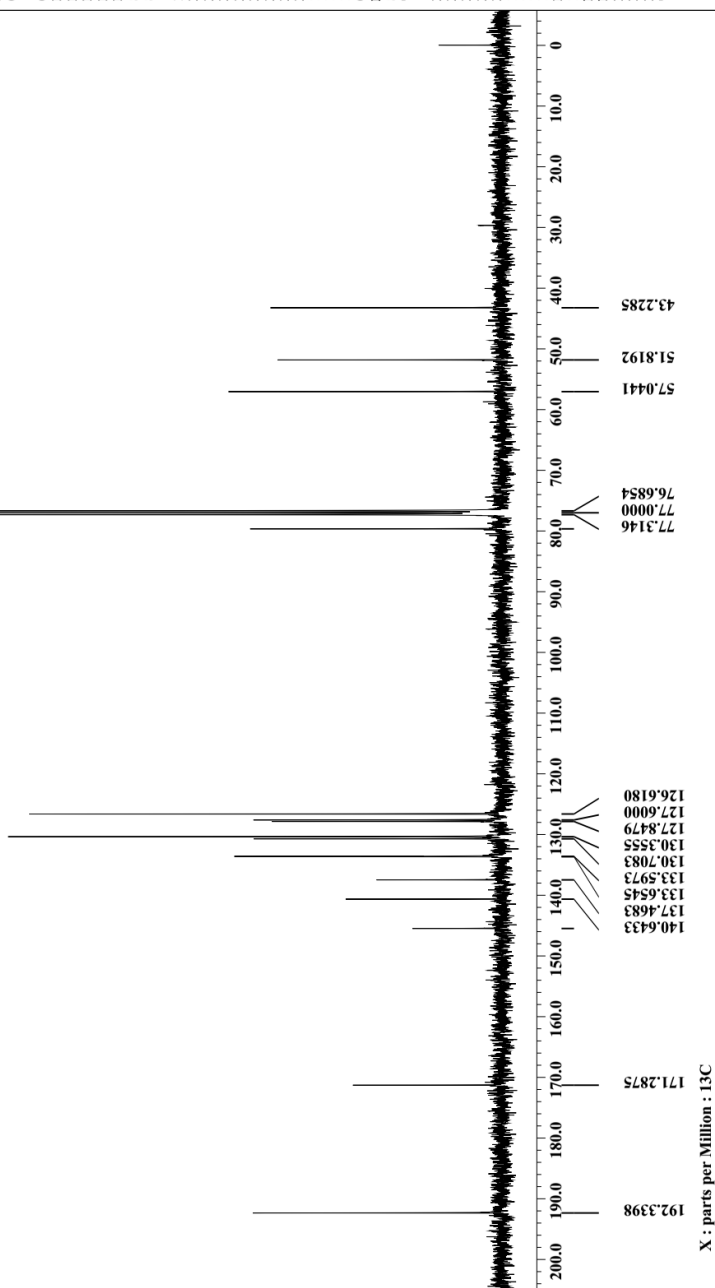
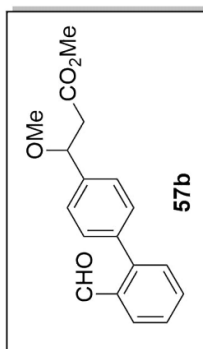


X : parts per Million : 1H



----- 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 = pn1-50colul14-27-3.jd
Author =
Experiment = single pulse_dec
Sample_id = #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 = ID COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389765[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[MHz]
X_sweep = 31.40703518[MHz]
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]
Irr_atn_dec = 2.73333333[us]
Irr_atn_aoe = 22.62948[db]
Decoupling = WALTZ
Pulse_program = TRUE
Initial_wait = 1[s]
Noe_time = 2[s]
Recvr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get_time = 21.8[dc]



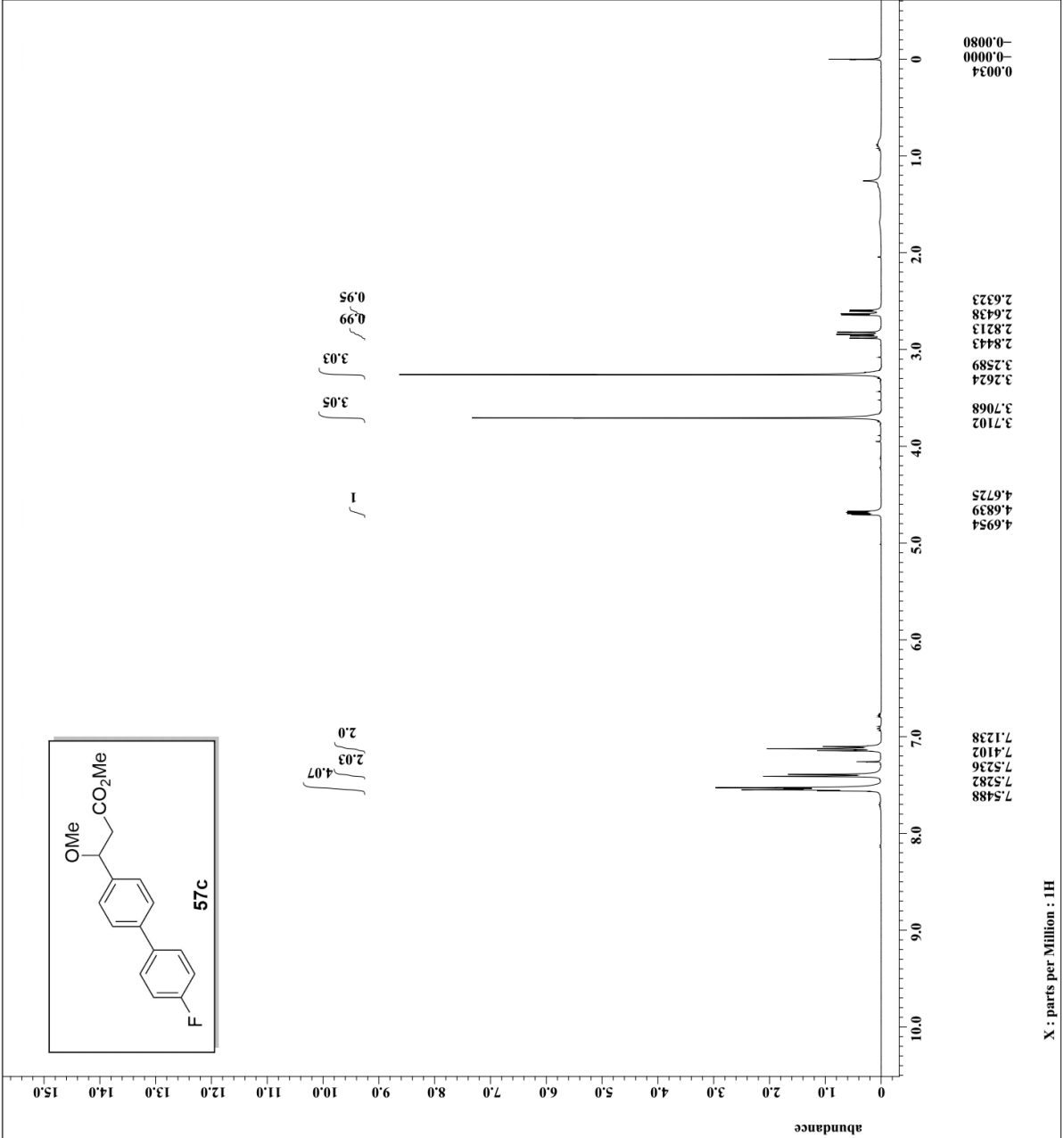


```

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

```

Filename = pn1-5scolumn-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 = ID COMPLEX
Dim_size = 13107
Dim_units = Hz
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]
Mapped = FALSE
Mode_return = 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_preset = FALSE
Initial_wait = 1 [s]
Recvr_gain = 36
Relaxation_delay = 5 [s]
Repetition_time = 7.18365952 [s]
Temp_get = 19.7 [C]
  
```

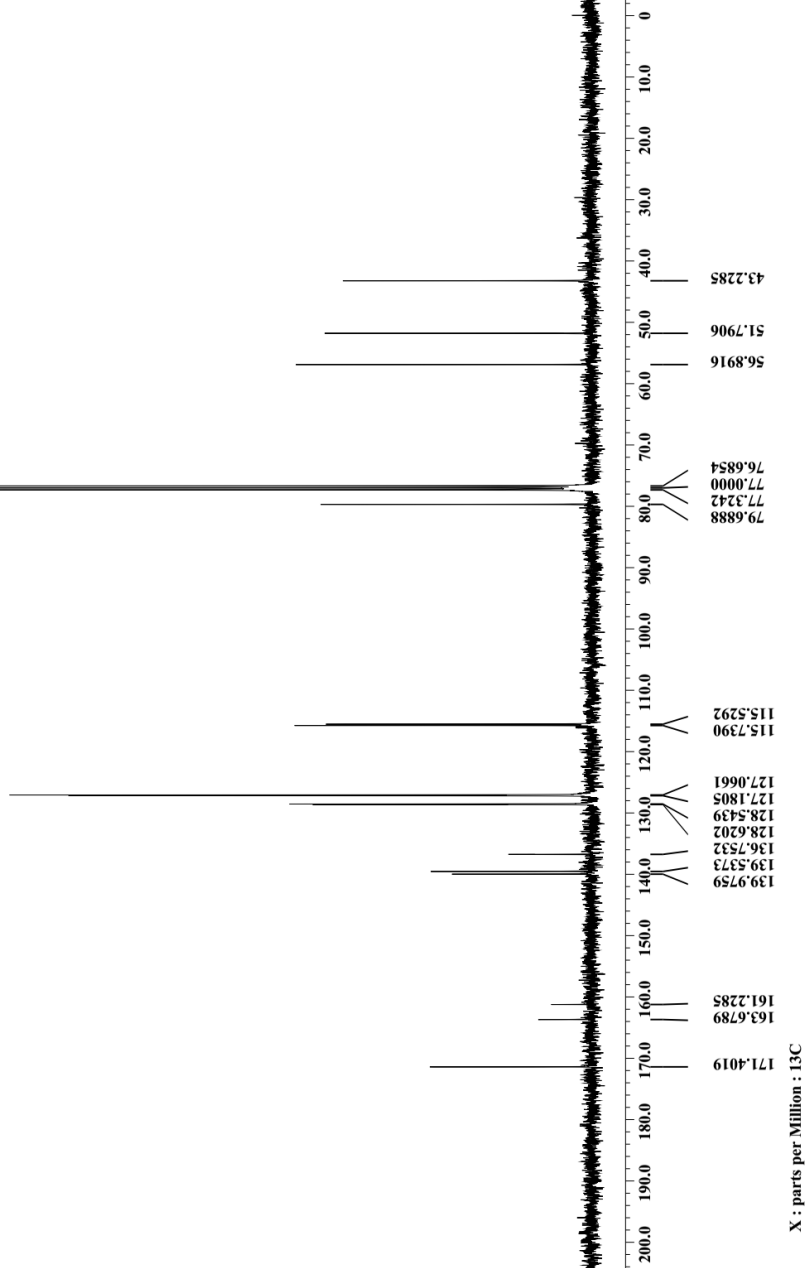
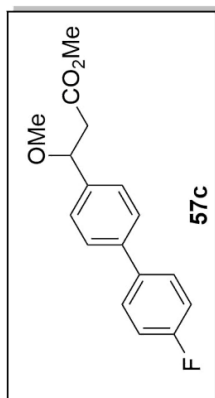


X : parts per Million : 1H



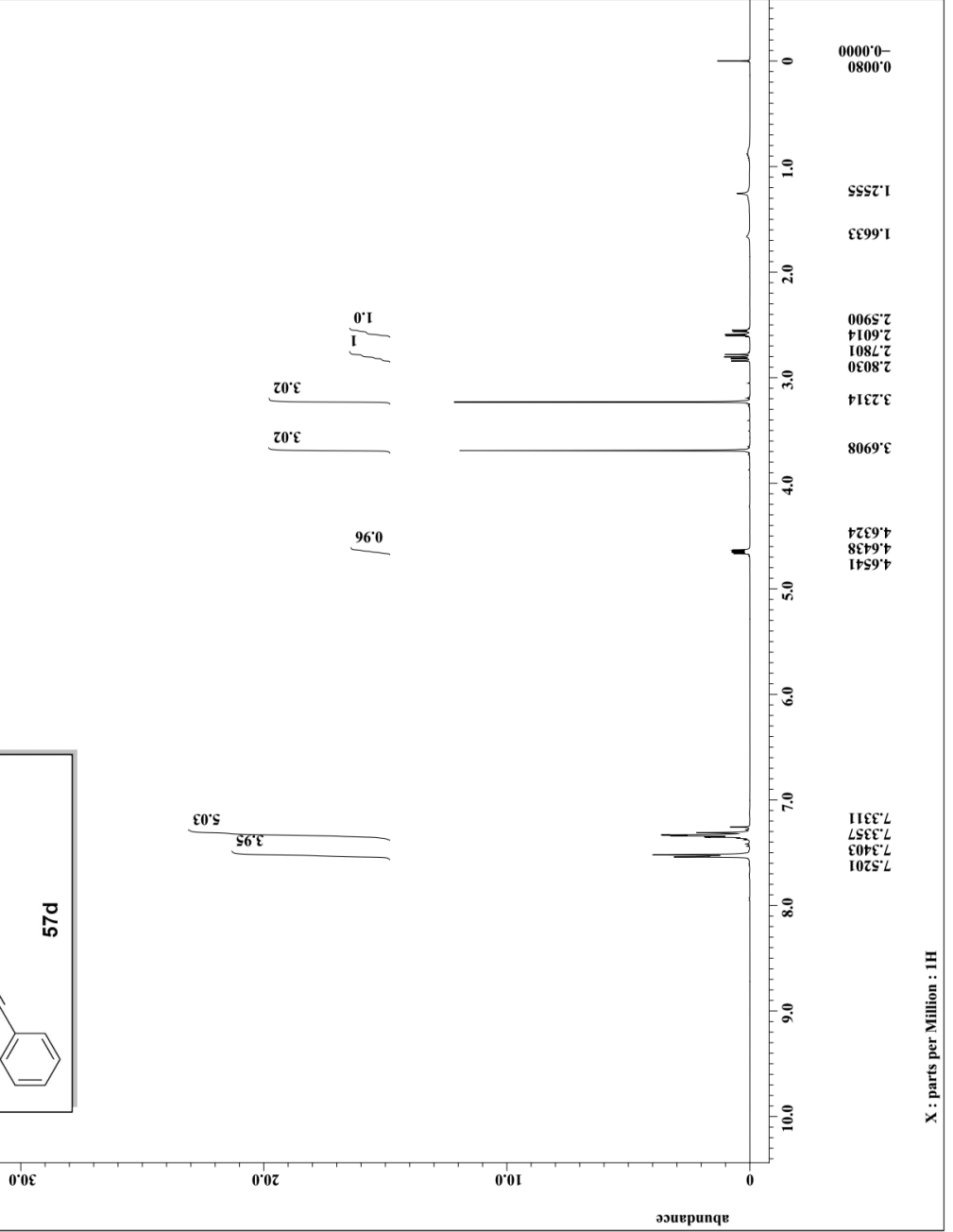
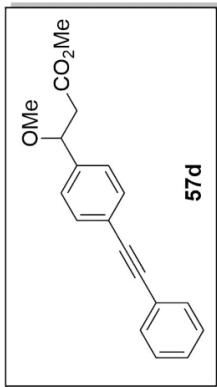
----- PROCESSING PARAMETERS -----
dc balance : 0 : FALSE
sexp : 2.0 [Hz] : 0.0 [s]
trapezoid3 : 0 [%] : 80 [%] : 100 [%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm
auto_reference : 5 [%] : TRUE

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 = ID 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 = 6
X_resolution = 6.95846665 [Hz]
X_resolution = 31.40703516 [kHz]
Irr_delay = 1H.40703516 [kHz]
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 = 2.7333333 [us]
Irr_atn_dec = 22.65948 [dB]
Irr_atn_noe = 22.65948 [dB]
Decoupling = WALTZ
Initial_wait = [s]
Noe_time = 2 [s]
Recvr_gain = 60
Relaxation_delay = 2 [s]
Repetition_time = 3.043333312 [s]
Temp_get = 19.9 [deg]



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

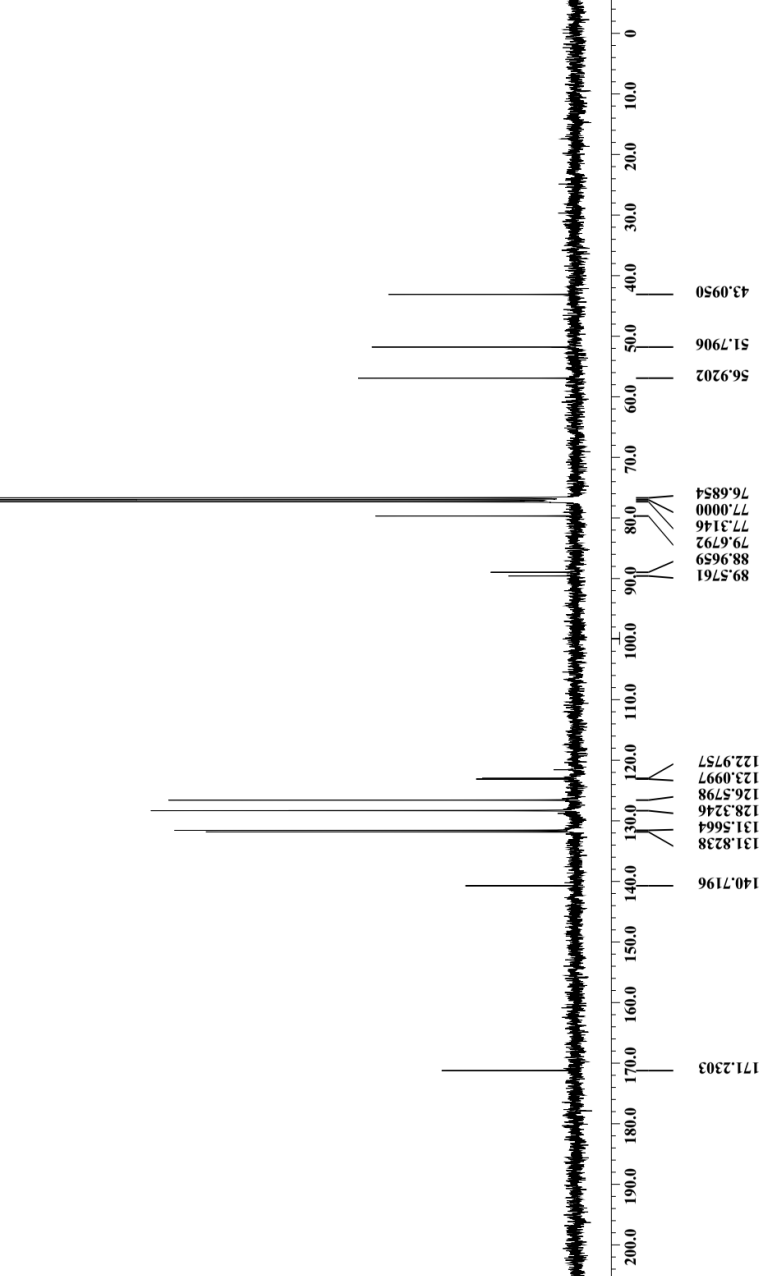
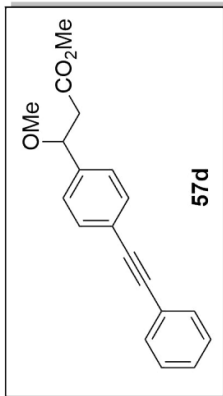
Filename = pn1-58column-5.jdf
 Author = det
 Experiment = single pulse.ex2
 Sample_id = SH2531E
 Solvent = CHLOROFORM-D
 Creation_time = 30-OCT-2015 16:51:37
 Revision_time = 17-JAN-2018 15:51:14
 Current_time = 17-JAN-2018 15:51:27
 Comment = single pulse
 Data_format = 1D COMPLEX
 Dim_size = 13107
 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]
 Irr_domain = 1H
 Irr_freq = 399.78219838[MHz]
 Irr_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]
 Tri_mode = Off
 Tri_mode = Off
 DanTE_preset = FALSE
 Initial_wait = 1[s]
 Recvr_gain = 36
 Relaxation_delay = 5[s]
 Repetition_time = 7.18365952[s]
 Temp_get = 19.9[dc]



X : parts per Million : 1H

```

Filename = pn1-58-5.jdf
Author = delta
Experiment = single_pulse_dec
Sample_id = S47976
Sample_name = CHLOROPRM-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_swept_freq = 31.40703518[kHz]
IRF_domain = 1H
IRF_freq = 399.78219838[MHz]
IRF_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]
IRF_atn_dec = 22.65948[db]
IRF_atn_noe = 22.65948[db]
IRF_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe_time = 2[us]
Noe_time = 2[s]
Relaxation = 0
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get_time = 19.5[dc]
  
```

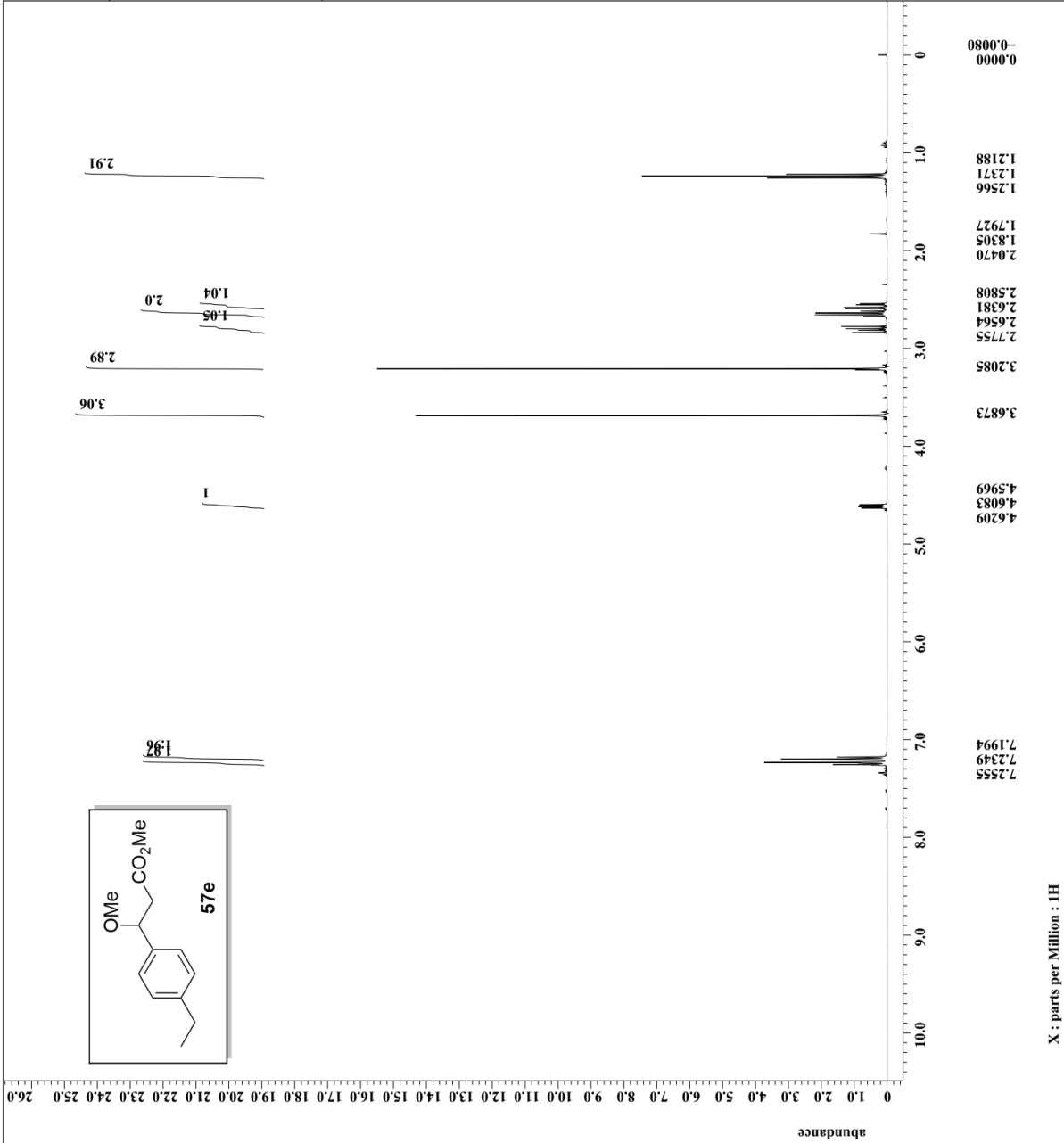


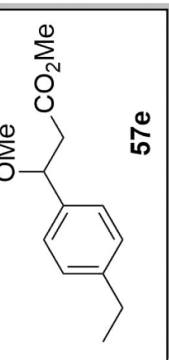
X : parts per Million : 13C



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

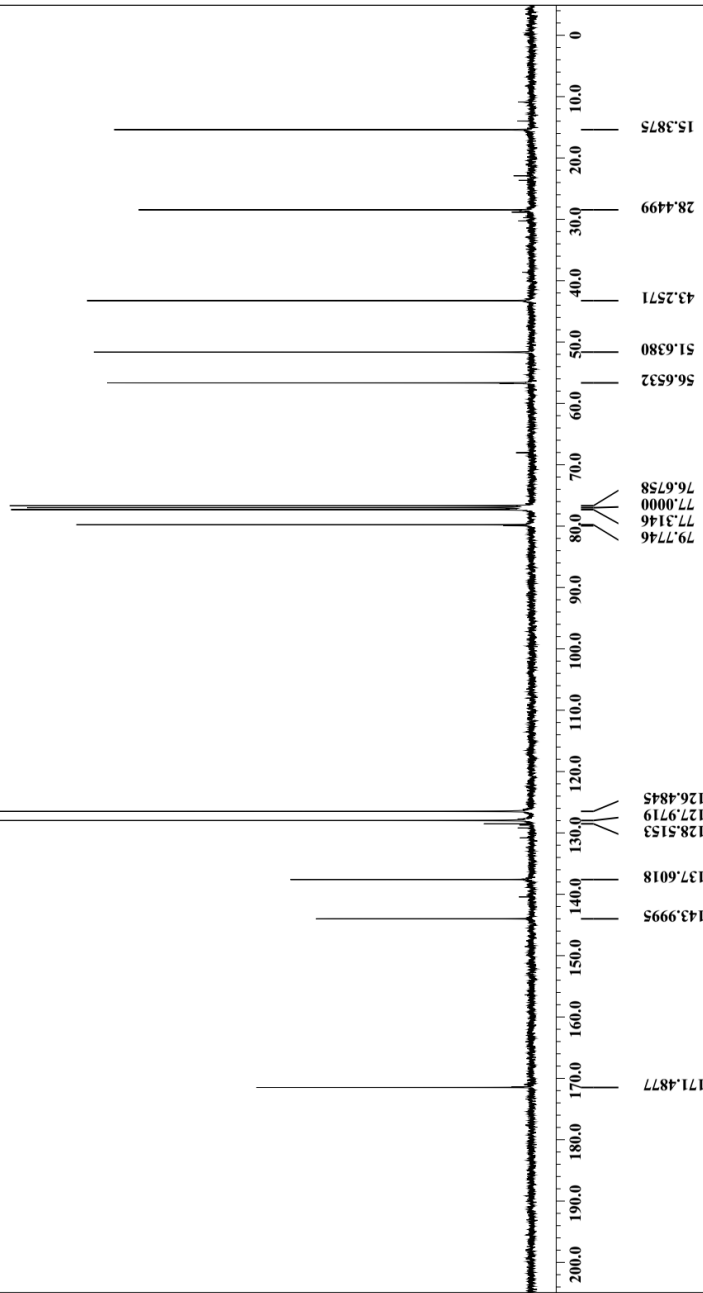
Filename = pn1-60column-5.jdf
 Author = delta
 Experiment = single_pulse.ex2
 Sample_id = S#603785
 Solvent = CHLOROFORM-D
 Creation_time = 9-NOV-2015 16:15:37
 Revision_time = 17-JAN-2018 15:52:37
 Current_time = 17-JAN-2018 15:52:50
 Comment = single_pulse
 Data_format = 1D COMPLEX
 Dim_size = 13107
 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 = 16384
 X_points = 0
 X_prescans = 0
 X_resolution = 0.45794685[Hz]
 X_sweep = 7.5030012[kHz]
 Irr_domain = 1H
 Irr_freq = 399.78219838[MHz]
 Irr_offset = 1H
 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_gate = 45[us]
 X_atc = 1[us]
 X_pulse = 4.75[us]
 Irr_mode = Off
 Tri_mode = Off
 Data_preset = FALSE
 Initial_wait = 1[s]
 Recvr_gain = 24
 Relaxation_delay = 5[s]
 Repetition_time = 7.18365952[s]
 Temp_get = 20.2[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 = 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 = ID 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 = 100.52530333[MHz]
X_freq = 100.52530333[MHz]
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 = WAHZ
Decoupling = TRUE
Initial_wait = 2[s]
Noe_time = 60
Reacr_gain = 60
Relaxation_delay = 2[s]
Repetition_time = 3.04333312[s]
Temp_get = 20.5[dc]





```

----- PROCESSING PARAMETERS -----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapzoid3 : 0[%] : 80[%] : 100[%]
fft_dir : 1 : TRUE
ppm : 1 : TRUE
machinephase :
ppm
auto_reference : 5[%] : TRUE
  
```

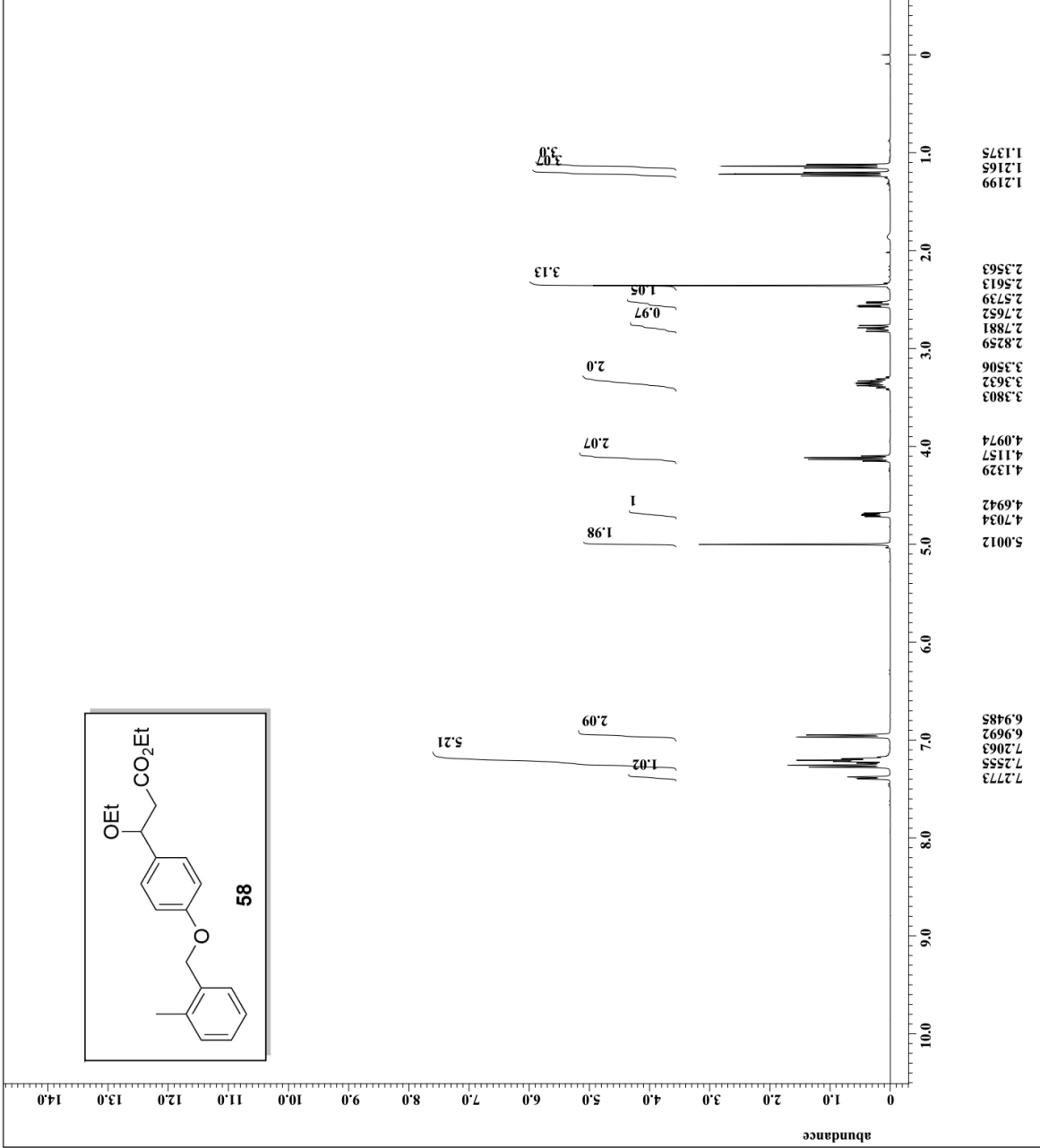
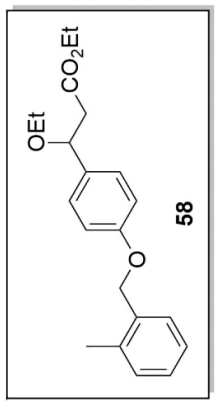
```

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

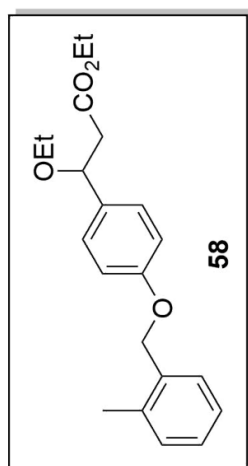
Comment = single_pulse
Data_format = 130MPLX
Dim_units = 1H
Dimensions = X[ppm]
Site = ECS 400
Spectrometer = JNM-ECS400

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]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_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_preset = FALSE
Initial_wait = 1[s]
Recvr_gain = 22
Relaxation_delay = 5[s]
Repetition_time = 7.18365952[s]
Temp_get = 460.0[dc]
  
```



X : parts per Million : 1H



```

----- 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
  
```

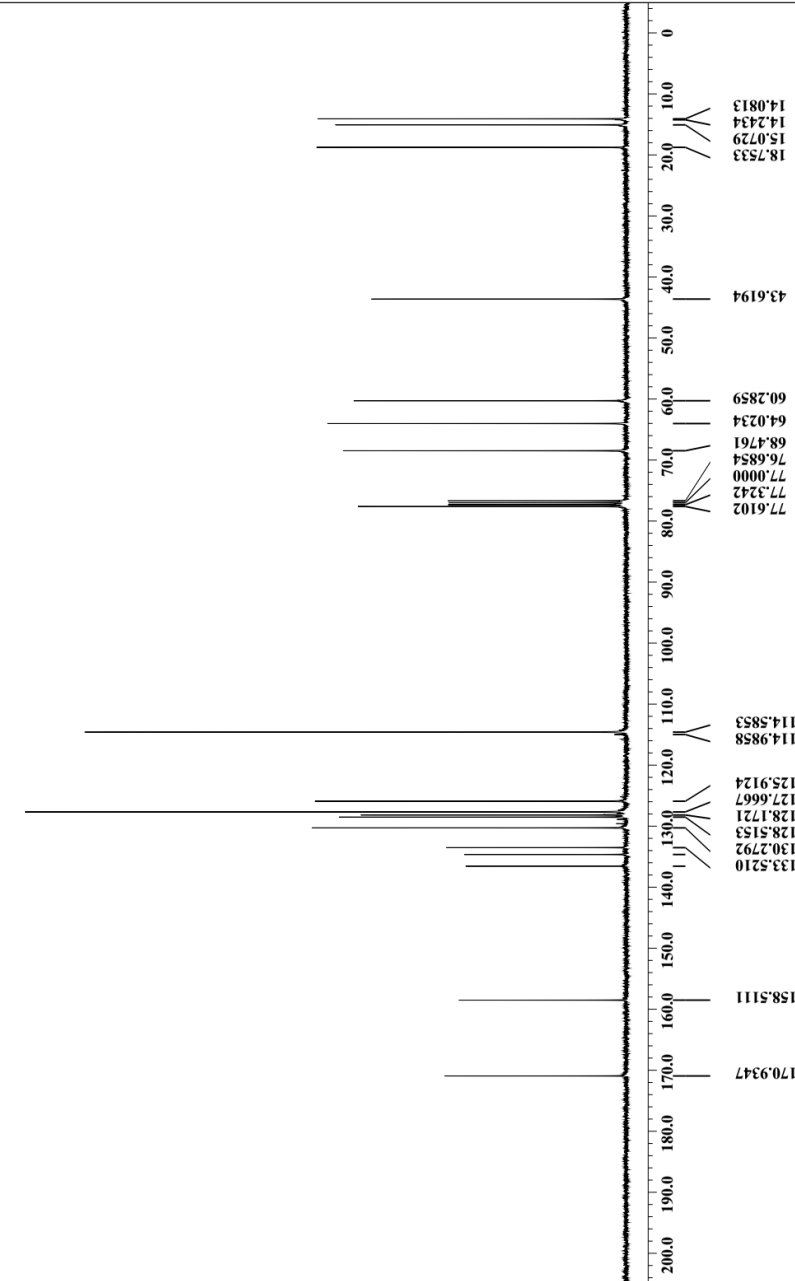
```

Filename = pn3-180cl3-3.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 = 10.52530333[MHz]
X_freq = 100.625[MHz]
X_offsets = 327.68
X_pulses = 4
X_prescans = 4
X_resolution = 0.95846665[Hz]
X_sweep = 31.40703518[kHz]
Irr_domain = 1H
Irr_sweep = 399.78219838[MHz]
Irr_freq = 5[ppm]
Irr_offset = FALSE
Clipped = 1
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 = WALTZ
Decoupling = IRUZ
Initial_wait = [s]
Noe_time = TRUE
Relaxation_delay = 21[s]
Repetition_time = 3.04333312[s]
Temp_get = 460.0[dc]
  
```



X : parts per Million : 13C