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Asymmetric conjugate reduction of enones with Co(II)-Salox complexes

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1 Introduction

In organic synthesis, α,β-unsaturated compounds represent a useful class of electrophiles due to their availability and their particular reactivity towards convenient chemical transformations such as reductions, Michael additions, Diels-Alder reactions, etc. Moreover, downstream products can be further modified into a variety of useful building blocks via well-established transformations. For α,β-unsaturated carbonyl compounds, the reactivity might be driven towards 1,2 or 1,4 additions. The factors governing the selectivity can be accounted for by the hard-soft acid-base (HSAB) paradigm and by the substrate's electronic properties, which contribute to the determination of the outcome of the reaction. More specifically, the carbonyl moiety presents a harder electrophilic character than the β-position.

Reductions are among the transformations that can be operated on α,β-unsaturated compounds and are the focus of this thesis work.

Many stoichiometric reductants can afford 1,2- or 1,4-reductions of α,β-unsaturated aldehydes or ketones in variable selectivity. To control the hydride addition, additives can be used that increase 1,2-selectivity. For example, while α,β-unsaturated ketones usually lead to a mixture of 1,2-, 1,4-addition, and over-reduction, by adding $CeCl_3$ selective 1,2-reduction can be achieved (Luche conditions). In addition to stoichiometric reactions, catalytic and enantioselective methods exist that allow achieving selective 1,2-reduction of α,β-unsaturated ketones (e.g. Corey-Bakshi-Shibata or Noyori reactions). In the case of esters however, the 1,2-reduction is more difficult due to the reduced reactivity of the carbonyl group when compared to ketones and aldehydes, which poses the bases for accessing efficient and selective 1,4 (conjugate) reductions.

The conjugate reduction of α,β-unsaturated compounds can be achieved using milder reducing agents such as molecular hydrogen H_2 in presence of a metallic catalyst (Pd/C, Rh), Hantzsch esters in combination with

organocatalysts, or via hydrometallation reactions with hydrogen sources such as silanes or boranes. Hydrogenations are widely employed on an industrial scale and highly efficient. However, these suffer some limitations in the context of functional group compatibility and costs. For instance, H_2 in the presence of Rh or Pd can easily reduce also unactivated double bonds possibly present in the substrate or result in partial dehalogenation in case of halogenated substrates. Moreover, this requires the availability of pressurized H_2 gas and expensive apparatus needed for its use. The transfer of formal hydrogen from solid and stable Hantzsch esters to the substrate with concomitant organocatalytic activation of the substrate is an attractive alternative. This is limited to the reduction of α,β-unsaturated aldehydes and ketones that can be activated via iminium catalysis (not suitable for esters and amides). Finally, hydrometallation reactions promoted by first row transition metal catalysts (typically Cu or Co) have been proven to be applicable to any type of α,β-unsaturated compounds with excellent functional group compatibility and using a variety of available reductants such as inexpensive silanes (e.g. polymethylhydrosiloxane PMHS, tetramethyldisiloxane TMDS, and others) or boranes (e.g. $NaBH_4$, HBpin).

This thesis work focuses on this latter case of conjugate reductions. Moreover, because of the general interest of synthetic chemists in accessing chiral building blocks for drug and agrochemical applications, the accent will be given to enantioselective 1,4-reductions of prochiral α,β-unsaturated compounds, namely Asymmetric Conjugate Reductions (ACR).

1.1 Asymmetric Conjugate Reductions (ACR)

Products generally attainable via catalytic ACR are useful building blocks in total synthesis. Tertiary stereogenic centers are ubiquitous in biologically active compounds such as drugs or agrochemicals. In the case of prochiral alkenes, ACR would build such stereogenic centers and, by using chiral metal complexes in a catalytic system, enantioselectivity can be afforded. In terms of stereoselectivity, the use of chiral ligands in transition metal catalysis can

induce the preferential formation of one of the two possible enantiomeric products by selecting one of the two enantiotopic faces of the C=C double bond. In this context, ACRs are most often used to form stereocenters in β-position rather than in the α-position. Indeed, the reaction pathway involves a stereo-determining hydrometallation step (i.e. hydride attack at the β-position) leading to the formation of a metal-enolate. Subsequent protonation, either with a proton source in situ or by reaction quench, renders the saturated product (*Figure 1*).

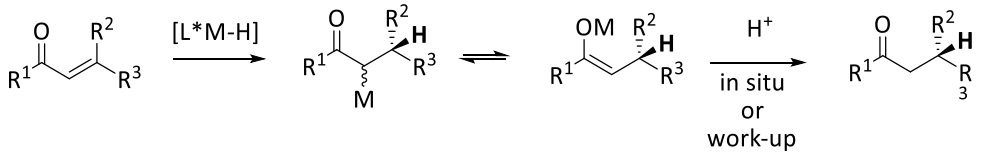


Figure 1: Transition metal catalyzed ACRs

There exist different catalytic systems which allow obtaining excellent results in ACR using different classes of ligands and metals. The most widely used are based on earth-abundant transition metals such as Co and Cu.

1.2 Copper catalyzed ACR

In the last three decades, Cu gained importance in catalysis due to its versatility and abundance, and is currently the most widely employed metal in ACRs. Chiral phosphines are employed as ligands, which are often commercially available even though generally expensive. Other classes of ligands have been proposed in recent literature (e.g. NHC), but these typically provide poorer performances.[1],[2]

ACRs with Cu follow the general mechanism depicted in *Figure 2*.

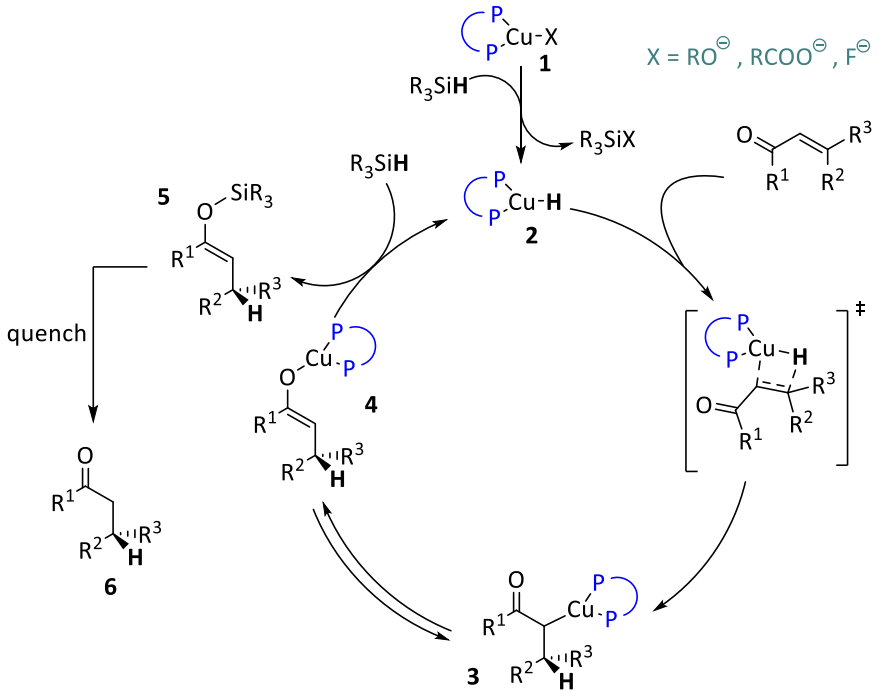


Figure 2: General reaction mechanism of Cu-catalyzed ACRs

Here, the catalyst **1** is formed in situ starting from a Cu(I) salt. The first step of the cycle is the transmetallation with a silane, which is the hydride source. The thermodynamics of this step is crucial since the catalyst's counterion X must form a sufficiently stable bond with Si to drive the reaction forward. For this reason fluorides, carboxylates or alkoxides are preferentially used. The so formed chiral catalytic hydride species LCu-H **2** can then undergo hydrocupration of the C=C bond, which results in the formation of a Cu enolate **3**. Tautomerization of this intermediate is possible and constitutes a key step for the formation of the LCu-O bond in **4**, which will then withstand transmetallation with the silane, thus starting a new catalytic cycle. The silylated product **5** persists in solution until quenching of the reaction, when hydrolysis affords the saturated final product.

In a pioneering work by Buchwald and co-workers it was shown that the use of (S)-tol-BINAP and PMHS as the hydride source could afford the enantioselective formation of linear esters with β-stereocenters in high yields and 80-92% *ee* (*Figure 3*).[3] The use of a co-catalytic strong base such as

t-BuONa was needed in this case to form CuO*t*-Bu in situ from CuCl, which could then undergo transmetallation with the hydride source.

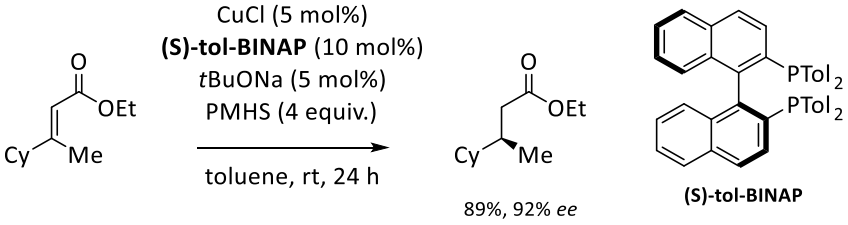


Figure 3: First example of ACR of enones with Cu

Aiming at further optimization of the reaction performances, several research groups engaged in the design of new ligands that could increase enantioselectivity, yield, and scope of this reaction. In 2004, the Lipshutz group reported that Josiphos (**L1**) and DTBM-Segphos (**L2**) (*Figure 4*) were capable of remarkable performances.[4] Over 90% yield and 95% ee were obtained in all of the substrates tested with **L1** for the ACR of enoates. Here, $[(PPh_3)_3CuH]_6$ (Stryker's reagent) was used as the Cu source and the catalyst loading was lowered down to ca. 0.01 mol%. A stoichiometric amount of *t*-BuOH was found to notably increase the reaction rate by facilitating the transmetallation step from intermediates **3** or **4** to **2** (see *Figure 2*). The requirement for alcoholic additives was also reported in other Cu-catalyzed ACRs. For instance, Buchwald and co-workers found that in the ACR of cyclic esters and amides, *t*-amyl alcohol is needed.

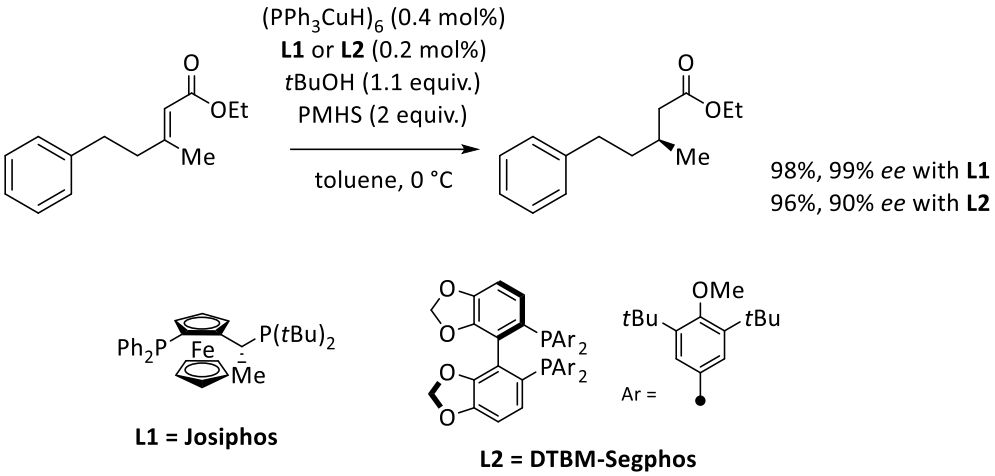


Figure 4: Lipshutz work on ACR of enones with Cu

Sawamura and co-workers reported that chiral Cu-NHC complexes such as [(**L3**)Cu] were also suitable for achieving ACR of enoates, obtaining good yields and 70-90% ee (*Figure 5*).[2]

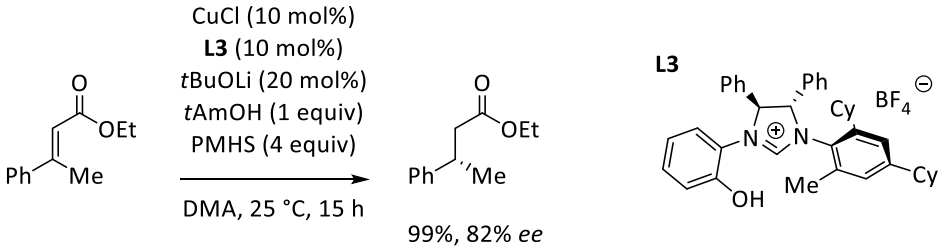


Figure 5: Sawamura work on ACR of enones with Cu

Cu-H catalysis has proven to be highly tolerant towards a variety of reactive functional groups. Thus, in addition to simple benchmark β-aryl or alkyl substituted chiral esters, also substrates bearing useful functionalities have been explored. In 2008, Zheng and co-workers developed the enantioselective reduction of γ-phthalimido enoates using (*S*)-BINAP (**L4)** giving 77-94% yields and 91-96% ee (*Figure 6a*).[5] Hu and co-workers further expanded the scope of substrate's scaffolds, managing ACR of γ-phosphonate unsaturated esters in 85-95% yields and 90-94% *ee* (*Figure 6b*).[6]

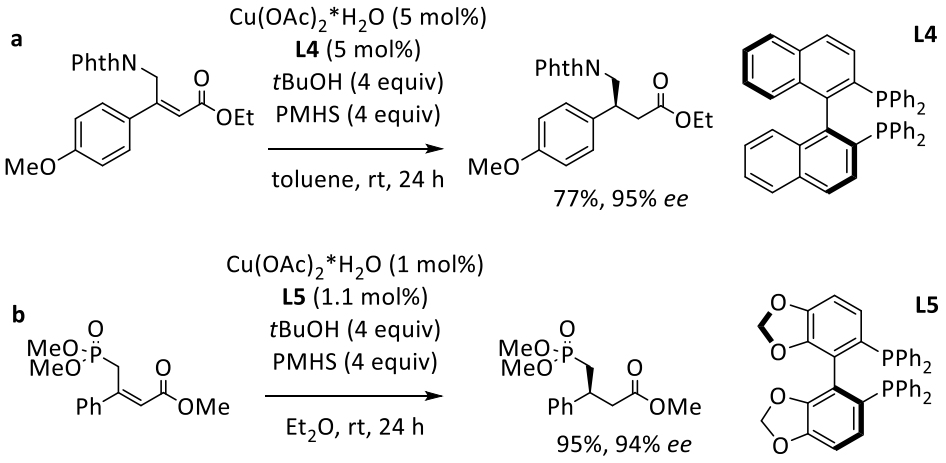


Figure 6: (a) Zheng - 2008, (b) Hu – 2011 work on Cu catalyzed ACR of enones

The reduction of β-enamino esters is also possible with Cu-H catalysis. Wu and coworkers demonstrated that either acetyl or aryl groups can be used as *N*-protecting groups, thus accessing different chiral β-amino ester derivatives

in up to 99% yield and *ee* (*Figure 7*).[7] The extended scope of Cu catalyzed ACR reaches ketones as suitable substrates. Reduction of α,β-unsaturated ketones is generally more challenging than the one of esters and amides since competitive 1,2 reduction or overreduction are possible issues. In 2000, Buchwald and co-workers showed that prochiral unsaturated cyclopentanones, cyclohexanones and cycloheptanones could be reduced in over 80% yield and 87-98% *ee* using (S)-tol-BINAP as a ligand (*Figure 7*).[8]

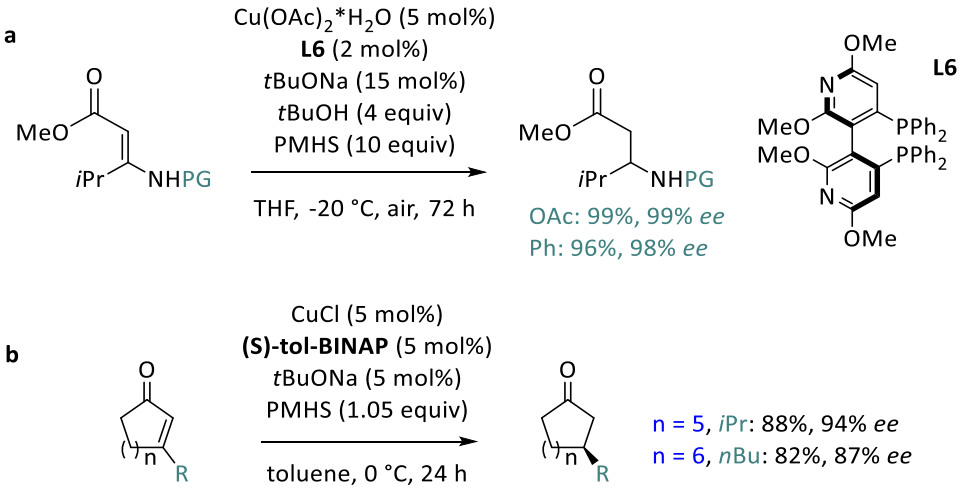


Figure 7: (a) Wu's work on protecting groups tolerance in Cu ACR, (b) Buchwald's work on Cu ACR of cyclic enones

In the following years, Cu catalyzed ACRs have proved to be of great versatility still maintaining good to excellent performances towards unsaturated substrates bearing different EWG such as NO_2 or CN. Cu catalysis is widely employed and currently the most convenient way to carry out ACRs.

1.3 Cobalt catalyzed ACR

Cobalt hydride (Co-H) chemistry is also flourishing. For this metal, complexes of bidentate or tridentate N-ligands are often the best choice. The first catalytic ACR was reported in 1979 by Fischli and Süss at Hoffman-La Roche using Co.[9-10] This transformation was catalyzed by cyanocobalamine (*Figure 8*) in the presence of Zn/AcOH as the reductant and proton source.

This catalytic system was applied to the reduction of a β,β-dialkyl substituted unsaturated ester to give the saturated product in 78% yield and 26% ee (*Figure 8*). The reaction mechanism was investigated due to the relevance that cobalamine (vitamin B12) covers in biological systems. It was hypothesized that the cyanocobalamine complex is first reduced to a nucleophilic Co(I) species which can then undergo Michael addition to the substrate's double bond.

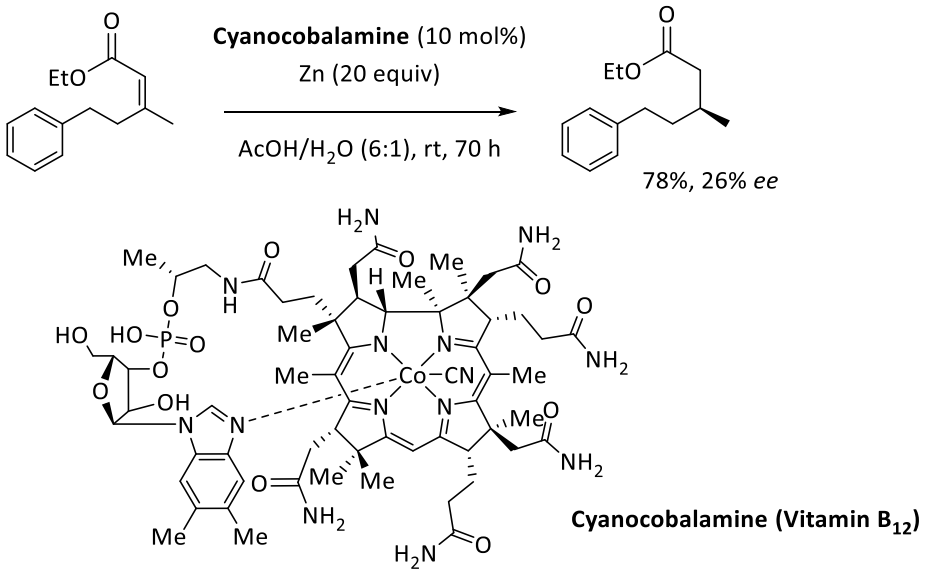


Figure 8: first example of Co catalyzed ACR

Subsequent reductive protonation with retention of configuration would afford the reduced product and restore the catalyst.[9], [10] Beside this pioneering example, other Co-catalyzed ACR rely on the formation of catalytic Co-H species.[11], [12] $NaBH_4$ is commonly used as the hydride source, and since the mechanism of this class of reactions is poorly known, the involvement of borohydride as ligand or direct reductant cannot be presently ruled out.[13], [14]

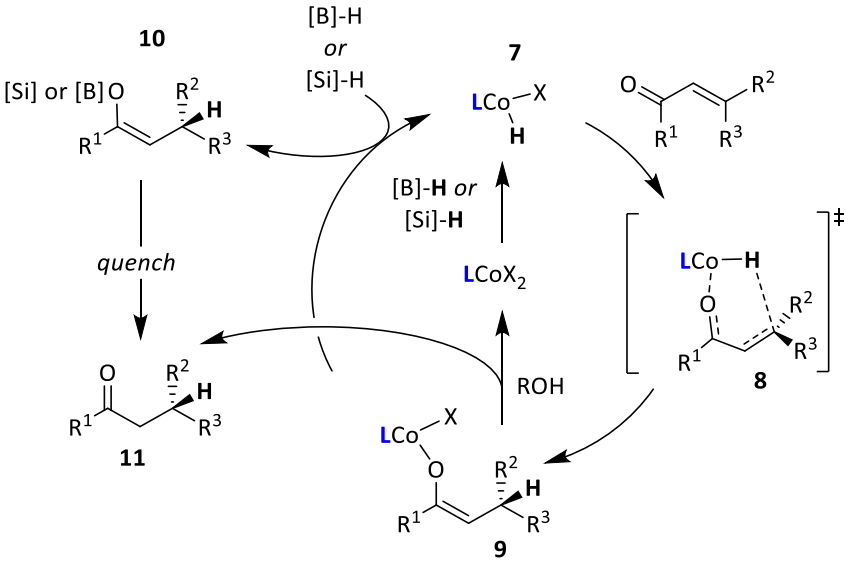


Figure 9: Generally accounted reaction mechanism for ACR with Co

Nevertheless, although no in-depth mechanistic study has been carried out to date, a general mechanism for these systems has been proposed and is nowadays generally accepted (*Figure 9*). The reaction starts with formation of **7** in situ from a Co(II) source, usually a Co dihalide via hydride donation from the reducing agent. Co(II) in this complex likely acts as a Lewis acid via binding of the carbonyl O-atom of the substrate. Contextually, the β position accepts the hydride from Co-H, via a six membered cyclic transition state **8**. The resulting Co-enolate **9** is then quenched by the proton source, typically an alcohol, to give tautomerization of the enolate forming the final product **11**. The Co-enolate can else undergo quenching with the proton source to free the final product and a Co alkoxide complex **10**. The reducing agent can then restore the Co hydride complex closing the catalytic cycle. Although $NaBH_4$ is a bench stable and commonly available reductant, its capability to reduce the aldehydes and ketones raises a significant problem in terms of selectivity. For this reason, only unsaturated esters and amide can be efficiently and selectively reduced by this manifold using $NaBH_4$ as the terminal reductant, while for ketones milder reducing agents such as silanes or boranes are required. The first highly enantioselective Co-catalyzed ACR was reported by Pfaltz and coworkers in 1989.[15] The authors found that $CoCl_2$ complexes of the anionic ligand Semicorrin **L7** was effective in the reduction of several

enoates even with catalyst loading as low as 1 mol% (*Figure 10*). The reaction with β,β-dialkyl substrates afforded nearly quantitative yields and 90-96% ee, even though the selectivity was lower in the case of cinnamate derivatives (73-81% ee). The same catalytic system was applied to the ACR of unsaturated amides.[16] With these substrates, the use of EtOH:diglyme mixtures as solvent allowed for the catalyst loading to be lowered down to 0.1 mol%, obtaining the desired products in >90% yield and 92-99% ee even though with long reaction times (68-118 h). Another example of anionic ligands suitable for Co-catalyzed ACR was reported by the Yamada group in 1998. The authors found that tetradentate β-ketoiminato complexes of Co(II) in the presence of borohydride **12** (generated in situ from $NaBH_4$ and tetrahydrofurfuryl alcohol, THFA) gave reduction of several enoates and corresponding amides in generally 90-99% yield and 62-91% *ee* (*Figure 10*).[17]

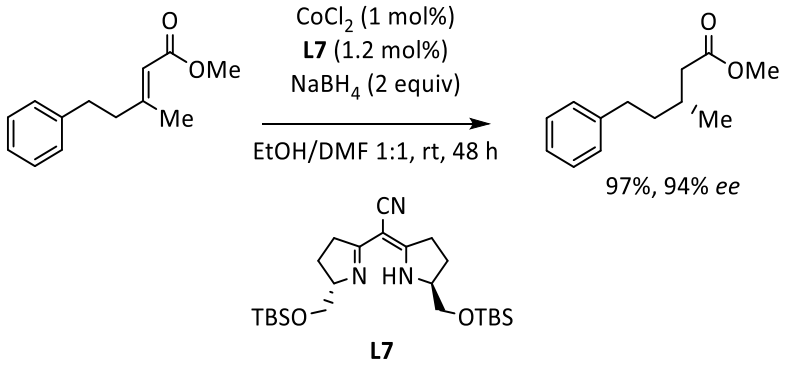


Figure 10: first highly enantioselective Co catalysed ACR by Pfaltz

This catalytic system offered lower performances than semicorrin ligand made by Pfaltz et al. Nevertheless, the authors undertook mechanistic experiments, and observed that β-ketoiminato complex in the presence of borohydride forms Co-H species (detected by FAB-MS analysis).[18] Moreover, submitting an α-substituted amide to the reaction conditions resulted in the formation of enantioenriched reduced product**.** This supports a mechanistic hypothesis involving the formation of a chiral Co-enolate complex, which would undergo enantioselective α-protonation. The use of anionic ligands is not a strict condition for the reaction. Neutral chelating

ligands are also possible if they are electrondonating enough. This was highlighted by Reiser and coworkers in 2004.[19]

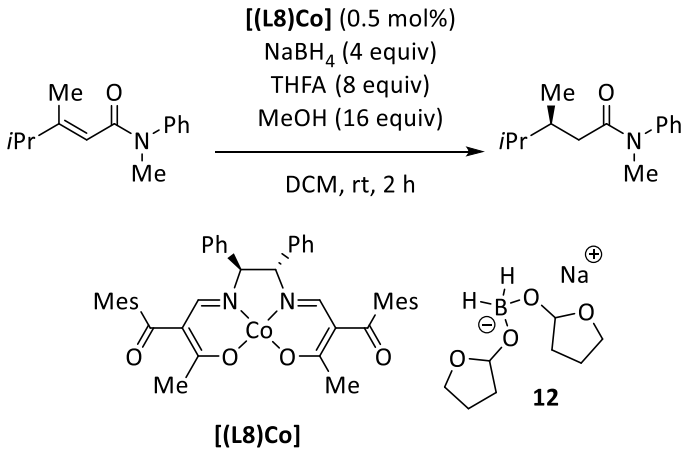


Figure 11: β-ketoiminato Co(II) complex to achieve ACR of enones by Pfaltz

They showed that bisoxazoline (BOX) ligands give sluggish reactivity in the enantioselective reduction of enoates with $NaBH_4$, while the structurally related aza-BOX ligand **L9**, which shows a more electrondonating character, provided efficient reactivity (*Figure 12*). Yields in the range 81-89% and 92-96% ee were obtained in the reduction of linear α,β-unsaturated esters and amides, while lactones provided diminished performances. In 2015, Kitamura and coworkers employed an N,N chelate complex **[(L10)Co]** (*Figure 12*) in the ACR of enoates with $NaBH_4$. The complex they obtained proved effective, allowing for the reduction of an array of substrates in >90% yield and up to >99% *ee* in 1 h.[20]

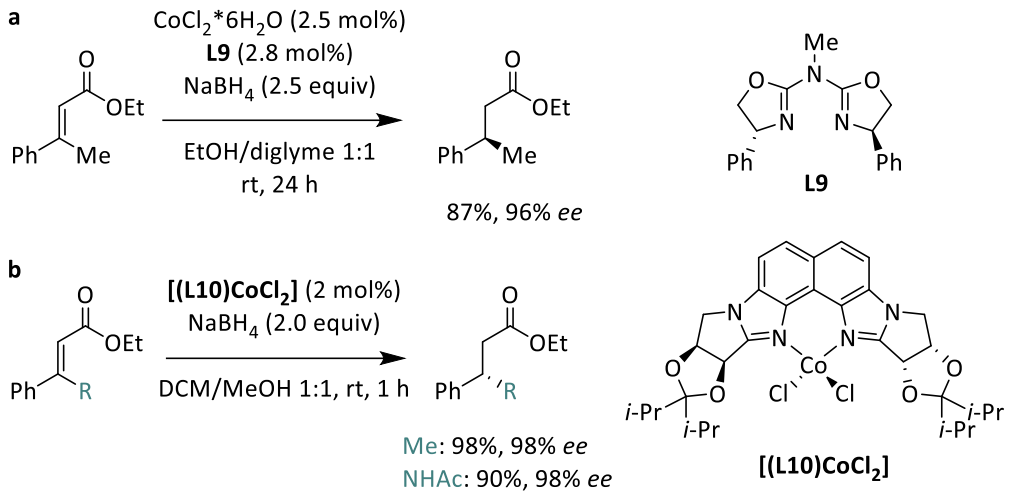


Figure 12: (a) Reiser's and (b) Kitamura's work on Co catalyzed ACR of enones

Interestingly, β-enamino esters and β,β-diaryl enoates were suitable substrates, making this catalytic system of wide generality. Moreover, the preliminary studies they made proved the mechanism to be polar. N,N,N-tridentate ligands are also useful in ACR of enones. Interestingly, the use of such ligands favors the formation of reactive hydride complexes using milder hydride donors than $NaBH_4$ such as silanes. This feature was first exploited by Nishiyama and coworkers in 2010, who employed bisoxazoline-phenylaniline (BOPA) ligands such as **L11** in order to access the selective 1,4-reduction of enones with diethoxymethylsilane (DEMS) as the hydride source (*Figure 13*).[21]

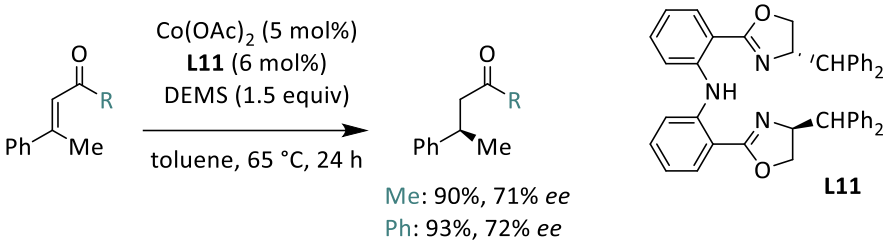


Figure 13: Nishiyama's work on Co catalyzed ACR of enones

The corresponding reduced chiral ketones were obtained in 90-93% yield and 65-75% *ee*.[21] More recently, the Lu group reported the ACR of enones via hydroboration with HBpin (*Figure 14*). The geometrical and steric features

of the tested tridentate ligands were shown to have a dramatic effect on the 1,2 vs. 1,4 selectivity. The best compromise between regio- and enantioselectivity was found to be the quinolinic ligand **L12**.[22]

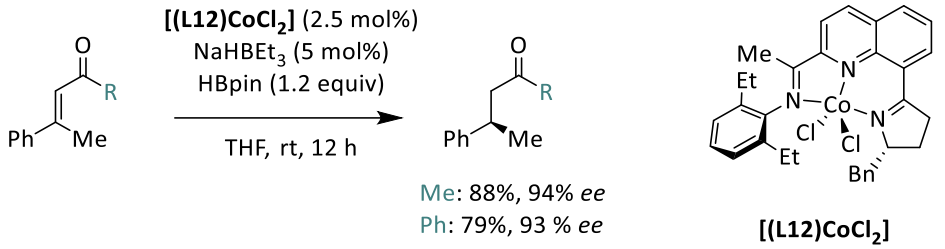
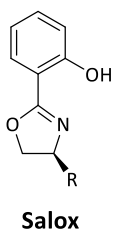


Figure 14: Lu's work on Co catalyzed ACR of enones

With this catalytic system, a variety of chiral ketones were obtained in 63-97% yield and 78-98% *ee*. $NaHBEt_3$ is present in the reaction as a co-catalytic activator enabling the initial formation of the LCo-H species. Interestingly, β,β-dialkyl enones were also suitable substrates in these reaction conditions. There are not many examples of ACR performed on different unsaturated compounds, such as nitriles, phosphonates, or sulfones. Only Pfaltz and coworkers managed to achieve ACR on this type of substrates using their semicorrin derivative as ligands (e.g. **L7**). Nevertheless, the saturated chiral compounds were only obtained in 40-95% yield and 40-69% ee, which was not considered satisfactory. Co catalysis appears to be less efficient than that of Cu or other precious metals. However, it offers a solid method which is relatively tolerant and does not require strict attention to in the reaction set up.

1.4 Objective of the thesis

With this thesis, we propose the use of Salox-Co complexes to be employed in ACR of α,β-unsaturated compounds. These ligands contain a phenol and an oxazoline ligating moieties and they can be synthetized in only one step from commercially available and inexpensive materials. While Cu imposed itself in the field of



Salox

enantioselective ACR due to its versatile and performing reactivity, Co remains less explored. Our choice to use Co in this study relies on the possibility to deepen our knowledge of Co chemistry and maybe open the way to new and efficient Co catalyzed reactions. Mechanistic hypothesis will be presented in light of preliminary studies which may constitute the basis for further optimizations.

2 Results and discussion

2.1 Preliminary data

The starting conditions for the reaction set up took inspiration from previous work of Pfaltz and co-workers report in 1991. A mixture of EtOH:Diglyme 1:1 was used as solvent with a concentration of 0.25 M for the substrate (substrate = 0.2 mmol, total volume = 800μL). The reaction was run on ethyl β-methyl-cynnamate **S1** which was synthetized following the procedure described in the experimental section of this thesis. (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol **L13** (easily accessed from *o*-cyanophenol and valinol as described in the experimental section) was used as the ligand and $CoCl_2$ as the metal source with loadings of 5.5 and 5 mol% respectively. Under these conditions, a preliminary experiment afforded the saturated product **P1** in 88% yield and 76% *ee*. No 1,2-reduction byproduct was observed. Having this experiment as a reference, other reaction conditions were explored, starting from the evaluation of other types of ligands.

2.2 Ligand scope

Steric hindrance of the oxazoline substituent of the ligand was investigated first (*Figure 15*). An intuitive correlation between the steric properties of the ligand and the *ee* of the corresponding catalytic test was missing (*Table 1*). However, some observations are in order:

1. Increasing the bulkiness of the amino alcohol's side chain with a *t*-butyl group (*Entry 2*) resulted in lower yield and enantioselectivity. Mixing ligands **L13** or **L15-L19** with $CoCl_2$ in EtOH:Diglyme 1:1 generally resulted in a deep blue color solution. However, in the case of bulky **L14** the complex solution appeared of a green color, suggesting complexation with different coordination sphere for this

ligand when compared to other electronically similar but less hindered analogues.

2. Reducing the steric hindrance by employing the phenyl alanine derived ligand **L17** also resulted in diminished enantioselectivity (*Entry 5*). These first two points suggest the requirement for a balance in the ligand steric hindrance in other to access higher *ee* values.
3. Phenyl glycinol derivative **L15** afforded **P1** with very similar performances than **L13** (cfr respectively *Entry 3* and *Entry 1*). On the other hand, the rigid aminoindanol scaffold of **L16** offered comparable yield but much lower *ee* (*Entry 4*).
4. The electronic properties of the ligand were also investigated. To this end, ligands **L18** and **L19** were employed that bear an electronwithdrawing or an electrondonanting group onto the phenolate moiety. Interestingly, this modulation did not produce any major change in reactivity or enantioselectivity (*Entries 6* and *7*).

From these experiments we concluded that the *i*-Pr substituent was an optimal choice as a bulky group.

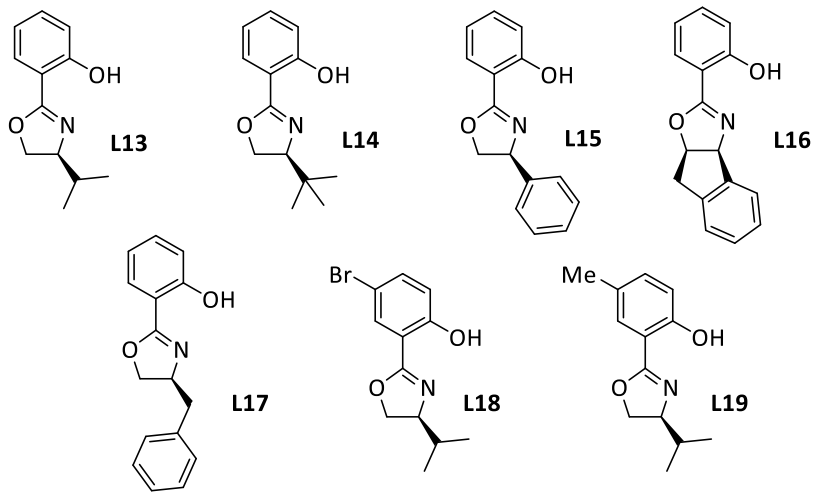
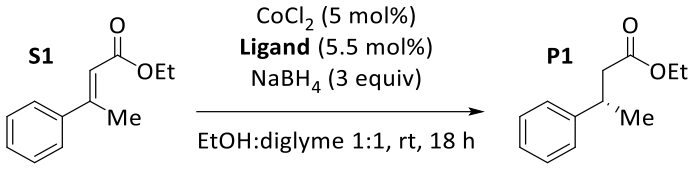


Figure 15: synthetized Salox igands



Entry	Ligand	Yield (%)	*ee* (%)
1	**L13**	90	76
2	**L14**	63	56
3	**L15**	88	74
4	**L16**	91	24
5	**L17**	99	64
6	**L18**	87	76
7	**L19**	80	72

Table 1: results with Salox ligands

Different chelating moieties were explored next (*Figure 16, Table 2*). Keeping in mind the affinity of Co for *N*-ligands and aiming at keeping the *L*,*X*-type coordination, amido-oxazoline **L20-L25** were synthesized. Using these ligands, nearly quantitative yields were obtained in every case. However, these were also proven to be much less efficient in terms of enantioselectivity (< 34% *ee*). Noteworthy are the data obtained with aniline **L20** and sulfonamide **L22** (*Entries 1 and 3, Table 2*). Differently from other *N*,*N*-ligands, lower yields were observed when employing these ligands, suggesting that electronic properties of the supposedly anionic nitrogen is of importance.

It has been previously reported that, for Co-catalyzed asymmetric hydroboration of styrenes with tridentate ligands, the *ee* was greatly improved by adding a 2-methyl group on the ligand's pyridine moiety. Thus, we also explored ligands **L24** and **L25** (*Entries 5 and 6*). While we observed an improved *ee* as reported, these ligands did not provide satisfactory performances in our transformation.

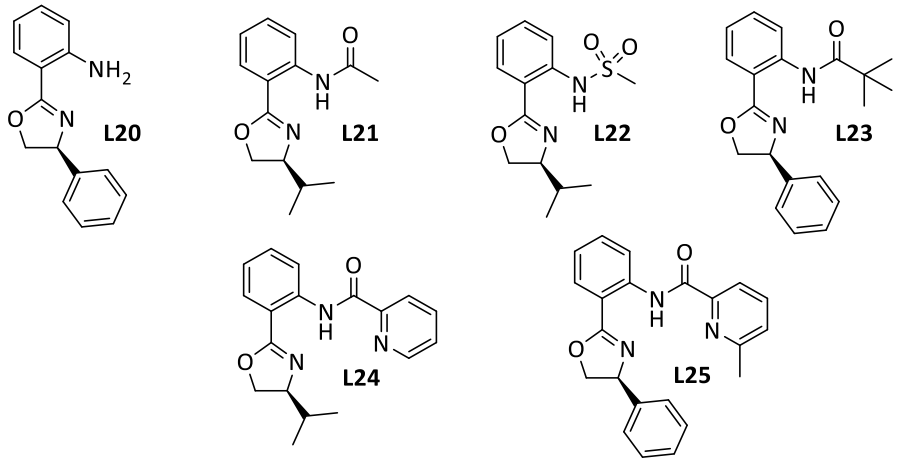
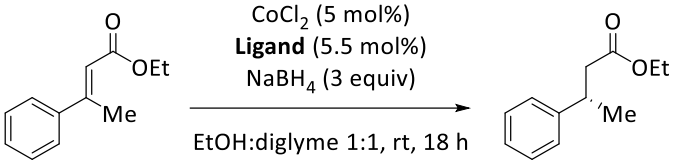


Figure 16: synthetized amidic ligands



Entry	Ligand	Yield (%)	*ee* (%)
1	**L20**	23	4
2	**L21**	>99	20
3	**L22**	73	29
4	**L23**	>99	34
5	**L24**	>99	24
6	**L25**	>99	34

Table 2: Amidic ligands performances

Given the results obtained with the ligand set evaluated, we moved forward to the optimization of other reaction conditions keeping **L13** as the optimal choice of ligand for the catalyst.

2.3 Reaction conditions optimization

2.3.1 Solvent

The effect of the solvent on the reaction yield and *ee* was explored (*Table 3*). While yields obtained in the different solvents were generally comparable, drastic changes in enantioselectivity were observed when changing the solvent's polarity. Although dimethoxyethane (DME) and diglyme present the same relative polarity, these provided very different results, pointing out how polarity is not the only factor involved in the determination of enantioselectivity of the reaction. However, the correlation between relative solvent's polarity and natural logarithm of the corresponding enantiomeric ratio (*er*) resulted in a linear trend (*Figure 17*).[23] In this plot, the reaction $\Delta\Delta G^{\ddagger}$ was employed which was calculated according to the Curtin-Hammett principle (*Eqn 1*, *Eqn 2*). The existence of a correlation between polarity of the solvent and enantioselectivity ($\Delta\Delta G^{\ddagger}$) highlights how solvation is an important factor in the relative stability the transition states leading to the two enantiomeric products.

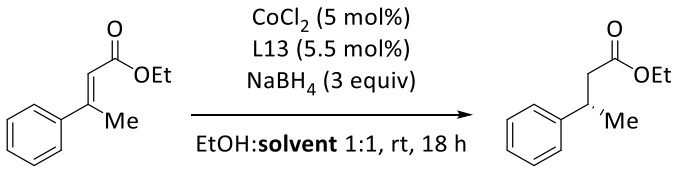
Among the solvents explored, dioxane appeared to be the solvent of choice to maximize the *ee* of the reaction (95% yield, 86% *ee*).

$$er = \frac{[E1]}{[E2]} \approx e^{-\Delta\Delta G^{\ddagger}/RT} \qquad \textit{Eqn 1}$$

$$\ln(er) = \frac{-\Delta\Delta G^{\ddagger}}{RT} \qquad \textit{Eqn 2}$$

The use of EtOH as the alcohol co-solvent was found to be crucial. MeOH and *i*-PrOH were also tested. We observed copious H_2 evolution in the case of MeOH, which eventually resulted in 20% yield of **P1**. In the case of EtOH this side reaction was much suppressed. The difference in this side-reactivity between MeOH and EtOH might be kinetic, as ascribable to the different sizes of the two alcohols. In fact, by employing an even more sterically hindered

alcohol such as *i*-PrOH, no H_2 evolution was observed, even though only 20% of **P1** was detected at the end of the reaction.



Entry	Solvent	Yield (%)	*ee* (%)	Rel. Polarity
1	1,4-Dioxane	95	84	0.164
2	THF	93	68	0.207
3	1,2-Dimethoxyethane	91	38	0.231
4	ACN	73	22	0.46
5	EtOH	90	12	0.654
6	Diglyme	90	76	0.231

Table 3: Effect of the solvent on yield and ee

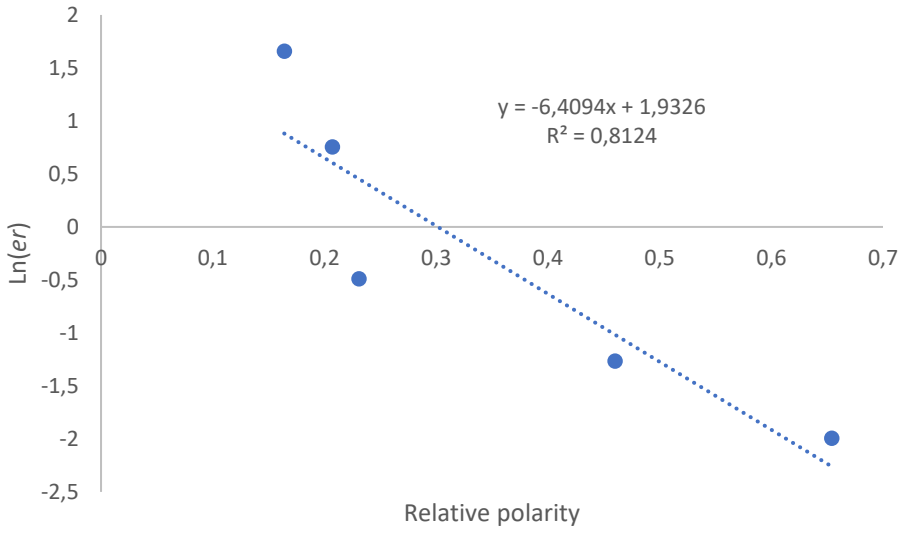


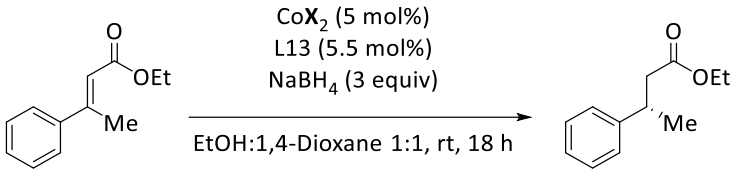
Figure 17: Plot of Ln(er) vs relative polarity of the corresponding solvents

Additional studies of the solvent role in this reaction are in order to understand the factors that influence reactivity and selectivity, and will be explored in the

future. Certainly, based on the information we obtained in this thesis, the solvent has multiple roles than just being a solvating agent or a proton source.

2.3.2 Metal salt

One of the key differences between Co and Cu catalyzed ACRs is the first step of the catalytic cycle. Indeed, using silanes as the hydride source in the case of Cu, a transmetallation step is required which is often rate determining. For this reason, the counter anion of Cu is very important for the reactivity. In our case, the reducing agent is supposed to act as a simple hydride donor, and the Co counter-anion loses importance. Nevertheless, a brief evaluation of different Co sources was carried out (*Table 4*).



Entry	X	Yield (%)	ee (%)
1	OAc	95	76
2	Br	96	84
3	Cl	95	84

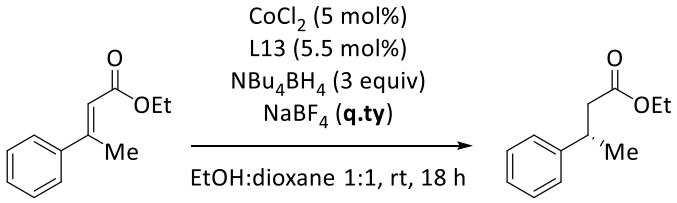
Table 4: Counteranion effect on yield and ee

We observed that $Co(OAc)_2$ afforded a good yield while offering lower enantioselectivity. As expected, $CoBr_2$ and $CoCl_2$ gave nearly identical results (*Entry 2,3*). Thus, $CoCl_2$ was kept as metal salt for further reaction development.

2.3.3 Reducing agent

In doing catalytic reactions in EtOH:1,4-dioxane, solubility of the reagents was generally poor. Particularly, $NaBH_4$ was soluble in the alcoholic fraction but did not dissolve in less polar solvents such as dioxane. Without complete

dissolution of all the reagents, the possibility of having different reaction mechanisms at the interphase or mass transfer effects persist. To gain insights into these factors, we evaluated more soluble reductants that could be suitable hydride donors for the reaction. HBpin was tested together with co-catalytic amounts of a hydride donor such as NaH_2BPin in order to favor the initial formation of the Co-H species. Under these conditions, no product formation was observed. Moving forward, we tested the reactivity of NBu_4BH_4 as the reducing agent. By using a lipophilic organic counter-cation, an homogeneous reaction mixture was obtained, yet no conversion was observed. This led us to hypothesize that the sodium cation had a significant role in some steps of the reaction pathway. To evaluate the role of sodium cation in the reaction, we performed our benchmark reaction with progressive amounts of $NaBF_4$ as an exogenous sodium source while maintaining the amount of NBu_4BH_4 fixed to 3 equivalents (*Table 5*). Interestingly, we observed an enhancement of both the yield and enantioselectivity with increasing sodium concentration until the reference value of *ee* in the standard reaction was eventually almost reached. It should be noted that by adding an equimolar amount of $NaBF_4$ with respect to NBu_4BH_4 the enantioselectivity of the reaction was lower than in the reference case (76% vs. 84% *ee*). Nevertheless, the effect was proven to be linear as shown in the plot of $\Delta\Delta G^{\ddagger}$ against the number of equivalents of $NaBF_4$ added (*Figure 18*).



Entry	q.ty (equiv)	Yield (%)	ee (%)
1	0	traces	2
2	0.3	56	16
3	1	80	30
4	3	93	76

Table 5: Yield and ee trend with increasing amounts of sodium added in solution

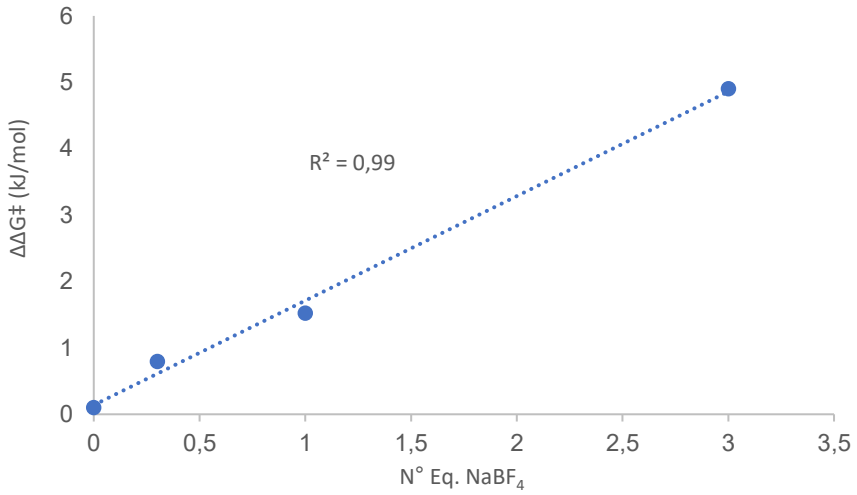
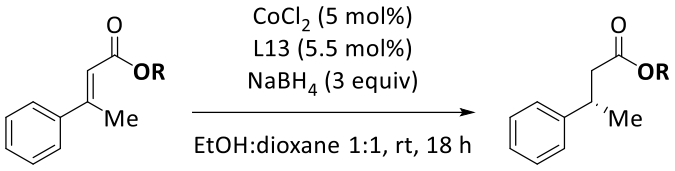


Figure 18: correlation plot between ΔΔG‡ and sodium equivalents added

The plot showed excellent linear correlation (R^2=0.99), suggesting a direct role of sodium in the reaction rate and stereo-determining step(s). Further studies on this line should include a cation scope in order to understand if Lewis acidity is the main factor that influences the transition states stabilization. However, it should be noted that such studies are not supposed to be trivial due to likely competitive 1,2-reduction in the case of more Lewis acidic cations (e.g. Li, Zn). In any case, the experiments we carried out demonstrate that the case reaction where a Co-Salox catalyst is used proceeds with a more complex reaction mechanism than anticipated.

2.3.4 Ester scope

Being enantioselectivity often related to the steric interaction between the catalyst and the substrate, we sought to test different esters for the ACR (*Table 6*). We observed sluggish reactivity with the bulky *t*-butyl ester **P1**^{tBu}. On the other hand, the less hindered methyl ester **P1**^{Me} offered better results also in terms of enantioselectivity, giving 95% yield and 90% *ee* (*Entry 1*). The corresponding benzyl ester was also reduced with high *ee*, but lower yield (*Entry 3*).

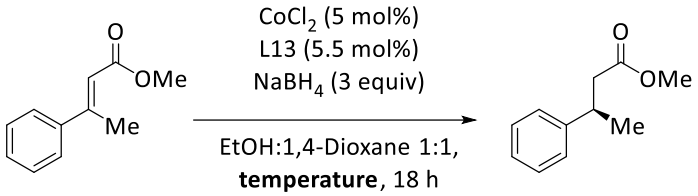


Entry	R	Yield (%)	ee (%)
1	Me	95	90
2	t-Bu	41	/
3	Bn	74	86
4	Et	90	84

Table 6: Influence of ester moiety on yield and ee

2.3.5 Temperature influence

Aiming at improving the reaction performances, temperature's effect was studied (*Table 7*). In particular we monitored the progress of *ee* while diminishing the temperature. The main issue we encountered is the freezing point of the reaction solvent. 1,4-Dioxane has indeed a melting point of around 12 °C, and besides the presence of EtOH, the reaction solvent froze below 0 °C. Thus, in trying to run the reaction at 0 °C and -20 °C we were forced to change the solvent composition. In particular, to avoid freezing of the reaction at 0 °C, the switch from EtOH:1,4-Dioxane 1:1 to EtOH:1,4-Dioxane 2:1 was sufficient (*Entry 2*). However, to maintain the liquid state of the reaction at -20 °C, a solvent mixture THF:EtOH:1,4-Dioxane 2:1:1 (*Entry 3*) was needed. These forced changes in the solvent composition make it hard to take any conclusion about temperature's effect in the reaction. The general lowering of the *ee* with the decrease of temperature might come from an actual temperature effect, from the lower concentration of Dioxane in the reaction solvent, or to lower solubility of the reductant (and therefore sodium) in solution as well.



Entry	Temperature (°C)	Yield (%)	ee (%)
1	40	88	88
2	rt	95	90
3	0[a]	76	82
4	-20[b]	30	58
5	-20[c]	80	62

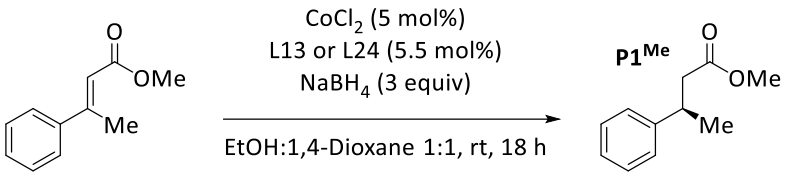
[a]: EtOH:1,4-Dioxane as solvent; [b]: EtOH:1,4-Dioxane:THF 1:1:2 as solvent, [c]: EtOH:THF 1:1 as solvent

Table 7: Temperature influence on yield and ee

To gain additional insights, an independent run was carried out at -20°C in EtOH:THF (*Entry 5*). The reason for the choice of THF in this case is his low melting point and the fact that we had a reference run carried at room temperature. This way we were able to find that by lowering the reaction temperature, a slight decrease of enantioselectivity occurs. Moreover, almost the same results as the run at rt were observed when the reaction was run at 40°C (*Entry 1*). Room temperature thus proved to be the ideal temperature for the reaction performances.

2.3.6 Concentration

To further optimize the reaction conditions, concentration's effect on the outcome of the reaction was explored (*Table 8*). By doubling the concentration from the standard 0.25 M to 0.5 M (*Entry 1*), no appreciable change in the enantioselectivity was found. Surprisingly, running the reaction with half of the concentration (0.13 M) ended in no substantial changes in yield but a drop of the *ee* (*Entry 3*).



Entry	Concentration (M)	Ligand	Yield (%)	ee (%)
1	0.5	**L13**	88	88
2	0.25	**L13**	95	90
3	0.13	**L13**	74	42
4	0.25	**L24**	>99	24
5	0.13	**L24**	>99	16

Table 8: Concentration effect on yield and ee

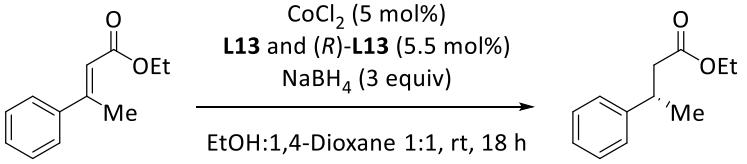
Another concentration study was taken using the tridentate ligand **L24** (*Entry 5*). When the solvent volume was doubled, the enantioselectivity of the reaction was considerably lower on a relative scale.

2.4 Additional mechanistic experiments

The results we obtained from the optimization of the reaction conditions highlighted how the reaction mechanism might be different from expectations (see paragraph 1.3 of the introduction). In particular, the effect of sodium, concentration, temperature, and of the identity of the alcohol co-solvent on the reaction performances suggested that higher order supramolecular species of Co-Salox complexes (aggregates) might be in place. Examples of Co-catalysis affected by the formation of dimeric structures using phenoxyimine ligands (structurally related to Salox) have been reported.[24] To corroborate this hypothesis we ran different experiments that could discern whether the nature of the catalyst is molecular or aggregated.

To gain insight into the structure of the competent catalyst, we explored the metal to ligand ratio. While under standard conditions a 1:1 ratio was employed, we ran a test introducing the catalyst as a preformed complex [Co(**L13**)$_2$]. The reaction gave 95% yield yet only 31% *ee*, indicating that the active Co complex in the stereo-determining step is likely mono-chelated.

Additional evidence was gained by running a Non-Linear Effect experiment (NLE). In asymmetric synthesis, the enantiopurity of the chiral ligands for metals or chiral auxiliaries often influence the enantiopurity of the product in a linear fashion. This might not be true whenever other factors come in play during the reaction, such as catalyst-product inhibition, the presence of supramolecular structures in the stereo determining step, autocatalysis, catalyst dimerization, etc. We performed a NLE experiment by running different reactions where the ligand enantiopurity was changed. The plot of the *ee* of the reaction product **P1** versus the *ee* of the ligand **L13** shall return a linear interpolation whenever none of the above-mentioned phenomenon are in place, or a non-linear correlation in case of the presence of two or more ligands at the stereo-determining step. (*R*)-**L13** was therefore synthetized (see Experimental section) and employed in different ratios with (*S*)-**L13** to variate the catalyst *ee* (*Table 9*). The plot of the *ee* of **P1** versus the catalyst's *ee* showed an unequivocal linear trend (R^2=0.99, *Figure 19*). Based on these results, we concluded that at the stereo-determining step, the catalytically active species only presents one ligand, and that aggregates involving more than one ligands are most likely not present in solution.



Entry	Ligand ee (%)	ee (%)
1	20	22
2	40	32
3	60	50
4	80	67
5	100	80

Table 9: Non linear effect experiment

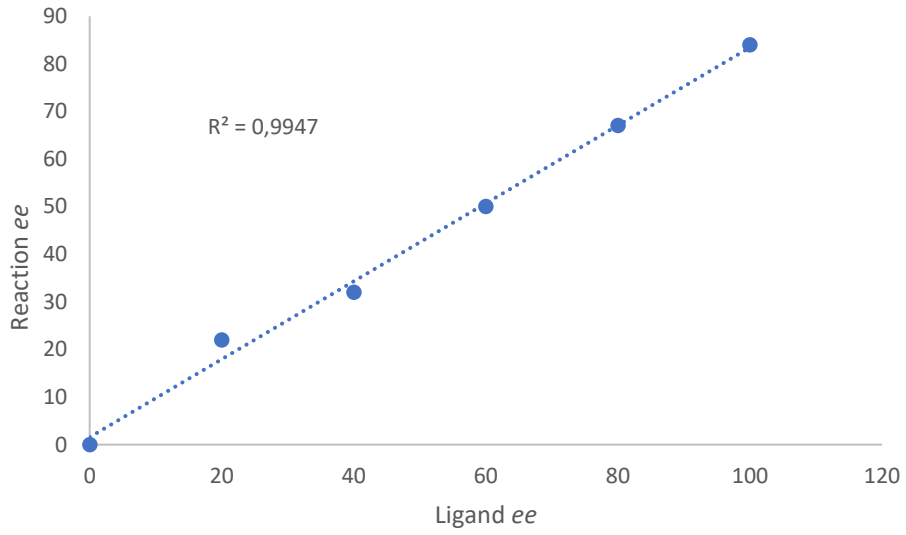


Figure 19: Non linear effect experiment

2.5 Reaction scope

Given the optimized reaction conditions, we moved to explore the reaction scope. The substrates shown in *Figure 20* were synthetized following the procedures described in the experimental part of this work. Generally, good to excellent yields and high enantioselectivity were achieved with *E*-alkenes. On the other hand, significantly lower selectivity was obtained when *Z*-alkenes were employed. Switching from Ethyl to Methyl ester often afforded enhanced yields and *ee* (e.g. **S5** vs **S6**). However, we observed an inverted trend in some cases (e.g. **S12** vs **S14**). Unsurprisingly, the reaction with more electrophilic substrates generally gave enhanced yields, reaching quantitative reactions in some cases (**S14**, **S20**). However, for these substrates, no substantial enhancement of the enantioselectivity was observed. In general, no intuitive trend in enantioselectivity could be deduced from the different performances of the catalytic system in the reaction with *p*-substituted alkenes. It should be noted that bulkier *p*-substituents on the phenyl moiety did not enhance the stereoselectivity. Interestingly, opposite tendencies were observed in the enantioselectivity when **S16** and **S19** were reduced. Indeed,

by enhancing the steric hindrance of the bulky substituent of the alkene (**S16**), about the same yield was given, but a lower *ee* was observed.

The scope was briefly extended to different classes of compounds such as nitriles (**S20**) and amides (**S21**). In the case of **S20**, although we afforded a remarkable quantitative yield, the enantioselectivity for this reaction was not satisfying. The reduction of **S21**, on the other hand, gave the best result among all the other substrates tested.

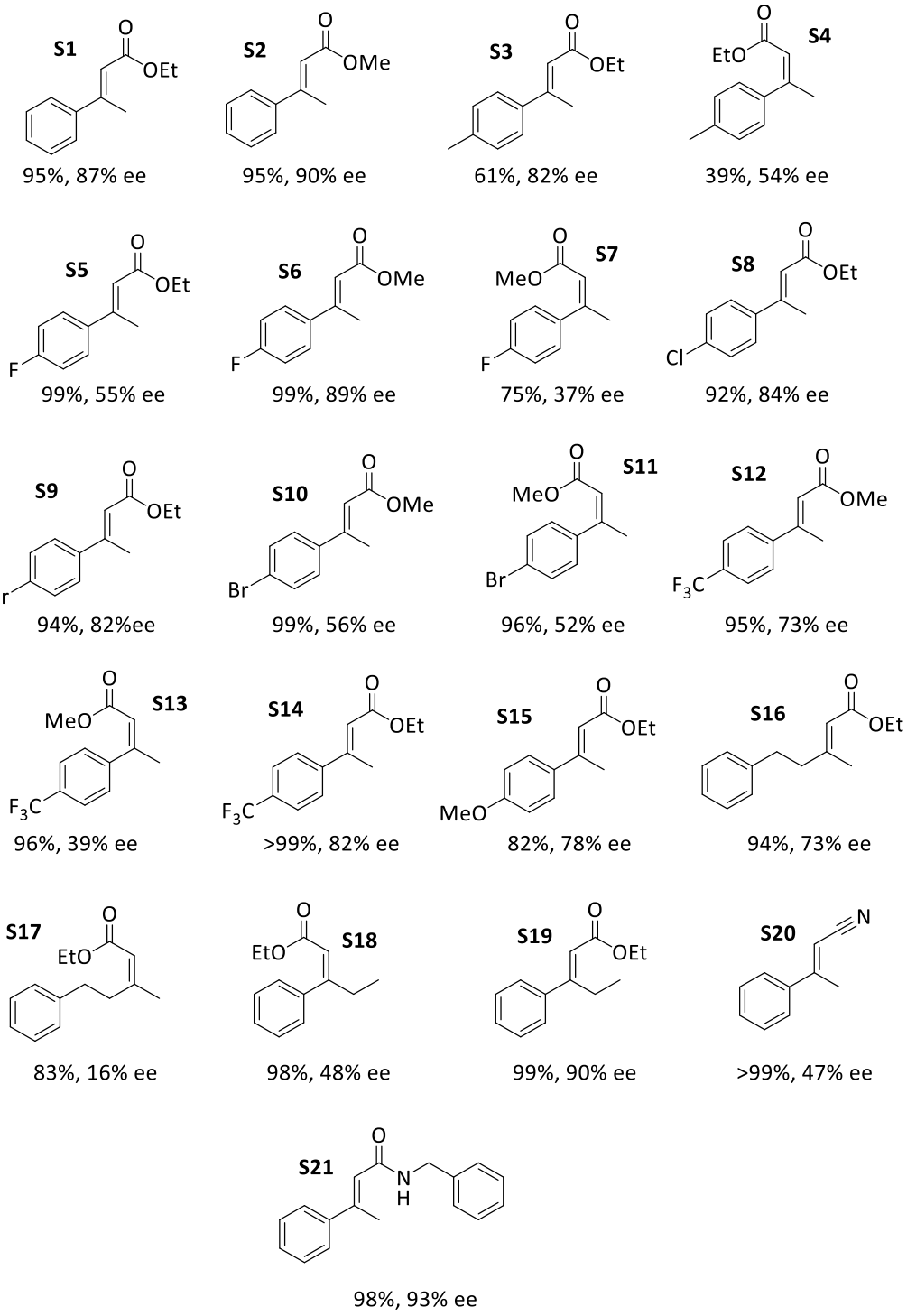


Figure 20: reaction scope

3 Conclusions

A Salox-type ligand was employed for the first time to achieve Co catalyzed ACR of enones in good to excellent yields and good enantioselectivity. Although being less efficient than other reported catalytic systems in some cases, our catalyst is simpler and of easier preparation.

The ACR of enoates, when conducted using Co-Salox complexes, was proven to follow a more complex reaction pathway than we expected. The preliminary mechanistic studies we took outlined the necessity for additional work on the topic in order to understand the importance of many factors that herein we briefly investigated. Future research will include kinetic analysis for the identification of the kinetically competent species in the RDS, and a scope of the counter-cation in the reducing agent that will give information about its role in the stereo determining step.

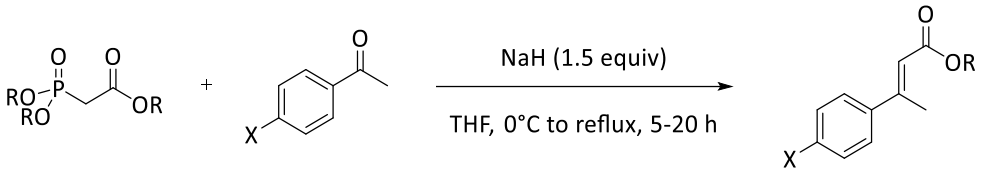
4 Materials and methods

All reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry Nitrogen unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using Merck pre-coated silica gel plates with F254 indicator. Visualization was accomplished by UV light (254 nm), with combination of Potassium Permanganate solution as an indicator. Flash column chromatography was performed using silica gel pore size 60 Å, 230-400 mesh particle size, 40-63 μm particle size or Aluminium oxide 90 active neutral. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted. Commercial grade reagents and solvents were used without further purification. 1H NMR, 13C NMR and 19F spectra were recorded on Bruker Avance300 spectrometer. The proton spectra are reported as follows δ (position of proton, multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (sextet), m (multiplet) and br (broad). Enantiomeric excess was determined on a Shimadzu HPLC SPD-10A with a variable wavelength detector using chiral stationary phase columns (0.46 cm x 25 cm) from Phenomenex or Daicel. Unless otherwise noted, all reagents were obtained commercially and used without further purification. NMR yields were collected using Ethylene carbonate as internal standard.

5 Experimental

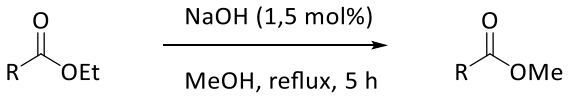
5.1 General procedures

General procedure A



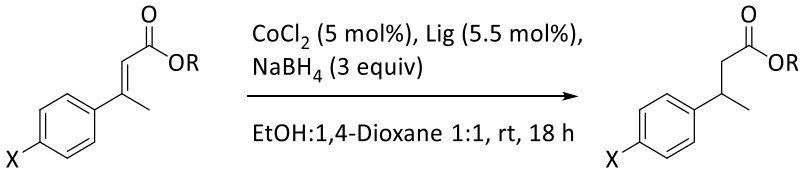
NaH (60 wt% in mineral oil, 1.5 equiv) was introduced in a flask under inert atmosphere, followed by anhydrous THF (0.2 M). The solution was cooled to 0 °C and the corresponding phosphonoacetate (1.5 equiv) was added dropwise. After the bubbling stopped, the solution was left reaching room temperature and then the corresponding ketone (1 equiv) was added dropwise. The solution was brought to reflux and left stirring for 5-20 hours. The reaction was quenched with distilled H_2O and the aqueous layer was extracted three times with EtOAc. The organic phases were collected, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel) to yield the target compound.

General procedure B



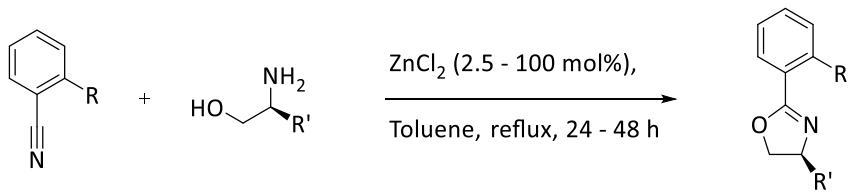
The starting material was introduced in a flask, followed by MeOH (0.4 M) and NaOH (1.5 mol%). The solution was left stirring at reflux for 5 hours and then concentrated in vacuo. Excess distilled water was added to the crude mixture and the aqueous phase was extracted three times with EtOAc. The collected organic fractions were concentrated in vacuo to yield the target compound.

General procedure C



In a vial, the reducing agent (3 equiv) was introduced and suspended in 400 µL of dry 1,4-dioxane. In a second vial, the anhydrous Cobalt salt (Standard solution in EtOH, 5 mol%), the ligand (5.5 mol%) and the starting material were introduced and dissolved in dry EtOH to reach an overall volume of 400 µL. The content of the two vials were merged and the resulting solution was left stirring at room temperature for 18 hours. The solvent was then evaporated with flow of N_2 and 1 M HCl (1 mL) was added to the reaction crude mixture. The resulting aqueous phase was extracted three times with Et_2O and the collected organic phases were filtered over a short plug of silica gel. A known amount of internal standard was then added and the mixture was analyzed via ^{1}H-NMR to determine the reaction yield. The crude reaction mixture was then purified by flash chromatography column (silica gel) to yield the target compound. A chiral HPLC analysis was then carried out for the determination of the reaction *ee*.

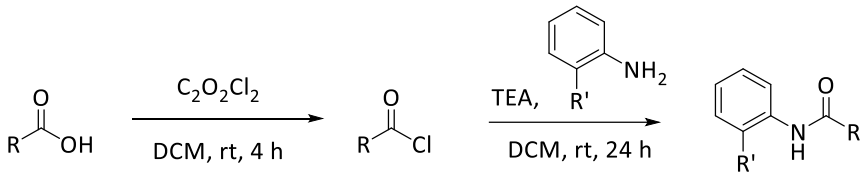
General procedure D



In a flask, the chosen aminoalcohol (1.5 equiv), the corresponding nitrile (1 equiv) and anhydrous $ZnCl_2$ were introduced under inert atmosphere (N_2). Anhydrous Toluene (0.25 M) was added and the solution was left stirring for 24-48 hours. The reaction was quenched with distilled H_2O and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The crude reaction

mixture was purified by flash chromatography column (silica gel) to yield the target compound.

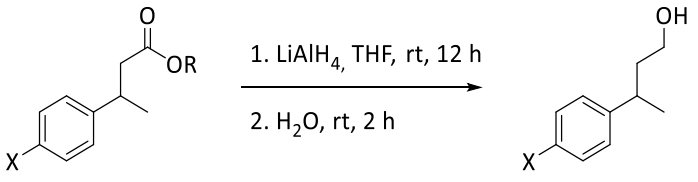
General procedure E



The chosen carboxylic acid (1.5 equiv) was dissolved in DCM (0.25 M) under inert atmosphere (N_2) and $C_2O_2Cl_2$ (3 equiv) was added dropwise. The solution was left stirring for 4 hours at room temperature and the solvent was then stripped under N_2 flow. The crude reaction mixture was used in the next step directly.

The crude mixture was re-dissolved in DCM (0.25 M) and the chosen aniline (1 equiv) was added together with TEA (2.5 equiv). The solution was left stirring for 24 hours and then quenched with distilled H_2O. The aqueous phase was extracted three times with DCM and the combined organic phases were collected, dried over Na_2SO_4, filtered with through cotton and concentrated under vacuum. The crude reaction mixture was purified with flash chromatography column (silica gel) to yield the target compound.

General procedure F

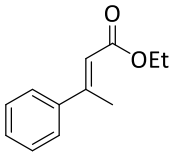


The crude ACR product was dissolved in dry THF (0.25 M) and $LiAlH_4$ (2 M solution in THF, 10 equiv) was added dropwise under magnetic stirring. The solution was left stirring for 12 hours and was then quenched with distilled H_2O. The resulting suspension was left stirring for 2 hours and then

extracted three times with EtOAc. The collected organic fractions were dried over Na_2SO_4, filtered through cotton and concentrated under vacuum. The crude reaction mixture was purified with flash chromatography column (silica gel) to yield the target compound.

5.2 Substrate synthesis and characterization

Ethyl (E)-3-phenylbut-2-enoate



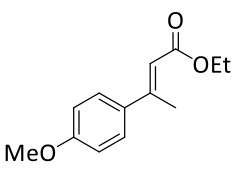
Following **General procedure A**, NaH (60 wt% in mineral oil, 1.912 g, 47.3 mmol, 1.5 equiv), Acetophenone (3.8 mL, 31.5 mmol) and Triethyl Phosphonoacetate (9.5 mL, 47.8 mmol, 1.5 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 5 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc 20:1) afforded the name compound as a colorless oil (4.626 g, 24.3 mmol, 77%).

R_f (Hexane:EtOAc 9:1) = 0.41.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 – 7.31 (m, 5H), 6.13 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 168.34, 156.96, 143.75, 130.44, 129.97, 127.79, 118.71, 61.30, 19.42, 15.83.

Ethyl 3-(4-methoxyphenyl)-2-butenoate



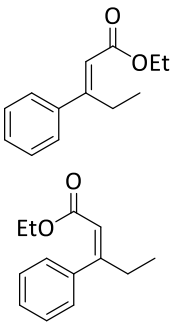
Following **General procedure A**, NaH (60 wt% in mineral oil, 826 mg, 20.7 mmol, 1.5 equiv), Acetanisole (2.126 g, 14.2 mmol) and Triethyl Phosphonoacetate (4.4 mL, 22.2 mmol, 1.6 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 18 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc

20:1) afforded the name compound as a colorless oil (E/Z = 64:36, 2.454 g, 11.1 mmol, 78%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.11 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.56 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 168.56, 161.92, 156.33, 135.86, 129.14, 116.85, 115.32, 61.18, 56.82, 19.14, 15.86.
R_f (Hexane:EtOAc 9:1) = 0.20.

Ethyl 3-phenylpent-2-enoate



Following **General procedure A**, NaH (60 wt% in mineral oil, 647 mg, 16.2 mmol, 1.5 equiv), Ethyl Phenyl Ketone (1.4 mL, 10.5 mmol) and Triethyl Phosphonoacetate (3.2 mL, 16.1 mmol, 1.5 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 16 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc 14:1) afforded the name compound as a colorless oil (E/Z= 56:44, 1.611 g, 7.89 mmol, 75%).

E isomer:

R_f (Hexane:EtOAc 9:1) = 0.44.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.51 – 7.40 (m, 2H), 7.40 – 7.31 (m, 3H), 6.01 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.11 (q, *J* = 7.5 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 167.93, 163.50, 142.66, 130.30, 129.98, 128.18, 118.30, 61.29, 25.82, 15.80, 15.01.

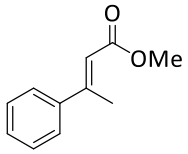
Z isomer:

R_f (Hexane:EtOAc 9:1) = 0.33.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 – 7.27 (m, 3H), 7.21 – 7.10 (m, 2H), 5.88 (s, 1H), 2.54 – 2.39 (m, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 2.47 (q, *J* = 7.4, 1.4 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 167.69, 162.48, 142.00, 129.31, 128.97, 128.50, 117.84, 61.21, 34.85, 15.43, 13.57.

Methyl (E)-3-phenylbut-2-enoate



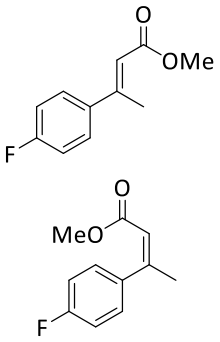
A solution of β-Methyl Cinnamic Acid (0.585 g, 3.6 mmol) in MeOH (0.4 M) was prepared and subsequently, five drops of concentrated H_2SO_4 were added. The solution was left stirring at reflux for 5 h. The solvent was evaporated under vacuum and distilled water was added to the crude reaction mixture. The pH was raised to 7 by adding saturated $NaHCO_3$ solution. The aqueous phase was extracted three times with EtOAc and the combined organic fractions were dried over Na_2SO_4 and filtered through cotton. The solvent was evaporated under vacuum to afford the name compound as a colorless oil (0.628 g, 3.56 mmol, 99%).

R_f (Hexane:EtOAc 9:1) = 0.40.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.54 – 7.42 (m, 2H), 7.42 – 7.29 (m, 3H), 6.14 (s, 1H), 3.75 (s, 3H), 2.58 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 168.74, 157.35, 143.68, 130.51, 130.00, 127.80, 118.21, 52.58, 19.47.

Methyl 3-(4-fluorophenyl)-but-2-enoate



Following **General procedure A**, NaH (60 wt% in mineral oil, 302 mg, 7.5 mmol, 2.1 equiv), p-Fluoroacetophenone (696 mg, 3.6 mmol) and Trimethyl Phosphonoacetate (1.368 g, 7.5 mmol, 2.1 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 5 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc 20:1) afforded the name compound as a colorless oil (E/Z= 79:21, 414 mg, 2.1 mmol, 59%).

E isomer:

R_f (Hexane:EtOAc 9:1) = 0.43.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.52 – 7.38 (m, 2H), 7.12 – 6.98 (m, 2H), 6.09 (s, 1H), 3.75 (s, 3H), 2.56 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 168.60, 166.39, 163.09, 156.06, 139.62, 129.65, 129.54, 118.12, 117.09, 116.80, 52.62, 19.48.

^{19}F NMR (188 MHz, Chloroform-*d*) δ -112.82.

Z isomer:

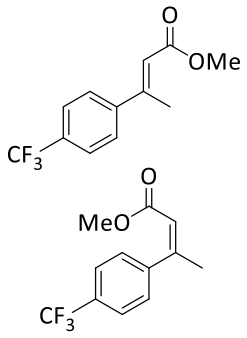
R_f (Hexane:EtOAc 9:1) = 0.35.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.23 – 7.12 (m, 2H), 7.11 – 6.96 (m, 2H), 5.92 (s, 1H), 3.57 (s, 3H), 2.17 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 168.60, 166.39, 163.09, 156.06, 139.62, 129.65, 129.54, 118.12, 117.09, 116.80, 52.62, 19.48.

^{19}F NMR (188 MHz, Chloroform-*d*) δ -114.46.

Methyl 3-(4-(trifluoromethyl)phenyl)-but-2-enoate



Following **General procedure A**, NaH (60 wt% in mineral oil, 300 mg, 7.5 mmol, 1.5 equiv), p-Trifluoromethylacetophenone (948 mg, 5.0 mmol) and Trimethyl Phosphonoacetate (1.375 g, 7.5 mmol, 1.5 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 18 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:OAc 19:1) afforded the name compound as a colorless oil (E/Z= 57:43, 911 mg, 3.7 mmol, 74%).

E isomer:

R_f (Hexane:EtOAc 19:1) = 0.22.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.69 – 7.48 (m, 4H), 6.15 (s, 1H), 3.76 (s, 3H), 2.58 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.78, 154.14, 145.70, 131.06, 130.63, 126.66, 125.75, 125.49 (q, *J* = 3.8 Hz), 122.14, 118.46, 51.26, 17.95.

^{19}F NMR (188 MHz, Chloroform-*d*) δ -63.12.

Z isomer:

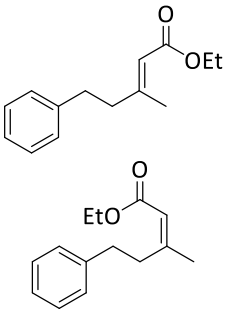
R_f (Hexane:EtOAc 19:1) = 0.15.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.98 (s, 1H), 3.57 (s, 3H), 2.19 (d, *J* = 1.5 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.81, 154.64, 144.55, 129.98, 129.54, 127.18, 125.07, 125.02, 124.97, 124.92, 122.32, 118.17, 51.14, 27.08.

^{19}F NMR (188 MHz, Chloroform-*d*) δ -62.96.

Methy 3-methyl-5-phenylpent-3-enoate



Following **General procedure A**, NaH (60 wt% in mineral oil, 304 mg, 7.6 mmol, 1.5 equiv), Benzylacetone (746 mg, 5 mmol) and Triethyl Phosphonoacetate (1.682 g, 7.5 mmol, 1.5 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 24 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc 14:1) afforded the name compound as a colorless oil (E/Z= 80:20, 454 mg, 2.2 mmol, 44%).

Z isomer:

R_f (Hexane:EtOAc 14:1) = 0.45.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 – 7.11 (m, 5H), 5.69 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.91 (dd, *J* = 10.2, 6.4 Hz, 2H), 2.77 (dd, *J* = 10.3, 6.4 Hz, 2H), 1.87 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.23, 159.48, 141.70, 128.47, 128.34, 125.94, 116.65, 59.51, 35.58, 34.58, 25.49, 14.36.

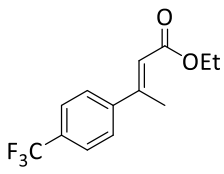
E isomer:

R_f (Hexane:EtOAc 14:1) = 0.38.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.15 (m, 5H), 5.74 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.91 – 2.74 (m, 2H), 2.55 – 2.41 (m, 2H), 2.25 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.77, 158.91, 141.12, 128.48, 128.29, 126.13, 116.03, 59.53, 42.73, 33.97, 18.94, 14.35.

Ethyl (E)-3-(4-(trifluoromethyl)phenyl)but-2-enoate



Following **General procedure A**, NaH (60 wt% in mineral oil, 243 mg, 6 mmol, 1.5 equiv), 1-(4-trifluoromethylphenyl)ethanone (740 mg, 4 mmol) and Triethyl Phosphonoacetate (1.2 mL, 6 mmol, 1.5 equiv) in dry THF (0.20 M). The solution was left stirring at reflux for 4 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc 19:1) afforded the name compound as a colorless oil (646 mg, 2.5 mmol, 63%).

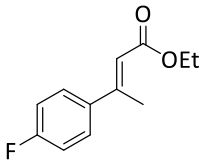
R_f (Hexane:EtOAc 19:1) = 0.25

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 6.15 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 167.89, 155.22, 147.30, 128.15, 127.05, 127.00, 126.94, 126.89, 120.47, 61.58, 19.44, 15.78.

^{19}F NMR (188 MHz, Chloroform-*d*) δ -63.10.

Ethyl (E)-3-(4-fluorophenyl)but-2-enoate



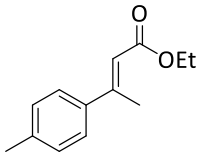
Following **General procedure A**, NaH (60 wt% in mineral oil, 300 mg, 7.5 mmol, 1.5 equiv), p-Fluoroacetophenone (690 mg, 5.0 mmol) and Triethyl Phosphonoacetate (1.359 g, 7.5 mmol, 1.5 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 18 h under inert atmosphere. The purification by flash chromatography column (Silica gel, Hexane:Ethyl Acetate 9:1) afforded the name compound as a colorless oil (E/Z = 64:36, g, 3.9 mmol, 78%).

R_f (Hexane:EtOAc 9:1) = 0.39.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 – 7.36 (m, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 6.08 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 168.19, 166.35, 163.05, 155.66, 139.74, 129.63, 129.52, 118.61, 117.05, 116.76, 61.36, 31.80, 19.42, 15.80.
^{19}F NMR (188 MHz, Chloroform-*d*) δ -112.96.

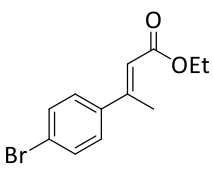
Ethyl 3-p-tolylbut-2-enoate



Following **General procedure A**, NaH (60 wt% in mineral oil, 244 mg, 6 mmol, 1.5 equiv), p-Methylacetophenone (540 µL, 4 mmol) and Triethyl Phosphonoacetate (1.2 mL, 6 mmol, 1.5 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 18 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc 24:1) afforded the name compound as a colorless oil (E/Z = 64:36, 598 mg, 2.93 mmol, 73%).

R_f (Hexane:EtOAc 24:1) = 0.26.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.13 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 2.37 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 167.01, 155.41, 139.26, 139.13, 129.19, 126.22, 116.30, 59.77, 21.18, 17.81, 14.36.

Ethyl (E)-3-(4-bromophenyl)but-2-enoate



Following **General procedure A**, NaH (60 wt% in mineral oil, 245 mg, 6 mmol, 1.5 equiv), p-Bromoacetophenone (798 mg, 4 mmol) and Triethyl Phosphonoacetate (1.2 mL, 6 mmol, 1.5 equiv) in dry THF (0.20 M). The solution was left stirring at reflux for 4 h under inert

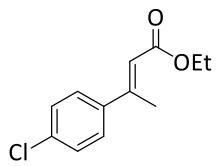
atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc 19:1) afforded the name compound as a colorless oil (711 mg, 2.65 mmol, 66%).

R_f (Hexane:Ethyl Acetate 19:1) = 0.27.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 6.11 (s, 0H), 4.21 (q, *J* = 7.1 Hz, 1H), 2.54 (s, 1H), 1.31 (t, *J* = 7.1 Hz, 2H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 168.08, 155.51, 142.56, 133.14, 129.38, 124.69, 119.10, 61.44, 19.25, 15.81.

Ethyl (E)-3-(4-chlorophenyl)but-2-enoate



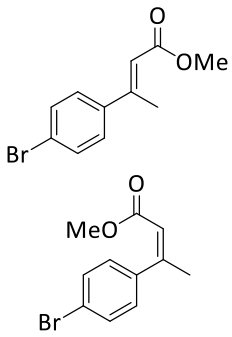
Following **General procedure A**, NaH (60 wt% in mineral oil, 606 mg, 15 mmol, 1.5 equiv), p-Chloroacetophenone (1.543 g, 10 mmol) and Triethyl Phosphonoacetate (3.205 g, 1.7 mmol, 1.7 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 5 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc 19:1) afforded the name compound as a white solid (1.307 g, 7.2 mmol, 72%).

R_f (Hexane:EtOAc 19:1) = 0.27.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.46 – 7.25 (m, 4H), 6.09 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.53 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.58, 153.96, 140.54, 134.96, 128.67, 127.59, 117.53, 59.93, 17.76, 14.32.

Methyl 3-(4-bromophenyl)but-2-enoate



Following **General procedure A**, NaH (60 wt% in mineral oil, 302 mg, 7.5 mmol, 1.5 equiv), p-Bromocetophenone (998 mg, 5.0 mmol) and Trimethyl Phosphonoacetate (1.367 g, 7.5 mmol, 1.5 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 6 h under inert atmosphere. The purification by flash chromatography column (silica gel, Hexane:EtOAc 14:1) afforded the name compound as a white solid (E/Z= 81:19, 891 mg, 3.5 mmol, 70%).

***Z isomer*:**

R_f (Hexane:EtOAc 14:1) = 0.19.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 – 7.41 (m, 2H), 7.14 – 7.01 (m, 2H), 5.93 (s, 1H), 3.57 (s, 3H), 2.16 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.01, 154.71, 139.49, 131.14, 128.61, 121.94, 117.67, 51.11, 27.07.

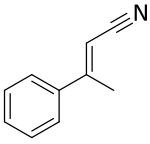
***E isomer*:**

R_f (Hexane:EtOAc 14:1) = 0.29.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.51 – 7.40 (m, 2H), 7.34 – 7.24 (m, 2H), 6.08 (s, 1H), 3.72 (s, 3H), 2.52 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.91, 154.35, 140.89, 131.66, 127.87, 123.29, 117.06, 51.16, 17.74.

(E)-3-phenyl-2-butenenitrile



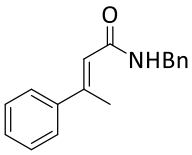
Following **General procedure A**, NaH (60 wt% in mineral oil, 299 mg, 7.5 mmol, 1.5 equiv), Acetophenone (595 mg, 5.0 mmol) and Diethyl cyanomethylphosphonate (1.331 g, 7.5

mmol, 1.5 equiv) in dry THF (0.25 M). The solution was left stirring at reflux for 10 h under inert atmosphere. The purification by flash chromatography column (silica gel, Pentane:Et_2O 50:1) afforded the name compound as a colorless oil (603 mg, 4.2 mmol, 84%).

R_f (Pentane:Et_2O 50:1) = 0.26.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 – 7.29 (m, 5H), 5.62 (q, *J* = 1.1 Hz, 1H), 2.47 (d, *J* = 1.1 Hz, 3H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 159.78, 138.24, 130.27, 128.84, 125.87, 117.63, 95.56, 20.20.

(E)-N-benzyl-3-phenylbut-2-enamide



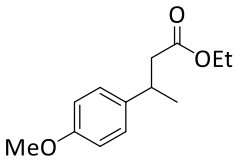
β-methyl cinnamic acid (302 mg, 1.85 mmol), EDC hydrochloride (394 mg, 2.0 mmol, 1.1 equiv) and HBTU (770 mg, 2.0 mmol, 1.1 equiv) were dissolved in DCM (0.2 M) and the solution was left stirring for 15 min. Then, TEA (390 µL, 2.8 mmol, 1.5 equiv) and Benzylamine (320 µL, 2.8 mmol, 1.5 equiv) were added and the solution was left stirring at room temperature for 15 h. The reaction was then quenched with 1 M HCl, and the organic fraction was dried over Na_2SO_4, filtered through cotton, and concentrated in vacuo. Purification by flash chromatography column (silica gel, Hexane:EtOAc:DCM 3:1:1) afforded the name compound as an orange oil.
R_f (Hexane:EtOAc:DCM 3:1:1) = 0.30.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 – 7.23 (m, 10H), 6.14 – 5.94 (m, 2H), 4.52 (d, *J* = 4.8 Hz, 2H), 2.58 (d, *J* = 1.2 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.72, 151.39, 142.69, 138.45, 128.73, 128.55, 128.47, 127.90, 127.50, 126.17, 119.65, 43.52, 17.74.

5.3 Products synthesis and characterization

Ethyl 3-(4-methoxyphenyl)butanoate



Following **General procedure C**, $NaBH_4$ (23.26 mg, 0.61 mmol, 3.6 equiv), Ethyl 3-(4-methoxyphenyl)-2-butenoate (37.84 mg, 0.17 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 6 mol%), **L13** (2.44 mg, 12 μmol, 7 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 49:1, then 19:1) afforded the name compound as a colorless oil.

NMR yield = 82%.

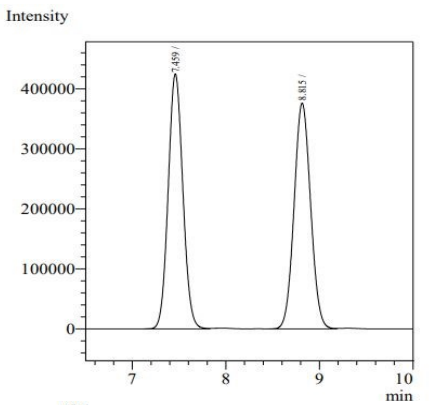
ee = 77%.

R_f (Hexane:EtOAc 9:1) = 0.39.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.14 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.23 (h, *J* = 7.2 Hz, 1H), 2.54 (t, *J* = 7.4 Hz, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

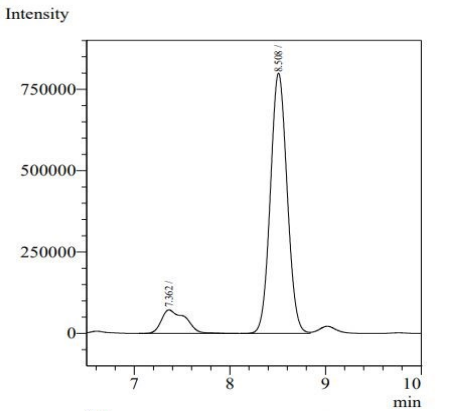
^{13}C NMR (75 MHz, Chloroform-*d*) δ 173.93, 159.57, 139.37, 129.15, 115.33, 61.69, 56.71, 44.75, 37.22, 23.45, 15.67.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 99:1, 0.5 mL/Min, 214 nm) t_R: 7.36 Min; 8.51 Min (maj).



AD1

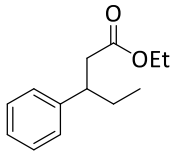
Peak#	Ret.Time	Area	Height	Conc.
1	7.459	4624469	425037	50.005
2	8.815	4623468	376330	49.995
Total		9247937	801367	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	7.362	1261731	72226	11.468
2	8.508	9740002	800514	88.532
Total		11001733	872740	

Ethyl 3-phenylpentanoate



Following **General procedure C**, $NaBH_4$ (22.70 mg, 0.60 mmol, 3 equiv), Ethyl (E)-3-phenylpent-2-enoate (40.40 mg, 0.20 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.26 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 49:1) afforded the name compound as a colorless oil.

NMR yield = 99%.

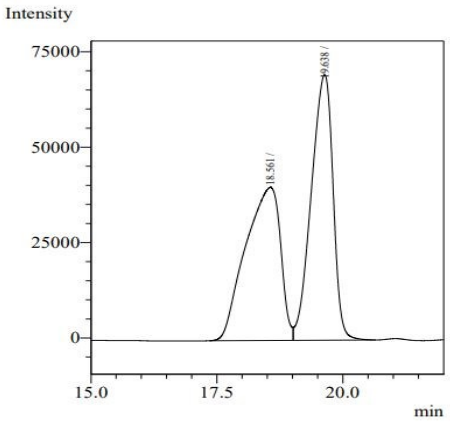
ee = 90%.

R_f (Hexane:EtOAc 49:1) = 0.17.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.35 – 7.11 (m, 5H), 1.81 – 1.51 (m, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.01 (p, *J* = 8.2 Hz, 1H), 2.60 (ddd, 2H), 1.66 (dddd, *J* = 28.0, 16.2, 13.9, 7.4 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H).

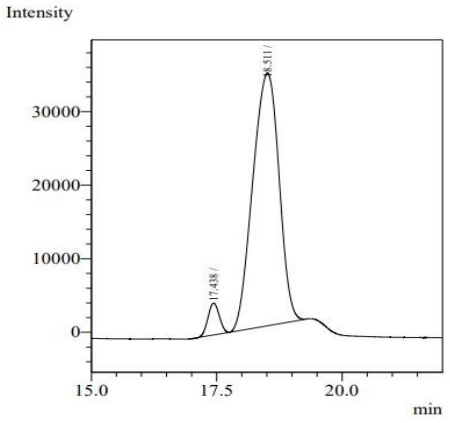
^{13}C NMR (75 MHz, Chloroform-*d*) δ 173.97, 145.41, 129.81, 129.03, 127.86, 61.65, 45.45, 43.00, 30.62, 15.60, 13.39.

HPLC (Lux Cellulose 5, Hexane:*i*-PrOH 999:1, 1.0 mL/Min, 214 nm) t_R: 17.44 Min; 18.51 Min (maj).



AD1

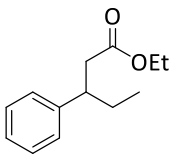
Peak#	Ret.Time	Area	Height	Conc.
1	18.561	1946323	40092	48.218
2	19.638	2090218	69650	51.782
Total		4036541	109742	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	17.438	67401	4341	5.107
2	18.511	1252325	34303	94.893
Total		1319727	38644	

Ethyl 3-phenylpentanoate



Following **General procedure C**, $NaBH_4$ (22.92 mg, 0.60 mmol, 3 equiv), Ethyl (Z)-3-phenylpent-2-enoate (44.80 mg, 0.22 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.26 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:Et_2O 49:1) afforded the name compound as a colorless oil.

NMR yield = 98%.

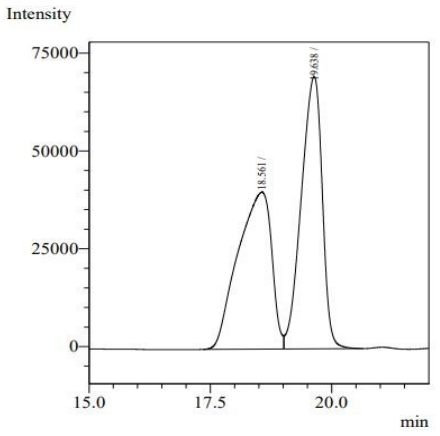
ee = 48%.

R_f (Hexane:EtOAc 49:1) = 0.17.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.35 – 7.11 (m, 5H), 1.81 – 1.51 (m, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.01 (p, *J* = 8.2 Hz, 1H), 2.60 (ddd, 2H), 1.66 (dddd, *J* = 28.0, 16.2, 13.9, 7.4 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H).

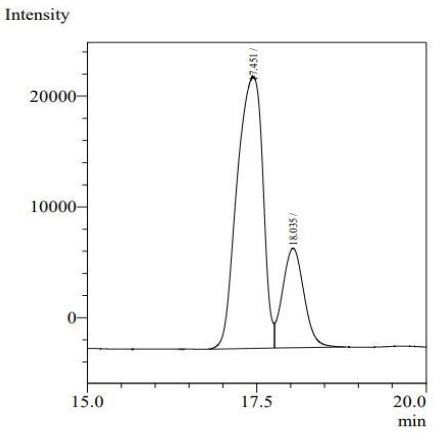
^{13}C NMR (75 MHz, Chloroform-*d*) δ 173.97, 145.41, 129.81, 129.03, 127.86, 61.65, 45.45, 43.00, 30.62, 15.60, 13.39.

HPLC (Lux Cellulose 5, Hexane:*i*-PrOH 999:1, 1.0 mL/Min, 214 nm) t_R: 17.45 Min (maj); 18.04 Min.



AD1

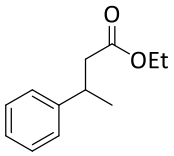
Peak#	Ret.Time	Area	Height	Conc.
1	18.561	1946323	40092	48.218
2	19.638	2090218	69650	51.782
Total		4036541	109742	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	17.451	650656	24532	76.686
2	18.035	197808	8993	23.314
Total		848464	33525	

Ethyl 3-phenylbutanoate



Following **General procedure C**, $NaBH_4$ (22.73 mg, 0.60 mmol, 2.6 equiv), Ethyl (E)-3-phenylbut-2-enoate (43.05 mg, 0.23 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 4 mol%), **L13** (2.26 mg, 11 μmol, 5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 19:1) afforded the name compound as a colorless oil.

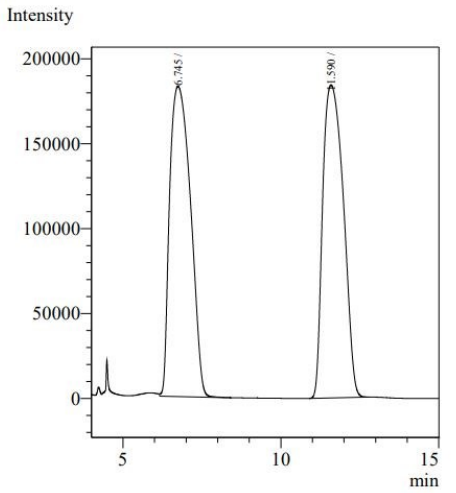
NMR yield = 95%.

ee = 87%.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.37 – 7.15 (m, 5H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.28 (h, *J* = 7.2 Hz, 1H), 2.58 (ddd, 2H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

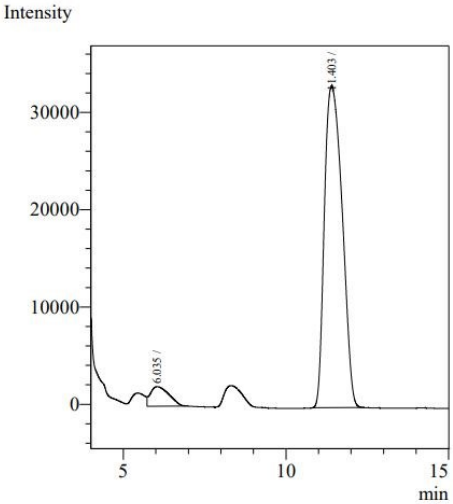
^{13}C NMR (75 MHz, Chloroform-*d*) δ 173.87, 147.25, 129.95, 128.25, 127.85, 61.73, 44.49, 38.01, 23.28, 15.65.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 99:1, 0.9 mL/Min, 214 nm) t_R: 6.04 Min; 11.40 Min (maj).



AD1

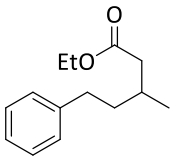
Peak#	Ret.Time	Area	Height	Conc.
1	6.745	8390063	182747	50.005
2	11.590	8388292	184247	49.995
Total		16778355	366994	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	6.035	78975	2002	5.920
2	11.403	1255092	33041	94.080
Total		1334067	35043	

Methy 3-methyl-5-phenylpent-3-anoate



Following **General procedure C**, $NaBH_4$ (23.96 mg, 0.63 mmol, 3.3 equiv), Methy (Z)-3-methyl-5-phenylpent-3-enoate (41.51 mg, 0.19 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.22 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 19:1) afforded the name compound as a colorless oil.

NMR yield = 83%.

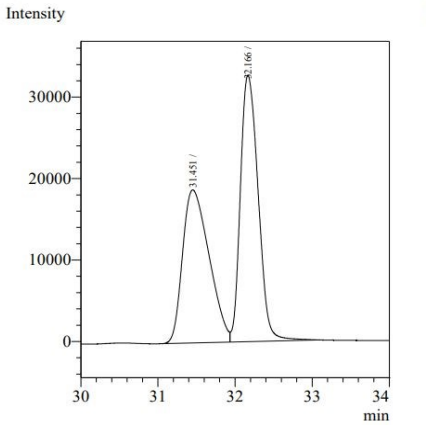
ee = 16%.

R_f (Hexane:EtOAc 19:1) = 0.35.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 – 7.23 (m, 2H), 7.23 – 7.13 (m, 3H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.63 (dtd, *J* = 16.3, 13.7, 7.2 Hz, 2H), 2.36 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.18 (dd, *J* = 14.6, 7.9 Hz, 1H), 2.02 (oct, *J* = 13.5, 6.7 Hz, 1H), 1.78 – 1.42 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H).

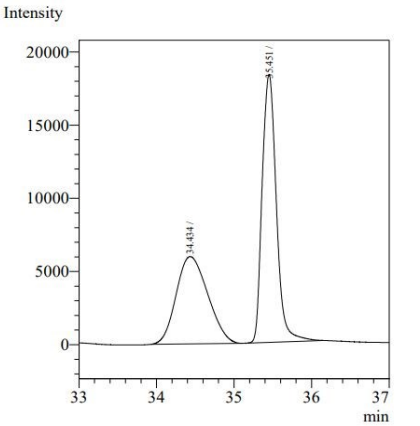
^{13}C NMR (75 MHz, Chloroform-*d*) δ 174.56, 143.90, 129.83, 129.80, 127.22, 61.62, 43.28, 40.03, 34.81, 31.63, 21.13, 15.76.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 999:1, 0.5 mL/Min, 260 nm) t_R: 34.43 Min; 35.45 Min (maj).



AD1

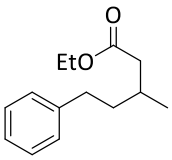
Peak#	Ret.Time	Area	Height	Conc.
1	31.451	448504	18793	46.118
2	32.166	524005	32706	53.882
Total		972510	51499	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	34.434	168774	5967	42.085
2	35.451	232253	18311	57.915
Total		401027	24278	

Methy 3-methyl-5-phenylpent-3-anoate



Following **General procedure C**, $NaBH_4$ (22.88 mg, 0.60 mmol, 3 equiv), Methy (E)-3-methyl-5-phenylpent-3-enoate (41.06 mg, 0.19mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.39 mg, 12 μmol, 6 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 19:1) afforded the name compound as a colorless oil.

NMR yield = 94%.

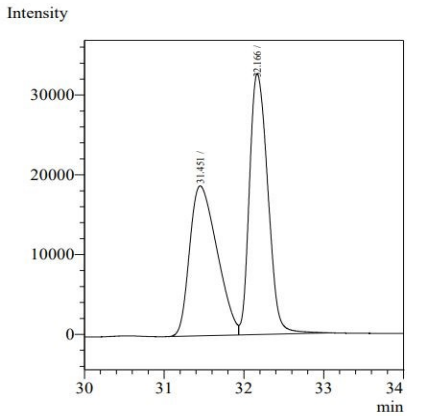
ee = 73%.

R_f (Hexane:EtOAc 19:1) = 0.35.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 – 7.23 (m, 2H), 7.23 – 7.13 (m, 3H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.63 (dtd, *J* = 16.3, 13.7, 7.2 Hz, 2H), 2.36 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.18 (dd, *J* = 14.6, 7.9 Hz, 1H), 2.02 (oct, *J* = 13.5, 6.7 Hz, 1H), 1.78 – 1.42 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H).

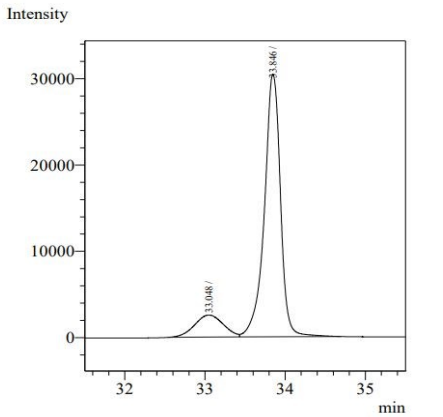
^{13}C NMR (75 MHz, Chloroform-*d*) δ 174.56, 143.90, 129.83, 129.80, 127.22, 61.62, 43.28, 40.03, 34.81, 31.63, 21.13, 15.76.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 999:1, 0.5 mL/Min, 260 nm) t_R: 33.05 Min; 33.85 Min (maj).



AD1

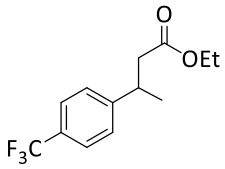
Peak#	Ret.Time	Area	Height	Conc.
1	31.451	448504	18793	46.118
2	32.166	524005	32706	53.882
Total		972510	51499	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	33.048	63537	2555	13.010
2	33.846	424828	30419	86.990
Total		488365	32974	

Ethyl 3-(4-trifluoromethylphenyl)butanoate



Following **General procedure C**, $NaBH_4$ (22.66 mg, 0.60 mmol, 3 equiv), Ethyl (E)-3-(4-(trifluoromethyl)phenyl)but-2-enoate (45.07 mg, 0.17 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 6 mol%), **L13** (2.29 mg, 11 μmol, 7 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 24:1) afforded the name compound as a colorless oil.

NMR yield = >99%.

ee = 82%.

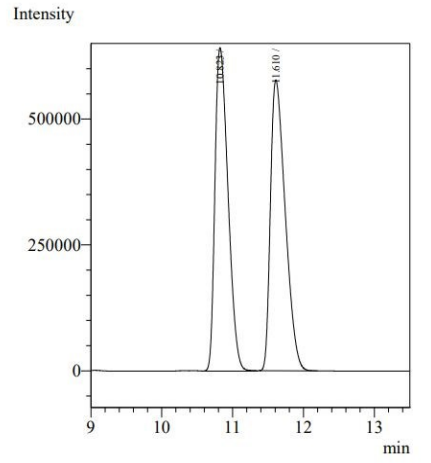
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.35 (h, *J* = 7.2 Hz, 1H), 2.58 (ddd, 4H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 173.38, 151.25, 128.66, 126.95, 126.90, 61.90, 44.05, 37.86, 23.19, 15.60.

^{19}F NMR (188 MHz, Chloroform-*d*) δ -62.78.

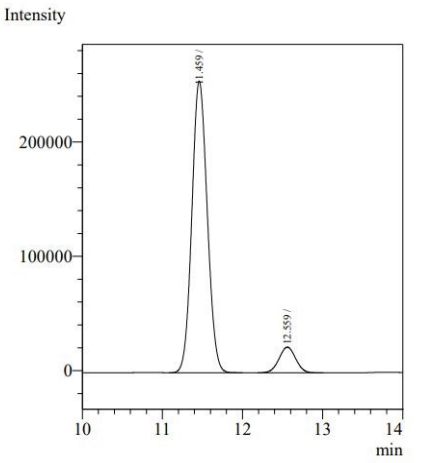
R_f (Hexane:EtOAc 4:1) = 0.38.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 999:1, 1.0 mL/Min, 214 nm) t_R: 33.05 Min; 33.85 Min (maj).



AD1

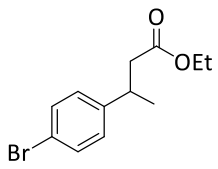
Peak#	Ret.Time	Area	Height	Conc.
1	10.823	8233782	642388	49.599
2	11.610	8366855	577367	50.401
Total		16600636	1219755	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	11.459	3405319	255209	91.317
2	12.559	323817	22432	8.683
Total		3729136	277641	

Ethyl 3-(4-bromophenyl)butanoate



Following **General procedure C**, $NaBH_4$ (22.73 mg, 0.60 mmol, 3 equiv), Ethyl (E)-3-(4-bromophenyl)but-2-enoate (51.30 mg, 0.19 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.17 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 24:1) afforded the name compound as a colorless oil.

NMR yield = 94%.

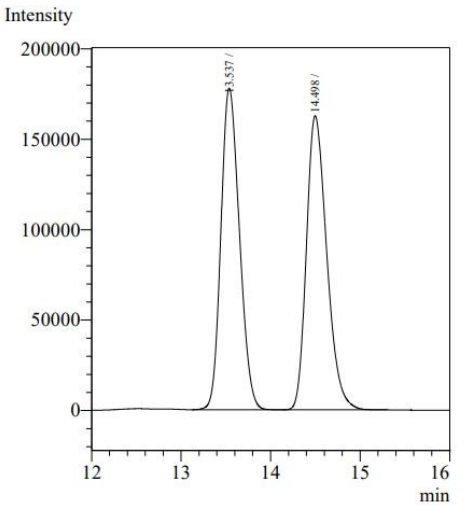
ee = 82%.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.46 – 7.36 (m, 2H), 7.15 – 7.04 (m, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.24 (h, *J* = 7.2 Hz, 1H), 2.63 – 2.44 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

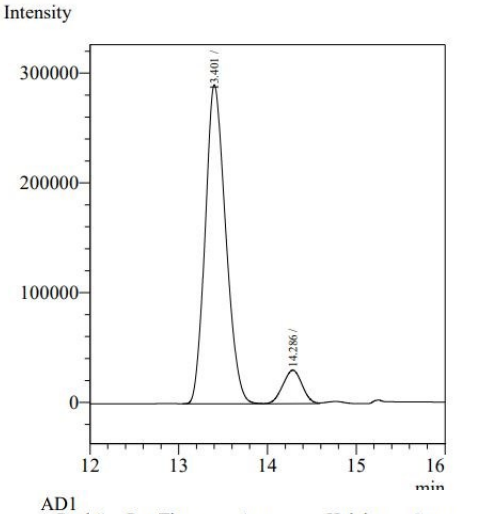
^{13}C NMR (75 MHz, Chloroform-*d*) δ 172.06, 144.70, 131.53, 128.58, 120.06, 60.36, 42.75, 36.01, 21.77, 14.16.

R_f (Hexane:EtOAc 4:1) = 0.43.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 999:1, 1.0 mL/Min, 214 nm) t_R: 13.40 Min (maj); 14.29 Min.



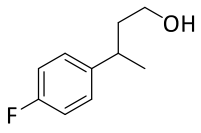
Peak#	Ret.Time	Area	Height	Conc.
1	13.537	2559404	177816	49.896
2	14.498	2570096	162592	50.104
Total		5129500	340409	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	13.401	4672148	290645	91.024
2	14.286	460729	30561	8.976
Total		5132876	321206	

Methyl 3-(4-fluoromethylphenyl)butanoate



Following **General procedure C**, $NaBH_4$ (22.73 mg, 0.60 mmol, 3 equiv), Ethyl (E)-3-(4-Fluorophenyl)but-2-enoate (51.30 mg, 0.19 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.17 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The crude reaction mixture was purified by flash chromatography column (silica gel, Hexane:EtOAc 29:1). Then, following **General procedure F**, $LiAlH_4$ (2 M solution in THF, 1 mL, 2.0 mmol, 10 equiv) in dry THF (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 2:1) afforded the name compound as a colorless oil.

NMR yield = 99%.

ee = 55%.

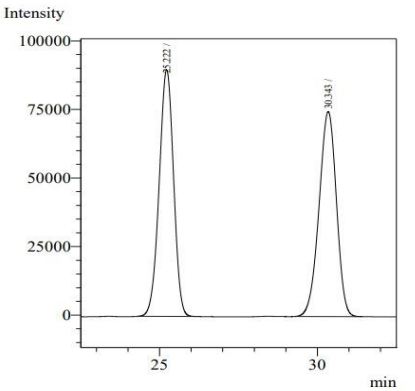
R$_f$ (Hexane:EtOAc 2:1) = 0.29.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.20 – 7.09 (m, 2H), 7.04 – 6.91 (m, 2H), 3.65 – 3.43 (m, 2H), 2.89 (h, *J* = 8.3 Hz, 1H), 1.94 – 1.70 (m, 2H), 1.43 (s, 1H), 1.25 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.90, 159.67, 142.45, 128.31, 115.31, 115.04, 61.03, 41.05, 35.66, 22.51.

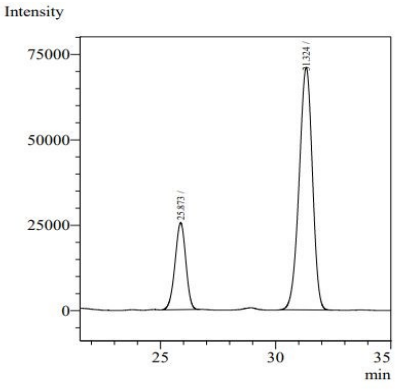
^{19}F NMR (188 MHz, Chloroform-*d*) δ -117.78.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 98:2, 1.0 mL/Min, 214 nm) t_R: 25.87 Min; 31.32 Min (maj).



AD1

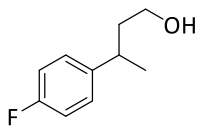
Peak#	Ret.Time	Area	Height	Conc.
1	25.222	2853303	89941	49.967
2	30.343	2857045	74755	50.033
Total		5710348	164697	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	25.873	825664	25415	22.501
2	31.324	2843718	70984	77.499
Total		3669383	96399	

Methyl 3-(4-fluoromethylphenyl)butanoate



Following **General procedure C**, $NaBH_4$ (22.73 mg, 0.60 mmol, 3 equiv), Methyl (Z)-3-(4-Fluorophenyl)but-2-enoate (51.30 mg, 0.19 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.17 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The crude reaction mixture was purified by flash chromatography column (silica gel, Hexane:EtOAc 29:1). Then, following **General procedure F**, $LiAlH_4$ (2 M solution in THF, 1 mL, 2.0 mmol, 10 equiv) in dry THF (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 2:1) afforded the name compound as a colorless oil.

NMR yield = 75%.

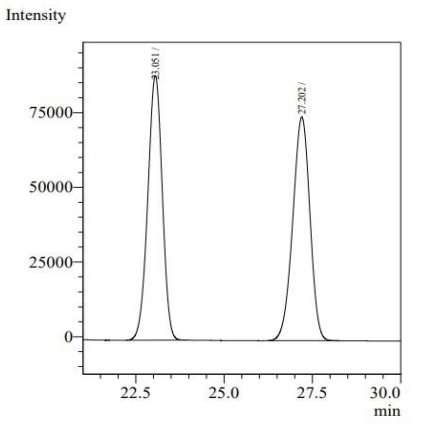
ee = 37%.

R_f (Hexane:EtOAc 2:1) = 0.29.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.20 – 7.09 (m, 2H), 7.04 – 6.91 (m, 2H), 3.65 – 3.43 (m, 2H), 2.89 (h, *J* = 8.3 Hz, 1H), 1.94 – 1.70 (m, 2H), 1.43 (s, 1H), 1.25 (d, *J* = 7.0 Hz, 3H).

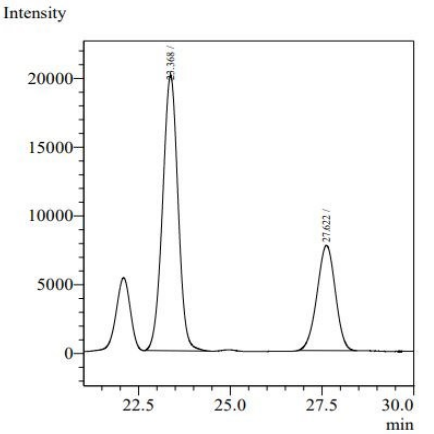
^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.90, 159.67, 142.45, 128.31, 115.31, 115.04, 61.03, 41.05, 35.66, 22.51.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 98:2, 1.0 mL/Min, 214 nm) t_R: 23.37 Min (maj); 27.62 Min.



AD1

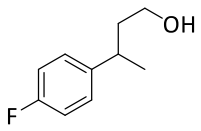
Peak#	Ret.Time	Area	Height	Conc.
1	23.051	2526481	88552	49.892
2	27.202	2537409	74895	50.108
Total		5063889	163448	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	23.368	585071	20000	68.858
2	27.622	264612	7643	31.142
Total		849683	27642	

Methyl 3-(4-fluoromethylphenyl)butanoate



Following **General procedure C**, $NaBH_4$ (22.73 mg, 0.60 mmol, 3 equiv), Methyl (E)-3-(4-Fluorophenyl)but-2-enoate (51.30 mg, 0.19 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.17 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The crude reaction mixture was purified by flash chromatography column (silica gel, Hexane:EtOAc 29:1). Then, following **General procedure F**, $LiAlH_4$ (2 M solution in THF, 1 mL, 2.0 mmol, 10 equiv) in dry THF (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 2:1) afforded the name compound as a colorless oil.

NMR yield = 99%.

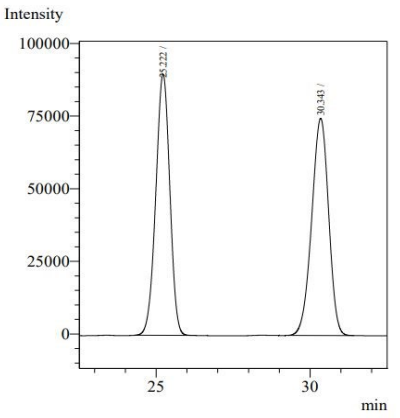
ee = 89%.

R$_f$ (Hexane:EtOAc 2:1) = 0.29.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.20 – 7.09 (m, 2H), 7.04 – 6.91 (m, 2H), 3.65 – 3.43 (m, 2H), 2.89 (h, *J* = 8.3 Hz, 1H), 1.94 – 1.70 (m, 2H), 1.43 (s, 1H), 1.25 (d, *J* = 7.0 Hz, 3H).

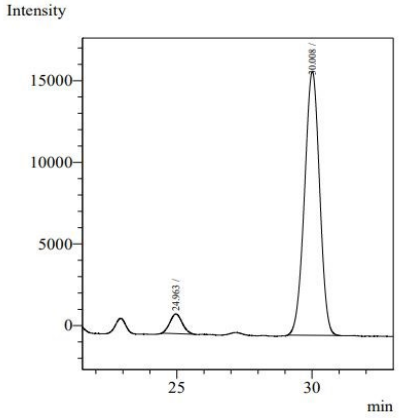
^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.90, 159.67, 142.45, 128.31, 115.31, 115.04, 61.03, 41.05, 35.66, 22.51.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 98:2, 1.0 mL/Min, 214 nm) t_R: 24.96 Min; 30.01 Min (maj).



AD1

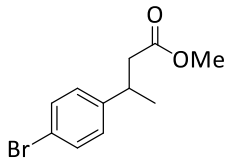
Peak#	Ret.Time	Area	Height	Conc.
1	25.222	2853303	89941	49.967
2	30.343	2857045	74755	50.033
Total		5710348	164697	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	24.963	38512	1211	5.790
2	30.008	626589	16161	94.210
Total		665101	17371	

Methyl 3-(4-bromophenyl)butanoate

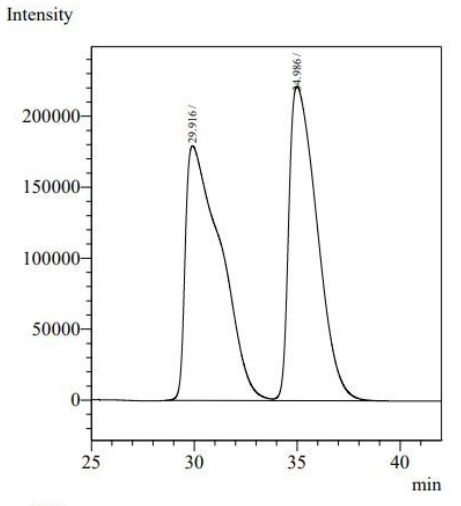


Following **General procedure C**, $NaBH_4$ (23.66 mg, 0.63 mmol, 3.3 equiv), Methyl (E)-3-(4-Bromophenyl)but-2-enoate (48.45 mg, 0.19 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 µmol, 5 mol%), **L13** (2.19 mg, 11 µmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 14:1) afforded the name compound as a colorless oil.
NMR yield = 96%.

ee = 52%

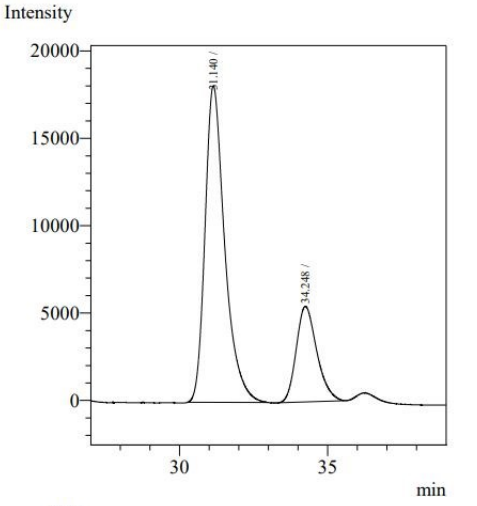
R_f (Hexane:EtOAc 14:1) = 0.18.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.46 – 7.37 (m, 2H), 7.15 – 7.05 (m, 2H), 3.61 (s, 3H), 3.25 (h, *J* = 7.2 Hz, 1H), 2.64 – 2.47 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 172.51, 144.65, 131.58, 128.53, 120.11, 51.57, 42.49, 35.94, 21.75.
HPLC (Lux Cellulose 3, Hexane:*i*-PrOH 999:1, 0.5 mL/Min, 214 nm) t_R: 31.14 Min (maj); 34.25 Min.



AD1

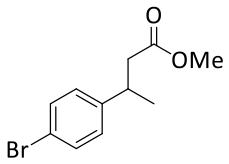
Peak#	Ret.Time	Area	Height	Conc.
1	29.916	21447023	179465	50.472
2	34.986	21045517	221543	49.528
Total		42492540	401009	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	31.140	838301	18116	76.004
2	34.248	264661	5474	23.996
Total		1102962	23591	

Methyl 3-(4-bromophenyl)butanoate



Following **General procedure C**, $NaBH_4$ (23.65 mg, 0.63 mmol, 3.5 equiv), Ethyl (E)-3-(4-Bromophenyl)but-2-enoate (46.11 mg, 0.18 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 µmol, 5 mol%), **L13** (2.15 mg, 11 µmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 14:1) afforded the name compound as a colorless oil.

NMR yield = 99%.

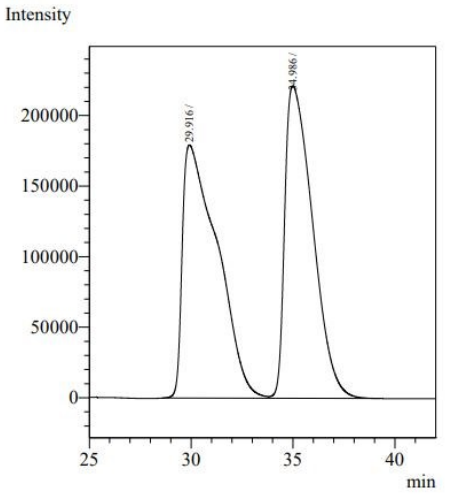
ee = 56%.

R_f (Hexane:EtOAc 14:1) = 0.18.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.46 – 7.37 (m, 2H), 7.15 – 7.05 (m, 2H), 3.61 (s, 3H), 3.25 (h, *J* = 7.2 Hz, 1H), 2.64 – 2.47 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H).

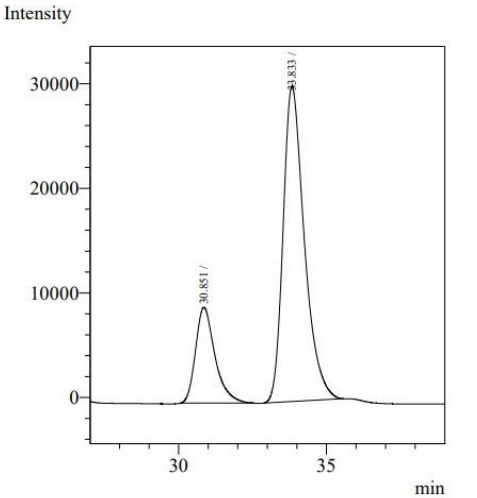
^{13}C NMR (75 MHz, Chloroform-*d*) δ 172.51, 144.65, 131.58, 128.53, 120.11, 51.57, 42.49, 35.94, 21.75.

HPLC (Lux Cellulose 3, Hexane:*i*-PrOH 999:1, 0.5 mL/Min, 214 nm) t_R: 30.85 Min; 33.83 Min (maj).



AD1

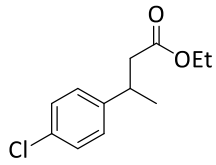
Peak#	Ret.Time	Area	Height	Conc.
1	29.916	21447023	179465	50.472
2	34.986	21045517	221543	49.528
Total		42492540	401009	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	30.851	418819	9163	21.777
2	33.833	1504411	30142	78.223
Total		1923230	39306	

Ethyl 3-(4-Chlorophenyl)butanoate



Following **General procedure C**, $NaBH_4$ (23.25 mg, 0.61 mmol, 3 equiv), Ethyl (E)-3-(4-bromophenyl)but-2-enoate (49.91 mg, 0.22 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.26 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 19:1) afforded the name compound as a colorless oil.

NMR yield = 92%.

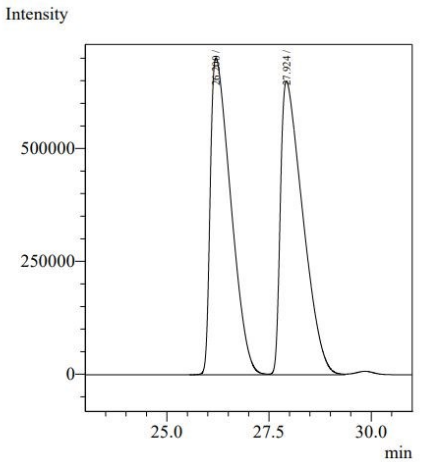
ee = 84%.

R_f (Hexane:EtOAc 19:1) = 0.23.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31 – 7.22 (m, 2H), 7.19 – 7.11 (m, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.26 (h, *J* = 7.2 Hz, 1H), 2.54 (ddd, *J* = 8.1, 3.1 Hz, 2H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

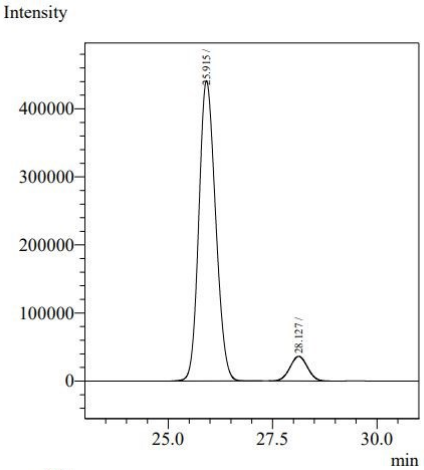
^{13}C NMR (75 MHz, Chloroform-*d*) δ 172.09, 144.17, 132.01, 128.58, 128.17, 60.36, 42.83, 35.96, 21.83, 14.16.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 999:1, 0.5 mL/Min, 214 nm) t_R: 25.92 Min (maj); 28.13 Min.



AD1

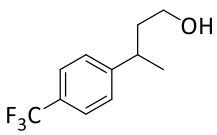
Peak#	Ret.Time	Area	Height	Conc.
1	26.200	24397417	701932	49.627
2	27.924	24764189	650062	50.373
Total		49161605	1351994	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	25.915	12288773	441280	92.105
2	28.127	1053332	36248	7.895
Total		13342106	477527	

3-methyl-3-p-trifluoromethylphenylpropanol



Following **General procedure C**, $NaBH_4$ (22.64 mg, 0.60mmol, 3 equiv), Methyl (E)-3-(4-(trifluoromethyl)phenyl)but-2-enoate (43.45 mg, 0.18 mmol) anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 µmol, 5 mol%), **L13** (2.26 mg, 11 µmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25M). The crude reaction mixture was purified by flash chromatography column (silica gel, Hexane:EtOAc 19:1). Then, following **General procedure F**, $LiAlH_4$ (2 M solution in THF, 1 mL, 2.0 mmol, 11 equiv) in dry THF (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 1:1) afforded the name compound as a colorless oil.
NMR yield = 96%.

ee = 73%.

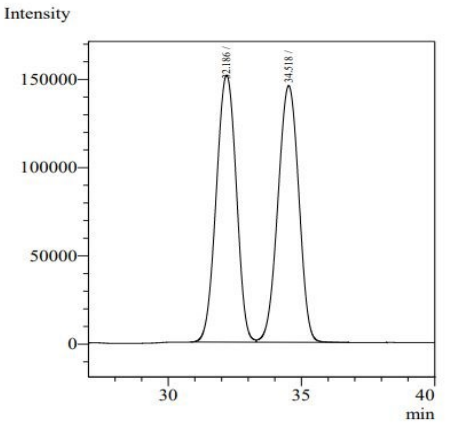
R_f (Hexane:EtOAc 1:1) = 0.17.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.67 – 3.44 (m, 2H), 2.99 (h, *J* = 7.1 Hz, 1H), 1.96 – 1.78 (m, 2H), 1.39 (s, 1H), 1.29 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 150.98, 127.33, 125.49, 125.44, 125.39, 125.34, 60.80, 40.65, 36.21, 22.08.

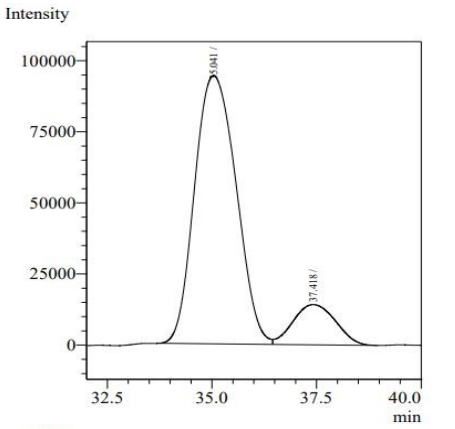
^{19}F NMR (188 MHz, Chloroform-*d*) δ -62.72.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 98:2, 0.5 mL/Min, 214 nm) t_R: 35.04 Min (maj); 37.42 Min.



AD1

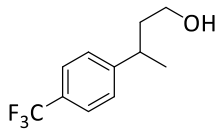
Peak#	Ret.Time	Area	Height	Conc.
1	32.186	7900501	151319	50.015
2	34.518	7895647	145425	49.985
Total		15796148	296744	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	35.041	6507497	94317	86.718
2	37.418	996683	14133	13.282
Total		7504180	108450	

3-methyl-3-p-trifluoromethylphenylpropanol



Following **General procedure C**, $NaBH_4$ (23.06 mg, 0.61mmol, 3 equiv), Methyl (Z)-3-(4-(trifluoromethyl)phenyl)but-2-enoate (42.97mg, 0.18mmol) anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.26 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25M). The crude reaction mixture was purified by flash chromatography column (silica gel, Hexane:EtOAc 19:1). Then, following **General procedure F**, $LiAlH_4$ (2 M solution in THF, 1 mL, 2.0 mmol, 11 equiv) in dry THF (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 1:1) afforded the name compound as a colorless oil.
NMR yield = 95%.

ee = 39%.

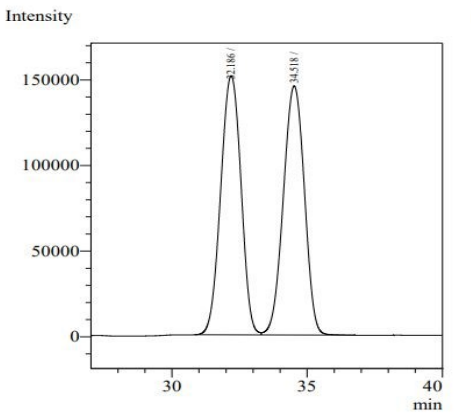
R_f (Hexane:EtOAc 1:1) = 0.17.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.67 – 3.44 (m, 2H), 2.99 (h, *J* = 7.1 Hz, 1H), 1.96 – 1.78 (m, 2H), 1.39 (s, 1H), 1.29 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 150.98, 127.33, 125.49, 125.44, 125.39, 125.34, 60.80, 40.65, 36.21, 22.08.

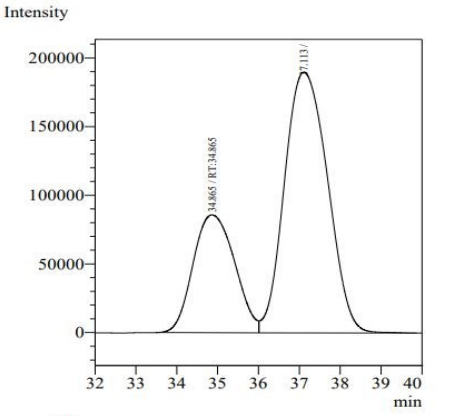
^{19}F NMR (188 MHz, Chloroform-*d*) δ -62.72.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 98:2, 0.5 mL/Min, 214 nm) t_R: 34.87 Min; 37.11 Min (maj).



AD1

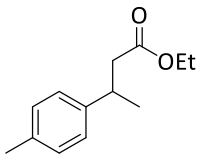
Peak#	Ret.Time	Area	Height	Conc.
1	32.186	7900501	151319	50.015
2	34.518	7895647	145425	49.985
Total		15796148	296744	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	34.865	6071290	85820	30.385
2	37.113	13910080	189876	69.615
Total		19981371	275696	

Ethyl 3-p-tolylbutanoate



Following **General procedure C**, $NaBH_4$ (23.06 mg, 0.61 mmol, 3 equiv), Ethyl (E)-3-(4-methylphenyl)but-2-enoate (38.62 mg, 0.19 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.16 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 49:1) afforded the name compound as a colorless oil.

NMR yield = 61%.

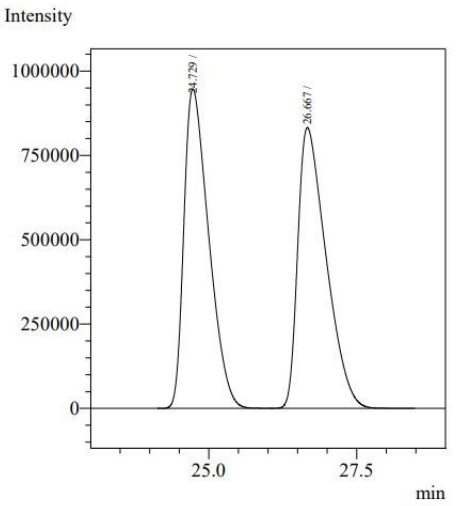
ee = 82%.

R_f (Hexane:EtOAc 49:1) = 0.16.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.11 (s, 3H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.25 (h, *J* = 7.0 Hz, 1H), 2.56 (ddd, *J* = 10.1, 7.6, 6.6 Hz, 2H), 2.32 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 4H), 1.20 (t, *J* = 7.1 Hz, 3H).

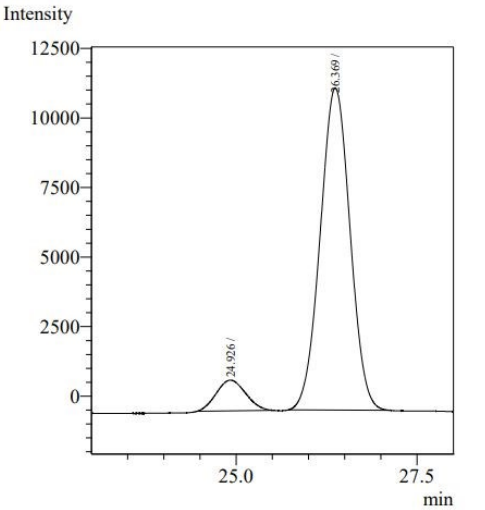
^{13}C NMR (75 MHz, Chloroform-*d*) δ 172.48, 142.77, 135.84, 129.14, 126.61, 60.23, 43.09, 36.10, 21.88, 20.99, 14.19.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 999:1, 0.5 mL/Min, 214 nm) t_R: 24.93 Min; 26.37 Min (maj).



AD1

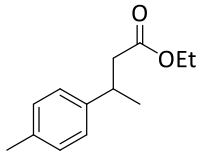
Peak#	Ret.Time	Area	Height	Conc.
1	24.729	27664120	947274	49.922
2	26.667	27750452	832397	50.078
Total		55414572	1779671	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	24.926	31289	1107	8.617
2	26.369	331822	11583	91.383
Total		363111	12690	

Ethyl 3-p-tolylbutanoate



Following **General procedure C**, $NaBH_4$ (22.70 mg, 0.60 mmol, 3 equiv), Ethyl (Z)-3-(4-methylphenyl)but-2-enoate (41.26 mg, 0.20 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.18 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 49:1) afforded the name compound as a colorless oil.

NMR yield = 39%.

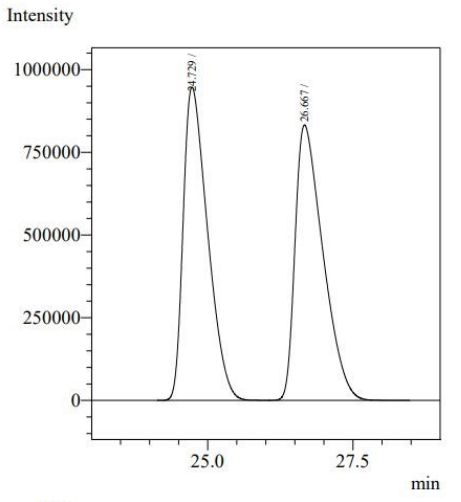
ee = 54%.

R_f (Hexane:EtOAc 49:1) = 0.16.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.11 (s, 3H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.25 (h, *J* = 7.0 Hz, 1H), 2.56 (ddd, *J* = 10.1, 7.6, 6.6 Hz, 2H), 2.32 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 4H), 1.20 (t, *J* = 7.1 Hz, 3H).

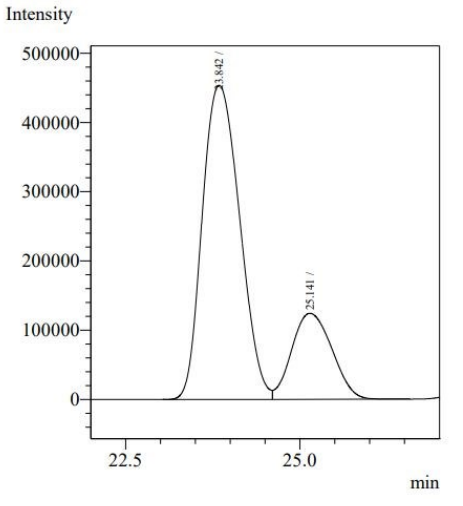
^{13}C NMR (75 MHz, Chloroform-*d*) δ 172.48, 142.77, 135.84, 129.14, 126.61, 60.23, 43.09, 36.10, 21.88, 20.99, 14.19.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 999:1, 0.5 mL/Min, 214 nm) t_R: 23.84 Min (maj); 24.14 Min.



AD1

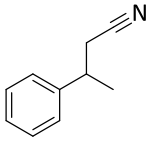
Peak#	Ret.Time	Area	Height	Conc.
1	24.729	27664120	947274	49.922
2	26.667	27750452	832397	50.078
Total		55414572	1779671	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	23.842	16904083	453795	77.232
2	25.141	4983463	124214	22.768
Total		21887546	578009	

(E)-3-phenyl-2-butanenitrile



Following **General procedure C**, $NaBH_4$ (23.00 mg, 0.61 mmol, 3 equiv), (E)-3-phenyl-2-butenenitrile (29.30 mg, 0.20 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.26 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 9:1) afforded the name compound as a colorless oil.

NMR yield = >99%.

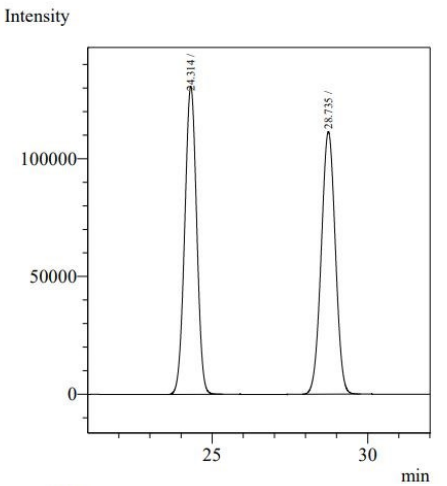
ee = 47%.

R_f (Hexane:EtOAc 9:1) = 0.25.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.32 (m, 2H), 7.31 – 7.21 (m, 3H), 3.17 (h, *J* = 7.0 Hz, 1H), 2.70 – 2.48 (m, 2H), 1.46 (d, *J* = 7.0 Hz, 3H).

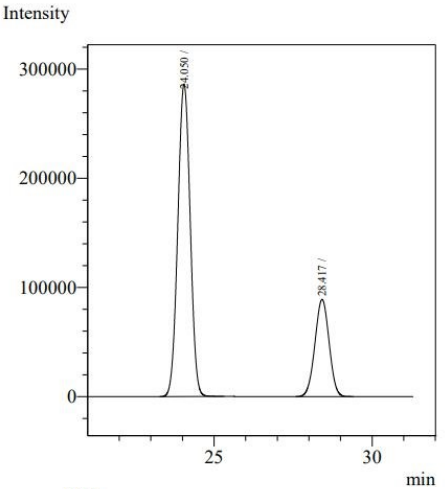
^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.16, 128.88, 127.34, 126.55, 118.58, 36.54, 26.36, 20.68.

HPLC (Lux Cellulose 1, Hexane:*i*-PrOH 90:10, 0.5 mL/Min, 214 nm) t_R: 24.05 Min (maj); 28.42 Min.



AD1

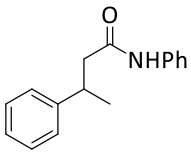
Peak#	Ret.Time	Area	Height	Conc.
1	24.314	3488601	130820	49.860
2	28.735	3508239	111463	50.140
Total		6996840	242284	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	24.050	7790598	286373	73.760
2	28.417	2771537	89104	26.240
Total		10562135	375477	

(E)-N-benzyl-3-phenylbutylamide



Following **General procedure C**, $NaBH_4$ (22.92 mg, 0.61 mmol, 3 equiv), (E)-N-benzyl-3-phenylbut-2-enamide (49.65 mg, 0.20 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 μmol, 5 mol%), **L13** (2.26 mg, 11 μmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25 M). The purification by flash chromatography column (silica gel, DCM:Acetone 9:1) afforded the name compound as a colorless oil.

NMR yield = 98%.

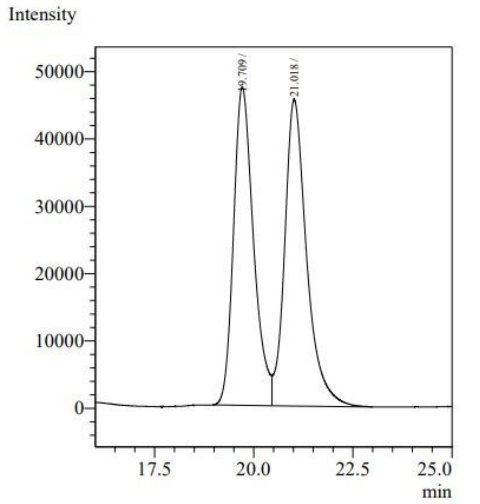
ee = 93%.

R_f (DCM:Acetone 9:1) = 0.46.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.35 – 7.17 (m, 8H), 7.08 – 6.96 (m, 2H), 5.63 (s, 1H), 4.33 (qd, *J* = 14.8, 5.7 Hz, 2H), 3.33 (h, *J* = 7.2 Hz, 1H), 2.46 (d, *J* = 7.5 Hz, 2H), 1.33 (d, *J* = 6.9 Hz, 3H).

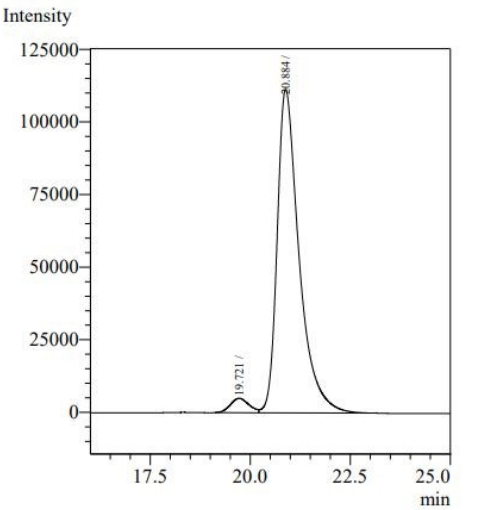
^{13}C NMR (75 MHz, Chloroform-*d*) δ 171.50, 145.76, 138.10, 128.64, 128.60, 127.59, 127.35, 126.86, 126.47, 45.85, 43.45, 37.11, 21.85.

HPLC (Lux Cellulose 3, Hexane:*i*-PrOH 90:10, 1.0 mL/Min, 214 nm) t_R: 19.72 Min; 20.88 Min (maj).



AD1

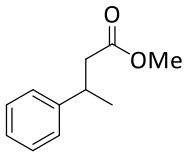
Peak#	Ret.Time	Area	Height	Conc.
1	19.709	1658530	47242	48.571
2	21.018	1756095	45523	51.429
Total		3414625	92765	



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	19.721	158716	4934	3.609
2	20.884	4239428	111358	96.391
Total		4398144	116292	

Methyl (E)-3-phenylbutanoate



Following **General procedure C**, $NaBH_4$ (22.73 mg, 0.60 mmol, 3 equiv), Methyl (E)-3-phenylbut-2-enoate (51.30 mg, 0.19 mmol), anhydrous $CoCl_2$ (Standard solution in EtOH, 1.28 mg, 10 µmol, 5 mol%), **L13** (2.17 mg, 11 µmol, 5.5 mol%) in 1,4-Dioxane:EtOH 1:1 (0.25M). The purification by flash chromatography column (silica gel, Hexane:EtOAc 24:1) afforded the name compound as a colorless oil.

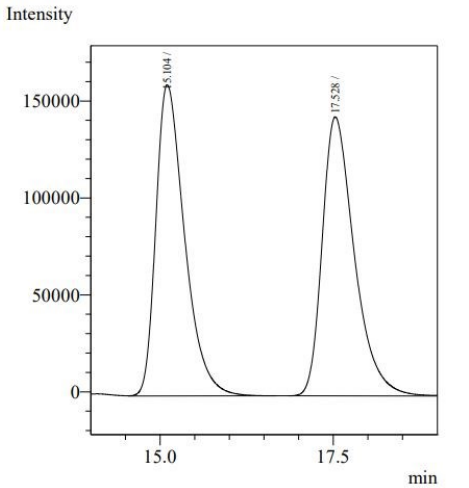
NMR yield = 95%.

ee = 90%.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.37 – 7.13 (m, 5H), 3.62 (s, 3H), 3.28 (h, *J* = 7.2 Hz, 1H), 2.59 (ddd, 2H), 1.30 (d, *J* = 7.0 Hz, 3H).

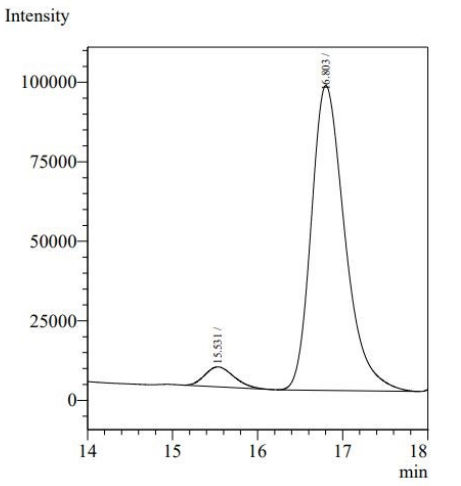
^{13}C NMR (75 MHz, Chloroform-*d*) δ 174.33, 147.20, 129.99, 128.19, 127.89, 52.96, 44.23, 37.92, 23.25.

HPLC (Lux Cellulose 3, Hexane:*i*-PrOH 99:1, 0.5 mL/Min, 214 nm) t_R: 15.53 Min; 16.80 Min (maj).



AD1

Peak#	Ret.Time	Area	Height	Conc.
1	15.104	4628496	160508	49.881
2	17.528	4650496	143943	50.119
Total		9278992	304451	

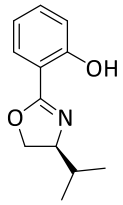


AD1

Peak#	Ret.Time	Area	Height	Conc.
1	15.531	149012	6253	5.359
2	16.803	2631433	95852	94.641
Total		2780445	102105	

5.4 Ligands synthesis and charachterization

(S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol

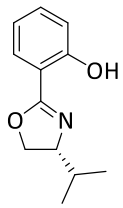


Following **General procedure D**, L-valinol (2.045 g, 19.8 mmol, 1.1 equiv), o-Cyanophenol (2.151 g, 18.0 mmol), $ZnCl_2$ (120.0 mg, 0.9 mmol, 5.0 mol%) in Toluene (0.4 M) at reflux for 24 h. Purification by flash chromatography column (silica gel, Hexane:EtOAc 9:1), yielded the name compound as a pale yellow oil (3.166 g, 15.5 mmol, 86%).

R_f (Hexane:EtOAc 9:1) = 0.39

NMR data match with **(R)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol.**

(R)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol



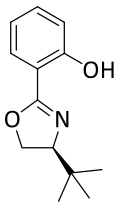
Following **General procedure D**, D-valinol (1.444 g, 14 mmol, 1.2 equiv), o-Cyanophenol (1.370 g, 11.5 mmol), $ZnCl_2$ (163 mg, 1.2 mmol, 10 mol%) in Toluene (0.25 M) at reflux for 24 h. Purification by flash chromatography column (silica gel, Hexane:EtOAc 9:1), yielded the name compound as a colorless oil (2.060 g, 10 mmol, 87%).

R_f (Hexane:EtOAc 9:1) = 0.39.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.37 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J* = 8.4 Hz, 1H), 4.50 – 4.33 (m, 1H), 4.20 – 4.04 (m, 2H), 1.80 (oct, *J* = 6.7 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.07, 159.98, 133.23, 127.98, 118.53, 116.68, 110.70, 71.51, 69.84, 33.02, 18.67, 18.58.

(S)-4-tert-butyl-2-(2-hydroxyphenyl)-2-oxazoline

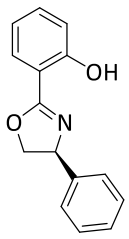


Following **General procedure D**, L-*t*-Butylglycinol (493 mg, 4.2 mmol, 1.1 equiv), o-Cyanophenol (446 mg, 3.7 mmol), $ZnCl_2$ (12.00 mg, 88 μmol, 2.4 mol%) in Toluene (0.4 M) at reflux for 24 h. Purification by flash chromatography column (silica gel, Hexane:EtOAc 4:1), yielded the name compound as a colorless oil (325 mg, 1.48 mmol, 40%).

R_f (Hexane:EtOAc 9:1) = 0.42.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.42 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 4.34 (dd, *J* = 10.0, 8.6 Hz, 1H), 4.22 (t, *J* = 8.2 Hz, 1H), 4.11 (dd, *J* = 10.0, 7.8 Hz, 1H), 0.95 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.09, 160.07, 133.25, 128.00, 118.51, 116.69, 110.64, 74.97, 68.02, 33.79, 25.75.

(S)-2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenol

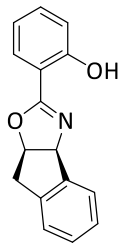


Following **General procedure D**, L-Phenylglycinol (509 mg, 3.6 mmol, 1.1 equiv), o-Cyanophenol (396 mg, 3.3 mmol), $ZnCl_2$ (14.20 mg, 104 μmol, 3.2 mol%) in Toluene (0.4 M) at reflux for 24 h. Purification by flash chromatography column (silica gel, Hexane:EtOAc 9:1), yielded the name compound as a pale yellow oil (563 mg, 2.4 mmol, 71%).

R_f (Hexane:EtOAc 9:1) = 0.29.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.35 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.31 (m, 6H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 5.49 (t, *J* = 10.1 Hz, 1H), 4.79 (t, *J* = 10.1 Hz, 1H), 4.27 (t, *J* = 8.3 Hz, 1H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.43, 160.30, 141.74, 133.81, 128.98, 128.45, 128.00, 126.62, 118.88, 117.00, 110.66, 74.12, 68.92.

2-((3aS,8aR)-3a,8a-dihydro-8H-indeno[1,2-d]oxazol-2-yl)phenol



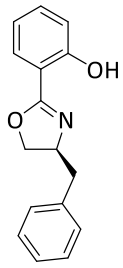
Following **General procedure D**, (1S,2R)-1-amino-2-indanol (517 mg, 3.5 mmol, 1.2 equiv), o-Cyanophenol (361 mg, 3.0 mmol), $ZnCl_2$ (26.21 mg, 192 μmol, 6.4 mol%) in Toluene (0.4 M) at reflux for 24 h. Purification by flash chromatography column (silica gel, Hexane:EtOAc 4:1), yielded the name compound as a brown solid (363mg, 1.4 mmol, 48%).

R_f (Hexane:EtOAc 9:1) = 0.25.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.11 (s, 1H), 7.64 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.50 (dt, *J* = 4.6, 2.1 Hz, 1H), 7.39 – 7.22 (m, 4H), 6.97 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.84 (td, *J* = 7.5, 1.1 Hz, 1H), 5.78 (d, *J* = 7.7 Hz, 1H), 5.47 (ddd, *J* = 8.0, 6.6, 1.8 Hz, 1H), 3.54 (dd, *J* = 18.1, 6.6 Hz, 1H), 3.40 (dd, *J* = 18.0, 1.7 Hz, 1H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.40, 159.79, 141.40, 139.45, 133.34, 128.75, 128.09, 127.65, 125.53, 125.33, 118.55, 116.71, 110.77, 82.65, 75.49, 39.48.

(S)-2-(4-benzyl-4,5-dihydrooxazol-2-yl)phenol



Following **General procedure D**, L-Phenylalaninol (512 mg, 3.4 mmol, 1.1 equiv), o-Cyanophenol (355 mg, 3.0 mmol), $ZnCl_2$ (22.16 mg, 163 μmol, 5.4 mol%) in Toluene (0.4 M) at reflux for 24 h. After purification by flash chromatography column (silica gel, Hexane:EtOAc 9:1), the name compound was obtained as a brownish oil (538 mg, 2.1 mmol, 71%).

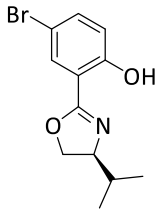
R_f (Hexane:EtOAc 9:1) = 0.27.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.22 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.47 – 7.22 (m, 6H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 4.74 –

4.57 (m, 1H), 4.42 (t, *J* = 8.9 Hz, 1H), 4.16 (t, *J* = 8.5 Hz, 1H), 3.14 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.85 (dd, *J* = 13.7, 7.5 Hz, 1H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.47, 159.94, 137.57, 133.43, 129.24, 128.66, 128.04, 126.71, 118.64, 116.76, 110.64, 71.20, 66.74, 41.91.

(S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-4-bromophenol



In a flask, L-valinol (700 mg, 6.8 mmol), EDC Hydrochloride (2.633 g, 13.7 mmol, 2.0 equiv), HOBT (1.847 g, 13.7 mmol, 2.0 equiv) and 4-Bromosalicylic acid (1.778 g, 8.2 mmol, 1.2 equiv) were added together with $CHCl_3$ (0.2 M) under inert atmosphere (N_2). The solution was left stirring at room temperature for 18 h and then extracted three times with a saturated Na_2CO_3 aqueous solution. The aqueous phase was then neutralized with 1 M HCl and concentrated in vacuo. The crude reaction mixture was used directly in the following step.

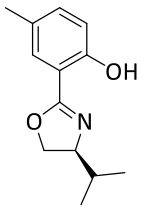
The crude reaction mixture was dissolved in DCM (0.4 M) and $SOCl_2$ (1.5 mL, 7.7 mmol, 1.1 equiv) was added dropwise. The solution was left stirring at room temperature overnight and then quenched with a saturated $NaHCO_3$ aqueous solution. The aqueous phase was then extracted three times with DCM and the collected organic phases were dried over Na_2SO_4, filtered through cotton and concentrated in vacuo. Purification by flash chromatography column (silica gel, Hexane:EtOAc 9:1) yielded the name compound as a brownish oil (852 mg, 3.01 mmol, 44%)

R$_f$ (Hexane:EtOAc 9:1) = 0.34.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 2.5 Hz, 1H), 7.43 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.50 – 4.36 (m, 1H), 4.21 – 4.06 (m, 2H), 1.81 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 164.10, 159.00, 135.91, 130.35, 118.61, 112.24, 110.13, 71.57, 70.07, 32.95, 18.63, 18.53, 14.15.

(S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-4-methylphenol



In a flask, L-valinol (700 mg, 6.8 mmol), EDC Hydrochloride (2.621 g, 13.7 mmol, 2.0 equiv), HOBT (1.860 g, 13.8 mmol, 2.0 equiv) and 4-Methylsalicylic acid (1.241 g, 8.2 mmol, 1.2 equiv) were added together with $CHCl_3$ (0.2 M) under inert atmosphere (N_2). The solution was left stirring at room temperature for 18 h and then extracted three times with a saturated Na_2CO_3 aqueous solution. The aqueous phase was then neutralized with 1 M HCl and concentrated in vacuo. The crude reaction mixture was used directly in the following step.

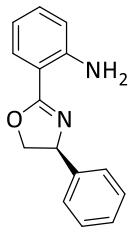
The crude reaction mixture was dissolved in DCM (0.4 M) and $SOCl_2$ (1.5 mL, 7.7 mmol, 1.1 equiv) was added dropwise. The solution was left stirring at room temperature overnight and then quenched with a saturated $NaHCO_3$ aqueous solution. The aqueous phase was then extracted three times with DCM and the collected organic phases were dried over Na_2SO_4, filtered with cotton and concentrated in vacuo. Purification by flash chromatography column (silica gel, Hexane:EtOAc 19:1) yielded the name compound as a brownish oil (781 mg, 3.6 mmol, 52%)

R_f (Hexane:EtOAc 4:1) = 0.46.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.12 (s, 1H), 7.44 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 4.50 – 4.33 (m, 1H), 4.21 – 4.03 (m, 2H), 2.28 (s, 3H), 1.80 (oct, *J* = 6.5 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.03, 157.78, 134.08, 127.84, 127.64, 116.44, 110.24, 71.51, 69.76, 33.00, 20.39, 18.66, 18.55.

(S)-2-(4-phenyl-4,5-dihydrooxazol-2-yl)aniline

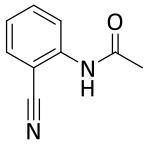


Following **General procedure D**, L-phenylglycinol (483 mg, 4.7 mmol, 1.5 equiv), 2-Aminobenzonitrile (498 mg, 3.1 mmol), $ZnCl_2$ (42.03 mg, 309 μmol, 10 mol%) in Toluene (0.4 M) at reflux for 96 h. Purification by flash chromatography column (silica gel, Hexane:EtOAc 3:1), yielded the name compound as a white solid (622 mg, 2.6 mmol, 84%).

R_f (Hexane:EtOAc 4:1) = 0.33.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.48 – 7.16 (m, 5H), 6.83 – 6.61 (m, 2H), 6.17 (s, 2H), 5.47 (t, *J* = 10.0 Hz, 1H), 4.71 (t, *J* = 10.0 Hz, 1H), 4.15 (t, *J* = 8.2 Hz, 1H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.08, 148.86, 142.80, 132.33, 129.83, 128.74, 127.57, 126.64, 116.05, 115.74, 108.72, 73.11, 70.23.

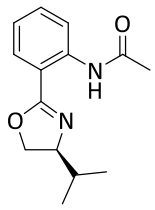
2-Acetamidobenzonitrile



In a flask, 2-Cyanoaniline (3.824 g, 32.4 mmol) was dissolved in DCM (0.25 M) under inert atmosphere (N_2) and the solution was cooled to 0 °C using an ice bath. Acetic anhydride (6.0 mL, 64.6 mmol, 2.0 equiv) was added dropwise and the solution was left stirring at reflux for 24 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the aqueous phase was extracted with DCM. The collected organic phases were dried over Na_2SO_4, filtered through cotton and concentrated under vacuum. Precipitation with Hexane from a DCM solution yielded the name compound as a white solid (4.020 g, 25.1 mmol, 77%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 8.9 Hz, 1H), 7.95 (s, 1H), 7.69 – 7.40 (m, 2H), 7.14 (t, *J* = 7.7 Hz, 1H), 2.24 (s, 3H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 168.97, 140.56, 134.11, 132.39, 124.23, 121.90, 116.49, 102.29, 24.59.
R_f (Hexane:EtOAc 1:1) = 0.23.

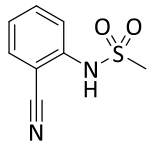
(S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenylacetamide



Following **General procedure D**, L-valinol (483 mg, 4.7 mmol, 1.5 equiv), 2-Acetamidobenzonitrile (498 mg, 3.1 mmol), $ZnCl_2$ (42.03 mg, 309 μmol, 10 mol%) in Toluene (0.4 M) at reflux for 96 h. Purification by flash chromatography column (silica gel, Hexane:EtOAc 3:1), yielded the name compound as a white solid (73 mg, 0.3 mmol, 10%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.39 (s, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 8.8 Hz, 1H), 7.05 (t, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 4.21 – 3.99 (m, 2H), 2.21 (s, 3H), 1.78 (oct, *J* = 13.4 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 169.14, 163.52, 140.11, 132.52, 129.06, 122.11, 119.51, 112.88, 72.78, 69.54, 33.35, 25.37, 19.02, 18.80.
R_f (Hexane:EtOAc 4:1) = 0.23.

2-Sulfonamidobenzonitrile



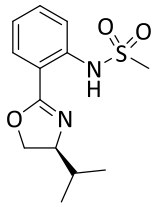
In a flask, 2-Cyanoaniline (3.824 g, 32.4 mmol) and Pyridine (3.8 mL, 47.1 mmol, 1.5 equiv) were dissolved in DCM (0.25 M) under inert atmosphere (N_2). Then, Mesyl Chloride (3.8 mL, 48.5 mmol, 1.5 equiv) was added dropwise and the solution was left stirring at reflux for 60 h. The reaction was then quenched with distilled water and washed with HCl 1 M. The aqueous phase was extracted three times with DCM and the collected organic fractions were dried over Na_2SO_4, filtered through cotton and concentrated in vacuo. Precipitation with Hexane from a DCM solution yielded the name compound as a white solid (2.630 g, 13.4 mmol, 41%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80 – 7.54 (m, 2H), 7.37 – 7.19 (m, 2H), 3.14 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 139.43, 134.57, 133.25, 125.54, 122.01, 116.14, 104.69, 40.72.

R_f (Hexane:EtOAc 1:1) = 0.26.

(S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenylsulfonamide



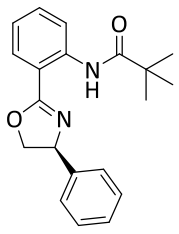
Following **General procedure D**, L-valinol (468 mg, 4.5 mmol, 1.5 equiv), 2-Sulfonamidobenzonitrile (589 mg, 3.0 mmol), $ZnCl_2$ (30.11 mg, 220 µmol, 7 mol%) in Toluene (0.4 M) at reflux for 20 h. Purification by flash chromatography column (silica gel, Hexane:EtOAc 2:1), yielded the name compound as a white solid (481 mg, 1.7 mmol, 57%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.28 (s, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.46 (t, 1H), 7.09 (t, 1H), 4.41 (t, *J* = 7.5 Hz, 1H), 4.22 – 4.00 (m, 2H), 3.01 (s, 3H), 1.79 (oct, *J* = 6.7 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.38, 139.52, 132.72, 129.65, 122.48, 117.35, 113.47, 72.40, 69.68, 39.85, 33.16, 18.79, 18.67.

R_f (Hexane:EtOAc 4:1) = 0.13.

(S)-2-(4-phenyl-4,5-dihydrooxazol-2-yl)pivaloylamide



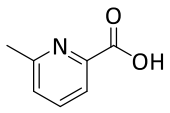
In a flask, (S)-2-(4-phenyl-4,5-dihydrooxazol-2-yl)aniline (477 mg, 2.0 mmol) and TEA (420 µL, 3.0 mmol, 1.5 equiv) were dissolved in THF (0.4 M). Then, Pivaloyl chloride (370 µL, 3.0 mmol, 1.5 equiv) was added dropwise and the solution was left stirring at RT for 4 h. The reaction was quenched with distilled H_2O and the aqueous layer was extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered

through cotton and concentrated in vacuo to yield the name compound as a yellow oil (483 mg, 1.5 mmol, 75%).

R_f (Hexane:EtOAc 4:1) = 0.34.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.84 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.42 – 7.21 (m, 4H), 7.09 (t, *J* = 7.5 Hz, 1H), 5.50 (t, *J* = 9.0 Hz, 1H), 4.75 (t, *J* = 9.3 Hz, 1H), 4.24 (t, *J* = 8.3 Hz, 1H), 1.27 (s, 2H), 1.19 (s, 7H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 179.92, 143.23, 142.19, 134.34, 130.87, 130.29, 129.34, 128.01, 123.48, 121.41, 74.81, 71.57, 29.06, 28.01.

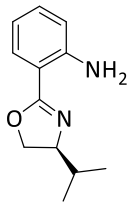
6-Methylpicolinic acid



In a flask, 2,6-Lutidine (10.737 g, 100 mmol) was dissolved in distilled H_2O (0.2 M) and the solution was brought to 60 °C. $KMnO_4$ (23.770 g, 150 mmol, 1.5 equiv) was added in 10 portions during the course of 4 h and the solution was left stirring for 2 h at 60 °C. The solution was filtered through celite, and its pH was adjusted to 5 using 1 M HCl. The aqueous phase was extracted several times with DCM and the combined organic phases were dried over Na_2SO_4, filtered through cotton and concentrated in vacuo. Precipitation with Hexane from a DCM solution of the crude reaction mixture yielded the name compound as a white solid (2.284 g, 17 mmol, 17%).

^{1}H NMR (300 MHz, Deuterium Oxide) δ 8.51 (t, *J* = 7.5 Hz, 1H), 8.08 (dd, *J* = 68.9, 7.8 Hz, 2H), 2.87 (s, 3H).
^{13}C NMR (75 MHz, Deuterium Oxide) δ 154.12, 146.81, 145.16, 129.45, 123.62, 18.98.

(S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)aniline

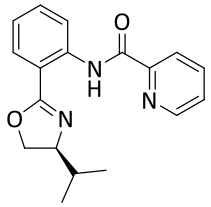


Following **General procedure D**, L-valinol (314 mg, 3.0 mmol, 1.5 equiv), 2-Aminobenzonitrile (231 mg, 1.9 mmol), $ZnCl_2$ (264 mg, 1.9 mmol, 100 mol%) in Toluene (0.4 M) at reflux for 48 h. Purification by flash chromatography column (Silica gel, Hexane:EtOAc 9:1), yielded the name compound as a white solid (200 mg, 1.0 mmol, 50%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.32 – 7.10 (m, 1H), 6.79 – 6.55 (m, 1H), 6.15 (s, 2H), 4.33 (d, *J* = 9.2 Hz, 1H), 4.19 – 4.06 (m, 1H), 4.01 (t, *J* = 7.8 Hz, 1H), 1.80 (oct, *J* = 6.7 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.52, 148.62, 131.90, 129.58, 115.96, 115.63, 109.19, 72.93, 68.74, 33.22, 18.99, 18.63.

(S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)picolinamide

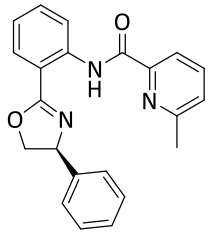


Following **General procedure E**, Picolinic acid (74 mg, 0.6 mmol, 1.5 equiv), Oxalyl chloride (78 µL, 0.9 mmol, 2.25 equiv) in DCM (0.1 M). The crude reaction mixture was reacted directly with TEA (150 µL, 1.1 mmol, 2.7 equiv) and (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)aniline (81 mg, 0.4 mmol) in Toluene (0.05 M). Purification by flash chromatography column (silica gel, Hexane:EtOAc 20:1) yielded the name compound as a white solid (52 mg, 0.17 mmol, 42%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.06 (d, *J* = 8.5 Hz, 1H), 8.74 – 8.51 (m, 1H), 8.30 (d, *J* = 7.9 Hz, 1H), 8.00 – 7.76 (m, 2H), 7.61 – 7.35 (m, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 4.43 (t, *J* = 9.6 Hz, 1H), 4.26 (q, *J* = 9.2, 8.7 Hz, 1H), 4.06 (t, *J* = 8.2 Hz, 1H), 1.85 (oct, *J* = 13.2 Hz, 1H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.65, 164.39, 149.70, 141.11, 138.68, 133.73, 130.89, 127.57, 124.38, 124.17, 121.80, 116.20, 74.97, 71.04, 34.96, 20.67, 20.24.

(S)-2-(4-phenyl-4,5-dihydrooxazol-2-yl)-6-methylpicolinamide



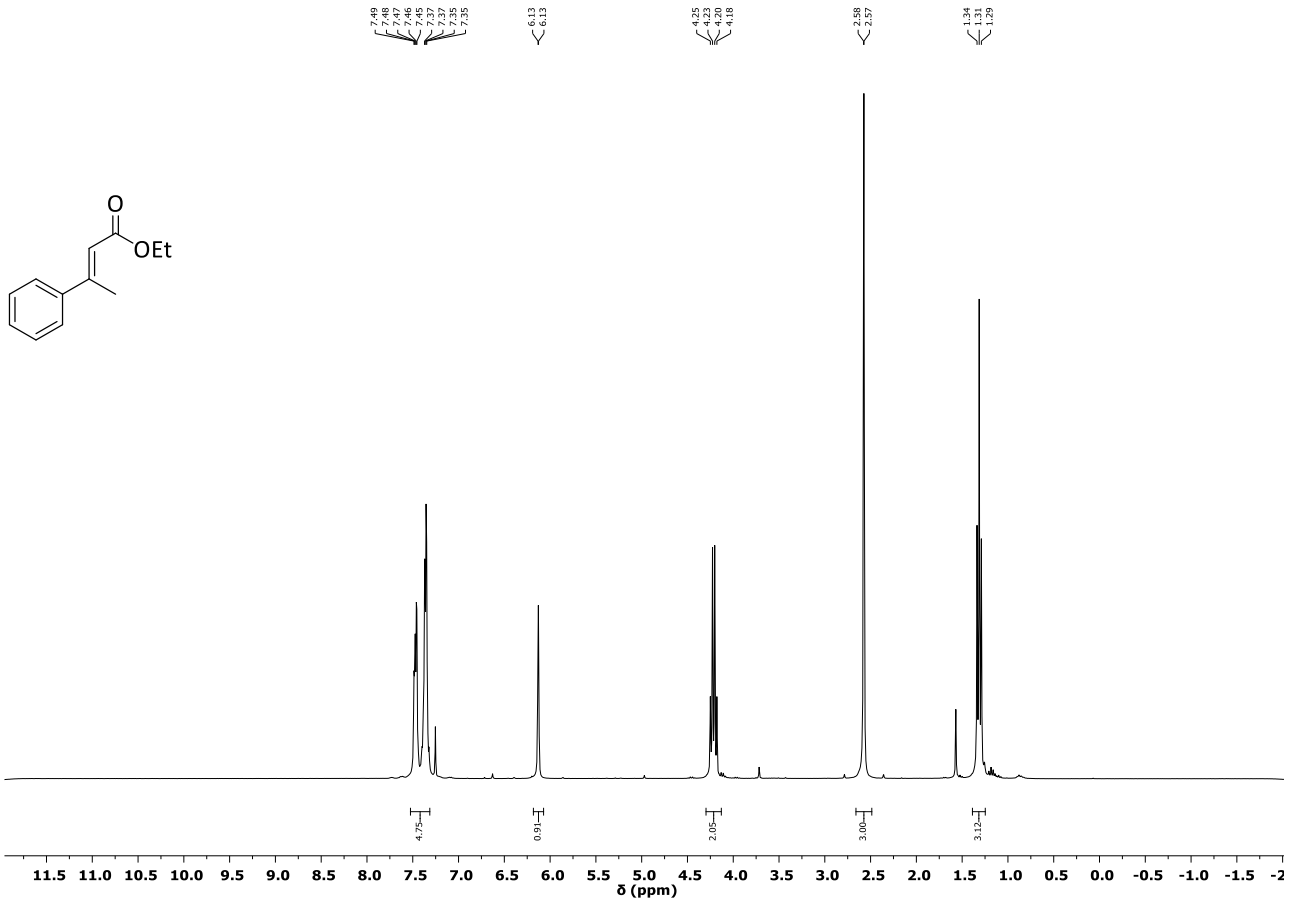
Following **General procedure E**, 6-Methylpicolinic acid (86 mg, 0.6 mmol, 1.5 equiv), Oxalyl chloride (125 µL, 1.5 mmol, 3.5 equiv) in DCM (0.1 M). The crude reaction mixture was reacted directly with TEA (150 µL, 1.1 mmol, 2.5 equiv) and (S)-2-(4-phenyl-4,5-dihydrooxazol-2-yl)aniline (100 mg, 0.4 mmol) in Toluene (0.05 M). Purification by flash chromatography column (silica gel, Hexane:EtOAc 19:1) yielded the name compound as a white solid (112 mg, 0.31 mmol, 75%).

R$_f$ (Hexane:EtOAc 9:1) = 0.09.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 13.86 (s, 1H), 9.09 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 8.8 Hz, 1H), 7.45 – 7.23 (m, 5H), 7.17 (ddd, *J* = 8.8, 5.7, 1.4 Hz, 2H), 5.64 (t, *J* = 10.1 Hz, 1H), 4.81 (t, *J* = 10.2 Hz, 1H), 4.19 (t, *J* = 8.5 Hz, 1H), 2.04 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 164.45, 157.49, 150.17, 142.26, 139.93, 137.28, 132.67, 129.60, 128.69, 127.63, 126.85, 125.74, 122.62, 120.32, 119.71, 114.35, 73.76, 70.51, 23.40.

5.4 NMR spectra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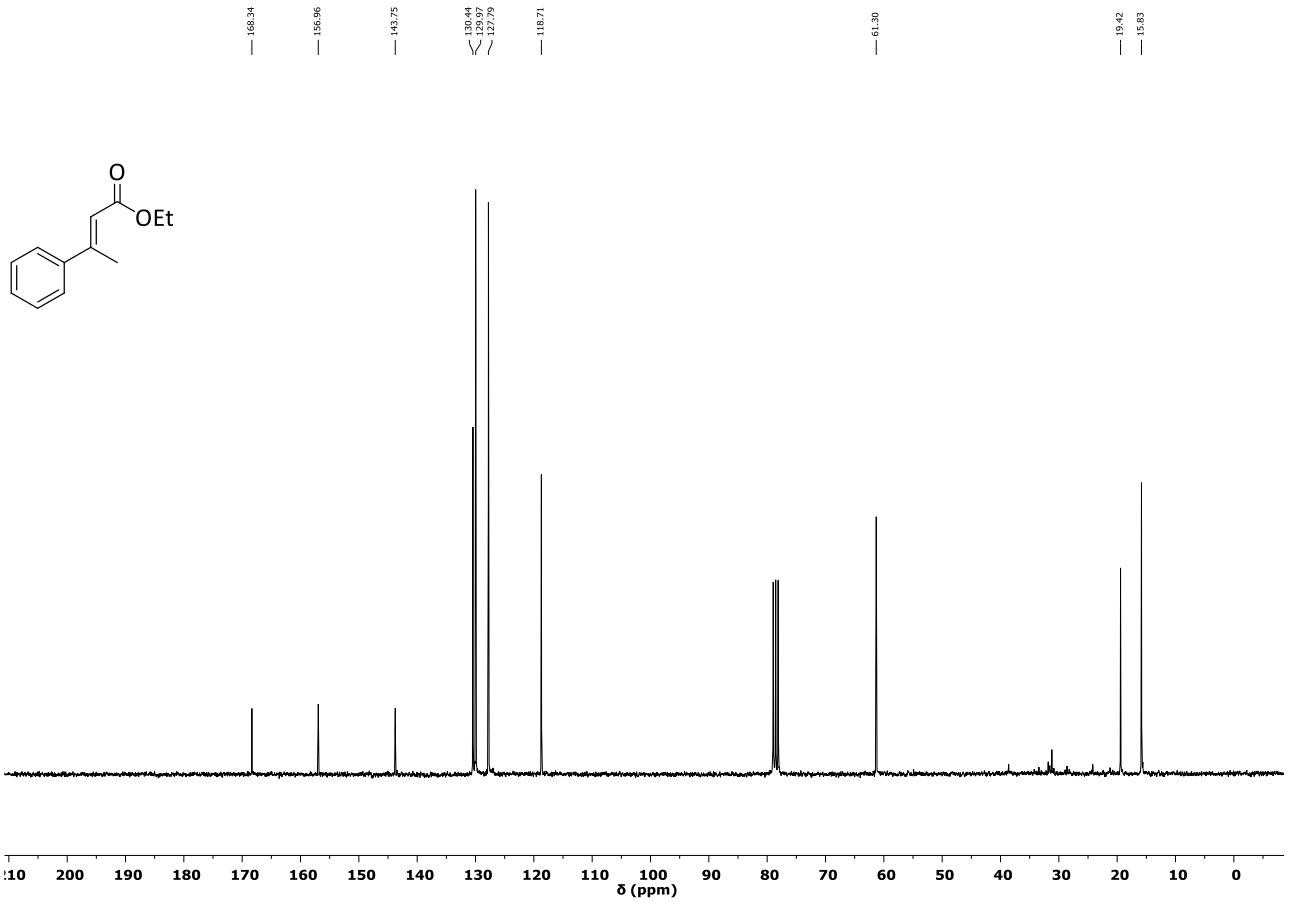
4.20
4.18
2.58
2.57
1.34
1.31
1.29
O
OEt
4.75
0.91
2.05
3.00
3.12
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2
δ (ppm)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OEt
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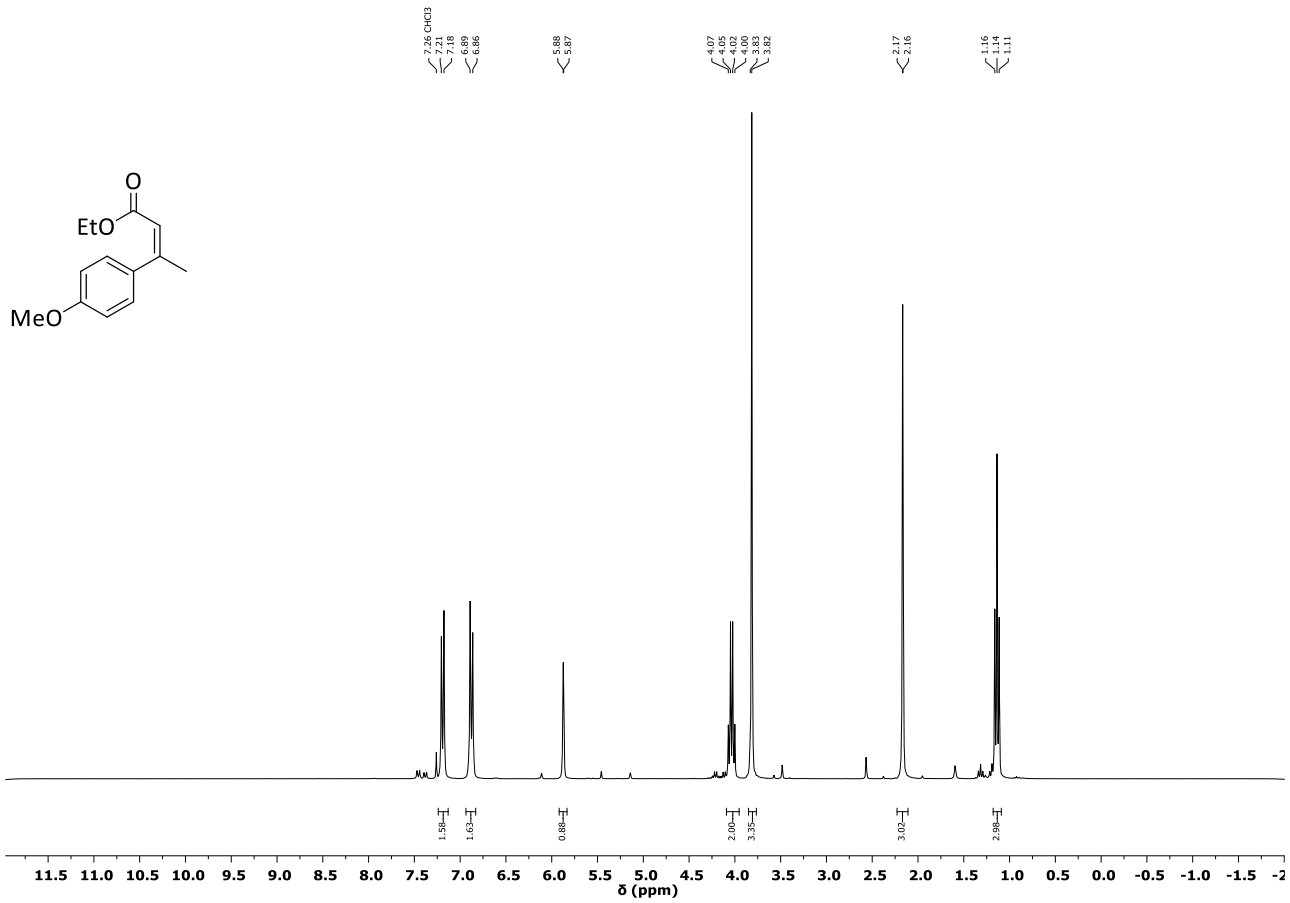
δ (ppm)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2.16
1.16
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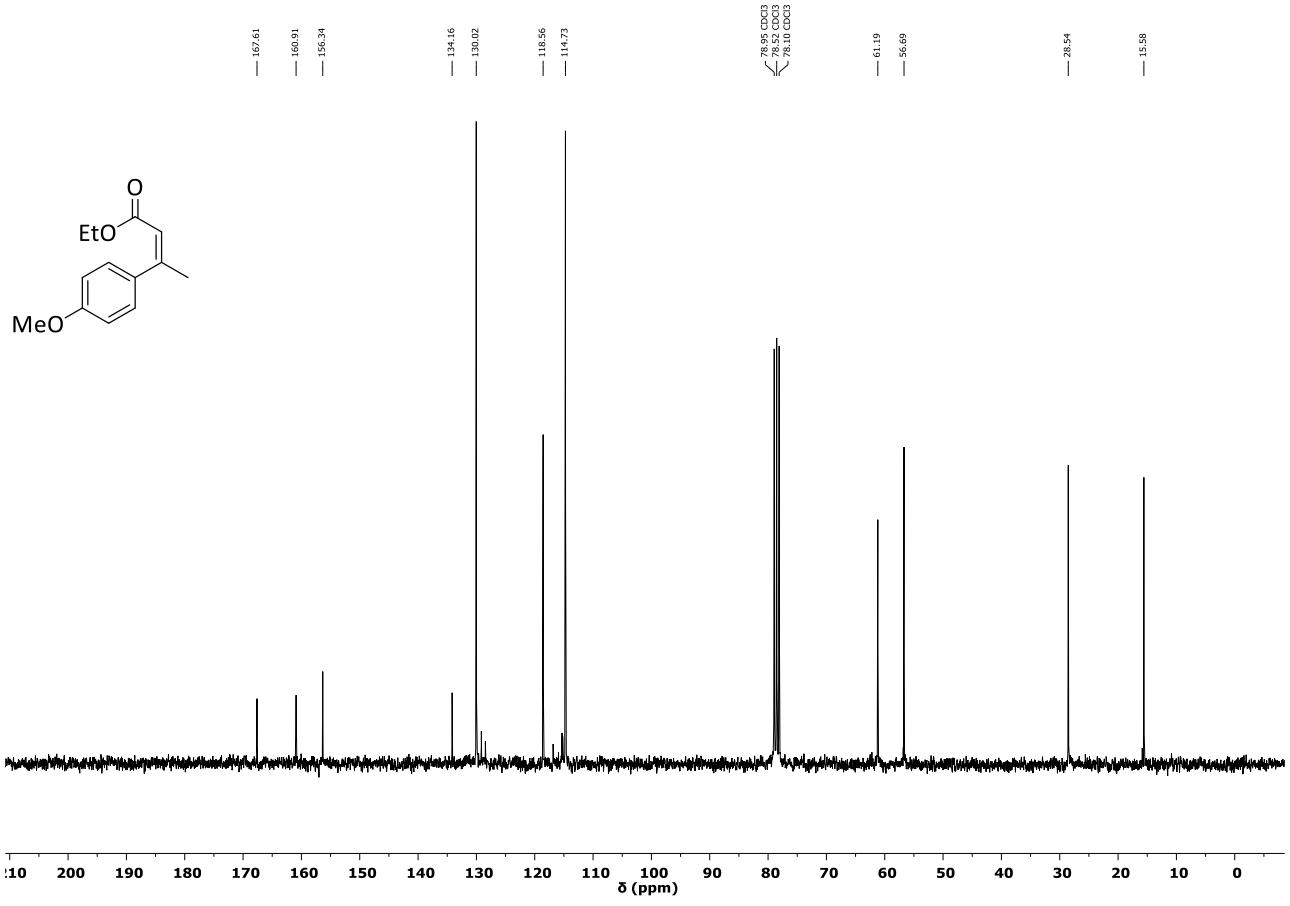
δ (ppm)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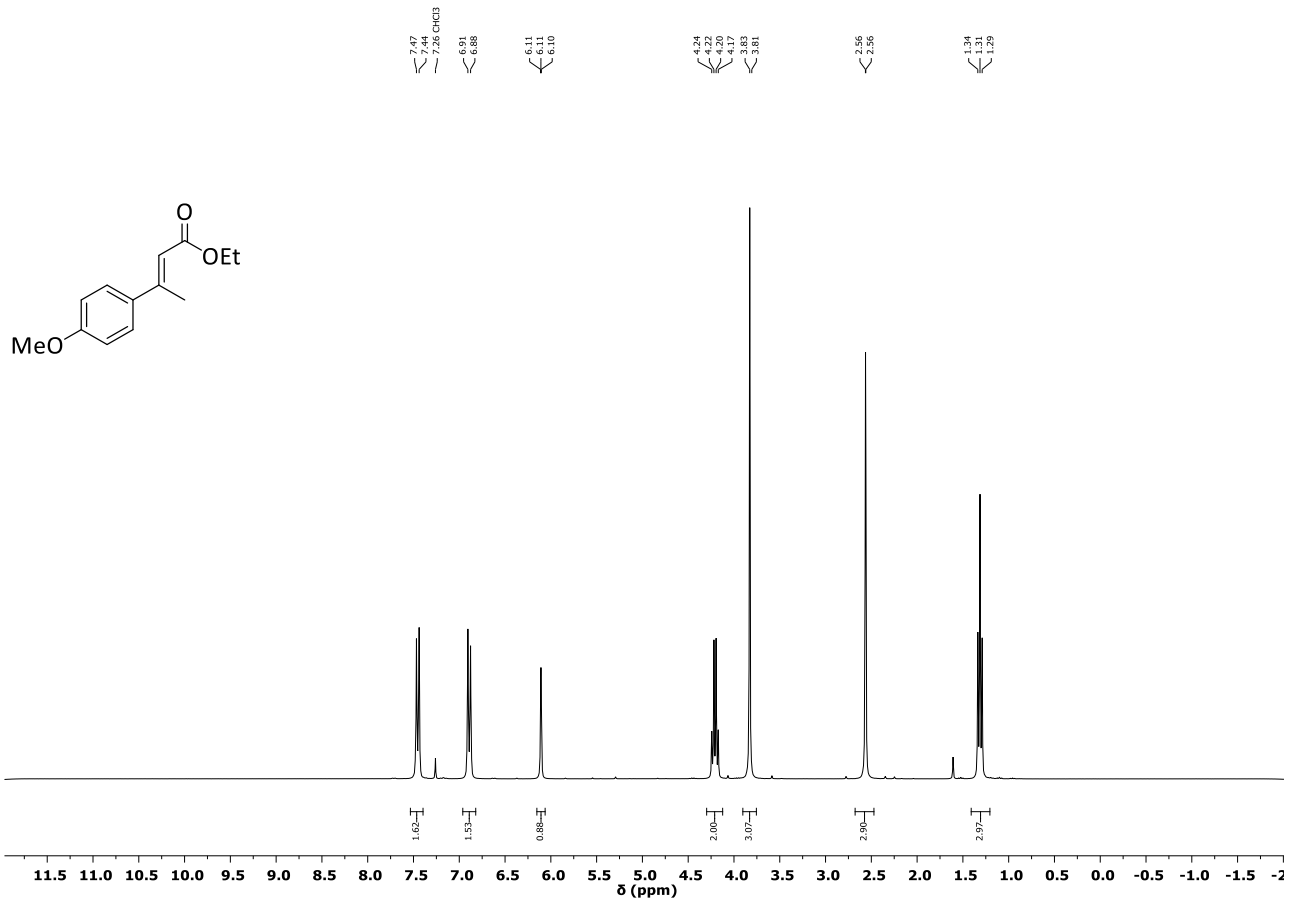
δ (ppm)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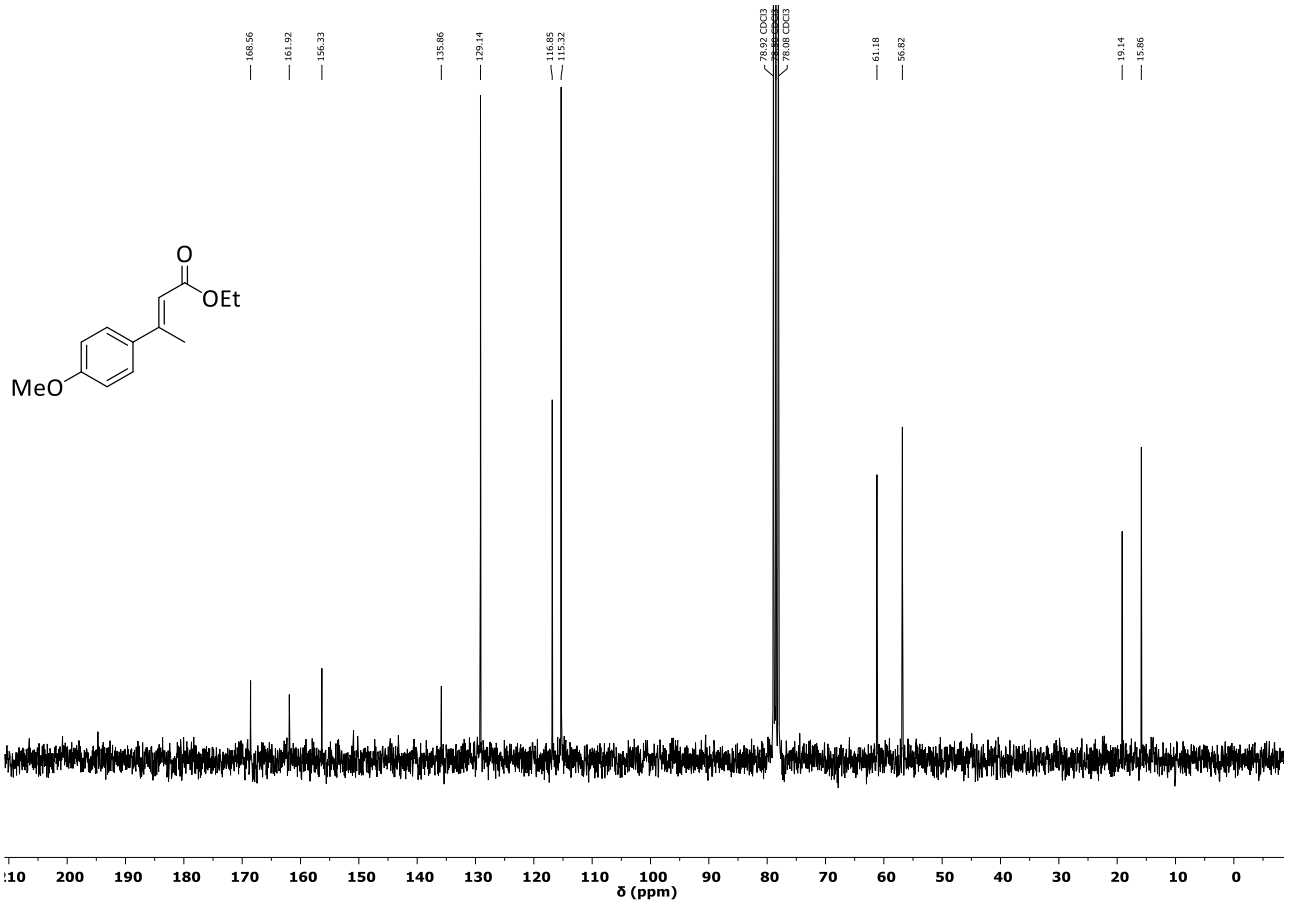
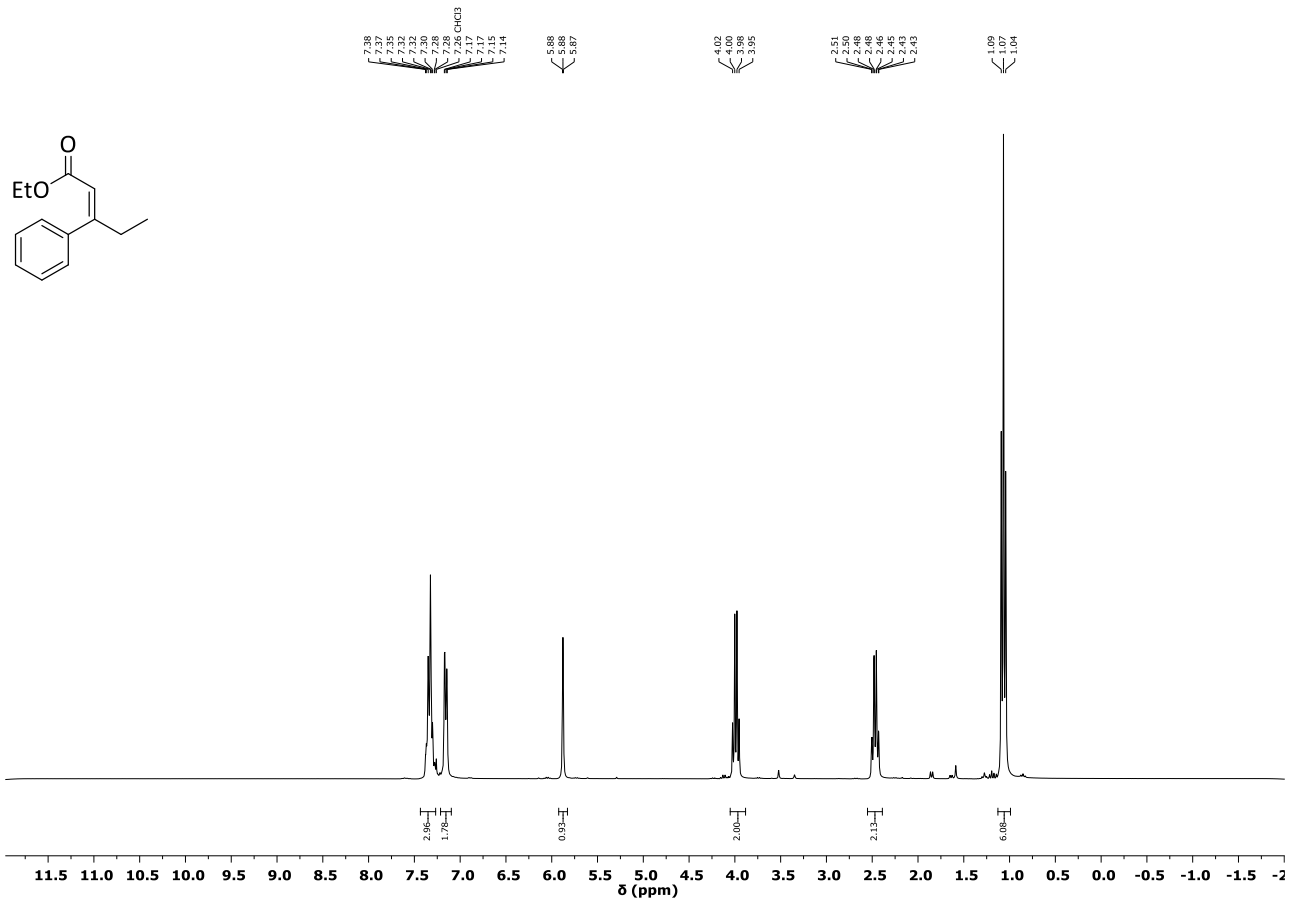
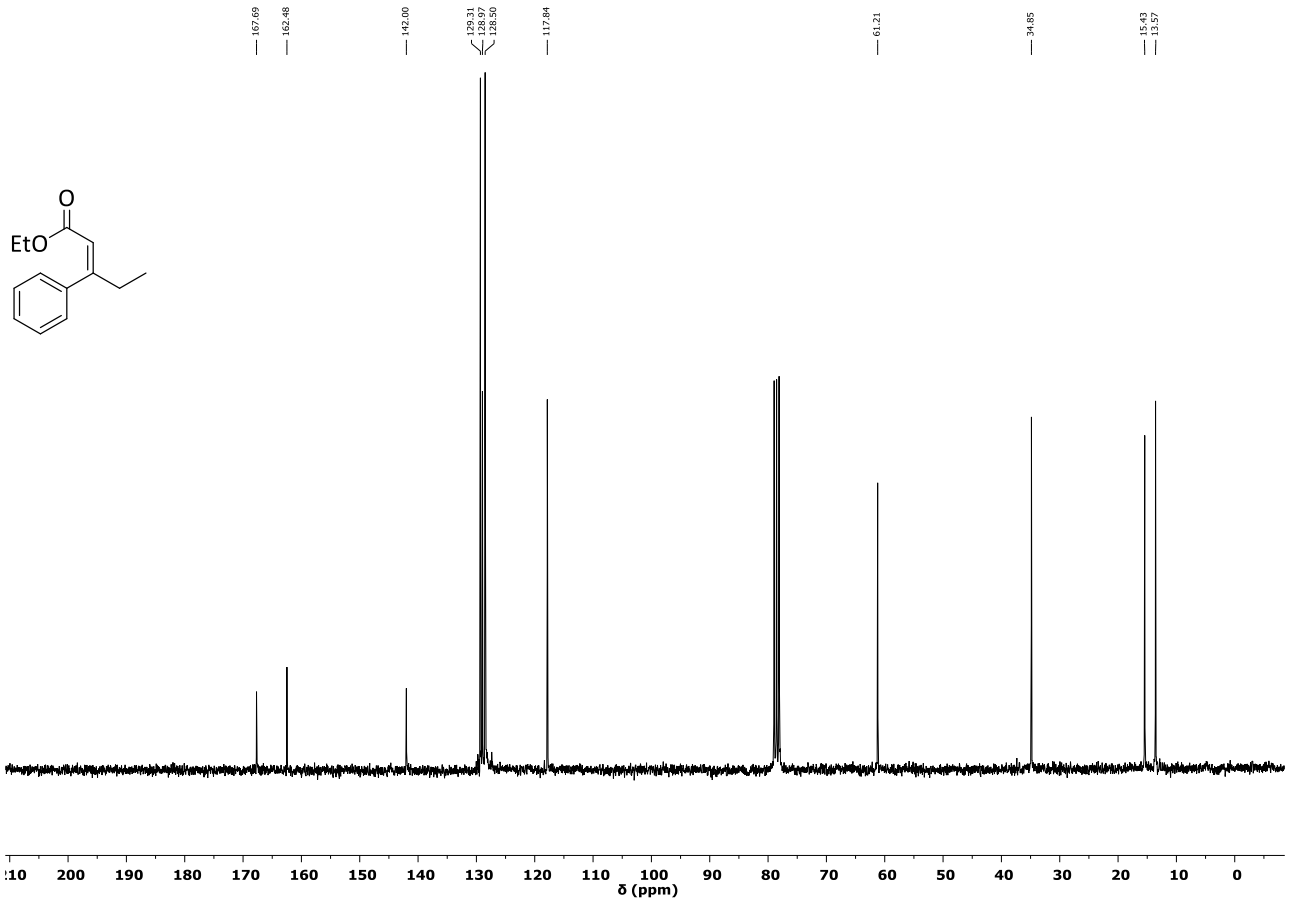
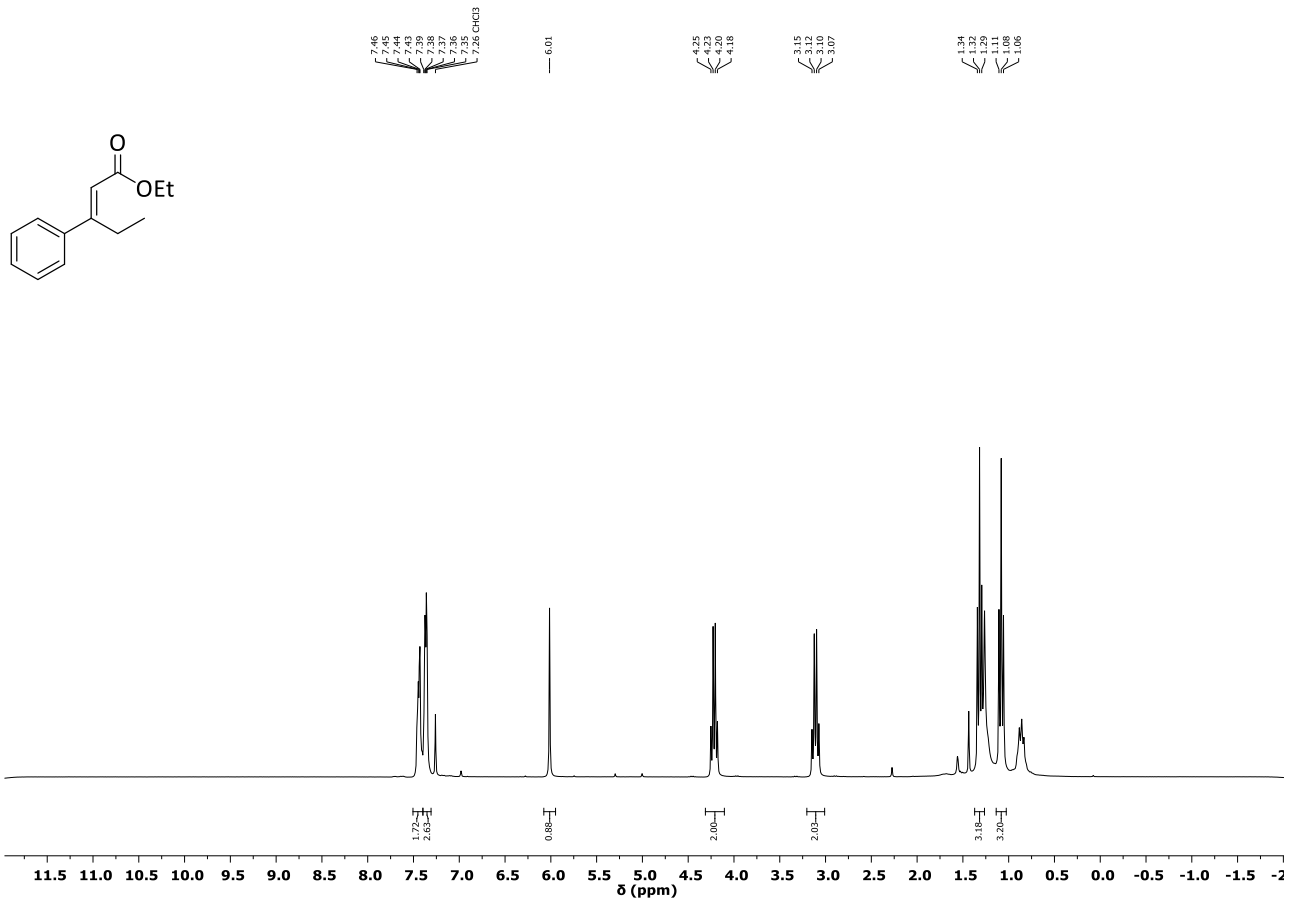
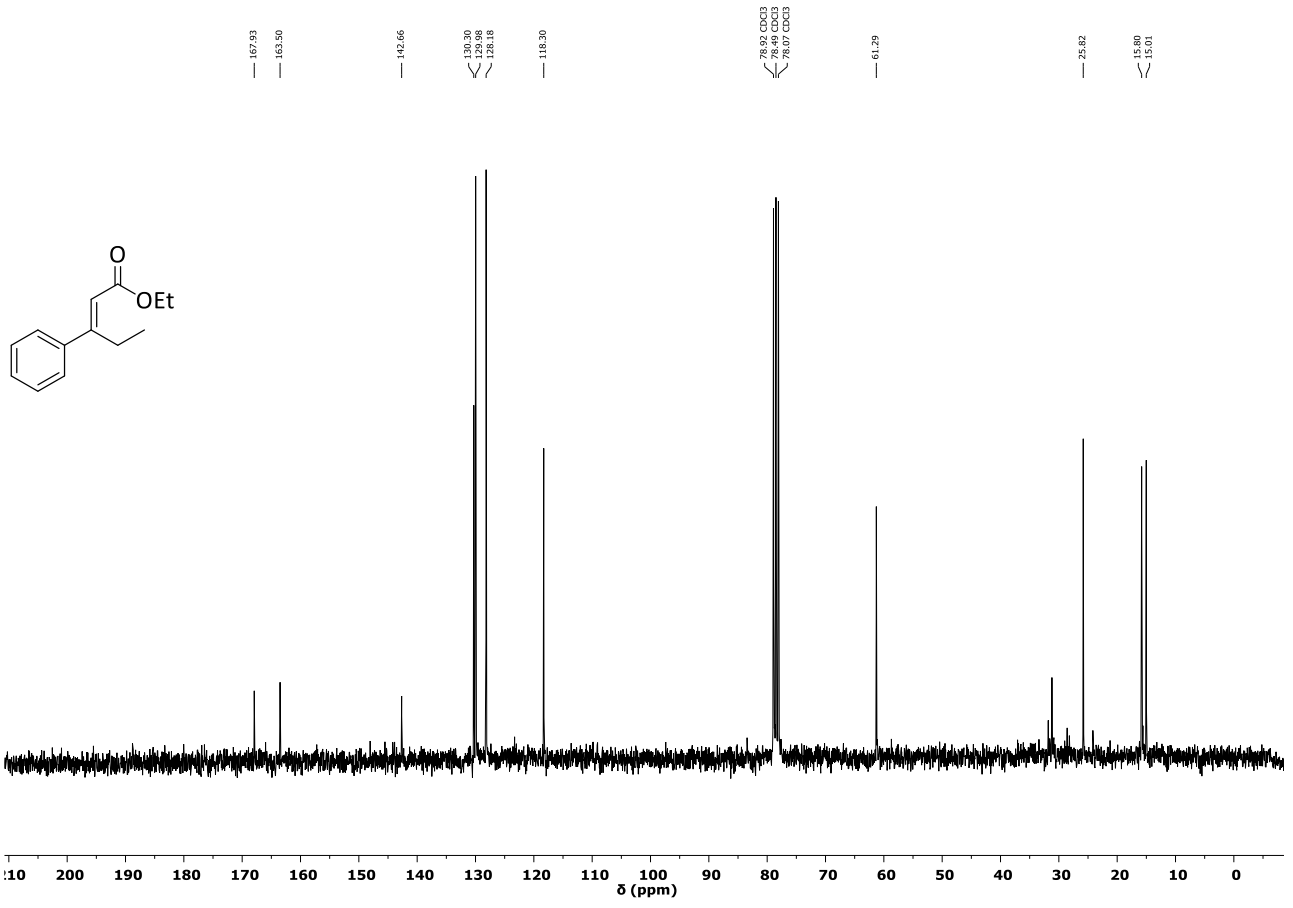
4.17
3.83
3.81
2.56
2.56
1.34
1.31
1.29
O
OEt
MeO
1.62
1.53
0.88
2.00
3.07
2.90
2.97
δ (ppm)

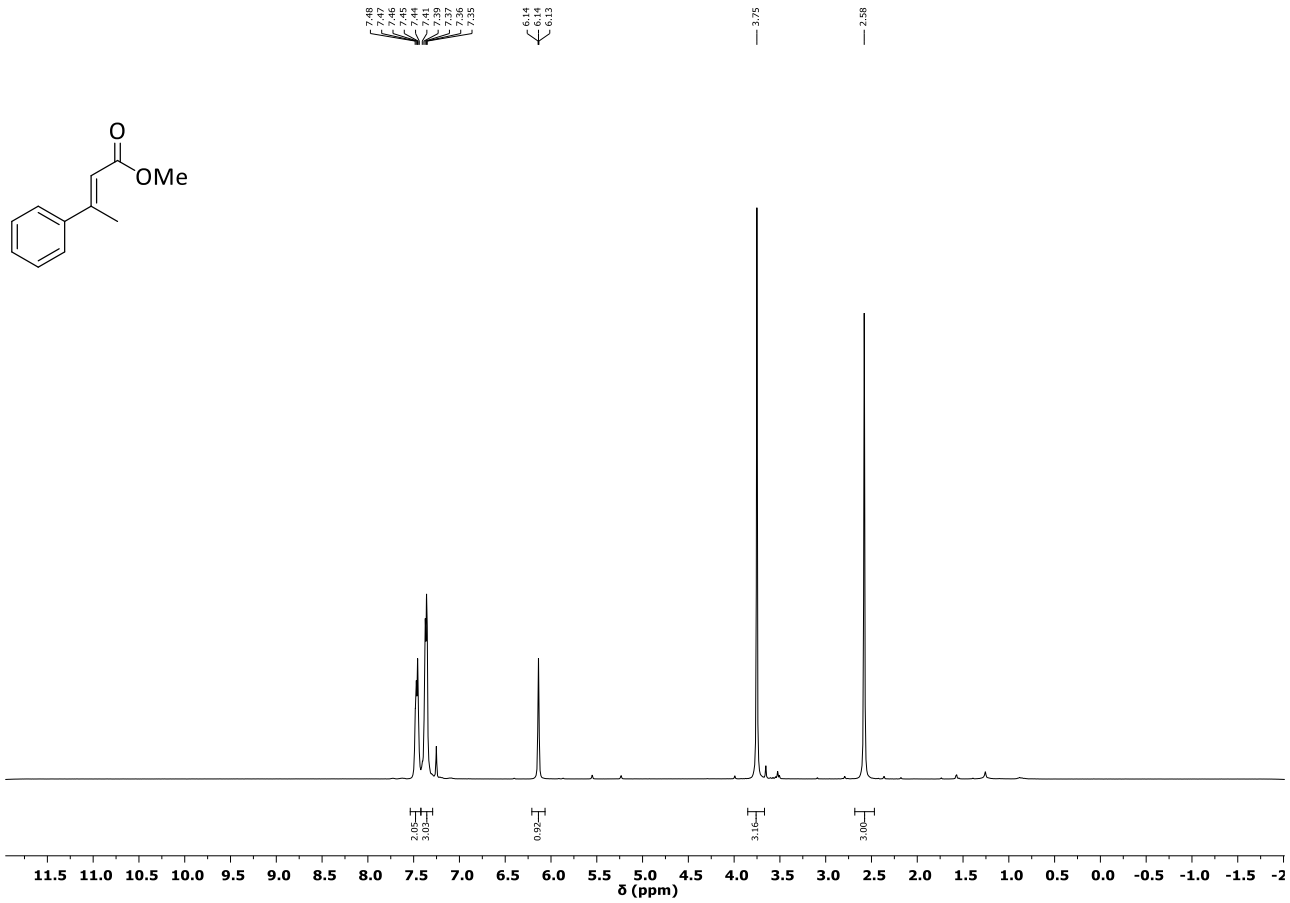

168.56
161.92
156.33
135.86
129.14
116.85
115.32
78.92 CDCl3
78.08 CDCl3
61.18
56.82
19.14
15.86
O
OEt
MeO
δ (ppm)

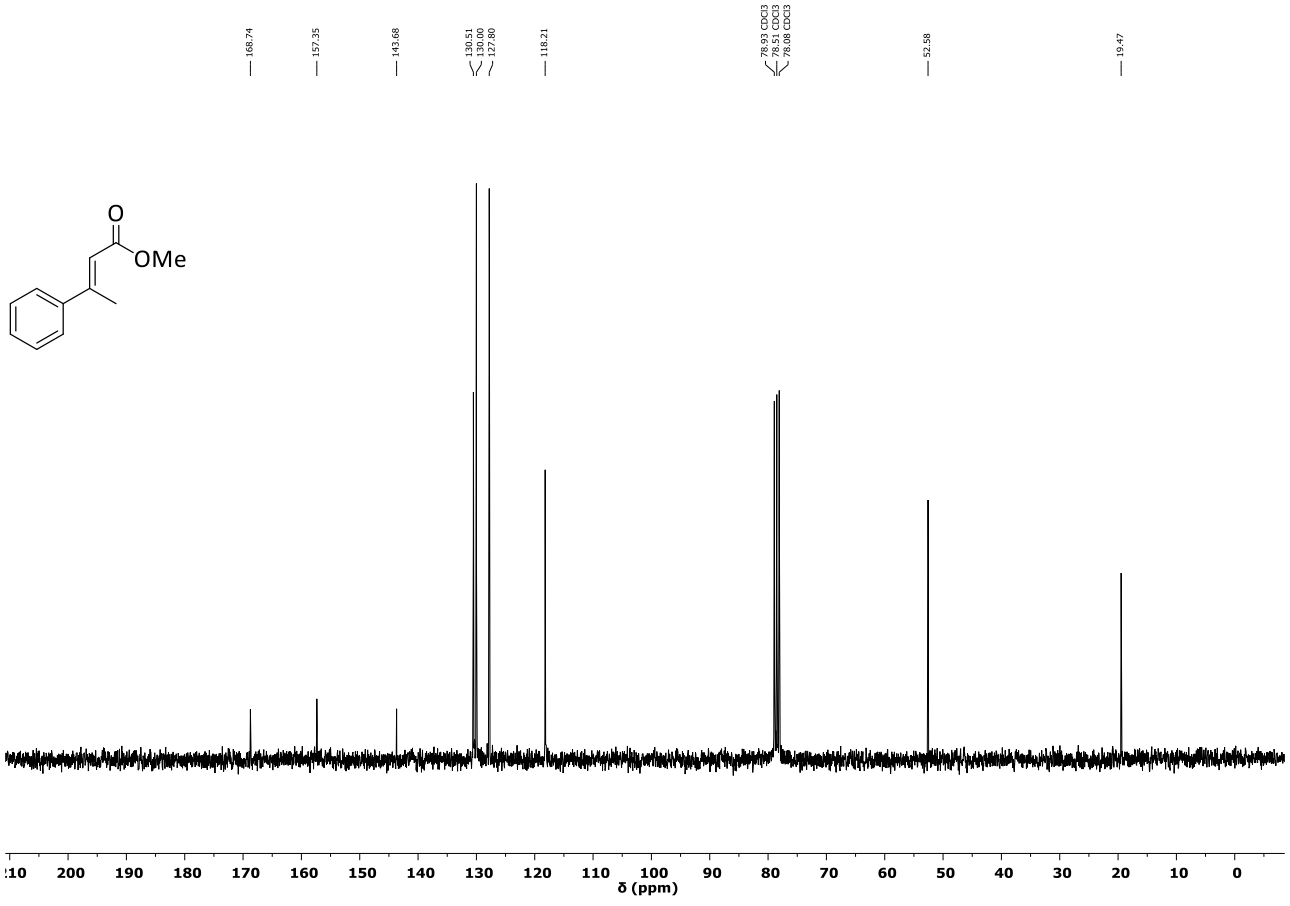

7.38
7.37
7.35
7.32
7.32
7.30
7.28
7.28
7.26 CHCl3
7.17
7.17
7.15
7.14
5.88
5.88
5.87
4.02
4.00
3.98
3.95
2.51
2.50
2.48
2.46
2.46
2.45
2.43
2.43
1.09
1.07
1.04
O
EtO
2.96
1.78
0.93
2.00
2.13
6.08
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
δ (ppm)

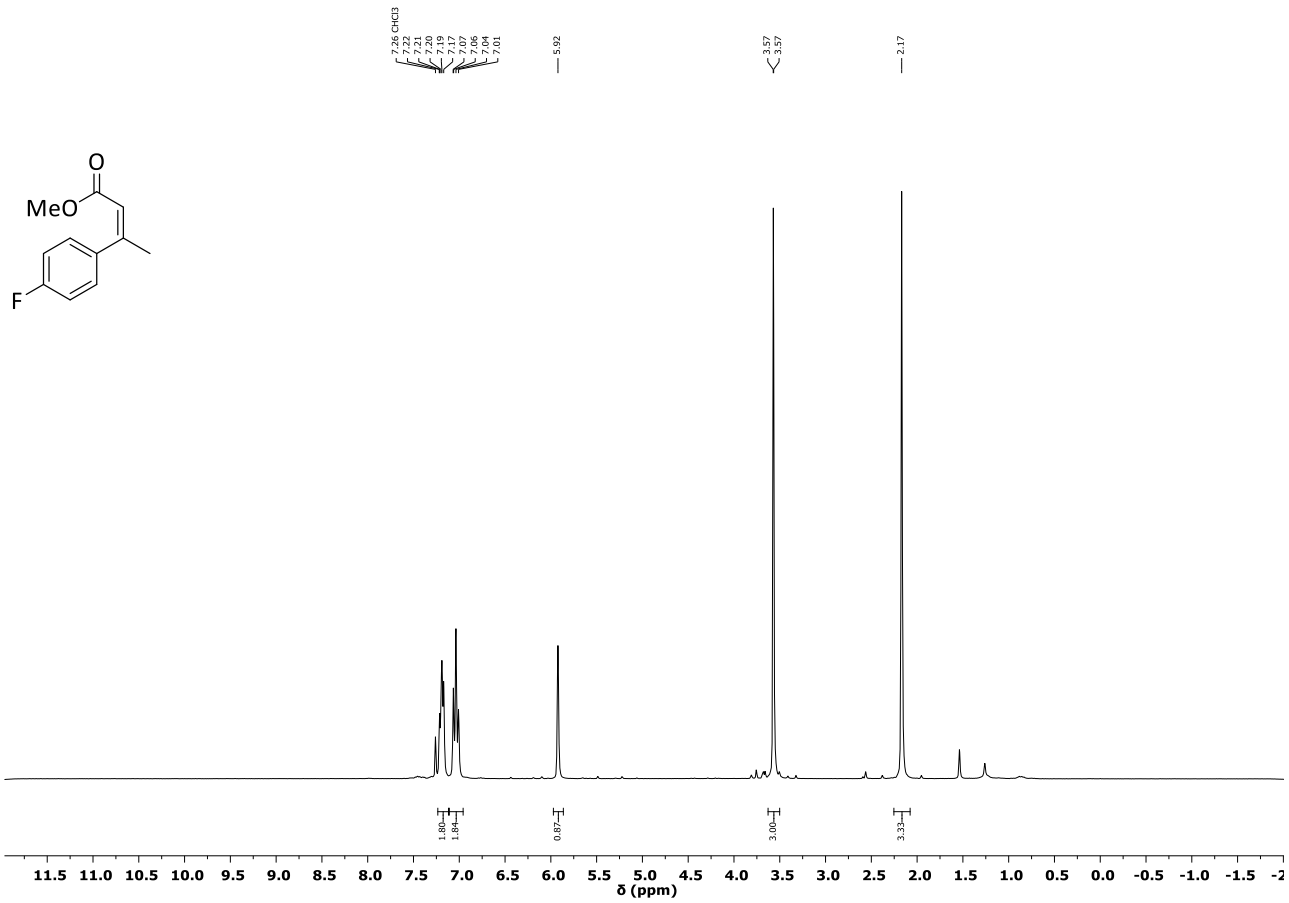

167.69
162.48
142.00
129.31
128.97
128.50
117.84
61.21
34.85
15.43
13.57
O
EtO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
δ (ppm)

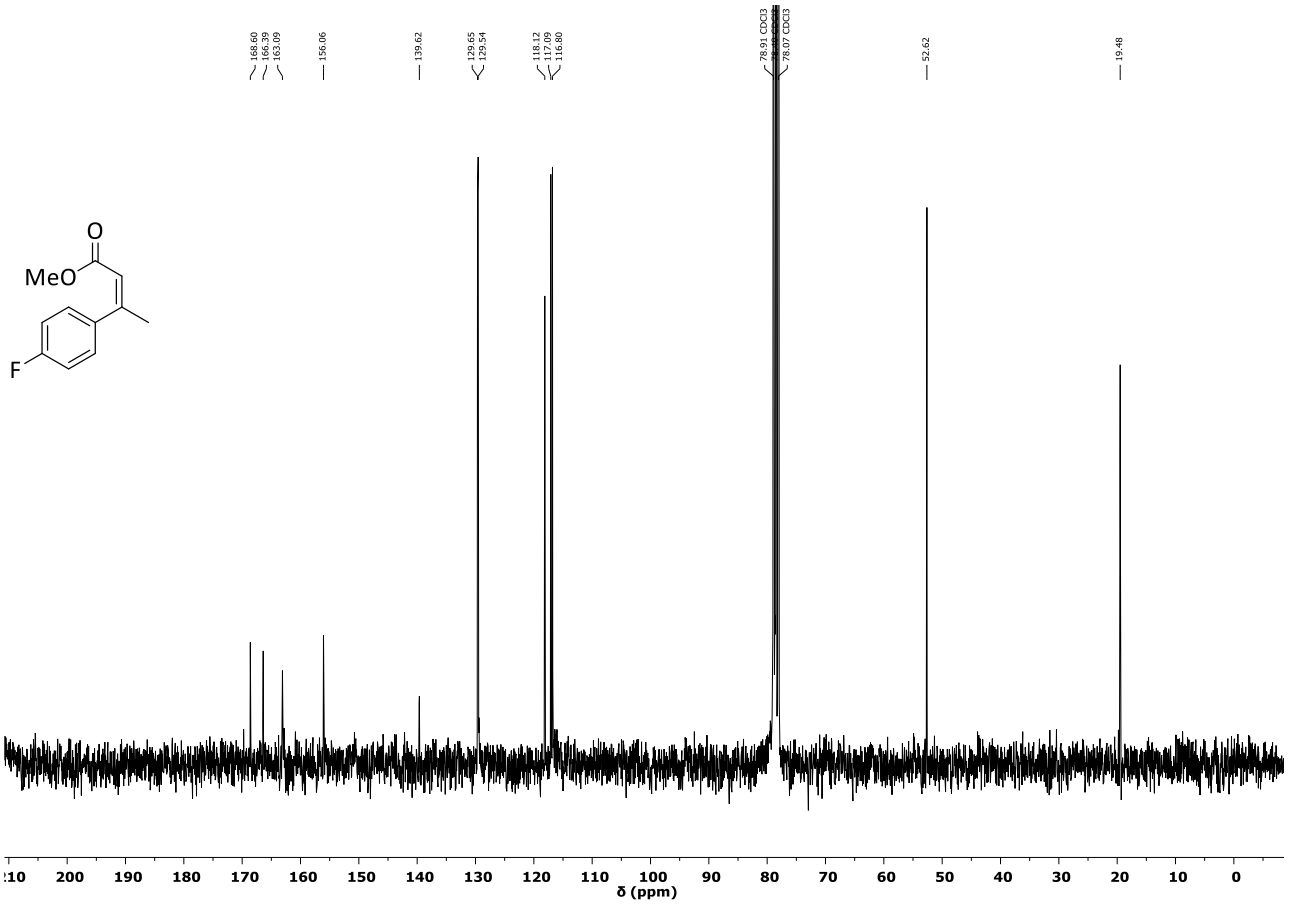

7.46
7.45
7.44
7.43
7.39
7.38
7.37
7.36
7.35
7.26 CHCl3
6.01
4.25
4.23
4.20
4.18
3.15
3.12
3.10
3.07
1.34
1.32
1.29
1.11
1.08
1.06
O
OEt
1.72
2.83
0.88
2.00
2.03
3.18
3.20
δ (ppm)

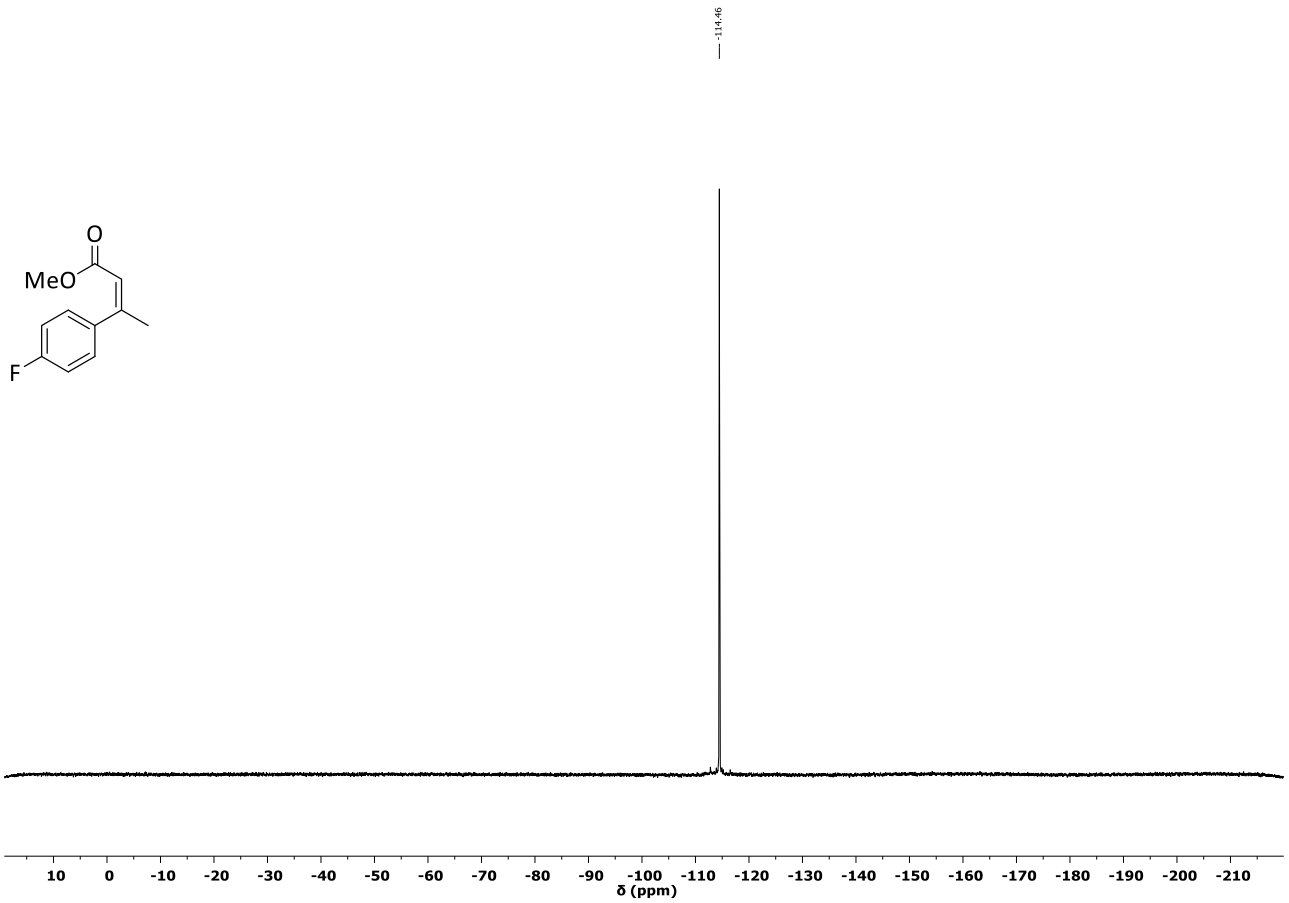

167.93
163.50
142.66
130.30
129.98
128.18
118.30
78.92 CDCl3
78.49 CDCl3
78.07 CDCl3
61.29
25.82
15.80
15.01
O
OEt
δ (ppm)

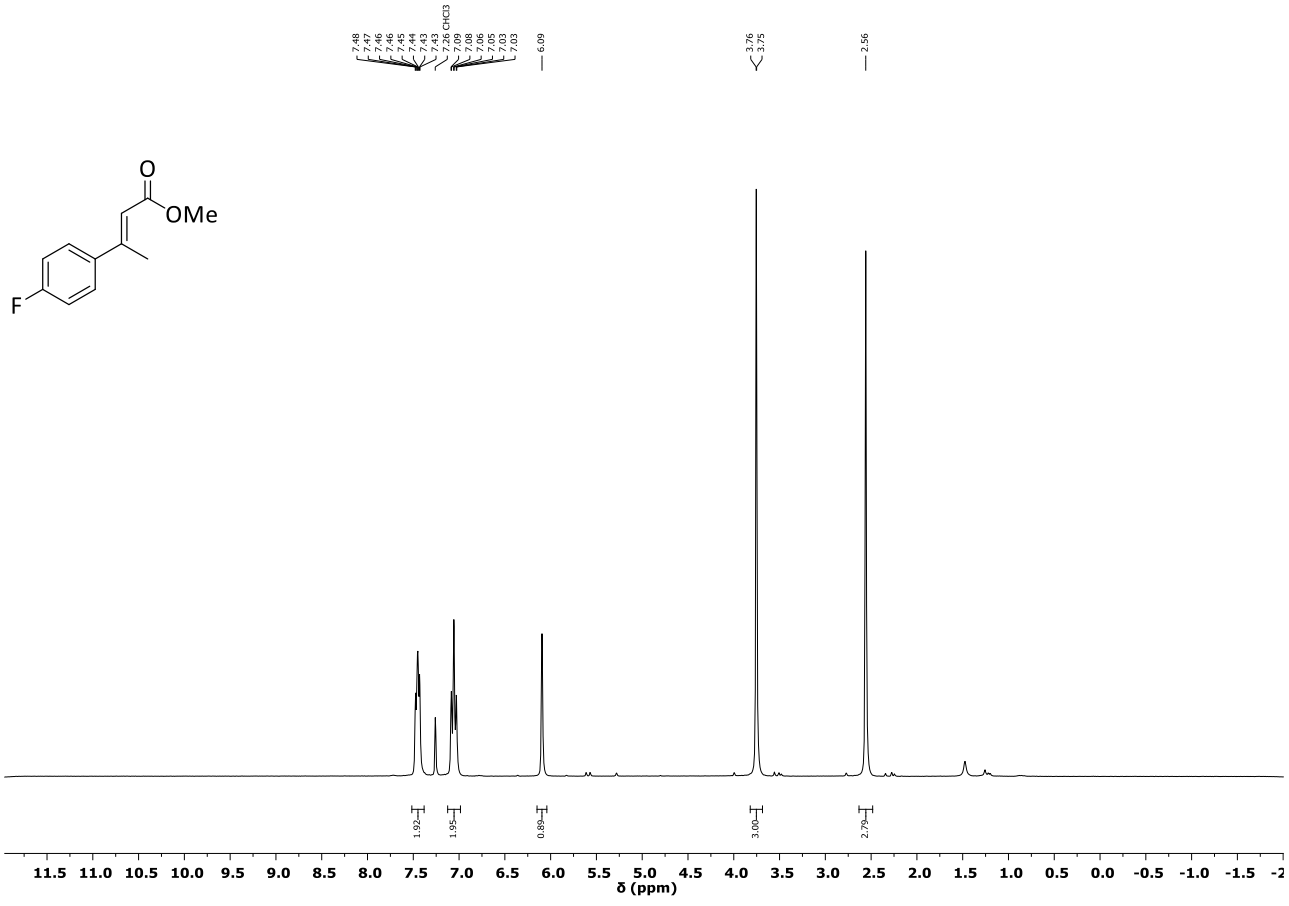

7.48
7.47
7.46
7.45
7.44
7.41
7.39
7.37
7.36
7.35
6.14
6.14
6.13
3.75
2.58
O
OMe
2.05
3.03
0.92
3.16
3.00
δ (ppm)

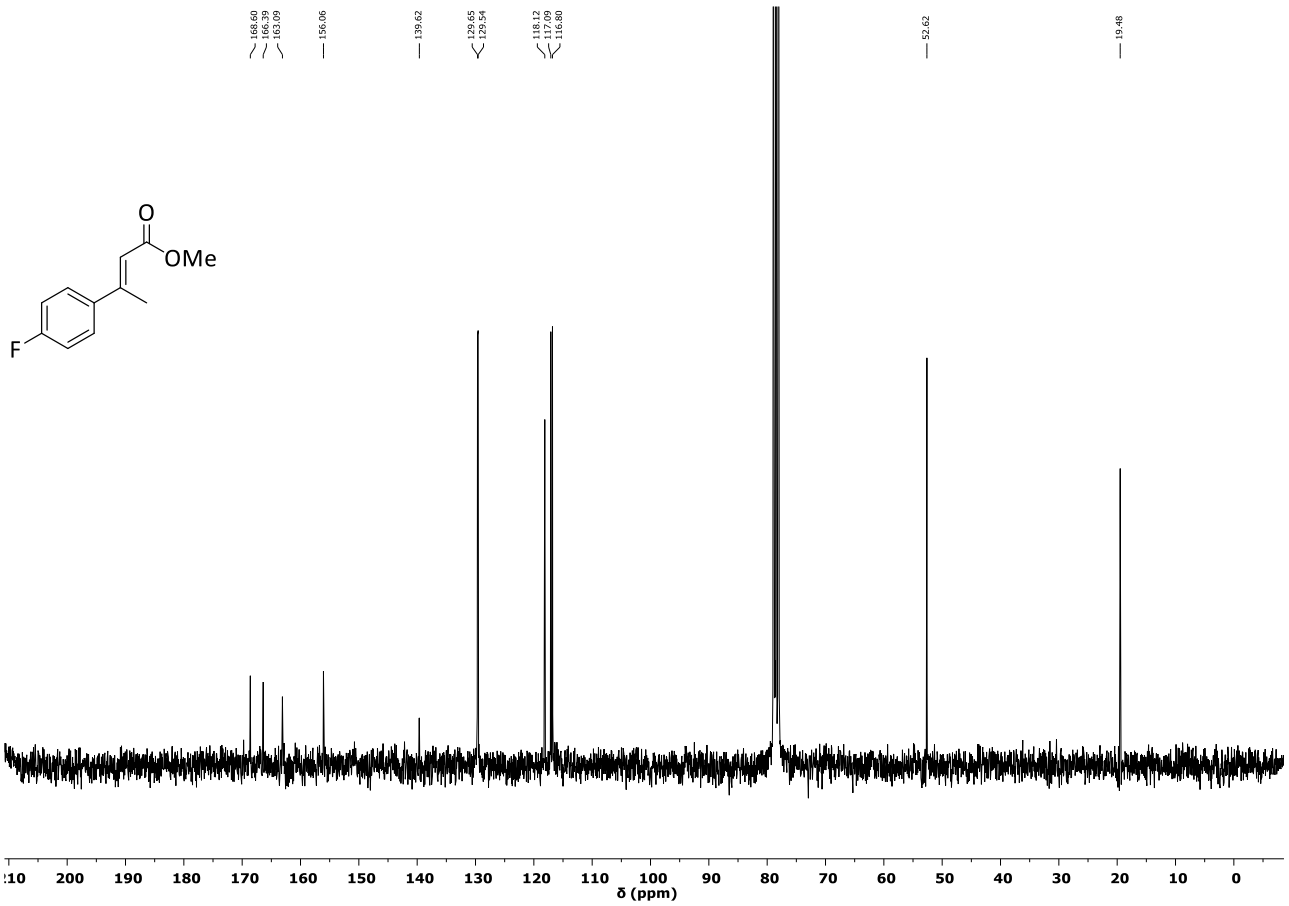

168.74
157.35
143.68
130.51
130.00
127.80
118.21
78.93 CDCl3
78.51 CDCl3
78.08 CDCl3
52.58
19.47
O
OMe
δ (ppm)

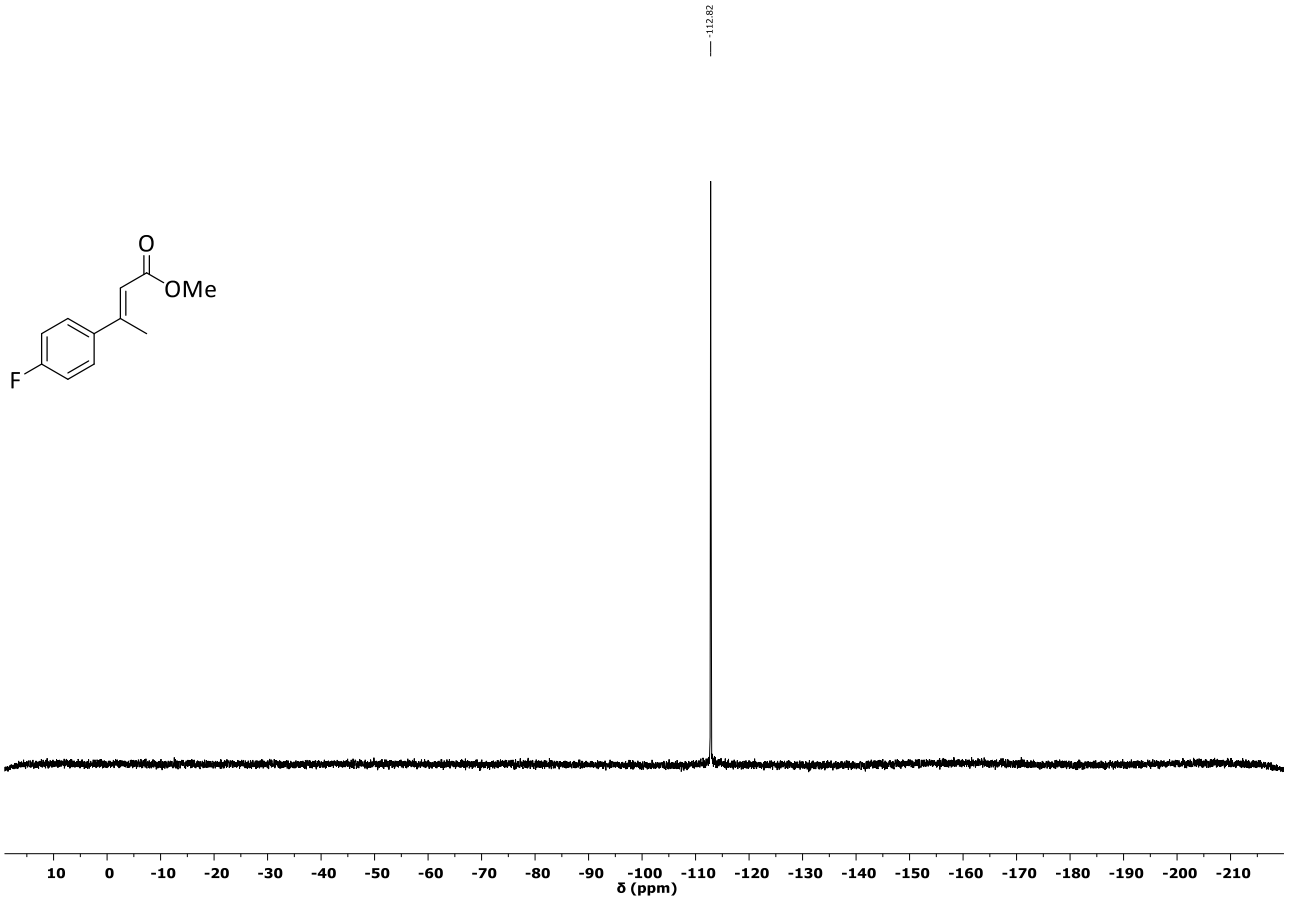

7.26 CHCl3
7.22
7.21
7.20
7.19
7.17
7.07
7.06
7.04
7.01
5.92
3.57
3.57
2.17
O
MeO
F
1.00
1.84
0.87
3.00
3.33
δ (ppm)

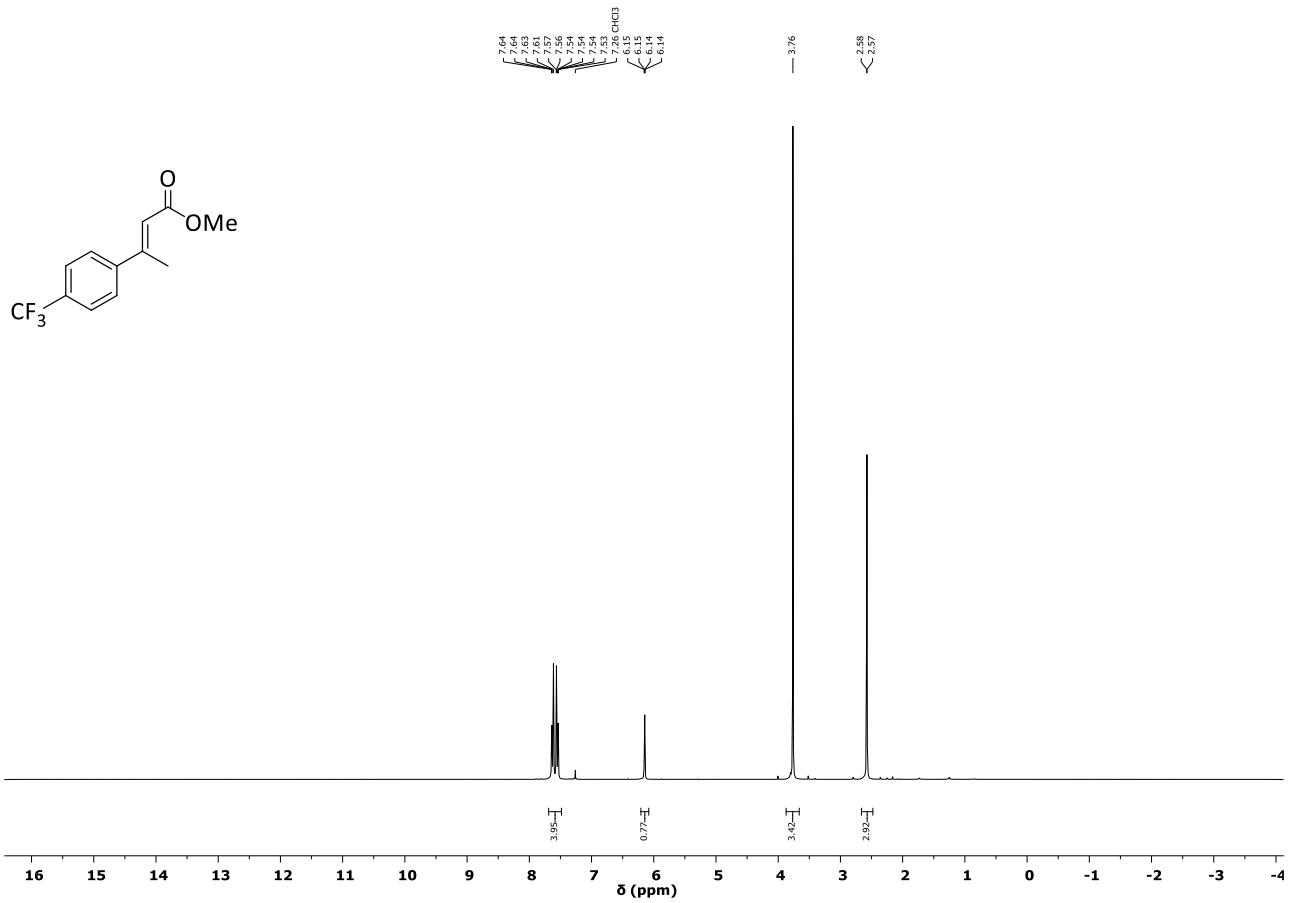

168.60
166.39
163.09
156.06
139.62
129.65
129.54
118.12
117.09
116.80
78.91 CDCl3
78.07 CDCl3
52.62
19.48
O
MeO
F
δ (ppm)

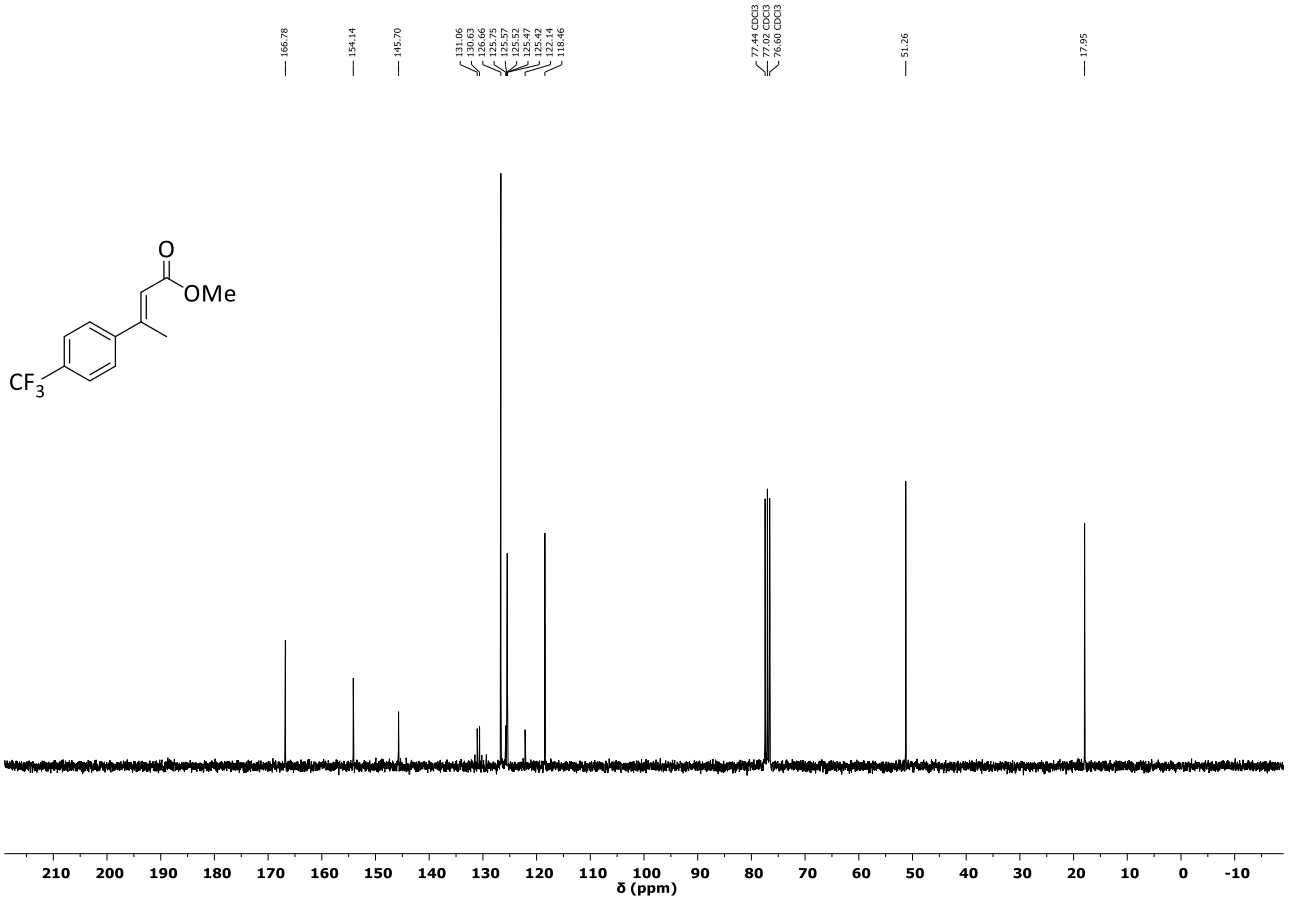

-114.46
O
MeO
F
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
δ (ppm)

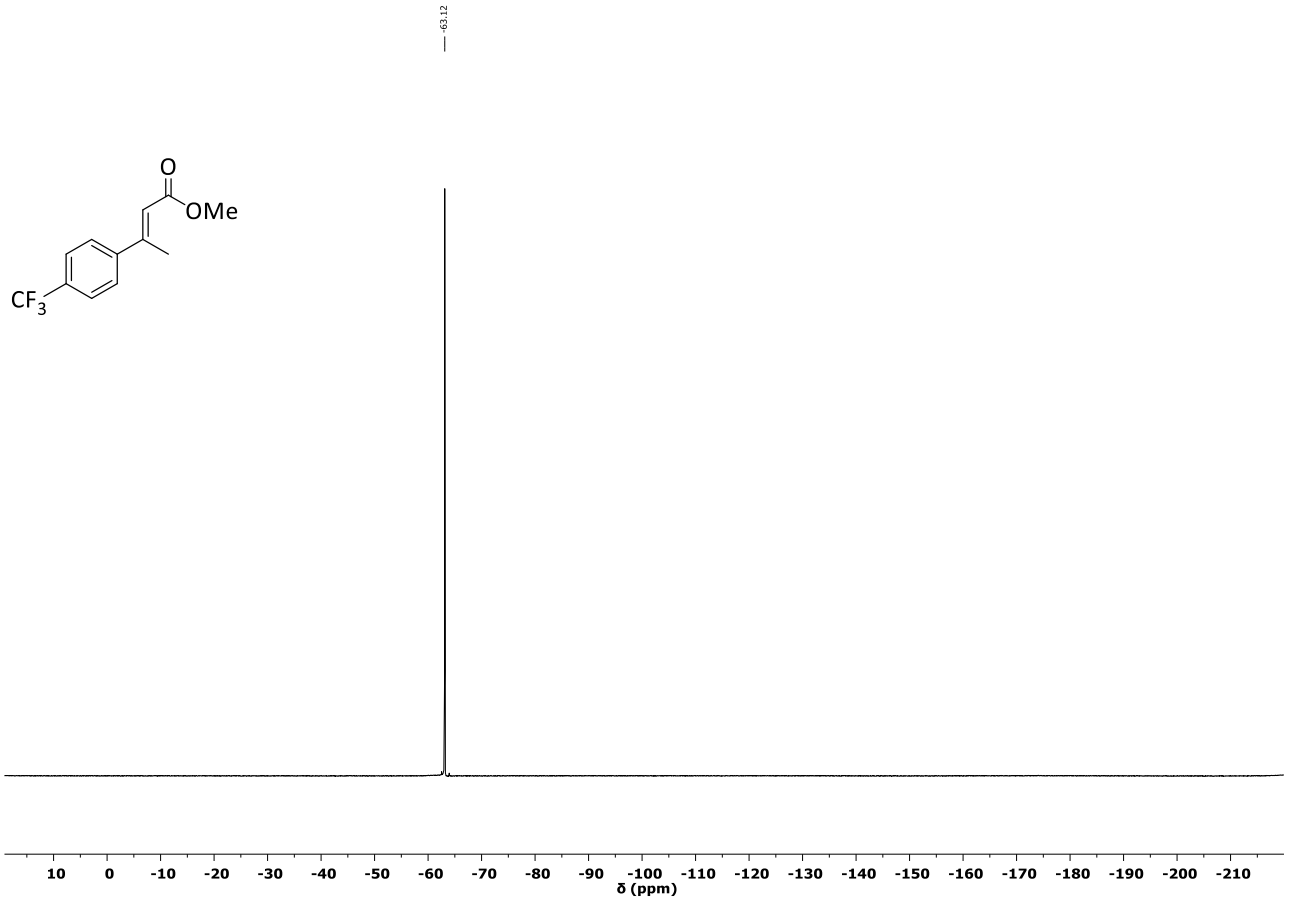

7.48
7.47
7.46
7.46
7.45
7.44
7.43
7.43
7.26 CHCl3
7.09
7.08
7.06
7.05
7.03
7.03
6.09
3.76
3.75
2.56
O
OMe
F
1.92
1.95
0.89
3.00
2.79
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
δ (ppm)

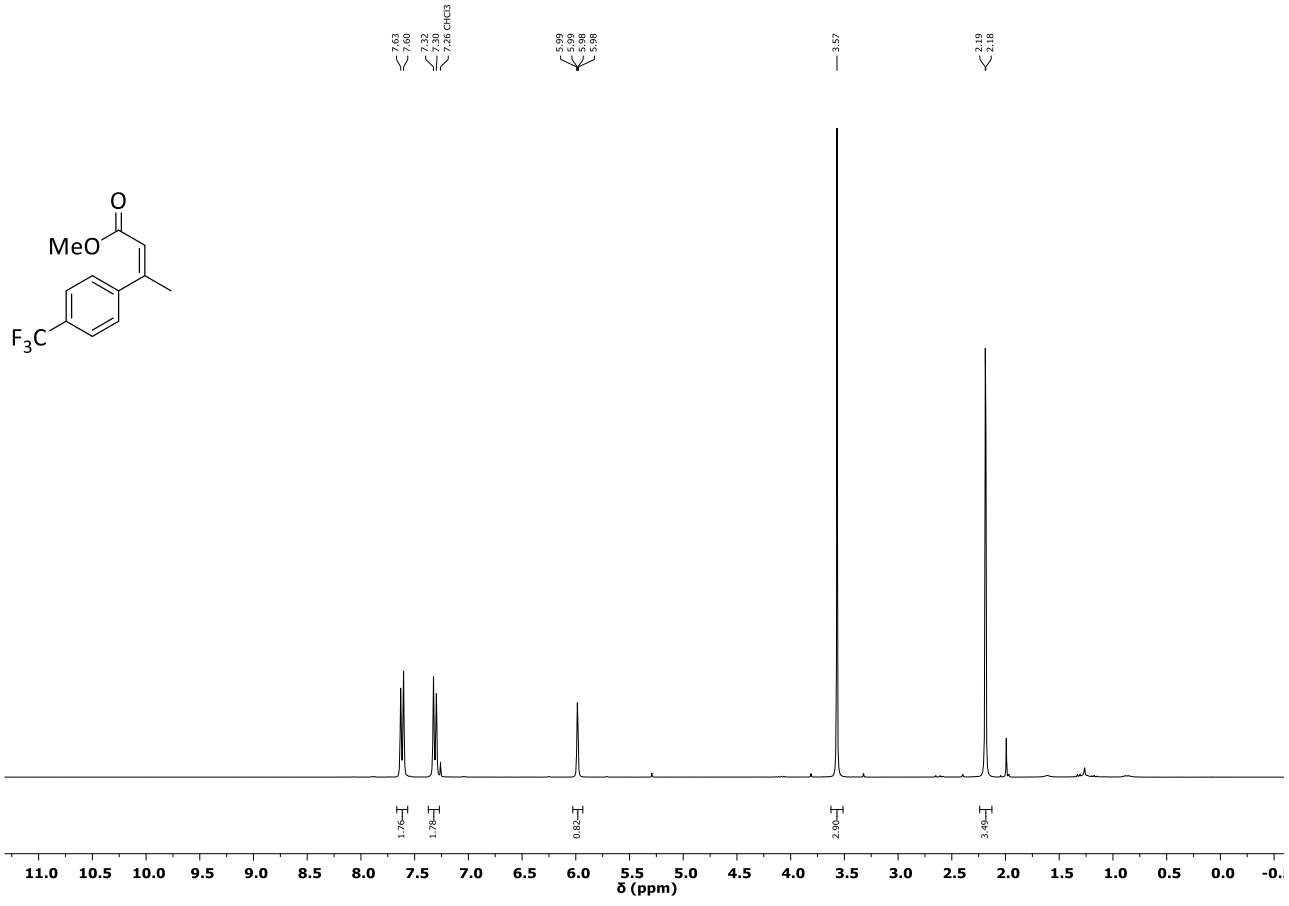

168.60
166.39
163.09
156.06
139.62
129.65
129.54
118.12
117.09
116.80
52.62
19.48
O
OMe
F
δ (ppm)

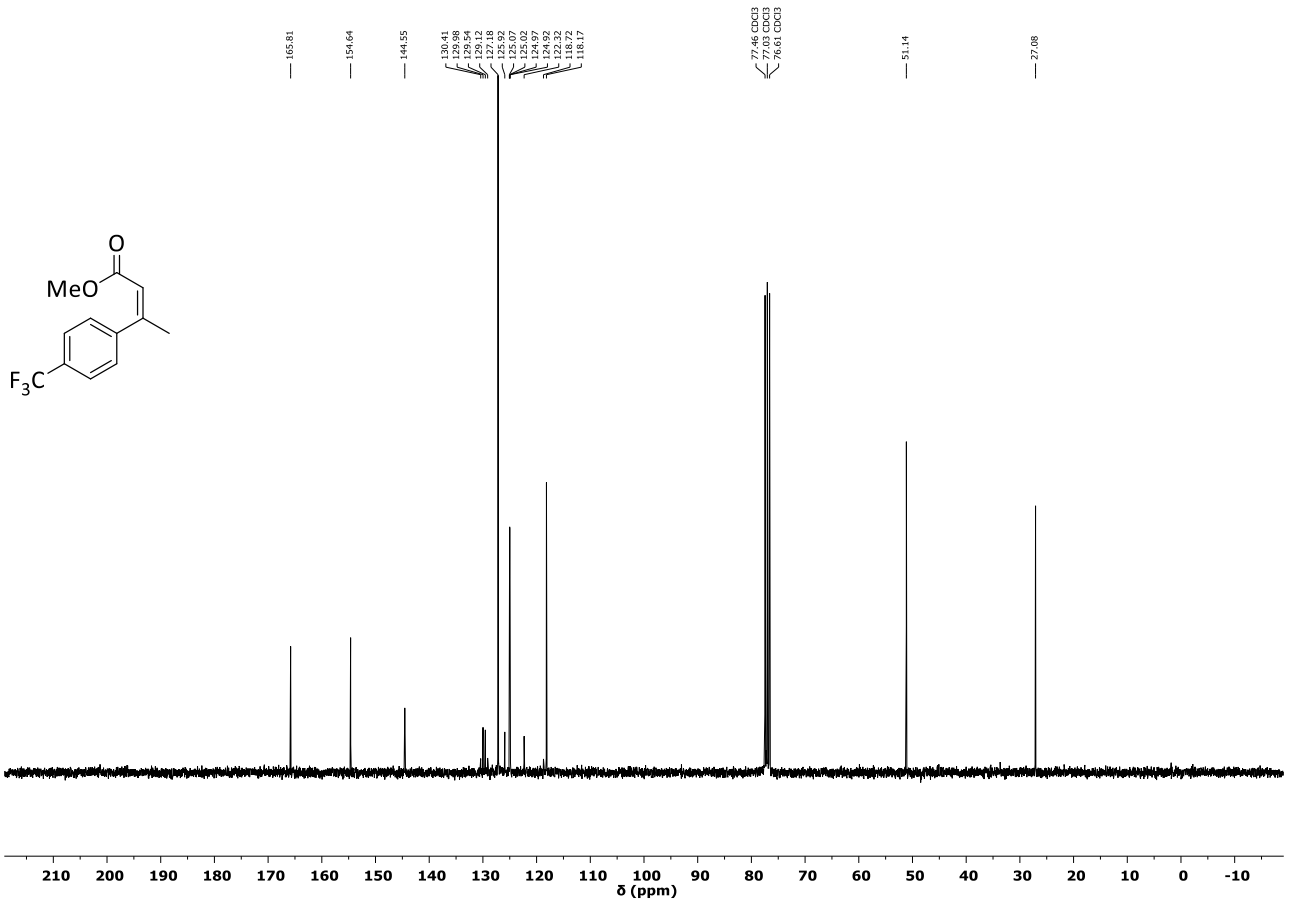

-112.82
O
OMe
F
δ (ppm)

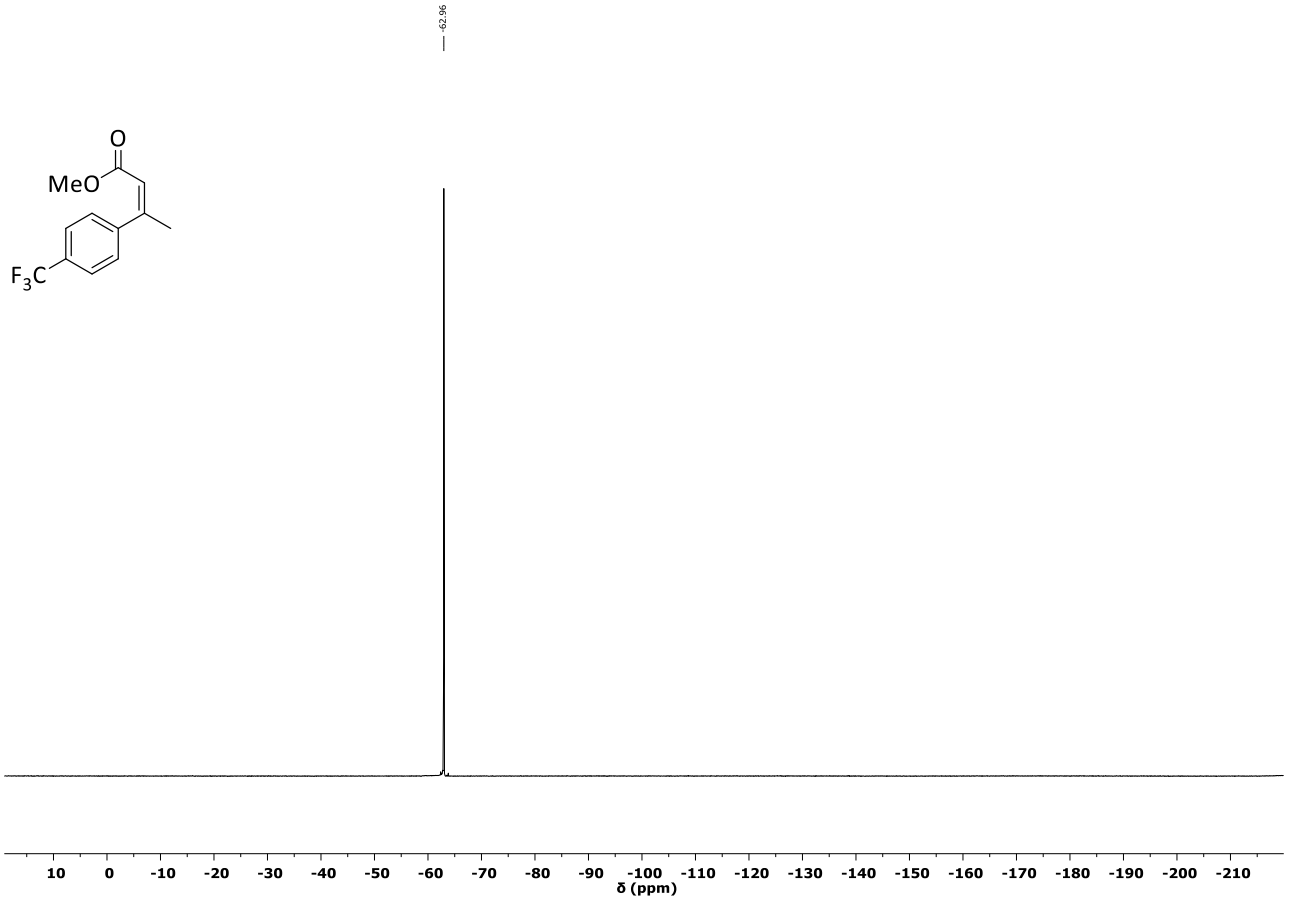

7.64
7.64
7.63
7.61
7.57
7.56
7.54
7.54
7.53
7.26 CHCl3
6.15
6.14
6.14
3.76
2.58
2.57
O
OMe
CF3
3.95
0.77
3.42
2.92
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
δ (ppm)

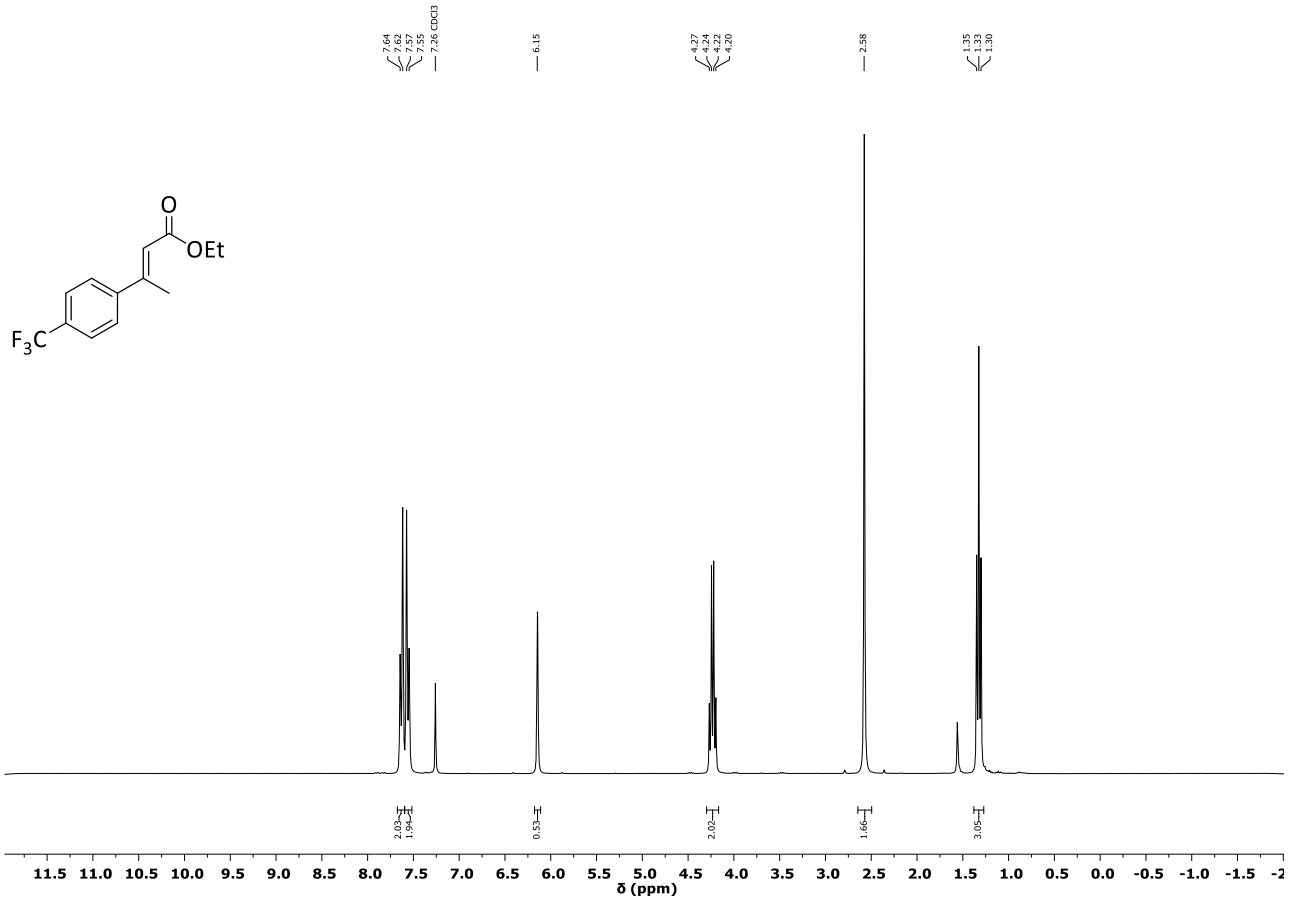

166.78
154.14
145.70
131.06
130.63
126.66
125.75
125.57
125.52
125.47
125.42
122.14
118.46
77.44 CDCl3
77.02 CDCl3
76.60 CDCl3
51.26
17.95
O
OMe
CF3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

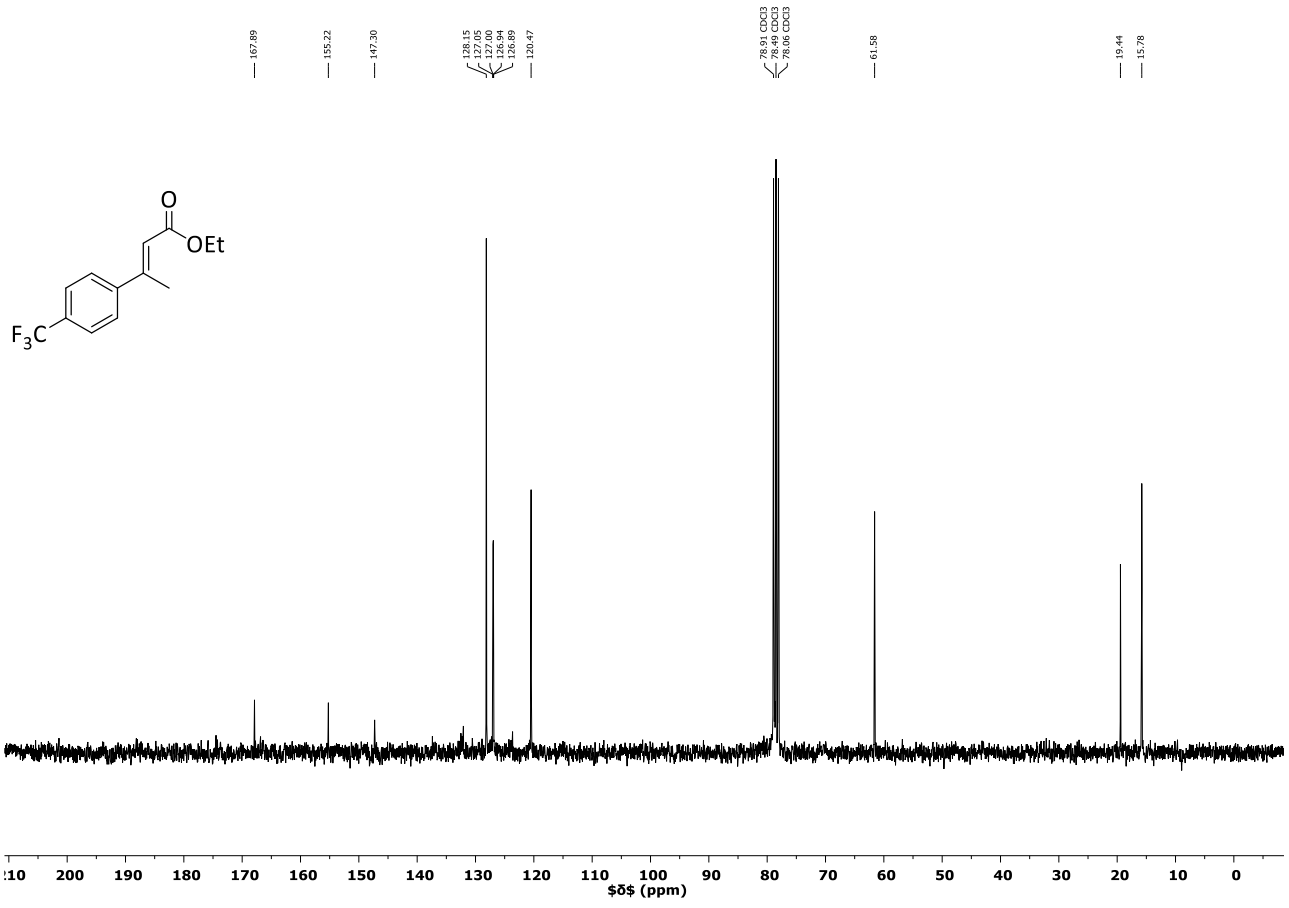

-63.12
O
OMe
CF3
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
δ (ppm)

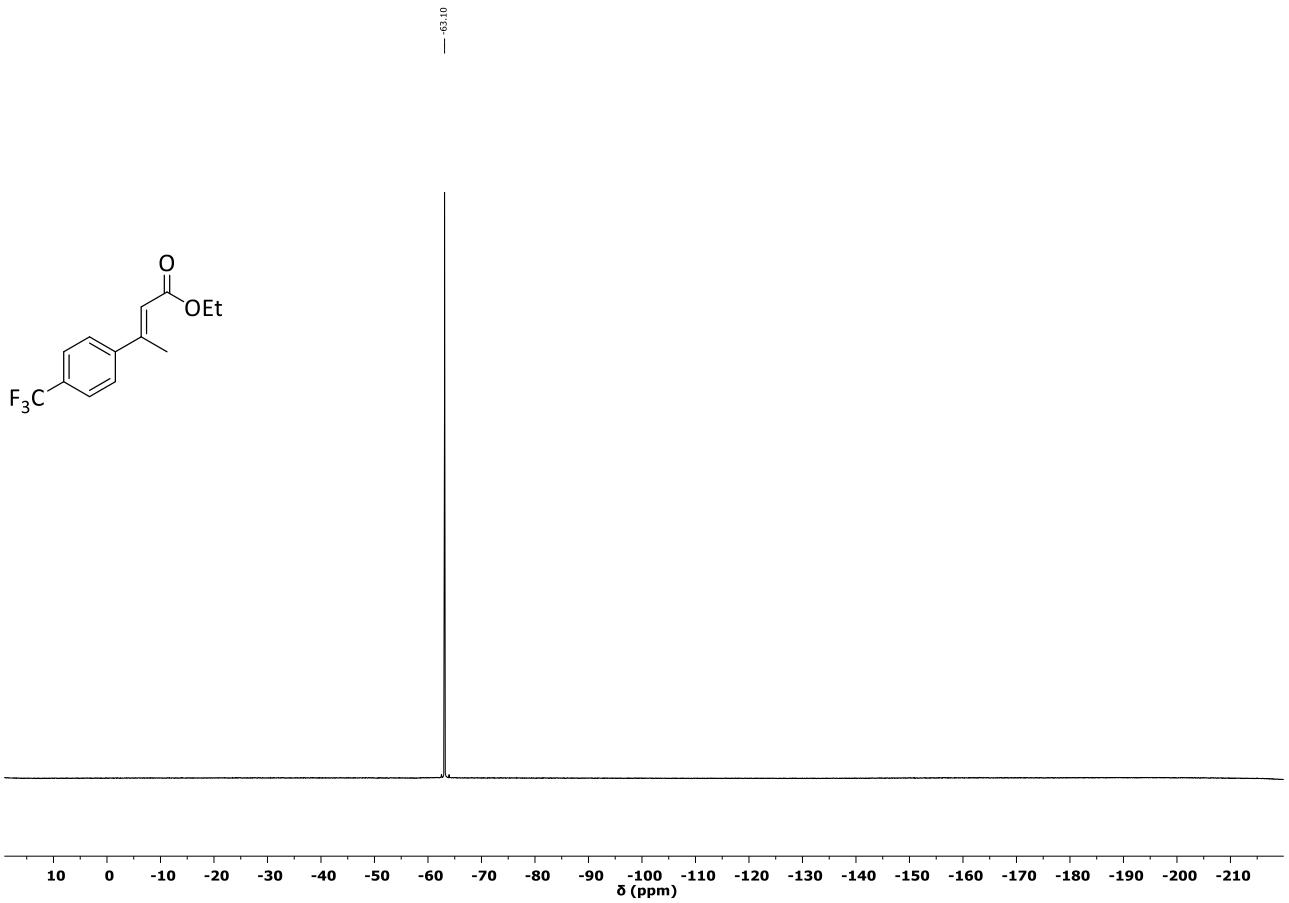

7.63
7.60
7.32
7.30
7.26 CHCl3
5.99
5.99
5.98
5.98
3.57
2.19
2.18
O
MeO
F3C
1.76
1.78
0.82
2.90
3.49
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

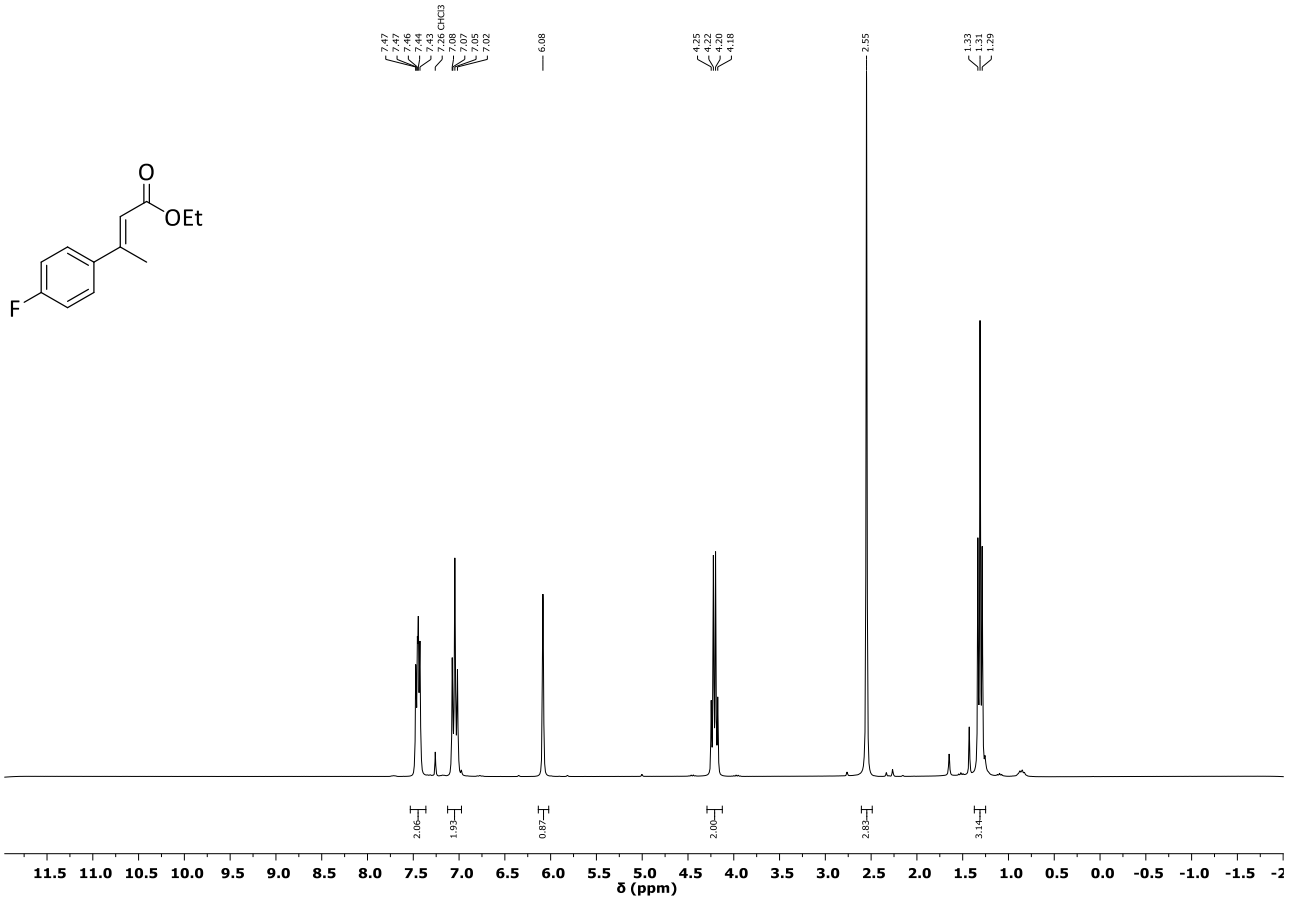

165.81
154.64
144.55
130.41
129.98
129.54
129.12
127.18
125.92
125.07
125.02
124.97
124.92
122.32
118.72
118.17
77.46 CDCl3
77.03 CDCl3
76.61 CDCl3
51.14
27.08
O
MeO
F3C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

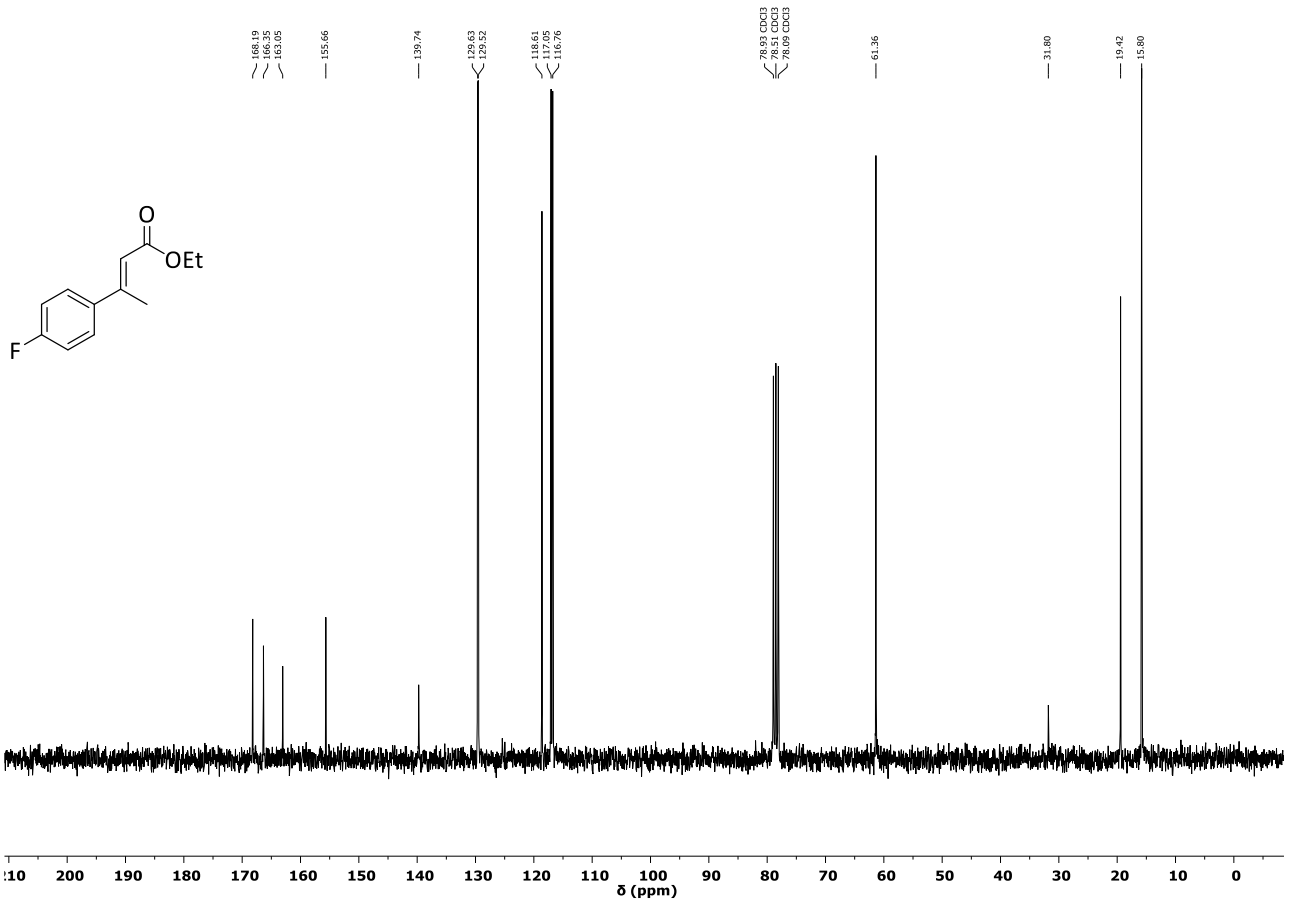

62.96
O
MeO
F3C
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
δ (ppm)

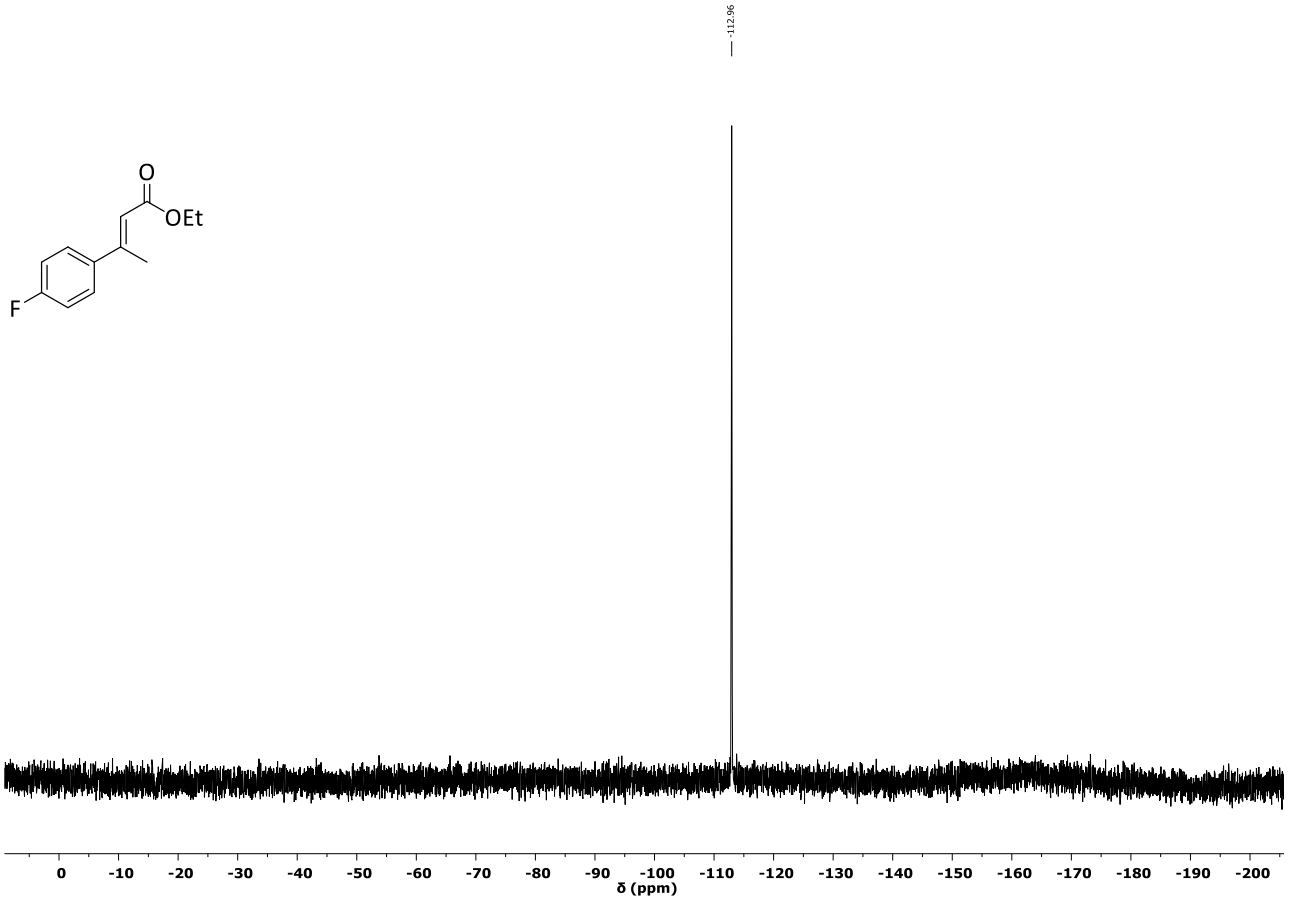

7.64
7.62
7.57
7.55
7.26 CDCl3
6.15
4.27
4.24
4.22
4.20
2.58
1.35
1.33
1.30
O
OEt
F3C
2.03
1.94
0.53
2.02
1.66
3.05
δ (ppm)

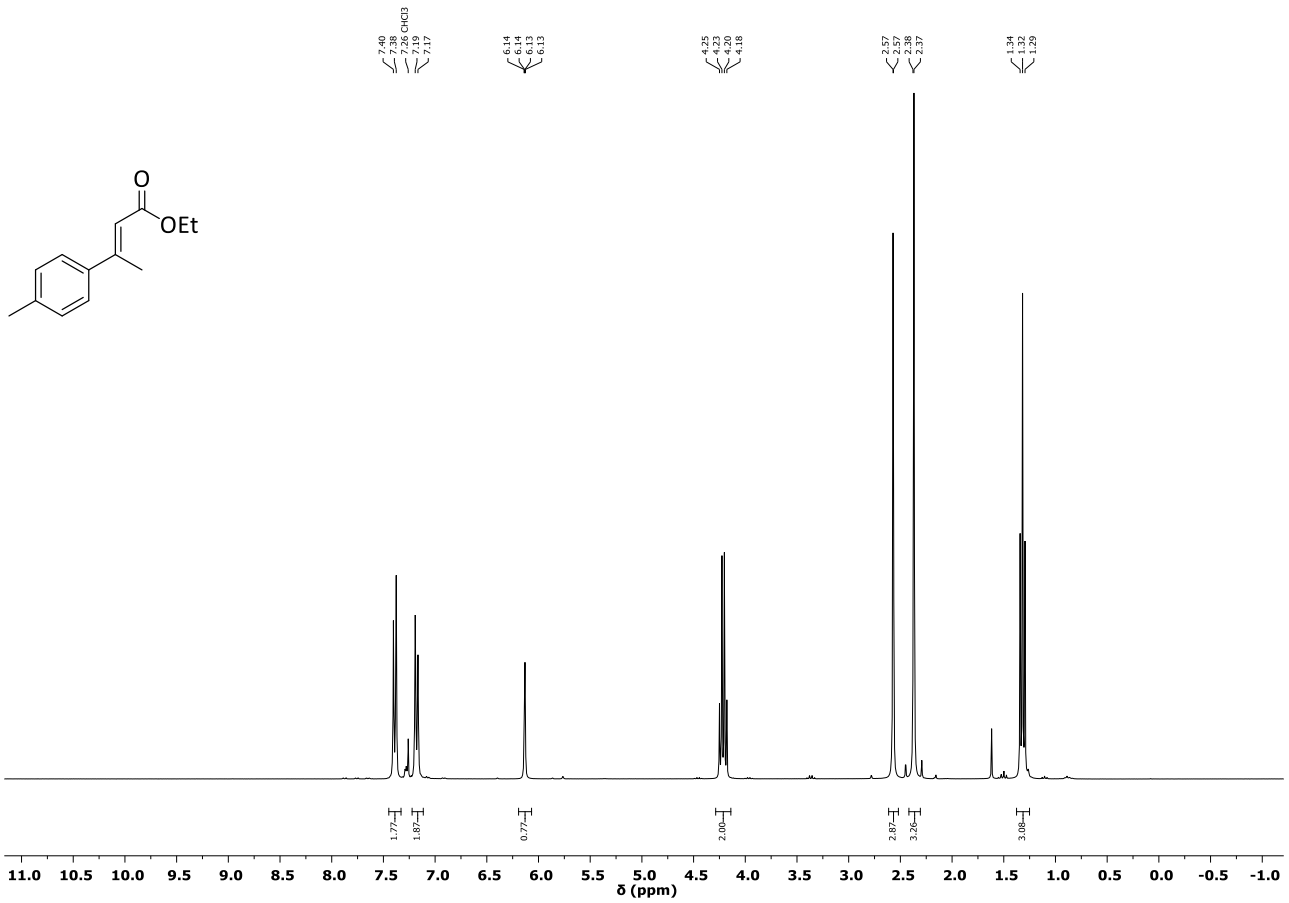

167.89
155.22
147.30
128.15
127.05
127.00
126.94
126.89
120.47
78.91 CDCl3
78.49 CDCl3
78.06 CDCl3
61.58
19.44
15.78
O
OEt
F3C
$δ$ (ppm)

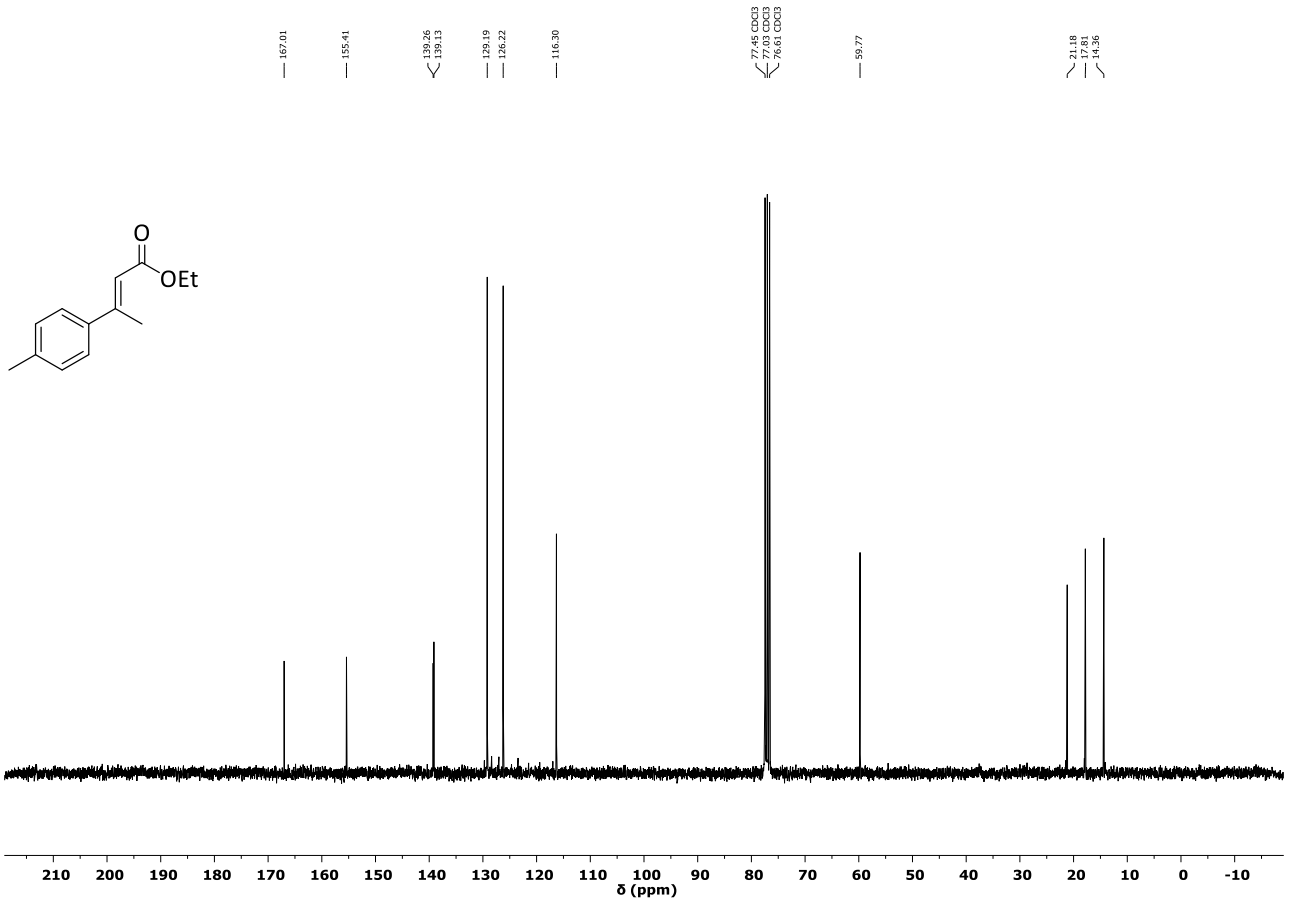

-63.10
O
OEt
F3C
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
δ (ppm)

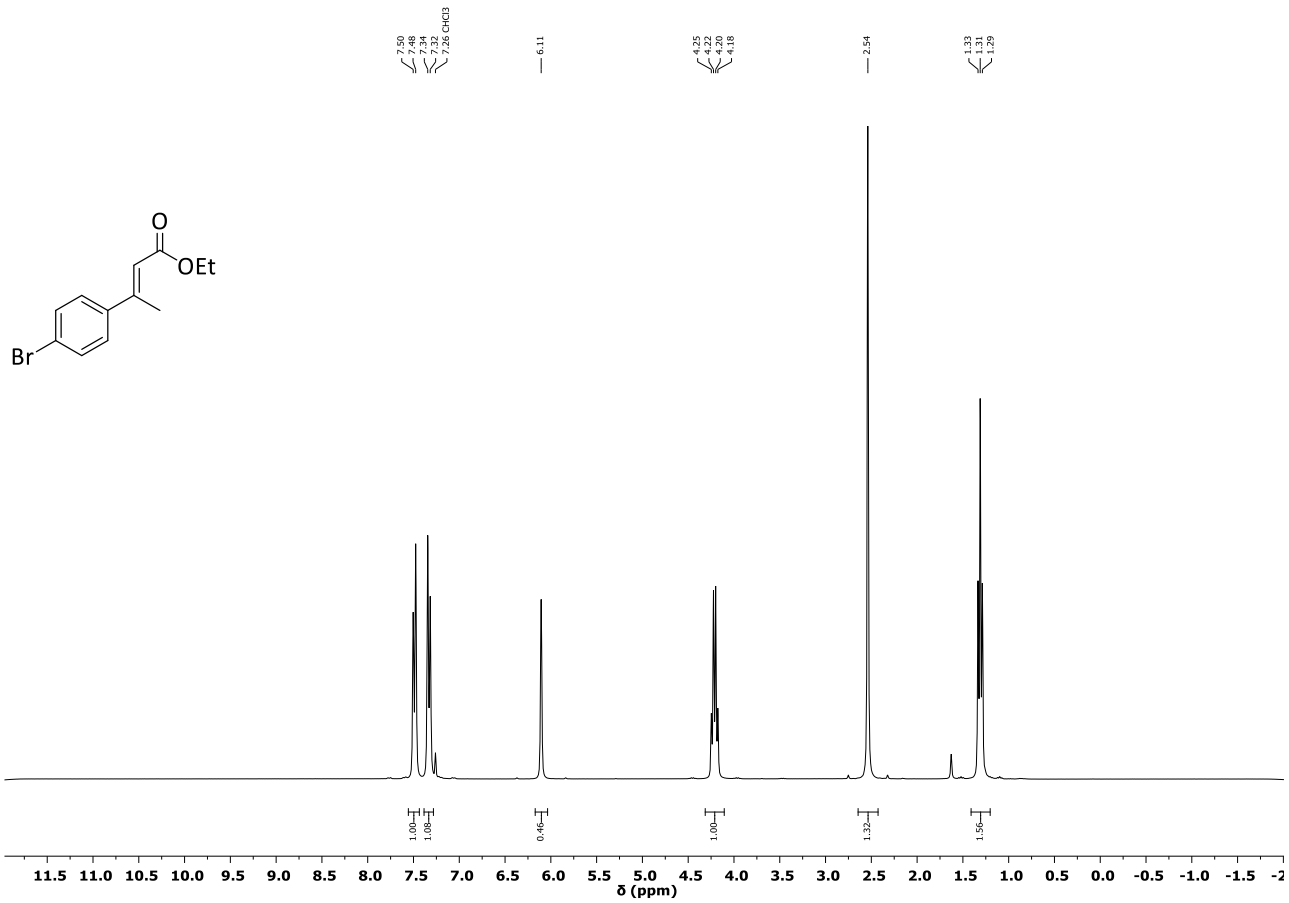

7.47
7.47
7.46
7.44
7.43
7.26 CHCl3
7.08
7.07
7.05
7.02
6.08
4.25
4.22
4.20
4.18
2.55
1.33
1.31
1.29
O
OEt
F
2.06
1.93
0.87
2.00
2.83
3.14
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
δ (ppm)

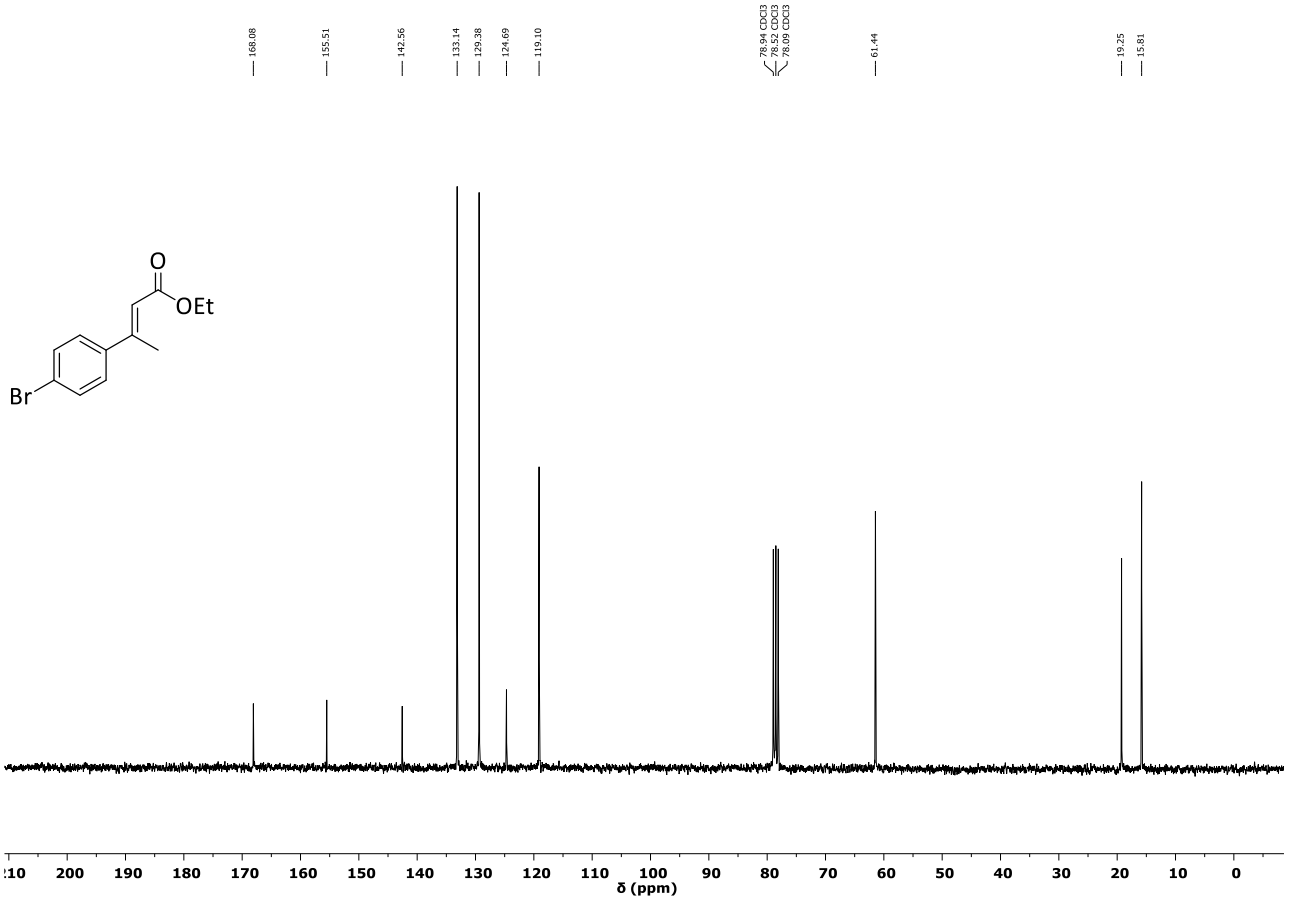

168.19
166.35
163.05
155.66
139.74
129.63
129.52
118.61
117.05
116.76
78.93 CDCl3
78.51 CDCl3
78.09 CDCl3
61.36
31.80
19.42
15.80
O
OEt
F
δ (ppm)

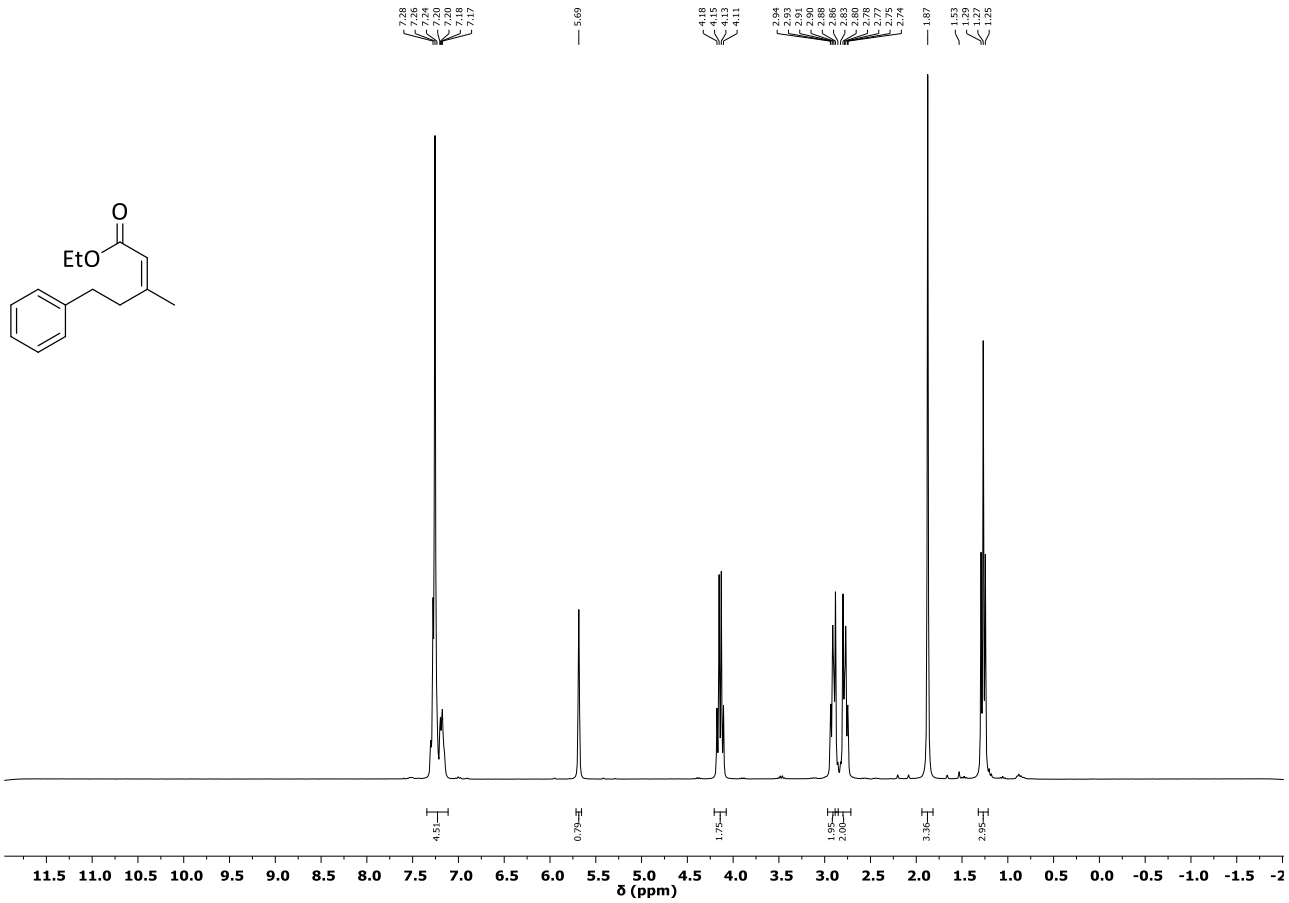

-112.96
O
OEt
F
δ (ppm)

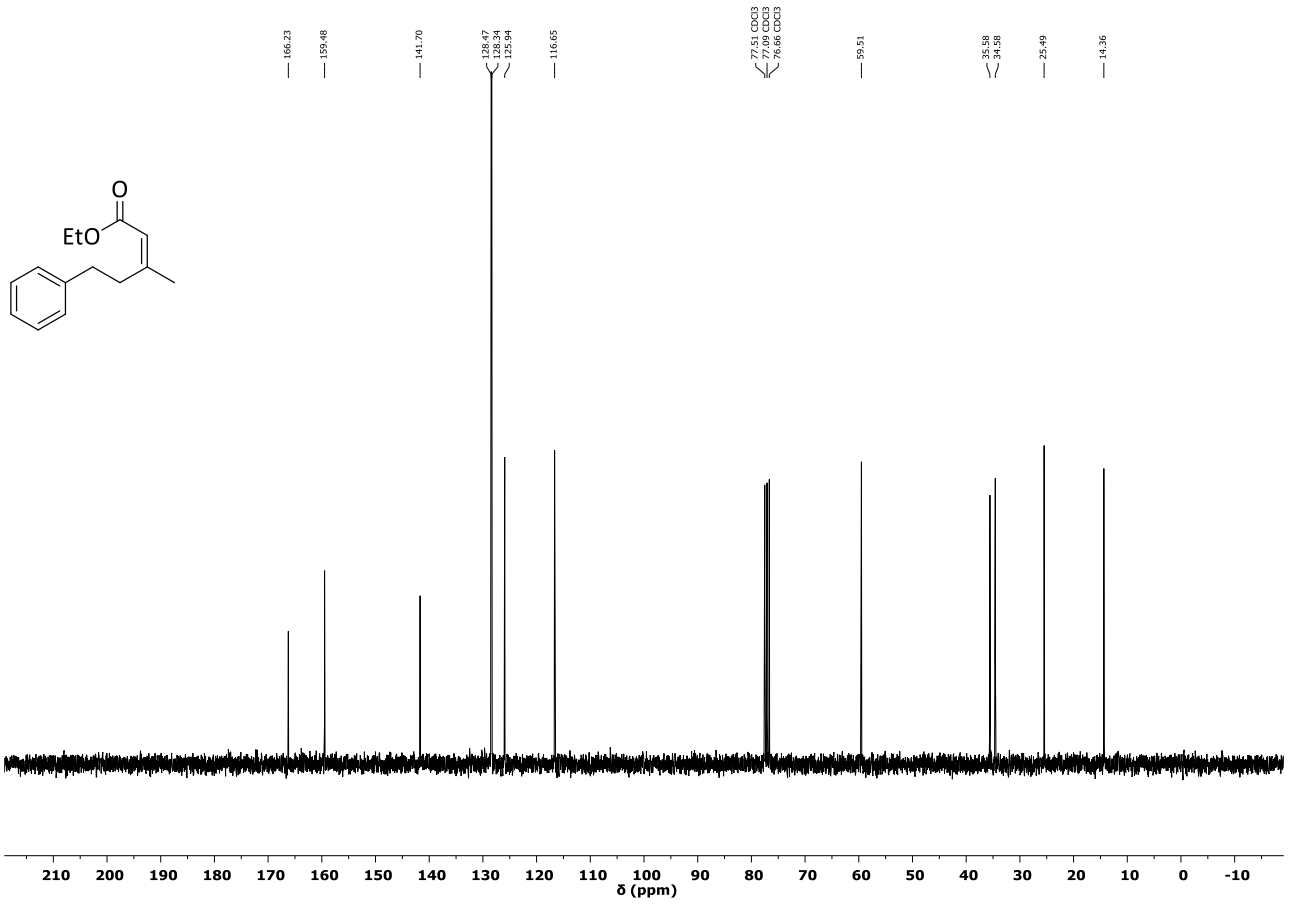

7.40
7.38
7.26 CHCl3
7.19
7.17
6.14
6.14
6.13
6.13
4.25
4.23
4.20
4.18
2.57
2.57
2.38
2.37
1.34
1.32
1.29
O
OEt
1.77
1.87
0.77
2.00
2.87
3.26
3.08
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
δ (ppm)

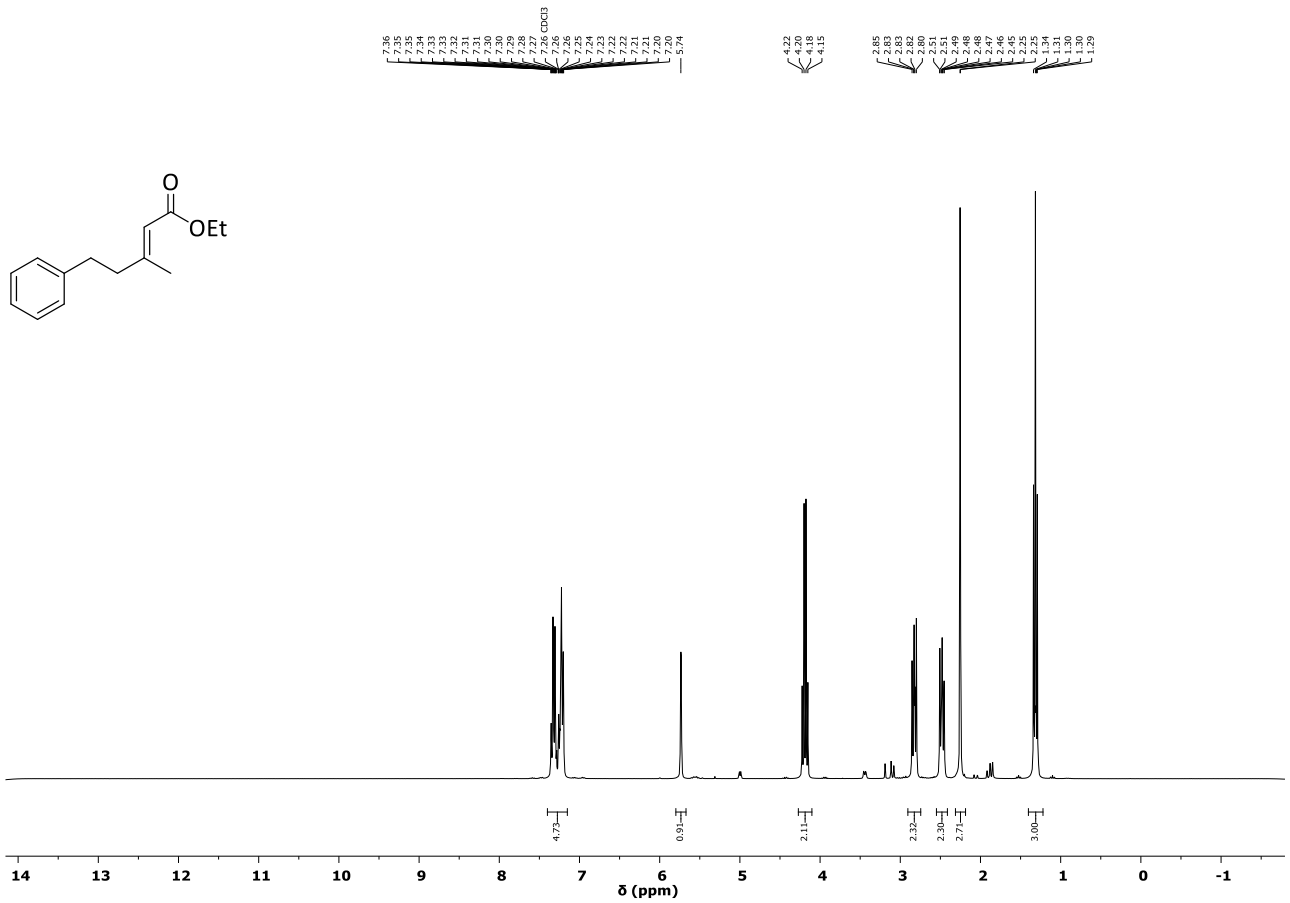

167.01
155.41
139.26
139.13
129.19
126.22
116.30
77.45 CDCl3
77.03 CDCl3
76.61 CDCl3
59.77
21.18
17.81
14.36
O
OEt
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

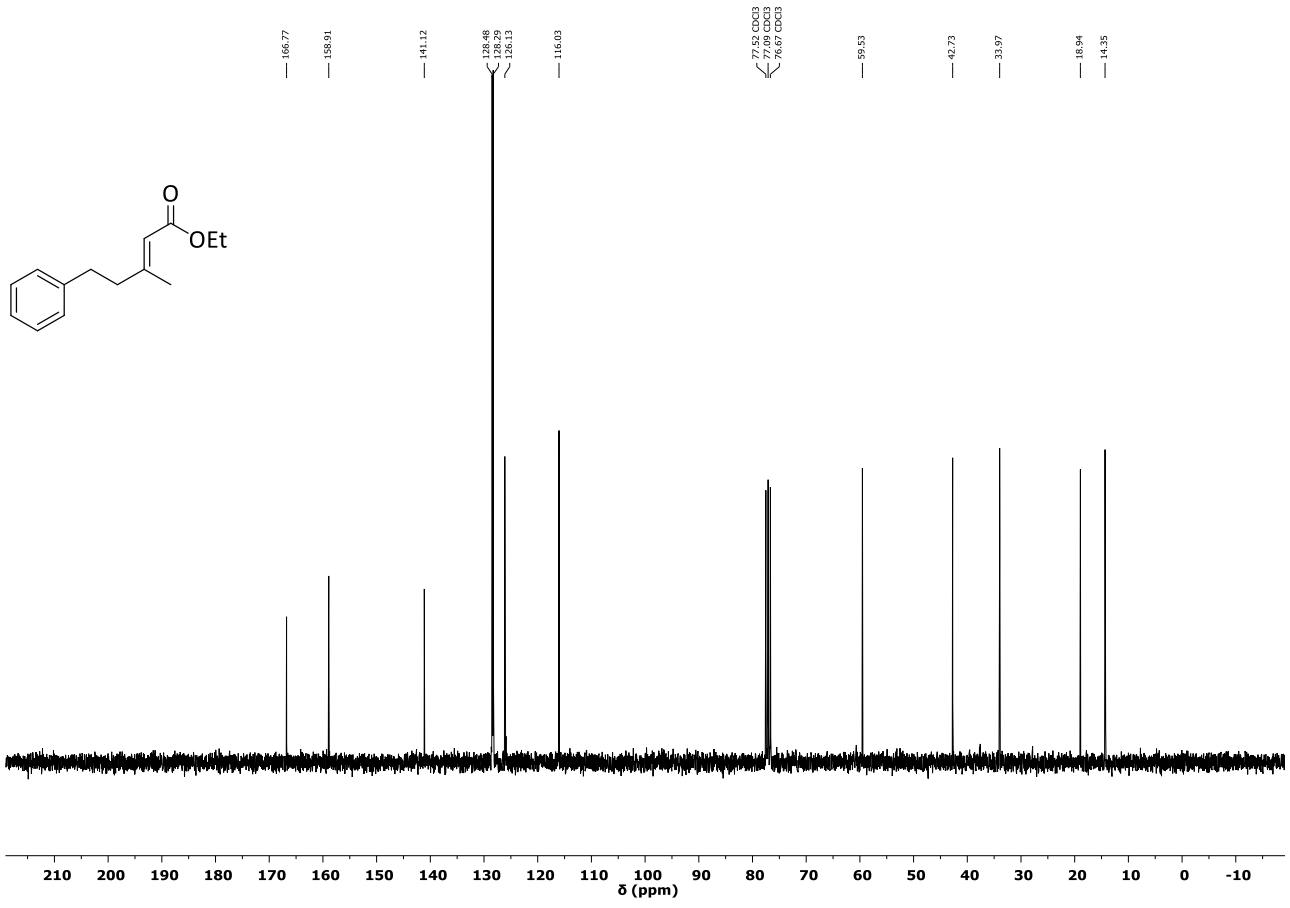

7.50
7.48
7.34
7.32
7.26 CHCl3
6.11
4.25
4.22
4.20
4.18
2.54
1.33
1.31
1.29
O
OEt
Br
1.00
1.08
0.46
1.00
1.32
1.56
δ (ppm)

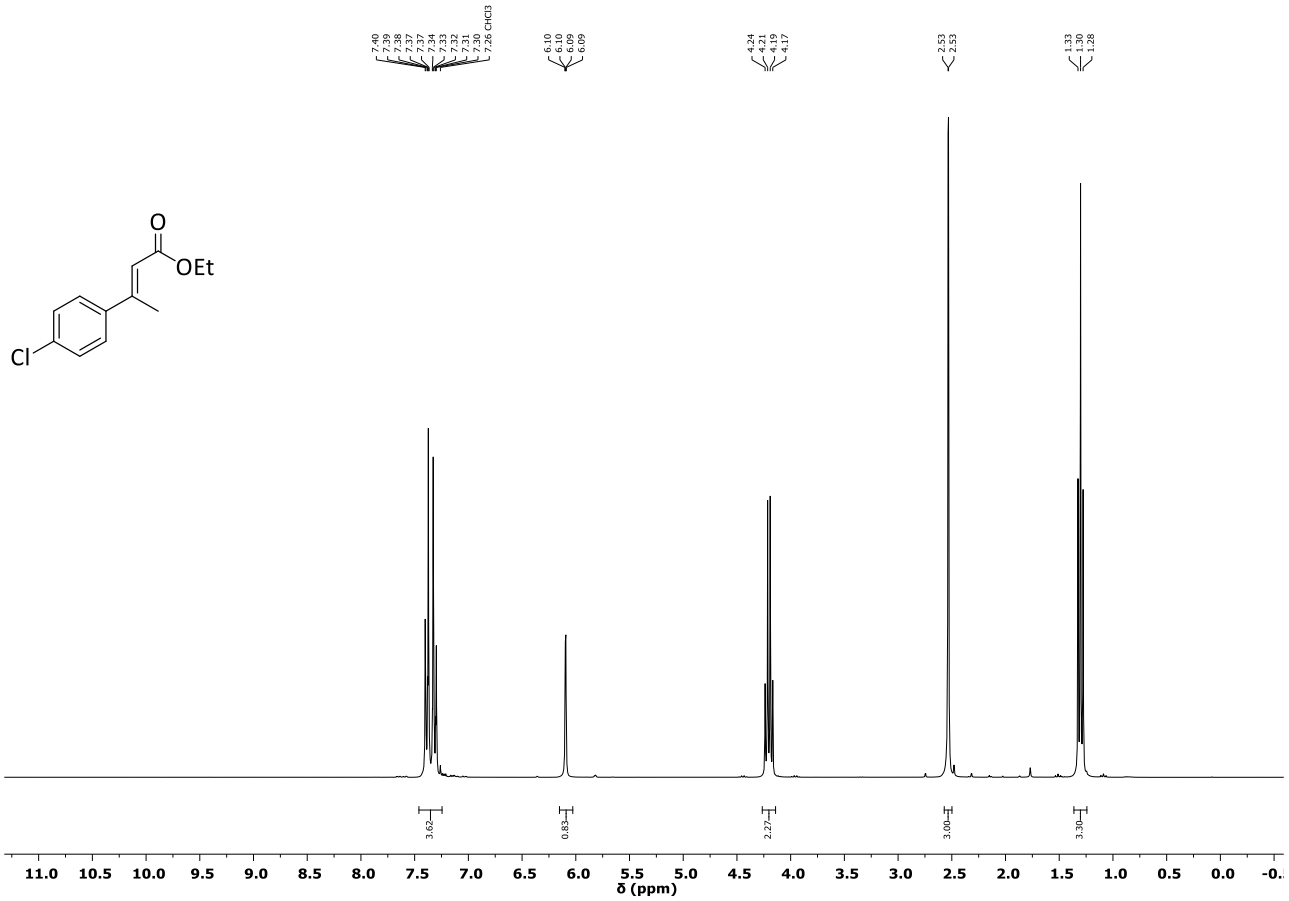

168.08
155.51
142.56
133.14
129.38
124.69
119.10
78.94 CDCl3
78.52 CDCl3
78.09 CDCl3
61.44
19.25
15.81
O
OEt
Br
δ (ppm)

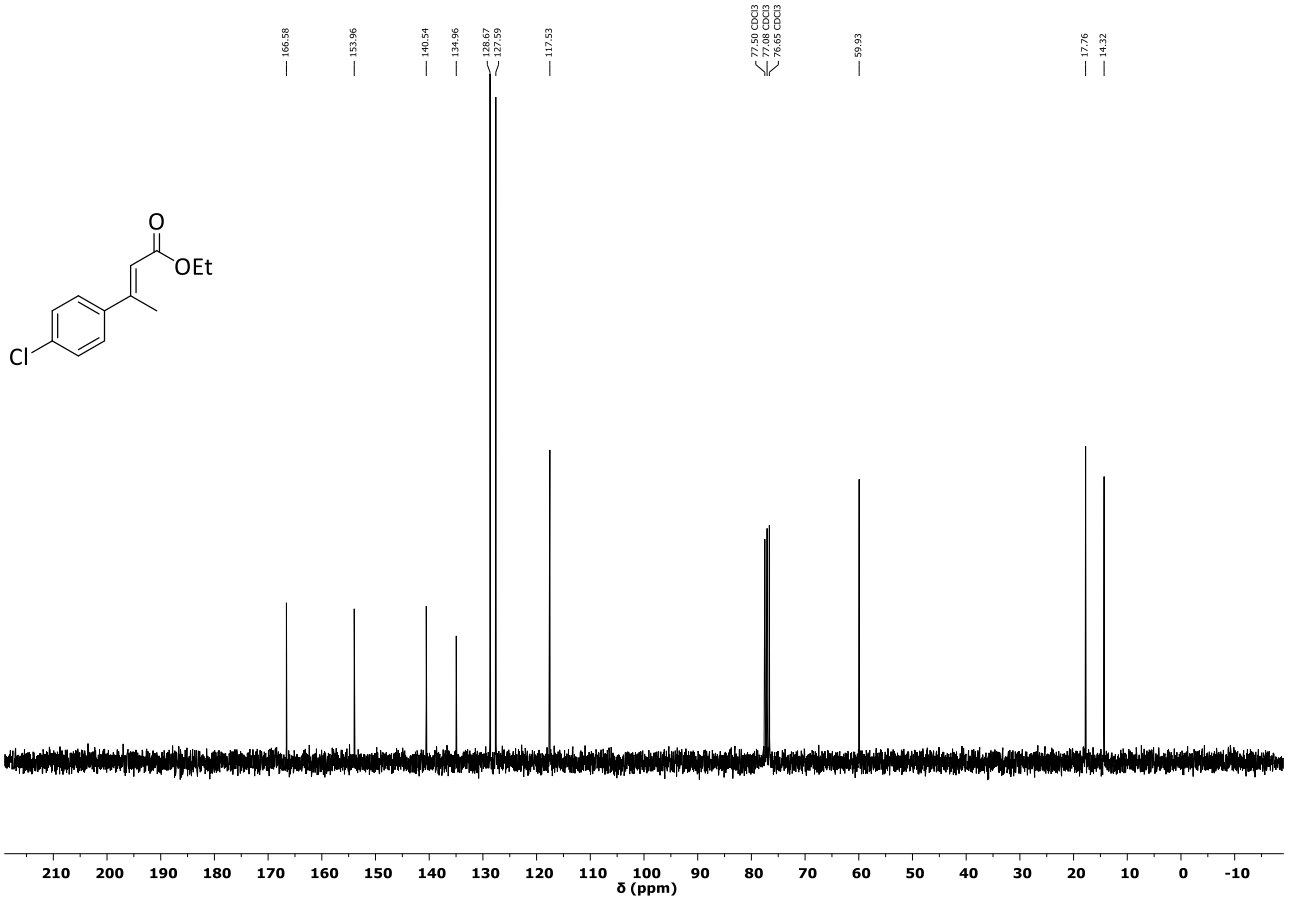

7.28
7.26
7.24
7.20
7.20
7.18
7.17
5.69
4.18
4.15
4.13
4.11
2.94
2.93
2.91
2.90
2.88
2.86
2.83
2.80
2.78
2.77
2.75
2.74
1.87
1.53
1.29
1.27
1.25
O
EtO
4.51
0.79
1.75
1.95
2.00
3.36
2.95
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2
δ (ppm)


166.23
159.48
141.70
128.47
128.34
125.94
116.65
77.51 CDCl3
77.09 CDCl3
76.66 CDCl3
59.51
35.58
34.58
25.49
14.36
O
EtO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)


7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.28
7.27
7.26 CDCl3
7.26
7.26
7.25
7.24
7.23
7.22
7.22
7.21
7.21
7.20
7.20
5.74
4.22
4.20
4.18
4.15
2.85
2.83
2.83
2.82
2.80
2.51
2.51
2.49
2.48
2.48
2.47
2.46
2.45
2.25
2.25
1.34
1.31
1.31
1.30
1.30
1.29
O
OEt
4.73
0.91
2.11
2.32
2.30
2.71
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
δ (ppm)


166.77
158.91
141.12
128.48
128.29
126.13
116.03
77.52 CDCl3
77.09 CDCl3
76.67 CDCl3
59.53
42.73
33.97
18.94
14.35
O
OEt
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
δ (ppm)


7.40
7.39
7.38
7.37
7.37
7.34
7.33
7.32
7.31
7.30
7.26 CHCl3
6.10
6.10
6.09
6.09
4.24
4.21
4.19
4.17
2.53
2.53
1.33
1.30
1.28
O
OEt
Cl
3.62
0.83
2.27
3.00
3.30
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)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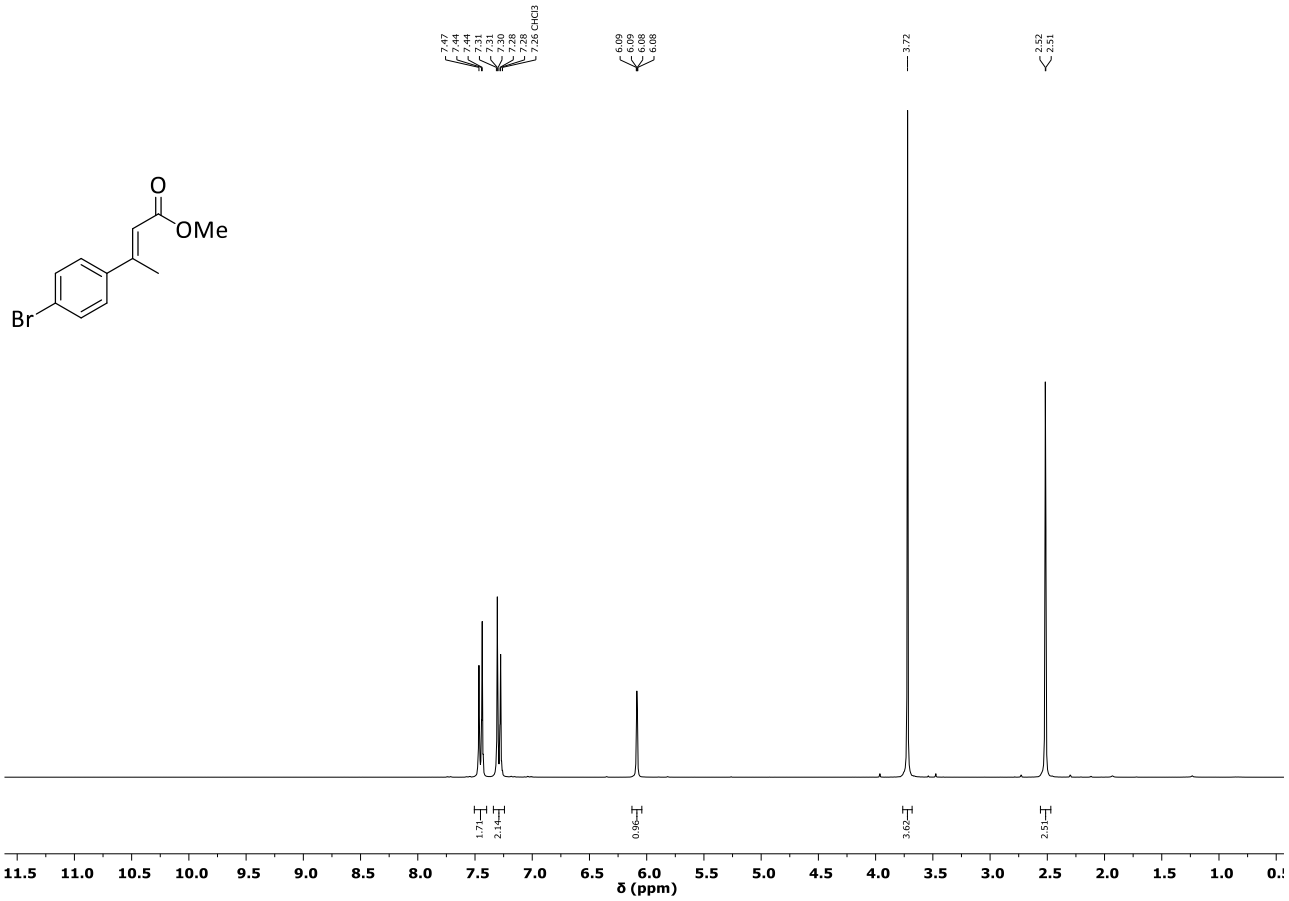
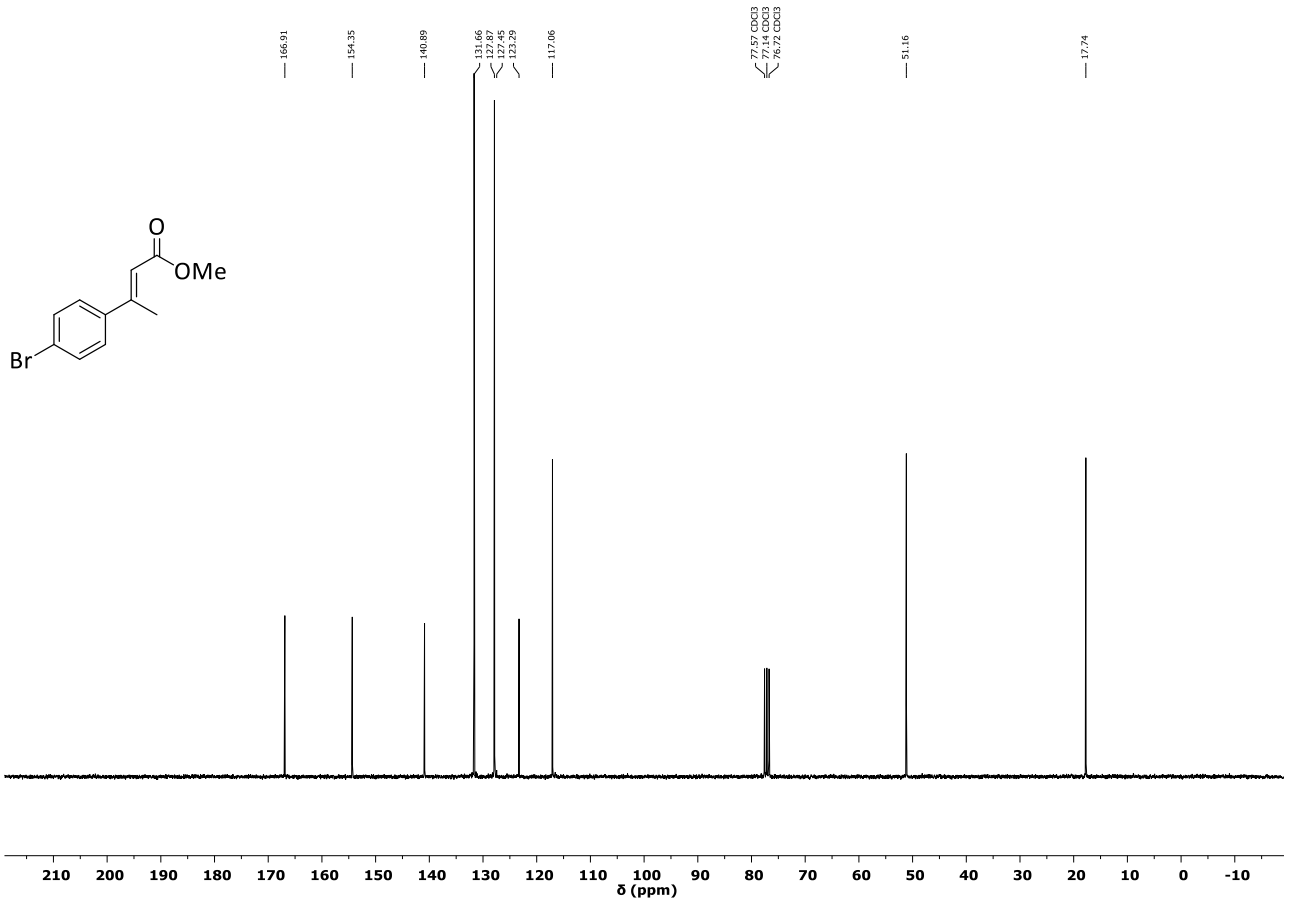
153.96
140.54
134.96
128.67
127.59
117.53
77.50 CDCl3
77.08 CDCl3
76.65 CDCl3
59.93
17.76
14.32
O
OEt
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)


7.47
7.44
7.31
7.30
7.28
7.26 CHCl3
6.09
6.09
6.08
6.08
3.72
2.52
2.51
O
OMe
Br
1.71
2.14
0.96
3.62
2.51
δ (ppm)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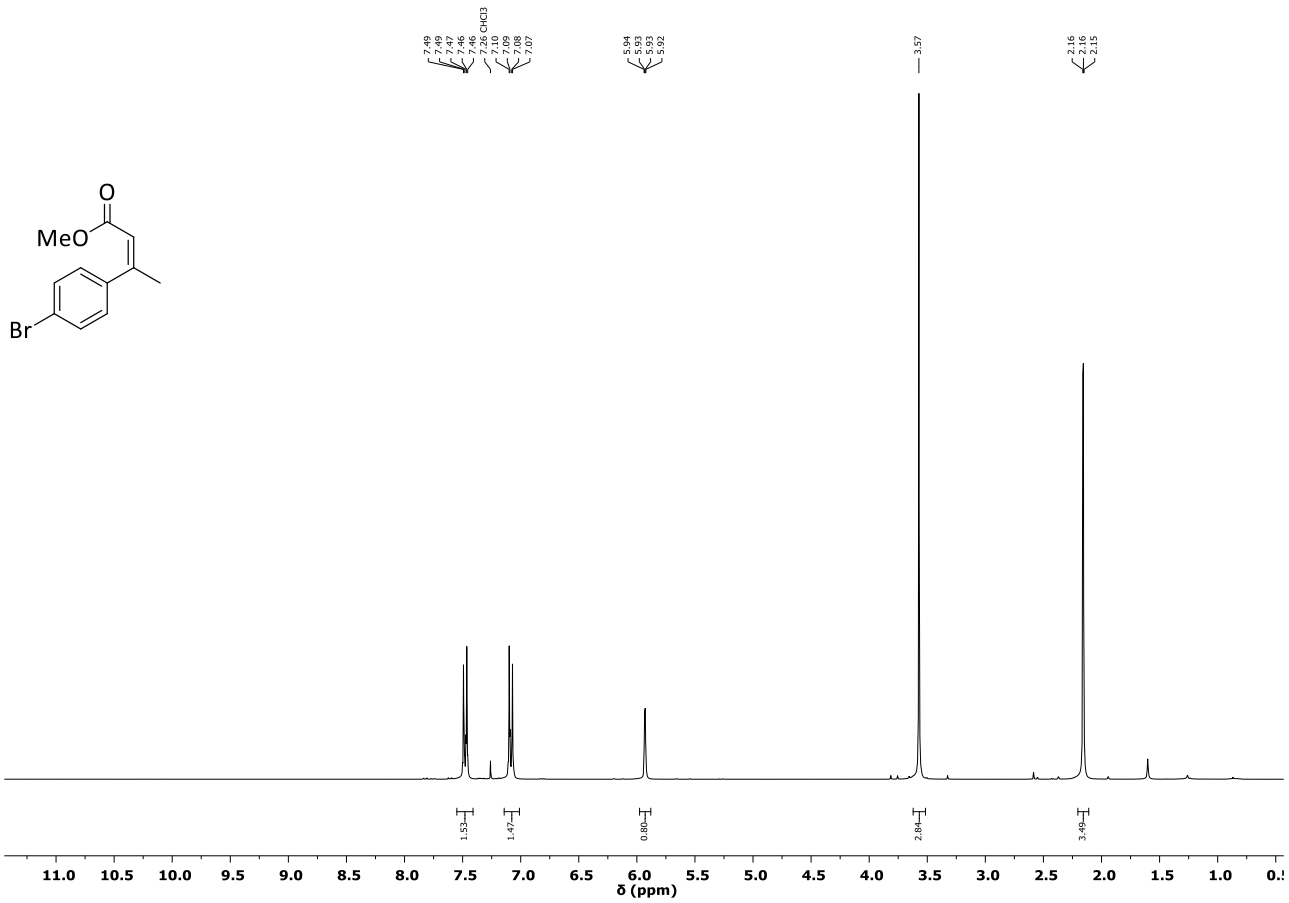
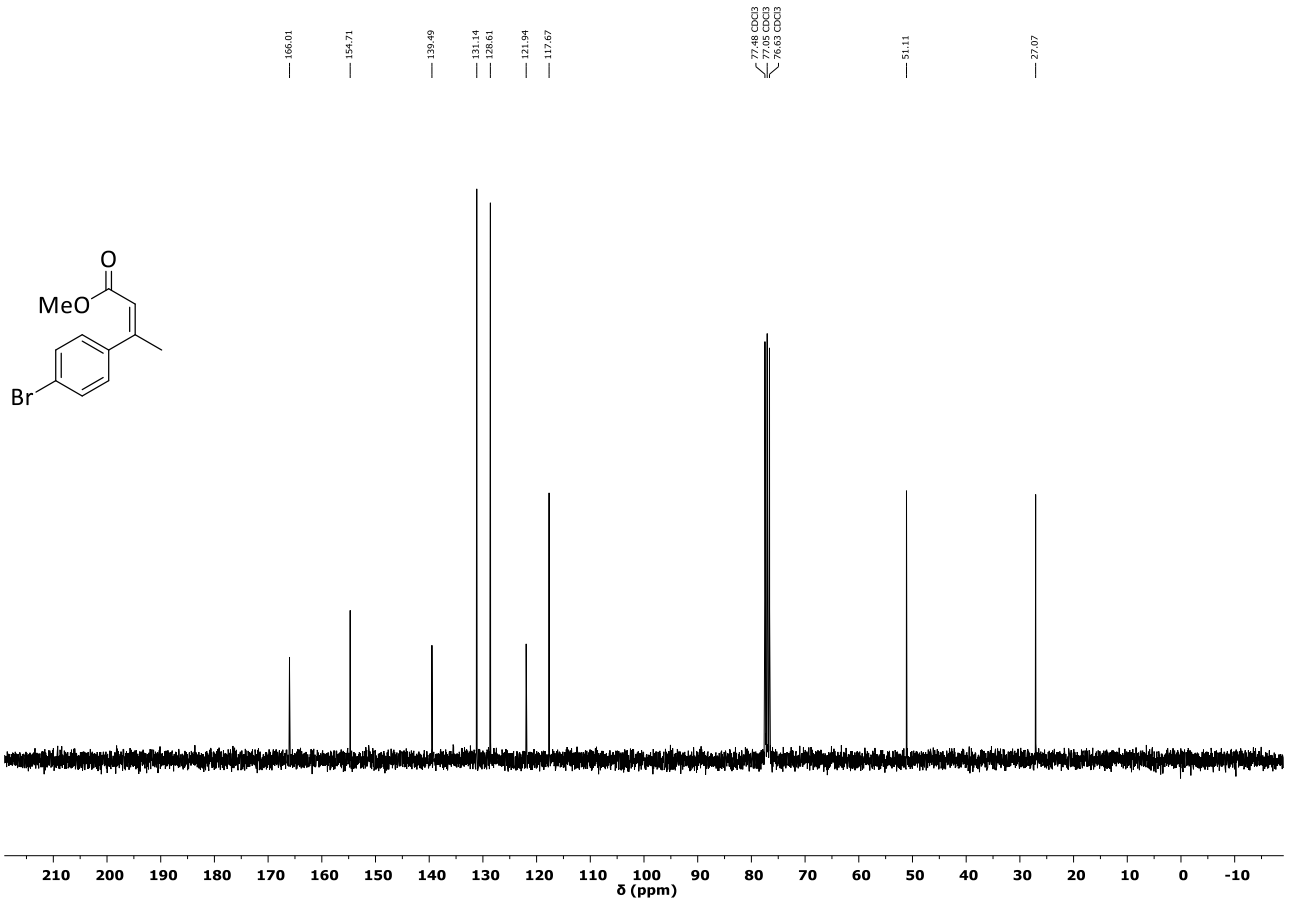
154.35
140.89
131.66
127.87
127.45
123.29
117.06
77.57 CDCl3
77.14 CDCl3
76.72 CDCl3
51.16
17.74
O
OMe
Br
δ (ppm)


7.49
7.49
7.47
7.46
7.46
7.26 CHCl3
7.10
7.09
7.08
7.07
5.94
5.93
5.93
5.92
3.57
2.16
2.16
2.15
O
MeO
Br
1.53
1.47
0.80
2.84
3.49
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
δ (ppm)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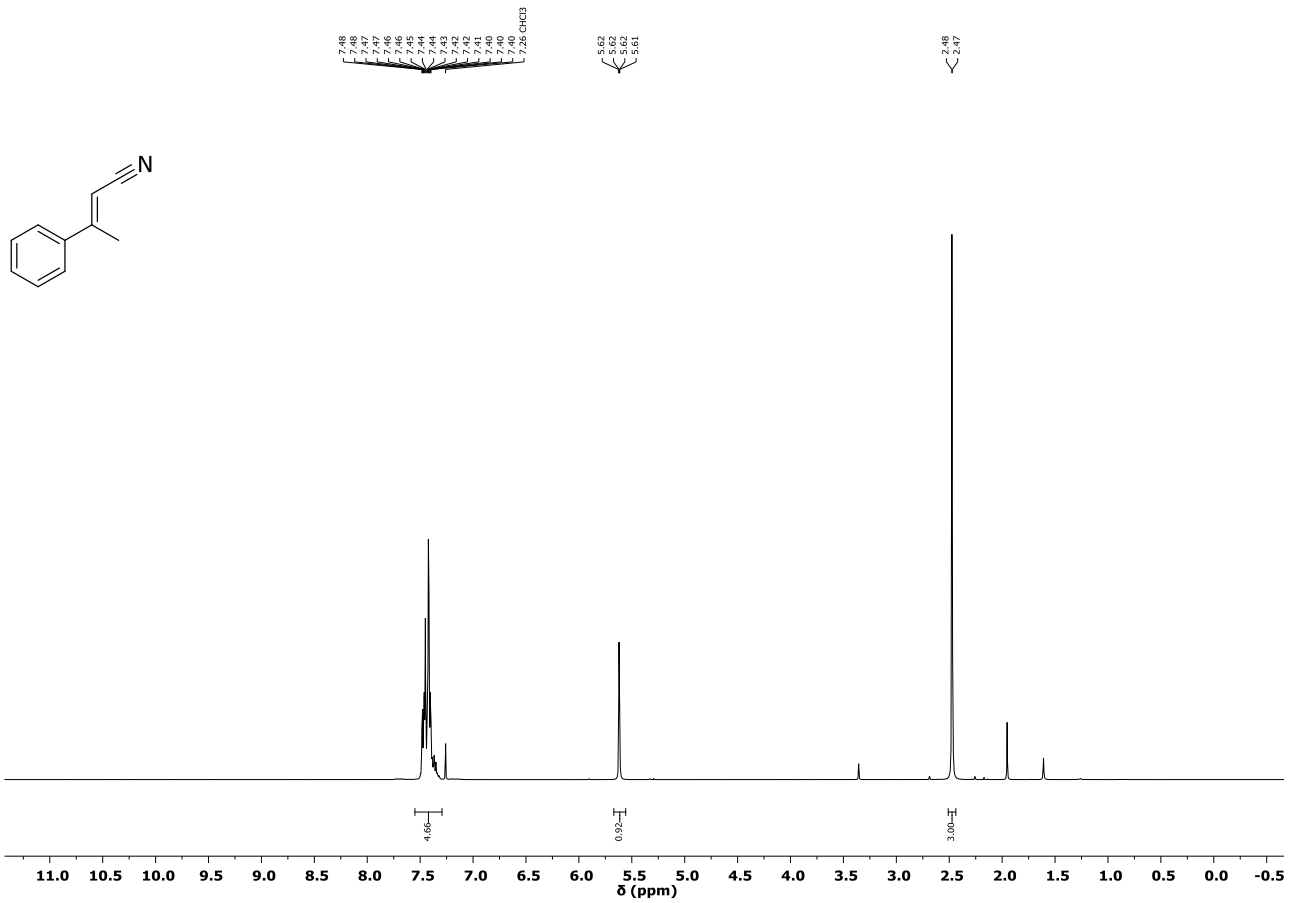
154.71
139.49
131.14
128.61
121.94
117.67
77.48 CDCl3
77.05 CDCl3
76.63 CDCl3
51.11
27.07
O
MeO
Br
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)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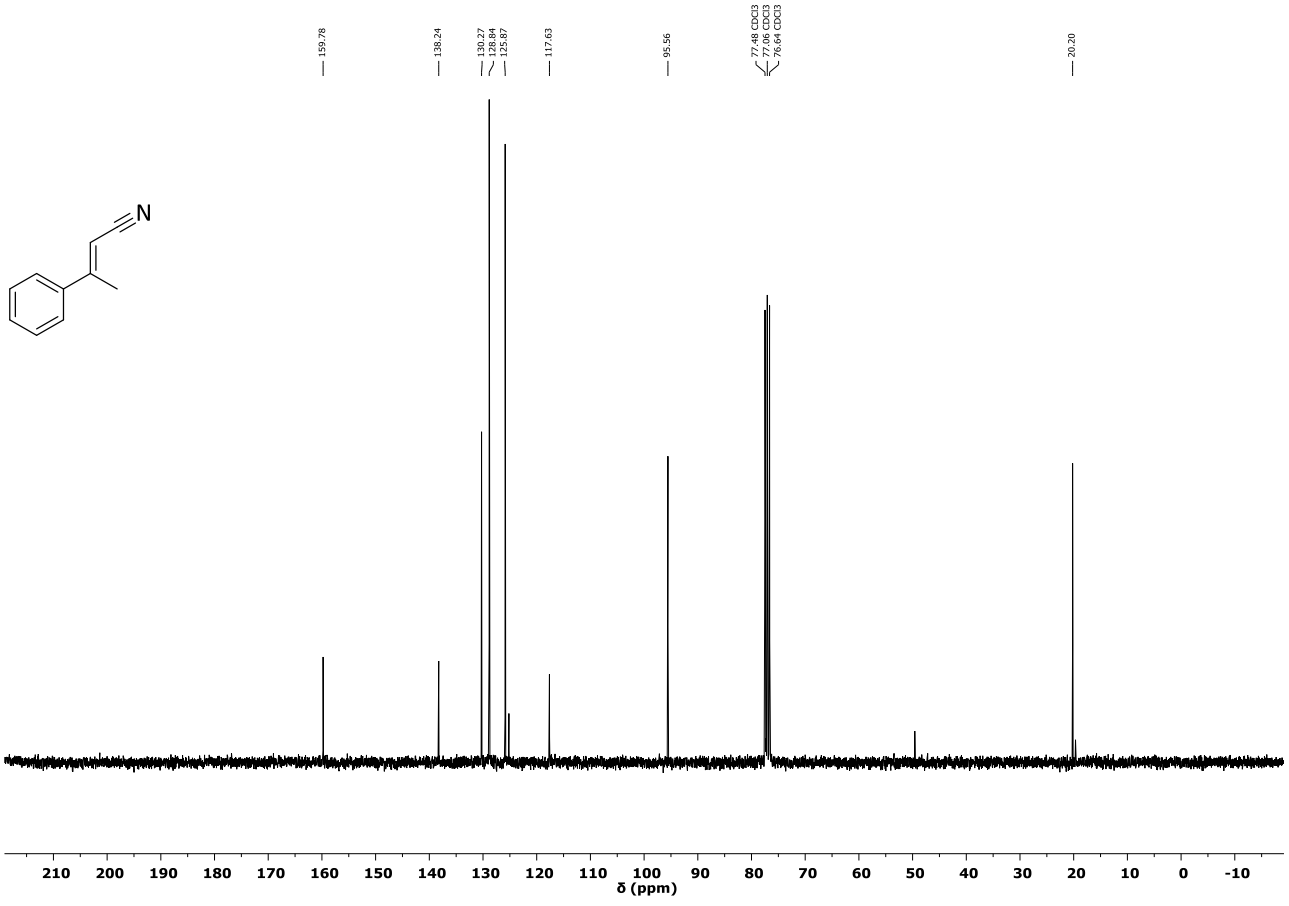
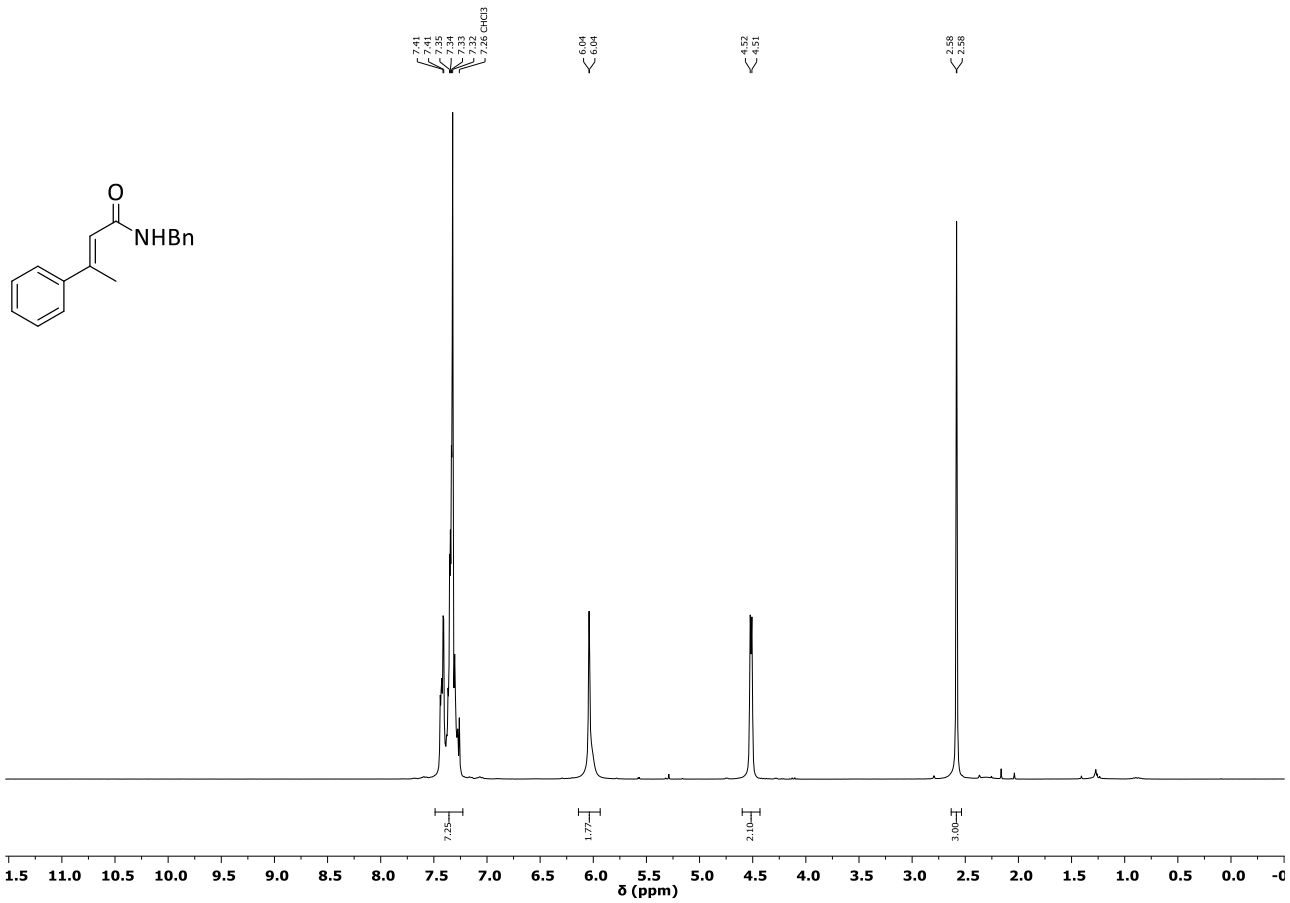
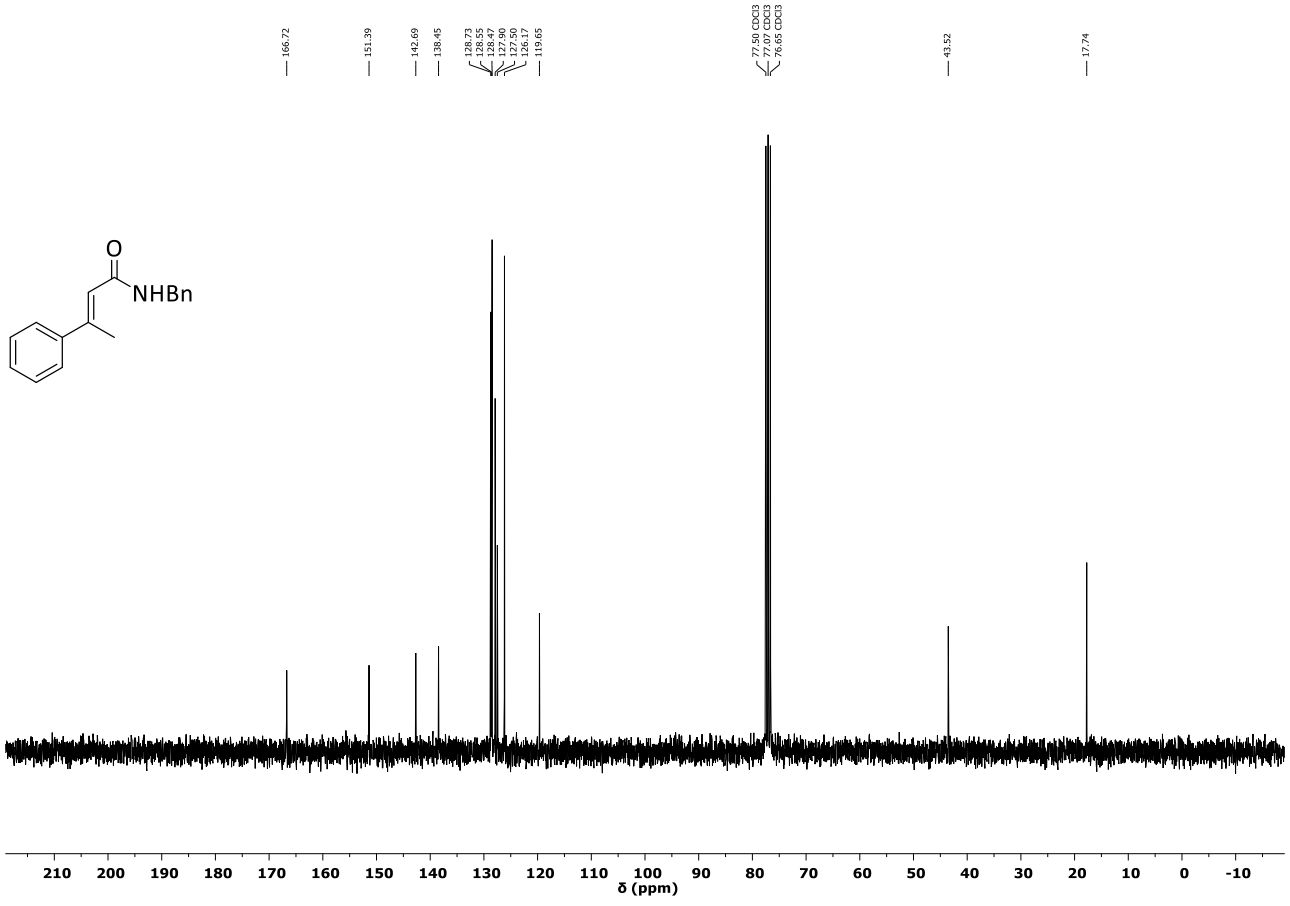
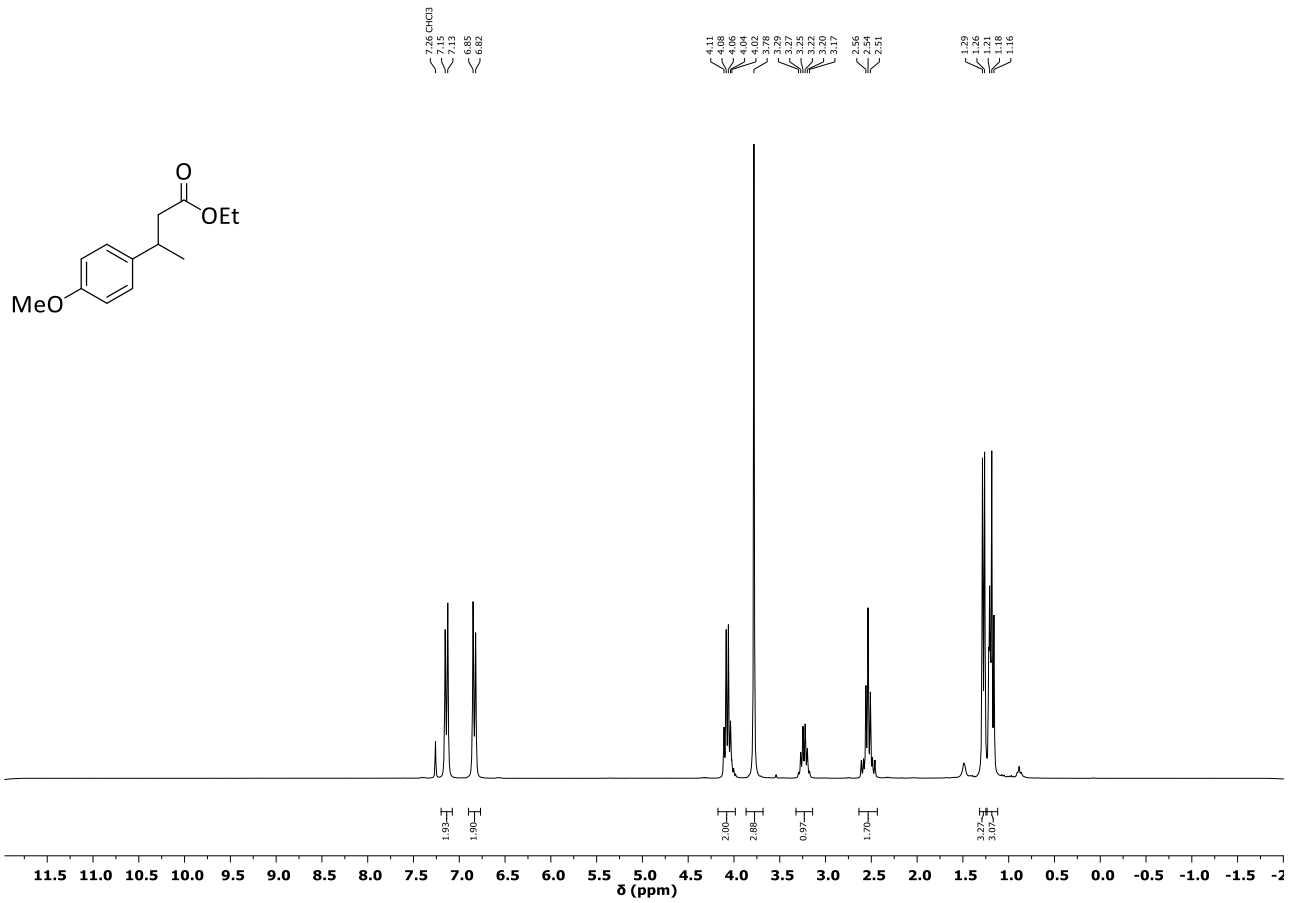
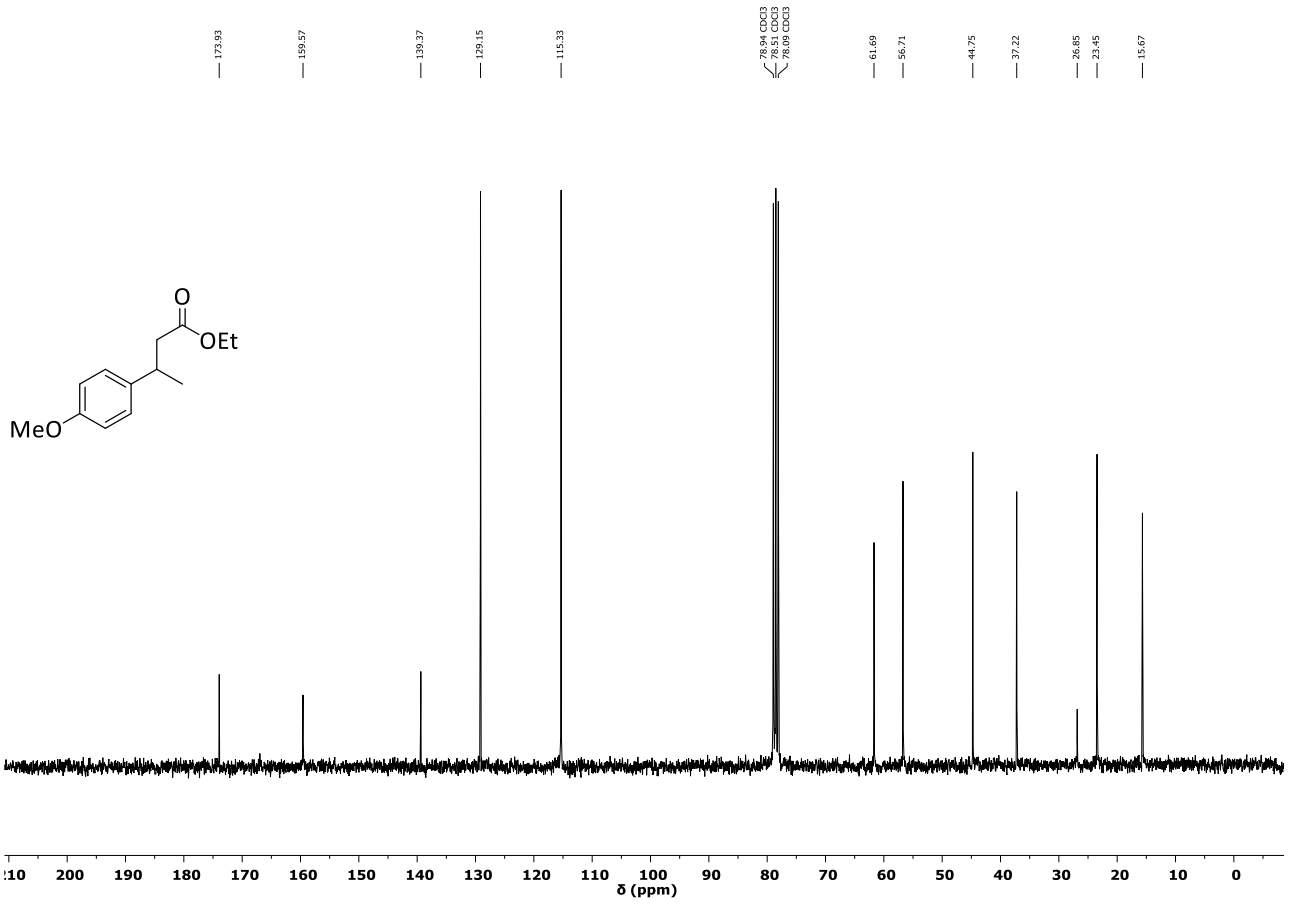
7.48
7.47
7.47
7.46
7.46
7.45
7.44
7.44
7.43
7.43
7.42
7.41
7.40
7.40
7.40
7.26 CHCl3
5.62
5.62
5.62
5.61
2.48
2.47
N
4.66
0.92
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
δ (ppm)

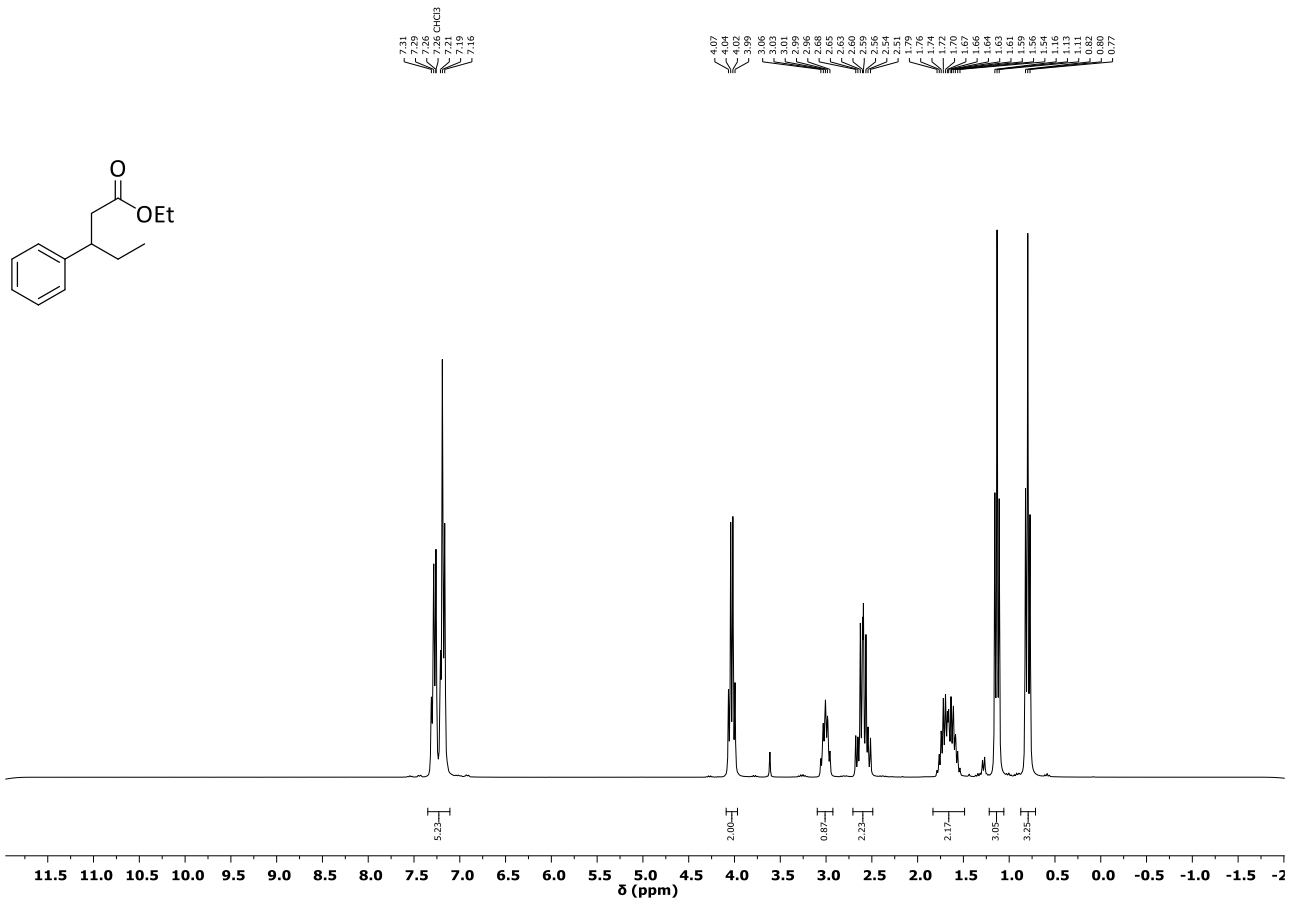

159.78
138.24
130.27
128.84
125.87
117.63
95.56
77.48 CDCl3
77.06 CDCl3
76.64 CDCl3
20.20
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

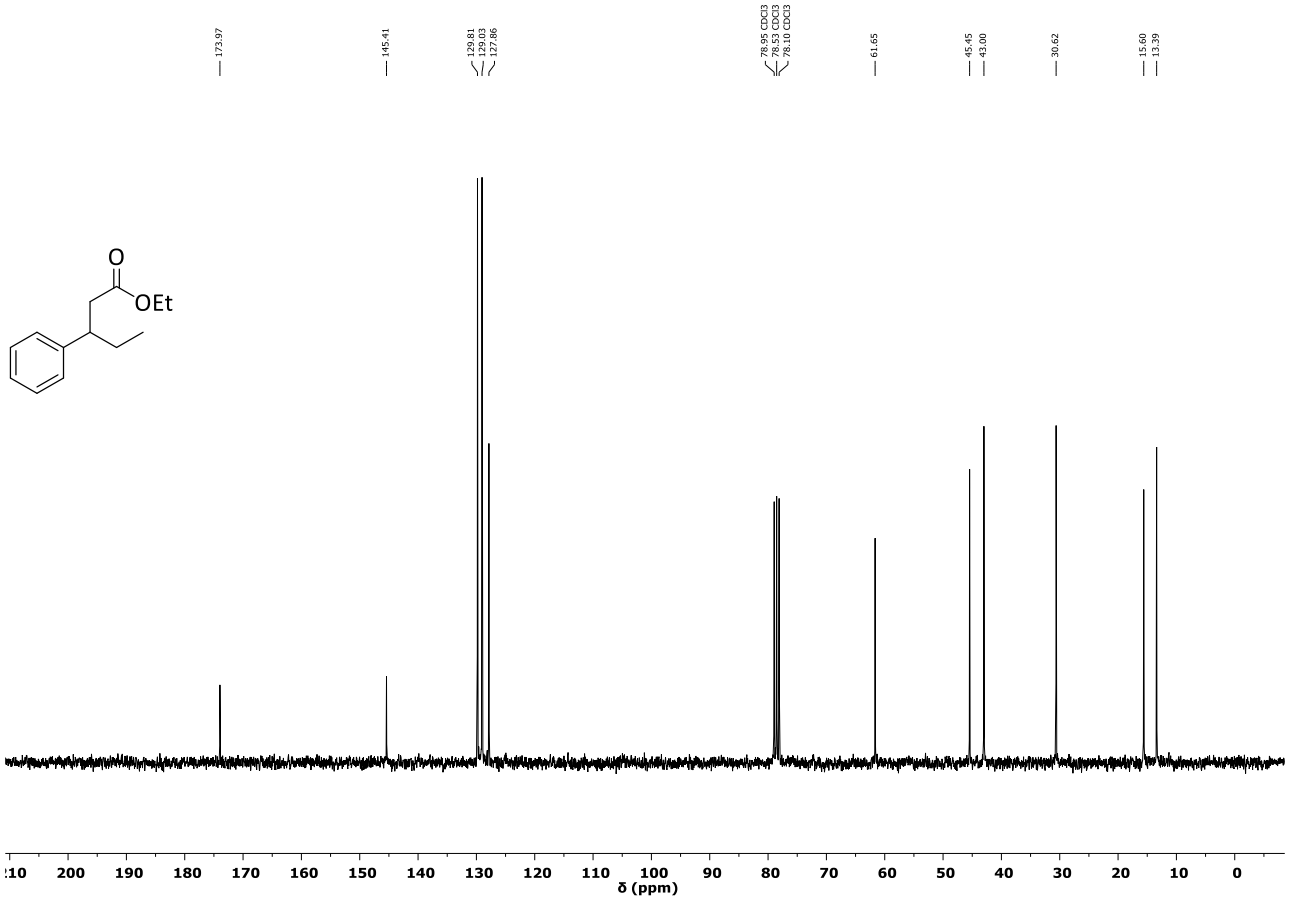

7.41
7.41
7.35
7.34
7.33
7.32
7.26 CHCl3
6.04
6.04
4.52
4.51
2.58
2.58
O
NHBn
7.25
1.77
2.10
3.00
δ (ppm)

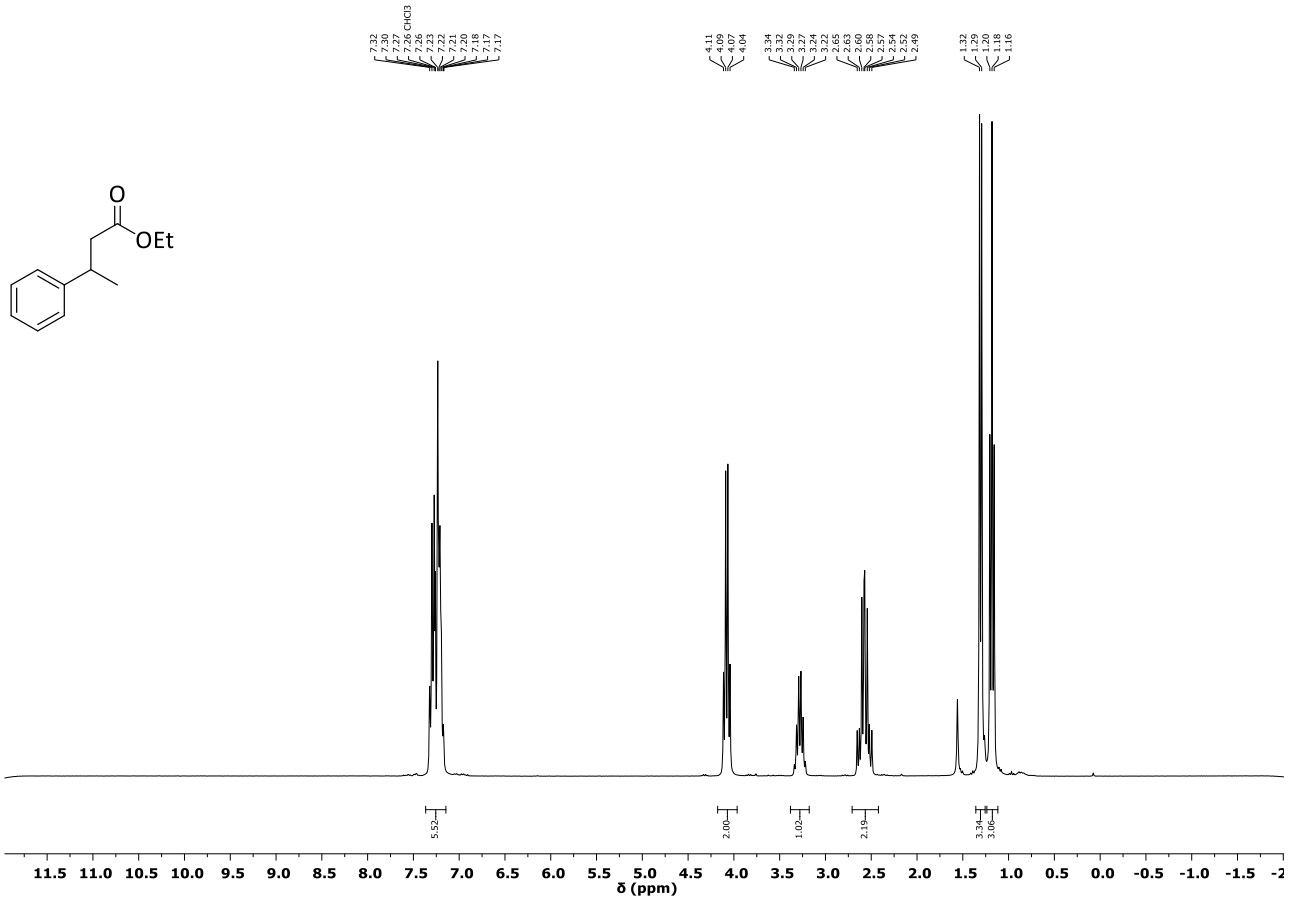

166.72
151.39
142.69
138.45
128.73
128.55
128.47
127.90
127.50
126.17
119.65
77.50 CDCl3
77.07 CDCl3
76.65 CDCl3
43.52
17.74
O
NHBn
δ (ppm)

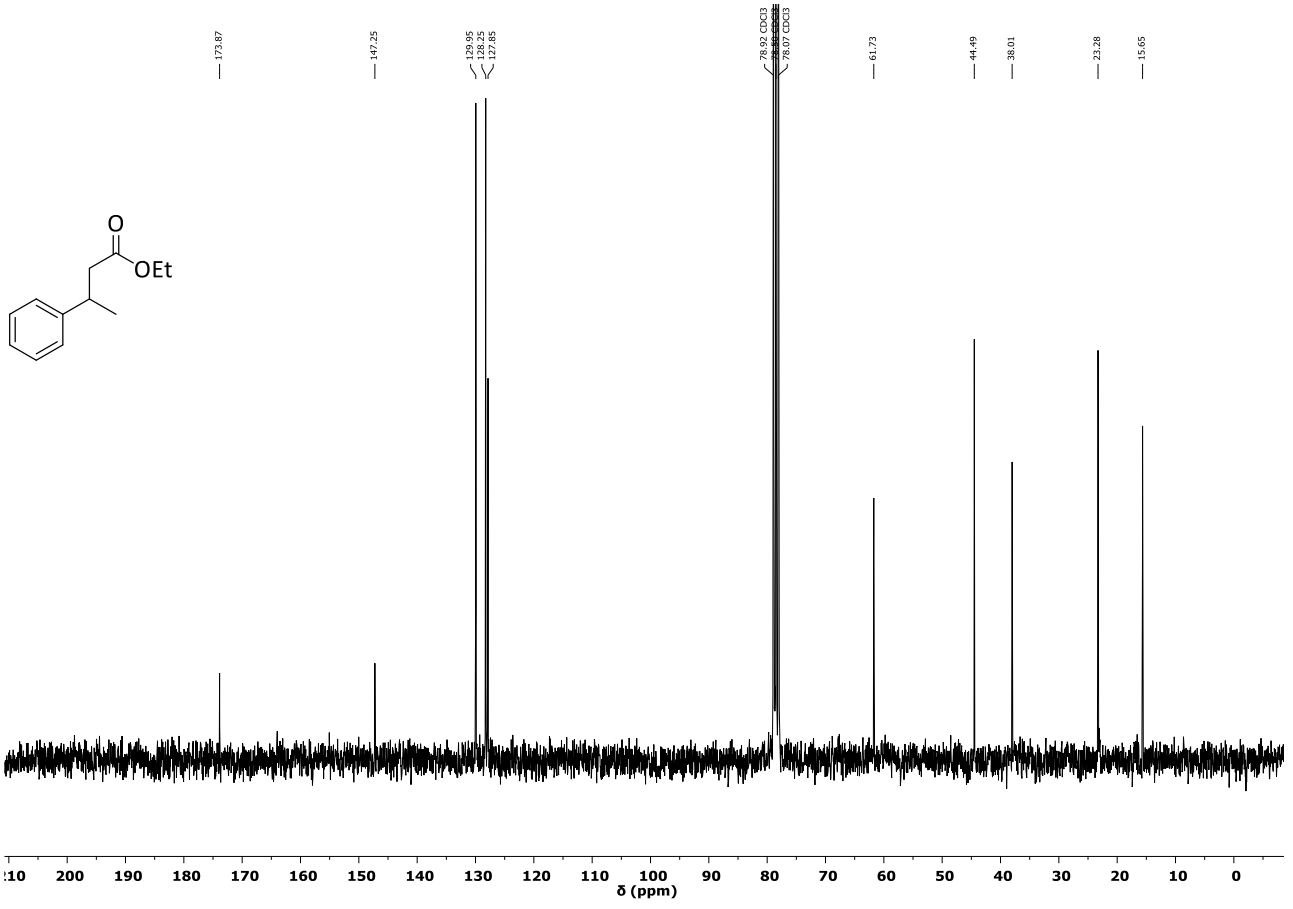

7.26 CHCl3
7.15
7.13
6.85
6.82
4.11
4.08
4.06
4.04
4.02
3.78
3.29
3.27
3.25
3.22
3.20
3.17
2.56
2.54
2.51
1.29
1.26
1.21
1.18
1.16
O
OEt
MeO
1.93
1.90
2.00
2.88
0.97
1.70
3.27
3.07
δ (ppm)

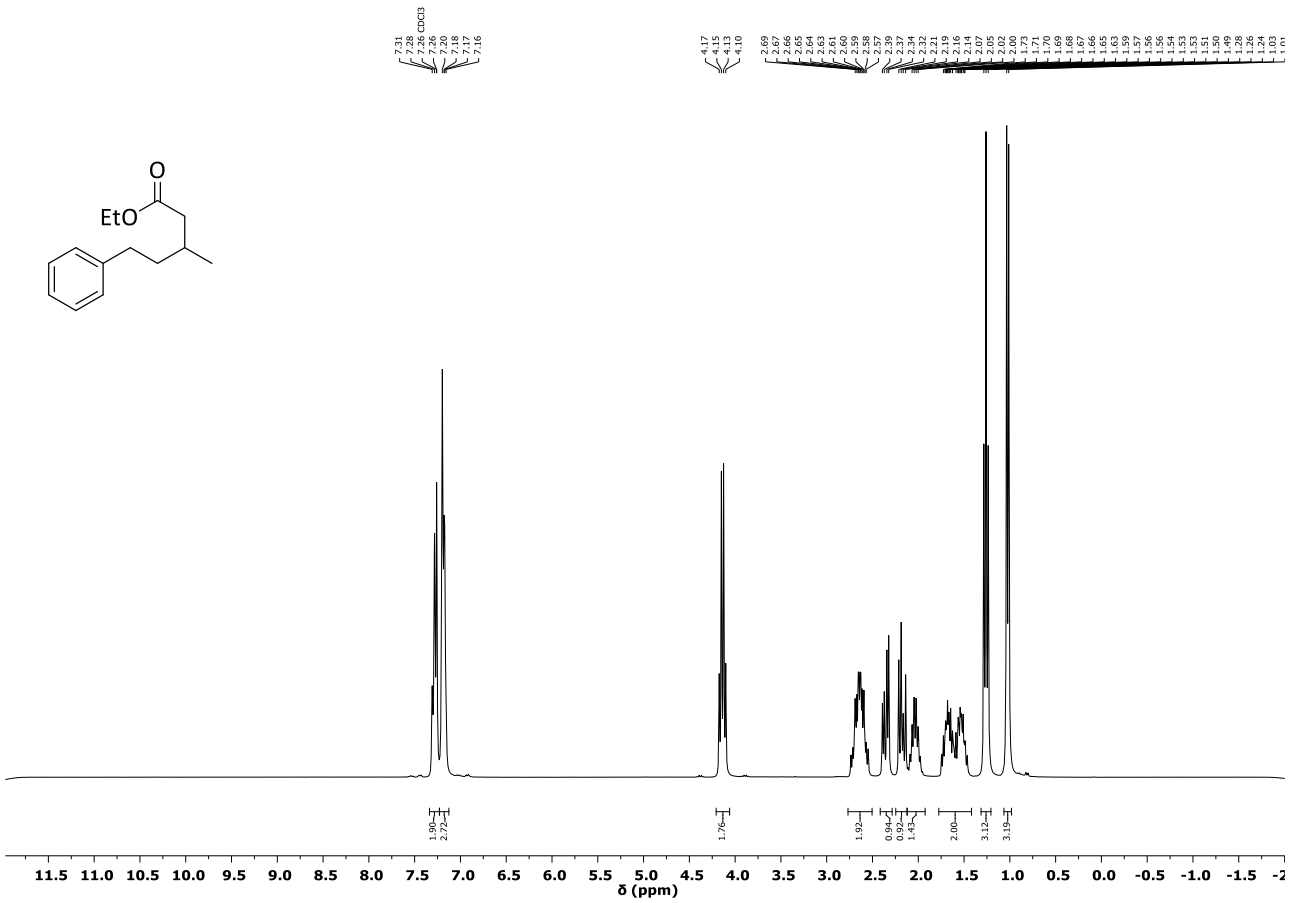

173.93
159.57
139.37
129.15
115.33
78.94 CDCl3
78.51 CDCl3
78.09 CDCl3
61.69
56.71
44.75
37.22
26.85
23.45
15.67
O
OEt
MeO
δ (ppm)

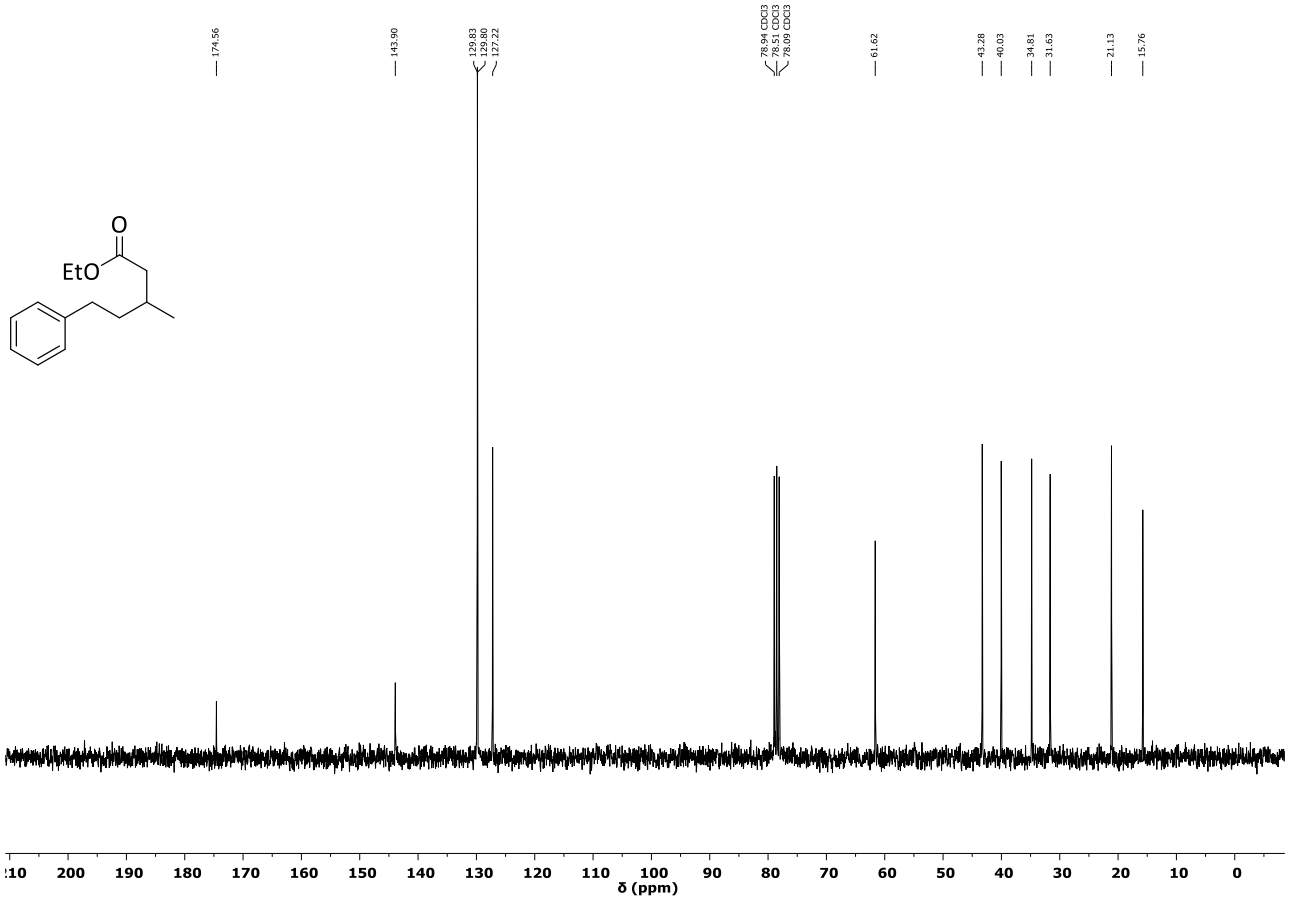

7.31
7.29
7.26 CHCl3
7.21
7.19
7.16
4.07
4.04
4.02
3.99
3.06
3.03
3.01
2.99
2.96
2.68
2.65
2.63
2.60
2.59
2.56
2.54
2.51
1.79
1.76
1.74
1.72
1.70
1.67
1.66
1.64
1.63
1.61
1.59
1.56
1.54
1.16
1.13
1.11
0.82
0.80
0.77
O
OEt
5.23
2.00
0.87
2.23
2.17
3.05
3.25
δ (ppm)


173.97
145.41
129.81
129.03
127.86
78.95 CDCl3
78.53 CDCl3
78.10 CDCl3
61.65
45.45
43.00
30.62
15.60
13.39
O
OEt
δ (ppm)


7.32
7.30
7.27
7.26 CHCl3
7.23
7.22
7.21
7.20
7.18
7.17
7.17
4.11
4.09
4.07
4.04
3.34
3.32
3.29
3.27
3.24
3.22
2.65
2.63
2.60
2.58
2.57
2.54
2.52
2.49
1.32
1.29
1.20
1.18
1.16
O
OEt
5.52
2.00
1.02
2.19
3.34
3.06
δ (ppm)


173.87
147.25
129.95
128.25
127.85
78.92 CDCl3
78.07 CDCl3
61.73
44.49
38.01
23.28
15.65
O
OEt
δ (ppm)


7.31
7.28
7.26 CDCl3
7.26
7.20
7.18
7.17
7.16
4.17
4.15
4.13
4.10
2.69
2.67
2.66
2.65
2.64
2.63
2.61
2.60
2.59
2.58
2.57
2.39
2.37
2.34
2.32
2.21
2.19
2.16
2.14
2.07
2.05
2.02
2.00
1.73
1.71
1.70
1.69
1.68
1.67
1.66
1.65
1.63
1.59
1.57
1.56
1.54
1.53
1.53
1.51
1.50
1.49
1.28
1.26
1.24
1.03
O
EtO
1.90
2.72
1.76
1.92
0.94
0.92
1.63
2.00
3.12
3.19
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
δ (ppm)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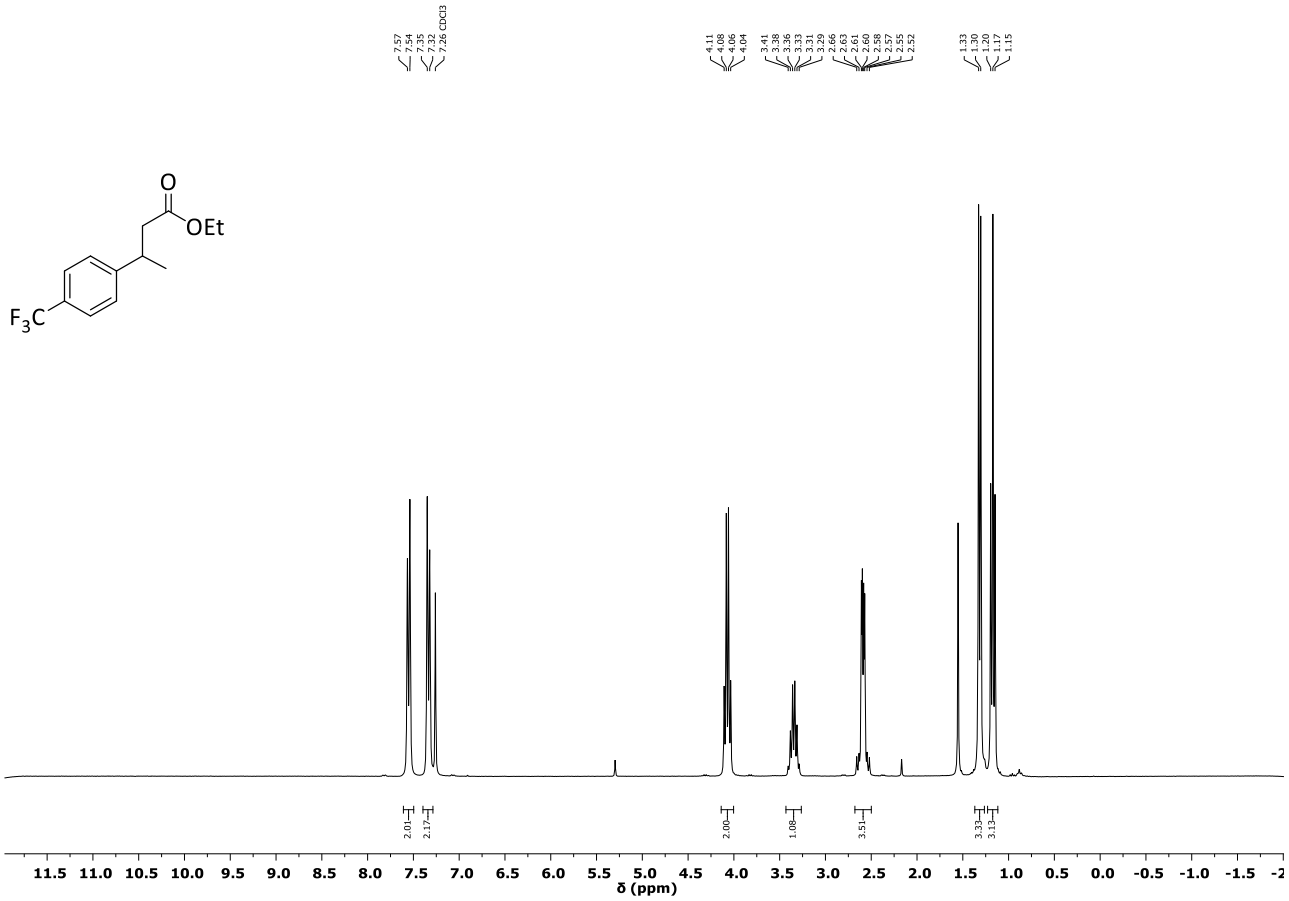
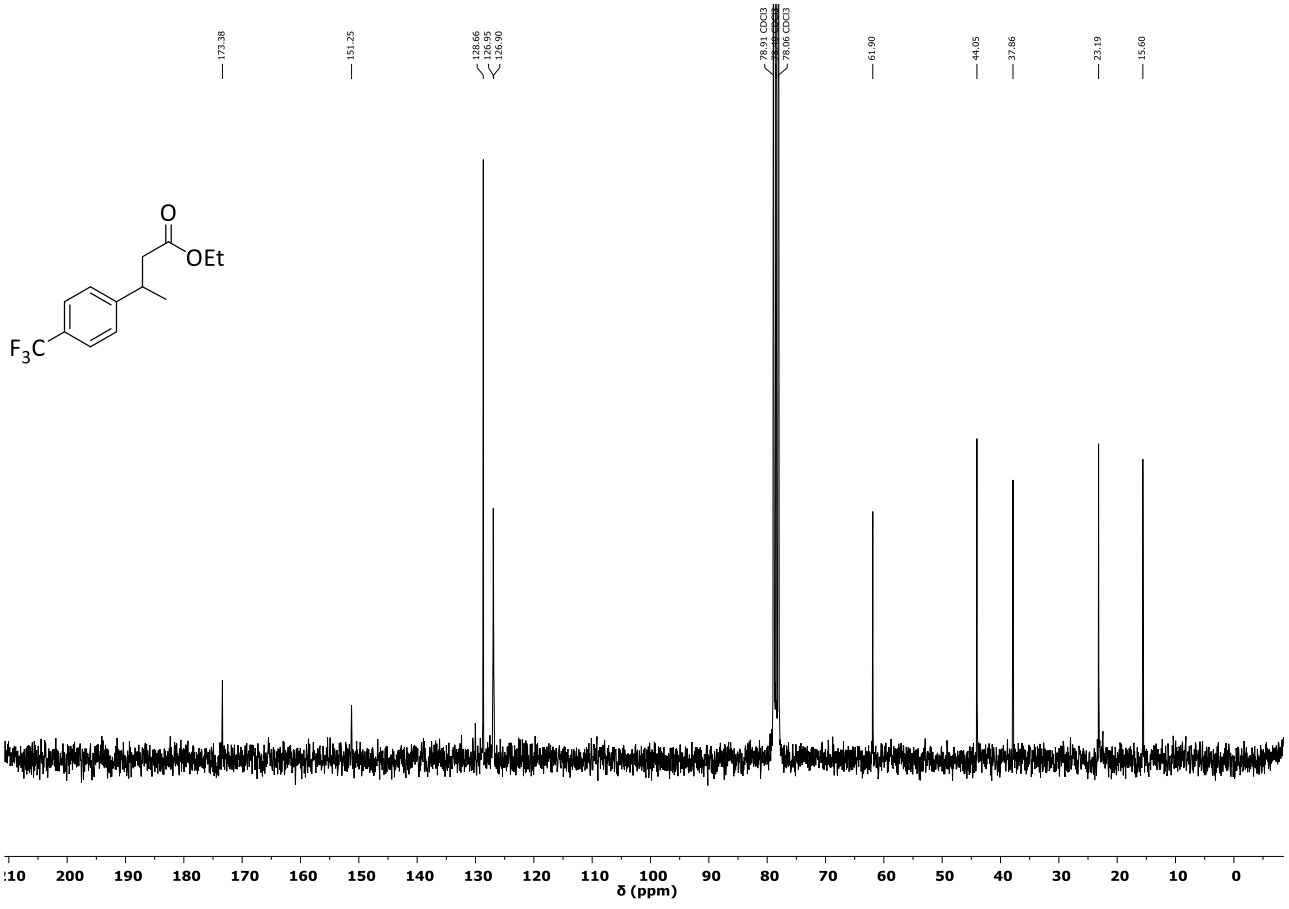
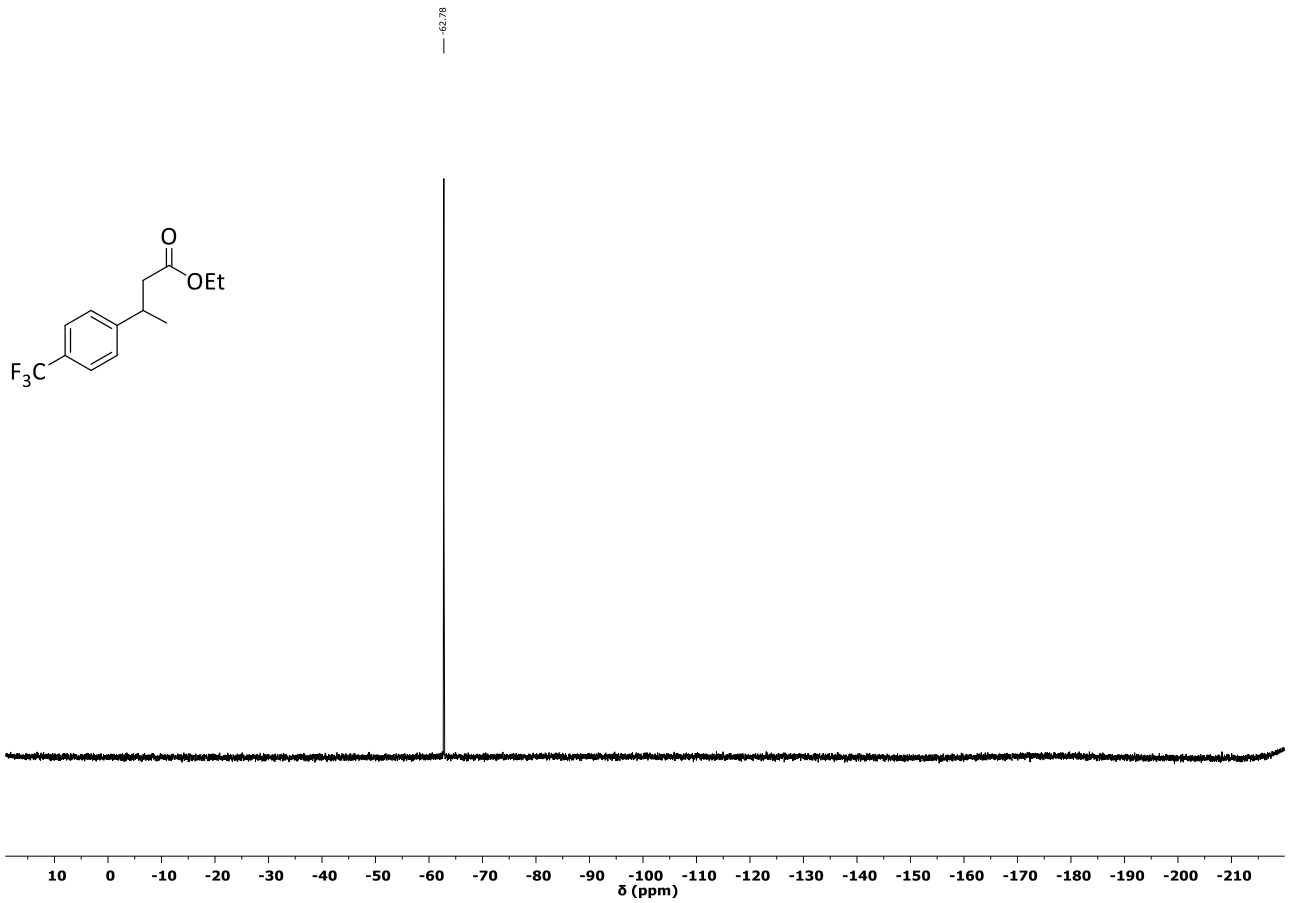
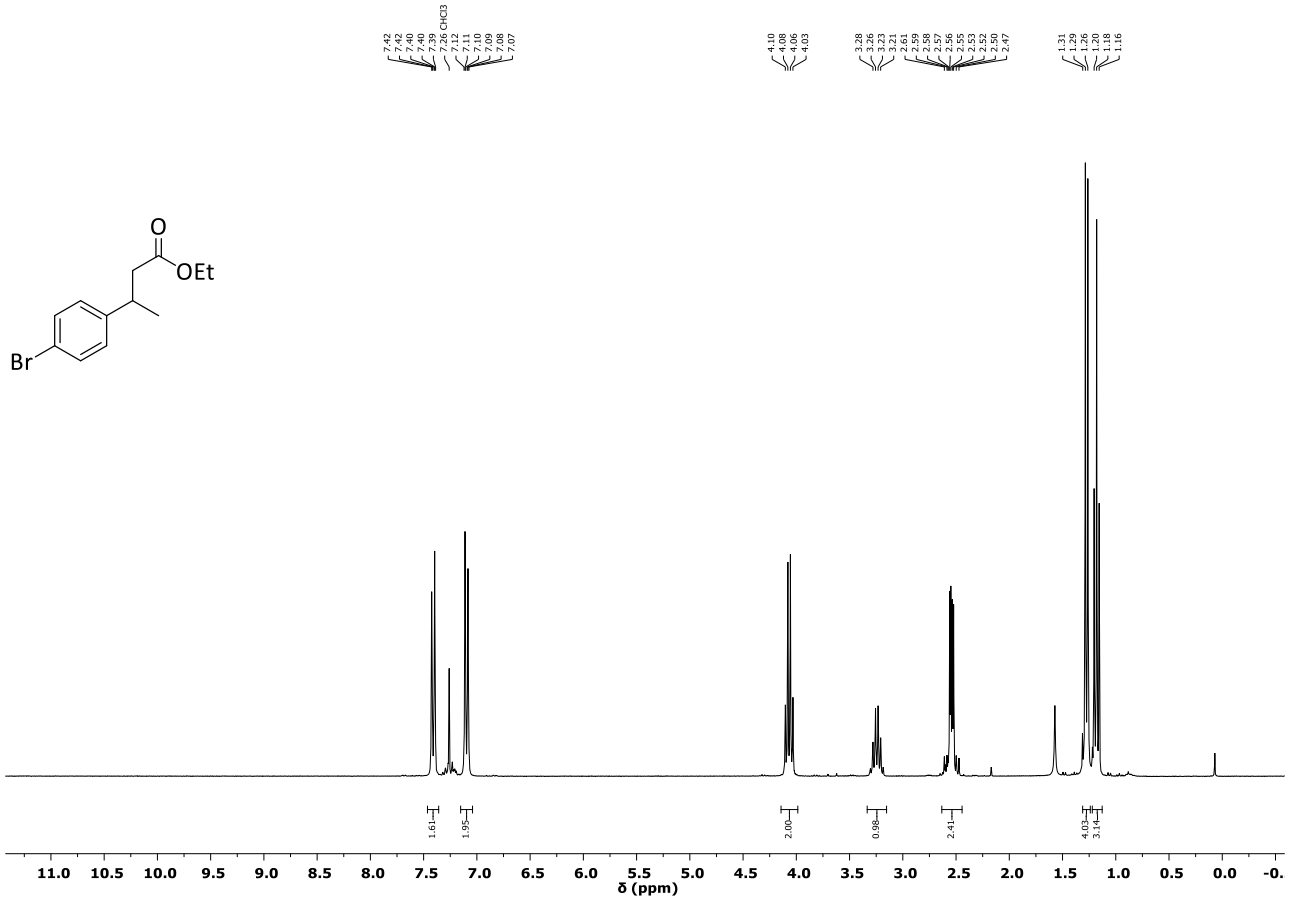
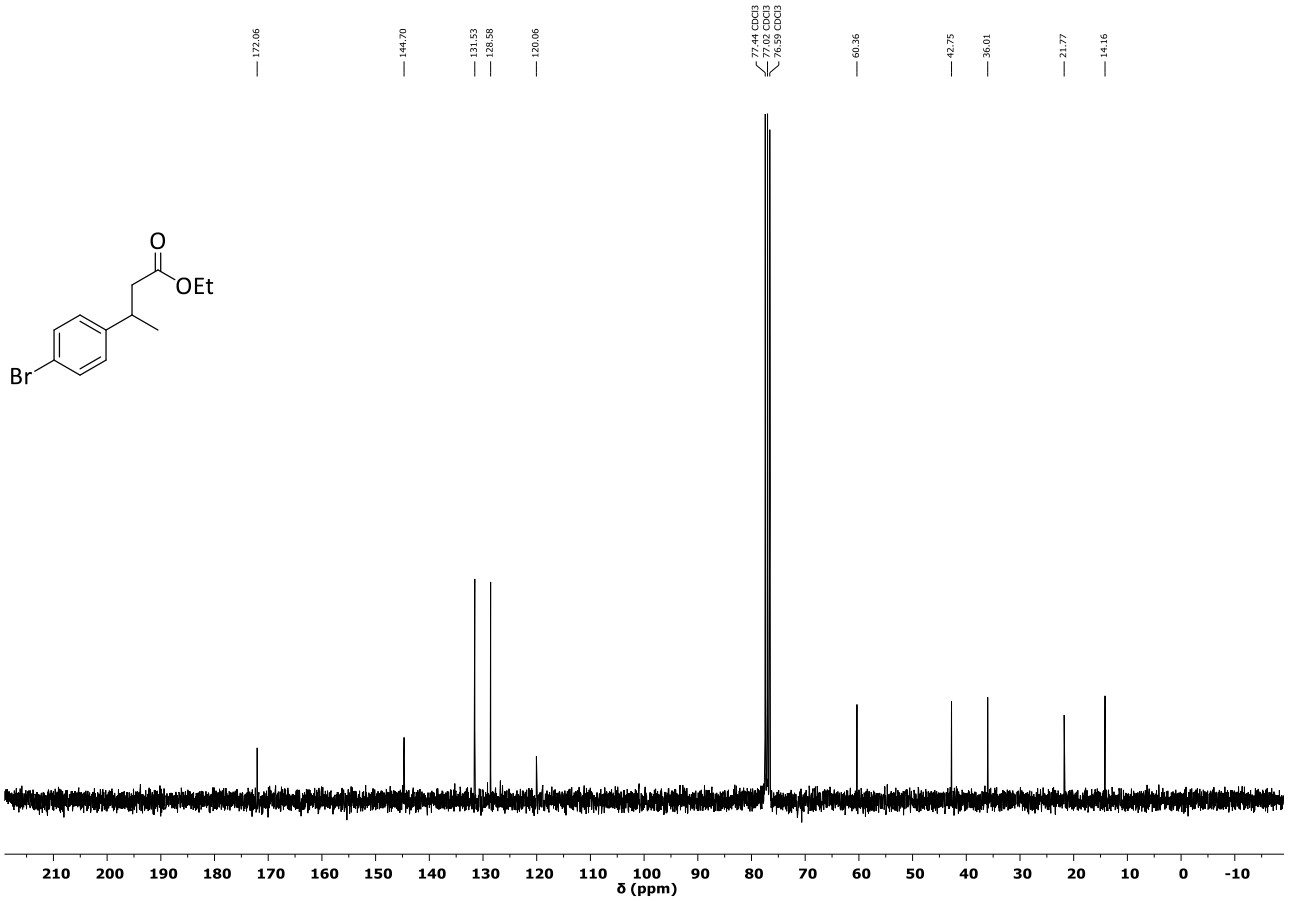
143.90
129.83
129.80
127.22
78.94 CDCl3
78.51 CDCl3
78.09 CDCl3
61.62
43.28
40.03
34.81
31.63
21.13
15.76
O
EtO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
δ (ppm)

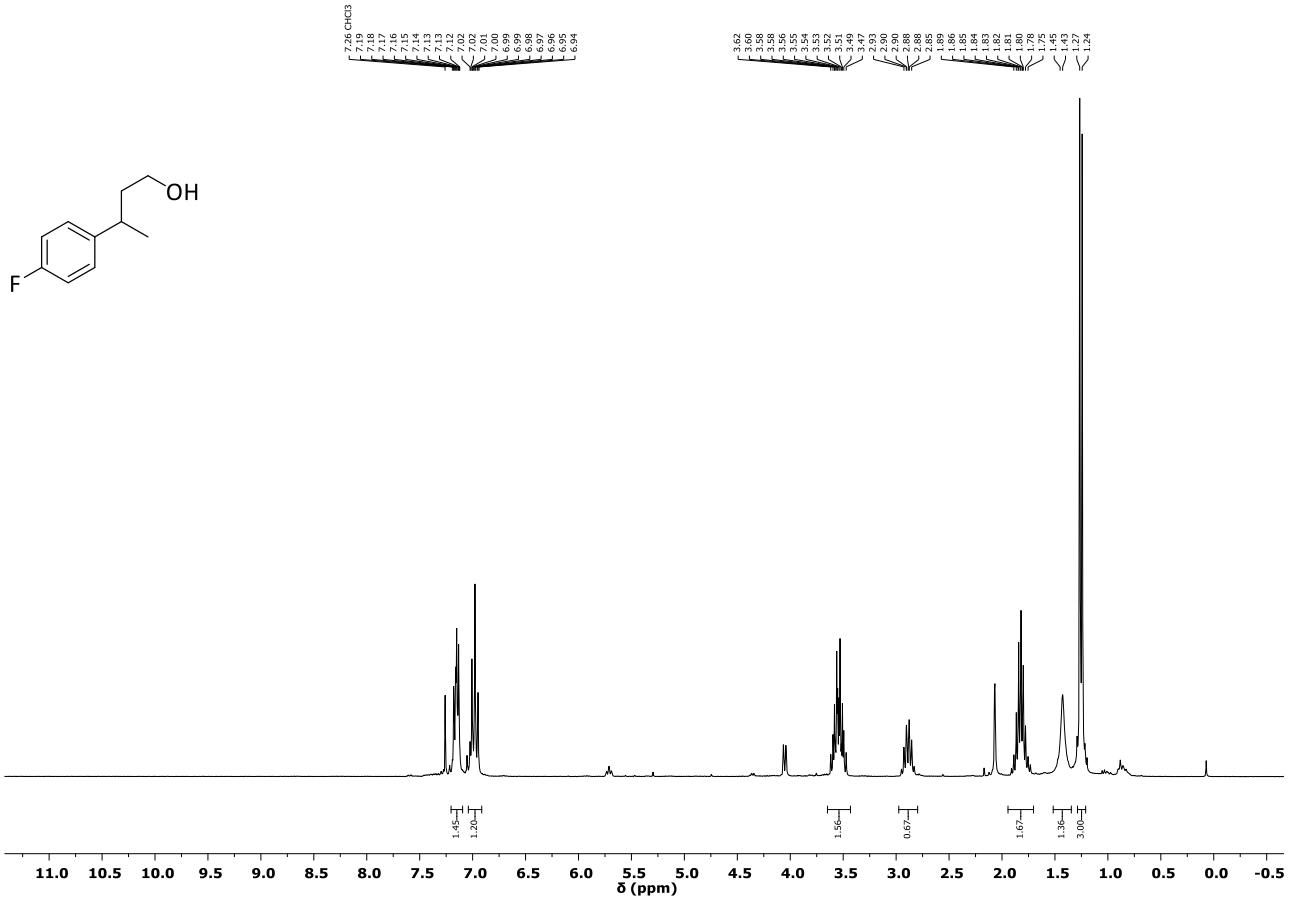

7.57
7.54
7.35
7.32
7.26 CDCl3
4.11
4.08
4.06
4.04
3.41
3.38
3.36
3.33
3.31
3.29
2.66
2.63
2.61
2.60
2.58
2.57
2.55
2.52
1.33
1.30
1.20
1.17
1.15
O
OEt
F3C
2.01
2.17
2.00
1.08
3.51
3.33
3.13
δ (ppm)

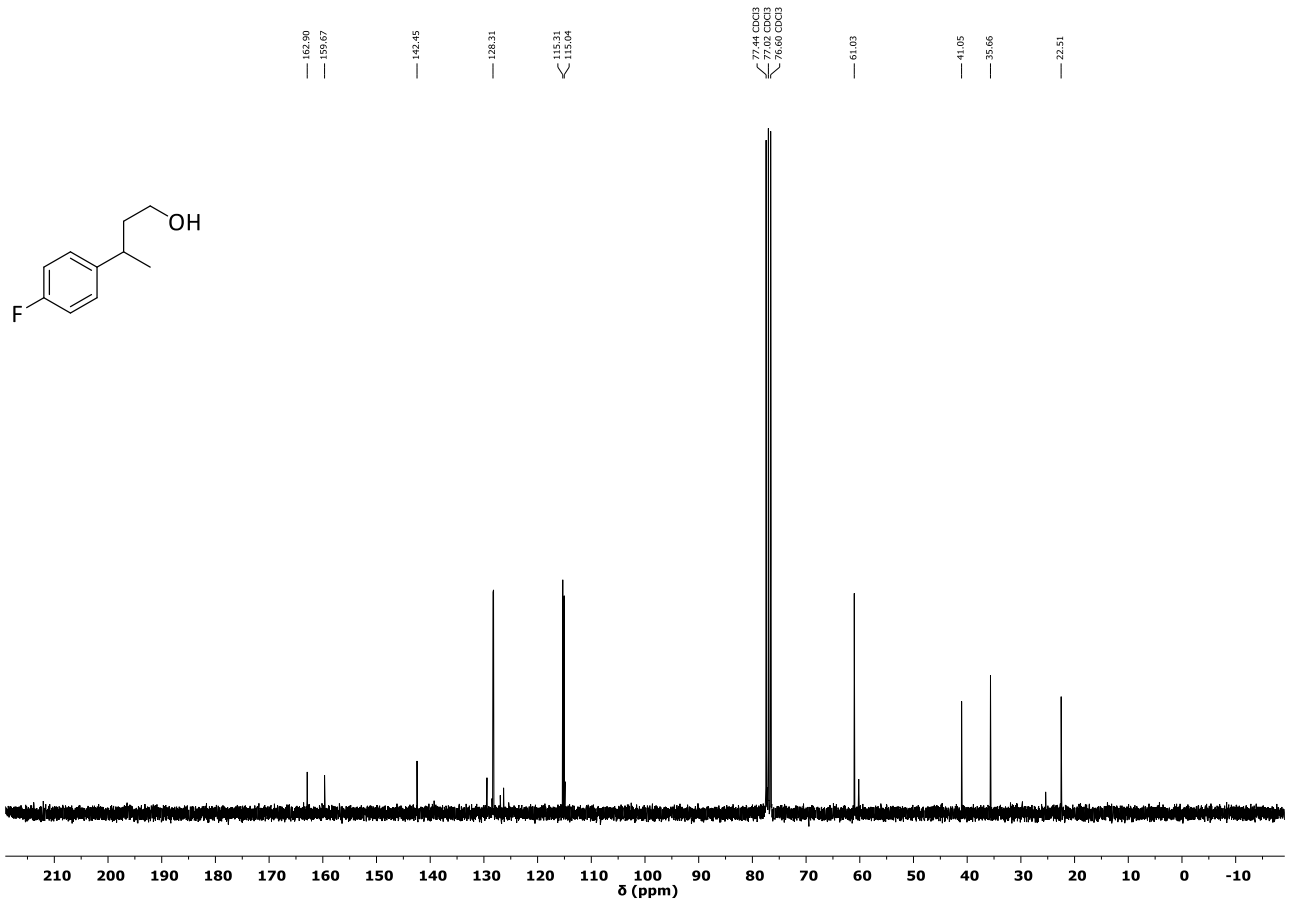

173.38
151.25
128.66
126.95
126.90
78.91 CDCl3
78.06 CDCl3
61.90
44.05
37.86
23.19
15.60
O
OEt
F3C
δ (ppm)

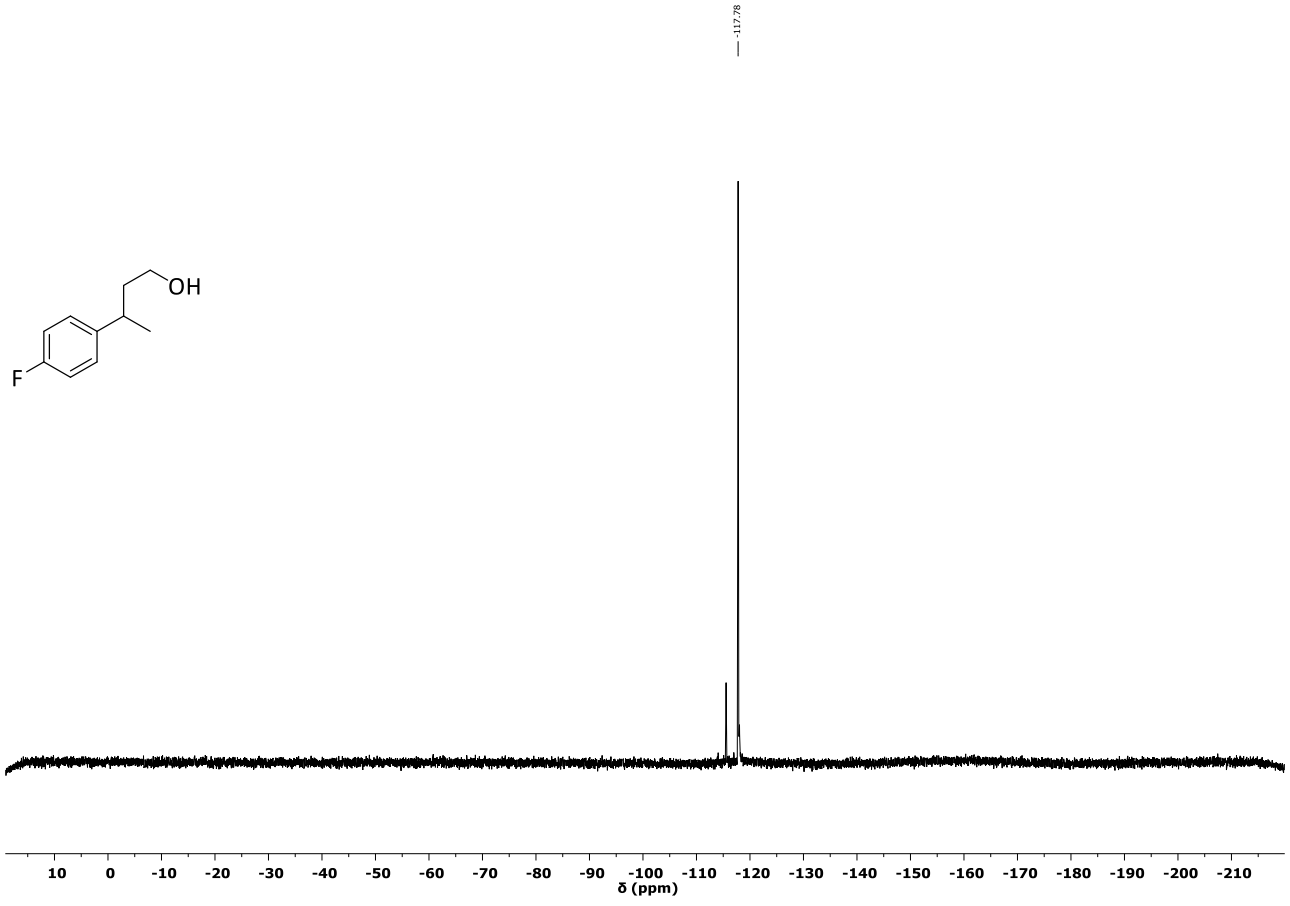

-62.78
O
OEt
F3C
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
δ (ppm)

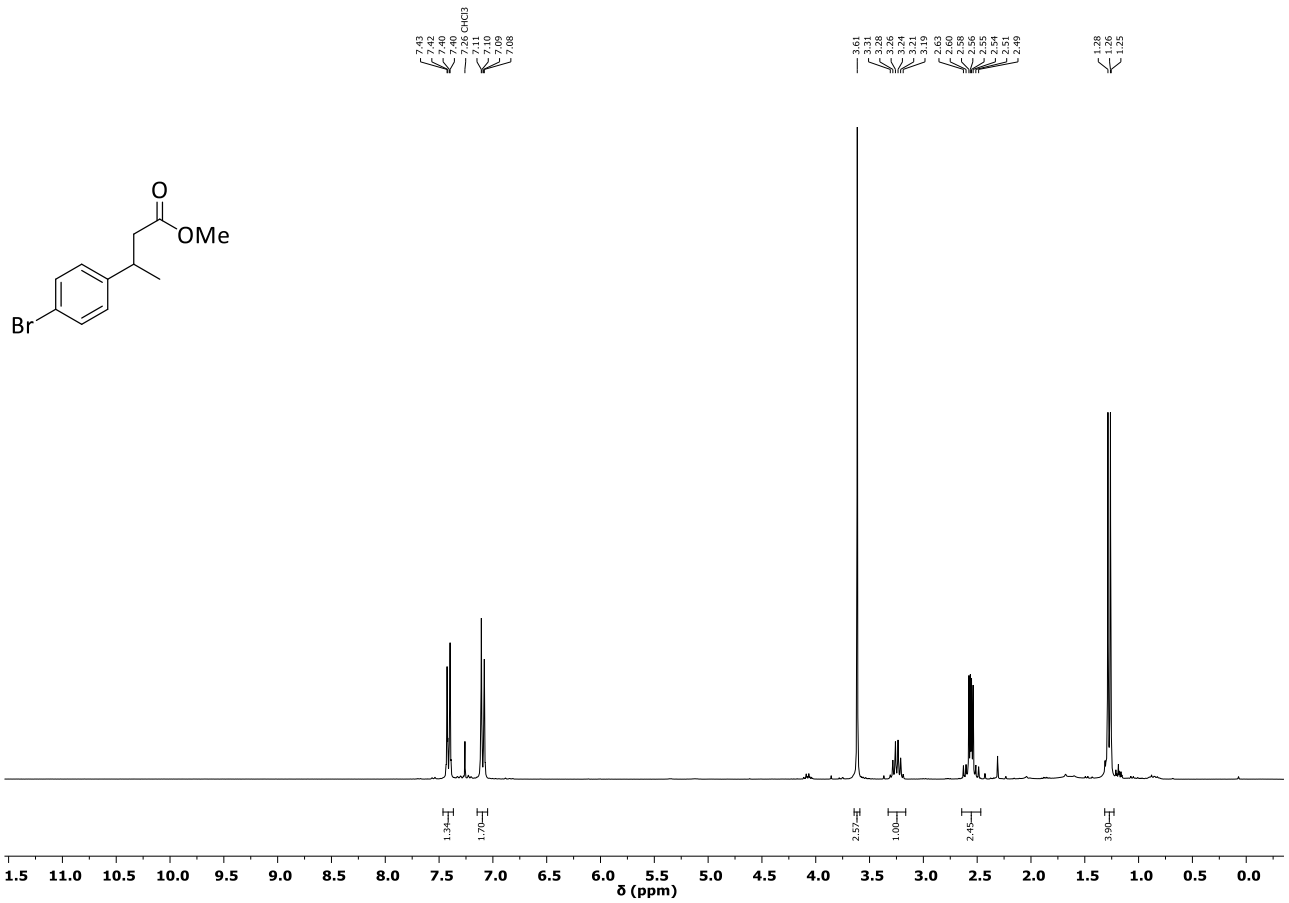

7.42
7.42
7.40
7.40
7.39
7.26 CHCl3
7.12
7.11
7.10
7.09
7.08
7.07
4.10
4.08
4.06
4.03
3.28
3.26
3.23
3.21
2.61
2.59
2.58
2.57
2.56
2.55
2.53
2.52
2.50
2.47
1.31
1.29
1.26
1.20
1.18
1.16
O
OEt
Br
1.61
1.95
2.00
0.98
2.41
4.03
3.14
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
δ (ppm)

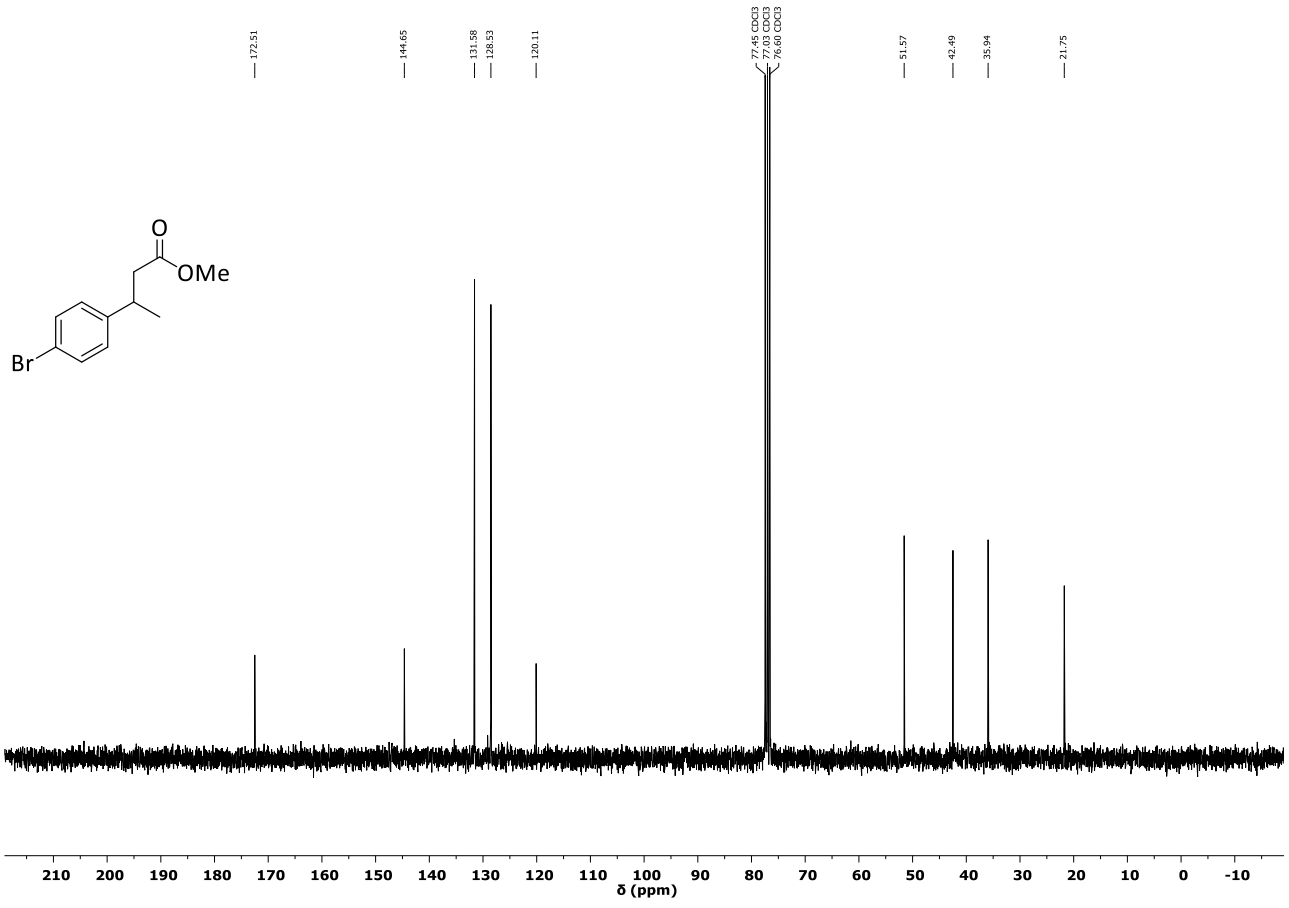

172.06
144.70
131.53
128.58
120.06
77.44 CDCl3
77.02 CDCl3
76.59 CDCl3
60.36
42.75
36.01
21.77
14.16
O
OEt
Br
δ (ppm)

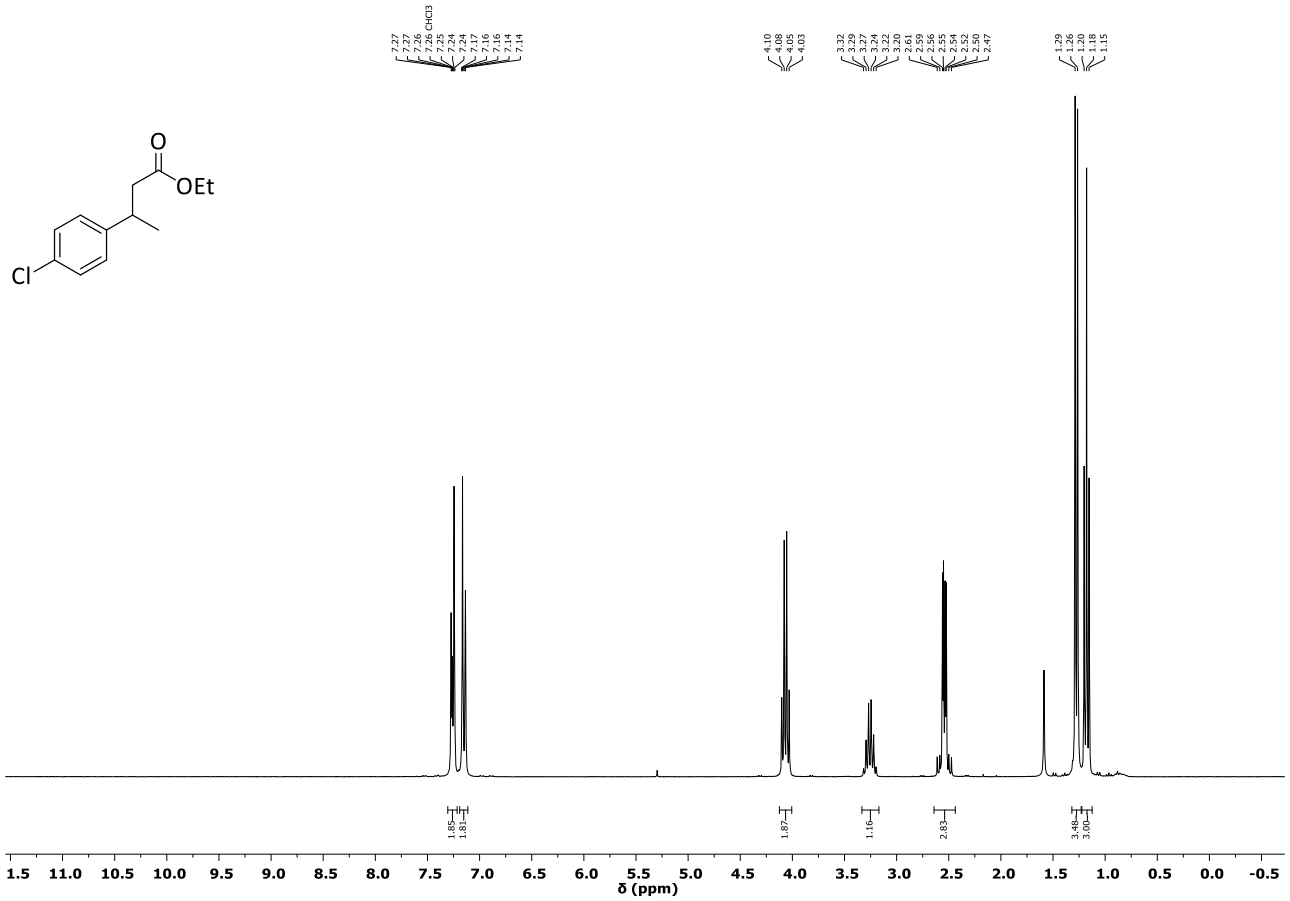

7.26 CHCl3
3.62
3.60
3.58
3.56
3.55
3.54
3.53
3.52
3.51
3.49
3.47
2.93
2.90
2.88
2.86
2.85
1.89
1.86
1.85
1.84
1.83
1.82
1.81
1.80
1.78
1.75
1.45
1.43
1.27
1.24
OH
F
1.45
1.20
1.56
0.67
1.67
1.36
3.00
δ (ppm)

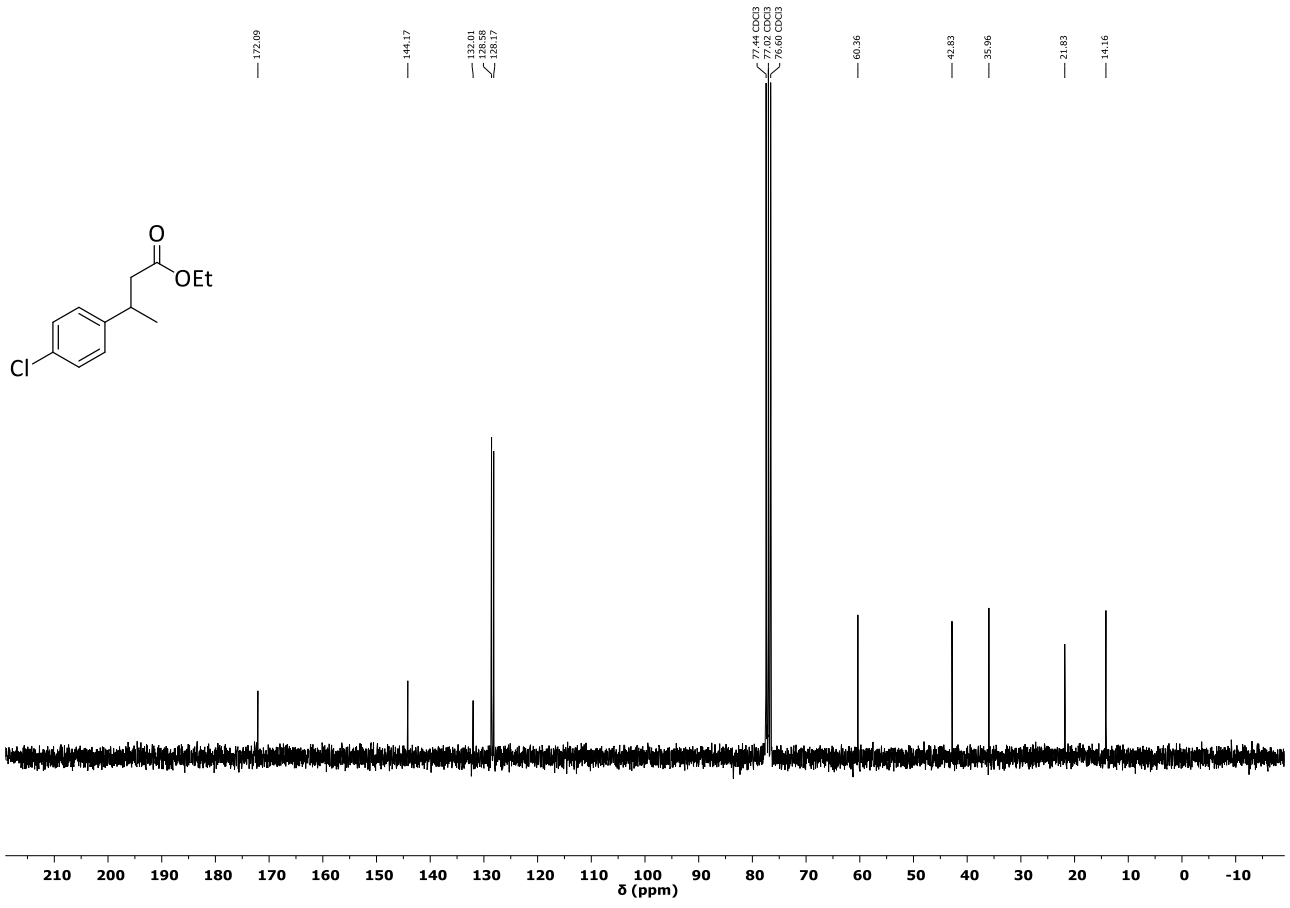

162.90
159.67
142.45
128.31
115.31
115.04
77.44 CDCl3
77.02 CDCl3
76.60 CDCl3
61.03
41.05
35.66
22.51
OH
F
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

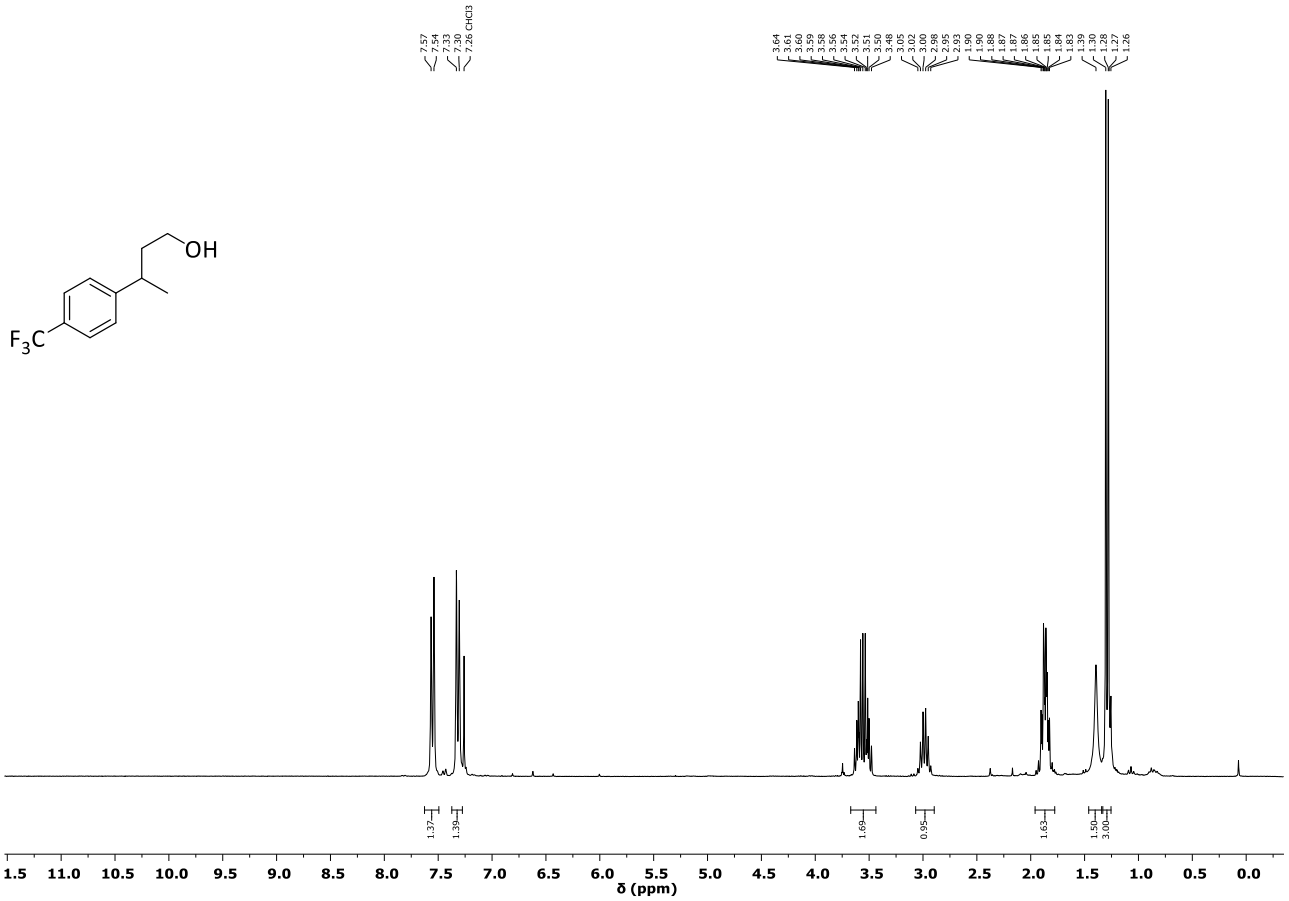

-117.78
OH
F
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
δ (ppm)

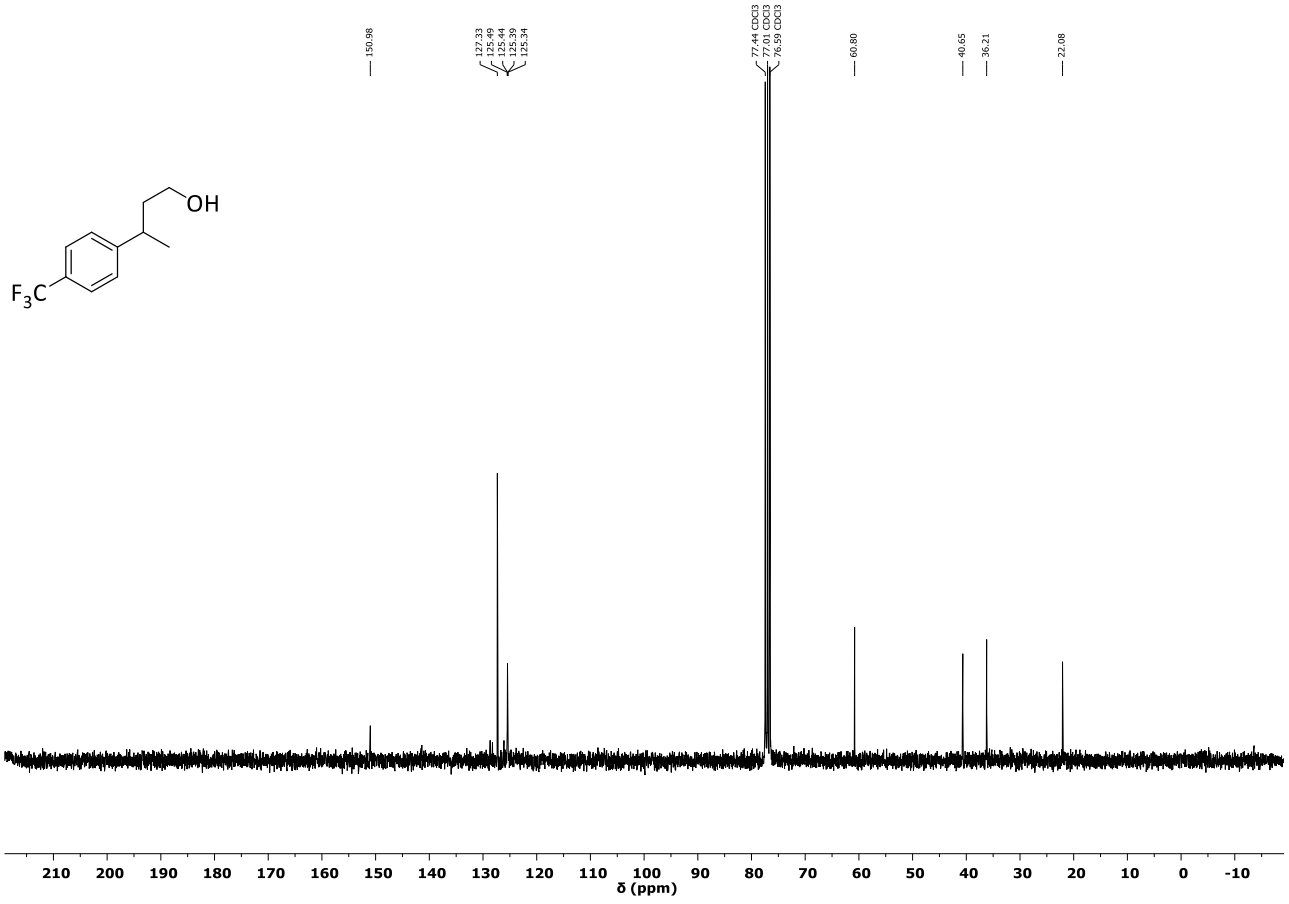

7.43
7.42
7.40
7.40
7.26 CHCl3
7.11
7.10
7.09
7.08
3.61
3.31
3.28
3.26
3.24
3.21
3.19
2.63
2.60
2.58
2.56
2.55
2.54
2.51
2.49
1.28
1.26
1.25
O
OMe
Br
1.34
1.70
2.57
1.00
2.45
3.90
1.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

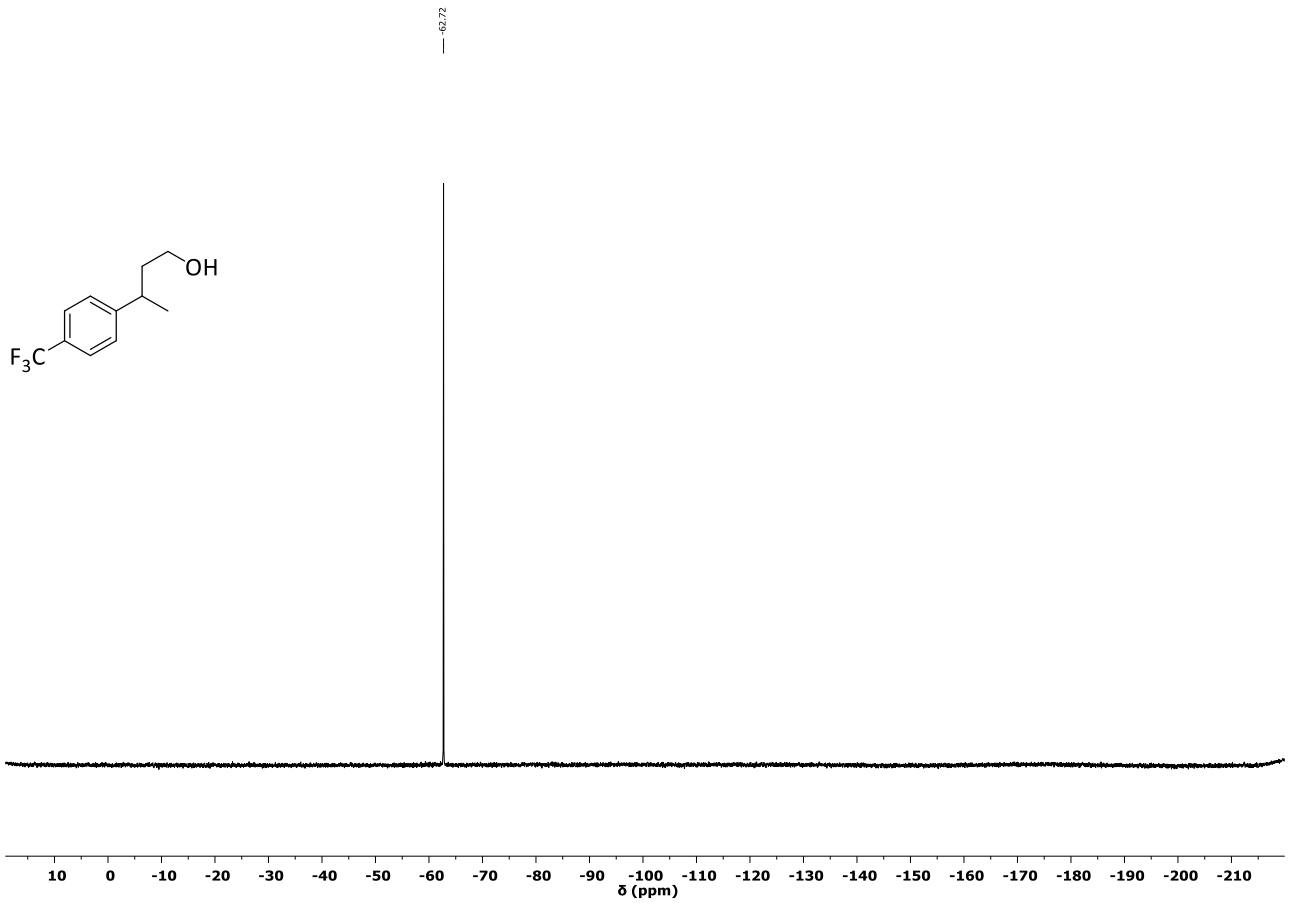

172.51
144.65
131.58
128.53
120.11
77.45 CDCl3
77.03 CDCl3
76.60 CDCl3
51.57
42.49
35.94
21.75
O
OMe
Br
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

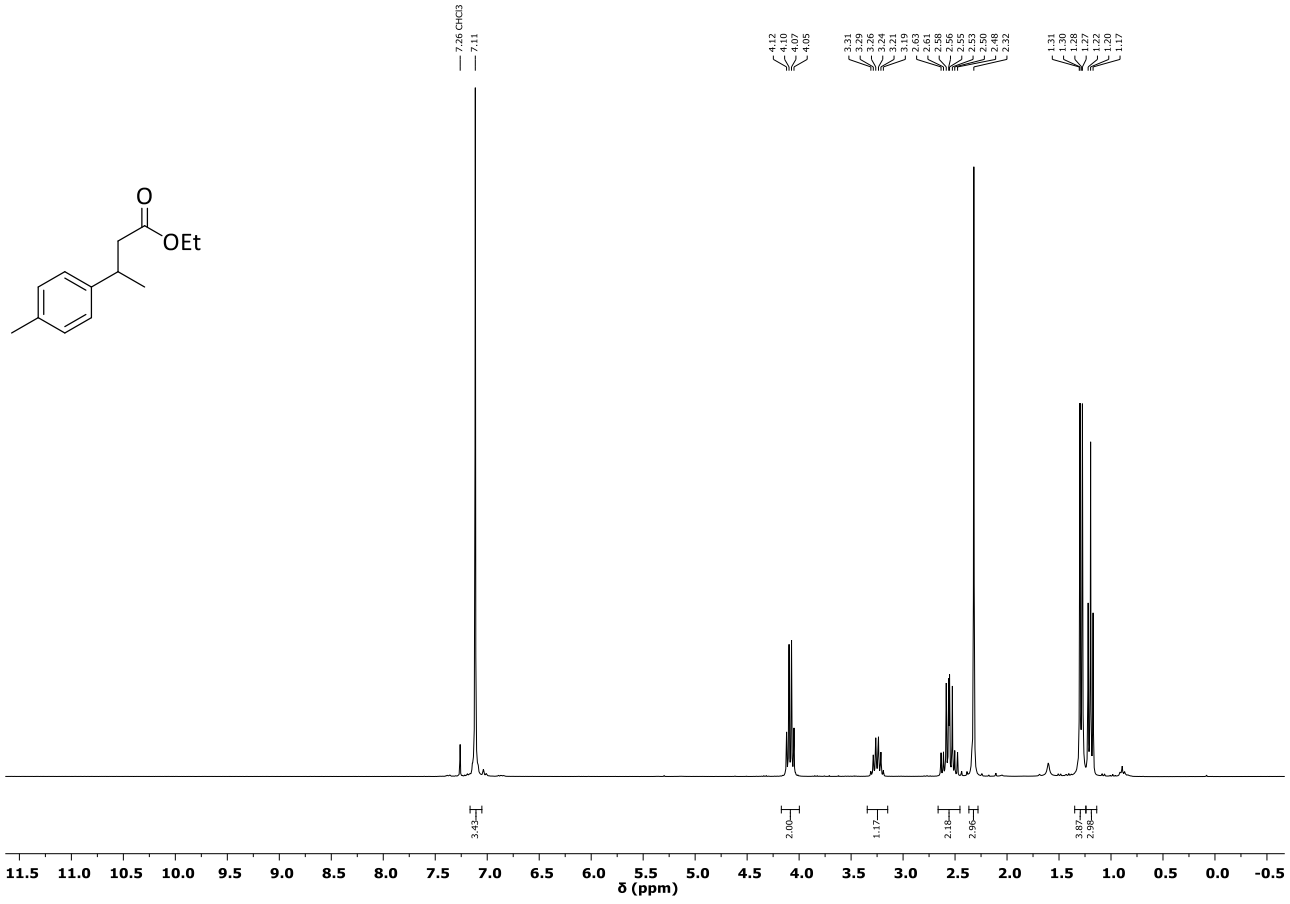

7.27
7.27
7.26
7.26 CHCl3
7.25
7.24
7.24
7.17
7.16
7.16
7.14
7.14
4.10
4.08
4.05
4.03
3.32
3.29
3.27
3.24
3.22
3.20
2.61
2.59
2.56
2.55
2.54
2.52
2.50
2.47
1.29
1.26
1.20
1.18
1.15
O
OEt
Cl
1.85
1.81
1.87
1.16
2.83
3.48
3.00
1.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
δ (ppm)

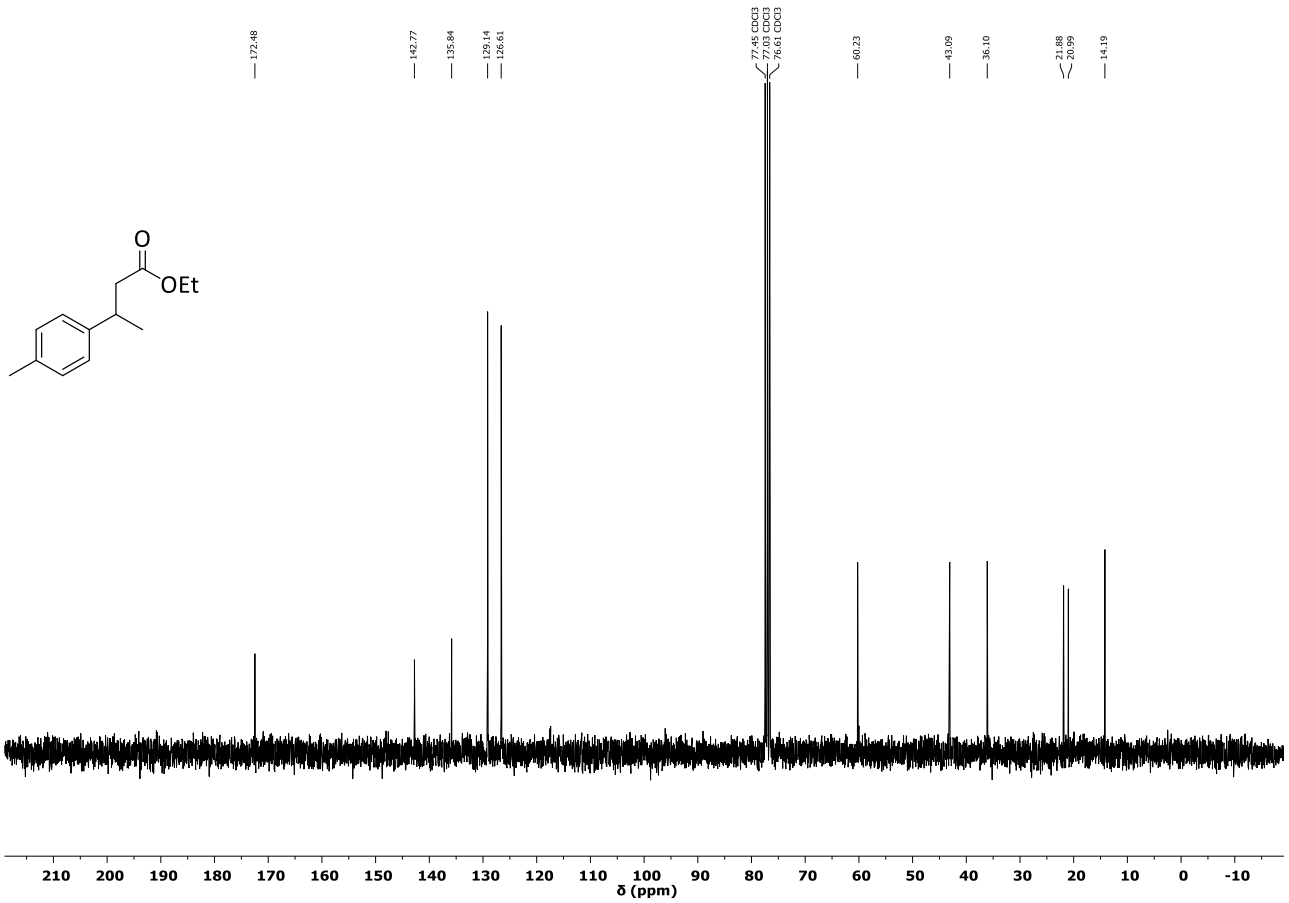

172.09
144.17
132.01
128.58
128.17
77.44 CDCl3
77.02 CDCl3
76.60 CDCl3
60.36
42.83
35.96
21.83
14.16
O
OEt
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

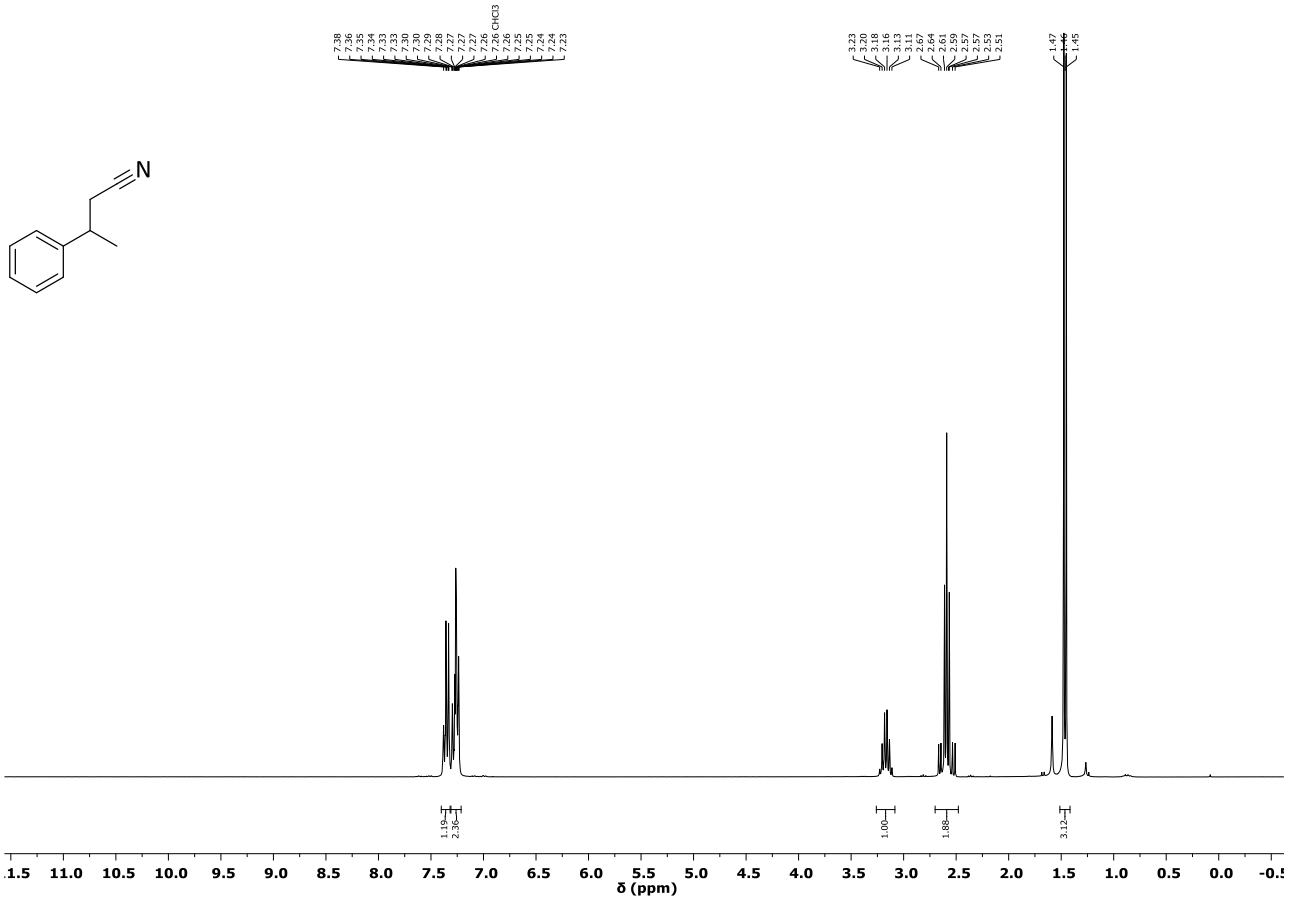

7.57
7.54
7.33
7.30
7.26 CHCl3
3.64
3.61
3.60
3.59
3.58
3.56
3.54
3.52
3.51
3.50
3.48
3.05
3.02
3.00
2.98
2.95
2.93
1.90
1.90
1.88
1.87
1.87
1.86
1.85
1.85
1.84
1.83
1.39
1.30
1.28
1.27
1.26
OH
F3C
1.37
1.39
1.69
0.95
1.63
1.50
3.00
1.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

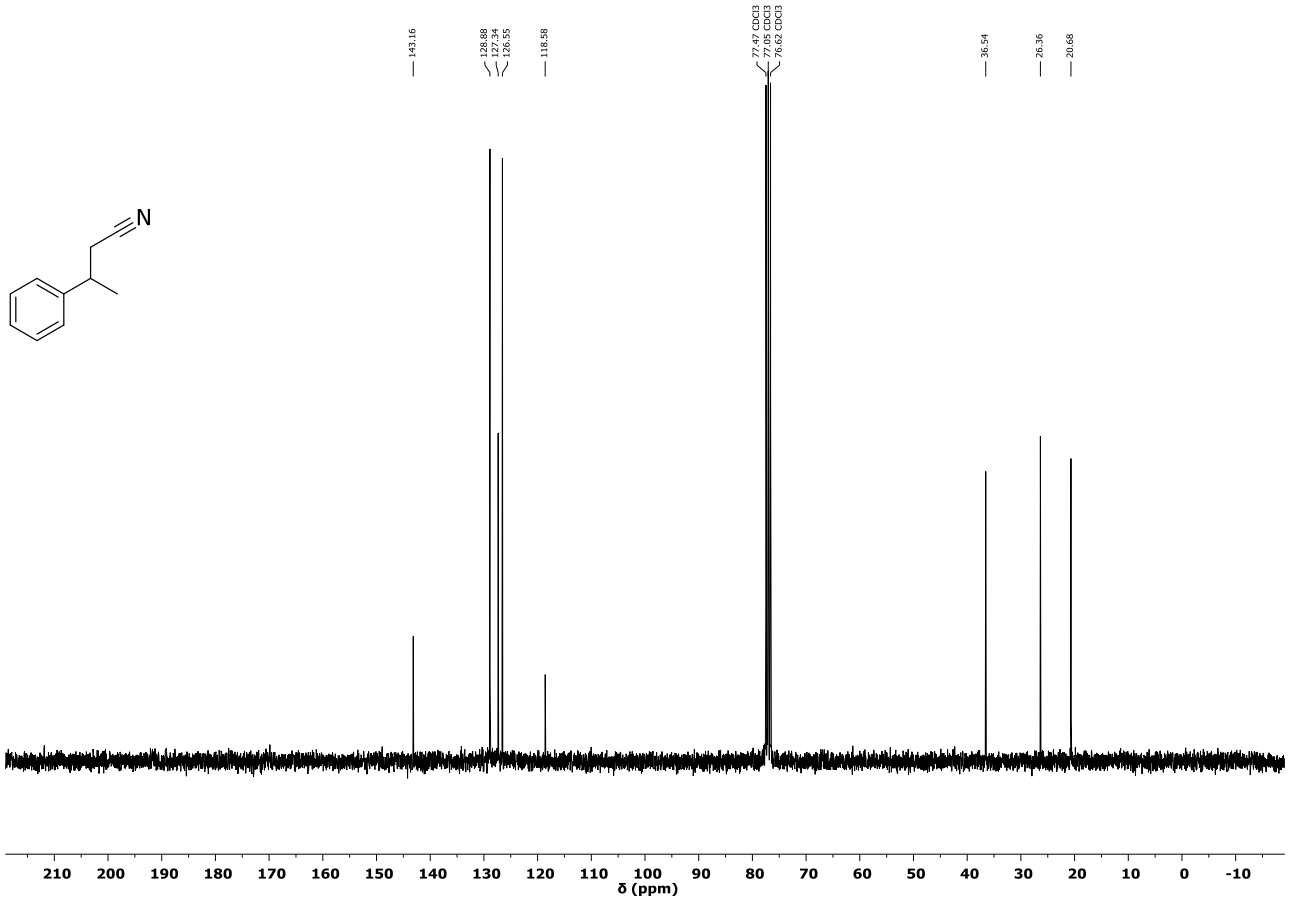

150.98
127.33
125.49
125.44
125.39
125.34
77.44 CDCl3
77.01 CDCl3
76.59 CDCl3
60.80
40.65
36.21
22.08
OH
F3C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

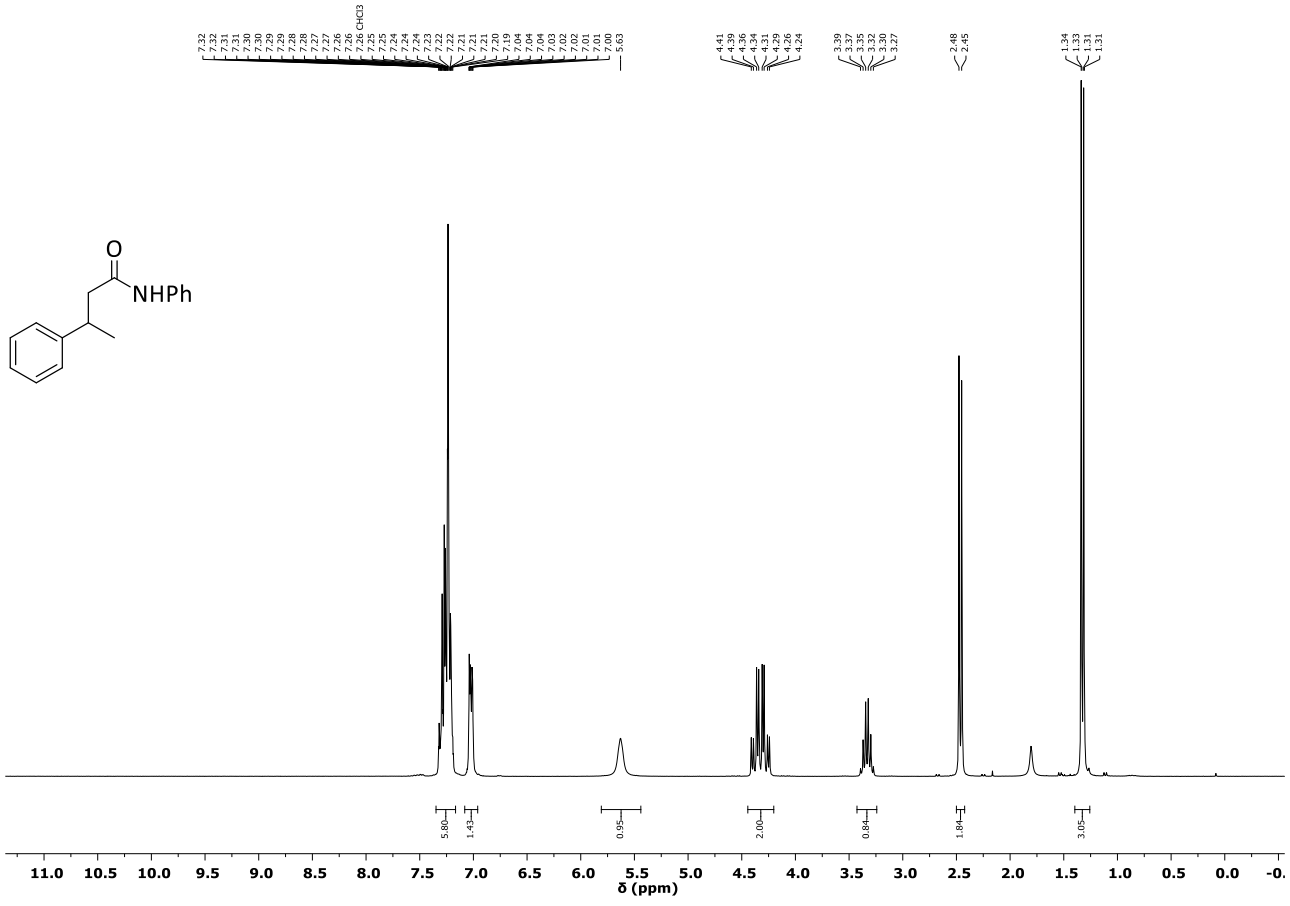

-62.72
OH
F3C
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
δ (ppm)

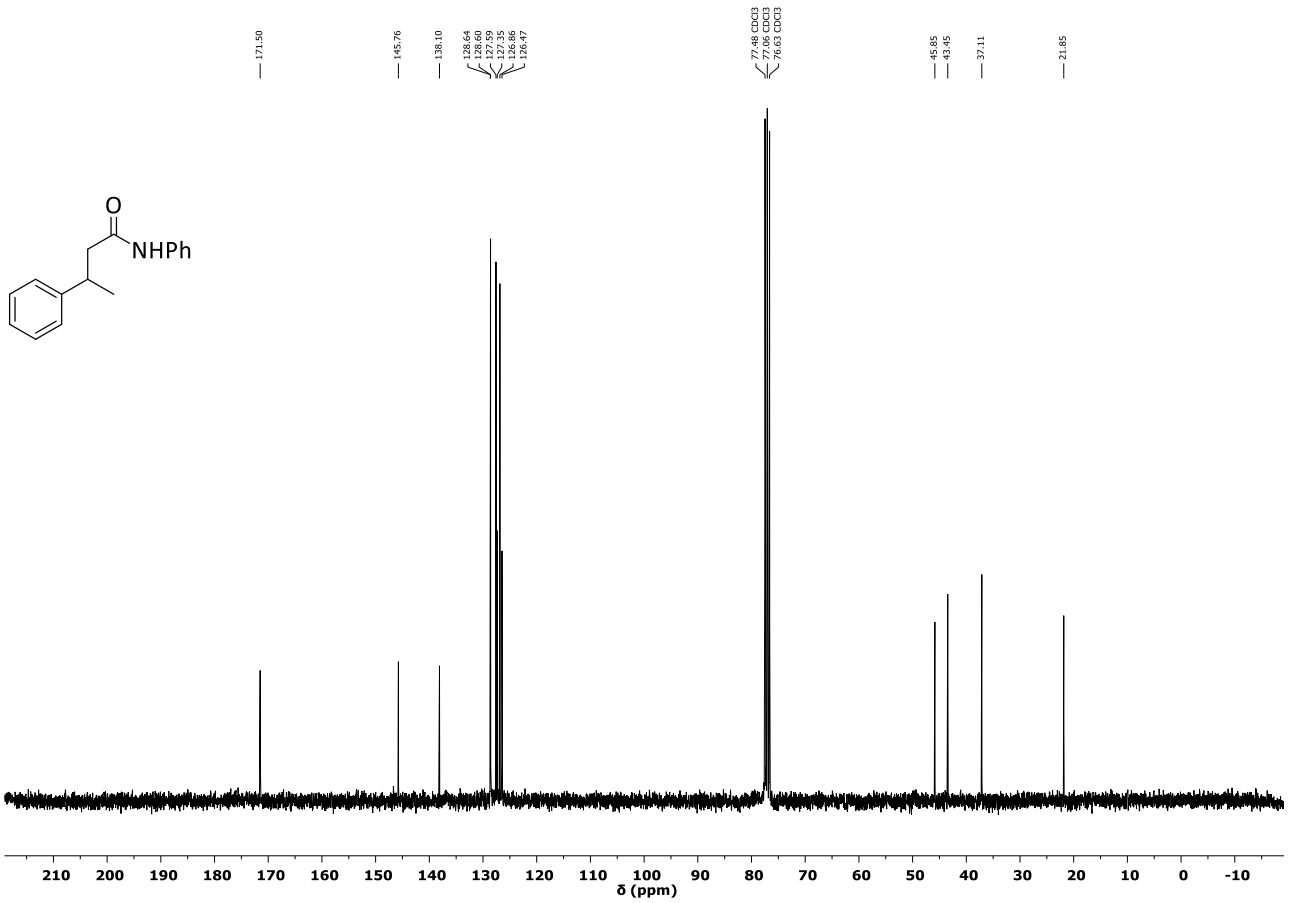

7.26 CHCl3
7.11
4.12 4.10 4.07 4.05
3.31 3.29 3.26 3.24 3.21 3.19
2.63 2.61 2.58 2.56 2.55 2.53 2.50 2.46 2.32
1.31 1.30 1.28 1.27 1.22 1.20 1.17
O
OEt
3.43
2.00
1.17
2.18
2.96
3.87
2.98
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
δ (ppm)

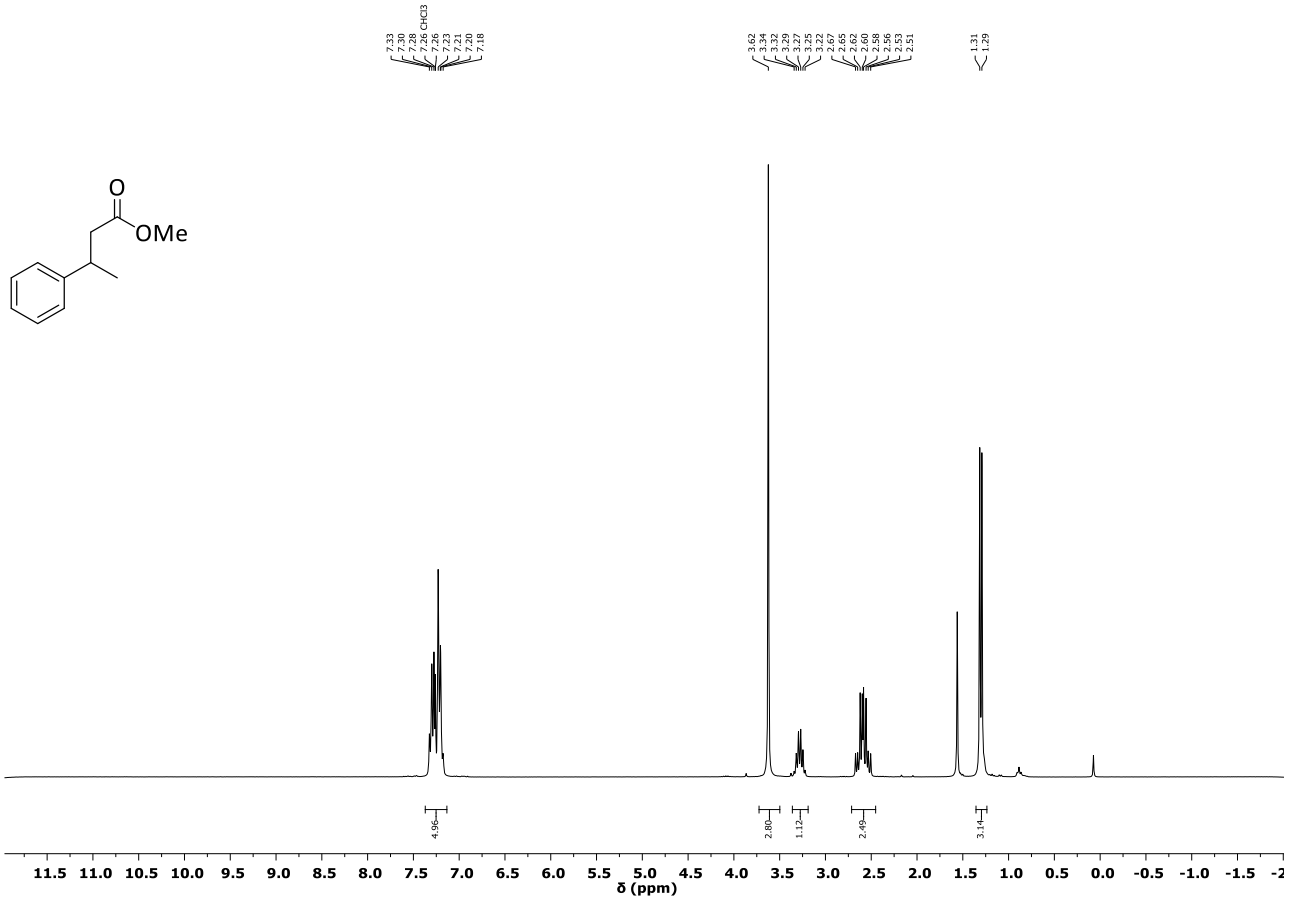

172.48
142.77
135.84
129.14
126.61
77.45 CDCl3
77.03 CDCl3
76.61 CDCl3
60.23
43.09
36.10
21.88
20.99
14.19
O
OEt
δ (ppm)

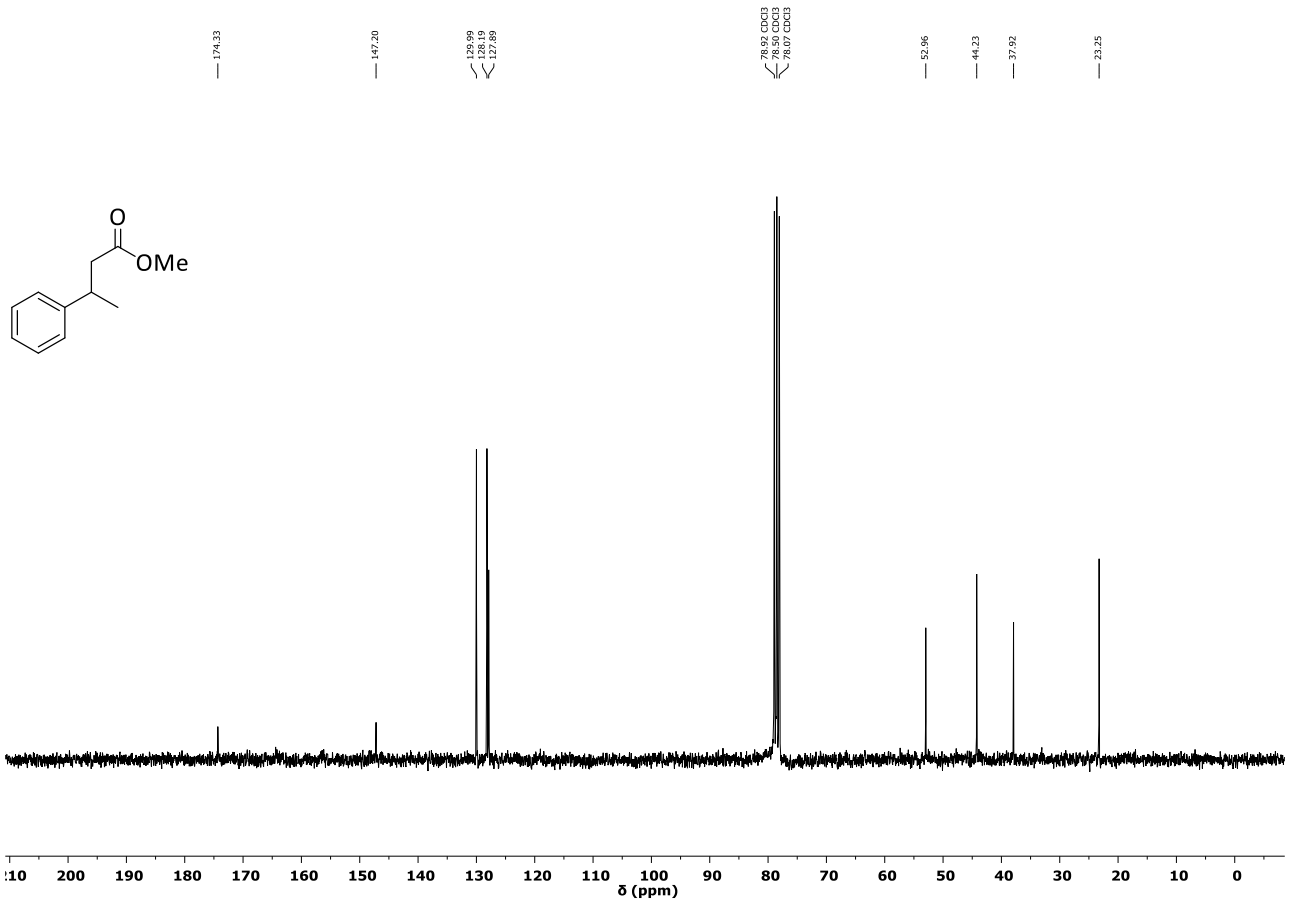

CHCl3
N
1.19
2.36
1.00
1.88
3.12
δ (ppm)

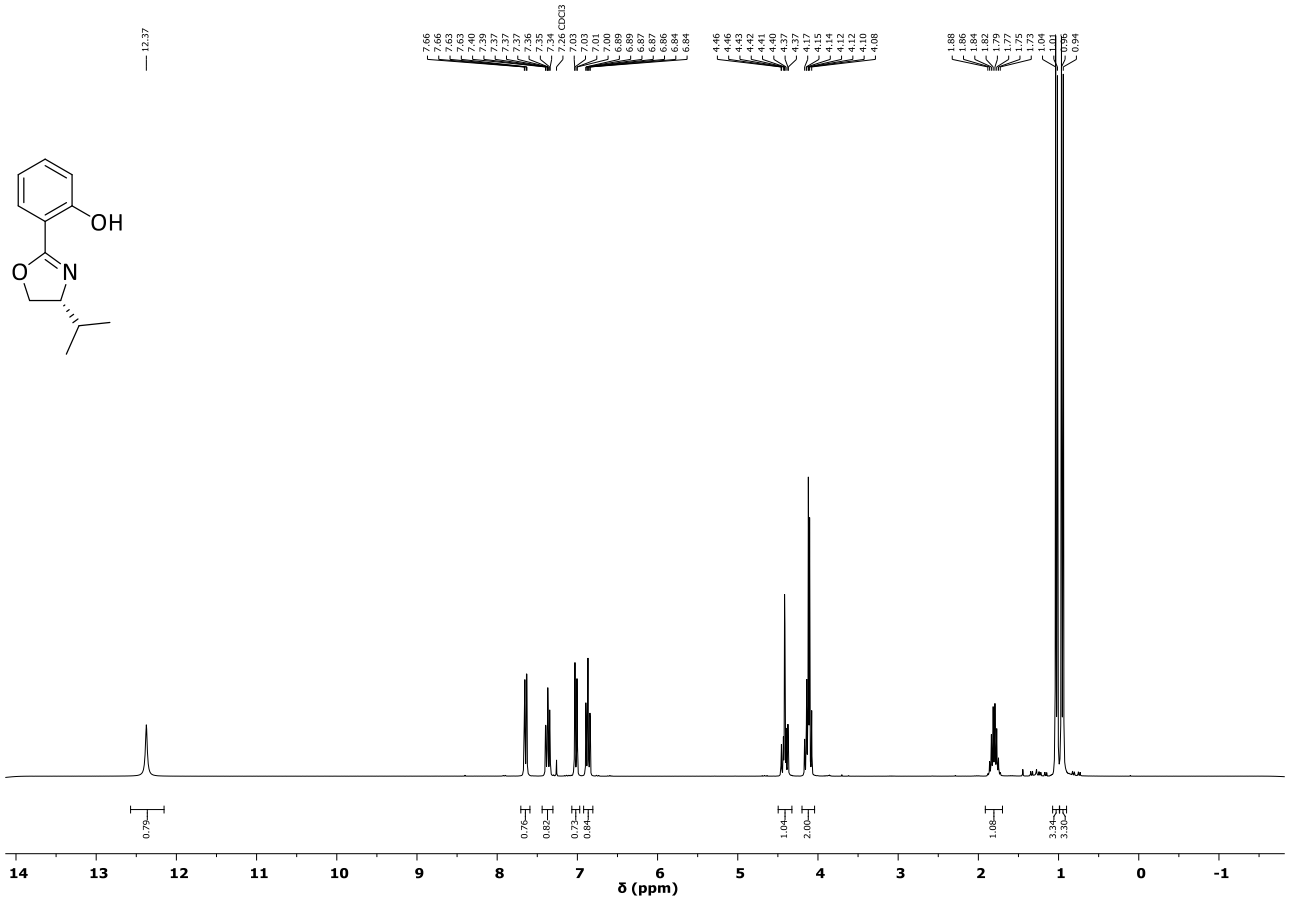

143.16
128.88
127.34
126.55
118.58
77.47 CDCl3
77.05 CDCl3
76.62 CDCl3
36.54
26.36
20.68
N
δ (ppm)

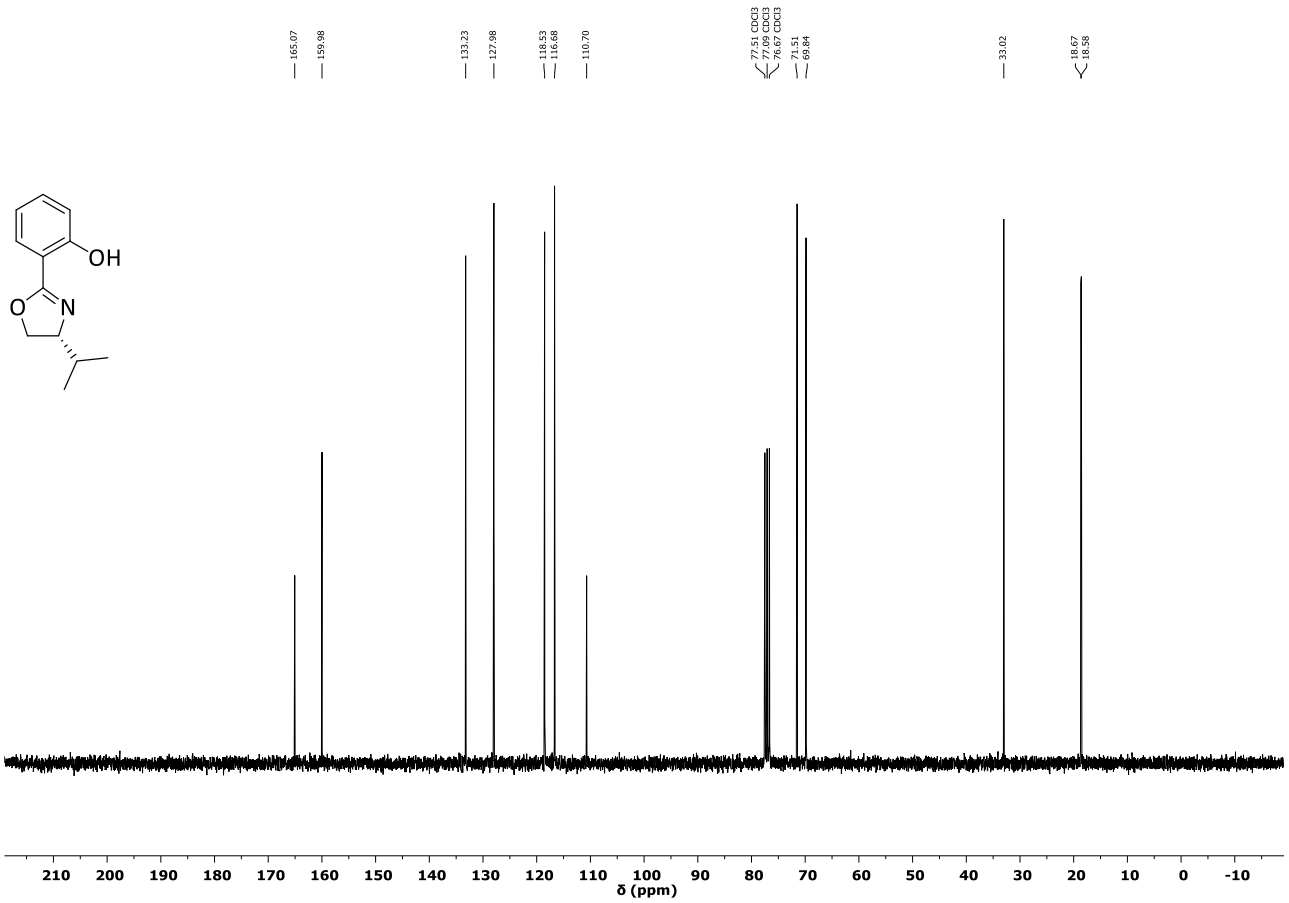

7.26 CHCl3
5.63
4.41
4.39
4.36
4.34
4.31
4.29
4.26
4.24
3.39
3.37
3.35
3.32
3.30
3.27
2.48
2.45
1.34
1.33
1.31
1.31
5.80
1.43
0.95
2.00
0.84
1.84
3.05
O
NHPh
δ (ppm)

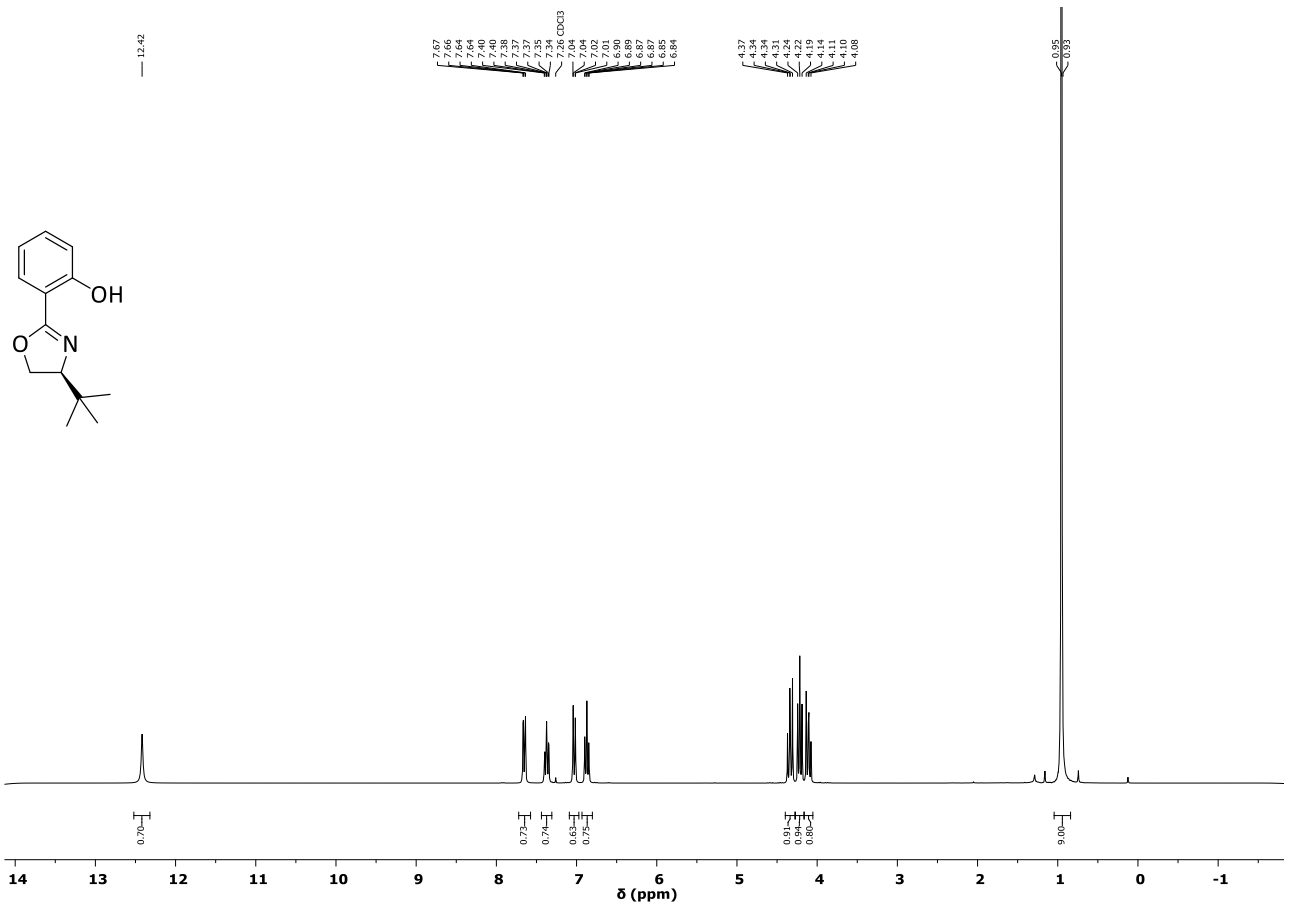

171.50
145.76
138.10
128.64
128.60
127.59
127.35
126.86
126.47
77.48 CDCl3
77.06 CDCl3
76.63 CDCl3
45.85
43.45
37.11
21.85
O
NHPh
δ (ppm)

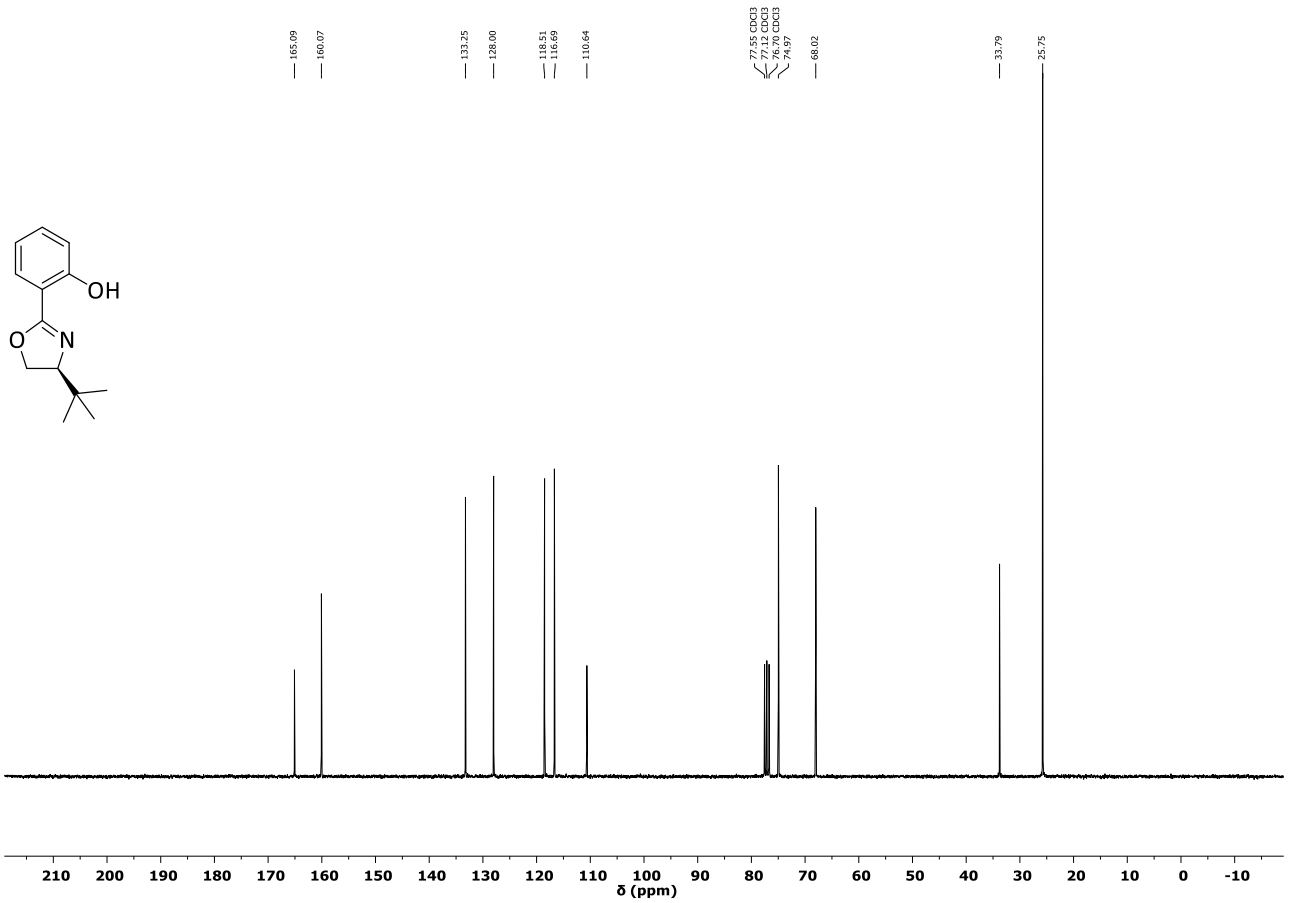

7.33
7.30
7.28
7.26 CHCl3
7.23
7.21
7.20
7.18
3.62
3.34
3.32
3.29
3.27
3.25
3.23
3.07
2.65
2.62
2.60
2.58
2.56
2.53
2.51
1.31
1.29
4.96
2.80
1.12
2.49
3.14
O
OMe
δ (ppm)

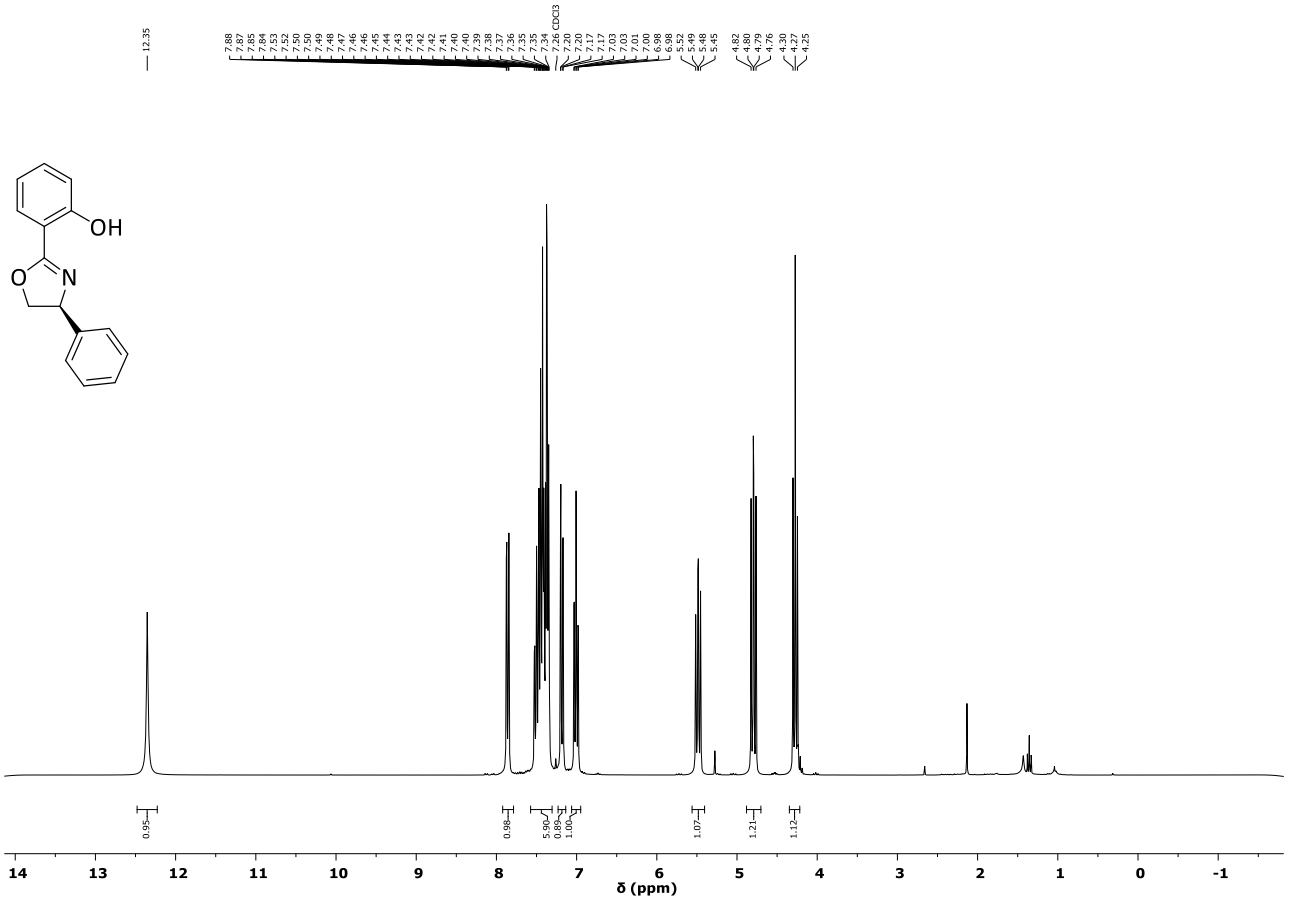

174.33
147.20
129.99
128.19
127.89
78.92 CDCl3
78.50 CDCl3
78.07 CDCl3
52.96
44.23
37.92
23.25
O
OMe
δ (ppm)

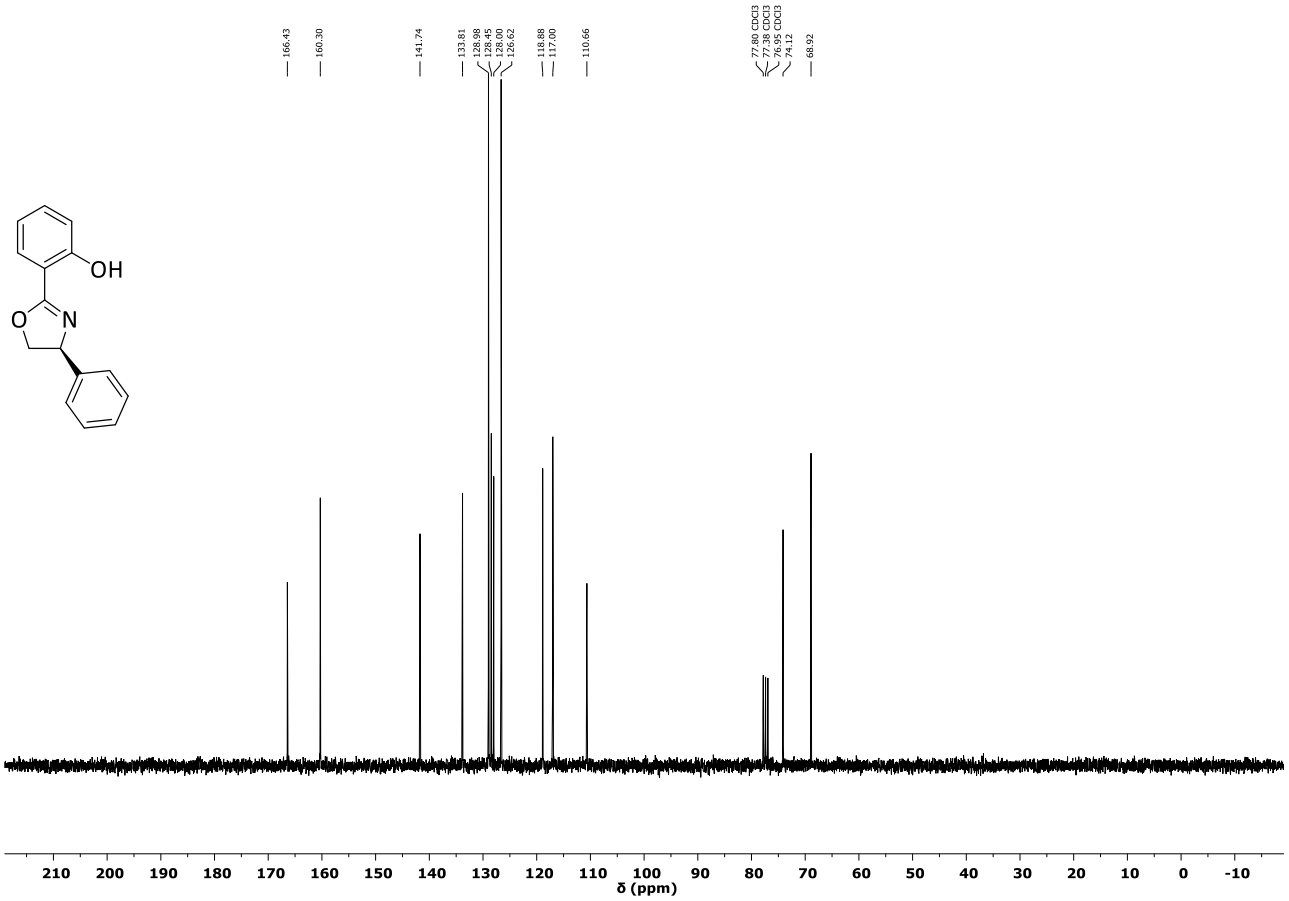

12.37
7.66
7.66
7.65
7.63
7.40
7.39
7.37
7.37
7.37
7.36
7.35
7.34
7.26 CDCl3
7.03
7.01
7.00
6.89
6.89
6.87
6.87
6.86
6.84
6.84
4.46
4.46
4.43
4.42
4.41
4.40
4.37
4.37
4.17
4.15
4.14
4.12
4.12
4.10
4.08
1.88
1.86
1.84
1.82
1.79
1.77
1.75
1.73
1.04
1.01
0.96
0.94
OH
O
N
0.79
0.76
0.82
0.73
0.84
1.04
2.00
1.08
3.34
3.30
δ (ppm)

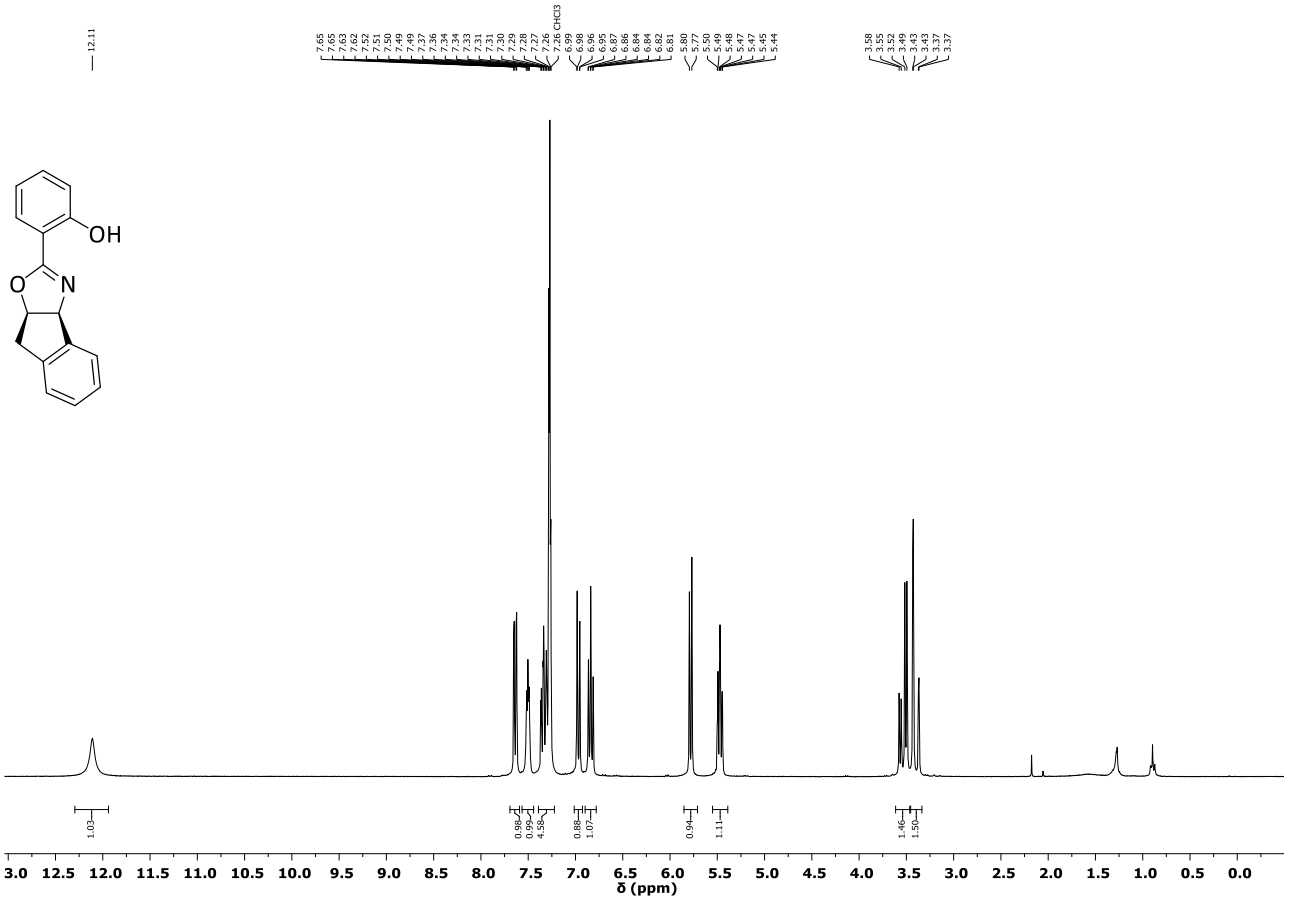

165.07
159.98
133.23
127.98
118.53
116.68
110.70
77.51 CDCl3
77.09 CDCl3
76.67 CDCl3
71.51
69.84
33.02
18.67
18.58
OH
O
N
δ (ppm)

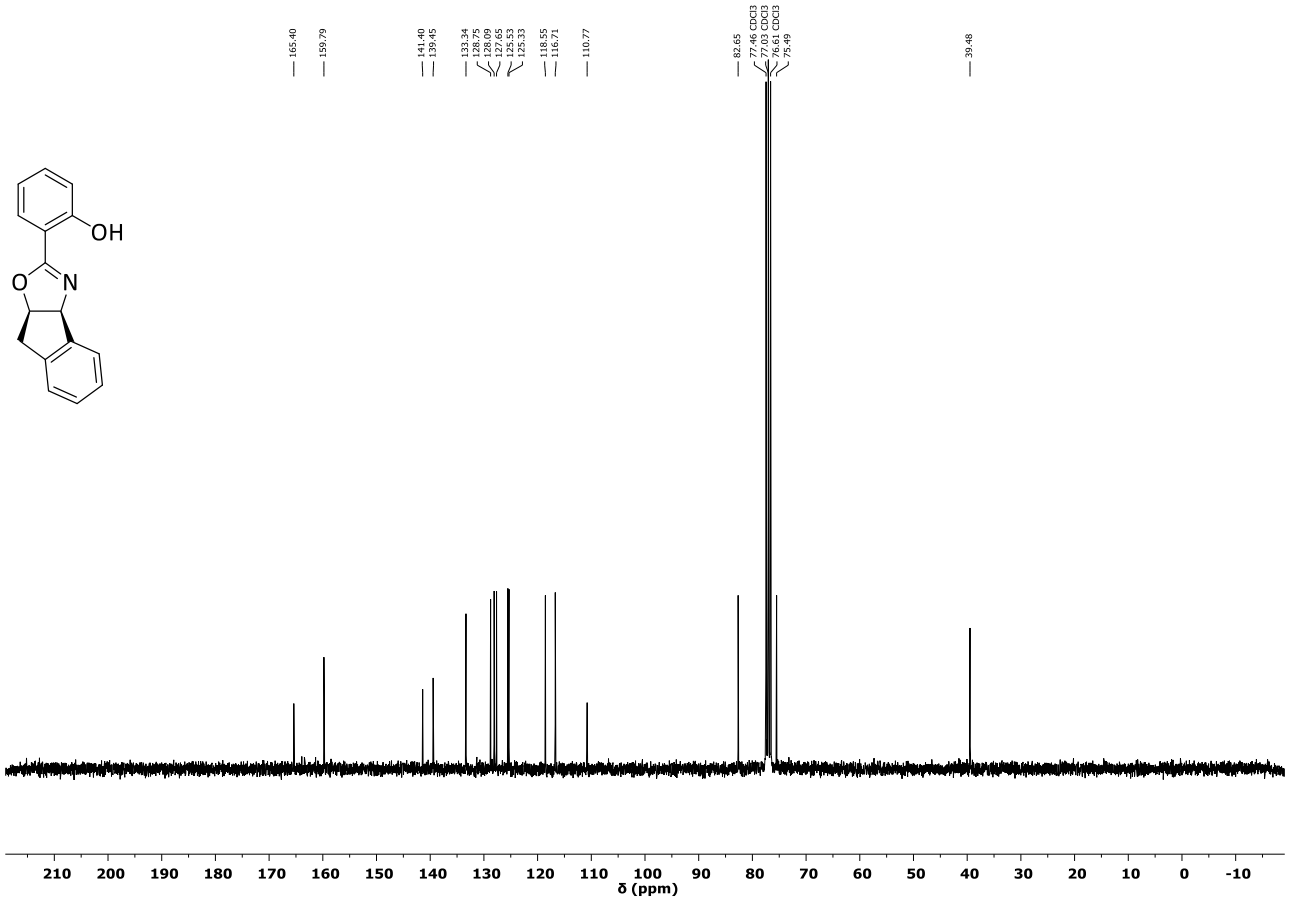

12.42
7.67
7.66
7.64
7.64
7.40
7.40
7.38
7.37
7.37
7.35
7.34
7.26 CDCl3
7.04
7.04
7.02
7.01
6.90
6.89
6.87
6.87
6.85
6.84
4.37
4.34
4.34
4.31
4.24
4.22
4.19
4.14
4.11
4.10
4.08
0.95
0.93
0.70
0.73
0.74
0.63
0.75
0.91
0.94
0.80
9.00
OH
O
N
δ (ppm)

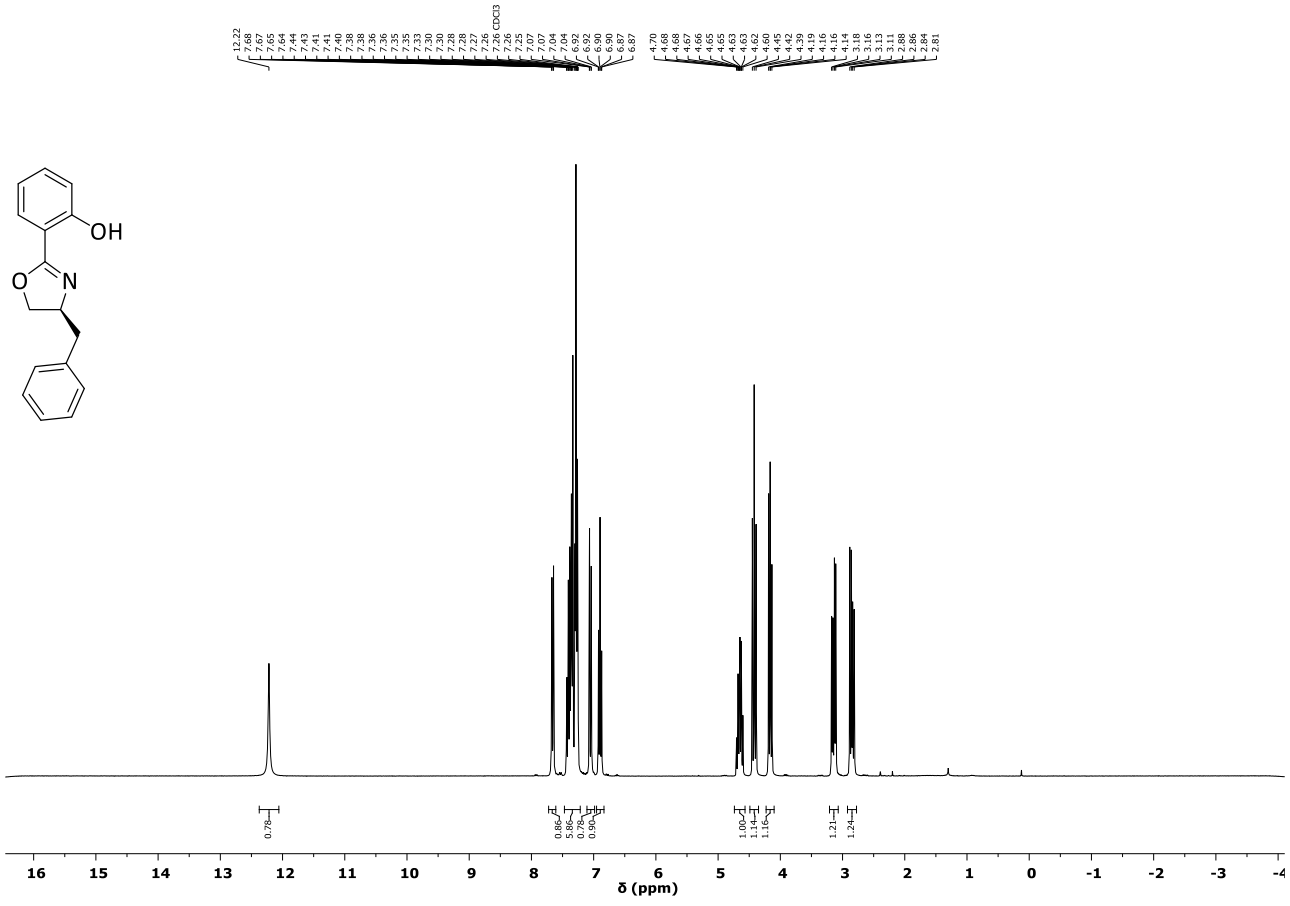

165.09
160.07
133.25
128.00
118.51
116.69
110.64
77.55 CDCl3
77.12 CDCl3
76.70 CDCl3
74.97
68.02
33.79
25.75
OH
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

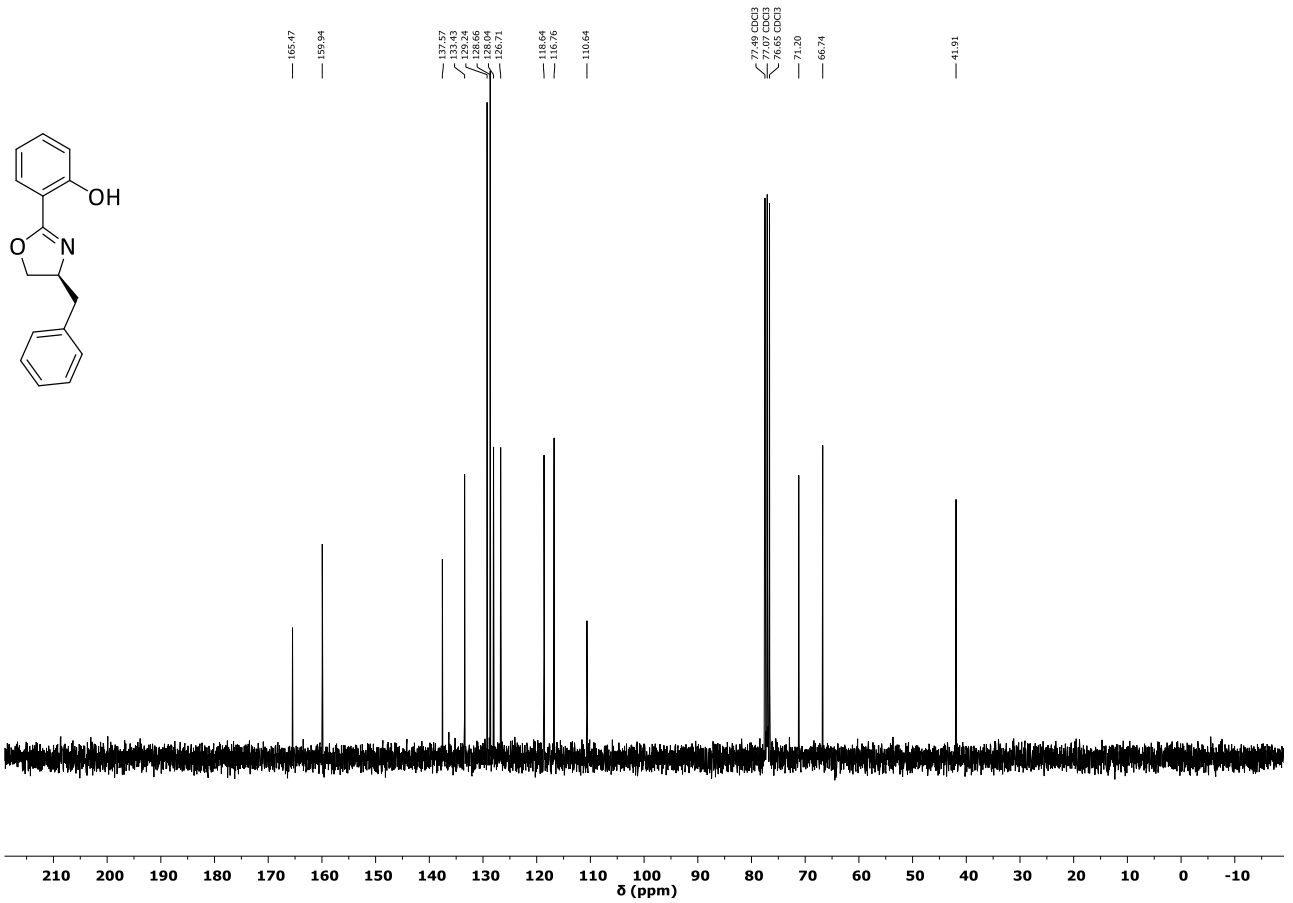

12.35
7.88
7.87
7.86
7.84
7.53
7.52
7.50
7.50
7.49
7.48
7.47
7.46
7.46
7.45
7.44
7.43
7.43
7.42
7.42
7.41
7.40
7.40
7.39
7.38
7.37
7.36
7.35
7.35
7.34
7.26 CDCl3
7.20
7.17
7.17
7.17
7.03
7.01
7.00
7.00
6.98
5.52
5.49
5.48
5.48
5.45
4.82
4.80
4.79
4.76
4.30
4.27
4.25
OH
O
N
0.95
0.98
5.90
0.89
1.00
1.07
1.21
1.12
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
δ (ppm)

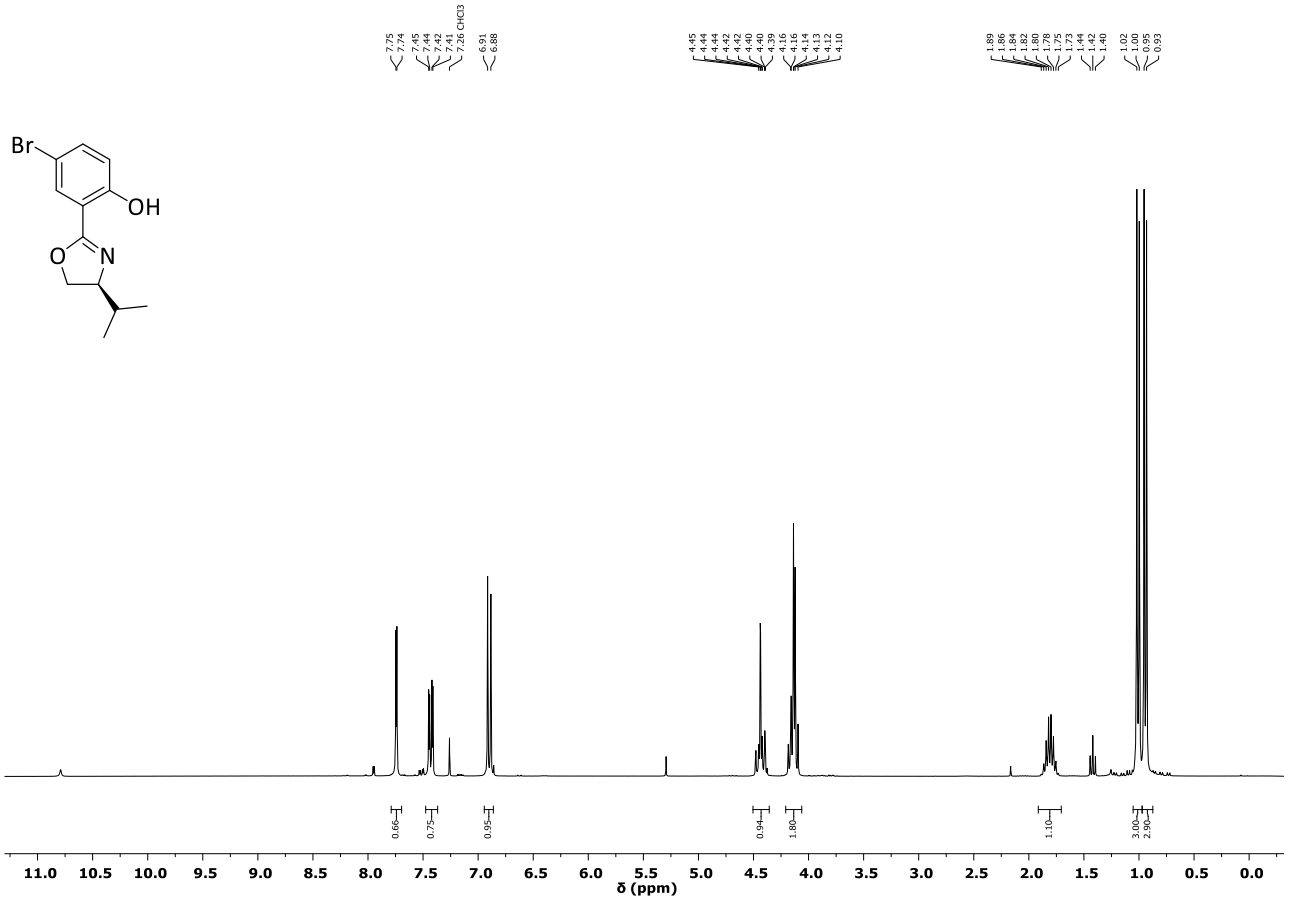

166.43
160.30
141.74
133.81
128.98
128.45
128.00
126.62
118.88
117.00
110.66
77.80 CDCl3
77.38 CDCl3
76.95 CDCl3
74.12
68.92
OH
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

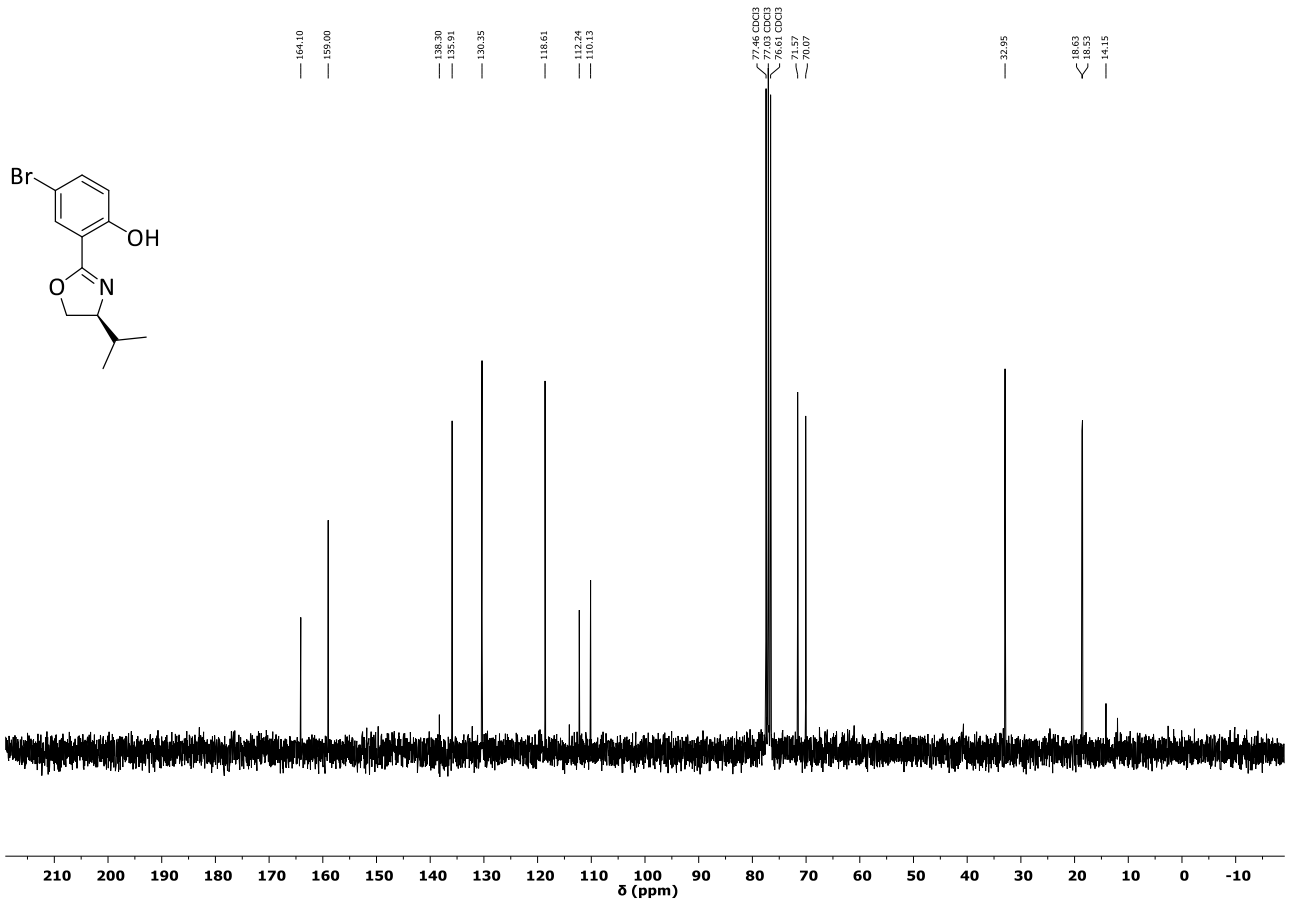

12.11
7.65
7.65
7.63
7.62
7.52
7.51
7.50
7.49
7.49
7.37
7.36
7.34
7.33
7.31
7.31
7.30
7.29
7.28
7.27
7.26
7.26 CHCl3
6.99
6.98
6.96
6.95
6.87
6.86
6.84
6.84
6.82
6.81
5.80
5.77
5.50
5.49
5.48
5.47
5.47
5.45
5.44
3.58
3.55
3.52
3.49
3.43
3.43
3.37
3.37
OH
O
N
1.03
0.98
0.99
4.38
0.88
1.07
0.94
1.11
1.46
1.50
3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)


OH
O
N
165.40
159.79
141.40
139.45
133.34
128.75
128.09
127.65
125.53
125.33
118.55
116.71
110.77
82.65
77.46 CDCl3
77.03 CDCl3
76.61 CDCl3
75.49
39.48
δ (ppm)


OH
O
N
δ (ppm)


165.47
159.94
137.57
133.43
129.24
128.66
128.04
126.71
118.64
116.76
110.64
77.49 CDCl3
77.07 CDCl3
76.65 CDCl3
71.20
66.74
41.91
OH
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)


7.75
7.74
7.45
7.44
7.42
7.41
7.26 CHCl3
6.91
6.88
4.45
4.44
4.44
4.42
4.42
4.40
4.40
4.39
4.16
4.16
4.14
4.13
4.12
4.10
1.89
1.86
1.84
1.82
1.80
1.78
1.75
1.73
1.44
1.42
1.40
1.02
1.00
0.95
0.93
Br
OH
O
N
0.66
0.75
0.95
0.94
1.80
1.10
3.00
2.90
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)


Br
OH
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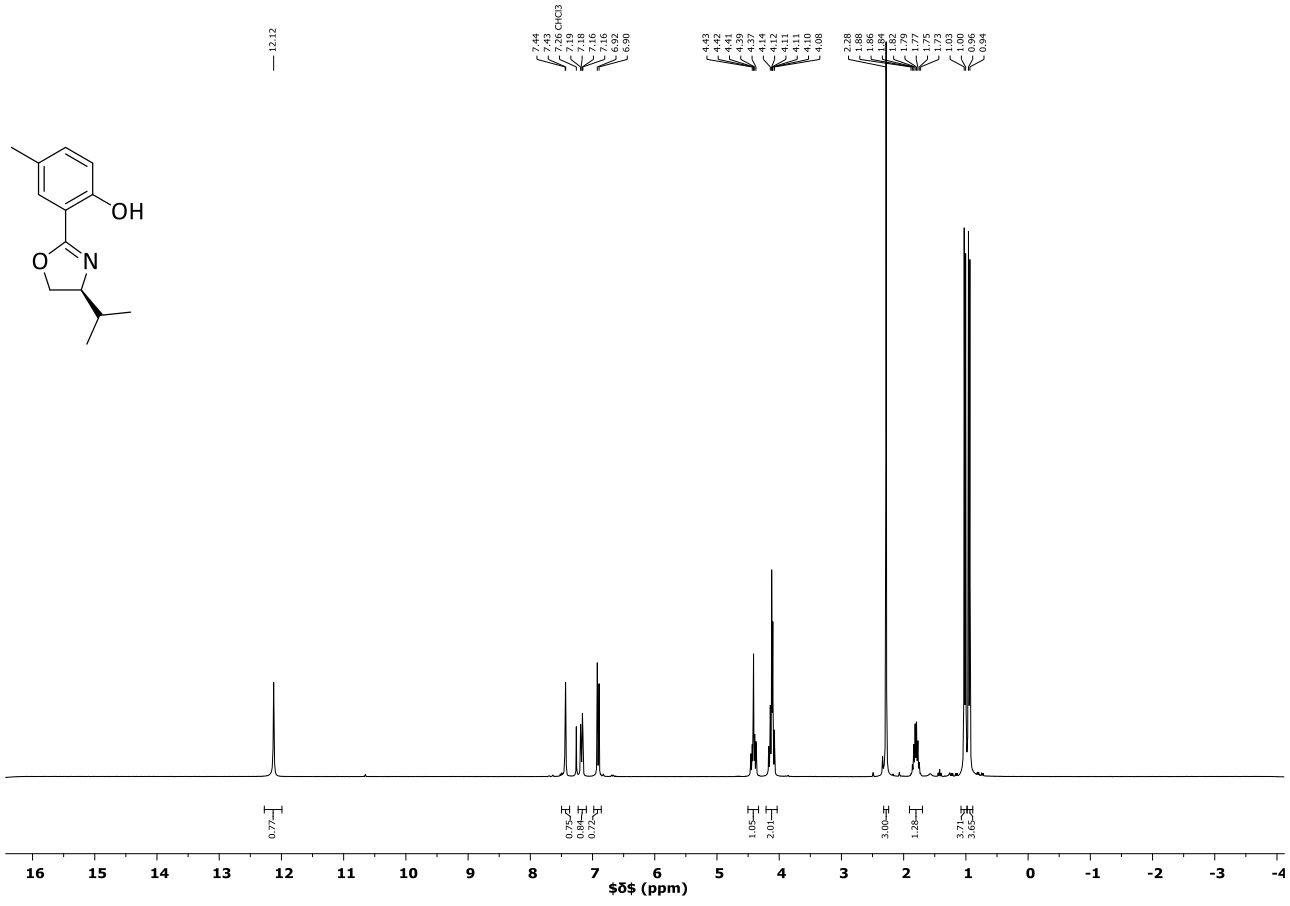
76.61 CDCl3
71.57
70.07
32.95
18.63
18.53
14.15
δ (ppm)


OH
O
N
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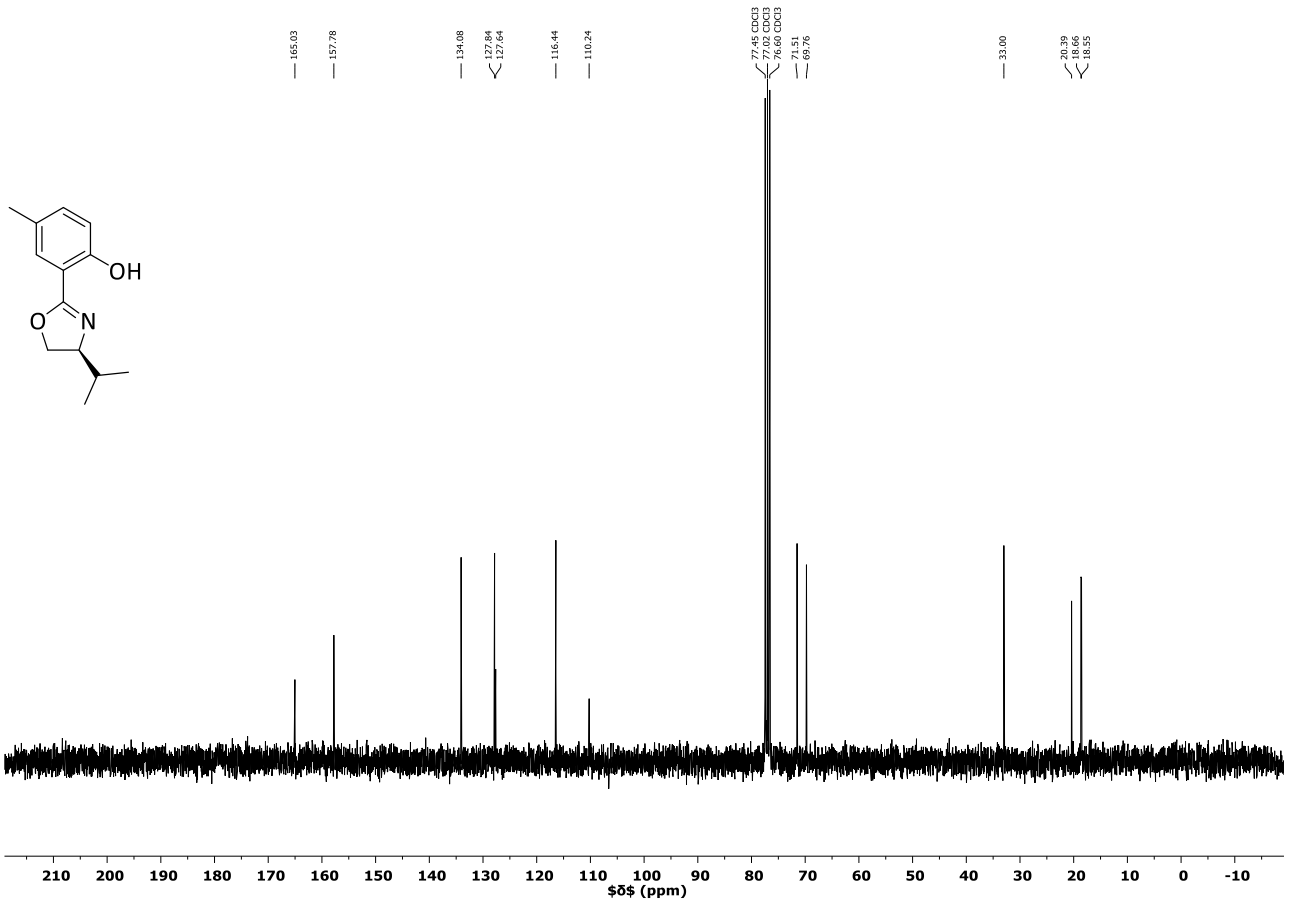
6.90
4.43
4.42
4.41
4.39
4.37
4.14
4.12
4.11
4.11
4.10
4.08
2.28
1.88
1.86
1.84
1.82
1.79
1.77
1.75
1.73
1.03
1.00
0.96
0.94
0.77
0.75
0.84
0.72
1.05
2.01
3.00
1.28
3.71
3.65
$δ$ (ppm)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127.64
116.44
110.24
77.45 CDCl3
77.02 CDCl3
76.60 CDCl3
71.51
69.76
33.00
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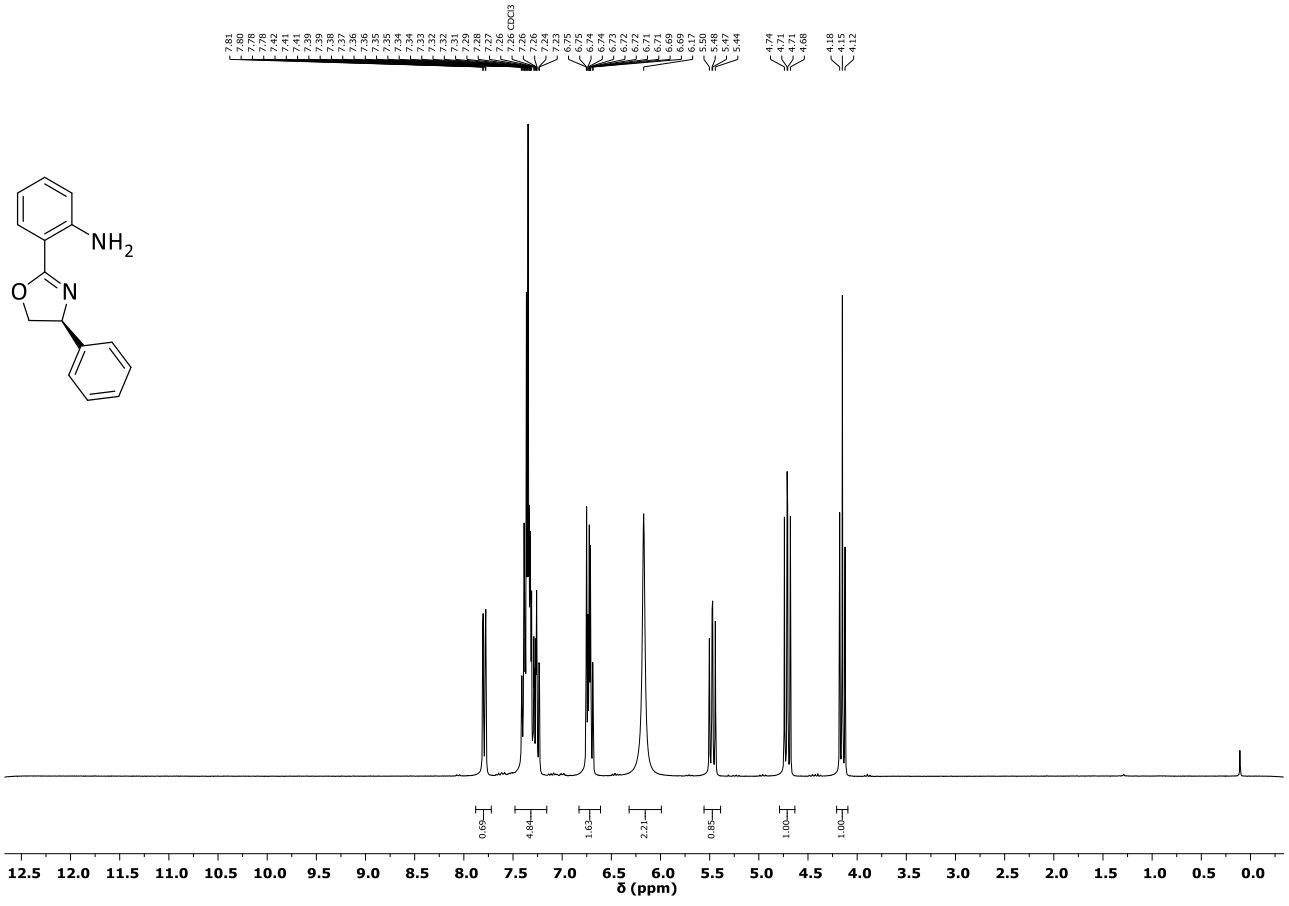
18.55
OH
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
$δ$ (ppm)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7.35
7.35
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7.24
7.23
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6.75
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6.74
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6.72
6.71
6.71
6.69
6.69
6.67
5.50
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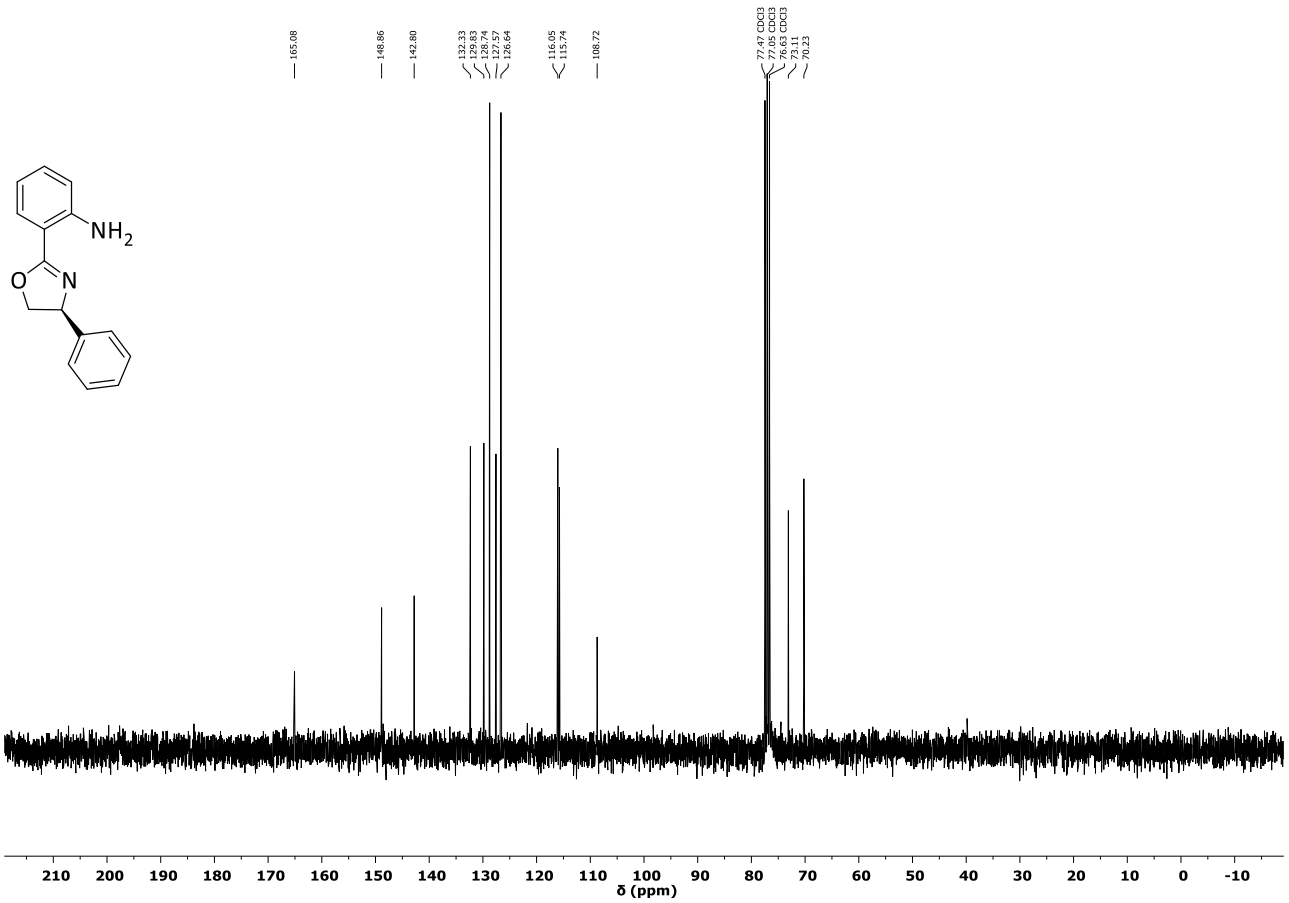
5.47
5.44
4.74
4.71
4.71
4.68
4.18
4.15
4.12
NH2
O
N
0.69
4.84
1.63
2.21
0.85
1.00
1.00
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)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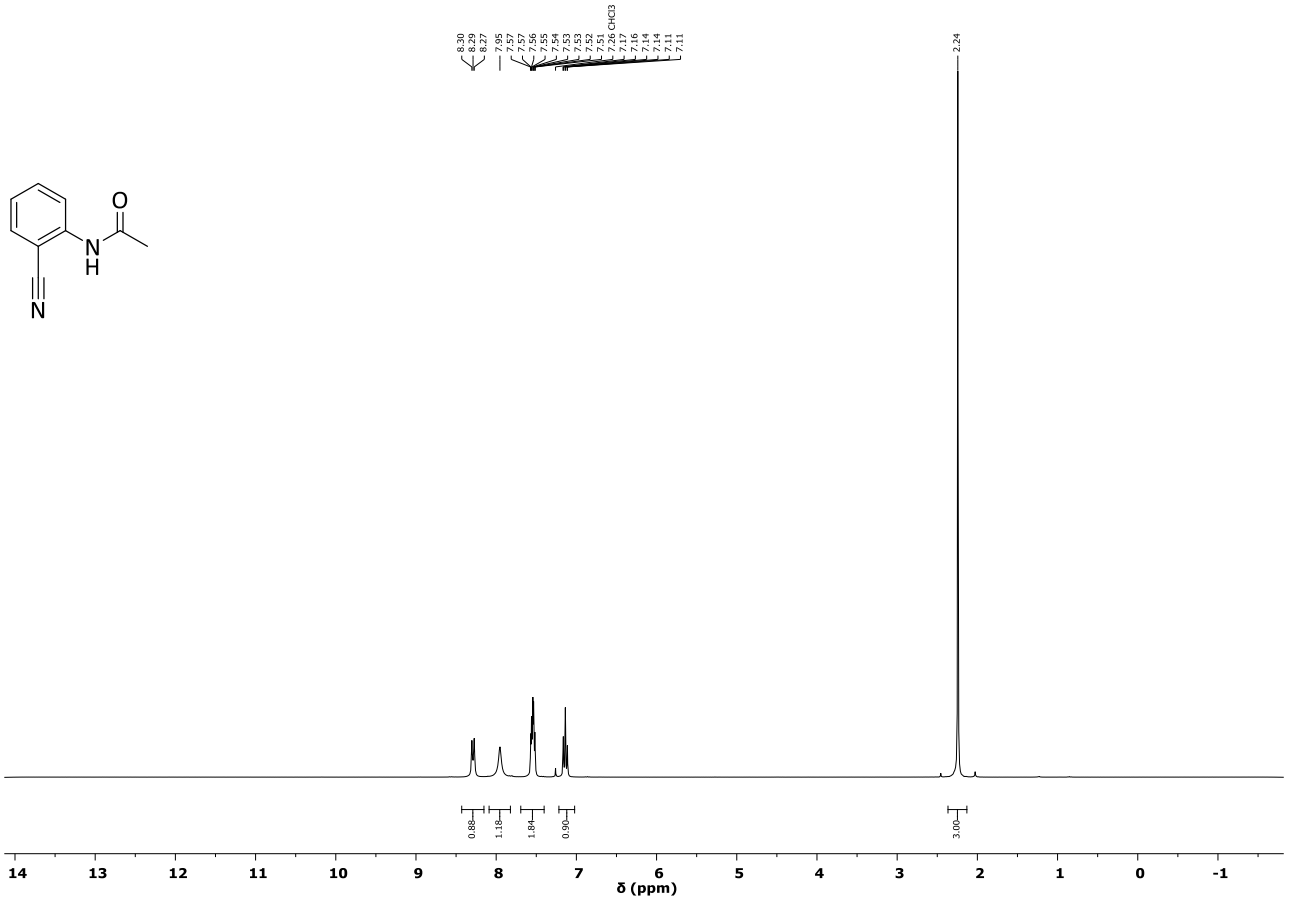
77.05 CDCl3
76.65 CDCl3
73.11
70.23
NH2
O
N
δ (ppm)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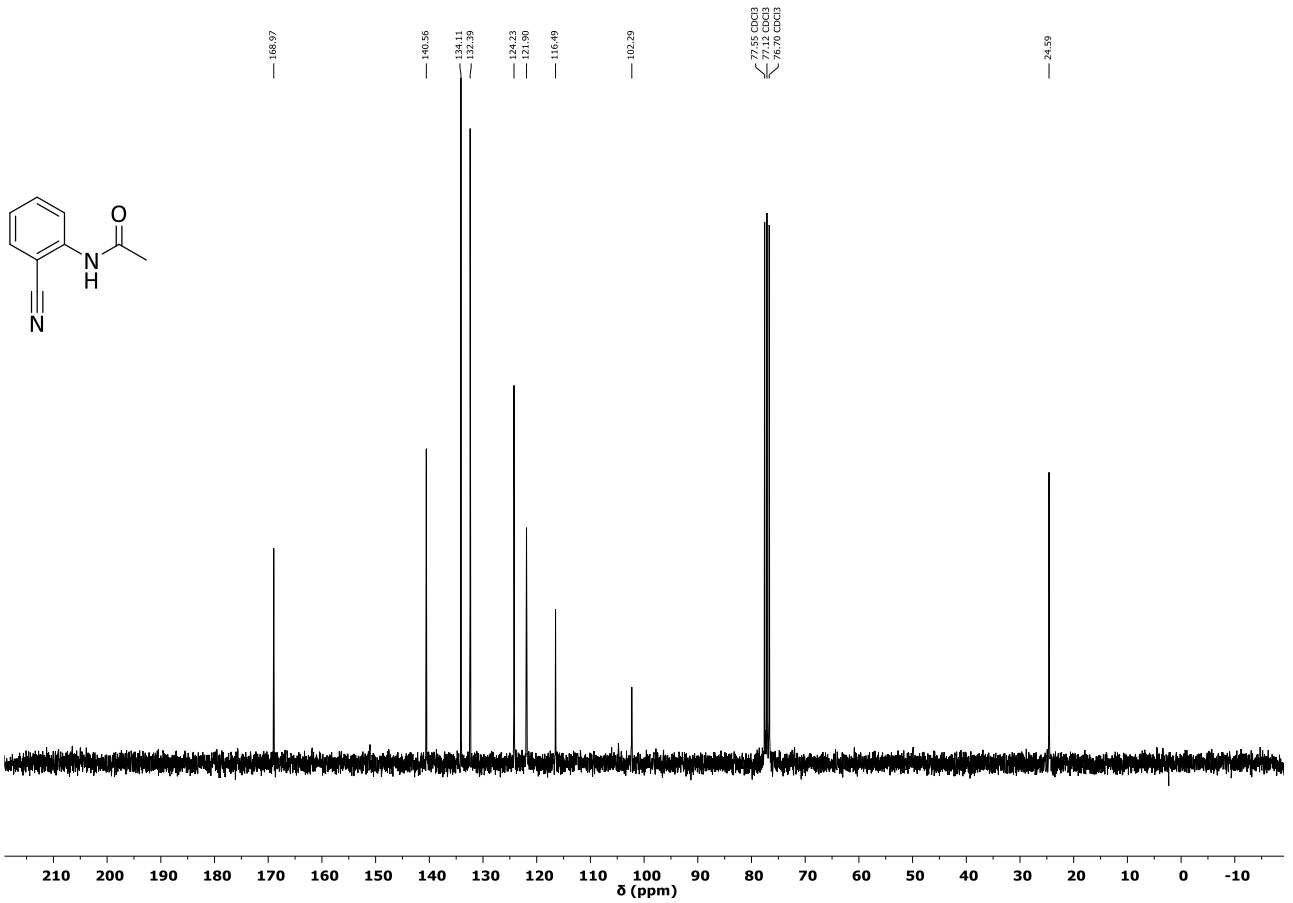
7.55
7.54
7.53
7.53
7.51
7.26 CHCl3
7.17
7.16
7.14
7.14
7.11
7.11
2.24
O
N
H
N
0.88
1.18
1.84
0.90
3.00
δ (ppm)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134.11
132.39
124.23
121.90
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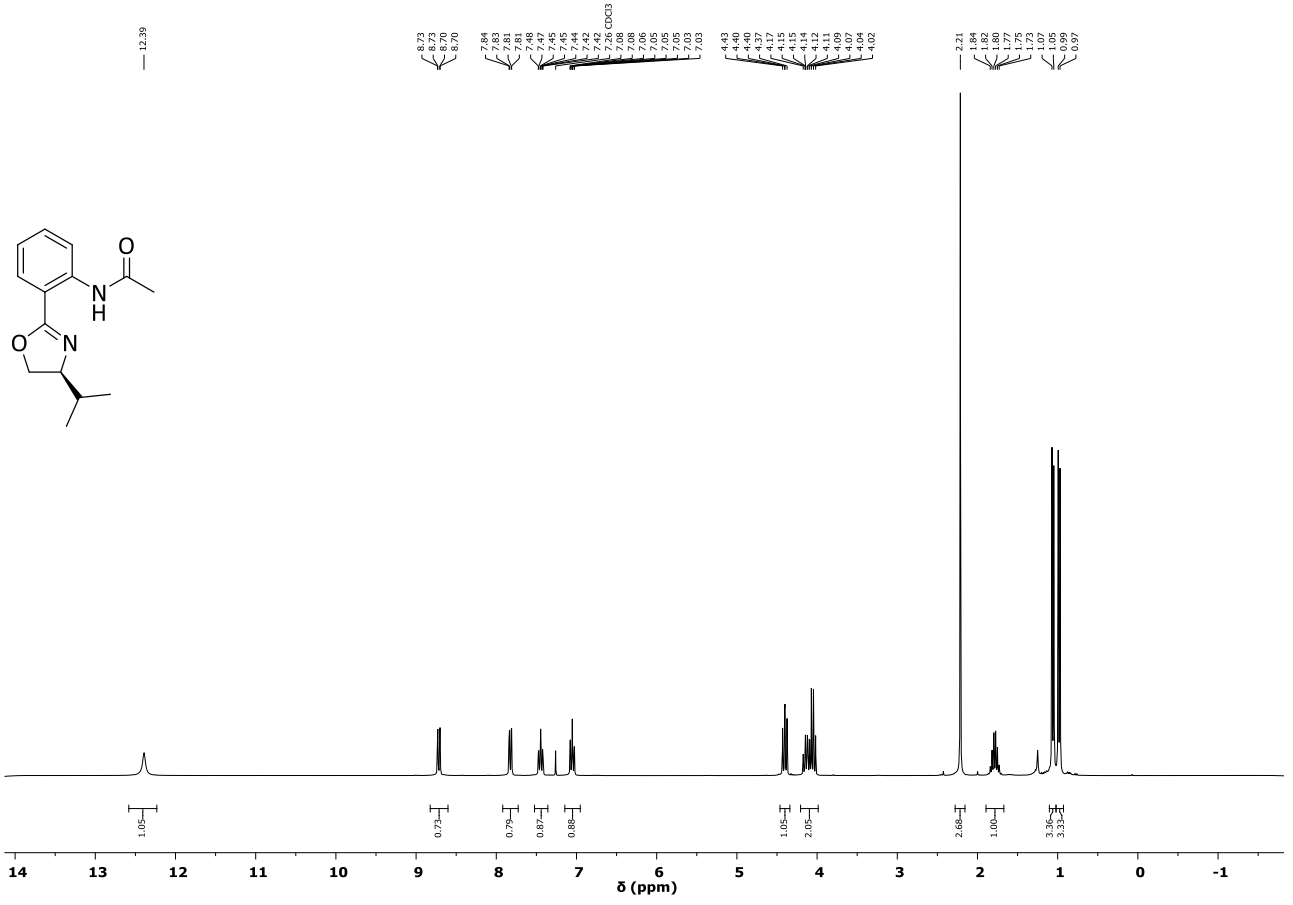
102.29
77.55 CDCl3
77.12 CDCl3
76.70 CDCl3
24.59
O
N
H
N
δ (ppm)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8.73
8.70
8.70
7.84
7.83
7.81
7.81
7.48
7.47
7.45
7.45
7.44
7.42
7.42
7.42 CDCl3
7.08
7.08
7.06
7.05
7.05
7.05
7.03
7.03
4.43
4.40
4.40
4.37
4.17
4.15
4.15
4.14
4.12
4.11
4.09
4.07
4.04
4.02
2.21
1.84
1.82
1.80
1.77
1.75
1.73
1.07
1.05
0.99
0.97
1.05
0.73
0.79
0.87
0.88
1.05
2.05
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1.00
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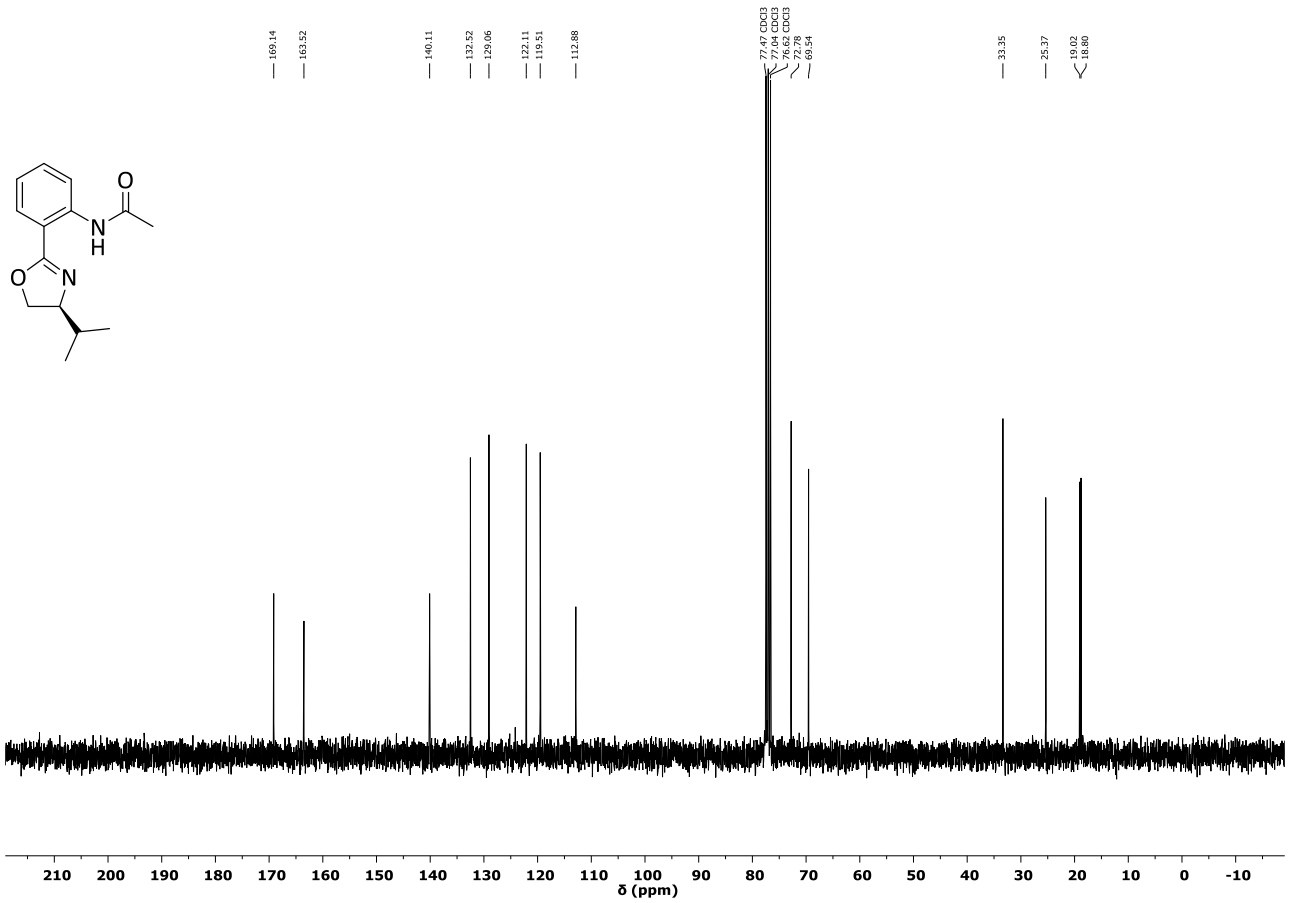
N
H
O
N
δ (ppm)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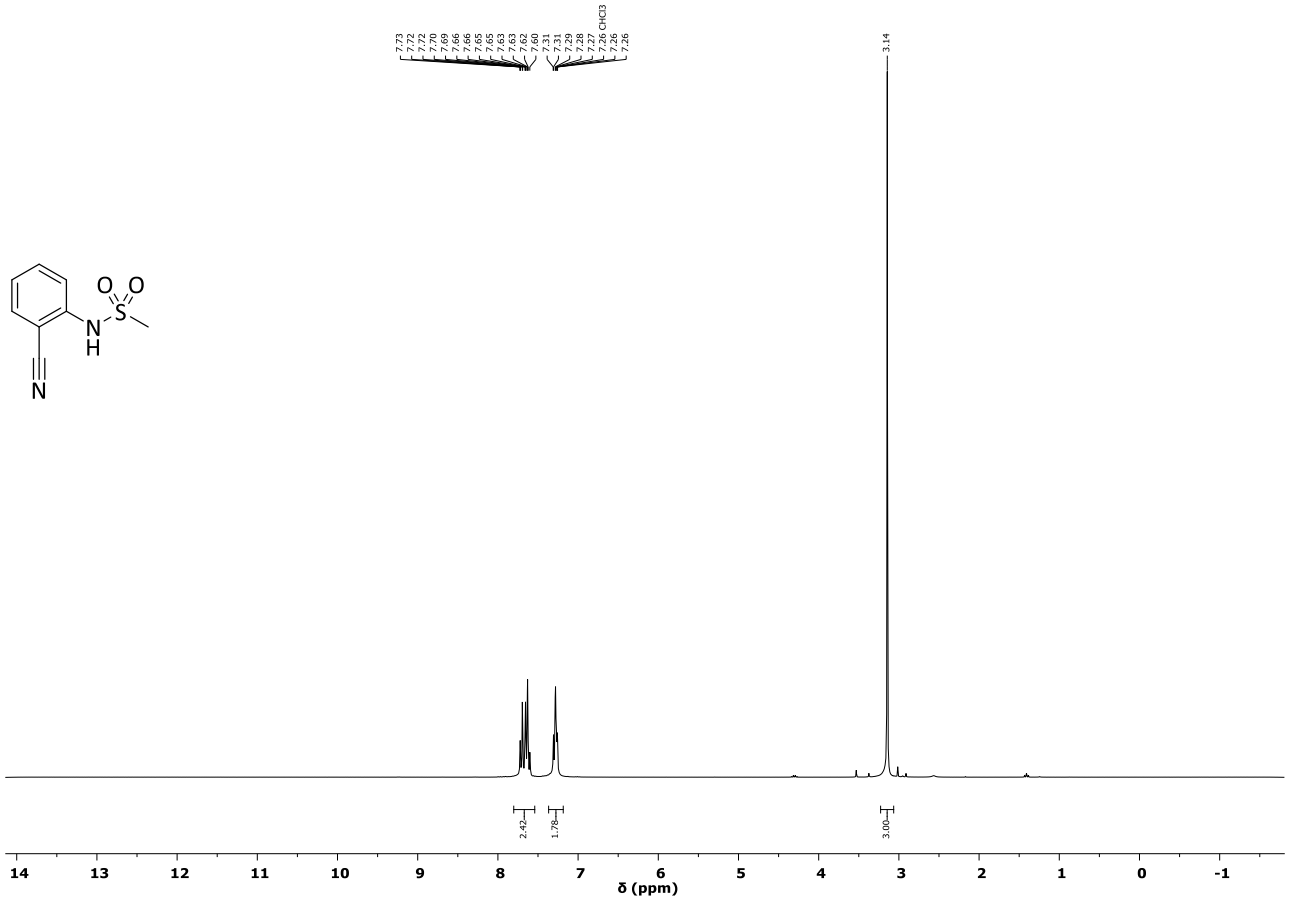
140.11
132.52
129.06
122.11
119.51
112.88
77.47 CDCl3
77.04 CDCl3
76.62 CDCl3
72.78
69.54
33.35
25.37
19.02
18.80
O
N
H
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)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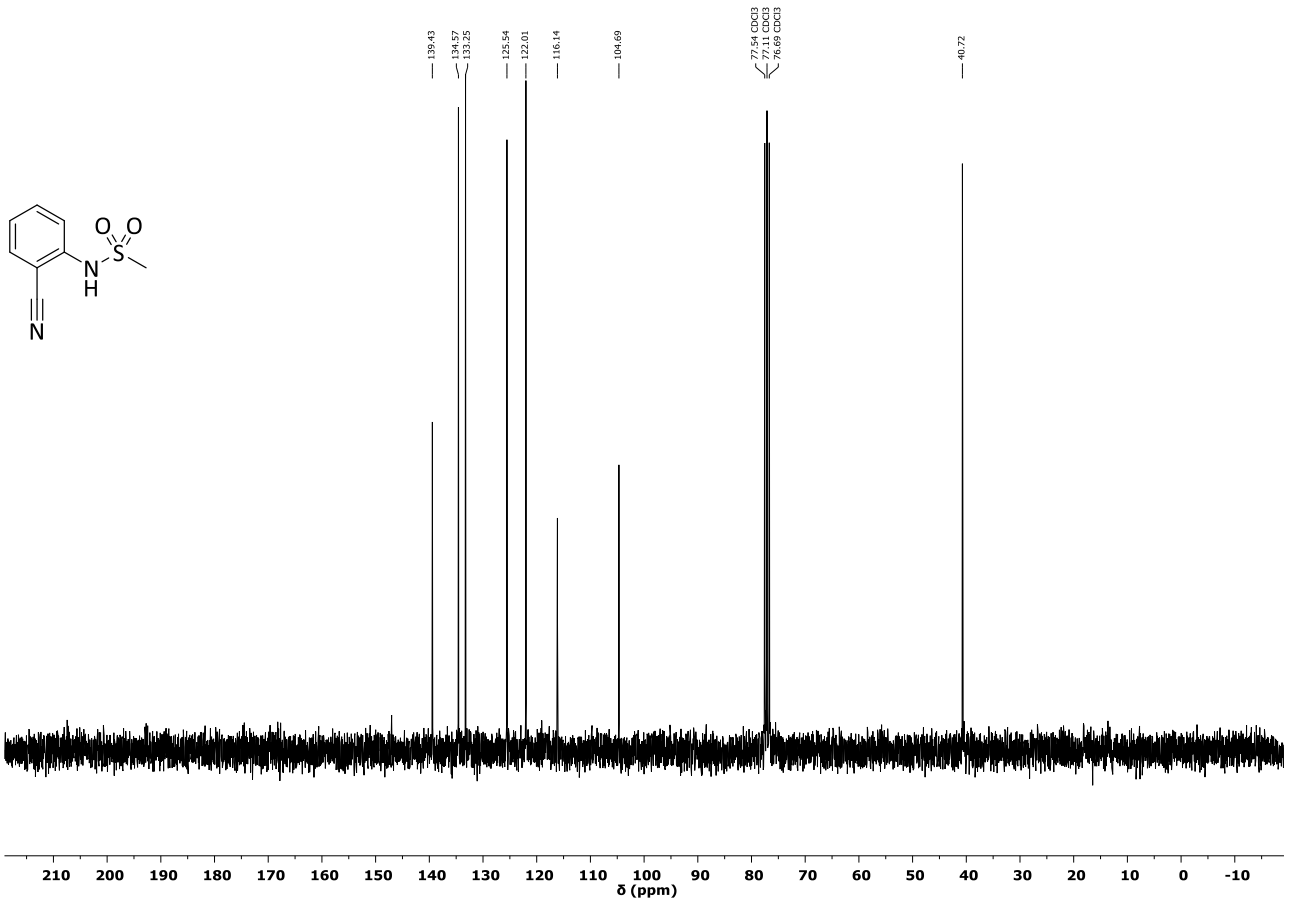
7.72
7.72
7.70
7.69
7.66
7.66
7.65
7.65
7.63
7.63
7.62
7.60
7.31
7.31
7.29
7.28
7.27 CHCl3
7.26
7.26
3.14
O
O
S
N
H
N
2.42
1.78
3.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
δ (ppm)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134.57
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116.14
104.69
77.54 CDCl3
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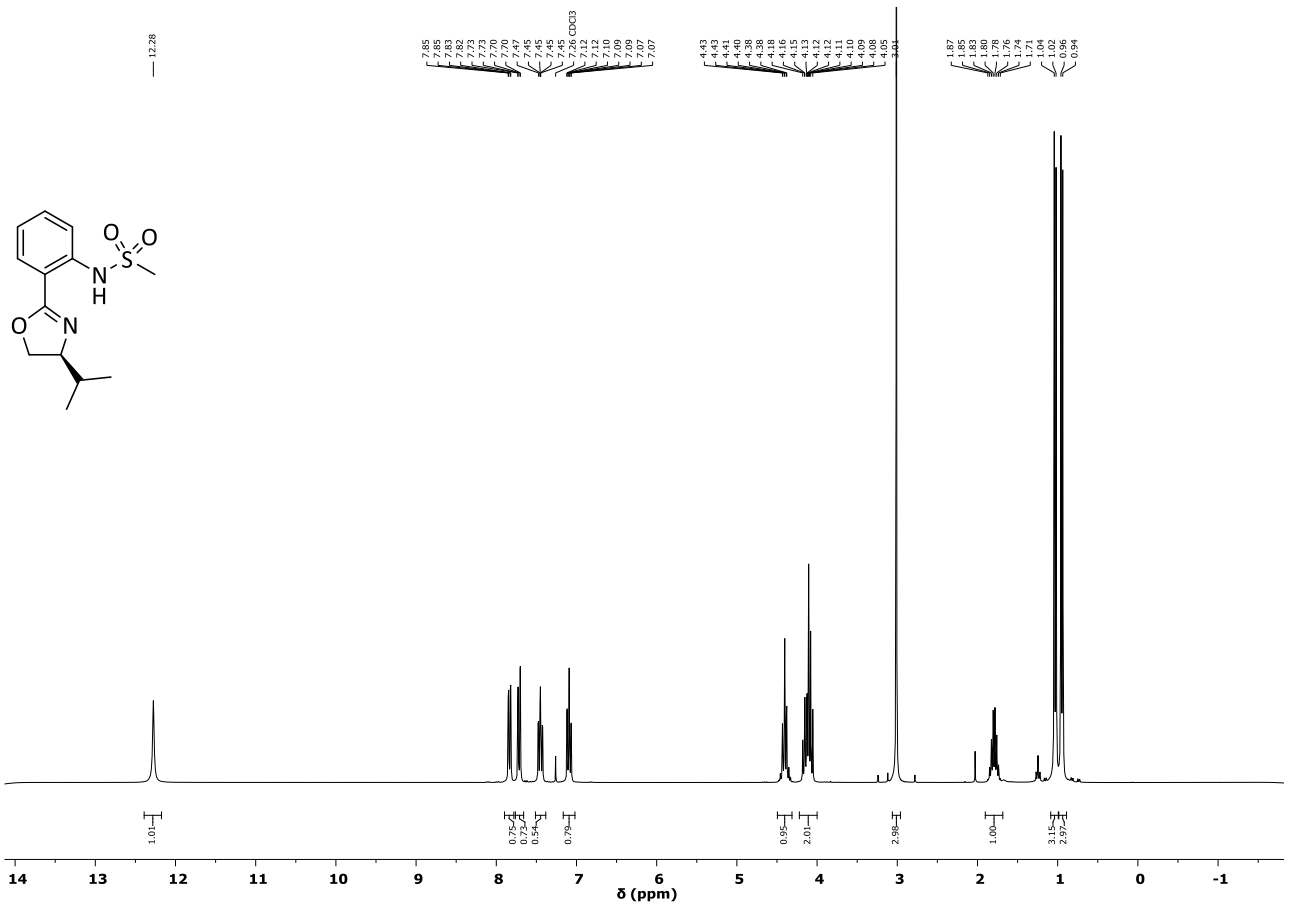
76.69 CDCl3
40.72
δ (ppm)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7.45
7.45
7.45
7.45
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7.10
7.10
7.09
7.09
7.07
7.07
4.43
4.43
4.41
4.40
4.38
4.38
4.18
4.16
4.15
4.13
4.12
4.12
4.11
4.10
4.09
4.08
4.05
3.01
1.87
1.85
1.83
1.80
1.78
1.76
1.74
1.71
1.04
1.02
0.96
0.94
1.01
0.75
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0.54
0.79
0.95
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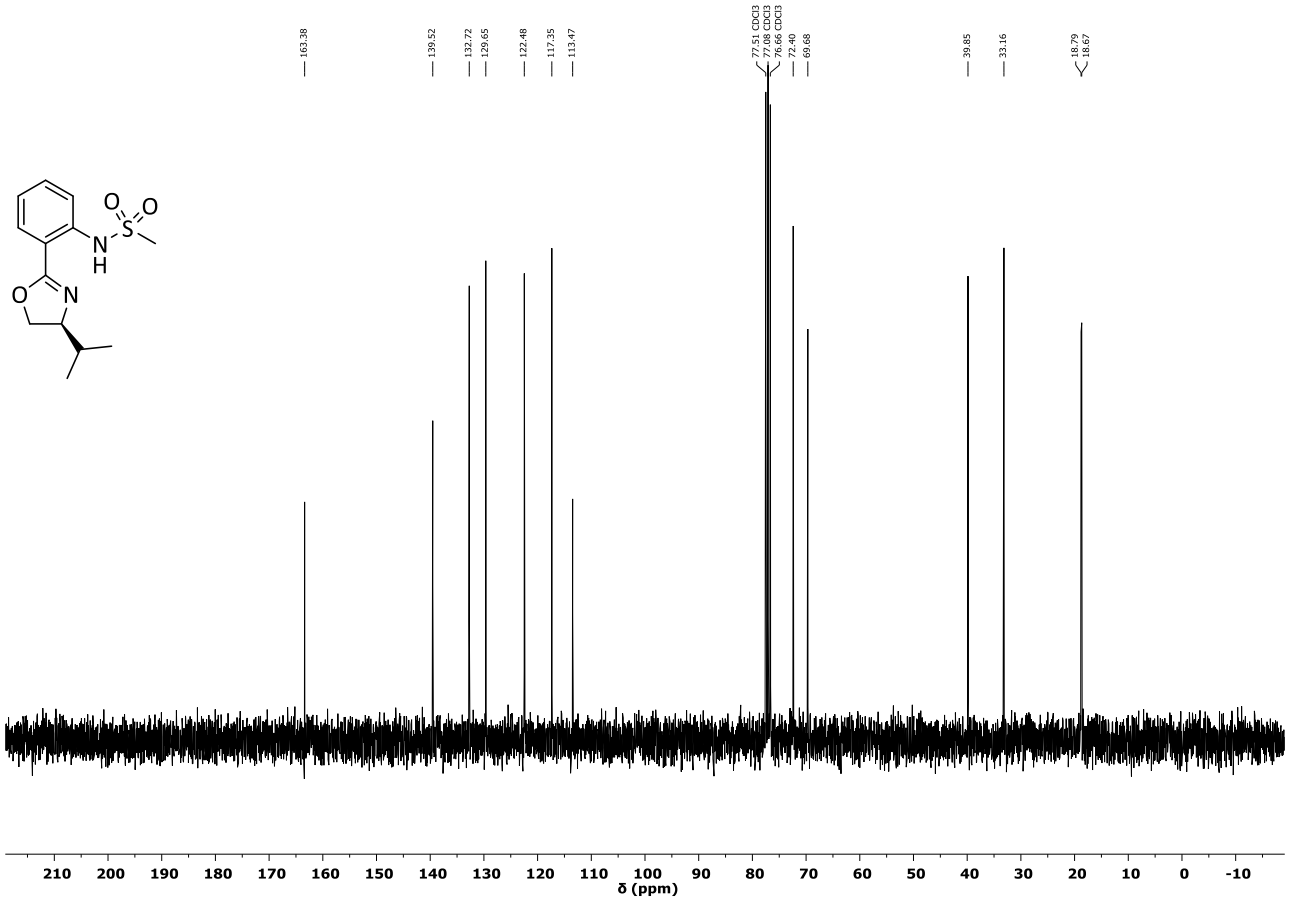
1.00
3.15
2.97
δ (ppm)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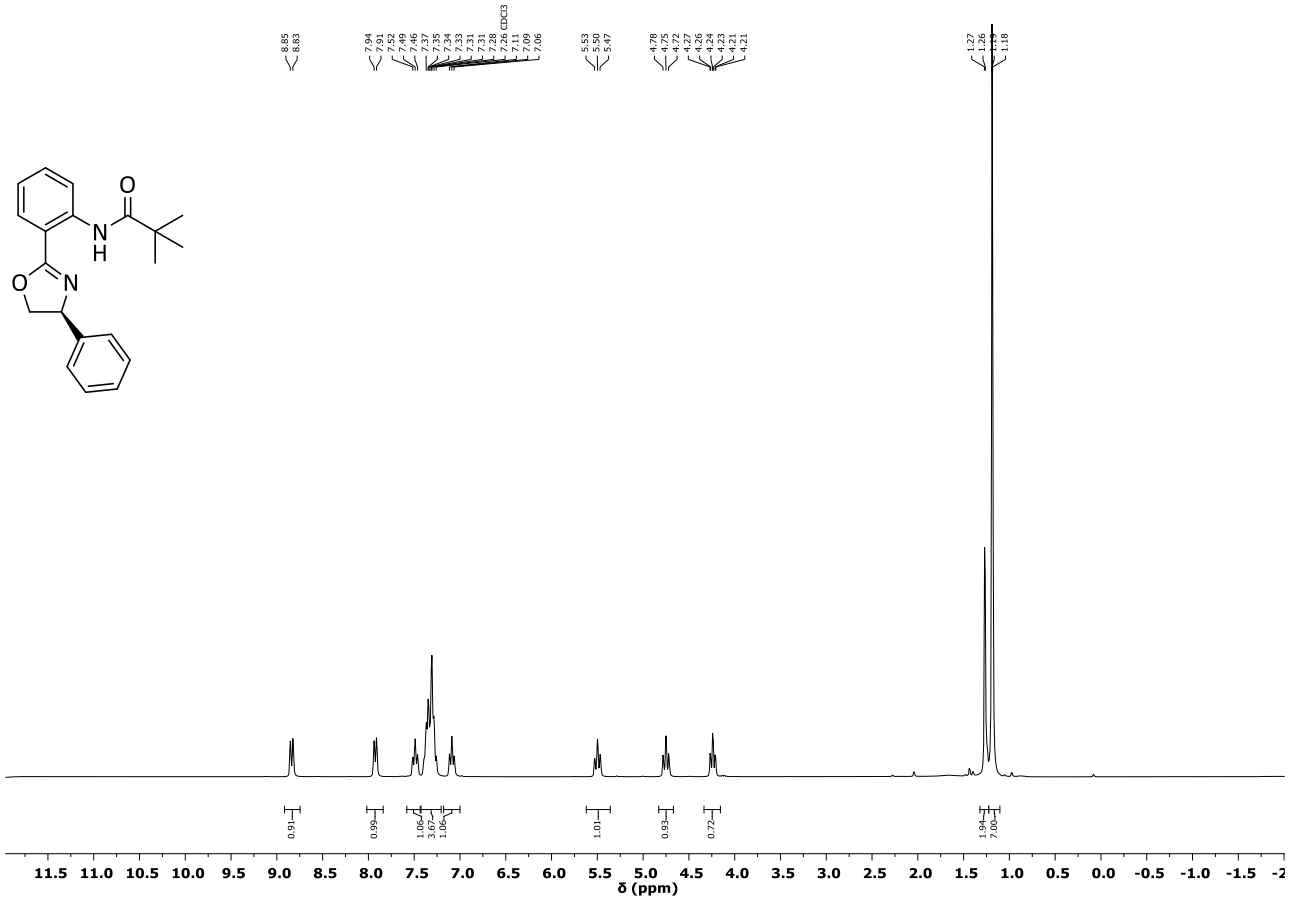
122.48
117.35
113.47
77.51 CDCl3
77.08 CDCl3
76.66 CDCl3
72.40
69.68
39.85
33.16
18.79
18.67
O
O
S
N
H
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)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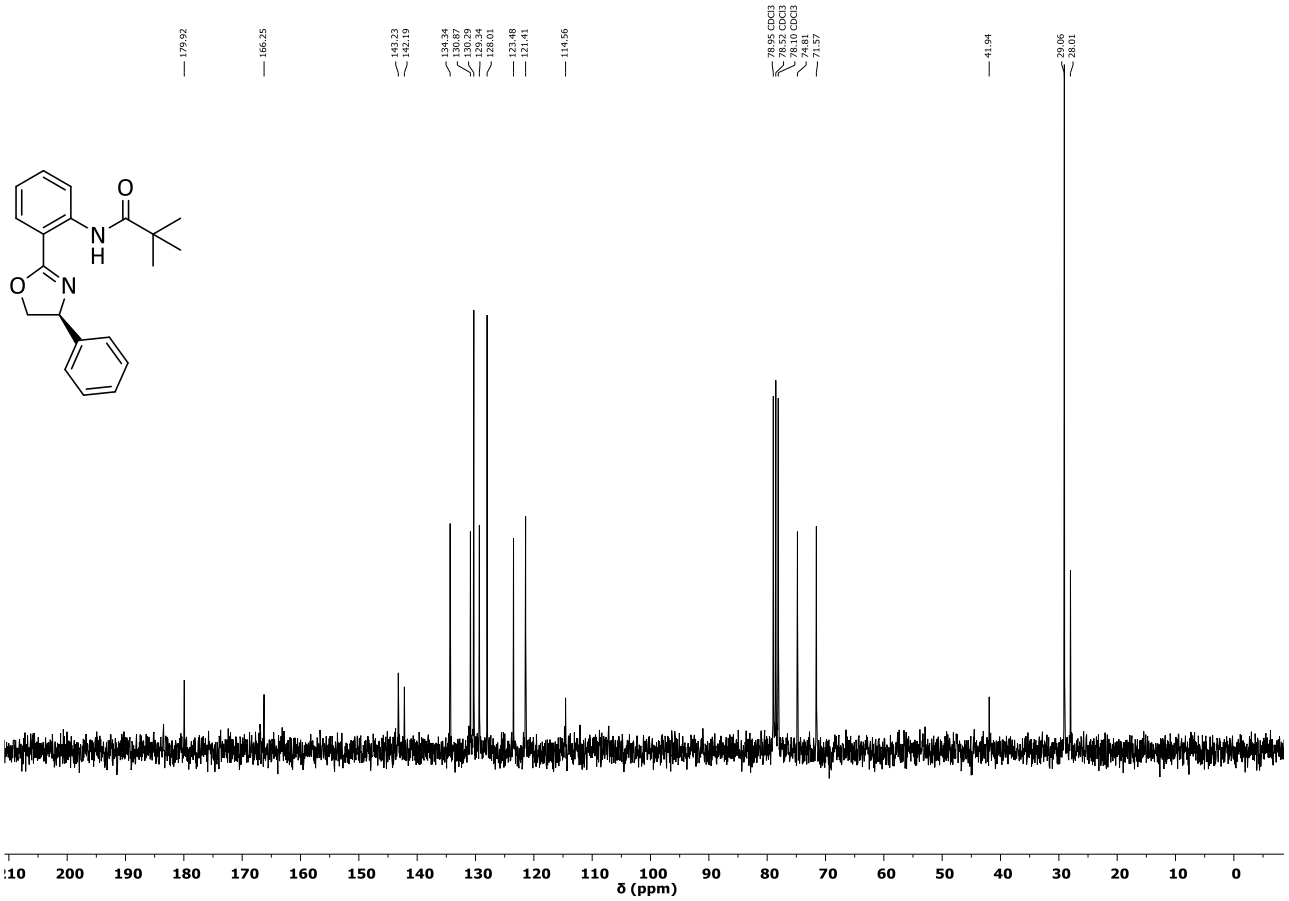
8.83
7.94
7.91
7.52
7.49
7.46
7.37
7.35
7.34
7.33
7.31
7.31
7.28
7.26 CDCl3
7.11
7.09
7.06
5.53
5.50
5.47
4.78
4.75
4.72
4.27
4.26
4.24
4.23
4.21
4.21
1.27
1.26
1.19
1.18
O
N
H
O
N
0.91
0.99
1.06
3.67
1.06
1.01
0.93
0.72
1.94
7.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
δ (ppm)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142.19
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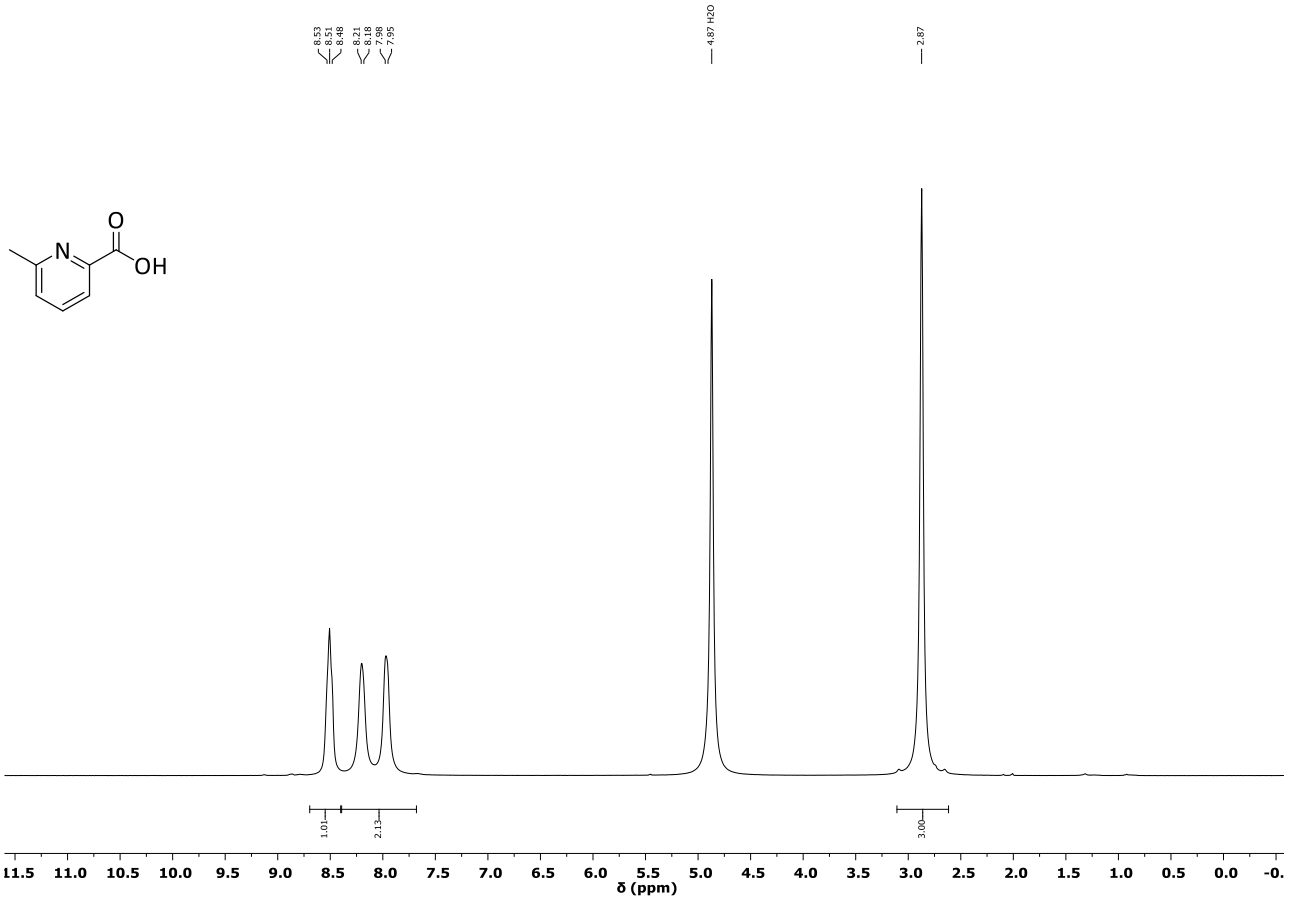
130.87
130.29
129.34
128.01
123.48
121.41
114.56
78.95 CDCl3
78.52 CDCl3
78.10 CDCl3
74.81
71.57
41.94
29.06
28.01
O
N
H
O
N
δ (ppm)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8.48
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8.18
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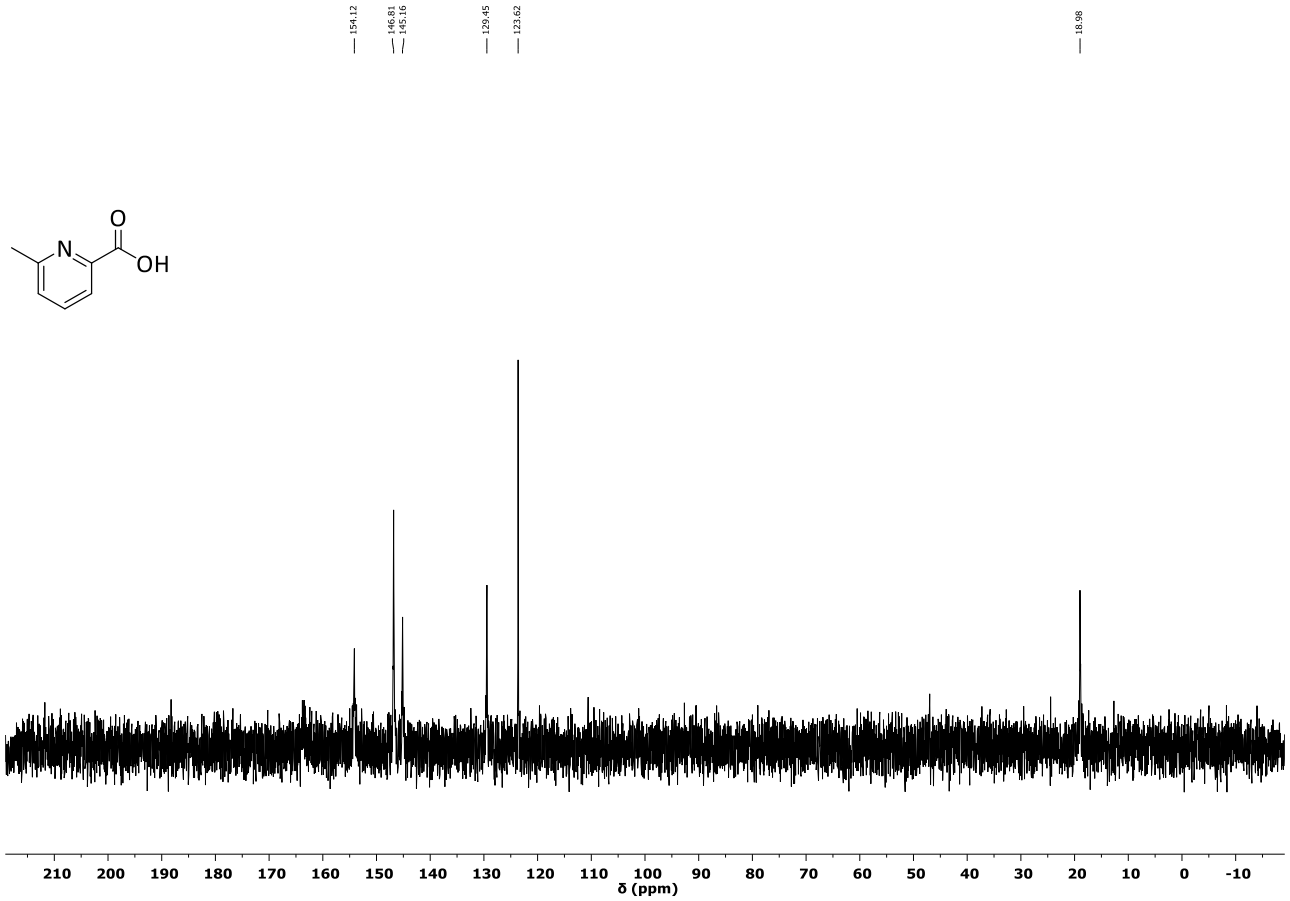
7.95
4.87 H2O
2.87
1.01
2.13
3.00
N
O
OH
δ (ppm)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O
N
OH
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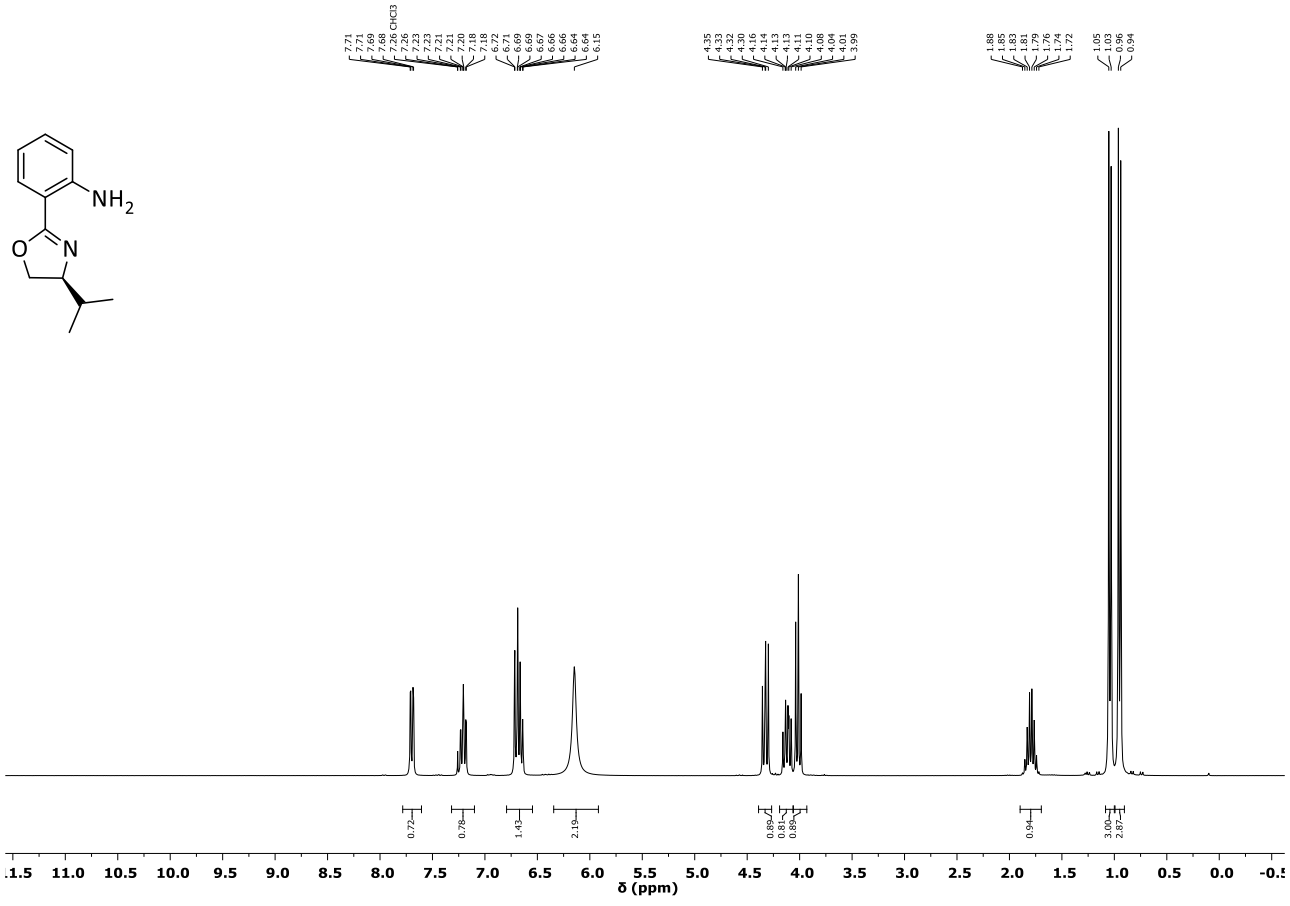
δ (ppm)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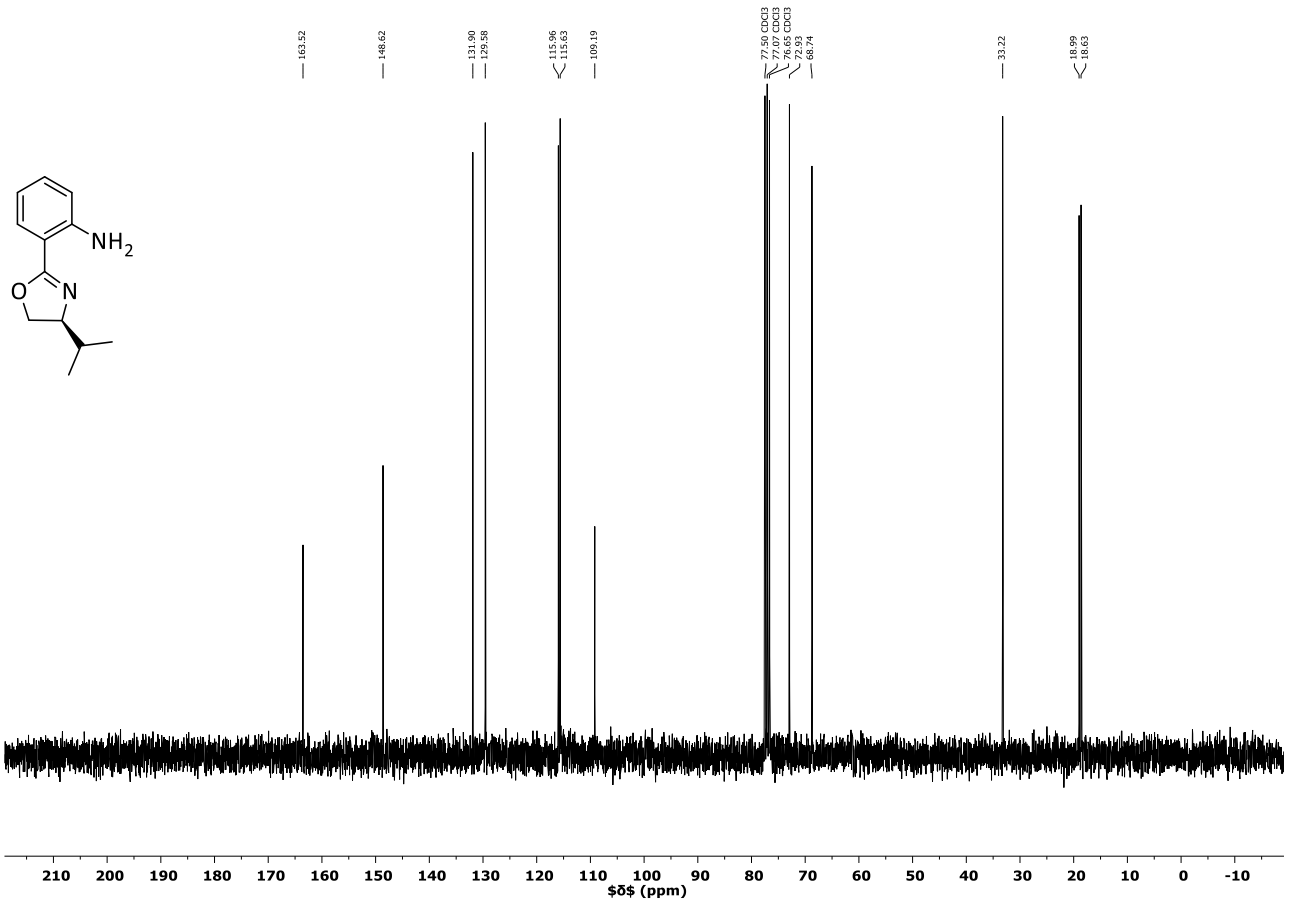
7.18
6.72
6.71
6.69
6.69
6.67
6.66
6.66
6.64
6.64
6.15
4.35
4.33
4.32
4.30
4.16
4.14
4.13
4.13
4.11
4.10
4.08
4.04
4.01
3.99
1.88
1.85
1.83
1.81
1.79
1.76
1.74
1.72
1.05
1.03
0.96
0.94
NH2
O
N
0.72
0.78
1.43
2.19
0.89
0.81
0.89
0.94
3.00
2.87
.1.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
δ (ppm)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77.07 CDCl3
76.65 CDCl3
72.93
68.74
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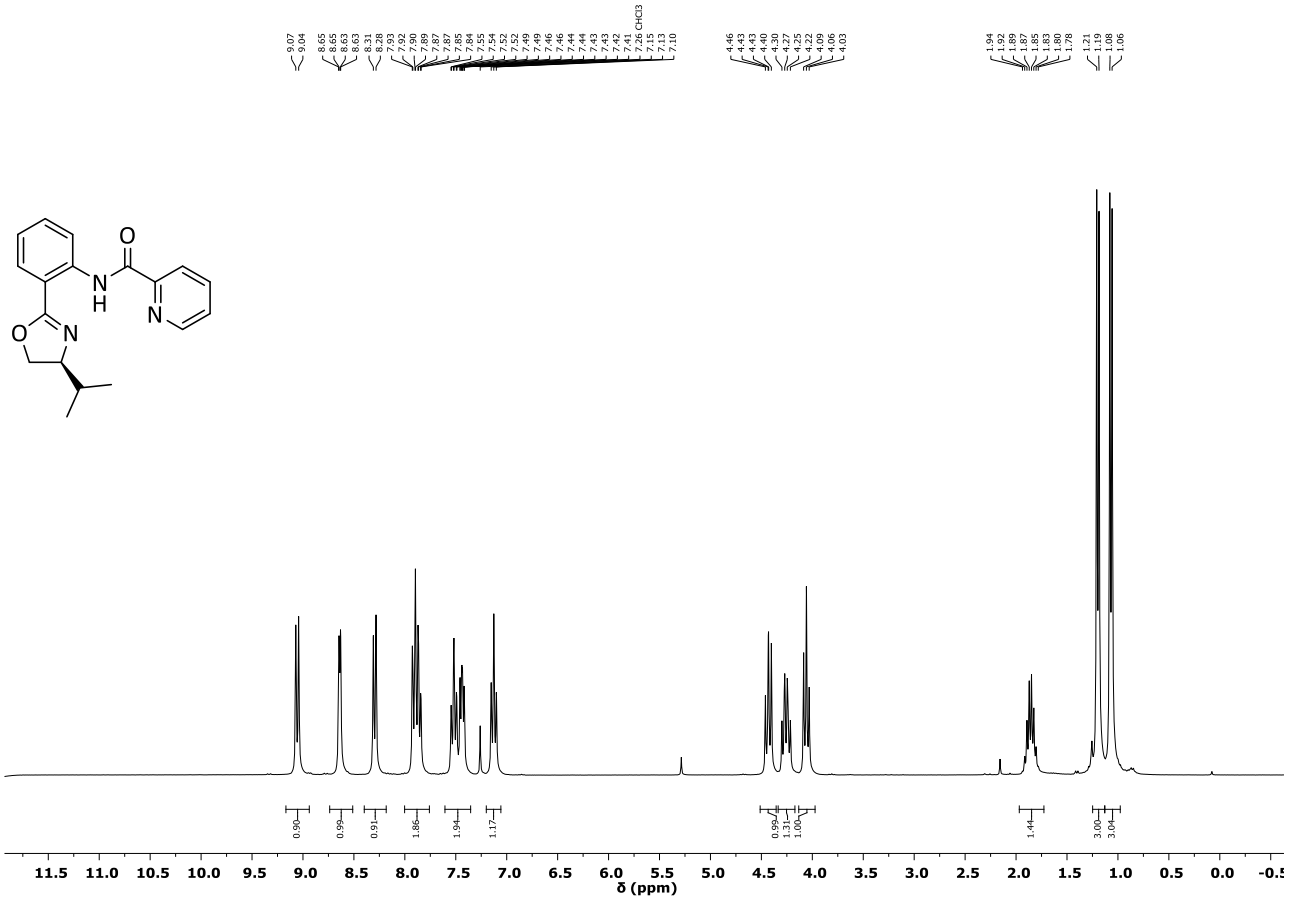
18.63
NH2
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
$δ$ (ppm)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7.84
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7.52
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7.44
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7.41
CHCl3
7.26
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7.13
7.10
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4.43
4.40
4.30
4.27
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4.09
4.06
4.03
1.94
1.92
1.89
1.87
1.85
1.83
1.80
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1.21
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1.08
1.06
O
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H
N
O
N
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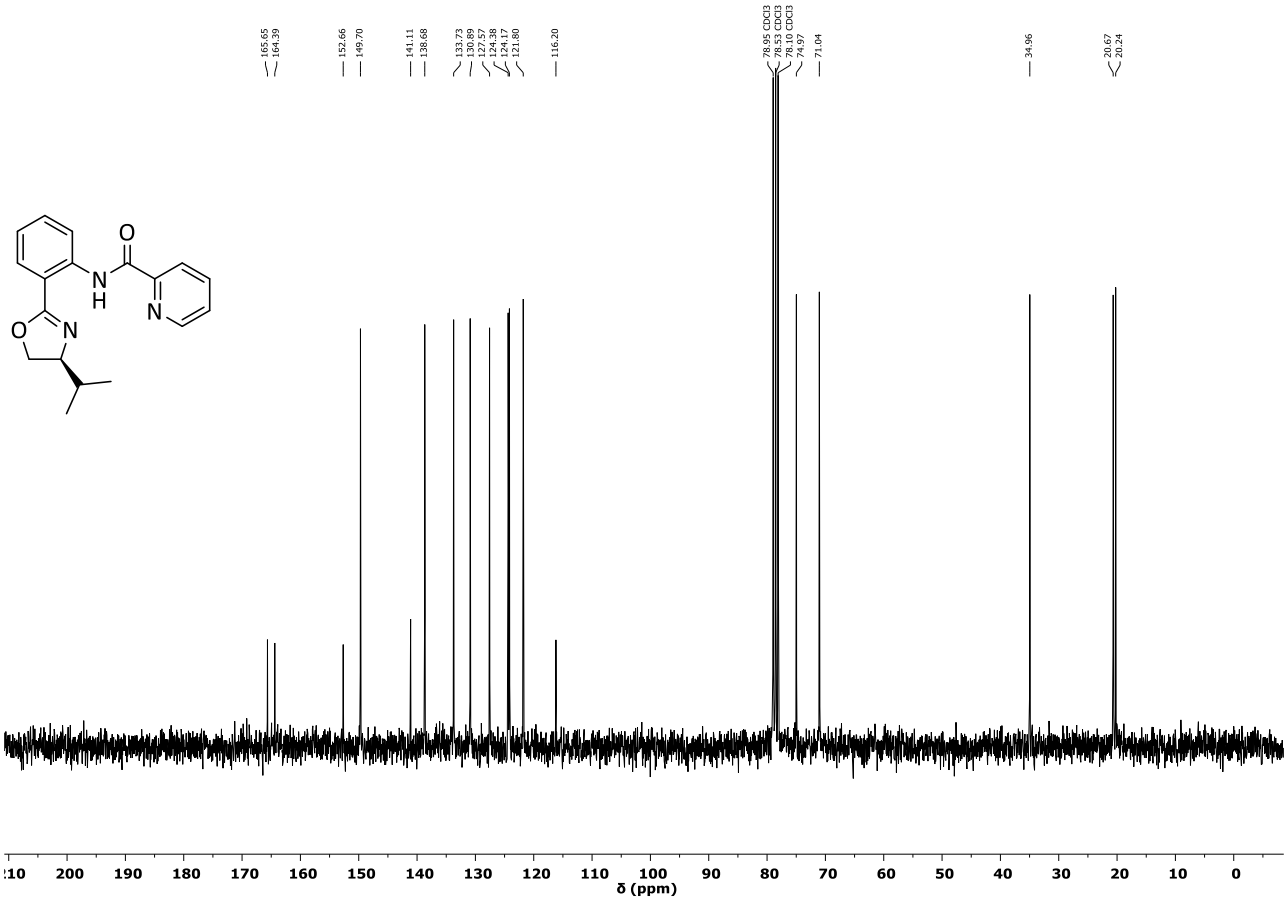
0.99
0.91
1.86
1.94
1.17
0.99
1.31
1.00
1.44
3.00
3.04
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
δ (ppm)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124.38
124.17
121.80
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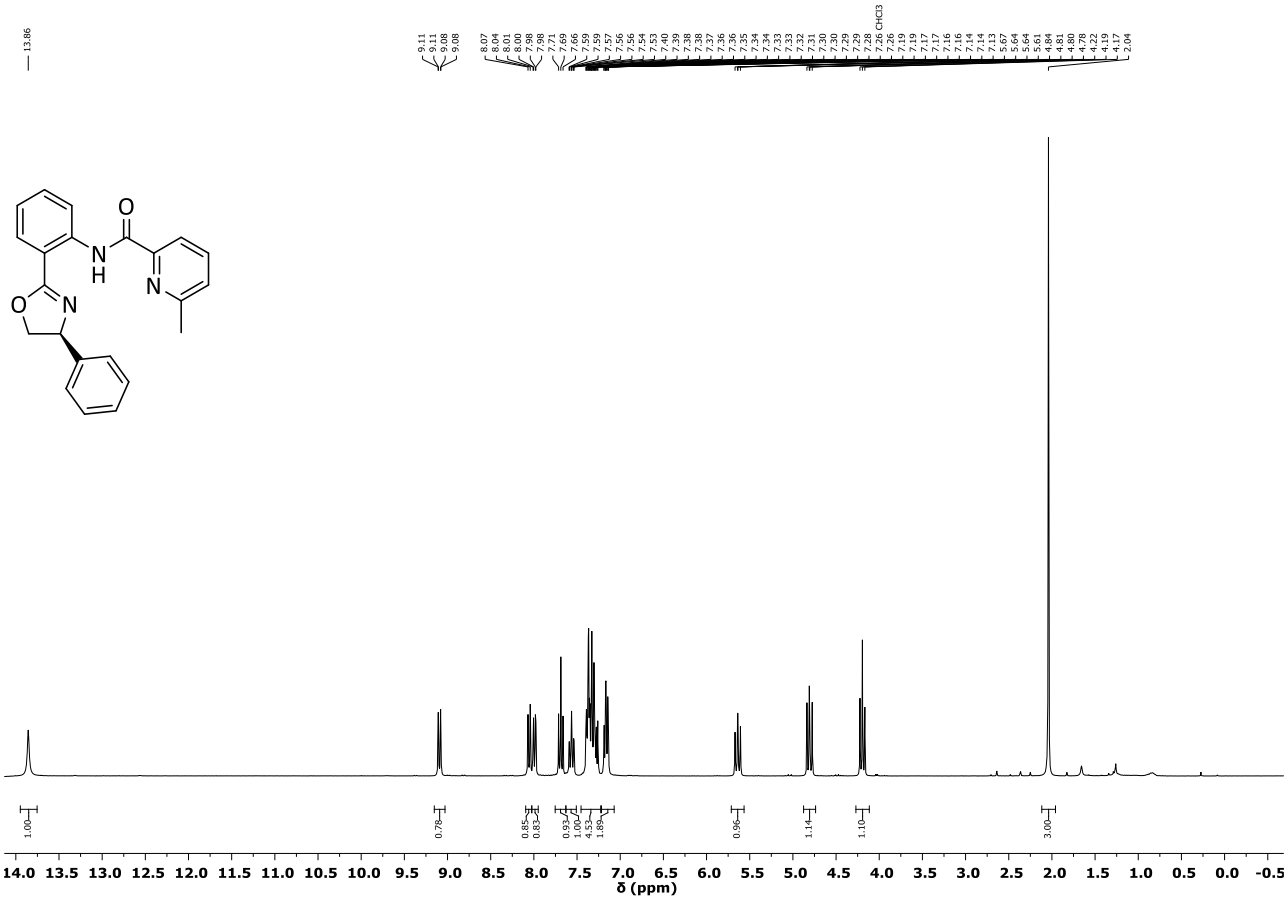
78.53 CDCl3
78.10 CDCl3
74.97
71.04
34.96
20.67
20.24
δ (ppm)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5.64
5.61
4.84
4.81
4.80
4.78
4.22
4.19
4.17
2.04
1.00
0.78
0.85
0.83
0.93
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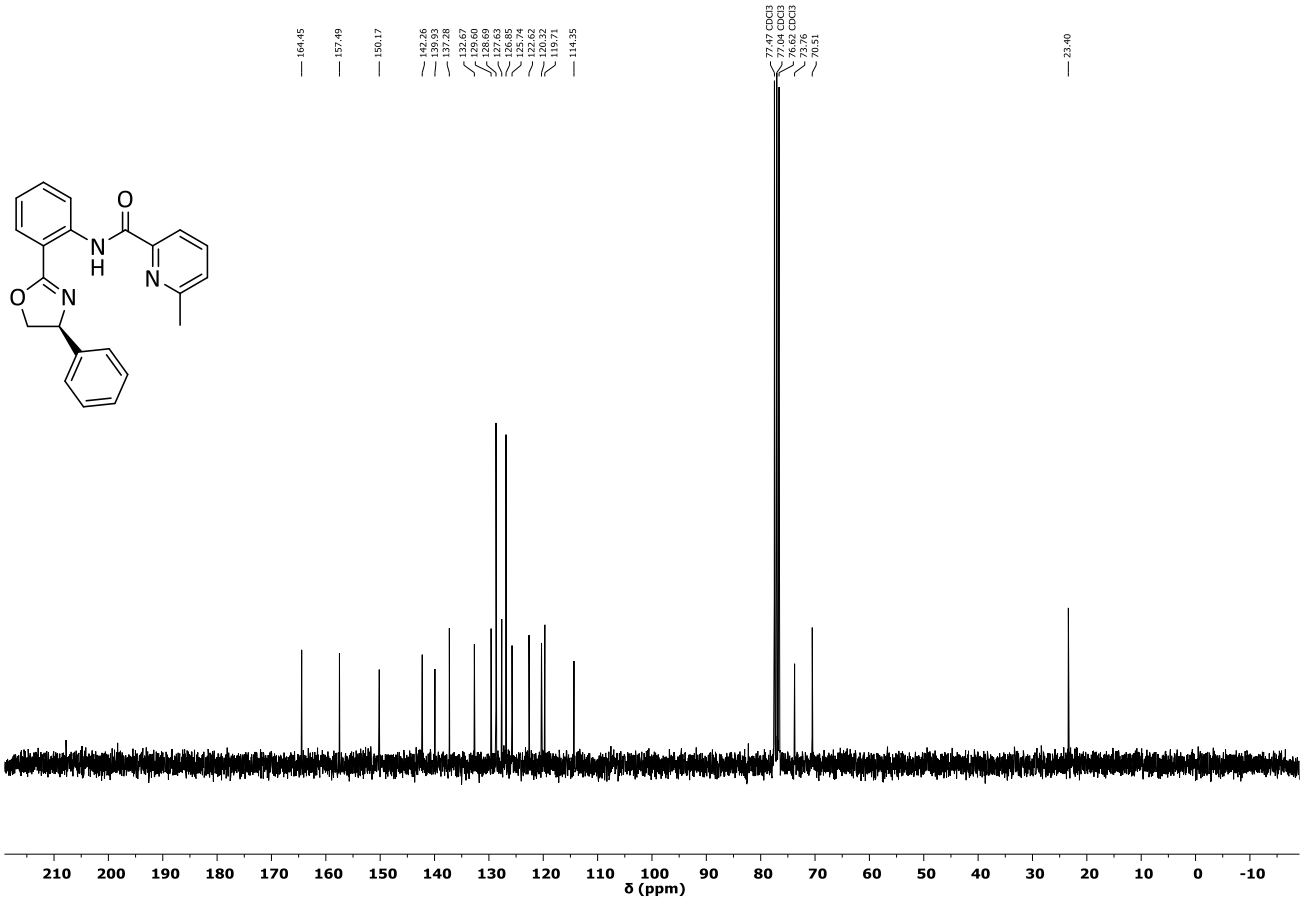
1.89
0.96
1.14
1.10
3.00
δ (ppm)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132.67
129.60
128.69
127.63
126.85
125.74
122.62
120.32
119.71
114.35
77.47 CDCl3
77.04 CDCl3
76.62 CDCl3
73.76
70.51
23.40
O
N
H
O
N
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

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