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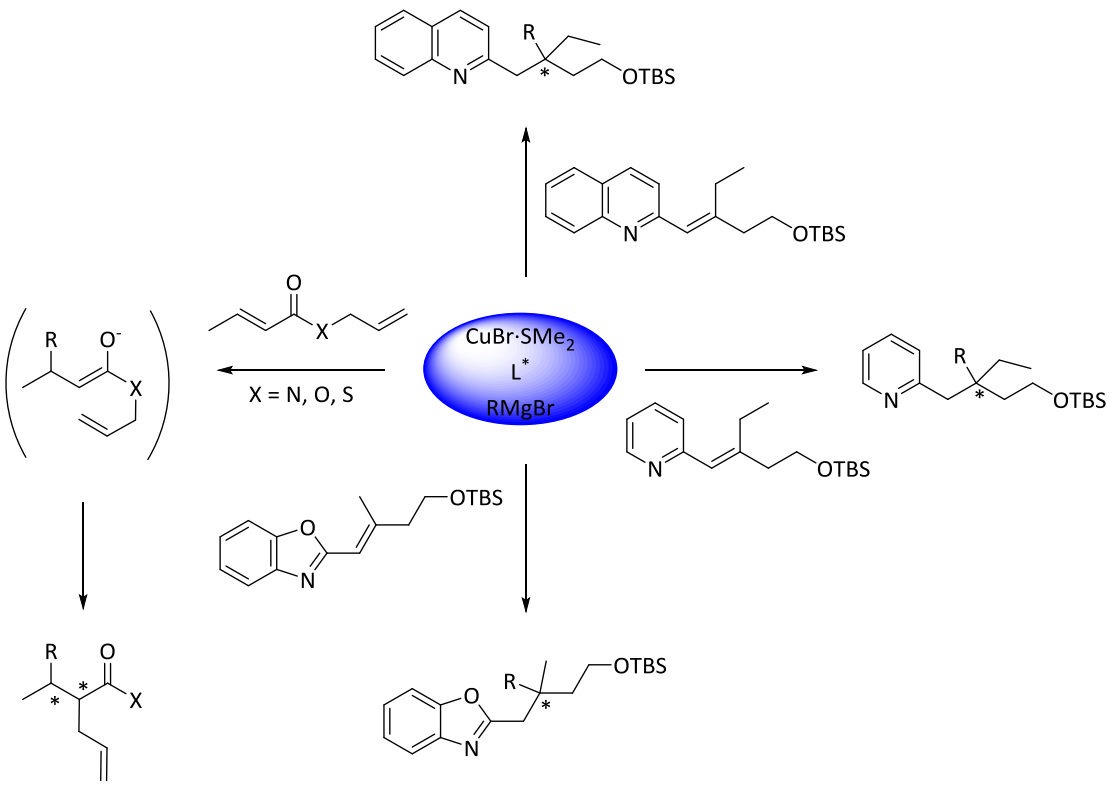
Expanding the Scope of the Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents



Master Research Project Submitted by

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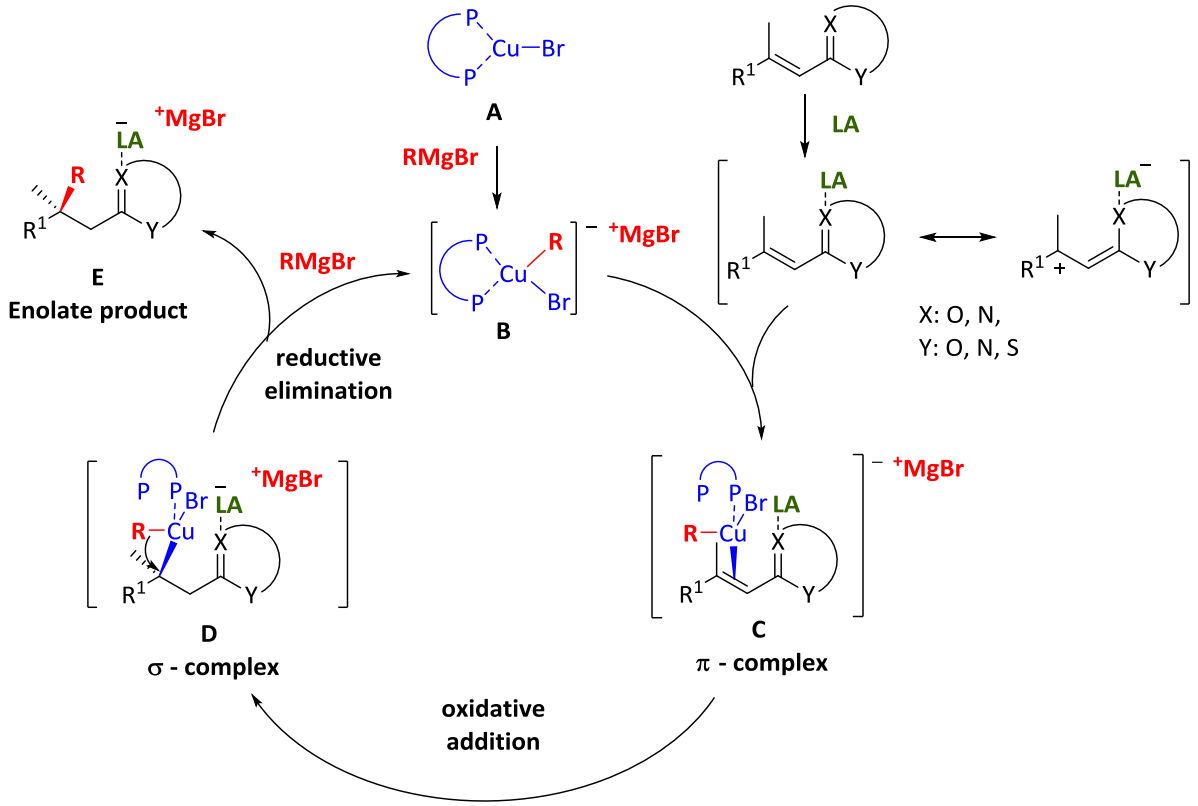
1. INTRODUCTION

Copper-catalyzed asymmetric conjugate addition (ACA) of organometallic reagents to electron-deficient conjugated systems has become one of the most useful tools in organic chemistry for the formation of new carbon-carbon bonds.[1] The basis of numerous advances in the synthesis of natural products, pharmaceuticals and agrochemicals have been done thanks to the ability to prepare homochiral compounds.

This transformation involves the reaction of an α,β-unsaturated system activated by an electron-withdrawing group (EWG). The addition takes places at the β-carbon of the unsaturated system, resulting in the formation of a stabilized enolate or derivative. After protonation of the enolate, the β-adduct is formed with a single stereocenter, whereas when it is quenched with an electrophile, it results in the α,β-disubstituted product with two new contiguous stereocenters. It offers a wide scope of possibilities and further functionalization of all kind of Michael acceptors (heteroarenes, carbonyl derivatives…). However, some of the substrates are not sufficiently reactive for the addition; therefore, some activation is required by means of Lewis Acids (LA).[2,3]

The proposed catalytic cycle for the LA copper-catalyzed ACA could be explained as follows: first, the CuBr/diphosphine ligand complex is formed, **A**. Then, this complex is transmetallated by the Grignard reagent forming complex **B**, which will coordinate with the α,β-unsaturated compound (either heterocyclic compounds or different carbonyl derivatives) to form the π-complex **C**. The α,β-unsaturated carbonyl compound, should in same cases be activated by a LA. For pyridines and amides, it is completely necessary, in contrast, not for thioesters, which are reactive enough towards the nucleophilic attack. After that, complex **C** will suffer oxidative addition, Cu(II) will be oxidized to Cu(III) forming a new σ bond at the β-position, leading to σ-complex **D**. To finalize the catalytic cycle, a reductive elimination occurs affording the conjugate addition product **E**, while the initial cuprate complex **B** is recovered by reacting with another molecule of Grignard reagent (Scheme 1).



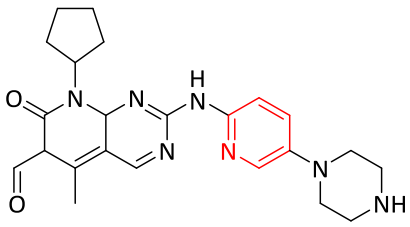
Scheme 1. Copper Catalyzed ACA of Grignard Reagents to Different Substrates and Proposed Catalytic Cycle.

In these master research project, based on the copper-catalyzed ACA of Grignard reagents, two different projects were carried out. The main focus of the first one was the formation of challenging all-carbon quaternary stereocenters after the synthesis of β,β-disubstituted alkenyl heteroaromatic compounds. For the second project, after the conjugate addition of organometallic reagents to α,β-unsaturated compounds, taking advantage of the resulting enolate, a system for the further functionalization was developed based on [3,3]-sigmatropic rearrangements, especially on Cope Rearrangement.

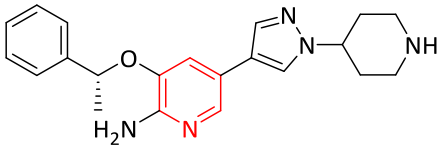
1.1 SYNTHESIS OF β,β-DISUBSTITUTED ALKENYL-HETEROAROMATIC COMPOUNDS AND THEIR APPLICATION IN THE SYNTHESIS OF ALL-CARBON QUATERNARY STEREOCENTERS

Chiral pyridines are present in many natural compounds, likewise in pharmaceutical products. It is known that most of the active pharmaceutical ingredients (APIs) contain heterocycles bearing a nitrogen atom.[4] Besides, half of these compounds have at least one stereogenic center on the molecule but only one of the two enantiomers is usually active for the desired function (Scheme 2).[5] Pyridines are relevant molecules in chemical processes and they are often used as additives or ligands. Hence, despite the direct functionalization of pyridines have been widely described in the literature, introducing stereogenic centers is still a challenge.[6]

During the last few years, many reports have been published about conjugate addition of carbon nucleophiles towards olefins adjacent to heterocycles. For instance, asymmetric conjugated addition of Grignard reagents has become one of the most relevant reactions for the formation of new carbon-carbon bonds;[7] this reaction is widely used by organic chemists for the synthesis of chiral building blocks.



Palbociclib
Advanced ovarian cancer



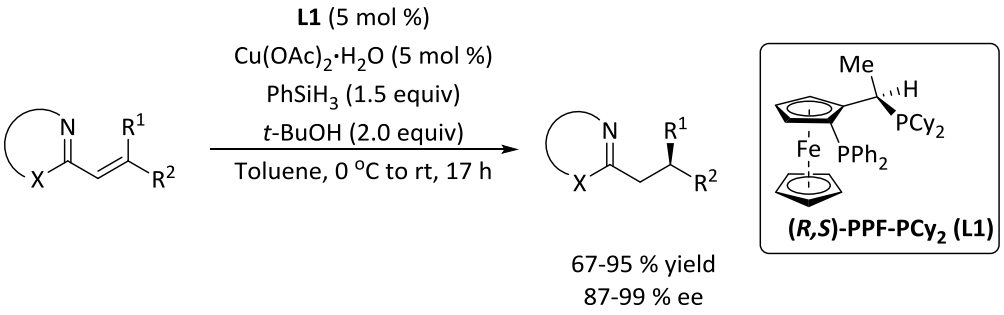
Crizotinib
Late-stage non-small-cell lung carcinoma

Scheme 2. Pyridine Containing Pharmaceutical Products.

For the conjugate addition (CA) of Grignard reagents to electron-deficient substrates, depending on their reactivity, activation by means of a Lewis Acid should be required. This is the case of nitrogen containing heterocycles.[2] Whereas, for the more reactive carbonyl compounds like ketones or thioesters additional LA activation is not necessary.

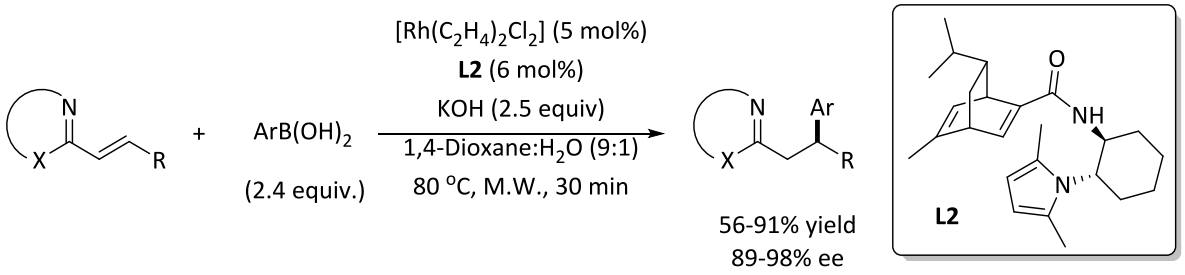
As it is stated above, direct functionalization of the pyridine ring is a known methodology.[8] Nevertheless, methods to further activate an olefin adjacent to the *N*-containing heterocycle have been recently developed during the last few years, due to the low reactivity of this moiety.[2,9-12]

One important methodology was described by Lam et al. in 2009.[9] In this work, after the synthesis of β,β-disubstituted 2-alkenyl heteroarenes the copper-catalyzed ACA was studied. On the other hand, it is recognized, that the ACA to substrates containing 2-vinyl heteroarenes is relatively common, however, the presence of substituents at β-position makes the attack of the Grignard difficult due to steric reasons. Thus, the effort was put on the addition of the smallest nucleophile possible, the hydride, and using benzoxazole as a substrate (Scheme 3). After finding the optimal reaction conditions, a highly enantioselective copper-catalyzed reductive system was achieved for a wide substrate scope, such as benzothiazoles, pyridines or quinolines. The adjacent alkene was activated enough by the nitrogen-containing aromatic heterocycle. Nevertheless, it was demonstrated that the conjugation between the alkene and the C=N moiety was very important, when the nitrogen was at 2- or 4- positions the addition was successful, in contrast, when it was at the 3-position the activation was not sufficient and consequently the addition did not proceed.



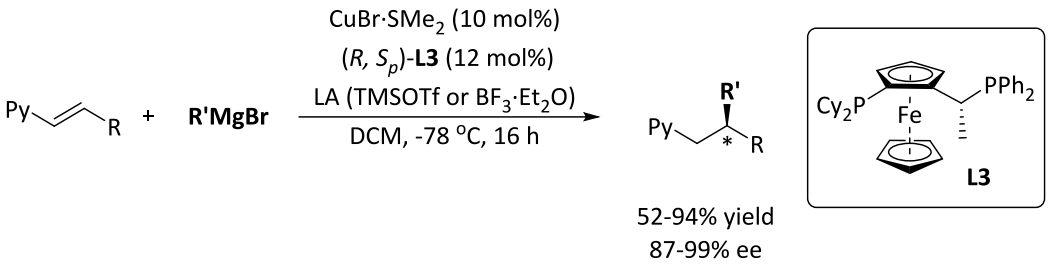
Scheme 3. Enantioselective Reduction of β,β-disubstituted 2-alkenylheteroarenes.

After this work, the same author was also able to carry out the asymmetric addition of organoboronic acids to different kind of π-deficient or π-excessive heteroarenes promoted by rhodium(I) catalyst using microwave irradiation.[10] In this case, the substrates were *N*-containing heterocycles with a single substituent at the β position. A wide substrate scope with good yields and excellent enantioselectivities could be acomplished (Scheme 4). Moreover, Lautens' group synthesized dihydrodibenzoxepines with high enantioselectivities by a tandem reaction involving the rhodium-catalyzed addition of borates and palladium-catalyzed C-O coupling.[11]



Scheme 4. Asymmetric Rh-Catalyzed Arylation of Alkenylheteroarenes.

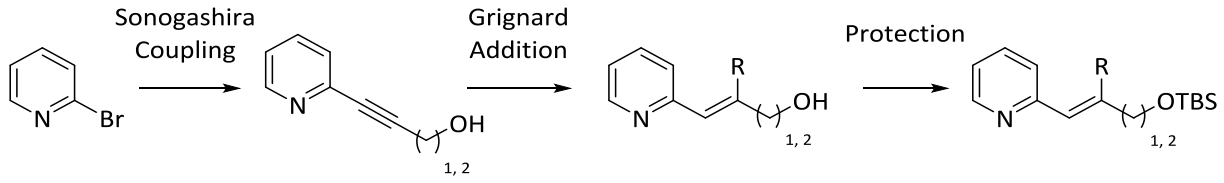
More recently, our research group have published other examples of functionalization of olefins adjacent to nitrogen-based heterocycles.[2] The alkenyl group was not reactive enough for the ACA due to the low activation by the pyridine ring. Therefore, the following system was developed: the use of a very reactive nucleophile and the further activation of the pyridine ring by means of Lewis acids. After all, a highly enantioselective method was presented, which gave as a result alkylated chiral pyridines (Scheme 5). The methodology was as simple as, enhancing the reactivity of the pyridine using a LA, and adding a reactive Grignard in a chiral environment formed by a copper catalyst complexed with a ferrocenyl diphosphine ligand. This process was applicable for a broad substrate scope. Different substituents at the aromatic ring or at the β position were well tolerated and the Grignard scope included linear, branched and functionalized examples. This transformation could be carried out even with MeMgBr, which was known to be barely reactive in this kind of transformations.



Scheme 5. Enantioselective Addition of Grignard Reagents to Alkenyl Pyridines.

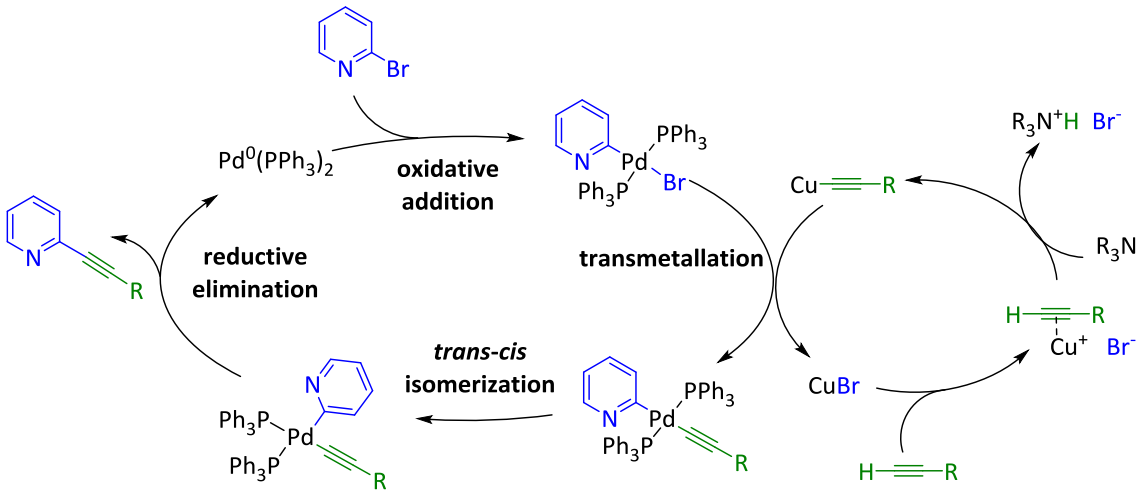
In all of the previous examples, the asymmetric alkylation or arylation took place at the β position respect to the *N*-containing heterocycle ending with tertiary stereogenic centers. Nevertheless, there were no examples where all-carbon quaternary stereocenters were formed for those kind of substrates. Alexakis published in 2010[1a] one of the only examples where all-carbon quaternary stereocenters were formed in cyclic ketones. In the mentioned work, a broad scope of different organometallic reagents could be added in high yields and excellent enantioselectivities.

Consequently and taking into account the knowledge acquired above, the first objective of the master research project was the design of a system, in order to achieve the enantioselective copper-catalyzed ACA of Grignard reagents to β,β-disubstituted *N*-containing heterocycles towards the adjacent olefin, to form all-carbon quaternary stereocenters. The synthesis of this kind of substrates was quite challenging because it was not so straightforward. Three steps were necessary: first Sonogashira Coupling between the heterocycle and an alkyne, then copper-catalyzed ACA of Grignard reagents and finally protection of the alcohol with a silyl group (Scheme 6).



Scheme 6. Synthesis of β,β-disubstituted Alkenyl-heterocycles.

Sonogashira Coupling[12] involves the palladium catalyzed C-C bond formation by coupling of a terminal *sp* hybridized carbon from an alkyne with a sp^2 carbon of an aryl or vinyl halide. Sonogashira, Tohda and Hagihara discovered that it was possible to perform the reaction at mild conditions using a Pd(0) catalyst, in combination with a Cu(I) co-catalyst. The mechanism of the reaction consists of two cycles. Although the real mechanism is still under study, the most common supposition involves a Pd(0) complex, which is needed, so in case of starting with a Pd(II) catalyst the first step is the reductive elimination to give the desired Pd(0). After the Pd(0) complex has been formed, the cycle is initiated by the oxidative addition of the aryl halide. Then, this complex is transmetallated with an in situ formed copper acetylide, previously formed in the copper-cycle (the copper complexes the terminal alkyne and in the presence of a base the acetylide is liberated). This adduct suffers reductive elimination after a *trans-cis* isomerization, to get the proper geometry and liberates the demanded alkyne, with the recovery of the catalyst (Scheme 7).[13]



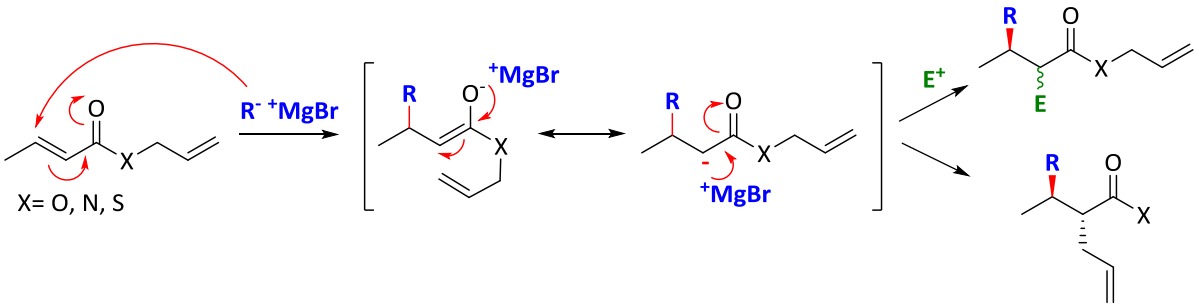
Scheme 7. Catalytic Cycle of the Sonogashira Coupling Reaction.

Since the discovery of this reaction, many papers have been published starting from different types of substrate and aryl moieties.[14] The type of palladium catalyst has also been studied in the last few years due to the difficulty to recover it after the reaction. Different palladium-phospine ligands have been tried, also palladium(0) on charcoal or even in charcoal nanoparticles.[15]

1.2 ASYMMETRIC CONJUGATE ADDITION TO CARBONYL DERIVATIVES FOLLOWED BY [3,3]-SIGMATROPIC REARRANGEMENT

Enantiopure β-substituted carbonyl derivatives (amides, esters, and thioesters) have an enormous synthetic potential as building blocks for natural product synthesis. In order to access these adducts different research groups have been working on the metal-based catalyzed ACA[1,16] to carbonyl derivatives. The enantiodiscrimination can be reached taking advantage of catalytic amount of chiral auxiliaries, which are able to form complexes with a copper source, such as ferrocenyl ligands or phosphoramidites.[17] They provide a chiral environment where the nucleophile performs the attack only from the less hindered side of the molecule, giving as a result preferably one of the two possible enantiomers.

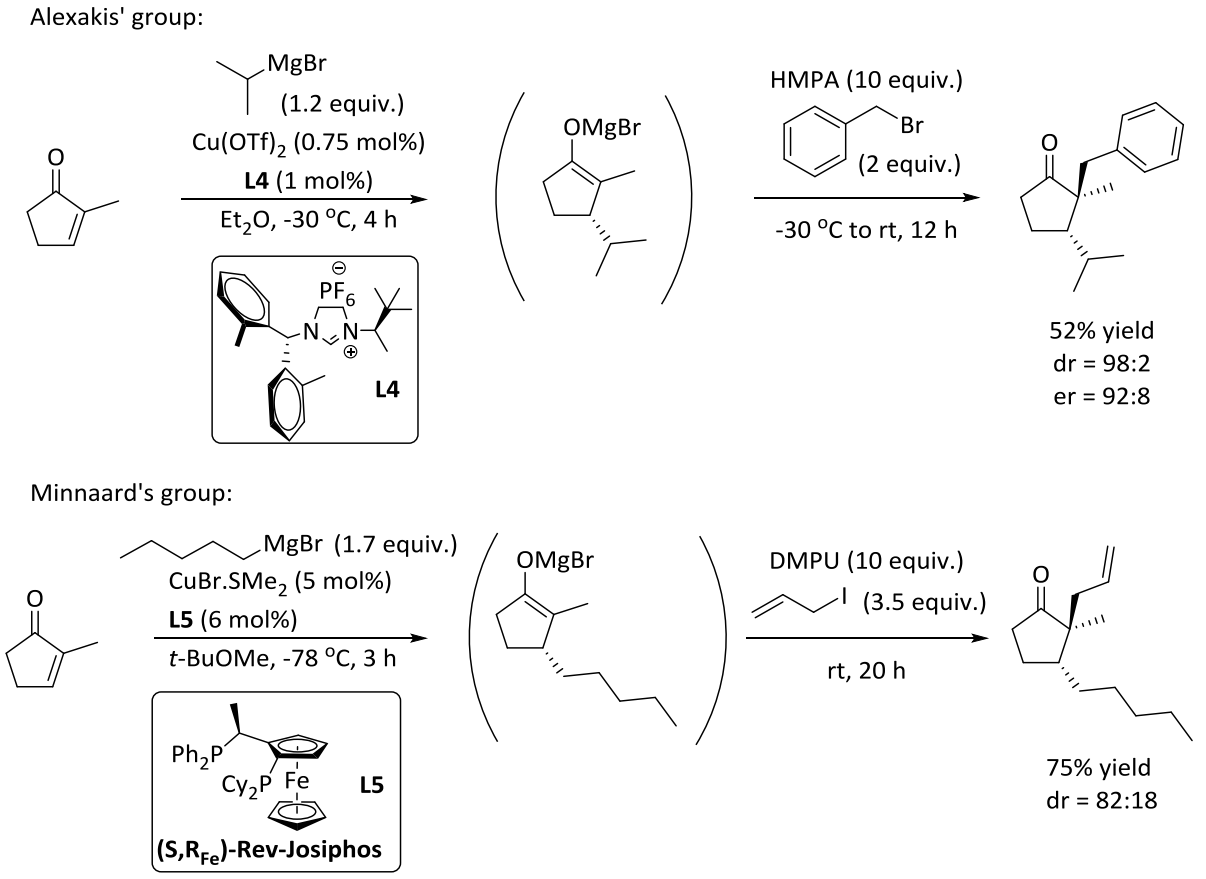
As it was previously mentioned, ACA is one of the most useful methods to form C-C bonds via addition of a nucleophile, but it is also possible to subsequently functionalize the resulting enolate using different procedures (Scheme 8). Many examples, where the β position with respect to the carbonyl or derivative group is modulated, are known.[3,18] However, the α position is quite unreactive, and examples where two contiguous stereocenters are formed have not been widely described in the literature. Therefore, in order to access the desired adducts, a tandem reaction is necessary. The conjugate addition is performed, followed by in situ trapping the enolate with different electrophiles or by the use of pericyclic reactions. In this way, it will be possible to generate two contiguous stereogenic centers.[19]



Scheme 8. Conjugated Addition and Formation of the Enolate with Further Functionalization.

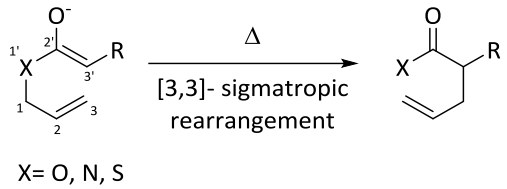
Some ACA examples have been reported for cyclic ketones,[20] where the Michael acceptor had a substituent at the α position. After the 1,4-addition, when the nucleophile was added at the β position, by alkylating or allylating the enolate, two vicinal stereogenic centers were formed, a quaternary stereocenter next to a tertiary one (Scheme 9). This was very interesting for obtaining biologically active pharmaceutical ingredients.[21]

In order to achieve the tandem reaction, after the 1,4-Michael addition, some additives were necessary due to the low reactivity of the magnesium enolate. For example, both hexamethylphosphoramide (HMPA) or *N,N*'-dimethylpropyleneurea (DMPU) are polar aprotic solvents that increase the nucleophility of the reagents, increasing the reactivity of the enolates for further alkylation or allylation. Although HMPA was more effective, it could be replaced by a higher amount of DMPU, which it was found to be nonmutagenic in contrast to HMPA. With the described methodology, the authors were able to broaden the scope for many different nucleophiles and electrophiles. However, this reaction has not been possible when using less reactive starting materials, such as, amides. In fact, there are no currently reports of highly diastereoselective products derived from these substrates and a few ones with ester or thioester substrates.[22]



Scheme 9. Previous Work in Enolate Trapping with Cyclic Enones.

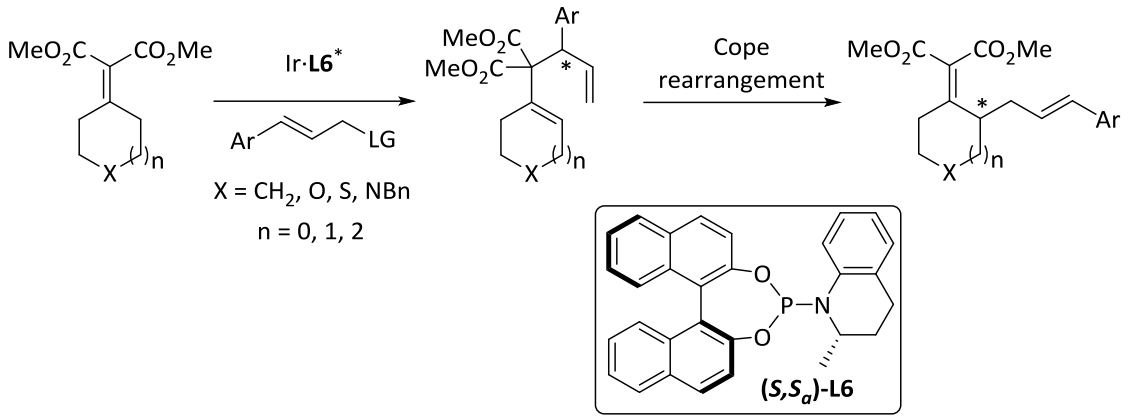
On the other hand, in order to obtain the same sort of products, pericyclic reactions[23] with an enolate and an allyl moiety seemed a good alternative. The mechanism of this type of reactions is known to proceed in a single step, where there are not any ionic intermediates or any charges involved; there is not indeed an intermediate. The transition state of the reaction has a cyclic geometry and it proceeds in a concerted fashion, meaning that often occurs with high stereospecificity. Therefore, taking advantage of the enolate after the asymmetric conjugate addition, [3,3]-sigmatropic rearrangement can occur in a diastereoselective fashion when an allyl moiety is present at the molecule (Scheme 10).[24]



Scheme 10. General Scheme of [3,3]-Sigmatropic Rearrangements.

Since the discovery of Claisen rearrangement,[25] this reaction has become a really useful synthetic route for organic chemists in the formation of new C-C bonds. The procedure is so efficient because it can be chemo-, regio-, diastereo- and enantioselective. Moreover, it can also be performed under mild conditions and it allows the use of many polyfunctionalized molecules. The rearrangement can happen wherever a 1,5-diene is present in the system. There are some heteroatoms which favor the reaction and examples can be found in the literature.[26] A drawback of this method is its reversibility. This means that the strategy of synthesis should be designed to shift the equilibrium towards the final product. For example, an interesting approach could be to obtain as the rearrangement product an enol. This adduct will be immediately tautomerized to the keto form which is normally more stable, so that the transformation becomes shifted towards the product. Other approach could be to trap the product with other reagent. For instance, when the rearrangement has happened in an allyl ester, (Scheme 10, X= O) the remaining acid could be treated with a base and a methylating agent could be added, shifting the equilibrium to the product.

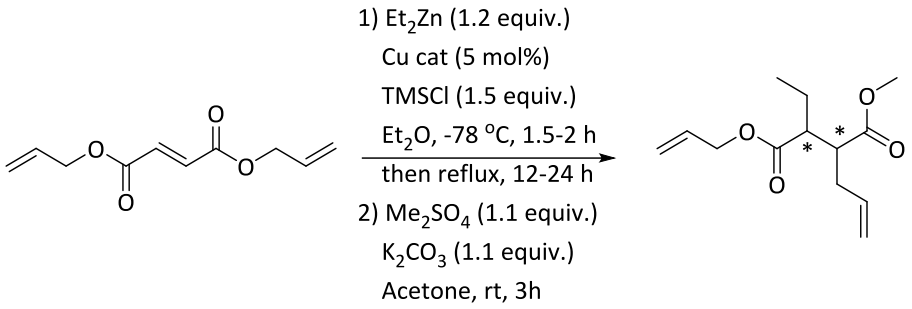
This method has not only been employed for the formation of α,α-disubstituted enolates[27] (with stereocontrol) but also for the synthesis of two adjacent stereogenic centers with high diastereoselectivity.[28] Recently, an asymmetric allylic alkylation combined with a Cope rearrangement of α,β-unsaturated malonates and ketoesters has been reported.[29] In this work, the authors described a regio- and enantioselective iridium-catalyzed α-alkylation of an enolate of such substrates, which was afterwards placed at the γ-position by Cope rearrangement with the retention of the stereoselectivity (Scheme 11). The main advantage of this tandem process was the retention of the chirality in the process. The stereogenic center formed with the alkylation of the substrate was transferred to a different position of the molecule, with the retention of the stereoselectivity.[27,28,29]



Scheme 11. General Scheme of the Sequential Asymmetric Allylic Alkylation Followed by Cope Rearrangement.

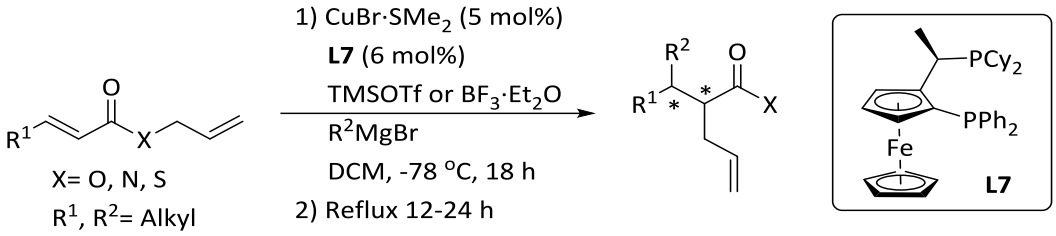
Nevertheless, the publication that really attracted our attention was published by Jeffrey S. Johnson et al.[30] The aim of this work was to perform the conjugate addition of dialkylzinc reagents to allyl fumarates followed by Ireland-Claisen rearrangement to obtain a non-symmetric moiety of the product. There are many reports published in the literature dealing with the conjugate addition of this kind of organozinc reagents to different diesters.[31]

However, the authors' work was based on accomplishing the organometallic addition to the allyl fumarates and taking advantage of the in situ formed silyl enolate, which should be reactive enough to undergo an ester enolate Claisen rearrangement (Scheme 12). After that, it was possible to further functionalize the carbonyl which gave the rearrangement. This process proceeded with good diastereoselectivity (up to 9:1 diastereomeric ratio (dr)).



Scheme 12. General Scheme of the Tandem Michael Addition/Ireland-Claisen Rearrangement.

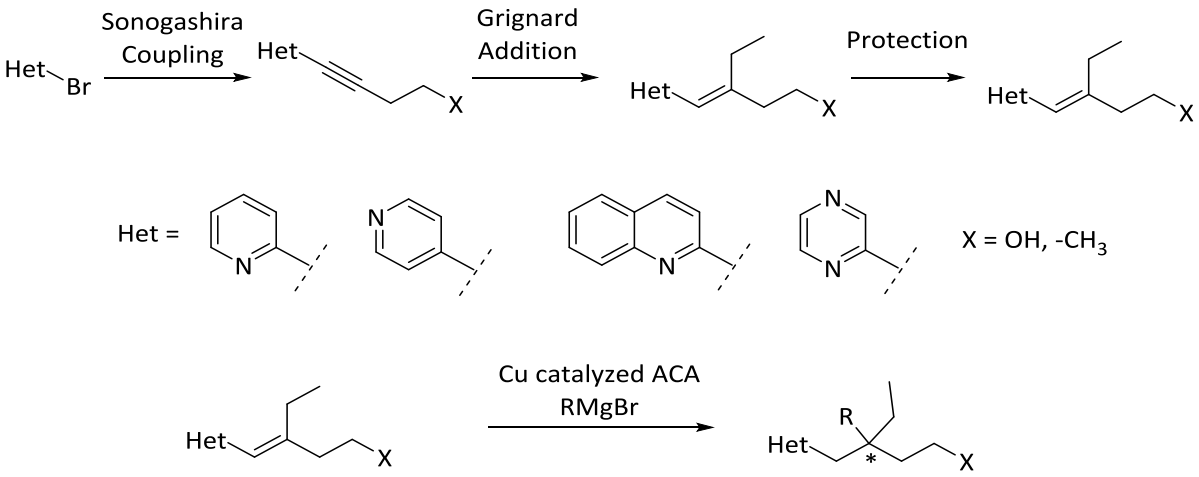
With all this information in hand, taking into account that to control the diastereoselectivity in the trapping processes cyclic substrates were necessary, enolate Claisen rearrangement could be an alternative to form selective contiguous stereocenters in carbonyl derivatives. The idea was to perform the copper-catalyzed ACA of organometallic reagents, followed by the enolate Claisen rearrangement of the resulting enolate with the allyl moiety. Our main focus was to study α,β-unsaturated amides, which were quite challenging substrates due to their intrinsic low reactivity. We envisioned that in case the system would work for the amides, we could broaden the substrate scope to more reactive carbonyl derivatives. Thus, as the asymmetric addition was already known for many different amides,[3] it would be really interesting to study the tandem reaction of ACA of Grignard reagents to *N*-allylic amides (and other carbonyl derivatives) followed by [3,3]-sigmatropic rearrangement (Scheme 13).



Scheme 13. General Scheme of the Tandem Reaction.

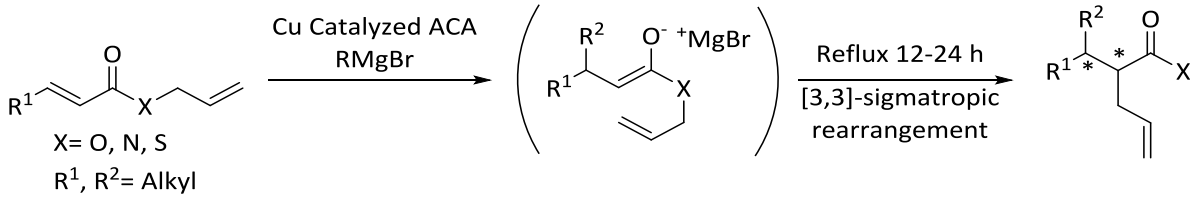
2. AIM OF THE PROJECT

The formation of all-carbon quaternary stereocenters at the β-position with respect to the *N*-containing heterocycles is rare in the literature. Therefore, the aim of the project in order to achieve highly enantioselective all-carbon quaternary stereogenic centers at the β-position was to synthesize β,β-disubstituted alkenyl heteroaromatic compounds and to study the copper-catalyzed ACA of Grignard reagents (Scheme 14).



Scheme 14. Aim of the First Part of the Master Research Project.

Enolate Claisen rearrangements with an allylic moiety could be an alternative to improve the diastereoselectivity achieved by the enolate trapping, due to the specificity of the reaction. Pericyclic reactions are known to proceed via concerted mechanism, usually with high stereocontrol. Thus, the aim of the second part of this master research project was to obtain highly selective contiguous stereogenic centers at α- and β-positions. For this purpose, it was necessary to synthesize different α,β-unsaturated carbonyl derivatives, and after the copper-catalyzed ACA subject them to high temperatures to favor the Claisen rearrangement, resulting on the desired adducts. (Scheme 15).

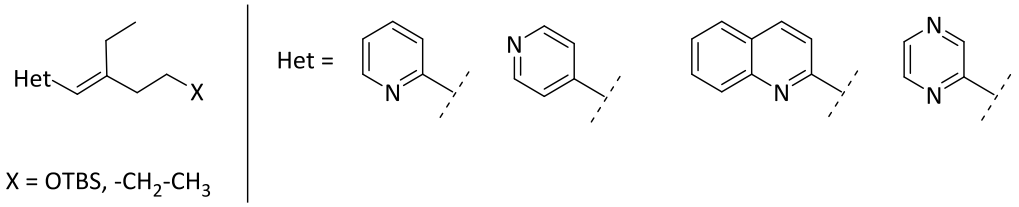


Scheme 15. Aim of the Second Part of the Master Research Project.

3. RESULTS AND DISCUSSION

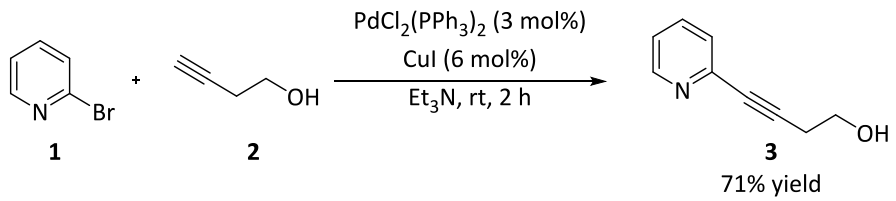
3.1 SYNTHESIS OF β,β-DISUBSTITUTED ALKENYL HETEROAROMATIC COMPOUNDS AND THEIR APPLICATION IN THE SYNTHESIS OF ALL-CARBON QUATERNARY STEREOCENTERS

For the purpose of generating all carbon quaternary stereocenters β-to the heteroaromatic moiety, the following β,β-disubstituted 2-alkenyl heteroaromatic compounds were synthesized. The selection was based on the previous work done in our research group:[2] in order to have the sufficient activation towards the conjugate addition at the olefin, the nitrogen in the heteroaromatic ring should be in 2- or 4-position respect to the olefin. Other important fact related to the 2-pyridines, was that a hydroxyl group should be placed in the aliphatic chain for the addition to proceed when an electron-withdrawing group was not present in the aromatic ring. Therefore, the following β,β-disubstituted 2-alkenyl heteroaromatic compounds substrates were synthesized (Scheme 16).



Scheme 16. Substrates to Be Synthesized.

As a starting point, β,β-disubstituted 2-alkenyl pyridine was chosen as model substrate for the optimization of the reaction. Sonogashira Coupling was the first step of the synthesis to prepare this compound. The reaction was performed according to a procedure described in the literature,[32] affording product **3** in a good yield, 71% (Scheme 17).

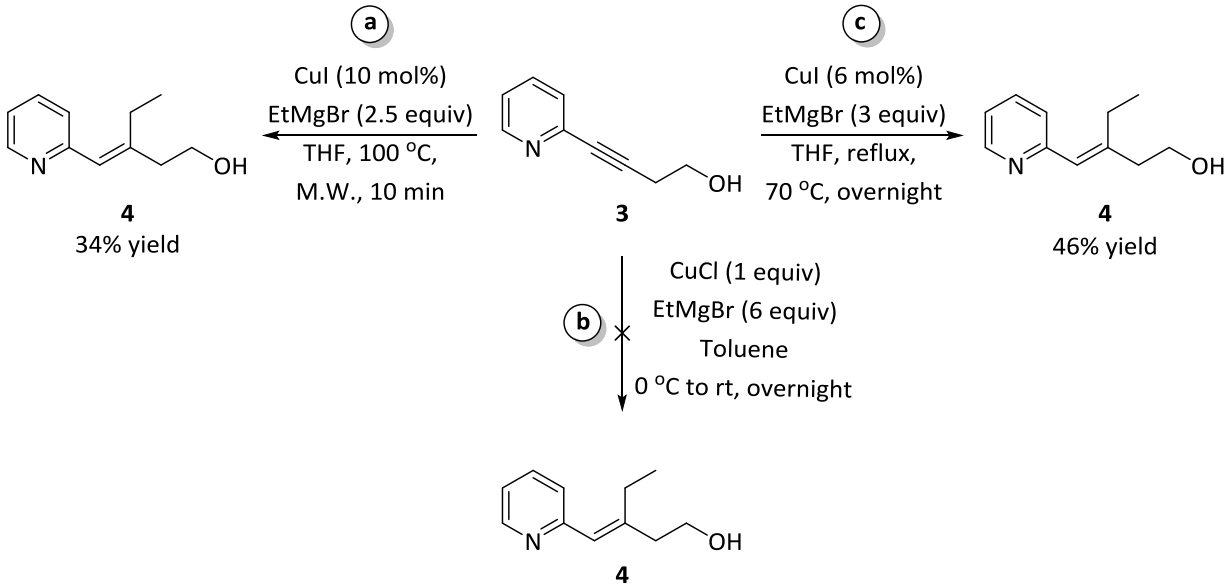


Scheme 17. Sonogashira Coupling for the Synthesis of Product **3**.

After that, in order to obtain the conjugate Grignard addition at the alkyne moiety, different procedures described in the literature were tried.[9,,33] The first attempt was performed in the presence of a copper(I) catalyst in THF and under microwave irradiation (Scheme 18, a). Even though product **4** was obtained, the yield was low, 34%. As a result, we decided to explore more methods to afford the conjugate addition.

Consequently, to check whether the yield could be improved, other methodology consisting of adding the Grignard reagent at 0 °C, and running the reaction overnight at room temperature was tried (Scheme 18, b). The reaction was warmed up to reflux until the consumption of the starting material because no conversion was observed. Unfortunately, the desired product **4** was not formed. It could be stated that double addition had happened by the analysis in the GC-MS. In addition, by ^{1}H-NMR the result was further confirmed, due to the absence of the characteristic signal of the proton of the alkene.

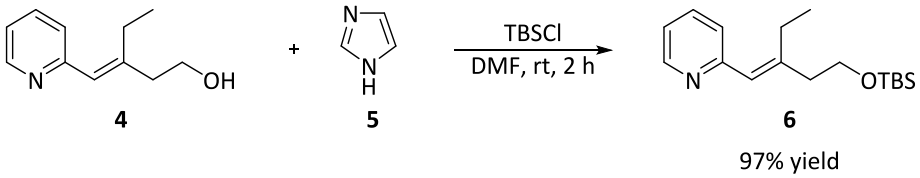
Finally, as it is known, the microwave irradiation accelerates the rate of the reaction; hence, the reaction was let for longer time. The same conditions used in the microwave synthesizer were repeated, but instead, the reaction was left under reflux overnight (Scheme 18, c). A slightly better yield of product **2** was obtained by the use of this procedure; therefore, it was further used for the alkene formation during the synthesis of the rest of the compounds.



Scheme 18. Copper-Catalyzed Grignard Addition.

It was confirmed by 2D NMR studies, Nuclear Overhauser Effect SpectroscopY (NOESY), that the alkene formed **4,** was only the *E* alkene shown in the scheme, because the proton of the alkene (H_d) was correlated to the protons (H_g) at the β-positions with respect to the hydroxyl group (See Appendix, compound **4**).

The last step for the synthesis of the substrate **6** was the protection of the alcohol with a silyl group. This step was quite straightforward; product **6** could be obtained in 97% yield by the use of a base and the silylating agent (Scheme 19).

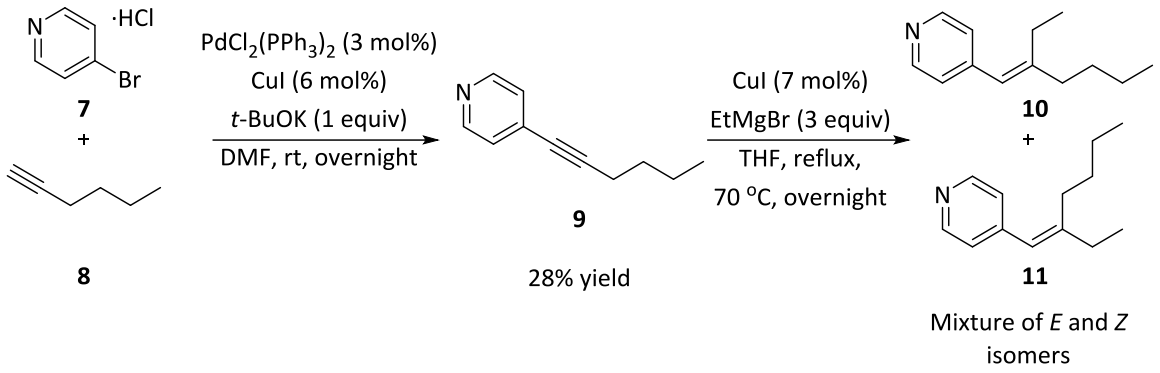


4 **5** **6**

97% yield

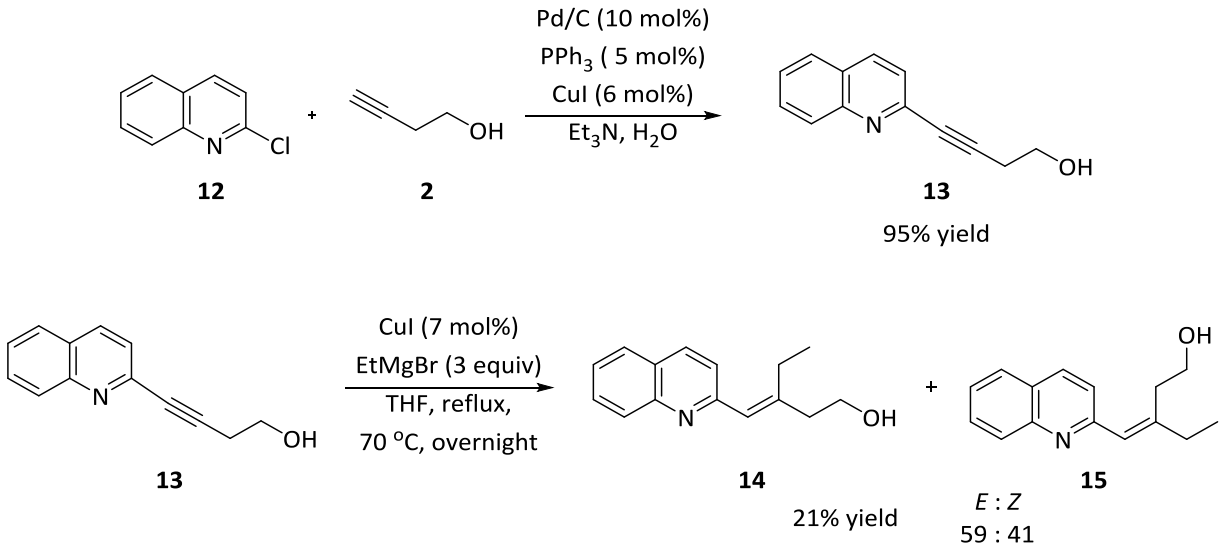
Scheme 19. Protection of the Alcohol.

After the synthesis of the 2-pyridine compound, in order to obtain the 4-pyridine adduct, the same methodology was applied (Scheme 20). Based on previous works, the presence of the hydroxyl group was not necessary for the 4-pyridine ring. Instead, in the first step of the synthesis, which consists on Sonogashira Coupling, an aliphatic chain was added, obtaining the desired product **9** in a low yield (28%). Next, the copper-catalyzed 1,4-addition was performed. However, by using the optimized Grignard addition methodology, a mixture of both *Z* and *E* isomers was formed (**10** and **11**), and it was not possible to separate them. The mixture of isomers could be a consequence of the lack of the nitrogen in 2-position. Somehow, when the copper was complexed to the substrate, it was coordinated with the nitrogen as well in case of being at 2-position. Consequently, the conformation was blocked and the attack on the alkyne could only happen from one side, resulting on the single *E* isomer.



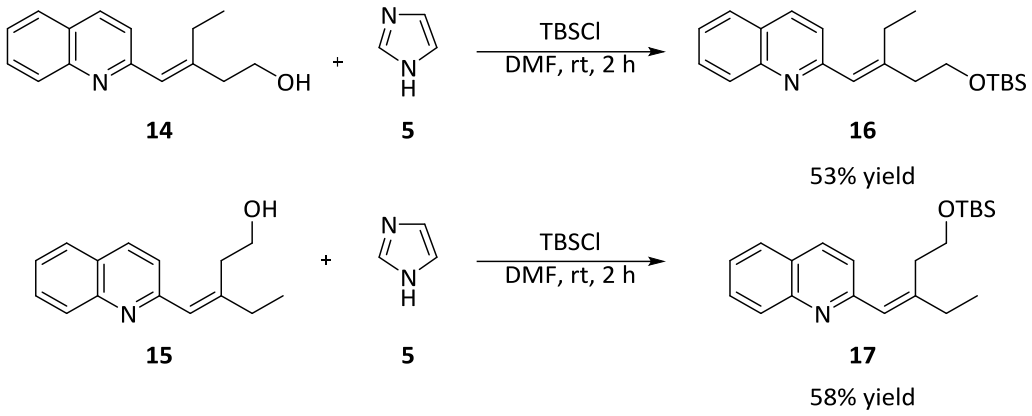
Scheme 20. Unsuccessful Synthesis of the 4-Pyridine Substrate.

Taking into account the need to have the nitrogen in position two of the aromatic ring, 2-quinoline substrate was the next substrate to be synthesized. Using palladium(0) in carbon and triphenylphosphine together with the copper(I) co-catalyst, compound **13** was successfully synthesized according to a literature procedure[15a] with excellent yield, 95%. Next, in order to obtain the alkene compound, the previously optimized standard conditions were used. For our surprise, the Grignard addition was not only successful, but it was also possible to separate the *E* and *Z* isomers (respectively **14** and **15**) during the purification step. The structures were confirmed by 2D NMR NOESY analysis (See Appendix, compounds **14**, **15**). The overall yield of the reaction was 21% and the ratio between the isomers was determined to be 59:41 (*E*:*Z*) by the isolated mass of each compound (Scheme 21).



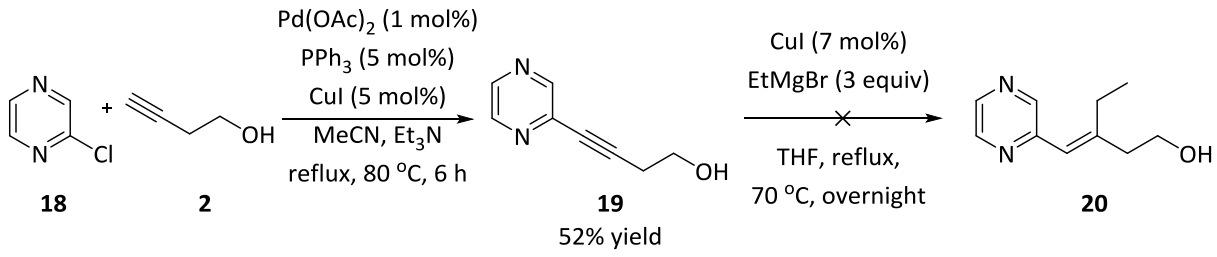
Scheme 21. Synthesis of Alkenyl Pyridine and Consequent Grignard Addition.

The last step of the synthesis to obtain the desired β,β-disusbtituted alkenyl quinoline, was the protection of the alcohol by the use of imidazole as a base in combination with a silylating agent (Scheme 22). In this case, the protection step was not as successful as in the previous substrate, but products **16** and **17** were synthesized in moderate yields, 53% and 58% respectively.



Scheme 22. Protection of the Alcohol in *E* and *Z* Isomers.

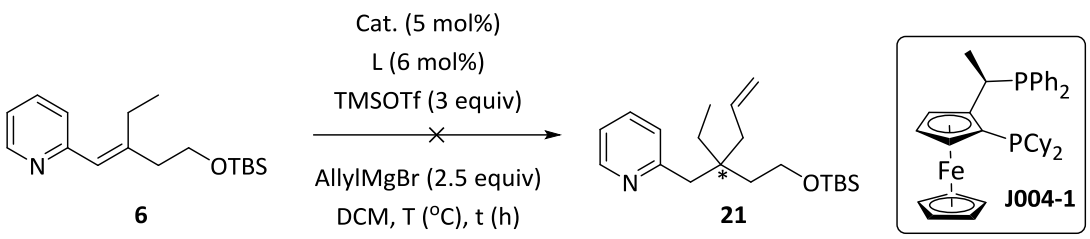
After the synthesis of the quinoline, the next substrate to be synthesized was the pyrazine substrate (Scheme 23). The first step was Sonogashira Coupling, in this case, the palladium(0) catalyst source was $Pd(OAc_2)$, which together with triphenylphosphine and the copper(I) co-catalyst gave product **19** in moderate yield, 52%. In the next step, using the methodology optimized before, Grignard addition was performed. The starting material was consumed, but after a difficult purification, none of the isolated fractions was the desired product **20**.



Scheme 23. Synthesis of Pyrazine substrate and Unsuccessful Grignard Addition.

With these substrates in hand, we decided to start trying some ACA reactions to the test substrate **6**. Grignard reagents have not been added to those kinds of substrate; therefore, the reaction conditions had to be explored from the beginning (Table 1).

Table 1. Optimization of the Reaction Conditions for the Addition of Allylmagnesium Bromide.[a]



Entry	Catalyst	Ligand	T (°C)	time (h)	Conv. (%)[b]
1[c]	-	-	0	2	0
2	-	-	0	2	0
3	$CuBr{\cdot}SMe_2$ (5)	-	0	2	0
4	-	-	-50	2	0
5	-	-	-78	2	0
6	$CuBr{\cdot}SMe_2$ (5)	J004-1 (6)	-78	2	Traces
7	$CuBr{\cdot}SMe_2$ (5)	J004-1 (6)	-78	16	50[d]
8	$CuBr{\cdot}SMe_2$ (5)	J004-1 (6)	0	2	0

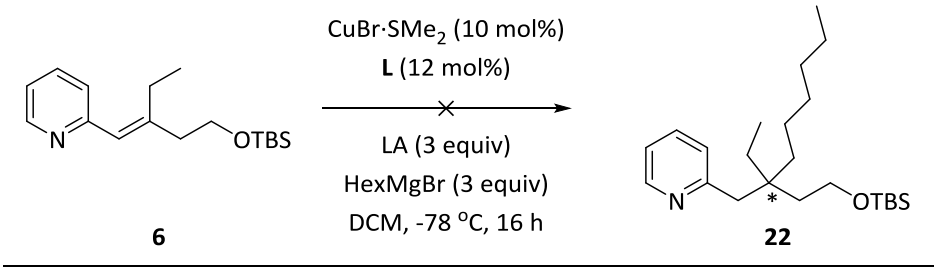
[a] Reaction carried out using 0.1 mmol substrate, 1 mL DCM; [b] Determined by ^{1}H-NMR spectroscopy; [c] No TMSOTf used; [d] Conversion to an unknown product.

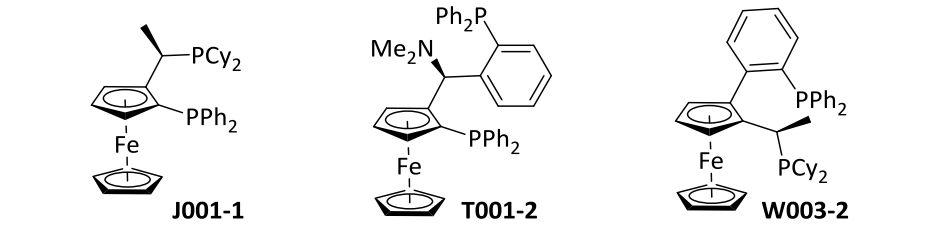
To compensate the low reactivity of the substrate a highly reactive Grignard reagent was chosen (allylmagnesium bromide). First of all, the blank reaction was tried (Table 1, entry 1) where as expected, no conversion was observed. In order for the addition to take place, a higher activation was necessary; the heterocycle should be activated by the use of a LA. Secondly, the same reaction was tried in the presence of a strong LA, TMSOTf (Table 1, entry 2) because our research group[2] has previously demonstrated that the 2-pyridine with the hydroxyl group at the end of the aliphatic chain reacts enantioselectively in the presence of TMSOTf. However, unfortunately, no conversion was achieved, probably due to the short reaction time.

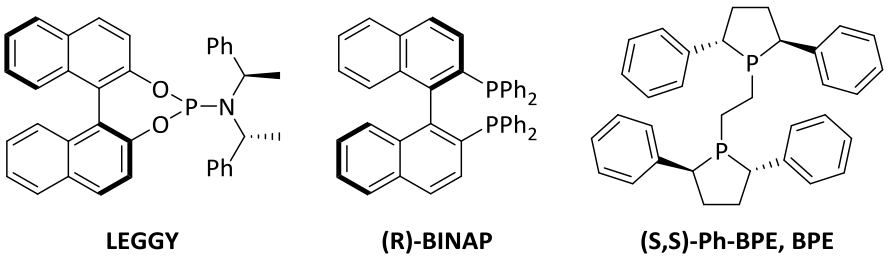
Then, the copper(I) catalyst was added, but just the starting material was observed (Table 1, entry 3). In addition, in case of having a lower temperature, (Table 1, entries 4-5) no conversion was observed either. Therefore, the screening was continued by adding a catalytic amount of a ferrocenyl ligand that has been demonstrated to give good results in the synthesis of β-tertiary chiral pyridines.[2] The standard conditions described in that publication were tried for two hours (Table 1, entry 6) and some conversion could be appreciated in the crude ^{1}H-NMR. Therefore, the reaction was carried out for longer time (Table 1, entry 7). The conversion to the product was 50% and after the purification, the isolated fraction was not the desired compound **21**. The same conditions were also tried at 0 °C, (Table 1, entry 8) but the reaction did not proceed, only the starting material was observed.

In order to find alternatives to perform the desired copper-catalyzed ACA, using a less reactive Grignard was another possibility. Since by the use of a LA the heterocycle should be sufficiently activated for the addition, with a less reactive Grignard the reaction was expected to be more selective and to proceed towards the β-position. Therefore, hexylmagnesium bromide was chosen as the reagent for the following tests because it was not possible to use ethylmagnesium bromide (Table 2).

Table 2. Ligand Screening for the Addition of Hexylmagnesium Bromide.[a]







Entry	Ligand	LA	Conv. (%)[b]
1	J004-1	TMSOTf	100
2	J001-1	TMSOTf	100
3	T001-2	TMSOTf	100
4	W003-2	$BF_3{\cdot}Et_2O$	100
5[c]	LEGGY	$BF_3{\cdot}Et_2O$	100
6	BINAP	$BF_3{\cdot}Et_2O$	100
7	S,S-Ph-BPE,BPE	$BF_3{\cdot}Et_2O$	100

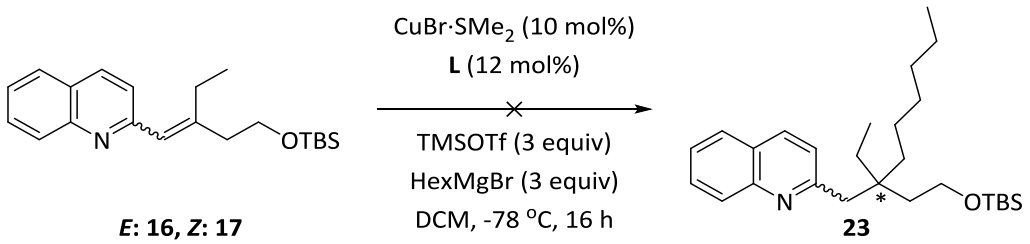
[a] Reaction carried out by using 0.1 mmol substrate, 1 mL DCM;
[b] Determined by ^{1}H-NMR spectroscopy, [c] 10 mol% catalyst used.

Different ferrocenyl based ligands were used from the Josiphos and the Taniaphos family (Table 2, entries 1-3). Despite having full conversion of the starting material, the desired product **22** was not observed. The characteristic proton of the alkene was still visible. Even after purification of the crude, it was not possible to determine the structure of the by-product. Then, we decided to switch the LA to $BF_3{\cdot}Et_2O$, which was proved to work for the addition towards the olefin of 2-pyridines. One different ferrocenyl ligand from the Walphos family was tried (Table 2, entry 4) but a complex mixture was obtained. Then, taking into account that all the previous catalysts were metal based, some organocatalysts that have been demonstrated to be effective in these kind of transformations were tested. First, a phosphoramidite ligand was chosen (Table 2, entry 5). In this case, the reaction did not result in the desired product. Finally, two more organobased ligands were tried (Table 2, entries 6-7) but unfortunately, no presence of product **22** was observed.

Once again, the starting material was always consumed but the representative signal of the alkene proton was always present as it was previously observed for the addition of allylmagnesium bromide. Thus, it could be stated as a conclusion that the addition was happening, but somewhere else at the molecule. It was likely that the addition proceeded at 4- or 6-position of the pyridine ring, due to the high steric hindrance present in the alkene. The Lewis Acid activates the pyridine, becoming those positions highly reactive for the nucleophilic addition of the Grignard reagent.

In vision of the obtained results, we decided to move on to the next substrate, which was the quinoline substrate. Some preliminary tests to both the *E* and *Z* enantiomers were performed to see whether the addition product could be observed (Table 3).

Table 3. Copper-Catalyzed ACA to Quinoline Substrates.[a]



***E*: 16, *Z*: 17** **23**

Entry	Quinoline	Ligand	Conv. (%)[b]
1	*E*	J004-1	60[c]
2	*E*	T001-2	0
3	*Z*	J004-1	0
4	*Z*	T001-2	100

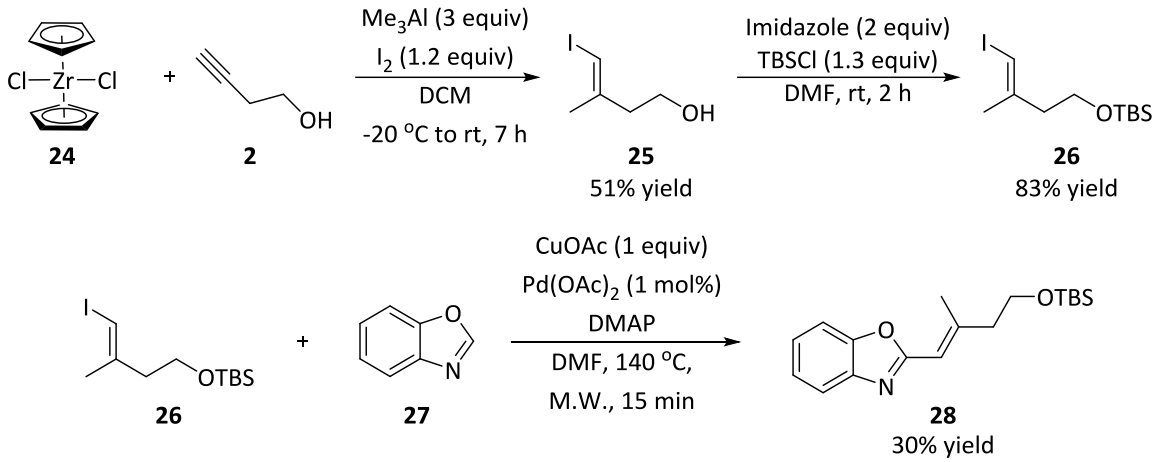
[a] Reaction carried out by using 0.1 mmol substrate, 1 mL DCM;
[b] Determined by ^{1}H-NMR spectroscopy; [c] Conversion to an unknown product.

First, a Josiphos family ligand was tried with the *E* isomer achieving 60% of conversion (Table 3, entry 1). However, once again it could be seen that it was not the desired product **23** due to the presence of the alkene proton. The other attempt was done in the presence of a Taniaphos ligand but no conversion was observed (Table 3, entry 2). Then, two more attempts with the *Z* isomer were tried using the same conditions (Table 3, entries 3-4). In this case, no conversion was observed with the Josiphos ligand and full conversion with Taniaphos. However, the obtained product was not the desired one, the representative proton from the alkene was still visible.

After all this attempts, it could be concluded that the copper-catalyzed ACA was taking place, but it was not happening at the desired β-position. As the NMR showed no starting material left, we could come to the conclusion that the addition was proceeding somewhere else at the molecule. Probably, it was happening at 4- or 6-position in the heterocycle, this could be due to β-position being highly sterically hindered; therefore, this position was not so accessible.

With those results in hand, we considered to synthesize other kind of starting material, because the copper-catalyzed ACA did not work as expected towards the olefin adjacent to the pyridine and quinoline rings. The position was always so hindered for the addition, and the Grignard that was being added was a long chain, which indeed contributed more to the steric problem. Therefore, we decided to switch to benzoxazole substrates, because of their known higher reactivity compared to pyridines and derivatives. A route to get benzoxazole moieties was found, where the β-position was not as hindered as before. A methyl substituent was present at the β-position and thanks to this fact, a smaller Grignard reagent could be added, which might favor the ACA.

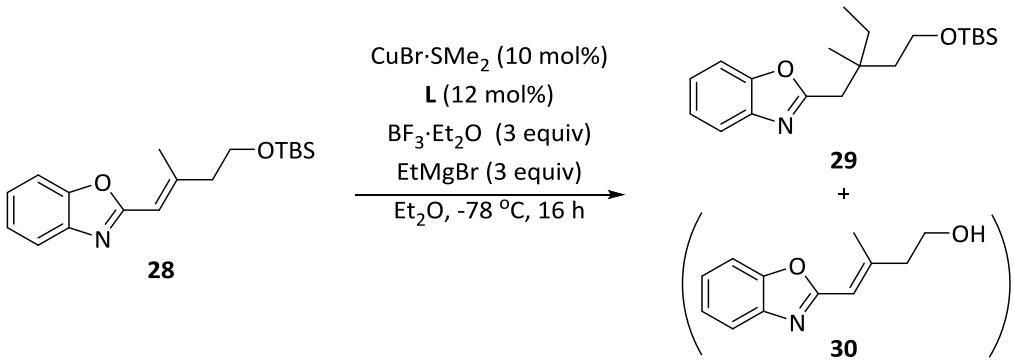
The formation of benzoxazole substrate proceeded through a multi-step synthesis. First, the vinyl iodide was synthesized following a procedure described in the literature (Scheme 24).[27] A terminal hydroxyl alkyne was coupled with trimethylamine and iodide in the presence of a zirconium(II) catalyst, giving as a result the *E* isomer **25** in a moderate yield, 51%. The next step was the protection of the alcohol by the use of a base (imidazole) in the presence of a silylating agent. The protection step afforded **26** in a good yield, 83%. Finally, the last step for the synthesis of the substrate was the coupling reaction of **26** with benzoxazole (**27**). By mixing the benzoxazole with the alkene in presence of a base, together with Cu(I) and Pd(II) co-catalysts, and heating the mixture up in the microwave synthesizer, product **28** could be obtained in 30% yield.



Scheme 24. Synthesis of Benzoxazole Substrate.

Once the benzoxazole substrate was synthesized, different optimization reactions were carried out. Only two tests could be performed due to the small quantity of the desired product **28** (Table 4).

Table 4. Copper-Catalyzed ACA to Benzoxazole Substrate.[a]

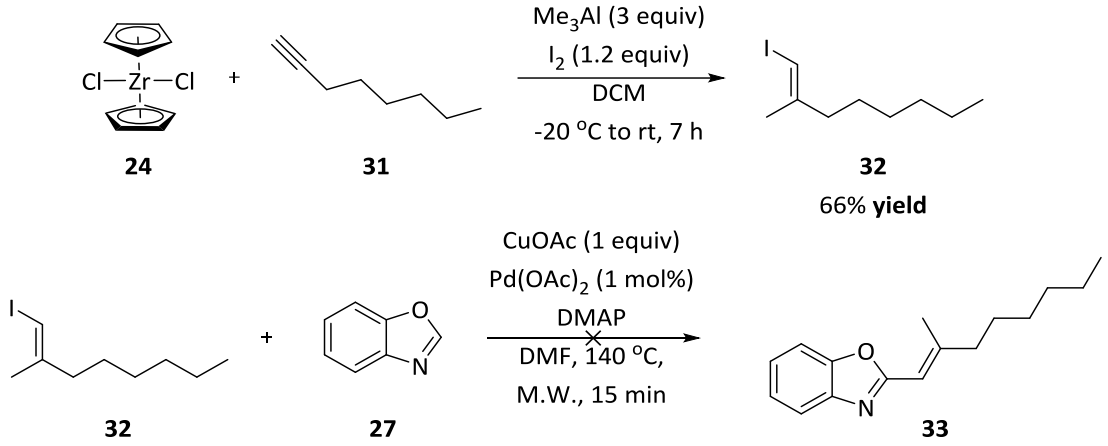


Entry	Ligand	Conv. (%)[b]
1	J004-1	100
2	(S,S)-Ph-BPE,BPE	100

[a] Reaction carried out by using 0.1 mmol substrate, 1 mL of Et_2O; [b] Determined by ^{1}H-NMR spectroscopy.

In order to broaden the ligand scope two different ligands were used, one ferrocenyl based ligand and an organobased ligand. In both cases (Table 4, entries 1-2) a full conversion was achieved, nevertheless, not to the desired product **29**. After purification, the obtained product was confirmed by ^{1}H-NMR to be the deprotected alcohol **30**.

Therefore, in the last attempt to obtain the enantiopure β,β-disubstituted heterocyclic compound, the synthesis of another benzoxazole substrate was tried. In the previous substrate, the alcohol played a role; the addition towards the olefin did not proceed. Instead, the deprotection of the alcohol happened. Consequently, in order to avoid that fact, we decided to replace the alcohol for an aliphatic chain (**31**) (Scheme 25). Following the same methodology to obtain the vinyl iodide, the synthesis of product **32** was successful; it was obtained in a 66% yield. Nevertheless, it was not possible to isolate coupling product **33** after several attempts. A complex mixture was observed in the ^{1}H-NMR and a mixture of five different compounds with the same mass was observed by GC-MS.



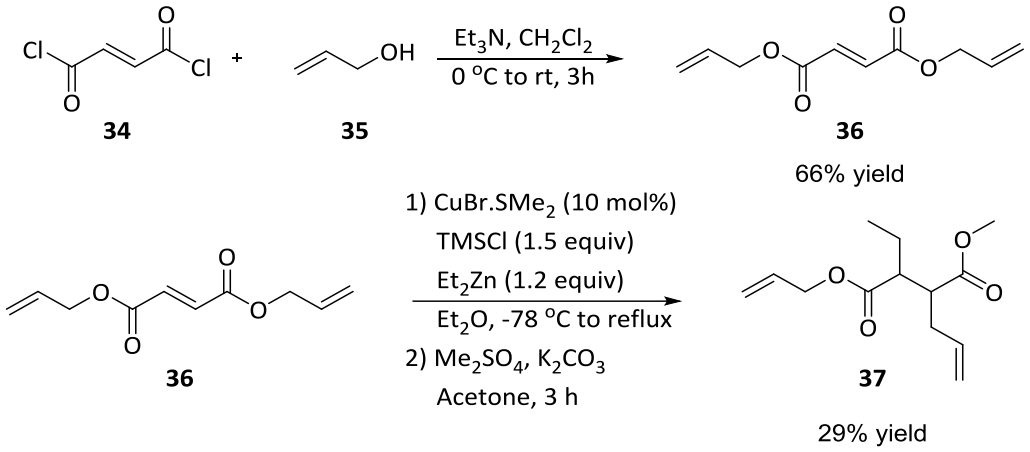
Scheme 25. Attempt to Synthesize other Benzoxazole Substrate.

After the unsuccessful tries to synthesize the benzoxazole substrate and taking into account that the ACA was not successful towards β,β-disubstituted alkenyl heteroaromatic substrates, probably due to the steric hindrance to reach the β-position, a new methodology should be developed to access all-carbon quaternary stereocenters.

3.2 ASYMMETRIC CONJUGATE ADDITION TO CARBONYL DERIVATIVES FOLLOWED BY [3,3]-SIGMATROPIC REARRANGEMENT

In order to obtain highly diastereoselective contiguous stereocenters in carbonyl derivatives, a tandem reaction was developed. First, conjugate addition was performed, resulting in a β-substituted enolate and this was followed by enolate Claisen rearrangement, getting the α,β-susbtituted adduct. For this purpose, the carbonyl derivatives needed to have an allylic group at the terminal position, owing to the need to have a 1,5-diene system present at the molecule. The idea was based on a procedure published by J. Johnson et al.[30]

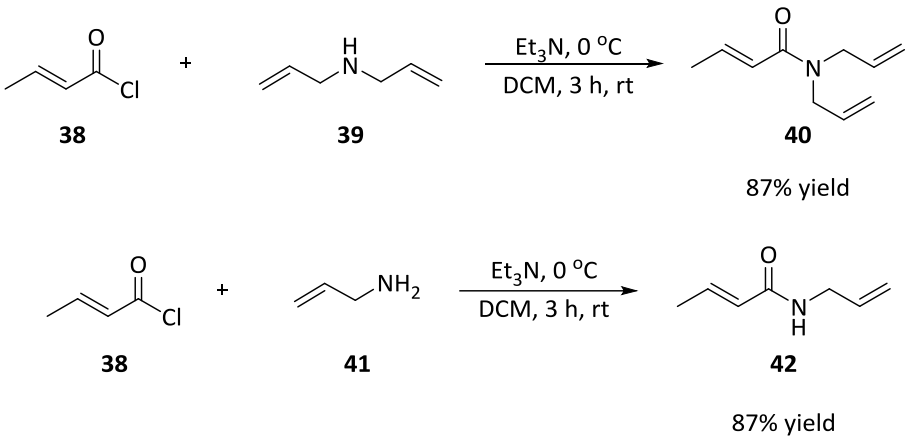
To start, the reaction of the diesters done by the mentioned group was reproduced. Therefore, the synthesis of the starting material diallyl fumarate was carried out by the use of fumaroyl chloride and allyl alcohol in the presence of a base. The reaction gave the desired product **36** in a good yield (66%). Then, the developed methodology was apply to perform the conjugate addition of diethyl zinc in the presence of a LA at low temperature. After the addition, the reaction was warmed up to reflux to favor the [3,3]-sigmatropic rearrangement. Product **37** was obtained in low yield together with other side products (Scheme 26). Nevertheless, it was demonstrated that the rearrangement was possible.



Scheme 26. Synthesis of Diallyl Fumarate and Tandem Reaction.

Once we saw the tandem reaction was proceeding, we started working with the desired carbonyl derivatives. As it was mentioned in the introduction, amides were the first substrate to be tested, not only because they are one of the most interesting products for the pharmaceutical industry, but also because in case the tandem reaction works for these substrates (the least reactive carbonyl derivatives), we envisioned that it was going to work with the rest of the carbonyl derivatives such as esters, or thioesters.

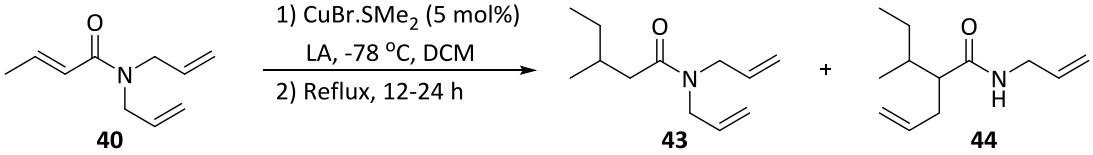
Consequently, different amide substrates were synthesized with the necessary allyl moiety for the [3,3]-sigmatropic rearrangement. Diallyl amide **40** and allyl amide **42** were synthesized in a high yield, (87%), according to a literature procedure[3] used in our research group for the synthesis of the substrates for the highly enantioselective copper-catalyzed ACA (Scheme 27).



Scheme 27. Synthesis of Allyl Amides.

Highly enantioselective copper-catalyzed Grignard Addition to amide substrates has been already described in our research group,[3] so in the first attempts, the reaction conditions developed by them were applied. Nevertheless, the first objective of our work was to check whether the rearrangement was achievable; therefore, the addition was not performed in an asymmetric fashion due to the big cost of the chiral catalysts used (Table 5).

Table 5. Screening of Reaction Conditions for the Tandem Reaction.[a]



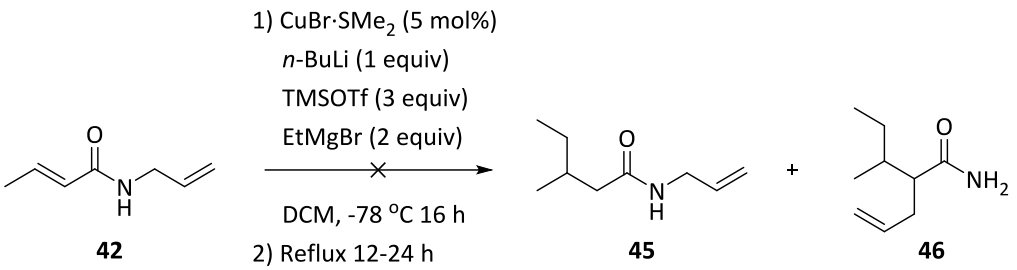
Entry	LA (equiv)	Organometallic reagent (equiv)	Conv. (%)[b] to 43	Conv. (%)[b] to 44
1[c]	$BF_3{\cdot}Et_2O$ (2)	EtMgBr (2)	0	-
2	TMSOTf (1)	EtMgBr (1)	100	0
3	TMSCl (1.5)	Et_2Zn (2)	0	-
4	TMSOTf (1.5)	Et_2Zn (2)	0	-
5[d]	TMSOTf (2)	Et_2Zn (2)	0	-

[a] Reaction carried out by using 0.5 mmol substrate, 5 mL DCM; [b] Determined by ^{1}H-NMR spectroscopy; [c] Reaction performed for 5 hours; [d] Reaction performed at rt for 2h.

When $BF_3{\cdot}Et_2O$ was used, no conversion was observed, likely because the reaction was not let for sufficient time (Table 5, entry 1). In contrast, when TMSOTf was used full conversion to the addition product **43** was observed, but no rearrangement product **44** was visible (Table 5, entry 2). The obtained product was not the desired one, because the representative two protons α to the carbonyl group were still visible in the ^{1}H-NMR. In addition, the addition product is described in literature and the ^{1}H-NMR was comparable.

Taking into account the obtained results, a silyl enolate was necessary for the rearrangement to proceed. When Grignard reagents were added, the magnesium enolate was present, which was not reactive enough for the rearrangement. Therefore, we decided to use the conditions described in the paper of allyl fumarates. Meaning, addition of diethylzinc reagents was going to be done (Table 5, entries 3-6). Unfortunately, after different tries, starting from a weak LA (TMSCl) to a stronger one (TMSOTf), or even performing the reaction at room temperature not even the addition product **43** was observed in any case.

Therefore, it was decided to switch to the next more reactive substrate due to the fact that it was not possible to favor the rearrangement. Consequently, the reaction was tried with amide **42**. Nevertheless, some groupmates tried to optimize the reaction conditions for the addition in this substrate, and using those conditions, only a low conversion to the addition product **45** could be observed, but not the desired rearrangement product **46** (Scheme 28).



42 **45** **46**

Scheme 28. Conjugated Addition followed by [3,3]-Sigmatropic Rearrangement.

In the view of the results, we could conclude that amides were not reactive enough for the [3,3]-sigmatropic rearrangement. However, a last hope was put into diamide substrate. As in the publication by Johnson et al. authors were using diesters, more reactive moieties than esters, perhaps this was also applicable to diamides. Consequently, by the use of fumaroyl chloride and diallylamine in the presence of a base, product **47** was afforded in 41% yield (Scheme 29).

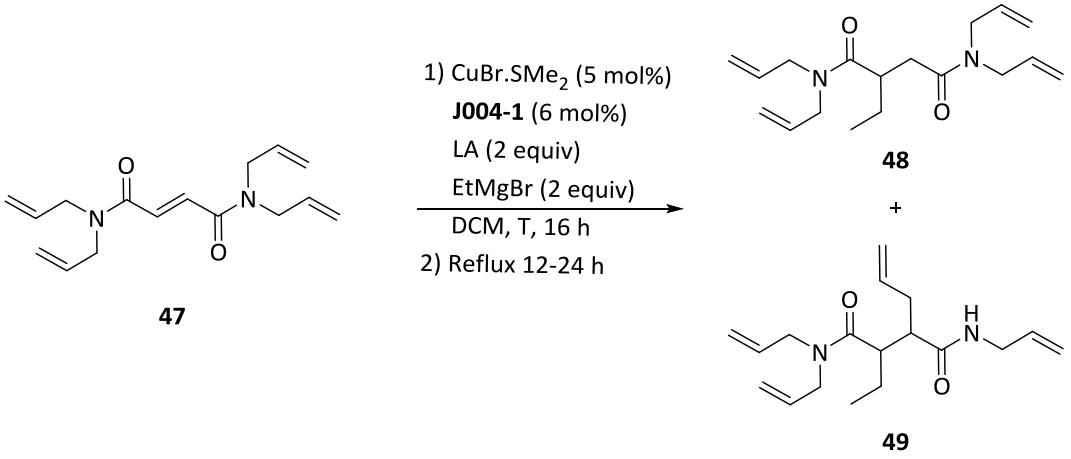
34 **39** **47**

41% yield

Scheme 29. Synthesis of Diamide Substrate.

With the substrate in hand some tests were performed. The copper-catalyzed asymmetric conjugate addition has not been performed to these kind of diamides before. Therefore, two different Lewis Acids were used, together with the optimized conditions for the addition of amides (Table 6).

Table 6. Copper-Catalyzed ACA to Diamide Substrate Followed by [3,3]-Sigmatropic Rearrangement.[a]



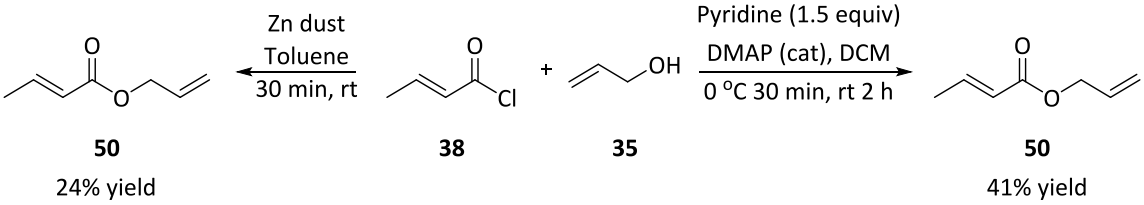
47 **48** + **49**

Entry	LA	T (°C)	Conv. (%)[b] to 48	Conv. (%)[b] to 49
1	TMSOTf	rt	60	0
2	$BF_3{\cdot}Et_2O$	-78	80	0

[a] Reaction was carried out by using 0.4 mmol substrate, 4 mL DCM;
[b] Determined by ^{1}H-NMR spectroscopy.

Depending on the LA different conversions were observed, but in both cases, the addition product **48** was obtained. In order to confirm that the rearrangement product **49** was not obtained, 2D NMR studies were carried out. By Heteronuclear Single Quantum Coherence (HSQC) analysis, it was confirmed that two protons were present in the position adjacent to the carbon where the 1,4-addition have happened, meaning that the allylic moiety have remained at the nitrogen (See Appendix, compound **48**).

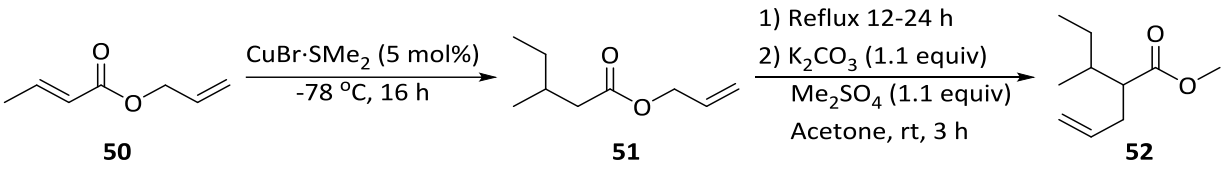
After the failed attempts to achieve the rearrangement product in the amides, we decided to move on to the next more reactive carbonyl derivatives, the esters. Allylic ester **50** was synthesized by two different methodologies (Scheme 30), obtaining respectively 24% and 41% yield. In both cases, the yields were low, because the product was so volatile and part of it was lost during the evaporation of the solvent.



Scheme 30. Different Methodologies for the Synthesis of Allyl Ester.

Taking into account the results obtained before, in order to ensure to have the silyl enolate for the rearrangement the CA was first carried out by the use of diethyl zinc reagent (Table 7).

Table 7. Copper-catalyzed ACA to Ester Substrate Followed by [3,3]-sigmatropic Rearrangement.[a]

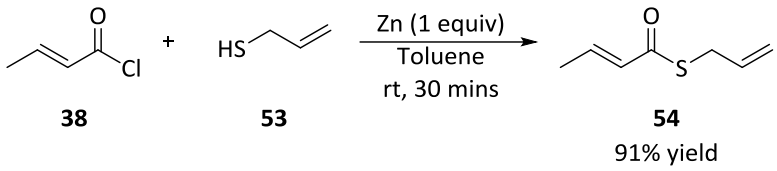


Entry	LA (equiv)	Organometallic reagent (equiv)	Solvent	Conv. (%)[b] to 51	Conv. (%)[b] to 52
1[c]	TMSCl (1.5)	Et_2Zn (2)	DCM	0	-
2[c]	TMSBr (1.5)	Et_2Zn (1.2)	DCM	100	-
3[c,d]	TMSOTf (2)	Et_2Zn (2)	DCM	0	-
4	TMSOTf (2)	Et_2Zn (2)	Et_2O	100	0
5	TMSOTf (2)	EtMgBr (2)	Et_2O	100	0

[a] Reaction carried out by using 0.5 mmol substrate, 5 mL Solvent; [b] Determined by ^{1}H-NMR spectroscopy; [c] Only addition was performed; [d] Reaction performed at rt for 2 hours.

In the first three attempts (Table 7, entries 1-3) only the addition reaction was performed promoted by different LA. The first reaction showed no conversion to the desired addition product **51** (Table 7, entry 1); as a result, more reactive LAs were tried. When using TMSBr (Table 7, entry 2) full conversion was obtained, and after purification and GC-MS analysis, it was confirmed that the addition had happened, however, the reaction was not properly quenched due to the presence of the silyl enolate in the remaining product. Nevertheless, this result was promising, because it was possible to confirm the presence of the necessary silyl enolate for the rearrangement to proceed. Then, a more reactive LA was used to prove whether the addition could occur at room temperature for shorter time (Table 7, entry 3), but unfortunately, no conversion was achieved. Two more attempts were tried using different organometallic reagents in the presence of TMSOTf (Table 7, entries 4-5). Even though full conversion was observed, after the purification in any case was possible to isolate the desired fractions of product **52**, due to the volatility of the compound.

Simultaneously, other substrate was also synthesized, consisting on a α,β-unsaturated thioester.[34] By taking advantage of the activated Zinc dust, which reacted with the chloride of the acyl chloride enhancing the electrophilicity of the carbonyl compound, allylthiol performed the nucleophilic attack affording α,β-unsaturated thioester **54** in a high yield (91%) (Scheme 31).

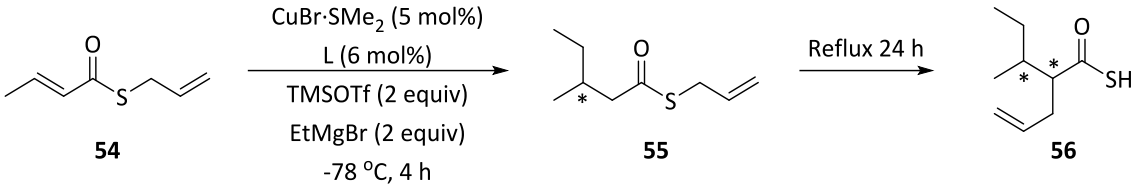


38 **53** **54**
91% yield

Scheme 31. Synthesis of α,β-Unsaturated Thioester Substrate

The copper-catalyzed ACA of Grignard addition has already been described for α,β-unsaturated thioesters,[35] however, not exactly with the allylic moiety at the sulfur. It could be possible to extrapolate the methodology used for a broad scope of thioester substrates to product **54**. Therefore, some preliminary tests were performed (Table 8).

Table 8. Copper-catalyzed ACA to α,β-Unsaturated Thioester Followed by [3,3]-Sigmatropic Rearrangement.[a]



54 **55** **56**

Entry	Ligand	Solvent	Conv. (%)[b] to 55	ee (%)[c]	Conv. (%)[b,d] to 56
1[e,f]	-	Et_2O	0	-	-
2[f]	-	Et_2O	100	racemic	-
3	J001-1	MTBE	100	40%	-
4	J001-4	MTBE	100	60%	-
5[g]	-	MTBE	100	-	100 (dr 1:1)

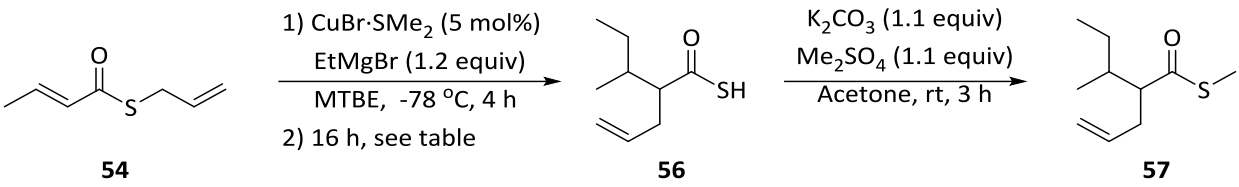
[a] Reaction carried out by using 0.8 mmol, 8 mL Solvent; [b] Determined by ^{1}H-NMR spectroscopy; [c] Determined by chiral HPLC; [d] Determined by GC-MS; [e] 2 equivalents of Et_2Zn used as the nucleophile; [f] Reaction left for 16 hours; [g] Rearrangement tried.

First of all, the optimization of the addition reaction was performed (Table 8, entries 1-4) using different reaction conditions. By using slightly same conditions as the ones described in the malonate's publication, no conversion was observed (Table 8, entry 1). Grignard reagents have been added to thioesters but not exactly to the one with the allylic moiety; therefore, we first performed the addition without a chiral catalyst, getting the racemic product **55**.(Table 8, entry 2). Although the yield was quite low due to the volatility of the product, it was possible to fully characterize it. Then, in order to check the enantioselectivity of the addition, two different ligands were tried, obtaining respectively 40% and 60% ee (Table 8, entries 3-4). Finally, one preliminary test was done to determine whether the rearrangement product could be achieved (Table 8, entry 5). After the purification process the desired rearrangement product **56** was isolated. However, the product was lost during the characterization process due to the terminal SH, but it could be observed by GC-MS analysis that the diastereomeric ratio (dr) was around 1:1. This last result had to be further confirmed. Usually based on the mechanism of [3,3]-sigmatropic rearrangements, one major diastereomer should be obtained, due to the stereospecificity of these reactions. This fact, lead us to think that the rearrangement could proceed via radical mechanism, because it is known that the selectivity in radical reactions is very difficult to control.

On the other hand, the enantioselectivities achieved in the addition step were not comparable to the ones observed in the original publication. After checking the procedure, it was recognized that in case of thioester substrates the use of LA was not necessary, and that the addition order of the reactants was also different. α,β-Unsaturated thioesters were sufficiently reactive for the 1,4-conjugated addition and after the transmetallation of the copper-salt with the Grignard in a chiral environment, by adding the substrate dropwise, up to 99% of enantioselectivity could be accomplished.

Taking into account the previously discussed facts, to analyze whether the mechanism of the reaction followed a radical mechanism, three more experiments were performed (Table 9). The methylation step was done to ease the purification.

Table 9. Screening of Conditions for the Rearrangement Step.[a]



54 **56** **57**

Entry	Conv. (%)[b] to 56	Rearrangement conditions	Rearrangement[b]
1	100	No *hv*, reflux	Yes
2	100	No *hv*, rt	Yes
3	100	Reflux, TEMPO (1 equiv)	Yes

[a] 0.7 mmol, 7 mL MTBE; [b] Determined by ^{1}H-NMR spectroscopy.

The addition was performed as described in literature[35] with the exception of the use of a chiral ligand. The aim was to test whether the rearrangement could proceed, so the diastereoselectivity was not important for the moment. In the first attempt, the reaction was heated up to reflux, but the Schlenk was covered from the light (Table 9, entry 1). After the methylation of the crude product **56**, the desired methylated product **57** was obtained. When the reaction was left overnight at room temperature, also covered from the light, the rearrangement product was observed as well (Table 9, entry 2).

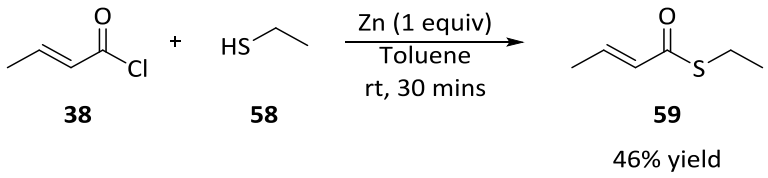
Finally, in the last attempt to check whether the reaction proceeded via radical mechanism, in order to catch the radical specie and stop the reaction, a radical scavenger was added ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl, (TEMPO)). For our surprise, the reaction proceeded anyway, affording product **57** after the methylation.

In order to determine the diastereomeric ratio of the product, the reaction was performed once more by using the chiral ligand J004-1 and letting the reaction stirring overnight. Product **57** was fully characterized by different NMR analysis HSQC, Correlation Spectroscopy (COSY), NOESY and Heteronuclear Multiple Bond Correlation (HMBC) (See Appendix, compound **57**) and the diastereomeric ratio was 1:0.65 determined by ^{1}H-NMR and confirmed by ^{13}C-NMR analysis.

From one hand, when a reaction is stopped in presence of a radical scavenger means that the reaction proceeds via radical mechanism. However, when it does not stop it does not necessarily mean that it is not via radical mechanism. Perhaps the reaction is too fast, and the radical scavenger cannot catch the radical before the rearrangement occurs. Further experiments should be done to confirm this theory but due to the lack of time, it was not possible to develop a new methodology to prove it.

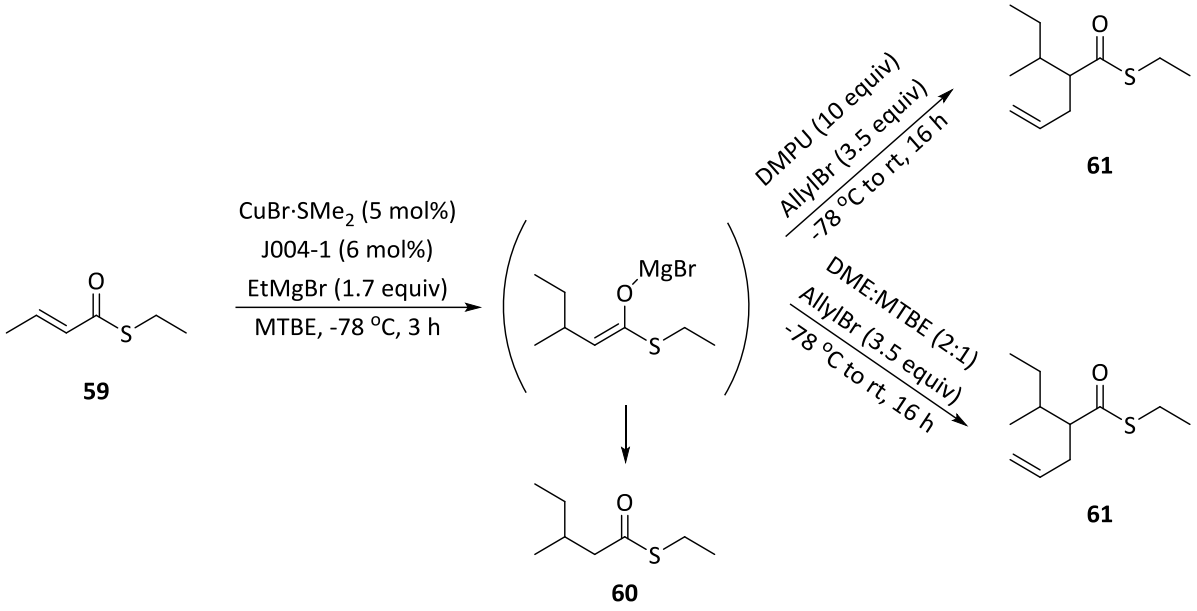
Few more experiments to broad the scope of temperature in the rearrangement step were performed. After the addition, the reaction was left stirring for 16 h at -50, -20 and 0 ^{o}C and in any case the rearrangement product **57** could be observed. At least room temperature was necessary for the rearrangement to proceed.

In the introduction, is stated that sigmatropic rearrangements have advantages for the functionalization of carbonyl derivatives respectively at α and β positions, over methods for further functionalization of enolates by trapping them with an electrophile. In order to compare the diastereomeric ratio that could be achieved by both methods, a new substrate (**59**) was synthesized following the same procedure as before for the synthesis of α,β-unsaturated thioester (Scheme 32).



Scheme 32. Synthesis of α,β-Unsaturated Thioester.

Authors have described methodologies for enolate trapping of cyclic and acyclic ketones in the literature.[20] In order to enhance the nucleophility of the magnesium enolate for the trapping with an electrophile different additives should be added to the enolate. DMPU and co-solvent DME have been reported to give successful diastereomeric ratios for the trapping of the mentioned substrates. Therefore, the previously mentioned conditions were employed (Scheme 33).



Scheme 33. Different Additives to Get the Enolate Trapping Product **61**.

More conversion to the trapping product **61** was achieved by the use of DMPU, which is known to be a reactant that enhances the nucleophilicity of the enolate. Even though it was not possible to separate the addition (**60**) from the trapping product, it was proven by ^{1}H-NMR and ^{13}C-NMR analysis that both products were synthesized in a 1:4 ratio (**60**:**61**) (See Appendix, compound **60**, **61**). The diastereomeric ratio for the trapping product was also determined to be 1:0.66. On the other hand, when DME was used the ratio between addition and trapping product was 1.5:1 (**60**:**61**).

According to the obtained results, the diastereomeric ratios were comparable, so the [3,3]-sigmatropic rearrangement did not improve the diastereoselectivity of the reaction as it was expected. Presumably because the reaction for the α,β-unsaturated thioester proceeded via radical mechanism, but further experiments should be done to confirm this theory.

4. CONCLUSION

In the first part of the project, the synthesis of β,β-disusbtituted alkenyl heteroaromatic compounds was performed to study subsequently the copper-catalyzed asymmetric conjugate addition of Grignard reagents to form all-carbon quaternary stereocenters. For the synthesis of the substrates, three steps were necessary, but it in overall, the desired compounds were synthesized in moderate to good yields depending on the heteroaromatic compound. However, the copper-catalyzed ACA of Grignard reagents to such substrates could not be performed at the targeted position due to the big steric hindrance. Therefore, in order to achieve the desired enantiorich all-carbon quaternary stereocenters, new methodologies should be developed.

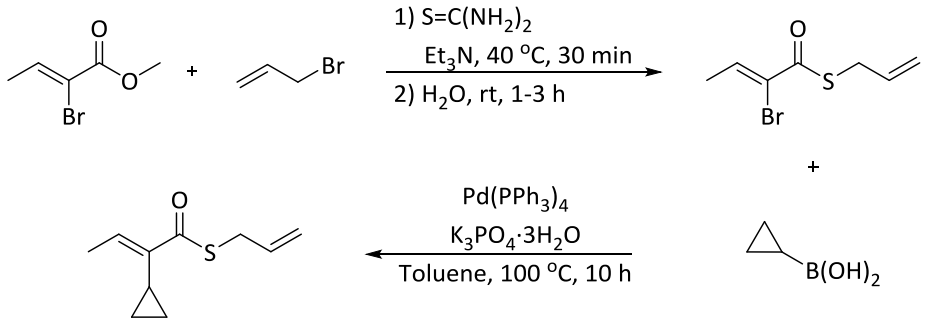
In the second part of the project, different carbonyl derivatives were synthesized to prove the efficiency of [3,3]-sigmatropic rearrangements over the common enolate trapping methodologies. Pericyclic reactions are known to be diastereoselective because they proceed via concerted mechanism. Thus, after performing the copper-catalyzed ACA, taking advantage of the formed enolate, by placing an allyl group that will form a 1,5-diene system the rearrangement could occur, giving as a result two adjacent stereogenic centers at α- and β-positions. α,β-Unsaturated amides, diamides and esters were not sufficiently reactive to give the rearrangement product. Nevertheless, thioesters proved to be reactive towards the tandem reaction, even though it did not proceed in a diastereoselective fashion. This fact lead us to contemplate the possibility that the rearrangement was happening via a radical mechanism. To conclude, in order to prove this theory, some tests were performed, such as adding a radical scavengers or avoiding the light, but the rearrangement was still proceeding. Perhaps due to the fact that proceeded too fast that the radical scavenger could not catch it. Therefore, it is not completely proven and further experiments should be performed.

5. PROSPECTIVE

Even though some test were made to prove the radical mechanism, it was not still clear whether the Cope Rearrangement was proceeding via concerted mechanism or radical mechanism, due to the lack of diastereoselectivity of the process. The concerted reactions are usually diastereoselective in contrast to radical reactions. Therefore, in order to study the mechanism, making use of radical clocks could be an interesting strategy.[36]

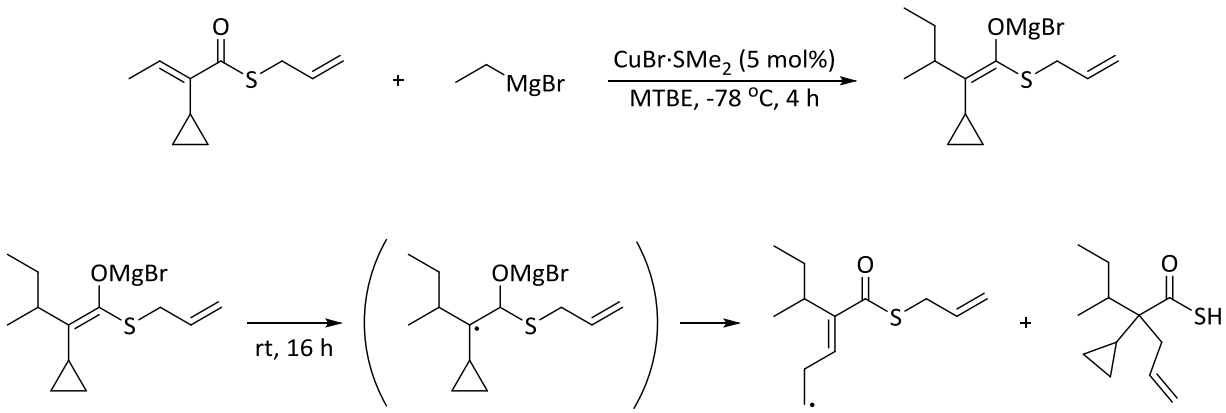
Radical clocks are unimolecular radical reactions that are kinetically calibrated and can be applied in a competition study to 'time' a particular radical reaction. They are also use for synthetic applications because most radical-based methods involve chain reactions that commonly have several competing reaction steps. In our case, radical clocks are going to be used to prove whether the rearrangement is proceeding via radical mechanism. In case this is happening, more than one product are going to be synthesized due to the presence of other radical in the media.

First of all, a synthesis pathway should be developed to synthesize the desired α-substituted α,β-unsaturated thioester. For that, the following route will be followed (Scheme 34).[37] By the use of the methyl crotonate derivative and urea, in presence of allyl bromide, the desired thioester will be formed. Then by using the borane reagent, the required starting material will be synthesized.



Scheme 34. Synthesis of α-Substituted α,β-Unsaturated Thioester.

After the conjugated addition, when the enolate is formed and the rearrangement has happened, in case there is a radical in the system, which could compete with the formation of the product, not only one product would be formed, but also a side product (Scheme 35). One of the fastest radical clocks is the cyclopropyl radical, which will immediately open to give the alkyl chain. Therefore, by the use of this methodology, it could be possible to prove whether the reaction proceeds via radical mechanism due to the formation of two different products.



Scheme 35. Synthesis of Possible Side Products via Radical Mechanism.

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8. APPENDIX

8.1 GENERAL INFORMATION

All reactions using oxygen- and/or moisture-sensitive materials were carried out with anhydrous solvents (vide infra) under a nitrogen atmosphere using oven-dried glassware and standard Schlenk techniques. Reactions were monitored by ^{1}H NMR and GC-MS. Purification of the products was performed by column chromatography using Merck 60 Å 230-400 mesh silica gel. Components were visualized by UV, I_2 and KMnO4 staining. NMR data was collected on Varian VXR400 (^{1}H at 400.0 MHz or 600.0 MHZ; ^{13}C at 100.58 MHz or 151 MHz) equipped with a 5 mm z-gradient broadband probe. Chemical shifts are reported in parts per million (ppm) relative to residual solvent peak (CDCl3, ^{1}H: 7.26 ppm; ^{13}C: 77.16 ppm; D_2O, ^{1}H: 4.79 ppm). Coupling constants are reported in Hertz. Multiplicity is reported with the usual abbreviations (s: singlet, br s: broad singlet, d: doublet, dd: doublet of doublets, t: triplet, tdt: triplet doublet of triplets, tqt: triplet quartet of triplets, ttq: triplet triplet of quartets, q: quartet, m: multiplet, if an apparent multiplicity is observed the actual multiplicity will be noted in brackets). Variable-temperature NMR spectra were acquired on a Bruker Avance III spectrometer paired with an Ascend 400 MHz magnet and BBFO dual-resonance probe. All temperatures were calibrated prior to acquisition with an external pure MeOH reference. Exact mass spectra were recorded on a LTQ Orbitrap XL apparatus with ESI ionization. Enantiomeric excess (ee) were determined by chiral HPLC analysis using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector.

8.2 CHEMICALS

Unless otherwise indicated, reagents and substrates were purchased from commercial sources and used as received. Solvents not required to be dry were purchased as technical grade and used as received. Dry solvents were freshly collected from a dry solvent purification system prior to use. Inert atmosphere experiments were performed with standard Schlenk techniques with dried (P_2O_5) nitrogen gas. Grignard reagents were purchased from Sigma-Aldrich (EtMgBr, MeMgBr, PhMgBr (3.0 M in Et_2O), HexMgBr, (2.0 M in Et_2O) AllylMgBr (1.0 M in Et_2O)). All other All Grignard reagents were titrated by NMR before use. Chiral ligands were purchased from Sigma Aldrich and Solvias. All reported compounds were characterized by ^{1}H and ^{13}C NMR and compared with literature data. All new compounds were fully characterized by ^{1}H and ^{13}C NMR and HRMS techniques.

8.3 GENERAL PROCEDURES

8.3.1 SYNTHESIS OF β,β-DISUBSTITUTED ALKENYL-HETEROAROMATIC COMPOUNDS

General procedure for the Grignard addition to alkynes (A)

To a solution of CuI (7 mol%) in THF at room temperature, EtMgBr (3.0 equiv) was added. The resulting dark brown solution was stirred for 10 min. After that, a solution of the corresponding substrate (1.0 equiv) in THF was added. The mixture was then refluxed at 70 ^{o}C overnight. After cooling to room temperature, the reaction was quenched carefully with 2M HCl and saturated Na_2CO_3 (pH basic) solution was added carefully. The mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatrography on silica gel to afford the corresponding β,β-disubstituted alkenyl heteroatom.

General procedure for the protection of the alcohol (B)

To a solution of the corresponding substrate (1.0 equiv) and imidazole (2.5 equiv) in DMF at room temperature, TBSCl (1.3 equiv) was added in one portion. The mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to afford the corresponding product.

General procedure for the synthesis of vinyl iodides (C)[38]

To a magnetically stirred solution of zirconocene dichloride (1 mmol, 0.2 equiv) in DCM (25 mL) at -20 °C trimethylaluminium (2M in hexane, 15 mmol, 3.0 equiv) was added dropwise. After 10 min, water (7.5 mmol, 1.5 equiv) was added dropwise. Caution: Exothermic reaction! After an additional 10 min, 3-butyn-1-ol (5 mmol, 1.0 equiv) (pretreated with trimethyl aluminium (2M in hexane, 1.5 mmol, 0.3 equiv) in DCM (5 mL) at 0 °C) was added slowly. The reaction mixture was allowed to warm to room temperature and was stirred for 2.5 h. The mixture was then cooled to -20 °C and I_2 (6 mmol, 1.2 equiv) in ether (7.5 mL) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction was quenched by the careful addition of water. The resulting biphasic mixture was filtered through Celite, washed with $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (20% ether-hexanes) to afford vinyl iodide.

8.3.2 COPPER-CATALYZED ACA OF GRIGNARD REAGENTS TO β,β-DISUBSTITUTED ALKENYL HETEROAROMATIC COMPOUNDS

General procedure for the optimization of copper-catalyzed ACA (D)

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, $CuBr{\cdot}SMe_2$ and ligand were dissolved in the solvent (1 mL/0.1 mmol substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (1.0 equiv) was added at once. After stirring for 5 min at room temperature the reaction mixture was cooled to - 78 °C and the LA (TMSOTf or BF_3 Et_2O) was added followed by RMgBr. After stirring at the right temperature and time, the reaction was quenched with MeOH (1 mL) followed by saturated aqueous solution of NH_4Cl and warmed to room temperature. The reaction mixture was extracted with DCM (3 × 10 mL). Combined organic phases were dried over $MgSO_4$, filtered and solvents were evaporated on rotary evaporator. The oily crude was purified by flash column chromatography on silica using mixture of pentane and EtOAc as eluent.

8.3.3 SYNTHESIS OF CARBONYL DERIVATIVE STARTING MATERIALS

General procedure for the synthesis of amide/diamide substrates (E)[39]

To a cold 0 °C solution of the corresponding acyl chloride (5.0 mmol) in DCM (4 mL) was added the corresponding amine (8.0 mmol). Dry triethylamine (6.6 mmol) was added and stirring was continued at ambient temperature for 3 h. The solvent was removed under reduced pressure and DCM (14 mL) was added. The organic phase was washed with dilute hydrochloric acid (2.0 M, 2 mL × 2), water (3 mL × 2), and brine (4 mL), dried over $MgSO_4$ and filtered. After removal of the solvent, the corresponding amides were obtained.

General procedure for the synthesis of thioester substrates (F)[40]

To a solution of crotonoyl chloride (1.0 equiv) in toluene (2 mL/1 mmol substrate), activated zinc dust (1.0 equiv) was added and the suspension was stirred for 10 min. Then the toluene solution of the thiol (1.0 equiv, 2 mL/1 mmol substrate) was added and stirring continued for 30 min. After completion of the reaction, the mixture was filtered and the solid washed with ether. Combined organic layers were washed with $NaHCO_3$ solution, water, dried over $MgSO_4$ and filtered. Evaporation of the solvent gives thioester in good yield and high purity.

8.3.4 COPPER-CATALYZED ACA TO α,β-UNSATURATED CARBONYL DERIVATIVES FOLLOWED BY [3,3]-SIGMATROPIC REARRANGEMENT

General procedure for the optimization of the Tandem reaction of amides/esters/thioesters (ACA + [3,3]-sigmatropic rearrangement) (G)

A flame-dried round-bottomed flask equipped with a stirring bar was charged with amide substrate (1.0 equiv) and copper catalyst (5 mol%). The flask was sealed with a septum and purged with nitrogen. DCM was added and cooled to -78 ^{o}C. After 15 min, LA (1.0-2.0 equiv) was added, followed by the addition of the organometallic reagent (1.0-2.0 equiv). This was stirred at the same temperature overnight and warmed to 23 ^{o}C. A reflux condenser was attached and the reaction was heated at reflux for 12-24 h. The reaction was cooled and quenched with 5 mL of 1M HCl. The aqueous layer was extracted with DCM. The organic extracts were combined and washed once with brine, dried over $MgSO_4$, filtered and the solvent was removed with a rotary evaporator. The reaction mixture was filtered through silica eluting with acetone and the solvent was removed in the rotavap. The product was purified by flash column chromatography 10% EtOAc/hexane.

General procedure for the optimization of the Tandem reaction of diamides (ACA + [3,3]-sigmatropic rearrangement) (H)

In a flame-dried Schlenk tube equipped with septum and magnetic stirring bar, copper catalyst (5 mol%) and chiral ligand (6 mol%) were dissolved in DCM and stirred under nitrogen atmosphere for 20 min. The diamide substrate was added at once. After stirring for 5 min at room temperature the reaction was cooled down to -78 ^{o}C, followed by addition of LA (TMSOTf or $BF_3{\cdot}Et_2O$ 2.0 equiv). After 20 min EtMgBr (2.0 equiv) was added by hand in about 1 min. After stirring for 18 h, a reflux condenser was attached to the reaction and was kept under reflux for 24 h. After that, the reaction was quenched with MeOH followed by addition of saturated aqueous NH_4Cl solution. The reaction mixture was extracted with DCM (10 mL x 3). Combined organic phases were dried over $MgSO_4$, filtered and solvents were evaporated on a rotary evaporator. The crude was purified by flash column chromatography on silica gel 50% Et_2O/hexane.

General procedure for the optimization of addition reaction of thioesters (ACA) (I)

A flame-dried round-bottomed flask equipped with a stirring bar was charged with copper catalyst (5 mol%) and ligand (6 mol%) in MTBE were stirred at room temperature for 15 min. After that, the substrate was added at once (1.0 equiv) and stirred for additional 10 min. The mixture was cooled to -78 ^{o}C. After 15 min, LA (1.0-2.0 equiv) was added, followed by the addition of the organometallic reagent (1.0-2.0 equiv). This was stirred at the same temperature for 4 h. The reaction was quenched with 5 mL of 1M HCl. The aqueous layer was extracted with DCM. The organic extracts were combined and washed once with brine, dried over $MgSO_4$, filtered and the solvent was removed with a rotary evaporator. The reaction mixture was filtered through silica eluting with acetone and the solvent was removed in the rotavap. The product was purified by flash column chromatography 10% EtOAc/hexane.

General procedure for the optimization of Tandem reaction of thioesters (ACA) + [3,3]-sigmatropic rearrangement (J)

A flame-dried round-bottomed flask equipped with a stirring bar was charged with copper catalyst (5 mol%) and ligand (6 mol%) in MTBE and the mixture was stirred at room temperature for 15 min. After that, the substrate was added at once (1.0 equiv) and stirred for additional 10 min. The mixture was cooled to -78 ^{o}C. After 15 min, LA (1.0-2.0 equiv) was added, followed by the addition of the organometallic reagent (1.0-2.0 equiv). This was stirred at the same temperature for 4 h and warmed to 23 ^{o}C. A reflux condenser was attached and the reaction was heated at reflux for 12-24 h. The reaction was let to cool down and it was quenched with 5 mL of 1M HCl. The aqueous layer was extracted with DCM. The organic extracts were combined and washed once with brine, dried over $MgSO_4$, filtered and the solvent was removed with a rotary evaporator. The reaction mixture was filtered through silica eluting with acetone and the solvent was removed in the rotavap. The product was purified by flash column chromatography 100% hexane.

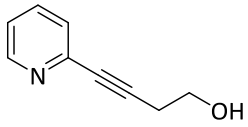
Optimized procedure for the Tandem reaction of thioesters (ACA + [3,3]-sigmatropic rearrangement (K)

$CuBr{\cdot}SMe_2$ (0.04 mmol, 5 mol%) and ligand (0.04 mmol, 6 mol%) were dissolved in MTBE (6.3 mL) and stirred at room temperature for 30 min under nitrogen. The mixture was cooled to -78 ^{o}C and EtMgBr (0.84 mmol, 1.2 equiv) was added dropwise. After stirring for 10 min, a solution of thioester substrate (0.7 mmol, 1.0 equiv) in MTBE (0.7 mL) was added via a syringe pump over 2 h. The reaction mixture was stirred at -78 ^{o}C for 4 h, then the reaction was let at room temperature and stirred overnight. After the time, the reaction was quenched with MeOH and HCl was added. The aqueous phase was extracted with Et_2O, dry it over $MgSO_4$, filtrate it and remove the solvent in the rotary evaporator. The crude product mixture was dissolved in acetone in a round-bottomed flask and Me_2SO_4 (1.76 mmol, 1.1 equiv) and K_2CO_3 (1.93 mmol, 1.1.equiv) were added. The reaction was stirred open to the atmosphere for 3 h. The reaction mixture was filtered through silica eluting with acetone and the solvent was removed in the rotavap. The product was purified by column chromatography 100% hexane.

8.4 CHARACTERIZATION DATA

4-(Pyridin-2-yl)but-3-yn-1-ol (3)

Compound **3** was synthesized according to a literature procedure:[41]



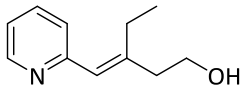
A solution of bromopyridine (5 mmol, 1.0 equiv), 3-butyn-1-ol (6 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (3 mol%), CuI (6 mol%) in dry Et_3N (5 mL) was stirred at room temperature for 2 h. Silica gel was added, and the resulting mixture was evaporated and separated by flash chromatography (SiO_2, hexane/EtOAc = 1/2), providing compound **4** (71% yield) as an oil.

^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.52 (dd, *J* = 5.1, 1.8 Hz, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.19 (ddd, *J* = 7.6, 4.9, 1.3 Hz, 1H), 3.86 (q, *J* = 6.4 Hz, 2H), 3.28 (s, 1H, OH), 2.72 (t, *J* = 6.4 Hz, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 149.8, 143.6, 134.6, 127.1, 122.9, 88.7, 81.7, 60.9, 24.1.

(*E*)-3-(Pyridin-2-ylmethylene)pentan-1-ol (4)

Compound **4** was synthesized according to **general procedure A**. Light yellow oil, 46% yield.



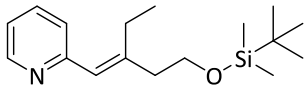
^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.56 (s, 1H), 7.62 (td, *J* = 7.7, 1.7 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 6.2, 1H), 6.36 (s, 1H), 3.82 (t, *J* = 6.5 Hz, 2H), 2.53 (q, *J* = 7.5 Hz, 2H), 2.48 (t, *J* = 6.5 Hz, 2H), 2.34 (s, 1H, OH), 1.09 (td, *J* = 7.5, 1.0 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 157.1, 149.4, 146.3, 136.4, 126.7, 124.0, 121.3, 61.1, 40.8, 24.4, 13.2.

HRMS (ESI$^+$): m/z calcd. for $C_{11}H_{15}NO$ ([M+H$^+$]) 177.1154, found: 178.1211.

(*E*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)-2-ethylbut-1-en-1-yl)pyridine (6)

Compound **6** was synthesized according to a **general procedure B**. Colorless oil, 97% yield.



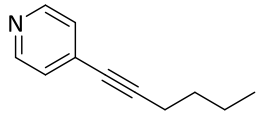
^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.55 (d, *J* = 4.2 Hz, 1H), 7.58 (td, *J* = 7.7, 1.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.04 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 6.29 (s, 1H), 3.80 (t, *J* = 7.3 Hz, 2H), 2.52 (q, *J* = 7.5 Hz, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 157.3, 149.4, 136.2, 126.1, 123.8, 121.0, 62.9, 41.0, 26.3, 26.0, 24.9, 18.6, 13.1, -5.0.

HRMS (ESI^{+}): m/z calcd. for $C_{17}H_{29}NOSi$ ([M+H^{+}]) 292.20912, found: 292.20953.

4-(Hex-1-yn-1-yl)pyridine (9)

Compound **9** was synthesized according to a literature procedure:[42]

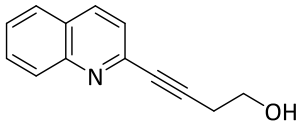


To a stirred suspension of 4-bromopyridine (2 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), and CuI (10 mol%) in Et_3N (14 mL) 1-hexyne (2.4 mmol, 1.2 equiv) was added dropwise at room temperature, and stirring was continued for 5 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel with hexane/Et_2O (75/25) as eluent to give **9** (28% yield) as a colorless oil.

^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.50 (d, *J* = 4.7 Hz, 2H), 7.24–7.17 (m, 2H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.64–1.51 (m, 2H), 1.51–1.36 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

4-(Quinolin-2-yl)but-3-yn-1-ol (13)

Compound **13** was synthesized according to a literature procedure:[43]



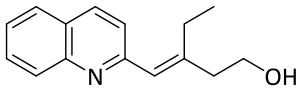
A mixture of 2-chloroquinoline (18 mmol, 1.0 equiv), Pd/C (10 mol%), PPh_3 (5 mol%), CuI (5 mol%), and triethylamine (54 mmol, 3.0 equiv) in water (100 mL) was stirred at 25-30 °C for 30 min under nitrogen. 3-Butyn-1-ol (27 mmol, 1.5 equiv) was added, and the mixture was initially stirred at room temperature for 1 h and then at 80 °C for 10 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc (200 mL), and filtered through Celite. The organic layers were collected, washed with water, dried over anhydrous $MgSO_4$, and concentrated under vacuo. The crude residue was purified by precipitation (EtOAc-hexane), obtaining product **13** (95% yield) as a pink solid.

^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.11–8.01 (m, 2H), 7.77 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 3.93 (t, *J* = 6.5 Hz, 2H), 3.24 (s, 1H, OH), 2.79 (t, *J* = 6.4 Hz, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 150.5, 146.2, 138.9, 132.7, 131.6, 130.1, 129.7, 129.7, 126.8, 91.3, 85.1, 63.4, 26.6.

(*E*)-3-(Quinolin-2-ylmethylene)pentan-1-ol (14)

Compound **14** was synthesized according to **general procedure A**. Yellow oil, 8% yield.



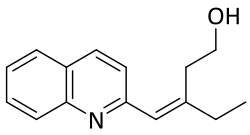
^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.08 (dd, *J* = 8.5, 0.8 Hz, 1H), 8.03 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.77 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.68 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.53 (s, 1H), 3.89 (t, *J* = 6.5 Hz, 2H), 2.71– 2.63 (m, 2H), 2.56 (td, *J* = 6.5, 1.2 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 156.9, 148.0, 147.8, 135.8, 129.4, 129.3, 127.4, 126.7, 126.4, 126.0, 122.3, 60.9, 40.7, 24.5, 12.9.

HRMS (ESI$^+$): m/z calcd. for $C_{15}H_{17}NO$ ([M+H$^+$]) 228.13829, found: 228.13801.

(*Z*)-3-(Quinolin-2-ylmethylene)pentan-1-ol (15)

Compound **15** was synthesized according to **general procedure A.** Yellow oil, 12% yield.



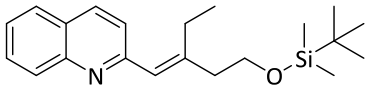
^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.12–8.08 (m, 2H), 7.77 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 1.5 Hz, 1H), 4.07–4.01 (m, 2H), 2.81–2.75 (m, 2H), 2.37 (qd, *J* = 7.4, 1.5 Hz, 2H), 1.22 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 155.9, 150.8, 146.8, 146.8, 137.0, 130.2, 128.6, 127.7, 127.1, 126.5, 125.5, 122.8, 61.5, 34.8, 30.9, 12.7.

HRMS (ESI^{+}): m/z calcd. for $C_{15}H_{17}NO$ ([M+H^{+}]) 228.13829, found: 228.13825.

(*E*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)-2-ethylbut-1-en-1-yl)quinoline (16)

Compound **16** was synthesized according to **general procedure B**. Clear oil, 53% yield.



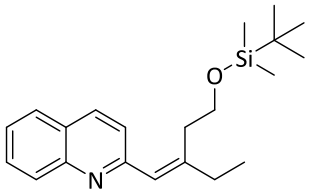
^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.06 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.47 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 6.48 (s, 1H), 3.86 (t, *J* = 7.3 Hz, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.51 (td, *J* = 7.3, 1.1 Hz, 2H), 1.17 (t, *J* = 7.5 Hz, 9H), 0.09 (d, *J* = 0.6 Hz, 6H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 157.6, 148.9, 148.4, 135.9, 129.7, 129.6, 127.7, 126.7, 126.4, 126.1, 122.6, 62.9, 41.2, 26.3, 25.4, 18.7, 13.2, -4.9.

HRMS (ESI^{+}): m/z calcd. for $C_{21}H_{31}NOSi$ ([M+H^{+}]) 342.22477, found: 342.22474.

(*Z*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)-2-ethylbut-1-en-1-yl)quinoline (17)

Compound **17** was synthesized according to **general procedure B**. Clear oil, 53% yield.



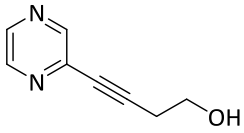
^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.04 (t, *J* = 9.4 Hz, 2H), 7.79–7.73 (m, 1H), 7.69 - 7.64 (m, 1H), 7.46 (dd, *J* = 13.7, 7.9 Hz, 2H), 6.55 (s, 1H), 3.86 (t, *J* = 7.1 Hz, 1H), 2.94 - 2.89 (m, 2H), 2.40 - 2.29 (m, 2H), 1.19 (t, *J* = 7.4 Hz, 3H), 0.87 (d, *J* = 2.9 Hz, 9H), 0.02 (s, 6H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 157.8, 148.9, 148.4, 135.9, 129.7, 129.5, 129.5, 127.6, 126.7, 126.0, 125.6, 123.0, 62.6, 35.6, 31.9, 26.3, 18.6, 12.9, -5.0.

HRMS (ESI^{+}): m/z calcd. for $C_{21}H_{31}NOSi$ ([M+H^{+}]) 342.22477, found: 342.22420.

4-(Pyrazin-2-yl)but-3-yn-1-ol (19)

Compound **19** was synthesized according to a literature procedure:[44]

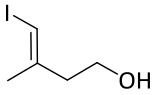


A solution of 2-chloropyrazine (28 mmol, 1.0 equiv) and 3-butyn-1-ol (30.8 mmol, 1.1 equiv) in acetonitrile (30 mL) and triethylamine (15 mL) was degassed under vacuum. Then $Pd(OAc)_2$ (1 mol%), PPh_3 (5 mol%), and CuI (5 mol%) were added. The reaction mixture was heated under reflux for 6 h. After evaporation of organic solvents, the obtained solid residue was diluted with water and extracted with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$ and then concentrated in vacuum. Purification by precipitation EtOAc-hexane, obtaining product **19** (52% yield) as a light brown solid.

^{1}H-NMR (400 MHz, Chloroform-*d*): δ 8.64 (s, 1H), 8.51 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 3.87 (dd, J = 6.9, 5.4 Hz, 2H), 2.77 (t, J = 6.4 Hz, 2H).

(*E*)-4-Iodo-3-methylbut-3-en-1-ol (25)

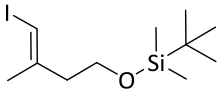
Compound **25** was synthesized according to **general procedure C**. Colorless oil, 51% yield.



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 6.02 (q, *J* = 1.1 Hz, 1H), 3.72 (t, *J* = 6.3 Hz, 2H), 2.48 (td, *J* = 6.3, 1.1 Hz, 2H), 1.87 (d, *J* = 1.1 Hz, 3H), 1.43 (s, 1H, OH).

(*E*)-tert-butyl((4-iodo-3-methylbut-3-en-1-yl)oxy)dimethylsilane (26)

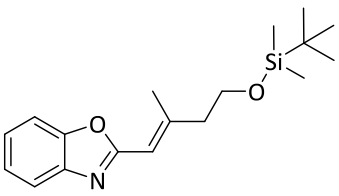
Compound **26** was synthesized according to **general procedure B**. Colorless oil, 85% yield.



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 5.93 (q, *J* = 1.2 Hz, 1H), 3.68 (t, *J* = 6.6 Hz, 2H), 2.41 (td, *J* = 6.6, 1.1 Hz, 2H), 0.88 (s, 9H), 0.05 (d, *J* = 7.0 Hz, 6H).

(*E*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)-2-methylbut-1-en-1-yl)benzo[*d*]oxazole (28)

Compound **28** was synthesized according to a literature procedure:[45]

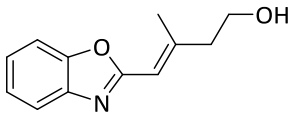


Benzoxazole (2 mmol, 2.0 equiv) and vinyl iodide (1 mmol, 1.0 equiv), $Pd(OAc)_2$ (1 mol%), CuOAc (1 mmol, 1.0 equiv) and DMAP (2 mmol, 2.0 equiv) in DMF (2 mL) were heated at 140 °C for 15 min in a microwave synthesizer. The mixture was diluted with Et_2O and washed with saturated aqueous NH_4Cl solution. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography (hexane to 2% hexane/EtOAc) to give a colorless oil (30% yield).

^{1}H-NMR (400 MHz, Chloroform-*d*): δ 7.71–7.67 (m, 1H), 7.50–7.46 (m, 1H), 7.32–7.27 (m, 2H), 6.29 (q, *J* = 1.3 Hz, 1H), 3.84 (t, *J* = 6.6 Hz, 2H), 2.50 (td, *J* = 6.6, 1.1 Hz, 2H), 2.38 (d, *J* = 1.3 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

(*E*)-4-(benzo[*d*]oxazol-2-yl)-3-methylbut-3-en-1-ol (30)

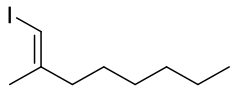
Compound **30** was synthesized according to **general procedure D**.



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 7.73–7.67 (m, 1H), 7.52–7.43 (m, 1H), 7.33–7.28 (m, 2H), 6.35 (q, *J* = 1.3 Hz, 1H), 3.88 (t, *J* = 6.3 Hz, 2H), 2.56 (td, *J* = 6.3, 1.1 Hz, 2H), 2.39 (d, *J* = 1.2 Hz, 3H).

(*E*)-1-iodo-2-methyloct-1-ene (32)

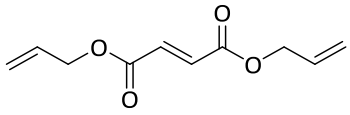
Compound **32** was synthesized according to **general procedure C**. Colorless oil, 66% yield.



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 5.85 (q, *J* = 1.2 Hz, 1H), 2.19 (td, *J* = 7.5, 1.2 Hz, 2H), 1.82 (d, *J* = 1.1 Hz, 3H), 1.46–1.38 (m, 2H), 1.33–1.22 (m, 8H), 0.91–0.85 (m, 3H).

Diallyl fumarate (36)

Compound **36** was synthesized according to a literature procedure:[46]



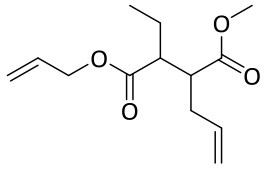
A flame-dried 100 mL 2-necked round-bottomed flask equipped with a magnetic stirring bar and addition funnel was charged with fumaroyl chloride (3.27 mmol, 1.0 equiv) and 10 mL of DCM under nitrogen and the flask was cooled to 0 °C. After 15 min, a solution of triethylamine (6.54 mmol, 2.0 equiv) and allyl alcohol (6.87 mmol, 2.1 equiv) in 10 mL of DCM was added via addition funnel.

The solution was stirred for 15 min at the same temperature, then warmed to 23 °C. After stirring for 60 min, 25 mL of DCM was added and the organic layer was washed with 15 mL of 1 M HCl, 15 mL of H_2O, and 15 mL of brine respectively. The organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed with a rotary evaporator. The crude product was purified by flash column chromatography with 10% EtOAc/hexane affording product **36** as a clear oil (66 %yield).

^{1}H-NMR (400 MHz, Chloroform-*d*): δ 6.88 (s, 2H), 5.92 (ddt, *J* = 17.1, 10.3, 5.7 Hz, 2H), 5.40–5.20 (m, 4H), 4.68 (dt, *J* = 5.8, 1.4 Hz, 4H).

1-Allyl 4-methyl 3-allyl-2-ethylsuccinate (37)

Compound **37** was synthesized according to a literature procedure.[37]

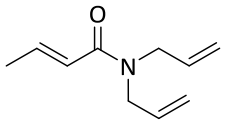


A flame-dried round-bottomed flask equipped with a stirring bar was charged with **36** (1 mmol, 1.0 equiv) and copper catalyst (10 mol%). The flask was sealed with a septum and purged with nitrogen. Et_2O was added and cooled to -78 °C. After 15 min, TMSCl (1.5 mmol, 1.5 equiv) was added, followed by Et_2Zn (1.2 mmol, 1.2 equiv). This was stirred at the same temperature for 2 h and warmed to 23 °C. A reflux condenser was attached and the reaction was heated at reflux for 12-24 h. The reaction was cooled and quenched with 10 mL of 1M HCl. The aqueous layer was extracted with Et_2O. The organic extracts were combined and washed once with brine. The organic extracts were dried ($MgSO_4$), filtered and the solvent was removed with a rotary evaporator. The crude product mixture was dissolved in acetone in a round-bottomed flask and Me_2SO_4 and K_2CO_3 were added. The reaction was stirred open to the atmosphere for 6h. The reaction mixture was filtered through silica eluting with acetone and the solvent was removed in the rotavap. The product was purified by flash column chromatography 10% EtOAc/hexane. Clear liquid 29% yield.

^{1}H-NMR (400 MHz, Chloroform-*d*): δ 6.00–5.83 (m, 1H), 5.79–5.60 (m, 1H), 5.39–5.19 (m, 2H), 5.08–4.95 (m, 2H), 4.60 (dt, *J* = 5.1, 1.5 Hz, 2H), 3.66 (s, 3H), 2.85–2.71 (m, 1H), 2.61 (td, *J* = 9.8, 4.1 Hz, 1H), 2.40–2.14 (m, 2H), 1.74–1.40 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H).

(*E*)-*N*,*N*-Diallylbut-2-enamide (40)

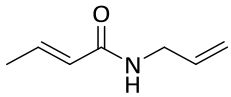
Compound **40** was synthesized according to **general procedure E**. Clear oil, 87% yield.



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 6.81 (dq, *J* = 13.9, 6.8 Hz, 1H), 6.06 (dq, *J* = 15.0, 1.5 Hz, 1H), 5.76–5.56 (m, 2H), 5.04 (dt, *J* = 17.7, 9.7 Hz, 4H), 3.85 (dd, *J* = 27.2, 5.3 Hz, 4H), 1.74 (dd, *J* = 7.0, 1.7 Hz, 3H).

(*E*)-*N*-Allylbut-2-enamide (42)

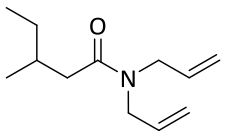
Compound **42** was synthesized according to **general procedure E.** Clear oil, 87% yield.



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 6.94–6.76 (m, 1H), 5.99–5.74 (m, 3H), 5.26–5.04 (m, 2H), 3.93 (dtt, *J* = 5.8, 3.9, 1.8 Hz, 2H), 1.84 (dt, *J* = 7.1, 1.6 Hz, 3H).

***N*,*N*-Diallyl-3-methylpentanamide (43)**

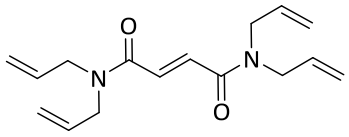
Compound **43** was synthesized according to **general procedure G**.



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 5.76 (ddt, *J* = 17.0, 10.3, 5.0 Hz, 2H), 5.23–5.05 (m, 4H), 4.03–3.96 (m, 1H), 3.87 (dt, *J* = 4.9, 1.8 Hz, 2H), 2.29 (dd, *J* = 14.8, 5.8 Hz, 2H), 2.10 (dd, *J* = 14.8, 8.0 Hz, 1H), 1.38 (ddd, *J* = 13.2, 7.5, 5.6 Hz, 1H), 1.29–1.05 (m, 2H), 0.96–0.81 (m, 6H).

***N*^{1},*N*^{1},*N*^{4},*N*^{4}-Tetraallylfumaramide (47)**

Compound **47** was synthesized according to **general procedure E**. Clear oil, 41% yield.

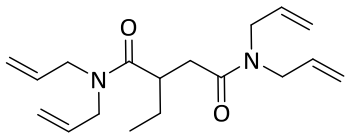


^{1}H-NMR (600 MHz, Chloroform-*d*): δ 7.31 (s, 2H), 5.82–5.72 (m, 4H), 5.24–5.11 (m, 8H), 4.04 (dt, *J* = 6.1, 1.5 Hz, 4H), 3.98 (dt, *J* = 5.0, 1.8 Hz, 4H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 165.3, 132.7, 132.6, 131.8, 117.8, 117.3, 49.3, 48.6.

***N*^{1},*N*^{1},*N*^{4},*N*^{4}-Tetraallyl-2-ethylsuccinamide (48)**

Compound **48** was synthesized according to **general procedure H**.



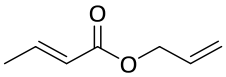
^{1}H-NMR (600 MHz, Chloroform-*d*): δ 5.86 (dddd, *J* = 17.4, 9.9, 6.0, 4.9 Hz, 1H), 5.81–5.67 (m, 3H), 5.21–5.05 (m, 8H), 4.26–4.20 (m, 1H), 4.07–3.96 (m, 3H), 3.94–3.77 (m, 4H), 3.18 (dtd, *J* = 8.9, 6.8, 4.5 Hz, 1H), 2.84 (dd, *J* = 15.9, 9.0 Hz, 1H), 2.36 (dd, *J* = 15.9, 4.5 Hz, 1H), 1.63 (ddd, *J* = 14.0, 7.6, 6.5 Hz, 1H), 1.53–1.45 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 175.6, 171.8, 133.9, 133.3, 133.2, 132.9, 117.1, 117.0, 116.7, 116.7, 49.7, 49.3, 48.0, 47.8, 39.3, 35.5, 26.1, 11.9.

HRMS (ESI$^+$): m/z calcd. for $C_{18}H_{28}N_2O_2$ ([M+H$^+$]) 305.22235, found: 305.22271.

Allyl (*E*)-but-2-enoate (50)

Compound **50** was synthesized according to a literature procedure:[47]

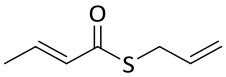


A solution of allyl alcohol (7.5 mmol, 1.0 equiv) and crotonoyl chloride (11.25 mmol, 1.5 equiv) in DCM (10 mL) pyridine (11.25 mmol, 1.5 equiv) and a catalytic amount of DMAP were added at 0 °C. After stirring the reaction for 30 min the reaction was allowed to room temperature and was stirred for 2 h. The solution was diluted with ether, and the organic phase was washed with HCl, water and brine and then dried. After removing the solvent, the residue was subjected to silica gel chromatrography to give the desired ester **50** in 41% yield (volatile product).

^{1}H-NMR (400 MHz, Chloroform-*d*): δ 7.00 (dqd, *J* = 15.1, 6.9, 1.1 Hz, 1H), 6.01–5.91 (m, 1H), 5.9–5.78 (m, 1H), 5.37–5.17 (m, 2H), 4.61 (dt, *J* = 5.7, 1.4 Hz, 2H), 1.87 (dt, *J* = 7.0, 1.4 Hz, 3H).

***S*-Allyl (*E*)-but-2-enethioate (54)**

Compound **54** was synthesized according to **general procedure F**. Clear oil, 91% yield.



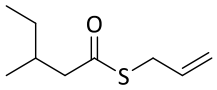
^{1}H-NMR (400 MHz, Chloroform-*d*): δ 6.91 (dq, *J* = 15.4, 6.9 Hz, 1H), 6.13 (dq, *J* = 15.4, 1.6 Hz, 1H), 5.81 (ddt, *J* = 16.9, 10.0, 6.9 Hz, 1H), 5.24 (dq, *J* = 16.9, 1.4 Hz, 1H), 5.09 (dq, *J* = 10.0, 1.1 Hz, 1H), 3.58 (dt, *J* = 7.0, 1.2 Hz, 2H), 1.87 (dd, *J* = 6.9, 1.7 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ 191.8, 143.7, 135.9, 132.6, 120.4, 34.1, 20.6.

HRMS (ESI$^+$): m/z calcd. for $C_7H_{12}OS$ ([M+H$^+$]) 143.05251, found: 143.05259.

_S_-Allyl 3-methylpentanethioate (55)

Compound **55** was synthesized according to **general procedure I**.

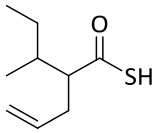


^{1}H-NMR (600 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.23 (dq, *J* = 16.9, 1.4 Hz, 1H), 5.09 (dq, *J* = 10.0, 1.1 Hz, 1H), 3.54 (dt, *J* = 7.0, 1.2 Hz, 2H), 2.55 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.36 (dd, *J* = 14.5, 8.1 Hz, 1H), 2.03–1.89 (m, 1H), 1.44–1.31 (m, 1H), 1.23 (dt, *J* = 13.6, 7.4 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (151 MHz, Chloroform-*d*): δ 198.9, 133.6, 118.0, 51.2, 33.0, 32.1, 29.6, 19.4, 11.6.

2-(*sec*-Butyl)pent-4-enethioic S-acid (56)

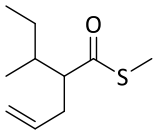
Compound **56** was synthesized according to **general procedure J**.



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 5.84–5.66 (m, 1H), 5.08–4.93 (m, 2H), 2.46–2.29 (m, 2H), 2.28–2.11 (m, 1H), 1.79–1.59 (m, 1H), 1.55–1.46 (m, 1H), 1.44 (d, *J* = 1.0 Hz, 1H), 1.27–1.08 (m, 1H), 0.97–0.81 (m, 5H).

_S_-Methyl 2-(*sec*-butyl)pent-4-enethioate (57)

Compound **57** was synthesized according to **general procedure K**.



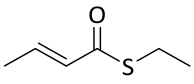
^{1}H-NMR (600 MHz, Chloroform-*d*): δ 5.74 (ddtd, *J* = 17.1, 10.2, 7.0, 4.4 Hz, 1H), 5.05 (ddq, *J* = 17.0, 4.8, 1.6 Hz, 1H), 5.00 (dddd, *J* = 11.3, 4.5, 2.1, 1.1 Hz, 1H), 2.61–2.55 (m, 1H), 2.46–2.37 (m, 1H), 2.28 (d, *J* = 1.8 Hz, 3H), 2.23 (dddd, *J* = 14.0, 6.7, 3.1, 1.6 Hz, 1H), 1.73 (ddtd, *J* = 40.2, 8.6, 6.7, 4.4 Hz, 1H), 1.53–1.41 (m, 1H), 1.23–1.15 (m, 1H), 0.96–0.86 (m, 6H).

^{13}C-NMR (151 MHz, Chloroform-*d*): δ 202.7, 202.4, 135.7, 135.6, 116.6, 116.5, 59.0, 58.7, 37.2, 37.0, 34.4, 33.0, 27.3, 26.6, 16.3, 15.9, 11.7, 11.5, 11.5, 11.3.

HRMS (ESI$^+$): m/z calcd. for $C_{10}H_{18}OS$ ([M+H$^+$]) 187.11511, found: 187.11532.

_S_-Ethyl (_E_)-but-2-enethioate (59)

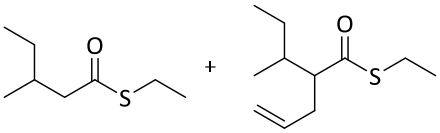
Compound **59** was synthesized according to **general procedure F**. Clear oil, 46% yield.



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 7.06–6.69 (m, 1H), 6.12 (dt, *J* = 15.4, 1.7 Hz, 1H), 2.92 (q, *J* = 7.4 Hz, 2H), 1.86 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.33–1.19 (m, 3H).

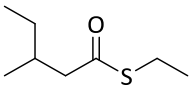
Complex mixture 60 + 61:

The mixture of compounds **60** and **61** was synthesized based on a literature procedure: [48]



To a flame dried Schlenk tube, containing a magnetic stirring bar, CuBr·SMe_2 (0.04 mmol, 5 mol%) and J004-1 (0.04 mmol, 6 mol%) and 6.3 mL of MTBE were added. The mixture was left to stir for 15 min. After that, thioester substrate (0.7 mmol, 1.0 equiv) dissolved in 0.7 mL of MTBE was added to the solution. The mixture was left to stir for 30 min at -78 °C. EtMgBr (3.0 equiv) was added dropwise over 15 min and the reaction mixture was left to stir for 3 h at the same temperature. Dry DMPU (7 mmol, 10.0 equiv) was added to the reaction mixture which was left to stir for 10 min at - 78 °C. Allyl bromide (2.45 mmol, 3.5 equiv) was added, the reaction mixture was allowed to warm up to room temperature and was left to stir for 16 h. The mixture was diluted with Et_2O, NH_4Cl was added and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed at reduced pressure. After the purification by column chromatography (100% hexane) a mixture of addition (**60**) and trapping (**61**) product was obtained.

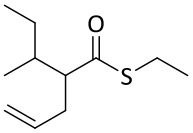
***S*-Ethyl 3-methylpentanethioate (60)**[49]



^{1}H-NMR (400 MHz, Chloroform-*d*): δ 2.86 (qd, *J* = 7.4, 2.4 Hz, 2H), 2.56–2.51 (m, 2H), 1.40–1.33 (m, 1H), 1.24 (q, *J* = 7.3 Hz, 2H), 0.90 (ddt, *J* = 7.5, 5.4, 2.4 Hz, 9H).

^{13}C-NMR (151 MHz, Chloroform-*d*): δ 199.7, 51.3, 34.7, 29.5, 22.9, 19.3, 14.4, 11.9.

***S*-ethyl 2-(*sec*-butyl)pent-4-enethioate (61)**

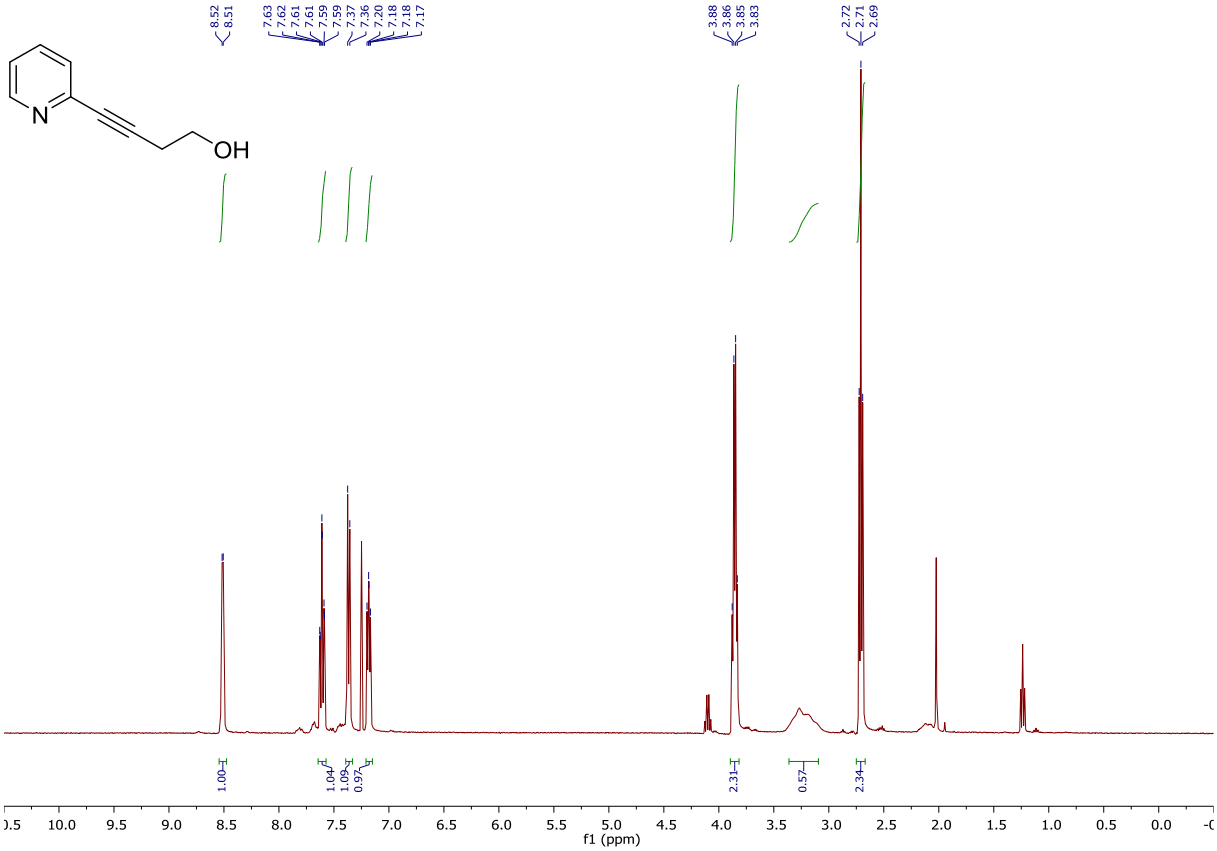


^{1}H-NMR (400 MHz, Chloroform-*d*): δ 5.79–5.68 (m, 1H), 5.08–4.95 (m, 2H), 2.56–2.50 (m, 2H), 2.46–2.37 (m, 1H), 2.28–2.19 (m, 1H), 1.72 (ddtd, *J* = 42.3, 8.7, 6.8, 4.5 Hz, 1H), 1.56–1.43 (m, 1H), 1.21–1.14 (m, 2H), 0.94–0.82 (m, 9H).

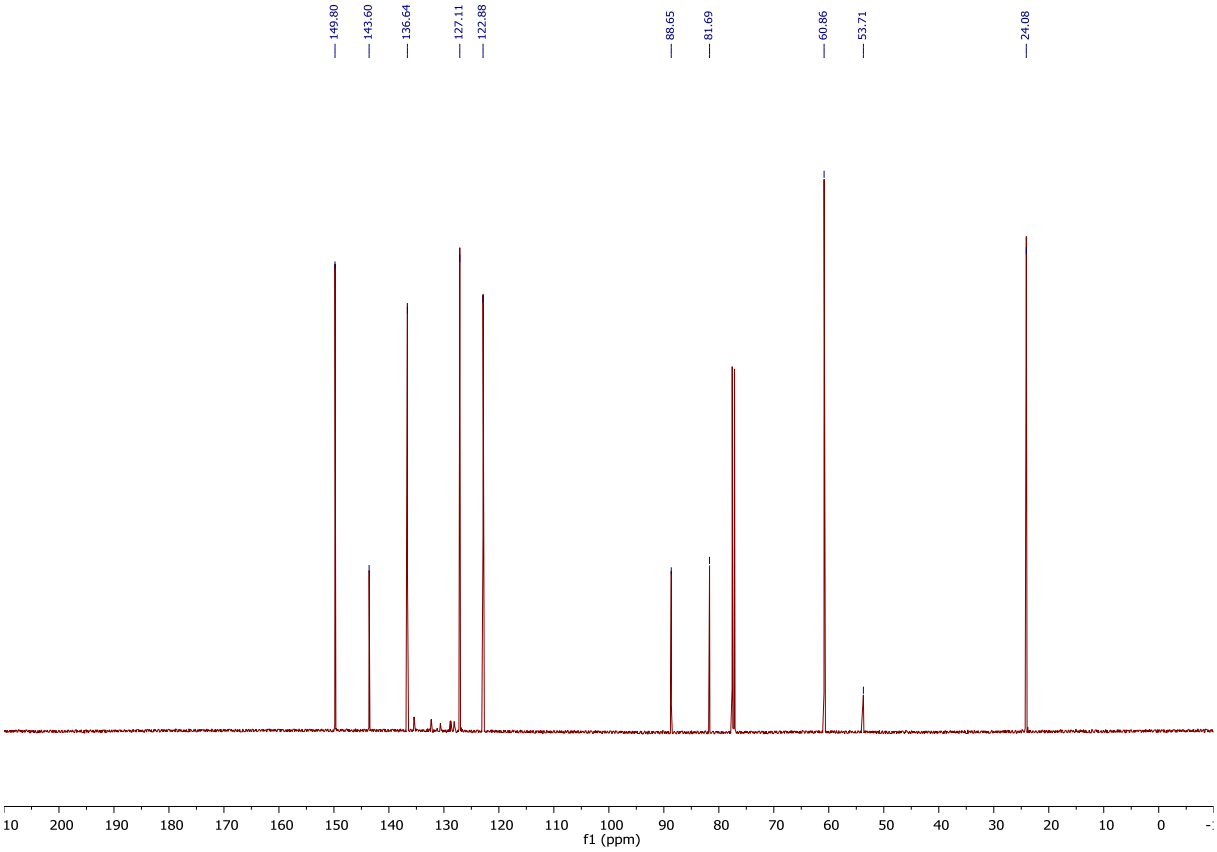
^{13}C-NMR (151 MHz, Chloroform-*d*): δ 202.6, 202.4, 136.0, 135.9, 116.9, 116.8, 59.2, 59.0, 37.5, 37.3, 34.7, 33.3, 31.9, 27.65, 26.9, 23.5, 23.5, 16.6, 16.1, 15.1, 15.1, 11.5.

8.5 COPIES OF NMR SPECTRUMS

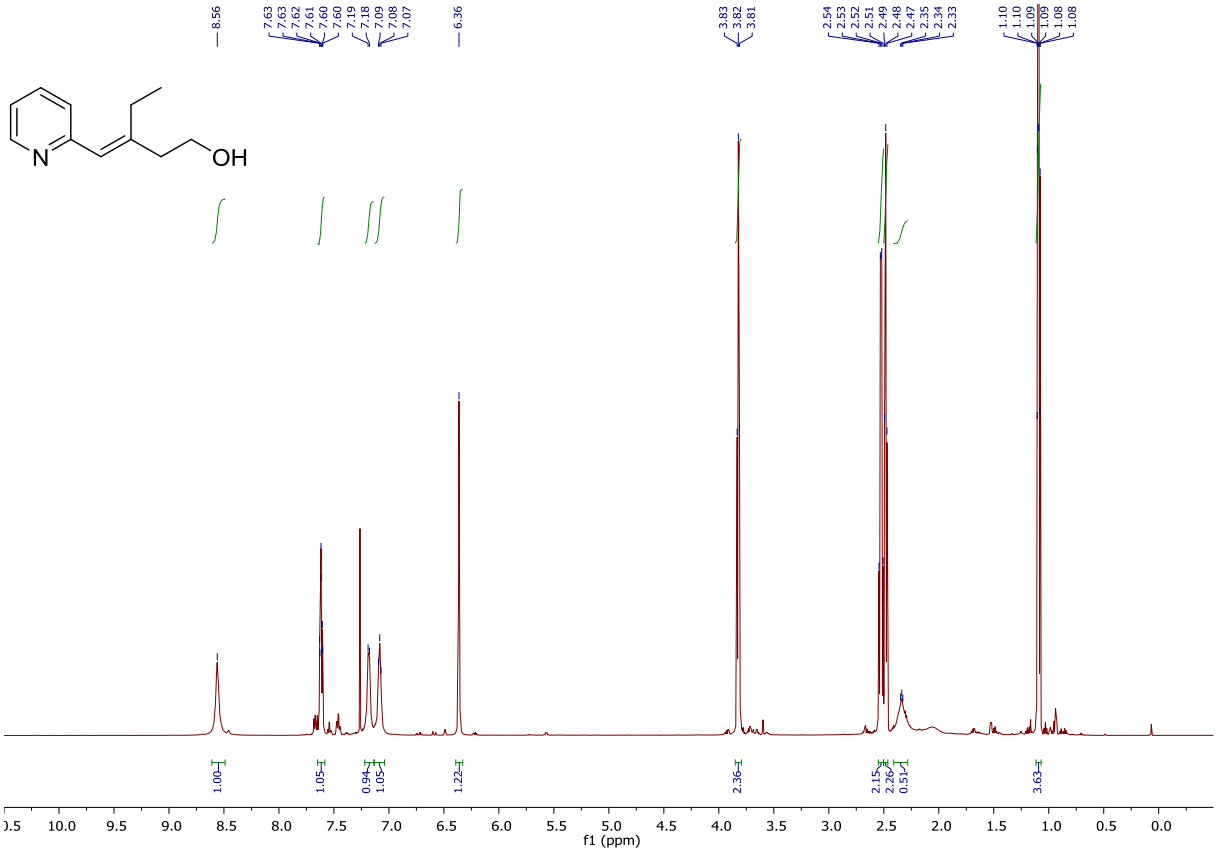
3, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



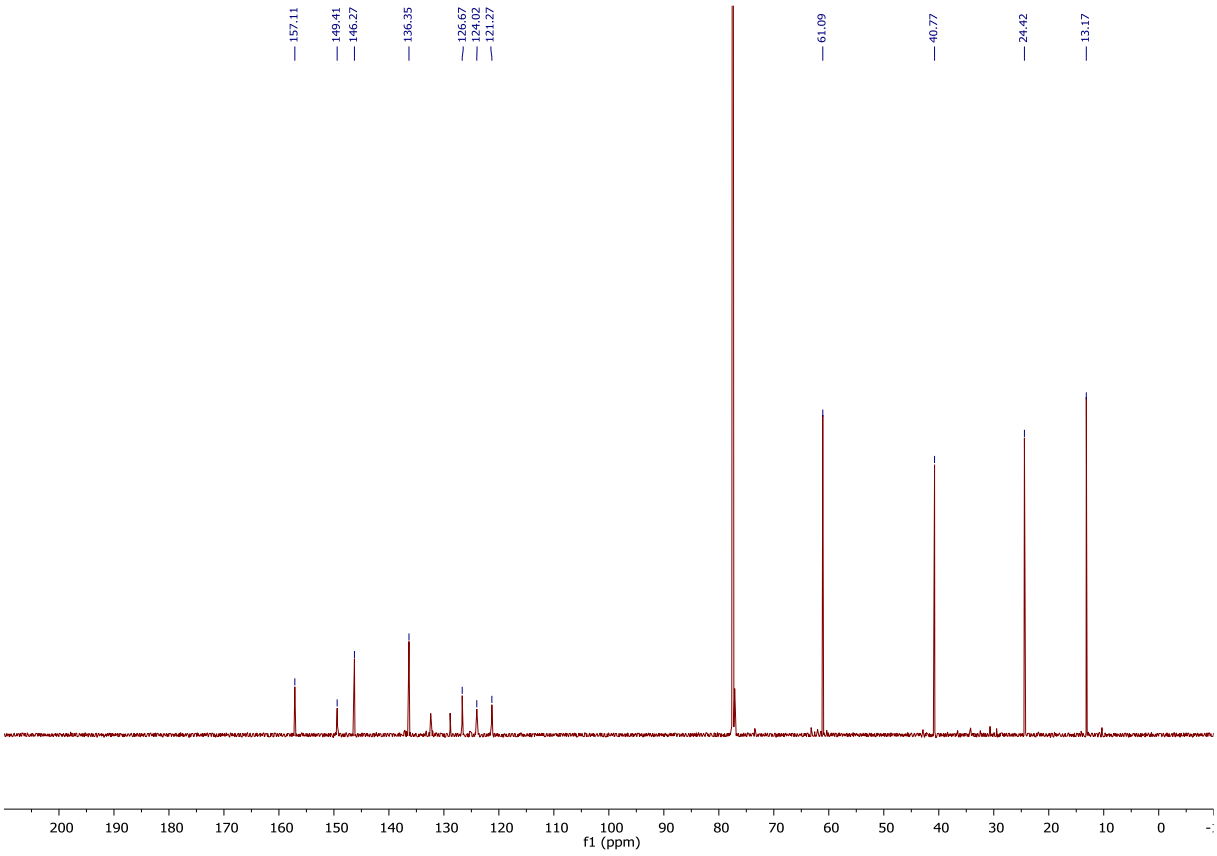
3, 101 MHz, ^{13}C NMR spectrum, $CDCl_3$.



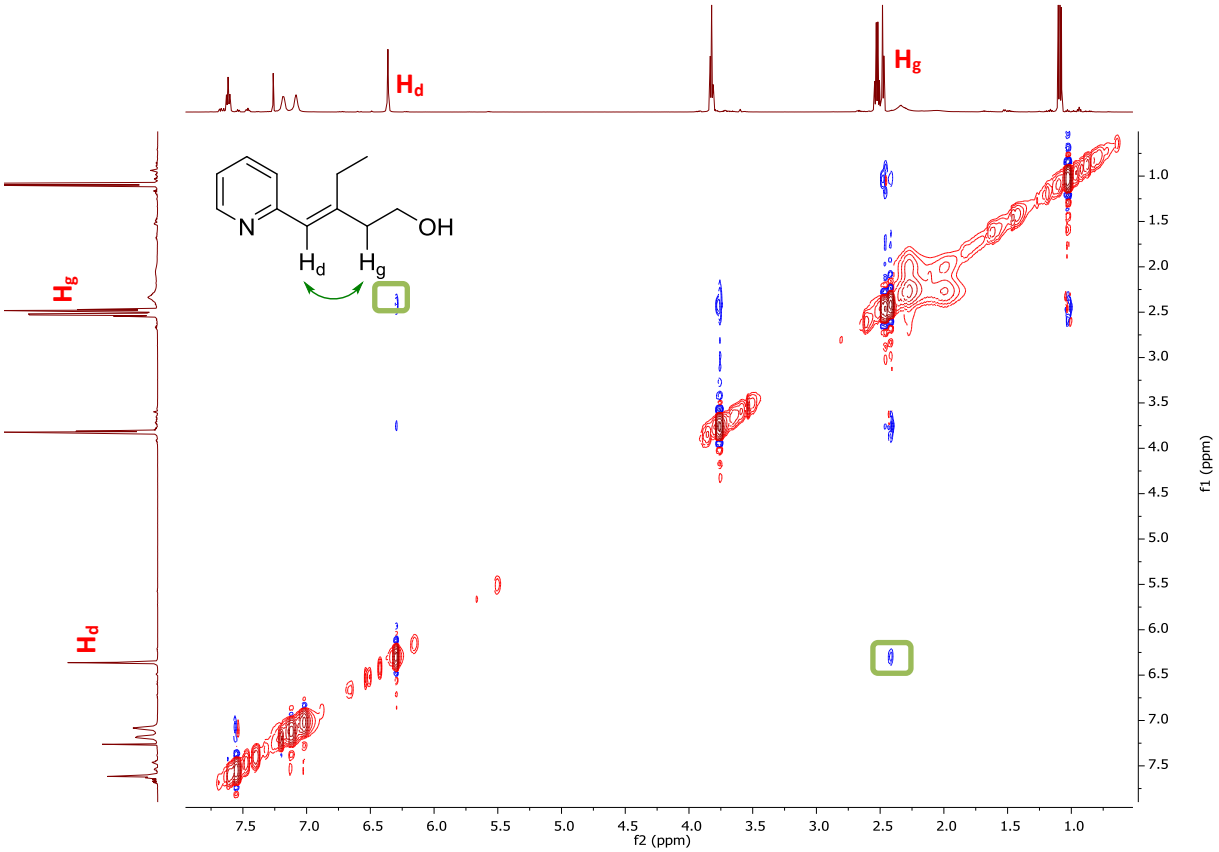
4, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



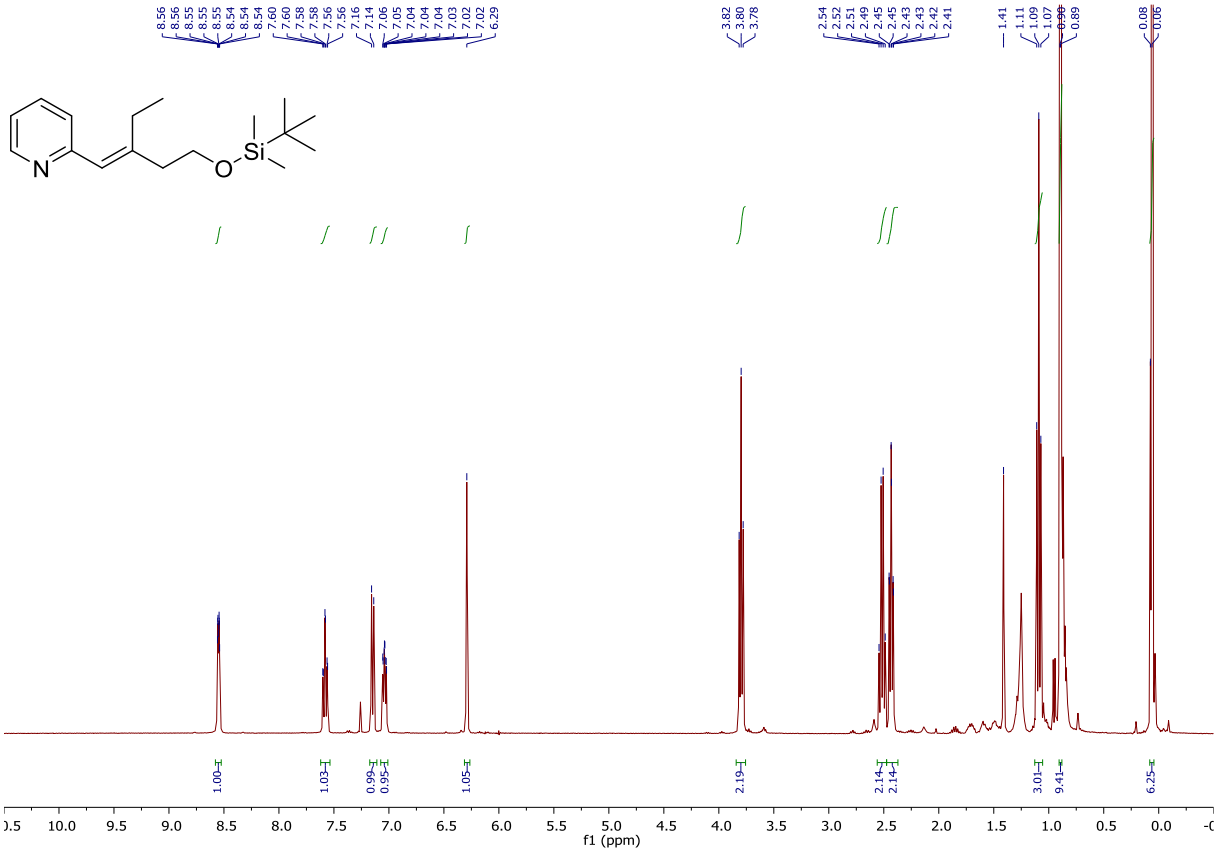
4, 101 MHz, ^{13}C NMR spectrum, $CDCl_3$.



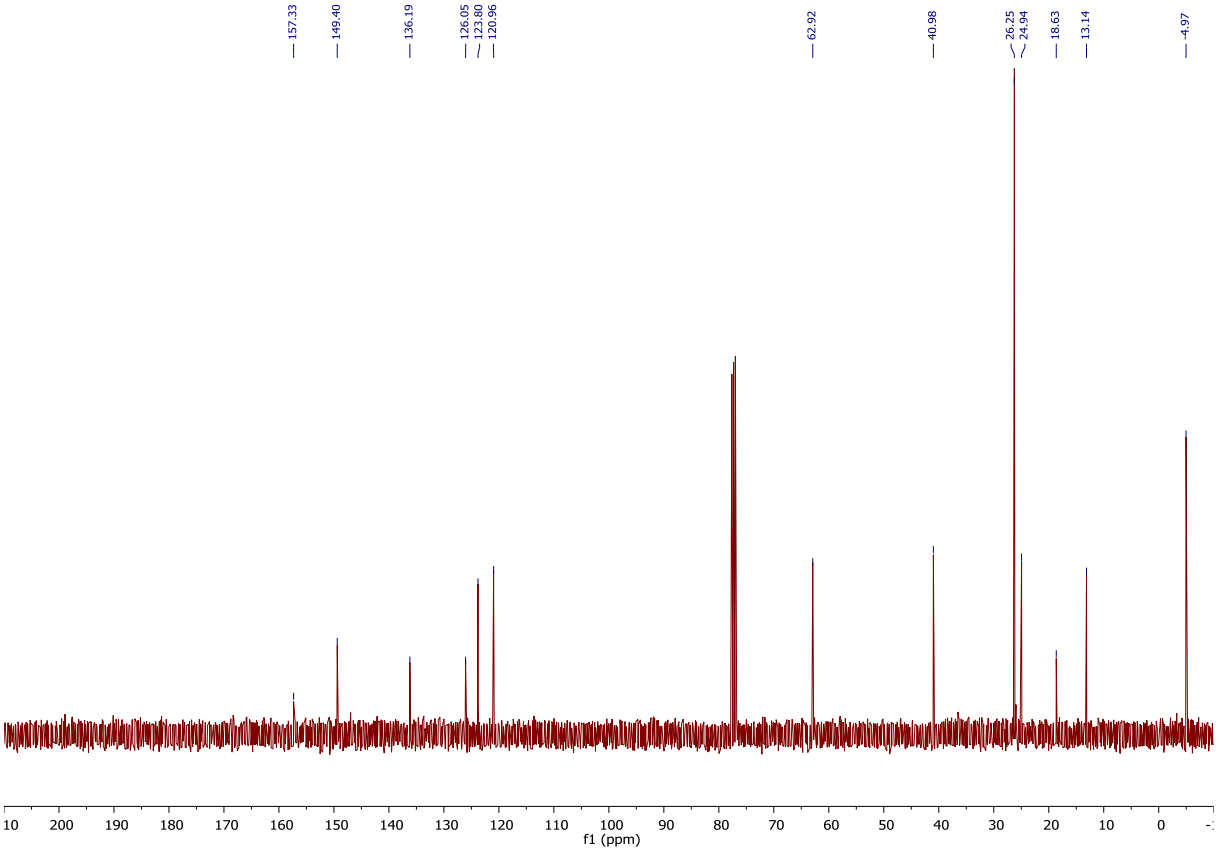
4, 2D NOESY spectrum, $CDCl_3$.



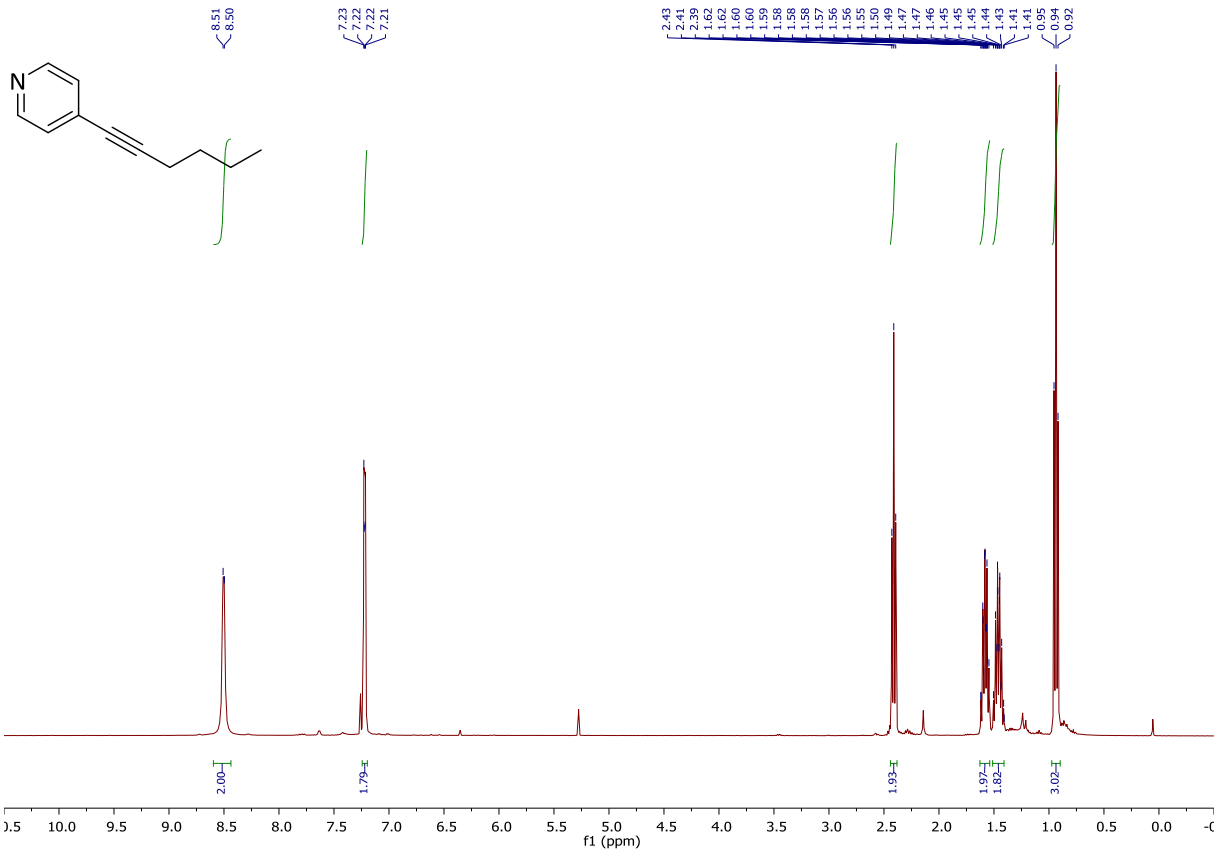
6, ^1H NMR spectrum, $CDCl_3$.



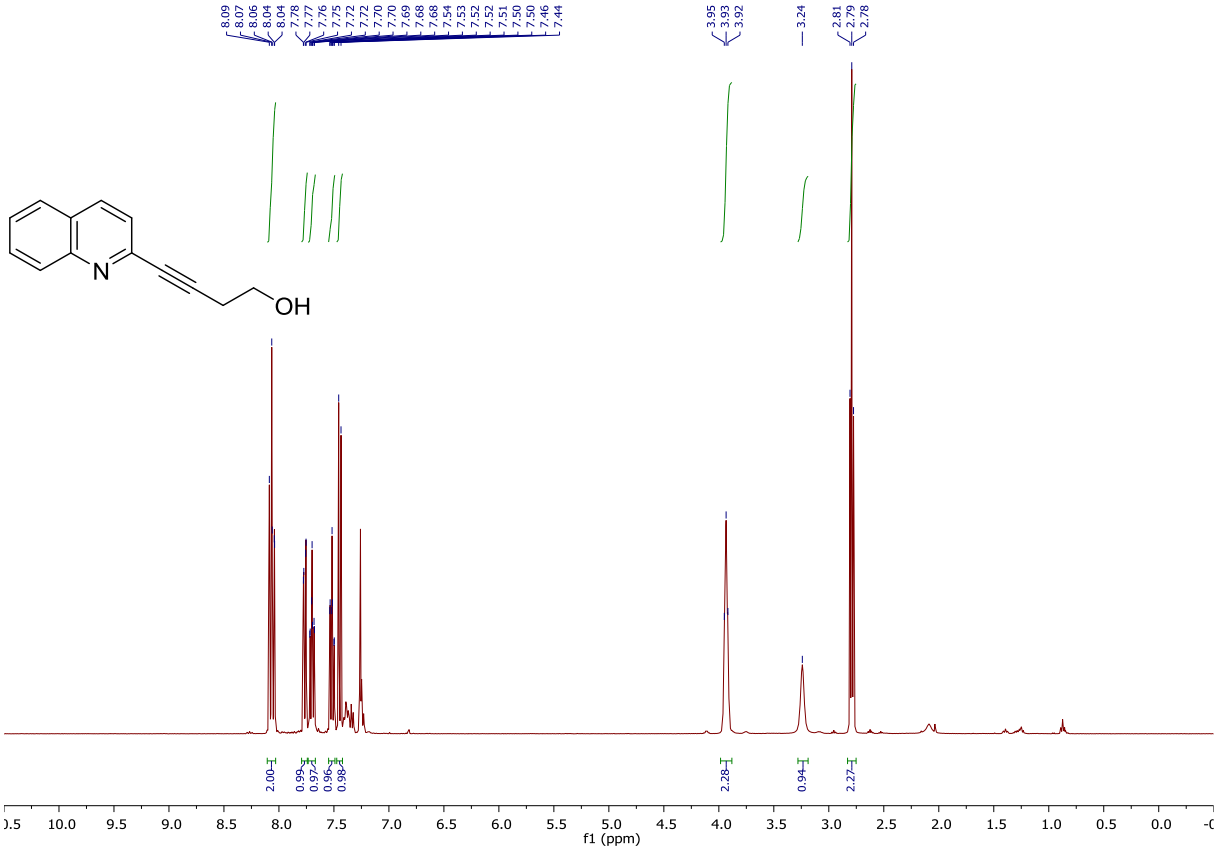
6, 101 MHz, ^{13}C NMR spectrum, $CDCl_3$.



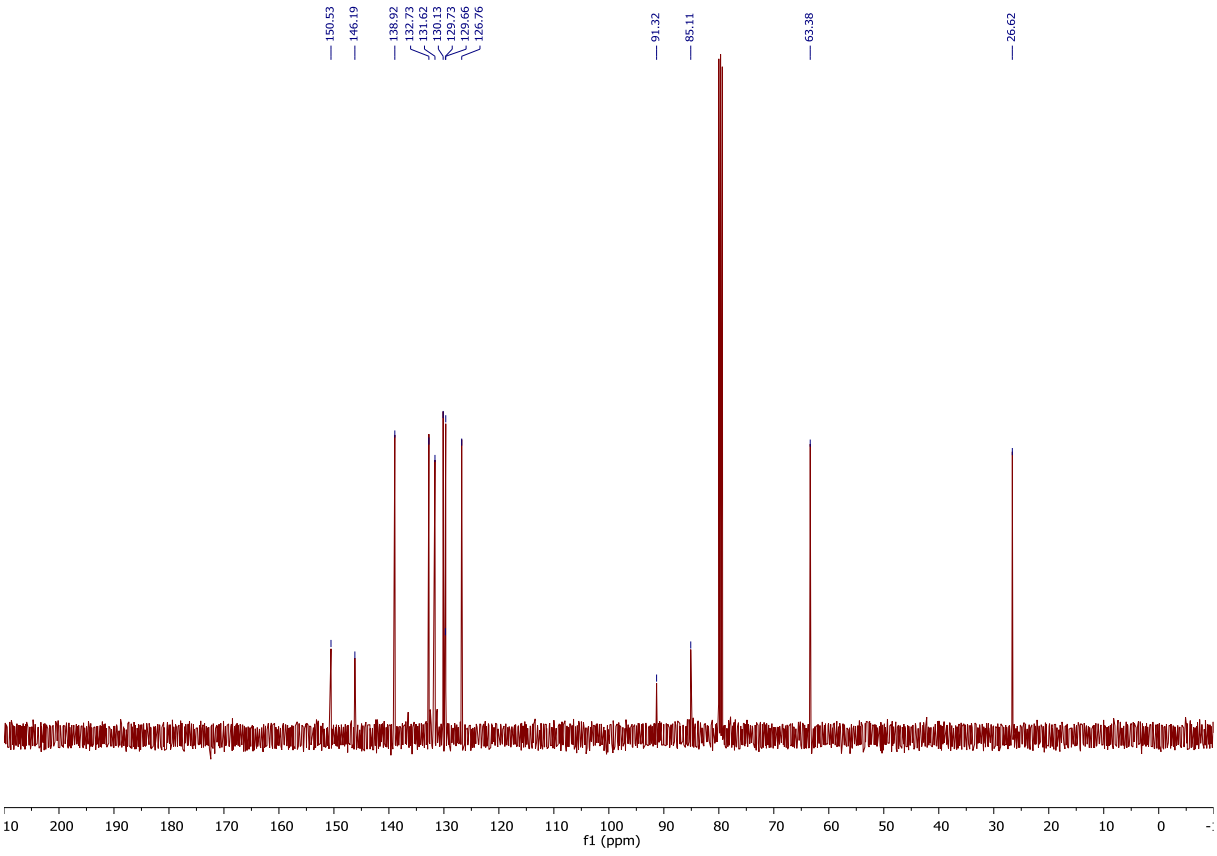
9, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



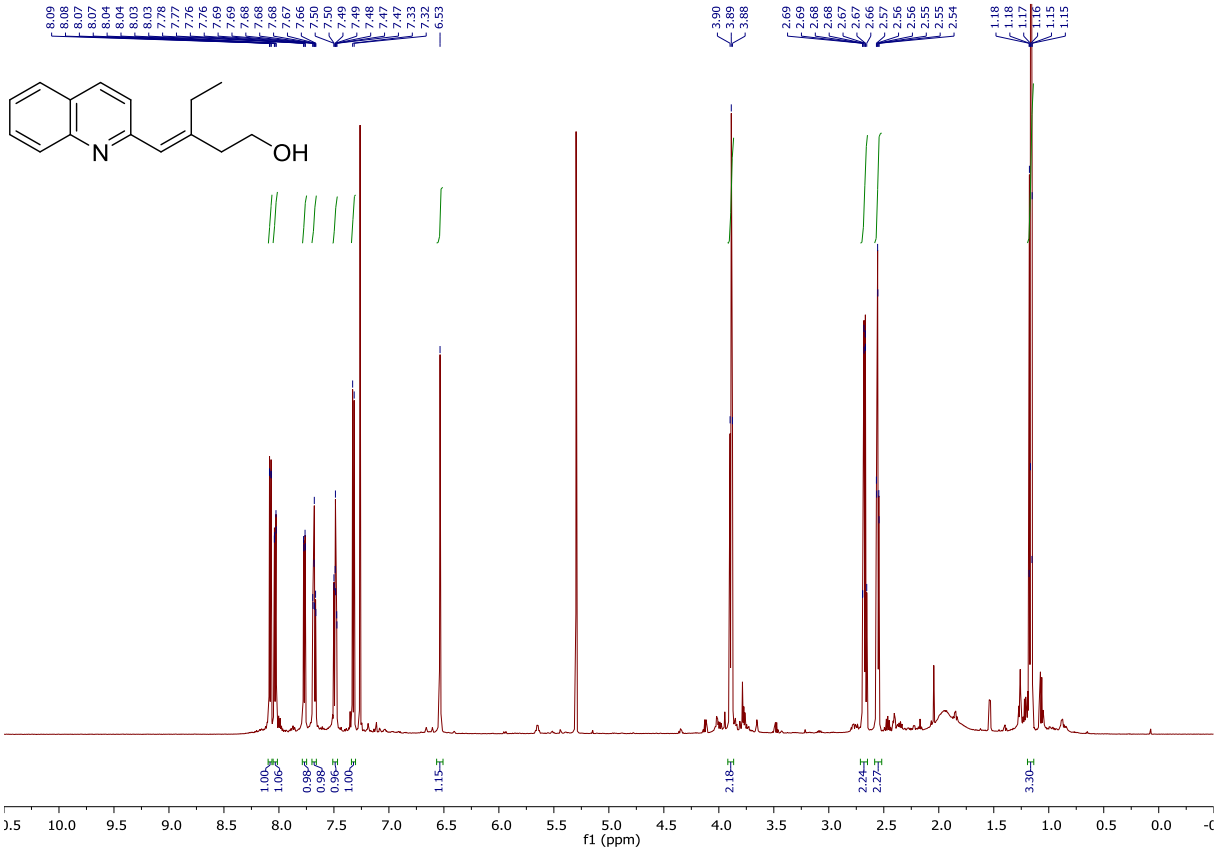
13, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



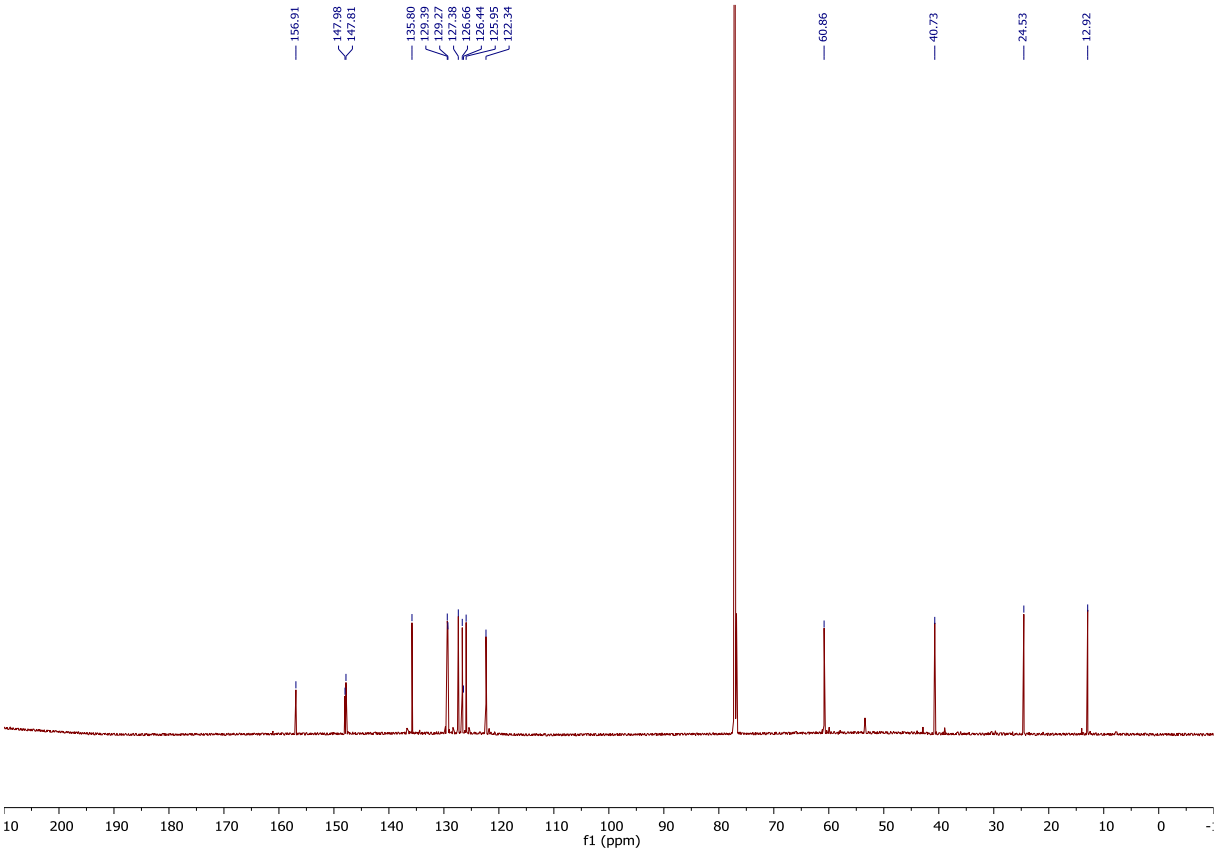
13, 101 MHz, ^{13}C NMR spectrum, $CDCl_3$.



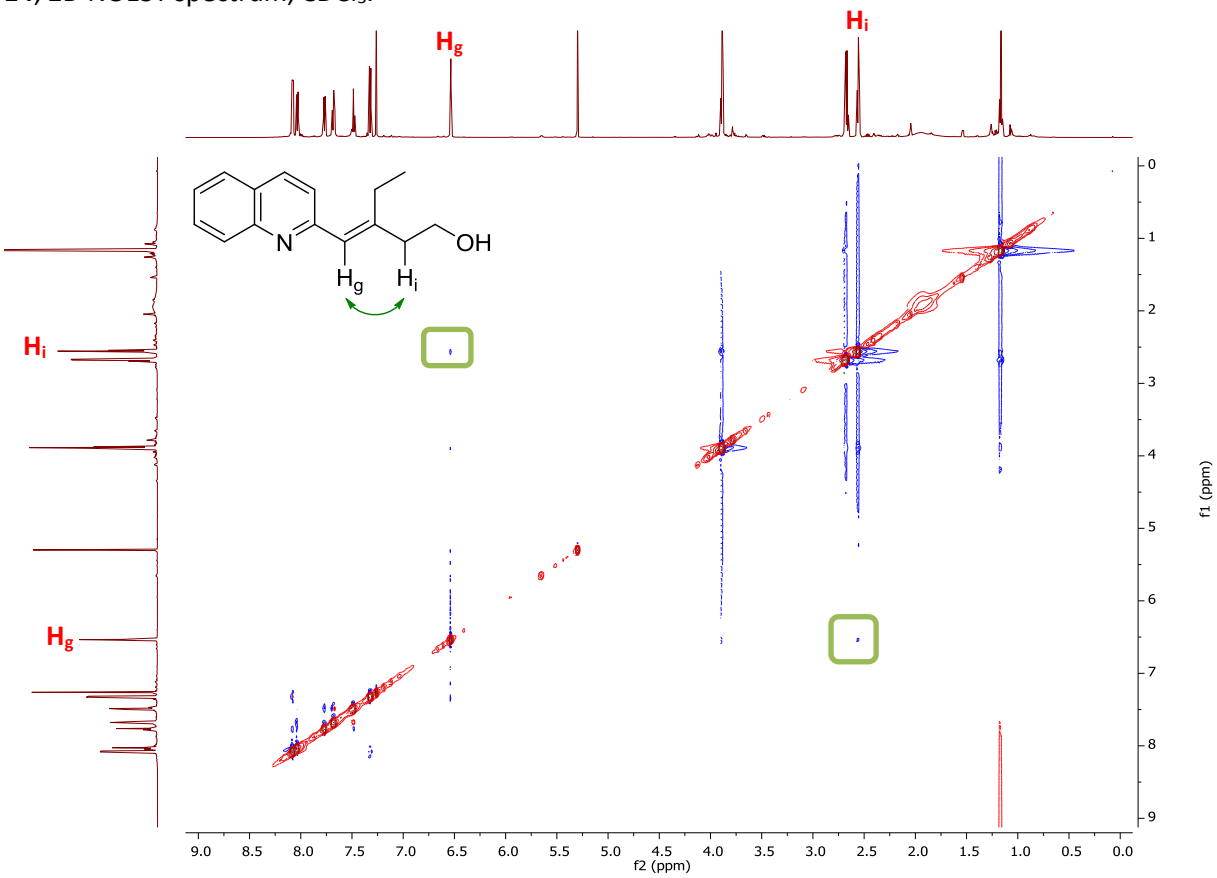
14, 600 MHz, ^{1}H NMR spectrum, $CDCl_3$.



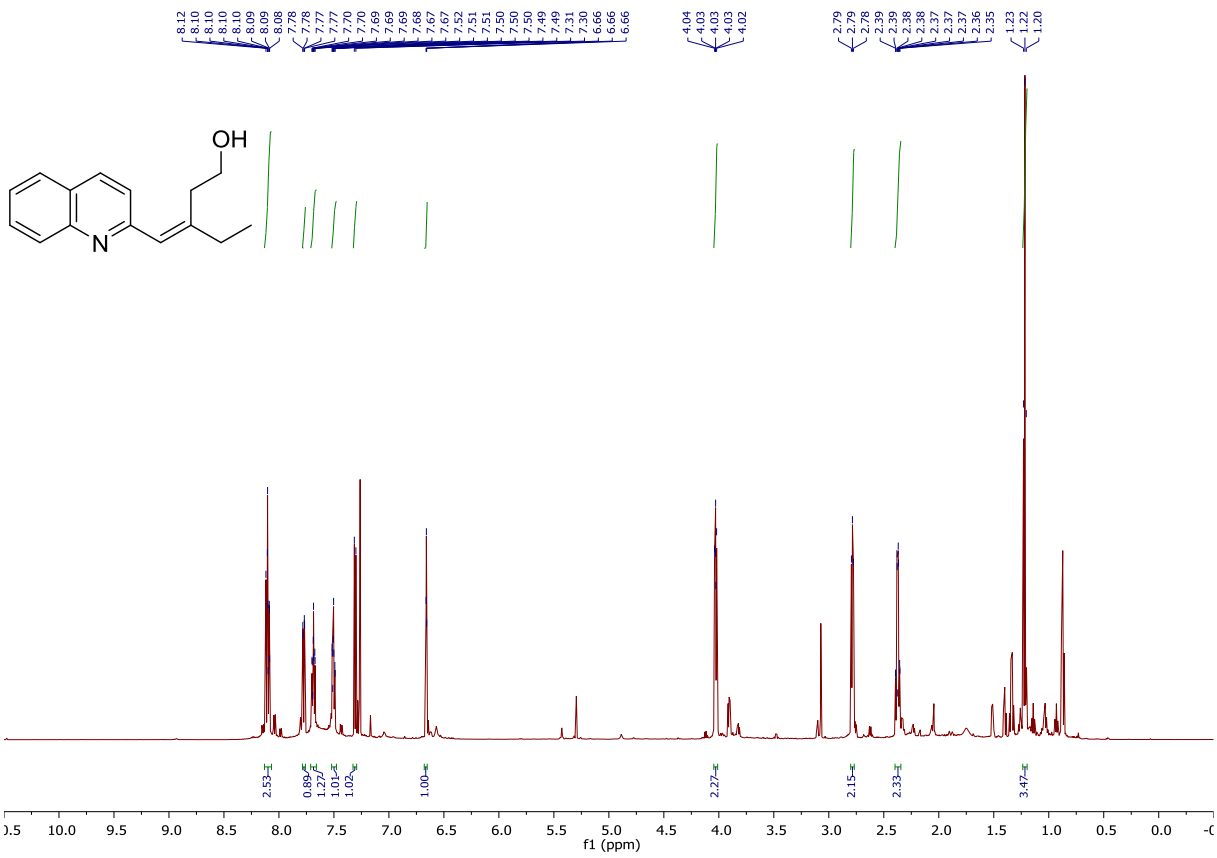
14, 151 MHz, ^{13}C NMR spectrum, $CDCl_3$.



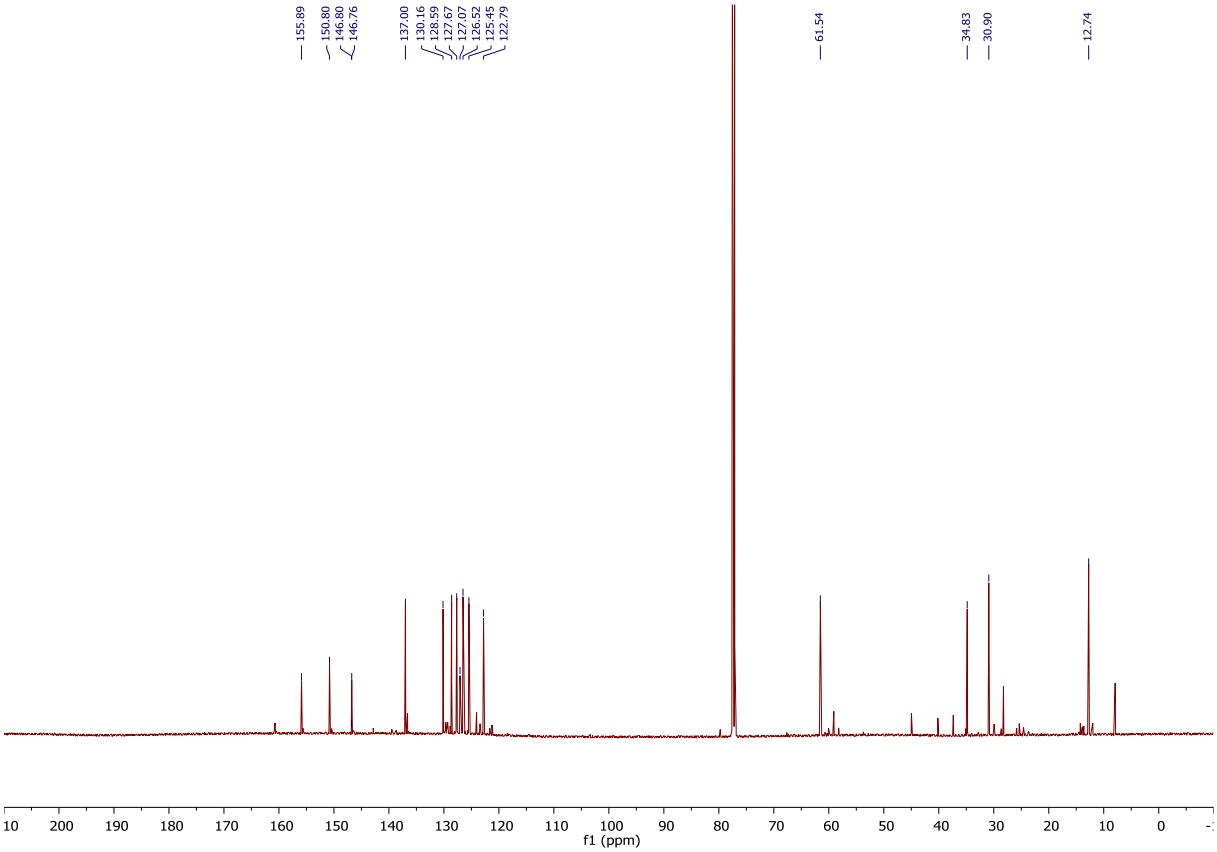
14, 2D NOESY spectrum, $CDCl_3$.



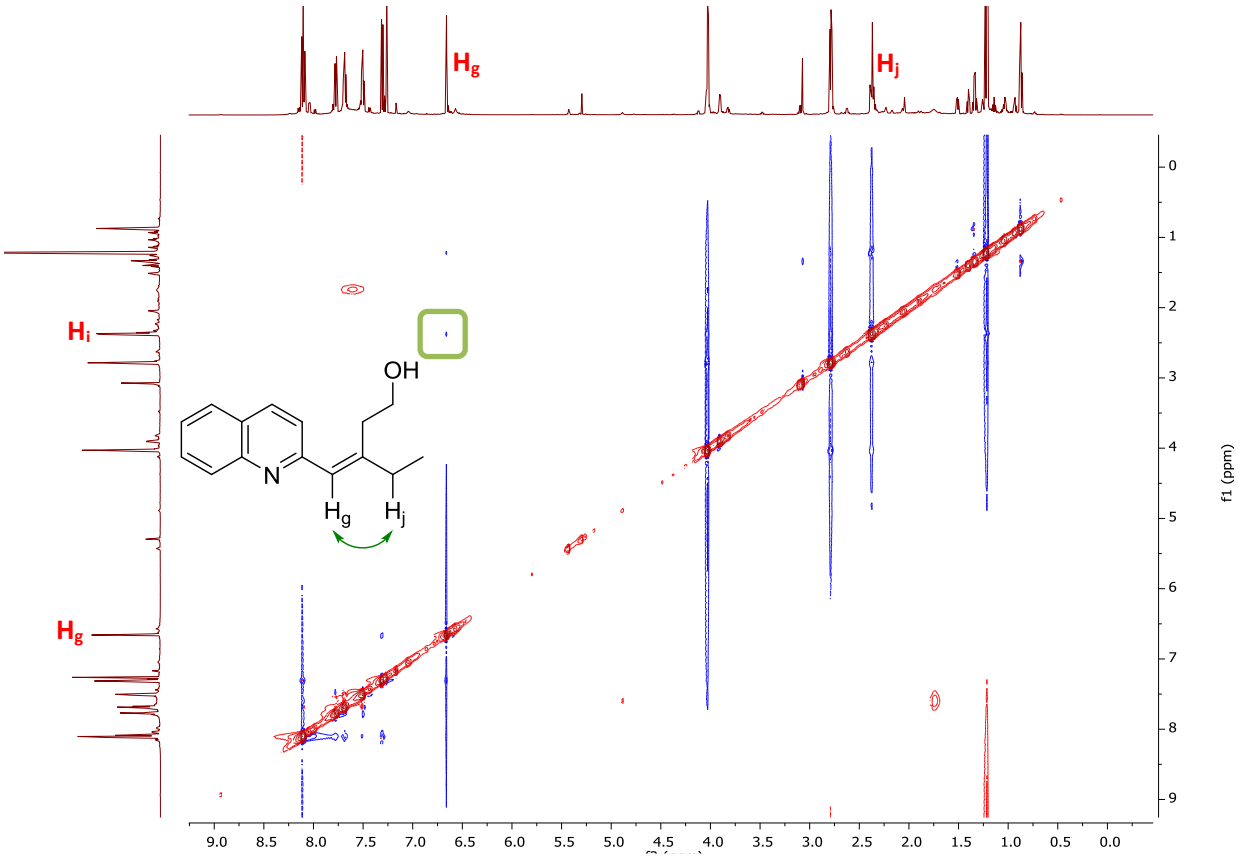
15, 600 MHz, ^1H NMR spectrum, $CDCl_3$.



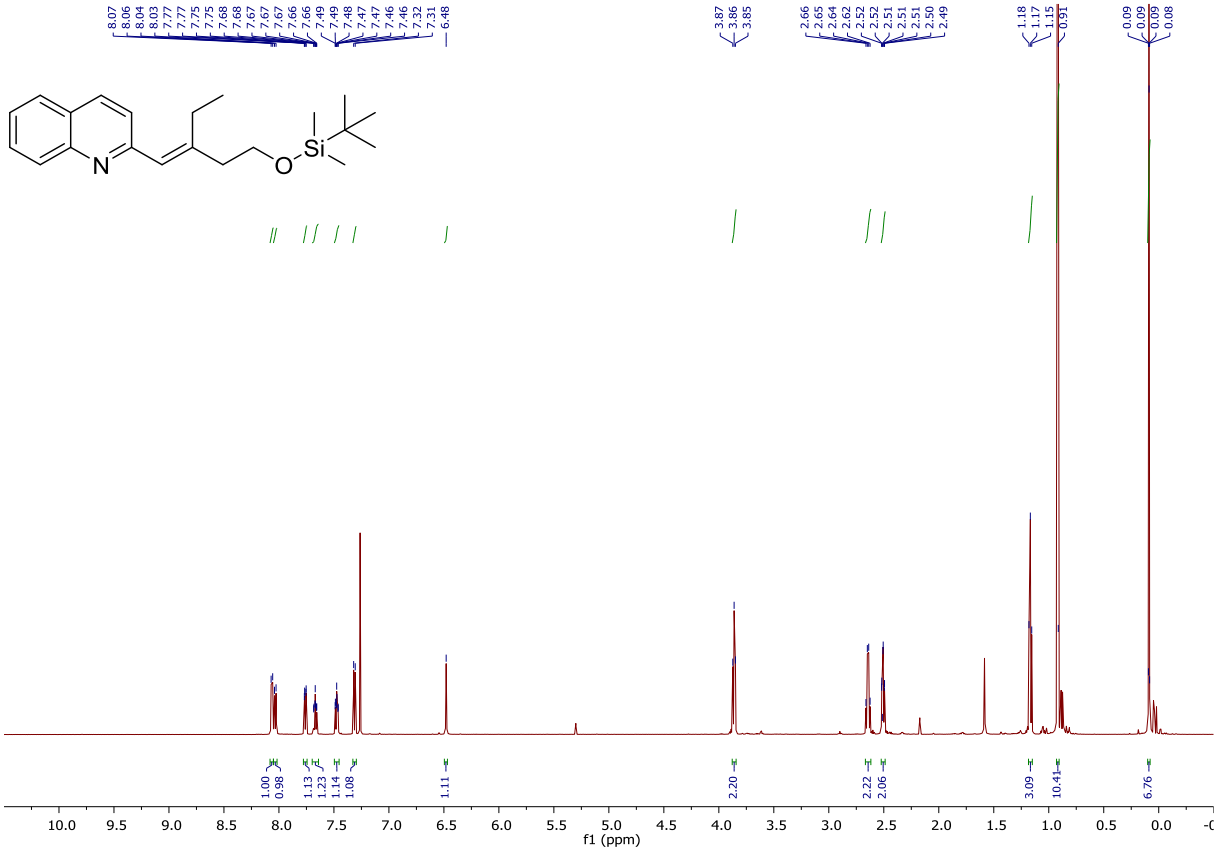
15, 151 MHz, ^{13}C NMR spectrum, $CDCl_3$.



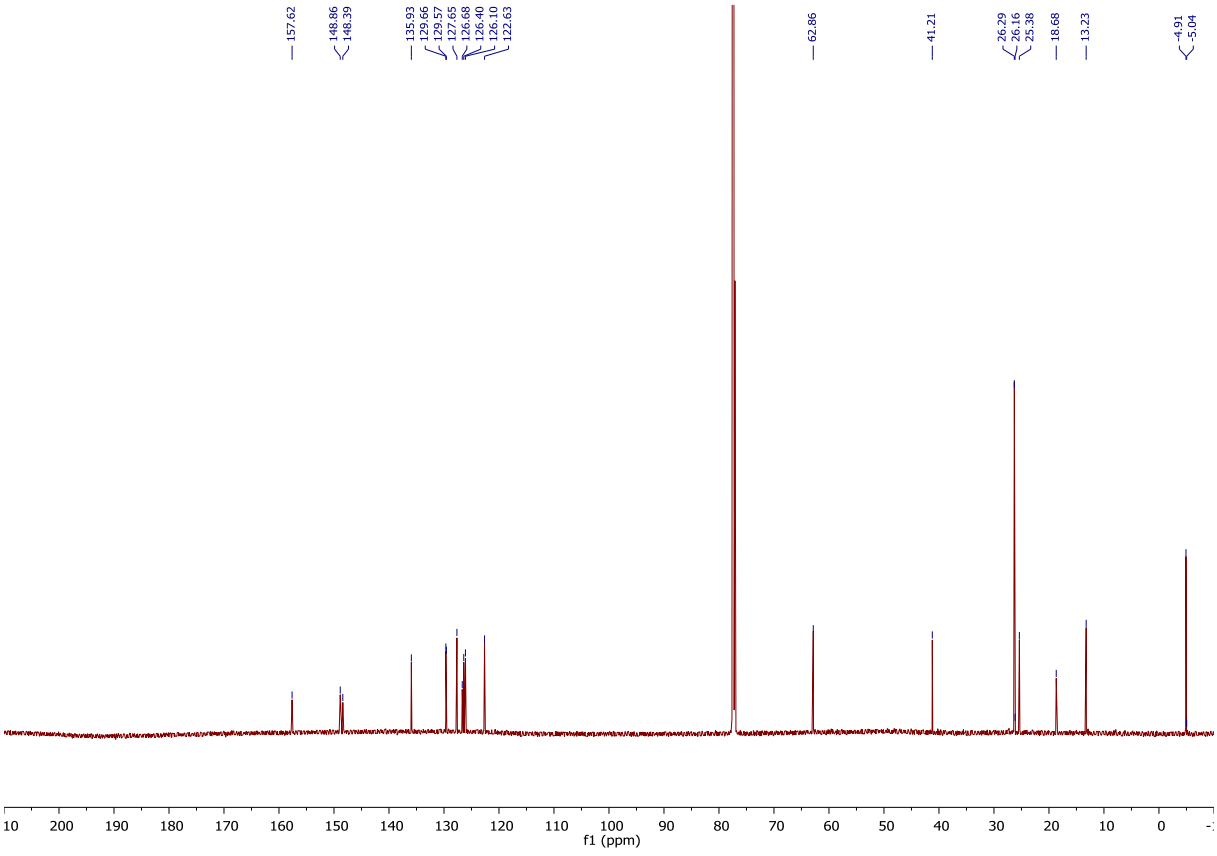
15, 2D NOESY spectrum, $CDCl_3$.



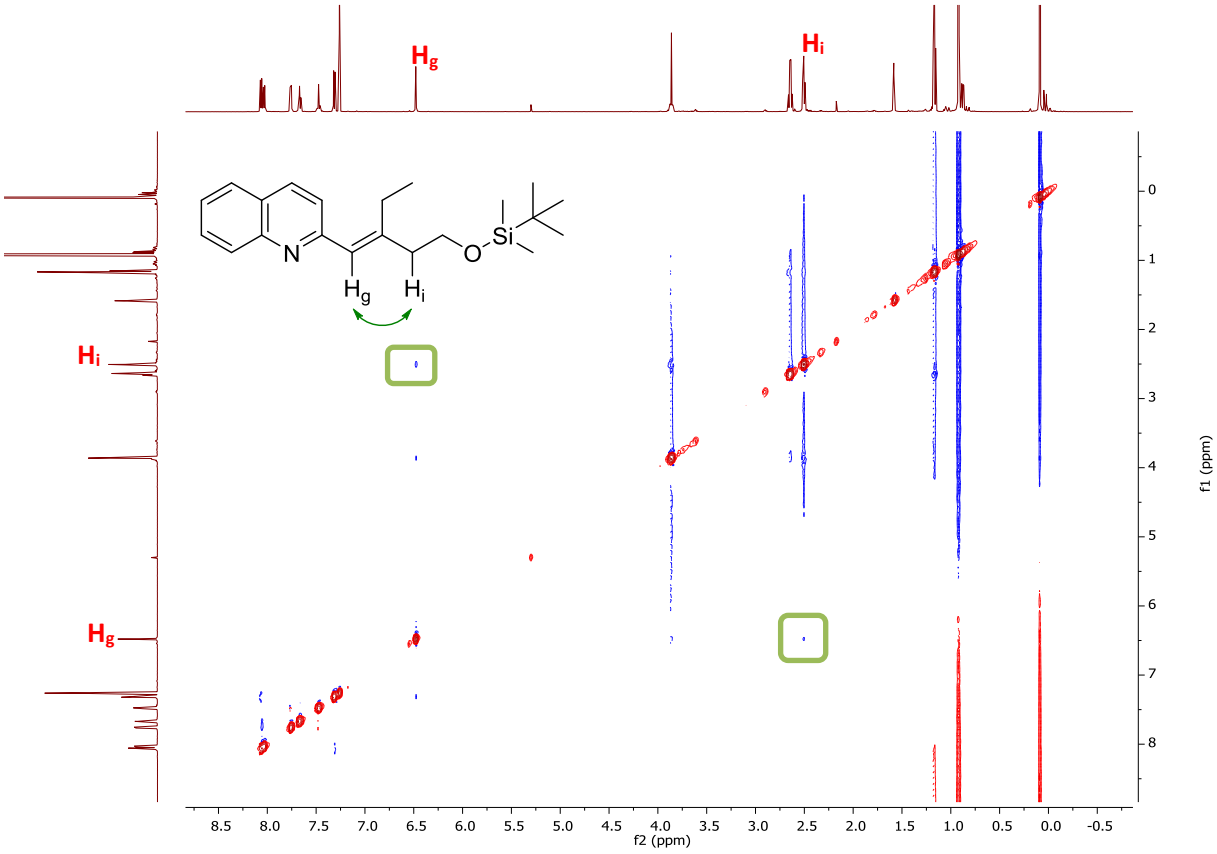
16, 600 MHz, ^{1}H NMR spectrum, $CDCl_3$.



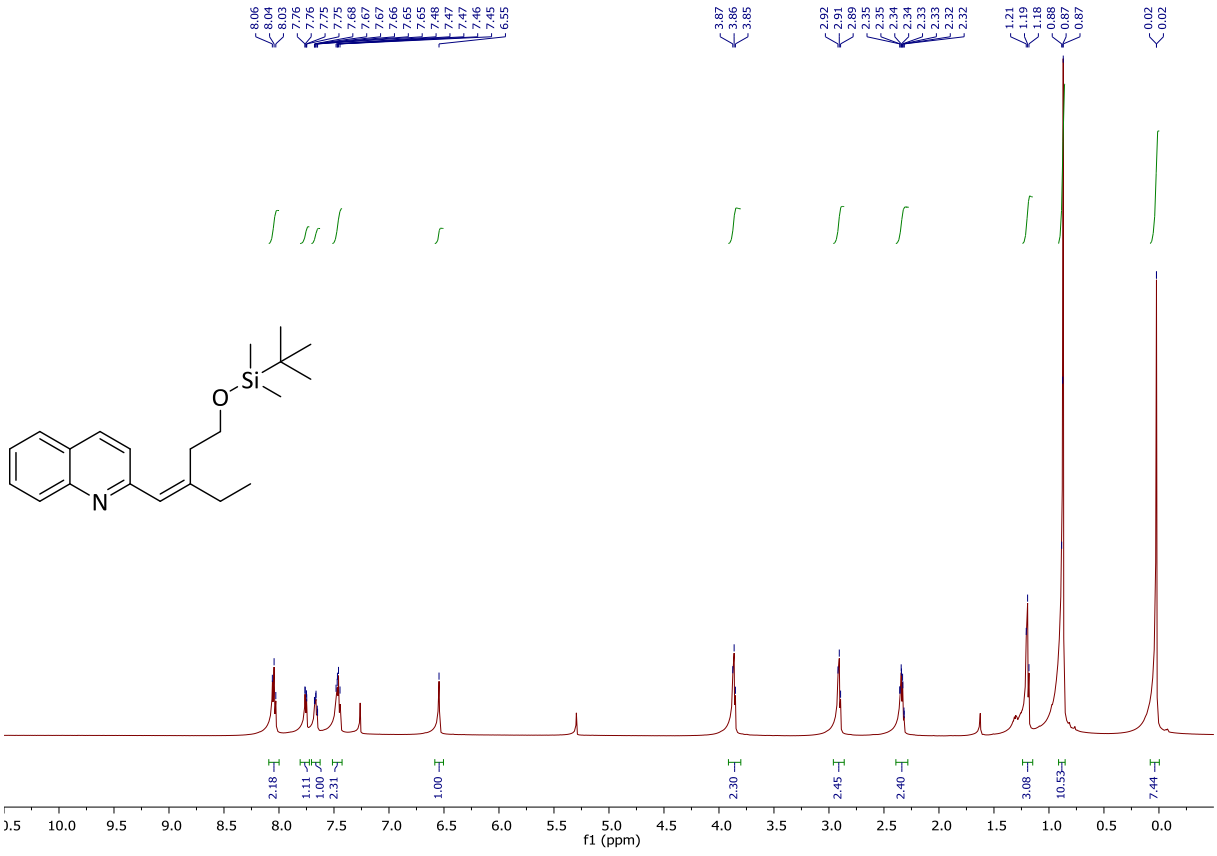
16, 151 MHz, ^{13}C NMR spectrum, $CDCl_3$.



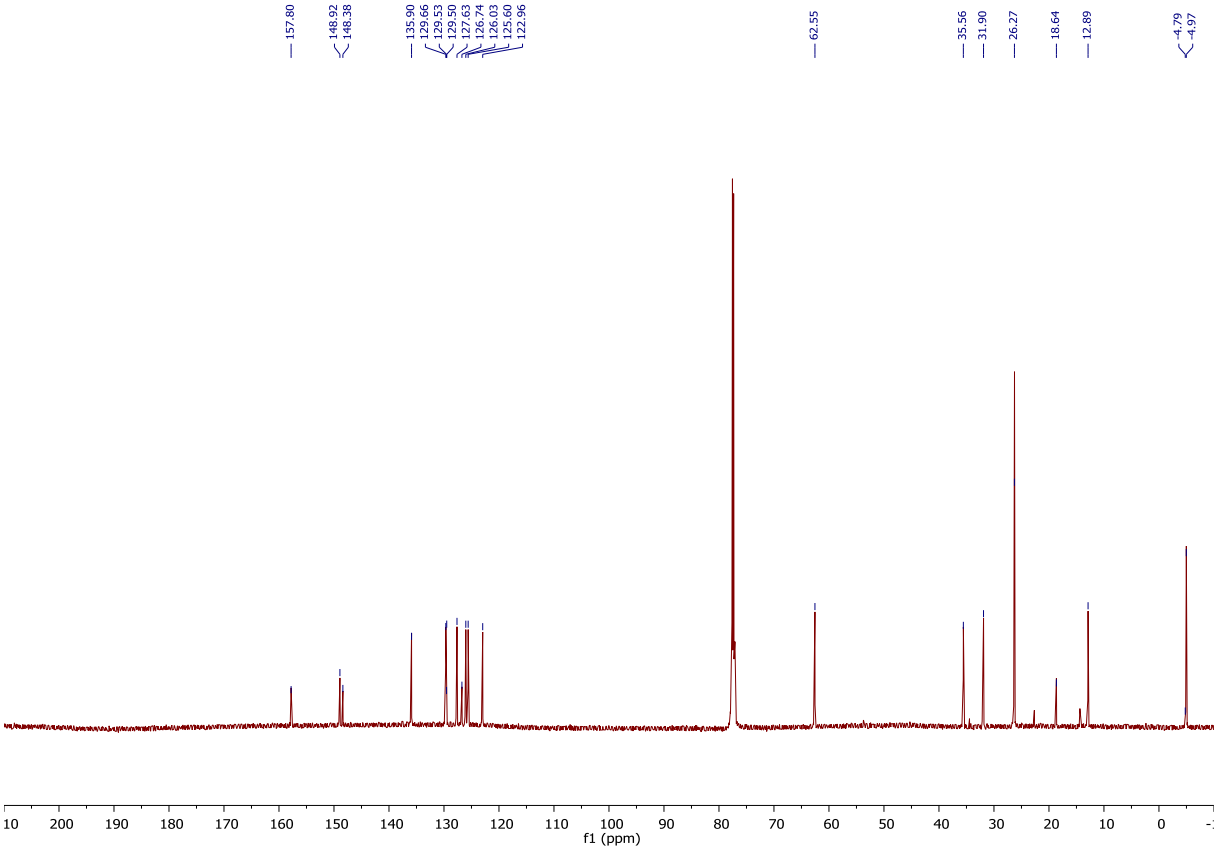
16, 2D NOESY spectrum, $CDCl_3$.



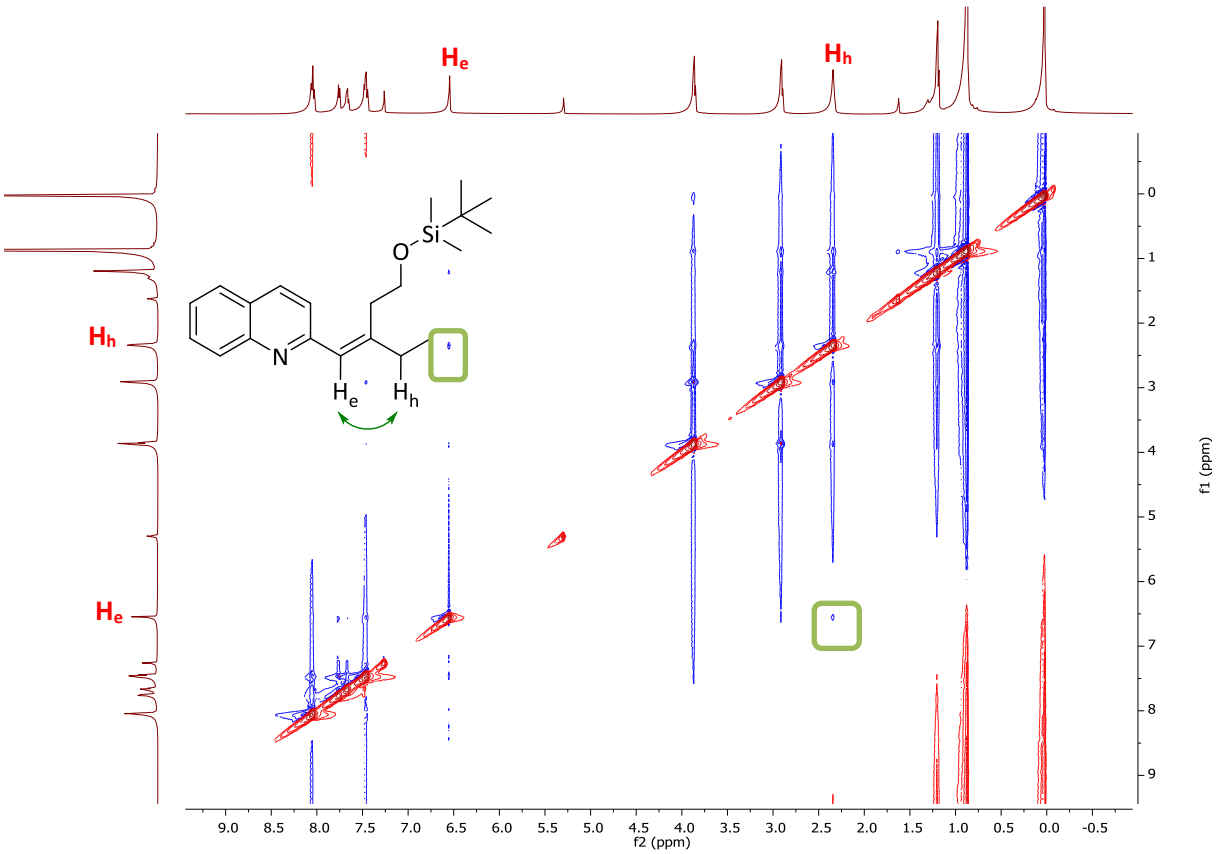
17, 600 MHz, ^1H NMR spectrum, $CDCl_3$.



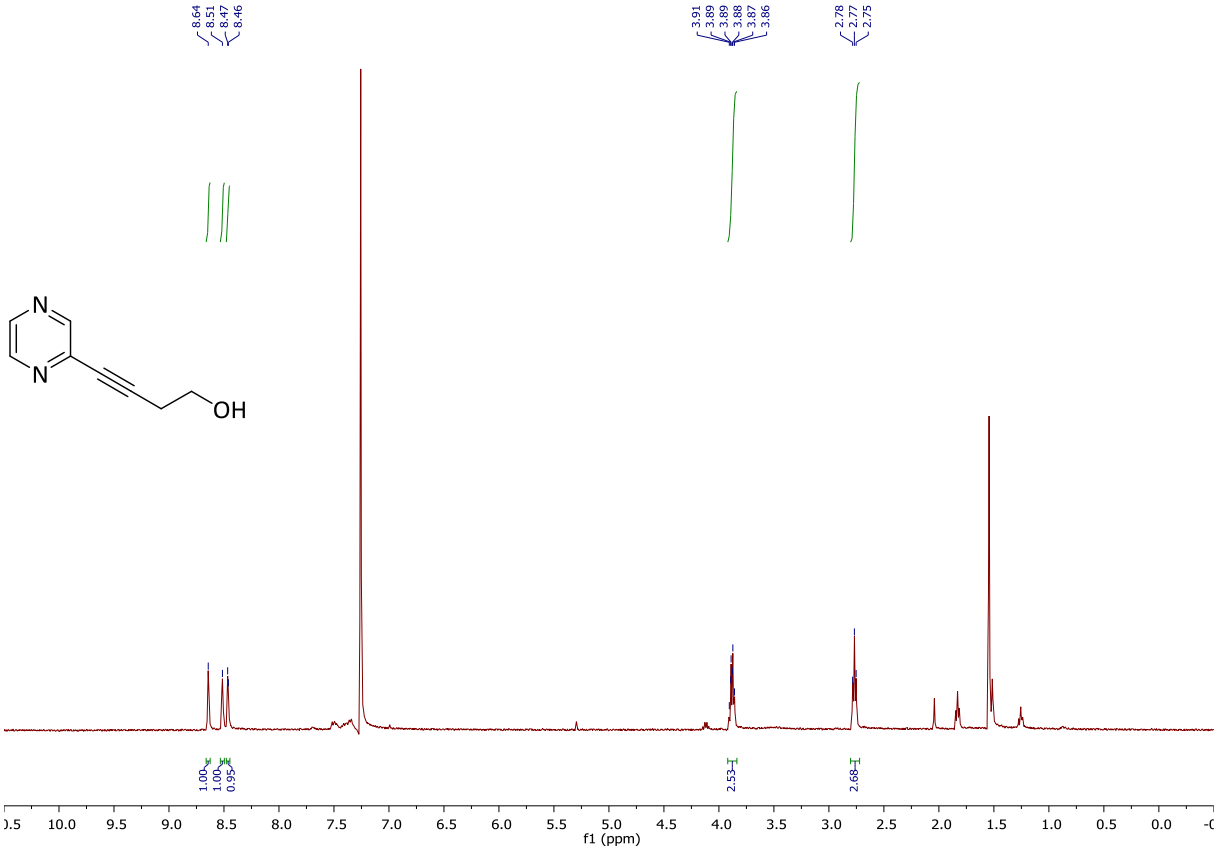
17, 151 MHz, ^{13}C NMR spectrum, $CDCl_3$.



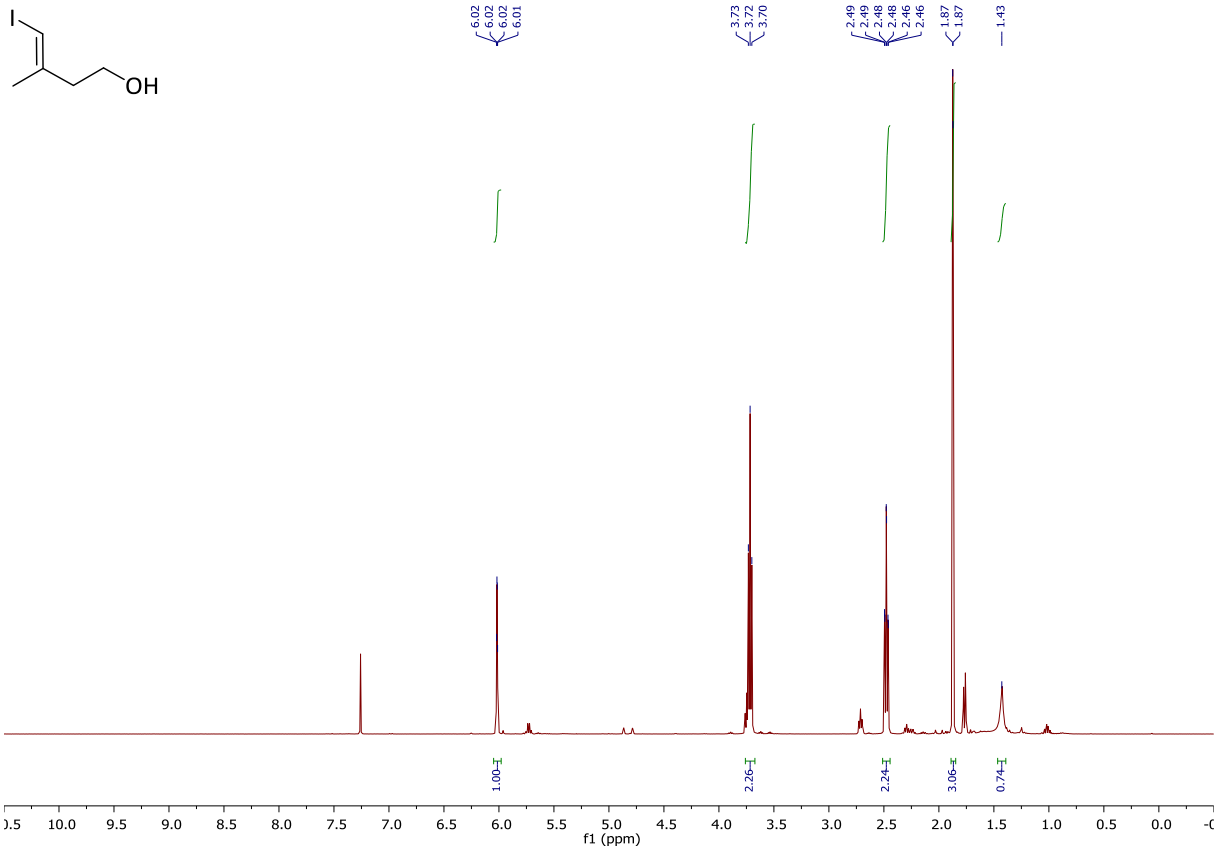
17, 2D NOESY spectrum, $CDCl_3$.



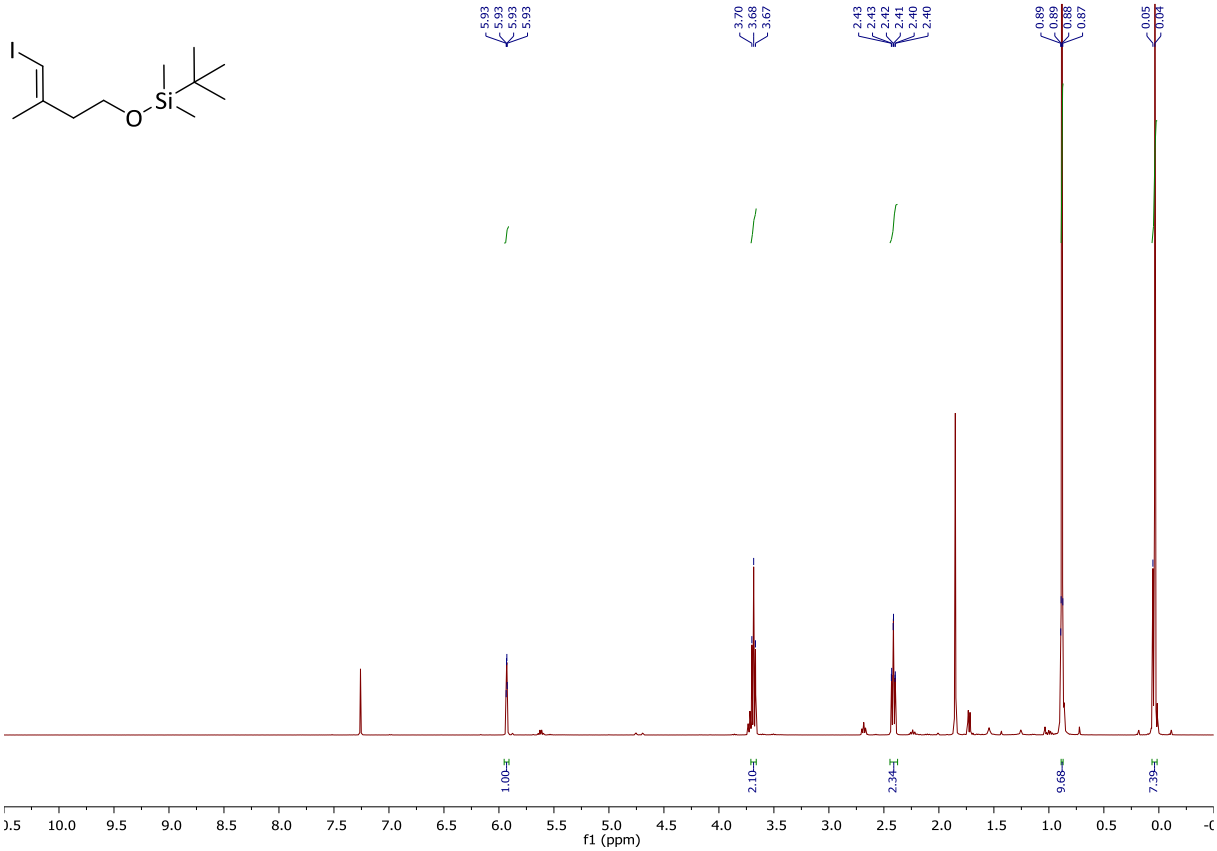
19, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



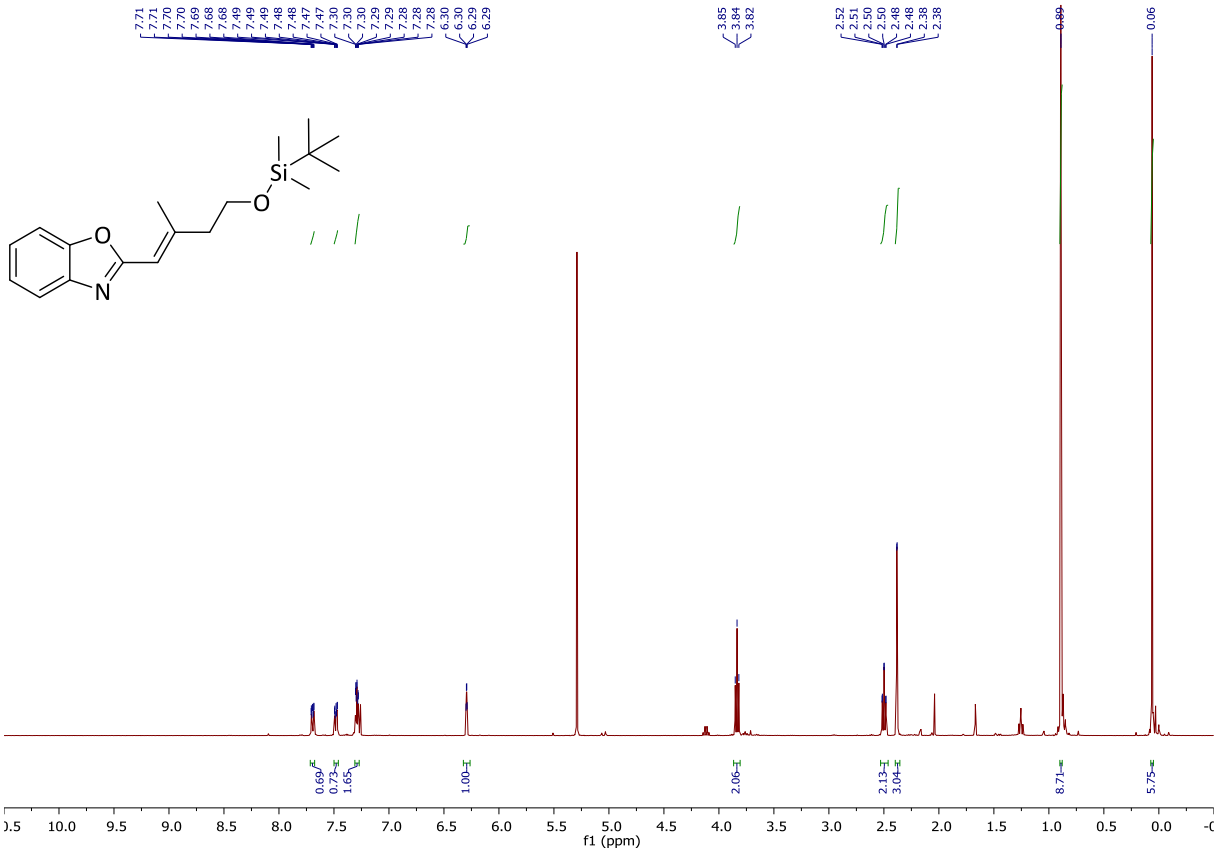
25, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



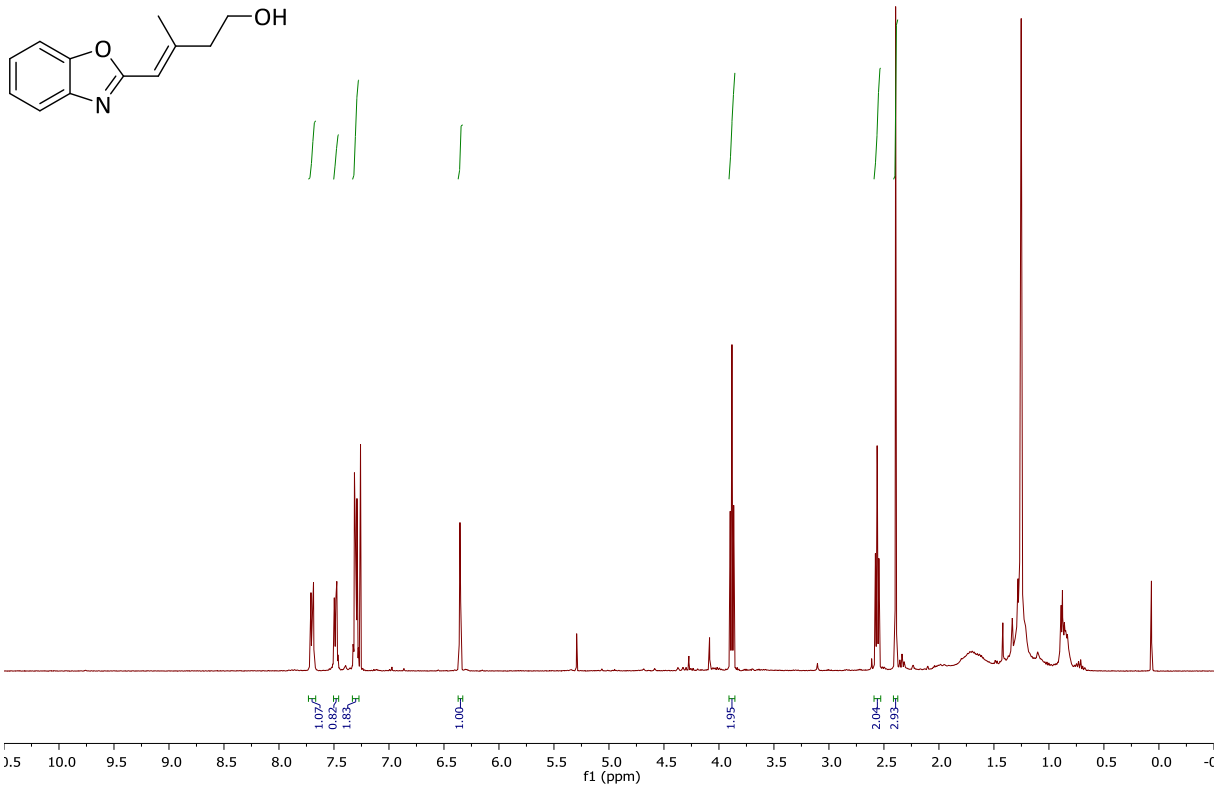
26, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



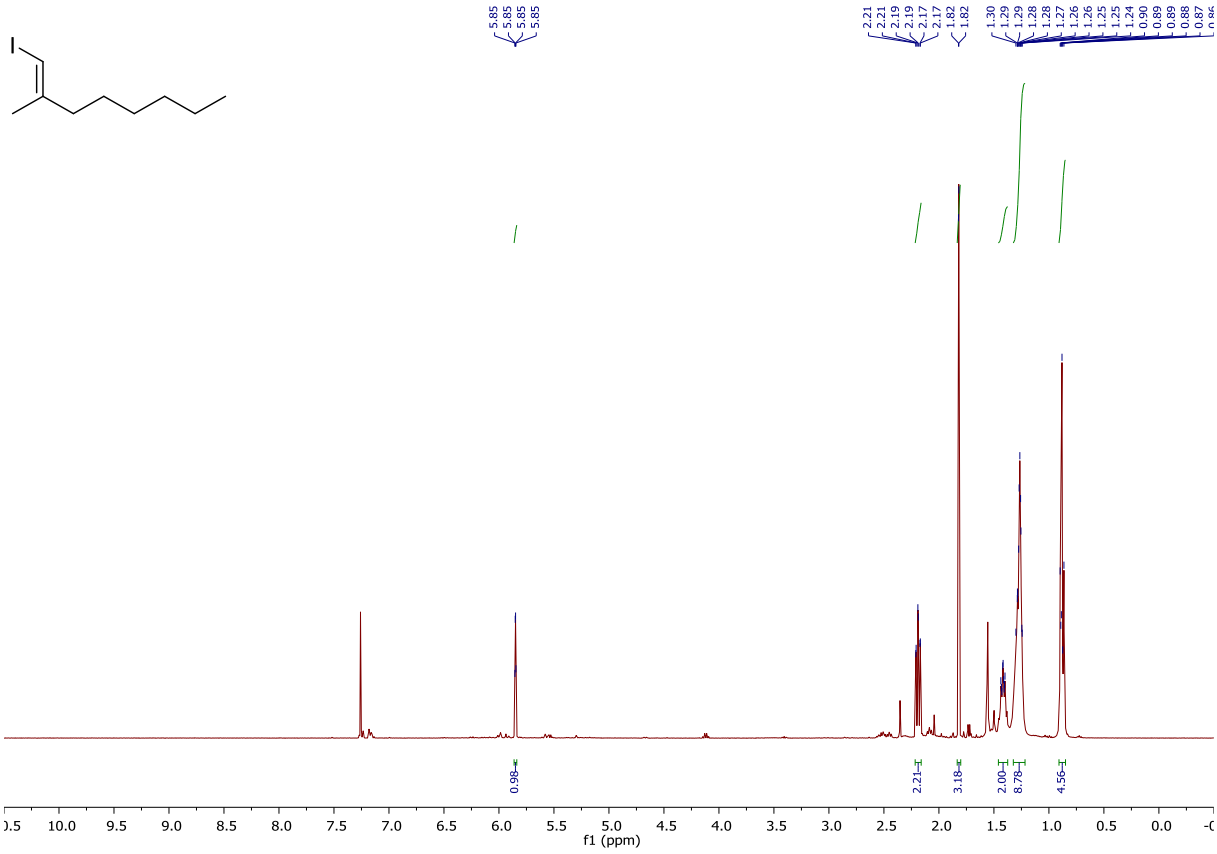
28, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



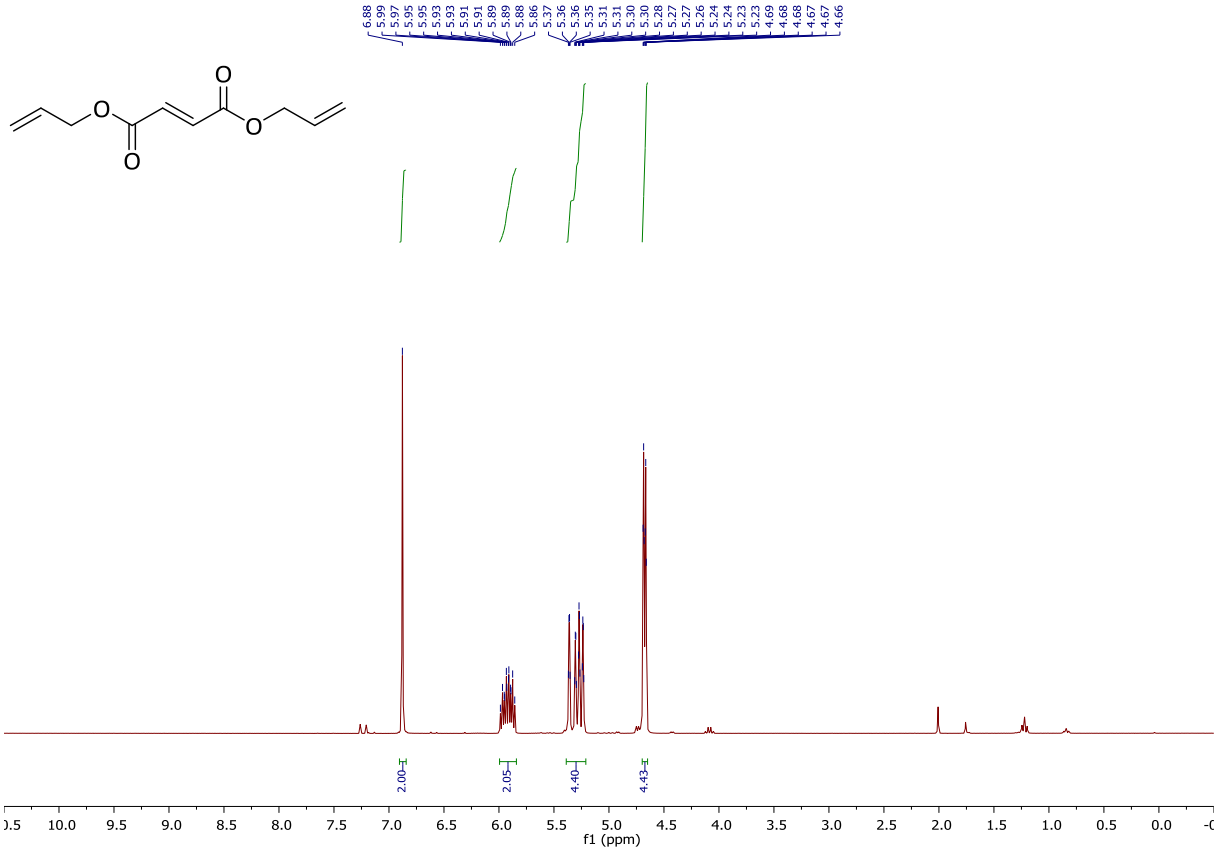
30, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



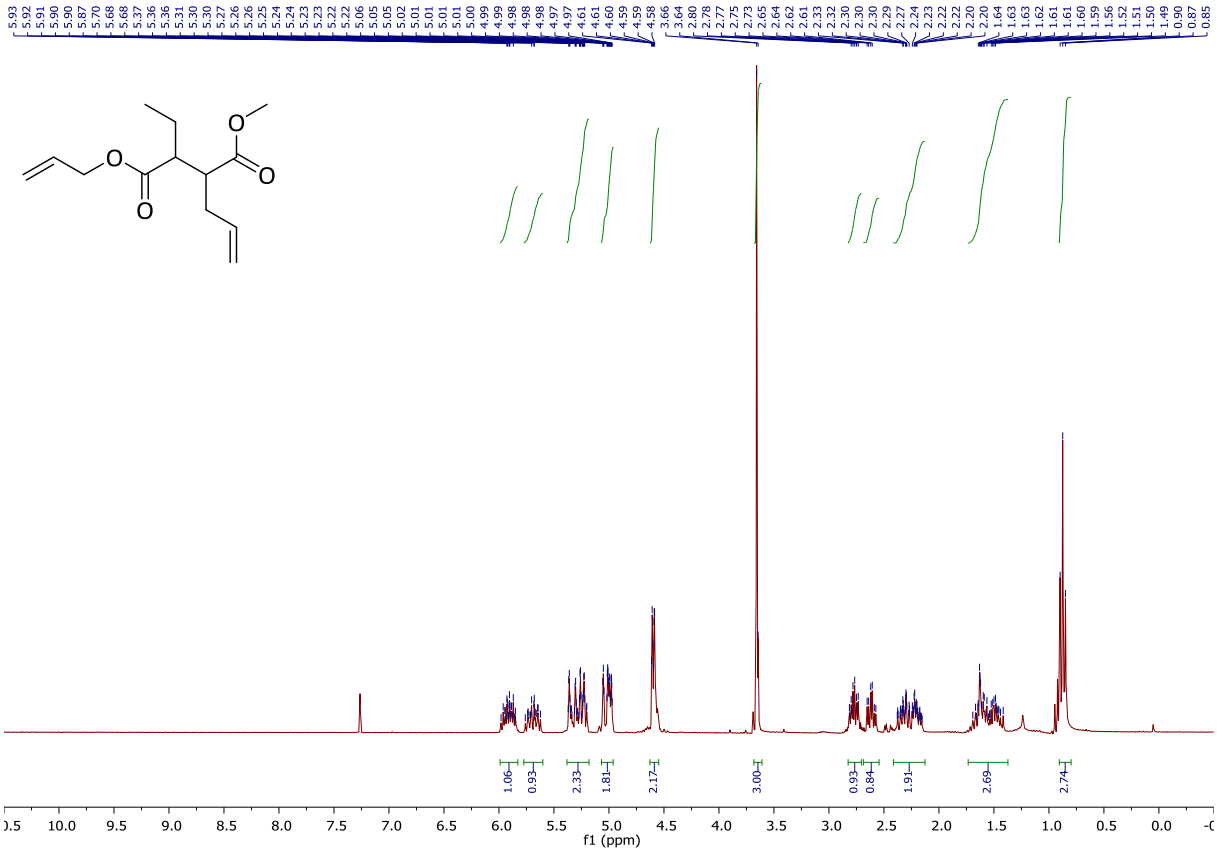
32, 400 MHz, ^{1}H NMR spectrum, $CDCl_3$.



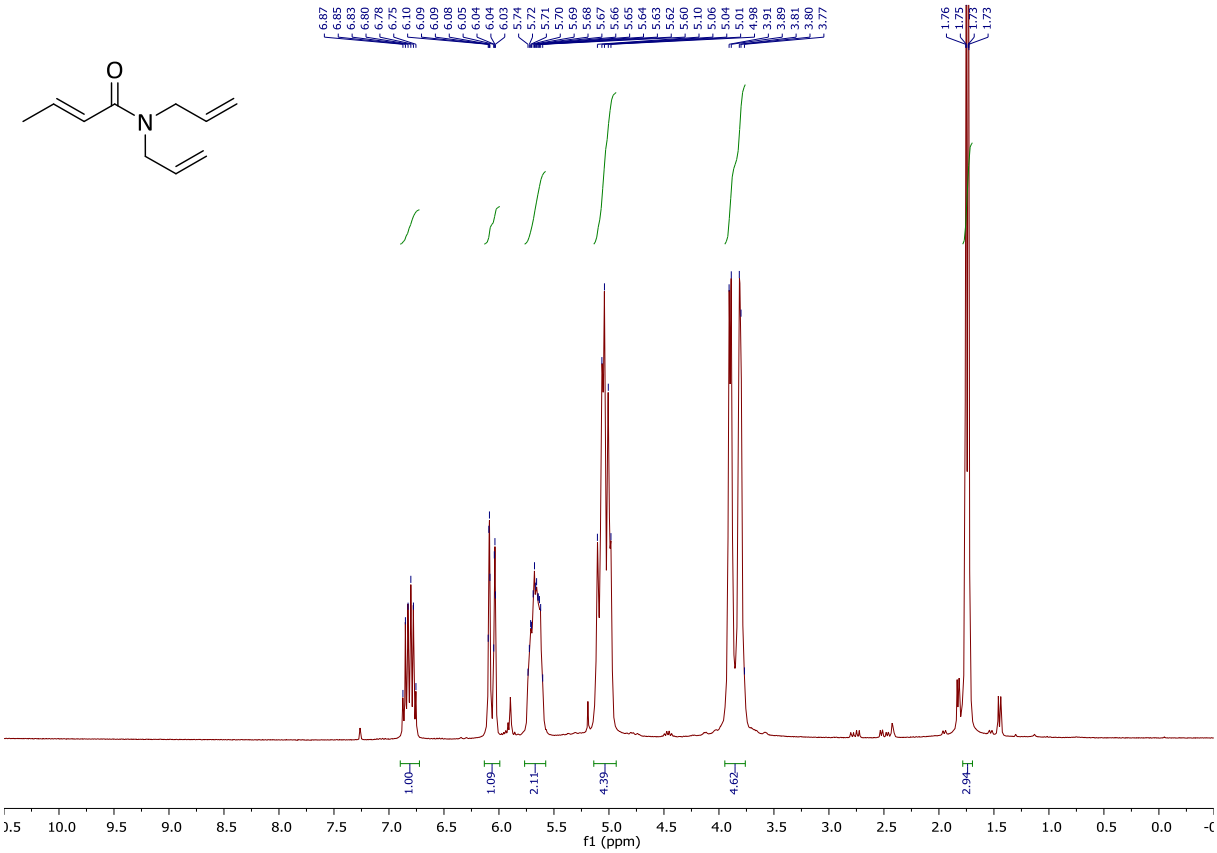
36, 400 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



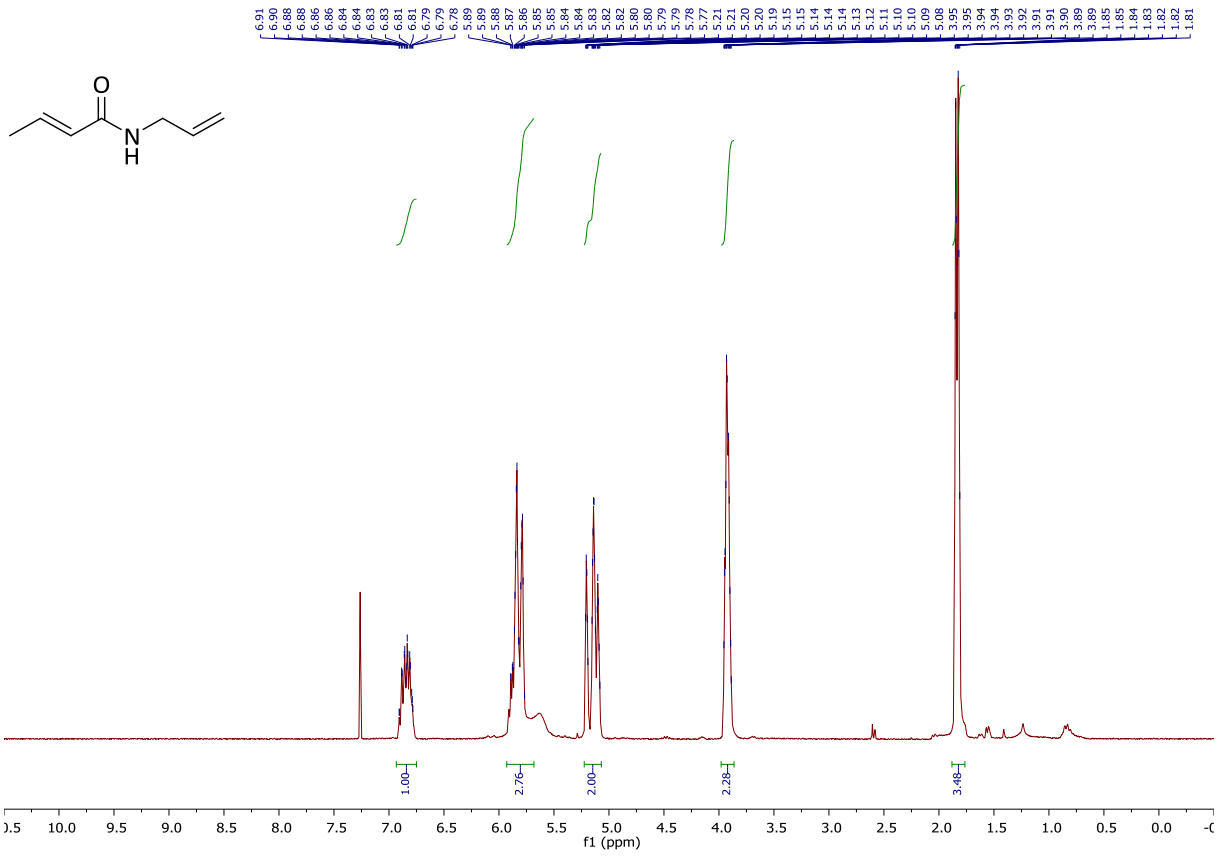
37, 400 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



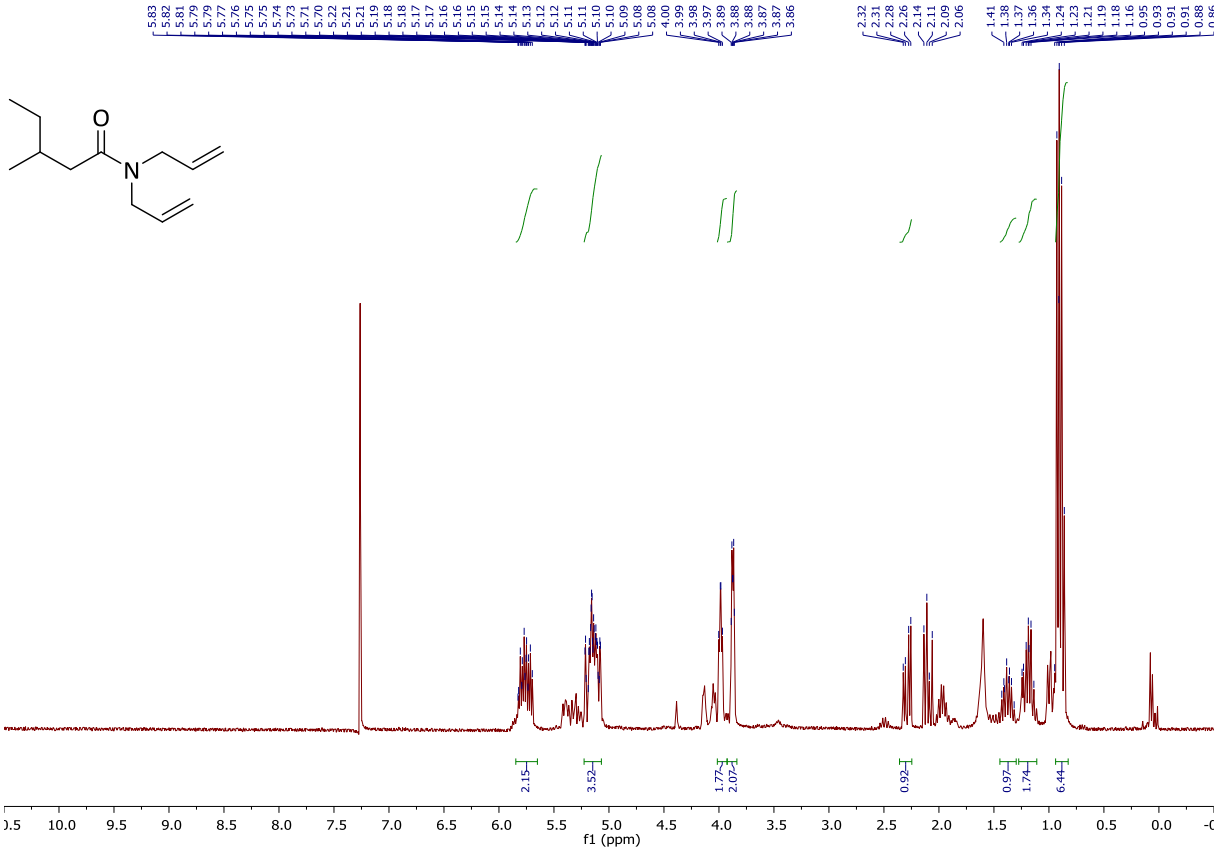
40, 400 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



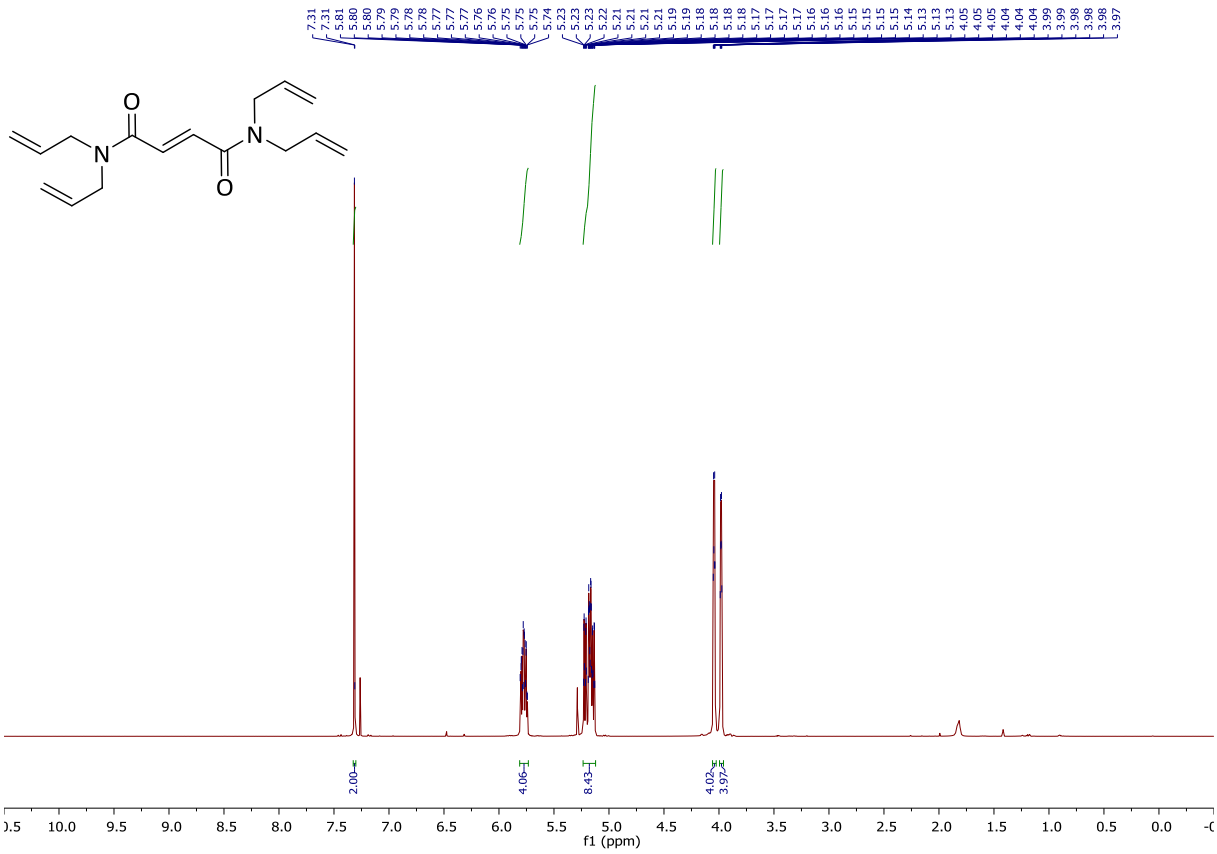
42, 400 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



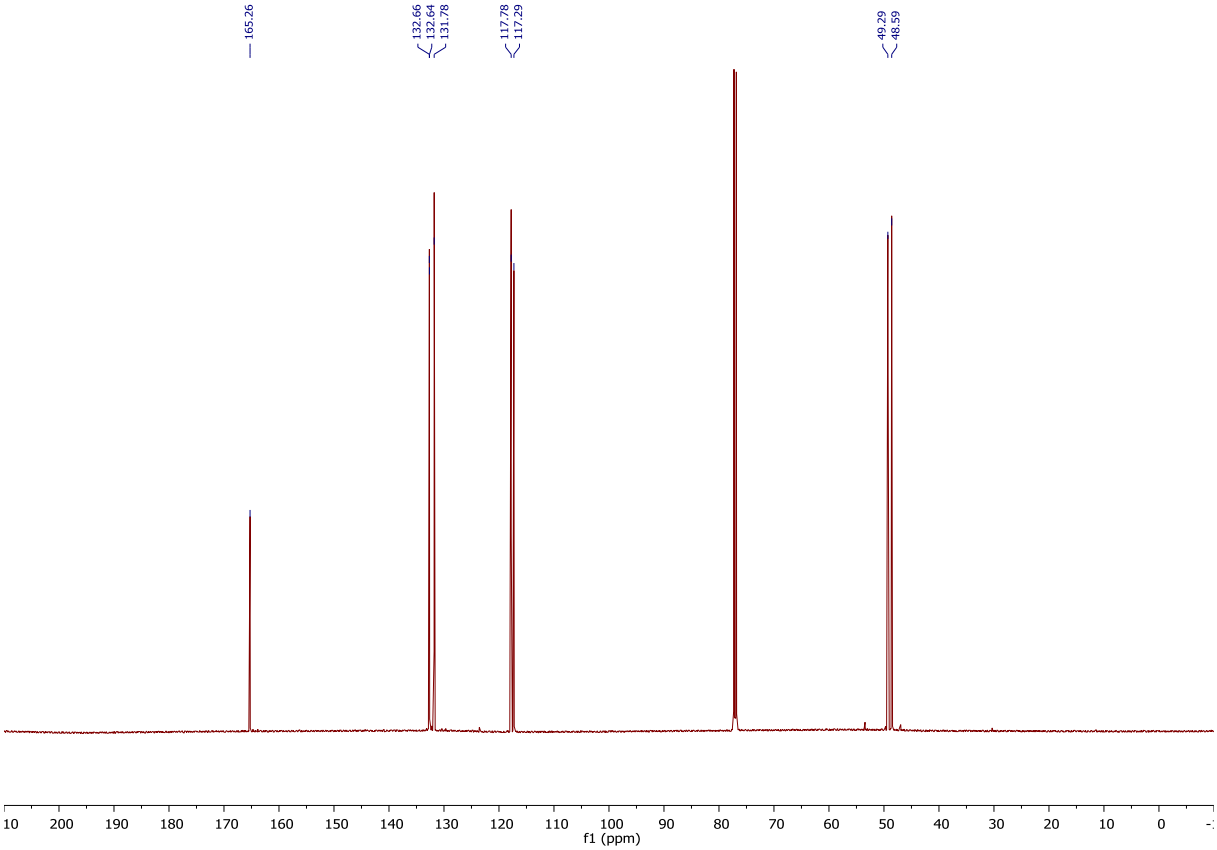
43, 400 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



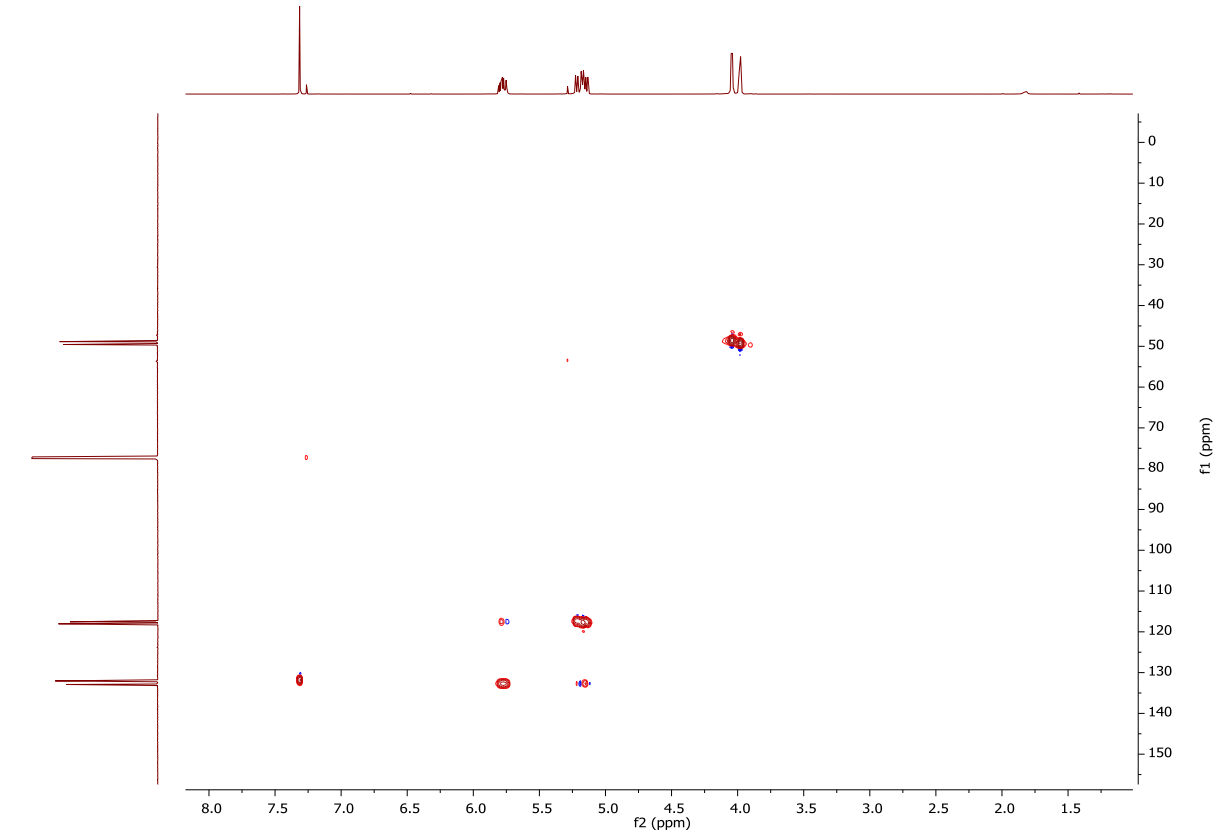
47, 600 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



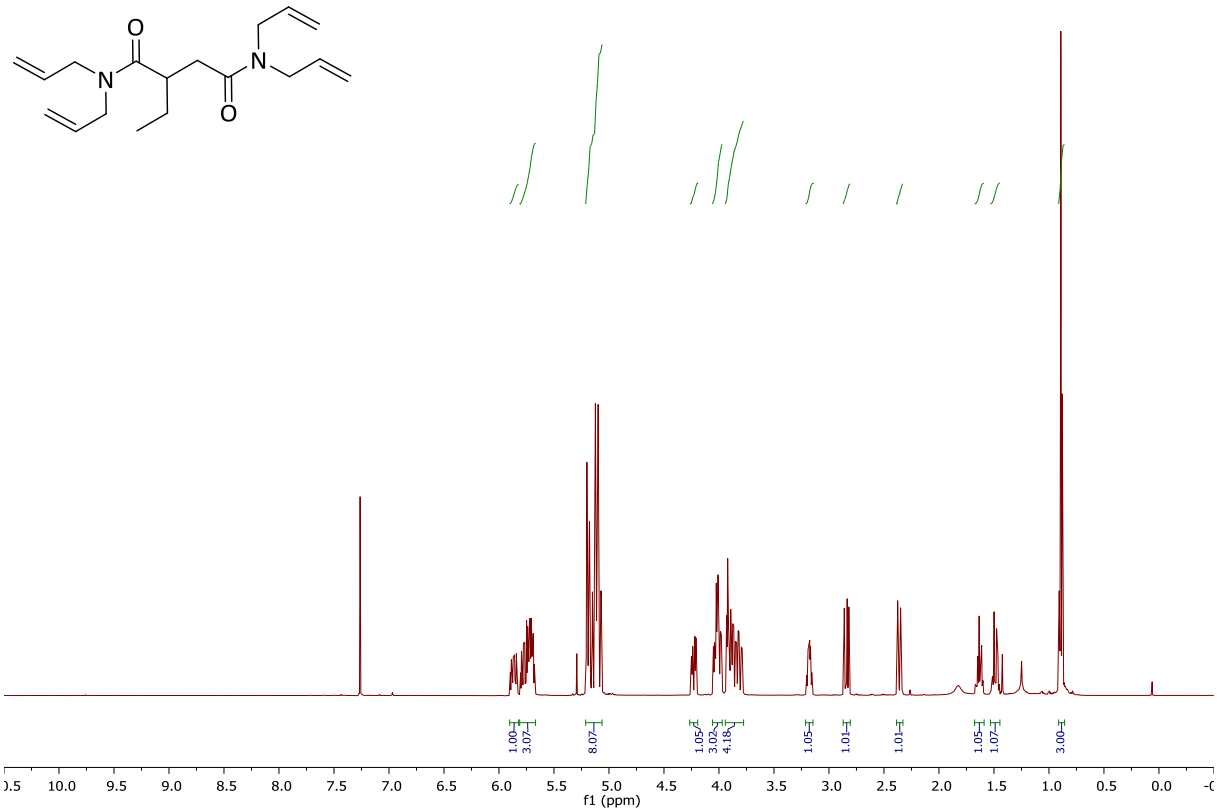
47, 151 MHz, ^{13}C-NMR spectrum, $CDCl_3$.



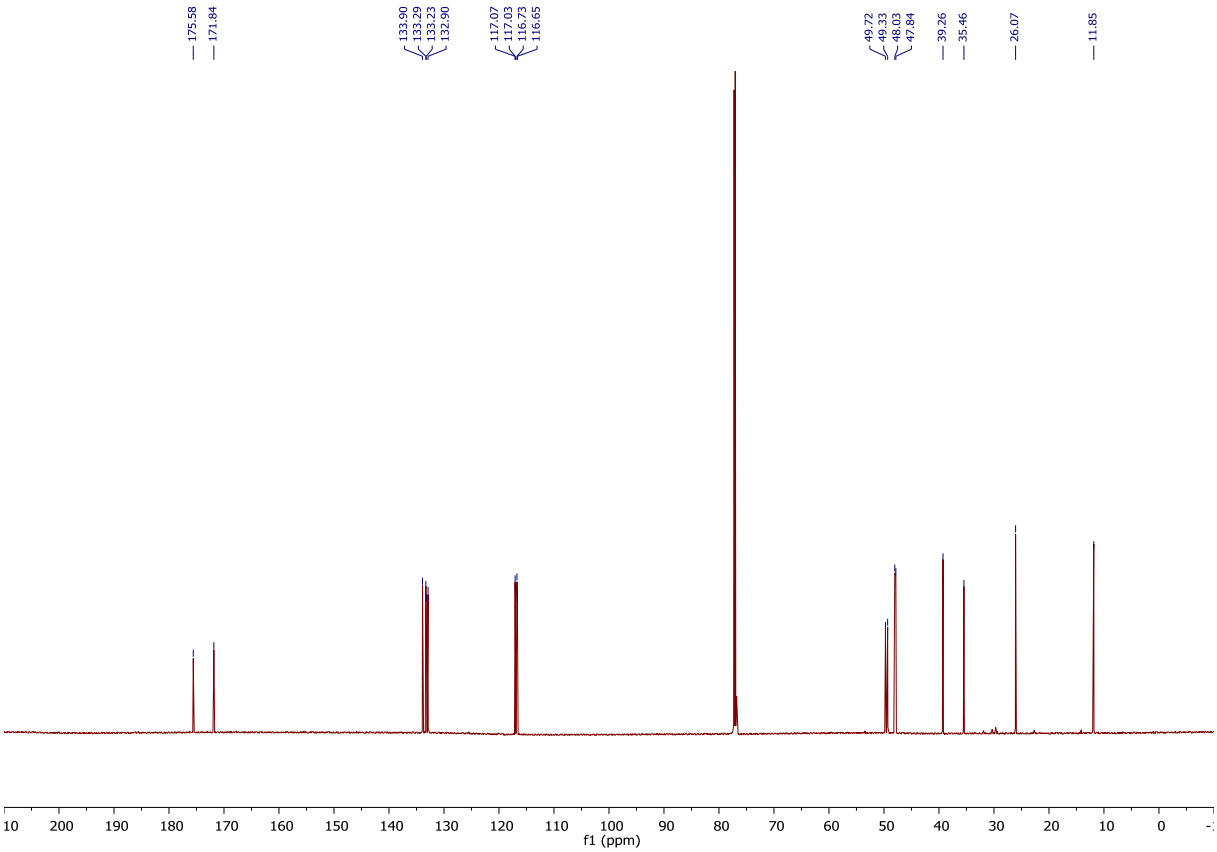
47, 2D HSQC-NMR spectrum, $CDCl_3$.



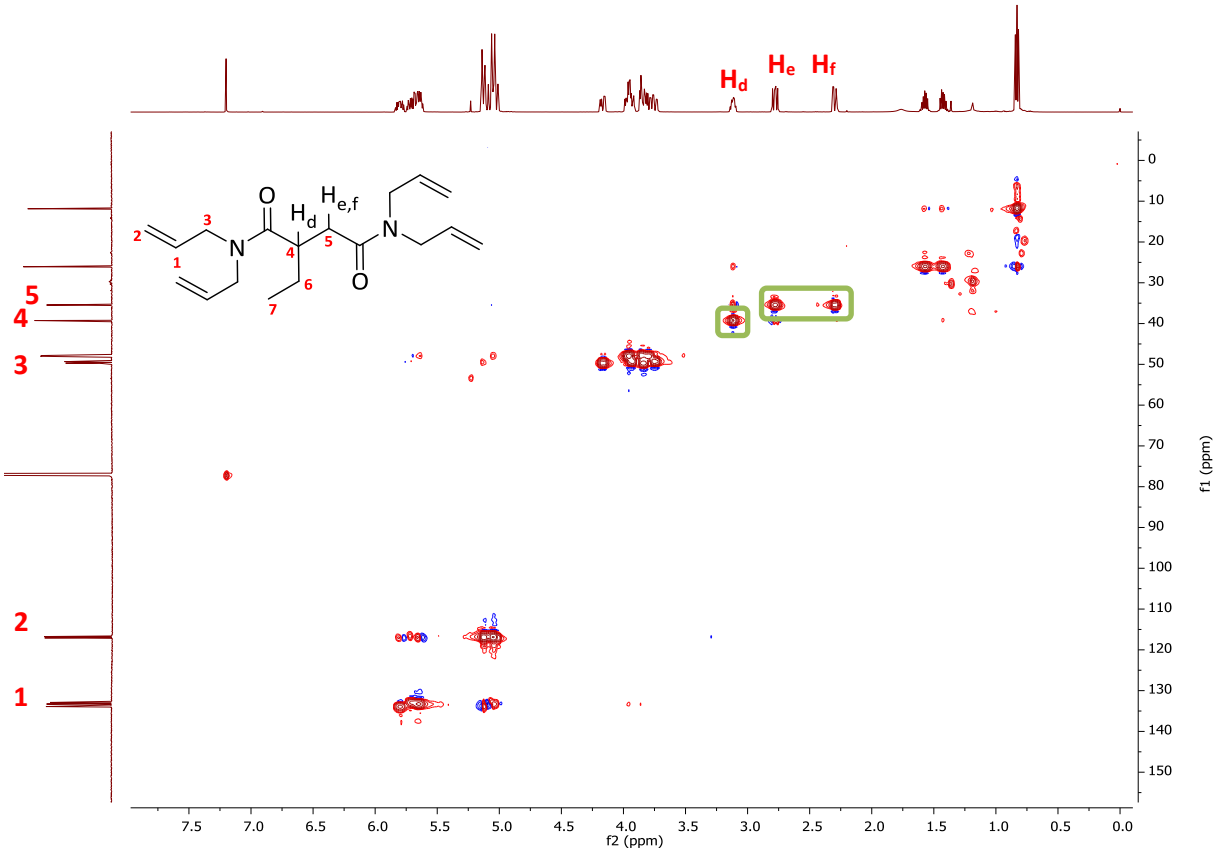
48, 600 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



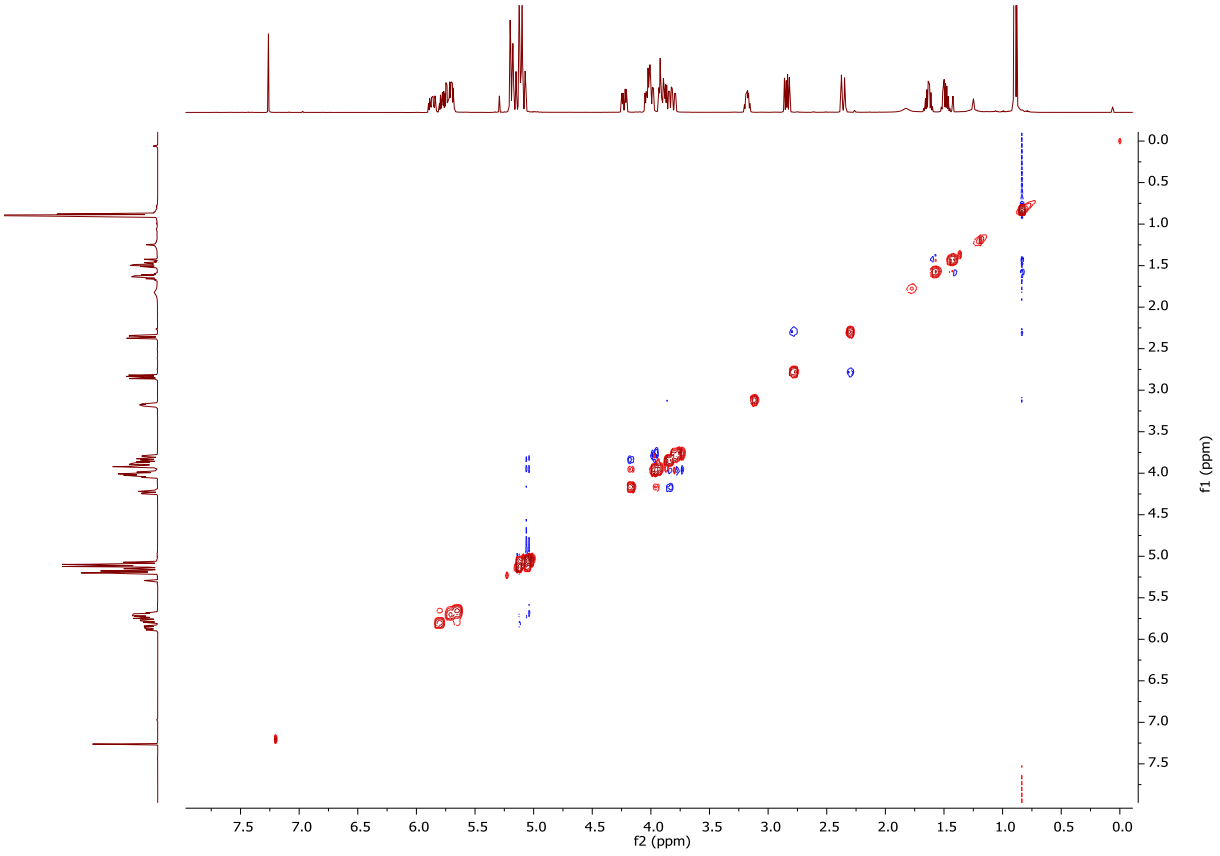
48, 151 MHz, ^{13}C-NMR spectrum, $CDCl_3$.



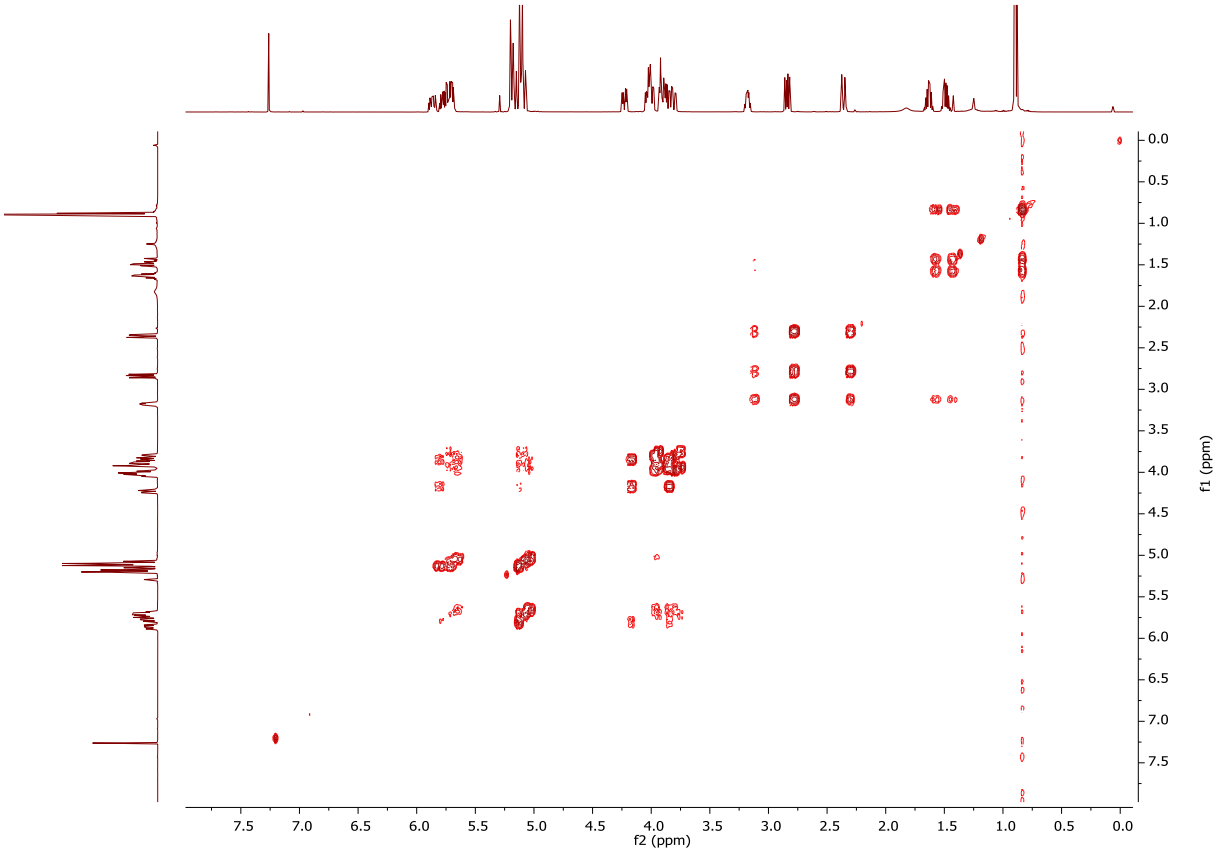
48, 2D-NMR HSQC spectrum, $CDCl_3$.



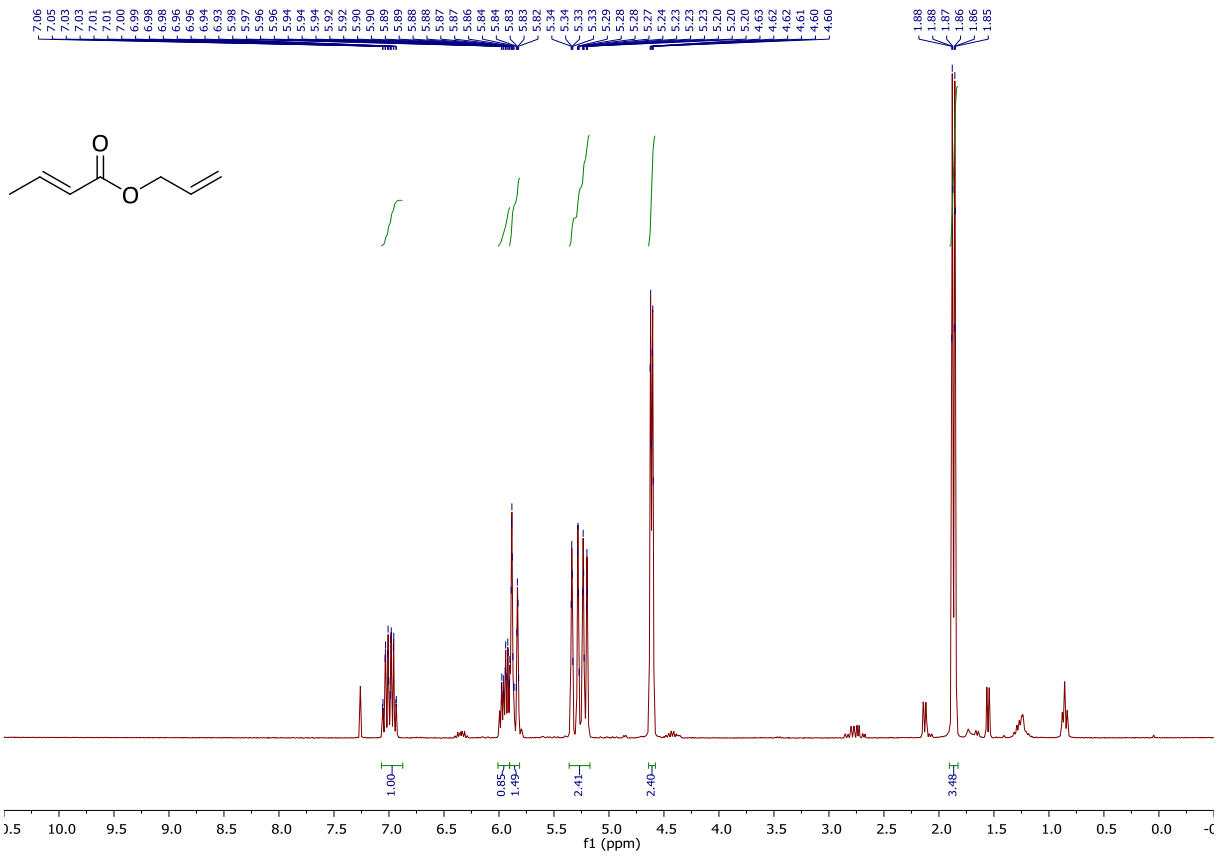
48, 2D-NMR COSY spectrum, $CDCl_3$.



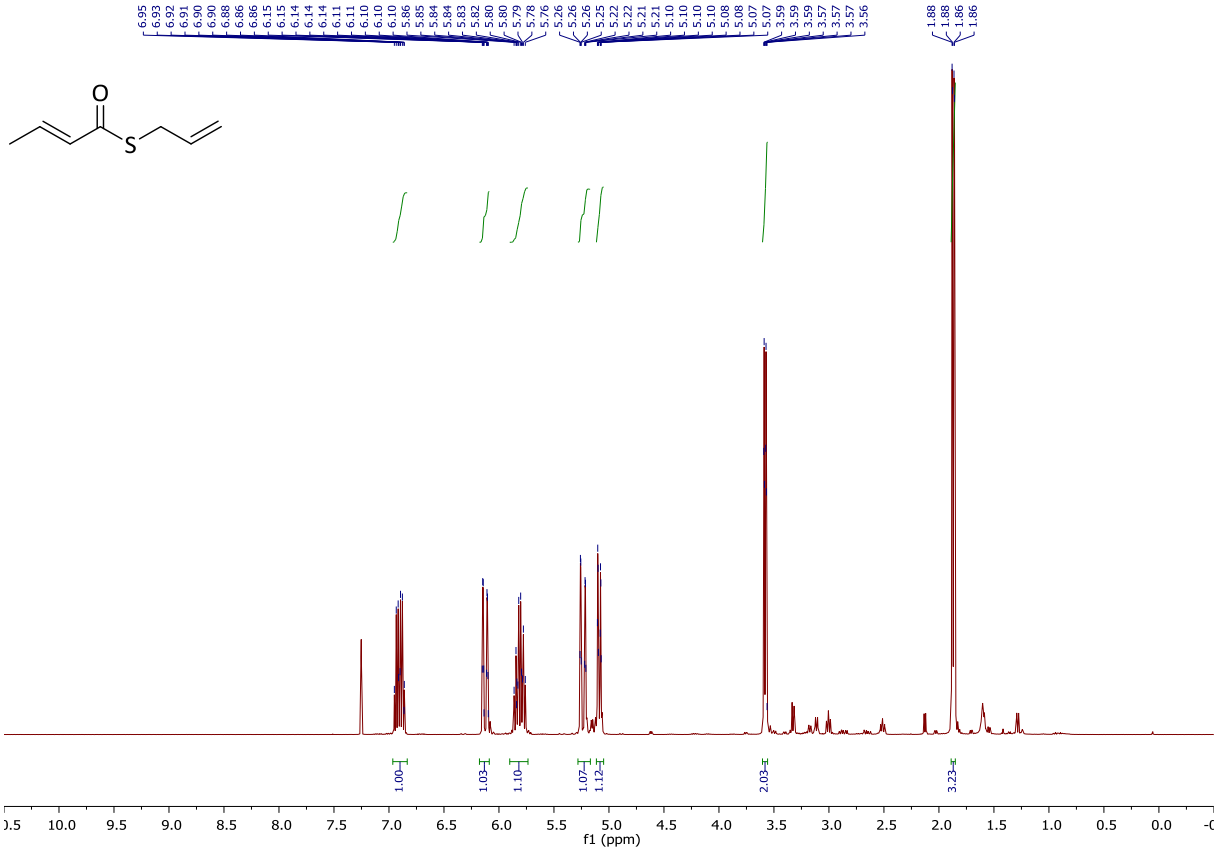
48, 2D-NMR NOESY spectrum, $CDCl_3$.



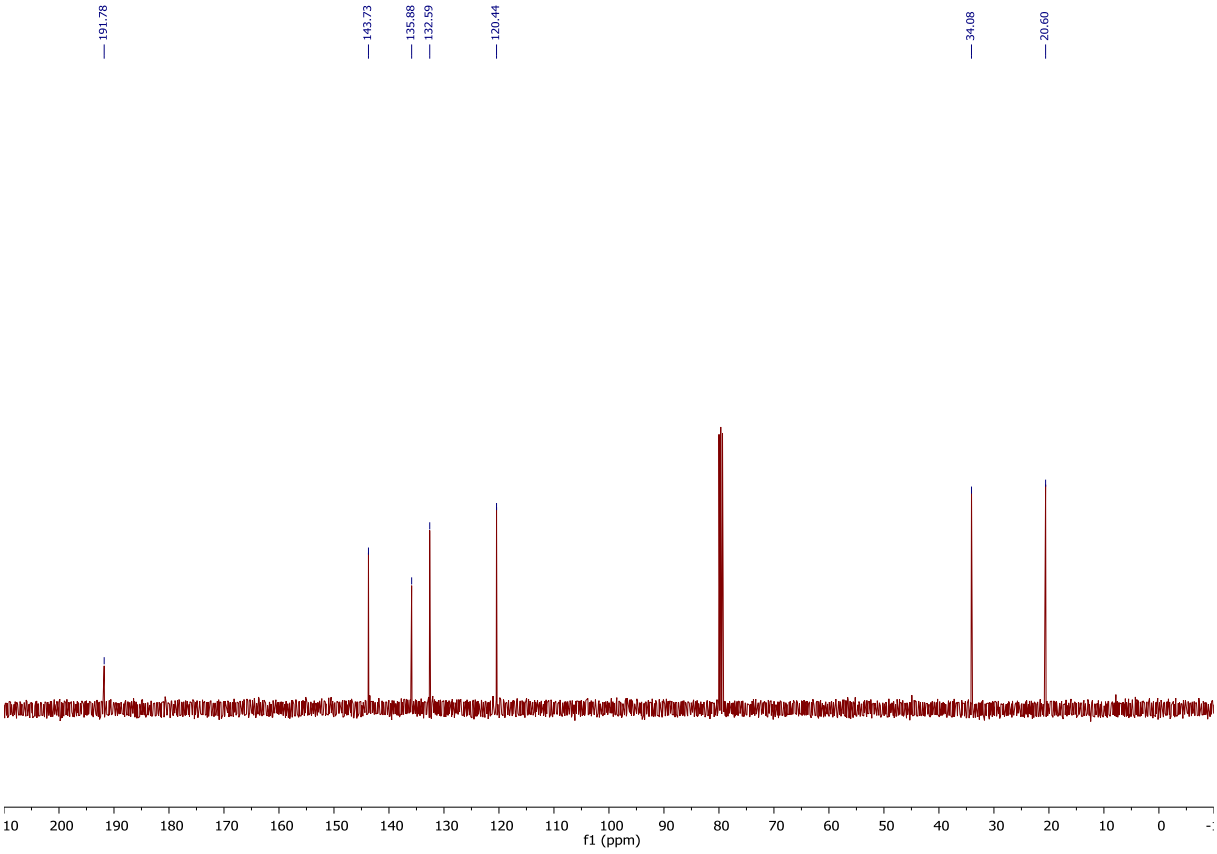
50, 400 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



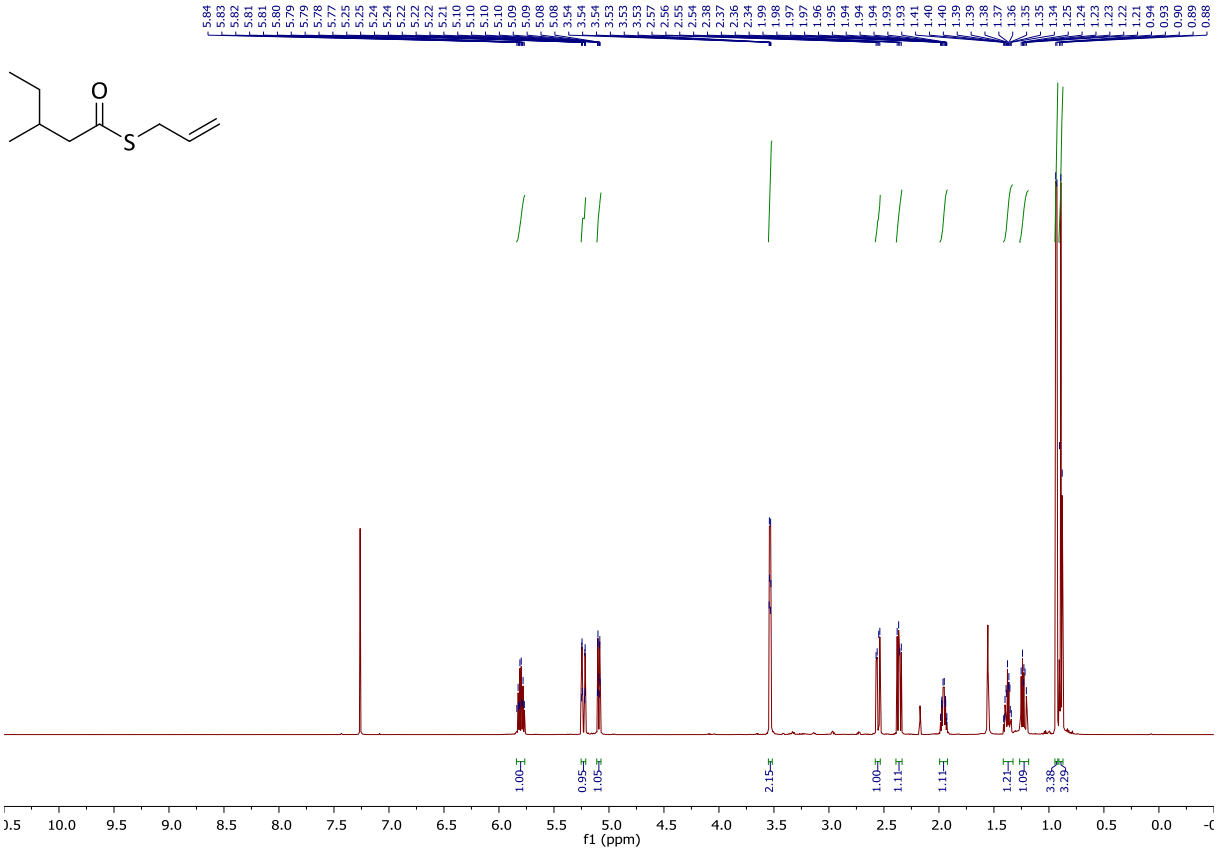
54, 400 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



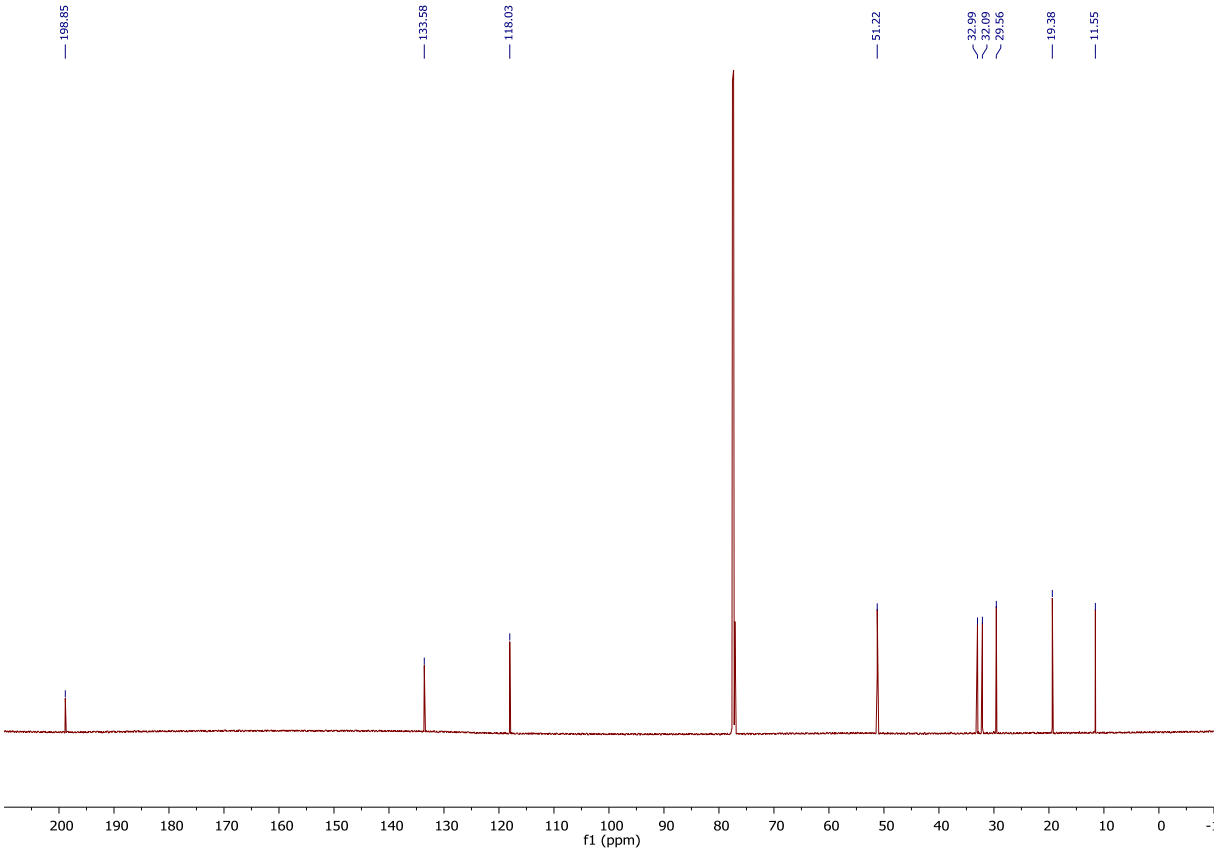
54, 101 MHz, ^{13}C-NMR spectrum, $CDCl_3$.



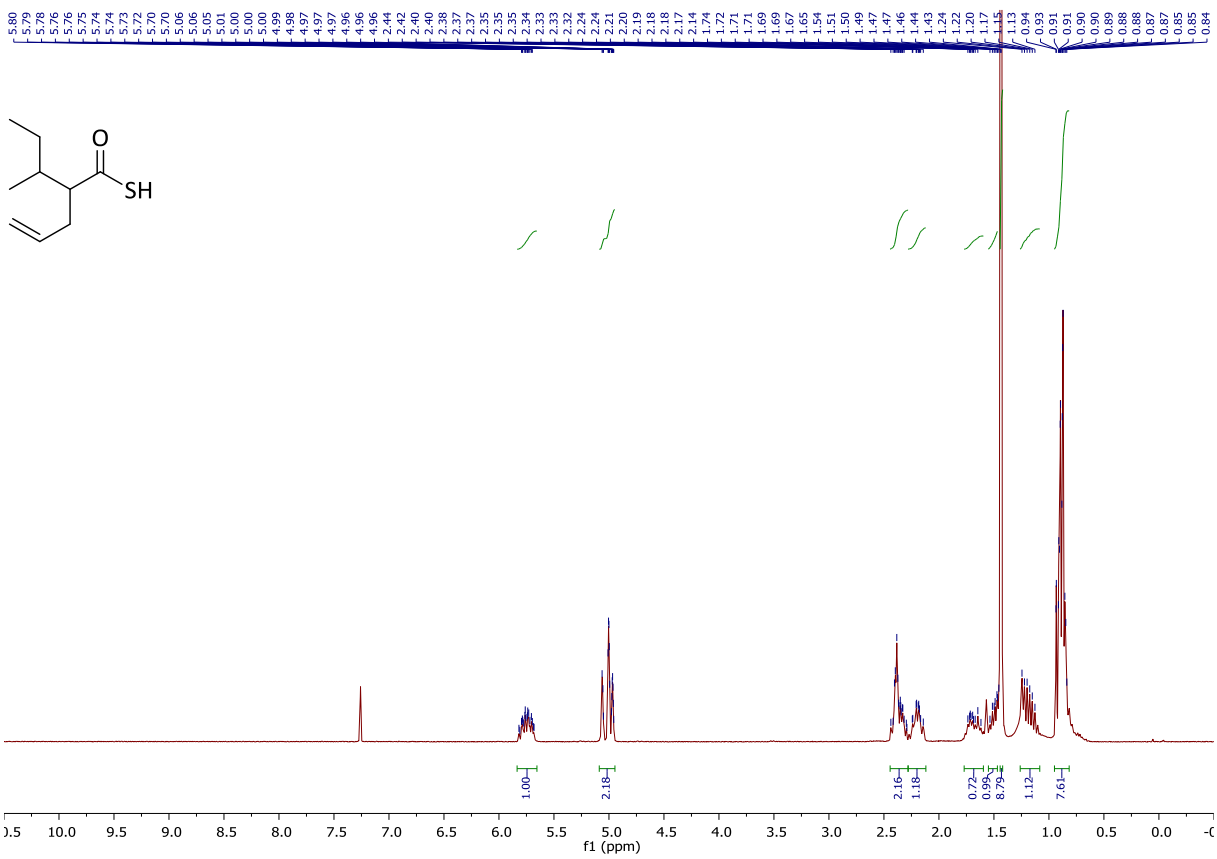
55, 600 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



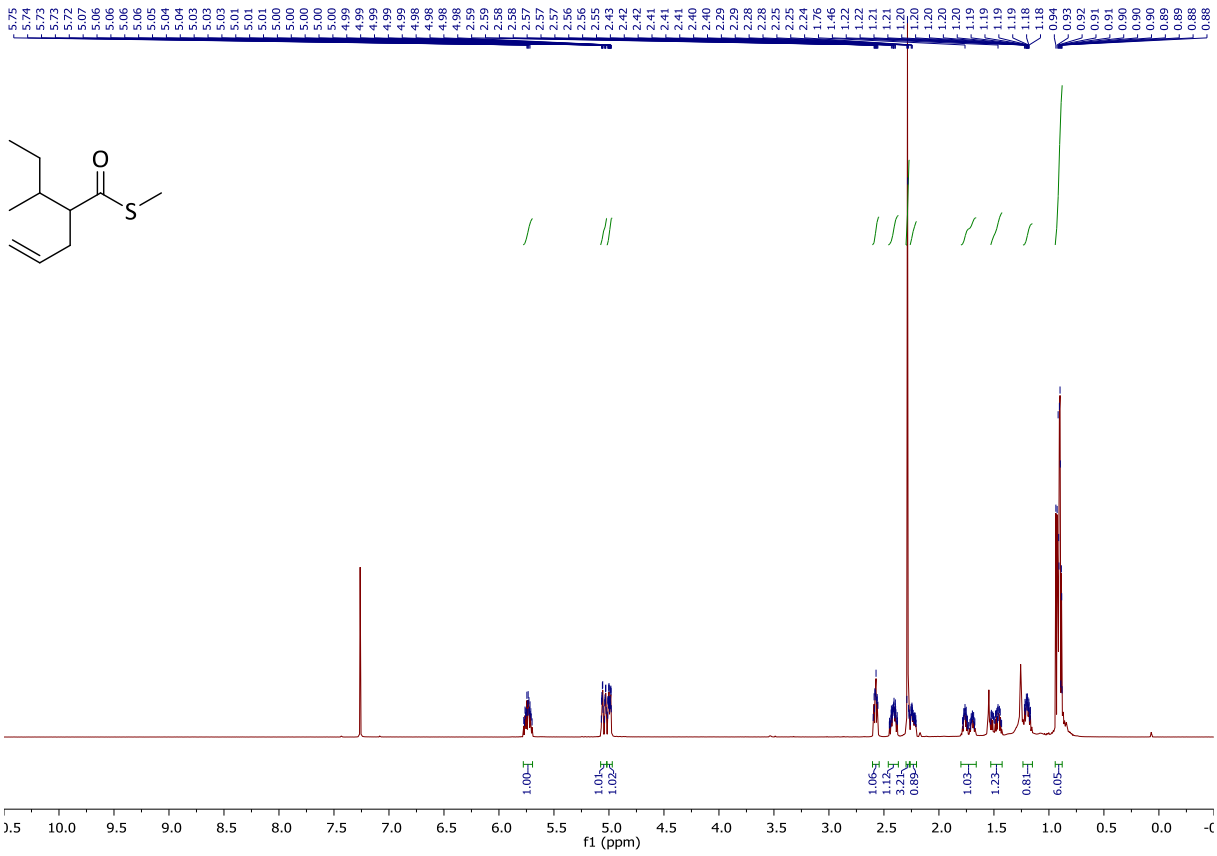
55, 151 MHz, ^{13}C-NMR spectrum, $CDCl_3$.



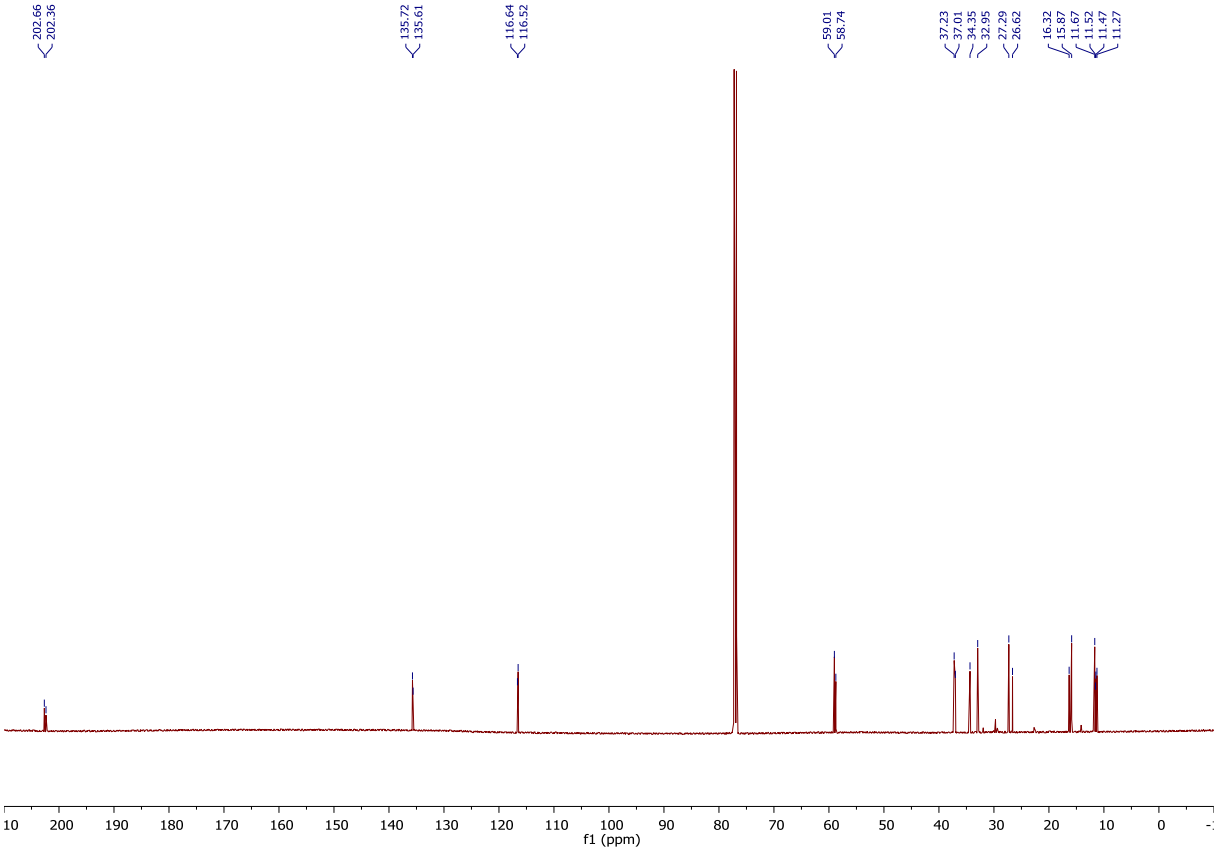
56, 400 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



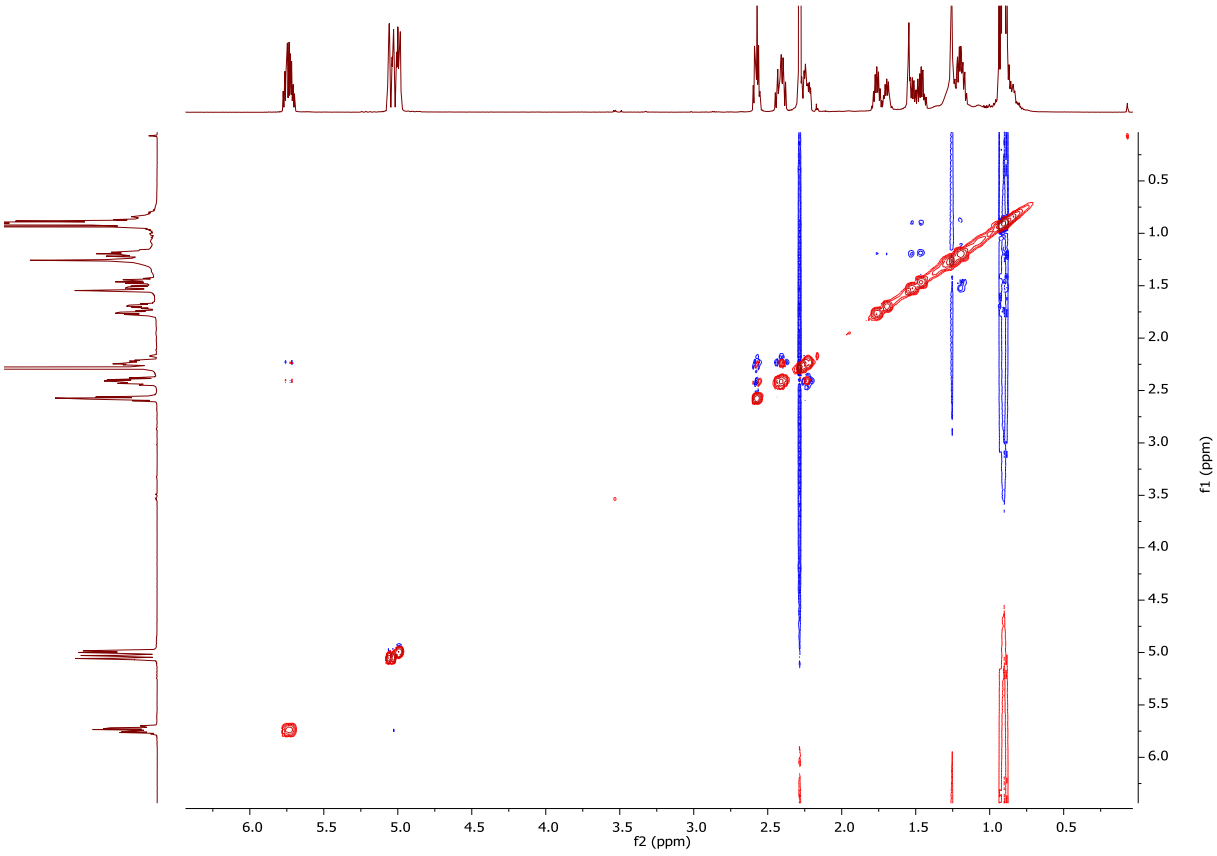
57, 600 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



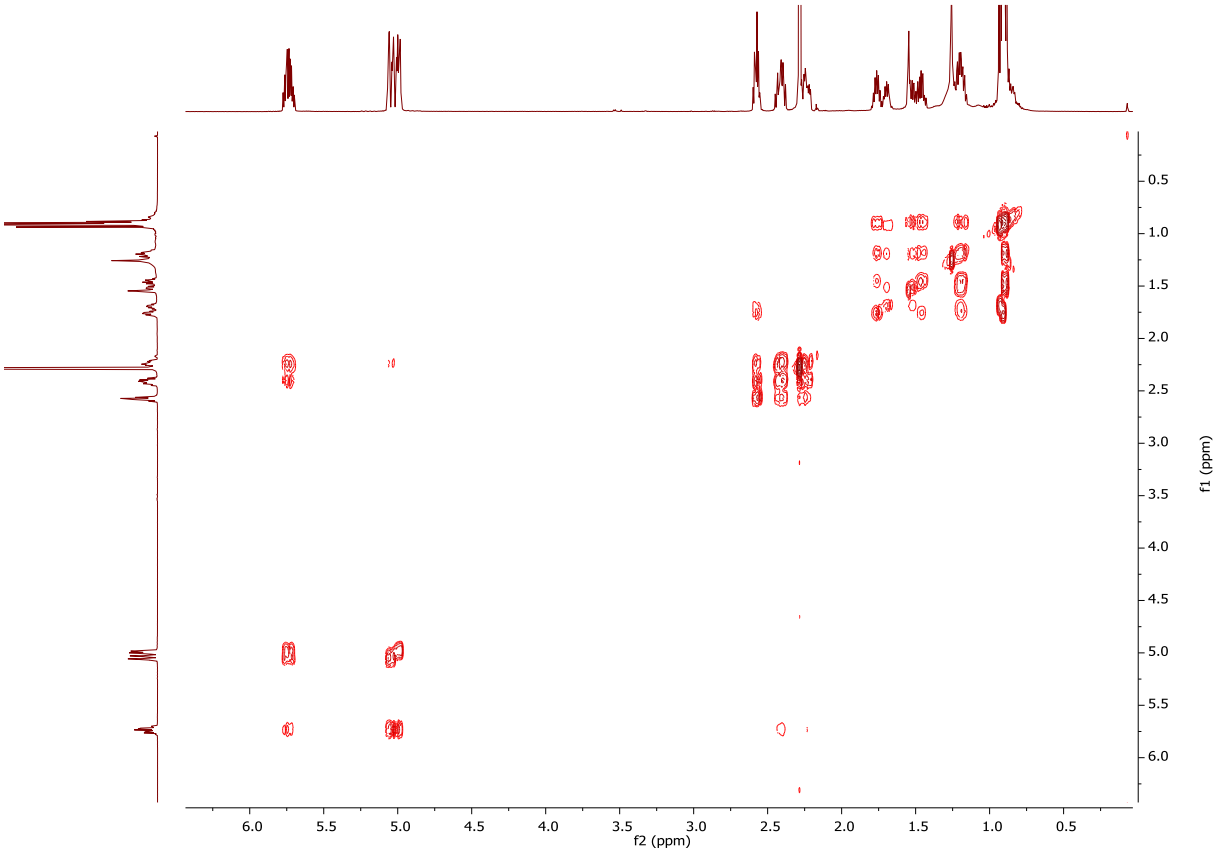
57, 151 MHz, ^{13}C-NMR spectrum, $CDCl_3$.



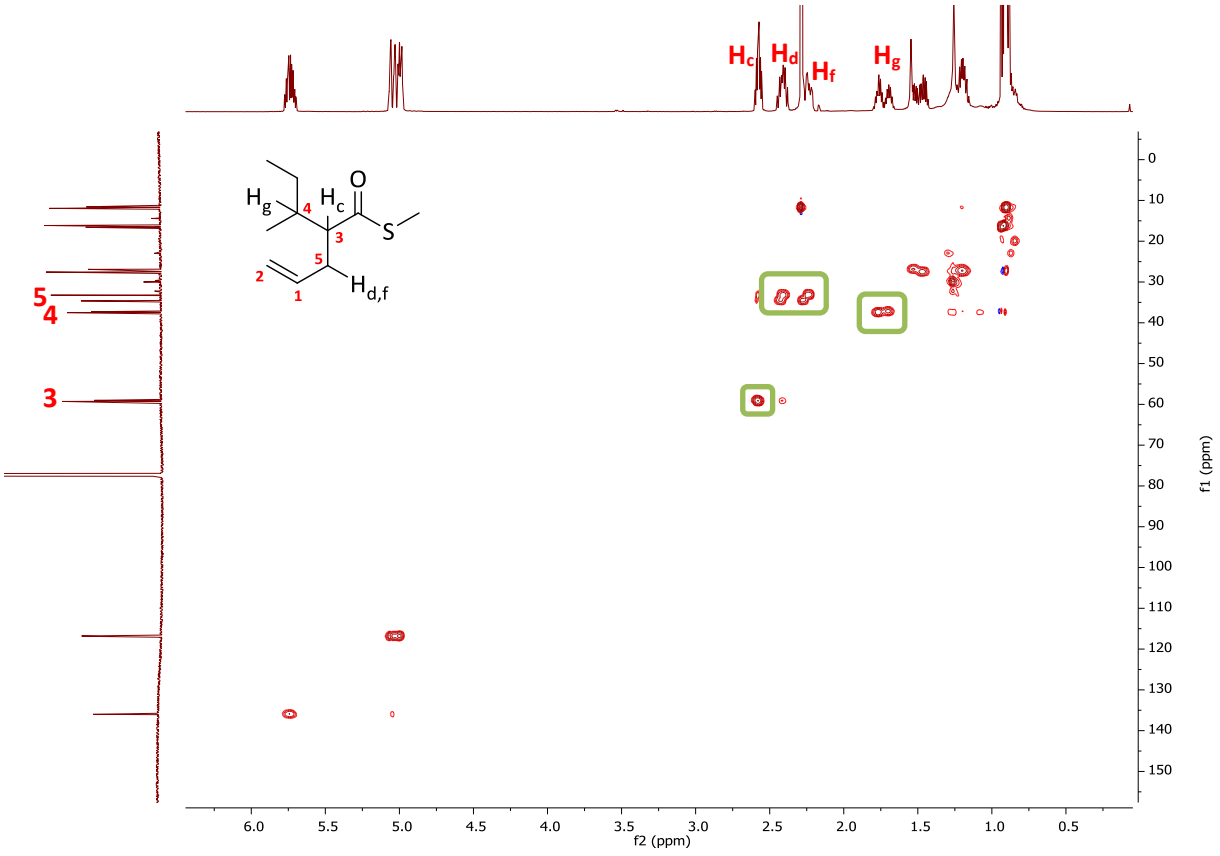
57, 2D-NMR COSY spectrum, $CDCl_3$.



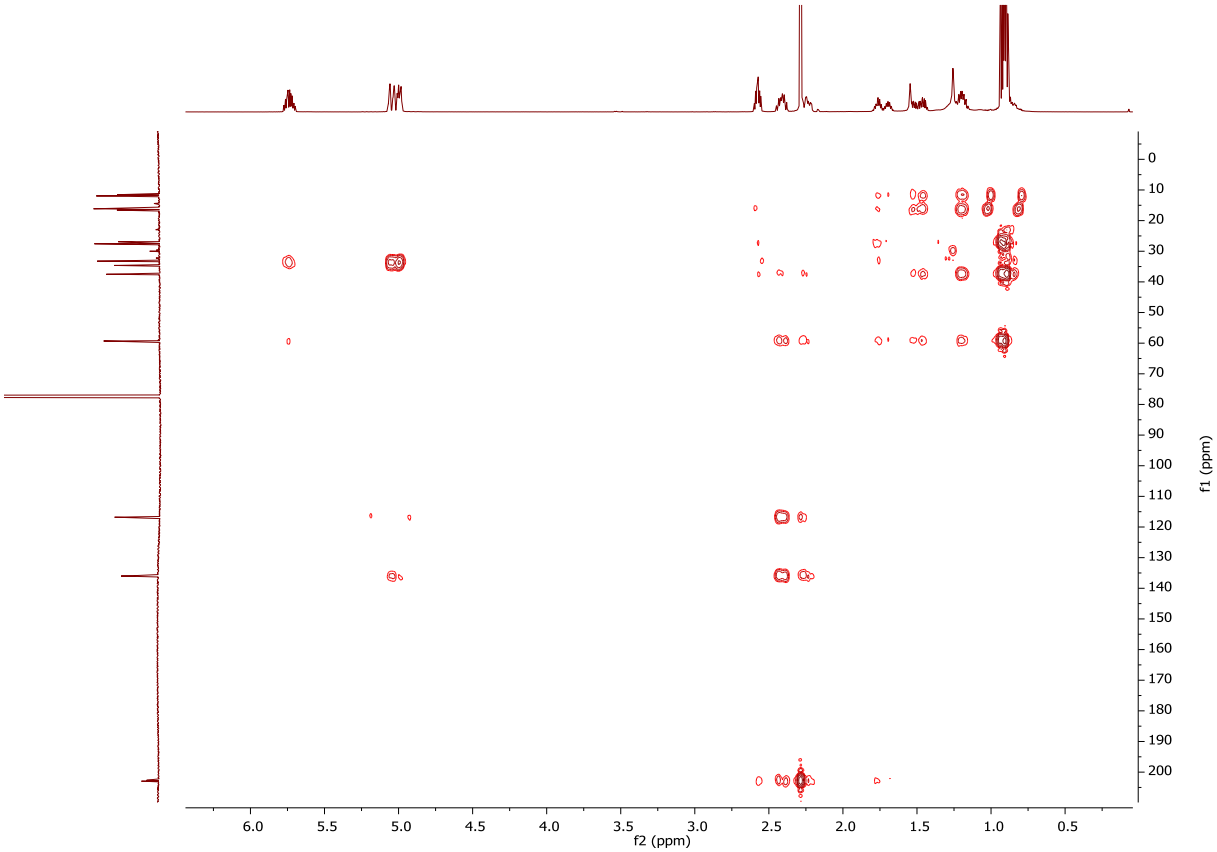
57, 2D-NMR NOESY spectrum, $CDCl_3$.



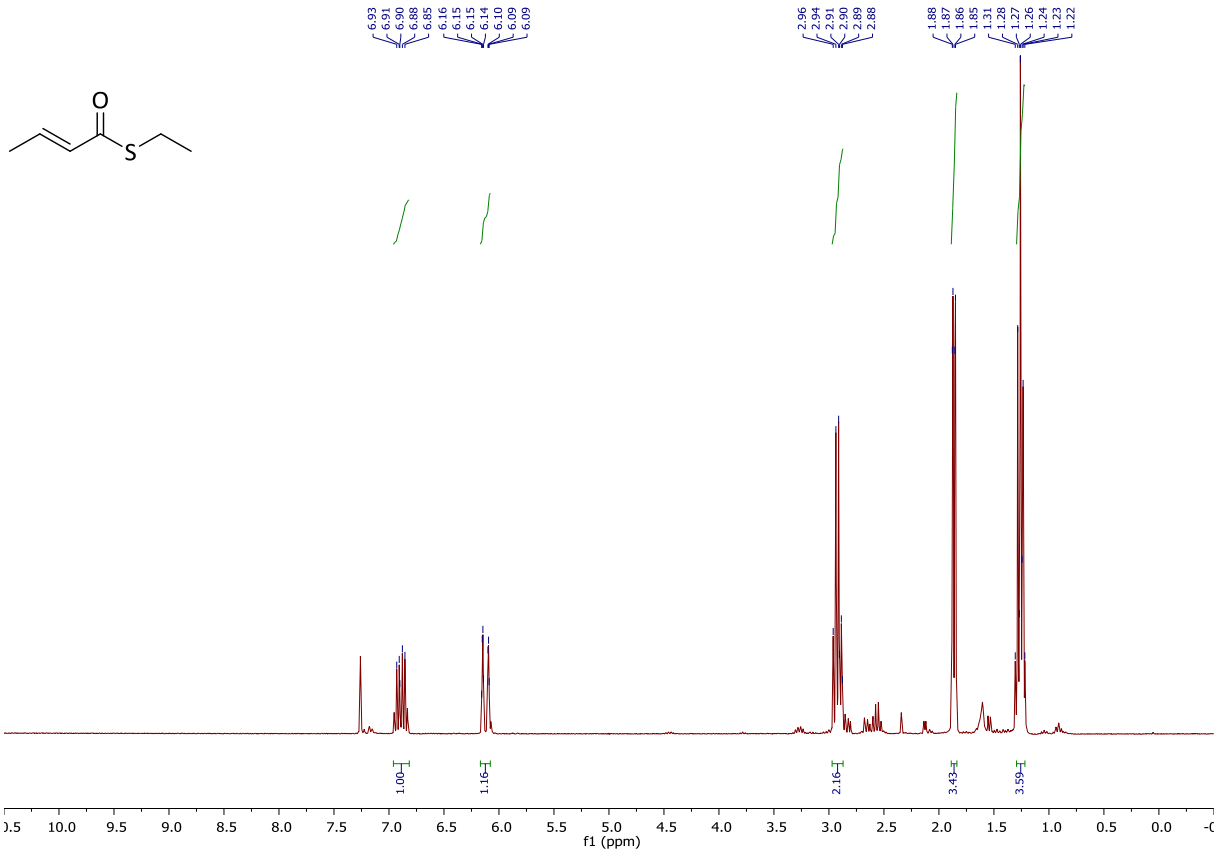
57, 2D-NMR HSQC spectrum, $CDCl_3$.



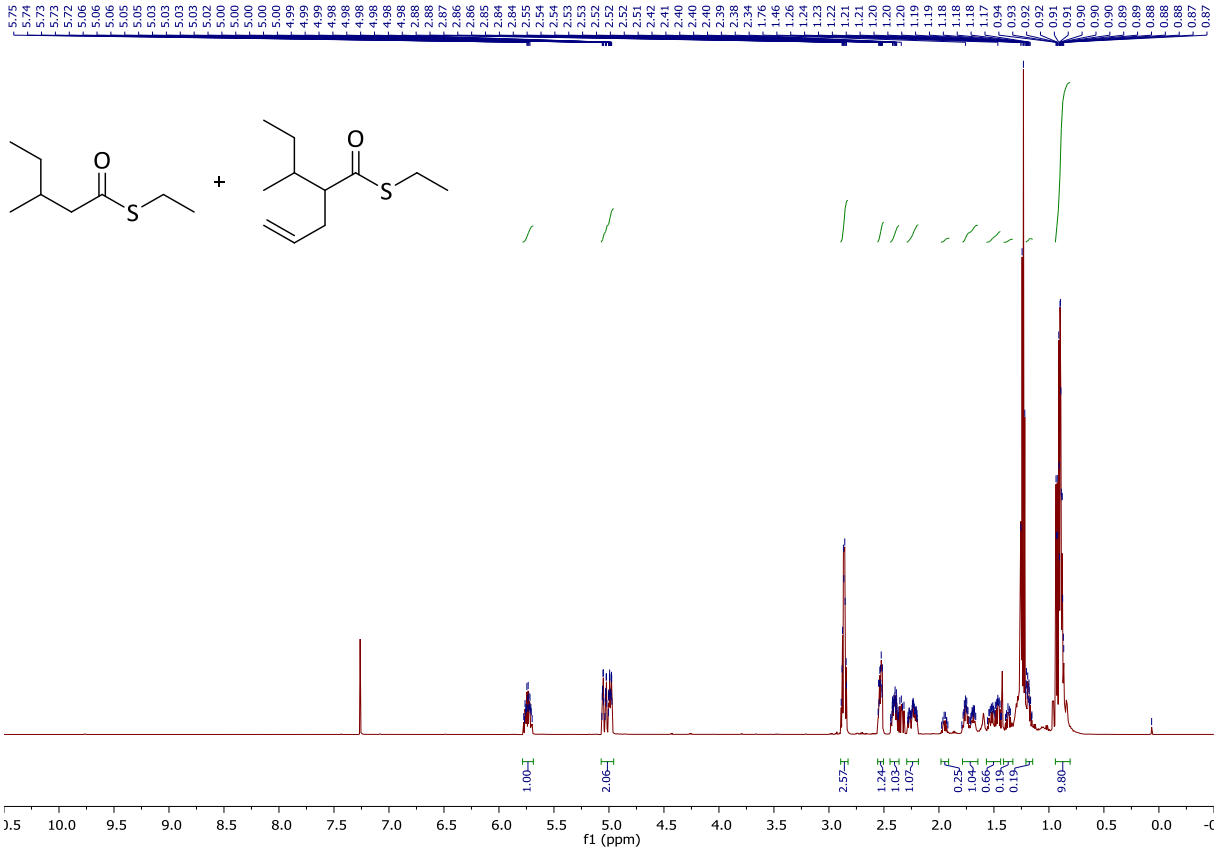
57, 2D-NMR HMBC spectrum, $CDCl_3$.



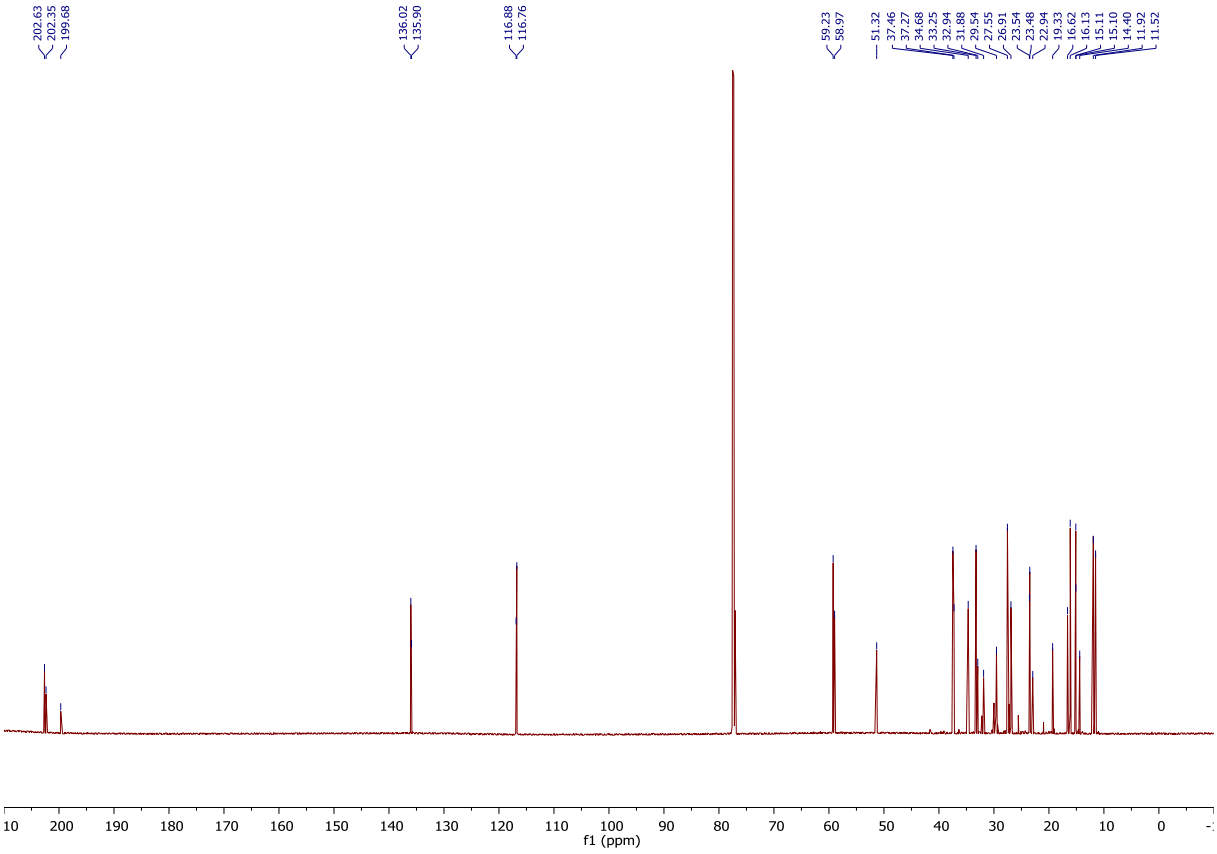
59, 400 MHz, ^{1}H-NMR spectrum, $CDCl_3$.



60 + **61**, 600 MHz, ^{1}H-NMR spectrum, $CDCl_3$.

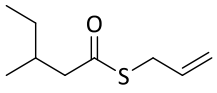


60 + **61**, 151 MHz, ^{13}C-NMR spectrum, $CDCl_3$.



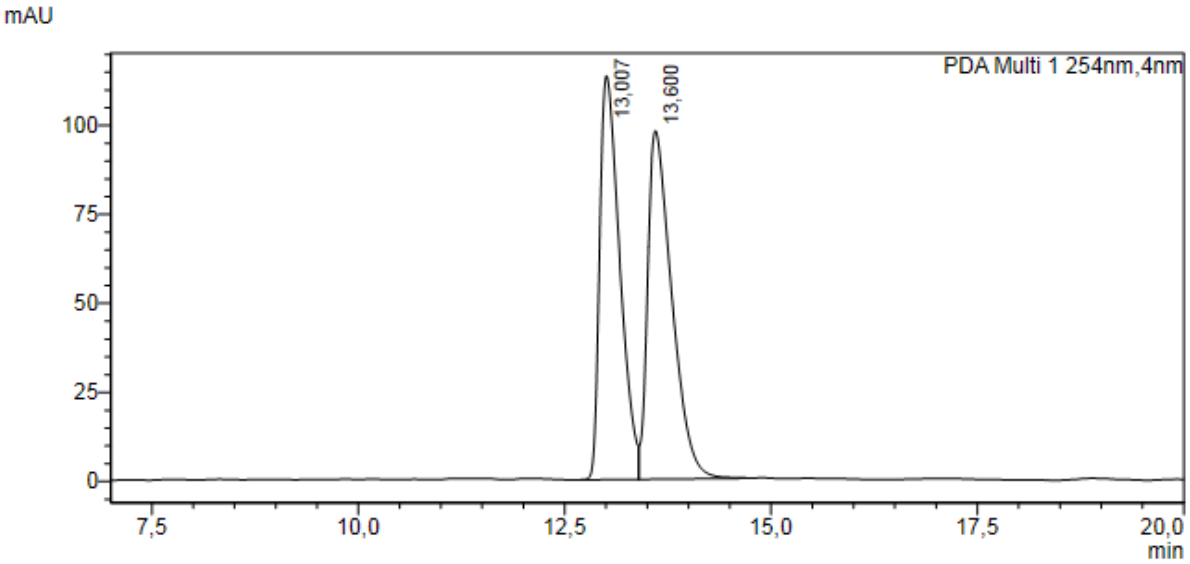
8.6 HPLC DATA

_S_-Allyl 3-methylpentanethioate (55)



CSP-HPLC: (254nm, Chiralpack ADH), *n*-heptane = 100%, 25 °C, 0.5 mL/min), t_R= 13.007 min, t_R= 13.600 min.

Racemic

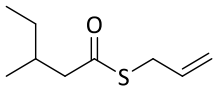


<Peak Table>

PDA Ch1 254nm

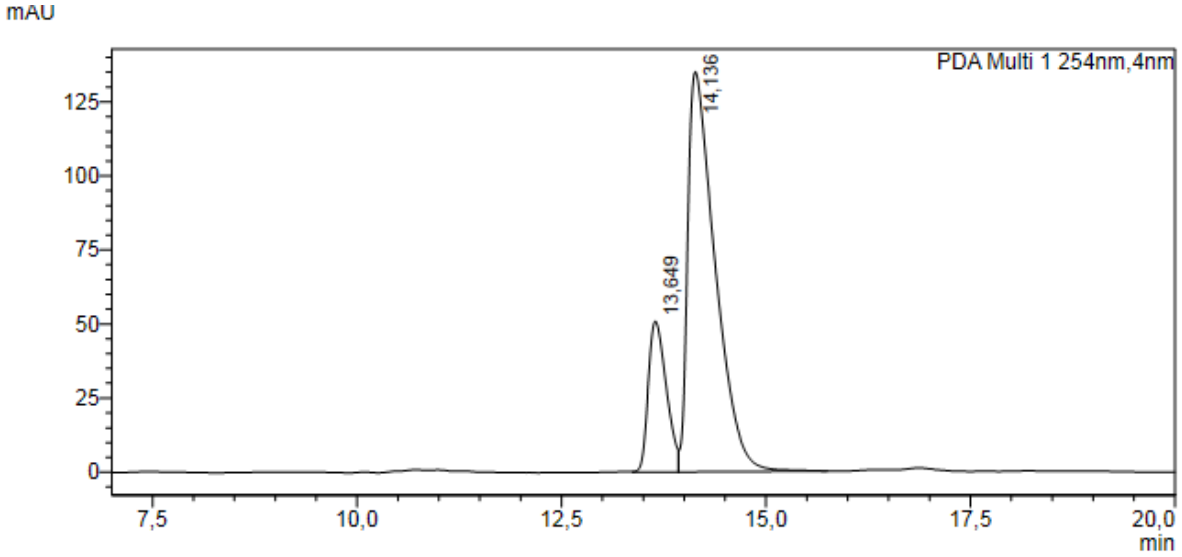
Name	Area	Ret. Time	Area%
	1919694	13,007	48,971
	2000391	13,600	51,029
	3920085		100,000

***S*-Allyl 3-methylpentanethioate (55)**



CSP-HPLC: (254nm, Chiralpack ADH), *n*-heptane = 100%, 25 °C, 0.5 mL/min), t_R= 13.649 (minor) min, t_R= 14.136 (major) min.

By the use of J001-1 (60% ee).

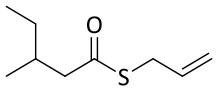


<Peak Table>

PDA Ch1 254nm

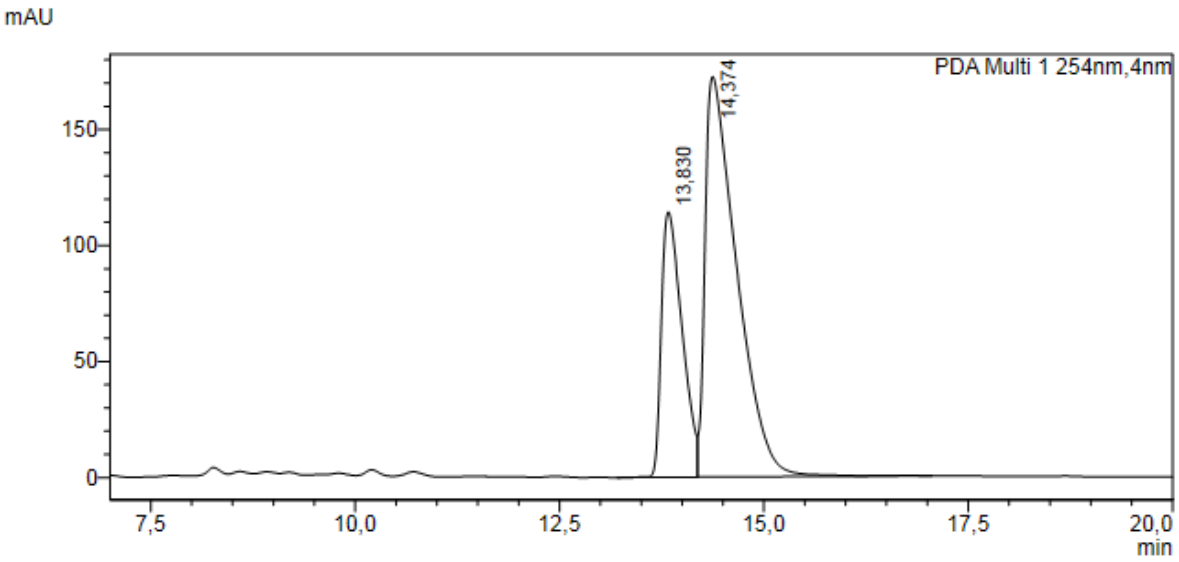
Name	Area	Ret. Time	Area%
	783569	13,649	19,970
	3140137	14,136	80,030
	3923706		100,000

***S*-Allyl 3-methylpentanethioate (55)**



CSP-HPLC: (254nm, Chiralpack ADH), *n*-heptane = 100%, 25 °C, 0.5 mL/min), t_R= 13.830 (minor) min, t_R= 14.374 (major) min.

By the use of J004-1 (40% ee)



<Peak Table>

PDA Ch1 254nm

Name	Area	Ret. Time	Area%
	2022533	13,830	30,256
	4662183	14,374	69,744
	6684716		100,000

8.7 REFERENCES

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