Pd(0)-Catalyzed Arylation of *O*-Carbamates via Negishi cross-coupling

and

Intermolecular Pd(0)-Catalyzed Atroposelective Csp^2-H Bond Activation

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Abstract

Over the past decades, the transition-metal catalyzed C-H bond functionalization has emerged as a powerful tool for the straightforward access to molecular complexity, while respecting the principles of atom- and step-economy.

The research at the Baudoin group mainly focuses on the activation and the functionalization of C-H bonds with palladium. The investigation led to the development of new methodologies including intramolecular Csp^3-H bond activation, and the arylation of remote Csp^3-H bond via migrative cross-couplings. These methodologies were applied in the synthesis of biologically active complex molecules.

The ligand-controlled regioselective arylation of cyclic and acyclic *N*-Boc-amines via Pd(0)-catalyzed migrative Negishi cross-coupling was recently developed within our group. In light of this work, the enantioselective α-arylation of *O*-carbamates was achieved by combining Hoppe's sparteine-mediated enantioselective lithiation-deprotonation and Pd(0)-catalyzed Negishi cross-coupling.

We then focused on the ligand-controlled migrative arylation of *O*-carbamates. The attempts toward the selective β-arylation were unsuccessful but led us to the discovery of a ligand-controlled γ-arylation of γ,δ-unsatured *O*-carbamates. The reaction proceeds via a non-canonical haptotropic rearrangement of the palladium intermediate.

As a follow-up, we examined the feasibility of an intermolecular Pd(0)-catalyzed atroposelective Csp^2-H arylation. Our investigation led us to the discovery of a catalytic system involving newly introduced bifunctionnal ligands.

Key words: C-H functionalization, C-H activation, organometalic catalysis, palladium, Negishi coupling, migrative arylation, enantioselectivity, haptrotropic rearrangement, atroposelectivity

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Abbreviations

(+)- or (−)-sp.	(+)- or (−)-sparteine
Ad	adamantyl
API	active pharmaceutical ingredient
Boc	*tert*-butyloxycarbonyl
C-H bond	carbon-hydrogen bond
CPME	cyclopentyl methyl ether
dba	dibenzilideneacetone
d.e.	diastereomeric ratio
DFT	density functional theory
DMAc	dimethylacetamide
DME	1,2-dimethoxyethane
DMF	dimethylformamide
e.e.	*enantiomeric excess*
eq.	equivalent
e.r.	*enantiomeric ratio*
e.s.	*enantiospecificity*
F-TOTP	tris(5-fluoro-2-methylphenyl)phosphine
GCMS	gas-chromatography/mass-spectrometry
HPLC	high-performance liquid chromatography
i-Bu	*iso*-butyl
i-Pr	*iso*-propyl
MS XÅ	molecular sieves XÅ

NASA	National Aeronautics and Space Administration
n-Bu	*n*-butyl
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
n-Pr	*n*-propyl
s-Bu	*sec*-butyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TEMPO	2,2,6,6-tetramethylpiperidinyloxyl
TMEDA	tetramethylethylenediamine
TMP-Zn base	2,2,6,6-tetramethylpiperidinyl

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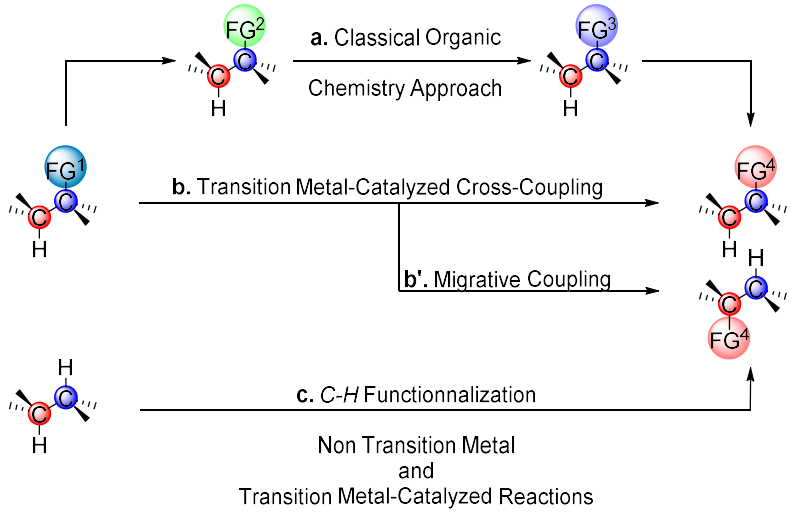
1. General bibliography

In the early 21st century, major technological developments led to the manufacture of reusable space rockets, the discovery of Earth-like planets, and the detection of water on Mars. The NASA launched a wide space programm with the aim of sending human to the Red Planet in 2030. While all of this is happening, Voyager I and II probes are travelling out of our solar system.

In contrast, climate variations, inequal growth of wealthiness and population, as well as massive production are proposed as linked to the harmful pollution and the unstoppable impoverishment of ressources.

In this context, scientists put many efforts in finding solutions to stemthe potential worldwide lack of ressources.

In organic chemistry, this evolution is reflected in the development of more concise syntheses, involving less protecting groups and minimal changes of oxidation states as well as atom economical transformations.[1] The traditional approach consists in an iterative change of functional group to obtain the desired chemical function. This strategy requires a prefunctionalized starting material, and often uses a stoichiometric amount of reactants. Despite the wide variety of known chemical transformations, and their application to solve chemo- and regioselectiviy issues, the synthetic routes remain very long and laborious.[2] This led chemists to investigate on less atom and step demanding alternatives (Scheme 1**a.**).



Scheme 1. *An overview for the functionalization of organic compounds*

In the early 80's, the comprehension and the development of transition metal catalysis revolutionized organic synthesis by providingnew tools for the construction of carbon-carbon bonds.This synthetic approach allowed new disconnections to access molecular complexity in a reduced number of steps with high selectivity thus enabling convenient and straightforward syntheses (Scheme 1**b.**).[3] In particular, palladium-catalysis cross-couplings witnessed an exponential growth of interest in academia and industry, as shown by the positive evolution of literature in the field (Figure 1). Moreover, Heck, Negishi and Suzuki received the Nobel Prize in Chemistry in 2010 for their contribution to these developments.[4]

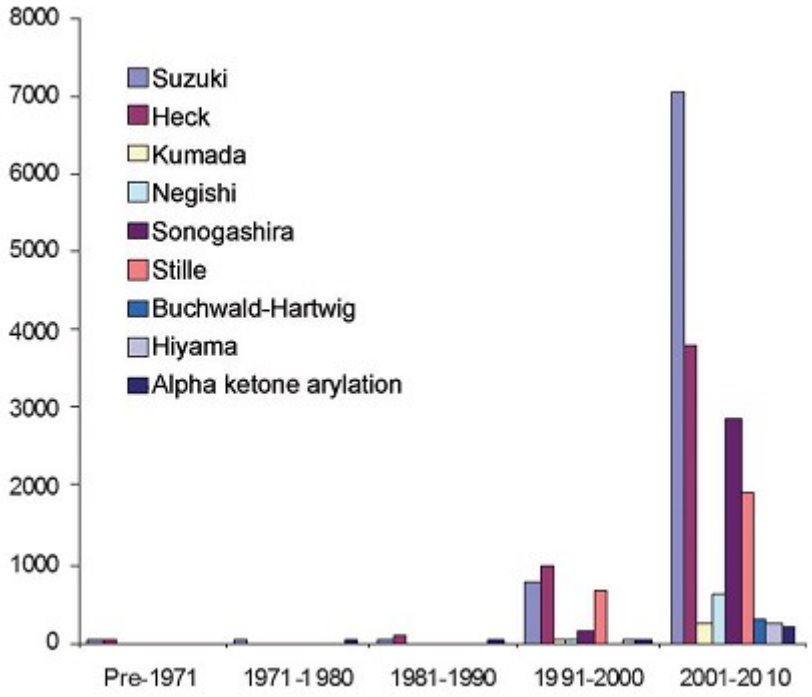
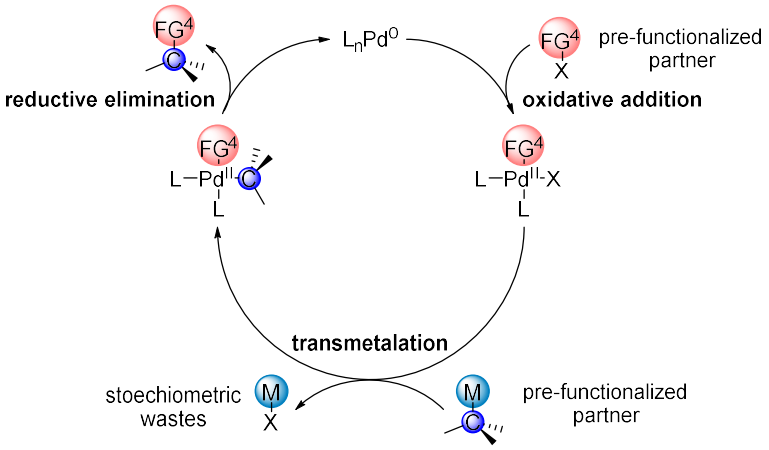


Figure 1.*Growth in the number of publications and patents on metal-catalyzed cross-coupling*

The catalytic cycle of this type of transition metal-catalyzed cross-coupling, as depicted in Scheme 2 with palladium, generally involves the oxidative addition of a catalytically active Pd^0complexto a carbon-halide or pseudohalide bond. The resulting electrophilic Pd^{II} organometallic species undergoes transmetalation with a nucleophilic organometallic compound, thus generating a Pd^{II} intermediate bearing the two organic coupling partner fragments. Subsequent reductive elimination produces the desired cross-coupling compound via the formation of a carbon-carbon bond, while regenerating the Pd^0 species that enters a new catalytic cycle. This catalytic system offers various advantages, notably step-economy in synthesis, enabling versatile retrosynthetic analyses[5]and alsonovel industrial applications.[6]

The system still encounters limitations, such as the use of pre-functionalized coupling partners, but also the production of a stoichiometric amount of toxic metal wastes.

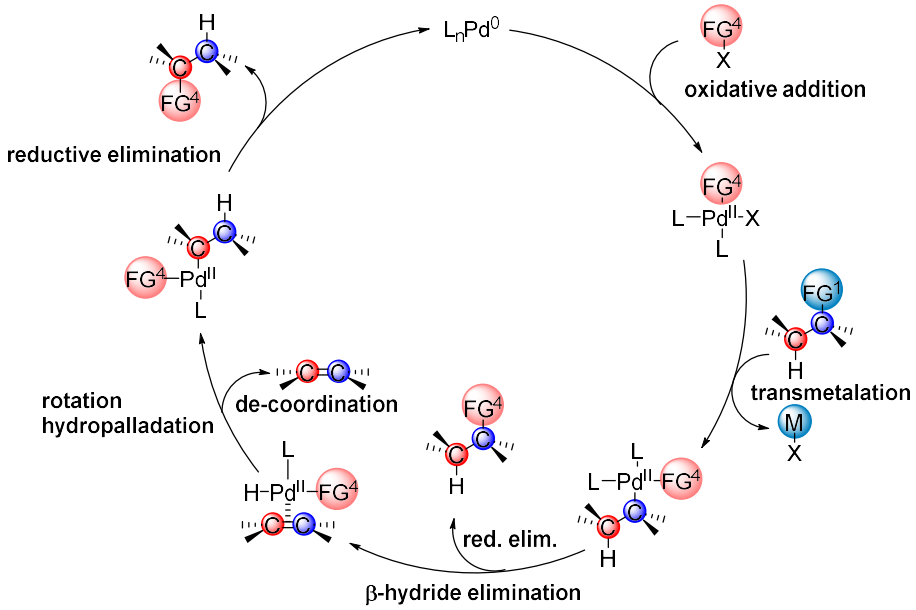


Scheme 2. *General catalytic cycle for palladium-catalyzed cross-coupling reaction*

Despite the universality of these cross-couplings, their drawbacks pushed chemists to turn their attention to the C-H bond functionalization. Indeed, the ubiquity of the C-H bond in organic compounds makes them perfect candidates for selective functionalization, while respecting the atom and step economy principlesto the benefit of more flexible and versatile retrosynthetic analyses.The C-H bond functionalization has longly been occulted because of the relative inertness of these bonds, as reflected by the high bond dissociation energy (BDE) of 104 kcal/mol in methane,[7]even if very reactive species such as radicals, carbenes and highly acidic compounds can react with aliphatic C-H bonds.[8]

During the development of transition-metal catalyzed cross-couplings, Kumada,[9]Negishi[10] and Hayashi[11] observed the ability of these metals to migrate along an aliphatic chain via a chain walking process, thus opening an access to the functionalization of aliphatic C-H bonds from a pre-functionalized substrate(Scheme 1**b'.**). A typical mechanism for this transformation, as illustrated in Scheme 3with palladium, involvesthe oxidative addition of the catalytic Pd^0 in the (pseudo)halide electrophile. The newly formed Pd^{II} complex undergoes transmetalation with the organometallic nucleophile. Once installed, the direct reductive elimination event leads to the classical cross-coupling product, while the β-hydride elimination provides the olefin π-complex which can undergo rotation and hydropalladation to give rise to an isomerized Pd-alkyl complex.The latter, after reductive elimination, yields the C-H functionalized productof the migrative cross-coupling. Noteworthy the

decomplexation of the olefin π-complex releases the unsaturated product along with the palladium-hydride complex.

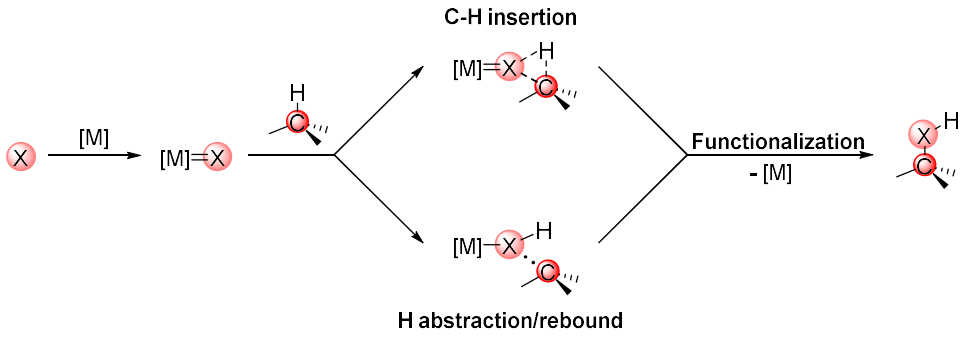


Scheme 3. *Typical mechanism for C-H functionalization via migrative cross-coupling*

Even if the migrative cross-couplings offer new synthetic disconnections, this approach suffers the same drawbacks as the direct cross-couplings due to the need of pre-functionalized starting materials.The direct C-H functionalization of non-acidic C-H bonds has emerged as the ideal path toward the rapid and efficient construction of molecular complexity (Scheme 1**c.**). The discoveries of Shul'pin and Shilov, Fujiwara, and Felkin and Crabtree in the 70'sdemonstrated the feasibility of transition-metal catalyzedfunctionalization of aromatic, as well as aliphatic C-H bonds via C-H bond activation.[12]The contemporary developments led chemists to overcome the challenging chemoselectivity and site selectivity in "first functionalization" and in late stage functionalization, making directed and non-directed C-H bond functionalizationspowerful tools for organic synthesis.[13]

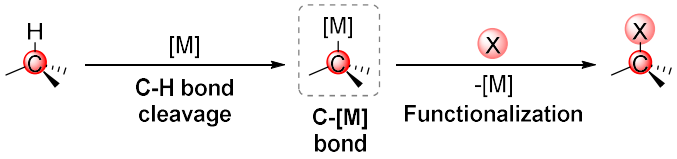
The transition metal C-H bond functionalization can proceed via an outer sphere mechanism or an inner sphere mechanism, the latter being commonly called "authentic" C-H activation.[14] In the outer sphere process, the activable C-H bond interacts first with a highly-activated ligand of a metal complex, such as a carbene,[15] a nitrene[16] or an oxene,[17] before the C-H bond cleavage/functionalization event. Two different pathways can be considered: the first involves the C-H insertion of the activated ligand, whereas the second proceeds via H abstraction and radical rebound of the coupling partner. In both cases, the metal doesn't interact directly with

the carbon bearing the activated proton (Scheme 4). Due to the involvement of a radical and/or cationic character at the carbon center, the transformation is more likely to be selective of weak C-H bonds (benzylic, allylic, tertiary or in α to heteroatoms).



Scheme 4. *C-H functionalization by outer sphere mechanism*

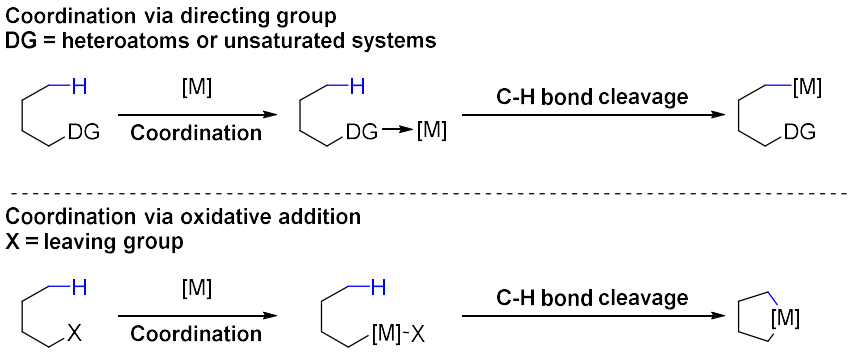
In the inner sphere mechanism, an organometallic intermediate is formed by C-H bond cleavage. This intermediate then reacts with an external reagent or at the metal center to obtain the C-H functionalized product. The C-H bond cleavage involves an agostic interaction between the metal center and the C-H bond prior to the proper C-H activation, via oxidative addition or CMD (Scheme 5).[18] The regio- and the stereoselectivity are mainly governed by the structural and electronic requirements of the organometallic intermediate, and other factors such as the ligand environment at the metal center can also influence these selectivities. In contrast to the outer sphere mechanisms, this C-H activation proceeds in principle with high selectivity for less sterically hindered C-H bonds, but this approach generally favors Csp^2-H activation over Csp^3-H activation, which is in agreement with the relative acidity of these bonds. Moreover, the Csp^3-H bonds in alkanes do not contain π-electrons, thus not allowing any π-metal pre-coordination, making the Csp^3-H bond activation more challenging.[19]



Scheme 5. *C-H functionalization by inner sphere mechanism (C-H activation)*

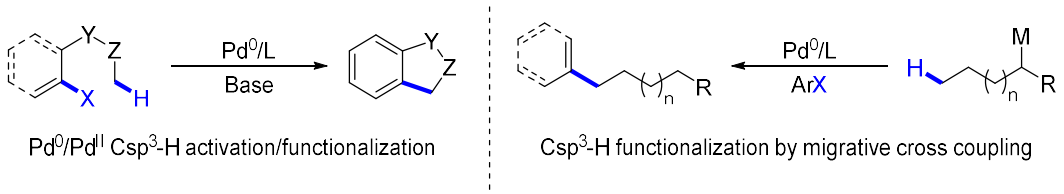
The metalation event in the C-H activation can be facilitated by the installation of a directing group that pre-coordinates the metal complex to the substrate. This complexation can modulate the reactivity of the substrate, but particularly enhances the selectivity and the

reactivity of the targeted C-H bond, thus triggering the intramolecular C-H activation. The oxidative addition of a C-(pseudo)halide bond followed by intramolecular C-H activation is another reliable approach. An example of the principle is depicted for C-H activation of aliphatic bonds in Scheme 6. The intermolecular C-H activation/functionalization constitutes an elegant but more challenging approach since no proximity between the metal center and the targeted C-H bond are induced.[20]



Scheme 6. *Pre-coordination of the metal to trigger C-H activation*

The Baudoin group research is mainly focused on the palladium oxidative-addition-initiated Csp^3-H activation for the control of selectivity in the Csp^3-H bond functionalization, in addition to the palladium catalyzed migrative cross-coupling of organometallics (Scheme 7), for the construction of APIs and in application to the total synthesis of natural compounds. The control of stereoselectivity is of major interest to enhance the power of these novel and step economical synthetic approaches.

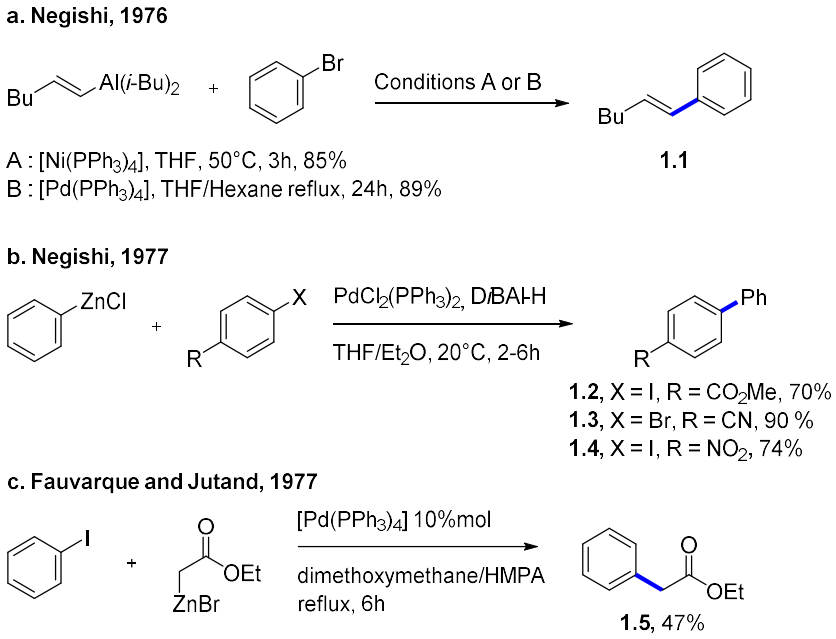


Scheme 7. *Current research topics at the Baudoin group*

Before the description of the projects developed during the course of this PhD, a summary of the development and the recents advances in the Negishi cross-coupling will be presented, followed by an overview of the use of palladium in migrative cross-coupling, to introduce the first research topic of this thesis. A third part will present the achievements of the Baudoin group in the field of C-H activation and the current investigation which led to the second subject of this thesis.

1.1. Negishi cross-couplings : development and recent advances

In 1976, Negishi first reported on the cross-coupling reaction of organoaluminum partners, employing nickel catalysts (Scheme 8**a.**).[21] However, a significant deterioration of stereospecificity was observed when organoaluminum reagents were involved in the synthesis of conjugated dienes. This drawback was overcome by replacing nickel with palladium. The following year, Negishi[22] and Fauvarque and Jutand[23] reported the use of organozinc reagents as coupling partners (Scheme 8**b** and **c**). The former authors highlighted the remarkable chemoselectivity of organozincs thanks to their tolerance toward sensitive functionalities such as esters, nitriles or nitros. Moreover, a screen of organometallic reagents showed that the palladium-catalyzed cross-coupling of an aryl iodide with zinc-, boron-, and tin-based partners was efficient.[24]



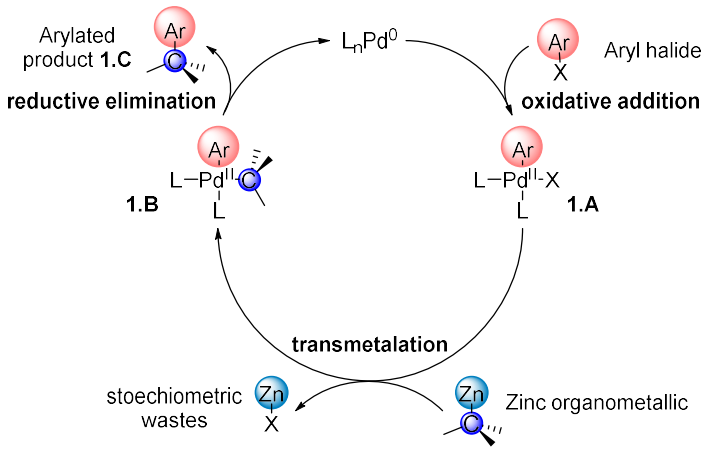
Scheme 8. *Development of the Negishi cross-coupling reaction*

Since then, the palladium-catalyzed Negishi cross-coupling found a myriad of applications in academia and industry, which were the topic of numerous publications and discussions, thus completing the scope of the transition metals catalyzed cross-couplings. It is noteworthy that the Negishi cross-coupling has also been studied with other transition-metals such as nickel or cobalt, and iron or copper catalysts were reported as being efficient for this type of coupling.[25]

1.1.1. General considerations

The general catalytic cycle for the palladium-catalyzed Negishi cross-coupling of zinc organometallics with aryl halides involves the oxidative addition of the catalytically active

Pd^0 to the carbon-halide bond. The intermediate Pd^{II}complex**1.A**transmetallates the organozinc, releasing zinc salt as a waste. The newly formed Pd^{II}complex**1.B**bearing the two organic coupling partners fragment undergoes reductive elimination to produce the arylated product **1.C** and thus regenerate the Pd^0 catalyst (Scheme 9). This coupling finds its advantage in the fast transmetalation of the organozinc to palladium, compared to boronic acids used in Suzuki coupling.[4a] Nevertheless, organozinc are mostly air and moisture sensitive, where boronic acids and esters are stable in these conditions, but also broadly available.[26]



Scheme 9. *General mechanism for palladium-catalyzed Negishi cross-coupling*

Common ligands used for the palladium-catalyzed Negishi cross-coupling are aryl(alkyl)phosphines and NHCs (Figure 2). The use of more hindered aryl(alkyl)phosphine generally suppresses the undesired isomerization by β-hydride elimination/migratory insertion in the coupling of secondary alkylzinc reagent. Thus, Buchwald and coworkers developed a panel of biphenyl-based hindered phosphinesand integrated them to aminobiphenyl-based palladacycle precatalysts, giving the advantage to be air and moisture stable but also to easily release the catalytically active Pd^0 species under basic conditions and at room temperature, then allowing Negishi couplings under milder conditions.[27]Organ and coworkers developed a series of hindered NHC-based Pd-complexes, which proved to be efficient for Negishi cross-couplings of secondary alkylzinc reagent with good selectivities.[28] The use of a very bulky imidazole-based phosphine developed by Baudoin and coworkers also allowed the direct coupling of functionalized secondary alkylzinc with high selectivities.[29]

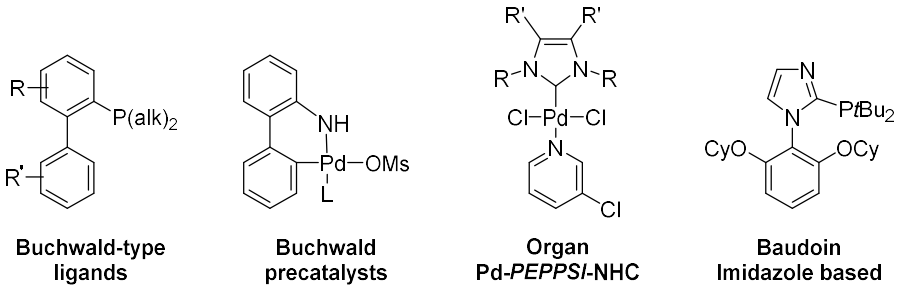
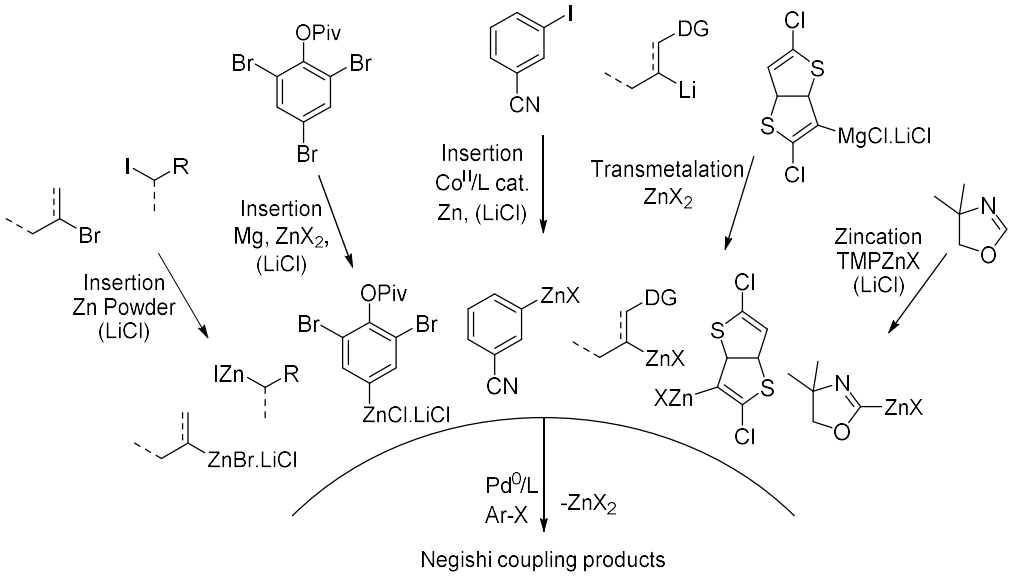


Figure 2.*Common ligands and palladium complexes for Negishi coupling*

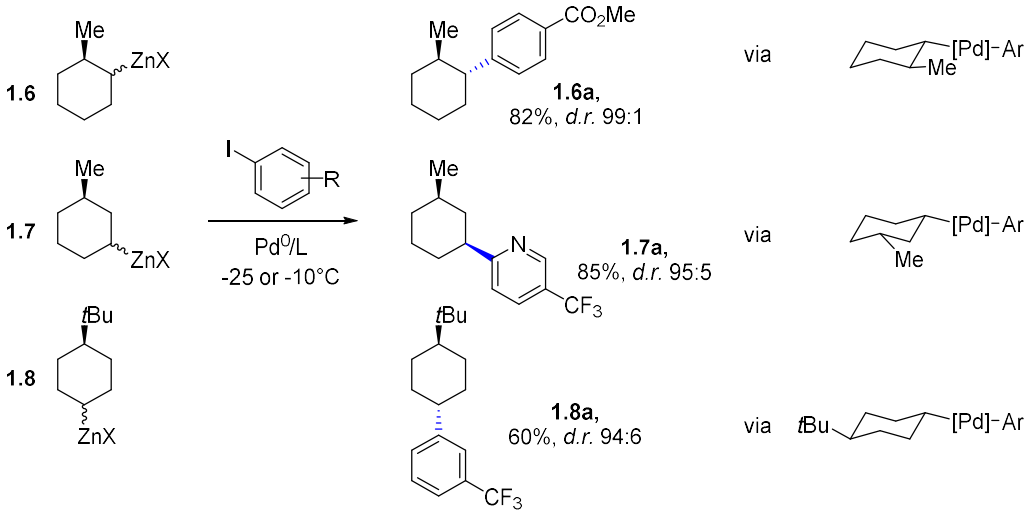
The organozinc partner can be prepared by oxidative addition of zinc powder to various aromatic, heterocyclic, benzylic, andalkyl bromides or iodides.[30] The highly activated Rieke-zinc is prepared by reduction of zinc chloride using lithium naphtalenide in THF,[31] and the commercial zinc powder insert more easily in presence of LiCl. The reaction scope of this insertion was increased by replacing zinc with bimetallic reagents couples such as Mg, $ZnCl_2$,[32]or Mg, $Zn(OPiv)_2$.[33]Gosmini showed that cobalt halides catalyze the preparation of various zinc reagents.[34] Yoshikai demonstrated that the latters undergo efficient palladium catalyzed Negishi cross-coupling.[35] The transmetalation of lithium, magnesium and aluminum organometallics generated from halogen/metal exchange[36], directed metalation,[37] or carbometalation[38]also provided zinc organometallics which were shown to be suitable for cross-coupling reactions. Alternatively, the directed zincation using TMP-zinc bases proved to be efficient for the cross-coupling of sensitive heterocycles (Scheme 10).[39]



Scheme 10. *Formation of zinc organometallics for Negishi cross-coupling*

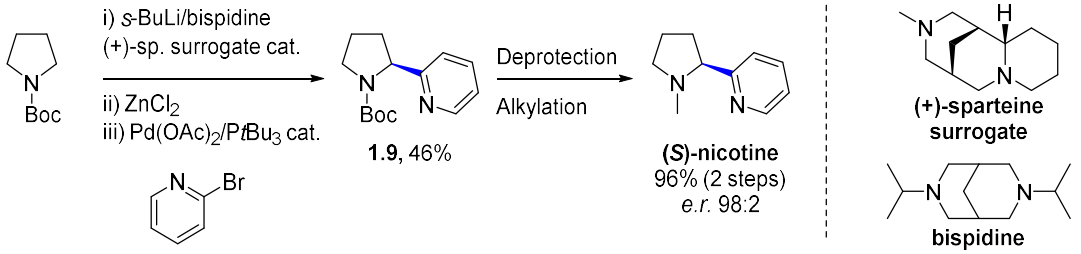
1.1.2. Stereo-induction in palladium-catalyzed Negishi coupling

A highly diastereoselective version of the Negishi cross-coupling was developed by Knochel and coworkers (Scheme 11). The treatment of cyclic organozinc reagents**1.6-1.8** with various arylhalides in presence of a palladium catalyst at low temperatures gave *cis*- or *trans*-disubstituted product with high *d.r.*. In this case, the substrates govern the selectivity. Indeed, 1,2- and 1,4-disubstituted organozincs**1.6** and **1.8** lead to the corresponding*trans*-arylated products**1.6a** and **1.8a** ; whereas the 1,3-disubstituted organozinc reagent **1.7** leads to the *cis*-arylated product **1.7a**. In all cases, the C-Pd bond in the Pd-complex intermediate is in equatorial position, thus explaining the induction.[40]



Scheme 11. *Highly diastereoselective arylation of cyclohexane derivatives*

Campos and O'Brien described the stereospecific Negishi coupling of enantioenriched pyrrolidylzinc with arylbromides leading to a precursor of (*S*)-nicotine.[41] The enantioselective lithiation of *N*-Boc-pyrrolidine in presence of catalytic (+)-sparteine surrogate and bispidine followed by the transmetalation to zinc and cross-coupling with 3-bromopyridine in presence of palladium acetate and P*t*Bu$_3$ afforded the Boc-protected arylated intermediate**1.9** in 46% yield. Its subsequent deprotection and methylation provided (*S*)-nicotine in 44% yield and 98:2 *e.r.* over the 3 steps, thus illustrating the application of this formal enantioselective Negishi coupling in natural and active product synthesis.



Scheme 12. *Enantioselective arylation of N-Boc-pyrrolidine*

In the scope of this arylation reaction, the authors also observed relevant amounts (up to 8%) of products resulting from the β-elimination pathway (olefin or isomerized arylated product) despite the use of a hindered ligand.

While many scientists were investing their efforts in the improvement of the direct Negishi cross-coupling, other groups took benefit of the lack of selectivity observed with certain transition metals to develop novel approaches for the functionalization of surrounding C-H bonds.

1.2. Csp^3-H bond functionalization via migrative cross-coupling

The "chain walking, chain running, or metal walk" is defined as a process in which discrete alkyl metal species undergo an iterative sequence of 1,2 or 1,3-hydride shifts along a single hydrocarbon chain. This constitutes a remote Csp^3-H bond functionalization relying on the ability of transition-metal complexes to undergo rapid olefin isomerization. The first catalytic examples were observed with titanium and zirconium in the early 60's, and the development of industrial processes notably with ruthenium, rhodium and iridium led to a deeper interest in the migrative processes in the 70's. In the last decades have also been taken into account iron and cobalt, while nickel has been the subject of major innovations.Those advances in the field were recently summarized by Martin and Marek.[42] Only migrative coupling with palladium will be discussed in this section, after the presentation of historical examples.

1.2.1. Heck-type migrative cross-couplings

In 1976, Heck[43] as well as Magennis[44] observed isomerized products in the palladium catalyzed arylation of unsaturated aliphatic alcohols with aryl halides. The corresponding arylated aldehydes**1.10-1.13**were obtained in low yield and selectivities under harsh conditions. Nevertheless, these examples gave rise to the development of Larock's remote functionalization of longer olefinic alcohols using Heck cross-coupling to install the

palladium on the olefin. The corresponding carbonyl compounds**1.14** and **1.15** were obtained in good yields at only 50°C (Figure 3).[45]

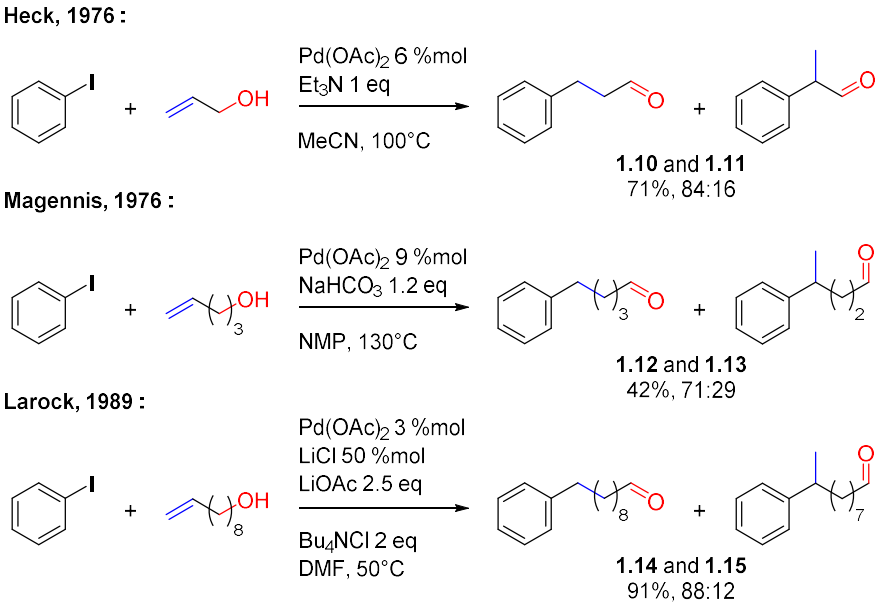


Figure 3: *Historical examples of migratory Heck cross-coupling reactions*

This work established the basis of the leading improvements, such as Marek's remote functionalization of olefinic alcohols that include a cyclopropane in the chain, which undergoes selective ring cleavage;[46] Mazet's long range redox isomerization of olefinic alcohols, initiated by hydropalladation;[47]or Sigman's enantioselective construction of remote quaternary stereocenters via redox-relay Heck reaction.[48]

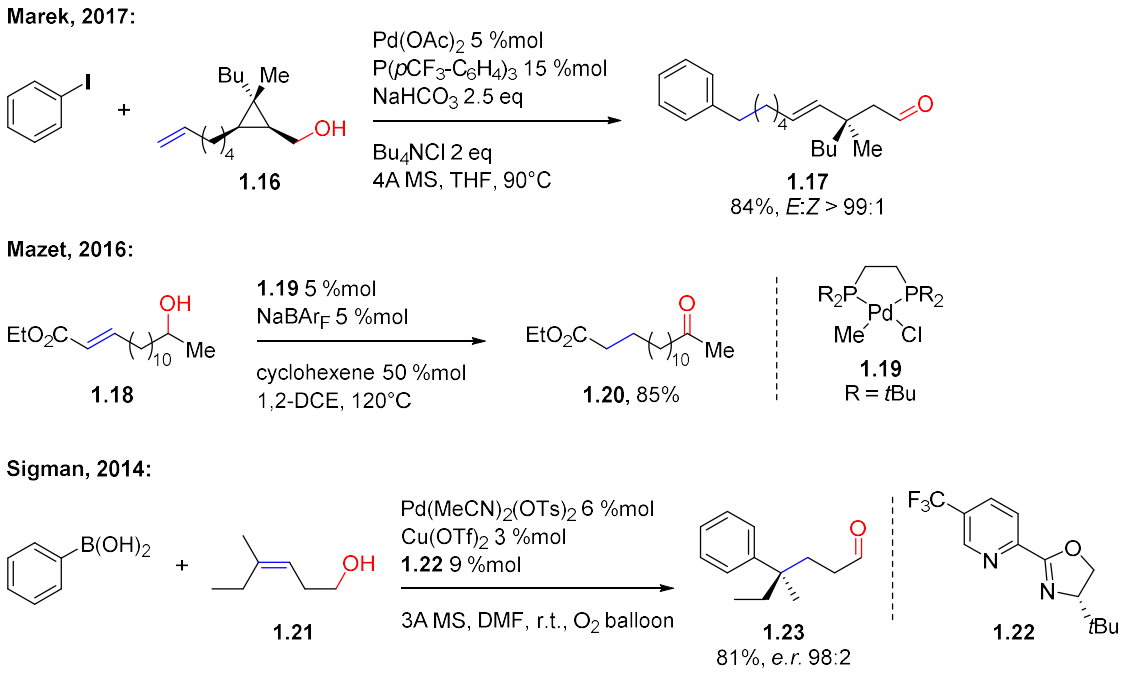
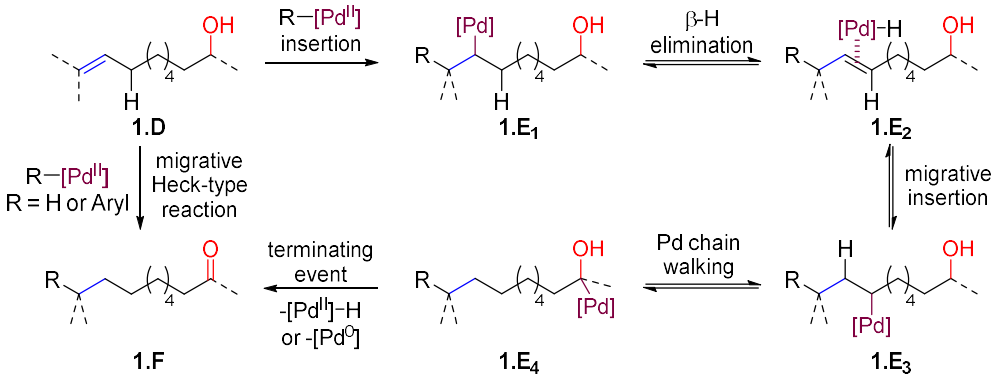


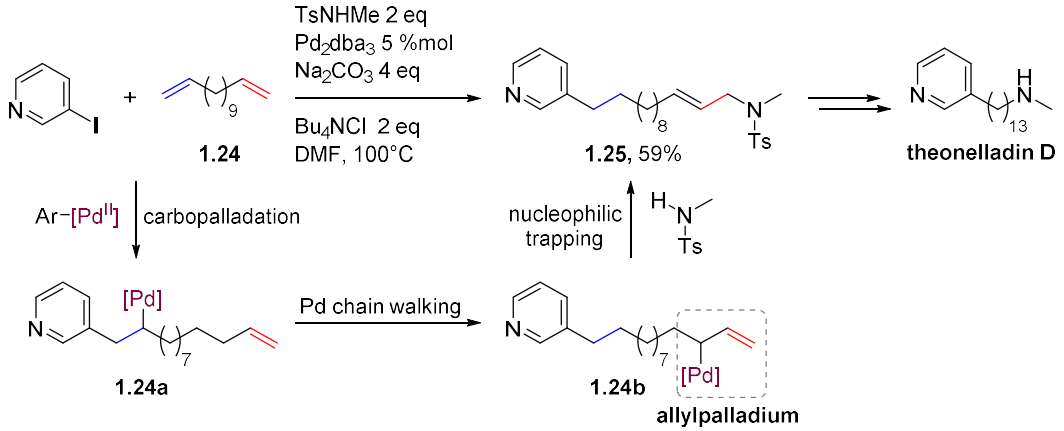
Figure 4. *Recent advances in the migrative Heck-type reactions*

The common path in the reactions proceeds with the coordination of the Pd^{II} species to the unsaturation of **1**.D-type olefinic alcohols, followed by the corresponding carbo- or hydropalladation giving rise to **1.E$_1$**-type intermediates. The regio- and stereoselectivity is determined during this step. Once the Pd^{II} is installed on the chain, the metal undergoes β-hydride elimination and migratory insertion to give complex **1.E$_3$** through Pd-hydride complex **1.E$_2$**. The process is repeated toward the alcohol via the chain walking process, in which the elementary steps are reversible and potentially bidirectional. The ultimate α-oxopalladium species **1.E$_4$** furnishes the corresponding enol by β-hydride elimination (palladium assisted tautomerization)[47]or the corresponding carbonyl product by concomitant oxidative deprotonation of the substrate and reduction of the Pd^{II} to Pd^0 (Scheme 13).[49] The initial Csp^2 center in **1.D** is transformed to a functionalized Csp^3 center in the migration product **1.F**.



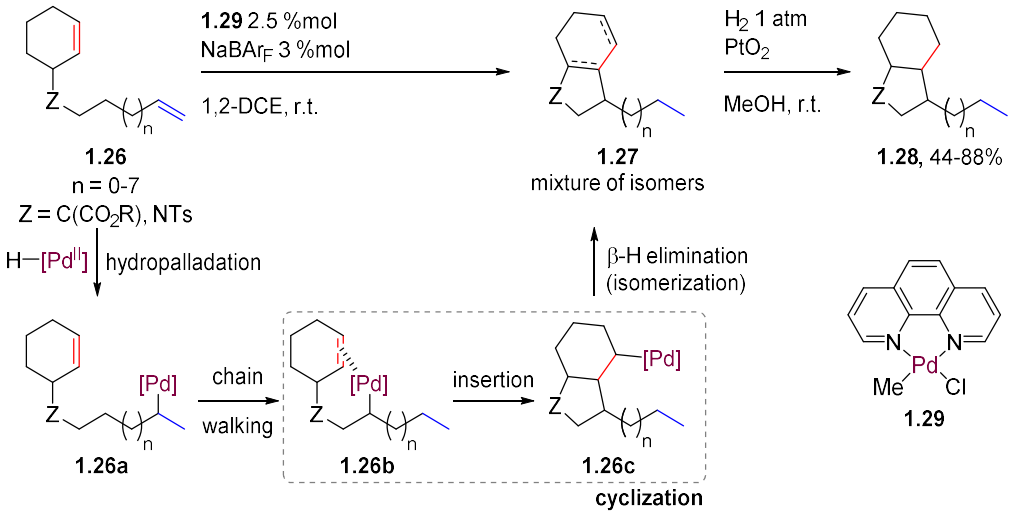
Scheme 13. *Common palladium chain walking in migrative Heck-type reactions*

Another strategy relies on the stability of allylpalladium species. After migration of complex **1.24a**, the terminating event is not anymore the carbonyl formation, but the formation of a stabilized allylpalladium in the insaturation distal to the introduction site of the palladium, as in **1.24b**. This intermediate complex is trapped by a nucleophile, thus releasing Pd^0 catalyst (Scheme 14). This approach was used by Larock for the synthesis of naturally occurring pyridine alkaloids.[50]



Scheme 14. *Larock's remote difunctionalization via migrative Heck coupling*

Kochi and coworkers recently proposed a sequence of chain-walking/cyclisation. A substrate containing a strategically placed olefin such as **1.26** has undergone cyclisation after hydropalladation on a terminal unsaturation and migration (respectively **1.26a** and **1.26b**). The insertion of the olefin provides a five membered ring organopalladium intermediate of type **1.26c**. The subsequentβ-hydride eliminations/isomerizations furnish a mixture of olefin isomers of type **1.27** which after hydrogenation provides valuable (hetero)cyclic compounds of type **1.28** (Scheme 15).[51]



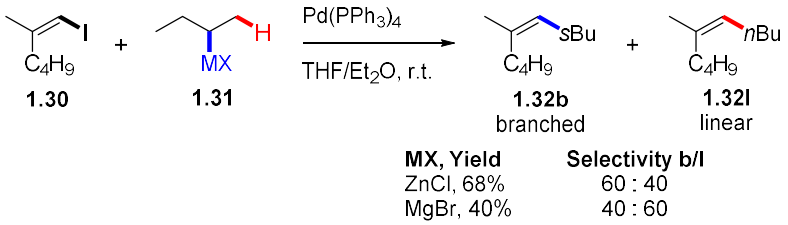
Scheme 15. *Kochi's chain walking cycloisomerization/hydrogenation of remote dienes.*

All those examples are based on palladium catalyzed Heck-type couplings, requiring an unsaturation to install the Pd^{II} catalytic intermediate on the olefinic chain, and a remote functionality such as an alcohol or another unsaturation to terminate the migration. The methods provide the product of a formal remote Csp^3-H functionalization. We have seen in the previous section that researchers put many efforts in the direct cross-coupling of

secondary alkyl organometallics, such as in the Negishi coupling, to avoid the migration of the palladium intermediates notably by using hindered ligands. But those organometallics are also the starting materials of choice for a proper remote Csp^3-H functionalization via migrative cross-coupling.

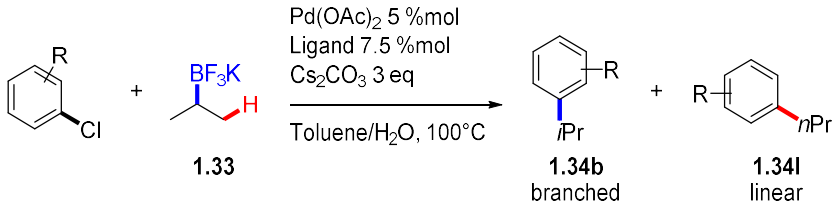
1.2.2. Transmetalation-induced migrative cross-couplings

In 1980, Negishi and coworkers observed the formation of the migration product in the coupling of an elaborated iodoalkene**1.30** with *sec*-butyl organometallics**1.31** (Scheme 16). The use of a zinc or a magnesium based sec-butyl metal under palladium catalysis provided the coupling products**1.32** in 68% and 40% yield respectively. The low selectivity of 60:40 was in favor of the direct couplingproduct**1.32b**in the case where the organozinc was used, and a reversed selectivity in favor of **1.32l** was observed with the organomagnesium.[52]



Scheme 16. *Historical example of palladium catalyzed Negishi cross-coupling*

While exploring the scope of the Suzuki coupling of secondary alkyltrifluoroborates with arylchlorides and bromides, Molander also observed the formation of non desired linear migratory coupling products**1.34l** (Scheme 17).[53]



Scheme 17. *Migrative coupling in the palladium catalyzed Suzuki cross-coupling*

In this study, the use of the hindered ligand P*t*Bu$_3$ conducted to the major formation of the branched product (*i*Pr) via direct coupling, but surprisingly the use of PAd$_2$*n*Bu led to a higher rate of the linear product (*n*Pr) via migrative coupling. The substitution effect of the aryl chloride is remarkable. *Ortho*-substituted aryls tend to undergo migrative coupling more than the *para*-substituted aryls. Moreover, the electronic effect is notable. Indeed, the use of rich

(methoxy) or poor (methylbenzoate) aryl nucleophiles leads to higher ratios of branched to linear product, in contrast to neutral aryls (methyl) (Figure 5).

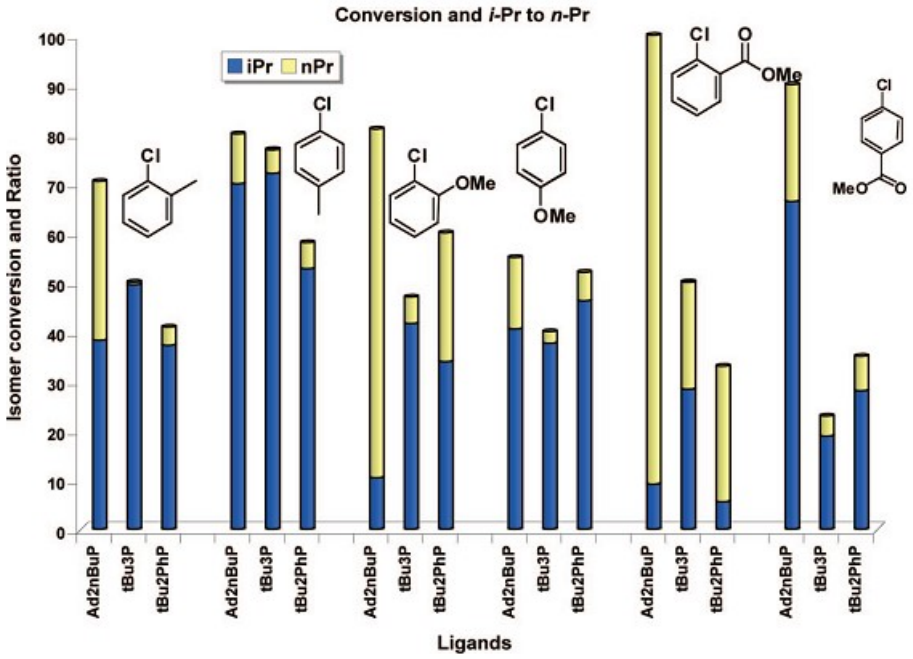
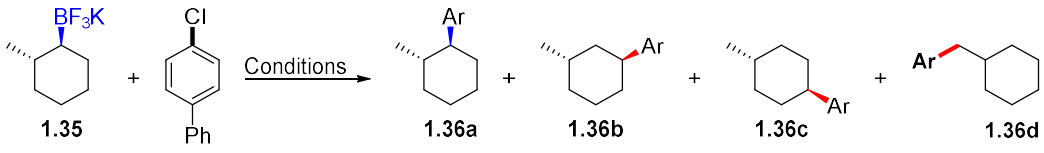


Figure 5. *Ligand and aryl effects in the branched to linear product ratio*

Next, the coupling of the diastereomerically pure potassium *trans*-2-methylcyclohexyl-trifluoroborate**1.35** with 4-chlorobiphenyl in presence of PAd$_2$*n*Bu, P*t*Bu$_3$, andP*t*Bu$_2$Ph always led to a mixture of 4 products, comprising 3 products of migration. In every case, the productof direct coupling **1.36a**was mainly obtained (Table 1). Interestingly, the biphenyl moiety can be coupled to the methyl substituent via two successive β-H eliminations/migratory insertions, to obtain substrate **1.36d**. The migration occurs through a tertiary carbon center.



Entry	Ligand	Conditions[a]	a	b	c	d	Yield (%) of 1.36
1	PAd$_2$*n*Bu	A	4.4	1.0	2.0	1.4	80
2	P*t*Bu$_3$	B	16.0	1.0	1.0	6.0	48
3	P*t*Bu$_2$Ph	B	27.7	1.6	1.0	8.1	72

[a] Conditions : A) Pd(OAc)$_2$ 2 %mol, Ligand 3% mol, RBF$_3$K 1.1 eq, Cs$_2$CO$_3$ 3 eq, toluene/H$_2$O (10:1), 100°C, 24h. B) Pd(OAc)$_2$ 5 %mol, Ligand 3% mol, RBF$_3$K

1.3 eq, toluene/H_2O (10:1), 100°C, 72h.

Table 1. *Selectivity in the cross-coupling of potassium* trans*-2-methylcyclohexyl-trifluoroborate*

Buchwald and coworkers observed a similar trend in the palladium catalyzed Negishi coupling of *iso*propylzinc bromide with *ortho*-substituted aryl bromides.[54] The important ligand effect is highlighted by the reversal of selectivity between **1.37** and **1.38**when XPhos (**1.L^3**) is used in place of CPhos (**1.L^6**) with arylbromides bearing either an electroattracting group (nitrile) or an electrodonating group (methoxy) (Figure 6).

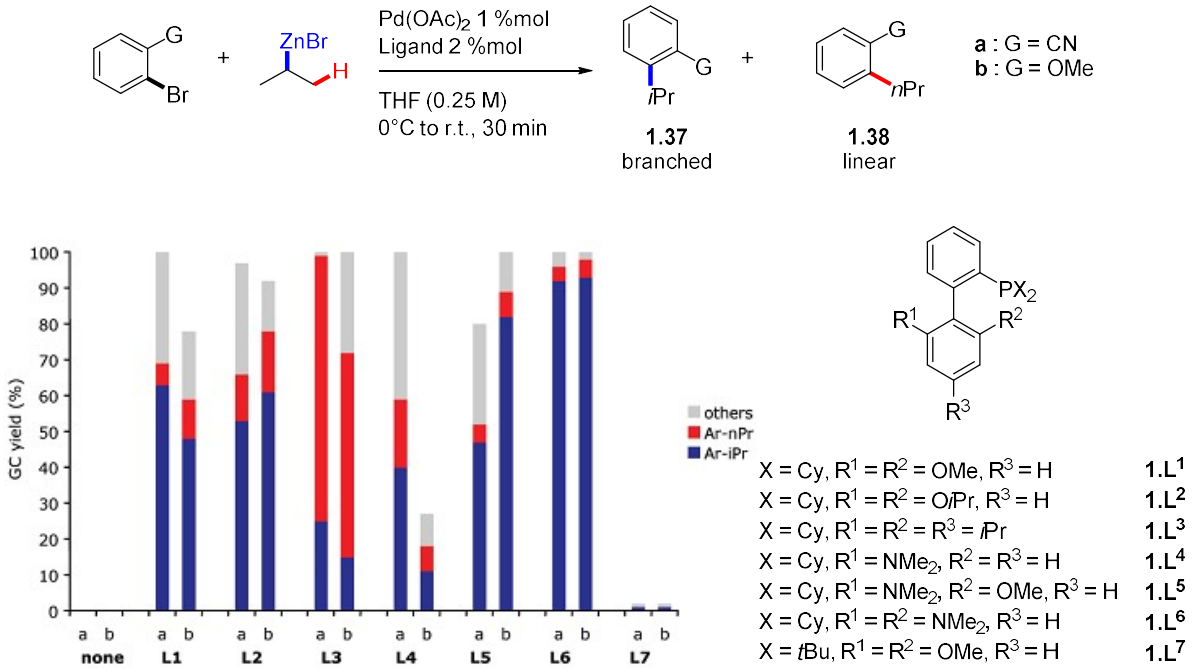
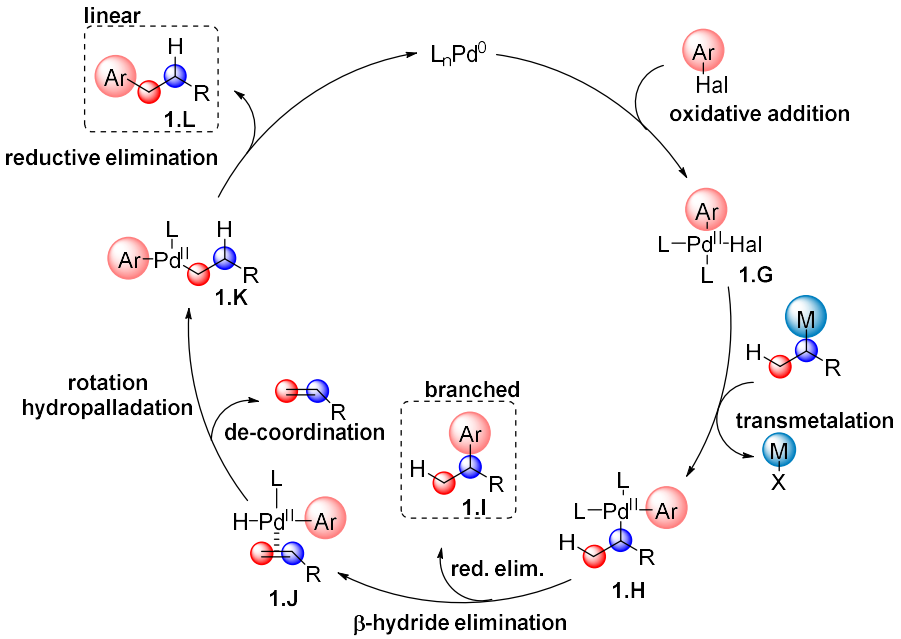


Figure 6. *Ligand effect on the selectivity of branched to linear Negishi coupling product*

1.2.3. Mechanistic insights and ligand design

The common mechanism of these palladium catalyzed cross-couplings involves the oxidative addition of the Pd^0 into the aryl (pseudohalide) bond to form the catalytically active Pd^{II} species**1.G** bearing the aryl moiety. This complex undergoes transmetalationwith the secondary alkyl organometallic nucleophile to give intermediate **1.H**. Once installed, the direct reductive elimination event leads to the classical cross-coupling product **1.I** (*i.e.* the branched product). The β-hydride elimination event triggers the migration process and provides the olefin π-complex**1.J** which undergoes rotation and hydropalladation to give rise to the isomerized Pd-alkyl complex**1.K**. The subsequent reductive elimination gives rise to the arylated product **1.L** via migrative cross-coupling (*i.e.* the linear product) (Scheme 18). In

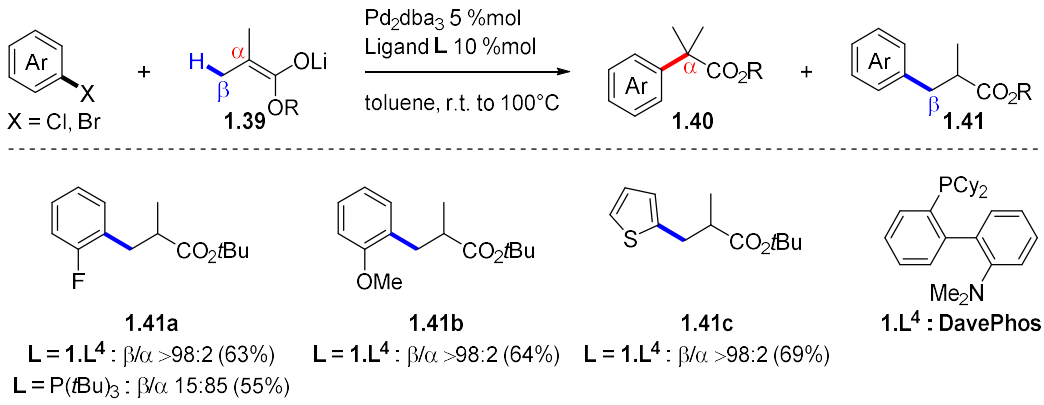
the reaction, a non activated Csp^3-H bond is transformed to a Csp^3-C bond, thus constituting a proper remote Csp^3-H bond functionalization.



Scheme 18. *Csp^3-H bond arylation via palladium catalyzed cross-coupling*

As shown by Molander and Buchwald in the previous examples, the substitution of the aryl halide as well as the ligand play an important role in the migration of the palladium complex. Both studies show that the *ortho* substitution of the aryl electrophile tends to favor the migration in spite of the direct coupling. The design and choice of the ligand is essential for the regioselectivity of the arylation. Surprisingly, in said examples, hindered ligands originally designed to favor the direct coupling are allowing the migrative coupling with high selectivities.

Based on a report from Hartwig and coworkers,[55] Baudoin and coworkers studied the selectivity control in the palladium-catalyzed arylation of the lithium enolates of isobutyric esters **1.39** with aryl halides (Scheme 19).[56] The combination of *ortho* substituted (hetero)aryl halides with DavePhos **1.L**[4] as the ligand afforded the β-arylated products **1.41** in good yields and excellent selectivities. In contrast, the use of P*t*Bu$_3$ favored the formation of the α-arylated product **1.40**, via direct cross-coupling. The installation of the Pd^{II} proceeds via lithium-palladium transmetalation of the lithium enolate,[57] followed by migration and reductive elimination.



Scheme 19. *Palladium-catalyzed β-arylation of carboxylic esters*

The pathway leading to the direct or migrative coupling products, *i. e.*α- or β-arylation, of the methyl isobutyrates were computed by DFT, enlightening the role of the aryl substitution and of the ligand.[58] The electronegative *ortho* substitution disfavors the α-reductive elimination, whereas a very bulky ligand favors this event. Moreover, the use of a more flexible ligand such as the DavePhos**1.L**^{4} decreases the energy barrier of the 180° rotation of the intermediate π-complex arising from β-hydride elimination, thus the palladium complex undergoes more easily migratory insertion (Figure 7).[59]

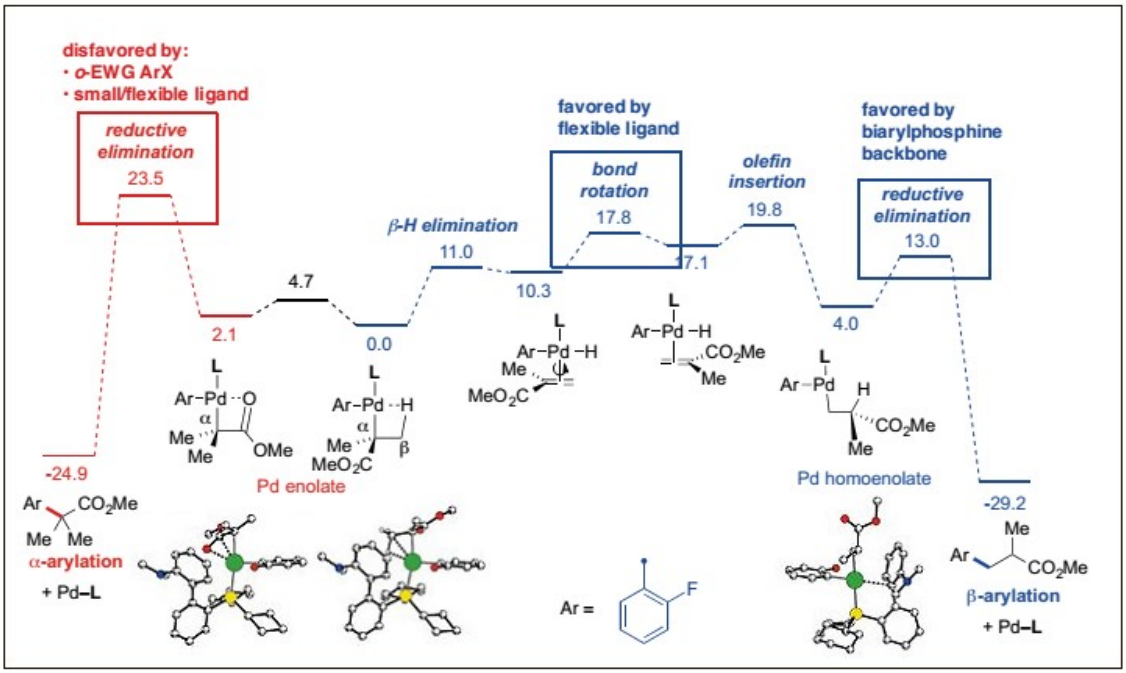
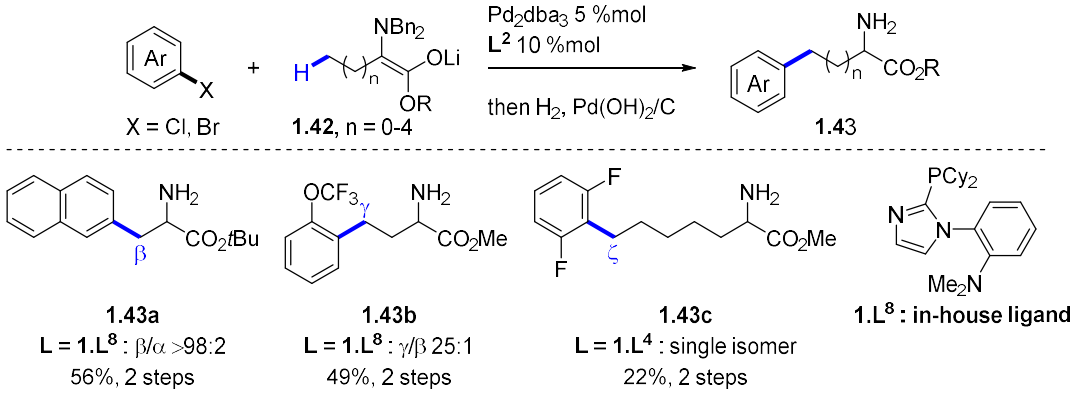


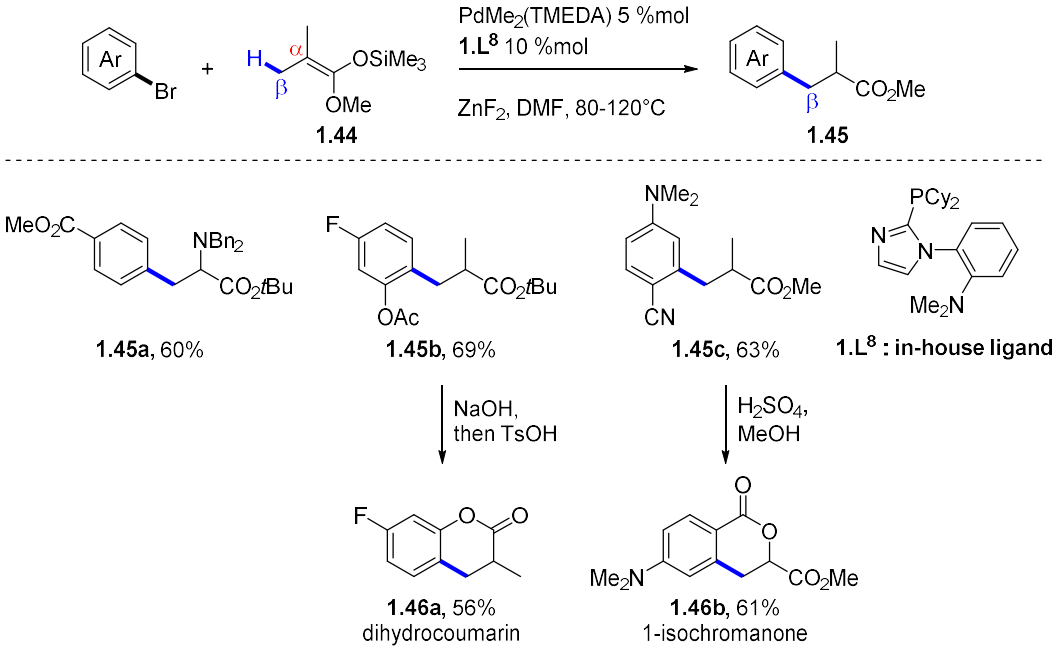
Figure 7. *Analysis of selectivity factors using DFT calculations (B3PW91/6-31G**), SDD, PCM). Values refer to Gibbs free energies in kcal mol*$^{-1}$

The method was extended in the long range arylation of α-aminoesters enolates**1.42**.[60] The use of a more flexibleimidazole-based ligand[61]**1.L^8** provides complete selectivity for the β-arylated products **1.43**,after deprotection of the amine, independent of the aryl bromide substitution. The terminal alkylation occurs on longer side-chains, but requires an electronegative *ortho* substitution. Nevertheless, γ- to ζ-arylation could be achieved in modest yields but excellent selectivities (**1.43b** and **1.43c**), via a chain walking process. The amine was deprotected in a subsequent hydrogenation to obtain the free arylalanine homologues (Scheme 20).



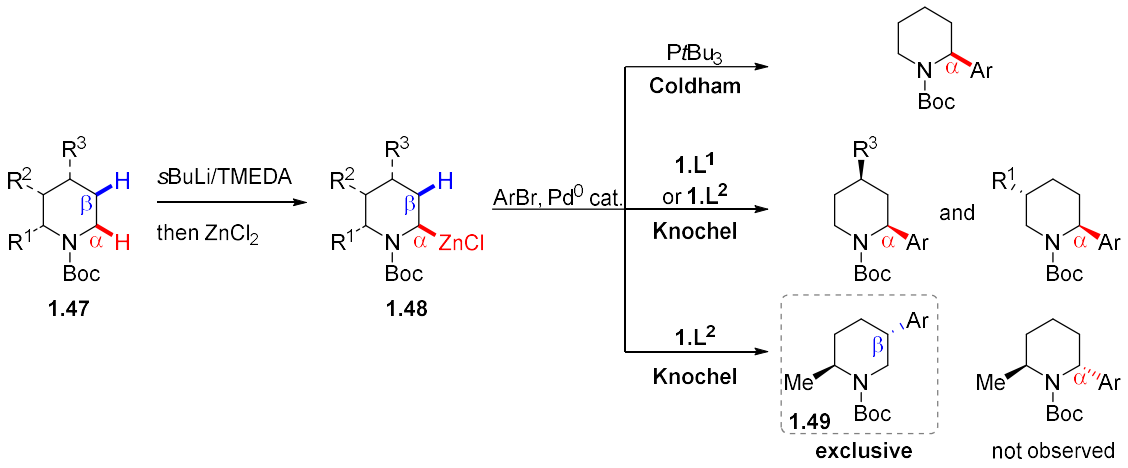
Scheme 20. *Long range arylation of α-aminoesters lithium enolates*

A similar methodology was developed using silyl ketene acetals**1.44** as an alternative to lithium enolates.[62] This novel approach was applied in the synthesis of benzo-fused δ-lactones**1.46a-b** (Scheme 21).



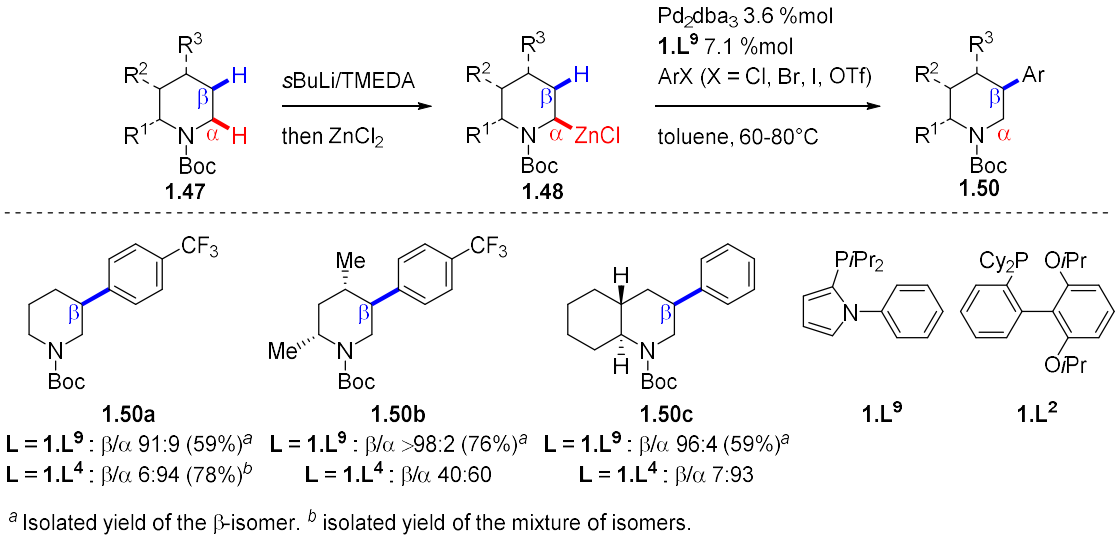
Scheme 21.*Migrative arylation of silyl ketene acetals and application to the synthesis of valuable compounds*

Coldham described in 2008 the Negishi coupling of α-piperidinylzinc**1.48**obtained by directed lithiation and transmetalation to zinc, in presence of P*t*Bu$_3$.[63]Following this study, Knochel described the diastereoselective arylations of substituted *N*-Boc-piperidines.[64] In this report, the α-organozinc, formed by directed lithiation/deprotonation, undergoes Negishi coupling in presence of SPhos**1.L^1**orRuPhos **1.L^2**. Surprisingly, when a 2-methyl-*N*-Boc-piperidine was submitted to the α-arylation condition, the β-arylated product**1.49** was formed exclusively. The regioselectivity, obtained by migration of the intermediate palladium complex, was shown to be induced by the hindrance of the 2-methyl substitution. Thus the selectivity in this case is controlled by the substrate (Scheme 22).



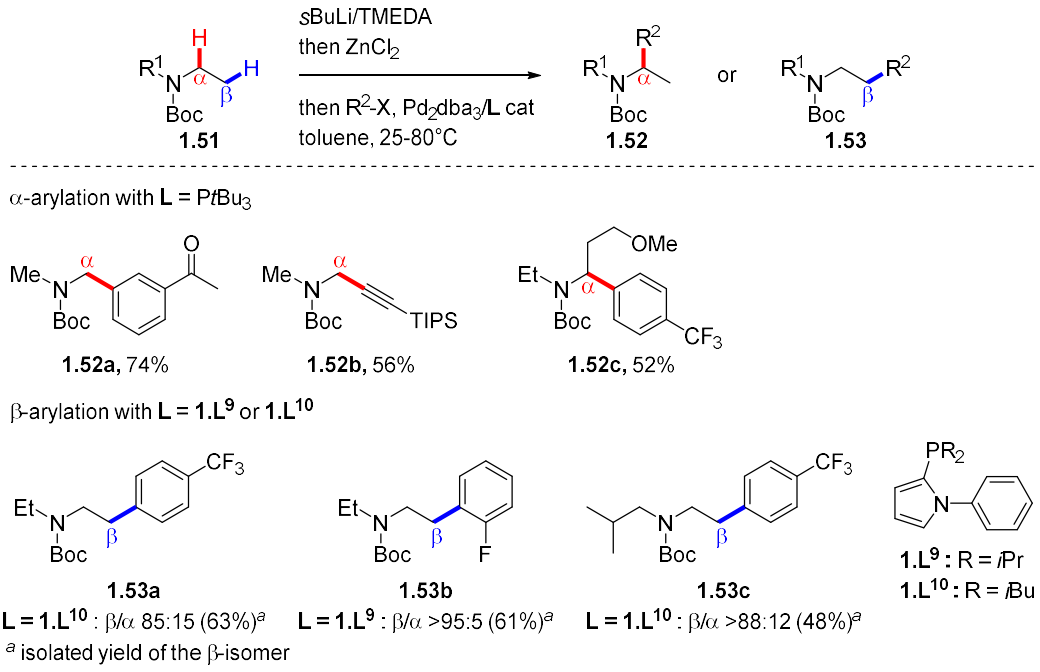
Scheme 22.*Selectivity in the Negishi coupling of piperidinylzinc chloride*

Following their work on the controlled migrative arylation for remote C-sp^3-H bond functionalization, Baudoin and coworkers developed the ligand-controlled β-arylation of *N*-Boc-piperidines**1.47** (Scheme 23).[65] A new flexible *N*-phenyl-pyrrole-based phosphine ligand**1.L^9** allows the selective β-arylation in good yields and excellent selectivities, contrasting with the opposite α-arylation obtained in presence of RuPhos**1.L^4**. The mild basic and nucleophilic character of the intermediate organozinc allows the use of sensitive functional groups on the arylbromide partner.



Scheme 23. *Ligand controlled β-selective Csp³-H arylation of N-Boc-piperidines*

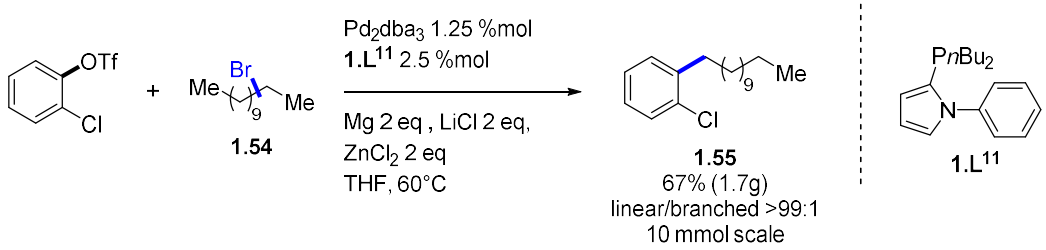
The methodology was extended to the selective α- and β-arylations of acyclic *N*-Boc-amines via Negishi coupling (Scheme 24).[66] The coupling in presence of P*t*Bu$_3$ provides the α-products **1.52**, whereas the flexible ligands such as**L**^{9} afford the migration products**1.53**.A similar mechanism as for the arylation of isobutyric esters was determined by DFT calculation, thus questioning the generalization of this methodology to other organometallic starting materials.



Scheme 24. *Ligand controlled α- and β-arylation of acyclic N-Boc-amines*

Nevertheless, this methodology did not give access to a longer range arylation. Indeed, the efficiency of the lithiation got dramatically affected by the bulkiness of the amine substituents, and suitable substrates for longer migration, such as the di-*n*-propyl-*N*-Boc-amine, only gave a poor conversion along with poor selectivities. The γ-arylated *N*-Boc-amines were accessed via the Negishi coupling of zincated *N*-Boc-allylamines.[67]

An alternative approach to the long range arylation was found in the Negishi coupling of secondary alkylzinc chloridesformedby *in-situ*transmetalation of the corresponding Barbier reagents. The linear products were selectively obtained by the fine tuning of the ligand. This powerful strategy was notably exemplified by the terminal Csp^3-H arylation of regioisomeric mixture of brominated alkanes**1.54** in presence of **1.L[11]** (Scheme 25).[68]



Scheme 25. *Terminal selective functionalization of alkyl chains via regioconvergent cross-coupling*

This last example illustrates the most recent advances in the field of palladium-catalyzed migrative cross-coupling, which is still actively under investigation within the Baudoin group.

1.2.4. Task 1 : ligand-controlled migrative coupling of aliphatic alcohols

Motivated by the successful ligand-controlled regioselectivity in the arylation of cylic and acyclic *N*-Boc-amines, and by the study and the understanding of the migration mechanism, the ligand controlled α-, β- and longer range arylation of protected aliphatic alcohols has been proposed as a novel access to various arylated alcohols, which the derivatives are widely represented in bioactive molecules of interest (Figure 8).

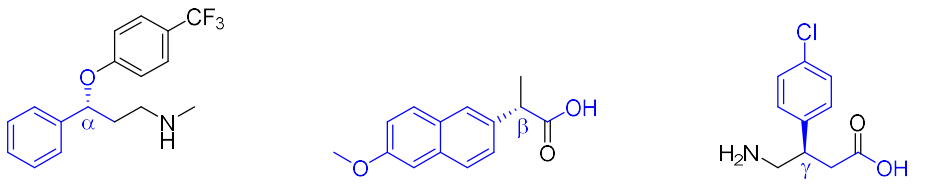
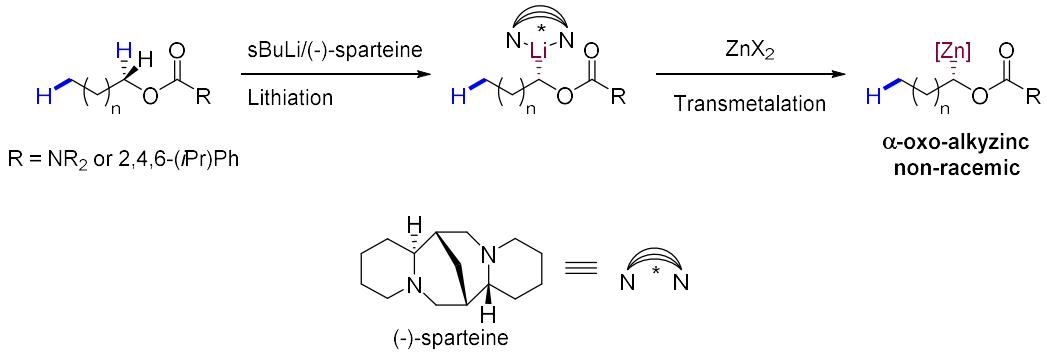


Figure 8. *Examples of arylated alcohols derivatives in bioactive molecules*

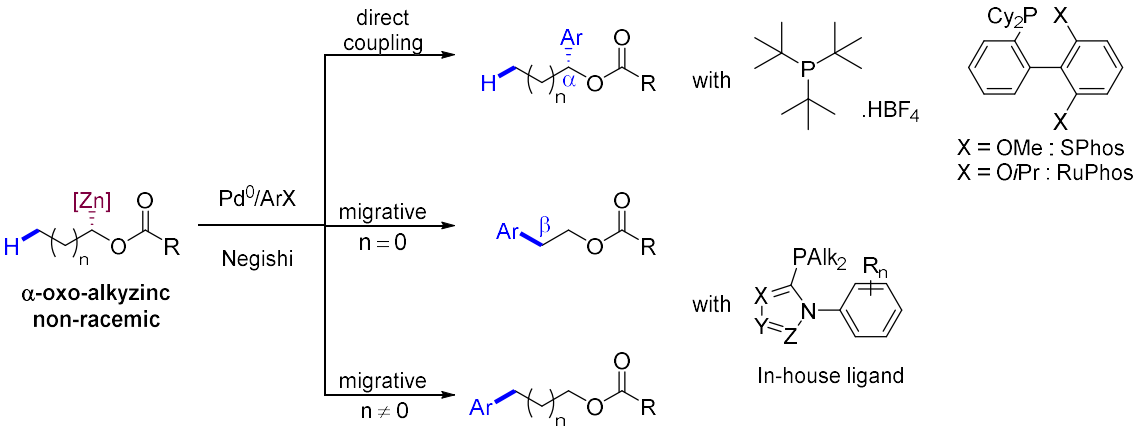
The formation of an (chiral) organozinc reagent in α-position of a nitrogen atom has proven to be feasible by transmetalation of an organolithium obtained by deprotonation/lithiation. Moreover, this type of organozinc reagent undergoes efficient direct and migrative Negishi cross-couplings.

In the same way, the preparation of α-oxo-alkylzinc reagent has been envisioned. The direct α-lithiation of hindered carbamates derived from aliphatic alcohols is a well established method for the introduction of functionality at the α-position of the oxygen upon electrophilic quenching. The methods developed by Hoppe allow the deprotonation/lithiation of secondary and activated tertiary carbons, also in asymmetric manner thanks to the use of sparteine as the ligand.[69] With the introduction of the hindered TIB ester, Aggarwal could allow the stereoretentive deprotonation of stereogenic tertiary carbons.[70]In addition, it has been shown that the lithiation of α-stereogenic carbamates and the transmetalation with a zinc halide are both stereoretentive, and the electrophilic quenching afforded enantioenriched secondary alcohols derivatives.[71]Thus, non-racemic α-oxo-alkylzinc reagent could be prepared (Scheme 26).



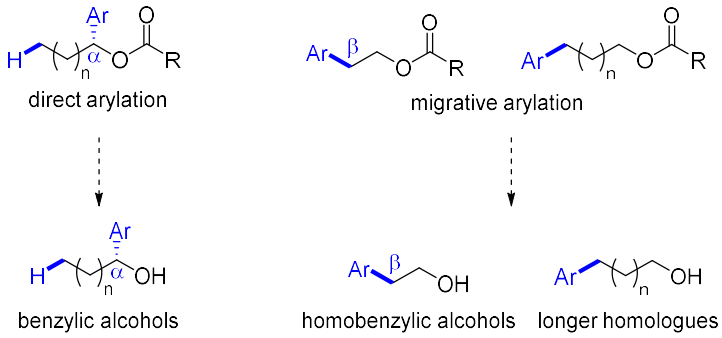
Scheme 26. *Preparation of the non racemic α-oxo-alkylzinc*

The investigation would focus in a first time on thepreparation of the intermediate α-oxo-organozinc species and its evaluation in both the direct and migrative Negishi cross-couplings. The variation of the ligand would allow the regio-selectivity in the arylation reaction, and hence new ligands could be designed and synthesized to improve the selectivity in the coupling.The use of hindered, non-flexible ligands would favor the direct coupling, whereas (in-house) flexible ligands would trigger the migration (Scheme 27). The enantioselective version of the reaction must be explored.



Scheme 27. *Envisioned ligand-controlled direct and migrative Negishi cross-couplings*

The deprotection of the arylated targets would give rise to a variety of benzylic, homobenzylic and longer homologues of arylated alcohols, thus demonstrating the synthetic utility of the methodology (Scheme 28).



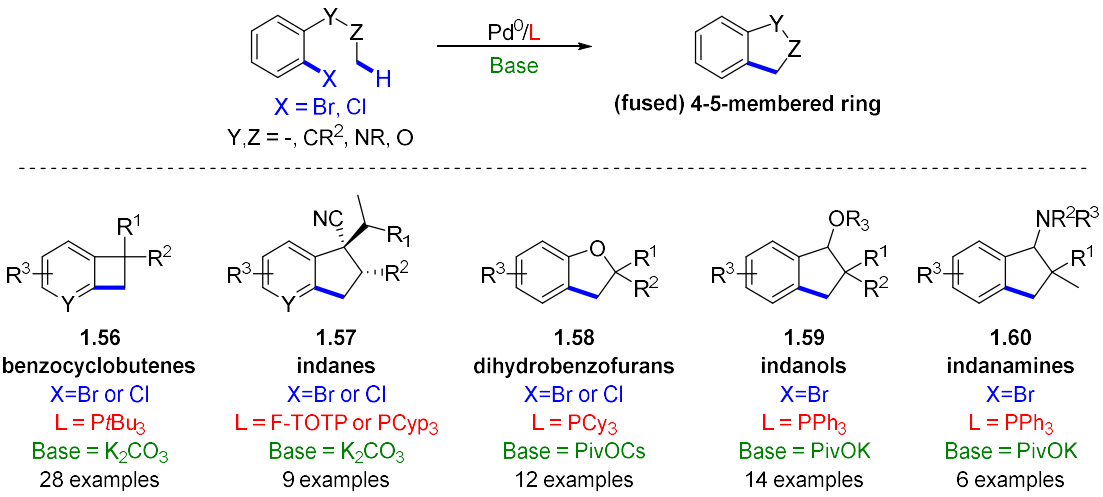
Scheme 28. *Obtention of various arylated alcohols after deprotection*

1.3. Palladium-catalyzed C-H bond activation/functionalization

1.3.1. Baudoin's approach to C-H activation/functionalization

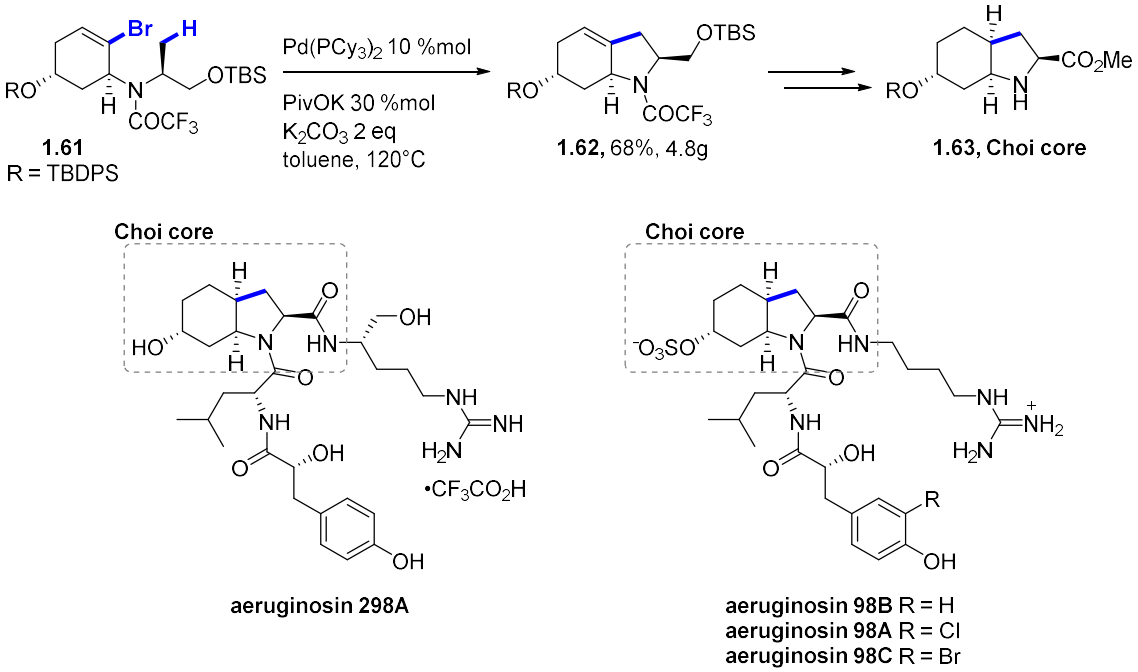
Over the last 15 years, Baudoin and coworkers developed many methodologies for the construction of four and five members (hetero)cyclic rings through Pd^0/Pd^{II} catalyzed Csp^3H functionalization (Scheme 29).[72] A first report in 2003 described the formation of benzocyclobutenes **1.56** via the C-H activation of benzylic *gem*-dialkyl groups.[73] The development of the catalytic system, and notably the ligand, allowed the synthesis of functionalized indanes**1.57**.[74]From the experience acquired, the synthesis of benzocyclobutene**1.56** was improved and made general, including a full mechanistic study.[75] A further work in collaboration with Fagnou established the first example of an efficient and general palladium-catalyzed intramolecular Csp^3-H arylation of (hetero)aryl chlorides for the

synthesis of cyclobutarenes**1.56**, indanes**1.57**, indolines, dihydrobenzofurans**1.58**, and indanones.[76] An extension of this work to indanols**1.59** and indanamines**1.60** was reported in 2014.[77]



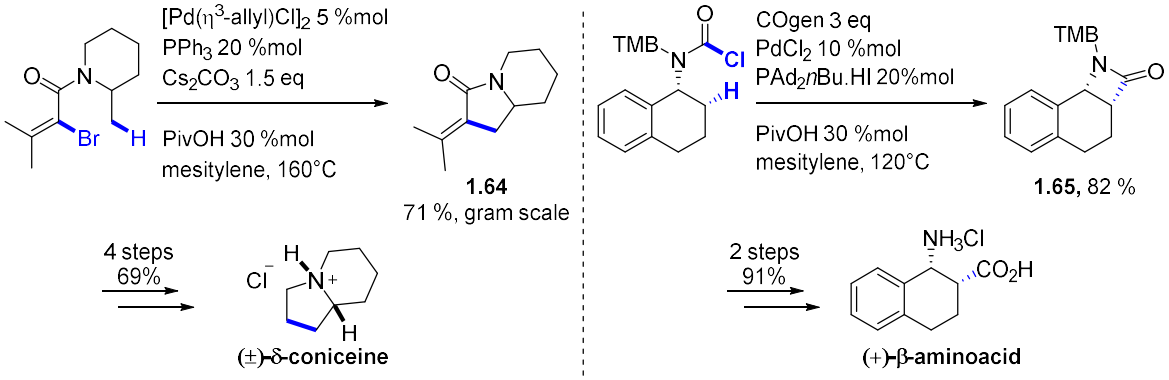
Scheme 29. *Examples of intramolecular Csp^3-H activation/arylation of unactivated C-H bond*

These methodologies were nevertheless restricted to the synthesis of fused benzo(hetero)cycles, even if the latter are important scaffolds included in natural products and active pharmaceutical ingredients. In 2012, it was demonstrated that the Csp^3-H alkenylation allows the access to more Csp^3-rich compounds, which are also important in the synthesis of bioactive compounds of interests. The synthesis of the Choi core**1.63** (2-carboxy-6-hydroxyoctaindole core) has been made possible by a novel intramolecular Csp^{3}H alkenylation of substrate **1.61** (Scheme 30). This Csp^3-H activation strategy has proven its efficiency in the synthesis of congeners of the aeruginosin, a family of natural products.[78]



Scheme 30. *Divergent synthesis of aeruginosins based on Csp^3-H activation strategy*

Various cyclic alkaloid precursors were obtained via the synthesis of strained γ-lactamssuch as**1.64** by Csp^3-H alkenylation. The methodology was applied in the synthesis of δ-coniceine.[79] The synthesis of β-lactamssuch as**1.65** by Csp^3-H carbamoylation allowed the synthesis of enantiopure non-natural β-aminoacid (Scheme 31).[80]

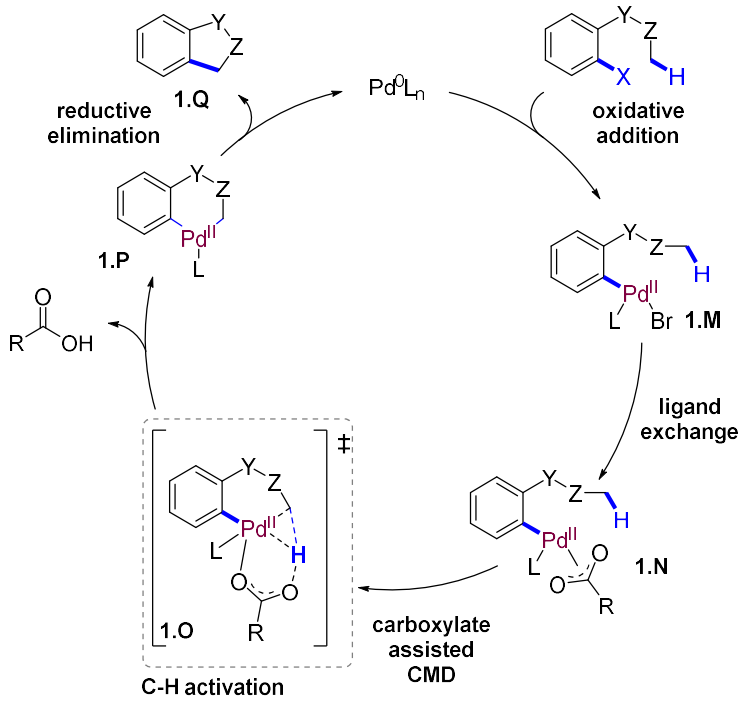


Scheme 31. *Csp^3-H activation strategy for the synthesis of bioactive compounds*

1.3.2. General mechanism and enantiocontrol

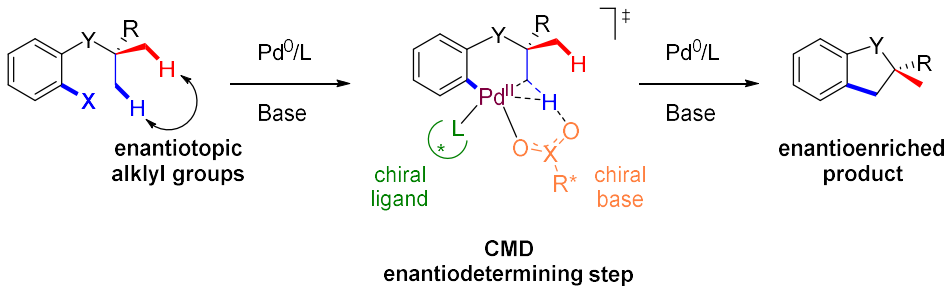
On the mechanistic level, the experimental and computational studies of Davies and McGregor[81] as well as Echavarren and Maseras[82] on the palladium catalyzed Csp^2-H activation/arylation discarded the outdated mechanisms for the C-H activation step (carbopalladation, electrophilic aromatic substitution, σ-bond methatesis)[83] in favor of the

concerted metalation deprotonation (CMD) mechanism.[84] Thanks to their mechanistic studies on Csp^2-H and Csp^3-H functionalization, Baudoin and Fagnou proposed the CMD to be involved in the activationof these C-H bonds.[85] A general mechanism for the above mentioned reaction starts with the oxidative addition of a monoligated Pd^0 complex into the carbon-(pseudo)halide bond of the substrate to form complex **1.M** (Scheme 32). A ligand exchange with a base such as a carboxylate or a carbonate forms the following Pd^{II} intermediate complex **1.N**. This complex undergoes C-H activation with the assistance of the base to form the intermediate palladacycle **1.P** (favored 5-membered > 6-membered >7-membered ring) via the transition state **1.O**. After reductive elimination of **1.P**, the cyclized product **1.Q** is formed and the Pd^0 catalyst is regenerated. The formation of the olefinic product from β-hydride elimination has been previously investigated.[86]



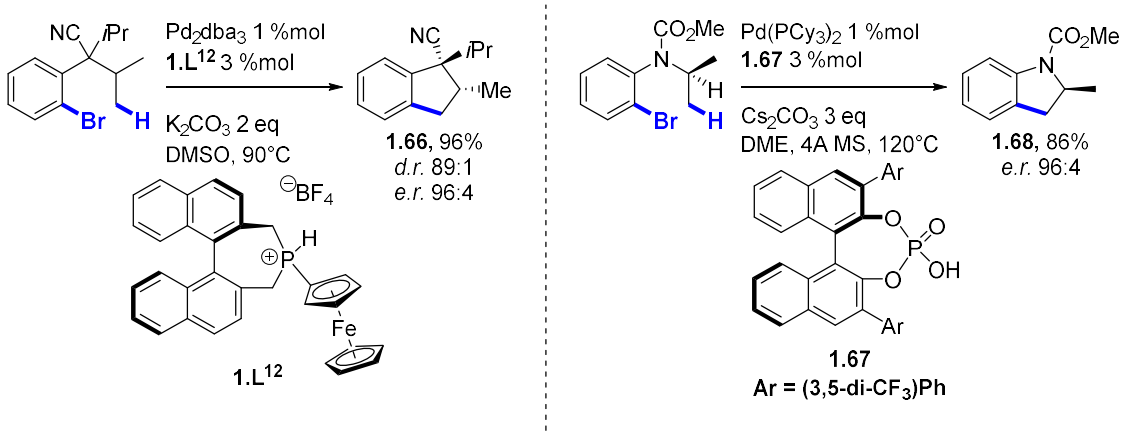
Scheme 32.*General mechanism for the intramolecular Csp^3-H activation/arylation*

Because of the importance of chirality in chemistry, the control of selectivity is of major interest, especially for the synthesis of biologically relevant compounds. The involment of the base and the ligand in the the CMD of the intramolecular Csp^3-H arylation opens two strategies for the enantiocontrol of the functionalized product. Indeed, their respective stereochemical information could be transferred during the CMD to discriminate two enantiotopic activable alkyl groups, thus the CMD would be the enantiodetermining step leading to enantioenriched products (Scheme 33).



Scheme 33. *Two strategies for the enantioselective Csp^3-H activation/arylation*

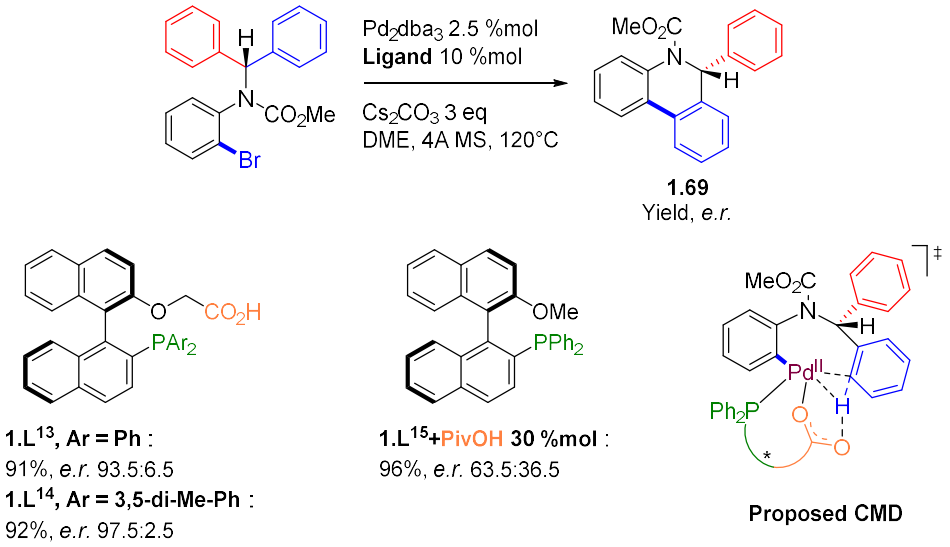
The enantioselective C-H bond activation/functionalization has been mostly investigated in the last decade.[87] Baudoin and coworkers utilized binepine ligand**1.L**^{12} for the enantio- and diastereo-selective synthesis of fused cyclopentanes such as **1.66**. The methodology have shown to be applicable for the activation of methylene C-H bond, but no general method in this case could be elaborated.[88] More recently, the same group reported the first highly enantioselective Pd^0 catalyzed Csp^3-H activation with a BINOL derived phosphoric base**1.67** in presence of an achiral ligand for the synthesis of chiral indolines **1.68**(Scheme 34).[89]This catalytic system was competitive with the previously described methodologies involving chiral phosphines or chiral NHCs.[87b]



Scheme 34. *Application of the ligand and the base stereocontrol in Csp^3-H activation*

The presence of the ancillary ligand and the base at the CMD opens also the opportunity to combine them in a unique bifunctional molecule. The use of bifunctional ligands in Pd^{II}-catalyzed C-H activation has been previously described.[90] In 2018, Baudoin developed the first example of Pd^0-catalyzed enantioselective C-H activation with a chiral binaphtyl-based bifunctional ligandsuch as **1.L**^{13} including a phosphine moiety and a carboxylic acid (Scheme 35).[91] The ligands showed high efficiency and enantioselectivity for a desymmetrizing Csp^2-H arylation providing 5,6-dihydrophenantridines such as **1.69**. The corresponding

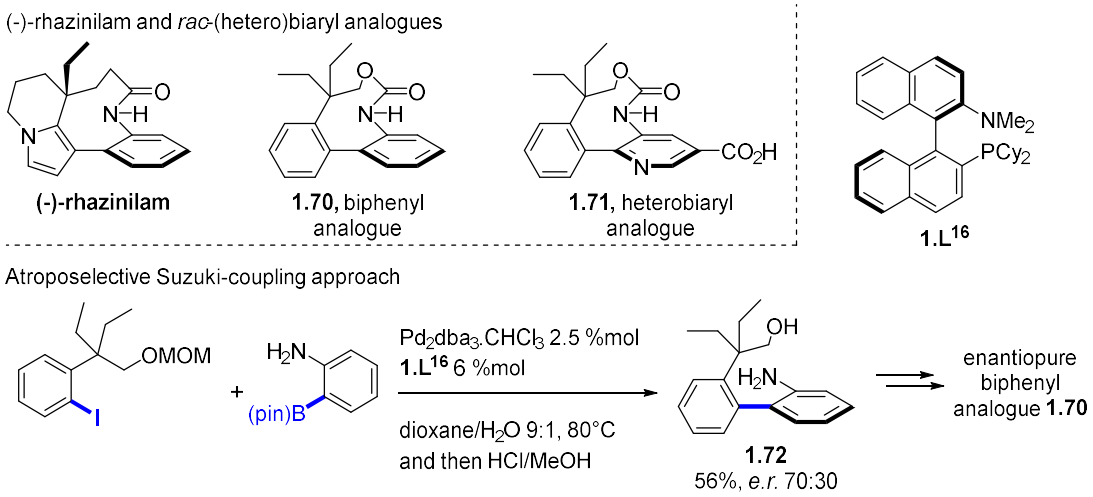
monofunctionnal ligand such as the MOP**1.L**[15], lacking the carboxylic acid function, only induced low enantioselectivities, thus demonstrating the necessity of the bifunctionality in this case. The proposed enantiodetermining step involves a more organized structure at the CMD transition step.



Scheme 35. *First example of Pd*^{0} *C-H activation with a chiral bifunctional ligand*

1.3.3. Early syntheses of bioactive biaryl compounds

The construction of biaryl scaffolds has been an early topic of interest for Baudoin and coworkers. The investigation was focused on the synthesis and the biological evaluation of (–)-rhazinilam analogues (Scheme 36).[92] This natural tetracyclic alkaloid was isolated from various *Apocynaceae*. The molecule posseses an axially chiral phenyl-pyrrole subunit, and a 9-membered median lactam-ring. It was found to have antimitotic properties, with inhibition of tubulin assembly. In addition, the molecule presents activity against various cancer cell lines. As part of a program directed toward the synthesis of (-)-rhazinilam, the authors showed that the biphenyl analogue**1.70** exhibited enhanced properties against tubulin assembly and similar activities against cancer cell lines. Various approaches, including a palladium-catalyzed borylation/Suzuki-coupling, allowed the synthesis of racemic (hetero)biaryl analogues of type **1.71**.[92a,e] An atroposelective Suzuki-coupling was proposed for the synthesis of enantiopure analogues. A large screen of ligand only led to moderate yields and low level of selectivity for the chiral biaryl **1.72** when KenPhos **1.L**[16]was used.[92b]



Scheme 36. *An early approach for the construction of enantiopure rhazinilam analogues.*

Allocolchicine and steganacin are two naturally occurring chiral biaryls that were found to inhibit the tubulin assembly in a similar way to colchicine. A prodrug of *N*-actetyl colchinol caused the selective destruction of tumor vasculature, thus having potential anticancer properties. The stereogenic biaryl axis in steganacin bears a stable a*R* configuration, thanks to the height membered bridging ring conformation that prevents from racemization. On the other hand, the seven-membered ring of allocochicine and *N*-acetylcolchinol allows atropisomerization, and these molecules occur as mixture of equilibrating isomers (Figure 9). The absolute configuration of their biaryl axis has been found to be crucial for their targeted bioactivity. Indeed, the activity is often restricted to the a*R* atropisomers.Baudoin and coworkers proposed enantioselective syntheses of hybrid analogues**1.73**, as well as amino analogues of *N*-acetylcolchinol**1.74**, in order to evaluate their biological properties.[93]

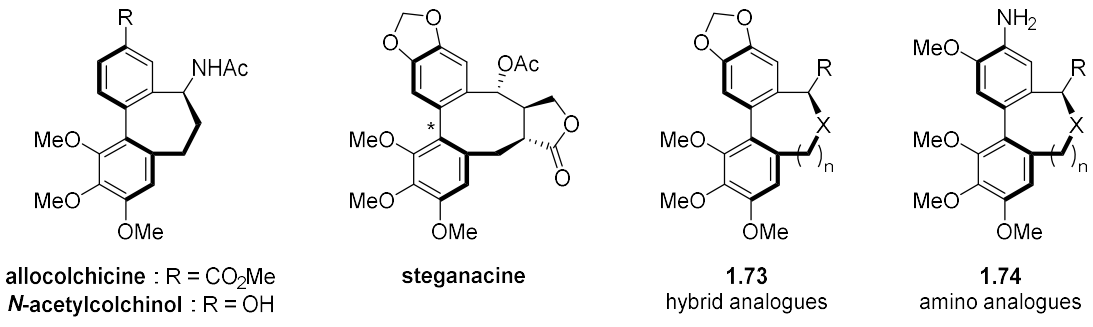
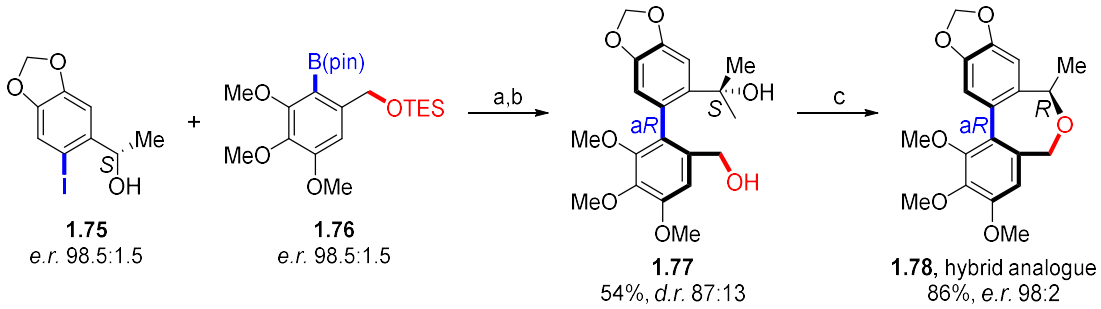


Figure 9. *Bioactive chiral biaryls*

A developed approach consisted in the atropo-diastereoselective construction of the biaryl axis of by Suzuki coupling of a chiral aryl iodide**1.75** with of an achiral pinacol arylborane **1.76**. The selectivity arises from the transfer of chirality from the chiral stereocenter to the

axial bond. Then, the biaryl axis in the intermediate **1.77** relays its stereochemical information to the temporarly destroyed stereocenter in a S_N1-type dehydrative cyclization. *N*-acetylcolchinol hybrid analogues such as **1.78** could be accessed in good yield and high enantiopurity(Scheme 37).[93b]

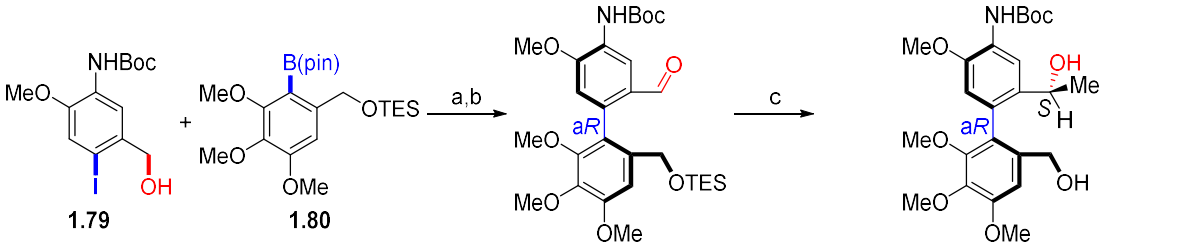


1.75 *e.r.* 98.5:1.5 + **1.76** *e.r.* 98.5:1.5 → **1.77** 54%, *d.r.* 87:13 → **1.78**, hybrid analogue 86%, *e.r.* 98:2

Reaction conditions : a) Pd(OAc) 5 %mol, DavePhos **1.L4** 10 %mol, $Ba(OH)_2.8H_2O$ 1.1 eq, dioxane/H_2O 9:1, 100°C. b) $n$$Bu_4NF$, THF, 20°C. c) TFA 5eq, CH_2Cl_2, -50°C.

Scheme 37. *Access to a N-acetylcholinol hybrid analogue via diasereoselective Suzuki cross-coupling*

Another approach involved the construction of the biaryl axis of **1.81** by racemic Suzuki coupling followed by a subsequent Grignard addition to obtain a diastereoenriched intermediate**1.82** in the synthesis ofthe target racemic amino analogues (Scheme 38).[93d]



1.79 + **1.80** → **1.81** 47%, 2 steps → **1.82** major diastereoisomer + minor (*R*, a*R*) 66%, *d.r.* 87:13

Reaction conditions : a) Pd(OAc) 5 %mol, SPhos **1.L1** 10 %mol, $Ba(OH)_2.8H_2O$ 1.1 eq, dioxane/H_2O 9:1, 100°C (63%). b) TPAP 0.02 eq, NMO 3 eq, CH_2Cl_2, 20°C (75%). c) MeMgBr 3 eq, THF, -78°C.

Scheme 38. *Suzuki coupling and diastereoselective Grignard addition toward a N-acetylcholinol amino analogue intermediate*

1.3.4. Modern syntheses of axially chiral biaryls

The importance of biaryl-based compounds exhibiting an axis of chirality is no longer to demonstrate. Various natural and synthetic biologically active substances bear at least one chiral axis, such as steganacin (*vide supra*) or gossypol.[94] Stereogenic ligands such as BINOL or BINAP are non-negligible inductors for enantioselective synthesis. Moreover, new

materials such as liquid crystals[95] and dyes[96], found their properties based on atropisomeric architecture (Figure 10).

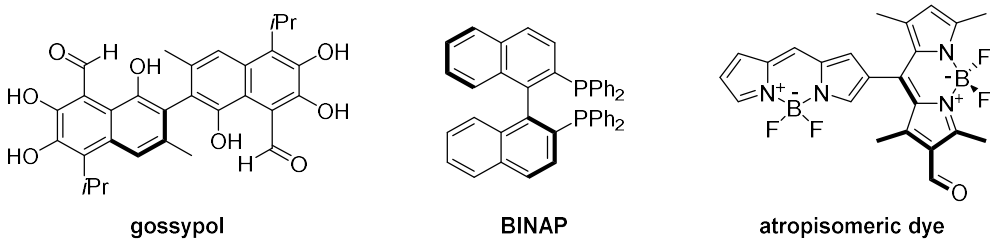
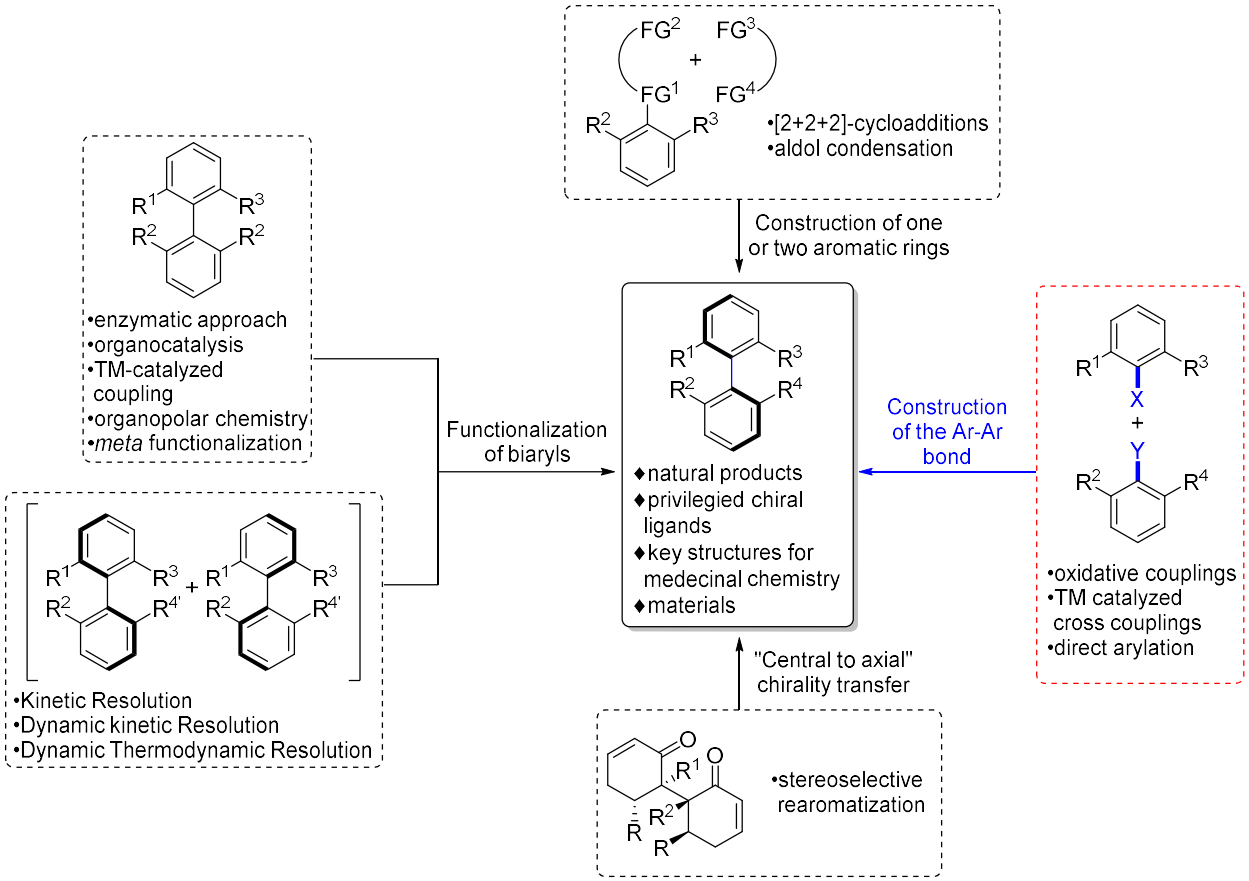


Figure 10. *Examples of stereo-enriched atropisomeric compounds*

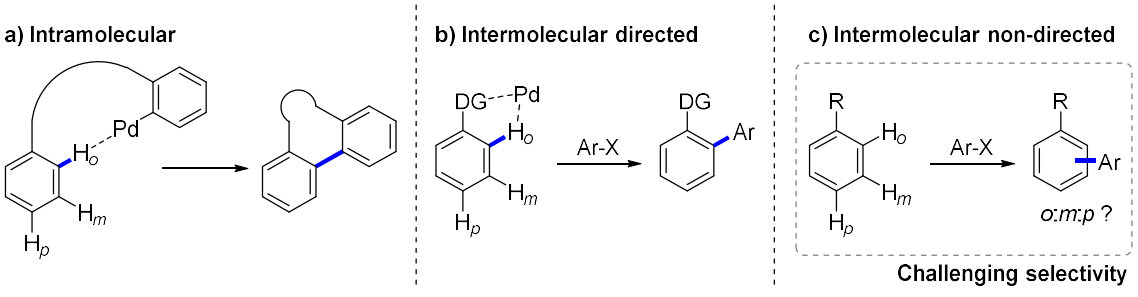
The historical access to atropisomerically enriched backbones was the resolution of racemic mixtures. The advances and development in organic and organometallic chemistry over the 21st century gave new accesses to these scaffolds. To date, numerous methodologies allow the construction of stereoenriched biaryls.[97] The modern approaches generally involve the stereoselective functionalization of racemic or prochiral biaryls, the construction of aromatic ring(s), the stereoselective rearomatization via "central to axial" chirality transfer, but notably the direct construction of the biaryl axis (Scheme 39).[98] These approaches often lie on the use of the appropriate organo- or organometallic catalyst.[99] The use of transition metal catalyzed asymmetric synthesis of axially chiral biaryl compounds has been extensively investigated and recently reviewed;[100] and the discussion will focus on the palladium-catalyzed Csp^2-H activation/arylation for the synthesis of biaryl scaffolds.



Scheme 39. *Modern approaches toward atropisomeric biaryls*

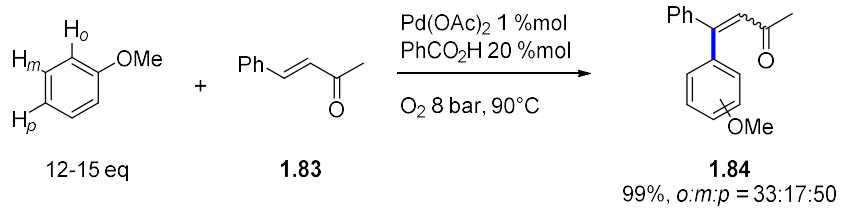
1.3.5. Challenges in palladium catalyzed Csp^2-H functionalization

The first occurrences of the Pd^0 catalyzed intramolecular Csp^2-H arylation appeared in the early 80's, notably with the work of Ames and Bull,[101] for the synthesis of valuable heterocycles.[102] Tajima independently reported the direct arylation of isoxazoles with aryl iodide in presence of a heterogeneous palladium catalyst.[103] These early works interrogated the *o,m,p*-regioselectivity in the direct Csp^2-H arylation of (hetero)arenes; and this challenging point was mainly overcome by intramolecular and/or directed C-H activation/arylation (Scheme 40).[104]



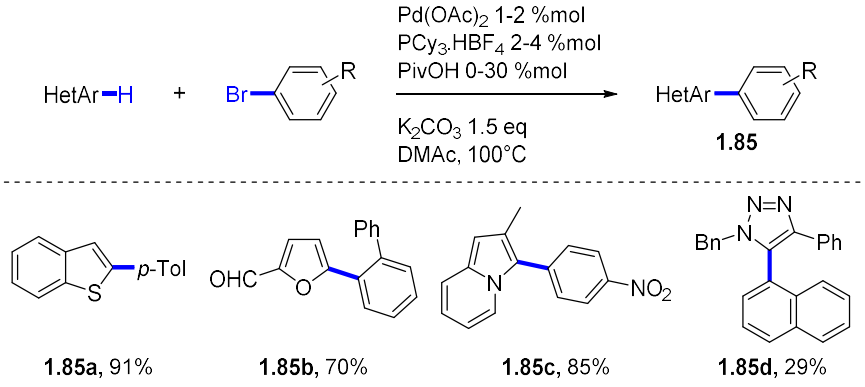
Scheme 40. *Challenges in the selectivity of the Pd-catalyzed C-H arylation*

The very challenging intermolecular undirected Csp^2-H activation/functionalization[105] has been firstly discussed by Fujiwara in the late 60's.[106] In recent reports by Jacobs[107] and Yu,[108] the authors developed a palladium-catalyzed oxidative olefination of arenes, and observed that the functionalized arenes lacking directing groups undergo Csp^2-H activation preferentially at the most electron-rich C-H bond. Nevertheless, no clear regioselectivity was obtained, as depicted for Jacobs's system (Scheme 41).



Scheme 41. *Lack of selectivity in Jacobs's Pd^{II} Csp^2-H olefination*

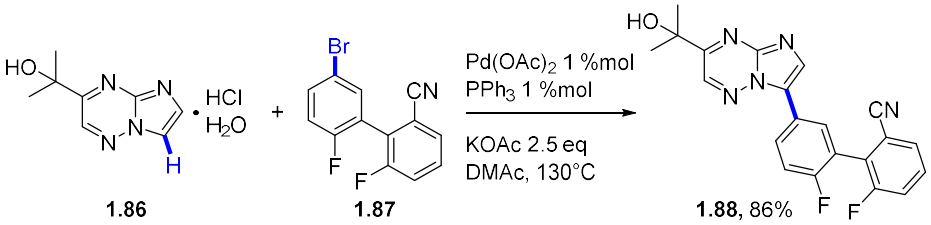
In contrast, the regioselectivity in the Csp^2-H activation of heteroarenes can be high and is mainly influenced by the electronic properties of the C-H bond, as well as its steric accessibility. Fagnou reported a systematic study of the regioselectivity in the direct arylation of heteroarenes under Pd^0 catalysis (Scheme 42). The reaction occurs at the most acidic or nucleophilic C-H bond of the heteroarene, to give various heterobiaryls **1.85**.[109] DFT calculations of the energy barriers for the C-H bond cleavage by CMD correlated well with the experimental observations.[110]



Scheme 42. *Selected examples of Fagnou's directed Csp^2-H arylation*

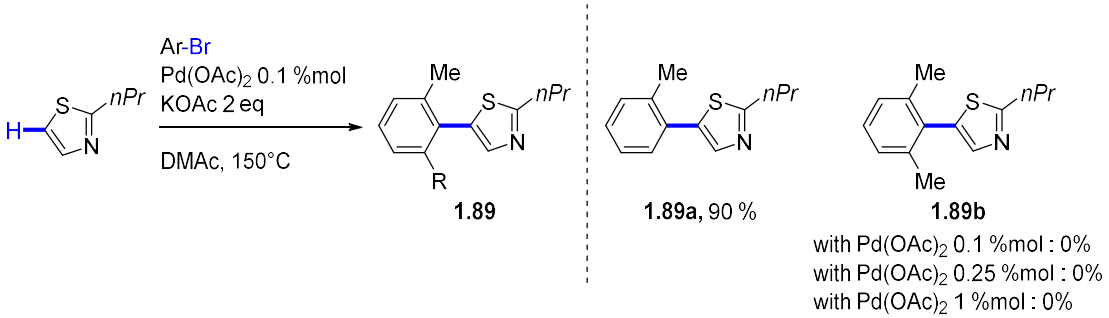
The preferential site selectivity in the non-directed intermolecular arylation of (hetero)arenes had already been taken in account by several research groups for the synthesis of bioactive compounds[111] and new materials.[112] The researchers at Merck demonstrated in 2005 the first

application of transition-metal catalyzed intermolecular Csp^2-H arylation of arenes to the synthesis of GABA agonists such as **1.88** (Scheme 43).[113]



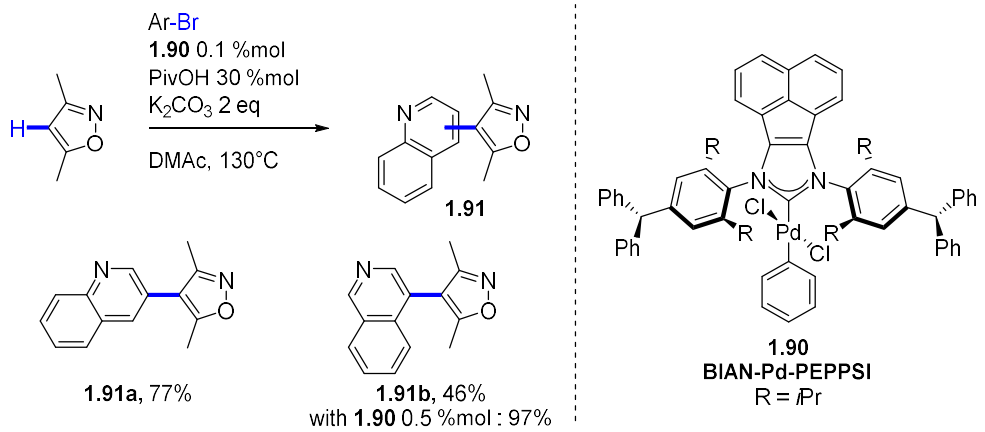
Scheme 43. *First application of intermolecular Pd^0 catalyzed Csp^2-H activation/arylation to the synthesis of bioactive compound*

The developed methodologies generally suffer from the hindrance around the newly formed axis. Indeed, the addition of *ortho* groups commonly shuts the reaction off; and harsher conditions are required, such as the increaseof palladium loading or of the temperature; as well as reaction times. In his ligand-free Pd^0 catalyzed direct arylation of thiazoles, Doucet described the formation of the mono-*ortho*-methylated product**1.89a** in 90% yield, whereas no product **1.89b** could be obtained when using the di-*ortho*-methylbromobenzene, even with higher catalyst loading (Scheme 44).[114]



Scheme 44. *Steric hindrance blocking the formation of biaryl axis*

The new NHC based catalyst **1.90** used by Liu in 2017 proved to be efficient in the direct coupling of several heteroarenes.[115] The arylation of dimethyl isoxazole with 3-bromoquinoline gave **1.91a** in 77% in presence of 0.1 %mol of catalyst at 130°C. In the same condition, the reaction with 4-bromoquinoline only afforded 46% yield of **1.91b**, in consequence of the increased steric hindrance at the *ortho* position. An excellent yield of 97% could be achieved by increasing the catalyst loading to 0.5 %mol (Scheme 45).

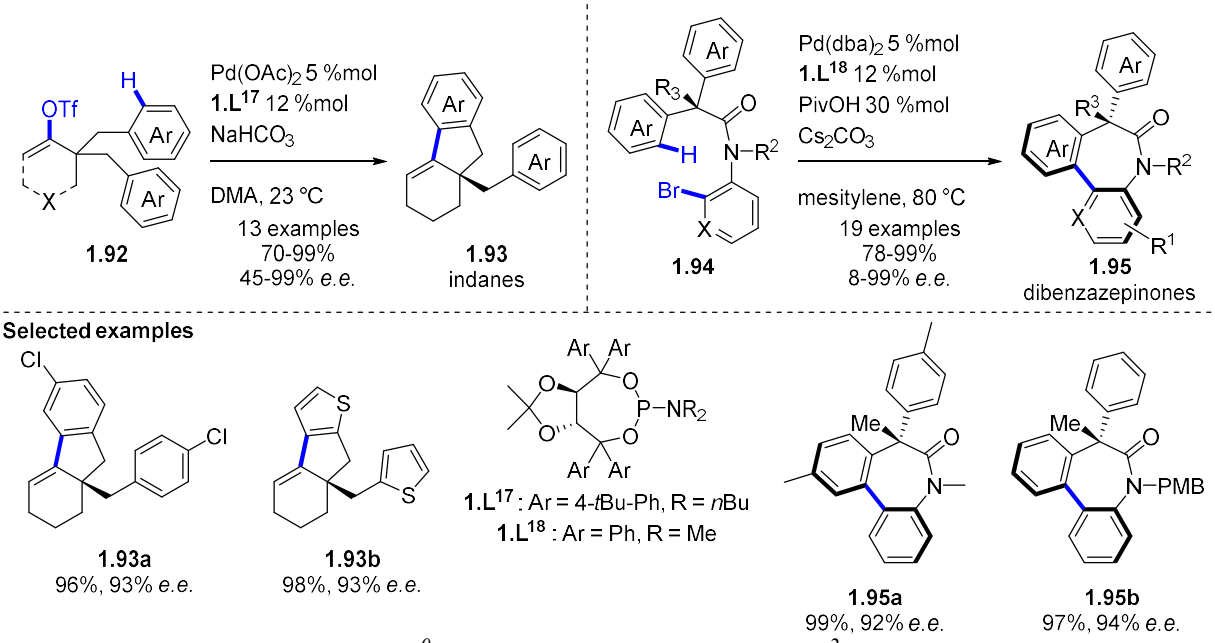


Scheme 45. *Harscher conditions for the formation of congested biaryl axis*

The syntheses of restricted (hetero)biaryl bearing a potential axis of chirality by palladium-catalyzed Csp^2-H arylation are commonly concealed due to the poor reactivity encountered in the construction of the biaryl axis.

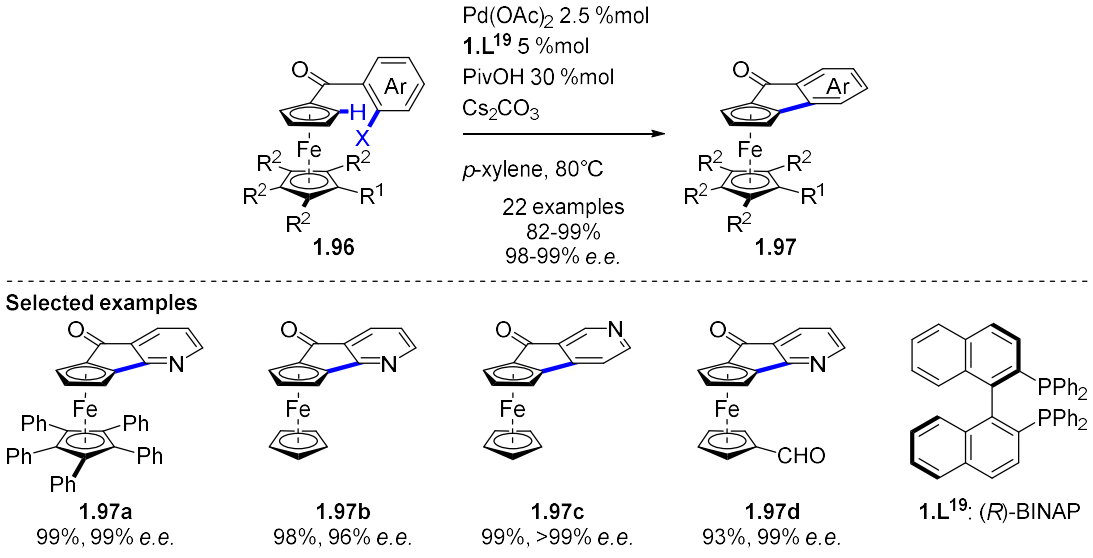
1.3.6. Enantiocontrol in palladium-catalyzed Csp^2-H arylation

The construction of chiral elements by Pd^0-catalyzed Csp^2-H arylation was scarcely reported and only central or planar chirality could be accessed via intramolecular reaction.[116] Cramer and coworkers disclosed in 2009 the first Pd^0-catalyzed enantioselective Csp^2-H desymmetrizing arylation involving the intramolecular arylation of vinyl triflates **1.92** providing chiral indanes **1.93** bearing an all-carbon quaternary stereocenter.[117] The authors discovered that monophosphine ligands displayed high reactivity, and the TADDOL-derived phosphoramidites such as **1.L**[17] provided excellent enantiocontrol. Based on the mechanistic studies of Maseras, Echavarren, Fagnou and Baudoin,[118] the enantiodetermining step was proposed to be the carboxylate-assisted CMD. The methodology was extended to the synthesis of dibenzazepinones **1.95** in 2013 (Scheme 46).[119]



Scheme 46. *First example of Pd^0 catalyzed enantioselective Csp^2-H activation/arylation, and an extension of methodology*

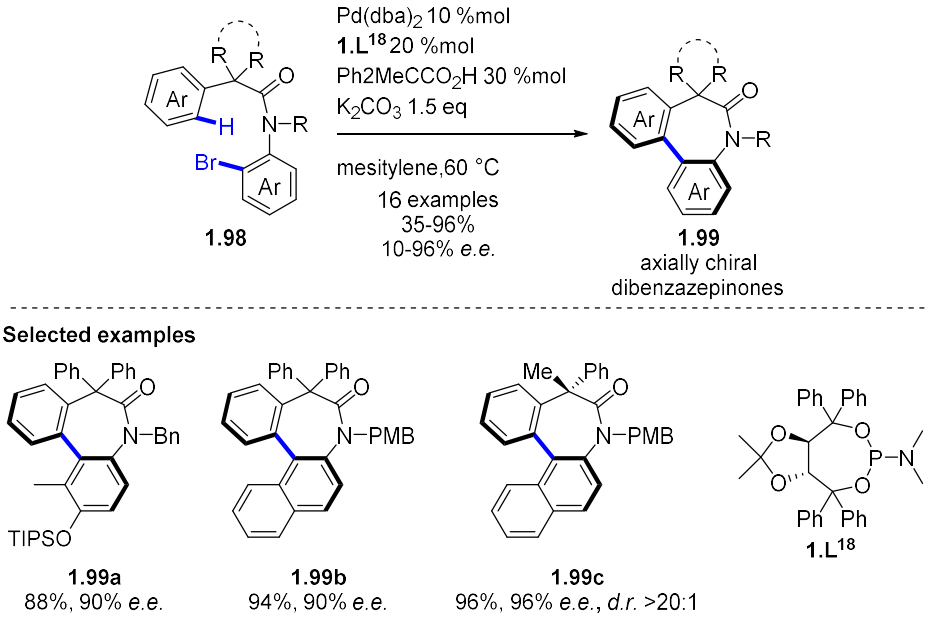
Very high levels of enantioselectivity were obtained in the synthesis of fluoreno- and pyridylferrocenes (planar chirality), notably by employing simple and general reaction conditions comprised of catalytic $Pd(OAc)_2$ and BINAP in presence of Cs_2CO_3 as an inorganic base.[120] Selected examples of the scope of Gu and You in 2015 are depicted in Scheme 47.



Scheme 47. *Construction of planar chirality by Pd^0 catalyzed Csp^2-H arylation*

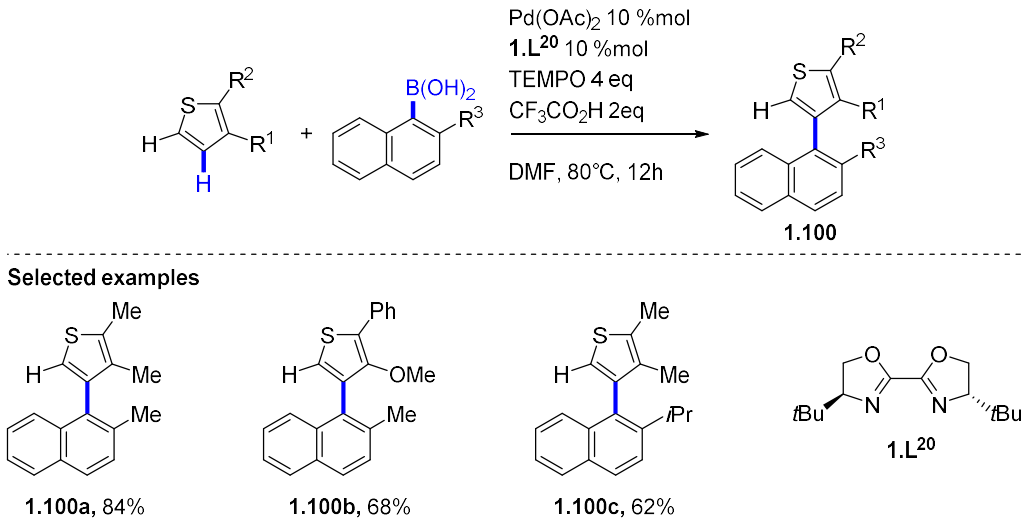
During the writing of this manuscript, Cramer and coworker established the first atroposelective Pd^0-catalyzed Csp^2-H arylation for the synthesis of axially chiral

dibenzazepinones**1.99** in an intramolecular fashion.[121] The direct arylation proceeds in mild conditions and tolerates both electron rich and poor aryls. The hindrance in the *ortho*-position was found necessary to obtain configurationally stable products (Scheme 48).



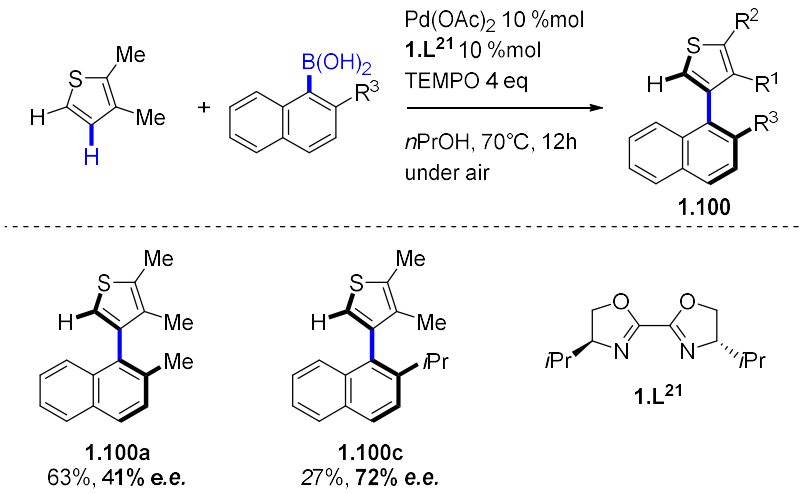
Scheme 48. *Cramer's first atroposelective Pd^0-catalyzed Csp^2-H activation/arylation*

To date, only Itami and Studer have provided an access to the intermolecular Pd-catalyzed atroposelective C-H arylation.[122] In 2012, the authors developed a Pd^{II}-catalyzed direct arylation of thiophenes with hindered arylboronic acid. The reaction proceeds at 80°C in presence of a chiral bisoxazoline**1.L^{20}** as the ligand. Good yields of **1.100** were obtained along with excellent C4 regioselectivities (Scheme 49). The reaction is applicable to other heteroaryls such as benzofurans or indoles.



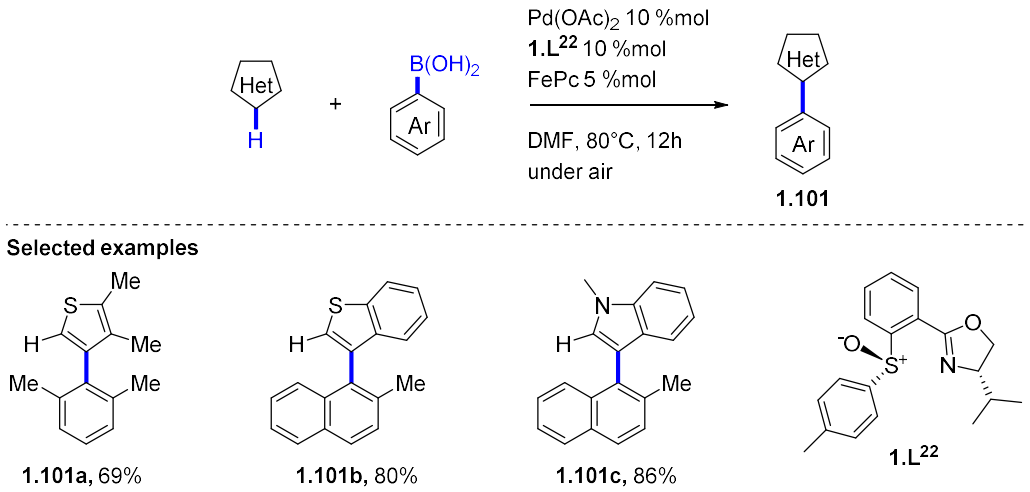
Scheme 49. *Itami and Studer's synthesis of hindered biaryl*

Since the optimal ligands for this reaction are chiral, the selective construction of the biaryl axis was investigated. In first place, the stability of the substituted thiophenes**1.100**toward racemization was evaluated. The rotational barrier of 3-methyl-4-(2-methylnaphtalen-1-yl)thiophene**1.100a** was calculated. The activation energies for the two modes of racemization, comprised between 33.2 kcal/mol and 33.5 kcal/mol, were found to be high enough for the two isomers to exist as stable atropisomers at room temperature. After an extensive screening of conditions, an asymmetric induction was observed. After 12h at 70°C, the enantioenriched **1.100a** was obtained in 41% *e.e.* and in 63% yield. When the steric encumbrance in *ortho*-position was increased by addition of an *i*Pr group, the enantiomeric excess rose up to 72% *e.e.*, to the detriment of the yield. Indeed, the biaryl **1.100c** was obtained in only 27% yield (Scheme 50).[122a]



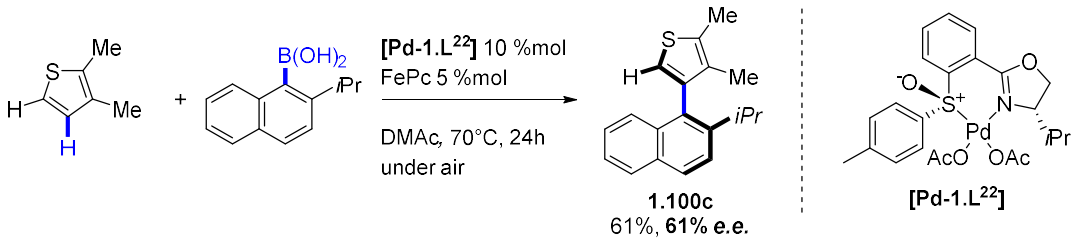
Scheme 50. *First intermolecular Pd-catalyzed atroposelective Csp^2-H arylation*

Despite the clear reactivity-selectivity dilemma, this example established the first step into intermolecular enantioselective biaryl coupling via C-H activation. The following year, Itami improved his catalytic system by using a catalytic iron-based oxidant instead of a stoichiometric TEMPO (Scheme 51).[122b] The reactivity for hindered coupling partner was enhanced and the reaction was also applicable to the oxidative coupling of alkenes. Various heterobiaryls **1.101** were isolated in good yield.



Scheme 51. *Itami's improved Pd-catalyzed C-H arylation*

With this catalytic system, the enantioenriched product**1.100c**was obtained in 61 % *e.e.* and in 61% yield under the optimal conditions (70°C, 24h), thus the enantioselectivity was not increased but the yield was greater than in the previous methodology (Scheme 52). Further mechanistic studies indicated that, contrary to the Pd^0 catalyzed atroposelective C-H arylation, no enantiodetermining CMD step occurs.[123]



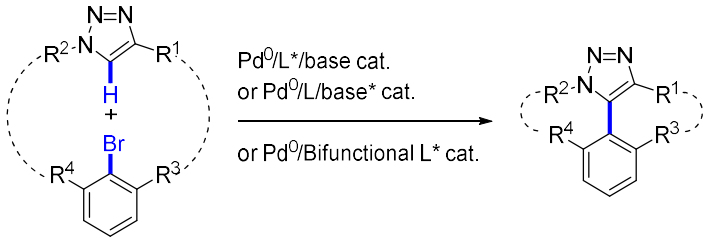
Scheme 52. *Itami's modification for the intermolecular atroposelective Csp^2-H arylation*

1.3.7. Task 2 : atroposelective Pd^0-catalyzed Csp^2-H activation/arylation

Axially chiral (hetero)biaryls became more importants and investigated molecular scaffolds, especially for the development of new active pharmaceutical ingredients. With the experience of the Baudoin group in both atroposelective cross-couplings and catalytic enantioselective C-H activation/ functionalization, the objective is to develop an efficient, general and scalable atropo-enantioselective method based on Pd^0-catalyzed Csp^2-H activation. The aim is to access new (hetero)biaryl scaffolds which could find their application in the synthesis of drugs or drug candidates.

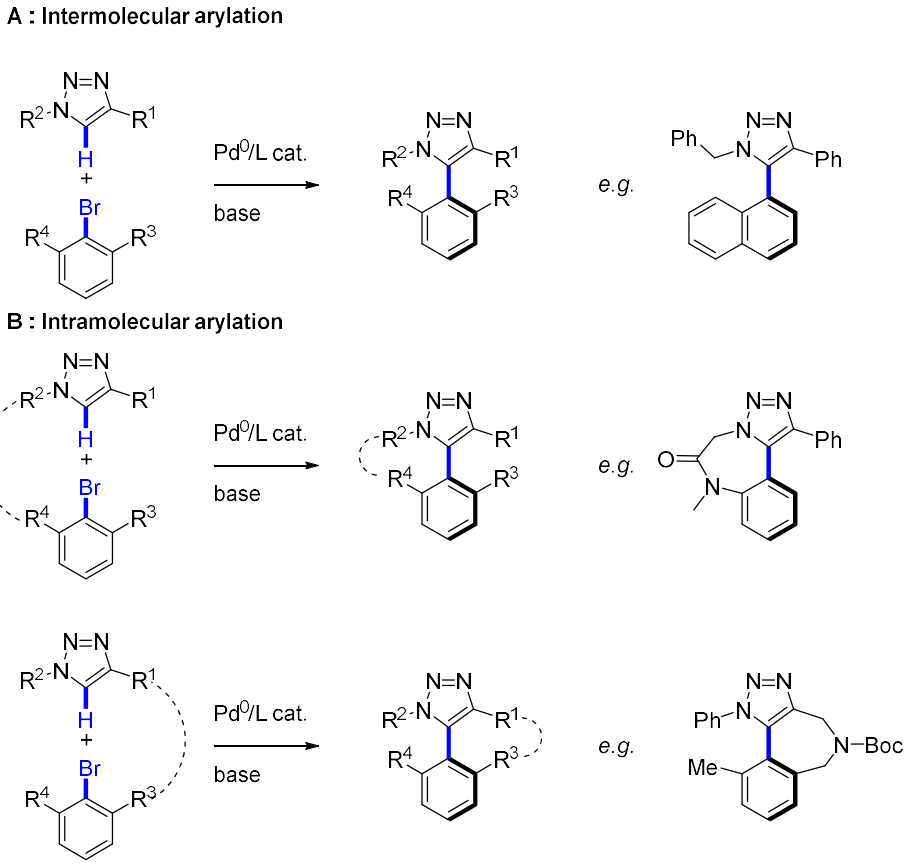
Both intra- and intermolecular C-H arylation has been originally considered, with 1,2,3-triazoles as a starting point. The induction of chirality would arise from 1. the use of a chiral

monodentate ligand in combination with an achiral base, 2. the combination of an achiral ligand with a chiral base, 3. ideally, the use of a chiral bifunctionnal ligand including the ligand and the base (Scheme 53).



Scheme 53. *Proposed model system and inductions*

The model substrates for the C-H activation would be substituted 1,2,3-triazoles in combination with encoumbered aryl bromides. Indeed, close examples of palladium catalyzed arylation in racemic fashion have been reported, and the starting materials are easily accessible through copper-catalyzed azide-alkyne cycloaddition (CuAAC ; "Click" chemistry). The intermolecular reaction would give rise to 5-aryltriazoles, whereas intramolecular reactions would furnish various bridged triazoles (Scheme 54).



Scheme 54. *Model substrates for the atroposelective Csp^2-H arylation*

It will be important to evaluate the configurational stability of our products toward racemization under the reaction conditions. The usually high temperatures (>100°C) required for C-H activation could lower down the selectivity by gradual erosion of the enantiomeric excess over time, and the choice of the substitution around the biaryl axis must be judicious.

A screening of the different types of ligands and/or bases would allow us to identify the most promising catalyst, and the optimization of the reaction conditions as well as a ligand design/synthesis (if necessary) would furnish high levels of enantiocontrol (*e.r.*>95:5).

2. Arylation of *O*-carbamates via Negishi cross-coupling

2.1. Enantioselective α-arylation of *O*-carbamates

2.1.1. Introduction

All along this chapter, the following notation will be used for the protecting/directing groups borne by the alcohols (Figure 11):

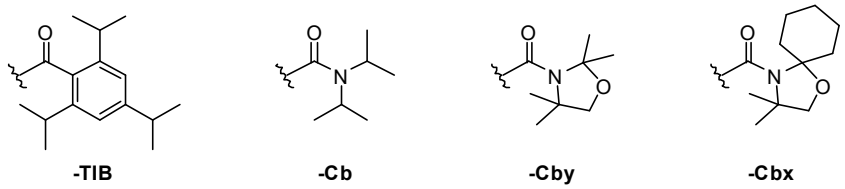
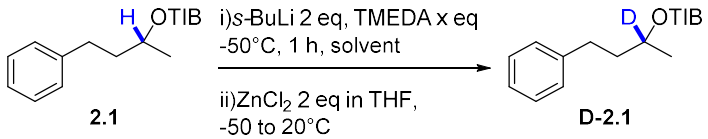


Figure 11. *The protecting/directing groups and their names*

2.1.2. Preliminary study

We started our investigation on the arylation of protected aliphatic alcohols using the deprotonation/lithiation conditions developed within the Aggarwal research group (Table 2).[124] The TIB-protected secondary alcohol **2.1** was deprotonated with *s*-BuLi/TMEDA (2/6 eq.) for 1h at -50°C in CPME, and subsequently quenched with MeOD to obtain the α-deuterated alcohol **D-2.1** in 85% D-integration (entry 1). A lower loading of TMEDA in CPME resulted in a decrease of D-integration (entry 2), as well as in other solvents (entries 3-5). The transmetalation of the organolithium to the organozinc was also attempted by addition of $ZnCl_2$ (2 eq. in THF) to the organolithium at -78°C, and then the warm up to 20°C, but the following quench with MeOD only led to variable proportions of the deuterated alcohol (entry 6). This deuteration was furthermore not reflecting whether or not the transmetalation to zinc occurred and if this complex was stable toward the variation of temperature.



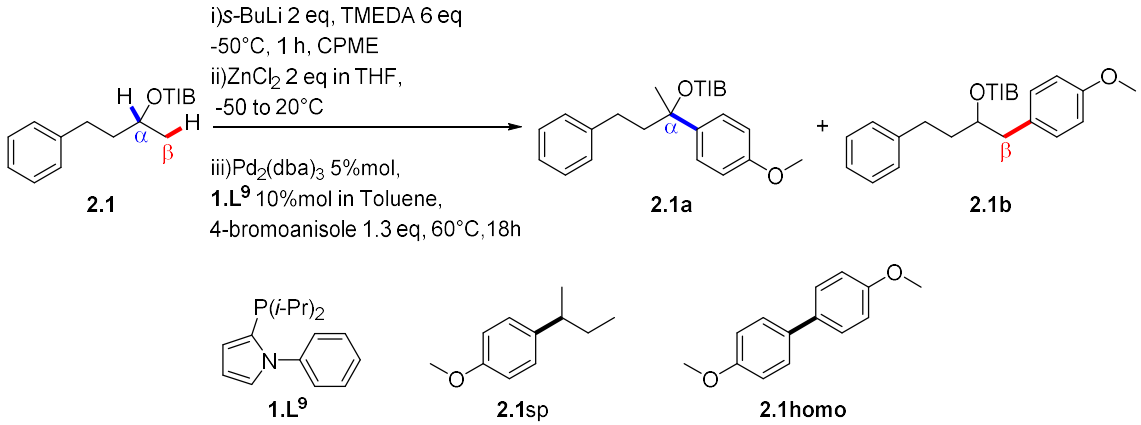
Entry	Conditions	TMEDA eq.	Solvent	Yield D-2.1%[a]	(D-int.%)[a]
1	i), then MeOD	6	CPME	90	90
2	i), then MeOD	2	CPME	90	52
3	i), then MeOD	2	Et_2O	75	40
4	i), then MeOD	2	THF	100	0

5	i), then MeOD	2	Toluene	50	20
6	i), then ii) then MeOD	6	CPME	<50	n.d.

[a]Yields and D-integration determined by ^{1}H NMR.

Table 2. *Variation of conditions for the metalation of* ***2.1***

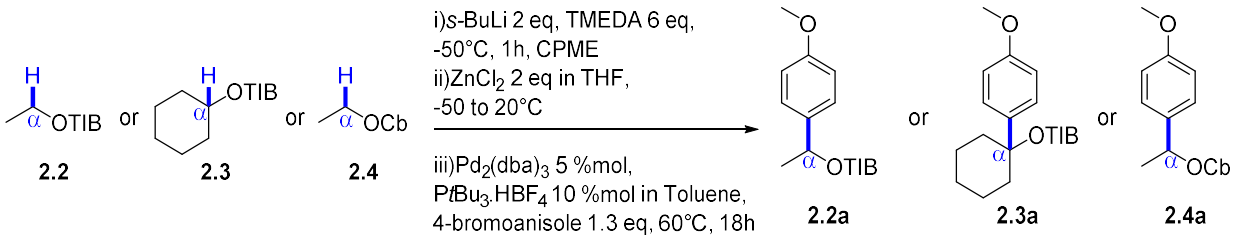
The Negishi cross-croupling was nevertheless attempted. After evaporation of the volatiles under high-vacuum, the assumed α-zincated ester was reacted with 4-bromoanisole (1.3 eq.) in presence of $Pd_2(dba)_3$ (5 %mol) and the ligand (10 %mol), at 60°C for 18h in toluene (Table 3). In presence of the hindered P*t*-Bu_3, the expected α-arylated product **2.1a** was not observed (entry 1). Instead, the side-product **2.1sp** resulting from transmetalation and subsequent coupling of *s*-BuLi, was mainly observed. Likewise, with the more flexible ligand **1.L**[9], no terminal β-arylation product **2.1b** was formed (entry 2). The direct coupling of the organolithium[125] was attempted, but only led to the homocoupling product **2.1homo** (entry 3).



Entry	Conditions	Ligand	Product
1	i), ii), then iii)	P*t*-Bu_3.HBF_4	only **2.1sp**
2	i), ii) then iii)	**1.L**[9]	no **2.1b**
3	i), then iii)	P*t*-Bu_3.HBF_4	only **2.1homo**

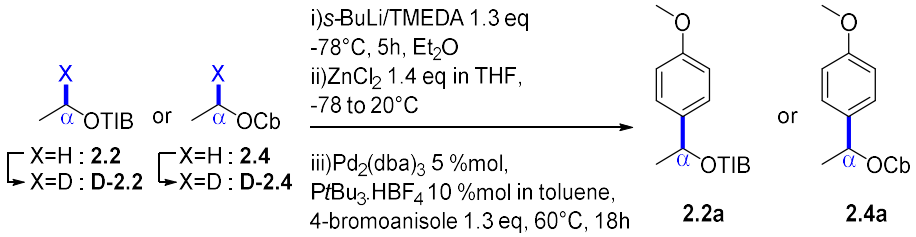
Table 3. *Arylation attempts on* ***2.1***

The TIB-protected ethanol **2.2** and cyclohexanol **2.3** were engaged in the same conditions, with Pt-Bu_3 as the ligand, without success. The reaction with the Cb-protected ethanol **2.4** did not show any efficiency as well (Scheme 55).



Scheme 55. *Arylation attempts on other protected alcohols*

We then turned our attention to the reaction system involving the deprotonation/lithiation step developed by Beak and Hoppe (Table 4).[126] The protected alcohols **2.2** and **2.4** were lithiated with *s*-BuLi/TMEDA (1.3 equivalents) for 5h at -78°C, and then quenched with MeOD. The compound **D-2.2** was obtained in 82% yield and 100% D-integration (entry 1), and **D-2.4** was obtained with a similar yield and D-integration (entry 2), showing the efficiency of the lithiation conditions. The corresponding organozinc intermediates were formed by addition of $ZnCl_2$ (1.4 eq. in THF) at -78°C, before being allowed to warm up to 20°C. After evaporation of the volatiles, the organozinc was subsequently coupled with 4-bromoanisole in presence of $Pd_2(dba)_3$ (5 %mol) and P*t*-Bu_3 (10 %mol) at 60°C for 18h in toluene. The coupling product **2.2a** was not observed (entry 3), but to our delight, the α-zincated carbamate **2.4** underwent Negishi cross-coupling to give **2.4a** in 72% yield (entry 4). This discovery established the feasibility of the α-arylation of protected alcohols.

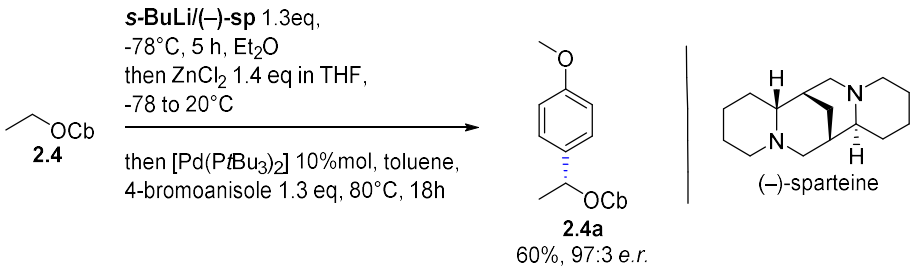


Entry	Substrate	Conditions	Product	Yield% (D-int.%)[a]
1	**2.2**	i), then MeOD	**D-2.2**	82 (100)
2	**2.2**	i), then MeOD	**D-2.4**	86 (100)
3	**2.4**	i), ii), then iii)	**2.2a**	not observed
4	**2.4**	i),ii), then iii)	**2.4a**	72%

[a]Yields and D-integration determined by ^{1}H NMR

Table 4. *Arylation attempts using Beak's deprotonation/lithiation sequence.*

To finish the preliminary study, the substrate **2.4** was deprotonated in presence of (–)-sparteine over 5h at -78°C in Et_2O and the enantioenriched organolithium intermediate was transmetalated to zinc and subjected to Negishi cross-coupling in presence of preformed Pd(P*t*-Bu_3)$_2$. We were pleased to obtain the enantioenriched α-arylated carbamate **2.4a** in 60% yield and with 97:3 *e.r.* (Scheme 56).



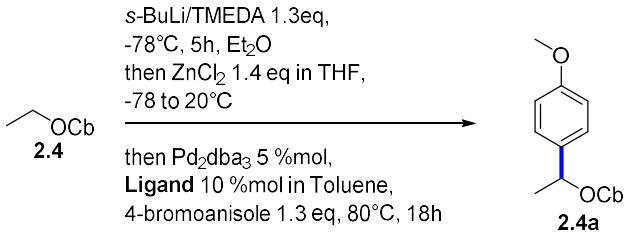
Scheme 56.*Enantioselective α-Arylation attempt with XX4*

This preliminary study established the feasibility of the α-arylation of protected alcohols and its enantioselective version, via a sequential deprotonation/lithiation, transmetalation to zinc and palladium-catalyzed Negishi cross-coupling. The reaction conditions were optimized.

2.1.3. Optimization of the reaction conditions

Optimization of the ligand

The ligand plays an essential role in the reactivity and the (regio)selectivity of the arylation under Negishi cross-coupling conditions. To evaluate the impact of the different ligands on this coupling, the racemic α-zincated carbamate formed from **2.4** was arylated with 4-bromoanisole (1.3 eq) in presence of Pd^0 (from Pd_2dba_3, 5 %mol) and the ligand (10 %mol) (Table 5). Other hindered trialkyl phosphines such as P(Cy)$_3$ and CataCXium A gave lower yields than P*t*-Bu_3 (entries 1-3). Nevertheless, the latter suffered a lack of constancy in the yield of arylated product, using either its HBF_4 adduct or the preformed Pd(P*t*-Bu_3)$_2$ from different provider, in the same stoichiometry (entries 3-5). Buchwald-type ligands, which are known for their efficiency in numerous direct and migrative arylation reactions, were screened. JohnPhos **2.L**[23] and CPhos **1.L**[6], bearing respectively a –P*t*-Bu_2 and a –PCy_2 moiety, gave yields below 3% (Table 5, entries 6-7). PhDavePhos **2.L**[24] gave a lower yield than its more electron-rich analog DavePhos **1.L**[4] and comparable yield to XPhos **1.L**[3] and BrettPhos **2.L**[25], in a range of 20% to 29% (entries 8-11). The arylation in presence of RuPhos **1.L**[2] showed a higher reactivity (43% yield). A comparable yield was obtained when the preformed RuPhos Pd G3 [**1.L**[2]**-PdG3]** was used (Entries 12-13).



Entry	Ligand	Yield%[b]
1	$P(Cy)_3$	<5
2	CataCXiumA	19
3	P*t*-Bu_3.HBF_4	(72)
4[a]	Pd(P*t*-Bu_3)$_2$ (Sigma-Aldrich)	22
5[a]	Pd(P*t*-Bu_3)$_2$ (Strem)	(50)
6	JohnPhos **2.L**[23]	<3
7	CPhos **1.L**[6]	<3
8	PhDavePhos **2.L**[24]	20
9	DavePhos **1.L**[4]	29
10	XPhos **1.L**[3]	25
11	BrettPhos **2.L**[25]	20
12	RuPhos **1.L**[2]	43 (39)
13[a]	RuPhos PdG3 [**1.L**[2]**-PdG3]**	46

[a]The Pd complex (10 %mol) was used. [b]GCMS yield with dodecane as an internal standard, isolated yield in brackets.

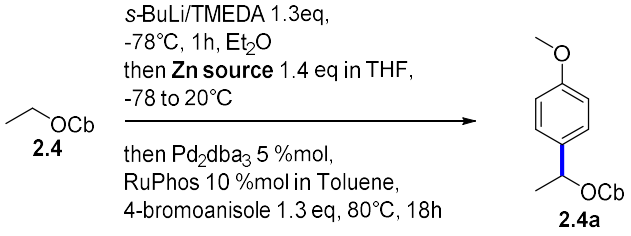
Table 5.*Effect of the ligand on the α-arylation reaction*

The free RuPhos **1.L**[2]was selected as the ligand of choice for this reaction, in combination with Pd_2dba_3. Indeed, this ligand was also more readily available than its preformed catalytic precursor [**1.L**[2]**-PdG3]**.

Optimization of the zinc source

$ZnCl_2$ in THF was used in the first place as it has been the zinc source for transmetalation in, for example, the direct and migrative arylations of *N*-Boc-amines. The racemic organolithium was formed with *s*-BuLi/TMEDA (1.3 eq.) as in the above optimizations, but only for 1h at -78°C in Et_2O. Indeed, a control experiment on the deuteration step showed that 1h only was necessary for the complete deprotonation/lithiation of the carbamate **2.4**. The organolithium was then transmetalated with the corresponding zinc source (1.4 eq. in THF) at -78°C for 30 min and then warmed-up to 20°C over 30 min. After

evaporation of the volatiles, the organozinc was submitted to a Negishi cross-coupling under the previously defined conditions (Table 6). $ZnBr_2$ and ZnI_2gave lower yields than $ZnCl_2$ (entries 2-3), where ZnF_2 did not provide any arylated product (entry 4). Surprisingly, the carboxylates provided higher yields than the halides. Commercially available $Zn(OAc)_2$ increased the yield to 63%, whereas $Zn(OPiv)_2$ and $Zn(OTFA)_2$ afforded the arylated product in average yields (entries 5-7).



Entry	Zinc Source	Yield%[a]
1	$ZnCl_2$	43 (39)
2	$ZnBr_2$	29
3	ZnI_2	16
4	ZnF_2	0
5	$Zn(OAc)_2$	63 (55)
6	$Zn(OPiv)_2$	55 (51)
7	$Zn(OTFA)_2$	51

[a]GCMS yield with dodecane as an internal standard, isolated yield in brackets.

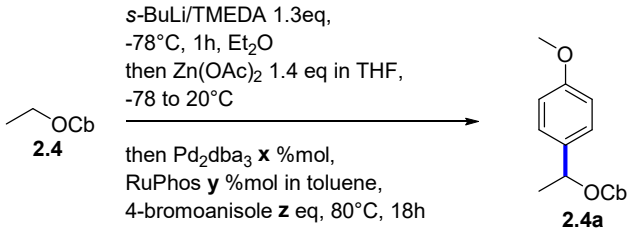
Table 6.*Variation of the zinc source for the transmetalation step*

A critical effect of the zinc salt on the outcome of the reaction was observed. $Zn(OAc)_2$ proved to be superior to $ZnCl_2$, and was selected as the ideal zinc source for the transmetalation step in our standard procedure.

Variation of the catalyst and the electrophile loadings

The catalyst loading was decreased to evaluate the possibility of using less palladium and less ligand in this arylation reaction (Table 7). This also reflects the robustness of the catalytic system for this Negishi cross-coupling. The loading was divided by two to reach 5 %mol of Pd/L, and afforded a similar yield than with 10 %mol of Pd/L(entries 1-2). A significantly decreased yield was observed with only 2.5 %mol of the catalytic system (entry 3). When the latter was decreased to 1 %mol, the yield decreased to only 25% (entry 4). A

loading of 5 %mol of the catalytic system, with respect to the carbamate, was chosen to continue the optimization. The stoichiometry of the electrophile was also decreased to 0.7 eq. with respect to the carbamate, and we were pleased to observe a crucial increase to 77% yield of the arylated product (entry 5). With this lower load of 4-bromoanisole, the stoichiometry of the catalytic system was also tested. The decrease of Pd/L loading to 10 %mol with respect to the arylbromide (equivalent to 7 %mol with respect to the carbamate) afforded a slightly lower yield, as well as with 5 %mol with respect to the arylbromide (entries 6-7). Further lowering of the catalyst loading resulted in a poor yield (entry 8).



Entry	x %mol	y %mol	z eq.	Yield% [a]
1	5	10	1.3	63 (55)
2	2.5	5	1.3	58
3	1.25	2.5	1.3	51
4	0.5	1	1.3	25
5	5	10	0.7	77 (70)
6	3.5	7	0.7	(73)
7	1.75	3.5	0.7	(71)
8	0.88	1.75	0.7	(39)

[a]GCMS yield with dodecane as an internal standard, isolated yield in brackets.

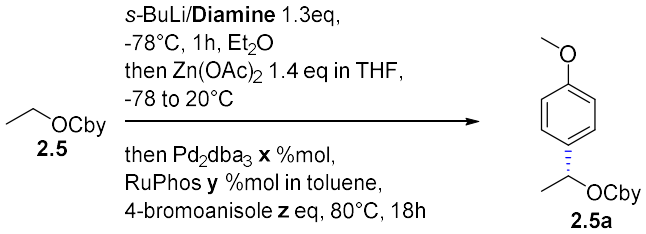
Table 7. *Variation of the catalyst and the electrophile equivalents*

With the variation of the catalyst and the electrophile loading, **2.4a** was afforded with 71% yield in presence of a minimized amount of catalyst (Pd_2dba_3 1.75 %mol / RuPhos 3.5 %mol) and of the electrophile (0.7 eq.) ; thus defining the new standard catalyst loading for this Negishi cross-coupling.

Alternative directing group

In parallel, the Cby-protected alcohol **2.5** has been submitted to the same reaction conditions, in order to estimate the potential of another directing group (Table 8). The intermediate racemic organozinc was formed, and engaged with 10 %mol of the catalytic

system in presence of 1.3 eq of 4-bromoanisole, to afford an average yield (entry 1). Furthermore, the α-zincated **2.5** was prepared in an enantioselective fashion and engaged in the Negishi cross-coupling. We were very satisfied to obtain a similar yield, but with an excellent *e.r.* of 99:1 when using (–)-sparteine as the diamine (entry 2). The equivalents of catalyst and electrophile were switched to those defined in the previous section. We were then enchanted to obtain more than 80% yield of **2.5a** with both protocols, and an excellent *e.r.* of 99.5:0.5 (entry 3-4), showing the efficiency of the protocols and a full transfer of chirality along all the steps of the arylation sequence.



Entry	x %mol	y %mol	z eq	diamine	Yield %[a]	*e.r.*[b]
1	5	10	1.3	TMEDA	44	*rac*
2	5	10	1.3	(–)-sp	44	99:1
3	1.75	3.5	0.7	TMEDA	81	*rac*
4	1.75	3.5	0.7	(–)-sp	86%	99.5:0.5

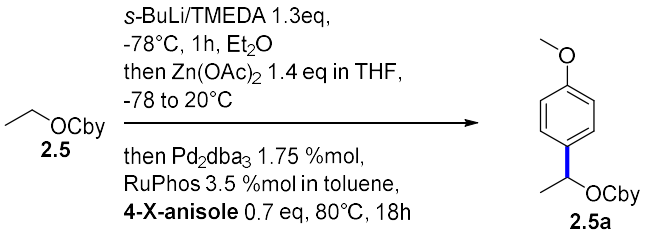
[a]Isolated yields.[b]*e.r.* valuedetermined by HPLC analysis on a chiral stationnary phase.

Table 8. *α-arylation on an alternative carbamate*

This study sealed our standard conditions and brought us to the last step of optimization, which was the evaluation of the most suitable electrophile.

Evaluation of the ideal electrophile

The coupling partner is of critical importance in cross-coupling reactions (Table 9). The electrophiles propose different reactivities toward the insertion of palladium in the (pseudo)halide bond, thus changing the outcome of the reaction. The optimization was carried out with 4-bromoanisole (entry 1) and other (pseudo)halides were engaged in the Negishi cross-coupling with the α-zincated **2.5** as the coupling partner. The yield decreased to 70% when 4-iodoanisole was used (entry 2), and the reaction was dramatically shut down when using 4-chloroanisole to afford only 7% of the **2.5a** (entry 3). The corresponding triflate only generated 40% yield (entry 4).



Entry	4-X-anisole	Yield%[a]
1	4-Br-anisole	81
2	4-I-anisole	70
3	4-Cl-anisole	7
4	4-OTf-anisole	41

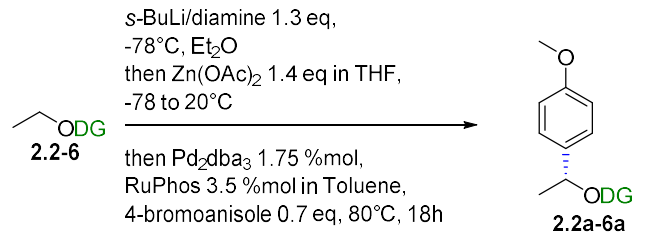
[a]Isolated yields.

Table 9. *Effect of the electrophile*

Bromo-electrophiles were selected as the coupling-partner of choice. With these conditions in hand, two additional directing groups were evaluated in this coupling as the first part of the reaction scope.

2.1.4. Study of the directing group

The known directing groups allowing the deprotonation/lithiation in α-position of protected alcohols were screened under the previously optimized conditions, in both racemic and enantioselective fashion, with 4-bromoanisole as the coupling partner (Table 10). The racemic protocol involves the deprotonation/lithiation step in presence of TMEDA for 1h, while the enantioselective protocol involves the initial deprotonation/lithiation in presence of (–)-sparteine for 5h, under otherwise identical conditions. The Cb carbamate **2.4** afforded **2.4a** in 71% for the racemic protocol, and furnished the enantioenriched **2.4a** in 51% yield and 98:2 *e.r.* (entry 1). The aminal derived Cby **2.5** and Cbx **2.6** gave improved yields and *e.r.* for both protocols (entry 2-3). In addition, the TIB ester **2.2** proved to be a competent reaction partner in this coupling, despite reduced yield and *e.r.* (entry 4).



	Yields[a]

Entry	Product	DG	TMEDA	(–)-sparteine	*e.r.*[b]
1	**2.4a**	Cb	71	50	98:2
2	**2.5a**	Cby	81	86	99.5:0.5
3	**2.6a**	Cbx	87	70	99.5:0.5
4	**2.2a**	TIB	47	62	92.5:7.5

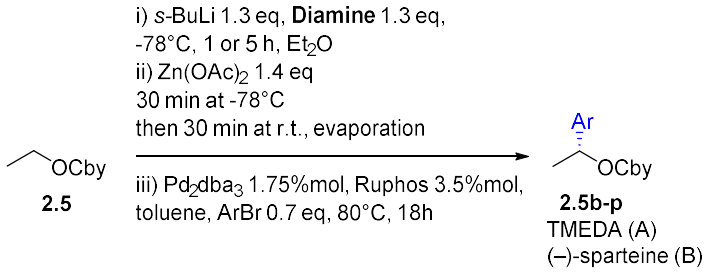
[a]Isolated yields.[b]*e.r.* valuedetermined by HPLC analysis on a chiral stationnary phase.

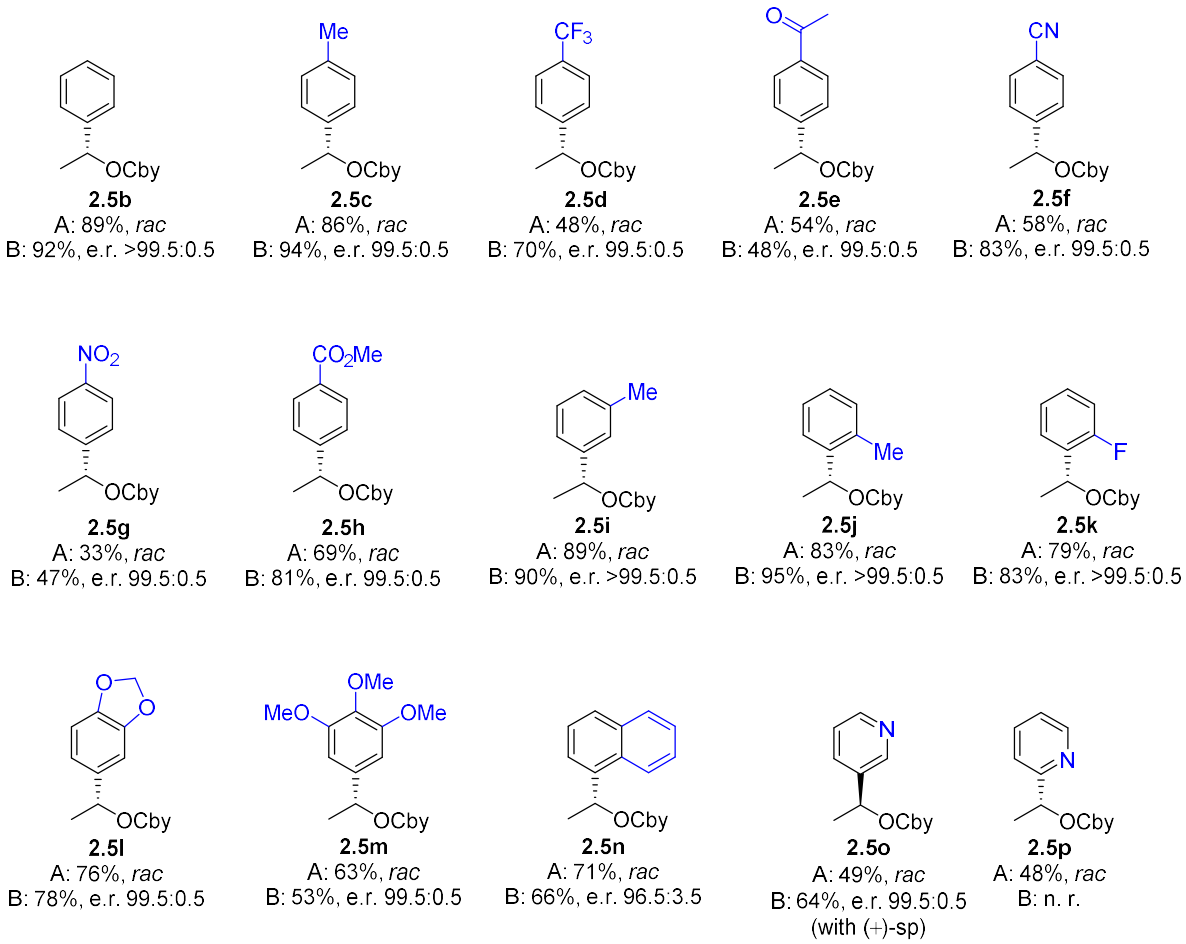
Table 10. *Study of the directing groups under the optimized conditions.*

The Cby carbamate was selected for the study of the reaction scope and limitations with respect to the bromo-electrophile.

2.1.5. Scope and limitations of the electrophile

The reaction proved to be compatible with a variety of aryl bromides, in both racemic (with TMEDA,for 1h, A) and enantioselective (with (–)-sparteine, for 5h, B) protocols (Scheme 57), including unsubstituted (**2.5b**), *para*- (**2.5a**,**c-h**), *meta*- (**2.5i**), *ortho*- (**2.5j-k**), as well as polysusbtituted arenes (**2.5l-n**). The mild conditions of the Negishi coupling step also tolerated sensitive functional groups such as a ketone (**2.5e**), nitrile (**2.5f**), nitro (**2.5g**) and methyl ester (**2.5h**). In all cases, excellent enantioselectivities were obtained, when (–)-sparteine was used as the diamine. 3-bromopyridine was also reacted successfully in both protocols (**2.5o**), whereas the 2-bromo isomer only reacted in the racemic reaction (**2.5p**).





Scheme 57.*Scope with respect to the aryl electrophile*

The absolute configuration of the compound **2.5f** was determined to be (*R)* by X-Ray diffraction analysis and the configurations of the other products were therefore assigned as (*R)* by analogy (Figure 12).

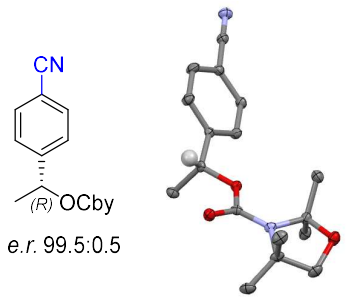


Figure 12. *X-Ray diffraction analysis of* ***2.5f***

The scope of the electrophile was nevertheless limited (Figure 13). Methyl 2-bromobenzoate did not undergo Negishi coupling, presumably because of the steric hindrance at the *ortho-*

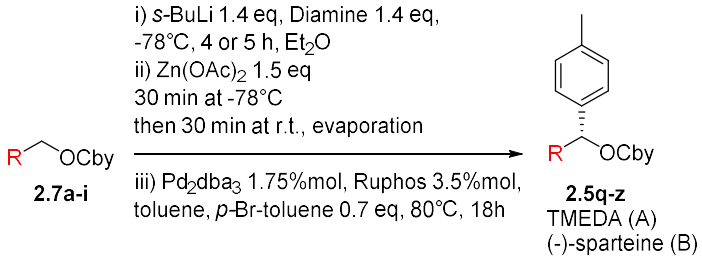
position. The other heteroarylhalides gave only low coupling yields (below 15%), as well as the alkenyl and the alkynyl electrophiles. Thus, there use was not further explored.

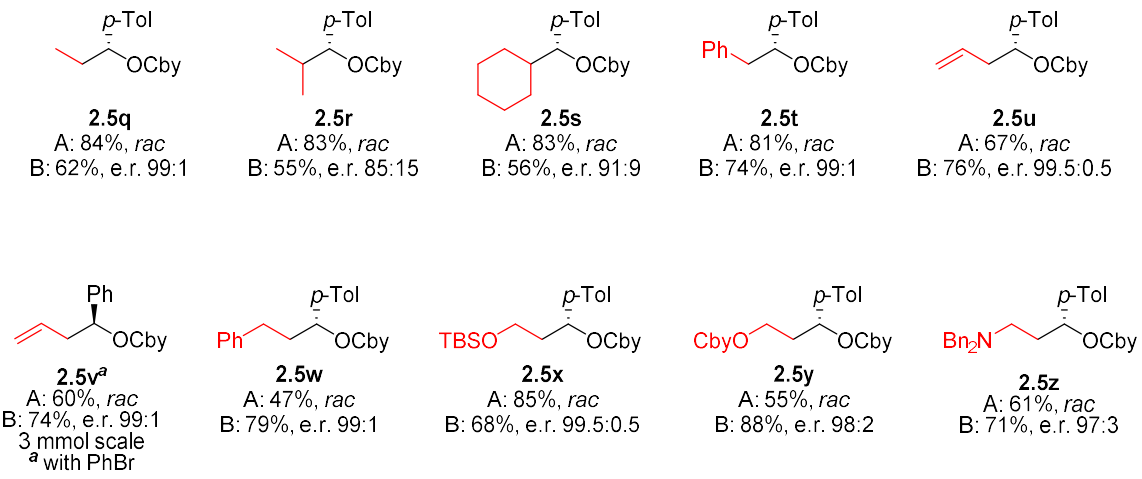
Figure 13. *Unsuccessfull electrophiles in the α-arylation conditions*

Next, the scope with respect to the carbamate was investigated.

2.1.6. Scope with respect to the carbamate reactant

Both protocols allowed the arylation in moderate-to-very good yields with *p*-bromotoluene as the coupling partner (Scheme 58). The reaction time for the lithiation in the racemic version was nevertheless increased to allow a complete deprotonation. Excellent *e.r.* were achieved using (−)-sparteine for the carbamates bearing a secondary carbon at the β-position (**2.5q**, **t-u**, **w-z**). Lower yields and *e.r.* were obtained for carbamates containing a more hindered tertiary βcarbon (**2.5r-s**). Several usefull functional groups were tolerated, such as a benzene ring (**2.5t, w**), an olefin (**2.5u-v**), a TBS-protected alcohol (**2.5x**) and a dibenzyl-amine (**2.5z**). The bis-carbamate **2.5y** underwent an efficient and exclusive monoarylation. The reaction could also be scaled-up to 3 mmol (5-folds scale) with (+)-sparteine and phenylbromide to offer equally good performance (74% yield, *e.r.* 99:1), as shown with compound **2.5v**.





Scheme 58. *Scope of the a-arylation in carbamate*

A variety of other carbamates were not successful with these protocols (Figure 14). The *N*-substituted aminoethanols **2.8a-b** only provided low yields. The Cby-protected benzylic alcohol underwent Negishi coupling in 39% yield of **2.9**, after tuning of the lithiation time, but was not further considered. Surprisingly, benzyl protected propanediol was arylated exclusively at the benzylic position to give **2.10** in a rather low yield of 36%. *N*-Boc-*N*-methyl propanolamine was found to react selectively in α-position to the nitrogen to afford **2.11** in 33% yield.

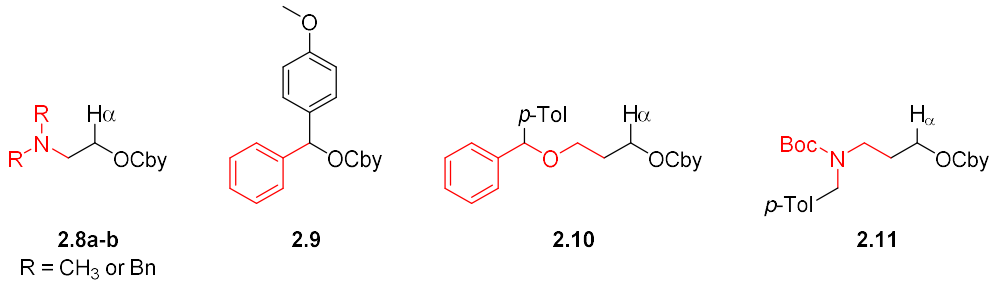


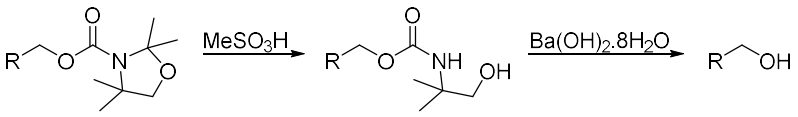
Figure 14.*Unsuccessfull carbamates under the α-arylation conditions*

In our aim to synthesize valuable building blocks and to demonstrate the versatility of this methodology, the deprotection of the scalemic α-arylated carbamates was performed.

2.1.7. Deprotection of the carbamates

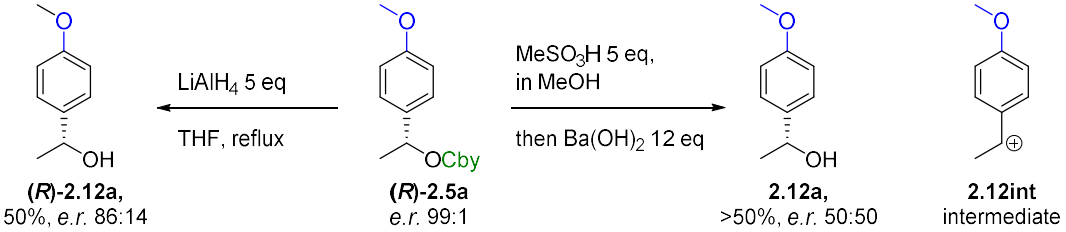
The Cby group was also chosen for its relative easy removal. Where the Cb group is nearly impossible to cleave, even under really harsh conditions, typically 10 equivalents of $LiAlH_4$ in refluxing THF for several days; the *N,O*-acetonide of the Cby is opened with

$MeSO_3H$ in refluxing methanol, and thereafter the hydroxyl group plays a role in presence of $Ba(OH)_2.8H_2O$ to release the free alcohol (Scheme 59).



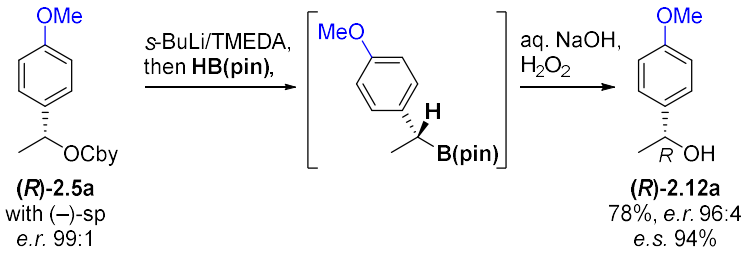
Scheme 59.*Standard deprotection of the Cby group.*

On the one hand, the cleavage of the directing group was attempted on the enantioenriched ***(R)*-2.5a**(*e.r.* 99:1) by reduction with $LiAlH_4$. The benzylic alcohol ***(R)*-2.12a** was obtained in 50% yield, but with a reduced *e.r.* of 86:14. On the other hand, the acido-basic conditions were applied and the free alcohol was obtained in average to good yields. Unfortunately, the *e.r.* was completely eroded during the deprotection to give only the racemic alcohol. We assumed that the benzylic carbocation **2.12int** formed under these conditions, leading to the racemic **2.12a** (Scheme 60).



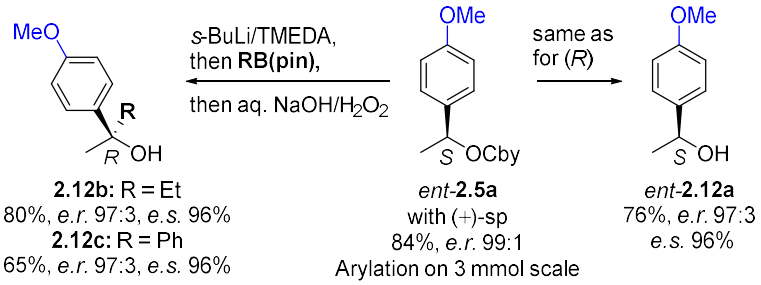
Scheme 60. *Deprotection attempt on the α-arylated carbamate* ***2.5a****.*

The protocols reported by Aggarwal and co-workers[127] for the Cb group were adapted as a formal deprotection of these benzylic carbamates. The lithiation/borylation/oxydation sequence was performed with HB(pin) from carbamate ***(R)*-2.5a**to give the desired alcohol in 78% yield and an *e.r.* of 96:4, thus exhibiting a very good enantiospecificity (*e.s.* 94%, Scheme 61).



Scheme 61. *Deprotection of* ***(R)-2.5a*** *via Aggarwal's lithiation/borylation sequence.*

Likewise, the (*S*)-enantiomer of **2.5a** was obtained using (+)-sparteine in a 3 mmol scale asymmetric arylation, and its lithiation/borylation/oxidation afforded **(*S*)-2.12a** with a similar yield and enantiospecificity. The (*R*)-configured tertiary alcohols **2.12b** and **2.12c** were obtained similarly using the organoboronates EtB(pin) and PhB(pin), respectively, in place of the pinacolborane. Both showed an excellent preservation of the optical purity (*e.s.* 96%, Scheme 62).

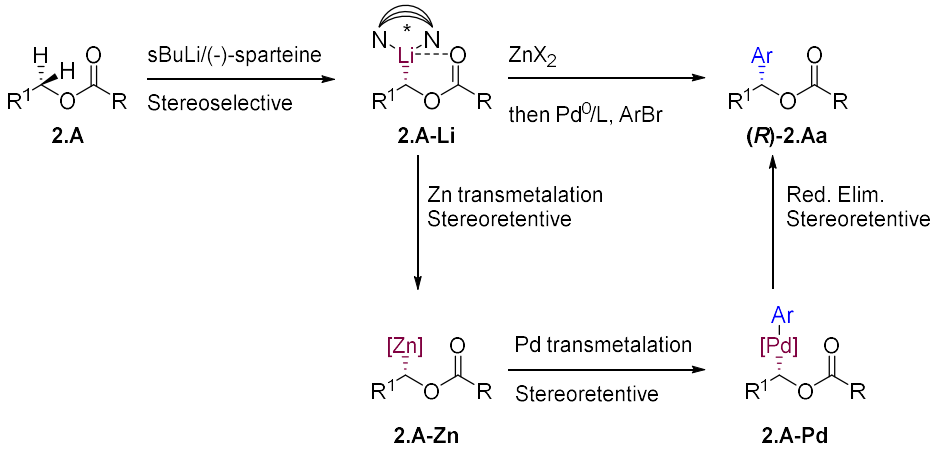


Scheme 62. *Access to 2° and 3° alcohols using Aggarwal's methods.*

The deprotection of the carbamates demonstrated the versatility of the α-arylation methodology, which coupled to Aggarwal's lithiation/borylation methodology provides a divergent access to very enantioenriched secondary and tertiary alcohols as valuable building blocks, with an excellent enantiospecifity all along the transmetalation steps.

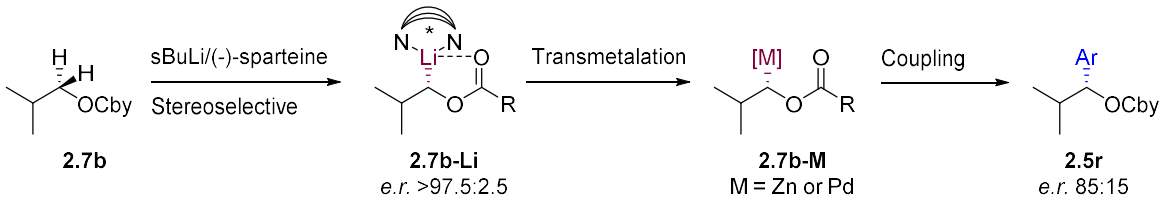
2.1.8. Mechanistic insights

As shown earlier, the methodology provides highly enantioenriched α-arylated *O*-carbamates. The chiral diamine controls the selectivity during the deprotonation/lithiation step. The use of (–)-sparteine induces the deprotonation of the pro-*S* proton in α-position to give intermediate **2.A-Li**, which undergoes transmetalation to zinc in a stereoretentive manner to give **2.A-Zn**. The stereospecific course of the transmetalation has been studied by Nakai and co-workers[128] and exemplified in the methodology of Taylor and co-workers.[129] The reductive elimination takes place without inversion of configuration and the products were assigned as being (*R*) thanks to the crystal structure of **2.5f**, thus demonstrating the enantioretention of the transmetalation to the organopalladium **2.A-Pd** during the Negishi coupling (Scheme 63).



Scheme 63. *Stereoretentive course of the α-arylation.*

Carbamates **2.5r** and **2.5s** bearing a more hindered tertiary carbon at the β-position were obtained in lower *e.r.*, but the (−)-sparteine mediated lithiation of the carbamate precursor of **2.5r** was reported to occur with an *e.r.*>97.5:2.5.[130] This erosion of *e.r.* arises thus more likely from the partial racemization of the corresponding organozinc or organopalladium intermediate, due to the neighboring steric hindrance (Scheme 64).



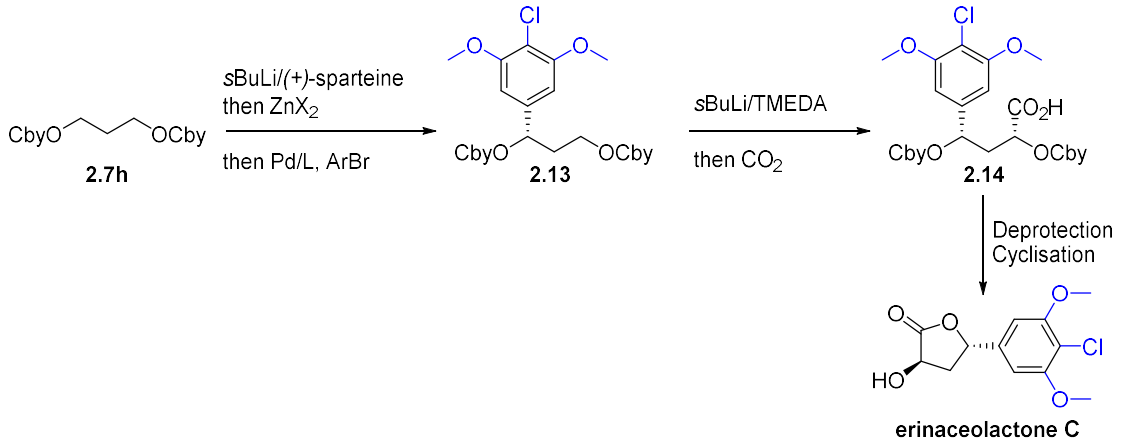
Scheme 64. *Partial racemization in the arylation of **2.7b***

It is remarkable to observe that the configuration of secondary and tertiary alcohols **2.12a-c** is controlled by the initial sparteine-mediated lithiation of the primary carbamate**2.5**, followed by a sequence of 5 discrete stereospecific steps, including :

- Li-Zn transmetalation
- Zn-Pd transmetalation and reductive elimination affording **2.5a**
- Stereoretentive lithiation
- Borylation followed by the 1,2-rearrangement
- Oxidation of the boronic ester

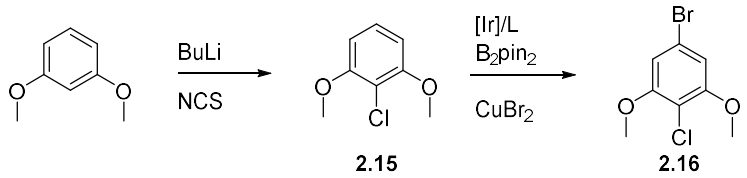
2.1.9. Application in total synthesis

With the collaboration of Yann Baumgartner,[131] we attempted to apply the enantioselective arylation methodology in total synthesis. The first target was Erinceolactone C, a natural lactone isolated from the culture broth of *Hericium Erinaceus*, and known as a plant growth inhibitor. No synthesis of this compound has yet been described. The synthetic approach involves the enantioselective arylation of bis-carbamate **2.7h** using our new methodology, a substrate-directed asymmetric carboxylation, and a deprotection/lactonisation sequence (Scheme 65).[132]



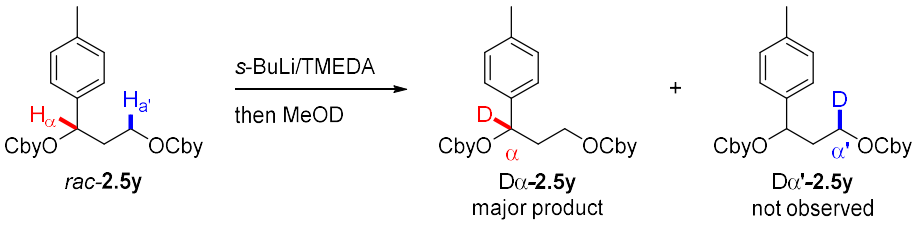
Scheme 65. *Proposed synthetic approach of Erinaceolactone C*

A synthetic pathway for the synthesis of the required trisubstituted aryl bromide **2.16** involves a directed *ortho*-lithiation/chlorination step to access **2.15** followed by an iridium-catalyzed *meta*-selective borylation/copper mediated bromination sequence (Scheme 66).[133]



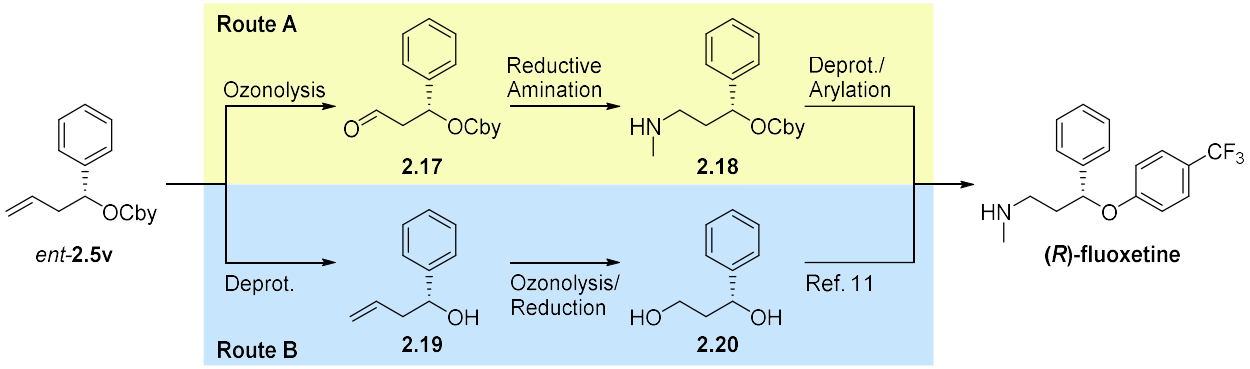
Scheme 66. *Proposed pathway for the synthesis of the trisubstituted aryl bromide*

In a first time, a deuteration experiment was run on product *rac*-**2.5y**to determine the regioselectivity of the deprotonation/lithiation sequence in view of the carboxylation step. Indeed, the directed deprotonation with s-BuLi in presence of TMEDA could occur either on the activated but hindered benzylic α-position, or at the desired α'-position. Unfortunately, only benzylic deuteration was observed and the synthesis was not further explored (Scheme 67).



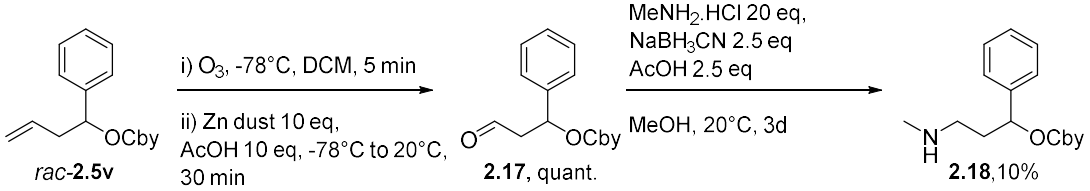
Scheme 67. *Regioselectivity of the deprotonation/lithiation of rac-7y*

We then turned our attention to the synthesis of fluoxetine (Prozac), a blockbuster antidepressant. Two routes were envisaged from the arylation product product **2.5v** (Scheme 68). The first approach involves the ozonolysis of the terminal insaturation, followed by the reductive amination with $MeNH_2$ to obtain the key *O*-α-arylated 1,3-aminopropanol (Route A). The latter would subsequently be deprotected and arylated to obtain the desired target. The second route involves the deprotection of **2.5v**, the ozonolysis of the insaturation and the subsequent carbonyl reduction to obtain the enantiopure *O*-α-arylated 1,3-propanediol **2.20**, a key intermediate in a synthetic approach of (*R*)-fluoxetine by Genêt and coworkers (Route B).[134]



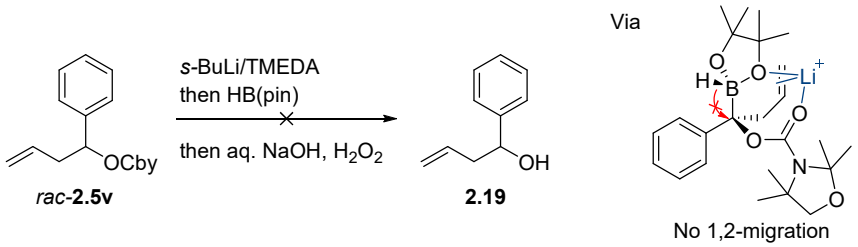
Scheme 68. *Synthetic approaches to (R)-fluoxetine from* ***2.5v***

The ozonolysis followed by the addition of zinc dust (10 eq) and acetic acid (10 eq) in Route A afforded the aldehyde **2.17** in quantitative yield. Unfortunetly, the following reductive amination was low yielding, and after a screen of numerous reducing agents, only 45% of the 1,3-aminopropanol was observed in the crude mixture. The desired compound **2.18** was isolated in only 10% yield (Scheme 69), which was not sufficient for a further application.



Scheme 69. *Development of Route Atoward Fluoxetine*

The second route also proved to be challenging. Indeed, Aggarwal's deprotonation/lithiation/borylation sequence with pinacolborane, followed by oxidation, did not lead to the deprotected product **2.19**. Only starting material or degraded product could be observed under classical conditions. It is proposed that the coordination of the unsaturation to the lithium in the intermediate boronate complex blocks the 1,2-migration of the hydride, as discussed by Aggarwal and coworkers in a previous report (Scheme 70).[135] The addition of 12-crown-4, water and TMSCl, as disclosed in the latter report, did not trigger the reaction.

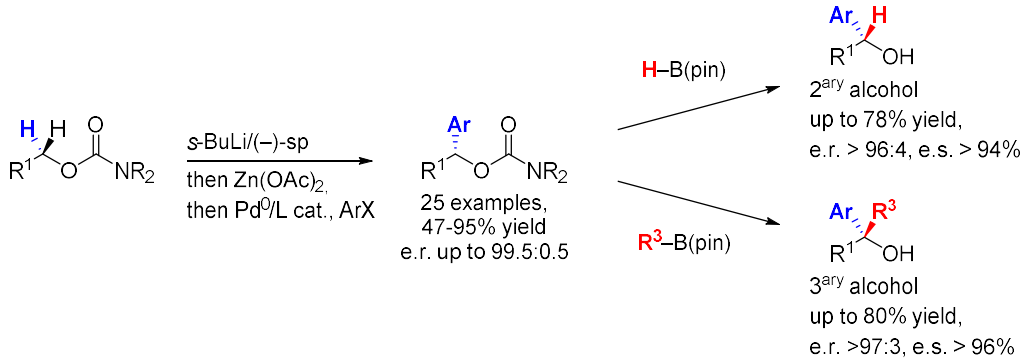


Scheme 70. *Unsuccessful deprotection of* ***2.5v***

In the same time, the scope of the reaction was completed and the training period of Yann Baumgartner ended. No further development for the method application was investigated.

2.1.10. Conclusion

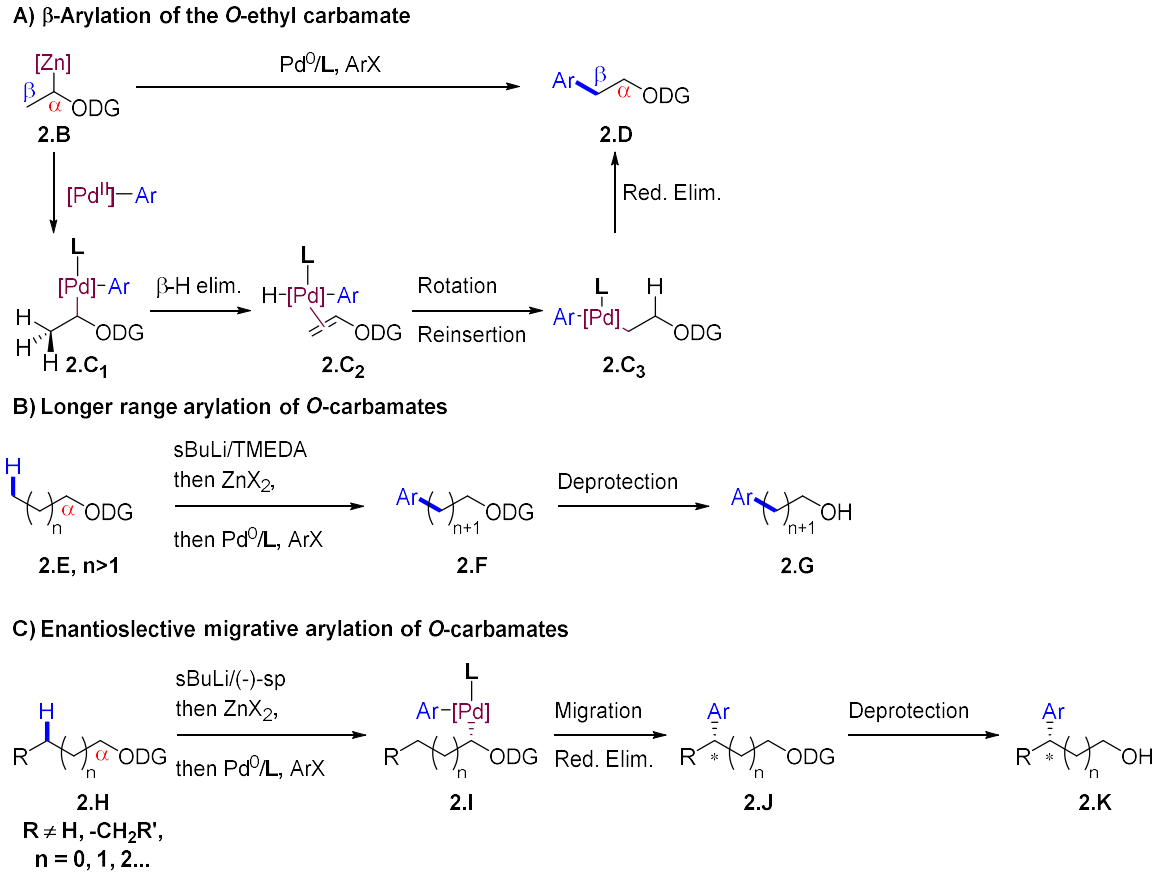
In this chapter, a general methodology for the enantioselective α-arylation of *O*-carbamates was described. The high enantioenrichment of the benzylic carbamates relies on the stereoselective deprotonation/lithiation with sparteine. The mild conditions of the Negishi cross-coupling allow the use of various useful and sensitive functional groups. This method, combined with Aggarwal's lithiation/borylation/oxidation sequence, provides a concise and divergent access to enantioenriched secondary and tertiary benzylic alcohols that complements other enantioselective methods (Scheme 71).[136]



Scheme 71. *Enantioselective α-arylation of O-carbamates*

2.2. Attempts toward the β-Arylation of *O*-carbamates

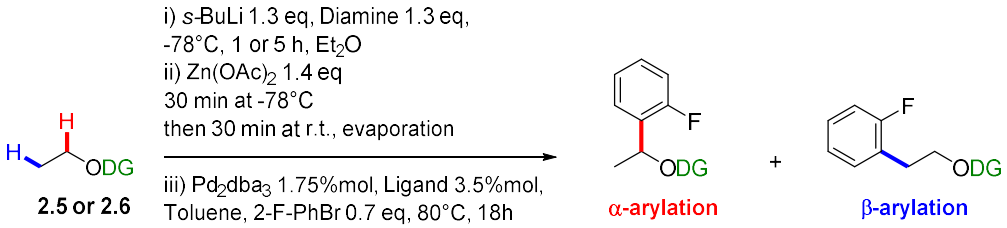
Greatly motivated by our results, and in view of the previous successful projects on the migrative arylation of *N*-Boc amines, we aimed the ligand-controlled migrative arylation of *O*-carbamates. The initial proposition involved the formation of the α-zincated carbamate of type **2.B** with the protocol developed for the α-arylation. The organozinc would be submitted to Negishi cross-coupling in presence of the adapted ligand. After installation of the palladium in the α-position such as in **2.C$_1$**, the favored β-hydride elimination, followed by rotation and reinsertion, would give rise, after reductive elimination, to the corresponding β-arylated carbamate of type **2.D** (Scheme 72, A). The methodology could ideally be adapted to longer chains such as **2.E** and the migration to the terminal position as in **2.F** would afford an array of terminal arylated alcohols of type **2.G** after deprotection (Scheme 72, B). In addition, the migration could occur toward a non-terminal position, thus forming a stereogenic center. The application of Hoppe's technology to install enantioselectively the palladium at the α-position (**2.I**) would potentially result in the enantiospecific migrative arylation (**2.J**) to obtain highly valuable building blocks of type **2.K** after deprotection (Scheme 72, C).



***Scheme 72.** β-arylation and longer range arylation of the O-carbamates*

2.2.1. Ligand controlled β-arylation of *O*-carbamates

In a first time, carbamate **2.5** was lithiated and transmetalated to zinc. The organozinc was engaged in the Negishi cross-coupling under the α-arylation conditions, in presence of 1-bromo-2-fluorobenzene, but with different ligands (Table 11). Not surprisingly, only the α-arylated product was observed when RuPhos **1.L**[2] was used (entry 1). The use of more flexible pyrrole-based ligands (**1.L**[9-10], **2.L**[26]) which proved to be effective in previous migrative couplings in the Baudoin group, led exclusively to the α-arylated carbamate (entries 2-4). The imidazole-based cataCXium PICy underwent the same pathway (entry 5). The steric bulk of the more hindered Cbx group of **2.6**, in combination with bulky Buchwald-type ligands, did not bring the desired push effect to force the migration (entries 7-8). The use of more flexible pyrrole- or imidazole- based ligands was unsuccessful as well (entries 9-13). In all cases, no β-arylated product was observed.



Entry	S.M.	DG	Ligand	α/β ratio[a]
1	2.5	Cby	RuPhos **1.L**[2]	100/0
2	2.5	Cby	**1.L**[10]	n.r.
3	2.5	Cby	**1.L**[9]	100/0
4	2.5	Cby	**2.L**[26]	100/0
5	2.5	Cby	CataCXium PICy **2.L**[27]	100/0
6	2.6	Cbx	RuPhos **1.L**[1]	100/0
7	2.6	Cbx	BrettPhos **2.L**[25]	100/0
8	2.6	Cbx	DavePhos **1.L**[4]	100/0
9	2.6	Cbx	**1.L**[11]	n.r.
10	2.6	Cbx	**1.L**[9]	100/0
11	2.6	Cbx	**2.L**[26]	100/0
12	2.6	Cbx	**1.L**[8]	100/0
13	2.6	Cbx	CataCXium PICy **2.L**[27]	100/0

[a]The ratios were determined by GCMS

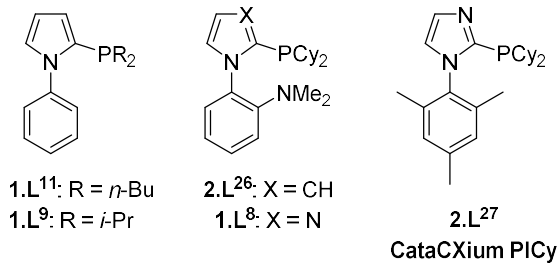
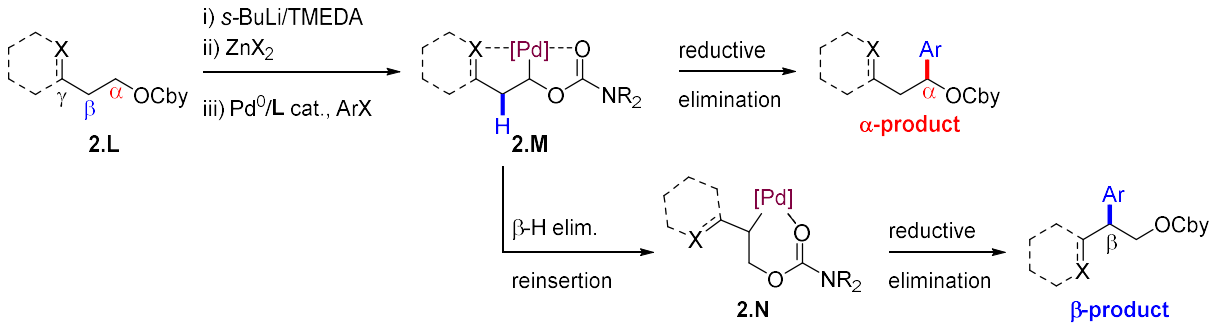


Table 11. *First attempts toward the ligand controlled β-arylation*

With the catalytic system being inefficient for the observation of the β-arylated products, we envisaged to design the substrate in order to stabilize the potential palladated intermediate.

2.2.2. Design of the substrate for β-arylation

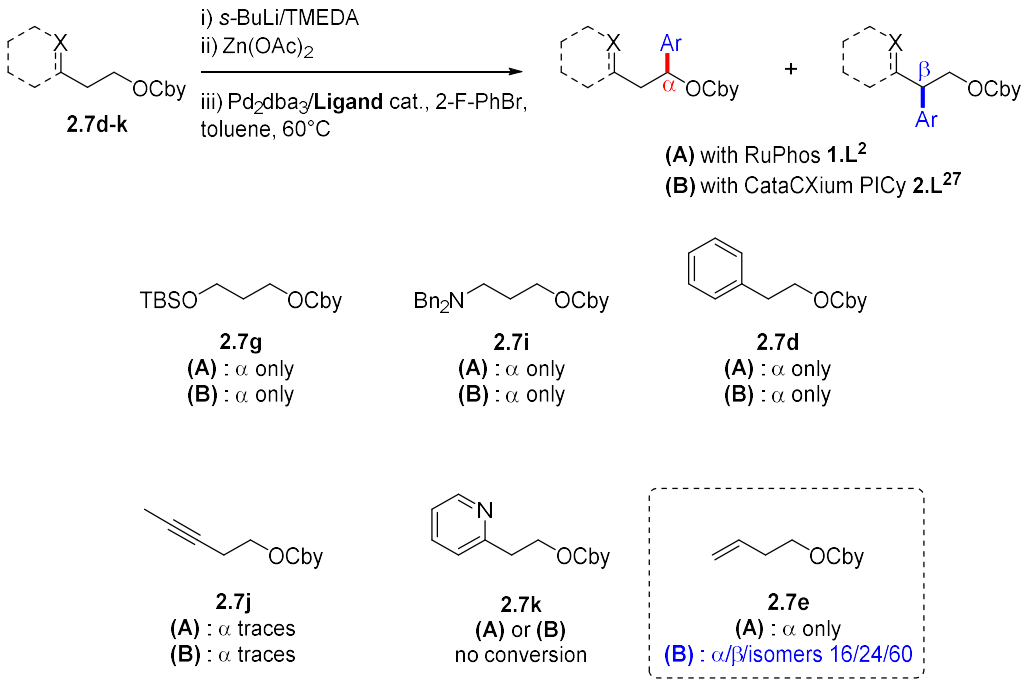
As a first step, the substrates were designed to bear a functional group in the γ-position of the carbamate, or a γ,δ-insaturation (**2.L**). In this way, after installation of the palladium in the α-position of the carbamate (**2.M**), the interaction with these functional groups would lead to an enhanced reactivity toward the β-hydride elimination, thus triggering the migration of the palladium complex to intermediate **2.N** (Scheme 73).



Scheme 73. *First design of substrate for the β-arylation of O-carbamates*

The designed carbamates were submitted to the α-arylation protocol with 1-bromo-2-fluorobenzene as the electrophile. The cross-couplings were conducted at 60°C with RuPhos **1.L**^{2} as the ligand to establish our reference α-products, and then with CataCXium PICy **2.L**^{27} (selected ligands among others for β-arylation attemps) to induce the migration (Scheme 74). The carbamates **2.7g** and **2.7i**, bearing a silyl-ether and a dibenzyl-amine respectively, underwent exclusive α-arylation in both protocols. The γ,δ-unsaturated carbamate **2.7d** bearing a phenyl ring did not lead to any arylation at the benzylic position. The alkyne **2.7j** and the pyridine **2.7k** only afforded poor conversion and no migrative arylation product was observed. But to our delight, the alkene **2.7e** gave the expected α-arylated product with

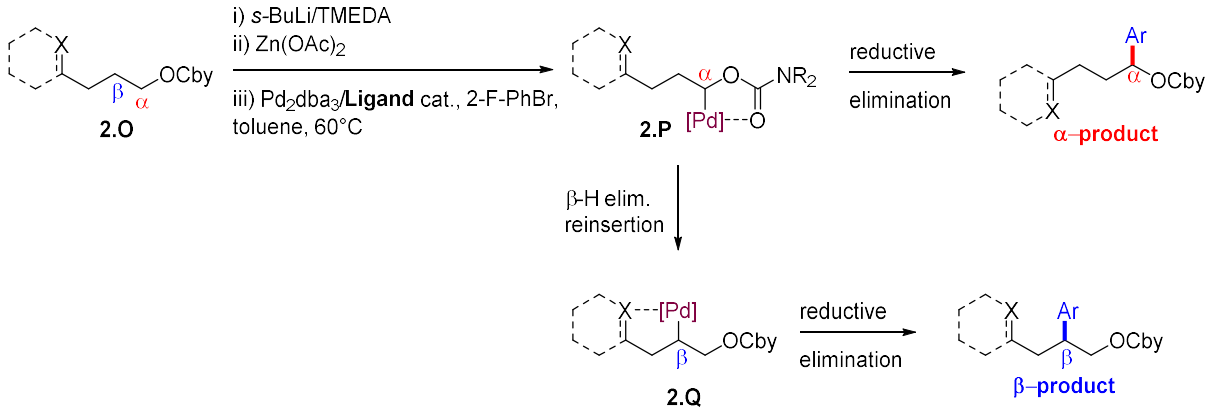
RuPhos as the ligand, and a distribution of regioisomers when arylated in presence of CataCXium PICy.



***Scheme 74.** β-arylation attempts on designed susbtrates I*

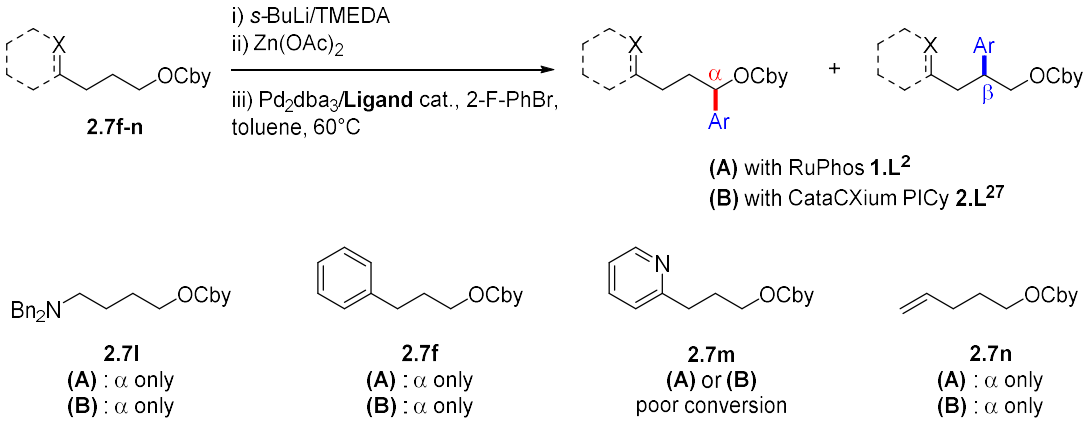
The different isomers included 16% of the α-arylated product and 24% of the β-arylated product, as well as 60% of other isomers, constituting the first discovery toward a new type of migration, which will be developed in the next section.

At the same time, the substrates were also designed in order to catch the palladium at the β-position, in the course of its migration (Scheme 75, **2.O**). After the first β-H eliminitation (**2.P**), rotation and reinsertion, the palladium complex would be stabilized thanks to a functional group located at the δ-position or a δ,ε-unsaturation (**2.Q**). The subsequent reductive elimination would lead to the β-arylated product.



Scheme 75. *Second design of substrates for the β-arylation of O-carbamates*

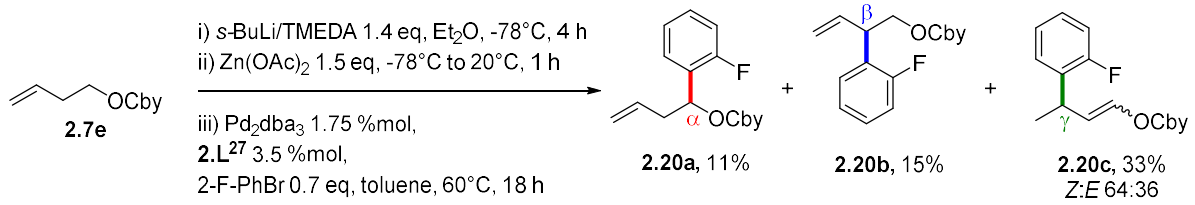
In the same way, carbamates **2.7f** and **2.7l-n** were engaged following the α-arylation protocol, at 60°C with 1–bromo-2-fluorobenzene as the coupling partner (Scheme 76). With RuPhos as the ligand, only the α-arylation products were obtained, for both δ-substituted and δ,ε-unsaturated substrates. These latter reacted equally when CataCXium PICy was used for the arylation, to deliver exclusively the corresponding α-arylated products. Of note, the carbamate **2.7m** bearing a pyridine moiety only gave poor conversion and an unexploitable mixture of products, probably due to a non-effective lithiation in this case. Surprisingly, the δ,ε-unsaturated carbamate **2.7n** did not provide any migrationproduct, enlightening the critical effect of the γ,δ-unsaturation in **2.7e** (above in Scheme 74).



Scheme 76. *β-arylation attempts on designed susbtrates II*

This study led us to the discovery of a potent substrate for the migrative arylation of *O*-carbamates (Scheme 77). In this regard, the arylation products of **2.7e** were analysed and their structures were determined. Surprisingly, the expected α- and β-arylated carbamates **2.20a** and **2.20b** were obtained in 11% and 15% ^{19}F-NMR yield respectively, along with a mixture

of the *Z* and *E* isomers of the γ-arylated product **2.20c** in 33% ^{19}F-NMR yield. The δ-arylation product was not detected.



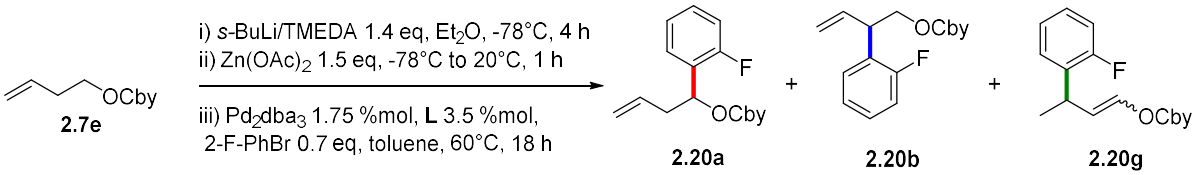
Scheme 77.*Observation of migrative arylation products*

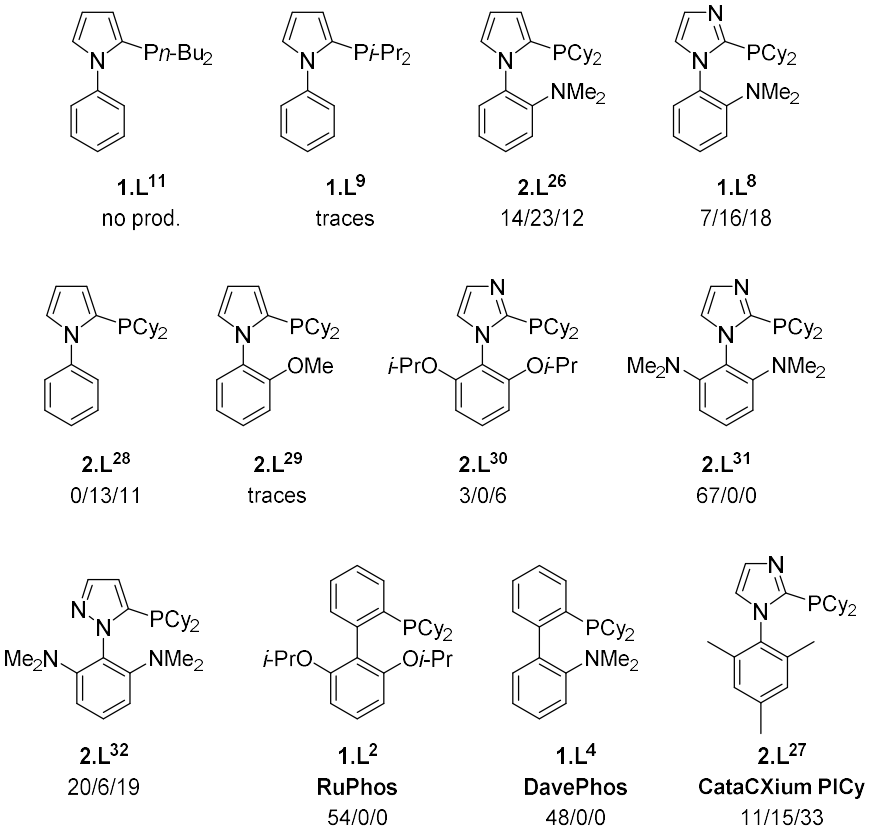
The different screens of ligands and designed substrates for the β-arylation of *O*-carbamates were unsuccessful. Nevertheless, the carbamate **2.7e** afforded a mixture of α-, β-, and γ-arylated products, the latter being the major one. With this result in hand, we turned our attention to the synthesis of the γ-arylated product, as well as the study of the mechanism leading to this regioselectivity in the coupling step.

2.3. Ligand-controlled γ-arylation of *O*-carbamates

2.3.1. Ligand screen

In a first place, a large screening of ligand was operated on substrate **2.7e** (>25 ligands were tested). Selected results are compiled in Scheme 78. The α-organozinc was formed under standard conditions, and then coupled with 2-F-bromobenzene in presence of Pd_2dba_3 and the ligand. The phenylpyrrole based ligands **1.L**[11]and **1.L**[9], known for their good selectivity control in previous migrative arylations, were in this case inefficient. Switching the alkyl groups to cyclohexyl moieties in **2.L**[28] allowed the observation of migration products in reasonable amounts. The phosphine bearing cyclohexyl chains was kept and the *o*-NMe_2 substitution of the lower ring in **2.L**[26]led to 49% yield of arylated products, but including only 12% of **2.20g**. The substitutions with an *o*-OMe in **2.L**[29] or the 2,6-di*O*i-Pr in **2.L**[30] completely shut down the reactivity. When the upper ring was changed to a more flexible imidazole such as **1.L**[8], a larger ratio of γ-product was obtained. The pyrazole congenere **2.L**[32] provided a better global yield of arylated product, but with a higher selectivity for the α-product. The more hindered 2,6-diNMe_2 substituted **2.L**[31]underwent exclusive α-arylation in good yield, likewise the biphenyl ligands RuPhos **1.L**[2] and DavePhos **1.L**[4]. The CataCXium PICy **2.L**[27] was found to give a better global yield of isomers in this series, with 59% ^{19}F-NMR yield. Moreover, an interesting proportion of γ-product (33%) was obtained, thus this ligand was selected for further optimization steps.

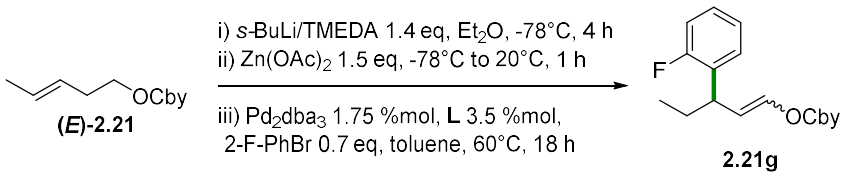


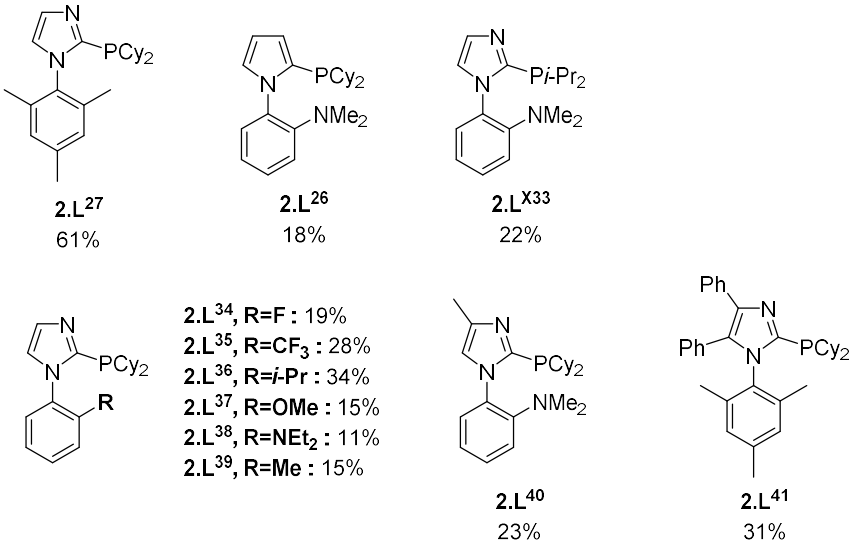


yields % of $\alpha/\beta/\gamma$ determined by ^{19}F-NMR of the crude reaction mixture, with trifluorotoluene as the reference.

Scheme 78. *Selected ligands for the γ-arylation of γ,δ-unsaturated O-carbamates*

Despite this result, the regioselectivity in this reaction was not yet satisfying. The substrate was furthermore modified to bear a simple methyl substitution on the terminal double bond, in order to observe its effect on the outcome of the reaction (Scheme 79). Thus, the substrate **(*E*)-2.21** was arylated in presence of **2.L^{27}**, which delightfully gave rise to 61% yield of the γ-products **2.21g**. The pyrrole-based **2.L^{26}** afforded a way lower yield of 18%, and the –P*i*-Pr$_2$ imidazole analogue **2.L^{33}**slightly improved this result (22% yield). The series of imidazole-based ligand **2.L$^{34\text{-}39}$** bearing an *o*-subtitution on the lower ring only gave yield in a range of 11%-34%. The methyl substitution on the imidazole in **2.L^{40}** did not bring a notable modification of the yield; and the disubstituted **2.L^{41}** was not favorable for this reaction, despite a higher yield than the said series.





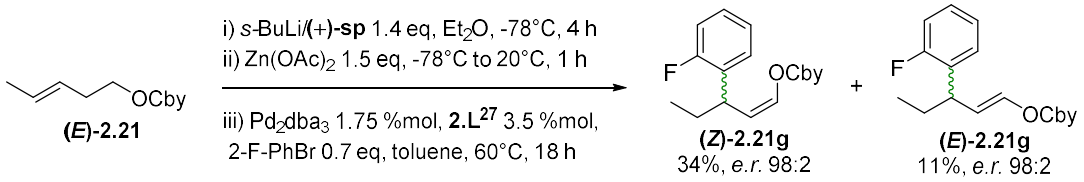
Yields % of γ-product determined by ^{19}F-NMR of the crude reaction mixture, with trifluorotoluene as the reference.

Scheme 79. *Effect of the ligand on the methyl substituted γ,δ-unsaturated O-carbamate*

Strong of our result with **2.L^{27}**, the reaction was tested in an enantioselective fashion.

2.3.2. Enantioselective migrative cross-coupling

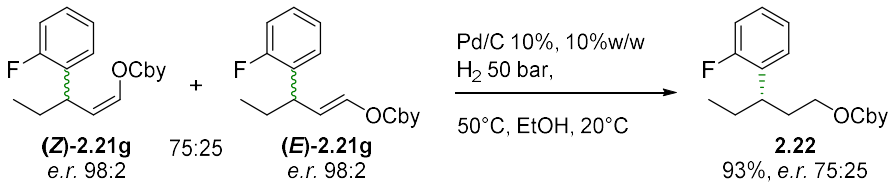
The substrate **(*E*)-2.21** was lithiated enantioselectively in presence of (+)-sparteine, and transmetalated to zinc. The enantioenriched α-organozinc was then engaged in the migrative Negishi cross-coupling with **2.L^{27}**as the ligand (Scheme 80). The reaction outcome was comparable to that of the racemic version and **2.21g** was obtained in 45% yield, with a ratio *Z*/*E* of 75:25. Both *cis*- and *trans*-products exhibited an excellent *e.r.* of 98:2, but were not separable by a standard silica gel column chromatography or by preparative HPLC.



Product isolated by preparative HPLC, *Z*:*E* ratio determined by ^{1}H NMR of the pure product.
e.r. determined by HPLC using chiral columns

Scheme 80.*Enantioselective γ-arylation*

The enantioenriched *Z*/*E* mixture of γ-products **2.21g** was hydrogenated to determine the relative configuration of the stereocenter at the γ-position. The reaction proceeded in 93% yield with 1% of palladium under 50 bar of H_2 at 50°C for 20h. Unfortunately, the hydrogenated product was obtain with 75:25 *e.r.*.



Scheme 81.*Hydrogenation of the scalemic mixture*

The ratio of this scalemic mixture reflects the opposite configuration at the stereocenter in γ-position (Figure 15). In consequence, any post-arylation modification of the enantioenriched substrate would lead to a dramatic loss of enantioenrichment. Nevertheless, this reversed selectivity at the γ-position also informed us about the mechanism of this arylation, that will be developed later.

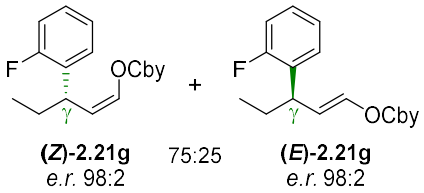


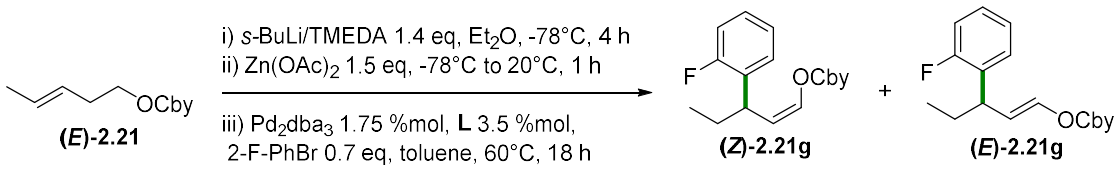
Figure 15. *Opposite configurations at the γ-position*

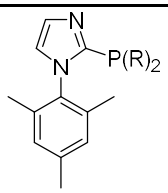
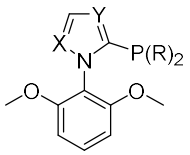
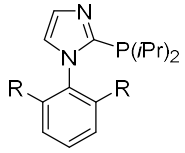
An amelioration of the *Z*/*E* ratio of the γ-product was thus necessary and new ligands were thereby synthesized and tested in this coupling.

2.3.3. Ligand design for selectivity

A series of imidazole-based ligands bearing a 2,6-substitution on the lower ring was synthesized and tested in the racemic γ-arylation of **(*E*)-2.21** (Table 12). The change from Cy to *i*-Pr on the **2.L**[27] core in **2.L**[42]resulted in a critical loss of reactivity, despite comparable *Z*/*E* selectivities (entries 1-2). In contrast, the same change from ligand **2.L**[43] to ligand **2.L**[44], bearing a *N-(*2,6-dimethoxyphenyl), resulted in an enhanced reactivity, along with a lower selectivity for the **(*Z*)-2.21g** isomer (entries 3-4). Of note, ligand **2.L**[43] provided a suitable selectivity but a lower yield. At the exception of the *t*-Bu, providing only the α-product with a rather good conversion, any other P-substitution shut down drastically the reactivity (entries 5-9, **2.L**[45-50]). When the imidazole was changed to the pyrazole in **2.L**[51], the γ-product **2.21g** was afforded in 50% ^{19}F-NMR yield, with a lower selectivity than for **2.L**[44] (entries 11 and 4). The effect of the substitution on the lower ring was also investigated. When bulkier 2,6-alkyloxy groups were used in **2.L**[52]and **2.L**[53], the reactivity slightly increased but the selectivity remained at 88:12 *Z*/*E* (entries 12-13 and 4). The 2,6-diethyl substitution in **L**[54]

gave a lower selectivity than **2.L**[27] (entry 14). To finish, the ligand **2.L**[55] bearing a 2,6-difluorophenyl moiety proposed a good reactivity, but the *Z*/*E* selectivity was importantly lowered to 68:32.



Entry	Structure	Ligand	X	Y	R	yield [a] % 2.21g	ratio *Z*:*E* [a]
1		**2.L**[27]	-	-	Cy	61	75:25
2		**2.L**[42]	-	-	*i*Pr	8	75:25
3		**2.L**[43]	CH	N	Cy	23	91:9
4		**2.L**[44]	CH	N	*i*-Pr	44	88:12
5		**2.L**[45]	CH	N	*t*-Bu	0, only α	n.d.
6		**2.L**[46]	CH	N	Ph	n.r.	n.d.
7		**2.L**[47]	CH	N	*n*-Bu	n.r.	n.d.
8		**2.L**[48]	CH	N	Et	n.r.	n.d.
9		**2.L**[49]	CH	N	*i*-Bu	n.r.	n.d.
10		**2.L**[50]	CH	N	Np	n.r.	n.d.
11		**2.L**[51]	N	CH	*i*-Pr	50	80:20
12		**2.L**[52]	-	-	OEt	51	88:12
13		**2.L**[53]	-	-	O*i*Pr	48	88:12
14		**2.L**[54]	-	-	Et	50	82:18
15		**2.L**[55]	-	-	F	53	68:32

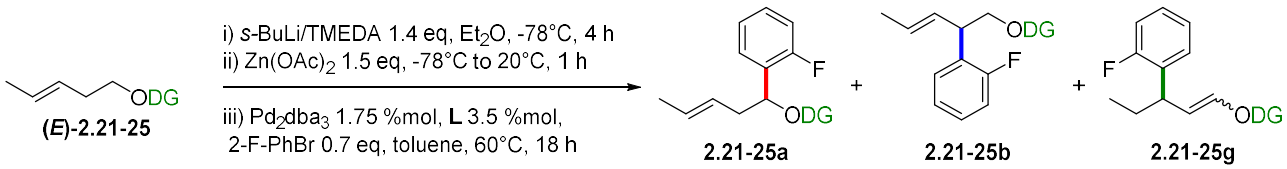
[a]The yield and the ratios were determined by ^{19}F-NMR with trifluorotoluene as the reference.

Table 12. *Effect of the designed ligand on the γ-arylation of* ***(E)-2.21***

With this last screen, the ligand bearing a *N*-(2,6-alkyloxyphenyl)imidazole, in combination with a diisopropylphosphine gave the best compromise in terms of yield of γ-product **2.21g** and *Z*/*E* selectivity, but the latter was not suitable for the development of an enantioselective version of the reaction. Moreover, the syntheses of the precursors of the ligands **2.L**[52] and **2.L**[53] were lacking efficiency. The other parameters of the reaction were then optimized with 2.L[27], simply due to its availability within our chemical library.

2.3.4. Variation of the directing group

The selectivity of the arylation was studied with respect to the directing group, with either **1.L**[2]or **2.L**[27] as the ligand, for α- and γ-arylation respectively (Table 13). The use of the more hindered Cbx group in **(*E*)-2.23** led to a similar outcome than with Cby, under the conditions for both α- and γ-conditions (entries 3-4). A fraction of the product was isolated via preparative HPLC, containing only the *Z* product in 3% yield. Of note, the conversion was low, leading to a complex separation even by preparative HPLC. The less elaborated Cb-protected substrate **(*E*)-2.24** underwent arylation in both cases, but with rather low yield, and showed a lower selectivity for the major*cis*-product **(*Z*)-2.25g** (entries 5-6). The γ-product was isolated in 18% yield with a ratio *Z*/*E*of 70:30. The TIB ester **(*E*)-2.25** was also engaged, but provided the α-arylated product as the major isomer in both protocols, despite the observation of only one migration product by GCMS (entries 7-8).



Entry	S.M.	DG	Ligand	ratio[a] α/β/γZ/γE	γ-product[b]
1	**(*E*)-2.21**	Cby	RuPhos	70/0/22/7	n.d.
2	**(*E*)-2.21**	Cby	CataCXium PICy	9/6/64/21	**2.21g**, 48%, 75:25 *Z*/*E*
3	**(*E*)-2.23**	Cbx	RuPhos	76/0/24/0	n.d.
4	**(*E*)-2.23**	Cbx	CataCXium PICy	6/6/69/18	**2.23g**, 3%, 100:0 *Z*/*E*
5	**(*E*)-2.24**	Cb	RuPhos	69/3/20/7	n.d.
6	**(*E*)-2.24**	Cb	CataCXium PICy	4/10/59/28	**2.24g**, 18%, 70:30 *Z*/*E*
7	**(*E*)-2.25**	TIB	RuPhos	96/0/4/0	n.d.
8	**(*E*)-2.25**	TIB	CataCXium PICy	57/0/43/0	n.d.

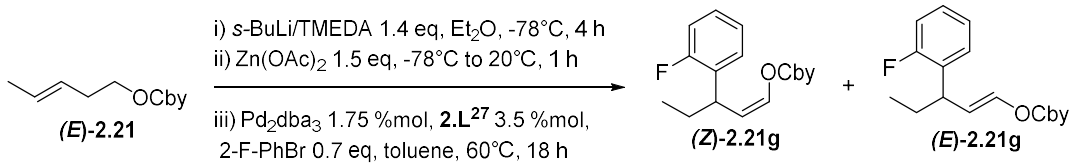
[a]Ratio determined by GCMS. [b]Isolated yield, *Z*/*E* ratio determined by ^{1}H-NMR.

Table 13.*Effect of the directing group on the γ-arylation*

This study indicated that the Cby group was the most adapted for this reaction, in terms of reactivity and selectivity, as well as for purification purpose. Indeed, the corresponding γ-products **2.21g** were more likely separable from the other isomers by preparative HPLC.

2.3.5. Variation of conditions

Different conditions for the arylation of **(*E*)-2.21** were tested, varying from the standard conditions (Table 14). The use of $ZnCl_2$ instead of $Zn(OAc)_2$ lowered the yield of **2.21g** to 35%, as well as the *Z*/*E* ratio to 71:29, following the same trend as for the α-arylation (entry 2). The lowering or the increase of the electrophile loading decreased the yield, with a more pronounced impact when 1 eq was engaged in the reaction (entries 3,4). The increase of the catalytic loading proved to be beneficial to the reaction and a yield of 54% of **2.21g** was obtained with 7 %mol of the catalytic system (entry 5). Also, 14 %mol of catalytic system brought a similar result, with no further amelioration of the yield (entry 6). A run over 40 h led to the same ^{19}F-NMR yield and was not considered more efficient despite a higher isolated yield (entry 7). The other sources of palladium impacted the reaction outcome and surprisingly the desired product was obtained in an average yield when 3.5 %mol of $[PdCl_2(MeCN)_2]$ was used (entries 8-10). The solvent for the arylation step was changed (entries 11-15). The reactivity in benzene was comparable, but decreased in *n*-hexane (entries 11-12). The use of polar solvents dramatically lowered the yield and no conversion was observed in DMAc or 1,4-dioxane (entries 14-15). To finish, the temperature of the coupling step was changed, and also resulted in a loss of reactivity in any case (entries 16-17). It is important to observe that, for every variation of the conditions, no significant variation of the *Z*/*E* ratio of **2.21g** was observed, exposing the essential role of the ligand in this selectivity.



Entry	Deviation	NMR yield%[a]	yield, *Z*/*E* ratio
1	-	49/12	48%, 75:25
2	ii) $ZnCl_2$ i/o $Zn(OAc)_2$	n.d.	35%, 71:29
3	iii) 0.5 eq ArBr	38/9	44%, 75:25
4	iii) 1 eq ArBr	32/9.5	35%, 75:25
5	iii) 3.5 %mol Pd_2dba_3, 7 %mol **2.L**^{27}	46/14	54%, 75:25
6	iii) 7 %mol Pd_2dba_3, 14 %mol **2.L**^{27}	44/13	n.d.
7	iii) reaction 40h	44/14	55%, 75:25
8	iii) 3.5 %mol $Pd(dba)_2$, 3.5 %mol **2.L**^{27}	14/4	n.d.
9	iii) 3.5 %mol $Pd(OAc)_2$, 7 %mol **2.L**^{27}	20/6	n.d.
10	iii) 3.5 %mol $[PdCl_2MeCN_2]$, 7 %mol **2.L**^{27}	45/14	50%, 75:25

11	iii) in benzene	39/11	47%, 76:24
12	iii) in *n*-hexane	26/4	29%, 73:27
13	iii) in THF	31/2	19%, 71/29
14	iii) in DMAc	n.r.	n.d.
15	iii) in 1,4-dioxane	n.r.	n.d.
16	iii) at 80°C	44/16	33%, 71/29
17	iii) at 40°C	40/11	31%, 77/23

[a]Yield determined by ^{19}F-NMR with trifluorotoluene as the reference [b]Isolated yield, *Z*/*E* ratio determined by ^{1}H-NMR.

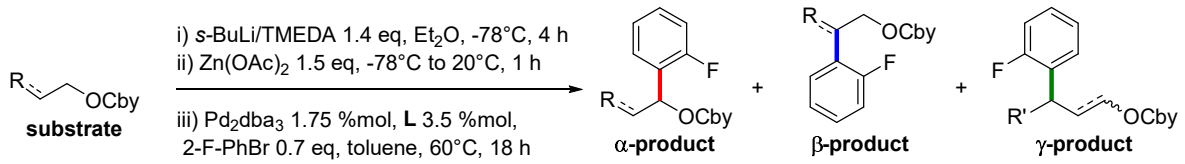
Table 14. *Variations of the standard conditions for the g-arylation of* ***(E)-2.21****.*

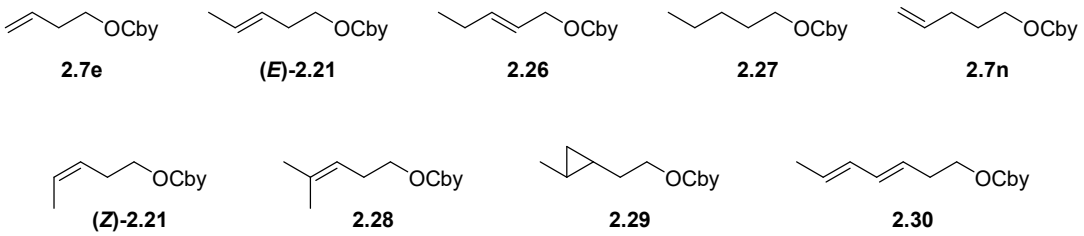
Only slight ameliorations were brought by this screening of conditions, and the initial ones were kept as the standard conditions, mainly for practical reasons, and also because of the availability of the palladium sources. Indeed, the slight increase of yield observed when the catalyst loading is two folds higher doesn't justify the use of 7 %mol of this Pd/L combination. Furthermore, [$PdCl_2MeCN_2$] is more expensive than Pd_2dba_3 (Sigma-Aldrich catalog, June 2018).

2.3.6. Evaluation of the γ,δ-unsaturation effect

The essential role of the γ,δ-unsaturation could be observed earlier, during the attemps for β-arylation (see part 2.2) and the screen of ligands on **2.7e** and **(*E*)-2.21** (part 2.3.1). In addition, the carbamates **(*Z*)-2.21**, **2.7n** and **2.26-2.30** were engaged in the α- and the γ-arylation reactions to verify the necessity of this insaturation and to evaluate the scope of this reaction with respect to the carbamate (Table 15). The allylcarbamate **2.26** was poorly converted in both protocols (entries 5-6). Interestingly, the GCMS ratios of isomers were similar to the one observed with **(*E*)-2.21** and different stereoisomers of the starting material were observed. The saturated carbamate **2.27** underwent exclusively α-arylation in both protocols, as well as the δ,ε-unsaturated carbamate **2.7n** (entries 7-10).The *Z* isomer **(*Z*)-2.21** reacted in a similar manner as **(*E*)-2.21**, providing an average yield with a lower selectivity for **(*Z*)-2.21g** (entries 11-12). Of note, **(*Z*)-2.21** is also less prompt to migrative coupling than its ***E***-isomer, in the α-arylation reaction, as observed by GCMS (entries 11 and 3). Unfortunately, when the γ,δ-unsaturation was more substituted, as in **2.28**, the reactivity was dramatically shut down to observe only a poor conversion and traces of the desired products (entries 13-14). Nevertheless, the GCMS ratios clearly showed a similar selectivity induced by the ligand, as for the less hindered carbamates. The carbamate **2.29**, bearing a *trans*-

cyclopropyl instead of the double bond, did not undergo any opening or activation of the 3-membered ring and only the corresponding α-arylation product was observed, with poor conversion (entries 15-16). This result also suggested that no radical pathway was involved in this migrative arylation. Traces of migration products were detected on GCMS when **2.30** was engaged in the γ-arylation protocol (entry 18).



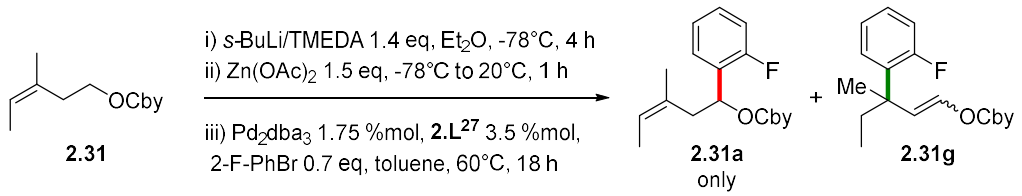


Entry	Susbtrate	Ligand	ratio [a] α/β/γZ/γE	γ-product [b]
1	**2.7e**	**1.L**[2]	100/0/0/0	only **2.20a**
2	**2.7e**	**1.L**[27]	18/25/40/18	**2.20g**, 33%, *Z*/*E* 64:36
3	(***E***)**-2.21**	**1.L**[2]	70/0/22/7	n.d. (42% **2.21a**)
4	(***E***)**-2.21**	**1.L**[27]	9/6/64/21	**2.21g**, 48%, 75:25 *Z*/*E*
5	**2.26**	**1.L**[2]	10/5/63/22	traces
6	**2.26**	**1.L**[27]	12/6/60/22	traces
7	**2.27**	**1.L**[2]	100/0/0/0	only α
8	**2.27**	**1.L**[27]	100/0/0/0	only α
9	**2.7n**	**1.L**[2]	100/0/0/0	only α
10	**2.7n**	**1.L**[27]	100/0/0/0	only α
11	(***Z***)**-2.21**	**1.L**[2]	85/3/8/3	n.d.
12	(***Z***)**-2.21**	**1.L**[27]	13/9/56/22	**2.21g**, 51%, 73:27 *Z*/*E*
13	**2.28**	**1.L**[2]	80/0/10/10	traces
14	**2.28**	**1.L**[27]	12/7/58/12	traces
15	**2.29**	**1.L**[2]	100/0/0/0	only α
16	**2.29**	**1.L**[27]	100/0/0/0	only α
17	**2.30**	**1.L**[2]	100/0/0/0	traces
18	**2.30**	**1.L**[27]	α→δ	traces

[a]Ratio determined by GCMS. [b]Isolated yield, *Z*/*E* ratio determined by ^{1}H-NMR.

Table 15. *Evalutation of the γ,δ-unsaturation effect*

The arylation of substrate **2.31** was attempted under the conditions favoring the migration (Scheme 82). The γ-arylation would provide a quaternary carbon center, which has, to date, not been accessed by palladium-catalyzed migrative cross-coupling. Unfortunately, only the direct coupling was observed.

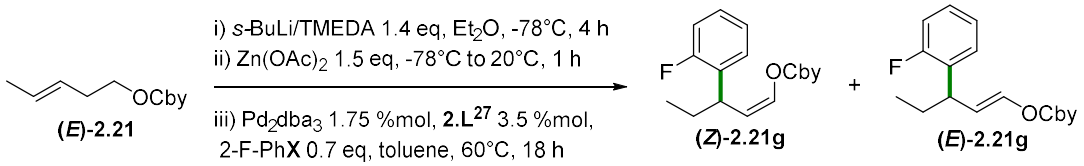


Scheme 82. *γ-Arylation attempt on* ***2.31***

The γ,δ-unsaturation is vital to observe this γ-arylation. When this insaturation is more substituted, as in **2.28**, the reaction is shut down. With a conjugated double-bond, as in **2.30**, only traces of a long range coupling are observed. When the unsaturation is located in the β,γ-position, *i.e.* when the allylic *O*-carbamate **2.26** is engaged, only traces of the desired product are obtained; in contrast to the outcome observed when allylic *N*-Boc-amines are engaged. It is assumed that the lithiation and/or the transmetalation steps are not efficient in this case. Hence, the study was continued uniquely with the substrate **2.21** and the substrate scope became narrower. Then, the potential of other aryl halides was rapidly evaluated.

2.3.7. Determination of the ideal aryl halide

The 1-iodo- and the 1-chloro-2-fluorobenzene were engaged as coupling partners in the γ-arylation reaction (Table 16). The same trend as for the α-arylation was observed. The iodo- partner is less efficient than the bromo- (entry 2 and 1) and the reaction is shut down when the chloro- is used (entry 3). No effect on the *Z*/*E* ratio was observed.



Entry	X	ratio [a] α/β/γZ/γE	NMR yield % [b]	yield, *Z*/*E* ratio [c]
1	Br	8/7/65/20	49/12	48%, 75:25 Z/E
2	I	7/7/64/22	33/8	37%, 75:25 Z/E

3	Cl	7/7/63/24	10/2	< 5%, 75:25 Z/E

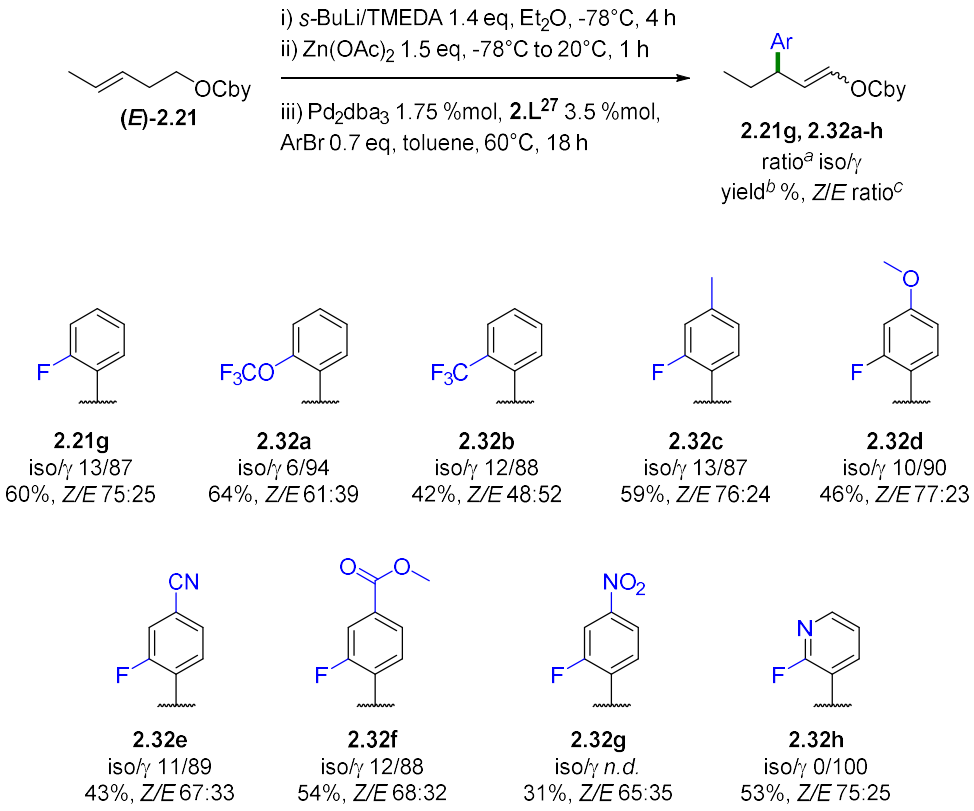
[a]Ratio determined by GCMS. [b] Yield determined by ^{19}F-NMR with trifluorotoluene as the reference [c]Isolated yield, *Z*/*E* ratio determined by ^{1}H-NMR.

Table 16. *Evaluation of the ideal aryl halide for the γ-arylation*

The final conditions for the γ-arylation were fixed, and the scope of the reaction was processed.

2.3.8. Scope and limitations of the electrophile

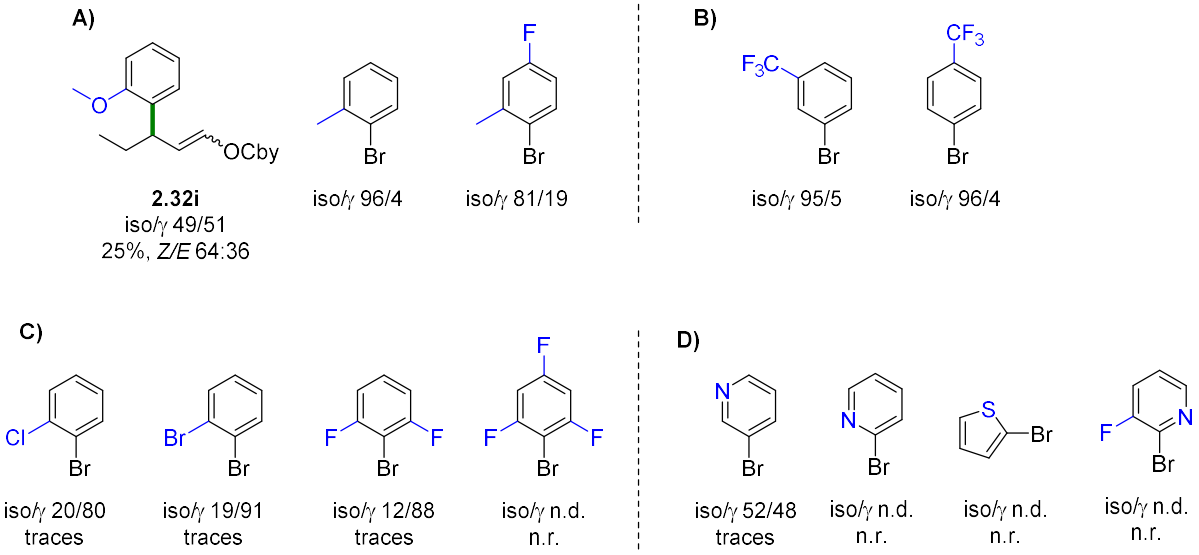
The scope of the reaction with respect to the arylbromide was examinated, to exhibit the synthetic potential of the methodology, and to dismiss the possibility that this reactivity would be limited to a unique substrate (Figure 16). After improvement of the quality of *s*-BuLi (filtration on celite before titration and use), **2.21g** was obtained in 60% isolated yield, with a *Z*/*E* ratio of 75:25. The variation of the *o*-substitution to *o*-OCF_3 provided a clear selectivity for the γ-product, and **2.32a** was isolated in 64% yield, nevertheless the *Z*/*E* ratio was lowered to 61:39. The effect of the *o*-CF_3 was more pronounced, indeed **2.32b** was obtained in 42% yield and with no selectivity for one of the two Z/E stereoisomers. The arylation proved to be efficient in the cases where the *p*-position was substituted. Products **2.32c** and **2.32d** bearing a *p*-Me and a *p*-OMe, respectively, were obtained with a good selectivity for the γ-product. Sensitive functionalities were compatible with the mild conditions of the Negishi coupling, such as a methyl ester or a nitrile, providing **2.32e** and **2.32f** in average yields. The *p*-NO_2-arene underwent Negishi coupling to afford **2.32g** in 31% yield, showing a similar reactivity as in the α-arylation. The reaction also took place with a heteroaryl to afford the fluoropyridine derivative **2.32h** with an exclusive selectivity toward the γ-product.



[a] Ratio of isomers/γ-product determined by GCMS. [b] Yield of the isolated product (%). [c] *Z/E* ratio determined by 1H-NMR.

Figure 16. *Scope of the γ-arylation with respect to the (hetero)aryl bromide*

Nevertheless, the scope of this reaction was very limited, and many arylbromides did not undergo a successful migrative coupling (Figure 17). With a less electronegative substituent on the *o*-position, such as an OMe, the migration occurs less likely (only 49:51 iso/γ, and 25% isolated yield of **2.32i**). This effect is enhanced with an *o*-Me, for which the α-arylated product is largely predominant, even when a fluorine is added on the *p*-position (**2A**). The *o*-effect is also obvious when the -CF_3 is moved to the *m*- or *p*- position. In this case the formation of the α-arylated product is favored with very good conversion (**2B**). Other halides on the *o*-position led only to poor conversion, but with similar selectivities toward the γ-products. The double *o*-F-substitution was not more efficient and no reaction occurred with the bromo-2,4,6-trifluorobenzene (**2C**), suggesting also that the electronic balance of the aryl halide must be finely tuned. 3-bromopyridine afforded traces of coupling with a 1:1 selectivity for the desired migration product to the other isomers. The other heteroarylbromides, even containing an *o*-fluoro substitution, were not efficient (**2D**).

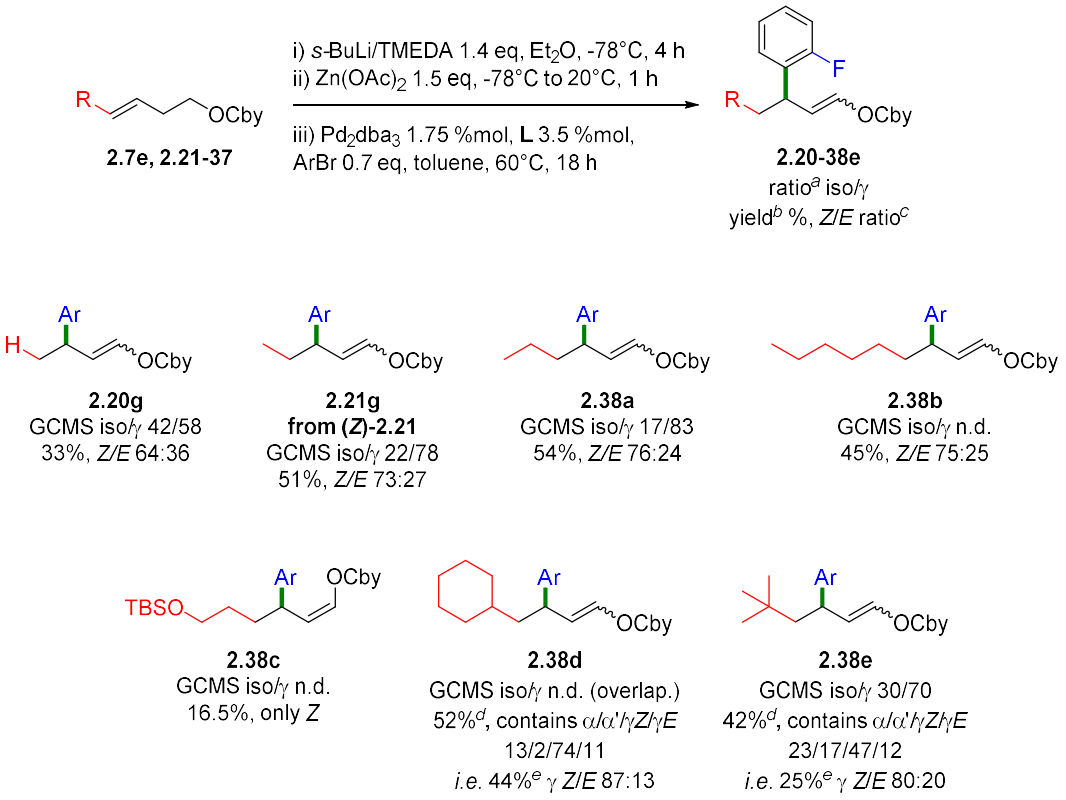


[a] Ratio of isomers/γ-product determined by GCMS. [b] Yield of the isolated product (%). [c] *Z/E* ratio determined by 1H-NMR.

Figure 17. *Unsuccessful γ-arylation of some (hetero)aryl bromides*

2.3.9. Scope with respect to the carbamate reactant

Others γ,δ-unsaturated carbamates were consecutively synthesized and engaged in the γ-arylation reaction (Figure 18). As seen in part 2.3.6, **2.20g** was obtained in 33% yield with a moderate selectivity. The γ-arylated product **(*E*)-2.21g** was also obtained from **(*Z*)-2.21**, with a lower yield and selectivity. Nevertheless, this example shows a type of convergence to **2.21g**from the *E* or *Z* starting material **2.21**, suggesting a common mechanistic pathway. Thus, the starting material could be a mixture of *E* and *Z* isomers, but the synthesis of the starting γ,δ-carbamates remained challenging. The carbamates **2.33** and **2.34** bearing a longer side chain underwent γ-arylation to provide **2.38a** and **2.38b** in average yield, with no relevant modification of the *Z*/*E* ratio. The product **2.38c** bearing a TBS protected alcohol was isolated in the pure *Z* isomeric form, despite a low yield of 17%. The hindrance of the ε-position induced a slight effect on the selectivity, which could also be attributed to the difficulties faced during the purification of the corresponding products. Indeed the arylation of **2.36** gave a mixture of four defined regioisomers (as seen in 2D ^{1}H NMR spectroscopy), containing a total yield of 44% of the desired γ-product **2.38d** with a *Z*/*E* ratio of 87:13, bearing a cyclohexyl chain at the δ-position. In the same way, the arylation of **2.37**, bearing a *t*-Bu group at the δ-position, afforded a mixture of four regioisomers, which contained 25% of the desired compound **2.38e** in 80:20 *Z*/*E* ratio.



[a] Ratio of isomers/γ-product determined by GCMS. [b] Yield of the isolated γ-products. [c] Z/E ratio determined by 1H-NMR. [d] Yield of the isolated mixture of isomers. [e] Calculated yield of corresponding γ-products.

Figure 18. *Scope of the γ-arylation with respect to the carbamate*

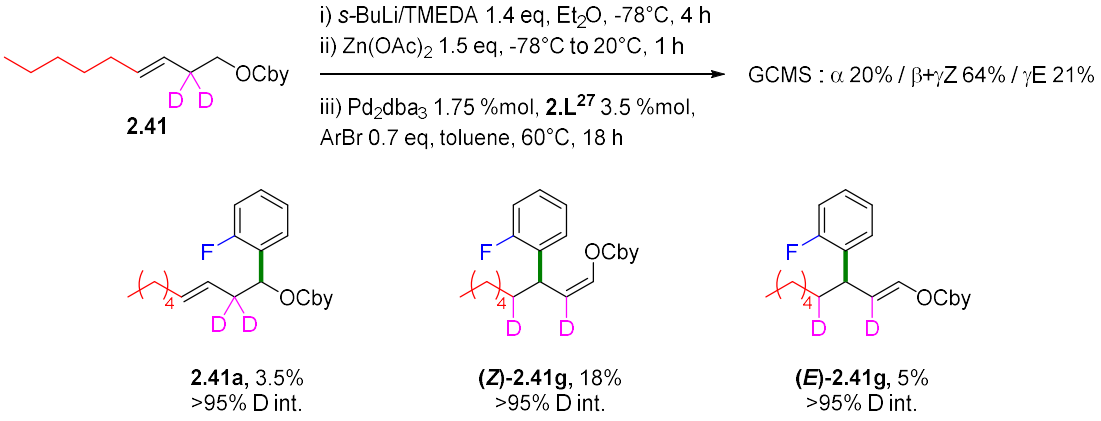
In addition to the unfruitful carbamates presented in 2.3.6, Table 15, biscarbamate **2.39** only underwent poor conversion under the γ-arylation conditions. Carbamates **2.40a-b** suffered a challenging synthetic approach and were not synthesized (Figure 19).

Figure 19. *Other γ,δ-unsaturated carbamates*

The study of the scope of the γ-arylation reaction led us to examine more closely the mechanism of this transformation. Indeed, the migration path is not obvious and the γ,δ-unsaturation is vital for the selective arylation to occur in presence of the appropriated ligand. In order to gain more insights on the mechanism, the suitable deuterated substrate was synthesized.

2.3.10. Deuterium labeling

The β-deuterated carbamate **2.41** was synthesized and then engaged in the γ-arylation reaction in presence of **2.L**[27] with Pd_2dba_3 as the palladium source (Scheme 83). The GCMS trace showed similar signals as for the arylation product **2.38b**, suggesting no dramatic isotopic effect on the arylation. The α- and γ- products **2.41a**, **(*Z*)-2.41g** and **(*E*)-2.41g** were isolated, and only traces of β-product were observed. Moreover, no scrambling and no longer range arylation occurred on the side chain of the γ,δ-insaturation, providing us more information about the probable reaction intermediates.



Scheme 83. *γ-Arylation of the deuterium-labelled substrate*

Thus, all the elements discovered during the study of this γ-arylation led us to postulate a non-canonical mechanism for this migrative coupling.

2.3.11. Mechanistic insights

The first step of the proposed mechanism is the installation of the palladium in the α-position of the carbamate by transmetalation of the non-racemic organozinc intermediate arising from the enantioselective deprotonation/lithiation with (+)-sparteine. The newly formed Pd^{II} species could then undergo two different β-hydride eliminations. Indeed, the rotation of the C_α-C_β bond can place each of the two diastereotopic β-hydrogen in the required *syn*-coplanar position to the metal center. After the subsequent elimination the (*Z*)-enol-carbamate (from $\mathbf{A_Z}$) or the (*E*)-enol-carbamate (from $\mathbf{A_E}$) can be formed (Scheme 84, **A**). Since the major product of the reaction is the (Z)-enol-carbamate, the elimination of $H_Z$in A_Z is favored and the formation of B_Z is predominant. Ligand optimization could not improve the elimination ratio of H_Z:H_E 88:12 leading to the corresponding (*E*)- or (Z)-products and no rational relashionship between the ligand structure and the selectivity could be established.

The newly formed conjugated (*E*),(*Z*)-dienolcarbamate $\mathbf{B_Z}$ and (*E*),(*E*)-dienolcarbamate $\mathbf{B_E}$couldallow the palladium to undergo haptotropic rearrangement[137] along the conjugated π-system in *trans*-conformation (Scheme 84, **B**). A cross-over experiment indicates that the palladium complex doesn't de-coordinate from the elongated π-system. Indeed, when the installation of the metal is carried out in asymmetric fashion, the two diastereomeric products are obtained separately with very high enantiomeric excesses. Nevertheless, the absolute configuration of the chiral C_γ center hasn't been determined yet. Thus the *trans*- or *cis*-conformation of the intermediate dienes has not been determined yet.

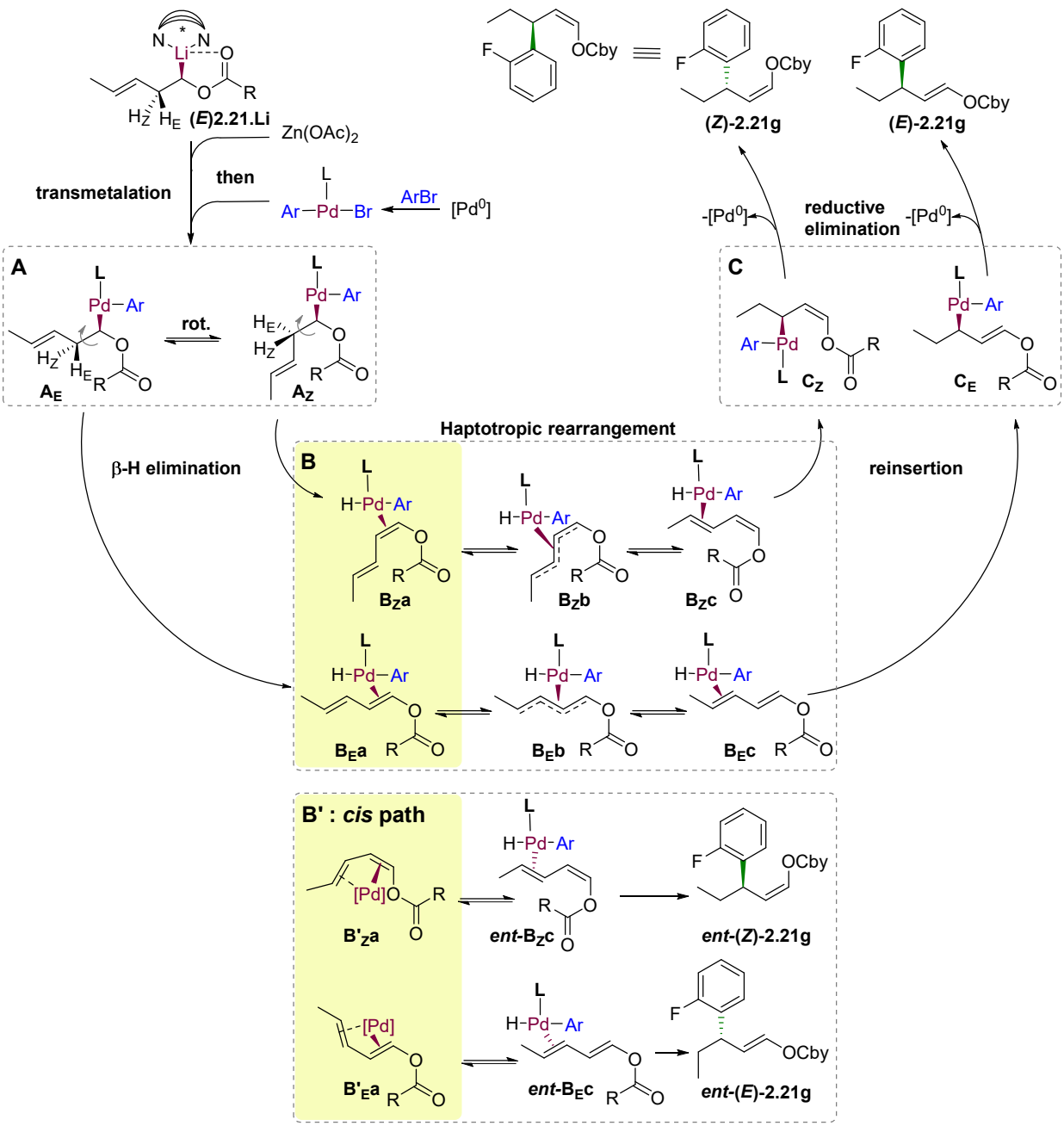
Only small amounts of β-product could be observed, suggesting that the haptotropic rearrangement is kinetically and/or thermodynamically favored over the rotation and the subsequent insertion of the metal center leading to the β-arylation. Moreover, no δ-arylated product could be observed, confirming that only the haptotropic rearrangement takes place before the insertion of the palladium hydride complexe into the C_γ-C_δ unsaturation, and no rotation of the complex occurs.

It is not excluded that the fluxional behavior of the palladium along the conjugated π-system is caused by a steric effect of the carbamate moiety, "pushing" the palladium complex toward the less hindered part of the chain. On similar but less hindered homoallylic systems, only allylic arylation is obtained after exclusive migration to the β-position.[138] However this effect must be added to the electronic and the steric effects of the ligand and the aryl substitution on the metal center.

After coordination of the palladium to the γ-δ unsaturation via the above mentioned haptrotropic rearrangement, possible complexes $\mathbf{B_Z}$**c** and $\mathbf{B_E}$**c**undergo stereospecific insertion on the predetermined face of the diene to give complexes $\mathbf{C_Z}$ and $\mathbf{C_E}$, respectively (Scheme 84, **C**). Their stereospecific reductive elimination gives rise to the γZ- and the γE-products, respectively, which bear an opposite configuration at the C_γ stereocenter.

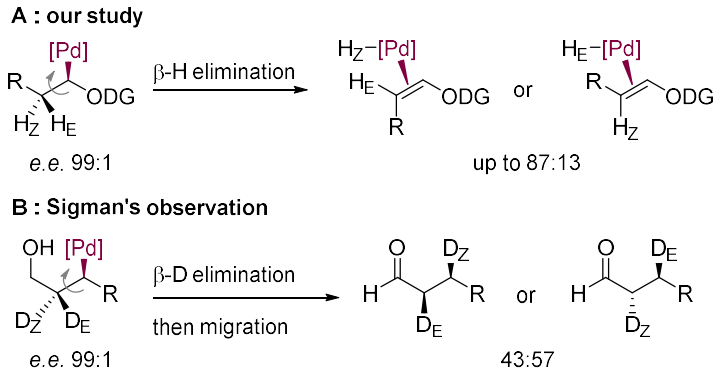
However the palladium might also undergo haptotropic rearrangement along the conjugated π-system in *cis*-conformation. In this case, the other enantiomers of both (*Z*) and (*E*) products would be obtained (Scheme 84, **B'**). It is to note that the migration occurs on the face of the α,β-unsaturation which was defined during the β-H elimination step, and on the face of the γ,δ-unsaturation wich is defined by the *trans*- or *cis*- conformation of the diene. Importantly, the migration occurs exclusively in *trans*- or in *cis*- configuration. Equilibrium between those

configurations on one of the (*Z*) or (*E*) precursors would lead to lower level of enantioselectivity. Moreover if a product precursor would be in *trans* while the other's product precursor would be in *cis*, then no opposite configuration would be observed at the C_γ.



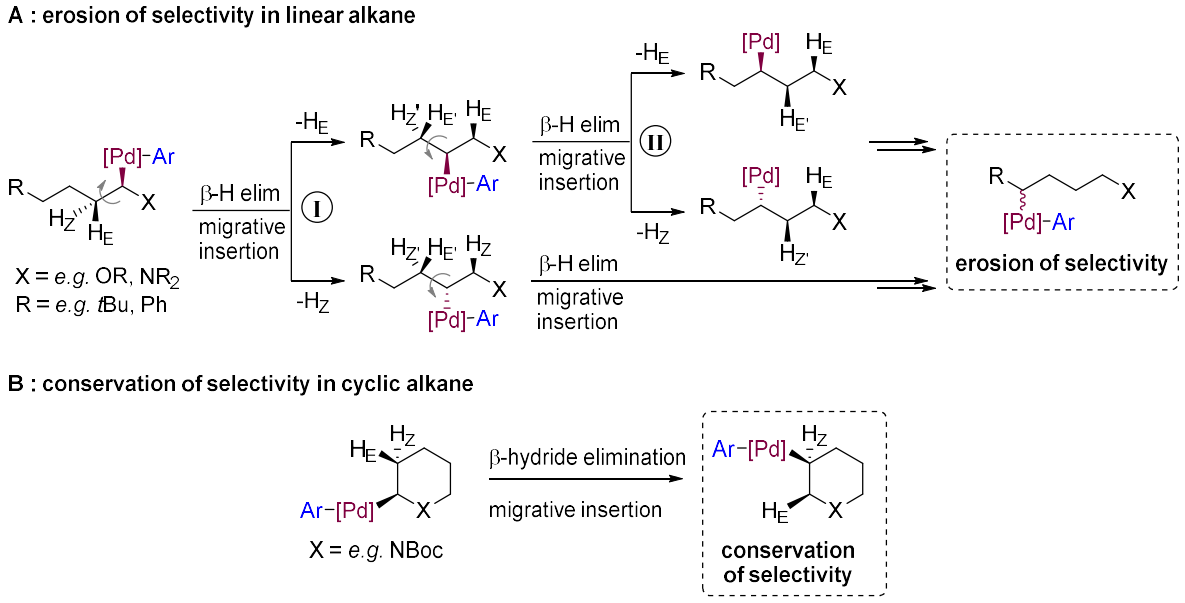
Scheme 84. *Proposed mechanism for the γ-arylation of O-carbamates*

This mechanism also brings to the fore the selectivity issues which would be associated to an enantioselective migrative coupling along an acyclic saturated aliphatic chain. In our case, the first β-hydride elimination leading to the (*Z*) or (*E*) alkene intermediate is critical for the stereochemical outcome of the reaction. The metal center is installed on the chain in α-position with a very high selectivity (99:1 *e.e.*, as seen in the corresponding α-arylation), and the selectivity is eroded during the β-hydride elimination step, because of the unselective abstraction of the H_Z or H_E. Thus the metal center is installed on one of the diastereoisomeric faces of the rising alkene. In this study, the palladium undergoes only one β-hydride elimination/migration event, and the selectivity H_Z:H_E could not be increased to 87:13, giving rise to two diastereoisomeric compounds (Scheme 85, **A**). Moreover, a study involving deuterium labeling has been provided by Sigman and coworkers.[139] A poor selectivity of 43:57 H_Z:H_E could be obtain on the β-deuteride elimination/migrative insertion of a stereochemically well defined palladium complex intermediate (Scheme 85, **B**).



Scheme 85. *Lack of selectivity in the β-hydride elimination*

Considering an acyclic saturated chain where the metal center migrates in one direction in a nondissociative process, the erosion could be repeated for each β-hydride elimination/migrative insertion step (**I** and then **II**), thus leading to a complete loss of stereochemical information (Scheme 86, **A**). In a cyclic system, no complete rotation is allowed on the C_α-C_β bond, hence the β-hydride elimination/migrative insertion would conserve the stereochemical information by exclusive abstraction of the hydride *syn* to the palladium (Scheme 86, **B**).[140] Since the steric and electronic effects of the ligand, the aryl and the substrate are not fully understood, the enantioselective migrative cross-coupling along an acyclic saturated aliphatic chain seems *a priori* challenging.

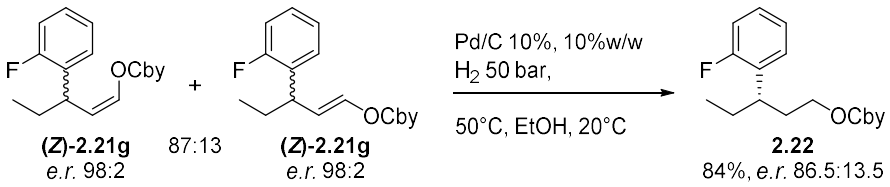


Scheme 86. *Stereospecific migration in linear vs cyclic alkanes*

A derivatization of the products has been attempted in order to determine the absolute configuration of the products. Because the configuration of the asymmetric deprotonation/lithiation and transmetalation is known, the absolute configuration of the products would give us the key to determine the *trans*- or *cis*- conformation of the diene intermediate, which is required to validate our proposed mechanism.

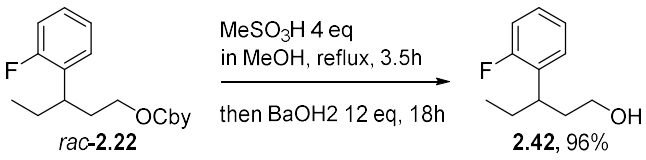
2.3.12. Product derivatization

First, a mixture of γZ and γE-isomer was hydrogenated with Pd/C and 50 bars of hydrogen (see Scheme 81). The hydrogenation of a 87:13 mixture of enantiopure *Z*/*E* products (*e.e.*>98:2, respectively) obtained from the enantioselective arylation with ligand **2.L**[44], provided the hydrogenated carbamate **2.22** in 84% yield and 86.5:13.5 *e.e.* (Scheme 87), thus confirming the opposite configuration at the C_γ in the two isomers .



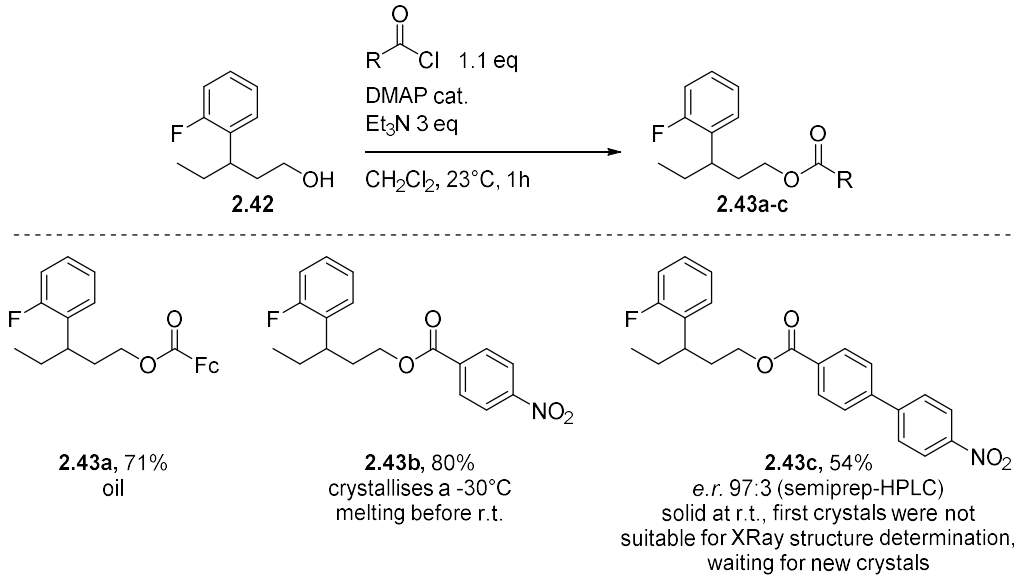
Scheme 87. *Hydrogenation of a 87:13 mixture of γ-products*

A subsequent deprotection of a recemic mixture of **2.22** took place in quantitative yield by using $MeSO_3H$ in refluxing methanol to open the acetonide, and then $Ba(OH)_2$ to remove the opened carbamate. The racemic alcohol **2.42** was obtained in 96% yield (Scheme 88).



Scheme 88. *Deprotection of the γ-arylated saturated carbamate*

In our aim to obtain a crystal to determine the absolute configuration, we envisaged to esterify the alcohol with a bulky and heavy acid to obtain a solid ester (Scheme 89). The ester of ferrocene carboxylic acid **2.43a** was accessed, but was oily at ambient temperature, even in its enantiopure form. The ester of *p*-nitrobenzoic acid **2.43b** was obtained as an oil which crystallized in solution at -30°C, but the obtained crystals were not suitable for analysis. Based on this observation, the biphenyl congener was synthesized and its ester **2.43c** was synthesized in a racemic fashion. To our delight, the product was a solid. The separation by semi-preparative HPLC provided a sample with >97:3 *e.e.*. Again, the crystals were not suitable for structure determination. The crystallization of this compound is still currently under investigation.



Scheme 89. *Attempts for the formation of a crystalline ester*

2.3.13. Conclusion

Our attempts toward the β- and longer range arylation of protected aliphatic alcohol via migrative Negishi cross-coupling remained unfruitful. In this study, a non-classical migration process was discovered. When using the adequate ligand, the γ,δ-unsaturated α-oxoalkylzinc reagents formed by directed lithiation and transmetalation undergo migrative Negishi

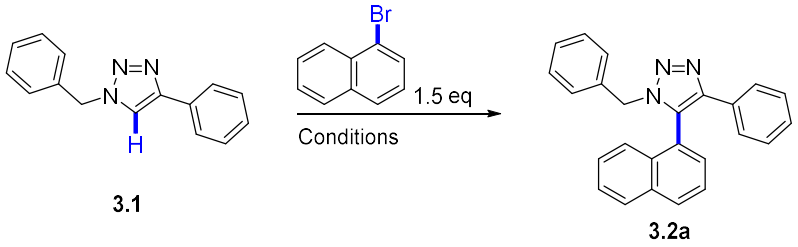
coupling to obtain γ-arylated *O*-carbamates. The reaction tolerates only a tight range of aryl bromides and homoallyl alcohol carbamates. Mechanistic studies, such as a deuterium labeling and a cross-over experiment, allowed us to propose a non-canonical mechanism which involves a haptotropic rearrangement of the intermediate palladium complex along an extended π-system. This type of rearrangement has, to date, not been reported for synthetic methodologies with palladium, nor for cross-coupling reactions. Only rare occurrences of palladium haptotropic rearrangements appear in the literature.[141] The determination of the absolute configuration of the product would be the key to validate the *trans*- or *cis*- pathway involved in the postulated mechanism.

The control of stereoselectivity in this arylation has been a major issue and our efforts to design and synthesize new ligands did not lead to an ideal selectivity. No proper rationalization could be obtained. Nevertheless, this study also enlightened us about the possible challenges for the control of regio- and stereo-selectivity in palladium-catalyzed migrative cross-couplings, which are currently under investigation in the Baudoin group.

3. Intermolecular atroposelective Csp^2-H arylation

3.1. Early development

We started our investigation by attempting the racemic Csp2-H arylation of the 1,2,3-triazole **3.1** with 1-bromonaphtalene (Table 17). The use of the conditions described by Gevorgyan[142] led us to 9% of **3.2a** (entry 1), where the arylation gave 66% yield in the original report. More classical conditions for C-H activation allowed us to obtain the desired product in 39% yield (entry 2). The reactivity dramatically decreased when the temperature was lowered to 70°C (entry 3). The reaction in DME provided a reactivity which is comparable as the one in mesitylene (entry 4). In the more polar DMF, in the absence of pivalic acid, the product was afforded in a modest yield of 23% (entry 5).



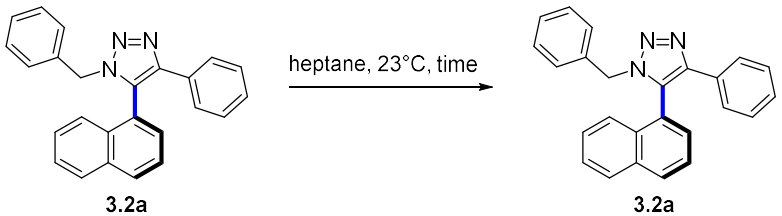
3.1 3.2a

Entry	Conditions	Yield 3.2a (%)
1	$Pd(OAc)_2$ 5 %mol, Bu_4NOAc 2 eq, NMP, 100°C, 18h	9
2	$Pd(OAc)_2$ 5 %mol, $P(Cy)_3$ 10 %mol, PivOH 30 %mol, Cs_2CO_3 1.5 eq, Mesitylene, 100°C, 18h	39
3[a]	Entry 2 at 70°C	< 3%
4[a]	Entry 2 in DME	42%
5[a]	Entry 2 in DMF, no PivOH	23%

[a] ^{1}H NMR yield with trichloroethylene as the reference.

Table 17. *Determination of conditions for the Csp^2-H arylation of* ***3.1***

The racemic mixture was separated by semi-preparative HPLC on chiral phase, and the enantiopurity of the scalemic sample was determined with respect to time (Table 18). The assumed enantiopure sample was always observed with an erosion of *e.e.* when being analyzed within an hour after the purification. When the sample was aged at 23°C in heptane, a fast racemization occurred. Starting from a 86:14 *e.r.* sample, the enantioenrichment tumbled down to 55:45 *e.r.* after 6h, and a total racemization was observed after 18h.



3.2a
86:14 *e.r.*

3.2a
e.r.

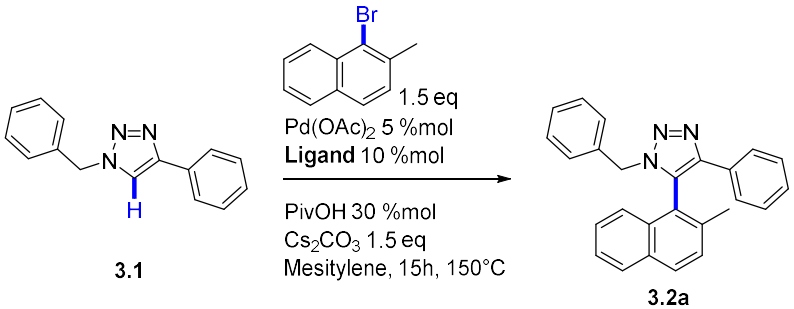
Entry	Time (h)	*e.r.*[a]
1	1	86:14
2	6	55:45
3	18	50:50
4	36	50:50

[a]*e.r.* valuedetermined by HPLC analysis on a chiral stationary phase.

Table 18. *Evolution of the e.r. of* ***3.2a*** *with respect to time at 23°C*

This first substrate was not adapted for Csp2-H arylation at high temperature (>100°C) and long reaction times (>15h). This study encouraged us to use a more hindered coupling partner, in order to increase the rotational barrier of the system, thus allowing us to study the enantioselective version of this arylation.

The racemic arylation of **3.1** was then studied with 1-bromo-2-methylnaphtalene as the coupling partner (Table 19). The reaction in classical conditions with $P(Cy)_3$ as the ligand at 120°C provided 12% of the isolated product **3.2b** for racemization tests (entry 1). The NMR yield increased to 35% when the reaction was conducted at 150°C (entry 2). The use of $P(n\text{-}Bu)_3$ was not efficient, and the product could be afford in only 11% with $P(Ph)_3$ (entries 3-4). Interestingly, with PAd_2n-Bu (CataXCium A), the product was afforded in 42% yield (entry 5). Moreover, an amelioration of the yield was observed at higher temperature and with a longer reaction time (entries 6-7). In contrast, RuPhos and the classical NHCs IPr and IBiOx did not provide any product in these conditions (entries 8-10). The reaction in more polar solvents such as NMP or DMAc showed to be inefficient a 120°C (entries 11-12).

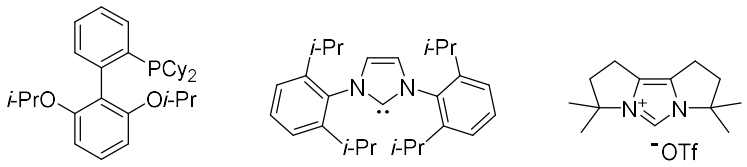


3.1

3.2a

Entry	Conditions deviation	Ligand	Yield[a] 2.a (%)
1	120°C	$P(Cy)_3$	12[b]
2	/	$P(Cy)_3$	35
3	72h	$P(n\text{-}Bu)_3$	no prod.
4	/	$P(Ph)_3$	11
5	/	$PAd_2n\text{-}Bu$	42
6	72h	$PAd_2n\text{-}Bu$	50
7	170°C, 72h	$PAd_2n\text{-}Bu$	50
8	/	**1.L²**	no prod.
9	/	**3.L⁵⁶**	no prod.
10	/	**3.L⁵⁷**	no prod.
11	$Pd(OAc)_2$ 2.5 %mol, NMP	$PAd_2n\text{-}Bu$	no prod.
12	K_2CO_3 1.5 eq, DMAc	$PAd_2n\text{-}Bu$	no prod.

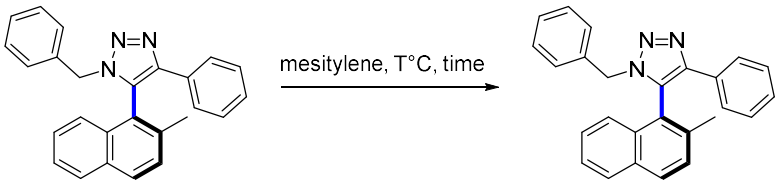
[a] ^1H NMR yield with trichloroethylene as the reference. [b] Isolated yield.



1.L² RuPhos | 3.L⁵⁶ IPr NHC | 3.L⁵⁷ IBiOx.HOTf

Table 19. *Study of the Csp2-H arylation of **A1***

The enantiomers of **3.2b** were separated by semi-preparative HPLC on chiral phase, and the enantiopurity of the scalemic sample was determined with respect to time at different temperatures in mesitylene (Table 20). No erosion of the enantiopurity of a 98:2 *e.r.* sample was observed at 23°C over 20h (entry 1). Gratifyingly, no decline was observed also at 120°C over 2.5h (entry 2). Furthermore, the enantiomeric ratio stayed intact a 150°C over 2.5h (entry 3).



3.2b 98:2 *e.r.* → **3.2b** *e.r.*

Entry	Temperature (°C)	Time (h)	*e.r.*[a]
1	23	20	98:2

2	120	2.5	98:2
3	150	2.5	98:2

[a] *e.r.* valuedetermined by HPLC analysis on a chiral stationary phase.

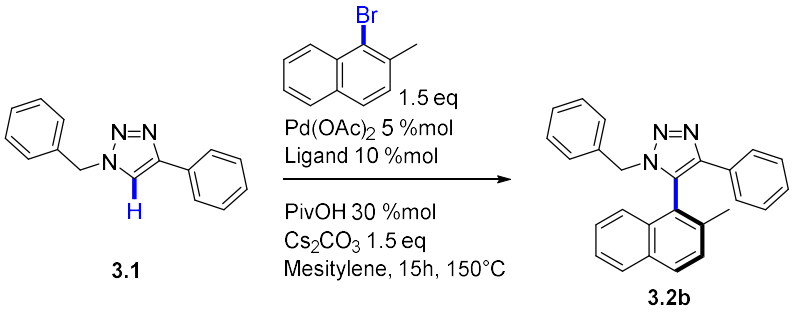
Table 20. *Evolution of the e.r. of enantiopure* ***3.2b*** *with respect to time and temperature*

Since a scalemic mixture of **3.2b** would not suffer an erosion of *e.e.* at high temperatures, we envisioned to develop the enantioselective version of this Csp2-H arylation reaction with **3.1** in presence of 1-bromo-2-methylnaphtalene.

3.2. System optimization with 1-bromo-2-methylnaphtalene

3.2.1. Ligand screen

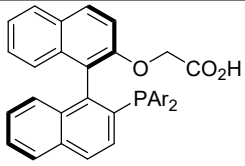
As a first step, different families of ligand were screened in combination with Pd_2dba_3 as the metal catalyst (Table 21). In these conditions, the reactivity with CataXCium A got lower than with $Pd(OAc)_2$ (entry 1). The achiral NHCs **3.L**[56] nd **3.L**[57] were also inefficient (entries 2-3). We were satisfied to observe that the bifunctional ligand **3.L**[58] in absence of PivOHprovided 13% NMR yield, and a 70:30 *e.r.* of the isolated product (entry 4). Other classes of ligand, such as binepines, phosphoramidite, and taddol-derived phosphonites did not show any reactivity (entries 5-9). The use of the chiral phosphoric **3.L**[64] acid in presence of $P(Cy)_3$ did not lead to the product (entries 10). A quick screen of conditions did not bring any major amelioration of the result obtained with the **3.L**[58] (entries 11-15).



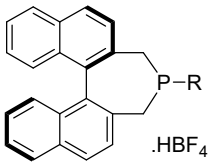
Entry	Condition deviations	Ligand	Yield[a] A1b (%)	*e.r.*[b]
1	/	PAd_2n-Bu	16	*rac*
2	/	**3.L**[56]	no prod.	n.d.
3	/	**3.L**[57]	no prod.	n.d.
4	No PivOH	**3.L**[58]	13 (10)[c]	70:30
5	/	**3.L**[59]	no prod.	n.d.
6	/	**3.L**[60]	no prod.	n.d.

7	/	**3.L[61]**	no prod.	n.d.
8	/	**3.L[62]**	no prod.	n.d.
9	/	**3.L[63]**	no prod.	n.d.
10	$Pd(PCy_3)_2$	**3.L[64]**	no prop.	n.d.
11	$PdCl_2MeCN_2$	**3.L[58]**	14	70:30
12	$[Pd(\pi\text{-cin})Cl]_2$	**3.L[58]**	14	70:30
13	$PdMe_2TMEDA$	**3.L[58]**	18.5	70:30
14	DME	**3.L[58]**	13.5	66:33
15	Rb_2CO_3	**3.L[58]**	14.5	70:30

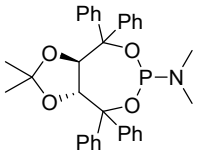
[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* valuedetermined by HPLC analysis on a chiral stationary phase. [c] Isolated yield in brackets.



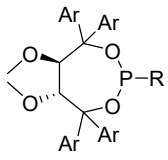
3.L[58] : Ar=3,5-diMePh



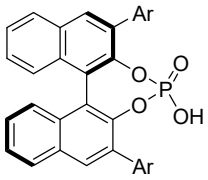
3.L[59] : R= *o*-Tolyl
3.L[60] : R= Cy



3.L[61]



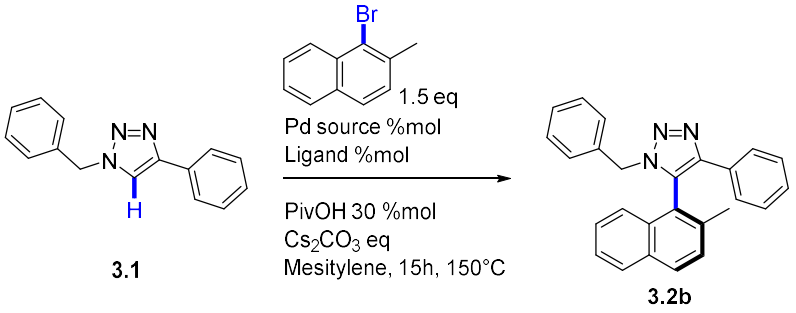
3.L[62] : Ar= 3,5-diCF_3Ph ; R = Ph
3.L[63] : Ar= 3,5-diCF_3Ph ; R = Cy



3.L[64]
Ar = 3,5-diCF_3Ph

Table 21. *First screen of ligand*

The effect of the catalyst loading was evaluated in both the racemic and enantioselective fashion, with respect to the base equivalents (Table 22). The yield increased to 22% with a double loading of the catalyst, from 5 %mol to 10 %mol, in presence of 1.5 eq of base for the racemic procedure (entries 1-2). The increase of base stoichiometry was not more effective (entries 3-4). A stoichiometry of 1:2 Pd/L also provided a similar yield (entry 5). This stoichiometry proved to be much for efficient when used for the enantioselective protocol, with $Pd(OAc)_2$ as the metal source and **3.L[58]** as the ligand (entries 6-7). Nevertheless, the reaction afforded 30% yield of the desired product when Pd_2dba_3 was the catalyst (entry 8). As a side note, the *e.r.* of 70/30 remained unaffected in this screen.



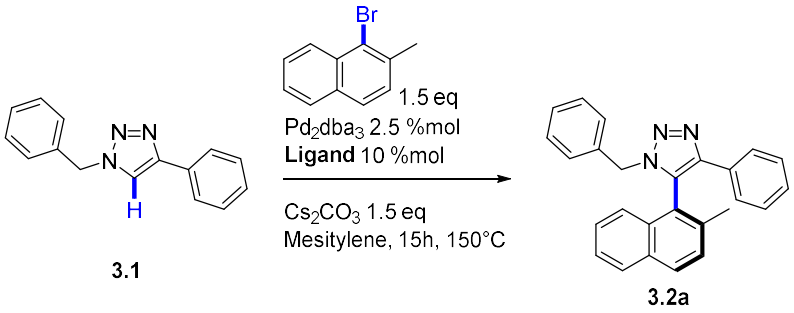
Entry	Pd source	%mol	Ligand	% mol	Cs_2CO_3 eq	Yield[a] A1b (%)	*e.r.*[b]
1	Pd_2dba_3	2.5	$PdAd_2n$-Bu	5	1.5	14	*rac*
2	Pd_2dba_3	5	$PdAd_2n$-Bu	10	1.5	22	*rac*
3	Pd_2dba_3	2.5	$PdAd_2n$-Bu	5	3	14	*rac*
4	Pd_2dba_3	5	$PdAd_2n$-Bu	10	3	20	*rac*
5	Pd_2dba_3	2.5	$PdAd_2n$-Bu	10	1.5	20	*rac*
6	$Pd(OAc)_2$, no PivOH	2.5	**3.L**[58]	5	1.5	16	70:30
7	$Pd(OAc)_2$, no PivOH	2.5	**3.L**[58]	10	1.5	28	70:30
8	Pd_2dba_3, no PivOH	2.5	**3.L**[58]	10	1.5	30 (20)[c]	70:30

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* valuedetermined by HPLC analysis on a chiral stationary phase. [c] Isolated yield in brackets.

Table 22. *Evalutation of the catalyst loading for both protocols*

With these last conditions in hands, we varied the parameters of the bifunctional ligand, such as the chain length to the acid, the aryl substitution and the hindrance of the chain (Table 23). The change in the 3,5-disubstition caused a decrease of reactivity. Yields between 10% and 18% were obtained (entries 2-4), and interestingly the opposite configuration of the product was induced with the fluorinated ligand **3.L**[66] (entry 3). Nevertheless, the selectivity was not ameliorated. When the 3,5-disubstitution was suppressed in **3.L**[68], the reactivity got recovered, and the selectivity rose up (entry 5) ; suggesting an negative effect of the close congestion at the reactive site. The ethyl ester **3.L**[68E] and the MOP were engaged in the same conditions (entries 6-7). Surprisingly, the product was obtained with a higher selectivity, but in low yield. In this case, it is assumed that the carbonate could perform the deprotonation. When the same experiments were run in presence of PivOH (entries 8-10), similar results were obtained, thus showing that the acid inductor in the bifunctional ligand is not crucial; and may not play an essential role in this reaction. The selectivity may be predominantly

induced by the phosphine moiety. Despite these ambiguous observations, the chain length to the acid was screened (entries 11-15); an enhanced reactivity and selectivity were found when the chain was 5 carbon-long in **3.L**[73]. The hindrance at the α-position of the acid dramatically decreased the reactivity and the selectivity when **3.L**[75] was used (entry 16). Furthermore, no more reaction occurred with **3.L**[77] as the ligand (entry 17).



Entry	Additive	Bifunct. Ligand	Ar	n	Yield[a] A1b (%)	*e.r.*[b]
1	/	**3.L**[58]	3,5-diMePh	1	30 (20)	70:30
2	/	**3.L**[65]	3,5-diOMePh	1	15	67.5:32.5
3	/	**3.L**[66]	3,5-diCF_3Ph	1	18	40:60
4	/	**3.L**[67]	3,5-di*t*-BuPh	1	10	68:32
5	/	**3.L**[68]	Ph	1	26	73:27
6	/	**3.L**[68E]	-	-	20	77:23
7	/	**3.L**[69]	-	-	11	80:20
8	PivOH 30 %mol	**3.L**[68]	Ph	1	26	75:25
9	PivOH 30 %mol	**3.L**[68E]	-	-	25	75:25
10	PivOH 30 %mol	**3.L**[69]	-	-	17	78:22
11	/	**3.L**[70]	Ph	2	14	76:24
12	/	**3.L**[71]	Ph	3	12	77:23
13	/	**3.L**[72]	Ph	4	13	78:22
14	/	**3.L**[73]	Ph	5	24	78:22
15	/	**3.L**[74]	Ph	6	15	77:23
16	/	**3.L**[75]	-	-	7	58.5:41.5
17	/	**3.L**[76]	-	-	no prod.	n.d.

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* valuedetermined by HPLC analysis on a chiral stationary phase.

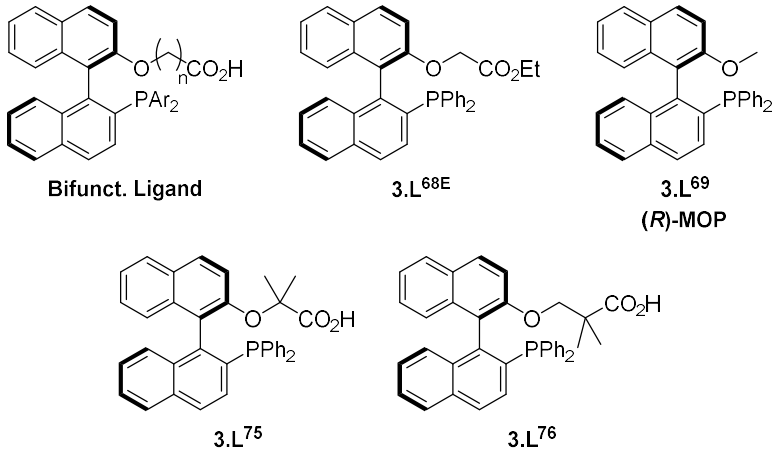
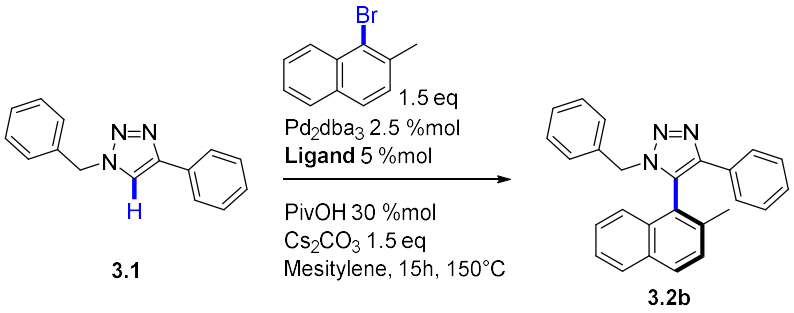


Table 23. *Variation of the bifunctional ligand*

The variation of the parameters of the bifunctional ligand showed us that the reaction is very sensitive to congestion at the reaction site. The role of the acid moiety of this bifunctional ligand is ambiguous, but its presence (in **3.L**[68]) affects positively the outcome of the reaction when compared to the corresponding ester or to the MOP. The best result was obtained with **3.L**[73], the bifunctional ligand bearing a $-PPh_2$ moiety and a $(CH_2)_5$ spacing chain to the acid.

A last screen of chiral ligand was operated in previously used conditions (Table 24). The NHC **3.L**[77] developed by Kunding did not provide any product (entry 1). The Cramer type ligand **3.L**[78], a chiral phosphine based on the Buchwald type ligand, afforded the desired product in 14% yield and a reverse selectivity (entry 2), comparable to the one obtained with the previously screened bifunctional ligands. The (*S*)-KenPhos**3.L**[79] was ineffective in the coupling (entry 3), while the (*S*)-Quinap **3.L**[80] and the (*R*)-Binap **3.L**[81] afforded very low yields of **3.2b** as near racemic mixtures (entries 4-5).



Entry	Ligand	Yield[a] A1b (%)	*e.r.*[b]
1	**3.L**[77]	no prod.	n.d.
2	**3.L**[78]	14	30:70
3	**3.L**[79]	no prod.	n.d.

4	**3.L[80]**	8	51:49
5	**3.L[81]**	15	49:51

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* valuedetermined by HPLC analysis on a chiral stationary phase.

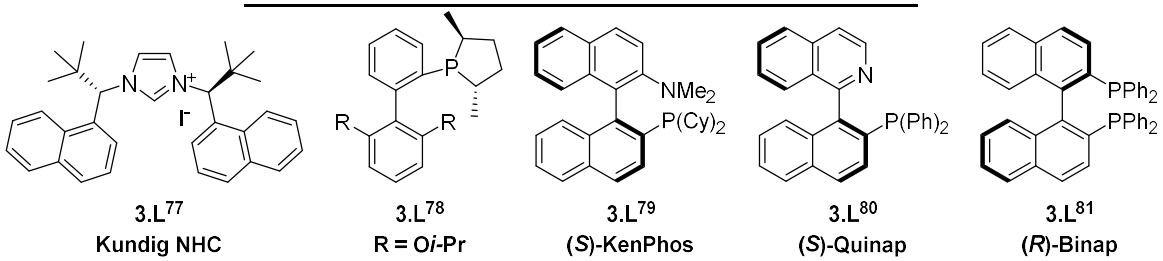
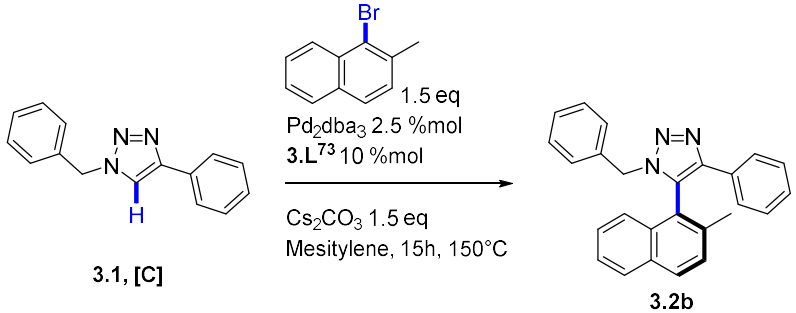


Table 24. *Additional ligand screen*

These other ligands did not provide any satisfactory results. Interestingly, the Cramer type ligand gave a comparable result as with the bifunctional ligand. Nevertheless, this class of ligand suffers a challenging synthesis and only a small sample was available in our chemical library for testing purpose. The reaction in presence of **3.L[73]** was then optimized.

3.2.2. Optimization of the reaction conditions

The different parameters of the reaction were optimized. The concentration of the reaction was varied (Table 25). The ligand optimization was run at a concentration in starting material of 0.25 M. The dilution of the reaction was negative in terms of yield but favorable for selectivity (entries 1-2). On the other hand, when the concentration was increased, the yield followed the trend while the selectivity slightly decreased (entries 5-6). Note that the reaction in neat 1-bromo-2-methylnaphtalene provided 36% yield with a near average *e.e.*(entry 7). The optimal concentration was 0.5 M (entry 4).



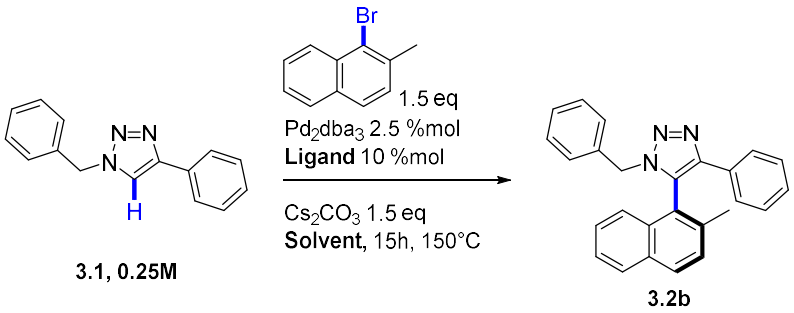
Entry	3.1 Concentration (mol/L)	Yield 3.2b (%)	*e.r.*
1	0.0625	23	80:20

2	0.125	26	79:21
3	0.25	27	78:22
4	0.5	36	78:22
5	0.75	33	77:23
6	2.5	32	76:24
7	Neat in 10 eq BrAr	34	75.5:24.5

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* value determined by HPLC analysis on a chiral stationary phase.

Table 25. *Concentration optimization*

The optimal solvent was also determined for the reaction in presence of **3.L**[73], and also the MOP **3.L**[73] with or without PivOH (Table 26). Polar solvents were not suitable for the reaction (entries 1-4). Heavy ethers provided the product in respectable yield with **3.L**[69] (entries 5-6). Apolar aromatic solvents proved to be efficient (entries 7-13), and the optimal solvent for the reaction with **3.L**[73] was the mixture of xylenes, which provided **3..2b** in 36% yield and 78:22 *e.r.* (entry 11). The optimal solvent for the reaction with **3.L**[69] in presence of PivOH was the 1,2,4-trimethylbenzene, which afforded the desired product in 23% yield and 73:27 *e.r.* (entry 7). The reactivity was dramatically decreased when the **3.L**[69] was used without PivOH. It is important to notice that no relevant variation of selectivity is observed in this series.



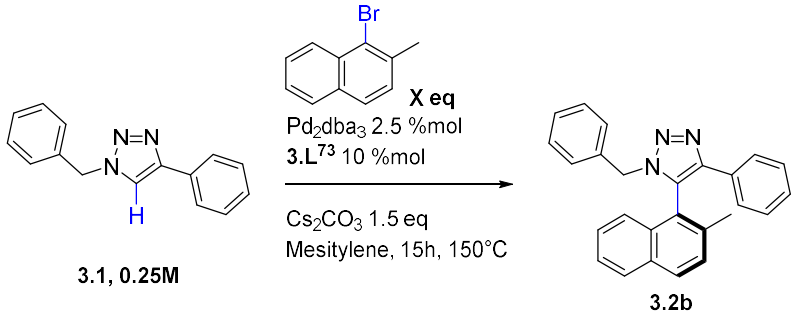
Entry	Solvent	**3.L**[73] yield[a], *e.r.*[b]	**3.L**[69]+PivOH 30 %mol yield[a], *e.r.*[b]	**3.L**[69] yield[a], *e.r.*[b]
1	NMP	5%, n.d.	6%, n.d.	4%, n.d.
2	DMAc	3%, n.d.	4%, n.d.	3%, n.d.
3	DMF	3%, n.d.	3%, n.d.	3%, n.d.
4	Benzonitrile	traces	traces	no prod.
5	Diethoxyethane	5%, n.d.	15%, 74:26	8%, n.d.
6	Dibutylether	17%, 75:25	16%, 71:29	6%, n.d.

7	1,2,4-Trimethylbenzene	27%, 78:22	23%, 73:27	8%, n.d.
8	*p*-Cymene	32%, 78:22	12%, 76:24	11%, 74:26
9	Cumene	30%, 78:22	20%, 75:25	7%, n.d.
10	Anisole	26%, 76:24	14%, 73:27	4%, n.d.
11	Xylenes	36%, 78:22	17%, 74:26	13%, 73:27
12	*p*-Xylene	14%, 78:22	15%, 74:26	9%, n.d.
13	*m*-Xylene	36%, 78:22	15%, 74:26	6%, n.d.

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* valuedetermined by HPLC analysis on a chiral stationary phase.

Table 26. *Solvent screen the the atroposelective arylation*

The stoichiometry of the bromide was surveyed and the addition of molecular sieves was examined, in presence of **3.L**[73] (Table 27). The yield increased when the proportion of the aryl increased (entries 1-5). In contrast, the selectivity was not influenced by this variation. A ratio of bromide/**3.1** 1.5:1 was found ideal (entry 3). In these conditions, the addition of molecular sieves proved to be very effective (entries 6-8). The 4Å MS was kept as the additive of choice, thanks to its availability.

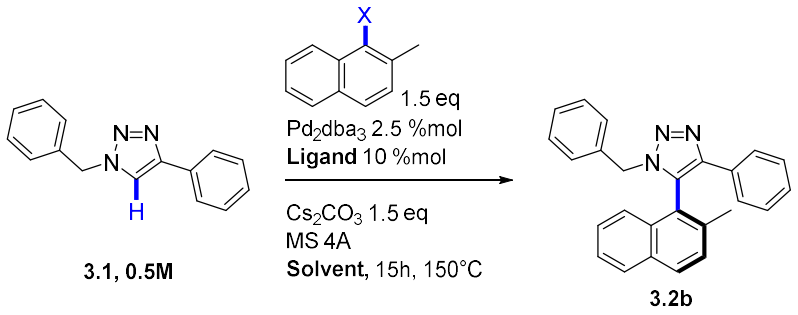


Entry	X/3.1 eq, additive	Yield[a] 3.2b (%)	*e.r.*[b]
1	0.75:1	23[c]	78:22
2	1:1	26	78:22
3	1.5:1	27	78:22
4	3:1	27	78:22
5	5:1	30	78:22
6	1.5:1, MS 3Å	35	77.5:22.5
7	1.5:1, MS 4Å	33	78:22
8	1.5:1, MS 5Å	35	78.5:21.5

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* valuedetermined by HPLC analysis on a chiral stationary phase. [c] Yield calculated with respect to the bromide.

Table 27. *Survey of the stoichiometry of the bromide*

The optimal conditions for **3.L**[73] and the MOP were combined and evaluated on the bromide as well as the iodide (Table 28). We were satisfied to obtain **3.2b** in 48% isolated yield in 77.5:22.5 *e.r.* with the bifunctional ligand (entry 1). The use of the 1-iodo-2-methylnaphtalene did not bring any amelioration (entry 2). When the MOP **3.L**[69] was used, the product was obtained in 34% yield in 75:25 *e.r.* (entry 3). The iodide did not affect the outcome of the reaction (entry 4).

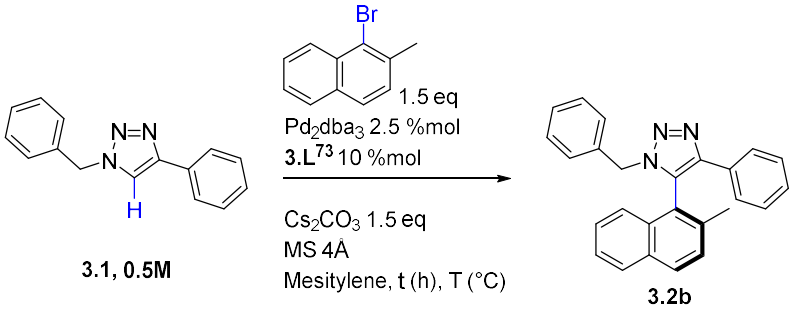


Entry	Ligand	Solvent	X	Yield[a] 3.2b (%)	*e.r.*[b]
1	**3.L**[73]	Xylenes	Br	57 (48)[c]	77.5:22.5
2	**3.L**[73]	Xylenes	I	56	78:22
3	**3.L**[69]+PivOH 0.3 eq	1,2,4-trimethylbenzene	Br	34	75:25
4	**3.L**[69]+PivOH 0.3 eq	1,2,4-trimethylbenzene	I	34	75:25

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* valuedetermined by HPLC analysis on a chiral stationary phase. [c] Isolated yield in brackets.

Table 28. *Arylation in the optimized conditions.*

To ensure that we reached the maximum potential of this reaction, a kinetic study of the arylation was done at 150°C, and the reaction was run at lower temperatures over 15h (Table 29). The yield rapidly increases over 2h and stabilizes over 55% after 4h at 150°C (entries 1-5). The enantiomeric ratio slowly decreases over 15h to reach 77.5:22.5. The reactivity shut down quickly when the temperature is lowered in a range of 140-120°C, despite a slightly better selectivity (entries 6-8).

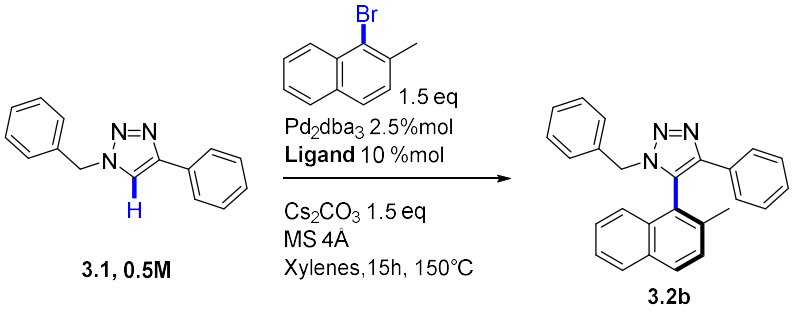


Entry	T (°C)	t (h)	Yield[a] 3.2b (%)	*e.r.*[b]
1	150	1	39	79:21
2	150	2	53	78.2:21.8
3	150	4	55	78:22
4	150	7	59	78:22
5	150	15	57	77.5:22.5
6	140	15	45	77:23
7	130	15	36	80:20
8	120	15	29	80:20

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* value determined by HPLC analysis on a chiral stationary phase.

Table 29. *Kinetic study of the arylation reaction*

In the end, more elaborated bifunctional ligands **3.L$^{82a\text{-}b}$** and **3.L$^{82aE\text{-}bE}$** bearing a lactyl moiety were engaged in the arylation reaction and compared to the ligand **3.L^{68}** (Table 30). A match/mismatch effect was observed for both the free acids and the corresponding methyl esters in presence of PivOH 0.3 eq, and a global decrease of reactivity was observed, showing again the negative effect of a steric congestion at the reaction site (entries 2-5). The (*S*) configuration of the lactyl moiety in **3.L^{82a}** and **3.L^{82aE}** provoked a mismatch effect, reflected by a clear drop of yield and selectivity (entries 2 and 4). The match effect with the (*R*) configuration of the lactyl in **3.L^{82b}** and **3.L^{82bE}** was also pronounced and only a reduction of yield was observed, along with a rise of the selectivity (entries 3 and 5). The reactivities of the esters were similar to their free acid counterparts, denoting again a non substancial effect of the acid.



Entry	Additive	Ligand	Yield[a] A1b (%)	*e.r.*[b]
1	/	**3.L**[68]	43	71.5:28.5
2	/	**3.L**[82a]	18	59:41
3	/	**3.L**[82b]	25	78:22
4	PivOH 30 %mol	**3.L**[82aE]	21	66:34
5	PivOH 30 %mol	**3.L**[82bE]	28	77.5:23.5

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* value determined by HPLC analysis on a chiral stationary phase.

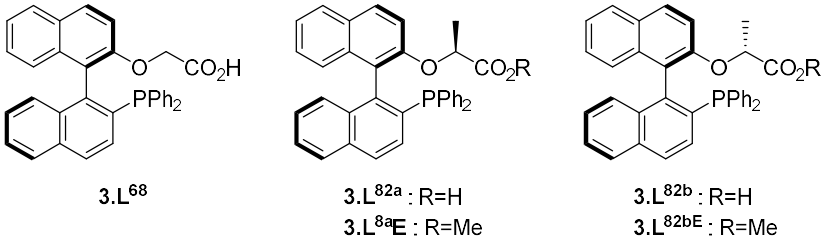


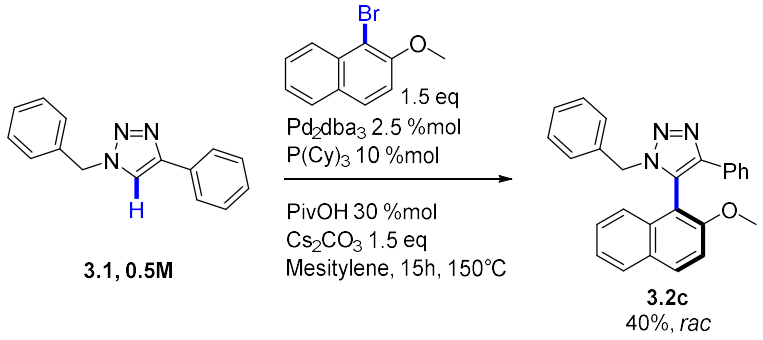
Table 30. *Evaluation of a match/mismatch effect with ligands* ***3.L***[77]

All those results led us to reconsider the substrate and/or the bromide. Indeed, the 2-Me substitution of the naphthalene brings an important hindrance blocking the axial rotation, making this system suitable for high temperature and reaction times; but this hindrance also limits the reactivity and the selectivity in this arylation reaction. This suggests that the high limit of our system was reached with this combination of substrate, in contrast to the initially proposed arylation with 1-bromonaphalene, proving to be reactive but not adapted to the harsh reaction conditions for enantioselective Csp2-H activation.

We then decided to change the bromoelectrophile engaged in the reaction, while keeping the optimized conditions.

3.3. Development with 1-bromo-2-methoxynaphtalene

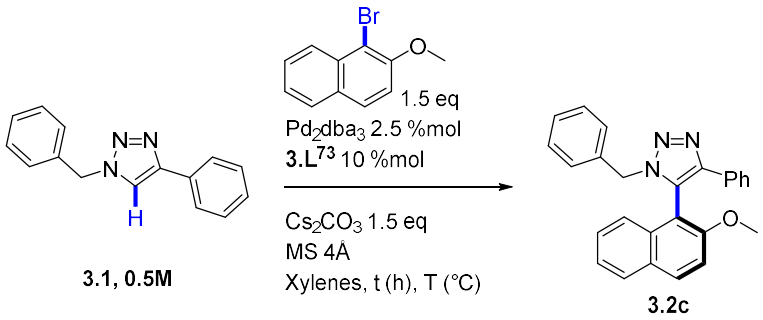
The arylation with 1-bromo-2-methoxynaphtalene as the coupling partner was examined. The racemic coupling proceeded in 40% yield with PCy_3 as the ligand in xylenes (Scheme 90). The product **3.2c** was isolated for analytical purpose.



Scheme 90. *Racemic arylation with 1-bromo-2-methoxynaphtalene*

3.3.1. Optimization with the bifunctional ligands

The enantioselective version of the reaction was directly studied with respect to time and temperature, with **3.L**[73] as the ligand, in the previously optimized conditions (Table 31). The observed yield rapidly reached more than 90% after only 1h at 150°C, with 76:24 *e.r.* (entry 1). The enantiopurity got dramatically affected by time and a near racemic mixture was obtained after 15h of reaction (entries 2-5). The reaction at 140°C for 15h afforded **3.2c** in 90% yield, in a better enantiomeric ratio of 66.5:33.5 (entry 6). Under 130°C, the reactivity started to decrease (entry 7-8), despite a higher conservation of the enantioenrichment over 15h.



Entry	T (°C)	t (h)	Yield[a] 3.2c (%)	*e.r.*[b]
1	150	1	> 90	76:24
2	150	2	> 90	70:30
3	150	4	> 90	66.5:33.5

4	150	7	> 90	59:41
5	150	15	> 90	53:47
6	140	15	> 90	66.5:33.5
7	130	15	75	68:32
8	120	15	65	74:26

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* value determined by HPLC analysis on a chiral stationary phase.

Table 31. *Time and temperature variation for the arylation toward* ***3.2c***

The reaction time was optimized at 140°C (Table 32). The yield reached 70% after 1h of reaction (entries 1-5) and topped 90% after 2h of reaction, affording 75:25 *e.r.*(entries 6). A longer reaction time provoked a depletion of the selectivity (entries 7-8). The optimal time of 2h was selected for the further study.

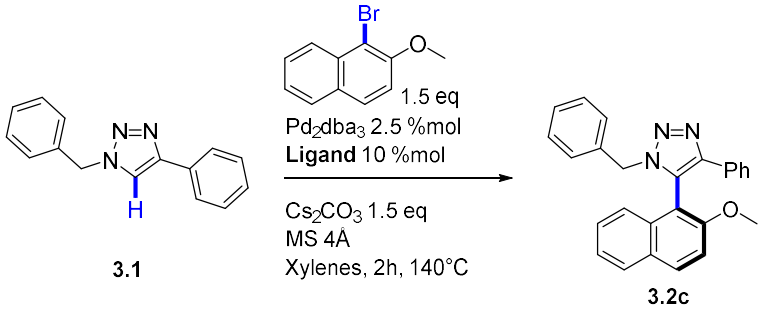
Entry	t (min)	Yield[a] 3.2c (%)	*e.r.*[b]
1	10	26	77:23
2	20	47	77:23
3	30	57	77:23
4	45	61	77:23
5	60	70	77:23
6	120	> 95	75:25
7	240	> 95	70:30
8	420	> 95	66:34

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* value determined by HPLC analysis on a chiral stationary phase.

Table 32. *Optimization of the reaction time for the arylation toward* ***3.2c***

At this step, it was necessary to re-evaluate the bifunctional ligands in order to ensure that **3.L**[73] was the most suitable ligand for this transformation. The reactions were run after being stirred for 1 min at 23°C, for the sake of reproducibility. Indeed, notable variations in the results were observe when the reaction were run directly after addition of the solvent to the reactants. The variation of the chain length (entries 1-6) followed the same trend as the arylation with 1-bromo-2-methylnaphtalene, and the 5 carbons spacer in **3.L**[73] prove to be the most efficient, providing **3.2c** in more than 95% yield and 73:27 *e.r.* (entry 2). The variation of the 3,5-disubstitution on the aryl moiety only induced a drop of reactivity, as well as a drop of selectivity (entries 7-10). The fluorinated ligand also reversed the selectivity (entry 9). The

ester **3.L**^{68E} turned down the reactivity, despite a conservation of the selectivity (entry 11). No reaction was observed with the MOP **3.L**^{69} in the absence of acid (entry 12). Interestingly, in presence of PivOH, **3.L**^{68} provided a better yield and a slight amelioration of selectivity (entry 13). The reactivity was recovered with the ester, and a similar enantiomeric ratio was obtained (entry 14). The MOP also proved to be efficient in presence of PivOH, and the product was obtained in 55% yield and 66:34 *e.r.* in this case, thus providing another optimizable system that will be discuss in the next part. The hindrance in **3.L**^{75} and **3.L**^{76} shut down the reactivity (entries 16-17). A near racemic mixture was obtained with **3.L**^{75} (entry 16), reinforcing the suggestion of a negative effect of the hindrance at the reactive site. The match effect with **3.L**^{82b} was also observed with this coupling partner. The selectivity was increased and **3.2c** was obtained in 20% yield but with 74:26 *e.r.* (entry 19). The switch to the $-P(Cy)_2$ moiety in **3.L**^{68Cy} was neither profitable for the reactivity nor for the selectivity (entry 18).



Entry	Additive	Ligand	Ar	n	Yield[a] A1c (%)	*e.r.*[b]
1	/	**3.L**^{74}	Ph	6	80	73:27
2	/	**3.L**^{73}	Ph	5	> 95	73:27
3	/	**3.L**^{72}	Ph	4	61	73:27
4	/	**3.L**^{71}	Ph	3	18	71:28
5	/	**3.L**^{70}	Ph	2	27	70:30
6	/	**3.L**^{68}	Ph	1	42	66:34
7	/	**3.L**^{58}	3,5-diMePh	1	22	64:36
8	/	**3.L**^{65}	3,5-diOMePh	1	13	63:37
9	/	**3.L**^{66}	3,5-diCF_3Ph	1	21	38:62
10	/	**3.L**^{67}	3,5-di*t*-BuPh	1	28	65:35
11	/	**3.L**^{68E}	-	-	9	72:27
12	/	**3.L**^{69}	-	-	no prod.	n.d.
13	PivOH 30 %mol	**3.L**^{68}	Ph	1	55	70:30
14	PivOH 30 %mol	**3.L**^{68E}	-	-	26	70:30
15	PivOH 30 %mol	**3.L**^{69}	-	-	55	66:34

16	/	**3.L[75]**	-	-	13	53:47
17	/	**3.L[76]**	-	-	traces	n.d.
18	/	**3.L[68Cy]**	-	-	10	61:39
19	/	**3.L[82b]**	-	-	20	74:26

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* valuedetermined by HPLC analysis on a chiral stationary phase.

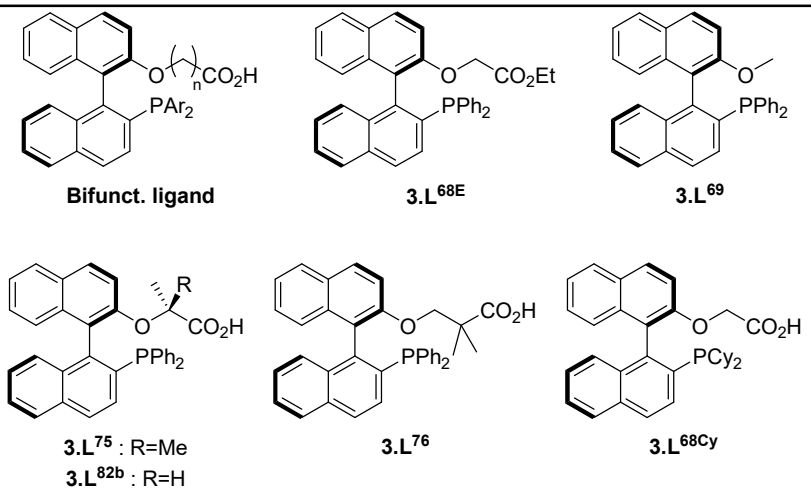
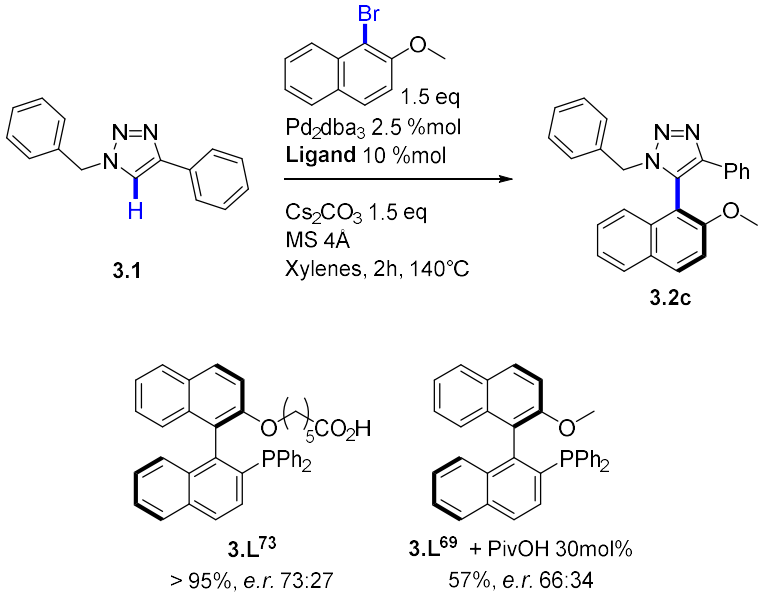


Table 33. *Ligand screen for the arylation toward* ***3.2c***

This ligand screen confirmed us the efficiency of the bifunctional ligand **3.L[73]**for this Csp^2-H arylation reaction. Nevertheless, the recovery of reactivity with the 1-bromo-2-methoxynaphtalene did not compensate the lack of selectivity. The product **3.2c** was observed in more than 95% yield but with an *e.r.* which stagnates at 73:27. Because the **3.L[69]** exhibited an interesting reactivity, it was chosen to optimize this system in parallel, since other combined parameters such as the acid could be varied under this arylation conditions.

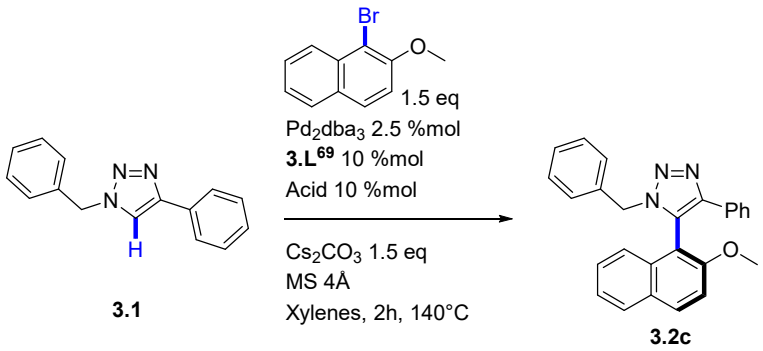
3.3.2. Optimization with the MOP**3.L[69]**

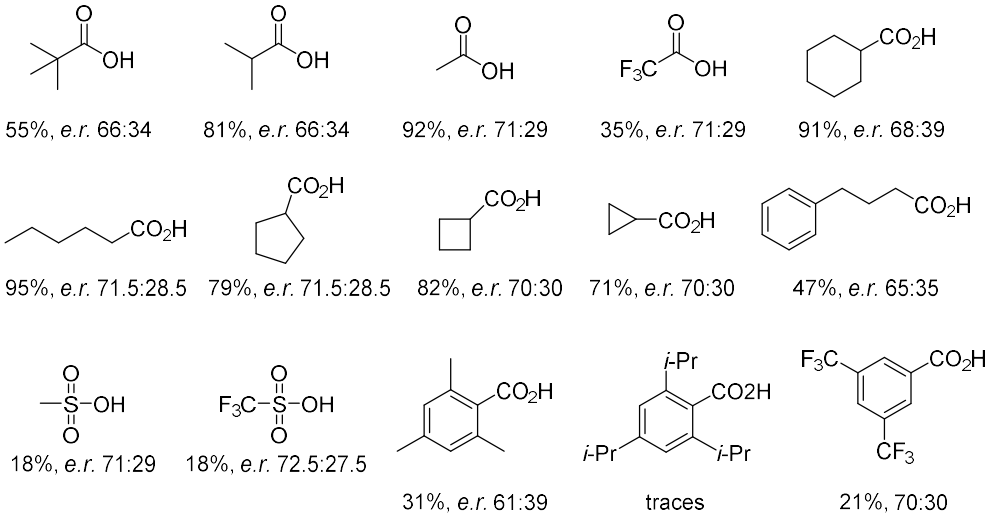
The study suggested us that the combination of MOP as the ligand and an acid could be an alternative to bifunctional ligands in this atroposelective Csp2-H arylation reaction (Scheme 91). Moreover, different congeners of **3.L[69]**and the acid could be rapidly screened.



Scheme 91. *MOP as an alternative to bifunctional ligands*

A broad range of organic acids was examined in 10 %mol toward the starting material, equivalent to 1:1 of (*R*)-MOP:acid ratio, to compare to the use of 10 %mol of bifunctional ligand (Scheme 92). The yield of the reaction was increased to up to 95% when the hexanoic acid was used, reaching 71.5:28.5 *e.r.*, in comparison to the use of PivOH.





Scheme 92. *First screen of organic acid*

The aminoacids and protected derivatives proved to be non suitable for this reaction (Figure 20). The use of the two enantiomers of the protected acid introduced by Cramer afforded **3.2c** in around 20% yield, with no notable match/mistmach effect. Indeed, the product was obtained in both case with near 10% *e.e.*.

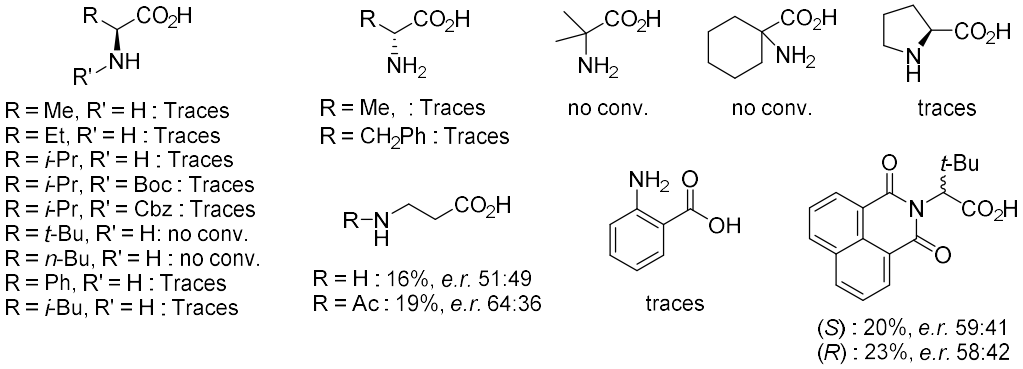


Figure 20. *Aminoacids screened in combination with MOP*

Additional acids were screened (Figure 21), and the racemic methoxy-lactic acid provided the desired product in 36% yield with 72:28 *e.r.*, thus showing a reduced reactivity despite the conservation of the selectivity. On a side note, the pyridinone introduced as the acid in C-H activation by Yu and coworkers was not efficient in this coupling.

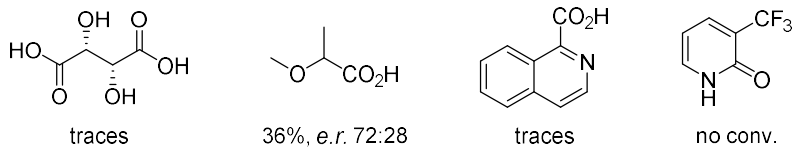
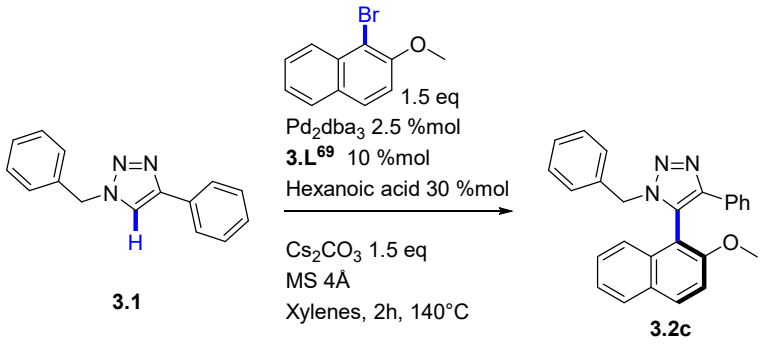


Figure 21. *Additional acids screened in combination with* ***3.L***[69]

The hexanoic acid was kept as the ideal partner with **3.L**[69] as the ligand for this arylation. The reactivity in this case was increased, and **3.2c** was obtained in 95% yield. Unfortunately, the enantiomeric ratio was only ameliorated to reach 70:30, which is comparable to the selectivity observed with the bifunctional ligand. No further amelioration of this ratio was observed for this arylation.

Control experiments were run to address the necessity of each reactant, this time involving the acid in 30 %mol (Table 34). The removal of a component of the catalytic system (entries 3-6), or of the base (entry 2) totally shut the reaction down. Also, no reaction happened in the absence of the acid (entry 5-6), suggesting that the carbonate alone is not involved in the proton abstraction.



Entry	Condition deviation	Yield[a] 3.2c (%)	*e.r.*[b]
1	/	> 95 (85)[c]	70:30
2	no Cs_2CO_3	0	n.d.
3	no **3.L**[69]	0	n.d.
4	no Pd_2dba_3	0	n.d.
5	no hexanoic acid	0	n.d.
6	no **3.L**[69], no hexanoic acid	0	n.d.

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* value determined by HPLC analysis on a chiral stationary phase. [c] yield of the isolated product.

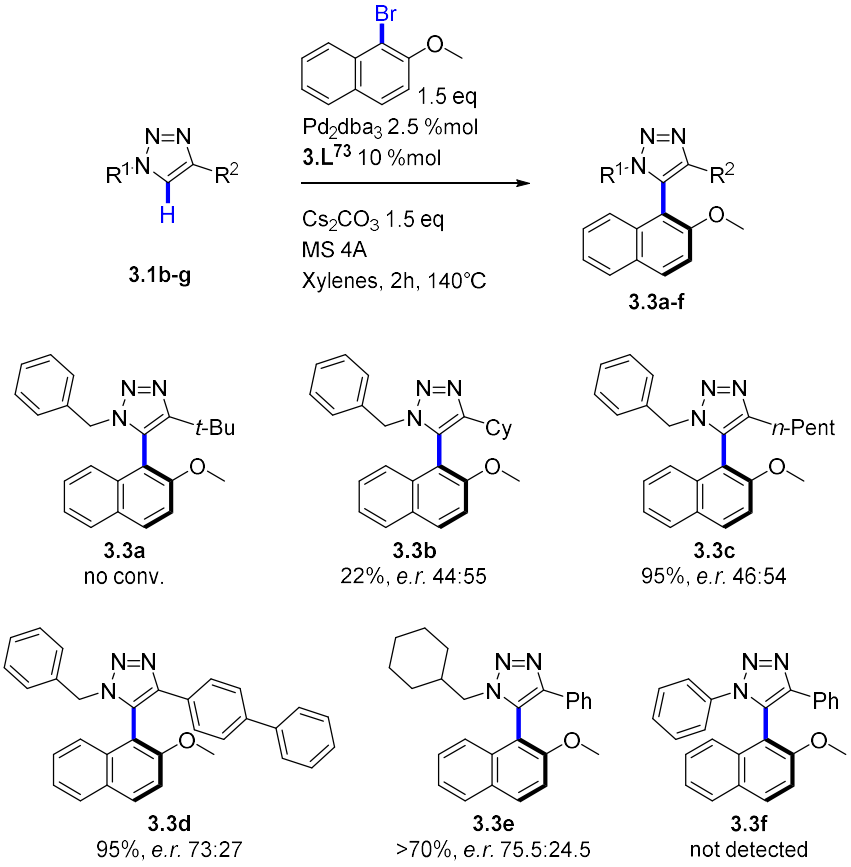
Table 34. *Control experiments with* ***3.L***[69]

Because no notable improvement of the selectivity was observed in the whole study, in spite of the discovery of two comparable system providing the arylated product in more than 90% yield and up to 73:27 *e.r.*, we decided to design the substrate and to vary the substituent borne by the triazole moiety.

3.4. Variation of the starting materials

3.4.1. Variation of the triazole

A variety of triazole was synthesized and engaged in the arylation reaction with 1-bromo-2-methoxynaphtalene, in presence of the bifunctional ligand **3.L**[73] (Scheme 93). No product **3.3a** was obtained when the phenyl moiety was replaced by a *t*-Bu group. The less hindered cyclohexyl or pentyl moieties afforded the corresponding products **3.3b** and **3.3c** in 22% and 95% yield, respectively, but with a very low selectivity. The product **3.3d** bearing an extended aromaticity on the biphenyl moiety was obtained in a similar fashion to **3.2c**, with 95% yield and 73:27 *e.r.*A slight amelioration of *e.r.* was observed when the benzyl was replaced by the corresponding saturated moiety, thus **3.3e** was obtained in more than 70% yield and 75.5:24.5 *e.r.*. The totally conjugated product **3.3f** was not detected in the crude mixture.

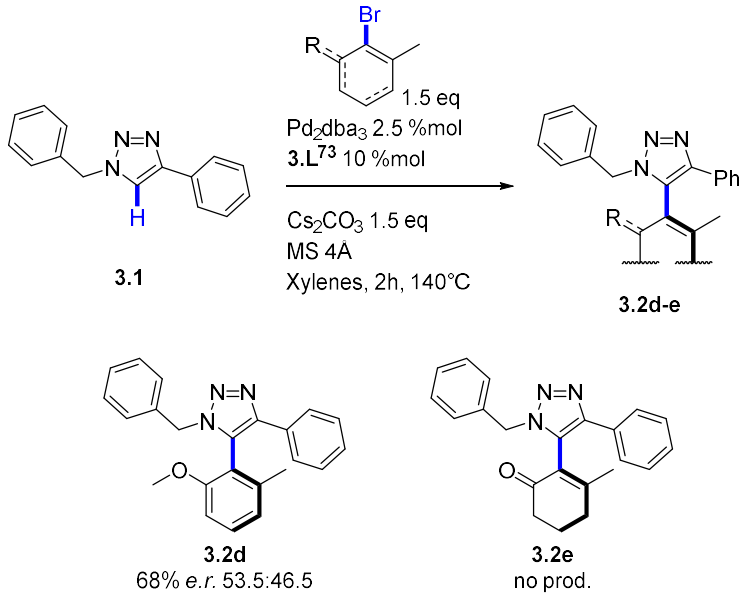


Scheme 93. *Variation of the triazole*

To our delight, several tested triazole underwent Csp2-H arylation in acceptable to good yield. But in contrast, no remarkably positive amelioration of the selectivity was observed, and near racemic mixtures were obtained in some cases.

3.4.2. Variation of the bromo-electrophile

The arylation was attempted on A1with less hindered bromo-electrophiles (Scheme 94). The product **3.2d** was obtained in a satisfying yield of 68%, but in less than 10% *e.e.*. The reaction with the α-bromo-3-methylcyclohexenone did not lead to **3.2e**, despite a total conversion of the bromide.



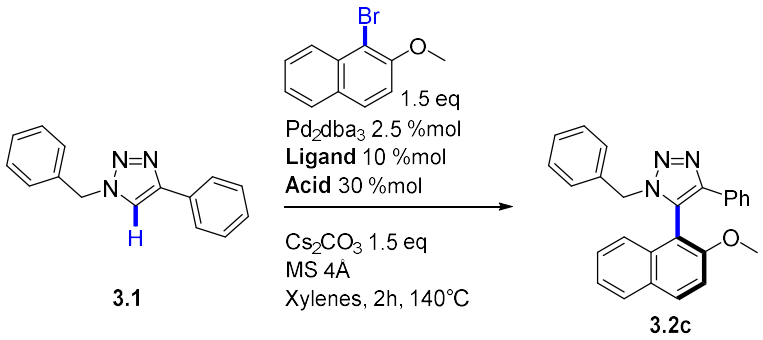
Scheme 94. *Variation of the bromo-electrophile*

After this quick evaluation of starting coupling partners, no further investigation was conducted, to leave space for the writing of this thesis. During this period, Cramer and coworkers reported a palladium-catalyzed intramolecular atroposelective Csp2-H arylation (see part1.3.6). To ensure of the uniqueness of our catalytic system, confirmation reaction were run.

3.5. Comparison with Cramer's report

In order to confirm the our catalytic system was unique, we tested our optimized conditions for **3.L**[69] with Cramer's phosphoramidite **3.L**[61] as the ligand (Table 35). Contrary to the efficiency observed in the intramolecular arylation, this monophosphine ligand only provided 11% yield of the desired biaryl, in 59:41 *e.r.* (entry 1). The 2,2-diphenylpropanoic acid was also tested in combination with the MOP (entry 2). But the effect of the steric bulk in

the acid completely shut down the reactivity and 19% yield of arylation was obtained. As in the screening of acids, the *e.e.* was not particularly affected and a ratio of 69.5:30.5 was observed. The reaction conditions of Cramer were tested and, not surprisingly, no reaction occurred at 60°C (entry 3-4). In addition, our system involves only 5% of palladium and 10 %mol of ligand against 10% and 20%, respectively, in Cramer's catalytic system.



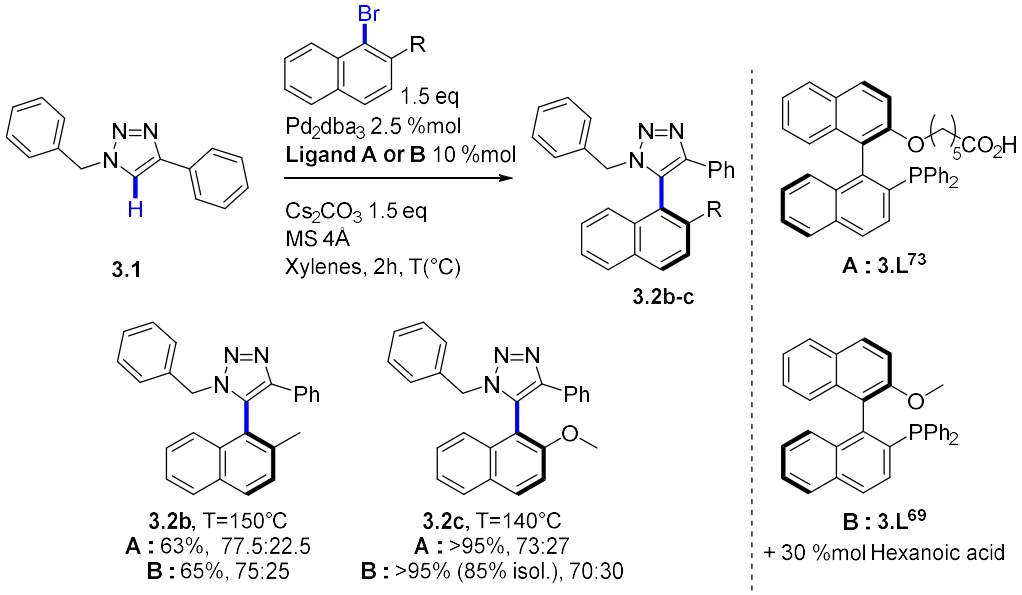
Entry	Ligand	Acid	Yield[a] 3.2c (%)	*e.r.*[b]
1	Cramer	Hexanoic	11	59:41
2	MOP	2,2-diPh-propanoic	19	69.5:30.5
3[c]	Cramer	2,2-diPh-propanoic	n.r.	n.d.
4[d]	MOP	Hexanoic	n.r	n.d.

[a] ^{1}H NMR yield with trichloroethylene as the reference. [b] *e.r.* value determined by HPLC analysis on a chiral stationary phase. [c] $Pd(dba)_2$ 10 %mol, ligand 20 %mol, K_2CO_3 1.5 eq, mesitylene, 60°C, 10h. [d] at 60°C.

Table 35.*Intermolecular arylation with Cramer's conditions.*

3.6. Conclusion

After the determination of suitable coupling partners for the palladium-catalyzed intermolecular Csp^2-H arylation, the reaction conditions were optimized and two catalytic systems which, to date, proved to be efficient to date for the atroposelective arylation of triazoles. One catalytic system uses the recently developed bifunctional ligands bearing the phosphine and the acid on a chiral binaphtyl core. The selectivity obtained in these conditions is slightly higher than when the MOP is used in combination with the hexanoic acid. Both catalytic systems were efficient, in particular for the coupling of triazole **3.1** with 1-Br-2-methylnaphtalene and with 1-Br-2-methoxynaphtalene.



Scheme 95. *Two advanced catalytic systems for the intermolecular Pd(0)-catalyzed atroposelective Csp^2-H arylation*

The screen of acids, ligands, and substrates brings to the fore the sensitivity of the reaction toward the steric hindrance nearby the metal center. The increase of bulk in the acid, as well as in the α-position to the ether in the bifunctional ligands, resulted in lower reactivities. The stereochemical outcome of the reaction was affected by the temperature of the reaction (dynamic racemization of the biaryl), but also and mainly by the decoration of the ligands. Nevertheless, the products obtained from our chosen coupling partners only slowly racemize in our reaction conditions.

According to Cramer's study, the enantiodetermining step of the reaction is the CMD-step, thus the induction chirality would fully rise from the ligand. Considering this case, our binaphtyl-based ligands seem to be not fully adapted for the reaction we develop, and a screen of MOP-type ligand based on other backbones should be privileged. In another scenario, the palladium intermediate obtained after the CMD-step, bearing the two aryl fragments, could favor one isomer or also racemize before reductive elimination, thus leading to low levels of selectivity. In this case, the selectivity would be linked to the difference of stability between the two enantiomeric intermediates, and a ligand favouring the reaction at a lower temperature could be investigated to solve the selectivity issue. So far, our results do not allow us to conclude clearly on the stereocontrol in this reaction

A global observation is that for our system, a clear dilemma between reactivity and selectivity is present, as already reported by Itami. Nevertheless, and to our delight, the results

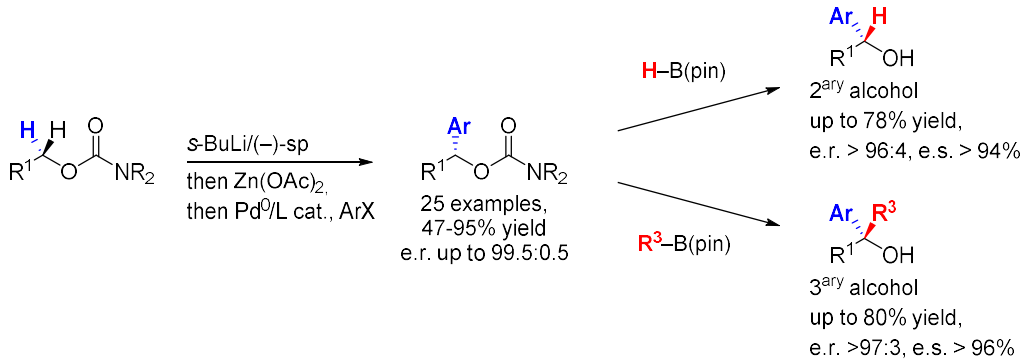
we obtained with our optimized catalytic systems show that our Pd^0 system provides , to date, comparable yields and selectivities as Itami's Pd^{II} catalytic system.

4. General conclusion

Over the past decades, the transition-metal catalyzed C-H bond functionalization has emerged as a powerful tool for the straightforward access to molecular complexity, while respecting the principles of atom- and step-economy.

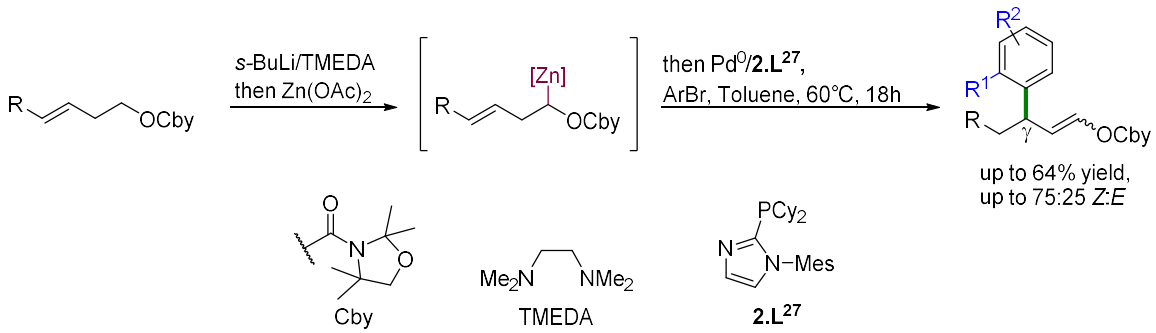
Within our group, many advances have been made in the development of the functionalization of remote Csp^3-H bonds via Pd(0)-catalyzed migrative cross-couplings, and in the intramolecular Pd(0)-catalyzed Csp^3-H bond activation.

In this context and in light of the work on the ligand-controlled arylation of *N*-Boc-piperidines, a versatile and highly enantioselective α-arylation of *O*-carbamates derived from primary alcohols was developed by combining Hoppe's sparteine-mediated enantioselective lithiation and Negishi coupling. This method, combined with Aggarwal's lithiation/borylation/oxidation sequence, provides a concise and divergent access to enantioenriched secondary and tertiary benzylic alcohols (Scheme 96).



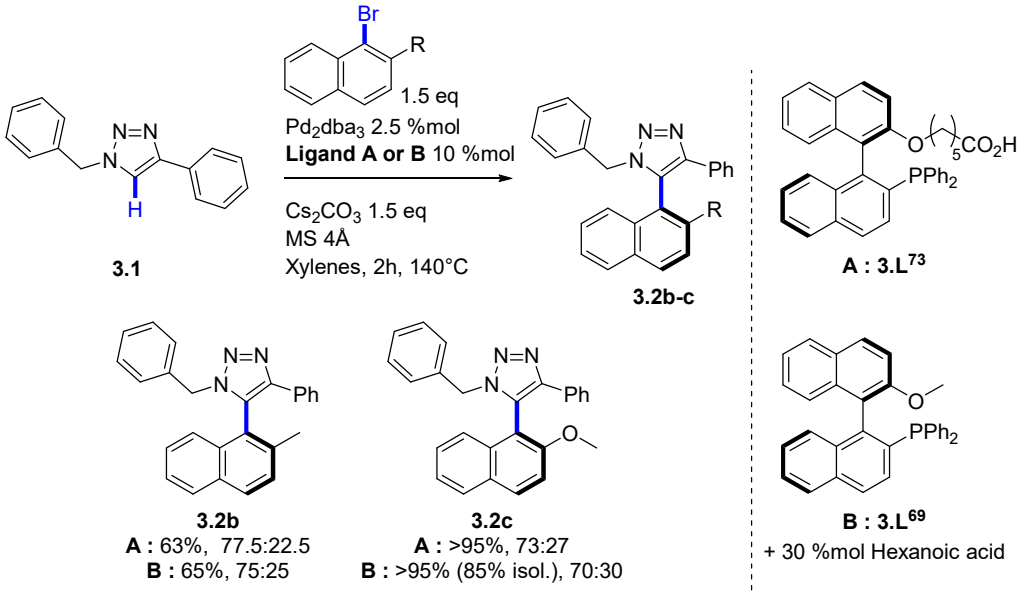
Scheme 96.*Enantioselective α-arylation of O-carbamates and application*

The attempts toward the β-arylation of *O*-carbamates remained unsuccessful, but led to the discovery of a new migration system. Indeed, the γ,δ-unsaturated *O*-carbamates underwent selective γ-arylation with the appropriate ligand under Pd(0)-catalyzed Negishi cross-coupling conditions (Scheme 97). The scope of the reaction was limited, but the mechanistic study led to the discovery of an unconventional migration involving a haptotropic rearrangement of the palladium intermediate. The lack of selectivity in the reaction enlightened us about the potential challenges in the enantiospecific migrative cross-coupling, which is currently under investigation within our group.



Scheme 97. *Ligand controlled γ-arylation of γ,δ-unsaturated O-carbamates*

The investigation on the very challenging intermolecular atroposelective Pd(0)-catalyzed Csp^2-H arylation led us to the discovery of two efficient catalytic systems. Despite the clear reactivity/selectivity dilemma, comparable yield and selectivities to the ones reported by Itami could be achieved (Scheme 98). The ligand still requires to be improved. The recent publication of Cramer on the intramolecular version of this reaction made us consider a potential collaboration with this research group on the intermolecular Csp^2-H arylation developed in this thesis.



Scheme 98. *Advances in the intermolecular atroposelective Pd(0)-catalyzed Csp^2-H arylation*

5. Supporting information

5.1. Enantioselective α-arylation of *O*-carbamates

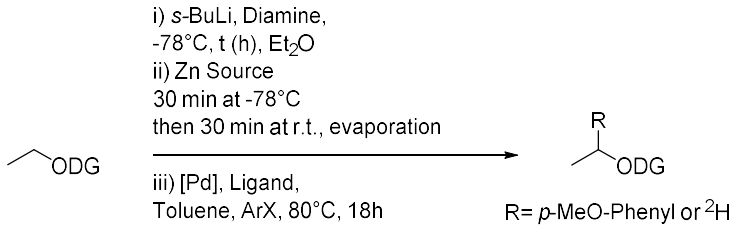
General information

All reactions were performed under an argon atmosphere (unless otherwise noted) in Pyrex glassware equipped with a magnetic stir bar. GC/MS analyses were run on a Shimadzu QP2010 apparatus using aRTx®-5ms column lined with a mass (EI 0.86 kV) detection system.^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a *BrukerAvance III* (400 MHz) spectrometer at 298 K in $CDCl_3$ (residual peaks ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm). Chemical shifts (δ) are reported in ppm relative totetramethylsilane (0.00 ppm). Data are reported as follows: chemical shift in parts per million (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br. for broad), integration value, coupling constant in Hz if applicable. Analytical Thin Layer Chromatography (TLC) was performed using pre-coated *Merck silica gel 60 F254* plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains (Phosphomolybdic acid or $KMnO_4$) Flash chromatographies were performed using *SilicycleSiliaFlash P60* (230-400 mesh) with the indicated solvents. High resolution mass spectrometry recorded by Dr. H. Nadig of the University of Basel on a *BrukermaXis 4G QTOF* ESI mass spectrometer. Infrared spectra were measured on a*ATR Varian Scimitar 800* FT-IR spectrometer and reported in cm^{-1}. HPLC analyses were done using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, $DGU\text{-}20A_3$ degasser and SPD-M20A Diode Array or UV/Vis detector. Chiralcel OD-H, OJ, or OJ-H and Chiralpak AD-H, IA or IC columns from Daicel Corporation were used for separation. Optical rotationwere measured on a Perkin Elmer 341Polarimeter in a 1 mL cuvette (cell length 100 mm) with Na_D-Line (λ = 589 nm) at 20°C. The concentration (c) is given in g/dL.

Commercially available reagents were used without further purification unless otherwise stated. Anhydrous solvents (Diethyl ether, THF, Toluene) were purchased form Sigma Aldrich and used as received.Tetramethylethylenediamine (TMEDA) was freshly distilled over CaH_2 under argon atmosphere. (−)-Sparteine and (+)-sparteine were respectively purchased from Sigma Aldrich and Fluorochem, distillated over CaH_2 under argon atmosphere, degassed under high vacuum via freeze-pumping process, and conserved at -30°C. 2-Dicyclohexylphosphino-2',6'-diisopropoxy-biphenyl (RuPhos) was purchased from

Strem. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was purchased from Strem and ABCR. Zinc acetate ($Zn(OAc)_2$)was purchased from Sigma Aldrich and thinly powdered. (RuPhos), ($Pd_2(dba)_3$), and ($Zn(OAc)_2$) were conserved in a glove box.

Optimization table



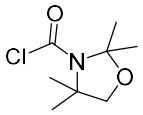
N°		DG	i)	ii)	iii)	Yield (GCMS Yield%)
1	Preliminary Studies	Cb or TIB	*s*-BuLi 2 eq, TMEDA 6 eq,-50°C, 30 min, CPME	$ZnCl_2$ 2 eq 30 min at -50°C then 30 min at r.t.	$Pd_2(dba)_3$ 5%mol, $PtBu_3.HBF_4$ 10%mol in Toluene, *p*-MeO-PhBr 1 eq, 60°C, 18h	0%
2		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, **5 h**, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**$Pd_2(dba)_3$ 5%mol, $PtBu_3.HBF_4$ 10%mol**in Toluene, *p*-MeO-PhBr 1 eq, 80°C, 18h	~72%
3		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, **3 h**, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**$Pd_2(dba)_3$ 5%mol, $PtBu_3.HBF_4$ 10%mol**in Toluene, *p*-MeO-PhBr 1.3 eq, 80°C, 18h	50%
4		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, **3 h**, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**[$Pd(PtBu_3)_2$] 10%mol** in Toluene, *p*-MeO-PhBr 1.3 eq, 80°C, 18h	50%
5		Cb	*s*-BuLi 1.3 eq, **(-)-Sparteine** 1.3 eq, -78°C, **5 h**, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**[$Pd(PtBu_3)_2$] 10%mol**in Toluene, *p*-MeO-PhBr 1.3 eq, 80°C, 18h	60%, *e.r.* 97:3
6	Ligands	Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 5 h, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**[$Pd(PtBu_3)_2$] 10%mol (Sigma)** in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	(22)
7		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 5 h, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**[$Pd(PtBu_3)_2$] 10%mol (Strem)** in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	50%
8		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 5 h, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**$Pd_2(dba)_3$ 5%mol, RuPhos 10%mol** in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	39% (43)
9		Cb	*s*-BuLi 1.3 eq, TMEDA	$ZnCl_2$ 1.4 eq	**RuPhos Pd G3 10%mol** in Toluene,	(46)

			1.3 eq,-78°C, 5 h, Et_2O	30 min at -78°C then 30 min at r.t.	*p*-MeO-PhBr 1.3 eq, 80°C, 18h	
10		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 5 h, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**$Pd_2(dba)_3$ 5%mol, DavePhos 10%mol** in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	(29)
11		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 5 h, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**$Pd_2(dba)_3$ 5%mol, CataCXium A 10%mol** in Toluene, *p*-MeO-PhBr 1.3 eq, 80°C, 18h	(20)
12		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 5 h, Et_2O	$ZnCl_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**$Pd_2(dba)_3$ 5%mol, $P(Cy)_3$ 10%mol** in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	(<5)
13	ControlDeuteration	Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C**, 1 h**, Et_2O	**MeOD**		86% (100% D-int)
14	Zinc Sources	Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	**$ZnBr_2$** 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 5%mol, RuPhos 10%mol in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	(29)
15		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	**$Zn(OAc)_2$** 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 5%mol, RuPhos 10%mol in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	55% (63)
16		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	**$Zn(OPiv)_2$** 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 5%mol, RuPhos 10%mol in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	51% (55)
17		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	**$Zn(OTFA)_2$**1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 5%mol, RuPhos 10%mol in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	(51)
18	Catalyst Loading	Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**$Pd_2(dba)_3$ 2.5%mol, RuPhos 5%mol** in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	(58)
19		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**$Pd_2(dba)_3$ 1.25%mol, RuPhos 2.5%mol** in Toluene, *p*-MeO-PhBr 1.3 eq, 80°C, 18h	(51)
20		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	**$Pd_2(dba)_3$ 0.5%mol, RuPhos 1%mol** in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	(25)
21	Alternative DG	Cby	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 5%mol, RuPhos 10%mol in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	44%
22		Cby	*s*-BuLi 1.3 eq, (-)-Sparteine 1.3 eq,	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C	$Pd_2(dba)_3$ 5%mol, RuPhos 10%mol in Toluene,*p*-MeO-PhBr 1.3 eq, 80°C, 18h	44%, *e.r.* 99:1

			-78°C, 1 h, Et_2O	then 30 min at r.t.		
23	Lower Cat/ArBr Charge	Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq, -78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 3.5%mol, RuPhos 7%mol in Toluene,***p*-MeO-PhBr 0.7 eq**, 80°C, 18h	73%
24		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 1.75%mol, RuPhos 3.5%molin Toluene,***p*-MeO-PhBr 0.7 eq**, 80°C, 18h	71%
25		Cb	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 1.23%mol, RuPhos 1.75%mol in Toluene,***p*-MeO-PhBr 0.7 eq**, 80°C, 18h	39%
26		Cby	*s*-BuLi 1.3 eq, TMEDA 1.3 eq, -78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 1.75%mol, RuPhos 3.5%mol in Toluene, ***p*-MeO-PhBr 0.7 eq**, 80°C, 18h	81%
27		Cby	*s*-BuLi 1.3 eq, (-)-Sparteine 1.3 eq, -78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 1.75%mol, RuPhos 3.5%mol in Toluene,***p*-MeO-PhBr 0.7 eq**, 80°C, 18h	86%, *e.r.* 99.4:0.6
28	ArX Variation	Cby	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 1.75%mol, RuPhos 3.5%mol in Toluene,***p*-MeO-PhCl**0.7 eq, 80°C, 18h	7%
29		Cby	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 1.75%mol, RuPhos 3.5%mol in Toluene,***p*-MeO-PhI**0.7 eq, 80°C, 18h	70%
30		Cby	*s*-BuLi 1.3 eq, TMEDA 1.3 eq,-78°C, 1 h, Et_2O	$Zn(OAc)_2$ 1.4 eq 30 min at -78°C then 30 min at r.t.	$Pd_2(dba)_3$ 1.75%mol, RuPhos 3.5%mol in Toluene,***p*-MeO-PhOTf**0.7 eq, 80°C, 18h	41%

Synthesis of carbamates ***2.4-6a*** *and* ***2.2a*** *:*

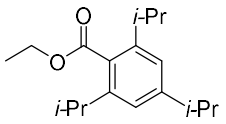
2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carbonyl chloride**S1** :



The reaction must be carried out in a well-vented fumehood, in dry conditions ! A solution of 2,2,4,4-tetramethyl-1,3-oxazolidine (26.4 g, 204 mmol, 1 eq) and triethylamine (34.4 mL, 245 mmol, 1.2 eq) in benzene (100 mL) was added dropwise via a dropping funnel to a solution of bis(trichloromethyl) carbonate (triphosgene, 20.6 g, 69.4 mmol, 0.34 eq) in benzene (400 mL) at 0°C. After addition, the mixture was heated to reflux for 20 h. The orange slurry was cooled down, poured into a 2 M aq. HCl solution (150 mL), and the aqueous phase was extracted with Et2O (2 x 150 mL). The combined organic phases were washed with sat. NaHCO3 (150 mL), dried over MgSO4, and evaporated under vacuum. The residue was distillated (55°C, 0.1 mbar) to afford 30.5 g (78%) of the carbamoyl chloride as a colorless oil which slowly crystallized as a white solid. The analytical data were in accordance with the literature.[143]

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) :δ = 3.81 (3.75) (2 br. s, 2H), (1.71) 1.59 (2 br. s, 6H), 1.53 (1.45) (2 br. s, 6H).**^{13}C-{1H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 143.8/142.6, 99.2/97.4, 76.9/75.3, 64.9/62.4, 26.8/25.5, 24.5/23.5

Ethyl 2,4,6-triisopropylbenzoate**2.2** :

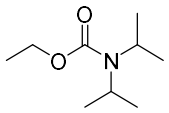


DIAD (2.1 mL, 10.5 mmol, 1.2 eq) was added dropwise over 10 min to a stirred solution of PPh_3 (2.75 g, 10.5 mmol, 1.2 eq), 2,4,6-triisopropyl benzoic acid (2.5 g, 10.1 mmol, 1.1 eq), and ethanol (0.52 mL, 8.75 mmol, 1 eq) in THF (50 mL) at 0°C. The reaction mixture was stirred for 4 h at r.t., then the solvent was evaporated under vacuum, and the residue was dissolved in pentane (15mL) for 5 min. The white suspension was filtered and the cake was washed with pentane (100 mL). The solvent was removed under vacuum, to obtain a yellow oil.The crude mixture was purified by column chromatography (pentane/Et_2O 99:1) to give

2.1 g (86 %) of the ester as a colorless oil. The analytical data were in accordance with the literature.[144]

^{1}H NMR (400 MHz, $CDCl_3$) :δ = 7.01 (s, 2H), 4.38 (q, *J* = 7.2), 2.93-2.82 (m, 3H), 1.37 (t, *J* = 7.2, 3H), 1.27-1.24 (m, 18H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 171.0, 150.3, 144.9, 130.8, 121.0, 61.0, 34.6, 31.6, 24.2, 24.1, 14.4.

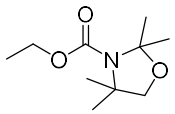
Ethyl *N*,*N*-diisopropylcarbamate**2.4** :



Ethyl chloroformate (7.2 mL, 75mmol, 1 eq) was added to a stirred mixture of diisopropyl amine (10.6 mL, 75 mmol, 1 eq) and K_2CO_3 (10.4 g, 75 mmol, 1 eq) in dichloromethane (80 mL) at 0°C. After addition, the mixture was refluxed for 4h. After cooling, the mixture was filtrated and washed with a 10% KOH aq. solution (2 x 100 mL), and water (100 mL). The organic phase was dried over $MgSO_4$, filtrated, and concentrated under vacuum. The residue was purified by column chromatography (pentane/Et_2O 9:1) to give 9.8 g (75%) of the carbamate as an oil. The analytical data were in accordance with the literature.[145]

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) :δ = 4.11 (q, 2H, *J* = 7.1), 3.88 (br. s, 2H), 1.24 (t, 3H, *J* = 7.1), 1.18 (d, 12H, *J* = 6.9).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 156.0, 60.5, 45.8 (br.), 21.1 (br.), 14.8

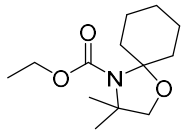
Ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5** :



Ethyl chloroformate (11.1 mL, 116 mmol, 1.5 eq) was added to a stirred mixture of 2,2,4,4-tetramethyl-1,3-oxazolidine (10 g, 77.4 mmol, 1 eq) and Na_2CO_3 (12.3 g, 116 mmol, 1.5 eq) in dichloromethane (100 mL) at 0°C. The mixture was stirred at r.t. for 5h and then filtrated. The solution was quenched with 1M aq. NaOH (100 mL) and washed with water (100 mL). The organic phase was dried over $MgSO_4$, filtrated, and concentrated under vacuum. The residue was purified by column chromatography (pentane/Et_2O 85:15) to give 12.5 g (80.2 %) of the carbamate as an oil. The analytical data were in accordance with the literature.[146]

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) :δ = 4.17–4.11 (m, 2H), 3.72 (s, 2H), 1.56 (1.52) (2 br. s, 6H), (1.42) 1.36 (2 br. s, 6H), 1.30-1.25 (m, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.0/152.3, 95.8/94.9, 76.5/76.2, 60.6/59.8, 60.4, 26.6/25.44, 25.38/25.3, 14.6.

Ethyl 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate**2.6** :



Ethyl chloroformate (2.4 mL, 24.6 mmol, 1 eq) was added to a stirred solution of 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane (5 g, 29.5 mmol, 1.2 eq) in dry dichloromethane (15 mL) at 0°C. The mixture was stirred at r.t. for 20h. The reaction mixture was quenched with 2 M aq. HCl (20 mL), the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic phases were dried over $MgSO_4$, and concentrated under vacuum. The residue was distillated (84°C, 0.6 mbar) to afford 2.8g (48 %) of the carbamate as a white solid. The analytical data were in accordance with the literature.[147]

^{1}H NMR (400 MHz, $CDCl_3$) :δ = 4.11 (q, 2H, *J* = 7.1), 3.67 (s, 2H), 2.41-2.16 (m, 2H), 1.58-1.34 (m, 14H), 1.26 (t, 3H, *J* = 7.1).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.1, 97.25/96.4, 76.4/76.0, 60.4/60.0, 60.3, 34.2/32.9, 25.6/24.8, 25.0/24.5, 23.6/23.4, 14.6.

*Arylation of carbamates **2.2** and **2.4-6***

General procedure A : arylation with TMEDA

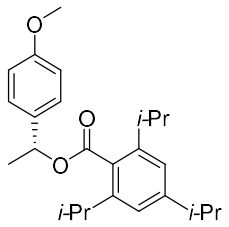
In a tubular reactor (100 mm x 16 mm)capped with a rubber septum, a solution of the carbamate**2.2** or **2.4-6**(0.6 mmol, 1 eq) and TMEDA (118 µL, 0.78 mmol, 1.3 eq) in dry diethyl ether (2 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (0.78 mmol, 1.3 eq, solution in hexane) was added dropwise, and the mixture was stirred for 1 h. A suspension of zinc acetate (154 mg, 0.84 mmol, 1.4 eq) in dry THF (2 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat to 20°C over 30 min. The solvents were evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (9.62 mg, 10.5 µmol, 1.75 %mol) and Ruphos (9.85 mg, 21 µmol, 3.5 %mol) in dry toluene (2 mL) was added, followed by the aryl bromide (0.42 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 80°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (5mL) and separated. The aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by column chromatography (pentane/Et_2O) to afford the benzylic alcohols.

General procedure B : enantioselective arylation with (-)-sparteine

In a tubular reactor (100 mm x 16 mm) capped with a rubber septum, a solution of the protected alcohol**2.2** or **2.4-6** (0.6 mmol, 1 eq) and (-)-sparteine (178 µL, 0.78 mmol, 1.3 eq) in dry diethyl ether (2 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (0.78 mmol, 1.3 eq, solution in hexane) was added dropwise, and the mixture was stirred for 5 h. A suspension of zinc acetate (154 mg, 0.84 mmol, 1.4 eq) in dry THF (2 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat to 20°C over 30 min. The solvents where evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (9.62 mg, 10.5 µmol, 1.75 %mol) and Ruphos (9.85 mg, 21 µmol, 3.5 %mol) in dry toluene (2 mL) was added, followed by the arylbromide (0.42 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 80°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (5mL) and separated. The aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic

layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by column chromatography (pentane/Et_2O) to afford the protected benzylic alcohols.

(*R*)-(+)-1-(4-Methoxyphenyl)ethyl 2,4,6-triisopropylbenzoate **2.2a**:

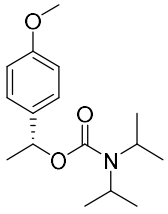


Following the general procedure A, ethyl 2,4,6-triisopropylbenzoate (166 mg) was arylated with 4-bromoanisole (52.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 75 mg (47%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,4,6-triisopropylbenzoate (166 mg) was arylated with 4-bromoanisole (52.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 100 mg (62%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400MHz) :δ =7.40-7.37(m, 2H), 6.99 (s, 2H), 6.91-6.88(m, 2H), 6.17 (q,1H, *J* = 6.6Hz), 3.82 (s, 3H), 2.88 (sept, 1H, *J* = 6.9Hz), 2.76 (sept, 1H, *J* = 6.8Hz), 1.65 (d, 3H,*J* = 6.6Hz), 1.24(d, 6H,*J* = 6.9Hz), 1.20 (d, 6H, *J* = 6.8Hz), 1.16(d, 6H, *J* = 6.8Hz).**^{13}C-{^{1}H} NMR ($CDCl_3$,100 MHz) :**δ =170.2, 159.6, 150.2, 145.0, 133.5, 130.7, 128.2, 121.0, 113.9, 72.9, 55.5, 34.6, 31.3, 24., 24.2, 24.1, 21.9.**HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 6.1 min for (*R*)-enantiomer (major) and t_R 11.4 min for (*S*)-enantiomer (minor). *e.r.* = 92.5:7.5.**$[\alpha]_D^{20}$** = +15.9° (c=1.1, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{25}H_{34}O_3Na$ ($[M + Na]^+$): 405.2406; found: 405.2398.**IR (neat) *ν* :** 2961, 1721, 1247.

(*R*)-(+)-1-(4-Methoxyphenyl)ethyl*N*,*N*-diisopropylcarbamate**2.4a** :



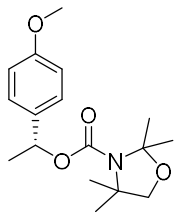
Following the general procedure A, ethyl *N*,*N*-diisopropylcarbamate(104 mg) was arylated with 4-bromoanisole (52.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 83 mg (71%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl N,N-diisopropylcarbamate (104 mg) was arylated with 4-bromoanisole (52.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 60 mg (51%) of the enantioenriched arylated product as an oil.

The analytical data were in accordance with the literature.[148]

^{1}H NMR (400 MHz, $CDCl_3$) :δ = 7.32–7.28 (m, 2H), 6.89-6.85 (m, 2H), 5.80 (q, 1H, *J* = 6.6), 4.10-3.80 (br. m, 5H), 1.53 (d, 3H, *J* = 6.6), 1.19-1.17 (m, 12H).**^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$) :** δ = 159.1, 155.4, 135.1, 127.6, 113.9, 72.5, 55.4 (b.s.), 22.8, 21.3 (b.s.).**HPLC separation conditions :** Chiralpak AD-H column,*n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 10.0 min for (*R*)-enantiomer (major) and t_R 16.2 min for (*S*)-enantiomer (minor). *e.r.* = 98.2:1.8.**$[\alpha]_D^{20}$** = +12.3° (*c*=1.1, $CHCl_3$).

(*R*)-(+)-1-(4-Methoxyphenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5a** :



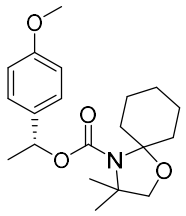
Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 4-bromoanisole (52.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 105 mg (81%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 4-bromoanisole (52.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 111 mg (86%) of the enantioenriched arylated product as an oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) :δ = 7.31–7.27 (m, 2H), 6.89-6.87 (m, 2H), 5.81 (q, 1H, *J* = 6.6), 3.80 (s, 3H), 3.72-3.70 (m, 2H), 1.60-1.33 (m, 15H).**^{13}C-{^{1}H} NMR (100 MHz,**

$CDCl_3$, rotamers) :δ = 159.2, 152.2/151.5, 134.5/134.4, 127.6, 113.9, 96.0/94.9, 76.5/76.2, 72.5, 60.7/59.8, 55.3, 26.9/26.8, 25.6/25.6, 25.5, 24.3, 22.6/22.5. **HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 8.1 min for (*R*)-enantiomer (major) and t_R 9.8 min for (*S*)-enantiomer (minor). *e.r.* = 99.4:0.6.**$[\alpha]_D^{20}$** = +11.5° (c=0.5, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{17}H_{25}NO_4Na$ ([M + Na]$^+$): 330.1676; found: 330.1671. **IR (neat) *ν* :** 2978, 1695, 1395, 1093, 1064.

(*R*)-(+)-1-(4-Methoxyphenyl)ethyl 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate**2.6a** :

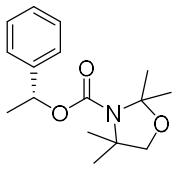


Following the general procedure A, ethyl 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate (145 mg) was arylated with 4-bromoanisole (52.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 127 mg (87%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate (145 mg) was arylated with 4-bromoanisole (52.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 103 mg (70%) of the enantioenriched arylated product as an oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) :δ = 7.31−7.27 (m, 2H), 6.89-6.86 (m, 2H), 5.78 (q, 1H, *J* = 6.6), 3.79 (s, 3H), 3.70-3.67 (m, 2H), 2.43-2.12 (m, 2H), 1.69-1.25 (m, 17H).**^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) :**δ = 159.2, 152.4/151.8, 134.6, 127.6/127.6, 113.9, 97.4/96.5, 76.4/76.0, 72.7/72.5, 60.5/59.7, 55.4, 34.5/34.2, 32.9, 25.9/25.8, 25.2, 24.8, 24.5, 23.7/23.6, 23.44/23.39, 22.9, 22.6.**HPLC separation conditions :** Chiralcel OJ-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 12.0 min for (*R*)-enantiomer (major) and t_R 17.5 min for (*S*)-enantiomer (minor). *e.r.* = 99.4:0.6.**$[\alpha]_D^{20}$** = +18.7° (c=1.0, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{20}H_{29}NO_4Na$ ([M + Na]$^+$): 370.1994; found: 370.1995.**IR (neat) *ν* :** 2931, 1692, 1394, 1247, 1065.

(*R*)-(+)-1-Phenylethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5b**:



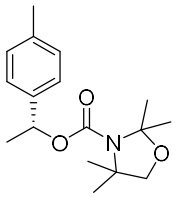
Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with bromobenzene (44.3 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 104 mg (89%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with bromobenzene (44.3 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 108 mg (92%) of the enantioenriched arylated product as an oil.

The analytical data were in accordance with the literature.[149]

^{1}H NMR ($CDCl_3$, 400MHz, rotamers) : δ = 7.36–7.26 (m, 5H), 5.84 (q, 1H,*J* = 6.6 Hz), 3.76-3.69 (m, 2H), 1.62-1.37 (m, 15H).**^{13}C-{^{1}H} NMR ($CDCl_3$,100 MHz, rotamers) :** δ =152.2/151.5, 142.5/142.4, 128.6, 127.8, 126.2, 96.1/95.0, 76.5/76.2, 72.9, 60.8/58.8, 26.9/26.8, 25.7/25.6, 25.49/25.45, 24.32/24.30, 22.8/22.7.**HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 6.0 min for (*R*)-enantiomer (major) and t_R 6.5 min for (*S*)-enantiomer (minor). *e.r.* = 99.6:0.4.**$[\alpha]_D^{20}$**= +11° (c=1.1, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{16}H_{23}NO_3Na$ ($[M + Na]^+$): 300.1576; found: 300.1573.**IR (neat) *ν* :** 2979, 1696, 1394, 1376, 1064.

(*R*)-(+)-1-(*p*-Tolyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5c**:



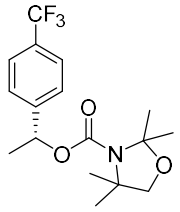
Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with p-bromotoluene (51.8 µL). The crude residue was purified by column

chromatography (pentane/Et_2O 98:2 to 80:20) to give 106 mg (86%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with p-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 116 mg (94%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400MHz, rotamers) : δ = 7.27−7.23 (m, 2H), 7.16-7.14 (m, 2H), 5.81 (q, 1H, *J* = 6.6 Hz), 3.75-3.68 (m, 2H), 2.34 (s, 3H), 1.61-1.35 (m, 15H).**^{13}C-{^{1}H} NMR ($CDCl_3$,100 MHz,rotamers) :**δ = 152.2/151.5, 139.5, 137.4, 129.3, 126.2, 96.0/94.5.0, 76.5/76.2, 72.9, 60.8/59.8, 26.9/26.8, 25.7/25.6, 25.49/25.46, 24.3, 22.8/22.7, 21.3.**HPLC separation conditions :**Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 6.0 min for (*R*)-enantiomer (major) and t_R 7.1 min for (*S*)-enantiomer (minor). *e.r.* = 99.4:0.6.**$[\alpha]_D^{20}$**= +14.2° (c=1.5, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{17}H_{25}NO_3Na$ ($[M + Na]^+$): 314.1727; found: 314.1723.**IR (neat) *ν* :** 2981, 1697, 1394, 1376, 1065.

(*R*)-(-)-1-(4-(Trifluoromethyl)phenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5d** :

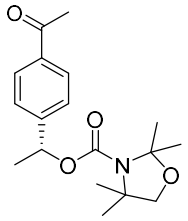


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 4-bromobenzotrifluoride (59.2 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 70 mg (48%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 4-bromobenzotrifluoride (59.2 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 102 mg (70%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 7.62–7.60 (m, 2H), 7.47-7.43 (m, 2H), 5.86 (q, 1H, *J* = 6.6), 3.77-3.70 (m, 2H), 1.61-1.35 (m, 15H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.0/151.2, 146.6/146.5, 130.1/129.8, 126.34/126.32, 125.7 (q, *J* = 3.6 Hz), 122.9, 96.2/95.0, 76.5/76.2, 72.3, 61.0/60.0, 27.0/26.9, 25.7/25.6, 25.44/25.39, 24.26, 22.72/22.66. **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** -62.54/-62.55.**HPLC separation conditions :** Chiralpak IA column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 6.0 min for (*R*)-enantiomer (major) and t_R 7.1 min for (*S*)-enantiomer (minor). *e.r.* = 99.3:0.7. **$[\alpha]_D^{20}$** = -1.5° (c=1.0, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{17}H_{22}F_3NO_3Na$ ($[M + Na]^+$): 368.1449; found: 368.1444. **IR (neat) *ν* :** 2982, 1697, 1325, 1067.

(*R*)-1-(4-Acetylphenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5e** :



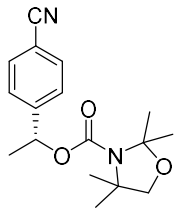
Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 4-bromoacetophenone (83.7 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 73 mg (54%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 4-bromoacetophenone (83.7 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 64 mg (48%) of theenantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400MHz, rotamers) : δ = 7.95–7.93 (m, 2H), 7.44-7.40 (m, 2H), 5.84 (q, 1H, *J* = 6.6 Hz), 3.75-3.68 (m, 2H), 2.58 (s, 3H), 1.60-1.34 (m, 15H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 197.8, 151.4/151.2, 147.9/147.7, 136.6, 128.84, 126.2, 96.1/95.0, 76.5/76.2, 72.4, 60.9/59.9, 26.9/26.8, 26.8, 25.7/25.6, 25.42/25.36, 24.3, 22.62/22.56.**HPLC separation conditions:** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 17.1 min for (*R*)-enantiomer (major) and t_R 37.7 min for (*S*)-enantiomer (minor). *e.r.* = 99.6:0.4.**$[\alpha]_D^{20}$**= ±0° (c=1.5, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for

$C_{18}H_{25}NO_4Na$ ([M + Na]$^+$): 342.1676; found: 342.1680.**IR (neat) *ν* :** 2980, 1683, 1375, 1263, 1064.

(*R*)-(-)-1-(4-Cyanophenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5f**:

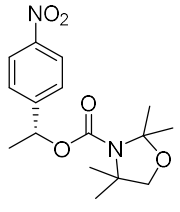


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 4-bromobenzonitrile (76.6 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 74 mg (58%) of the racemic arylated product as a white solid.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 4-bromobenzonitrile (76.6 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 106 mg (83%) of the enantioenriched arylated product as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 7.67–7.65 (m, 2H), 7.47-7.44 (m, 2H), 5.85 (q, 1H, *J* = 6.7), 3.78-3.71 (m, 2H), 1.62-1.36 (m, 15H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 151.7/150.9, 147.9/147.8, 132.5, 126.6, 118.7, 111.5, 96.0/94.9, 76.3/76.0, 72.0, 60.9/59.9, 26.8, 25.7/25.4, 25.3/25.2, 24.1, 22.44/22.38. **HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 21.3 min for (*R*)-enantiomer (major) and t_R 28.7 min for (*S*)-enantiomer (minor). *e.r.* = 99.3:0.7. **$[\alpha]_D^{20}$** = -5.3° (c=1.25, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{17}H_{22}N_2O_3Na$ ([M + Na]$^+$): 325.1523; found: 325.1526. **IR (neat) *ν* :** 2980, 2229, 1696, 1377, 1066.**M.p.**=91-93°C.

(*R*)-(-)-1-(4-Nitrophenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5g** :

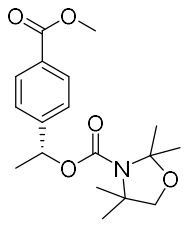


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 1-bromo-4-nitrobenzene (85 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 45 mg (33%) of the racemic arylated product as a yellow solid.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 1-bromo-4-nitrobenzene (85 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 64 mg (47%) of the enantioenriched arylated product as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 8.22-8.18 (m, 2H), 7.50-7.47 (m, 2H), 5.87 (q, 1H, *J* = 6.7 Hz), 3.76-3.69 (m, 2H), 1.60-1.33 (m, 15H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 151.7/151.0, 150.0/149.9, 147.7, 126.76/126.73; 124.1, 96.2/95.0, 76.4/76.1, 71.9, 61.0/50.0, 26.9, 25.8/25.5, 25.36/25.29, 24.2, 22.6/22.5.**HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 16.1 min for (*R*)-enantiomer (major) and t_R 32.7 min for (*S*)-enantiomer (minor). *e.r.* = 99.3:0.7. **$[\alpha]_D^{20}$** = -6.2° (c=0.8, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{16}H_{22}N_2O_5Na$ ($[M + Na]^+$): 345.1421; found: 345.1421. **IR (neat) *ν* :** 2981, 1693, 1341, 1092.**M.p.**=136-138°C.

(*R*)-(+)-1-(4-(Methoxycarbonyl)phenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5h**:

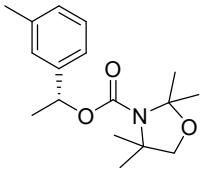


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with methyl-4-bromobenzoate (90.5 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 97 mg (69%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with methyl-4-bromobenzoate (90.5 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 95:5 to 80:20) to give 115 mg (81%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 8.02-8.00 (m, 2H), 7.41-7.38 (m, 2H), 5.85 (q, 1H, *J* = 6.6 Hz), 3.90-3.88 (m, 3H), 3.75-3.68 (m, 2H), 1.60-1.33 (m, 15H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 166.9, 151.9/151.2, 147.6/147.5, 130.0, 129.6, 126.0, 96.1/95.0, 76.5/76.1, 72.4, 60.9/59.89, 52.2, 26.9/26.8, 25.7/25.6, 25.41/25.37, 24.25, 22.6/22.5. **HPLC separation conditions** : Chiralcel OJ column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 24.7 min for (*R*)-enantiomer (major) and t_R 33.8 min for (*S*)-enantiomer (minor). *e.r.* = 99.:0.5. **$[\alpha]_D^{20}$** = +0.7° (c=0.9, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{18}H_{25}NO_5Na$ ($[M + Na]^+$): 358.1625; found: 358.1629. **IR (neat) *ν* :** 2980, 1723, 1695, 1376, 1275, 1065.

(*R*)-(+)-1-(*m*-Tolyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5i** :

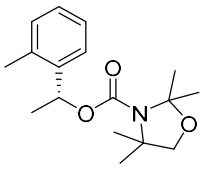


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with m-bromotoluene (51 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 109 mg (89%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with m-bromotoluene (51 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 110 mg (90%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 7.26-7.22 (m, 1H), 7.17-1.14 (m, 2H), 7.10-7.08 (m, 1H), 5.81 (q, 1H, *J* = 6.6 Hz), 3.76-3.69 (m, 2H), 2.35 (s, 3H), 1.62-1.37 (m, 15H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.2/151.5, 142.5/142.3, 138.1, 128.53/128.47, 127.0, 123.1, 96.0/95.0, 76.5/76.2, 73.0, 60.8/59.8, 26.9/26.8, 25.7/25.6, 25.5/25.4, 24.3, 22.9/22.8, 21.6. **HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 6.3 min for (*R*)-enantiomer (major) and t_R 7.1 min for (*S*)-enantiomer (minor). *e.r.* = 99.6:0.4. **$[\alpha]_D^{20}$** = +9,0° (c=1.75, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{17}H_{25}NO_3Na$ ($[M + Na]^+$): 314.1727; found: 314.1728. **IR (neat) *ν* :** 2979, 1692, 1374, 1063.

(*R*)-(-)-1-(*o*-Tolyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5j** :

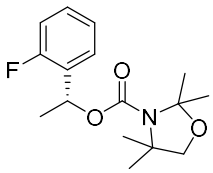


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with o-bromotoluene (50.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 102 mg (83%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with o-bromotoluene (50.7 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 117 mg (95%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 7.42-7.36 (m, 1H), 7.25-7.12 (m, 3H), 6.07 (q, 1H, *J* = 6.5 Hz), 3.76-3.69 (m, 2H), 2.39 (s, 3H), 1.64-1.36 (m, 15H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.2/151.5, 140.9/140.8, 134.5, 130.57, 127.5/126.3, 125.2/125.1, 96.1/94.9, 76.5/76.2, 69.6, 60.8/59.8, 27.0/26.8, 25.7/25.6, 25.5/25.4, 24.33/24.29, 22.0, 19.2. **HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 5.0 min for (*R*)-enantiomer (major) and t_R 5.4 min for (*S*)-enantiomer (minor). *e.r.* = 99.7:0.3. **$[\alpha]_D^{20}$**= -0.3° (c=1.1, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{17}H_{25}NO_3Na$ ($[M + Na]^+$): 314.1727; found: 314.1728. **IR (neat) *ν* :** 2979, 1694, 1376, 1064.

(*R*)-1-(2-Fluorophenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5k** :

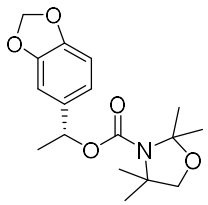


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 1-bromo-2-fluorobenzene (46 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 90:10) to give 98 mg (79%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 1-bromo-2-fluorobenzene (46 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 90:10) to give 103 mg (83%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400MHz, rotamers) : δ = 7.41−7.33 (m, 1H), 7.27-7.24 (m, 1H), 7.15-7.11 (m, 1H), 7.04-7.02 (m, 1H), 6.08 (q, 2H, *J* = 6.6 Hz), 3.77-3.70 (m, 2H), 1.62-1.37 (m, 15H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 159.9 (d, *J* = 247.4 Hz), 151.9/151.2, 129.7/129.6, 129.4-129.2 (m), 127.5 (d, *J* = 4.3 Hz), 124.3 (d, *J* = 3.5 Hz), 115.8 (d, *J*= 21.8 Hz), 96.1/95.0, 76.5/76.2, 67.8/67.7, 60.9/59.9, 26.9/26.7, 25.6/25.51, 25.46/25.4, 24.29/24.26, 21.7/21.6.**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** -118.0/-118.04.**HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 99:1, flow rate 0.5 mL/min, 25°C, t_R 14.7 min for (*R*)-enantiomer (major) and t_R 15.4 min for (*S*)-enantiomer (minor). *e.r.* = 99.7:0.3.**$[\alpha]_D^{20}$**= ±0° (c=1.75, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{16}H_{22}F_1NO_3Na$ ([M + Na]$^+$): 318.1476; found: 318.1480.**IR (neat) *ν* :** 2980, 1695, 1376, 1062, 756.

(*R*)-(+)-1-(Benzo[1,3]dioxol-5-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5l** :



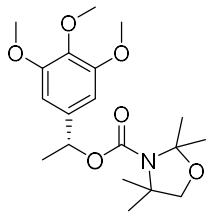
Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 1-bromo-3,4-(methylenedioxy)benzene (50.6 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 103 mg (76%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 1-bromo-3,4-(methylenedioxy)benzene (50.6 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 105 mg (78%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 6.84-6.80 (m, 2H) , 6.76-6.74 (m, 2H), 5.93-5.92 (m, 2H), 5.73 (q, 1H, *J* = 6.5 Hz), 3.73-3.67 (m, 2H),1.58-1.34 (m, 15H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.1/151.4, 147.8/147.1, 136.4/136.3, 119.8, 108.3,

106.7, 101.1, 96.0/94.9, 76.5/76.1, 72.7, 60.8/59.8, 26.9, 25.7/25.6, 25.4, 24.3, 22.8/22.7. **HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 9.9 min for (*R*)-enantiomer (major) and t_R 11.6 min for (*S*)-enantiomer (minor). *e.r.* = 99.3:0.7. **$[\alpha]_D^{20}$** = +28.9° (c=1.5, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{17}H_{23}NO_5Na$ ($[M + Na]^+$): 344.1468; found: 344.1472. **IR (neat) *ν* :** 2979, 1693, 1367, 1246, 1064.

(*R*)-(+)-1-(3,4,5-Trimethoxyphenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5m** :

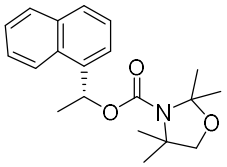


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 5-bromo-1,2,3-trimethoxybenzene (104 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 60:40) to give 98 mg (63%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 5-bromo-1,2,3-trimethoxybenzene (104 mg in 1 mL of toluene). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 60:40) to give 82 mg (53%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 6.54-6.52 (m, 2H), 5.74 (q, 1H, *J* = 6.5), 3.82-3.80 (m, 9H), 3.71-3.69 (m, 2H), 1.59-1.35 (m, 15 H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.3, 152.0/151.3, 138.3/138.2, 137.3, 102.8, 96.0/94.8, 76.4/76.1, 72.8, 60.9, 60.8/59.8, 26.80/26.77, 25.6/25.5, 25.3, 24.3/24.2, 22.9/22.8. **HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 33.3 min for (*R*)-enantiomer (major) and t_R 42.0 min for (*S*)-enantiomer (minor). *e.r.* = 99.4:0.6. **$[\alpha]_D^{20}$** = +8.3° (c=1.4, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{19}H_{29}NO_6Na$ ($[M + Na]^+$): 390.1887; found: 390.1889. **IR (neat) *ν* :** 2978, 1691, 1375, 1236, 1127, 1092.

(*R*)-(-)-1-(Naphthalen-1-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5n** :

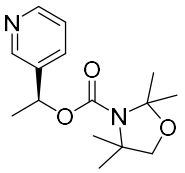


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 1-bromonaphtalene (58.9 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 98 mg (71%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 1-bromonaphtalene (58.9 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 91 mg (66%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400MHz, rotamers) : δ = 8.13–8.11 (m, 1H), 7.89-7.80 (m, 2H), 7.63-7.47 (m, 4H), 6.68 (q, 1H, *J* = 6.6), 3.78-3.73 (m, 2H), 1.75-1.35 (m, 15H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.3/151.6, 138.4, 134.0, 130.4, 129.0, 128.3, 126.4, 125.8, 125.5, 123.4, 123.0, 96.2/95.0, 76.6/76.2, 69.7, 60.9/59.9, 27.0/26.7, 25.7/25.6, 25.54/25.45, 24.37/24.31, 22.2.**HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 6.5 min for (*R*)-enantiomer (major) and t_R 7.8 min for (*S*)-enantiomer (minor). *e.r.* = 96.3:3.7.**$[\alpha]_D^{20}$** = -38.0° (c=0.9, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{20}H_{25}NO_3Na$ ($[M + Na]^+$): 350.1757; found: 350.1728.**IR (neat) *ν* :** 2979, 1689, 1372, 1059, 776.

(*S*)-(-)-1-(Pyridin-3-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5o** :

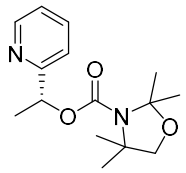


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 3-bromopyridine (40.5 µL). The crude residue was purified by column chromatography (pentane/Et_2O 90:10 to 50:50) to give 57 mg (49%) of the racemic arylated product as an oil.

Following the general procedure B, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 3-bromopyridine (40.5 µL) in presence of (+)-sparteine (178 µL, 0.78 mmol, 1.3 eq). The crude residue was purified by column chromatography (pentane/Et_2O 20:80 to 0:100) to give 75 mg (64%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 8.66-8.64 (m, 1H), 8.56-8.55 (m, 1H), 7.69-7.67(m, 1H), 7.31-7.28 (m, 1H), 5.88 (q, 1H, *J* = 6.6 Hz), 3.77-3.73 (m, 2H), 1.62-1.36 (m, 15H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 151.8/151.1, 149.2, 148.0, 137.8/137.7, 133.8/133.7, 123.5, 96.1/94.9, 76.4/76.1, 70.7, 60.9/59.9, 26.83/26.76, 25.7/25.5, 25.3, 24.19/24.15, 22.4/.22.3.**HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 97:3, flow rate 1 mL/min, 25°C, t_R13.0 min for (*R*)-enantiomer (minor) and t_R 15.7 min for (*S*)-enantiomer (major). *e.r.* = 0.7:99.3.**$[\alpha]_D^{20}$** = -6.2° (c=0.92, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{15}H_{22}N_2O_3Na$ ($[M + Na]^+$): 301.1523; found: 301.1519. **IR (neat) *ν* :** 2979, 1693, 1392, 1063.

1-(Pyridin-2-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5p** :

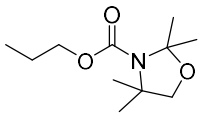


Following the general procedure A, ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (121 mg) was arylated with 2-bromopyridine (40.3 µL) at 110°C. The crude residue was purified by column chromatography (pentane/Et_2O 90:10 to 50:50) to give 56 mg (48%) of the racemic arylated product as an oil.

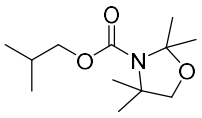
^{1}H NMR ($CDCl_3$, 400MHz, rotamers) : δ = 8.56 (m, 1H), 7.68-7.64 (m, 1H), 7.32-7.28 (m, 1H), 7.18-7.15 (m, 1H), 5.88 (q, 1H, *J* = 6.6 Hz), 3.76-3.69 (m, 2H), 1.62-1.36 (m, 15H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 161.4/161.2, 152.1, 149.3, 136.8, 122.6, 120.2, 96.1/95.1, 76.6/76.2, 73.7, 60.9/60.0, 26.9/26.8, 25.7/25.6, 25.5/25.3, 24.31/24.27, 20.94/20.88. **HRMS (ESI) m/z:** calcd. for $C_{15}H_{22}N_2O_3Na$ ($[M + Na]^+$): 301.1523; found: 301.1521.**IR (neat) *ν* :** 2980, 1695, 1376, 1091, 1067.

*Preparation of 2,2,4,4-tetramethyloxazolidine-3-carboxylates **2.7a-i***

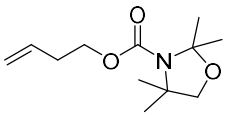
The carbamates**2.7a-b,d-f,** were synthesized following the procedures of Sardina *et al.* and Hoppe *et al.*.[150]



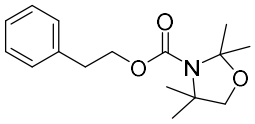
2.7a



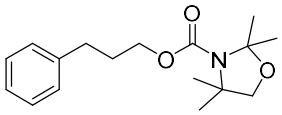
2.7b



2.7e



2.7d

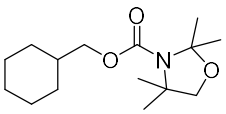


2.7f

General procedure :

A solution of the corresponding alcohol (1.0 eq) in THF (10 mL) was addeddropwise to a suspension of sodium hydride (60% in mineral oil, 1.1 eq) in THF (30 mL) and the mixture was stirred for 30 min at room temperature. A solution of 2,2,4,4-tetramethyloxazolidine-3-carbonyl chloride (1.05 eq.) in THF (10 mL) was then added dropwise and the mixture was stirred for 12 h. After quenching with water, the solvent was removed under reduced pressure and Et_2O (50 mL) was added to the crude mixture. The organic phase was washed with sat. aq. $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain the corresponding carbamate.

Cyclohexylmethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.7c** :

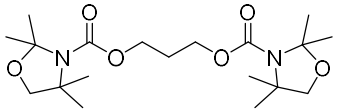


Following the general procedure, cyclohexanemethanol (0.71 mL, 5 mmol) gave 1.35 g (quant.) of the title carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 3.91-3.88 (m, 2H), 3.73 (s, 2H), 1.76-1.67 (m, 5H),1.56 (1.53) (2 br. s., 6H), (1.42) 1.37 (2 br. s., 6H), 1.31-1.15 (m, 4H), 1.06-0.96 (m, 2H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.1/152.4, 95.9/94.8, 76.4/76.2, 70.09/70.05, 60.6/50.7, 37.5, 30.1, 26.7/26.5, 25.8, 25.45/25.41, 24.2.**HRMS (ESI) m/z :**

calcd. for $C_{15}H_{27}NO_3Na$ ([M + Na]$^+$): 292.1883; found: 292.1886.**IR neat (υ/cm^{-1}) :**2926, 1694, 1340, 1065.

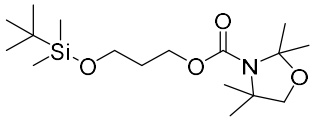
Propane-1,3-diyl bis(2,2,4,4-tetramethyloxazolidine-3-carboxylate) **2.7h** :



Following the general procedure, 1,3-propanediol (0.73 mL, 10 mmol) was reacted with NaH (60% in mineral oil, 880 mg, 22 mmol, 2.2 eq) and 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl chloride (4.03 g, 21 mmol, 2.1 eq) to give 3.85 g (99%) of the title dicarbamate as a white solid (recryst. from <0°C cold pentane).

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 4.19-4.15 (m, 4H), 3.69 (s, 4H), 2.03-1.98 (m, 4H), 1.52 (1.48) (2 br. s., 12H), (1.38) 1.33 (2 br. s., 12H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.6/151.9, 95.9/94.7, 76.4/76.1, 61.4, 60.7/59.8, 28.7, 26.6, 25.4, 25.3, 24.2.**HRMS (ESI) m/z :** calcd. for $C_{19}H_{34}N_2O_6Na$ ([M + Na]$^+$): 409.2309; found: 409.2310.**IR neat (υ/cm^{-1}) :**2936, 1683, 1363, 1066.

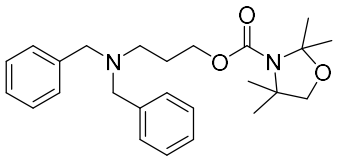
3-((*tert*-Butyldimethylsilyl)oxy)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7g**:



Following the general procedure, 3-(*tert*-butyldimethylsilyloxy)propan-1-ol[151](761 mg, 4 mmol) gave 1.1 g (80%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ =4.17-4.11 (m, 2H), 3.71-3.65 (m, 4H), 1.85-1.81 (m, 2H), 1.52 (1.48) (2 br. s., 6H), (1.38) 1.32 (2 br. s., 6H), 0.85 (s, 9H), 0.01 (s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.9/152.2, 95.9/94.9, 76.5/76.2, 61.6, 60.7/59.7, 60.0, 32.3, 26.7, 26.0, 25.4, 24.3, 18.4, -5.3.**HRMS (ESI) m/z :** calcd. for $C_{17}H_{35}NO_4SiNa$ ([M + Na]$^+$): 368.2228; found: 368.2226.**IR neat (υ/cm^{-1}) :**2930, 1698, 1068, 834.

3-(Dibenzylamino)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7i**:



Following the general procedure, 3-(*N*,*N*-dibenzylamino)propanol[152] (2.0 g, 7.83 mmol) gave 1.85 g (58%) of the title carbamate as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ =7.38-7.22 (m, 10 H), 4.14-4-09 (m, 2H), 3.68-3.65 (m, 2H), 3.57 (s, 4H), 2.57-2.51 (m, 2H), 1.90-1.84 (m, 2H), 1.54 (1.40) (2 br s, 6H), (1.30) 1.14 (2 br s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.9/152.2, 139.8, 128.8, 128.4, 127.0, 95.9/94.9, 76.4/76.2, 63.0, 60.6/59.7, 58.7, 50.6, 26.9, 26.5/25.4, 25.3/24.3.**HRMS (ESI) m/z :** calcd. for $C_{25}H_{34}N_2O_3H_1$ ($[M + H]^+$): 411.2642; found: 411.2645.**IR neat (υ/cm^{-1}) :** 2973, 2800, 1683, 1337, 1095, 1067.**Melting point :** 65 °C.

*Arylation of the carbamates **2.7a-i***

General procedure C : arylation with TMEDA

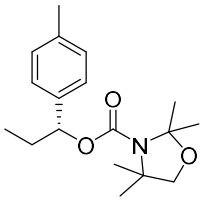
In a tubular reactor (100 mm x 16 mm) set up with a rubber septum, a solution of the protected alcohol**2.7a-i** (0.6 mmol, 1 eq) and TMEDA (127 µL, 0.84 mmol, 1.4 eq) in dry diethyl ether (2 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (0.84 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 4 h. A suspension of zinc acetate (165 mg, 0.9 mmol, 1.5 eq) in dry THF (2 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat to 20°C over 30 min. The solvents where evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (9.62 mg, 10.5 µmol, 1.75 %mol) and Ruphos (9.85 mg, 21 µmol, 3.5 %mol) in dry toluene (2 mL) was added to solve the residue, followed by the bromoaryl (0.42 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 80°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (5mL) and separated. The aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by column chromatography (Et_2O/pentane) to afford the benzylic alcohols.

General procedure D : enantioselective arylation with (-)-sparteine

In a tubular reactor (100 mm x 16 mm) set up with a rubber septum, a solution of the protected alcohol **2.7a-i** (0.6 mmol, 1 eq) and (-)-sparteine (193 µL, 084 mmol, 1.4 eq) in dry diethyl ether (2 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (0.84 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 5 h. A suspension of zinc acetate (165 mg, 0.9 mmol, 1.5 eq) in dry THF (2 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat to 20°C over 30 min. The solvents where evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (9.62 mg, 10.5 µmol, 1.75 %mol) and Ruphos (9.85 mg, 21 µmol, 3.5 %mol) in dry toluene (2 mL) was added tosolve the residue, followed by the bromoaryl (0.42 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 80°C for 18h. After cooling down, the reaction was

quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (5mL) and separated. The aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by column chromatography (Et_2O/pentane) to afford the protected benzylic alcohols.

(*R*)-(+)-1-(*p*-Tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5q**:

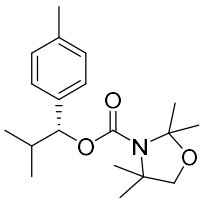


Following the general procedure C, propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (129 mg) was arylated with p-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 108 mg (84%) of the racemic arylated product as an oil.

Following the general procedure D, propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (129 mg) was arylated with p-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 80 mg (62%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.23-7.14 (m, 4H), 5.60 (t, 1H, *J* = 6.8 Hz), 3.75-3.68 (m, 2H), 2.33 (s, 3H), 2.00-1.78 (m, 2H), 1.63-1.34 (m, 12H), 0.89 (q, 3H, *J* = 7.2 Hz).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.4/151.7, 138.2/138.1, 137.4/137.2, 129.2, 126.7, 96.1/94.9, 78.0, 76.5/76.2, 60.8/59.8, 29.8/29.7, 27.0/26.9, 25.7, 25.52/25.45, 21.3, 10.3/10.2.**HPLC separation conditions:** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 5.5 min for (*R*)-enantiomer (major) and t_R 7.1 min for (*S*)-enantiomer (minor). *e.r.* = 98.8:1.2.**$[\alpha]_D^{20}$** = +18.2° (c=1.5, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{18}H_{27}NO_3Na$ ($[M + Na]^+$): 328.1883; found: 328.1881.**IR (neat) *ν* :** 2975, 1697, 1377, 1094.

(*R*)-(+)-2-Methyl-1-(*p*-tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5r**:

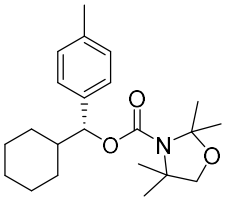


Following the general procedure C, isobutyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (138 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 112 mg (83%) of the racemic arylated product as an oil.

Following the general procedure D, propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (138 mg) was arylated with p-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 74 mg (55%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.18-7.12 (m, 4H), 5.46 (d, 1H, *J* = 7 Hz), 3.76-3.69 (m, 2H), 2.33 (s, 3H), 2.17-2.10 (m, 1H), 1.66-1.32 (m, 12H), 1.01-0.98 (m, 3H), 0.84-0.82 (m, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.9/151.7, 137.3, 137.2, 128.9, 127.2, 96.2/94.9, 81.6, 76.6/76.3, 60.9/59.8, 34.0, 27.1, 25.9/25.8, 25.6/25.4, 24.41/24.38, 21.3, 19.08/19.04,18.95. **HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 99:1, flow rate 0.5 mL/min, 25°C, t_R 10.1 min for (*R*)-enantiomer (major) and t_R 12.4 min for (*S*)-enantiomer (minor). *e.r.* = 85.2:14.8.**$[\alpha]_D^{20}$** = +4.8° (c=0.5, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{19}H_{29}NO_3Na$ ($[M + Na]^+$): 342.2040; found: 342.2039.**IR (neat) *ν* :** 2967, 1694, 1375, 1091, 1060.

(*R*)-(+)-Cyclohexyl(*p*-tolyl)methyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5s**:

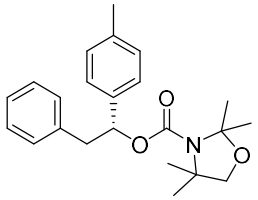


Following the general procedure C, cyclohexylmethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (162 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 125 mg (83%) of the racemic arylated product as an oil.

Following the general procedure D cyclohexylmethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (162 mg) was arylated with p-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 85 mg (56%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.17-7.11 (m, 4H), 5.48 (d, 1H, *J* = 7.3 Hz), 3.75-3.68 (m, 2H), 2.33 (s, 3H), 1.76-0.88 (m, 23H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ =152.5/151.8, 137.3, 137.2, 129.0, 127.2, 96.2/94.9, 81.1, 76.6/76.2, 60.9/59.8, 43.6, 29.44/29.37, 27.2/27.1, 26.5, 26.2, 26.0/25.8, 25.7/25.5, 24.4, 21.3.**HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 99:1, flow rate 0.5 mL/min, 25°C, t_R 10.2 min for (*R*)-enantiomer (major) and t_R 11.8 min for (*S*)-enantiomer (minor). *e.r.* = 90.8:9.2.**$[\alpha]_D^{20}$**= +5.4° (c=0.5, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{22}H_{33}NO_3Na$ ([M + Na]$^+$): 382.2353; found: 382.2353.**IR (neat) *ν* :** 2927, 1693, 1374, 1058.

(*R*)-(-)-2-Phenyl-1-(*p*-tolyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5t**:



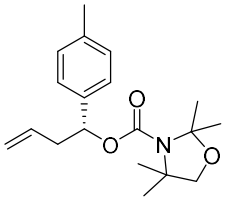
Following the general procedure C, phenethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (167 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 125 mg (81%) of the racemic arylated product as an oil.

Following the general procedure D, phenethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (167 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 114mg (74%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 7.23-7.09 (m, 9H), 5.94 (t, 1H, *J* = 7.1 Hz), 3.26-3.08 (m, 2H), 2.31 (s, 3H), 1.50-1.30 (m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :** δ = 152.0/151.3, 137.7/137.6, 137.4, 137.21/137.15, 129.6, 129.1, 128.3, 126.67/126.64, 126.5, 96.1/94.9, 77.2, 76.5/76.1, 60.8/59.8, 43.51/43.46, 27.0/26.6, 25.6/25.5, 25.3, 24.3/24.2, 21.3. **HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-

PrOH 99:1, flow rate 0.5 mL/min, 25°C, t_R 11.7 min for (*R*)-enantiomer (major) and t_R 13.7 min for (*S*)-enantiomer (minor). *e.r.* = 99.2:0.8. **$[\alpha]_D^{20}$**= -17.3° (c=1.0, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{23}H_{29}NO_3Na$ ($[M + Na]^+$): 390.2040; found: 390.2045. **IR (neat) *v* :** 2979, 1692, 1376, 1091, 1059.

(*R*)-(+)-1-(*p*-Tolyl)but-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5u**:

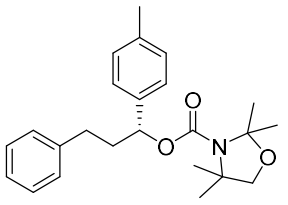


Following the general procedure C, but-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (137 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 90 mg (67%) of the racemic arylated product as an oil.

Following the general procedure D, but-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (137 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 102 mg (76%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.24-7.20 (m, 2H), 7.16-7.14 (m, 2H), 5.77-5.68 (m, 1H), 5.10-5.03 (m, 1H), 3.75-3.68 (m, 2H), 2.71-2.55 (m, 2H), 2.33 (s, 3H), 1.61-1.34 (m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 151.1/151.4, 137.9/137.7, 137.5, 133.93/133.86, 129.2, 126.6, 117.9, 96.1/95.0, 76.5/76.2, 75.9, 60.8/59.9, 41.4/41.3, 26.9, 25.71/25.67, 25.5/25.4, 24.33/24.27, 21.3. **HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 10.8 min for (*R*)-enantiomer (major) and t_R 13.0 min for (*S*)-enantiomer (minor). *e.r.* = 99.7:0.3. **$[\alpha]_D^{20}$** = +19.3° (c=1.25, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{19}H_{27}NO_3Na$ ($[M + Na]^+$): 340.1883; found: 340.1886. **IR (neat) *v* :** 2979, 1694, 1375, 1060.

(*R*)-(+)-3-Phenyl-1-(*p*-tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5w**:

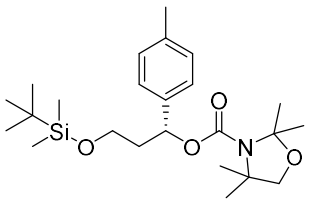


Following the general procedure C, 3-phenylpropyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (175 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 75 mg (47%) of the racemic arylated product as an oil.

Following the general procedure D, 3-phenylpropyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (175 mg, 0.375 mmol) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 127 mg (79%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.28-7.23 (m, 4H), 7.19-7.13 (m, 5H), 5.73 (t, 1H, *J* = 6.8 Hz), 3.76-3.68 (m, 2H), 2.71-2.50 (m, 2H), 2.34-2.28 (m, 4H), 2.13-2.07 (m, 1H), 1.65-1.35 (m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.2/151.5, 141.6, 138.0/137.9, 137.60/137.56, 129.3, 128.6, 128.4, 126.7, 126.1, 96.1/94.9, 76.9/76.2, 76.3, 38.7/38.6, 32.2, 27.1/27.0, 25.8/25.7, 25.5/25.4, 24.3, 21.3. **HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 10.6 min for (*R*)-enantiomer (major) and t_R 11.9 min for (*S*)-enantiomer (minor). *e.r.* = 98.7:1.3. **$[\alpha]_D^{20}$** = +17.4° (c=1.05, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{24}H_{31}NO_3Na$ ($[M + Na]^+$): 404.2196; found: 404.2198. **IR (neat) *ν* :** 2979, 1692, 1375, 1058.

(*R*)-(+)-3-((*tert*-Butyldimethylsilyl)oxy)-1-(*p*-tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5x**:

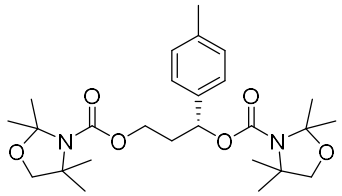


Following the general procedure C, 3-((*tert*-butyldimethylsilyl)oxy)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (208 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 156 mg (85%) of the racemic arylated product as an oil.

Following the general procedure D, 3-((*tert*-butyldimethylsilyl)oxy)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (208 mg) was arylated with p-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 125 mg (68%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.24-7.21 (m, 2H), 7.15-7.13 (m, 2H), 5.82-5.78 (m, 1H), 3.75-3.57 (m, 4H), 2.33 (s, 3H), 2.24-2.14 (m, 1H), 2.02-1.94 (m, 1H), 1.61-1.32 (m, 12H), 0.89 (s, 9H), 0.05-0.00 (m, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.1/151.4, 138.4/138.3, 137.44/137.39, 129.3, 126.6, 96.1/94.9,76.5/76.2, 73.7, 60.8/59.8, 40.0/39.9, 27.06/27.03, 26.1, 25.9/25.8, 25.6/25.4, 24.4/24.3, 21.3, 18.5, -5.22/-5.23.**HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 4.0 min for (*R*)-enantiomer (major) and t_R 4.8 min for (*S*)-enantiomer (minor). *e.r.* = 95:0.5.**$[\alpha]_D^{20}$** = +5.5° (c=0.8, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{24}H_{41}NO_4SiNa$ ($[M + Na]^+$):458.2697; found: 458.2703.**IR (neat) *ν* :** 2929, 1697, 1375, 1057, 833.

(*R*)-(+)-1-(*p*-Tolyl)propane-1,3-diyl bis(2,2,4,4-tetramethyloxazolidine-3-carboxylate) **2.5y**:



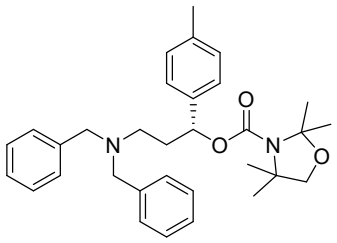
Following the general procedure C, propane-1,3-diyl bis(2,2,4,4-tetramethyloxazolidine-3-carboxylate) (232 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 110 mg (55%) of the racemic arylated product as an oil.

Following the general procedure D, propane-1,3-diyl bis(2,2,4,4-tetramethyloxazolidine-3-carboxylate) (232 mg) was arylated with *p*-bromotoluene (51.8 µL). The crude residue was purified by column chromatography (pentane/Et_2O 98:2 to 80:20) to give 176 mg (88%) of the enantioenriched arylated product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.22-7.20 (m, 2H), 7.14-7.12 (m, 2H), 5.79 (q, 1H, *J* = 6.1 Hz) , 4.13-4.05 (m, 2H), 3.73-3.65 (m, 2H), 2.35-2.10 (m, 5H), 1.52-1.30 (m, 24H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.6/151.9, 151.8/151.1, 137.8/137.7, 137.6, 129.4, 126.5, 96.1/95.0, 95.9/94.8, 76.4/76.1, 73.5, 61.1/59.79/59.76,

60.8/60.7, 36.2/.36.1, 27.0, 26.69/26.67, 25.8, 25.7, 25.48/25.45, 25.4/25.3, 24.23/24.19, 21.2. **HPLC separation conditions :** Chiralpak AD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 25°C, t_R 16.3 min for (*R*)-enantiomer (major) and t_R 19.6 min for (*S*)-enantiomer (minor). *e.r.* = 97.9:2.1. $[\alpha]_D^{20}$ = +3.8° (c=2.0, $CHCl_3$). **HRMS (ESI) m/z:** calcd. for $C_{26}H_{40}N_2O_6Na$ ($[M + Na]^+$): 499.2779; found: 499.2777. **IR (neat) *ν* :** 2978, 1698, 1345, 1063.

(*R*)-(+)-3-(Dibenzylamino)-1-(*p*-tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5z** :



Arylation with TMEDA :

In a tubular reactor (100 mm x 16 mm) set up with a rubber septum, a solution of 3-(dibenzylamino)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.7i** (247 mg, 0.6 mmol, 1 eq) and TMEDA (181 µL, 1.2 mmol, 2 eq) in dry diethyl ether (2 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (1.2 mmol, 2 eq, solution in hexane) was added dropwise, and the mixture was stirred for 4 h. A suspension of zinc acetate (232 mg, 1.26 mmol, 2.1 eq) in dry THF (2 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat to 20°C over 30 min. The solvents where evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (9.62 mg, 10.5 µmol, 1.75 %mol) and Ruphos (9.85 mg, 21 µmol, 3.5 %mol) in dry toluene (2 mL) was added to solve the residue, followed by p-bromotoluene (51.8 µL, 0.42 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 80°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (5mL) and separated. The aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by column chromatography (pentane/Et_2O 98:2 to 50:50) to afford 128mg (61%) of the racemic arylated product.

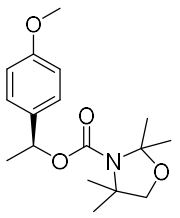
Enantioselective arylation with (-)-sparteine :

In a tubular reactor (100 mm x 16 mm) set up with a rubber septum, a solution of the protected alcohol**2.7i** (247 mg, 0.6 mmol, 1 eq) and (-)-sparteine (276 µL, 1.2 mmol, 2 eq) in dry diethyl ether (2 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (1.2 mmol, 2 eq, solution in hexane) was added dropwise, and the mixture was stirred for 5 h. A suspension of zinc acetate (232 mg, 1.26 mmol, 2.1 eq) in dry THF (2 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat to 20°C over 30 min. The solvents where evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (9.62 mg, 10.5 µmol, 1.75 %mol) and Ruphos (9.85 mg, 21 µmol, 3.5 %mol) in dry toluene (2 mL) was added to solve the residue, followed by the bromoaryl (0.42 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 80°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (5mL) and separated. The aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by column chromatography (pentane/Et_2O 98:2 to 50:50) to afford 150mg (71%) of the enantioenriched arylated product.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.34-7.19 (m, 10H), 7.13-7.08 (m, 4H), 5.71-5.58 (m, 1H), 3.65-3.64 (m, 2H), 3.54 (s, 4H), 2.53-2.48 (m, 2H), 2.32 (s, 3H), 2.16-1.98 (m, 2H), 1.52-1.13 (m, 12H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.1/151.3, 139.7, 138.7/138.5, 137.33/137.29, 129.3, 129.0, 128.4, 127.0, 126.4, 96.0/94.9, 76.4/76.2, 74.9, 60.8/59.7, 58.6, 50.1, 34.8/34.7, 26.9/26.8, 25.7, 25.51/25.49, 24.4, 21.3.**HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 99:1, flow rate 0.5 mL/min, 25°C, t_R 11.9 min for (*R*)-enantiomer (major) and t_R 13.7 min for (*S*)-enantiomer (minor). *e.r.* = 97.2:2.8.**$[\alpha]_D^{20}$**= +1.5° (c=0.5, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{32}H_{40}N_2O_3H_1$ ($[M + H]^+$): 501.3112; found: 501.3116.**IR (neat) *ν* :**3026, 2932, 1694, 1375, 1093, 1060.

*Arylation on a 3 mmol scale for ent-**2.5a** and **2.5v***

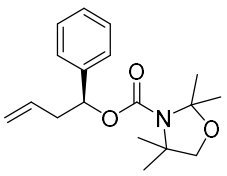
(*S*)-(-)-1-(4-Methoxyphenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate *ent*-**2.5a** :



In a oven-dried Schlenck tube (75 mm x 40 mm) set up with a rubber septum, a solution of 2,2,4,4-tetramethyl-1,3-oxazolidine (604 mg, 3 mmol, 1 eq) and (+)-sparteine (896 µL, 3.9 mmol, 1.3 eq) in dry diethyl ether (10 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (3.9 mmol, 1.3 eq, solution in hexane) was added dropwise, and the mixture was stirred for 5 h. A suspension of zinc acetate (771 mg, 4.2 mmol, 1.4 eq) in dry THF (10 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat to 20°C over 30 min. The solvents where evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (48.1 mg, 52.5 µmol, 1.75 %mol) and Ruphos (49 mg, 105 µmol, 3.5 %mol) in dry toluene (10 mL) was added to solve the residue, followed by the 4-bromoanisole (264 µL, 2.1 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 80°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (10 mL), and the organic phase was diluted with EtOAc (25 mL) and separated. The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with water and dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by column chromatography (Et_2O/pentane) to afford 542 mg (84%) of the enantioenriched benzylic alcohol ((*S*), *e.r.* 1:99).

$\mathbf{[\alpha]_D^{20}}$ = -13° (c=0.6, $CHCl_3$).

(*S*)-(-)-1-Phenylbut-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5v** :



Arylation with TMEDA :

In a oven-dried Schlenck tube (75 mm x 40 mm) set up with a rubber septum, a solution of but-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate(684 mg, 3 mmol, 1 eq) and TMEDA (634 µL, 4.2 mmol, 1.4 eq) in dry diethyl ether (10 mL) under argon was stirredand cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (4.2 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 5 h. A suspension of zinc acetate (826 mg, 4.5 mmol, 1.5 eq) in dry THF (10 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat to 20°C over 30 min. The solvents where evaporated over 30 min under high

vacuum, and a solution of $Pd_2(dba)_3$ (48.1 mg, 52.5 µmol, 1.75 %mol) and Ruphos (49 mg, 105 µmol, 3.5 %mol) in dry toluene (10 mL) was added to solve the residue, followed by thebromobenzene (224 µL, 2.1 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 80°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (10 mL), and the organic phase was diluted with EtOAc (25 mL) and separated. The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with water and dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by column chromatography (Et_2O/pentane) to afford 380 mg (60%) of the racemic benzylic alcohol.

Enantioselective arylation with (+)-sparteine :

In a oven-dried Schlenck tube (75 mm x 40 mm) set up with a rubber septum, a solution of but-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (684 mg, 3 mmol, 1 eq) and (+)-sparteine (965 µL, 4.2 mmol, 1.4 eq) in dry diethyl ether (10 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (4.2 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 5 h. A suspension of zinc acetate (826 mg, 4.5 mmol, 1.5 eq) in dry THF (10 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat to 20°C over 30 min. The solvents where evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (48.1 mg, 52.5 µmol, 1.75 %mol) and Ruphos (49 mg, 105 µmol, 3.5 %mol) in dry toluene (10 mL) was added to solve the residue, followed by the bromobenzene (224 µL, 2.1 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 80°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (10 mL), and the organic phase was diluted with EtOAc (25 mL) and separated. The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with water and dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by column chromatography (Et_2O/pentane) to afford 474 mg (74%) of the enantioenriched benzylic alcohol.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.37-7.25 (m, 5H), 5.80-5.68 (m, 2H), 5.10-5.03 (m, 2H), 3.75-3.69 (m, 2H), 2.72-2.58 (m, 2H), 1.62-1.34 (m, 12H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.1/151.4, 140.9/140.8, 133.82/133.75, 128.6, 127.8, 126.6, 118.1, 96.1, 95.0,76.5/76.2, 76.1, 60.9/60.0, 41.5/41.4, 26.98/26.96, 25.73/27.70, 25.5/25.4, 24.33/24.29.**HPLC separation conditions :** ChiralcelOJ column, *n*-heptane/*i*-PrOH 98:2,

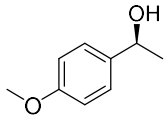
flow rate 0.3 mL/min, 25°C, t_R18.4min for (*R*)-enantiomer (minor) and t_R 20.4 min for (*S*)-enantiomer (major). *e.r.* = 1:99.**$[\alpha]_D^{20}$** = -8° (c=0.3, $CHCl_3$).**HRMS (ESI) m/z:** calcd. for $C_{18}H_{25}NO_3Na$ ($[M + Na]^+$): 326.1727; found: 326.1725.**IR (neat) *ν* :**3077, 2980, 1693, 1377, 1060, 1027, 761, 651.

Synthesis of secondary and tertiary alcohols ***2.12a-c*** *via Aggarwal's lithiation-borylation method*

General procedure :

To a stirred solution of 1-(4-methoxyphenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (100 mg, 0.325 mmol, 1 eq) and TMEDA (54 µL, 0.358 mmol, 1.1 eq) in Et_2O (2 mL) at -78°C under argon was added *s*-BuLi (0.345 mmol, 1.06 eq) dropwise over 3 min. The mixture was stirred for 5 min at -78°C, and then a 1 M solution of boron reagent (1.1 to 3 eq) in Et_2O was added dropwise under vigorous stirring. The solution was kept at -78°C for 20 min, and then at ambient temperature for 2 h after cooling bath removal (unless otherwise stated). The mixture was diluted with THF (2 mL), cooled to ~0°C with an ice bath, and a mixture of 3 M NaOH (1.1 mL) and 30% aqueous H_2O_2 (0.8 mL) per 1 mmol of boron reagent employed was added. After removal of the ice bath, the reaction mixture was stirred at room temperature for 2 h, then diluted with water (3 mL) and extracted with Et_2O (4 x 5 mL). The combined organic layer were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/Et_2O) to afford the pure secondary or tertiary alcohol. The analytical data of these latter were consistent with those reported in the literature[153].

1-(4-Methoxyphenyl)ethan-1-ol**2.12a** and *ent*-**2.12a** :



Synthesis of (±)-**2.12a**: to a stirred solution of racemic 1-(4-methoxyphenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (150 mg, 0.49 mmol, 1 eq) in Et_2O (2 mL) at -78°C under argon was added *s*-BuLi (0.54 mmol, 1.1 eq) dropwise over 3 min. The mixture was stirred for 20 min at -78°C, and then a 1 M solution of BH_3.THF (0.54 mL, 0.36 mmol, 1.1 eq) was added dropwise under vigorous stirring. The solution was kept at -78°C for 20 min, and then at ambient temperature for 2 h after cooling bath removal. The work-up was performed according to the general procedure. The crude product was purified (pentane/Et_2O 80:20 to 50:50) to afford 52 mg (70%) of the racemic secondary alcohol as a colorless oil.

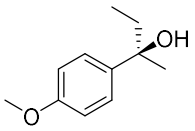
Synthesis of (*R*)-(+)-**2.12a**: according to the general procedure, the (*R*)-(-)-carbamate (80 mg, 0.26 mmol, 1 eq, *e.r.*99:1) was reacted with HB(pin) (113 µL, 0.78 mmol, 3 eq). The solution

was kept at -78°C for 2h, and then at -30°C for 3 h. The cooling bath was removed before the oxydation step in the sequence. The crude product was purified (pentane/Et_2O 80:20 to 50:50) to afford 31 mg (78%) of the (*R*)-(+)-enantioenriched secondary alcohol**2.12a** as a colorless oil.

Synthesis of (*S*)-(-)-**2.12a**: according to the general procedure, the (*S*)-(+)-carbamate (*e.r.* 1:99) was reacted with HB(pin) (113 µL, 0.78 mmol, 3 eq). The solution was kept at -78°C for 2h, and then at -30°C for 3 h. The cooling bath was removed before the oxidation step in the sequence. The crude product was purified (pentane/Et_2O 80:20 to 50:50) to afford 37.5 mg (76%) of the (*S*)-(-)-enantioenriched secondary alcohol *ent*-**2.12a** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) :δ = 7.31-7.28 (m, 2H), 6.90-6.87 (m, 2H), 4.85 (q, 1H, *J* = 6.4 Hz), 3.80 (s, 3H), 1.85 (br. s, 1H), 1.48 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR (100 MHz, $CDCl_3$) :**δ = 153.2, 138.2, 126.8, 114.0, 70.2, 55.5, 25.2. **HPLC separation conditions :** Chiralcel OD-H column, *n*-heptane/*i*-PrOH 98:2, flow rate 1 mL/min, 25°C. For **2.12a**: t_R 20.9 min for (*R*)-enantiomer (major) and t_R 24.5 min for (*S*)-enantiomer (minor). *e.r.* = 96:4. **$[\alpha]_D^{20}$** = +40.2° (c=1.5, $CHCl_3$). For *ent*-**2.12a** :t_R 21.5 min for (*R*)-enantiomer (minor) and t_R 25.9 min for (*S*)-enantiomer (major). *e.r.* = 3:97. **$[\alpha]_D^{20}$ =** -41.6° (c=1.5, $CHCl_3$).

(R)-(+)-2-(4-Methoxyphenyl)butan-2-ol **2.12b**:



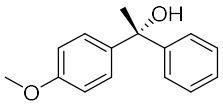
Synthesis of (±)-**2.12b**: according to the general procedure, the racemic carbamate was reacted with EtB(pin) (87 µL, 0.49 mmol, 1.5 eq). The crude product was purified (pentane/Et_2O 80:20 to 50:50) to afford 50 mg (85%) of the racemic tertiary alcohol as a colorless oil.

Synthesis of (*R*)-**2.12b**: according to the general procedure, the (*S*)-(+)-carbamate (*e.r.* 1:99) was reacted with EtB(pin) (87 µL, 0.49 mmol, 1.5 eq). The crude product was purified (pentane/Et_2O 80:20 to 50:50) to afford 47 mg (80%) of the (*R*)-(+)-enantioenriched tertiary alcohol as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) :δ = 7.36-7.34 (m, 2H), 6.88-6.86 (m, 2H), 3.80 (s, 3H), 1.86-1.78 (m, 3H), 1.53 (s, 3H), 0.79 (t, 3H). **^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$) :**δ = 158.3, 140.1, 126.2, 113.5, 74.8, 55.4, 36.9, 29.7, 8.5. **HPLC separation conditions :** Chiralcel OD-

H column, *n*-heptane/*i*-PrOH 99:1, flow rate 0.8 mL/min, 25°C, t_R 21.2 min for (*R*)-enantiomer (major) and t_R 25.3 min for (*S*)-enantiomer (minor). *e.r.* = 97:3. $[\alpha]_D^{20}$ = +22.2° (c=1.1, $CHCl_3$).

(*R*)-(+)-1-(4-Methoxyphenyl)-1-phenylethan-1-ol **2.12c**:



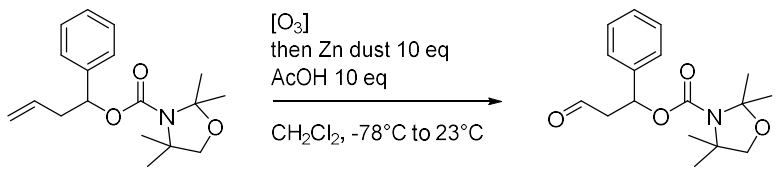
Synthesis of (±)-**2.12c**: according to the general procedure, the racemic carbamate was reacted with PhB(pin) (73 mg, 0.36 mmol, 1.1 eq,). The crude product was purified (pentane/Et_2O 80:20 to 50:50) to afford 58 mg (78%) of the racemic tertiary alcohol as a colorless oil.

Synthesis of (*R*)-**2.12c**: according to the general procedure, the (*S*)-(+)-carbamate (*e.r.* 1:99) was reacted with PhB(pin) (87 µL, 0.49 mmol, 1.5 eq). The crude product was purified (pentane/Et_2O 80:20 to 50:50) to afford 48 mg (65%) of the (*R*)-(+)-enantioenriched tertiary alcohol as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) :δ = 7.37-7.35 (m, 2H), 7.29-7.24 (m, 4H), 7.20-7.16 (m, 1H), 6.81-6.77 (m, 2H), 3.73 (s, 1H), 2.16 (s, 1H), 1.88 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) :**δ = 158.6, 148.5, 140.5, 128.3, 127.3, 127.0, 125.9, 113,6, 76.1, 55.4, 31.2. **HPLC separation conditions :** Chiralcel OJ column, *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25°C, t_R 33.9 min for (*R*)-enantiomer (major) and t_R 41.6 min for (*S*)-enantiomer (minor). *e.r.* = 97:3. $[\alpha]_D^{20}$ = +19.4° (c=0.9, $CHCl_3$).

Toward the synthesis of fluoxetine

3-oxo-1-phenylpropyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.17** :

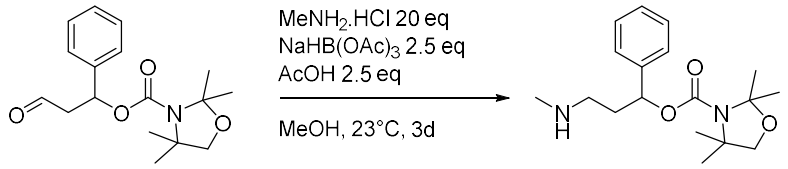


A solution of 1-phenylbut-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5v** (300 mg, 1 mmol, 1 eq) in CH_2Cl_2 (20 mL) was cooled down to -78°C. A stream of ozone was bubbled through the solution. The ozone stream was stopped 5 minutes after the reaction mixture turned blue and then a stream of oxygen was bubbled through the solution to evacuate

the excess of ozone. Zn dust (647 mg, 9.9 mmol, 10 eq) and AcOH (0.6 mL, 9.9 mmol, 10 eq) were added to the reaction mixture before it was allowed to warm up to 23 °C over 30 minutes. The reaction mixture was filtered through a pad of celite and sat. aq. $NaHCO_3$ (15 mL) was added to the filtrate. The aqueous phase was extracted with CH_2Cl_2 (3x30 mL) and the comined organic layer was washed with water (40 mL), and brine (40 mL), and then dried over $MgSO_4$. The solvent was evaporated under vacuum to obtain the title compound (302 mg, quant.) as a yellow oil, which is air sensitive.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 9.73 (s, 1H), 7.34-7.23 (m, 5H), 6.19 (dd, *J* = 8.5Hz, *J* = 4.8 Hz, 1H), 3.69-3.65 (m, 2H), 3.03-2.95 (m, 1H), 2.85-2.79 (m, 1H), 1.50-1.28 (m, 12H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 400 MHz, rotamers) :**δ = 199.1, 139.7, 129.0, 128.4, 126.4, 96.3/95.0, 76.5/76.1, 71.5, 61.1/60.0, 53.6, 50.7, 26.92/26.89, 25.7, 25.4, 24.2. **HRMS (ESI) m/z:** calcd. for $C_{17}H_{23}NO_4Na$ ($[M + Na]^+$): 328.1519; found: 328.1520. **IR (neat) *ν* :**not measured, compound not stable.

3-(methylamino)-1-phenylpropyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.18** :



To a solution of 3-oxo-1-phenylpropyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (300 mg, 1 mmol, 1 eq) in MeOH (15 mL) were added $MeNH_2$.HCl (1.36 g, 19.6 mmol, 20 eq), $NaHB(OAc)_3$ (520 mg, 2. 5 mmol, 2.5 eq), and acetic acid (0.1 mL, 2.5 mmol, 2.5 eq). The mixture was sitirred at 23°C for 3 days. The reaction mixture was quenched with aq. 1M NaOH (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3x30 mL). The combined organic layer was washed with sat. aq. $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified by colomn chromatography (CH_2Cl_2 to CH_2Cl_2/(NH_3 7M in MeOH) 95:5) followed by reversed phase preparative HPLC to obtain 31.5 mg (10%) of the title compound as a yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 7.35-7.27 (m, 5H), 5.81-5.78 (m, 1H), 3.75-3.68 (m, 2H), 2.65-2.58 (m, 2H), 2.39 (s, 3H), 2.18-2.96 (m, 2H), 1.65-1.34 (m, 12H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 400 MHz, rotamers) :**δ = 152.2/151.5, 141.1/140.0, 128.6, 127.9, 126.6, 96.2/95.0, 76.5/76.2, 74.8, 60.9/59.9, 48.4, 37.2, 36.6, 27.0/26.9, 25.8/25.7, 25.44/25.38, 24.3.

HRMS (ESI) m/z: calcd. for $C_{18}H_{28}N_2O_3H$ ($[M + H]^+$): 321.2173; found: 321.2177. **IR (neat) *v* :**2935, 1689, 1394, 1092, 1058, 762, 698.

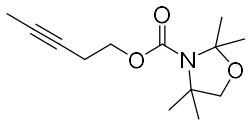
5.2. Attempts toward the β-arylation of *O*-carbamates

*Preparation of 2,2,4,4-tetramethyloxazolidine-3-carboxylates **2.7j-n***

General procedure :

A solution of the corresponding alcohol (1.0 eq) in THF (10 mL) was addeddropwise to a suspension of sodium hydride (95% in mineral oil, 1.1 eq) in THF (30 mL) and the mixture was stirred for 30 min at room temperature. A solution of 2,2,4,4-tetramethyloxazolidine-3-carbonyl chloride (1.05 eq.) in THF (10 mL) was then added dropwise and the mixture was stirred for 12 h. After quenching with water, the solvent was removed under reduced pressure and Et_2O (50 mL) was added to the crude mixture. The organic phase was washed with sat. aq. $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated and the residue was purified by silica gel column chromatography (Pent/Et_2O 98:2 to 80:20).

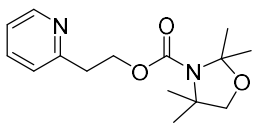
Pent-3-yn-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.7j**:



Following the general procedure, 3-pentyn-1-ol (550 µL, 5.9 mmol) gave 1.3 g (91%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 4.14-4.10 (m, 2H), 3.72 (s, 2H), 2.48-2.43 (m, 2H), 1.74 (t, J_5 = 2.5 Hz, 3H), 1.54 (s, 6H), (1.40) 1.38 (2 br. s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.6/151.9, 95.9/95.2, 77.2, 76.5/76.2, 75.6, 63.0, 60.7/60.0, 26.5/25.4, 25.3/24.2, 19.6, 3.5. **HRMS (ESI) m/z:**calcd. for $C_{13}H_{21}NO_3Na$ ($[M + Na]^+$): 262.1414; found: 262.1418**. IR neat (υ/cm^{-1}) :** 2980, 2870, 2360, 1702, 1408, 1349, 1260, 1099.

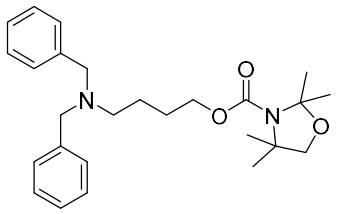
2-(pyridin-2-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7k**:



Following the general procedure, 2-(pyridin-2-yl)ethan-1-ol (0.85 mL, 7.5 mmol) gave 1.85 g (89%) of the title carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 8.56-8.54 (m, 1H), 7.62-7.58 (m, 1H), 7.21-7.1 (m, 2H), 4.52-4.48 (m, 2H), 3.67-3.66 (m, 2H), 3.17-3.12 (m, 2H), 1.53 (1.39) (2 br. s., 6H), (1.30) 1.16 (2 br. s., 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 158.4, 152.2, 151.8, 149.4, 136.3, 123.3, 121.5, 95.7/94.8, 76.3/76.0, 63.7, 60.5/59.6, 37.7, 26.2, 25.2, 249, 24.1. **HRMS (ESI) m/z :** calcd. for $C_{15}H_{22}N_2O_3H$ ($[M + H]^+$): 279.1703; found: 279.1699.**IR neat (υ/cm^{-1}) :**2980, 1697, 1582, 1407, 1343, 1260, 1097.

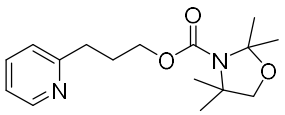
4-(dibenzylamino)butyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.7l**:



Following the general procedure, 4-(dibenzylamino)butan-1-ol (1.08g, 3.64 mmol) gave 850mg (50%) of the title carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 7.37-7.29 (m, 8H), 7.25-7.21 (m, 2H), 4.05-4.00 (m, 2H), 3.72 (s, 2H), 3.56 (s, 4H), 2.48-2.43 (m, 2H), 1.64-1.34 (m, 14H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :** δ = (C=O missing), 139.9, 128.88, 128. 85, 128.3, 126.9, 95.9/94.9, 76.5/75.2, 64.6, 60.6/59.7, 58.4, 53.0, 27.0, 26.7, 26.4, 25.5, 24.3, 24.0, 23.7. **HRMS (ESI) m/z :** calcd. for $C_{26}H_{36}N_2O_3H$ ($[M + H]^+$): 425.2799; found: 427.2807.**IR neat (υ/cm^{-1}) :** 2940, 2798, 1697, 1453, 1408, 1363, 1259, 1067.

3-(pyridin-2-yl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.7m**:

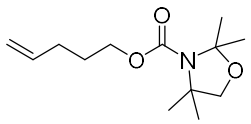


Following the general procedure, 3-(pyridin-2-yl)propan-1-ol (500mg, 3.64 mmol) gave 1.00 g (94%) of the title carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 8.54-8.52 (m, 1H), 7.61-7.57 (m, 1H), 7.15-7.1 (m, 2H), 4.17-4.13 (m, 2H), 3.73 (s, 2H), 2.91-2.85 (m, 2H), 2.17-2.08 (m, 2H), 156 (1.54 (2br. s., 6H), (1.42) 1.38 (2br. s., 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :** δ = 161.0, 152.9, 152.2, 149.5, 136.5, 122.9, 121.3, 95.9/94.9, 76.4/76.2, 64.2, 60.6/59.8,

35.0, 28.9, 26.7/25.44, 25.38/24.2. **HRMS (ESI) m/z :** calcd. for $C_{16}H_{24}N_2O_3H$ ($[M + H]^+$): 293.1860; found: 293.1859.**IR neat (υ/cm^{-1}) :** 2980, 1693, 1409, 1364, 1260, 1098.

Pent-4-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7n**:



Following the general procedure, Pent-4-en-1-ol (600 µL, 5.8 mmol) gave 1.3 g (93%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.86-5.78 (m, 1H), 5.07-4.98 (m, 2 H), 4.12-4.08 (m, 2H), 3.73 (s, 2H), 2.19-2.12 (m, 2H), 1.80-1.72 (m, 2H), 1.56 (1.53) (2 br. s, 6H), (1.42) 1.37 (2 br. s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.0/152.2, 137.7, 115.4, 95.9/94.9, 76.5/76.2, 64.0, 60.7/59.8, 30.5, 28.3, 26.7, 25.4, 24.3. **HRMS (ESI) m/z:**calcd. for $C_{13}H_{23}NO_3Na$ ($[M + Na]^+$): 264.1570; found: 264.1570**. IR neat (υ/cm^{-1}) :** 2979, 2361, 1695, 1406, 1359, 1259, 1067, 914.

5.3. Ligand-controlled γ-arylation of *O*-carbamates

Generalinformation

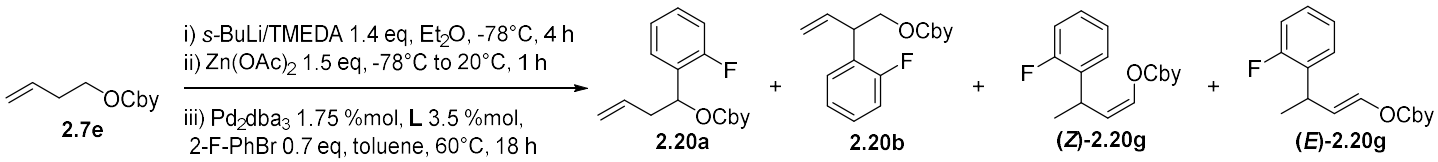
All reactions were performed under an argon atmosphere (unless otherwise noted) in Pyrex glassware equipped with a magnetic stir bar. GC/MS analyses were run on a Shimadzu QP2010 apparatus using aRTx®-5ms column lined with a mass (EI 0.86 kV) detection system.^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a *BrukerAvance III* (400 MHz) spectrometer at 298 K in $CDCl_3$ (residual peaks ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm). Chemical shifts (δ) are reported in ppm relative totetramethylsilane (0.00 ppm). Data are reported as follows: chemical shift in parts per million (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br. for broad), integration value, coupling constant in Hz if applicable. Analytical Thin Layer Chromatography (TLC) was performed using pre-coated *Merck silica gel 60 F254* plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains (Phosphomolybdic acid or $KMnO_4$) Flash chromatographies were performed using *SilicycleSiliaFlash P60* (230-400 mesh) with the indicated solvents. High resolution mass spectrometry recorded by Dr. H. Nadig of the University of Basel on a *BrukermaXis 4G QTOF* ESI mass spectrometer. Infrared spectra were measured on a*ATR Varian Scimitar 800* FT-IR spectrometer and reported in cm^{-1}. HPLC analyses were done using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, $DGU\text{-}20A_3$ degasser and SPD-M20A Diode Array or UV/Vis detector. Chiralcel OD-H, OJ, or OJ-H and Chiralpak AD-H, IA or IC columns from Daicel Corporation were used for separation. Optical rotationwere measured on a Perkin Elmer 341Polarimeter in a 1 mL cuvette (cell length 100 mm) with Na_D-Line (λ = 589 nm) at 20°C. The concentration (c) is given in g/dL.

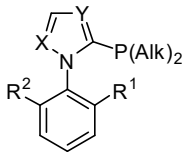
Commercially available reagents were used without further purification unless otherwise stated. Anhydrous solvents (Diethyl ether, THF, Toluene) were purchased form Sigma Aldrich and used as received.Tetramethylethylenediamine (TMEDA) was freshly distilled over CaH_2 under argon atmosphere. (-)-Sparteine and (+)-sparteine were respectively purchased from Sigma Aldrich and Fluorochem, distillated over CaH_2 under argon atmosphere, degassed under high vacuum via freeze-pumping process, and conserved at -30°C. 2-Dicyclohexylphosphino-2',6'-diisopropoxy-biphenyl (RuPhos) was purchased from Strem. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was purchased from Strem and

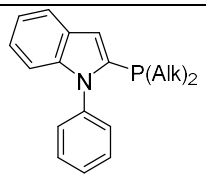
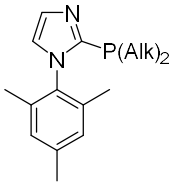
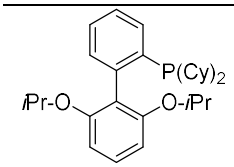
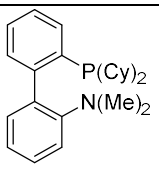
ABCR. Zinc acetate ($Zn(OAc)_2$)was purchased from Sigma Aldrich and thinly powdered. (RuPhos), ($Pd_2(dba)_3$), and ($Zn(OAc)_2$) were conserved in a glove box.

Additional optimization results

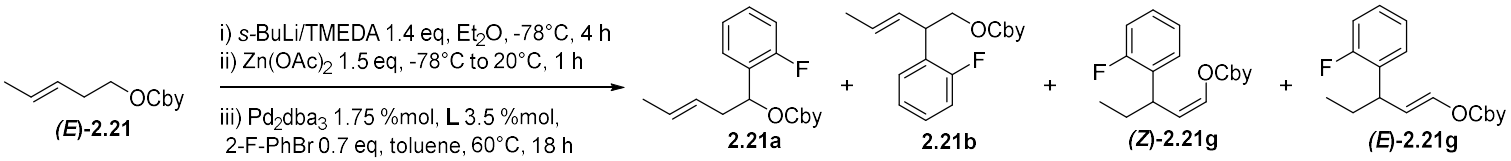
First ligand screen :

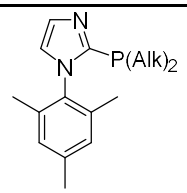
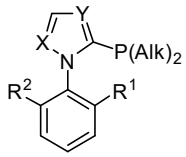
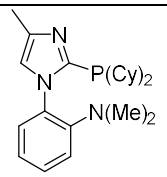
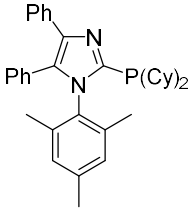


Structure	Ligand	X	Y	R^1	R^2	Alk	Product ratio GCMS (α/β/γZ/γE)	^{19}F NMR Yield % (α/β/γZ/γE)
	2.L[11]	CH	CH	H	H	*n*Bu	No prod.	n.d.
	2.L[10]	CH	CH	H	H	*i*Bu	No prod.	n.d.
	2.L[9]	CH	CH	H	H	*i*Pr	9/44/16/31	Traces
	2.L[28]	CH	CH	H	H	Cy	12/37/17/33	0/13/0/11
	5.L[83]	CH	CH	H	H	*t*Bu	100/0/0/0	n.d.
	5.L[84]	CH	CH	$N(Me)_2$	H	*i*Pr	24/50/17/8	7.5/20/4/2
	2.L[26]	CH	CH	$N(Me)_2$	H	Cy	27/45/15/11	14/23/7/5
	5.L[85]	CH	CH	$N(Me)_2$	H	*t*Bu	23/50/17/10	n.d
	2.L[8]	CH	N	$N(Me)_2$	H	Cy	18/36/25/21	7/16/10/8
	**5.L[86]**	CH	N	$N(Me)_2$	H	*t*Bu	100/0/0/0	56/0/0/0
	2.L[29]	CH	CH	OMe	H	Cy	29/27/17/27	Traces
	5.L[87]	CH	CH	OMe	H	*t*Bu	100/0/0/0	n.d.
	2.L[30]	CH	N	O*i*Pr	O*i*Pr	Cy	33/6/51/11	3/0/6/0
	5.L[88]	CH	N	O*i*Pr	O*i*Pr	*t*Bu	100/0/0/0	60/0/0/0
	5.L[89]	N	CH	O*i*Pr	O*i*Pr	*t*Bu	100/0/0/0	20/0/0/0
	2.L[31]	CH	N	$N(Me)_2$	$N(Me)_2$	Cy	88/1/9/3	67/0/0/0
	5.L[890]	CH	N	$N(Me)_2$	$N(Me)_2$	*t*Bu	100/0/0/0	31/0/0/0
	2.L[32]	N	CH	$N(Me)_2$	$N(Me)_2$	Cy	48/15/30/8	20/6/16/3
	5.L[91]	N	CH	$N(Me)_2$	$N(Me)_2$	*t*Bu	100/0/0/0	9/0/0/0
	5.L[92]	CH	N	OCy	OCy	*t*Bu	No prod.	n.d
	5.L[93]	CH	N	O*i*Pr	O*i*Pr	Ad	100/0/0/0	38/0/0/0

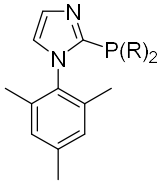
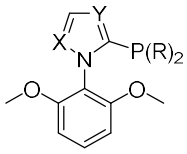
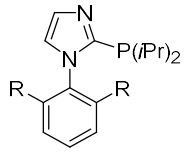
	**5.L[94]**	-	-	-	-	Cy	20/36/12/33	3/7/0/3
	5.L[95]	-	-	-	-	*t*Bu	100/0/0/0	n.d.
	**2.L[27]**	-	-	-	-	Cy	18/25/40/48	11/15/21/12
	**1.L[2]** **RuPhos**	-	-	-	-	-	100/0/0/0	54/0/0/0
	**1.L[4]** **DavePhos**	-	-	-	-	-	93/7/0/0	n.d.

Second ligand screen :

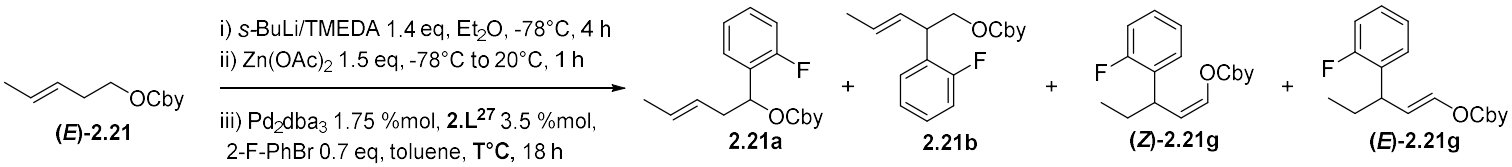


Structure	Ligand	X	Y	R^1	R^2	Alk	Product ratio GCMS (α/β/γZ/γE)	^{19}F NMR Yield % γZ/γE
	**2.L[27]**	-	-	-	-	Cy	9/6/64/21	49/12
	**2.L[26]**	CH	CH	$N(Me)_2$	H	Cy	17/33/34/15	12/6
	2.L[33]	CH	N	$N(Me)_2$	H	*i*Pr	9/19/46/26	16/6
	2.L[34]	CH	N	F	H	Cy	6/9/36/49	9/10
	2.L[35]	CH	N	CF_3	H	Cy	4/16/41/39	15/13
	2.L[36]	CH	N	*i*Pr	H	Cy	8/5/52/35	20/14
	2.L[37]	CH	N	OMe	H	Cy	13/4/47/37	9/6
	2.L[38]	CH	N	$N(Et)_2$	H	Cy	7/12/57/24	7/4
	2.L[39]	CH	N	Me	H	Cy	7/14/46/33	9/6
	**2.L[40]**	-	-	-	-	-	12/14/51/23	14/9
	**2.L[41]**	-	-	-	-	-	13/10/57/20	31/10

Third ligand screen :

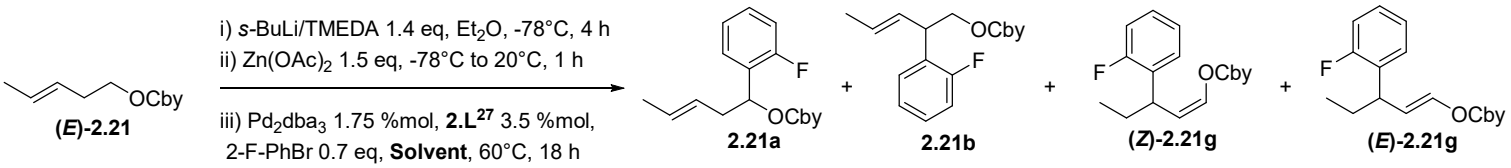
Structure	Ligand	X	Y	R	Product ratio GCMS (α/β/γZ/γE)	^{19}F NMR Yield % γZ/γE
	**2.L**^{27}	-	-	Cy	9/6/65/20	49/12
	2.L^{42}	-	-	*i*Pr	7/14/60/20	6/2
	**2.L**^{46}	CH	N	Ph	No traces	n.d.
	2.L^{43}	CH	N	Cy	16/0/76/8	21/2
	2.L^{44}	CH	N	*i*Pr	16/1/74/10	39/5
	2.L^{47}	CH	N	*n*Bu	traces	n.d.
	2.L^{48}	CH	N	Et	No traces	n.d.
	2.L^{45}	CH	N	*t*Bu	100/0/0/0	n.d.
	2.L^{49}	CH	N	*i*Bu	No traces	n.d.
	2.L^{50}	CH	N	Np	No traces	n.d.
	2.L^{51}	N	CH	*i*Pr	29/15/46/10	40/10
	**2.L**^{52}	-	-	OEt	10/1/76/12	45/6
	2.L^{53}	-	-	O*i*Pr	9/0/79/12	42/6
	2.L^{54}	-	-	Et	10/12/62/16	41/9
	2.L^{55}	-	-	F	5/20/44/31	36/17

Temperature screen :



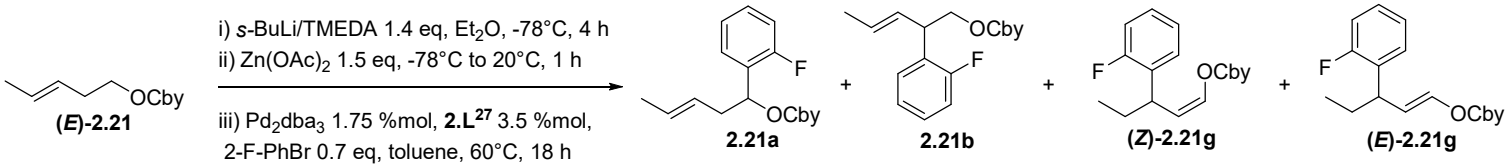
Entry	T°C	Product ratio GCMS (α/β/γZ/γE)	^{19}F NMR Yield% (γZ/γE)	Isolated Yield γ-product
1	100	18/8/51/22	32/14	31%, 68/32 Z/E
2	80	11/7/59/22	44/16	33%, 71/29 Z/E
3	60	9/6/64/21	49/12	48%, 75/25 Z/E
4	40	4/6/70/19	40/11	31%, 77/23 Z/E
5	20	traces	<6/1	n.d.
6	0	traces	<2/1	n.d.

Solvent screen :



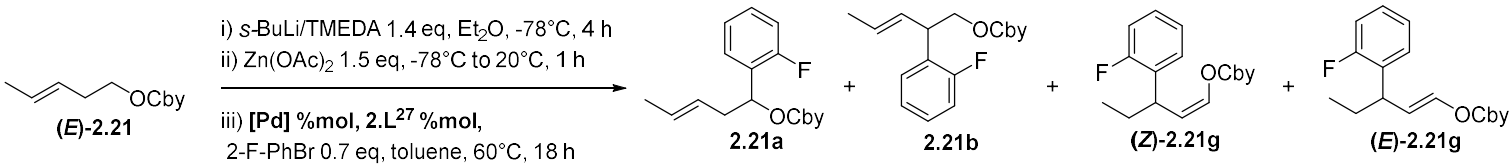
Entry	Solvent	Product ratio GCMS (α/β/γZ/γE)	^{19}F NMR Yield% (γZ/γE)	Isolated Yield γ-product
1	toluene	9/6/64/21	49/12	48%, 75/25 Z/E
2	THF	8/4/67/22	31/2	19%, 71/29 Z/E
3	dimethylacetamide	no conversion	n.d.	n.d.
4	1,2-dichloroethane	13/0/75/13	<3/3	n.d.
5	1,2-dimethoxyethane	0/0/86/14	7/<1	n.d.
6	*n*-hexane	10/12/60/19	26/4	29%, 73/27 Z/E
7	1,4-dioxane	no conversion	n.d.	n.d.
8	cyclopentyl methyl ether	10/6/65/19	<2/2	n.d.
9	benzene	7/6/66/21	39/11	47%, 76/24 Z/E
10	cyclohexane	10/6/65/19	<3/3	n.d.
11	α,α,α-trifluorotoluene	8/0/65/27	n.d.	12%, 72/28 Z/E
12	mesitylene	8/8/63/21	20/7	18%, 60/40 Z/E
13	perfluorobenzene	13/8/59/19	20/5	n.d.

Additives/conditions deviations :



Entry	Additive / deviation	Product ratio GCMS (α/β/γZ/γE)	^{19}F NMR Yield% (γZ/γE)	Isolated Yield γ-product
1	i) *s*-BuLi/TMEDA 2 eq ii) Zn(OAc) 2,1 eq	6/7/68/16	29/8	31.5%, 74/26 Z/E
2	i) *s*-BuLi/TMEDA 1.05 eq ii) Zn(OAc) 1.1eq	11/5/70/14	42/13	43%, 75/25 Z/E
3	ii) $ZnCl_2$ i/o $Zn(OAc)_2$	8/4/67/21	n.d.	35%, 71/29 Z/E
4	iii) 0.5 eq ArBr	7/7/66/20	38/9	44%, 75/25 Z/E
5	iii) 0.5 eq ArBr, 2.5 %mol cat.	7/5/67/21	42/10	44%, 74/26 Z/E
6	iii) 0.6 eq ArBr	6/6/67/20	32/9	n.d.
7	iii) 1 eq ArBr	8/8/64/20	32/9.5	35%, 75/25 Z/E
8	iii) 1 eq ArBr, 5 %mol cat.	7/6/67/20	33/9.5	35%, 75/25 Z/E
9	iii) 1.5 eq ArBr	8/7/64/21	32/9.5	n.d.
10	iii) 3.5 %mol Pd_2dba_3, 7 %mol **2.L^{27}**	8/7/67/19	46/14	53.5%, 75/25 Z/E
11	iii) 7 %mol Pd_2dba_3, 14 %mol **2.L^{27}**	7/7/67/20	44/13	n.d.
12	iii) 1.75 %mol Pd_2dba_3, 5.25 %mol **2.L^{27}**	8/5/67/20	43/13	42%, 75/25 Z/E
13	iii) 1.75 %mol Pd_2dba_3, 7 %mol **2.L^{27}**	6/7/66/21	34/10	n.d.
14	iii) reaction 40h	7/7/65/21	44/14	55%, 75/25 Z/E
15	iii) + 12-Crown-4 1.5 eq	8/6/67/20	44/13	n.d.
16	iii) + $MgCl_2$ 1.5 eq	8/7/67/18	41/12	n.d.
17	iii) + ZnF_2 1.5 eq	8/7/67/18	29/10	n.d.
18	iii) + $BF_3.Et_2O$ 1.5 eq	no traces	n.d.	n.d.
19	iii) + CO atmosphere	No reaction, no insertion		
20	iii) + *t*BuNC	Lower conversion, no insertion		

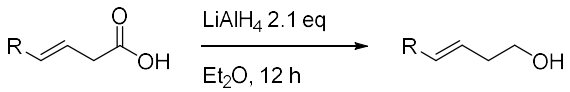
Palladium source screen :



Entry	Additive / deviation	Product ratio GCMS (α/β/γZ/γE)	^{19}F NMR Yield% (γZ/γE)	Isolated Yield γ-product
1	3.5 %mol $Pd(dba)_2$, 3.5 %mol **2.L^{27}**	6/6/66/21	14/4	n.d.
2	**L20** Pd G3 precatalyst 5 %mol	6/7/67/20	32/10	n.d.
2	3.5 %mol $PdCl_2$, 7 %mol **2.L^{27}**	6/6/66/21	24/8	n.d.
4	3.5 %mol $Pd(OAc)_2$, 7 %mol **2.L^{27}**	7/6/67/20	20/6	n.d.
5	1.75 %mol $[CinnamylPdCl]_2$, 7 %mol **2.L^{27}**	7/7/66/20	35/11	n.d.
6	3.5 %mol $[PdCl_2MeCN_2]$, 7 %mol **2.L^{27}**	7/7/67/20	45/14	50%, 75/25 Z/E
7	7 %mol $[PdCl_2MeCN_2]$, 14 %mol **2.L^{27}**	7/5/67/21	43/15	44%, 74/26 Z/E
8	7 %mol $[PdCl_2PhCN_2]$, 14 %mol **2.L^{27}**	7/6/67/20	45/14	45%, 75/25 Z/E
9	7 %mol $[PdMe_2TMEDA]$, 14 %mol **2.L^{27}**	7/6/67/20	43/13	n.d.
10	7 %mol $[PdCl_2(SMe)_2]$, 14 %mol **2.L^{27}**	7/5/67/20	44/14	n.d.
11	7 %mol $[Pd(CH_2SiMe_3)_2$ COD], 14 %mol**2.L^{27}**	7/6/68/20	44/14	n.d.

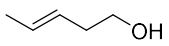
Starting material synthesis

- General procedure for the synthesis of homoallyl alcohols **S2-S4** from 3-alkenoic acids



A solution of the corresponding carboxylic acid (1 eq) in Et_2O was added dropwise to a suspension of $LiAlH_4$ (2.1 eq) in Et_2O at 0°C over 30 min. The resulting mixture was stirred at 20°C for 12 h, quenched with 20% aq. NaOH, and then filtrated over celite. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (Pent/Et_2O 95:5 to 50:50) to obtain the corresponding alcohol.

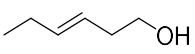
(*E*)-Pent-3-en-1-ol **S2**:



Following the general procedure, (*E*)-pent-3-enoic acid (1.5 mL, 14.7 mmol) in Et_2O (10 mL) was reacted with $LiAlH_4$ (1.2 g, 30.9 mmol) in Et_2O (20 mL) to obtain 1.1 g (87%) of the title alcohol as a colorless oil. The spectral data are consistent with those reported in the literature.[154]

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 5.62-5.53 (m, 1H), 5.44-5.36 (m, 1H), 3.62 (t, J_3 = 6.3 Hz, 2H), 2.28-2.23 (m, 2H), 1.70-1.67 (m, 3H), 1.49 (br. s, 1H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :** δ = 128.7, 127.2, 62.1, 36.1, 18.2. **GCMS (EI) m/z (intensity %) :**41 (100), 54 (0.2).**IR neat (υ/cm^{-1}) :** 3330, 3024, 2936, 2363, 1757, 1449, 1045, 966.

(*E*)-Hex-3-en-1-ol **S3**:

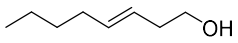


Following the general procedure, (*E*)-hex-3-enoic acid (1.5 g, 12.8 mmol) in Et_2O (10 mL) was reacted with $LiAlH_4$ (1.0 g, 26.9 mmol) in Et_2O (20 mL) to obtain 1.0 g (78%) of the title

alcohol as a colorless oil.The spectral data are consistent with those reported in the literature.[155]

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 5.64-5.57 (m, 1H), 5.41-5.33 (m, 1H), 3.63 (t, J_3 = 6.3 Hz, 2H), 2.29-2.23 (m, 2H), 2.08-2.00 (m, 2H), 1.48 (br. s, 1H), 0.98 (t, J_3 = 7.4 Hz, 3H).**^{13}C-{^{1}H}NMR ($CDCl_3$, 100 MHz) :**δ = 135.9, 124.9, 62.2, 36.1, 25.8, 13.9. **GCMS (EI) m/z (intensity %) :**43 (100), 61 (34), 89 (27), 70 (25), 45 (20)**.IR neat (υ/cm^{-1}) :** 3342, 2963, 2360, 1441, 1047, 967.

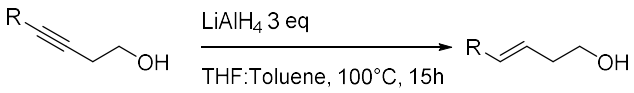
(*E*)-Oct-3-en-1-ol **S4**:



Following the general procedure, (*E*)-oct-3-enoic acid (570 mg, 4 mmol) in Et_2O (10 mL) was reacted with $LiAlH_4$ (320 mg, 8.4 mmol) in Et_2O (20 mL) to obtain 460 mg (90%) of the title alcohol as a colorless oil. The spectral data are consistent with those reported in the literature.[156]

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 5.59-5.52 (m, 1H), 5.41-5.33 (m, 1H), 3.62 (t, J_3 = 6.3 Hz, 2H), 2.29-2.23 (m, 2H), 2.04-1.99 (m, 2H), 1.48 (br. s, 1H), 1.35-1.29 (m, 4H), 0.89 (t, J_3 = 7.1 Hz, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 134.5, 125.8, 62.2, 36.1, 32.5, 31.8, 14.1. **GCMS (EI) m/z (intensity %):**55 (100) 41 (59), 68 (34), 81 (33), 95 (8), 110 (8)**.IR neat (υ/cm^{-1}) :** 3345, 2926, 2362, 1462, 1047, 968.

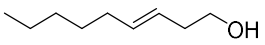
- General procedure for the synthesis of homoallyl alcohols **S5-S7** from homopropargylic alcohols



The homopropargylic alcohol (1 eq) was added dropwise to a suspension of $LiAlH_4$ (3 eq) in THF:Toluene (1:1 v:v) at 0°C. After the addition the mixture was stirred at 100°C for 15 h and then cooled down to room temperature. The reaction was quenched by a sequential addition of water (1µL/mg of $LiAlH_4$), 15% aq. NaOH (1µL/mg of $LiAlH_4$), and water (3µL/mg of $LiAlH_4$). The precipitate was filtered off on celite with Et_2O. The resulting organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The oily

residue was purified by silica gel column chromatography (Pent/Et_2O 95:5 to 50:50) the corresponding (*E*)-homoallyl alcohol as an oil.

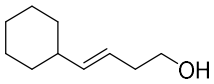
(*E*)-non-3-en-1-ol **S5**:



Following the general procedure, non-3-yn-1-ol (2.2 g, 15.7 mmol) was reacted with $LiAlH_4$ (reagent grade 95%, 1.9 g, 47.1 mmol) in THF:Toluene (50 mL) to obtain 1.4 g (63%) of the title compound as a colorless oil. The spectral data are consistent with those reported in the literature.[144]

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 5.59-5.52 (m, 1H), 5.41-5.33 (m, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 2.28-2.23 (m, 2H), 2.03-1.98 (m, 2H), 1.48 (br. s., 1H), 1.36-1.25 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 2H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 134.6, 125.8, 62.1, 36.1, 32.8, 31.5, 29.3, 22.7, 14.2. **GCMS (EI) m/z (intensity %):**41 (100), 55 (93), 69 (68), 81 (42), 95 (24), 124 (5). **IR neat (υ/cm^{-1}) :** 3333, 2924, 2856, 2361, 1461, 1335, 1048, 968.

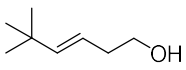
(*E*)-4-cyclohexylbut-3-en-1-ol **S6**:



Following the general procedure, 4-cyclohexylbut-3-yn-1-ol (200 mg, 1.3 mmol) was reacted with $LiAlH_4$ (reagent grade 95%, 157 mg, 3.9 mmol) in THF:Toluene (4 mL) to obtain 190 mg (94%) of the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 5.54-5.48 (m, 1H), 5.36-5.29 (m, 1H), 3.61 (t, *J* = 6.3 Hz, 2H), 2.27-2.22 (m, 2H), 1.97-1.89 (m, 1H), 1.73-1.62 (m, 5H), 1.48 (s, 1H), 1.31-1.00 (m, 5H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz) :**δ = 140.6, 123.2, 62.2, 40.9, 36.2, 33.3, 26.3, 26.2. **IR neat (υ/cm^{-1}) :** 3328, 2922, 2851, 2362, 1448, 1047, 968.

(*E*)-5,5-dimethylhex-3-en-1-ol **S7**:

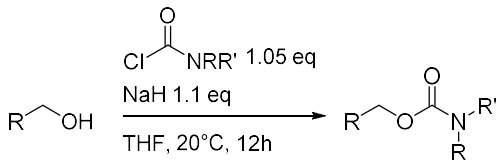


Following the general procedure, (*E*)-5,5-dimethylhex-3-yn-1-ol (200 mg, 1.6 mmol) was reacted with $LiAlH_4$ (reagent grade 95%, 189 mg, 4.7 mmol) in THF:Toluene (4 mL) to

obtain 145 mg (71%) of the title compound as a colorless oil. The spectral data are consistent with those reported in the literature.[4 ref above]

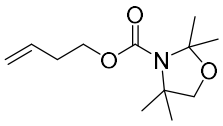
^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 5.59 (dt, *J* = 15.6 Hz, *J* = 1.3 Hz, 1H), 5.29 (dt, *J* = 15.6 Hz, *J* = 7.0 Hz, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 2.29-2.23 (m, 2H), 1.42 (s, 1H), 1.00 (s, 9H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz) :**δ = 145.6, 120.3, 62.2, 36.2, 33.2, 29.9. **IR neat (υ/cm^{-1}) :** 3727, 2956, 2362, 1748, 1634, 1460, 1046, 972.

- General procedure for the synthesis of 2,2,4,4-tetramethyloxazolidine-3-carboxylates **2.7e**, **2.21**, **2.23-31**, **2.33-37**, **2.39**



A solution of the corresponding alcohol (1.0 eq) in THF (10 mL) was added dropwise to a suspension of sodium hydride (95% in mineral oil, 1.1 eq) in THF (30 mL) and the mixture was stirred for 30 min at room temperature. A solution of 2,2,4,4-tetramethyloxazolidine-3-carbonyl chloride (unless otherwise stated) (1.05 eq) in THF (10 mL) was then added dropwise and the mixture was stirred for 12 h. After quenching with water, the solvent was removed under reduced pressure and Et_2O (50 mL) was added to the crude mixture. The organic phase was washed with sat. aq. $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated and the residue was purified by silica gel column chromatography (Pent/Et_2O 98:2 to 80:20).

But-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7e**:

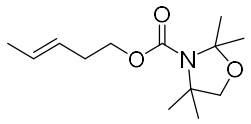


Following the general procedure, 3-buten-1-ol (652 µL, 7.5 mmol) gave 1.55 g (91 %) of the corresponding carbamate as a colorless oil. The analytical data were in accordance with the literature.[157]

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.85-5.76 (m, 1H), 5.14-5.05 (m, 2H), 4.16-4.12 (m, 2H), 3.71 (s, 2H), 2.44-2.37 (m, 2H), 1.55 (1.50) (2 br. s, 6H), (1.41) 1.34 (2 br. s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.9/152.2, 134.8, 117.2, 95.9/95.0,

76.5/76.2, 63.8, 60.7/59.9, 33.6, 26.6/25.42, 25.39/24.3. **HRMS (ESI) m/z:**calcd. for $C_{12}H_{21}NO_3Na$ ($[M + Na]^+$): 250.1414; found: 250.1416.**IR neat (υ/cm^{-1}) :** 2980, 2361, 1695, 1404, 1343, 1259, 1207, 1068, 991, 768, 652.

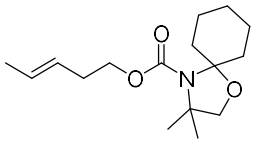
(*E*)-Pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate ***(E)*-2.21**:



Following the general procedure, (*E*)-pent-3-en-1-ol (1.2 g, 13.9 mmol) gave 3.2 g (95%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.57-5.49 (m, 1H), 5.45-5.39 (m, 1H), 4.11-4.07 (m, 2H), 3.72 (s, 2H), 2.37-2.32 (m, 2H), 1.66 (dd, J_3 = 6.2 Hz, J_4 = 1.1 Hz, 3H), 1.56 (1.51) (2 br. s, 6H), (1.42) 1.35 (2 br. s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.0/152.2, 127.9, 127.2, 95.9/95.0, 76.5/76.2, 64.3, 60.6/59.9, 35.5, 26.5/25.4, 25.3/24.3, 18.1. **HRMS (ESI) m/z:**calcd. for $C_{13}H_{23}NO_3Na$ ($[M + Na]^+$): 264.1570; found: 264.1572**. IR neat (υ/cm^{-1}) :** 2972, 2573, 2361, 1696, 1406, 1343, 1258, 1067, 966.

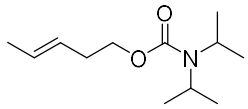
(*E*)-pent-3-en-1-yl 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate**2.23**:



Following the general procedure, (*E*)-pent-3-en-1-ol (100 mg, 1.16 mmol) was reacted with 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carbonyl chloride (271 mg, 1.17 mmol, 1.01 eq) to give 200 mg (61%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.57-5.49 (m, 1H), 5.45-5.38 (m, 1H), 4.08 (t, *J* = 6.5 Hz, 2H), 3.68 (s, 2H), 2.41-2.31 (m, 3H), 2.22-2.15 (m, 1H), 1.66-1.50 (m, 11H), (1.41) 1.34 (br. s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.1/152.5, 127.9, 127.5, 127.2, 97.3/96.6, 76.4/76.0, 64.2, 60.4/59.8, 34.1, 32.9, 32.5, 25.5, 24.9, 24.7, 24.5, 23.6, 23.4, 18.1. **HRMS (ESI) m/z:**calcd. for $C_{16}H_{27}NO_3Na$ ($[M + Na]^+$): 304.1883; found: 304.1885**. IR neat (υ/cm^{-1}) :** 3300, 2929, 2856, 2361, 1697, 1407, 1346, 1269, 1226, 1099, 965.

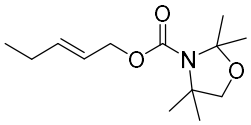
(E)-pent-3-en-1-yl diisopropylcarbamate **2.24**:



Following the general procedure, (*E*)-pent-3-en-1-ol (250 mg, 2.9 mmol) was reacted with *N,N*-diisopropylcarbamoyl chloride (522 mg, 3.2 mmol, 1.1 eq) to give 300 mg (48%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 5.54-5.47 (m, 1H), 5.45-5.37 (m, 1H), 4.15-3.53 (m, 4H), 2.34-2.29 (m, 2H), 1.65-1.63 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 12H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 156.0, 127.7, 127.3, 64.4, 45.6 (br. s), 32.7, 21.1 (br. s), 18.1. **HRMS (ESI) m/z:**calcd. for $C_{12}H_{23}NO_2Na$ ($[M + Na]^+$): 236.1621; found: 236.1619**. IR neat (υ/cm^{-1}) :** 2969, 2360, 1695, 1437, 1370, 1311, 1219, 1157, 1066.

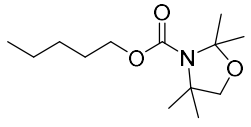
(*E*)-Pent-2-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.26** :



Following the general procedure, (*E*)-pent-2-en-1-ol (345 mg, 4 mmol) gave 850 mg (88%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.82-5.78 (m, 1H), 5.61-5.54 (m, 1H) 4.54-4.52 (m, 2H), 3.73 (s, 2H), 2.11-2.04 (m, 2H), 1.56 (1.52) (2 br. s, 6H), (1.42) 1.36 (2 br. s, 6H), 1.00 (t, J_3 = 7.4 Hz, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.8/152.1, 137.2/137.1, 123.6/123.6, 95.9/95.0, 76.5/76.26, 65.4, 60.7/59.8, 26.6, 25.4, 24.3, 13.4. **HRMS (ESI) m/z:**calcd. for $C_{13}H_{23}NO_3Na$ ($[M + Na]^+$): 264.1570; found: 264.1575**. IR neat (υ/cm^{-1}) :** 2968, 2871, 2361, 1701, 1405, 1348, 1261, 1065.

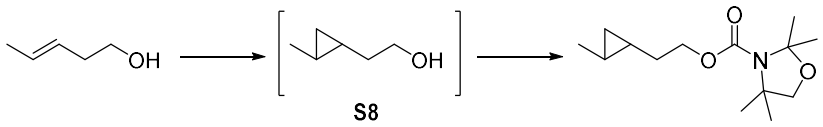
Pentyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.27**:



Following the general procedure, pentanol (650 µL, 4 mmol) gave 820 mg (84%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 4.09-4.05 (m, 2H), 3.73 (s, 2H), 1.68-1.63 (m, 2H), 1.56 (1.52) (2 br. s., 6H), 1.44-1.31 (m, 10H), 0.93-0.89 (m, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.1/152.4, 95.9/94.9, 76.5/76.2, 64.7, 60.6/59.7, 28.7, 28.5, 26.6/25.43, 25.39/24.3, 22.4, 14.1. **HRMS (ESI) m/z:**calcd. for $C_{13}H_{25}NO_3Na$ ([M + Na]$^+$): 266.1727; found: 266.1729.**IR neat (υ/cm^{-1}) :** 2961, 2867, 2360, 1700, 1408, 1348, 1260, 1096.

2-(2-methylcyclopropyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.29** :

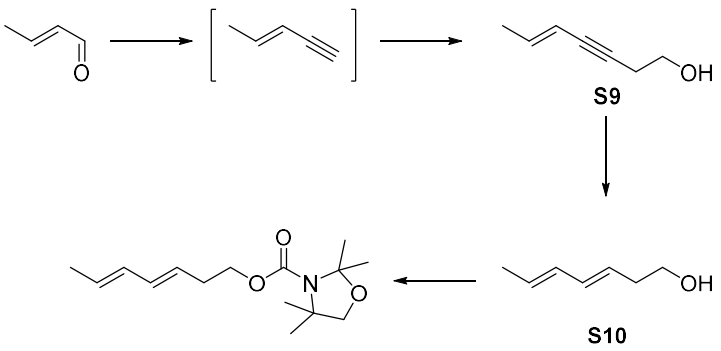


To a solution of (*E*)-Pent-3-en-1-ol (300 mg, 3.5 mmol, 1 eq) in dichloromethane (25 mL) at -20°C (acetone bath, cryostat) was carefully added diethylzinc (8.7 mL of a 1.5 M solution in toluene, 8.7 mmol, 2.5 eq) followed by addition of diiodomethane (0.56 mL, 7 mmol, 2 eq). The mixture was stirred for 5 min at this temperature, and was allowed to warm up to 20°C and stirred for 15h. Sat. aq. NH_4Cl was added (15 mL) and the aqueous phase was extracted with Et_2O (3x20 mL). The combined organic phase was washed with sat. aq. $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, filtrated, and then concentrated under vacuum. The residue was filtrated by silica gel column chromatography (Pent/Et_2O 80:20) to obtain 200 mg (ca. 60%) of the intermediate 2-(2-methylcyclopropyl)ethan-1-ol**S8** (containing ~15% inseparable starting material) as a colorless oil.

Following the general procedure, the intermediate 2-(2-methylcyclopropyl)ethan-1-ol **S8** (200 mg, ca.2 mmol, containing ~15% inseparable alkene) gave 250 mg (ca. 45%) of the corresponding carbamate (containing ~10% inseparable corresponding alkene) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 4.11-4.07 (m, 2H), 3.70 (s, 2H), 1.54-1.48 (m, 8H), (1.40) 1.34 (2 br. s, 6H), 0.99 (d, *J* = 5.9 Hz, 3H), 0.47-0.38 (m, 2H), 0.24-0.15 (m, 2H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.1/152.4, 95.9/94.9, 76.5/76.2, 64.8, 60.6/59.7, 33.7, 26.6/25.6, 25.4/24.3, 19.0, 16.7, 19.9, 12.6. **HRMS (ESI) m/z:**calcd. for $C_{14}H_{25}NO_3Na$ ([M + Na]$^+$): 278.1727; found: 278.1728**. IR neat (υ/cm^{-1}) :** 2984, 2361, 1701, 1408, 1352, 1261, 1098.

(3E,5E)-hepta-3,5-dien-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.30** :



(*E*)-hept-5-en-3-yn-1-ol**S9** was synthesised using a modified procedure from the literature.[158] To a 3-neck 100 mL round-bottomed flask equipped with a dry ice condenser was added trimethylsilyldiazomethane (4 mL of a 2 M solution in hexane, 8 mmol, 1.1 eq) and THF (10 mL). The solution was cooled to -78°C (acetone bath, cryostat) and *n*-BuLi (3.25 mL of a 2.5M solution in hexanes, 8 mmol, 1.1 eq) was added slowly. The resulting orange solution was stirred for 10 min at this temperature, and then a solution of crotonaldehyde (0.59 mL, 7.27 mmol, 1 eq) in THF (5 mL) was added. Stirring was continued at -78°C for 10 min, and then at 0°C (water, ice) for 10 min, before being cooled back to -78°C. *n*-BuLi (4.43 mL of a 2.5M solution in hexanes, 10.9 mmol, 1.5 eq) was slowly added and the reaction was allowed to stir for 15 min. $BF_3.Et_2O$ (2.88 mL of a 48% solution in Et_2O, 10.9 mmol, 1.5 eq) was added and the solution was stirred for 15 min at this temperature before the addition of ethylene oxide (4.85 mL of a 3M solution in THF, 14.5 mmol, 2 eq). The solution was stirred for 1 h, quenched with MeOH (2 mL), stirred for an additional 5 min, and then allowed to warm up to room temperature. Water (20 mL) and Et_2O (20 mL) were added to the mixture. The aqueous layer was separated and extracted with Et_2O (2x20 mL). The organice layers were combined, washed with brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure at 0°C. The oily residue was filtrated by silica gel column chromatography (Pent/Et_2O 80:20) to obtain 400 mg of an oil containing the intermediate (*E*)-hept-5-en-3-yn-1-ol**S9** along with inseparable unknown products.

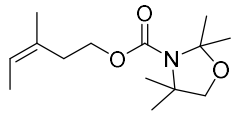
A solution of the intermediate (*E*)-hept-5-en-3-yn-1-ol**S9** (310 mg, ca. 2.8 mmol, ca. 1 eq) in THF (0.25 mL) was added to a suspension of $LiAlH_4$ (135 mg, 3.8 mmol, 1.2 eq) in THF:Triglyme (7.25 mL:2.5 mL) at 0°C (water, ice) over 5 min. After addition, the mixture was stirred at 80°C for 15 h and then cooled down to room temperature. The reaction was quenched by a sequential addition of water (200µL), 15% aq. NaOH (200µL), and water (1 mL). The precipitate was filtrated off on celite with Et_2O. The resulting organic phase was dried over $MgSO_4$, filtrated, and concentrated under vacuum. The oily residue was filtrated by

silica gel column chromatography (Pent/Et_2O 80:20) to obtain 130 mg of an oil containing (3*E*,5*E*)-hepta-3,5-dien-1-ol**S10** along with inseparable unknown products.

Following the general procedure, (3*E*,5*E*)-hepta-3,5-dien-1-ol**S10** (130 mg, ca. 1.2 mmol) gave 140 mg (9% on 3 steps) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 6.11-5.98 (m, 2H), 5.65-5.49 (m, 2H), 4.14-4.10 (m, 2H), 3.72 (s, 2H), 2.43-2.39 (m, 2H), 1.73 (d, *J* = 7.3Hz, 2H), 1.56 (1.50) (2 br. s, 6H), (1.42) 1.35 (2br. s, 6H), .**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = (C=O missing), 133.0, 131.40/131.37, 128.21/128.15, 126.97/126.91, 95.9/95.1, 76.5/76.2, 64.1, 60.7/59.9, 32.5/30.5, 26.6/25.5, 25.4/24.3, 18.2. **HRMS (ESI) m/z:**calcd. for $C_{15}H_{25}NO_3Na$ ($[M + Na]^+$): 290.1727; found: 290.1727**. IR neat (υ/cm^{-1}) :** 2973, 2361, 1693, 1408, 1345, 1259, 1207, 1067.

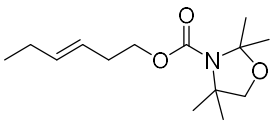
(*Z*)-3-methylpent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.31** :



Following the general procedure, (*Z*)-3-methylpent-3-en-1-ol[159] (300 mg, 3 mmol) gave 370 mg (48%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.35-5.30 (m, 1H), 4.15-4.11 (m, 2H), 3.72 s, 2H), 2.43-2.38 (m, 2H), 1.72-1.71 (m, 3H), 1.60-1.59 (m, 3H), 1.56 (1.50) (2 br. s., 6H), (1.42) 1.34 (2 br. s., 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.0/152.3, 131.8, 121.8, 95.9/95.0, 76.5/76.2, 62.4, 60.6/59.8, 31.0/30.9, 26.5, 25.4, 25.3, 24.3, 23.2/23.1, 13.5. **HRMS (ESI) m/z:**calcd. for $C_{14}H_{25}NO_3Na$ ($[M + Na]^+$): 278.1727; found: 278.1722**. IR neat (υ/cm^{-1}) :** 2976, 2361, 1699, 1454, 1407, 1348, 1260, 1069.

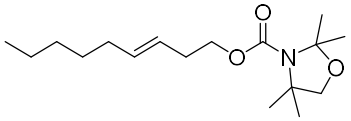
(E)-hex-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.33**:



Following the general procedure, (*E*)-hex-3-en-1-ol (407 mg, 4.1 mmol) gave 930 mg (90%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.58-5.51 (m, 1H), 5.41-5.33 (m, 1H), 4.10-4.06 (m, 2H), 3.70 (s, 2H), 2.35-2.29 (m, 2H), 2.03-1.96 (m, 2H), 1.54 (1.49) (2 br. s, 6H), (1.40) 1.33 (2 br. s, 6H), 0.94 (t, *J* = 7.5 Hz, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.0/152.2, 134.9, 125.0, 95.9/95.0, 76.5/76.2, 64.28/64.23, 60.6/59.8, 32.5, 26.6/25.42, 25.7, 25.36/24.3, 13.8. **HRMS (ESI) m/z:**calcd. for $C_{14}H_{25}NO_3Na$ ($[M + Na]^+$): 278.1727; found: 278.1729**. IR neat (υ/cm^{-1}) :** 2966, 2871, 2361, 1698, 1406, 1342, 1260, 1097, 967.

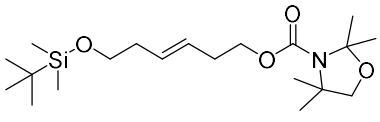
(*E*)-non-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.34**:



Following the general procedure, (*E*)-non-3-en-1-ol (500 mg, 3.52 mmol) gave 940 mg (90%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.55-5.48 (m, 1H), 5.42-5.34 (m, 1H), 4.11-4.07 (m, 2H), 3.72 (s, 2H), 2.37-2.30 (m, 2H), 2.00-1.95 (m, 2H), 1.55 (1.50) (2 br. s, 6H), 1.41-1.23 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 153.0/152.3, 133.5, 125.8, 95.9/95.0, 76.5/76.2, 64.34/64.30, 60.6/59.9, 32.7, 32.5, 31.5, 29.2, 26.6/25.5, 25.4/24.3, 22.7, 14.2. **HRMS (ESI) m/z:**calcd. for $C_{17}H_{31}NO_3Na$ ($[M + Na]^+$): 320.2196; found: 320.2199**. IR neat (υ/cm^{-1}) :** 2930, 2361, 1701, 1407, 1344, 1260, 1098.

(E)-6-((tert-butyldimethylsilyl)oxy)hex-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.35**:

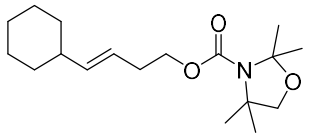


Following the general procedure, (*E*)-6-((tert-butyldimethylsilyl)oxy)hex-3-en-1-ol(130 mg, 0.56 mmol, *E*:*Z* 85:15) gave 120 mg (55%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.56-5.44 (m, 2H), 4.11-4.08 (m, 2H), 3.72 (s, 2H), 3.61-3.59 (m, 2H), 2.38-2.32 (m, 2H), 2.24-2.20 (m, 2H), 1.55 (1.50) (2 br. s, 6H), (1.41) 1.35 (2 br. s, 6H), 0.88 (s, 9H), -0.04 (s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz,**

rotamers) :δ = 153.0/152.2, 129.5, 128.2, 95.9/95.0, 76.5/76.3, 64.22/64.17, 63.2, 60.7/59.9, 36.5, 32.6, 26.6/25.5, 26.1, 25.4/24.3, 18.5, -5.11. **HRMS (ESI) m/z:**calcd. for $C_{20}H_{39}NO_4SiNa$ ([M + Na]$^+$): 408.2541; found: 408.2546**. IR neat (υ/cm^{-1}) :** 2956, 2361, 1701, 1461, 1407, 1344, 1257, 1098.

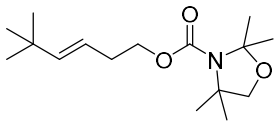
(*E*)-4-cyclohexylbut-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.36**:



Following the general procedure, (*E*)-4-cyclohexylbut-3-en-1-ol (150 mg, 0.97 mmol) gave 230 mg (76%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.49-5.44 (m, 1H), 5.39-5.30 (m, 1H), 4.12-4.07 (m, 2H), 3.72 (s, 2H), 2.36-2.29 (m, 2H), 1.94-1.86 (m, 1H), 1.69-1.65 (m, 5H), 1.55 (1.50) (2 br. s, 6H), (1.41) 1.35 (2 br. s, 6H), 1.30-0.98 (m, 5H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 153.0/152.3, 139.4, 123.44/123.40, 95.9/95.1, 76.5/76.3, 64.4/64.3, 60.6/59.9, 40.9, 33.2, 32.6, 26.7, 26.3, 26.2, 25.5, 24.3. **HRMS (ESI) m/z:**calcd. for $C_{18}H_{31}NO_3Na$ ([M + Na]$^+$): 332.2196; found: 332.2197**. IR neat (υ/cm^{-1}) :** 22925, 2853, 2361, 1697, 1450, 1406, 1343, 1259, 1208, 1097, 969.

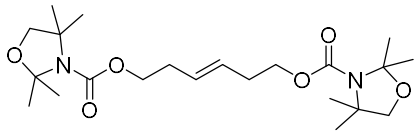
(*E*)-5,5-dimethylhex-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.37**:



Following the general procedure, (*E*)-5,5-dimethylhex-3-en-1-ol(125 mg, 0.98 mmol) gave 200 mg (72%) of the corresponding carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.56-5.52 (m, 1H), 5.35-5.26 (m, 1H), 4.12-4.08 (m, 2H), 3.71 (s, 2H), 2.36-2.30 (m, 2H), 1.55 (1.50) (2 br. s, 6H), (1.41) 1.34 (2 br. s, 6H), 0.97 (s, 9H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 153.0/152.3, 144.3, 120.78/120.74, 95.9/95.0, 765/76.3, 64.4/64.3, 60.6, 59.9, 33.1, 32.6, 29.8, 26.7, 25.5, 24.3. **HRMS (ESI) m/z:**calcd. for $C_{16}H_{29}NO_3Na$ ([M + Na]$^+$): 306.2040; found: 306.2036**. IR neat (υ/cm^{-1}) :** 2957, 2361, 1697, 1509, 1460, 1407, 1344, 1260, 1092, 972.

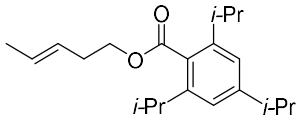
(*E*)-hex-3-ene-1,6-diyl bis(2,2,4,4-tetramethyloxazolidine-3-carboxylate)**2.39**:



Following the general procedure, (E)-hex-3-ene-1,6-diol(290 mg, 2.5 mmol, *E*:*Z* 85:15) was reacted withsodium hydride (95% in mineral oil, 2.15 eq) and 2,2,4,4-tetramethyloxazolidine-3-carbonyl chloride (2.1 eq) to give 311 mg (28%, E/Z) of the corresponding carbamate as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.53 (br. s, 1H), 4.12-4.07 (m, 2H), 3.71 (s, 2H), 2.44-2.42 (m, 2H, mino.), 2.37-2.35 (m, 2H, majo.), 1.54 (1.49) (2 br. s, 6H), (1.41) 1.34 (2 br. s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 152.9/152.1, 128.9 (majo.), 127.9 (mino.), 95.9/95.0, 76.5/76.2, 64.0, 60.7, 59.9, 32.6 (majo.), 27.4 (mino.), 26.6/25.43, 25.41/24.3. **HRMS (ESI) m/z:**calcd. for $C_{22}H_{38}N_2O_6Na$ ($[M + Na]^+$): 449.2622; found: 449.2626**. IR neat (υ/cm^{-1}) :** 2980, 2361, 1685, 1405, 1333, 1260, 1205, 1067.**M.p :** 67°C

- Synthesis of (*E*)-pent-3-en-1-yl 2,4,6-triisopropylbenzoate **2.25**

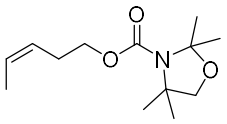


DIAD (0.68 mL, 3.5 mmol, 1.2 eq) was added dropwise over 10 min to a stirred solution of PPh_3 (913 mg, 3.5 mmol, 1.2 eq), 2,4,6-triisopropyl benzoic acid (792mg, 3.2 mmol, 1.1 eq), and (*E*)-Pent-3-en-1-ol (250 mg, 2.9 mmol, 1 eq) in THF (50 mL) at 0°C. The reaction mixture was stirred for 4 h at r.t., then the solvent was evaporated under vacuum, and the residue was dissolved in pentane (15mL) for 5 min. The white suspension was filtrated and the cake was washed with pentane (100 mL). The solvent was removed under vacuum, to obtain a yellow oil. The crude mixture was purified by column chromatography (Pent/Et_2O 100:0 to 90:10) to give 850mg (93%) of the ester as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.00 (s, 2H), 5.60-5.53 (m, 1H), 5.48-5.41 (m, 1H), 4.32 (t, *J* = 6.7 Hz, 2H), 2.92-2.81 (m, 3H), 2.45-2.39 (m, 2H), 1.67-1.65 (m, 3H), 1.25-1.23 (m, 18H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 171.1, 150.2, 144.9, 130.8, 128.1, 126.7, 121.0, 64.8, 34.6, 32.1, 31.6, 24.3, 24.1, 18.2. **HRMS (ESI) m/z:**calcd. for $C_{21}H_{32}O_2Na$ ($[M + Na]^+$):

339.2295; found: 339.2300**. IR neat (υ/cm^{-1}) :** 2962, 2361, 1727, 1460, 1384, 1250, 1137, 1075.

- Synthesis of (*Z*)-Pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **(*Z*)-2.21**



A mixture of pent-3-yn-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.7j** (800 mg, 3.3 mmol, 1 eq), quinoline (200 µL, 1.7 mmol, 0.5 eq) and Lindlar's catalyst (Pd 5% on $CaCO_3$, poisoned with Pb, 50 mg) in ethyl acetate (10 mL) was stirred under hydrogen atmosphere (balloon) at 20°C for 2 h. The reaction mixture was then filtrated through a pad of celite, and washed with 1 M aq. HCl (2x10mL). The organic layer was dried over $MgSO_4$, filtrated and then concentrated under vacuum. The oily residue was purified by silica gel column chromatography (Pent/Et_2O 98:2 to 90:10) to obtain 750 mg (93%) of the title product as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.49-5.41 (m, 1H), 5.32-5.26 (m, 1H), 4.00-3.96 (m, 2H), 3.60 (s, 3H), 2.31-2.28 (m, 2H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.44 (1.39) (2 br. s, 6H), (1.30) 1.23 (2 br. s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.9/152.2, 126.5/126.4, 126.2, 95.9/95.0, 76.5/76.2, 64.1, 60.6/59.8, 26.9, 26.5/25.4, 25.3/24.2, 13.0. **HRMS (ESI) m/z:** calcd. for $C_{13}H_{23}NO_3Na$ ($[M + Na]^+$): 264.1570; found: 264.1569**. IR neat (υ/cm^{-1}) :** 2979, 2361, 1699, 1407, 1345, 1260, 1208, 1096.

General procedures for the γ-arylation

General procedure A : arylation with TMEDA

In a tubular reactor (100 mm x 16 mm)capped with a rubber septum, a solution of the carbamate(0.207 mmol, 1 eq) and TMEDA (44 µL, 0.29 mmol, 1.4 eq) in dry diethyl ether (1.5 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (0.29 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 4 h. A suspension of zinc acetate (57 mg, 0.31 mmol, 1.5 eq) in dry THF (1.5 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to warm up to 20°C over 30 min. The solvents were evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (3.3 mg, 3.6 µmol, 1.75 %mol) and **2.L**[27] (2.8 mg, 7.3 µmol, 3.5 %mol) in dry toluene (1.5 mL) was added, followed by the aryl bromide (0.15 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 60°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (3 mL) and separated. The aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by preparative reversed-phase HPLC ($MeCN/H_2O$) to afford the γ-arylated products.

General procedure B : enantioselective arylation with (+)-sparteine

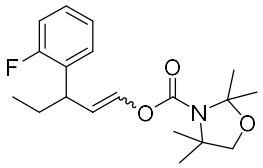
In a tubular reactor (100 mm x 16 mm)capped with a rubber septum, a solution of the carbamate(0.207 mmol, 1 eq) and (+)-sparteine (66 µL, 0.29 mmol, 1.4 eq) in dry diethyl ether (1.5 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (0.29 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 4 h. A suspension of zinc acetate (57 mg, 0.31 mmol, 1.5 eq) in dry THF (1.5 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat up to 20°C over 30 min. The solvents were evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (3.3 mg, 3.6 µmol, 1.75 %mol) and **2.L**[27] (2.8 mg, 7.3 µmol, 3.5 %mol) (unless otherwise stated) in dry toluene (1.5 mL) was added, followed by the aryl bromide (0.15 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 60°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (3 mL) and separated. The aqueous phase was extracted with EtOAc (2 x 3 mL). The combined

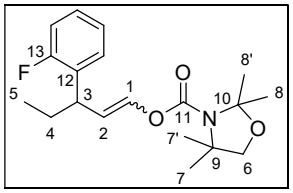
organic layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by preparative reversed-phase HPLC ($MeCN/H_2O$) to afford the γ-arylated products.

*Arylation of carbamate (E)-2.21 : products **2.21g**, **2.32a-i***

- Arylations with 1-bromo-2-fluorobenzene : products **2.21g** and isomers

3-(2-fluorophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.21g** :



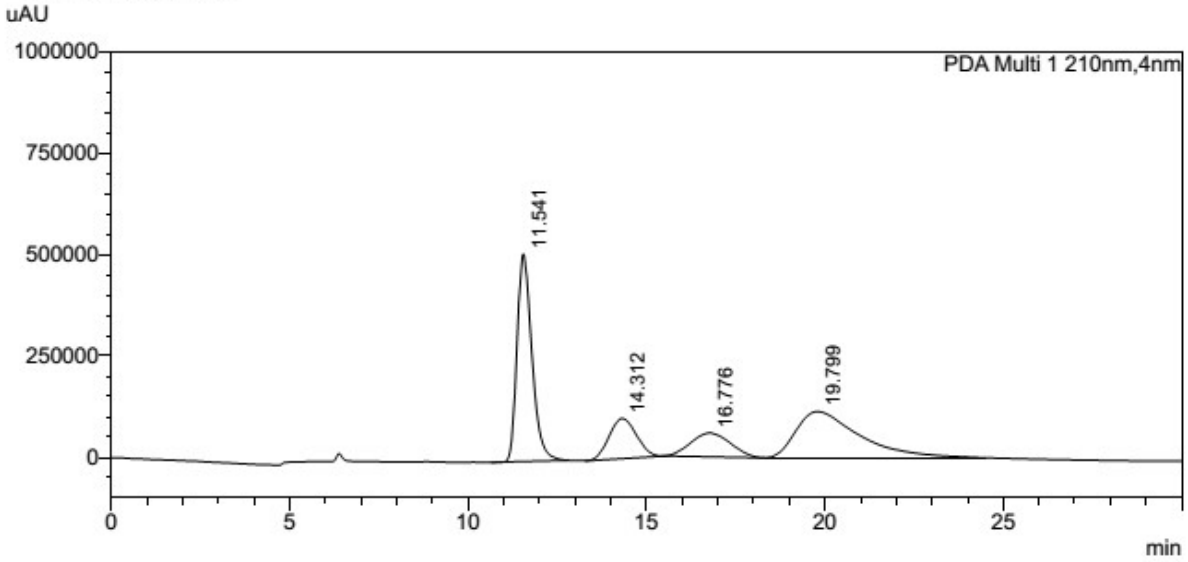


Following the general procedure A, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 29 mg (60%) of the title compound (75:25 *Z*:*E* ratio) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.24-7.06 (m, 4H, H_1, H_{Ar}), 7.02-6.97 (m, 1H, H_{Ar}), 5.54-5.47 (m, 1H, H_2E), 4.99-4.95 (m, 1H, H_2Z), 4.07-3.96 (m, 1H, H_3Z), 3.78-3.73 (m, 2H, H_6), 3.51-3.46 (m, 1H, H_3E), 1.79-1.62 (m, 2H, H_4), 1.64-1.32 (m, 12H, H_7, $H_{7'}$, H_8, $H_{8'}$), 0.92-0.87 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 162.0/161.9-159.6/159.5 (d of rotamers, *J* = 245.4 Hz, C_{13}), 150.0/149.1 (C_{11}), 136.8/136.6 (C_1E), 134.8/134.7 (C_1Z), 131.8/131.7 ($C_{12}Z$), 131.4/131.3 ($C_{12}E$), 128.8-128.5 (C_{Ar}), 127.9-127.6 (C_{Ar}), 124.3-124.2 (C_{Ar}), 115.8/115.4 (C_{Ar}), 114.7/114.6 (C_2E), 113.2/113.1 (C_2Z), 96.3/96.1/95.4 (C_{10}), 76.6/76.4/76.2 (C_6), 61.2/61.0/60.4/60.3 (C_9), 39.6 (C_3E), 36.63/36.56 (C_3Z), 29.4 (C_4Z), 28.4 (C_4E), 26.9-24.0 (C_7, $C_{7'}$, C_8, $C_{8'}$), 12.3 (C_5E), 12.2 (C_5Z)..**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -118.31/-118.32 ($F_{13}E$), -118.35/-118.41 ($F_{13}Z$). **HRMS (ESI) m/z:**calcd. for $C_{19}H_{26}FNO_3Na$ ($[M + Na]^+$): 358.1789; found: 358.1794**.IR neat (υ/cm^{-1}) :**2971, 2361, 1717, 1378, 1225, 1089.

References of the racemic products :

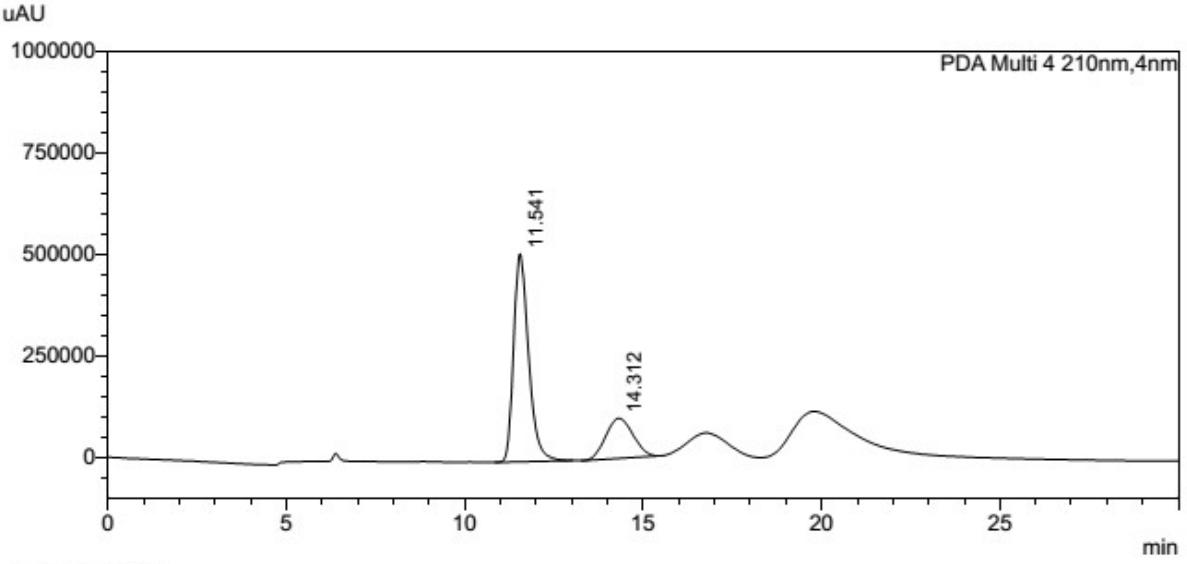
<Chromatogram>



<Peak Table>

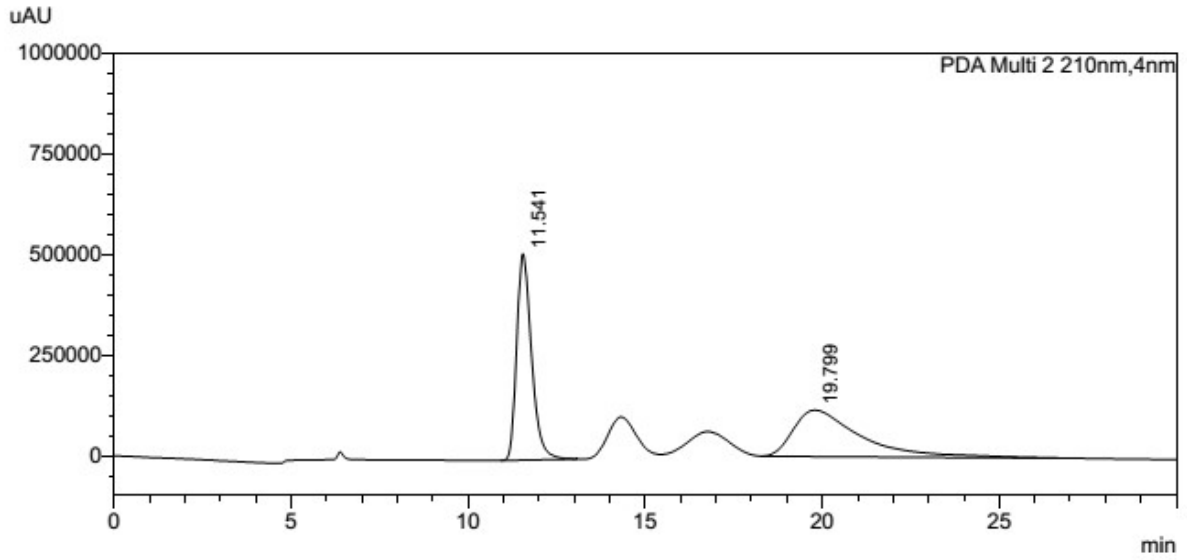
PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.541	38.373	14891598	511705	38.373		M
2	14.312	13.559	5261849	99023	13.559		M
3	16.776	11.640	4517160	58490	11.640		M
4	19.799	36.428	14137033	114514	36.428		M
Total		100.000	38807641	783732			



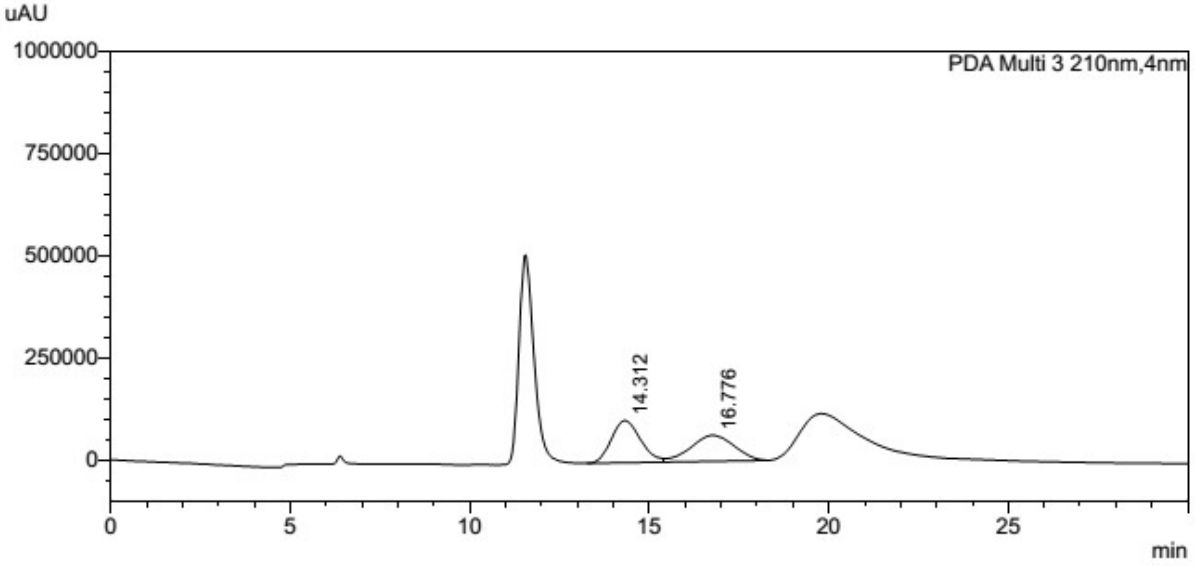
PDA Ch4 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.541	74.166	15022547	512578	74.166		M
2	14.312	25.834	5232829	98826	25.834		M
Total		100.000	20255375	611404			



PDA Ch2 210nm

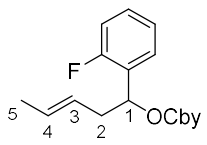
Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.541	49.837	15035407	512614	49.837		M
2	19.799	50.163	15133902	115479	50.163		M
Total		100.000	30169309	628094			



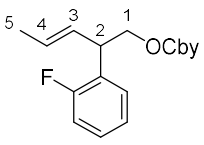
PDA Ch3 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	14.312	52.084	5790262	103097	52.084		M
2	16.776	47.916	5326903	63379	47.916		V M
Total		100.000	11117165	166476			

Observation and isolation of α- and β-products **(*E*)-2.21a** and **(*E*)-2.21b** :



(*E*)-2.21a



(*E*)-2.21b

After arylation following the general procedure A, 6 mg (12%) of amixture of α- and β-arylated products (ratio 47:57) was isolated for analytical purpose.

α-product **2.21a** :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 6.00-5.98 (m, 1H, H_1), 5.51-5.46 (m, 1H, H_4), 5.39-5.33 (m, 1H, H_3), 2.65-2.57 (m, 2H, H_2), 1.62-1.60 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 125.95/125.89 (C_3), 71.04/70.99 (C_1), 31.11/39.05 (C_2), 18.1 (C_5).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ =-117.65/-117.68.

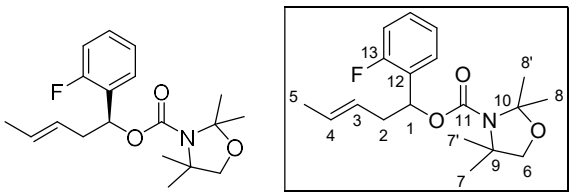
β-product **2.21b** :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 5.65-5.56 (m, 2H, H_3, H_4), 4.40-4.35 (m, 1H, H_1), 4.28-4.22 (m, 1H, H_1), 4.04-3.97 (m, H_2), 1.68-1.67 (m, 3H, H_5).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 66.7 (C_1), 42.03/41.98 (C_2), 18.2 (C_5). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ =-118.11/-118.13.

IR neat (υ/cm^{-1}) of the mixture : 2978, 2361, 1696, 1398, 1341, 1258, 1064, 966.

Selective α-Arylation of **(*E*)-2.21** : synthesis of enantiopure **(*E*)-2.21a** :

(−)-(*S*,*E*)-1-(2-fluorophenyl)pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate :



Arylation with TMEDA :

In a tubular reactor (100 mm x 16 mm)capped with a rubber septum, a solution of (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg, 0.207 mmol, 1 eq) and TMEDA (44 µL, 0.29 mmol, 1.4 eq) in dry diethyl ether (1.5 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (0.29 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 4 h. A suspension of zinc acetate (57 mg, 0.31 mmol, 1.5 eq) in dry THF (1.5 mL) was sonicated for 30 min and added

dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat up to 20°C over 30 min. The solvents were evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (3.3 mg, 3.6 µmol, 1.75 %mol) and RuPhos (3.4 mg, 7.3 µmol, 3.5 %mol) in dry toluene (1.5 mL) was added, followed by 1-bromo-2-fluorobenzene (15.8 µL, 0.15 mmol, 0.7 eq). The mixture was then vigorously stirred and heated to 60°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (3 mL) and separated. The aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by preparative reversed-phase HPLC ($MeCN/H_2O$) to afford 17 mg (35%) of the racemictitle compound as an oil.

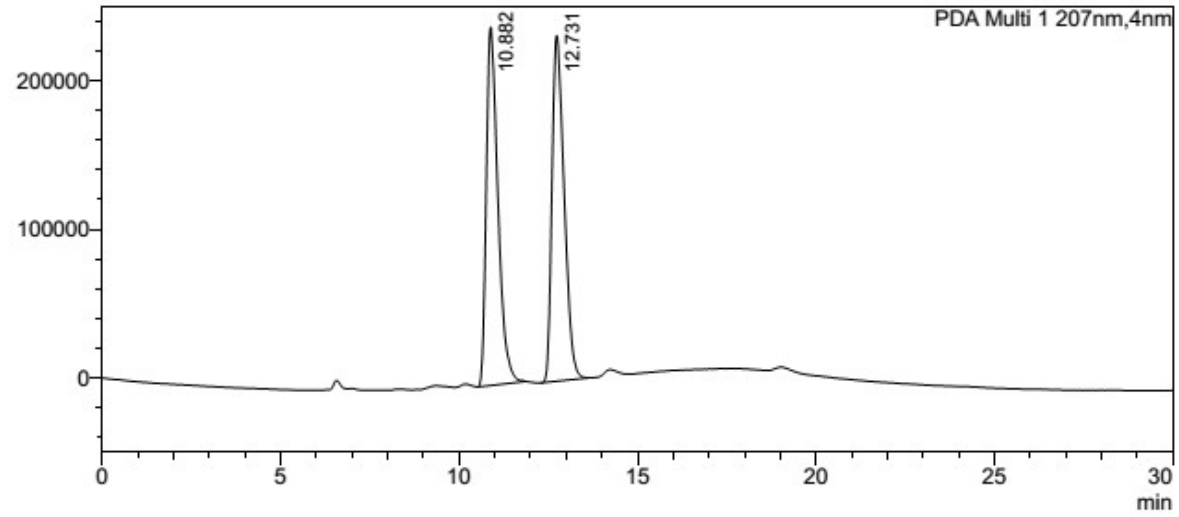
Arylation with (+)-sparteine :

The same procedure as for the arylation with TMEDA was used, using (+)-sparteine (88 µL, 0.29 mmol, 1.4 eq) as the diamine, instead of TMEDA. The crude residue was purified by preparative reversed-phase HPLC ($MeCN/H_2O$) to afford 20.5 mg (42%) of the enantioenrichedtitle compound as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.34-7.23 (m, 2H, H_{Ar}), 7.13-7.10 (m, 1H, H_{Ar}), 7.05-7.01 (m, 1H, H_{Ar}), 5.99 (t, *J* = 6.6 Hz, 1H, H_1), 5.50-5.32 (m, 2H, H_3, H_4), 3.76-3.70 (m, 2H, H_6, 2.65-2.57 (m, 2H, H_2), 1.62-1.34 (m, 15H, H_5, H_7, H_7', H_8, H_8'). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 161.0-159.0 (d of rotamers, *J* = 247.6 Hz, C_{13}), 152.0/151.2 (C_{11}), 129.24/129.17 (C_{Ar}), 128.9 (C_4), 128.5-128.2 (C_{12}), 128.1/128.0 (C_{Ar}), 126.0/125.9 (C_3), 124.12/124.09 (C_{Ar}), 115.8/115.7 (C_{Ar}), 96.2/95.1 (C_{10}), 76.6/76.2 (C_6), 71.0 (C_1), 60.9/60.0 (C_9), 39.1/39.0 (C_2), 26.8-24.3 (C_7, $C_{7'}$, C_8, $C_{8'}$), 18.1 (C_5).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -117.62/-117.64 (F_{13}). **HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 99:1, flow rate 0.5 mL/min, 25°C, t_R10.9 min for (*R*)-enantiomer (minor) and t_R 12.7 min for (*S*)-enantiomer (major). *e.r.* = 1:99.**$[\alpha]_D^{20}$** = +5.5° (c=0.8, $CHCl_3$).**HRMS (ESI) m/z:**calcd. for $C_{19}H_{26}NO_3Na$ ($[M + Na]^+$) : 358.1789; found: 358.1784**. IR neat (ʊ/cm^{-1}) :** 2960, 2361, 1701, 1397, 1258, 10630.**$[\alpha]_D^{20}$ =** -3.1° (c=1, $CHCl_3$).

<Chromatogram>

uAU



<Peak Table>

PDA Ch1 207nm

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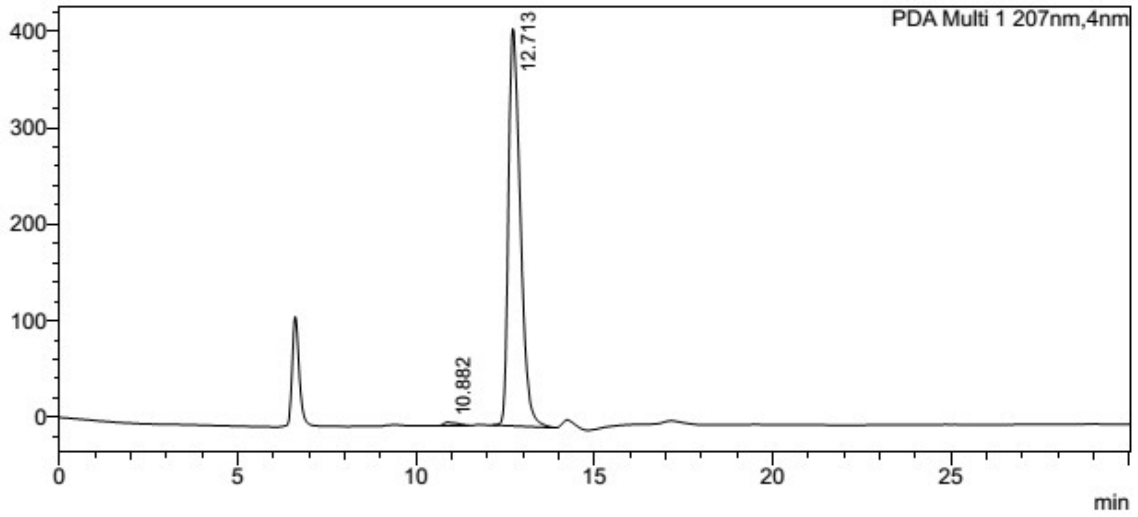
2	12.731	50.200	5492958	232430	50.200		M
Total		100.000	10942161	473279			

<Chromatogram>

mAU



<Peak Table>

PDA Ch1 207nm

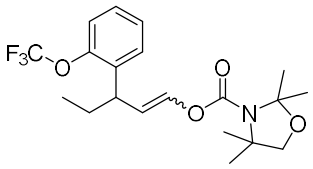
Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.882	0.959	92659	3660	0.000		M
2	12.713	99.041	9565229	411603	0.000		M
Total		100.000	9657888	415263			

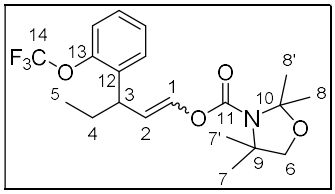
- Scale-up of the arylation of **2.21**

In a oven-dried Schlenck tube (75 mm x 40 mm) set up with a rubber septum, a solution of (*E*)-**2.21** (603 mg, 2.5 mmol, 1 eq) and TMEDA (530 µL, 3.5 mmol, 1.4 eq) in dry diethyl ether (10 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (3.5 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 4 h. A suspension of zinc acetate (688 mg, 3.8 mmol, 1.5 eq) in dry THF (10 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to warm-up to 20°C over 30 min. The solvents where evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (40.1 mg, 44 µmol, 1.75 %mol) and **2.L**[27] (33.5 mg, 88 µmol, 3.5 %mol) in dry toluene (10 mL) was added to solve the residue, followed by 1-Br-2-F-benzene (191 µL, 1.75 mmol, 0.7 eq). The mixture was then vigorously stirred at60°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (10 mL), and the organic phase was diluted with EtOAc (25 mL) and separated. The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with water and dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified bypreparative reversed-phase HPLC (MeCN/H_2O) to afford 397 mg (68%) of the γ-product **2.21g** (74:26 *Z*:*E* ratio).

- Products **2.32a-h**

3-(2-(trifluoromethoxy)phenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.32a** :

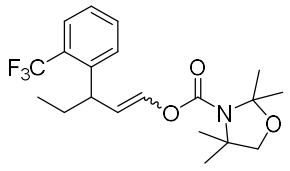


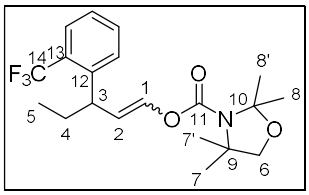


Following the general procedure, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 1-bromo-2-(trifluoromethoxy)benzene (21.6 µL) to give 37 mg (64%) of the title compound (61:39 *Z*:*E* ratio) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.34-7.21 (m, 4H, H_{Ar}), 7.10-7.07 (m, 1H, H_1), 5.48-5.40 (m, 1H, H_2E), 4.93-4.88 (m, 1H, H_2Z), 4.18-4.07 (m, 1H, H_3Z), 3.77-3.74 (m, 2H, H_6), 3.63-3.58 (m, 1H, H_3E), 1.80-1.38 (m, 14H, H_4, H_7, $H_{7'}$, H_8, $H_{8'}$), 0.92-0.85 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 150.2/150.0 ($C_{11}Z$), 149.3/149.2 ($C_{11}E$), 149.2/147.1 (C_{13}), 137.1-136.8 (C_1E, C_{Ar}), 135.0/134.9 (C_1Z), 128.7/128.5 (C_{Ar}), 127.5/127.4 (C_{Ar}), 127.2-126.9 (C_{Ar}), 122.1/122.0-119.52/119.46 (q of rotamers, J = 257 Hz, C_{14}), 120.7/120.0 (C_{Ar}), 96.4-95.4 (C_{10}), 76.6-76.2 (C_6), 61.2-60.4 (C_9), 38.7 (C_3E), 36.3 (C_3Z), 30.0 (C_4E), 29.8 (C_4Z), 26.9-24.0 (C_7, $C_{7'}$, C_8, $C_{8'}$), 12.1 (C_5).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -56.41/-56.43($F_{14}Z$), -56.74 ($F_{13}E$).**HRMS (ESI) m/z:**calcd. for $C_{20}H_{26}F_3NO_4Na$ ($[M + Na]^+$): 424.1706; found: 424.1700**. IR neat (ʊ/cm^{-1}) :**2972, 2876, 2361, 1718, 1377, 1256, 1164, 1088.

3-(2-(trifluoromethoxy)phenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.32b** :

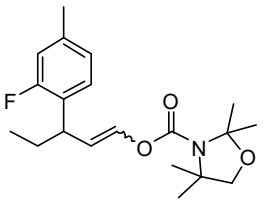


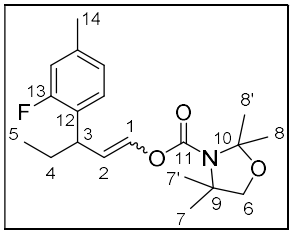


Following the general procedure, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 1-bromo-2-(trifluoromethyl)benzene(20.1 µL) to give 23.6 mg (42%) of the title compound (48:52 *Z*:*E* ratio) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.62-7.60 (m, 1H, H_{Ar}), 7.54-7.41 (m, 2H, H_{Ar}), 7.30-7.27 (m, 1H, H_{Ar}), 7.09-7.06 (m, 1H, H_1E), 7.03-7.01 (m, 1H, H_1Z), 5.50-5.42 (m, 1H, H_2E), 4.93-4.89 (m, 1H, H_2Z), 4.23-4.13 (m, 1H, H_3Z), 3.79-3.74 (m, 2H, H_6), 3.66-3.62 (m, 1H, H_3E), 1.81-1.37 (m, 14H, H_4, C_7, $C_{7'}$, C_8, $C_{8'}$), 0.89-0.84 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 150.2-149.3 (C_{11}), 144.0/143.9 (C_{12}), 136.9/136.8 (C_1E), 134.8/134.7 (C_1Z), 132.3/132.2 (C_{Ar}), 128.5/128.1 (C_{Ar}), 128.3 (q, J = 29.6 Hz, C_{13}), 126.2 (C_{Ar}), 126.1-125.8 (C_{Ar}), 124.7 (q of rotamers, J = 279.8 Hz, C_{14}), 115.52/115.46 (C_2E), 114.64/114.59 (C_2Z), 96.4-95.4 (C_{10}), 76.6-76.1 (C_6), 61.3-60.4 (C_9), 40.9 (C_3E), 38.7 (C_3Z), 31.2 (C_4Z), 29.8 (C_4E), 26.9-24.0 (C_7, $C_{7'}$, C_8, $C_{8'}$), 12.13/12.06 (C_5).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -58.30/-58.33(F_{14}).**HRMS (ESI) m/z:**calcd. for $C_{20}H_{26}F_3NO_3Na$ ($[M + Na]^+$): 408.1757; found: 408.1753**. IR neat (ʊ/cm^{-1}) :** 2972, 2361, 1715, 1374, 1314, 1122, 1071.

3-(2-fluoro-4-methylphenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.32c** :



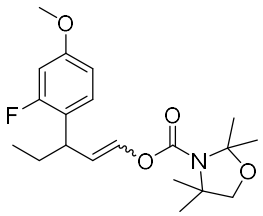


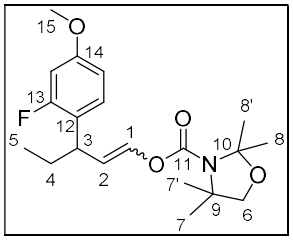
Following the general procedure, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 4-bromo-3-fluorotoluene (18.3 µL) to give 29.9 mg (59%) of the title compound (76:24 *Z*:*E* ratio) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.11-7.05 (m, 2H, H_1, H_{Ar}), 6.90-6.88 (m, 1H, H_{Ar}), 6.84-6.80 (m, 1H, H_{Ar}), 5.53-5.45 (m, 1H, H_2E), 4.98-4.93 (m, 1H, H_2Z), 4.02-3.91 (m, 1H, H_3Z), 3.77-3.74 (m, 2H, H_6), 3.46-3.41 (m, 1H, H_3E), 2.31 (s, 3H, $H_{14}E$), 2.30 (s, 3H, $H_{14}Z$), 1.76-1.34 (m, 14H, H_4, H_7, $H_{7'}$, H_8, $H_{8'}$), 0.91-0.86 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 161.9/161.7-159.4/159.3 (d of rotamers, J = 244.3 Hz, C_{13}), 150.0/149.2 (C_{11}), 138.1-137.9 (C_{Ar}), 136.6/136.5 (C_1E), 134.6/134.5 (C_1Z), 128.6-128.2 (C_{12}, C_{Ar}), 125.0-124.9 (C_{Ar}), 116.3-116.0 (C_{Ar}), 115.0/114.9 (C_2E), 113.5/113.3 (C_2Z), 96.3-95.4 (C_{10}), 76.6-76.2 (C_6), 61.1-60.3 (C_9), 39.3 (C_3E), 36.42/36.36 (C_3Z), 29.4 (C_4Z), 28.4 (C_4E), 26.9-24.0 (C_7, $C_{7'}$, C_8, $C_{8'}$), 21.01/21.99 (C_{14}), 12.3 (C_5E), 12.2 (C_5Z).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -119.3--119.4 (F_{13}).**HRMS (ESI) m/z:**calcd. for

$C_{20}H_{28}FNO_3Na$ ([M + Na]$^+$): 372.1945; found: 372.1953**. IR neat (υ/cm^{-1}) :**2970, 2361, 1718, 1377, 1258, 1089.

3-(2-fluoro-4-methoxyphenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.32d** :





Following the general procedure, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 4-bromo-3-fluoroanisole (29.7 mg) to give 24.1 mg (46%) of the title compound (77:23 *Z*:*E* ratio) as an oil.

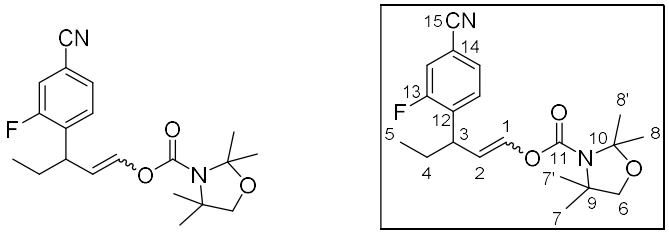
^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.12-7.06 (m, 3H, H_1, $2H_{Ar}$), 6.66-6.63 (m, 1H, H_{Ar}), 6.60-6.56 (m, 1H, H_{Ar}), 5.52-5.44 (m, 1H, H_2E), 4.96-4.91 (m, 1H, H_2Z), 3.97-3.87 (m, 1H, H_3Z), 3.79-3.74 (m, 5H, H_6, H_{14}), 3.43-3.38 (m, 1H, H_3E), 1.75-1.34 (m, 14H, H_4, H_7, $H_{7'}$, H_8, $H_{8'}$), 0.91-0.95 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 162.2/162.1-160.3/160.1 (d of rotamers, *J* = 244.2 Hz, C_{13}), 159.3-159.1 (C_{15}), 150.2-149.2 (C_{11}), 138.6/138.4 (C_1E), 134.6-134.4 (C_1Z), 129.1-128.8 (C_{Ar}), 123.7-123.6 ($C_{12}Z$), 123.2-123.1 ($C_{12}E$), 115.11/115.06 (C_2E), 113.6/113.5 (C_2Z), 110.1-109.9 (C_{Ar}), 101.9-101.7 (C_{Ar}), 93.3-95.4 (C_{10}), 76.6-76.2 (C_6), 61.2-60.3 (C_9), 55.6 (C_{15}), 40.0 (C_3E), 36.2/36.1 (C_3Z), 29.5 (C_4Z), 28.4 (C_4E), 26.9-24.1 (C_7, $C_{7'}$, C_8, $C_{8'}$), 12.3 (C_5E), 12.2 (C_5Z).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -119.28--119.33 (F_{13}).**HRMS (ESI) m/z:**calcd. for $C_{20}H_{28}FNO_4Na$ ([M + Na]$^+$): 388.1895; found: 388.1897**. IR neat (υ/cm^{-1}) :** 2968, 2361, 1714, 1624, 1507, 1376, 1353, 1259, 1090.

- Scale up of the arylation for the synthesis of **2.32d**

In a oven-dried Schlenck tube (75 mm x 40 mm) set up with a rubber septum, a solution of (*E*)-**2.21** (302 mg, 1.25 mmol, 1 eq) and TMEDA (264 µL, 1.75 mmol, 1.4 eq) in dry diethyl ether (10 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (1.75 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 4 h. A suspension of zinc acetate (344 mg, 3.8 mmol, 1.5 eq) in dry THF (10 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was

stirred for 30 min at -78°C, and then allowed to warm-up to 20°C over 30 min. The solvents where evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (20 mg, 22 µmol, 1.75 %mol) and **2.L**[27] (16.7 mg, 88 µmol, 3.5 %mol) in dry toluene (10 mL) was added to solve the residue, followed by 4-Br-3-F-anisole (112 µL, 0.88 mmol, 0.7 eq). The mixture was then vigorously stirred at60°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (10 mL), and the organic phase was diluted with EtOAc (25 mL) and separated. The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with water and dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified bypreparative reversed-phase HPLC ($MeCN/H_2O$) to afford 200 mg (44%) of the γ-product **2.32d** (76:24*Z*:*E* ratio).

3-(4-cyano-2-fluorophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.32e** :

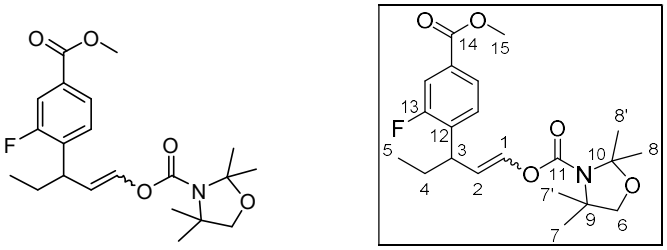


Following the general procedure, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 4-bromo-3-fluorobenzonitrile (29 mg) to give 22.5 mg (43%) of the title compound (67:33 *Z*:*E* ratio, contains ~10% α- and β-arylated products) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.42-7.40 (m, 1H, H_{Ar}), 7.37-7.29 (m, 2H, $2H_{Ar}$), 7.15-7.12 (m, 1H, H_1), 5.47-5.39 (m, 1H, H_2E), 4.93-4.88 (m, 1H, H_2Z), 4.10-4.00 (m, H_3Z), 3.78-3.73 (m, 2H, H_6), 3.55-3.50 (m, 1H, H_3E), 1.81-1.65 (m, 2H, H_4), 1.61-1.38 (m, 12H, H_7, $H_{7'}$, H_8, $H_{8'}$), 0.93-0.87 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 161.2-159.1 (d of rotamers, *J* = 248.4 Hz, C_{13}), 150.0-148.8 (C_{11}), 138.2-137.8 (C_{12}), 137.6/137.5 (C_1E), 136.0/135.8 (C_1Z), 130.0-129.7 (C_{14}, C_{Ar}), 128.48-128.45 (C_{Ar}), 119.5-119.1 (C_{Ar}), 117.8 (C_{15}), 113.04/112.99 (C_2E), 111.6-111.4 (C_2Z), 96.4-95.3 (C_{10}), 76.5-76.2 (C_6), 61.3-60.3 (C_9), 39.7 (C_3E), 36.72/36.67 (C_3Z), 29.2 (C_4Z), 28.2 (C_4E), 26.9-23.8 (C_7, $C_{7'}$, C_8, $C_{8'}$), 12.12 (C_5E), 12.05 (C_5Z).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = [-113.73/-113.74 ($F_{α\text{-prod}}$), -114.4 ($F_{β\text{-prod}}$)], -114.84/-114.85 ($F_{13}E$), -115.0/-

115.1 ($F_{13}Z$).**HRMS (ESI) m/z:**calcd. for $C_{20}H_{25}FN_2O_3Na$ ([M + Na]$^+$): 383.1741; found: 383.1739. **IR neat (υ/cm^{-1}) :**2970, 2874, 2361, 2234, 1713, 1376, 1257, 1088.

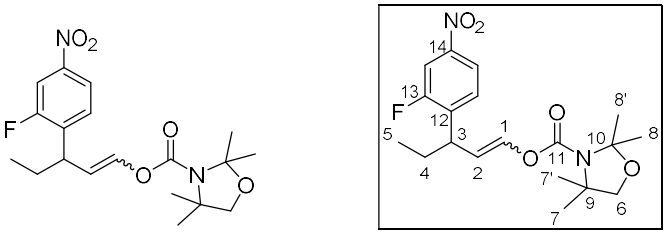
3-(2-fluoro-4-(methoxycarbonyl)phenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.32f** :



Following the general procedure, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with methyl 4-bromo-3-fluorobenzoate (33.8 mg, in 0.5 mL of toluene) to give 31 mg (54%) of the title compound (68:32 *Z*:*E* ratio) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.78-7.75 (m, 1H, H_{Ar}), 7.68-7.64 (m, 1H, H_{Ar}), 7.32-7.25 (m, 1H, H_{Ar}), 7.14-7.11 (m, 1H, H_1), 5.52-5.43 (m, 1H, H_2E), 4.98-4.92 (m, 1H, H_2Z), 4.11-3.99 (m, 1H, H_3Z), 3.90 (s, 3H, H_{15}), 3.75-3.74 (m, 2H, H_6), 3.55-3.48 (m, 1H, H_3E), 1.78-1.66 (m, 2H, H_4), 1.62-1.28 (m, 12H, H_7, $H_{7'}$, H_8, $H_{8'}$), 0.92-0.86 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 166.13/166.10 (C_{14}), 161.6/161.5-159.2/159.0 (d of rotamers, *J* = 245.3 Hz, C_{13}), 150.0/149.8 ($C_{11}Z$), 149.2/149.0 ($C_{11}E$), 137.4-137.0 (C_{Ar}, C_1E), 135.4/135.3 (C_1Z), 130.2-130.0 (C_{12}), 128.9-128.6 (C_{Ar}), 125.61-125.56 (C_{Ar}), 117.0-116.6 (C_{Ar}), 113.74/113.69 (C_2E), 112.2/112.1 (C_2Z), 96.3-95.3 (C_{10}), 76.5-76.1 (C_6), 61.2-60.3 (C_9), 52.4 (C_{15}), 39.7 (C_3E), 36.8/36.7 (C_3Z), 29.3 (C_4Z), 28.7 (C_4E), 26.7-24.0 (C_7, $C_{7'}$, C_8, $C_{8'}$), 12.2 (C_5E), 12.1 (C_5Z).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -117.37--117.38 ($F_{13}E$), -117.47--117.52 ($F_{13}Z$).**HRMS (ESI) m/z:**calcd. for $C_{21}H_{28}FNO_5Na$ ([M + Na]$^+$): 416.1844; found: 416.1838**. IR neat (υ/cm^{-1}) :**2969, 2874, 2361, 1720, 1353, 1290, 1210, 1089.

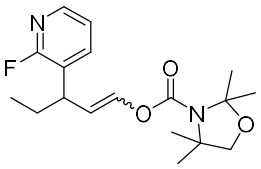
3-(2-fluoro-4-nitrophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.32g** :

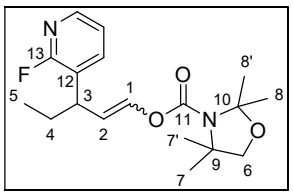


Following the general procedure, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 4-bromo-3-fluoronitrobenzene (32 mg) to give 17 mg (31%) of the title compound (65:35 *Z*:*E* ratio, contains ~5% α- and β-arylated products) as an orange oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 8.00-7.98 (m, 1H, H_{Ar}), 7.91-7.88 (m, 1H, H_{Ar}), 7.44-7.37 (m, 1H, H_{Ar}), 7.17-7.14 (m, 1H, H_1), 5.49-5.41 (m, 1H, H_2E), 4.96-4.91 (m, 1H, H_2Z), 4.15-4.04 (m, 1H, H_3Z), 3.78-3.74 (m, 2H, H_6), 3.60-3.55 (m, 1H, H_3E), 1.84-1.71 (m, 2H, H_4), 1.63-1.29 (m, 12H, H_7, $H_{7'}$, H_8, $H_{8'}$), 0.95-0.89 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 161.1-158.95 (d of rotamers, *J* = 248.5 Hz, C_{13}), 149.9-148.8 (C_{11}), 147.3-147.1 (C_{14}), 140.0-139.5 (C_{12}), 137.8/137.6 (C_1E), 136.1/136.0 (C_1Z), 129.4-129.2 (C_{Ar}), 119.62/119.59 (C_{Ar}), 112.90/112.86 (C_2E), 111.8-111.2 (C_2Z, C_{Ar}), 96.5-95.3 (C_{10}), 76.5-76.2 (C_6), 61.4-60.3 (C_9), 39.76/39.74 (C_3E), 36.8-36.7 (C_3Z), 29.3 (C_4Z), 28.2 (C_4E), 26.8-24.0 (C_7, $C_{7'}$, C_8, $C_{8'}$), 12.14 (C_5E), 12.07 (C_5Z).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = [-112.52/-112.53 ($F_{\alpha\text{-prod}}$), -113.2 ($F_{\beta\text{-prod}}$)], -113.67/-113.68 ($F_{13}E$), -113.86/-113.91 ($F_{13}Z$).**HRMS (ESI) m/z:** calcd. for $C_{19}H_{25}FN_2O_5Na$ ($[M + Na]^+$): 403.1640; found: 403.1633**. IR neat (υ/cm^{-1}) :** 2971, 2874, 2361, 1714, 1528, 1351, 1258, 1088.

3-(2-fluoropyridin-3-yl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.32h** :



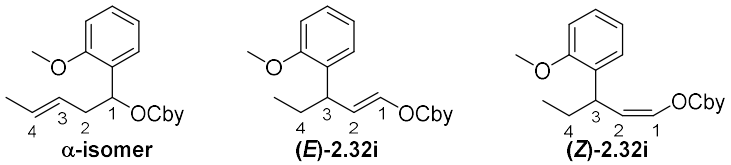


Following the general procedure, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 3-bromo-2-fluoropyridine (14.7 µL) to give 25.6 mg (52.5%) of the title compound (75:25 *Z*:*E* ratio, contains ~10% of other isomers) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 8.07-8.04 (m, 1H, H_{Ar}), 7.66-7.60 (m, 1H, H_{Ar}), 7.15-7.12 (m, 2H, H_1, H_{Ar}), 5.51-5.43 (m, 1H, H_2E), 4.95-4.90 (m, 1H, H_2Z), 4.00-3.89 (m, 1H, H_3Z), 3.77-3.73 (m, 2H, H_6), 3.42-3.37 (m, 1H, H_3E), 1.78-1.25 (m, 14H, H_4, H_7, $H_{7'}$, H_8, $H_{8'}$), 0.94-0.88 (m, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 162.6-160.9 (d of rotamers, *J* = 238.2 Hz, C_{13}), 150.0-148.9 (C_{11}), 145.5-145.2 (C_{Ar}), 139.4-139.0 (C_{Ar}), 137.4/137.3 (C_1E), 135.8-135.6 (C_1Z), 126.9-126.6 (C_{12}), 121.70/121.67 (C_{Ar}), 113.4-113.3 (C_2E), 111.8/111.7 (C_2Z), 96.4-95.4 (C_{10}), 76.5-76.2 (C_6), 61.3-60.4 (C_9), 40.0/39.9 (C_3E),

36.57/36.55 (C_3E), 29.1/29.0 (C_4Z), 28.2 (C_4E), 26.5-25.1 (C_7, $C_{7'}$, C_8, $C_{8'}$), 12.2-12.1 (C_5).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = [-69.53--70.2 (F other isomers)], -71.7/-71.8 ($F_{13}E$), -72.3 ($F_{13}Z$).**HRMS (ESI) m/z:** calcd. for $C_{18}H_{25}FN_2O_3Na$ ([M + Na]$^+$): 359.1741; found: 359.1740**. IR neat (υ/cm^{-1}) :** 2970, 2874, 1361, 1713, 1435, 1377, 1257, 1089.

- Arylation of (*E*)-2.21 with 2-bromoanisole : products **2.32i** and isomers



Following the general procedure, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 2-bromoanisole (18.1 µL) to give 15 mg (30%) of a mixture of isomeric arylated product (NMR ratio : α/γE/γZ 16/54/30). The calculated yield of combined γ-product **2.32i** was *ca*. 24% (64:36 *Z*:*E* ratio).

α-isomer :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 6.16-6.13 (m, 1H, H_1), 5.45-5.39 (m, 2H, H_3, H_4), 2.57-2.49 (m, 2H, H_2). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 71.4/71.3 (C_1), 39.1/39.0 (C_2).

γE-product **(*E*)-2.32i** :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 5.53-5.47 (m, 1H, H_2), 3.66-3.61 (m, 1H, H_3). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 38.8 (C_3).

γZ-product **(*Z*)-2.32i**:

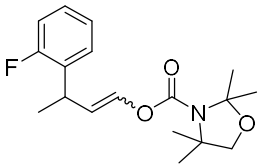
^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 5.01–4.97 (m, 1H, H_2), 4.20-4.09 (m, 1H, H_3), 1.75-1.67 (m, 2H, H_4).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 114.5/114.3 (C_2), 36.62/36.45 (C_3), 29.3/29.2 (C_4).

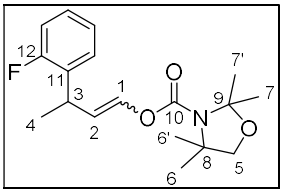
HRMS (ESI) m/z: calcd. for$C_{20}H_{29}NO_4Na$ ([M + Na]$^+$): 370.1989; found: 370.1989.**IR neat (υ/cm^{-1}) :** 2969, 2361, 1711, 1596, 1377, 1350, 1241, 1091.

*Arylation of carbamates **2.7e, 2.33-37***

- Arylation of **2.7e** : products **2.20g** and isomers

3-(2-fluorophenyl)but-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.20g** :

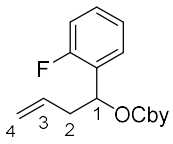




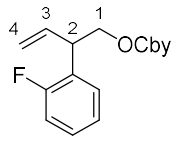
Following the general procedure, but-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (47 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 9.7 mg (21%) of the title compound (64:36 *Z*:*E* ratio) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.29-6.97 (m, 5H, H_1, H_{Ar}), 5.59-5.51 (m, 1H, H_2E), 5.01-4.97 (m, 1H, H_2Z), 4.30-4.19 (m, 1H, H_3Z), 3.95-3.79 (m, 1H, H_3E), 3.76-3.75 (m, 2H, H_5), 1.62-1.28 (m, 15H, H_4, H_6, $H_{6'}$, H_7, $H_{7'}$). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 161.5/159.5 (d of rotamers, J = 246.4 Hz, C_{12}), 150.2-149.1 (C_{10}), 136.4/136.3 (C_1E), 133.8/133.7 (C_1Z), 133.0-132.8 ($C_{11}Z$), 132.5-132.4 ($C_{11}E$), 128.3-127.7 (2 C_{Ar}), 124.28/124.25 (C_{Ar}), 116.0/115.9 (C_2E), 115.7-115.4 (C_{Ar}), 114.5/114.4 (C_2Z), 96.3-95.4 (C_9), 76.5-76.1 (C_5), 61.1-60.3 (C_8), 31.7 (C_3E), 29.6-24.0 (C_3Z, C_6, $C_{6'}$, C_7, $C_{7'}$), 22.1 (C_4Z), 20.7 (C_4E).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -118.57/-118.62 ($F_{12}Z$), -118.80/-118.81 ($F_{12}E$). **HRMS (ESI) m/z:**calcd. for $C_{18}H_{24}FNO_3Na$ ($[M + Na]^+$): 344.1632; found: 344.1638.**IR neat (υ/cm^{-1}) :** 2974, 2921, 2361, 1717, 1374, 1241, 1069.

Observation and isolation of α- and β-products **2.20a** and **2.20b** :



2.20a



2.20b

After arylation, <10% yield of amixture of α- and β-arylated products (ratio 50:50) was isolated for analytical purpose.

α-product **2.20a** :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 6.07-6.04 (m, 1H, H_1), 5.79-5.69 (m, 1H, H_3), 5.09-5.04 (m, 2H, H_4), 2.75-2.63 (m, 2H, H_2).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 133.5/133.4 (C_3), 118.3 (C_4), 70.74/70.69 (C_1), 40.2/40.1 (C_2).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ =-117.93/-117.96.

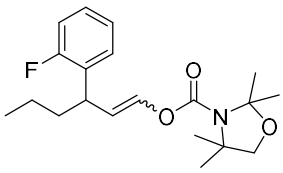
β-product **2.20b** :

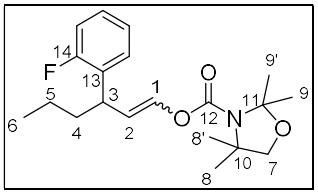
^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 6.02-5.97 (m, 1H, H_3), 5.19-5.14 (m, 2H, H_4), 4.48-4.43 (m, 1H, H_1), 4.33-4.27 (m, 1H, H_1), 4.10-4.04 (m, 1H, H_2).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 136.7-136.6 (C_3), 117.3 (C_4), 66.3 (C_1), 42.7/42.6 (C_2). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ =-117.51/-117.55.

IR neat (υ/cm^{-1}) : 2980, 2361, 1699, 1399, 1347, 1259, 1066.

- Arylation of carbamates **2.33-35** : products **2.38a-c**

3-(2-fluorophenyl)hex-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.38a** :



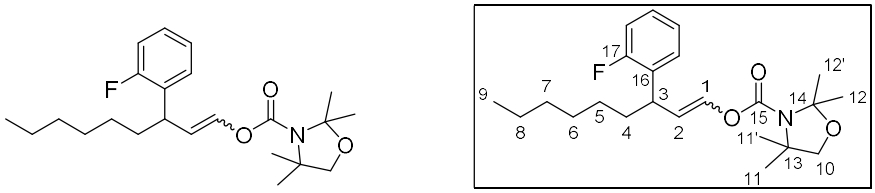


Following the general procedure, (*E*)-hex-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (53 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 27.2 mg (54%) of the title compound (76:24 *Z*:*E* ratio) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.24-7.06 (m, 4H, 3H_{Ar}, H_1), 7.01-6.97 (m, 1H, H_{Ar}), 5.55-5.47 (m, 1H, H_2*E*), 5.00-4.96 (m, 1H, H_2*Z*), 4.17-4.07 (m, 1H, H_3*Z*), 3.76-3.74 (m, 2H, H_7), 3.62-3.57 (m, 1H, H_3*E*), 1.73-1.21 (m, 16H, H_4, H_5, H_8, $H_{8'}$, H_9, $H_{9'}$), 0.92-0.88 (m, 3H, H_6). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 161.7/161.6-159.8/159.7 (d of rotamers, *J* = 245.1 Hz, C_{14}), 150.2/150.0 (C_{12}*Z*), 149.4/149.2 (C_{12}*E*), 136.6/136.5 (C_1*E*), 134.6/134.5 (C_1*Z*), 132.0-131.5 (C_{13}), 128.8-128.5 (C_{Ar}), 127.8-127.6 (C_{Ar}), 124.29/124.27 (C_{Ar}), 115.8-115.4 (C_{Ar}), 114.93/114.89 (C_2*E*), 113.5/113.4 (C_2*Z*), 96.3-95.4 (C_{11}), 76.6-76.2 (C_7), 61.2-60.4 (C_{10}), 38.7 (C_4*Z*), 37.6 (C_4*E*), 37.5 (C_3*E*), 34.74-34.65 (C_3*Z*), 26.9-24.0 (C_8, $C_{8'}$, C_9, $C_{9'}$), 20.80/20.76 (C_5), 14.1/14.0 (C_6).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :**

δ =-118.31/-118.32 ($F_{14}E$), -118.33/-118.39 ($F_{14}Z$).**HRMS (ESI) m/z:**calcd. for $C_{20}H_{28}FNO_3Na$ ($[M + Na]^+$): 372.1945; found: 372.1943**. IR neat (υ/cm^{-1}) :**2361, 1712, 1345, 1240, 1225, 1089.

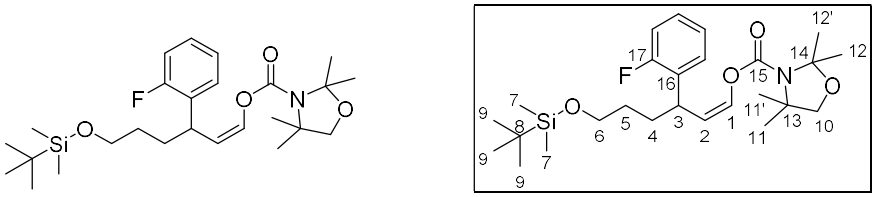
3-(2-fluorophenyl)non-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.38b** :



Following the general procedure, (*E*)-oct-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 22.9 mg (45%) of the title compound (77:23 *Z*:*E* ratio) as an oil.

^{1}H NMR ($CDCl_3$, 500 MHz, rotamers) :δ = 7.25-7.06 (m, 4H, H_1, H_{Ar}), 7.02-6.97 (m, 1H, H_{Ar}), 5.54-5.47 (m, 1H, H_2E), 5.00-4.95 (m, 1H, H_2Z), 4.15-4.04 (m, 1H, H_3Z), 3.76-3.74 (m, 2H, H_{10}), 3.59-3.54 (m, 1H, H_3E), 1.73-1.23 (m, 22H, H_4, H_5, H_6, H_7, H_8, H_{11}, $H_{11'}$, H_{12}, $H_{12'}$), 0.87-0.84 (m, 3H, H_9). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 161.7/161.6-159.8/159.7 (d of rotamers, *J* = 244.7 Hz, C_{17}), 150.2/150.0 ($C_{15}Z$), 149.4/149.2 ($C_{15}Z$), 136.6/136.5 (C_1E), 134.6/134.5 (C_1Z), 132.0/131.9 ($C_{16}Z$), 31.6/131.5 ($C_{16}E$), 128.8-128.5 (C_{Ar}), 127.8-127.6 (C_{Ar}), 124.29/124.26 (C_{Ar}), 115.8-115.4 (C_{Ar}), 115.01/115.95 (C_2E), 113.6/113.5 (C_2Z), 96.3-95.4 (C_{14}), 76.6-76.2 (C_{10}), 61.2-60.3 (C_{13}), 37.80/37.78 (C_3E), 36.5 (C_4Z), 35.4 (C_4E), 35.0-34.9 (C_3Z), 31.85/31.82 (C_5), 29.3/29.2 (C_6), 27.64/27.58 (C_7), 26.7-24.0 (C_{11}, $C_{11'}$, C_{12}, $C_{12'}$) 22.8 (C_8), 14.2 (C_9).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -118.30/-118.31 ($F_{17}E$), -118.34/-118.40 ($F_{17}Z$).**HRMS (ESI) m/z:**calcd. for $C_{23}H_{34}FNO_3Na$ ($[M + Na]^+$): 414.2415; found: 414.2414**. IR neat (υ/cm^{-1}) :**2929, 2361, 1711, 1372, 1258, 1128, 1069.

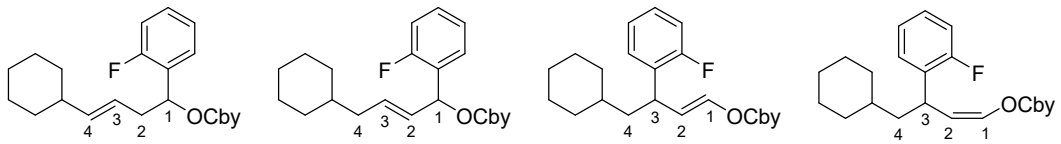
(*Z*)-6-((tert-butyldimethylsilyl)oxy)-3-(2-fluorophenyl)hex-1-en-1-yl 2,2,4,4-tetramethyloxa zolidine-3-carboxylate**2.38c** :



Following the general procedure, (*E*)-6-((tert-butyldimethylsilyl)oxy)hex-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (80 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 11.5 mg (16.5%) of the title compound as an oil.

^{1}H NMR ($CDCl_3$, 500 MHz, rotamers) :δ = 7.25-7.20 (m, 1H, H_{Ar}), 7.18-7.14 (m, 1H, H_{Ar}), 7.09-7.06 (m, 2H, H_1, H_{Ar}), 7.01-6.97 (m, 1H, H_{Ar}), 5.00-4.95 (m, 1H, H_2), 4.15-4.04 (m, 1H, H_3), 3.78-3.73 (m, 2H, H_{10}), 3.60-3.57 (m, 2H, H_6), 1.87-1.65 (m, 2H, H_4), 1.64-1.32 (m, 14H, H_5, H_{11}, $H_{11'}$, H_{12}, $H_{12'}$), 0.87 (s, 9H, H_9), 0.01 (m, 6H, H_7). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 161.6-159.7 (d of rotamers, *J* = 244.2 Hz, C_{17}), 150.0/149. (C_{15}), 134.7-134.6 (C_1), 131.8/131.6 (C_{16}), 128.6-128.5 (C_{Ar}), 127.8-127.7 (C_{Ar}), 124.4/124.3 (C_{Ar}), 115.7/115.5 (C_{Ar}), 113.3/113.2 (C_2), 96.3/95.4 (C_{14}), 76.6/76.2 (C_{10}), 63.07/63.05 (C_6), 61.2/60.3 (C_{13}), 34.9/34.8 (C_3), 32.7 (C_4), 31.1 (C_5), 26.8-24.0 (C_{11}, $C_{11'}$, C_{12}, $C_{12'}$), 26.1 (C_9), 18.5 (C_8), -5.2 (C_7).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -118.21/-118.27 (F_{17}). **HRMS (ESI) m/z:** calcd. for $C_{26}H_{42}FNO_4SiNa$ ($[M + Na]^+$): 502.2759 ; found: 502.2766**. IR neat (υ/cm^{-1}) :** 2935, 2863, 2361, 1719, 1400, 1349, 1256, 1091.

- Arylation of carbamate **2.36** : products **2.38d** and isomers



Following the general procedure A, (*E*)-4-cyclohexylbut-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (64.1 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 30 mg (52%) of a mixture of isomeric arylated product (NMR ratio : α/α'/γE/γZ 13/2/11/74). The calculated yield of combined γ-product **2.38d** was *ca*. 44% (87:13 *Z*:*E* ratio).

α-product :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 6.02-6.00 (m, 1H, H_1), 5.41-5.36 (m, 1H, H_4), 5.31-5.24 (m, 1H, H_3),2.66-2.52 (m, 2H, H_2). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 140.4 (C_4), 122.03/121.95 (C_3), 71.1/71.0 (C_1), 39.1/39.0 (C_2).).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -116.95.

α'-product :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 6.41-6.39 (m, 1H, H_1) 5.75-5.63 (m, 2H, H_2, H_3). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 72.0 (C_1). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -117.49/-117.53.

γE-product **(*E*)-2.38d** :

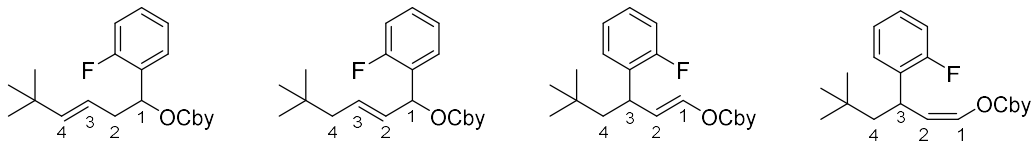
^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 5.52-5.45 (m, 1H, H_2). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 115.3/115.2 (C_2), 34.6 (C_3). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -118.34/-118.35

γZ-product **(*Z*)-2.38d** :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 4.97–4.93 (m, 1H, H_2), 4.30-4.19 (m, 1H, H_3). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 114.0/113.9 (C_2), 32.1-32.0 (C_3). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -118.6/-118.44.

HRMS (ESI) m/z: calcd. for$C_{24}H_{34}FNO_3Na$ ($[M + Na]^+$): 426.2415; found: 426.2412**.IR neat (υ/cm^{-1}) :** 2923, 2852, 2361, 1714, 1349, 1258, 1091.

- Arylation of carbamate **2.37** : products **2.38e** and isomers



Following the general procedure A, (*E*)-5,5-dimethylhex-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (58.7 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 23 mg (42%) of a mixture of isomeric arylated product (NMR ratio : α/α'/γE/γZ 24/17/12/47). The calculated yield of combined γ-product was *ca*. 25% (80:20 *Z*:*E* ratio).

α-product :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 6.04-6.02 (m, 1H, H_1), 5.46-5.42 (m, 1H, H_4), 5.29-5.21 (m, 1H, H_3),2.66-2.51 (m, 2H, H_2). **^{13}C-{^{1}H} NMR ($CDCl_3$,**

125 MHz, rotamers), characteristic peaks :δ = 145.4 (C_4), 119.4/119.3 (C_3), 71.1/71.0 (C_1), 39.1/39.0 (C_2).).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -117.52/-117.57.

α'-product :

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 6.44-6.41 (m, 1H, H_1) 5.82-5.76 (m, 2H, H_2), 5.70-5.65 ((m, 2H, H_3), 1.92 (d, *J* = 7.5 Hz, 1H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 71.9/71.8 (C_1), 132.2/132.1 (C_2), 129.7/129.6 (C_3), 46.8 (C_4). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -116.97/-116.99.

γE-product **(*E*)-2.38e**:

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 5.57-5.49 (m, 1H, H_2), 1.80 (ddd, *J* = 13.9 Hz, *J* = 7.3 Hz, *J* = 2.4 Hz, 1H, H_4). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 117.0/116.9 (C_2), 49.3 (C_4), 34.68/34.66 (C_3). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -117.99/-118.0.

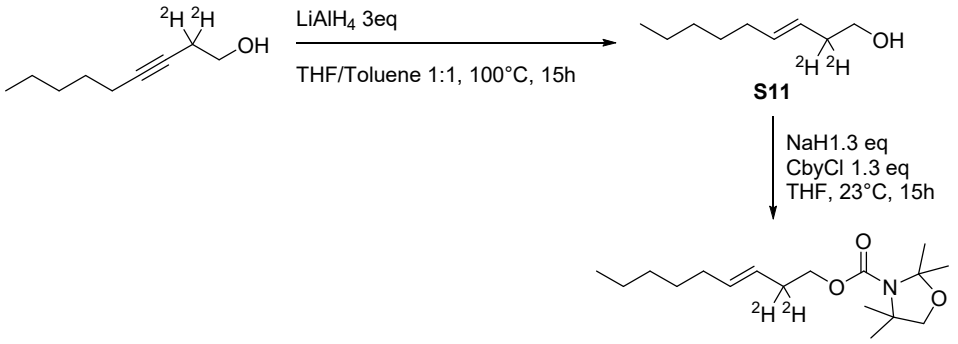
γZ-product **(*Z*)-2.38e**:

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers), characteristic peaks :δ = 5.07-5.02 (m, 1H, H_2), 4.30-4.21 (m, 1H, H_3). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers), characteristic peaks :**δ = 50.9 (C_4). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -117.86/-117.95.

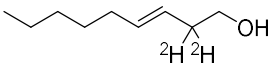
HRMS (ESI) m/z:calcd. for$C_{22}H_{32}FNO_3Na$ ($[M + Na]^+$): 400.2258; found: 400.2254.**IR neat (υ/cm^{-1}) :**2958, 2361, 1712, 1397, 1259, 1066.

Deuterium labeling

- Synthesis of the deuterated substrate **2.41**



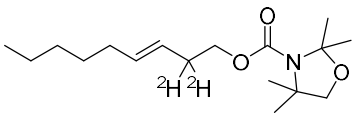
[2,2-$^2H_2$]-non-3(*E*)-en-1-ol **S11**:



$LiAlH_4$ (211 mg, 5.3 mmol, 3 eq) was added portionwise to a solution of [2,2-$^2H_2$] non-3-yn-1-ol[160] (250 mg, 1.8 mmol, 1 eq) in THF/Toluene (5 mL, 1:1 v:v) at 0°C (water, ice) over 5 min. The mixture was stirred at 100°C for 15 h and then cooled down to room temperature. The reaction was quenched by a sequential addition of water (250µL), 15% aq. NaOH (250µL), and water (750 µL). The precipitate was filtered off on celite with Et_2O. The resulting organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The oily residue was purified by silica gel column chromatography (Pent/Et_2O 95:5 to 50:50) to obtain 180 mg (71 %, 100 % (*E*), >98% ^2H int.) of the desired deuterated alcohol as a colorless oil.

^1H NMR ($CDCl_3$, 400 MHz) :δ = 5.55 (dt, *J* = 15.3 Hz, *J* = 6.7 Hz, 1H), 5.36 (br. d, *J* = 15.4 Hz, 1H), 3.60 (s, 2H), 2.03-1.98 (m, 2H), 1.51 (s, 1H), 1.39-1.22 (m, 6H), 0.88 (t, *J* = 6.95 Hz, 3H).**^{13}C-{^1H} NMR ($CDCl_3$, 100 MHz) :** δ = 134.6, 125.7, 62.1, 35.6/35.4/35.2 (C$^2H_2$), 32.8, 31.5, 29.3, 14.2. **GCMS (EI) m/z (intensity %) :** 70 (100), 41 (76), 57 (71), 83 (45), 97 (27), 126 (7), 111 (2), 144 (0.2)**.IR neat (υ/cm^{-1}) :** 2927, 2361, 1394, 1249, 1054.

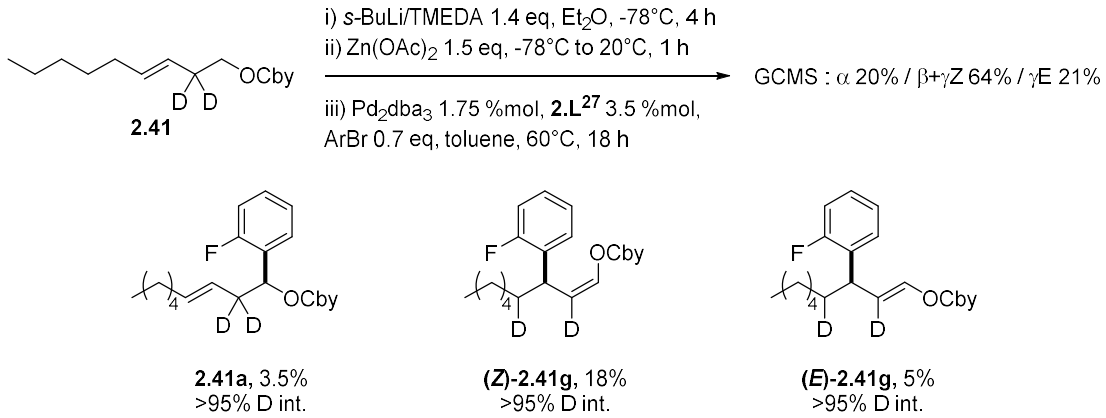
[2,2-$^2H_2$]-non-3(*E*)-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.41** :



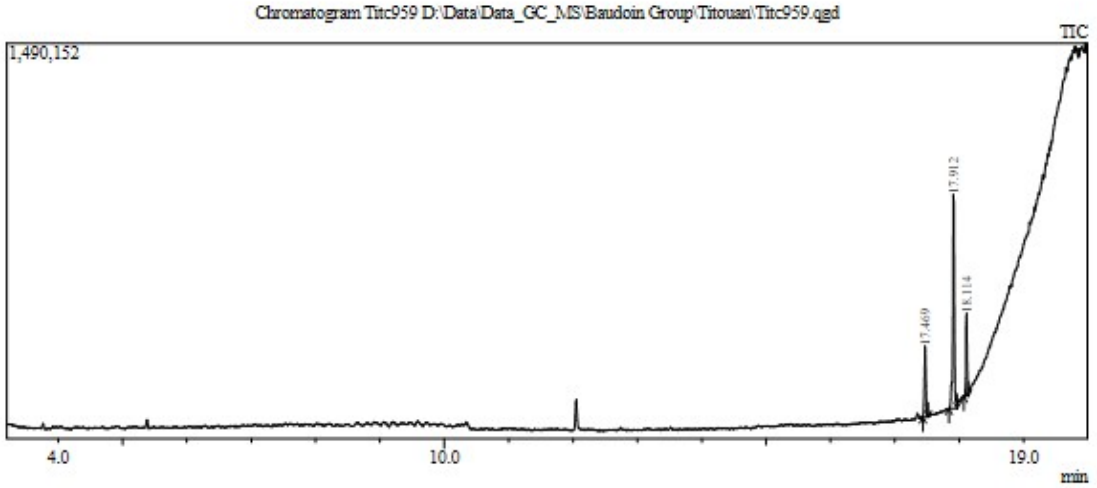
A solution of [2,2-$^2H_2$] non-3(*E*)-en-1-ol**S11** (150 mg, 1.0 mmol, 1 eq) in THF (1 mL) was added dropwise to a suspension of sodium hydride (34 mg, 1.4 mmol, 1.3 eq) in THF (4 mL) at 0°C (water, ice) over 5 min. The mixture was then stirred for 30 min at room temperature. A solution of 2,2,4,4-tetramethyloxazolidine-3-carbonyl chloride (259 mg, 1.4 eq, 1.3 eq) in THF (1 mL) was added dropwise and the mixture was stirred for 15 h at room temperature. After quenching with water, the solvent was removed under vacuum and the residue was diluted with Et_2O (10 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (10 mL), water (10 mL), brine (10 mL) and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (Pent/Et_2O 95:5 to 80:20) to obtain 215 mg (70 %, 100 % (*E*), >98% ^2H int.) of the desired deuterated carbamate as colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 5.55-5.48 (m, 1H), 5.39-5.34 (m, 1H), 4.08-4.07 (m, 2H), 3.71 (s, 2H), 2.00-1.95 (m, 2H), 1.55 (1.50) (2 br. s, 6H), 1.41-1.22 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :** δ = 153.0/152.3, 133.6, 125.7, 95.9/95.0, 76.5/76.2, 64.2, 60.6/59.9, 32.7, 31.8/31.6/31.5 ($\underline{C}^2H_2$ overlapped with CH_2), 29.2, 26.6/25.44, 25.38/24.3, 22.7, 14.2. **HRMS (ESI) m/z:** calcd. for $C_{17}H_{29}D_2NO_3Na$ ($[M + Na]^+$): 322.2322; found: 322.2327 **IR neat (υ/cm^{-1}) :** 2971, 1361, 1701, 1403, 1068.

- Arylation of **2.41** : products **2.41a** and **2.41g**



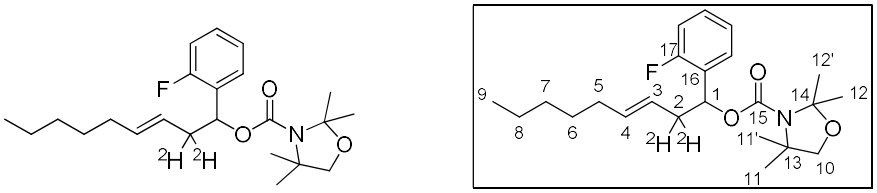
GCMS report



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	17.469	17.433	17.517	435049	19.69	267093	19.28	1.63	MI	
2	17.912	17.842	17.967	1358349	61.48	805227	58.13	1.69	MI	
3	18.114	18.075	18.142	416000	18.83	312801	22.58	1.33	MI	
				2209398	100.00	1385121	100.00			

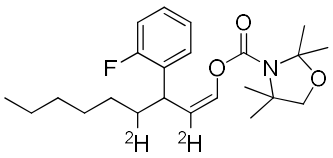
(*E*)-1-(2-fluorophenyl)-[2,2-$^{2}H_2$]-non-3-en-1-yl 2,2,4,4-tetramethyl oxazolidine-3-carboxylate **2.41a** :

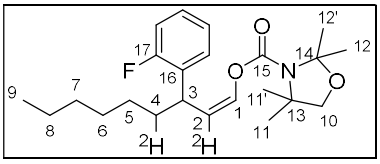


^{1}H NMR (CDCl$_3$, 500 MHz, rotamers) : δ = 7.33-7.28 (m, 1H, H_{Ar}), 7.27-7.23 (m, 1H,H_{Ar}), 7.13-7.10 (m, 1H, H_{Ar}), 7.05-7.01 (m,1H, H_{Ar}), 5.99 (s, 1H, H_1), 5.47-5.42 (m, 1H, H_3), 5.33-5.28 (m, 1H, H_4), 3.76-3.70 (m, 2H, H_{10}), 1.94-1.91 (m, 2H, H_5), 1.62-1.34 (m, 12H, H_{11},

$H_{11'}$, H_{12}, $H_{12'}$), 1.29-1.23 (m, 4H, H_6, H_7), 1.20-1.17 (m, 2H, H_8), 0.86 (t, J = 7.2 Hz, 3H, H_9). **^{2}H NMR ($CHCl_3$, 76 MHz, rotamers) :**δ = 7.62-7.55 (m, 2^2H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :** δ = (C_{17}, C_{16},C_{15}missing), 134.7 (C_3), 129.24/129.16 (C_{Ar}), 128.2/128.1 (C_{Ar}), 124.4/124.3 (C_{Ar}), 124.10/124.07 (C_4), , 115.8/115.7 (C_{Ar}), 96.2/95.1 (C_{14}), 76.6/76.2 (C_{10}), 71.1/71.0 (C_1), 60.9/60.0 (C_{13}), 32.7 (C_5), 31.4 (C_6), 29.9 (C_2), 29.1 (C_7), 26.9-24.3 (C_{11}, $C_{11'}$, C_{12}, $C_{12'}$), 22.7 (C_8), 14.2 (C_9). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = 117.53/117.56 (F_{17}). **HRMS (ESI) m/z:** calcd. for $C_{23}H_{32}D_2FNO_3Na$ ([M + Na]$^+$): 416.2540; found: 416.2547 **. IR neat (υ/cm^{-1}) :** 2969, 2361, 1702, 1395, 1260, 1063.

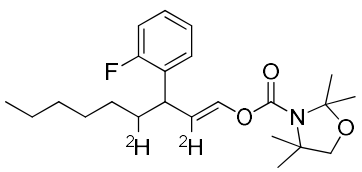
(*Z*)-3-(2-fluorophenyl)-[2,4-$^2H_2$]-non-1-en-1-yl 2,2,4,4-tetramethyl oxazolidine-3-carboxylate **(*Z*)-2.41g**:

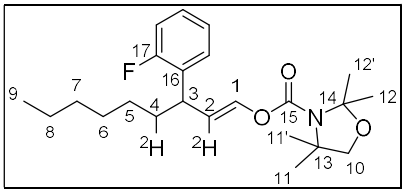




^{1}H NMR ($CDCl_3$, 500 MHz, rotamers) :δ = 7.24-7.20 (m, 1H, H_{Ar}), 7.17-7.14 (m, 1H, H_{Ar}), 7.08-7.06 (m, 2H, H_1, H_{Ar}), 7.00-6.97 (m, 1H, H_{Ar}), 4.12-4.04 (m, 1H, H_3), 3.78-3.72 (m, 2H, H_{10}), 1.64-1.21 (m, 21H, H_4, H_5, H_6, H_7, H_8, H_{11}, $H_{11'}$, H_{12}, $H_{12'}$), 0.86 (t, J = 7.0 Hz, 3H, H_9). **^{2}H NMR ($CHCl_3$, 76 MHz, rotamers) :**δ = 5.02 (s, 1^2H, $^2H_2$), 1.70 (s, 1^2H, $^2H_4$). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :** δ = 161.8-159.4 (d, J = 245.7 Hz, C_{17}), 150.0/149.2 (C_{15}), 134.6/134.4 (C_1), 132.0/131.9 (C_{16}), 128.60-128.51 (C_{Ar}), 127.7-127.6 (C_{Ar}), 124.30/124.26 (C_{Ar}), 115.6/115.4 (C_{Ar}), 96.3/95.4 (C_{14}), 76.6/76.2 (C_{10}), 61.2/60.3 (C_{13}), 36.3-36.0 (C_4), 34.84/34.77 (C_3), 31.9 (C_5), 29.2 (C_6), 27.6 (C_7), 26.7-24.0 (C_{11}, $C_{11'}$, C_{12}, $C_{12'}$), 22.8 (C_8), 14.2 (C_9).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = 118.3–118.40 (F_{17}). **HRMS (ESI) m/z:**calcd. for $C_{23}H_{32}D_2FNO_3Na$ ([M + Na]$^+$): 416.2540; found: 416.2548 **. IR neat (υ/cm^{-1}) :** 2926, 2361, 1716, 1375, 1258, 1141, 1087.

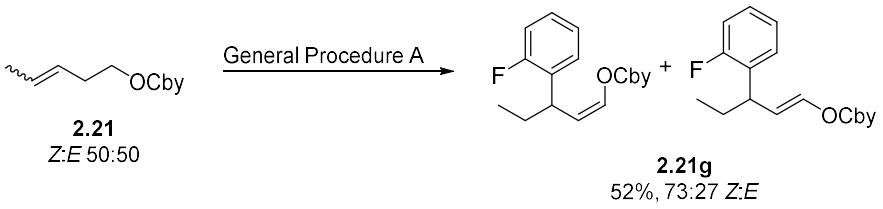
(*E*)-3-(2-fluorophenyl)-[2,4-$^2H_2$]-non-1-en-1-yl 2,2,4,4-tetramethyl oxazolidine-3-carboxylate **(*Z*)-2.41g**:





^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) : δ = 7.21-7.15 (m, 2H, H_{Ar}), 7.10-7.07 (m, 2H, H_1, H_{Ar}), 7.02-6.99 (m, 1H, H_{Ar}), 3.76-3.74 (m, 2H, H_{10}), 3.56-3.55 (m, 1H, H_3), 1.70-1.68 (m, 1H, H_4), 1.57-1.21 (m, 20H, H_5, H_6, H_7, H_8, H_{11}, $H_{11'}$, H_{12}, $H_{12'}$) , 0.86 (t, J = 7.1 Hz, 3H, H_9). **^{2}H NMR ($CHCl_3$, 76 MHz, rotamers) :** δ = 5.55 (s, 1^2H, $^2H_2$), 1.71 (s, 1^2H, $^2H_4$). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :** δ = 161.8-159.8 (d, J = 245.6 Hz, C_{17}), 150.2 (C_{15}), 136.6/136.4 (C_1), 131.7/131.5 (C_{16}), 128.84/128.80 (C_{Ar}), 127.8/127.7 (C_{Ar}), 124.32/124.29 (C_{Ar}), 115.8/115.6 (C_{Ar}), 96.2/95.4 (C_{14}), 76.5/76.2 (C_{10}), 61.0/60.4 (C_{13}), 37.68/37.64 (C_3), 35.2-34.9 (C_4), 31.8 (C_5), 29.2 (C_6), 27.5 (C_7), 26.9-24.1 (C_{11}, $C_{11'}$, C_{12}, $C_{12'}$), 22.8 (C_8), 14.2 (C_9). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = 118.31/118.32 (F_{17}). **HRMS (ESI) m/z:**calcd. for $C_{23}H_{32}D_2FNO_3Na$ ($[M + Na]^+$): 416.2540; found: 416.2548 **. IR neat (υ/cm^{-1}) :** 2926, 2361, 1714, 1374, 1258, 1126, 1071.

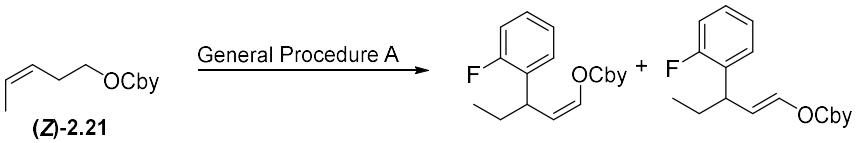
Regio- and stereoconvergence in the arylation of ***2.21***



2.21
Z:*E* 50:50

2.21g
52%, 73:27 *Z*:*E*

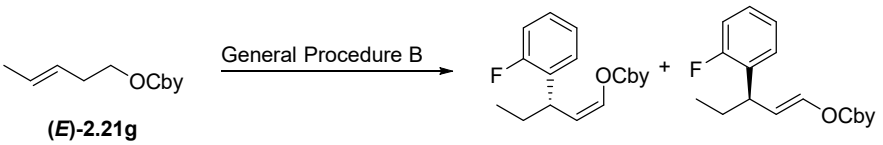
Following the general procedure A, a mixture of (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate and (*Z*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg, ratio 50:50) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 25.1 mg (52%) of the title compound (73:27 *Z*:*E* ratio) as an oil.



(*Z*)-2.21
Z:*E* 100:0

2.21g
51%, 73:27 *Z*:*E*

Following the general procedure A, (*Z*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 24.6 mg (51%) of the title compound (73:27 *Z*:*E* ratio) as an oil.

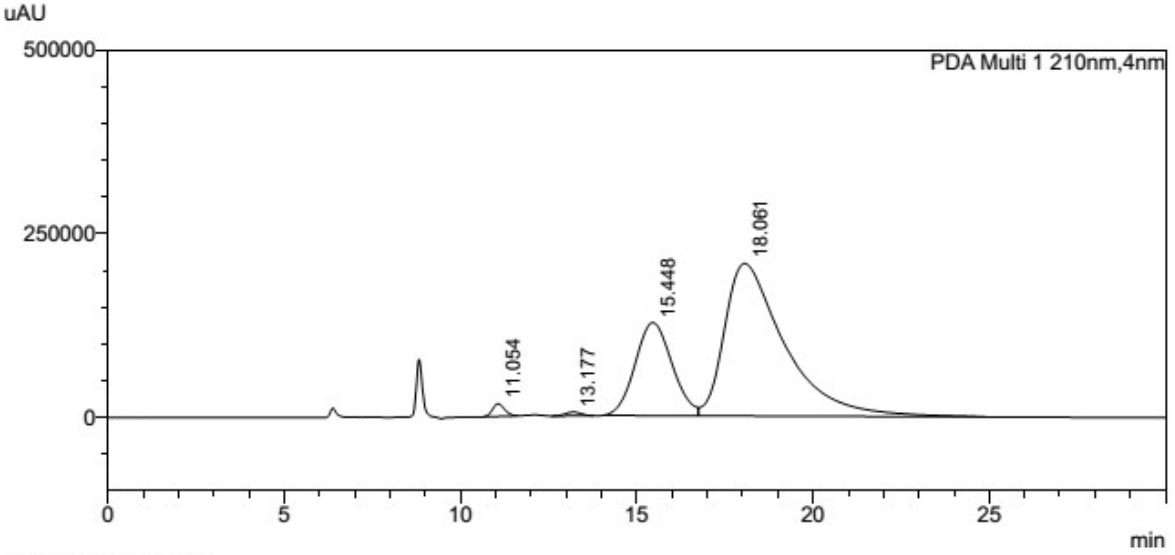


(*E*)-2.21g
Z:*E* 0:100

2.21g
61%, 74:26 *Z*(98:2 *er*):*E*(98:2 *er*)

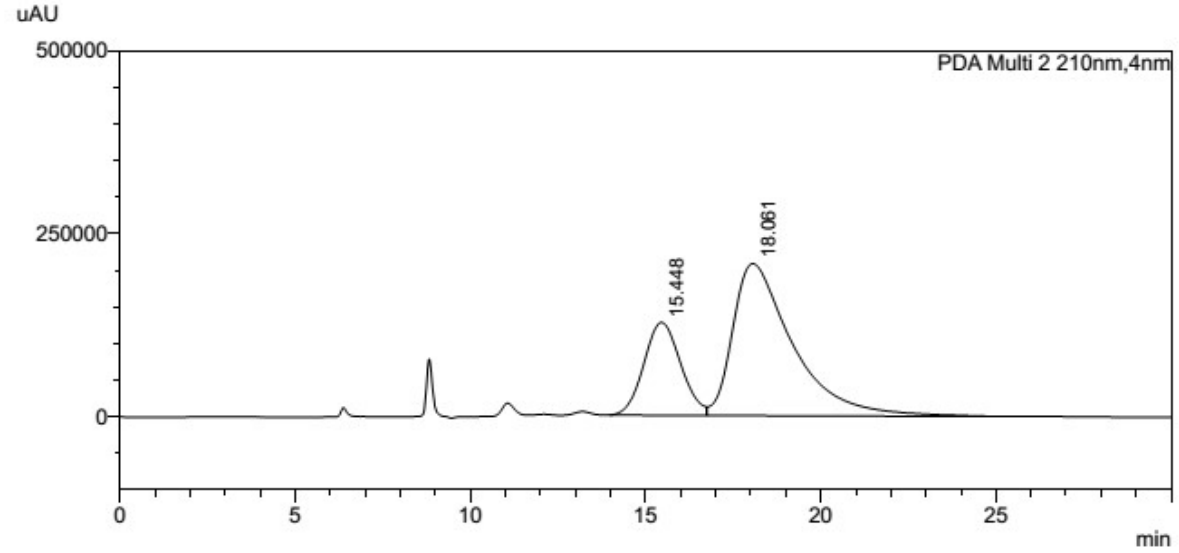
Following the general procedure B, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 29.6 mg (61%) of the title compound (74:26 *Z*:*E* ratio) as an oil. The *e.r.* were, respectively, 98:2 for the *Z*-isomer and 98:2 for the *E*-isomer.

<Chromatogram>



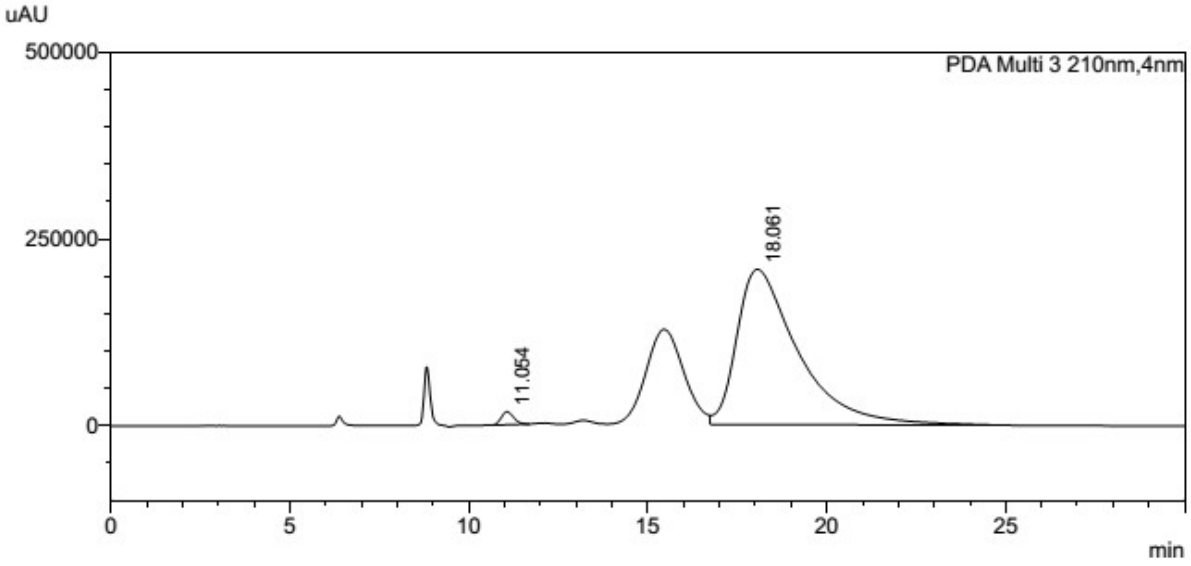
PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.054	1.188	408688	17272	0.000		M
2	13.177	0.474	163125	5048	0.000		M
3	15.448	26.815	9221055	126552	0.000		M
4	18.061	71.522	24595086	207452	0.000		V M
Total		100.000	34387954	356324			



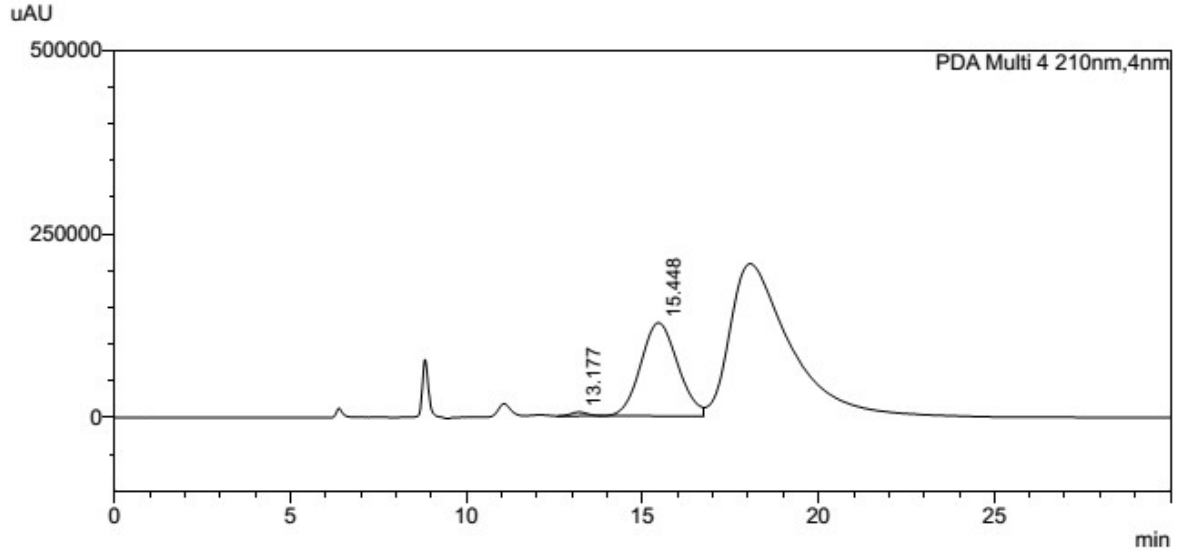
PDA Ch2 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	15.448	27.304	9290901	126976	0.000		M
2	18.061	72.696	24736243	207802	0.000		V M
Total		100.000	34027144	334777			



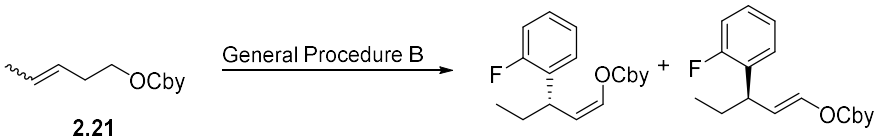
PDA Ch3 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.054	1.652	415247	17379	0.000		M
2	18.061	98.348	24723437	207866	0.000		M
Total		100.000	25138684	225244			



PDA Ch4 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	13.177	1.764	167317	5107	0.000		M
2	15.448	98.236	9319113	127141	0.000		M
Total		100.000	9486430	132248			

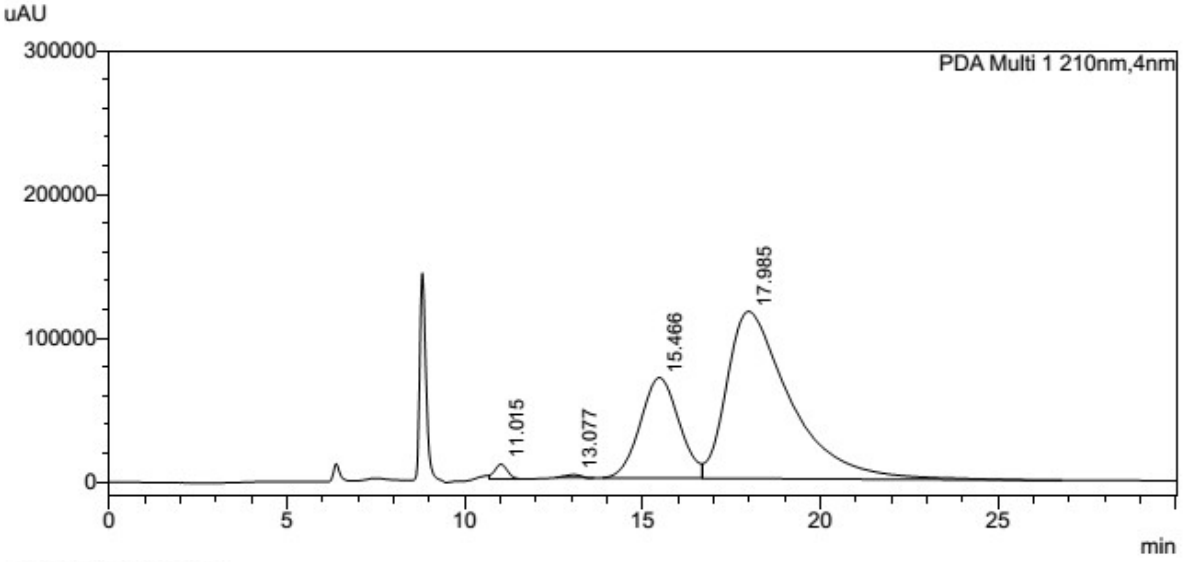


2.21
Z:*E* 50:50

2.21g
56%, 74:26 *Z*(98:2 *er*):*E*(98:2 *er*)

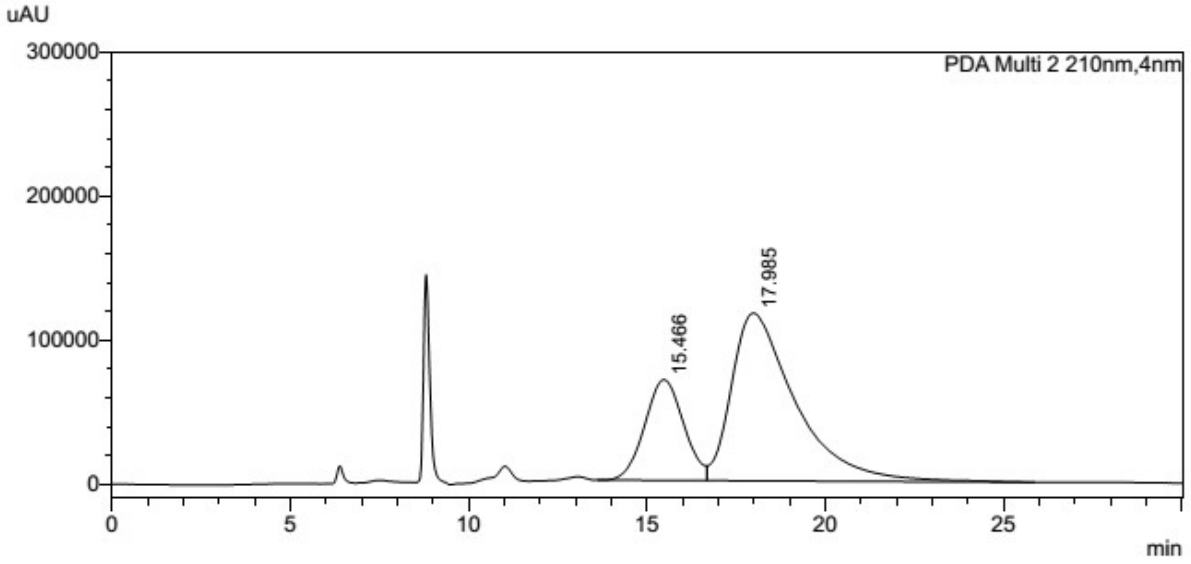
Following the general procedure B, a mixture of (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate and (*Z*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg, ratio 50:50) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 27.4 mg (56%) of the title compound (74:26 *Z*:*E* ratio) as an oil. The *e.r.* were, respectively, 98:2 for the *Z*-isomer and 98:2 for the *E*-isomer.

<Chromatogram>



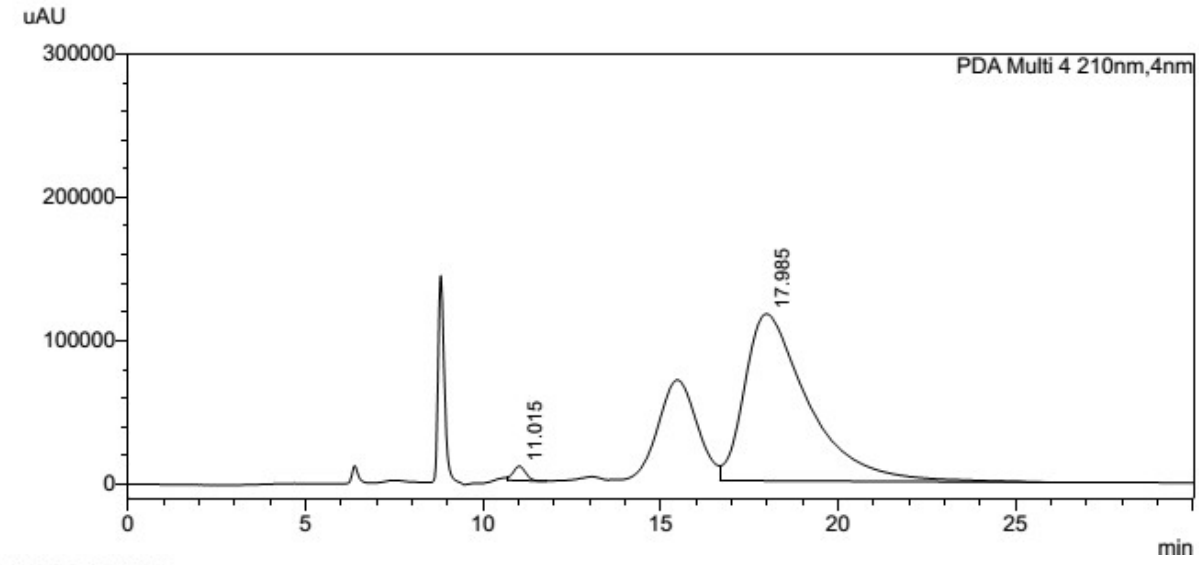
PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.015	1.320	265741	10497	0.000		M
2	13.077	0.302	60853	2063	0.000		M
3	15.466	26.363	5305621	69837	0.000		M
4	17.985	72.014	14493095	116287	0.000		V M
Total		100.000	20125310	198683			



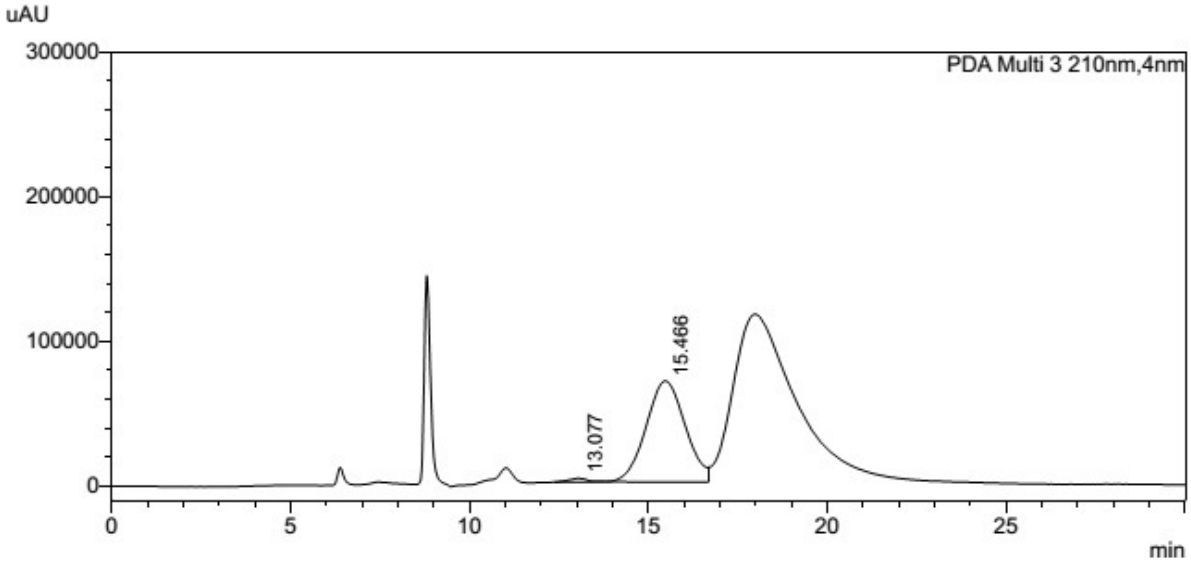
PDA Ch2 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	15.466	26.803	5311787	69872	0.000		M
2	17.985	73.197	14506447	116316	0.000		V M
Total		100.000	19818234	186187			



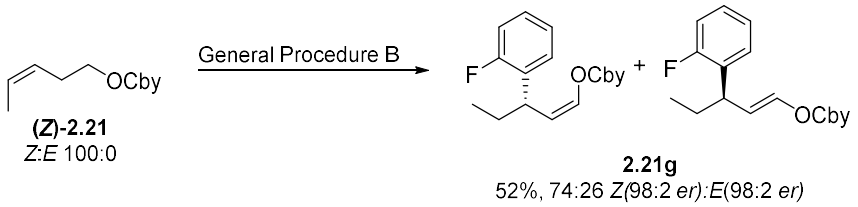
PDA Ch3 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	13.077	1.479	79757	2335	0.000		M
2	15.466	98.521	5311204	69869	0.000		M
Total		100.000	5390960	72205			



PDA Ch4 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.015	1.653	244013	10042	0.000		M
2	17.985	98.347	14516806	116324	0.000		M
Total		100.000	14760819	126365			

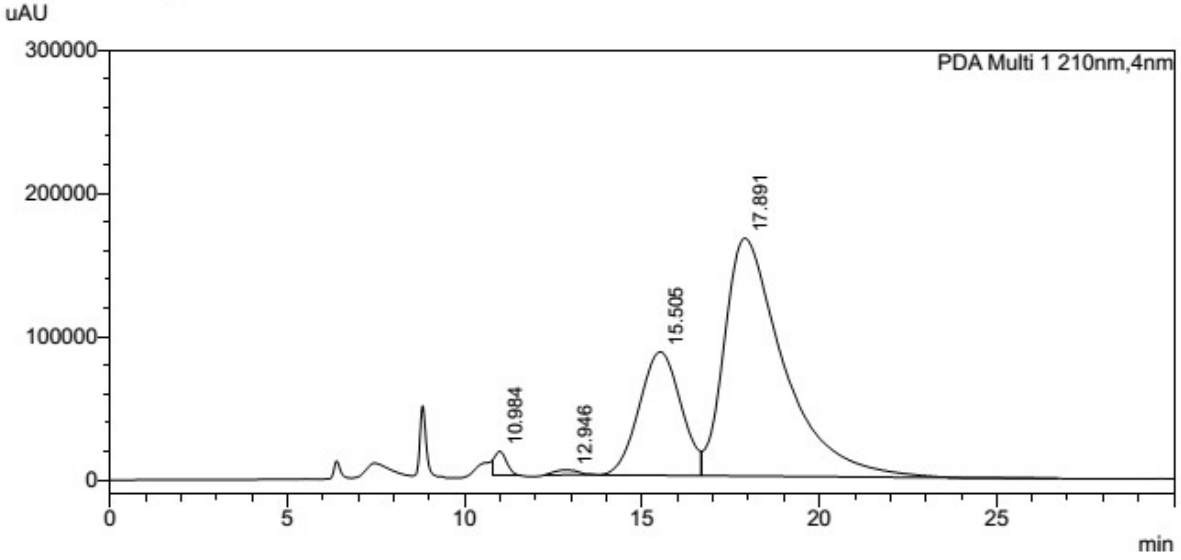


(*Z*)-2.21
Z:*E* 100:0

2.21g
52%, 74:26 *Z*(98:2 *er*):*E*(98:2 *er*)

Following the general procedure B, (*Z*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) to give 25.3 mg (52%) of the title compound (74:26 *Z*:*E* ratio) as an oil. The *e.r.* were, respectively, 98:2 for the *Z*-isomer and 98:2 for the *E*-isomer.

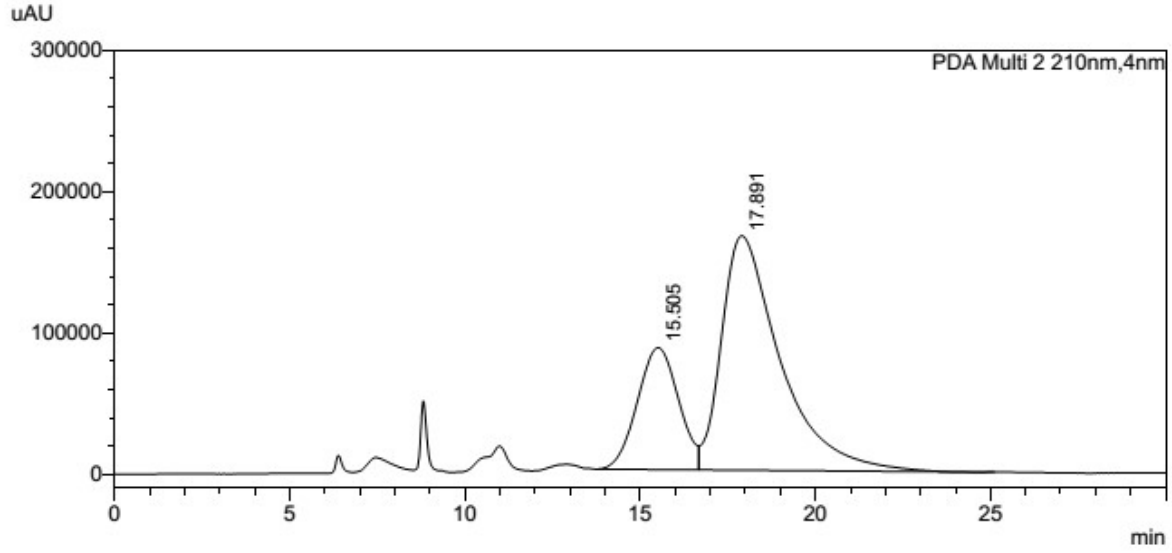
<Chromatogram>



<Peak Table>

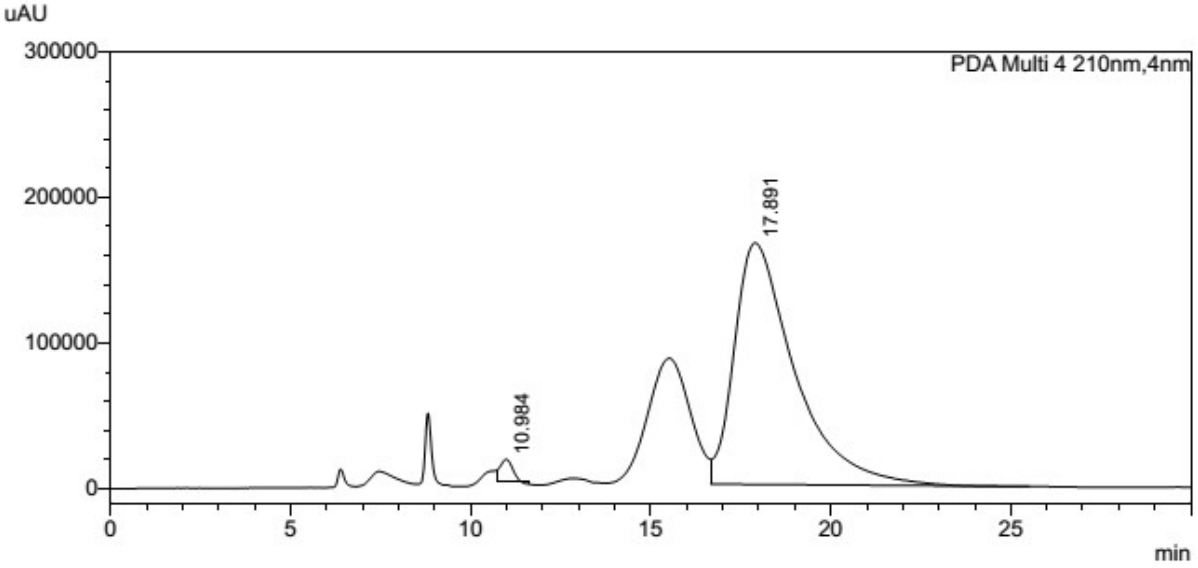
PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.984	1.380	372789	16303	0.000		M
2	12.946	0.604	163017	3385	0.000		M
3	15.505	26.134	7059236	86275	0.000		M
4	17.891	71.882	19416554	165906	0.000		V M
Total		100.000	27011595	271869			



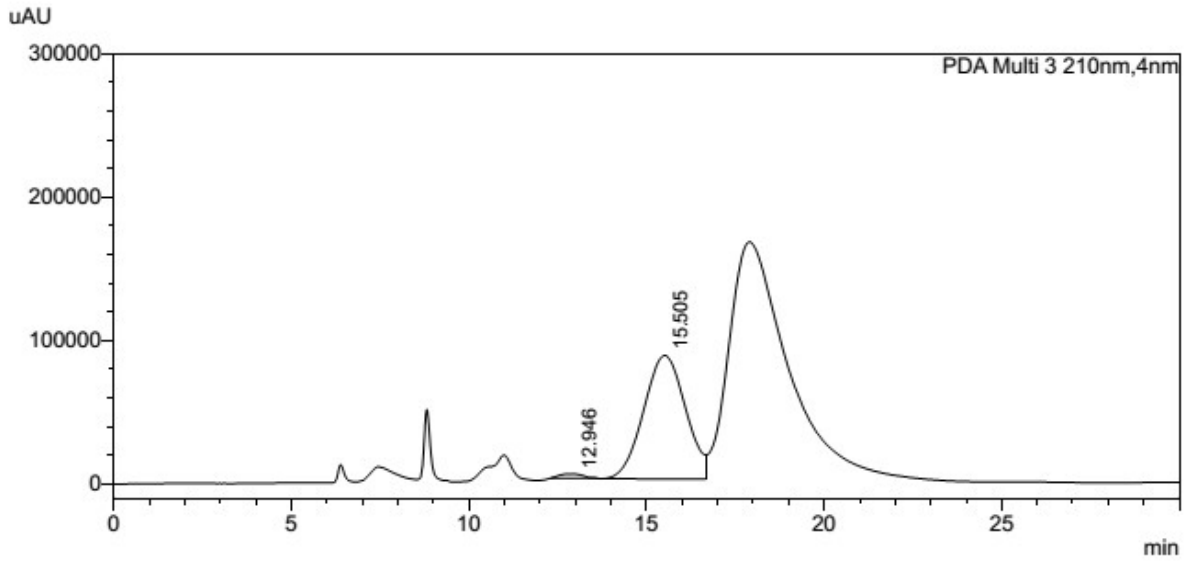
PDA Ch2 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	15.505	26.702	7056746	86258	0.000		M
2	17.891	73.298	19371515	165866	0.000		V M
Total		100.000	26428261	252123			



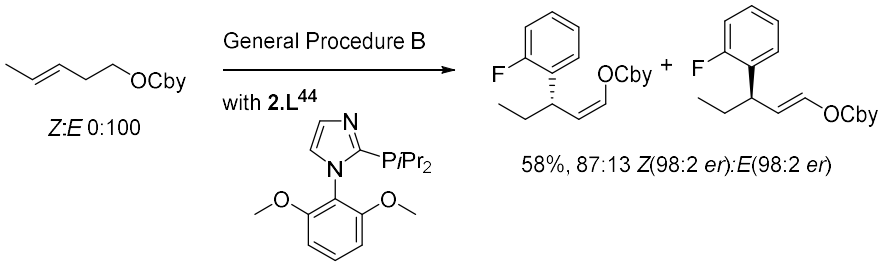
PDA Ch4 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.984	1.840	362907	15813	0.000		M
2	17.891	98.160	19356467	165832	0.000		M
Total		100.000	19719373	181646			

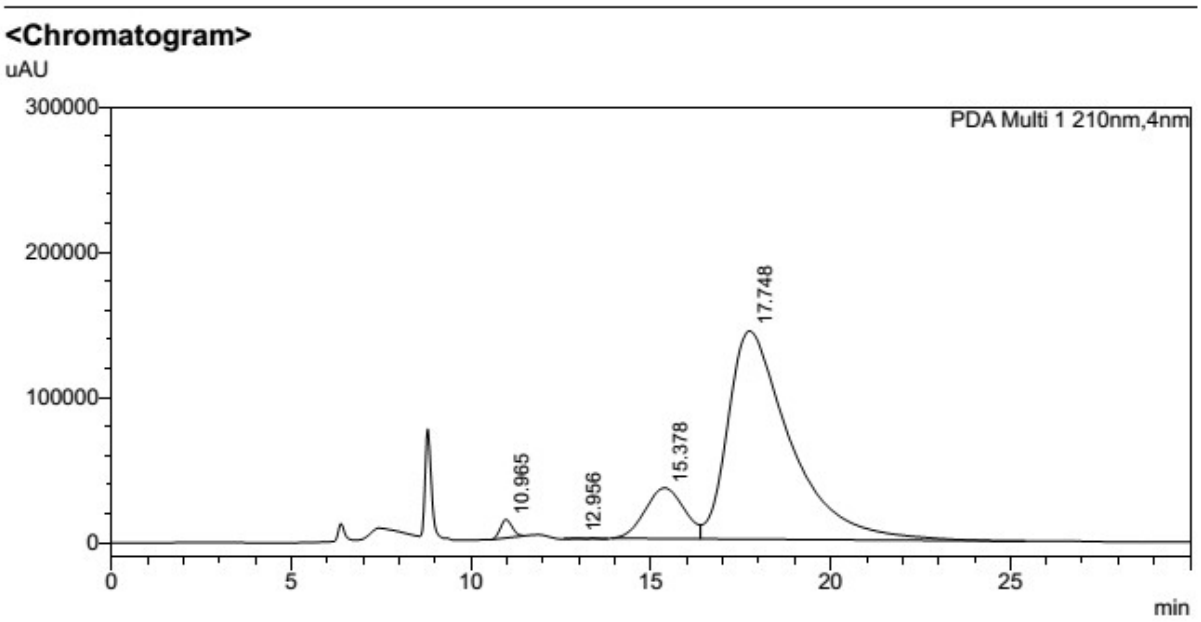


PDA Ch3 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	12.946	1.841	132335	3010	0.000		M
2	15.505	98.159	7056389	86255	0.000		M
Total		100.000	7188724	89265			

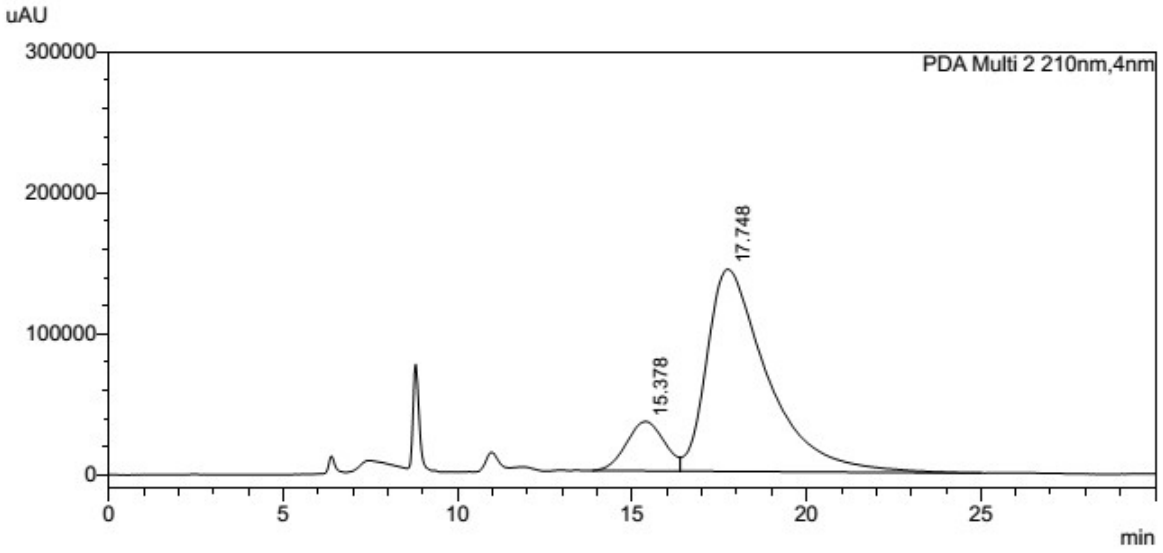


Following the general procedure B, (*E*)-pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg) was arylated with 1-bromo-2-fluorobenzene (15.8 µL) in presence of **2.L**^{44} to give 28 mg (58%) of the title compound (87:13 *Z*:*E* ratio) as an oil. The *e.r.* were, respectively, 98:2 for the *Z*-isomer and 98:2 for the *E*-isomer.



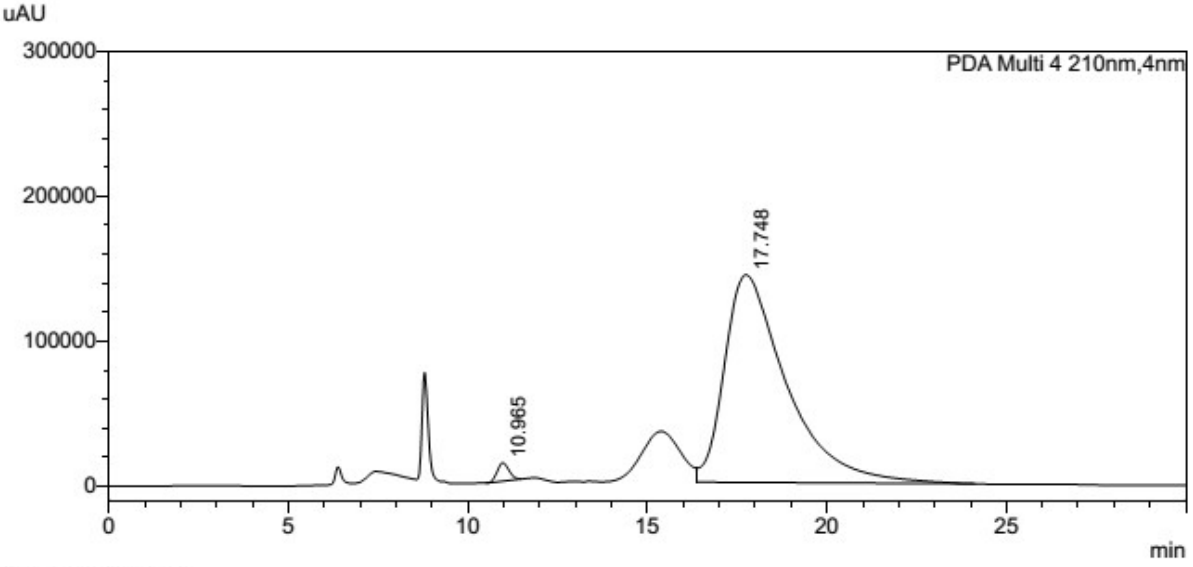
PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.965	1.419	288032	12518	0.000		M
2	12.956	0.101	20531	685	0.000		M
3	15.378	12.998	2638100	34938	0.000		M
4	17.748	85.482	17349918	143372	0.000		V M
Total		100.000	20296582	191514			



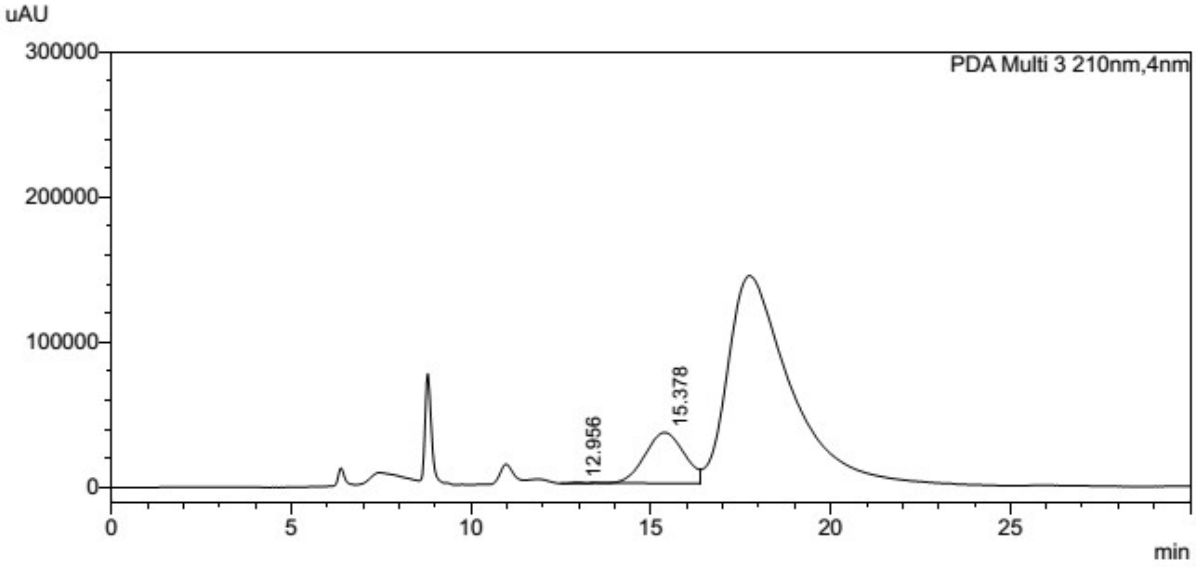
PDA Ch2 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	15.378	13.230	2654391	35047	0.000		M
2	17.748	86.770	17409568	143483	0.000		V M
Total		100.000	20063959	178530			



PDA Ch4 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.965	1.636	288032	12518	0.000		M
2	17.748	98.364	17312799	143328	0.000		
Total		100.000	17600832	155847			

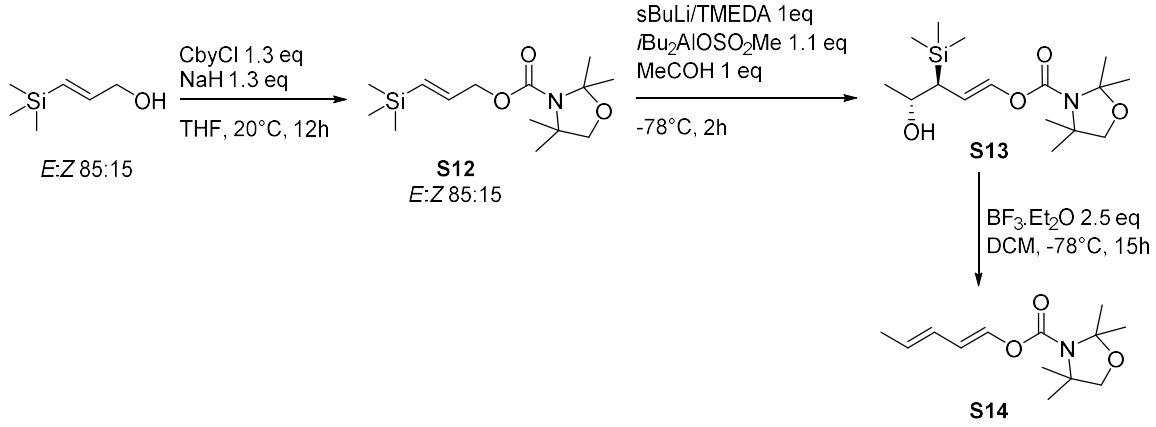


PDA Ch3 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	12.956	0.724	19352	701	0.000		M
2	15.378	99.276	2653216	35038	0.000		M
Total		100.000	2672568	35739			

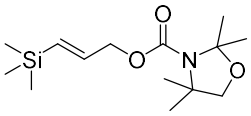
Cross over experiment

- Preparation of the diene**S14**



The diene **S14** was prepared following a procedure similar to the literature.[161]

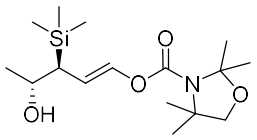
3-(trimethylsilyl)allyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**S12** :



Following the general procedure, (*E*)-3-(trimethylsilyl)prop-2-en-1-ol[162](621 mg, 5 mmol, E:Z 85:15) was reacted with sodium hydride (95% in mineral oil, 3 eq)and 2,2,4,4-tetramethyloxazolidine-3-carbonyl chloride (3 eq) to give 1.25 g (88%, *E*:*Z* 85:15) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 6.43-6.36 (m, 1H, mino.), 6.12-6.05 (m, 1H, majo.), 5.95-5.90 (m, 1H, majo.), 5.81-5.79 (m, 1H, mino.), 4.66-4.60 (m, 2H), 3.76-3.73 (m, 2H), 1.60-1.36 (m, 12H), 0.15-0.00 (m, 9H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 152.67/151.95, 142.0/141.9 (mino.), 140.3/140.2 (majo.), 134.4/134.3 (mino.), 132.84/132.75 (mino.), 96.0/95.1, 76.6/76.2 (majo.), 75.3 (mino.), 67.1 (majo.), 64.6/64.5 (mino), 60.8/59.9, 26.78/26.68, 25.5.48/25.46/25.42, 24.5, 24.3, 23.7/23.5, 0.12, -1.3. **HRMS (ESI) m/z:**calcd. for $C_{14}H_{27}NO_3SiNa$ ([M + Na]$^{+}$): 308.1652; found: 308.1658**. IR neat (υ/cm^{-1}) :** 2957, 2361, 1700, 1400, 1338, 1250, 1097.

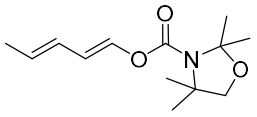
(*E*)-4-hydroxy-3-(trimethylsilyl)pent-1-en-1-yl2,2,4,4-tetramethyloxazolidine-3-carboxylate**S13** :



To a solution of 3-(trimethylsilyl)allyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (380 mg, 1.3 mmol, 1 eq, 85:15 *E*:*Z*) and TMEDA (199 µL, 1.3 mmol, 1 eq) in dry diethyl ether (5 mL) at -78°C (cryostat, acetone bath) was added *s*-Butyllithium (1.46 mmol, 1.1 eq, solution in hexane) over 5 min. The orange mixture was stirred for 1 h, before the addition of diisobutylaluminium methanesulfonate[163] (1.46 mmol, 1.1 eq, 0.5 M in Toluene:MTBE 1:1). The yellow mixture was then stirred for 1.5 h, before the addition of acetaldehyde (75 µL, 1.33 mmol, 1 eq). After 1 h, the mixture was stirred for 15 min at 20°C before the addition of Seignette's salt (10% in water, 20 mL) to quench the reaction. The aqueous layer was extracted with diethyl ether (3x 10 mL), and the combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under vacuum. The residue was purified by flash column chromatography (Pent/Et_2O 80:20 to 30:70) to give 195 mg (45%) of the desired compound as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz, rotamers) :δ = 6.97-6.94 (dd, *J* = 12.4 Hz, *J* = 2.4 Hz, 1H), 5.32-5.24 (m, 1H), 4.01-3.96 (m, 1H), 3.76-3.75 (m, 2H), 1.58-1.56 (m, 6H), 1.48-1.41 (m, 7H), 1.23-1.22 (m, 3H), 0.06 (m,9H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 150.3/149.5, 136.3/136.1, 109.5/109.4, 96.1/95.4, 76.5/76.2, 68.1, 61.0, 60.4, 37.19/37.17, 26.9/26.8, 25.8/25.7, 25.3/25.2, 24.2/24.1, 23.8, 1.8. **HRMS (ESI) m/z:**calcd. for $C_{16}H_{31}NO_4SiNa$ ($[M + Na]^+$): 352.1915; found: 352.1919**. IR neat (ʊ/cm^{-1}) :** 2969, 2872, 2361, 1695, 1373, 1255, 1118.

(1*E*,3*E*)-penta-1,3-dien-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**S14** :

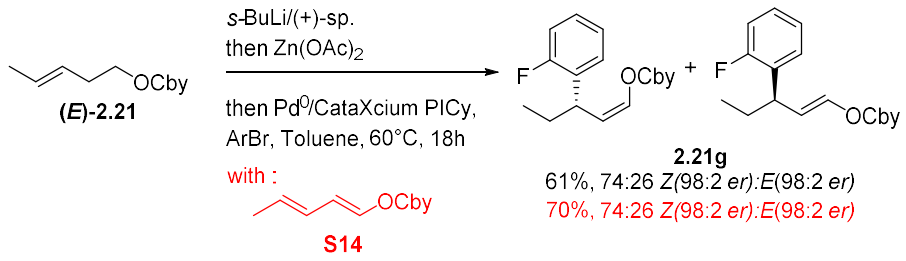


A solution of (*E*)-4-hydroxy-3-(trimethylsilyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (190 mg, 0.58 mmol, 1 eq) in dichloromethane (1.9 mL) was cooled down to -78°C (cryostat, acetone bath). $BF_3.Et_2O$ (0.38 mL, 1.44 mmol, 2.5 eq) was slowly added and the resulting yellowish mixture was stirred at -78°C for 15 h. The reaction was quenched at -78°C (total degradation of the product was observed when warmed up to 20°C before the quench) by addition of aq. sat. $NaHCO_3$ (1.5 mL) and stirred for 5 min, and then was allowed

to warm up to room temperature over 30 min under vigourous stirring. The organic phase was separated and the aqueous layer was extracted with dichloromethane (3x1.5 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under vacuum. The oily residue was purified by flash column chromatography (Pent/Et_2O 95:5 to 80:20) to give 107 mg (78%) of the desired compound as a colorless oil (the product appears also to be slightly volatile).

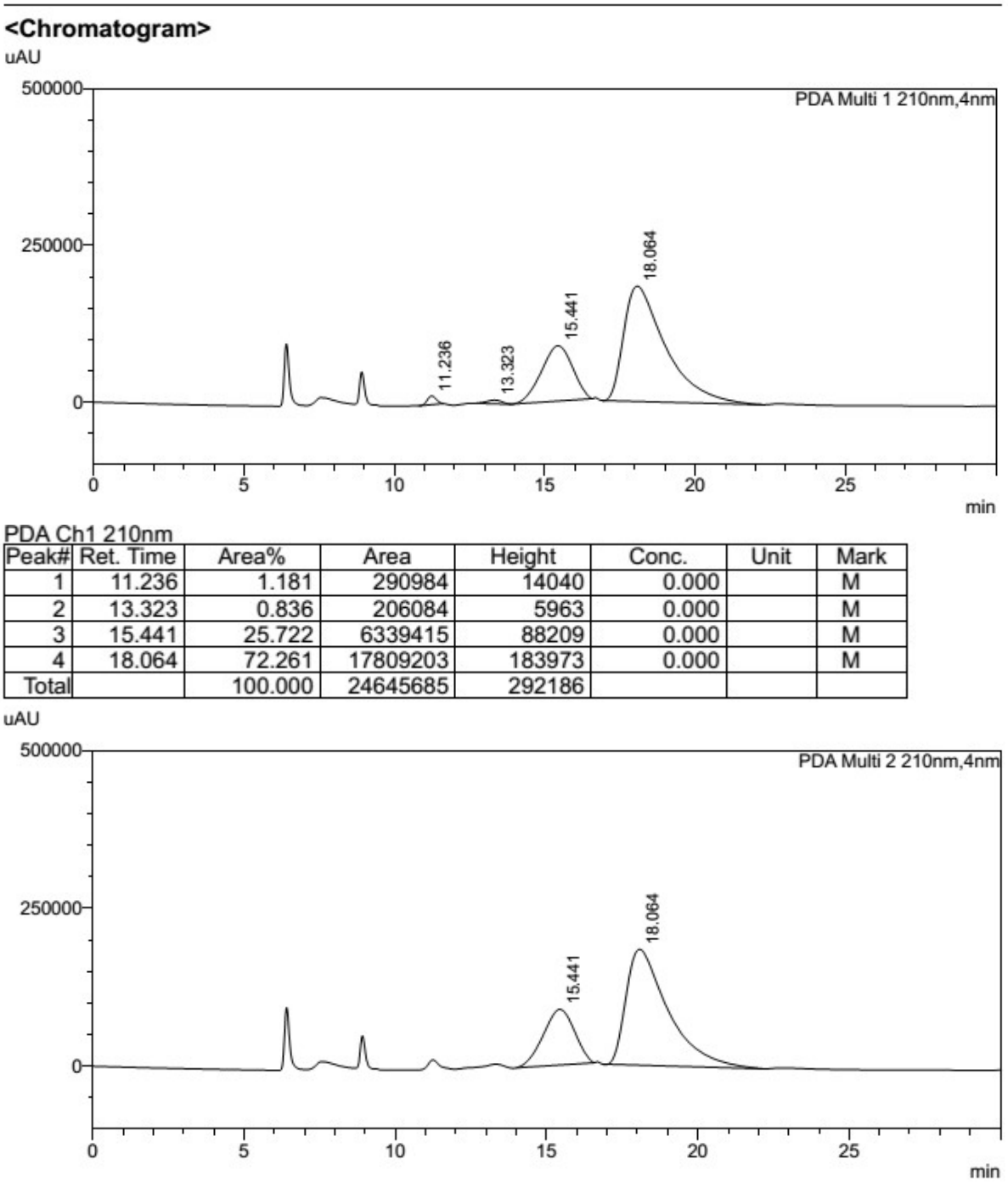
^{1}H NMR ($CDCl_3$, 500 MHz, rotamers) :δ = 7.25-7.21 (m, 1H), 6.00-5.88 (m, 2H), 5.66-5.59 (m, 1H), 3.75 (s, 1H), 1.75-1.74 (m, 3H), 1.57 (1.56) (2 br. s, 6H), (1.43) 1.41 (2 br. s, 6H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 150.00/149.2, 137.3/137.2, 128.13/128.10, 126.2/126.1, 113.72/113.66, 96.2/95.5, 76.4/76.2, 61.1/60.5, 26.9/25.7, 25.2/24.1, 18.4. **HRMS (ESI) m/z:**calcd. for $C_{13}H_{21}NO_3Na$ ([M + Na]$^+$): 262.1414; found: 262.1419**. IR neat (υ/cm^{-1}) :** 2980, 2361, 1716, 1372, 1258, 1133, 1068.

- Procedure for the cross-over experiment :



In a tubular reactor (100 mm x 16 mm)capped with a rubber septum, a solution of the carbamate**(*E*)-2.21**(50 mg, 0.207 mmol, 1 eq) and (+)-sparteine (67 µL, 0.29 mmol, 1.4 eq) in dry diethyl ether (1.5 mL) under argon was stirred and cooled down to -78°C (acetone bath, cryostat). *s*-Butyllithium (0.29 mmol, 1.4 eq, solution in hexane) was added dropwise, and the mixture was stirred for 4 h. A suspension of zinc acetate (57 mg, 0.31 mmol, 1.5 eq) in dry THF (1.5 mL) was sonicated for 30 min and added dropwise to the mixture. The resulting solution was stirred for 30 min at -78°C, and then allowed to heat up to 20°C over 30 min. The solvents were evaporated over 30 min under high vacuum, and a solution of $Pd_2(dba)_3$ (3.3 mg, 3.6 µmol, 1.75 %mol) and CataCXium PICy**2.L**[27] (2.8 mg, 7.3 µmol, 3.5 %mol) in dry toluene (1.0 mL) was added, followed by the aryl bromide (0.15 mmol, 0.7 eq) and the diene**S14**(49.5 mg, 0.207 mmol, 1 eq,) in toluene (0.5 mL). The mixture was then vigorously stirred and heated to 60°C for 18h. After cooling down, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the organic phase was diluted with EtOAc (3 mL) and separated. The

aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtrated over a pad of celite, and evaporated under vacuum. The residue was purified by preparative reversed-phase HPLC ($MeCN/H_2O$) to afford 34 mg (70%) of **2.21g** (74:26 *Z*:*E* ratio) as an oil. The *e.r.* were, respectively, 98:2 for the *Z*-isomer and 98:2 for the *E*-isomer.

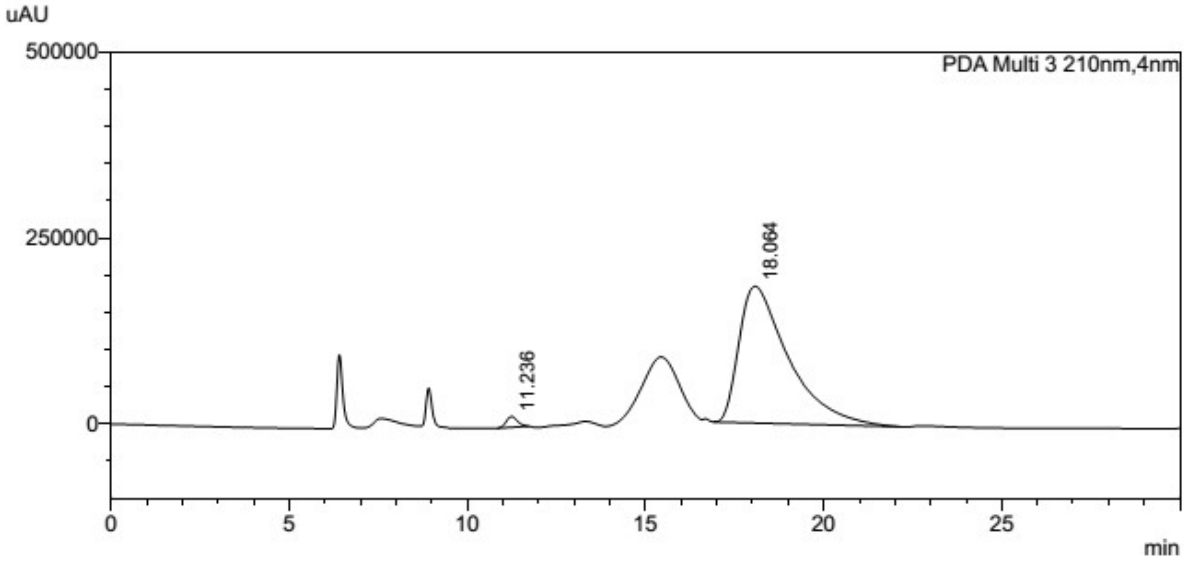


PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.236	1.181	290984	14040	0.000		M
2	13.323	0.836	206084	5963	0.000		M
3	15.441	25.722	6339415	88209	0.000		M
4	18.064	72.261	17809203	183973	0.000		M
Total		100.000	24645685	292186			

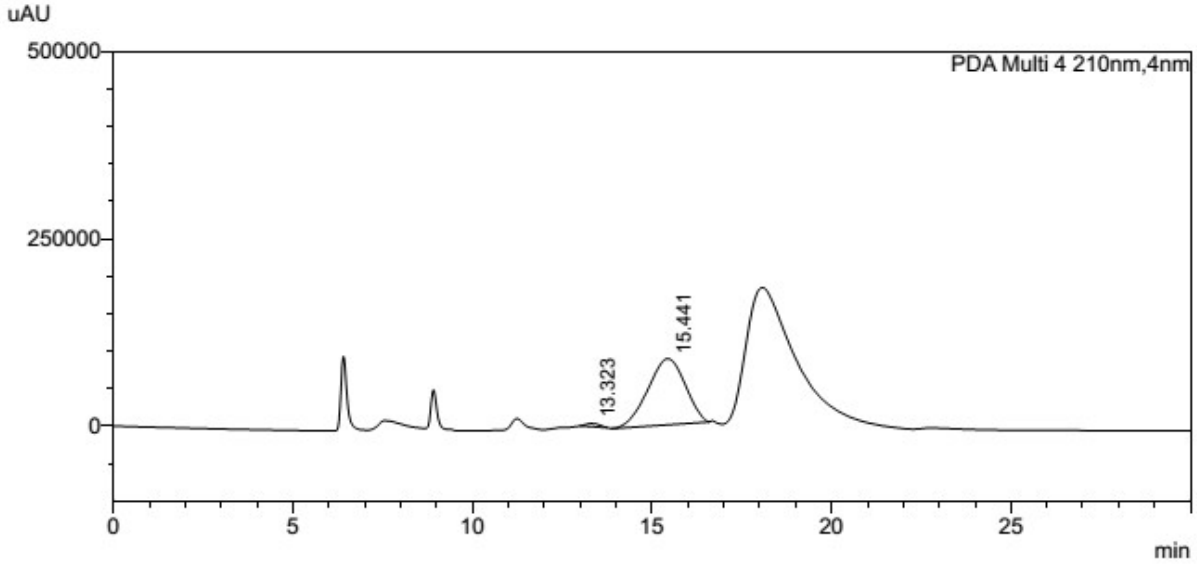
PDA Ch2 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	15.441	26.315	6327776	88138	0.000		M
2	18.064	73.685	17718201	183507	0.000		M
Total		100.000	24045978	271645			



PDA Ch3 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.236	1.756	317722	14574	0.000		M
2	18.064	98.244	17776643	183975	0.000		M
Total		100.000	18094365	198548			



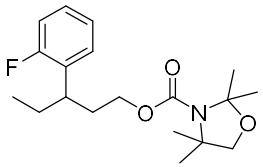
PDA Ch4 210nm

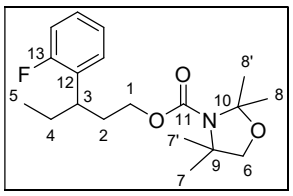
Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	13.323	1.738	112783	4259	0.000		M
2	15.441	98.262	6378143	88434	0.000		M
Total		100.000	6490926	92694			

Product derivatization

- Hydrogenation product **2.22**

3-(2-fluorophenyl)pentyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate :





rac-3-(2-fluorophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.21g**(75:25 *Z*:*E*) (206 mg, 0.6 mmol, 1 eq) was diluted with dry ethanol (6 mL) in a 10 mL glass vial. Pd/C 10%w/w (20 mg, 10% w/w) was added and the vial was loaded in an autoclave. The mixture was stirred at 50°C under H_2 (50 bar) for 24h. After cooling down, the reaction mixture was filtered on celite and the filtrated solution was concentrated under vacuum. The crude residue was filtered over a pad of silica gel (Pent/Et_2O 85:15) to afford 192 mg (93%) of the desired *rac*-carbamate as an oil.

Under the same conditions, an enantioenriched mixture of 3-(2-fluorophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (75:25 *Z*:*E*, *e.r.* 98:2 respectively) (7 mg, 0.02 mmol, 1 eq) was hydrogenated to give 7 mg (99 %) of the desired enantioenriched carbamate as an oil (*e.r.* 75:25)

Under the same conditions, an enantioenriched mixture of 3-(2-fluorophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (87:13 *Z*:*E*, *e.r.* 98:2 respectively) (20.2 mg, 0.06 mmol, 1 eq) was hydrogenated to give 17 mg (84%) of the desired enantioenriched carbamate as an oil (*e.r.* 86.5:13.5)

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.17-7.13 (m, 2H, H_{Ar}), 7.09-7.06 (m, 1H, H_{Ar}), 7.01-6.97 (m, 1H, H_{Ar}), 4.06-3.90 (m, 2H, H_1), 3.71 (s, 2H, H_6), 3.03-2.95 (m, 1H, H_3), 2.08-1.90 (m, 2H, H_2), 1.77-1.62 (m, 2H, H_4), 1.62-1.36 (m, 12H, H_7, $H_{7'}$, H_8, $H_{8'}$), 0.80 (t, *J* = 7.4 Hz, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 162.36/160.42 (d of rotamers, *J* = 243.9 Hz, C_{13}), 152.9/152.2 (C_{11}), 131.2/131.1 (C_{12}), 128.7/128.6 (C_{Ar}), 127.72/127.66 (C_{Ar}), 124.32/124.29 (C_{Ar}), 115.7/115.5 (C_{Ar}), 95.9/94.9 (C_{10}), 76.5/76.2 (C_6), 62.9 (C_1), 60.7/59.7 (C_9), 37.3 (C_3), 34.6 (C_2), 28.46/28.45 (C_4), 26.6-24.3 (C_7, $C_{7'}$, C_8, $C_{8'}$), 12.1 (C_5).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -118.30/-118.33 (F_{13}). **HPLC**

separation conditions : Chiralpak IC column, *n*-heptane/*i*-PrOH 99.5:0.5, flow rate 0.5 mL/min, 25°C, t_R19.4 min for ()-enantiomer (major) and t_R 21.3 min for ()-enantiomer (minor). *e.r.* = 86.5:13.5.**HRMS (ESI) m/z:**calcd. for $C_{19}H_{28}FNO_3Na$ ($[M + Na]^+$) : 360.1945; found: 360.1946**.IR neat (υ/cm^{-1}) :** 2970, 2361, 1699, 1408, 1364, 1258, 1068.

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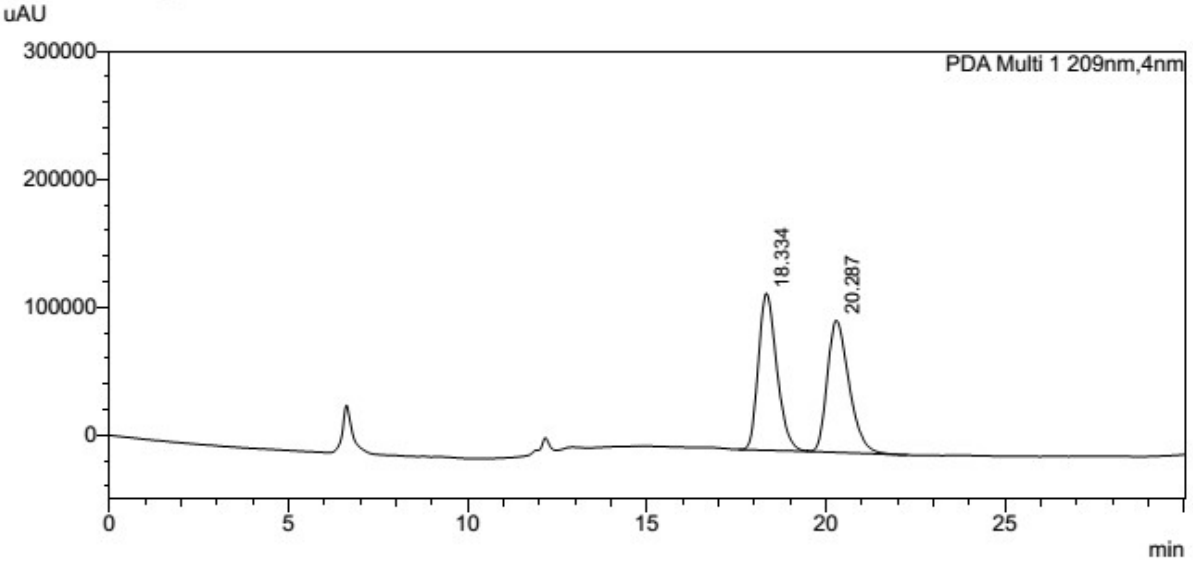

<Peak Table>

PDA Ch1 209nm

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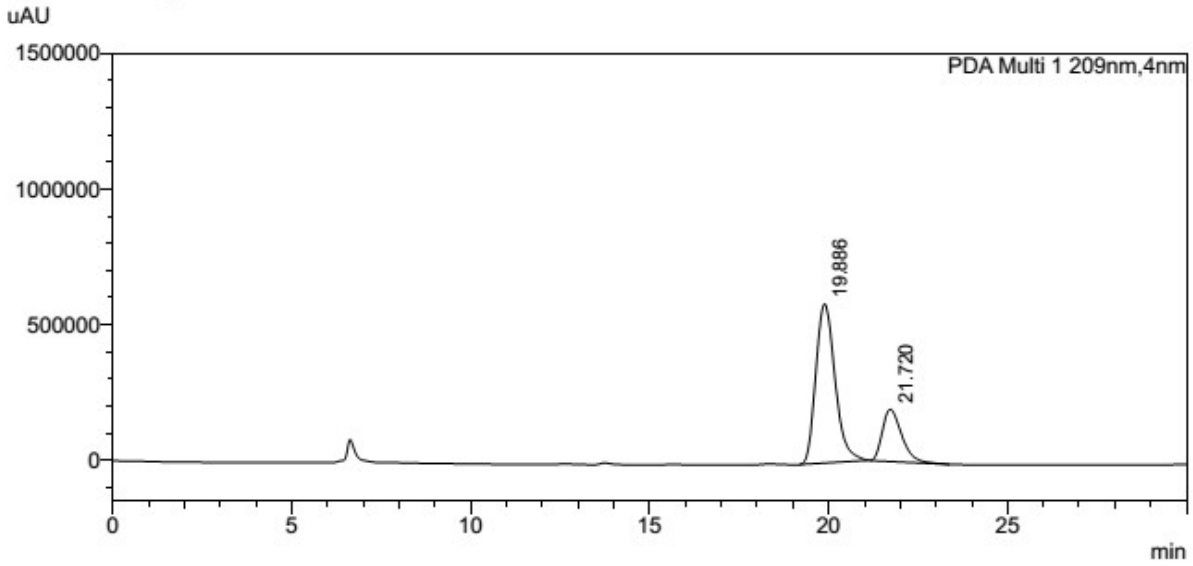
1	18.334	50.099	4377329	122698	50.099		M
2	20.287	49.901	4360114	103154	49.901		M
Total		100.000	8737443	225852			

<Chromatogram>

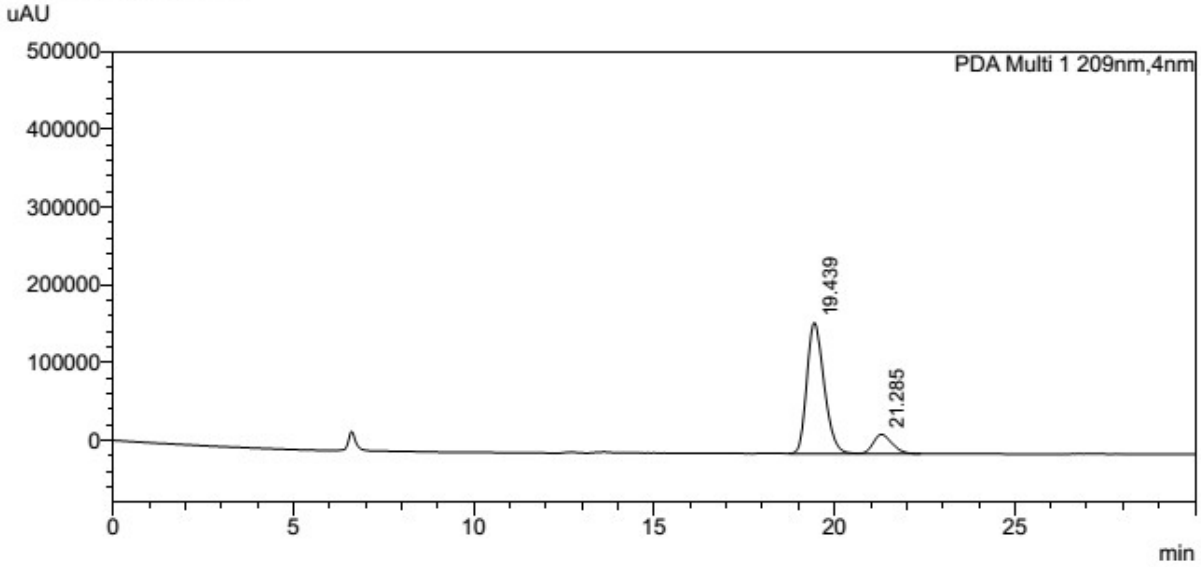


<Peak Table>

PDA Ch1 209nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	19.886	75.264	21939706	586283	75.264		M
2	21.720	24.736	7210596	192432	24.736		M
Total		100.000	29150302	778715			

<Chromatogram>



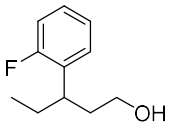
<Peak Table>

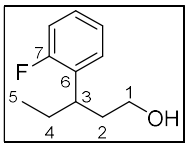
PDA Ch1 209nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	19.439	86.313	5605596	168170	86.313		V
2	21.285	13.687	888926	24629	13.687		
Total		100.000	6494522	192798			

- Deprotection product **2.42**

3-(2-fluorophenyl)pentan-1-ol :

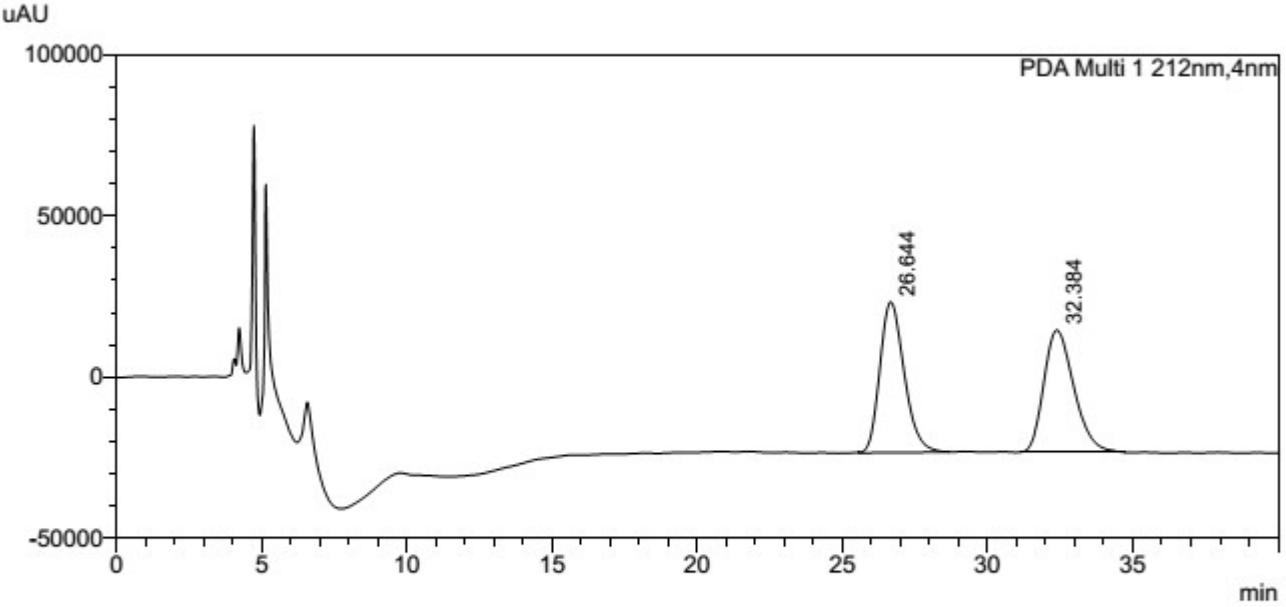




rac-3-(2-fluorophenyl)pentyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (50 mg, 0.15 mmol, 1 eq) was diluted in methanol (1mL) and $MeSO_3H$ (38 µL, 0.59 mmol, 4 eq) was added. The mixture was refluxed for 3.5h, cooled down to 20°C, and $Ba(OH)_2.8H_2O$ (304 mg, 1.78 mmol, 12 eq) was added. The mixture was then refluxed for 18h. After cooling down, the solids were filtrated on a pad silica with Et_2O (5 mL). After evaporation under vacuum, the residue was purified by silica gel column chromatography (Pent/Et_2O 80:20) to give the 25.8 mg (96%) of the racemic alcohol.

H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 7.20-7.15 (m, 2H, H_{Ar}), 7.11-7.08 (m, 1H, H_{Ar}), 7.02-6.99 (m, 1H, H_{Ar}), 3.57-3.45 (m, 2H, H_1), 3.03-2.97 (m, 1H, H_3), 2.01-1.80 (m, 2H, H_2), 1.77-1.60 (m, 2H, H_4), 0.81 (t, *J* = 7.4 Hz, 3H, H_5). **^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 162.47/160.53 (d, *J* = 244.8 Hz, C_7), 131.6/131.4 (C_6), 128.9/128.8 (C_{Ar}), 127.63/127.56 (C_{Ar}), 124.34/124.31 (C_{Ar}), 115.6-115.4 (C_{Ar}), 61.3 (C_1), 38.4 (C_3), 36.92/36.91 (C_2), 28.67/28.66 (C_4), 12.2 (C_5).**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -118.54 (F_7). **HPLC separation conditions :** ChiralcelOD-H column, *n*-heptane/*i*-PrOH 99:1, flow rate 0.8 mL/min, 25°C, t_R26.6 min for ()-enantiomer (major) and t_R 32.4 min for ()-enantiomer (minor). *e.r.* =.**HRMS (ESI) m/z:**calcd. for $C_{11}H_{15}FO_3Na$ ($[M + Na]^+$) : 205.0999; found: 205.0998**.IR neat (υ/cm^{-1}) :** 3352, 2963, 2361, 1224, 1052.

<Chromatogram>



<Peak Table>

PDA Ch1 212nm

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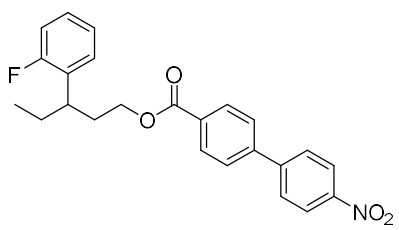
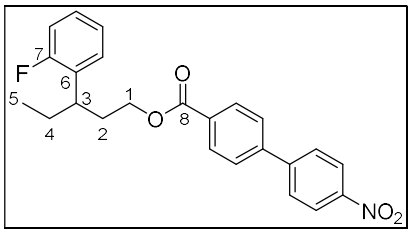
2	32.384	50.182	2742922	38046	50.182		SV
Total		100.000	5465983	84767			

- Esterification product **2.43c**

3-(2-fluorophenyl)pentyl 4'-nitro-[1,1'-biphenyl]-4-carboxylate :





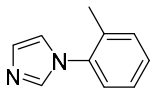
To a solution of *rac*-3-(2-fluorophenyl)pentan-1-ol (25 mg, 0.14 mmol, 1 eq) in CH_2Cl_2 (0.2 mL) were added 4'-nitro-[1,1'-biphenyl]-4-carbonyl chloride (39.4 mg, 0.15 mL, 1.1 eq), triethylamine (57 µL, 0.41 mmol, 3 eq), and DMAP (< 1mg, cat.). The mixture was stirred at 23°C for 45 min. After this time, the volatiles were evaporated under vacuum and the crude residue was purified by column chromatography (EtOAc:Cyclohexane 2.5:97.5) to give 30 mg (54%) of the title compound as a white solid.

H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 8.34-8.32 (m, 2H, H_{Ar}), 8.08-8.07 (m, 2H, H_{Ar}), 7.78-7.76 (m, 2H, H_{Ar}), 7.68-7.66 (m, 2H, H_{Ar}), 7.23-7.16 (m, 2H, $2H_{Ar}$), 7.12-7.03 (m, 1H, H_{Ar}), 7.03-7.00 (m, 1H, H_{Ar}), 4.33-4.28 (m, 1H, H_1), 4.21-4.16 (m, 1H, H_1), .3.12-3.06 (m, 1H, H_3), 2.24-2.17 (m, 1H, H_2), 2.13-2.06 (m, 1H, H_2), 1.82-1.66 (m, 2H, H_4), 0.84 (t, J = 7.4 Hz, 1H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz, rotamers) :**δ = 166.1 (C_8), 162.5/160.5 (d, J = 244.4 Hz, C_7), 147.7 (C_{Ar}), 146.6 (C_{Ar}), 143.1 (C_{Ar}), 131.1/131.0 (C_6), 130.8 (C_{Ar}), 130.5 (C_{Ar}), 128.80/128.76 (C_{Ar}), 128.2 (C_{Ar}), 127.82/127.75 (C_{Ar}), 127.5 (C_{Ar}), 124.41/124.38 (C_{Ar}), 124.35 (C_{Ar}), 115.8/115.6 (C_{Ar}), 63.9 (C_1), 37.6 (C_3), 34.2 (C_2), 28.8 (C_4), 12.2 (C_5). **^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz, rotamers) :** δ = -118.40 (F_7). **HPLC separation conditions :HPLC separation conditions :**Chiralpak AD-H column, *n*-heptane/*i*-PrOH 98:2, flow rate 0.5 mL/min, 25°C, t_R83.0 min for ()-enantiomer and t_R 88.4 min for ()-enantiomer. *e.r.***HRMS (ESI) m/z:** $C_{24}H_{22}FO_4Na$ ([M + Na]$^+$) : 430.1425; found: 430.1419**. IR neat (ʊ/cm^{-1}) :** 2963, 2361, 1716, 1598, 1519, 1343, 1275, 1109.**M.p :** 82°C

Preparation of ligands ***2.L***^{16} *and* ***2.L***$^{42\text{-}55}$.

- Synthesis of starting material heterocycles **S15-S21**

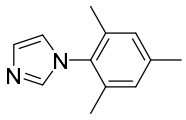
1-(*o*-tolyl)-1*H*-imidazole **S15** :



A 20 mL reaction tube was loaded in a glovebox with imidazole (680 mg, 10 mmol, 1 eq), CuI (286 mg, 1.5 mmol, 0.15 eq), and Cs_2CO_3 (4.89 g, 15 mmol, 1.5 eq). Out of the glovebox, 1-iodo-2-methylbenzene (1.56 mL, 12 mmol, 1.2 eq) and DMSO (10 mL) were added. The tube was sealed and placed in a microwave apparatus, stirred for 1 min at ambient temperature, and then stirred and heated at 150°C for 2 h under microwave irradiation. The reaction mixture was diluted with 100 mL of EtOAc:CyHex (50:50) and 100 mL of Brine:Water (50:50) were added. The organic layer was separated and the aqueus layer was extracted 3 times with 100 mL of EtOAc:CyHex (50:50). The combined organic layers were washed with 250 mL of Brine:Water (50:50), dried over $MgSO_4$, filtrated and then concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc) to afford 550 mg (35 %) of the desired product as a yellowish oil.The data were in accordance with the literature.[164]

^{1}H NMR (400 MHz, $CDCl_3$) :δ = 7.56 (s, 1H), 7.38-7.27 (m, 3H), 7.23-7.21 (m, 2H), 7.06 (s, 1H), 2.19 (s, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ =134.0, 131.4, 128.9, 127.0, 126.7, 17.75.

1-mesityl-1*H*-imidazole**S16** :

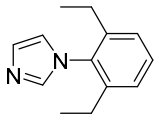


Formaldehyde (2.2 mL (37% solution in H_2O), 30 mmol, 1eq) and glyoxal (3.4 mL (40% solution in H_2O), 30 mmol, 1 eq) were dissolved in a mixture of acetic acid and toluene (8 mL, 1:1) and heated to 70°C for 15 min. A slurry of mesitylamine (4.2 mL, 30 mmol, 1 eq), ammonium acetate (2.3 g, 30 mmol, 1 eq), and acetic acid (4mL) was added to the reaction mixture. . The dark solution was stirred for 3 days, cooled down to room temperature, and

poured over a saturated solution of $NaHCO_3$ (100 mL). Powdered KOH was added to raise the pH to 8. The mixture was then extracted with THF (3x75 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The brown residue was purified by column chromatography (EtOAc:CyHex 20:80 to 100:0) to obtain a brown solid. Sublimation of this last under high vacuum afforded 2.62 g (47 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.43-7.42 (m, 1H), 7.22 (m, 1H), 6.96 (m, 1H), 6.88 (m, 1H), 2.33 (s, 3H), 1.98 (s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 139.0, 137.6, 135.6, 133.5, 129.7, 129.1, 120.2, 21.2, 17.5.

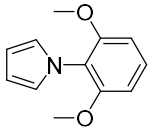
1-(2,6-diethylphenyl)-1H-imidazole**S17** :



A 20 mL reaction tube was loaded in a glovebox with imidazole (251 mg, 3.7mmol, 1 eq), CuI (105 mg, 0.55mmol, 0.15 eq), and Cs_2CO_3 (1.80 g, 5.5mmol, 1.5 eq). Out of the glovebox, 1,3-diethyl-2-iodobenzene (960 mg, 3.7 mmol, 1 eq) and DMSO (10 mL) were added. The tube was sealed and placed in a microwave apparatus, stirred for 1 min at ambient temperature, and then stirred and heated at 170°C for 3 h under microwave irradiation. The reaction mixture was diluted with 100 mL of EtOAc:CyHex (50:50) and 100 mL of Brine:Water (50:50) were added. The organic layer was separated and the aqueus layer was extracted 3 times with 100 mL of EtOAc:CyHex (50:50). The combined organic layers were washed with 250 mL of Brine:Water (50:50), dried over $MgSO_4$, filtrated and then concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc) to afford 160 mg (22 %) of the desired product as a white solid.

^{1}H NMR ($CDCl_3$, 500 MHz) :δ = 7.47 (b.s., 1H), 7.37-7.34 (m, 1H), 7.24 (b.s., 1H), 7.20-7.18 (m, 2H), 6.94 (b.s., 1H), 2.28 (q, *J* = 7.6 Hz, 4H), 1.08 (t, *J* = 7.6 Hz, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 126 MHz) :**δ = 142.0, 134.8, 129.6, 126.8, 24.3, 15.7.

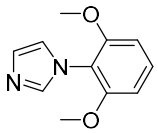
1-(2,6-dimethoxyphenyl)-1*H*-pyrrole**S18** :



In a 25 mL round bottom flask was dissolved 2,6-dimethoxyaniline[165](400 mg, 2.6 mmol, 1 eq) in glacial acetic acid (10 mL). After the solution became clear (ca. 2 min), dimethoxytetrahydrofuran (0.34 mL, 2.6 mmol, 1 eq) was added, and the mixture was heated to 100°C for 3 h. After cooling, the dark solution was slowly poored to a solution of $NaHCO_3$ (14.7 g in 200 mL of H_2O) to quench the acetic acid. Ethyl acetate (100 mL) was added and the aqueous layer was separated. The organic layer was rinced with water (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The brown solid residue was purified by silica gel chromatography (EtOAc:CyHex 10:80 to 50:50) to afford 220 mg (42 %) of the titled compound as a beige solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.29-7.25 (m, 1H), 6.76-6.75 (m, 2H), 6.67-6.65 (m, 2H), 6.32-6.31 (m, 2H), 3.77 (s, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 156.0, 128.5, 123.1, 119.4, 108.0, 104.7, 56.2.

1-(2,6-dimethoxyphenyl)-1*H*-imidazole **S19** :

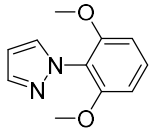


A 20 mL reaction tube was loaded in a glovebox with imidazole (680 mg, 10 mmol, 1 eq), CuI (286 mg, 1.5 mmol, 0.15 eq), and Cs_2CO_3 (4.89 g, 15 mmol, 1.5 eq). Out of the glovebox, 2-iodo-1,3-dimethoxybenzene (2.64 g, 10 mmol, 1 eq) and DMSO (10 mL) were added. The tube was sealed and placed in a microwave apparatus, stirred for 1 min at ambient temperature, and then stirred and heated at 160°C for 6 h under microwave irradiation. The reaction mixture was diluted with 100 mL of EtOAc:CyHex (50:50) and 100 mL of Brine:Water (50:50) were added. The organic layer was separated and the aqueous layer was extracted 3 times with 100 mL of EtOAc:CyHex (50:50). The combined organic layers were washed with 250 mL of Brine:Water (50:50), dried over $MgSO_4$, filtrated and then concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc:MeOH 100:0 to 95:5) to afford 480 mg (24%) of the desired product as anoff-white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.56 (s, 1H), 7.34-7.30 (m, 1H), 7.17 (s, 1H), 7.02 (s, 1H), 6.68-6.66 (m, 2H), 3.78 (s, 6H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 155.5, 139.2, 139.1, 129.6, 128.2, 121.3, 121.3, 104.6, 69.20. **HRMS (ESI) m/z:** calcd. for $C_{11}H_{12}N_2O_2H$ ([M +

H]$^+$): 205.0972; found: 205.0971**. IR neat (υ/cm^{-1}) :** 2954, 2877, 2359, 1594, 1449, 1254, 1110. **M.p :** 147°C

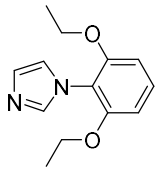
1-(2,6-dimethoxyphenyl)-1*H*-pyrazole**S20** :



A 20 mL reaction tube was loaded in a glovebox with pyrazole (258 mg, 3.8mmol, 1 eq), CuI (372 mg, 1.9mmol, 0.5eq), and Cs_2CO_3 (2.47 g, 7.6mmol, 2eq). Out of the glovebox, 2-iodo-1,3-dimethoxybenzene (1.0 g, 3.8mmol, 1 eq), TMEDA (0.29 mL, 1.9 mmol, 0.5 eq) and DMF (10 mL) were added. The tube was sealed and vigorously stirred at 130°C for 36 h. The reaction mixture was diluted with 100 mL of EtOAc:CyHex (50:50) and 100 mL of Brine:Water (50:50) were added. The organic layer was separated and the aqueous layer was extracted 3 times with 100 mL of EtOAc:CyHex (50:50). The combined organic layers were washed with 250 mL of Brine:Water (50:50), dried over $MgSO_4$, filtrated and then concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc:CyHex 20:80 to 100:0) to afford 280 mg (36%) of the desired product as an off-white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.78-7.77 (m, 1H), 7.51-7.50 (m, 1H), 7.38-7.31 (m, 1H), 6.67-6.64 (m, 1H), 6.45-6.43 (m, 1H), 3.76 (s, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ =156.7, 140.3, 132.6, 130.2, 118.9, 105.6, 104.4, 56.3.

1-(2,6-diethoxyphenyl)-1H-imidazole**S21** :

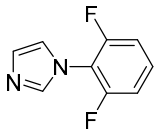


Formaldehyde (260µL (37% solution in H_2O), 3.5mmol, 1eq) and glyoxal (400 µL (40% solution in H_2O), 3.5mmol, 1 eq) were dissolved in a mixture of acetic acid and toluene (8 mL, 1:1) and heated to 70°C for 15 min. A slurry of 2,6-diethoxyaniline[2] (631 mg, 3.5mmol, 1 eq), ammonium acetate (268 mg, 3.5mmol, 1 eq), and acetic acid (4mL) was added to the reaction mixture. . The dark solution was stirred for 24 h, cooled down to room temperature, and poured over a saturated solution of $NaHCO_3$ (100 mL). Powdered KOH was added to

raise the pH to 8. The mixture was then extracted with THF (3x75 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The brown residue was purified by column chromatography (EtOAc:CyHex 20:80 to 100:0) to obtain 420 mg (52%) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.61-7.60 (m, 1H), 7.26-7.22 (m, 1H), 7.13 (m, 1H), 7.05-7.04 (m, 1H), 6.63-6.61 (m, 2H), 4.00 (q, *J* = 7 Hz, 4H), 1.28 (t, *J* = 7 Hz, 6H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ =154.6, 139.1, 129.2, 127.8, 121.3, 116.3, 105.7, 64.7, 14.8.

1-(2,6-difluorophenyl)-1H-imidazole **S22** :



Formaldehyde (577 µL (37% solution in H_2O), 7.75 mmol, 1 eq) and glyoxal (885 µL (40% solution in H_2O), 7.75 mmol, 1 eq) were dissolved in a mixture of acetic acid and toluene (10 mL, 1:1) and heated to 70°C for 15 min. A slurry of 2,6-difluoroaniline (1 g, 7.75 mmol, 1 eq), ammonium acetate (600 mg, 7.75 mmol, 1 eq), and acetic acid (5 mL) was added to the reaction mixture. . The dark solution was stirred for 24 h, cooled down to room temperature, and poured over a saturated solution of $NaHCO_3$ (100 mL). Powdered KOH was added to raise the pH to 8. The mixture was then extracted with THF (3x75 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The brown residue was purified by column chromatography (EtOAc:CyHex 50:50 to 100:0) to obtain 880 mg (63%) of the title compound as a yellowish oil.

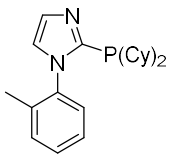
^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.73 (br. s, 1H), 7.38-7.31 (m, 1H), 7.22 (br. s, 1H), 7.17 (m, 1H), 7.11-7.05 (m, 2H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 157.86, 157.82, 155.34, 155.31, 138.1, 129.41, 129.39, 129.3, 129.2, 120.5, 115.4, 112.8, 112.74, 112.71, 112.57, 112.55, 112.52.**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz) :** δ = -120.4.

- General procedure for the preparation of ligands **2.L[16]** and **2.L[42-55]**

The preparation steps must be carried out under argon atmosphere as much as possible via the use of argon filled balloons and/or a schlenk ramp. A solution of the *N*-arylated heterocycle**S15-22** (1 eq)in THF (2 mL) was cooled down to -30°C (acetone, cryostat). *s*-Butyllithium (1 eq, solution in hexane) was added dropwise and the mixture was stirred for 30 min before addition of the chlorophosphine (1 to 1.05 eq) in THF (1 mL). The mixture was stirred for 30 min at -30°C and 30 min at 20°C. Then, the mixture was directly concentrated under reduced pressure (using an argon flushed rotavapor) and the residue was purified by column chromatography (Pent/Et_2O 95:5 to 0:100) to afford the corresponding phosphine ligand.

- Synthesis of ligands **2.L[16]** and **2.L[42-55]**

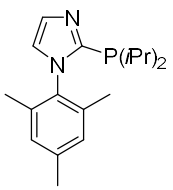
2-(dicyclohexylphosphanyl)-1-(*o*-tolyl)-1*H*-imidazole**2.L[16]** :



A solution of 1-(*o*-tolyl)-1*H*-imidazole (300 mg, 1.9 mmol, 1 eq) was reacted with chlorodicyclohexylphosphine (464 mg, 2 mmol, 1.05 eq) to afford 400 mg (59 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.38 (m, 1H), 7.36-7.34 (m, 1H), 7.31-7.24 (m, 2H), 7.15 (m, 1H), 7.04 (m, 1H), 2.30 (b.s., 1H), 2.04 (s, 3H), 1.88 (b.s., 1H), 1.88-1.56 (m, 10H), 1.38-0.91 (m, 10H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 147.5, 147.4, 137.8, 135.3, 130.9, 129.2, 128.98, 128.96, 126.2, 123.1, 35.0 (b.s.), 33.5 (b.s.), 30.1 (b.s.), 29.9 (b.s.), 29.1 (b.s.), 27.1 (b.s.), 26.5, 17.93, 17.89. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -23.5.

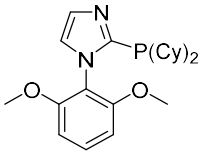
2-(diisopropylphosphanyl)-1-mesityl-1*H*-imidazole**2.L[42]** :



A solution of 1-mesityl-1*H*-imidazole (100 mg, 0.54mmol, 1 eq) was reacted with chlorodiisopropylphosphine (86 mg, 0.56mmol, 1.05eq) to afford 97 mg (60 %) of the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.40 (m, 1H), 6.96-6.95 (m, 3H), 2.33 (s, 3H), 2.28-2.21 (m, 2H), 1.97 (s, 6H), 1.09-1.03(m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 147.3, 138.8, 135.2, 134.1, 131.0, 129.1, 122.9, 24.5, 24.4, 21.2, 20.4, 20.3, 19.8, 19.7, 18.4, 18.3. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -12.5.

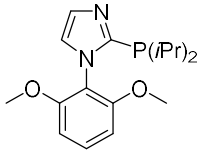
2-(dicyclohexylphosphanyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole **2.L^{43}** :



A solution of 1-(2,6-dimethoxyphenyl)-1*H*-imidazole (250 mg, 1.22 mmol, 1 eq) was reacted with chlorodicyclohexylphosphine (298 mg, 1.28 mmol, 1.05 eq) to afford 260 mg (53 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.40 (m, 1H), 7.38-7.34 (m, 1H), 6.97 (m, 1H), 6.63-6.61 (m, 2H), 3.73 (s, 3H), 2.08-2.03 (m, 2H), 1.69-1.61 (m, 10H), 1.28-1.14 (m, 10H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 156.1, 148.3, 148.2, 130.4, 130.2, 123.3, 116.0, 103.8, 55.6, 33.8, 33.7, 30.1, 29.9, 29.3, 29.2, 27.4, 27.3, 27.2, 27.1, 26.6. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -22.9.

2-(diisopropylphosphanyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole **2.L^{44}** :

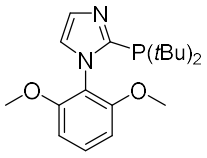


A solution of 1-(2,6-dimethoxyphenyl)-1*H*-imidazole (300 mg, 0.1.47 mmol, 1 eq) was reacted with chlorodiisopropylphosphine (236 mg, 0.1.54 mmol, 1.05 eq) to afford 310 mg (66 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.39-7.34 (m, 2H), 6.99-6.98 (m, 1H), 6.64-6.62 (m, 2H), 3.72 (s, 6H), 2.30-2.19 (m, 2H), 1.04-0.96 (m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz)**

:δ = 156.2, 130.4, 130.3, 123.5, 103.9, 55.7, 24.6, 24.50, 19.9, 19.7, 19.4, 19.3.. **^{31}P-{^{1}H} NMR (CDCl$_3$, 162 MHz) :**δ = -14.3.**HRMS (ESI) m/z:** $C_{17}H_{25}N_2O_2PH$ ([M + H]$^+$): 321.1726; found: 321.1725. **IR neat (υ/cm^{-1}) :** 2959, 2841, 2359, 1593, 1477, 1257, 1103, 986.**M.p :** 76°C

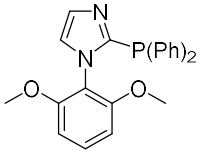
2-(di-*ter*t-butylphosphanyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole**2.L**[45] :



A solution of 1-(2,6-dimethoxyphenyl)-1*H*-imidazole (50 mg, 0.24 mmol, 1 eq) was reacted with chlorodi-*tert*-butylphosphine (44 mg, 0.24 mmol, 1 eq) to afford 61 mg (70 %) of the title compound as a white solid.

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.41-7.40 (m, 1H), 7.37-7.33 (m, 1H) 6.97-6.96 (m, 1H), 6.62-6.60 (m, 2H), 3.70 (s, 6H), 1.20-1.17 (m, 18H). **^{13}C-{^{1}H} NMR (CDCl$_3$, 100 MHz) :**δ =156.2, 148.6, 148.4, 130.2, 129.8, 123.7, 103.8, 55.4, 33.3, 33.1, 30.4, 30.3.. **^{31}P-{^{1}H} NMR (CDCl$_3$, 162 MHz) :**δ = 8.0.

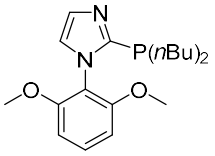
1-(2,6-dimethoxyphenyl)-2-(diphenylphosphanyl)-1*H*-imidazole**2.L**[46] :



A solution of 1-(2,6-dimethoxyphenyl)-1*H*-imidazole (150 mg, 0.74mmol, 1 eq) was reacted with chlorodiphenylphosphine (170 mg, 0.77mmol, 1.05 eq) to afford 150 mg (53 %) of the title compound as a white solid.

^{1}H NMR (CDCl$_3$, 400 MHz) :δ = 7.46-7.62 (m, 5H), 7.37-7.26 (m, 7H), 7.07-7.06 (m, 1H), 6.60-6.58 (m, 2H), 3.52 (s, 6H). **^{13}C-{^{1}H} NMR (CDCl$_3$, 100 MHz):**δ = 156.3, 147.79, 147.78, 136.6, 136.5, 133.9, 133.7, 131.34, 131.32, 130.4, 128.6, 128.3, 128.2, 124.10, 124.09, 104.1, 55.7. **^{31}P-{^{1}H} NMR (CDCl$_3$, 162 MHz) :**δ = -30.5.

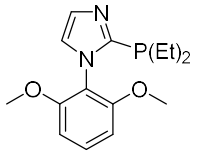
2-(dibutylphosphanyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole**2.L**[47] :



A solution of 1-(2,6-dimethoxyphenyl)-1*H*-imidazole (70 mg, 0.34 mmol, 1 eq) was reacted with chlorodibutylphosphine (62 mg, 0.34 mmol, 1 eq) to afford 68 mg (57 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.39-7.34 (m, 2H), 6.96-6.95 (m, 1H), 6.65-6.633 (m, 2H), 3.74 (s, 6H), 1.95-1.87 (m, 2H), 1.63-1.56 (m, 2H), 1.33-1.22 (m, 8H), 0.83 (t, *J* = 7.05 Hz, 6H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 156.2, 150.7, 150.6, 130.3, 130.1, 123.2, 115,8, 103.8, 55.7, 28.2, 28.1, 27.3, 27.3, 24.3, 24.2, 13.9. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -46.0.

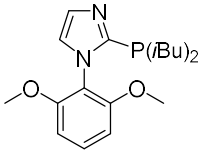
2-(diethylphosphanyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole **2.L**[48] :



A solution of 1-(2,6-dimethoxyphenyl)-1*H*-imidazole (50 mg, 0.24 mmol, 1 eq) was reacted with chlorodiethylphosphine (30 mg, 0.24 mmol, 1 eq) to afford 40 mg (56 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.39-7.36 m, 2H), 6.98-6.97 (m, 1H), 6.66-6.64 (m, 2H), 3.75 (s, 3H), 1.91-1.84 (m, 2H), 1.65-1.56 (m, 2H), 0.99-0.91 (m, 6H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 156.4, 150.3, 130.4, 130.4, 123.6, 115.9, 104.1, 55.9, 19.9, 19.80, 10.1, 9.9. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -37.0.

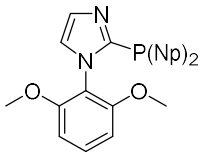
2-(diisobutyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole **2.L**[49]:



A solution of 1-(2,6-dimethoxyphenyl)-1*H*-imidazole (50 mg, 0.24 mmol, 1 eq) was reacted with chlorodiisobutylphosphine (44.1 mg, 0.24 mmol, 1 eq) to afford 45 mg (53 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.39-7.34 (m, 2H), 6.95-6.94 (m, 1H), 6.65-6.63 (m, 2H), 3.74 (s, 3H), 2.01-1.95 (m, 2H), 1.55-1.43 (m, 4H), 0.86-0.85 (m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 156.3, 151.5, 151.4, 130.4, 130.3, 123.2, 115.8, 103.9, 55.8, 39.0, 38.9, 26.4, 26.3, 24.5, 24.4, 24.0, 23.9. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -55.3.

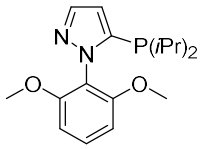
2-(dineopentyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole **2.L**[50] :



A solution of 1-(2,6-dimethoxyphenyl)-1*H*-imidazole (50 mg, 0.24 mmol, 1 eq) was reacted with chlorodineopentylphosphine (56 mg, 0.24 mmol, 1 eq) to afford 46 mg (50 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.38-7.34 (m, 1H), 7.32 (m, 1H), 6.93 (m, 1H), 6.64-6.62 (m, 2H), 3.74 (s, 3H), 2.15-2.10 (m, 2H), 1.57-1.53 (m, 2H), 0.84 (s, 18H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 156.4, 152.7, 152.6, 130.2, 130.1, 123.2, 115.8, 103.9, 55.8, 44.4, 44.3, 31.4, 31.2, 30.7, 30.6. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -64.0.

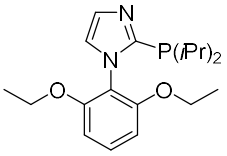
5-(diisopropylphosphanyl)-1-(2,6-dimethoxyphenyl)-1H-pyrazole**2.L**[51]:



A solution of 1-(2,6-dimethoxyphenyl)-1*H*-pyrazole (100 mg, 0.49mmol, 1 eq) was reacted with chlorodiisopropylphosphine (79 mg, 0.52mmol, 1.05 eq) to afford 45 mg (29 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.83 (m, 1H), 7.40-7.35 (m, 1H), 6.63-6.61 (m, 2H), 6.54 (m, 1H), 3.71 (s, 3H), 2.02-1.95 (m, 2H), 1.02-0.94 (m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ =156.9, 141.6, 141.4, 140.37, 140.35, 130.7, 118.5, 111.41, 111.37, 103.8, 55.7, 24.23, 24.15, 19.7, 19.5, 18.9, 18.8.**^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -17.7.

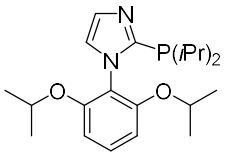
1-(2,6-diethoxyphenyl)-2-(diisopropylphosphanyl)-1*H*-imidazole**2.L**[52] :



A solution of 1-(2,6-diethoxyphenyl)-1*H*-imidazole (200 mg, 0.86 mmol, 1 eq) was reacted with chlorodiisopropylphosphine (138 mg, 0.90 mmol, 1.05 eq) to afford 234 mg (78 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.35 (m, 1H), 7.33-7.28 (m, 1H), 6.96-6.95 (m, 1H), 6.60-6.58 (m, 2H), 4.00-3.93 (m, 4H), 2.28-2.21 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 6H), 1.4-0.98 (m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 155.7, 148.4, 148.2, 130.04, 129.97, 123.7, 116.3, 104.4, 64.0, 24.6, 24.5, 19.9, 19.8, 19.69, 19.68, 14.6. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -14.4.

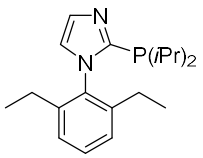
1-(2,6-diisopropoxyphenyl)-2-(diisopropylphosphanyl)-1H-imidazole**2.L**[53]:



A solution of 1-(2,6-diisopropoxyphenyl)-1*H*-imidazole (100 mg, 0.38 mmol, 1 eq) was reacted with chlorodiisopropylphosphine (62 mg, 0.40mmol, 1.05 eq) to afford 93 mg (65 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.25 (m, 1H), 7.22-7.18 (m, 1H), 6.81-6.80 (m, 1H), 6.52-6.50 (m, 2H), 4.40 (sept, *J* = 5.9 Hz, 2H), 2.24-2.13 (m, 2H), 1.16 (d, *J* = 6.1 Hz, 6H), 1.06 (d, *J* = 6.1 Hz, 6H), 1.00-0.93 (m, 12 H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 155.0, 148.7, 148.6, 129.8, 129.7, 123.6, 118.2, 105.9, 71.0, 24.7, 24.6, 22.13, 22.06, 20.2, 20.1, 20.0, 19.9. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -14.1.

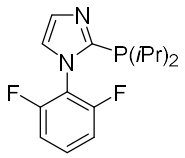
1-(2,6-diethylphenyl)-2-(diisopropylphosphanyl)-1*H*-imidazole**2.L**[54] :



A solution of 1-(2,6-diethylphenyl)-1*H*-imidazole (100 mg, 0.5mmol, 1 eq) was reacted with chlorodiisopropylphosphine (80 mg, 0.52mmol, 1.05 eq) to afford 68 mg (43 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.74-7.70 (m, 2H), 7.55-7.54 (m, 2H), 7.35-7.34 (m, 1H), 2.72-2.44 (m, 6H), 1.46 (t, *J* = 7.5 Hz, 6H), 1.41-1.36 (m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 148,0 , 147.9, 141.4, 135.2, 130.7, 129.5, 126.3, 123.8, 24.49, 24.46, 24.4, 24.3, 20.4, 20.3, 19.7, 19.6, 15.1. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -13.1.

1-(2,6-difluorophenyl)-2-(diisopropylphosphanyl)-1H-imidazole **2.L**[55] :



A solution of 1-(2,6-difluorophenyl)-1H-imidazole (100 mg, 0.56 mmol, 1 eq) was reacted with chlorodiisopropylphosphine (89 mg, 0.58 mmol, 1.05 eq) to afford 90 mg (55 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.46-7.39 (m, 2H), 7.09-7.03 (m, 3H), 2.32-2.22 (m, 2H), 1.03-0.97 (m, 12H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 159.4, 156.9, 149.1, 148.9, 131.4, 130.7, 130.6, 130.5, 123.2, 116.3, 112.2, 112.00, 111.97, 24.6, 24.4, 19.9, 19.7, 19.2, 19.1. **^{31}P-{^{1}H} NMR ($CDCl_3$, 162 MHz) :**δ = -13.9, -14, -14.1.**^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz) :** δ = -117.29, -117.35.

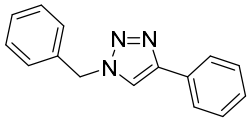
5.4. Atroposelective Csp^2-H arylation

*Preparation of triazoles **3.1a-g***

General procedure :

The alkyne (1 eq) and the azide (1 eq) were suspended in a 1:1 mixture of water and *t*BuOH (1 mol/L). Sodium ascorbate (10 %mol) was added, followed by $CuSO_4.5H_2O$ (1 %mol). The heterogeneous mixture was vigorously stirred at 80°C for 15 h. The reaction mixture was cooled down and ice-cold water was added to dilute the mixture by 2. In the case that precipitation occurred, the product was collected by filtration, washed with cold water and dried under vacuum. Int the case that no precipitation occurred, the mixture was extracted with EtOAc (3x). The combined organic phase was dried over $MgSO_4$. After filtration and evaporation of the volatile, the residue was purified by column chromatography (EtOAc/Cyclohexane) to afford the desired triazole.

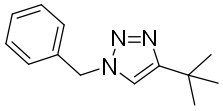
1-benzyl-4-phenyl-1*H*-1,2,3-triazole**3.1a** :



Phenylacetylene (3.2 mL, 29.2 mmol) and benzylazide (3.6 mL, 29.2 mmol) were reacted. Filtration of the precipitate gave 5.8 g (84%) of the desired triazole as a white solid. The analytical data were consistent with those reported in the literature.[166]

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.81-7.78 (m, 2H), 7.66 (s, 1H), 7.42-7.29 (m, 8H), 5.57 (s, 2H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 148.4, 134.8, 130.7, 129.3, 128.9, 128.3, 128.2, 125.8, 119.6, 54.4.

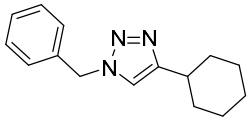
1-benzyl-4-(tert-butyl)-1*H*-1,2,3-triazole**3.1b** :



3,3-dimethyl-1-butyne (0.6 mL, 5.0 mmol) and benzylazide (0.6 mL, 5 mmol) were reacted. Purification of the crude residue by column chromatography (EtOAc/Cyclohexane 10:90 to 50:50) afforded 660 mg (61%) of the desired triazole as a white solid. The analytical data were consistent with those reported in the literature.[167]

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.30-7.28 (m, 3H), 7.20-7.13 (m, 3H), 5.40 (s, 1H), 1.25 (s, 9H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 135.2, 129.1, 128.7, 128.1, 54.1, 31.0, 30.4.

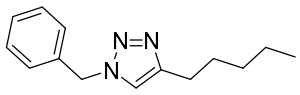
1-benzyl-4-cyclohexyl-1*H*-1,2,3-triazole**3.1c** :



Cyclohexaneacetylene (0.65 mL, 5.0 mmol) and benzylazide (0.6 mL, 5 mmol) were reacted. Purification of the crude residue by column chromatography (EtOAc/Cyclohexane 10:90 to 50:50) afforded 1.03 g (86%) of the desired triazole as a white solid. The analytical data were consistent with those reported in the literature.[168]

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.30-7.24 (m, 3H), 7.19-7.16 (m, 3H), 5.40 (s, 1H), 2.68 (br. s., 1H), 1.97 (br. s., 2H), 1.70-1.61 (m, 3H), 1.30 (br. s., 1H), 1.16 (br. s., 1H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 135.1, 129.1, 128.6, 128.1, 54.2, 35.4, 33.0, 26.2, 24.1.

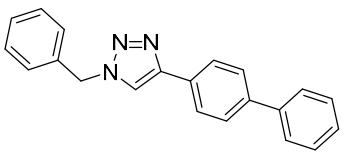
1-benzyl-4-pentyl-1*H*-1,2,3-triazole **3.1d** :



1-Heptyne (0.66 mL, 5.0 mmol) and benzylazide (0.6 mL, 5 mmol) were reacted. Purification of the crude residue by column chromatography (EtOAc/Cyclohexane 10:90 to 50:50) afforded 875 mg (75%) of the desired triazole as a white solid. The analytical data were consistent with those reported in the literature.[169]

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.37-7.30 (m, 3H), 7.24-7.22 (m, 2H), 7.18 (m, 1H), 5.47 (s, 2H), 2.68-2.64 (m, 2H), 1.66-1.59 (m, 2H), 1.34-1.27 (m, 4H), 0.88-0.84 (m, 3H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 149.0, 135.1, 129.1, 128.6, 128.0, 120.6, 54.0, 31.5, 29.2, 25.8, 22.5, 14.1.

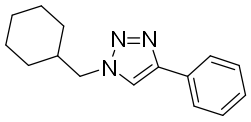
4-([1,1'-biphenyl]-4-yl)-1-benzyl-1*H*-1,2,3-triazole **3.1e** :



4-Ethynylbiphenyl (0.40 g, 2.25 mmol) and benzylazide (0.28 mL, 2.25 mmol) were reacted. Purification of the crude residue by column chromatography (EtOAc/Cyclohexane 10:90 to 50:50) afforded 250 mg (36%) of the desired triazole as a white solid. The analytical data were consistent with those reported in the literature.[170]

^{1}H NMR ($CDCl_3/C_6D_6$10:1, 400 MHz) :**δ = 8.12-8.10 (m, 2H), 7.87-7.82 (m, 4H), 7.77 (br. s., 1H), 7.66-7.63 (m, 2H), 7.57-7.54 (m, 4H), 7.47-7.45 (m, 2H), 5.66 (s, 1H). **^{13}C-{^{1}H} NMR ($CDCl_3$/MeOH10:1, 100 MHz) :δ = 141.0, 140.2, 134.4, 128.9, 128.8, 128.6, 127.9, 127.3, 126.7, 125.9, 120.1, 54.1.

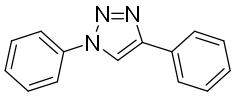
1-(cyclohexylmethyl)-4-phenyl-1*H*-1,2,3-triazole **3.1f** :



Phenylacetylene (0.8 mL, 7.2 mmol) and (azidomethyl)cyclohexane (1.0 g, 7.2 mmol) were reacted. Filtration of the precipitate gave 1.6 g (92%) of the desired triazole as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :δ = 7.84-7.81 (m, 2H), 7.71 (s, 1H), 7.43-7.39 (m, 2H), 7.34-7.29 (m, 1H), 4.20 (d, *J* = 7.2 Hz, 2H), 1.96-1.86 (m, 1H), 1.75-1.64 (m, 4H), 1.32-1.10 (m, 4H), 1.05-0.96 (m, 2H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :**δ = 147.6, 130.8, 128.9, 128.1, 125.8, 120.13, 56.6, 38.9, 30.6, 26.2, 25.6.**HRMS (ESI) m/z :** calcd. for $C_{15}H_{19}N_3H$ ([M + H]$^+$): 242.1652; found: 242.1652.**IR neat (υ/cm^{-1}) :** 3345,2923, 2361, 1447, 1222.**M.p :** 111°C

1,4-diphenyl-1*H*-1,2,3-triazole **3.1g**:



Phenylacetylene (0.28 mL, 2.5 mmol) and azidobenzene (~ 0.5 M in toluene, 5 mL, 2.5 mmol) were reacted. Purification of the crude residue by column chromatography (EtOAc/Cyclohexane 10:90 to 50:50) afforded 150 mg (27%) of the desired triazole as a white solid. The analytical data were consistent with those reported in the literature.[158]

^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) :δ = 8.12 (s, 1H), 7.85-7.82 (m, 2H), 7.73-7.70 (m, 2H), 7.49-7.44 (m, 2H), 7.40-7.33 (m, 3H), 7.31-7.25 (m, 1H). **^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz, rotamers) :**δ = 148.6,137.2, 1300.3, 129.9, 129.1, 128.9, 128.6, 126.0, 120.7, 117.8.

Procedure for the arylation reactions

A: Arylation in racemic fashion :

A Pyrex glass tube equipped with a stir bar was charged with the triazole (0.15 mmol, 1 eq) and the aryl bromide (0.225 mmol, 1.5 eq). The tube was introduced in an argon filled glove-box, and Pd_2dba_3 (3.43 mg, 3.75 µmol, 2.5 %mol), the ligand (10 %mol), PivOH (4.6 mg, 45 µmol, 30 %mol), Cs_2CO_3 (73.3 mg, 0.225, 1.5 eq), and the molecular sieves 4Å (50 mg) were loaded in the tube. The tube was sealed with a septum and taken out of the glovebox. Under an argon atmosphere, mesitylene (0.3 mL, 0.5 M) was added. The mixture was stirred at 20 °C for 1 min, and the septum was quickly removed and replaced with a phenolic screw cap before the tube was heated at 150°C for 18h in an aluminium block. After this time, the reaction mixture was diluted with ethyl acetate (1.5 mL), and was quenched with sat. aq. NH_4Cl (1.5 mL). The organic layer was removed and the aqueous fraction was extracted with ethyl acetate (3x1.5 mL). The combined organic layer was dried under vacuum. The residue was diluted with $CDCl_3$ (1.5 mL) and the NMR reference was added (75 µmol of trichloroethylene, equivalent to 50% of the possible maximum yield) in order to evaluate the NMR yield. After measurement, the crude fraction was recombined and dried under vacuum. The crude residue was purified by column chromatography (EtOAc/Cyclohexane 10:90 to 50:50) to afford a racemic sample of the biaryl product for HPLC analysis.

B : Enantioselective arylation with the (*R*)-MOP :

A Pyrex glass tube equipped with a stir bar was charged with the triazole (0.15 mmol, 1 eq) and the aryl bromide (0.225 mmol, 1.5 eq). The tube was introduced in an argon filled glove-box, and Pd_2dba_3 (3.43 mg, 3.75 µmol, 2.5 %mol), the MOP **3.L**[69] (7.0 mg, 15 µmol, 10 %mol), PivOH, Cs_2CO_3 (73.3 mg, 0.225 mmol, 1.5 eq), and the molecular sieves 4Å (50 mg) were loaded in the tube. The tube was sealed with a septum and taken out of the glovebox. Under an argon atmosphere, xylenes (0.3 mL, 0.5 M) were added, followed by addition of hexanoic acid (5.6 µL, 45 µmol, 30 %mol. The mixture was stirred at 20 °C for 1 min, and the septum was quickly removed and replaced with a phenolic screw cap before the tube was heated at 140°C for 2h in an aluminium block. After this time, the reaction tube was rapidly cooled down by immersion in fresh water for 1 min. The reaction mixture was diluted with ethyl acetate (1.5 mL), and was quenched with sat. aq. NH_4Cl (1.5 mL). The organic layer was removed and the aqueous fraction was extracted with ethyl acetate (3x1.5 mL). The combined organic layer was dried under vacuum. The residue was diluted with $CDCl_3$ (1.5

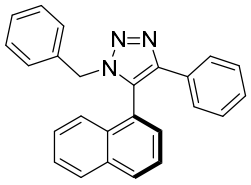
mL) and the NMR reference was added (75 µmol of trichloroethylene, equivalent to 50% of the possible maximum yield) in order to evaluate the NMR yield. After measurement, the crude fraction was recombined and dried under vacuum. The crude residue was purified by column chromatography (EtOAc/Cyclohexane 10:90 to 50:50) to afford an enantioenriched sample of the biaryl product for HPLC analysis.

C :Enantioselective arylation with the (*R*)-bifunctionnal ligand :

A Pyrex glass tube equipped with a stir bar was charged with the triazole (0.15 mmol, 1 eq) and the aryl bromide (0.225 mmol, 1.5 eq). The tube was introduced in an argon filled glove-box, and Pd_2dba_3 (3.43 mg, 3.75 µmol, 2.5 %mol), the bifunctionnal ligand (15 µmol, 10 %mol), Cs_2CO_3 (73.3 mg, 0.225 mmol, 1.5 eq), and the molecular sieves 4Å (50 mg) were loaded in the tube. The tube was sealed with a septum and taken out of the glovebox. Under an argon atmosphere, xylenes (0.3 mL, 0.5 M) were added. The mixture was stirred at 20 °C for 1 min, and the septum was quickly removed and replaced with a phenolic screw cap before the tube was heated at 140°C for 2h in an aluminium block. After this time, the reaction tube was rapidly cooled down by immersion in fresh water for 1 min. The reaction mixture was diluted with ethyl acetate (1.5 mL), and was quenched with sat. aq. NH_4Cl (1.5 mL). The organic layer was removed and the aqueous fraction was extracted with ethyl acetate (3x1.5 mL). The combined organic layer was dried under vacuum. The residue was diluted with $CDCl_3$ (1.5 mL) and the NMR reference was added (75 µmol of trichloroethylene, equivalent to 50% of the possible maximum yield) in order to evaluate the NMR yield. After measurement, the crude fraction was recombined and dried under vacuum. The crude residue was purified by column chromatography (EtOAc/Cyclohexane 10:90 to 50:50) to afford an enantioenriched sample of the biaryl product for HPLC analysis.

*Arylation products **3.2a-c***

1-benzyl-5-(naphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazole**3.2a**:

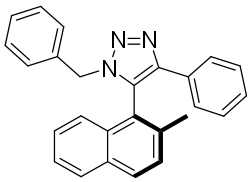


General procedure A : 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (35.5 mg) was reacted with 1-Br-naphtalene (31 µL) in presence of PCy_3 (4.2 mg) in DME (instead of mesitylene) to afford

42% NMR yield of the title compound. The purification of the crude gave a fraction of the racemic product for HPLC analysis and configurational stability evaluation. The analytical data were consistent with those reported in the literature.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ = 8.02-8.00 (m, 1H), 7.94-7.92 (m, 2H), 7.52-7.46 (m, 4H), 7.30-7.28 (m, 1H), 7.22-7.19 (m, 2H), 7.16-7.05 (m, 6H) 6.81-6.79 (m, 2H), 5.38 (d, *J* = 14.9 Hz, 1H), 5.09 (d, *J* = 14.9 Hz, 1H).. **HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25°C, t_R24.3 min and t_R 27.7 min.*e.r.* = 0:0 (racemizes under 1 day at 25°C).

1-benzyl-5-(2-methylnaphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazole**3.2b** :



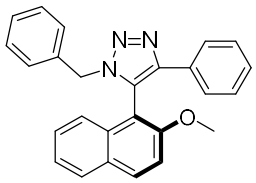
General procedure A : 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (35.5 mg) was reacted with 1-Br-2-Me-naphtalene (35 µL) in presence of PCy_3 (4.2 mg) to afford 35% NMR yield of the title compound. The purification of the crude gave a fraction of the racemic product for HPLC analysis and configurational stability evaluation.

General procedure B : 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (35.5 mg) was reacted with 1-Br-2-Me-naphtalene (35 µL) to afford 65% NMR yield of the title compound. The purification of the crude gave a fraction of the enantioenriched product that was 75:25 *e.r.*.

General procedure C : 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (35.5 mg) was reacted with 1-Br-2-Me-naphtalene (35 µL) in presence of **3.L**[73]to afford 63% NMR yield of the title compound. The purification of the crude gave a fraction of the enantioenriched product that was 77.5:22.5 *e.r.*.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ = 7.95-7.91 (m, 2H), 7.50-7.47 (m, 3H), 7.35-7.30 (m, 2H), 7.16-7.05 (m, 7H), 6.76-6.74 (m, 2H), 5.40 (d, *J* = 14.6 Hz, 1H), 4.87 (d, *J* = 14.6 Hz, 1H), 1.66 (s, 3H). **HPLC separation conditions :** Chiralpak IC column, *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25°C, t_R16.3 min for the major enantiomer and t_R 28.7 min for the minor enantiomer.

1-benzyl-5-(2-methoxynaphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazole**3.2c** :



General procedure A : 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (35.5 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of PCy_3 (4.2 mg) to afford 40% NMR yield of the title compound. The purification of the crude gave a fraction of the racemic product for HPLC analysis.

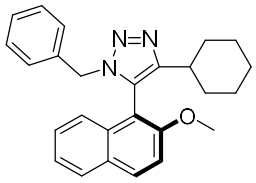
General procedure B : 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (35.5 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) to afford >95% NMR yield of the title compound. The purification of the crude gave 50 mg (85%) of the enantioenriched product that was 70:30 *e.r.*.

General procedure C : 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (35.5 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of **3.L**[73]to afford >95% NMR yield of the title compound. The purification of the crude gave a fraction of the enantioenriched product that was 73:27 *e.r.*.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ = 8.18-8.16 (m, 1H), 8.00-7.98 (m, 1H), 7.71-7.69 (m, 2H), 7.50-7.47 (m, 1H), 7.72-7.37 (m, 2H), 7.31-7.29 (m, 3H), 7.24-7.17 (m, 4H), 6.96-6.95 (m, 1H), 5.48 (d, *J* = 14.9 Hz, 1H), 5.23 (d, *J* = 14.9 Hz, 1H), 3.69 (s, 3H).**^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) :** δ = 155.9, 146.0, 134.9, 133.1, 132.5, 131.5128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 126.0, 124.3, 123.6, 112.8, 109.7, 56.0, 52.6. **HPLC separation conditions :** Chiralpak IA column, *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25°C, t_R16.3 min for the major enantiomer and t_R 28.7 min for the minor enantiomer.**HRMS (ESI) m/z :** calcd. for $C_{26}H_{21}N_3OH$ ($[M + H]^+$): 392.1757; found: 392.1753.**IR neat (υ/cm^{-1}) :** 3324, 2973, 1691, 2361, 1453, 1269, 1046.**M.p :** 175°C

*Arylation products **3.3b-e***

1-benzyl-4-cyclohexyl-5-(2-methoxynaphthalen-1-yl)-1*H*-1,2,3-triazole**3.3b**:

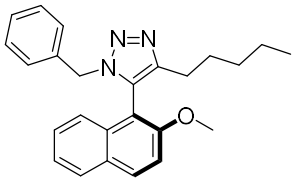


General procedure A : 1-benzyl-4-cyclohexyl-1*H*-1,2,3-triazole (36.2 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of PCy_3 (4.2 mg) to afford 28% NMR yield of the title compound. The purification of the crude gave a fraction of the racemic product for HPLC analysis.

General procedure C : 1-benzyl-4-cyclohexyl-1*H*-1,2,3-triazole (36.2 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of **3.L**[73]to afford 22% NMR yield of the title compound. The purification of the crude gave a fraction of the enantioenriched product that was 44.5:55.5 *e.r.*.

^{1}H NMR ($CDCl_3$, 400 MHz), characteristic peaks : δ = 6.90-6.86 (m, 2H), 5.40 (d, *J* = 14.8 Hz, 1H), 5.14 (d, *J* = 14.8 Hz, 1H), 3.70 (s, 3H).**HPLC separation conditions :** Chiralpak IA column, *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25°C, t_R14.9 min for the minor enantiomer and t_R 19.9 min for the major enantiomer.

1-benzyl-5-(2-methoxynaphthalen-1-yl)-4-pentyl-1H-1,2,3-triazole**3.3c**:

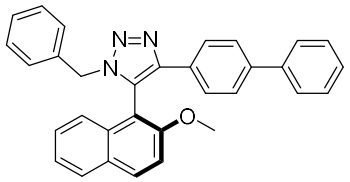


General procedure A : 1-benzyl-4-pentyl-1*H*-1,2,3-triazole (34.4 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of PCy_3 (4.2 mg) to afford 76% NMR yield of the title compound. The purification of the crude gave a fraction of the racemic product for HPLC analysis.

General procedure C : 1-benzyl-4-pentyl-1*H*-1,2,3-triazole (34.4 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of **3.L**[73]to afford 95% NMR yield of the title compound. The purification of the crude gave a fraction of the enantioenriched product that was 46:54 *e.r.*.

^{1}H NMR ($CDCl_3$, 400 MHz), characteristic peaks : δ = 6.93-6.1 (m, 2H), 5.42 (d, *J* = 14.9 Hz, 1H), 5.26 (d, *J* = 14.9 Hz, 1H), 3.76 (s, 3H).**HPLC separation conditions :** Chiralpak IA column, *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25°C, t_R14.1 min for the minor enantiomer and t_R 15.5 min for the major enantiomer.

4-([1,1'-biphenyl]-4-yl)-1-benzyl-5-(2-methoxynaphthalen-1-yl)-1*H*-1,2,3-triazole**3.3d**:

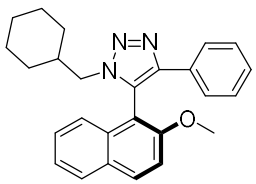


General procedure A : 4-([1,1'-biphenyl]-4-yl)-1-benzyl-1*H*-1,2,3-triazole (46.7 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of PCy_3 (4.2 mg) to afford 37% NMR yield of the title compound. The purification of the crude gave a fraction of the racemic product for HPLC analysis.

General procedure C : 4-([1,1'-biphenyl]-4-yl)-1-benzyl-1*H*-1,2,3-triazole (46.7 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of **3.L**[73]to afford 95% NMR yield of the title compound. The purification of the crude gave a fraction of the enantioenriched product that was 72:28 *e.r.*.

^{1}H NMR ($CDCl_3$, 400 MHz), characteristic peaks : δ = 6.79-6.77 (m, 2H), 5.29 (d, *J* = 14.9 Hz, 1H), 5.05 (d, *J* = 14.9 Hz, 1H), 3.48 (s, 3H).**HPLC separation conditions :** Chiralpak IA column, *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25°C, t_R71.9 min for the major enantiomer and t_R 77.9 min for the minor enantiomer.

1-(cyclohexylmethyl)-5-(2-methoxynaphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazole**3.3e** :



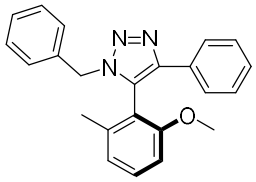
General procedure A : 1-(cyclohexylmethyl)-4-phenyl-1*H*-1,2,3-triazole (36.2 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of PCy_3 (4.2 mg) to afford % NMR yield of the title compound. The purification of the crude gave a fraction of the racemic product for HPLC analysis.

General procedure C : 1-(cyclohexylmethyl)-4-phenyl-1*H*-1,2,3-triazole (36.2 mg) was reacted with 1-Br-2-OMe-naphtalene (53.3 mg) in presence of **3.L**[73]to afford >70% NMR yield of the title compound. The purification of the crude gave a fraction of the enantioenriched product that was 75.5:24.5 *e.r.*.

^{1}H NMR ($CDCl_3$, 400 MHz), characteristic peaks : δ = 4.01 (dd, *J* = 13.6 Hz, *J* = 7.5 Hz, 1H), 3.96-3.90 (m, 4H).**HPLC separation conditions :** Chiralpak IA column, *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25°C, t_R34.2 min for the major enantiomer and t_R 36.9 min for the minor enantiomer.

*Arylation product **3.2d***

1-benzyl-5-(2-methoxy-6-methylphenyl)-4-phenyl-1H-1,2,3-triazole**3.2d**:



General procedure A : 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (35.5 mg) was reacted with 2-bromo-1-methoxy-3-methylbenzene (45.2 mg) in presence of PCy_3 (4.2 mg) to afford 21% NMR yield of the title compound. The purification of the crude gave a fraction of the racemic product for HPLC analysis.

General procedure C : 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (35.5 mg) was reacted with 2-bromo-1-methoxy-3-methylbenzene (45.2 mg) in presence of **3.L**[73]to afford 68% NMR yield of the title compound. The purification of the crude gave a fraction of the enantioenriched product that was 53.5:46.5 *e.r.*.

^{1}H NMR ($CDCl_3$, 400 MHz), characteristic peaks : δ = 5.58 (d, *J* = 14.7 Hz, 1H), 5.32 (d, *J* = 14.7 Hz, 1H), 3.76 (s, 3H), 1.71 (s, 3H).**HPLC separation conditions :** Chiralpak IA column, *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25°C, t_R16.0 min for the major enantiomer and t_R 18.4 min for the minor enantiomer.

6. References

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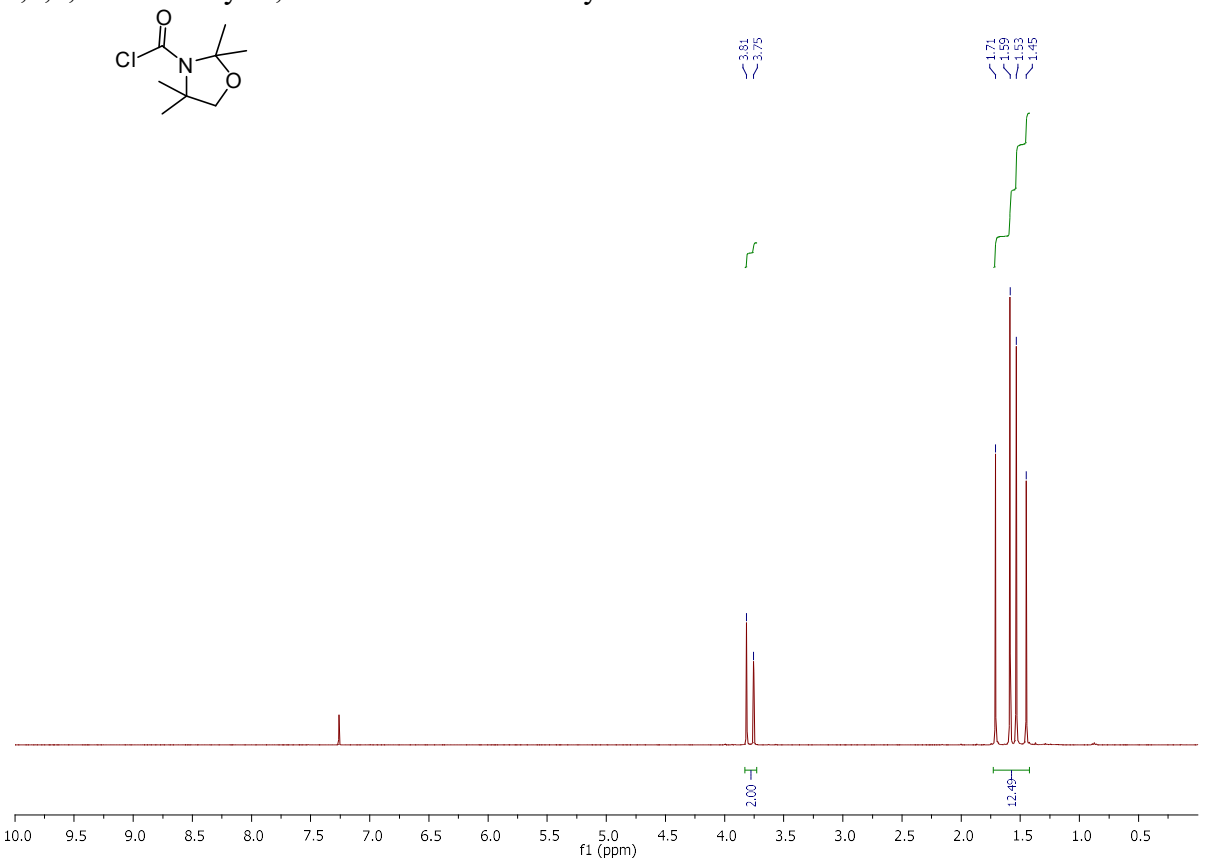
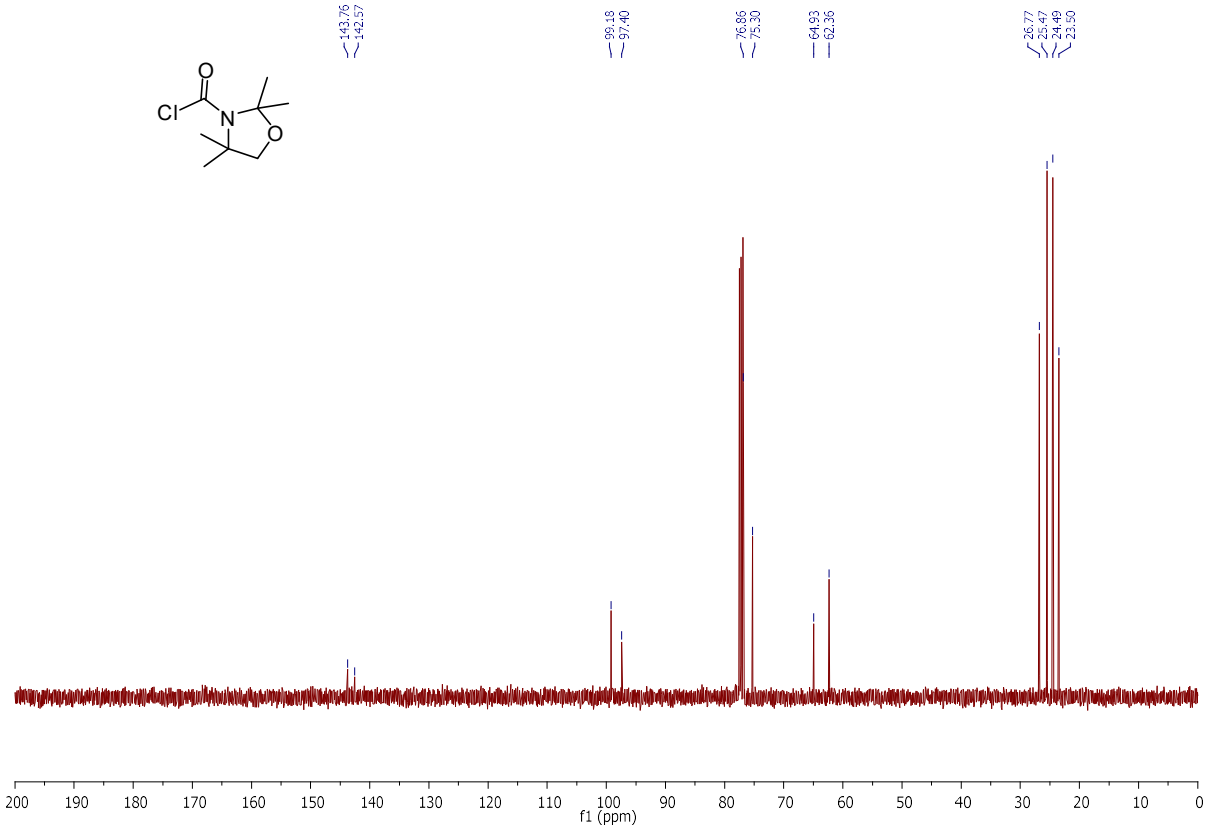
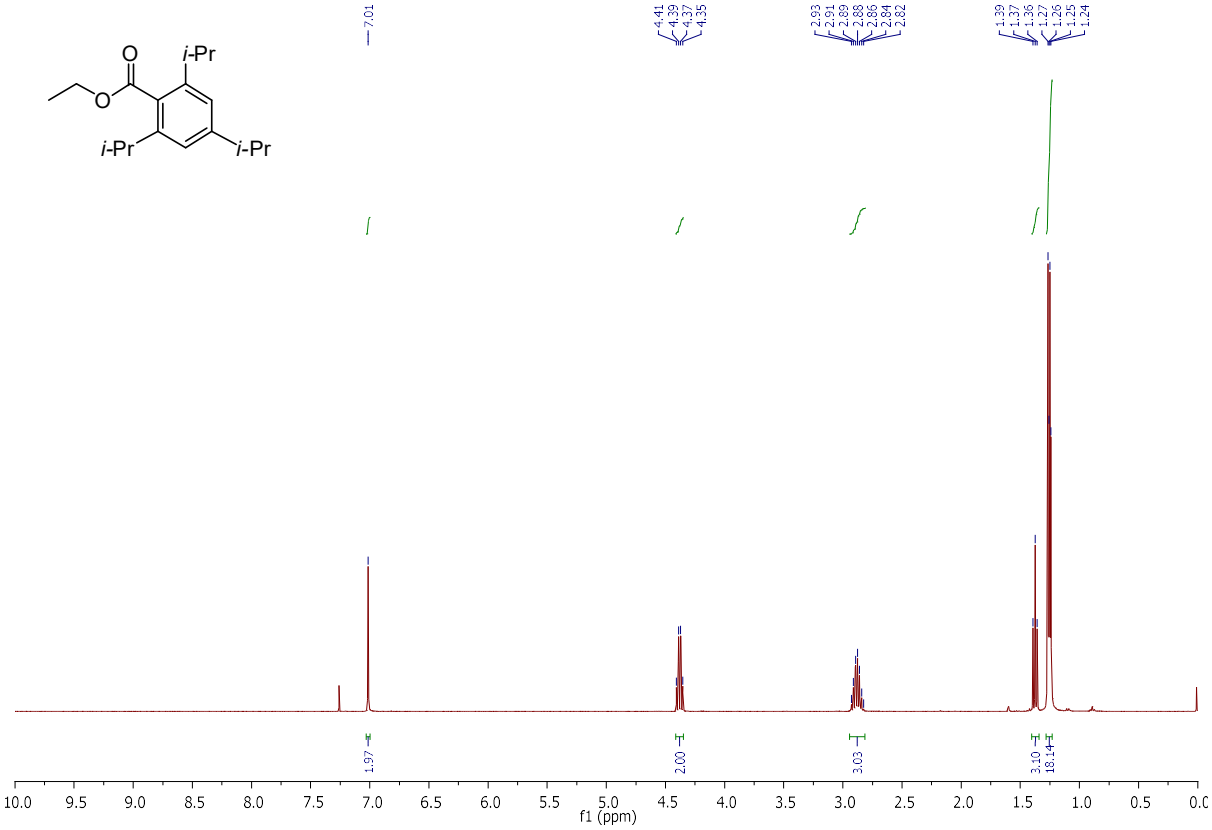
7. NMR Spectra and HPLC chromatograms

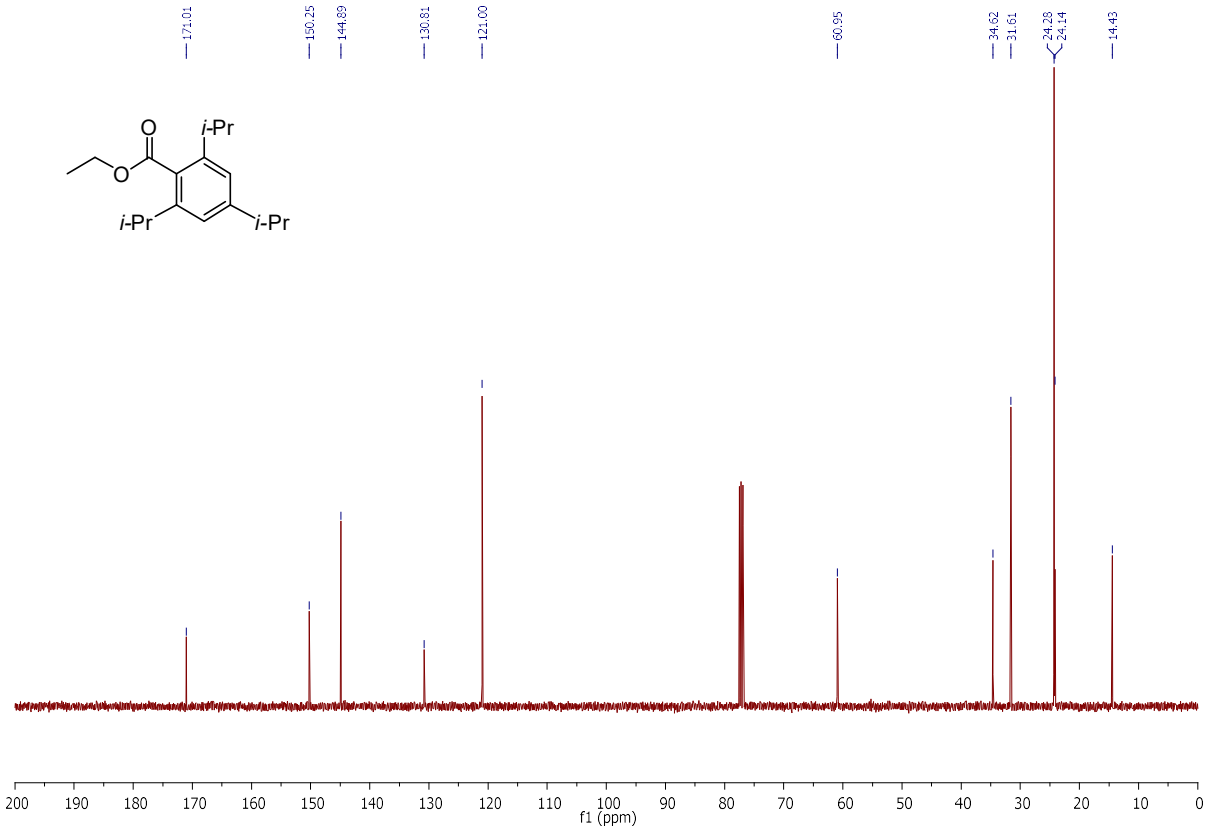
2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl chloride **S1** :



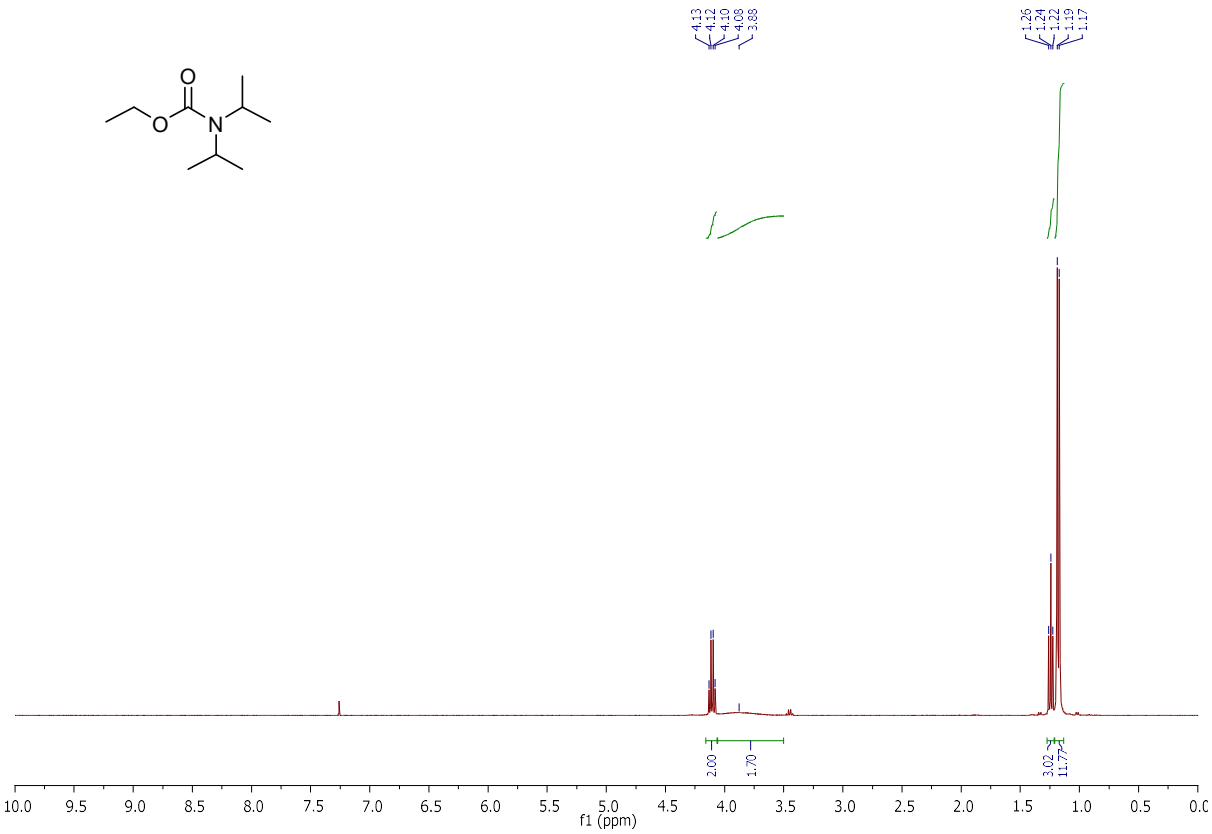


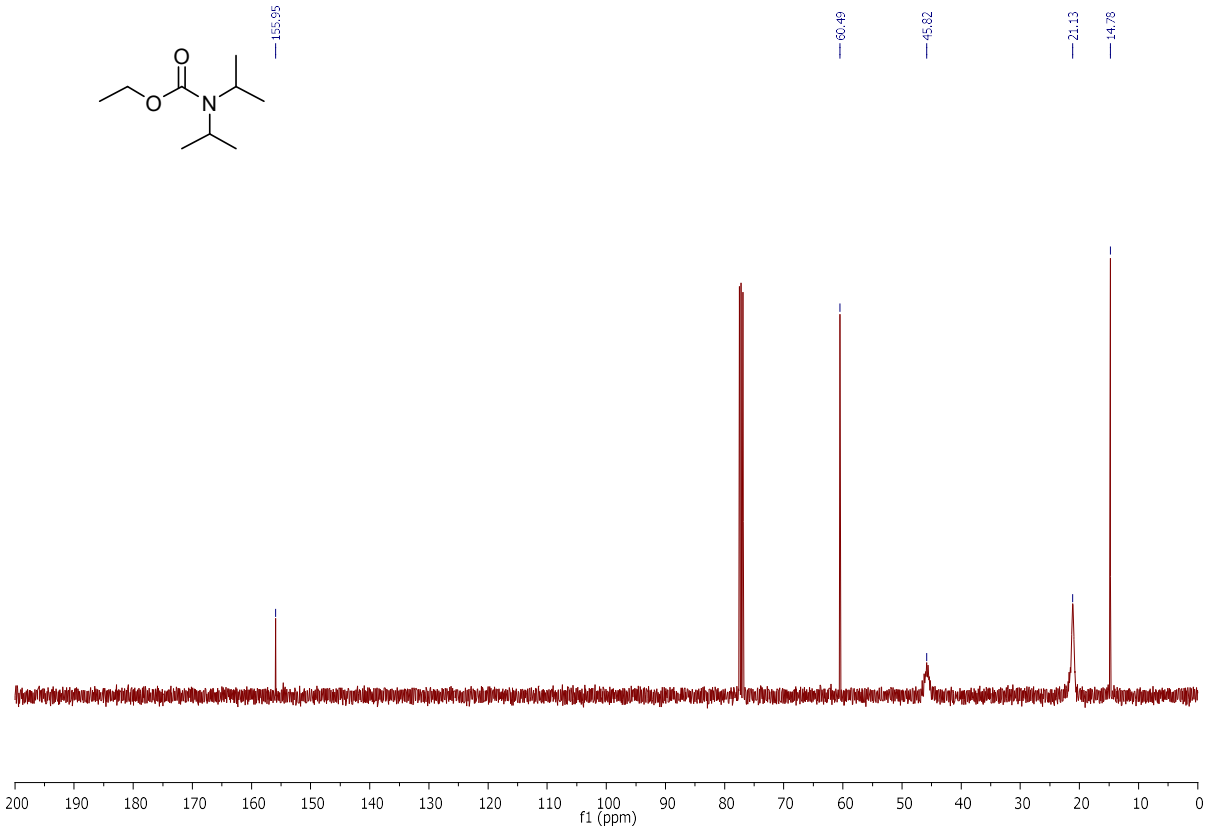
Ethyl 2,4,6-triisopropylbenzoate **2.2**:



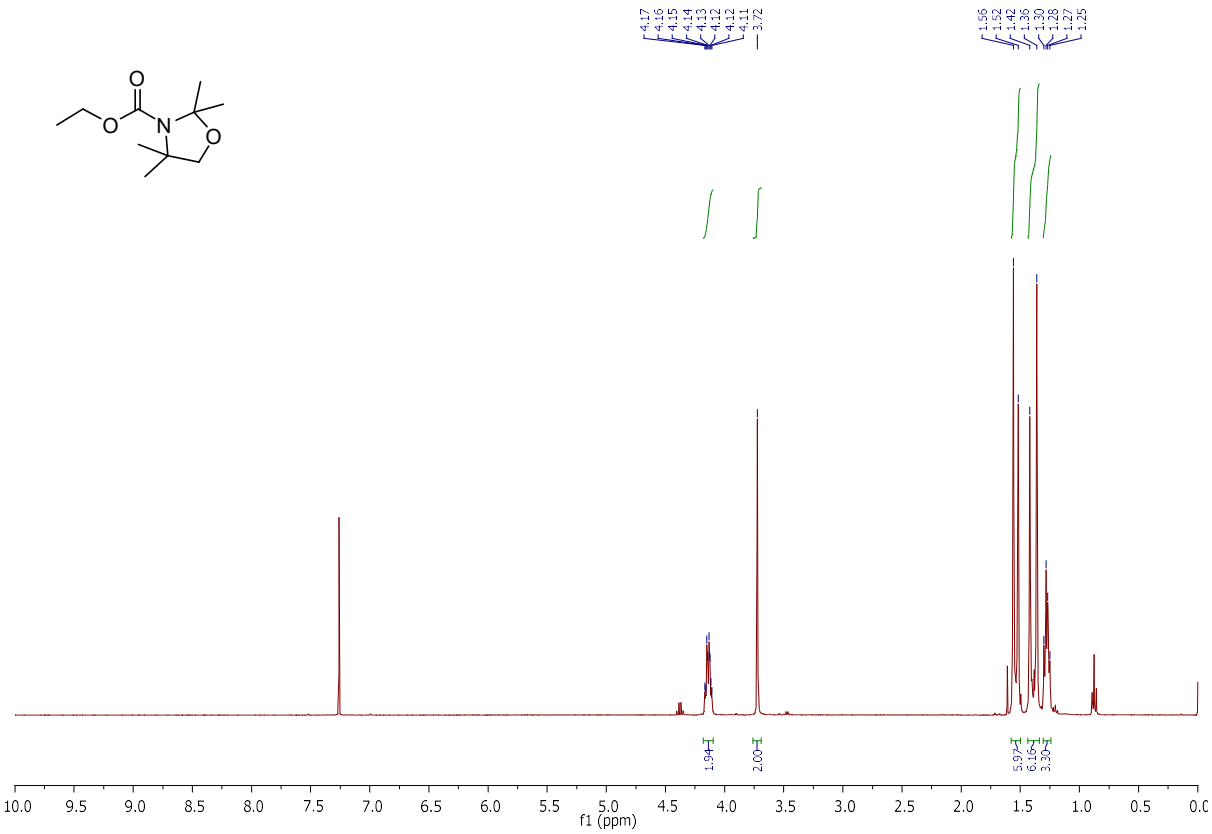


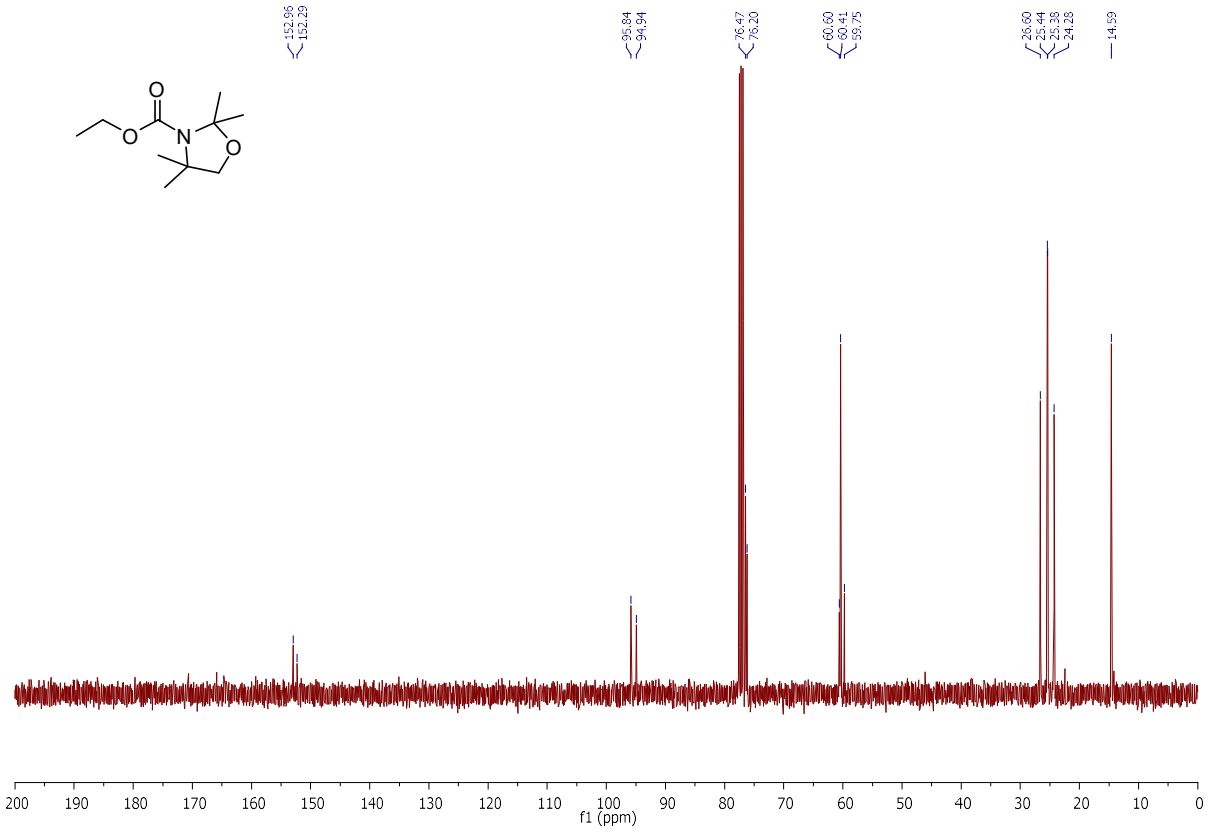
Ethyl N,N-diisopropylcarbamate **2.4** :





Ethyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate **2.5**:





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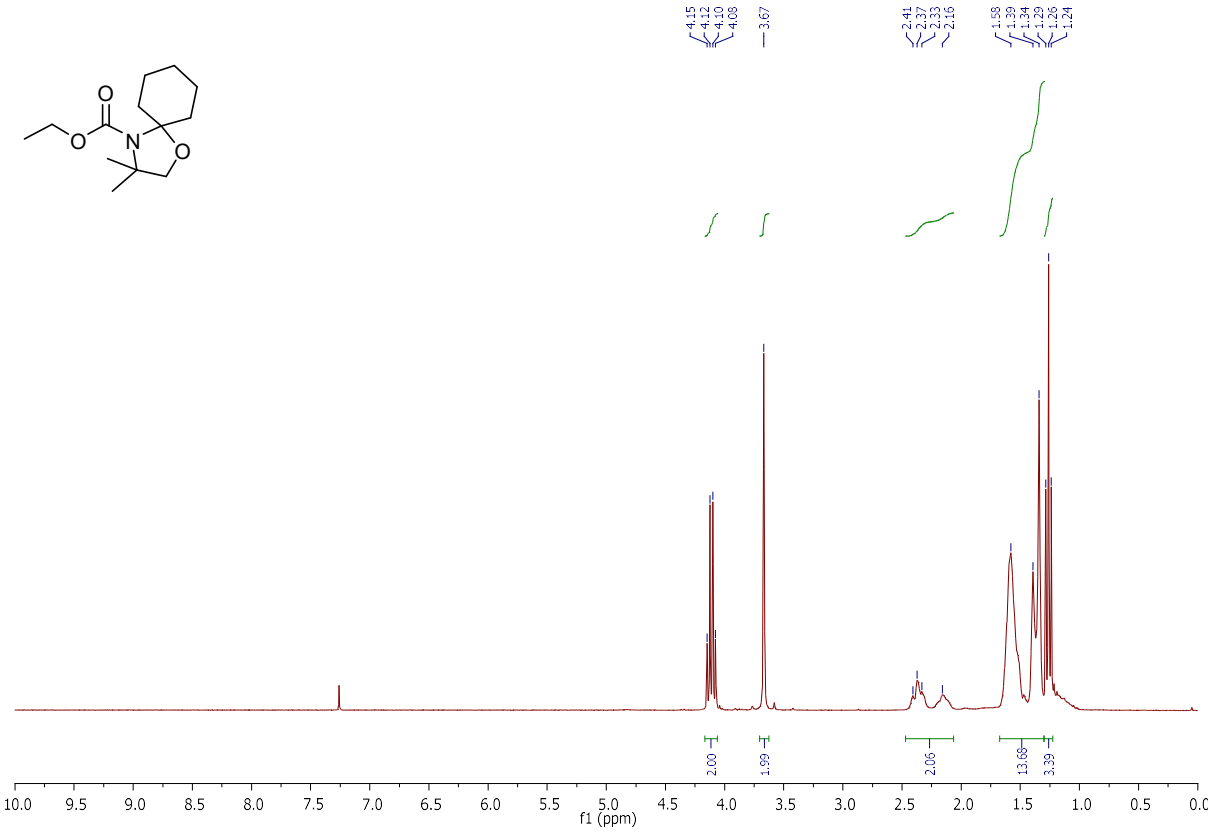
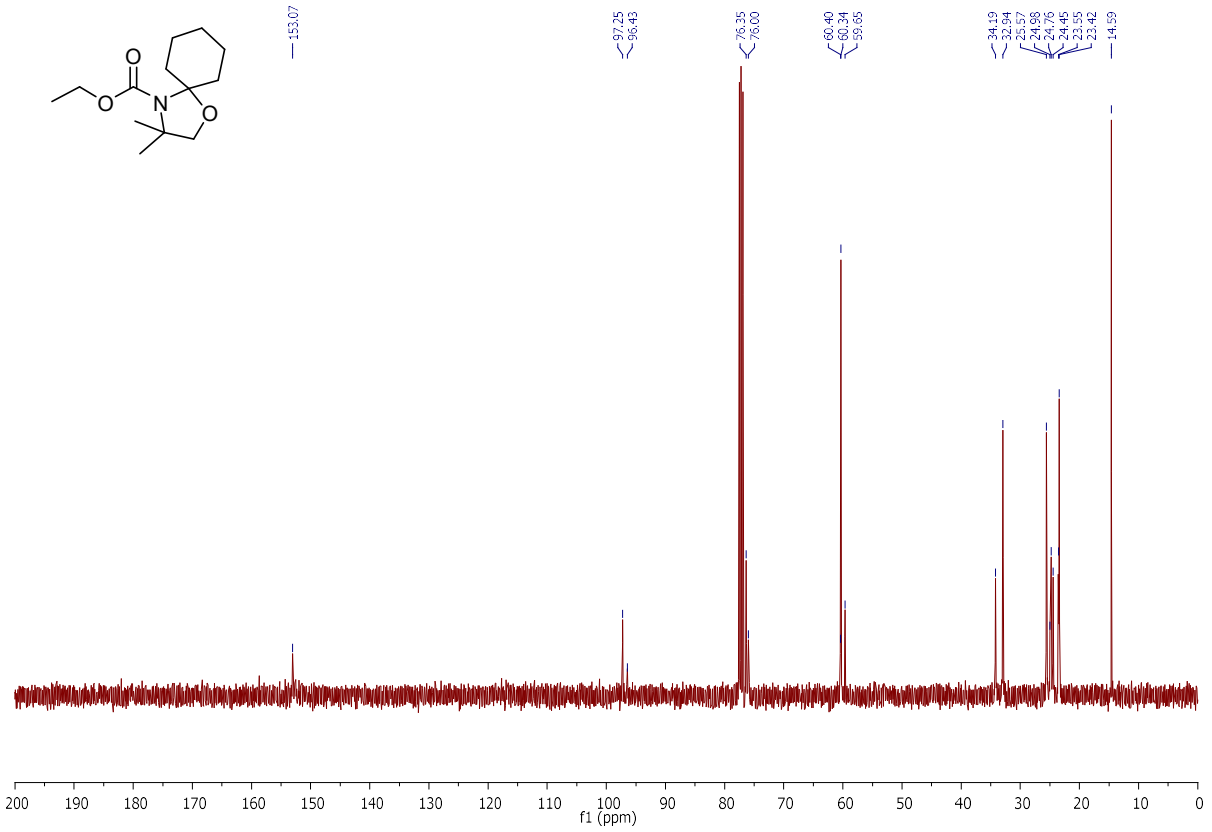
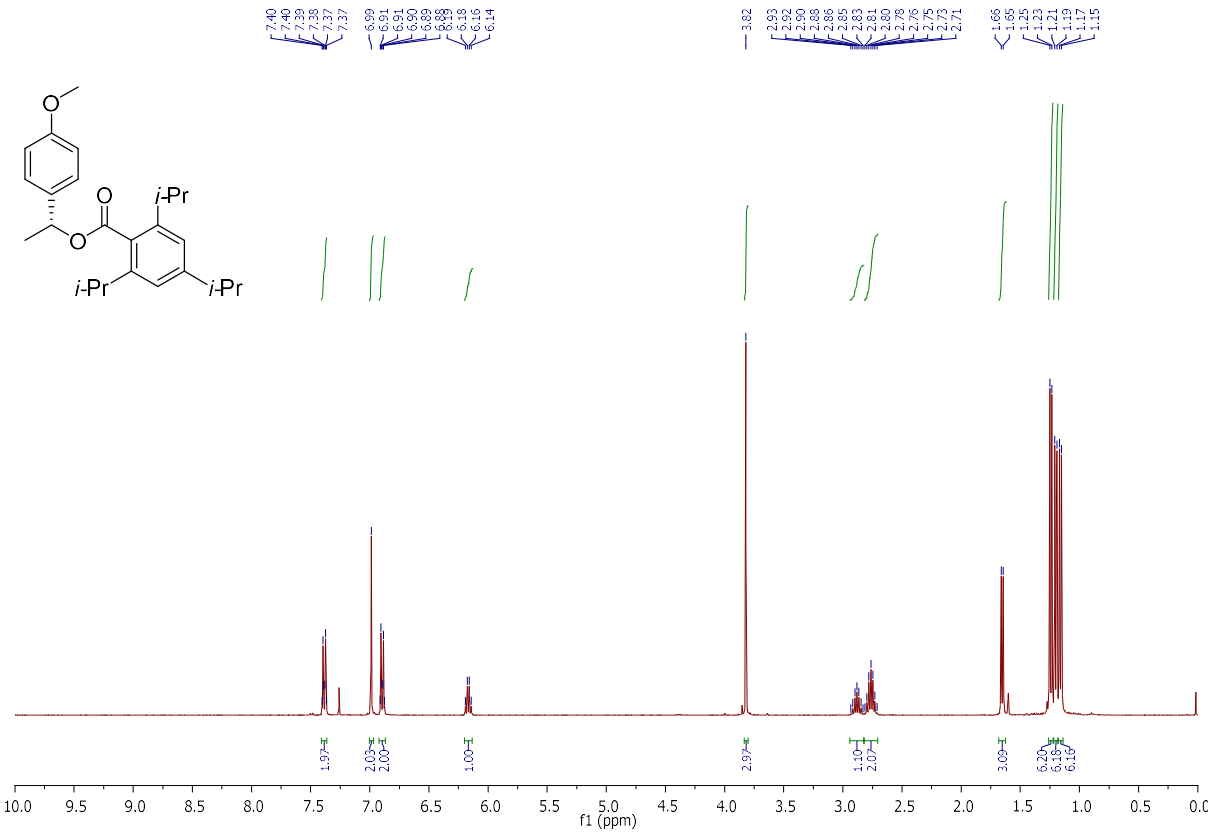
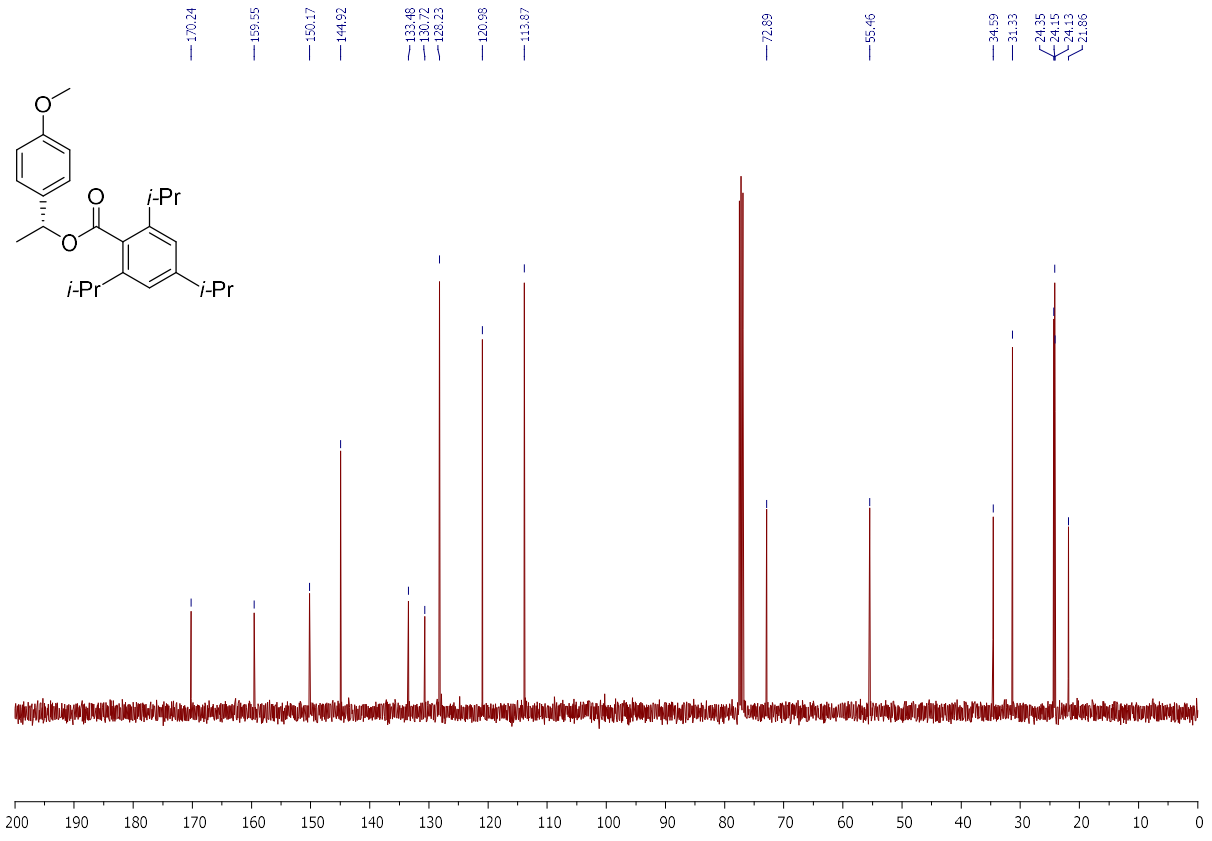




(*R*)-(+)-1-(4-methoxyphenyl)ethyl 2,4,6-triisopropylbenzoate **2.2a** :





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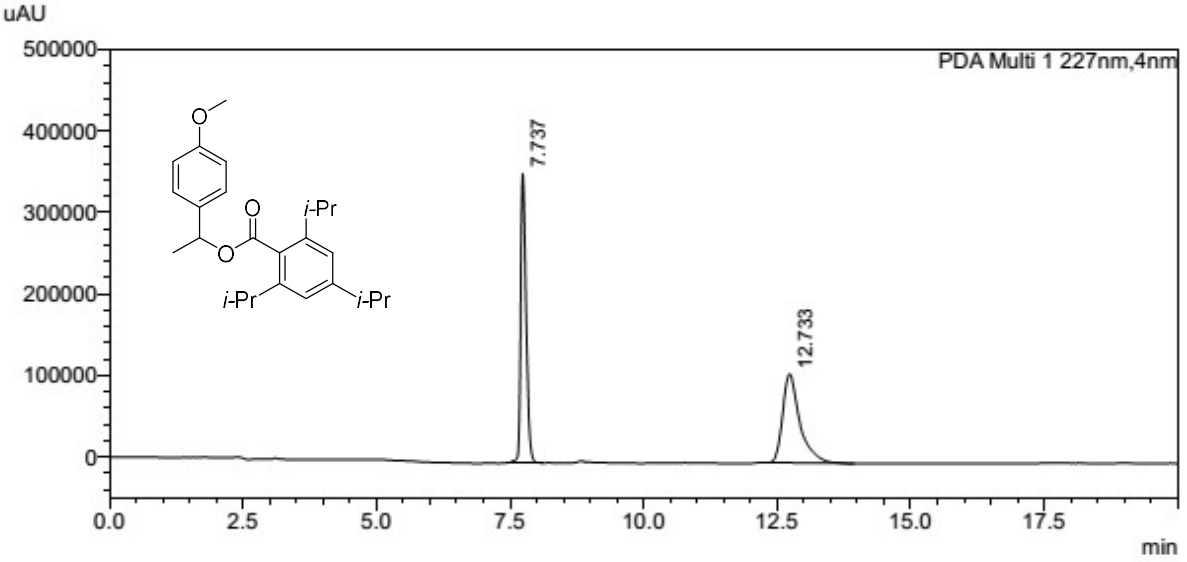

<Peak Table>

PDA Ch1 227nm

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1	7.737	50.679	2505149	355310	0.000		M
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Total		100.000	4943201	464254			

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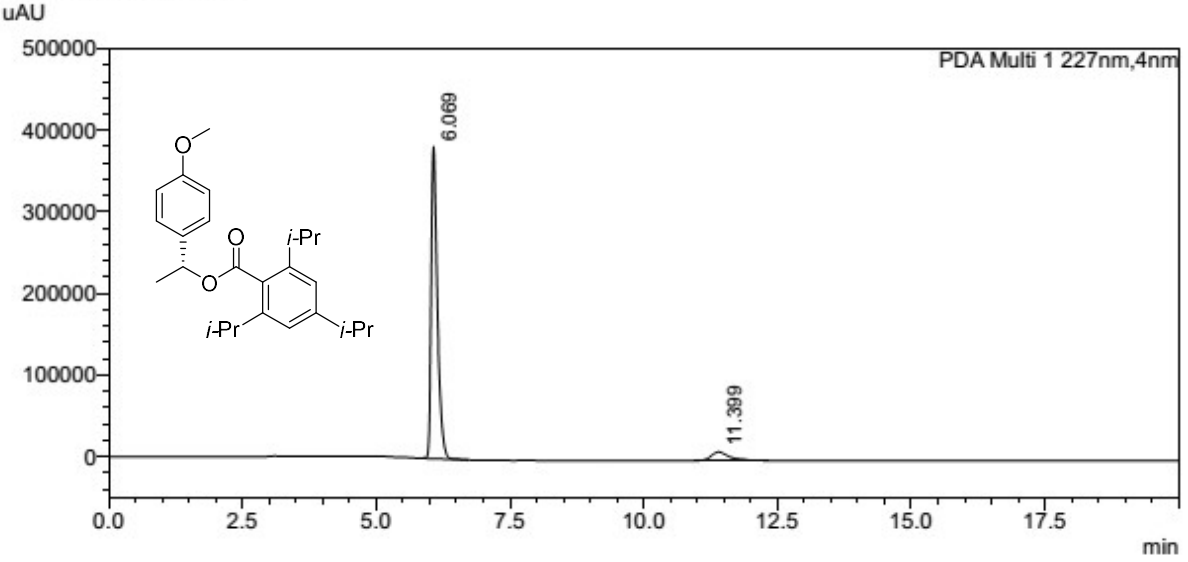

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PDA Ch1 227nm

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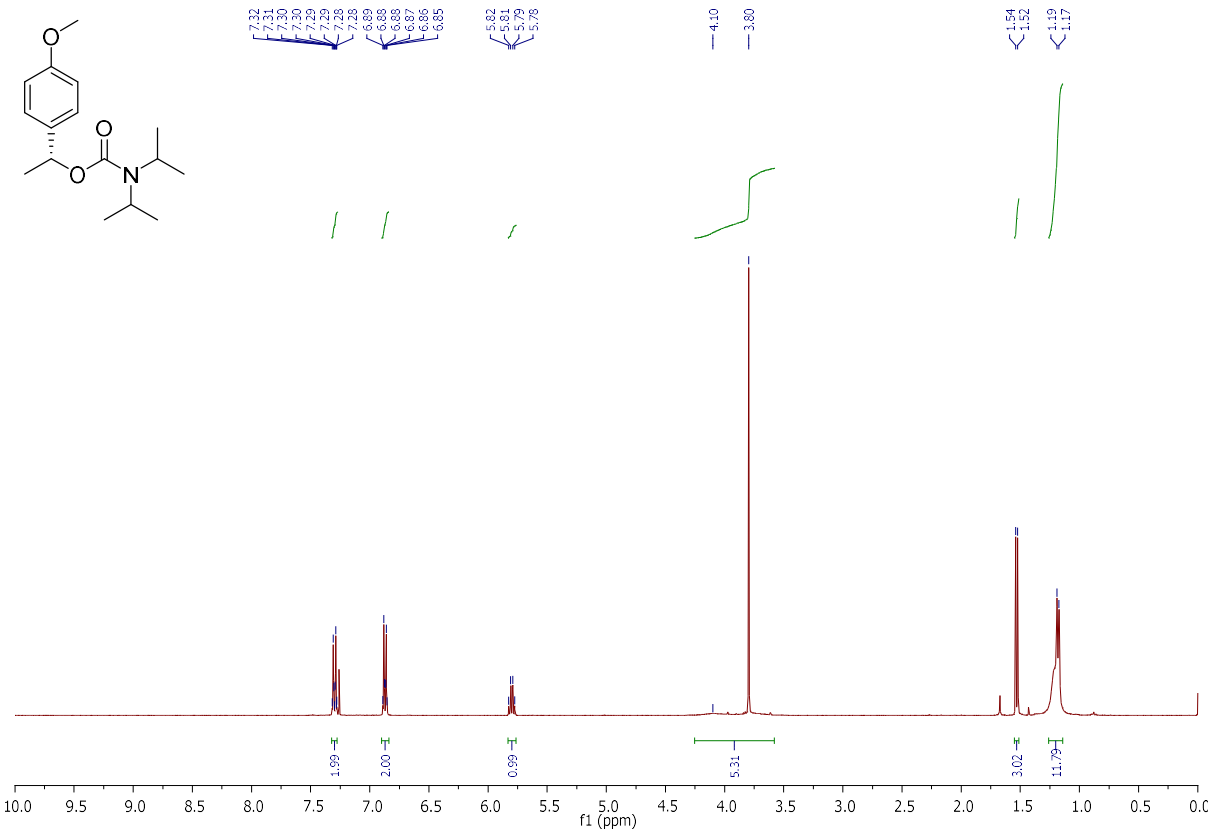
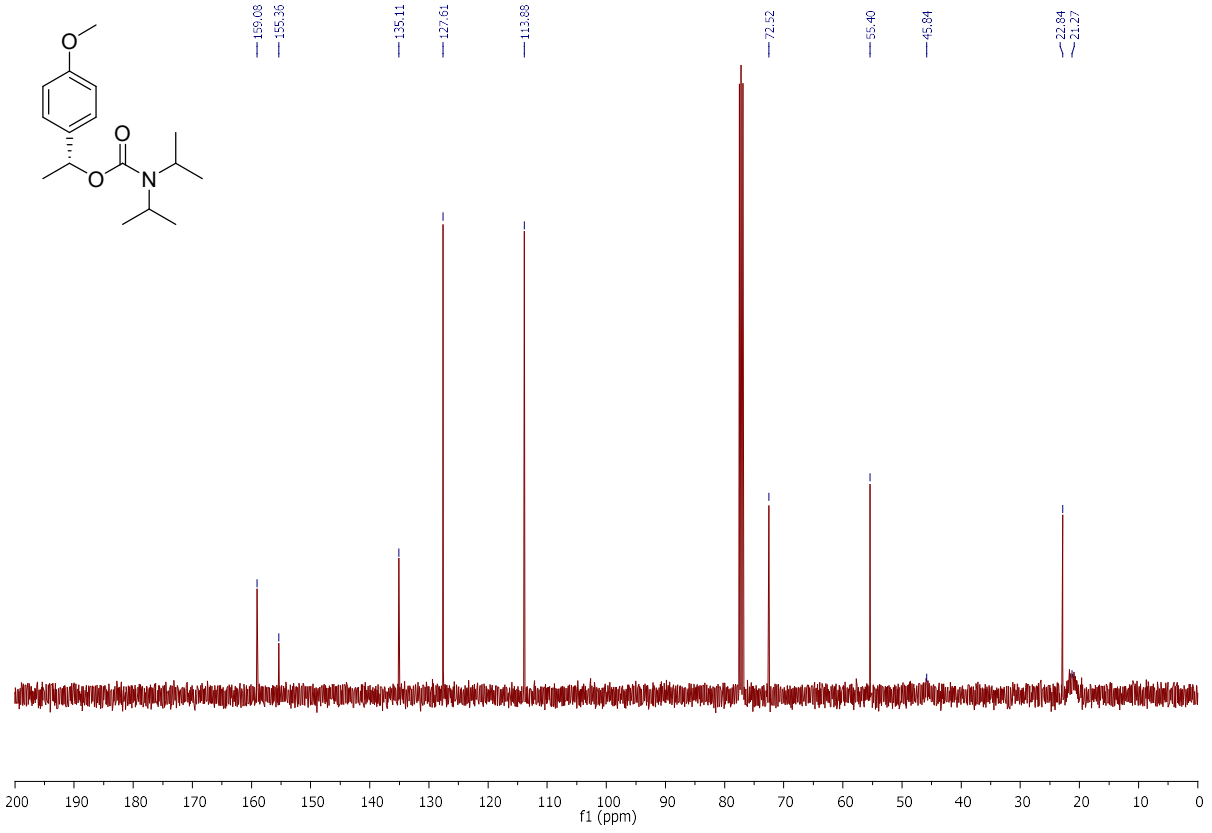
1	6.069	92.490	3046997	382929	0.000		M
2	11.399	7.510	247410	10456	0.000		M
Total		100.000	3294407	393386			

(*R*)-(+)-1-(4-methoxyphenyl)ethyl N,N-diisopropylcarbamate**2.4a**:





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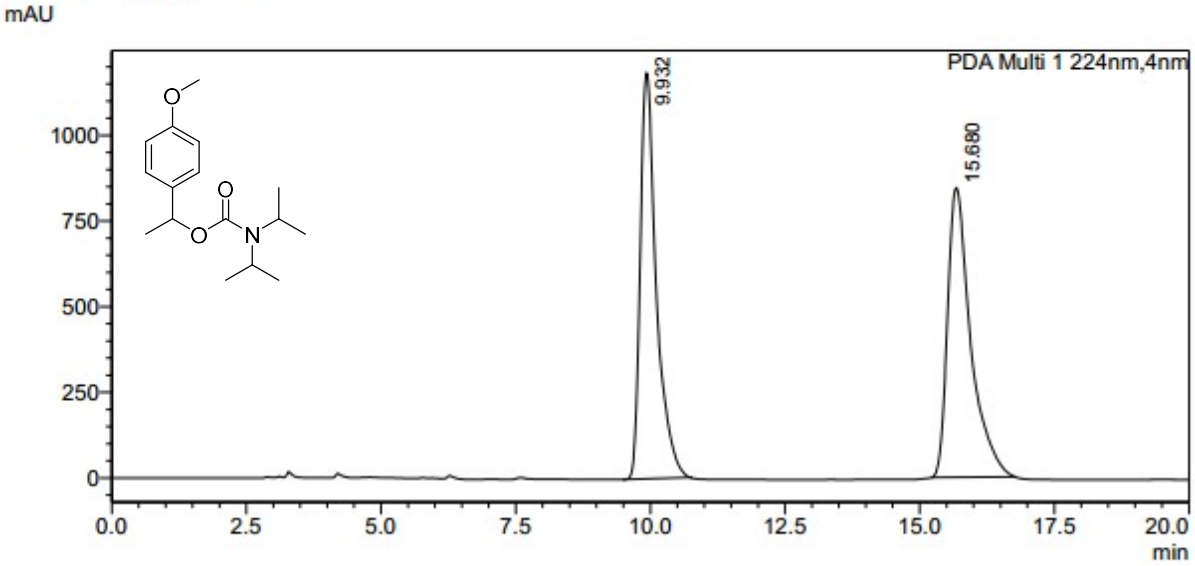

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PDA Ch1 224nm

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2	15.680	50.568	25177345	844920	50.568		M
Total		100.000	49789285	2028628			

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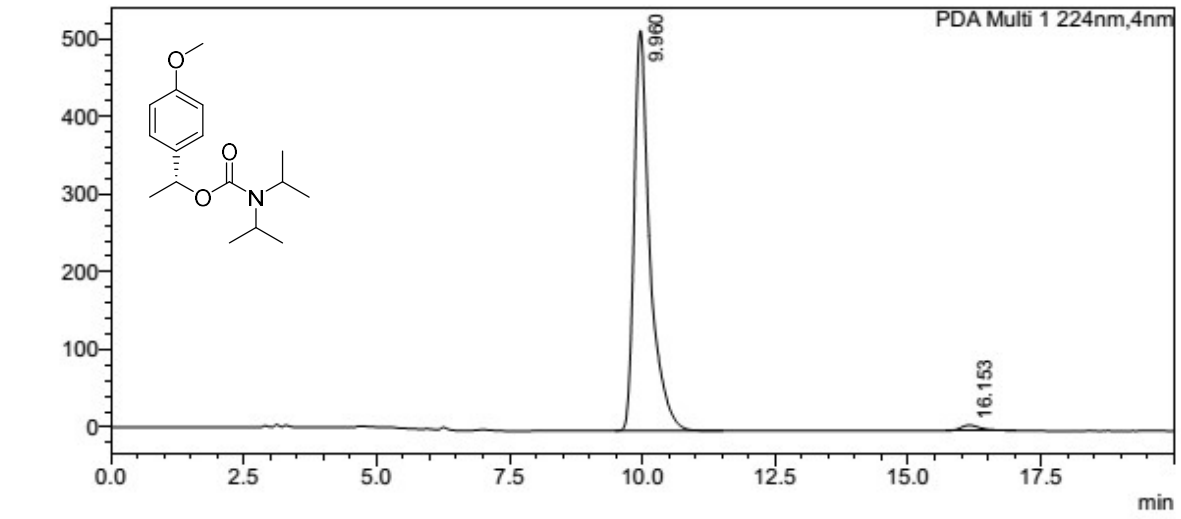

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PDA Ch1 224nm

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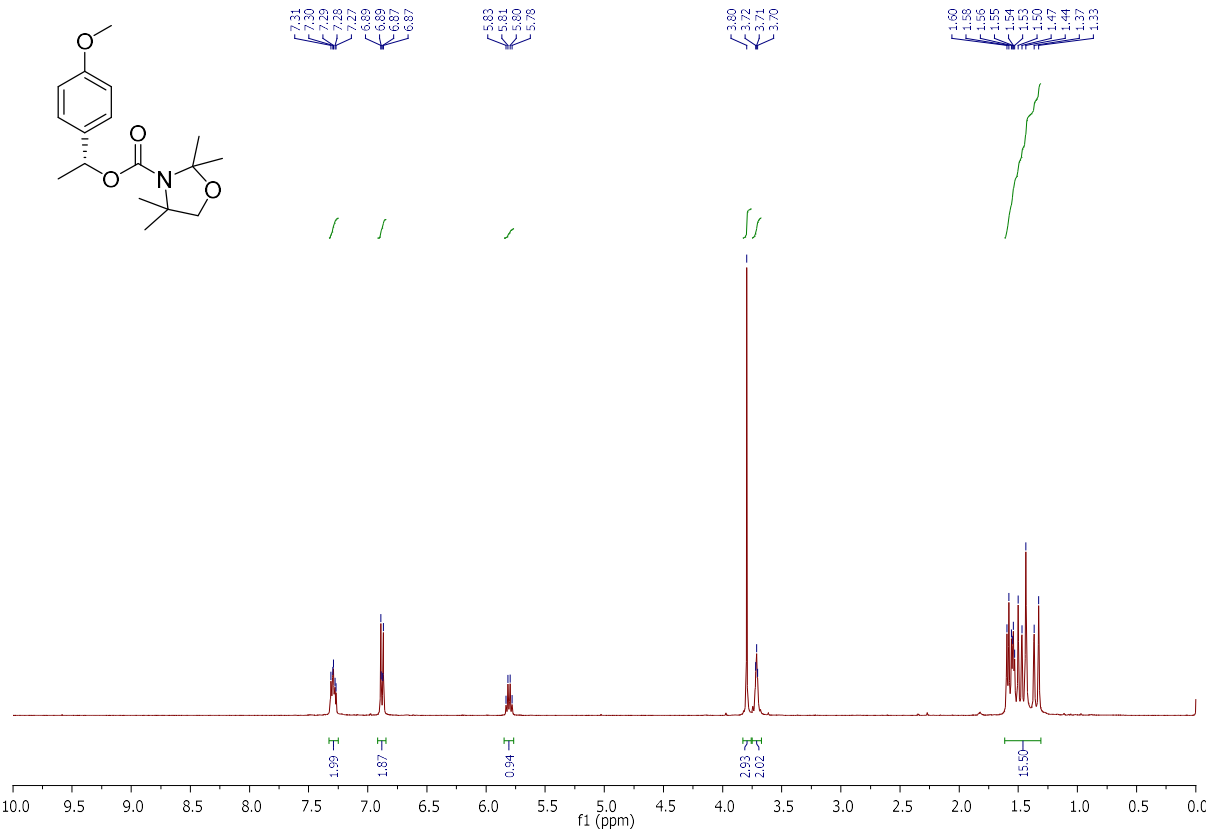
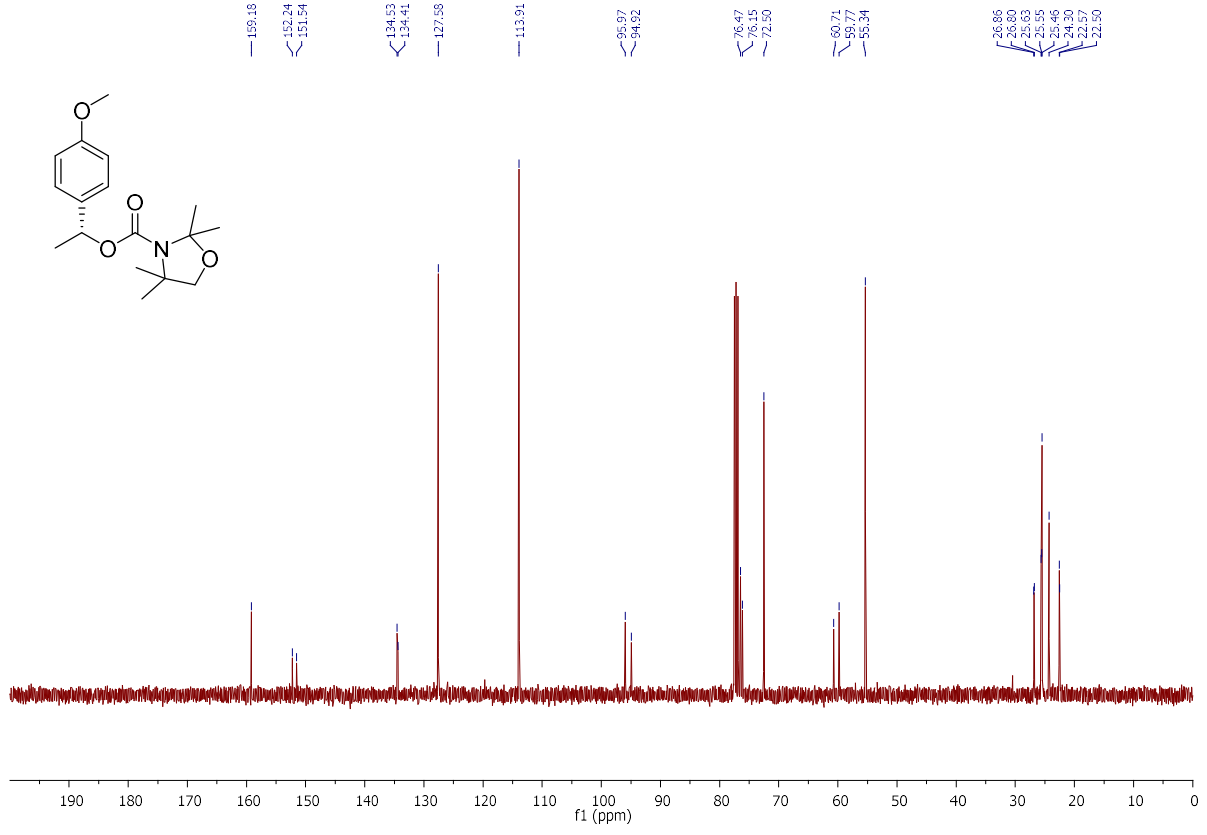
1	9.960	98.136	10619394	514965	0.000		M
2	16.153	1.864	201705	7309	0.000		M
Total		100.000	10821099	522274			

(*R*)-(+)-1-(4-methoxyphenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5a** :





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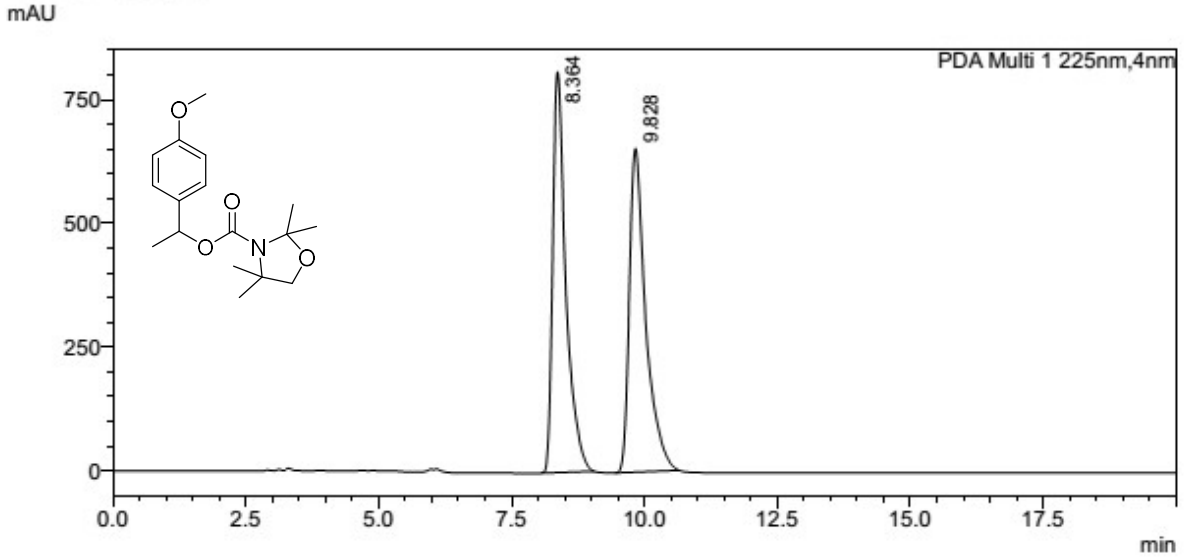

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PDA Ch1 225nm

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Total		100.000	27891601	1462143			

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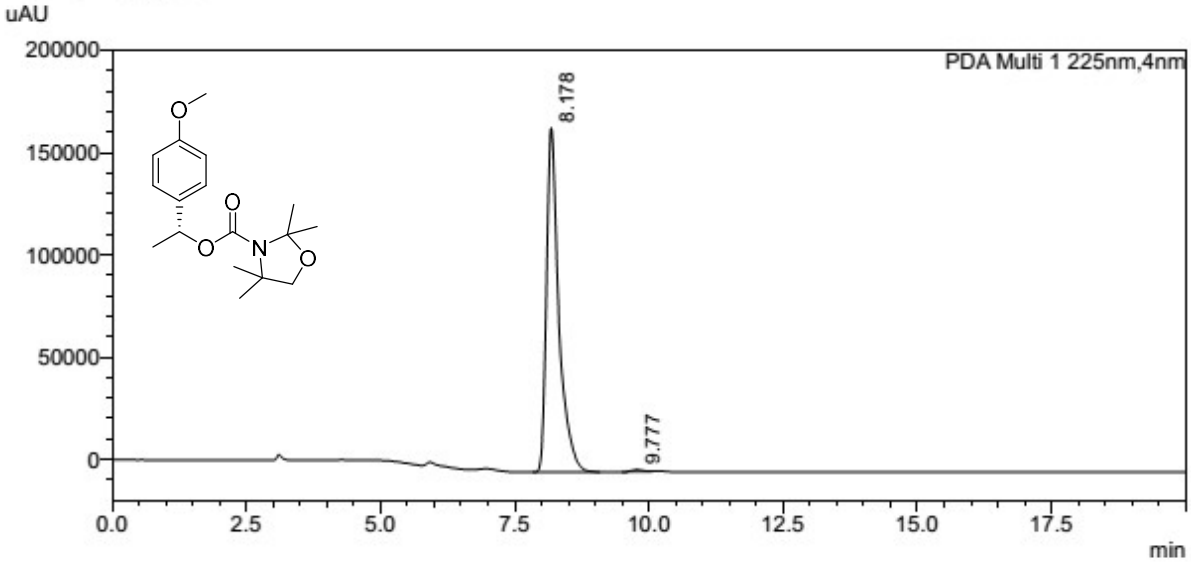

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PDA Ch1 225nm

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1	8.178	99.472	2685854	168295	0.000		M
2	9.777	0.528	14263	904	0.000		M
Total		100.000	2700117	169198			

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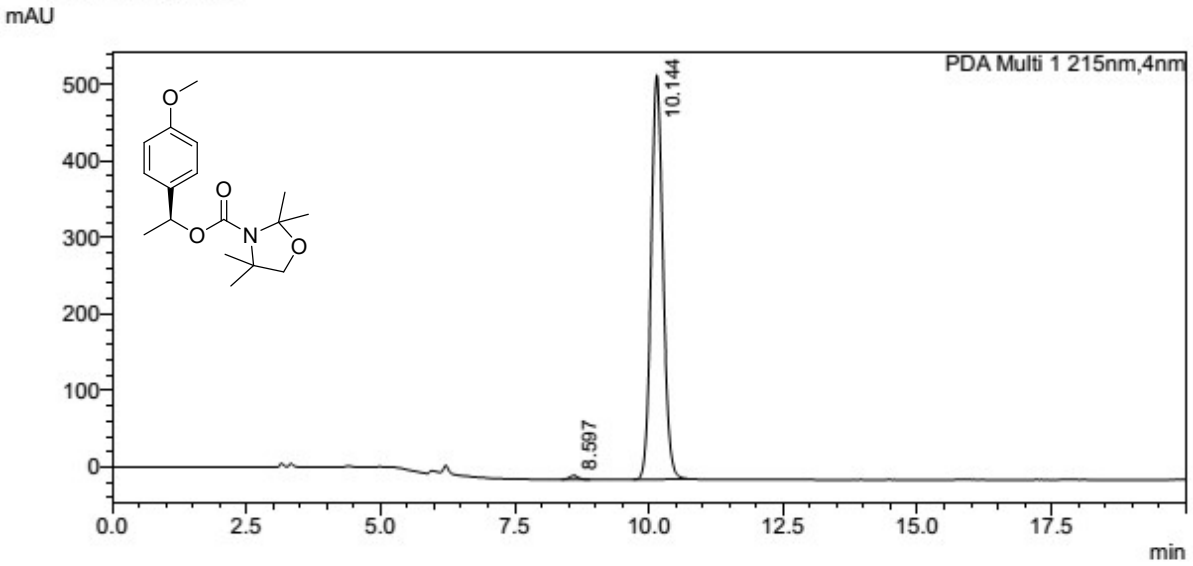

<Peak Table>

PDA Ch1 215nm

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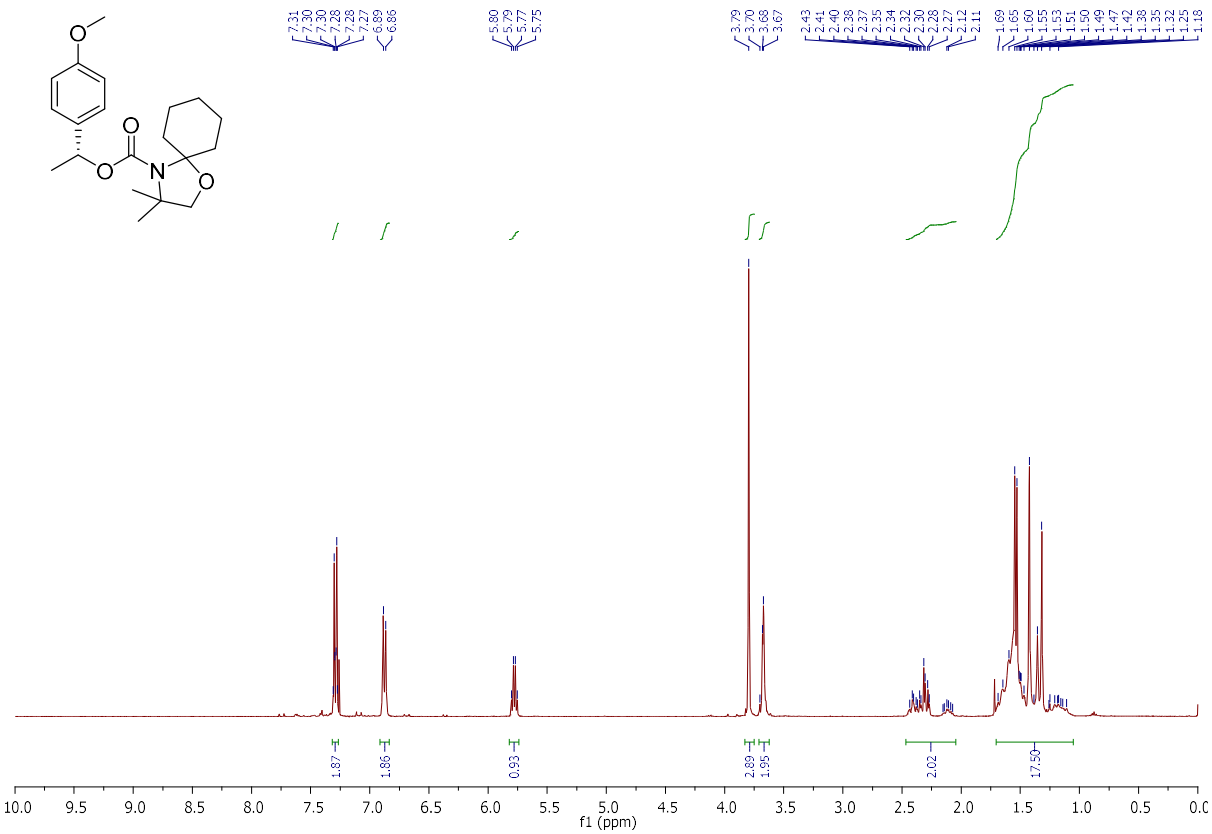
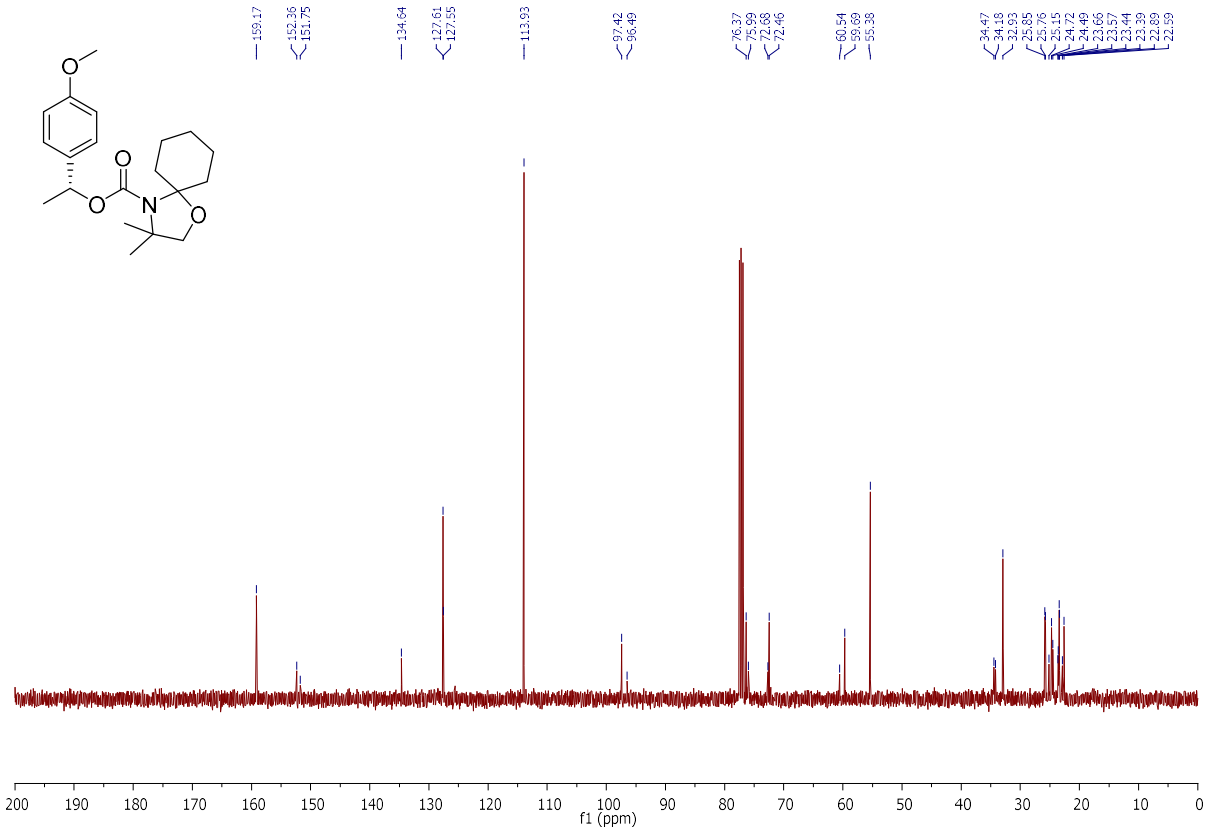
1	8.597	0.767	62729	5169	0.000		M
2	10.144	99.233	8118818	528091	0.000		M
Total		100.000	8181547	533260			

(*R*)-(+)-1-(4-methoxyphenyl)ethyl 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate **6a** :





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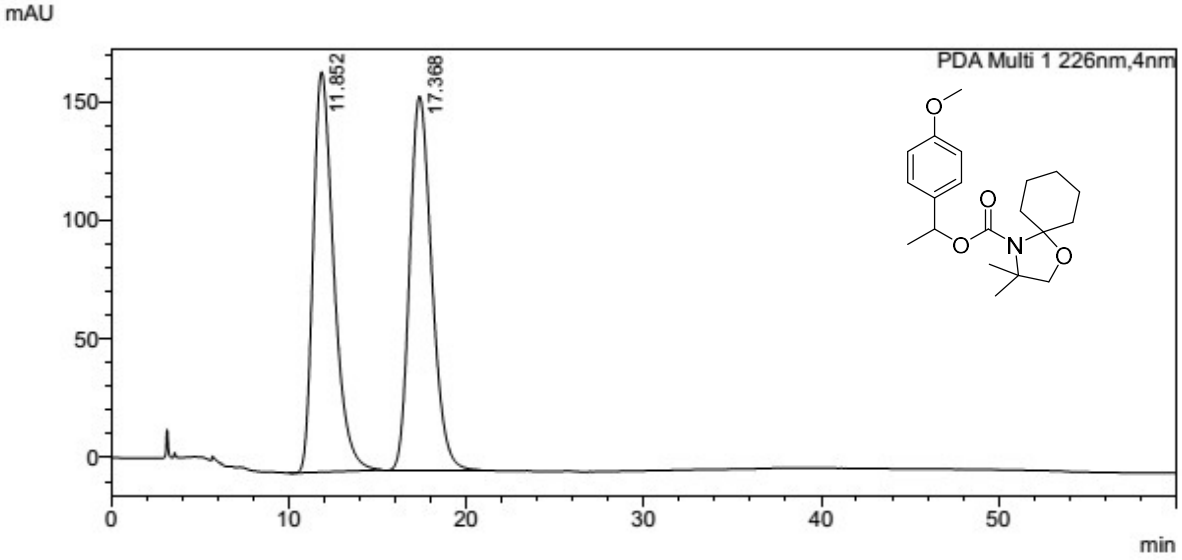

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PDA Ch1 226nm

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1	11.852	49.910	13572159	168712	0.000		M
2	17.368	50.090	13621105	157620	0.000		M
Total		100.000	27193264	326333			

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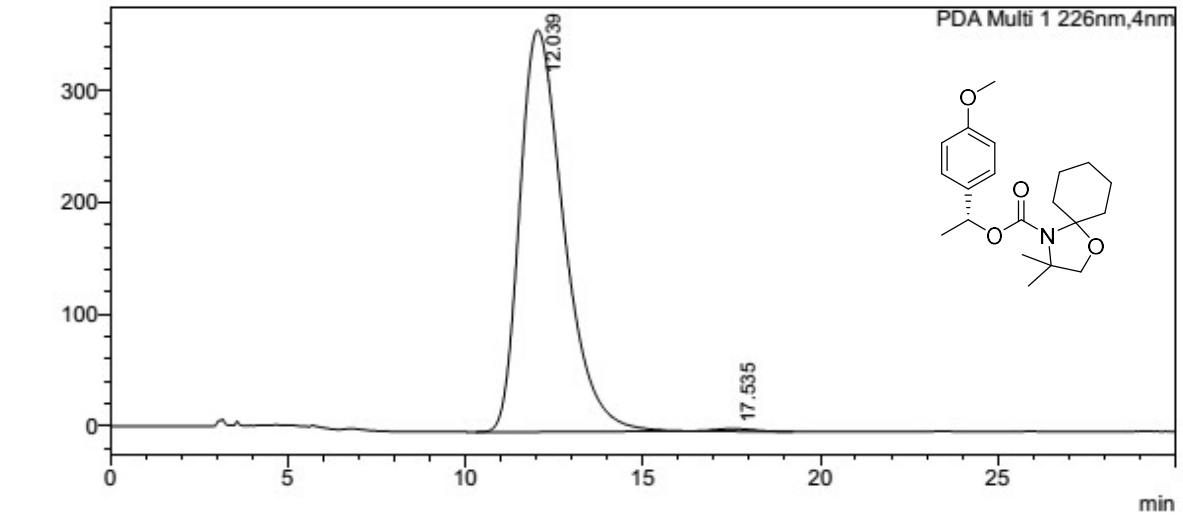

<Peak Table>

PDA Ch1 226nm

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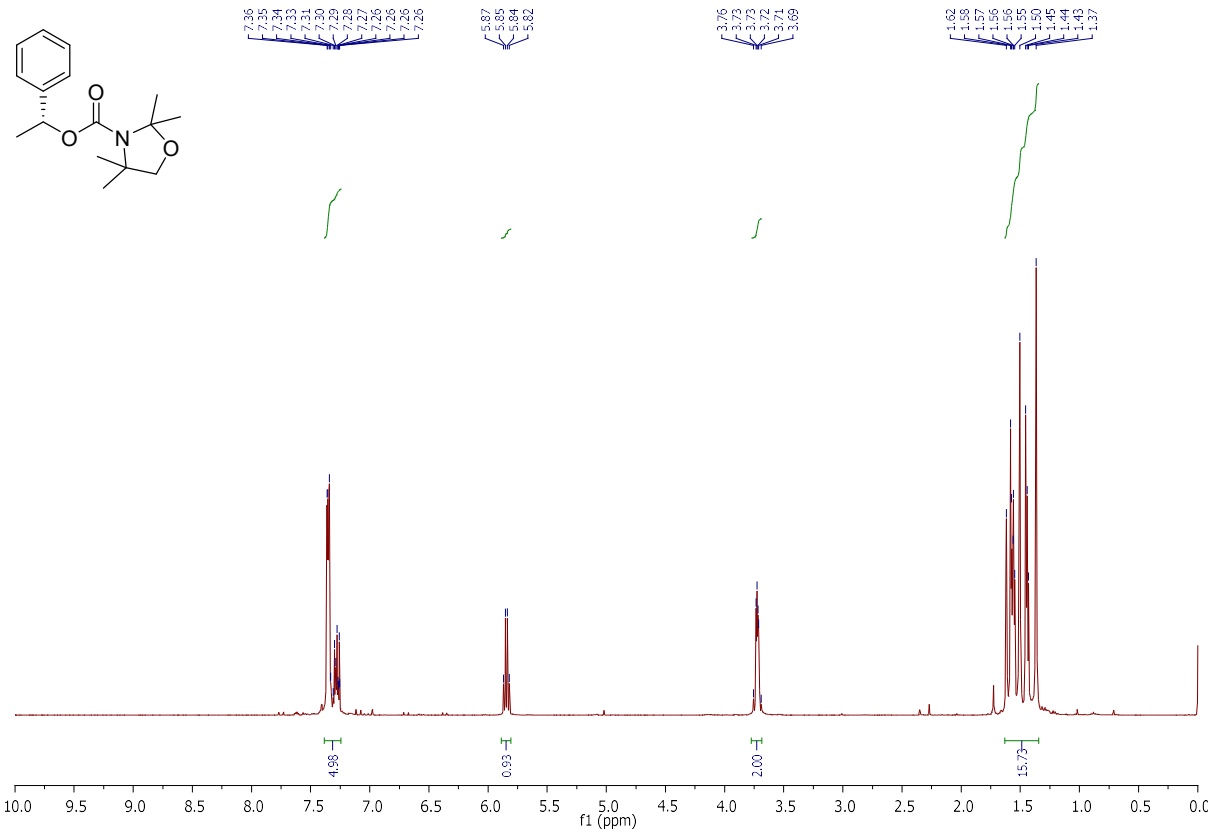
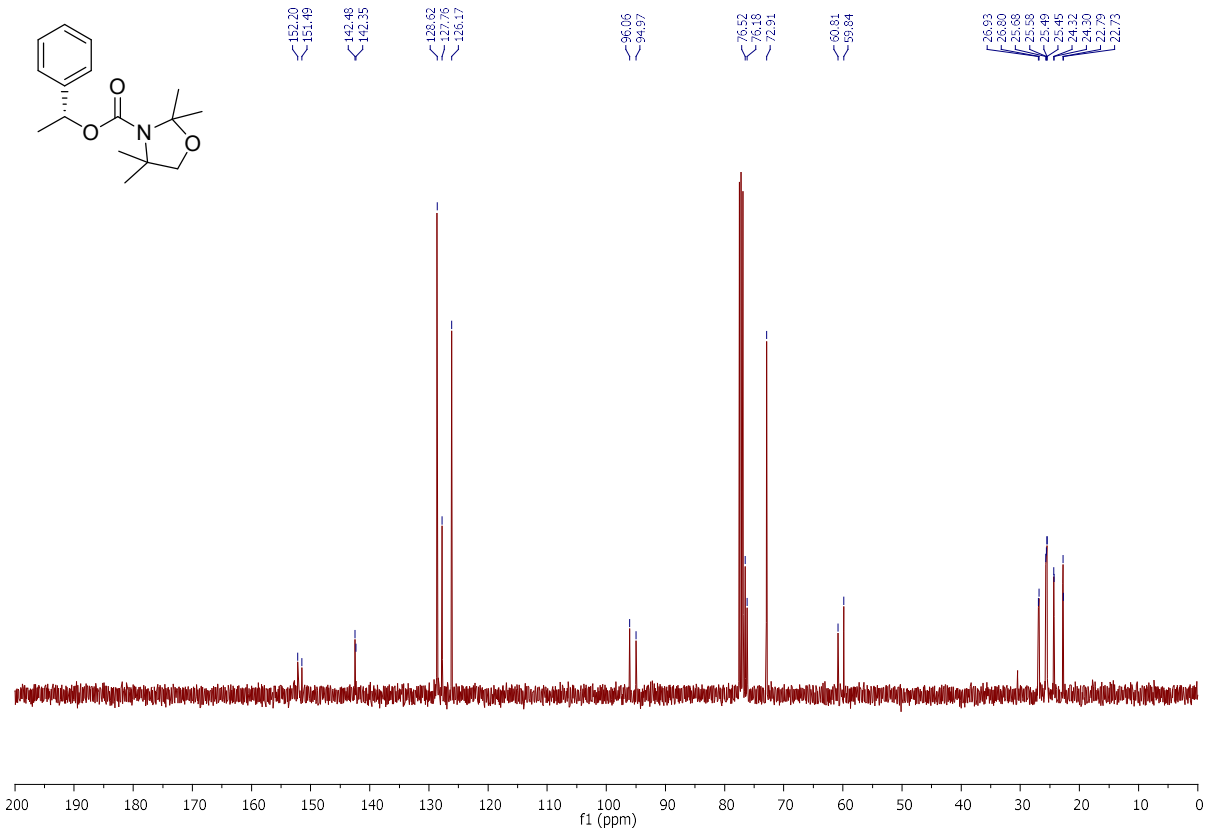
1	12.039	99.417	31072496	359632	0.000		M
2	17.535	0.583	182284	2469	0.000		M
Total		100.000	31254780	362101			

(*R*)-(+)-1-phenylethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5b**:





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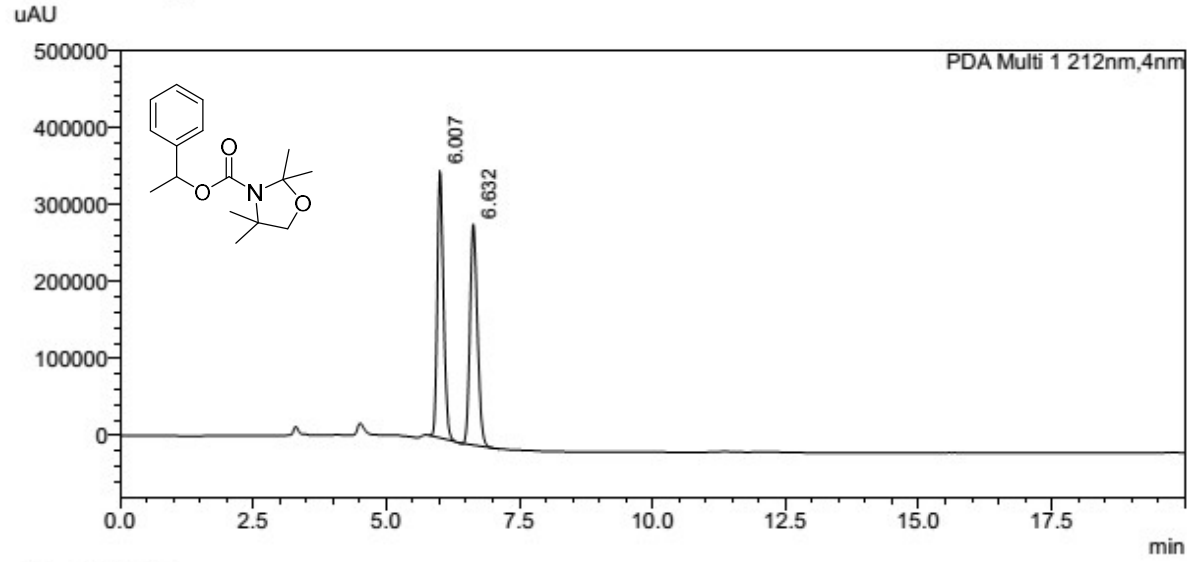

<Peak Table>

PDA Ch1 212nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	6.007	50.080	2822839	347168	0.000		M
2	6.632	49.920	2813813	286752	0.000		M
Total		100.000	5636652	633920			

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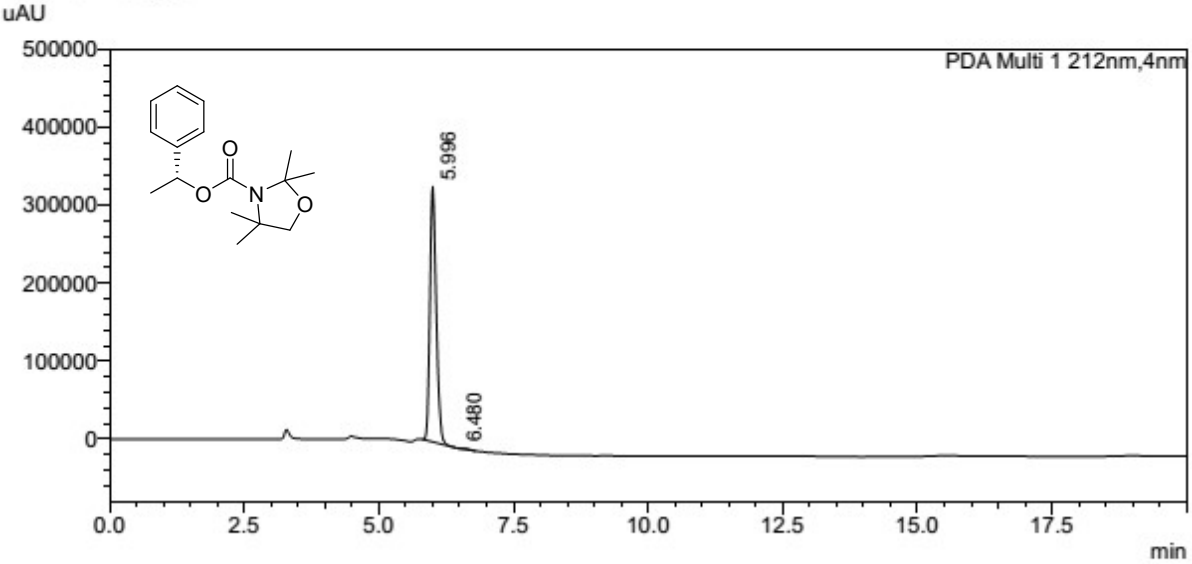
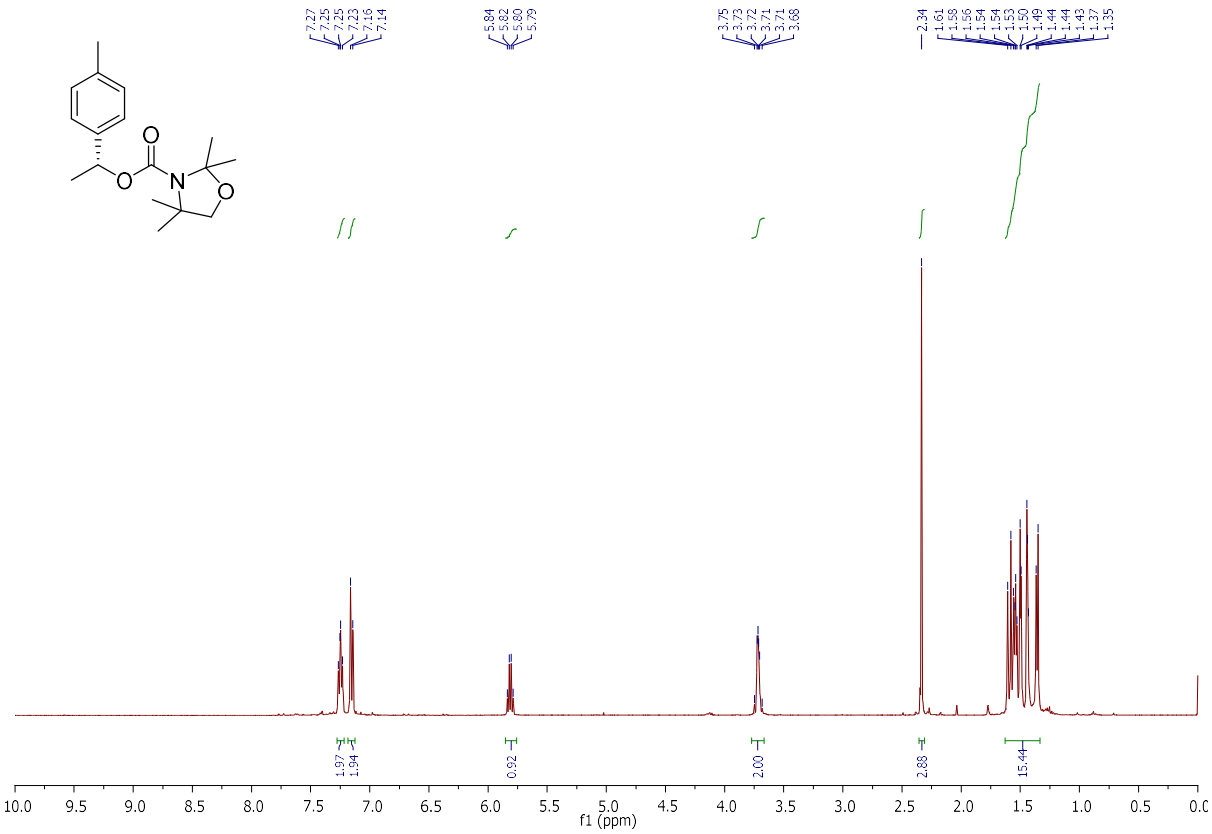


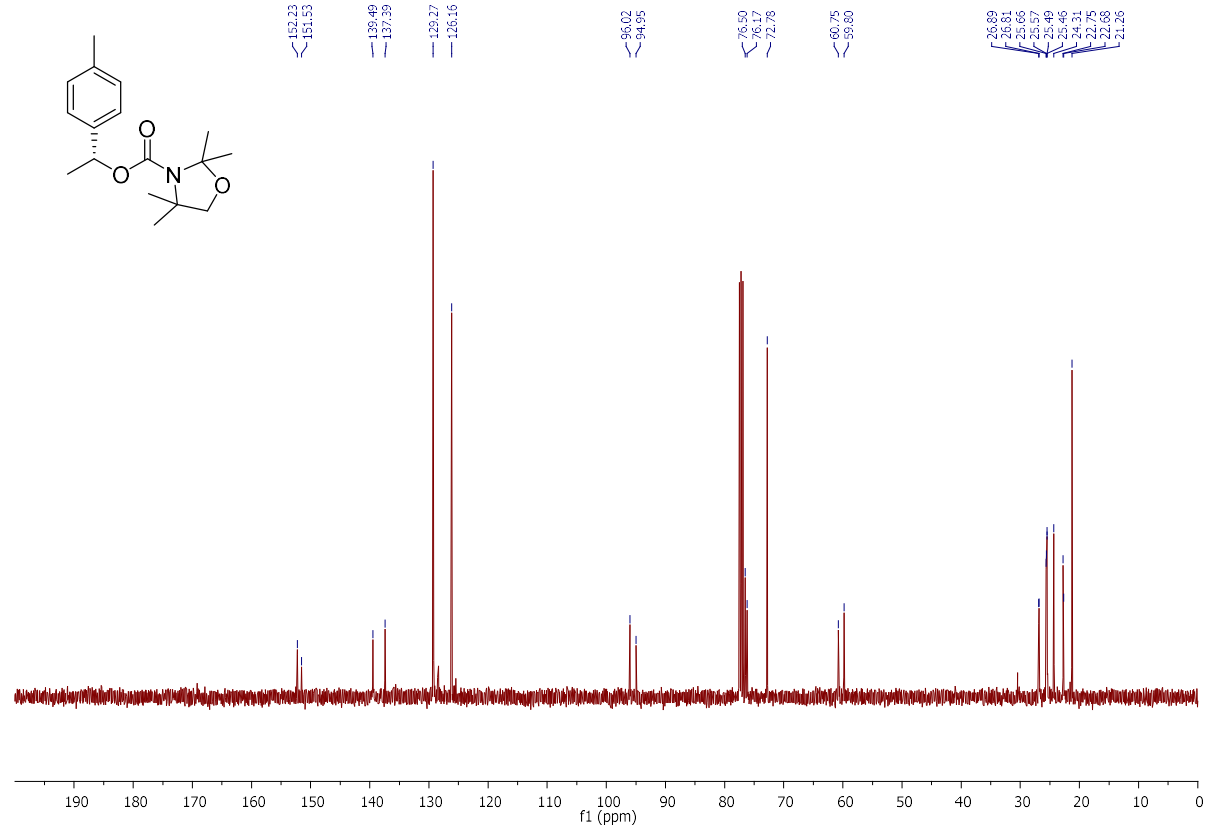
<Peak Table>

PDA Ch1 212nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	5.996	99.656	2691247	327890	0.000		M
2	6.480	0.344	9278	35	0.000		M
Total		100.000	2700525	327925			

(*R*)-(+)-1-(*p*-tolyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5c**:





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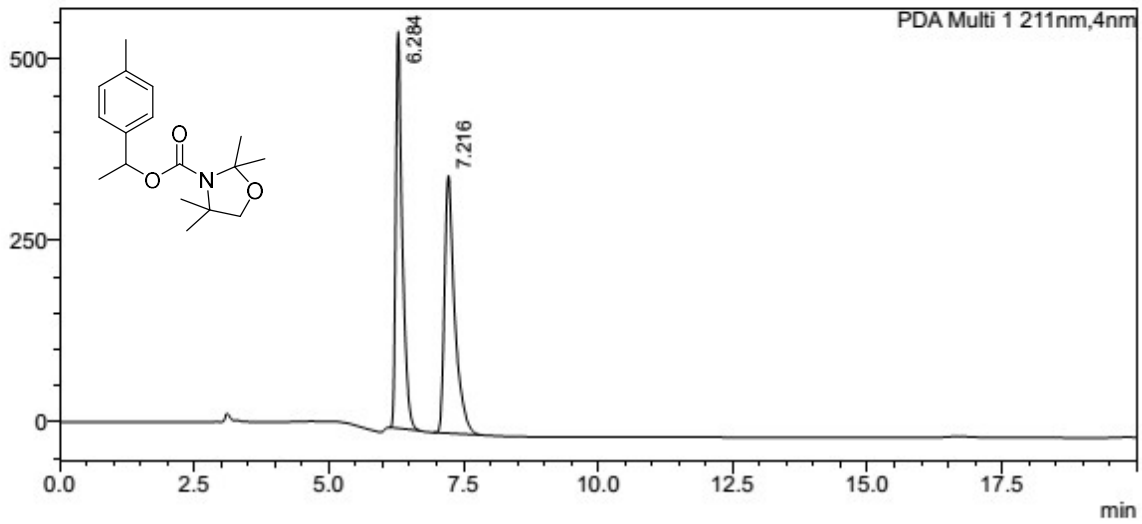
mAU



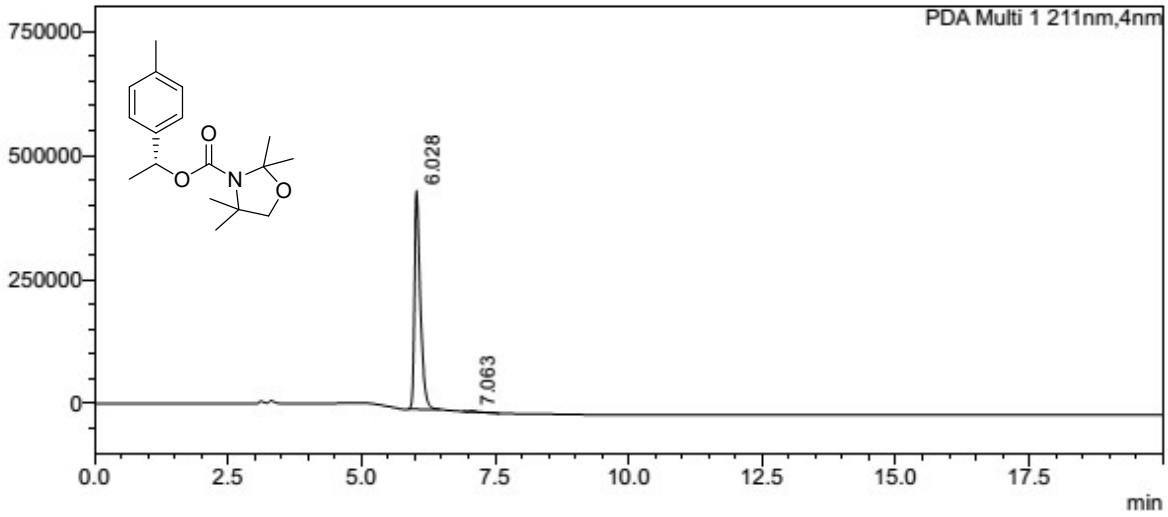
<Peak Table>

PDA Ch1 211nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	6.284	49.815	4637526	546916	0.000		M
2	7.216	50.185	4672024	354951	0.000		M
Total		100.000	9309550	901868			

<Chromatogram>

uAU

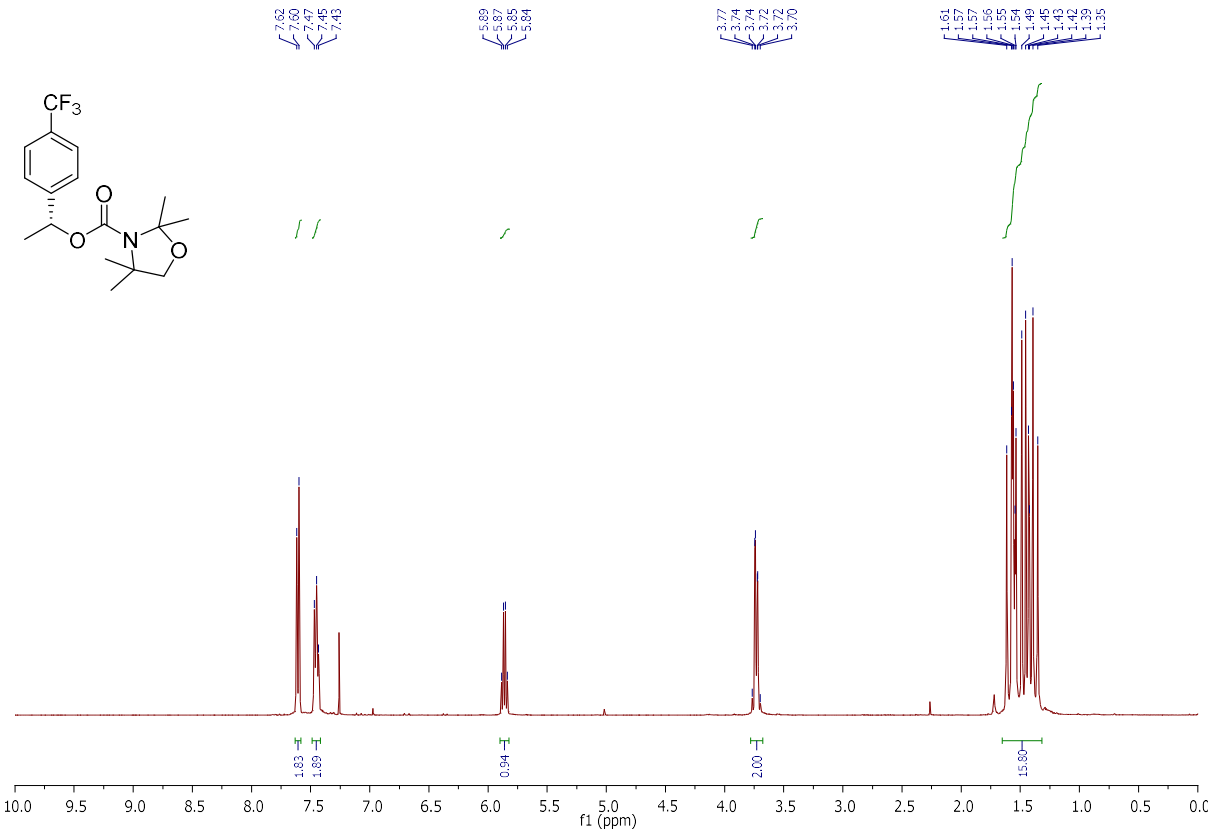


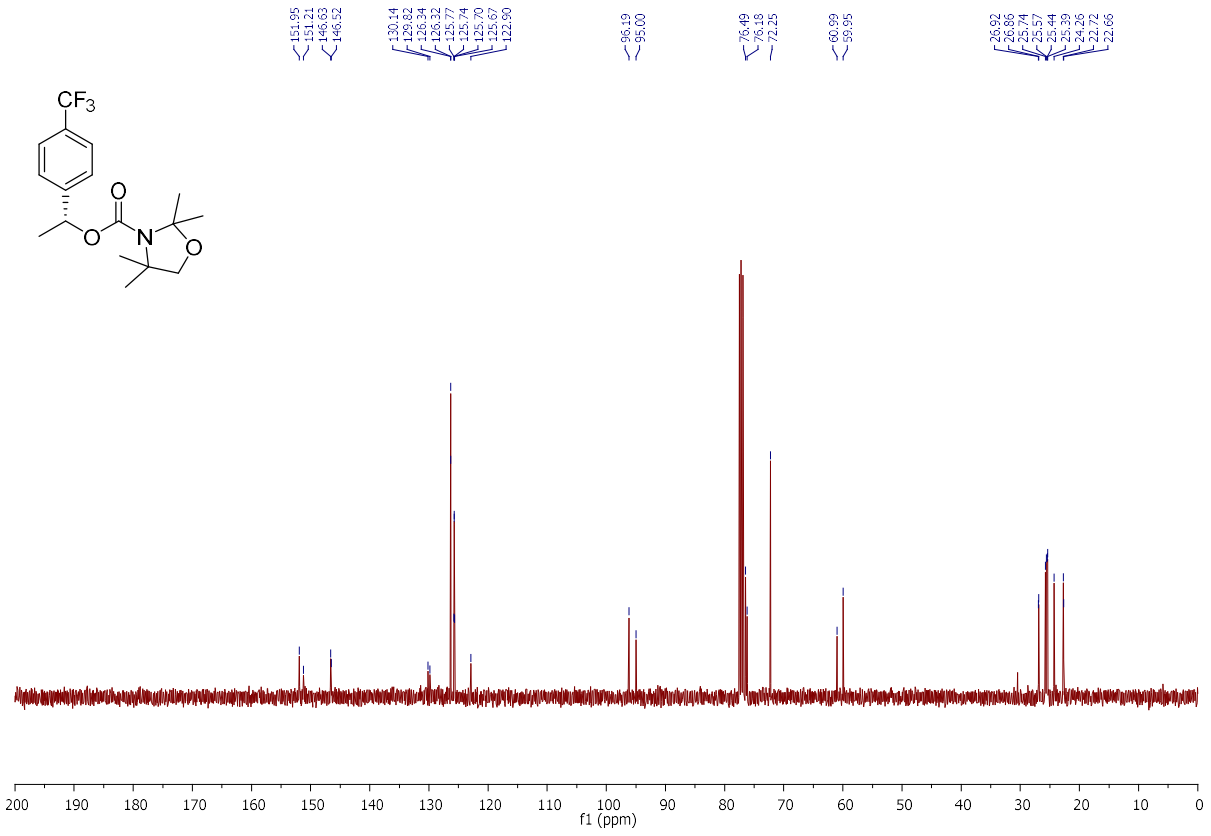
<Peak Table>

PDA Ch1 211nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	6.028	99.367	3378584	440863	0.000		M
2	7.063	0.633	21520	1690	0.000		M
Total		100.000	3400104	442553			

(*R*)-(-)-1-(4-(trifluoromethyl)phenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5d**:





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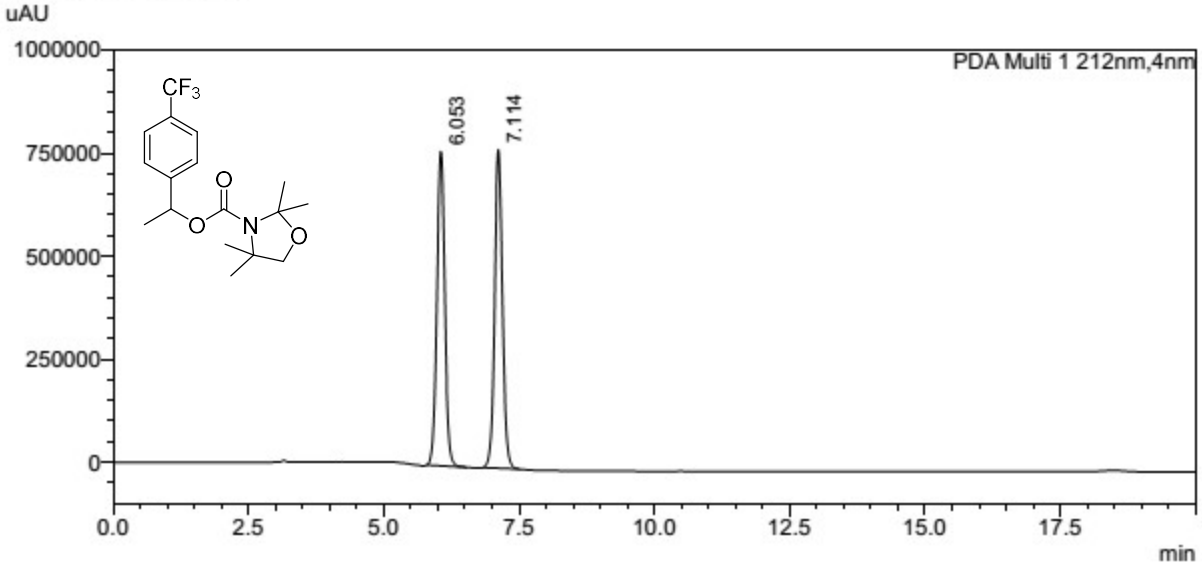
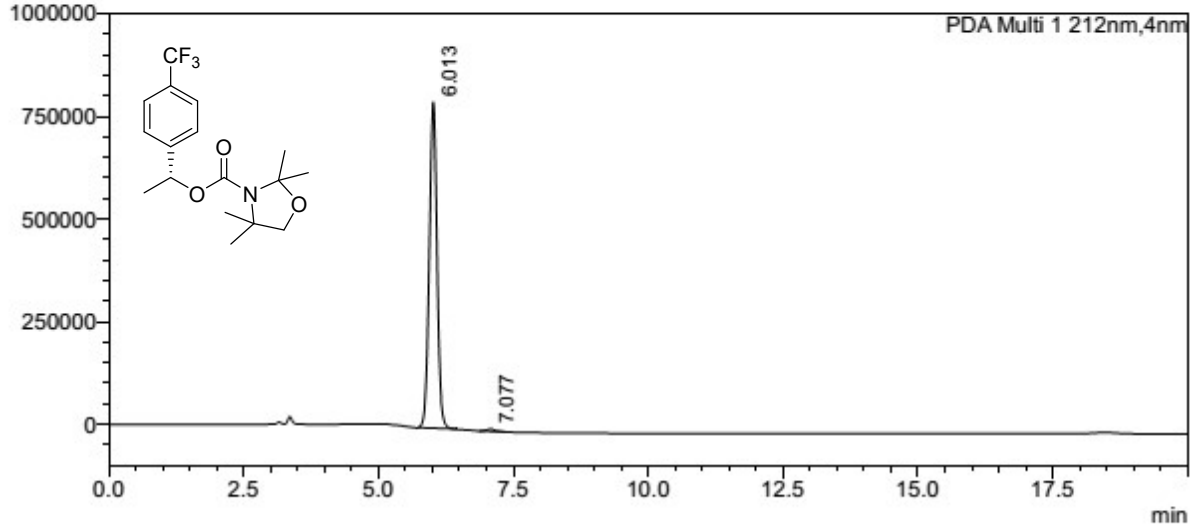


<Peak Table>

PDA Ch1 212nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	6.053	50.098	7741728	762321	0.000		M
2	7.114	49.902	7711544	773271	0.000		M
Total		100.000	15453272	1535592			

<Chromatogram>

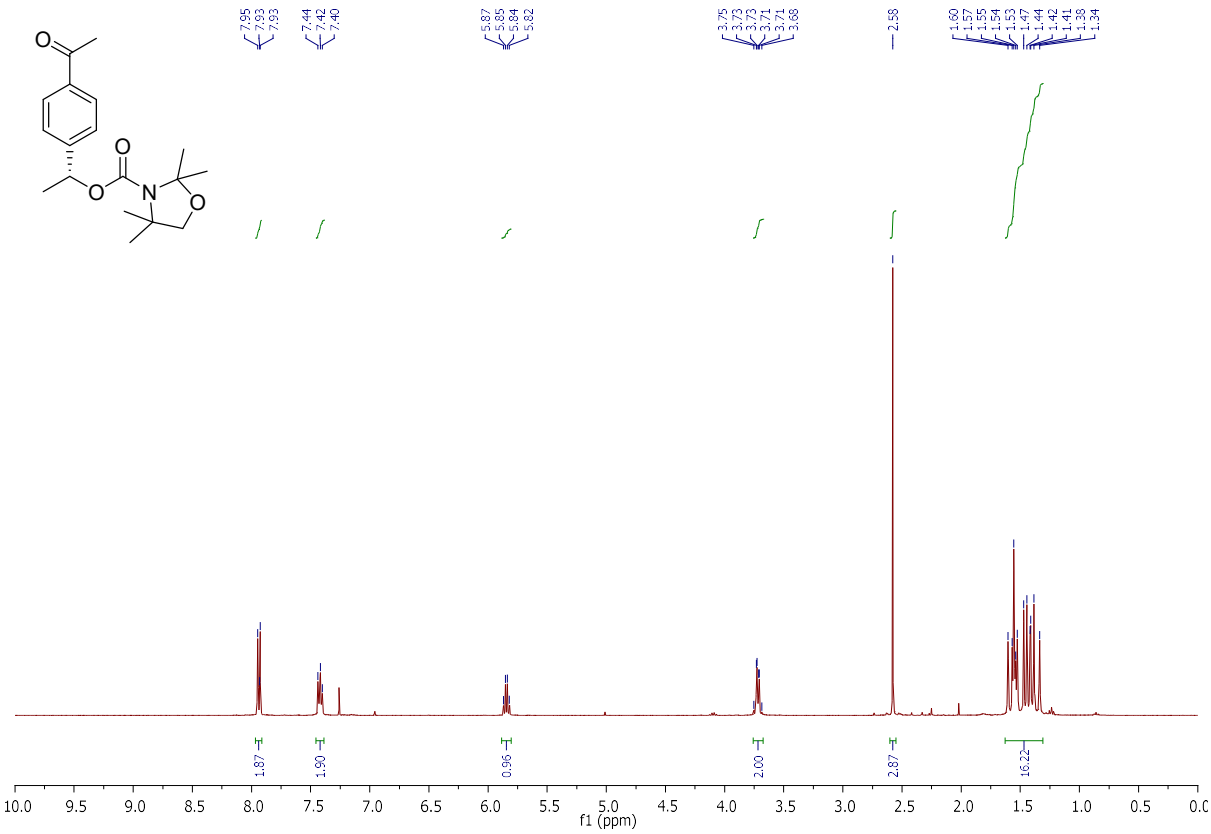


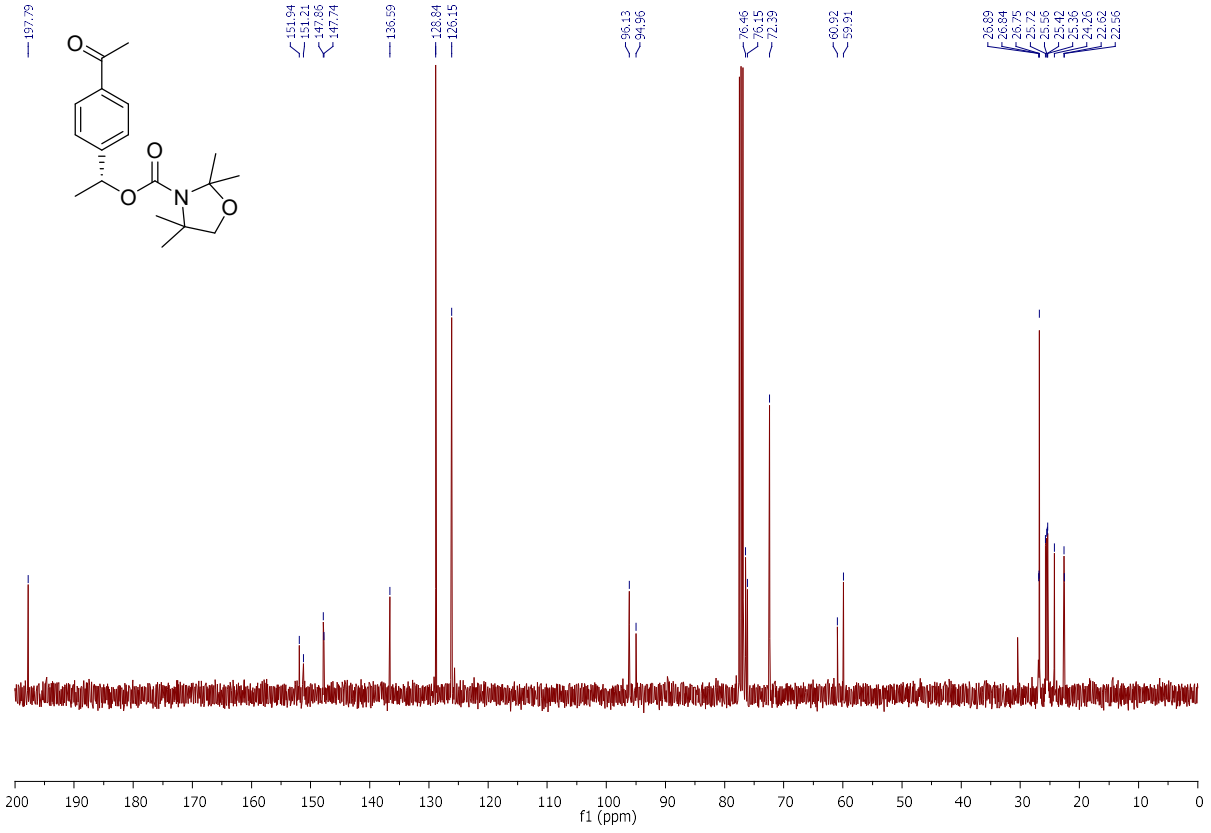
<Peak Table>

PDA Ch1 212nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	6.013	99.288	7950741	794641	0.000		M
2	7.077	0.712	56985	5713	0.000		M
Total		100.000	8007726	800354			

(*R*)-1-(4-acetylphenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5e** :





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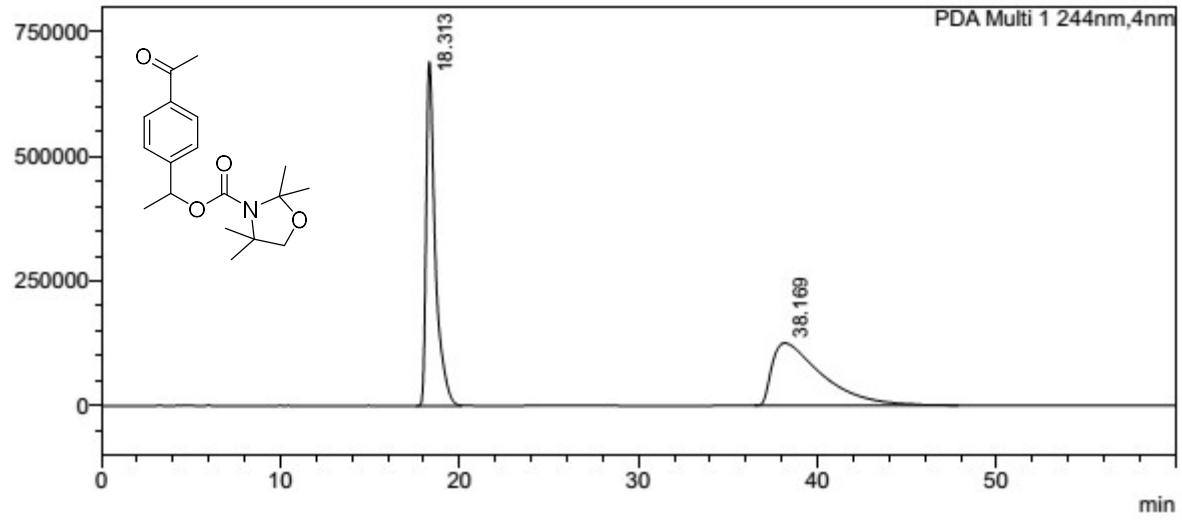


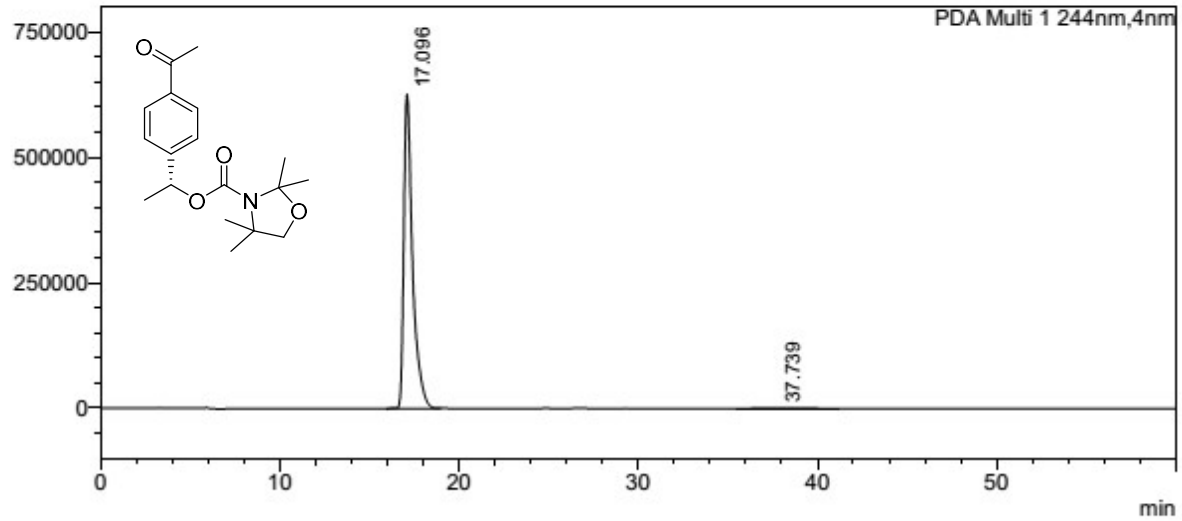
<Peak Table>

PDA Ch1 244nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	18.313	50.010	24456474	690064	0.000		M
2	38.169	49.990	24446567	125294	0.000		M
Total		100.000	48903041	815359			

<Chromatogram>

uAU

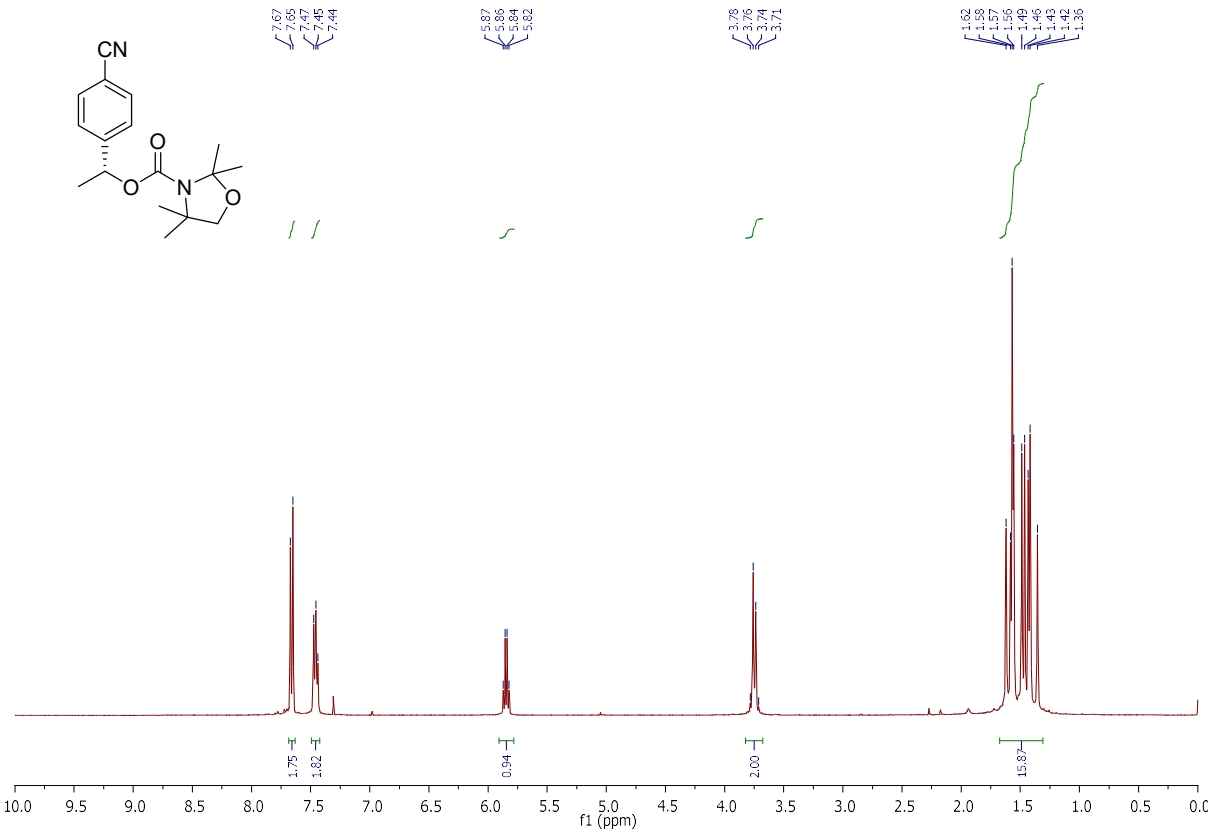


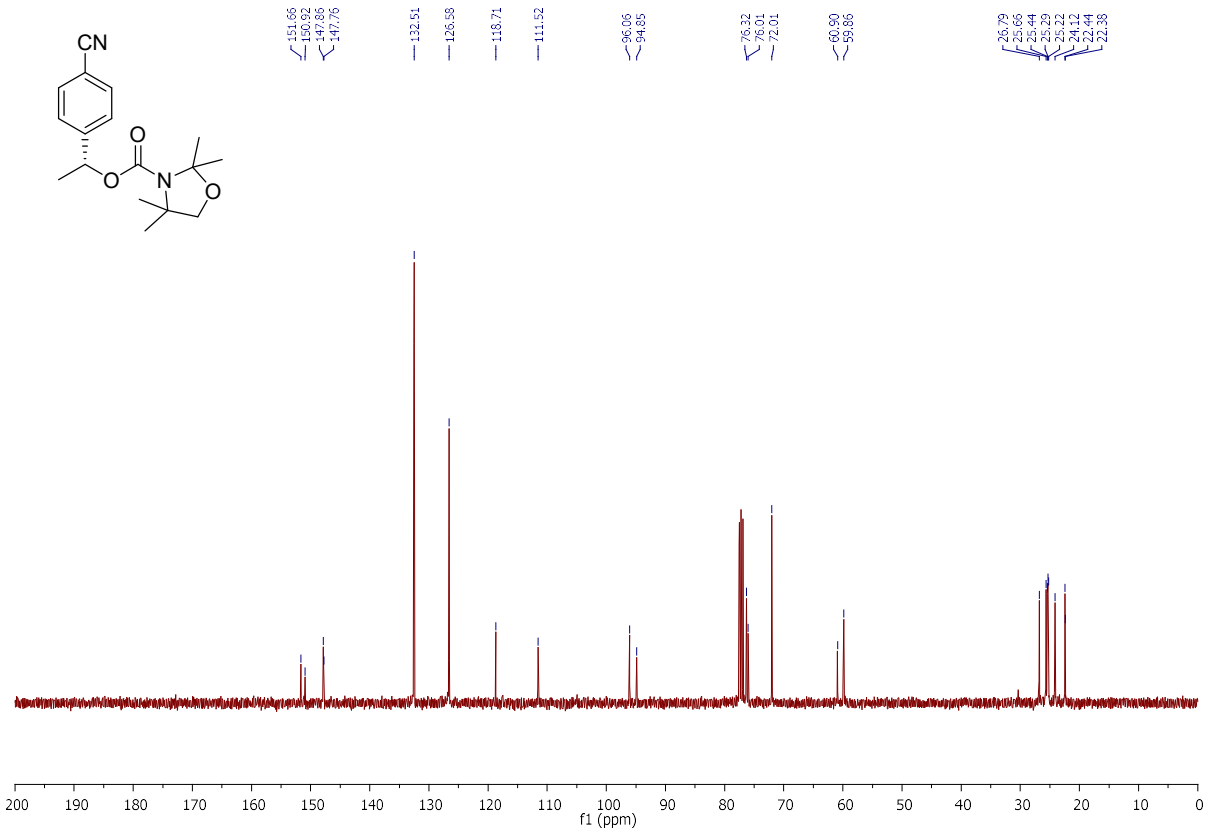
<Peak Table>

PDA Ch1 244nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	17.096	99.561	21282071	626756	0.000		M
2	37.739	0.439	93823	570	0.000		M
Total		100.000	21375895	627326			

(*R*)-(-)-1-(4-cyanophenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5f** :





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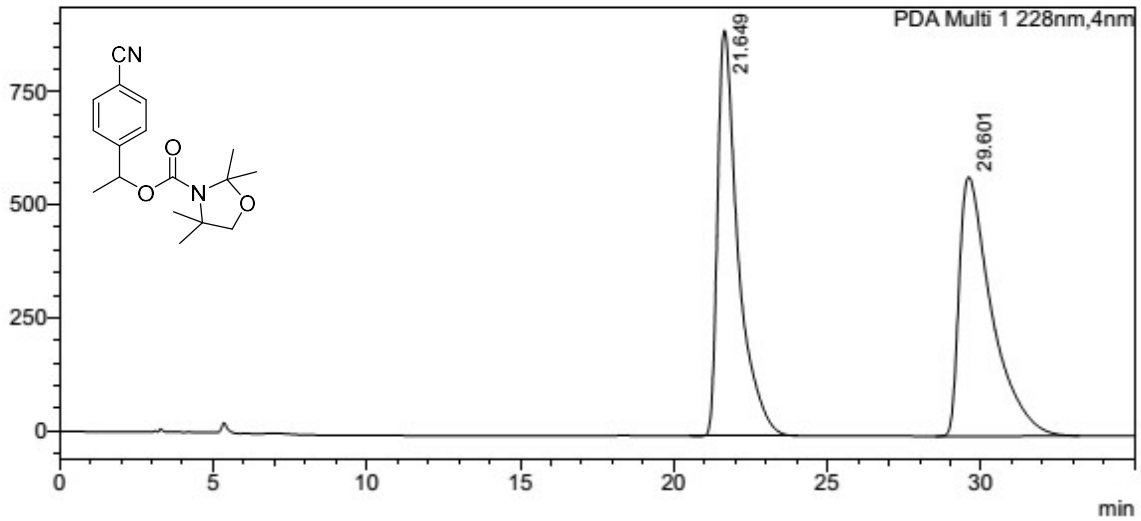


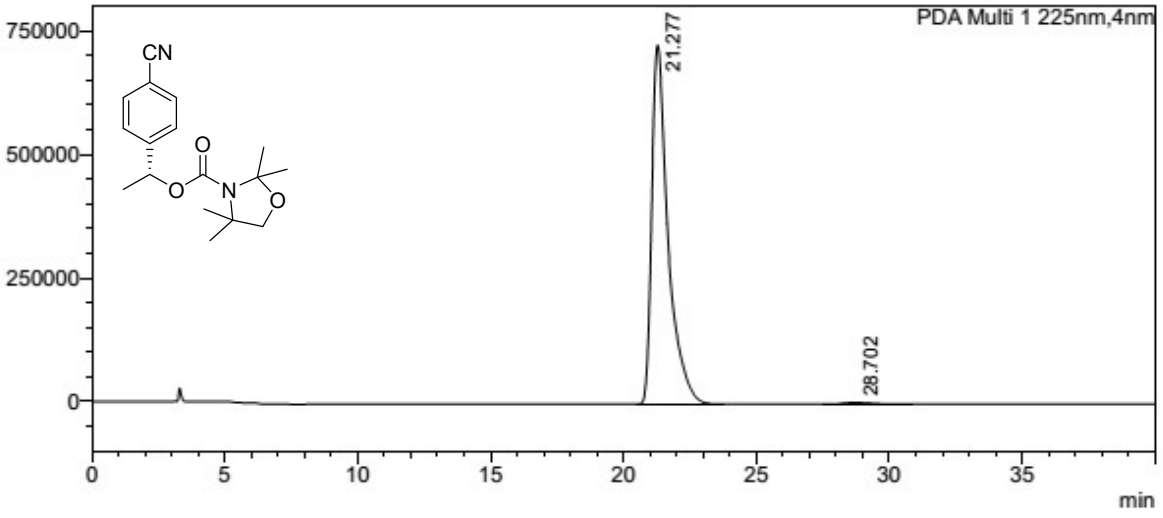
<Peak Table>

PDA Ch1 228nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	21.649	49.694	41665069	896677	0.000		M
2	29.601	50.306	42178598	572999	0.000		M
Total		100.000	83843667	1469676			

<Chromatogram>

uAU

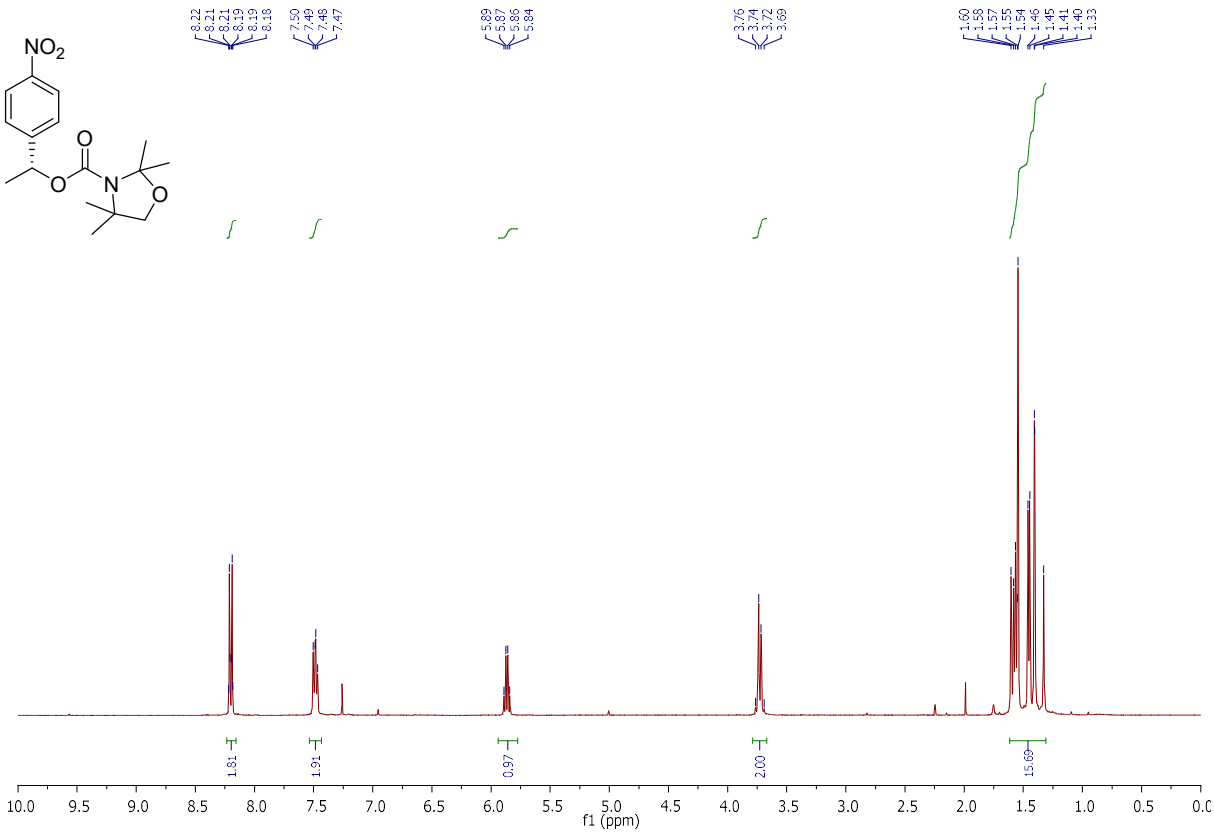


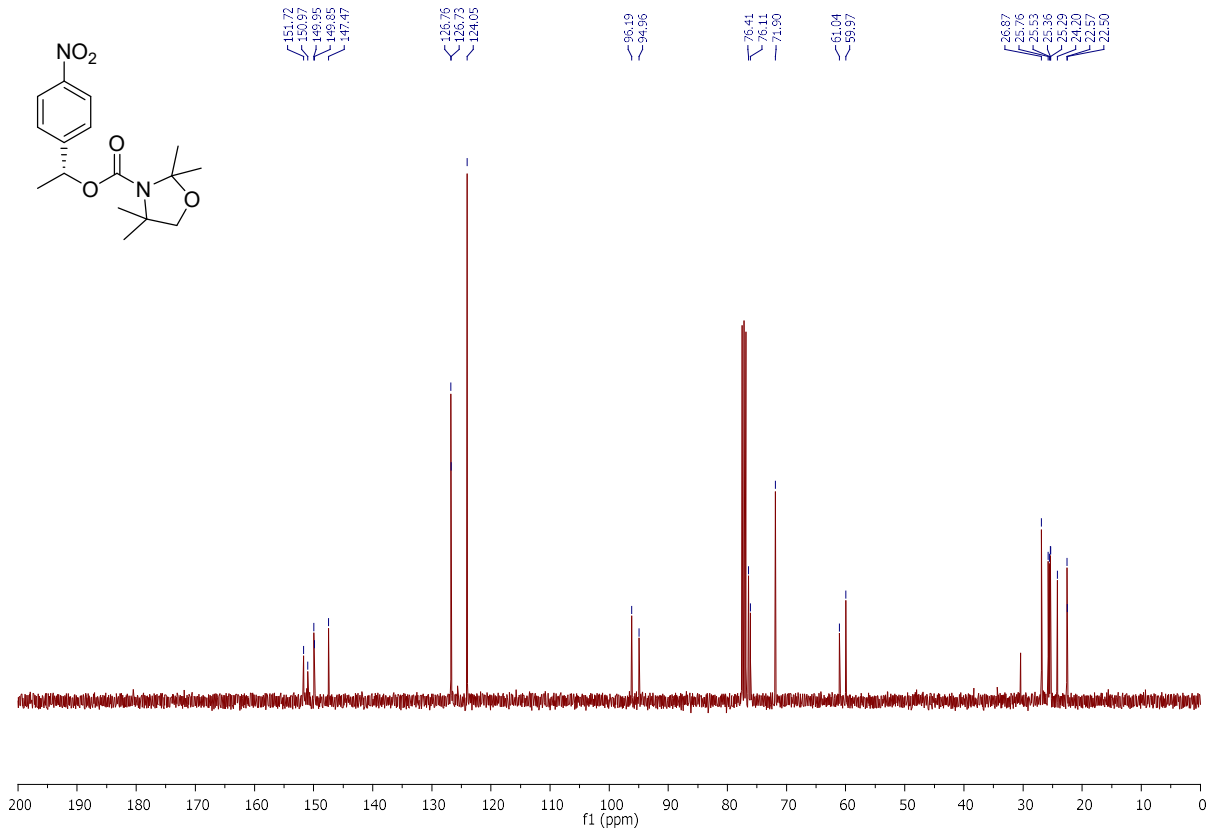
<Peak Table>

PDA Ch1 225nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	21.277	99.354	30971763	726127	0.000		M
2	28.702	0.646	201260	3189	0.000		M
Total		100.000	31173023	729316			

(*R*)-(-)-1-(4-nitrophenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5g** :





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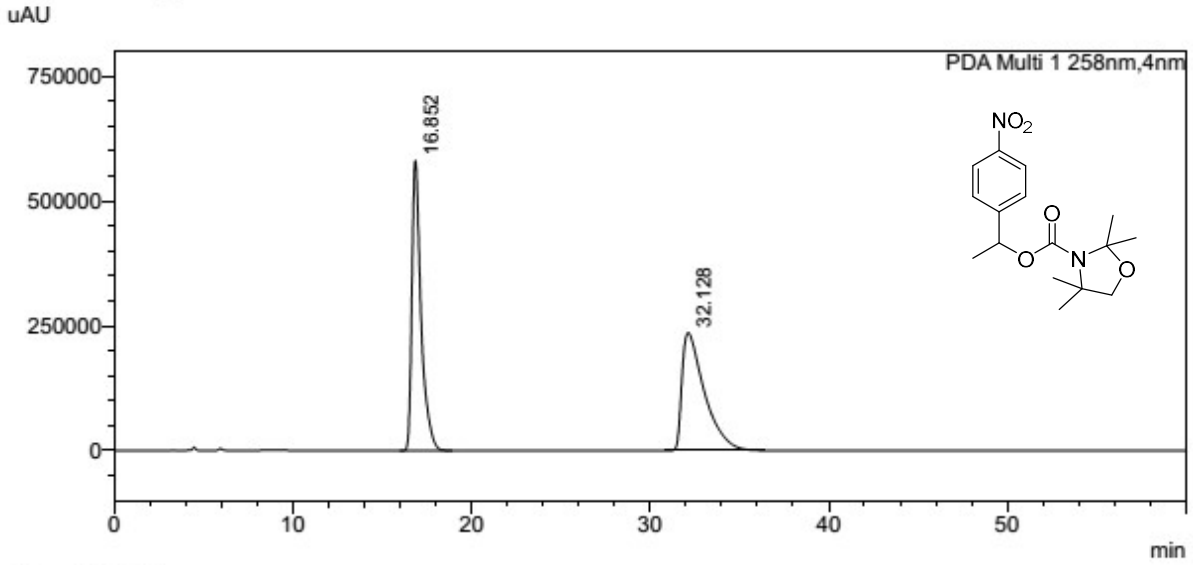
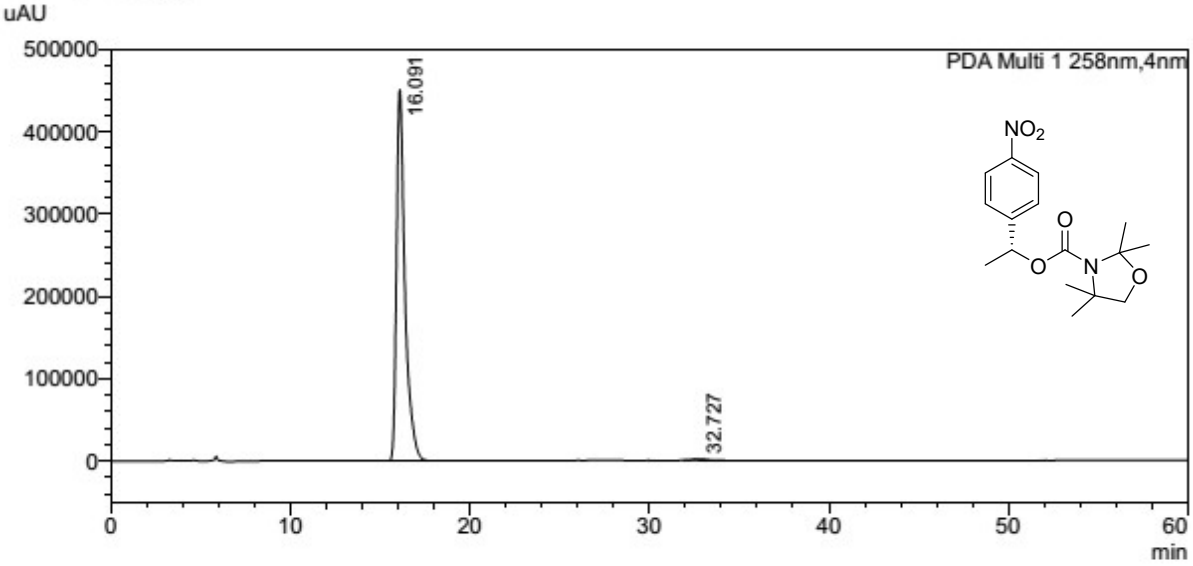


<Peak Table>

PDA Ch1 258nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	16.852	50.010	20722164	581688	0.000		M
2	32.128	49.990	20713573	235944	0.000		M
Total		100.000	41435736	817631			

<Chromatogram>

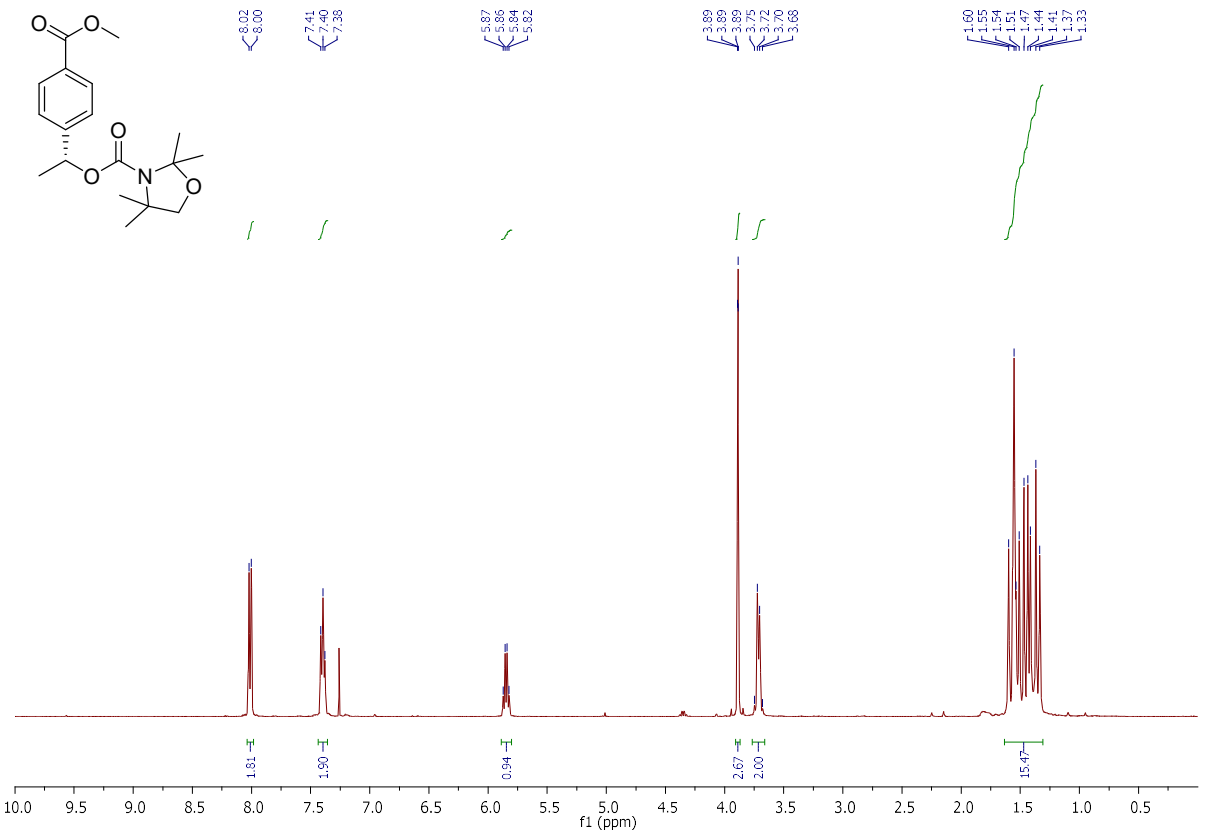


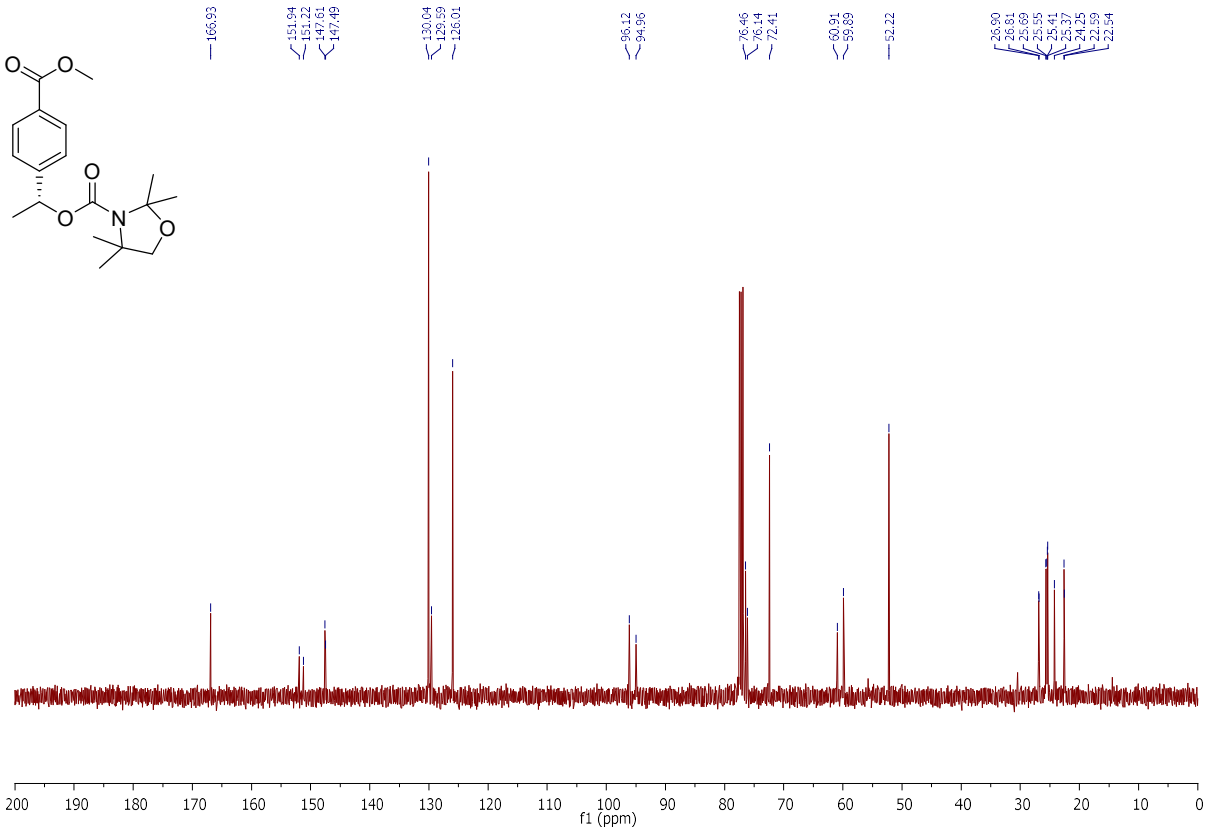
<Peak Table>

PDA Ch1 258nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	16.091	99.316	14798702	451461	0.000		
2	32.727	0.684	101864	1585	0.000		
Total		100.000	14900566	453045			

(*R*)-(+)-1-(4-(methoxycarbonyl)phenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5h** :





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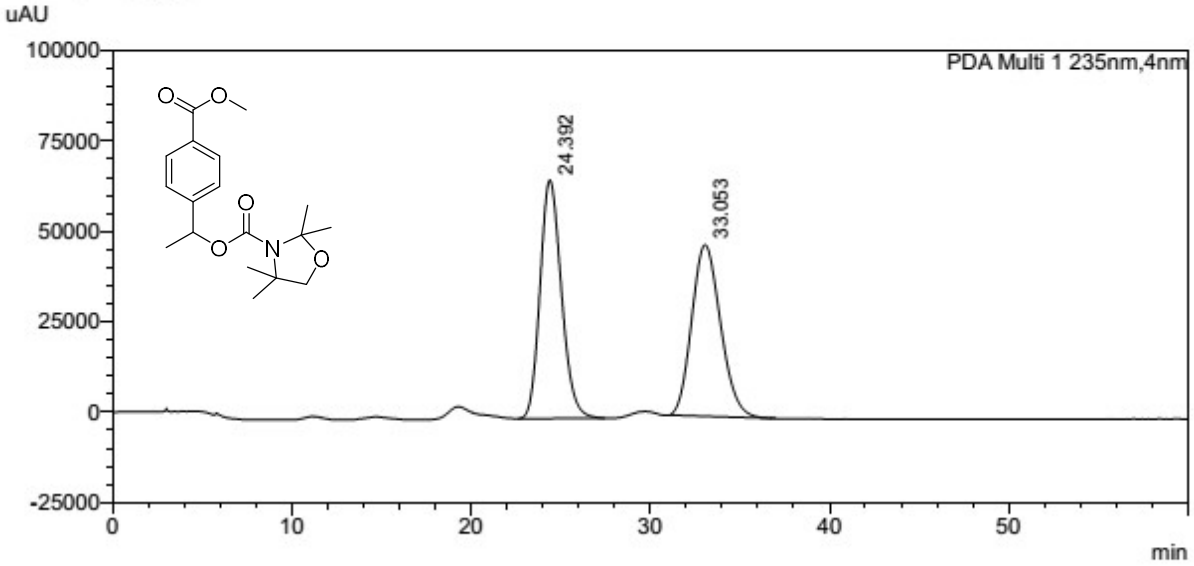
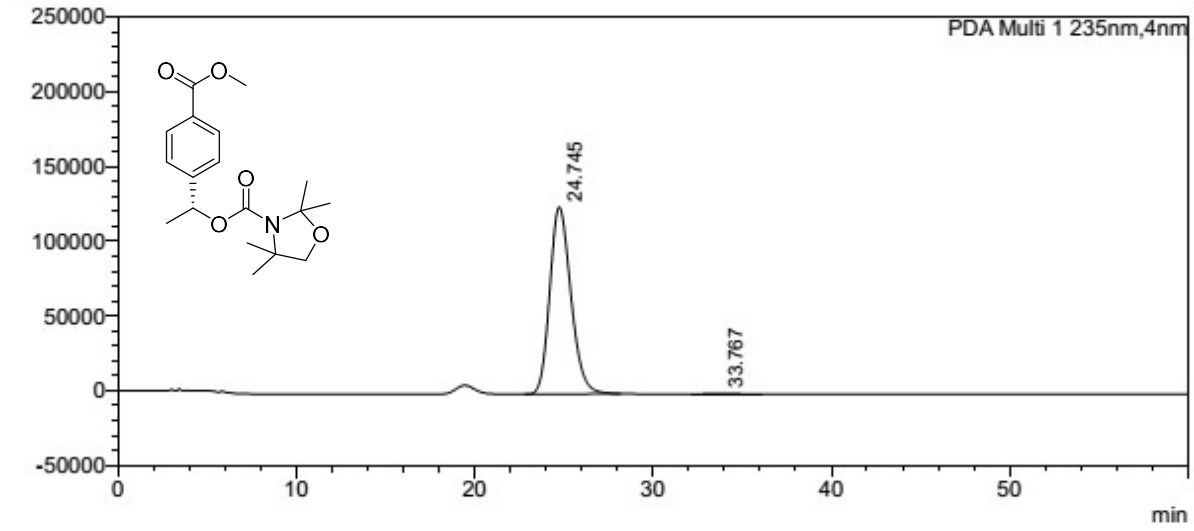


<Peak Table>

PDA Ch1 235nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	24.392	50.770	5477224	65982	0.000		M
2	33.053	49.230	5311090	47446	0.000		M
Total		100.000	10788314	113428			

<Chromatogram>

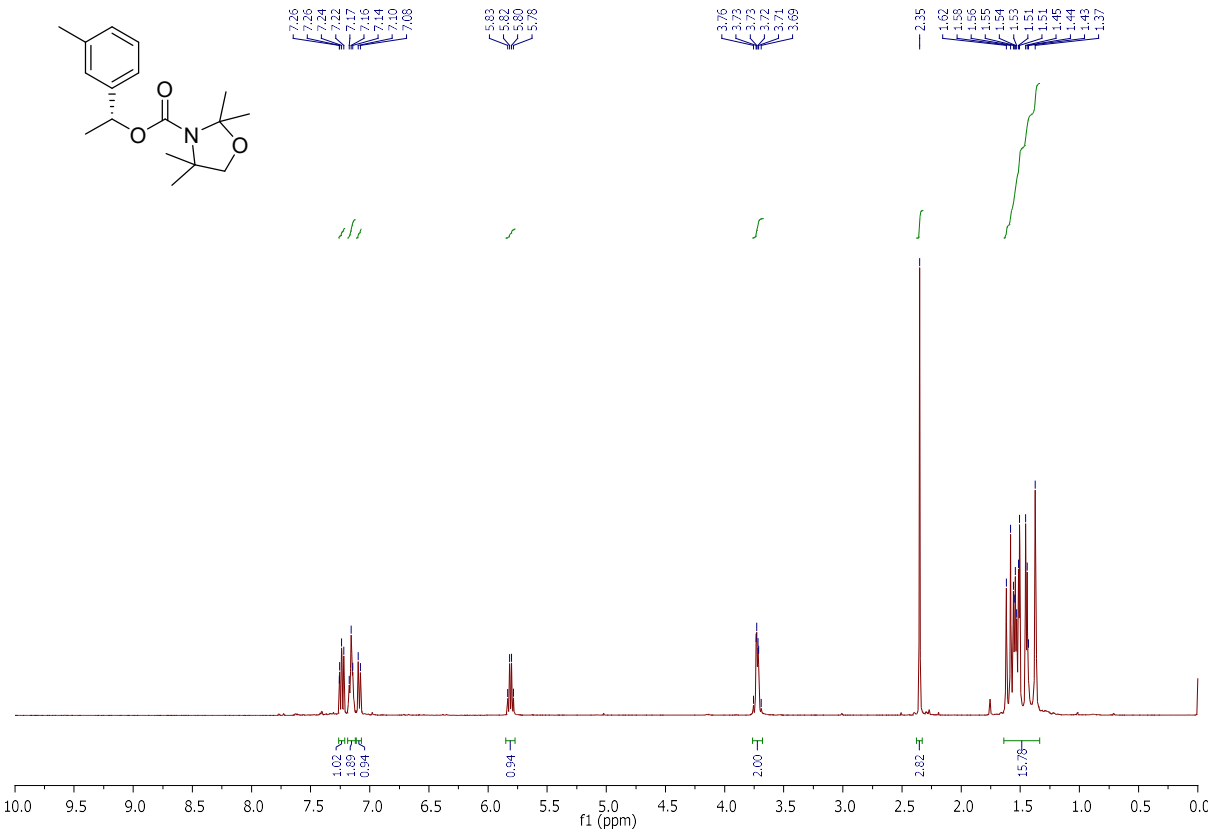


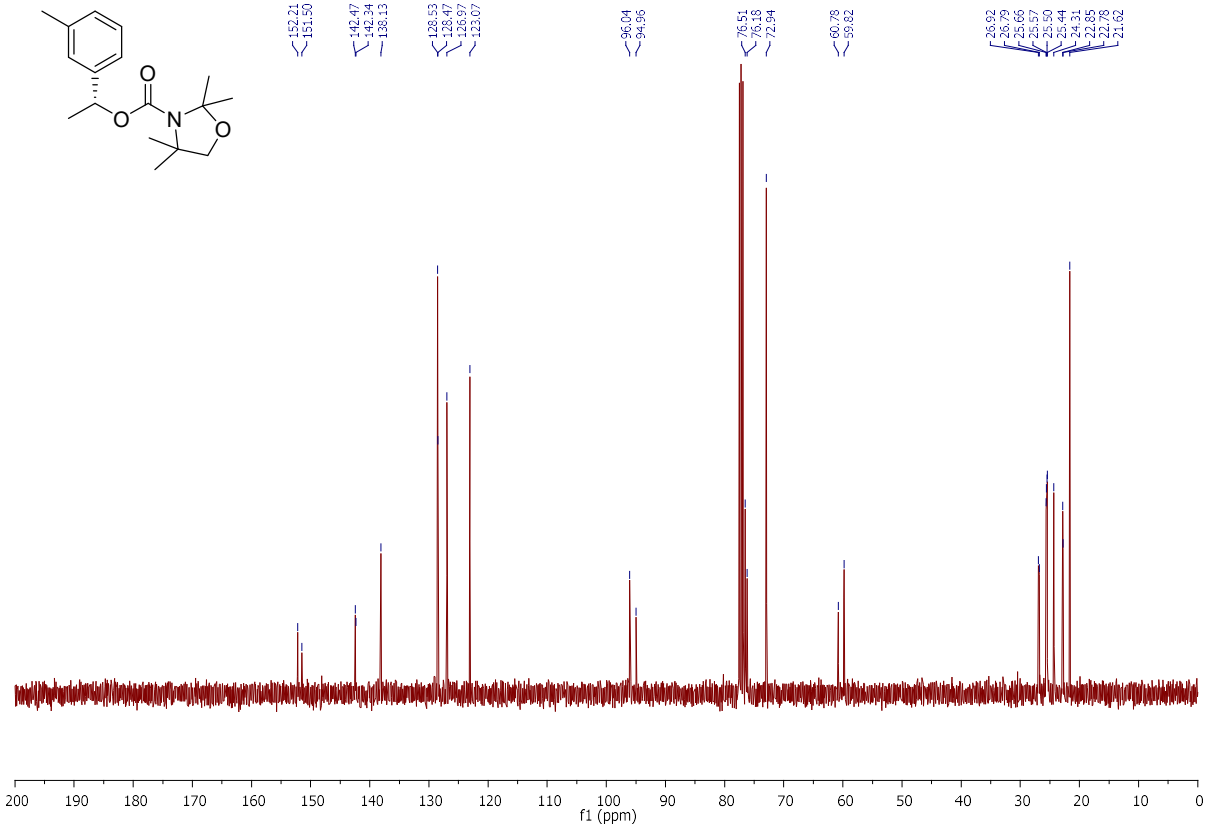
<Peak Table>

PDA Ch1 235nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	24.745	99.462	10317069	125147	0.000		M
2	33.767	0.538	55813	529	0.000		M
Total		100.000	10372882	125676			

(*R*)-(+)-1-(*m*-tolyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5i** :





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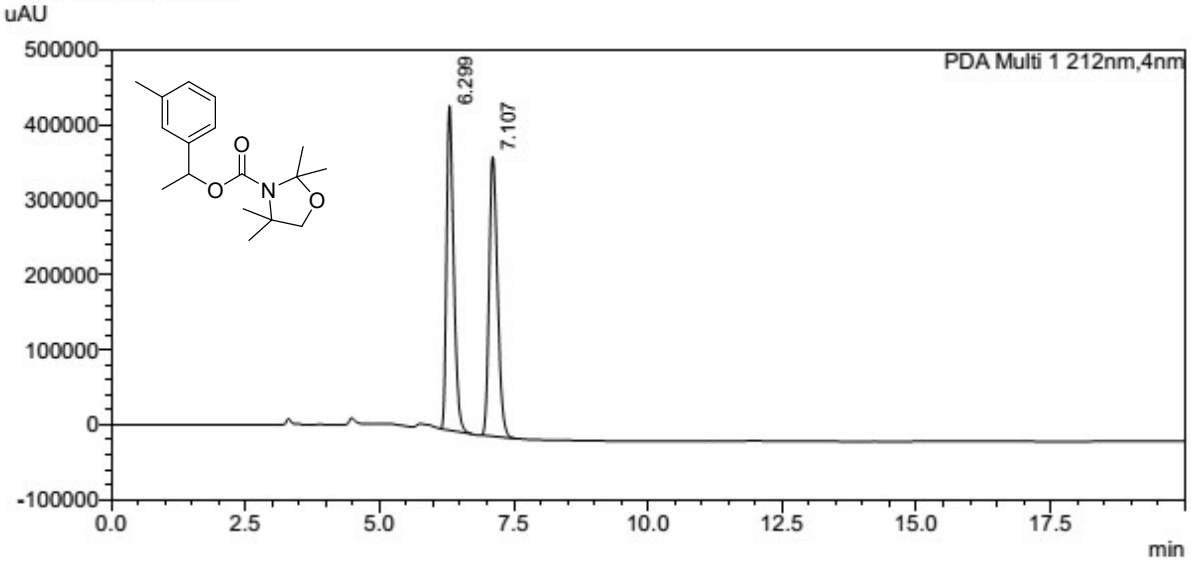

<Peak Table>

PDA Ch1 212nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	6.299	49.684	4012408	432727	0.000		M
2	7.107	50.316	4063427	373139	0.000		M
Total		100.000	8075835	805865			

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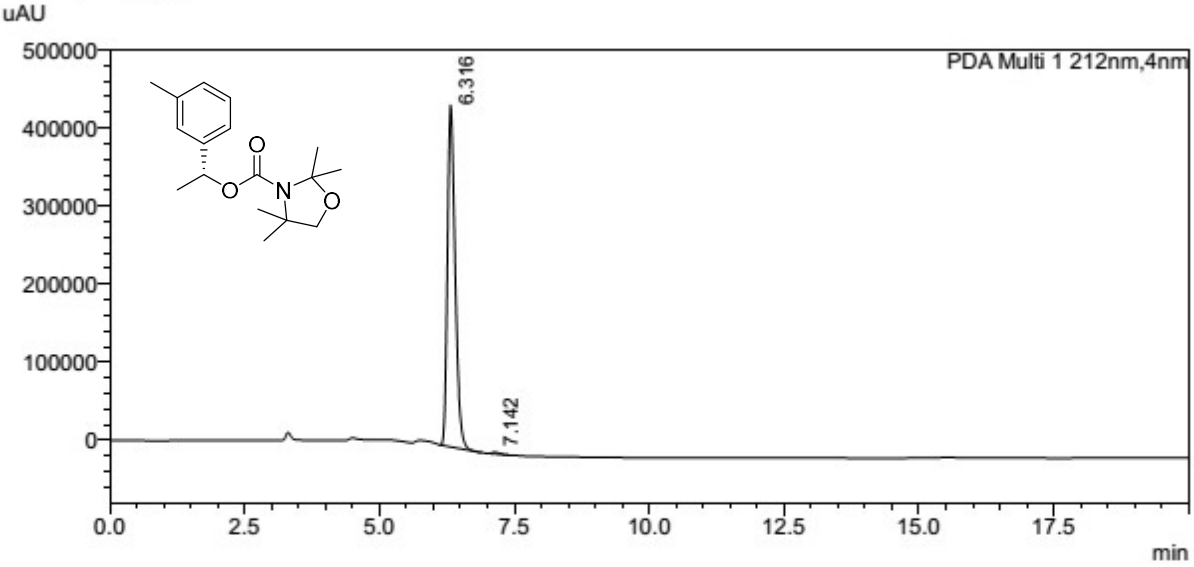
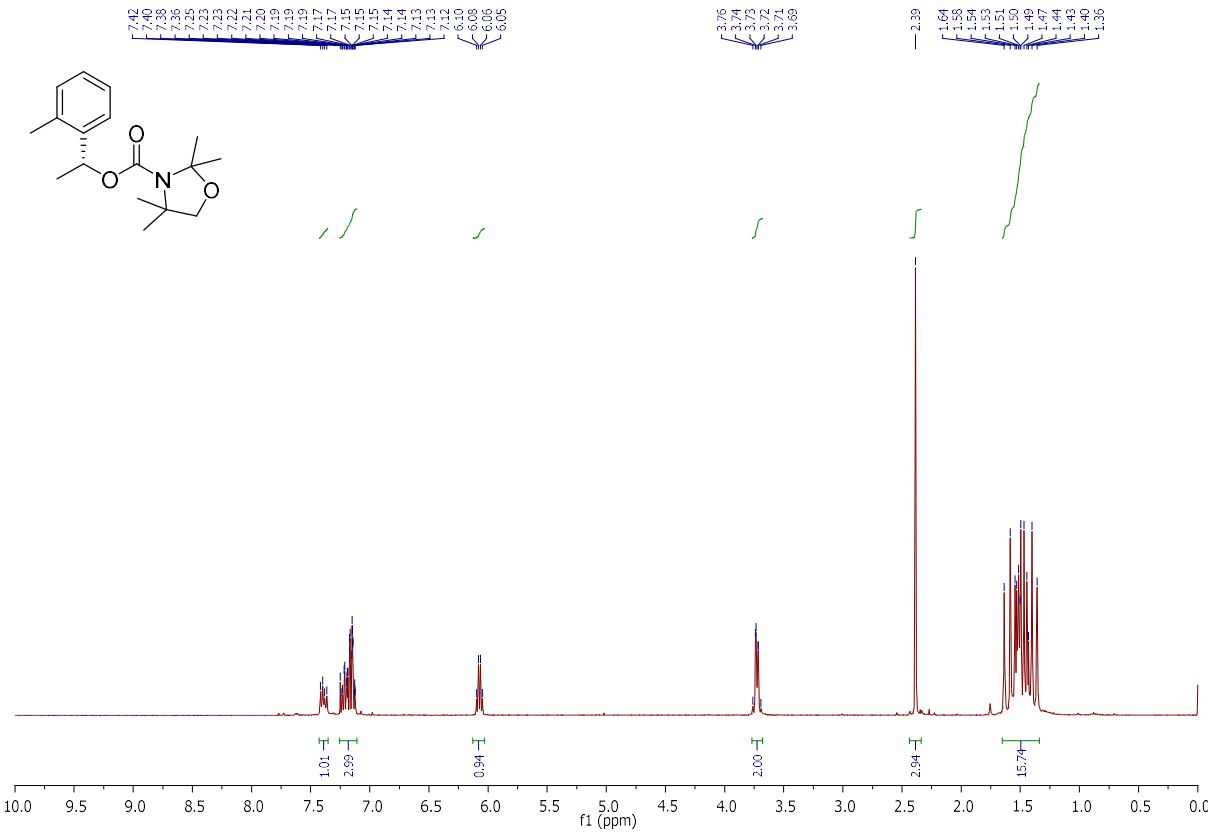


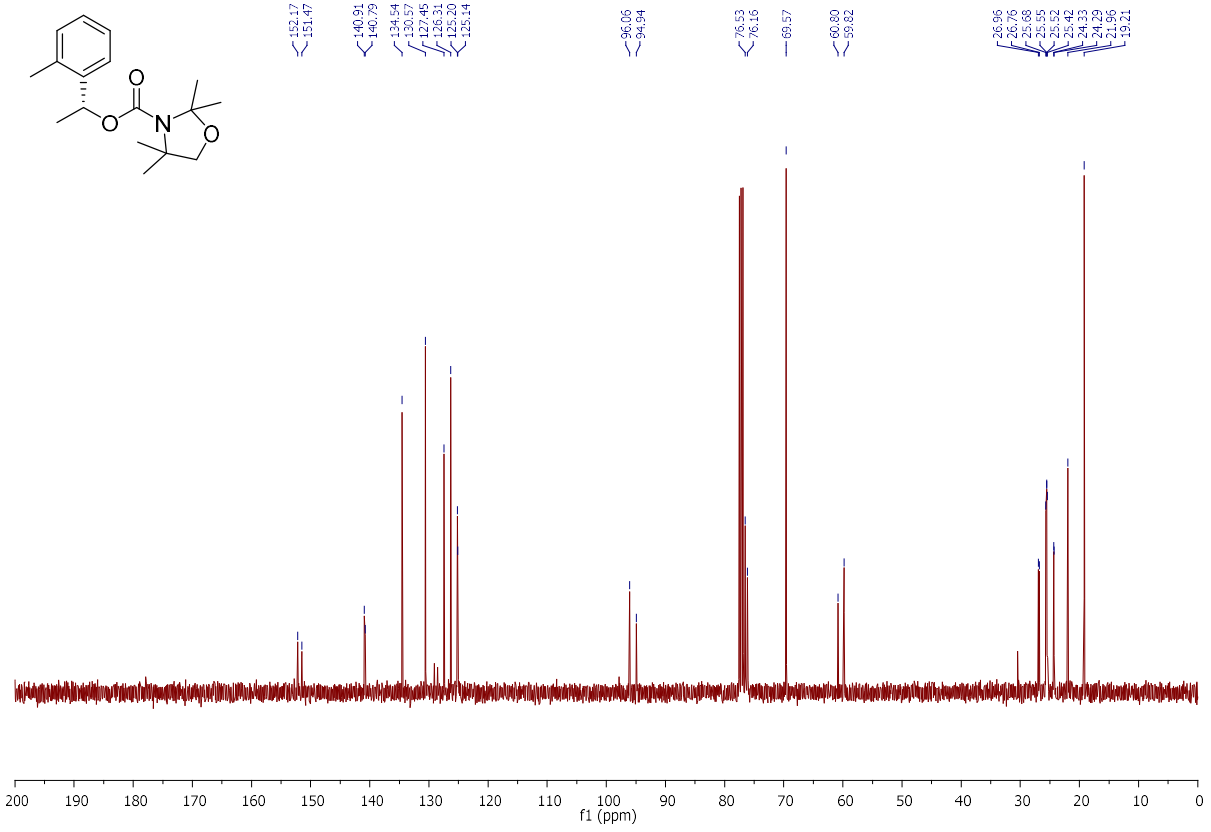
<Peak Table>

PDA Ch1 212nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	6.316	99.603	4356598	438058	0.000		M
2	7.142	0.397	17346	1916	0.000		M
Total		100.000	4373944	439974			

(*R*)-(-)-1-(*o*-tolyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5j** :





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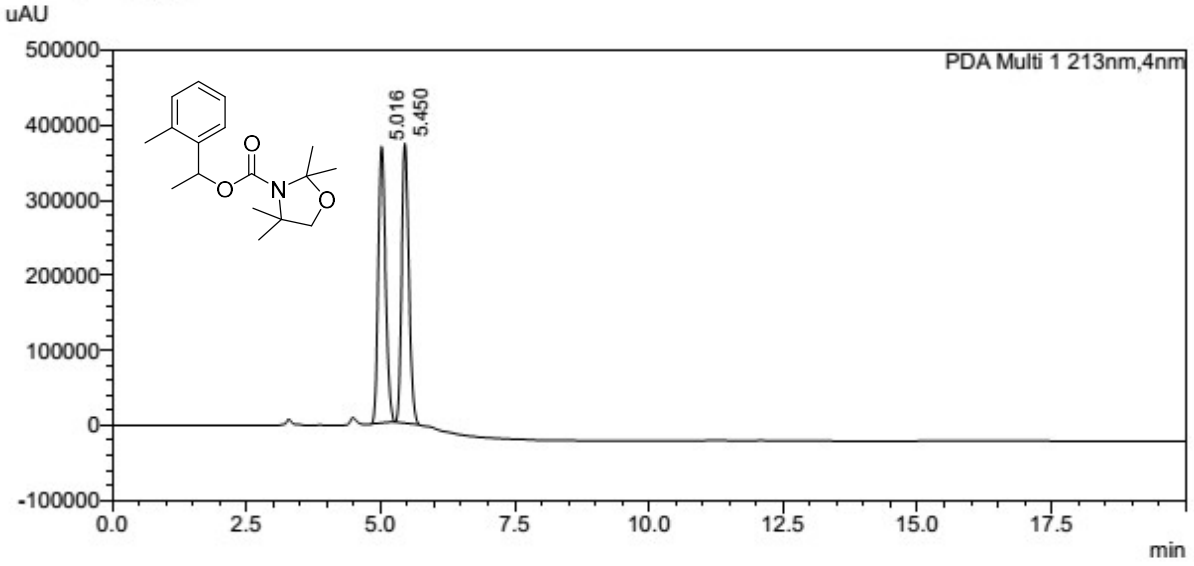

<Peak Table>

PDA Ch1 213nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	5.016	50.134	3483496	368861	0.000		M
2	5.450	49.866	3464921	372999	0.000		M
Total		100.000	6948417	741860			

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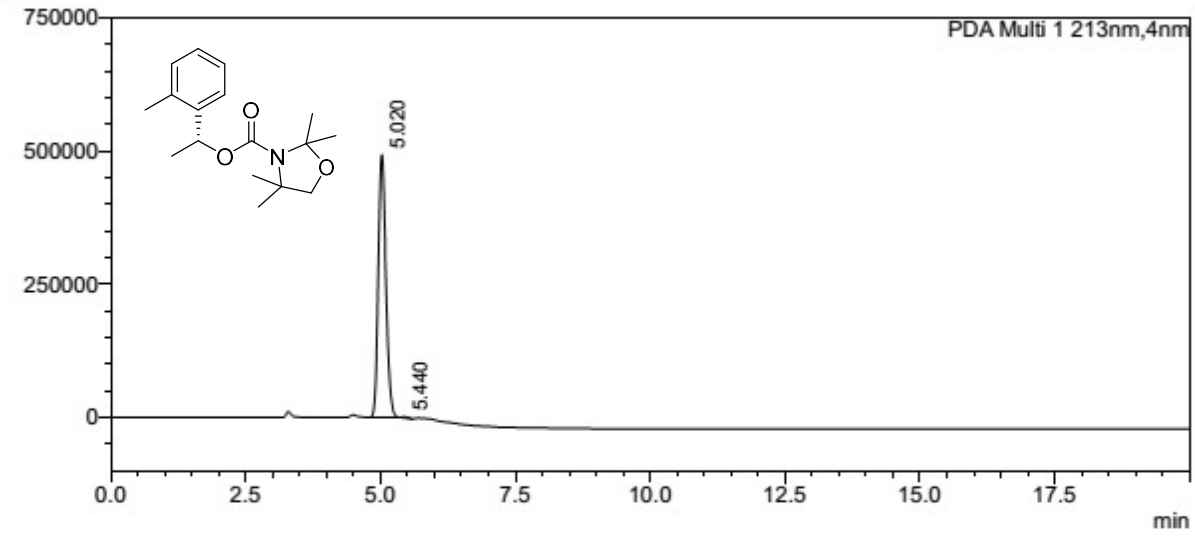
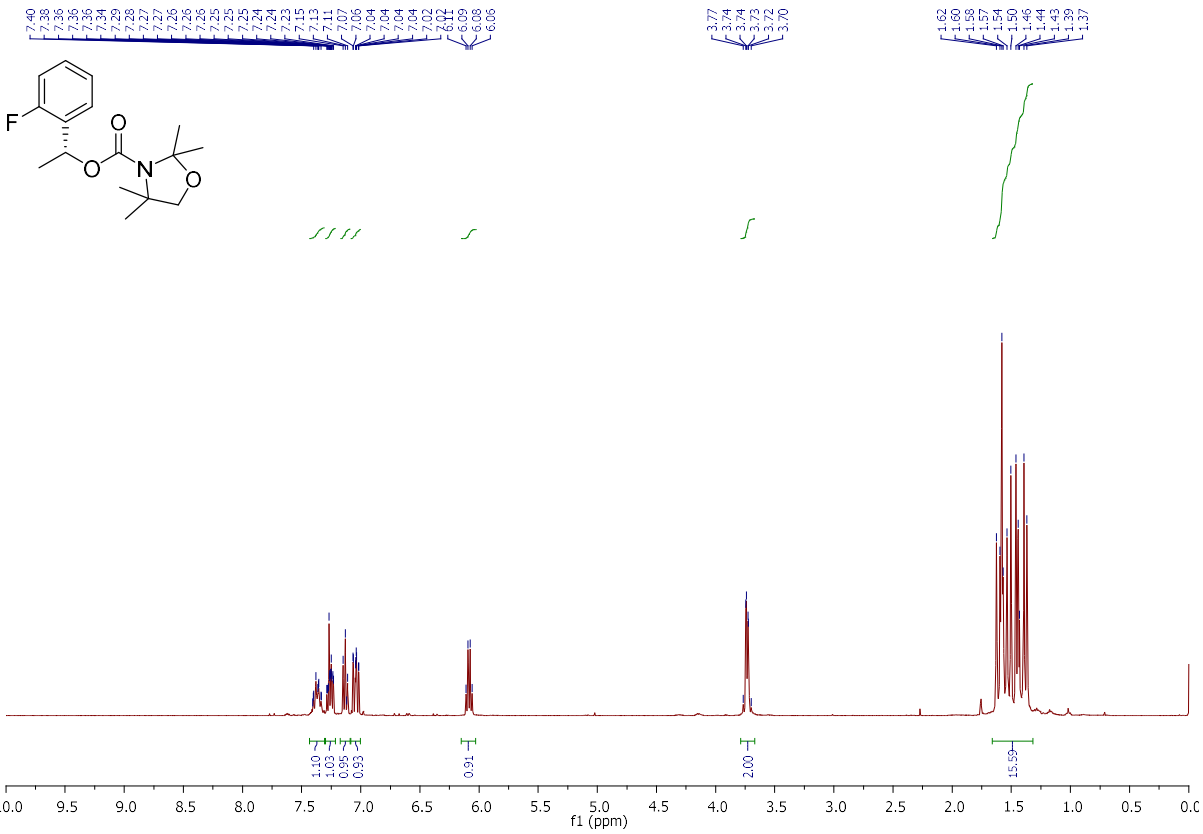


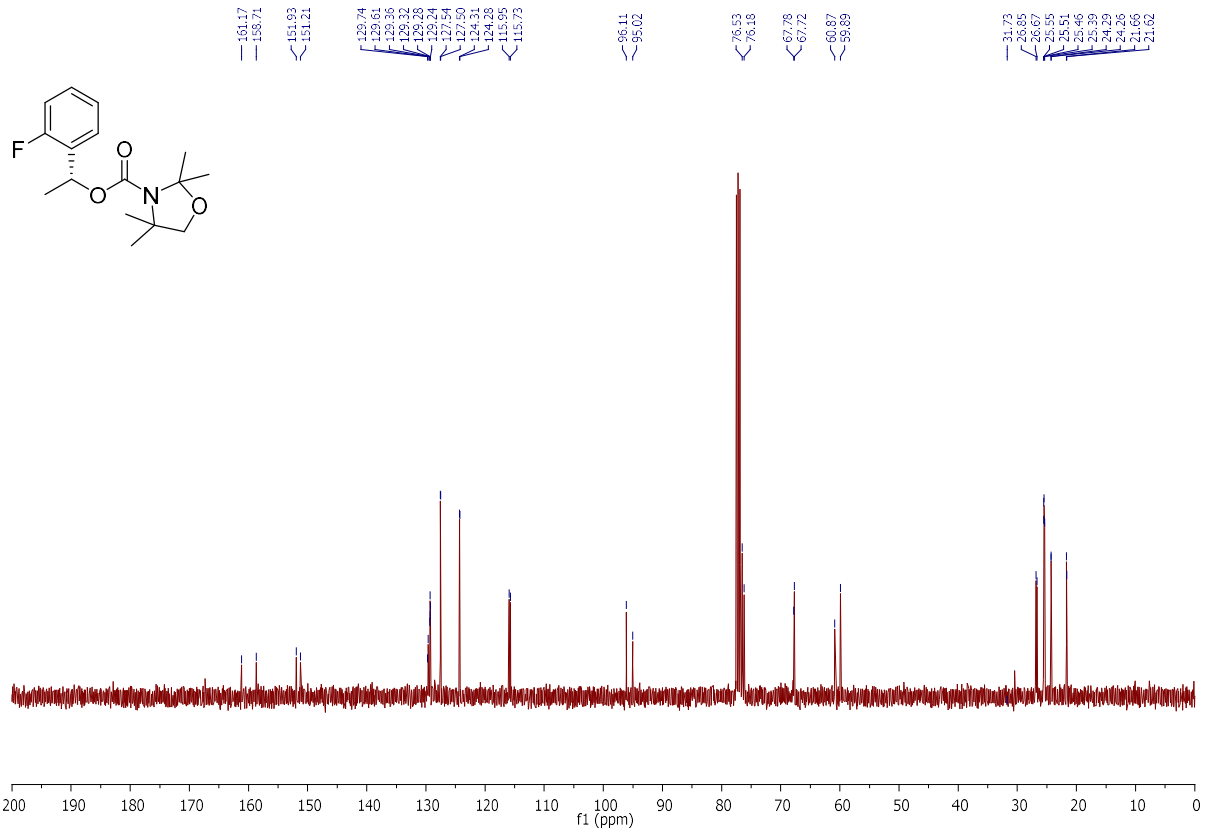
<Peak Table>

PDA Ch1 213nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	5.020	99.706	4803122	493245	0.000		M
2	5.440	0.294	14153	2160	0.000		M
Total		100.000	4817275	495404			

(*R*)-1-(2-fluorophenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5k** :





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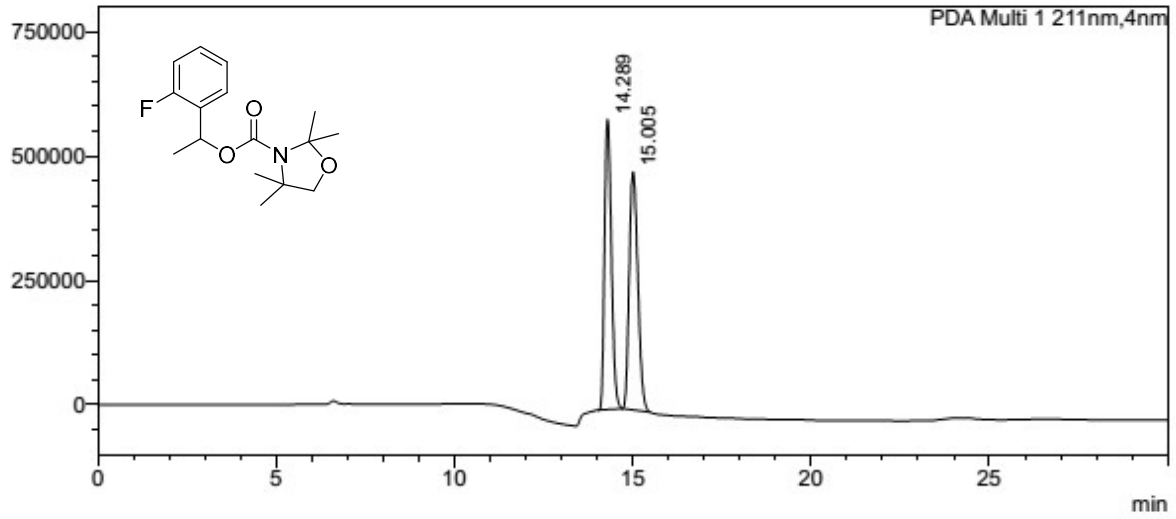


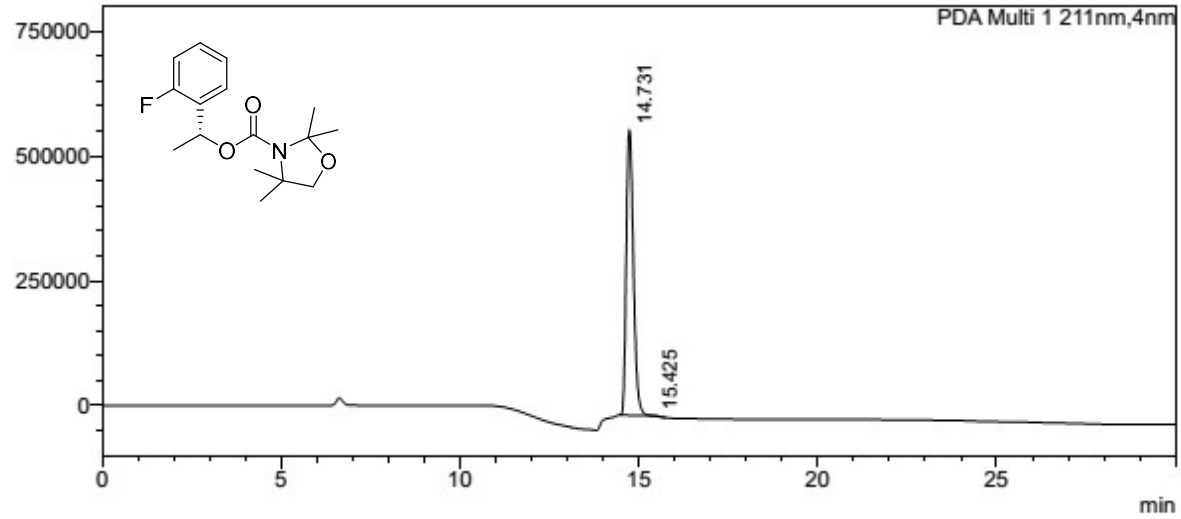
<Peak Table>

PDA Ch1 211nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	14.289	49.446	7846908	582933	0.000		M
2	15.005	50.554	8022630	477829	0.000		M
Total		100.000	15869538	1060762			

<Chromatogram>

uAU

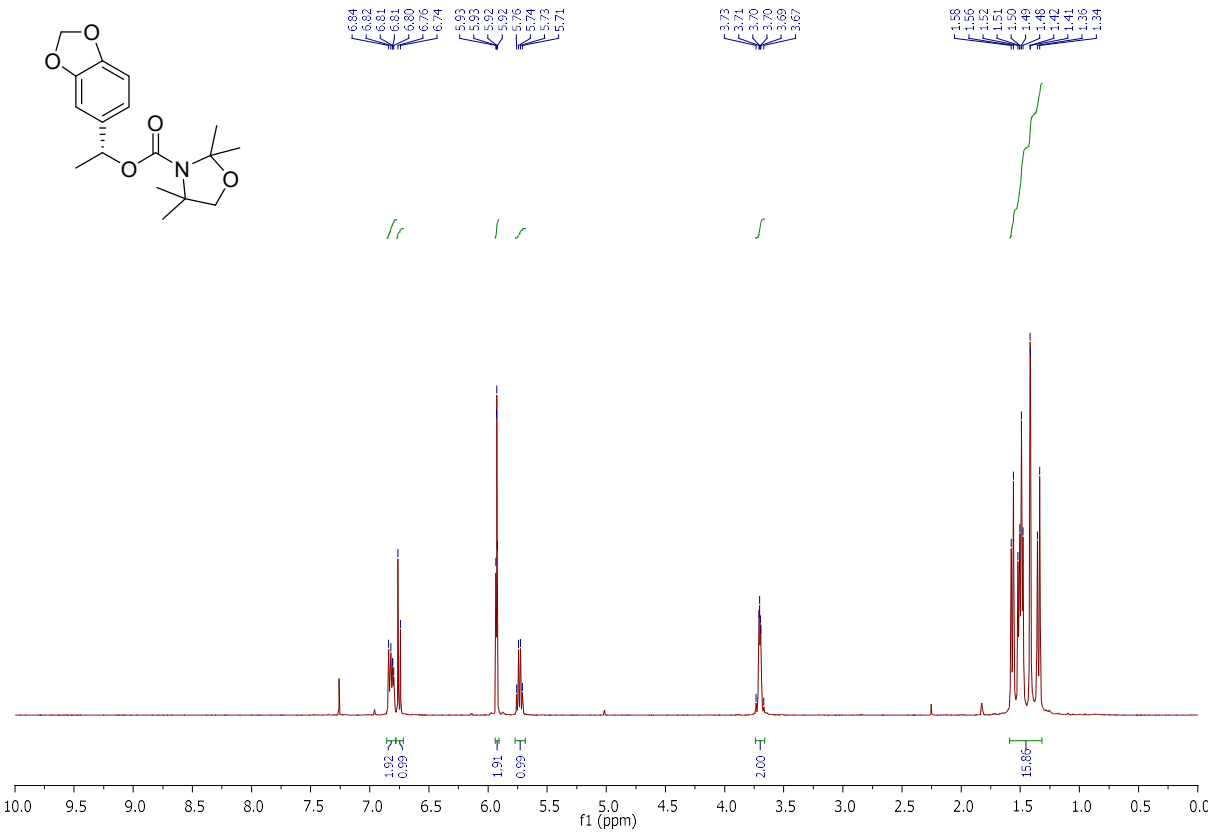


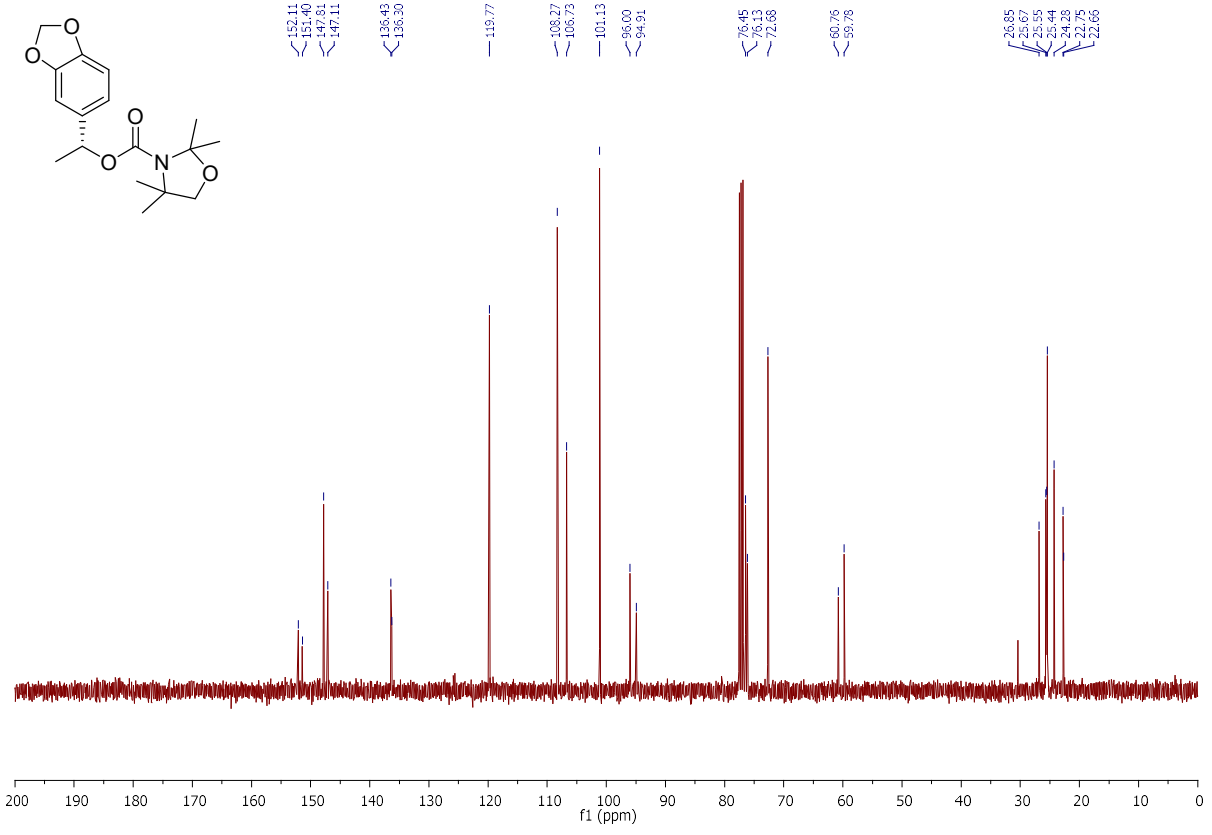
<Peak Table>

PDA Ch1 211nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	14.731	99.757	7949421	571860	0.000		M
2	15.425	0.243	19333	1463	0.000		M
Total		100.000	7968754	573323			

(*R*)-(+)-1-(benzo[1,3]dioxol-5-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5l** :





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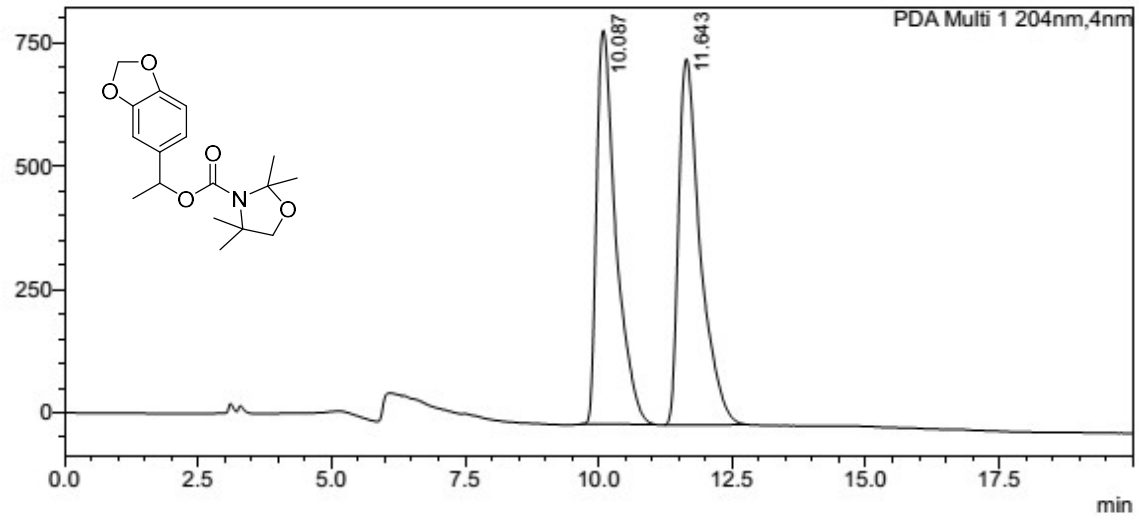


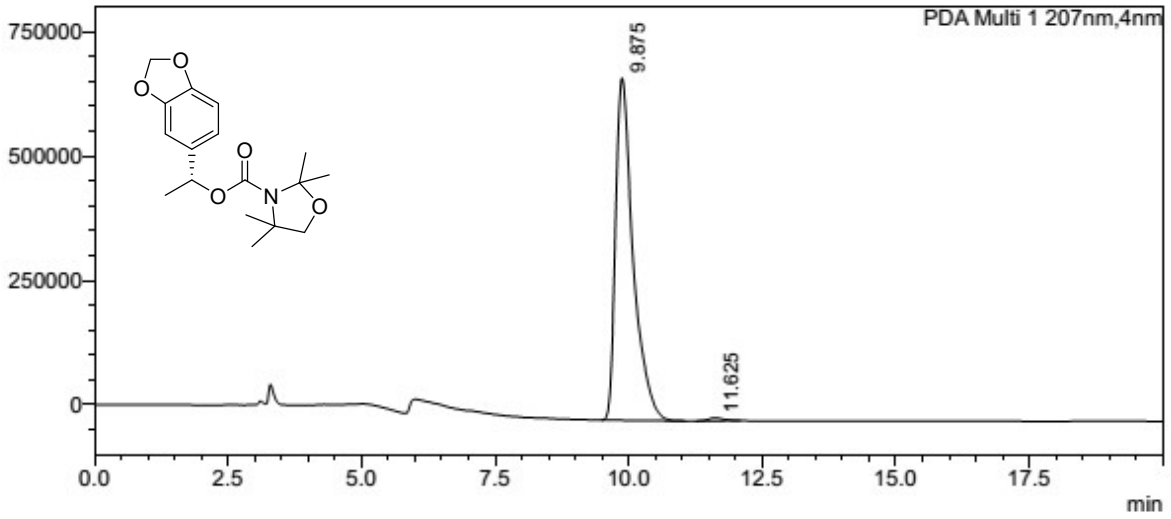
<Peak Table>

PDA Ch1 204nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.087	48.921	20146655	799670	48.921		M
2	11.643	51.079	21035156	742653	51.079		M
Total		100.000	41181811	1542323			

<Chromatogram>

uAU

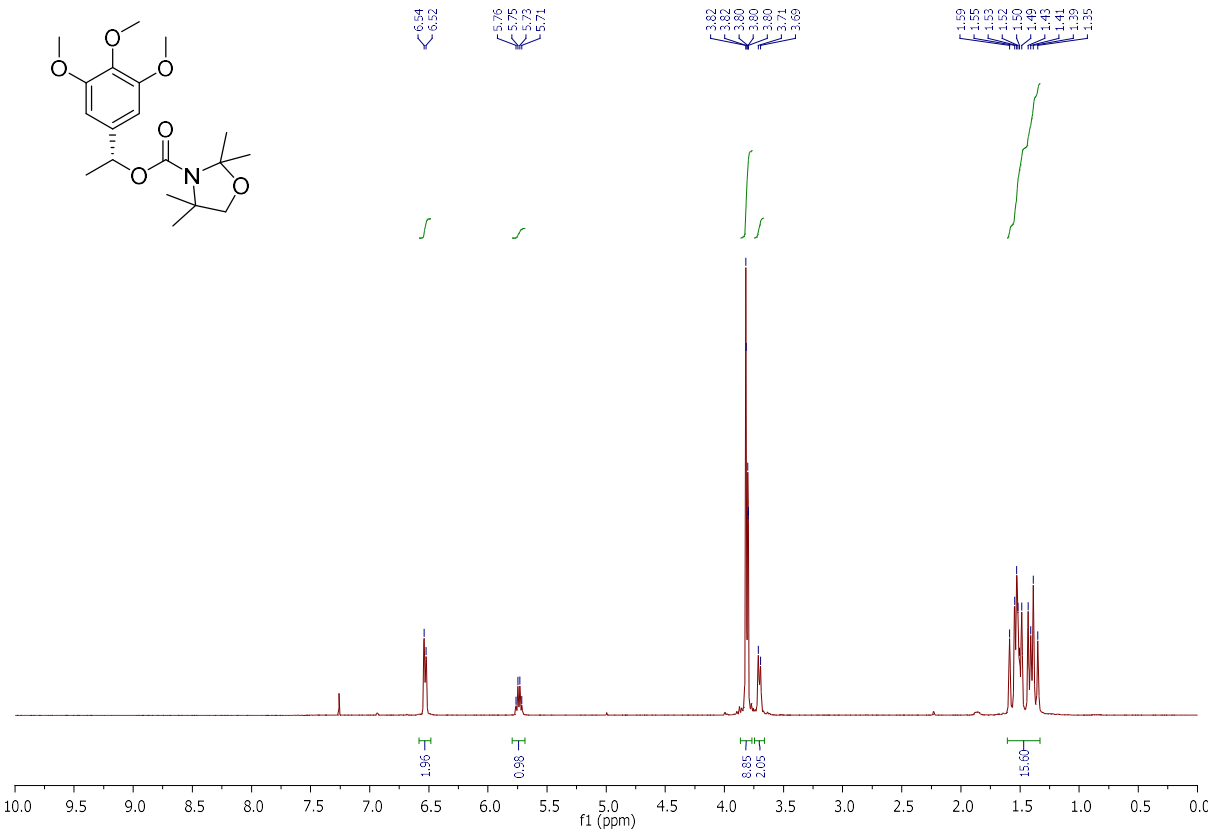


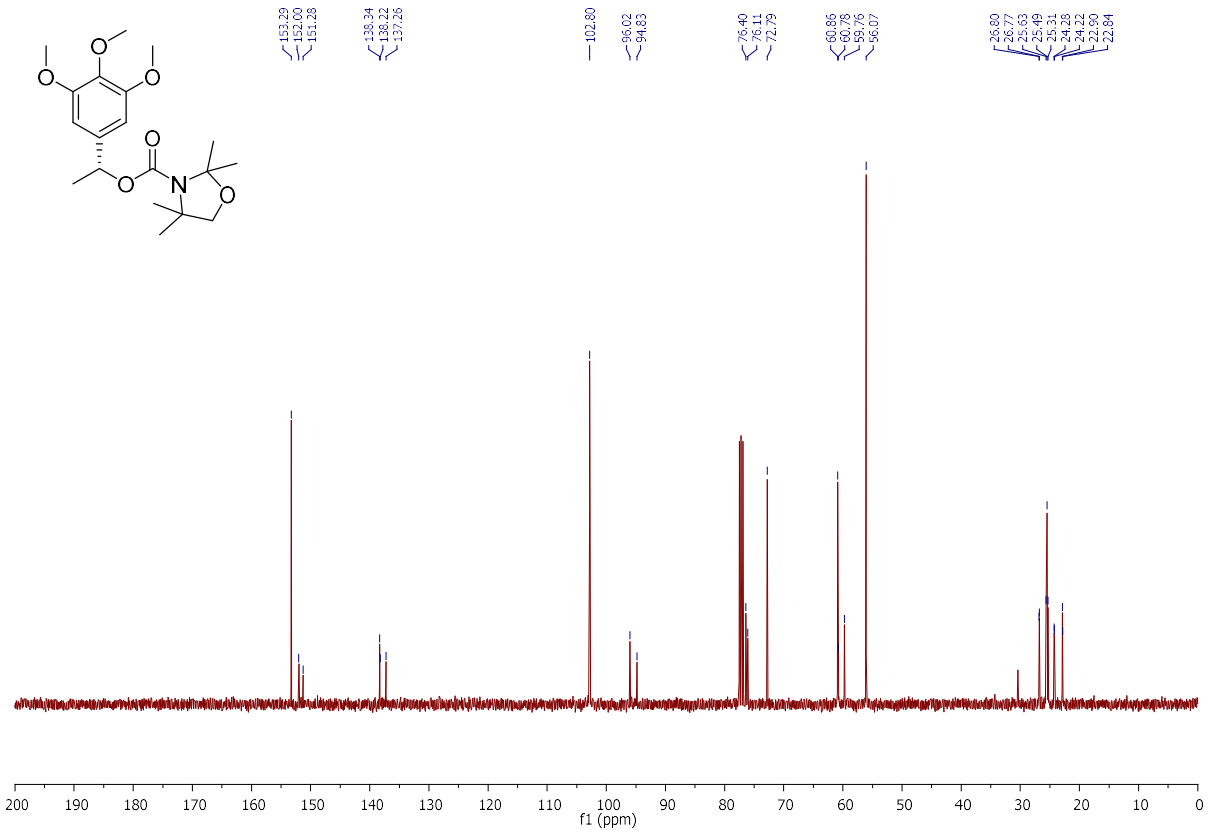
<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	9.875	99.307	15749744	687822	0.000		M
2	11.625	0.693	109928	5644	0.000		M
Total		100.000	15859672	693466			

(*R*)-(+)-1-(3,4,5-trimethoxyphenyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5m** :





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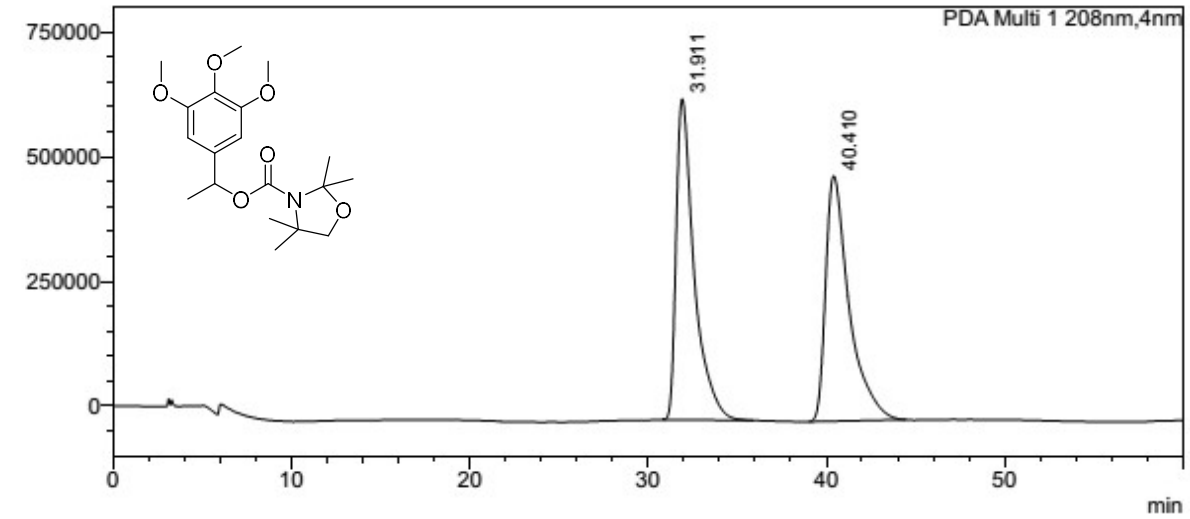


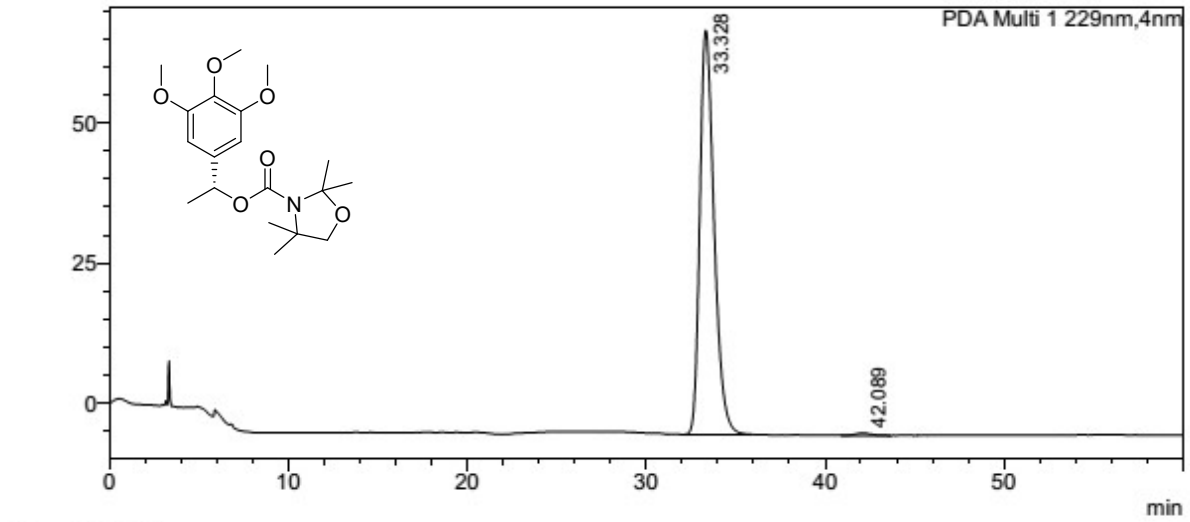
<Peak Table>

PDA Ch1 208nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	31.911	45271566	643665	0.000		M	
2	40.410	45145465	491616	0.000		M	
Total		90417030	1135281				

<Chromatogram>

mAU

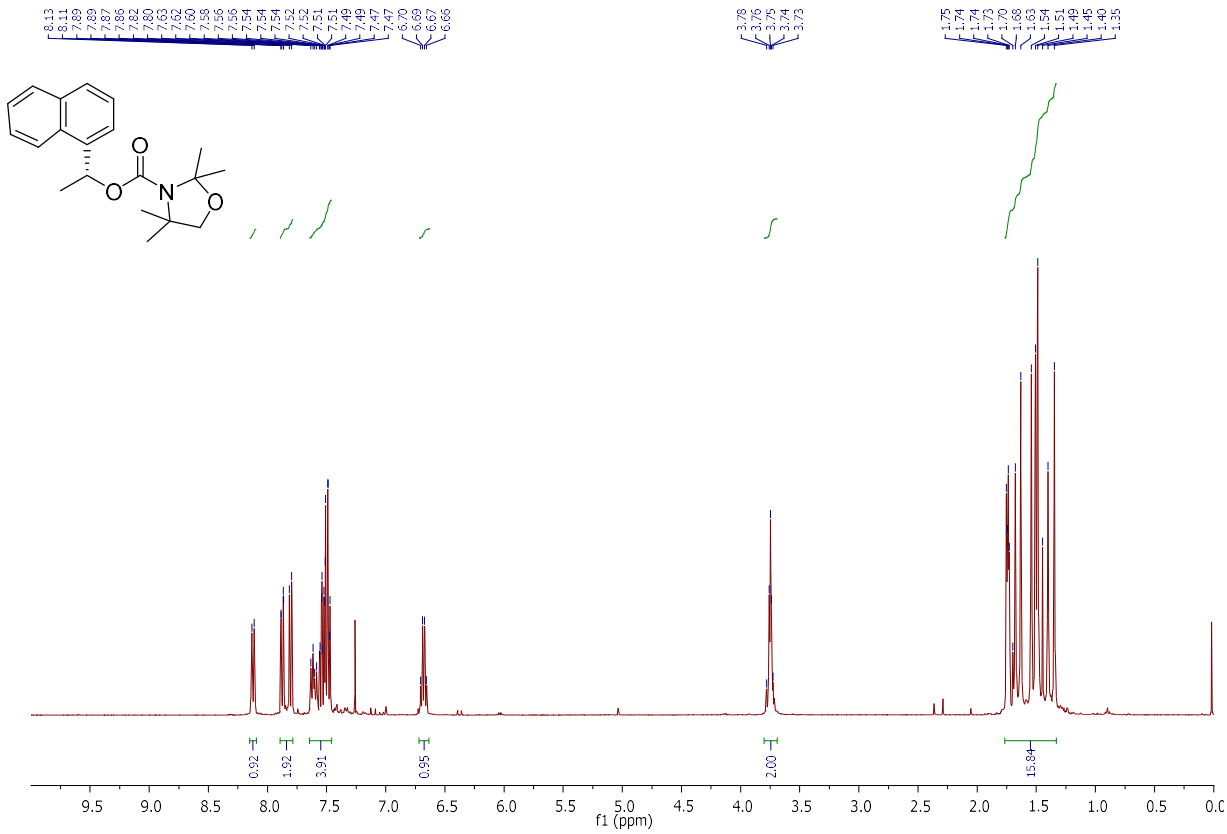


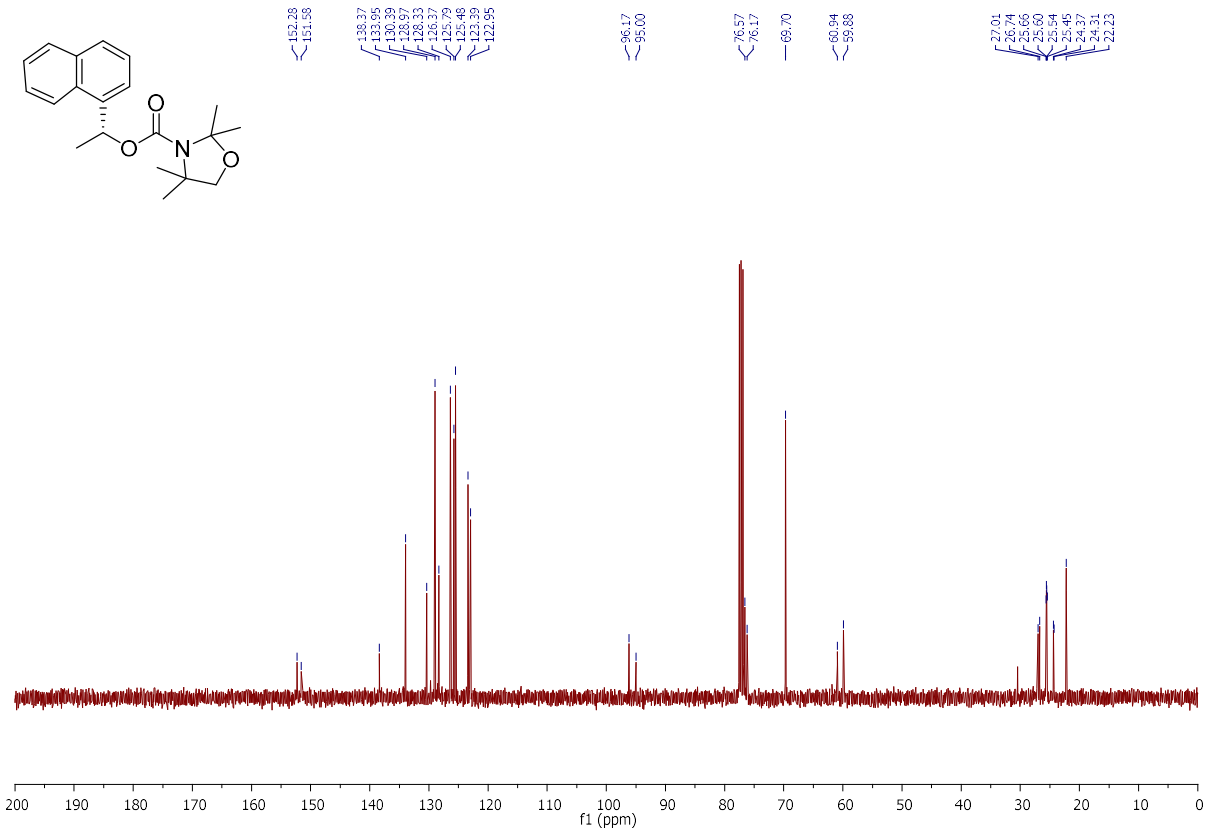
<Peak Table>

PDA Ch1 229nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	33.328	99.350	3997031	72016	0.000		M
2	42.089	0.650	26147	412	0.000		M
Total		100.000	4023178	72427			

(*R*)-(-)-1-(naphthalen-1-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5n** :





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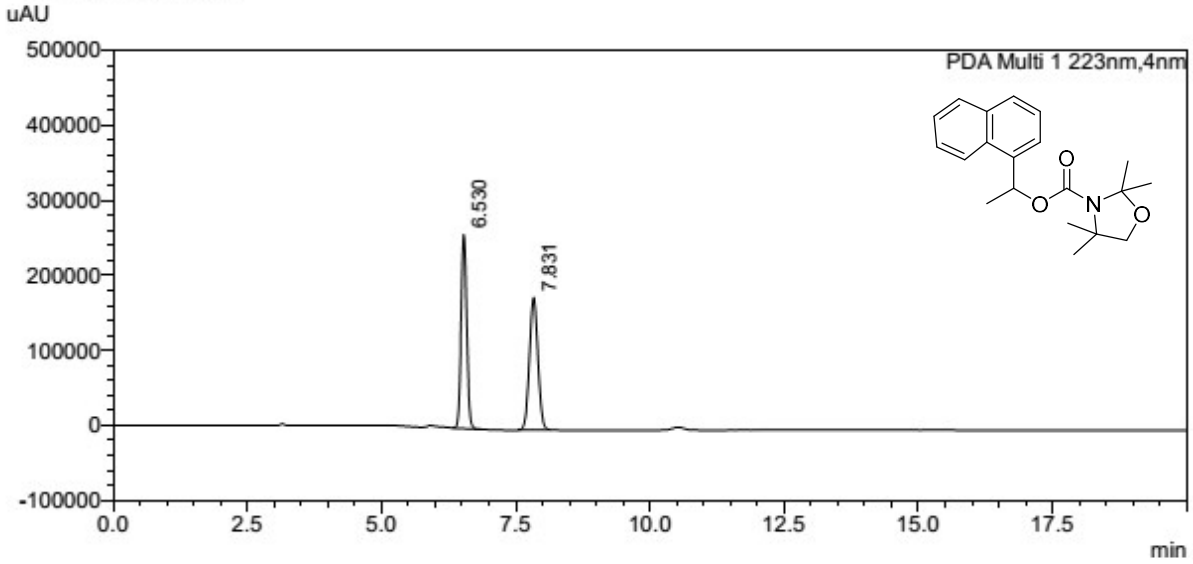
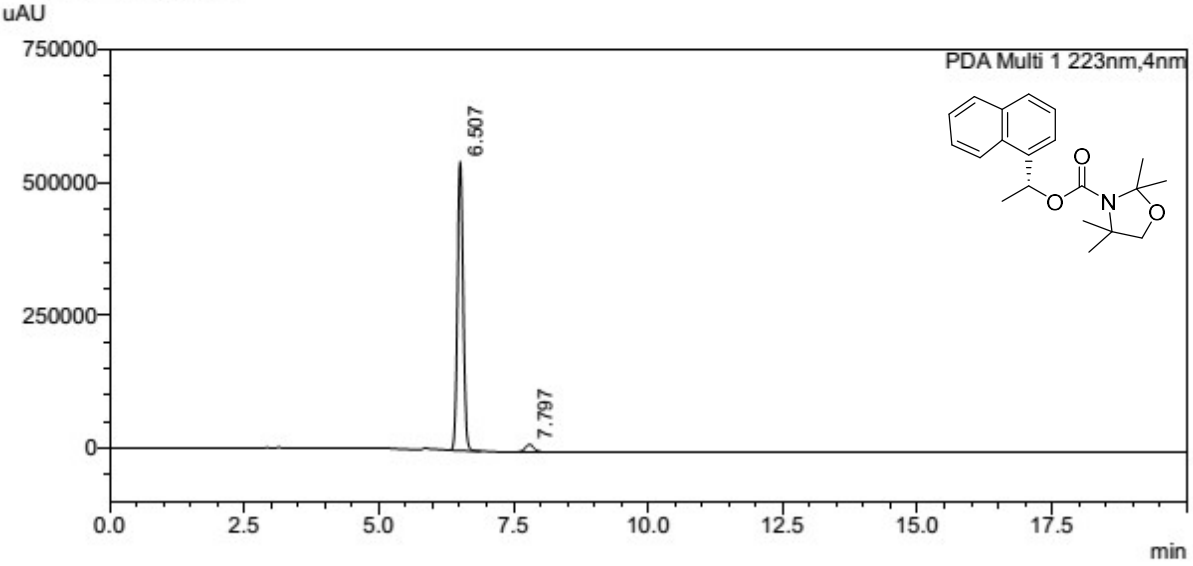


<Peak Table>

PDA Ch1 223nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	6.530	49.238	1882725	258944	0.000		M
2	7.831	50.762	1941037	176589	0.000		M
Total		100.000	3823762	435533			

<Chromatogram>

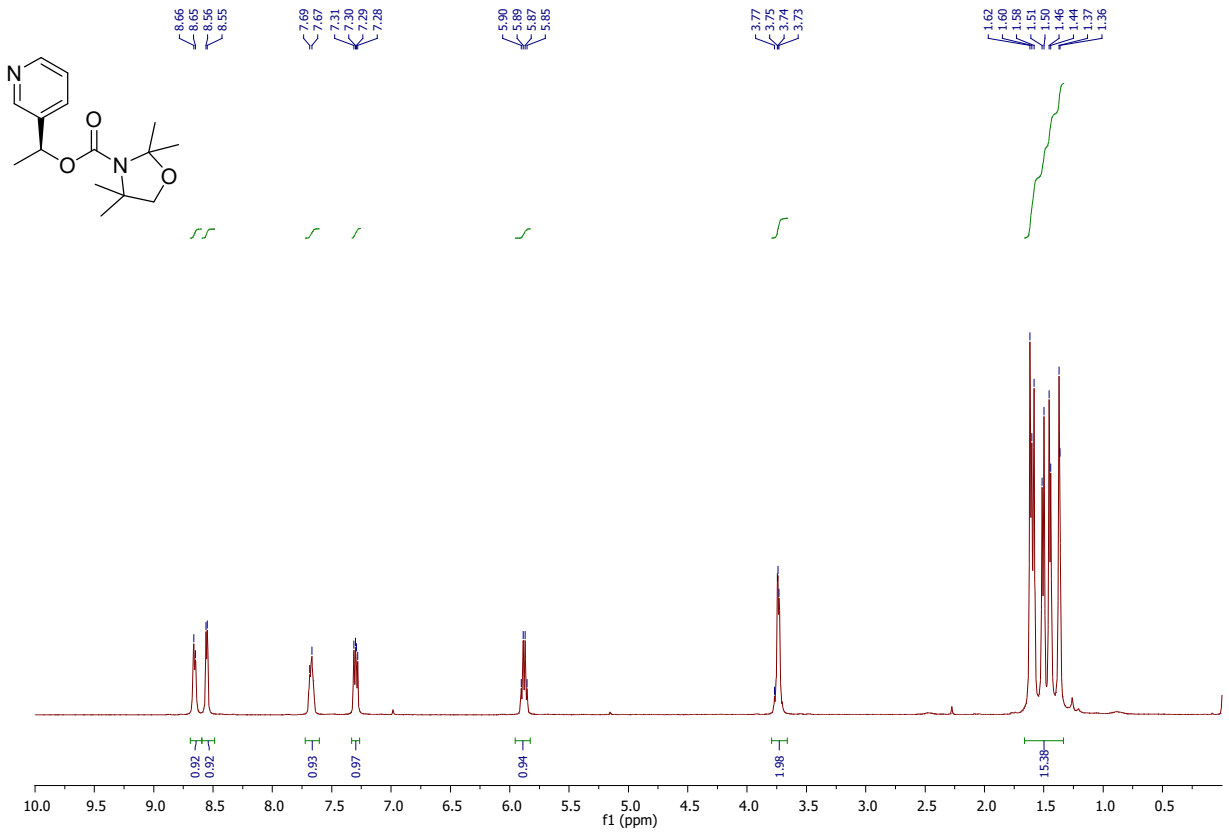


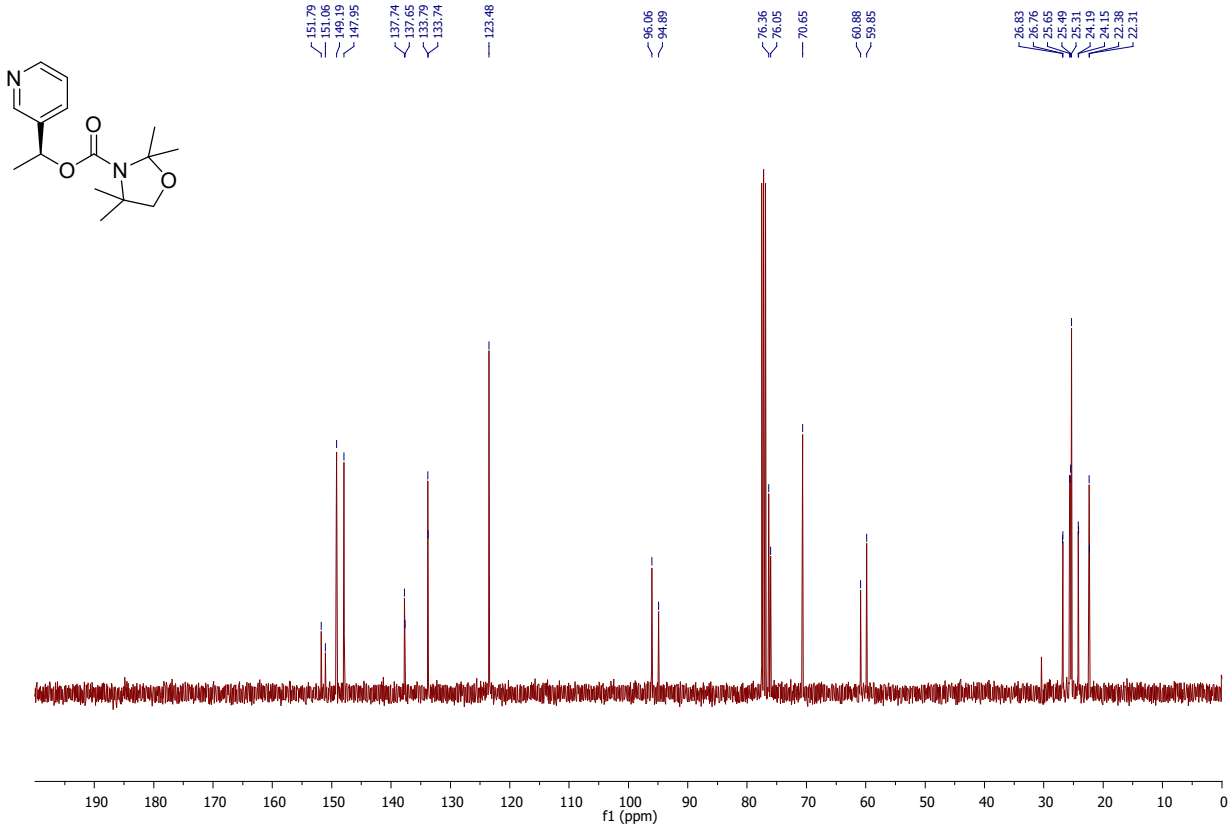
<Peak Table>

PDA Ch1 223nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	6.507	96.317	4014505	544391	0.000		M
2	7.797	3.683	153513	14162	0.000		M
Total		100.000	4168019	558554			

(*S*)-(-)-1-(pyridin-3-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5o** :





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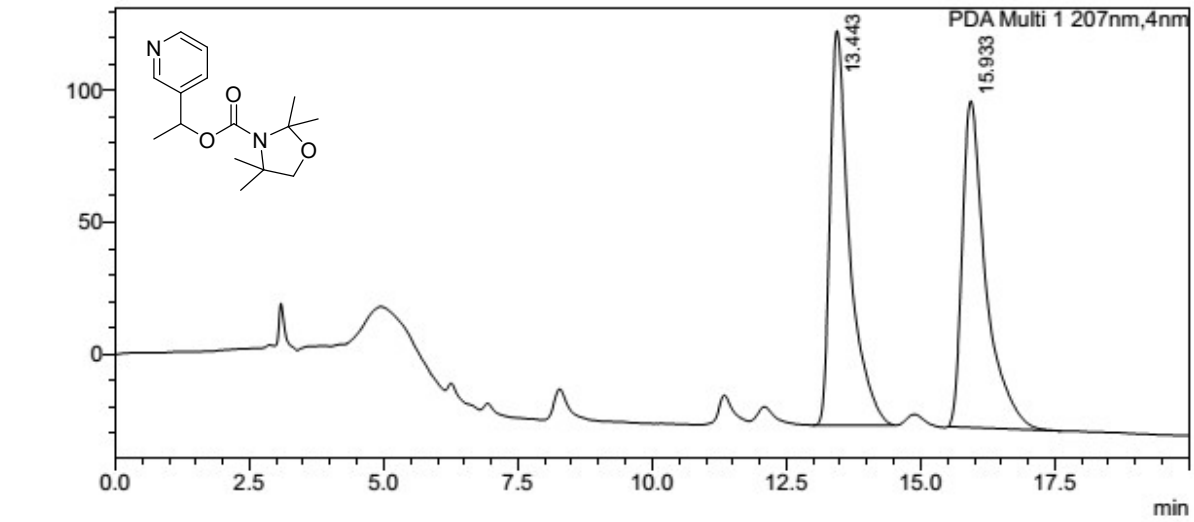

<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	13.443	50.185	3810315	149819	0.000		M
2	15.933	49.815	3782254	123909	0.000		M
Total		100.000	7592569	273728			

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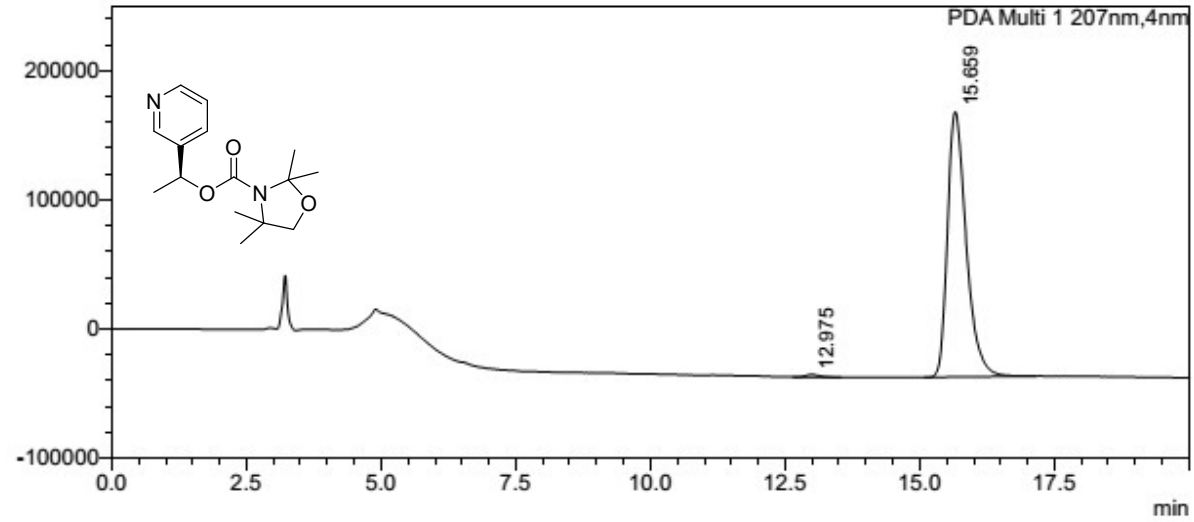
uAU

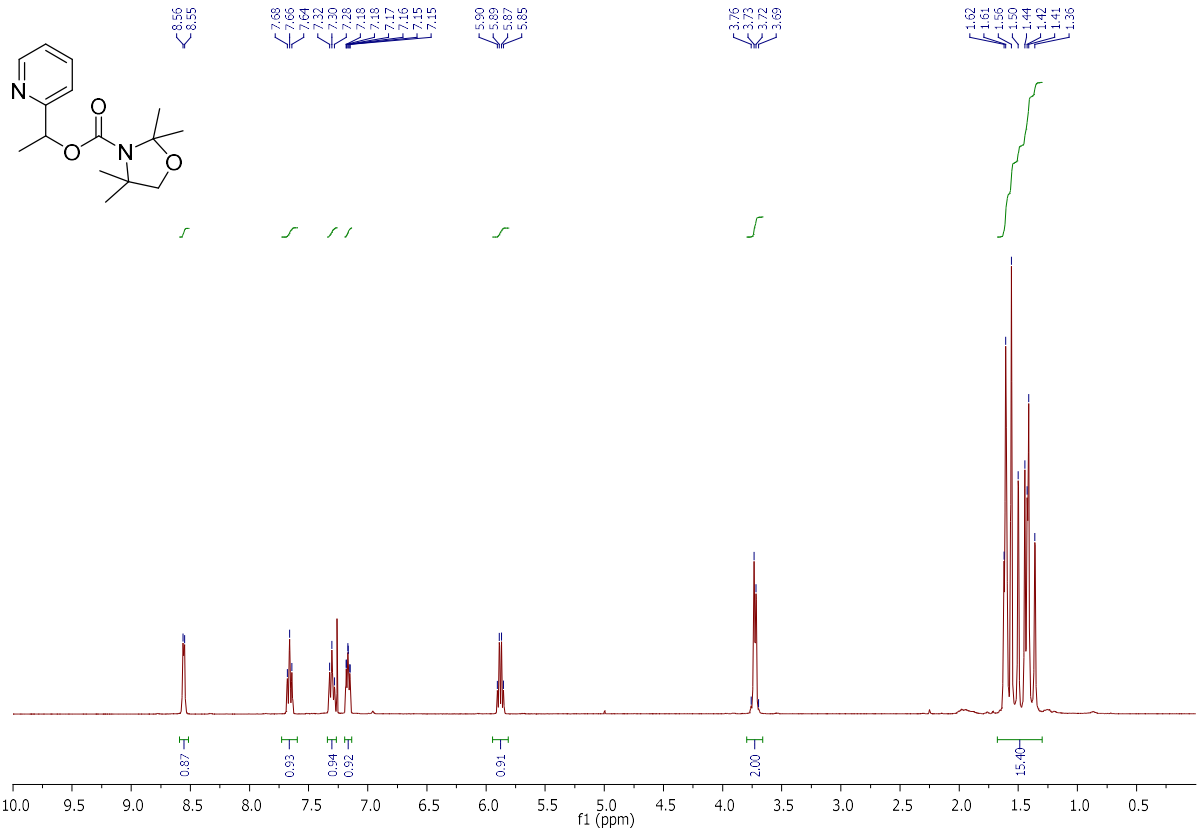


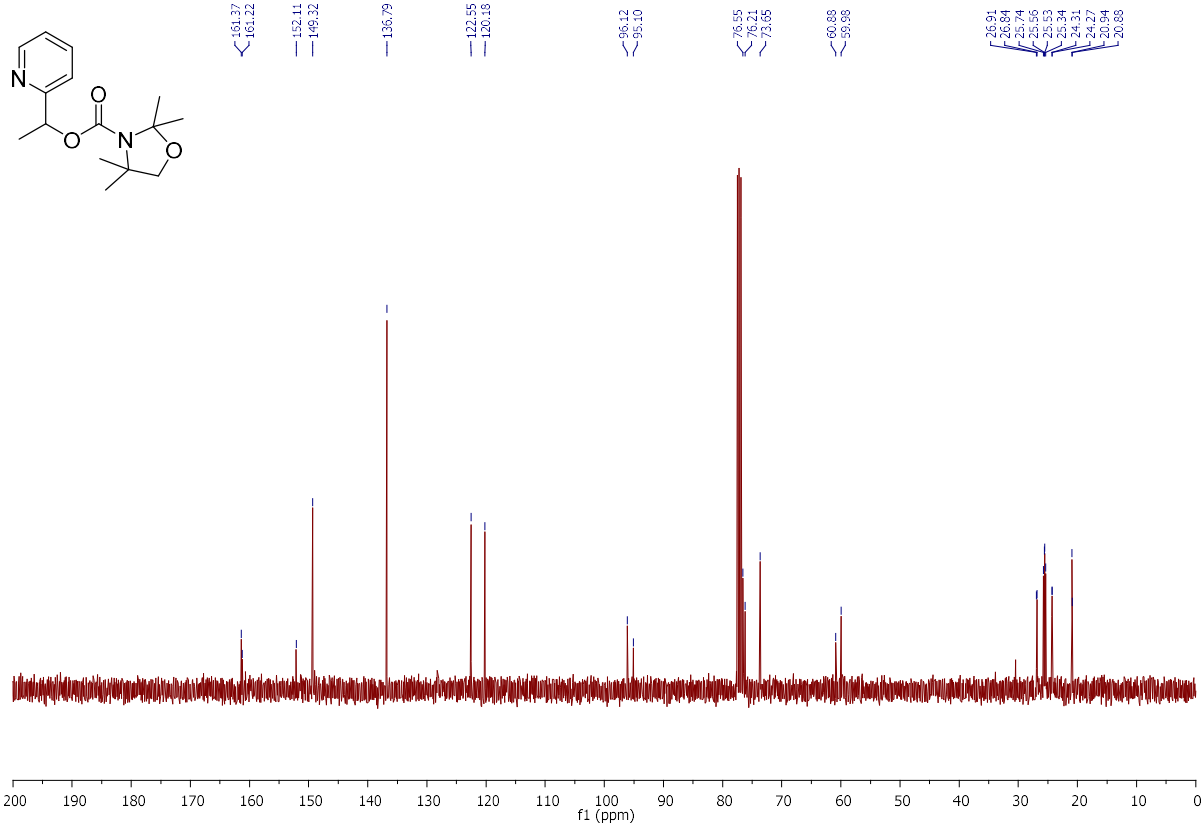
<Peak Table>

PDA Ch1 207nm

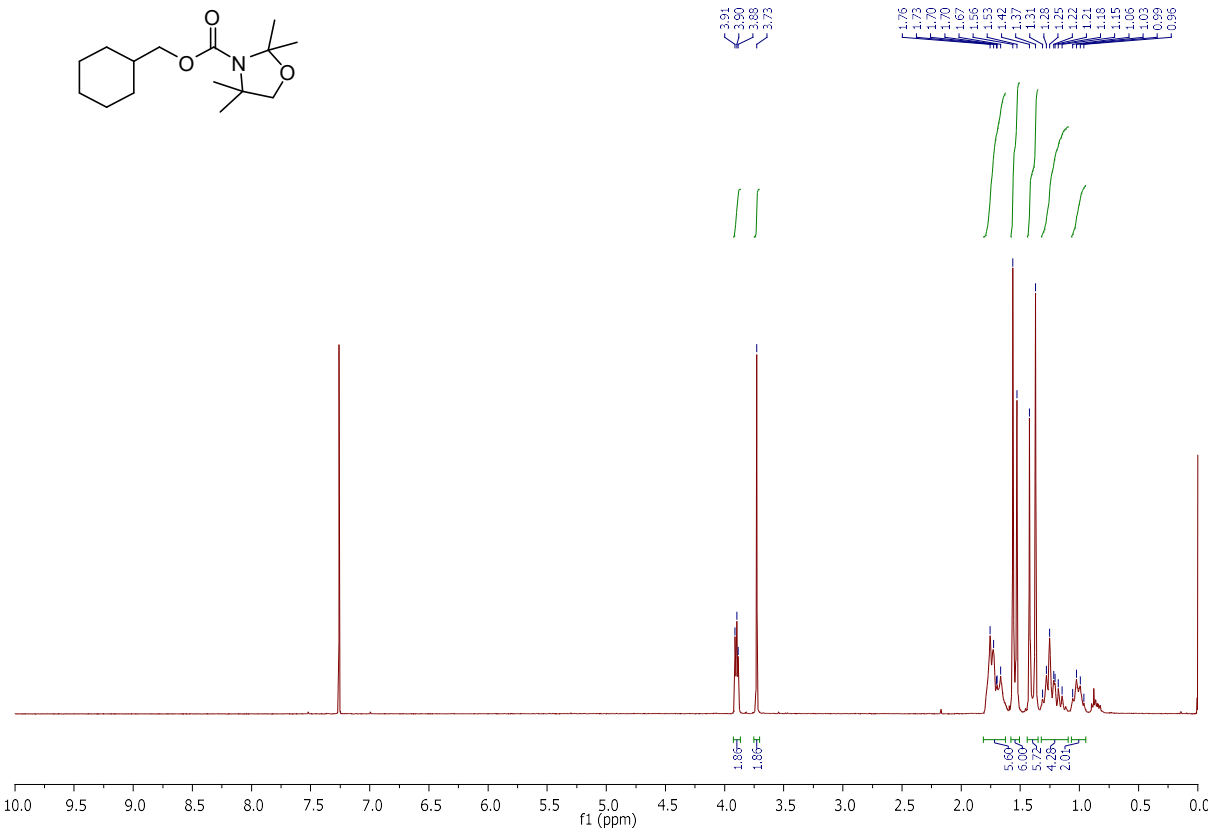
Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	12.975	0.665	33434	1886	0.000		M
2	15.659	99.335	4997659	205632	0.000		M
Total		100.000	5031093	207519			

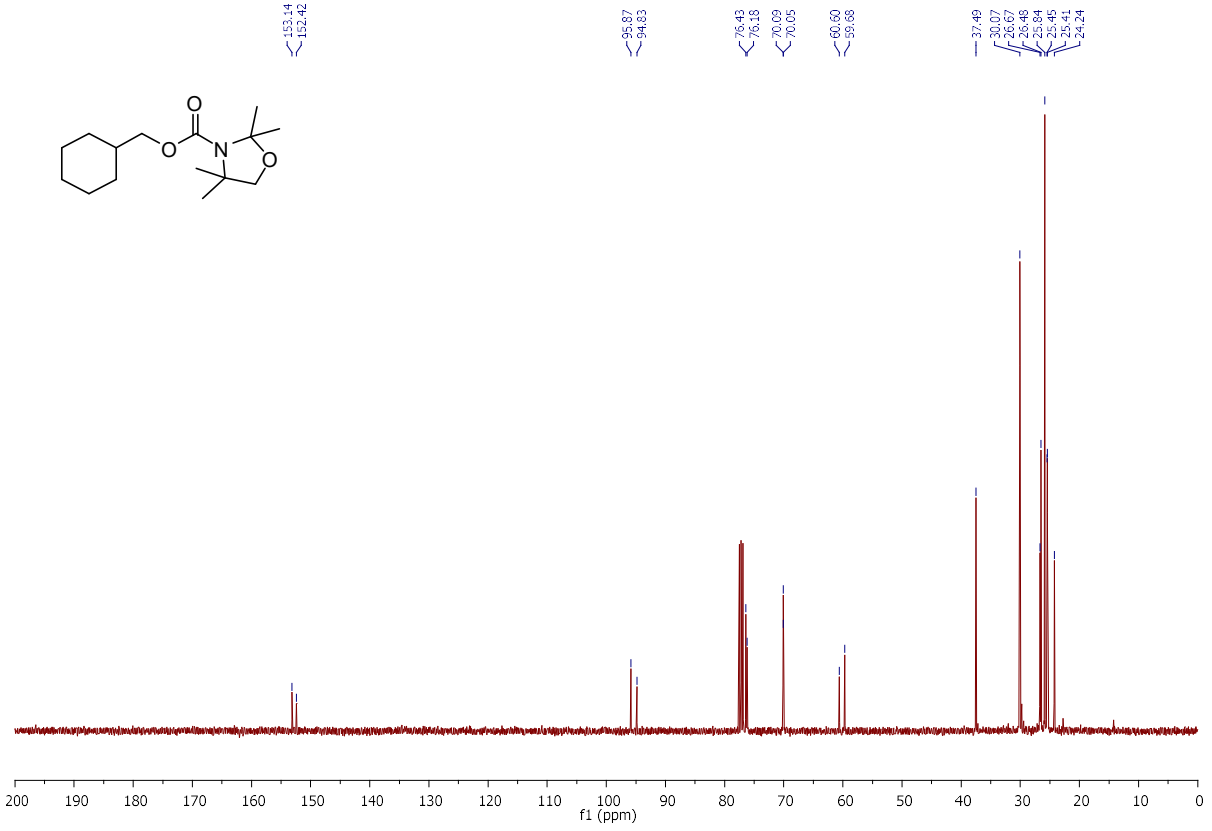
1-(pyridin-2-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5p** :



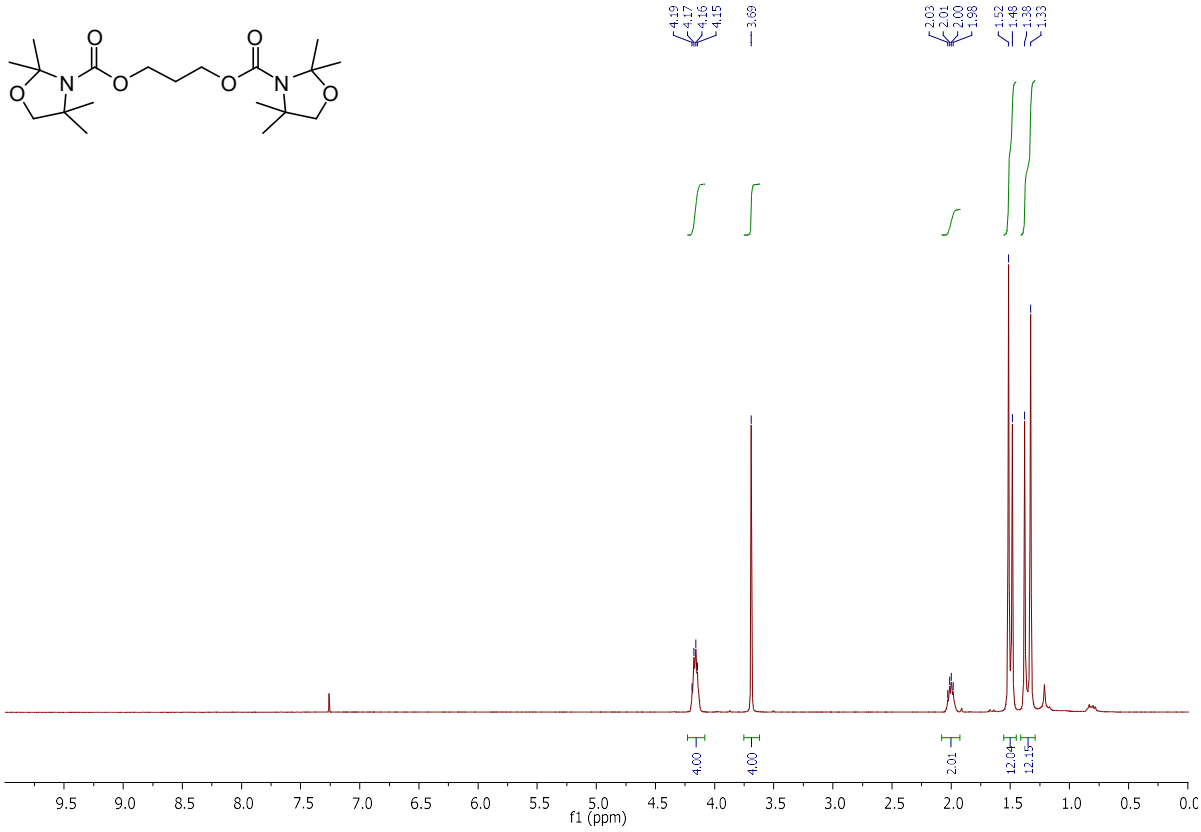


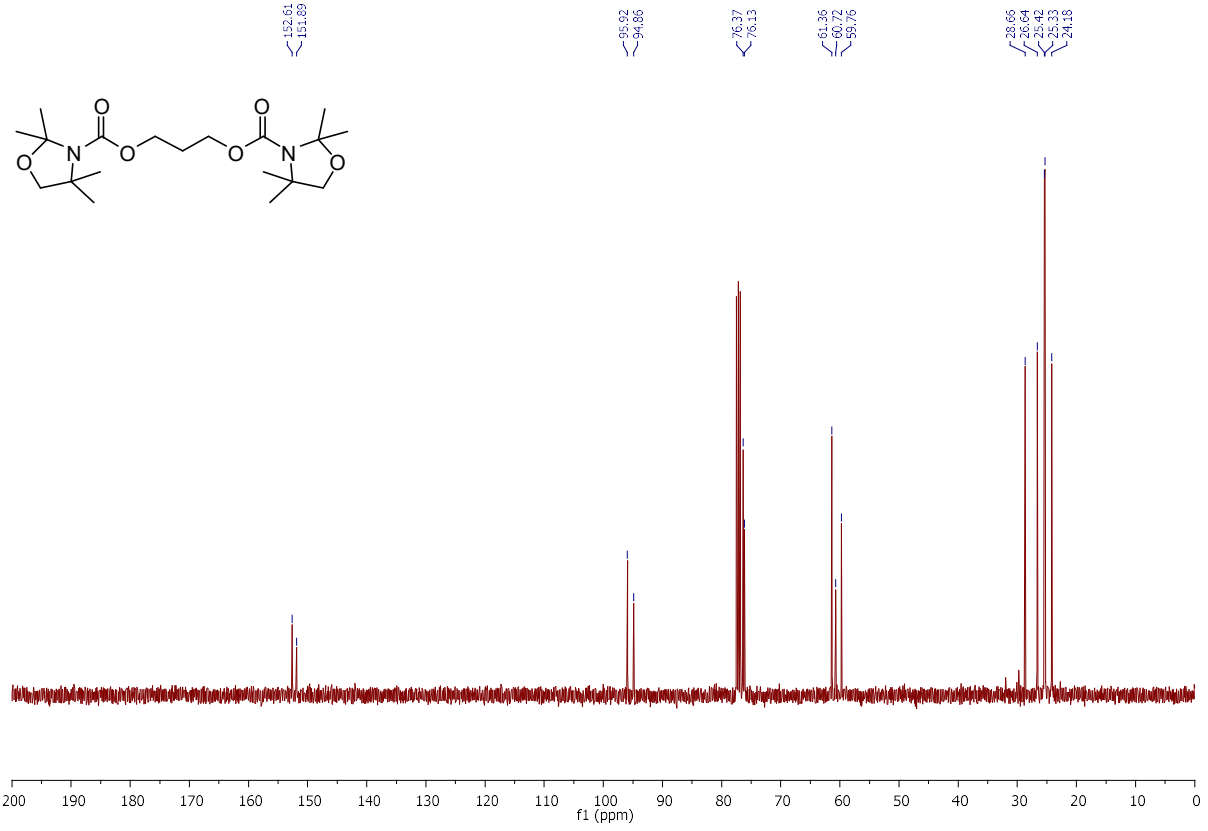
cyclohexylmethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7c** :



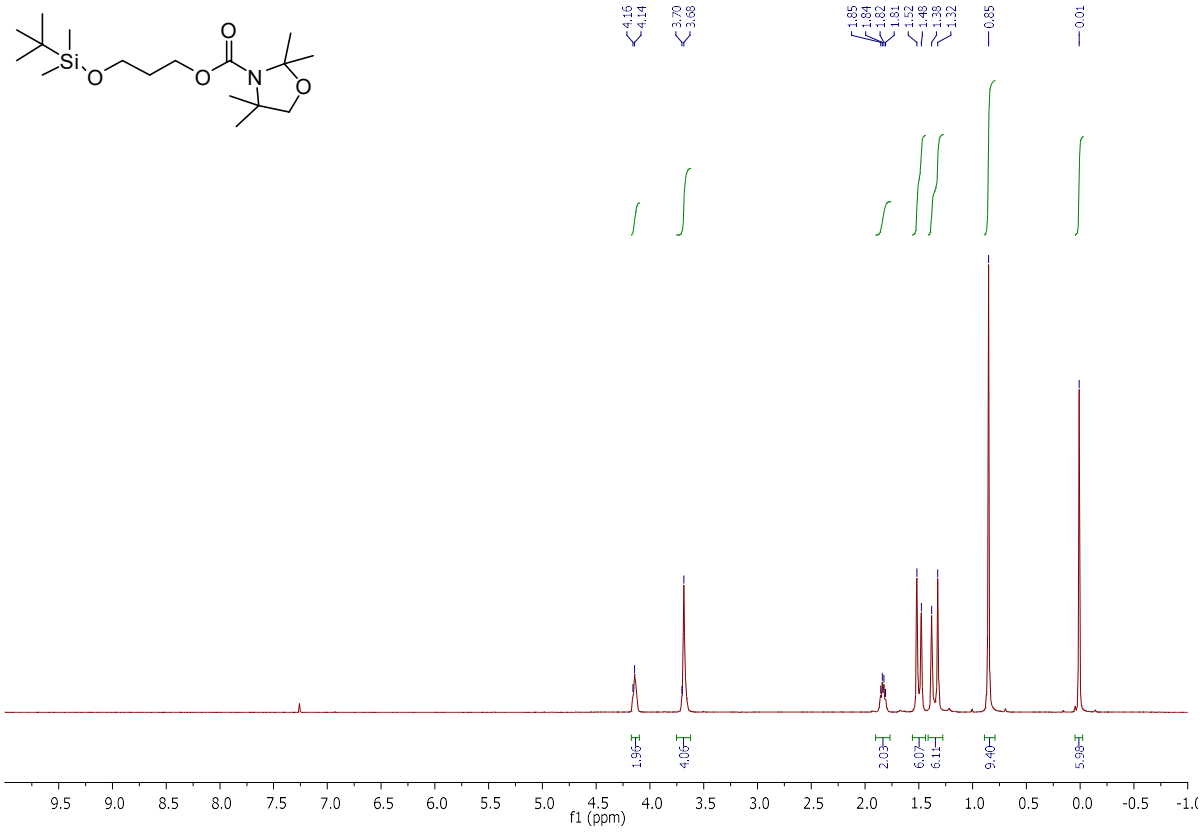


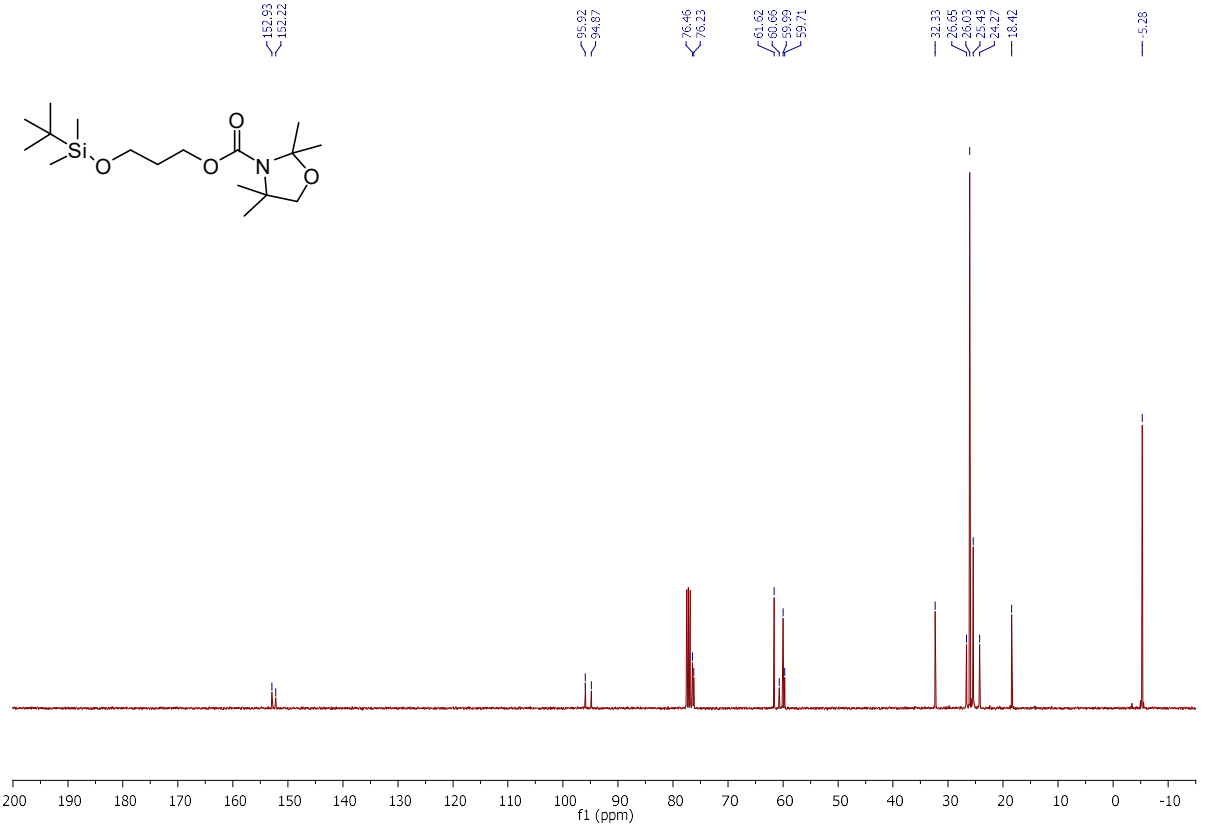
propane-1,3-diyl bis(2,2,4,4-tetramethyloxazolidine-3-carboxylate) **2.7h** :



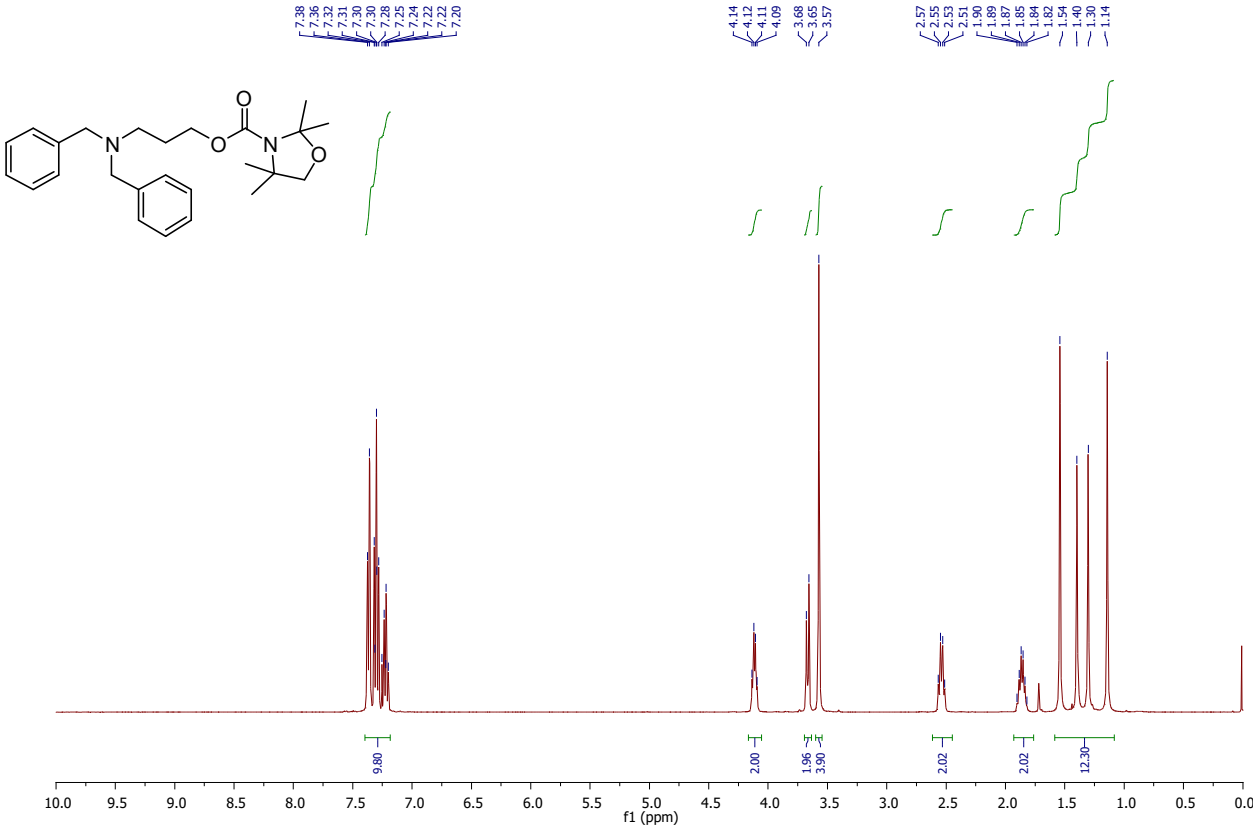


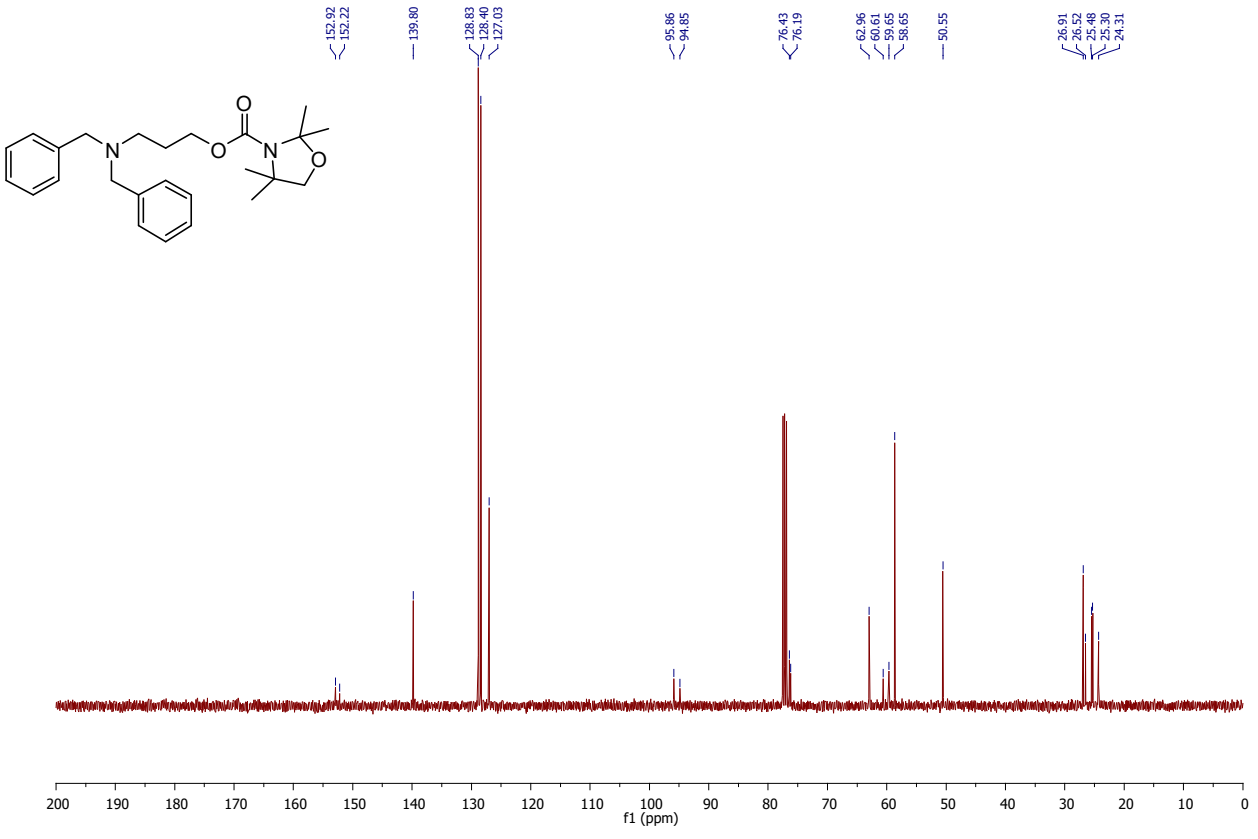
3-((tert-butyldimethylsilyl)oxy)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7g** :



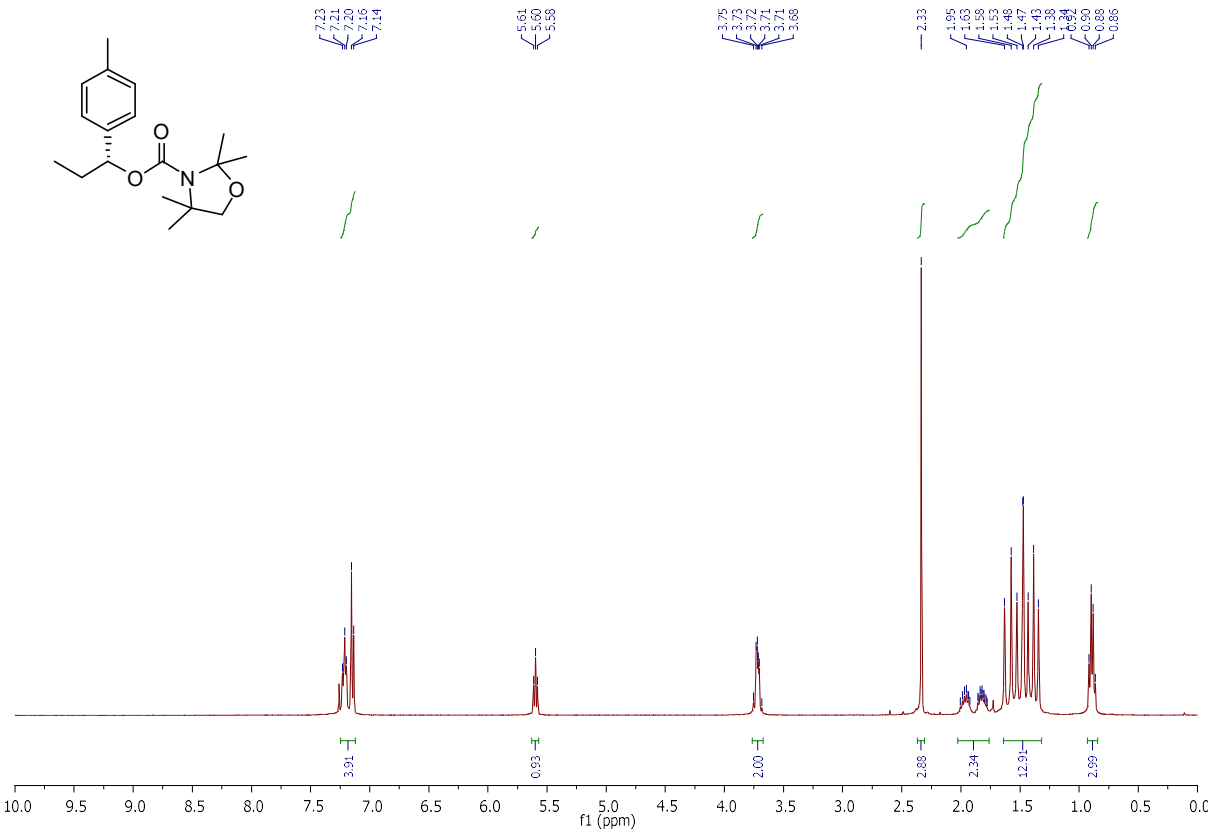


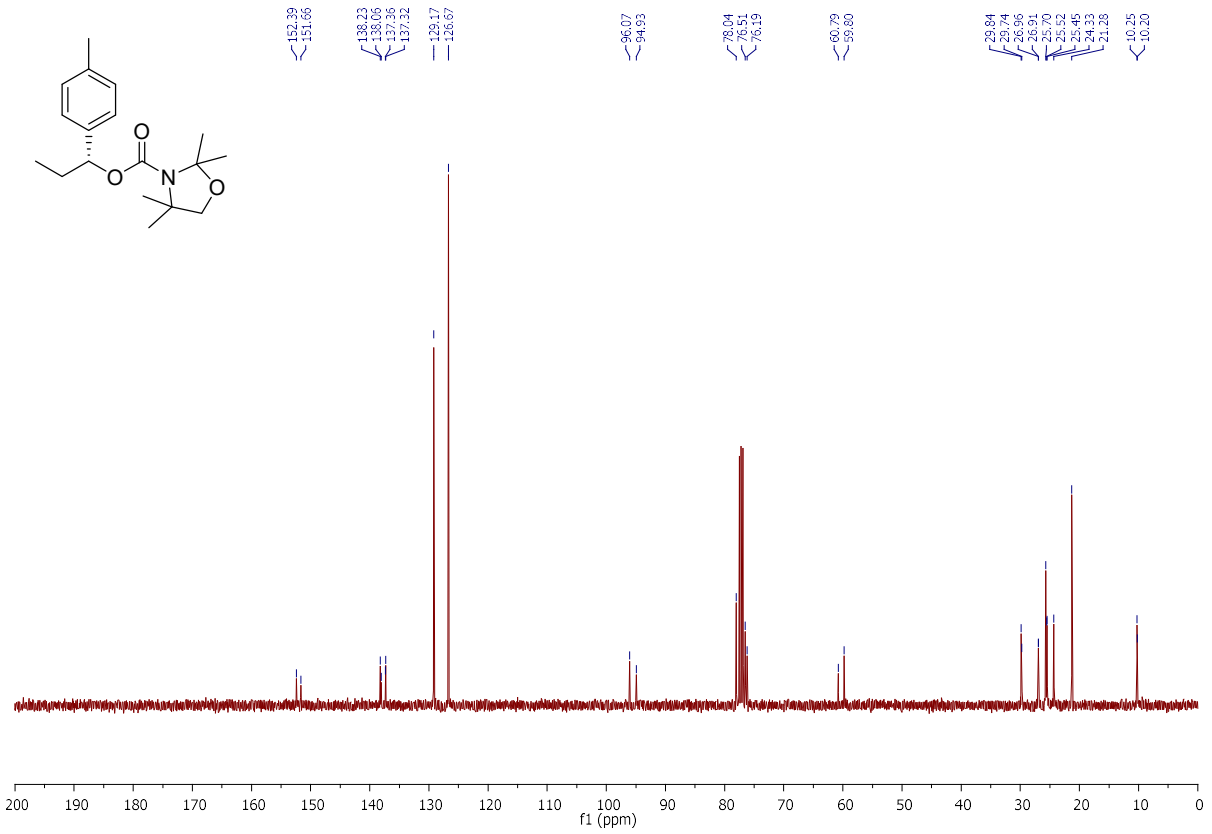
3-(dibenzylamino)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7i** :





(*R*)-(+)-1-(*p*-tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5q** :





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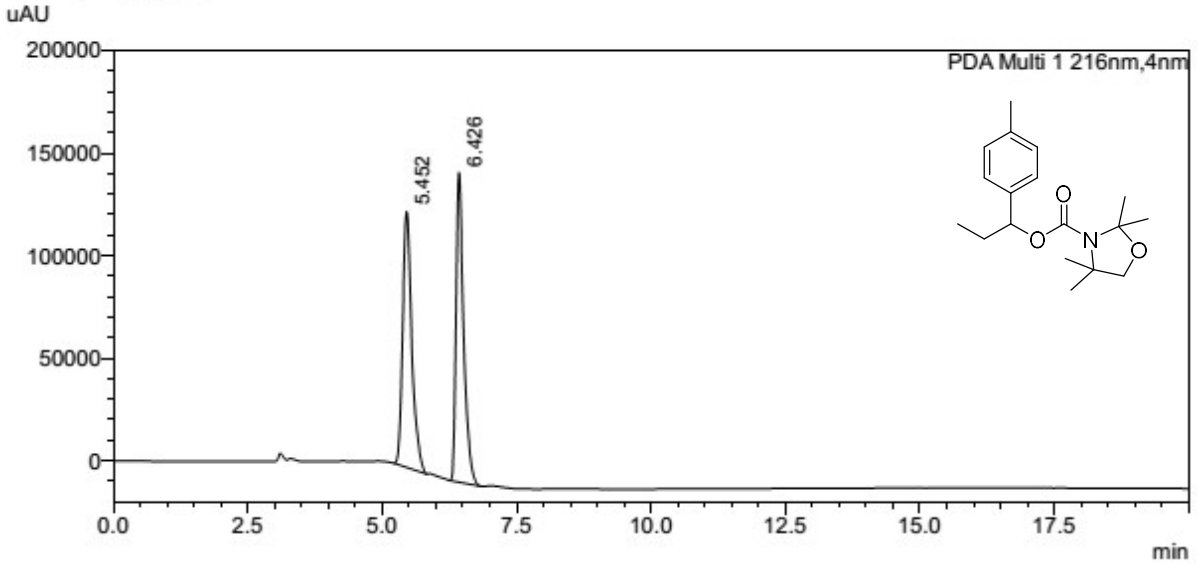

<Peak Table>

PDA Ch1 216nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	5.452	49.805	1465217	124804	0.000		M
2	6.426	50.195	1476697	151115	0.000		M
Total		100.000	2941914	275918			

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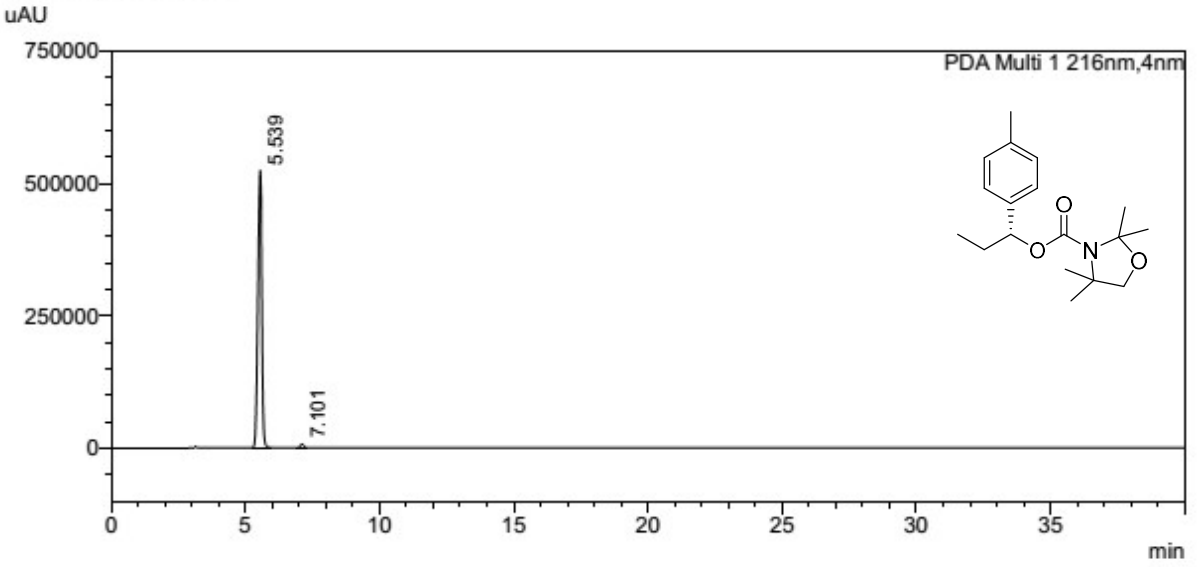
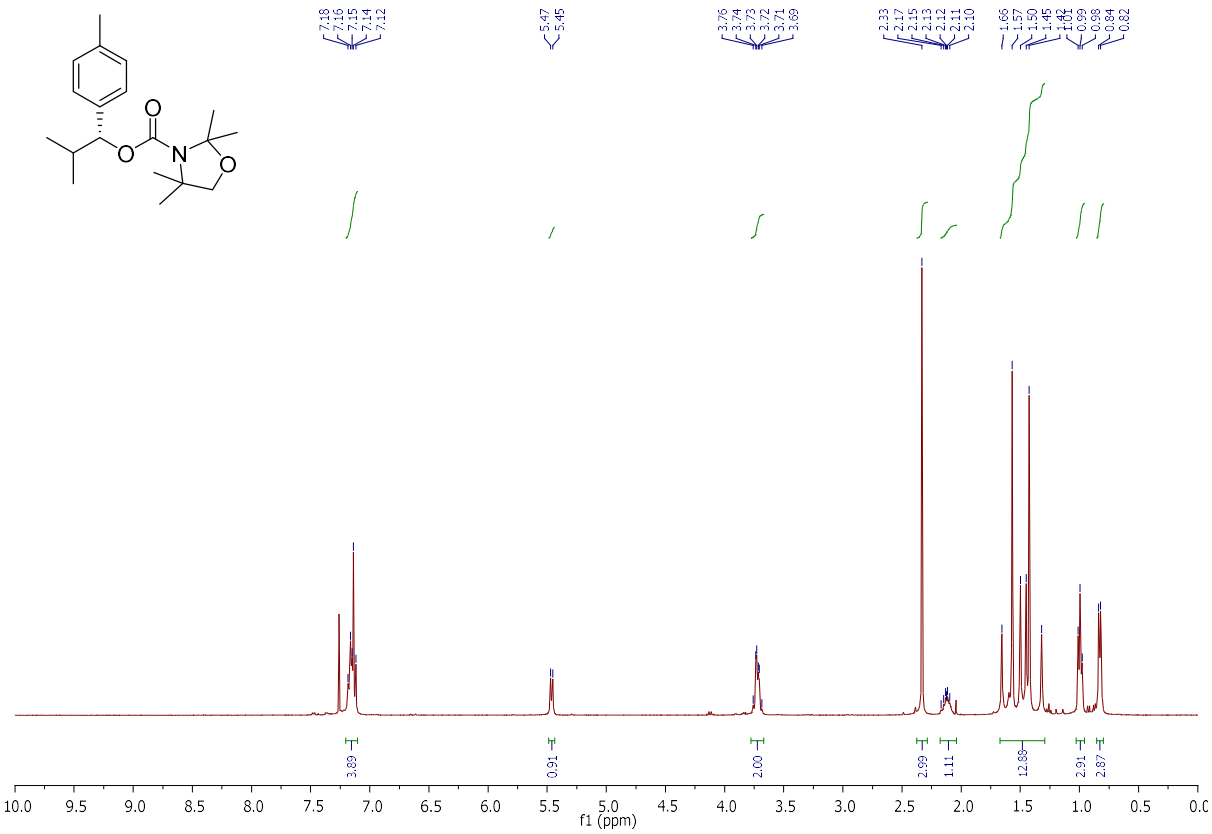


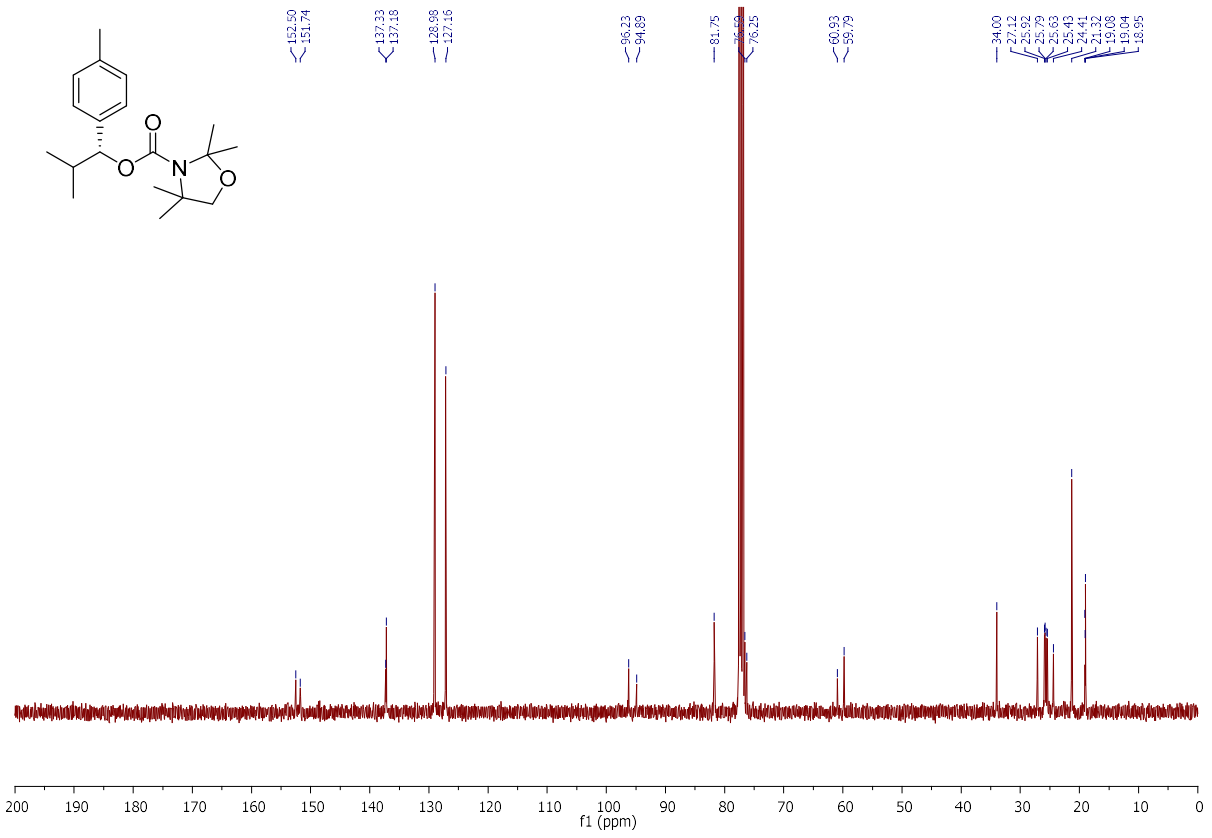
<Peak Table>

PDA Ch1 216nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	5.539	98.815	5401892	523572	0.000		M
2	7.101	1.185	64761	6828	0.000		M
Total		100.000	5466653	530399			

(*R*)-(+)-2-methyl-1-(*p*-tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5r**:





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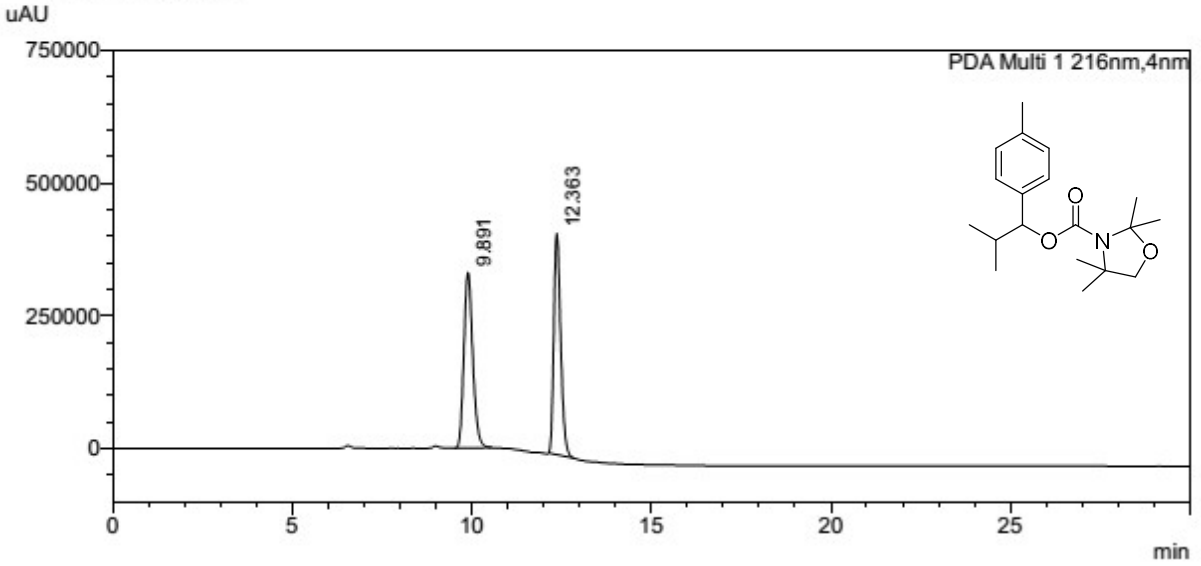

<Peak Table>

PDA Ch1 216nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	9.891	50.662	5687044	331036	0.000		M
2	12.363	49.338	5538385	416561	0.000		M
Total		100.000	11225429	747598			

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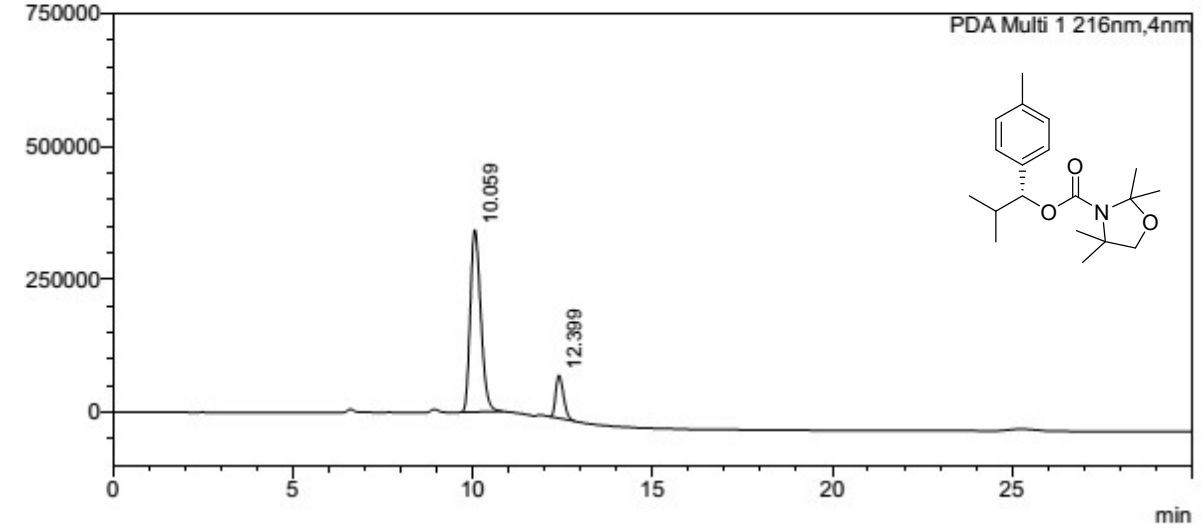
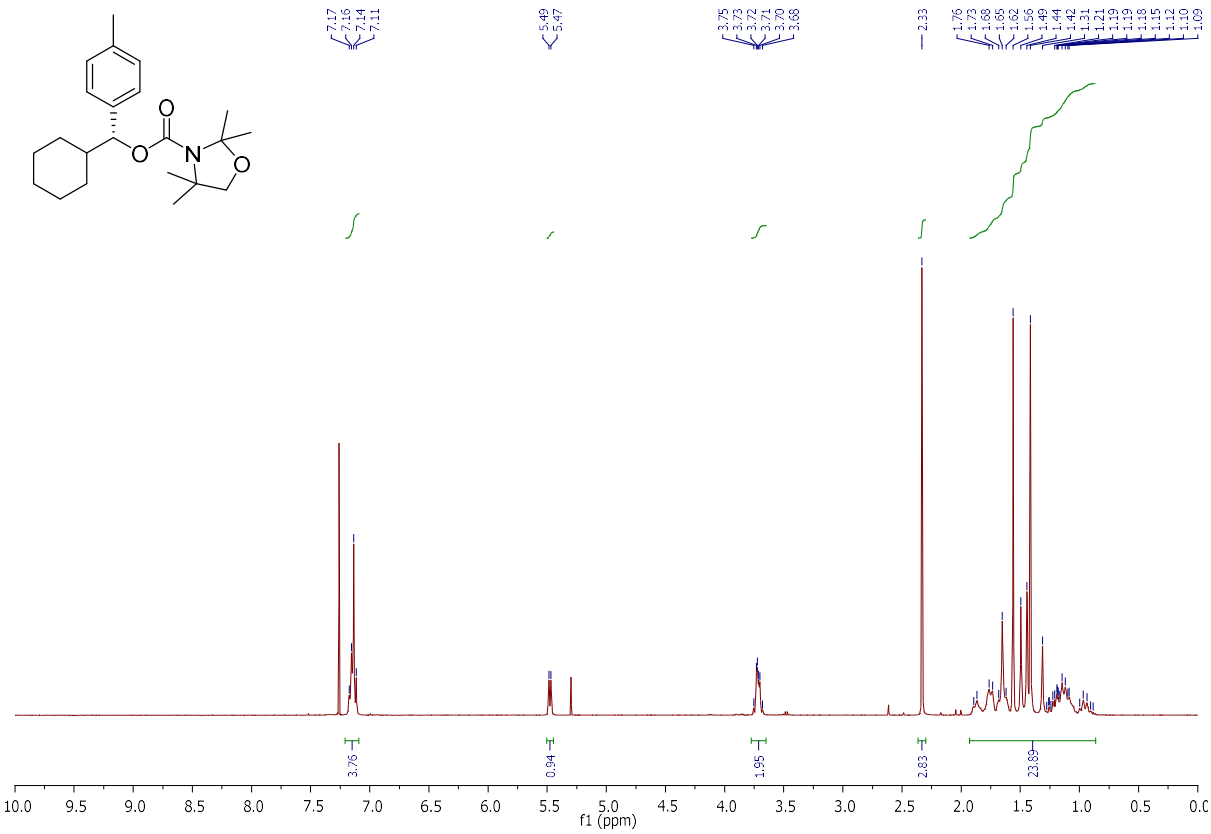


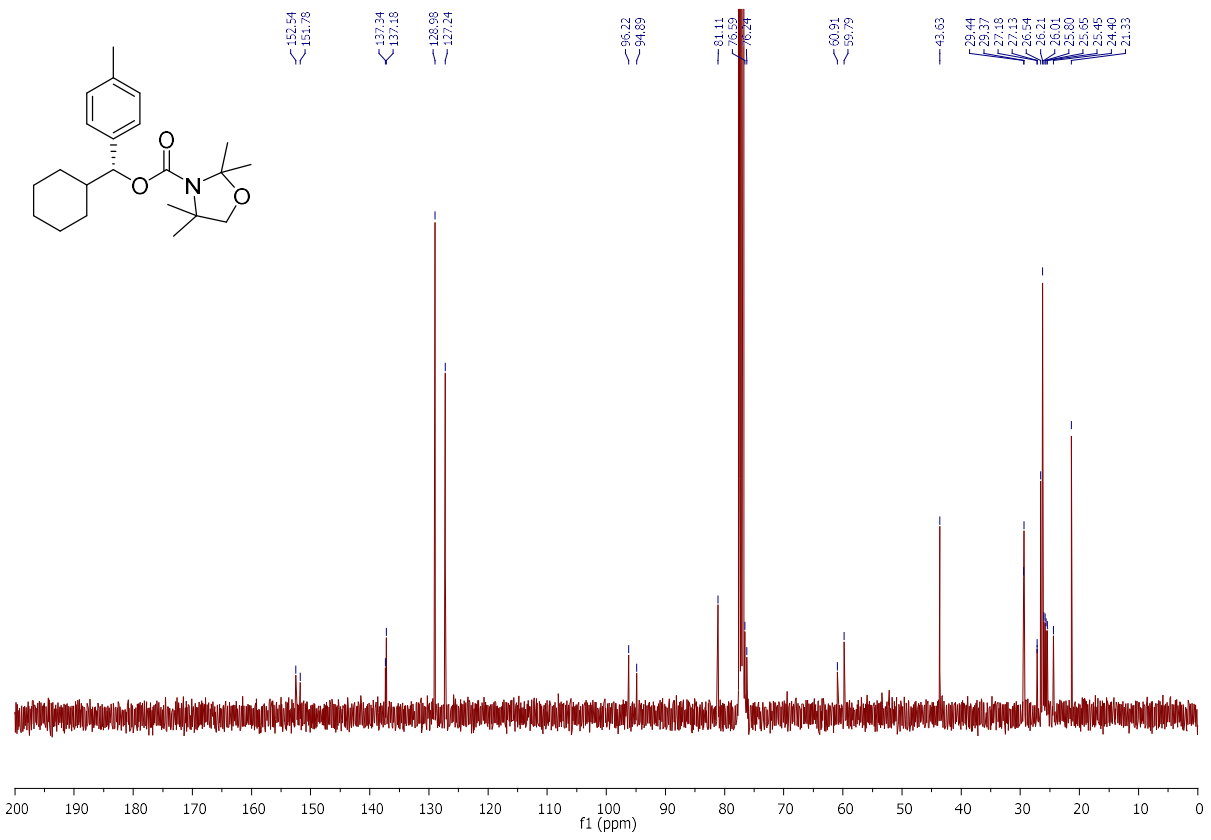
<Peak Table>

PDA Ch1 216nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.059	85.190	6983904	343172	0.000		M
2	12.399	14.810	1214140	80616	0.000		M
Total		100.000	8198044	423787			

(*R*)-(+)-cyclohexyl(*p*-tolyl)methyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5s** :





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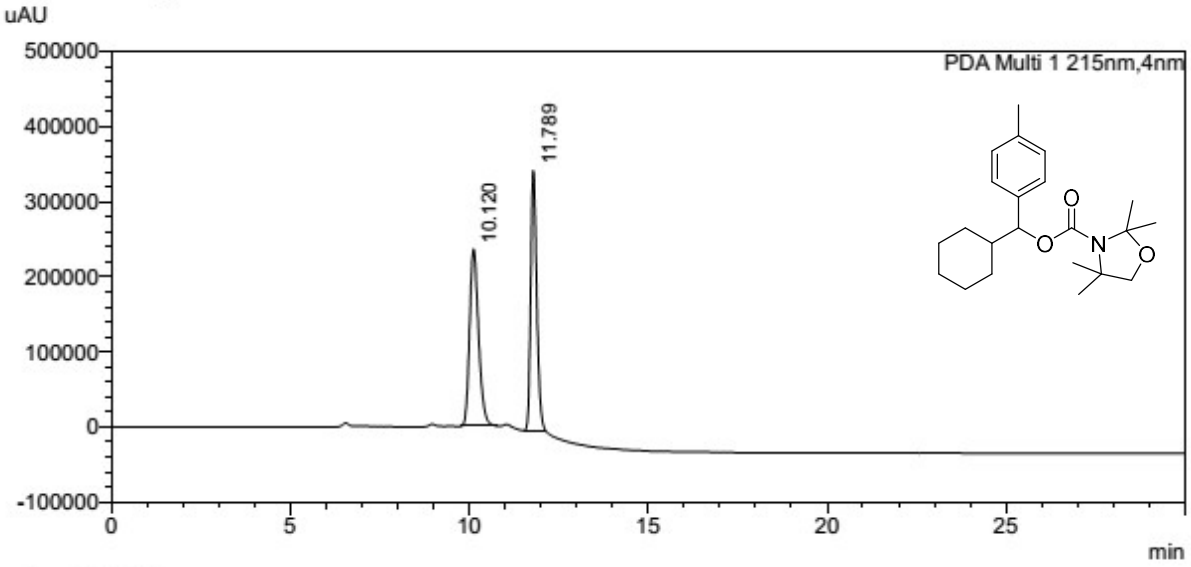

<Peak Table>

PDA Ch1 215nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.120	50.349	4131860	236125	0.000		M
2	11.789	49.651	4074616	346883	0.000		M
Total		100.000	8206475	583008			

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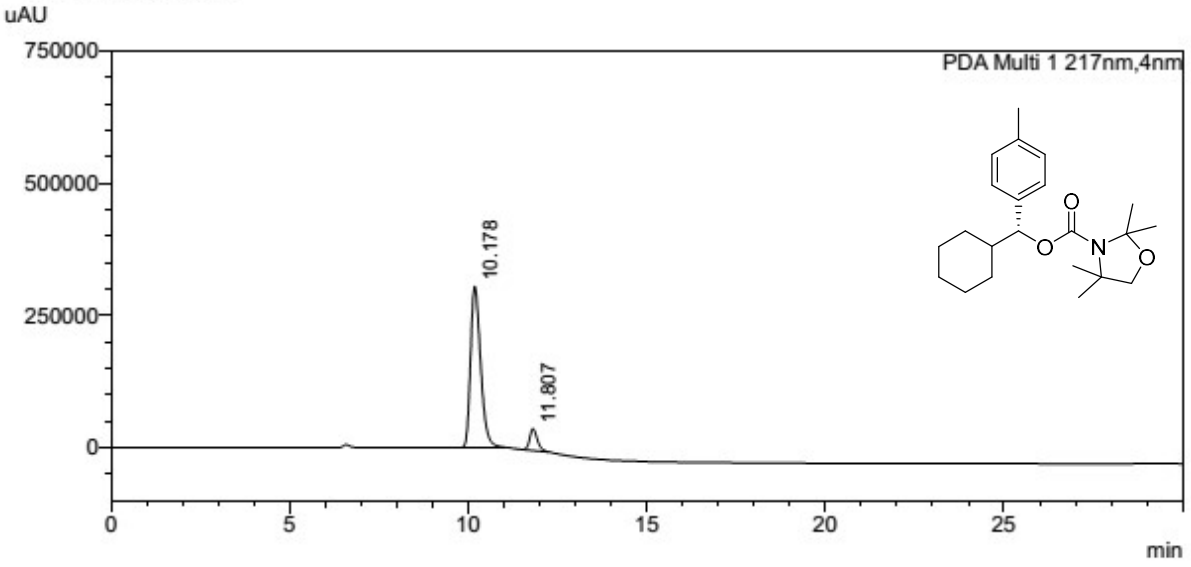
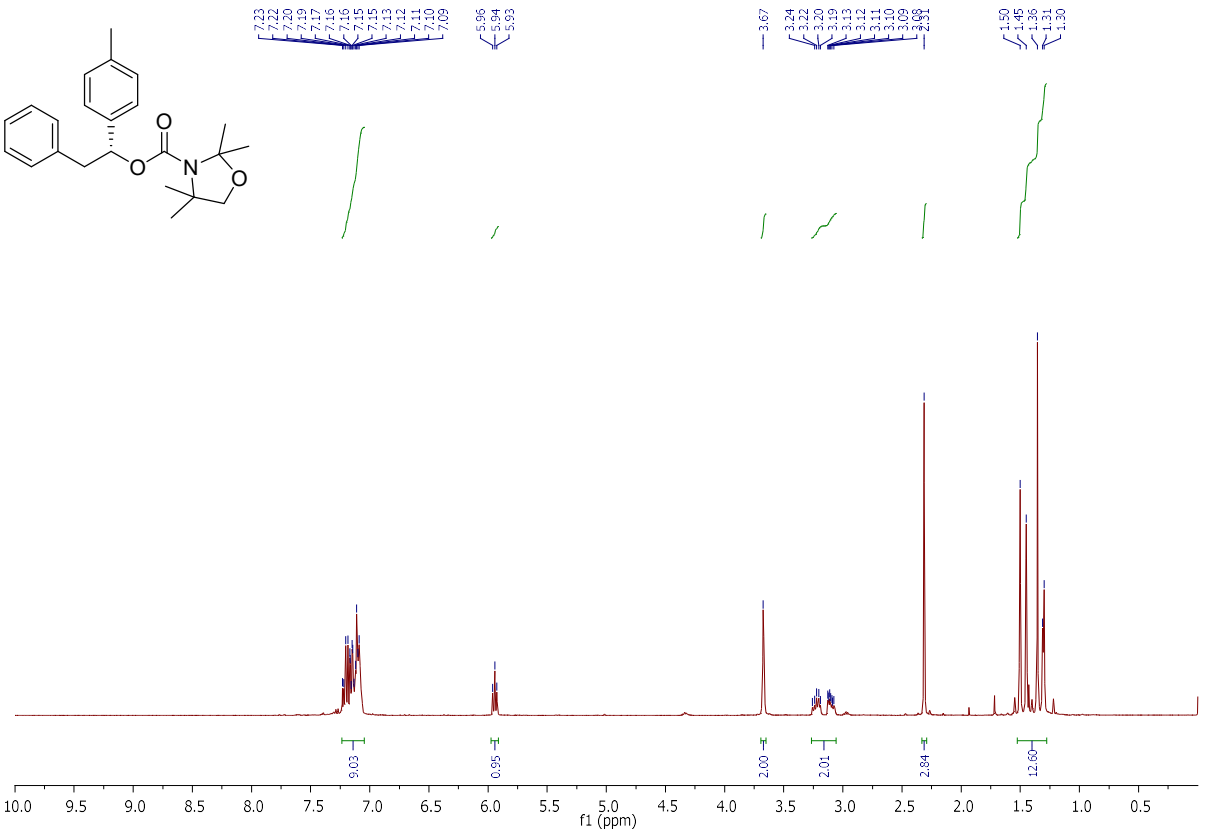


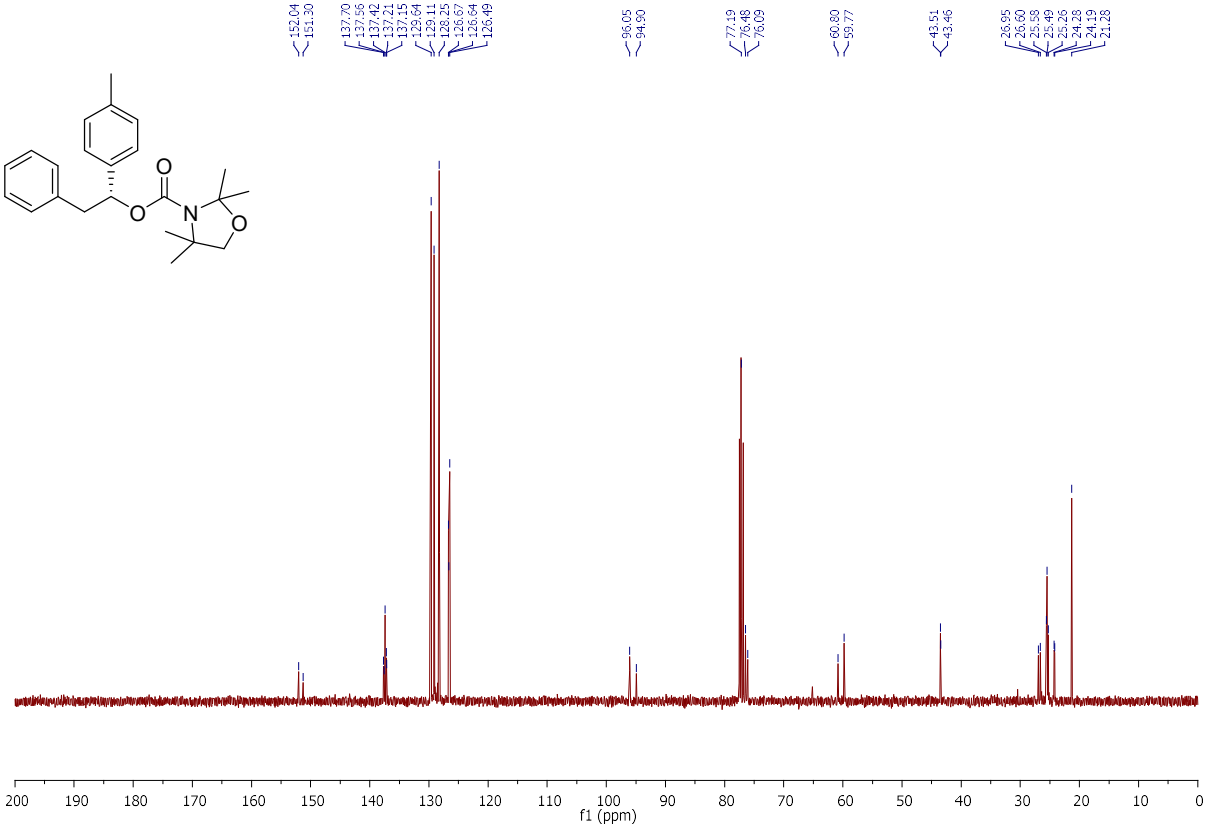
<Peak Table>

PDA Ch1 217nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.178	90.790	5980890	304793	0.000		M
2	11.807	9.210	606737	40949	0.000		M
Total		100.000	6587627	345742			

(*R*)-(-)-2-phenyl-1-(*p*-tolyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5t** :





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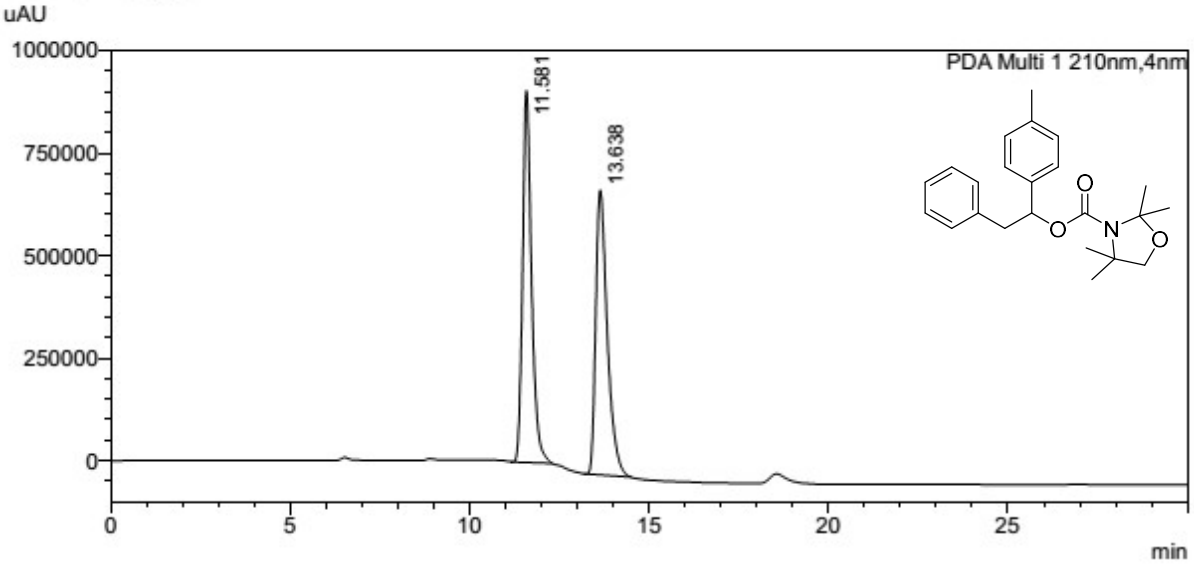

<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.581	50.235	15699669	906663	0.000		M
2	13.638	49.765	15552947	694241	0.000		M
Total		100.000	31252616	1600903			

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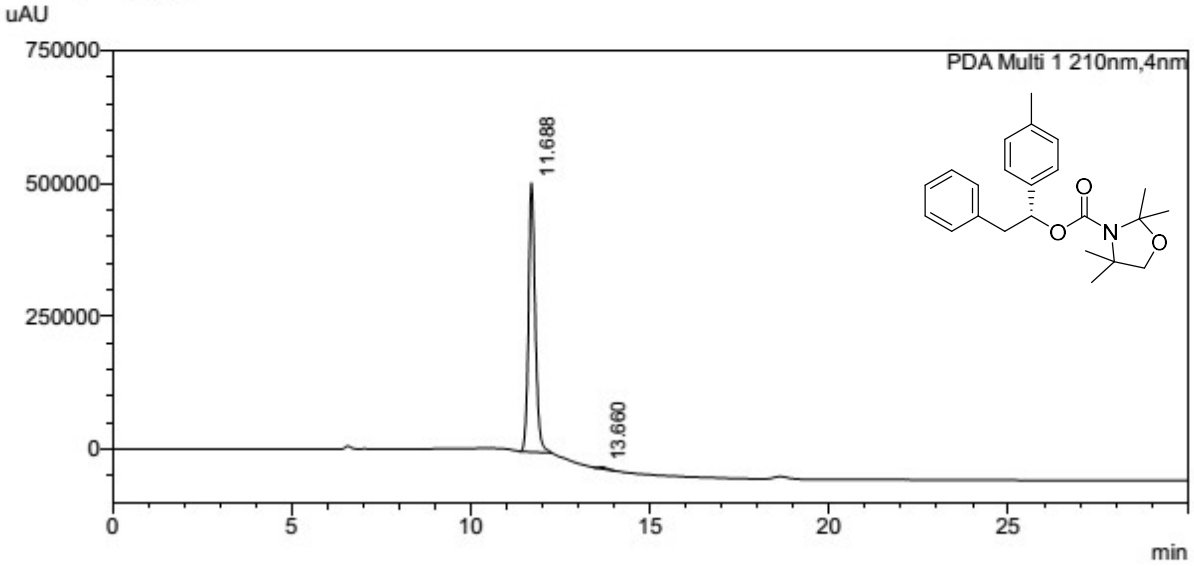
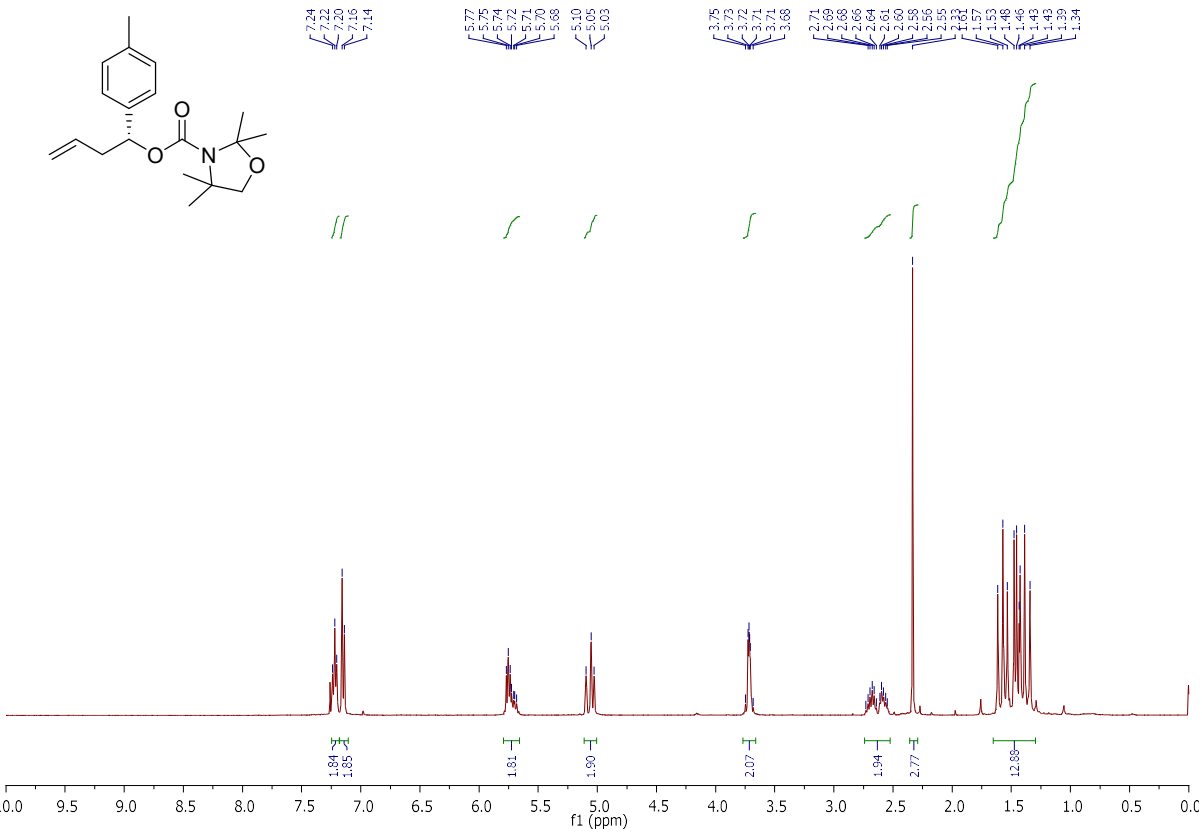


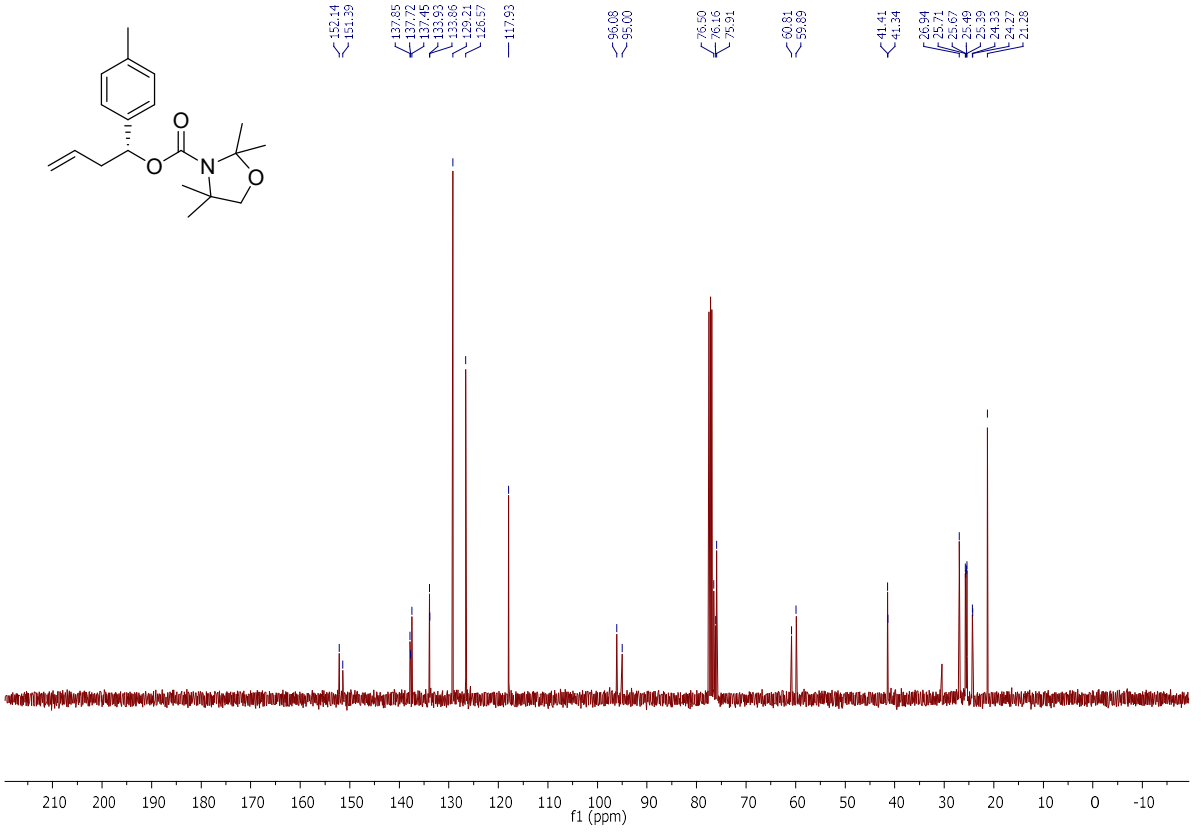
<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.688	99.236	6600105	506497	0.000		M
2	13.660	0.764	50840	3286	0.000		M
Total		100.000	6650945	509783			

(*R*)-(+)-1-(*p*-tolyl)but-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5u** :





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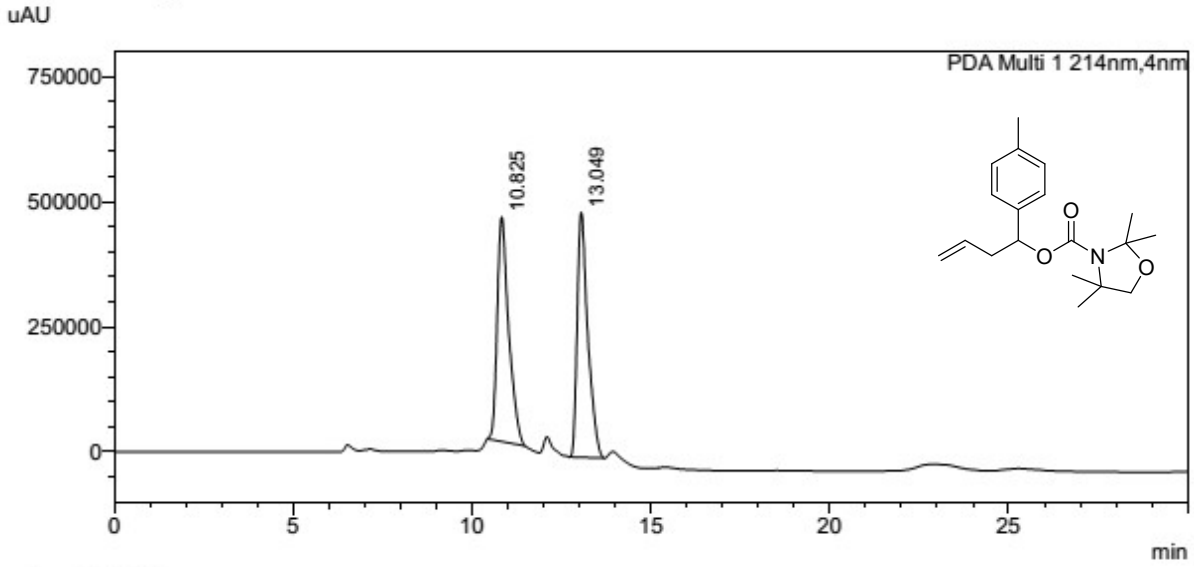

<Peak Table>

PDA Ch1 214nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.825	49.787	10012011	449168	0.000		M
2	13.049	50.213	10097782	489545	0.000		M
Total		100.000	20109794	938713			

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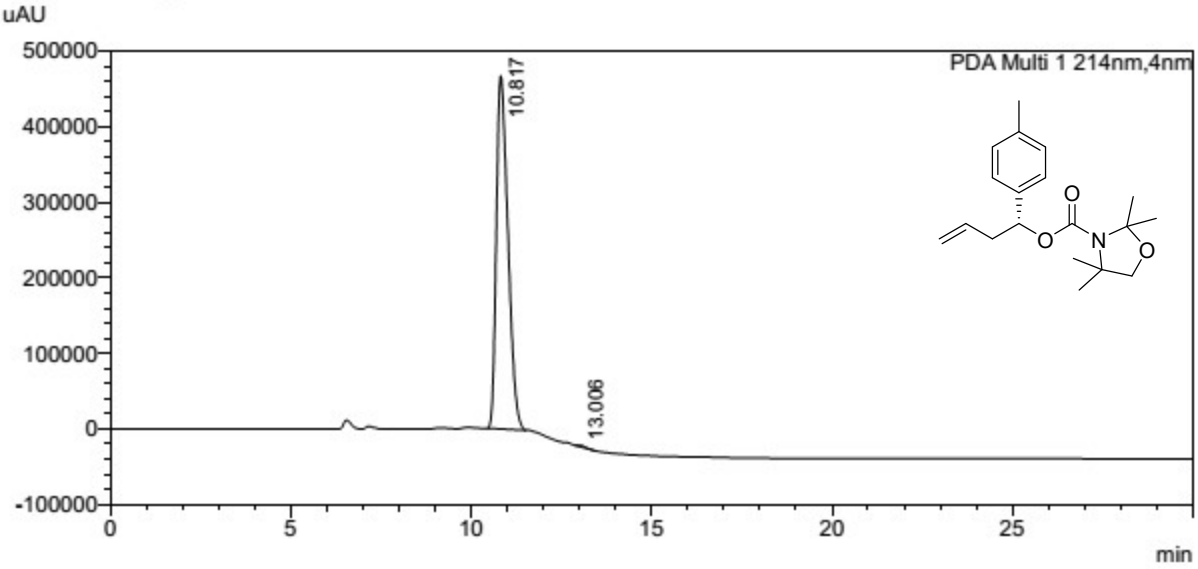
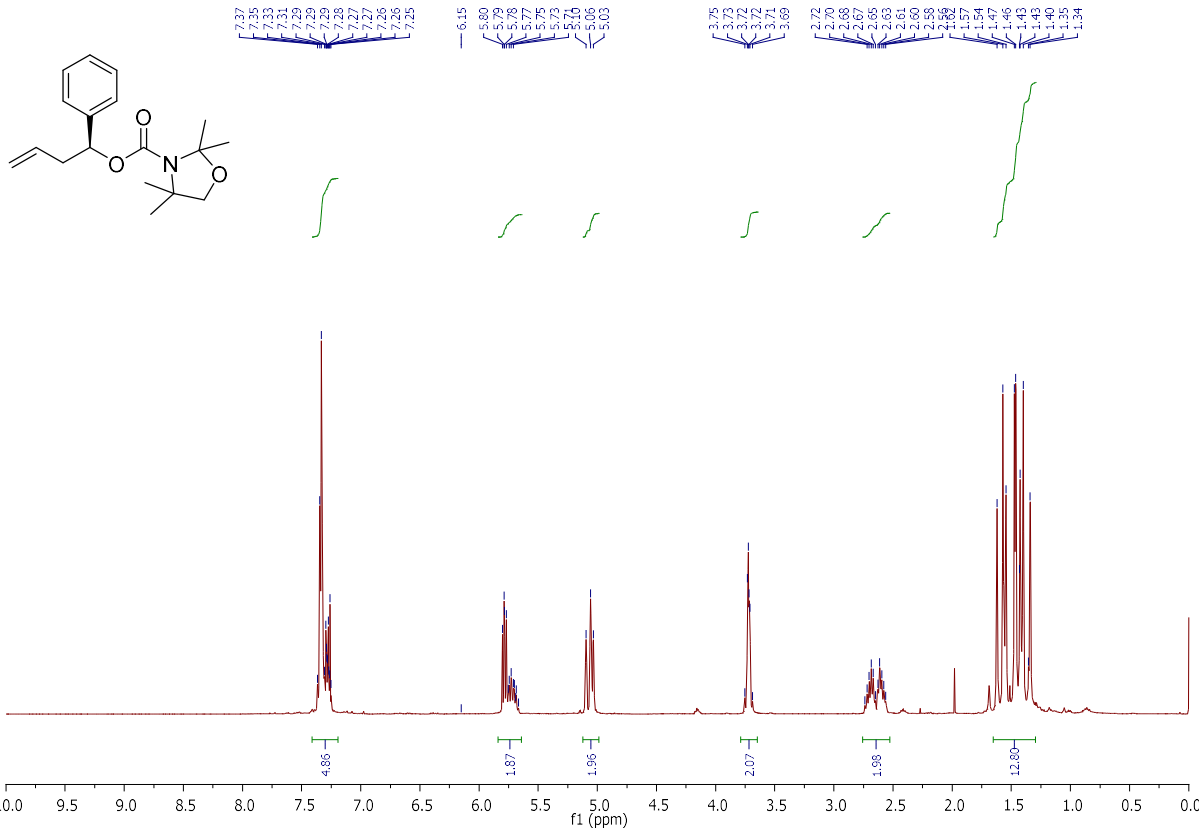


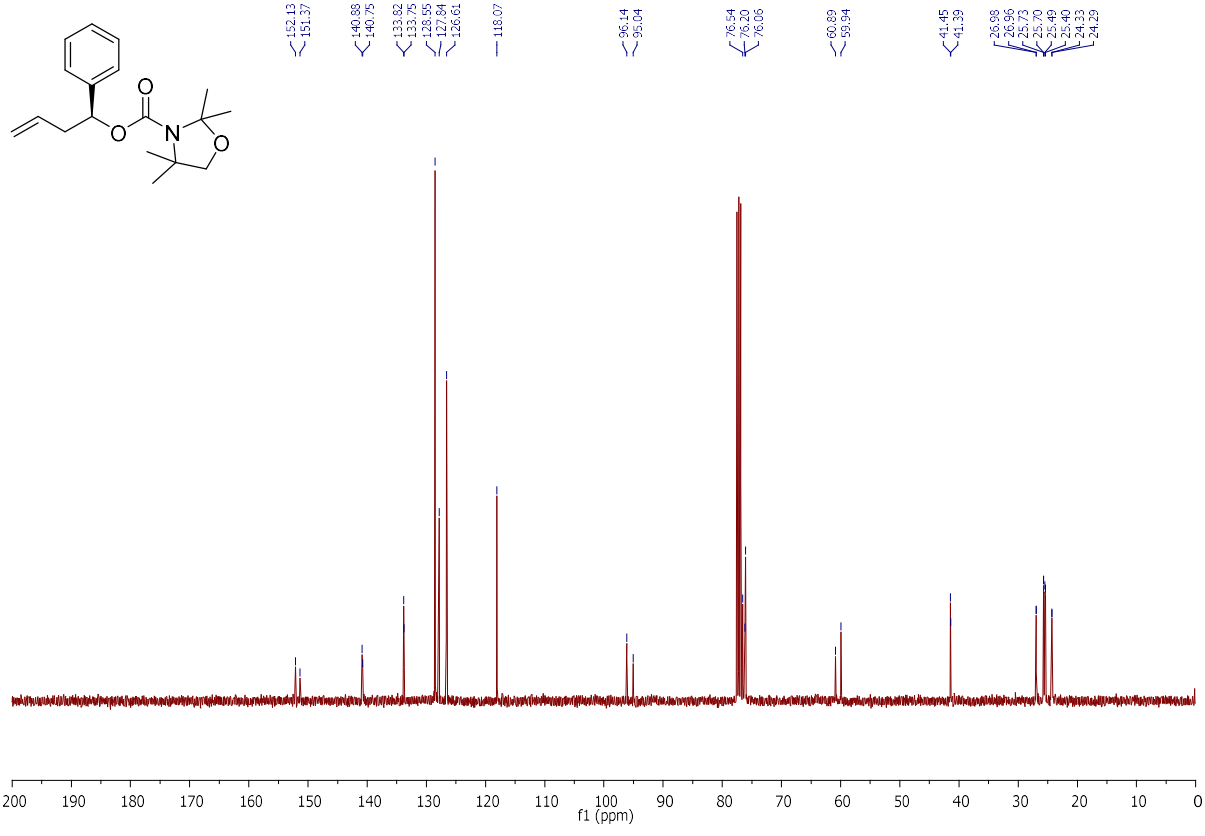
<Peak Table>

PDA Ch1 214nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.817	99.728	10451111	467409	0.000		M
2	13.006	0.272	28495	1706	0.000		M
Total		100.000	10479605	469116			

(*S*)-(-)-1-phenylbut-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5v** :





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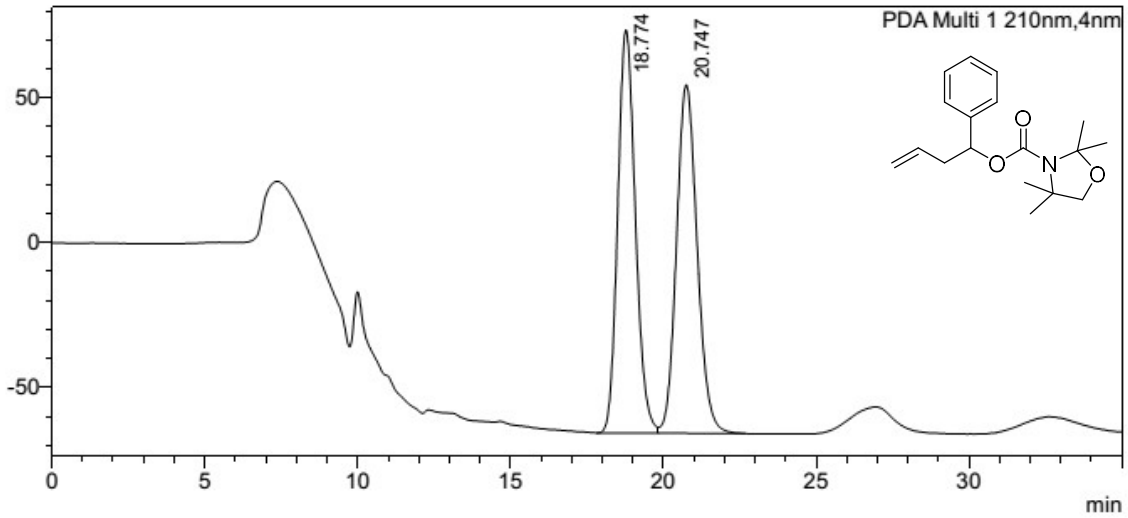

<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	18.774	49.737	5598202	139116	0.000		
2	20.747	50.263	5657384	120290	0.000		V
Total		100.000	11255586	259406			

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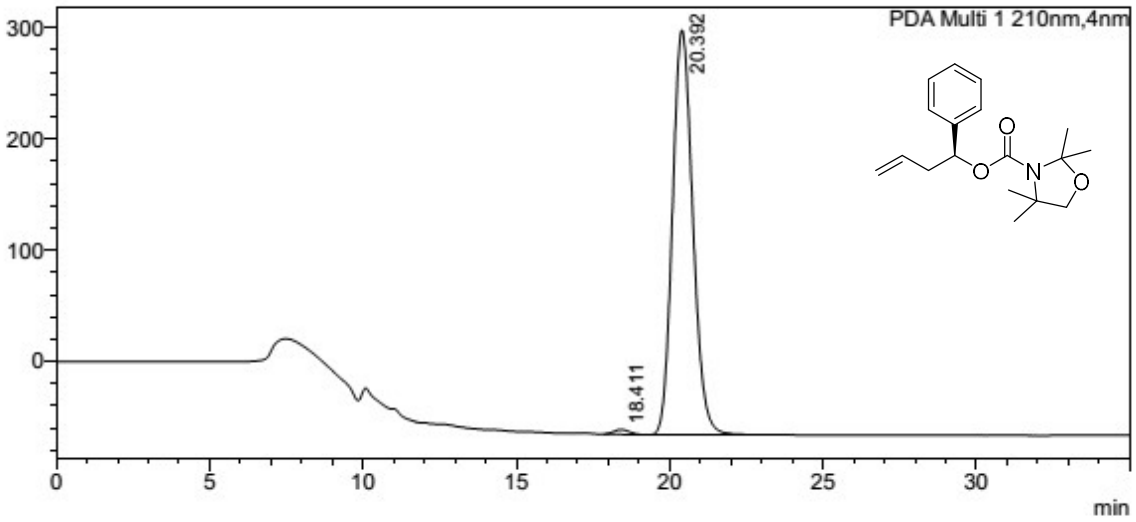
mAU

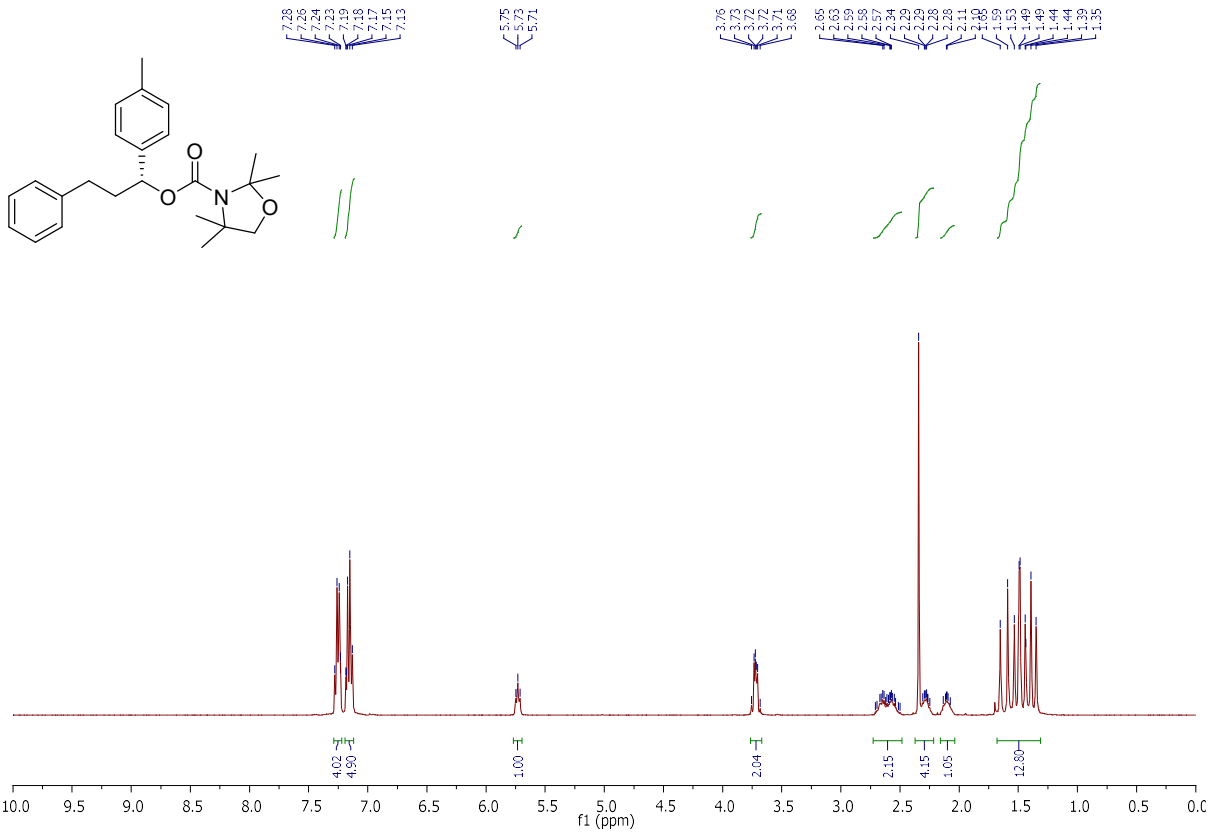


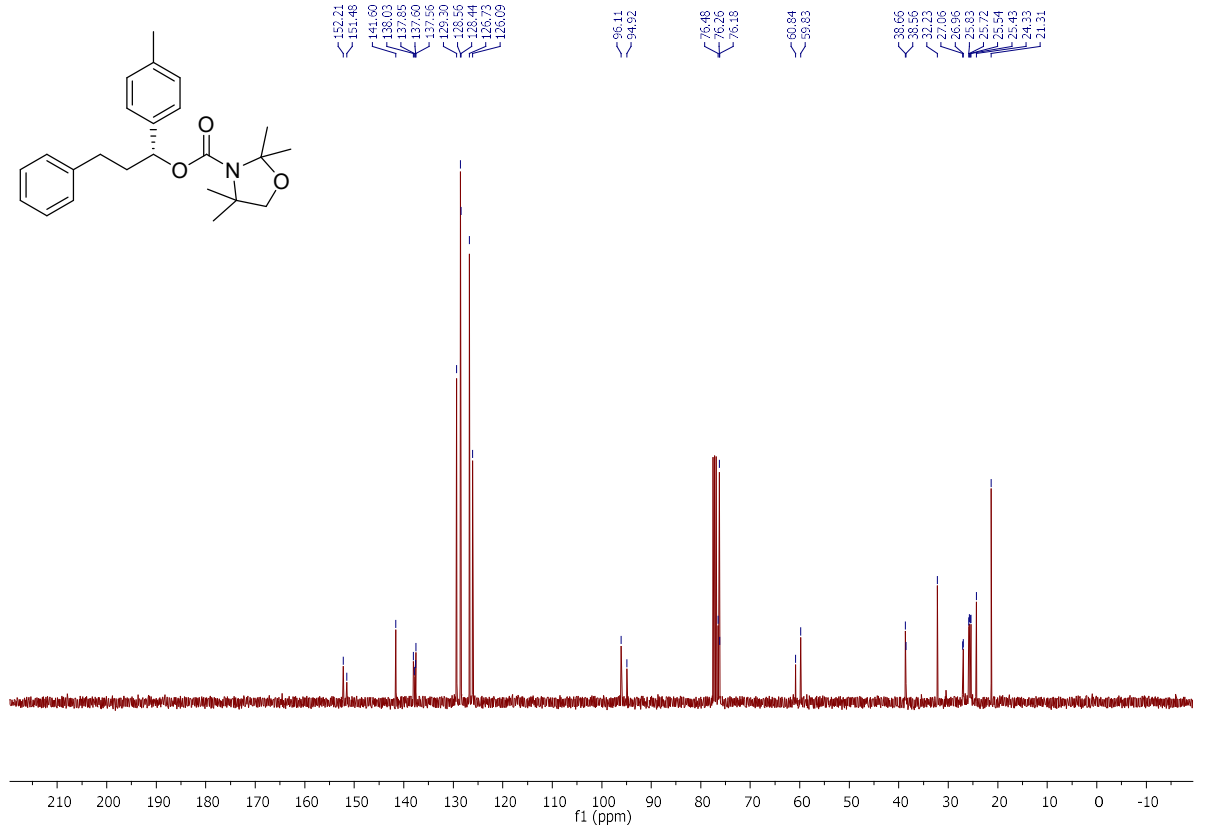
<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	18.411	0.880	148872	4240	0.000		M
2	20.392	99.120	16771009	363973	0.000		M
Total		100.000	16919881	368212			

(*R*)-(+)-3-phenyl-1-(*p*-tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.5w** :





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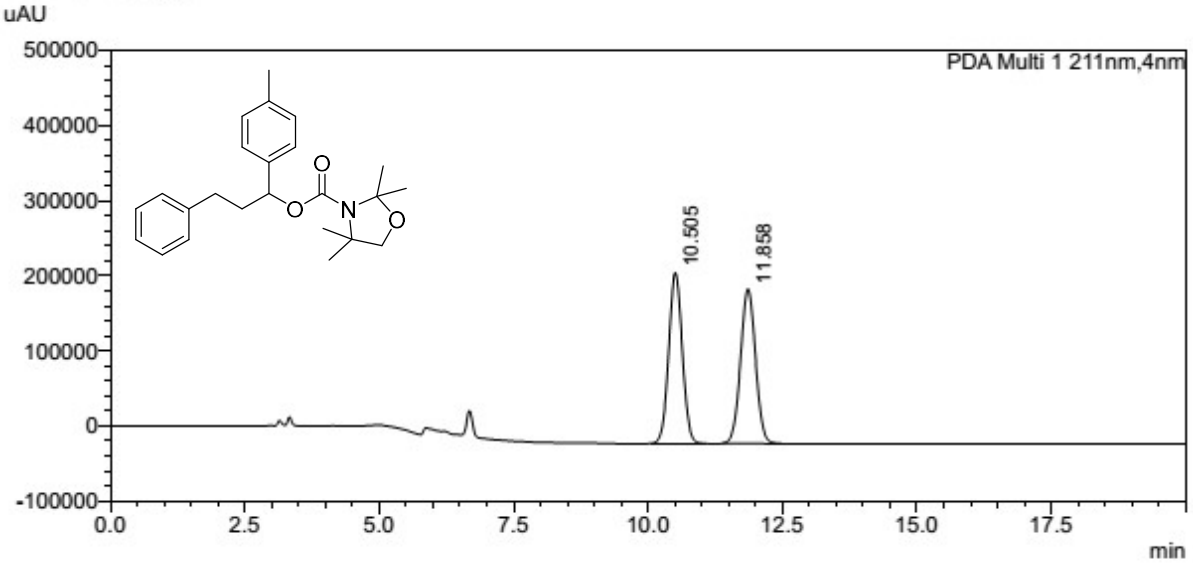

<Peak Table>

PDA Ch1 211nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.505	50.056	3996975	227590	0.000		M
2	11.858	49.944	3988031	206054	0.000		M
Total		100.000	7985007	433644			

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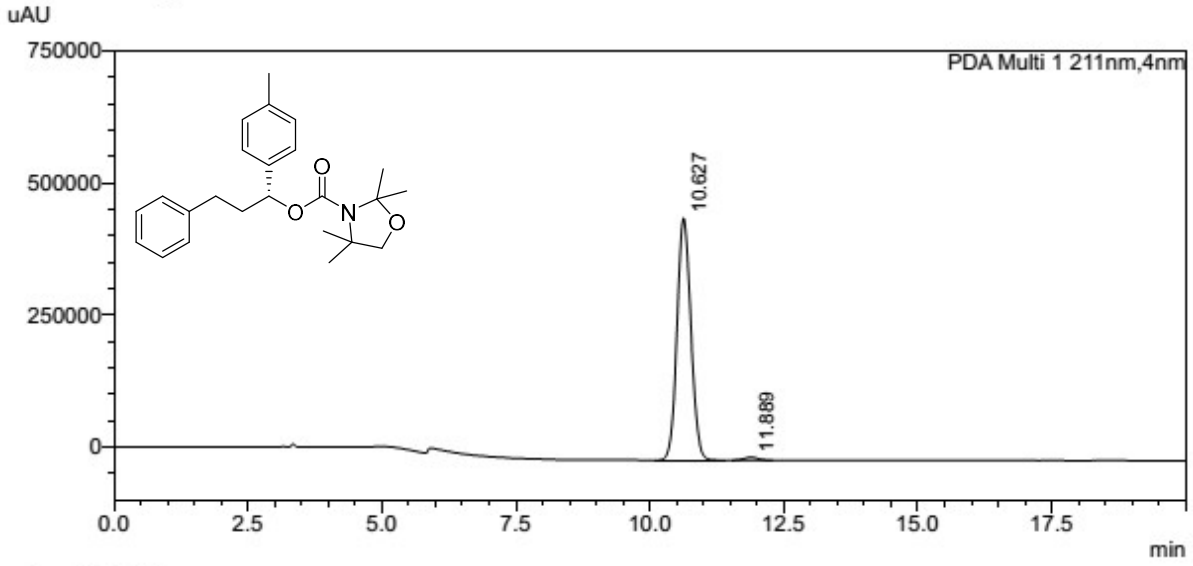
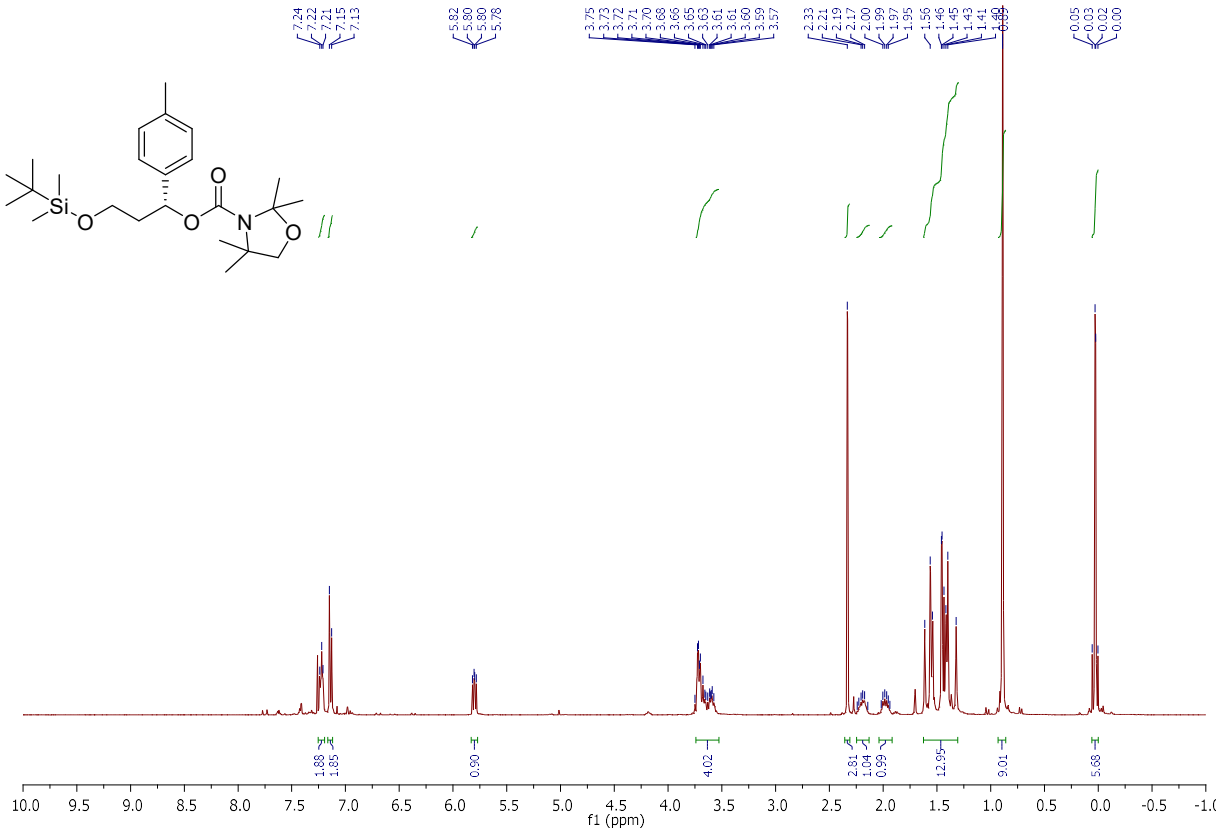


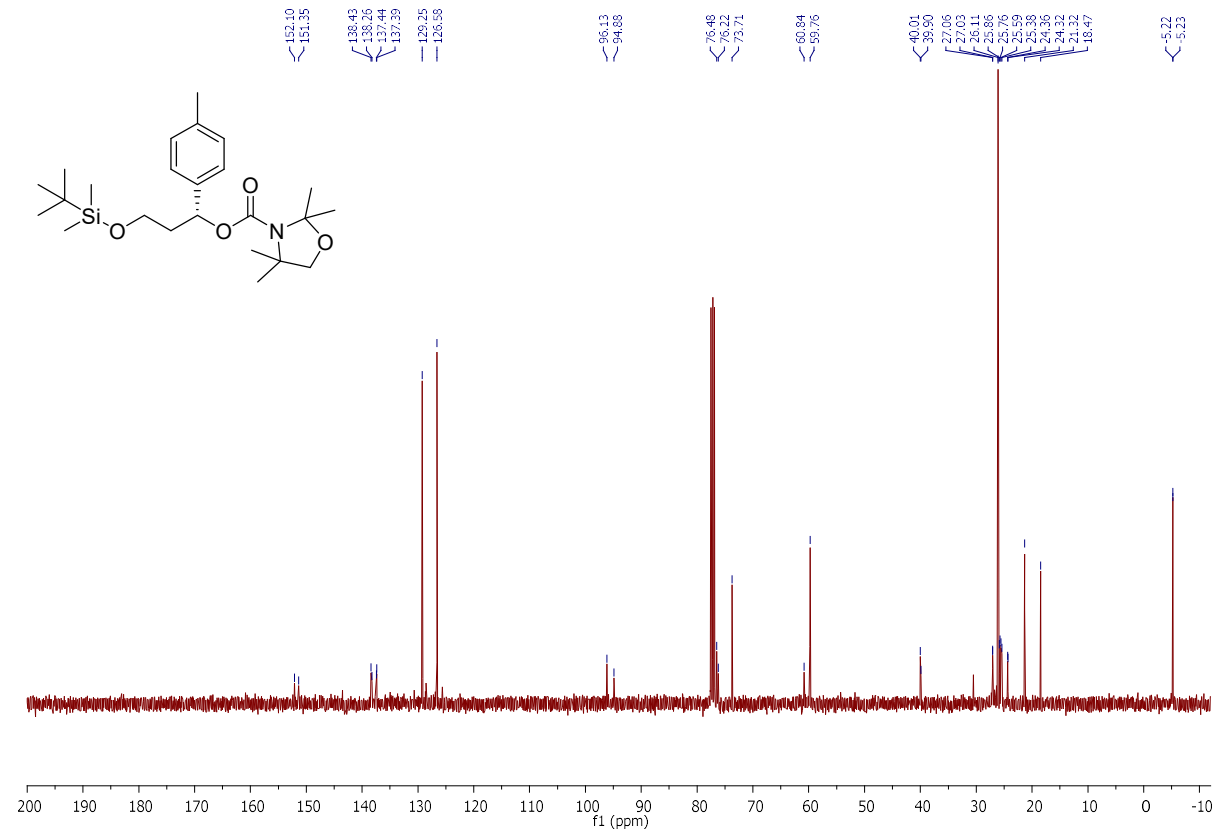
<Peak Table>

PDA Ch1 211nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.627	98.736	8270437	458829	0.000		M
2	11.889	1.264	105901	5718	0.000		M
Total		100.000	8376338	464547			

(*R*)-(+)-3-((tert-butyldimethylsilyl)oxy)-1-(*p*-tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5x** :





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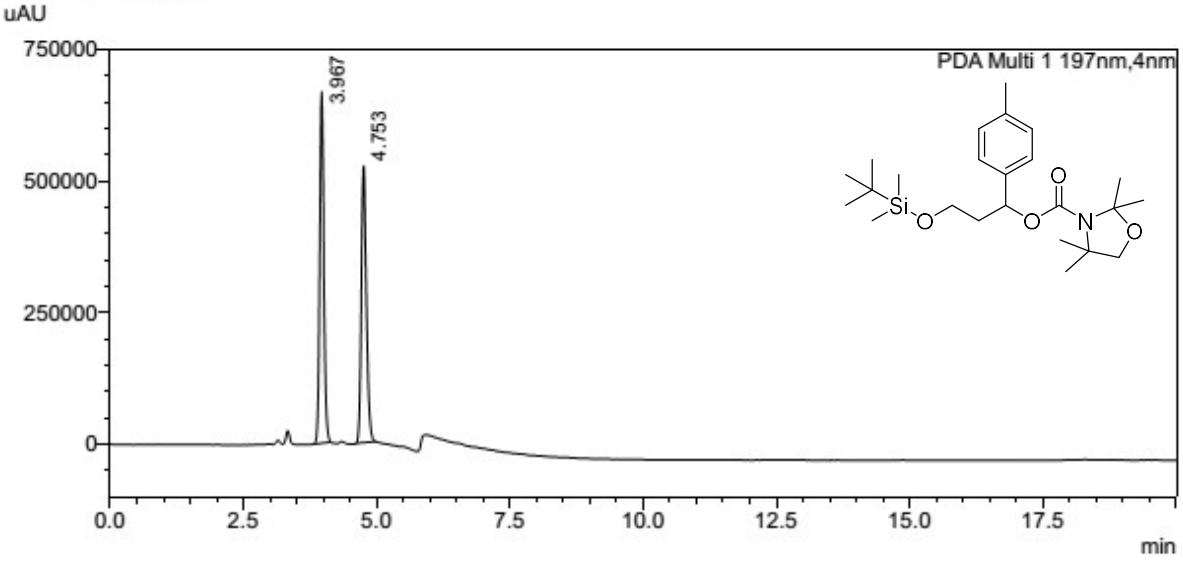

<Peak Table>

PDA Ch1 197nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	3.967	50.702	3580389	668413	0.000		M
2	4.753	49.298	3481285	525923	0.000		M
Total		100.000	7061674	1194336			

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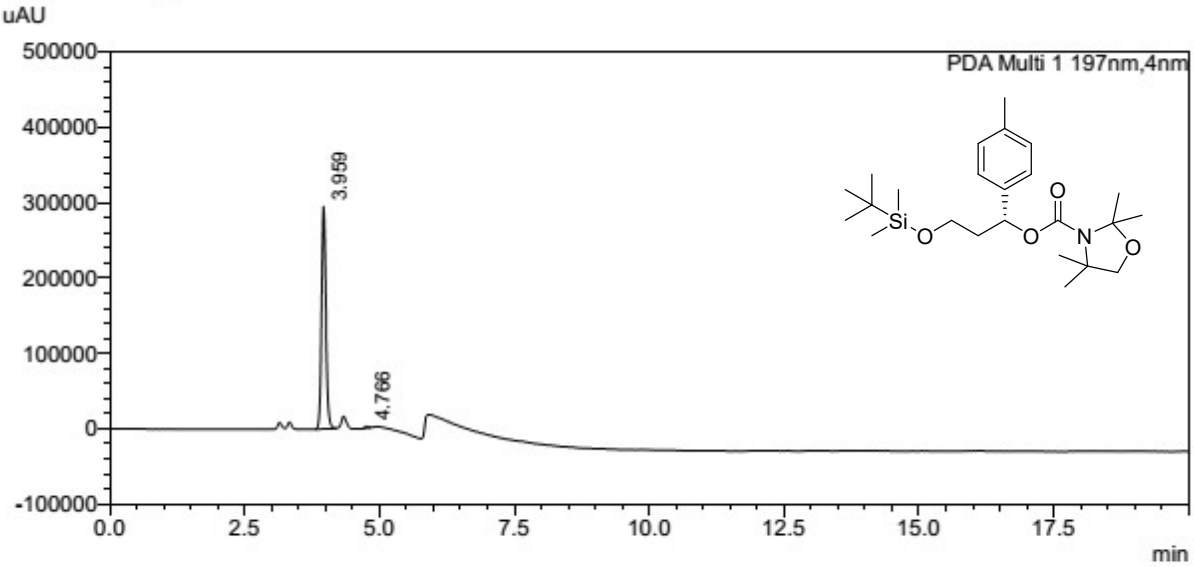
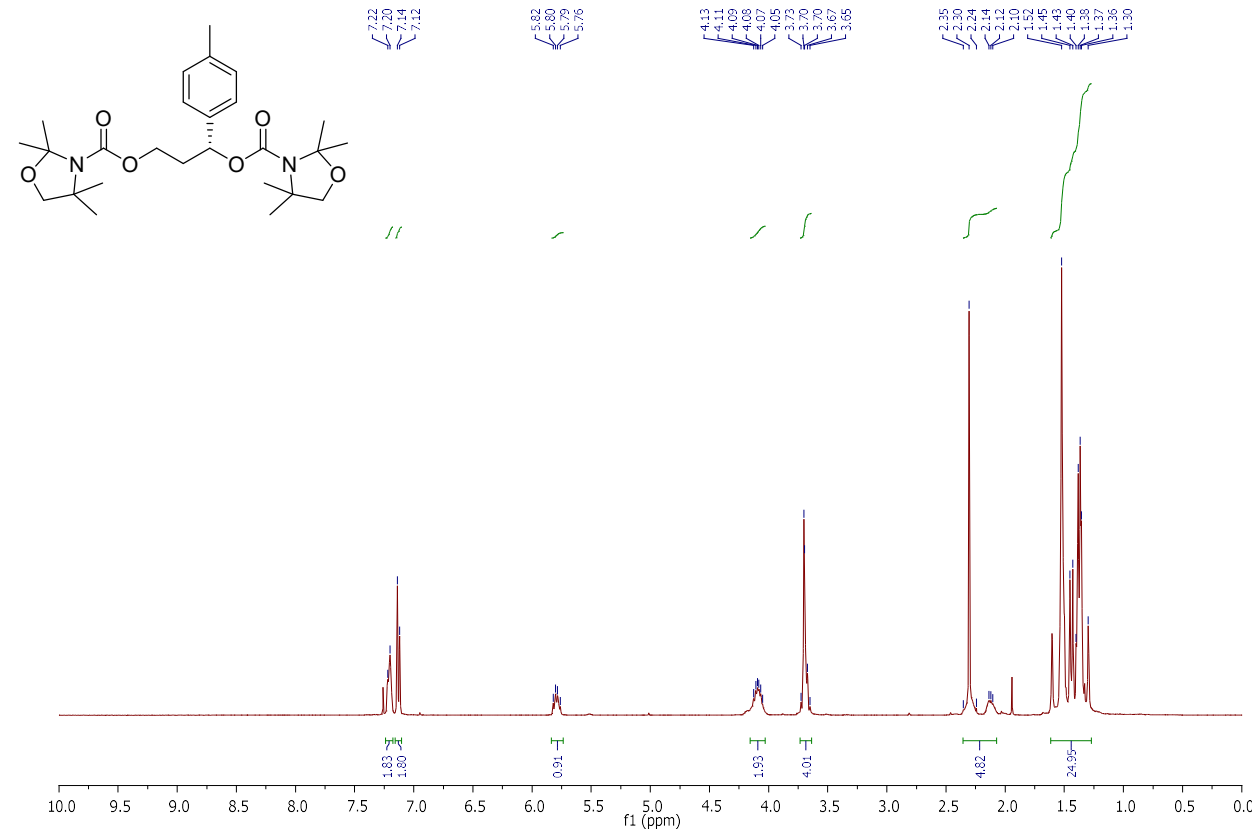


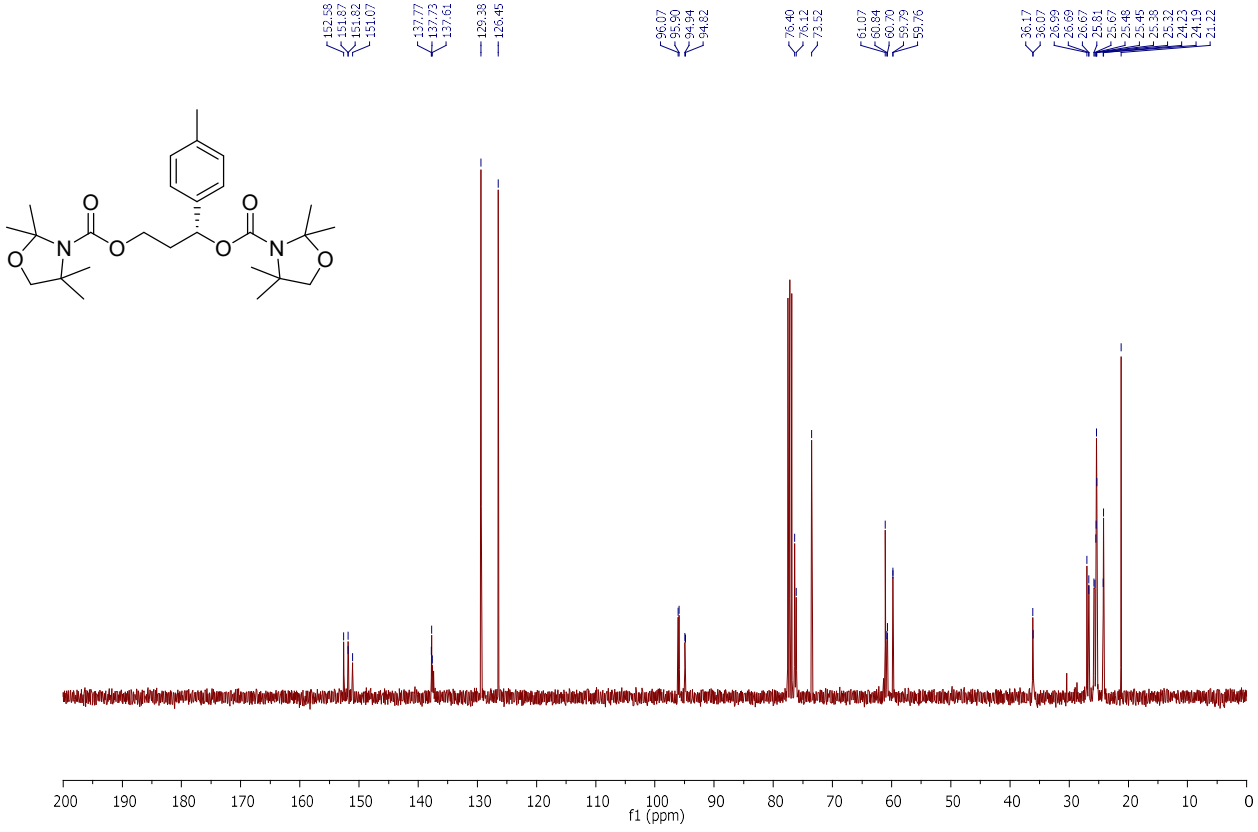
<Peak Table>

PDA Ch1 197nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	3.959	99.467	1627816	295073	99.467		M
2	4.766	0.533	8724	1969	0.533		M
Total		100.000	1636540	297042			

(*R*)-(+)-1-(*p*-tolyl)propane-1,3-diyl bis(2,2,4,4-tetramethyloxazolidine-3-carboxylate) **2.5y** :





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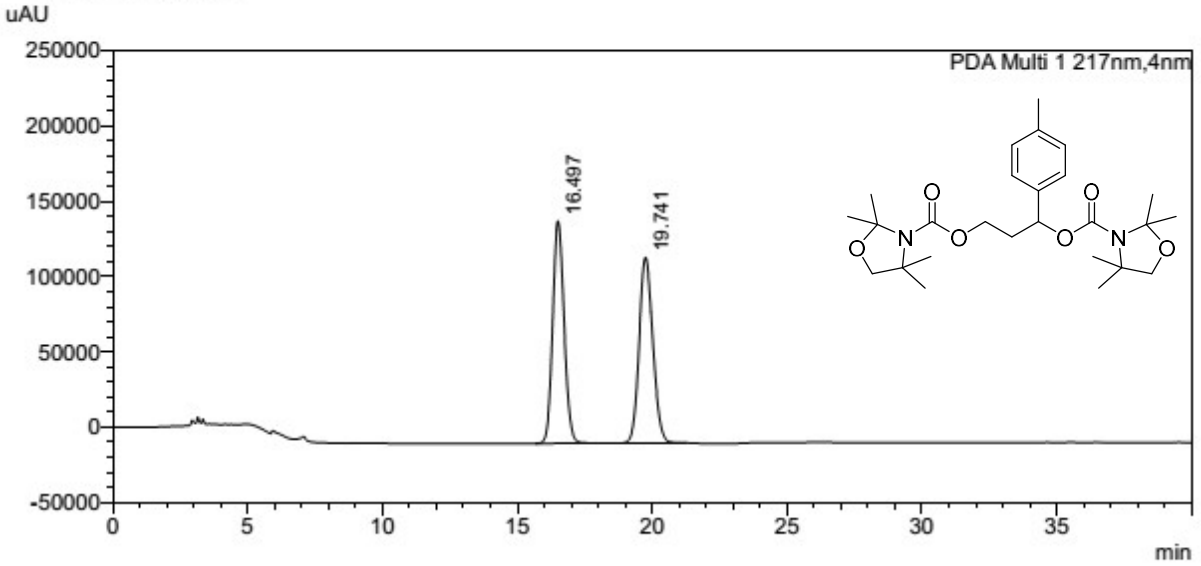

<Peak Table>

PDA Ch1 217nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	16.497	49.830	4335660	147665	0.000		
2	19.741	50.170	4365298	123362	0.000		
Total		100.000	8700958	271027			

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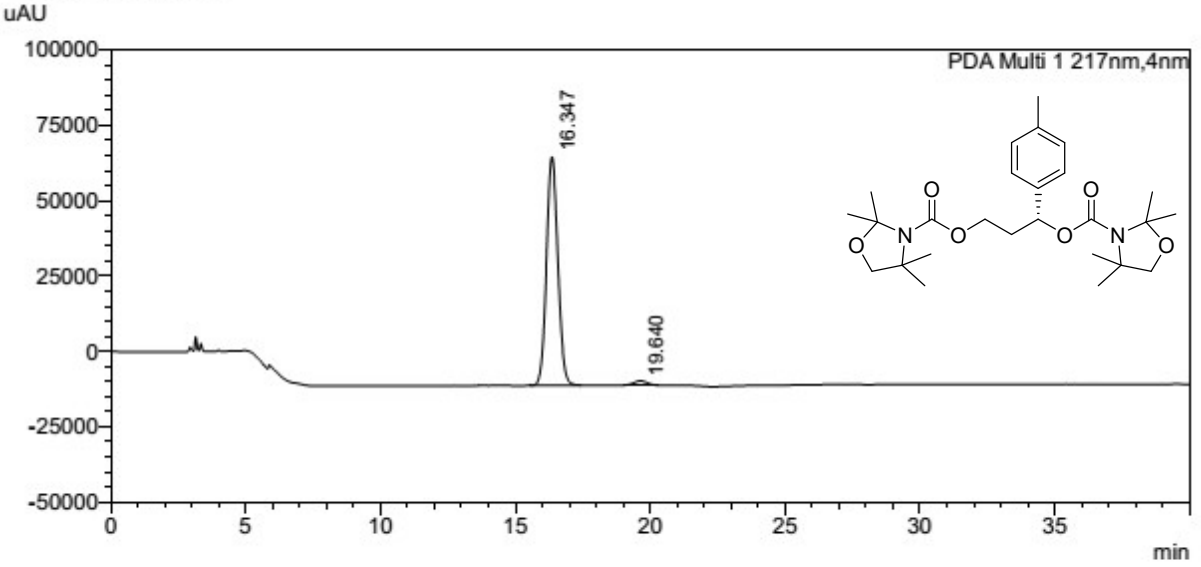
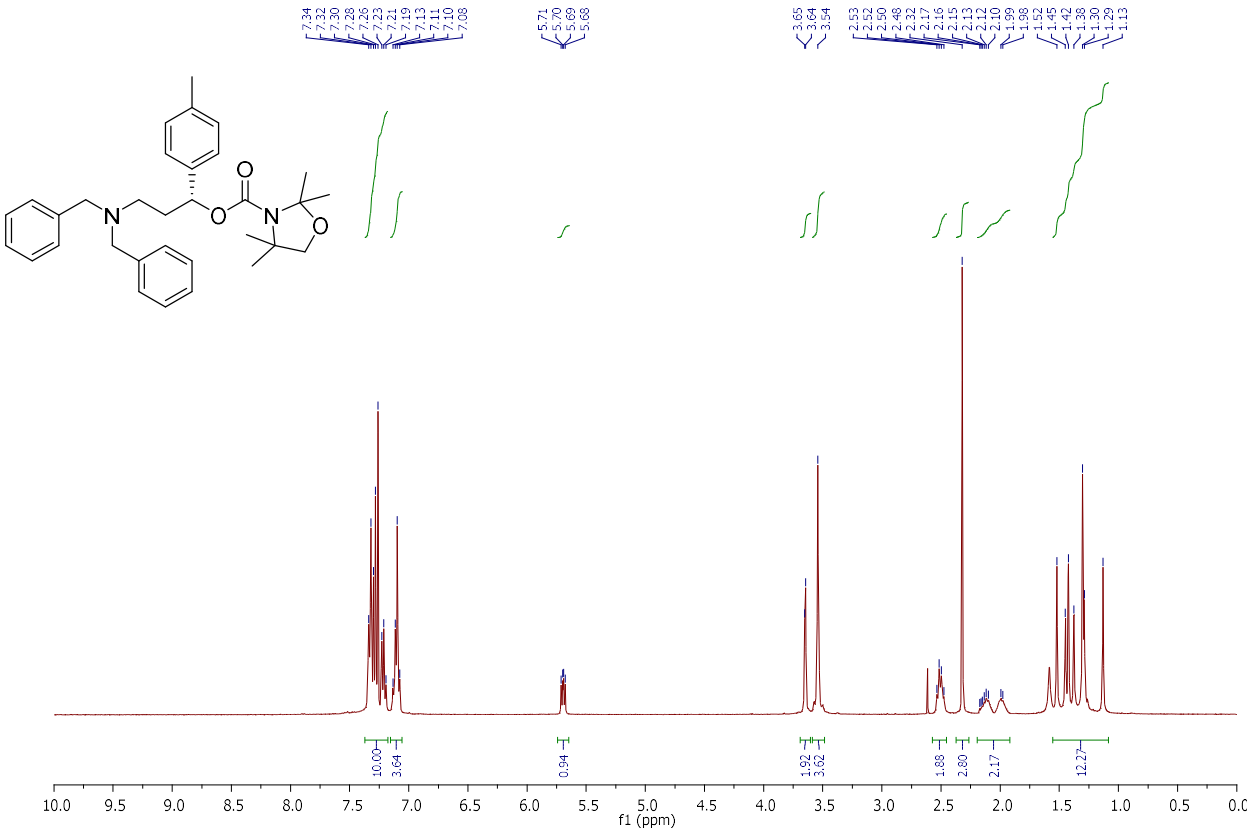


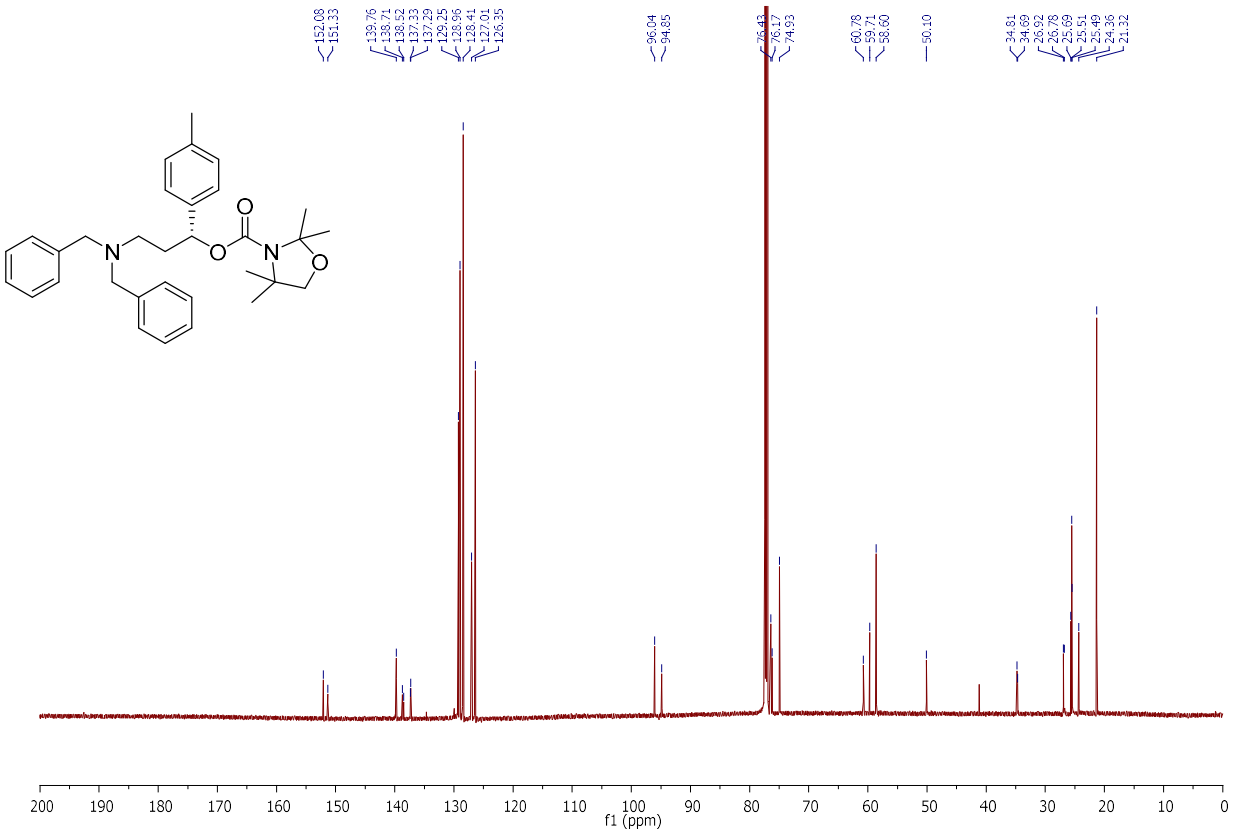
<Peak Table>

PDA Ch1 217nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	16.347	97.929	2221943	75743	0.000		
2	19.640	2.071	46999	1417	0.000		
Total		100.000	2268941	77160			

(*R*)-(+)-3-(dibenzylamino)-1-(*p*-tolyl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.5z** :





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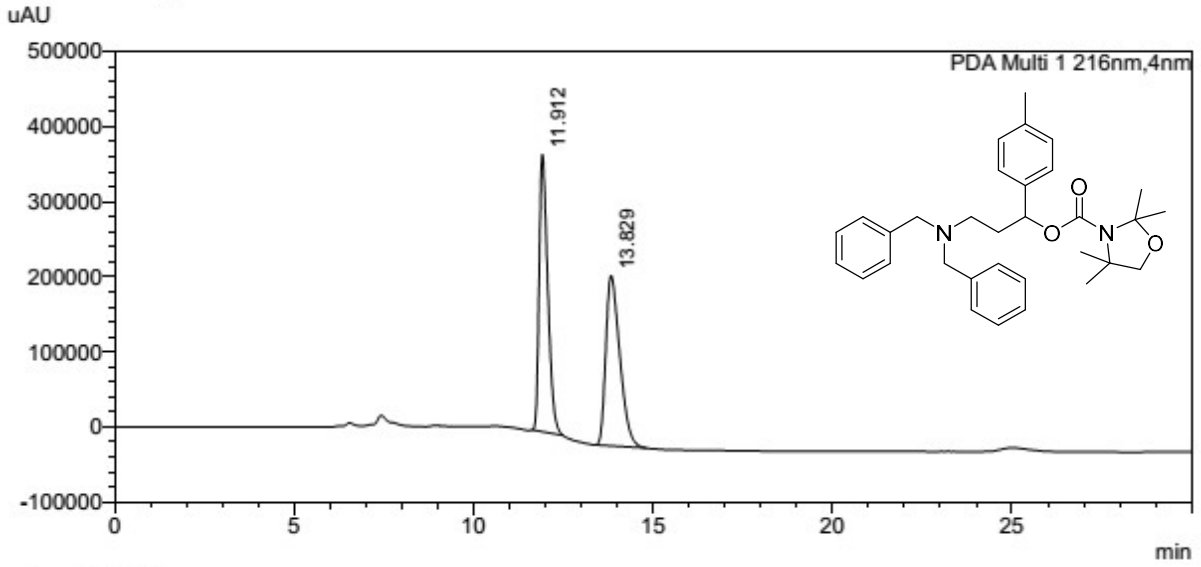

<Peak Table>

PDA Ch1 216nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.912	49.987	6151368	369644	0.000		M
2	13.829	50.013	6154486	226789	0.000		M
Total		100.000	12305854	596433			

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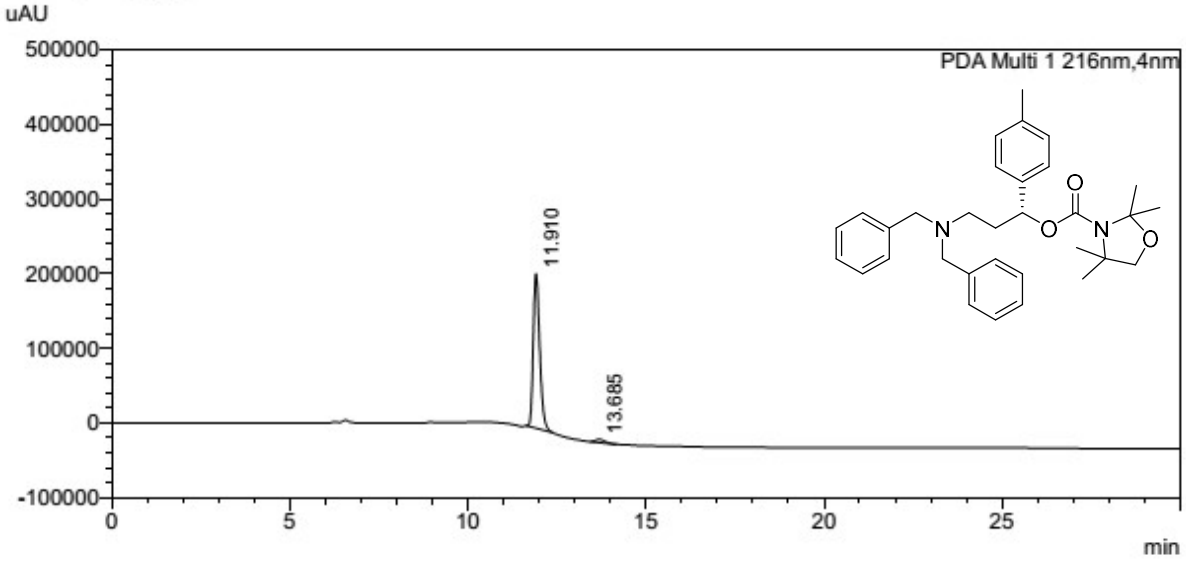
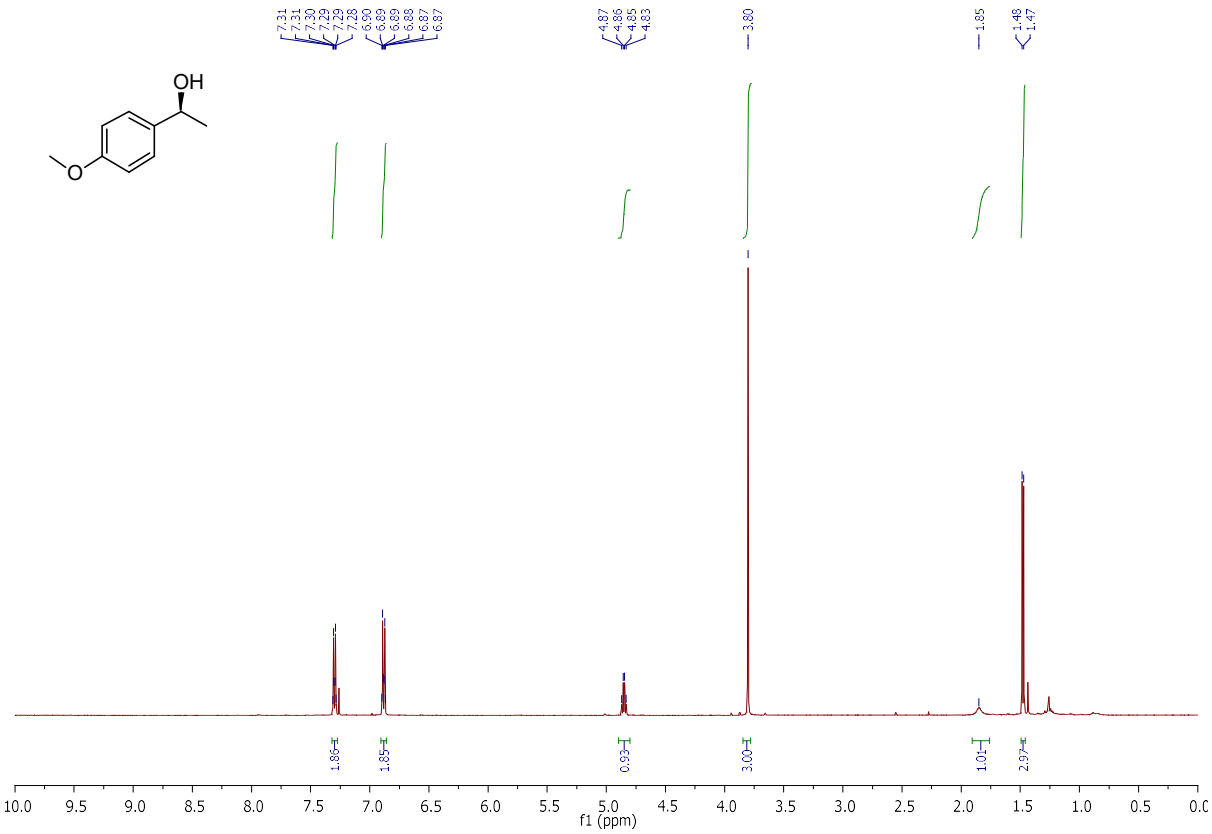


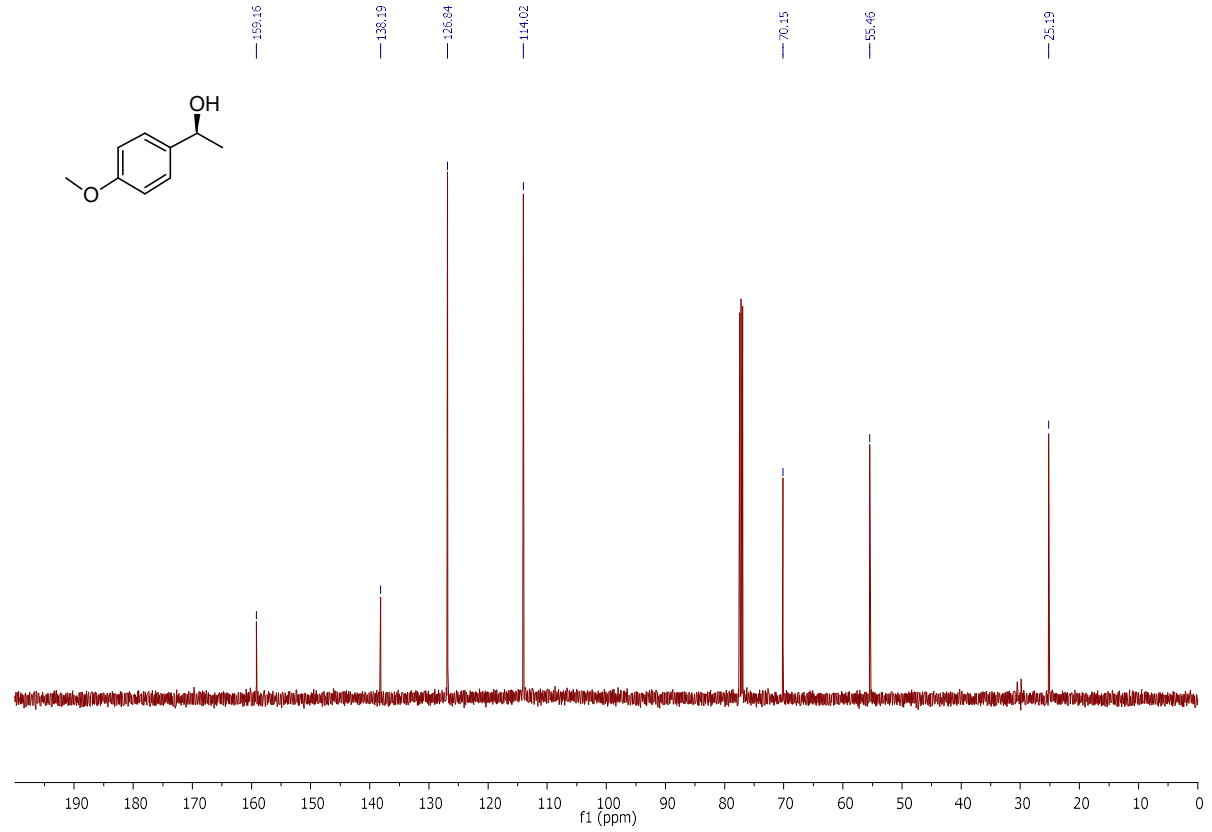
<Peak Table>

PDA Ch1 216nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	11.910	97.174	2624125	207016	0.000		M
2	13.685	2.826	76325	4142	0.000		M
Total		100.000	2700451	211158			

1-(4-methoxyphenyl)ethan-1-ol **2.12a** and *ent*-**2.12a**:





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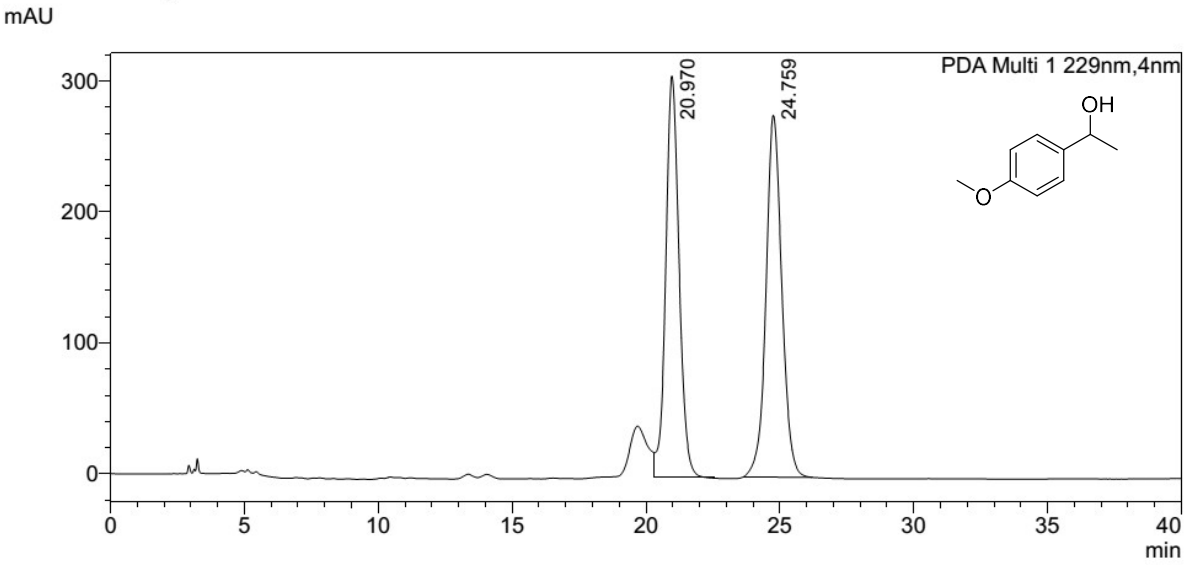

<Peak Table>

PDA Ch1 229nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	20.970	48.361	10615591	306678	0.000		M
2	24.759	51.639	11335041	276232	0.000		M
Total		100.000	21950632	582910			

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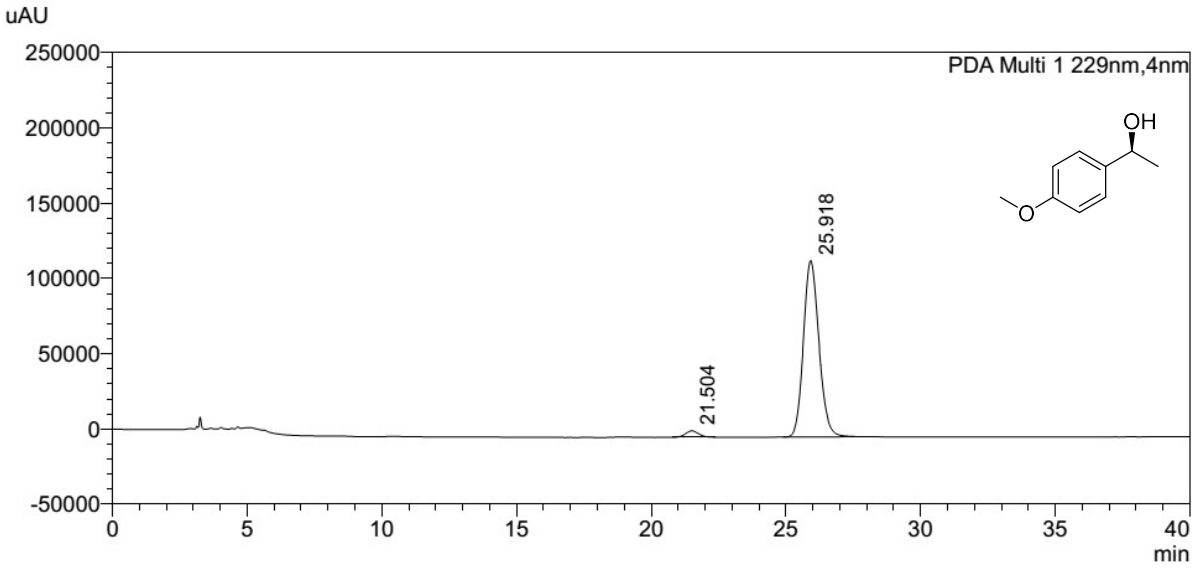
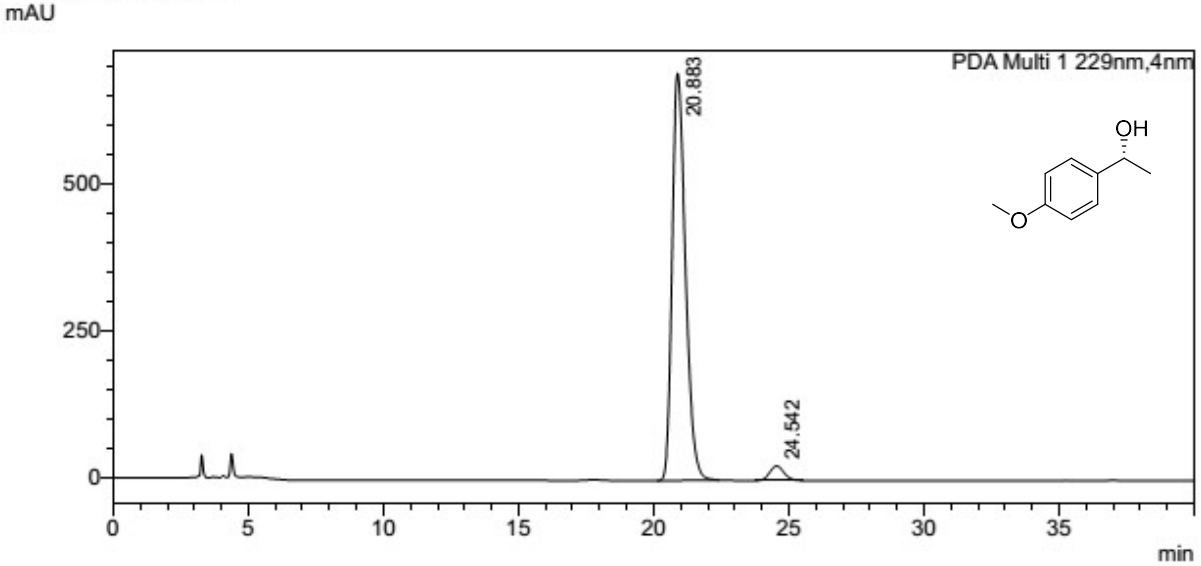


<Peak Table>

PDA Ch1 229nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	21.504	3.026	146597	4315	3.026		
2	25.918	96.974	4698294	117247	96.974		
Total		100.000	4844891	121562			

<Chromatogram>

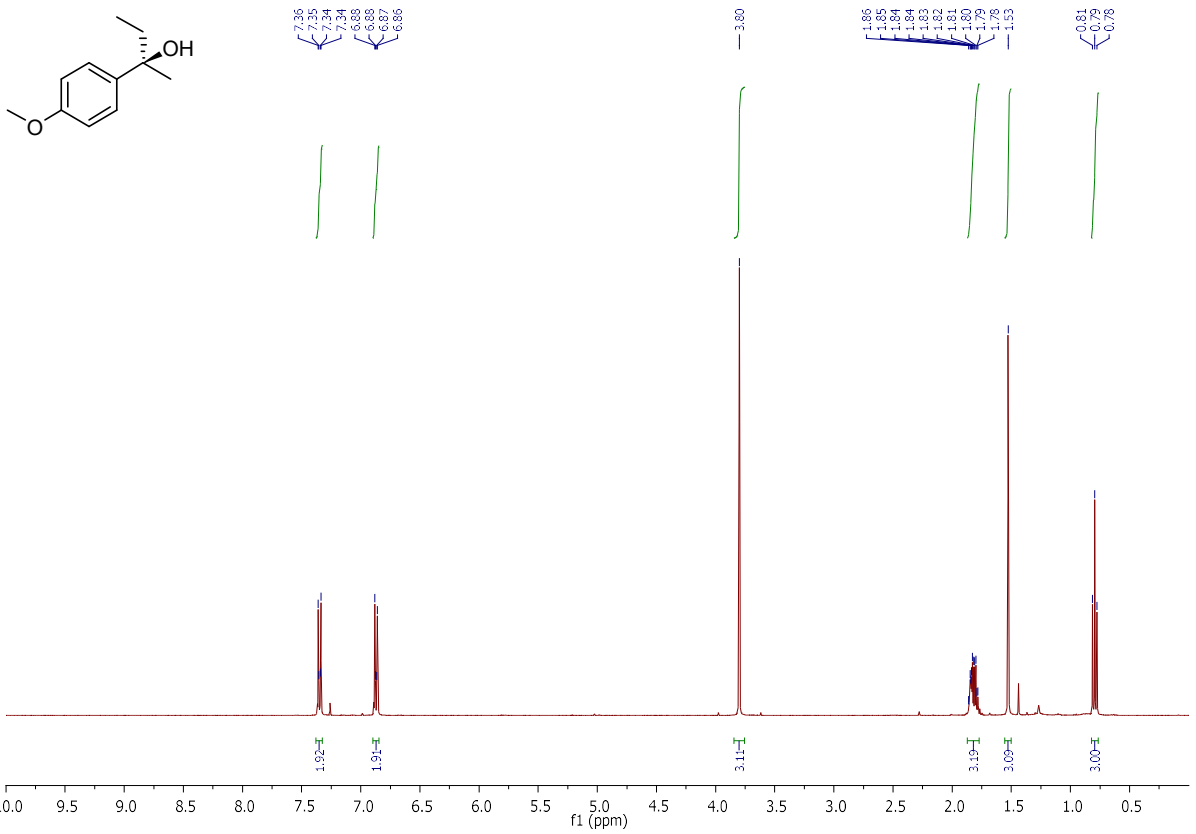


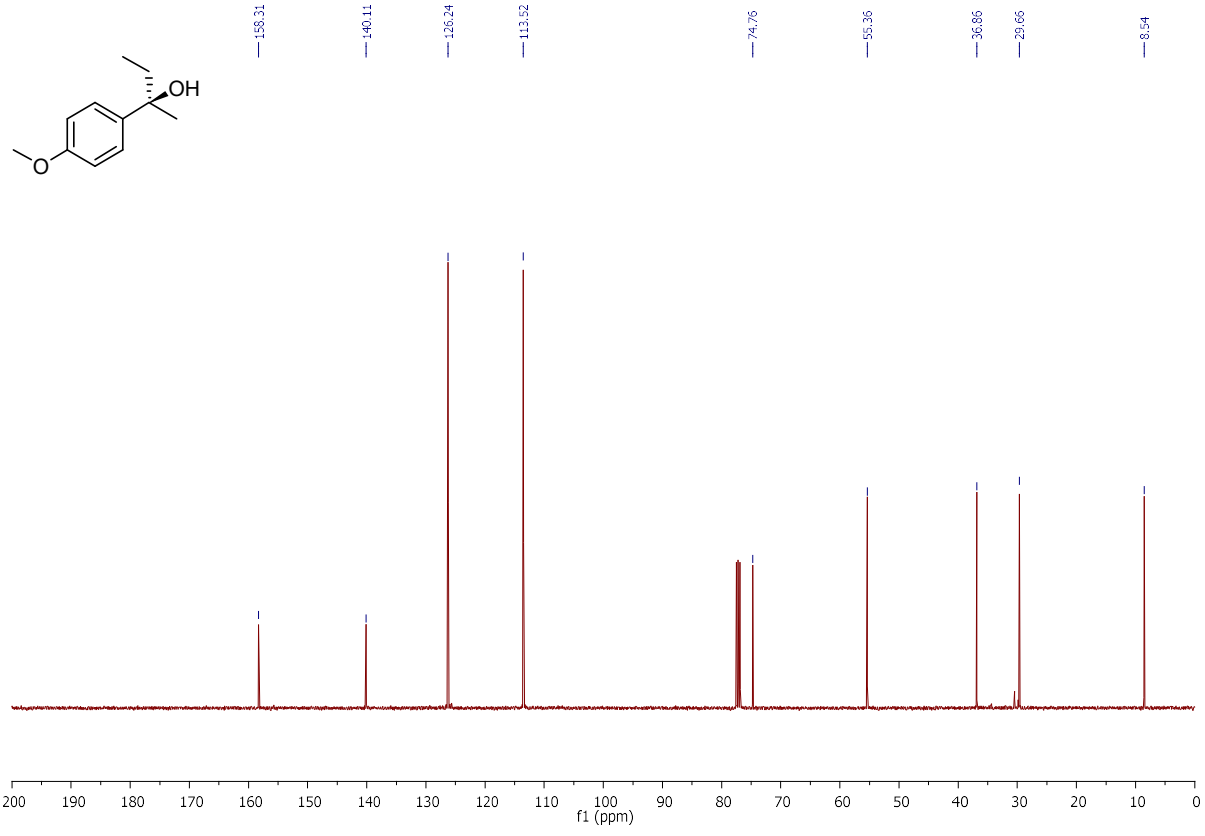
<Peak Table>

PDA Ch1 229nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	20.883	96.206	23719043	692372	0.000		M
2	24.542	3.794	935348	25128	0.000		M
Total		100.000	24654390	717500			

(R)-(+)-2-(4-methoxyphenyl)butan-2-ol**2.12b** :





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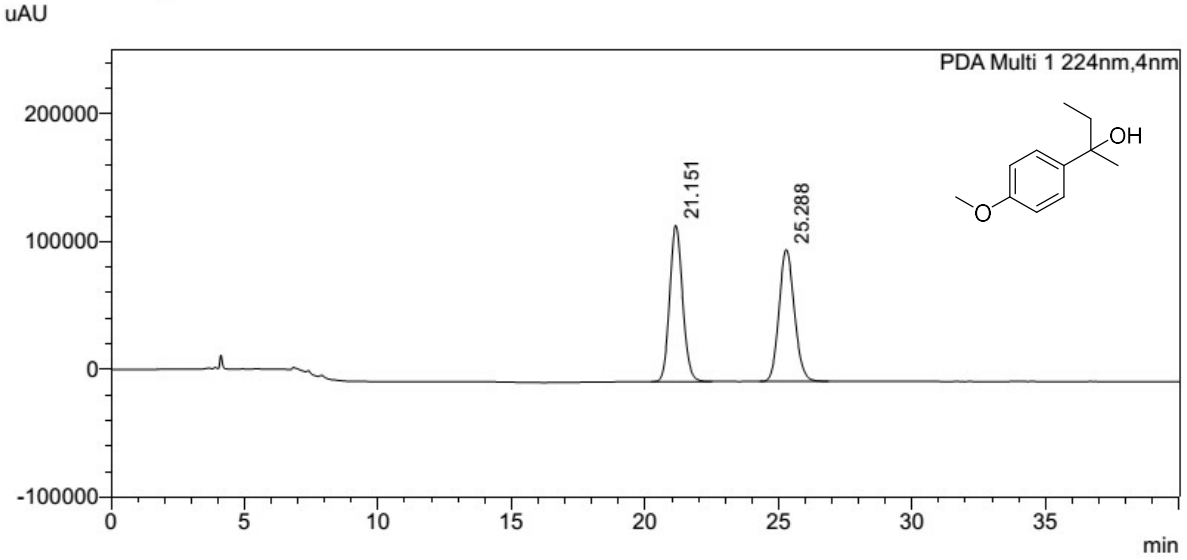
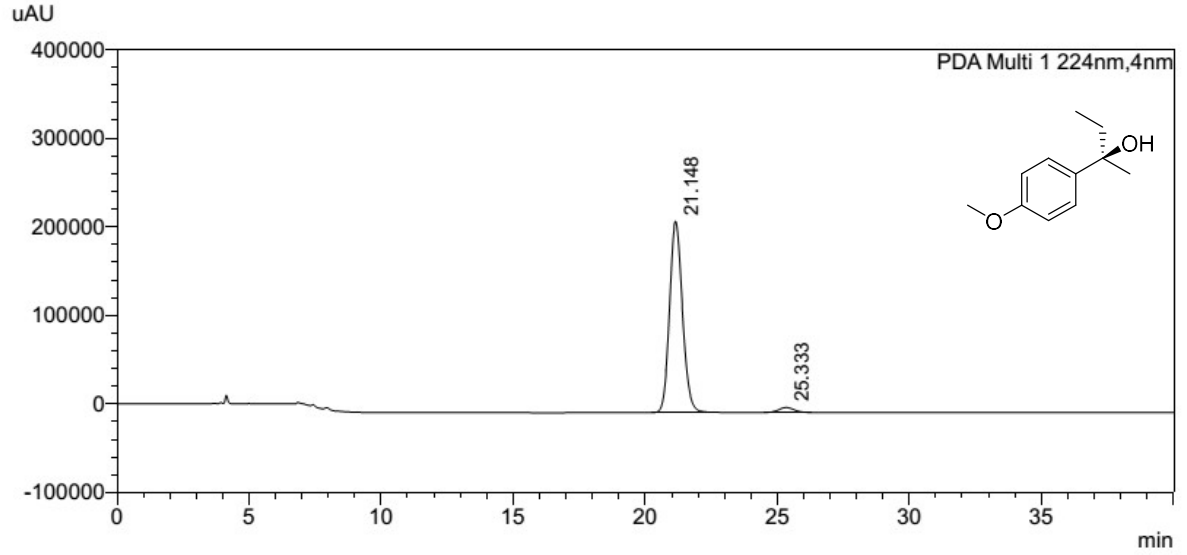


<Peak Table>

PDA Ch1 224nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	21.151	49.983	4121990	122258	0.000		
2	25.288	50.017	4124869	103121	0.000		
Total		100.000	8246858	225379			

<Chromatogram>

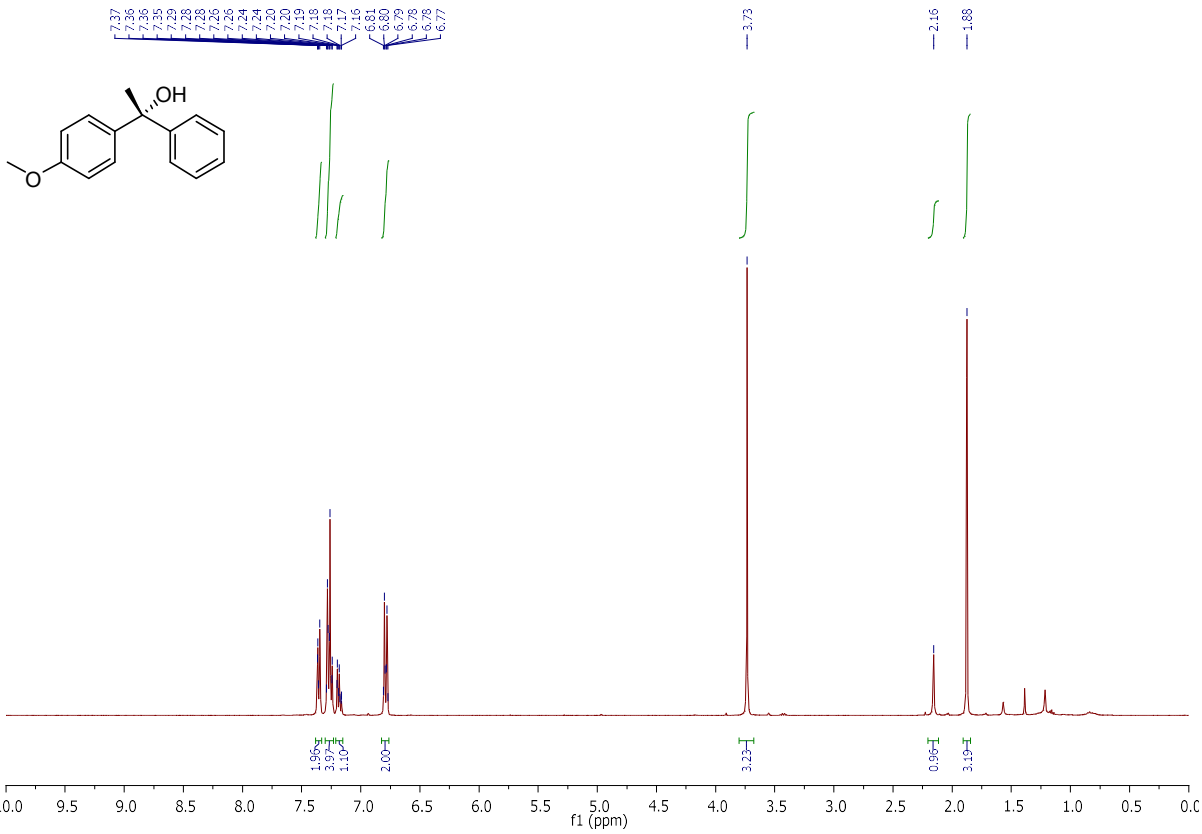


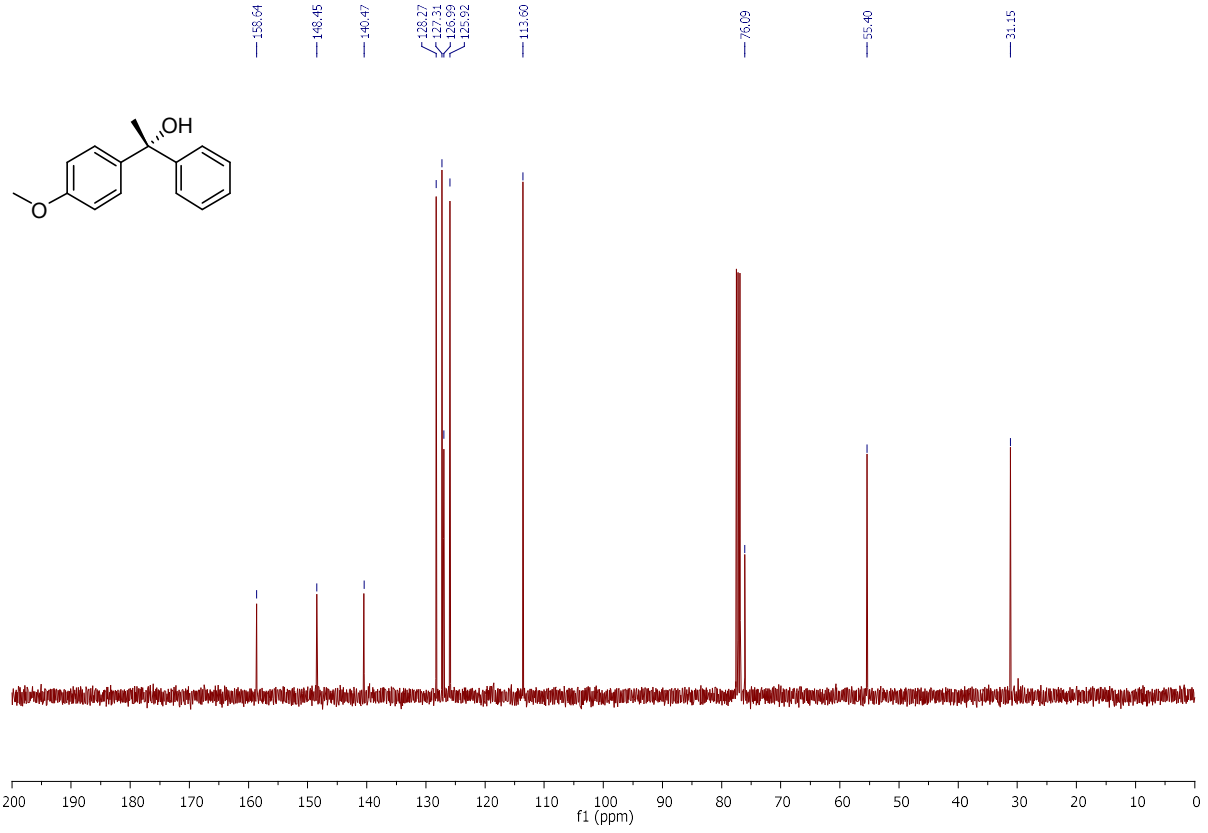
<Peak Table>

PDA Ch1 224nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	21.148	97.132	7322927	215685	0.000		
2	25.333	2.868	216190	5534	0.000		
Total		100.000	7539117	221219			

(R)-(+)-1-(4-methoxyphenyl)-1-phenylethan-1-ol **2.12c** :

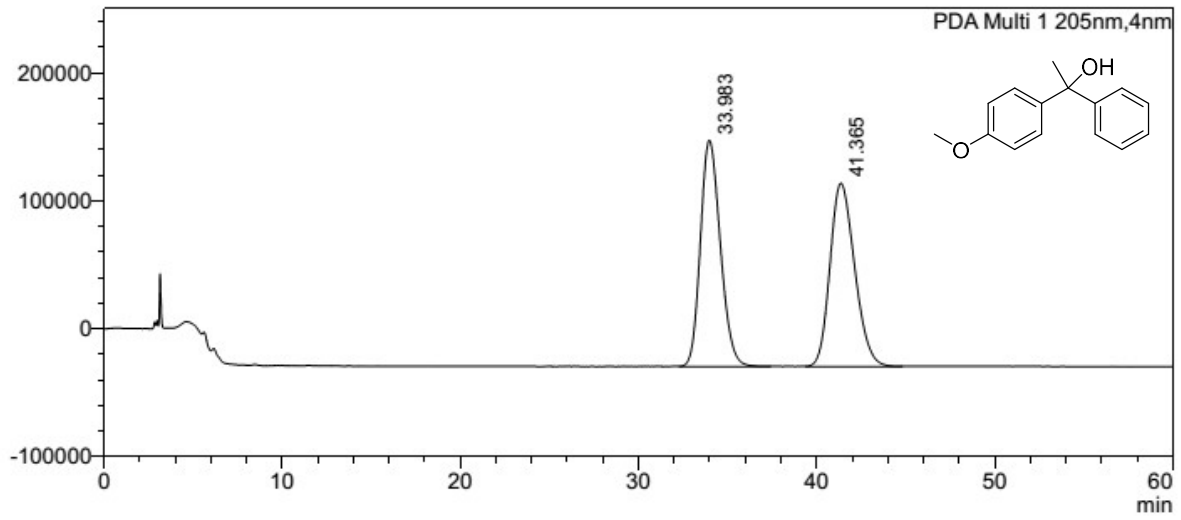




(R)-(+)-1-(4-methoxyphenyl)-1-phenylethan-1-ol :

<Chromatogram>

uAU



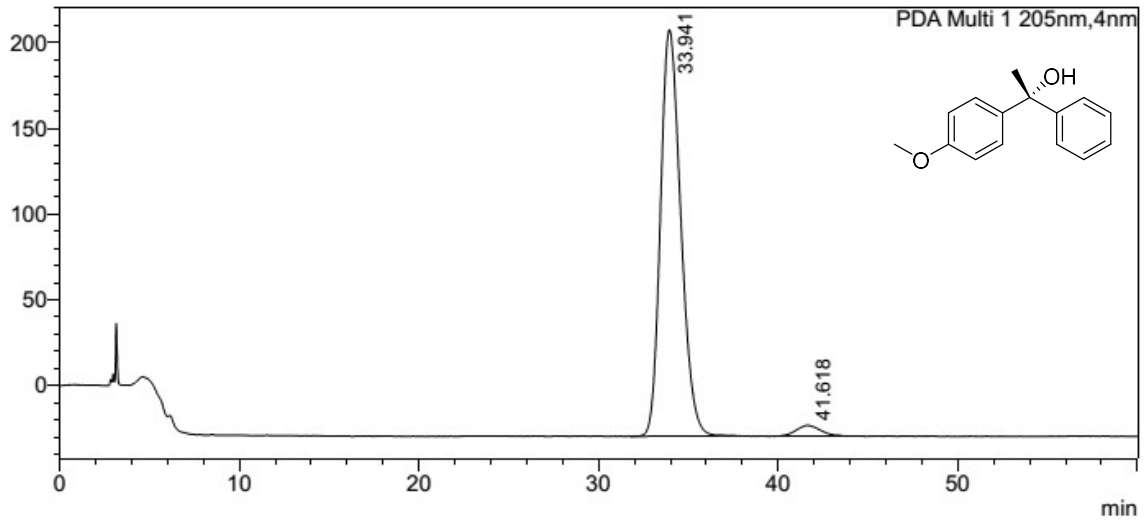
<Peak Table>

PDA Ch1 205nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	33.983	49.962	13757096	176681	0.000		SV
2	41.365	50.038	13777860	143154	0.000		SV
Total		100.000	27534956	319835			

<Chromatogram>

mAU

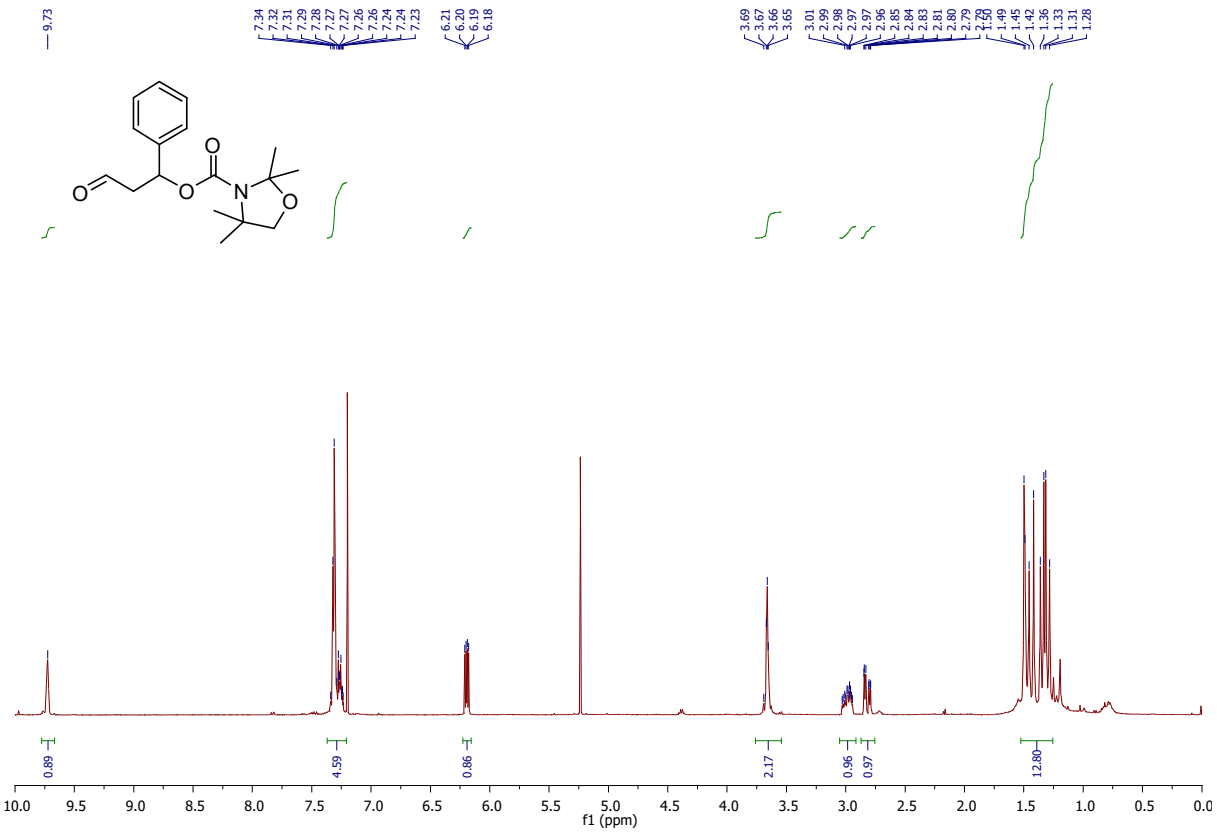


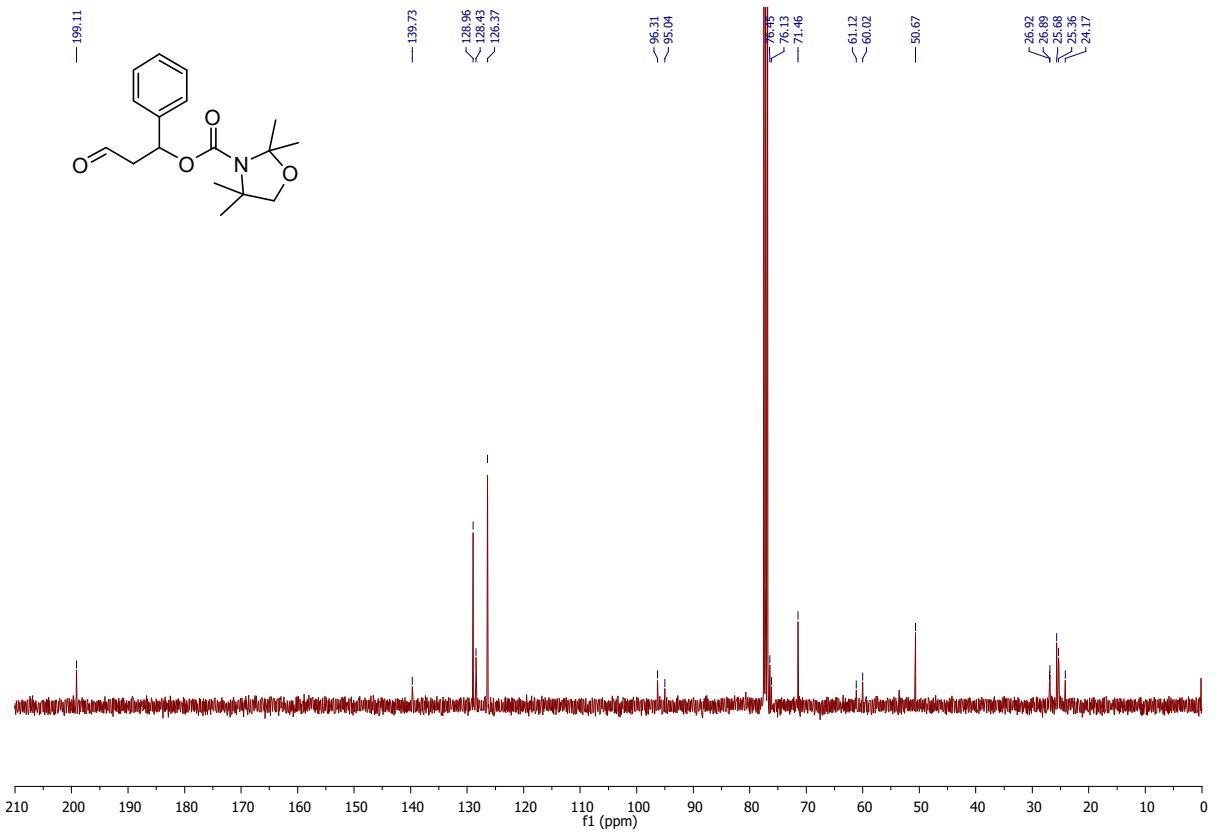
<Peak Table>

PDA Ch1 205nm

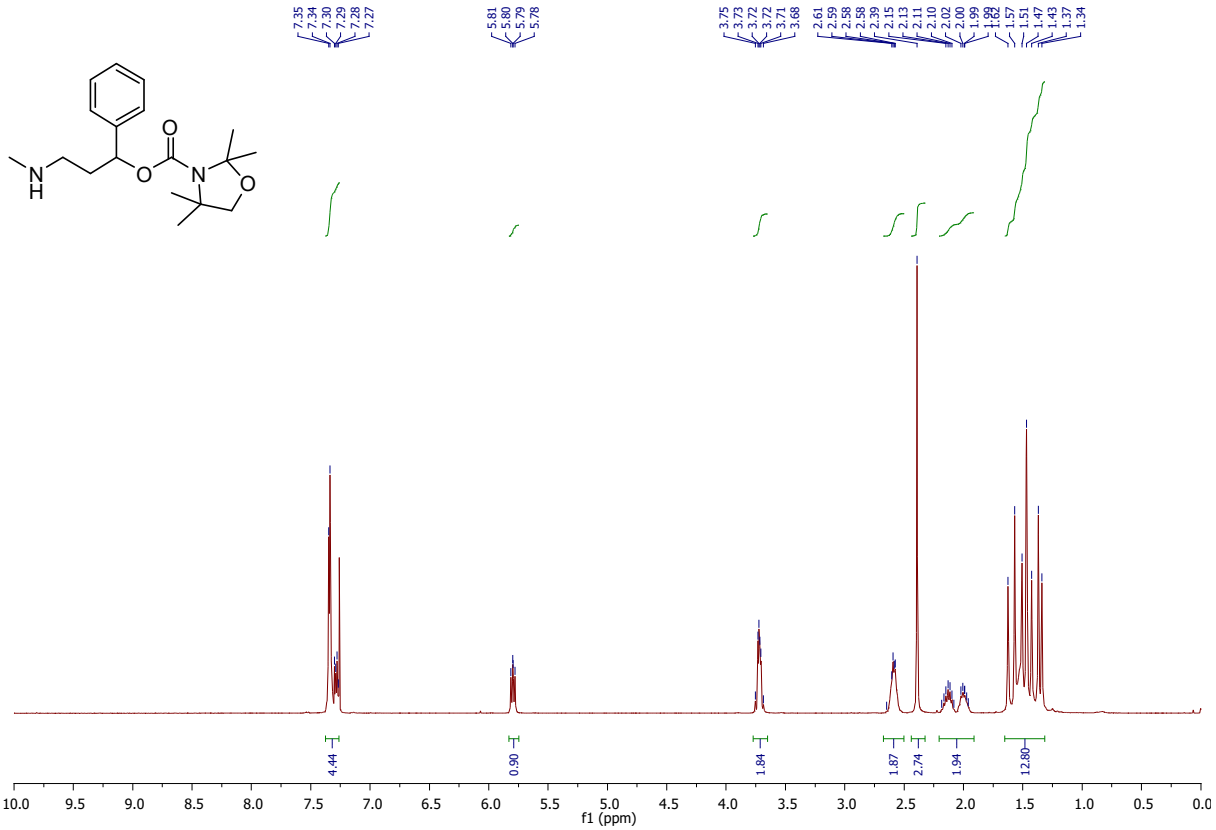
Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	33.941	96.956	18576811	236973	0.000		M
2	41.618	3.044	583269	6202	0.000		M
Total		100.000	19160080	243175			

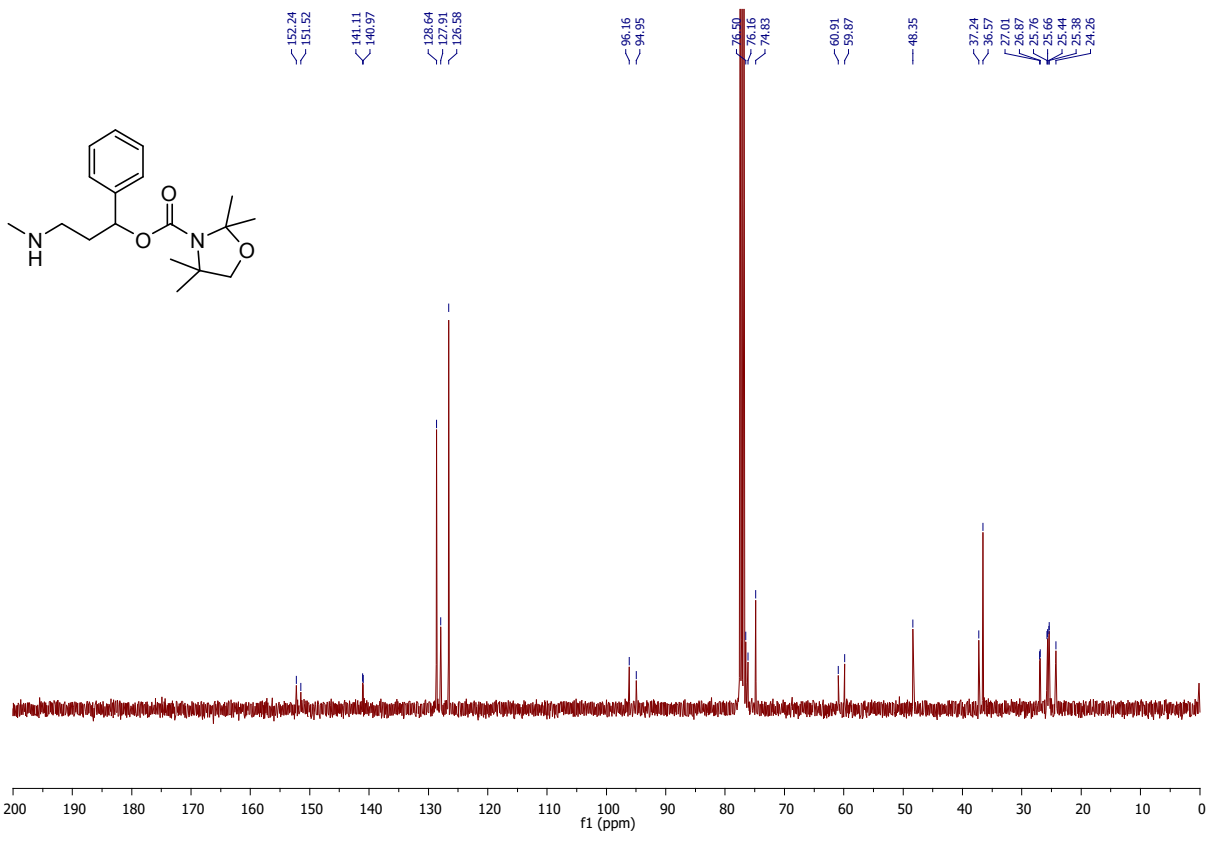
3-oxo-1-phenylpropyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.17**:



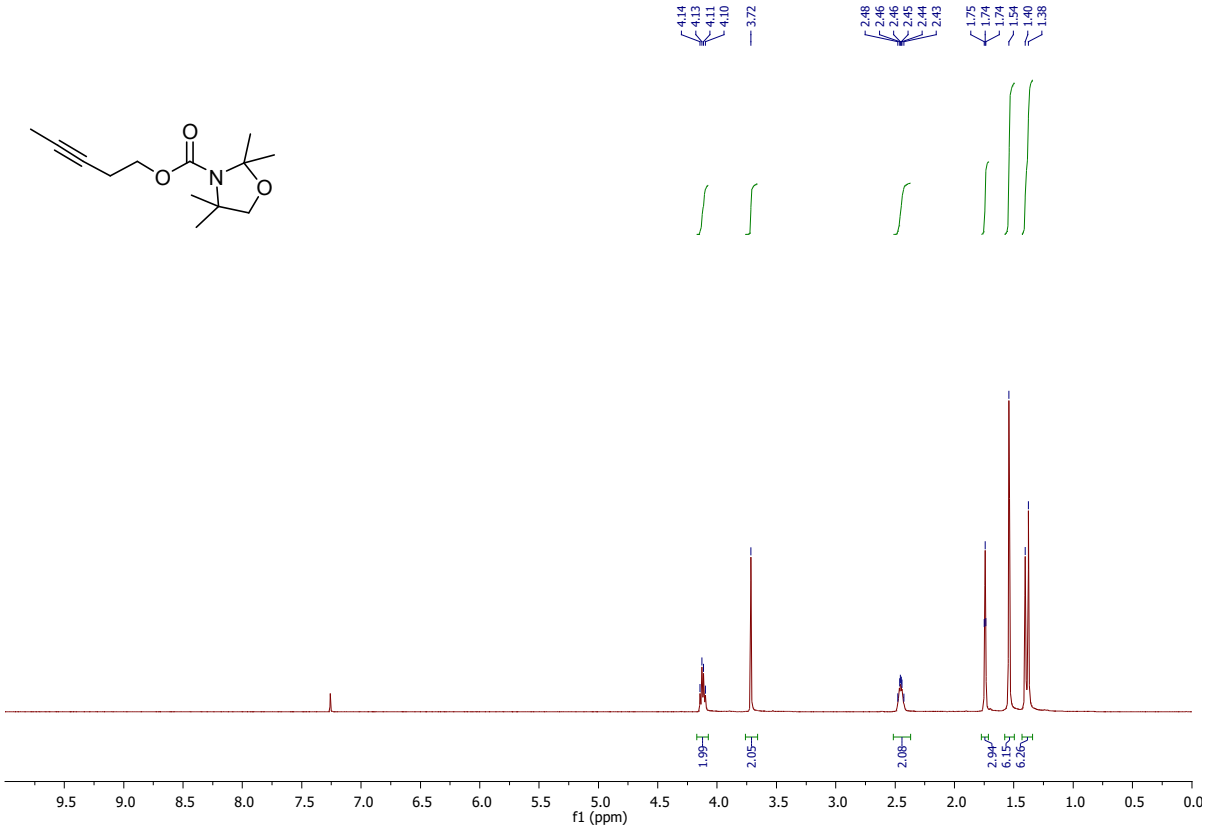


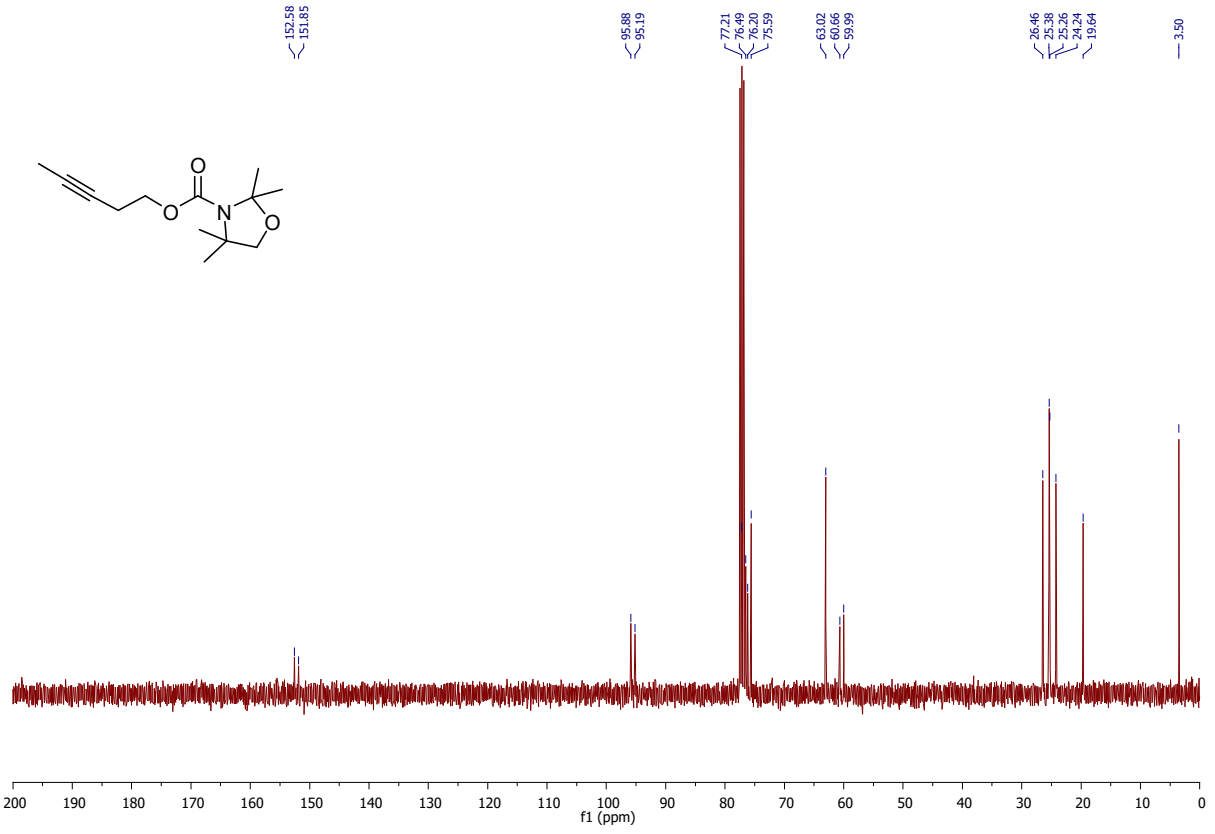
3-(methylamino)-1-phenylpropyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.18**:



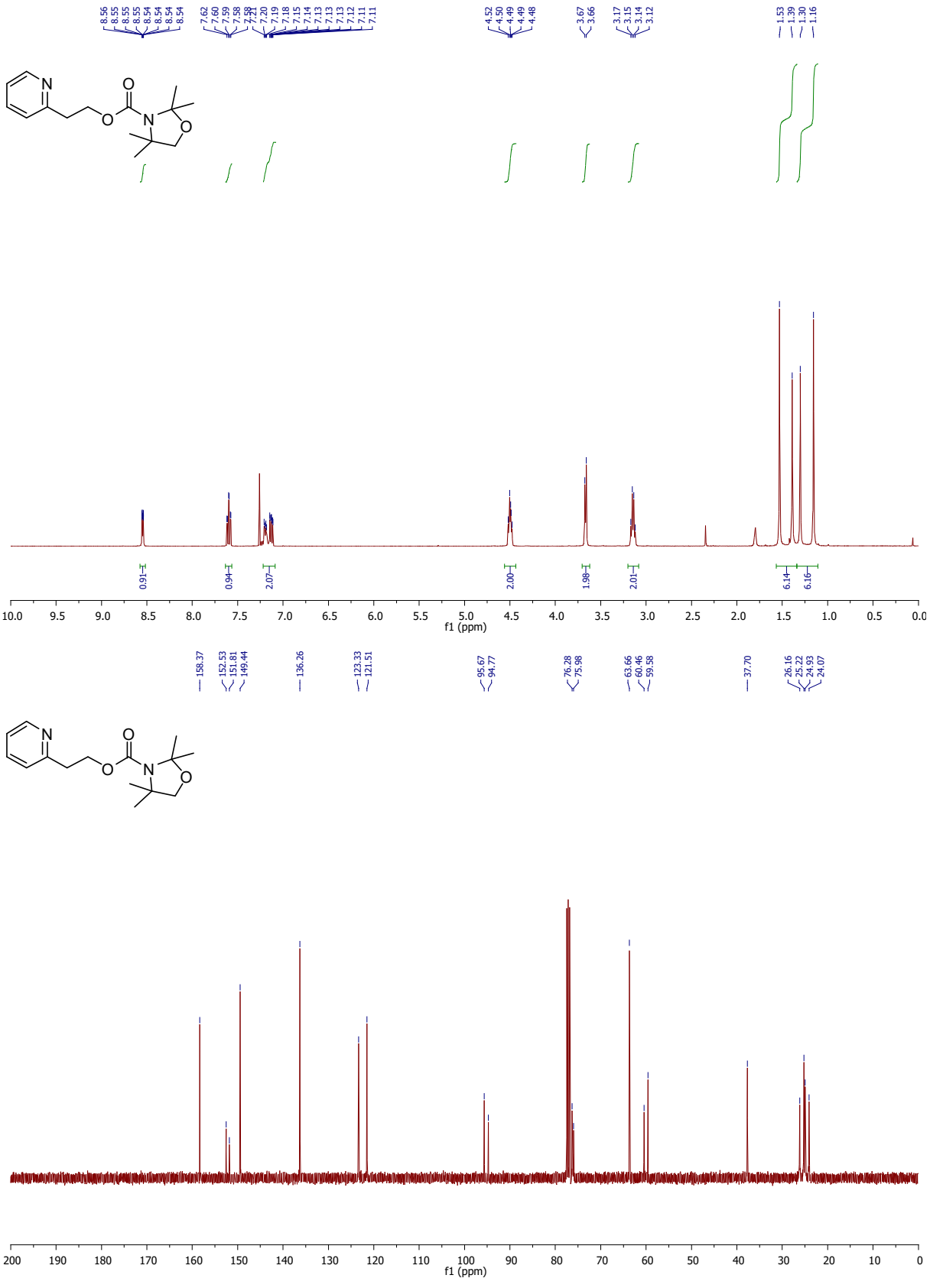


Pent-3-yn-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.7j** :

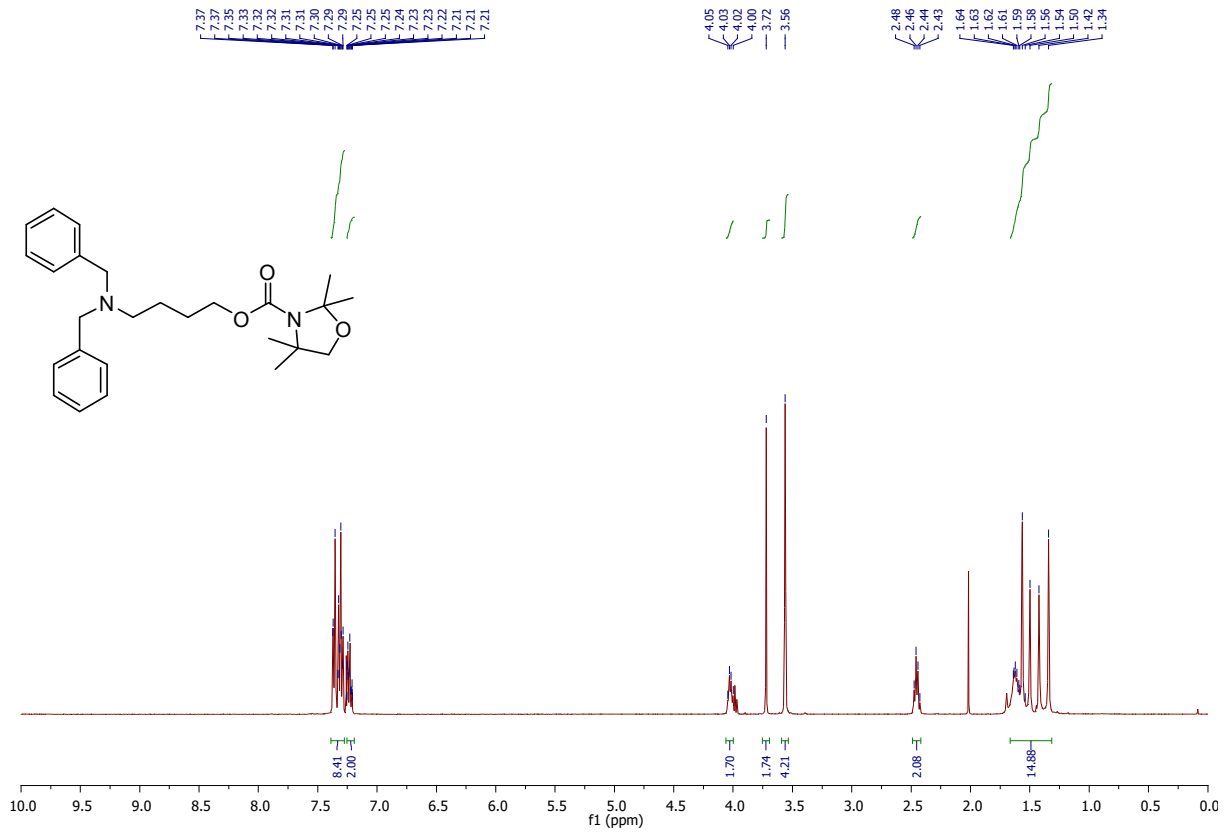


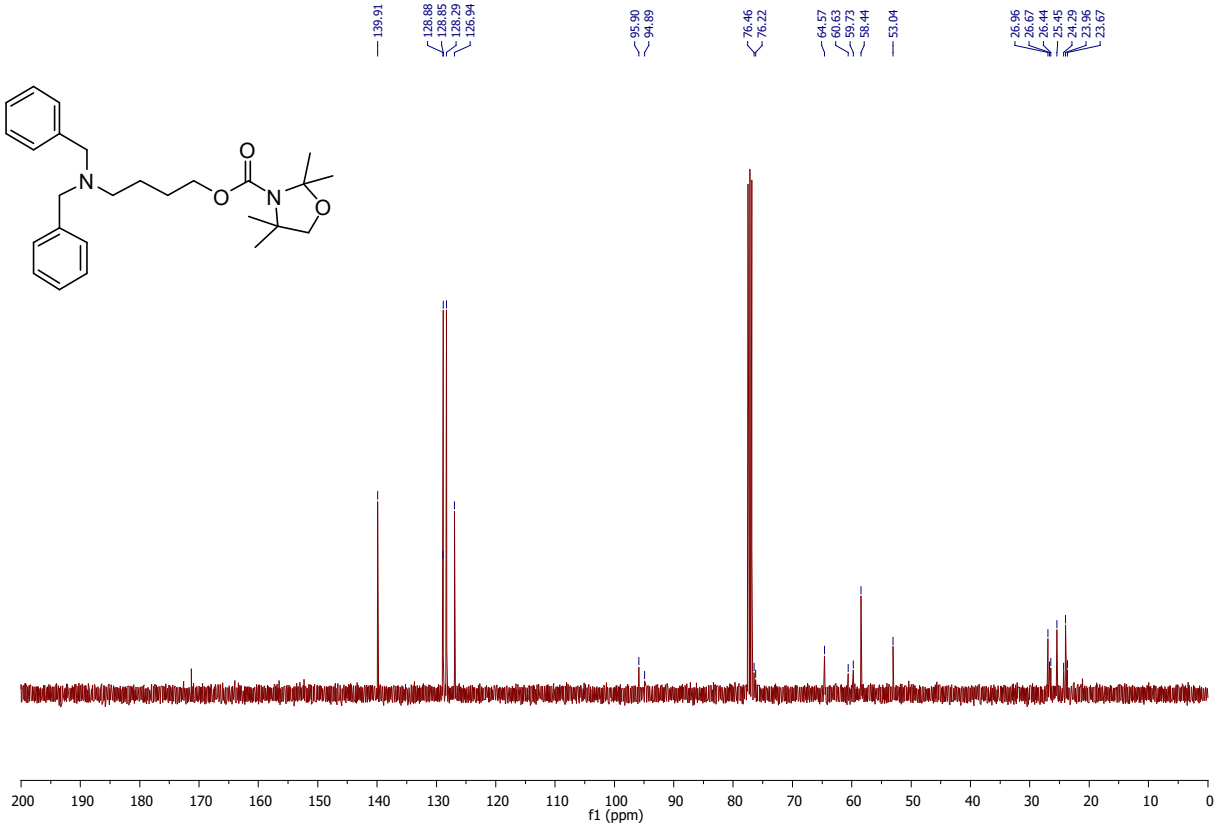


2-(pyridin-2-yl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7k**:

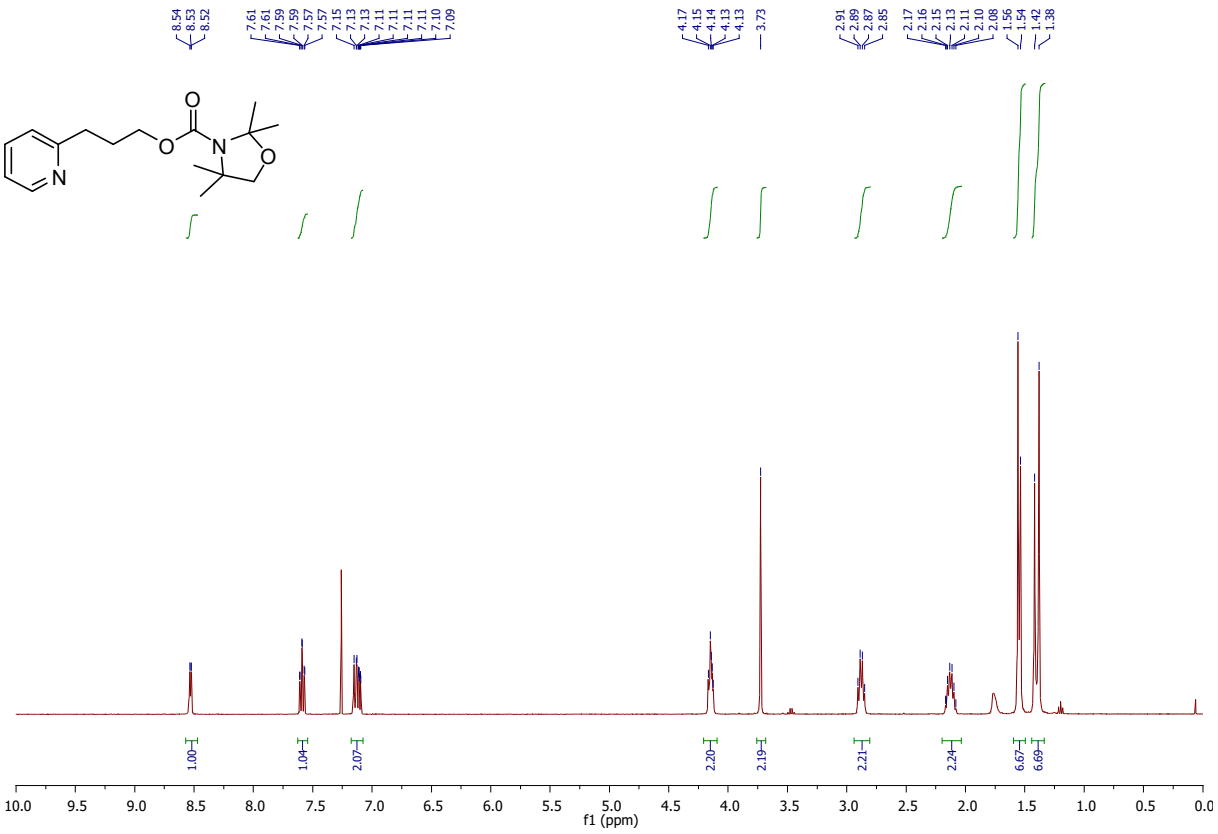


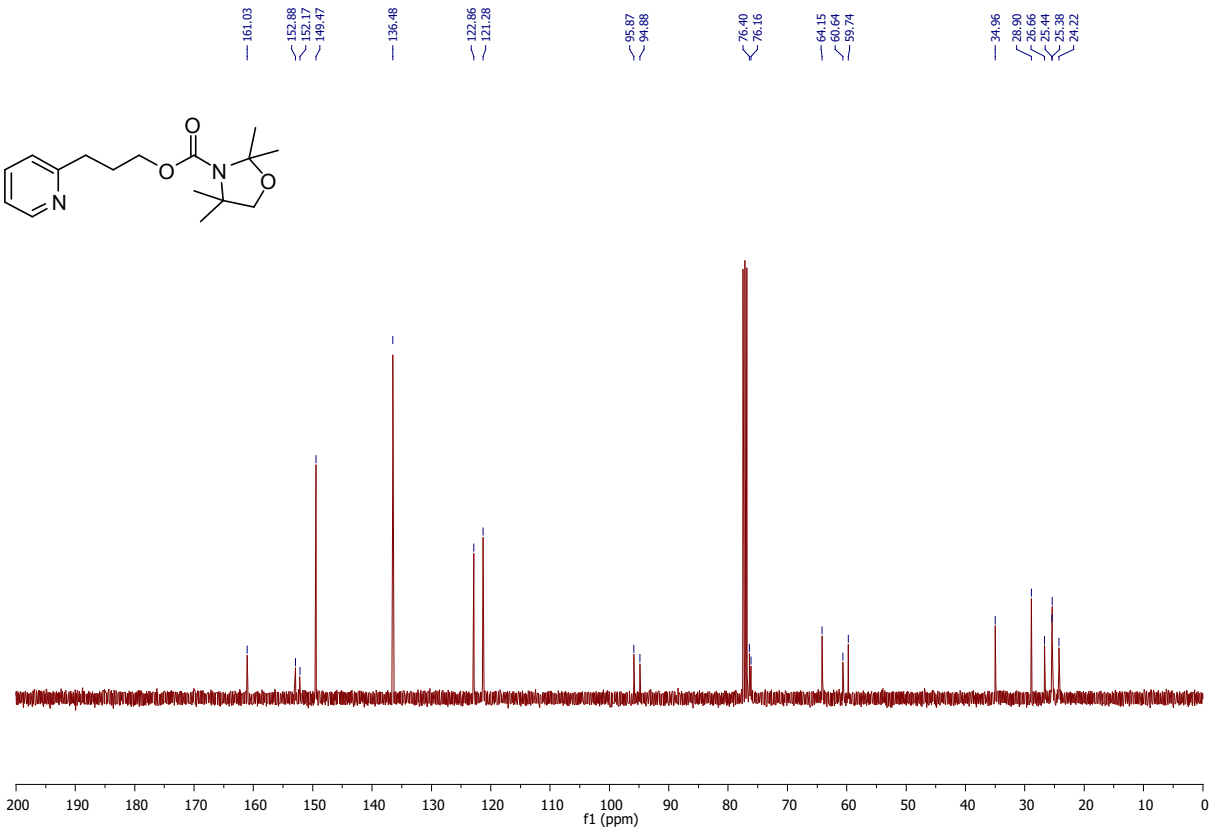
4-(dibenzylamino)butyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7l**:



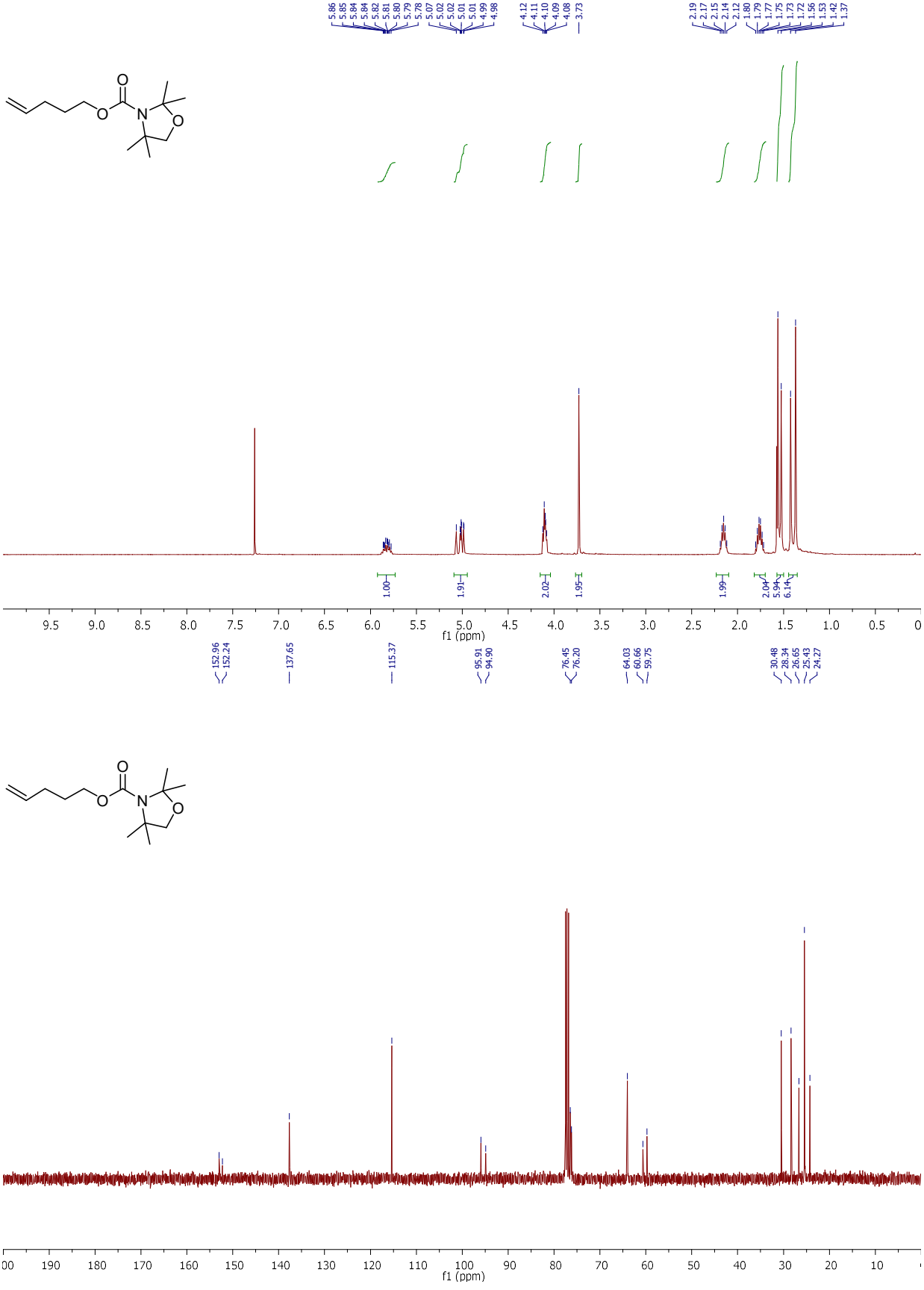


3-(pyridin-2-yl)propyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.7m**:

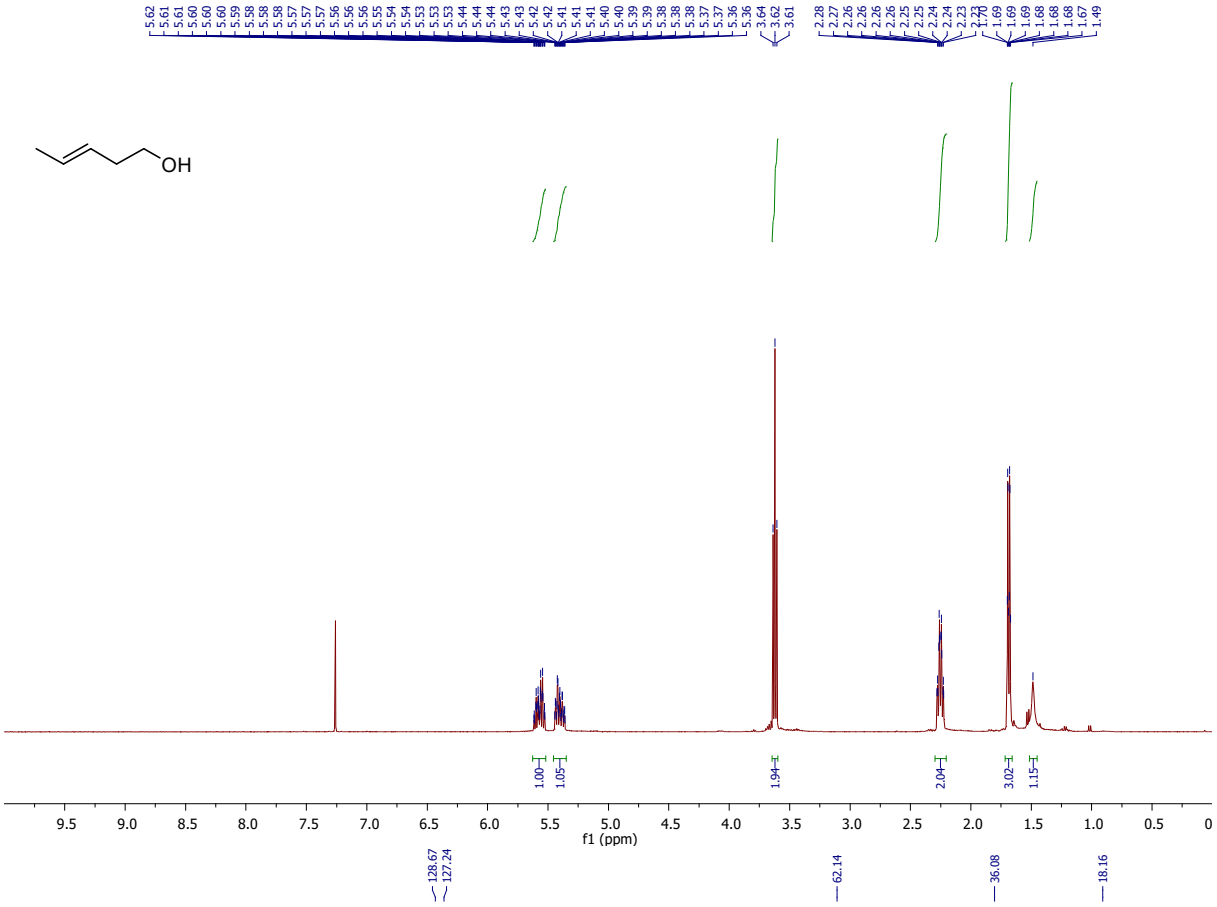


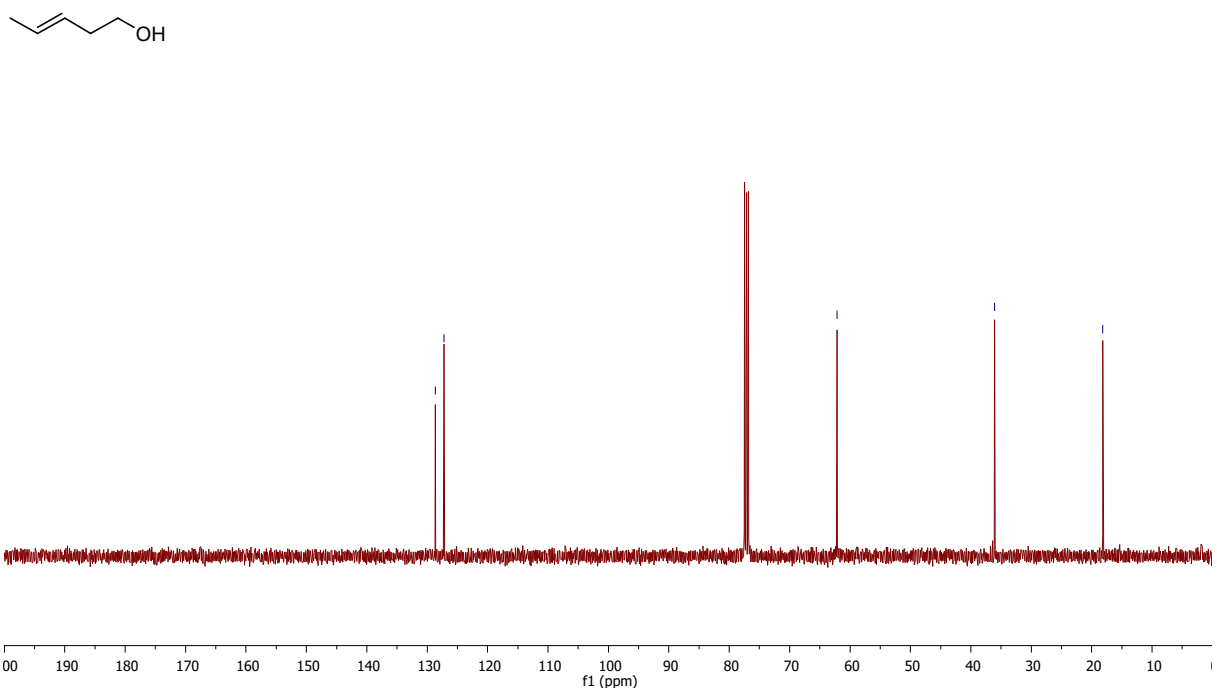


Pent-4-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7n**:

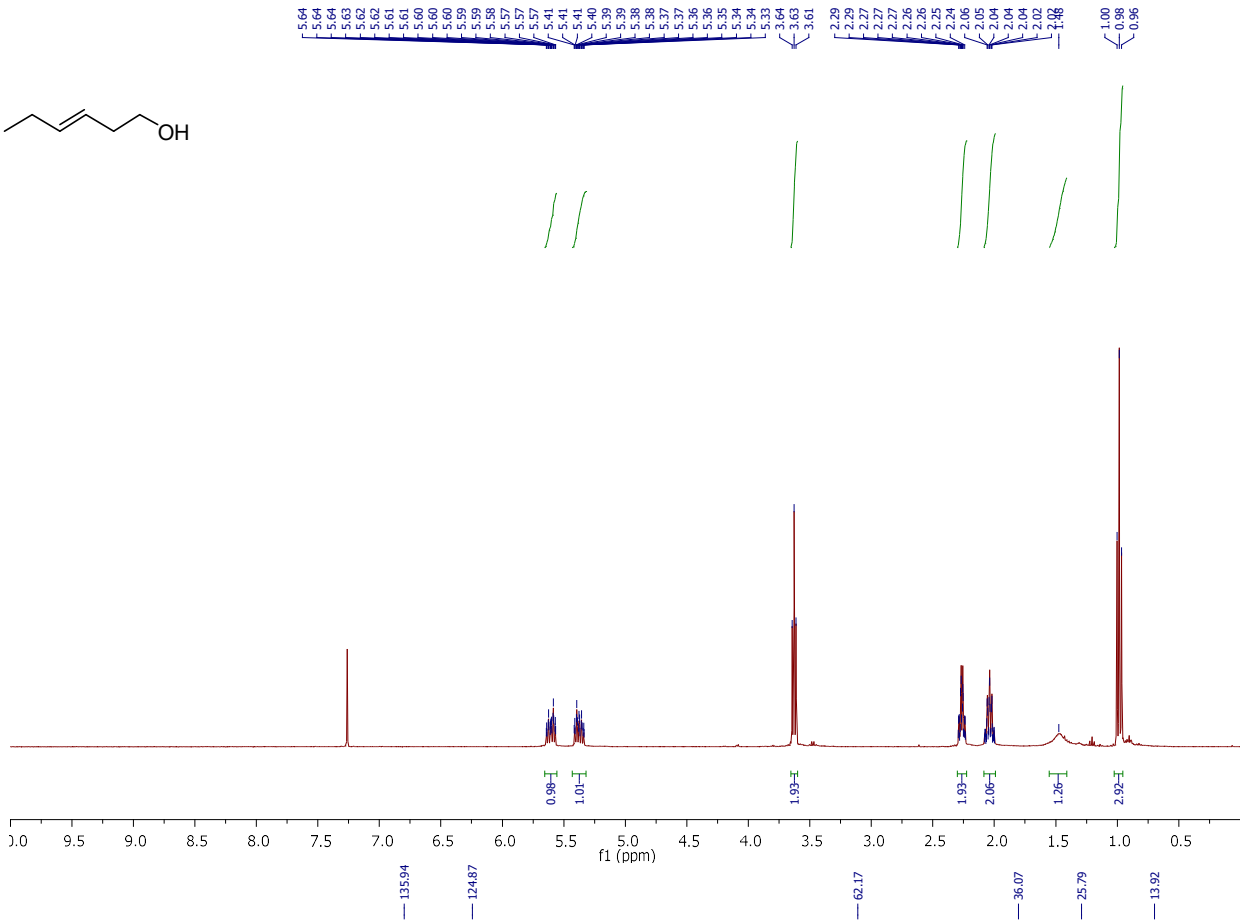


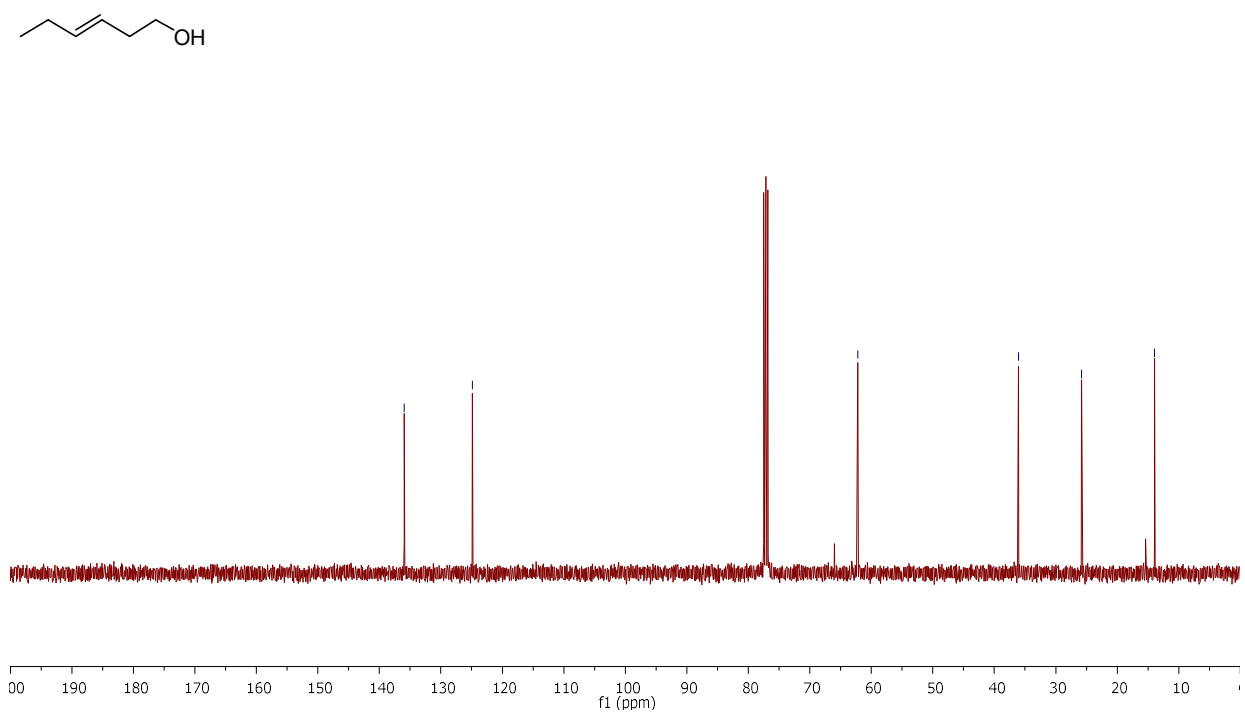
(*E*)-Pent-3-en-1-ol **S2** :



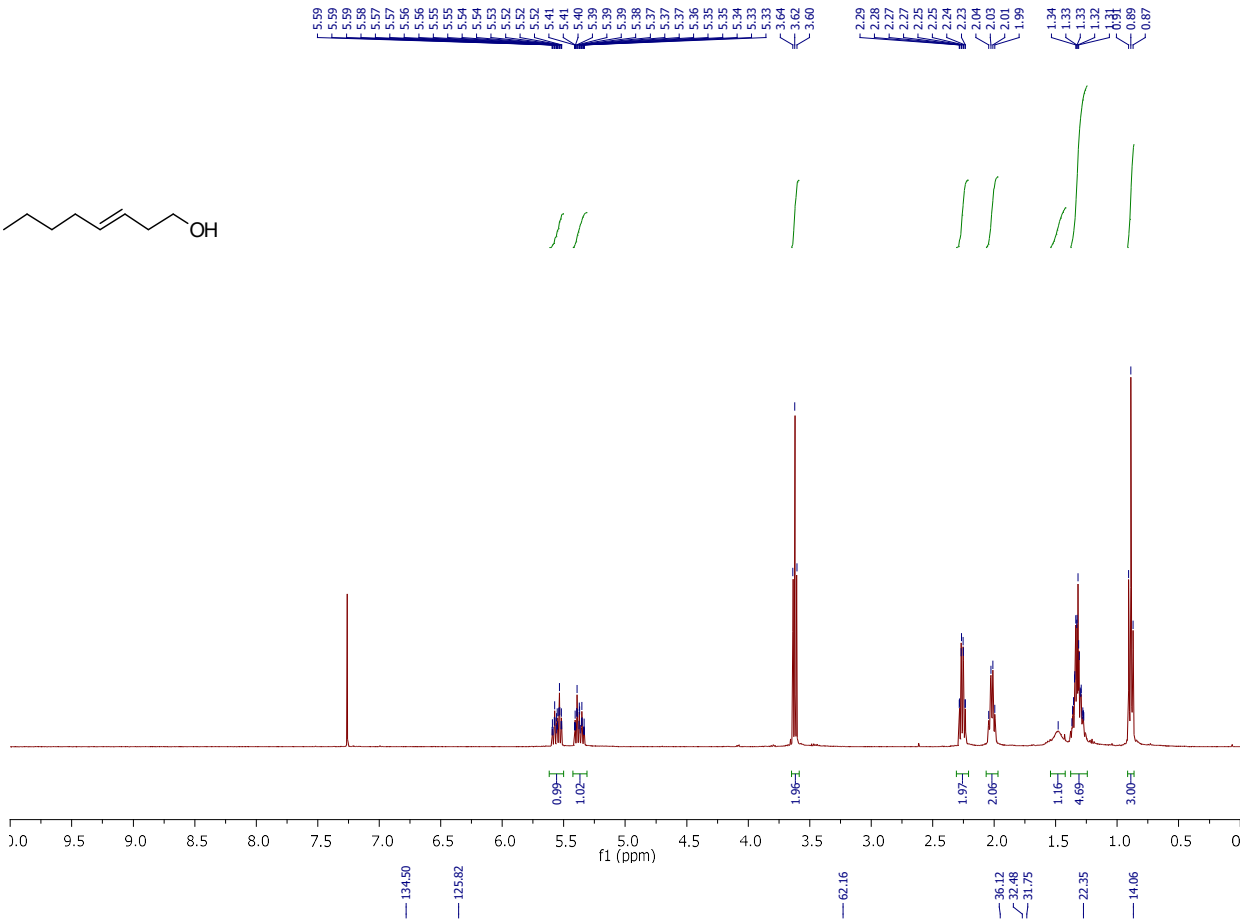


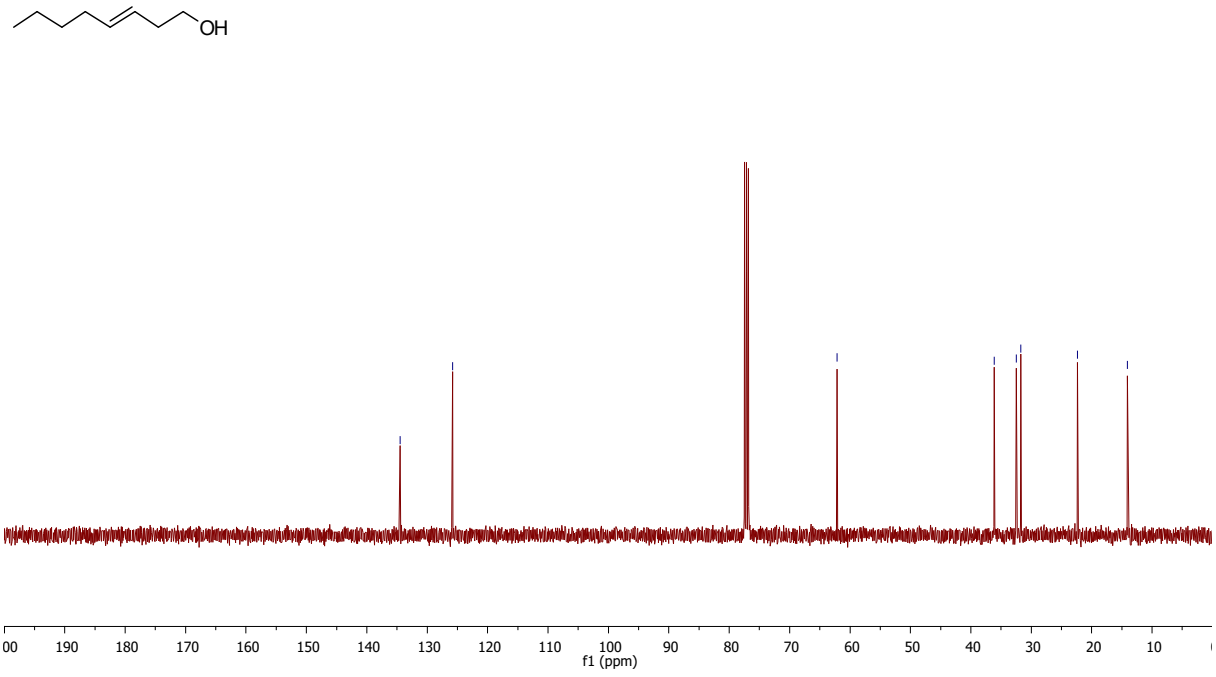
(*E*)-Hex-3-en-1-ol **S3** :



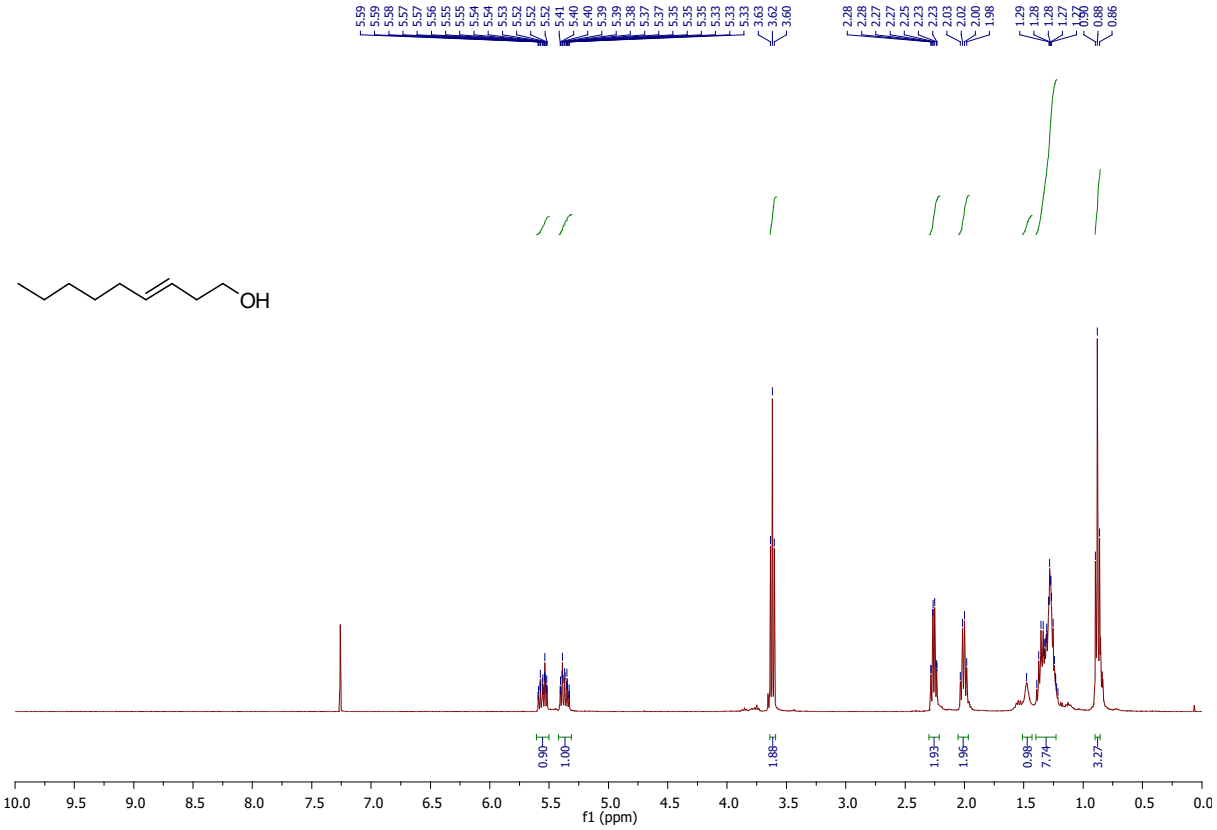


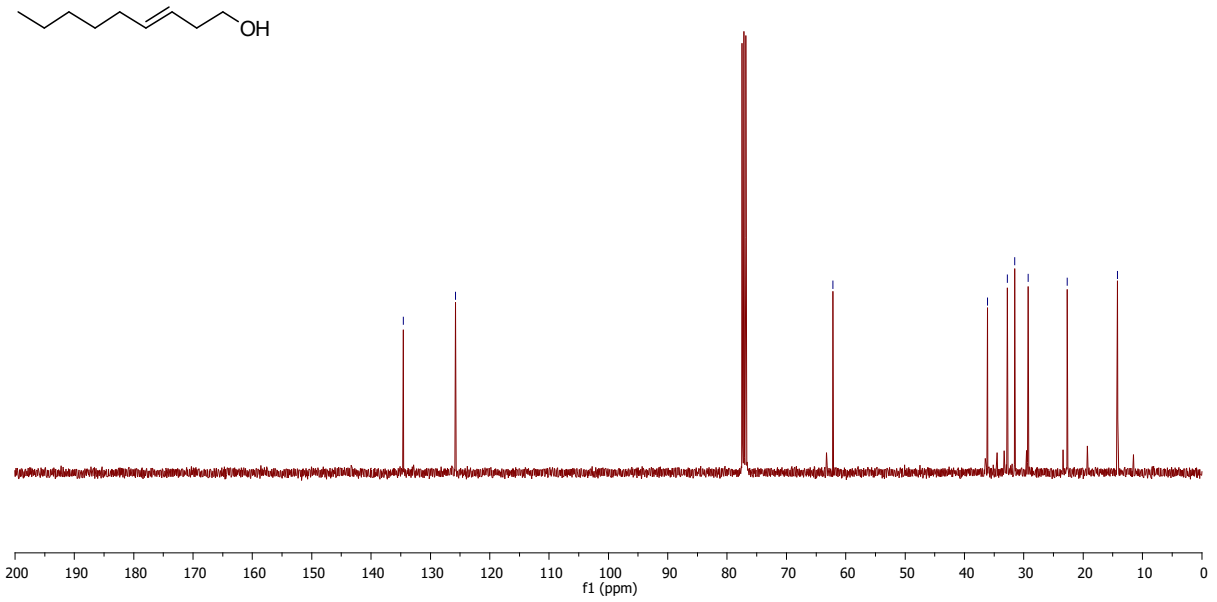
(*E*)-Oct-3-en-1-ol **S4** :



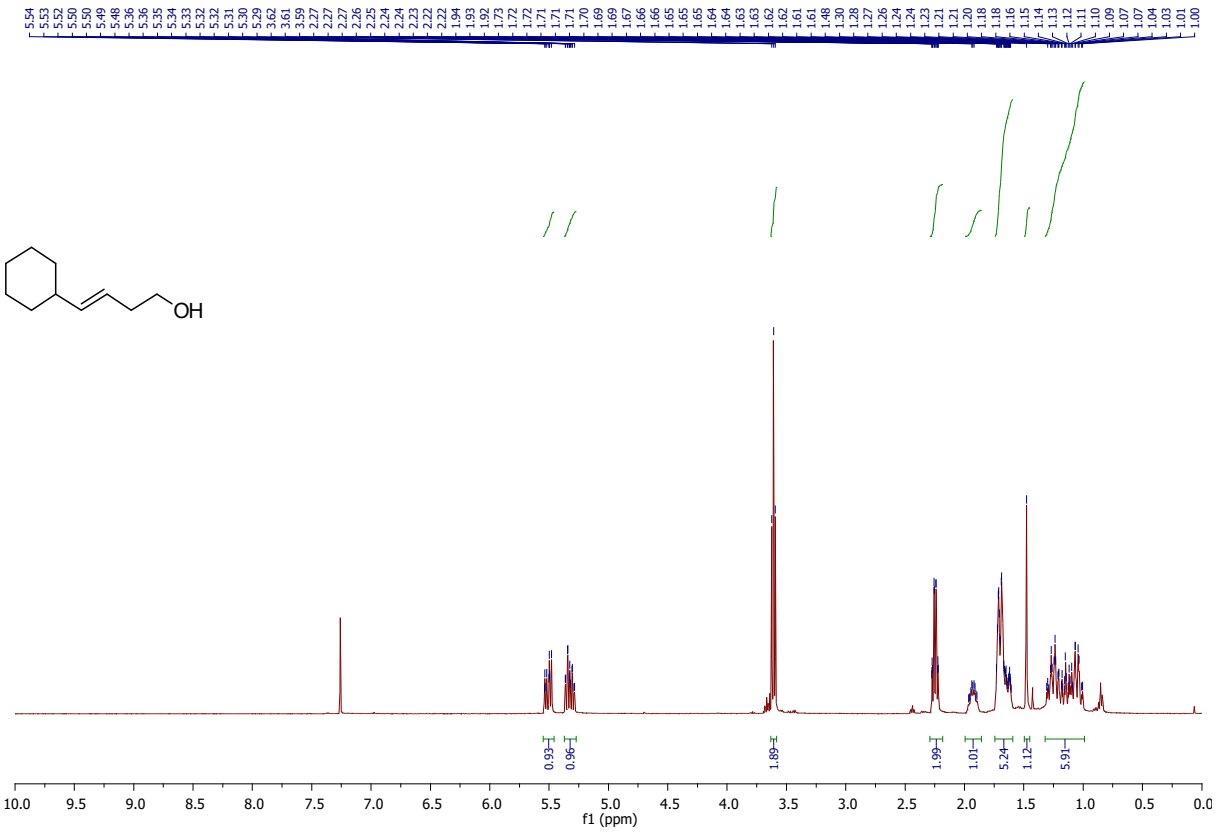


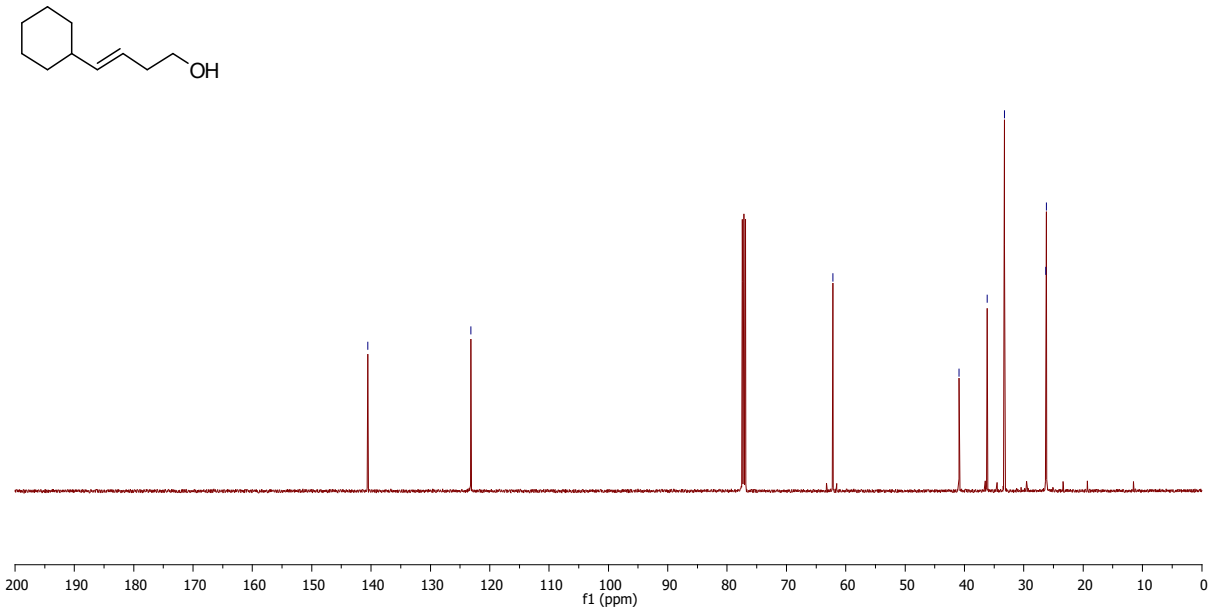
(*E*)-Non-3-en-1-ol **S5** :



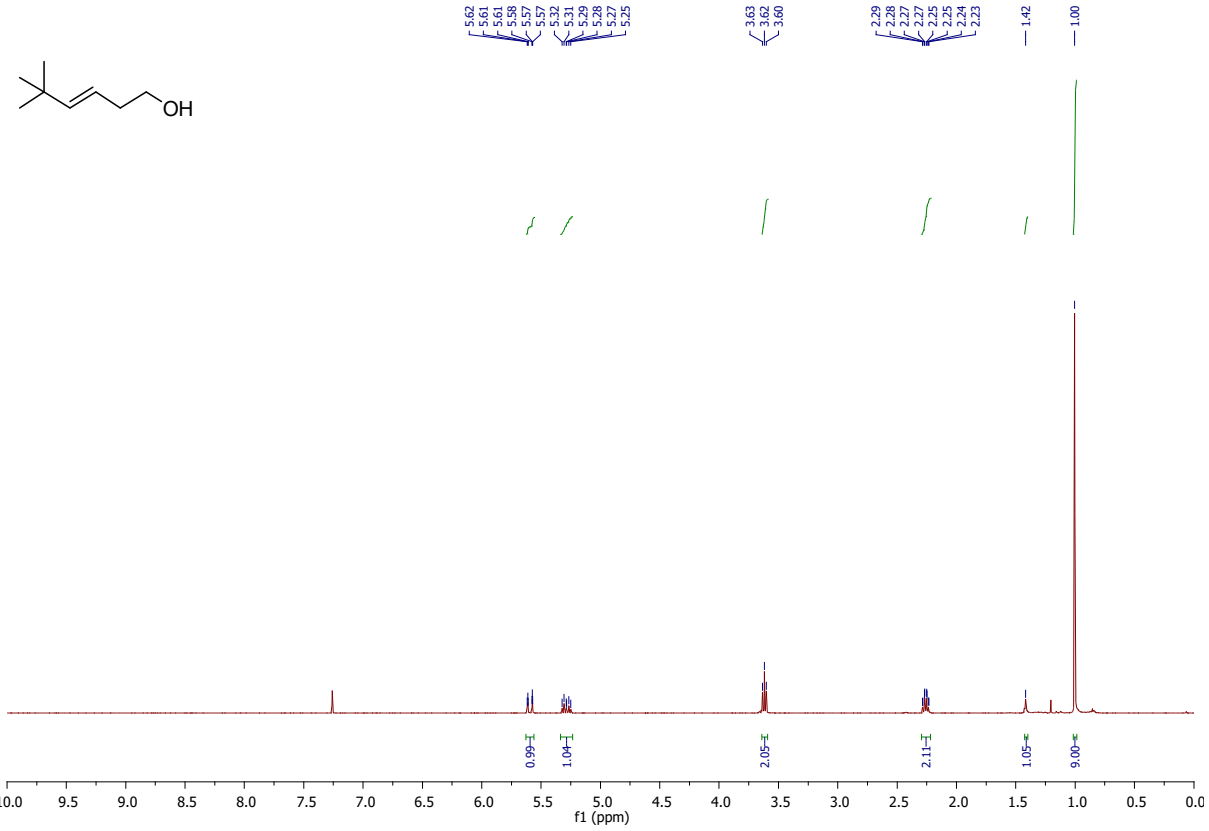


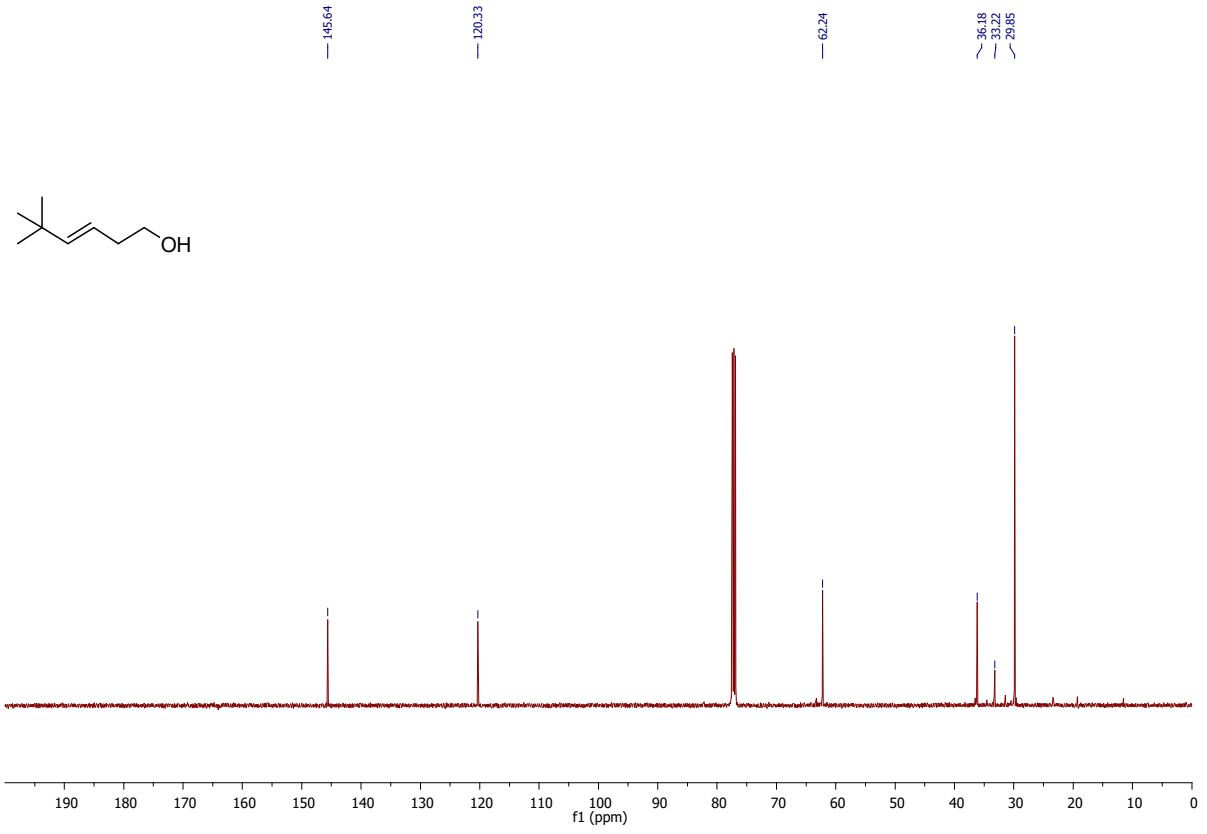
(*E*)-4-cyclohexylbut-3-en-1-ol **S6** :



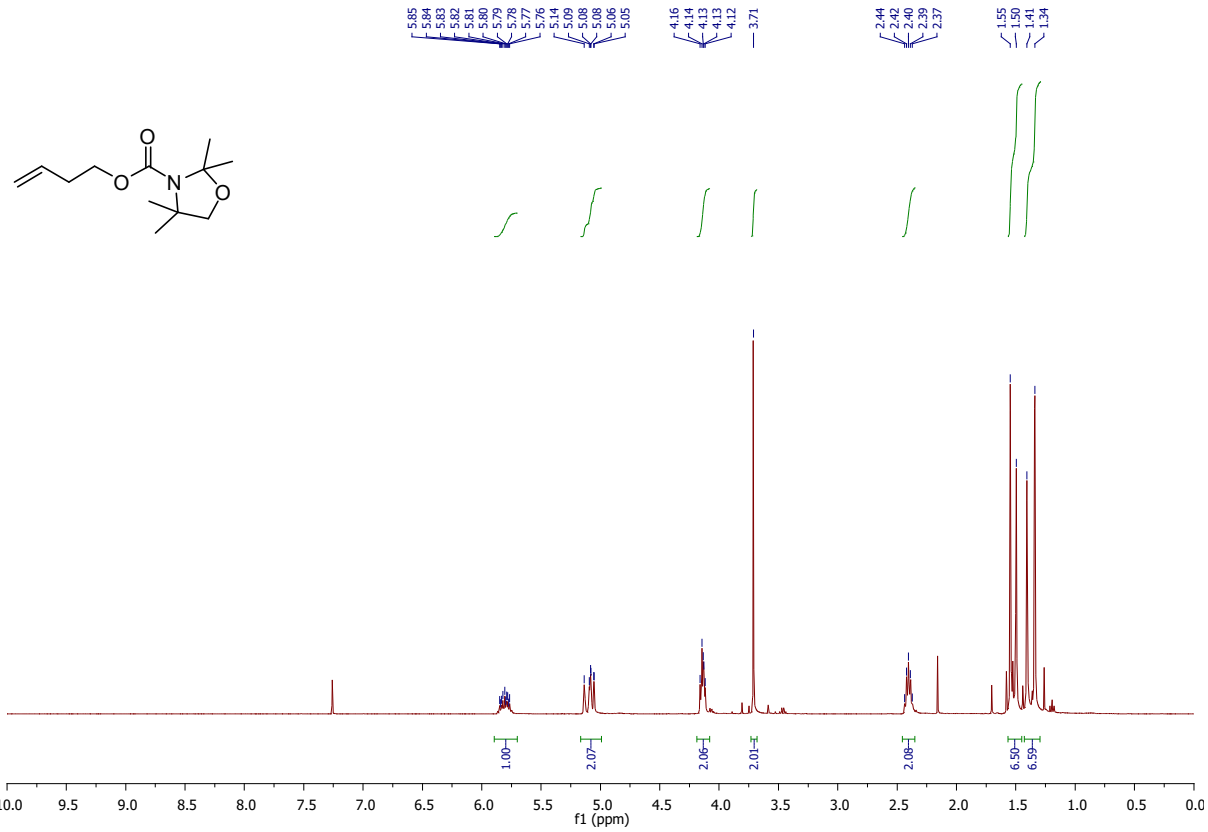


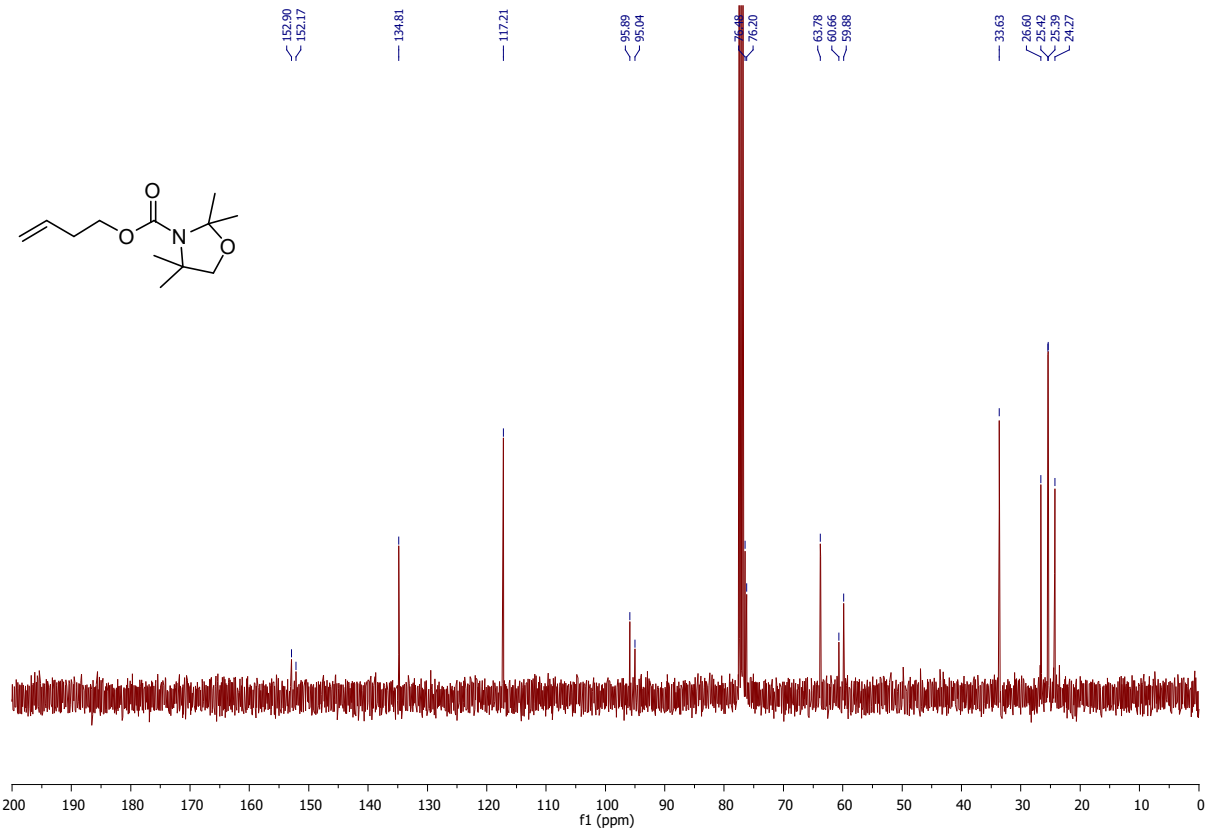
(*E*)-5,5-dimethylhex-3-en-1-ol **S7** :



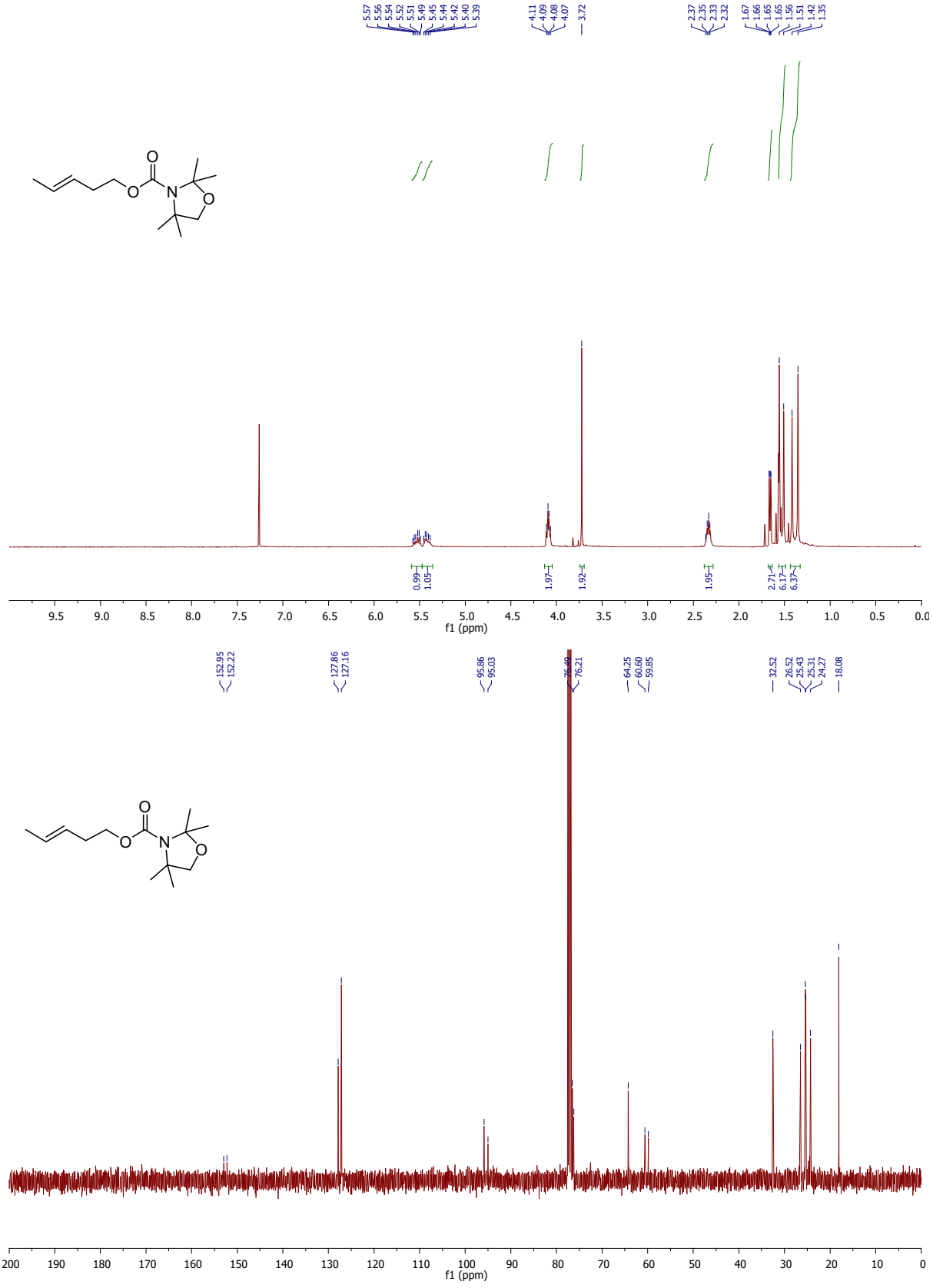


But-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.7e** :

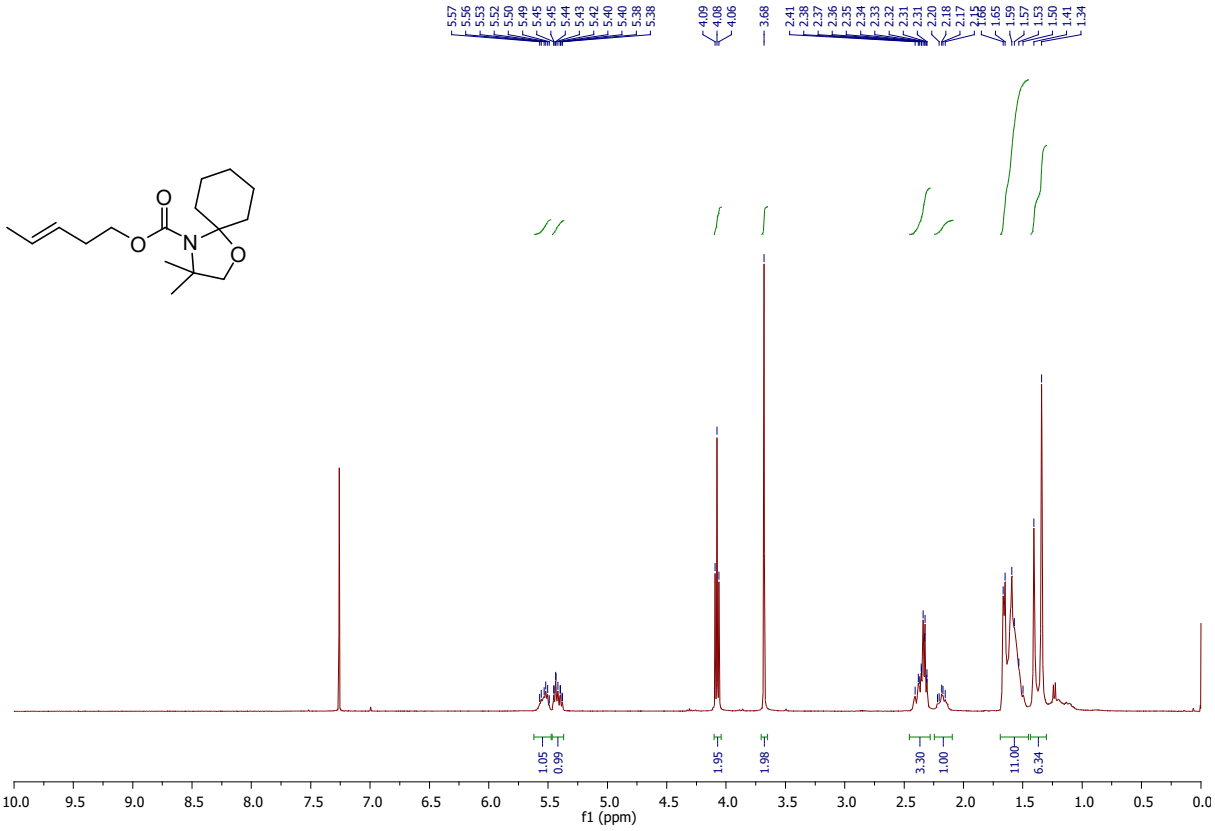


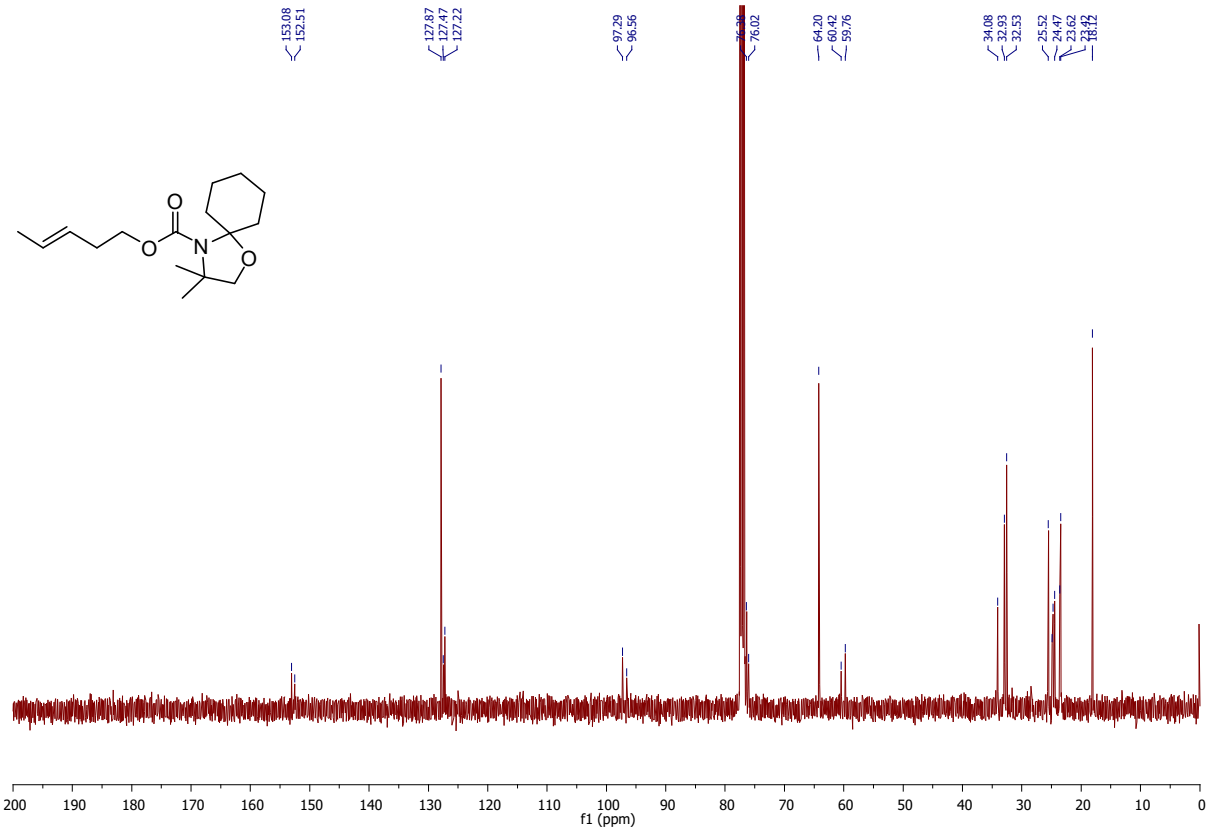


(*E*)-Pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **(*E*)-2.21g** :

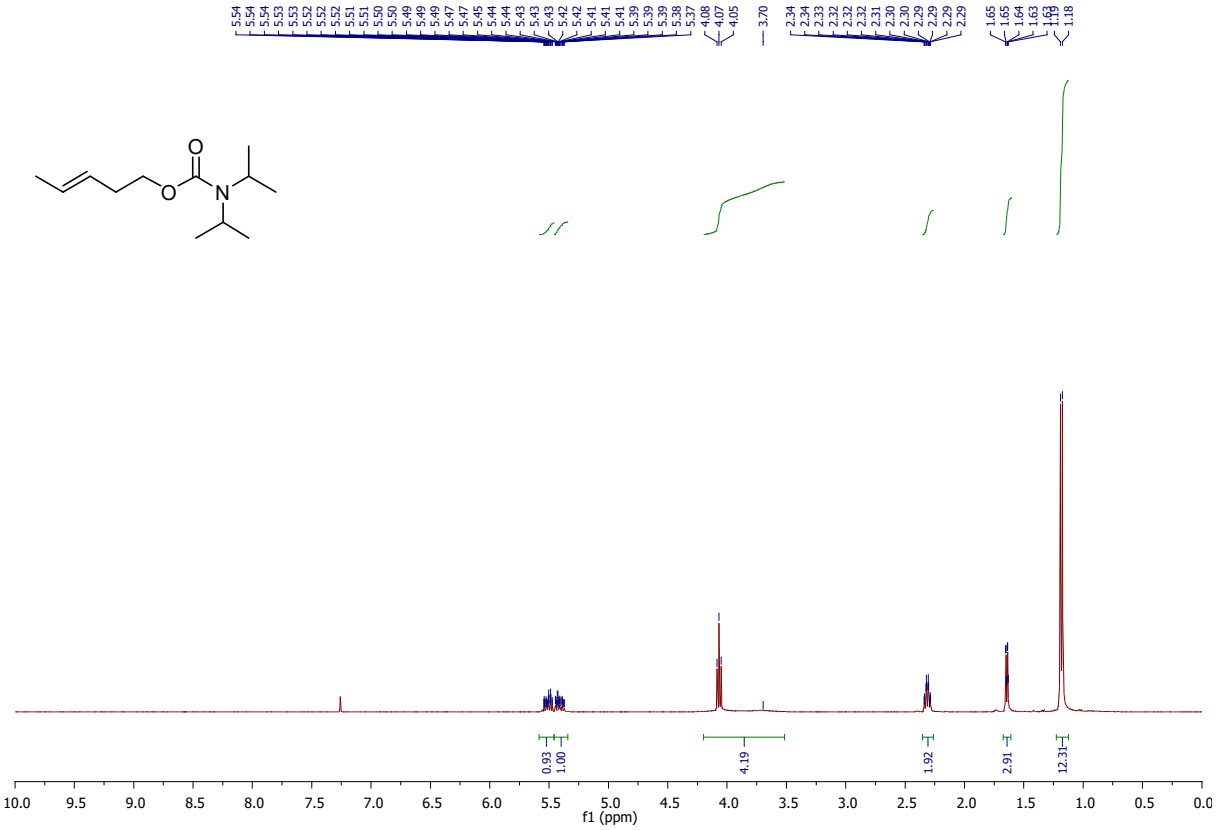


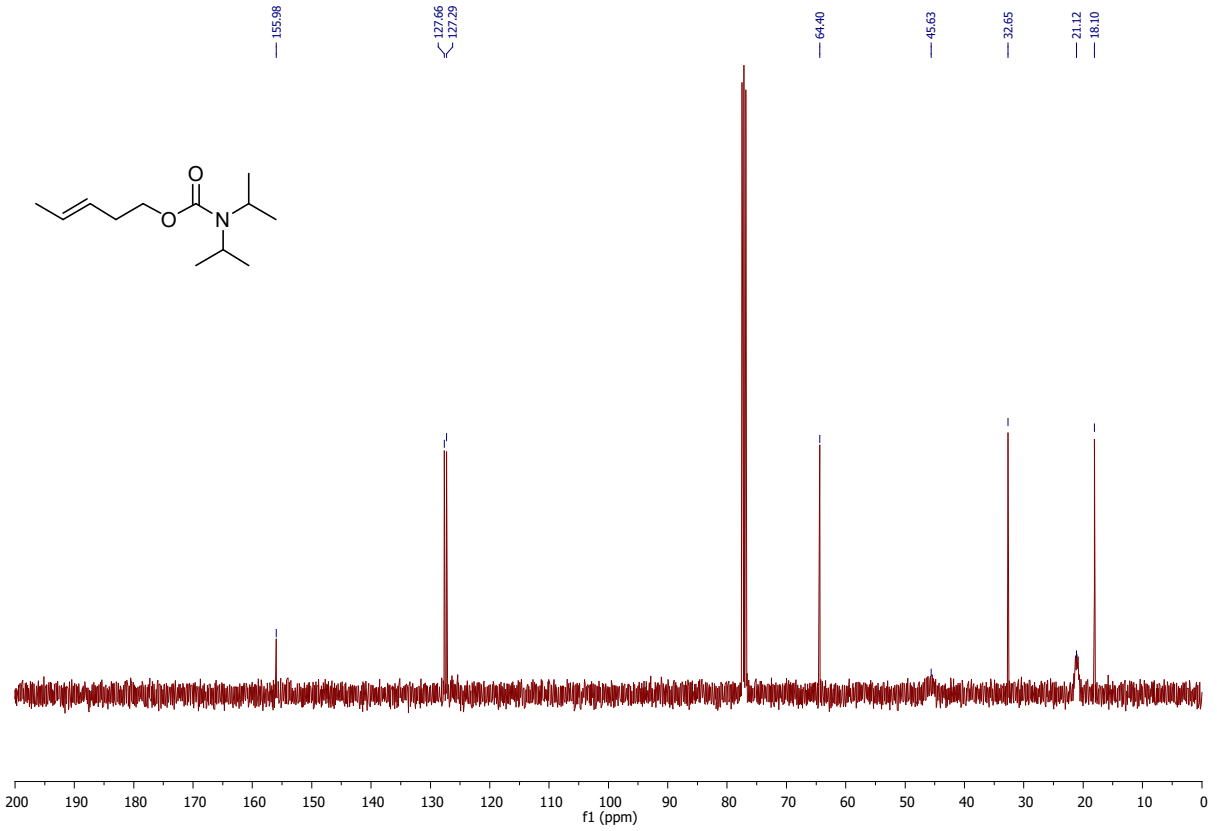
(*E*)-pent-3-en-1-yl 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate **2.23** :



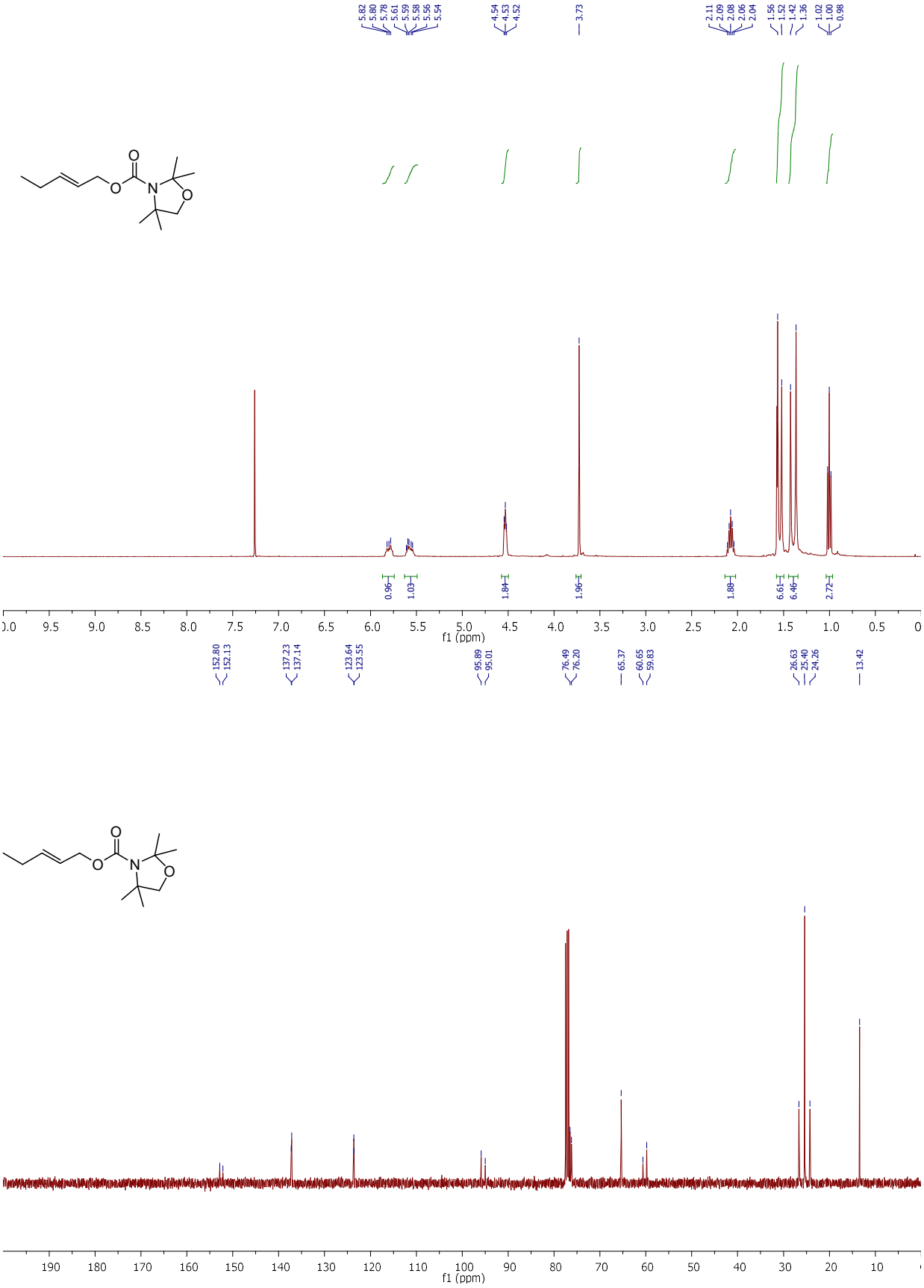


(E)-pent-3-en-1-yl diisopropylcarbamate **2.24** :

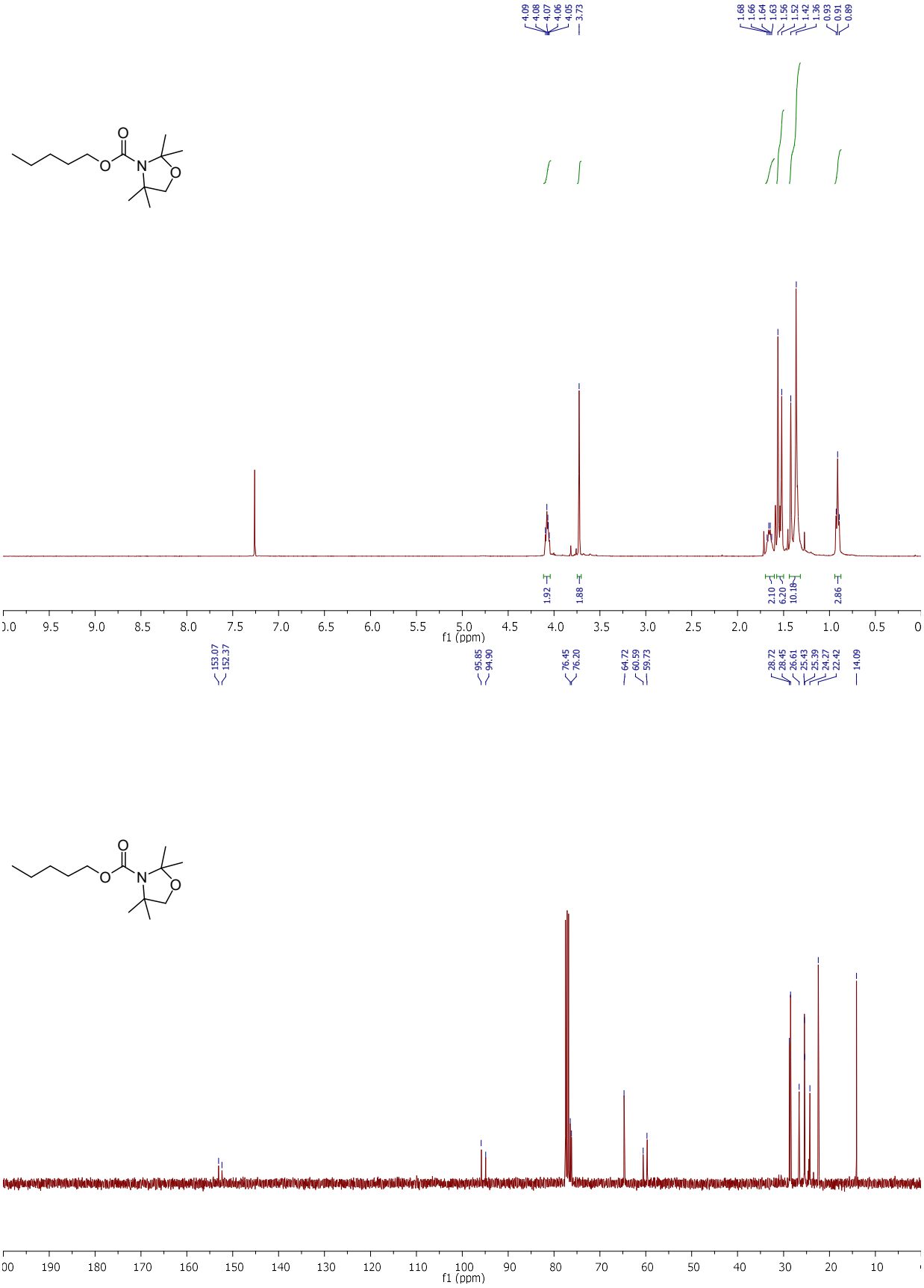




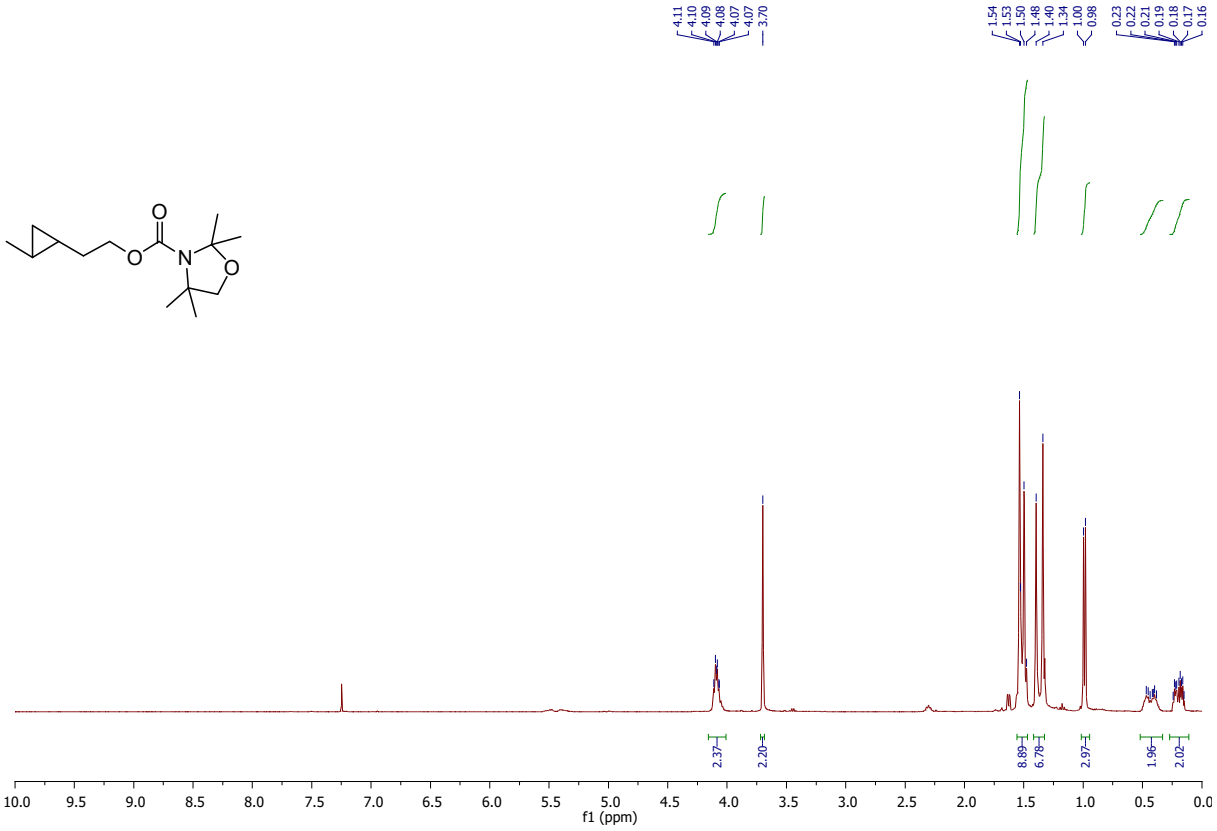
(*E*)-Pent-2-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.26** :

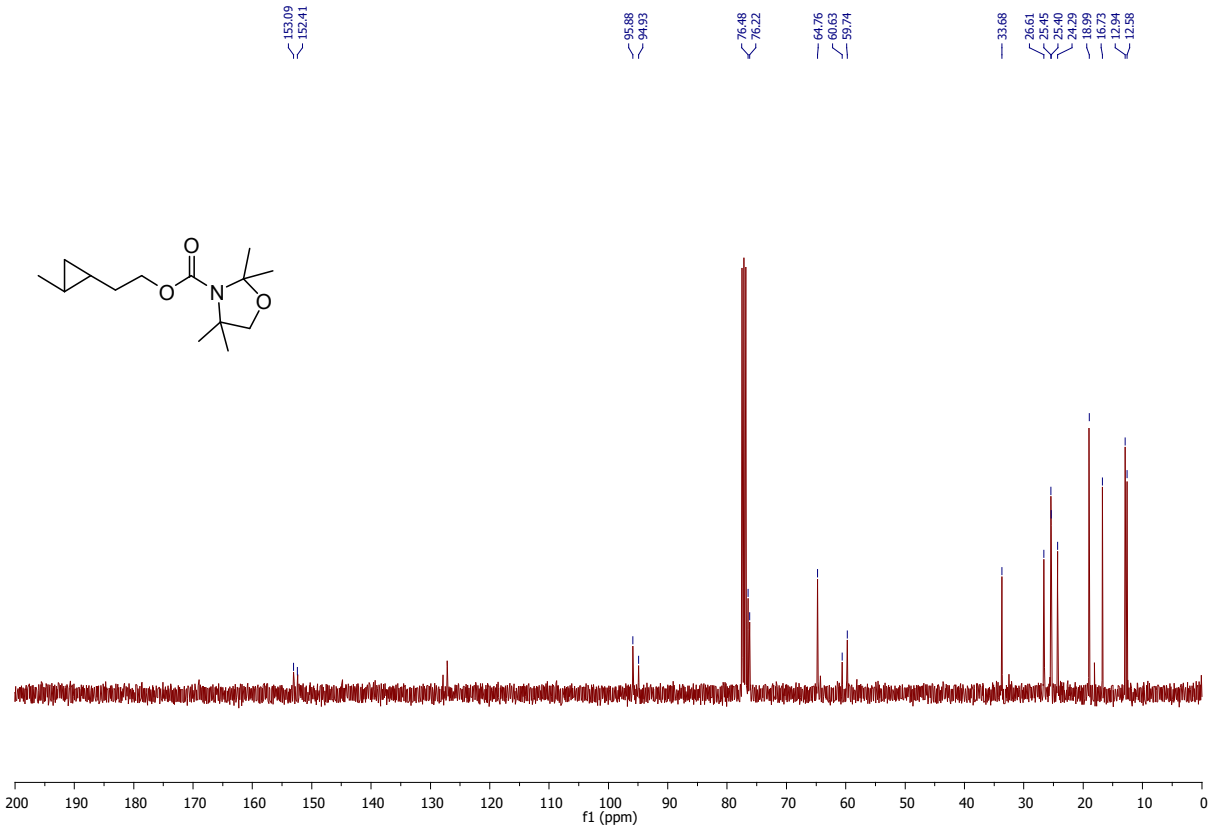


Pentyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.27** :

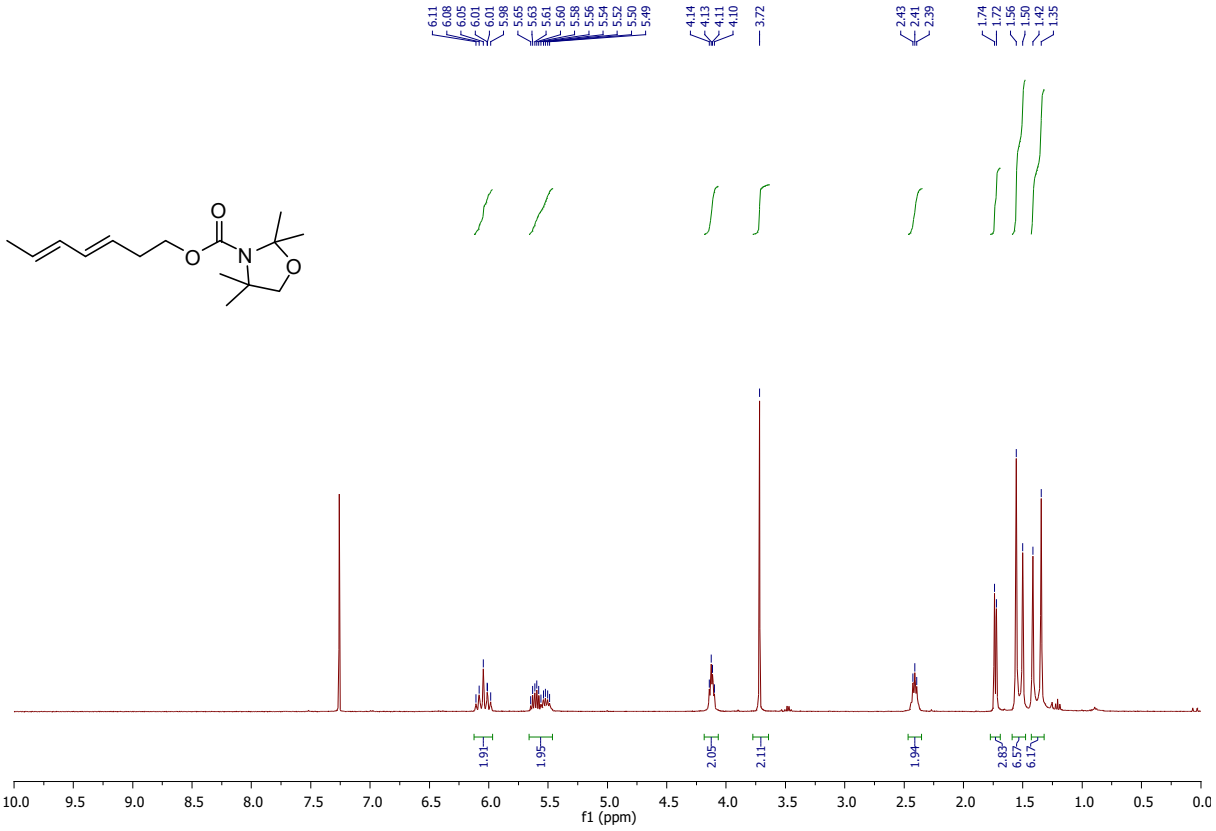


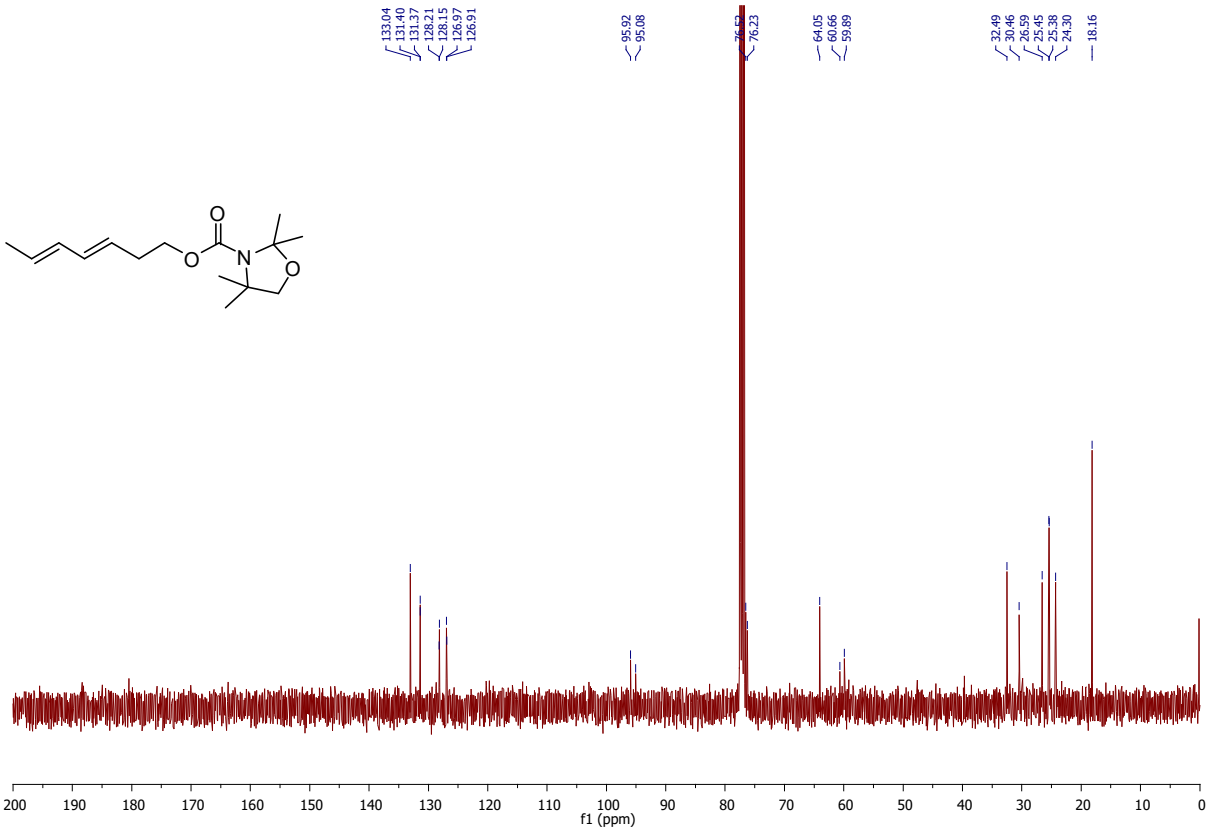
2-(2-methylcyclopropyl)ethyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.29** :



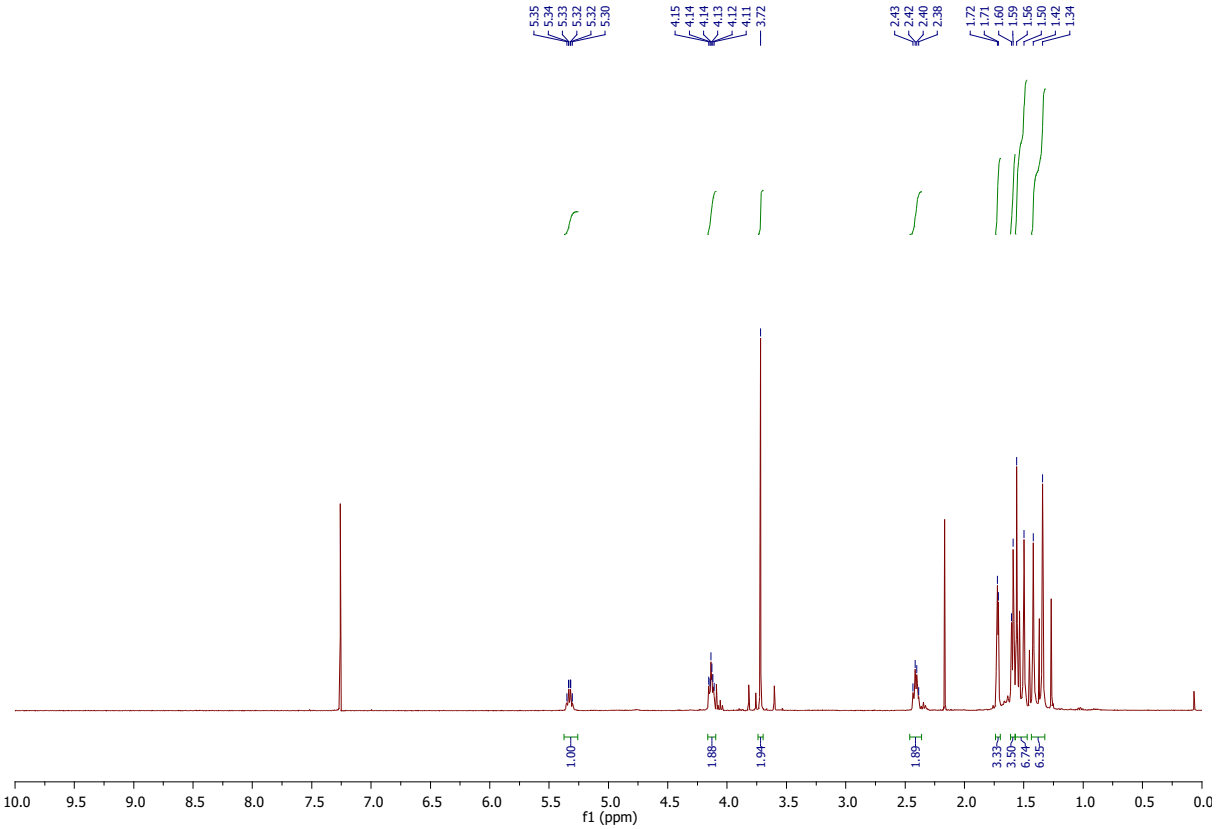


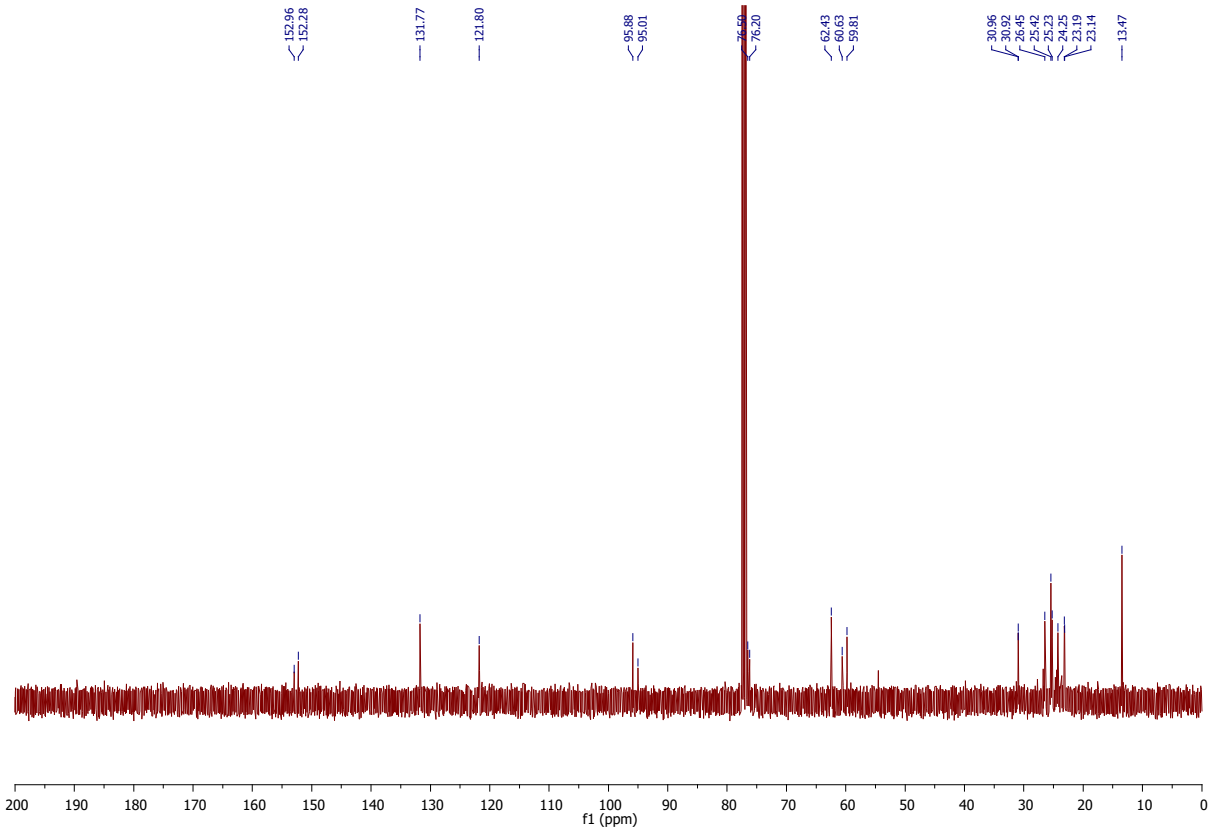
(3*E*,5*E*)-hepta-3,5-dien-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.30** :



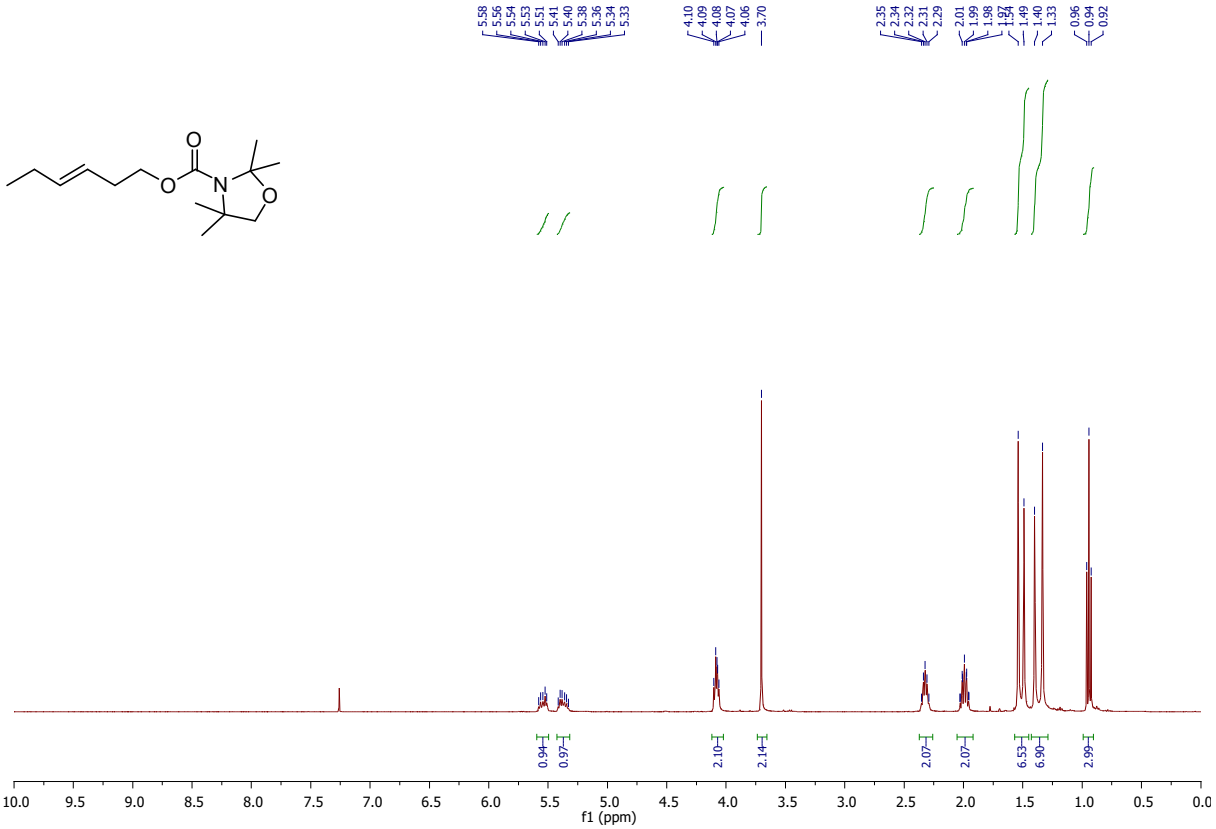


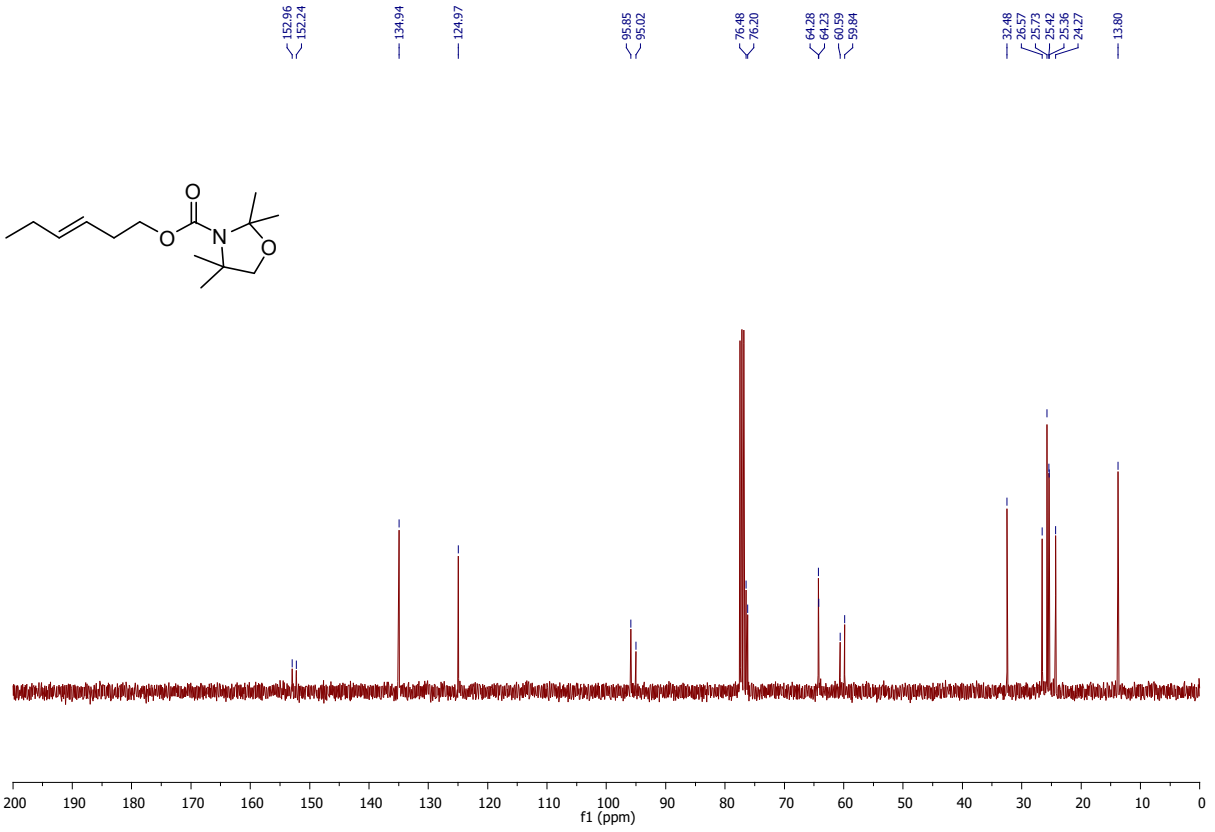
(*Z*)-3-methylpent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.31** :



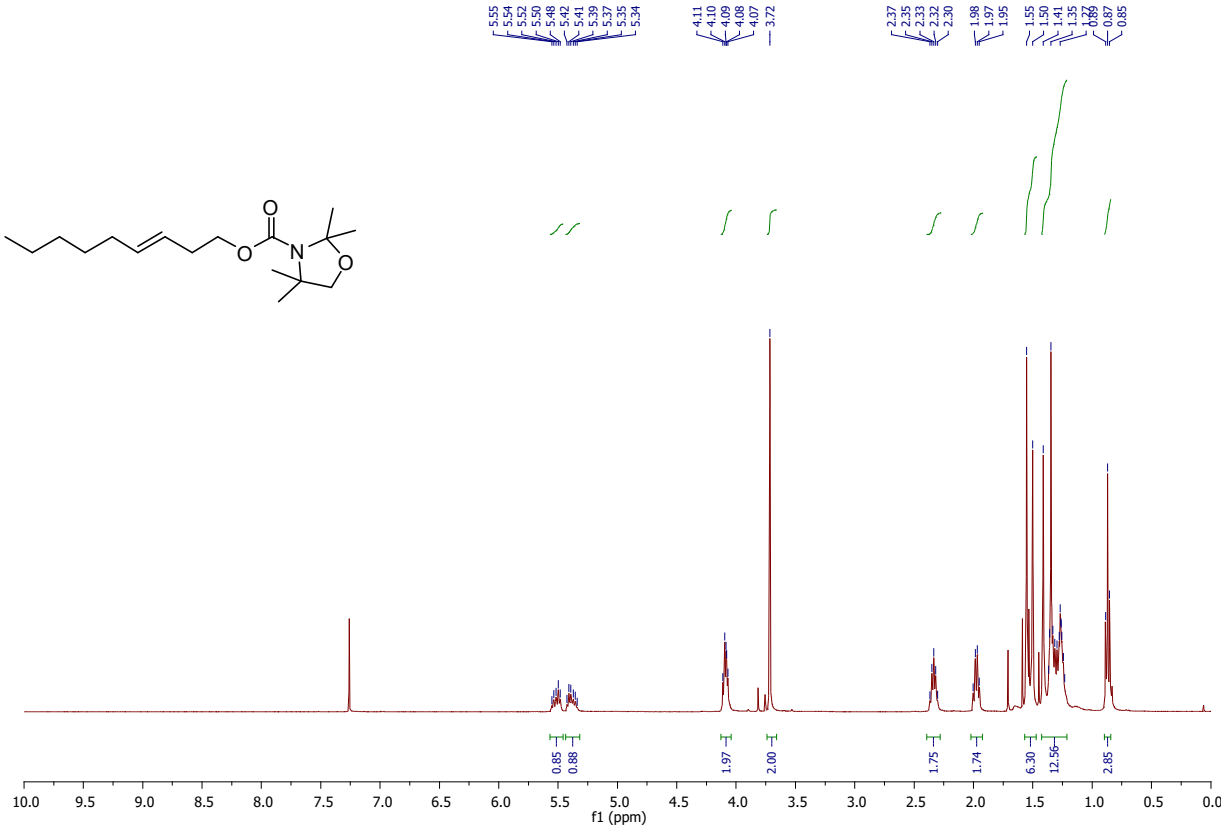


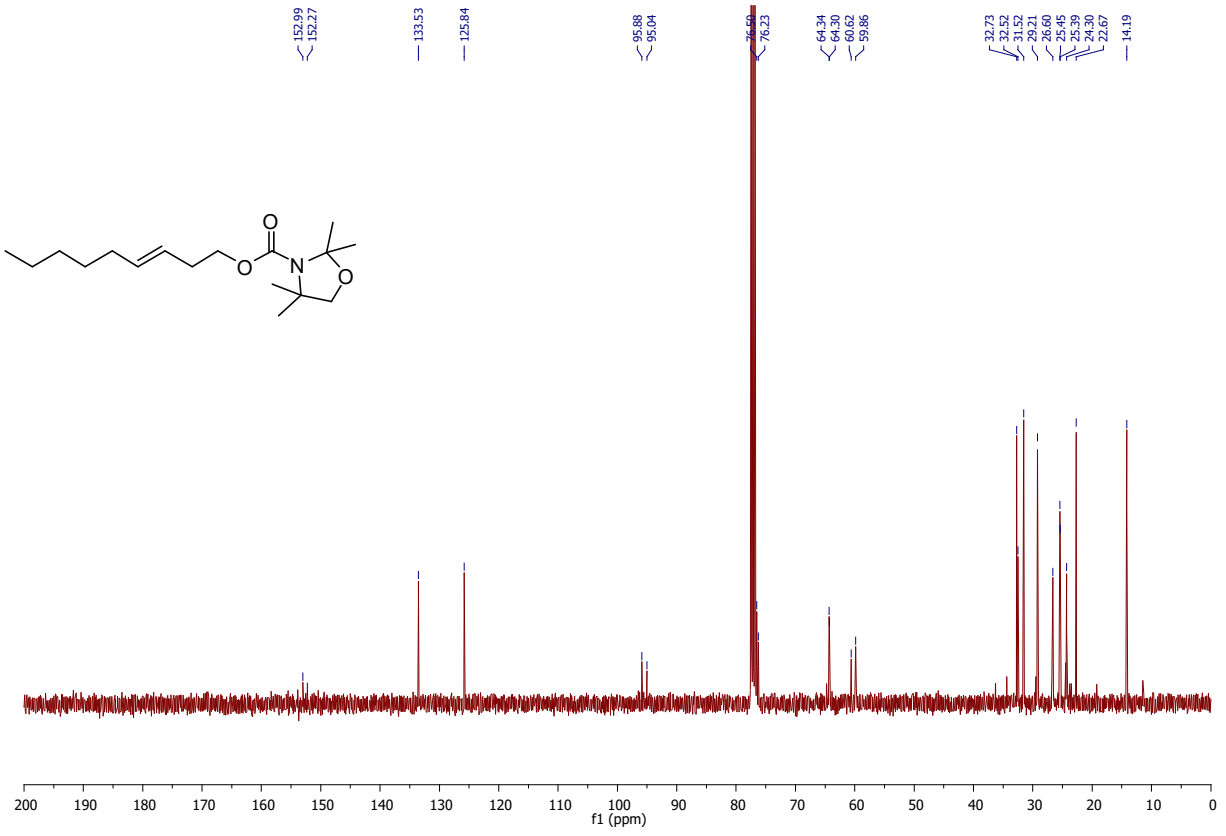
(*E*)-hex-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.33** :



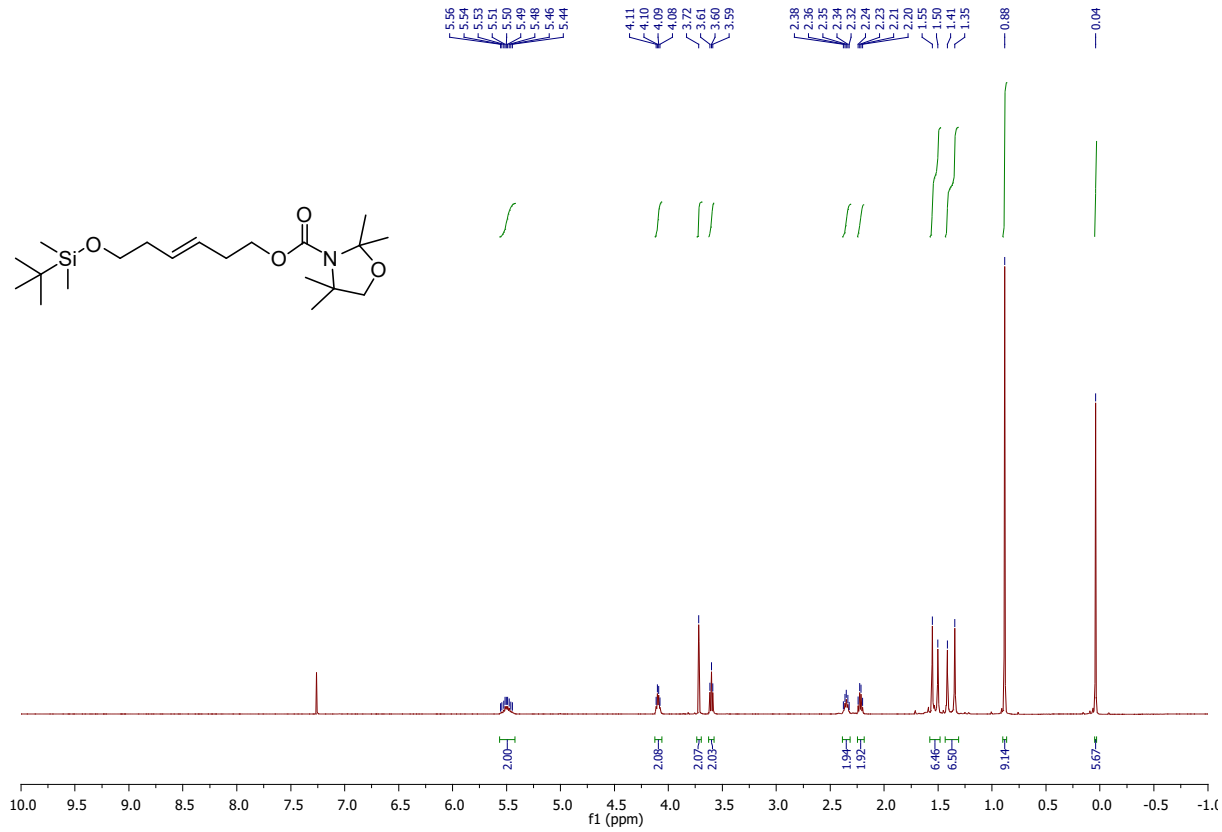


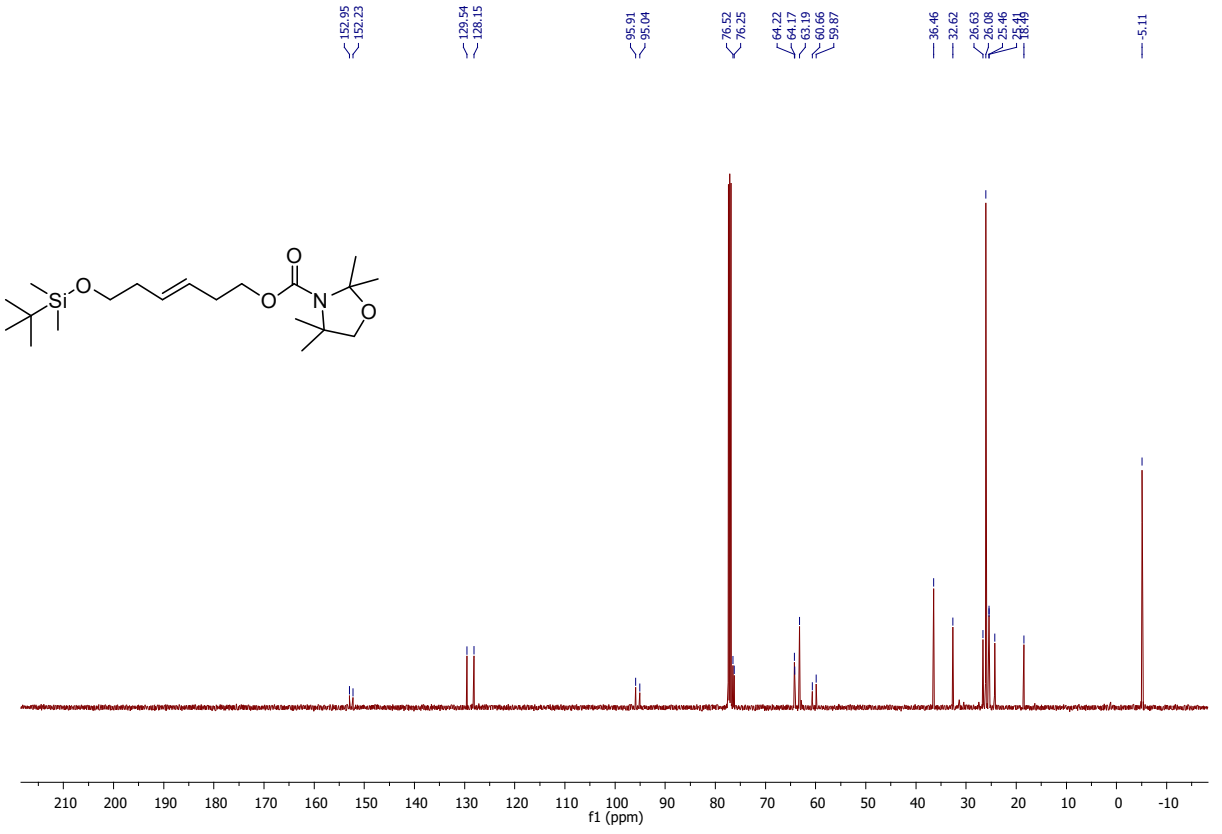
(*E*)-non-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.34** :



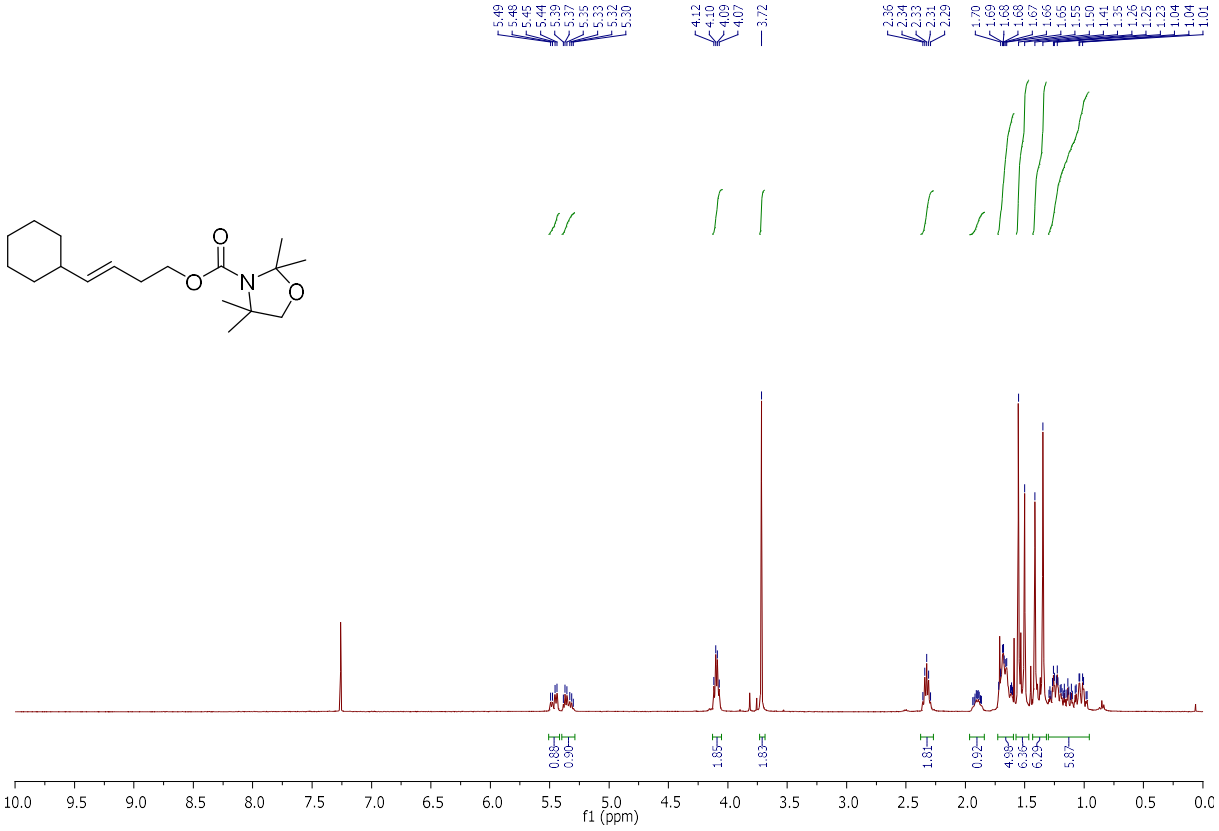


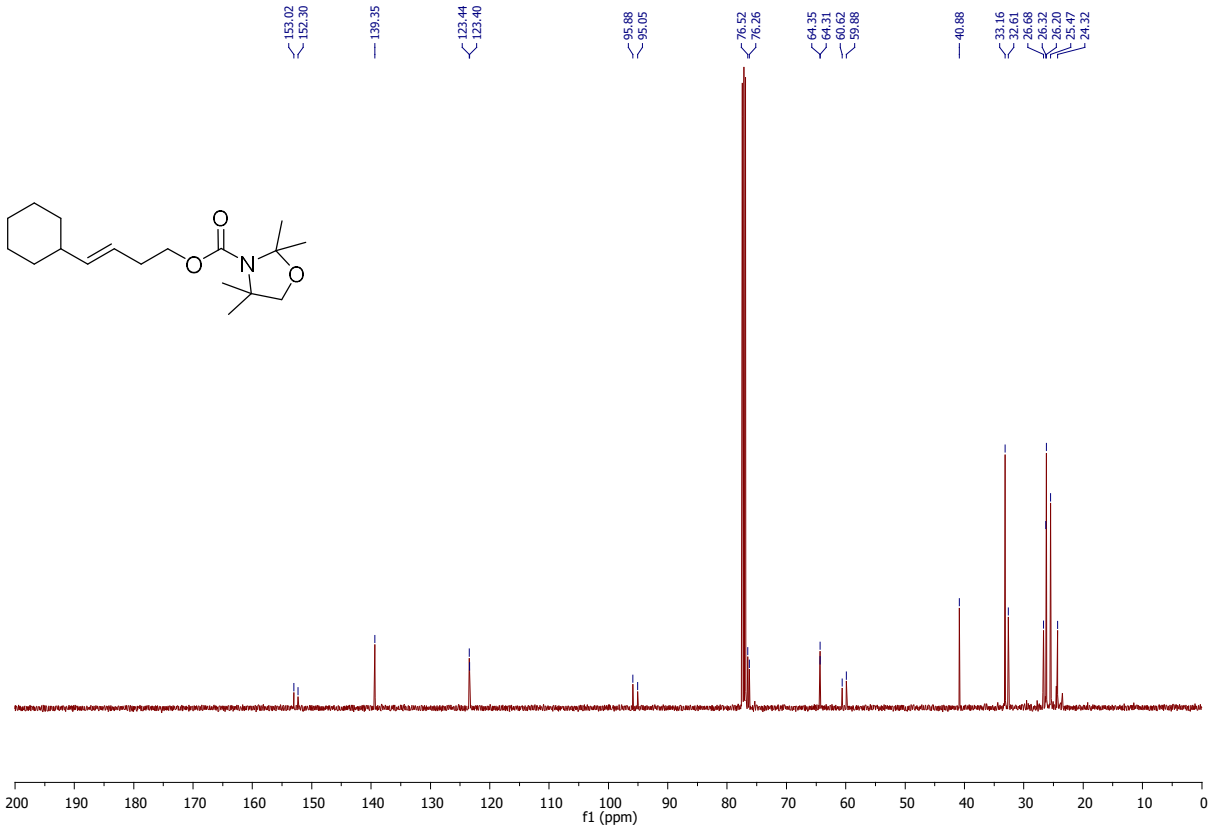
(*E*)-6-((tert-butyldimethylsilyl)oxy)hex-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.35** :



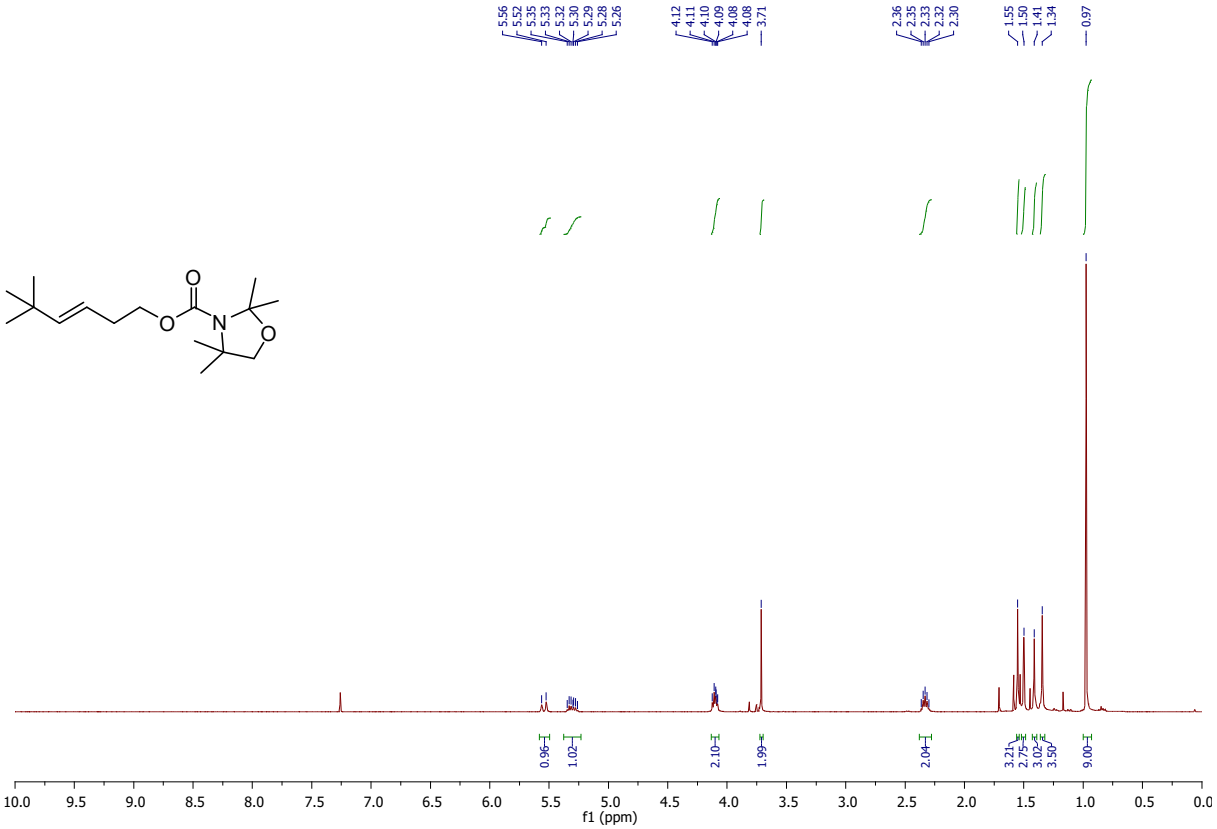


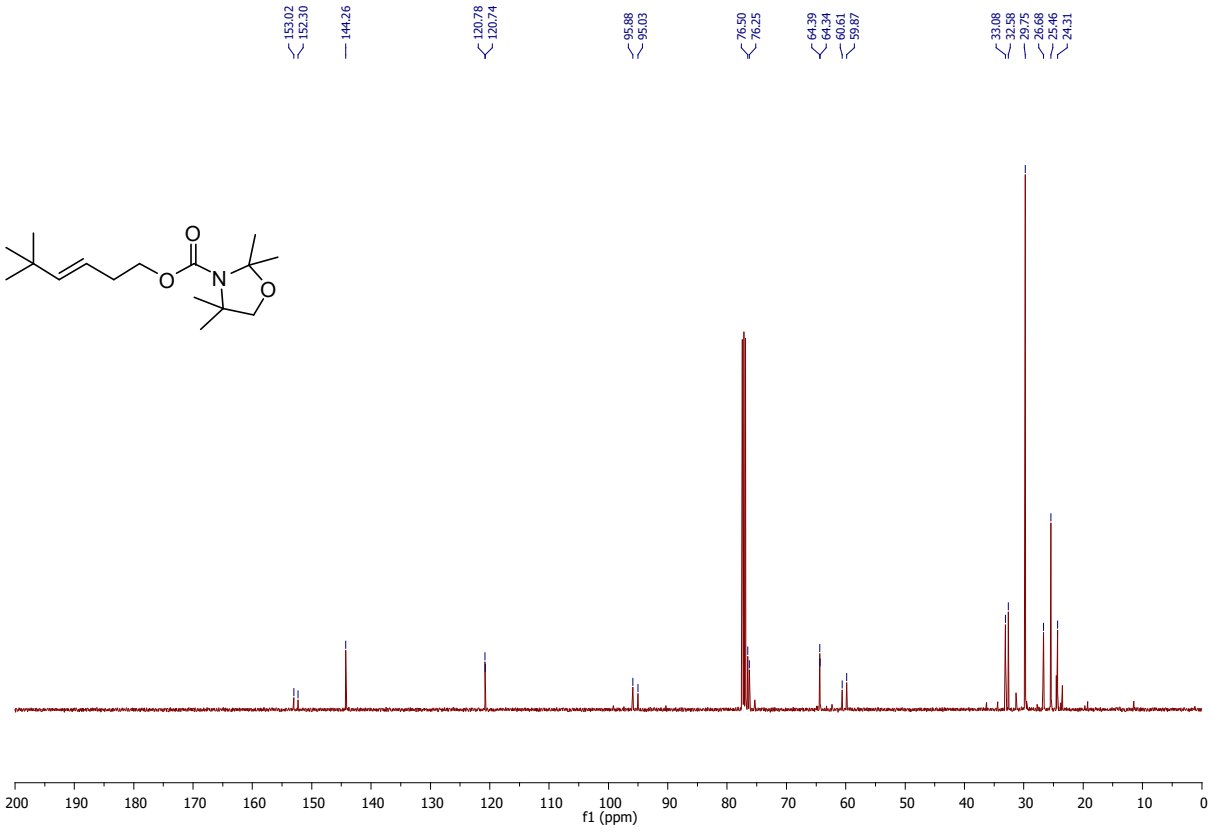
(*E*)-4-cyclohexylbut-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.36** :



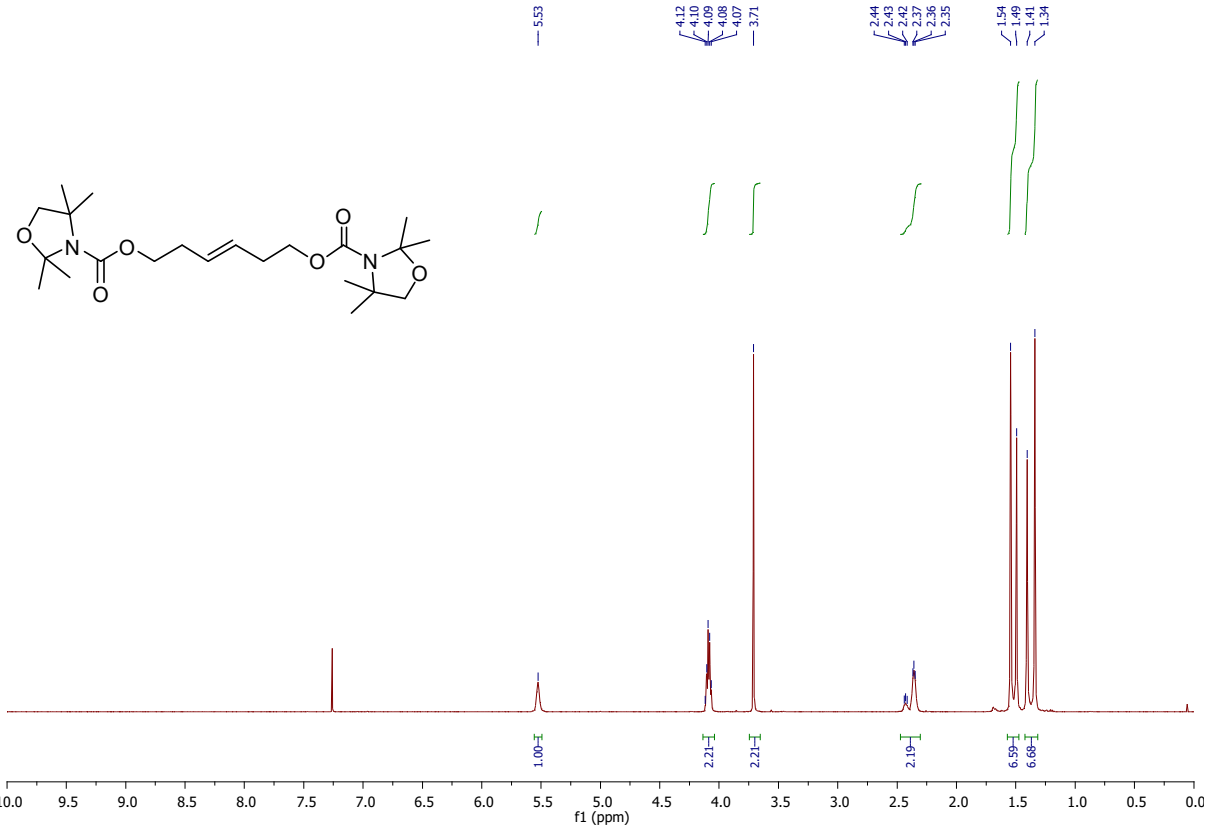


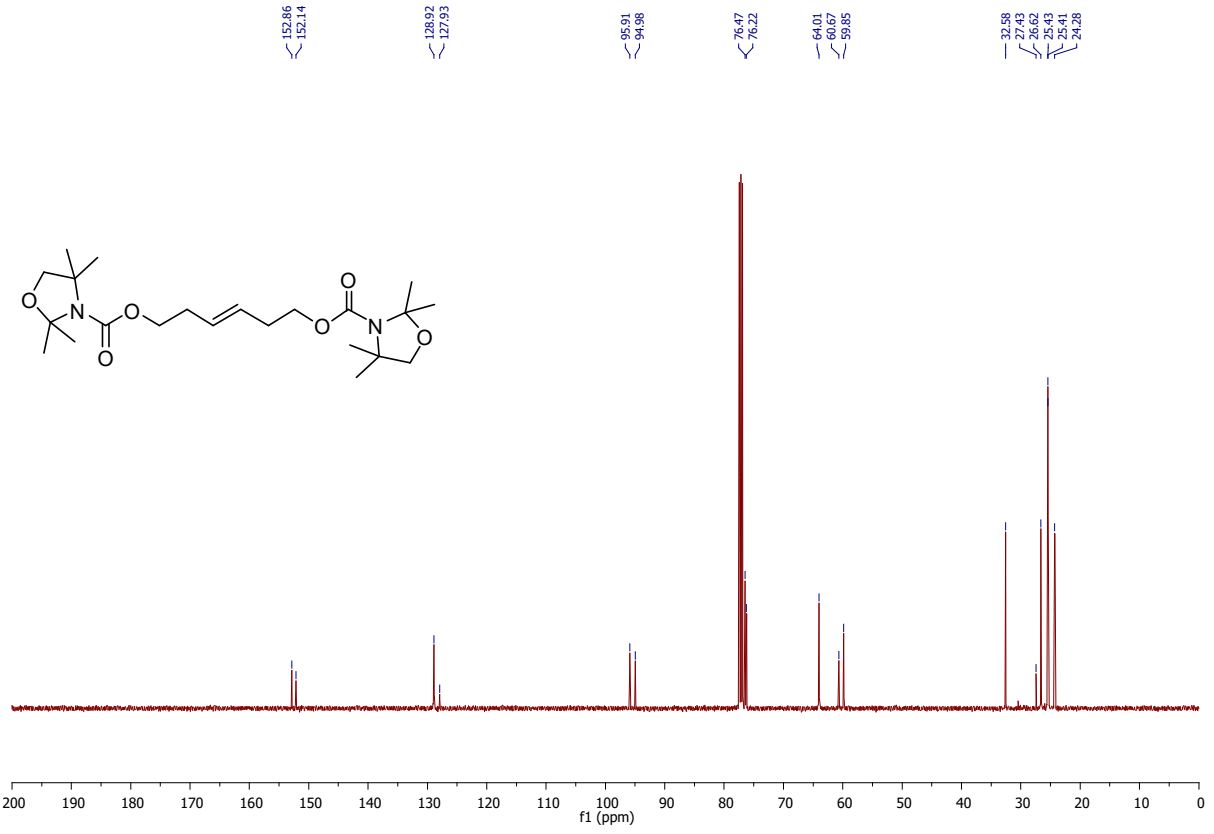
(*E*)-5,5-dimethylhex-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.37** :



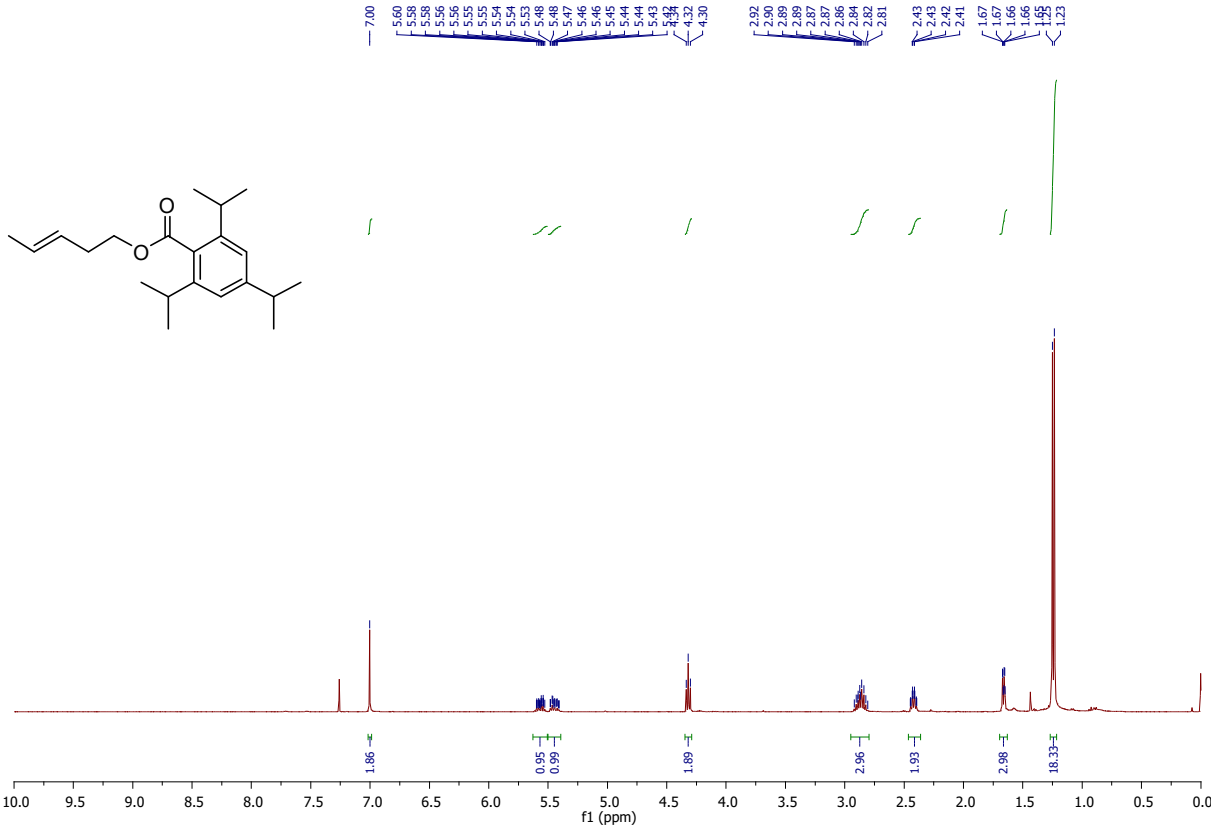


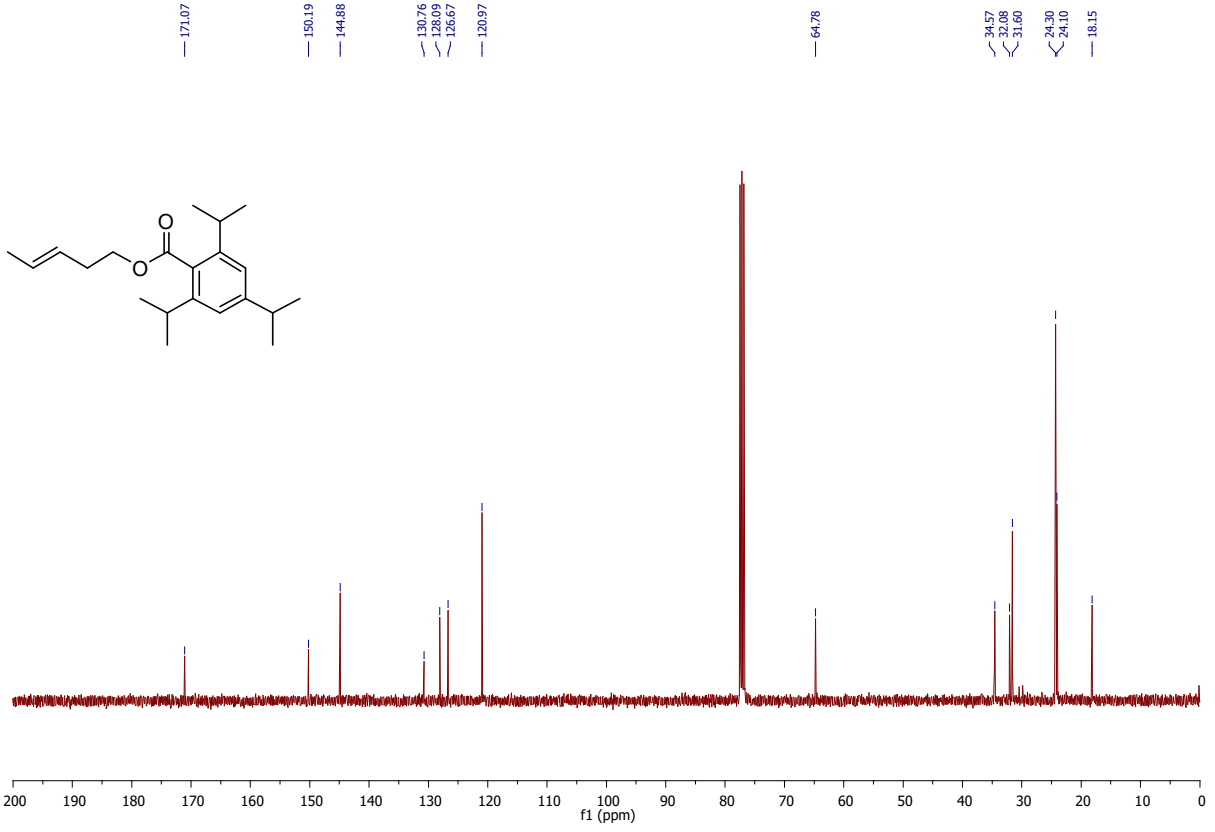
(*E*)-hex-3-ene-1,6-diyl bis(2,2,4,4-tetramethyloxazolidine-3-carboxylate) **2.39** :



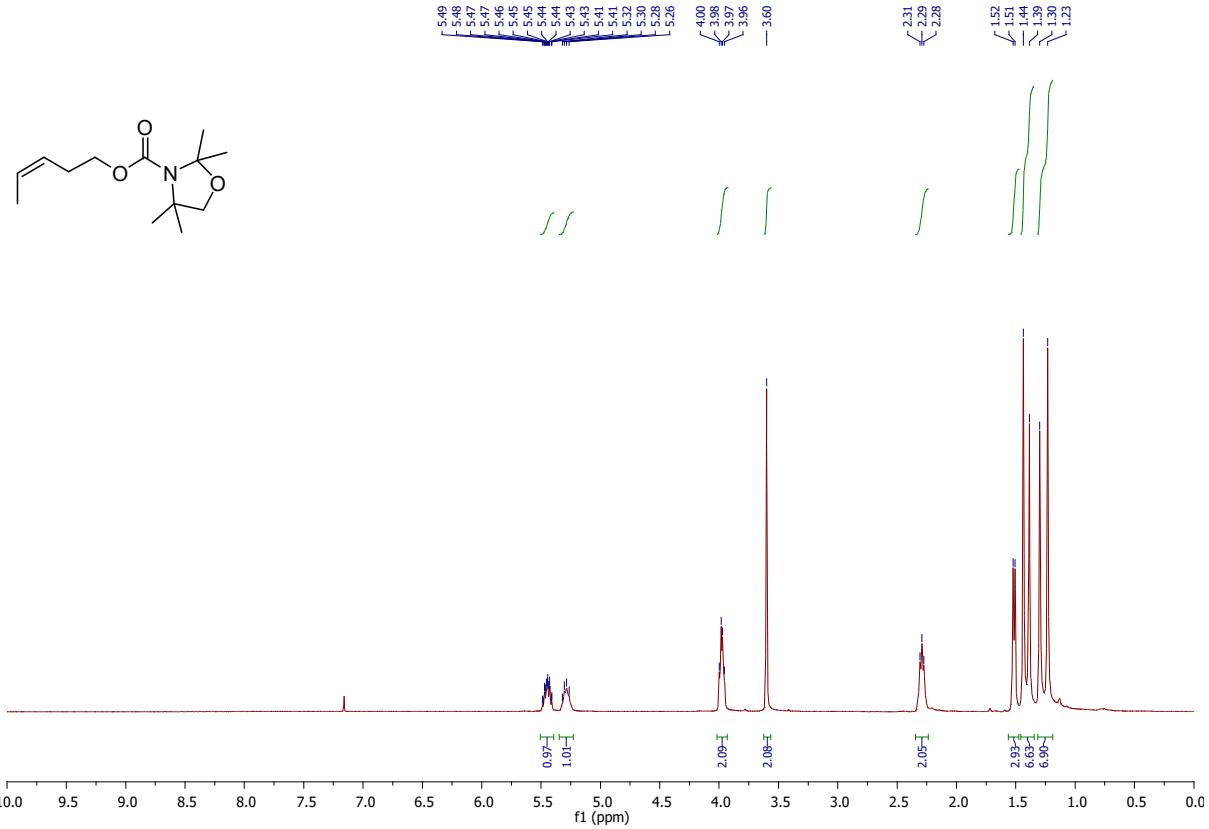


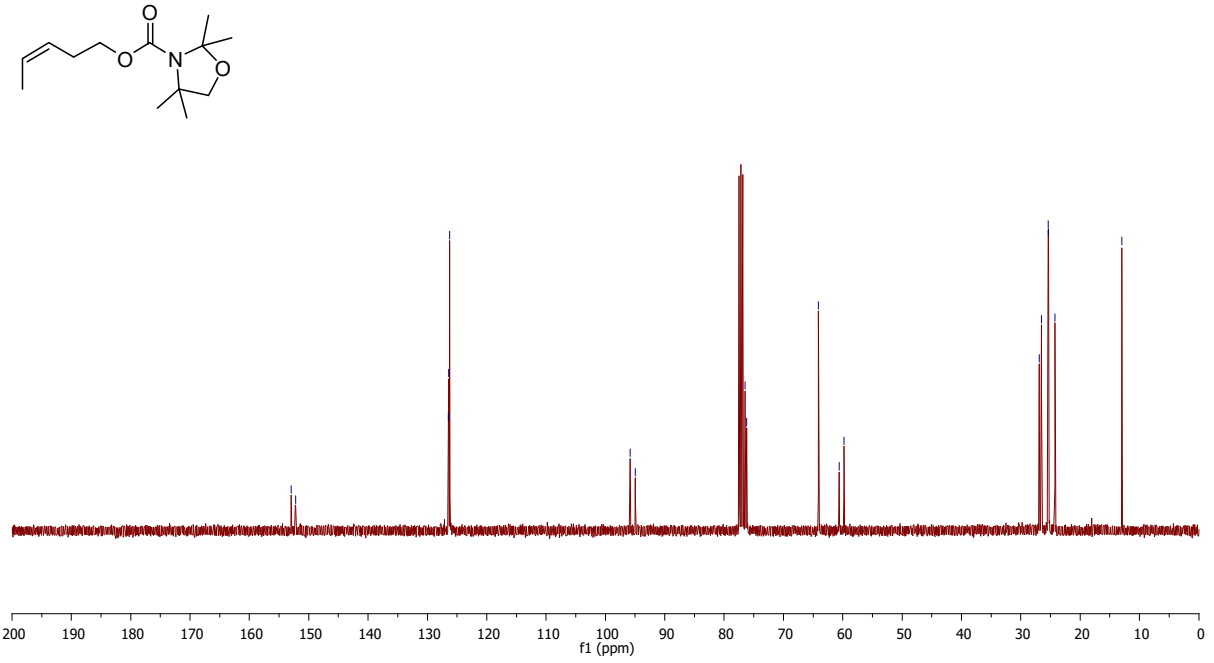
(*E*)-pent-3-en-1-yl 2,4,6-triisopropylbenzoate **2.25** :



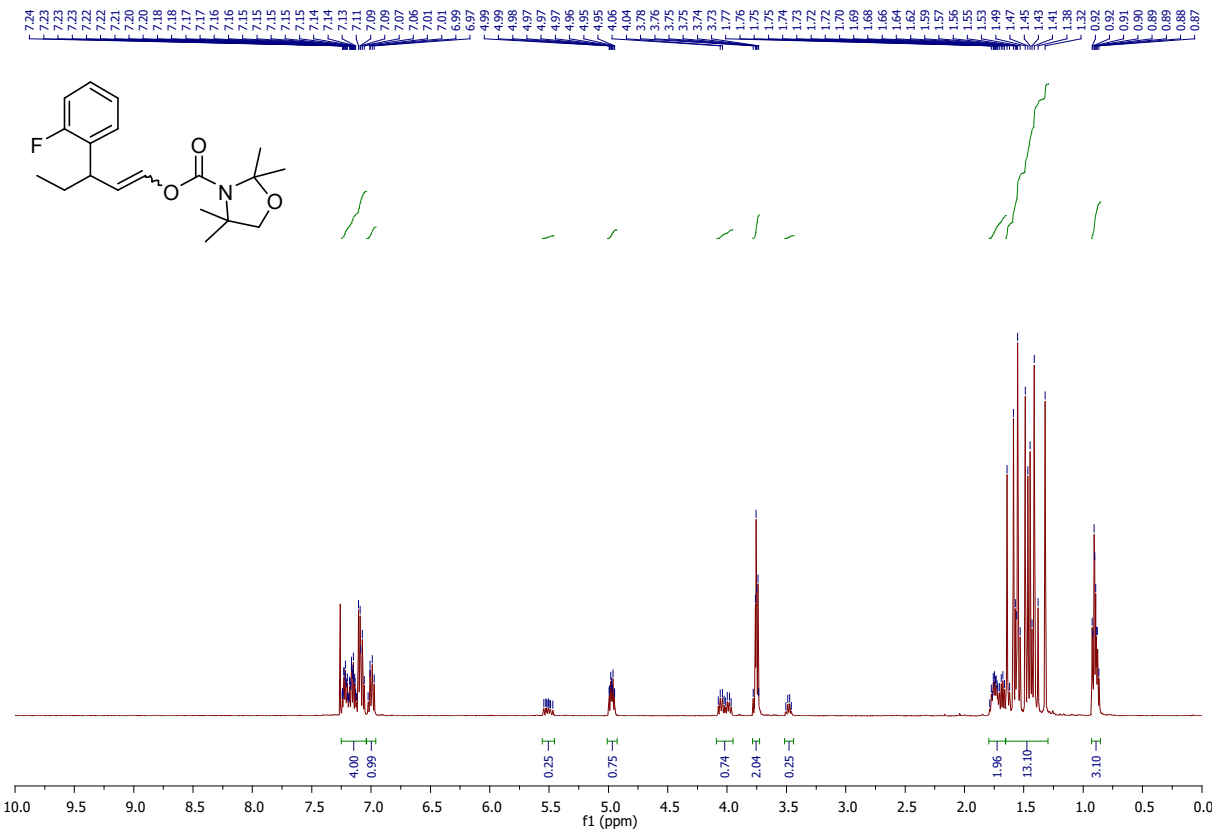


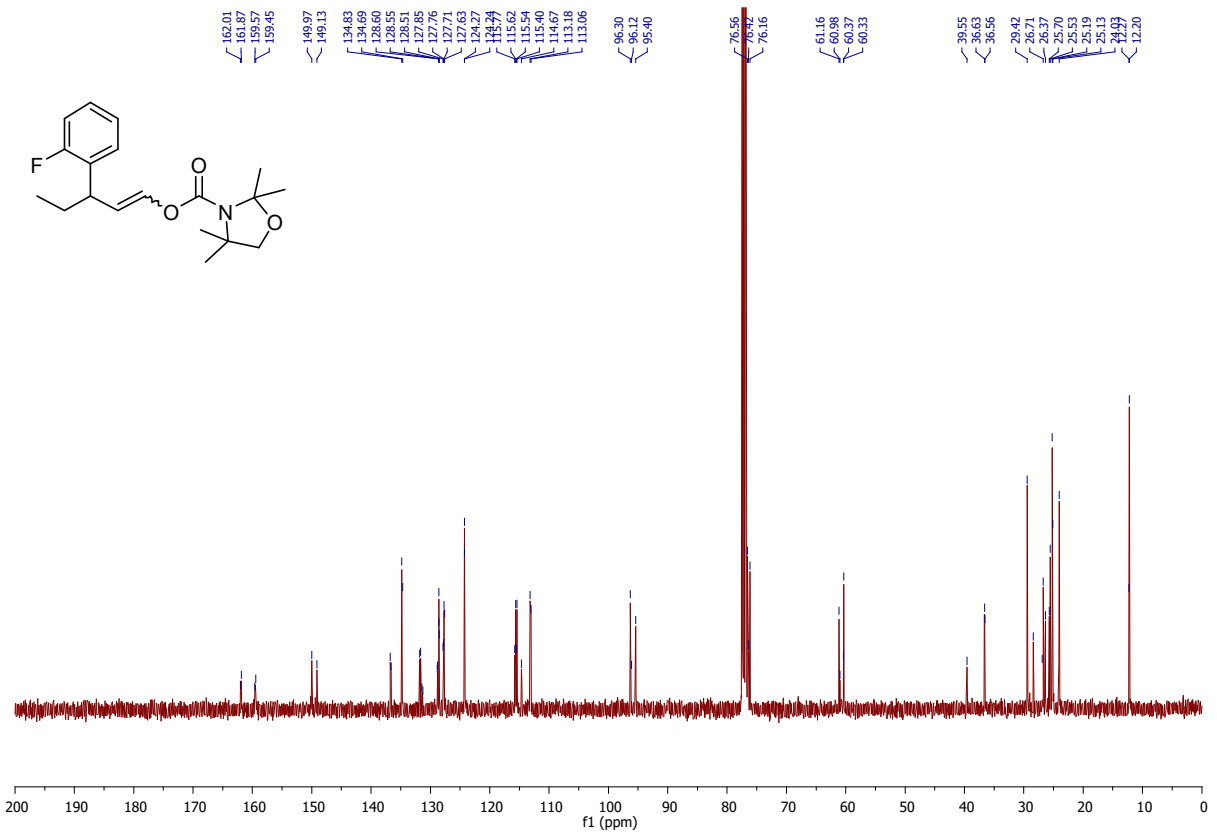
(*Z*)-Pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **(*Z*)-2.21**:



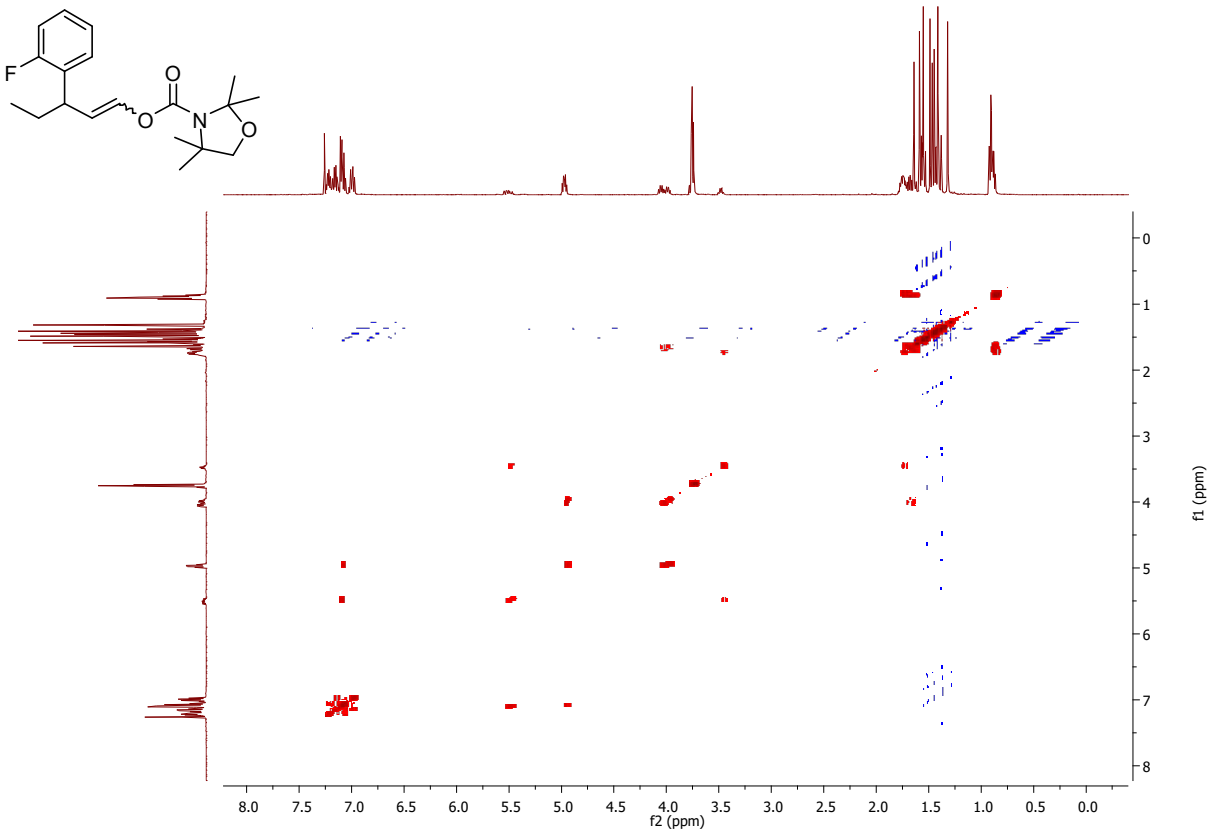


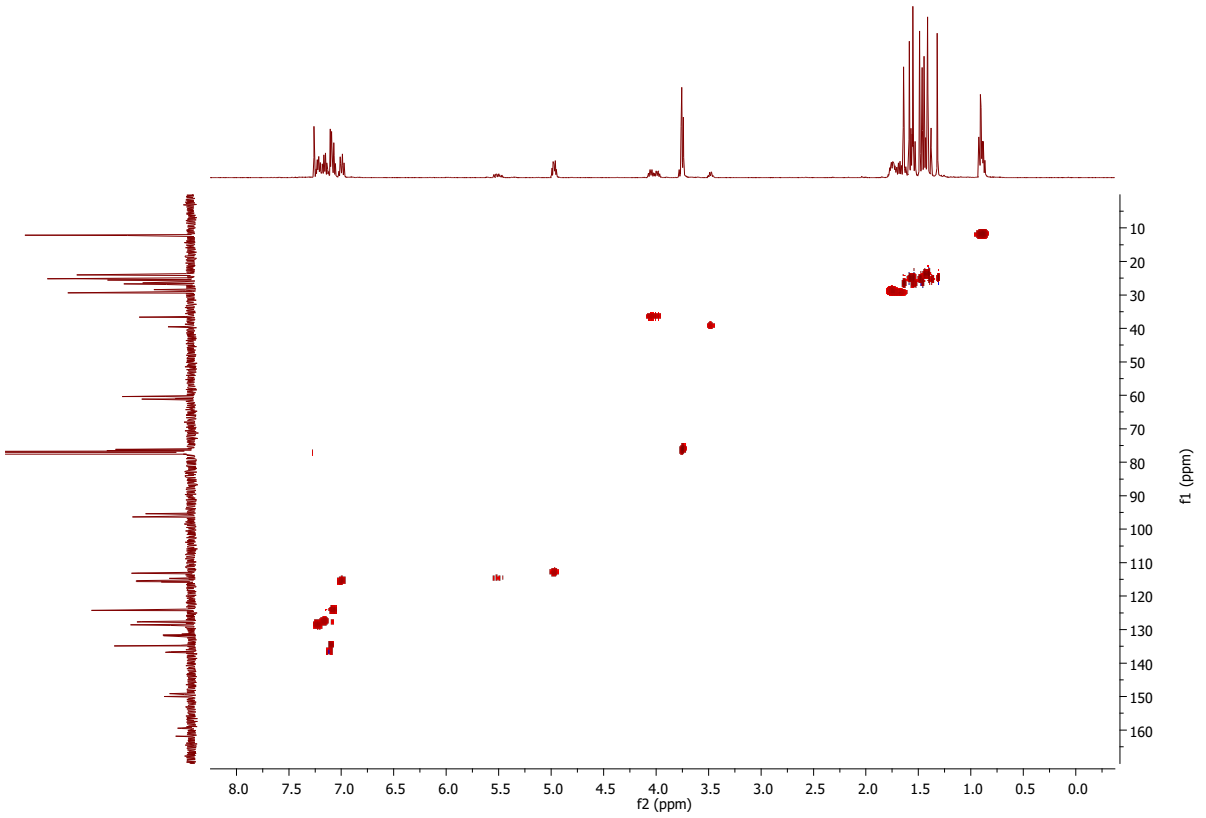
3-(2-fluorophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.21g** :

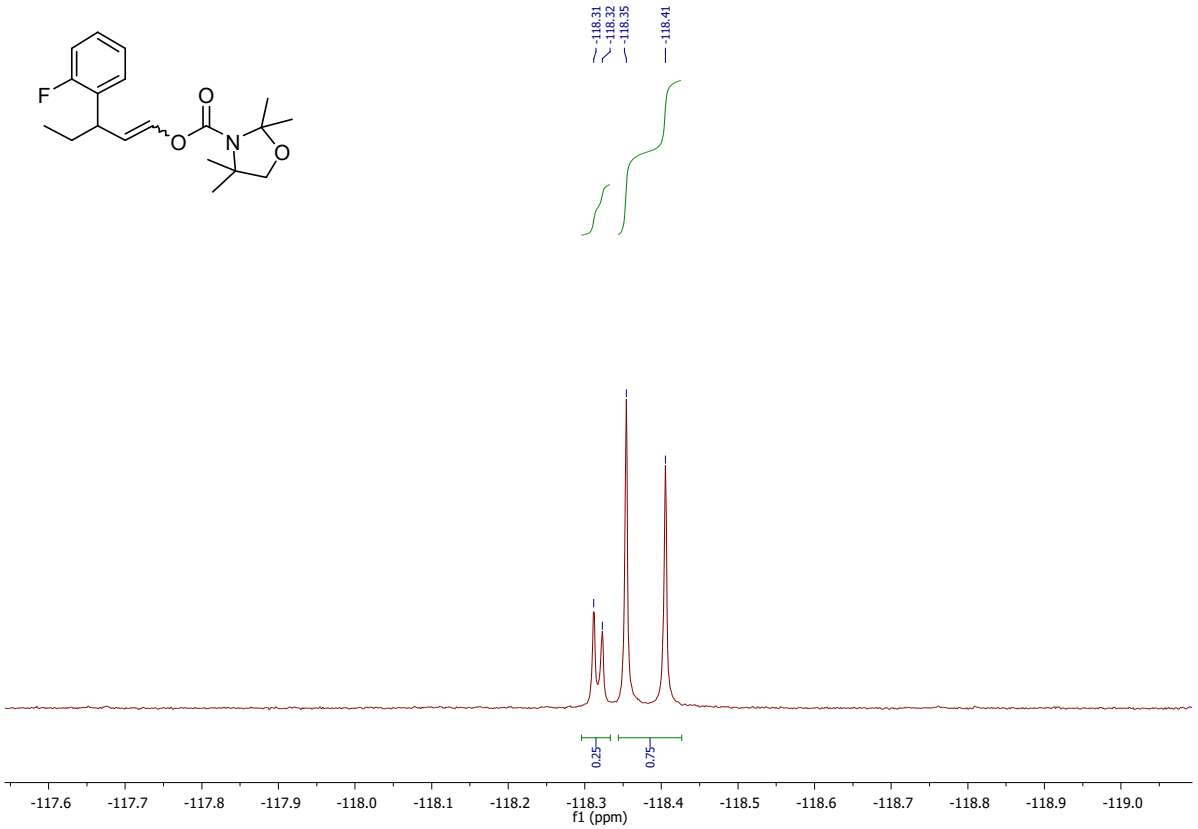




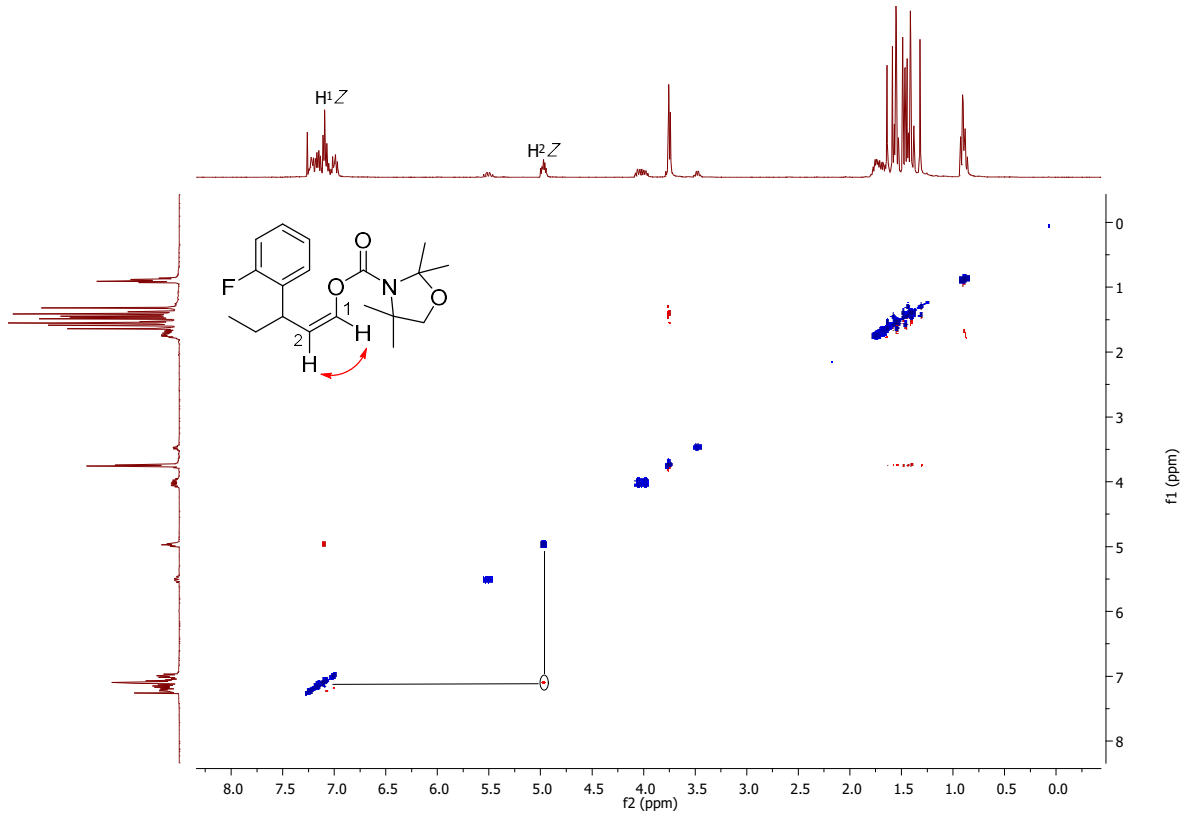
COSY and HMQC experiments :



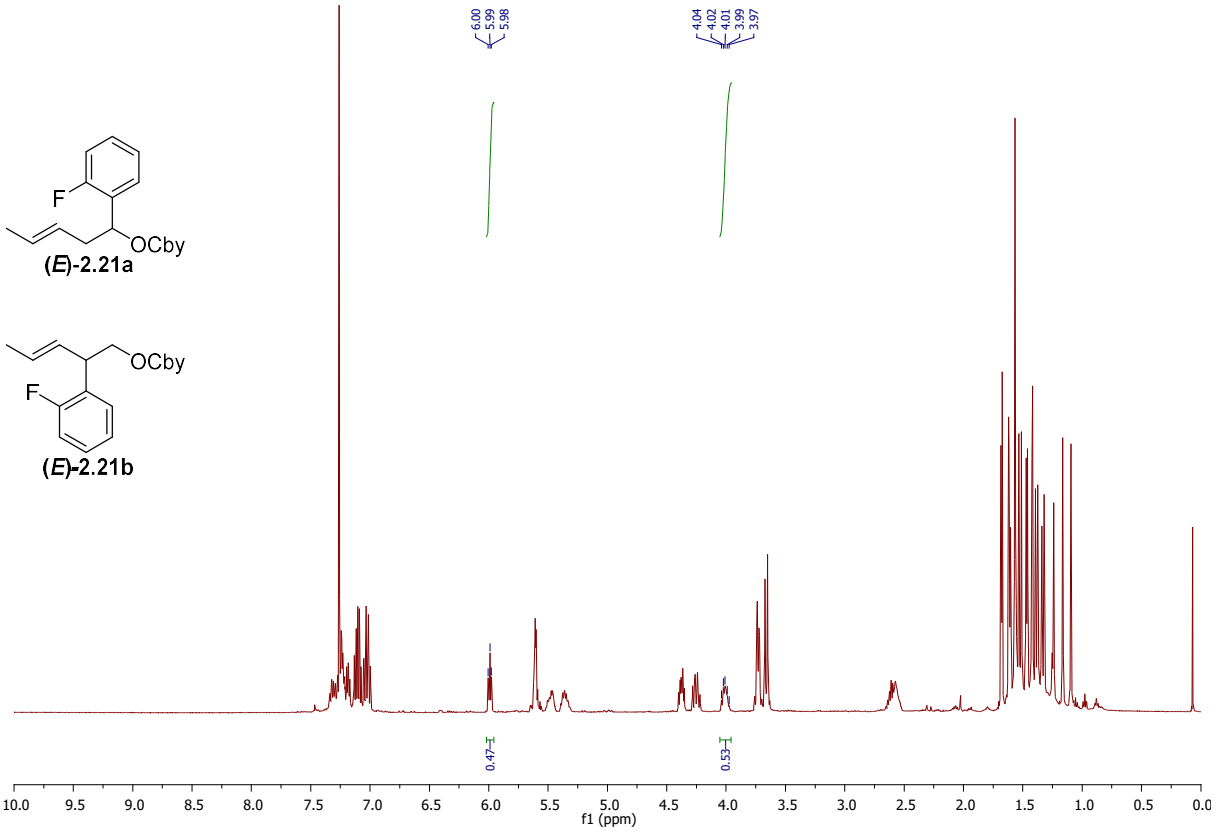


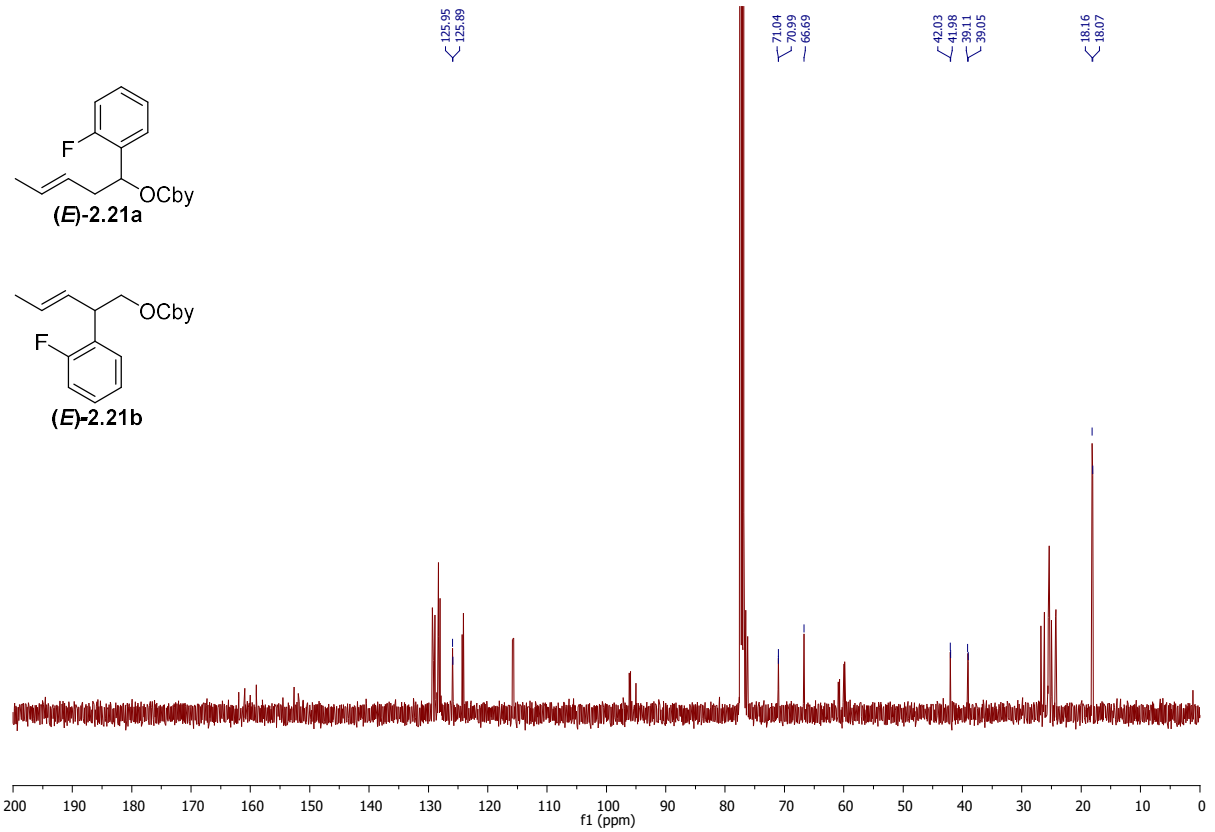


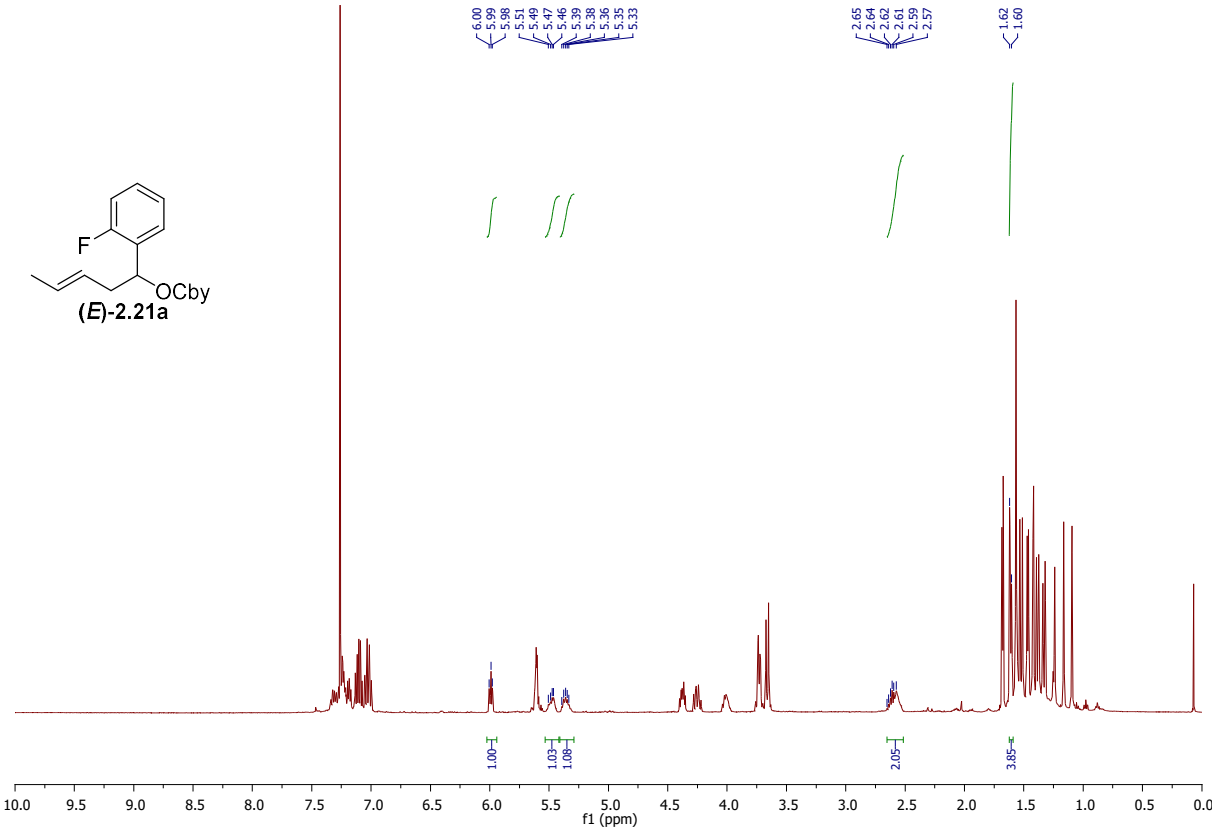
NOESY correlation between H_1Z and H_2Z :

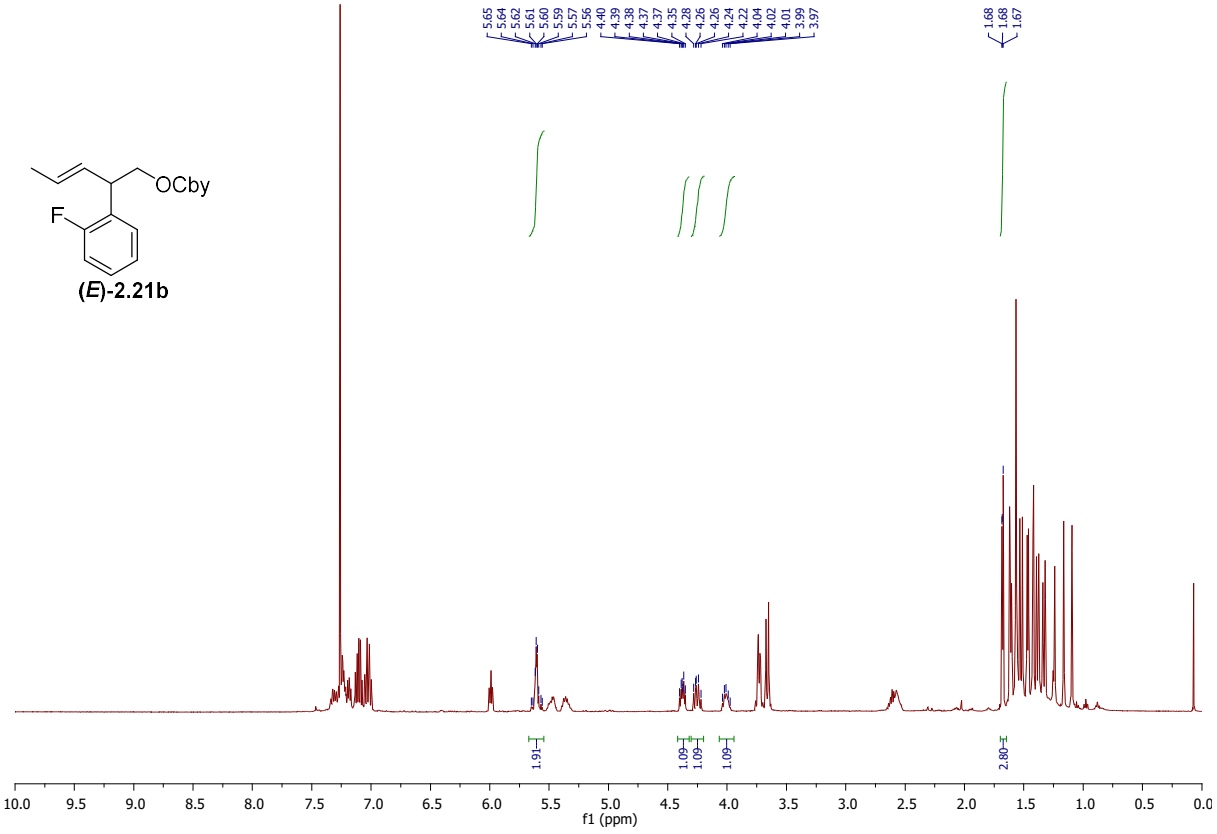


α- and β-products **(*E*)-2.21a** and **(*E*)-2.21b** :

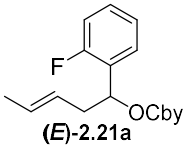




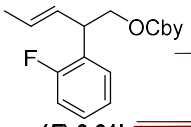

F
OCby
(E)-2.21a
6.00
5.99
5.98
5.51
5.49
5.47
5.46
5.39
5.38
5.36
5.35
5.33
2.65
2.64
2.62
2.61
2.59
2.57
1.62
1.60
1.00
1.03
1.08
2.05
3.85
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OCby
F
(E)-2.21b
5.65
5.64
5.62
5.61
5.60
5.59
5.57
5.56
4.40
4.39
4.38
4.37
4.37
4.35
4.28
4.26
4.26
4.24
4.22
4.04
4.02
4.01
3.99
3.97
1.68
1.68
1.67
1.91
1.09
1.09
1.09
2.80
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
f1 (ppm)

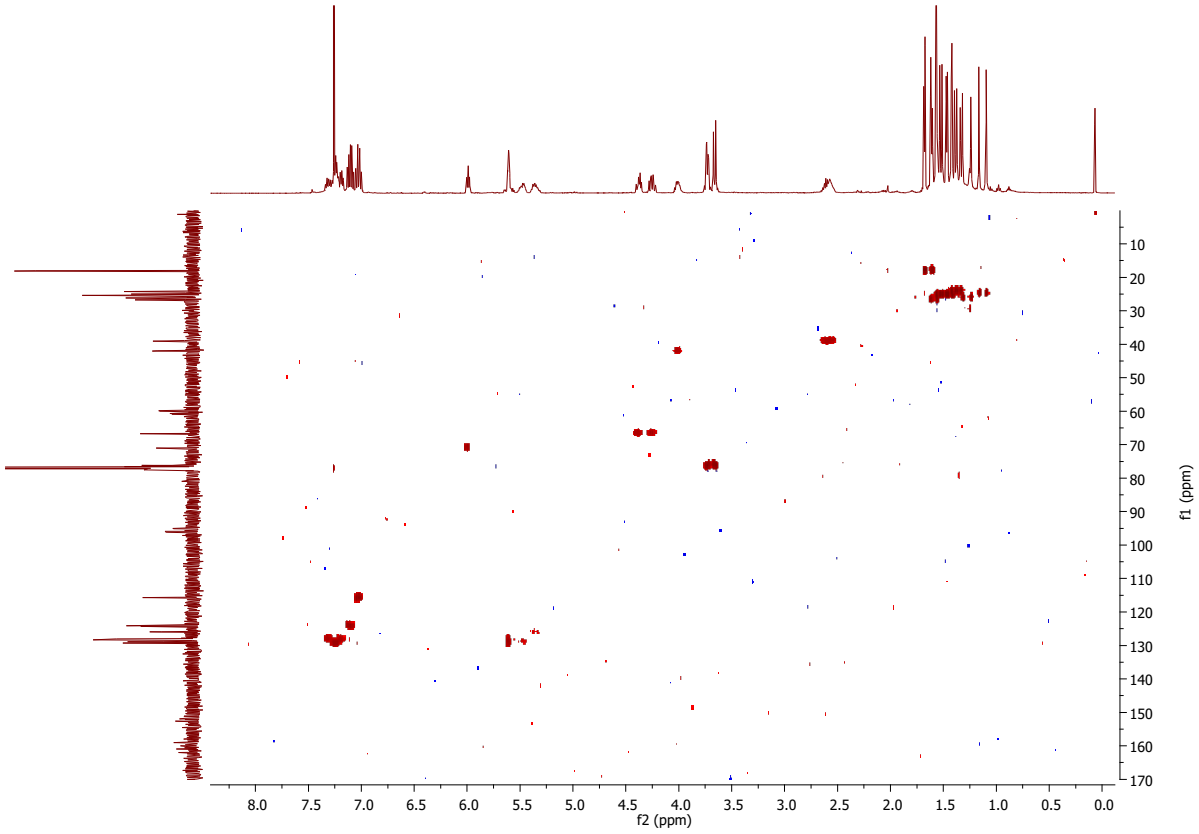
COSY and HMQC experiments :

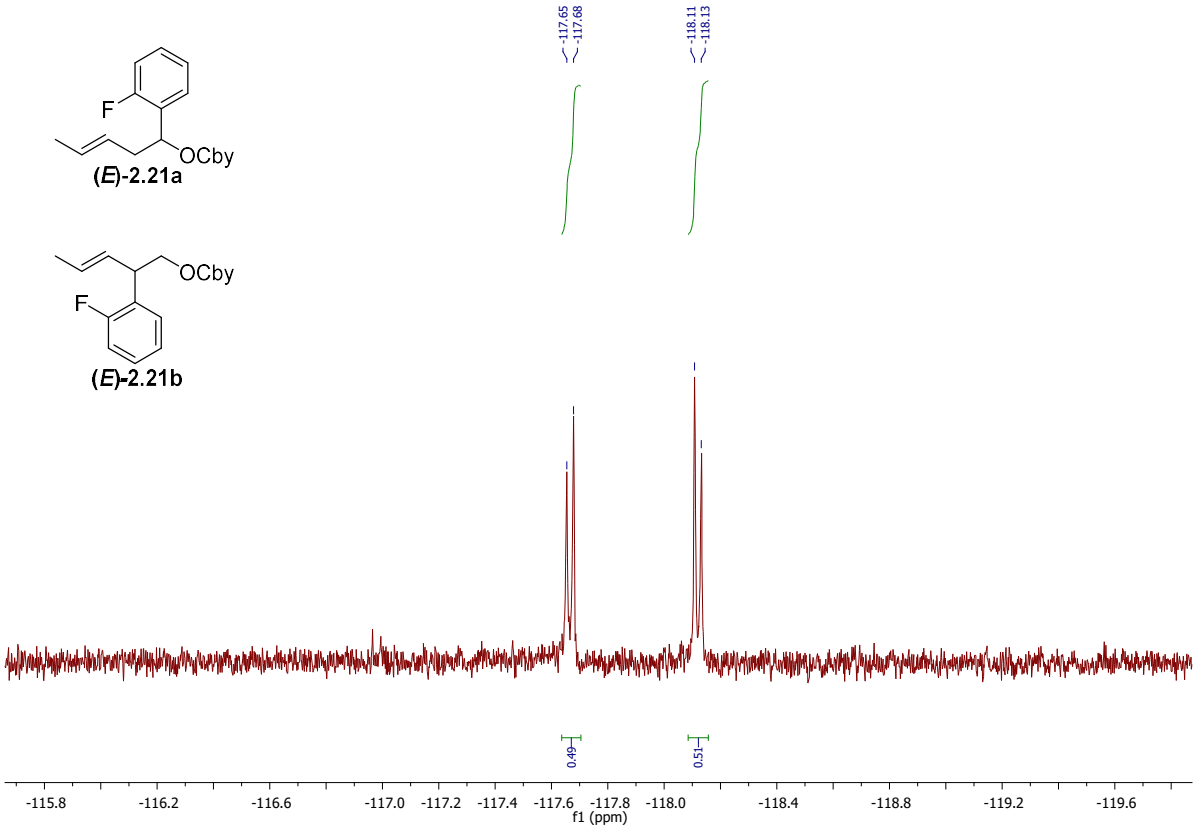


(*E*)-2.21a



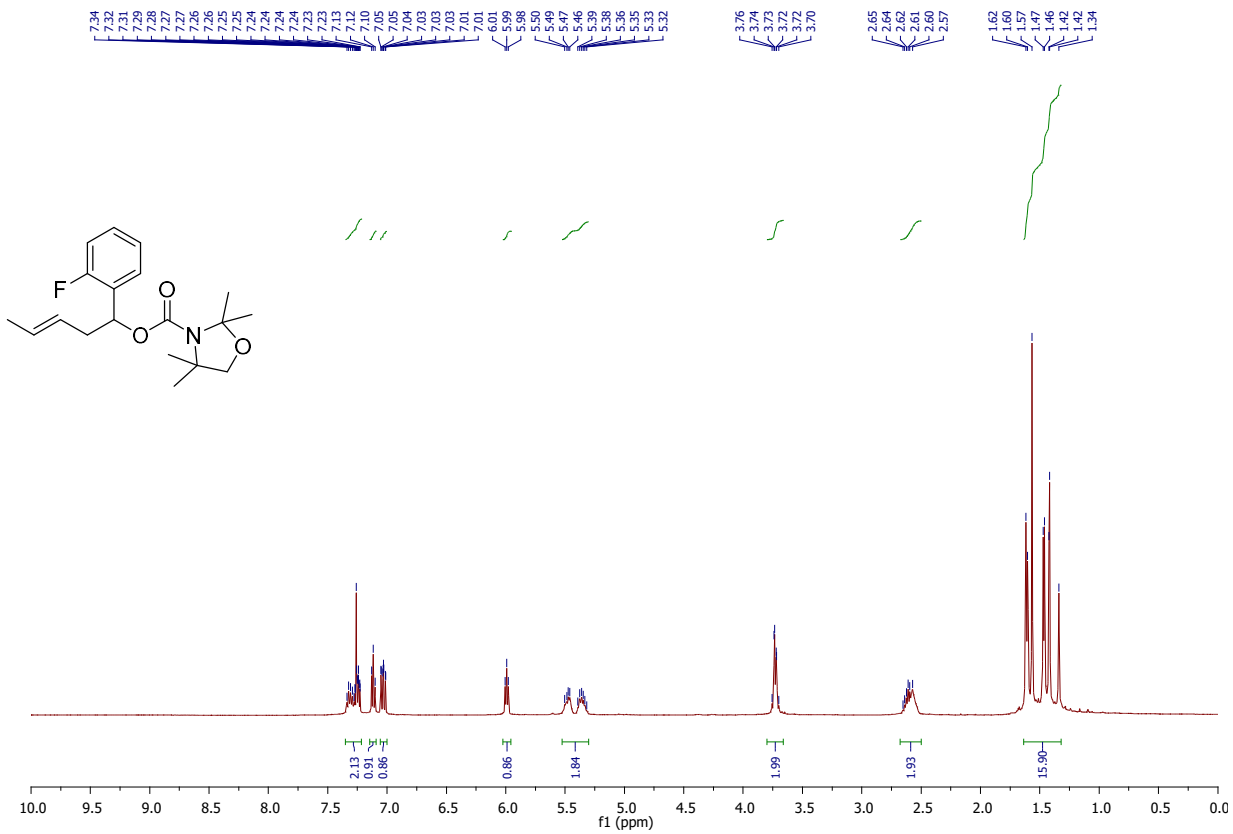
(*E*)-2.21b

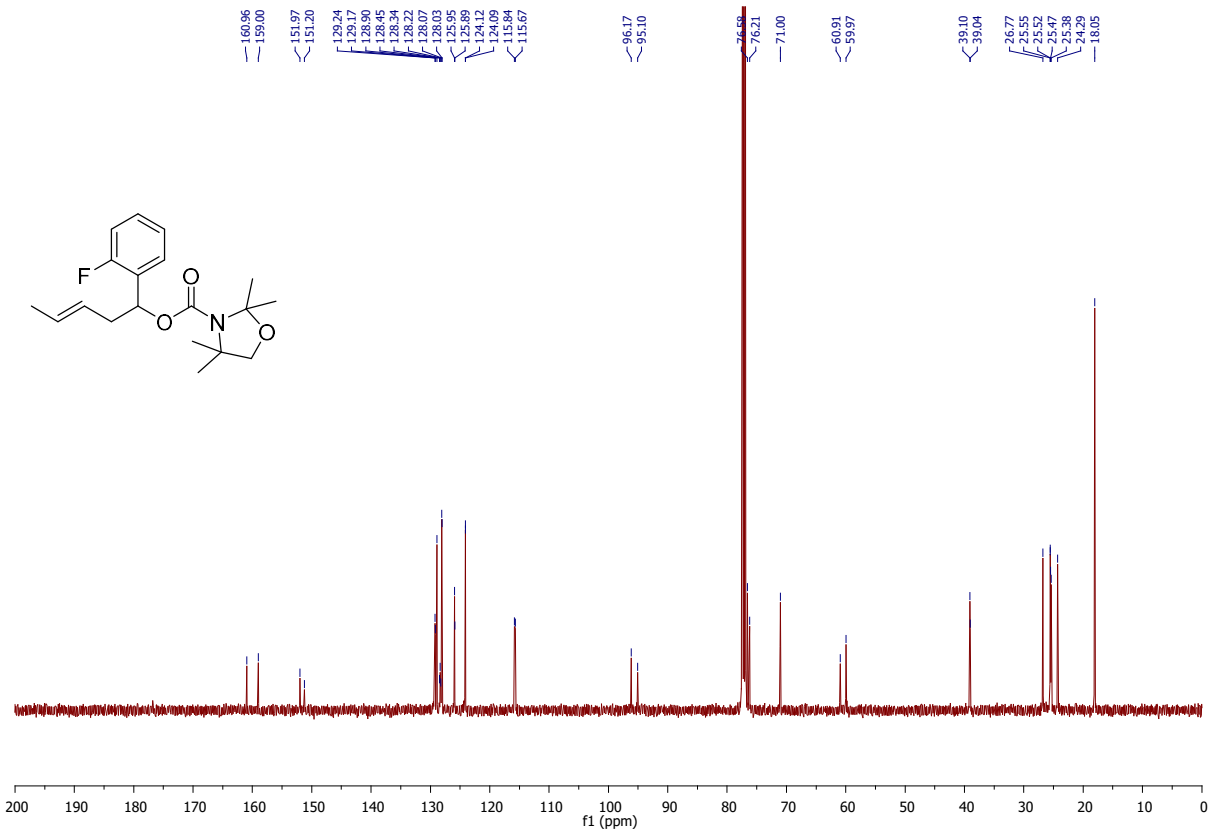



F
OCby
(E)-2.21a
OCby
F
(E)-2.21b
-117.65
-117.68
-118.11
-118.13
0.49
0.51
-115.8
-116.2
-116.6
-117.0
-117.2
-117.4
-117.6
-117.8
-118.0
-118.4
-118.8
-119.2
-119.6
f1 (ppm)

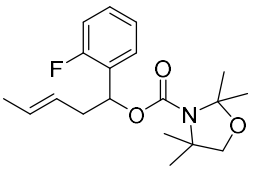
(*E*)-1-(2-fluorophenyl)pent-3-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **(*E*)-2.21a**

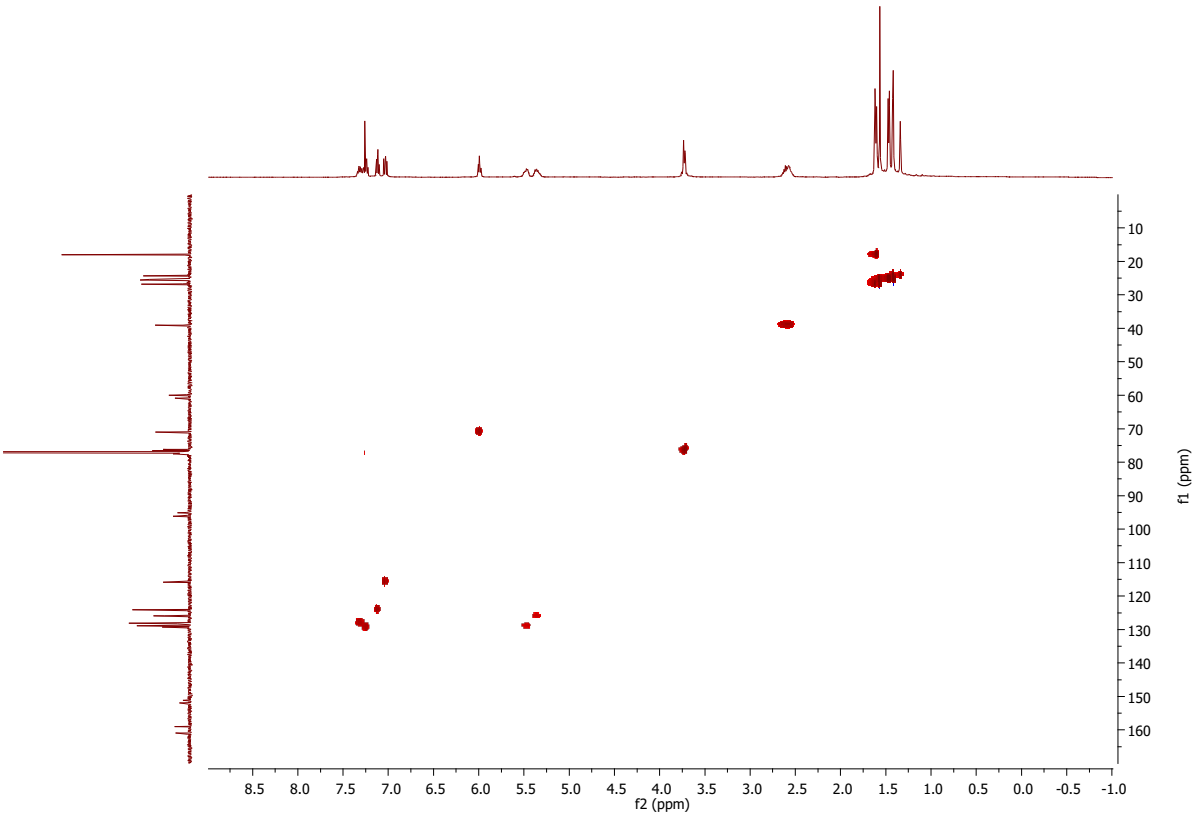
:

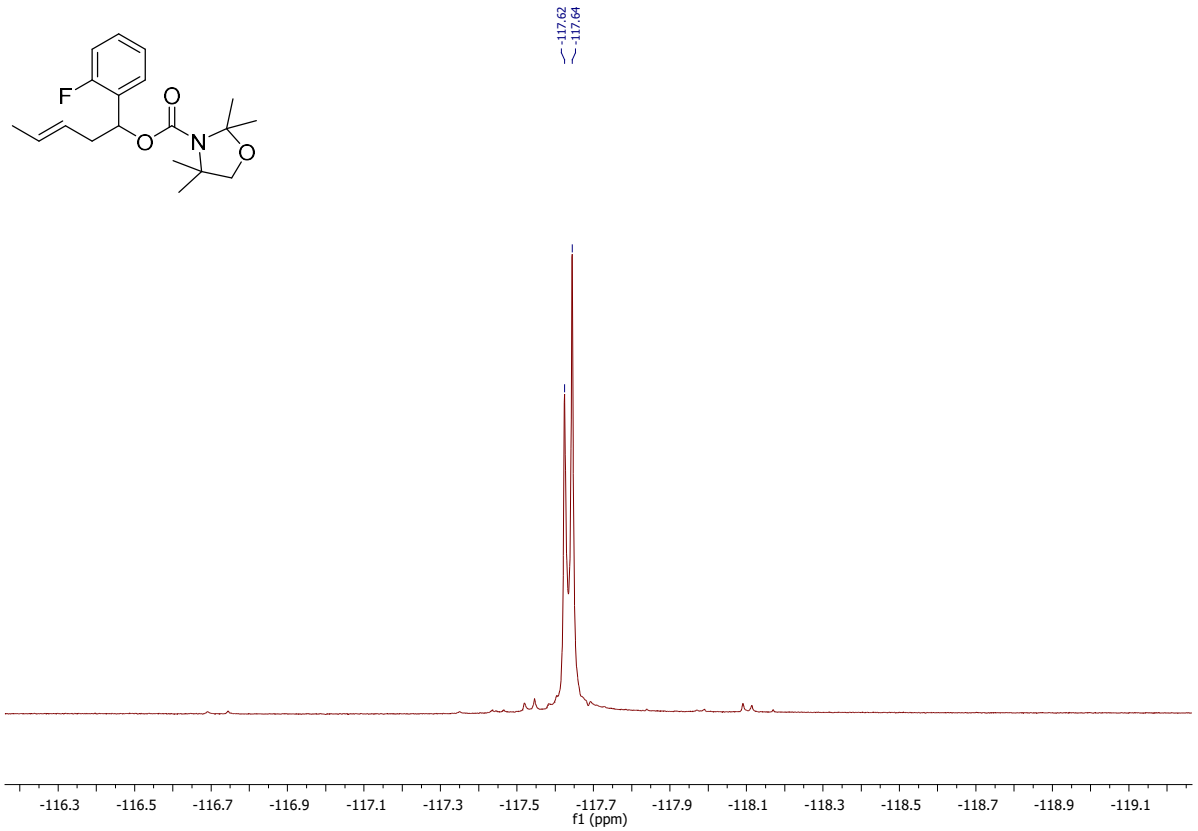




COSY and HMQC experiments :

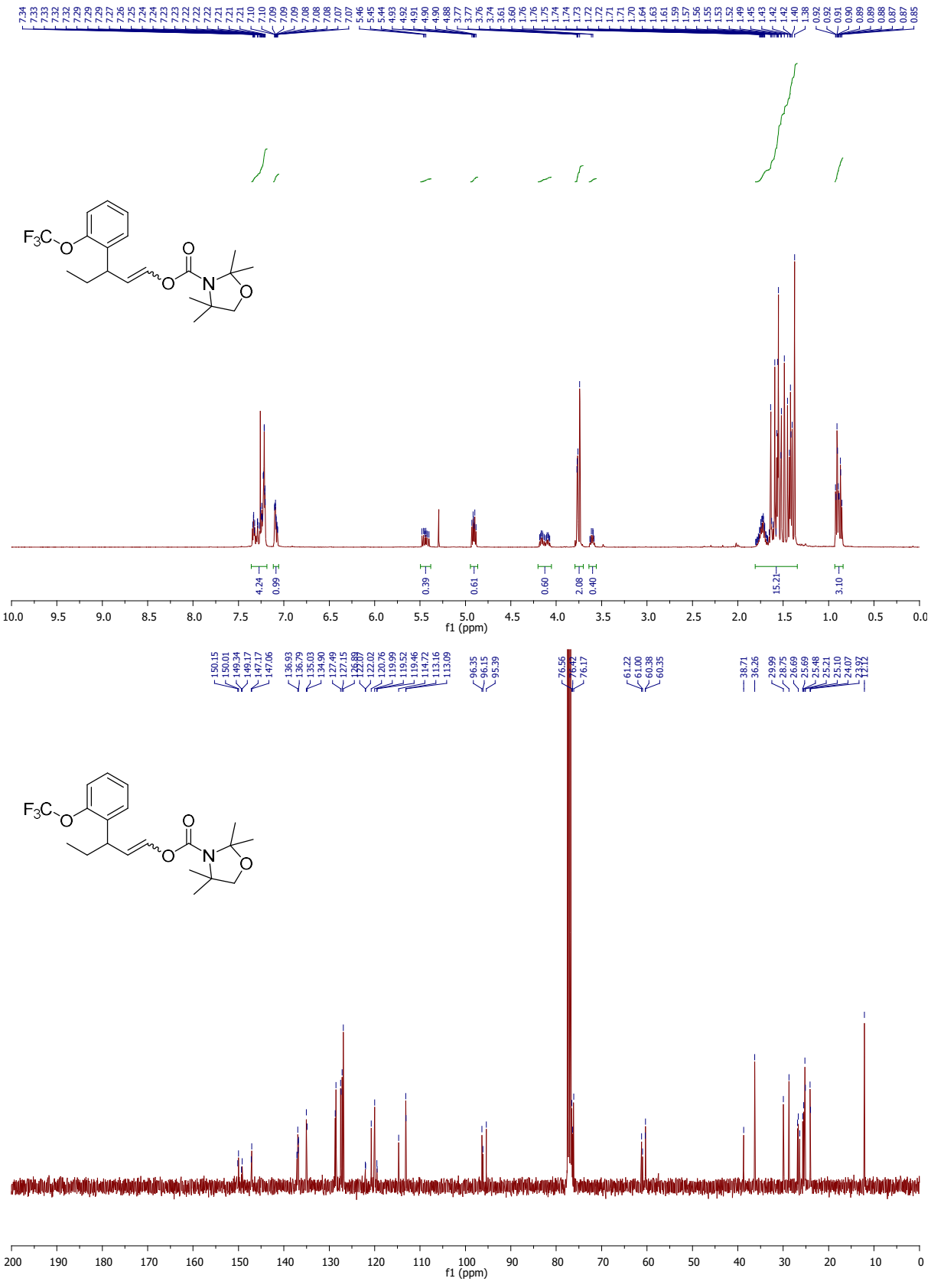




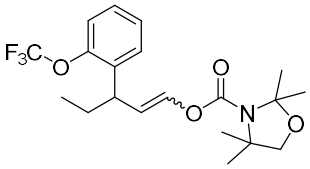

F
O
O
N
O
-117.62
-117.64
-116.3
-116.5
-116.7
-116.9
-117.1
-117.3
-117.5
-117.7
-117.9
-118.1
-118.3
-118.5
-118.7
-118.9
-119.1
f1 (ppm)

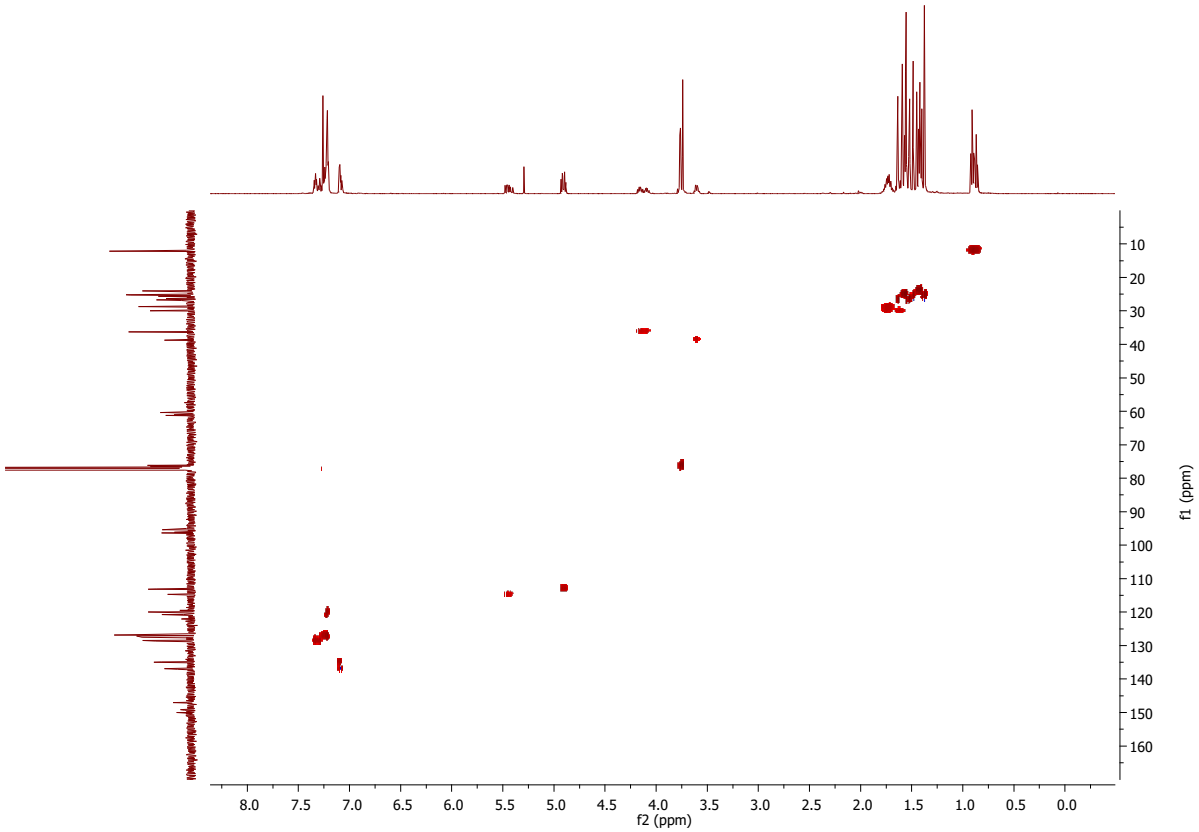
3-(2-(trifluoromethoxy)phenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate

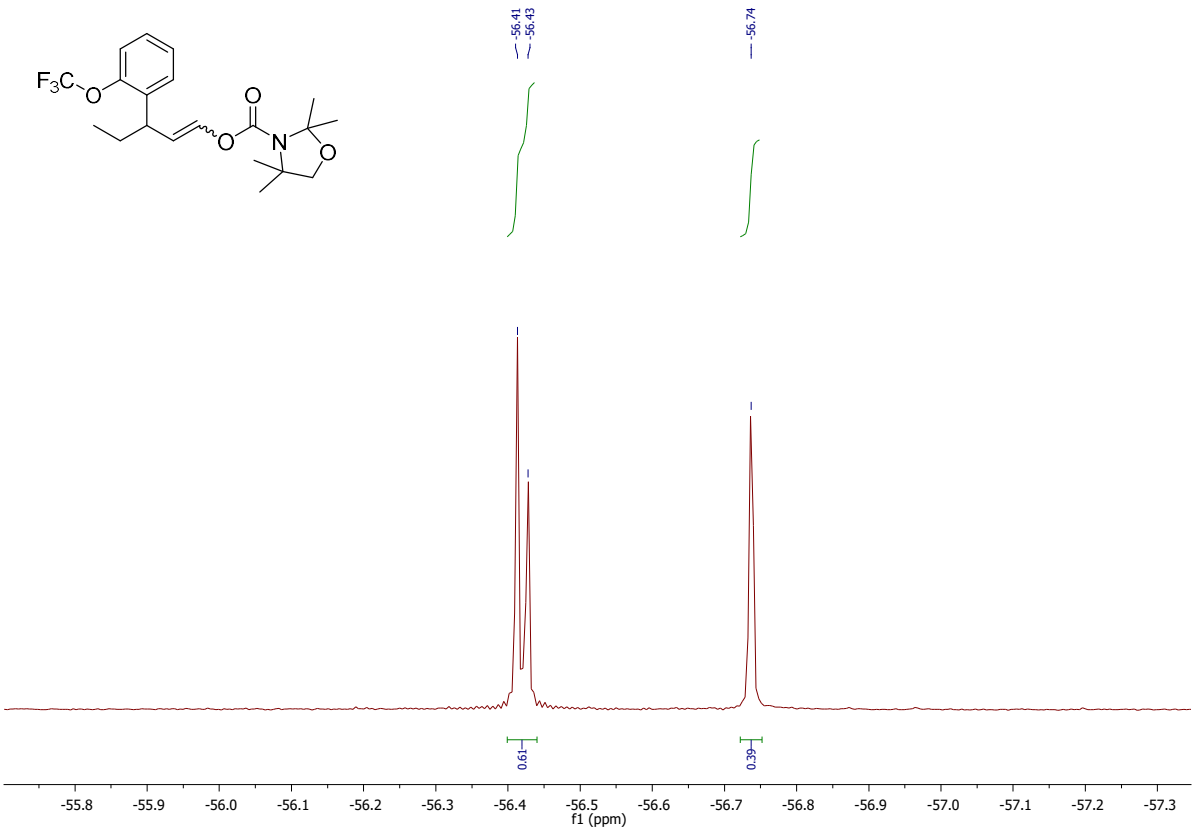
2.32a :



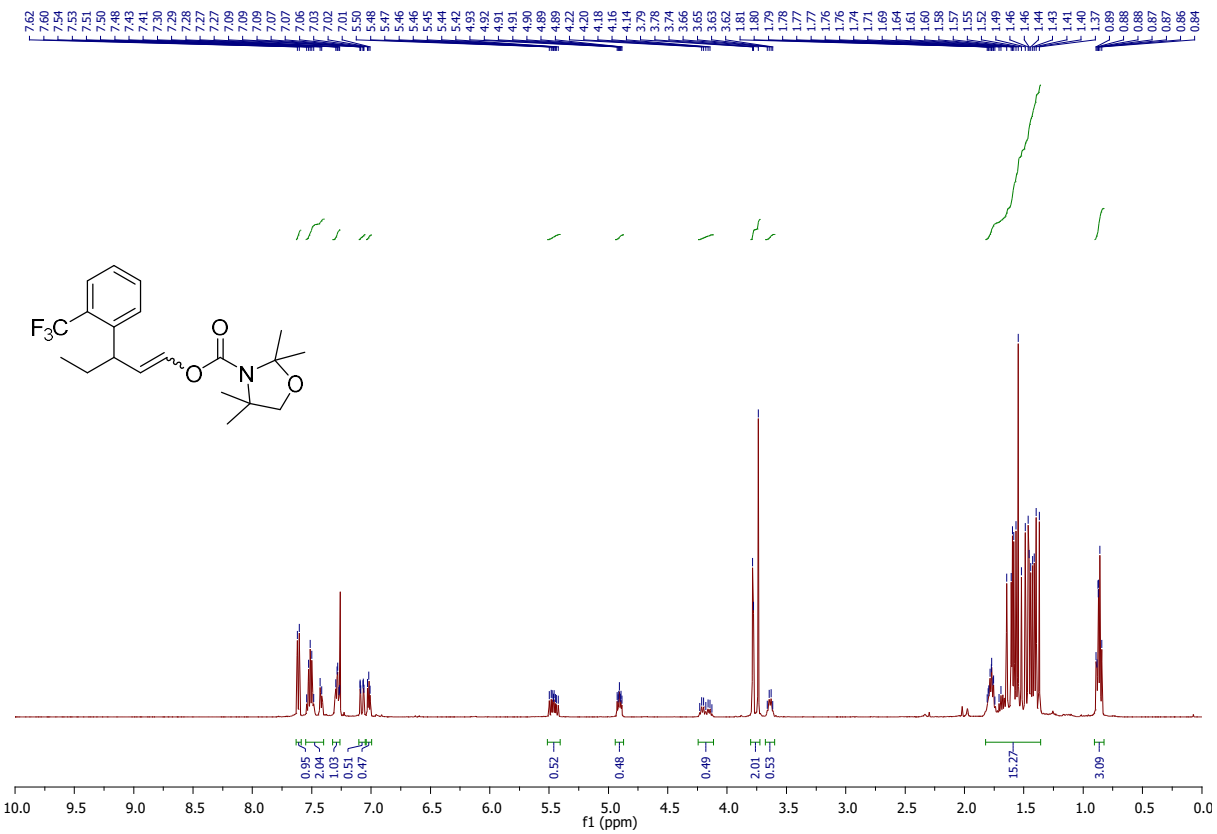
COSY and HMQC experiments :

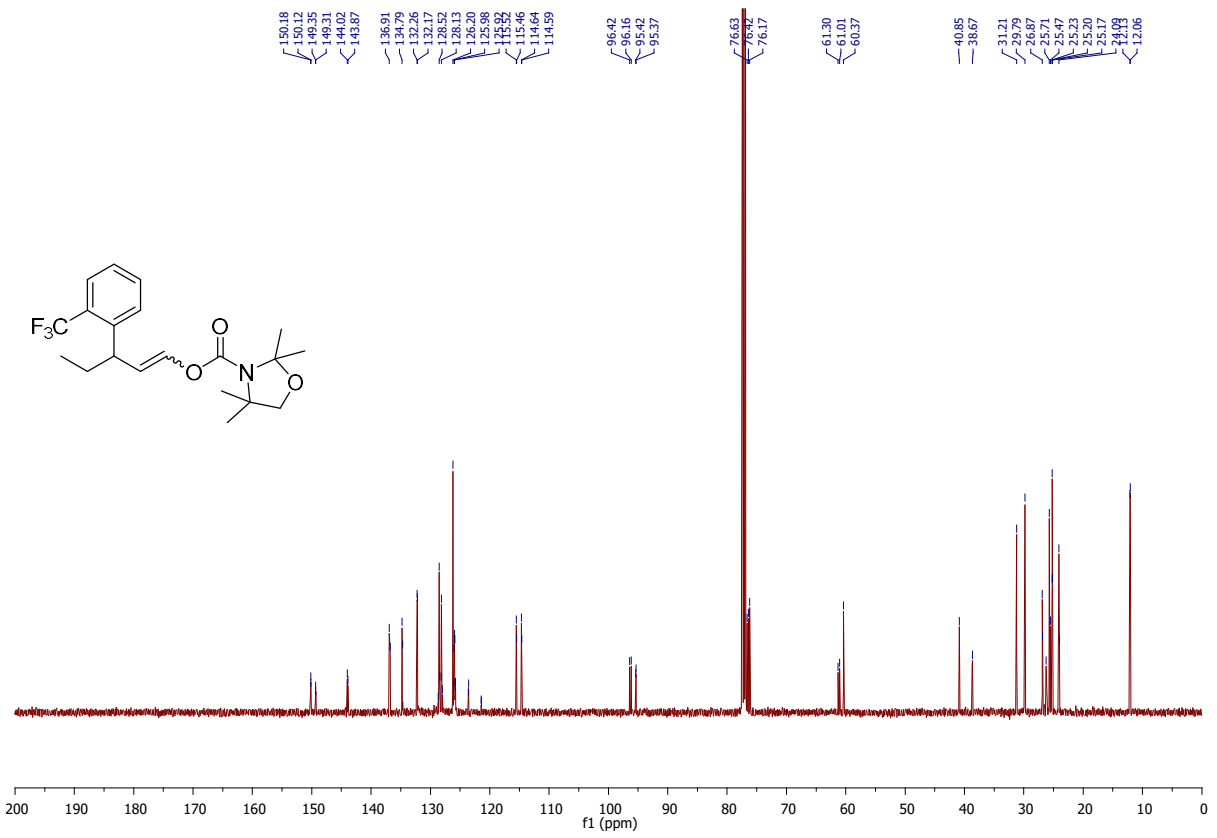




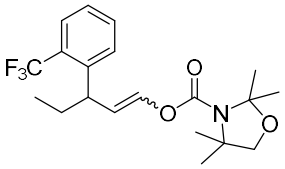

F3C
O
O
O
N
O
-56.41
-56.43
-56.74
0.61
0.39
-55.8
-55.9
-56.0
-56.1
-56.2
-56.3
-56.4
-56.5
-56.6
-56.7
-56.8
-56.9
-57.0
-57.1
-57.2
-57.3
f1 (ppm)

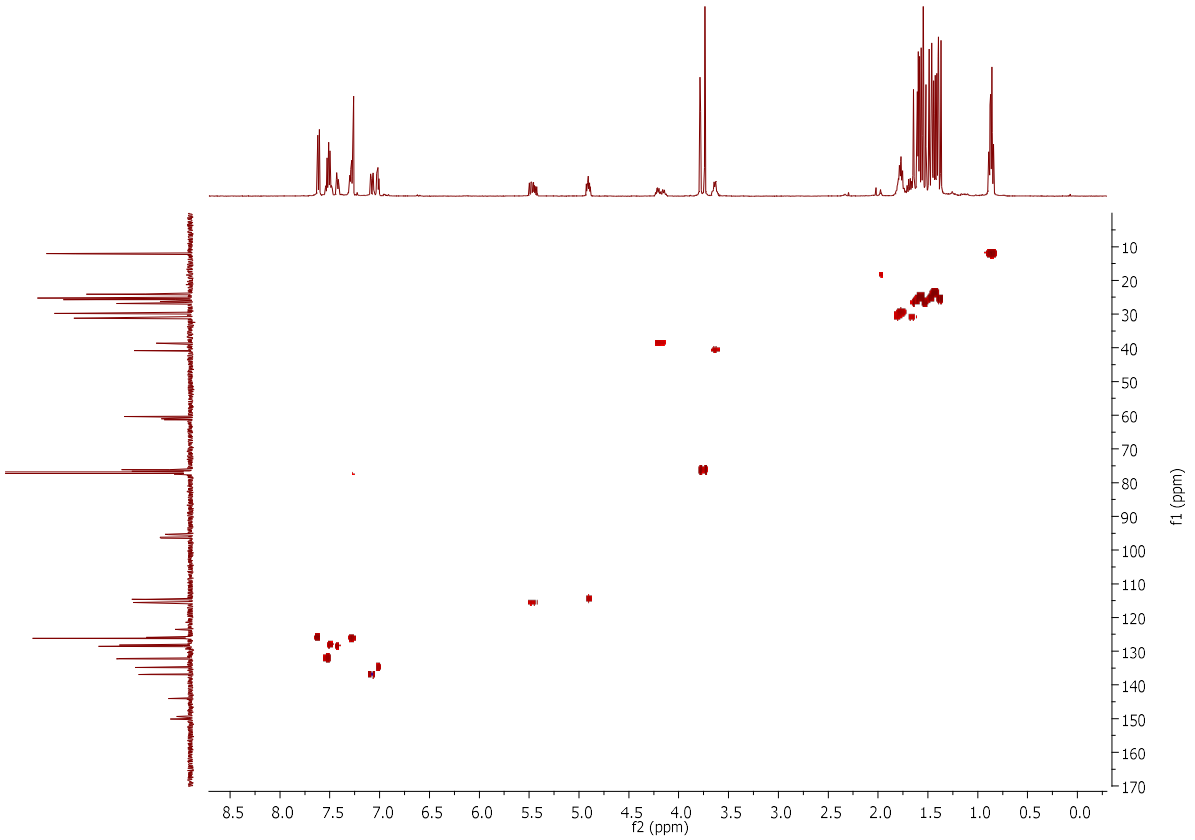
3-(2-(trifluoromethoxy)phenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.32b** :

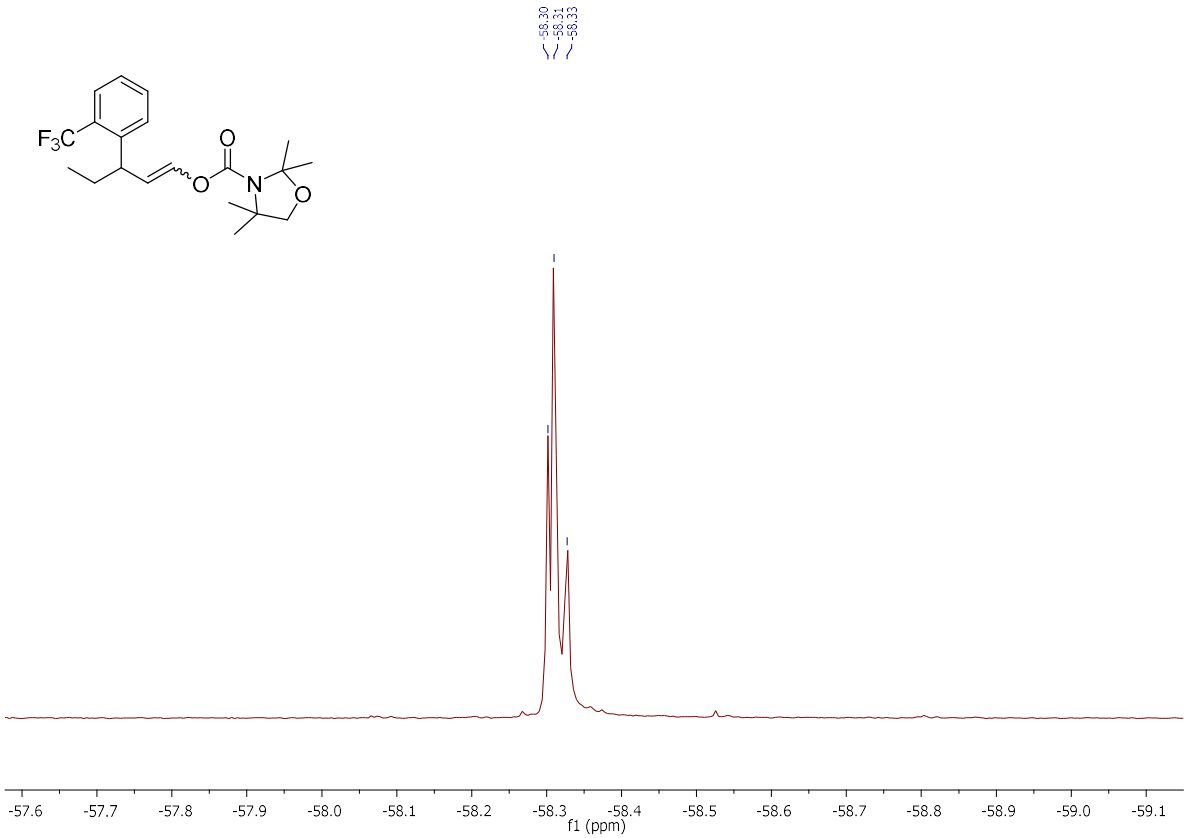




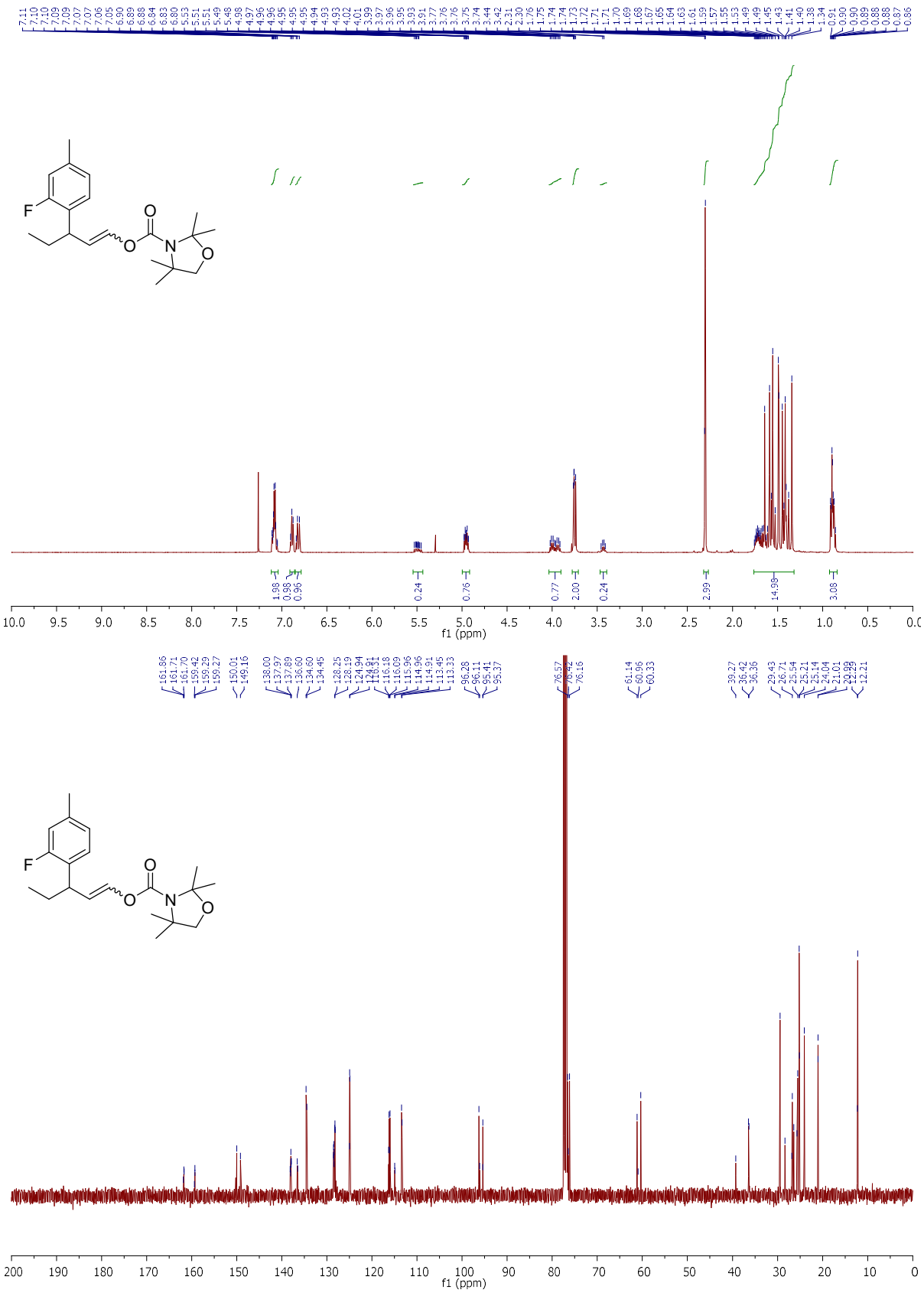
COSY and HMQC experiments :



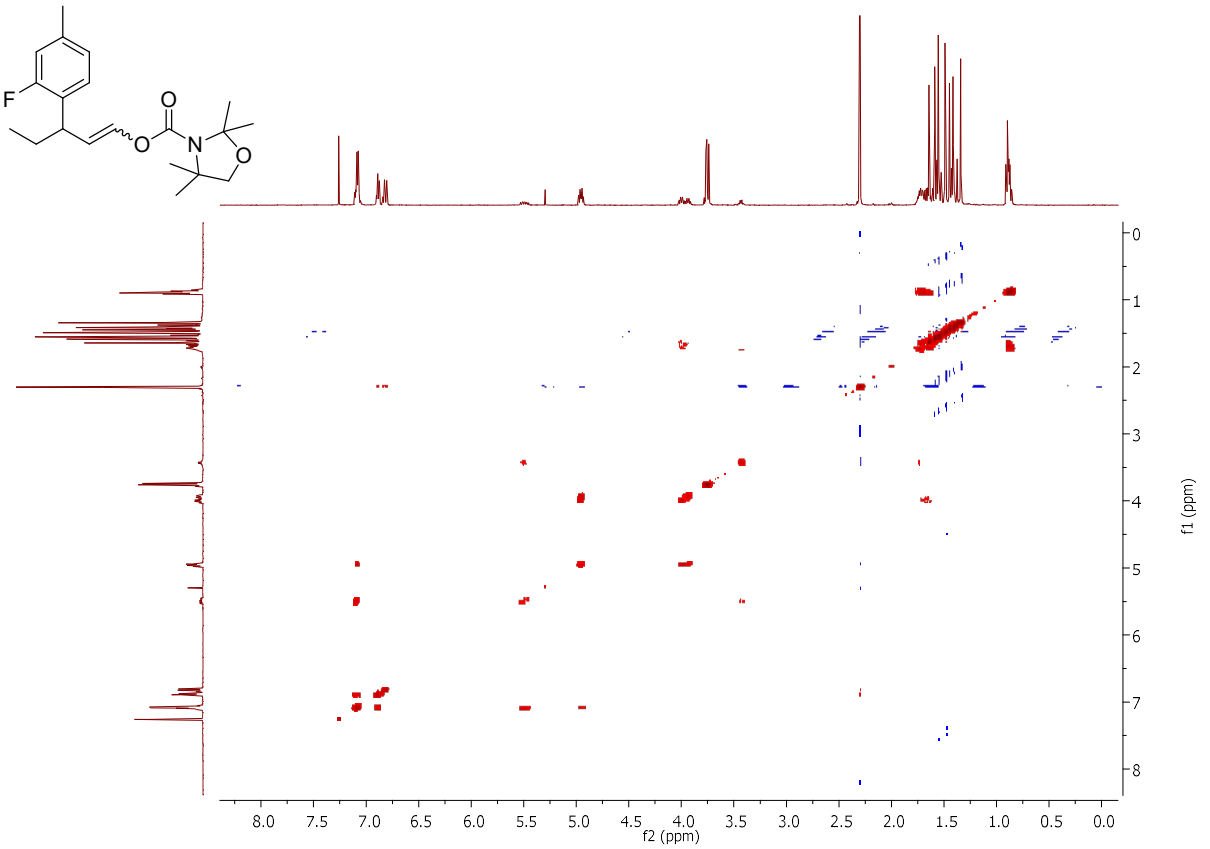


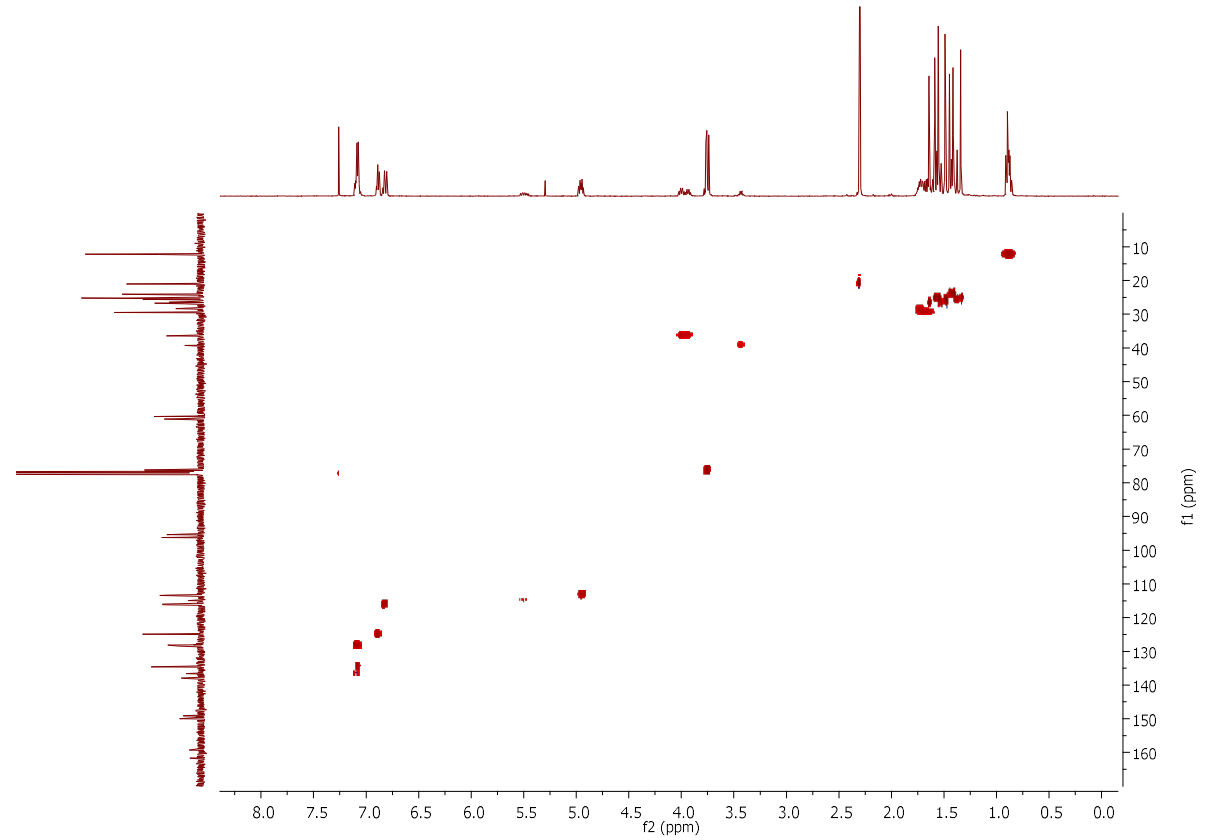

-58.30
-58.31
-58.33
F3C
O
O
N
O
-57.6
-57.7
-57.8
-57.9
-58.0
-58.1
-58.2
-58.3
-58.4
-58.5
-58.6
-58.7
-58.8
-58.9
-59.0
-59.1
f1 (ppm)

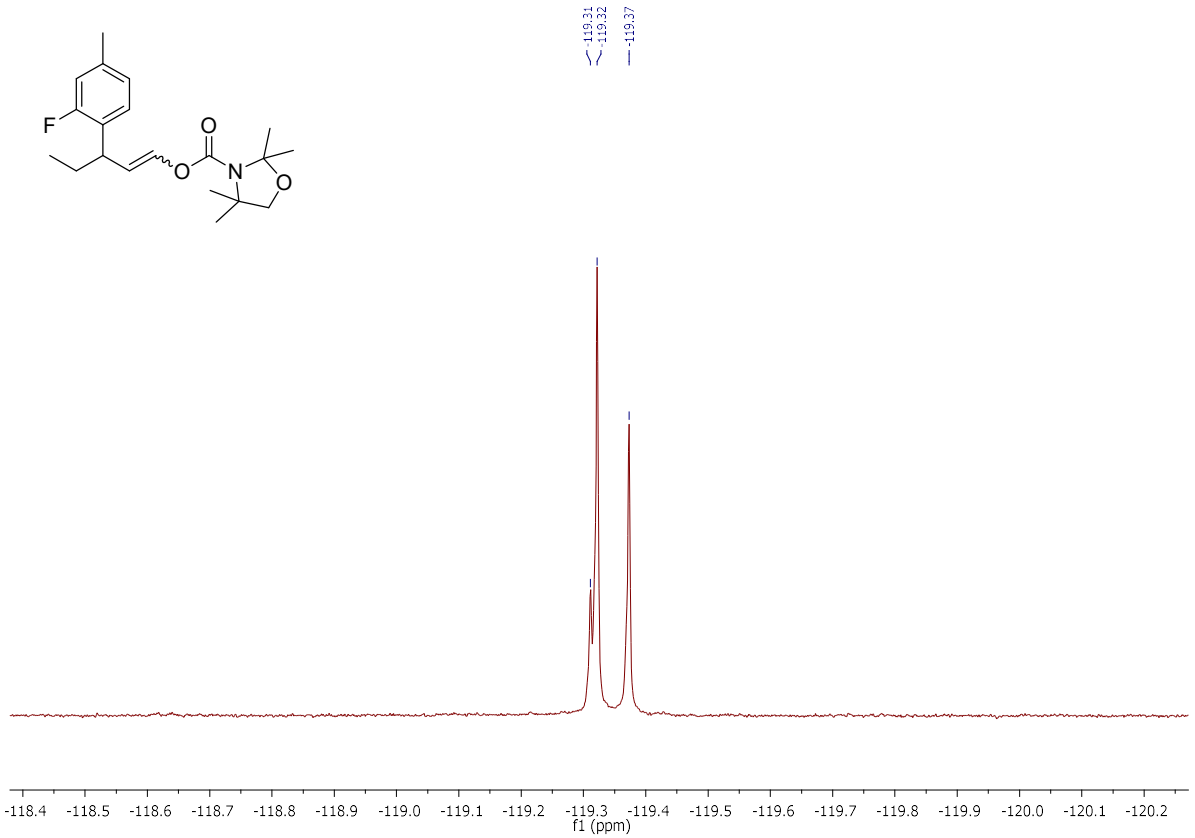
3-(2-fluoro-4-methylphenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.32c** :



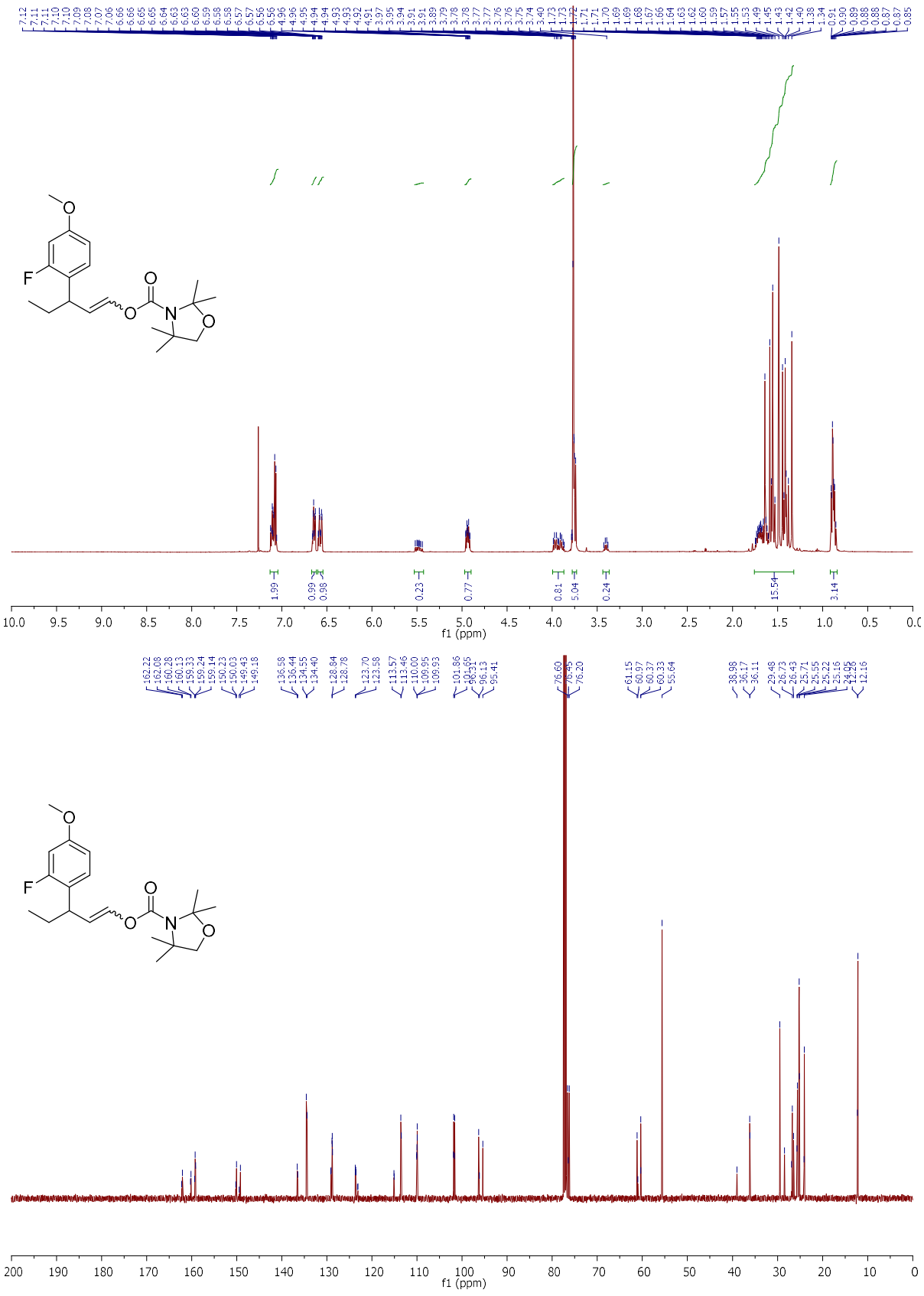
COSY and HMQC experiments :



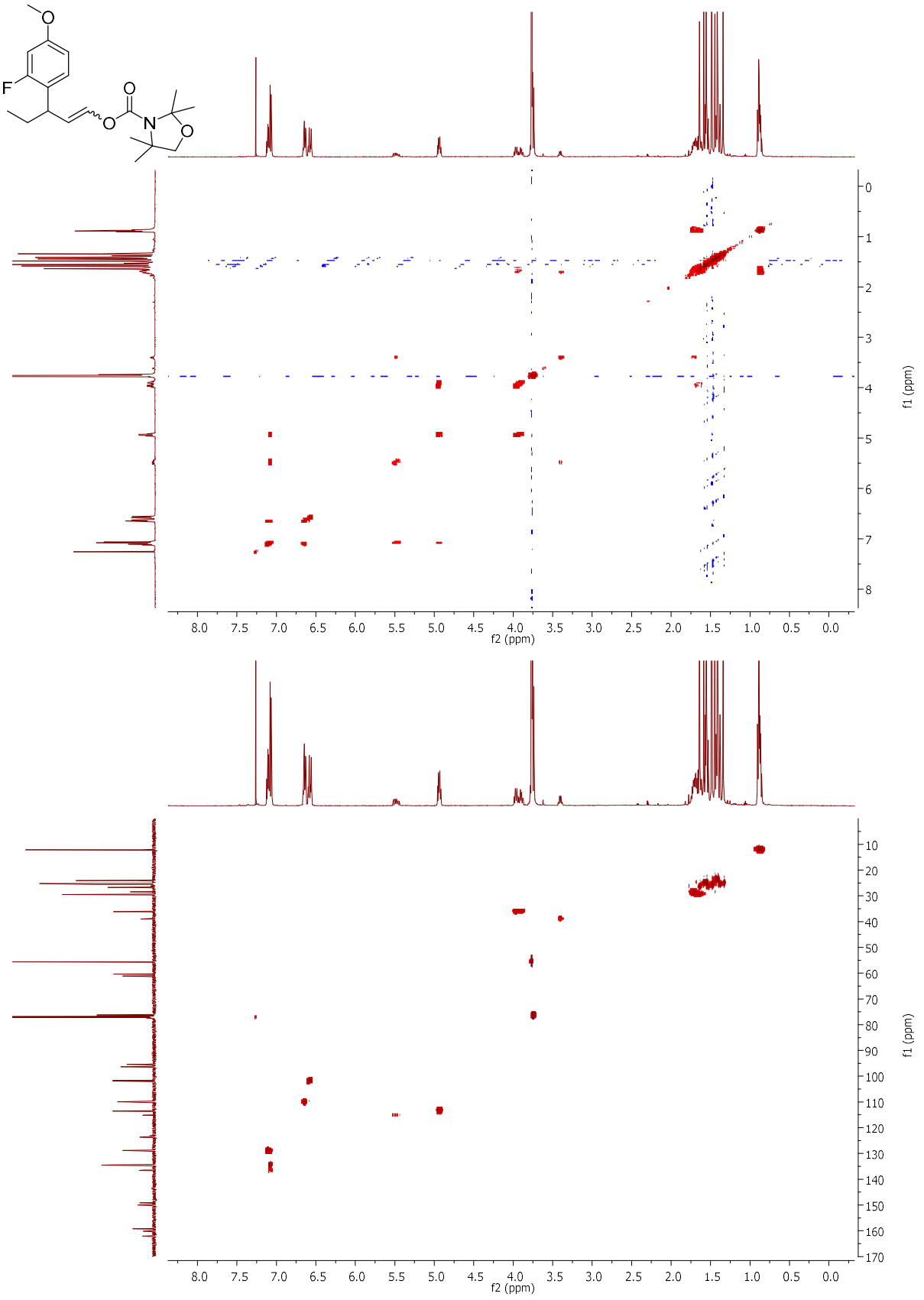


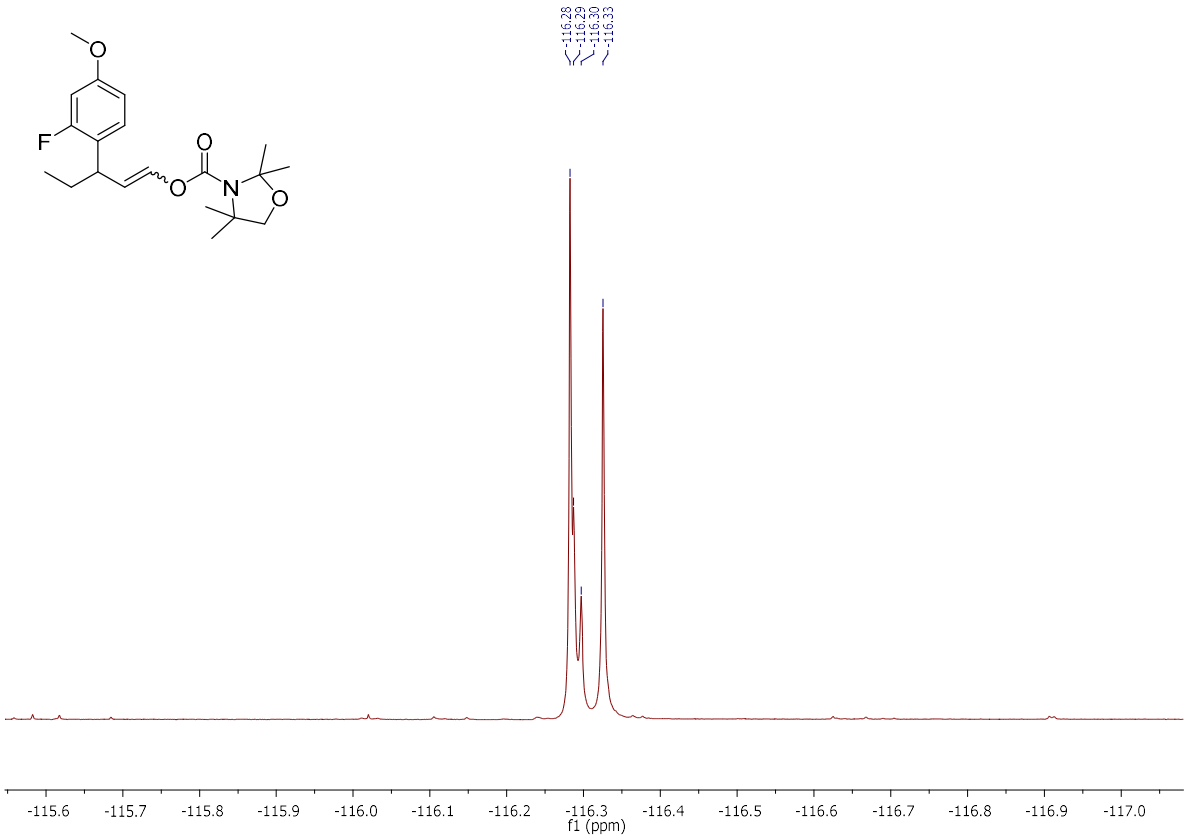

F
O
O
N
O
-119.31
-119.32
-119.37
-118.4
-118.5
-118.6
-118.7
-118.8
-118.9
-119.0
-119.1
-119.2
-119.3
-119.4
-119.5
-119.6
-119.7
-119.8
-119.9
-120.0
-120.1
-120.2
f1 (ppm)

3-(2-fluoro-4-methoxyphenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.32d** :



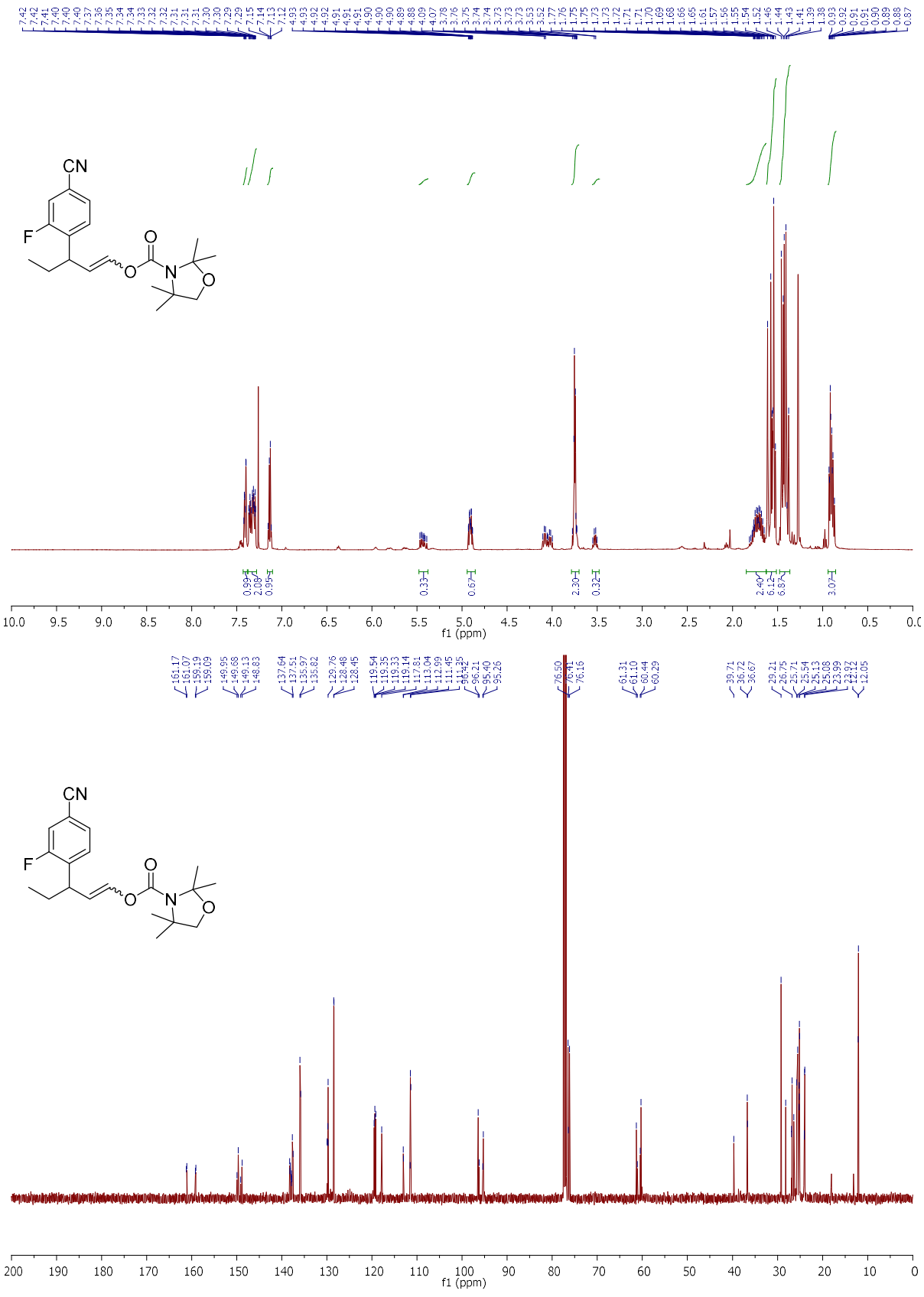
COSY and HMQC experiments :



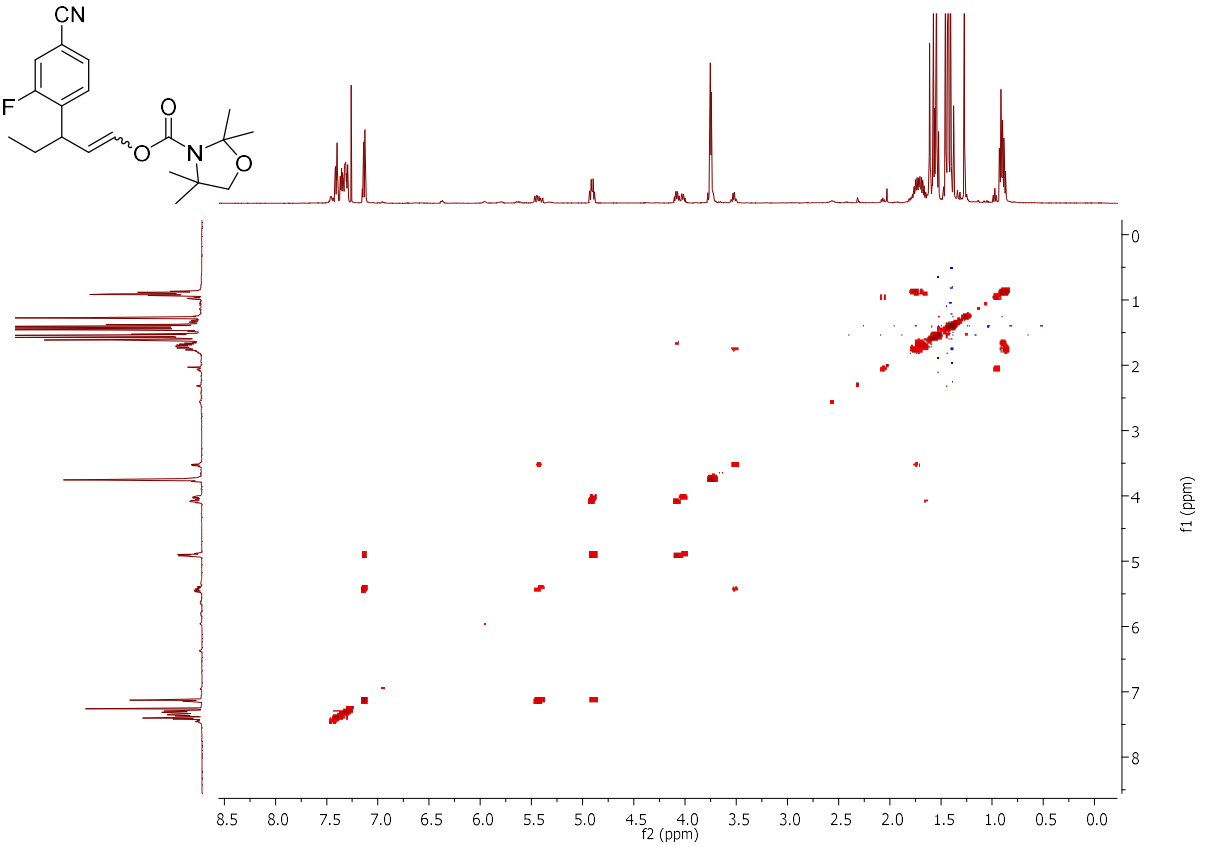

-116.28
-116.29
-116.30
-116.33
O
F
O
O
N
O
-115.6
-115.7
-115.8
-115.9
-116.0
-116.1
-116.2
-116.3
-116.4
-116.5
-116.6
-116.7
-116.8
-116.9
-117.0
f1 (ppm)

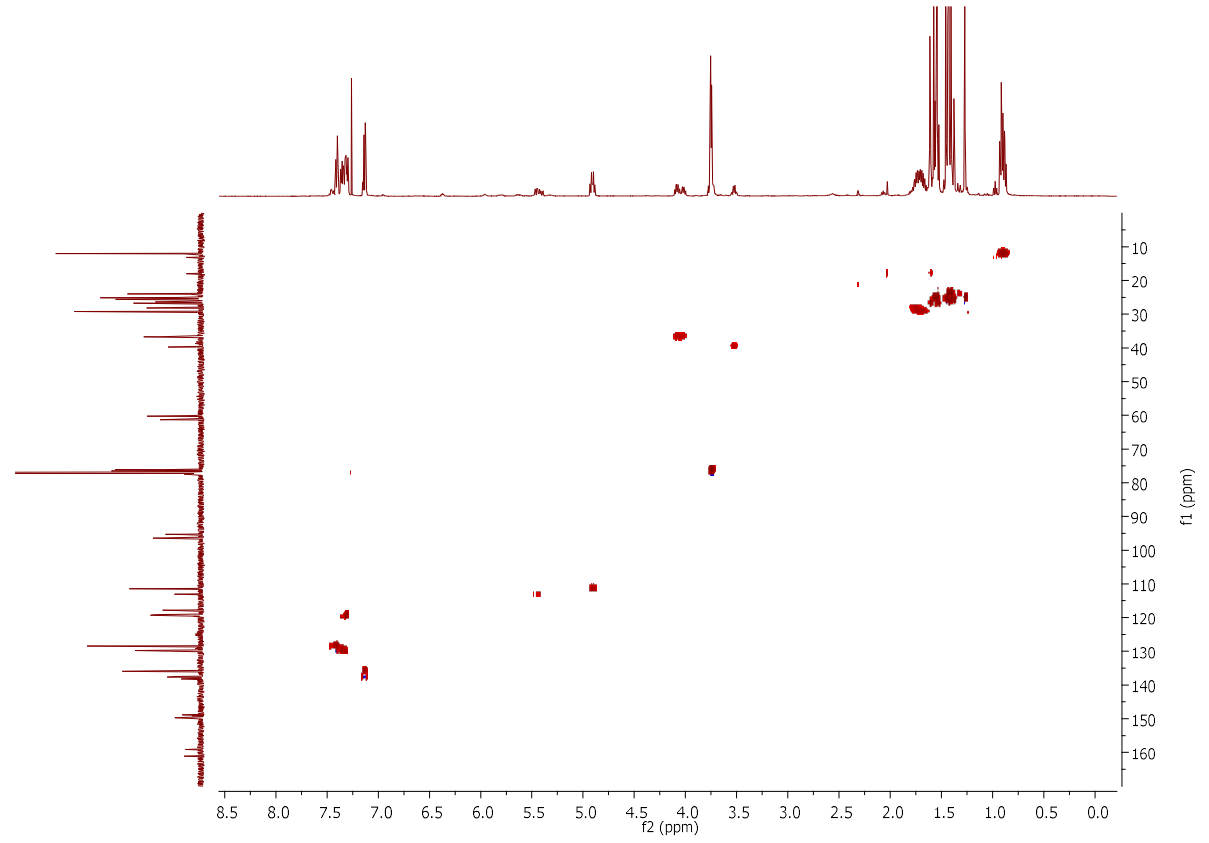
3-(4-cyano-2-fluorophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate

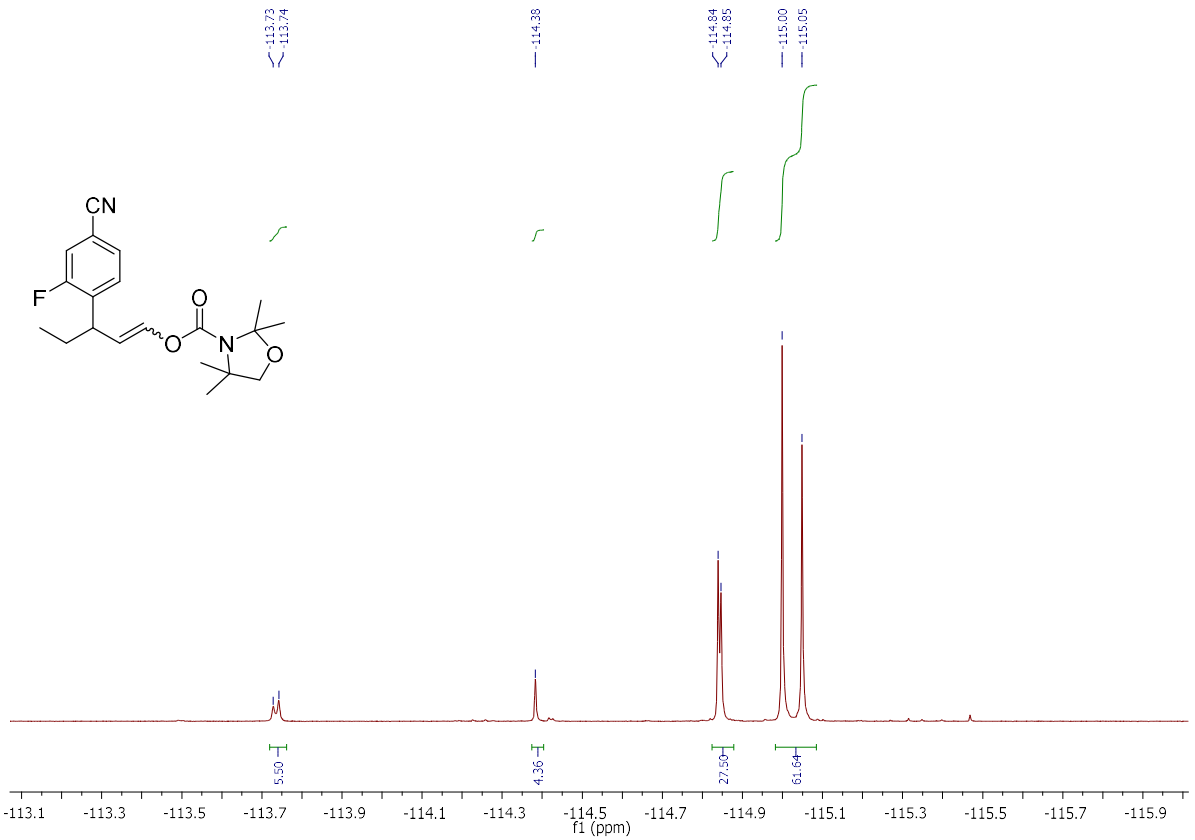
2.32e :



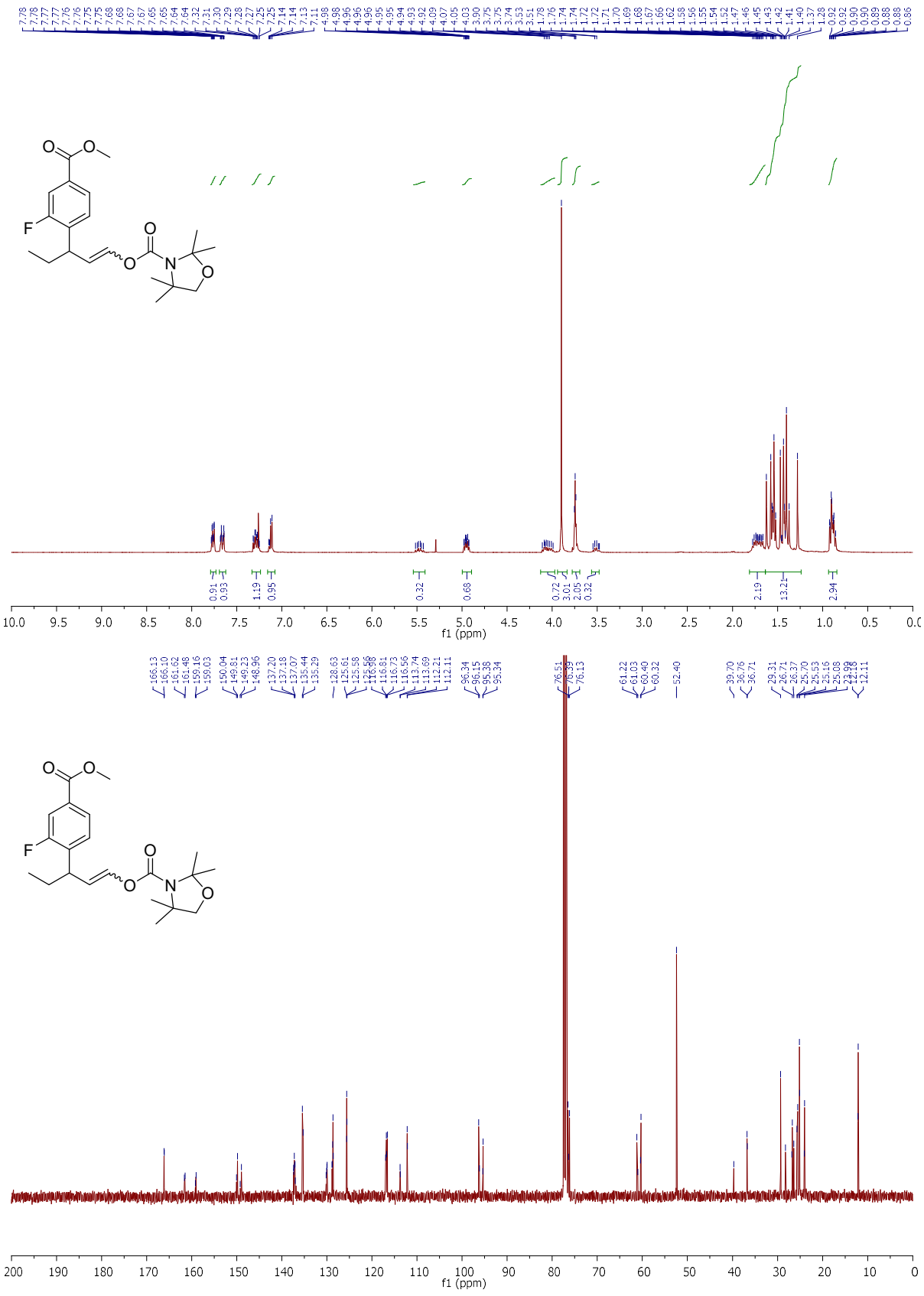
COSY and HMQC experiments :



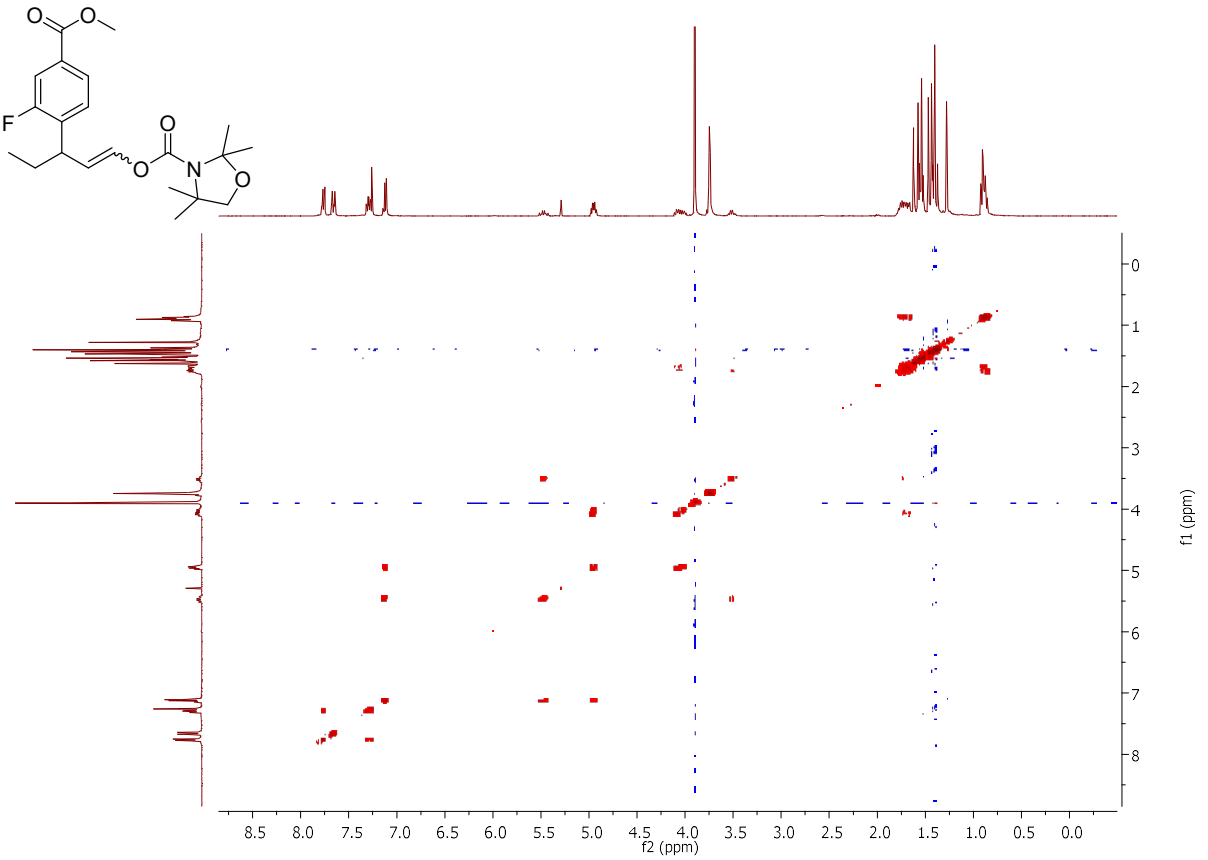


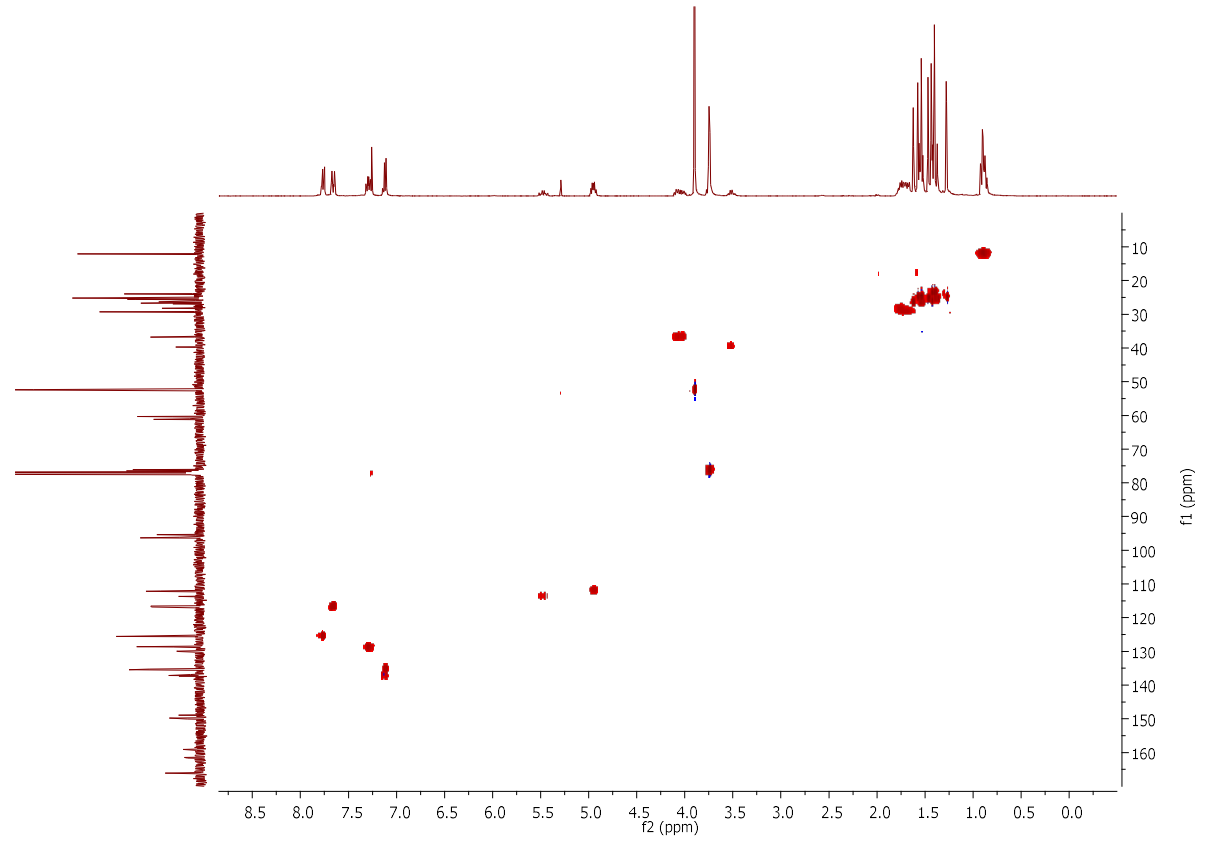

-113.73
-113.74
-114.38
-114.84
-114.85
-115.00
-115.05
CN
F
O
O
N
O
5.50
4.36
27.50
61.64
-113.1
-113.3
-113.5
-113.7
-113.9
-114.1
-114.3
-114.5
-114.7
-114.9
-115.1
-115.3
-115.5
-115.7
-115.9
f1 (ppm)

3-(2-fluoro-4-(methoxycarbonyl)phenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.32f** :

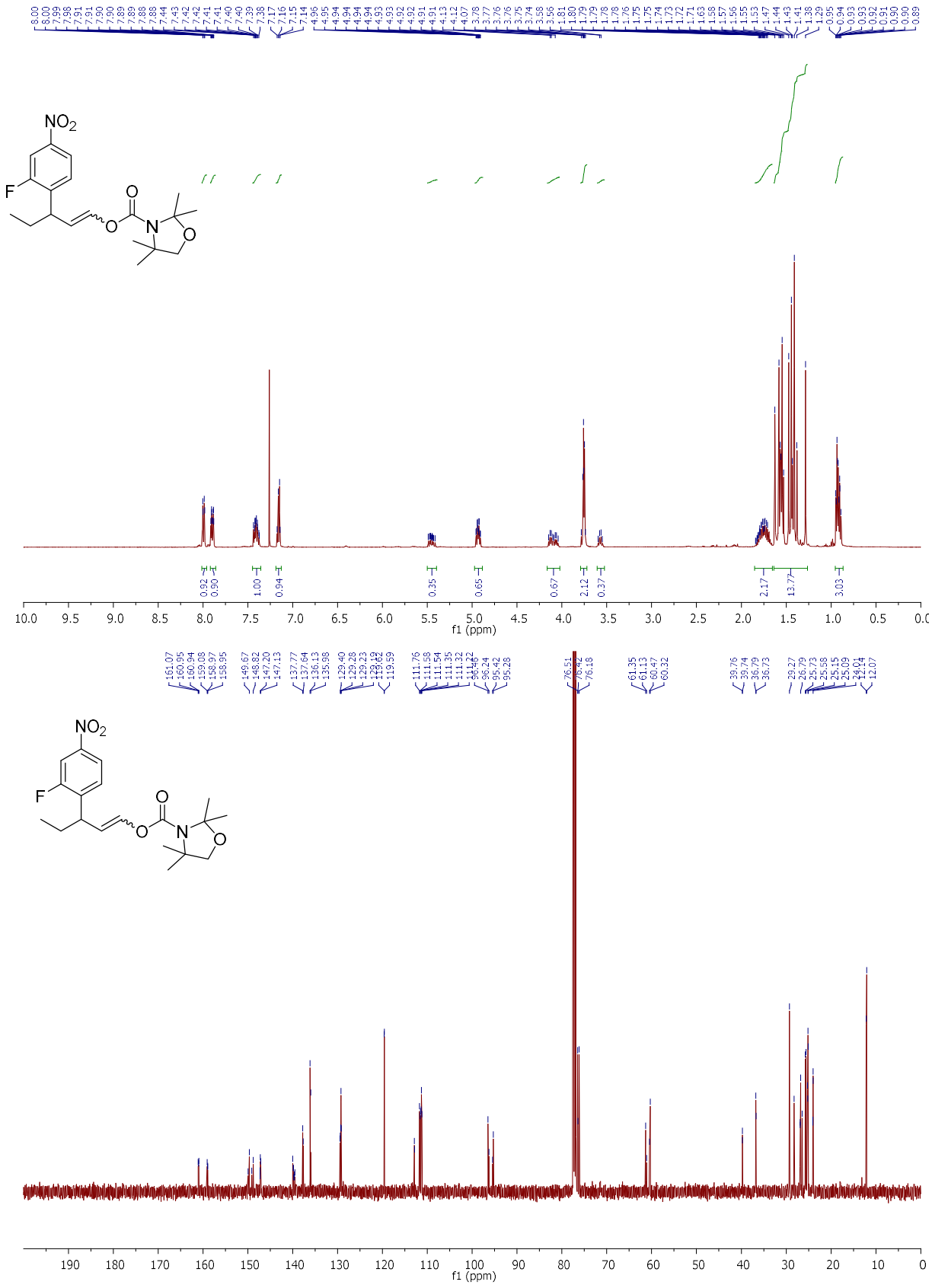


COSY and HMQC experiments :

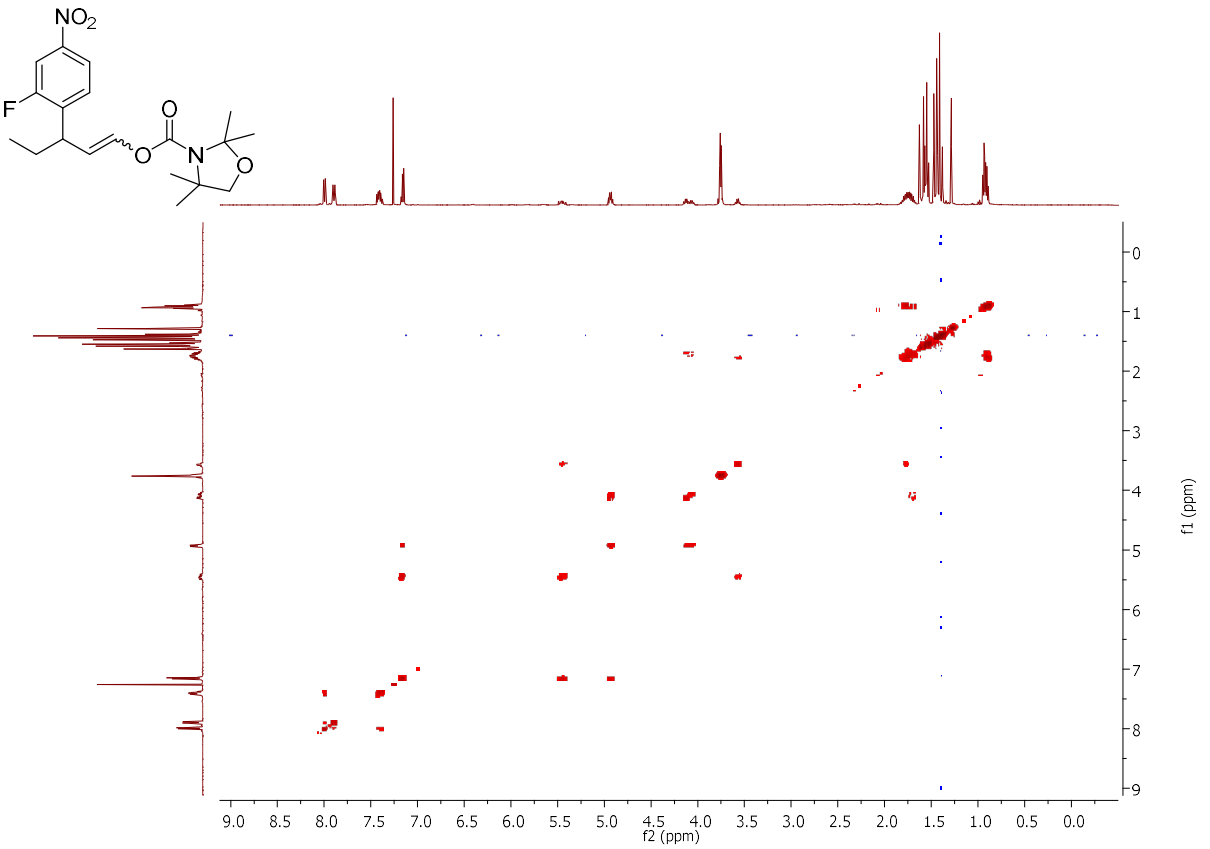


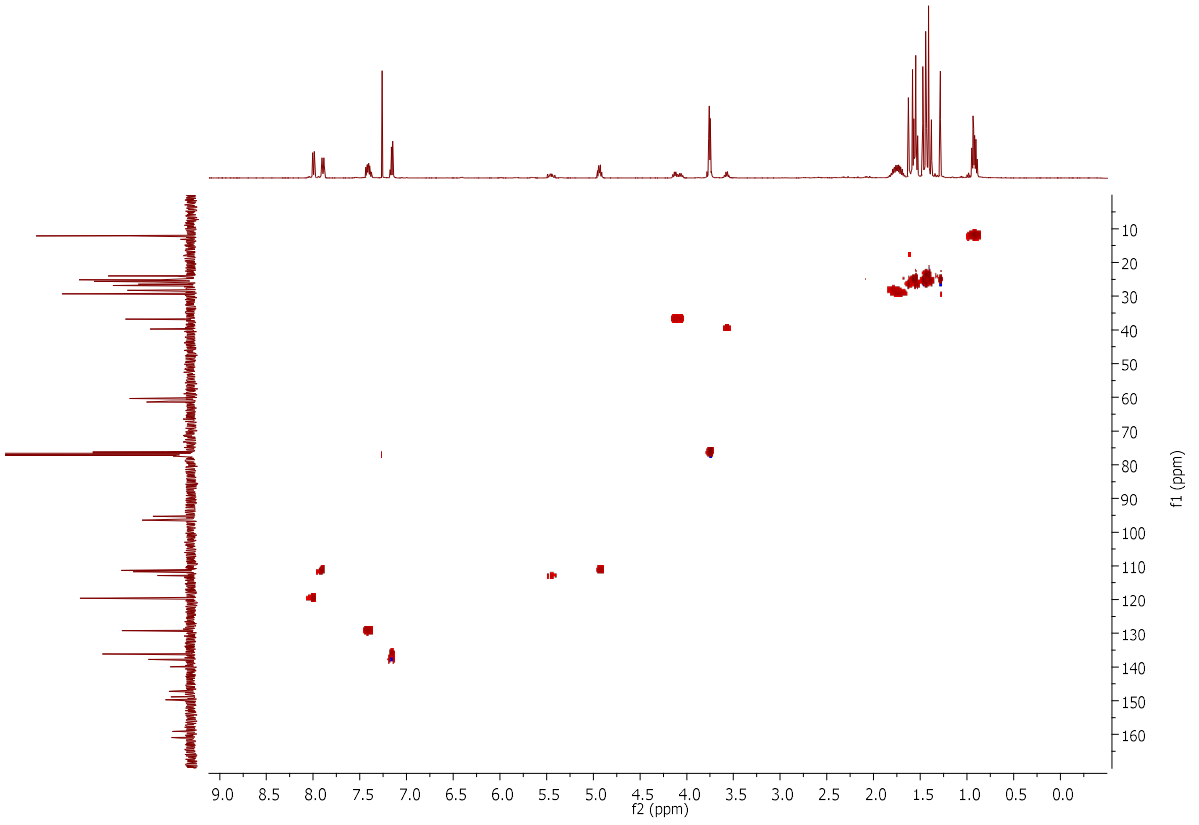


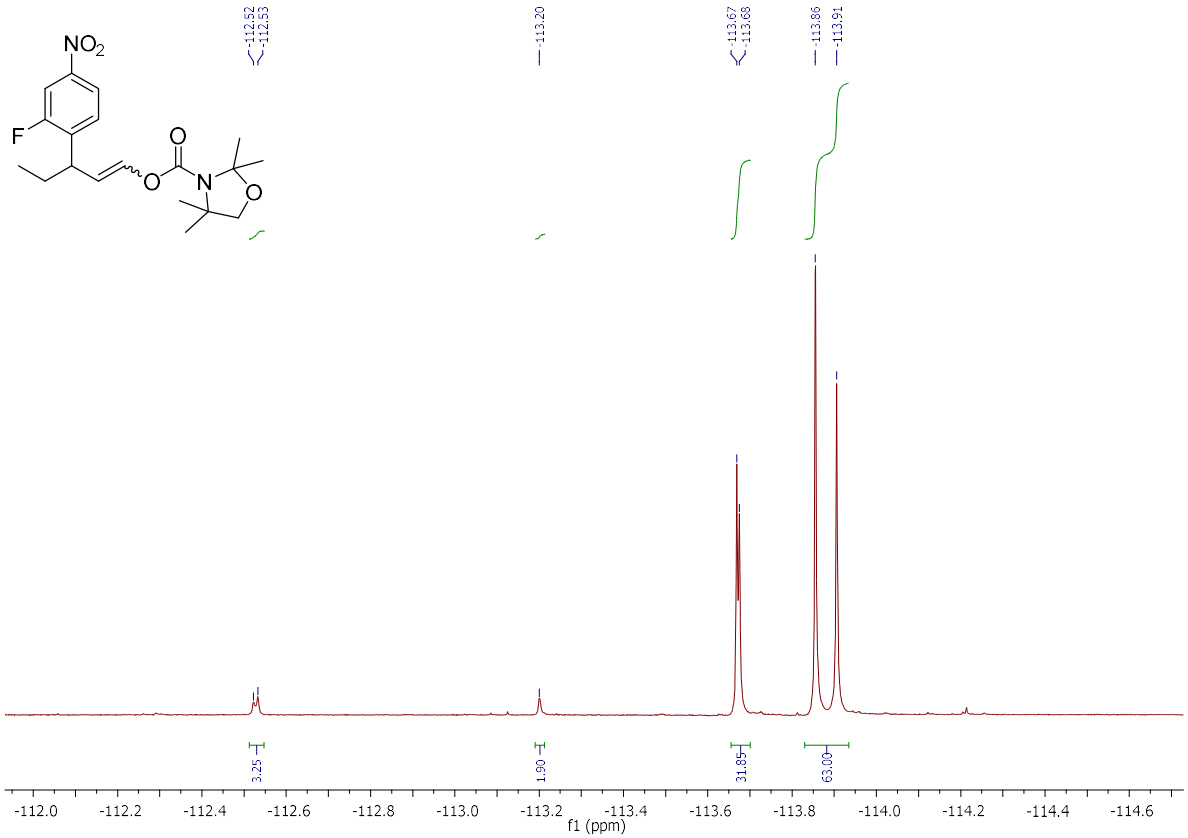
3-(2-fluoro-4-nitrophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.32g** :



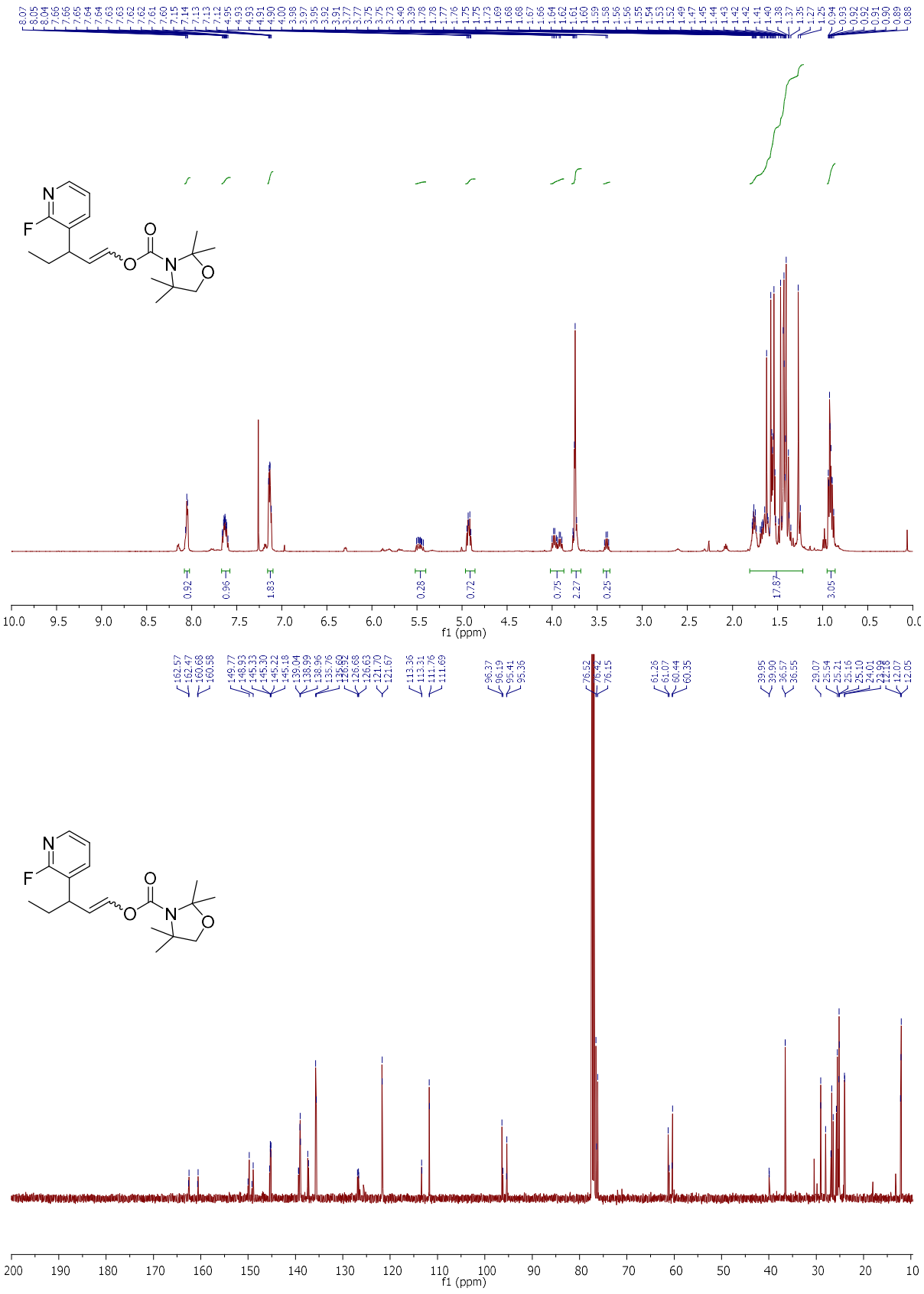
COSY and HMQC experiments :



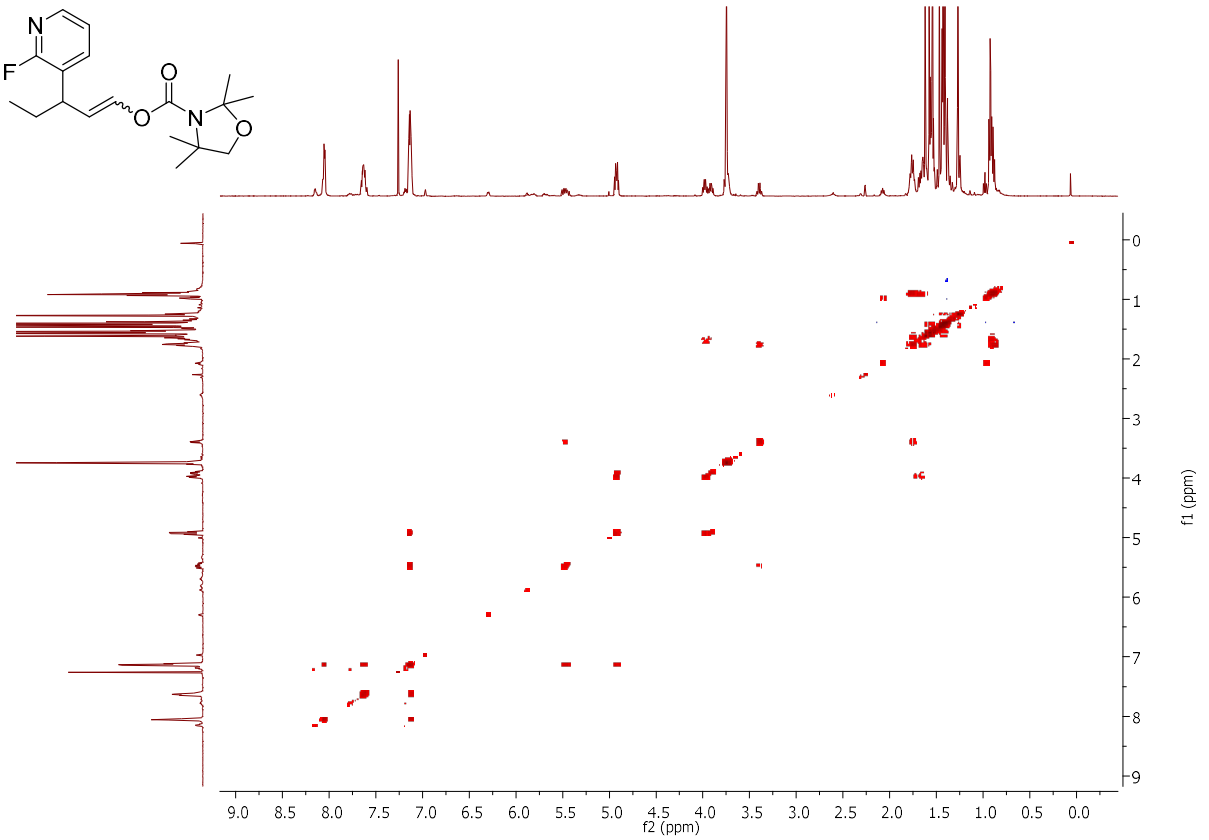


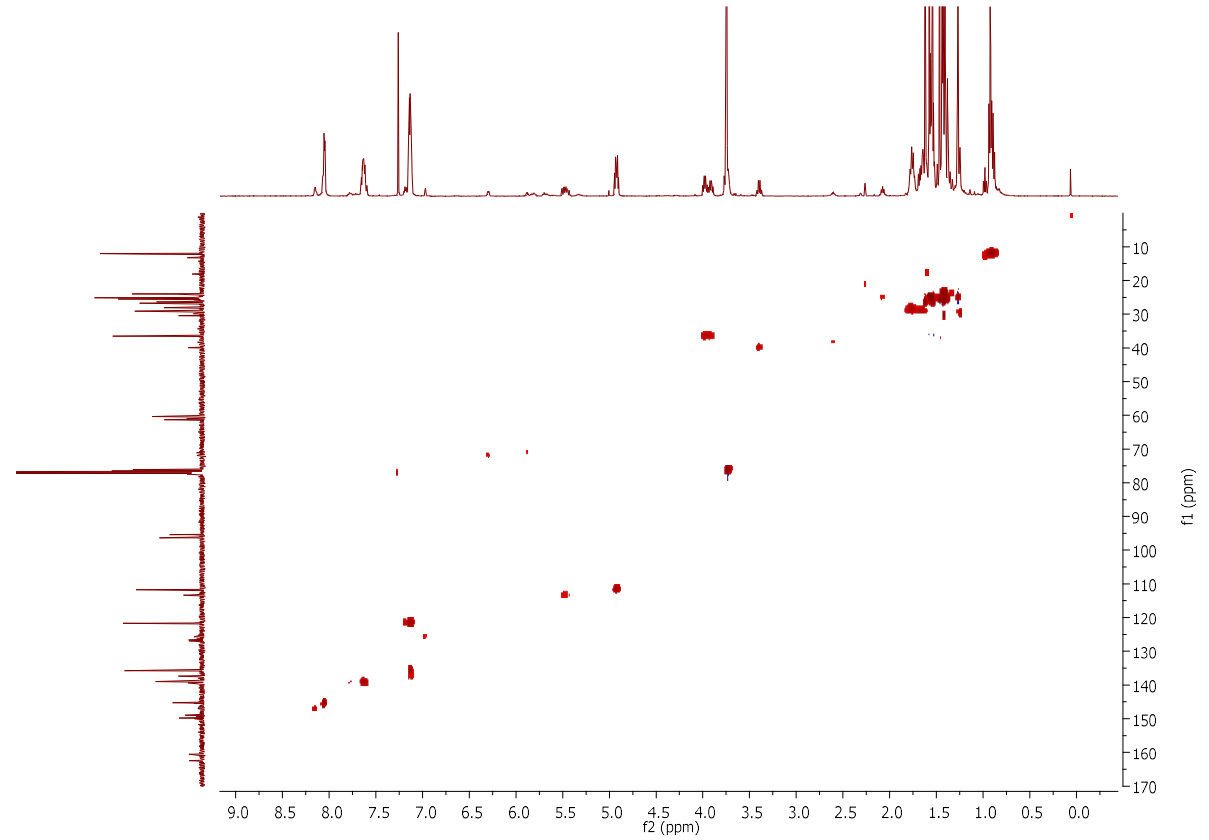

NO2
F
O
O
N
O
-112.52
-112.53
-113.20
-113.67
-113.68
-113.86
-113.91
3.25
1.90
31.85
63.00
-112.0
-112.2
-112.4
-112.6
-112.8
-113.0
-113.2
-113.4
-113.6
-113.8
-114.0
-114.2
-114.4
-114.6
f1 (ppm)

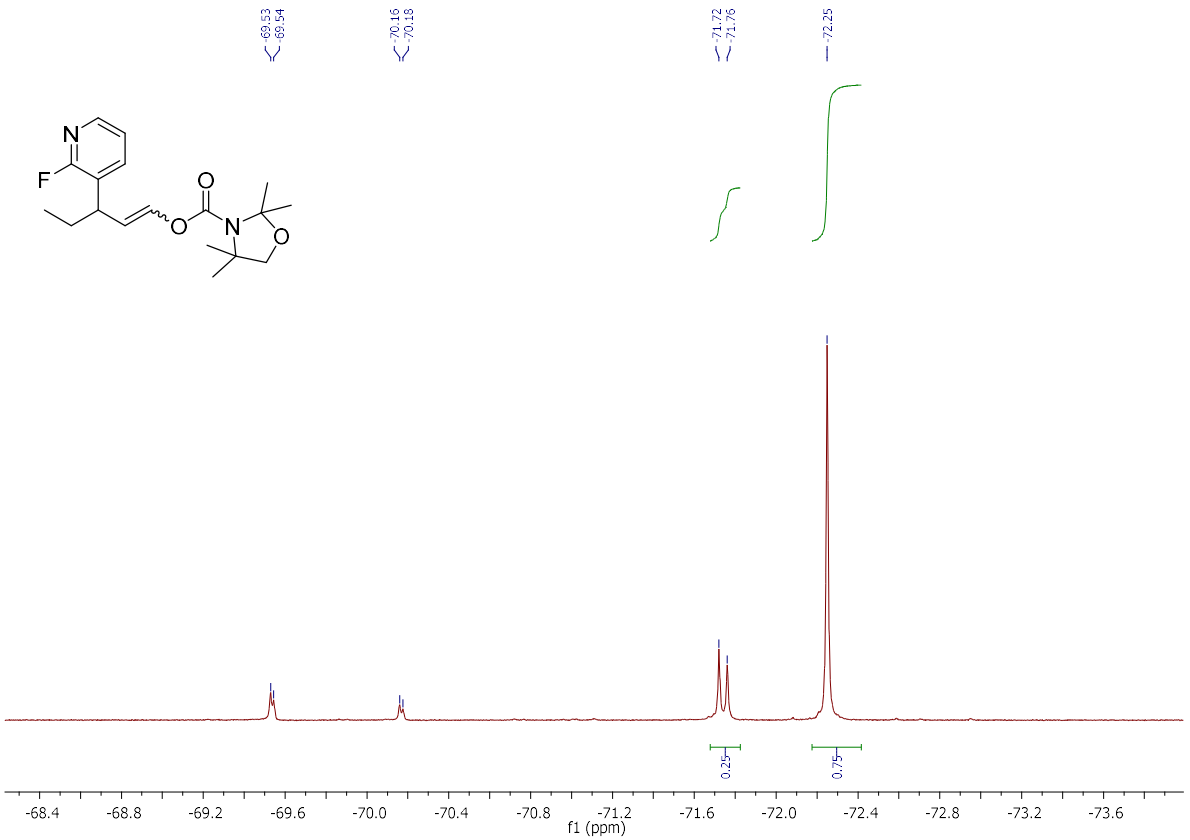
3-(2-fluoropyridin-3-yl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.32h** :



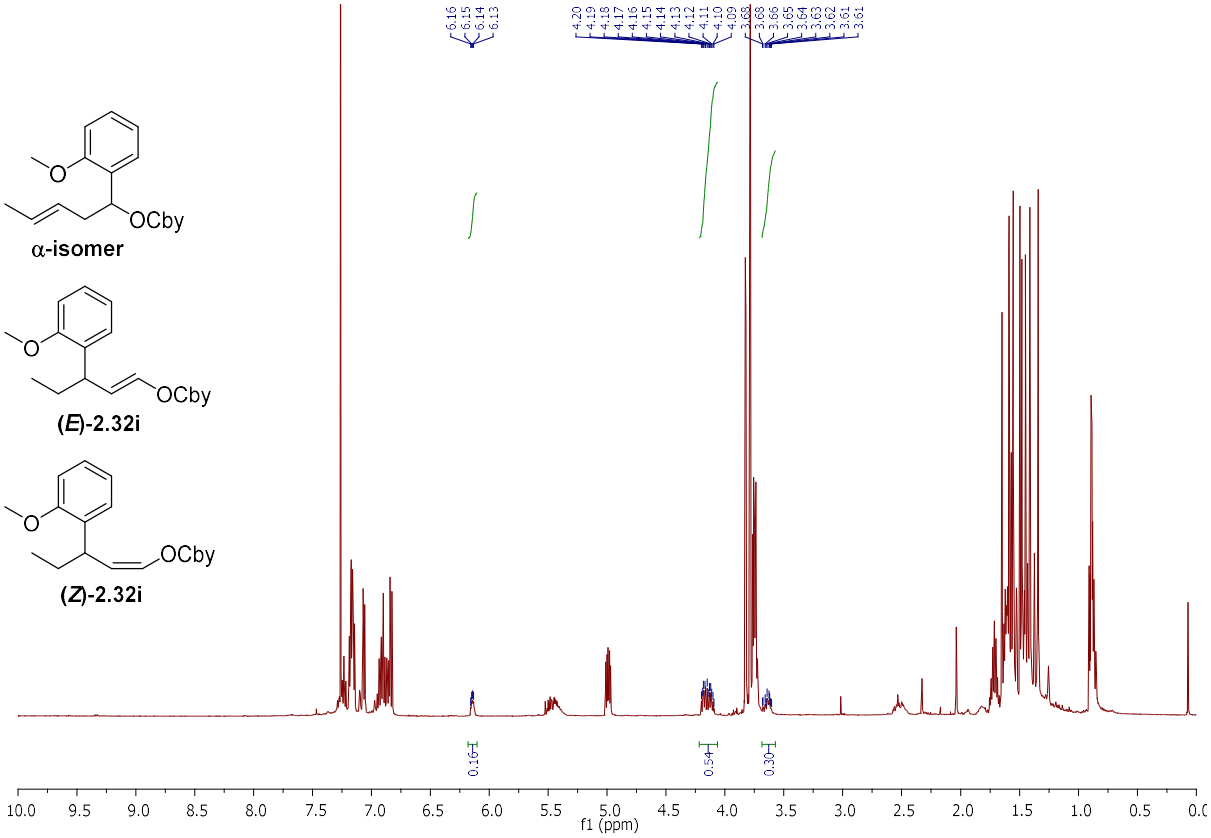
COSY and HMQC experiments :

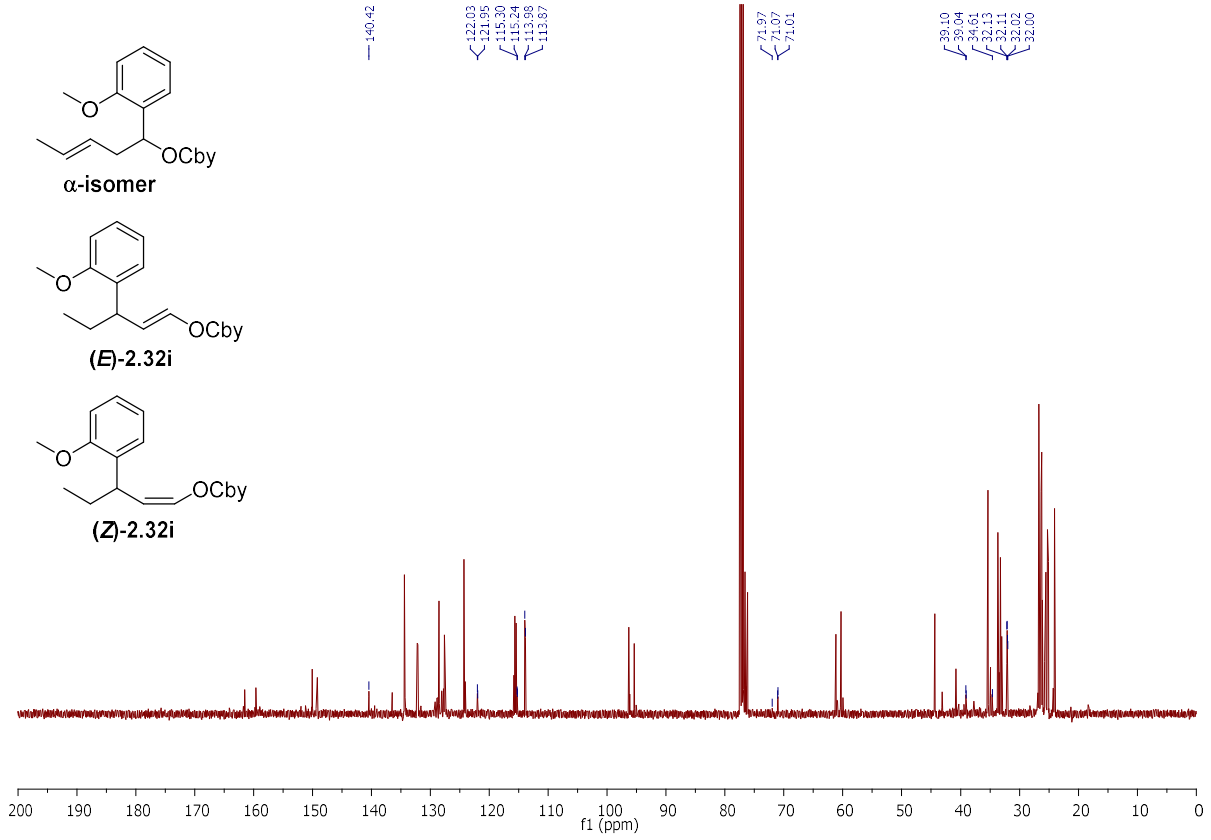


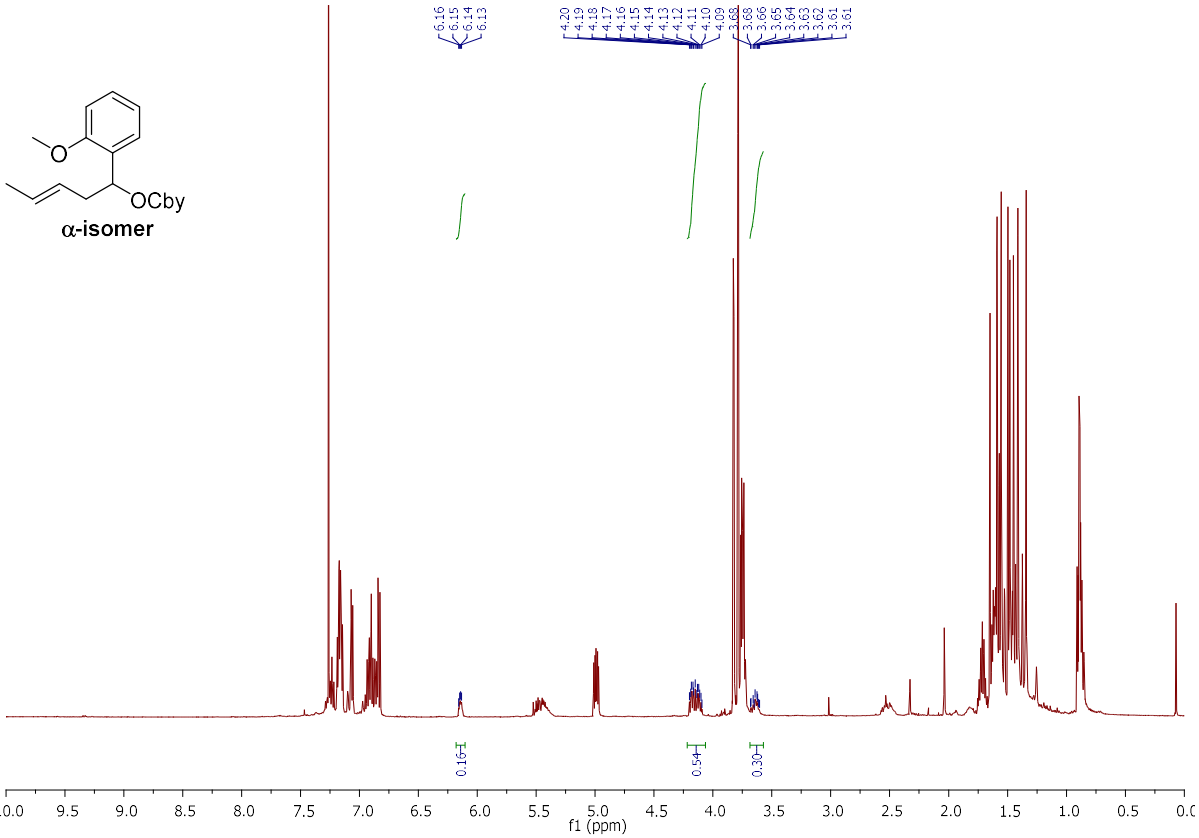


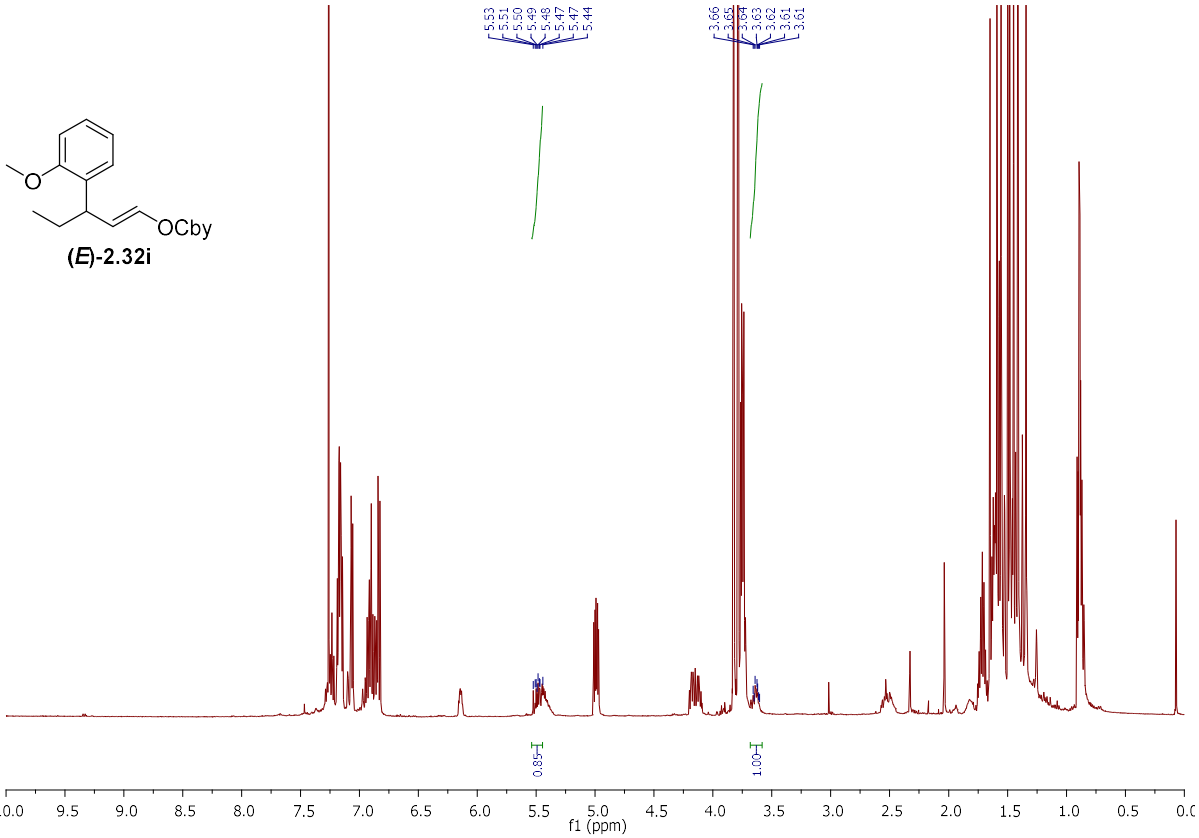

-69.53
-69.54
-70.16
-70.18
-71.72
-71.76
-72.25
N
F
O
O
N
O
0.25
0.75
-68.4
-68.8
-69.2
-69.6
-70.0
-70.4
-70.8
-71.2
-71.6
-72.0
-72.4
-72.8
-73.2
-73.6
f1 (ppm)

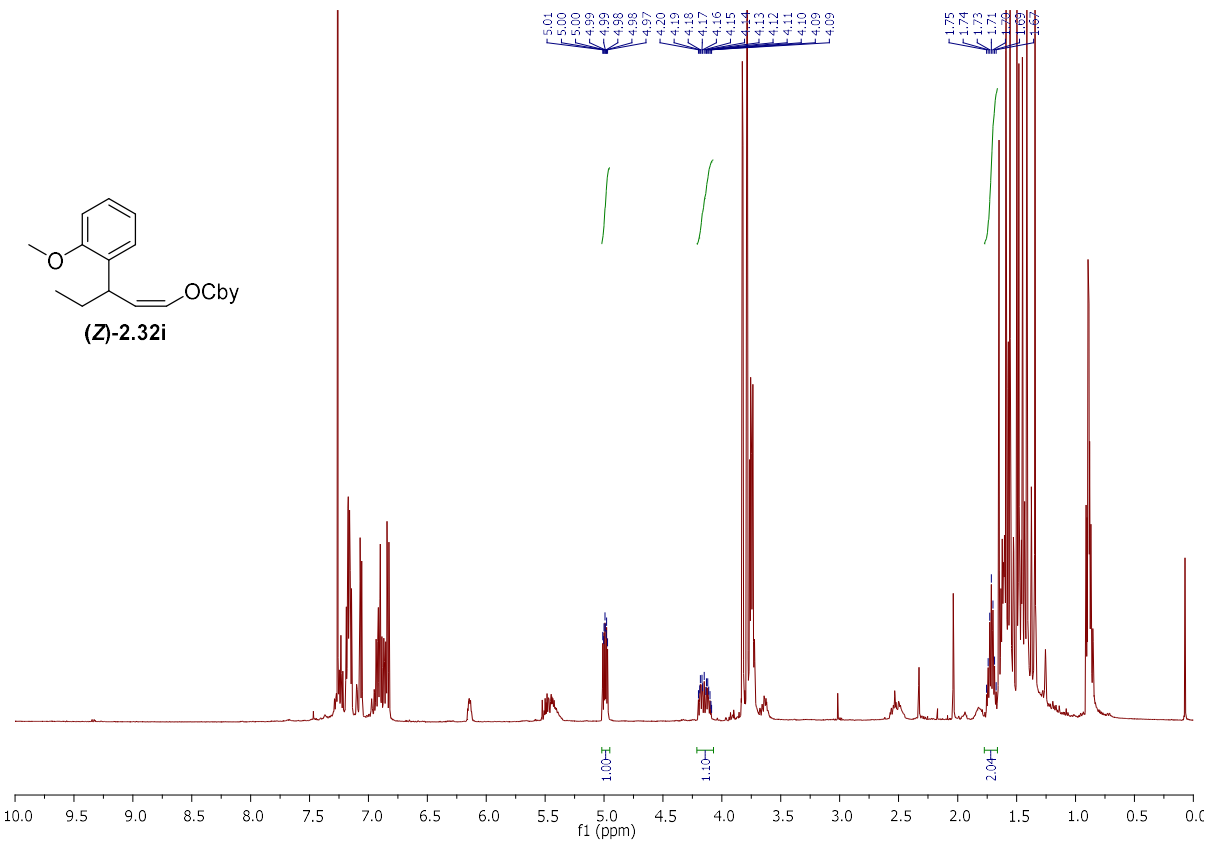
Arylation of **(*E*)-2.21** with 2-bromoanisole : product **2.32i** and isomers



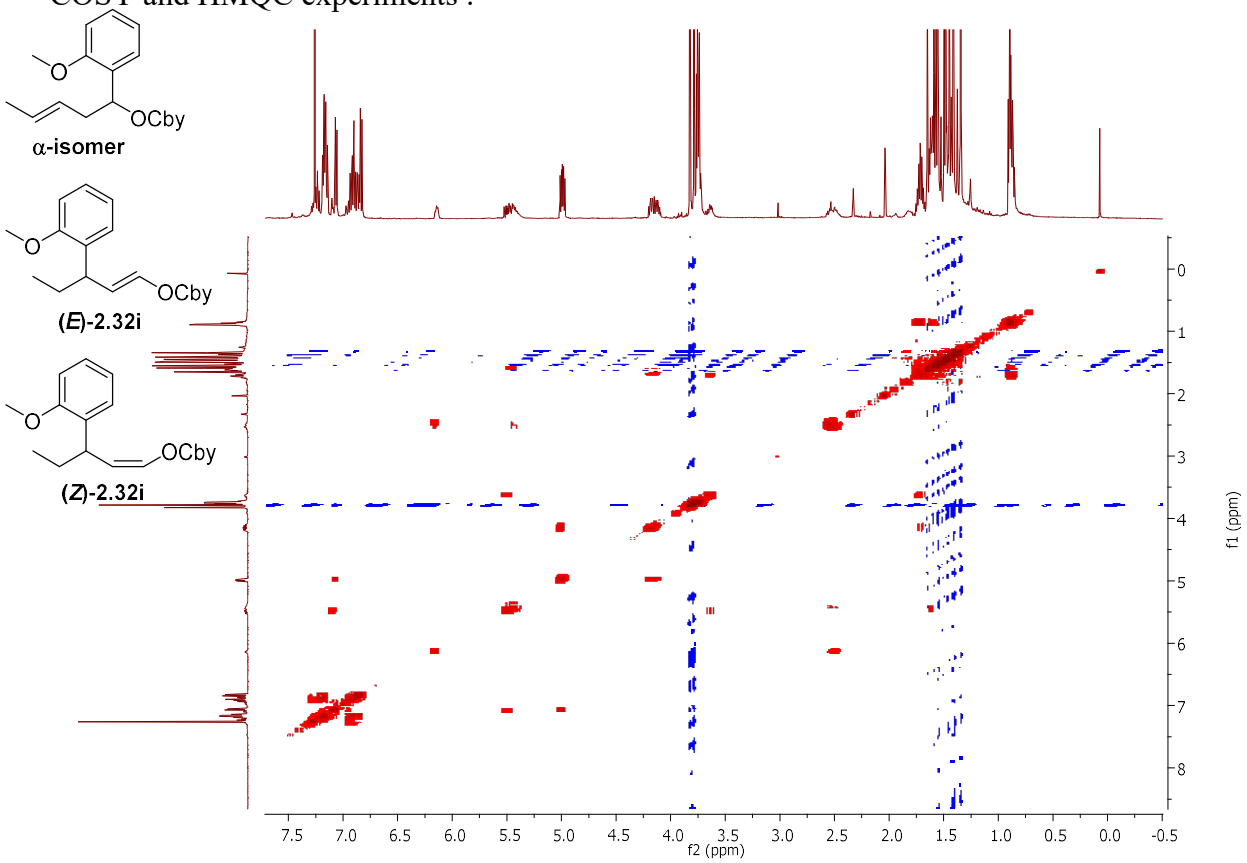


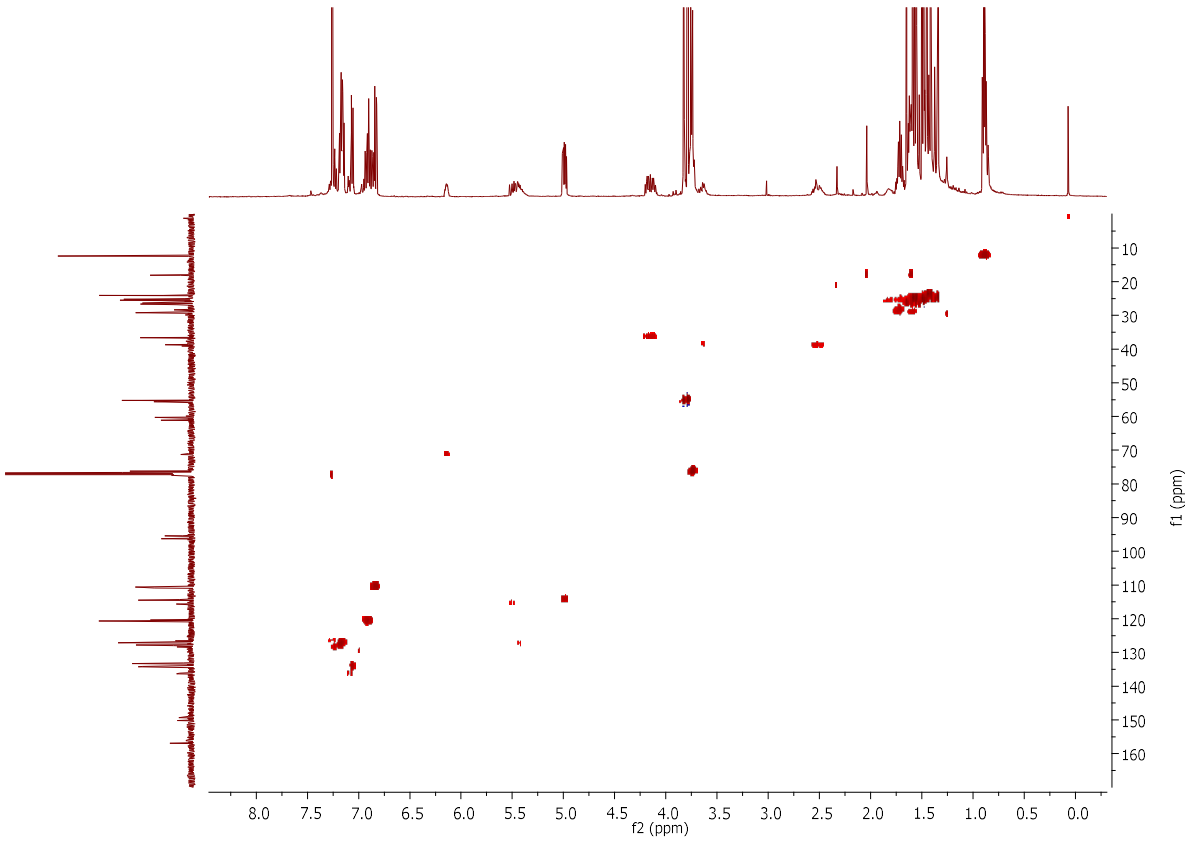

OCby
α-isomer
f1 (ppm)


OCby
(E)-2.32i
f1 (ppm)

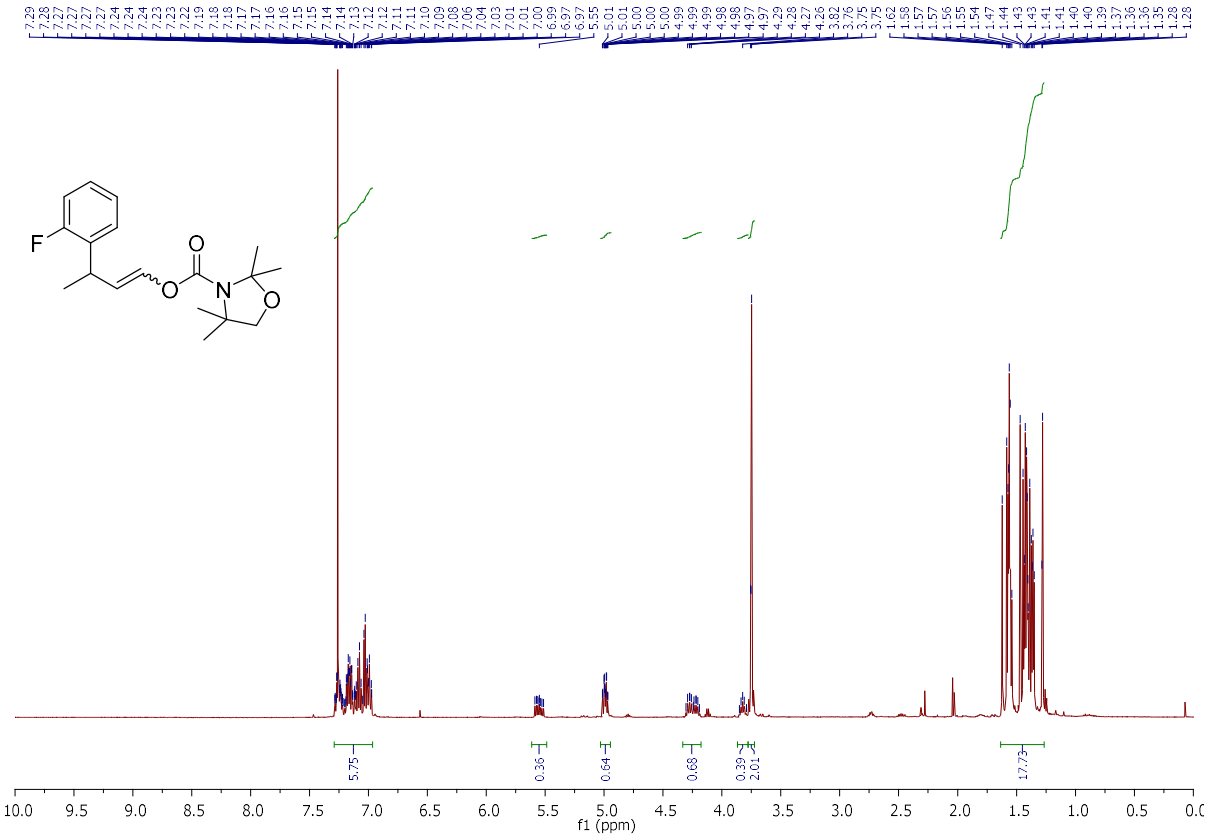

O
OCby
(Z)-2.32i
5.01
5.00
5.00
4.99
4.99
4.98
4.98
4.97
4.20
4.19
4.18
4.17
4.17
4.16
4.15
4.14
4.13
4.12
4.11
4.10
4.09
4.09
1.75
1.74
1.73
1.71
1.00
1.10
2.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

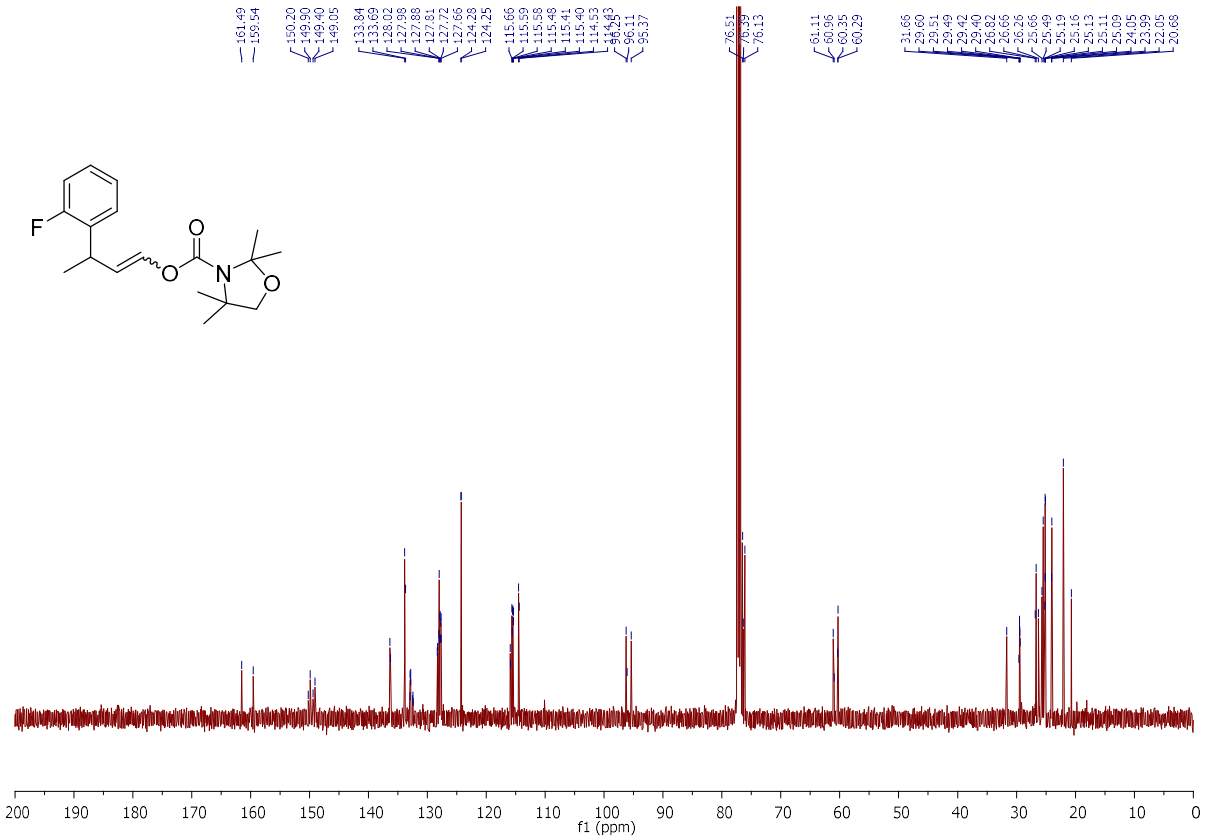
COSY and HMQC experiments :



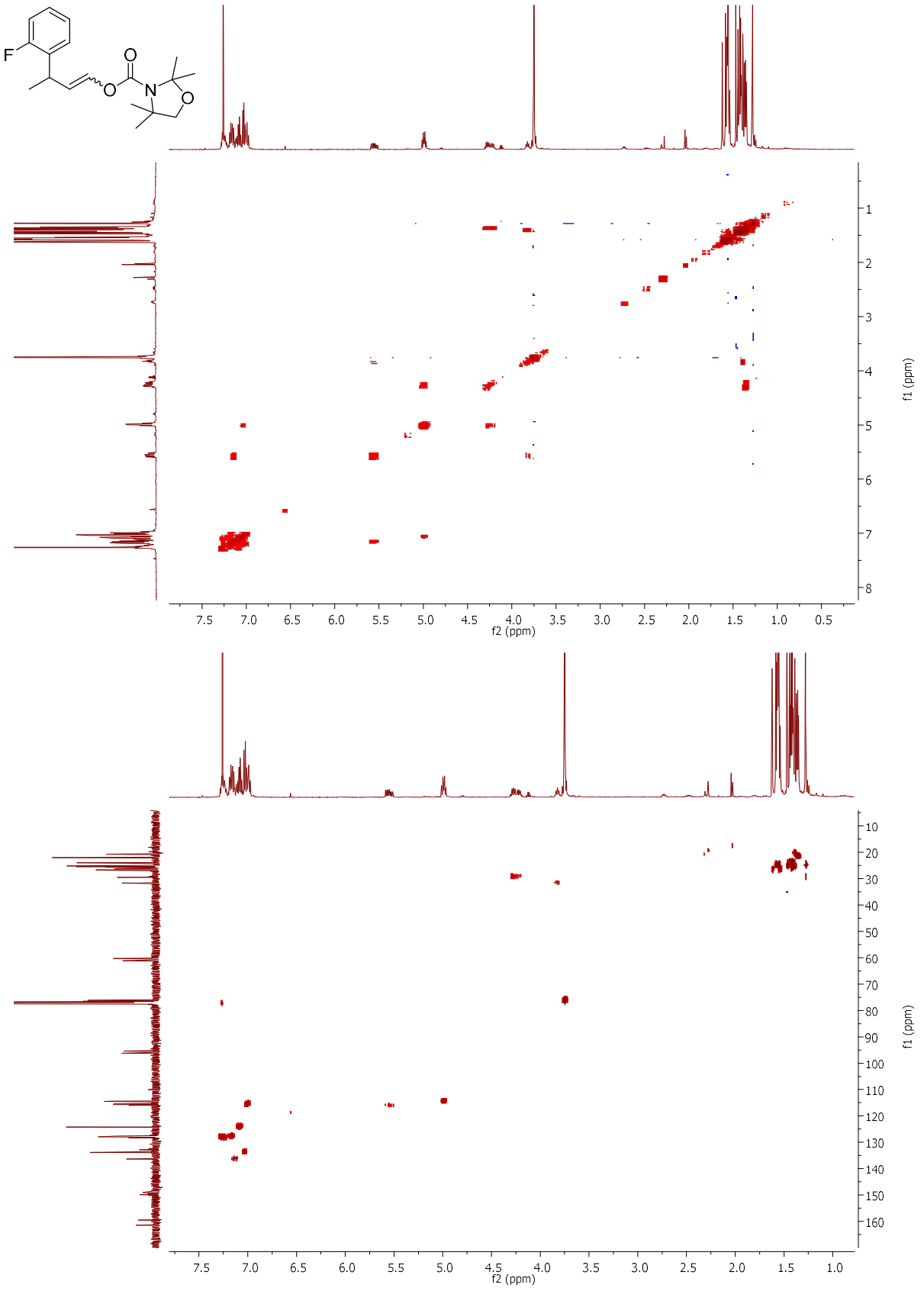


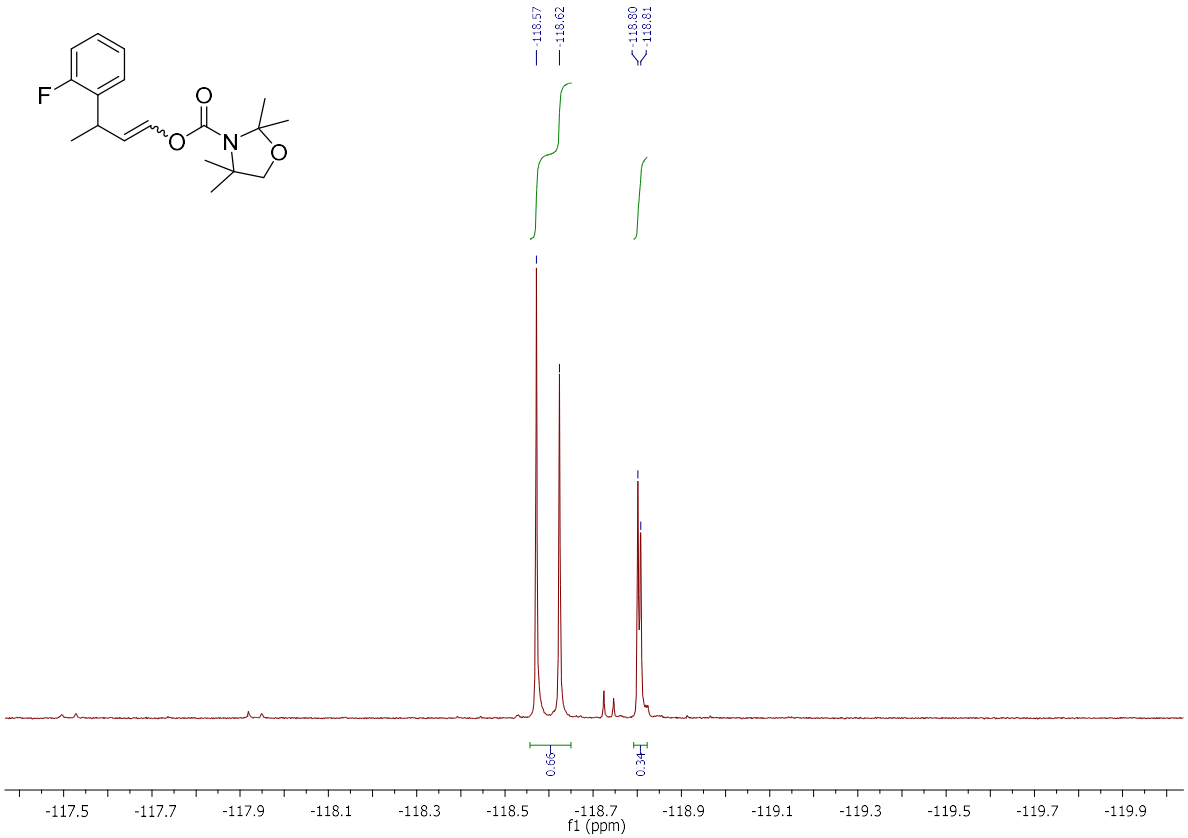
3-(2-fluorophenyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.20g** :



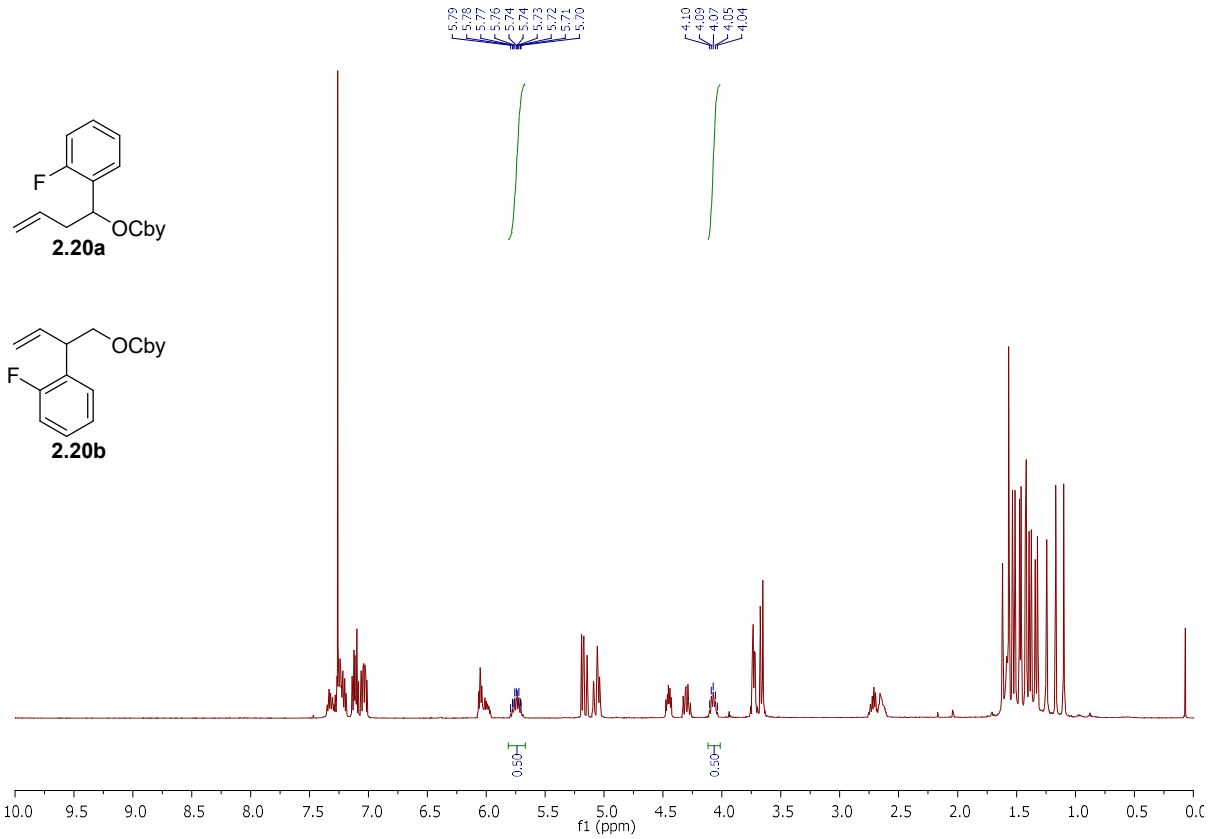


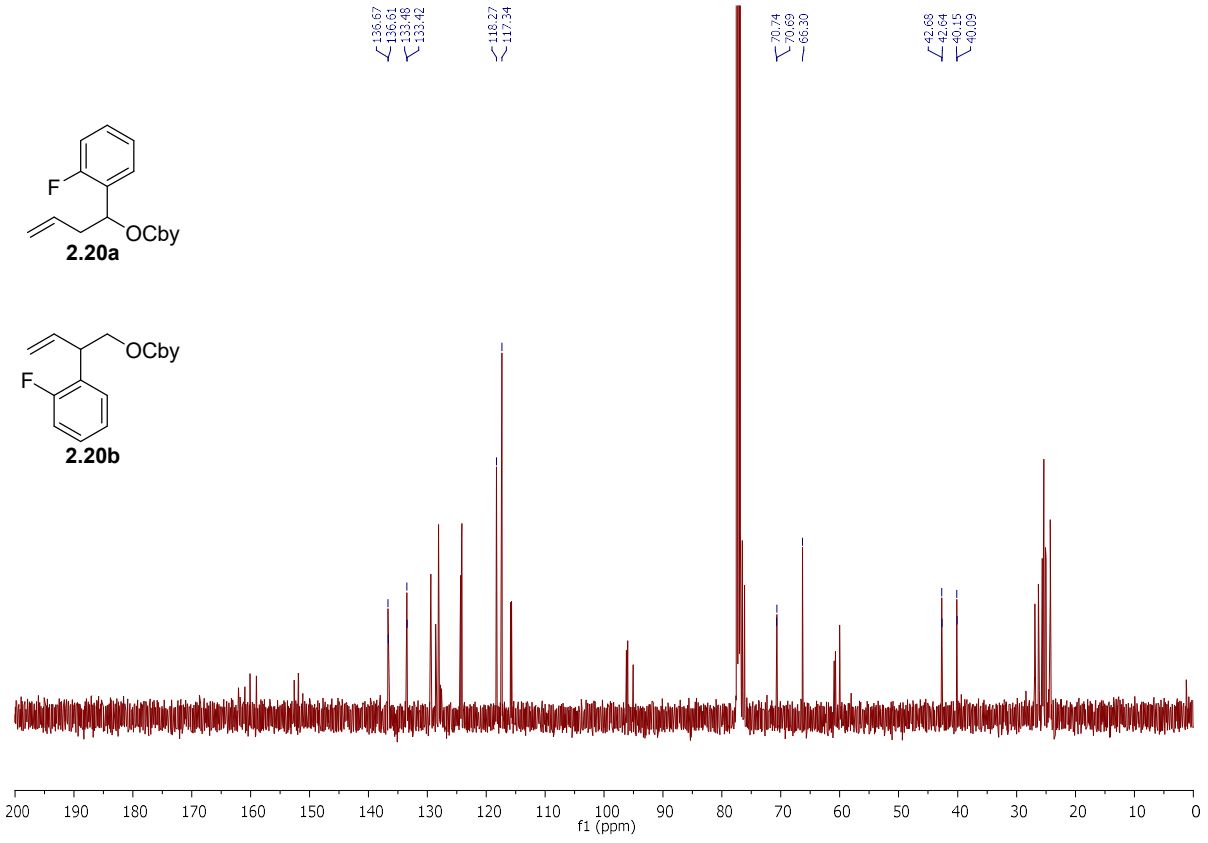
COSY and HMQC experiments :

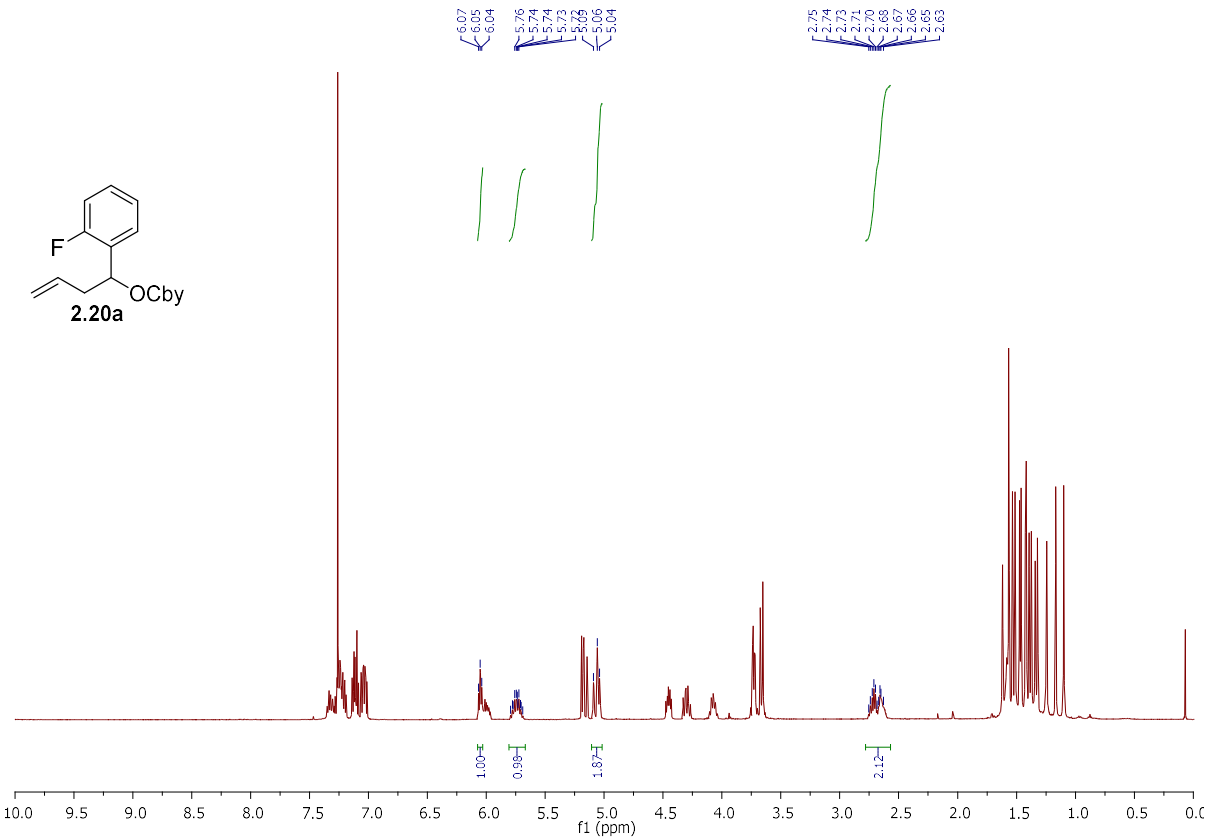


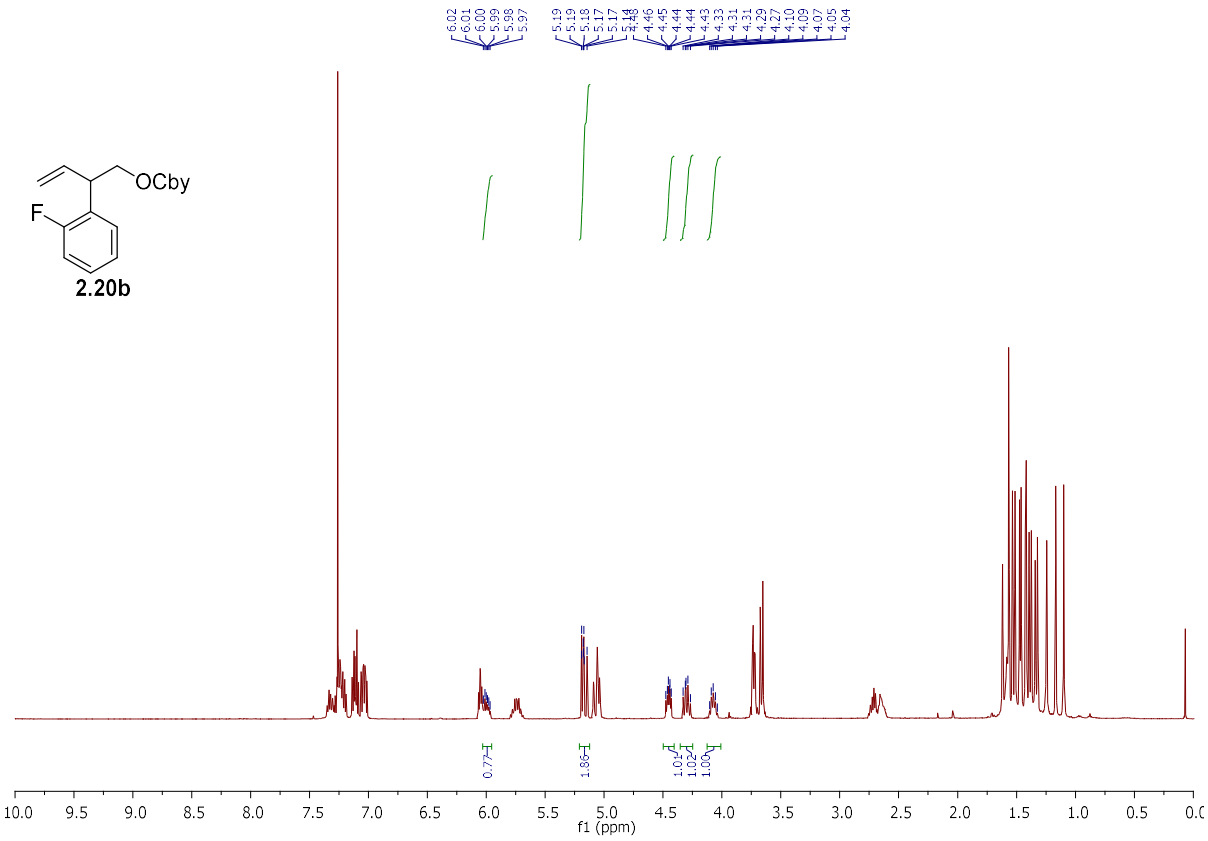

F
O
O
N
O
-118.57
-118.62
-118.80
-118.81
0.66
0.34
-117.5
-117.7
-117.9
-118.1
-118.3
-118.5
-118.7
-118.9
-119.1
-119.3
-119.5
-119.7
-119.9
f1 (ppm)

α- and β-products **(*E*)-2.20a** and **(*E*)-2.20b** :

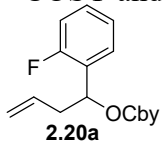




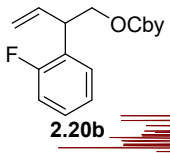

F
OCby
2.20a
f1 (ppm)


OCby
F
2.20b
f1 (ppm)

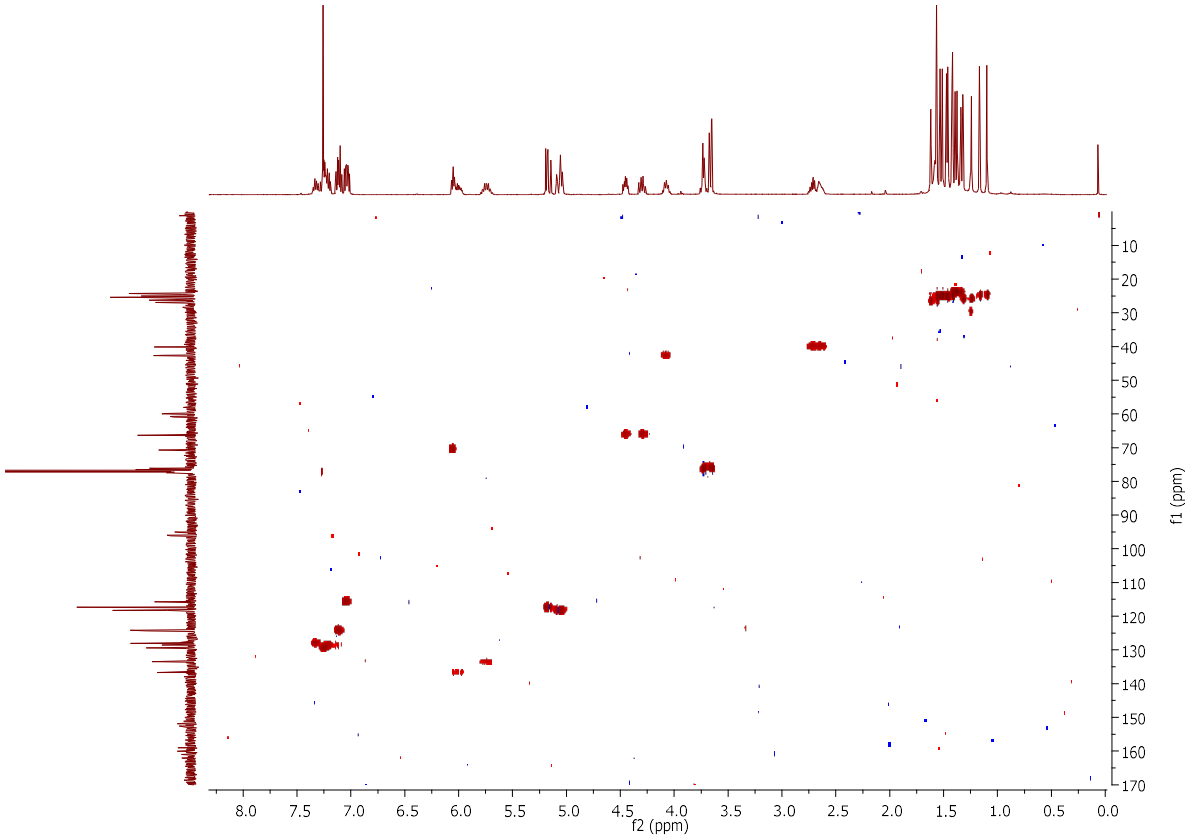
COSY and HMQC experiments :

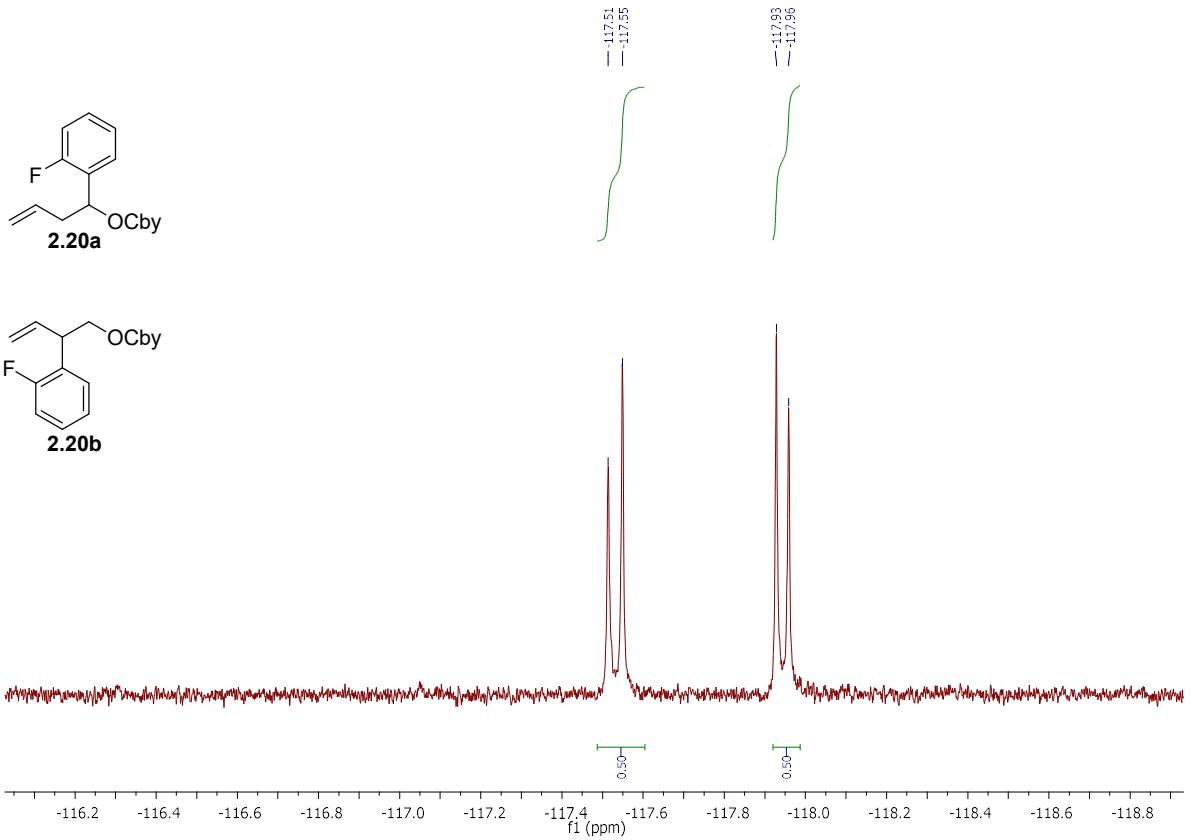


2.20a

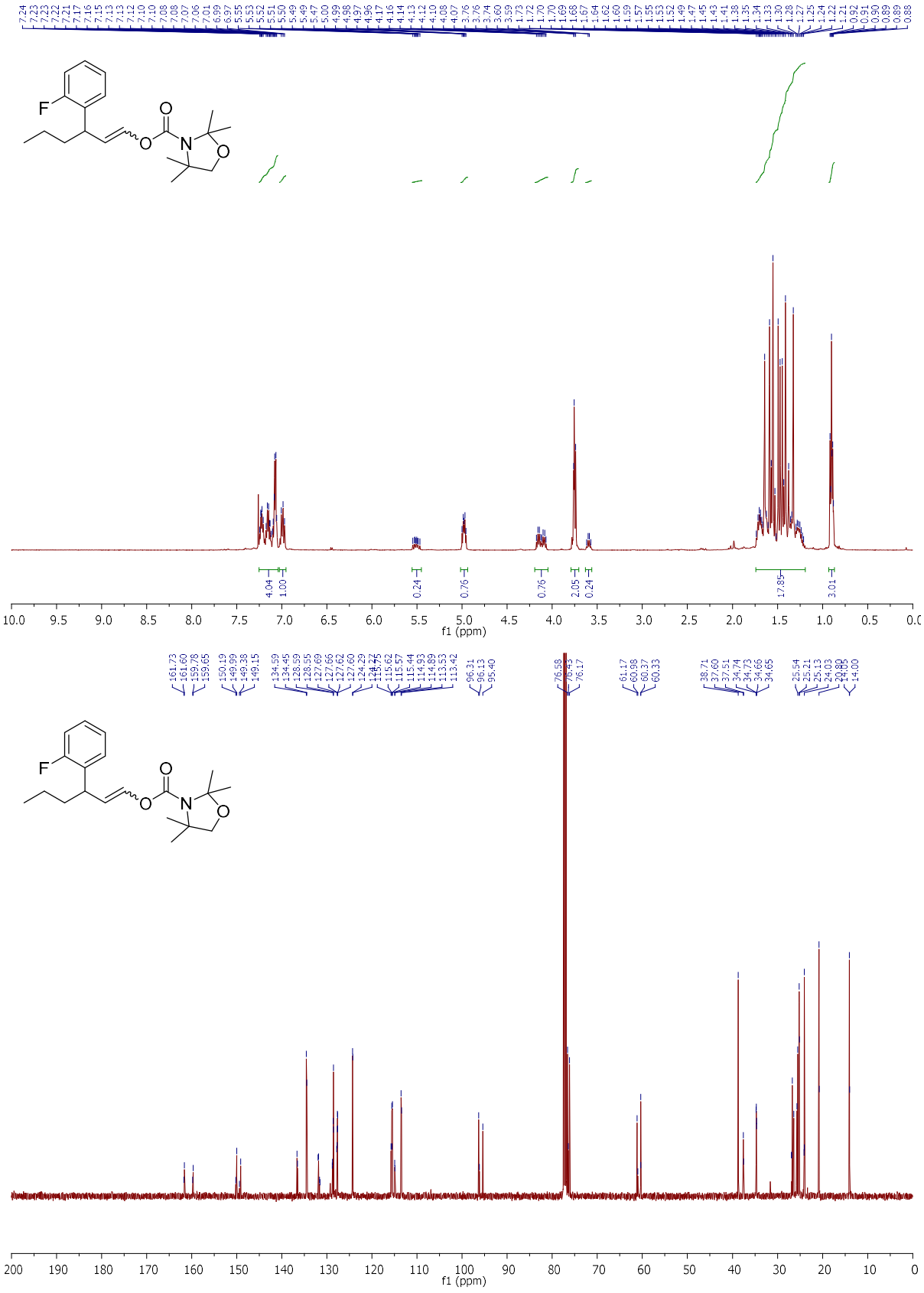


2.20b

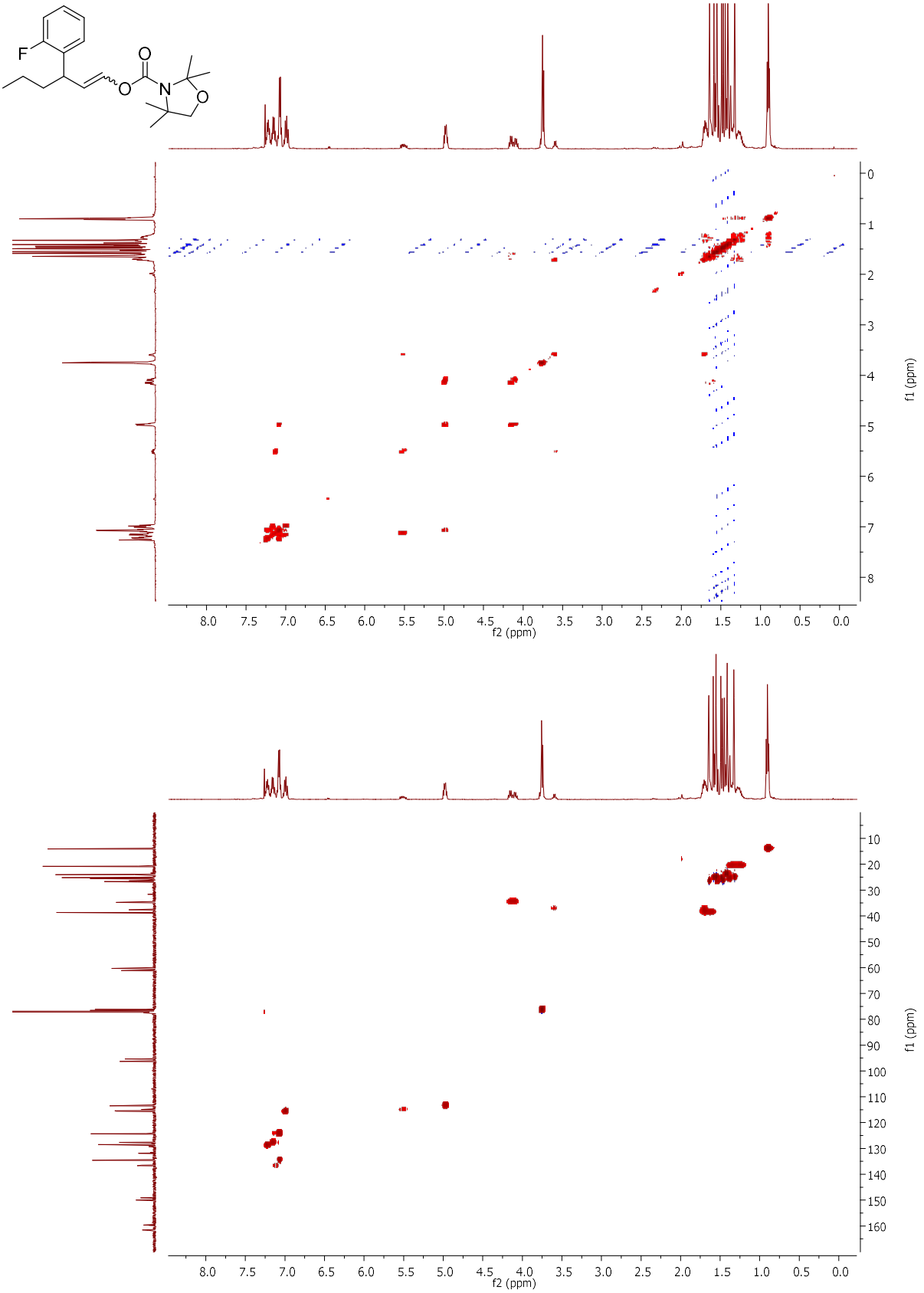


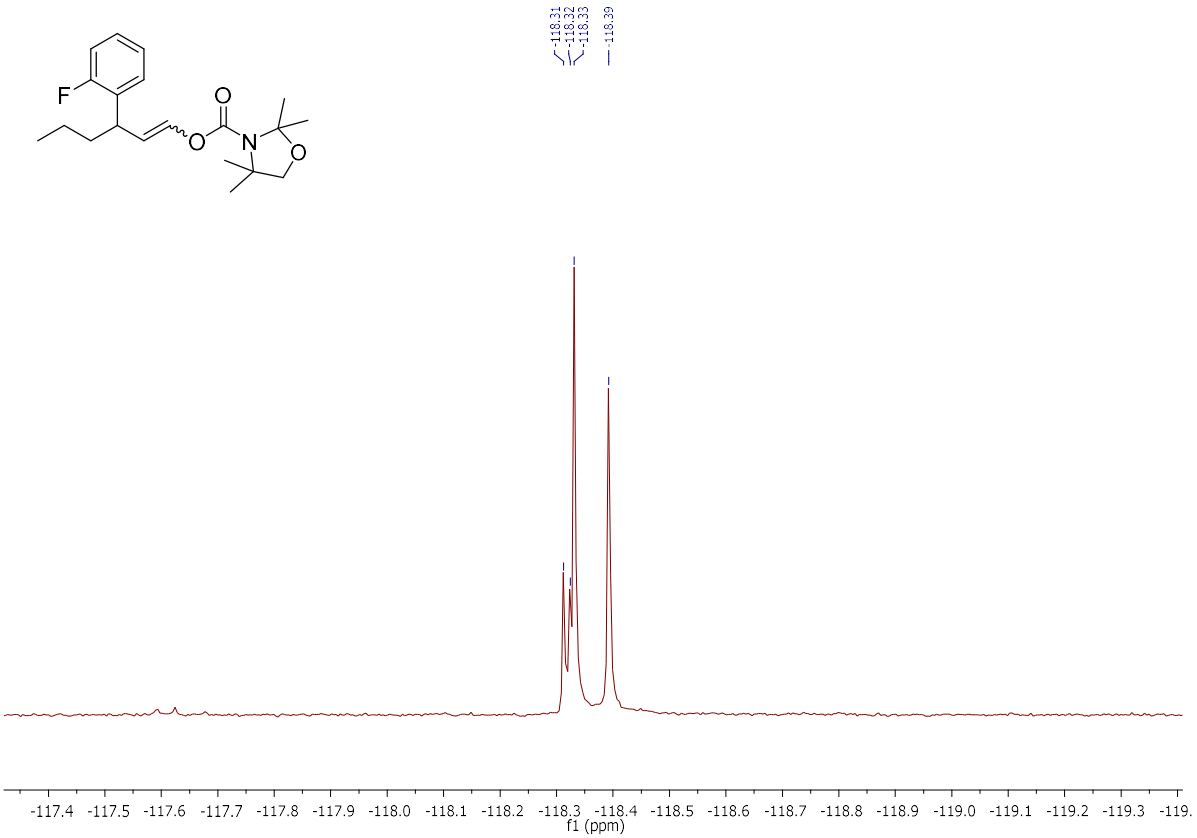

-117.51
-117.55
-117.93
-117.96
F
OCby
2.20a
OCby
F
2.20b
0.50
0.50
-116.2
-116.4
-116.6
-116.8
-117.0
-117.2
-117.4
-117.6
-117.8
-118.0
-118.2
-118.4
-118.6
-118.8
f1 (ppm)

3-(2-fluorophenyl)hex-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.38a** :

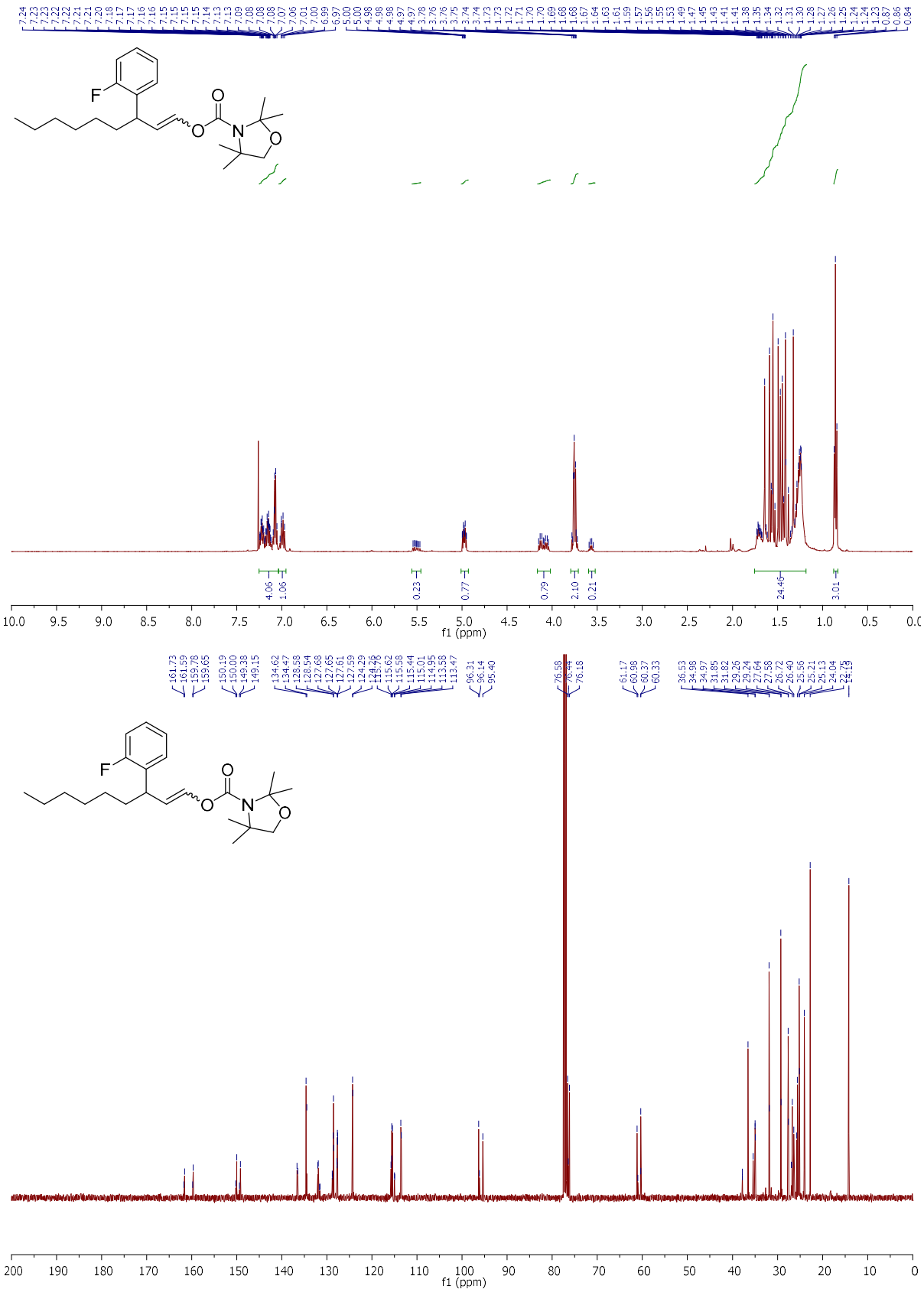


COSY and HMQC experiments :

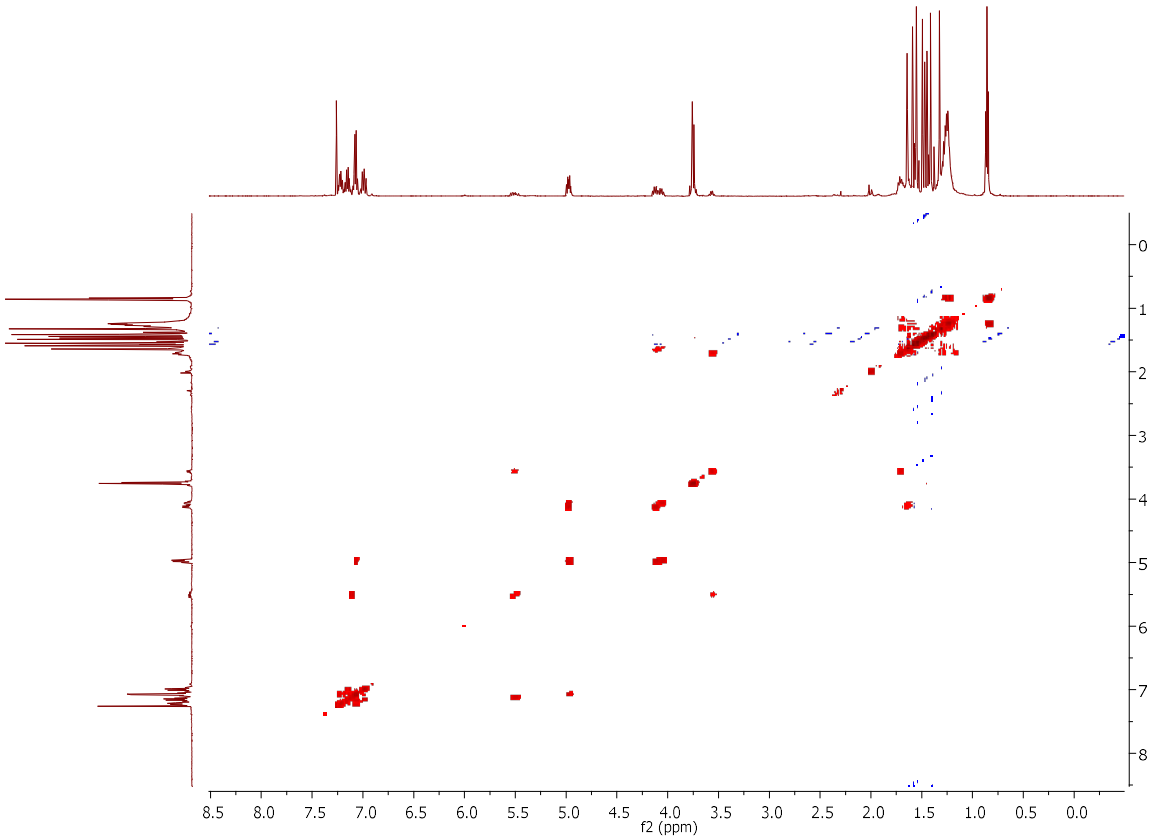


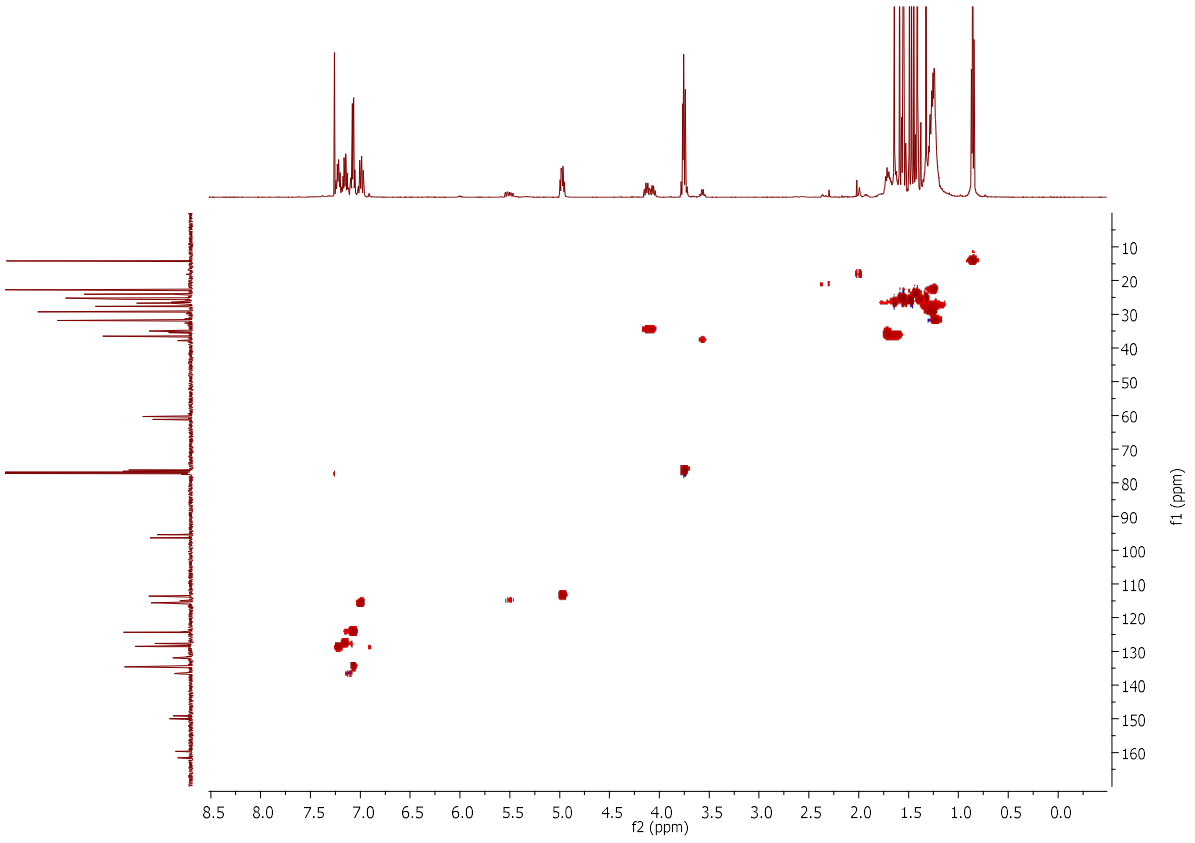

-118.31
-118.32
-118.33
-118.39
F
O
O
N
O
-117.4 -117.5 -117.6 -117.7 -117.8 -117.9 -118.0 -118.1 -118.2 -118.3 -118.4 -118.5 -118.6 -118.7 -118.8 -118.9 -119.0 -119.1 -119.2 -119.3 -119.
f1 (ppm)

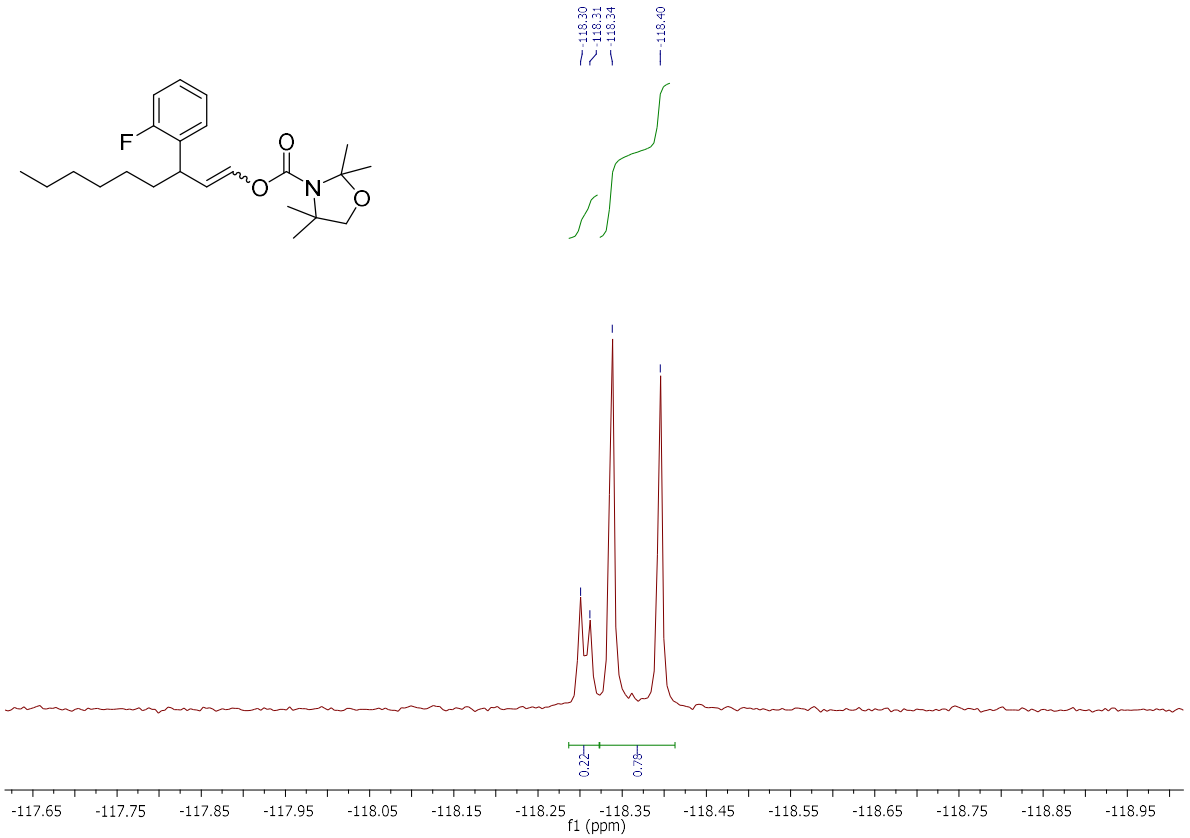
3-(2-fluorophenyl)non-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.38b** :



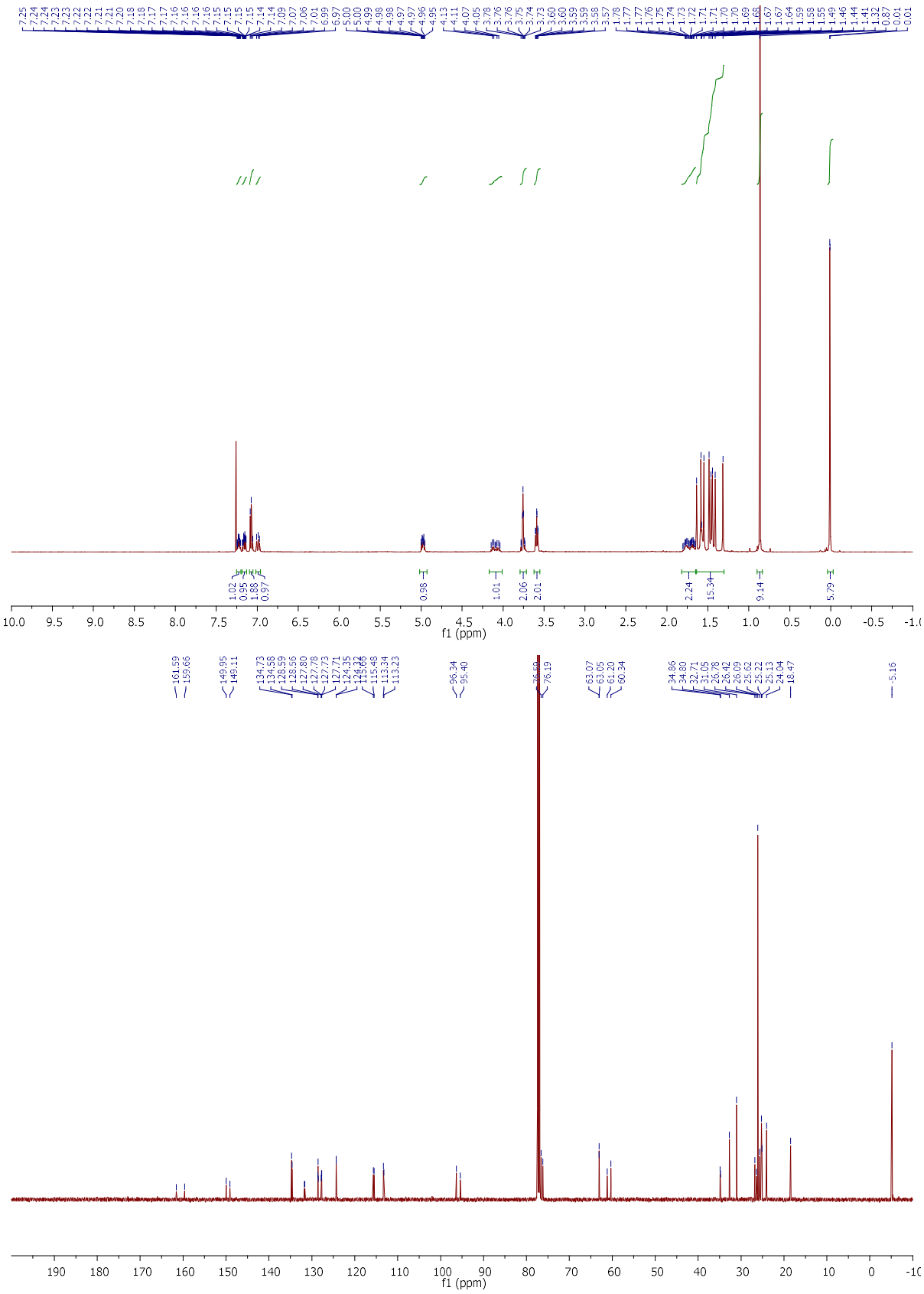
COSY and HMQC experiments :



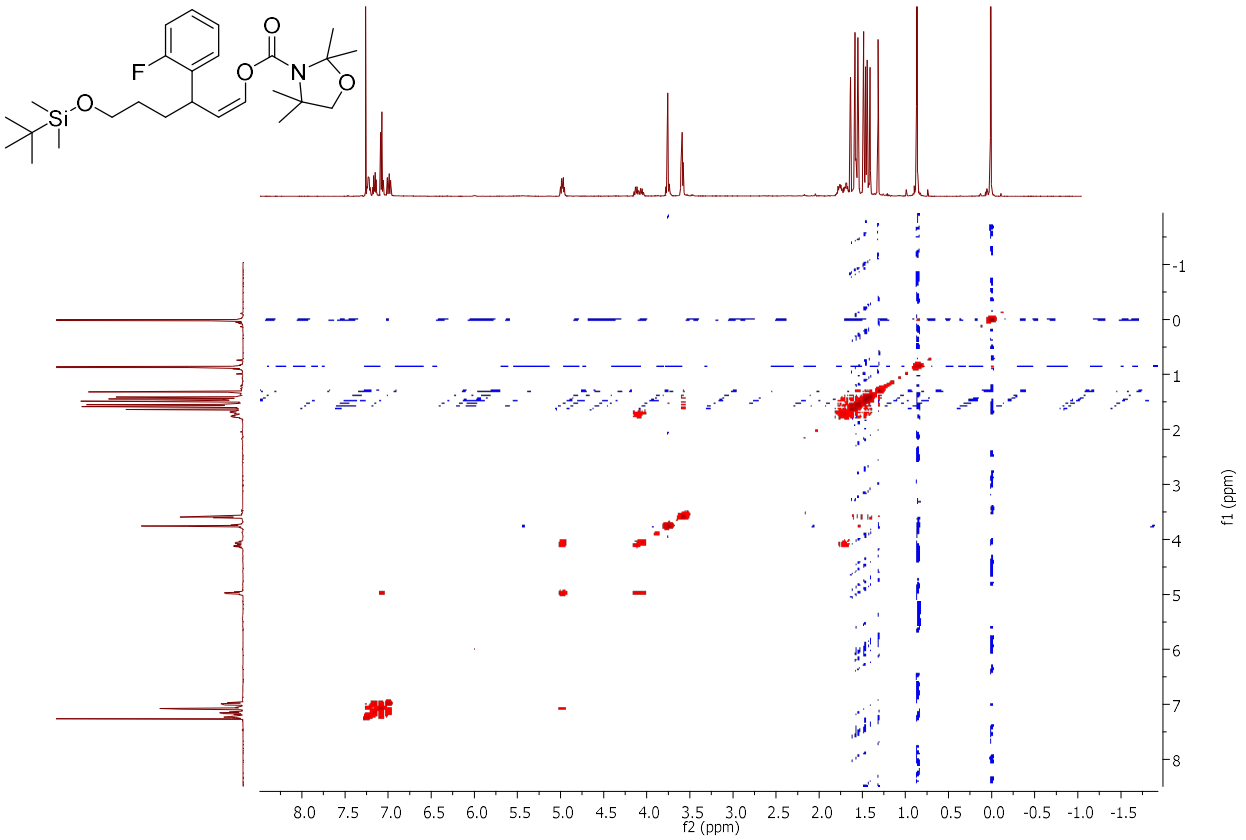


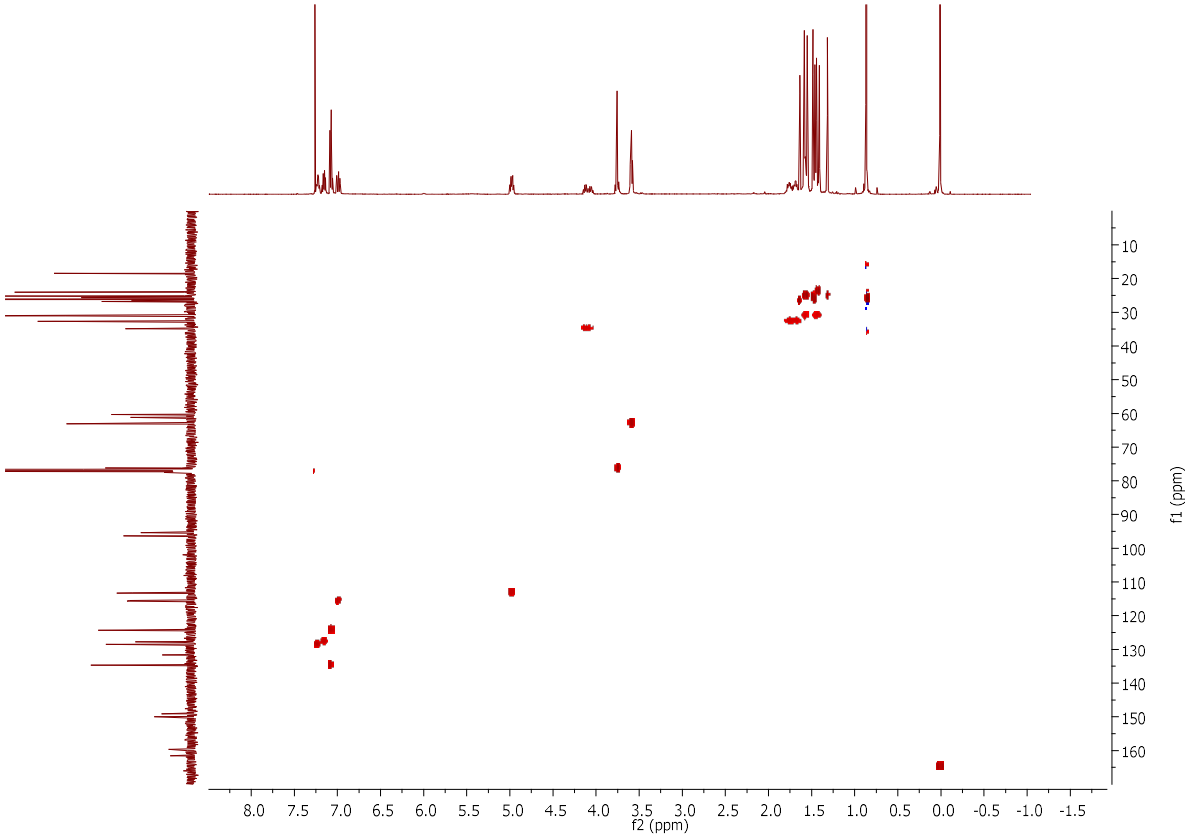

F
O
O
N
O
-118.30
-118.31
-118.34
-118.40
0.22
0.79
-117.65
-117.75
-117.85
-117.95
-118.05
-118.15
-118.25
-118.35
-118.45
-118.55
-118.65
-118.75
-118.85
-118.95
f1 (ppm)

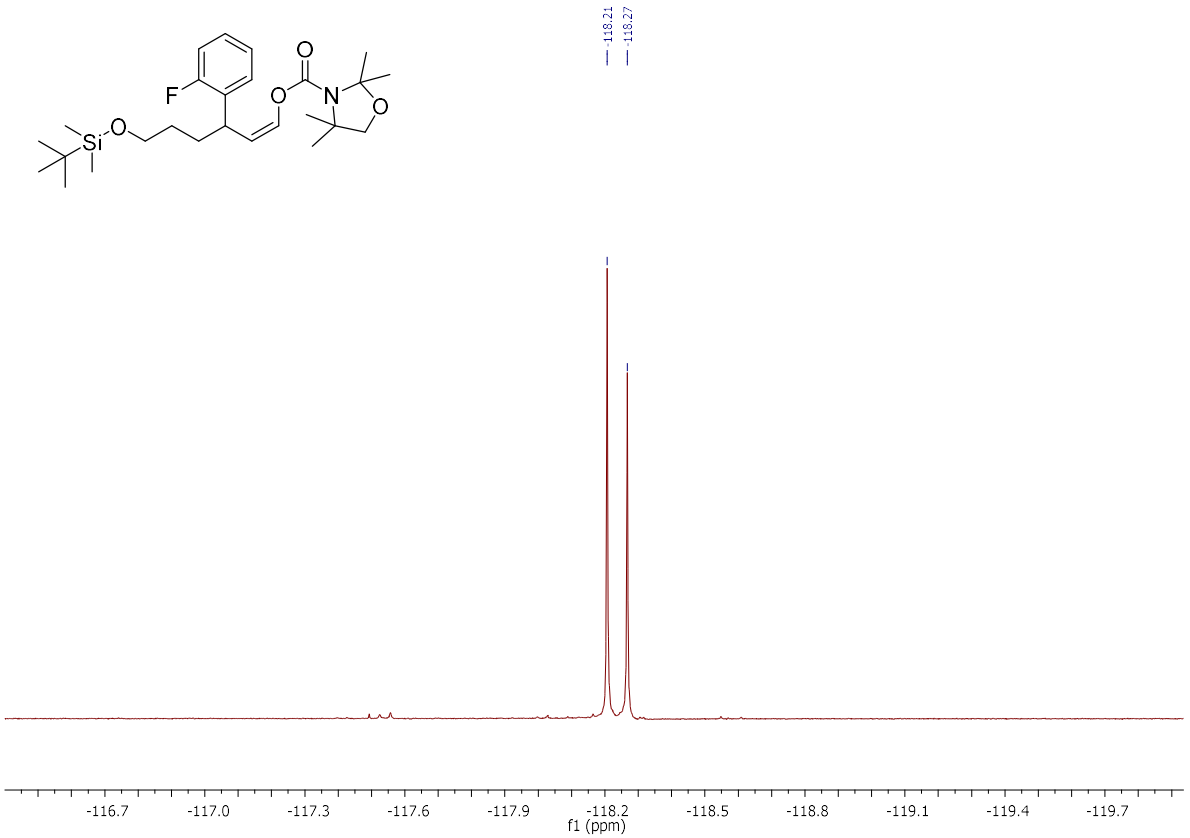
(*Z*)-6-((tert-butyldimethylsilyl)oxy)-3-(2-fluorophenyl)hex-1-en-1-yl2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.38c** :



COSY and HMQC experiments :

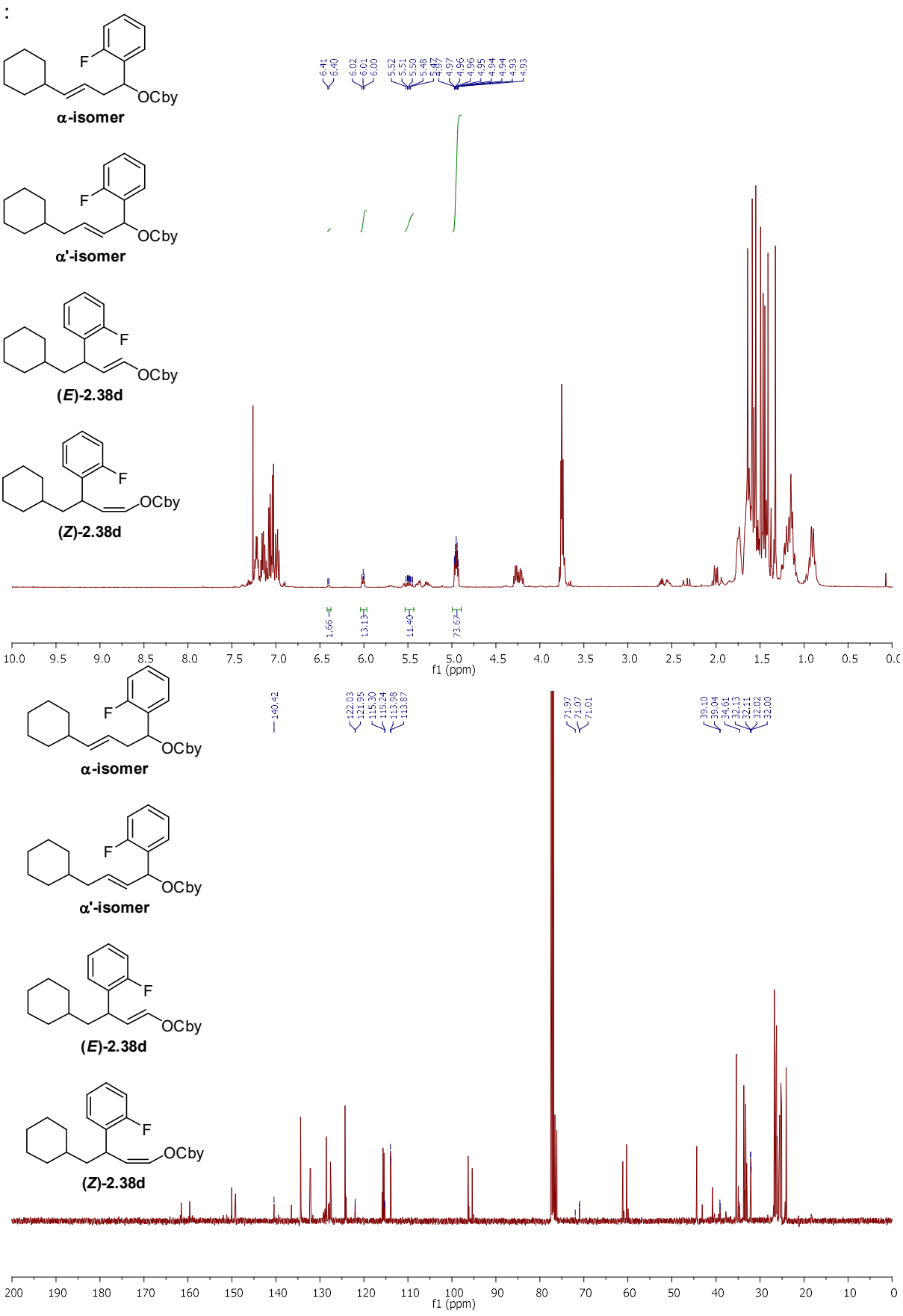


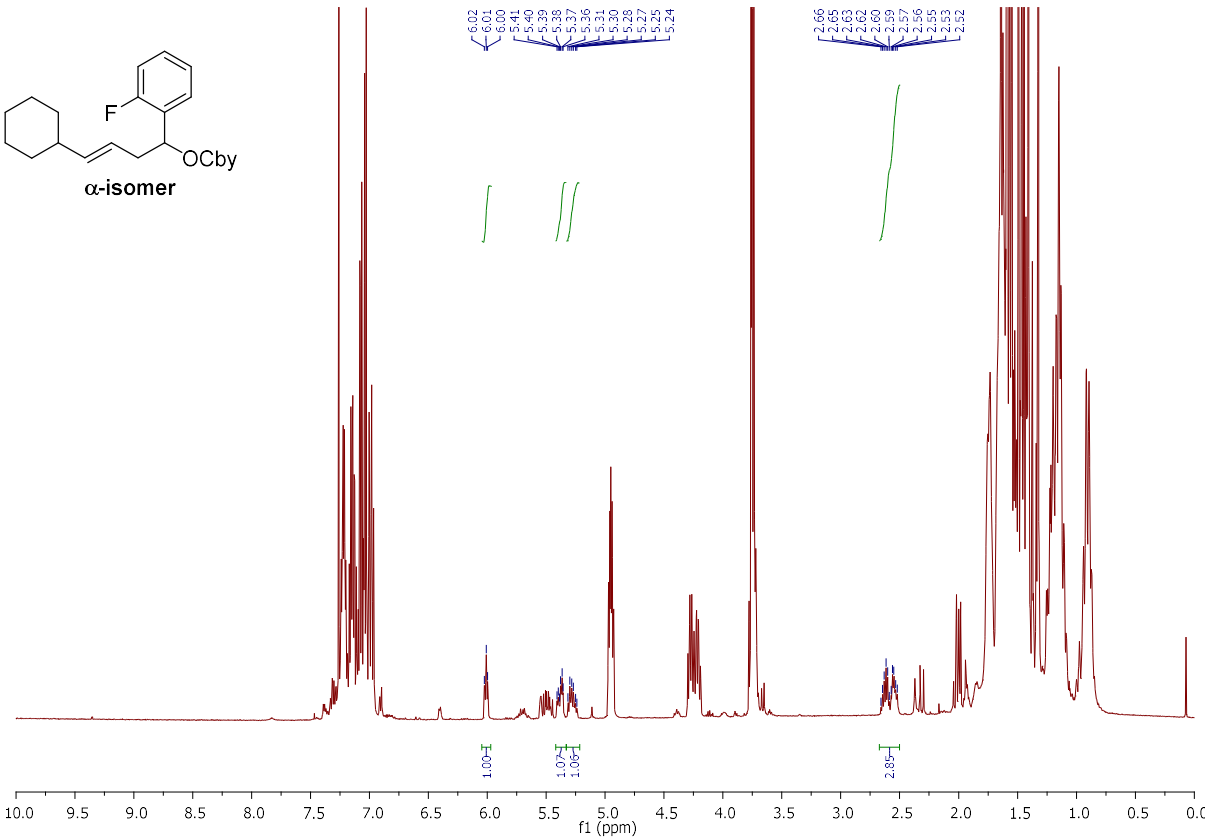


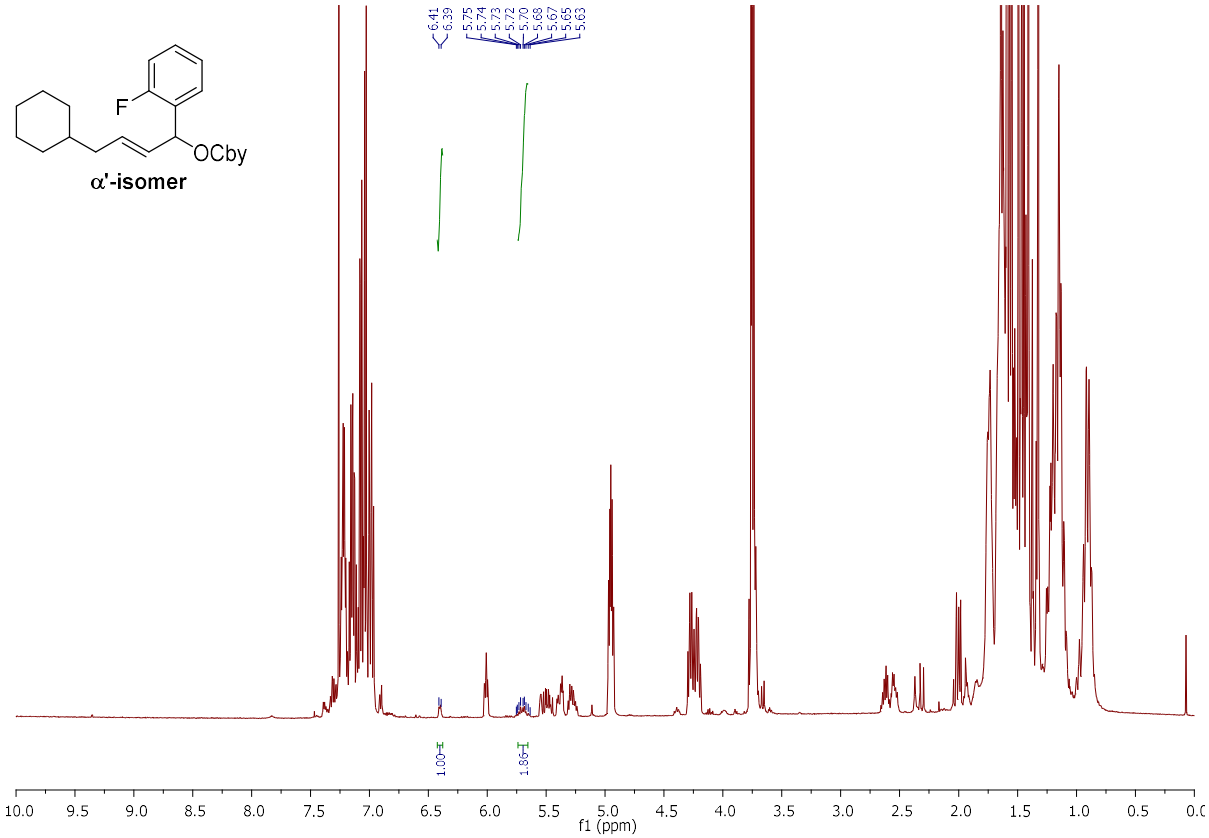

-118.21
-118.27
F
O
O
N
O
Si
O
-116.7
-117.0
-117.3
-117.6
-117.9
-118.2
-118.5
-118.8
-119.1
-119.4
-119.7
f1 (ppm)

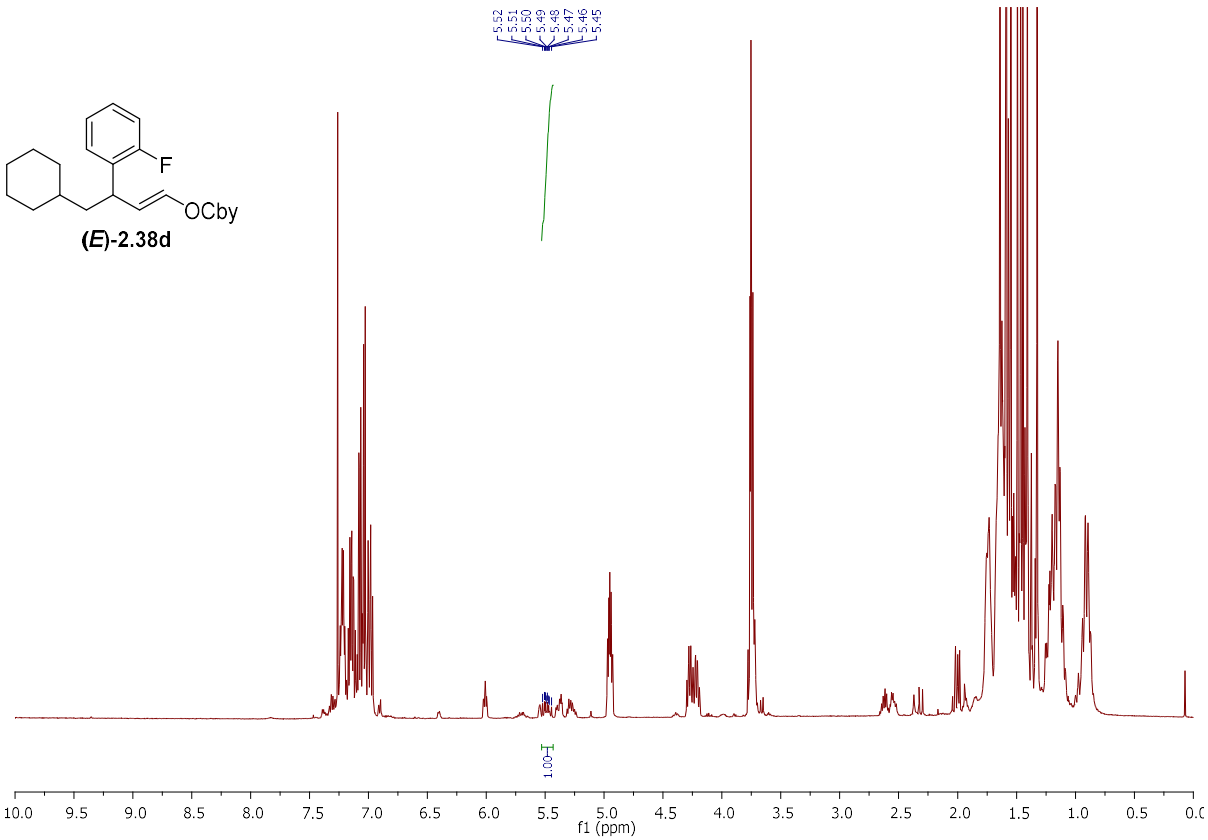
Arylation of **2.36** : products **2.38d** and isomers :

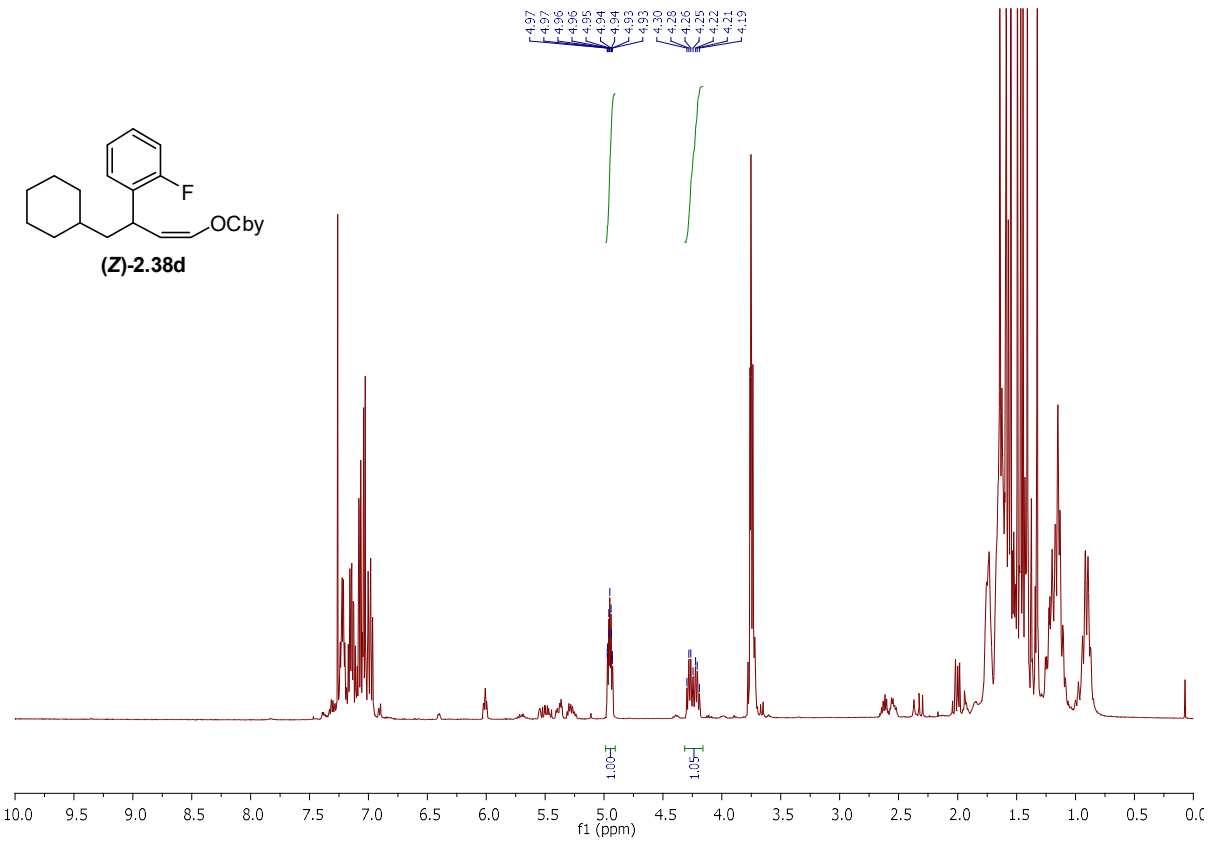
:



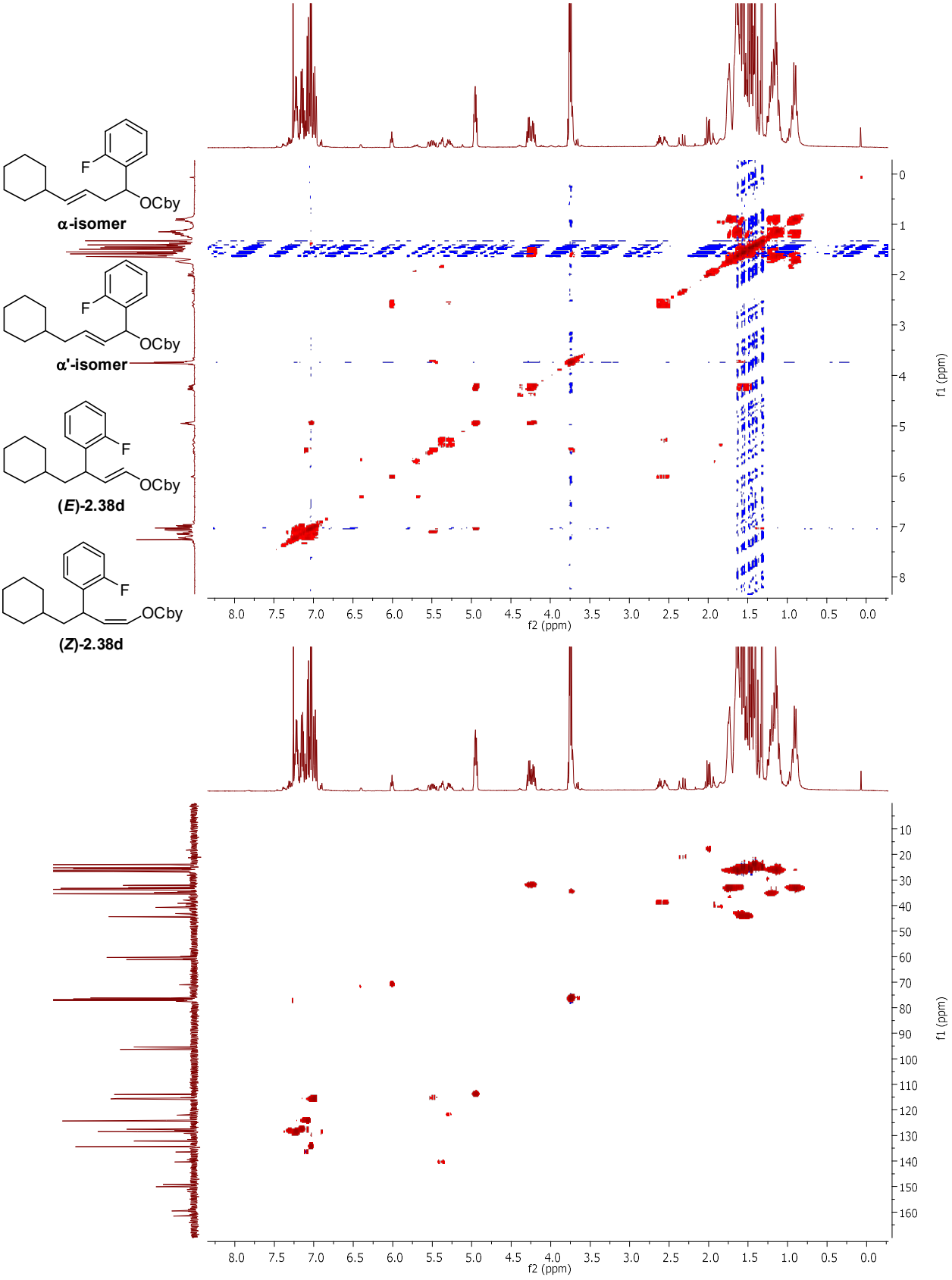

F
OCby
α-isomer
6.02
6.01
6.00
5.41
5.40
5.39
5.38
5.37
5.36
5.31
5.30
5.28
5.27
5.25
5.24
2.66
2.65
2.63
2.62
2.60
2.59
2.57
2.56
2.55
2.53
2.52
1.00
1.07
1.06
2.85
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

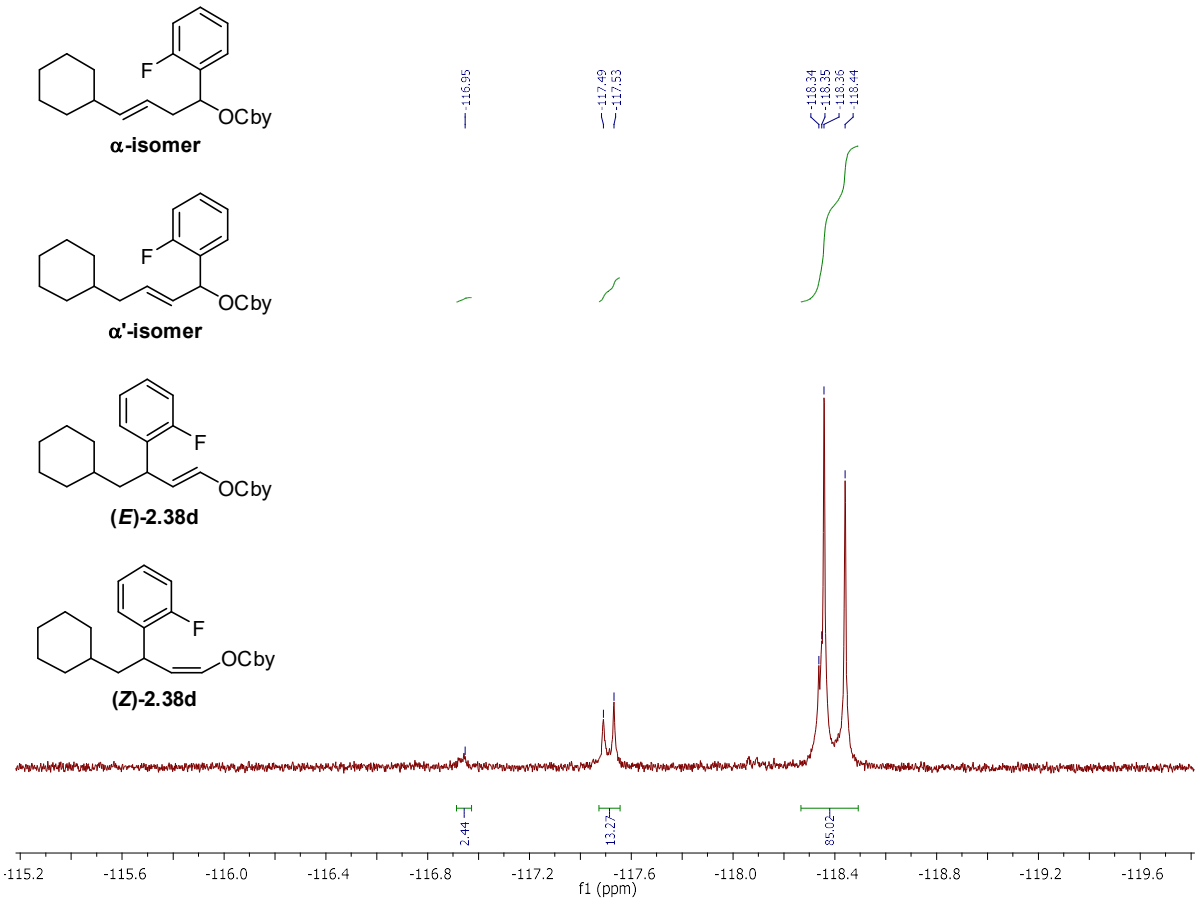

F
OCby
α'-isomer
6.41
6.39
5.75
5.74
5.73
5.72
5.70
5.68
5.67
5.65
5.63
1.00
1.86
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


F
OCby
(E)-2.38d
5.52
5.51
5.50
5.49
5.48
5.47
5.46
5.45
1.00
f1 (ppm)

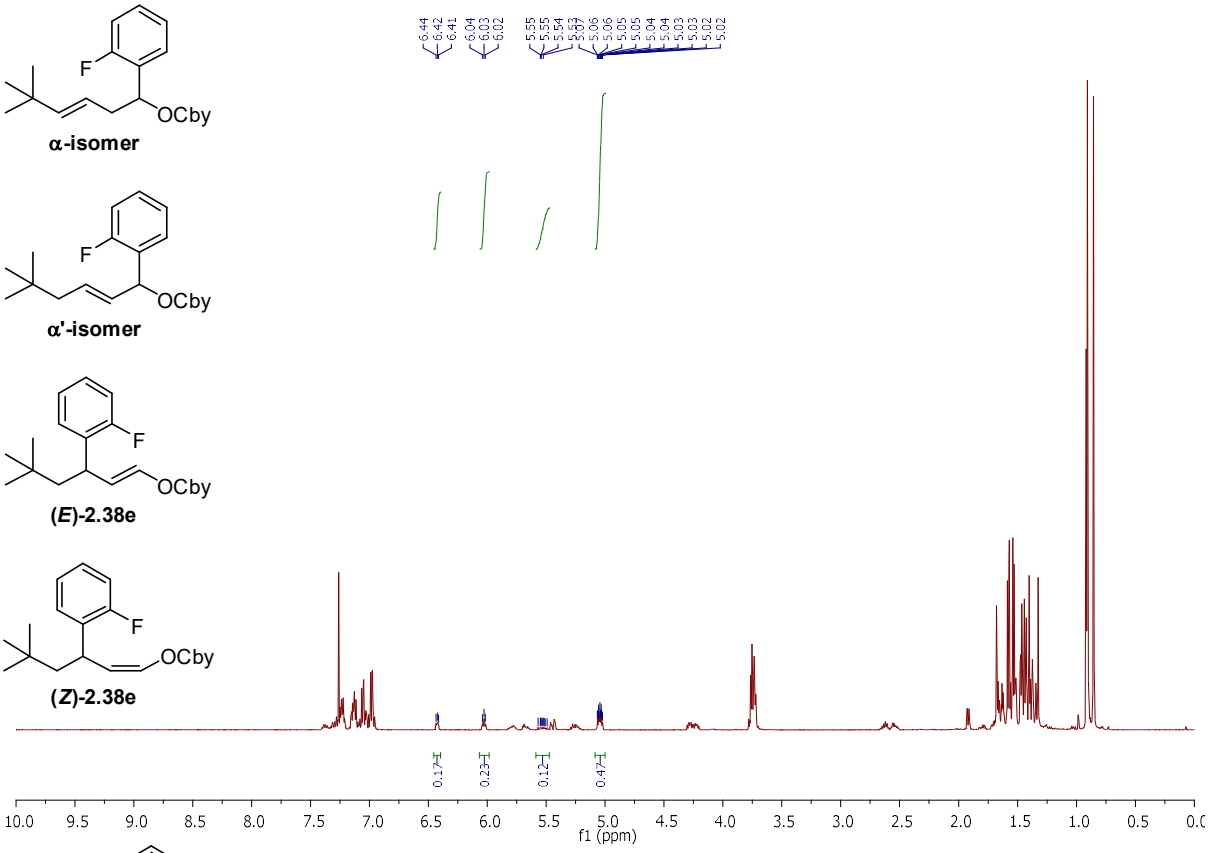

F
OCby
(Z)-2.38d
4.97
4.97
4.96
4.96
4.95
4.94
4.94
4.93
4.93
4.30
4.28
4.26
4.25
4.22
4.21
4.19
1.00
1.05
f1 (ppm)

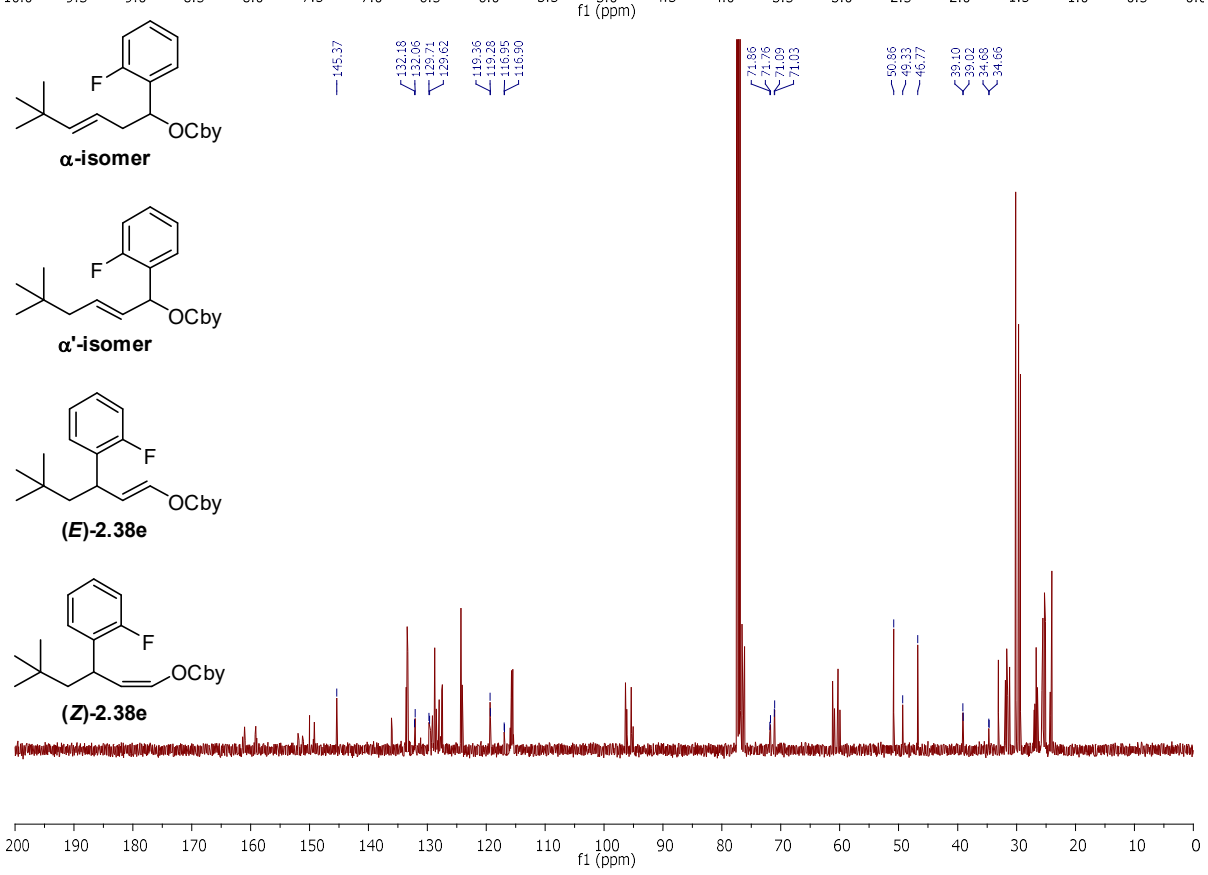
COSY and HMQC experiments :

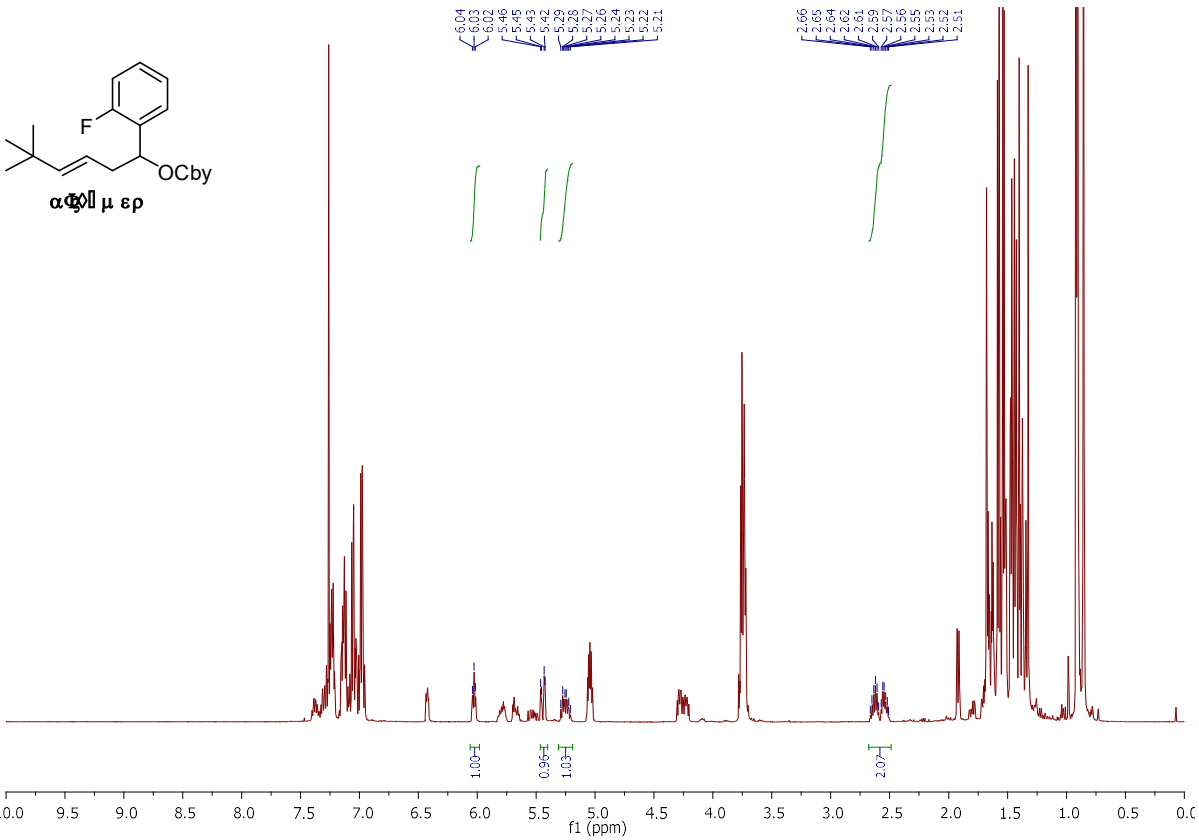


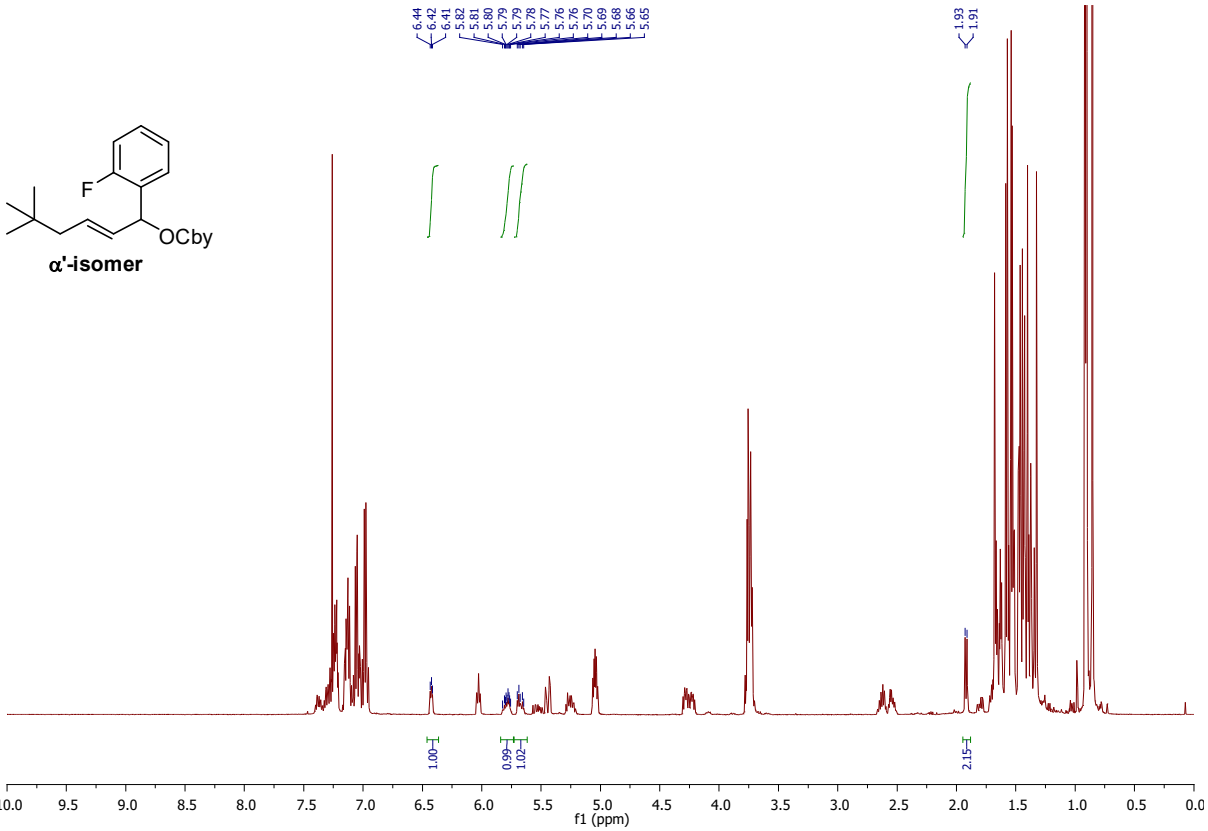

F
OCby
α-isomer
F
OCby
α'-isomer
F
OCby
(E)-2.38d
F
OCby
(Z)-2.38d
-116.95
-117.49
-117.53
-118.34
-118.35
-118.36
-118.44
2.44
13.27
85.02
-115.2
-115.6
-116.0
-116.4
-116.8
-117.2
-117.6
-118.0
-118.4
-118.8
-119.2
-119.6
f1 (ppm)

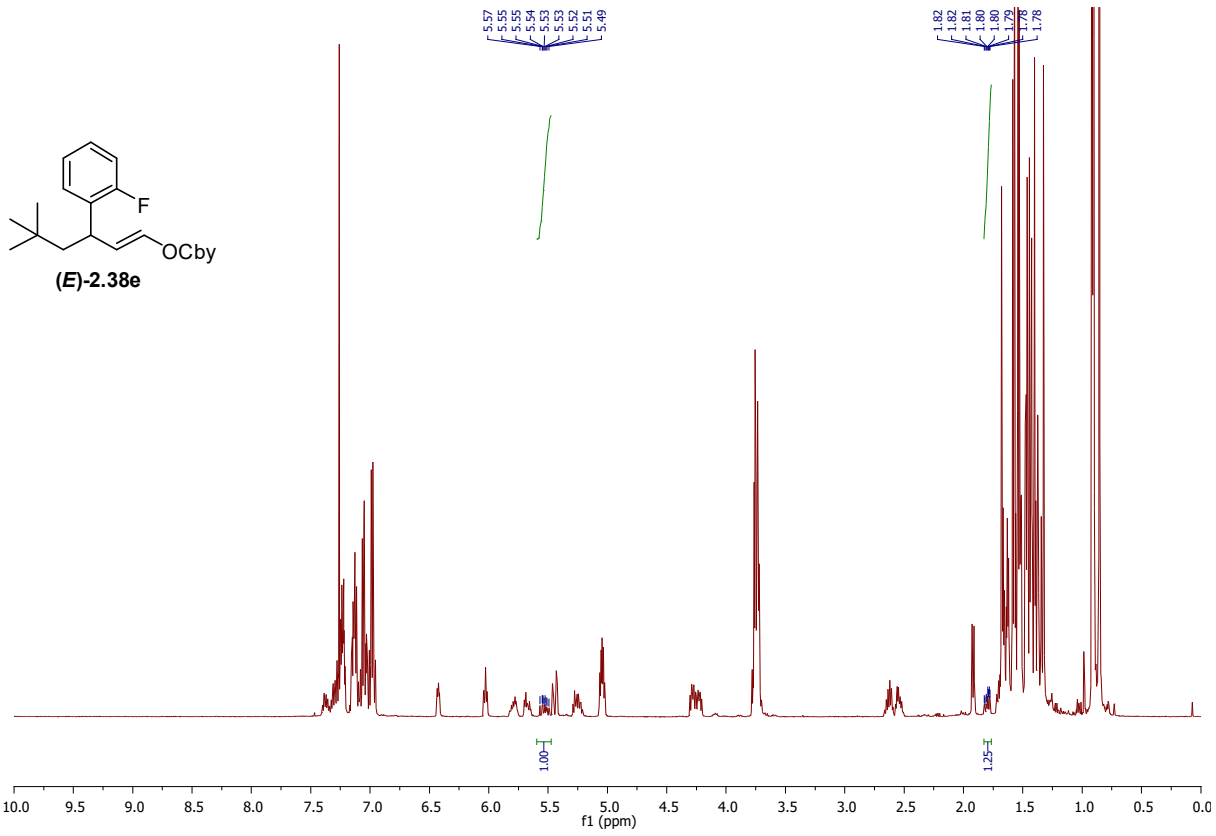
Arylation of **2.37** : products **2.38e** and isomers :



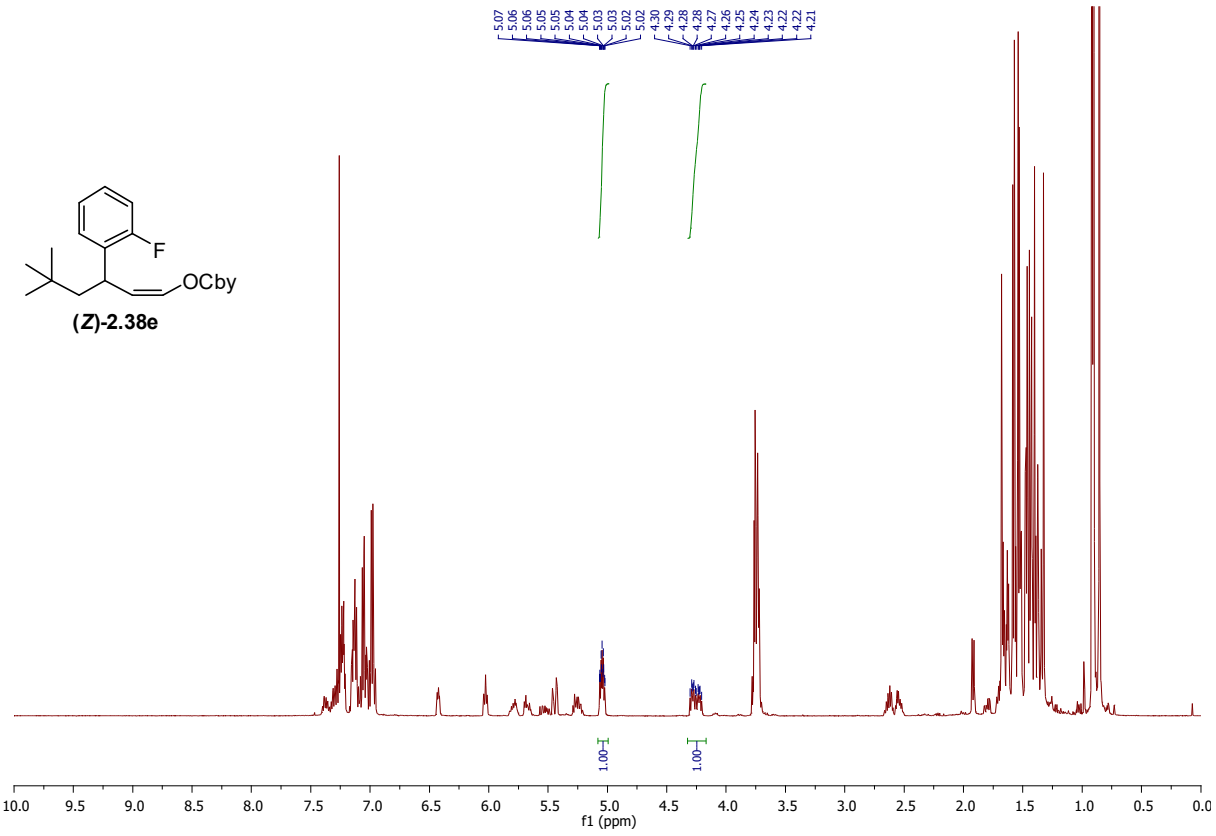



F
OCby
f1 (ppm)


F
OCby
α'-isomer
f1 (ppm)

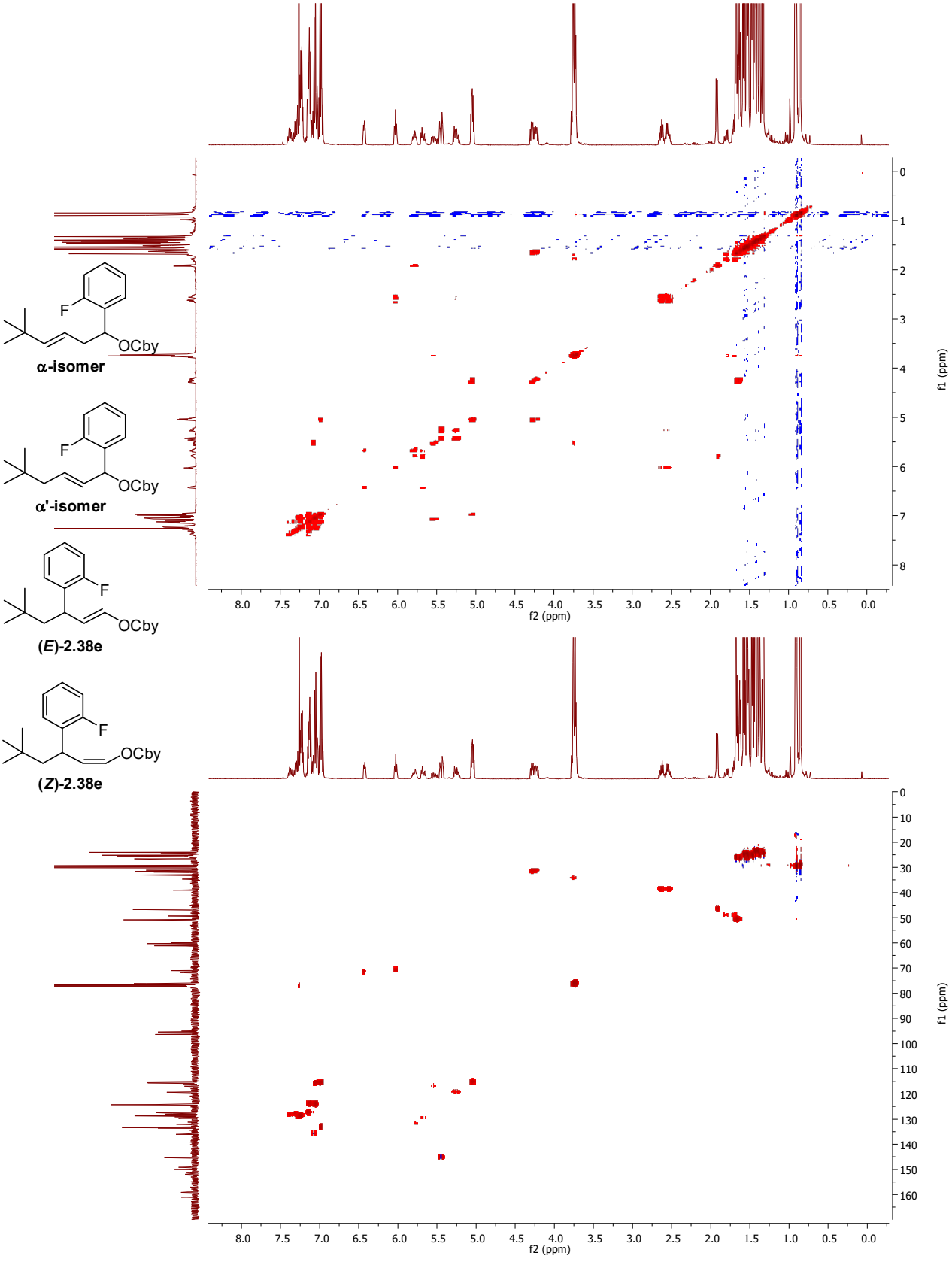

F
OCby
5.57
5.55
5.55
5.54
5.53
5.53
5.52
5.51
5.49
1.82
1.82
1.81
1.80
1.80
1.79
1.78
1.78
1.00
1.25
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

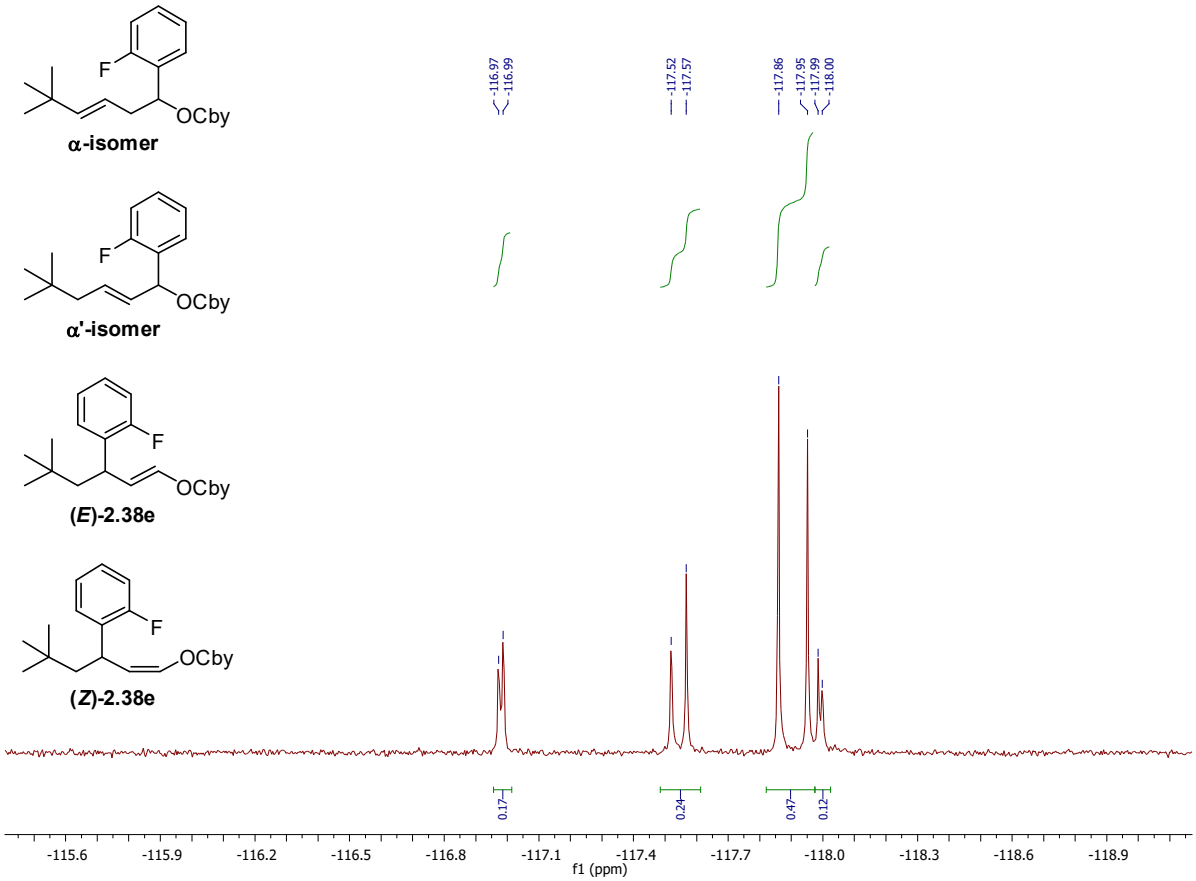
(*E*)-2.38e


F
OCby
5.07
5.06
5.06
5.05
5.05
5.04
5.04
5.03
5.03
5.02
5.02
4.30
4.29
4.28
4.28
4.27
4.26
4.25
4.24
4.23
4.22
4.22
4.21
1.00
1.00
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
f1 (ppm)

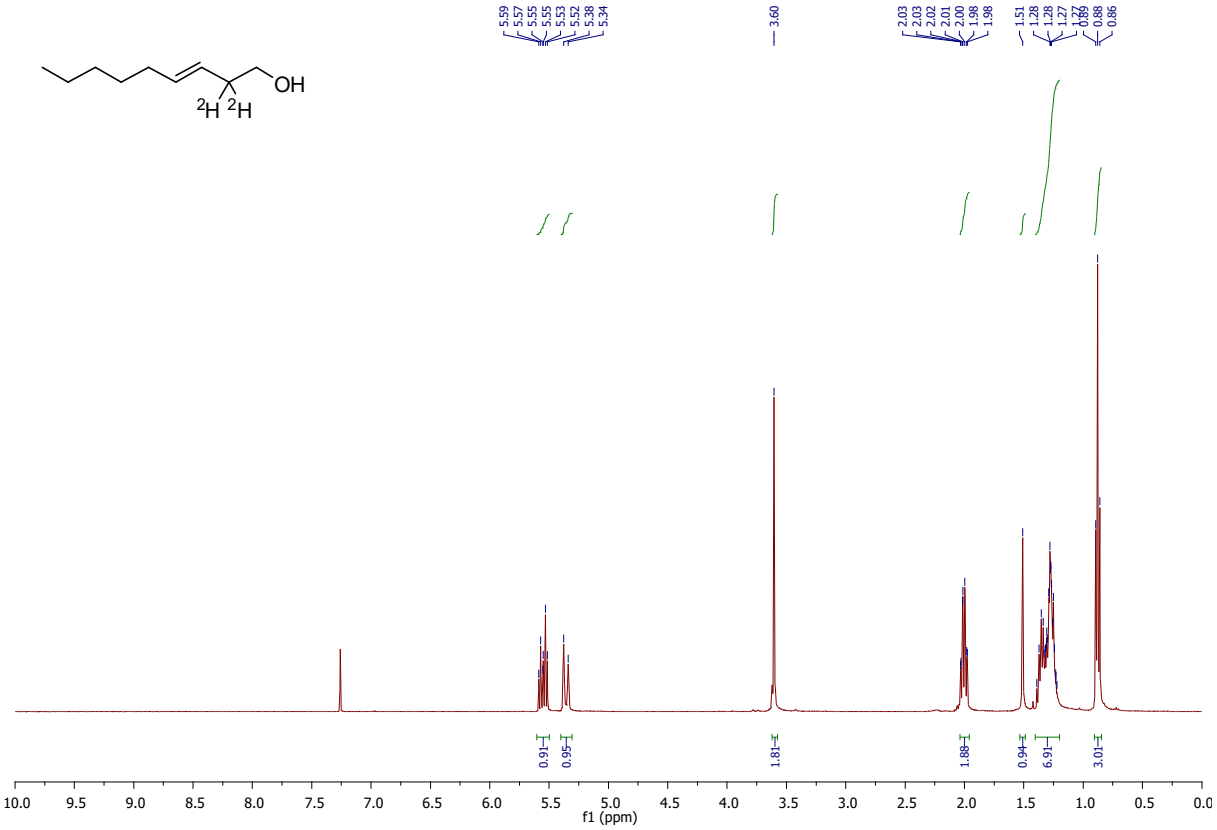
(*Z*)-2.38e

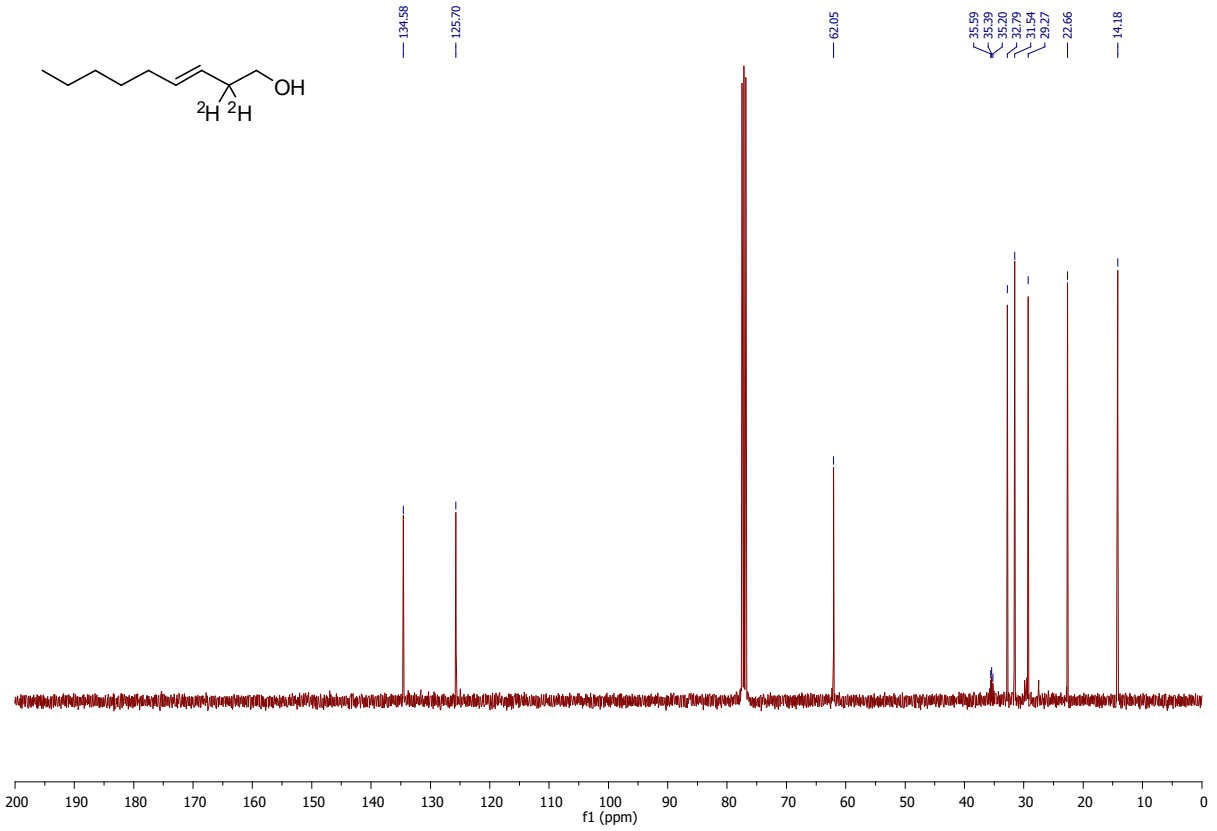
COSY and HMQC experiments :



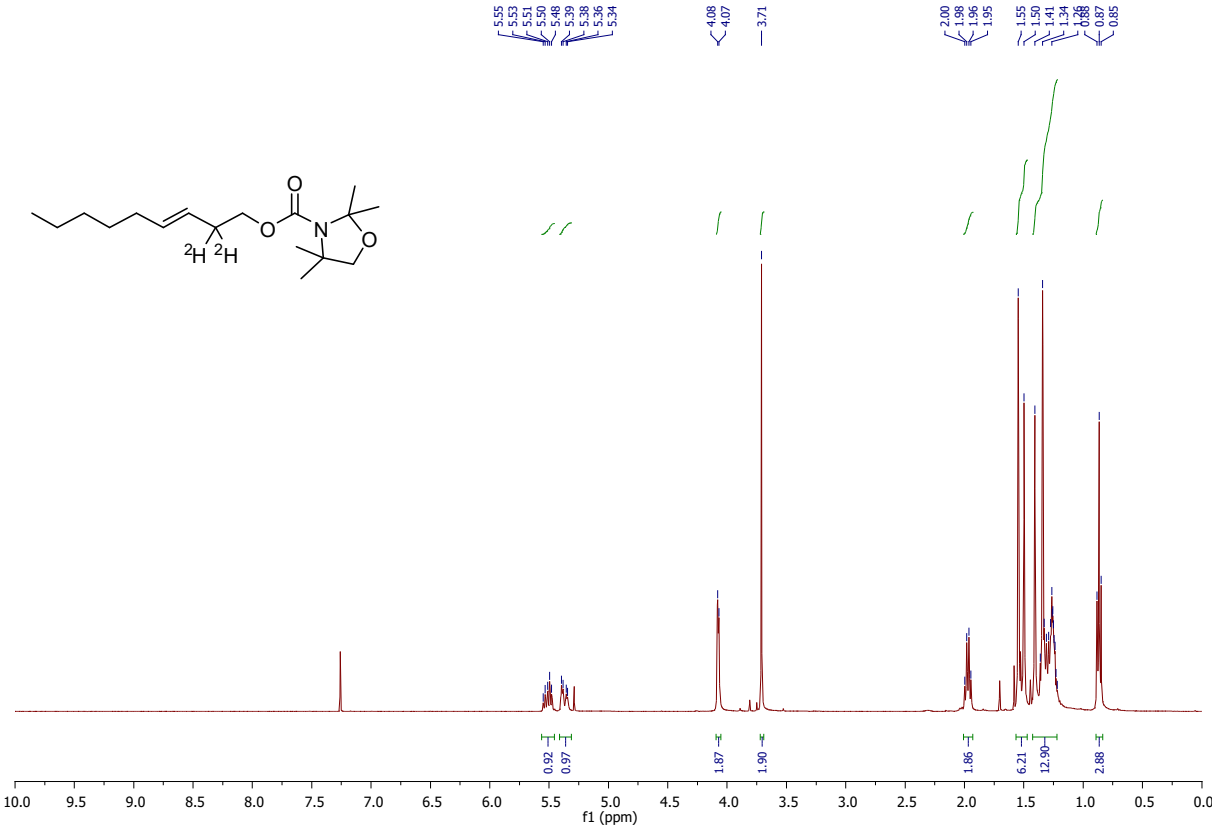

F
OCby
α-isomer
F
OCby
α'-isomer
F
OCby
(E)-2.38e
F
OCby
(Z)-2.38e
-116.97
-116.99
-117.52
-117.57
-117.86
-117.95
-117.99
-118.00
0.17
0.24
0.47
0.12
-115.6
-115.9
-116.2
-116.5
-116.8
-117.1
-117.4
-117.7
-118.0
-118.3
-118.6
-118.9
f1 (ppm)

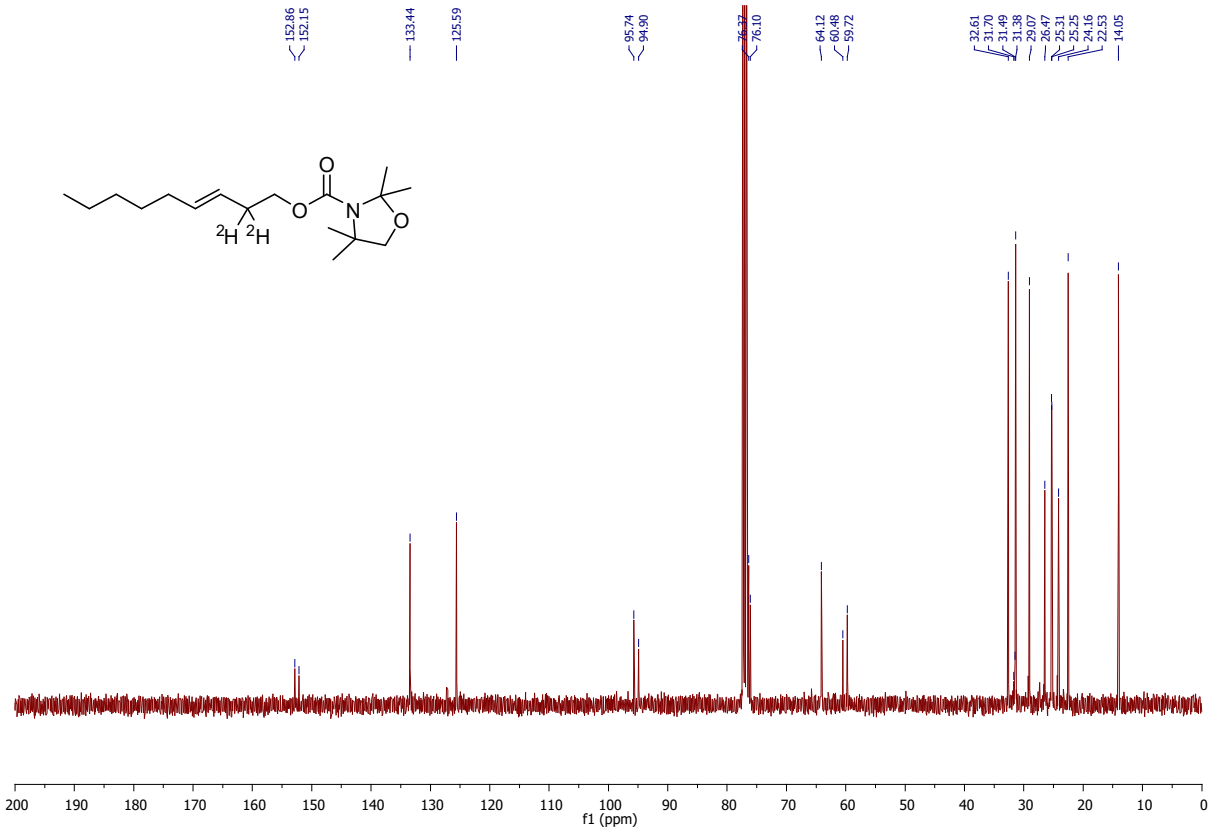
[2,2-$^{2}H_2$]-non-3(*E*)-en-1-ol **S11** :



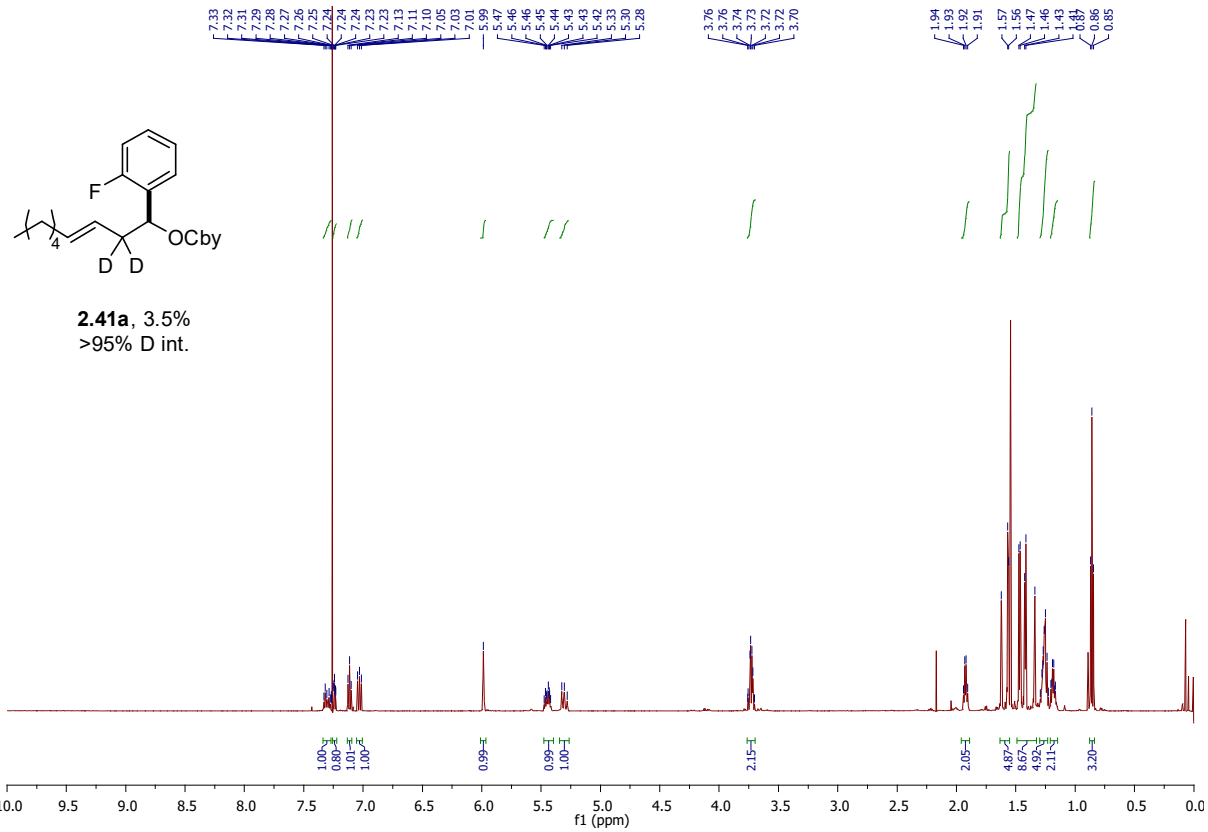


[2,2-$^{2}H_2$]-non-3(*E*)-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **2.41** :

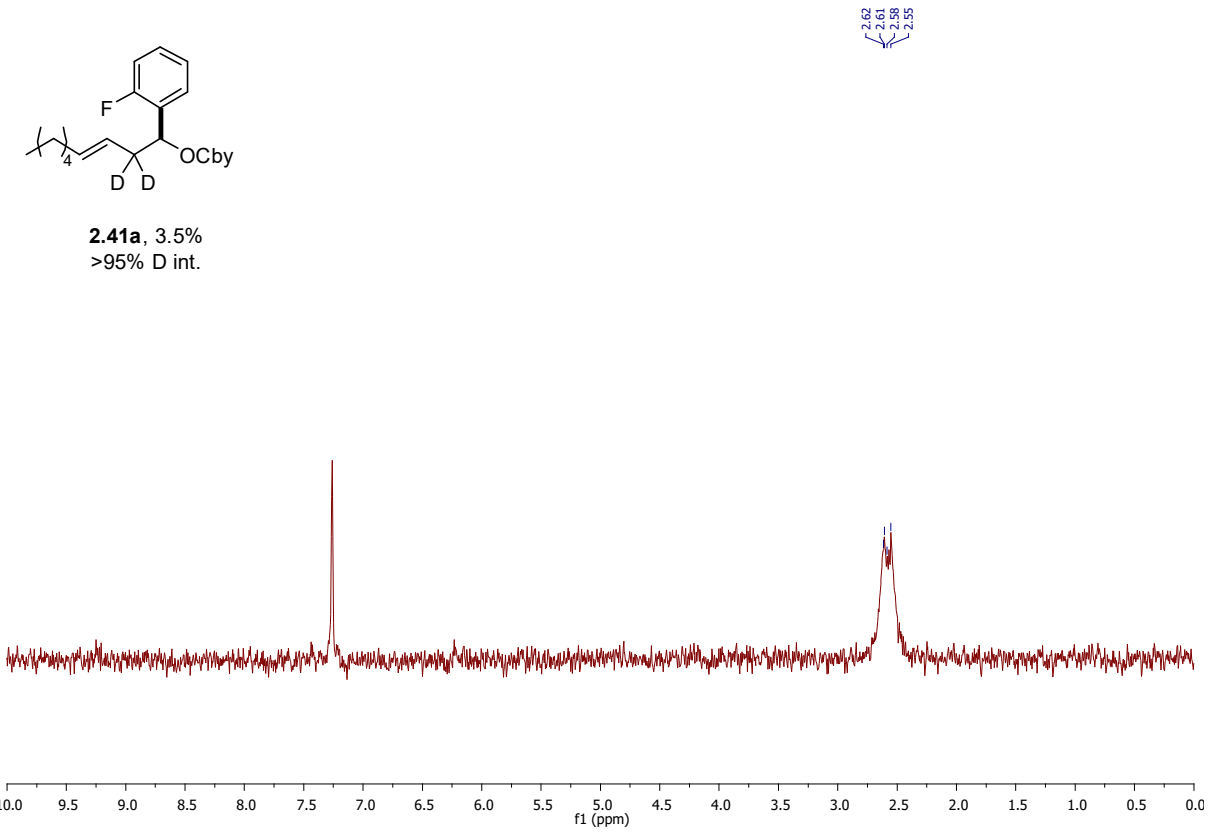




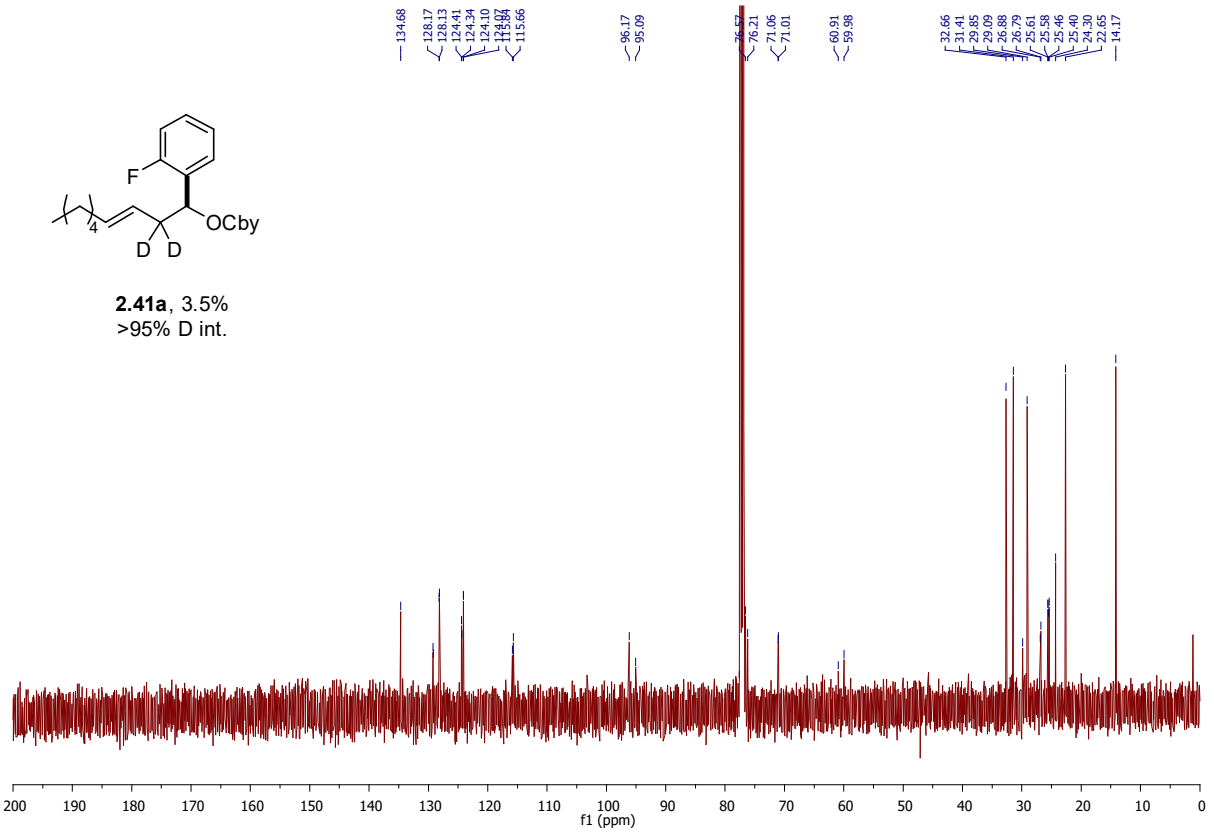
^{1}H NMR of the α-arylated product (rotamers) **2.41a**:



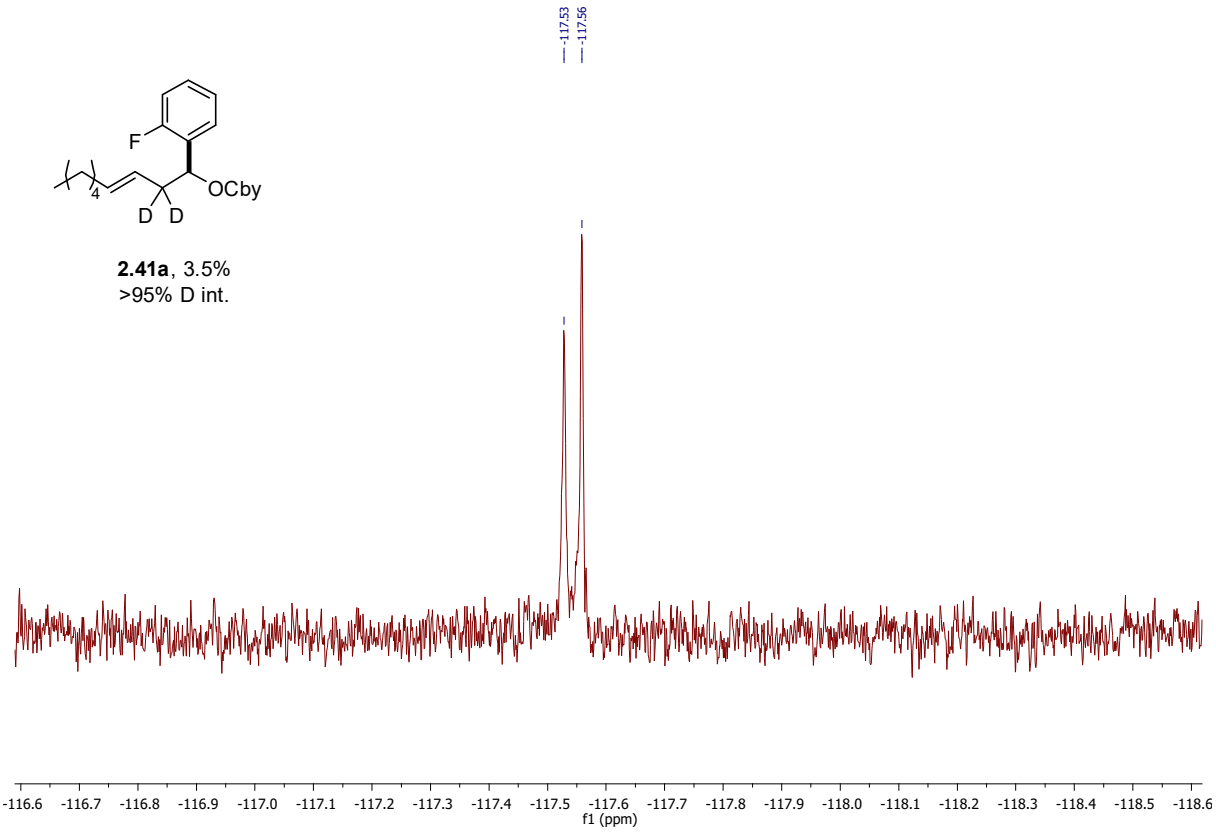
^{2}H NMR of the α-arylated product (rotamers) **2.41a**:



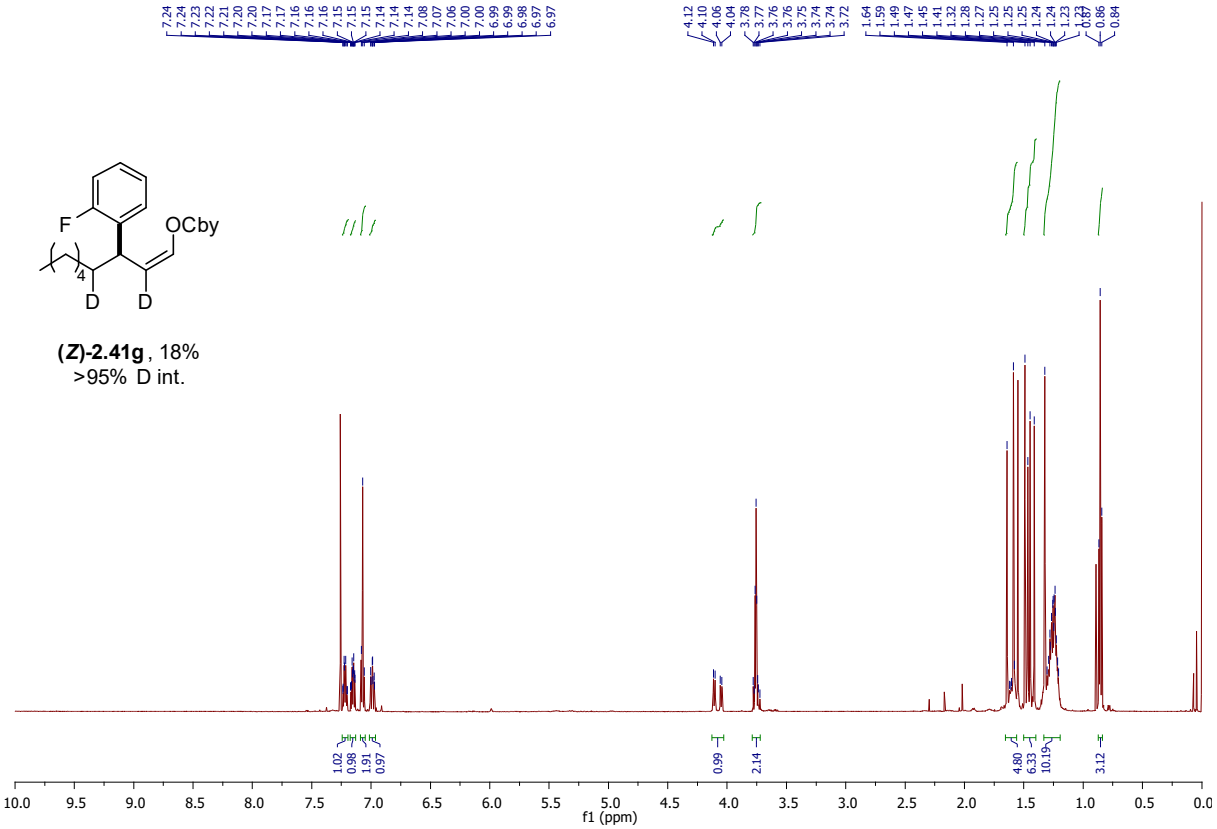
^{13}C NMR of the α-arylated product (rotamers) **2.41a**:



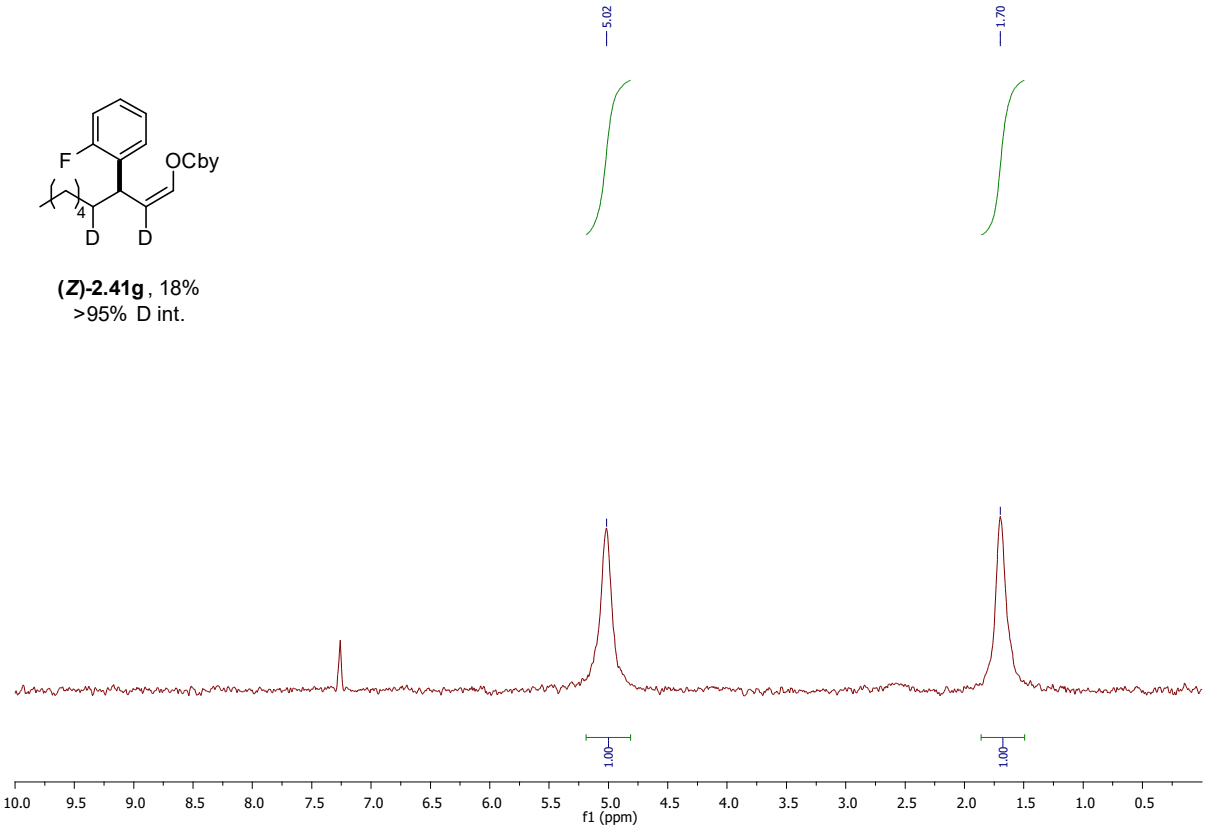
^{19}F NMR of the α-arylated product (rotamers) **2.41a**:



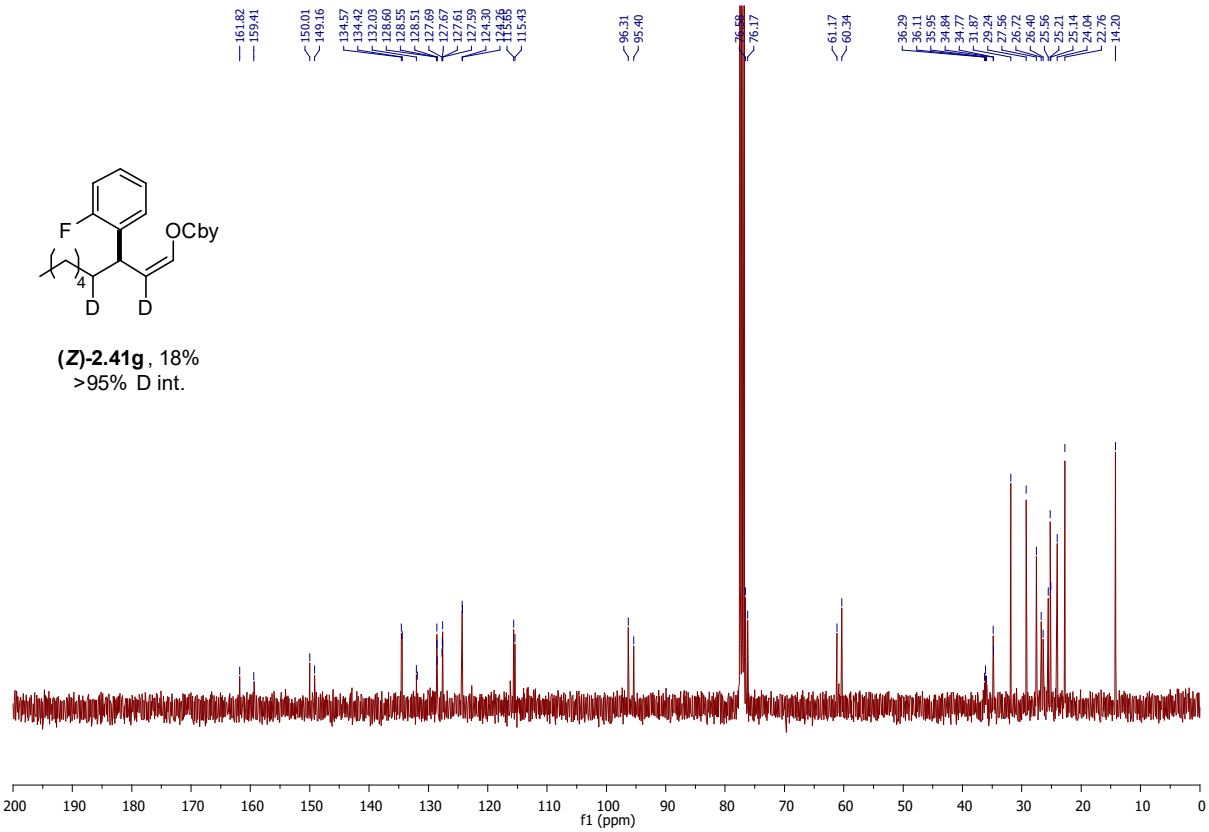
^{1}H NMR of the γ*Z*-arylated product (rotamers) **(*Z*)-2.41g**:



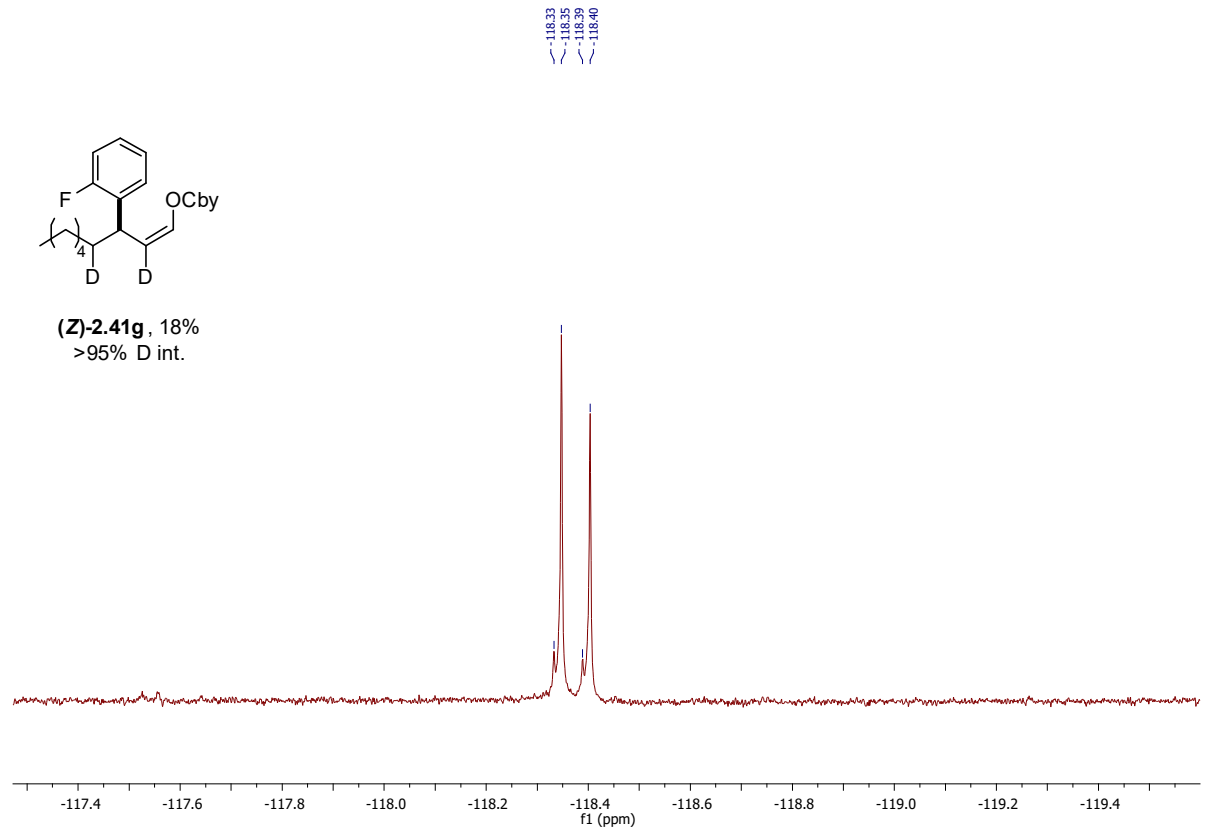
^{2}H NMR of the γ*Z*-arylated product (rotamers) **(*Z*)-2.41g**:



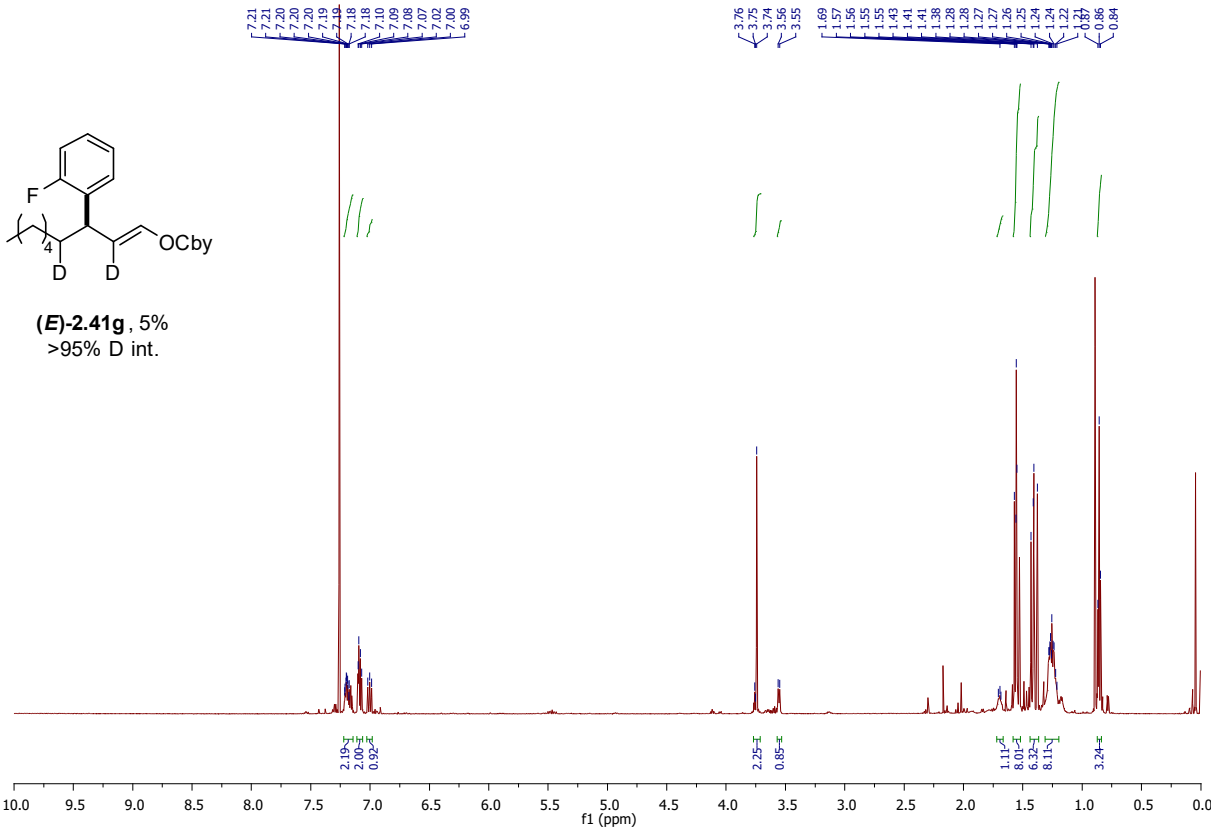
^{13}C NMR of the γ*Z*-arylated product (rotamers) **(*Z*)-2.41g**:



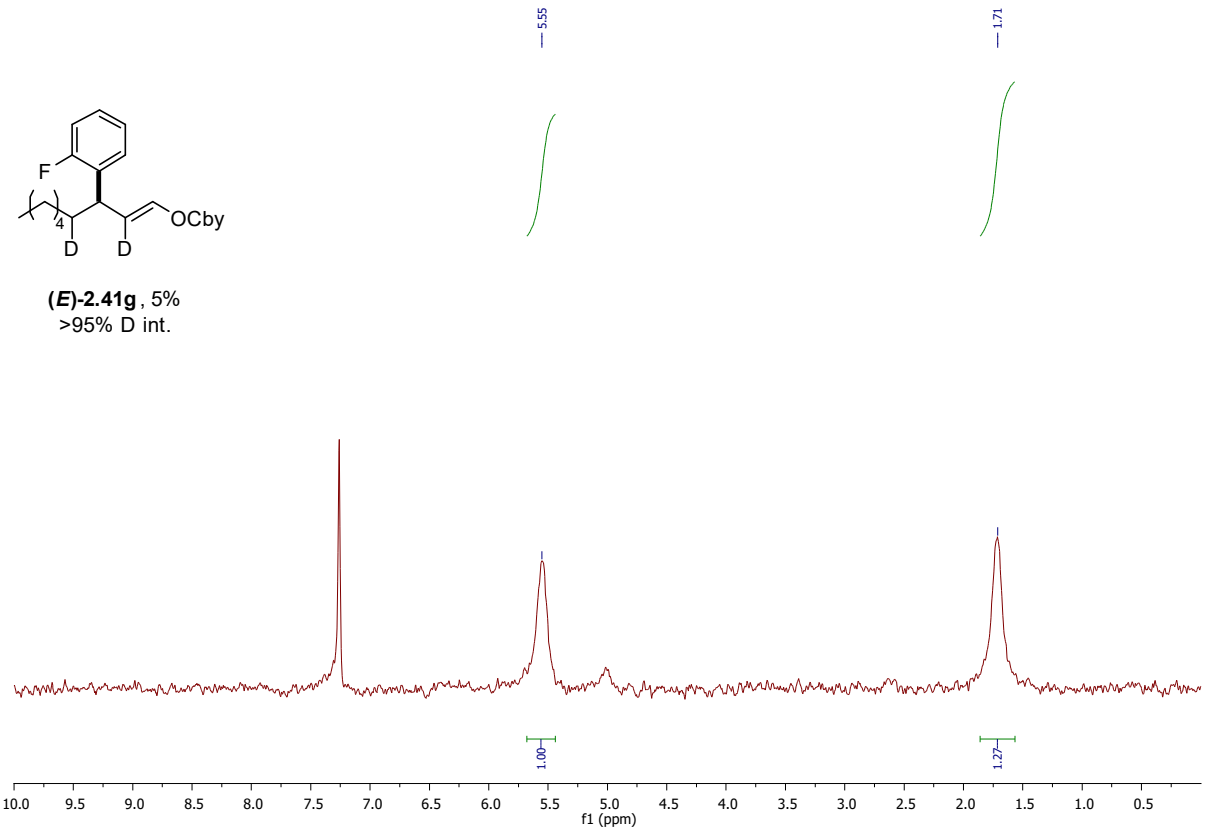
^{19}F NMR of the γ*Z*-arylated product (rotamers) **(*Z*)-2.41g**:



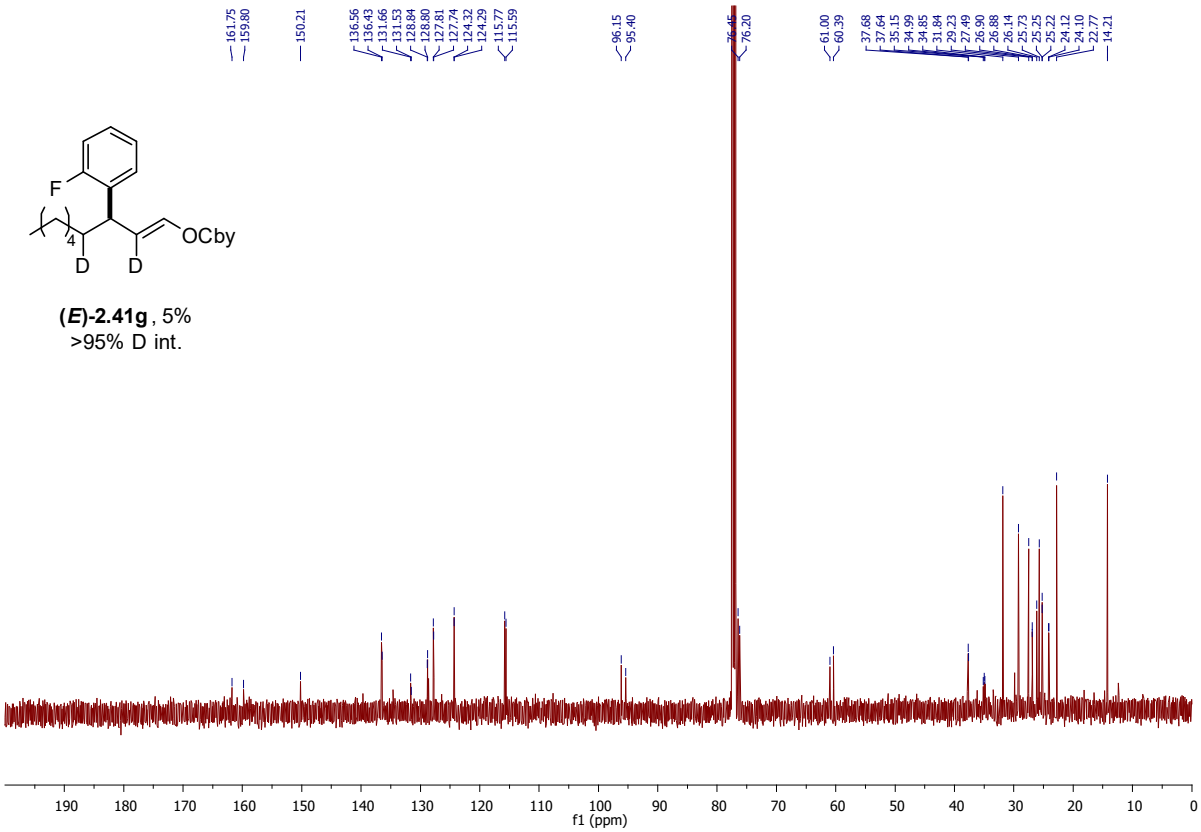
^{1}H NMR of the γ*E*-arylated product**(*E*)-2.41g** (rotamers, contains γ*Z* product):



^{2}H NMR of the γ*E*-arylated product**(*E*)-2.41g** (rotamers, contains γ*Z*product):

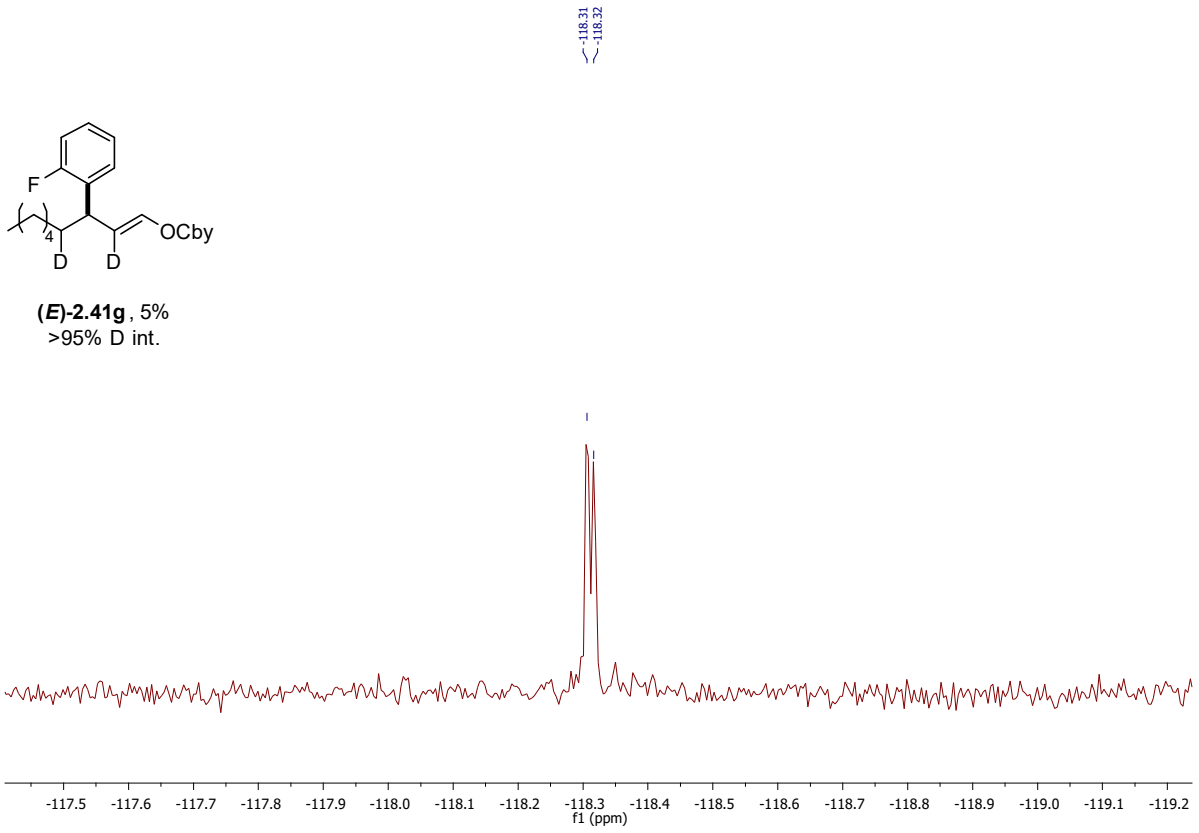


^{13}C NMR of the γ-arylated product(***E*)-2.41g** (rotamers, contains γ*Z* product):



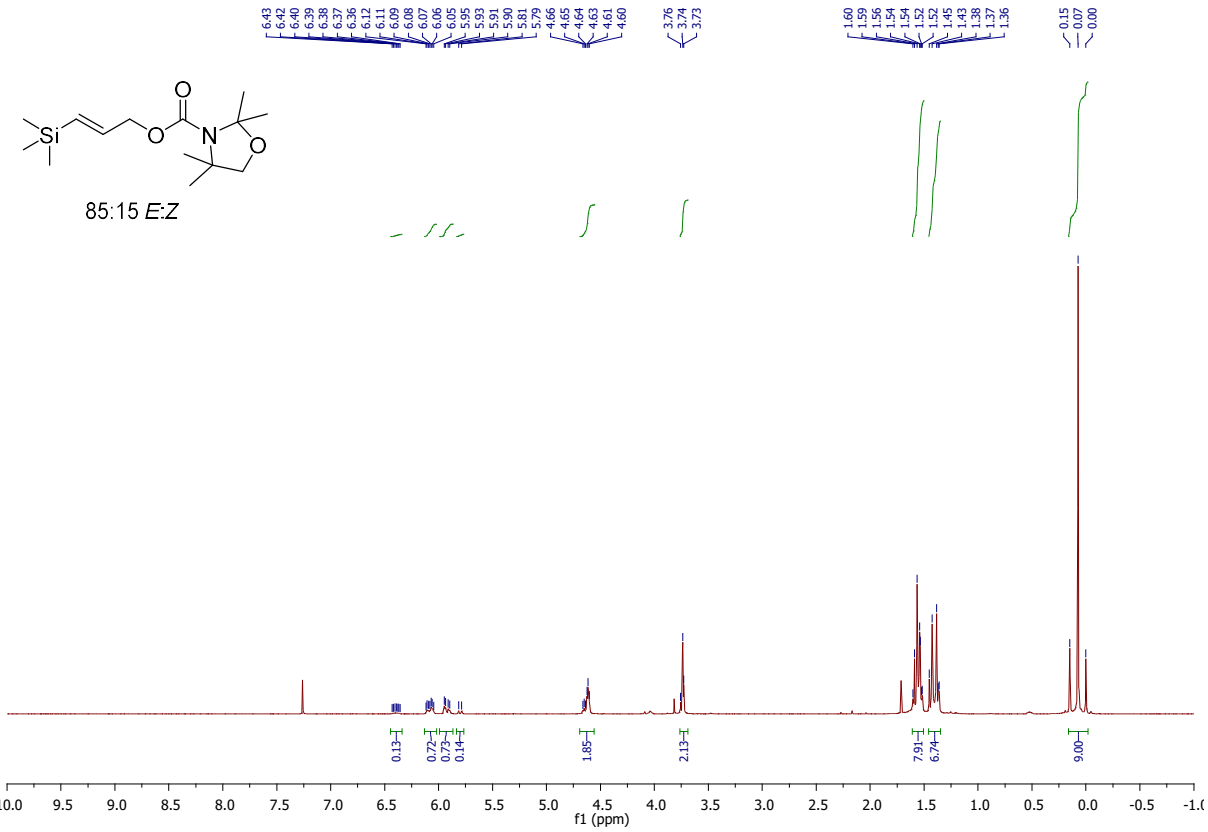
(*E*)-2.41g, 5%
>95% D int.

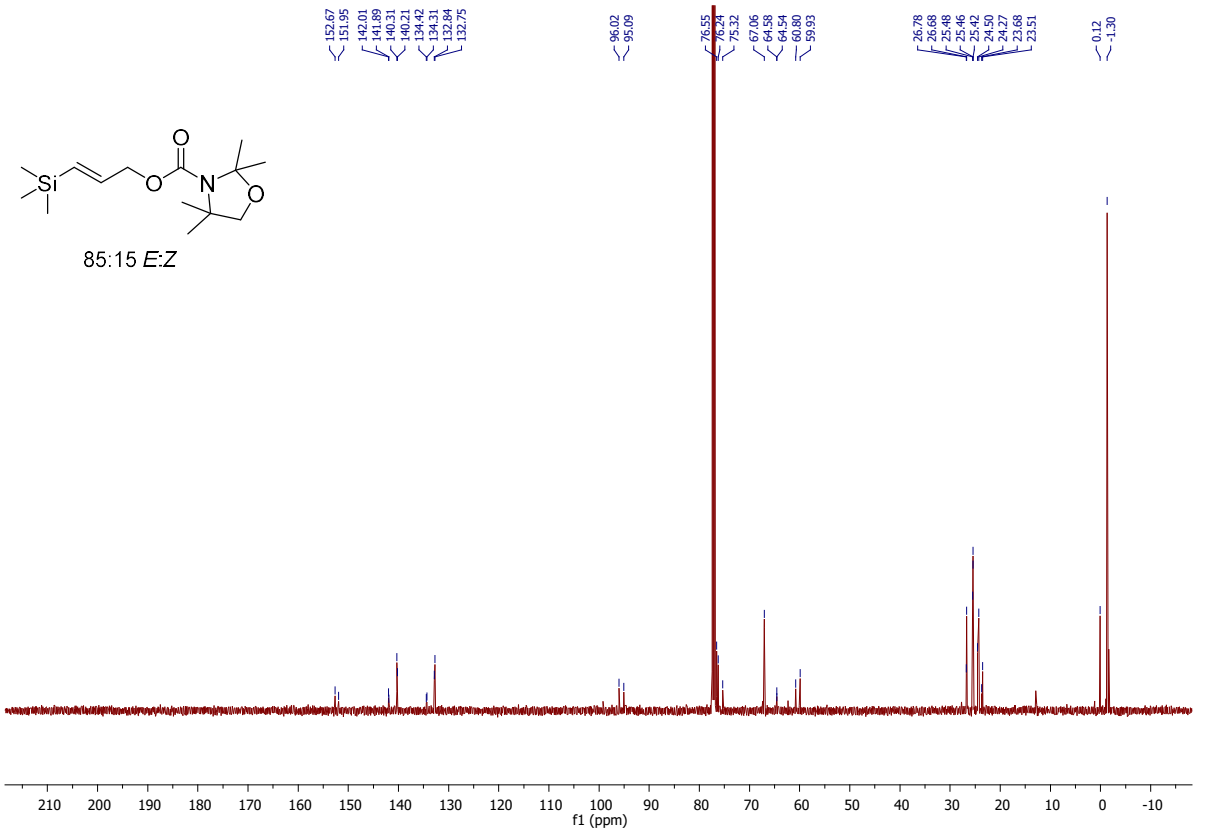
^{19}F NMR of the γ*E*-arylated product **(*E*)-2.41g**:



(*E*)-2.41g, 5%
>95% D int.

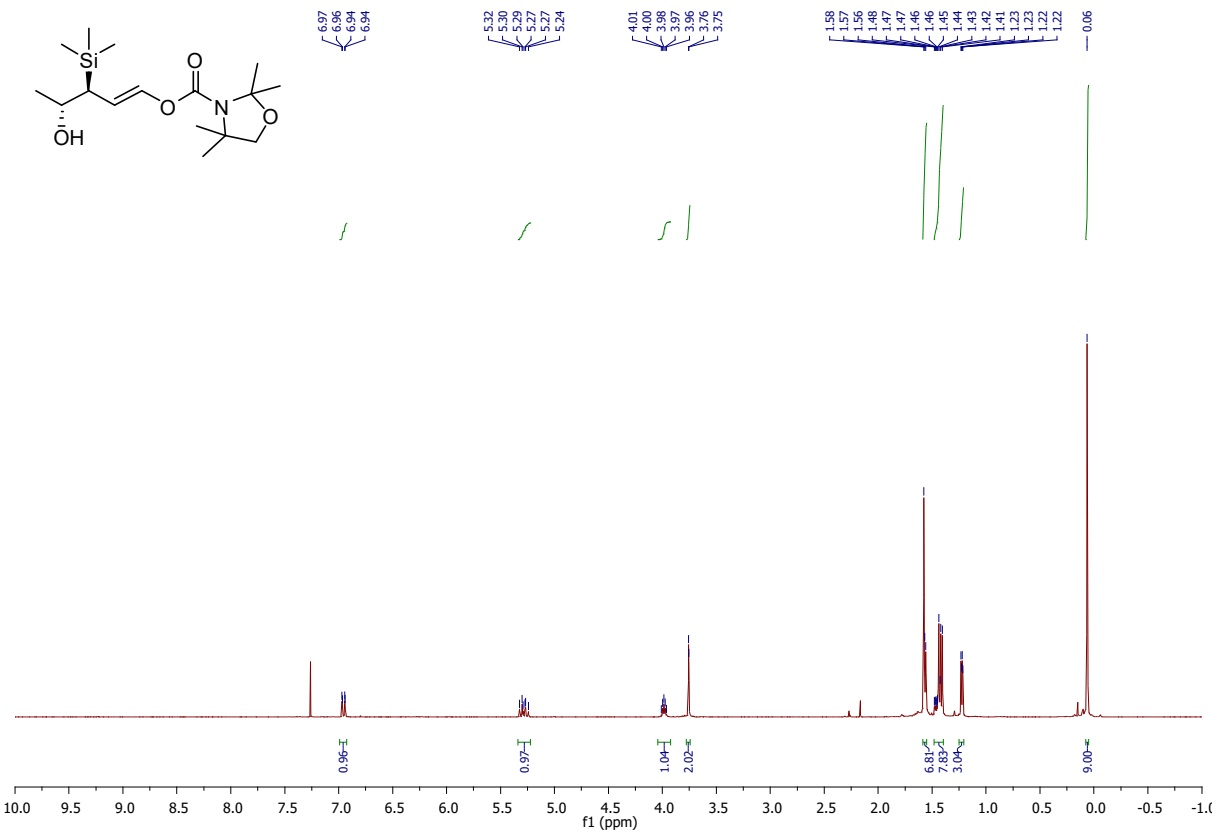
3-(trimethylsilyl)allyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **S12** :

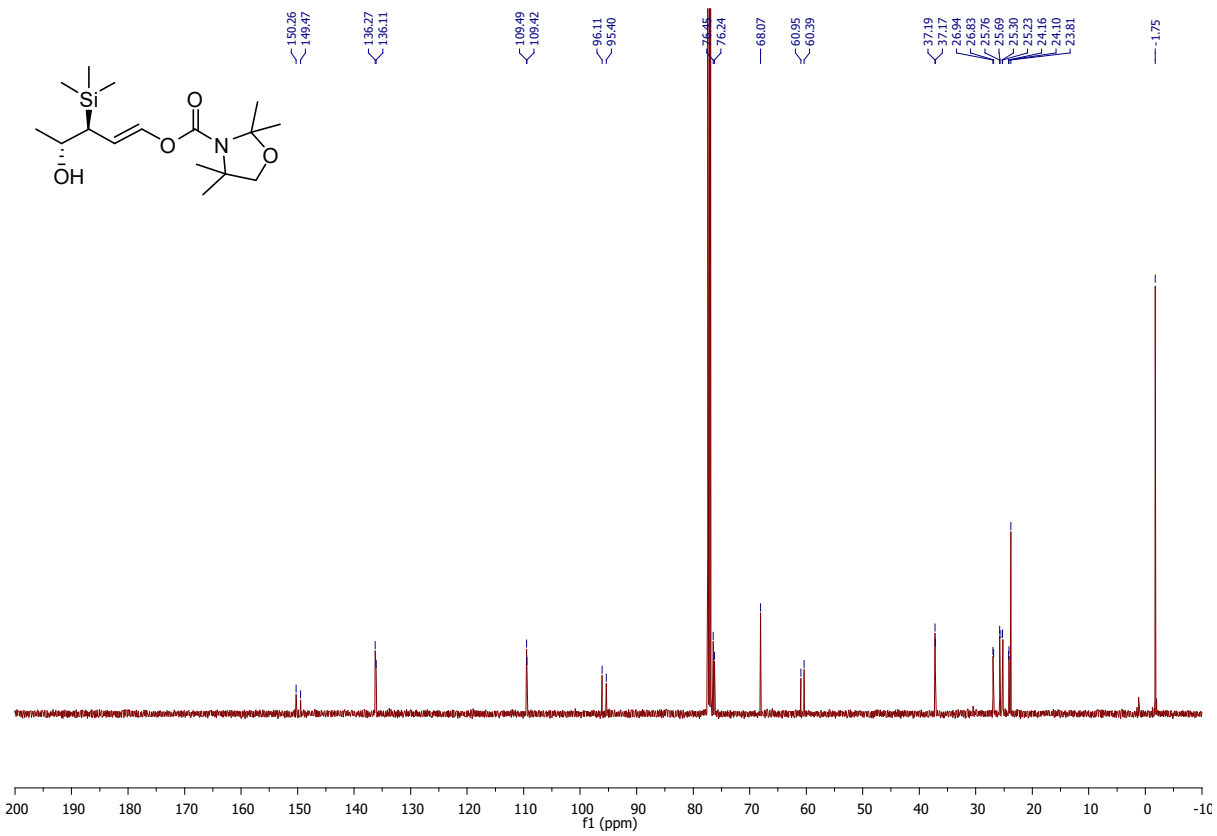




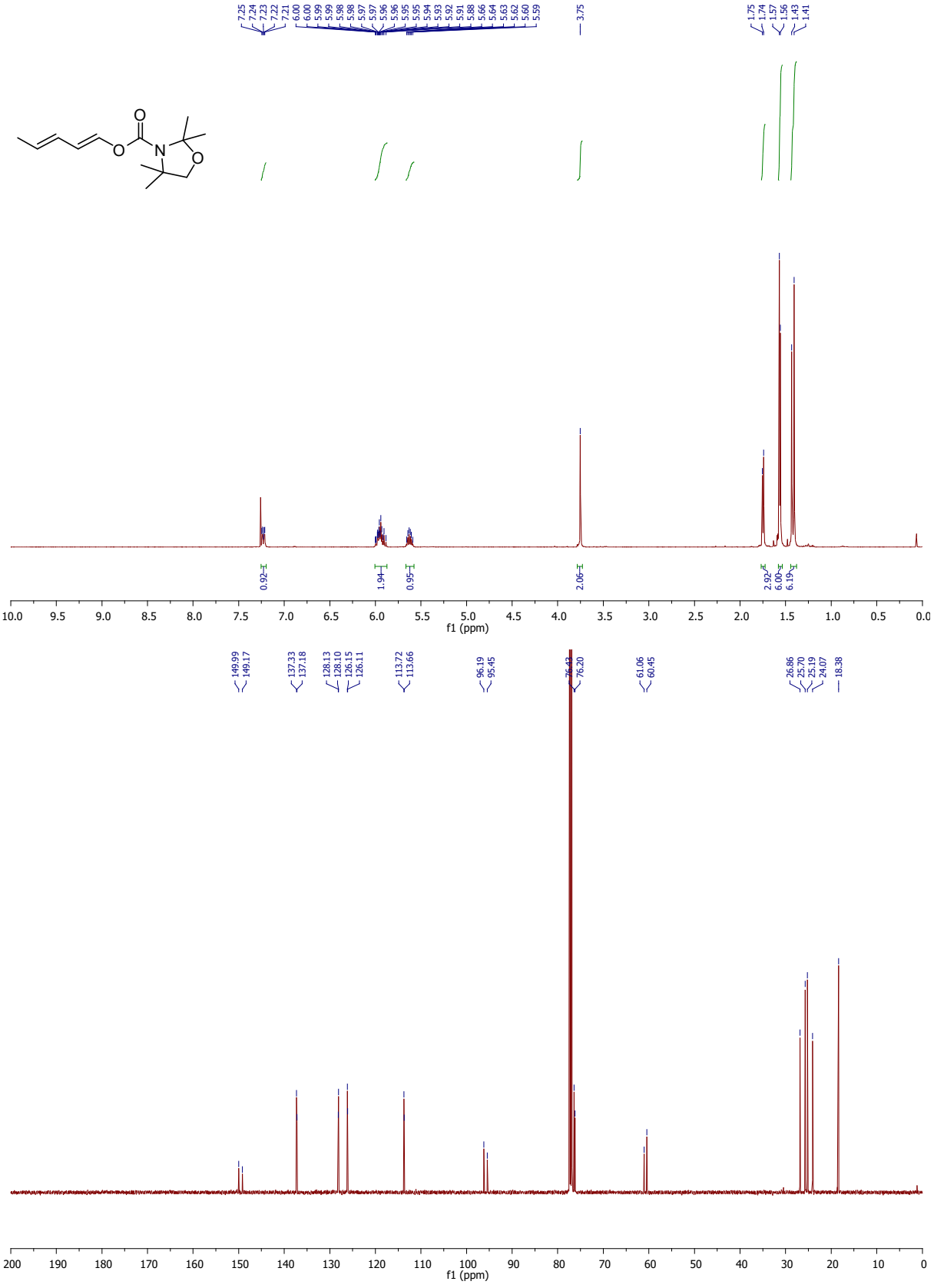
(*E*)-4-hydroxy-3-(trimethylsilyl)pent-1-en-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate

S13 :

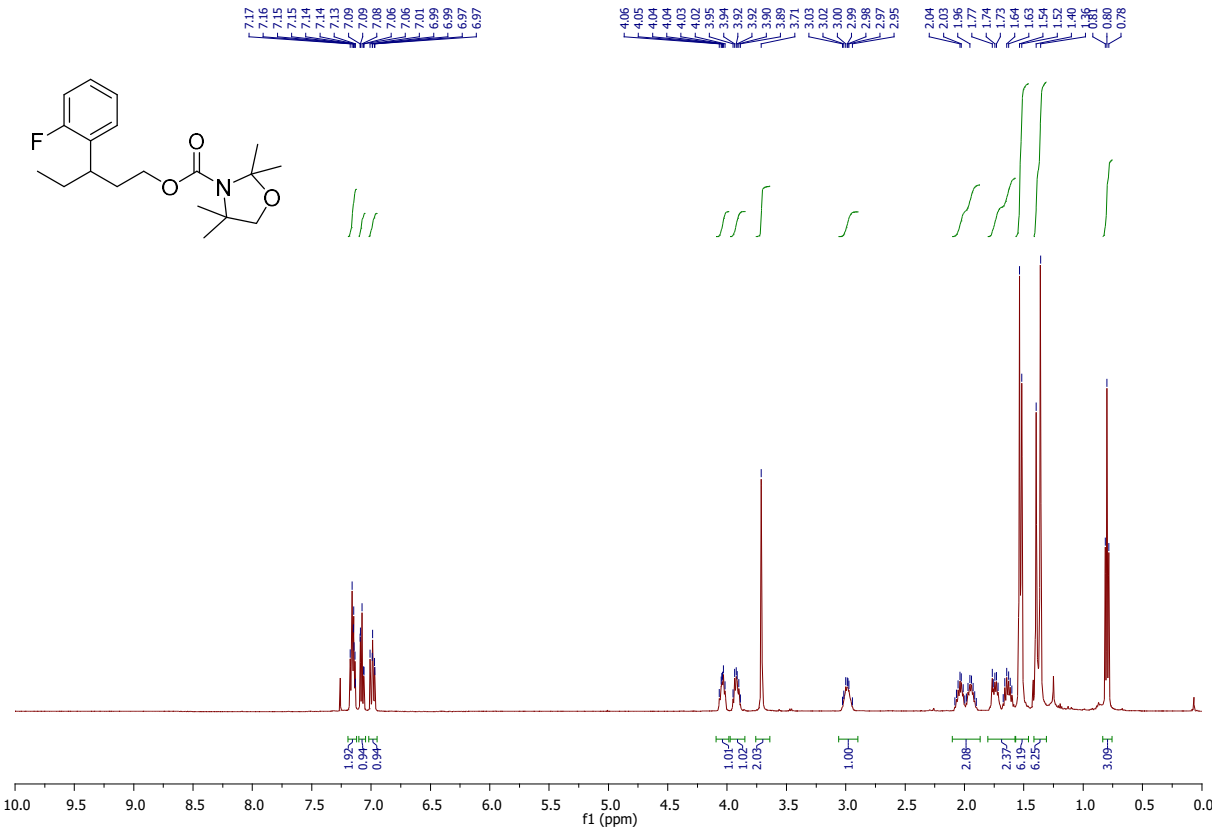


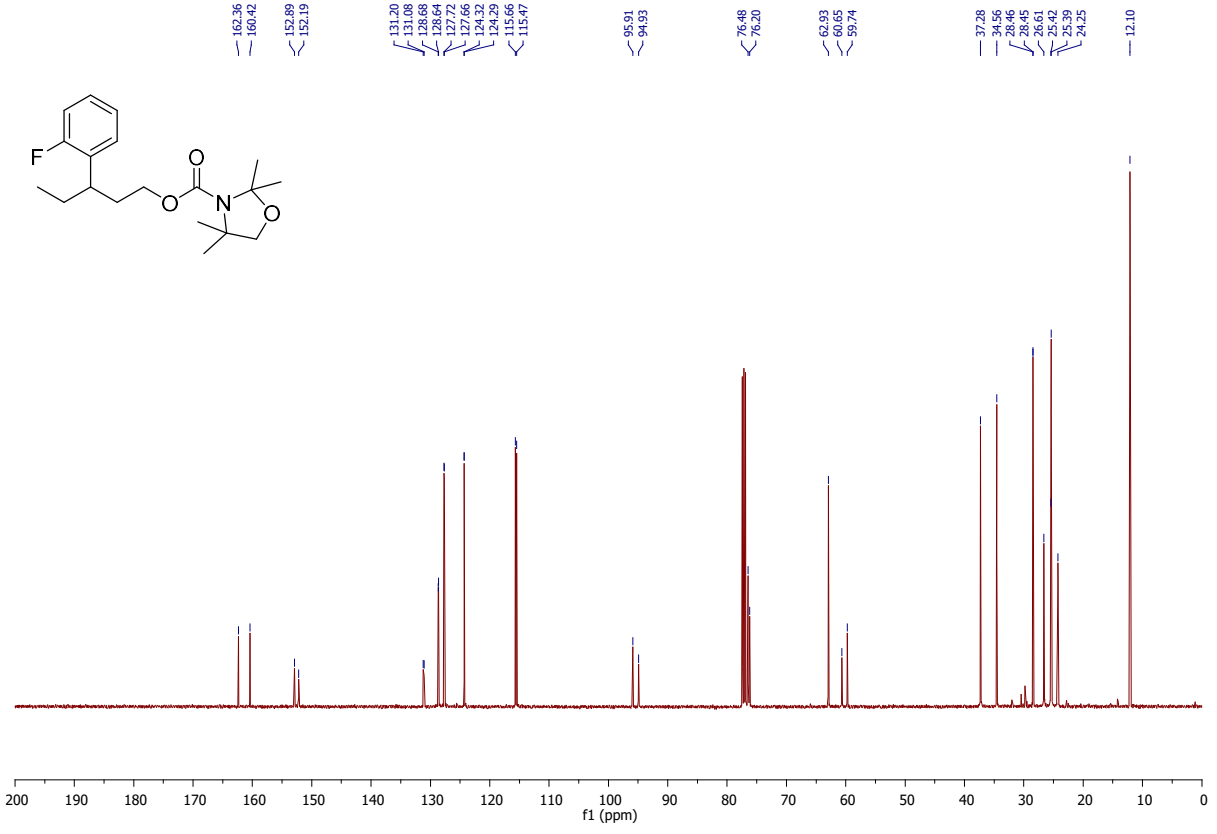


(1*E*,3*E*)-penta-1,3-dien-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate **S14** :

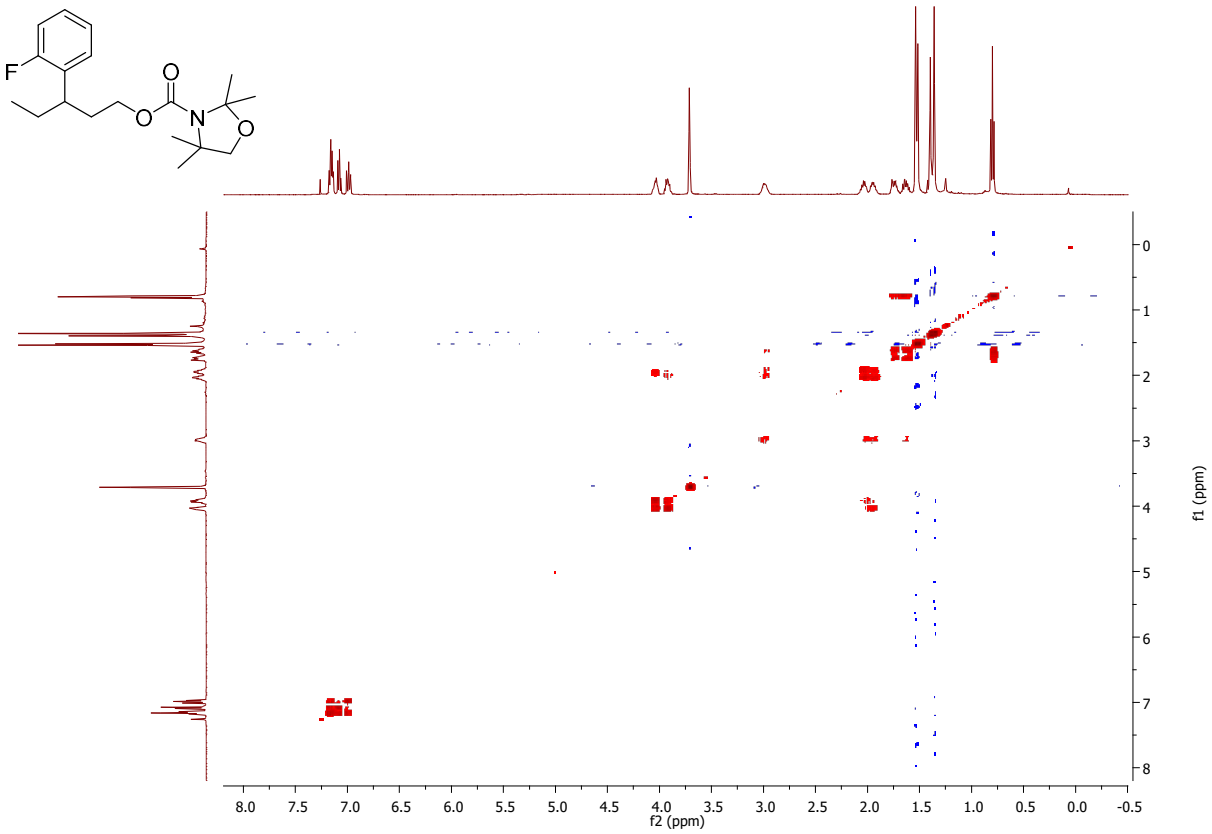


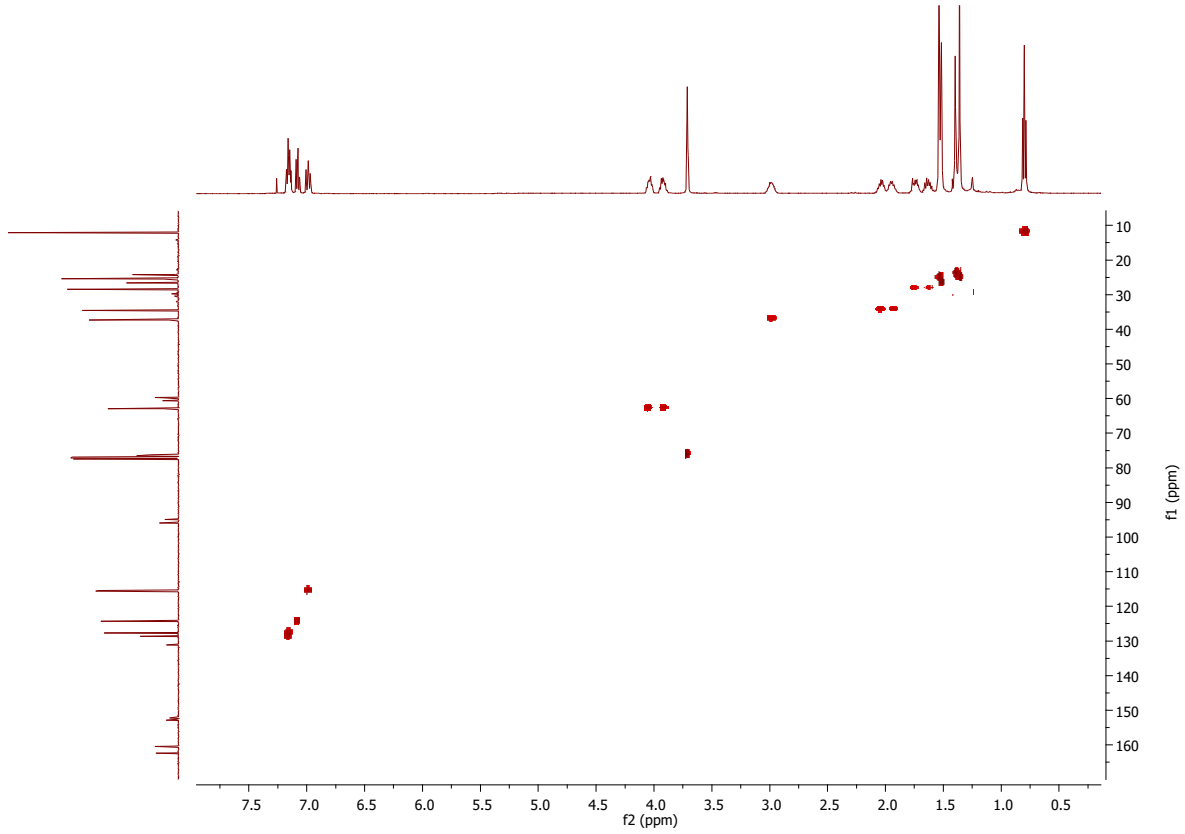
3-(2-fluorophenyl)pentyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.22**:

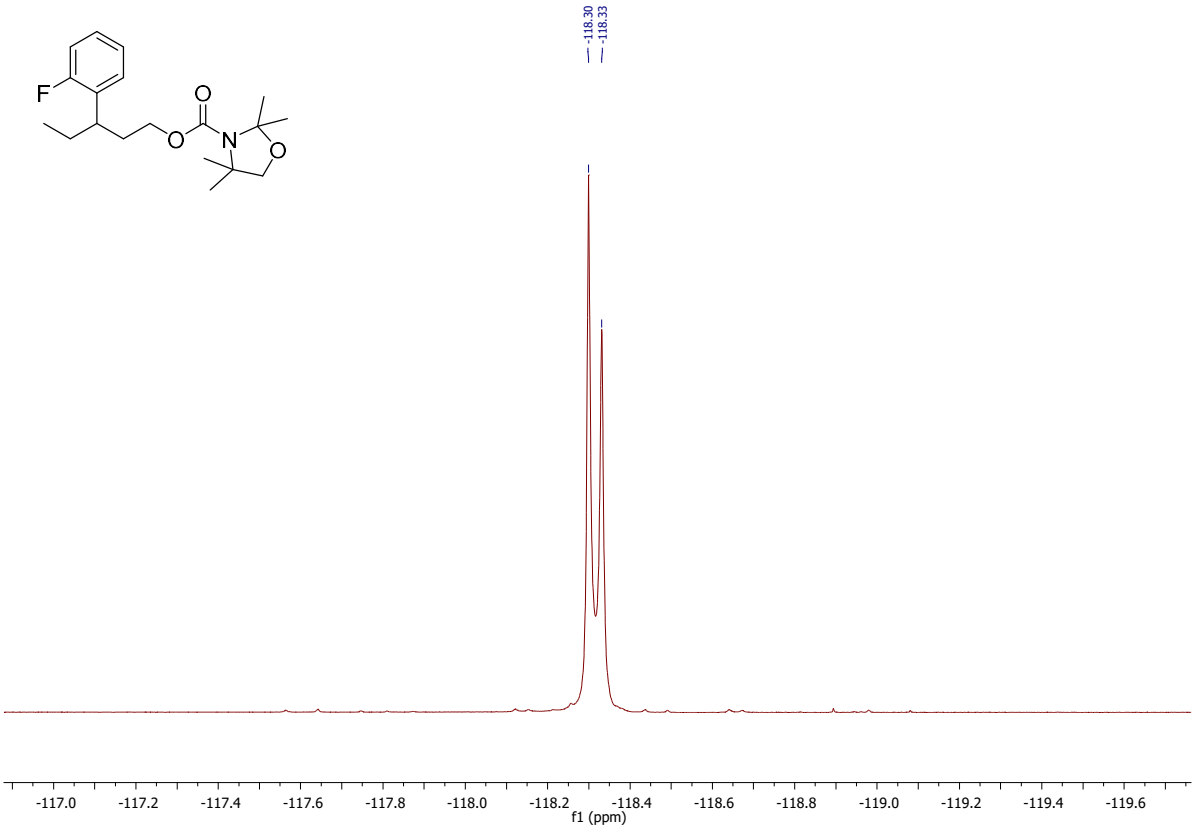




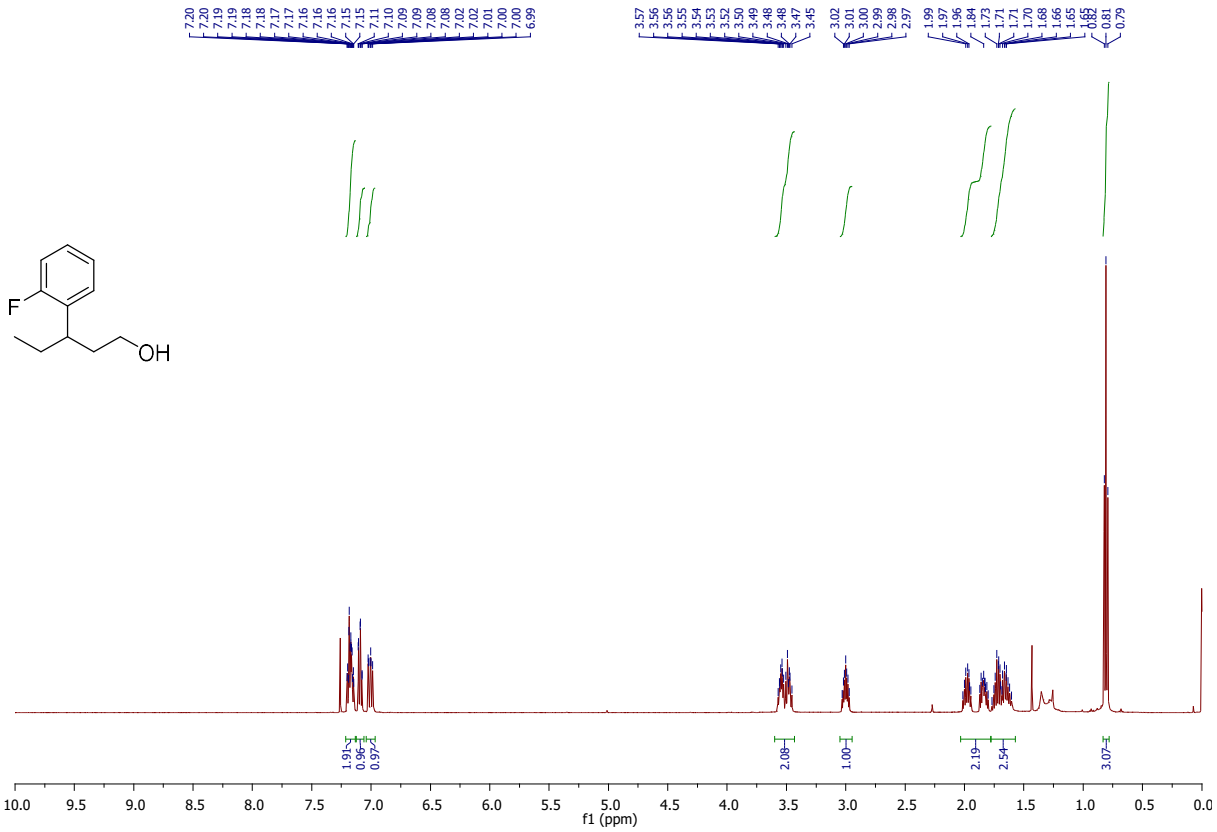
COSY and HMQC experiments :

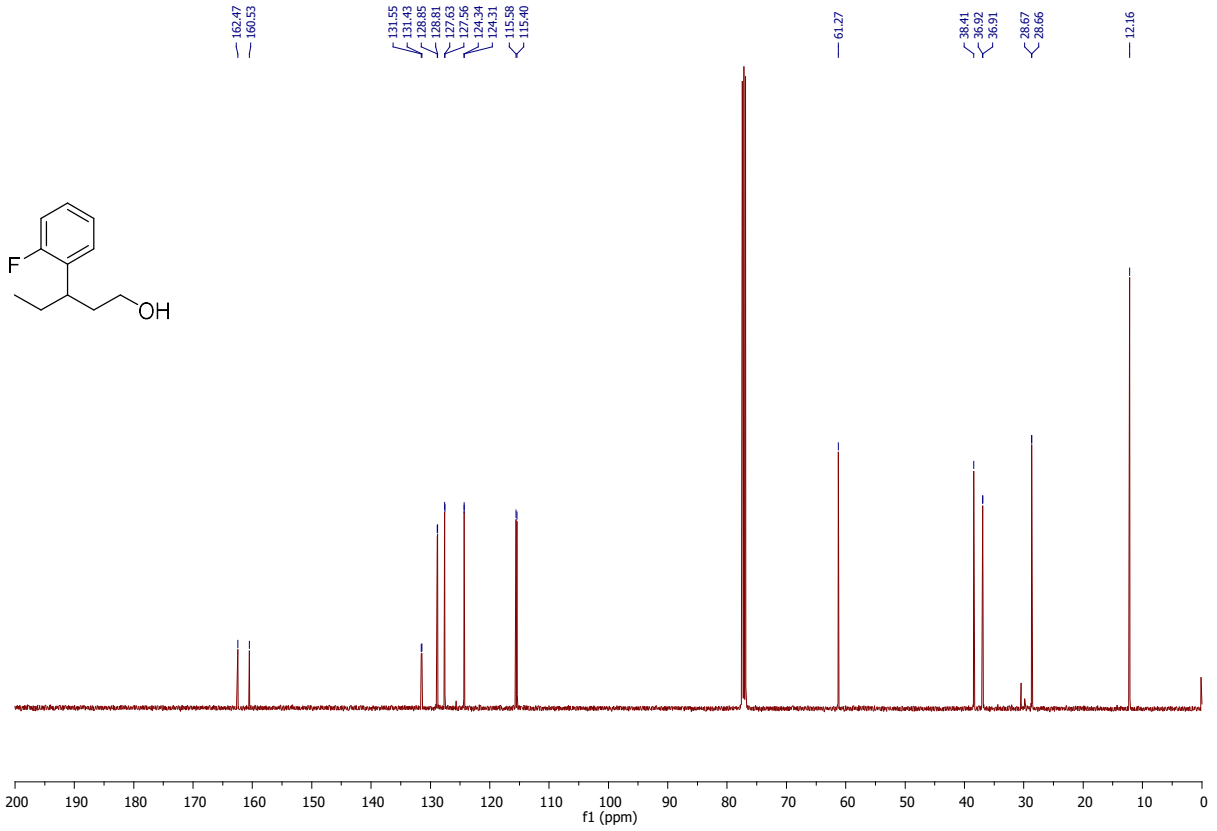




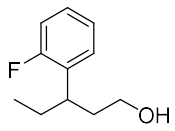

F
O
O
N
O
-118.30
-118.33
-117.0
-117.2
-117.4
-117.6
-117.8
-118.0
-118.2
-118.4
-118.6
-118.8
-119.0
-119.2
-119.4
-119.6
f1 (ppm)

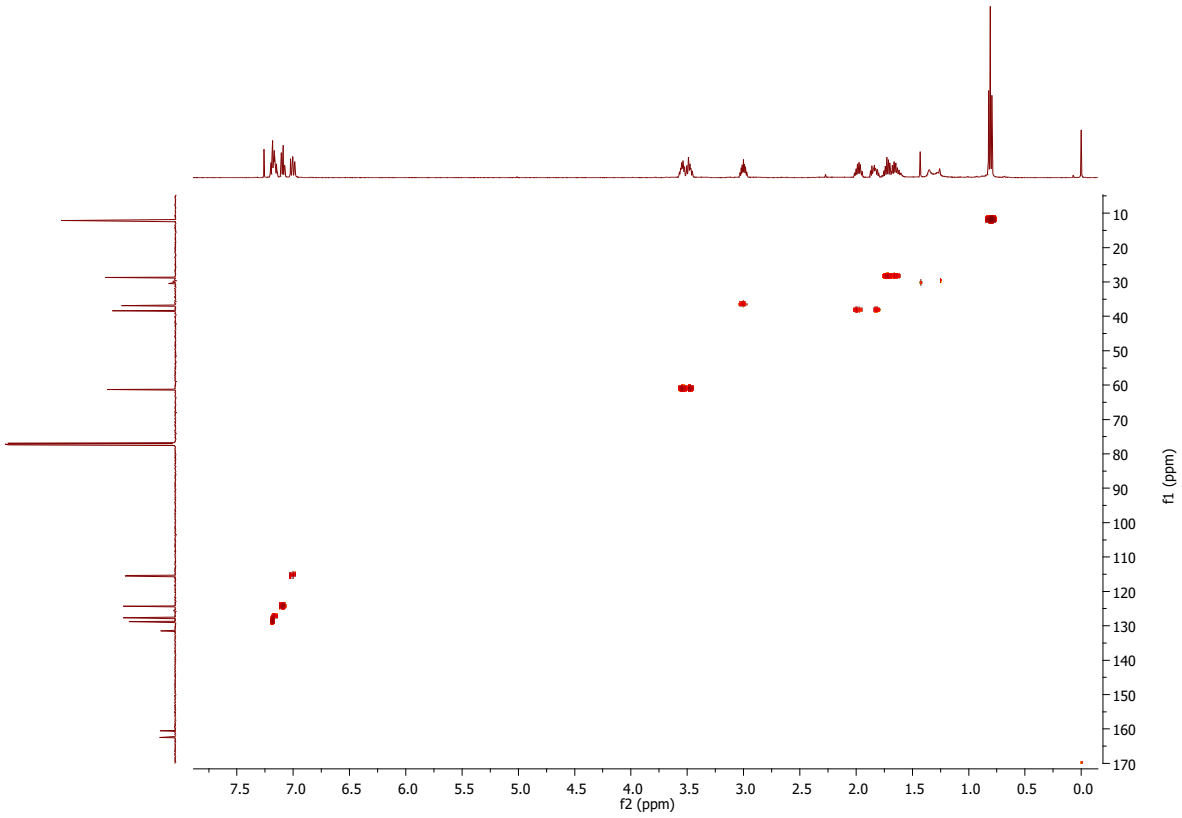
3-(2-fluorophenyl)pentyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate**2.42**:

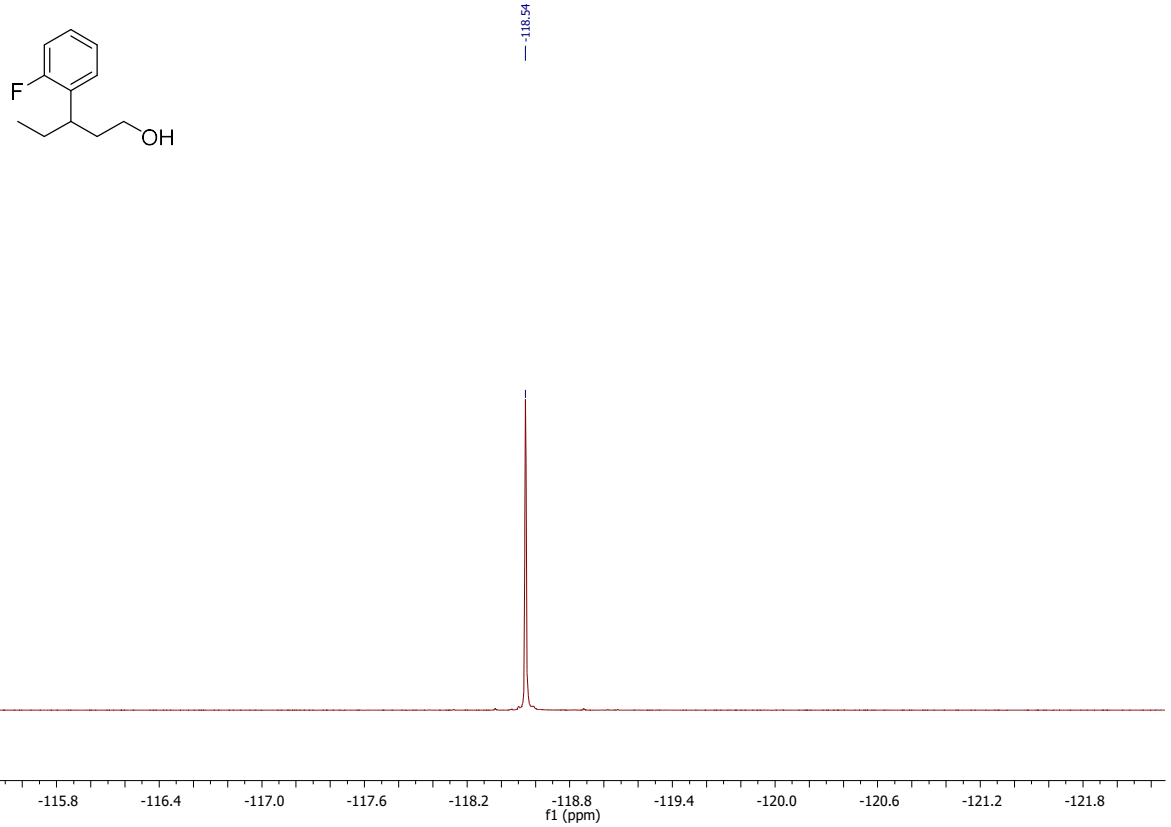




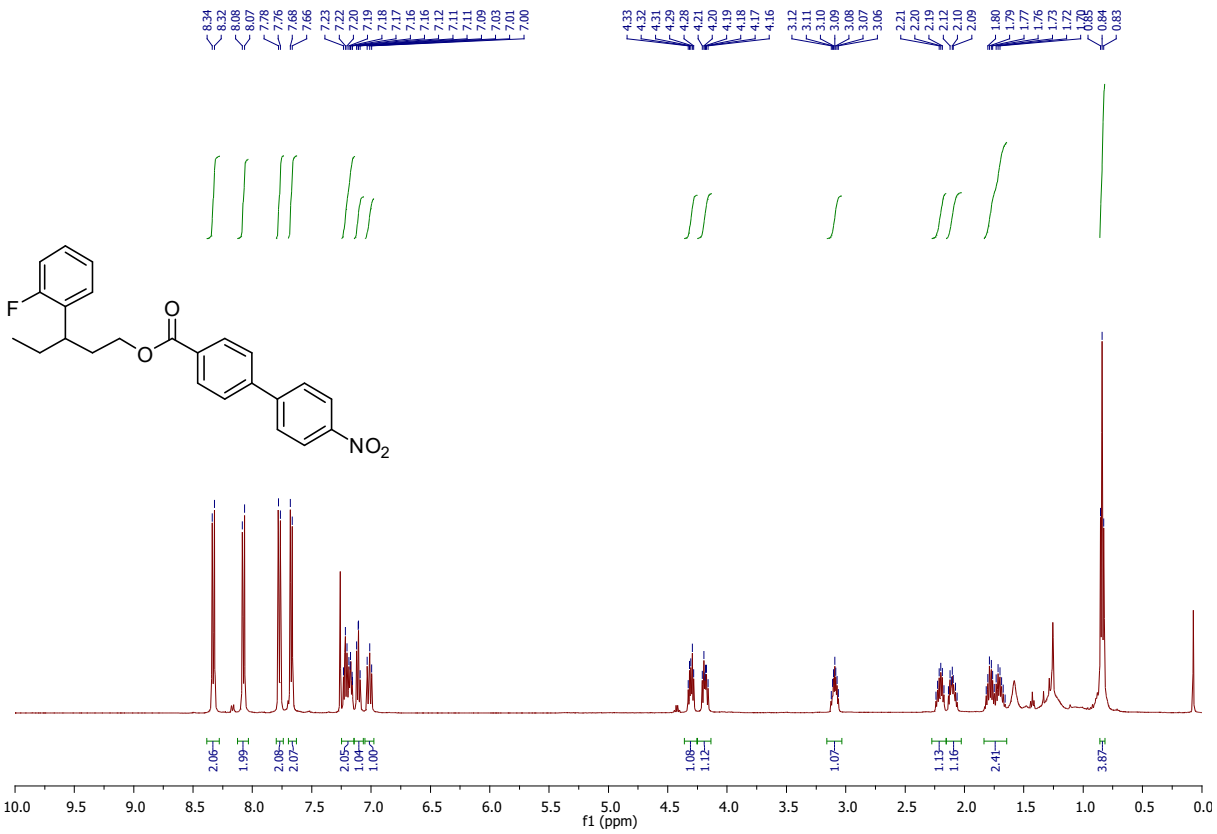
COSY and HMQC experiments :

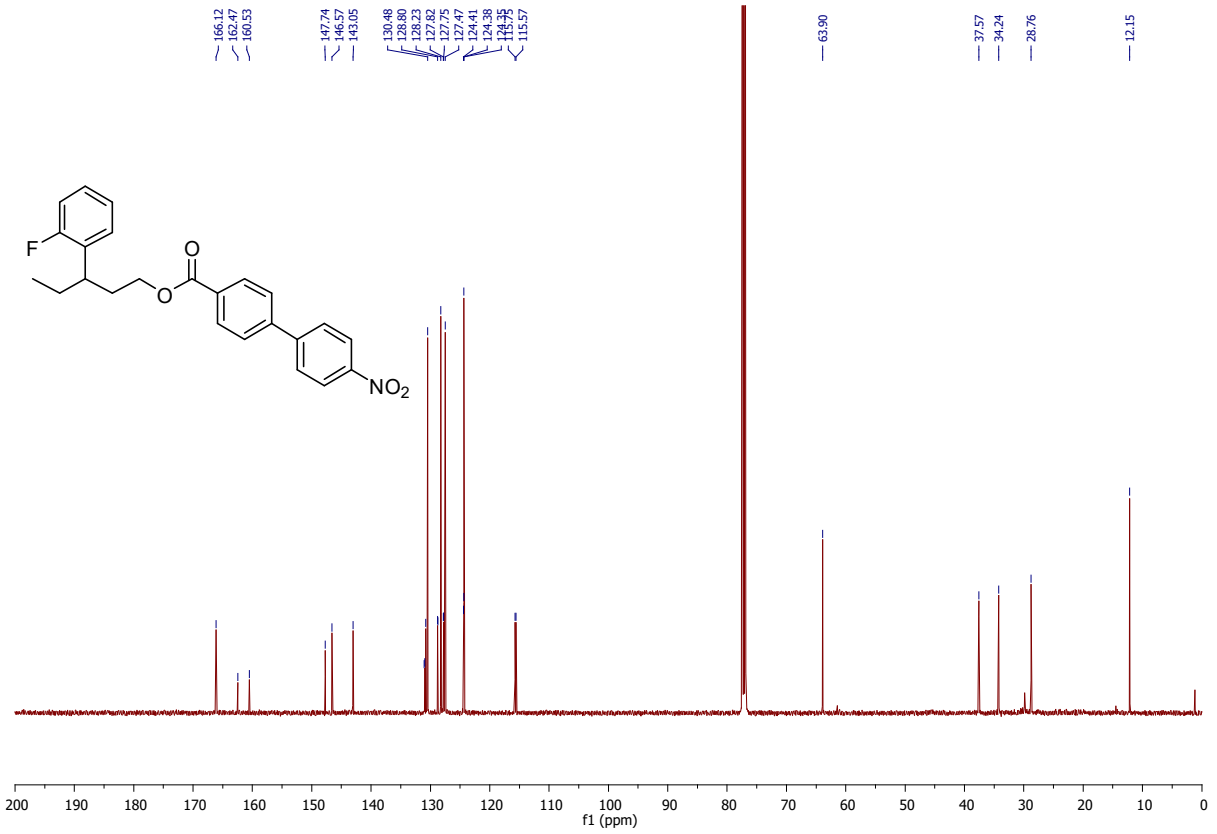




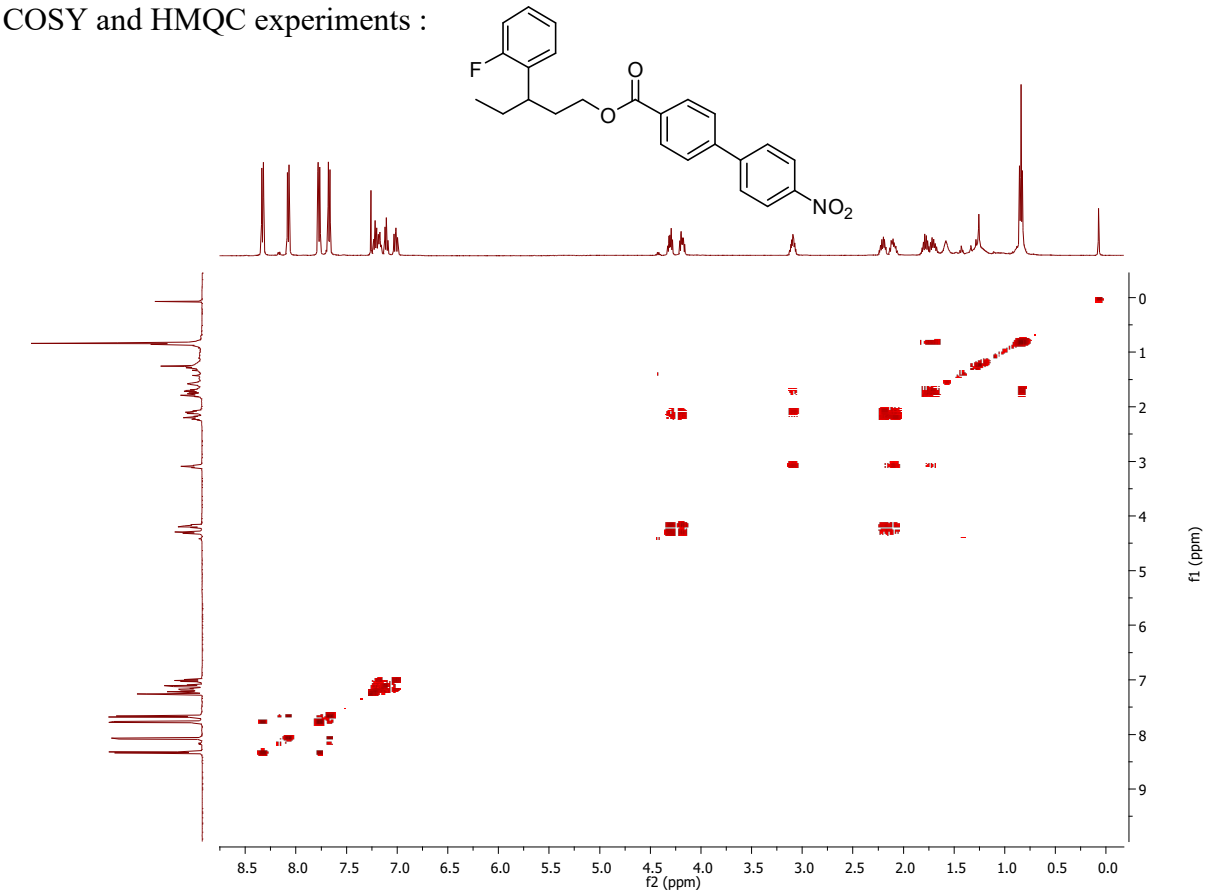

F
OH
-118.54
-115.8
-116.4
-117.0
-117.6
-118.2
-118.8
-119.4
-120.0
-120.6
-121.2
-121.8
f1 (ppm)

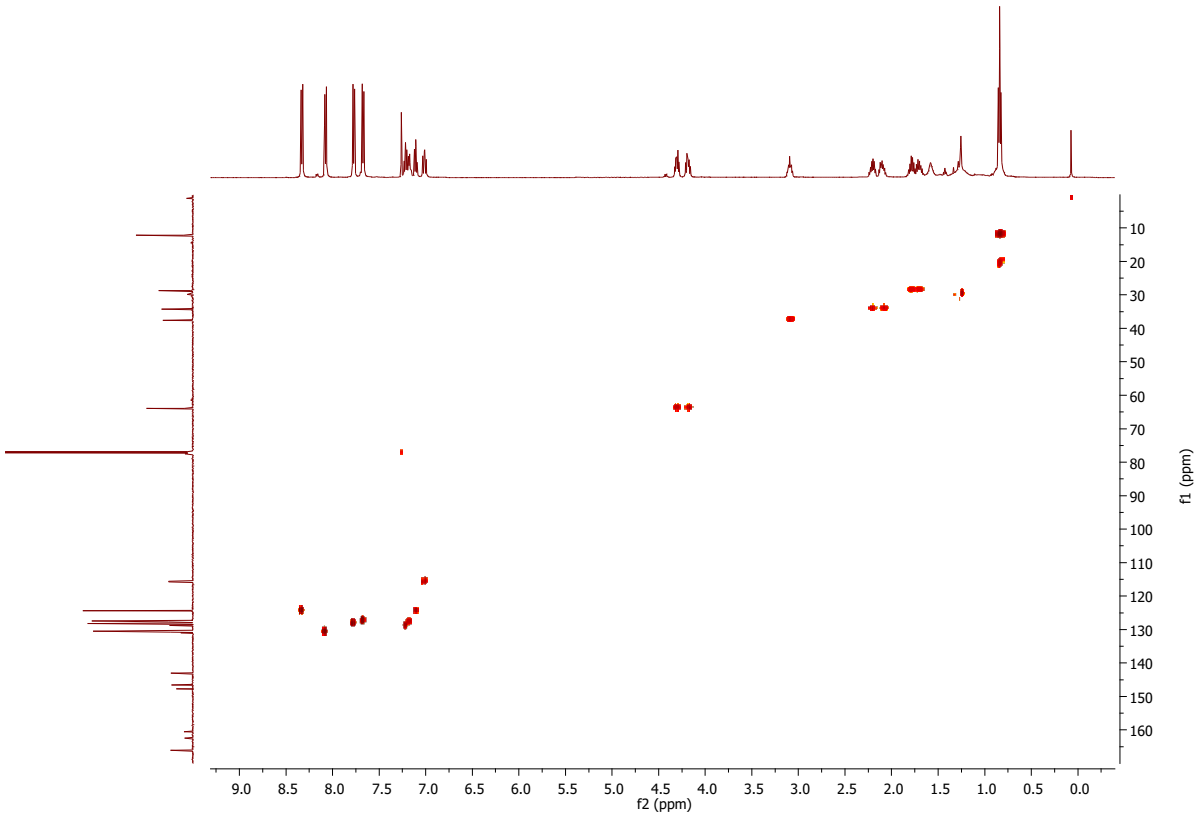
3-(2-fluorophenyl)pentyl 4'-nitro-[1,1'-biphenyl]-4-carboxylate**2.43c** :





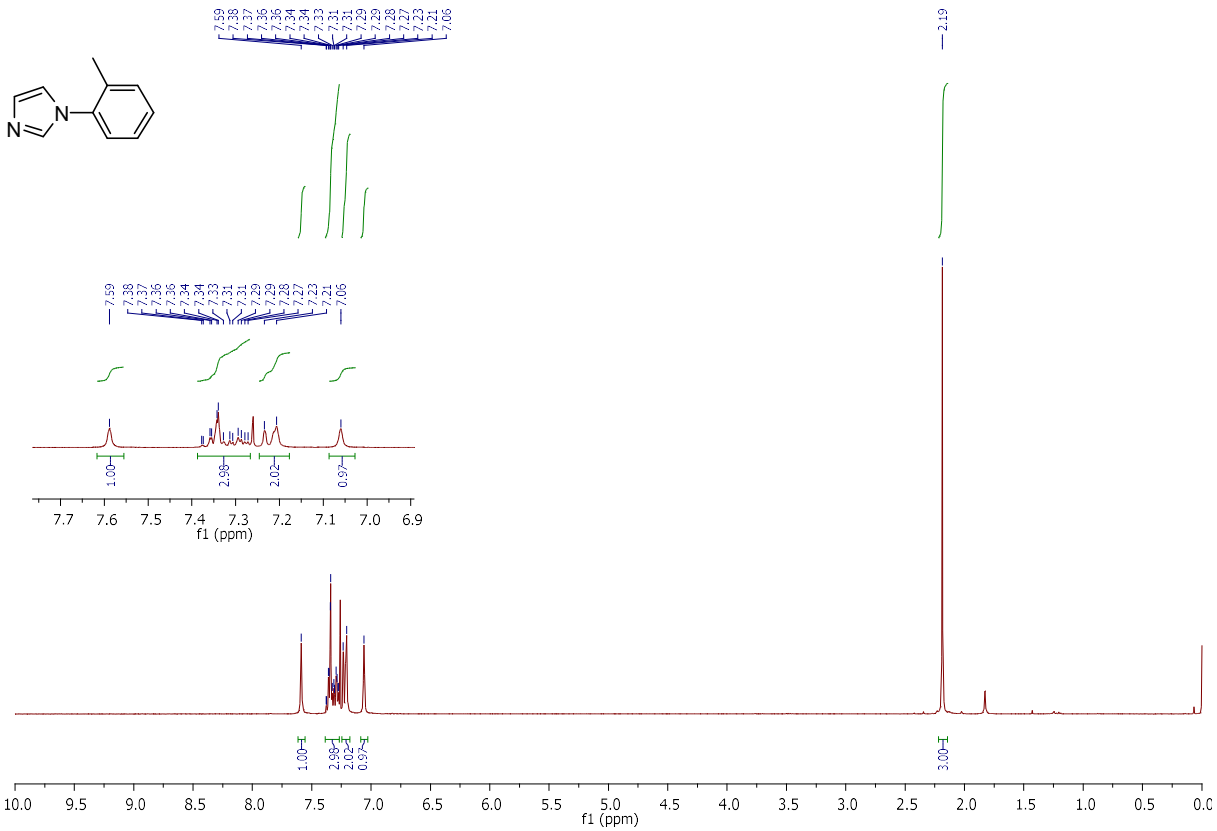
COSY and HMQC experiments :

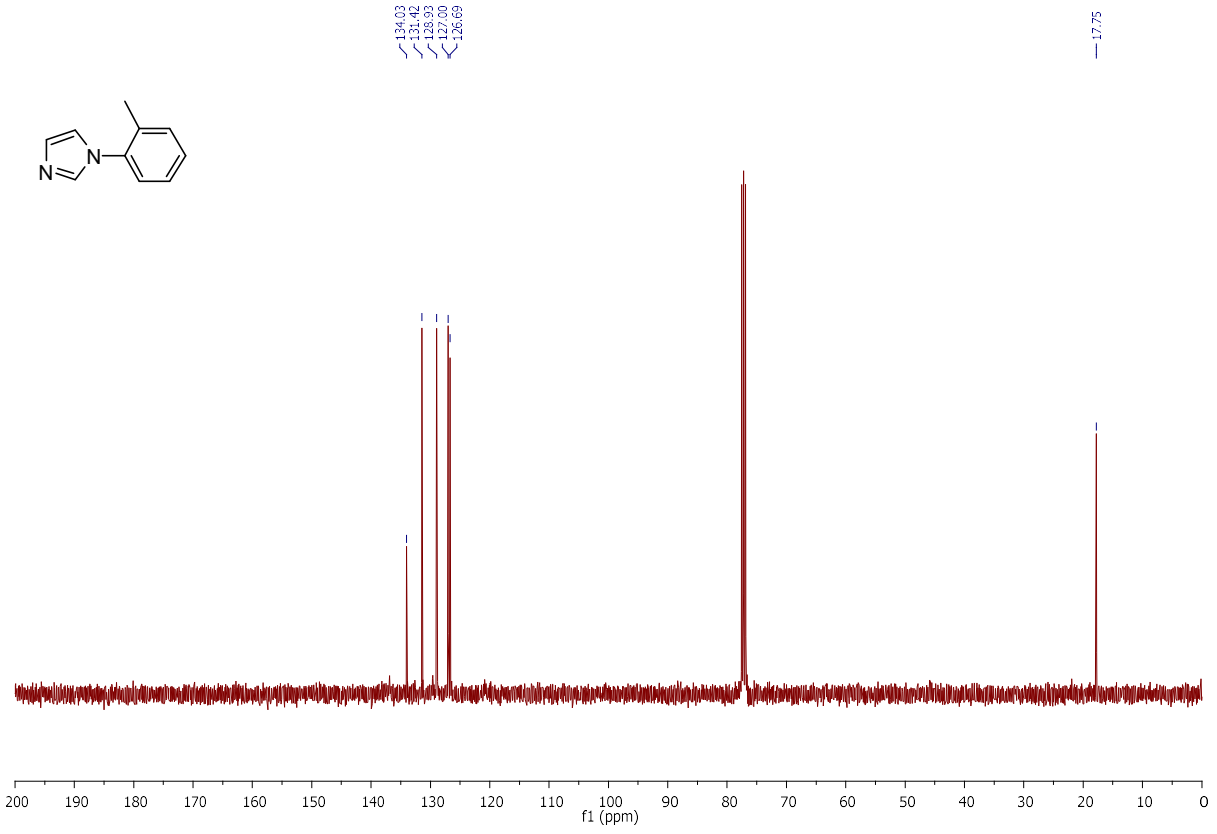




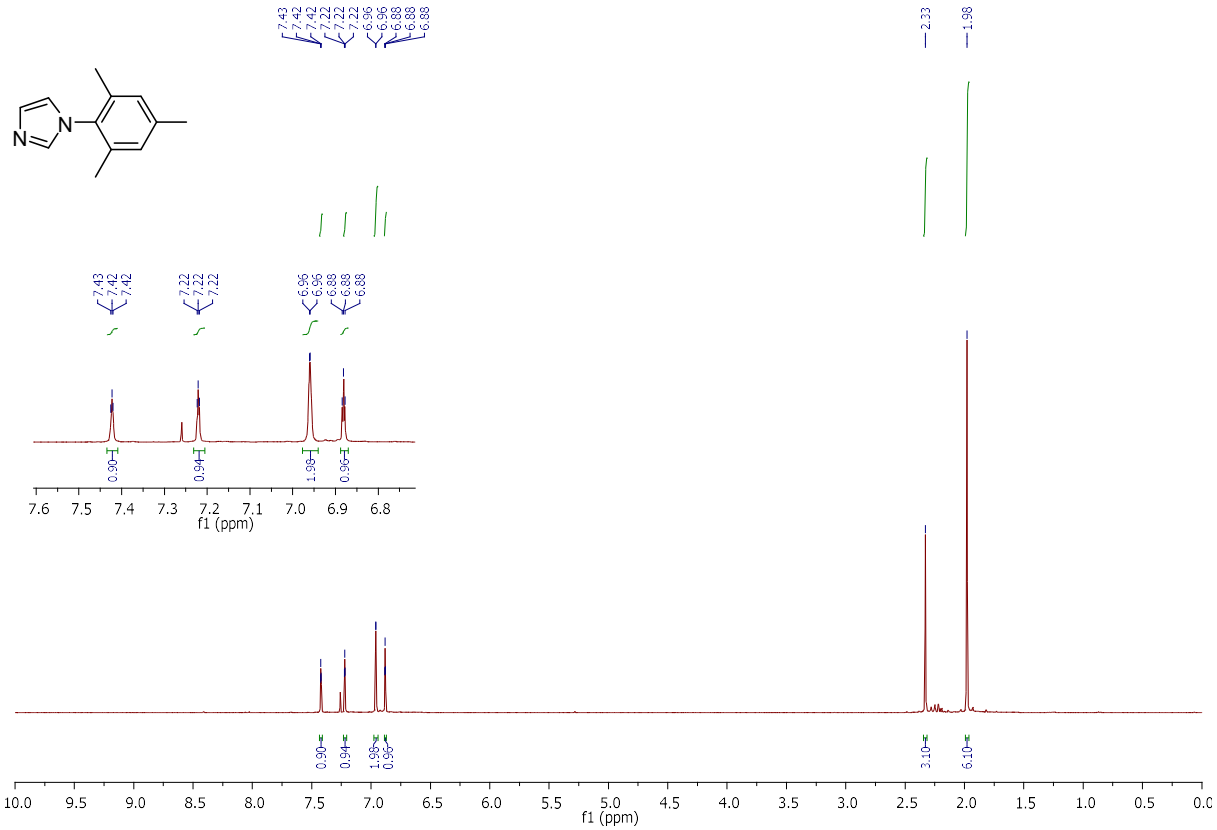

F
O
O
NO2
-118.40
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
f1 (ppm)

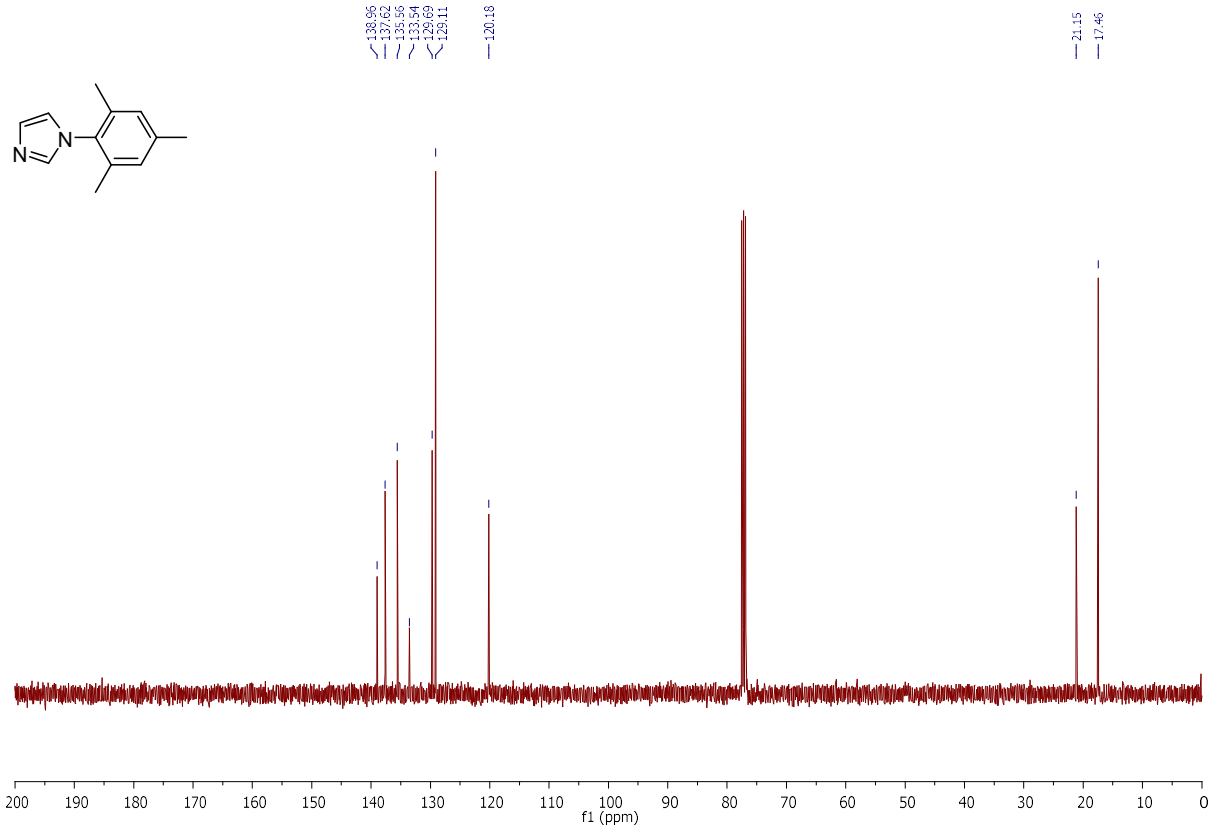
1-(*o*-tolyl)-1*H*-imidazole **S15** :



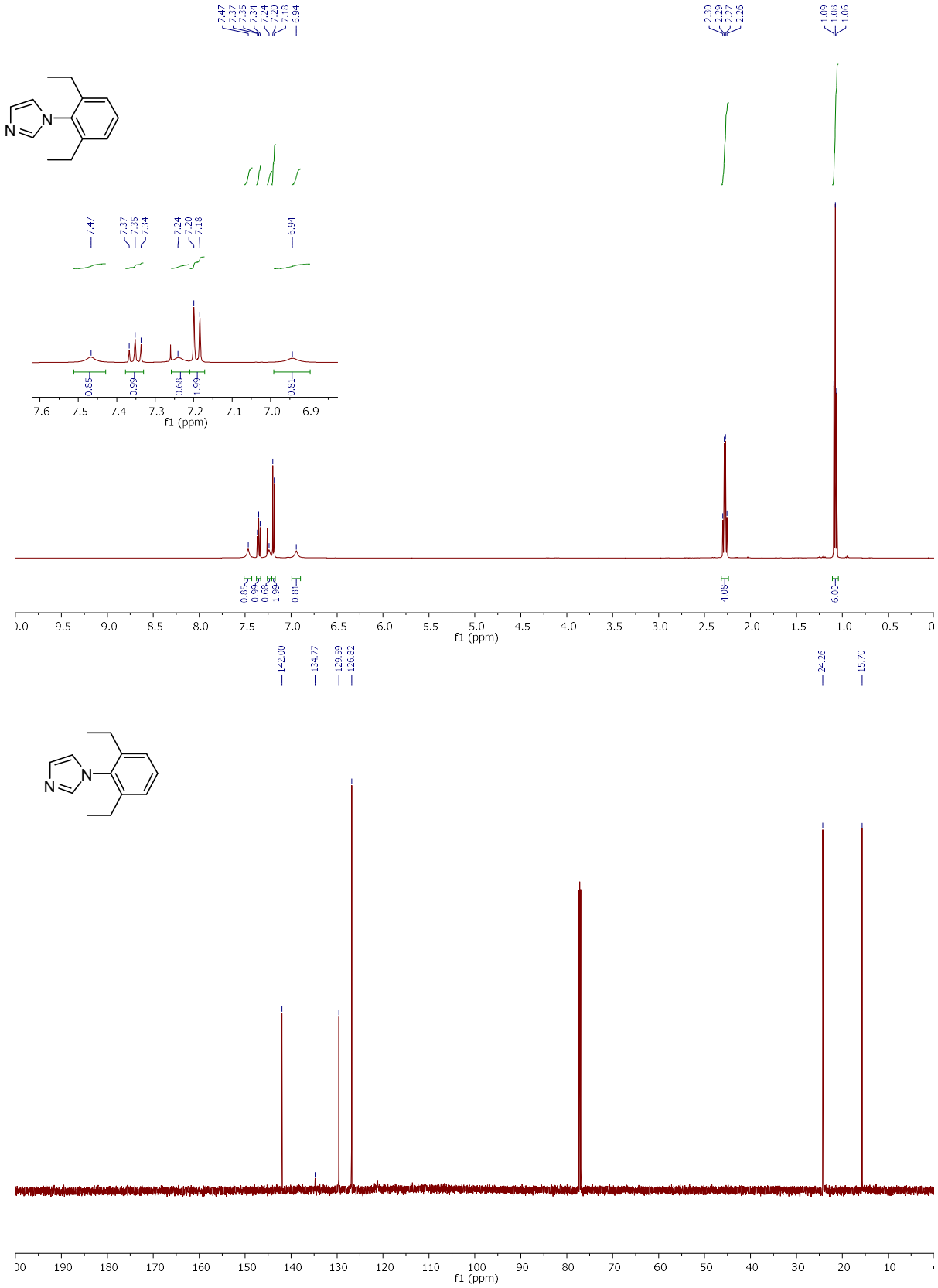


1-mesityl-1H-imidazole **S16** :

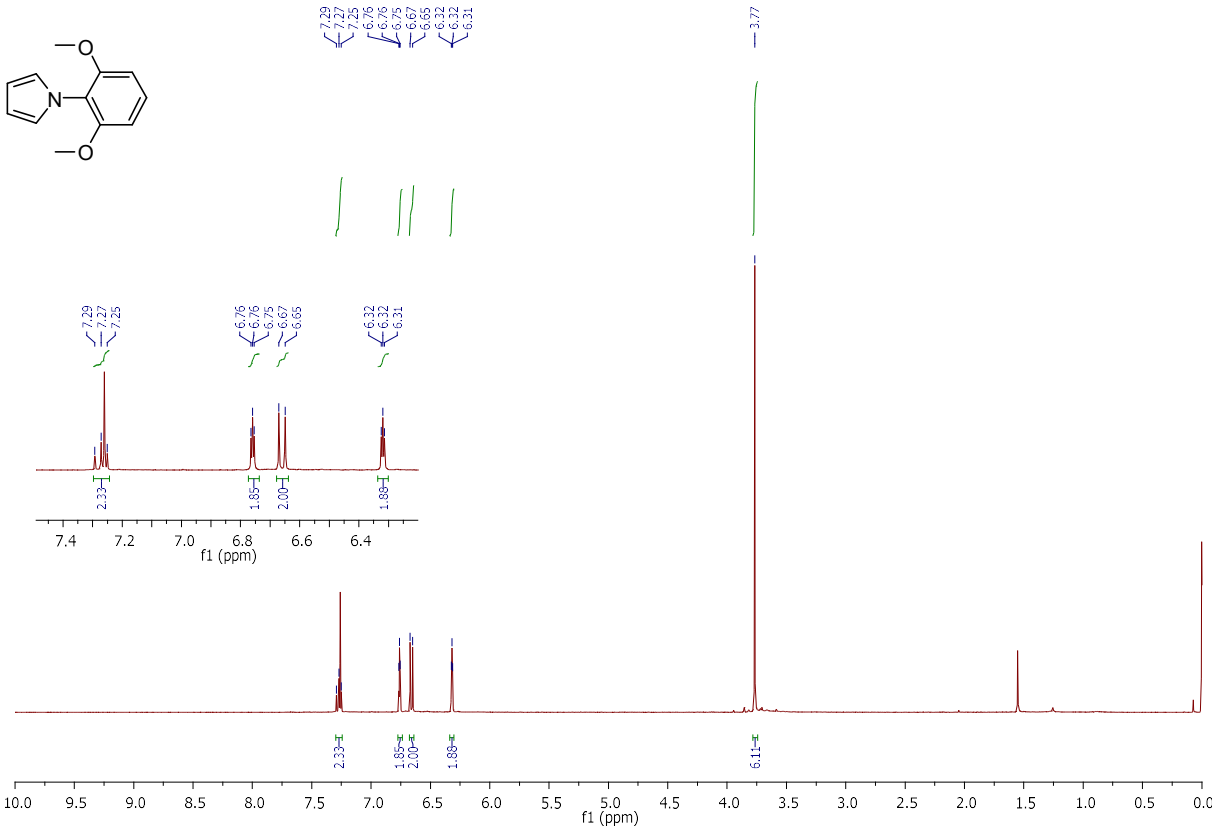


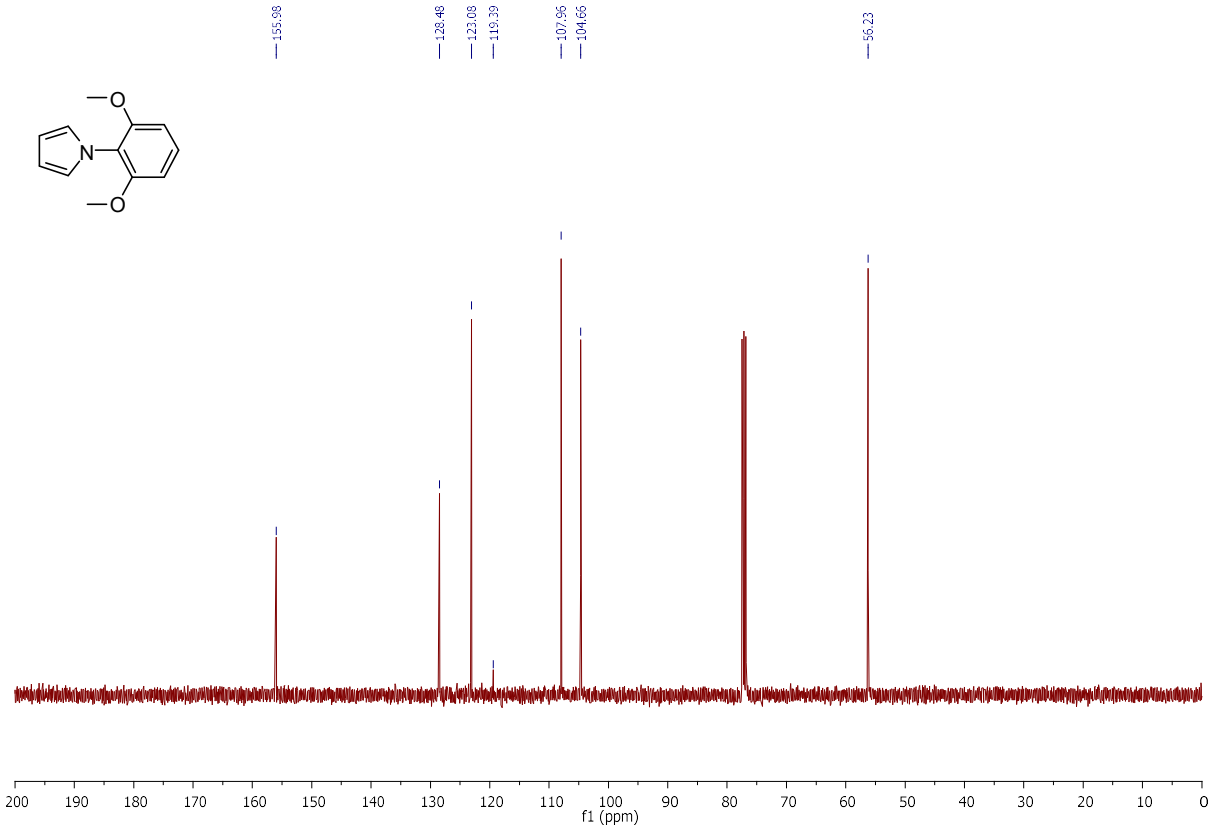


1-(2,6-diethylphenyl)-1H-imidazole **S17**:

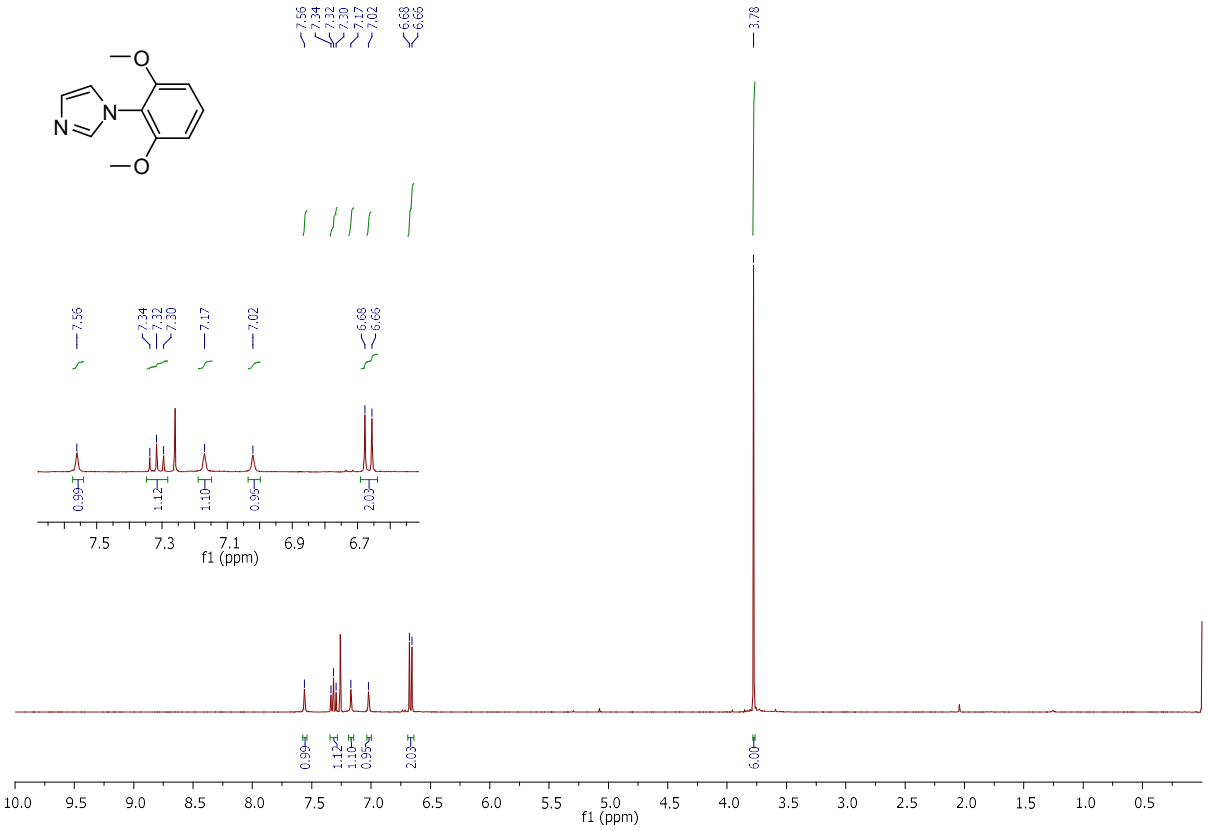


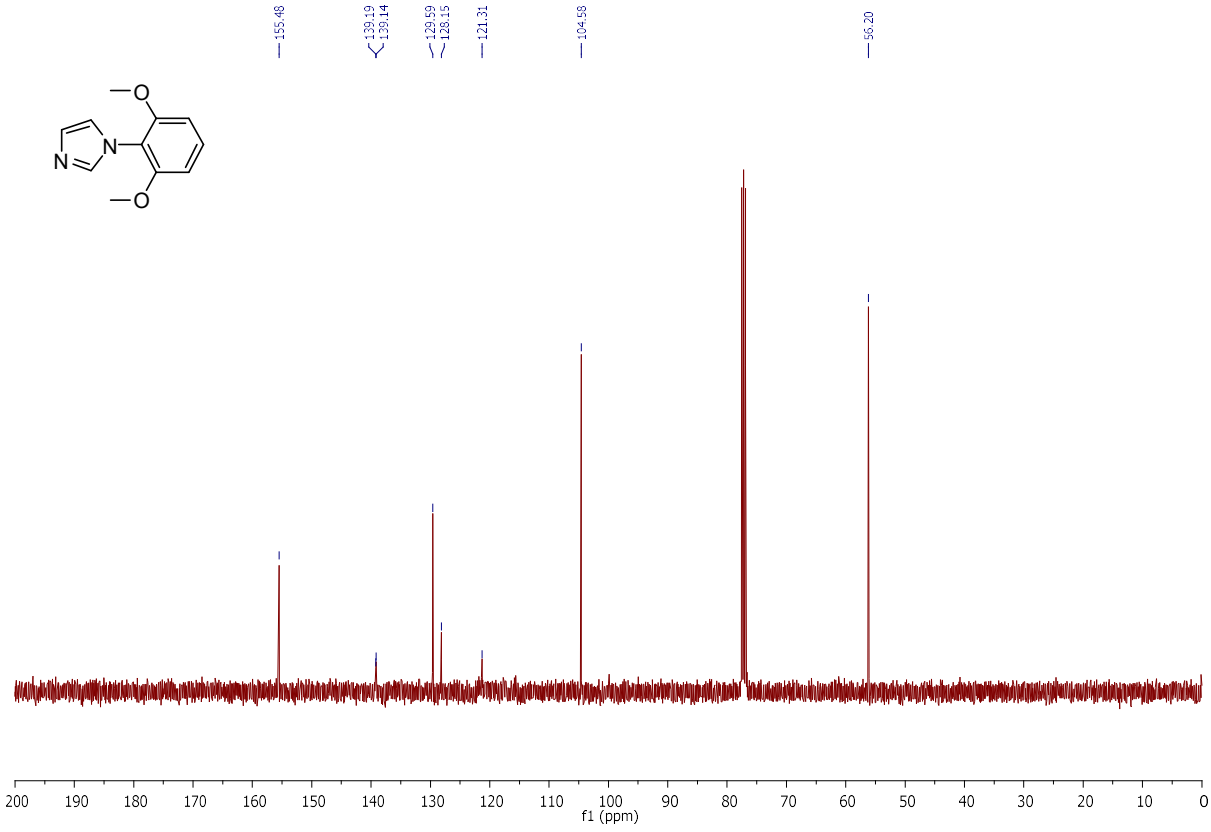
1-(2,6-dimethoxyphenyl)-1*H*-pyrrole**S18** :



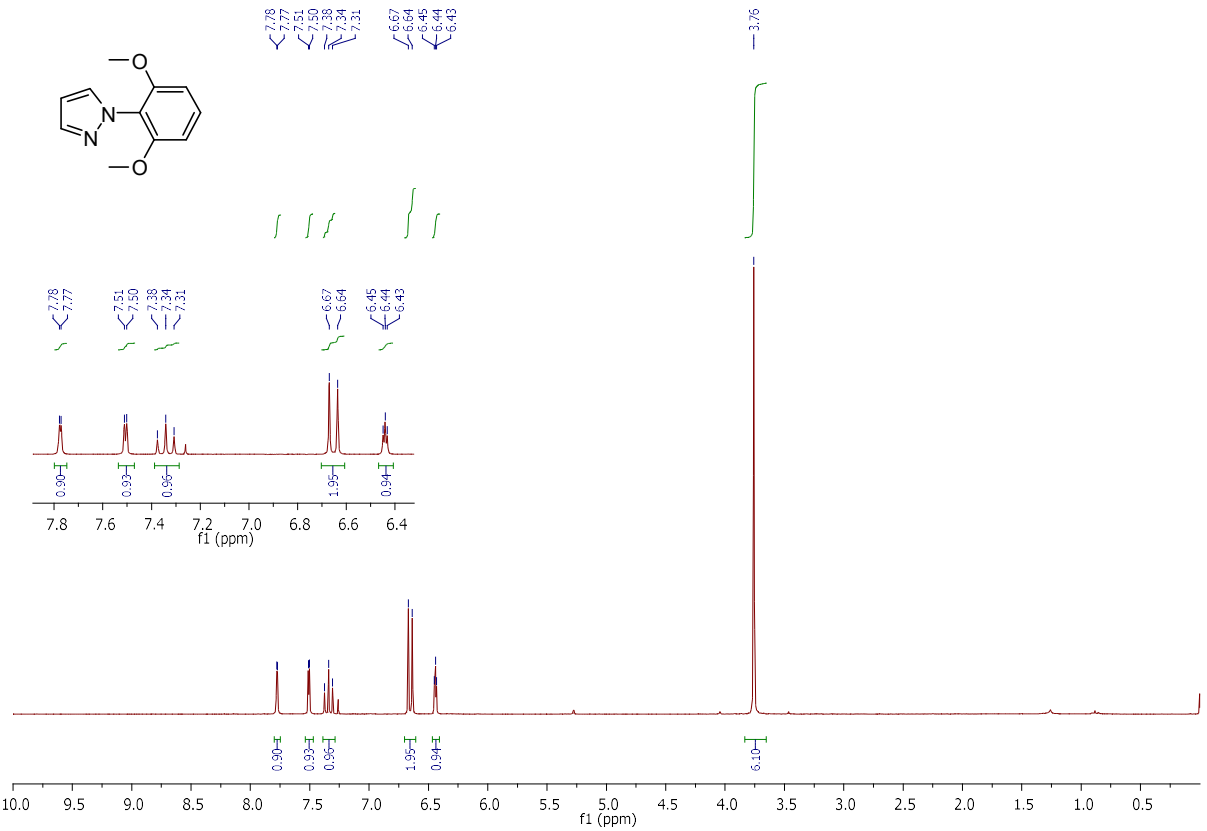


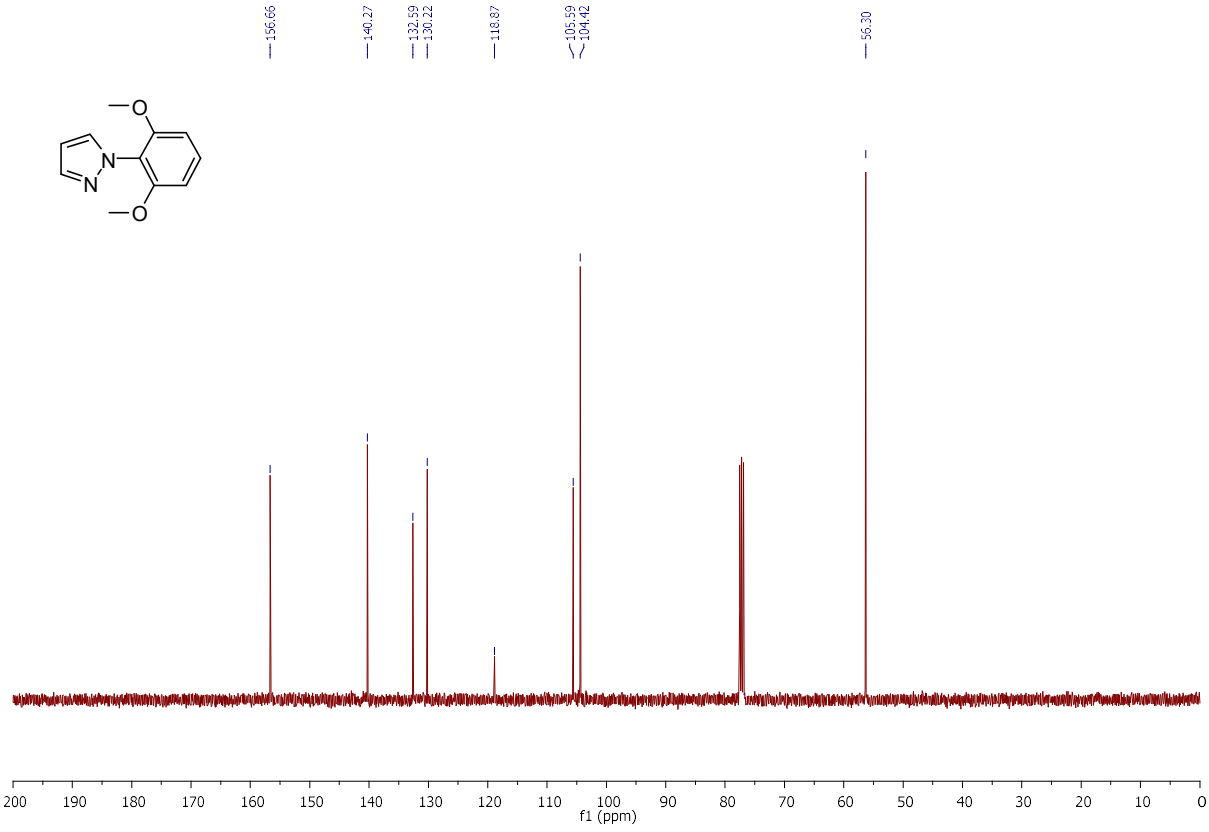
1-(2,6-dimethoxyphenyl)-1*H*-imidazole**S19** :



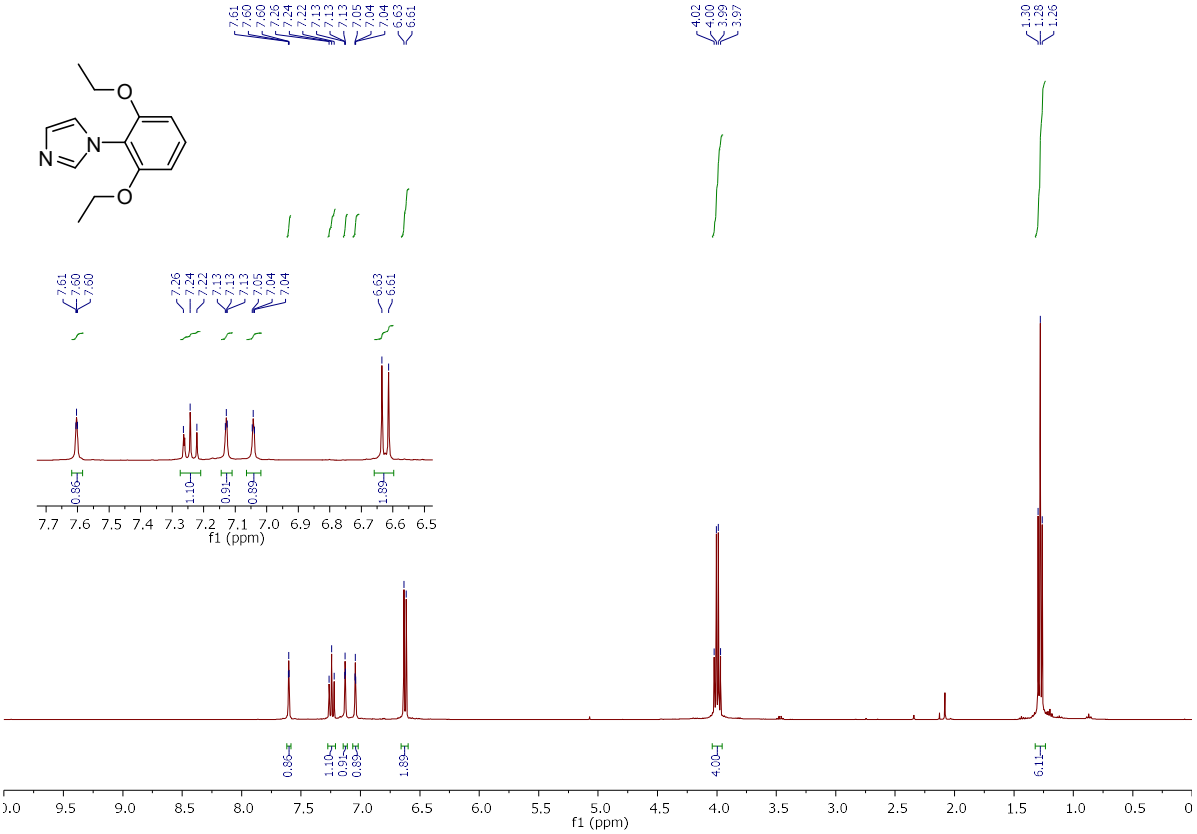


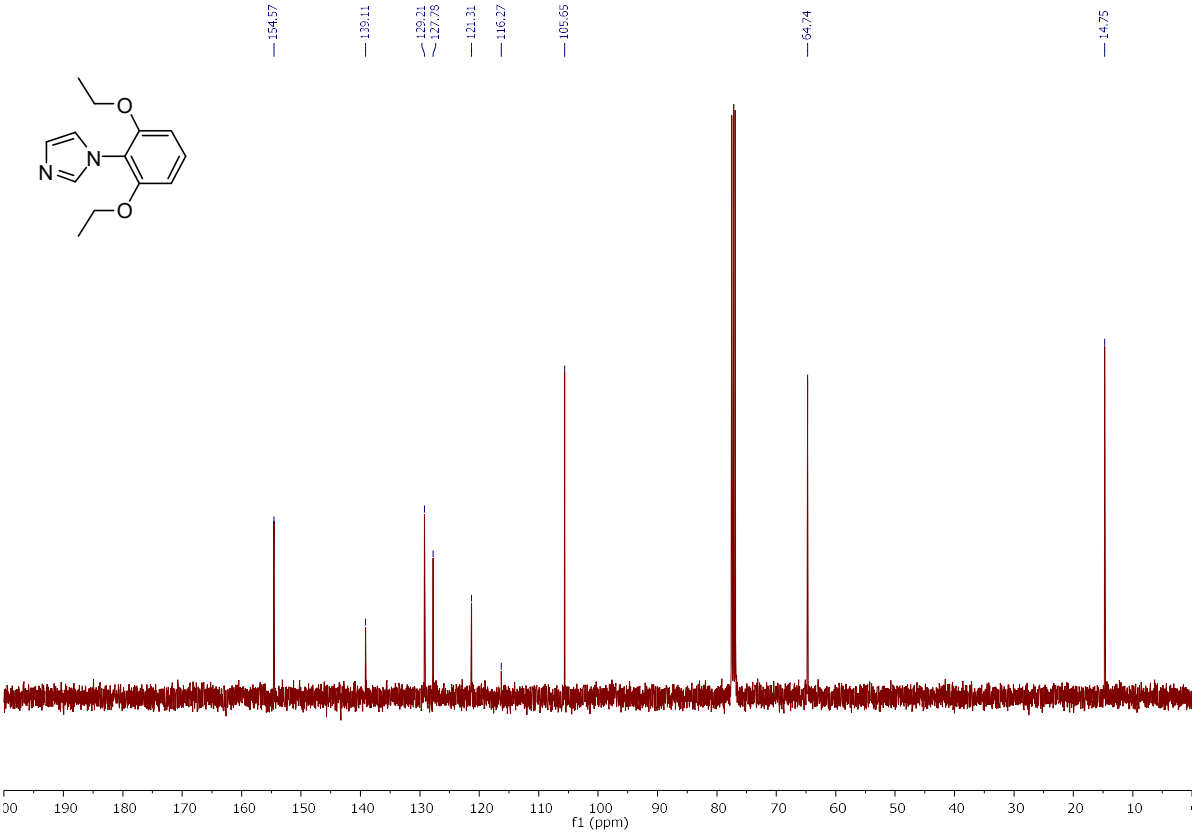
1-(2,6-dimethoxyphenyl)-1H-pyrazole**S20** :



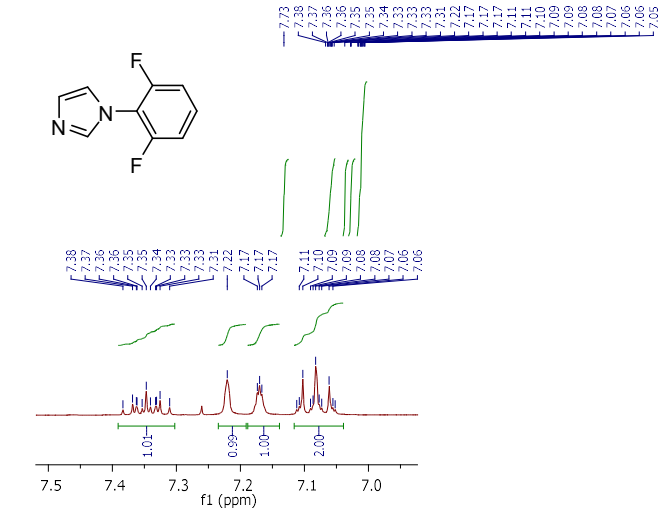


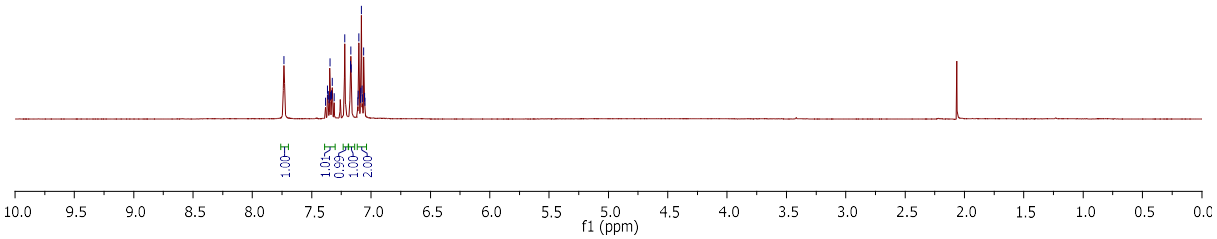
1-(2,6-diethoxyphenyl)-1H-imidazole**S21** :

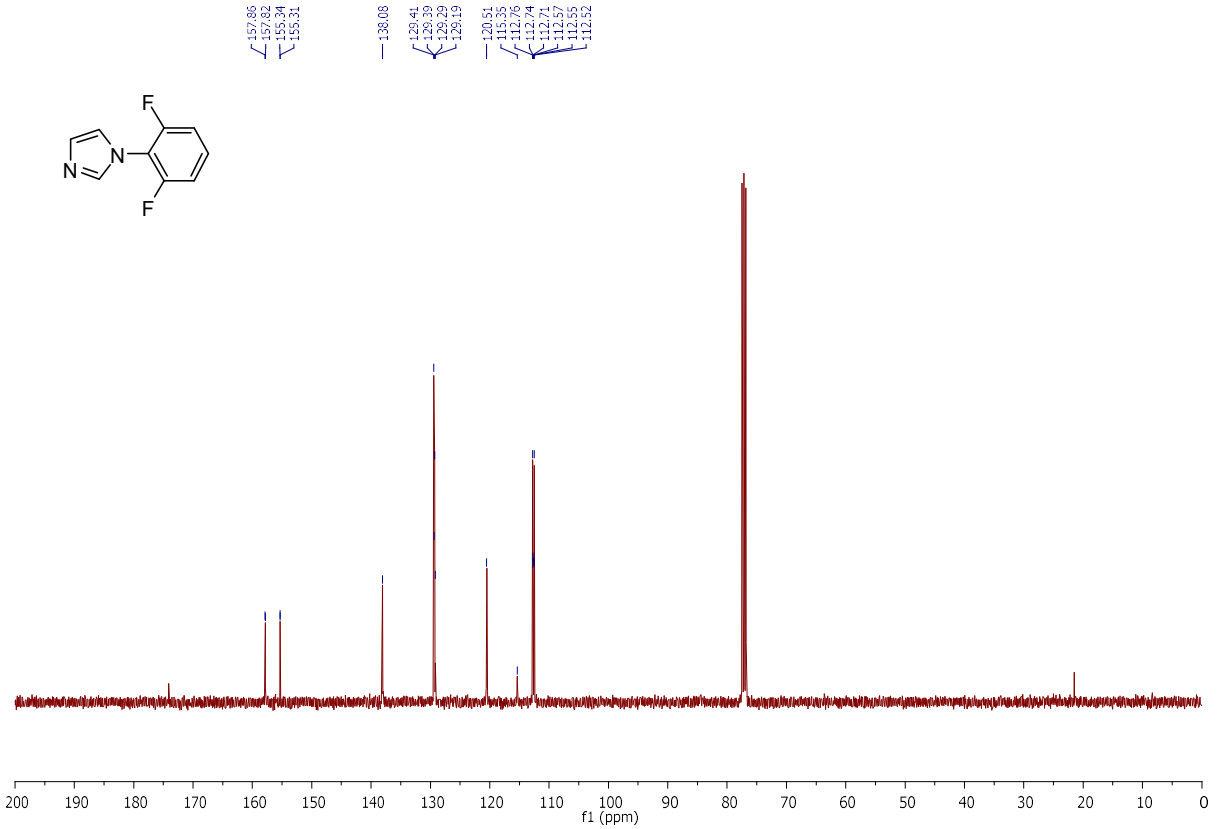


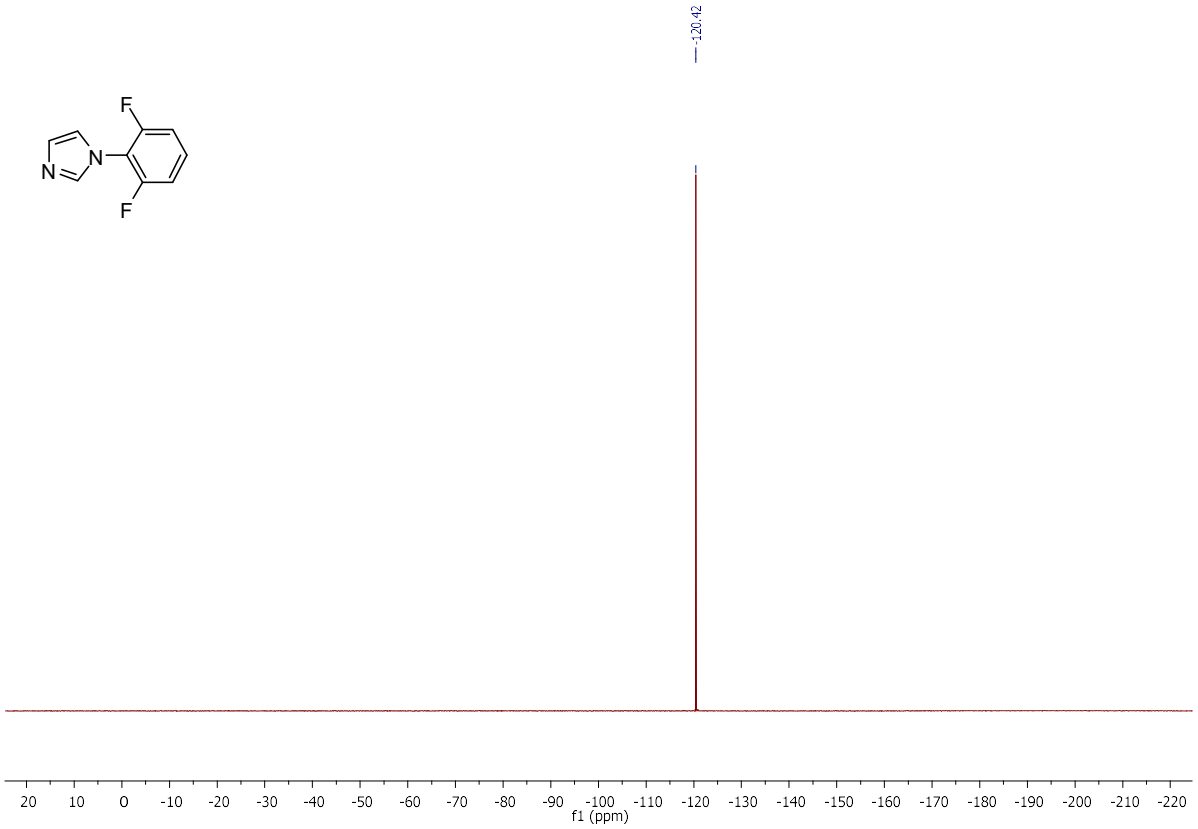


1-(2,6-difluorophenyl)-1H-imidazole**S22** :

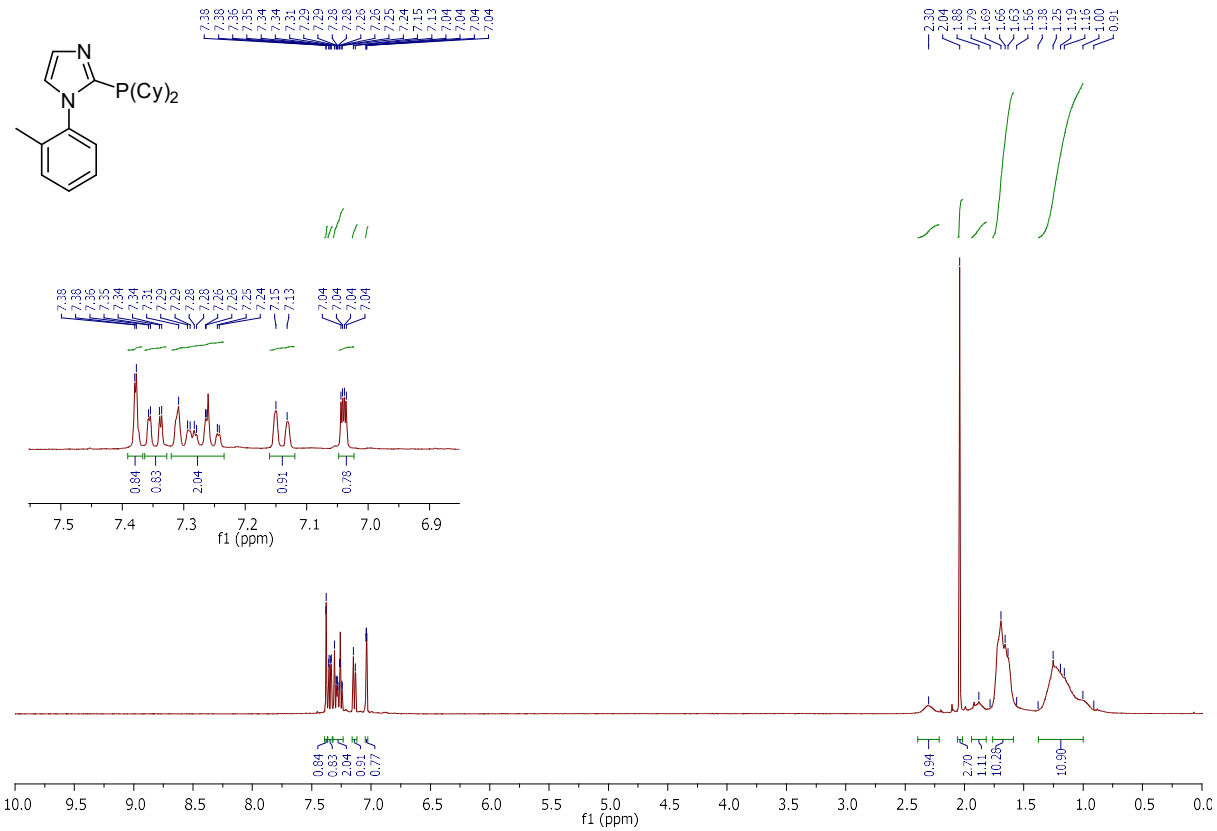


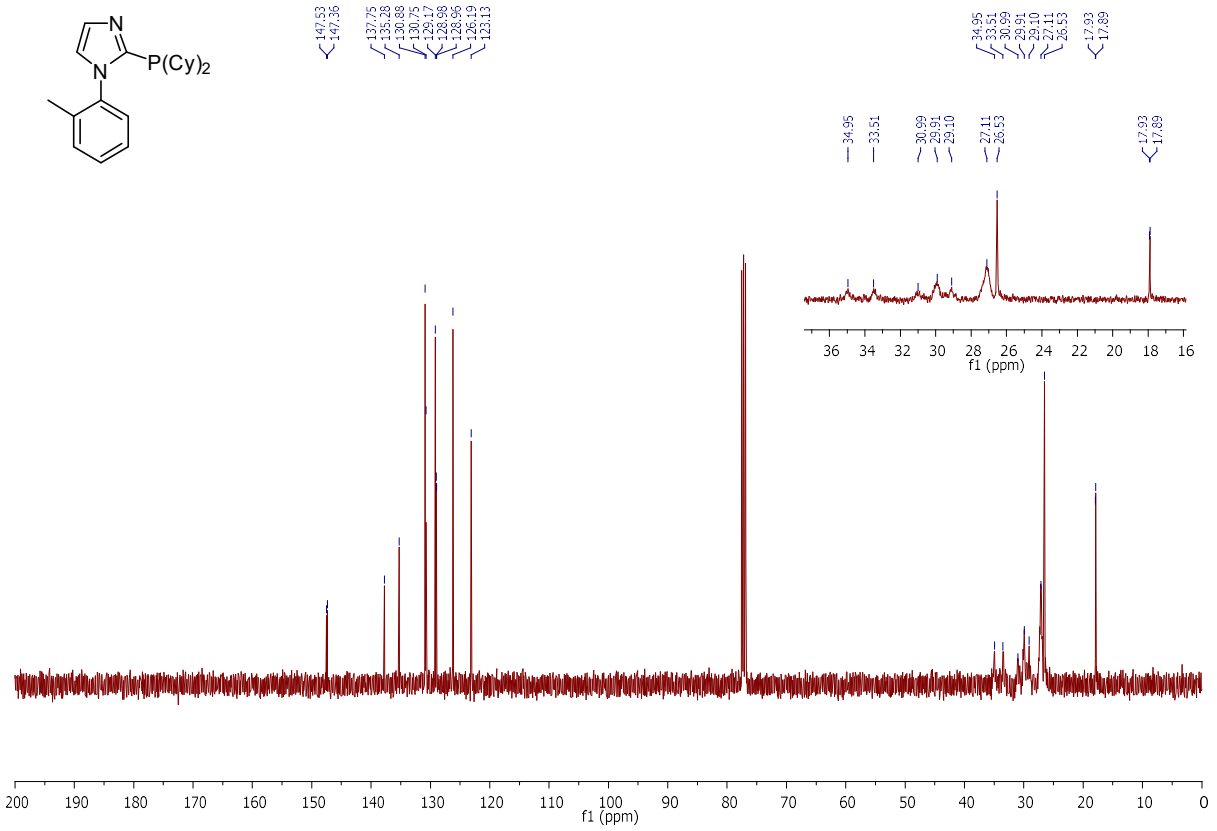


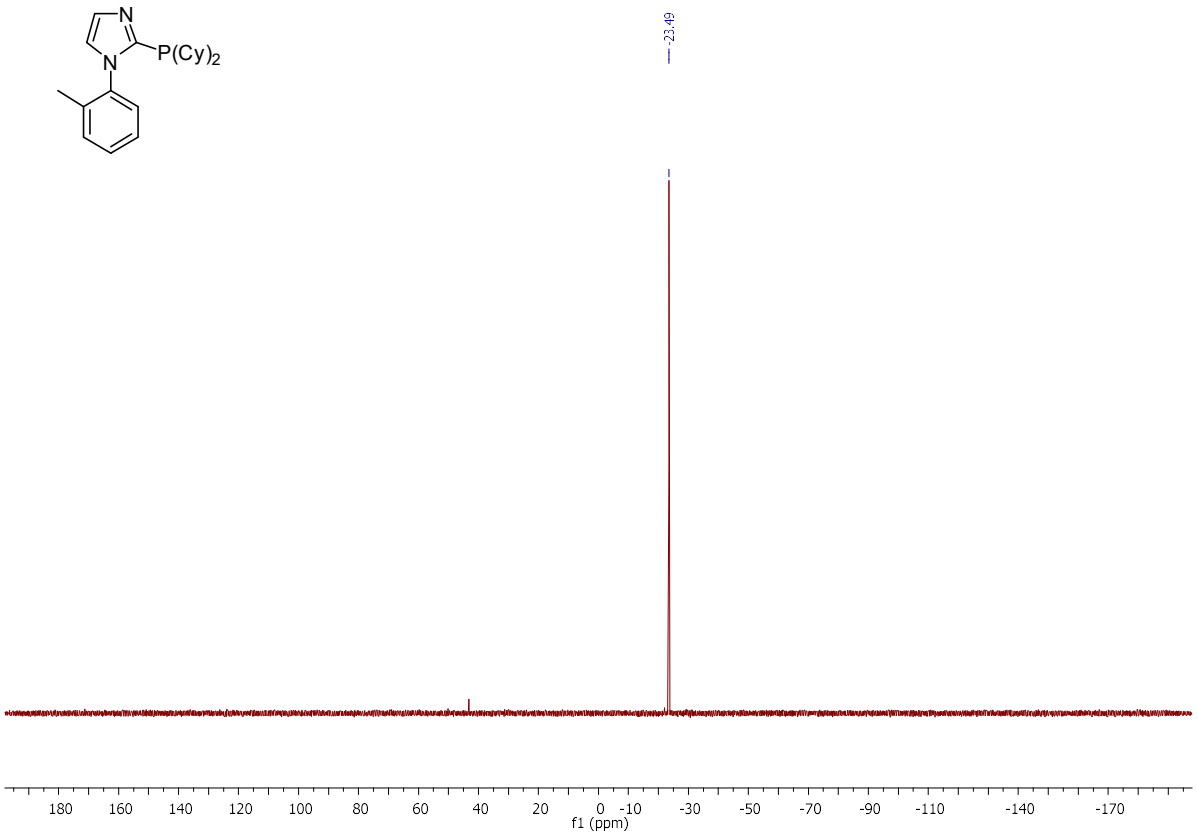



F
N
N
F
-120.42
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

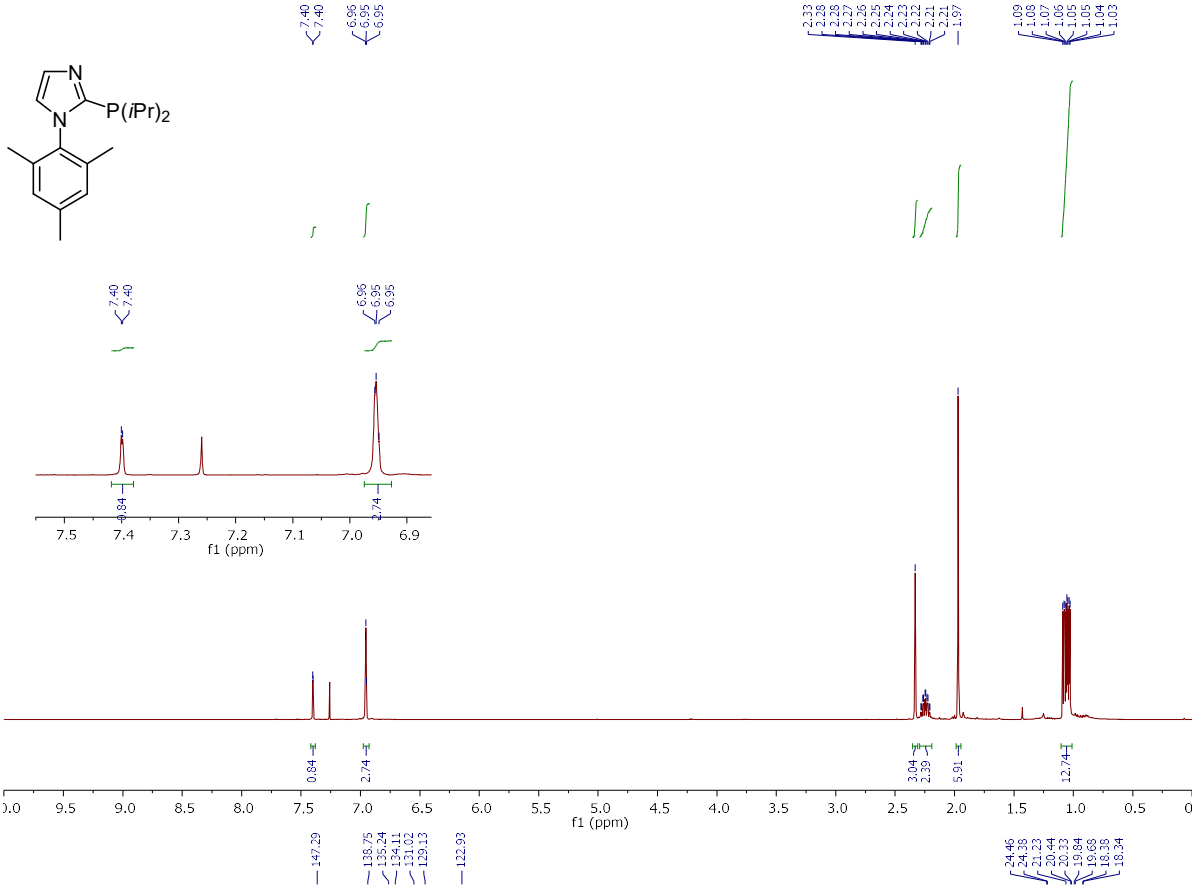
2-(dicyclohexylphosphanyl)-1-(*o*-tolyl)-1*H*-imidazole**2.L**[16] :

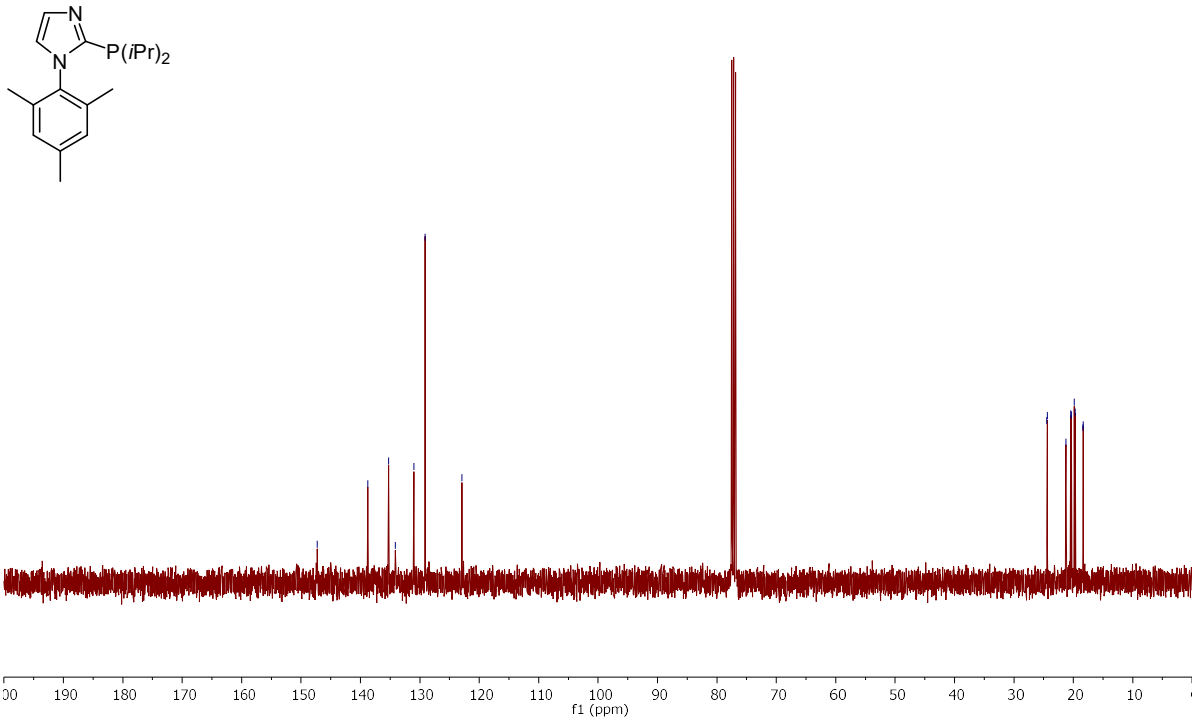


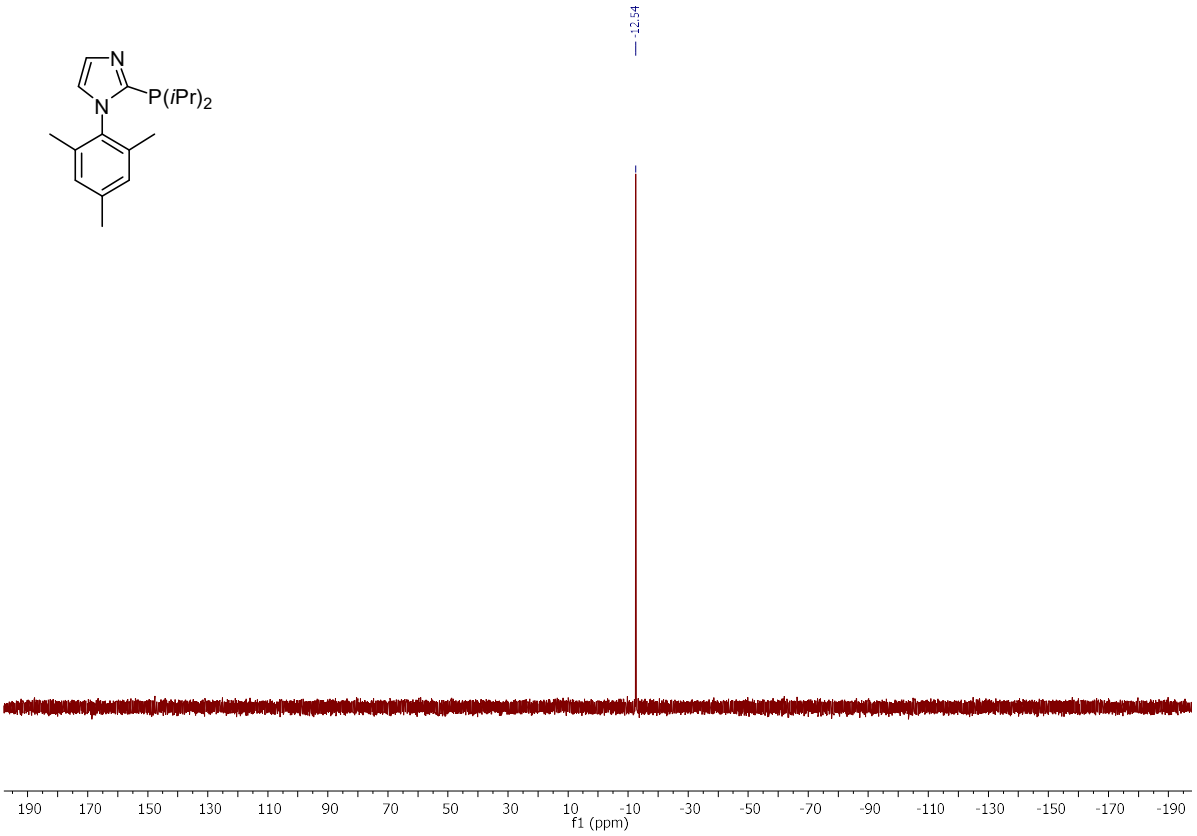



N
N
P(Cy)2
-23.49
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

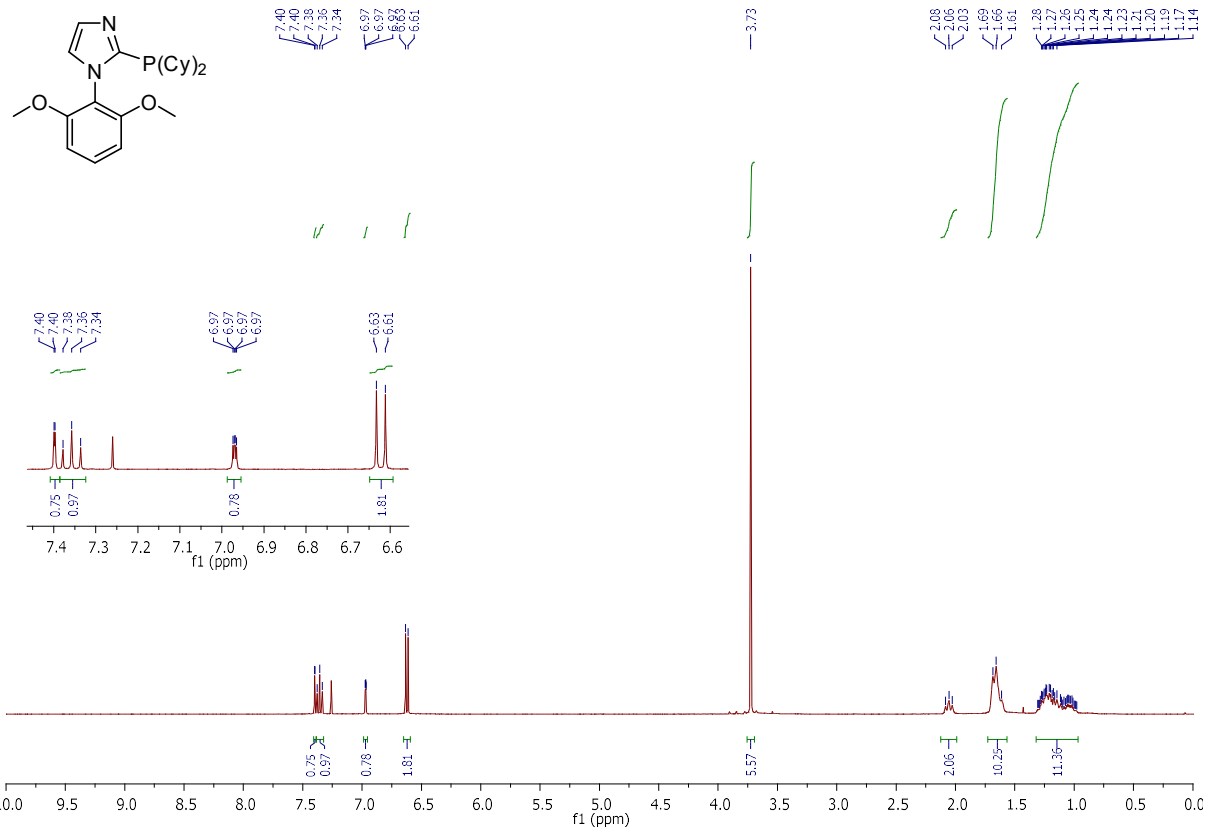
2-(diisopropylphosphanyl)-1-mesityl-1*H*-imidazole **2.L**[42] :

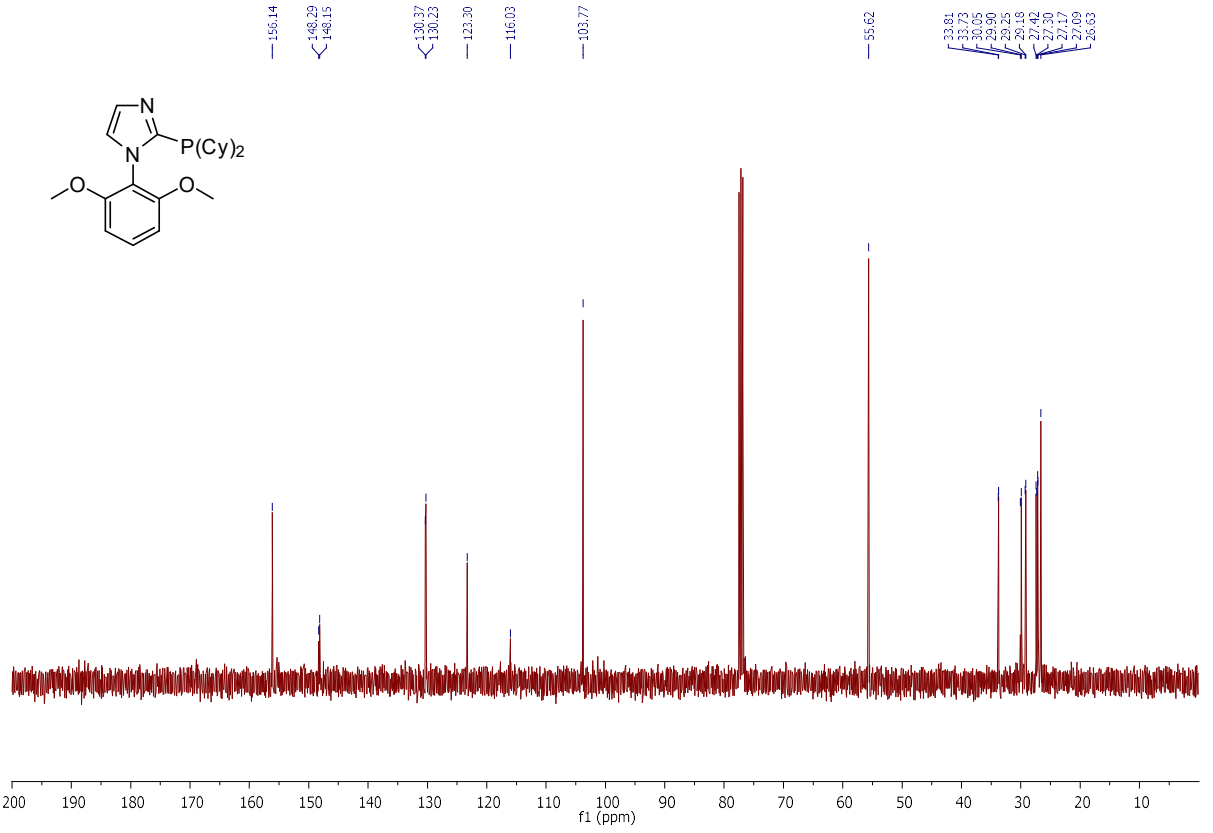


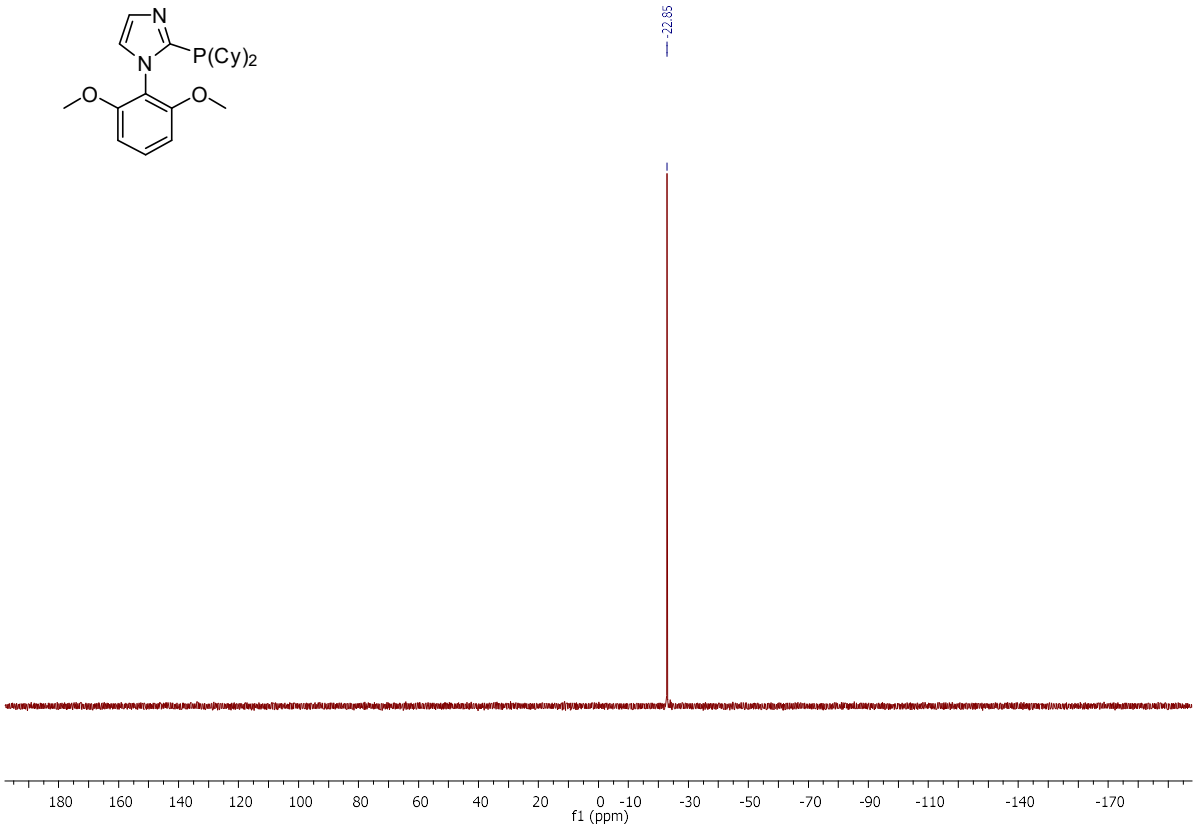



N
N
P(iPr)2
12.54
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

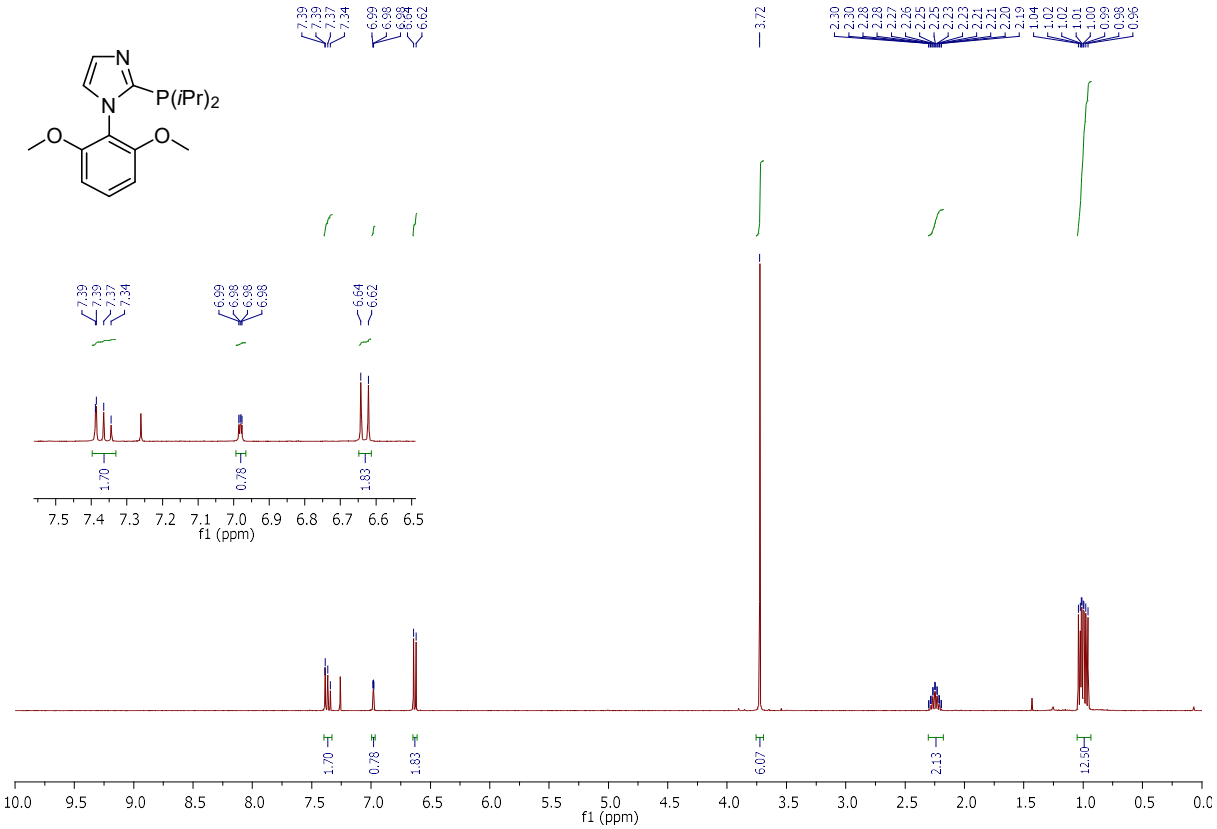
1-(2,6-dimethoxyphenyl)-2-(dicyclohexylphosphanyl)-1*H*-imidazole **2.L**[43] :

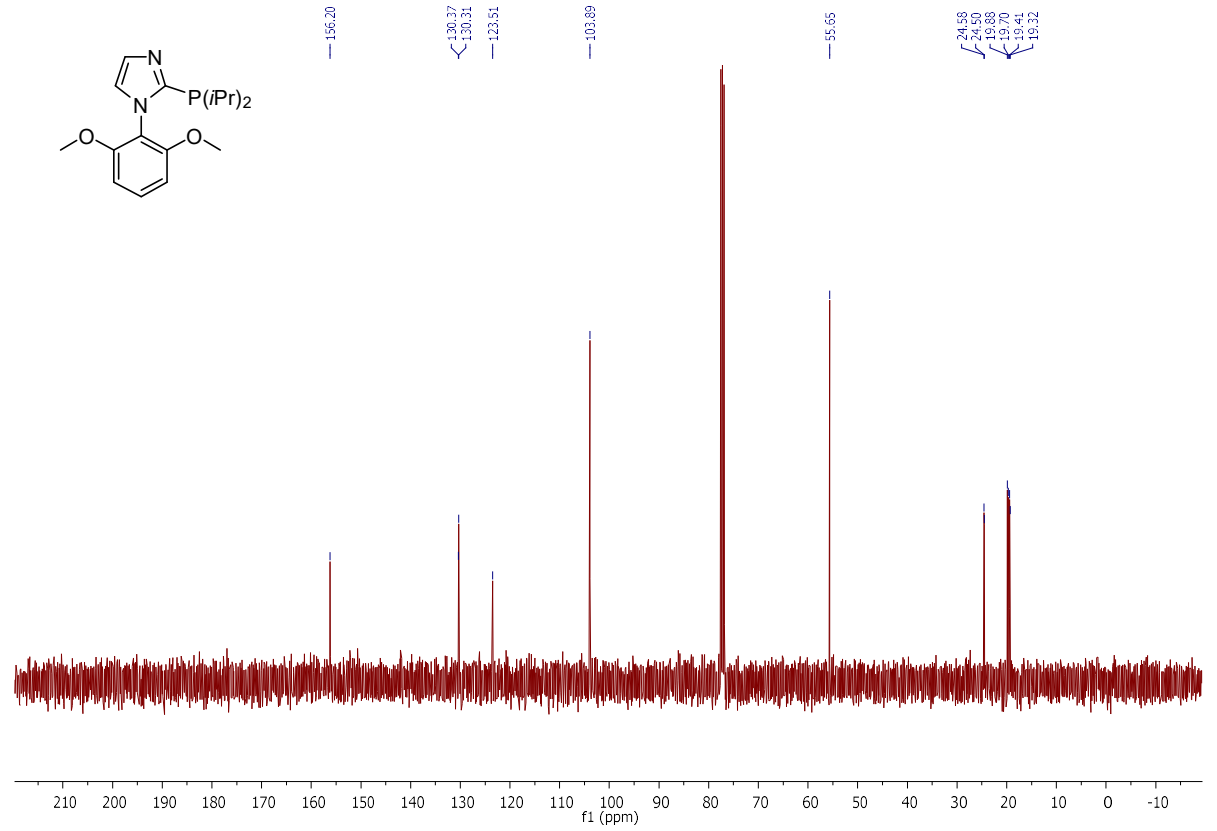


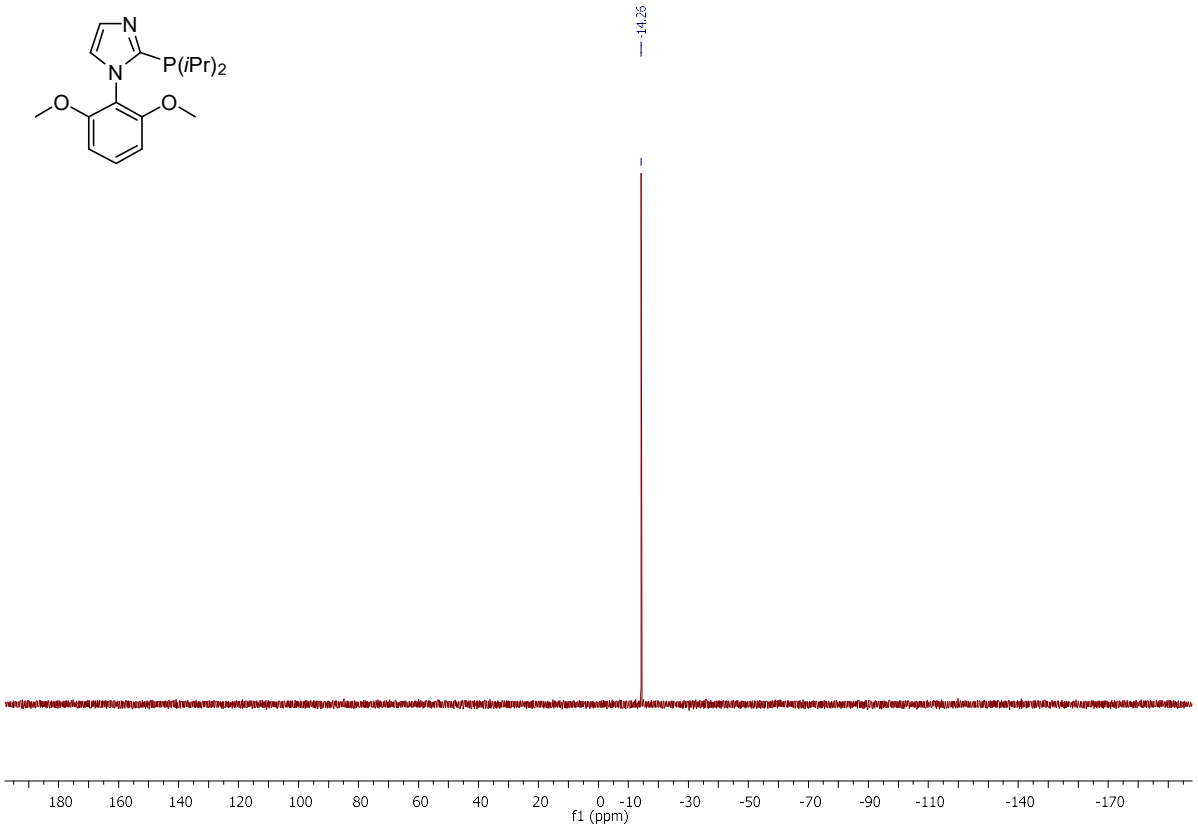



N
N
P(Cy)2
O
O
-22.85
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

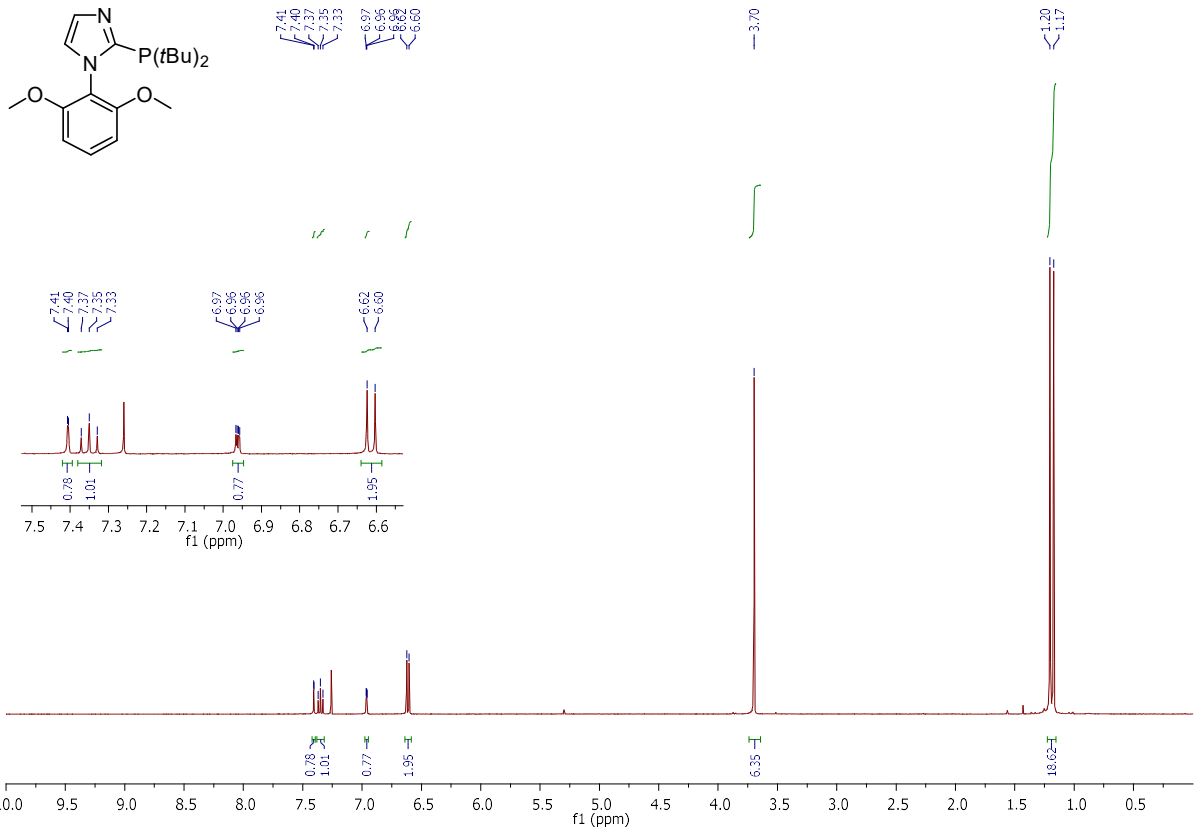
2-(diisopropylphosphanyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole **2.L**[44] :

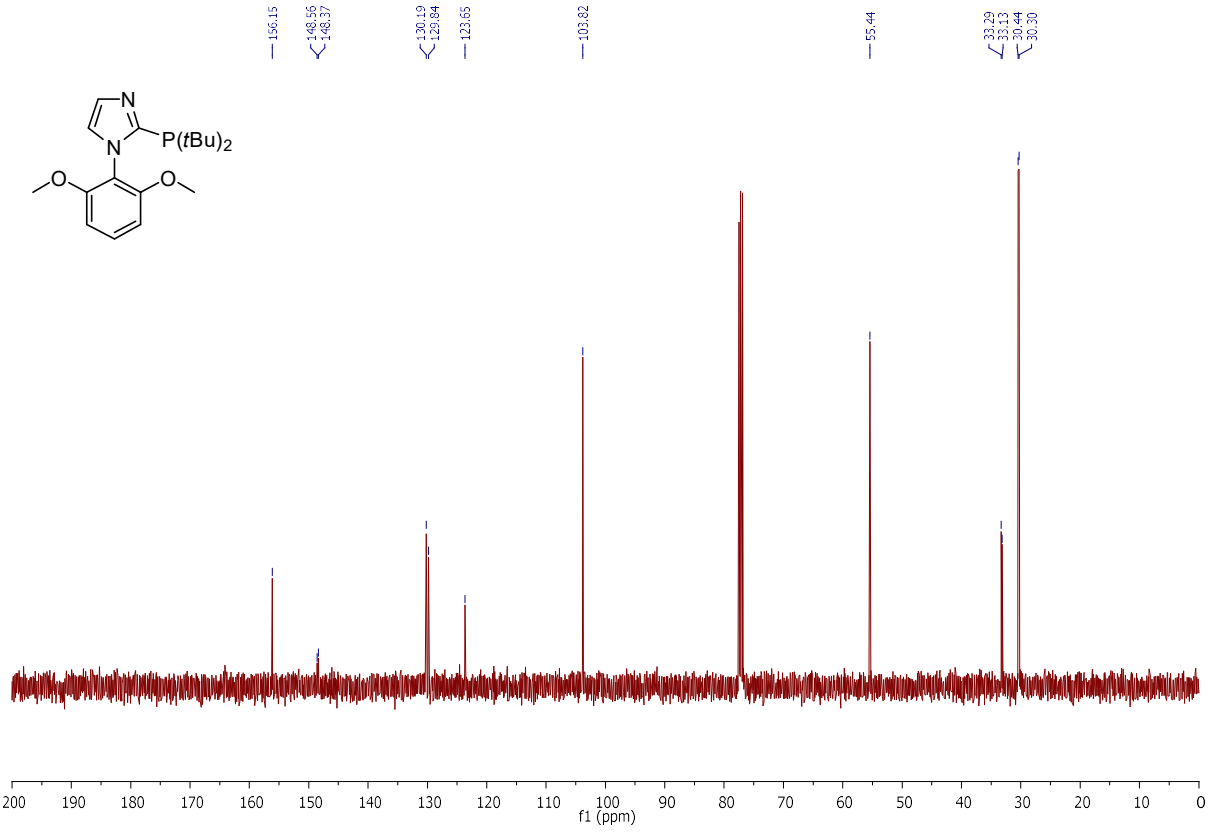


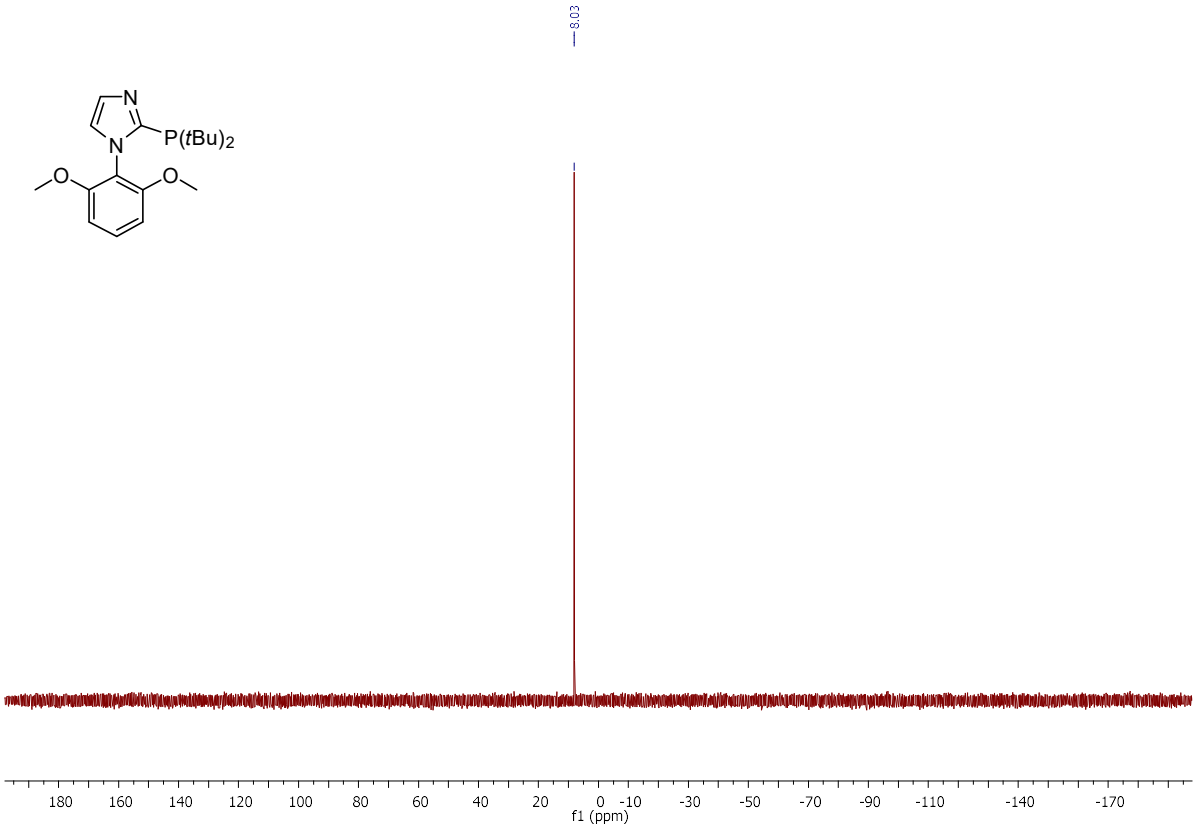



N
N
P(iPr)2
O
O
-14.26
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

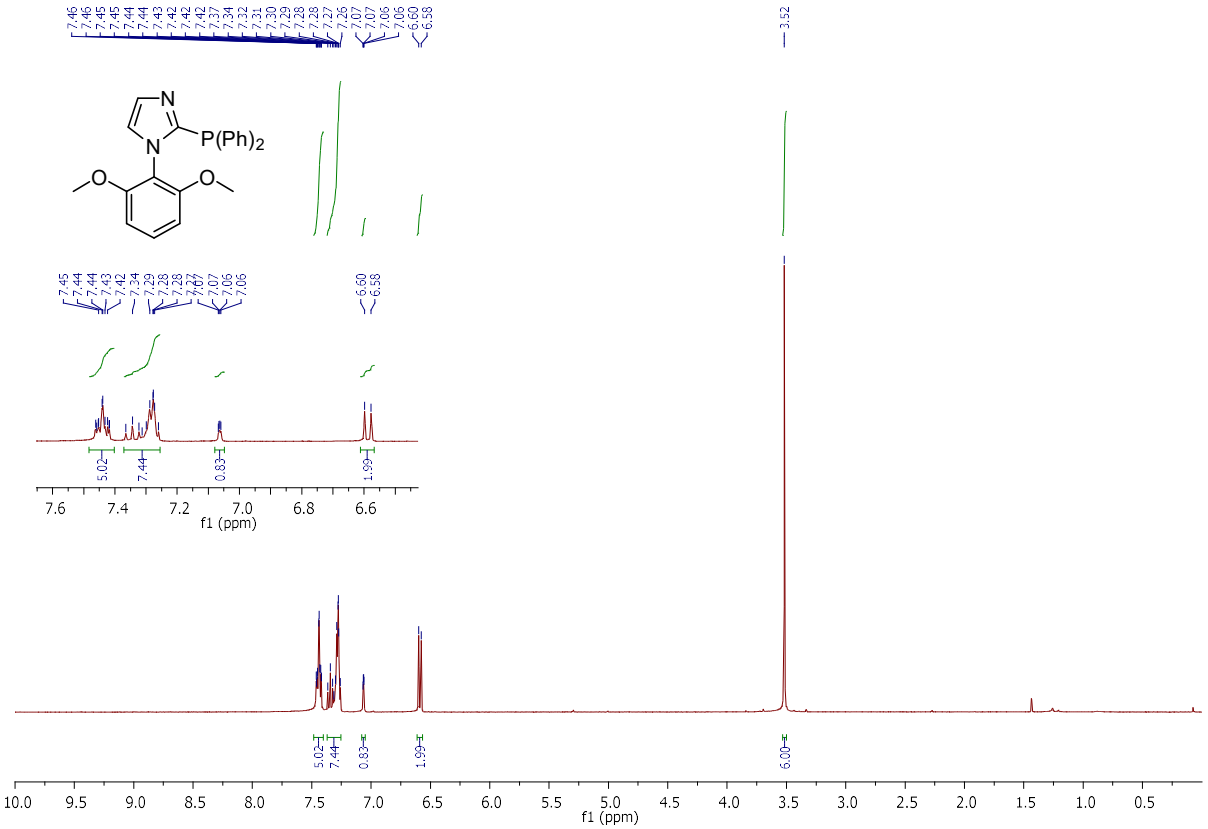
2-(di-*ter*t-butylphosphanyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole**2.L**[45] :

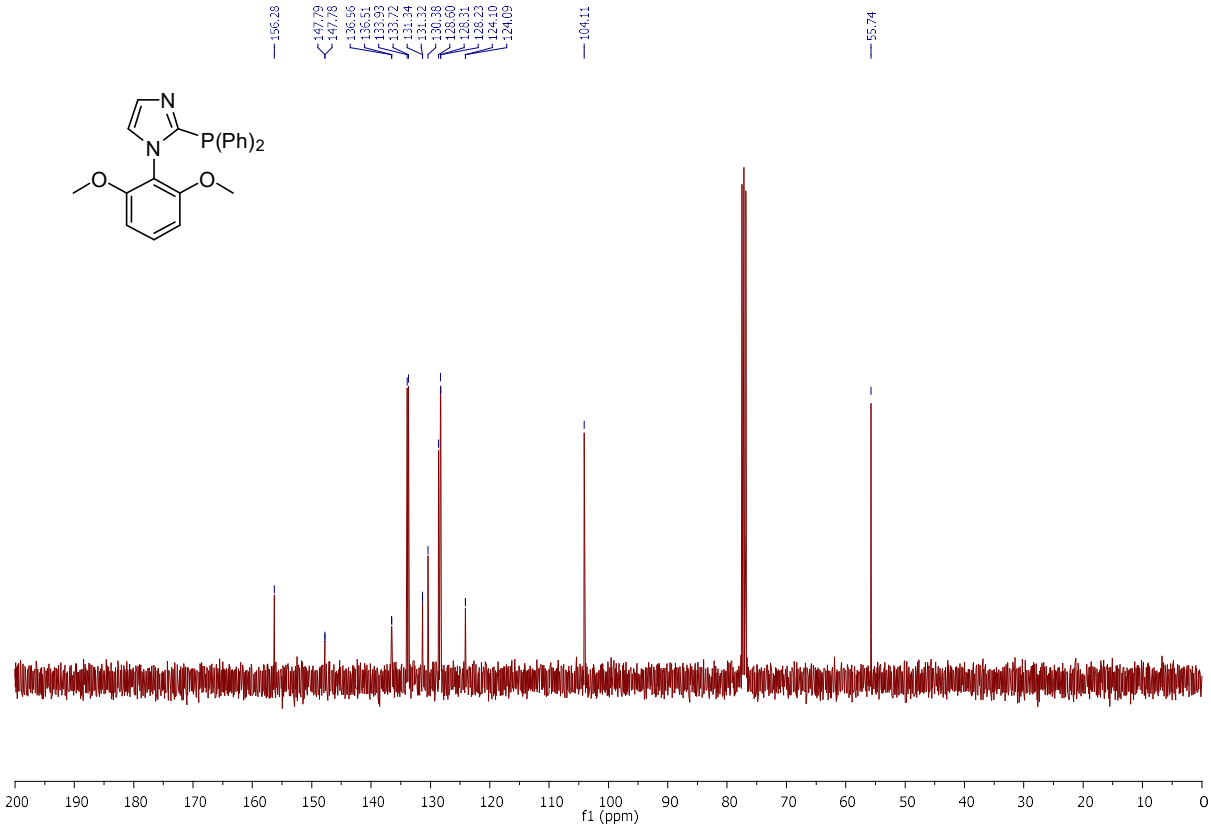


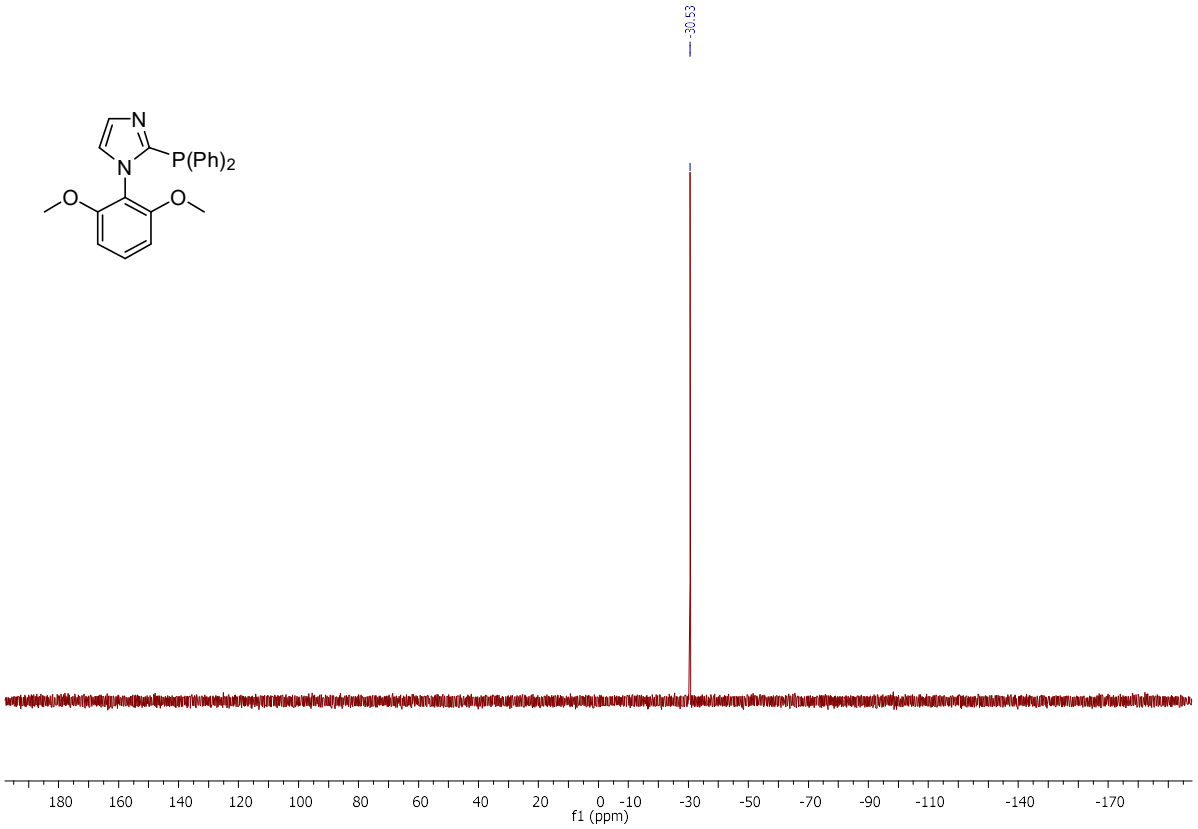



8.03
N
N
P(tBu)2
O
O
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

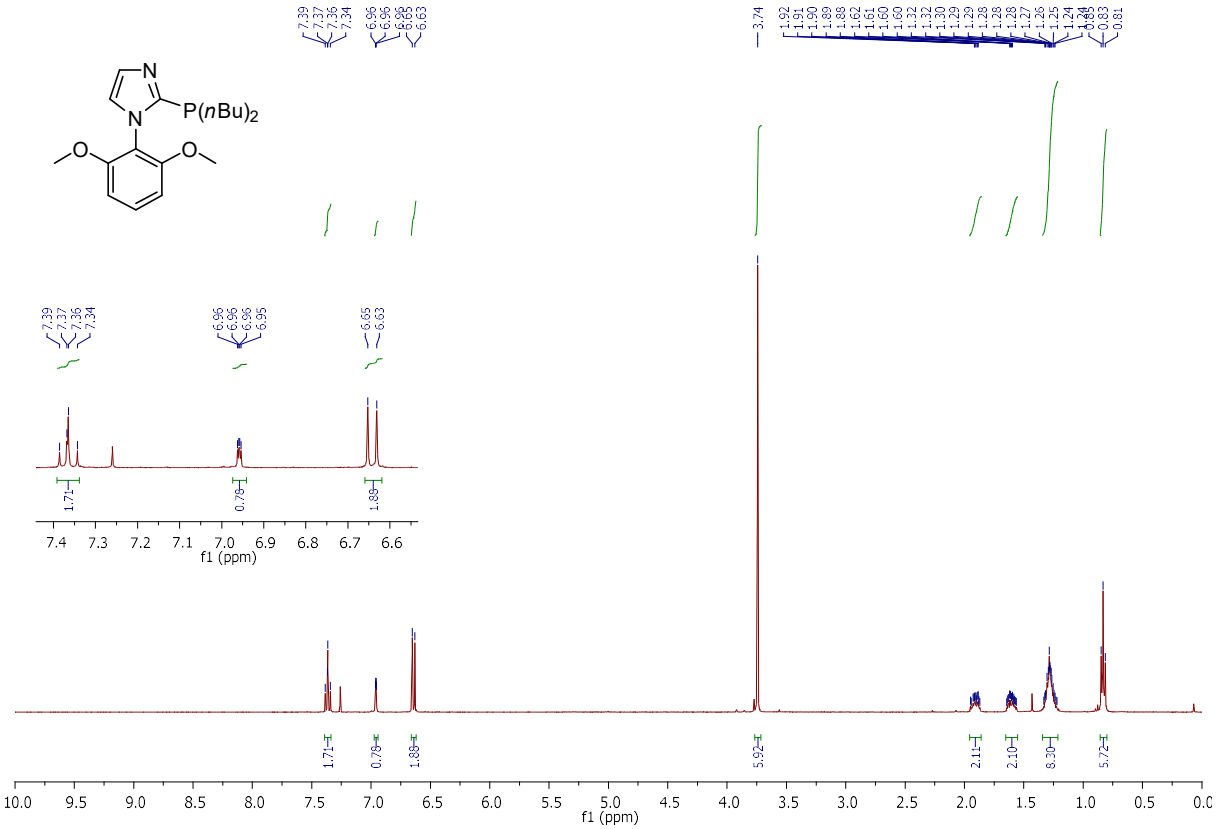
1-(2,6-dimethoxyphenyl)-2-(diphenylphosphanyl)-1*H*-imidazole**2.L**[46] :

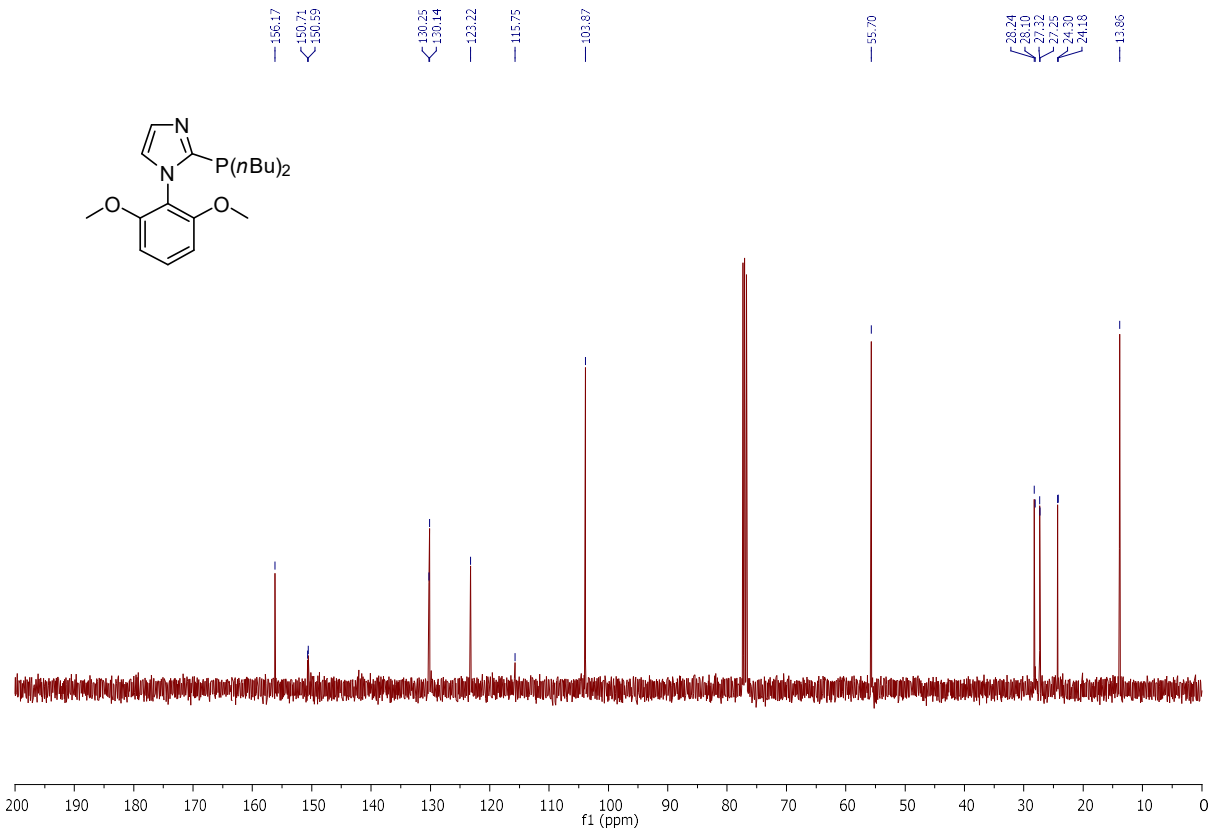


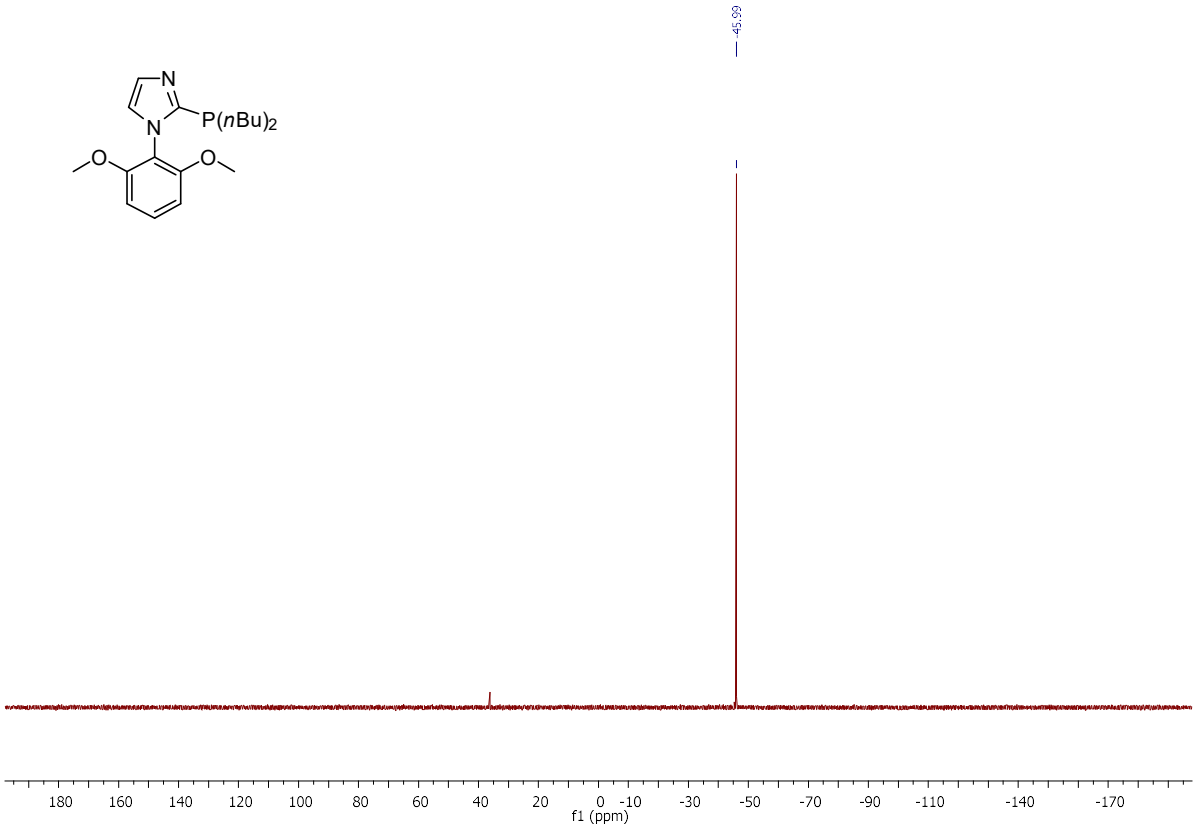



-30.53
N
N
P(Ph)2
O
O
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

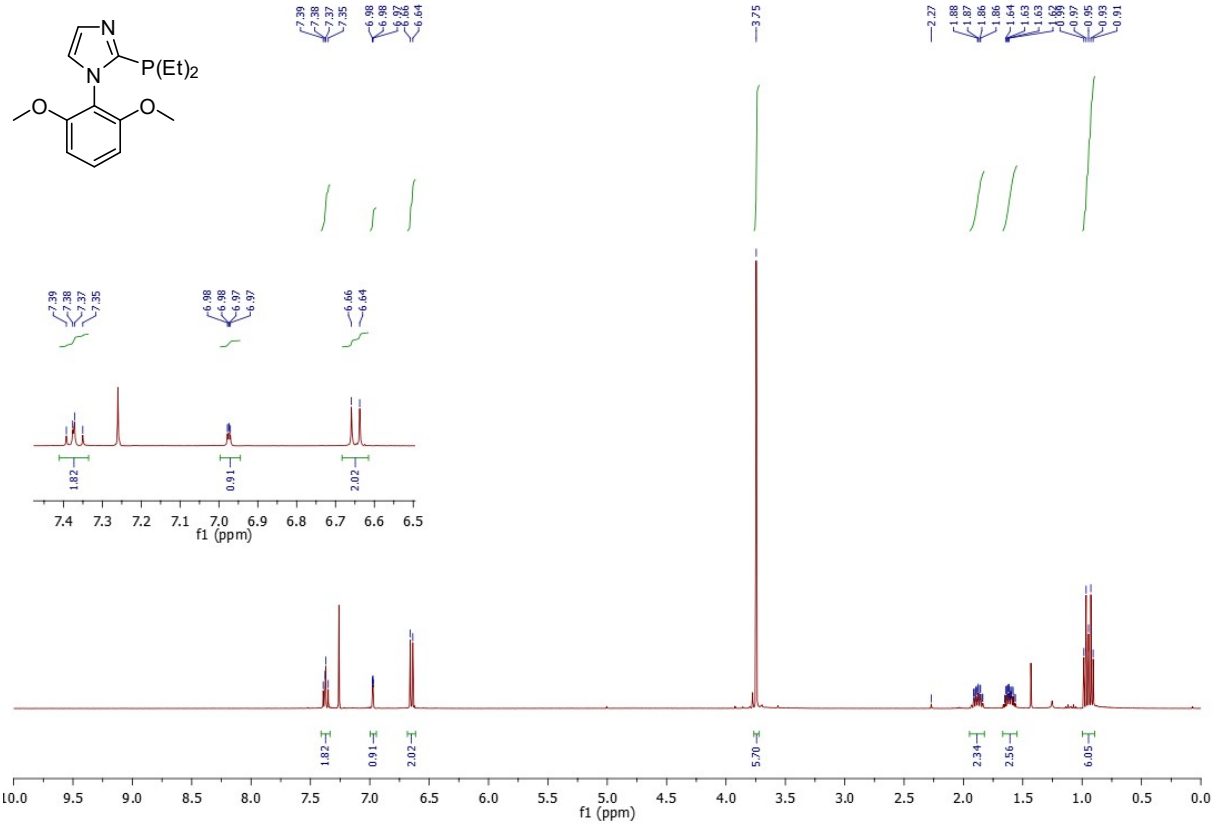
2-(dibutylphosphanyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole**2.L**[47] :

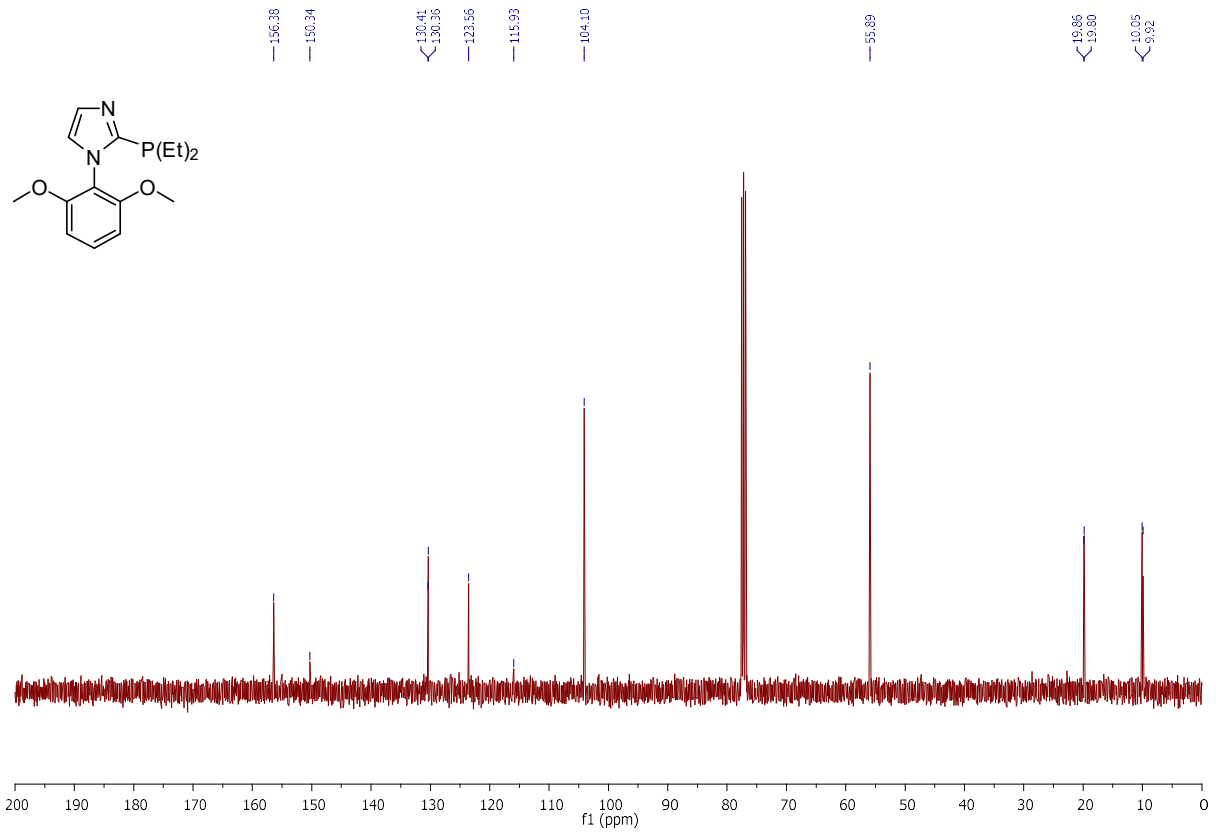


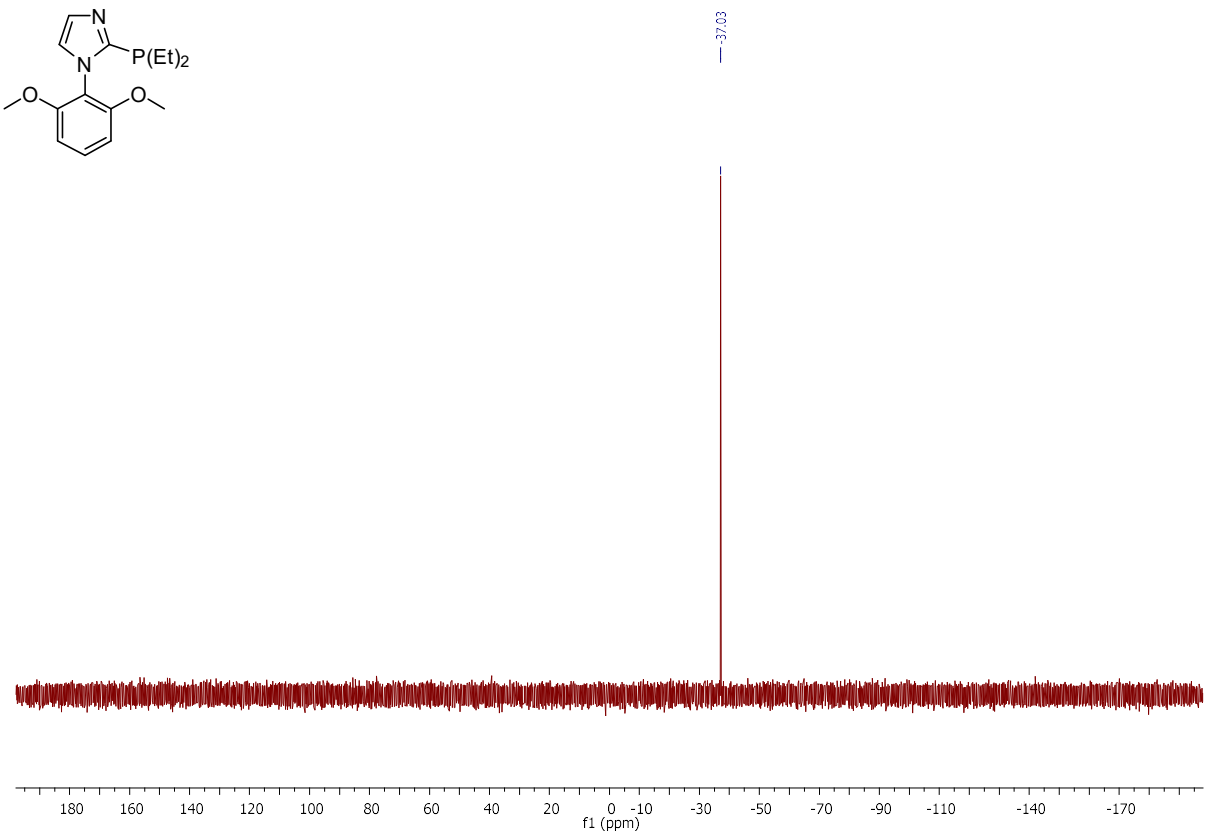



N
N
P(nBu)2
O
O
-45.99
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

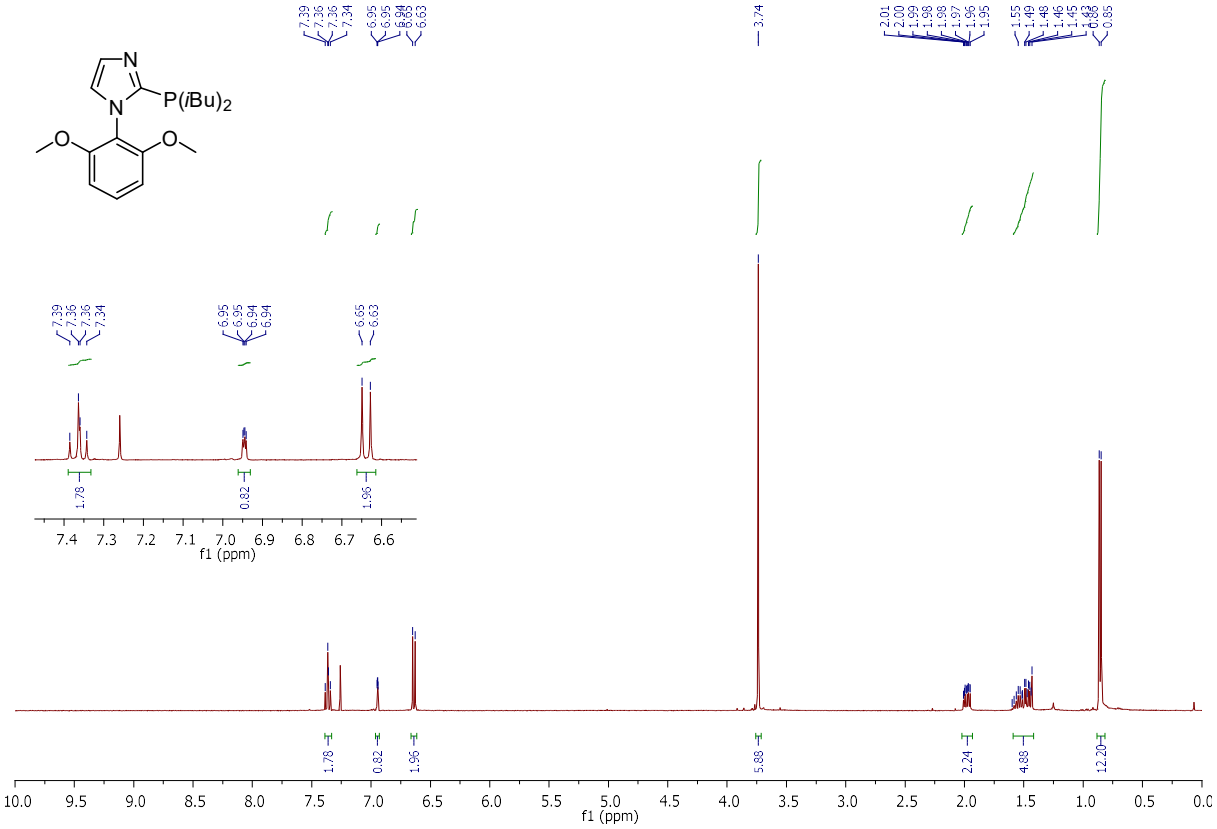
2-(diethylphosphanyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole**2.L**[48] :

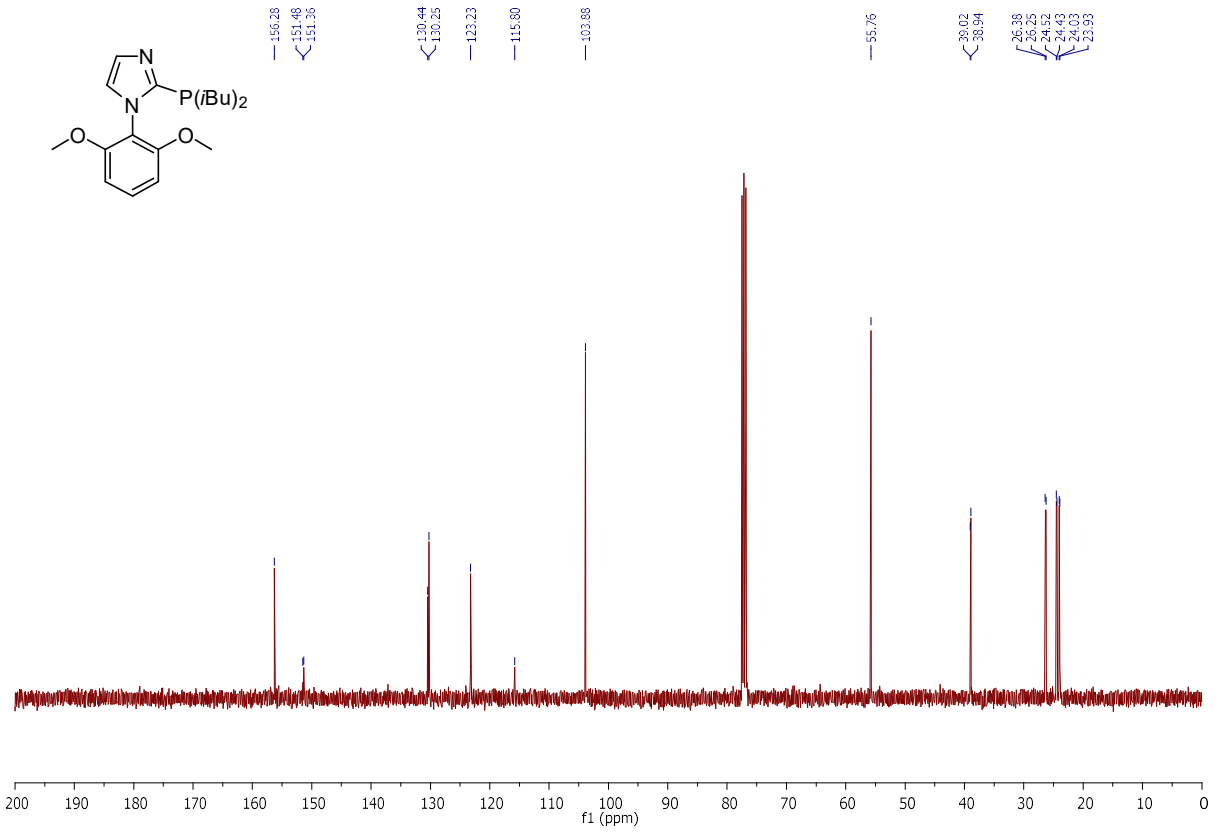


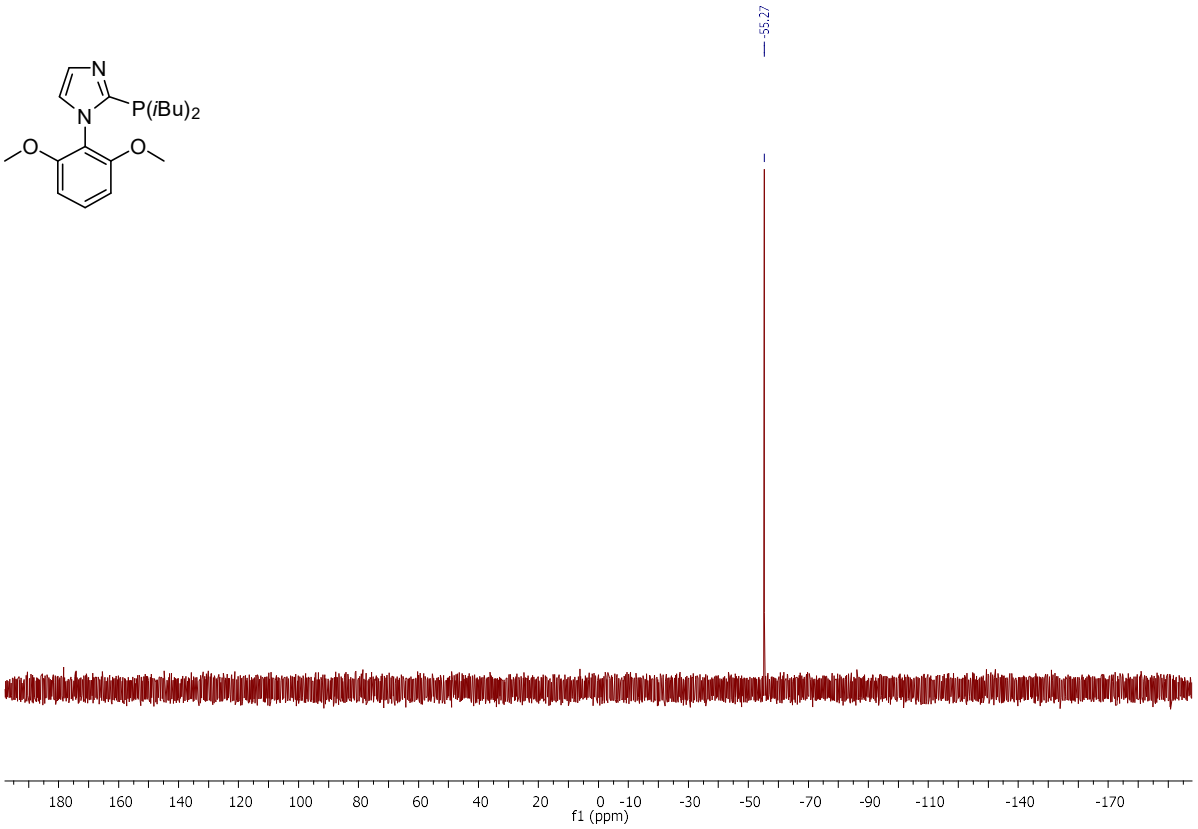



N
N
P(Et)2
O
O
-37.03
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

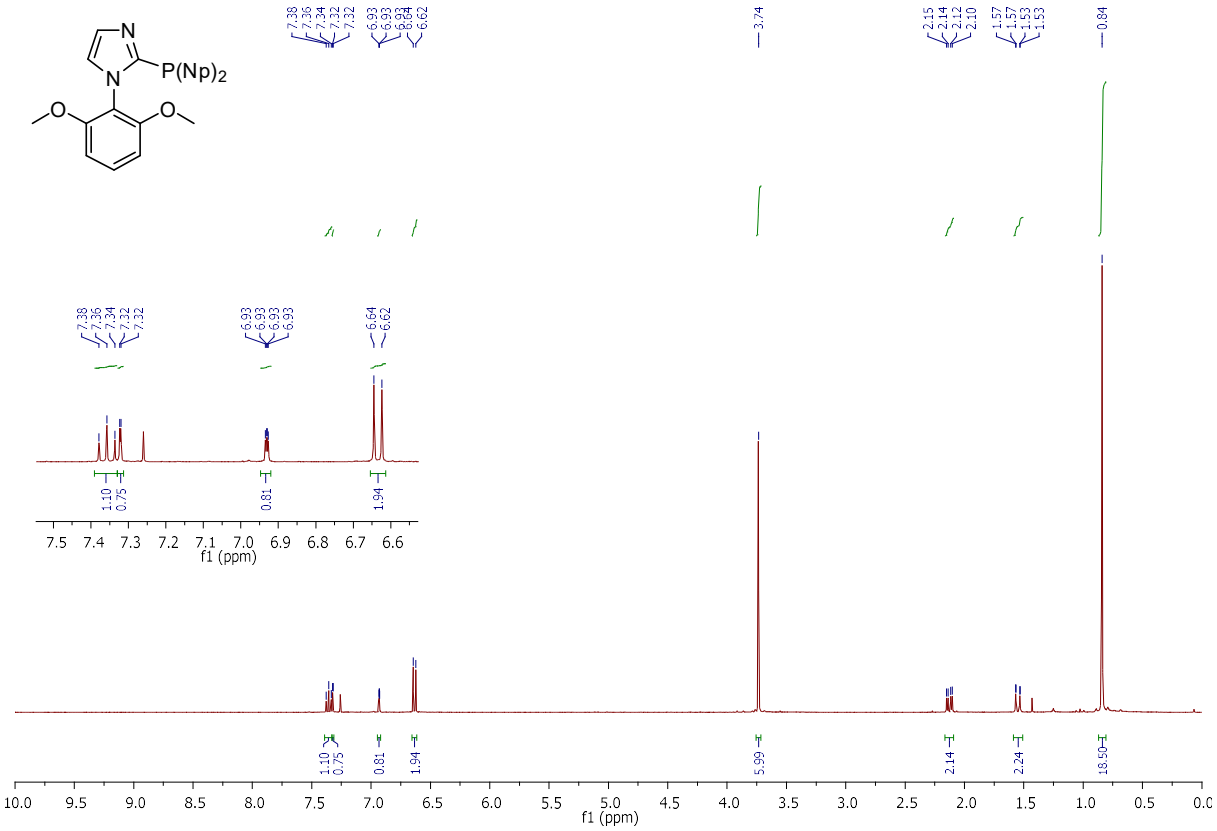
2-(diisobutyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole**2.L**[49] :

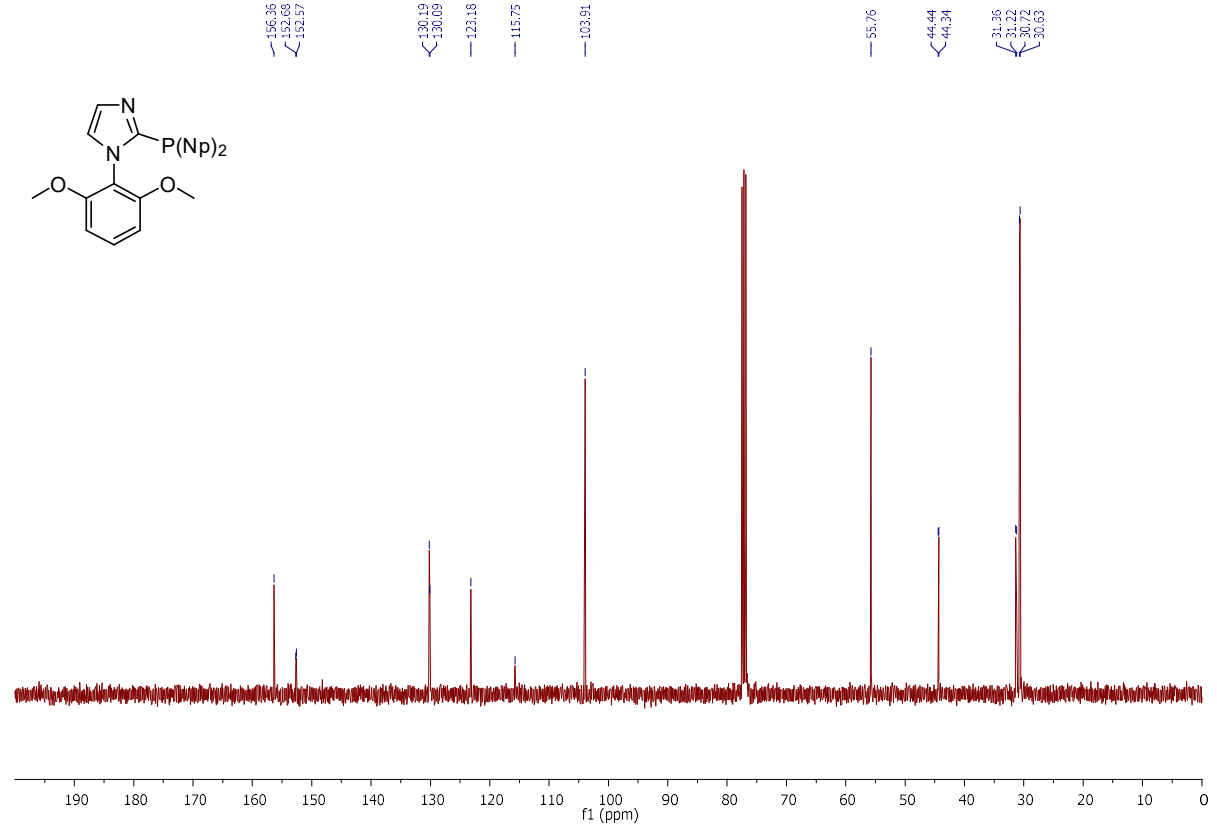


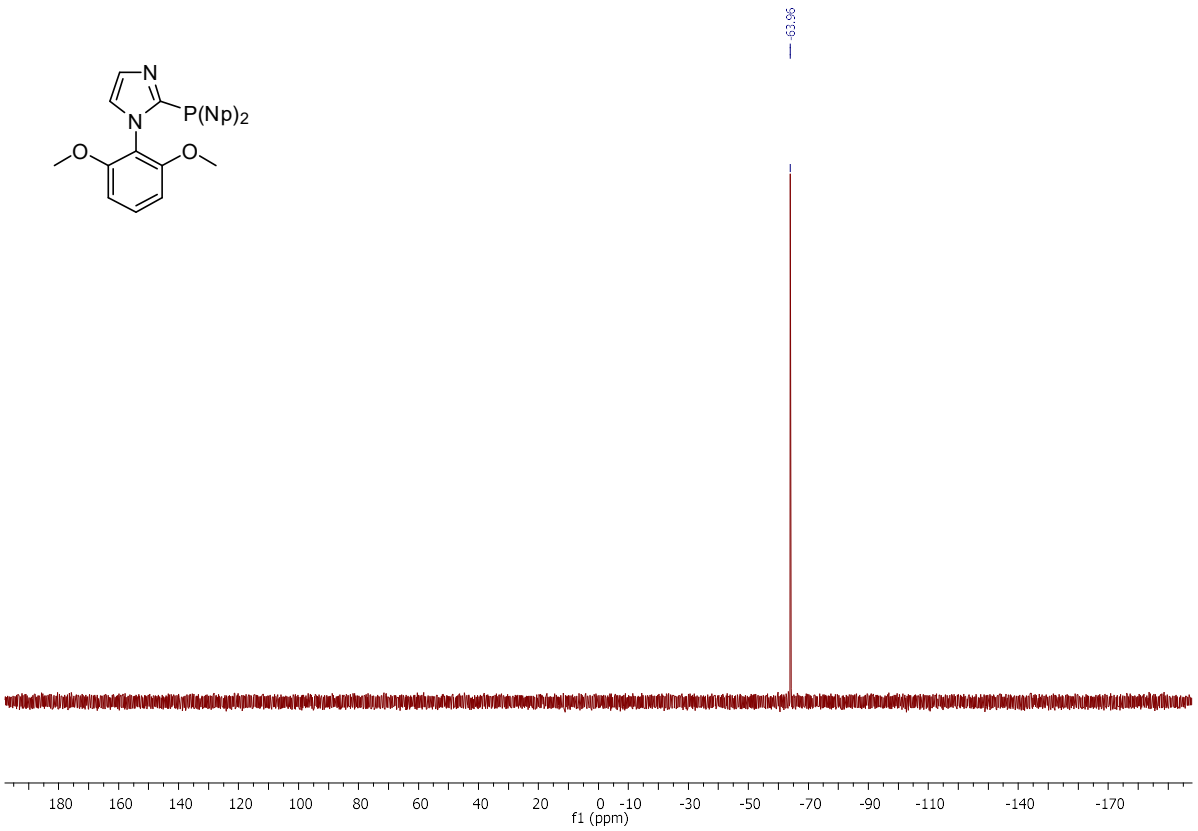



N
N
P(iBu)2
O
O
-55.27
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

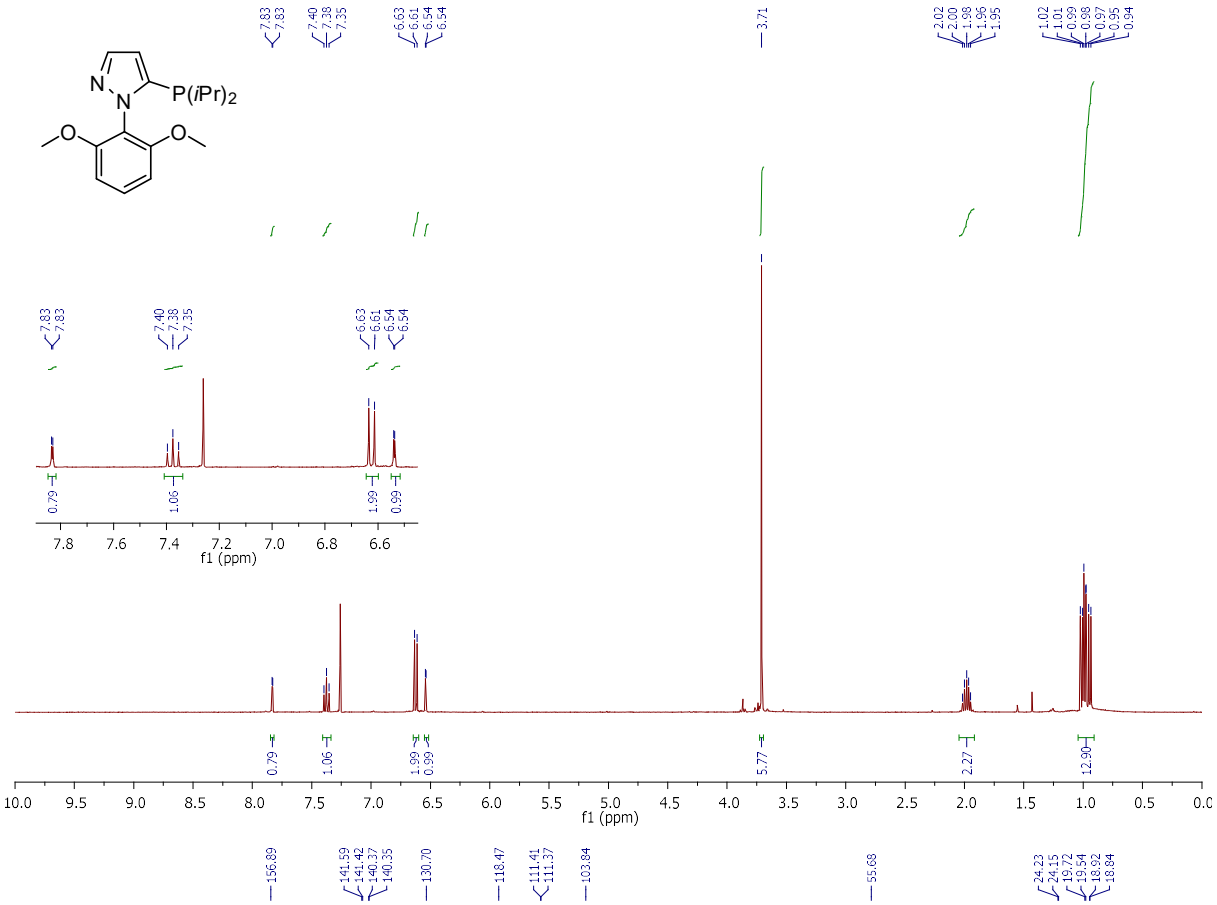
2-(dineopentyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole **2.L**[50] :

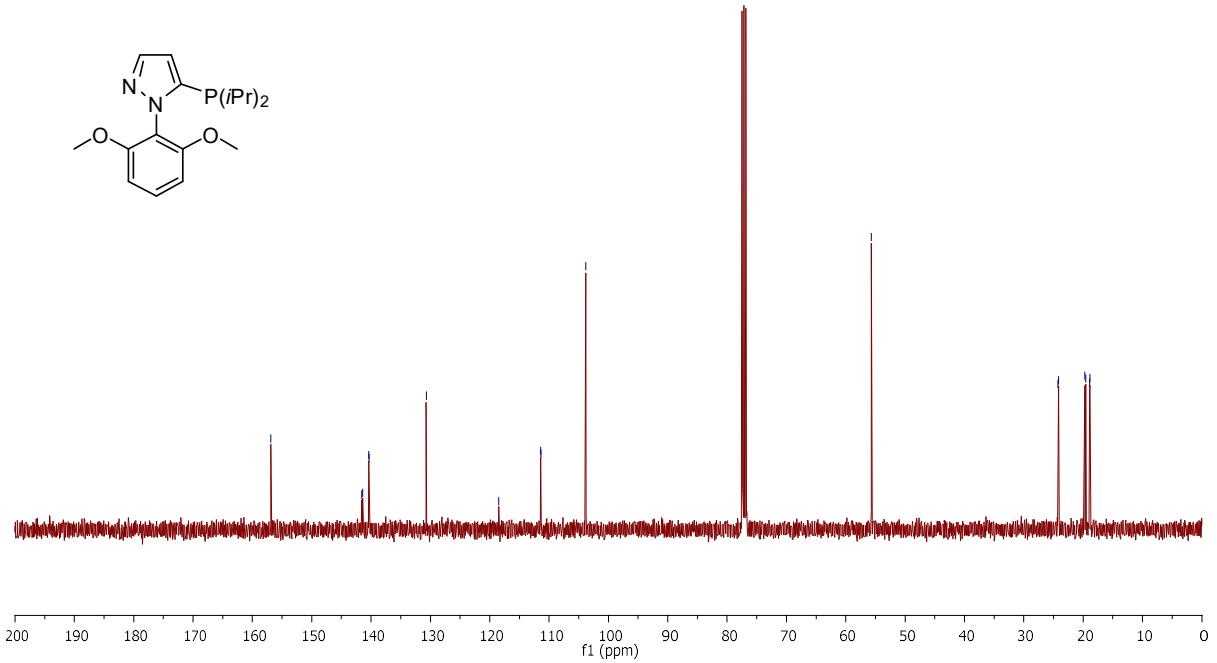


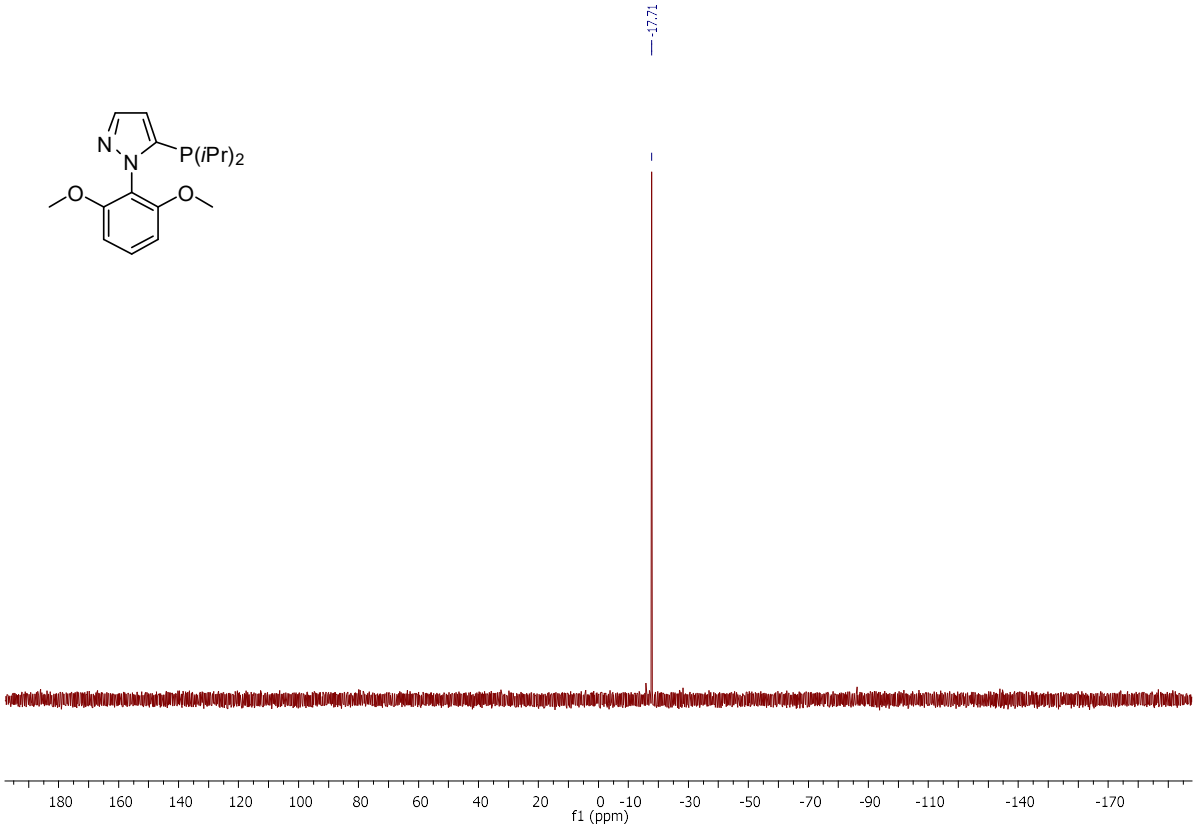



N
N
P(Np)2
O
O
-63.96
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

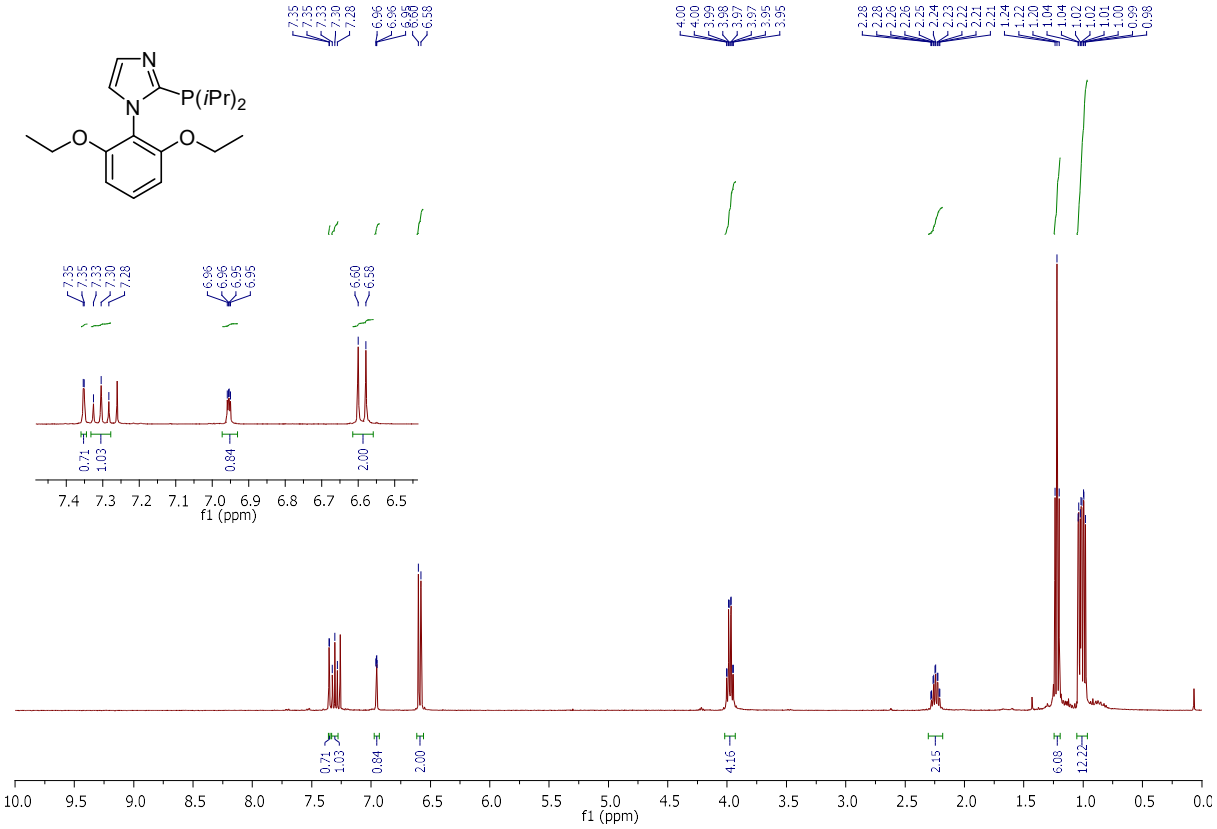
5-(diisopropylphosphanyl)-1-(2,6-dimethoxyphenyl)-1H-pyrazole **2.L**[51] :

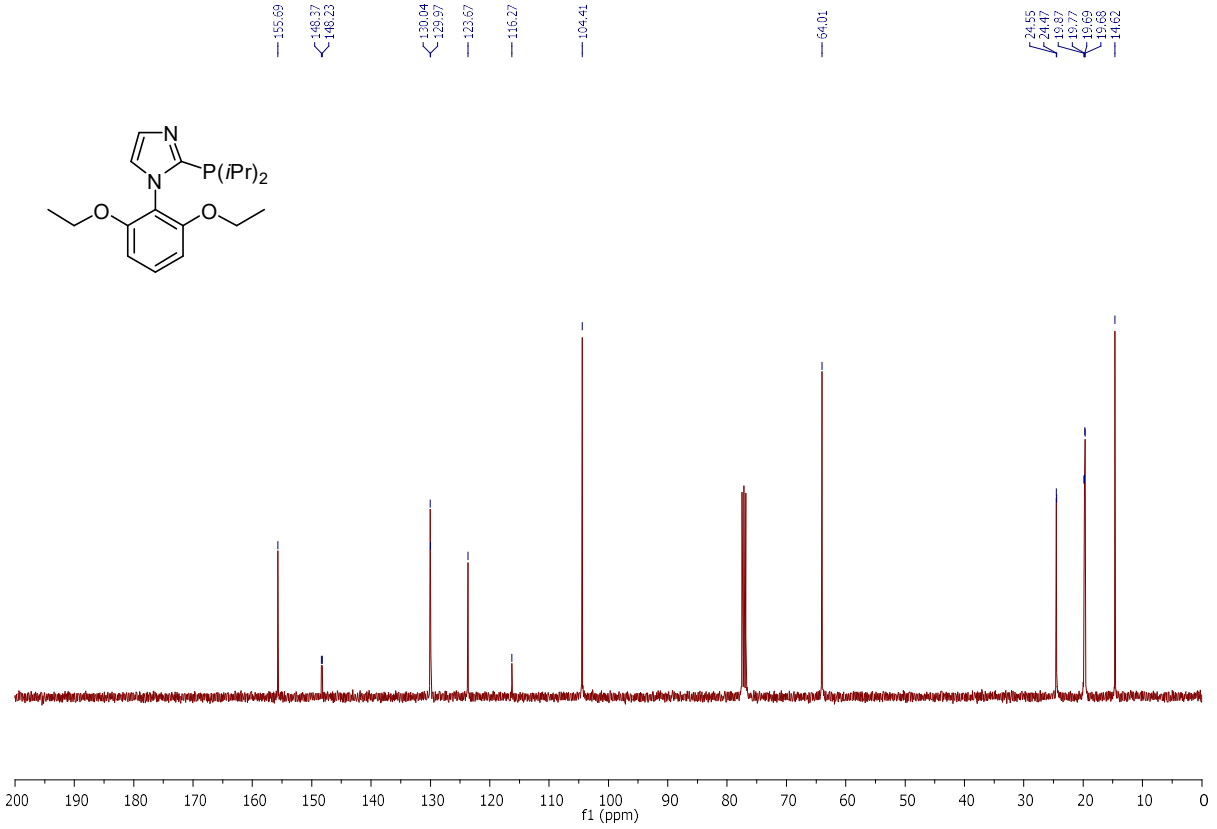


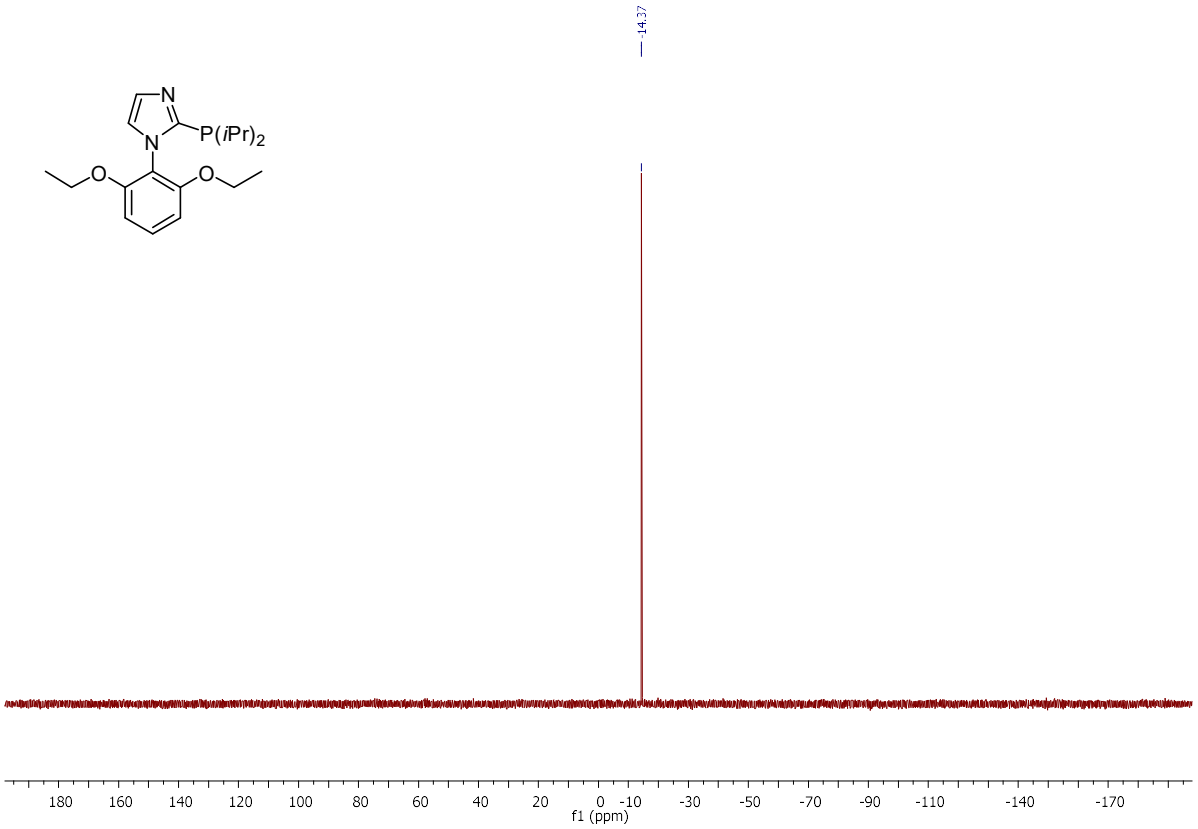



-17.71
N
N
P(iPr)2
O
O
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

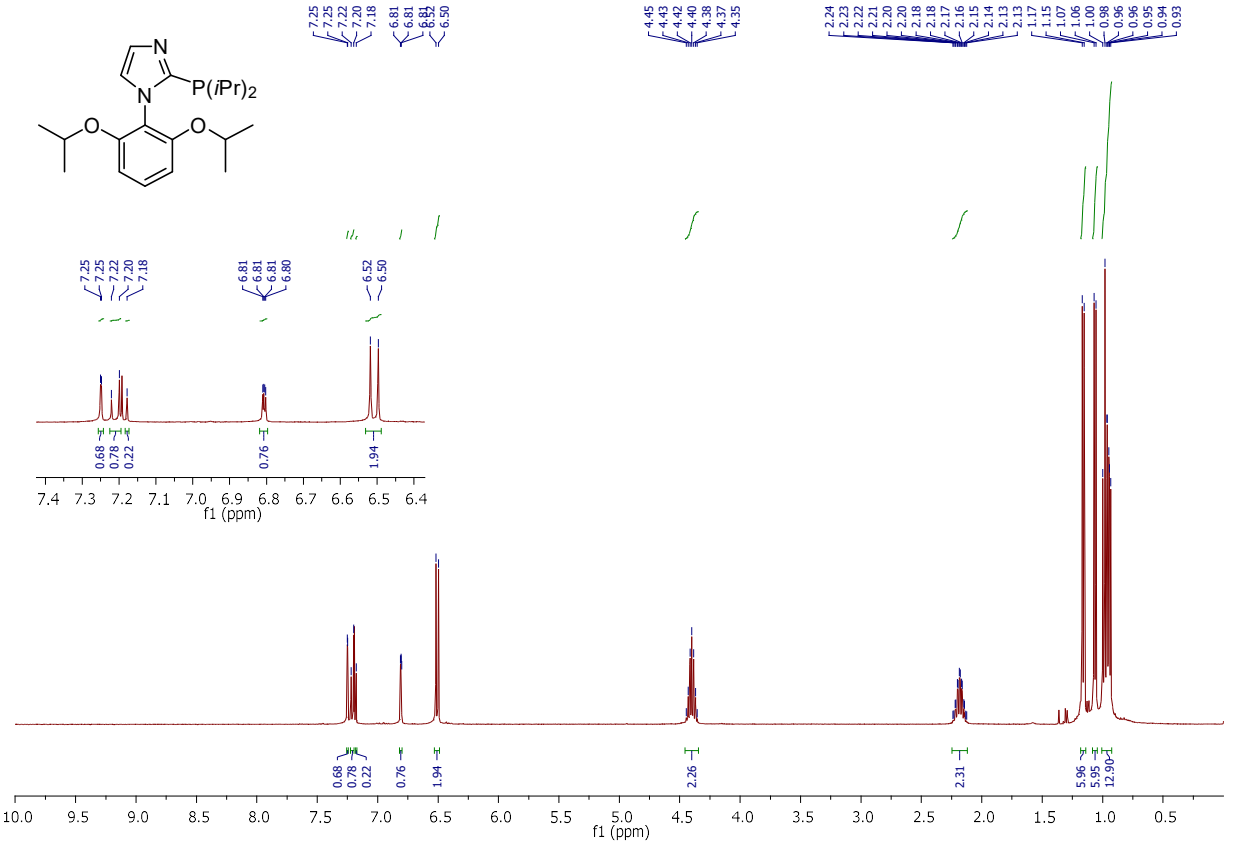
1-(2,6-diethoxyphenyl)-2-(diisopropylphosphanyl)-1*H*-imidazole**2.L**[52] :

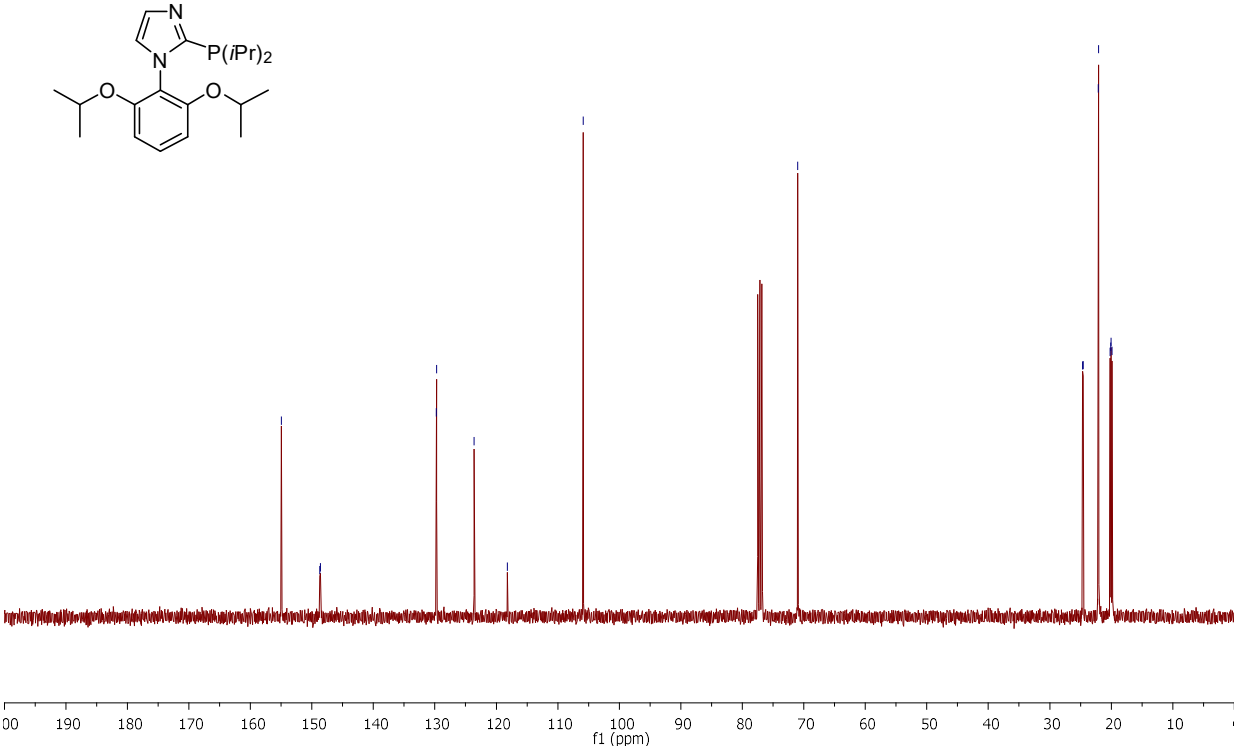


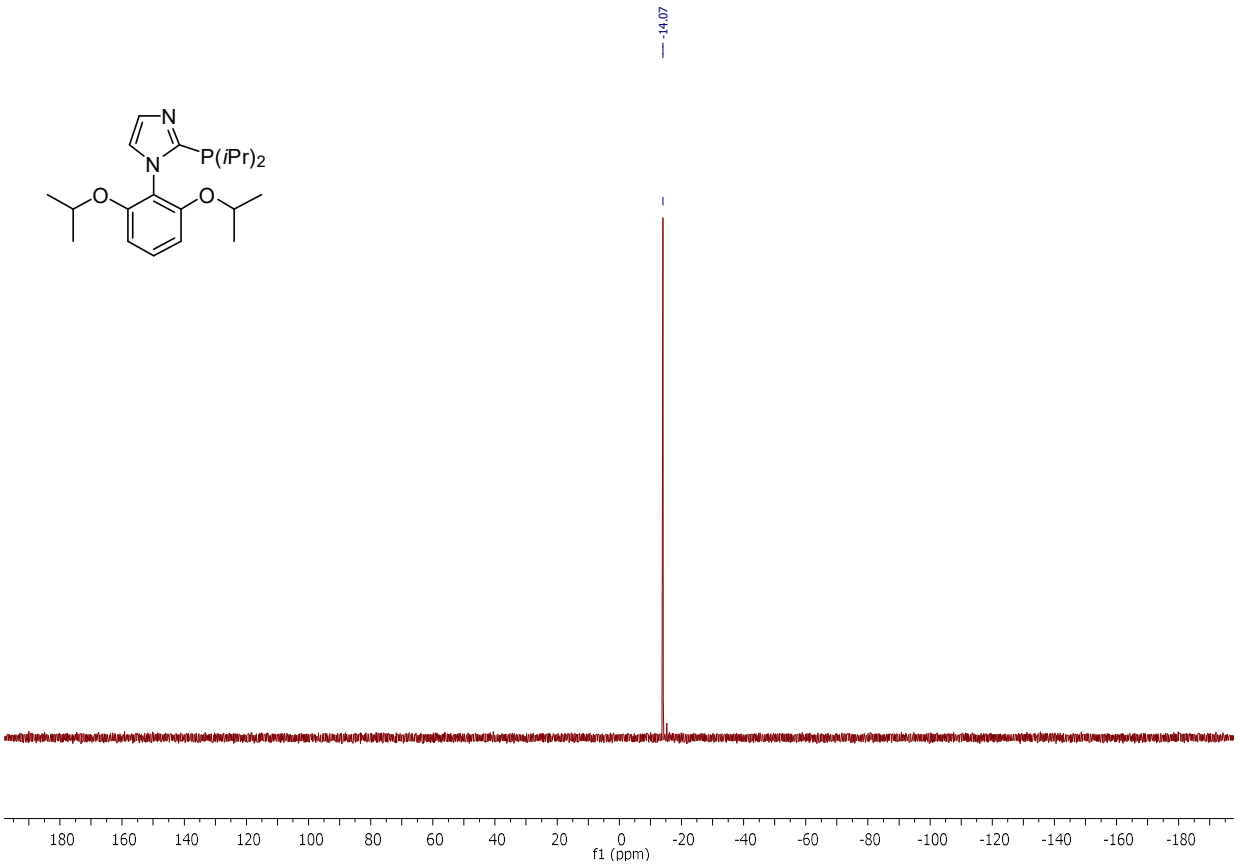



-14.37
N
N
P(iPr)2
O
O
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

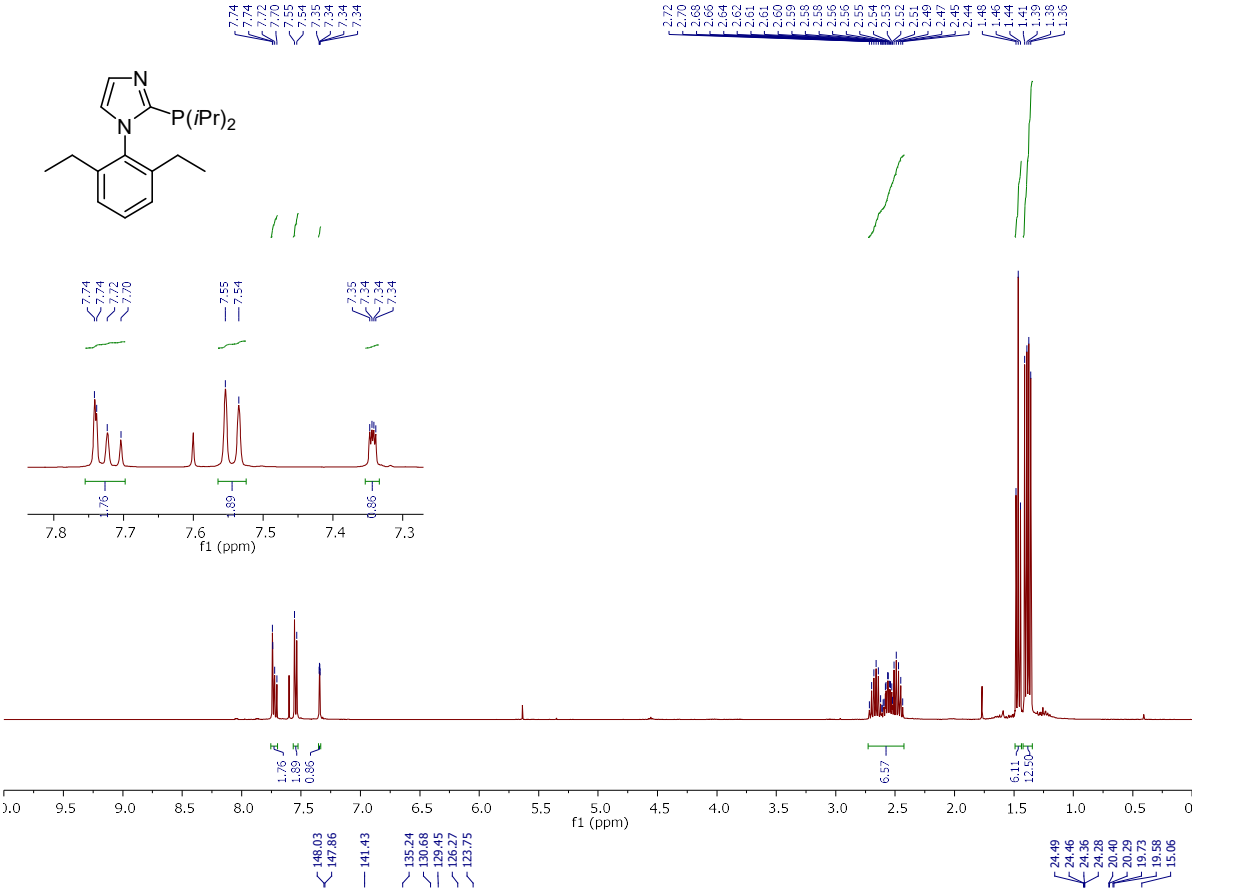
1-(2,6-diisopropoxyphenyl)-2-(diisopropylphosphanyl)-1H-imidazole **2.L**[53]:

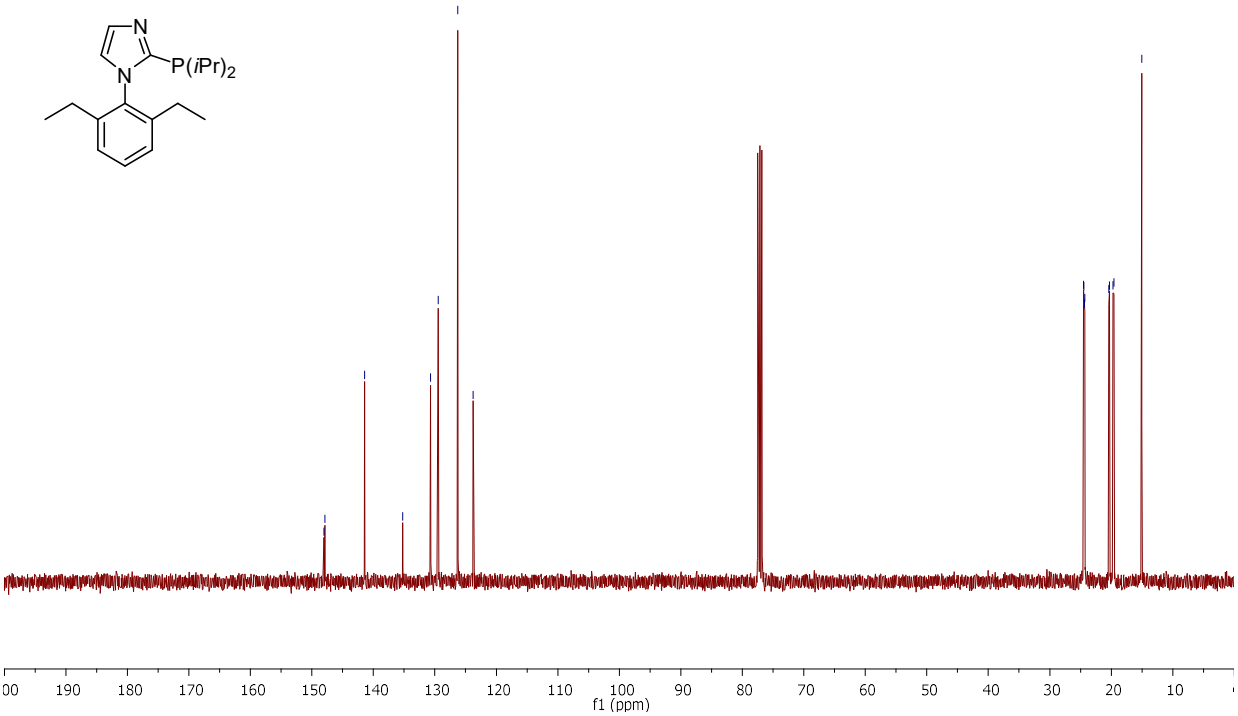


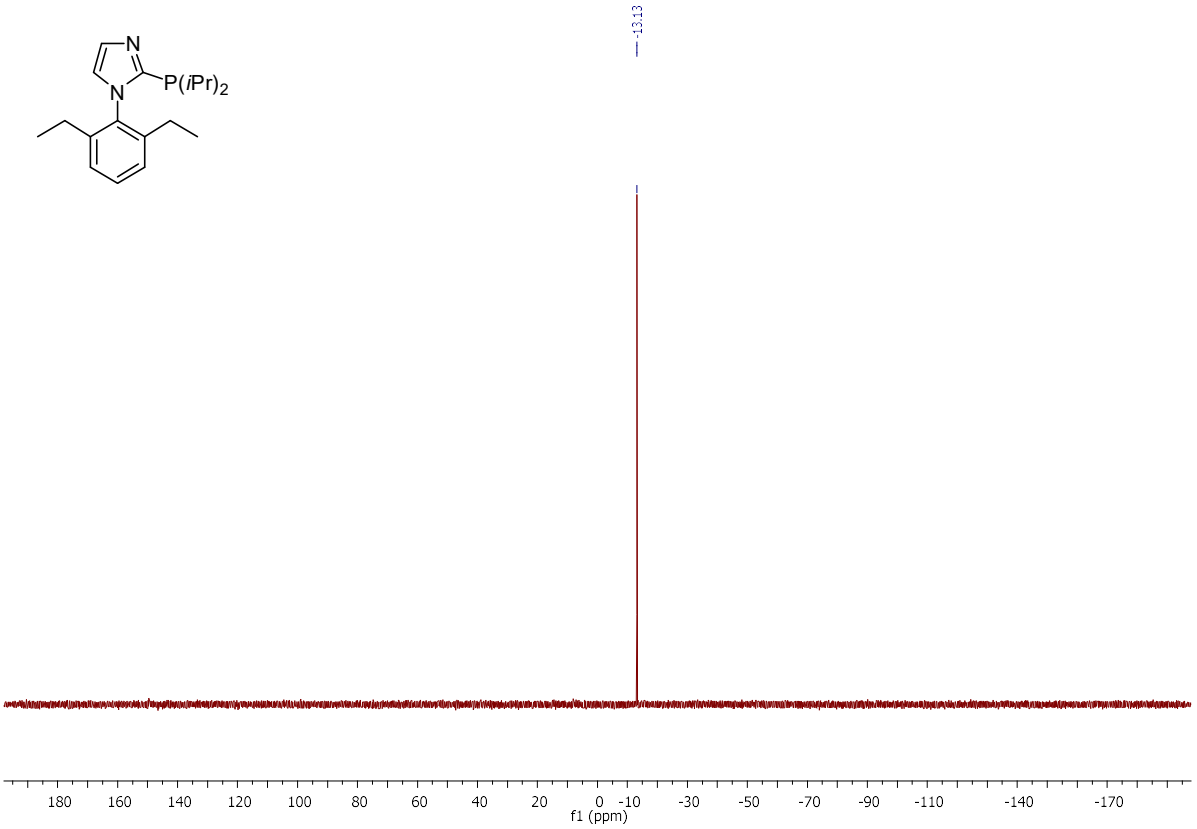



-14.07
N
N
P(iPr)2
O
O
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
f1 (ppm)

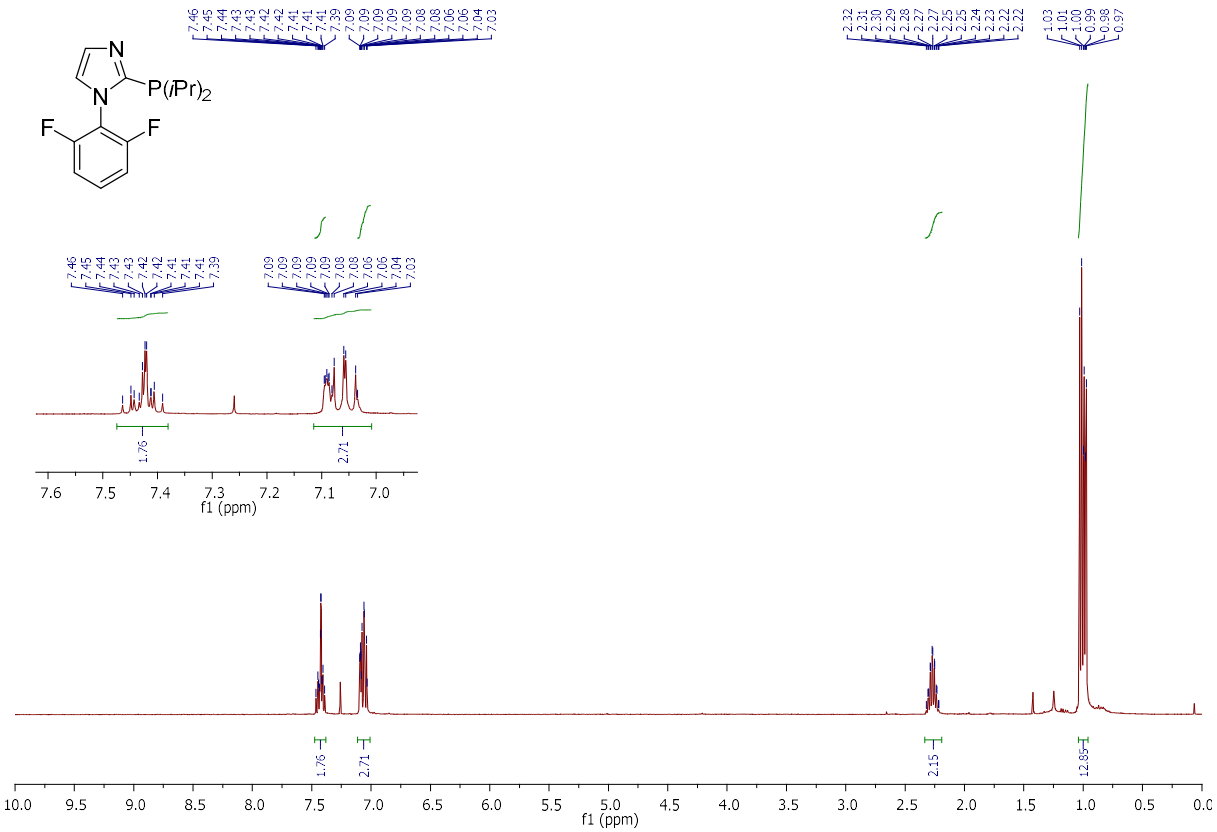
1-(2,6-diethylphenyl)-2-(diisopropylphosphanyl)-1*H*-imidazole**2.L**[54] :

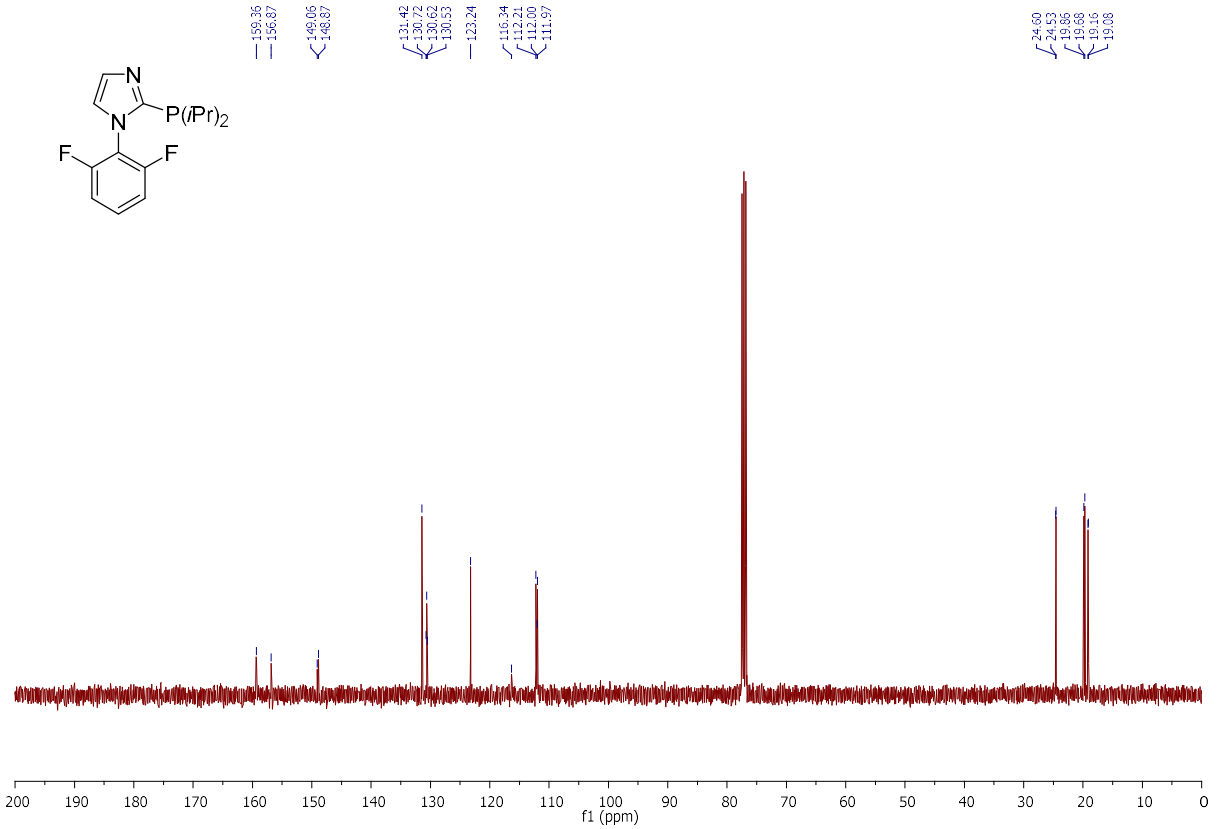


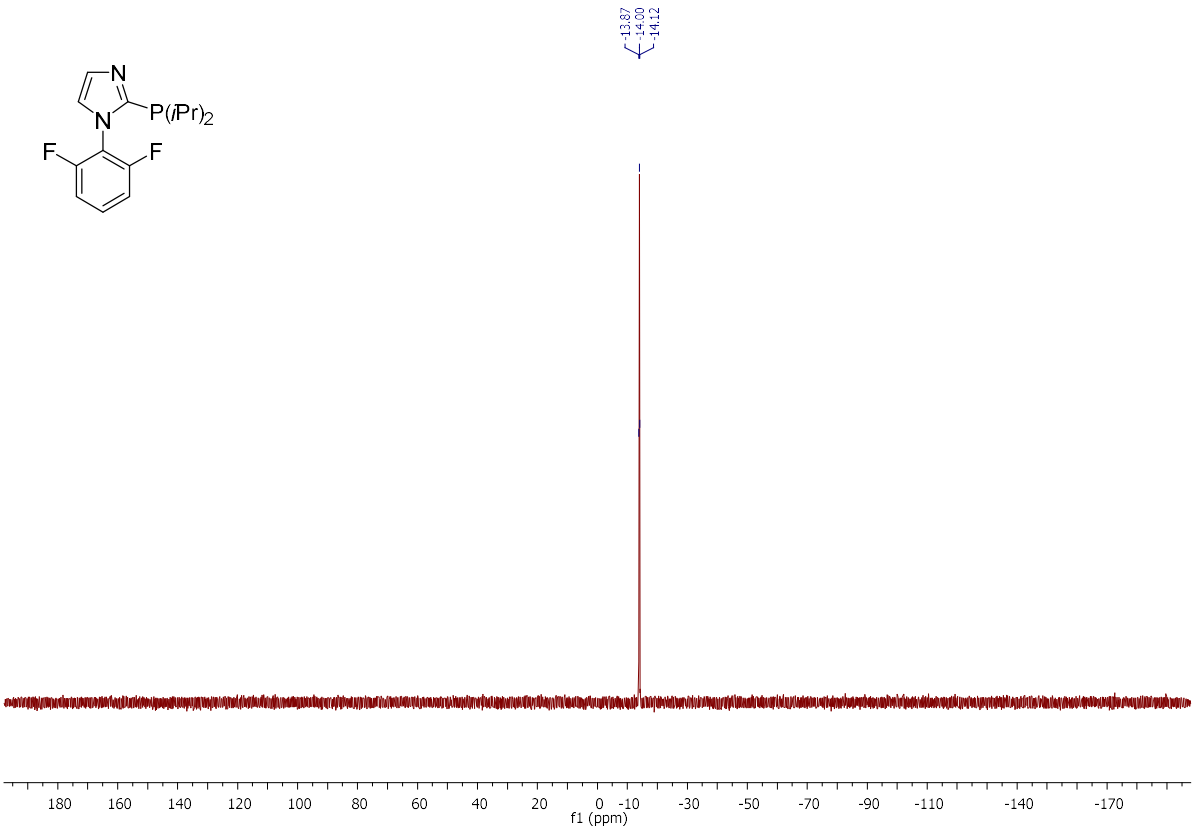


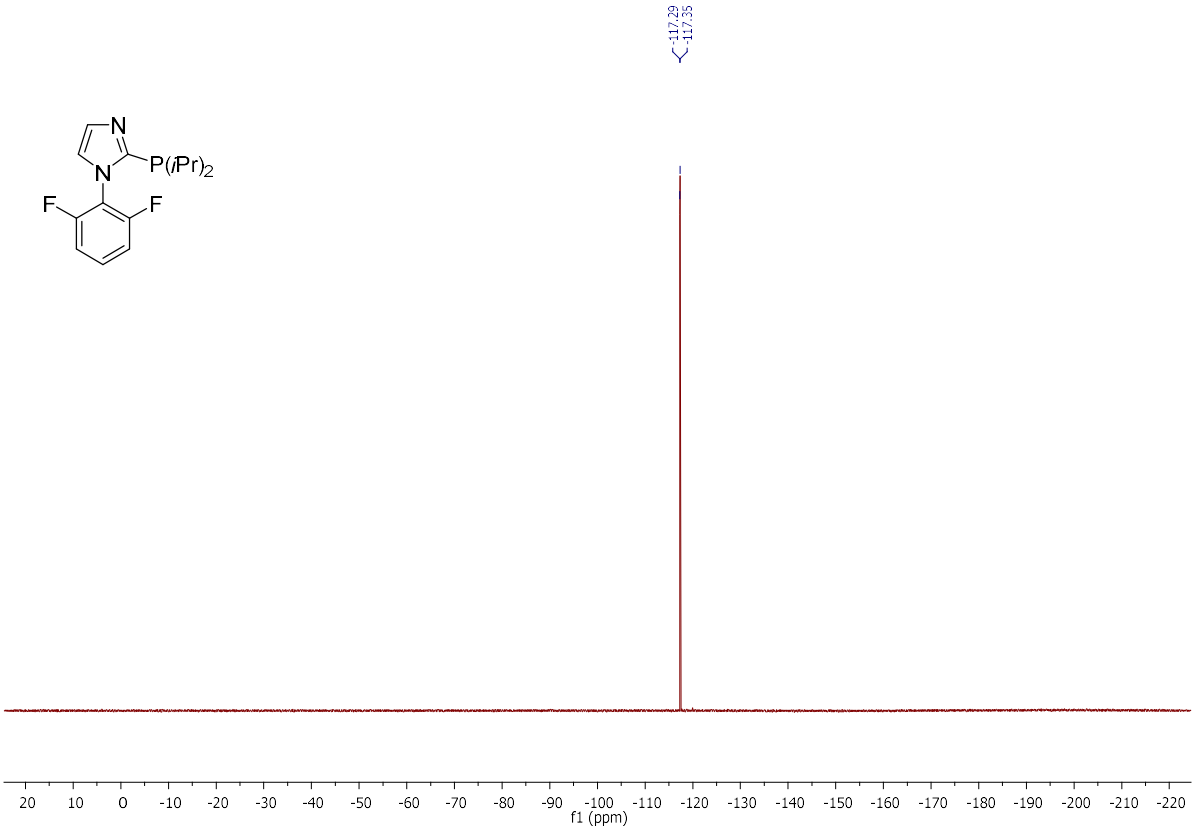

N
N
P(iPr)2
-13.13
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-110
-140
-170
f1 (ppm)

1-(2,6-difluorophenyl)-2-(diisopropylphosphanyl)-1H-imidazole**2.L**[55] :

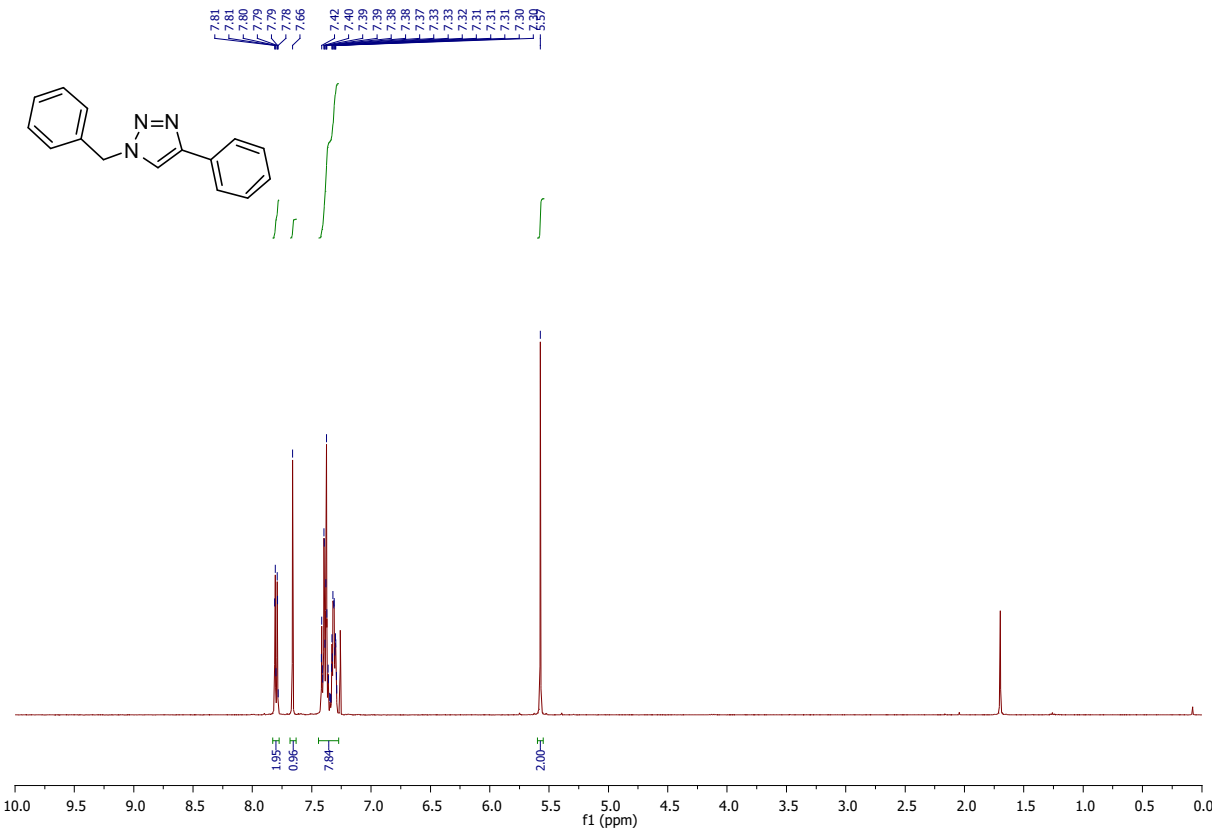


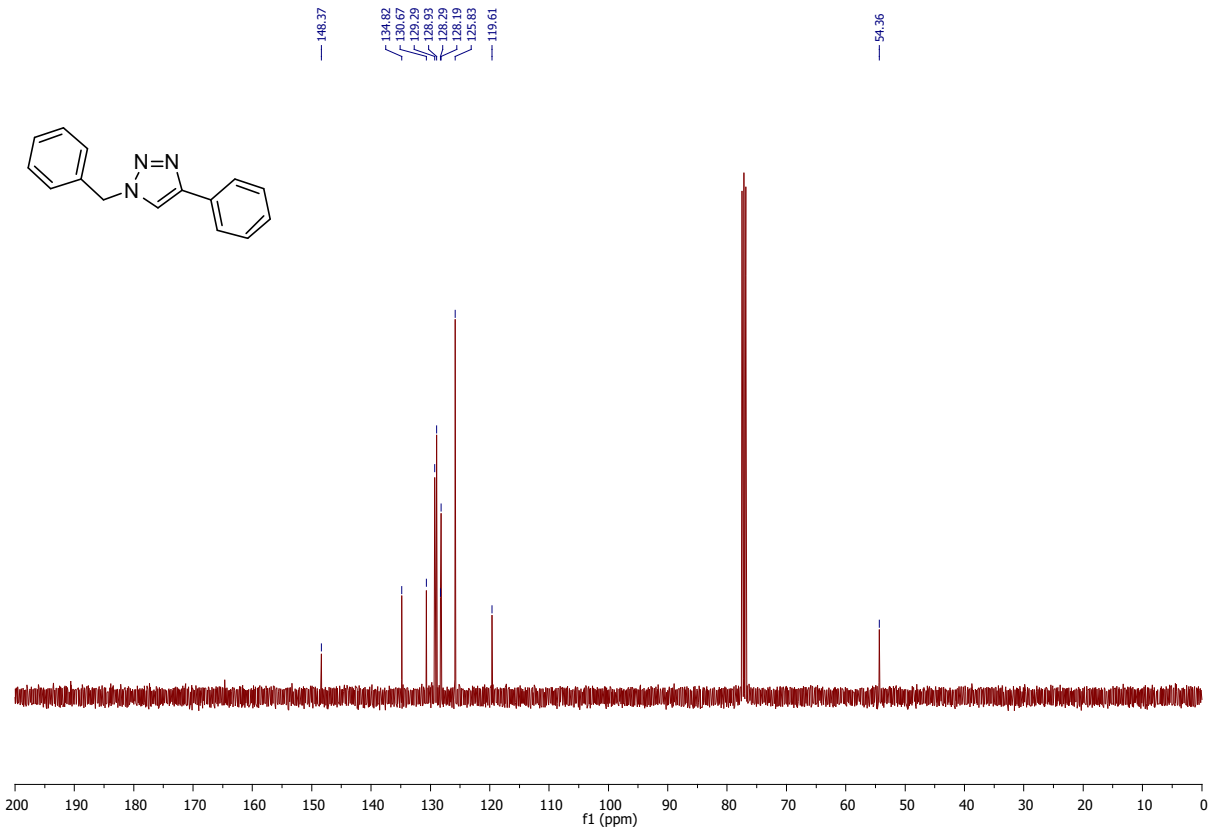



-13.87
-14.00
-14.12
N
N
P(iPr)2
F
F
180 160 140 120 100 80 60 40 20 0 -10 -30 -50 -70 -90 -110 -140 -170
f1 (ppm)

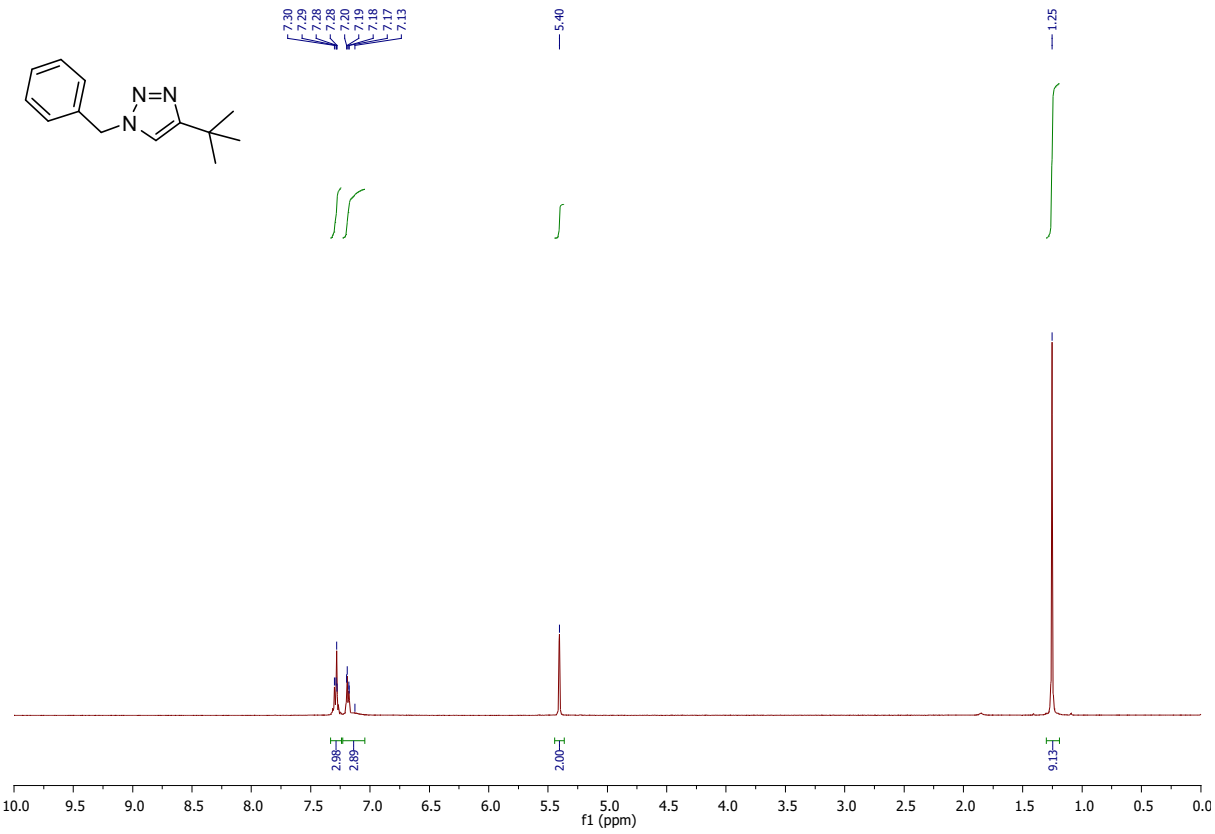

-117.29
-117.35
N
N
P(iPr)2
F
F
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

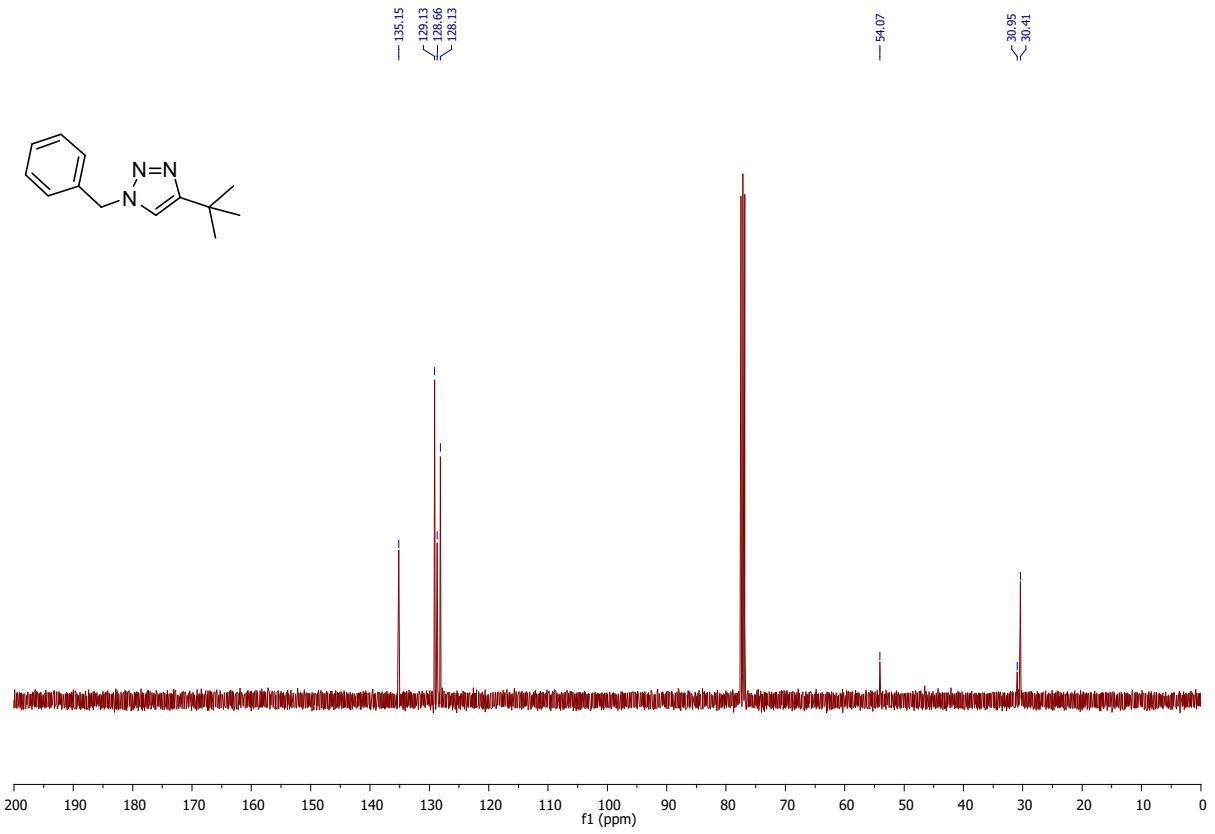
1-benzyl-4-phenyl-1*H*-1,2,3-triazole**3.1a**:



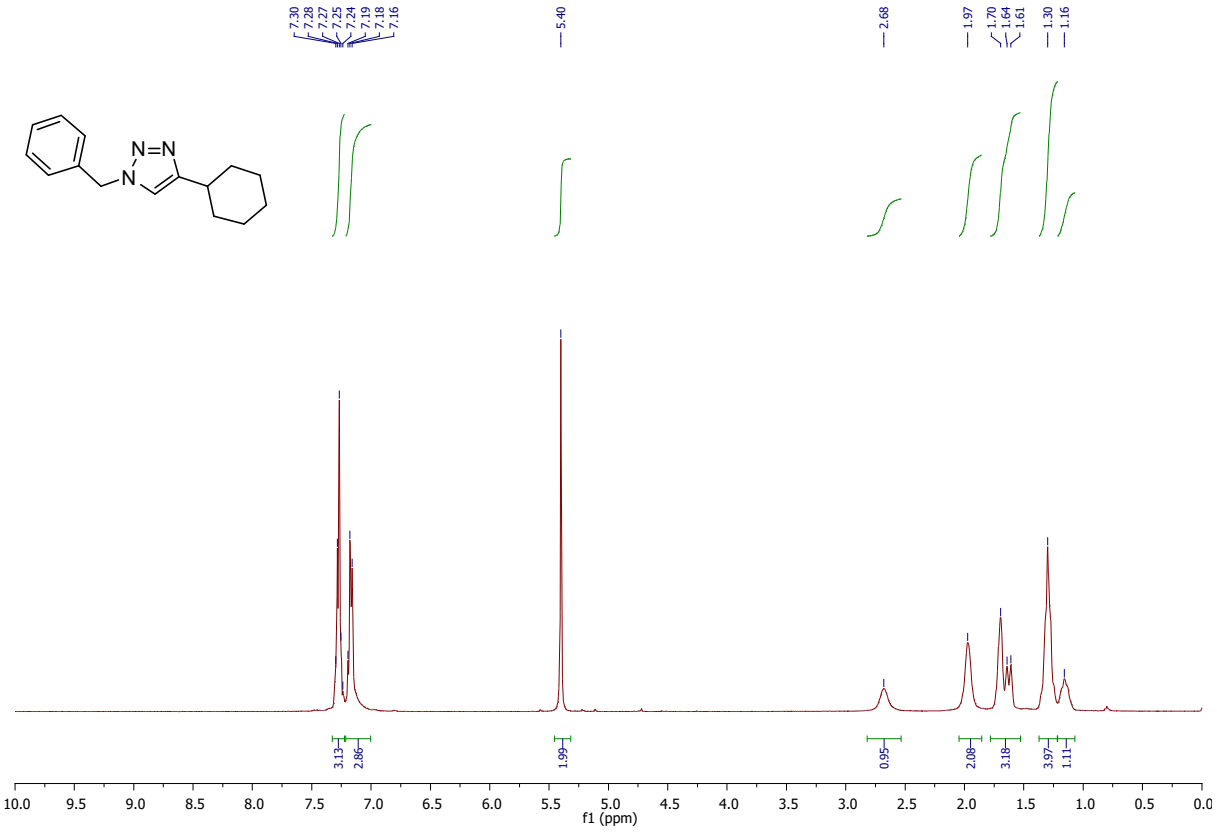


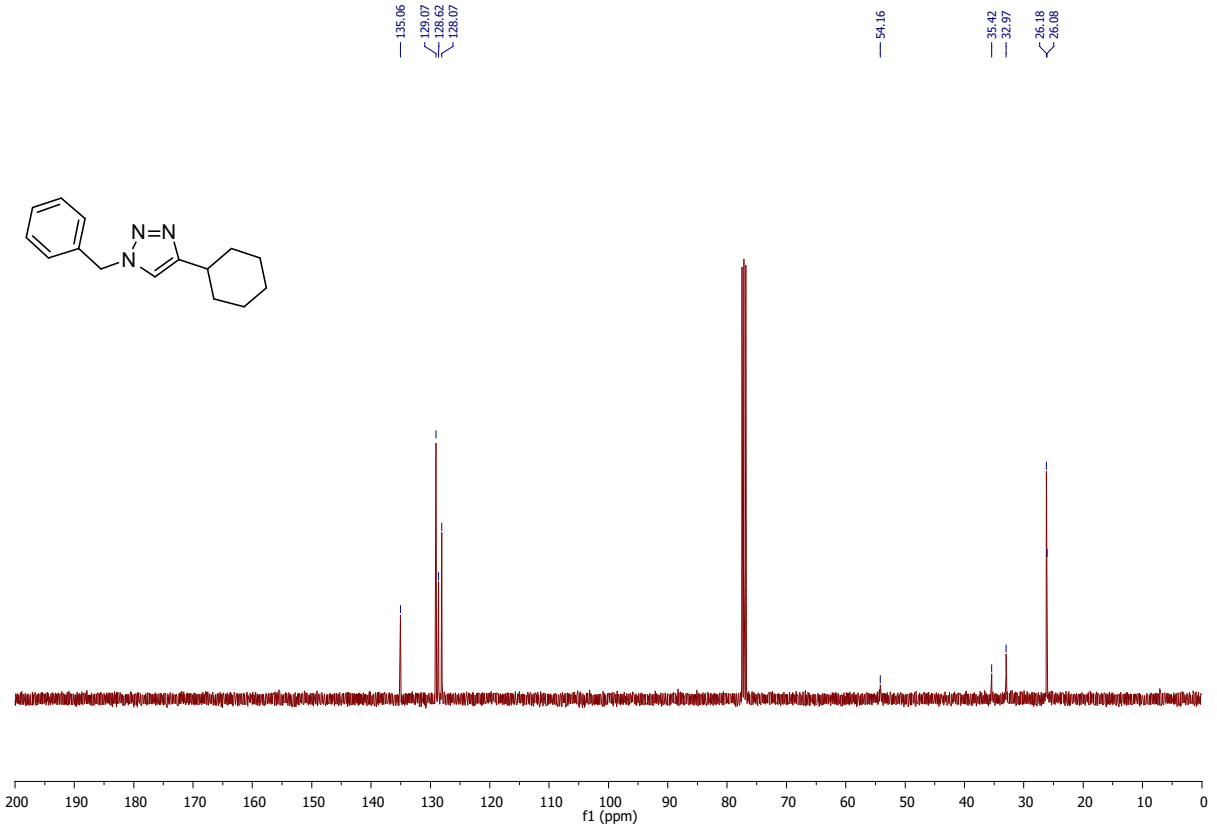
1-benzyl-4-(tert-butyl)-1*H*-1,2,3-triazole **3.1b**:



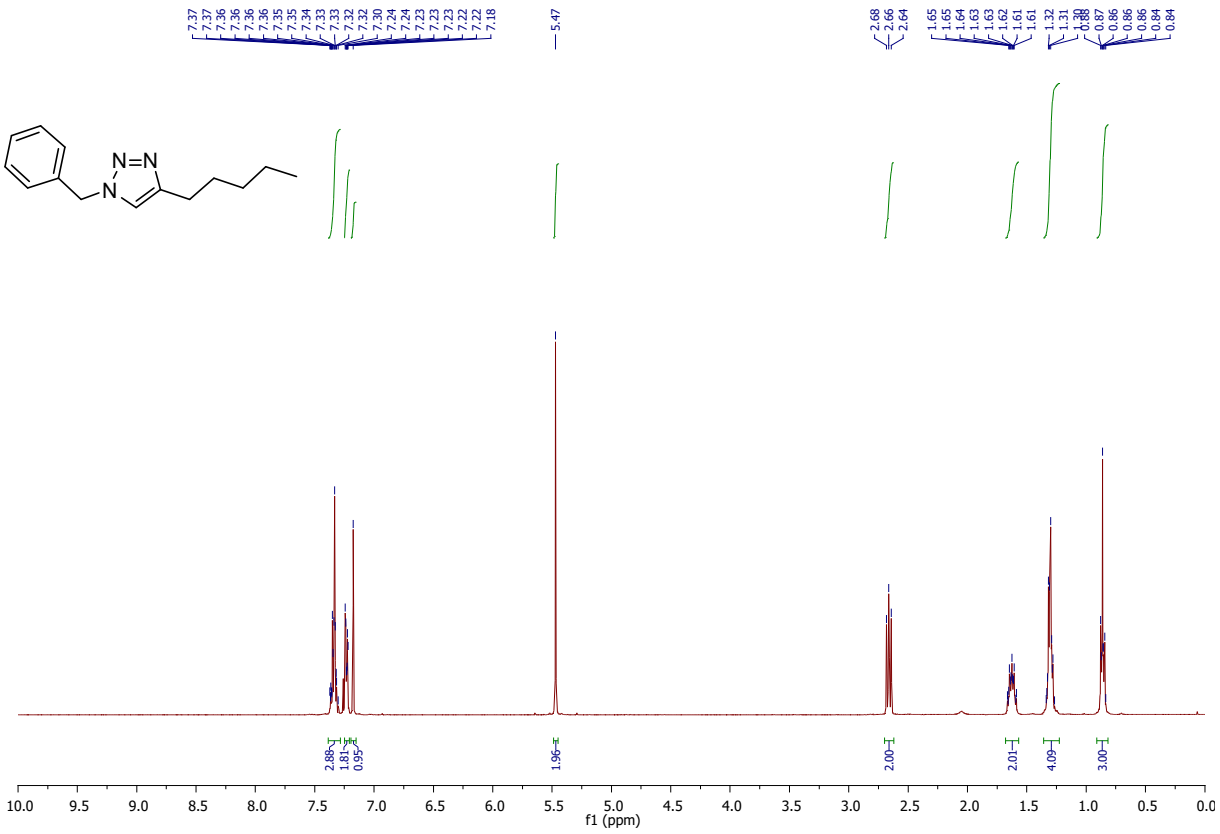


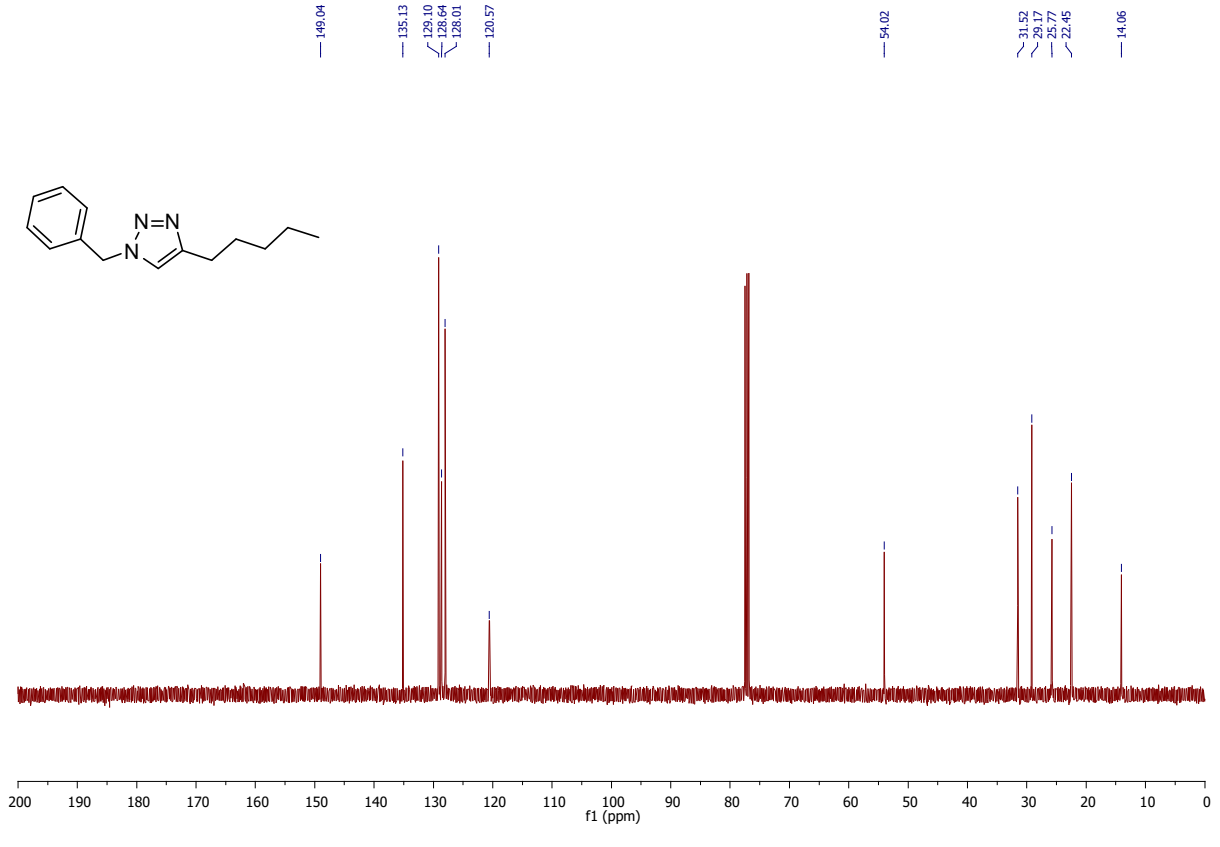
1-benzyl-4-cyclohexyl-1*H*-1,2,3-triazole **3.1c**:



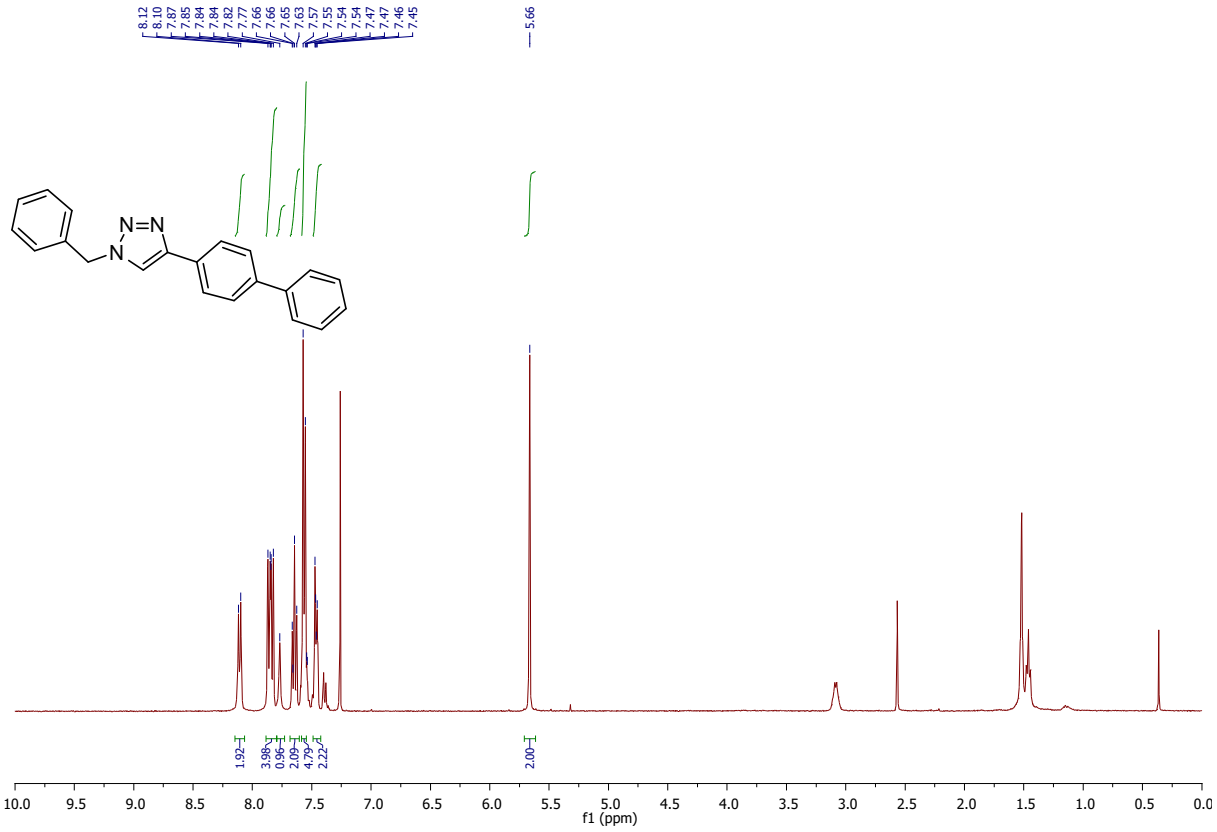


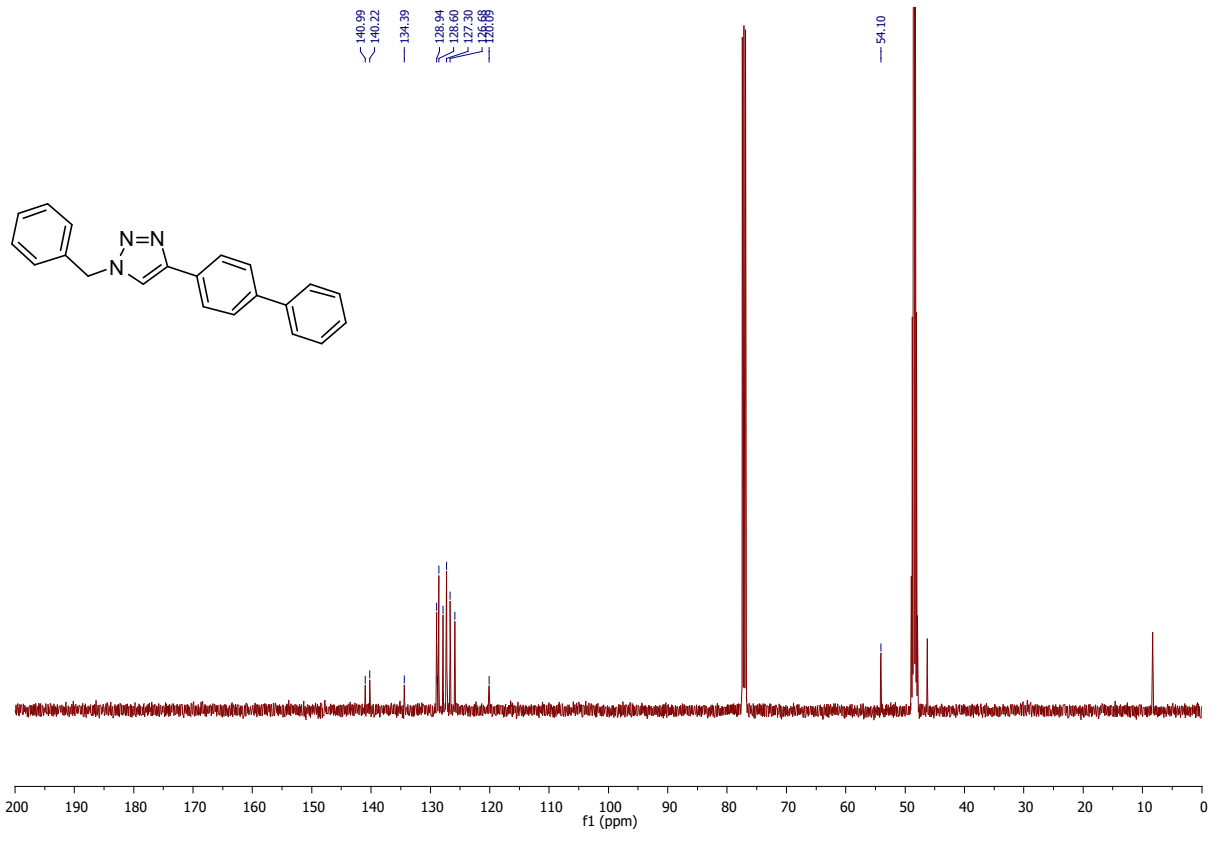
1-benzyl-4-pentyl-1*H*-1,2,3-triazole **3.1d** :



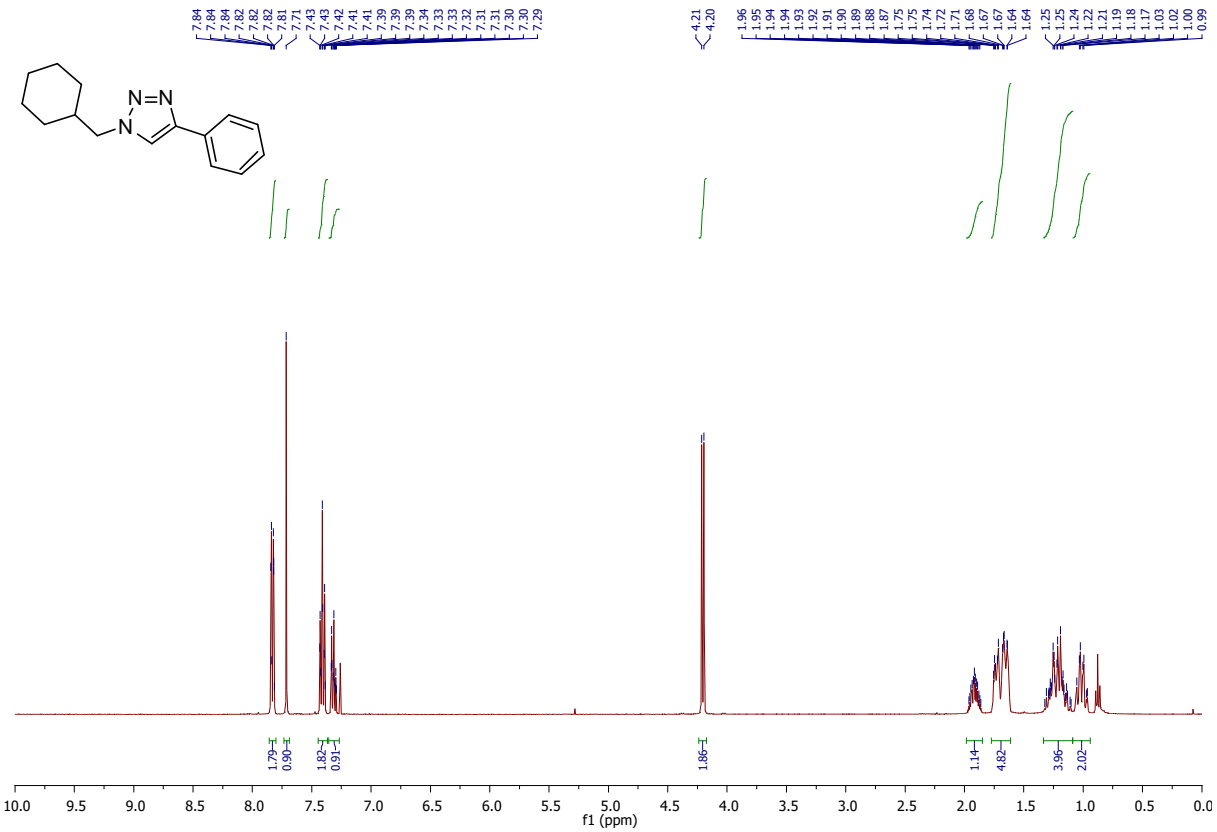


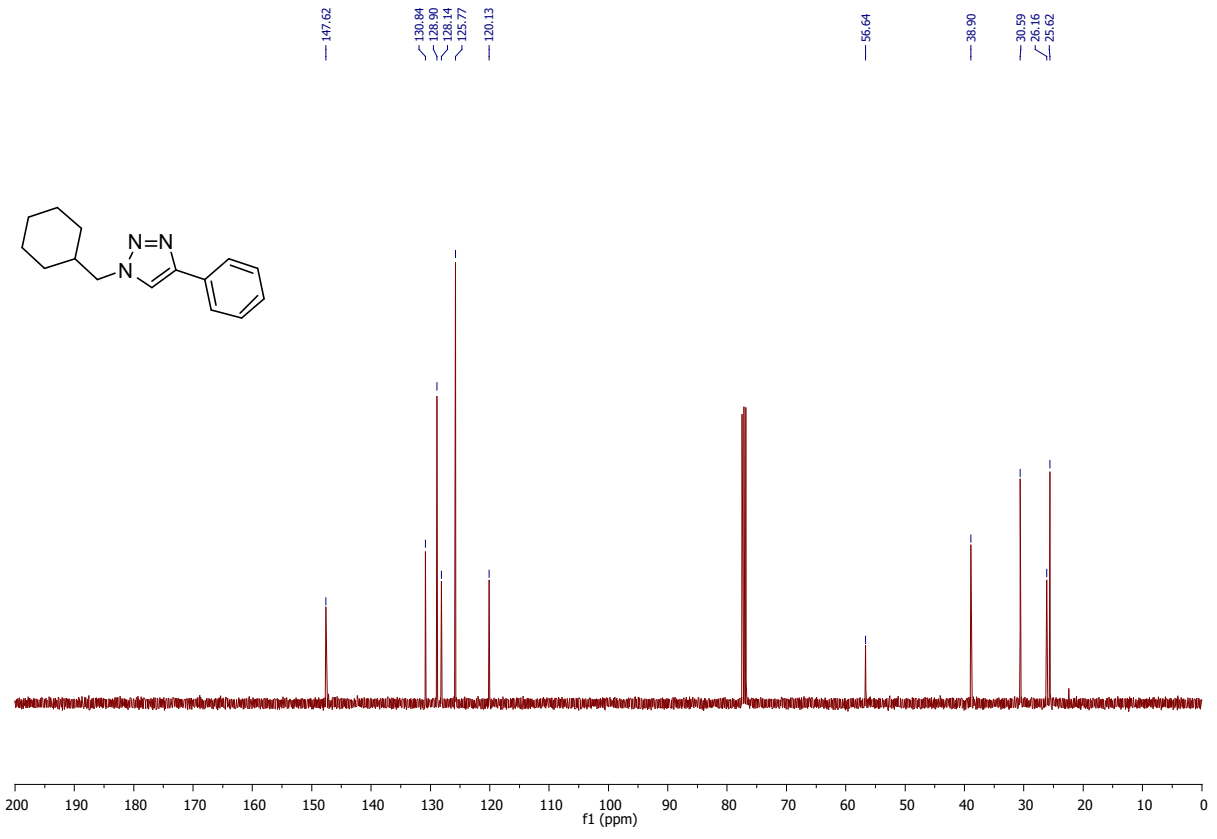
4-([1,1'-biphenyl]-4-yl)-1-benzyl-1*H*-1,2,3-triazole **3.1e** :



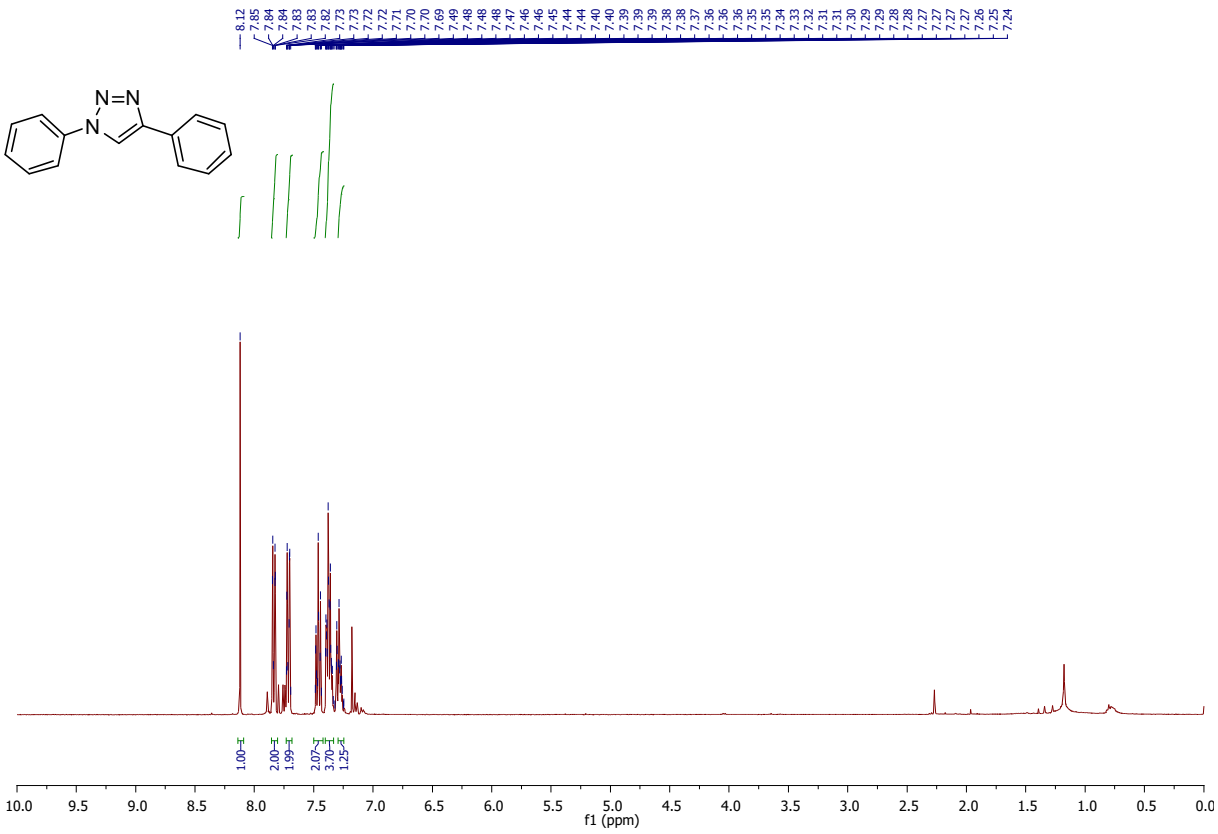


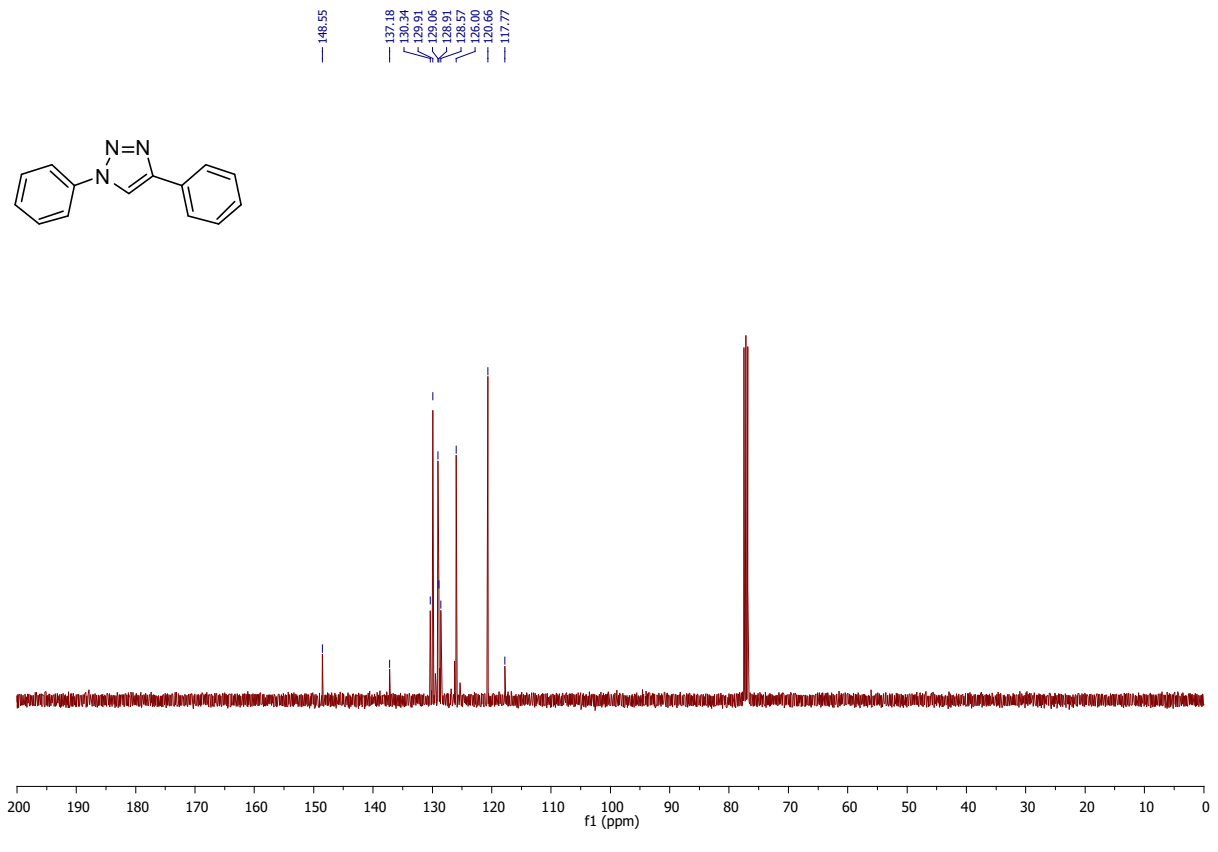
1-(cyclohexylmethyl)-4-phenyl-1*H*-1,2,3-triazole **3.1f** :



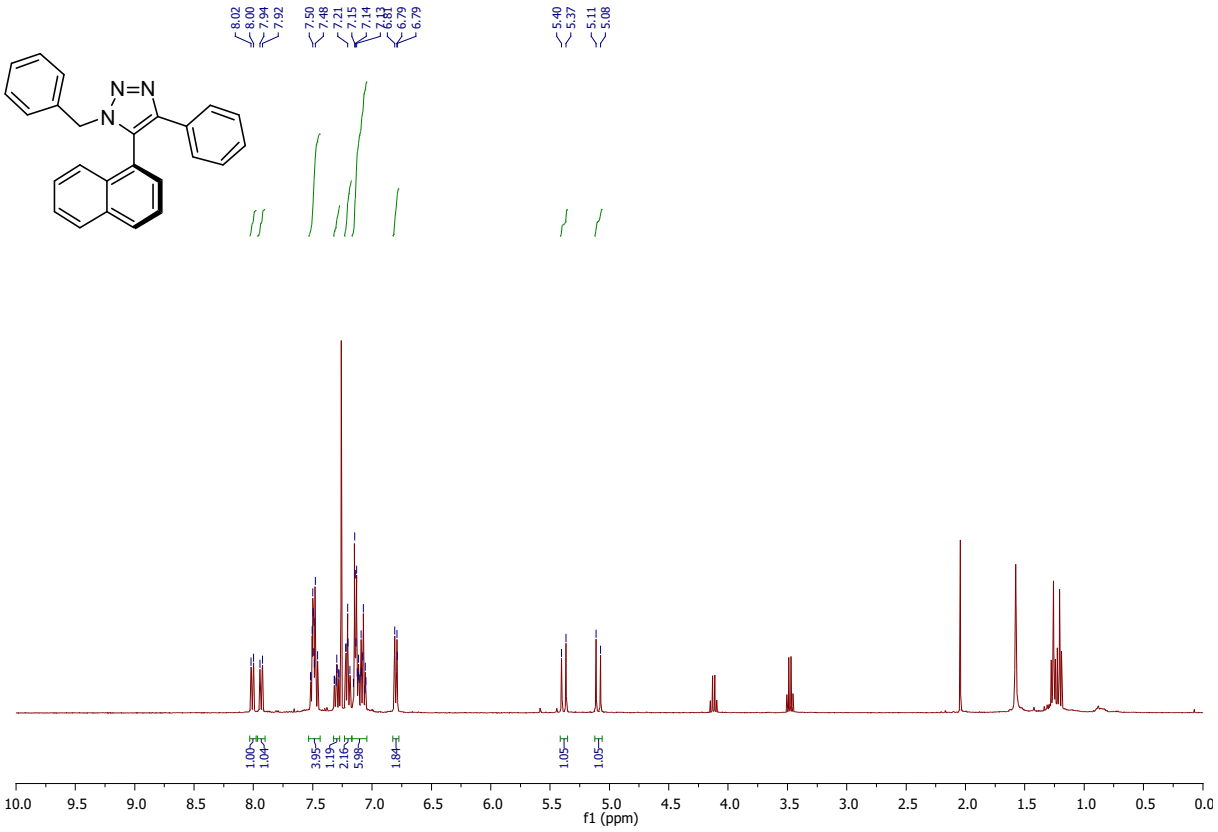


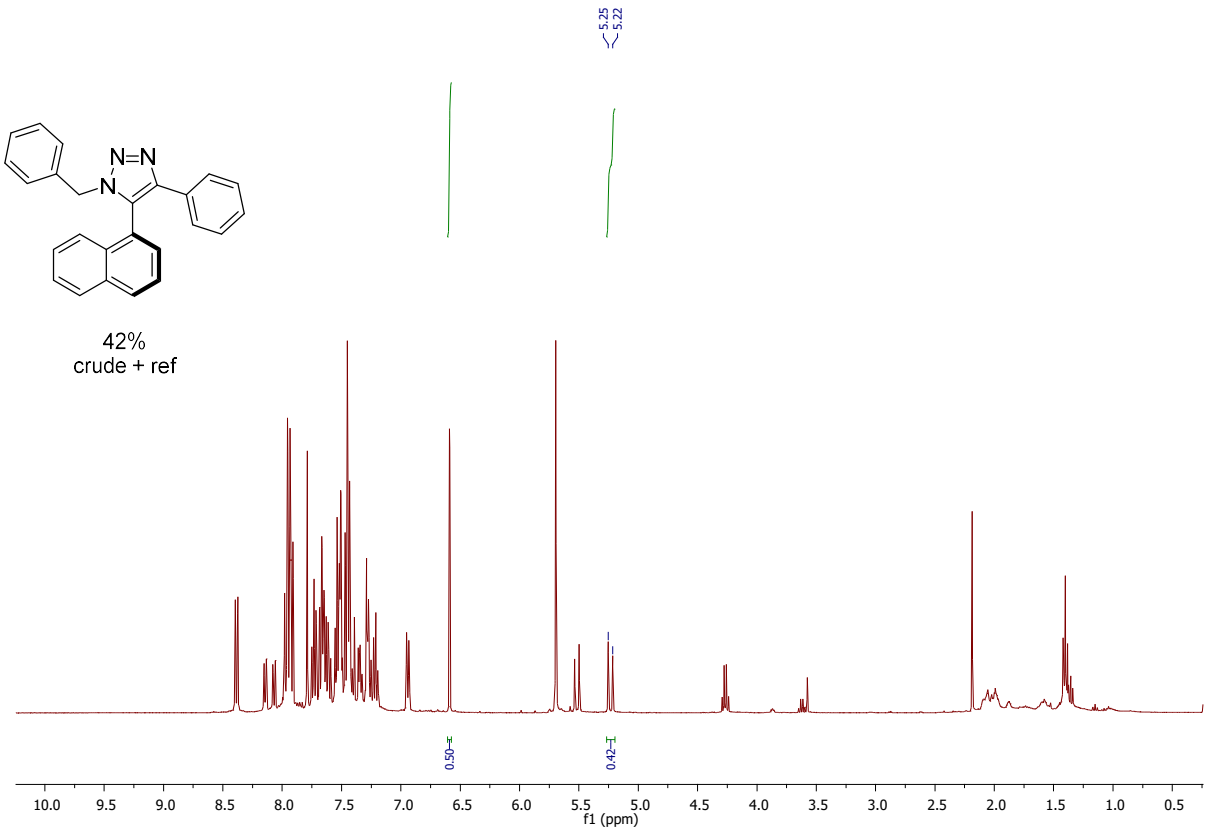
1,4-diphenyl-1*H*-1,2,3-triazole **3.1g** :



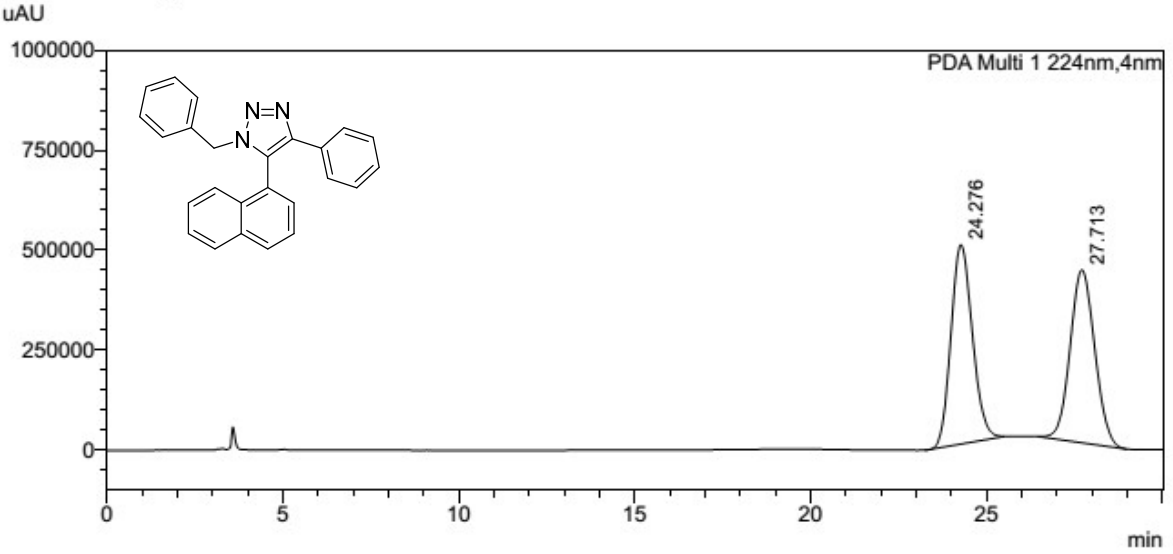


1-benzyl-5-(naphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazole **3.2a**:





<Chromatogram>

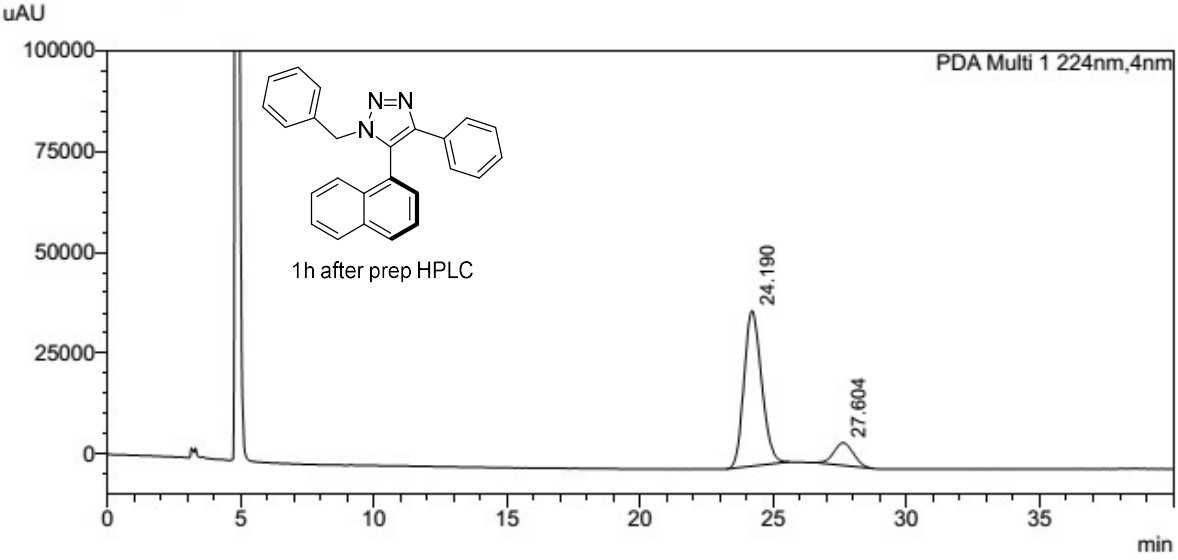


<Peak Table>

PDA Ch1 224nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	24.276	50.139	21144135	498295	50.139		M
2	27.713	49.861	21026646	432291	49.861		
Total		100.000	42170781	930586			

<Chromatogram>

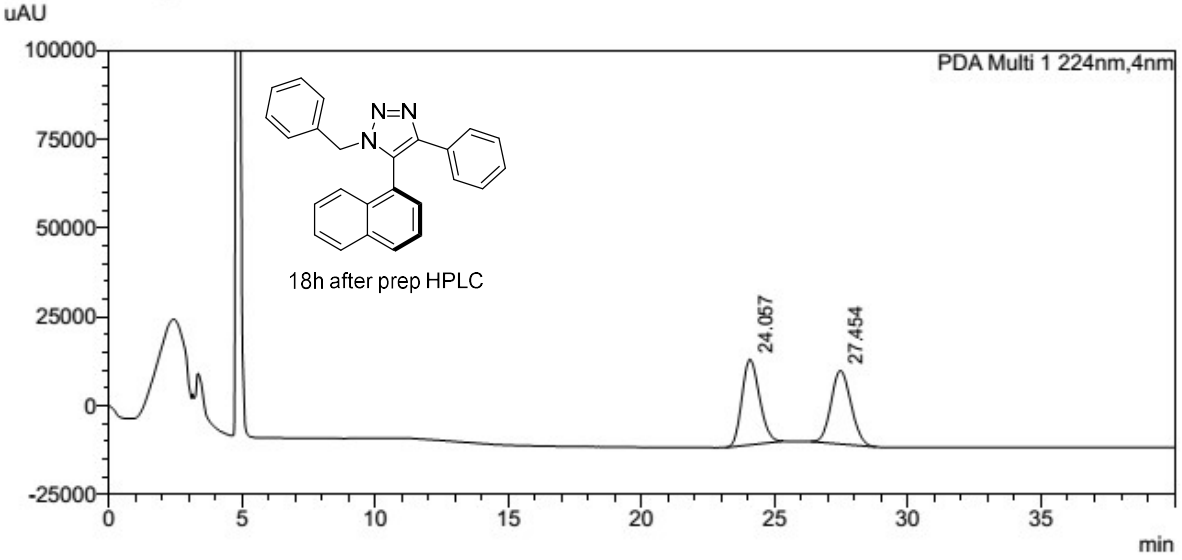


<Peak Table>

PDA Ch1 224nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	24.190	86.090	1768139	38487	86.090		
2	27.604	13.910	285683	5571	13.910		
Total		100.000	2053822	44058			

<Chromatogram>

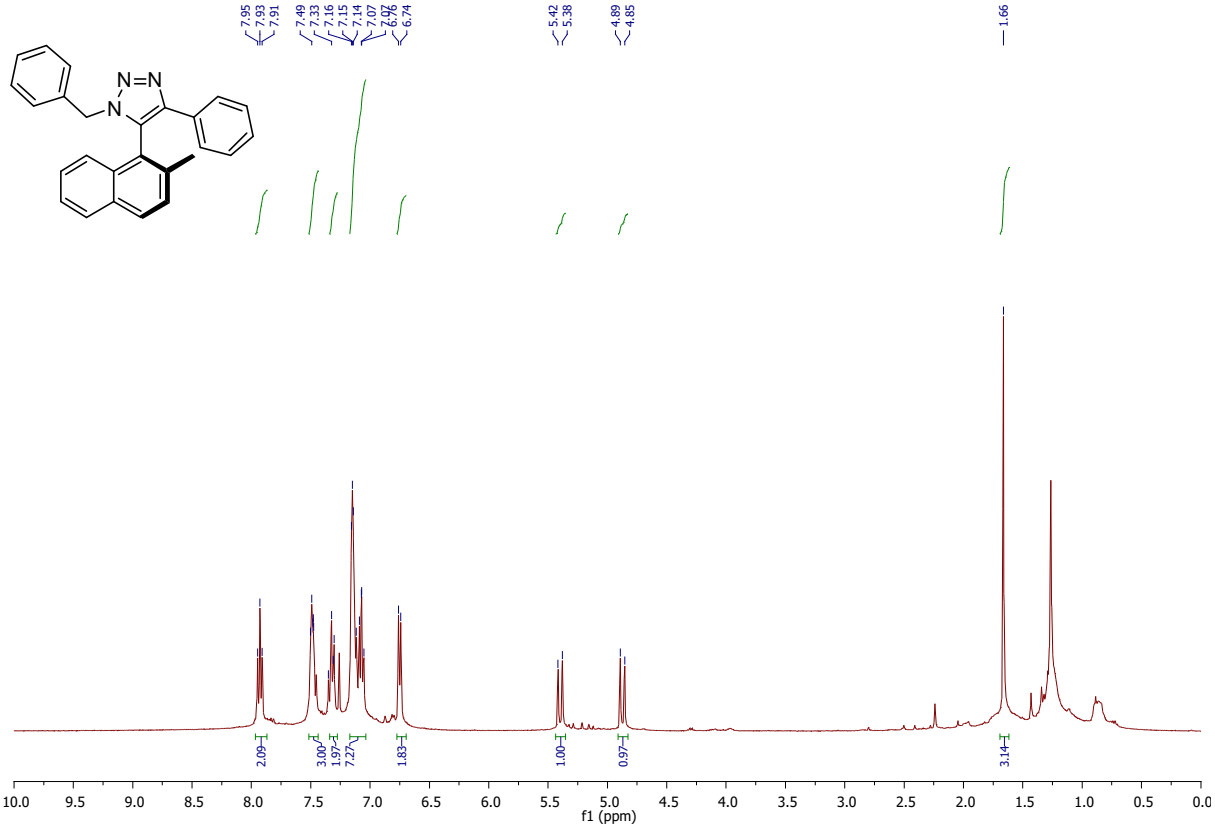


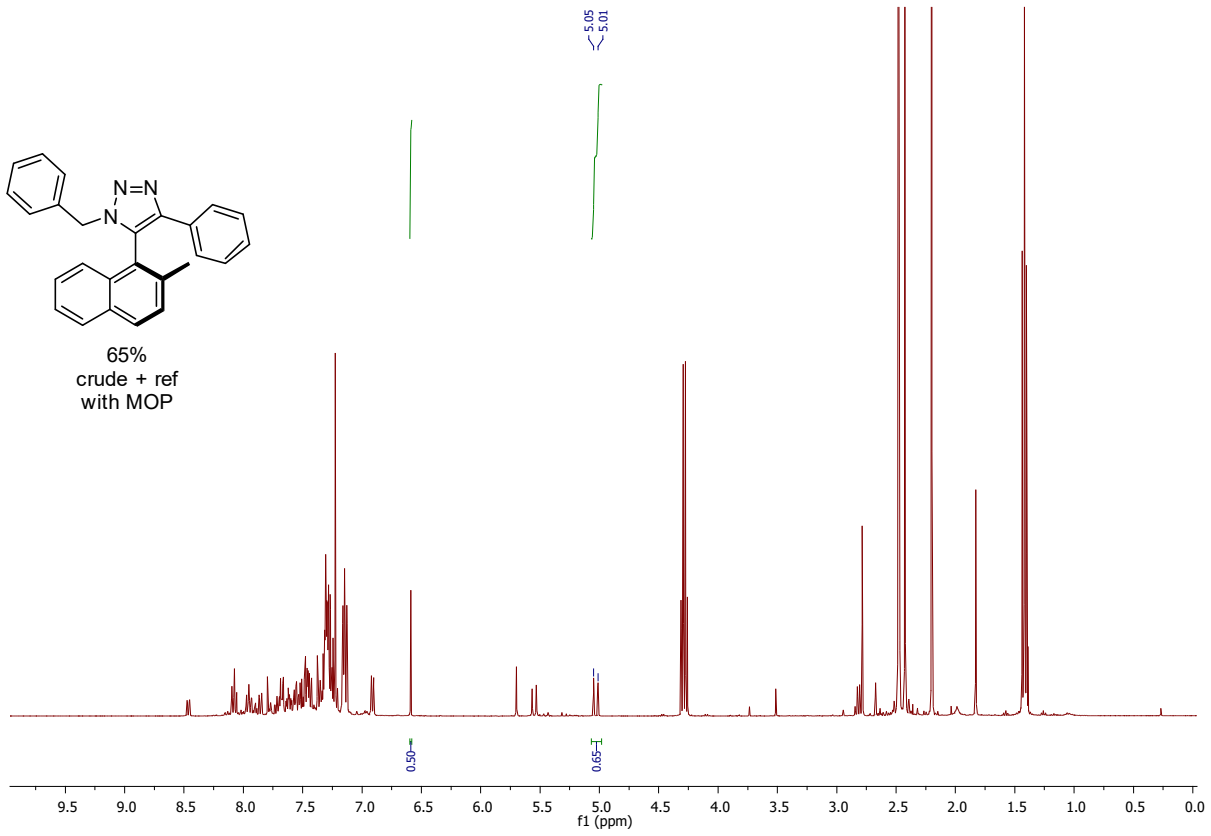
<Peak Table>

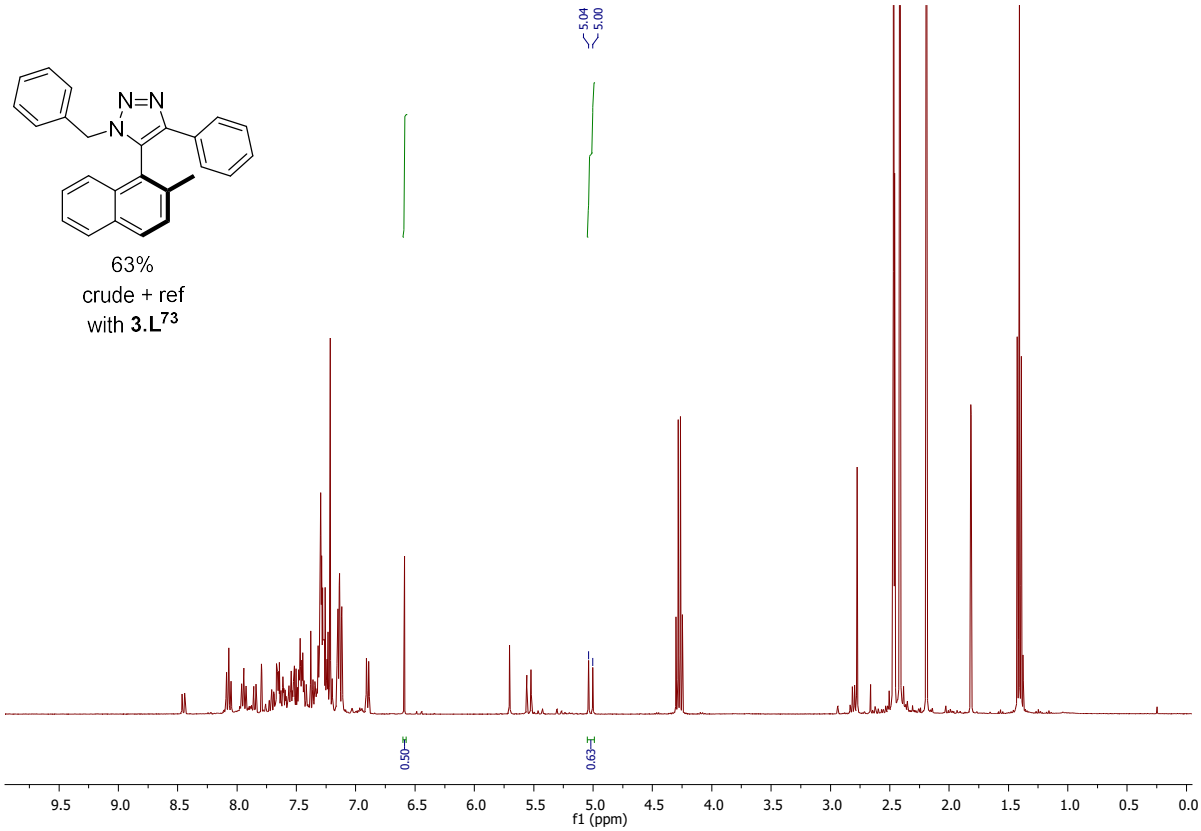
PDA Ch1 224nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	24.057	50.610	1103493	24067	0.000		
2	27.454	49.390	1076879	20648	0.000		
Total		100.000	2180373	44715			

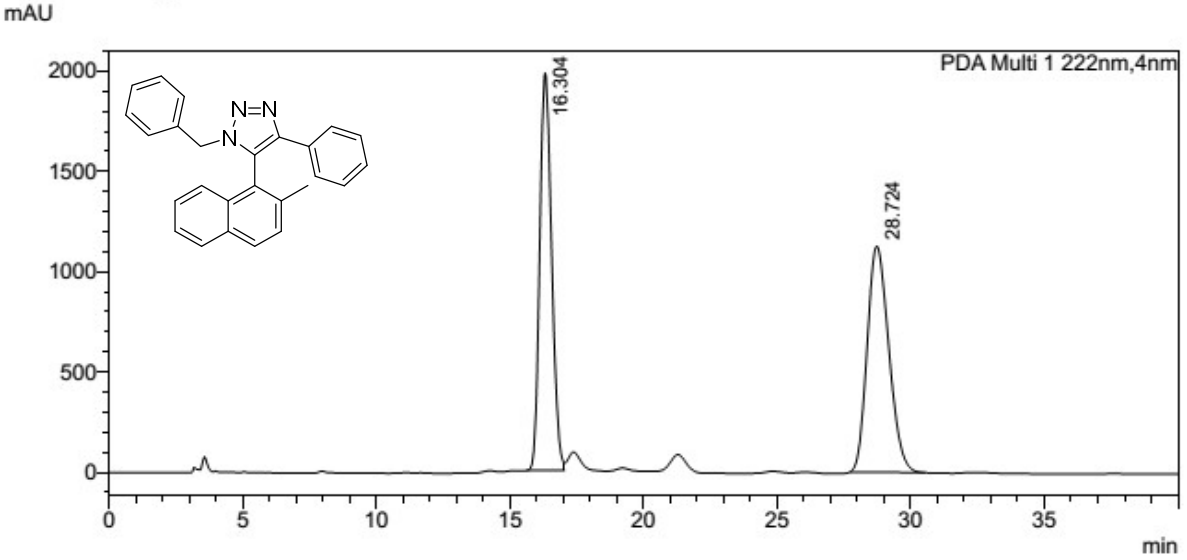
1-benzyl-5-(2-methylnaphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazole**3.2b**:






63%
crude + ref
with 3.L73
5.04
5.00
0.50
0.63
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
f1 (ppm)

<Chromatogram>

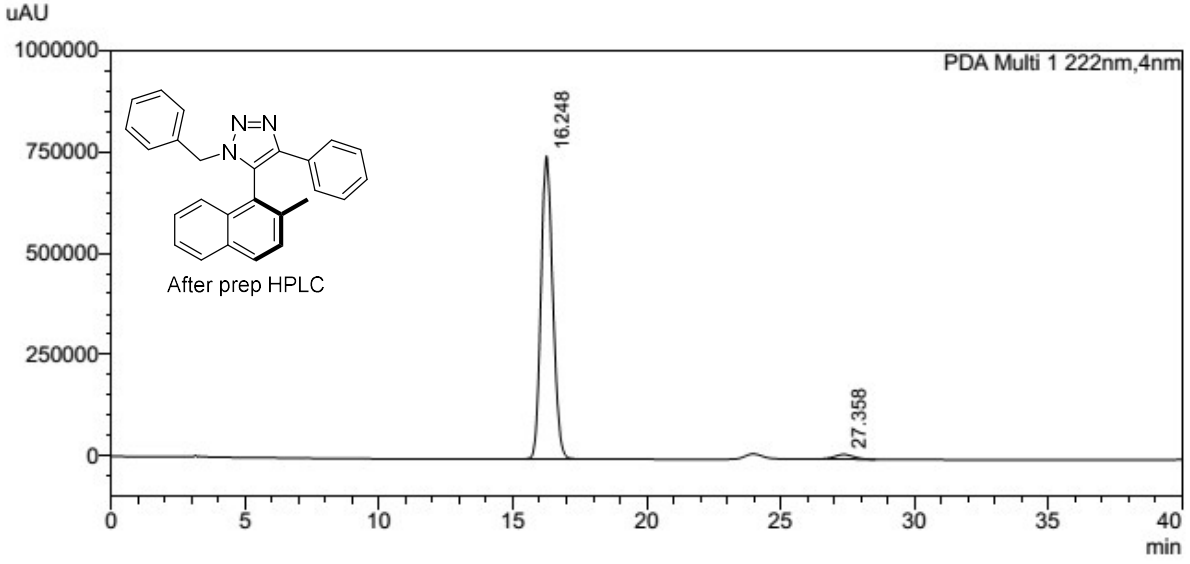


<Peak Table>

PDA Ch1 222nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	16.304	49.172	61298670	1980970	49.172		M
2	28.724	50.828	63362186	1127120	50.828		M
Total		100.000	124660856	3108089			

<Chromatogram>

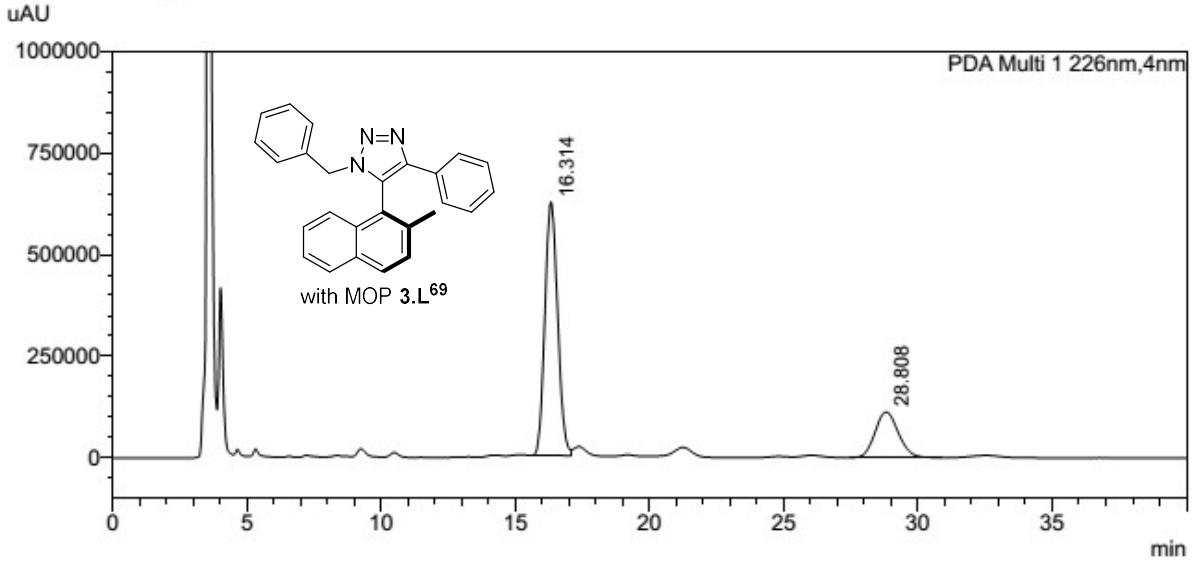


<Peak Table>

PDA Ch1 222nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	16.248	97.611	22945899	746461	0.000		
2	27.358	2.389	561508	11351	0.000		
Total		100.000	23507406	757812			

<Chromatogram>

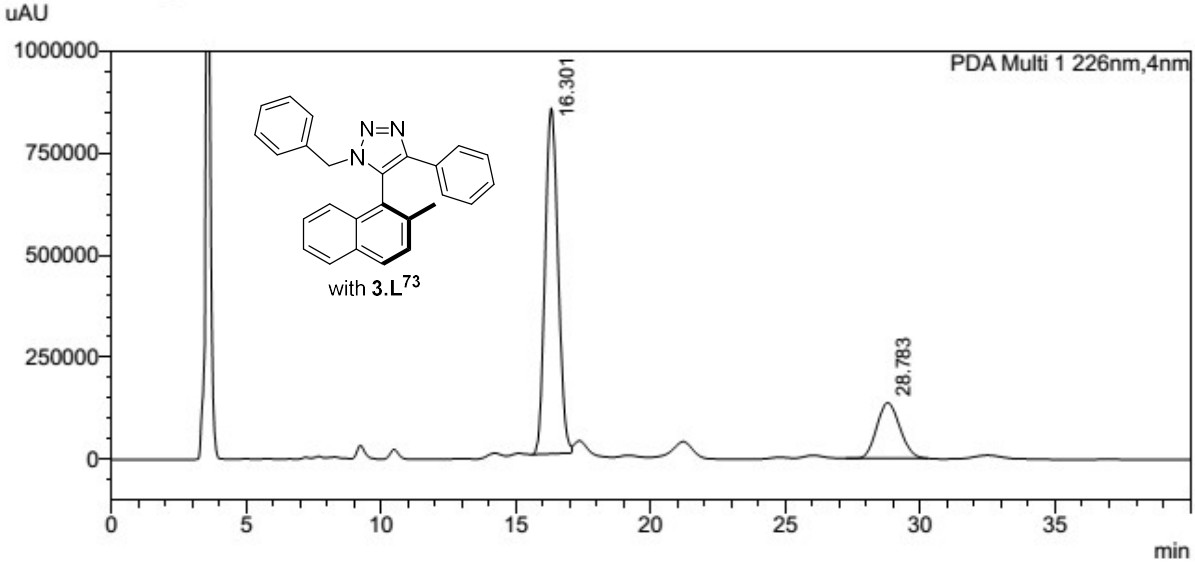


<Peak Table>

PDA Ch1 226nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	16.314	75.291	20508741	622975	0.000		M
2	28.808	24.709	6730676	111922	0.000		S
Total		100.000	27239418	734896			

<Chromatogram>

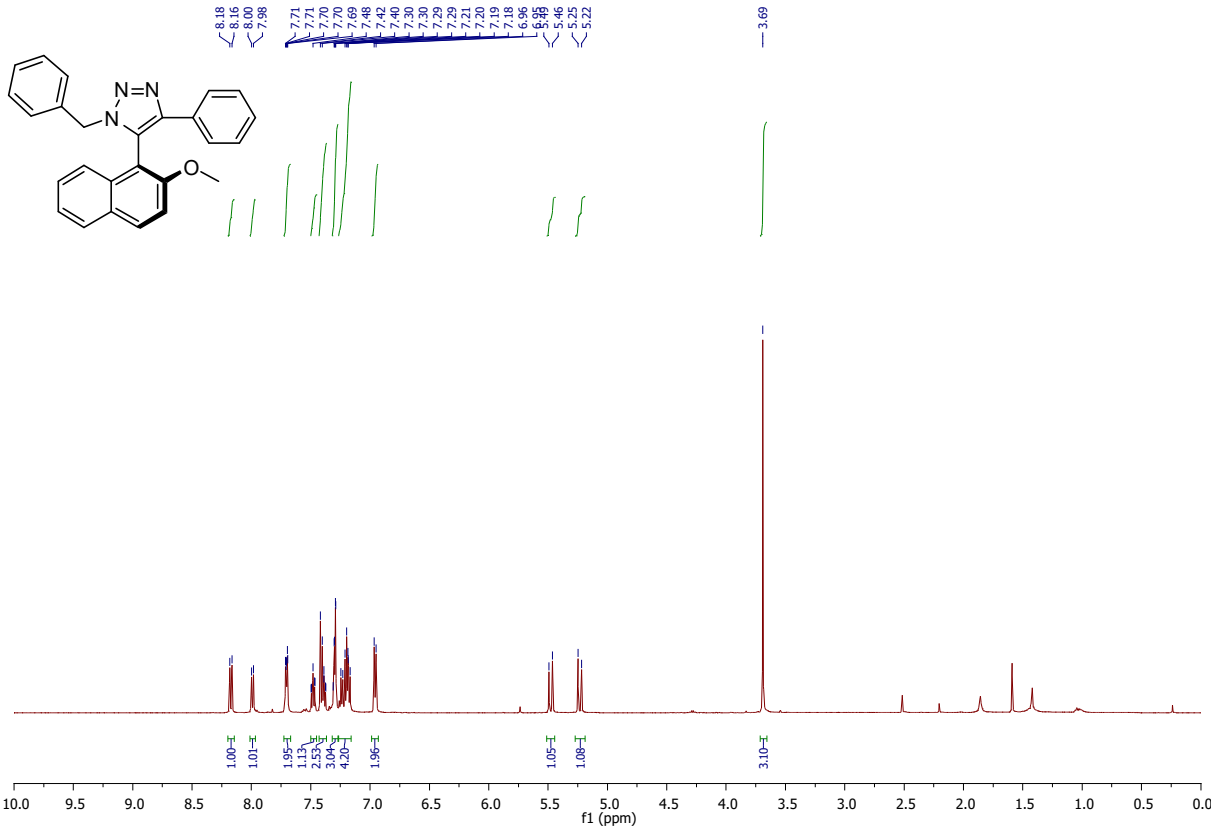


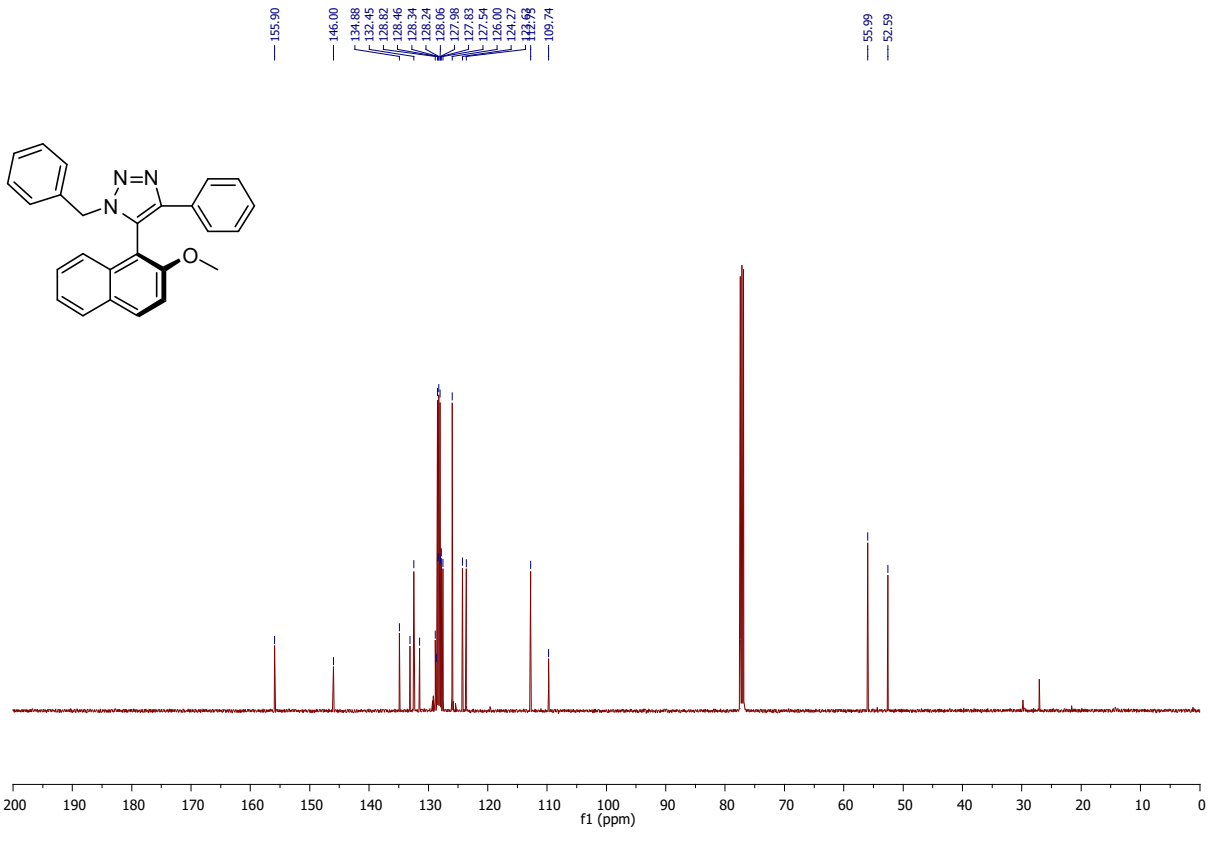
<Peak Table>

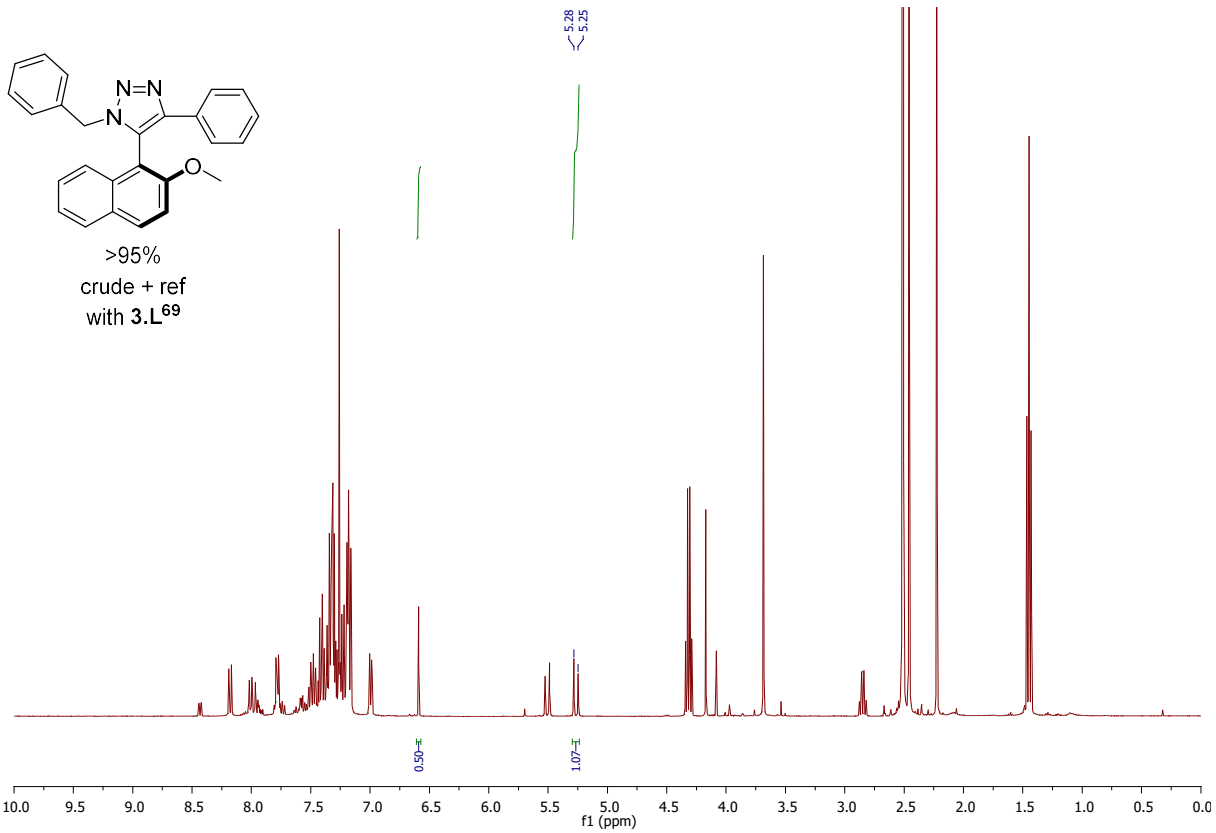
PDA Ch1 226nm

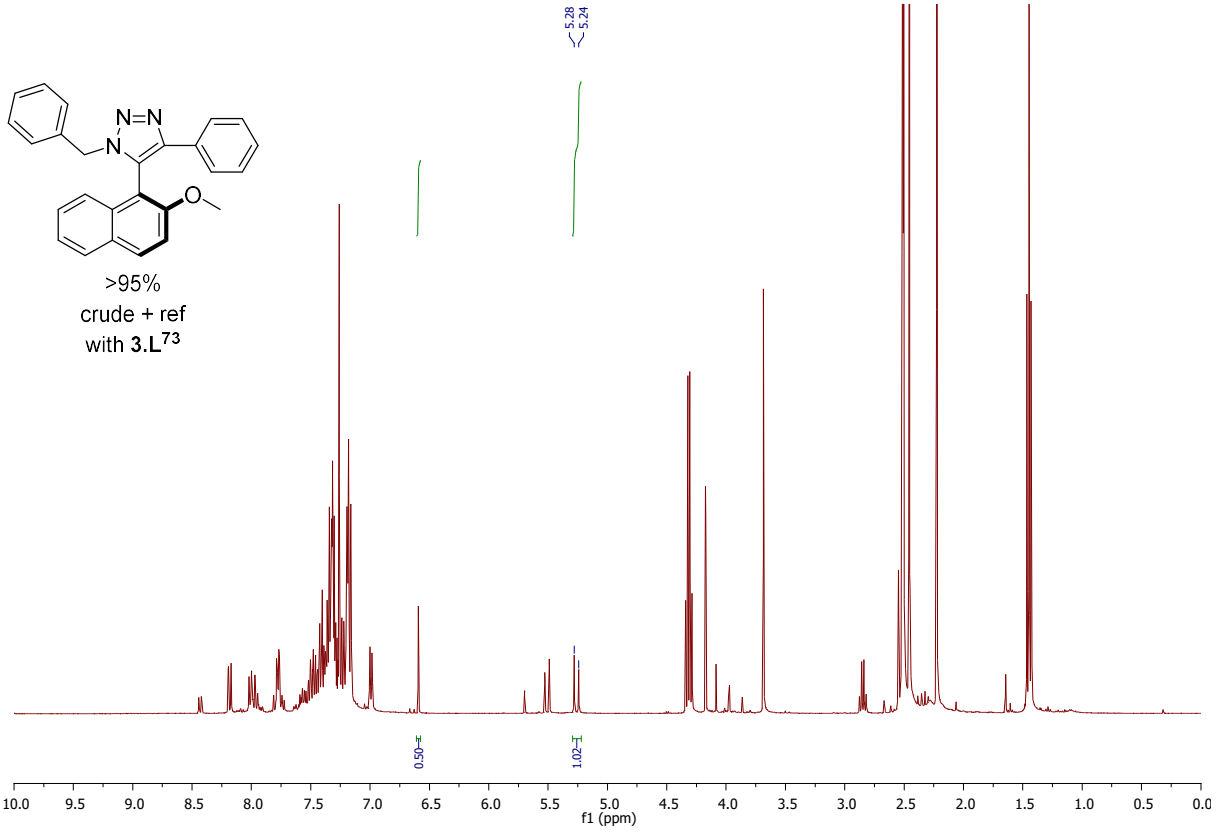
Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	16.301	77.690	28193958	845923	77.690		M
2	28.783	22.310	8096282	136074	22.310		M
Total		100.000	36290240	981997			

1-benzyl-5-(2-methoxynaphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazole**3.2c**:






N=N
N
O
>95%
crude + ref
with 3.L69
5.28
5.25
0.50
1.07
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
f1 (ppm)


N=N
N
O
>95%
crude + ref
with 3.L73
5.28
5.24
0.50
1.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

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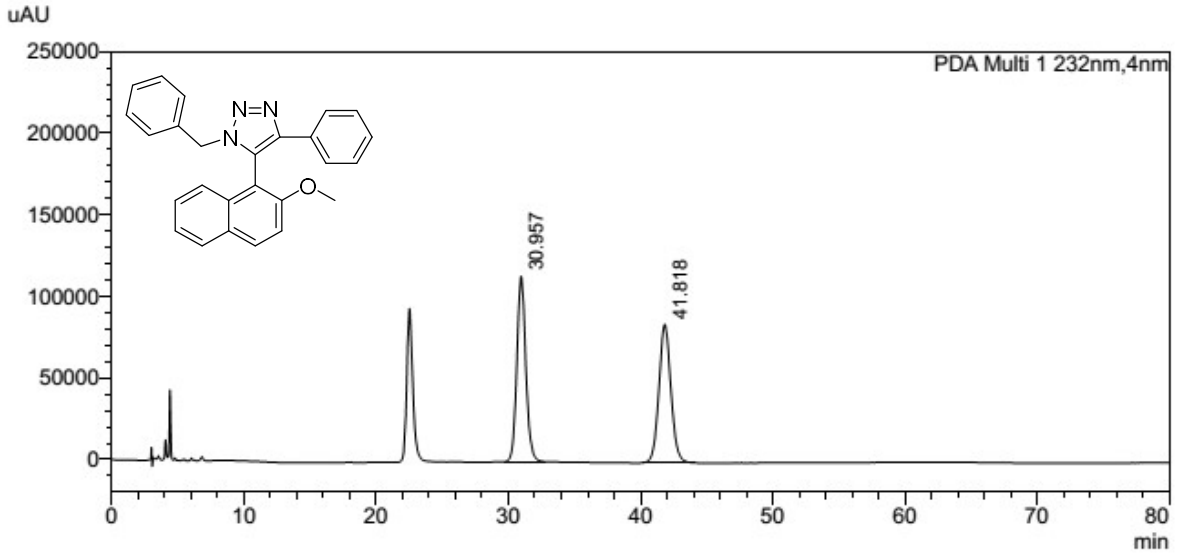

<Peak Table>

PDA Ch1 232nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	30.957	50.021	5350016	113643	0.000		
2	41.818	49.979	5345537	84894	0.000		
Total		100.000	10695554	198537			

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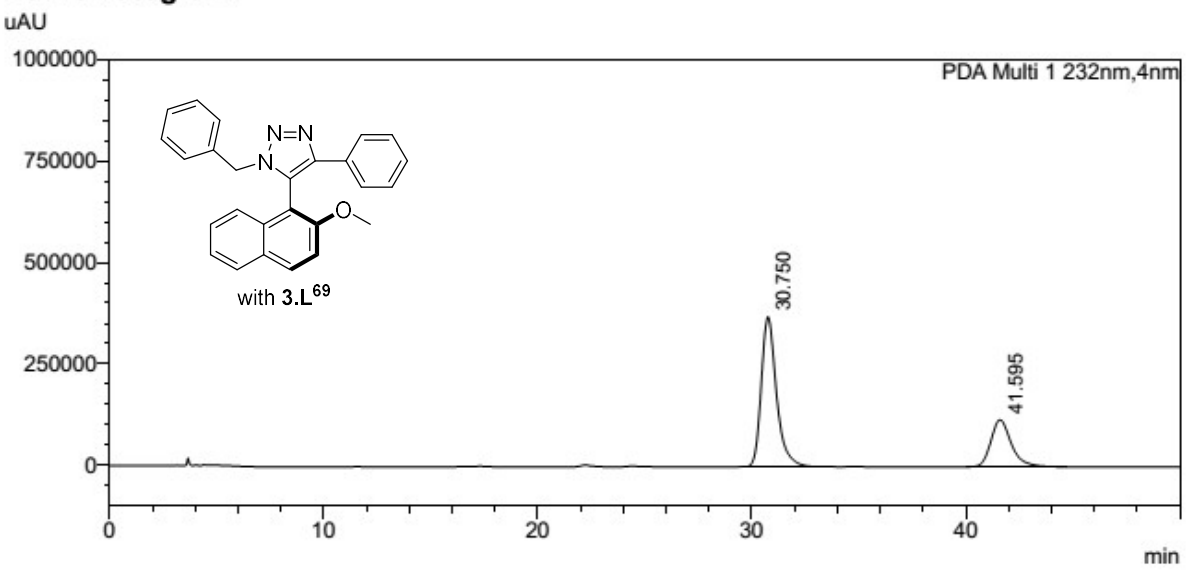
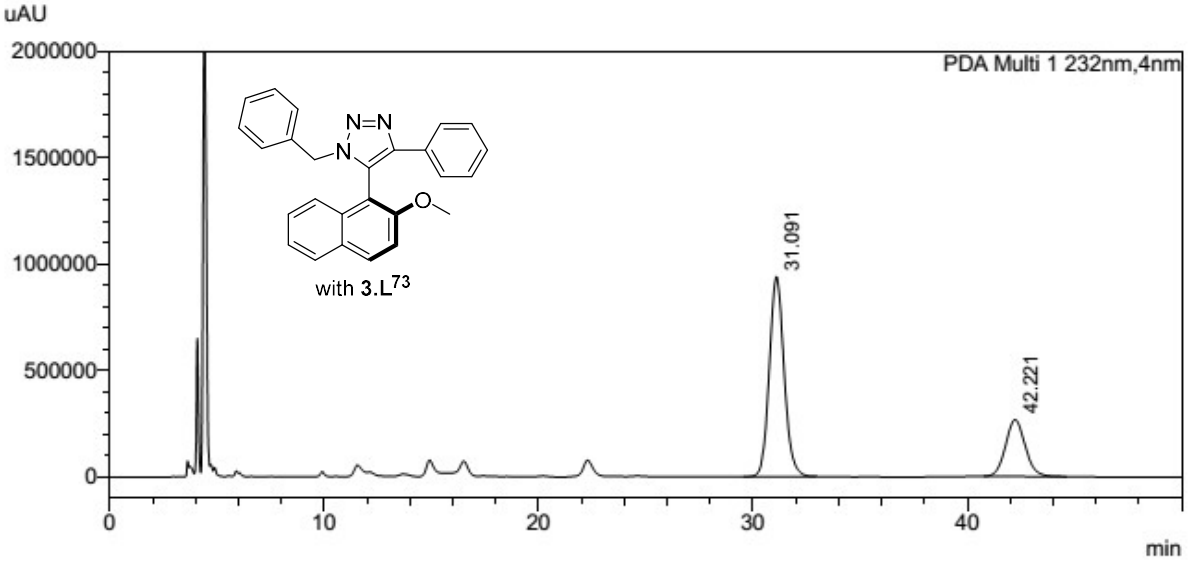


<Peak Table>

PDA Ch1 232nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	30.750	70.232	18257520	369315	0.000		S
2	41.595	29.768	7738489	116474	0.000		
Total		100.000	25996010	485789			

<Chromatogram>

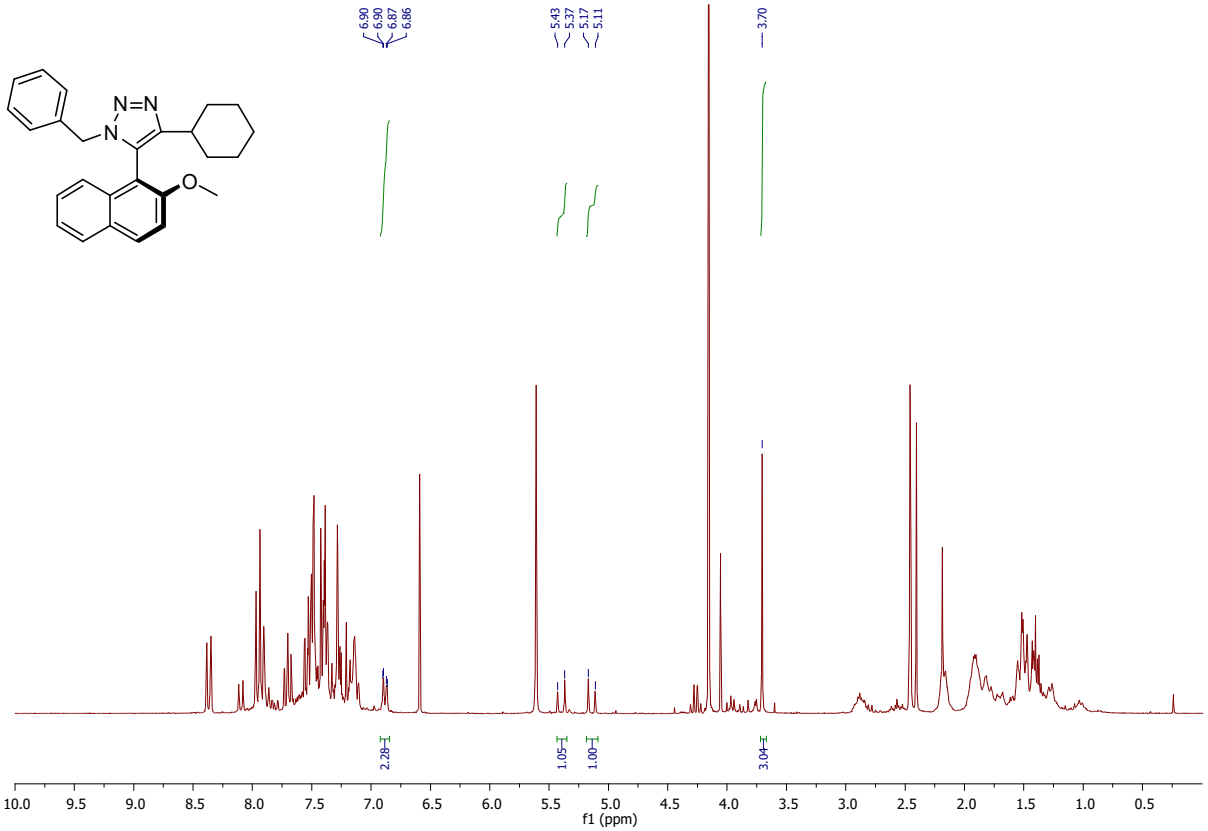


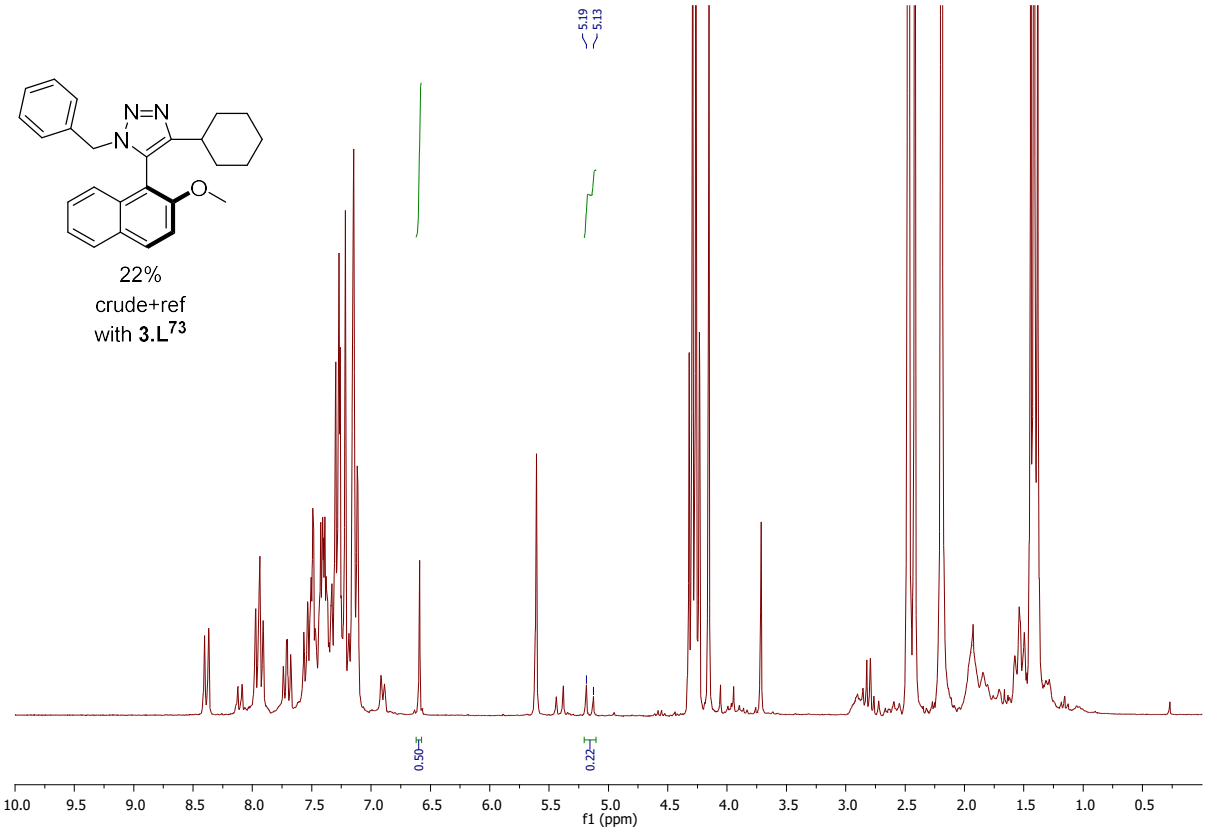
<Peak Table>

PDA Ch1 232nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	31.091	72.672	45178116	939676	0.000		M
2	42.221	27.328	16989178	266899	0.000		M
Total		100.000	62167294	1206575			

1-benzyl-4-cyclohexyl-5-(2-methoxynaphthalen-1-yl)-1*H*-1,2,3-triazole**3.3b** :





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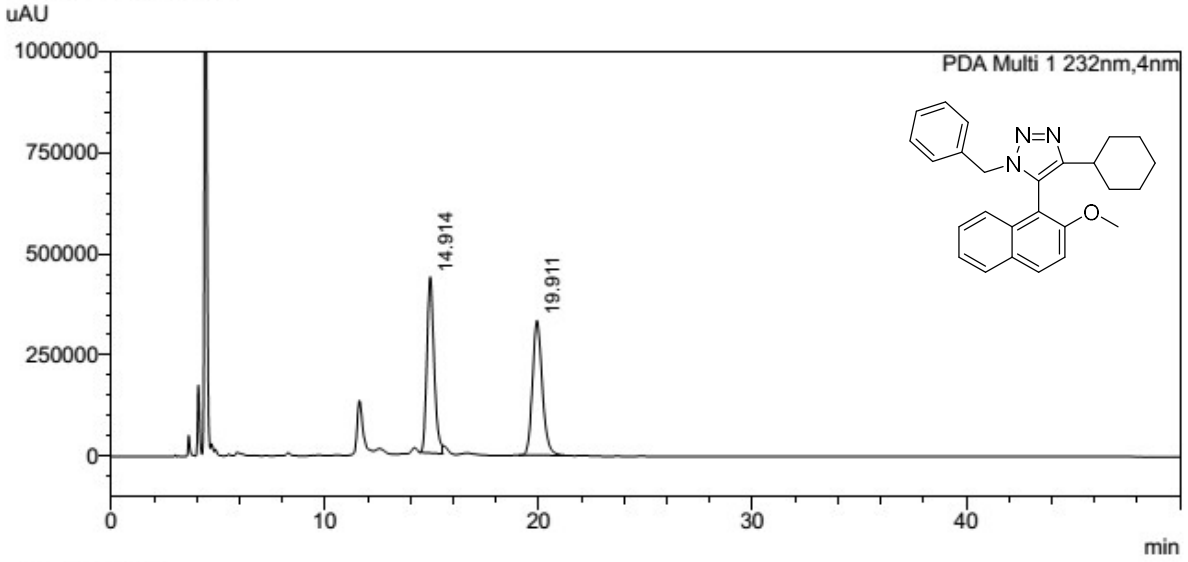

<Peak Table>

PDA Ch1 232nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	14.914	49.301	10320875	434805	0.000		M
2	19.911	50.699	10613501	332534	0.000		M
Total		100.000	20934375	767339			

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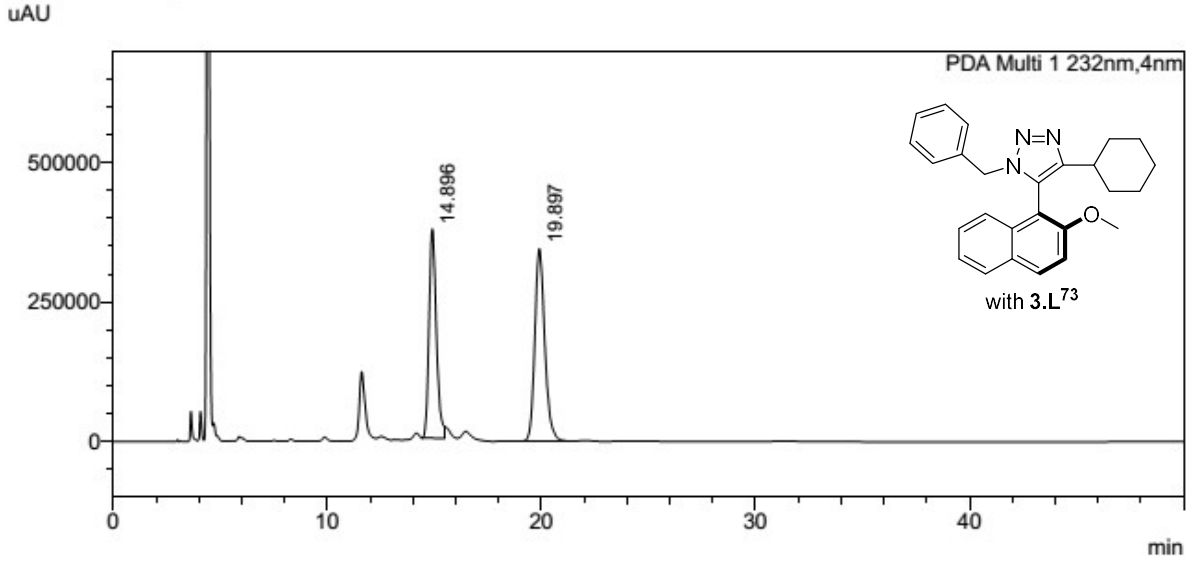
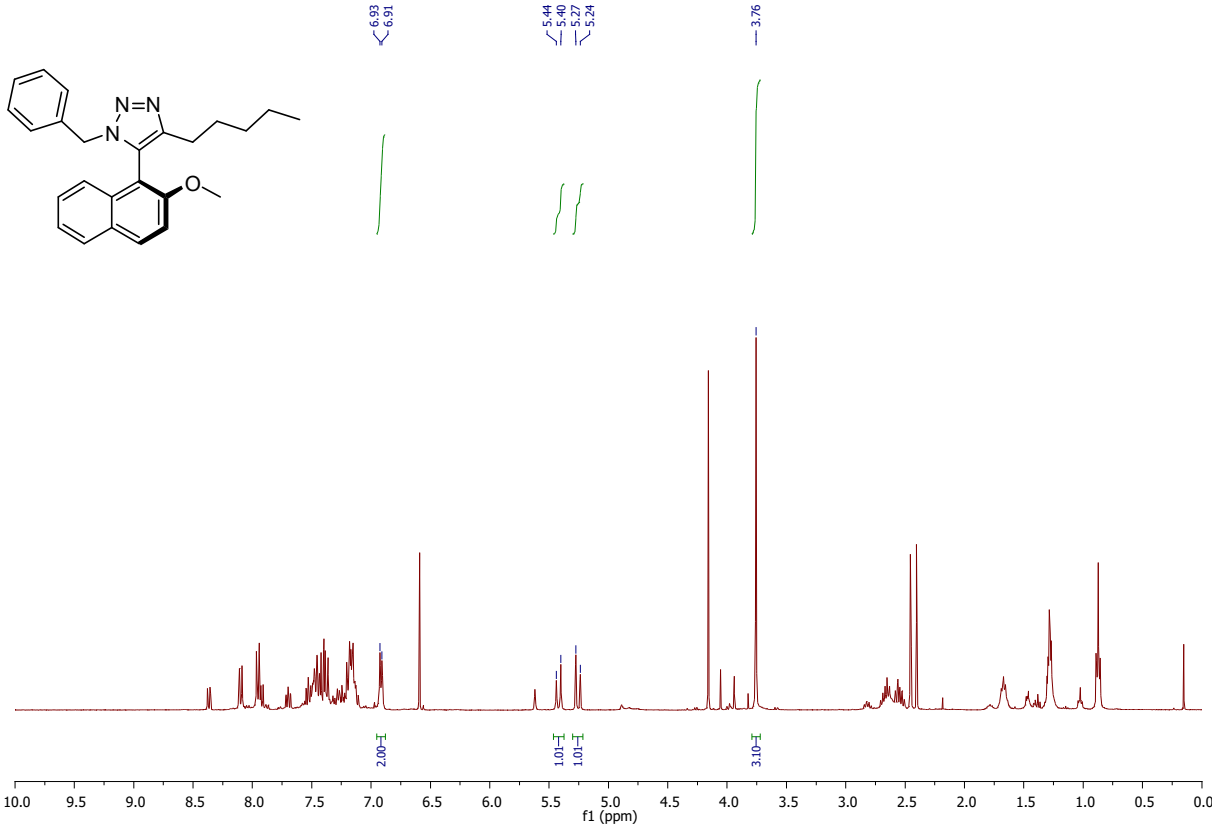


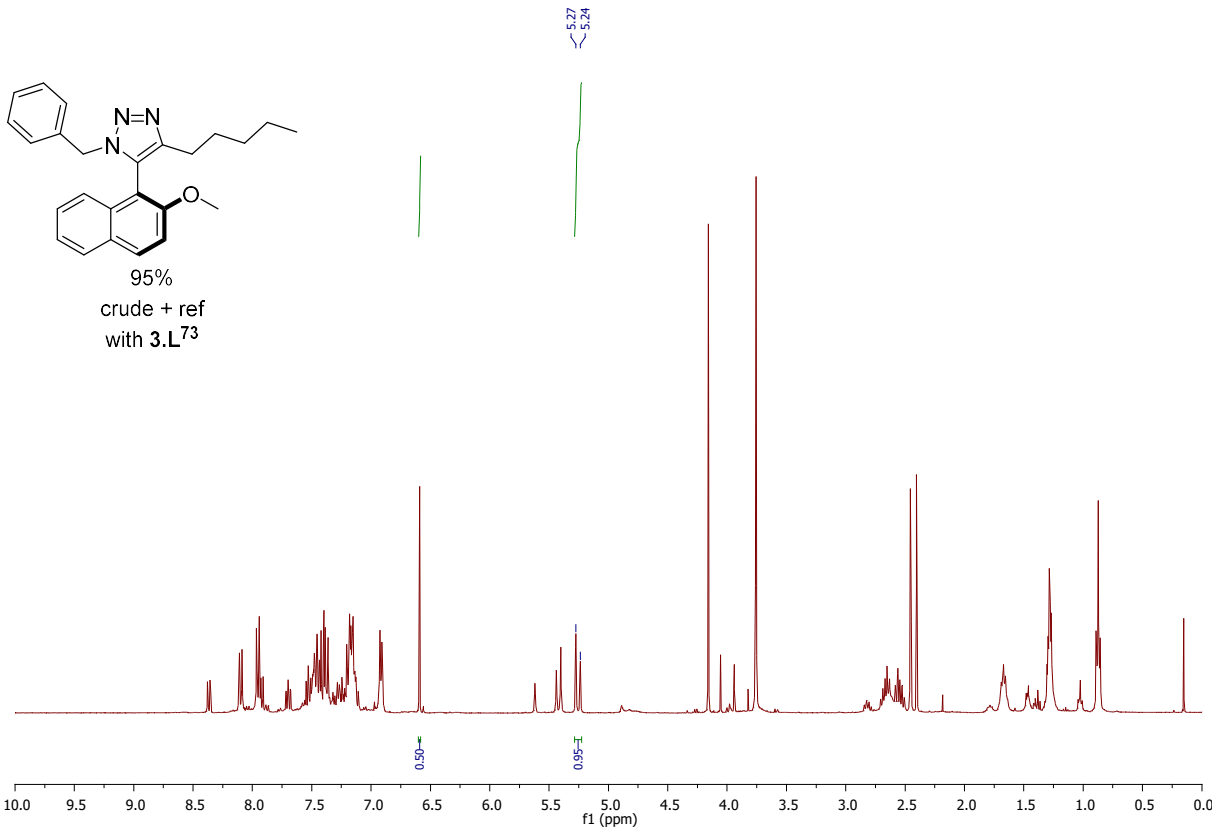
<Peak Table>

PDA Ch1 232nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	14.896	44.512	8896411	374763	0.000		M
2	19.897	55.488	11090171	344826	0.000		M
Total		100.000	19986582	719588			

1-benzyl-5-(2-methoxynaphthalen-1-yl)-4-pentyl-1H-1,2,3-triazole**3.3c**:





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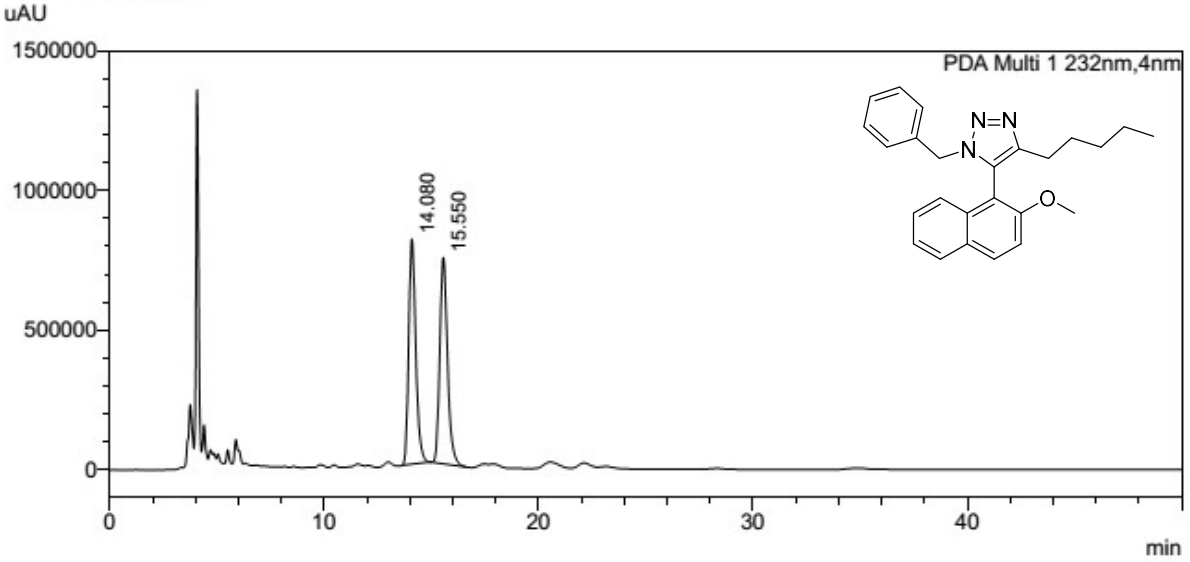
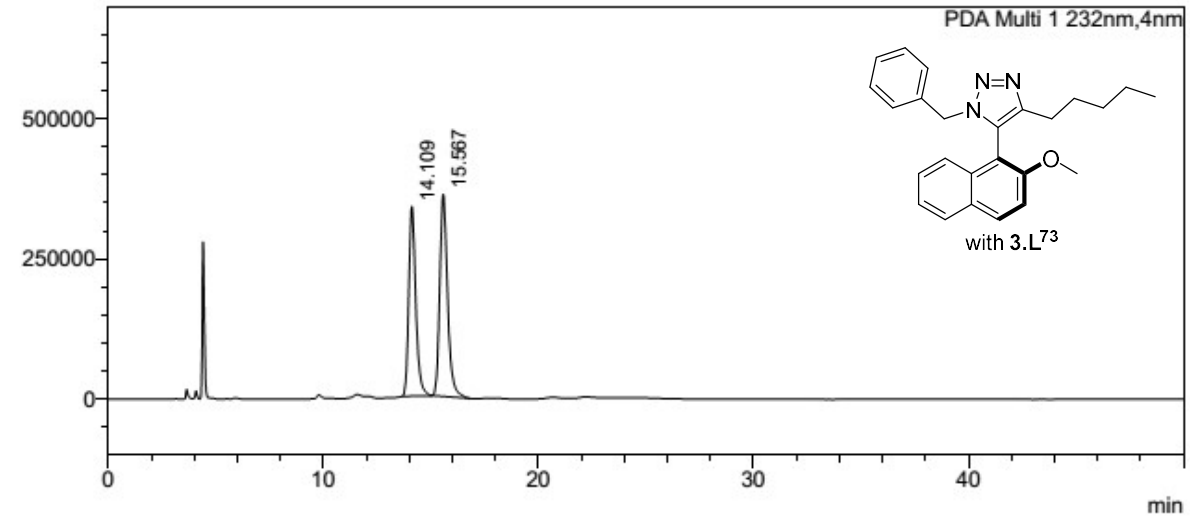


<Peak Table>

PDA Ch1 232nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	14.080	49.797	18375134	807062	0.000		M
2	15.550	50.203	18525104	739032	0.000		M
Total		100.000	36900238	1546094			

<Chromatogram>

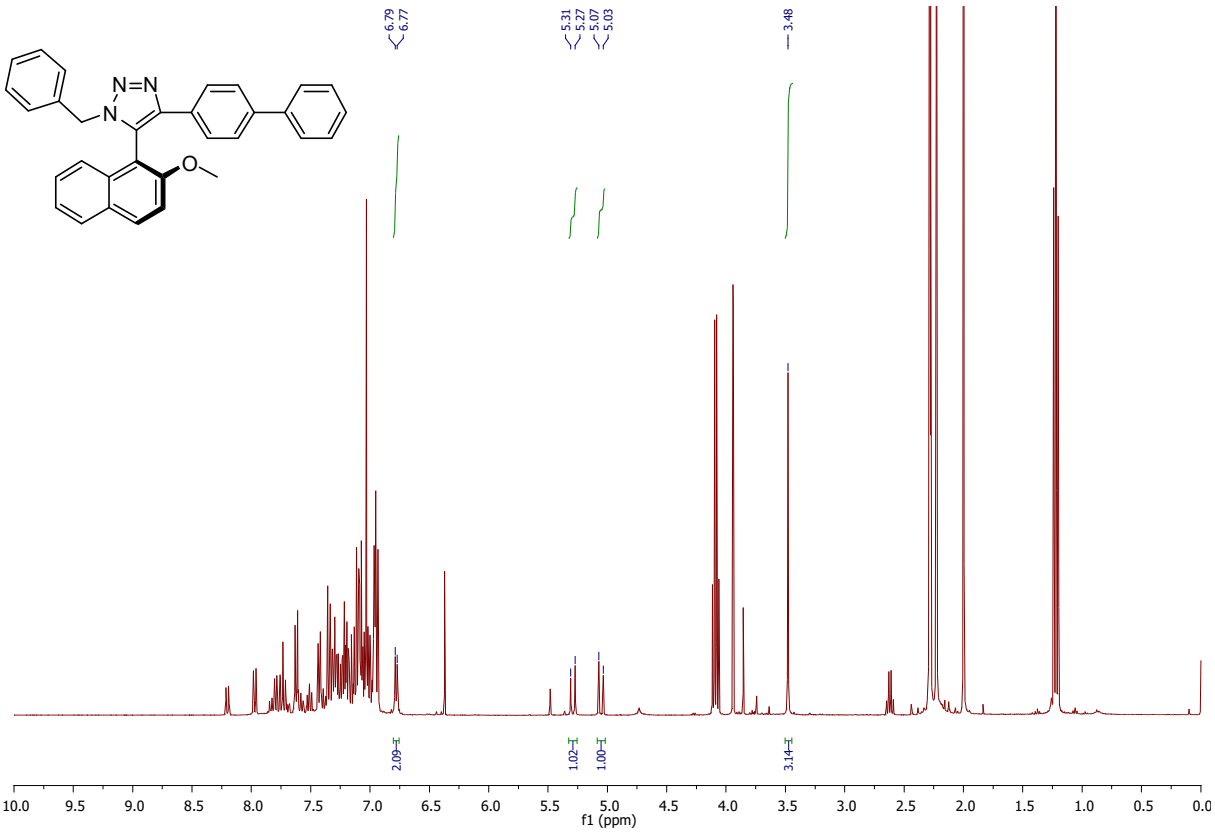


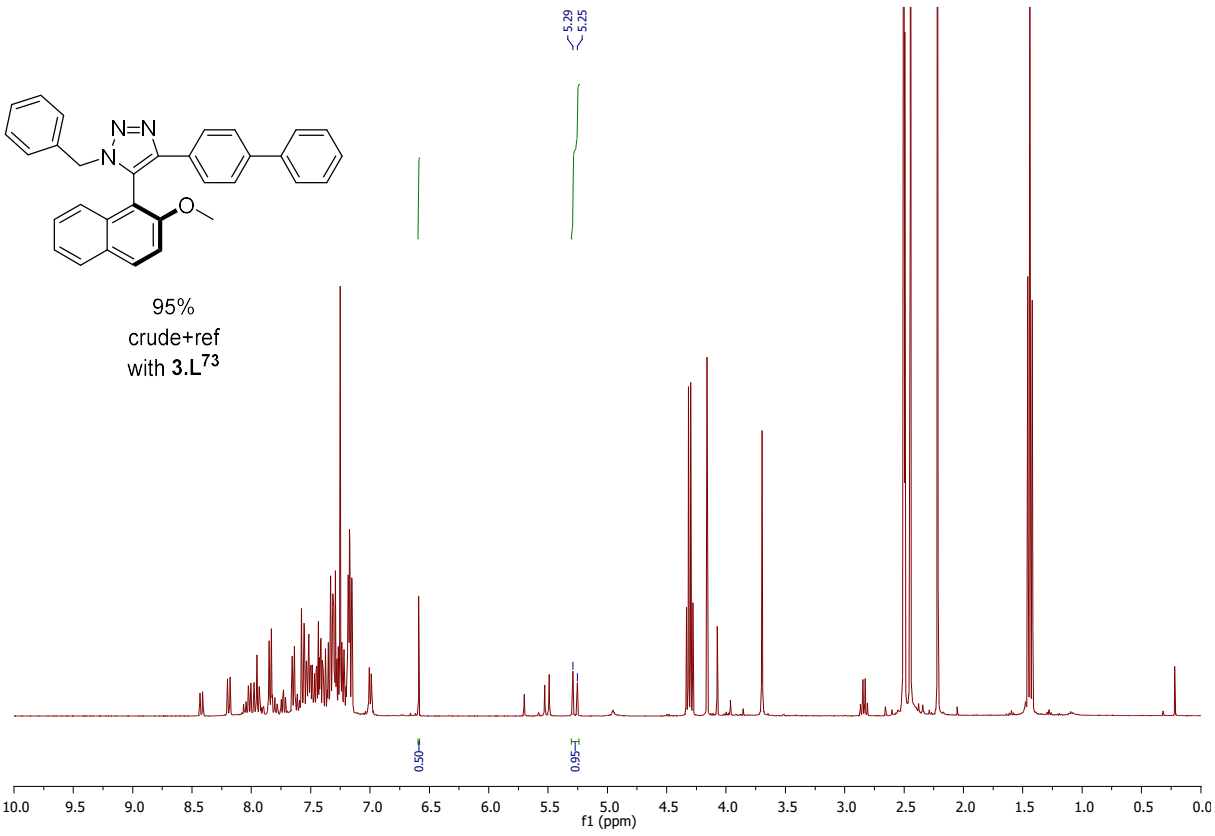
<Peak Table>

PDA Ch1 232nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	14.109	45.793	7668317	338194	0.000		M
2	15.567	54.207	9077403	360596	0.000		M
Total		100.000	16745720	698790			

4-([1,1'-biphenyl]-4-yl)-1-benzyl-5-(2-methoxynaphthalen-1-yl)-1*H*-1,2,3-triazole**3.3d**:





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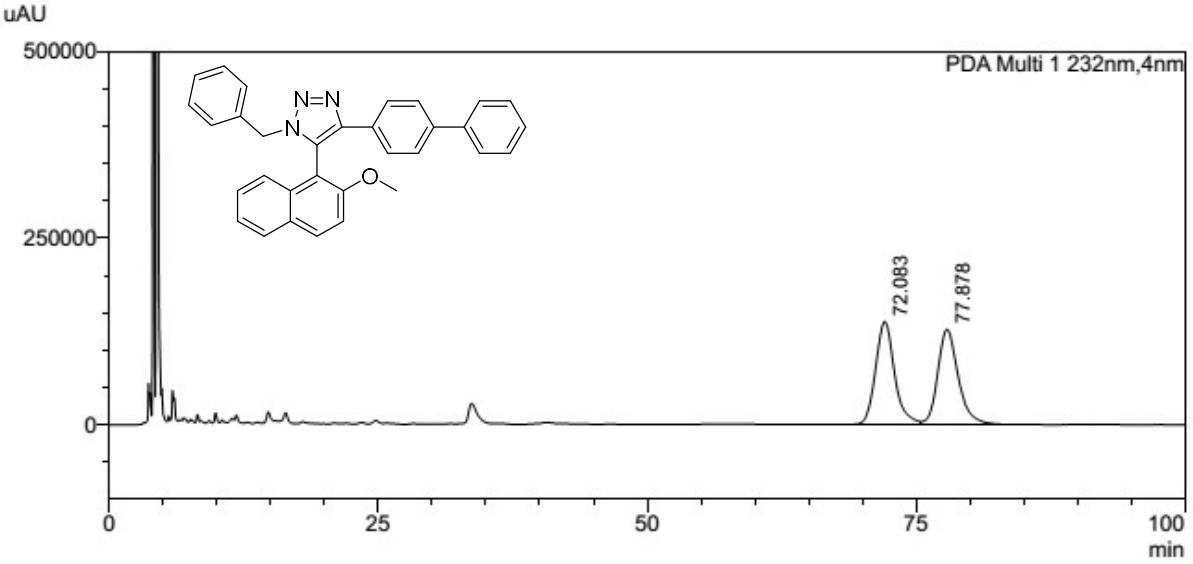

<Peak Table>

PDA Ch1 232nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	72.083	50.169	16859608	137659	0.000		
2	77.878	49.831	16746032	127204	0.000		SV
Total		100.000	33605640	264863			

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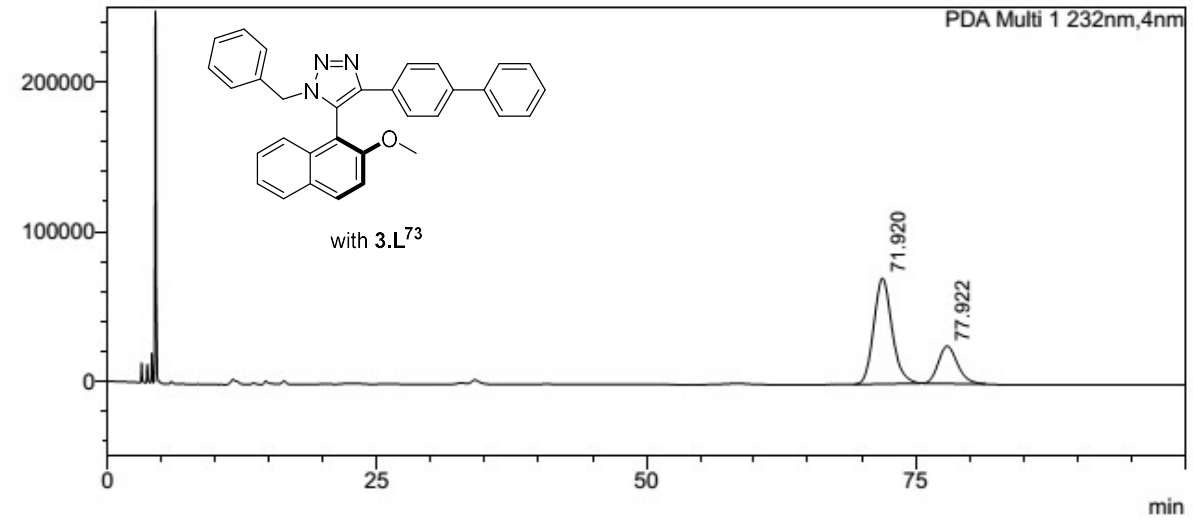
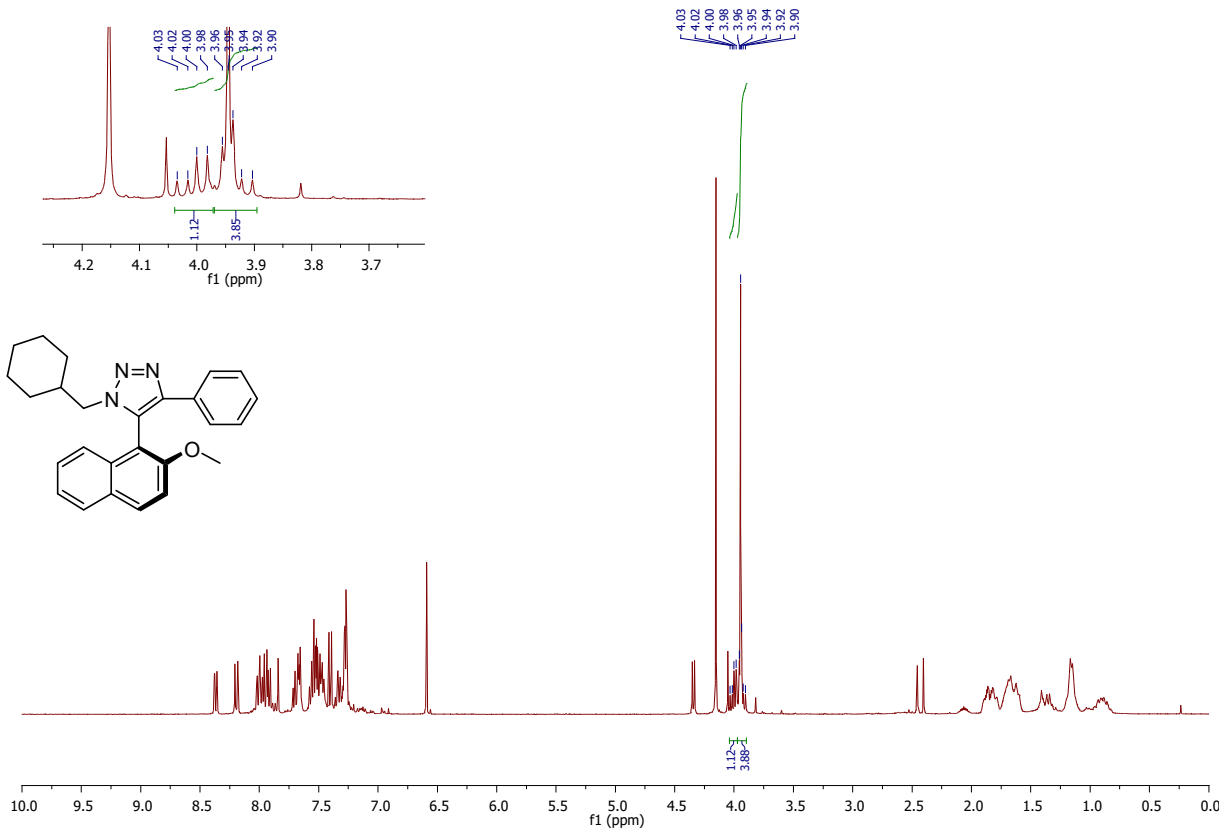


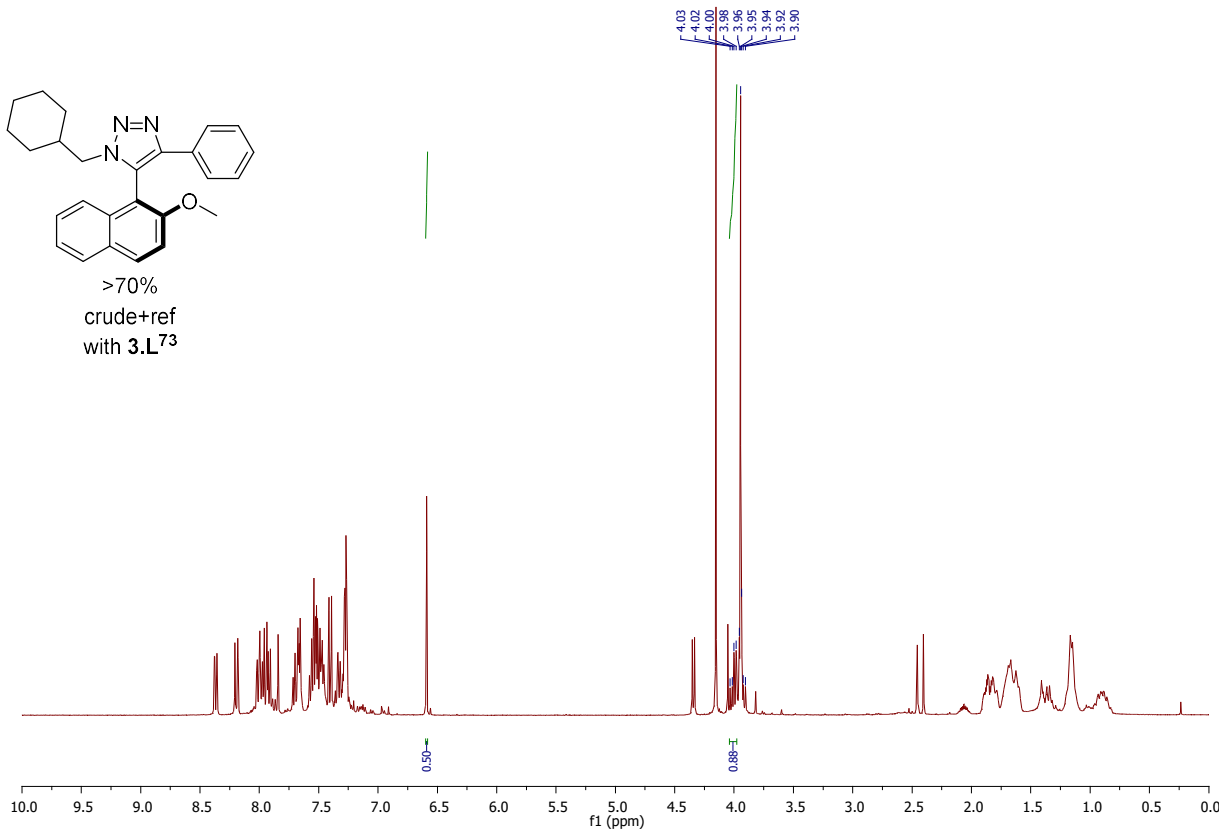
<Peak Table>

PDA Ch1 232nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	71.920	72.803	8338546	70529	0.000		
2	77.922	27.197	3115040	25046	0.000		
Total		100.000	11453586	95576			

1-(cyclohexylmethyl)-5-(2-methoxynaphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazole**3.3e**:





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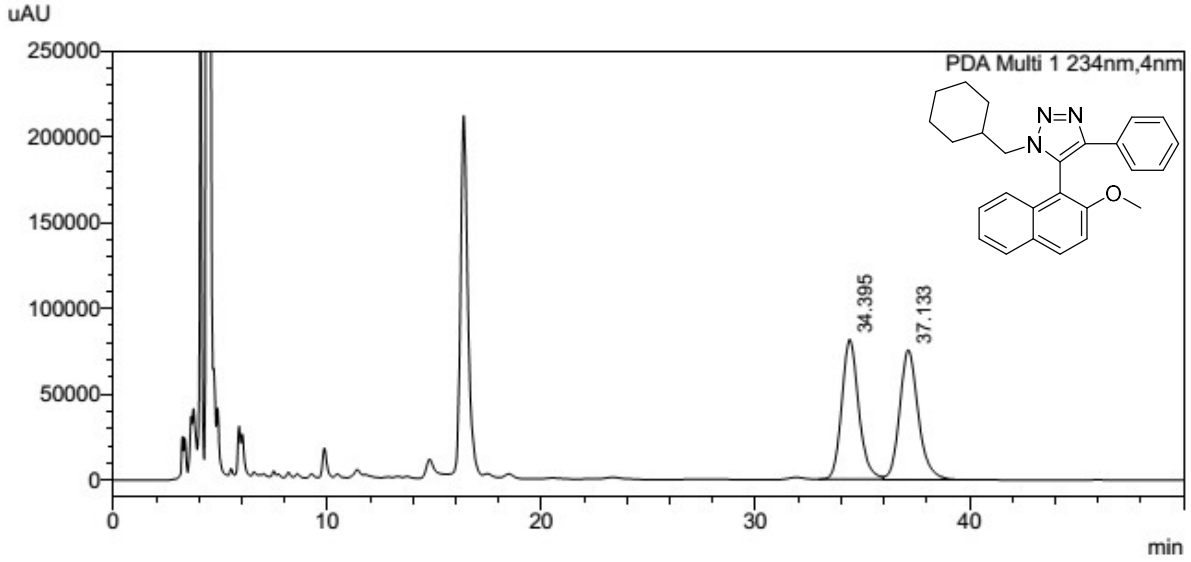

<Peak Table>

PDA Ch1 234nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	34.395	49.644	4501968	81543	0.000		
2	37.133	50.356	4566483	75510	0.000		V
Total		100.000	9068451	157054			

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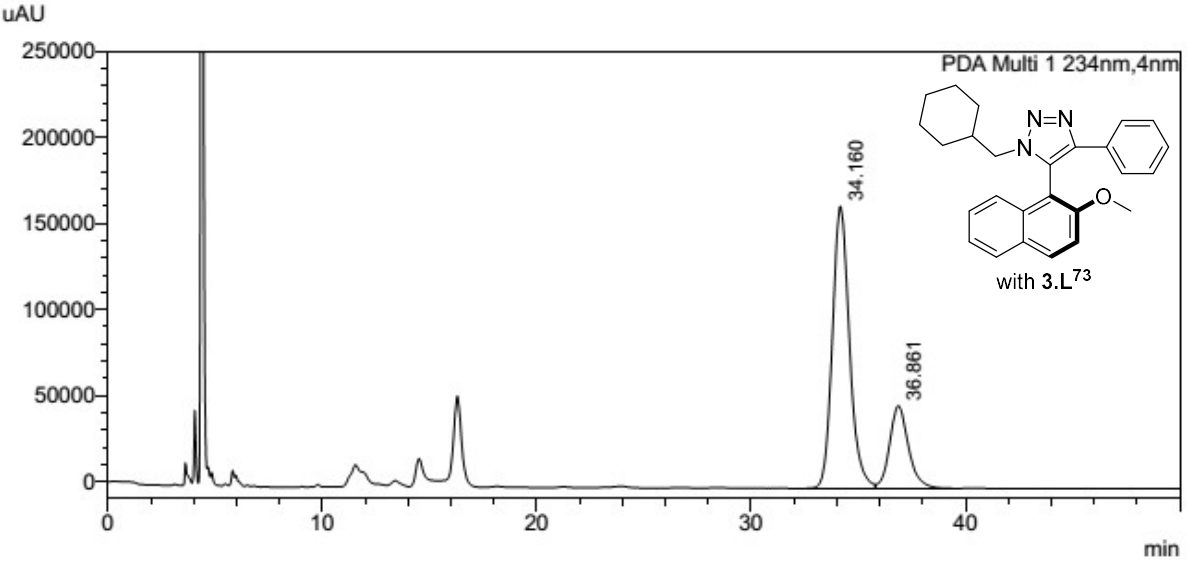
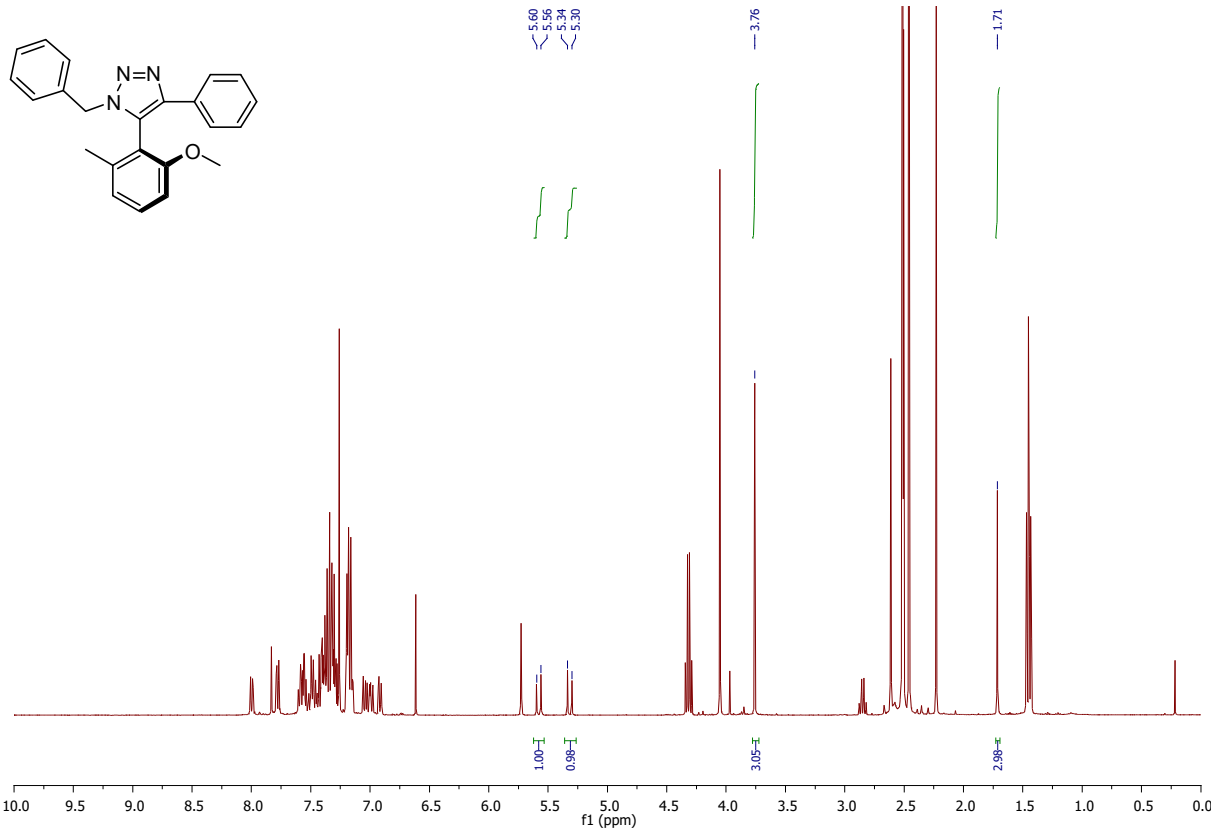


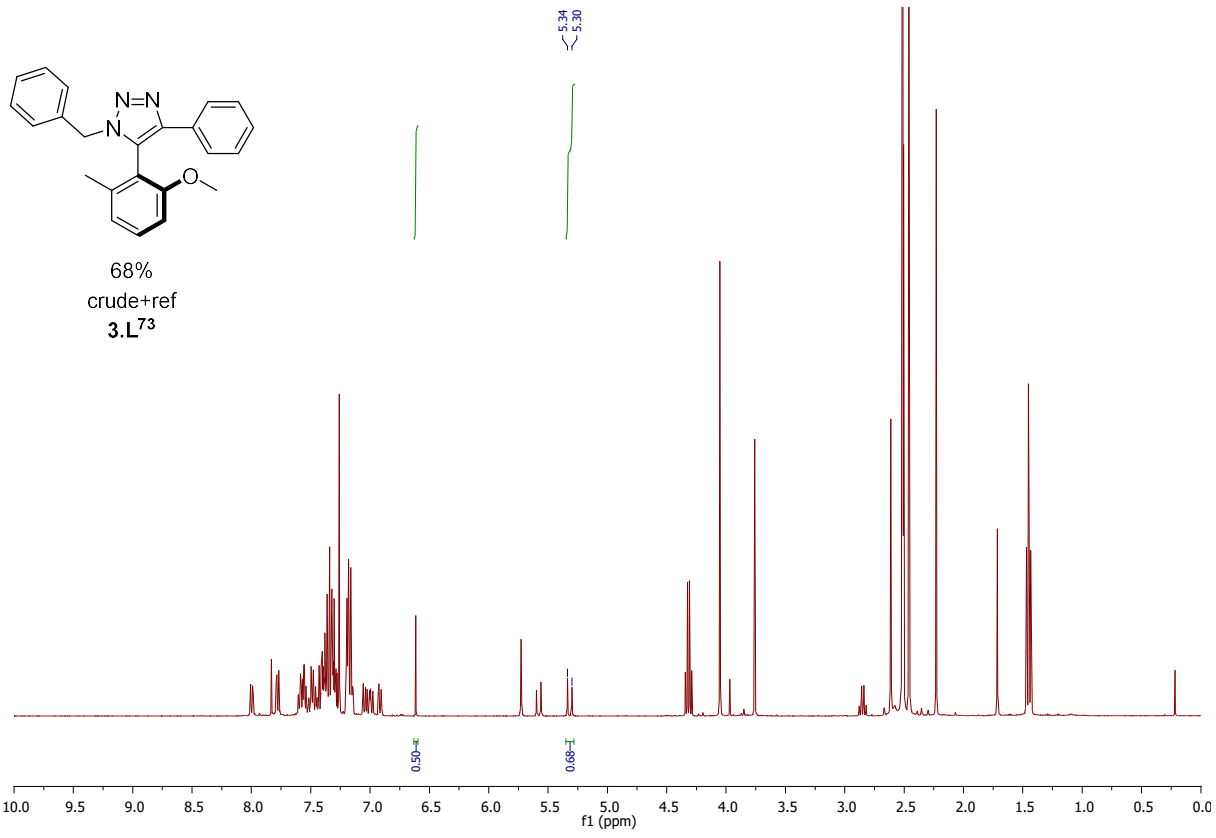
<Peak Table>

PDA Ch1 234nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	34.160	75.430	9050271	164020	0.000		
2	36.861	24.570	2947975	48135	0.000		SV
Total		100.000	11998246	212155			

1-benzyl-5-(2-methoxy-6-methylphenyl)-4-phenyl-1H-1,2,3-triazole**3.2d**:





68%
crude+ref
3.L[73]

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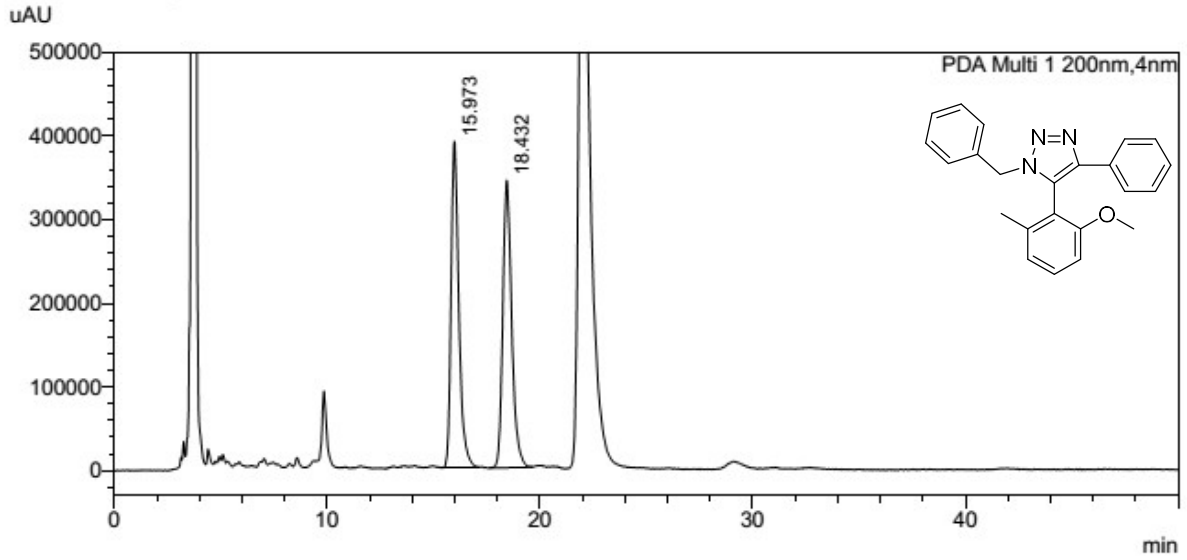

<Peak Table>

PDA Ch1 200nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	15.973	49.534	9831812	389678	0.000		M
2	18.432	50.466	10016614	343722	0.000		M
Total		100.000	19848426	733400			

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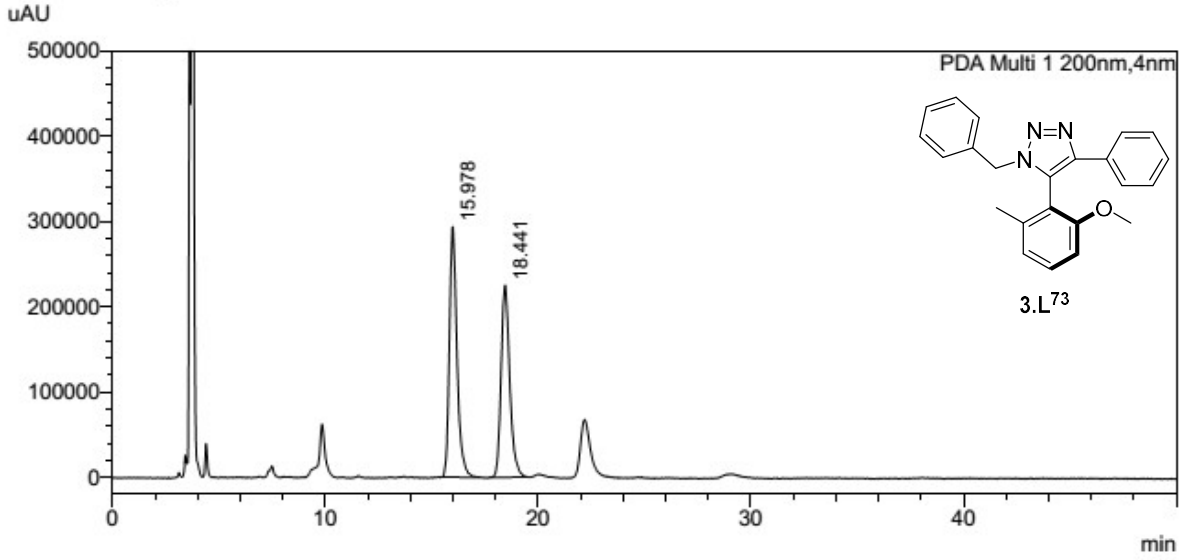

<Peak Table>

PDA Ch1 200nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	15.978	53.374	7312105	293953	0.000		M
2	18.441	46.626	6387705	225402	0.000		M
Total		100.000	13699810	519356			