Selenium-mediated allenylation and allylation reactions of N- and O-nucleophiles

Dissertation
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Poorva Ramadas Narasimhamurthy
aus Solapur, Indien

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Die Arbeit wurde angeleitet von: Prof Dr. Alexander Breder

Promotionsausschuss:
Vorsitzender: Apl. Prof. Dr. Rainer Müller
1. Gutachter: Prof. Dr. Alexander Breder
2. Gutachterin: Prof. Dr. Julia Rehbein
3. Prüfer: Prof. Dr. F.-M. Matysik

Tell me not, in mournful numbers,
Life is but an empty dream!
For the soul is dead that slumbers,
And things are not what they seem.

Not enjoyment, and not sorrow,
Is our destined end or way;
But to act, that each to-morrow
Find us farther than to-day.

Life is real! Life is earnest!
And the grave is not its goal;
Dust thou art, to dust returnest,
Was not spoken of the soul.

Not enjoyment, and not sorrow,
Is our destined end or way;
But to act, that each to-morrow
Find us farther than to-day.

Art is long, and Time is fleeting,
And our hearts, though stout and brave,
Still, like muffled drums, are beating
Funeral marches to the grave.

In the world's broad field of battle,
In the bivouac of Life,
Be not like dumb, driven cattle!
Be a hero in the strife!

Trust no Future, howe'er pleasant!
Let the dead Past bury its dead!
Act,— act in the living Present!
Heart within, and God o'erhead!

Lives of great men all remind us
We can make our lives sublime,
And, departing, leave behind us
Footprints on the sands of time;

Footprints, that perhaps another,
Sailing o'er life's solemn main,
A forlorn and shipwrecked brother,
Seeing, shall take heart again.

Let us, then, be up and doing,
With a heart for any fate;
Still achieving, still pursuing,
Learn to labor and to wait.

— H. W. Longfellow, *A Psalm of Life*

Acknowledgements

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Contents

1 Allenes

Allenes are a three-carbon species with two contiguous, mutually orthogonal double bonds (Figure 1.1).[1] Considered to be hybrids of alkenes and alkynes due to the presence of both sp^2 (terminal) and sp (central) hybridized carbon atoms, the reactivity patterns exhibited by allenes towards various nucleophiles, electrophiles and transition metals is comparable to that exhibited by alkenes and alkynes towards similar species.[2] Despite this similarity, allenes exhibit a unique structural feature known as axial chirality. Axial chirality is defined as a form of stereoisomerism arising from the non-planar arrangement of four substituents with respect to a chirality axis.[3] The substitution pattern at the termini of the propadiene subunit influences the electron density and by extension, the reactivity of each of the carbon atoms.[4] This feature is especially prominent when one or more heteroatomic residues are connected to one or both the allenic termini.[4] Some examples include allenol ethers, allenyl sulfides, allenamines, and allenamides (Figure 1.2).[5]

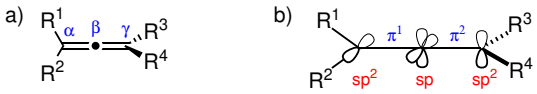


Figure 1.1: a) General structure of allenes b) Orientation and hybridization of p orbitals in an allenic system.[6]

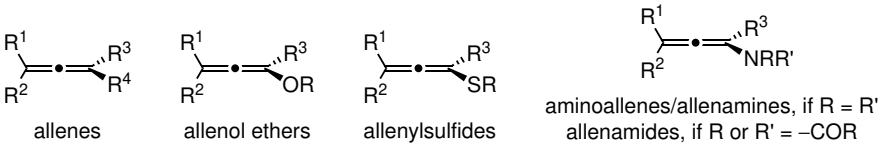
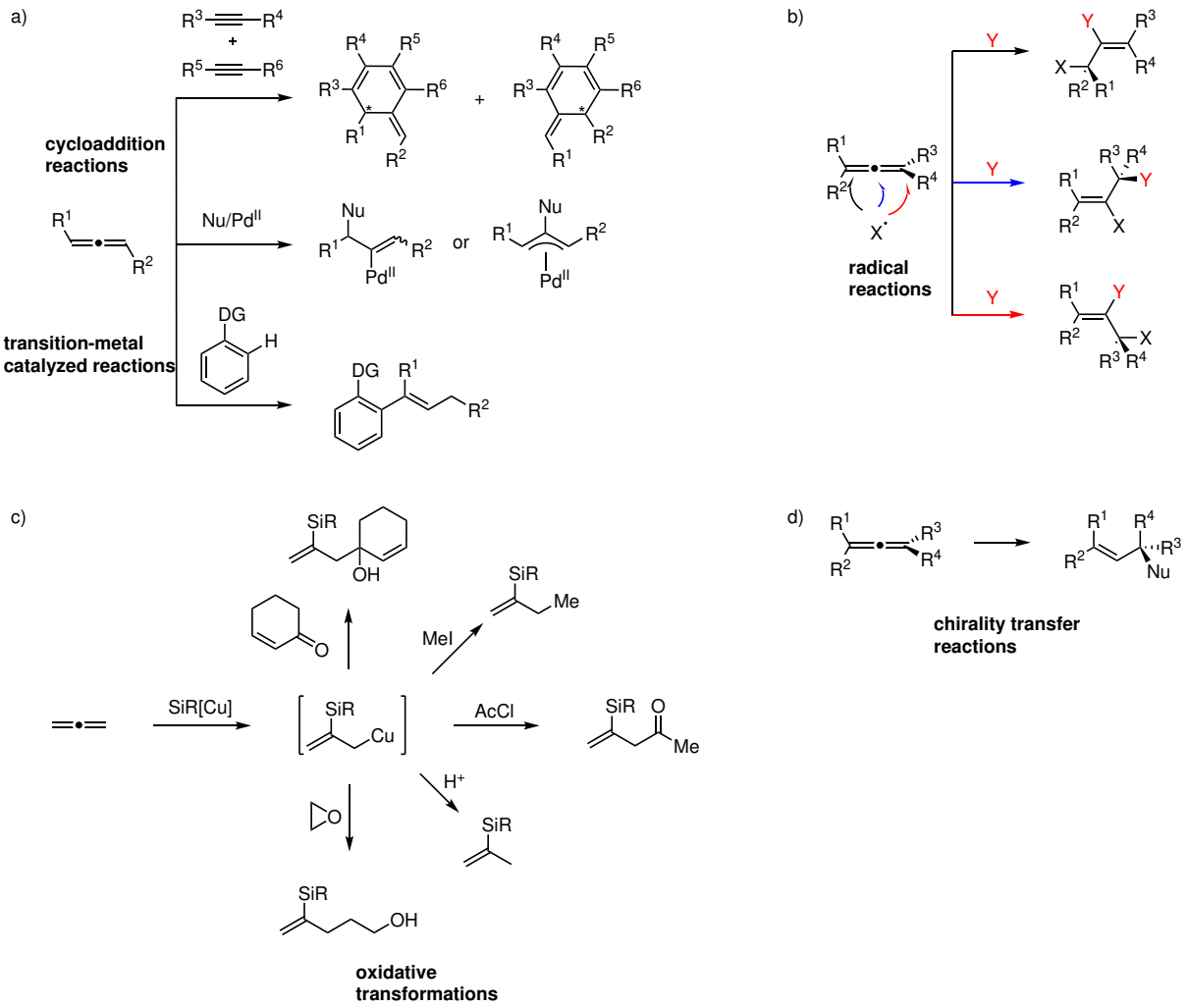


Figure 1.2: An illustration of heteroatom-substituted allenes.

1.1 Allenes in organic synthesis

The allenic moiety has been discovered in over 150 natural products till date.[7] Almost all of these natural products are chiral and have been isolated in non-racemic forms.[7]

Allenes are also known to exhibit biological activity, and have been incorporated into the existing backbone of steroids, prostaglandins, carbacyclins, and nucleosides to improve their bioavailability and metabolic stability.[8] Allenes have also been used in a number of organic transformations, including [2+2+2] cycloaddition reactions,[1] carbocyclic annulations,[9] addition reactions,[10] radical reactions on each of the three carbon atoms,[6] transition metal-catalyzed[11] C-H functionalization reactions[12] and oxidative transformations (Scheme 1.1).[13] Chiral allenes have been used in axial-to-central chirality transfer reactions, wherein the product is formed with a new stereocentre which is influenced by the substituents on the allene termini.[2] Apart from this, allenes have also been used in molecular materials such as shape-persistent macrocycles, foldamers, polymers, and liquid crystals, among others.[14]

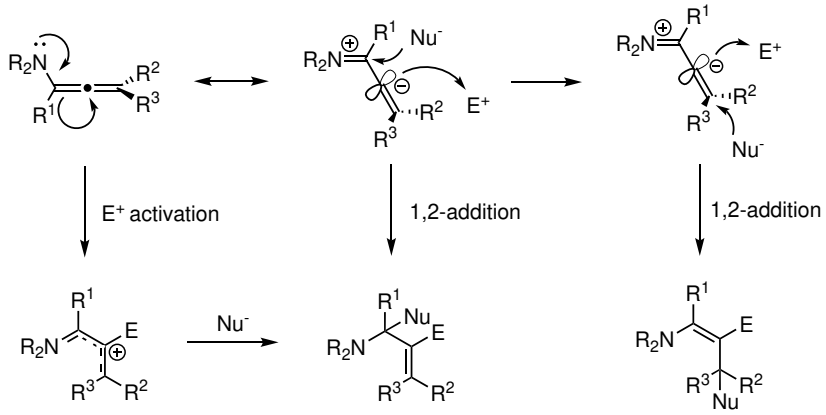


Scheme 1.1: Synthetic utilities of allenes as substrates in a) various cycloaddition[1] and transition-metal catalyzed reactions[12] b) radical reactions[6] c) oxidative transformations[13] d) axial-to-centre chirality transfer reactions.[2]

1.2 Aminoallenes

As briefly mentioned in the introduction, the electron density and therefore the reactivity of an allene is influenced by heteroatomic substitution on one or both of the allenic termini. In the case of aminoallenes, the π-donating ability of the nitrogen atom results in an increased electron density on the allenic backbone compared to simple allenes, making them better substrates for electrophilic functionalizations.[5] The ability of the nitrogen lone pair to undergo delocalization on the allenic moiety facilitates regioselective transformations by enabling a consecutive addition of an electrophile and a nucleophile, resulting in the

formation of 1,2-addition products (Scheme 1.2). Additionally, the trivalent nitrogen can be used for stereochemical induction, by functioning as a tether for a chirality-inducing moiety. The tether also simultaneously provides conformational rigidity to the molecule.[5]



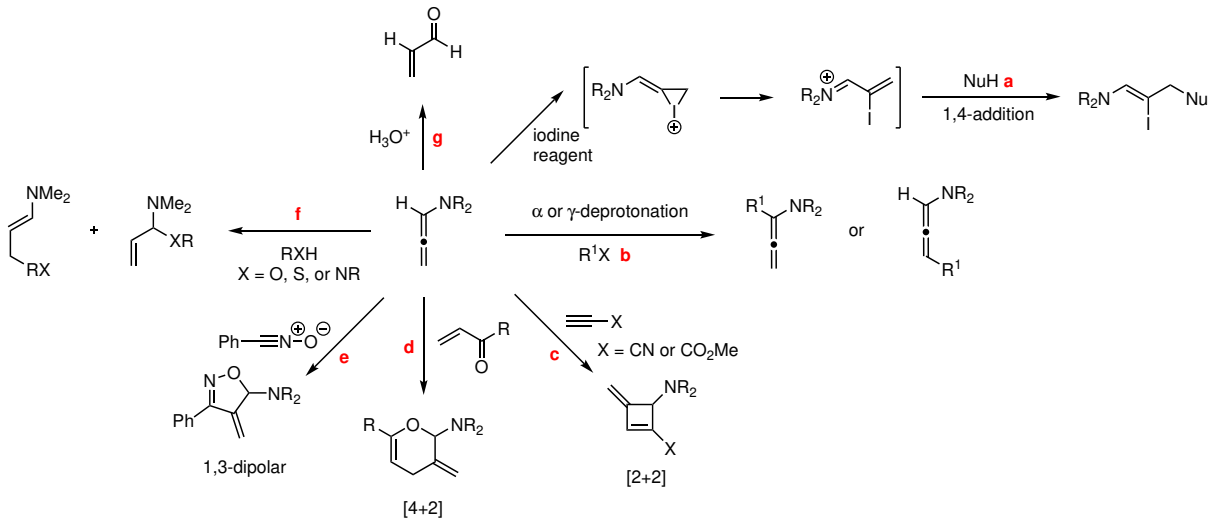
Scheme 1.2: Resonance structures of aminoallenes, followed by electrophilic and nucleophilic attack.[5]

Similar to simple allenes, electron-rich aminoallenes have also been used in a number of organic transformations (cf. Scheme 1.1). Scheme 1.3 below shows some illustrative examples.[15] The unique α-β- and β-γ- dual reactivity of allenes leading to 1,2-addition products, has been used to introduce both alkyl groups[16] and heteroatoms[17,18] into the carbon chain (Scheme 1.3, paths a and b). A deprotonation at the α-position or the γ-position leads to the formation of the 1,2- or 1,4-adduct, respectively (Scheme 1.3, path f). Aminoallenes have also been used to synthesize cyclobutene derivatives *via* a [2+2] cycloaddition reaction with functionalized alkynes,[19,20] dihydropyran derivatives *via* [4+2] cycloaddition with an α,β-unsaturated ketone,[19,21] and to synthesize 1,2-isoxazole derivatives *via* 1,3-dipolar addition with nitrile oxides,[22] respectively (Scheme 1.3, paths c, d, and e). Additionally, upon hydrolysis, α,β-aldehydes can be formed (Scheme 1.3, path g).[16]

Due to the synthetic versatility of aminoallenes, efforts have been made to streamline their synthesis, especially from easily accessible starting materials. The most commonly developed strategies will be discussed in the following sections.

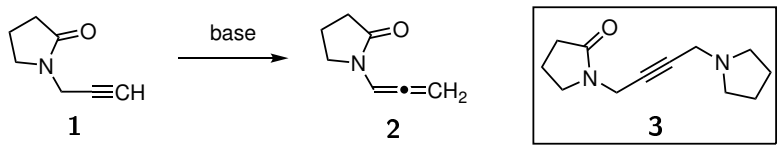
1.2.1 Base-catalyzed isomerization reactions of propargylic substrates

In 1967, Dickinson and co-workers reported the formation of aminoallene **2** *via* a base-catalyzed isomerization of acetylenic derivative **1**, a key intermediate in the synthesis



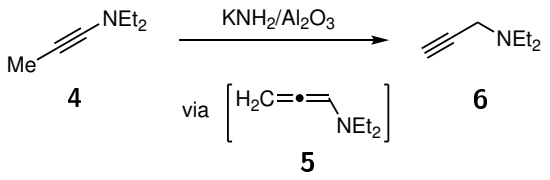
Scheme 1.3: Application of aminoallenes in various organic transformations.

of muscarinic agent oxotremorine (**3**) (Equation 1.1).[23] The presence of the allene was confirmed both *via* NMR and IR spectroscopy, with the allenic carbon backbone showing absorbtion at 5.2 μ (1 μ = 10^{-4} cm).



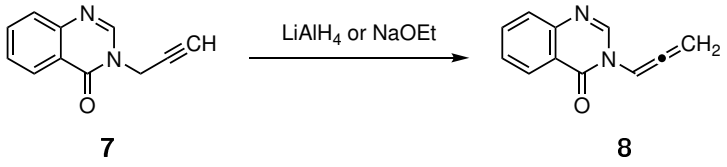
(1.1)

In 1968, Viehe and co-workers observed the formation of aminoallene **5** as an intermediate in the isomerization reaction of *N,N*-dialkylprop-2-ynylamines (**4**) to *N,N*-dialkylprop-1-ynylamines (**6**) using a dispersion of potassium amide on alumina as catalyst (Equation 1.2).[24] They reported that the unstable aminoallene intermediates decomposed upon distillation and also gave rise to olefinic dimers as side products. As a result, the formation of the aminoallene intermediate could only be confirmed spectroscopically. The absorption of the allenic moiety was in agreement with that reported by Dickinson and co-workers in 1967.[23] As a continuation of this work, Hubert and co-workers also reported a similar isomerization using *N*-Prop-2-ynyl heterocycles, with the aminoallenes being exclusively formed when 1-prop-2-ynyl-pyrrole, -pyrazole, and -imidazole were used as the starting material.[25]



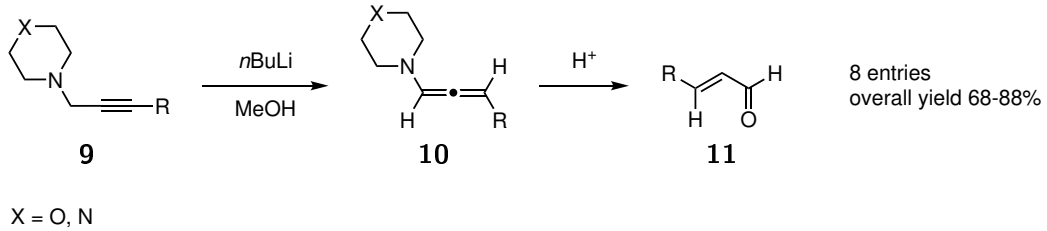
(1.2)

In the following year, Bogentoft and co-workers reported the formation of allene **8** while attempting to reduce the carbonyl moiety of 3-propargyl-3,4-dihydro-4-oxoquinazoline (**7**) with $LiAlH_4$ (Equation 1.3).[26] The same terminal allene was observed when compound **7** was treated with sodium in ethanol. The terminal allene was confirmed by a doublet at 4.35 ppm, belonging to the terminal allenic protons. In the IR spectrum however, no prominent absorption was observed in the expected range of 1920-2000 cm^{-1}. Only a weak band at 1955 cm^{-1} was observed. The authors here exercised caution in ruling out the formation of the aminoallene based only on the IR spectrum.



(1.3)

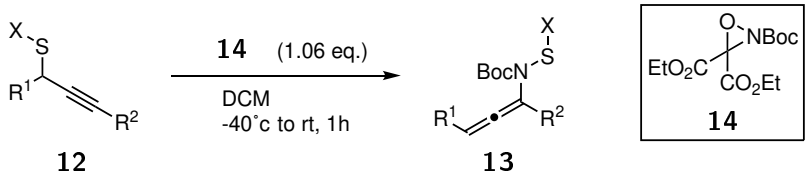
Another base-promoted prototropic rearrangement methodology for the synthesis of aminoallenes was reported by Craig and co-workers in 1980.[16] Treating the starting *N*-substituted alkyne (**9**) with an organometallic base such as *n*-BuLi followed by protonation with MeOH resulted in the formation of aminoallene **10**, confirmed both by NMR and IR spectroscopy. The authors used the aminoallenes to develop a novel method to synthesize α,β-unsaturated aldehydes **11** *via* acid hydrolysis of the aminoallene (Scheme 1.4).



Scheme 1.4: Synthesis of aminoallenes **10** *via* base-promoted prototropic rearrangement of N-substituted alkynes **9**.[16]

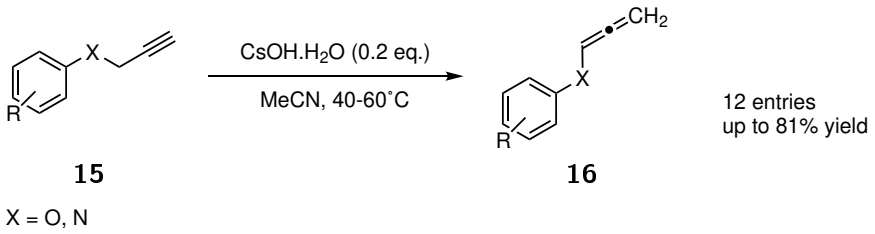
In 2003, Armstrong and co-workers reported the synthesis of *N*-allenylsulfimides **13** *via* [2,3]-sigmatropic rearrangement of propargylic sulfimides **12** using aziridine **14**.[27] The key feature of this method was the *tert*-butoxycarbonyl (Boc)-protected amino group, giving

the aminoallenes greater synthetic utility by allowing easy cleavage of the Boc group and further functionalization of the nitrogen moiety (Equation 1.4). In 2009, the authors published a similar method for the synthesis of benzyl chloroformate (Cbz)-protected chiral aminoallenes.[28]



(1.4)

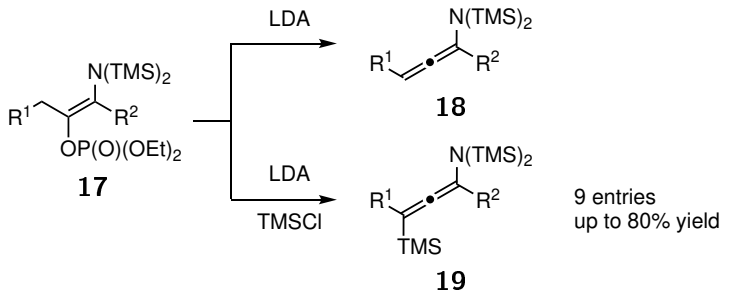
In 2015, during their investigation into the synthesis of 1,2-diselenoalkenes using catalytic amounts of caesium hydroxide monohydrate ($CsOH \cdot H_2O$) and a terminal alkyne (**15**), Li and co-workers reported the unexpected formation of an *O*-substituted allene (**16**).[29] Further investigations revealed that the method could also be used to synthesize aminoallenes, albeit at a slightly higher temperature of 60°C than the corresponding *O*-allenes, which were synthesized at 40°C. The reaction was performed exclusively using terminal alkynes (Equation 1.5). The CsOH promotes isomerization of the alkyne moiety to give an intermediate containing the anionic allene and the Cs^+ countercation. Addition of one molecule of water to this intermediate resulted in the formation of the desired allene and regeneration of the $CsOH \cdot H_2O$ catalyst.



(1.5)

1.2.2 Base-promoted elimination reactions

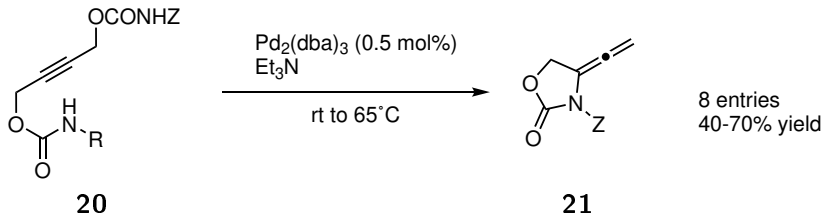
In 1995, Cunico and co-workers reported the synthesis of TMS-functionalized aminoallenes (**18**) starting from phosphoryl enol esters (**17**), which in the presence of LDA at 25°C underwent elimination to give TMS-functionalized aminoallenes (**18**) (Scheme 1.5). The products were isolated in yields of up to 80%. With more sterically hindered substrates, the LDA-induced elimination was done at a higher temperature of 65°C. Additionally, the authors also used the phosphoryl enol esters (**17**) to synthesize C-silyl aminoallenes (**19**) in yields of up to 74% using LDA and trimethylsilylchloride.



Scheme 1.5: Synthesis of aminoallenes **18** and **19** *via* LDA-promoted elimination from phosphoryl enolester **17**.[30]

1.2.3 Metal-catalyzed reactions

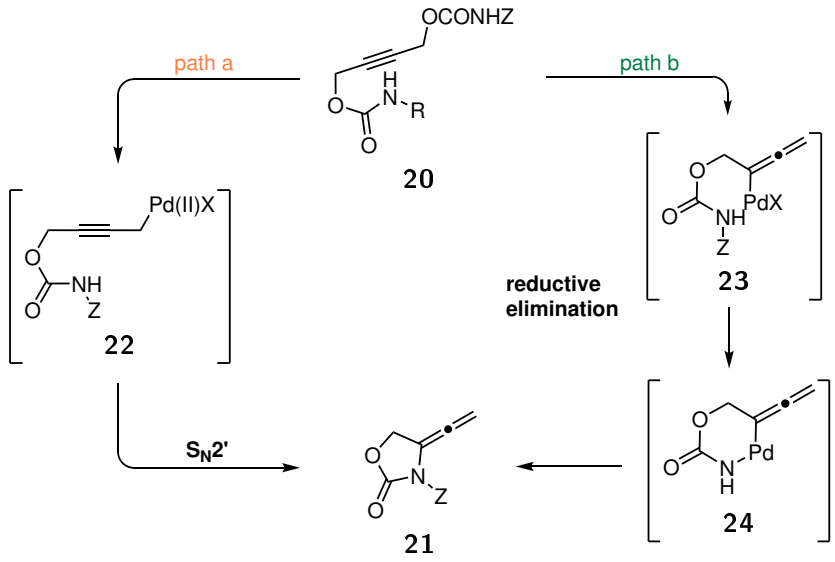
One of the first published methods to synthesize aminoallenes using a metal catalyst was published in 1997 by Kimura and co-workers.[31] They catalyzed the amidocyclization of 2-butyn-1,4-diol biscarbamates **20** to 2-oxazolidinone-substituted aminoallenes **21** using a Pd-catalyst (Equation 1.6).



(1.6)

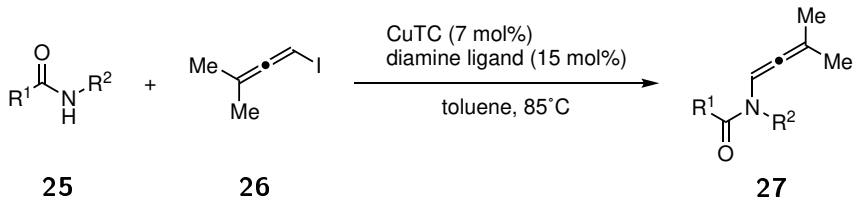
During the reaction, the authors observed the formation of intermediates **22**, **23**, and **24**. Therefore, they proposed two possible routes to the product. Intermediate **22** was proposed to undergo an S_N2' reaction to give product **21** (Scheme 1.6, path a). The other observed intermediate **23** is assumed to undergo a reductive elimination *via* palladacycle **24** to give the aminoallene (Scheme 1.6, path b). A similar intermediate was also reported by Mori and co-workers in 2001, in their synthesis of the carbapenam skeleton using a propargylic carbonate and a $Pd_2(dba)_3$ catalyst.[32]

In 2005, Trost and co-workers reported a Cu-catalyzed synthesis of aminoallenes *via* a coupling reaction between allenyl halides **26** and amides, carbamates, and ureas **25**.[33] The authors were focussed on the synthesis of 3,3-dimethyl-substituted aminoallenes **27**)towards the synthesis of a natural alkaloid and drew inspiration from the better known Cu-catalyzed cross-coupling reaction between amides and vinyl halides.[34] Using copper thiophenecarboxylate (CuTC) as catalyst and a diamine ligand, the authors were able to synthesize the desired aminoallenes in up to quantitative yields (Equation 1.7). Hsung and co-workers later used this strategy in a stereospecific amidation using chiral allenyl



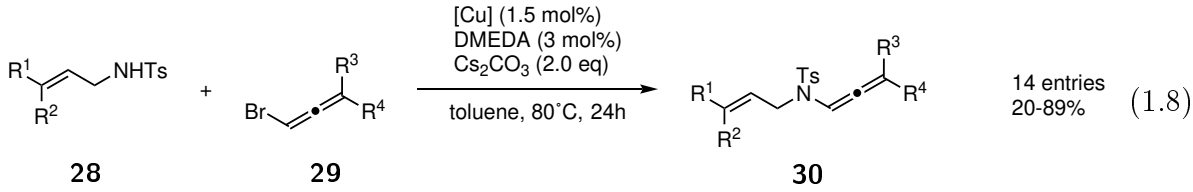
Scheme 1.6: Synthesis of 2-oxazolidinone-substituted aminoallenes reported by Kimura and co-workers and the intermediated formed upon oxidative addition of the Pd-catalyst to the substrate.[31]

iodides **26**.[35]



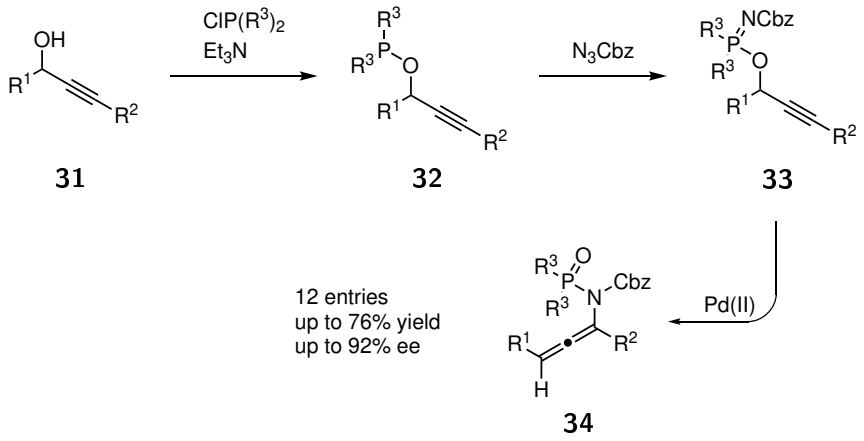
(1.7)

Continuing the trend of using allenyl halides as substrates, Persson and co-workers published a Cu-catalyzed cross-coupling reaction between allylic sulfonamides **28** and allenyl bromides **29** to synthesize allylic allenic amides **30**, with the aim to use them as potential substrates for further transition-metal-catalyzed transformations (Equation 1.8). Oxidative addition of the Cu-center to the allenyl halide followed by transmetallation and reductive elimination results in the formation of the desired product and regeneration of the catalyst.[36]



(1.8)

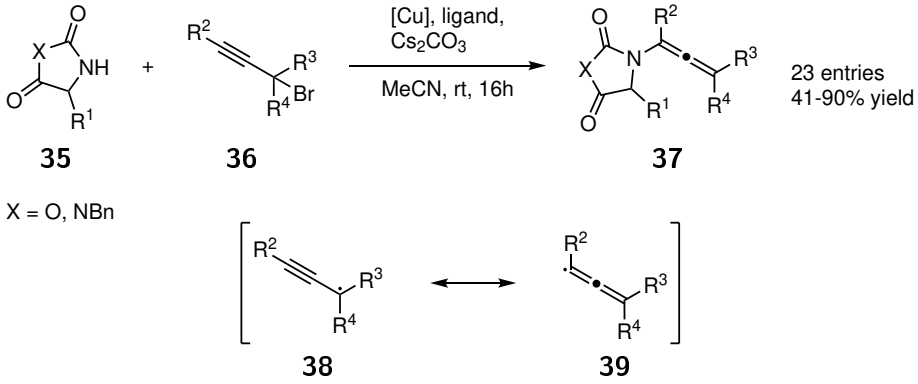
In 2010, Danowitz and co-workers published a Pd-catalyzed [3,3]-rearrangement reaction for the synthesis of chiral aminoallenes using a propargylic alcohol, a chlorophosphite, and a Cbz-azide.[37] A combination of the alcohol (**31**) with the chlorophosphite forms a propargylic phosphite (**32**), which upon oxidation with the azide *via* a Staudinger reaction[38] gives the key phosphorimidate intermediate (**33**). This intermediate then undergoes a [3,3]-rearrangement to give the desired aminoallene **34** in the presence of a Pd(II) catalyst (Scheme 1.7). The reaction worked well with internal as well as terminal alkynes, giving the desired aminoallenes in yields of up to 76% and 92% ee.



Scheme 1.7: Synthesis of Cbz-protected aminoallenes **34** *via* [3,3]-rearrangement from phosphorimidate intermediate **33**.[37]

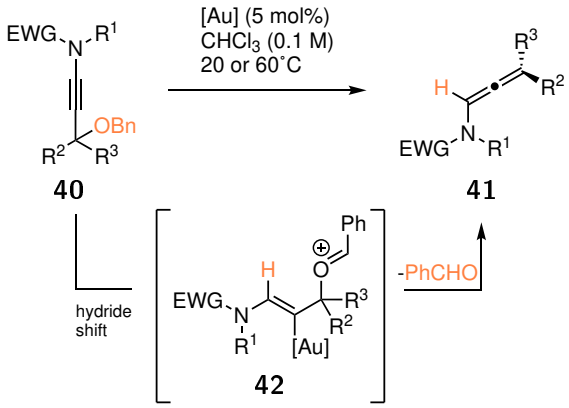
In 2016, Demmer and co-workers published a Cu-catalyzed method for the synthesis of *N*-oxazolidinone aminoallenes (**37**) starting from oxazolidinones **35** and readily available propargylic bromides **36**.[39] The key features of this method included mild reaction conditions, with most of the reactions taking place at room temperature, and the ability to synthesize mono-, di-, and trisubstituted aminoallenes. The reaction was also found to work with hydantoins, and could be used to synthesize chiral aminoallenes. The reaction was found to take place *via* a radical pathway, where an SET from the Cu-catalyst to the propargylic bromide resulted in the formation of the corresponding allenic radical *via*

rearrangement. Oxidative addition of the Cu-catalyst, followed by ligand exchange and reductive elimination resulted in the formation of the desired product and regeneration of the Cu(I) catalyst (Scheme 1.8).



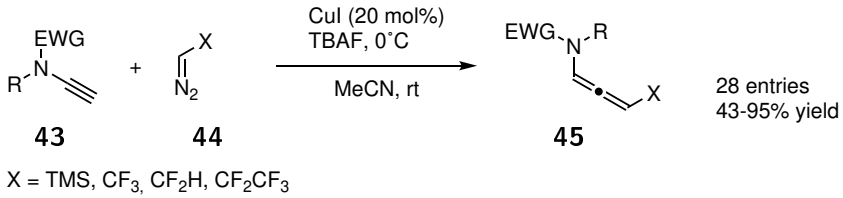
Scheme 1.8: Synthesis of *N*-oxazolidinone aminoallenes reported by Demmer and co-workers *via* intermediates **38** and **39**.[39]

Following this, Zhao and co-workers reported in 2017 a method to synthesize aminoallenes **41** *via* a gold-catalyzed hydride shift using ynamides **40**.[40] The benzyloxy group acts as an internal hydride donor and helps in the reduction of the carbon α to the nitrogen moiety when the alkyne is activated by the gold complex. Loss of benzaldehyde from the thus-formed intermediary oxocarbenium species **42** then results in the formation of the desired product and regenerates the catalyst (Scheme 1.9). The key features of this method are the mild reaction conditions which prevent further side reactions or decomposition of the aminoallenes, and the large functional group tolerance. Under these reaction conditions, aminoallenes with various substituents such as sulfonamido, phosphonamido, and urea were also synthesized.



Scheme 1.9: Gold-catalyzed synthesis of aminoallenes *via* intramolecular hydride shift.[40]

More recently, Zheng and co-workers published a Cu-mediated coupling reaction between ynamides **43** and diazo-compounds **44** to synthesize terminal aminoallenes with a TMS-group on the nitrogen, affording it large synthetic utility.[41] Furthermore, the authors were able to extend the method to synthesize tri-, di- and per-fluorinated aminoallenes by replacing the TMS-diazo- compound with fluorinated diazo-compounds (Equation 1.9). DFT calculations made during mechanistic investigations showed that the addition of the diazo-compound always occurred at the β-position of the ynamide, regardless of the polarization of the triple bond.



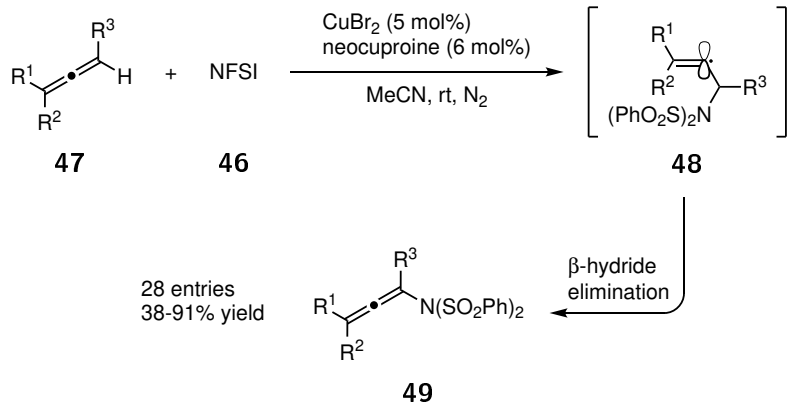
(1.9)

1.2.4 Synthesis of aminoallenes using NFSI (46)

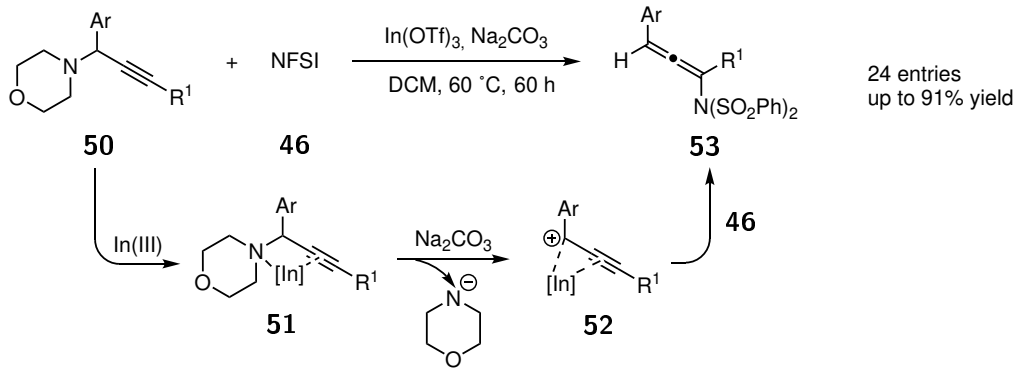
In the year 2015, Zhang and co-workers developed a novel copper-catalyzed radical C−H amination reaction for the synthesis of aminoallenes starting from terminal or internal allenes **47** and *N*-fluorobenzenesulfonimide (NFSI) (**46**).[42] The addition of NFSI to the allene in the presence of a suitable copper catalyst and neocuproine ligand results in the formation of a vinyl radical intermediate **48**. This intermediate undergoes β-hydride elimination to give the desired aminoallene **49** (Scheme 1.10). The reaction worked well with both electron donating and withdrawing substituents on the allene, with aminoallenes obtained in yields of up to 91%. With this method, the authors managed to solve a common problem associated with the transition-metal catalyzed direct C−H amination of allenes, namely, the regioselectivity of the formation of the C−N bond at either the central or terminal allenic carbon.[43]

Following this, Samanta and co-workers reported the In(III)-catalyzed, ligand-free synthesis of *N*-sulfonamide aminoallenes starting from propargylic amines **50** and NFSI (**46**).[44] Compared to the previous method, the authors proposed an ionic pathway for the reaction. Co-ordination of the In-centre to the alkyne in the presence of a base results in the elimination of morpholine to give propargylic cationic intermediate **52**. A nucleophilic attack by the NFSI then results in the formation of the desired aminoallene **53** (Scheme 1.11).

More recently in 2020, Muhammad and co-workers published a metal-free method to synthesize difluoromethylated aminoallenes (**55**) starting from both internal and terminal 1,3-enynes (**54**).[45] Addition of NFSI (**46**) to the 1,3-enyne results in the formation of inter-

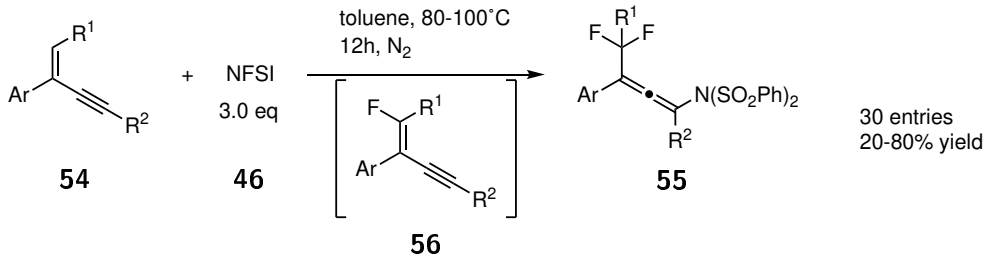


Scheme 1.10: Cu-catalyzed synthesis of *N*-sulfonamide aminoallenes (**49**) starting from internal or external allenes (**47**) and NFSI (**46**).[42]



Scheme 1.11: In-catalyzed synthesis of *N*-sulfonamide aminoallenes (**53**) starting from propargylic amines (**50**) and NFSI (**46**).[44]

mediary fluorinated 1,3-enyne **56**, which upon addition of another molecule of NFSI gives the final product. Here, NFSI (**46**) serves not only as the source of the amino functionality, but also as a source of electrophilic fluorine, resulting in a rare 1,3-trifunctionalization of the 1,3-enyne (Scheme 1.12).



Scheme 1.12: Metal-free synthesis of difluorinated aminoallenes **55** starting from 1,3-enynes **54** and NFSI (**46**) *via* intermediate **56**.[45]

The main feature of using NFSI (**46**) in the synthesis of aminoallenes was that no external oxidant or nucleophile was required to be added to the system to bring about the desired functionalization. Furthermore, as shown by Muhammed and co-workers,[45] the (counter)anion stemming from NFSI could also be used to functionalize the substrate. From these examples, the versatility of NFSI as a reagent is also to be noted, being applicable in the functionalization of both alkynes as well as allenes.

While all the above examples show a progression in the synthetic strategies towards the synthesis of aminoallenes, such as increased functional group tolerance, they either require highly functionalized alkynes as substrates, with the adjustment of the oxidation state to the desired allene taking place in one or more subsequent steps, or they require the allenic moiety to be already present in the substrate, with the nitrogen functionality introduced in one or more subsequent steps. Therefore, a synthetic methodology that combines both the modification of the oxidation state of the alkyne to the allene as well as the introduction of the nitrogen functionality to the allene in a single synthetic step would be a major breakthrough in the synthesis of aminoallenes. A further improvement could be made if simple, non-functionalized alkyes could be used for this transformation.

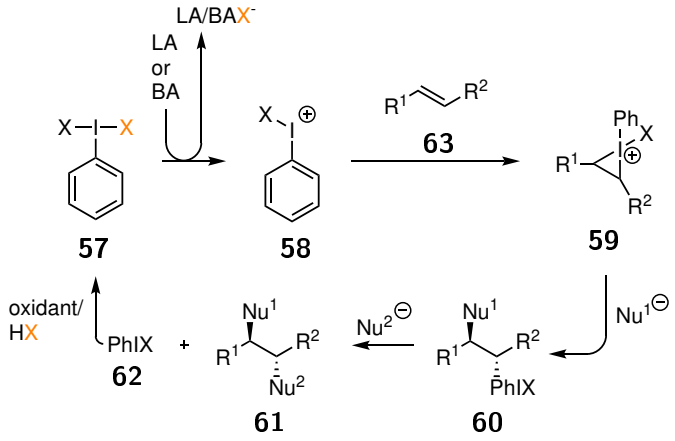
After this introduction into the different methods to synthesize aminoallenes starting from alkynes, different strategies for the functionlization of alkynes will be discussed in the following sections. The discussion begins with the functionalization of olefins, and continues towards the functionalization of alkynes.

1.3 Olefin functionalization

An important factor to consider while designing a synthetic transformation is the cost of the starting materials used. Consequently, inexpensive and easily available starting materials are highly sought after in organic syntheses. Due to their low cost and easy availability from petrochemical feedstocks, simple olefins are suitable candidates for organic transformations.[46] Therefore, the oxidative functionalization of olefins has been extensively investigated over the last few decades and a number of strategies have been developed for the construction of C–C,[47–49] C-N,[50,51] C–O,[50,52] C–S,[53] and C–X[54,55] bonds. Most of these strategies involve the use of transition metal catalysts such as palladium,[47,50,56,57] rhodium,[48,49] and copper.[52] Although these strategies have worked well with terminal olefins, the functionalization of internal olefins has been a challenge due to the tendency of the transition metal-olefin complex to isomerize to the terminal position, leading to a product mixture.[56] Therefore, the development of synthetic strategies using organocatalysts as an alternative to the more traditional transition metal-catalyzed processes has witnessed an increase over the last few decades. These strategies include the use of electrophilic, hypervalent iodine (III) reagents[58–62] and reagents containing electrophilic sulphur and selenium compounds, also known as chalcogens.[46,63]

1.3.1 Iodine(III)-mediated olefin functionalization reactions

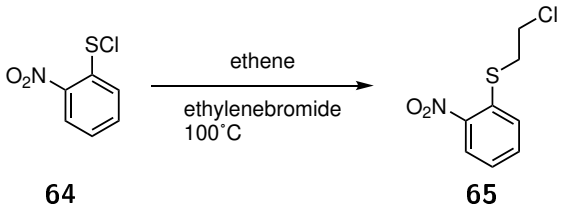
In olefin functionalizations using hypervalent iodine reagents, hypervalent iodine(III) reagent **57** undergoes activation by a Lewis or a Brønsted acid to give electrophilic species **58** which then adds on to the π-bond of the unactivated olefin to form iodonium species **59** (Scheme 1.13).[64] Substitution of the iodo moiety by a nucleophile results in the formation of iodoadduct **60**.[64] Substitution by a second nucleophile results in the formation of vicinal difunctionalized olefin **61**.[64] Alternatively, the iodo moiety can also be expelled *via* an elimination reaction, especially when attached to a tertiary-carbon centre.[65] This concept of olefin functinalization using hypervalent iodine was further developed into the corresponding catalytic versions.[64,66–68] In the catalytic version, the elimination or substitution step generates the corresponding allylic functionalized or vicinal difunctionalized product, respectively, and catalytically inactive iodine(I) species **62**. Consequently, a suitable oxidant is required to regenerate the catalytically active iodine(III) species. This terminal oxidation can either be done electrochemically, by the use of an acid,[69] or by the use of a suitable oxidizing agent such as *m*CPBA.[67,68]



Scheme 1.13: Vicinal difunctinalization of olefins using hypervalent iodine(III) reagents.[64]

1.3.2 Chalcogen-mediated olefin functionalization reactions

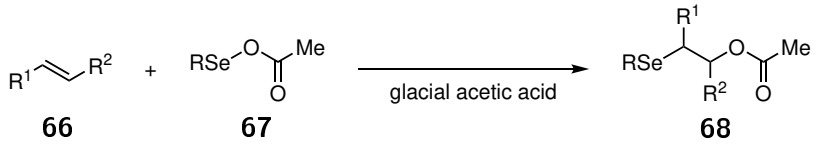
The principle of olefin functionalization using electrophilic chalcogen reagents is similar to that of the iodine(III)-promoted reactions. Similar to the previous case, reactions using stoichiometric amounts of organochalcogen reagents could be upgraded to catalytic versions when an appropriate terminal oxidant was used.[46,63] In 1925, Lecher and co-workers described the addition of phenyl sulfenyl chlorides (**64**) to ethene to give the corresponding adducts (**65**) (Equation 1.10).[70] This strategy was expanded to include other olefins such as cyclohexene and styrene, and phenyl sulfenyl chlorides bearing substituents such as Cl- and NO_2 on the phenyl ring of the sulfenyl chlorides.[71,72]



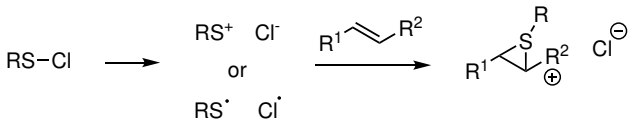
(1.10)

Following this, Jenny and co-workers reported the addition of selenic acid esters to various unpolar alkenes to give the corresponding selenoadducts (Equation 1.11).[73] With both chalcogens, the addition was found to proceed *trans*-selectively, where the addition products were predominantly formed according to Markovnikov's rule.[72,74–76] Fuson and co-workers explained the formation of the product by proposing a cyclic thiiranium ion intermediate which could further undergo a rearrangement.[77] Based on these findings, Kharasch and co-workers also proposed a similar cyclic thiiranium ion intermediate but ruled out the possbility of a rearrangement during attack of the nucleophile to give either the *normal* or *iso* regioisomers.[74] The cyclic intermediate could instead undergo

substitution with either the counter anion (in this case, a chloride) to give the β-chloro sulfide or with a solvent molecule to give a β-solvent substituted sulfide, or undergo an elimination to give the corresponding vinylic sulfide.[74] Mueller and co-workers proposed that the addition of the electrophilic sulfur species to the double bond can occur either *via* a homolytic cleavage or a heterolytic cleavage of the S – Cl bond, which generates the required radicals or the corresponding electrophilic and nucleophilic species necessary for the the addition/substitution reaction to occur (Scheme 1.14).[78]



(1.11)



Scheme 1.14: Formation of the thiiranium intermediate *via* either a heterolytic or homolytic cleavage of the RS – Cl bond.[74,77]

Indeed, evidence for the existence of these chalcogeniranium intermediates was provided when Pettit and co-workers isolated sulfonium intermediate **69**,[79,80] and later Garratt and co-workers isolated episelenurane **70** and a series of other seleniranium hexafluorophosphate or hexafluoroantimonate salts (**71**) (Figure 1.3).[81,82] Furthermore, they established that when the intermediate was exposed to nucleophiles, the same products were obtained as when the unactivated olefin reacts with the selenide reagents, thereby strongly supporting the theory that the three-membered chalcogeniranium ions are intermediates in the chalcogen-mediated functionalization reactions of olefins (Scheme 1.15).

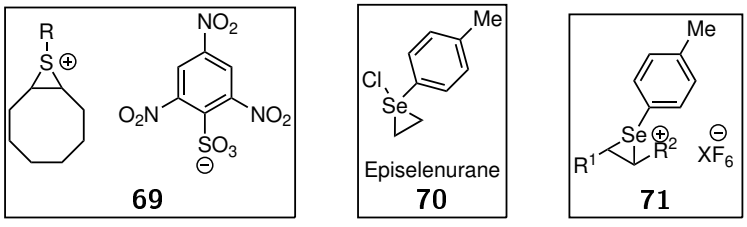
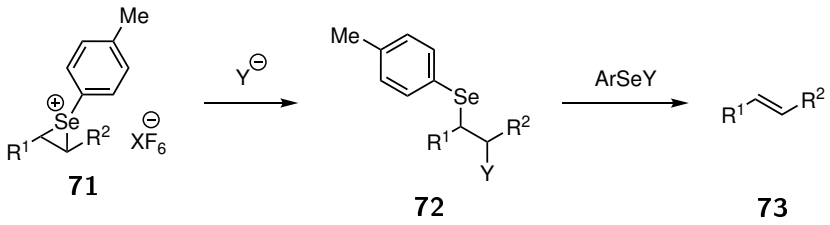


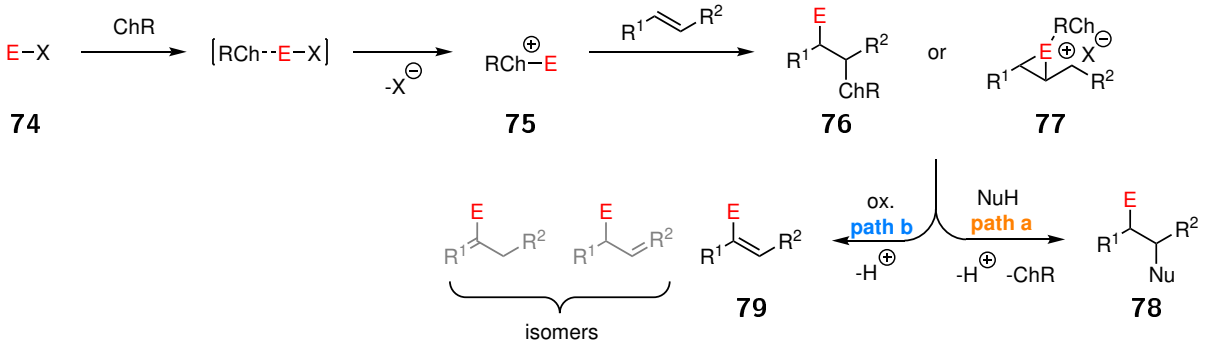
Figure 1.3: The first isolated thiiranium[79,80] and seleniranium intermediates[81,82] in the oxidative functionalization of alkenes.

The formation of the chalcogeniranium intermediate and the following adduct is due to the ability of the chalcogen atom to function in two different ways. In the first scenario,



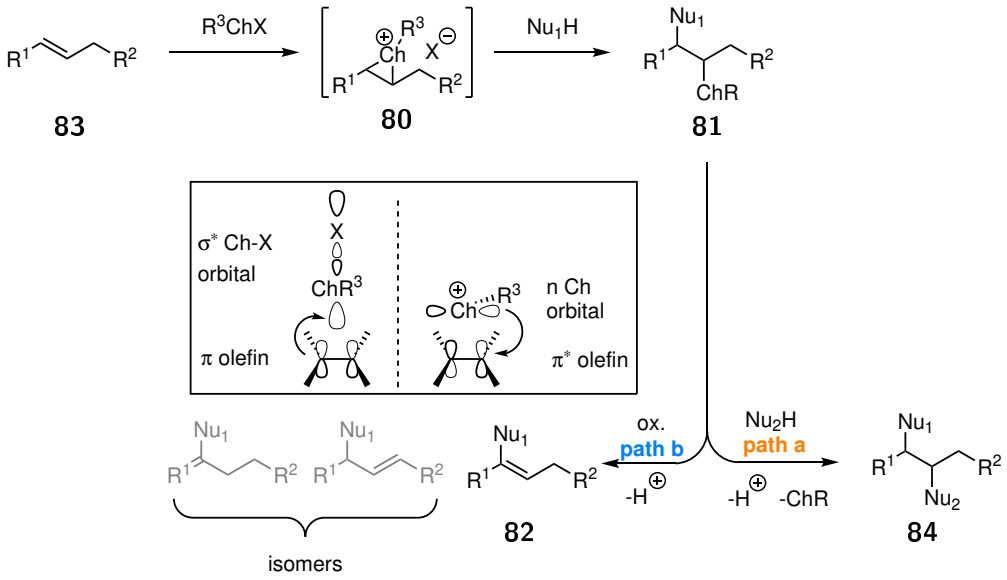
Scheme 1.15: Nucleophilic substitution of the intermediate to give the final product as reported by Garratt and co-workers.[81,82]

the chalcogen atom acts as a Lewis base and activates an electrophile **74**, which in its now-activated form **75** can react with the unactivated alkene to form a chalcogen-olefin-electrophile adduct **76** or cyclic species **77** (Scheme 1.16).[83] These intermediates can either undergo nucleophilic substitution to give a 1,2-difunctionalized product (Scheme 1.16, path a),[84,85] or they can undergo an elimination reaction in the presence of a suitable oxidant, resulting overall in a vinylic or allylic functionalization of the unactivated olefin (Scheme 1.16, path b).[54,86]



Scheme 1.16: Chalcogens as lewis-base activators of an electrophile.

In the second case, the electrophilic chalcogen atom acts as a π acid and activates the olefin towards a nucleophilic attack *via* the formation of a three-membered chalcogeniranium ion (**80**). Following mucleophilic attack, a chalcogen-olefin-nucleophile adduct **81** is formed (Scheme 1.17). Here, the antibonding σ* orbital of the Ch−X bond receives electron density from the π-orbital of the double bond, and the non-bonding n orbital of the chalcogen atom donates electron density into the π* orbital of the olefin.[46,87] This is similar to the interaction found in transition metal-olefin complexes, where the σ*-orbital of a metal-ligand bond (or an empty d orbital of the metal) receives electron density from the π-orbital of the olefin, and a back donation occurs from a filled d orbital on the metal into the π* orbital of the olefin.[88] Similar to the adduct from the lewis-base activation discussed above, adduct **81** can eundergo nucleophilic substitution to give a 1,2-difunctionalized product **82** (Scheme 1.17, path a)[84,85] or it can undergo an elimination reaction in the presence of a suitable oxidant, resulting overall in a vinylic or allylic functionalization of the unactivated olefin (Scheme 1.17, path b).[54,86]



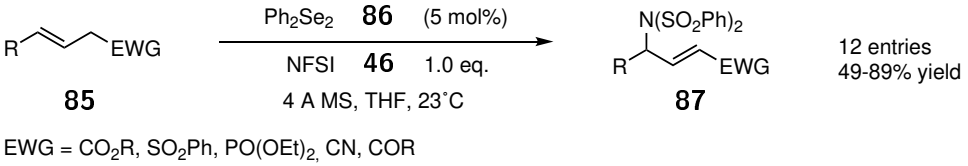
Scheme 1.17: Chalcogens as π-acid activators of olefins in the oxidative functionalization of olefins. The orbital interactions of the chalcogen atom and the π-bond are shown in the box.

The elimination reaction from the chalcogen-adducts, both in the Lewis-base activation as well as the π-acid activation, in the presence of a suitable oxidant is analogous to the elimination reaction of the hypervalent iodine adducts **60** briefly mentioned in Section 1.3. Adducts containing sulfur as the chalcogen atom require higher temperatures and longer reaction times for the elimination reaction. In contrast, seleno-adducts undergo elimination at room temperature or even at 0°C.[89] Consequently, selenium-catalyzed olefin

functionalizations have been gaining popularity over the last couple of decades. In some cases, the nucleophile which results in the opening of the chalcogeniranium intermediate stems from the oxidant (*endogenous nucleophile*), whereas in others, an external intra- or intermolecular nucleophile (*exogenous nucleophile*) is added to the reaction.[46] In cases where an exogenous nucleophile is required, a competing reaction can occur with the endogenous nucleophile.[86] Therefore, the choice of nucleophile and oxidant play an important role in determining the outcome of the reaction. Off late, a number of reactions have been published using NFSI (**46**) as the oxidant or both as the oxidant and as a source of the (endogenous) nucleophile, establishing a new strategy for the construction of C-heteroatom bonds using selenium catalysts.[90–92]

1.3.3 Se-catalyzed olefin functionalization using NFSI

The ability of NFSI (**46**) to functionalize different substrates and the advantages associated with it (cf. Subsection 1.2.4) has also been used in the Se-mediated functionalization of olefins. In 2013, Breder and co-workers developed a strategy for a Se-catalyzed intermolecular synthesis of an array of allylic and vinylic imides using NFSI (**46**) as both the terminal oxidant and source of nitrogen and diphenyl diselende (**86**) as the catalyst.[90] THF was determined to be the optimum solvent for the desired transformation. The advantage of using NFSI as the oxidant over the hitherto used *N*-halosuccinimides was twofold: firstly, the problem of a competing halogenation reaction was circumvented[54,55] and secondly, no extra nitrogen source had to be added to the reaction. The authors used acyclic allylic esters, sulfones, amides, among other functional groups as substrates and were able to synthesize the corresponding allylic imides in yields of up to 89% (Equation 1.12). Furthermore, the reaction was also found to work with cyclic alkenes, giving the corresponding vinylic imides in yields of up to 95% (Equation 1.13). For this transformation, 1,4-dioxane was determined to be the most suitable solvent.



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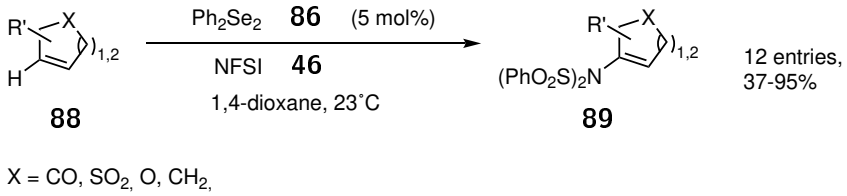
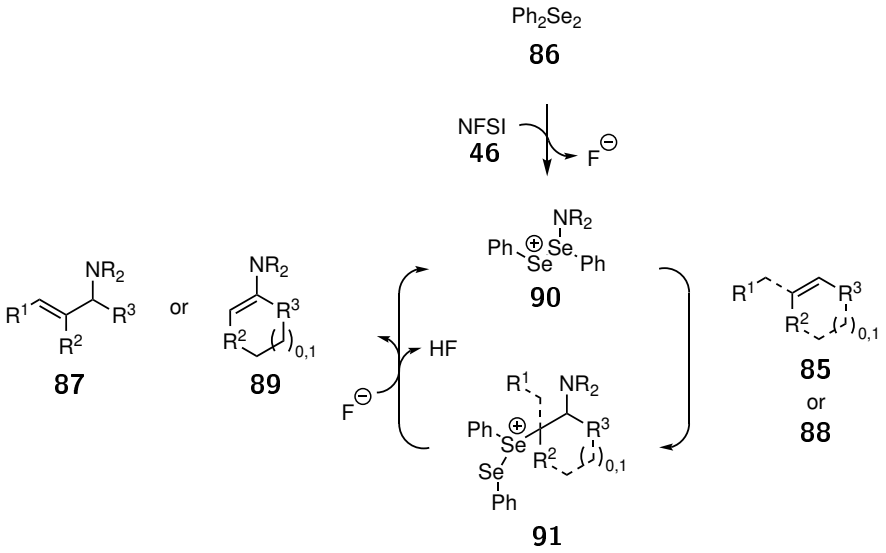


(1.13)

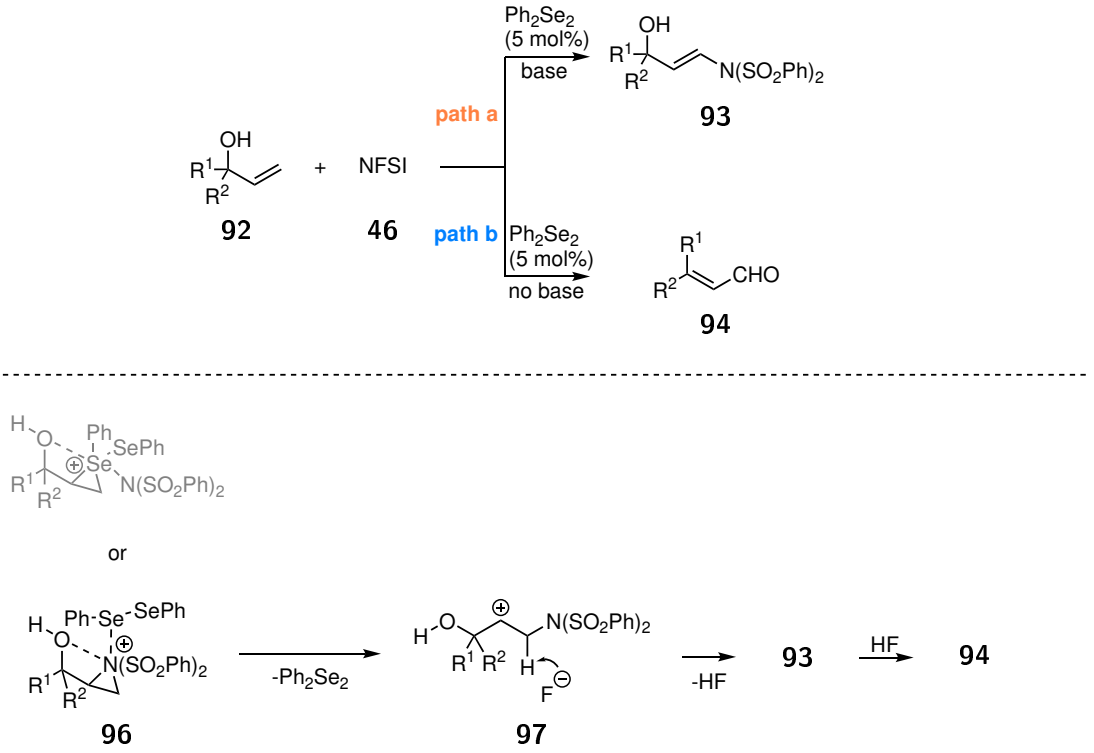
Control experiments revealed that the presence of an Se−Se bond is crucial for catalytic activity to occur, and that no intermediary species such as PhSeF or $PhSeN(SO_2Ph)_2$, formed as the result of a reaction between NFSI (**46**) and the selenium catalyst **86** was sufficient to bring about the desired reaction. The proposed mechanism is shown in Scheme 1.18. The NFSI undergoes nucleophilic attack to give cationic species **90**. Addition of this species to the alkene gives cationic adduct **91**, which then undergoes elimination promoted by the F^- anion to give the desired product and regenerate the diphenyl diselenide catalyst.



Scheme 1.18: Proposed mechanism of the Se-catalyzed intermolecular amination of alkenes using NFSI (**46**).[90]

In 2015, Zhao and co-workers improved these results by publishing a method for a single-step Se-catalyzed amination of terminal vinylic sp^2 C−H bonds starting from allylic alcohols.[93] When allylic alcohol **92** was treated with 5 mol% of diphenyl diselenide (**86**) and NFSI (**46**) in the presence of a base, *trans*-aminated alcohol **93** was formed (Scheme 1.19, path a). In the absence of a base, aldehyde **94** was formed instead (Scheme 1.19, path b). The authors were also able to apply this method to α,β-disubstituted alkenes, resulting in the formation of exclusively *cis*-amination products **95**. The authors hypothesized that

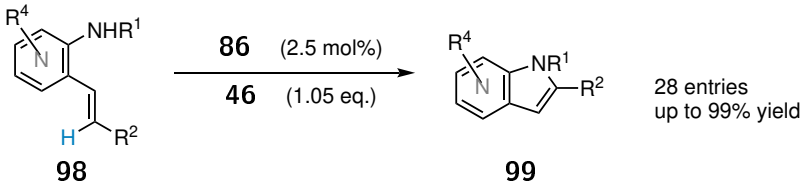
the lone pair of electrons on the oxygen atom of the hydroxy group could react with the selenium cation and consequently control regio- and stereoselectivity of the amination. Intermediate **96** formed by the addition of diphenyl diselenide (**86**) or NFSI (**46**) to the double bond undergoes a rapid elimination of diphenyl diselenide (**86**) to give cationic intermediate **97**, which under the loss of a proton gives *trans*-functionalized alcohol **93**. In the absence of a base to neutralize the *in-situ* produced HF, product **93** undergoes decomposition to give aldehyde **94**. This hypothesis was backed by various control experiments. With this method, the authors were no longer restricted by the need for an EWG in the allylic position as in case of Breder and co-workers,[90] and as a result published the first regio- and stereoselective method for the amination of olefins *via* Se-catalysis.



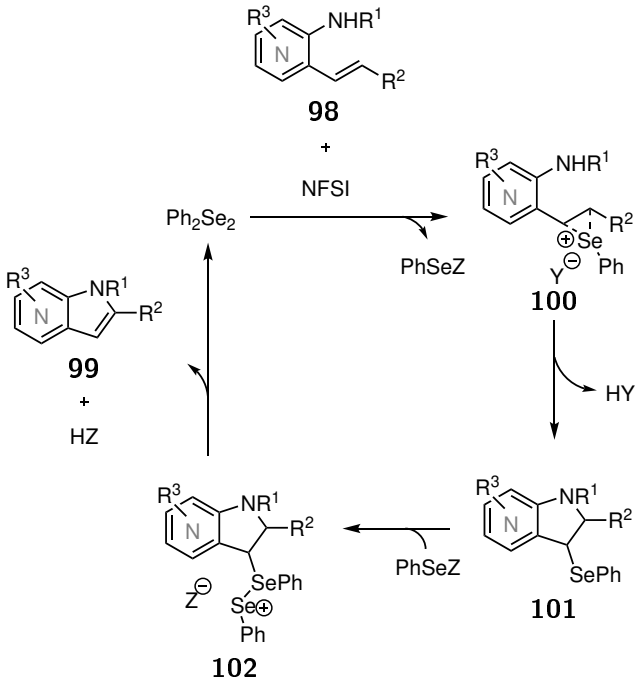
Scheme 1.19: Vinylic amination of allylic alcohols as reported by Zhao and co-workers.[93]

Following this, the Breder group published a method for an intramolecular synthesis of (aza)indoles *via* a Se-catalyzed Csp^2-H amination of unactivated alkenes using NFSI (**46**) as the terminal oxidant.[92] A large number of anilides **98** containing both various allylic and aromatic substituents were used as substrates, with the desired (aza)indoles (**99**) obtained in yields of up to 99% (Equation 1.14). The authors reported that a sufficient acidity of the N-H proton is necessary for the required deprotonation to take place. Furthermore, the electronic nature of the substituents on the aromatic ring was found to

have little to no effect on the outcome of the reaction. Consequently, the authors were able to extend the method to aminopyridines. The authors propose that the reaction proceeds *via* the formation of seleniranium intermediate **100**, which, upon nucleophilic attack by the nitrogen moiety forms adduct **101**. Nucleofugic activation of the Se-center by another electrophlic Se-species promotes the required elimination and consequently forms the desired product **99** and regenerates the diselenide catalyst (Scheme 1.20).



(1.14)

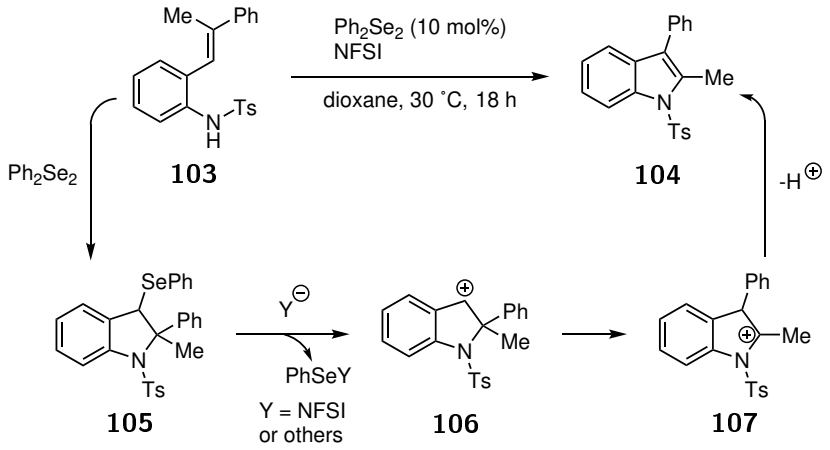


Y = $N(SO_2Ph)_2$ if Z = F or vice versa

Scheme 1.20: Mechanism of the Se-catalyzed intramolecular synthesis of (aza)indoles using NFSI as terminal oxidant.[92]

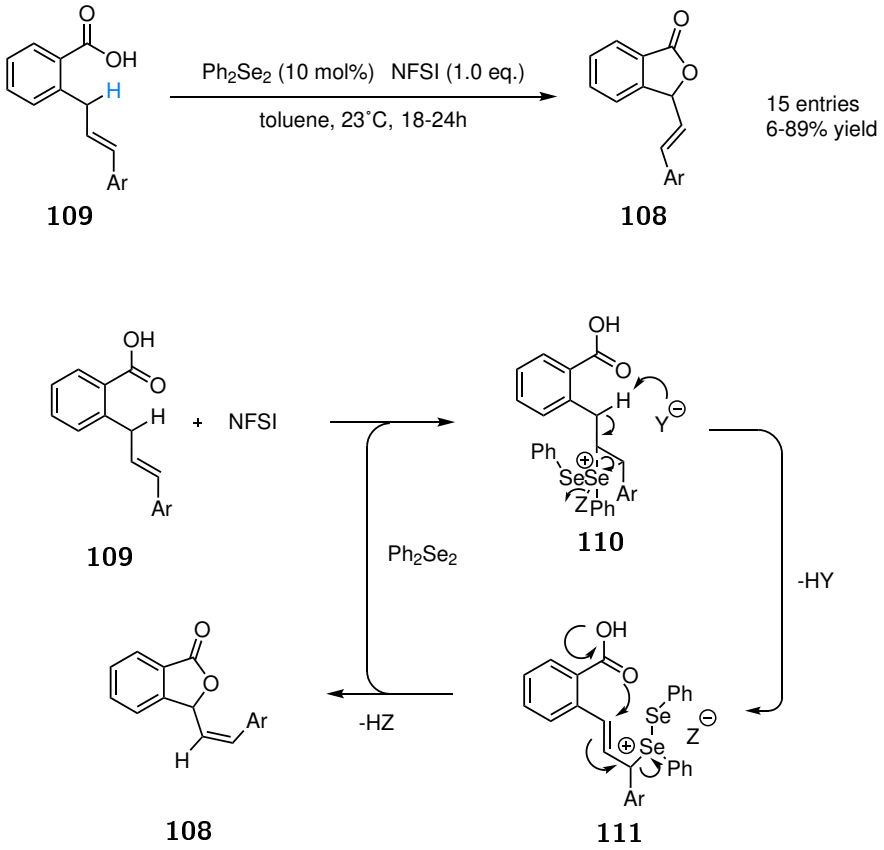
At about the same time, Zhao and co-workers published a similar method for the synthesis of indoles using NFSI (**46**) and diphenyl diselenide (**86**) as catalyst, albiet with a higher catalyst loading of 10 mol%.[94] Additionally, they were able to use this method to functionalize trisubstituted alkenes **103** (Scheme 1.21). When alkene **103** was treated with diphenyl diselenide (**86**) and NFSI (**46**) in dioxane, 2,3-disubstituted indole **104** was

formed, *via* a 1,2-phenyl group migration (Scheme 1.21). Attack of the selenide catalyst on to the double bond followed by ring closure gave intermediate **105**. Elimination of PhSeY to give **106**, accompanied by 1,2-migration of the phenyl group formed intermediate **107**. Elimination of a proton gave the 2,3-disubstituted indole product **104**. This was the first time that product **104** was formed *via* a 1,2-phenyl group migration.



Scheme 1.21: Synthesis of 2,3-disubstituted indoles **104** by Zhao and co-workers.[94]

Shortly afterwards, Breder and co-workers were able to expand this method to a Csp^3-H acyloxylation reaction to synthesize isobenzofuranones **108** using *o*-allyl benzoic acid derivatives **109** (Equation 1.15).[91] As in the previous case, both electron withdrawing and donating groups on the aromatic ring of the benzoic acid were tolerated well under the optimized reaction conditions. However, electronic differences in the substituents on the olefin significantly affected the yields of the corresponding products. Electron deficient substituents on the olefin were observed to give poor yields when compared to electron-neutral or electron donating subsitutents. Based on extensive control experiments, the authors suggest that the reaction occurs *via* an allylic selenation/S_N2' substitution domino reaction. The addition of an electrophilic selenium species to the double bond results in the formation of cationic intermediate **110**. This intermediate can undergo deprotonation to yield olefinic intermediate **111**, which can in turn undergo an S_N2' substitution by the carboxylic acid group to give the desired product **108** and regenerate the diselenide catalyst.

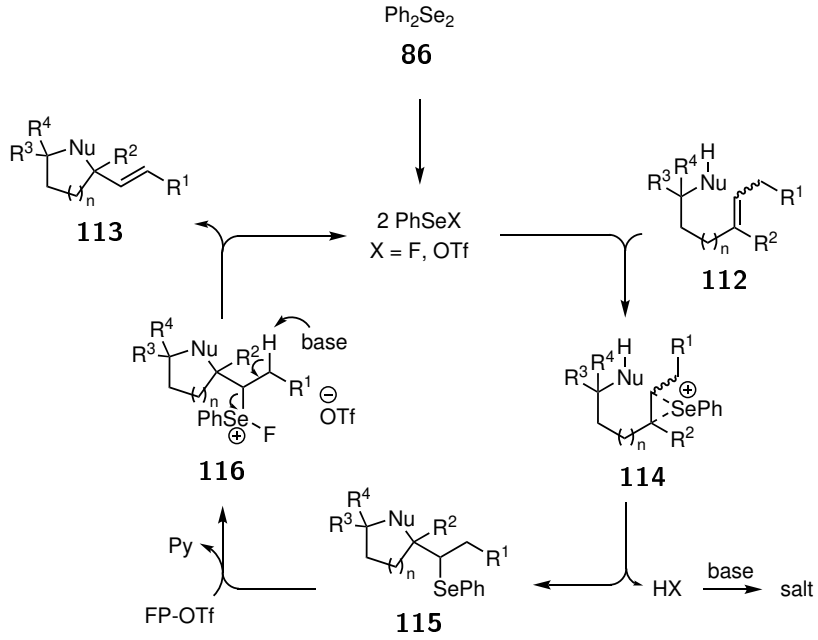


(1.15)

Scheme 1.22: Mechanism of the Se-catalyzed intramolecular synthesis of isobenzofuranones using NFSI as terminal oxidant.[91]

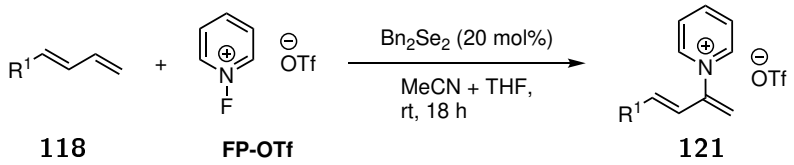
The method described above by Breder and co-workers was limited to the synthesis of benzoheterocycles. In 2016, Zhao and co-workers were able to apply Se-catalysis to the synthesis of other oxygen- and nitrogen-containing hetereocycles, such as tetrahydrofurans, tetrahydropyrans, pyrrolidines and piperidines.[95] When olefinic alcohols or olefinic sulfoniamides **112** were treated with diphenyl diselenide (**86**), NaF, and fluoropyridinium triflate (FP-OTf) in a suitable solvent, the corresponding *exo-trig* cyclization products **113** were formed (Equation 1.16). The proposed mechanism of the transformation is shown in Scheme 1.23. Diphenyl diselenide (**86**) reacts with FP-OTf to form a highly reactive PhSeX species (X = F, OTf), which adds on to the olefinic double bond to produce seleniranium ion **114**. Intramolecular attack of the nucleophile leads to ring opening and the formation of intermediate **115**. The phenylseleno group on intermediate **115** undergoes oxidation to form cationic intermediate **116**. Base-assisted deprotonation, followed by removal of the PhSe-group results in the formation of product **113** and regeneration of the PhSeX species, which reenters the catalytic cycle.

(1.16)



Scheme 1.23: Mechanism of the synthesis of O- and N-containing heterocycles by Zhao and co-workers.[95]

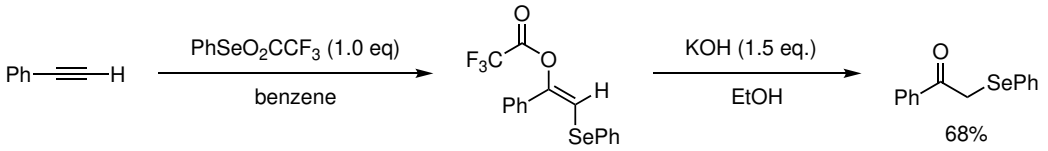
Lastly, Zhao and co-workers were able to apply Se-catalysis for the selective functionalization of 1,3-dienes selectively in the C-2 position, solving a long-standing problem associated with conjugated dienes, where the functionalization traditionally occurs in the C-1 position due to its high reactivity. When conjugated diene **118** was treated with 20 mol% of dibenzyl diselenide (**119**) and different pyridinium salts in a solvent mixture of MeCN and THF, the corresponding C-2 functionalized pyridinium salts **120** were formed in yields of up to 89% (Equation 1.17). They were also able to use this method to synthesize pyridinium salts of various styrene derivatives, with the functionalization taking place in the benzylic position.



118 FP-OTf 121 (1.17)

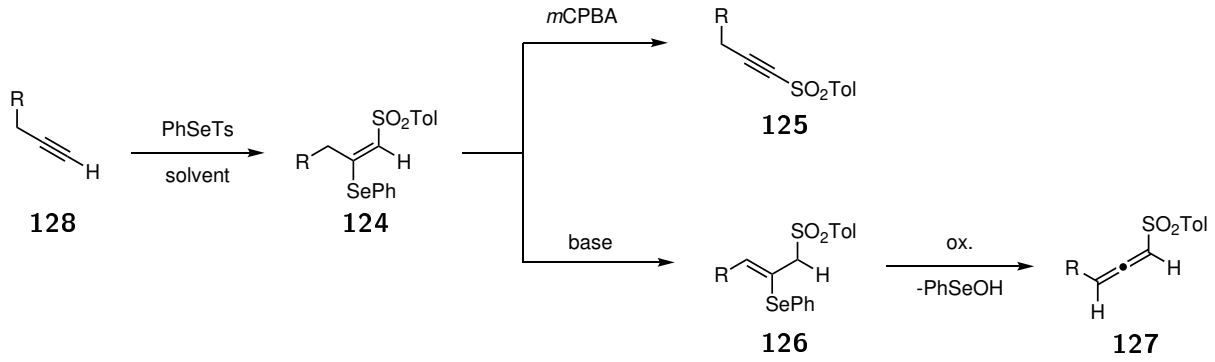
1.4 Se-catalyzed alkyne functionalization

After many successful examples of Se-catalyzed olefin functionalization, the next step was to investigate the Se-catalyzed oxidative functionalization of alkynes. The addition of a selenium reagent to a triple bond occurs analogously to that with a double bond, resulting in the formation of a vinylic selenofunctionalized adduct. Consequently, a nucleophilic substitution reaction is ruled out, and further functionalization is possible either *via* elimination or hydrolysis. The earliest example of Se-mediated functionalization of alkynes was reported by Reich and co-workers in 1974.[96] Here, the addition of phenylselenyl trifluoroacetate to phenyl acetylene (**122**) was demonstrated. The resulting vinylic selenofunctionalized adduct **123** was hydrolyzed to give a β-phenylselenyl ketone **117** in 68% yield (Equation 1.18).



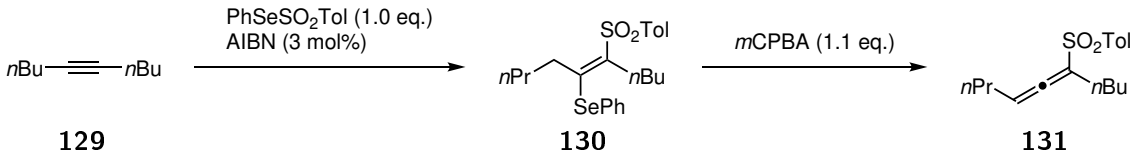
122 123 117 (1.18)

An elimination reaction of the vinylic selenofunctionalized adduct was first reported by Back and co-workers in 1981.[97] Here, the authors reported the addition of phenylselenyl *p*-tolueneselenosulfonate to terminal alkynes to give the corresponding β-(phenylseleno)vinyl sulfones (**124**). Oxidation of the adduct with *m*CPBA resulted in the formation of the corresponding acetylinic sulfone (**125**). In another synthetic transformation of the adduct, the authors reported that upon reaction with a base, the double bond undergoes isomerization to give the allylic β-(phenyl-seleno) sulfone **126**.[98,99] Oxidation of the isomerized adduct results in the formation of allenic sulfone **127** (Scheme 1.24).
Back and co-workers extended Se-mediated alkyne functionalization to include internal alkynes, when they treated 5-decyne (**129**) with phenylselenyl *p*-tolueneselenosulfonate in the presence of AIBN.[100] The resulting vinylic selenium-functionalized adduct **130**)un-



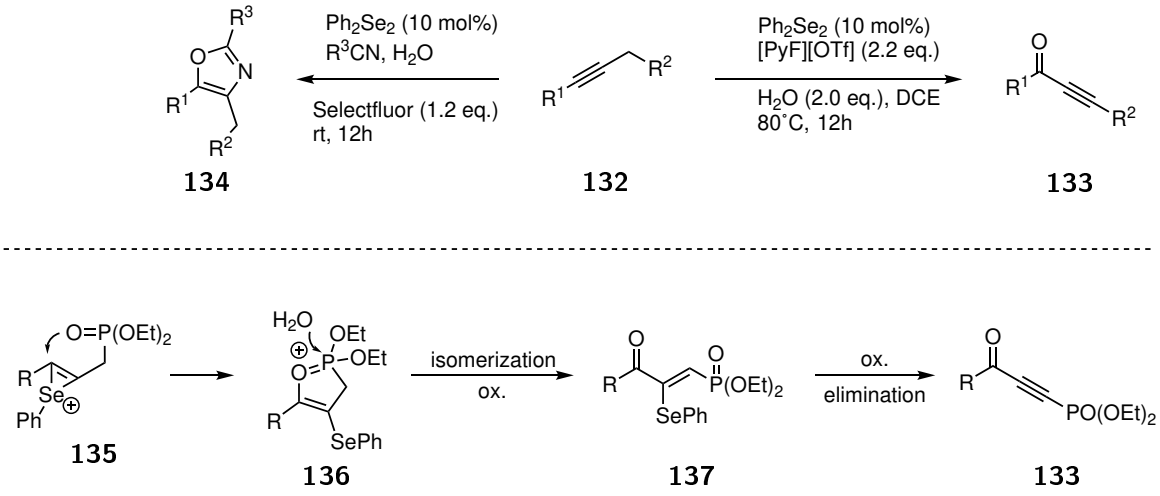
Scheme 1.24: Addition of a selenium reagent to a triple bond, as reported by Back and co-workers.[98,99]

dergoes oxidation with *m*CPBA followed by elimination of an allylic hydrogen to give the corresponding allene **131** (Scheme 1.25).



Scheme 1.25: Se-mediated oxidative functionalization of internal alkynes to give functionalized allene **131**.[100]

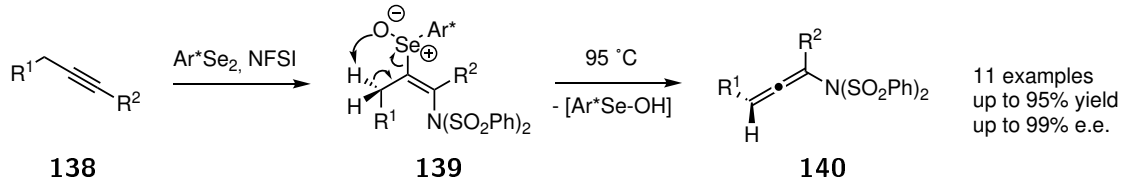
A major breakthrough was made by Zhao and co-workers in 2018, when they were able to establish the first catalytic protocol in the Se-π-acid-mediated functionalization of alkynes.[101] Ynones **133** were synthesized starting from propargylic phosphonates and esters (**132**) using diphenyldiselenide (**86**) as catalyst and [PyF][OTf] as the oxidant and water. They were also able to extend this method to synthesize oxazoles **134** (Scheme 1.26). The main drawback of this method is the need for prefunctionalized starting alkynes, wherein the synthesis of the ynones required the presence of an oxygen atom in the propargylic position in the substrate. This is because the oxygen atom is required to open the selenirenium intermediate **135** to form oxaphosphole **136**. Subsequent attack by H_2O leads to an allylic alcohol, which upon oxidation gives ketone **137**. Oxidation of the selenium moiety followed by elimination gives the desired product **133**.



Scheme 1.26: Se-catalyzed oxidative functionalization of alkynes reported by Zhao and co-workers.[101]

1.4.1 Se-catalyzed asymmetric alkyne functionalization

After the results discussed in the course of this thesis were published in 2021, Peixoto and co-workers in 2023 used a chiral lactamide-containing diselenide catalyst to synthesize enantioenriched aminoallenes **140** from simple alkynes *via* chiral vinyl selenoxide intermediates **139** in a two-step procedure, thereby becoming the first group to develop an asymmetric version of our method (Scheme 1.27).[102]



Scheme 1.27: Recent method for the enantioselective synthesis of aminoallenes.[102]

The authors were able to isolate a number of chiral selenoxide intermediates **139**, which were then converted to their corresponding aminoallenes *via* a β-syn-elimination reaction. The stereochemical outcome of the reaction was determined *via* a 5-center transition state, wherein the presence or the absence of sterical repulsion between the substituents on the aromatic group on the Se-species and the substituents on the olefinic double bond determines which of the two allylic protons will be deprotonated. The configuration of the Se−O bond is fixed *via* hydrogen bonds between each of the lactamide protons and the Se- and O-atoms, respectively (Figure 1.4).

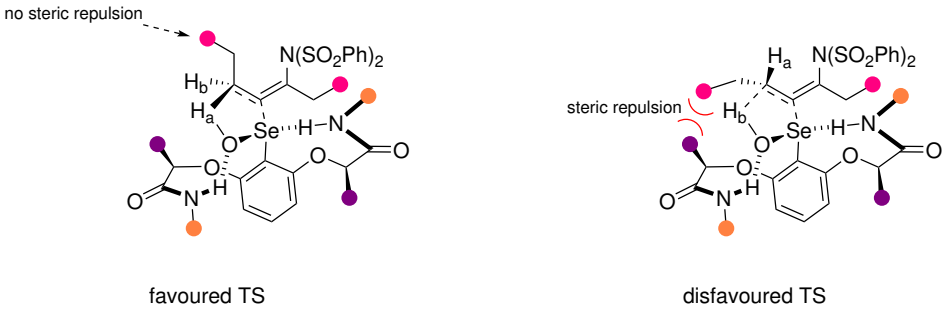
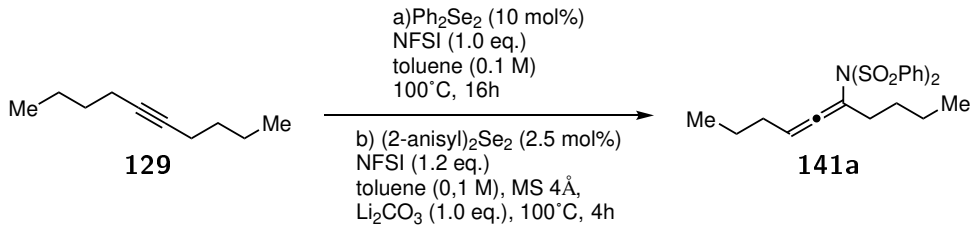


Figure 1.4: Structure of the five-membered, hydrogen bond-stabilized L: favoured TS and R: disfavoured TS of the selenoxide intermediates isolated by Peixoto and co-workers.[102]

As seen from the above examples, Se-catalysis can be used to functionalize simple, non-functionalized alkynes. Therefore, Se-catalysis could be a promising strategy towards the synthesis of aminoallenes starting from simple, non-functionalized alkynes. Additionally, if this strategy could combine the adjustment of the oxidation state and the introduction of the nitrogen moiety on the aminoallene in a single step, a major breakthrough would be achieved, not only in the field of Se-catalysis, but also in the synthesis of aminoallenes.

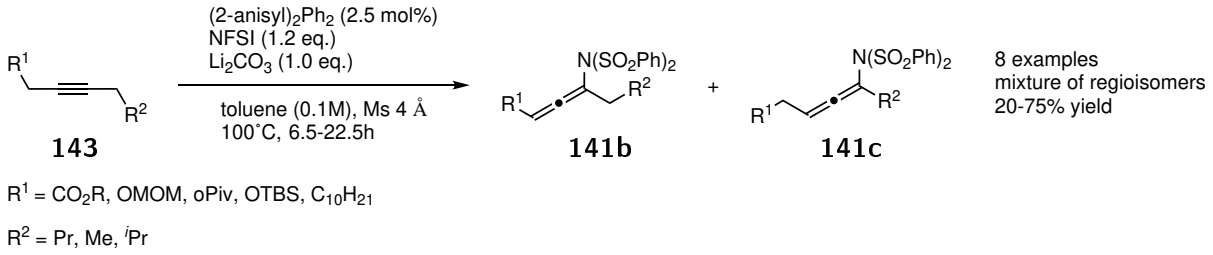
2 Objectives

After achieving multiple milestones in the Se-catalyzed functionalization of olefins,[46,91,92] our group wanted to test the applicability of selenium catalysts in the functionalization of alkynes, with a focus on using simple nonfunctionalized alkynes and an endogenous nucleophile, i.e., a nucleophile stemming from the oxidant. As NFSI (**46**) had proven to be a promising candidate both as the source of nucleophile and as the terminal oxidant in the oxidative functionalization of olefins,[90–92] the same strategy was decided to be used here. Initial experiments by Dr. Ortgies using 5-decyne (**129**), 10 mol% diphenyl diselenide (**86**) as catalyst, NFSI (**46**) (1.0 eq.) in toluene gave aminoallene (**141a**) in 38% yield (Equation 2.1a).[103] Further experiments conducted by Dr. Rode led to the following optimized conditions: using alkyne **129**, 2.5 mol% (2-anisyl)$_2$Se$_2$ (**142**) as catalyst, 1.0 eq. of Li_2CO_3 as base, 1.2 eq. of NFSI (**46**) as the source of nitrogen and terminal oxidant in toluene (0.1M) at 100°C, aminoallene (**141a**) was obtained with a yield of 77% (Equation 2.1b).[104]



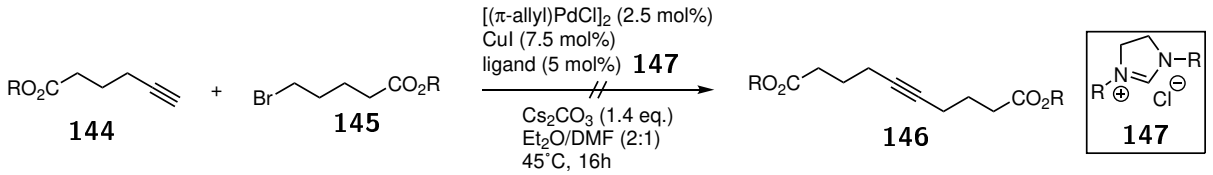
(2.1)

With optimized conditions in hand, the substrate scope of the reaction was investigated. The reaction was tested on both symmetric and unsymmetric alkynes. The reaction showed promising results with a number of unsymmetric alkynes, giving the corresponding aminoallenes in yields of up to 75%.[4] The reaction worked well with substitutents such as ethers, esters, and simple alkyl substituents. As expected, the product was obtained as a mixture of regioisomers, with a slightly higher preference for the aminoallene with the nitrogen group distal to the allenic moiety. The preference for a regioisomer was probably dictated by steric factors, wherein bulky substituents such as esters push the bulky selenium moiety away from the double bond to the less-hindered position, thus enabling nucleophilic attack at this distal position (Equation 2.2).

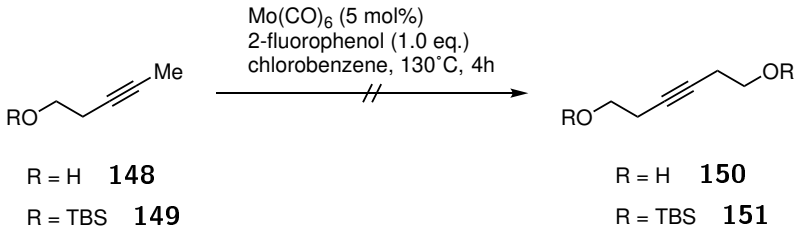


(2.2)

Following the success of the reaction with unsymmetric alkynes, our focus shifted to symmetric alkynes bearing different functional groups. However, the synthesis of suitable symmetric alkynes proved to be unexpectedly challenging. A Sonogashira coupling reaction performed by Dr. Rode using the corresponding methoxy esters of alkyne **144** and halide **145** failed to give the desired coupling products (Equation 2.3). Following these results, an alternative method for the synthesis of symmetric alkynes *via* alkyne metathesis was investigated. For this purpose, an alkyne metathesis reaction using 3-pentyne-1-ol (**148**) using $Mo(CO)_6$ was attempted. Unfortunately, no reaction was observed. The same results were obtained when the reaction was repeated with tert-butyldimethyl(pent-3-yn-1-yloxy)silane (**149**) (Equation 2.4).

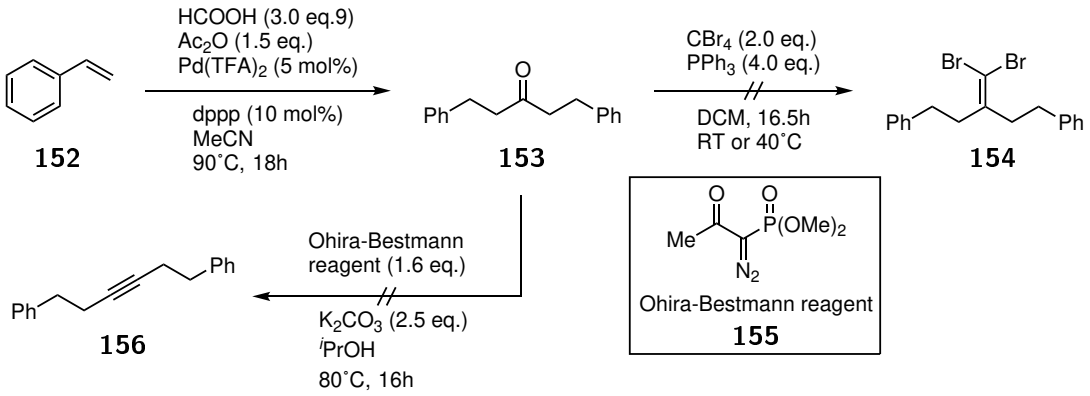


(2.3)



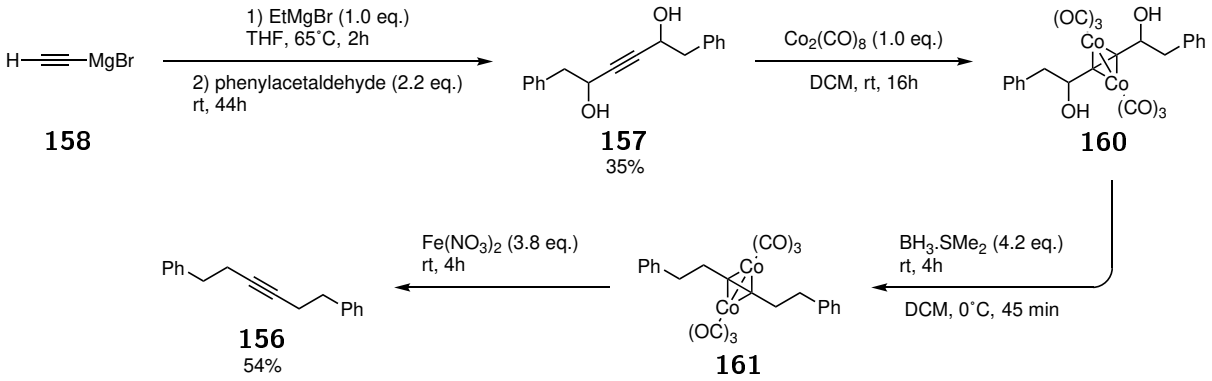
(2.4)

After the failure of the above two methods, a Corey-Fuchs reaction to synthesize symmetric alkynes was attempted. Ketone **153** was synthesized *via* a Pd-catalyzed carbonylation of styrene (**152**), obtained in a yield of 41%. However, the synthesis of dibromoalkene **154** from ketone **153** using carbon tetrabromide and triphenyl phosphine yielded no product. Consequently, a Seyferth-Gilbert homologation using the Ohira-Bestmann reagent (**155**) was attempted using ketone **153**. Unfortunately, no product formation was observed.



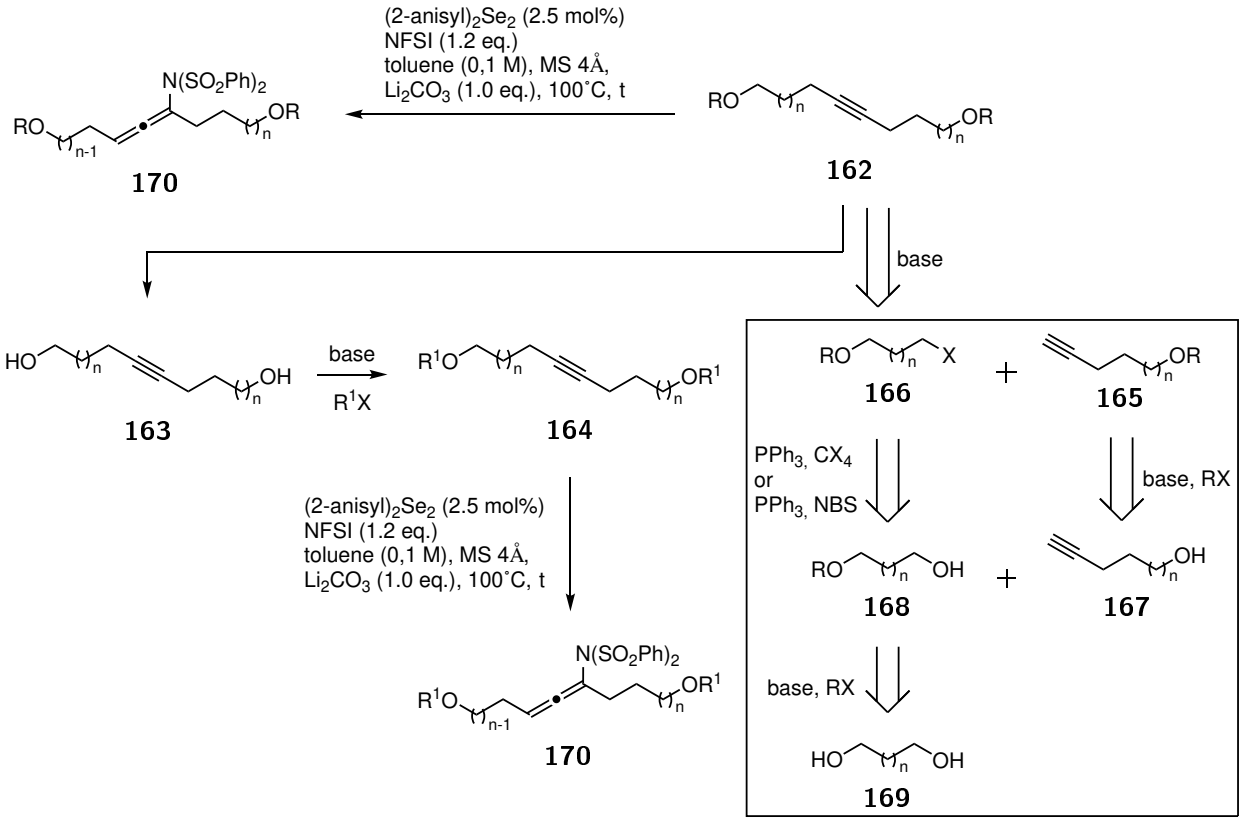
Scheme 2.1: Synthesis of ketone **153** from styrene (**152** and the attempted Corey-Fuchs and Seyferth-Gilbert homologation reactions).

As the transformation of a carbonyl moiety into a triple bond proved to be unsuccessful thus far, the incorporation of the triple bond as a whole in one of the starting materials was considered. To this effect, diol **157** was synthesized in 35% from a bis-Grignard reagent obtained by reacting ethinyl magnesium bromide (**158**) and ethyl magnesium bromide (**159**) (Scheme 2.2). To obtain an alkyne from diol **157**, a reduction of the hydroxyl groups while simultaneously leaving the alkyne triple bond unaffected was necessary. This was achieved by protecting the triple bond with a dicobalt compound in a Nicholas reaction[105] to give dicobalt complex **160**. The reduction of the diol was achieved with a borane dimethylsulfide complex to give cobalt complex **161**, which was deprotected using $Fe(NO_3)_2$ to give alkyne **156** in a 54% yield. However, due to the highly toxic and hazardous nature of both the cobalt and borane complexes, and also because the protection and deprotection added an extra step to the synthesis, an alternative route was sought.



Scheme 2.2: Synthesis of alkyne **156** from ethinylmagnesium bromide (**158**).

Therefore, the aim of this project was to identify a suitable alternative route to synthesize symmetric alkynes, which would further be used as substrates for the Se-catalyzed functionalization of alkynes. The method of choice should ideally allow for the introduction of a variety of functional groups on the alkyne using simple transformations, starting from commercially available, non-toxic starting materials (Scheme 2.3). In order to simplify the overall synthesis, it was important that one of the starting materials already contained the required triple bond. To achieve this, we envisioned a route incorporating protected diol **162**. Deprotection of the hydroxyl groups to diol **163**, followed by reprotection using a base and a suitable protecting group, would facilitate the incorporation of a variety of other rests on the alkynes, leading to an array of symmetric ethers and esters (**164**). The protected diol (**162**) itself could be synthesized *via* a coupling reaction between alkyne **165**, bearing a protecting group on the hydroxyl moiety, and halide **166**, also containing a protected hydroxyl group. The corresponding unprotected terminal alkyne **167** should ideally be commercially available. Halide **166** can be synthesized from the corresponding singly protected alcohol **168** using, for example, an Appel reaction. The singly protected alcohol can be synthesized from the corresponding diol **169**.



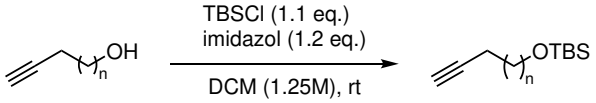
Scheme 2.3: Envisioned synthetic route to symmetric alkynes.

As a mechanism for the titular reaction was already proposed by Dr. Rode before the beginning of this work, the experiments pertaining to the mechanistic investigations lie beyond the scope of this thesis and will therefore not be discussed here.

3 Results and Discussion

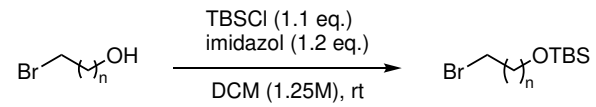
3.1 Synthesis of symmetric alkynes

Following the envisioned synthetic path, but-3-yn-1-ol (**172**) and 2-bromoethan-1-ol (**173**) were converted to their corresponding TBS ethers **174** and **175**, respectively, using TBSCl (1.1 eq.) and imidazole (1.2 eq.) in DCM (1.2 M) (Equation 3.1).[106] However, during the course of the substrate synthesis, it was observed that both the starting materials were volatile under reduced pressure. Therefore, the reactions were repeated with starting alcohols having a slightly longer chain length, and consequently a higher molecular weight and therefore higher boiling points. The reaction was repeated using hex-5-yn-1-ol (**176**) and 4-bromo-butan-1-ol (**177**) using the same reaction procedure. The corresponding TBS-ethers **178** and **179** were obtained in nearly quantitative yields (Equation 3.1 and Equation 3.2).



n = 1	**172**		n = 1	**174**	80%
n = 3	**176**		n = 3	**178**	>99%

(3.1)

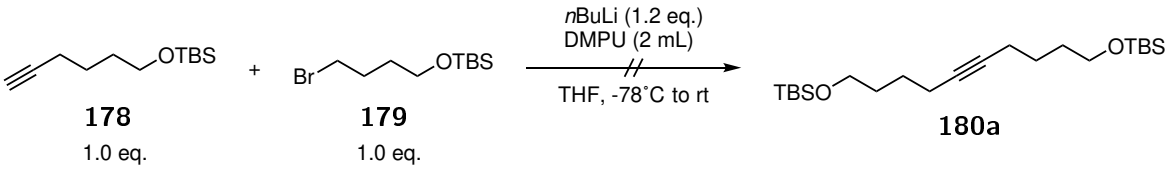


n = 1	**173**		n = 1	**175**	82%
n = 3	**177**		n = 3	**179**	>99%

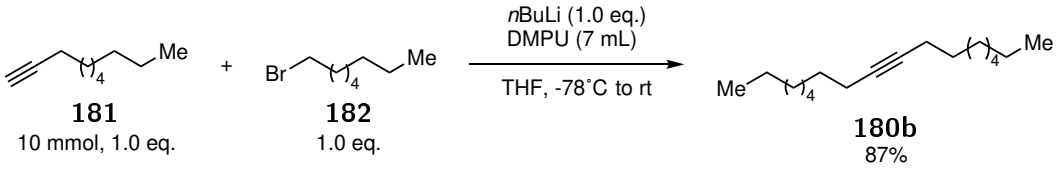
(3.2)

The coupling reaction was carried out between compounds **178** and **179** using *n*-BuLi (2-0 eq.) and DMPU in THF.[107] However, no coupling reaction was observed from the crude proton spectrum of the reaction mixture (Equation 3.3). The crude proton spectrum only showed signals belonging to both the starting materials and other small signals belonging probably to the retro-Brook rearrangement product, which TBS-ether containing terminal alkynes such as **178** are known to exhibit in the presence of a strong base such as *n*-

BuLi.[108] Purification of the reaction mixture using column chromatography led to the isolation of only the starting materials. To verify if the coupling reaction worked with other substrates, the coupling reaction was repeated with dec-1-yne (**181**) and 1-bromooctane (**182**) (Equation 3.4). To our delight, coupling product (**180b**) was obtained in a high yield of 87%. The proton NMR spectrum of the product showed two multiplets characteristic of the methyl group at 0.8 ppm, and the methylene protons directly attached to the triple bond at 2.14 ppm, respectively. The result was further corroborated by mass spectrometry.

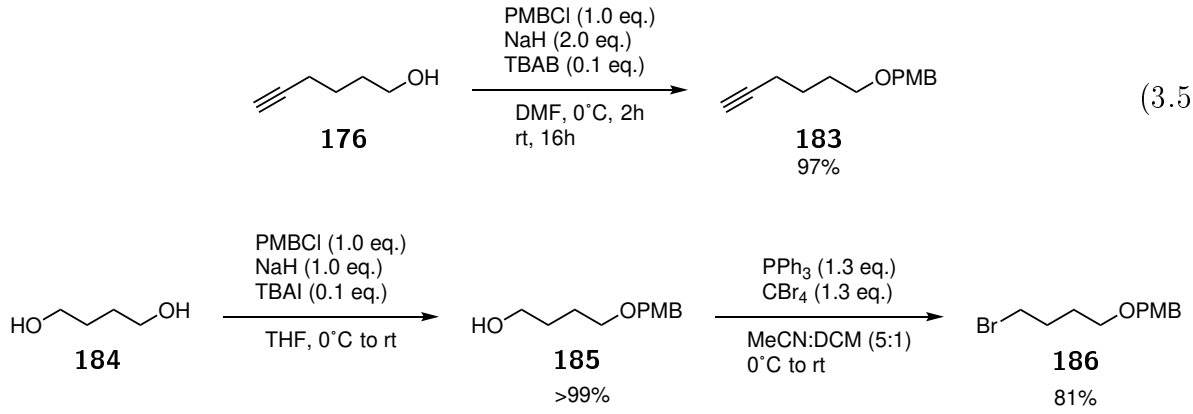


(3.3)



(3.4)

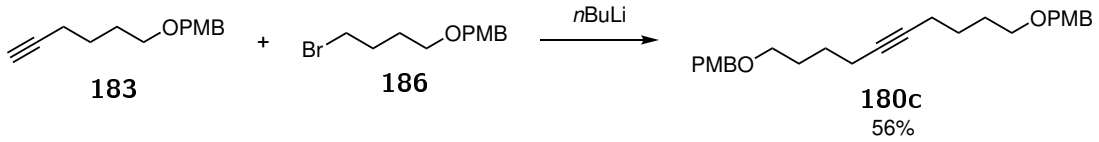
Following the success of the coupling reaction (Equation 3.4), we shifted our attention to other protecting groups for the alcohol moiety. The first protecting group of choice was the *p*-methoxybenzyl (PMB) group. PMB-ether **183** was obtained in nearly quantitative yield from alcohol **176**, PMBCl (1.0 eq.), NaH (2.0 eq.), and tetra-*n*-butylammonium bromide (0.1 eq.) in DMF at 0°C (Equation 3.5).[109] Apart from the proton NMR signals expected from the PMB-group, the methylene protons attached directly to the ether moiety showed an upfield shift from 3.64 ppm in the starting material to 3.47 ppm in the product. These shifts were in accordance with those reported in literature.[109] The required coupling partner **186** was obtained in a two-step process starting from diol **184**. First, one of the hydroxy groups on diol **184** was protected using NaH (1.0 eq.), PMBCl (1.0 eq.) and tetra-*n*-butylammonium iodide (0.1 eq.) in THF to give alcohol **185** in nearly quantitative yield (Scheme 3.1). The remaining hydroxy group in alcohol **185** was brominated *via* an Appel reaction[110] using PPh_3 and CBr_4 in a mixture of acetonitrile and chloroform (5:1).[111] The brominated coupling product **186** was obtained in 81% yield (Scheme 3.1). The product was identified by the NMR shifts of the methylene group protons directly attached to the bromide, appearing as two overlapping triplets at 3.45 ppm, compared to two separate triplets at 3.63 ppm and 3.49 ppm in alcohol **185**.



(3.5)

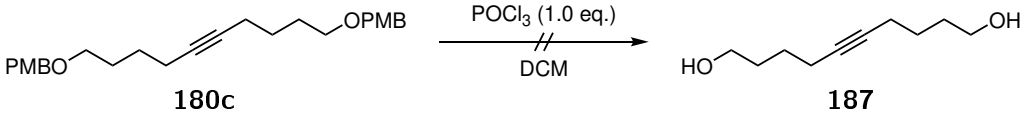
Scheme 3.1: Synthesis of bromide **186** to be used in the coupling reaction with alkyne **183**.

The coupling reaction between alkyne **183** and halide **186** was done using the same conditions as before (cf. Equation 3.3 and Equation 3.4). Coupling product **180c** was obtained in 56% yield (Scheme 3.2). The product was identified by the NMR signals of the methylene group protons in the vicinity of the triple bond, appearing as a multiplet between 2.24 ppm and 2.09 ppm. The corresponding methylene group protons in **183** appear as a doublet of triplets at 2.20 ppm. This result was further confirmed *via* mass spectrometry.



Scheme 3.2: Synthesis of molecule **180c**.

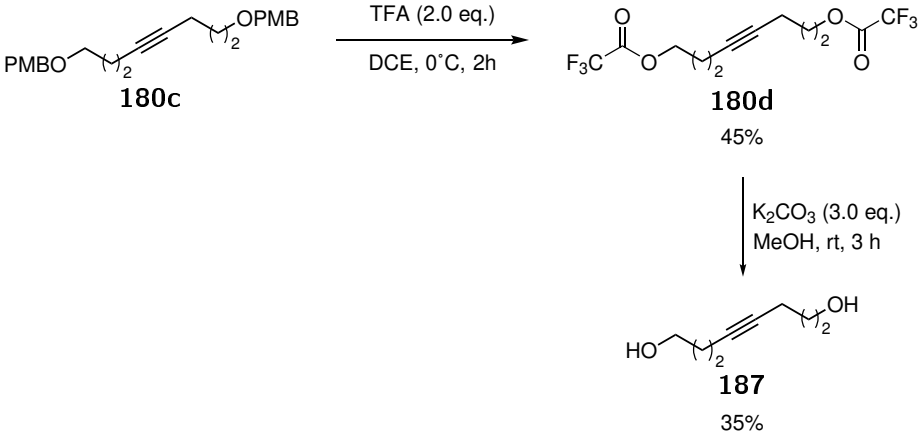
Encouraged by the success of the coupling reaction resulting in the formation of product **180c**, our attention shifted to finding a suitable procedure to cleave the PMB-protecting group. As mentioned earlier, this deprotection step followed by a reprotection using other protecting groups would grant access to an array of structurally diverse substrates for the titular reaction. In the first method tested, $POCl_3$ in dichloroethane was used to cleave the PMB-group (Equation 3.6).[112] TLC control after 1 hour revealed full conversion of the starting material. However, no product could be isolated after purification of the reaction mixture *via* column chromatography.



(3.6)

Consequently, a new method published by Silverman and co-workers was attempted. Alkyne **180c** was stirred with two eq. of trifluoroacetic acid in DCM at 0°C for 2 h

(Scheme 3.3). A clean fraction was isolated after column chromatographic separation. However, a comparison of the ^{1}H NMR spectra of the isolated product with that of the desired diol from previously published literature[113] showed that the triplet originating from the methylene group adjacent to the hydroxy group in the isolated product appeared at 4.37 ppm, instead of at 3.67 ppm as reported in literature. Mass spectroscopy showed that the isolated product was not the desired diol, but instead trifluoromethyl ester **180d** (Figure 3.1). Consequently, a procedure was sought which would cleave the trifluoromethyl ester groups and afford the desired diol. Therefore, according to a literature procedure, ester **180d** was stirred with 3 eq. of K_2CO_3 in MeOH for 3h at rt (Scheme 3.3).[114] Following work-up, diol **187** was obtained in 35% yield.



Scheme 3.3: Attempted cleavage of the PMB-protecting group on molecule **180c** resulting in the formation of trifluoromethyl ester **180d**, followed by the formation of diol **187**.

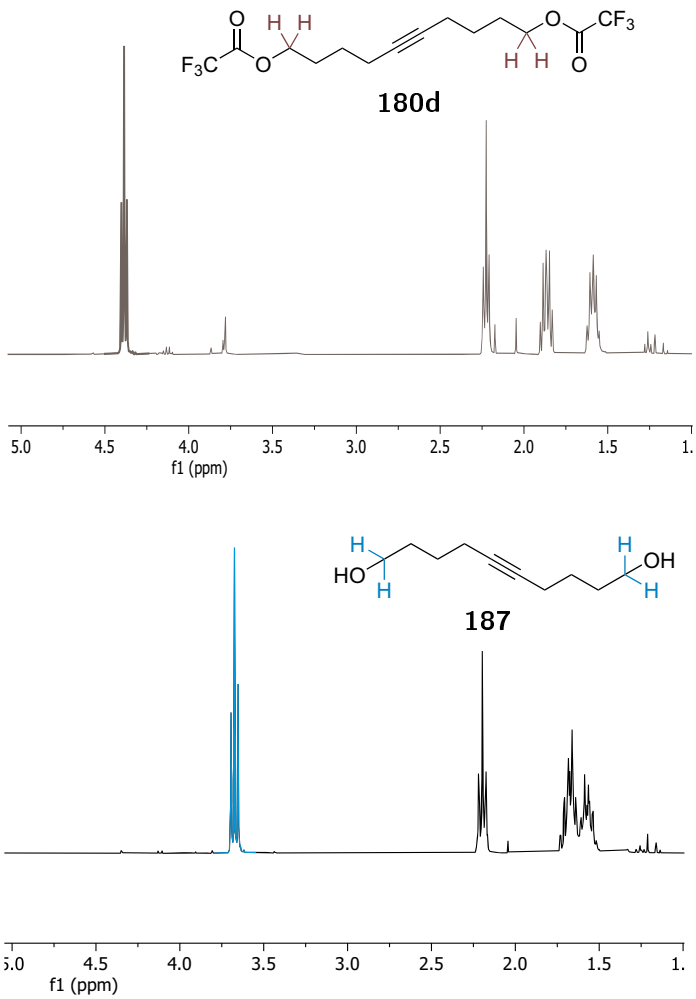
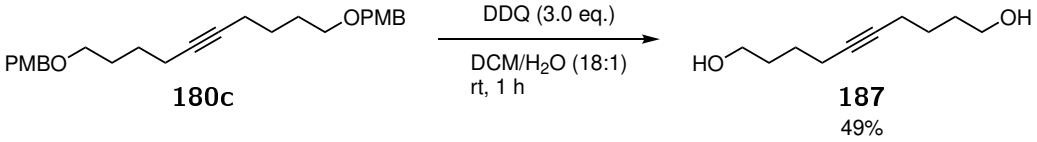


Figure 3.1: A comparison of the proton NMR spectra of trifluoromethyl ester **180d** with the free diol **187**. The NMR shifts are in accordance with existing literature.[114]

To avoid the synthesis of diol **187** over two steps, namely *via* the trifluoromethyl ester, an alternative method was sought that would enable access to the diol starting directly from compound **180c**. Following a method published by Horita and co-workers,[115] PMB-protected alkyne **180c** was treated with 3.0 eq. of DDQ in a mixture of DCM and water (18:1) and stirred at rt for 1 h (Equation 3.7). To our delight, diol **187** was obtained in a 49% yield, which provided direct access to the desired diol in a single step. The product was identified by the slight downward shift of the methylene group protons directly attached to the ether group from 3.45 ppm in **180c** to 3.61 ppm in the product (**187**). Additionally, the two alcoholic protons appeared as a broad singlet at 2.61 ppm.

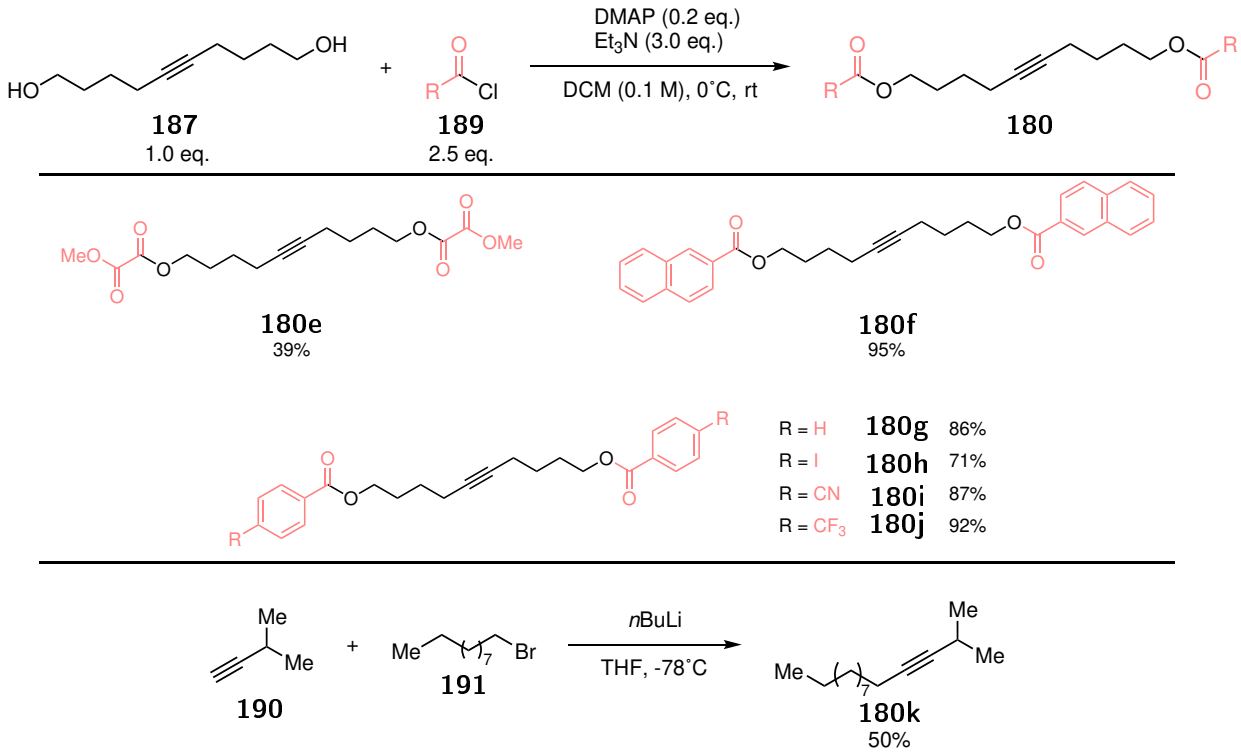


180c **187** 49% (3.7)

With the diol finally in hand, the next step was to introduce other protecting groups onto the hydroxy groups. Following a procedure by Studer and co-workers,[116] diol **187** was treated with DMAP (0.2 eq.), Et_3N (3.0 eq.), and methyl chlorooxacetate (**188**) (2.5 eq.) in DCM at 0°C. Product **180e** was obtained with a 39% yield. The same reaction was used to synthesize other symmetric alkynes such as naphthyl ester **180f** and benzylic esters **180g–j** containing different substituents on the aromatic ring, in yields ranging from 71 to 92 % (Table 3.1). The products were identified by the downfield shift of the methylene group protons directly attached to the ester group in the proton NMR spectrum to between 4.0 and 5.0 ppm, from 3.61 ppm in diol **187**.

In addition to the symmetric alkynes, unsymmetric alkyne **180k** was also synthesized as substrate for the titular reaction. The rationale behind this was to observe the effects, if any, of the branched carbon chain directly attached to the triple bond on the outcome of the allenylation reaction. To synthesize this substrate, 3-methylbut-1-yne (**190**) was treated with *n*BuLi in THF at −78°C. To this mixture, 1-decylbromide (**191**) was added. Product **180k** was obtained in yield of 50%. The product was identified from the proton NMR spectrum, where the methine proton changed from a doublet at 2.02 ppm in **190** to a triplet of doublets at 2.13 ppm. Additionally, the methylene group protons directly attached to the triple bond in product **180k** appeared as a doublet of triplet of doublets at 2.52 ppm.

Table 3.1: Synthesis of symmetric alkynes as substrates for the Se-catalyzed synthesis of aminoallenes.



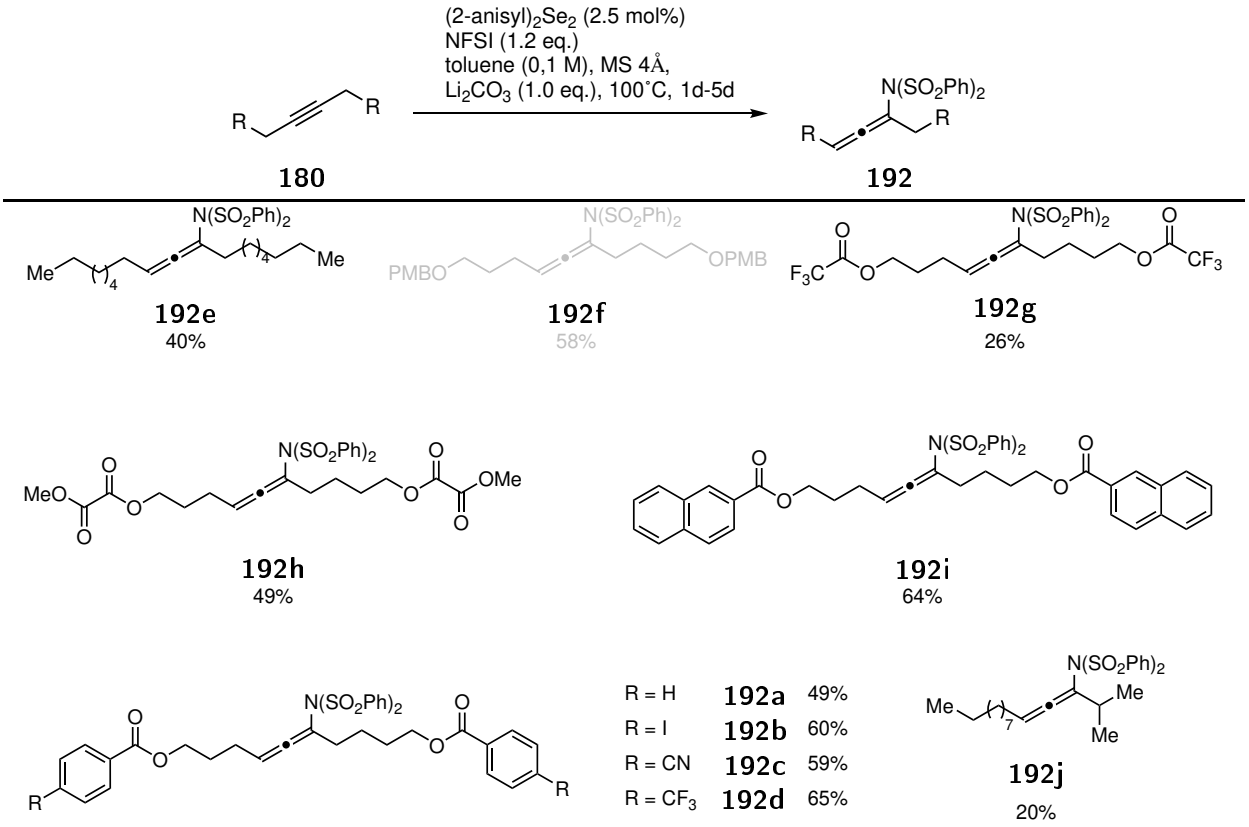
Scheme 3.4: Synthesis of unsymmetric alkyne **180k**.

3.2 Substrate scope

The allenylation reaction was performed using the optimized conditions with 2.5 mol% 2-anisyl$_2$Se$_2$, 1,2 equiv NFSI, 1.0 equiv Li_2CO_3 and molecular sieves in toluene at 100 °C (Table 3.2). The reaction was performed using the symmetric alkynes synthesized thus far (cf. Equation 3.4, Scheme 3.2, Scheme 3.3, and Table 3.1), as well as unsymmetric alkyne **180k**. The corresponding aminoallenes were obtained between 26% and 64% yields. The products were identified by the allenic proton signal in the ^{1}H NMR, appearing between 5.0 and 5.2 ppm in each case. Non-functionalized alkyne **180b** gave the corresponding aminoallene **192e** in a moderate yield of 40%. Alkyne **180c**, containing an electron donating PMB-ether group gave a slightly higher yield of 58% (**192f**). In comparison, alkyne **180d**, containing the highly electron withdrawing CF_3 group gave the corresponding aminoallene **192g** in a poor yield of 26%. Alkynes **180e–j** containing ester substituents gave the corresponding aminoallenes in moderate to good yields, between 49% and 65%. However, no clear trend could be observed here. Aminoallene **192a**, containing an aromatic ester without any substituents on the aromatic ring was obtained in a

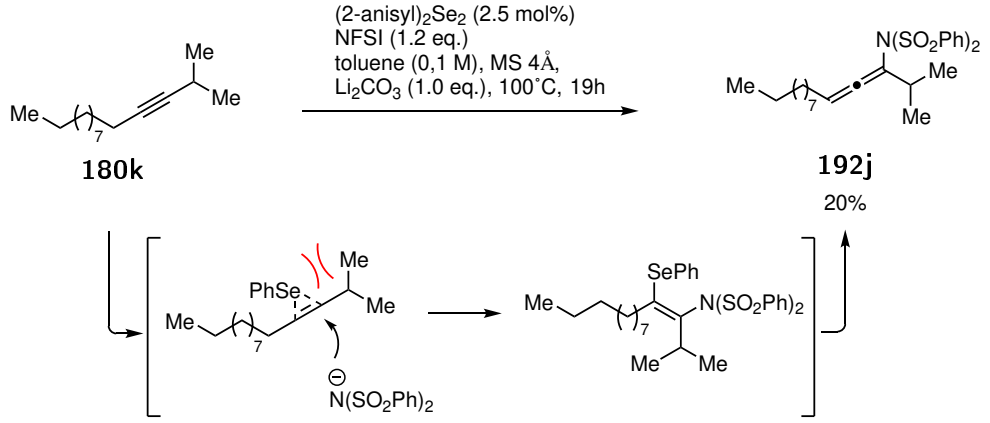
moderate yield of 48%. Higher yields of up to 65% were obtained with alkynes containing a substituent on the *para*-position of the aromatic ring of the ester group. Aminoallene **192b**, containing a *p*-iodo substituent was obtained in a 60% yield, aminoallene **192c**, with a *p*-cyano substituent was obtained in a yield of 59%, and aminoallene **192d**, with a *p*-CF_3 group was obtained in a yield of 65%.

Table 3.2: Substrate scope of the allenylation reaction. Greyed structure was synthesized by R. Rieger. Aminoallene **192g** was not isolated.



In the case of asymmetric alkyne **180k**, aminoallene **192j** was obtained in a poor 20% yield. Contrary to the allenlyation reactions performed by Dr. Rode and Dr. Krätzschmar with other asymmetric alkynes (cf. Chapter 2), regioisomer (**192j**) was the only product isolated, with a low yield of 20%. The product was identified by the characteristic allenic proton signal at 4.99 ppm. This could be due to the steric hindrance of the isopropyl group, which forces the bulky selenium moiety away from itself and as a result, facilitates the attack of the nucleophile on the carbon adjacent to the isopropyl group (Scheme 3.5). Additionally, the elimination of hydrogen from a methylene group, a secondary carbon, might be faster than the elimination from the tertiary carbon of the isopropyl group, which would have led to the formation of a tetra-substituted allene and therefore, shown

no characteristic signal for the allenic proton in the proton NMR spectrum.



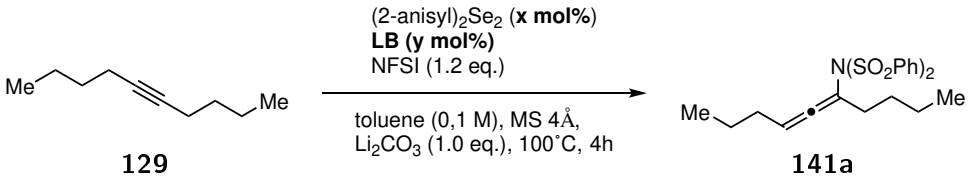
Scheme 3.5: Synthesis of aminoallene **192j** showing the potential direction of nucleophilic attack.

3.3 Mechanistic investigations

With the substrate scope of the optimized reaction established, the next step was to gain insights into the mechanism of the reaction. Two main aspects of the reaction mechanism had to be ascertained: 1) the mode of activation exhibited by the diselenide catalyst that drives the transformation and 2) the catalytic cycle itself, including, if possible, the formation of reaction intermediates and their subsequent transformation to the final product. As explained in Subsection 1.3.2, the diselenide catalyst can exhibit two modes of activation. It can either act as π-acid and activate the alkyne towards nucleophilic attack or it can act as a Lewis-base and consequently activate the nucleophile. If the reaction proceeded *via* a Lewis-basic activation of the nucleophile by the diselenide catalyst, the reaction should go towards completion even in the presence of other Lewis-bases and in the absence of the diselenide catalyst. When the reaction was carried out with alkyne **129** and 5 mol% $Se{=}PPh_3$ as the Lewis-base, product **141a** was formed in a low yield of 10% (Table 3.3, entry 1). No product formation was observed when 10 mol% of DMF was used as the Lewis-base (Table 3.3, entry 2). When a combination of 5 mol% $Se{=}PPh_3$ and 2.5 mol% 2-anisyl$_2$Se$_2$, product **141a** was formed with a 56% yield (Table 3.3, entry 3). Although this yield was not as high as that obtained when the optimized conditions were employed, it was a strong indication that the reaction did not take place *via* a Lewis-basic activation of the nucleophile by the diselenide catalyst.

During the optimization experiments with 5-decyne (**129**) conducted by Dr. Rode, the

Table 3.3: Allenylation of 5-decyne (**129**) using Lewis-bases. Experiments were conducted by Dr. Rode.

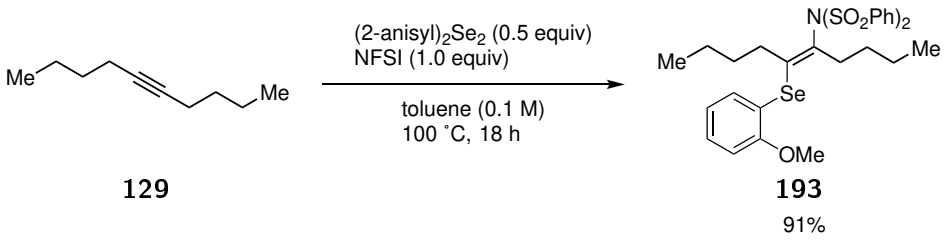


129 **141a**

Entry	(2-anisyl)$_2$Se$_2$ (**x mol%**)	LB (**y mol%**)	Yield[a]
1	-	Se=PPh$_3$ (5 mol%)	10%
2	-	DMF (10 mol%)	-
3	2.5 mol%	Se=PPh$_3$ (5 mol%)	56%

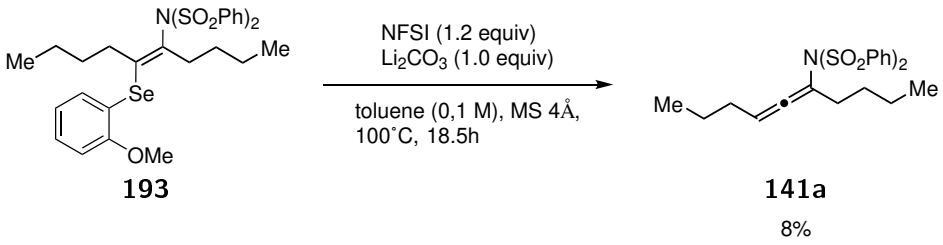
[a] NMR yield, standard: 1,3,5-trimethoxy benzene.

formation of adduct **193** was observed in many reactions. Consequently, this lead to the question whether adduct **193** was an intermediate in the catalytic cycle. To establish this, adduct **193** was synthesized from 5-decyne (**129**) using 0.5 equiv of (2-anisyl)$_2$Se$_2$ and 1.0 equiv NFSI in a 91% yield (Equation 3.8). A number of experiments were envisioned to convert it to the desired aminoallene **141a**.



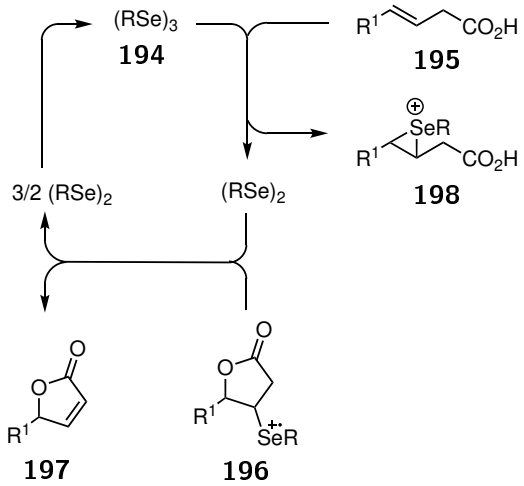
129 **193** 91% (3.8)

In their work reporting the Se-mediated functionalization of alkynes, Back and Reich showed that selenoadducts analogous to adduct **193** underwent elimination in the presence of an oxidizing agent such as *m*CPBA to give the desired allenic sulfone (cf. Scheme 1.24 and Scheme 1.25).[96–99] Based on these results, selenoadduct **193** was subjected to the optimized reaction conditions, albeit without the diselenide catalyst, to verify if the oxidation of the selenium functionalized species by NFSI resulted in the elimination step required for the formation of product **141a** (Equation 3.9). Contrary to expectations, however, product **141a** was formed in a low yield of 8%, indicating that a simple oxidation-elimination of the Se-moiety was not the dominant pathway in the catalytic cycle.

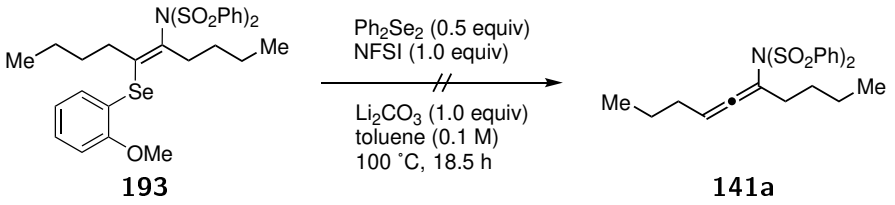


(3.9)

During investigations into the mechanism of the selenium-π-acid/photoredox catalyzed synthesis of lactones, the formation of trimeric selenium species from Ph_2Se_2 was observed.[117] This trimeric species (**194**) was not only hypothesized to transfer a phenyl selenide moiety on to another olefinic substrate **195**, but the thus-formed diselenide species $(RSe)_2$ was assumed to drive the elimination of the phenylselenide moiety from selenolactone **196** and as a consequence, result in the formation of the desired lactone **197** (Scheme 3.6). Subsequently, the question arose if a similar elimination of the selenide moiety from selenoadduct **193** could be achieved by the addition of extraneous Ph_2Se_2. In our case, it was also possible that the elimination would be induced not directly by the Ph_2Se_2, but by another selenium electrophile generated *in situ* from NFSI (**46**) and Ph_2Se_2. Therefore, the reaction was repeated with 0.5 equiv of Ph_2Se_2 (Equation 3.10) and 1.0 equiv of NFSI. Unfortunately, no product formation was observed. From the above observations, it was clear that neither the oxidation of the selenoadduct, nor the involvement of trimeric selenium species were dominant pathways in the catalytic cycles.

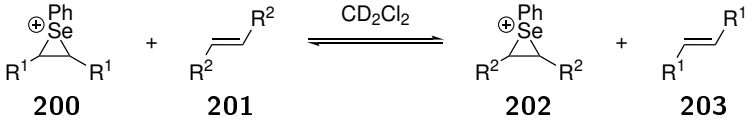


Scheme 3.6: An excerpt from the mechanism of the Se-catalyzed lactonization of alkenoic acids **195**.

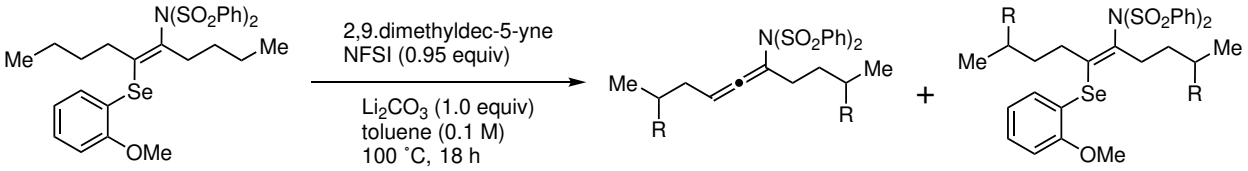


193 **141a** (3.10)

During optimization experiments, it was observed that the reaction came to a halt upon full consumption of alkyne **129**. Additionally, some amount of leftover selenoadduct **193** was observed. In their work regarding enantioselective selenoetherification reactions, Denmark and co-workers observed a transfer of selenenium ions from their corresponding seleniranium species **200** onto other olefinic species **201** present in the reaction, where the olefinic species served as a Lewis-basic activator of the seleniranium ion (Equation 3.11).[118,119] Based on these findings, it was speculated whether a similar transfer could take place in our case, where an additional alkyne molecule would induce elimination of an oxidized Se-moiety by functioning as a Lewis-basic activator to give the desired allene. It was hypothesized that the oxidized Se-centre and the alkyne would form a Lewis-acid/Lewis-base pair which would then form the desired allene as well as propagate the reaction. The oxidized Se-centre in this case would be the seleniranium ion equivalent used by Denmark and co-workers, and could be obtained *via* oxidation by NFSI. To verify if the reaction followed this mechanism, selenoadduct **193** was treated with 1.0 equiv 2,9-dimethyl-5-decyne und 0.95 equiv NFSI. To our delight, a mixture of allenes **141a** and **141d** derived from selenoadduct **193** and 2,9-dimethyl-5-decyne was obtained, along with selenoadducts **193** and **199**, and the regeneration of the diselenide catalyst (2-anisyl)$_2$Ph$_2$Se$_2$.



200 **201** **202** **203** (3.11)



193

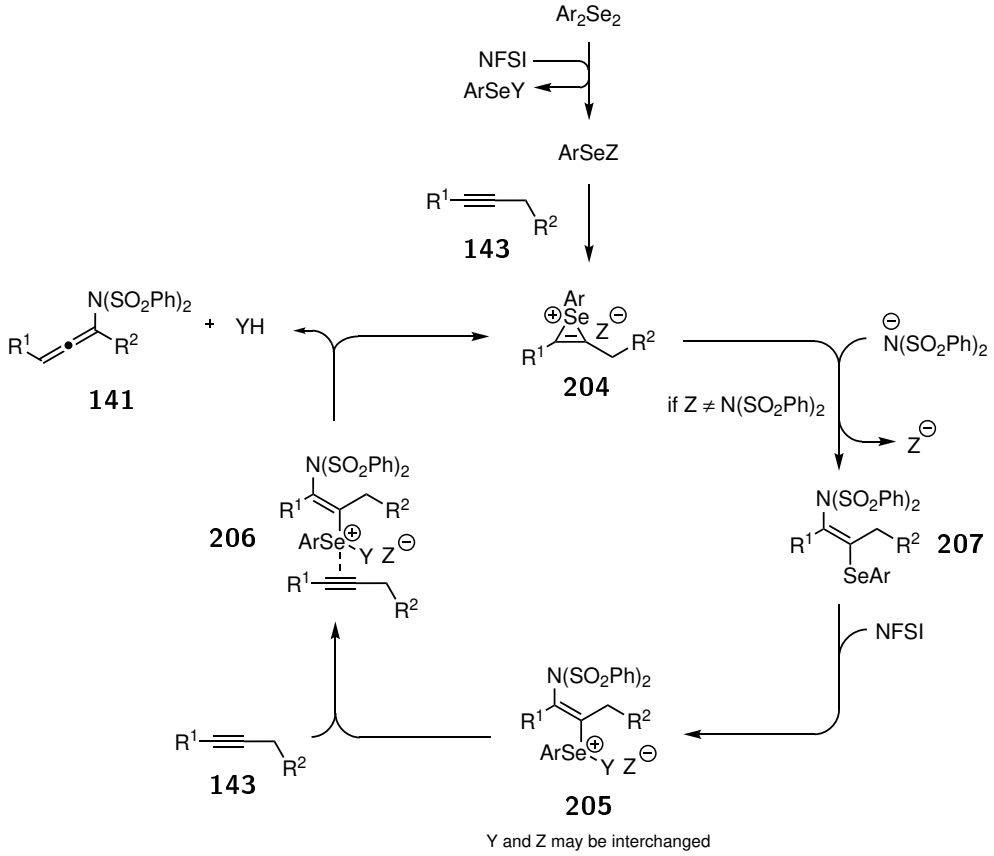
R = H: **141a** (33%)
R = Me: **141d** (18%)

R = H: **193** (24%)
R = Me: **199** (22%)

(3.12)

Based on these results, the following mechanism was proposed for the reaction (Scheme 3.7). First, oxidation of the diselenide catalyst by NFSI and its subsequent

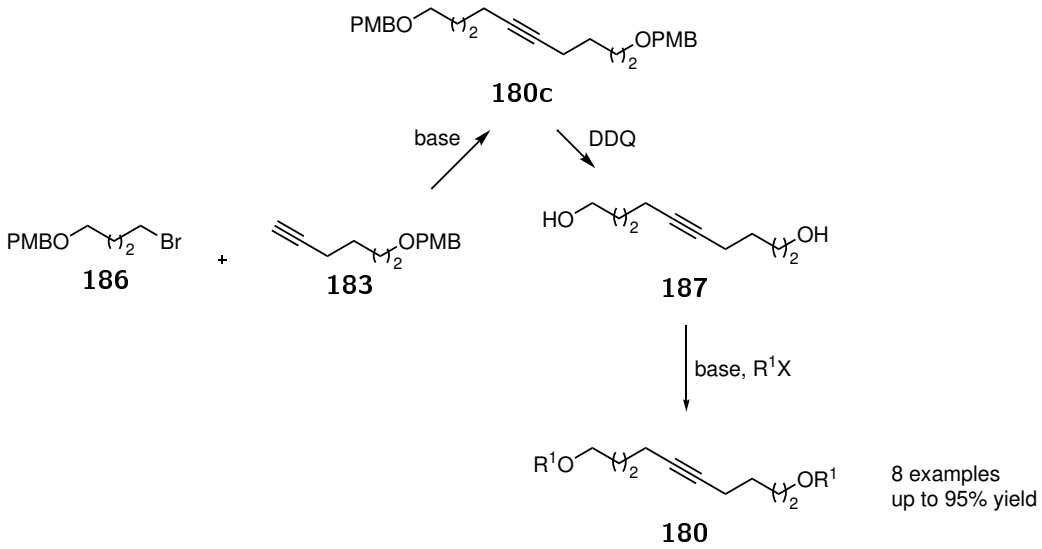
addition onto alkyne **143** forms seleniranium ion **204**. An attack by the sulfonimide anion to open the three-membered ring, followed by oxidation with another molecule of NFSI forms oxidized selenofunctionalized intermediate **205**. Coordination of this intermediate onto another alkyne molecule possibly forms Lewis-acid/Lewis-base pair **206**, from which elimination of the selenium moiety results in the formation of product **141** and the simultaneous formation of seleniranium ion **204**, which reenters the catalytic cycle.



Scheme 3.7: Proposed mechanism for the Se-catalyzed synthesis of aminoallenes.

4 Summary and outlook

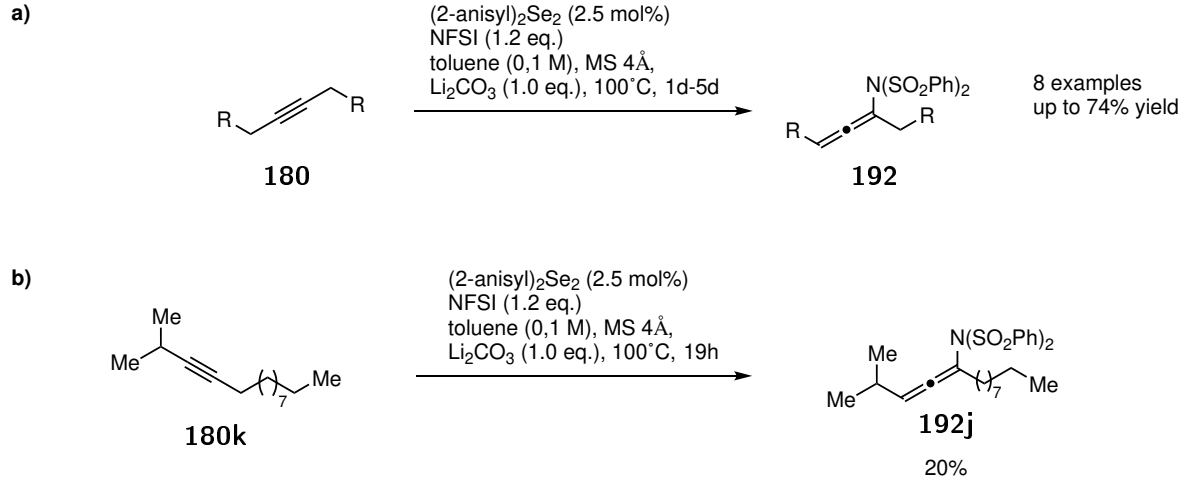
The aim of this project was to develop a route to synthesize symmetric alkynes and use them as substrates in the Se-catalyzed synthesis of aminoallenes optimized by Dr. Rode and co-workers, and consequently broadening the scope of the reaction.[4] The synthesis of symmetric alkynes was to be designed such that a number of symmetric alkynes could be obtained from a common path. This goal was achieved with the synthesis of alkyne **180c**, whose PMB-ether groups could be exchanged with other protecting groups such as esters and ethers *via* a simple transformation involving cleavage of the PMB-group using DDQ to give diol **187**, followed by re-protection of the free alcohol groups with other protecting groups to give symmetric alkynes **180** (Scheme 4.1). Alkyne **180c** was synthesized *via* a coupling reaction between terminal alkyne **183** and halide **186** using *n*-BuLi. A total of eight symmetric alkynes were synthesized using this route, in yields of up to 95%.



Scheme 4.1: Synthesis of symmetric alkynes developed during the course of this project.

In the second part of this project, the synthesized alkynes were subjected to the optimized reaction conditions. To our delight, aminoallenes synthesized from the symmetric alkynes were obtained in yields of up to 74% (Scheme 4.2, a). Additionally, unsymmetric alkyne **180k** was also synthesized to be used as a substrate for the titular transformation, in

order to study the effects, if any, of the relative position of the double bond to the triple bond on the outcome of the titular transformation. Contrary to the unsymmetric alkynes tested by Dr. Rode, which gave the corresponding aminoallenes in a regioisomeric mixture, unsymmetric alkyne **180k** yielded only one regioisomer of the corresponding aminoallene (**192j**), with a poor yield of 20% (Scheme 4.2, b). This was probably due to the greater steric hindrance of the isopropyl group, which pushes the bulky phenylselenium moiety to the less hindered position of the alkyne, and as a consequence promoting nucleophilic attack on the more hindered position.

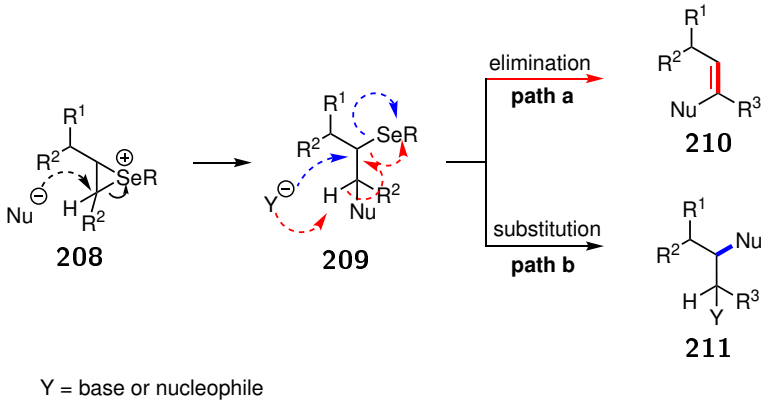


Scheme 4.2: Substrate scope of the titular transformation.

The success of this project enabled the synthesis of aminoallenes in a single step starting from unactivated alkynes with the adjustment of the oxidation state and the introduction of the amino group taking place in a single step. It also established Se-π-acid catalysis as an effective tool for the functionalization of unactivated alkynes, thus broadening the existing repertoire of Se-catalyzed alkyne functionalizations. As the application of Se-catalysis in the realm of alkyne functionalization is still in its infancy, there are a number of possibilities in which the method can be developed going forward. For instance, an enantioselective method using chiral selenium catalysts.[102] As photochemical tranformations involving selenium catalysts are gaining increasing attention, future investigations should focus on broadening the methodology by applying photochemistry, potentially employing other selenium catalysts. Another development in the area could be to extend the method to incorporate other functional groups containing heteroatoms such as oxygen, sulfur, phosphorous, etc., onto unactivated alkynes and as a result, enabling access to other substituted allenic moieties *via* Se-π-acid catalysis.

5 SN reactions

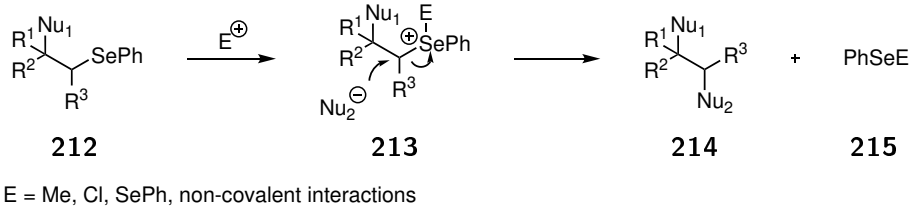
As already mentioned in Subsection 1.3.2, chalcogen-mediated olefin functionalizations, particularly selenium-mediated ones, have seen many developments over the last few years.[46,63] The reaction proceeds *via* an attack of the electrophilic selenium species on to the olefinic double bond to form a seleniranium cation **208**.[81,82] Attack of a nucleophile followed by ring-opening leads to the formation of seleno adduct **209**. A deselenenylation process, either *via* an elimination of the selenium moiety in the presence of a base (Scheme 5.1, path a), or *via* a nucleophilic substitution reaction in the presence of a suitable nucleophile (Scheme 5.1, path b), gives the corresponding final product **210** or **211**, respectively.



Scheme 5.1: Possible deselenenylation modes: nucleophilic substitution and elimination.

In many of the previous examples (cf. Subsection 1.3.2 and Subsection 1.3.3), the deselenenylation step begins *via* an oxidative activation of the selenium moiety by a PhSeX species. This results in a net reduction of electron density on the selenium-centre, and consequently enhances its nucleofugalicity. The modified nucleofugalicity of the selenium moiety facilitates deselenenylation *via* either an elimination reaction, generally in the presence of suitable base, or a nucleophilic substitution reaction, in the presence of a suitable nucleophile, at the selenium moiety.[120] In most cases, the kinetically favoured, fast elimination reaction is observed compared to the kinetically unfavoured slow substitution reaction (Scheme 5.1). One way to induce a nucleophilic substitution reaction could be

a softer activation of the selenium moiety. As a result, the C−Se bond in selenoadducts analogous to **209** might be polarized less strongly, allowing the slower nucleophilic substitution reaction to take place. Such a soft activation can be achieved by the addition of appropriate reagents, or through non-covalent interactions such as hydrogen bonds, both of which will be elucidated in the coming sections (Scheme 5.2). Combined with the potential effect of a soft activation of the selenium moiety, a strategic choice of the substrate could also suppress the faster elimination reaction. Ideally, this would be a substrate where elimination reactions are not possible. For example, tetrasubstituted olefins or systems where the positive charge arising due to the polarization of the C−Se bond can be stabilized, such as allenic systems, or secondary and tertiary carbon centres.



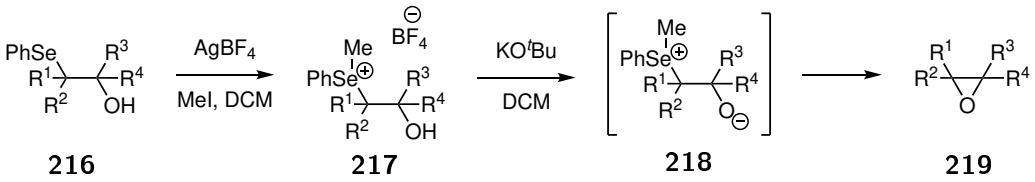
212 **213** **214** **215**

Scheme 5.2: Soft oxidative activation of the selenide moiety for nucleophilic substitution.

5.1 Oxidative activation at Se-centres

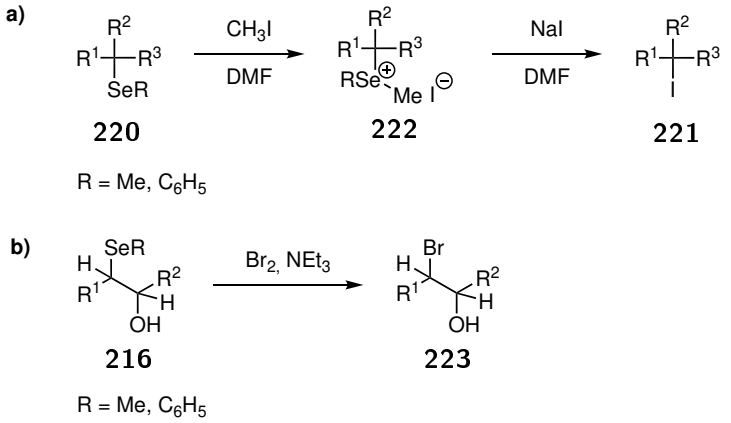
5.1.1 Oxidative activation using carbon reagents

A number of examples of nucleophilic substitution reactions at Se-centres using various reagents has been reported. In 1975, Krief and co-workers published a method for the synthesis of epoxides *via* the oxidative activation of selenohydrins (**216**).[121] Selenohydrins (**216**) were activated with MeI in the presence of $AgBF_4$ in DCM to form the corresponding methylselenonium salt **217**. Deprotonation of the alcohol with KO^{t}Bu in DCM gave the desired epoxide **219** in yields of up to 73 %.



Scheme 5.3: Synthesis of epoxides from β-hydroxyalkylphenyl selenides (**216**) by Krief and co-workers.[121]

Following this, Krief and co-workers established a new route for the synthesis of primary, secondary, and tertiary alkyliodides **221** starting from the corresponding alkyl selenides **220** using methyl iodide to activate the Se-moiety (Scheme 5.4, a).[122] This was the first example for an intermolecular nucleophilic substitution reaction at an activated Se-centre. Furthermore, they were able to convert selenohydrins **216** to the corresponding bromide, a precursor to the α-bromo ketone, in the presence of Br_2 und NEt_3 (Scheme 5.4, b). Although no mechanistic details are mentioned by the authors, the formation of the S_N2 substitution product instead of the formation of an epoxide as in the previous exammple maybe due to the absence of oxidative activation of the Se-centre.

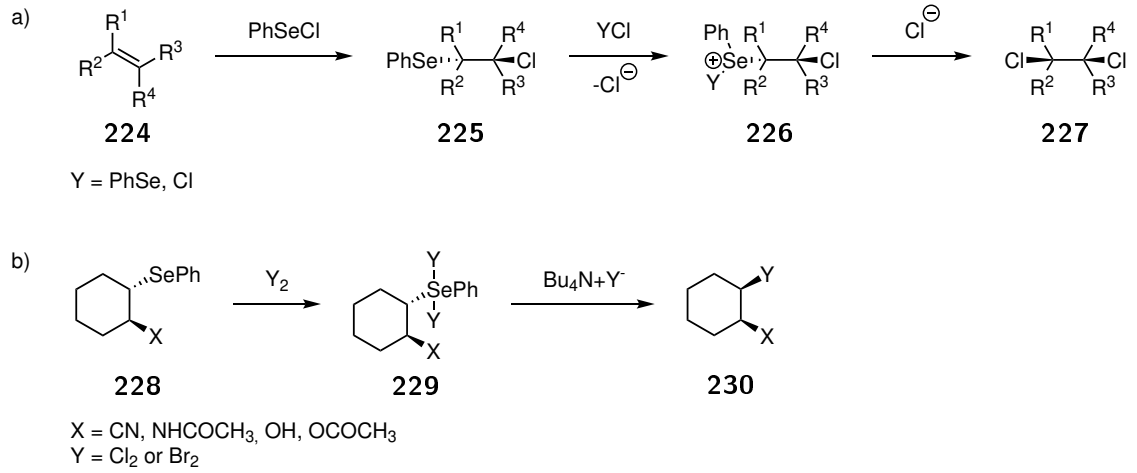


Scheme 5.4: a) Synthesis of alkyliodide **221** from the corresponding alkyl selenides **220**. b) Synthesis of α-bromo ketone precursor **223** from **216**.[122]

Krief and co-workers were also able to convert secondary alkyl alcohols to the corresponding secondary bromides *via* the intermediary secondary phenyl selenide, with retention of configuration.[123] This was the first example of a stereoselective nucleophilic substitution reaction at Se-centre. Here, no extra reagent was added for the activation of the Se-moiety. A combination of bromide and NEt_3 was used as the bromide source.

5.1.2 Oxidative activation using halide reagents

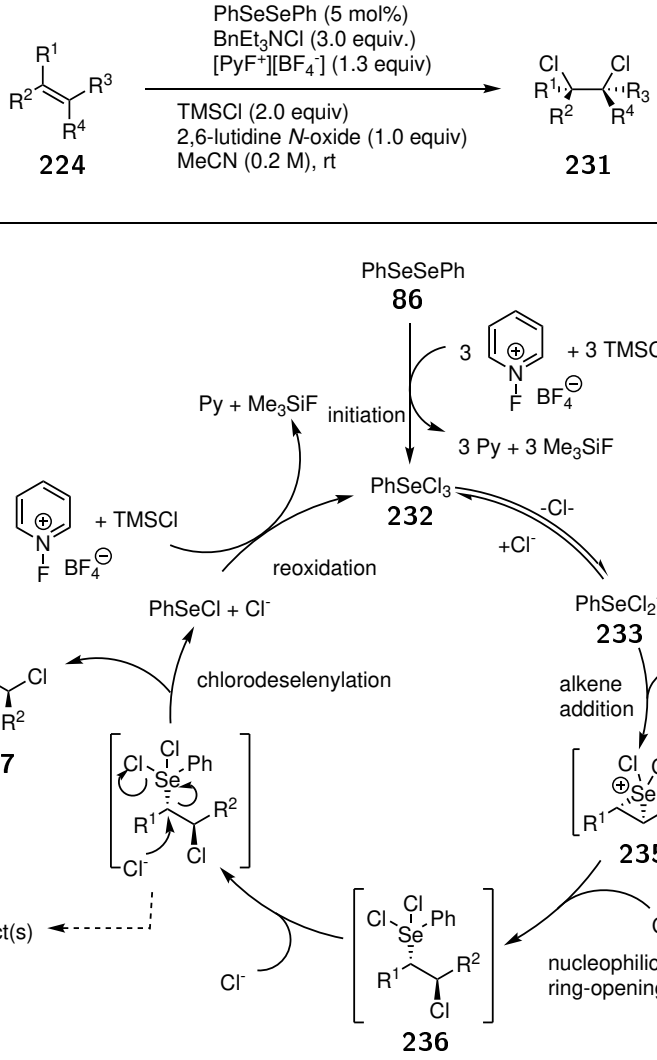
In 1984, Ward and co-workers published a method for the *cis*-dichlorination of alkenes using phenylselenyl chloride. Selenoadduct **225** is oxidized using a suitable chloride source to generate cationic selenium species **226**, which is attacked by the nucleophile to give the desired substitution product **227**, analogous to Scheme 5.2.[124] In the case of alkenes which can rapidly generate a tertiary carbonium ion, such as 1-phenylcyclohexne, the dichlorination took place without the addition of an additional chloride source and at temperatures as low as −78 °C, wherein the *trans*-isomer was the major product formed. When the same alkene was reacted with molecular chlorine, a mixture of products not limited to dichlorides was observed. In general, the authors observed that molecular chlorine was the better oxidising agent compared to PhSeCl. They attribute this to the higher stability of cationic species **226** when Y = Cl than when Y = PhSe, which, in a control experiment using dodecylphenylselenide as the substrate, was found to revert to the starting material. No such reversion was observed when molecular chlorine was used as the oxidizing agent. Shortly after, the same group published a method for the *cis*-1,2-difunctionalization of *trans*-1,2-phenylseleno acetate, acetamide, alcohol and nitrile of cyclohexane (**228**) *via* oxidation of the selenium-centre using chlorine to give the tetravalent selenium species **229**. The oxidized phenylseleno moiety is then displaced by a chloride anion obtained from a suitable source such as tetra-*n*-butylammonium chloride to give the *cis*-1,2-difunctionalized cyclohexane derivative (**230**).[125]



Scheme 5.5: SN reaction at Se-centres *via* a) monovalent and b) bivalent oxidative activation using halides as reported by Ward and co-workers.[124,125]

More recently, Denmark and co-workers published a method for the selenium-catalyzed *syn*-dichlorination of alkenes using PhSeSePh (**86**) as pre-catalyst, benzyltriethylammo-

nium chloride ($BnEt_3NCl$) as the chloride source, and an *N*-fluoropyridinium salt as the oxidant.[85] Unlike the previous methods where stoichiometric amounts of selenium were used, Denmark and co-workers employed an oxidant to convert the pre-catalytic Se(II) species into the catalytically active Se(IV) species. Here, the Se(IV) centre in selenointermediate **236** is substituted with a chloride anion from the $BnEt_3NCl$ to generate the 1,2-difunctionalized product **237** and PhSeCl, which upon oxidation with the *N*-fluoropyridinium salt, reenters the catalytic cycle.

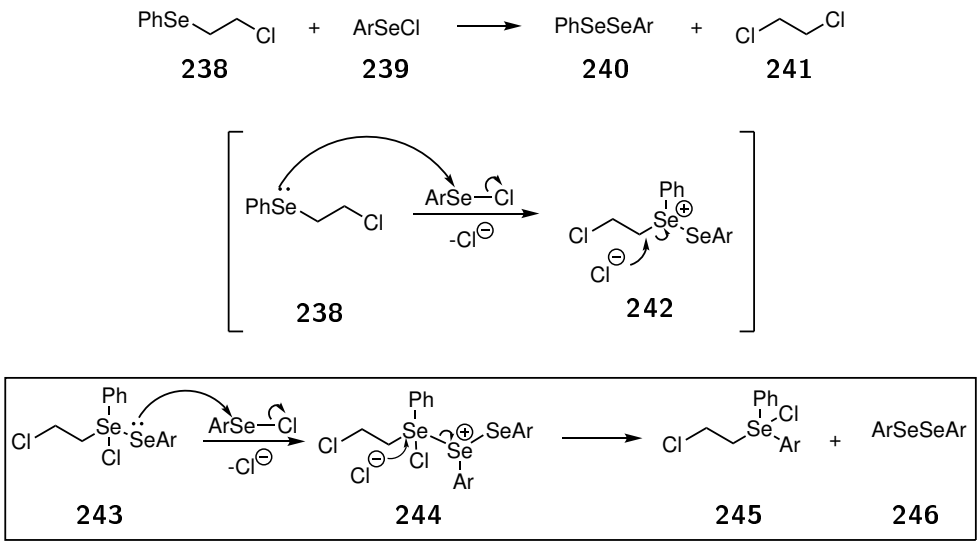


Scheme 5.6: Reaction mechanism of the *syn*-dichlorination of alkenes reported by Denmark and co-workers.[85]

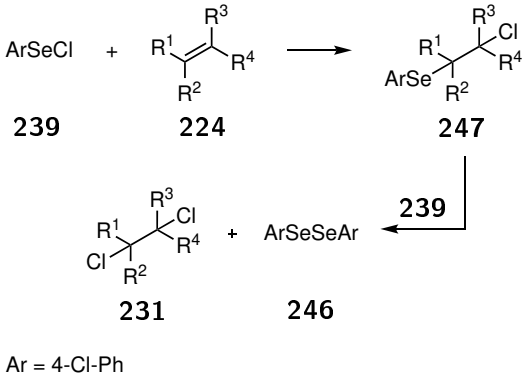
5.1.3 Oxidative activation using selenide reagents

In contrast to carbon- and halide-based reagents, selenide reagents have seen a broader application in nucleophilic substitution reactions at selenium-centres.[120] The oxidizing agent is a $PhSe^+$ species obtained for instance from PhSeCl, benzeneselenenyl trifluoroacetate ($PhSeOCOCF_3$), PhSeOTf, which does not have a nucleophilic counter-ion, or from an *in situ* oxidation of PhSeSePh (**86**) using $PhI(OAc)_2$ or ammonium persulfate. In 1985, Schmid and co-workers published an exemplary method for nucleophilic substitution at selenium centres *via* oxidative activation of organic selenides using PhSeCl.[126] In a reaction involving equimolar mixtures of 2-chlorophenylethyl selenide (**238**) and 4-

chlorobenzeneselenenyl chloride (**239**), mixed diselenide **240** and 1,2-dichloroethane (**241**) are formed. The products were explained by a mechanism where the selenium centre of the aromatic selenide undergoes oxidative activation by the selenium centre on **238**, resulting in the formation of cationic intermediate **242**. The *in situ* generated chloride nucleophile attacks the carbon atom, resulting in a nucleophilic substitution reaction (Scheme 5.7, top). The reaction was also found to work with an excess of 2-chlorophenylethyl selenide (**238**). In this case, the chloride ion attacks intermediate **242** at the selenium to give molecule **243**, while the selenium centre undergoes a second oxidative activation by 2-chlorophenylethyl selenide (**238**) to give intermediate **244** (Scheme 5.7, box). The chloride ion generated as a result of the second activation brings about the nucleophilic substitution reaction, resulting in the formation of Se(IV) species **245** and diselenide **246**. Contrary to the previous activation methods using carbon centres and halides, the main advantage of this method is that one of the reactants itself acts as the selenium-centre activator, eliminating the need for extra reagents. Furthermore, the authors were able to apply this strategy to unactivated olefins (**224**), resulting in the formation of a difunctionalized olefin (**231**). This opened the doors to a new method towards the difunctionalization of olefins (Scheme 5.8).

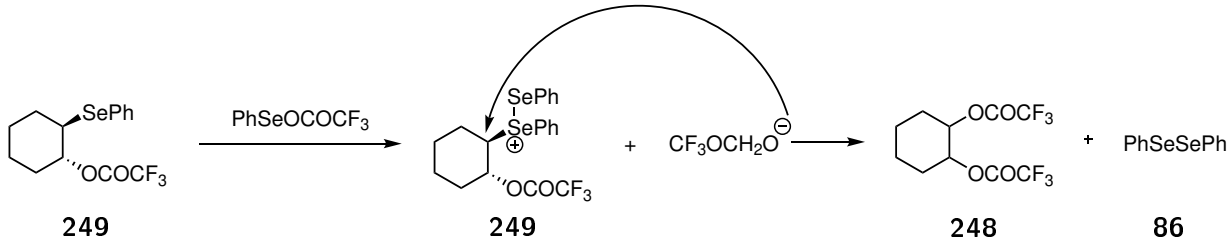


Scheme 5.7: Electrophilic activation of the selenide moiety using PhSeCl reported by Schmid and co-workers.[126]



Scheme 5.8: Se-mediated difunctionalization of olefins by Schmid and co-workers.[126]

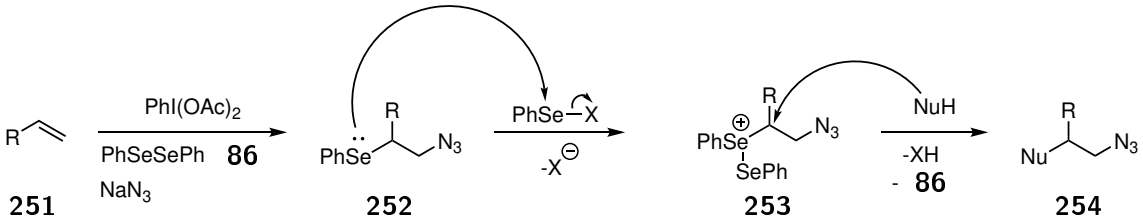
In 1992, Kutateladze and co-workers published a strategy for the synthesis of 1,2-bis-(trifluoroacetate) cyclohexane (**248**), a highly electrophilic source of the phenylseleno moiety.[127] Benzeneselenenyl trifluoroacetate ($PhSeOCOCF_3$) was reacted with cyclohexene in dry $CHCl_3$ to give a *trans*-addition product **249**. An excess of the reagent leads to the stable phenylselanylselenonium salt **250**, which, upon heating, undergoes substitution at the selenium moiety and forms the desired disubstituted cyclohexane product **248**. With this development, not only did the authors develop a new and easy route towards the synthesis of **248**, the authors discovered a new nucleophile that could substitute the Se-centre in addition to the hitherto-used halide nucleophiles.



Scheme 5.9: Synthesis of 1,2-bis-(trifluoroacetate)cyclohexane reported by Kutateladze and co-workers.[127]

Selenium-promoted deselenenylation reactions have also been used to synthesize substituted azides and oxazoline derivatives.[128–130] In the synthesis of substituted aziridines, vicinal azido selenides **252** are activated at the selenium centre by an electrophilic selenium species generated from PhSeX (X = Cl, Br, OTf), which then undergo nucleophilic attack by the counter anion to generate the corresponding halo-substituted azide **253** (Scheme 5.10). In addition to PhSeX, the deselenenylation was also achieved using PhSeOTf. When PhSeOTf in MeOH was used, the activated azido selenide underwent substitution with the MeO-group of the solvent, as the counter ion is non-nucleophilic.

Therefore, in the field of nucleophilic substitution reactions using Se-reagents as oxidative activators, after PhSeX and $PhSeOCOCF_3$, PhSeOTf was the next reagent used to activate a Se-centre towards nucleophilic substitution. Additionally, this method allowed the use of a nucleophile not coming from the oxidising agent itself, as seen in the previous examples.

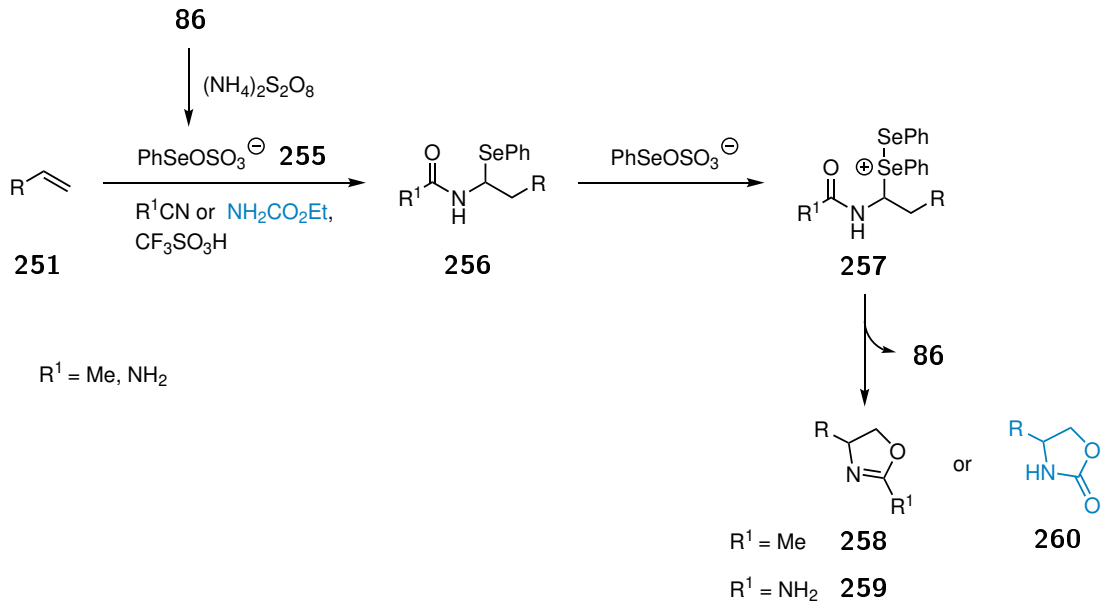


Scheme 5.10: Selenium-promoted synthesis of azides.

Building upon these results, Tiecco and co-workers were able to extend this methodology to an easy one-pot synthesis of oxazoline derivatives starting from unfuntionalized alkenes (**251**) (Scheme 5.10). Here, electrophilic phenylselenenyl sulfate (**255**), generated from the reaction between diphenyl diselenide (**86**) and $(NH_4)_2S_2O_8$, activates selenoadduct **256** to generate selenonium ion **257**. An intramolecular displacement at the carbon atom bearing the selenium moiety results in the formation of the oxazoline species **258**. Selenoadduct **256** itself was generated through the reaction between alkene **251**, $PhSeOSO_3^-$, acetonitrile, water, and triflic acid. They were also able to apply this method to the synthesis of 2-aminooxazolines (**259**) and oxazolidin-2-ones (**260**), when cyanamide (NH_2CN) or ethyl carbamate, respectively, was used instead of MeCN (Scheme 5.11). This method was the first reported method for the synthesis of heterocycles *via* nucleophilic substitution at a selenium centre *via* electrophilic activation. Furthermore, the authors were able to quantitatively recover diphenyl diselenide (**86**), which could be reused for further reactions.

5.2 Hydrogen bonds

As mentioned in Chapter 5, a soft activation of the Se-centre on selenoadducts such as **212** can probably also be brought about by non-covalent interactions, in addition to the examples above, where the Se-centre was activated by chemical reagents. These non-covalent interactions could be both intra- and intermolecular, and may also include solvent-substrate interactions. Some of the most common non-covalent interactions observed in solution include hydrogen bonds (HBs), halogen bonds, chalcogen bonds, and σ-hole bonds.[131] In



Scheme 5.11: Selenium-promoted synthesis of oxazolines.

the case of conventional hydrogen bonds (HBs), halogen bonds, and chalcogen bonds, the strength of the interaction is determined primarily by the electronegativity of the atom to which the participating hydrogen, halogen, or chalcogen atom is attached. Whereas in the case of σ-hole bonds, the polarizability of the atom on which the σ-hole is found also dictates the strength of the interaction, in addition to the electronegativity of the atom or group attached covalently to it. σ-hole bonding will be discussed in detail in Section 5.3. Conventionally, hydrogen bonds (HBs) are interactions between an electron-deficient hydrogen atom covalently bonded to an electronegative atom, also known as the hydrogen bond donor (HBD), and the lone pair of electrons of another electronegative atom, also known as the hydrogen bond acceptor (HBA) (Figure 5.1).[132] Although conventional HBs are thought of as being primarily electrostatic interactions, studies of various hydrogen-bonded complexes have shown that many HBs are shorter than the sum of the van der Waals radii of the donor and acceptor atoms, and also show angular constraints that are atypical for purely electrostatic interactions, indicating a partial covalent character occuring through orbital overlap between the participating atoms.[132,133] This multi-faceted nature of HBs can especially be observed in HBs involving weaker electronegative atoms such as selenium and sulfur, where additional properties such as atomic charge and polarizability of the HBA determine the strength of the hydrogen bond.[134] This will be discussed in detail in Section 5.4.

In conventional HBs, the transfer of electron density from the HBA into the σ^* orbital of the X−H bond (Figure 5.1b) results in the weakening of the X−H covalent bond. This

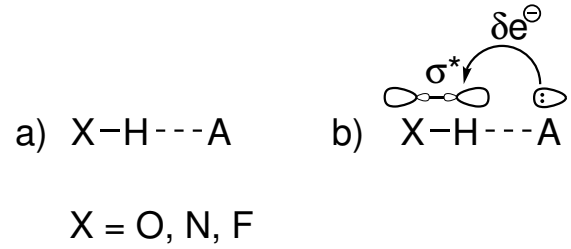


Figure 5.1: a) HB between donor X (X = O, N, F) and acceptor A (A = O, N, F, S, Se). b) Transfer of electron density between donor and acceptor in a HB.

results in a slight elongation of the X–H bond due to which the X–H bond stretch shifts to a lower frequency (red-shift), while increasing in breadth and intensity. The value of the red-shift is correlated to the strength of the HB formed. Due to the net shift of electron density from the HBA to the HBD, the H atom involved in the HB loses electrons and the electronegative atom X gains electron density. Additionally, all H atoms attached to the electronegative atom of the HBD gain electron density upon HB formation, whereas the largest loss of electron density occurs at the H or C atoms directly attached to the HBA.[135] Discovered in the early 20th century,[136–138] HBs play a key role in chemistry, physics, and biology, such as being responsible for the unique structure and properties of water,[139] and for the double-helix structure of our DNA as Franklin-Watson-Crick base pairs.[140] Additionally, HBs play an important role in many chemical transformations,[141,142] such as Bronsted-acid catalyzed reactions.[143,144]

5.2.1 Hydrogen bonds in solvents and the Kamlet-Taft parameters

In addition to hydrogen bonds between different reactants in a mixture, in some cases, the solvent used can also form HBs to one or more of the reactants. This results in the solvent acquiring the status of a catalyst, as the HBs formed from the solvent to one or more of the reactants can influence the kinetics of the reaction without the solvent itself being consumed during the reaction. Kamlet and co-workers defined in 1983 a scale to quantify these solvent effects based on the change in the absorption maximum of the UV spectrum of different solvatochromic dyes in common organic solvents.[145] The π^* scale is an index of the polarizability of the solvent, which measures the ability of a solvent to stabilize a charge or dipole by virtue of its dielectric constant. The higher the value of the π^* parameter, the higher is the polarizability of the solvent. The α scale is a measure of the solvent's HB donicity, which describes the ability of the solvent to donate a proton

in a solute-to-solvent HB. The β scale of HBA basicities is a measure of the ability of the solvent to accept a proton or donate a pair of electrons to the solute in a solute-to-solvent HB. For example, Water and 1,1,1,3,3,3-hexafluoro isopropanol (HFIP) have very high α (α H_2O = 1.17 and α HFIP = 1.96), and π* values (π* H_2O = 1.09 and π* HFIP = 0.65), and therefore high acidities and polarizabilities, while having very low β values (0.18 and 0.00), and therefore low basicities.

5.3 Sigma holes and chalcogen bonding

In additions to HBs, σ-holes and chalcogen bonds are also commonly observed non-covalent interactions. σ-Holes are regions of positive electrostatic potential collinear with and directionally opposite to covalent σ bonds.[146] Generally, a free, ground-state atom has a spherically-symmetrical electron charge distribution. When the atom forms a covalent bond, some of the charge is polarized towards the covalent bond, leading to a diminished electron density in the outer region opposite to the covalent bond and a simultaneous increase in electron density on the equatorial sides of the atom. This results in a positive potential on the outside of the atom, and a negative potential around the sides of the atom.[147] The larger the electronegativity of the covalently bonded atoms, and the higher the polarizability of the central atom, the higher the positive character of the electrostatic hole.[148] Therefore, by manipulating the covalently-bonded atoms, an electrostatic hole can be used to deliberately reduce electron density on an atom, and thereby increase the electrophilicity of the molecule. This strategy is summarized under the term σ-hole or hydrogen-bond catalysis.[149,150] These non-covalent interactions are further classified after the atom where the positive electrostatic potential is located. In general, a non-covalent, attractive interaction of a σ-hole with a negative site on another atom is known as σ-hole bonding. If the σ-hole is present on a halogen or chalcogen atom, the non-covalent interaction is known as halogen- or chalcogen-bonding, respectively. Other similar σ-hole bonding interactions include: 1) pnictogen bonding, where the σ-hole is present on P, As, or Sn, and 2) tetrel bonding, where the σ-hole is present on Si, Ge, or Sn. If the σ-hole is present on an hydrogen atom, the resulting non-covalent interaction is a hydrogen bond. Analogous to HBs, chalcogen bonding between two organic molecules is also a result of orbital interactions. Among the chalcogens, selenium is mostly divalent in nature and has an oxidation state of +II in addition to its two lone pairs of electrons. This results in two possible non-covalent orbital interactions that organoselenium compounds can exhibit with other molecules. In the first case, electron density is transferred from the lone pair of a heteroatom such as oxygen, nitrogen, or chlorine into the Se−R σ* orbital, resulting in

an overall increase in electron density at the selenium centre, with a simultaneous decrease in electron density on the heteroatom (Figure 5.2a). In other words, the σ-hole in this case is on the selenium atom. In the second case, electron density is transferred from one of the two lone pairs of a selenium atom, usually into the σ* orbital of an X−H covalent bond, resulting in an overall decrease in electron density at the selenium atom.[151,152] The resulting interaction is therefore a classical hydrogen bond, with the σ-hole present on the hydrogen atom (Figure 5.2b).

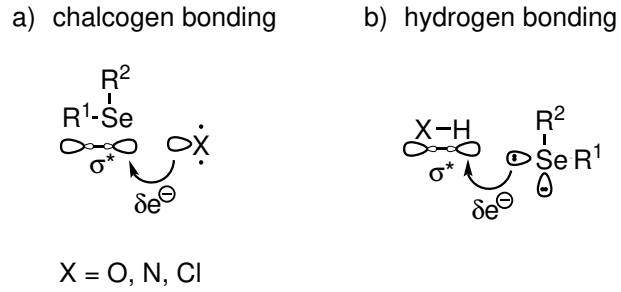


Figure 5.2: Orbital interactions of divalent selenides.

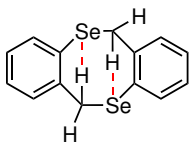
This dual reactivity of selenium was also observed by Shukla and co-workers in 2015 in their computational study of the influence of substituents on an XHSe species on Se−O noncovalent interactions in water.[153] The authors found that in most cases, an Se...O interaction was observed. However, in a couple of examples, they observed a hydrogen bond between the selenium and a water molecule. One of the factors contributing to this duality was the electronic nature of the X-group on the XHSe species. Higher the electron-withdrawing power of X, stronger the positive charge on the selenium, and therefore stronger the Se...O interaction. Therefore, in the case of non-covalent interactions using selenium species, the electronic nature of the participating molecules has an influence on the type of non-covalent interaction observed in solution.

5.4 Selenium-centred hydrogen bonds

For a nucleophilic substitution reaction mediated by non-covalent interactions to occur at a Se-moiety, the Se-atom itself should be capable of forming Se-centred HBs. Selenium-centred HBs play an important role in controlling the structures and functions of biomolecules, for example, as selenomethionine residues in proteins.[134,154] However, sulfur and selenium are considered to be 'poor' or 'weak' HB participants compared to their more electronegative counterparts such as nitrogen and oxygen. This is indeed the

case if only the electrostatic component is taken into account. However, the polarizabilities of sulfur and selenium are larger than that of oxygen and nitrogen, indicating that Se-centred HBs may indeed be stronger than anticipated. Using analytical techniques such as NMR and gas-phase laser spectroscopy and theoretical calculations, Biswal and co-workers found that Se-centred HBs have bond strengths comparable to those of oxygen and nitrogen, and are a combination of electrostatic, charge-transfer, and dispersion forces.[155]

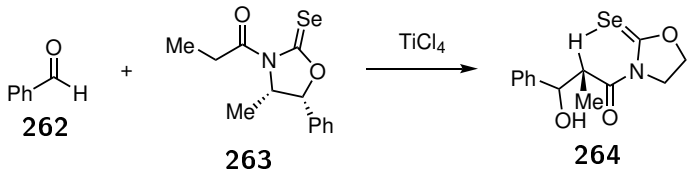
Se-centred HBs were first observed in 1986 by Mikenda through IR and X-ray spectroscopy.[156] In 1994, Tomoda and co-workers reported the first C−H/Se−H noncovalent interaction in diselenocin **261** (Figure 5.3), which was unexpectedly obtained from the reduction of 2,2'-diselenobis(benzyl chloride) with $NaBH_4$ in MeOH, using single crystal X-ray diffraction analysis and ^{77}Se NMR spectroscopy.[157] They observed that the hydrogen atom pointing towards the selenium is oriented perpendicularly to the plane containing the selenium and its immediate neighbouring C atoms, indicating that the hydrogen is directed towards the Se-lone pair as an electrophile. Furthermore, the angles of the HBs (C−H...Se) were in the range of 100°-107°, which is slightly larger than the 90° of normal HBs,[158] further indicating that orbital interaction between the Se-lone pair and the C−H bond plays a predominant role in the C−H/Se−H interaction.



261

Figure 5.3: The C−H/Se−H bond observed in diselenocin **261**.[157]

In 1998, Silks and co-workers reported in their study of chiral selones, the presence of an intramolecular Se-centred HB in some of their products, confirmed *via* ^{77}Se NMR spectroscopy. They also report noncovalent interactions between the Se-atom and water present in $CDCl_3$, which was used as the NMR solvent of choice for spectroscopical investigations.[159] In 2016, Bibelayi and co-workers showed the ability of selenoureas and selenoamides (**263**) to form HBs based on computational modelling studies. *ab initio* calculations confirmed that hydrogen bonding in these systems is the result of a resonance-induced dipole moment introduced in the C−Se double bonds by substituents present on the carbon atom, quite similar to the corresponding thiourea and thioamide derivatives.[160] Despite growing interest in noncovalent interactions involving selenium, no methods using Se-centred hydrogen bond catalysis in organic reactions are known till date.



(5.1)

The main advantage of using non-covalent interactions for oxidative activation of the selenium moiety to facilitate nucleophilic substitution reactions is that the addition of catalysts or other reagents for a similar activation can be avoided. As the aspired activation may either be intramolecular or intermolecular, or a combination of both, a judicious choice of the substrate and/or solvent are crucial for the success of this method. The incorporation of strategic functional groups in the substrate which can participate in intramolecular non-covalent interactions with the Se-moiety and/or hydrogen bond-forming solvents which can participate in intermolecular non-covalent interactions with the Se-moiety are therefore necessary requirements.

5.5 Photochemistry

Traditional oxidative and/or reductive deselenenylation processes suffer from various disadvantages including the usage of toxic substances such as liquid ammonia and Raney-Ni, and loss of functionality.[161] Therefore, more manageable conditions for the deselenenylation process are required. In addition to the ability of the Se-moiety to form hydrogen bonds (cf. Section 5.4), C−Se bonds exhibit photosensitivity to irradiation of specific wavelengths. Before going into the details of the photochemistry of C−Se bonds and their utility in organic synthesis, the basic principles of photochemistry of C−C bonds and the species formed as a result will be discussed, followed by the photochemistry of Se−Se bonds.

Photochemistry involves the study of chemical reactions which are caused by the absorption of light irradiation.[162][163] Typically, light belonging to the visible and UV (ultraviolet) regions with wavelengths between 800 nm and 200 nm is known to bring about such chemical reactions. The quantized energy levels of matter have the same order of separation as that of the energy of visible or UV light, and therefore, the absorption of such radiation can excite electrons to higher energy levels, generating electronically-excited species (Figure 5.4). Essentially, this involves the promotion of an electron from a bonding molecular orbital (BMO) to an anti-bonding molecular orbital (ABMO) when light of a suitable wavelength is provided to the system. An atom or molecule in such an excited state is more likely to undergo a chemical reaction than in the ground state.

The minimum energy which the system has to be supplied with in order to bring about this excitation is known as the activation energy. In photochemical reactions, the activation energy is acquired by the absorption of photons using monochromatic light from the UV-visible light region. This allows a single species in a reaction mixture to be selectively excited independent of the other constituents of the reaction system. In contrast, thermal reactions, where the activation energy is attained through random intermolecular collisions, does not allow such selectivity because the constituents of the reaction mixture are all excited to the same extent.

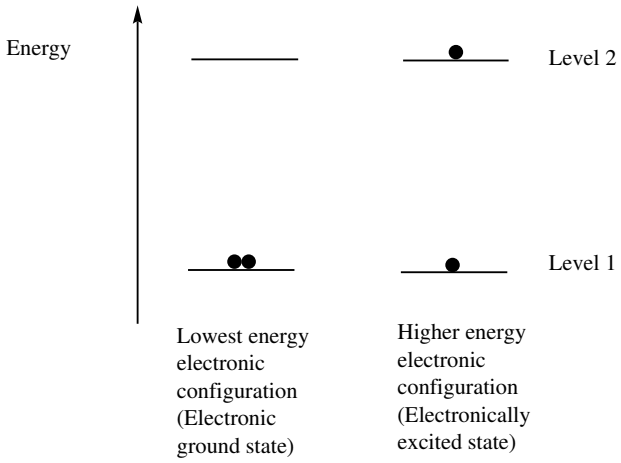
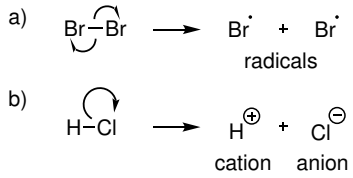


Figure 5.4: Quantized energy levels of matter where an electron may be found in either the ground state or the excited state

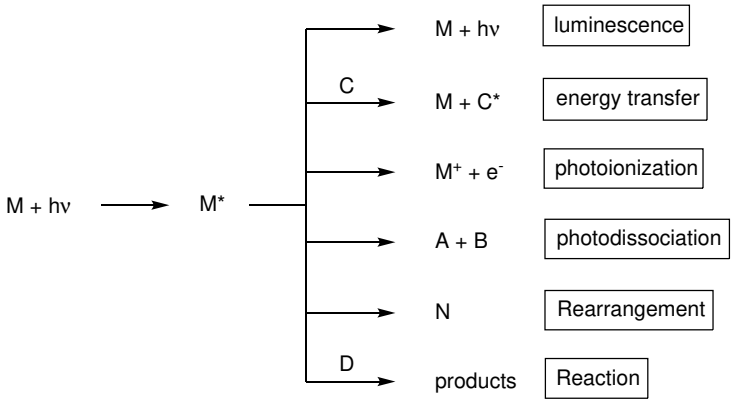
According to the **Grotthuss-Draper Law** of photochemistry, also known as the principle of photochemical activation, only that light which is absorbed by a system can result in a photochemical change.[163] These changes include non-radiative processes, where the excited molecule transfers its energy to another molecule *via* collisions, radiative processes such as fluorescence and phosphorescence, and bond-breaking processes known as photolysis, where the electron absorbing energy escapes the molecule and leaves behind a reactive intermediate. The type of reactive intermediate formed depends on the type of bond cleavage. During homolytic cleavage of a covalent bond, each of the atoms forming the bond retains a single electron resulting in the formation of intermediates known as radicals (Scheme 5.12a). During heterolytic cleavage of a covalent bond, one of the fragments retains both bonding electrons resulting in the formation of an electron-deficient or positive species known as a cation, and an electron-rich or negatively charged species known as an anion (Scheme 5.12b).[164]

The various methods that can be employed to generate such reactive species and the synthetic utility of these species are discussed in the following sections. In general, the



Scheme 5.12: Examples for a) homolysis and b) heterolysis.

various reactions possible as a result of light absorption by a species are summarized in Scheme 5.13:



Scheme 5.13: A summary of common photochemical transformations.

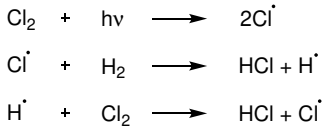
5.6 Photolysis

Photolysis is a chemical process in which chemical bonds are broken as a result of the transfer of light energy to these bonds. This process can be brought about by the irradiation itself (direct photolysis) or by the transfer of radiant energy from another molecule (indirect photolysis).[165] The general form of a direct photolysis reaction can be summarized as:

$$X + h\nu \longrightarrow Y + Z \tag{5.2}$$

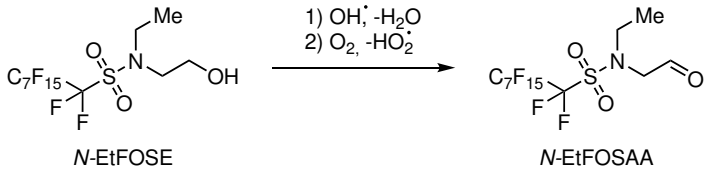
The photochemical mechanism of direct photolysis can be divided into three stages : (1) the absorption of light by the molecule which results in the excitation of its electrons, (2) primary photochemical processes which generate reactive intermediates or deexcite the molecule from its excited state, and (3) the secondary thermal reactions which transform the intermediates produced in the previous step into other products. An example of a primary photochemical reaction is the dissociation of a molecule *via* homolytic bond

cleavage into radicals. The secondary process may involve a chain reaction wherein the radical formed in the primary process may either attack a neutral molecule to generate another unstable radical, or combine with another radical to form a stable molecule. The reaction of hydrogen and chlorine gases in the presence of UV light to form HCl involves both these processes:



Scheme 5.14: Formation of HCl from hydrogen and chlorine gases in the presence of UV light.

In contrast, indirect or sensitized photolysis occurs when the light energy absorbed by one molecule (the sensitizer) is transferred to another molecule which in its turn undergoes further transformations. The sensitizer undergoes no net chemical change and as such functions as a catalyst. Indirect photolysis is most commonly observed in the photodegradation of enivornmental contaminants in the presence of sunlight.[166,167] For example, an indirected photolysis induced by a hydroxy radical, generated *via* homolysis of a water molecule under UV radiation, was observed in perfluorinated surfactant *N*ethyl perfluorooctane sulfonamidoethanol (*N*-EtFOSE), wherein the alcohol group was oxidised to the corresponding aldehyde to give *N*ethyl perfluorooctane sulfonamidoacetate (*N*-EtFOSAA) (Equation 5.3).[167]



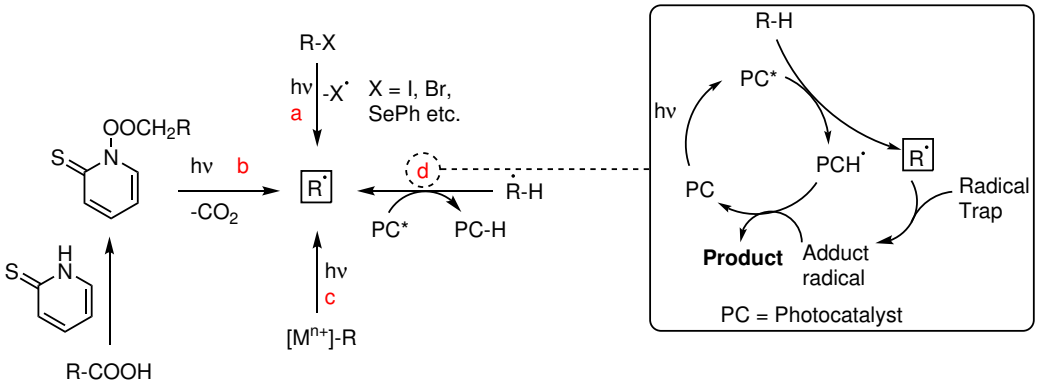
(5.3)

5.7 Photochemically generated intermediates

As mentioned above, different kinds of intermediates are generated depending on the type of photolytic bond cleavage, which then react further to give the final products. Additionally, the electronic properties of the atoms on either side of the bond exposed to irradiation also influence the type of intermediates formed. Photolytically generated intermediates include radicals, biradicals, radical ions, cations, anions, and carbenes. Each of these has been discussed briefly below.

5.7.1 Radicals

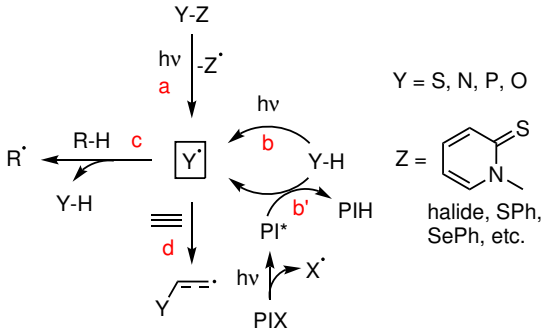
As mentioned in section Section 5.5, radicals are formed as a result of homolytic cleavage of a chemical bond. As a result, both carbon-centred and heteroatom-centred radicals can be generated, which can further be used in many useful synthetic transformations.[164] Scheme 5.15 shown below summarizes the various modes of photogeneration of carbon-centred radicals.[168] Although homolytic cleavage of a precursor molecule, usually involving a C–X or C–SePh bond (path a),[169] represents the simplest method of generating radicals, this method is often limited by poor light absorption of the halide substrates and/or competing heterolytic fragmentation resulting in the formation of ion pairs $R^+ + X^-$. Therefore, substrates with better light absorption properties such as Barton esters (path b)[170] or pre-formed metal complexes (path c) serve as better candidates to generate the desired radicals upon irradiation. More recently, radicals generated through cleavage of a strong C–H bond using a suitably excited species (S*) *via* a hydrogen atom transfer (HAT) process has been gaining importance.[168,171,172] In most cases S is a photocatalyst (PC), which in its excited state generates a carbon-centred radical *via* proton abstraction from the substrate. The thus generated radical is trapped by a suitable molecule such as an olefin or an alkyne to form a radical adduct, which upon hydrogen back-donation from PC–H• releases the product and regenerates the PC to re-enter the catalytic cycle.[172–174]



Scheme 5.15: Modes of photogeneration of C-radicals

Scheme 5.16 shows the different routes towards photogenerated heteroatom-based radicals.[168] Analogous to the generation of C-centred radicals, heteroatom-based radicals can also be generated *via* the homolytic cleavage of a weak Y–Z bond, which usually connects two heteroatoms such as N–X (*N*-halo-amines or amides), S–S (disulfides), X–X (dihalogens), or N–O bonds in Barton esters (path a). The direct cleavage of a Y–H bond is usually limited to S–H or P–H bonds (path b), but can be induced through the fragmentation of an excited photoinitiator (PI–X, path b'). The heteroatom-based radi-

cal thus generated can be further utilized to generate a C-centred radical in a secondary process either by H-abstraction (path c) or by addition to a double or triple bond (path d). These radicals then undergo further secondary reactions to generate stable molecules as products.[169]



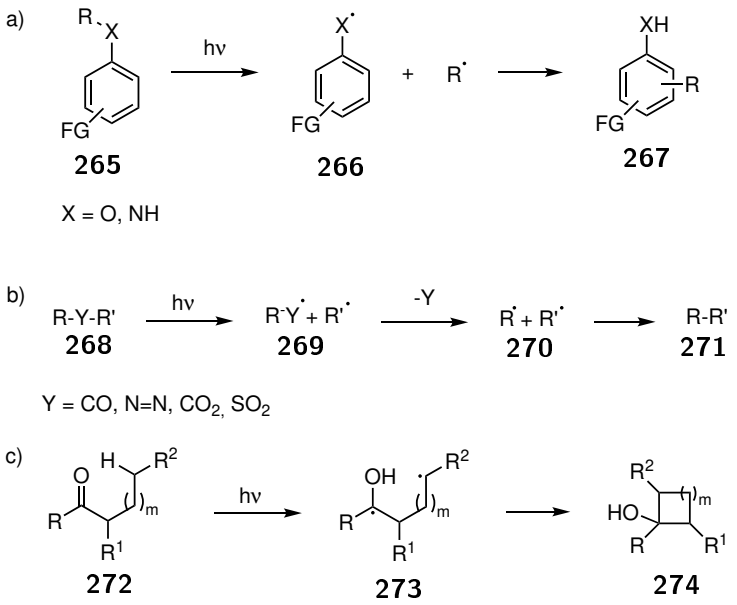
Scheme 5.16: Modes of photogeneration of heteroatom-based radicals and their secondary reactions.

5.7.2 Biradicals or Radical Pairs

Radical pairs are formed through the fragmentation of a single bond.[168] The high energy of the excited states makes the fragmentation of high energy bonds under mild conditions viable.[169] When these individual fragments are joined by a tether, the resulting species is known as a biradical. A reaction at one of the radical centres or radical recombination gives the final products. Scheme 5.17 summarizes the different modes of generation of radical pairs and biradicals. The *photo-Fries rearrangement* (Scheme 5.17a) illustrates the latter process, where the homolytically generated radicals recombine to form arylated end products.[175] A further possibility is the elimination of a small molecule preceding radical recombination, resulting in an overall extrusion process (Scheme 5.17b).[176] In the *Norrish Type II* reaction, these intermediates have been used in the construction of n-membered rings induced by an intramolecular H-abstraction from an excited carbonyl followed by the cyclization of the 1,n-biradical formed (Scheme 5.17c).[175]

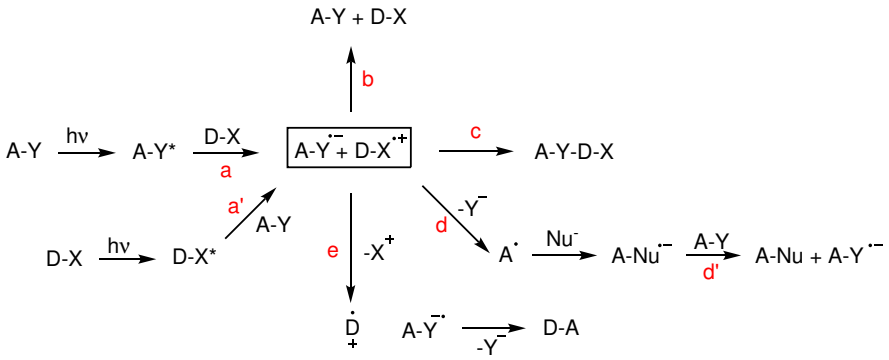
5.7.3 Radical Ions

Radical ions can be generated *via* photoinduced electron transfer (PET) reactions.[169,172,177–181] Usually, single electron transfer (SET) is achieved by irradiation of one of two (or more) organic molecules (A–Y and D–X) to form a radical ion pair (A-$Y^{\bullet-}$) and (D-$X^{\bullet+}$) (path a and path a' Scheme 5.18). However, the possibility of back



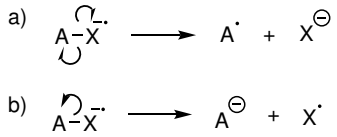
Scheme 5.17: Modes of photogeneration of (a and b) radical pairs and (c) biradicals

electron transfer (BET) resulting in the reformation of the starting materials limits the overall efficiency of the reaction (path b). Occasionally, the radicals can couple to form the adduct A−Y−D−X (path c). In successful cases, one of the radical ions is a stable species, and the other one undergoes a chemical reaction such as addition, rearrangement, or fragmentation to give another radical which then forms the products. If the fragment undergoing further reaction has a nucleofuge, the resulting ion can be trapped by a nucleophile to form a new radical anion($A-Nu^{\bullet -}$, path d), which in turn transfers an electron to the starting material initiating a chain process and giving the final product (A−Nu, path d'). If, however, the radical cation bears an electrofugal group, the thus-formed radical $D^{\bullet}$ can couple with the $A\text{-}Y^{\bullet -}$ to form an alternative substitution product (path e).



Scheme 5.18: Photogeneration and fate of radical ions from organic molecules A−Y and D−X.

Radical ions can further undergo fragmentation into radicals and ions in a process known as mesolysis, resulting in the redistribution of the unpaired electron which resides in a π orbital on one side of the scissile bond .[182] Two types of fragmentation, and therefore electron apportionment,[183] are possible. During the homolytic process, the charge remains localized on the same moiety (Scheme 5.19a), whereas a heterolytic fragementation results in the transfer of charge across the scissile bond (Scheme 5.19b).[184]



Scheme 5.19: Mesolysis of a radical anion undergoing a) homolytic and b) heterolytic cleavage

More recently, photoredox catalysis has grown to be a widely-used method to generate radical ions *via* PET processes.[185–187] The SET process can occur in two ways: in the first case, the SET takes place from an excited state photocatalyst (PC*) to a molecule to generate to a radical ion (Scheme 5.20). In the second case, the radical ion is generated *via* an SET from the reduced or the oxidised state of the photocatalyst, PC_{red} or PC_{ox}, respectively, to the molecule (Scheme 5.21). In the first variant of the process, PC* oxidises an organic molecule R–X to the corresponding radical cation (Scheme 5.20a, path a'), which can then take paths b', c', or d' to form the corresponding products with the concomitant regeneration of the reduced PC (PC_{red}). The reduced PC can react with either an intentionally added sacrificial electron acceptor (SEA) or an intermediate formed formed during one of the previous steps to regenerate the PC (Scheme 5.20a, path e'). Alternatively, PC* may reduce molecule R-Y (Scheme 5.20b, paths a') and the ensuing reactions are due to the corresponding radical anion (or radical) (Scheme 5.20b, paths b', c', and d'). Similar to the previous case, the PC is regenerated when the oxidised PC reacts with a sacrificial electron donor (SED) or an intermediate generated during one of the previous steps (Scheme 5.20b, paths e').

In the second variant of the process, the excited state PC reacts with either an SEA (Scheme 5.21a) or an SED (Scheme 5.21b), undergoes an SET with a molecule in the reaction and thus forms the radical. Depending on whether the excited PC reacts with an SEA or an SED, PC_{ox} (Scheme 5.21a, path a') or PC_{red} (Scheme 5.21b, path a') is generated, which acts as a ground state oxidant or reductant, and converts reagent R–X (Scheme 5.21a, path b') or R–Y (Scheme 5.21b, path b') into the corresponding radical ion, which can then undergo further reactions (Scheme 5.21a and b, paths c', d', and e'). However, an ideal process would be one which avoids the addition of sacrificial reagents,

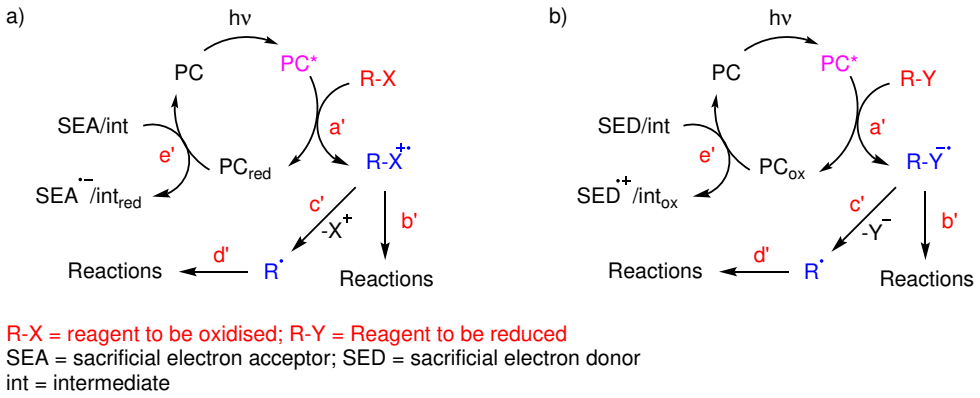
resulting in an overall redox neutral process.[186] This can be achieved by adding suitable X or Y groups which enhance the overall oxidisibility (or reducibility) of the molecule. Such electroauxiliary[188] groups, such as silyl groups, may then be lost in subsequent fragmentation processes, allowing the easy formation of the corresponding radicals ((Scheme 5.21a and b, paths c' and d').

5.7.4 Cations and Anions

As briefly mentioned earlier, carbocations and carbanions are usually generated by photoheterolysis (Scheme 5.22).[169] The photoheterolytic cleavage of C−X and in some cases C−O bonds (e.g. in sulfonates or phosphates) can be used to generate (rather unstable) carbocations such as vinylic or arylic carbocations,[189] which is made viable by the high energy of the respective excited states (Scheme 5.22a). As mentioned earlier, photohomolysis can hinder the efficiency of the process, unless an electron transfer within the radical pair leads to the desired ion pair.
Carbanions, on the other hand, have seen tremendous use in C−C bond forming reactions, particularly in the case of enolates (or similar anions), which are formed by *via* a deprotonation. The photogeneration of carbanions has seen a rather limited scope so far, mostly involving decarboxylation reactions (Scheme 5.22b).[169,190]

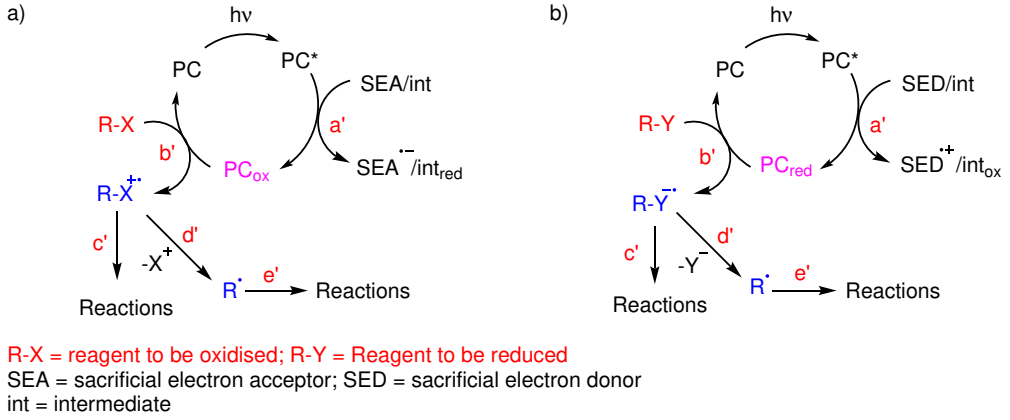
5.7.5 Carbenes

Carbenes **278** can be formed by the photolysis of either the corresponding diazo compound **277** (Scheme 5.23a, path a') or of a diazirine **279** (Scheme 5.23a, path b').[169] The *Wolff rearrangement* (Scheme 5.23, path c), for example, proceeds *via* a carbene **276** generated from α-diazocarbonyl or carboxyl compounds.[191,192] A recent approach by Priebbenow

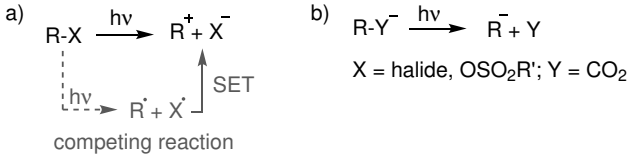


R-X = reagent to be oxidised; R-Y = Reagent to be reduced
SEA = sacrificial electron acceptor; SED = sacrificial electron donor
int = intermediate

Scheme 5.20: General scheme of photoredox catalysis

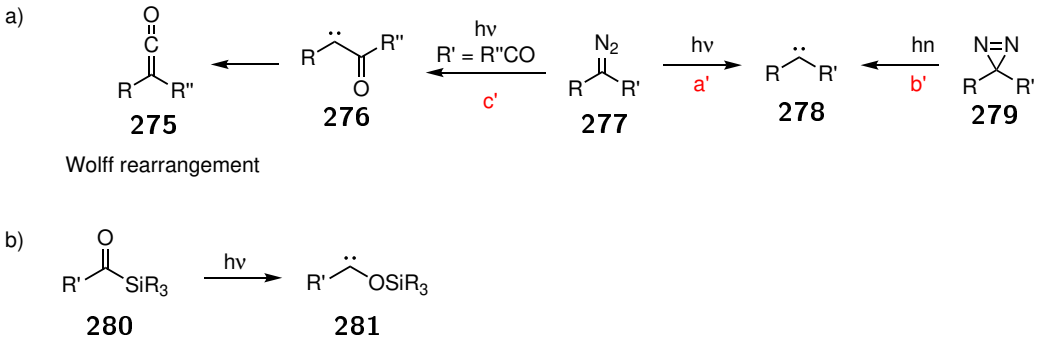


Scheme 5.21: Alternate mechanism of photoredox catalysis



Scheme 5.22: Modes of photogeneration of a) carbocations and b) carbanions

and co-workers made use of an acyl silane **280** to generate the corresponding siloxycarbene **281** (Scheme 5.23b).[193]



Scheme 5.23: Modes of photogeneration of carbenes

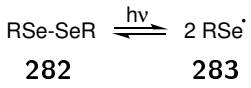
5.8 Photolysis of Se-Se Bonds

The selective introduction of heteroatomic funtional groups to organic molecules can be achieved through addition reactions of compounds bearing heteroatom-heteroatom single bonds, such as dihalides, diselenides, and disulfides, to unsaturated compounds such as alkynes, allenes, and alkenes.[194] Organoselenium compounds are synthetically useful in-

termediates, many of which have been shown to have biological activity.[195,196] In this regard, organic diselenides are useful precursors for the synthesis of selenium-containing compounds. The Se−Se single bond is easily susceptible to activation and cleavage under visible light irradiation to generate selenium-centred intermediates as active species, which can then add on to unsaturated organic molecules to form selenium-containing organic compounds. In the following subsections, the photochemical generation and synthetic utility of various selenium-centred intermediates will be discussed.

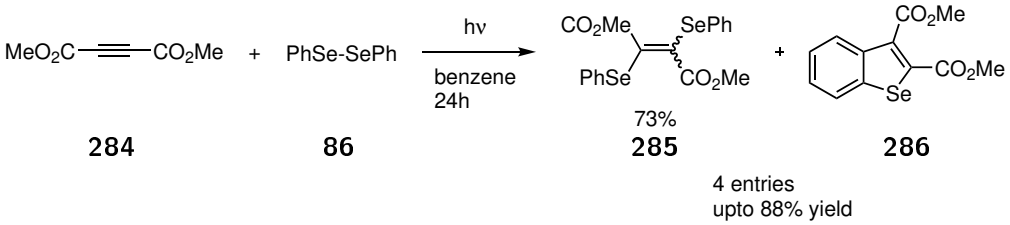
5.8.1 Photogenerated Se-centred radicals in organic syntheses

Selenium-centred radicals **283** can be obtained through the homolytic cleavage of the Se−Se bond present in organic diselenides under irradiation from (near-)UV light sources (Equation 5.4).[197] The seleno-radicals thus formed are labile species that can either undergo recombination to reform the starting diselenides, or add on to molecules such as alkenes and alkynes. In general, seleno-radicals are less reactive towards alkenes compared to other heteroatom-centred radicals such as Si, Ge, and Sn due to their faster rate of recombination and the reversible nature of their addition to the π-bond, thus limiting the overall efficiency of the addition reactions of seleno-radicals to alkenes.[198,199]



282 **283** (5.4)

The first radical addition of organic diselenides to alkynes was reported by Back and co-workers in 1988. Upon UV irradiation in benzene, diphenyl diselenide (**86**) adds onto electron deficient acetylenes such as dimethyl acetylenedicarboxylate (**284**) (DMAD) to form the desired seleno-adduct **285** in yields of up to 88 % along with small amounts of selenophene derivatives **286** (Equation 5.5).[199]

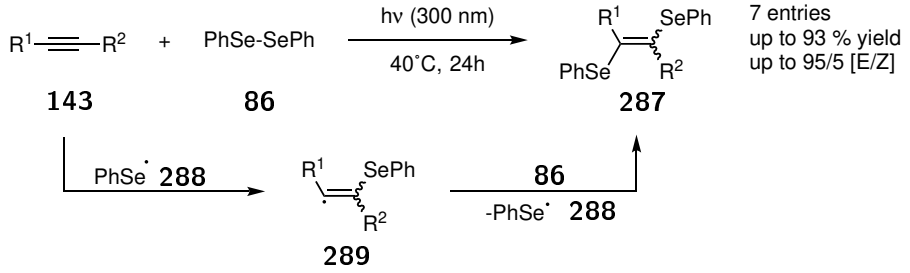


284 **86** **285** **286** (5.5)

4 entries
upto 88% yield

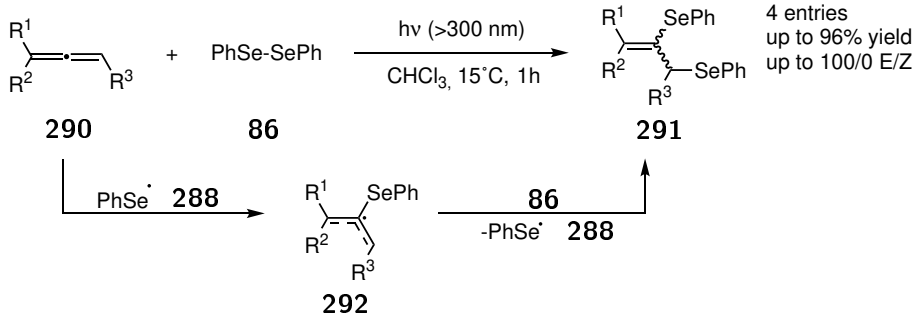
Following this, Ogawa and co-workers reported that upon irradiation with a tungsten lamp in the absence of a solvent, diphenyl diselenide (**86**) adds to a variety of alkynes to yield the corresponding vicinally diselenated alkenes **287** in yields of up to 93 % with *E*/*Z* ratios of up to 95:5 (Scheme 5.24).[200] The reaction also worked well with dibutyl diselenide, giving the corresponding vicinal diselenated alkene in a yield of 83 % (*E*/*Z* ratio 82:18). This was

the first reported method for the addition of diselenides to electronically undifferentiated acetylenes.[199] By taking high initial concentrations of the starting acetylene and diphenyl diselenide, the authors managed to overcome common challenges associated with such reactions, such as poor reactivity of the phenylseleno radical towards multiple bonds,[198] and the tendency of the radical to dimerize to re-form the starting diselenide.



Scheme 5.24: Addition of phenylseleno radical (**288**) to alkynes (**143**)[200]

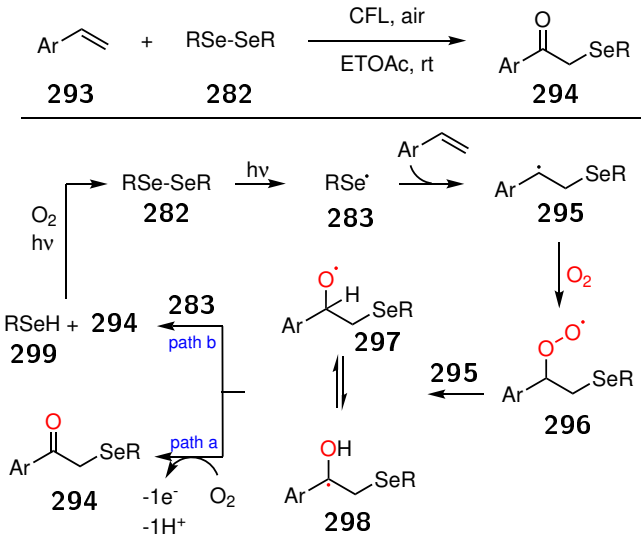
Ogawa and co-workers also reported the first example for the addition of a photogenerated selenoradical, obtained from diphenyl diselenide (**86**), to allenes **290** to give β(phenylseleno)allylic selenides **291** in high yields of up to 96 % (Scheme 5.25).[201]



Scheme 5.25: Addition of phenylseleno radical **288** to allenes (**290**)[201]

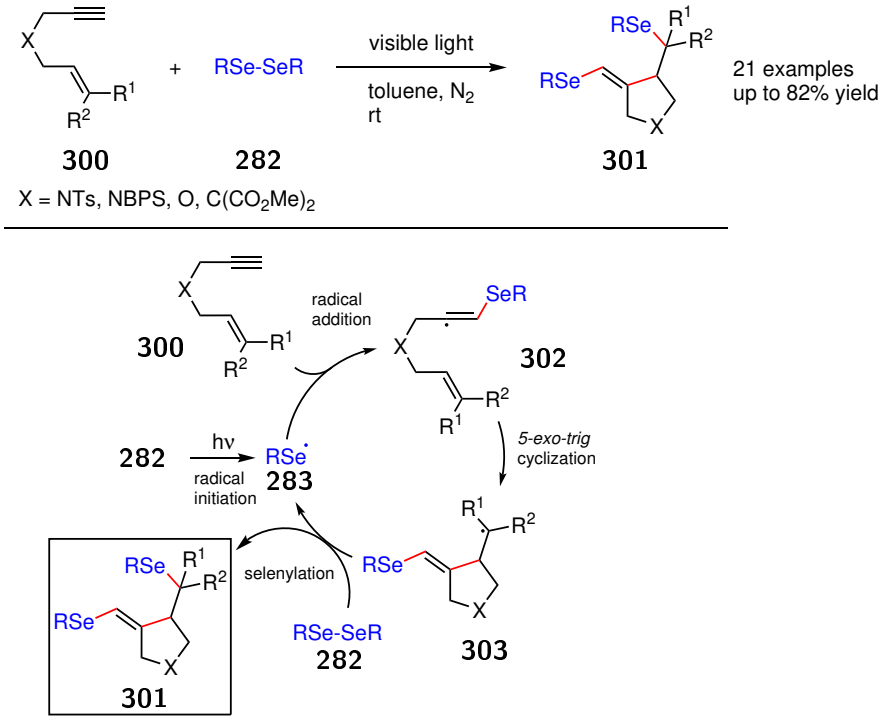
In 2021, Liu and co-workers reported the synthesis of α-aryl and α-alkyl selenomethyl ketones **294** *via* visible-light-induced oxidative coupling of vinyl arenes **293** with diselenides **282** (Scheme 5.26). According to their proposed mechanism, selenoradical **283** generated from diselenide **282** adds on to the double bond of the styrene to give benzyl radical species **295**, which is trapped by oxygen to give peroxy radical **296**. The combination of radicals **295** and **296** followed by homolysis of the O-O bond gives rise to alkoxy radical intermediate **297**, which is in equilibrium with intermediate **298** through a 1,2-H atom shift. Subsequent oxidation by O_2 of either intermediate **297** or **298** followed by racemization to lose H^+ gives the desired selenomethyl ketone **294** (Scheme 5.26, path a). Alternatively, intermediate **297** or **298** can react with selenoradical **283** to give the desired product,

along with selenol **299**, which is then oxidised to give the dimer[202] (**282**) for the next cycle (Scheme 5.26, path b). The main advantage of this method was that the reaction was performed using a green solvent (ethyl acetate), used air as the oxidant, and worked well under sunlight. Furthermore, additives such as photocatalysts, bases, and external oxidants were avoided.[203]



Scheme 5.26: Addition of phenylseleno radical to vinyl arenes to give α- alkyl or aryl selenomethylketones[203]

Another application of selenoradicals in organic transformations was published by Zhu and co-workers in 2021, where they used visible light-generated selenoradicals in the cyclization reactions of 1,6-enynes **300** in toluene under a N_2 atmosphere to obtain the corresponding seleno-functionalized cyclic product **301** in yields of up to 82 %. This was the first time where the final cyclization product contained not one,[204,205] but two selenide groups.[206] Aromatic diselenides with different substituents also gave the desired products in yields between 35 % and 76 %. According to their proposed mechanism, the addition of the selenoradical **283** generated *via* visible light excitation of the diselenide **282** to the triple bond of the enyne **300** results in the vinyl radical intermediate **302**. A *5-exo-trig* cyclization results in the tertiary carbon radical **303**, which upon reaction with the diselenide furnishes the desired cyclization product **301** and regenerates the selenoradical **283** (Scheme 5.27).

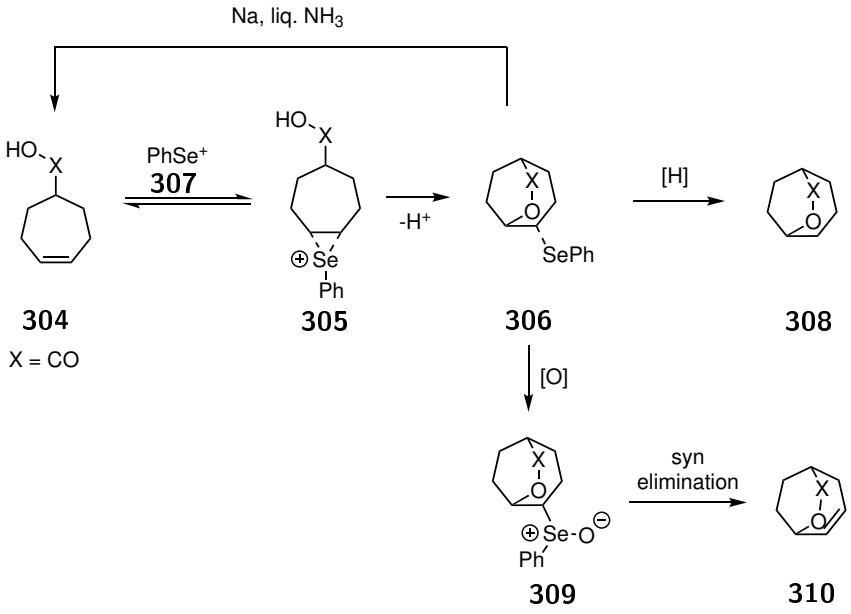


Scheme 5.27: Addition of seleno radical **283** to 1,6-enynes **300**.[206]

5.8.2 Photogenerated electrophilic selenium species in organic syntheses

In 1981, K.C. Nicolaou reported the first use of an electrophilic selenium species in phenylselenoetherification reactions (Scheme 5.28), starting from a suitably unsaturated carboxylic acid **304**.[207] The authors predicted that the cyclization occurs *via* the reversible addition of the electrophilic phenylselenonium ion to the double bond to give intermediate **305** which then undergoes intramolecular substitution to give the desired lactone (**306**).

However, due to the toxic and moisture-sensitive nature of PhSeX compounds in addition to their high costs, a need was identified for a more benign source of electrophilic selenium species. In this context, in 1989, Pandey and co-workers published for the first time the *in situ* generation of an electrophilic selenium species *via* photosensitized (SET) cleavage of the Se-Se bond in diphenyl diselenide (**86**) using 1,4-dicyanonaphthalene (^{1}DCNP*) as an electron acceptor.[208] Photoinduced electron transfer (PET) between ground and electronic excited states of such a donor-acceptor pair results in the formation of a radical ion pair, which then diffuses apart in polar solvents to form free radical ions. These radical ions generally undergo fragmentation to ions and neutral radicals which can then be used

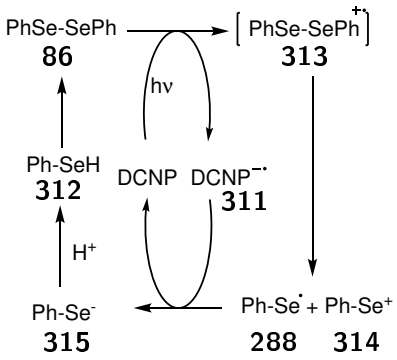


Scheme 5.28: Selenoetherification reaction using electrophilic selenium species reported by Nicolaou and co-workers.[207]

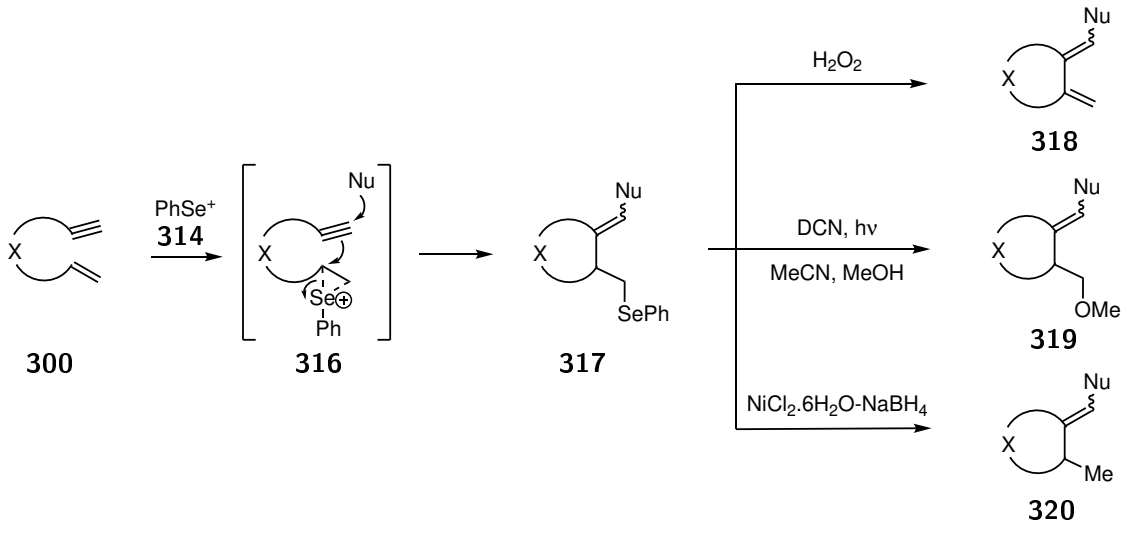
in various organic transformations. According to the mechanism proposed by Pandey and co-workers, a SET from PhSeSePh (**86**) to (^{1}DCNP*) produces the solvent-separated ion pair **311** and **313** (Scheme 5.29). In medium to high-polarity solvents, intramolecular electron transfer could occur within the free solvated radical ion **313** leading to cleavage of the Se−Se bond, leading to the formation of $PhSe^+$ (**314**) and $PhSe^\bullet$ (**288**), analogous to the C-C bond dissociation reported in the case of bibenzyl radical cation.[209] In solvents of low polarity, however, the transformation of the solvent separated ion pair **311** and **313** into a contact ion pair is favoured and back electron transfer competes with the dissociation of the solvent-separated ion pair to the free ion pair.[209–211] The electrophilic selenium species **314** was then used in phenylselenoetherification reactions.[208] The neutral phenylselenoradical **288** undergoes another SET with **311**, generating phenylselenol (**312**), which undergoes oxidation to regenerate diphenyl diselenide (**86**). After further auxiliary experiments, this proposed reaction mechanism was confirmed by the same group in 1992.[212]

In 1993, Pandey and co-workers used the same PET strategy using electrophilic selenium species $PhSe^+$ in enyne cyclization reactions to synthesize the corresponding monocyclic compound **317**, which could further undergo oxidation, reduction, or substitution reactions to produce other functionalized cyclic products **318**, **319**, and **320**, respectively (Scheme 5.30).[213]

However, in the cyclization of 3-(prop-2-yn-1-yloxy)prop-1-ene (**321**), the detection of



Scheme 5.29: Generation of an electrophilic selenium species *via* SET between diphenyl diselenide and DCNP.[208]



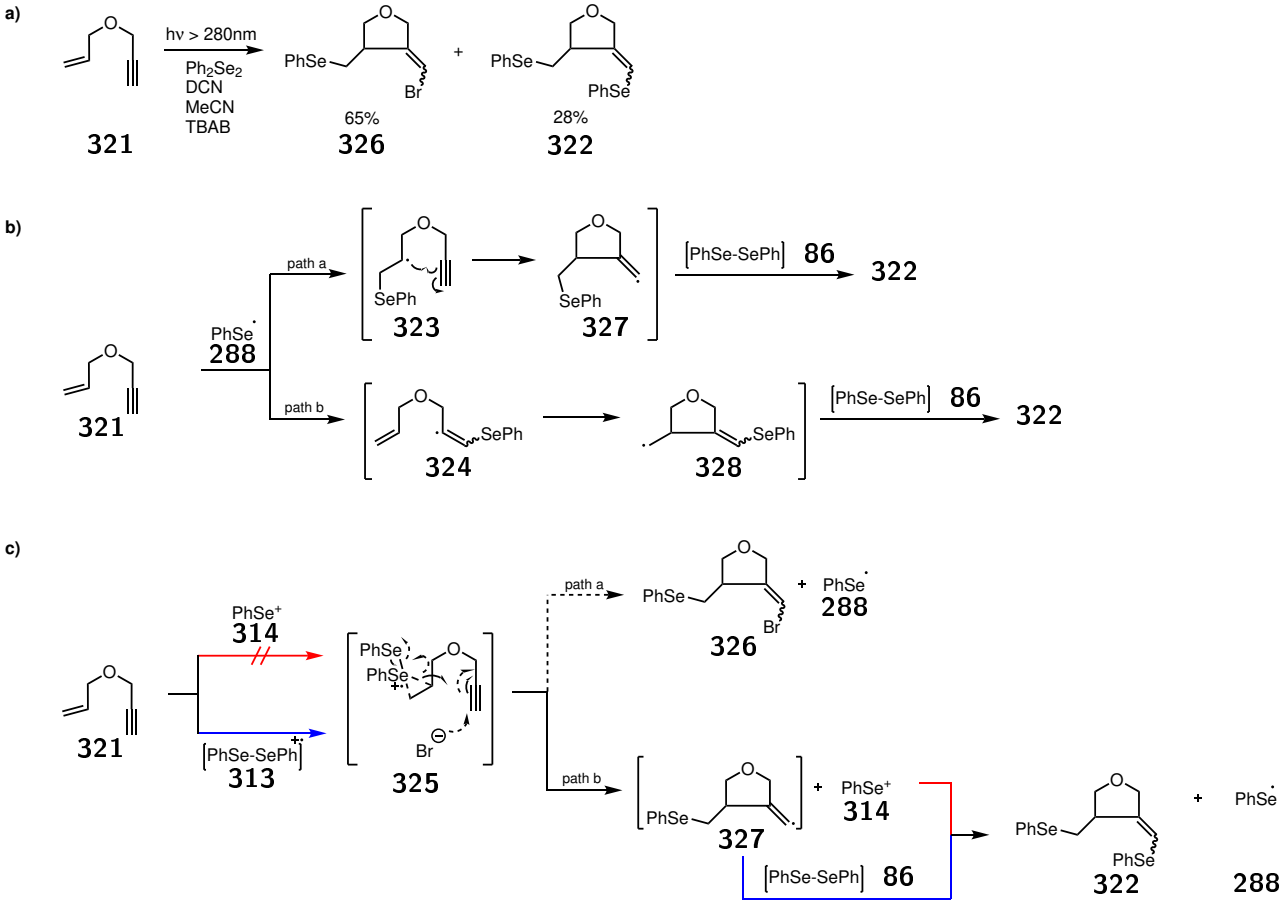
Scheme 5.30: Cyclization reactions of enynes using electrophilic selenium species.[213]

by-product **322** (Scheme 5.31a) made them reinvestigate their proposed mechanism for the cyclization reaction. With the mechanism propsed in Scheme 5.30 insufficient to explain the formation of side product **322**, the authors tried to rationalize its formation *via* radical intermediates **323** and **324**, wherein phenylselenoradical **288** adds either to the olefin (Scheme 5.31b, path a), or to the acetylene (Scheme 5.31b, path b), respectively. The authors however rejected this radical-based hypothesis due to literary evidence which showed that the addition of the phenylseleno radical **288** to the olefinic double bond is reversible in nature, and the addition of the radical to the acetylenic triple bond occurs only under special circumstances. Additionally, the phenylseleno radical (**288**) is known to undergo rapid recombination to form diphenyl diselenide (**86**). A control experiment done with the same reaction conditions but in the absence of DCN showed no formation of side product **322**, providing further evidence against a radical pathway. This led the authors to consider radical cation **313** to be the active electrophilic selenium species participating in the reaction (Scheme 5.31c). Radical cation **313** adds to the olefinic double bond to form intermediate **325**. Nucleophilic attack by the bromide anion at the acetylenic carbon leads to the formation of product **326**, and the formation of side product **322** was proposed *via* vinylic radical intermediate **327**, which reacts with a molecule of diphenyl diselenide (**86**) to give the observed side product (**322**). The authors were able to back up this hypothesis with further experiments. Therefore, this was the first reported example of a electrophilic selenium-mediated reaction where the active species was the diphenyl diselenide radical cation **313**.[214]

5.9 Photolysis of C-Se bonds

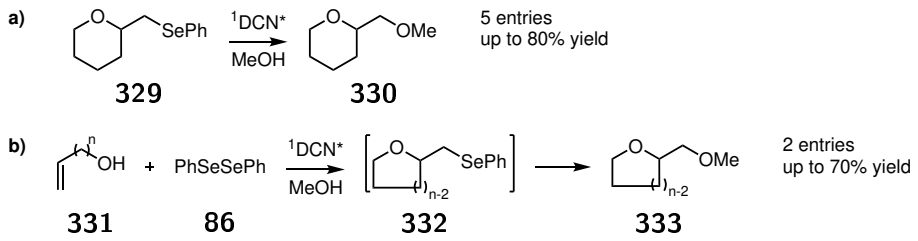
In 1990, Pandey and co-workers reported a light-mediated C−Se bond heterolytic cleavage methodology *via* a radical cationic intermediate generated through an SET process from the C−Se bond to ^{1}DCN*.[215] A mixture of selenoether **329** and DCN irradiated with a 450-W medium-pressure mercury lamp in methanol gave the corresponding MeO-substituted deselenenylated product **330** in up to 80 % yield (Scheme 5.32a). Additionally, they were able to harness this method for a sequential one-pot selenenylation and deselenenylation reaction by irradiating a mixture of an alken-1-ol **331**, PhSeSePh (**86**) and DCN in MeOH to obtain the desired MeO-substituted deselenenylated product **333** in yields of up to 70 % (Scheme 5.32b).

For the light-initiated C−Se bond cleavage, Pandey and co-workers proposed the mechanism shown below (Scheme 5.33).[216] An SET from the starting selenide **334** to the singlet excited electron acceptor DCN results in the formation of a charge-transfer (CT) exciplex



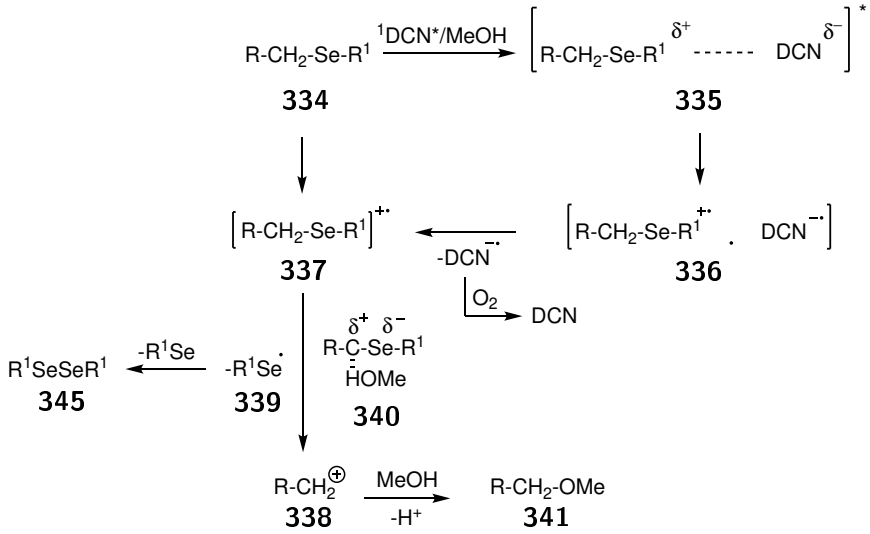
Scheme 5.31: **a)** Cyclization reaction of 3-(prop-2-yn-1-yloxy)prop-1-ene (**321**) **b)** An alternative radical pathway proposed by Pandey and co-workers for the cyclization of 3-(prop-2-yn-1-yloxy)prop-1-ene (**321**)[214] **c)** mechanism of the cyclization reactions of enynes using electrophilic selenium species. Red arrows represent the mechanism proposed by Pandey and co-workers in 1993.[213] Blue arrows represent the revised mechanism published in 1995.[214]

335. In aq. MeOH the exciplex dissociates into solvent-separated ion pairs (SSIP) **336** which dissociate further into free radical ion pairs (FRIP) **337** and $DCN^{-\bullet}$. This assumption was based on the findings of Gould and co-workers,[217] who reported that the reduced interaction of the anion radical with the cation radical in polar solvents favours the dissociation of the ions into SSIPs and FRIPs, whereas in non-polar solvents, a contact ion pair (CIP) between the ions is more prevalent.[218,219] The radical cation (**337**) can dissociate to form free carbocationic species **338** and radical species **339**, whereas $DCN^{-\bullet}$ is oxidised by the oxygen present in the reaction to DCN. The formation of cationic species **338** may also involve the addition of the nucleophile prior to the cleavage, *via* complex **340**. Carbocation **338** combines with MeOH to give the desired product (**341**) and radical species

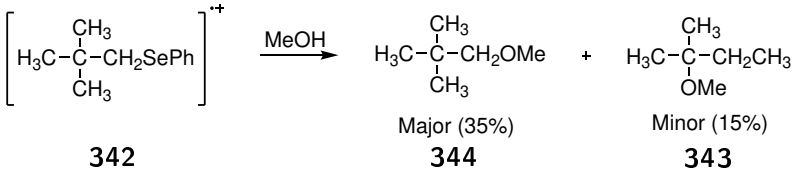


Scheme 5.32: Light-mediated C−Se bond cleavage by Pandey a) deselenenylation reaction b) one-pot selenenylation and deselenenylation reaction.[215]

349 undergoes recombination to give the corresponding diselenide (**345**). To establish the exact mode of cleavage of the radical cation (**337**), Pandey and coworkers studied the PET cleavage of neopentyl phenyl selenide (**342**) due to the fact that if the neopentyl carbocation were to be formed, the rearranged product (**343**) would be isolated.[220] Irradiation of a mixture of neopentyl phenyl selenide (**342**) with DCN in MeOH gave the unrearranged MeO-ether (**344**) as the major product (Equation 5.6), suggesting that the fragmentation of the radical cation does not involve the formation of the free cation, but instead might be aided by MeOH in the solvent cage (*via* complex **340**) before the rearrangement can occur. Through this method, Pandey and co-workers discovered yet another application of organoselenium reagents in organic transformations *viz.* as carbocation equivalents.



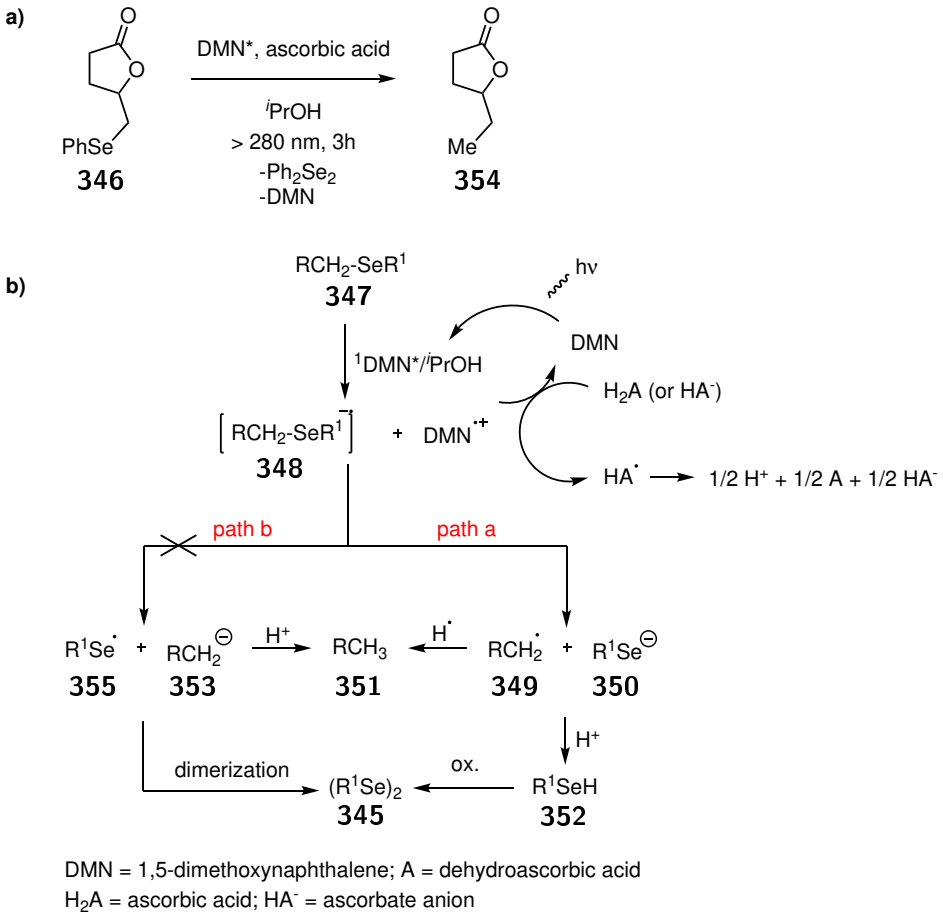
Scheme 5.33: Mechanism of the PET-induced one-pot selenenylation and deselenenylation reaction.[215]



342 344 343 (5.6)

Pandey and co-workers later published a PET-promoted reductive activation of C−Se bonds in unimolecular group transfer radical reactions[221] wherein the organoselenium reagent was reduced to a radical anion in the presence of a light-harvesting electron donor and a co-oxidant. The radical anion then undergoes mesolytic cleavage to generate the corresponding carbon radical and anionic selenium species. This was in contrast to their previous studies, where the organoselenium reagent was oxidised to a radical cation in the presence of an electron acceptor. A mixture of selenolactone **346**, 1,5-dimethoxy naphthalene (DMN) (0.4 eq.) and ascorbic acid (0.4 eq.) in ^{i}PrOH was irradiated ($\lambda >$ 280 nm) for 3 h in the presence of oxygen to give product **354** in a 83 % yield, along with diphenyldiselenide (**86**) and DMN (Scheme 5.34a). The DMN acts as the light-harvesting electron donor and ascorbic acid as the sacrificial electron donor (SED). According to the proposed mechanism, organoselenium compond **347** undergoes a PET with the excited electron donor (DMN*) to generate radical anion **348**, which dissociates to give radical (**349**) and anion (**350**). The alkyl radical combines with an H$^{\bullet}$ to give the desired product (**351**). The selenide anion (**350**) is converted to the corresponding diselenide (**345**) *via* selenol **352**. The authors were able to rule out the formation of the product *via* carbanion **353** when a control reaction performed in deuterated ^{i}PrOH did not give the corresponding deuterated product (Scheme 5.34b, path b).

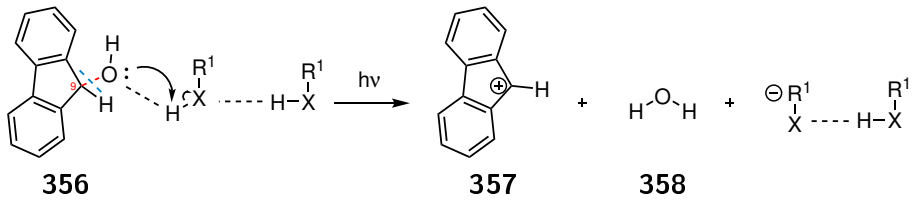
From the examples in Section 5.1, it is clear that selenoadducts can undergo nucleophilic substitution upon oxidative activation of the Se-atom. Based on the stated examples, this activation can be brought about by the use of an appropriate reagent. Additionally, Se-centres are known to participate in chalcogen- and hydrogen bond formation (cf. Section 5.2). A synthetic method which induces a substitution reaction at the Se-moiety *via* oxidative activation of the Se-centre using hydrogen bonds has not been developed as yet. Furthermore, harnessing the photosensitive nature of the C−Se bond (cf. Section 5.9) in such a method can potentially further augment the ability of selenoadducts analogous to **209** to undergo nucleophilic substitution reactions.



Scheme 5.34: PET-induced reductive activation of C−Se bonds to generate C-centred radicals.[221]

6 Objectives

In 2001, Gurzadyan and co-workers reported that the mechanism of the cleavage of the photochemically labile C9 – O bond in 9-fluorenol (**356**) depends on the polarity and dielectric constant of the solvent.[222] Nonpolar solvents resulted in a homolytic cleavage of the C9 – O bond, whereas polar protic solvents resulted in a heterolytic cleavage. The polarity of the solvent manifests as its ability to induce ionization in the solute, whereas the dielectric constant determines the ease with which the ions are separated from one another. Therefore, a polar protic solvent such as HFIP was observed to induce polarity into the 9-fluorenol molecule *via* a proton transfer, which results in a spatial redistribution of electron density on the 9-fluorenol molecule and makes the -OH group a better nucleofuge (Equation 6.1). The high dielectric constant of the solvent enables it to stabilize the ions formed as the result of a heterolytic scission, thus driving the overall process towards heterolysis. The absence of heterolysis in simple alcohols such as MeOH further confirmed that both proton-donicity and high polarity are crucial for a heterolytic cleavage to take place.



356 **357** **358** (6.1)

Recently, Breder and co-workers developed a new photocatalytic homologation strategy *via* a 1,2-carbon shift enabled by hydrogen-bond activation of mildly polar selenium-carbon σ-bonds in β-hydroxy selenides **359** under green light irradiation (528 nm) and using rose bengal disodium salt (**360**) as photocatalyst (**??**).[223] The choice of irradiation (green, 528 nm) corresponds to the absorption maximum of the photocatalyst, which lies between 500 and 570 nm. During optimization studies, they observed a linear correlation between the yield of the product formed and the HB donating ability of the solvent used (cf. Subsection 5.2.1). For instance, *N,N*-dimethylformamide ($\alpha = 0.0$) gave product **361** with a crude yield of only 3 % whereas HFIP ($\alpha = 1.96$) gave a crude yield of 75 %. Additionally, the absence of any correlation between product yield and other solvent

parameters such as dipole moment, and the presence of a high background reactivity (81 % conversion of starting material) even in the absence of a photocatalyst suggested that potential hydrogen bond networks between the reactant and the solvent might be playing a role in the outcome of the reaction. NMR investigations indeed confirmed the presence of a strong hydrogen bond interaction between the -OH group and the selenium atom. Additionally, the presence of an HB between the solvent HFIP and the hydroxy group of the β-hydroxy selenide (**362**) was also confirmed.

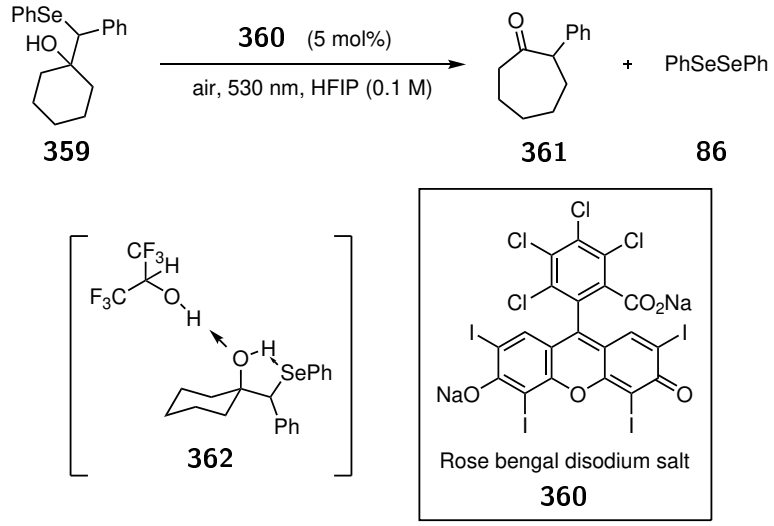
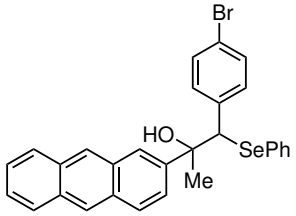


Figure 6.1: The photorearrangement reaction developed by Breder and co-workers.

As preliminary investigations indicated a dependency of the mechanism of cleavage of the C−Se bond on the solvent used, laser photolysis experiments using **363** were conducted in different solvents and the absorption spectrum of the reactive intermediate obtained in each case was studied. For instance, in DCM, the absorption spectrum of the reactive intermediate was observed to correlate with the absorption spectrum of phenylseleno radical $PhSe^{\bullet}$ (**288**). In HFIP, radical cationic species $PhSe^{+\bullet}$ (**364**) was detected instead. To gain more insight into the behaviour of both $PhSe^{\bullet}$ (**288**) and $PhSe^{+\bullet}$ (**364**) in HFIP, photolysis experiments using diphenyl diselenide (**86**) in HFIP were conducted. These studies revealed that in neat HFIP, radical species $PhSe^{\bullet}$ (**288**) remains unprotonated. In the presence of a proton donor in HFIP, however, the radical species was found to undergo protonation, consequently resulting in the formation of the corresponding radical cation $PhSe^{+\bullet}$ (**364**). Therefore, this led to the assumption that during the photolysis of compound **363** in HFIP, a proton transfer to the selenium moiety was taking place during, or shortly after, the cleavage of the C−Se bond. This proton transfer was presumed to be taking place from the −OH group of the β-hydroxy selenide to the selenium atom, resulting

in the formation of an intramolecular hydrogen bond, in addition to the intermolecular hydrogen bond observed between the solvent and the –OH group. Combining these observations, it was speculated that the main role of the solvent HFIP lay in compensating for the accumulation of negative charge on the O-atom of the –OH group during proton transfer from the oxygen to the selenium atom *via* intramolecular hydrogen bonding. This intramolecular hydrogen bond was additionally speculated to continuously withdraw electron density from the Se-atom, thus increasing its nucleofugacity and facilitating the 1,2-carbon shift (cf. 5).

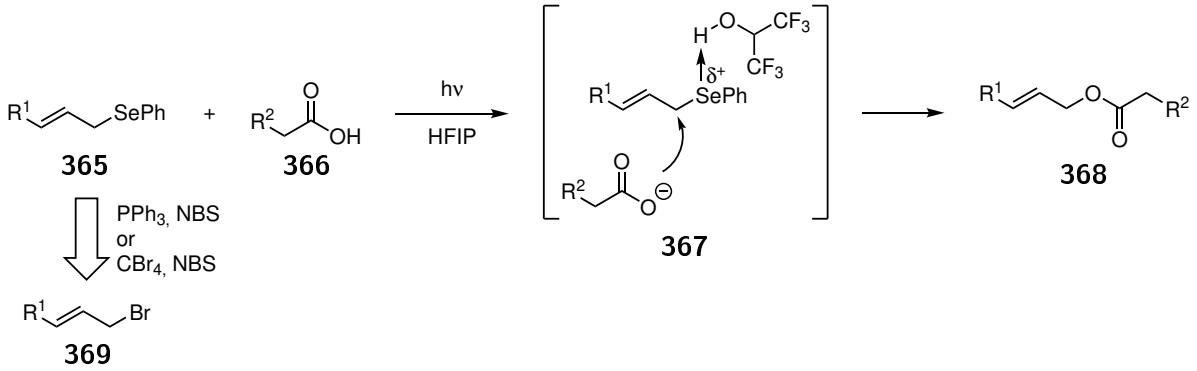


363

Figure 6.2: Molecule used for laser photolysis experiments.

Therefore, the main purpose of this work was to verify if the strategy developed by Breder and co-workers,[223] which combined the photolabile nature of the C–Se bond with the ability of the solvent HFIP to activate the selenium moiety *via* non-covalent interactions and consequently increase its nucleofugacity, could also be used to facilitate an intermolecular nucleophilic substitution reaction in other molecules containing a C–Se bond. By doing so, we would eliminate the need to add an extra PhSeX species to activate the selenium-centre, and also not be limited to a nucleophile generated from the PhSeX species. With a strong focus on easy to synthesize or commercially available reagents, we decided to use simple allylic phenylselenides as the test substrates due to the following reasons: (1) the intermediates generated upon photolytic cleavage of the C–Se bond, regardless homolytic or heterolytic, are stable in allylic systems, (2) allylic systems do not undergo disproportionation reactions,[224] which would limit the formation of side products formed due to photolysis to a minimum, and (3) allylic phenyl selenides can be synthesized easily from commercially available, inexpensive starting materials. For the nucleophile, we wanted a species that was neither too weak, nor too strong. If the nucleophile were too weak, the substitution would probably not take place at all, and if it were too strong, the substitution would probably take place in any solvent suitable for nucleophilic substitution reactions, thereby eliminating the non-covalent interactions that we hypothesized were needed for the success of our strategy. With this in mind, we decided to use carboxylic acids as the nucleophile. Apart from being mild nucleophiles, carboxylic acids with a

variety of substituents are inexpensive and easily available commercially.



Scheme 6.1: The planned nucleophilic substitution reaction at allylic selenides *via* electrophilic activation of the selenium-centre with hydrogen bond networks to the solvent.

Conceptually, the plan could be divided into two parts. In the first part, a simple allylic phenyl selenide (**365** would be used as a substrate to test carboxylic acids of differing electronic properties and substituents (**366**) as nucleophiles in the presence of irradiation (528 nm). In other words, for this series of substrates, R^1 on the selenide is kept constant, while the R^2 group on the carboxylic acid is varied. In the second part, a particular carboxylic acid would be used as a nucleophile with different allylic phenyl selenides, to gain an understanding into the variety of selenides that might be suitable substrates, and to observe the effects, if any, of different substituents present on the selenide on the outcome of the substitution reaction. In other words, for this series of substrates, the R^1 group on the selenide would be varied while the R^2 group on the carboxylic acid would remain unchanged. The allylic phenyl selenide (**365**) is easily accessible from the corresponding allylic bromide (**369**), many of which are commercially available. These experiments would hopefully offer some information about the mechanism of the substitution reaction. Dedicated mechanistic investigations, however, were beyond the scope of this thesis.
The reaction set-up was to be similar to the one used by Breder and co-workers in the homologation reaction of β-hydroxy selenides (Figure 6.3).[223] The set-up consisted of a custom-made metal block, which would allow irradiation of reaction vials *via* LEDs fitted below the block. The blocks were further equipped with an inlet and an outlet which allowed the vials to be heated or cooled to the desired temperatures.

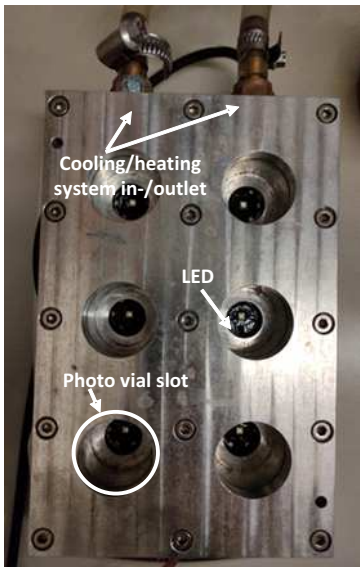


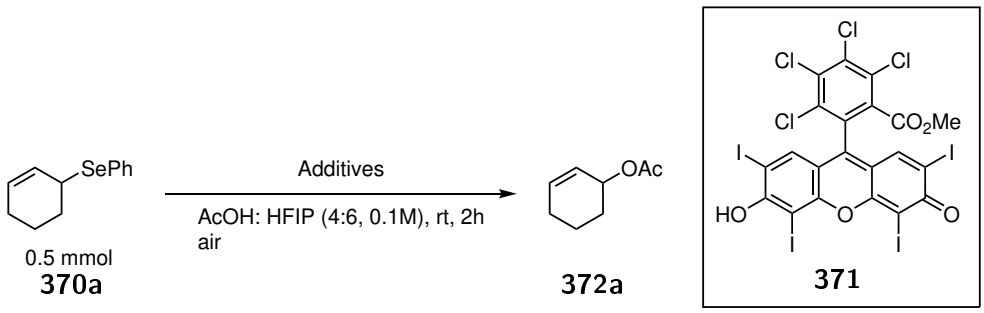
Figure 6.3: The custom-made cooling blocks for the planned photoreactions.

7 Results and Discussion

7.1 Initial Experiments

As mentioned in chapter 6, the reaction conditions used for the initial experiments in the green-light mediated nucleophilic substitution reaction at organic selenides were the same as those used for the rearrangement reactions. One equivalent of cyclohex-2-en-1-yl(phenyl)selane (**370a**) was dissolved in a photoreaction vial in a 4:6 AcOH:HFIP solution, such that an overall concentration of 0.1M was attained, with acetic acid acting as the nucleophile. The set-up was placed in the custom-made cooling block and stirred for 2 h at 400 rpm at 19°C. The first vial was irradiated with green LEDs (528 nm) in the presence of photocatalyst (PC) rose bengal monomethyl ester (RBME) (**371**), and the second one without. A control reaction was set up in the absence of both the green light and the PC (Table 7.1).

Table 7.1: Initial experiments on the green-light mediated nucleophilic substitution reaction at allylic selenides using acetic acid as the nucleophile.



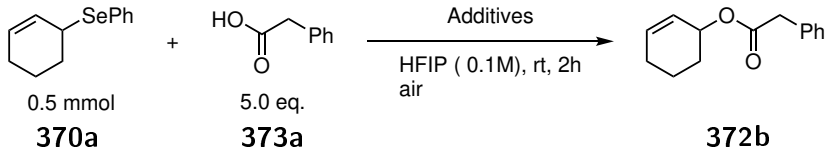
Entries	Additives	Irradiation	Conversion	NMR yield[a]
1	**371** (5 mol%)	528 nm	100%	29%
2	-	528 nm	100%	80%
3	-	-	46%	11%

[a] NMR standard: 1,3,5-trimethoxy benzene

Substitution product **372a** was formed both in the presence and absence of PC **371**. Contrary to expectations, however, the yield of the product was higher in the absence of PC

371, than in its presence (80% vs. 29%) (Table 7.1, entries 1 and 2). The product was identified *via* proton NMR spectroscopy, by the lowfield shift of both the allylic proton signal from 3.97 ppm to 5.26 ppm, and the olefinic proton signals from a region of 5.73-5.89 ppm to 5.67-6.02 ppm. The poor conversion and low yield of the product in the absence of irradiation (Table 7.1, entry 3), showed that the green light played a crucial role in the success of the reaction. To ensure that there were no discrepancies in the yields as a result of the volatility of acetic acid and product **372a**, the experiments were repeated with 5.0 equivalents of phenylacetic acid (**373a**) as the nucleophile (Table 7.2).

Table 7.2: Initial experiments on the green-light mediated SN reaction at allylic selenides using phenylacetic acid (**373a**) as the nucleophile.



Entries	Additives	Irradiation	Conversion	NMR yield[a]
1	**371** (5 mol%)	528 nm	100%	0%
2	-	528 nm	100%	65% (58%)
3	-	-	20%	0%

[a] NMR standard: 1,3,5-trimethoxy benzene; isolated yields in parentheses.

Similar to the reaction with acetic acid, the desired substitution product (**372b**) was observed under irradiation in the absence of the PC (Table 7.2, entry 2). The allylic proton of the product appears as a multiplet between 5.24 and 5.30 ppm. The two olefinic signals appear as two multiplets between 5.66 and 5.72 ppm, and 5.92 and 5.98 ppm, respectively. The benzylic protons appear as a sharp singlet at 3.61 ppm (Figure 7.1).

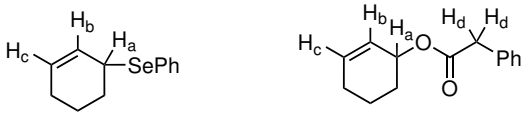


Figure 7.1: A part of the proton NMR spectra of substitution product **372b** and selenide **370a**.

Interestingly, in the presence of the PC **371**, the formation of difunctionalized product **374** was inferred from the proton NMR spectrum (Figure 7.2). This was characterized by the two multiplets between 5.19 and 5.33 ppm, which belong to the carbinolic protons, and the doublet of doublets at 3.44 ppm, belonging to the proton on the C−Se carbon. The aromatic protons with an integral of 15, appearing between 7.20 and 7.51 ppm, and the multiplet between 3.54 and 3.52 ppm, belonging to the methylene protons, also helped

identify the molecule. The methylene protons on the cyclohexene ring can be observed between 1.4 and 2.0 ppm, along with some impurities from the NMR solvent, between 0.8 and 1.2 ppm. The formation of the disubstituted product was further confirmed by mass spectrometry. As in the previous cases, the absence of irradiation led to a poor outcome with no product formation and only 20% conversion of selenide **370a**.

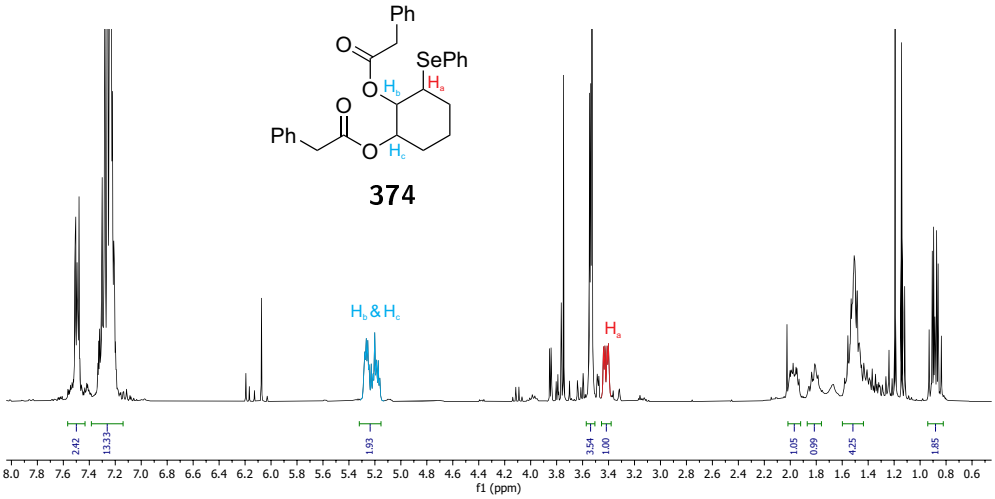


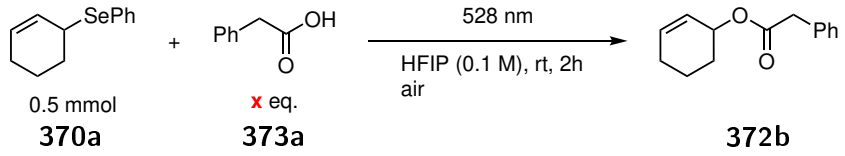
Figure 7.2: Proton NMR spectrum of the difunctionalized product (**374**) obtained in the photoreaction performed in the presence of PC **371**.

7.2 Optimization Experiments

7.2.1 Stoichiometry Screening at 0.1M concentration

As the product was formed in the absence of a PC and the addition of the PC only led to the formation of undesired products, all further optimization experiments were conducted without any additional PC in the reaction system. The first step in the optimization studies was to determine the optimum amount of the nucleophile required to bring about the desired substitution reaction. Selenide **370a** was stirred with different amounts of nucleophile **373a** in HFIP (0.1M). An increase in the amount of **373a** from one to three eqivalents showed a steady increase in the yield from 41% to 58% (Table 7.3, entries 1-3). A further increase to five equivalents had no significant influence on the yield of the product (Table 7.3, entries 4 and 5). Therefore, all further experiments were performed with three equivalents of the nucleophile.

Table 7.3: Optimization of the amount of nucleophile needed for the green-light mediated nucleophilic substitution reaction.



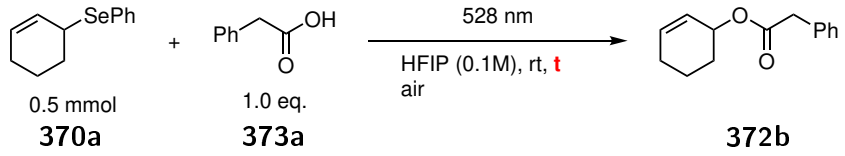
Entries	**373a** x eq.	Conversion	NMR yield[a]
1	1.0	92%	41%
2	2.0	94%	51%
3	3.0	96%	58%
4	4.0	95%	56%
5	5.0	100%	60%

[a] NMR standard: 1,3,5-trimethoxy benzene

7.2.2 Time taken for completion at 0.1M concentration

Since all previous reactions were terminated after only two hours, the outcomes of running the reaction both for a shorter duration as well as for a longer duration had to be examined. Running the reaction for a shorter duration would reveal if the two hours runtime was unnecessary, and the longer duration had to be studied in order to determine any potential decomposition of product **372b** under the reaction conditions. Therefore, the photoreaction was conducted simultaneously in multiple reaction vials containing 0.5 mmol of selenide **370a** and 1.0 eq. of phenyl acetic acid (**373a**) in HFIP (0.1M) (Table 7.4). At the end of each hour, one reaction was terminated and analysed using proton NMR spectroscopy for conversion of the starting selenide and NMR yield of the substitution product. After one hour, 67% conversion of the starting material was observed (Table 7.4, entry 1). Complete conversion of the starting material was observed after three hours (Table 7.4, entry 3).

Table 7.4: Optimization of the time required for completion of the reaction.



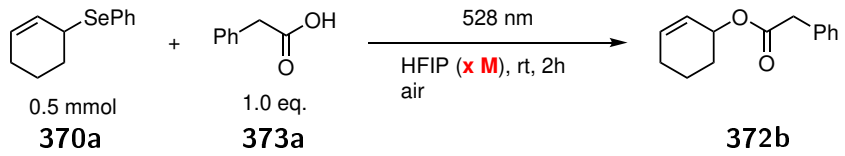
Entries	t	Conversion	NMR yield[a]
1	1h	67%	30%
2	2h	89%	40%
3	3h	94%	44%

[a] NMR standard: 1,3,5-trimethoxy benzene; concentration based on **370a**

7.2.3 Concentration Screening

To determine the optimum concentration of the reaction mixture, one equivalent of selenide **370a** was stirred with one equivalent of phenyl acetic acid (**373a**) in HFIP in varying concentrations (Table 7.5). The reactions with 0.2M and 0.5M solutions of the selenide in HFIP gave the desired substitution product in similar yields of 44% (Table 7.5, entries 1 and 2). Increasing the concentration to 1.0M increased the yield of the substitution product to 50%. Consequently, a 1.0M solution of the selenide in HFIP was determined to be optimum for obtaining the substitution product in good yields, while simultaneously keeping the amount of solvent used to a minimum. Higher concentrations were not attempted as the reactants did not dissolve completely in lower solvent volumes.

Table 7.5: Optimization of the concentration of the solution.



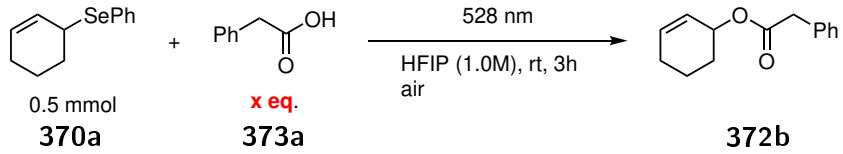
Entries	**373a** x molL^{-1}	Conversion	NMR yield[a]
1	0.2	87%	44%
2	0.5	92%	45%
3	1.0	95%	50%

[a] NMR standard: 1,3,5-trimethoxy benzene; concentration based on **370a**

7.2.4 Stoichiometry Screening at 1.0M concentration

Once the optimum concentration was determined, the next logical step was to re-examine the amount of nucleophile that gives the highest product yield at the higher concentration (cf. Subsection 7.2.1). Therefore, all reactions mentioned in Subsection 7.2.1 were repeated at a 1.0M concentration. These reactions were run for three hours, based on the results from Subsection 7.2.2 (Table 7.6). With one equivalent of the nucleophile, product **372b** was obtained in a moderate yield of 38% (Table 7.6, entry 1). Increasing the amount of nucleophile to two equivalents led to a slightly diminished yield of the product (Table 7.6, entry 2). As in the previous case, three equivalents of nucleophile **373a** gave the best results, giving product **372b** in a significantly higher yield of 79% (Table 7.6, entry 3). As these conditions were the best trade-off between the amount of nucleophile and solvent used, we decided to use these conditions as the benchmark for all further optimization experiments, with the aim being to find alternate conditions which would match the 79% yield. Reactions using greater than three equiv of the nucleophile were not conducted because the resulting reaction mixture could not be stirred sufficiently with the small amount of solvent (0.5 ml) present in the reaction mixture.

Table 7.6: Stoichiometry screening at 1.0M concentration.



Entries	**373a** x equiv	Conversion	NMR yield[a]
1	1.0	79%	38%
2	2.0	92%	34%
3	3.0	94%	79%

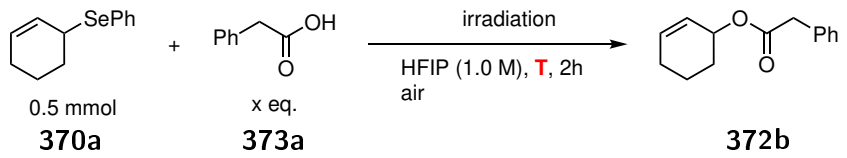
[a] NMR standard: 1,3,5-trimethoxy benzene; Conversion and NMR yields as an average of two determinations.

7.2.5 Temperature Screening

To verify if an increased reaction temperature in addition to the irradiation could improve the yield of product **372b**, one equivalent each of selenide **370a** and phenyl acetic acid (**373a**) was stirred in HFIP (1.0M) for 2h at 40 °C and 50 °C, respectively. The increase in temperature did not seem to have any effect on the outcome of the reactions, with product **372b** obtained with a 52% yield at both temperatures (Table 7.7, entries 1 and

2). Increasing the amount of nucleophile to two equivalents, however, raised the yield of the product to 71% (Table 7.7, entry 3). As the same reaction at RT gave only 34% yield of the product (Table 7.6, entry 2), the increased yield at 50 °C implied that a combined effect of both light and temperature could indeed enhance product yields. To verify the possibility of an entirely thermal reaction pathway, the reaction was repeated at 50°C in the absence of irradiation. This led to both poor conversion of the starting material and low yield of the substitution product (Table 7.7, entry 4). This was a strong indication that although higher temperatures in combination with irradiation could indeed improve product yields, the irradiation was the main driver of the reaction. As the boiling point of HFIP is 58°C and the current temperature set up did not allow the use of reflux condensers or pressure tubes, higher temperatures were not tested.

Table 7.7: Temperature screening experiments for the green-light mediated SN reaction.



Entries	**373a** (x eq.)	T	irradiation	Conversion	NMR yield
1	1.0	40°C	528 nm	100%	53%[a]
2	1.0	50°C	528 nm	100%	55%[b]
3	2.0	50°C	528 nm	100%	71%
4	2.0	50°C	-	17%	9%

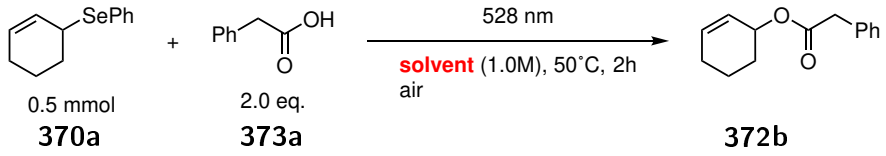
[a] NMR standard: 1,3,5-trimethoxy benzene
[b] NMR standard: dimethyl sulfone

7.2.6 Solvent Screening

With the optimum stoichiometry of the reagents established, the quality of the SN reaction in solvents other than HFIP had to be determined. As a combination of both irradiation and higher temperature was found to enhance reaction yields, the screening experiments were conducted at 50°C to investigate if the same combination could give comparable yields in solvents other than HFIP. As two equivalents of nucleophile **373a** at 50 °C in HFIP gave yields comparable to that of the benchmark, solvent screening experiments were conducted using two equiv of the nucleophile at 50 °C in a 1.0M solution in HFIP (Table 7.8). The standard reaction time was fixed at two hours, unless the half-hourly TLC controls indicated an earlier completion of the reaction.
The solvents in table (Table 7.8) have been arranged in order of increasing HBD ability.

Among solvents with HBD parameter $\alpha = 0.0$, toluene gave the highest yield of product at 23%, followed by EA at 14% (Table 7.8, entries 1 and 2). Ethereal solvents THF and 1,4-dioxane showed differing outcomes, despite their similar chemical properties (Table 7.8, entries 3 and 5.) While THF full conversion of the starting material was observed in THF without any product formation, 1,4-dioxane showed a lower conversion of 72%, but a higher yield of 10%. DMSO similarly showed a poor conversion of the starting material at 72%, with no product formation (Table 7.8, entry 4). This could be due to the higher HBA ability of DMSO compared to its HBD ability. Contrary to expectations, solvents with increasing HBD values did not necessarily lead to improved outcomes. Acetone and DCM both showed 100% conversion of starting material and no product formation (Table 7.8, entries 6 and 7). Acetonitrile showed full conversion *via* TLC control after only 1 h, but showed no product formation (Table 7.8, entry 8). The best outcome in relation to conversion was observed in nitromethane, where a 72% conversion of the starting material resulted in a yield of 26% of the desired product (Table 7.8, entry 9). Chloroform, however, showed poorer results than nitromethane, despite having a higher HBD value (Table 7.8, entry 10). Among alcohols, both ^{i}PrOH and ethanol showed no product formation, with ^{i}PrOH showing a conversion of only 72% (Table 7.8, entries 11 and 12). This could be because the HBA values for both these solvents are similar to higher than their respective HBD values. Trifluoroethanol, with a higher HBD value of 1.51, showed a higher product formation of 18% (Table 7.8, entry 13). Surprisingly, trifluorotoluene gave the desired product in a yield of 22%, despite having no proton which could participate in the formation of a hydrogen bond (Table 7.8, entry 14). This result is comparable to that obtained in toluene, indicating that factors such as pi-stacking interactions could also contribute to product formation. However, a poorer yield of 11% was observed in *o*-xylene. (Table 7.8, entry 15). No trends in product formation could be observed based on the HBD or HBA parameters of the solvents alone. This could be because of the much lower HBD values of these solvents when compared to HFIP, which has a HBD parameter α of 1.96. Speculating whether the addition of an acid to a solvent could enhance its ability to form stronger hydrogen bond networks, the photoreaction was repeated in nitromethane, which gave the highest product yield after HFIP, with additional *p*TsOH and TFA (Table 7.8, entries 16 and 17). However, the addition of acid resulted in immediate decomposition of the starting material. In the proton spectrum of the crude reaction mixture, the only identifiable signals belonged to phenyl acetic acid (**373a**), the NMR standard, and Ph_2Se_2 (**86**). The allylic selenide probably decomposes to give the observed Ph_2Se_2 (**86**) and the volatile cyclohexene rest, which is likely lost during the work-up.

Table 7.8: Solvent screening reactions for the green-light mediated SN reaction at allylic selenides using phenylacetic acid (**373a**) as nucleophile.



Entries	solvent	α	β	Conversion	NMR yield[a]
1	toluene	0.00	0.11	100%	23%
2	EA	0.00	0.45	100%	14%
3	THF	0.00	0.55	100%	0%
4	DMSO	0.00	0.76	72%	0%
5	1,4-dioxane	0.00	0.37	70%	10%
6	acetone	0.08	0.48	100%	0%
7	DCM	0.13	0.10	100%	0%
8	MeCN[b]	0.19	0.31	100%	7%
9	NO_2Me[b]	0.22	0.06	79%	26%
10	$CHCl_3$	0.44	0.00	100%	19%
11[e]	^{i}PrOH	0.48	0.95	78%	9%
12	EtOH	0.83	0.77	100%	0%
13	TFE[c]	1.51	0.00	96%	18%
14	TFT[b,d]	-	-	100%	22%
15	*o*-xylene	-	-	100%	11%
16	NO_2Me+*p*TsOH · H_2O	-	-	100%	0%
17	NO_2Me+TFA	-	-	100%	0%

[a] NMR standard: dimethyl sulfone [b] Reaction stirred for 1h [c] Trifluoroethanol
[d] α,α,α-trifluorotoluene [e] Reaction was performed by A. Tiefel

Interestingly, ketone **375**, identified by the olefinic signals at 6.0 and 7.0 ppm, was observed in all cases (Figure 7.3). In EtOH, the major product formed was ketone **375**, with a yield of 31%. The formation of the ketone can be attributed to possible radical cationic intermediates interacting with the triplet oxygen present in the air atmosphere in the reaction. Trace amounts of allylic alcohol **376** were also observed, except in ^{i}PrOH, ethyl acetate, toluene, and *o*-xylene. The alcohol could be identified from the olefinic protons between 5.72 and 5.86 ppm, and the allylic proton at 4.19 ppm. The NMR shifts are in accordance with those of the pure compounds measured from commercially available samples. As none of the tested solvents gave the desired product (**372b**) in yields comparable to those obtained in HFIP, HFIP was determined to be the best solvent for the green-light mediated nucleophilic substitution reaction at allylic selenides.

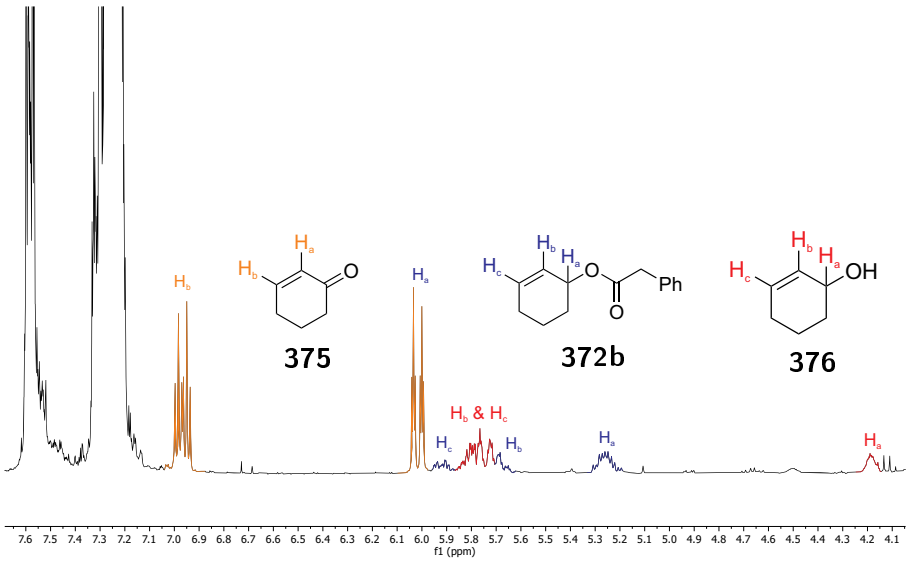


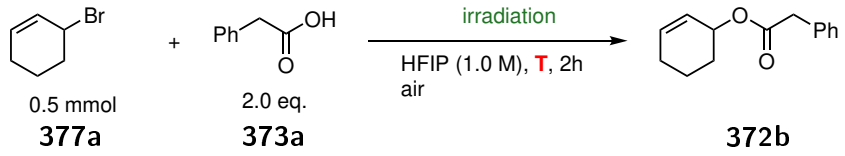
Figure 7.3: Side products observed in EtOH during solvent screening experiments.

7.2.7 Substrate Screening

Selenide **370a** was synthesized from the corresponding bromide **377a** in the presence of $NaBH_4$ in EtOH.[225] As C–Br bonds themselves are known to be photolabile,[226] the possibility of the nucleophilic substitution reaction taking place with the bromide had to be investigated. 0.5 mmol of bromide **377a** was reacted with two equivalents of nucleophile **373a** in a 1.0M solution in HFIP (Table 7.9). At 50°C, a rapid decomposition of the bromide was observed, regardless of whether the reaction was performed under irradiation or without (Table 7.9, entries 1 and 2). This was probably due to the the fact that bromide **377a** is temperature-sensitive and therefore, the higher temperature resulted in its immediate decomposition. Consequently, the reactions were repeated at room temperature. Product **372b** was obtained in yields of up to 25%, regardless of irradiation (Table 7.9, entries 3 and 4). This indicated that the bromide was highly reactive by itself, and could undergo substitution thermally rather than photochemically. The difference in conversion of the starting material and the yield of the product is a further indication that the bromide is unstable at room temperature and that it is the selenide which is required for the reaction to proceed photochemically.

Another interesting candidate for the substitution reaction was a species where the phenylselenide moiety is directly attached to a benzylic position. The rationale behind this was twofold: 1) to verify if the increased stability of the benzylic position was sufficient to stabilize the radical/cationic intermediate and thereby facilitate the substitution reaction and 2) to establish whether the double bond in the substrate must strictly be

Table 7.9: Screening of other substrates for the substitution reaction.



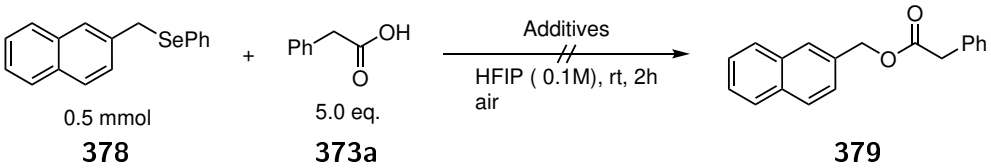
0.5 mmol **377a** | 2.0 eq. **373a** | **372b**

Entries	T	Irradiation	Conversion	NMR yield[a]
1	50°C	528 nm	100%	0%
2	50°C	-	100%	0%
3	19°C	528 nm	100%	23%
4	19°C	-	100%	22%

[a] NMR standard: dimethyl sulfone

in an allylic position or if it could be in an allylic position in conjugation with an aromatic system. To this end, selenide **378** was reacted with five equivalents of phenylacetic acid (**373a**) in HFIP (0.1M), replicating the conditions used for the initial optimization experiments (cf. Subsection 7.2.1). The reaction was carried out both in the presence and absence of photocatalyst **371**, with and without irradiation (Table 7.10). No reaction was observed under any of the reaction conditions, indicating that an actual allylic moiety might be requisite for the substitution reaction.

Table 7.10: Nucleophilic substitution reaction at the benzylic position.



0.5 mmol **378** | 5.0 eq. **373a** | **379**

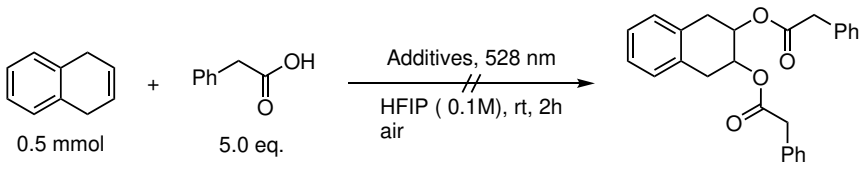
Entries	Additives	Irradiation	Conversion	NMR yield[a]
1	**371** (5 mol%)	528 nm	nr	nr
2	-	528 nm	nr	nr
3	-	-	nr	nr

[a] NMR standard: 1,3,5-trimethoxy benzene.

Difunctionalized product **374** was one of the side products observed during the initial optimization experiments where selenide **370a** was reacted with phenylacetic acid (**373a**) in the presence of PC **371** (Cf. Section 7.1). An idea arose to investigate the applicability of these conditions to induce difunctionalization in simple alkenes. To this effect, one equivalent of 1,4-dihydronaphthalene (**380**) was reacted with five equivalents of phenylacetic acid (**373a**) in the presence of PC **371** in HFIP (0.1M) under green light irradiation. As

the exact mechanism of the reaction was unknown, stoichiometric amounts of diphenyl diselenide (**86**) were also added to study any potential effects it might have on the substitution reaction. A control reaction without the PC was also set up (Table 7.11). However, none of the reaction conditions resulted in any chemical reaction. The proton spectra of the crude reaction mixture all showed signals belonging only to the starting materials.

Table 7.11: Attempted difunctionalization of simple olefins under green-light irradiation.



0.5 mmol 5.0 eq.

380 **373a** **381**

Entries	Additives	**86**	Conversion	NMR yield[a]
1	**371** 5 mol%	1.0 eq.	nr	nr
2	**371** 5 mol%	-	nr	nr
3	-	1.0 eq.	nr	nr
4	-	-	nr	nr

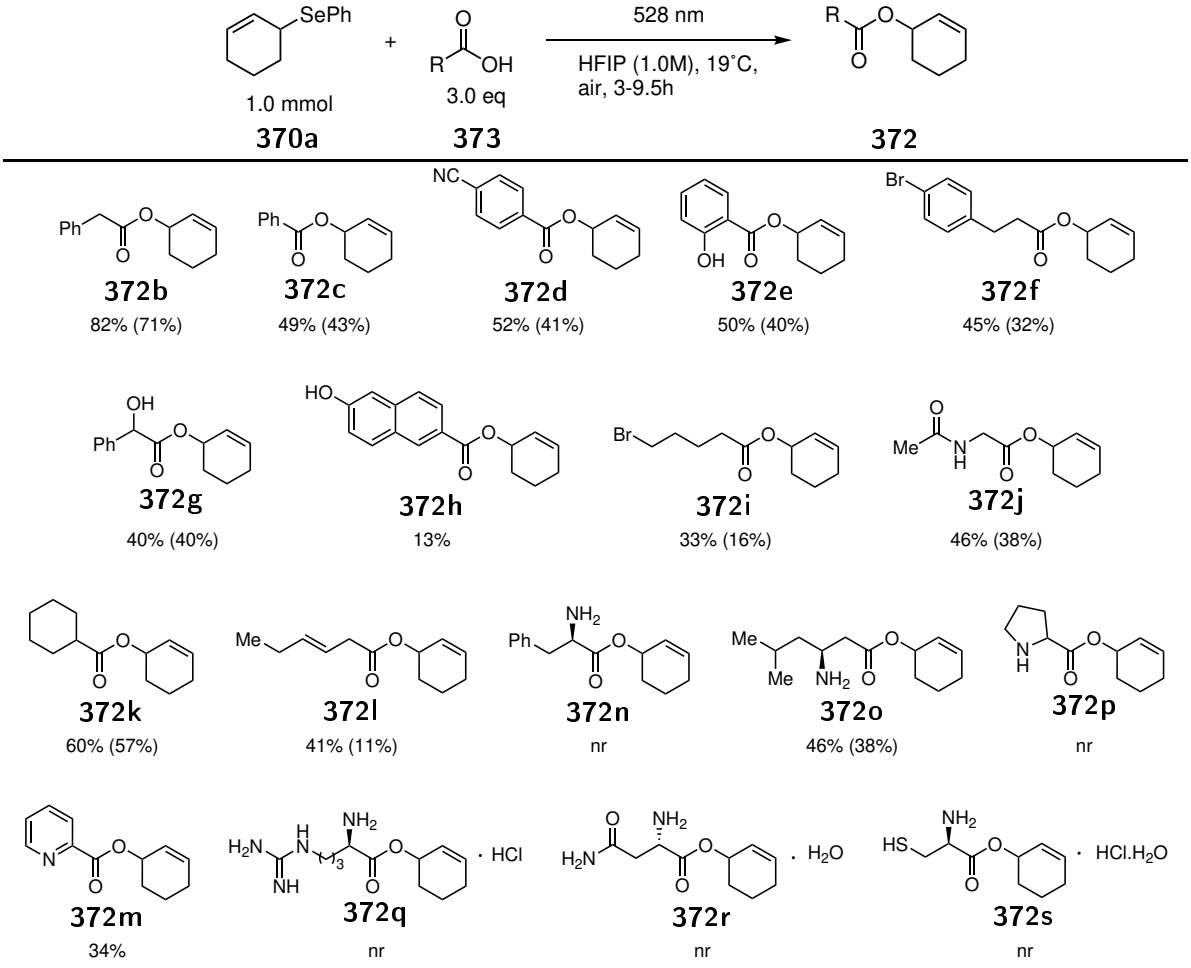
[a] NMR standard: 1,3,5-trimethoxy benzene.

7.3 Substrate scope: nucleophiles

With the optimized conditions established, the substrate scope of the green-light mediated nucleophilic substitution reaction of allylic selenides was investigated. For this purpose, a 1.0M solution of selenide **370a** in HFIP was reacted with three equivalents of various carboxylic acid nucleophiles at room temperature (Table 7.12). The reactions were monitored for completion *via* TLC control. The corresponding substitution products **372** were obtained in moderate to good yields. The products are identifiable from the broad multiplet of the allylic proton and from the olefinic proton signals. The allylic proton signal in the substitution product undergoes a downfield shift from 4.0 ppm in the selenide to 5.20-5.55 ppm in the product. With the phenylacetic acid (**373a**) as nucleophile, product **372b** was obtained in a high yield of 82%. Benzoic acid derivatives gave the corresponding products **372c–e** in moderate yields of up to 52%. 4-bromobenzyl propanoic acid **373b** and mandelic acid (**373c**) gave the corresponding products **372f**,**g** in moderate yields of 40-45%. The reaction with 6-hydroxy-2-naphthoic acid (**373d**), however, only showed a moderate conversion of 48% after 7 hours and a low yield of 13%, probably due to the steric bulk of the acid. The corresponding product (**372h**) was not isolated. With aliphatic

acids, the corresponding substitution products **372i–l** were obtained in yields between 33 and 70%. Picolinic acid (**373e**) gave the corresponding product (**372m**) in a yield of 34%. However, the product could not be isolated. The success of the reaction with *N*-acetyl glycine (**373f**), where the corresponding substitution product **372j** was obtained in a 46% yield, prompted the investigation of other amino acids as potential nucleophiles. However, no identifiable signals were observed in the proton spectra of any of these reactions. In the case of amino acid salts, the poor reaction outcome could be attributed to their low solubility in HFIP. No further attempts were made to improve the solubility of the amino acid salts in HFIP.

Table 7.12: Substrate scope of the green-light mediated nucleophilic substitution reaction.



[a] NMR yield, standard: dimethyl sulfone or 1,3-dinitrobenzene

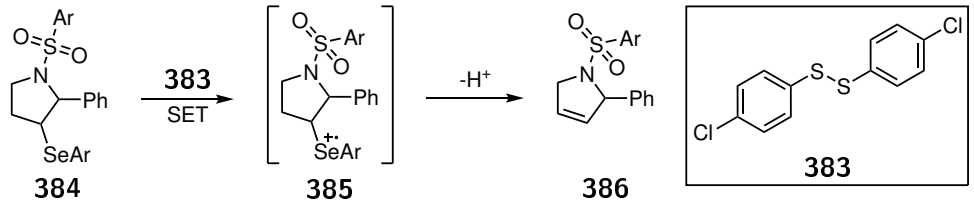
Apart from products **372b** and **372k**, all other products shown in Table 7.12 were formed in low to moderate yields. In an attempt to improve the outcome of the nucleophilic substitution reaction, it was decided that the screening of additives such as acids and

bases might be necessary.

7.4 Further optimization experiments

7.4.1 Singlet oxygen quencher and additional oxidising agent

Seeing as the product yields achieved thus far were below expectations, further optimization experiments were conducted with the aim to find suitable additives which might potentially improve the outcome of the reaction. In ongoing research on photoaerobic amination of olefins in the Breder group, it was found that competing side reactions occurring due to the presence of singlet oxygen in the reaction mixture, such as the Schenk-ene reaction,[227] interfered with the desired amination reaction. Therefore, a singlet oxygen quencher such as *o*-nitrobenzaldehyde (**382**)[228] was used to suppress such side reactions, which consequently increased the yield of the desired amination product. Additionally, Stern-Vollmer experiments revealed that a disulfide additive such as compound **383** oxidised seleno-intermediate **384** *via* an SET process and as a result promoted the elimination reaction required to give the final product.

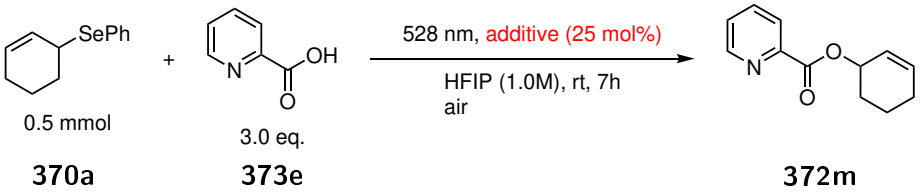


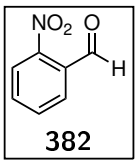
Scheme 7.1: Oxidation of selenointermediate **384** *via* SET using disulfide species **383** in the intramolecular amination reaction currently being investigated in the Breder group.

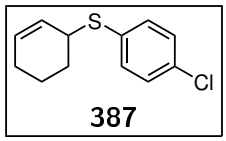
To verify whether similar singlet oxygen-promoted side reactions were hindering the substitution reaction at the allylic selenides, and whether the disulfide (**383**) could supplement the solvent HFIP in reducing electron density at the selenium centre and thus accelerate the substitution reaction, both *o*-nitrobenzaldehyde (**382**) and disulfide **383** were tested as additives in the green-light mediated nucleophilic substitution reaction using selenide **370a** and picolinic acid (**373e**) as the nucleophile (Table 7.13). In the absence of any additives, product **372m** was obtained in 34% yield (Table 7.13, entry 1). The addition of nitrobenzaldehyde (**382**) slightly decreased the yield of product **372m** to 30% (Table 7.13, entry 2). This indicated that singlet oxygen-mediated competing reactions were probably not hindering the desired substitution reaction. With additive **383**, the yield of the product remained almost unchanged (Table 7.13, entry 3), indicating that disulfide **383** does

not oxidise the selenide as observed in the amination reaction. Furthermore, side product **387** was also observed in 18% yield. The characteristic signals were in agreement with the NMR shifts of the pure compound as reported in literature.[229] A combination of both the additives also did not have any influence on the yield of the product (Table 7.13, entry 4). Consequently, the screening of other additives such as acids and bases was deemed necessary.

Table 7.13: Screening of additives **383** and **382** in the green-light mediated nucleophilic substitution using selenide **370a** and picolinic acid (**373e**)







Entry	Additive	Conversion	NMR Yield[a]
1	-	93%	34%
2	**382**	100%	30%
3	**383**	100%	34%
4	**382** + **383**	100%	33%

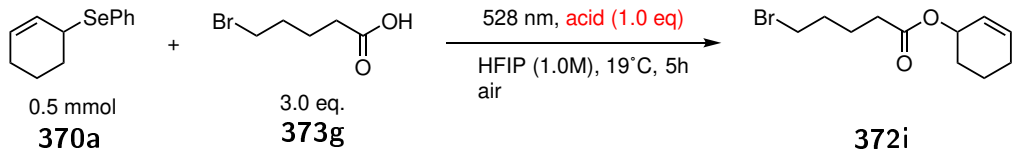
[a] NMR yield, standard: 1,3-dinitrobenzene

7.4.2 Screening of acids and bases

For the screening of additives, the substrate of choice had to be one where the product was obtained only in moderate yields under the hitherto used conditions, in order for a potential improvement in reaction yield to be observed clearly. Therefore, 5-bromovaleric acid (**373g**) was used as the nucleophile in the screening reactions. As shown in Table 7.12, substituted product **372i** was obtained in a moderate yield of 33% under the hitherto used reaction conditions. As already done in the solvent screening experiments (cf. Table 7.8), it was decided to once again verify the effect of an acid on the reaction in HFIP, this time at room temperature. It was speculated that the acid could supplement the already high hydrogen bond donating ability of the solvent and thus increase the overall electrophilicity of the selenide towards the nucleophile. However, similar to previous results, the addition of acid led to rapid decomposition of selenide **370a**. With these results, it was confirmed that the addition of acids to the reaction mixture had no influence on the electrophilicity

of the selenide substrate.

Table 7.14: Screening of acids as additives in the green-light mediated nucleophilic substitution reactions.

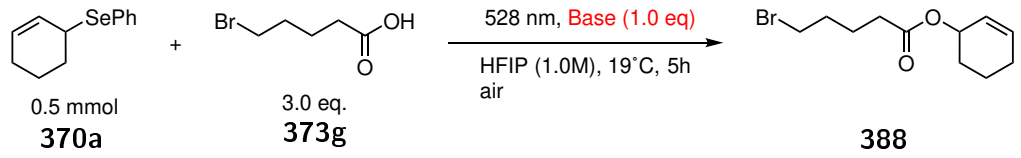


Entry	Acid	Conversion	NMR Yield[a]
1	pTsOH · H_2O	100%	0%
2	MsOH	100%	0%
3	BnSOH	100%	0%

[a] NMR yield, standard: 1,3-dinitrobenzene

As the electrophilicity of the selenide could not be regulated, enhancing the nucleophilicity of the acid *via* deprotonation was identified as an alternative to promote the nucleophilic subsitution reaction. Hence, one equivalent of various bases was added to the hitherto used reaction conditions. Among the carbonates tested, K_2CO_3 slightly increased the yield of product **372i** to 40% (Table 7.15, entry 1). $KHCO_3$ further increased the yield to 49% (Table 7.15, entry 2). The addition of Cs_2CO_3 resulted in no significant change in the yield and with Na_2CO_3, the yield decreased slightly to 29% (Table 7.15, entries 3 and 4). With $NaHCO_3$, the yield of product **372i** increased drastically to 62%, and Li_2CO_3 further increased the yield to 66% (Table 7.15, entries 5 and 6). These improvements strongly indicated that employing a base to enhance the nucleophilicity of the acid was a promising strategy to improve the yield of the substitution product. Apart from carbonates, fluorides and phosphates were also tested. Both CsF and KF resulted in an increase in the yield of product **372i** from 33% to 47 and 44%, respectively (Table 7.15, entries 8 and 9). The highest product yields of 71% and 77% were obtained with CaF_2 and NaF (Table 7.15, entries 7 and 10), respectively. On the other hand, AgF and TBAF gave the poorest outcomes, both in terms of conversion of starting material **370a** and the yield of the product (Table 7.15, entries 11 and 12). This could be attributed to the highly hygroscopic nature of both the compounds, which could result in their reaction with moisture present in the air atmosphere of the reaction and lead to side products. Among the phosphates tested, KF_6P gave product **372i** in a 71% yield (Table 7.15, entry 17). All other phosphates only resulted in a moderate increase in the yield of the product from 33% to up to 59% (Table 7.15, entries 13-16). As the best results were obtained with NaF, all further reactions were conducted using NaF as an additive.

Table 7.15: Screening of bases as additives in the green-light mediated nucleophilic substitution reaction.



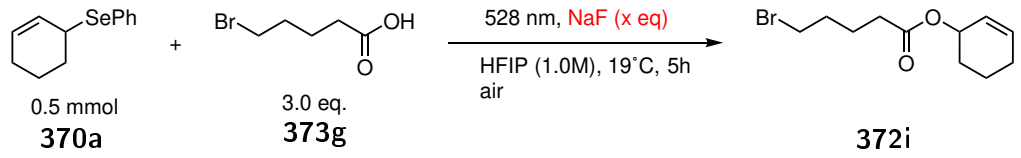
0.5 mmol **370a** | 3.0 eq. **373g** | **388**

Entry	Base	Conversion	Yield[a]	Entry	Base	Conversion	Yield[a]
1	K_2CO_3	100%	40%	10	NaF	100%	77%
2	$KHCO_3$	96%	49%	11	AgF	84%	22%
3	Cs_2CO_3	100%	35%	12	TBAF	48%	8%
4	Na_2CO_3	93%	29%	13	Na_2HPO_4	95%	53%
5	$NaHCO_3$	96%	62%	14	NaH_2PO_4	95%	51%
6	Li_2CO_3	95%	66%	15	Na_3PO_4	100%	59%
7	CaF_2	96%	71%	16	K_3PO_4	85%	47%
8	CsF	100%	47%	17	KF_6P	96%	71%
9	KF	94%	44%				

[a] NMR yield, standard: 1,3-dinitrobenzene

The next step in the optimization process was to determine the influence of varying amounts of NaF on the yield of the product. Selenide **370a** was treated with 5-bromovaleric acid (**373g**) and varying amounts of NaF in HFIP (1.0M) (Table 7.16). It was found that using NaF in substoichiometric amounts (Table 7.16, entries 1 and 2) as well as in excess (Table 7.16, entries 4 and 5) gave yields slightly lower than when one equivalent of NaF was used (Table 7.16, entry 3). Therefore, one equivalent of NaF was chosen to be the optimum amount of additive required to obtain the desired substitution products (**372**) in enhanced yields. A control reaction was performed with the optimized reagents in the absence of irradiation. No conversion of the selenide was observed after three hours, confirming once again that green light irradiation was crucial for the substitution reaction.

Table 7.16: Stoichiometric screening of NaF as an additive in the green-light mediated nucleophilic substitution reaction.

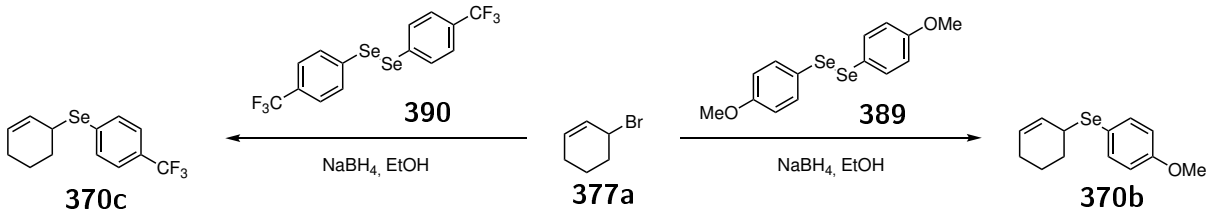


Entry	NaF (x eq)	Conversion	NMR Yield[a]
1	0.2	100%	68%
2	0.5	100%	69%
3	1.0	95%	75%
4	3.0	97%	63%
5	5.0	96%	65%

[a] NMR yield, standard: 1,3-dinitrobenzene

7.4.3 Effect of substituents on allylic phenyl selenides

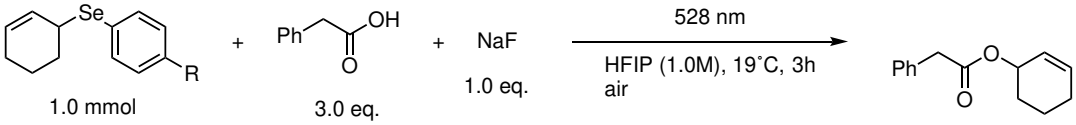
With the optimized conditions in hand, the effect of different substituents on the aromatic ring of the allylic selenide on the outcome of the nucleophilic substitution reaction were investigated. The rationale behind this was to verify if the hypothesized hydrogen bonding network required to reduce electron density on the selenium centre could alternatively be achieved by manipulating the electronic character of the aryl selenide leaving group. For this purpose, selenides **370b** and **370c** were synthesized from bromide **377a**, using $NaBH_4$ and the corresponding diselenides **389** and **390** in EtOH, respectively (Scheme 7.2).



Scheme 7.2: Synthesis of allylic selenides with different substituents on the aromatic ring.

The photoreaction was carried out using standard nucleophile **373a** (Table 7.17). With the *p*-MeO substituted selenide **370b**, product **372b** was obtained in a 67% yield, comparable to that achieved with selenide **370a** (Table 7.17, entry 1). With *p*-CF_3 substituted selenide **370c**, product **372b** was obtained in a lower yield of 50% (Table 7.17, entry 1). As the unsubstituted aromatic ring gave the best yields among the cyclohexene allylic selenide species, all further selenides were synthesized without any substituents on the aromatic ring.

Table 7.17: Green-light mediated nucleophilic substitution reaction with different substituents on the aromatic ring of allylic selenide **370**.



R = *p*-OMe **370b**

R = *p*-CF_3 **370c**

373a

372b

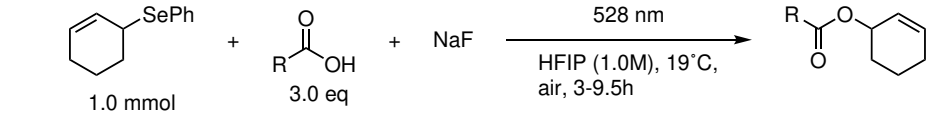
Entry	Selenide	Conversion	NMR Yield[a]
1	**370b**	100%	67%
2	**370c**	100%	50%

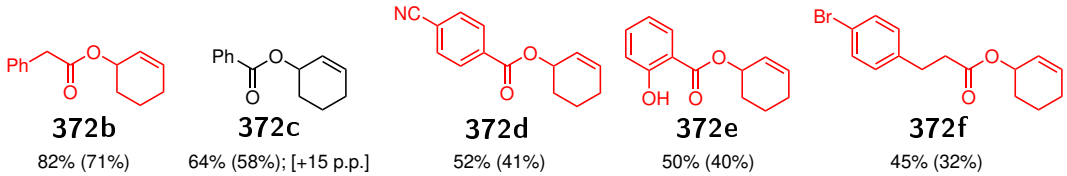
[a] NMR yield, standard: 1,3-dinitrobenzene

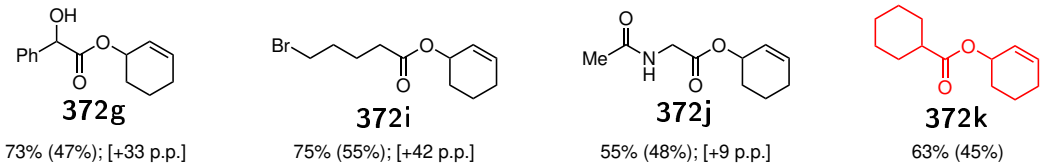
7.5 Substrate scope with NaF

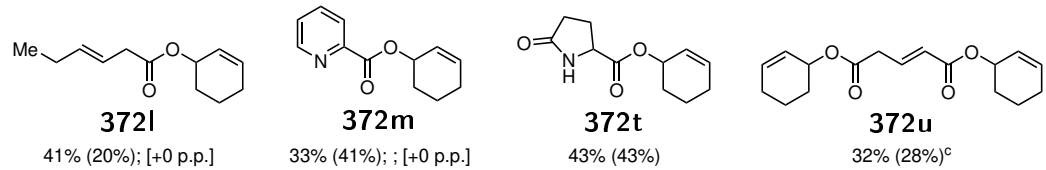
Following the success of the base screening experiments, the substrate scope of the green-light mediated nucleophilic allylic substitution reaction was repeated with one equivalent of NaF as an additive. Similar to the previous substrate scope, one equivalent of selenide **370a** was treated with three equivalents of a carboxylic acid nucleophile in the presence of one equivalent of NaF in HFIP (1.0 M) under green-light irradiation (Table 7.18). The addition of NaF improved the yields of the products in most cases. In the case of product **372c**, the yield of the product increased from 49% previously to 64% with NaF (Cf. Table 7.12). Products **372g** and **372i**,**j** also showed a drastic increase from their previous yields of 40% to 73%, 33% to 75%, and 46% to 55%, respectively. With hex-3-enoic acid (**373h**) and picolinic acid (**373e**), however, no change was observed in the yields of the corresponding substitution products **372l** and **372m**. Pyroglutamic acid (**373i**) and glutaconic acid (**373j**) gave the corresponding products **372t** and **372u** in moderate yields of 43% and 32%, respectively. For products **372b**,**d**–**f**,**k** the yields with NaF showed an increase of less than five percentage points when compared to the reactions performed without NaF. These products were therefore not isolated, and the yields were carried over from the previous substrate scope (Cf. Section 7.3).

Table 7.18: Substrate scope of the green-light mediated nucleophilic substitution reaction with one equivalent of NaF. Increase of yield in percentage points (p.p.) from the corresponding reaction without NaF (cf. Table 7.12) in brackets.









[a] NMR yield, standard: dimethyl sulfone or 1,3-dinitrobenzene
[b] Yields of structures shown in red carried over from the substrate scope without NaF.
[c] Reaction was performed using one equivalent of glutaconic acid (**373j**) and two equivalents of NaF.

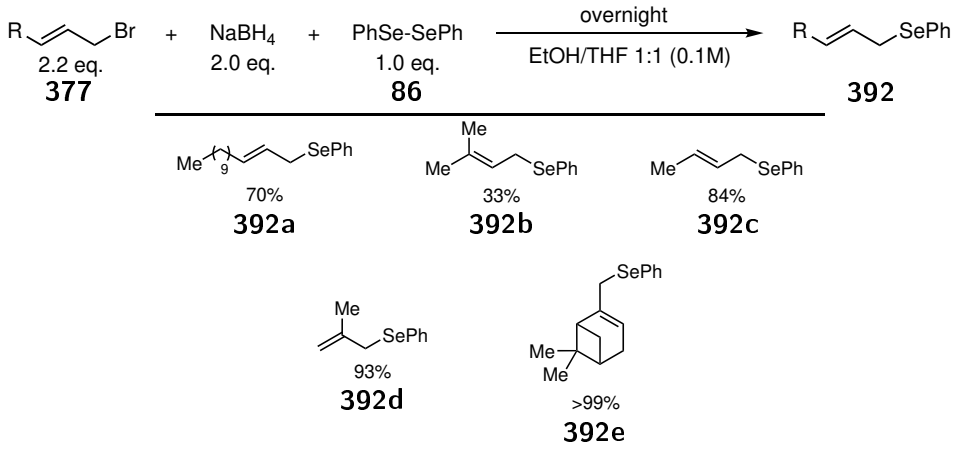
7.6 Substrate scope: selenides

7.6.1 Synthesis of primary selenides

In the second part of the substrate scope of the green-light mediated nucleophilic substitution reaction, various allylic selenides were to be tested as substrates. Commercially available primary allylic alcohols **391a** and **391b** were converted to their corresponding bromides **377b** and **377c** *via* the Appel reaction (Equation 7.1).[111] The bromides were then converted to the corresponding selenides using the previously described method with $NaBH_4$ and diphenyl diselenide (**86**) in EtOH or a mixture of EtOH and THF (Subsection 7.2.7).[225] Additionally, some commercially available allylic bromides were also converted to the corresponding selenides using the same method (Table 7.19).

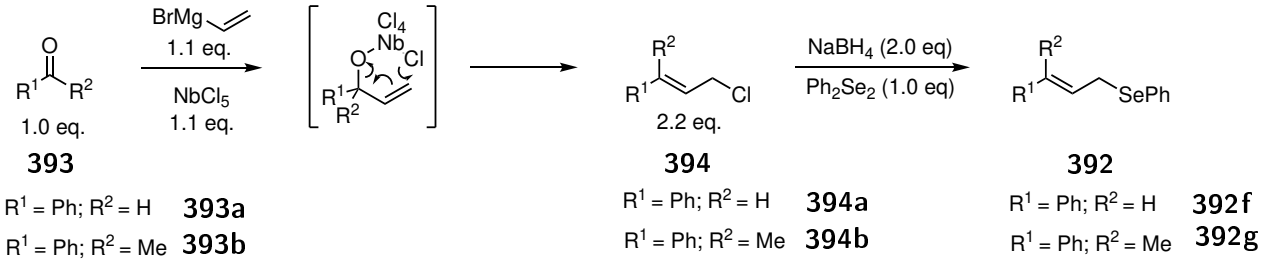
(7.1)

Table 7.19: Synthesis of primary allylic selenides starting from allylic bromides.



Due to both the lack of appropriate options and high costs of primary allylic alcohols, a new method to synthesize allylic selenides starting from commercially available ketones was employed. Ketones **393** were converted to the corresponding allylic alcohols **391** using a Grignard reagent.[230] The addition of $NbCl_5$ facilitates a rearrangement which generates

the corresponding allylic chlorides **394** (Scheme 7.3). Allylic chloride **394a** was identified from the proton NMR spectrum by the two olefinic proton signals between 6.7 ppm and 5.7 ppm, and from the methylene group protons at 4.25 ppm, respectively. Ketone **393b** was converted completely to the corresponding chloride **394b**, identified also from the proton NMR spectrum by the olefinic proton multiplet between 6.5 ppm and 6.2 ppm, and by the methylene group multiplet between 5.4 ppm and 5.2 ppm, respectively. The chlorides could be used without further purification to synthesize the respective selenides **392f** and **392g** using $NaBH_4$ and diphenyl diselenide (**86**), obtained with a yield of 30% and 41% over two steps, respectively.



Scheme 7.3: Synthesis of allylic selenides starting from commercially available ketones using $NbCl_5$.

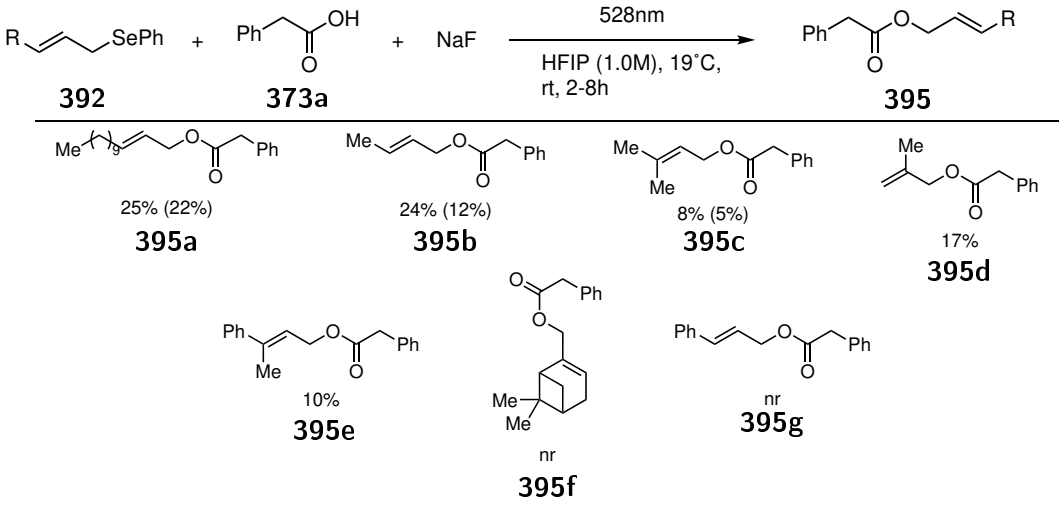
7.6.2 Photoreaction using primary allylic selenides

With the different selenides in hand, the green light-mediated nucleophilic substitution reaction was performed with one equivalent of the allylic selenide (**392**), three equivalents of standard nucleophile phenyl acetic acid (**373a**) and one equivalent of NaF in HFIP (1.0M) (Table 7.20).

Substitution product **395a** was isolated with a low yield of 22%. The reaction showed a conversion of only 75% despite a reaction time of 24h. Additionally, two singlets were observed at 9.5 ppm in the crude proton spectrum, which correspond to the chemical shift characteristic of an aldehyde proton. Product **395b** was also obtained in a low yield of 24%. Similar to the previous case, incomplete conversion of the starting material (63%) and low intensity aldehyde signals at 9.5 ppm were observed in the crude spectrum. Product **395c** was isolated as a mixed fraction containing NMR standard 1,3-dinitrobenzene, with a low yield of around 5%, despite full conversion of the starting material. The photoreaction with selenide **392d** showed 73% conversion after 5h but only 17% NMR yield of product **395d**. No other side products could be identified from the crude spectrum. Product **395e** was also obtained in a poor yield of 10%, despite full conversion of the starting material.

Even in this case, signals at 10.11 ppm were found in the crude proton NMR spectrum. However, no other signals belonging to a possible aldehyde side product could be clearly identified. With selenide **392e**, no clear signals, belonging either to the starting material, or to side products, could be identified. Apart from a triplet at 9.82 ppm, belonging possibly to the corresponding aldehyde, no other products could be isolated. Product **395g** was also formed only in trace amounts.

Table 7.20: Substrate scope of the green-light mediated nucleophilic substitution reaction using different primary allylic selenides.



[a] NMR yield, standard: 1,3-dinitrobenzene, isolated yield in parentheses.

The above results indicate that longer reaction times lead to competing side reactions, such as the incorporation of an oxygen atom into the carbon chain to give an aldehydic side product, as was observed in almost all the cases. In the photoreaction using selenide **392a**, apart from product **395a**, signals for aldehyde (**396**), and ketone (**397**) were observed (Figure 7.4). The NMR shifts observed in the crude spectrum were compared with those of the pure aldehyde and ketone isolated by A. Tiefel in a similar reaction. However, none of these side products could be isolated. This may have been due to the different solvents used for column chromatographic purification of the crude product mixture, with a mixture of PE and EA used in the former case, and PE and toluene in the latter. Additionally, the formation of the regioisomer could not be confirmed due to a strong overlapping of signals. The formation of these side products may be explained *via* the homolytic cleavage of the C−Se bond resulting in the formation of allylic radical intermediate **398** and its resonance structure **399** (Scheme 7.4a). Radical **398** can react with the oxygen present in the air atmosphere to form peroxide radical **400**, which can then react in one of two possible ways. In the first scenario, the peroxide radical can

combine with the phenylselenide radical (**288**) to form peroxide intermediate **401**, which, in the presence of a base (NaF) can undergo a Kornblum-like fragmentation[231] to form aldehyde **402** and phenylselenenic acid (PhSeOH). It was not possible to infer from the analytical data if the PhSeOH remained in the reaction mixture or reacted further with oxygen to form other Se-containing species such as diphenyldiselenide (**86**), among others. Alternatively, peroxide radical **400** may react with another allylic radical **398** to form a dimer. A Kornblum-like fragmentation of this species would result in the formation of equal amounts of aldehyde **402** and the corresponding allylic alcohol. However, no signals belonging to the allylic alcohol could be identified, making it unlikely that aldehyde **402** was formed this way. The formation of ketone **397** may be explained similarly starting from radical **399**. In the crude spectrum of the photoreaction with cinnamic acid (**373k**) as the nucleophile, aldehyde proton signals belonging both to benzaldehyde (**402a**) and cinnamaldehyde (**402b**) were observed. The formation of these side products can also be attributed to radical intermediates reacting with oxygen, as explained above.

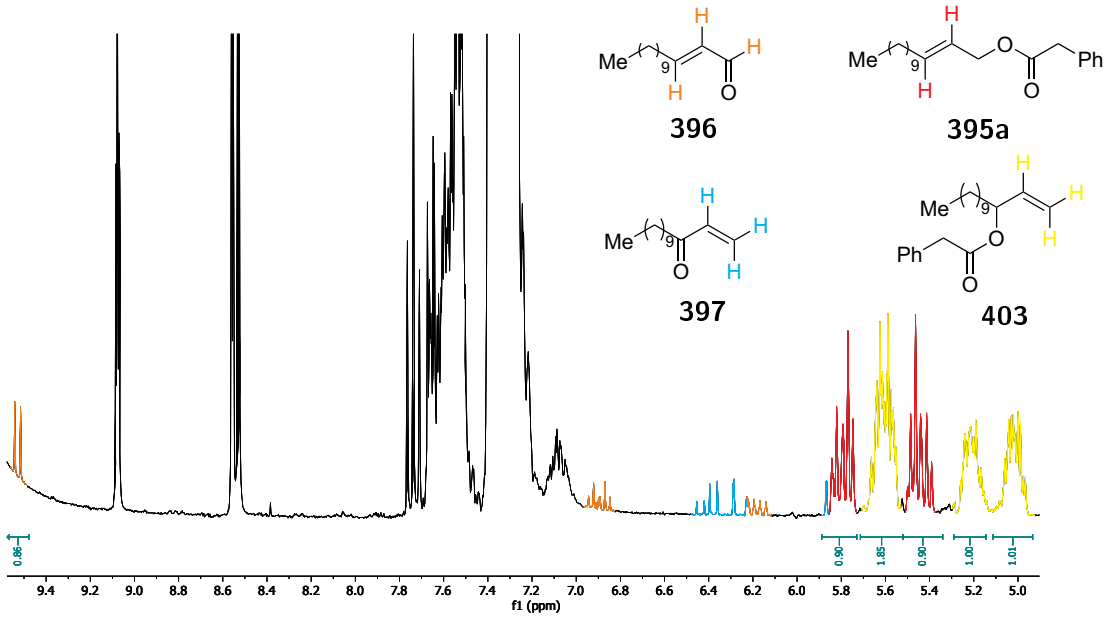
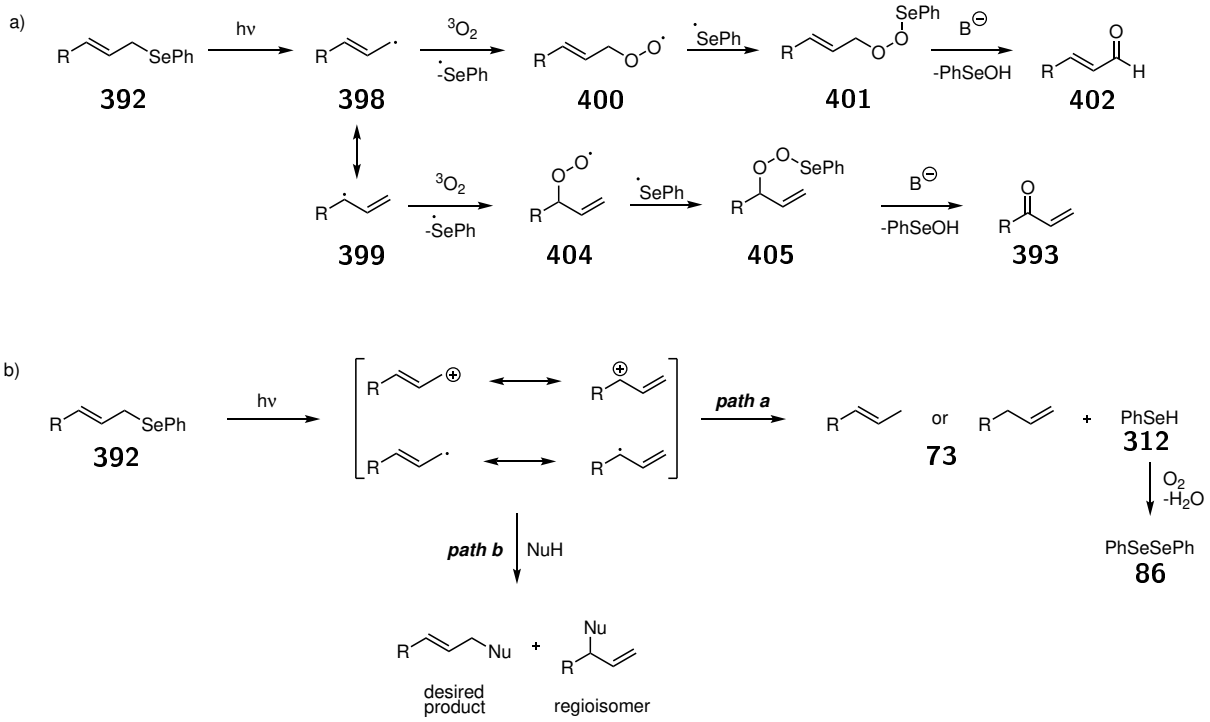


Figure 7.4: Crude proton spectrum of the photoreaction using **392a** showing all observed products: side products aldehyde **396** (orange), ketone **397** (blue), regioisomer **403** (yellow), and desired product **395a** (red).

Another possible side reaction which explains the high conversion and low product yield is the dehydrodeselenylation of the selenide substrate (Scheme 7.4b, path a). The cleavage of the C – Se bond results in the formation of phenylselenol (**312**) and the remaining carbon chain fragment. The phenylselenol is oxidised to diphenyl diselenide (**86**), and the carbon chain, which in most of the above cases is volatile due to low molecular weight, is lost



Scheme 7.4: Competing reactions in the green-light mediated S_N reaction using primary allylic selenides showing a) Kornblum-like fragmentation to give the aldehyde side product and b) dehydrodeselenylation reaction (path a) and isomerization of the intermediate to regioisomeric substitution products (path b).

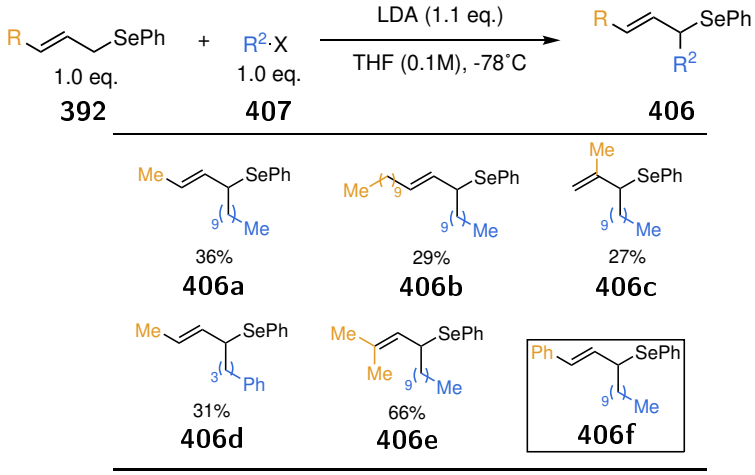
during the work-up. The radical/cationic intermediates formed as a result of the cleavage of the C−Se bond in primary allylic selenides can also undergo isomerization to give the better-stabilised secondary radical/cationic intermediate. The attack of the nucleophile on the isomerized intermediate to give the substitution product regioisomeric to those isolated can explain the descrepancy between high conversion and low yields observed thus far (Scheme 7.4b, path b). However, no characteristic terminal olefinic signals could be identified in any of the crude spectra due to other overlapping signals to confirm this possibility. Furthermore, the multiplet expected for the tertiary allylic proton could also not be identified in any of the reactions.

7.6.3 Synthesis of secondary selenides

As the substitution reaction with primary selenides gave the corresponding substitution products in poor yields, it was proposed that secondary selenides similar to cyclohexene phenylselenide (**370a**) could yield products in higher yields due to a better stabilisation of the radical/ionic intermediate at the secondary carbon centre. Therefore, secondary allylic

phenylselenides **406** were synthesized from primary allylic selenides **392** and a primary alkyl halide using LDA as base (Table 7.21). The desired secondary allylic selenides were obtained in yields between 27% and 66%.

Table 7.21: Synthesis of secondary allylic selenides starting from primary allylic selenides and alkyl/aryl halides. Encased product synthesized by A. Tiefel.



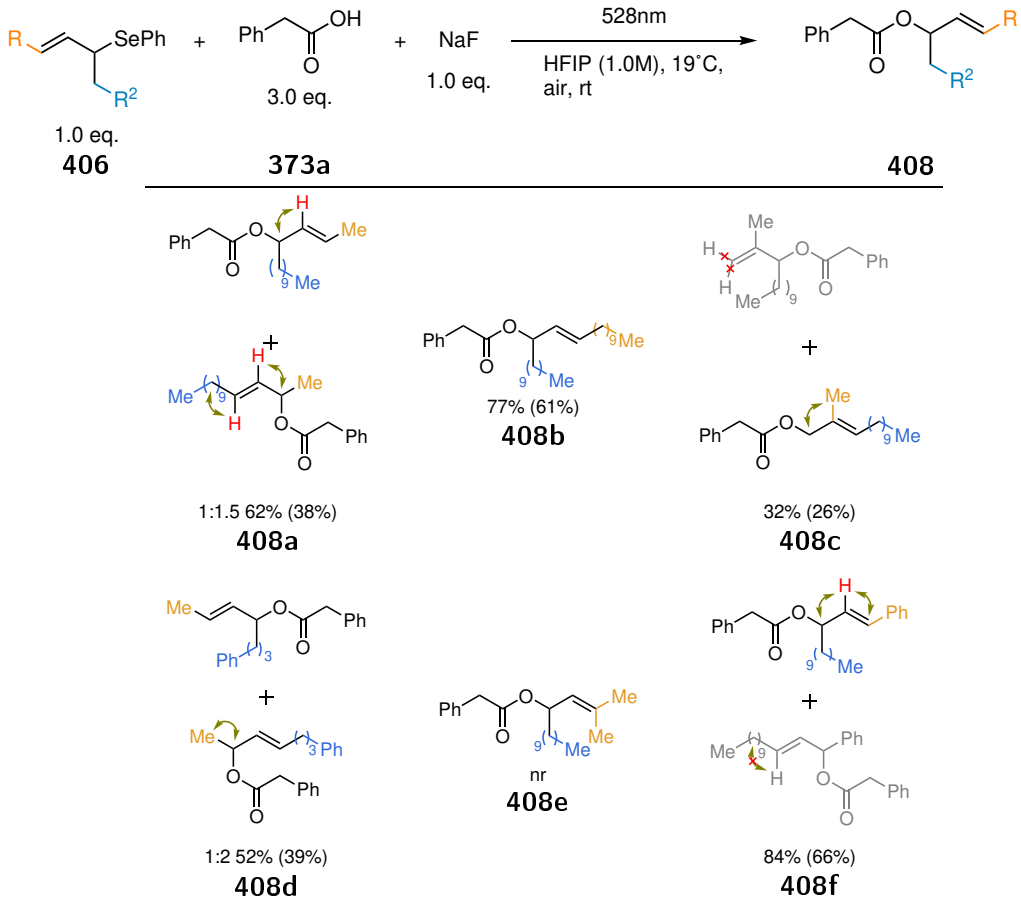
7.6.4 Substrate scope using secondary allylic selenides

The optimized photoreaction was performed using one equivalent of the secondary allylic selenide (**406**), three equivalents of phenyl acetic acid (**373a**) as the nucleophile and one equivalent of NaF in HFIP (1.0M) (Table 7.22).

As hypothesized, the photoreaction with secondary allylic selenides **406** gave much higher yields of the corresponding substitution products **408** than with primary allylic selenides **392**. Substitution products **408** were obtained in yields of up to 84%, as regioisomeric mixtures in certain cases (Table 7.22). Product **408a** was formed as a 1:1.5 mixture of regioisomers with a 62% yield overall, with the isomer containing the methyl group in the vinylic position being the minor isomer. The result was deduced from the HSQC and HMBC spectra, where a coupling of an olefinic proton (shown in red) with both the carbinolic proton as well as with a methylene group was observed. Product **408b** was formed as a single isomer, due to the symmetric nature of the corresponding selenide (**406b**), with a good yield of 77%. With selenide **406c** containing a terminal double bond, only the regioisomer containing the double bond internally was isolated, with a low yield of 32% (**408c**). The absence of the substitution product with the double bond in the terminal position (**408c**, grey, Table 7.22) was confirmed by the absence of NMR signals for both the vinylic protons as well as the vinylic carbon atom. Furthermore, it was deduced from

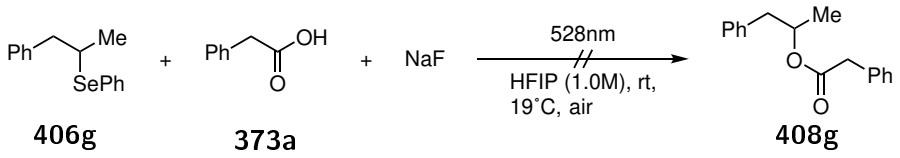
the HSQC and HMBC spectra that the methyl group in the vinylic position coupled with a neighbouring methylene group, which is only possible in the isomer that was isolated, indicated by the two-sided arrow in the structure. The absence of the either isomer could be due to the reduced stabilization of the cationic/radical intermediate on a primary carbon centre, which would be formed as a result of an isomerization of the terminal double bond. In comparison, the cationic/radical intermediate formed with the other secondary selenides shown in Table 7.21 is always at least on a secondary carbon atom. These results indicate that the outcome of the nucleophilic substitution reaction depends strongly on the stabilization of the reaction intermediate, with higher product yields obtained when the radical/ionic intermediate is found on a secondary carbon when compared to a primary carbon centre. Selenide **406d** gave the corresponding substitution products **408d** as a 1:2 mixture of regioisomers, wherein the structure with the more substituted double bond was the major product. This was confirmed *via* HMBC and HSQC spectra, where the carbinolic carbon at 70 ppm shows coupling with the protons of the methyl group at 1.28 ppm, in addition to coupling with the olefinic protons. Furthermore, the coupling constant of 6.7 Hz exhibited by methyl group protons is characteristic of a ^{3}J H−H coupling, exhibited here by the coupling between the carbinolic proton and the protons of the methyl group. Selenide **406e**, containing two vicinal methyl groups did not undergo any transformation. This could be due to the greater steric hindrance posed by the two methyl groups towards the incoming nucleophile. Selenide **406f** gave the corresponding product **408f**, containing the double bond in the benzylic position as the only substitution product. The absence of the other isomer (**408f**, grey, Table 7.22) was confirmed *via* HMBC and HSQC spectra, where no coupling between an olefinic proton and a methylene proton was observed. Additionally, no corresponding doublet of triplets for such an olefinic proton was observed in the proton NMR spectrum. The observed doublet of doublet at 6.0 ppm confirms the position of the double bond at the benzylic position, where the olefinic proton undergoes coupling with the other olefinic proton and the carbinolic proton.

Table 7.22: Substrate scope of the green-light mediated nucleophilic substitution reaction using secondary allylic selenides.



[a] NMR yield, standard: 1,3-dinitrobenzene, isolated yield in parentheses.

As a final control experiment, substrate **406g** was reacted with phenylacetic acid (**373a**) under reaction conditions used for all other optimization and control reactions. The rationale behind this was to verify once again the necessity of a double bond for the SN reaction, this time in the presence of NaF, as a similar reaction (cf. Section 7.3) using selenide **378** with the naphthyl rest was performed without NaF. After three hours, selenide **406g** showed a poor conversion of 7%, indicating once again, that under the optimized reaction conditions, a secondary allylic system was vital to the success of the green-light mediated SN reaction.

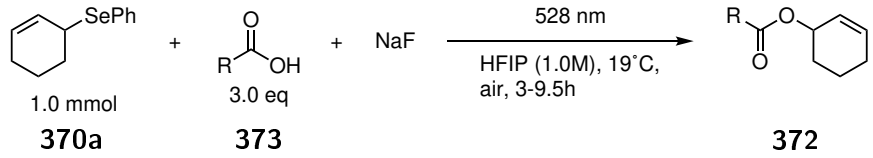


(7.2)

8 Summary and outlook

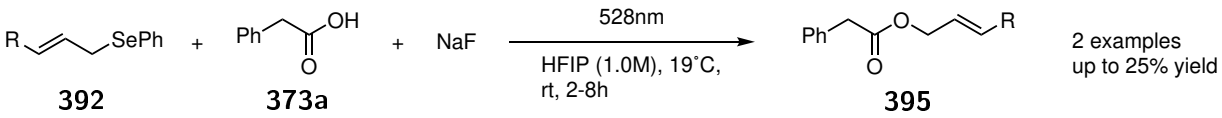
The aim of this project was to apply the strategy developed by Park and co-workers[223] to develop a new method for a nucleophilic substitution reaction at a Se-centre, *via* oxidative activation of the Se-centre through non-covalent interactions. The strategy included combining the ability of the Se-centre to participate in the formation of chalcogen- and hydrogen bonds with the photosensitive nature of the C−Se bond.

To our delight, initial experiments with allylic selenide **370a** and phenyl acetic acid (**373a**) as nucleophile gave the corresponding substitution product **372b** in 82% yield. The optimized conditions were determined to be 3.0 equiv of carboxylic acid as nucleophile and 1.0 equiv of NaF for 1.0 equiv of the allylic phenyl selenide in a 1.0 M solution in HFIP, under green-light irradiation (528 nm). The optimized conditions were applied to selenide **370a** and thirteen commercially available carboxylic acid nucleophiles **373**. The corresponding substitution products **372** were obtained in yields of up to 82% (Equation 8.1).



(8.1)

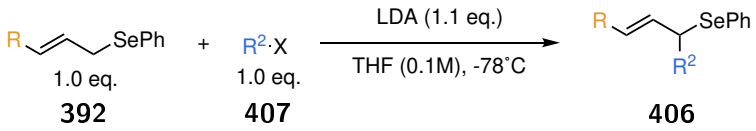
In the second part of this project, various primary allylic phenyl selenides **392** were tested as substrates for the titular transformation using phenyl acetic acid (**373a**) as the nucleophile (Equation 8.2). The corresponding substitution products were obtained in low yields of up to 25%. Only two products **395a** and **395b** could be isolated, with the other products obtained in yields of less than 10%. Due to a strong overlapping of signals in the crude spectra, it was not possible to ascertain if regioisomeric mixtures were formed.



(8.2)

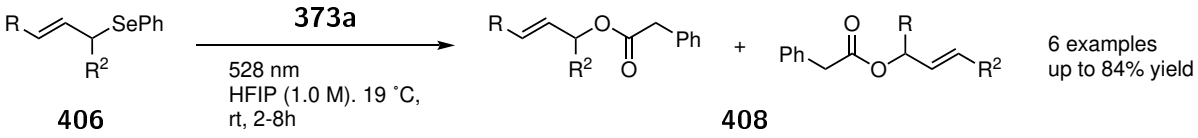
Therefore, the next step was to use secondary allylic phenylselenides **406** as substrates for the optimized reaction. Primary allylic selenides **392** were treated with LDA and

alkyl bromides **407** to give the desired secondary allylic selenides in yields of up to 66% (Equation 8.3). A total of five substrates were synthesized.



(8.3)

The titular transformation using these substrates gave the corresponding substitution products **408** in yields of up to 84%, as a mixture of regioisomers in some cases (Equation 8.4). In the case of sterically hindered selenide **406e**, no product formation was observed.



(8.4)

The success of the project has paved a way for nucleophilic substitution reactions at allylic selenides using a never-seen-before strategy. As the method is still in its infancy, it is crucial to conduct mechanistic investigations to gain a thorough understanding of the interplay of the non-covalent interactions between the solute and the solvent, and the green-light irradiation. The role played by NaF must also be identified. It can be speculated that NaF acts as a base to enhance the nuclophilicity of the carboxylic acid. Future investigations should also work on broadening the scope of the method to include other heteroatom-containing nucleophiles apart from oxygen, such as nitrogen and sulfur. Another aspect that can be investigated further is the selenium-containing substrate. The requirement of the allylic system in the success of the transformation must be investigated, in addition to exploring other Se-containing compounds as potential substrates, such as simple secondary and tertiary phenylselenides. Furthermore, developing a catalytic version of the transformation using a simple selenium catalyst, such as diphenyl diselenide, would further contribute to the grow field of Se-catalyzed transformations.

9 Experimental part

9.1 General Methods

Preparative Methods

If not indicated otherwise, all reactions were performed in heat-dried glassware, under a nitrogen atmosphere. Dry solvents were distilled and stored over molecular sieves under nitrogen or taken from an SPS (THF, toluene). If not mentioned otherwise, commercially available chemicals were used directly without further purification. For reactions at low temperatures, either an ice bath, or an acetone/dry ice freezing mixture was used. For reactions with a syringe pump, an LA-100 from *Landgraf Laborsysteme HLL* was used. For reactions at higher temperatures, a silicon oil bath or a thermostat CORDIO CD-601F from *Julabo* were used. Photo experiments were performed at $\lambda = 528$ nm using commercially available green LED strips in custom-made, water-cooled reaction blocks.

Chromatographic Methods

Thin Layer Chromatography (TLC): Analytical thin layer chromatography was performed on TLC plates from *MACHEREY NAGEL*, TLC plates Alugram® Sil G/UV 254. Visualization of the developed chromatogram was performed by fluorescence quenching at 254 nm and staining with *p*-anisaldehyde or potassium permanganate solutions.

Column Chromatography: Column chromatographic separations were performed on Merck Silica 60 (0.063-0.200 mm, 70-230 mesh ASTM) using forced flow.

Instrumental Analysis

IR Spectra: IR spectra were measured on a Cary 360 FT-IR Spectrometer.

NMR Spectra: NMR spectra were recorded at 300 MHz (^{1}H) and 76 MHz (^{13}C) with a *Bruker Avance* 300 in $CDCl_3$ solutions, if not specified otherwise. Chemical shifts are reported as δ-values in ppm relative to the residual peak of the deuterated solvent or its carbon atom. For characterization of the multiplicities, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), hept (heptet), m (multiplet), dd (doublet of doublet), td (triplet of doublet), and analogues. The coupling constants J are reported in hertz (Hz). Signals appearing at 0.8 ppm and 1.45 ppm in some of the ^{1}H spectra arise from the plastic syringes used to measure the respective NMR solvent and as such do not have any influence on the isolated yield of the products.

Mass Spectra: ESI and ESI-HRMS were measured on a Agilent Q-TOF 6540 UHD or Jeol Accu TOF GCX or ThermoQuest Finnigan TSQ 7000.

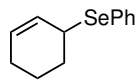
Melting Points: Melting Points were measured on a *Büchi* 540 apparatus or a *Krüss* M5000. The values were not corrected.

9.2 Synthesis of selenides

9.2.1 Synthesis of primary selenides

General procedure **A** for the synthesis of **primary selenides**: Diselenide (1.00 eq) was dissolved in a solvent in a two-necked flask under N_2 atmosphere and cooled to 0°C. $NaBH_4$ (1.50 equiv.) was added portionwise. The yellowish-brown solution was stirred at 0°C until a colourless solution was formed. Bromide (**377**) (2.00 equiv.) was added dropwise at 0°C. The reaction was warmed to rt and stirred until completion of reaction was observed *via* TLC control. The reaction was quenched with water and extracted with EtOAc (3*10.0 mL). The combined organic phases were washed with brine, dried over an. Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography (*n*-pentane) to give the desired product (**392**).[\textit {J}ana.2019]

cyclohex-2-en-1-yl(phenyl)selane **(370a)**

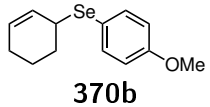


370a

Following general procedure **A**: **86** (3.12 g, 10.0 mmol, 1.00 equiv.) in EtOH (35.0 mL, 0.1 M); 3-bromocyclohex-1-ene **377a** (3.54 g, 22.0 mmol, 2.20 equiv.); $NaBH_4$ (0.945 g, 25.0 mmol, 2.50 equiv.); column chromatography (*n*-pentane);colourless to yellow oil; 4.66 g, 19.6 mmol, 89%.

$\mathbf{R}_f$ = 0.74 (*n*-pentane); IR (neat): ν [cm^{-1}] = 693, 738, 865, 999, 1021, 1070, 1178, 1252, 1439, 1476, 1580, 2863, 2930, 3027, 3056; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.64–7.46 (m, 2H), 7.33–7.13 (m, 3H), 5.93–5.80 (m, 1H), 5.81–5.69 (m, 1H), 4.03–3.92 (m, 1H), 2.11–1.81 (m, 5H), 1.70–1.55 (m, 1H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 134.1, 130.7, 129.8, 129.0, 127.8, 127.3, 41.2, 29.4, 24.9, 19.7; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 394.9; **HRMS**: (EI-MS) [$C_{12}H_{14}Se$] ($[M]^{+\bullet}$), obs.: 238.0252, calcd.: 238.0261.

cyclohex-2-en-1-yl(4-methoxyphenyl)selane **(370b)**



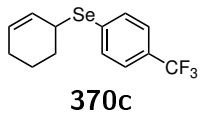
370b

Following general procedure **A**: **389** (1.86 g, 5.0 mmol, 1.0 equiv.) in EtOH (15.0 mL); 3-bromocyclohex-1-ene **377a** (1.77 g, 11.0 mmol, 2.20 equiv.); $NaBH_4$ (0.472 g, 12.5 mmol, 2.50 equiv.); column chromatography (*n*-pentane/toluene 100:0 to 50:1); colourless to yellow oil; 2.12 g, 7.94 mmol, 72%.

$\mathbf{R}_f$ = 0.10 (*n*-pentane/tol 10:1); IR (neat): ν [cm^{-1}] = 731, 820, 865, 1029, 1100, 1170,

1241, 1282, 1402, 1439, 1487, 1588, 2833, 2930, 3023; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.58 – 7.46 (m, 2H), 6.87 – 6.76 (m, 2H), 5.74 (dtd, J = 9.7, 3.7, 1.2 Hz, 1H), 2.07 – 1.79 (m, 5H), 1.71 – 1.52 (m, 1H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 267.2, 159.5, 137.0, 129.5, 128.0, 120.5, 114.6, 55.3, 41.8, 29.3, 24.9, 19.6.; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 395.1; **HRMS**: (EI-MS) [$C_{13}H_{16}OSe$] ([M]$^{+\bullet}$), obs.: 268.0353, calcd.: 268.0366.

cyclohex-2-en-1-yl(4-(trifluoromethyl)phenyl)selane **(370c)**

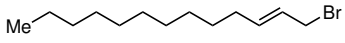


370c

Following general procedure **A**: **390** (2.24 g, 5.00 mmol, 1.00 equiv.) in EtOH (15.0 mL); 3-bromocyclohex-1-ene **377a** (1.77 g, 11.0 mmol, 2.20 equiv.); $NaBH_4$ (0.472 g, 12.5 mmol, 2.05 equiv.); column chromatography (n-pentane); colourless to yellow oil; 1.82 g, 6.00 mmol, 54%.

$\mathbf{R}_f$ = 0.35 (n-pentane); IR (neat): ν [cm^{-1}] = 686, 734, 820, 865, 1014, 1074, 1118, 1163, 1320, 1398, 1603, 2837, 2930, 3027; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.65 – 7.59 (m, 2H), 7.53 – 7.47 (m, 2H), 5.83 (q, J = 2.7 Hz, 2H), 4.09 (dt, J = 6.7, 3.2 Hz, 1H), 2.14 – 2.00 (m, 3H), 1.98 – 1.80 (m, 2H), 1.73 – 1.58 (m, 1H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 136.3, 132.9, 130.6, 126.9, 125.8, 125.7, 125.7, 125.6, 122.4, 41.1, 29.4, 24.9, 19.6; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 406.1, 445.8 (**390**, impurity); **HRMS**: (EI-MS) [$C_{13}H_{13}SeF_3$] ([M]$^{+\bullet}$), obs.: 302.0154, calcd.: 302.0156.

(E)-1-bromotridec-2-ene **(377b)**

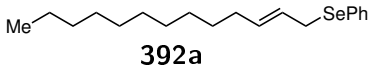


377b

To a mixture of (E)-1-bromotridec-2-en-1-ol (**391a**) (1.11 g, 5.90 mmol, 1.00 equiv.) and PPh_3 (1.60 g, 6.00 mmol, 1.00 equiv.) in DCM (20.0 mL) cooled to 0°C was added NBS (1.20 g, 6.60 mmol, 1.10 equiv.) in one portion. The mixture was stirred at 0°C for 20 min and overnight at rt. n-pentane was added until a white precipitate appeared, which was filtered over a silica plug. Concentration of the filtrate *in vacuo* gave bromide **377b** as a colourless oil (1.40 g, 5.20 mmol, 88%).

$\mathbf{R}_f$ = 0.88 (PE); IR (neat): ν [cm^{-1}] = 723, 924, 962, 1204, 1461, 1662, 2363, 2855, 2922; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 5.84 – 5.59 (m, 2H), 3.95 (d, J = 7.0 Hz, 2H), 2.05 (q, J = 6.7 Hz, 2H), 1.26 (s, 16H), 0.91 – 0.83 (m, 3H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 136.9, 126.2, 33.8, 32.1, 31.9, 29.6, 29.6, 29.5, 29.4, 29.1, 28.8, 22.7, 14.1; **HRMS**: (EI-MS) [$C_{13}H_{25}Br$] ([M]$^{+\bullet}$), obs.: 260.1141, calcd.: 260.1140.

(E)-phenyl(tridec-2-en-1-yl)selane (392a)

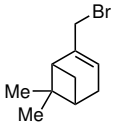


392a

Following general procedure **A**: **86** (4.30 g, 13.7 mmol, 1.00 equiv.) in EtOH/THF (1:1) (200 mL); **377b** (4.10 g, 30.0 mmol, 2.20 equiv.); $NaBH_4$ (1.10 g, 24.3 mmol, 2.00 equiv.); column chromatography (*n*-pentane); colourless to yellow oil; 3.80 g, 17.9 mmol, 59%.

$\mathbf{R}_f$ = 0.55 (*n*-pentane); IR (neat): ν [cm^{-1}] = 690, 734, 962, 1021, 1074, 1178, 1439, 1461, 1580, 2851, 2922, 3056; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.55 – 7.44 (m, 2H), 7.35 – 7.14 (m, 3H), 5.57 (dtt, J = 14.9, 7.4, 1.3 Hz, 1H), 5.40 (ddd, J = 15.0, 7.3, 6.1 Hz, 1H), 3.51 (dt, J = 7.5, 0.7 Hz, 2H), 1.96 (q, J = 6.7 Hz, 2H), 1.33 – 1.18 (m, 16H), 0.95 – 0.85 (m, 3H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 134.0, 133.4, 130.3, 128.8, 127.0, 125.7, 32.3, 32.0, 30.3, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 22.7, 14.2; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 332.2; **HRMS**: (EI-MS) [$C_{19}H_{30}Se$] ([M]$^{+\bullet}$), obs.: 334.1544, calcd.: 334.1534.

2-(bromomethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (377c)

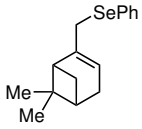


377c

To a solution of (6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methanol (**391b**) (1.52 g, 10.0 mmol, 1.00 equiv.) in MeCN/DCM 6:1 (15.0 mL + 3.0 mL) cooled to 0°C was added PPh_3 (3.41 g, 13.0 mmol, 1.30 equiv.). CBr_4 (4.31 g, 13.0 mmol, 1.30 equiv.) was added in one portion. The mixture was slowly warmed to rt and stirred overnight. The reaction mixture was concentrated *in vacuo* and purified *via* column chromatography to give the desired product as a colourless oil. As the product was found to be volatile, the eluent was not evaporated fully.

$\mathbf{R}_f$ = 0.81 (*n*-pentane); **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 6.83 (s, 1H), 5.67 (td, J = 2.9, 1.6 Hz, 2H), 4.12 (qd, J = 7.1, 0.7 Hz, 2H) (EtOAc), 3.94 (h, J = 1.1 Hz, 4H), 2.44 (dt, J = 8.8, 5.6 Hz, 2H), 2.32 – 2.17 (m, 5H), 2.09 (dtt, J = 5.6, 4.0, 2.5 Hz, 2H) (EtOAc), 1.34 – 1.22 (m, 7H), 0.82 (s, 5H) (EtOAc); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 144.2, 123.2, 60.4, 44.9, 40.3, 37.9 (d, J = 7.4 Hz), 31.5 (d, J = 18.6 Hz), 26.0, 21.1 (d, J = 4.7 Hz), 14.2, 9.8; **HRMS**: (EI-MS) [$C_{10}H_{15}Br$], obs.: 214.0348, calcd.: 214.0351.

((6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)(phenyl)selane (392e)

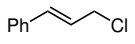


392e

Following general procedure **A**: **86** (1.42 g, 4.50 mmol, 1.00 equiv.) in EtOH (20.0 mL); **377c** (2.15 g, 10.0 mmol, 2.20 equiv.); $NaBH_4$ (0.430 g, 11.4 mmol, 2.50 equiv.); column chromatography (*n*-pentane); yellow oil; quantitative yield.

$\mathbf{R}_f$ = 0.80 (*n*-pentane); IR (neat): ν [cm^{-1}] = 690, 731, 794, 857, 965, 1096, 1182, 1264, 1297, 1364, 1435, 1476, 1580, 2829, 2915, 2982, 3023, 3056; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.56 – 7.47 (m, 1H), 7.33 – 7.23 (m, 2H), 5.39 (tt, J = 3.1, 1.6 Hz, 0H), 3.66 – 3.51 (m, 1H), 2.42 (dt, J = 8.7, 5.6 Hz, 1H), 2.31 – 2.19 (m, 1H), 2.17 – 2.03 (m, 1H), 1.12 (d, J = 8.5 Hz, 0H), 0.83 (s, 2H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 144.2, 123.2, 60.4, 44.9, 40.3, 37.9 (d, J = 7.4 Hz), 31.5 (d, J = 18.6 Hz), 26.0, 21.1 (d, J = 4.7 Hz), 14.2, 9.8; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 296.53; **HRMS**: (EI-MS) [$C_{16}H_{20}Se$], obs.: 288.0752, calcd.: 288.0751.

(E)-(3-chloroprop-1-en-1-yl)benzene (394a)

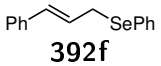


394a

To a solution of benzaldehyde (**393a**) (0.530 g, 5.00 mmol, 1.00 equiv.) in THF (6.00 mL), cooled to 10°C, was added vinyl magnesiumbromide (0.7 M in THF, 8.50 mL, 6.00 mmol, 1.20 equiv.) dropwise. The solution was stirred at 10°C for 30 min. 1,4-dioxane (24.0 mL) and $NbCl_5$ (3.38 g, 12.5 mmol, 2.50 equiv.) were added and the solution was stirred for 10 min at 10°C. The reaction was quenched by pouring onto 2 M HCl and was extracted with EtOAc (3*15.0 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The crude mixture was used for the next step without further purification (1.64 g).

cinnamyl(phenyl)selane (392f)

Method 1:



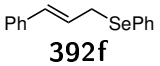
392f

Following general procedure **A**: **86** (1.53 g, 4.89 mmol, 1.00 equiv.) in EtOH (25.0 mL); **394a** (1.64 g, 10.8 mmol, 2.20 equiv.); $NaBH_4$ (0.462 g, 12.2 mmol, 2.50 equiv.); column chromatography (*n*-pentane); yellow oil; 0.407 g, 1.48 mmol, 30% over two steps.

$\mathbf{R}_f$ = 0.54 (*n*-pentane/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 686, 723, 805, 883, 913, 962, 1018, 1070, 1096, 1167, 1208, 1305, 1327, 1375, 1472, 1573, 1655, 1752, 1804, 1871,

2117, 2345, 2855, 2922, 3023, 3079; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.58 – 7.46 (m, 2H), 7.33 – 7.12 (m, 8H), 6.40 – 6.17 (m, 2H), 3.68 (d, J = 7.0 Hz, 2H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 136.9, 134.0, 132.1, 129.9, 129.0, 128.5, 127.4 (d, J = 7.1 Hz), 126.3, 125.9, 30.8; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 341.17; **HRMS**: (EI-MS) [$C_{15}H_{14}Se$], obs.: 274.0247, calcd.: 274.0255.

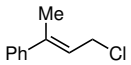
Method 2:



392f

Following general procedure **A**: **86** (4.30 g, 13.7 mmol, 1.00 equiv.) in EtOH/THF 1:1 (200 mL); **377d** (4.50 mL, 30.0 mmol, 2.20 equiv.); $NaBH_4$ (1.00 g, 27.3 mmol, 2.00 equiv.); column chromatography (*n*-pentane); yellow oil; 5.30 g, 19.5 mmol, 65%.

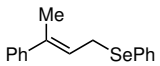
(E)-(4-chlorobut-2-en-2-yl)benzene (394b)



394b

To a solution of acetophenone (**393b**) (1.17 mL, 10.0 mmol, 1.00 equiv.) in THF (12.0 mL), cooled to 0°C, was added vinyl magnesiumbromide (0.7 M in THF, 15.7 mL, 11.0 mmol, 1.10 equiv.) dropwise. The solution was stirred at 0°C for 15 min. 1,4-dioxane (50.0 mL) and $NbCl_5$ (2.97 g, 11.0 mmol, 1.10 equiv.) were added and the solution was stirred for 10 min at 0°C. A colopur change from yellow to dark blue was observed. The reaction was quenched by pouring onto 2 M HCl and was extracted with EtOAc (3*15.0 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The crude mixture was used for the next step without further purification (1.67 g).

(E)-phenyl(3-phenylbut-2-en-1-yl)selane (392g)



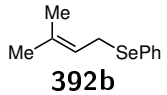
392g

Following general procedure **A**: **86** (1.42 g, 4.55 mmol, 1.00 equiv.) in EtOH (20.0 mL); **394b** (1.67 g, 10.0 mmol, 2.20 equiv.); $NaBH_4$ (0.343 g, 9.09 mmol, 2.00 equiv.); column chromatography (*n*-pentane); yellow oil; 1.18 g, 4.11 mmol, 41% over two steps.

$\mathbf{R}_f$ = 0.50 (PE/EtOAc 30:1); IR (neat): ν [cm^{-1}] = 686, 727, 753, 861, 1021, 1070, 1096, 1170, 1271, 1297, 1342, 1379, 1435, 1491, 1528, 1573, 1629, 1737, 1797, 1871, 1938, 1990, 2113, 2855, 2922, 2986, 3053; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.63 – 7.50 (m, 1H), 3.74 (d, J = 8.4 Hz, 1H), 1.83 (d, J = 1.5 Hz, 2H); **^{13}C NMR**

(75MHz, $CDCl_3$): δ [ppm] = 143.1, 137.9, 134.5, 129.8, 128.9, 128.2, 127.4, 127.1, 125.8, 123.5, 26.7, 15.4; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 337.2 (d, J = 135.2 Hz), 462.88 (**86**, impurity); **HRMS**: (EI-MS) [$C_{16}H_{16}Se$], obs.: 288.0401, calcd.: 288.0411.

(3-methylbut-2-en-1-yl)(phenyl)selane (392b)

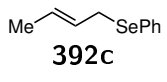


392b

Following general procedure **A**: **86** (4.20 g, 13.6 mmol, 1.00 equiv.) in EtOH/THF 1:1 (200 mL); **377e** (3.40 mL, 30.0 mmol, 2.20 equiv.); $NaBH_4$ (1.00 g, 27.3 mmol, 2.00 equiv.); column chromatography (*n*-pentane); yellow oil; 2.40 g, 10.8 mmol, 36%.

$\mathbf{R}_f$ = 0.50 (PE/EtOAc 30:1); IR (neat): ν [cm^{-1}] = 690, 731, 839, 1021, 1070, 1100, 1178, 1222, 1297, 1375, 1435, 1476, 1525, 1577, 1662, 1737, 1797, 1871, 2087, 2728, 2915, 2967, 3056; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.57 – 7.43 (m, 2H), 7.32 – 7.17 (m, 3H), 5.38 (tdq, J = 8.4, 2.9, 1.5 Hz, 1H), 3.55 (d, J = 8.2 Hz, 2H), 1.70 (d, J = 1.4 Hz, 3H), 1.49 (d, J = 1.5 Hz, 3H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 135.9, 133.6, 131.5, 130.6, 129.2, 128.8, 127.8, 127.0, 120.2, 26.1, 25.7, 17.4; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 327.6, 462.7 (**86**, impurity); **HRMS**: (EI-MS) [$C_{11}H_{14}Se$], obs.: 226.0260, calcd.: 226.0255.

(E)-but-2-en-1-yl(phenyl)selane (392c)

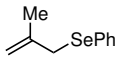


392c

Following general procedure **A**: **86** (1.42 g, 4.55 mmol, 1.00 equiv.) in EtOH (20.0 mL); **377f** (1.16 mL, 10.0 mmol, 2.20 equiv.); $NaBH_4$ (0.430 g, 11.4 mmol, 2.50 equiv.); column chromatography (*n*-pentane); yellow oil; 1.80 g, 8.40 mmol, 84%.

$\mathbf{R}_f$ = 0.54 (*n*-pentane/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 690, 731, 839, 917, 962, 1021, 1070, 1178, 1297, 1375, 1435, 1476, 1580, 1659, 1737, 1797, 1871, 1946, 2646, 2728, 2851, 2881, 2915, 2963, 3019, 3056; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.60 – 7.47 (m, 2H), 7.33 – 7.22 (m, 3H), 5.76 – 5.53 (m, 1H), 5.53 – 5.36 (m, 1H), 3.66 – 3.46 (m, 2H), 1.66 (dq, J = 6.3, 1.1 Hz, 2H), 1.59 – 1.43 (m, 1H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 133.7, 133.3, 130.4, 128.9 (d, J = 1.9 Hz), 128.4, 127.0 (d, J = 4.4 Hz), 30.1, 17.7; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 330.6 (d, J = 52.1 Hz); **HRMS**: (EI-MS) [$C_{15}H_{14}Se$], obs.: 274.0245, calcd.: 274.0255.

(2-methylallyl)(phenyl)selane **(392d)**

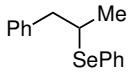


392d

Following general procedure **A**: **86** (1.42 g, 4.55 mmol, 1.00 equiv.) in EtOH (20.0 mL); **377g** (1.01 mL, 10.0 mmol, 2.20 equiv.); $NaBH_4$ (0.343 g, 9.09 mmol, 2.00 equiv.); column chromatography (*n*-pentane); yellow oil; 1.97 g, 9.32 mmol, 93%.

$\mathbf{R}_f$ = 0.73 (*n*-pentane); IR (neat): ν [cm^{-1}] = 690, 734, 809, 891, 1021, 1070, 1185, 1286, 1372, 1439, 1476, 1580, 1640, 1737, 1797, 1871, 1946, 2371, 2594, 2646, 2725, 2915, 2974, 3075; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.57 – 7.43 (m, 2H), 7.33 – 7.16 (m, 4H), 4.79 – 4.58 (m, 2H), 3.53 (d, J = 1.0 Hz, 2H), 1.87 (dd, J = 1.5, 0.8 Hz, 3H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 141.8, 133.5, 130.5, 128.9, 127.2, 113.5, 77.3, 36.1, 21.4; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 317.40; **HRMS**: (EI-MS) [$C_{10}H_{12}Se$], obs.: 212.0101, calcd.: 212.0098.

phenyl(1-phenylpropan-2-yl)selane **(406g)**



406g

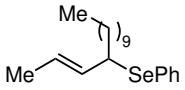
Following general procedure **A**: **86** (1.42 g, 4.50 mmol, 1.00 equiv.) in EtOH/THF 1:1 (100 mL); **377h** (1.54 mL, 10.0 mmol, 2.20 equiv.); $NaBH_4$ (0.343 g, 9.09 mmol, 2.00 equiv.); column chromatography (*n*-pentane); yellow oil; 0.483 g, 1.75 mmol, 18%.

$\mathbf{R}_f$ = 0.29 (*n*-pentane/toluene 10:1); IR (neat): ν [cm^{-1}] = 693, 731, 906, 1021, 1070, 1100, 1167, 1223, 1301, 1375, 1476, 1580, 2248, 2859, 2922, 2956, 3026, 3064; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.74 – 7.59 (m, 2H), 7.46 – 7.21 (m, 9H), 3.63 (dqd, J = 9.2, 6.8, 5.5 Hz, 1H), 3.27 – 3.10 (m, 1H), 2.87 (dd, J = 13.6, 9.2 Hz, 1H), 1.56 – 1.30 (m, 4H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 139.9, 135.1, 129.5, 129.1 (d, J = 9.4 Hz), 128.6, 128.4, 127.6, 127.0, 126.5, 44.2, 40.1, 21.2; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 413.1; **HRMS**: (EI-MS) [$C_{15}H_{16}Se$] ($[M]^{+\bullet}$), obs.: 276.040, calcd.: 276.041.

9.2.2 Synthesis of secondary selenides

General procedure **B** for the synthesis of **secondary selenides**: To a solution of selenide in THF (0.1 M) cooled to -78°C, LDA (1.10 equiv.) was added dropwise. The reaction was stirred at -78°C for 1 h. Bromide **377** was added dropwise. The reaction was warmed to 0°C and stirred overnight at rt. The reaction was quenched with aq. NH_4Cl, and extracted thrice with EtOAc (3*15.0 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 or $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography (*n*-pentane) to give the desired secondary selenide.

(E)-phenyl(tetradec-2-en-4-yl)selane **(406a)**

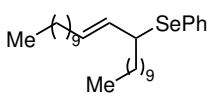


406a

Following general procedure **B**: **392c** (1.48 g, 7.00 mmol, 1.00 equiv.) in THF (70.0 mL); LDA (1.92 M in THF, 4.00 mL, 7.70 mmol, 1.10 equiv.); **377i** (1.55 g, 1.45 mL, 7.00 mmol, 1.00 equiv.); column chromatography (*n*-pentane);colourless to yellow oil; 0.891 g, 2.53 mmol, 36%.

$\mathbf{R}_f$ = 0.63 (*n*-pentane); IR (neat): ν [cm^{-1}] = 693, 738, 805, 842, 962, 1021, 1066, 1133, 1178, 1301, 1375, 1461, 1580, 1659, 2855, 2922, 3019, 3060; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.52 – 7.42 (m, 2H), 7.31 – 7.20 (m, 3H), 5.49 – 5.32 (m, 1H), 5.14 (dq, J = 15.1, 6.4 Hz, 1H), 3.69 (td, J = 9.0, 5.9 Hz, 1H), 1.69 (dddd, J = 17.0, 14.1, 7.8, 3.9 Hz, 2H), 1.60 (s, 0H), 1.25 (d, J = 3.7 Hz, 15H), 0.94 – 0.81 (m, 4H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 135.8, 132.4, 129.8, 128.6, 127.5, 126.1, 47.8, 35.1, 31.9, 29.6, 29.5, 29.3 (d, J = 6.0 Hz), 28.2, 22.7, 17.6, 14.2; ^{77}**Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 413.1; **HRMS**: (EI-MS) [$C_{20}H_{32}Se$] ([M]$^{+\bullet}$), obs.: 352.1661, calcd.: 352.1663.

(E)-phenyl(tricos-12-en-11-yl)selane **(406b)**



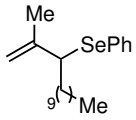
406b

Following general procedure **B**: **392a** (1.33 g, 3.94 mmol, 1.00 equiv.) in THF (40.0 mL); LDA (1.92 M in THF, 2.26 mL, 4.33 mmol, 1.10 equiv.); **377i** (0.814 mL, 3.94 mmol, 1.00 equiv.); column chromatography (*n*-pentane);colourless to yellow oil; 0.550 g, 1.15 mmol, 29%.

$\mathbf{R}_f$ = 0.58 (*n*-pentane); IR (neat): ν [cm^{-1}] = 693, 738, 910, 962, 1021, 1066, 1152, 1301, 1379, 1461, 1580, 2855, 2922; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 5.36 (ddt, J =

15.2, 9.4, 1.4 Hz, 1H), 5.13 (dt, J = 15.2, 6.8 Hz, 1H), 3.70 (td, J = 9.0, 5.7 Hz, 1H), 1.79 – 1.54 (m, 2H), 1.48 – 1.09 (m, 29H), 0.88 (td, J = 6.8, 1.4 Hz, 5H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 135.7, 131.8, 131.1, 129.8, 128.6, 127.4, 47.8, 35.1, 32.2, 32.0, 29.9 – 29.0 (m), 28.2, 22.7, 14.2; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 419.0; **HRMS**: (EI-MS) $[C_{29}H_{50}Se]$ ($[M]^{+\bullet}$), obs.: 478.3097, calcd.: 478.3072.

(2-methyltridec-1-en-3-yl)(phenyl)selane (406c)

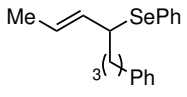


406c

Following general procedure **B**: **392d** (1.48 g, 7.00 mmol, 1.00 equiv.) in THF (70.0 mL); LDA (1.92 M in THF, 5.47 mL, 10.5 mmol, 1.50 equiv.); **377i** (1.45 mL, 7.00 mmol, 1.00 equiv.); column chromatography (*n*-pentane);colourless to yellow oil; 0.660 g, 1.81 mmol, 27%.

$\mathbf{R}_f$ = 0.50 (*n*-pentane); IR (neat): ν [cm^{-1}] = 690, 738, 887, 1021, 1066, 1156, 1297, 1372, 1461, 1580, 1636, 2855, 2922, 3075; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.55 – 7.44 (m, 2H), 7.33 – 7.18 (m, 4H), 4.66 (p, J = 1.5 Hz, 1H), 4.56 – 4.50 (m, 1H), 3.72 (t, J = 7.8 Hz, 1H), 1.80 (t, J = 1.1 Hz, 3H), 1.77 – 1.66 (m, 2H), 1.25 (s, 20H), 0.93 – 0.83 (m, 3H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 144.5, 135.3, 130.3, 128.8, 127.6, 112.7, 52.8, 33.3, 32.1, 30.2 – 29.1 (m), 28.4, 22.8, 18.7, 14.3; **HRMS**: (EI-MS) $[C_{20}H_{32}Se]$ ($[M]^{+\bullet}$), obs.: 352.1655, calcd.: 352.1663.

(E)-phenyl(7-phenylhept-2-en-4-yl)selane (406d)

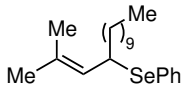


406d

Following general procedure **B**: **392c** (1.42 g, 6.72 mmol, 1.00 equiv.) in THF (80.0 mL); LDA (1.92 M in THF, 4.50 mL, 8.74 mmol, 1.30 equiv.); **377j** (1.02 mL, 6.72 mmol, 1.00 equiv.); column chromatography (*n*-pentane/toluene 10:1);colourless to yellow oil; 0.685 g, 2.07 mmol, 31%.

$\mathbf{R}_f$ = 0.43 (*n*-pentane/toluene 10:1); IR (neat): ν [cm^{-1}] = 693, 738, 805, 842, 910, 962, 1074, 1129, 1178, 1260, 1301, 1375, 1439, 1476, 1603, 1662, 1744, 1804, 1875, 1946, 2855, 2933, 3027, 3060; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.61 – 7.42 (m, 2H), 7.35 – 7.10 (m, 9H), 5.48 – 5.31 (m, 1H), 5.15 (dq, J = 15.0, 6.4 Hz, 1H), 3.70 (dt, J = 9.2, 4.9 Hz, 1H), 2.59 (dp, J = 6.1, 3.3, 2.8 Hz, 2H), 1.85 – 1.62 (m, 4H), 1.58 (dd, J = 6.4, 1.6 Hz, 3H), 1.35 – 1.24 (m, 1H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 142.2, 136.2, 135.9, 132.1, 129.6, 128.6, 128.4 (d, J = 7.3 Hz), 127.6, 126.4, 125.8, 47.5, 35.5, 34.6, 30.1, 17.6; **HRMS**: (EI-MS) $[C_{19}H_{22}Se]$ ($[M]^{+\bullet}$), obs.: 330.0881, calcd.: 330.0881.

(2-methyltetradec-2-en-4-yl)(phenyl)selane (406e)

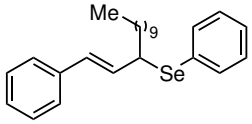


406e

Following general procedure **B**: **392b** (2.43 g, 10.8 mmol, 1.00 equiv.) in THF (90.0 mL); LDA (1.92 M in THF, 7.30 mL, 14.0 mmol, 1.30 equiv.); **377i** (2.23 mL, 10.8 mmol, 1.00 equiv.); column chromatography (*n*-pentane);colourless to yellow oil; 2.62 g, 7.16 mmol, 66%.

$\mathbf{R}_f$ = 0.40 (*n*-pentane); IR (neat): ν [cm^{-1}] = 693, 738, 850, 910, 984, 1021, 1066, 1141, 1234, 1301, 1375, 1439, 1580, 1662, 1748, 1871, 1946, 2855, 2922, 3056; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.59 – 7.49 (m, 2H), 7.34 – 7.17 (m, 4H), 5.10 (dp, J = 10.7, 1.4 Hz, 1H), 4.02 (ddd, J = 10.7, 9.1, 5.2 Hz, 1H), 1.82 – 1.45 (m, 4H), 1.43 – 1.21 (m, 17H), 0.93 – 0.82 (m, 3H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 136.4, 133.9, 132.4, 129.6, 129.0, 128.5, 127.6, 126.6, 43.6, 36.1, 31.9, 29.6 (d, J = 6.9 Hz), 28.3, 25.6, 22.7, 17.7, 14.2; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 422.3; **HRMS**: (EI-MS) [$C_{21}H_{34}Se$] ([M]$^{+\bullet}$), obs.: 366.1822, calcd.: 366.1820.

((E)-phenyl(1-phenyltridec-1-en-3-yl)selane (406f)



406f

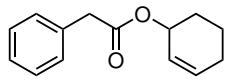
Following general procedure **B**: **392f** (2.19 g, 8.00 mmol, 1.00 equiv.) in THF (80.0 mL); LDA (1.92 M in THF, 4.60 mL, 8.80 mmol, 1.10 equiv.); **377i** (1.60 mL, 8.00 mmol, 1.00 equiv.); column chromatography (*n*-pentane);yellow oil; 0.90 g, 2.20 mmol, 28%.

$\mathbf{R}_f$ = 0.50 (*n*-pentane); IR (neat): ν [cm^{-1}] = 1215, 1372, 1748, 2005, 2359, 2851, 2926, 2963, 3034; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.56 – 7.47 (m, 2H), 7.34 – 7.12 (m, 8H), 6.15 (dd, J = 15.7, 9.5 Hz, 1H), 5.95 (d, J = 15.7 Hz, 1H), 3.85 (td, J = 9.0, 6.0 Hz, 1H), 1.91 – 1.65 (m, 2H), 1.42 (dtd, J = 11.4, 8.2, 7.4, 3.2 Hz, 2H), 1.36 – 1.18 (m, 16H), 0.93 – 0.82 (m, 3H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 137.0, 136.2, 131.2, 129.9, 129.1, 128.7, 128.4, 127.8, 127.2, 126.2, 48.3, 34.9, 31.9, 29.6, 29.5, 29.3, 29.3, 22.7, 14.1; **^{77}Se NMR** (76MHz, $CDCl_3$): δ [ppm] = 429.6; **HRMS**: (EI-MS) [$C_{25}H_{34}Se$] ([M]$^{+\bullet}$), obs.: 414.1831, calcd.: 414.1826.

9.3 Photoreactions

General procedure **C**: To a photoreaction vial was added selenide (1.0 equiv.), carboxylic acid **373** (3.0 equiv.), NaF (1.0 equiv.), and HFIP (1.0 M). the vial was fitted with an air balloon and stirred for t h at 19°C under irradiation (528 nm). After completion of the reaction, verified by TLC control, the reaction mixture was transferred to a round bottom flask with NMR standard (1,3-dinitrobenezene, unless otherwise specified) and concentrated *in vacuo*. Purification of the crude mixtrue *via* column chromatography afforded the desired product.

cyclohex-2-en-1-yl 2-phenylacetate (372b)

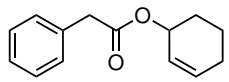


372b

Following general procedure **C**: **370a** (0.237 g, 1.0 mmol, 1.0 equiv.), **373a** (0.408 g, 3.0 mmol, 3.0 equiv); HFIP (1.00 mL); column chromatography (PE/Et_2O 200:1 to 100:1); colourless oil; NMR yield: 82%; isolated yield: 0.154 g, 0.712 mmol, 71%.

$\mathbf{R}_f$ = 0.55 (PE/EtOAc); IR (neat): ν [cm^{-1}] = 723, 760, 835, 906, 958, 1006, 1051, 1137, 1249, 1290, 1342, 1454, 1498, 1603, 1651, 2837, 2870, 2937, 3034, 3064; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.38 – 7.20 (m, 5H), 5.95 (dtd, J = 10.1, 3.7, 1.3 Hz, 1H), 5.70 (ddt, J = 10.0, 4.1, 2.2 Hz, 1H), 5.27 (dtq, J = 7.2, 3.5, 1.6 Hz, 1H), 3.61 (s, 2H), 2.16 – 1.95 (m, 2H), 1.92 – 1.82 (m, 1H), 1.77 – 1.51 (m, 3H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 206.5, 171.3, 134.3, 132.9, 129.3, 128.5, 127.0, 125.6, 68.6, 41.7, 28.2, 24.9, 18.8; **HRMS**: (EI-MS) [$C_{14}H_{16}O_2$] ([M]$^{+\bullet}$), obs.: 216.1143, calcd.: 216.1144.

cyclohex-2-en-1-yl benzoate (372c)



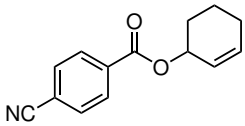
372c

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373l** (0.366 g, 3.00 mmol, 3.00 equiv); NaF(0.0420 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 10:1 to 1:1); colourless oil; NMR yield: 64%; isolated yield: 0.117 g, 0.578 mmol, 58%.

$\mathbf{R}_f$ = 0.47 (toluene); IR (neat): ν [cm^{-1}] = 708, 805, 854, 917, 1025, 1070, 1111, 1178, 1267, 1312, 1394, 1454, 1603, 1711, 2837, 2870, 2937, 3034, 3064; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.14 – 7.97 (m, 2H), 7.63 – 7.47 (m, 1H), 6.01 (dtd, J = 10.1, 3.6, 1.2 Hz, 1H), 5.84 (ddt, J = 10.0, 4.1, 2.1 Hz, 1H), 5.51 (dp, J = 5.2, 1.9 Hz, 1H), 2.24

– 1.61 (m, 7H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 166.3, 132.8 (d, J = 8.4 Hz), 130.8, 129.6, 128.3, 125.7, 68.6, 28.4, 25.0, 19.0; **HRMS**: (EI-MS) [$C_{13}H_{14}O_2$] ([M]$^{+\bullet}$), obs.: 202.0987, calcd.: 202.0988.

cyclohex-2-en-1-yl 4-cyanobenzoate (372d)

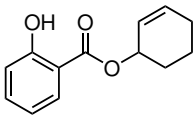


372d

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373m** (0.441 g, 3.00 mmol, 3.00 equiv); HFIP (1.00 mL); column chromatography (PE/tol 10:1); colourless oil; NMR yield: 52%; isolated yield: 0.0940 g, 0.410 mmol, 41%.

$\mathbf{R}_f$ = 0.34 (toluene); IR (neat): ν [cm^{-1}] = 686, 731, 764, 831, 857, 906, 1044, 1107, 1170, 1278, 1349, 1405, 1439, 1498, 1569, 1707, 1942, 2121, 2233, 2378, 2948, 3038, 3071, 3101; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.19 – 8.09 (m, 2H), 7.78 – 7.68 (m, 2H), 6.03 (dtd, J = 10.0, 3.7, 1.2 Hz, 1H), 5.81 (ddt, J = 10.1, 4.1, 2.2 Hz, 1H), 5.51 (tdq, J = 5.2, 3.3, 1.6 Hz, 1H), 2.24 – 1.61 (m, 5H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 164.6, 134.6, 133.6, 132.2, 130.1, 125.0, 118.1, 116.2, 69.6, 28.3, 24.9, 18.8; **HRMS**: (EI-MS) [$C_{13}H_{14}O_2$] ([M]$^{+\bullet}$), obs.: 227.0935, calcd.: 227.0940.

cyclohex-2-en-1-yl 2-hydroxybenzoate (372e)

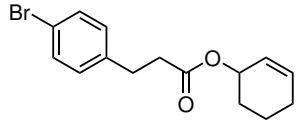


372e

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373n** (0.414 g, 3.00 mmol, 3.00 equiv); HFIP (1.00 mL); column chromatography (tol/EtOAc 100:1 to 5:1); colourless oil; NMR yield: 50%; isolated yield: 0.0870 g, 0.398 mmol, 40%.

$\mathbf{R}_f$ = 0.15 (PE/toluene 5:1); IR (neat): ν [cm^{-1}] = 727, 753, 798, 865, 910, 1003, 1051, 1088, 1156, 1211, 1249, 1290, 1361, 1398, 1431, 1484, 1610, 1662, 2837, 2870, 2937, 3034, 3150; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 10.90 (s, 1H), 7.86 (dd, J = 8.0, 1.8 Hz, 1H), 7.44 (ddd, J = 8.6, 7.2, 1.8 Hz, 1H), 6.97 (dd, J = 8.4, 1.2 Hz, 1H), 6.87 (ddd, J = 8.2, 7.2, 1.1 Hz, 1H), 6.10 – 5.98 (m, 1H), 5.83 (ddt, J = 10.0, 4.1, 2.2 Hz, 1H), 5.53 (ddt, J = 5.1, 3.5, 1.6 Hz, 1H), 2.24 – 1.62 (m, 5H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 169.9, 161.7, 135.5, 133.6, 131.5, 130.1, 129.2, 125.0, 119.1, 117.5, 112.9, 69.3, 28.3, 24.9, 18.8; **HRMS**: (EI-MS) [$C_{13}H_{14}O_3$] ([M]$^{+\bullet}$), obs.: 218.0940, calcd.: 218.0937.

cyclohex-2-en-1-yl 3-(4-bromophenyl)propanoate (372f)

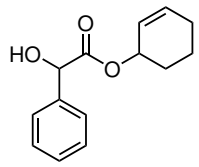


372f

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373o** (0.687 g, 3.00 mmol, 3.00 equiv); HFIP (1.00 mL); column chromatography (PE/EtOAc 20:1); colourless oil; NMR yield: 45%; isolated yield: 0.0990 g, 0.320 mmol, 32%.

$\mathbf{R}_f$ = 0.48 (PE/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 727, 813, 869, 910, 954, 1010, 1055, 1100, 1156, 1249, 1290, 1372, 1405, 1439, 1487, 1543, 1592, 1655, 1722, 2866, 2937, 3034; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.43 – 7.33 (m, 2H), 7.12 – 7.02 (m, 2H), 5.94 (dtd, J = 10.0, 3.7, 1.2 Hz, 1H), 5.65 (ddt, J = 10.1, 4.0, 2.2 Hz, 1H), 5.24 (tdq, J = 5.3, 3.2, 1.7 Hz, 1H), 2.90 (t, J = 7.6 Hz, 2H), 2.15 – 1.90 (m, 2H), 1.88 – 1.76 (m, 1H), 1.75 – 1.50 (m, 3H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 172.3, 139.5, 132.9, 131.5, 130.2, 125.5, 120.0, 68.2, 35.9, 30.5, 28.3, 24.9, 18.8; **HRMS**: (EI-MS) [$C_{15}H_{17}O_2Br$] ([M]$^{+\bullet}$), obs.: 308.0404, calcd.: 308.0406.

cyclohex-2-en-1-yl 2-hydroxy-2-phenylacetate (372g)

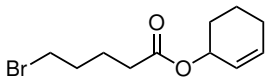


372g

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373c** (0.456 g, 3.00 mmol, 3.00 equiv); NaF (0.042 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (tol/EtOAc 100:0 to 75:1); colourless oil; NMR yield: 73%; isolated yield: 0.109 g, 0.469 mmol, 47%.

$\mathbf{R}_f$ = 0.23 (PE/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 701, 753, 787, 828, 854, 906, 1003, 1074, 1185, 1219, 1249, 1290, 1342, 1405, 1454, 1495, 1715, 2091, 2833, 2870, 2945, 3038, 3489; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.48 – 7.25 (m, 6H), 6.05 – 5.83 (m, 1H), 5.74 (ddt, J = 10.0, 4.1, 2.2 Hz, 1H), 5.56 – 5.46 (m, 0H), 5.31 (q, J = 5.1, 4.2 Hz, 1H), 5.16 (d, J = 6.0 Hz, 1H), 3.45 (dd, J = 10.4, 6.1 Hz, 1H), 2.14 – 1.85 (m, 1H), 1.86 – 1.59 (m, 1H), 1.60 – 1.45 (m, 2H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 173.4 (d, J = 6.5 Hz), 138.6 (d, J = 5.6 Hz), 133.8, 133.4, 128.5, 128.3, 126.4 (d, J = 2.0 Hz), 124.6 (d, J = 1.9 Hz), 72.9 (d, J = 1.8 Hz), 70.5, 70.1, 28.2, 27.9, 24.8 (d, J = 2.0 Hz), 18.7, 18.3; **HRMS**: (EI-MS) [$C_{15}H_{17}O_2Br$] ((M+H)+), obs.: 233.1174, calcd.: 233.1172.

cyclohex-2-en-1-yl 5-bromopentanoate (372i)

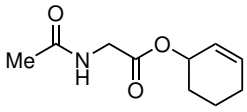


372i

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373g** (0.543 g, 3.00 mmol, 3.00 equiv); NaF (0.042 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 10:1 to 6.5:1); colourless oil; NMR yield: 75%; isolated yield: 0.143 g, 0.547 mmol, 55%.

$\mathbf{R}_f$ = 0.50 (PE/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 678, 731, 828, 913, 1010, 1055, 1163, 1252, 1375, 1435, 1651, 2837, 2870, 2937, 3034; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 5.96 (dtd, J = 10.1, 3.7, 1.3 Hz, 1H), 5.69 (ddt, J = 10.1, 4.0, 2.2 Hz, 1H), 5.33 – 5.21 (m, 1H), 3.41 (t, J = 6.5 Hz, 2H), 2.34 (t, J = 7.2 Hz, 2H), 2.17 – 1.96 (m, 1H), 1.95 – 1.46 (m, 6H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 172.8, 132.8, 125.6, 68.1, 33.6, 33.1, 32.0, 28.3, 24.9, 23.6, 18.8; **HRMS**: (EI-MS) [$C_{11}H_{17}O_2Br$] ((M+H)+), obs.: 261.0489, calcd.: 261.0485.

cyclohex-2-en-1-yl acetylglycinate (372j)

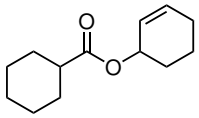


372j

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373f** (0.351 g, 3.00 mmol, 3.00 equiv); NaF (0.042 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (tol/EtOAc 100:0 to 1:1); colourless oil; NMR yield: 55%; isolated yield: 0.0780 g, 0.395 mmol, 40%.

$\mathbf{R}_f$ = 0.23 (EtOAc); IR (neat): ν [cm^{-1}] = 678, 731, 820, 910, 954, 1006, 1036, 1133, 1189, 1293, 1375, 1435, 1543, 1655, 1737, 2837, 2870, 2937, 3034, 3082, 3295; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 6.39 (s, 1H), 5.93 (dtd, J = 10.1, 3.7, 1.2 Hz, 1H), 5.64 (ddt, J = 10.1, 4.1, 2.2 Hz, 1H), 5.26 (tdt, J = 5.2, 3.6, 1.5 Hz, 1H), 4.13 – 3.87 (m, 2H), 2.19 – 1.36 (m, 8H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 170.3, 169.8, 133.5, 124.9, 69.5, 41.7, 28.1, 24.8, 23.0, 18.6; **HRMS**: (EI-MS) [$C_{10}H_{15}NO_3$] ((M+H)+), obs.: 198.1123, calcd.: 198.1125.

cyclohex-2-en-1-yl cyclohexanecarboxylate (372k)



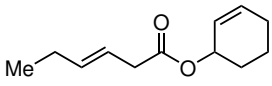
372k

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373p** (0.384 g, 3.00 mmol, 3.00 equiv); HFIP (1.00 mL); column chromatography (PE/tol 10:1 to 7.5:1); colourless oil; NMR yield: 60%;

isolated yield: 0.0940 g, 0.451 mmol, 45%.

$\mathbf{R}_f$ = 0.12 (tol/PE 1:2); IR (neat): ν [cm^{-1}] = 675, 727, 794, 846, 917, 1133, 1163, 1245, 1308, 1375, 1450, 1655, 1722, 2855, 2930, 3034; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.31 – 7.09 (m, 1H), 5.94 (dtd, J = 10.1, 3.7, 1.3 Hz, 1H), 5.68 (ddt, J = 10.1, 4.1, 2.2 Hz, 1H), 5.24 (tdq, J = 5.3, 3.4, 1.7 Hz, 1H), 2.38 – 2.19 (m, 2H), 2.17 – 1.96 (m, 1H), 1.96 – 1.80 (m, 3H), 1.80 – 1.54 (m, 5H), 1.54 – 1.35 (m, 2H), 1.35 – 1.14 (m, 3H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 175.8, 132.5, 125.9, 67.5, 43.4, 29.1 (d, J = 9.2 Hz), 28.3, 25.8, 25.5 (d, J = 3.6 Hz), 24.9, 18.9; **HRMS**: (EI-MS) [$C_{13}H_{20}O_2$] ([M]$^{+\bullet}$), obs.: 208.1461, calcd.: 208.1457.

cyclohex-2-en-1-yl (E)-hex-3-enoate (372l)

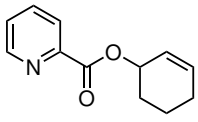


372l

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373h** (0.342 g, 3.00 mmol, 3.00 equiv); NaF (0.024 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 50:1 to 20:1); colourless oil; NMR yield: 38%; isolated yield: 0.0560 g, 0.288 mmol, 29%.

$\mathbf{R}_f$ = 0.46 (toluene); IR (neat): ν [cm^{-1}] = 727, 835, 910, 965, 1010, 1055, 1156, 1241, 1312, 1346, 1457, 1543, 1651, 1730, 2874, 2937, 3034; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 5.95 (dtd, J = 10.1, 3.7, 1.3 Hz, 1H), 5.69 (ddt, J = 10.1, 4.0, 2.2 Hz, 1H), 5.66 – 5.42 (m, 2H), 5.26 (ddtt, J = 7.1, 5.1, 3.4, 1.8 Hz, 1H), 3.05 – 2.97 (m, 2H), 2.16 – 1.94 (m, 3H), 1.92 – 1.79 (m, 1H), 1.79 – 1.54 (m, 3H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 267.1, 172.0, 136.2, 132.7, 128.9, 125.7, 120.8, 68.2, 38.4, 28.3, 25.5, 24.9, 18.9, 13.5; **HRMS**: (EI-MS) [$C_{12}H_{18}O_2$] ((M+H)+), obs.: 195.138, calcd.: 195.138.

cyclohex-2-en-1-yl picolinate (372m)



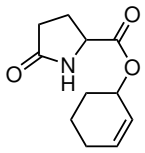
372m

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373e** (0.369 g, 3.00 mmol, 3.00 equiv); NaF (0.042 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (tol/EtOAc 100:0 to 0:100); colourless oil; NMR yield: 33%; isolated yield: 0.0830 g, 0.408 mmol, 41%.

$\mathbf{R}_f$ = 0.36 (tol/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 705, 746, 857, 910, 995, 1044, 1126,

1245, 1286, 1327, 1439, 1584, 1651, 1707, 2837, 2870, 2937, 3034; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.75 (ddd, J = 4.7, 1.8, 0.9 Hz, 1H), 8.10 (dt, J = 7.8, 1.1 Hz, 1H), 7.80 (td, J = 7.7, 1.8 Hz, 1H), 7.44 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 5.99 (dtd, J = 10.1, 3.7, 1.3 Hz, 1H), 5.83 (ddt, J = 10.2, 4.0, 2.2 Hz, 1H), 5.58 (tdq, J = 5.2, 3.4, 1.8 Hz, 1H), 2.21 – 1.58 (m, 6H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 164.9, 150.0, 148.6, 136.9, 133.2, 126.7, 125.4, 125.1, 77.3, 69.9, 28.3, 24.9, 19.1; **HRMS**: (EI-MS) [$C_{12}H_{13}NO_2$] ((M+H)+), obs.: 204.1022, calcd.: 204.1019.

cyclohex-2-en-1-yl 5-oxopyrrolidine-2-carboxylate (372t)

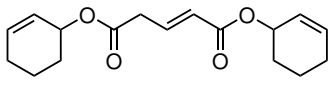


372t

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373i** (0.387 g, 3.00 mmol, 3.00 equiv); NaF (0.042 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (DCM/EtOAc 20:1 to 1:1); colourless oil; NMR yield: 45%; isolated yield: 0.0980 g, 0.468 mmol, 47%.

R$_f$ = 0.05 (DCM/EtOAc 1:1); IR (neat): ν [cm^{-1}] = 667, 727, 824, 910, 1010, 1100, 1189, 1323, 1383, 1424, 1692, 2870, 2937, 3034, 3228; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 6.82 (s, 1H), 6.01 – 5.89 (m, 1H), 5.65 (ddq, J = 9.6, 3.4, 1.9 Hz, 1H), 5.26 (tdp, J = 5.1, 3.2, 1.6 Hz, 1H), 4.20 (dd, J = 8.6, 5.3 Hz, 1H), 2.53 – 1.51 (m, 9H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 178.3, 171.8, 133.6, 124.8, 69.4 (d, J = 5.6 Hz), 55.7, 29.3 (d, J = 1.4 Hz), 28.1, 25.1 – 24.5 (m), 18.6 (d, J = 3.1 Hz); **HRMS**: (EI-MS) [$C_{11}H_{15}NO_3$] ((M+H)+), obs.: 210.1127, calcd.: 210.1125.

di(cyclohex-2-en-1-yl) (E)-pent-2-enedioate (372u)



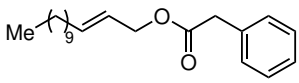
372u

Following general procedure **C**: **370a** (0.237 g, 1.00 mmol, 1.00 equiv.), **373j** (0.0650 g, 0.500 mmol, 0.500 equiv); NaF (0.083 g, 2.00 mmol, 2.00 equiv.); HFIP (1.0 mL); column chromatography (PE/tol 10:1 to 0:100 to tol/EtOAc 100:1); colourless oil; NMR yield: 32%; isolated yield: 0.041 g, 0.141 mmol, 28%.

R$_f$ = 0.36 (PE/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 678, 727, 839, 910, 1006, 1051, 1152, 1185, 1267, 1312, 1398, 1435, 1655, 1714, 2837, 2870, 2937, 3034; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.01 (dt, J = 15.7, 7.1 Hz, 0H), 6.01 – 5.87 (m, 2H), 5.70 (dddt, J = 10.1, 5.9, 4.0, 2.2 Hz, 1H), 5.30 (dtdq, J = 11.7, 5.0, 3.3, 1.6 Hz, 1H), 3.22 (dd, J = 7.2, 1.6 Hz, 1H), 2.18 – 1.54 (m, 4H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 169.6, 165.5,

139.8, 133.2, 132.8, 125.7, 125.2, 125.0, 69.0, 68.2, 37.8, 28.3, 28.2, 24.9 (d, J = 3.6 Hz), 18.9, 18.8; **HRMS**: (EI-MS) [$C_{17}H_{22}O_4$] ((M+NH_4)+), obs.: 308.186, calcd.: 308.1856.

(E)-tridec-2-en-1-yl 2-phenylacetate (395a)

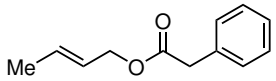


395a

Following general procedure **C**: **392a** (0.337 g, 1.00 mmol, 1.00 equiv.), **373a** (0.408 g, 3.00 mmol, 3.00 equiv); NaF (0.0420 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 100:0 to 7.5:1); colourless oil; NMR yield: 25%; isolated yield: 0.0700 g, 0.221 mmol, 22%.

R$_f$ = 0.38 (toluene); IR (neat): ν [cm^{-1}] = 723, 835, 969, 1029, 1144, 1245, 1301, 1327, 1379, 1454, 1498, 1603, 1737, 2855, 2922, 3034; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.39 – 7.20 (m, 6H), 5.75 (dtt, J = 16.5, 6.5, 1.1 Hz, 1H), 5.54 (dtt, J = 15.4, 6.4, 1.4 Hz, 1H), 4.54 (dd, J = 6.4, 1.1 Hz, 2H), 3.63 (s, 2H), 2.10 – 1.97 (m, 2H), 1.59 (s, 0H), 1.26 (s, 16H), 0.94 – 0.83 (m, 3H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 171.4, 136.8, 134.1, 129.3, 128.5, 127.1, 123.5, 65.7, 41.4, 32.3, 31.9, 29.6 (d, J = 2.6 Hz), 29.5, 29.4, 29.2, 28.9, 22.7, 14.1; **HRMS**: (EI-MS) [$C_{21}H_{32}O_2$] ((M+NH_4)+), obs.: 334.274, calcd.: 334.274.

(E)-but-2-en-1-yl 2-phenylacetate (395b)

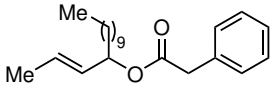


395b

Following general procedure **C**: **392c** (0.211 g, 1.00 mmol, 1.00 equiv.), **373a** (0.408 g, 3.00 mmol, 3.00 equiv); NaF (0.0420 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 100:0 to 1:1); colourless oil; NMR yield: 24%; isolated yield: 0.0220 g, 0.115 mmol, 12%.

R$_f$ = 0.58 (PE/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 697, 760, 965, 1029, 1077, 1137, 1241, 1301, 1331, 1375, 1454, 1498, 1603, 1733, 2941, 3030, 3064; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.41 – 7.21 (m, 6H), 5.89 – 5.67 (m, 1H), 5.58 (dddt, J = 14.4, 6.5, 4.9, 1.6 Hz, 1H), 4.72 – 4.50 (m, 2H), 3.63 (s, 2H), 1.72 (dq, J = 6.5, 1.2 Hz, 3H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 171.5, 134.1, 129.3, 128.6, 127.1, 125.0, 65.7, 41.4, 17.8; **HRMS**: (EI-MS) [$C_{12}H_{14}O_2$] ((M+H)+), obs.: 191.1067, calcd.: 190.10.

(E)-tetradec-2-en-4-yl 2-phenylacetate (408a)

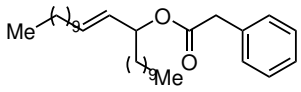


408a

Following general procedure **C**: **406a** (0.351 g, 1.00 mmol, 1.00 equiv.), **373a** (0.408 g, 3.00 mmol, 3.00 equiv); NaF (0.0420 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 100:0 to 0:100); colourless oil; NMR yield: 62%; isolated yield: 0.125 g, 0.380 mmol, 38%.

R$_f$ = 0.73 (PE/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 723, 764, 962, 1040, 1133, 1252, 1297, 1346, 1454, 1498, 1603, 1674, 1733, 2855, 2922, 3034; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.39 – 7.19 (m, 5H), 5.75 – 5.58 (m, 1H), 5.51 – 5.26 (m, 2H), 5.19 (d, J = 6.9 Hz, 0H), 3.61 (s, 2H), 1.99 (dd, J = 7.4, 5.9 Hz, 1H), 1.68 (dd, J = 6.5, 1.6 Hz, 1H), 1.66 – 1.43 (m, 1H), 1.39 – 1.16 (m, 19H), 0.95 – 0.84 (m, 3H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 170.9 (d, J = 7.1 Hz), 134.3 (d, J = 3.3 Hz), 133.6, 129.6, 129.3 – 129.1 (m), 128.5 (d, J = 1.4 Hz), 127.0, 75.5, 71.7, 41.8 (d, J = 4.2 Hz), 34.5, 32.2, 32.0, 29.7 (d, J = 2.2 Hz), 29.6 – 29.5 (m), 29.4 (d, J = 1.9 Hz), 29.2, 29.0, 25.1, 22.7, 20.4, 17.8, 14.2; **HRMS**: (EI-MS) [$C_{12}H_{14}O_2$] ((M+NH_4)+), obs.: 348.29, calcd.: 348.289.

(E)-tricos-12-en-11-yl 2-phenylacetate (408b)

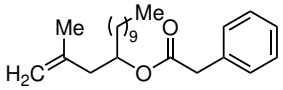


408b

Following general procedure **C**: **406b** (0.477 g, 1.00 mmol, 1.00 equiv.), **373a** (0.408 g, 3.00 mmol, 3.00 equiv); NaF (0.042 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 100:0 to 0:100); colourless oil; NMR yield: 77%; isolated yield: 0.280 g, 0.613 mmol, 61%.

R$_f$ = 0.84 (PE/toluene 10:1); IR (neat): ν [cm^{-1}] = 723, 764, 965, 1029, 1074, 1152, 1252, 1297, 1342, 1457, 1498, 1737, 2855, 2922; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.34 – 7.15 (m, 5H), 5.60 (dt, J = 15.3, 6.7 Hz, 1H), 5.32 (ddt, J = 15.2, 7.4, 1.5 Hz, 1H), 5.16 (q, J = 6.9 Hz, 1H), 3.57 (s, 2H), 1.95 (q, J = 6.9 Hz, 2H), 1.61 – 1.41 (m, 1H), 1.21 (d, J = 8.6 Hz, 33H), 0.91 – 0.80 (m, 5H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 170.9, 134.6, 134.4, 129.3, 128.5, 128.2, 127.0, 75.5, 41.8, 34.5, 32.2, 32.0, 29.7 – 29.5 (m), 29.4 – 29.3 (m), 29.1, 29.0, 25.1, 22.7, 14.2; **HRMS**: (EI-MS) [$C_{31}H_{52}O_2$] ((M+NH_4)+), obs.: 474.430, calcd.: 474.430.

2-methyltetradec-1-en-4-yl 2-phenylacetate (408c)

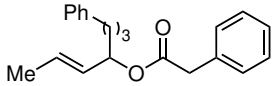


408c

Following general procedure **C**: **406c** (0.351 g, 1.00 mmol, 1.00 equiv.), **373a** (0.408 g, 3.00 mmol, 3.0 equiv); NaF (0.042 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 100:0 to 0:100); colourless oil; NMR yield: 32%; isolated yield: 0.085 g, 0.257 mmol, 26%.

$\mathbf{R}_f$ = 0.13 (PE/toluene 10:1); IR (neat): ν [cm^{-1}] = 723, 760, 857, 980, 1029, 1144, 1245, 1297, 1327, 1372, 1454, 1498, 1737, 2855, 2922, 3034, 3064; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.39 – 7.20 (m, 5H), 5.42 (tq, J = 7.2, 1.4 Hz, 1H), 4.48 (d, J = 1.1 Hz, 2H), 3.64 (s, 2H), 2.01 (q, J = 6.9 Hz, 2H), 1.60 (d, J = 1.2 Hz, 3H), 1.27 (s, 18H), 0.94 – 0.83 (m, 3H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 171.5, 134.2, 130.2, 129.7, 129.3, 128.6, 127.1, 70.7, 41.5, 31.9, 29.6 (d, J = 7.9 Hz), 29.5 – 29.2 (m), 27.7, 22.7, 14.2, 13.9; **HRMS**: (EI-MS) [$C_{22}H_{34}O_2$] ((M+NH_4)+), obs.: 348.290, calcd.: 348.289.

(E)-7-phenylhept-2-en-4-yl 2-phenylacetate (408d)

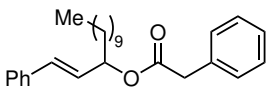


408d

Following general procedure **C**: **406d** (0.329 g, 1.00 mmol, 1.00 equiv.), **373a** (0.408 g, 3.00 mmol, 3.00 equiv); NaF (0.0420 g, 1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 100:0 to 0:100); colourless oil; NMR yield: 52%; isolated yield: 0.120 g, 0.389 mmol, 39%.

$\mathbf{R}_f$ = 0.60 (PE/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 697, 746, 910, 962, 1036, 1077, 1133, 1252, 1297, 1346, 1454, 1495, 1603, 1730, 2859, 2930, 2978, 3027, 3064; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.38 – 7.23 (m, 8H), 7.22 – 7.06 (m, 3H), 5.74 – 5.59 (m, 1H), 5.52 – 5.18 (m, 2H), 2.63 – 2.51 (m, 2H), 2.04 (q, J = 7.3 Hz, 1H), 1.76 – 1.55 (m, 4H), 1.28 (d, J = 6.4 Hz, 2H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 171.0, 142.3, 134.3, 133.0, 129.8, 129.3 (d, J = 1.9 Hz), 128.5 (d, J = 3.7 Hz), 128.4, 128.3, 127.0, 125.8, 75.2, 71.6, 41.8, 35.6, 35.3, 34.1, 31.6, 30.6, 27.0, 20.4, 17.8; **HRMS**: (EI-MS) [$C_{21}H_{24}O_2$] ((M+NH_4)+), obs.: 326.211, calcd.: 326.211.

(E)-1-phenyltridec-1-en-3-yl 2-phenylacetate (408f)



408f

Following general procedure **C**: **406f** (0.413 g, 1.00 mmol, 1.00 equiv.), **373a** (0.408 g, 3.00 mmol, 3.00 equiv); NaF (0.0420 g,

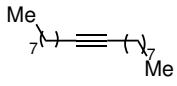
1.00 mmol, 1.00 equiv.); HFIP (1.00 mL); column chromatography (PE/tol 100:0 to 0:100); colourless oil; NMR yield: 84%; isolated yield: 0.260 g, 0.660 mmol, 66%.

$\mathbf{R}_f$ = 0.71 (PE/EtOAc 10:1); IR (neat): ν [cm^{-1}] = 719, 746, 842, 962, 1074, 1133, 1249, 1297, 1342, 1454, 1495, 1603, 1733, 2855, 2922, 3030, 3064; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.33 – 7.13 (m, 10H), 6.45 (dd, J = 16.0, 1.0 Hz, 1H), 6.06 (dd, J = 15.9, 7.1 Hz, 1H), 5.36 (q, J = 6.8 Hz, 1H), 3.60 (s, 2H), 1.62 (tt, J = 13.7, 6.7 Hz, 2H), 1.21 (dd, J = 6.6, 3.4 Hz, 16H), 0.89 – 0.78 (m, 3H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 170.9, 136.4, 134.2, 132.3, 129.3, 128.6, 127.9, 127.7, 127.1, 126.6, 75.2, 41.8, 34.6, 31.9, 29.7 – 29.5 (m), 29.4, 25.1, 22.7, 14.2; **HRMS**: (EI-MS) [$C_{27}H_{36}O_2$] ((M+NH_4)+), obs.: 410.305, calcd.: 410.305.

9.4 Synthesis of alkynes

General procedure **D** for the esterification of diol **187**: Deprotected alkyne (1.00 equiv), DMAP (0.20 equiv), Et3N (3.00 equiv) were dissolved in DCM (0.10 M) at 0 °C. Acid chloride (2.50 equiv) was added slowly, and the reaction was stirred overnight at RT. The reaction was quenched with Et_2O, the ppt. was filtered off, and the solvent was removed under reduced pressure. The residue was purified via column chromatography on silica gel to give the title compound.[116]

octadec-9-yne **(180b)**

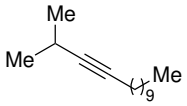


180b

To a freshly distilled solution of 1-decyne (**181**) (1.80 mL, 10.0 mmol, 1.00 equiv) in dry THF (15.0 mL) cooled to -78 °C was added *n*-BuLi (1.56 M in hexane, 6.41 mL, 10.0 mmol, 1.00 equiv) dropwise. The solution was stirred for 10 min, and freshly distilled 1-bromooctane (**182**) (1.73 mL, 10.0 mmol, 1.00 equiv) and freshly distilled DMAPU (7.00 mL) was added dropwise. The solution was warmed to RT and stirred for 4 days at rt. The reaction was quenched by adding sat. aq. NH_4Cl-sol. and extracted with EtOAc (3x). The combined organic phases were washed with brine, and dried over Na_2SO_4. The solvent was removed under pressure, and the residue was purified on silica gel (*n*-hexane) to give the product as a colourless oil in 83% yield.[107]

$\mathbf{R}_f = 0.47$ (*n*-hexane); IR (neat): ν [cm^{-1}] = 2922, 2855, 1461, 723; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 2.14 (s, 4H), 1.53 – 1.21 (m, 24H), 0.94 – 0.82 (m, 6H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 80.3, 31.9, 30.3 – 28.1 (m), 22.7, 18.8, 14.1; **HRMS**: (EI-MS) [$C18H34^{+\bullet}$] ([M]$^{+\bullet}$), obs.: 250.2669, calcd.: 250.2661.

2-methyltetradec-3-yne **(180k)**



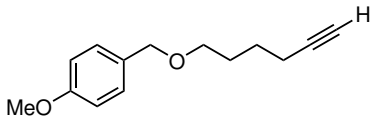
180k

To a solution of 3-methylbut-1-yne (**190**) (1.01 mL, 10.0 mmol, 1.00 equiv) in dry THF (8.00 mL) cooled to -78 °C was added *n*-BuLi (2.45 M in hexane, 10.0 mL, 22.0 mmol, 2.20 equiv.) dropwise. The reaction was stirred for 3h at -78 °C, after which 1-bromodecane (**191**) (2.08 mL, 10.0 mmol, 1.00 equiv.), and DMAPU (7.00 mL) was added dropwise. The solution was warmed to rt and stirred for 24 h. The reaction was quenched by adding sat. aq. NH_4Cl-sol. and extracted with EtOAc (3x). The combined organic phases were washed with brine, and dried over

Na_2SO_4. The solvent was removed under pressure, and the residue was purified on silica gel (*n*-pentane) to give the product as a colourless oil (1.04 g, 4.96 mmol, 50% yield).[107]

R$_f$ = 0.81 (*n*-pentane); IR (neat): ν [cm^{-1}] = 2963, 2922, 2855, 1461, 1379, 1320, 1185, 1107, 1051, 924, 723; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 2.52 (dtd, J = 13.7, 6.8, 2.2 Hz, 1H), 2.13 (td, J = 7.0, 2.2 Hz, 2H), 1.57 – 1.18 (m, 17H), 1.14 (d, J = 6.9 Hz, 6H), 0.96 – 0.81 (m, 3H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 86.1, 79.5, 32.1, 29.7 (d, J = 2.2 Hz), 29.5, 29.3 (d, J = 2.7 Hz), 29.0, 23.6, 22.8, 20.7, 18.9, 14.3; **HRMS**: (EI-MS) [C15H28$^{+\bullet}$] ([M]$^{+\bullet}$), obs.: 208.2188, calcd.: 208.2185.

1-((hex-5-yn-1-yloxy)methyl)-4-methoxybenzene (183)

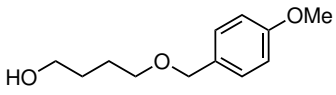


183

To a stirred solution of 5-hexyn-1-ol (4.91 g, 50.0 mmol, 1.00 equiv) and 4-methoxy benzoyl chloride (6.75 mL, 50.0 mmol, 1.00 equiv) in DMF (50.0 mL) at 0 °C was added NaH (4.00 g, 100 mmol, 2.00 equiv) portionwise, and then $Bu_4N^+Br^-$ (1.61 g, 5.00 mmol, 0.10 equiv), under N_2. The reaction was stirred at 0 °C for 2 h, and then for 16 h at RT. The reaction was quenched by pouring onto ice and extracted with EtOAc (3x). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under pressure, and the residue was purified on silica gel (PE/EtOAc 20:1) to give the product as a colourless oil in quantitative yield.[109]

R$_f$ = 0.46 (PE/EtOAc, 20:1); IR (neat): ν [cm^{-1}] = 3295, 2937, 2858, 1610, 1513, 1461, 1360, 1300, 1244, 1174, 1092, 1036, 820, 756; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.32 – 7.18 (m, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.47 (t, J = 6.2 Hz, 2H), 2.21 (td, J = 6.9, 2.7 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.78 – 1.52 (m, 4H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 159.1, 130.6, 129.2, 113.8, 84.4, 72.6, 69.4, 68.4, 55.3, 28.8, 25.3, 18.2; **HRMS**: (EI-MS) [C14H17O2$^{\bullet}$] ([M−H]$^{\bullet}$), obs.: 238.0252, calcd.: 238.0261.

4-((4-methoxybenzyl)oxy)butan-1-ol (185)



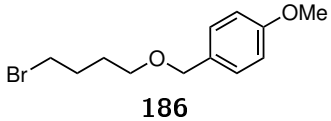
185

To a suspension of NaH (2.00 g, 50.0 mmol, 1.00 equiv) in THF (50.0 mL) at 0 °C was added 1,4-butandiol (4.51 g, 50.0 mmol, 1.00 equiv) dropwise. The reaction was stirred at

0 °C for 10 min. $Bu_4N^+I^-$ (1.85 g, 5.00 mmol, 0.100 equiv), and 4-methoxy benzoyl chloride (6.78 mL, 50.0 mmol, 1.00 equiv) were added, and the reaction was stirred at 0 °C for 30 min. The reaction was warmed to RT and stirred for 17 h at RT. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified on silica gel (PE/EtOAc 4:1) to give the product as a colourless oil in quantitative yield.[111]

$\mathbf{R}_f$ = 0.32 (PE/EtOAc, 1:1); IR (neat): ν [cm^{-1}] = 3380, 3000, 2937, 2862, 1610, 1587, 1513, 1461, 1360, 1300, 1244, 1174, 1088, 1058, 1032, 957, 816, 752, 708; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.34 – 7.13 (m, 2H), 6.97 – 6.80 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.63 (td, J = 5.9, 1.0 Hz, 2H), 3.49 (t, J = 5.6 Hz, 2H), 2.26 (s, 1H), 1.80 – 1.56 (m, 4H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 129.4, 113.8, 72.8, 70.1, 62.8, 55.3, 30.3, 26.8; **HRMS**: (EI-MS) [$C_{12}H_{18}O_3$] ([M]), obs.: 210.13, calcd.: 210.12.

1-((4-bromobutoxy)methyl)-4-methoxybenzene **(186)**



186

To a solution of 4-((4-methoxybenzyl)oxy)butan-1-ol (5.14 g, 24.4 mmol, 1.00 equiv.) in MeCN/DCM 5:1 at 0 °C was added PPh_3 (11.5 g, 31.7 mmol, 1.30 equiv) and CBr_4 (10.5 g, 31.7 mmol, 1.30 equiv.) in portions. The solution was warmed to RT stirred overnight. The precipitate was filtered over a plug of silica gel and the solvent was removed under reduced pressure. The residue was purified on silica gel (PE/EtOAc 30:1) to give the title compound as a yellow oil (5.40 g, 19.8 mmol, 81%).

$\mathbf{R}_f$ = 0.26 (PE/EtOAc, 10:1); IR (neat): ν [cm^{-1}] = 3004, 2937, 2840, 1736, 1684, 1610, 1513, 1461, 1364, 1300, 1244, 1174, 1095, 1032, 872, 820, 756; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.29 – 7.21 (m, 2H), 6.92 – 6.83 (m, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.45 (dt, J = 13.5, 6.5 Hz, 4H), 2.04 – 1.87 (m, 2H), 1.83 – 1.65 (m, 2H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 158.8, 130.2, 113.5, 72.2, 68.6, 54.9, 33.5, 29.4, 28.0; **HRMS**: (EI-MS) [$C_{12}H_{17}BrO_2$] ([M]), obs.: 272.06, calcd.: 272.04.

1,10-bis((4-methoxybenzyl)oxy)dec-5-yne **(180c)**

180c

To a solution of **183** (1.09 g, 5.00 mmol, 1.00 equiv.) was added *n*-BuLi (2M in cyclohexane, 3.75 mL, 7.50 mmol, 2.00 equiv.) dropwise at -78 °C and stirred for 3 h at -78 °C. **186** (1.37 g, 5.00 mmol, 1.00 equiv.) and DMAPU (3.50 mL) were added dropwise. The solution was warmed slowly to RT and was stirred for 3 days. The reaction was quenched by adding sat. aq. NH_4Cl-sol. and the aqueous phase extracted with EtOAc (3x). The combined organic layers were washed with brine, washed with anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified via column chromatography on silica gel (PE/EtOAc 10:1) to obtain the title compound as colourless oil (1.15 g, 2.80 mmol, 56%).

$\mathbf{R}_f$ = 0.56 (PE/EtOAc, 1:1); IR (neat): ν [cm^{-1}] = 2937, 2855, 1736, 1610, 1513, 1401, 1360, 1300, 1244, 1174, 1092, 1036, 816; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.26 (dt, 4H), 6.94 – 6.80 (m, 4H), 4.43 (s, 4H), 3.80 (s, 6H), 3.45 (t, J = 6.4 Hz, 4H), 2.24 – 2.09 (m, 4H), 1.78 – 1.61 (m, 4H), 1.55 (dtd, J = 9.4, 6.8, 4.9 Hz, 4H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 159.1, 130.7, 129.2, 113.8, 80.1, 72.5, 69.6, 55.3, 28.9, 25.8, 18.6; **HRMS**: (ES-MS) [$C_{26}H_{35}O_4$+] ([M^+H]$^+$), obs.: 411.2537, calcd.: 411.2530.

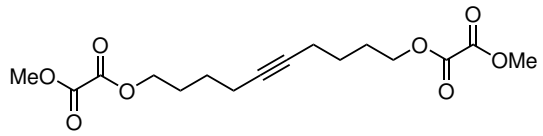
dec-5-yne-1,10-diol **(187)**

187

To a solution of **180c** (1.20 g, 3.00 mmol, 1.00 equiv.) in DCM/H_2O (19:1; 3.00 mL) at 0°C was added DDQ (2.00 g, 9.00 mmol, 3.00 equiv.). The mixture was stirred overnight at RT. The reaction was quenched with sat. aq. $NaHCO_3$-sol. and extracted with DCM (3x). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvent removed under pressure. The residue was purified via column chromatography on silica gel (PE/EtOAc 1:1) to obtain the title compound (0.040 g, 0.230 mmol, 49% yield.[115]

$\mathbf{R}_f$ = 0.07 (PE/EtOAc, 1:1); IR (neat): ν [cm^{-1}] = 3317, 2937, 2862, 1736, 1651, 1435, 1371, 1334, 1259, 1207, 1162, 1054, 980, 931, 905; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 3.61 (t, J = 6.4 Hz, 4H), 2.61 (s, 2H), 2.16 (td, J = 6.7, 6.0, 1.9 Hz, 4H), 1.64 (dqd, J = 9.5, 6.1, 5.6, 1.4 Hz, 4H), 1.58 – 1.45 (m, 4H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 80.4, 62.3, 31.8, 25.3, 18.6; **HRMS**: (APCI) [$C_{10}H_{19}O_2$+] ([M^+H]$^+$), obs.: 171.1387, calcd.: 171.1380.

O,O'-(dec-5-yne-1,10-diyl) dimethyl dioxalate (180e)

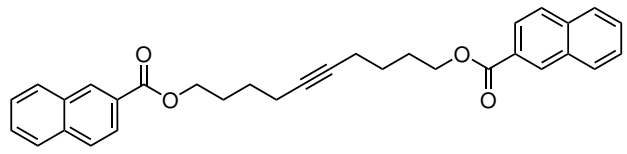


180e

Following general procedure **D** dec-5-yne-1,10-diol **187** (0.550 g, 3.23 mmol, 1.00 equiv), DMAP (0.078 g, 0.646 mmol, 0.200 equiv), Et_3N (1.08 mL, 7.75 mmol, 2.40 equiv), methyl chlorooxoacetate (0.89 mL, 9.69 mmol, 3.00 equiv). Eluting with PE/EtOAc 10:1 to 2:1; yield: 0.435 g, 1.27 mmol, 39%, white solid.

$\mathbf{R}_f$ = 0.25 (PE/EtOAc, 2:1); IR (neat): ν [cm^{-1}] = 3485, 2952, 2907, 2870, 1736, 1654, 1438, 1326, 1267, 1207, 1162, 1043, 924, 790, 745; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 4.27 (t, J = 6.6 Hz, 4H), 3.85 (s, 2H), 2.21 – 2.09 (m, 1H), 1.87 – 1.72 (m, 1H), 1.60 – 1.47 (m, 4H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 158.2, 157.6, 79.9, 66.8, 53.6, 27.4, 25.1, 18.3; **HRMS**: (ESI) [$C_{16}H_{23}O_8$+] ($[M]^+$), obs.: 343.139, calcd.: 343.138.

dec-5-yne-1,10-diyl bis(2-naphthoate) (180f)



180f

Following general procedure **D** dec-5-yne-1,10-diol **187** (0.354 g, 2.08 mmol, 1.00 equiv), DMAP (0.050 g, 0.415 mmol, 0.200 equiv), Et_3N (0.869 mL, 6.24 mmol, 3.00 equiv), 2 naphthoyl chloride (0.989 g, 5.20 mmol, 2.50 equiv). Eluting with PE/EtOAc 20:1; yield: 0.948 g, 1.98 mmol, 95%, white solid.

$\mathbf{R}_f$ = 0.31 (PE/EtOAc, 10:1); **mp.**: 82 °C; IR (neat): ν [cm^{-1}] = 3056, 2944, 2117, 1707, 1628, 1595, 1505, 1468, 1435, 1394, 1356, 1271, 1230, 1196, 1103, 1010, 965, 864, 823, 779; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.63 – 8.57 (m, 2H), 8.05 (dd, J = 8.6, 1.7 Hz, 2H), 7.99 – 7.91 (m, 2H), 7.90 – 7.83 (m, 4H), 7.63 – 7.48 (m, 4H), 4.41 (t, J = 6.5 Hz, 4H), 2.33 – 2.24 (m, 4H), 1.94 (tt, J = 8.7, 6.2 Hz, 4H), 1.77 – 1.64 (m, 4H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 166.8, 135.5, 132.5, 131.0, 129.4, 128.2 (d, J = 5.5 Hz), 127.8, 127.6, 126.6, 125.3, 80.2, 64.8, 28.0, 25.7, 18.6; **HRMS**: (ESI) [$C_{32}H_{30}O_4$+] ($[M]^+$), obs.: 479.223, calcd.: 479.221.

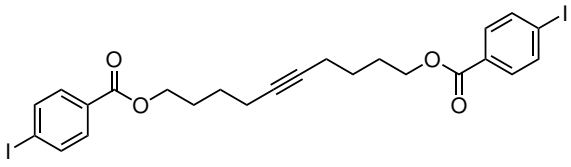
dec-5-yne-1,10-diyl dibenzoate (180g)

180g

Following general procedure **D** dec-5-yne-1,10-diol **187** (0.275 g, 1.62 mmol, 1.00 equiv), DMAP (0.040 g, 0.323 mmol, 0.200 equiv), Et_3N (0.673 mL, 4.84 mmol, 3.00 equiv), benzoyl chloride (0.566 g, 4.03 mmol, 2-50 equiv). Eluting with PE/EtOAc 20:1; yield: 0.528 g, 1.39 mmol, 86%, yellow oi.l

$\mathbf{R}_f$ = 0.35 (PE/EtOAc, 5:1); IR (neat): ν [cm^{-1}] = 3063, 2948, 2866, 1714, 1453, 1386, 1315, 1267, 1177, 1114, 1069, 1025, 939, 853, 805, 708; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.08 – 8.00 (m, 4H), 7.59 – 7.49 (m, 2H), 7.47 – 7.39 (m, 4H), 4.34 (t, J = 6.4 Hz, 4H), 2.31 – 2.18 (m, 4H), 1.88 (tt, J = 8.7, 6.1 Hz, 4H), 1.72 – 1.57 (m, 4H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 166.6, 132.9, 129.6, 128.3, 80.1, 64.6, 27.9, 25.7, 18.5; **HRMS**: (ESI) [$C_{24}H_{27}O_4$+] ([M]$^+$), obs.: 379.191, calcd.: 379.190.

dec-5-yne-1,10-diyl bis(4-iodobenzoate) (180h)

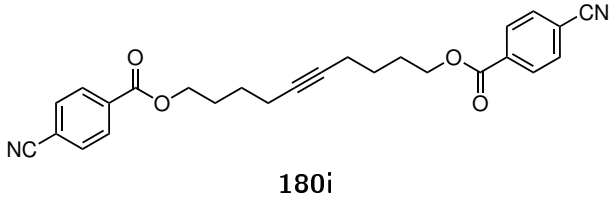


180h

Following general procedure **D** dec-5-yne-1,10-diol **187** (0.500 g, 2.93 mmol, 1.00 equiv), DMAP (0.071 g, 0.586 mmol, 0.200 equiv), Et_3N (1.22 mL, 8.79 mmol, 3.00 equiv), 4 iodobenzoyl chloride (1.95 g, 7.32 mmol, 2.50 equiv). Eluting with PE/EtOAc 20:1; yield: 1.31 g, 2.08 mmol, 71%, white solid.

$\mathbf{R}_f$ = 0.41 (PE/EtOAc, 10:1); **mp.**: 68.8 °C; IR (neat): ν [cm^{-1}] = 2940, 2899, 2866, 2109, 1703, 1584, 1468, 1390, 1312, 1267, 1170, 1118, 961, 928, 842, 749, 682; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 7.87 – 7.65 (m, 8H), 4.32 (t, J = 6.5 Hz, 4H), 2.36 – 2.13 (m, 4H), 1.87 (tt, J = 8.6, 6.3 Hz, 4H), 1.75 – 1.55 (m, 4H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 166.1, 137.7, 131.0, 129.8, 100.7, 80.1, 64.9, 27.9, 25.6, 18.5; **HRMS**: (ESI) [$C_{24}H_{25}I_2O_4$+] ([M^+H]$^+$), obs.: 630.984, calcd.: 630.983.

dec-5-yne-1,10-diyl bis(4-cyanobenzoate) (180i)



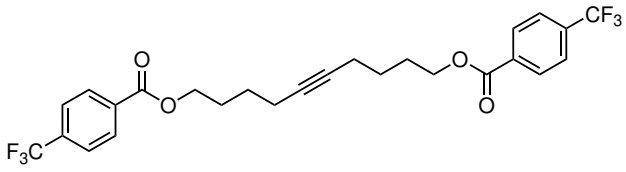
180i

Following general procedure **D** dec-5-yne-1,10-diol **187** (0.203 g, 1.19 mmol, 1.00 equiv), DMAP (0.029 g, 0.238

mmol, 0.200 equiv), Et_3N (0.497 mL, 3.57 mmol, 3.00 equiv), 4-cyanobenzoyl chloride (0.491 g, 2.97 mmol, 2.50 equiv). Eluting with PE/EtOAc 10:1 to 5:1; yield: 0.441 g, 1.03 mmol, 87%, white solid.

R_f = 0.28 (PE/EtOAc, 2.5:1); **mp.**: 110.8 °C; IR (neat): ν [cm^{-1}] = 3101, 2940, 2873, 2232, 2119, 1722, 1476, 1405, 1367, 1312, 1274, 1118, 1017, 946, 868, 767, 738, 689; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.23 – 8.07 (m, 4H), 7.81 – 7.66 (m, 4H), 4.37 (t, J = 6.5 Hz, 4H), 2.33 – 2.16 (m, 4H), 1.98 – 1.80 (m, 4H), 1.64 (dd, J = 8.9, 6.1 Hz, 4H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 164.9, 134.0 (d, J = 14.1 Hz), 132.2 (d, J = 1.5 Hz), 130.1 (d, J = 2.3 Hz), 128.8 (d, J = 28.9 Hz), 118.0, 116.4 (d, J = 3.3 Hz), 106.9, 98.1, 80.1, 65.5 (d, J = 10.5 Hz), 64.6, 33.0, 27.7 (d, J = 12.1 Hz), 25.5, 24.8, 23.2, 18.4; **HRMS**: (ESI) [$C_{16}H_{25}N_2O_4$+] ($[M]^+$), obs.: 429.181, calcd.: 429.180.

dec-5-yne-1,10-diyl bis(4-(trifluoromethyl)benzoate) (180j)



180j

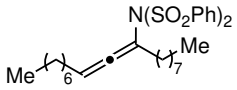
Following general procedure **D** dec-5-yne-1,10-diol **187** (0.009 g, 0.528 mmol, 1.00 equiv), DMAP (0.012 g, 0.105 mmol, 0.200 equiv), Et_3N (0.221 mL, 1.59 mmol, 3.00 equiv), 4-(Trifluoromethyl) benzoyl chloride (0.196 mL, 1.32 mmol, 2.50 equiv). Eluting with PE/EtOAc 20:1; yield: 0.251 g, 0.48 mmol, 92%, colourless oil.

R_f = 0.28 (PE/EtOAc, 10:1); IR (neat): ν [cm^{-1}] = 2948, 1722, 1412, 1323, 1271, 1166, 1118, 1017, 861, 775, 704; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.15 (dp, J = 7.8, 0.8 Hz, 4H), 7.76 – 7.65 (m, 4H), 4.38 (t, J = 6.5 Hz, 4H), 2.33 – 2.20 (m, 4H), 1.90 (tt, J = 8.5, 6.3 Hz, 4H), 1.74 – 1.57 (m, 4H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 266.6, 165.4, 129.9, 125.4 (d, J = 3.7 Hz), 80.1, 65.2, 27.8, 25.6, 18.5; **^{19}F NMR** (377MHz, $CDCl_3$): δ [ppm] = -63.6; **HRMS**: (ES) [$C_{26}H_{25}F_6O_4$+] ($[M^+H]^+$), obs.: 515.1655, calcd.: 515.17.

9.5 Synthesis of allenes

General procedure **E** for the synthesis of allenes: Alkyne **180** (1 mmol, 1.0 equivuiv), (2-anisyl)$_2$Se$_2$ (9.0 mg, 25.0 µmol, 2.5 mol%), Li_2CO_3 (74.0 mg, 1.0 mmol, 1.0 equivuiv) and molecular sieves (4 Å, powdered, 30.0 mg) are suspended in dry toluene (4.0 mL) and heated to 100°C. A solution of NFSI (378.0 mg, 1.2 mmol, 1.2 equiv.) in dry toluene (6.0 mL) is added via syringe pump over 3.5 h. The reaction is controlled for completion by TLC and NMR. The solvent is removed under reduced pressure and the residue is purified on silica gel to afford the title compound.

N-(octadeca-9,10-dien-9-yl)-N-(phenylsulfonyl)benzenesulfonamide (192e)

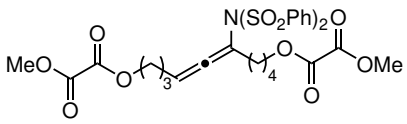


192e

Following general procedure **E**: octadec-9-yne (**180b**) (0.250 g, 1.00 mmol, 1.00 equiv); 51 h; eluting with *n*-pentane/EtOAc 10:1; NMR yield (standard 1,1,2,2-tetrachloroethane): 42%; isolated yield: 0.210 g, 0.391 mmol, 40%, colourless oil.

$\mathbf{R}_f$ = 0.29 (*n*-pentane/EtOAc, 10:1); IR (neat): ν [cm^{-1}] = 2922, 2851, 1449, 1375, 1166, 1084, 902, 752, 719, 685; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.00 (d, J = 7.7 Hz, 4H), 7.73-7.47 (m, 6H), 5.02 (tt, J = 7.4, 3.8 Hz, 1H), 2.26 (ddd, J = 7.9, 6.2, 3.8 Hz, 2H), 1.78 (dq, J = 10.2, 7.5 Hz, 2H), 1.24 (tt, J = 14.5, 6.4 Hz, 18H), 1.02-0.79 (m, 6H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 206.0, 133.6, 128.8, 106.7, 99.1, 33.5, 31.8 (d, J = 7.9 Hz), 29.5, 29.3, 29.0 (dd, J = 11.5, 5.3 Hz), 28.4, 26.8, 22.7 (d, J = 2.1 Hz), 14.1 (d, J = 1.8 Hz); **HRMS**: (ES) [$C_{30}H_{44}NO_4S_2$+] ([M$^+$H]$^+$), obs.: 546.268, calcd.: 545.27.

dimethyl O,O'-(6-(N-(phenylsulfonyl)phenylsulfonamido)deca-4,5-diene-1,10-diyl) dioxalate (192h)



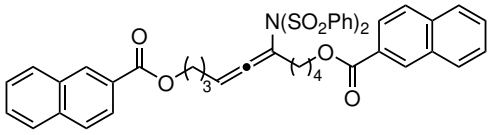
192h

Following general procedure **E**: O,O'-(dec-5-yne-1,10-diyl) dimethyl dioxalate(**180e**) (0.342 g, 1.00 mmol, 1.00 equiv); 4d; eluting with PE/EtOAc, 10:1 to 1:1; NMR yield (standard 1,3,5-trimethoxybenzene): 49%; isolated yield: 0.313 g, 0.490 mmol, 49%, yellow oil.

$\mathbf{R}_f$ = 0.25 (PE/EtOAc, 1:1); IR (neat): ν [cm^{-1}] = 2955, 1740, 1449, 1371, 1312, 1162, 1084, 902, 723, 685; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.01 (d, J = 7.6 Hz, 4H),

7.71-7.61 (m, 2H), 7.56 (dd, J = 8.4, 6.8 Hz, 4H), 5.05 (tt, J = 7.1, 3.7 Hz, 1H), 4.28 (td, J = 6.6, 0.9 Hz, 2H), 4.16 (t, J = 6.4 Hz, 2H), 3.90 (d, J = 1.0 Hz, 6H), 2.33 (td, J = 7.4, 3.7 Hz, 2H), 1.95 (q, J = 7.3 Hz, 2H), 1.86 1.62 (m, 4H), 1.49 (p, J = 7.6 Hz, 2H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 205.7, 158.5 – 156.7 (m), 133.5, 129.9 – 125.2 (m), 106.4, 97.6, 66.4 (d, J = 6.4 Hz), 65.6, 53.2, 32.4, 26.8 (d, J = 15.7 Hz), 24.1, 22.5; **HRMS**: (ESI) [$C_{28}H_{32}NO_{12}S_2$+] ([M^+H]$^+$), obs.: 638.137, calcd.: 638.136.

6-(N-(phenylsulfonyl)phenylsulfonamido)deca-4,5-diene-1,10-diyl bis(2-naphthoate) (192i)

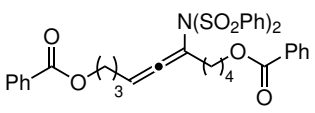


192i

Following general procedure **E**: dec-5-yne-1,10-diyl bis(2-naphthoate) (**180f**) (0.478 g, 1.00 mmol, 1.00 equiv); 4d; eluting with PE/EtOAc, 10:1 to 1:1; NMR yield (standard 1,3,5-trimethoxybenzene): 64%; isolated yield: 0.517 g, 0.613 mmol, 61%, yellow oil.

$\mathbf{R}_f$ = 0.52 (PE/EtOAc, 1:1); IR (neat): ν [cm^{-1}] = 3063, 2952, 2102, 1710, 1468, 1371, 1278, 1226, 1192, 1162, 1129, 1084, 1021, 954, 894, 827, 779, 719, 685; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.57 (dt, J = 4.8, 1.4 Hz, 2H), 8.02 (ddd, J = 8.4, 4.0, 2.6 Hz, 6H), 7.97-7.89 (m, 2H), 7.85 (ddd, J = 9.3, 5.0, 1.8 Hz, 5H), 7.66-7.44 (m, 10H), 5.13 (tt, J = 7.2, 3.7 Hz, 1H), 4.37 (t, J = 6.5 Hz, 2H), 4.28-4.19 (m, 2H), 2.42 (td, J = 7.5, 3.7 Hz, 2H), 2.02 (ddd, J = 8.4, 7.2, 6.3 Hz, 2H), 1.93-1.80 (m, 2H), 1.68 (dp, J = 39.3, 7.5, 7.0 Hz, 3H); **^{13}C NMR** (101MHz, $CDCl_3$): δ [ppm] = 206.3, 171.2, 166.7 (d, J = 10.2 Hz), 135.5 (d, J = 2.9 Hz), 133.8, 132.5, 131.0 (d, J = 3.7 Hz), 129.3 (d, J = 2.6 Hz), 128.9, 128.6, 128.2 (dd, J = 6.6, 2.9 Hz), 127.7 (d, J = 2.0 Hz), 127.6, 127.4, 126.7, 125.2, 107.0, 98.3, 64.5 (d, J = 70.4 Hz), 60.4, 33.1, 28.0 (d, J = 7.2 Hz), 25.0, 23.5, 21.1, 14.2; **HRMS**: (ESI) [$C_{44}H_{40}NO_8S_2$+] ([M^+H]$^+$), obs.: 774.220, calcd.: 774.219.

6-(N-(phenylsulfonyl)phenylsulfonamido)deca-4,5-diene-1,10-diyl dibenzoate (192a)



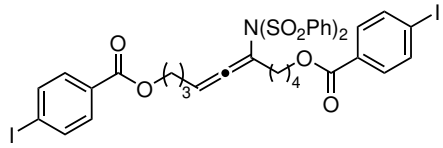
192a

Following general procedure **E**: dec-5-yne-1,10-diyl dibenzoate (**180g**) (0.378 g, 1.00 mmol, 1.00 equiv); 4d; eluting with PE/EtOAc, 10:1 to 1:1; NMR yield (standard 1,3,5-trimethoxybenzene): 49%; isolated yield: 0.288 g, 0.427 mmol,

43%, yellow oil.

$\mathbf{R}_f$ = 0.52 (PE/EtOAc, 2:1); IR (neat): ν [cm^{-1}] = 3063, 2952, 1714, 1449, 1371, 1315, 1271, 1162, 1114, 1084, 1025, 894, 752, 708, 685; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.02 (tt, J = 6.4, 3.1 Hz, 9H), 7.63-7.35 (m, 14H), 5.10 (tt, J = 7.2, 3.7 Hz, 1H), 4.29 (t, J = 6.4 Hz, 2H), 4.18 (td, J = 6.4, 1.4 Hz, 2H), 2.38 (td, J = 7.5, 3.8 Hz, 2H), 2.02-1.87 (m, 2H), 1.87-1.74 (m, 2H), 1.69 (dtd, J = 9.9, 8.4, 7.6, 6.2 Hz, 2H), 1.63-1.48 (m, 2H); ^{13}**C NMR** (101MHz, $CDCl_3$): δ [ppm] = 206.1, 166.4 (d, J = 9.2 Hz), 133.8, 132.9 (d, J = 5.9 Hz), 130.2 (d, J = 11.4 Hz), 129.5 (d, J = 2.3 Hz), 128.9, 128.7-128.0 (m), 106.9, 98.3, 64.7, 63.8, 33.0, 27.8 (d, J = 7.5 Hz), 24.9, 23.3; **HRMS**: (ESI) [$C_{36}H_{36}NO_8S_2$+] ([M^+H]$^+$), obs.: 674.186, calcd.: 674.187.

6-(N-(phenylsulfonyl)phenylsulfonamido)deca-4,5-diene-1,10-diyl bis(4-iodobenzoate) (192b)

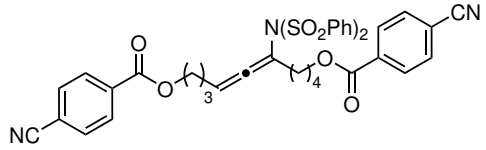


192b

Following general procedure **E**: dec-5-yne-1,10-diyl bis(4-iodobenzoate) [**180h**] (0.630 g, 1.00 mmol, 1.00 equiv); 4d; eluting with PE/EtOAc, 10:1 to 1:1; NMR yield (standard 1,3,5-trimethoxybenzene): 60%; isolated yield: 0.564 g, 0.609 mmol, 61%, yellow oil.

$\mathbf{R}_f$ = 0.74 (PE/EtOAc, 1:1); IR (neat): ν [cm^{-1}] = 3067, 2952, 2109, 1714, 1476, 1446, 1371, 1267, 1162, 1084, 1006, 902, 846, 719, 682; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.05-7.95 (m, 4H), 7.83-7.74 (m, 4H), 7.75-7.68 (m, 4H), 7.67-7.59 (m, 2H), 7.58-7.48 (m, 4H), 5.07 (tt, J = 7.1, 3.7 Hz, 1H), 4.28 (t, J = 6.5 Hz, 2H), 4.17 (t, J = 6.4 Hz, 2H), 2.36 (td, J = 7.4, 3.7 Hz, 2H), 1.97 (q, J = 7.3 Hz, 2H), 1.87-1.61 (m, 4H), 1.63-1.45 (m, 3H); ^{13}**C NMR** (75MHz, $CDCl_3$): δ [ppm] = 204.2, 163.9 (d, J = 8.8 Hz), 135.8 (d, J = 2.9 Hz), 132.0, 129.1 (d, J = 1.9 Hz), 127.8, 127.7, 127.0, 126.6, 105.0, 98.9 (d, J = 7.1 Hz), 96.3, 63.1, 62.1, 31.1, 25.8 (d, J = 9.7 Hz), 23.0, 21.4; **HRMS**: (ESI) [$C_{36}H_{34}I_2NO_8S_2$+] ([M^+H]$^+$), obs.: 925.982, calcd.: 925.981.

6-(N-(phenylsulfonyl)phenylsulfonamido)deca-4,5-diene-1,10-diyl bis(4-cyanobenzoate) (192c)



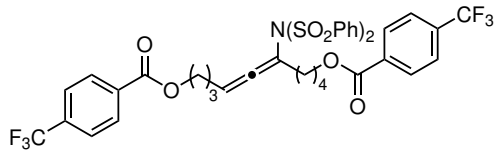
192c

Following general procedure **E**: dec-5-yne-1,10-diyl bis(4-cyanobenzoate) (**180i**) (0.428 g, 1.00 mmol,

1.00 equiv); 4d; eluting with PE/EtOAc, 10:1 to 1:1; NMR yield (standard 1,3,5-trimethoxybenzene): 59%; isolated yield: 0.411 g, 0.560 mmol, 56%, yellow oil.

$\mathbf{R}_f$ = 0.69 (PE/EtOAc, 1:1); IR (neat): ν [cm^{-1}] = 3067, 2952, 2232, 1718, 1584, 1449, 1371, 1271, 1162, 1110, 1021, 898, 861, 752, 719, 685; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.19-8.04 (m, 4H), 8.04-7.93 (m, 4H), 7.71 (dq, J = 8.2, 1.6 Hz, 4H), 7.69-7.55 (m, 2H), 7.58-7.46 (m, 4H), 5.06 (dh, J = 7.1, 3.8 Hz, 1H), 4.32 (t, J = 6.6 Hz, 2H), 4.24-4.16 (m, 2H), 2.45-2.31 (m, 2H), 1.99 (td, J = 7.6, 7.0, 5.9 Hz, 2H), 1.88-1.63 (m, 4H), 1.54 (dq, J = 10.1, 7.5 Hz, 2H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 164.7, 134.0, 132.0, 129.9, 117.8, 116.2, 79.8, 65.2, 27.6, 25.3, 18.2; **HRMS**: (ESI) [$C_{38}H_{34}N_3O_8S_2$+] ([M^+H]$^+$), obs.: 724.179, calcd.: 724.178.

6-(N-(phenylsulfonyl)phenylsulfonamido)deca-4,5-diene-1,10-diyl bis(4-(trifluoromethyl)benzoate) (192d)

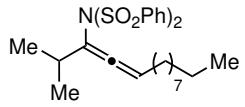


192d

Following general procedure **E**: dec-5-yne-1,10-diyl bis(4-(trifluoromethyl)benzoate) (**180j**) (0.514 g, 1.00 mmol, 1.00 equiv); 4d; eluting with PE/EtOAc, 10:1 to 1:1; NMR yield (standard 1,3,5-trimethoxybenzene): 65%; isolated yield: 0.515 g, 0.635 mmol, 64%, yellow oil.

$\mathbf{R}_f$ = 0.15 (n-pentane/EtOAc, 3:1); IR (neat): ν [cm^{-1}] = 2855, 1722, 1449, 1412, 1375, 1326, 1274, 1162, 1121, 1017, 905, 864, 775, 726; **^{1}H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.2-8.1 (m, 5H), 8.1-8.0 (m, 4H), 7.7-7.6 (m, 7H), 7.5 (dd, J = 8.4, 6.8 Hz, 4H), 5.1 (tt, J = 7.2, 3.7 Hz, 1H), 4.3 (t, J = 6.5 Hz, 2H), 4.2 (t, J = 6.4 Hz, 2H), 2.4 (td, J = 7.6, 3.7 Hz, 2H), 2.0 (q, J = 7.4 Hz, 2H), 1.9-1.7 (m, 4H), 1.6 (q, J = 8.0 Hz, 4H); **^{13}C NMR** (75MHz, $CDCl_3$): δ [ppm] = 206.3, 165.2 (d, J = 9.1 Hz), 134.5 (d, J = 4.3 Hz), 134.0 (d, J = 4.2 Hz), 133.9, 133.6, 133.4, 129.9 (d, J = 1.8 Hz), 128.9, 128.5, 126.2-124.7 (m), 121.8, 107.0, 98.2, 65.3, 64.3, 33.1, 30.8, 27.7 (d, J = 11.2 Hz), 24.8, 23.3; **^{19}F NMR** (377MHz, $CDCl_3$): δ [ppm] = -63.6 (d, J = 7.2 Hz); **HRMS**: (ESI) [$C_{38}H_{34}F_6NO_8S_2$+] ([M^+H]$^+$), obs.: 810.1629, calcd.: 810.1625.

N-(2-methyltetradeca-3,4-dien-3-yl)-N-(phenylsulfonyl)benzenesulfonamide (192j)



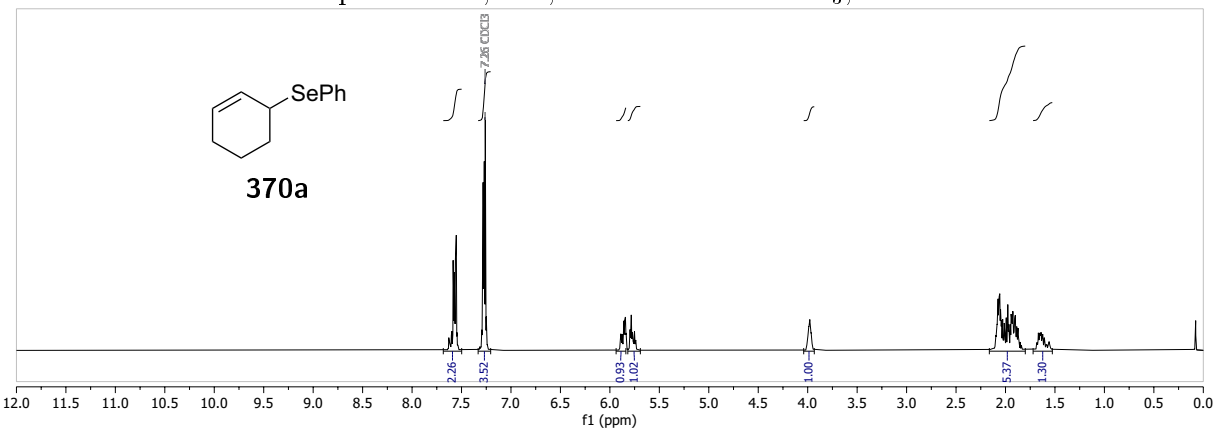
192j

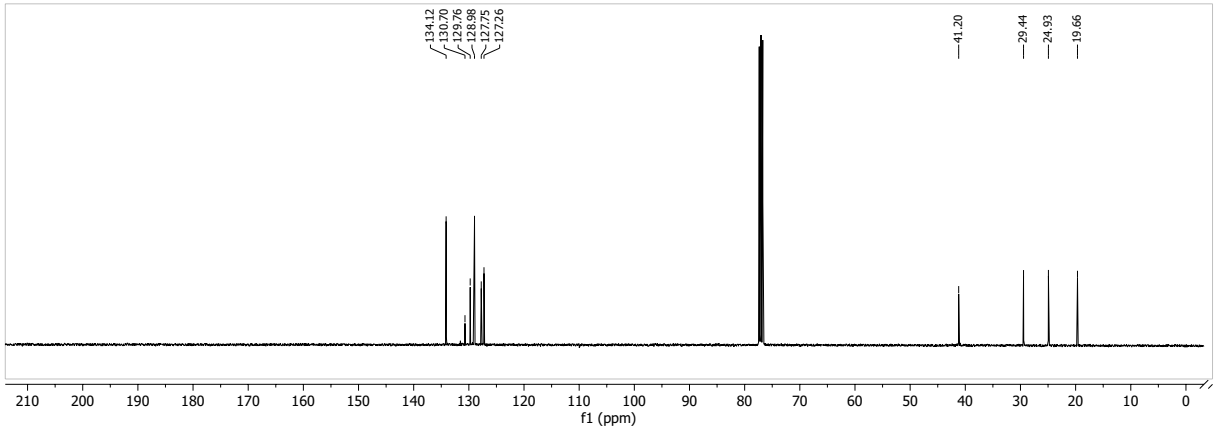
Following general procedure **E**: 2-methyltetradec-3-yne (**180k**) (0.208 g, 1.0 mmol, 1.00 equiv); 19 h; eluting with *n*-pentane/EtOAc 10:1; NMR yield (standard 1,1,2,2-tetrachloroethane): 42%; isolated yield: 0.0730 g, 0.145 mmol, 15%, colourless oil.

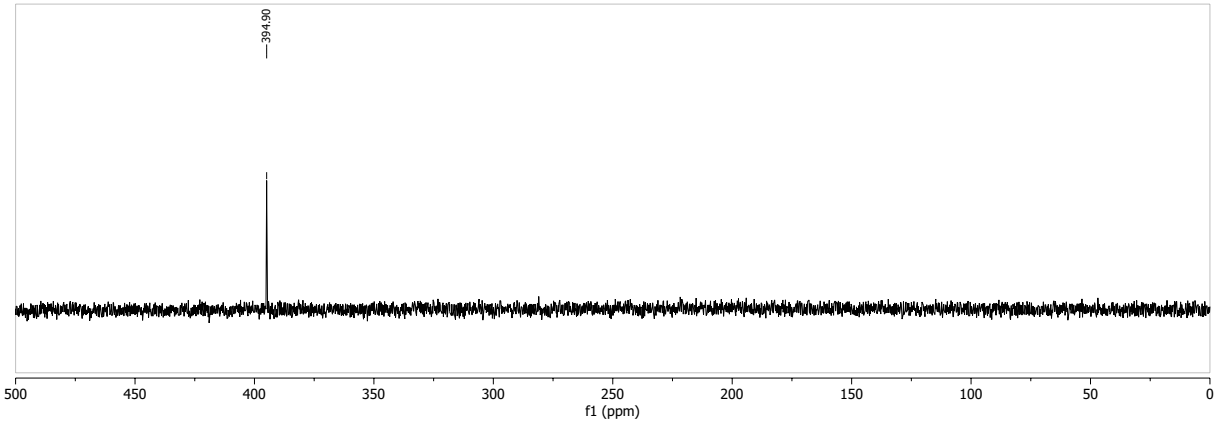
$\mathbf{R}_f$ = 0.47 (n-pentane/EtOAc, 10:1); IR (neat): ν [cm^{-1}] = 3068, 2926, 2855, 1587, 1449, 1375, 1166, 1085, 887, 820.8, 753, 719, 686; ^{1}**H NMR** (300MHz, $CDCl_3$): δ [ppm] = 8.05 – 7.87 (m, 4H), 7.70 – 7.58 (m, 2H), 7.56 – 7.45 (m, 5H), 4.99 (td, J = 7.3, 2.9 Hz, 1H), 2.60 (heptd, J = 6.8, 2.8 Hz, 1H), 1.79 (qd, J = 7.1, 4.6 Hz, 2H), 1.39 – 1.13 (m, 17H), 1.09 (dd, J = 6.9, 4.1 Hz, 6H), 0.98 – 0.82 (m, 3H); ^{13}**C NMR** (75MHz, $CDCl_3$): δ [ppm] = 205.4, 133.7, 130.6 – 127.1 (m), 112.1, 99.5, 32.3, 31.9, 29.5, 29.4 (d, J = 4.5 Hz), 29.0 (d, J = 5.9 Hz), 28.3, 22.7, 21.6, 21.2, 14.2; **HRMS**: (ESI) [$C_{27}H_{37}NO_4S_2$+] ([M^+H]$^+$), obs.: 504.2236, calcd.: 504.2237.

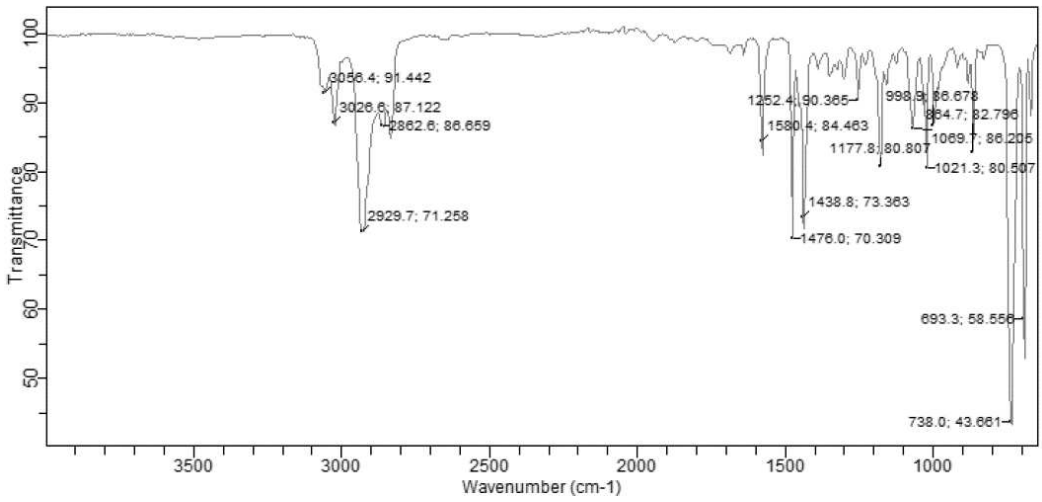
10 Spectra

Spectra: ^{1}H, ^{13}C, ^{77}Se NMR in $CDCl_3$; IR

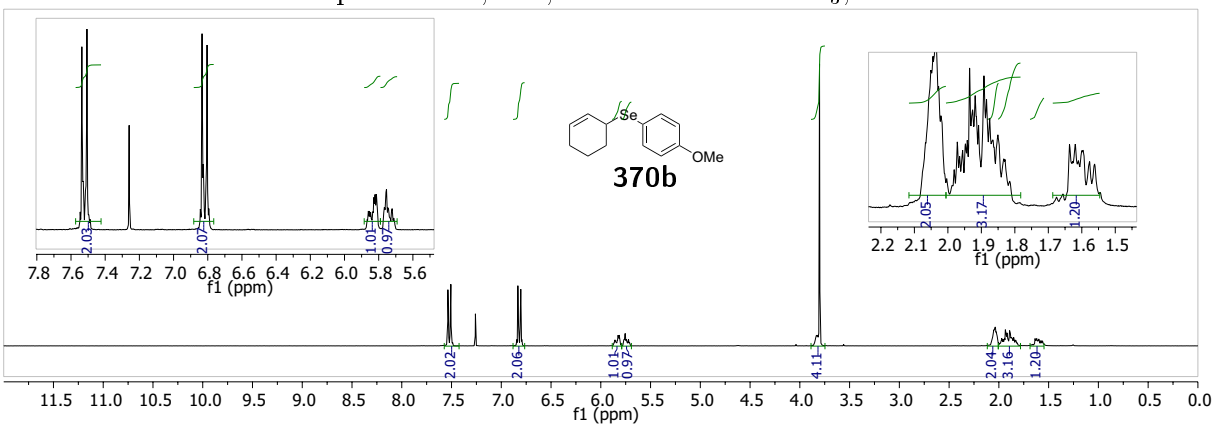


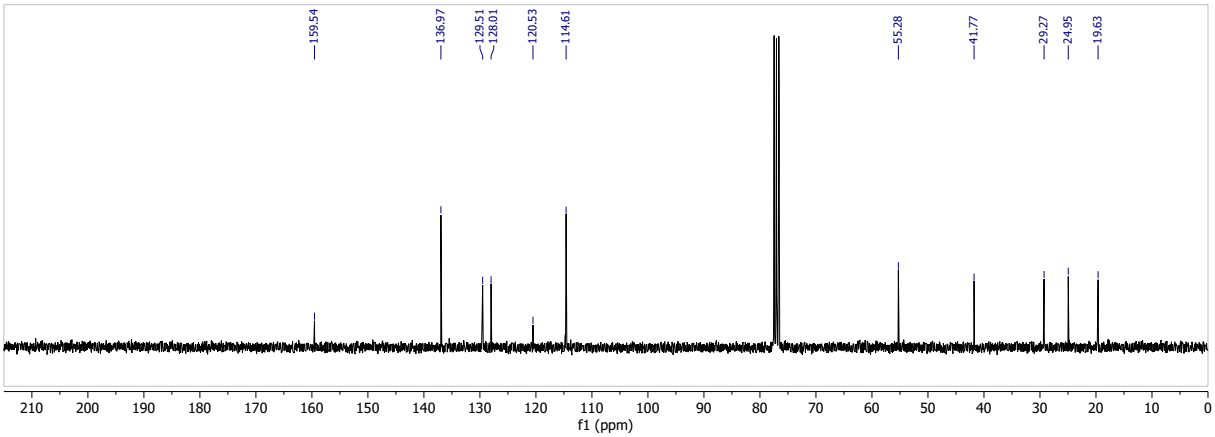


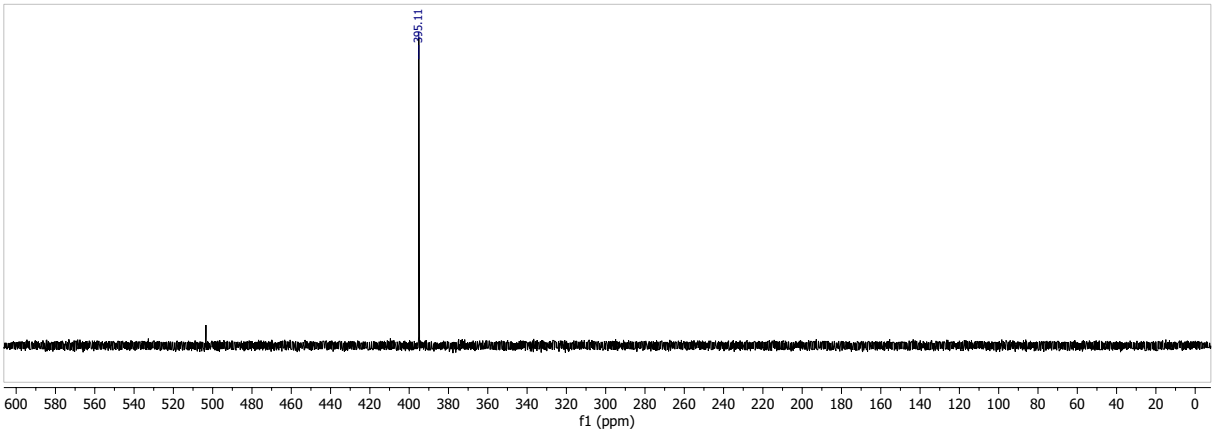


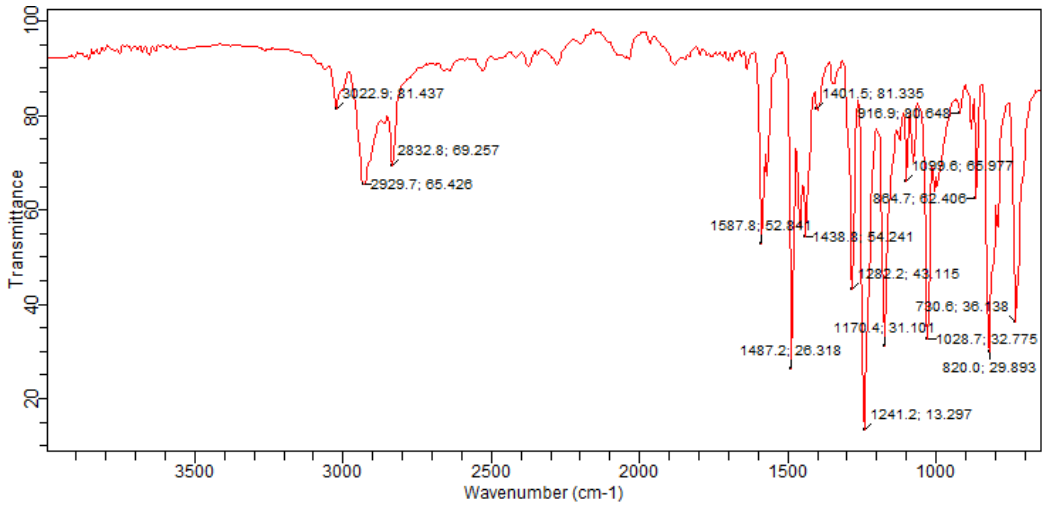


Spectra: ^{1}H, ^{13}C, ^{77}Se NMR in $CDCl_3$; IR

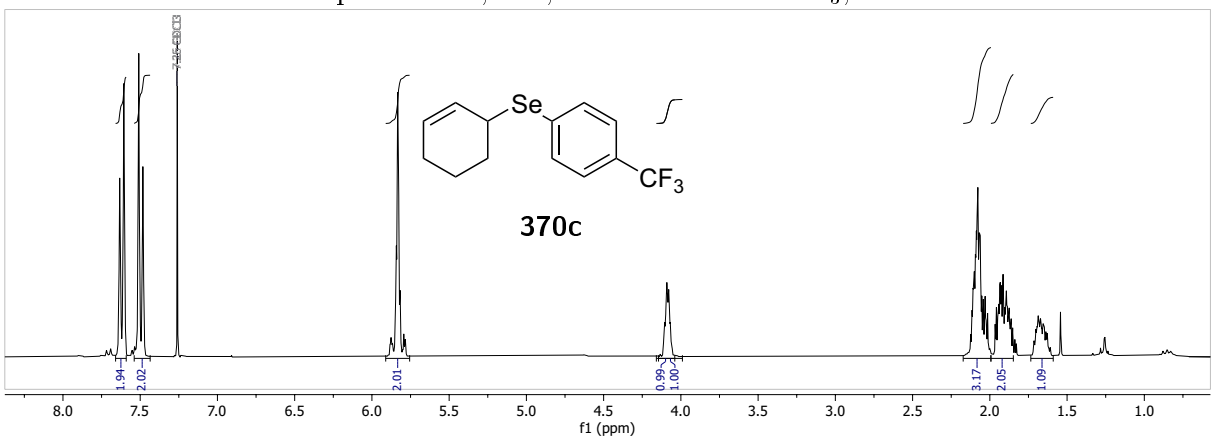


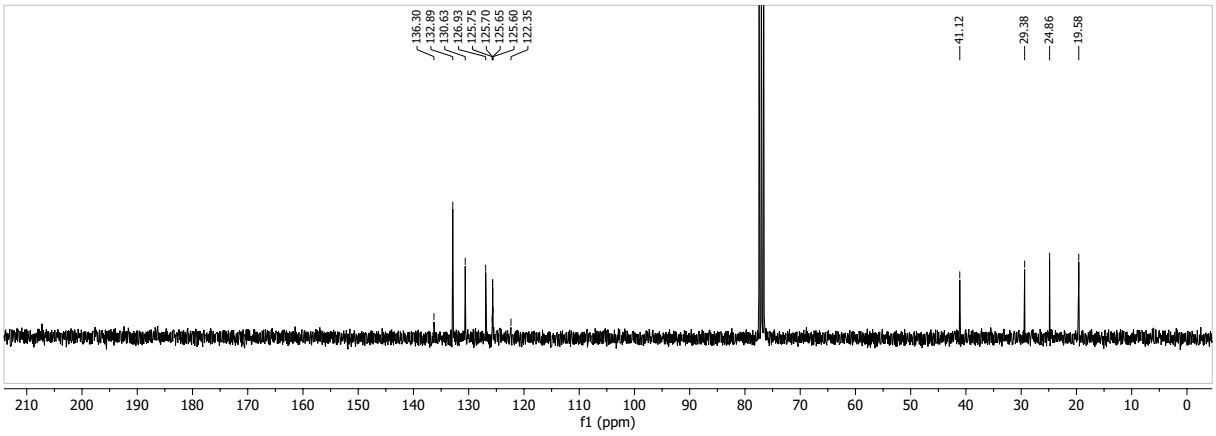


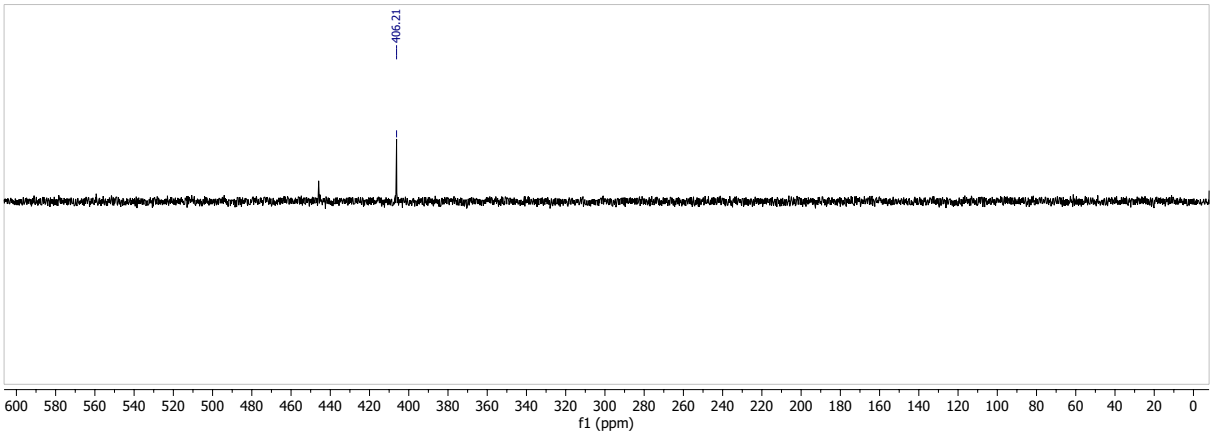


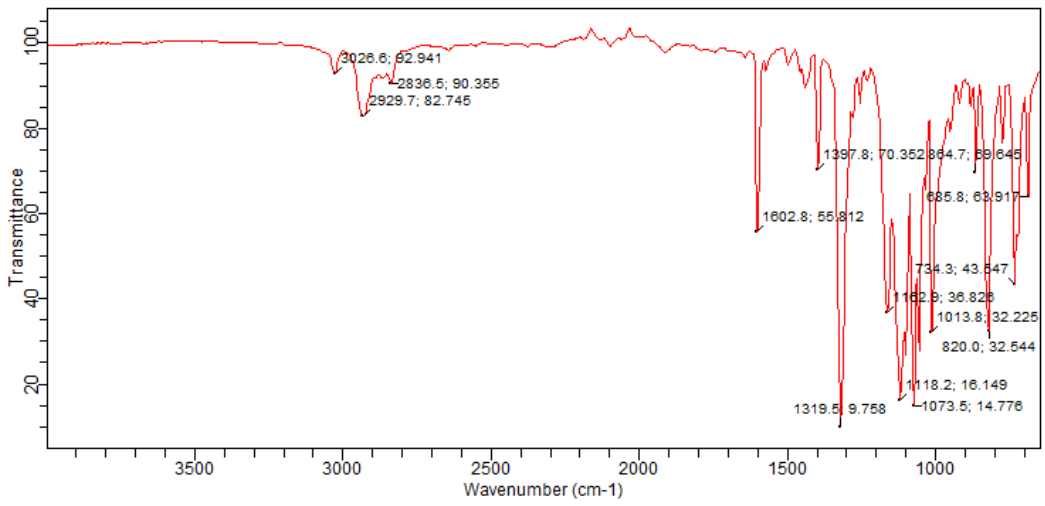


Spectra: ^{1}H, ^{13}C, ^{77}Se NMR in $CDCl_3$; IR

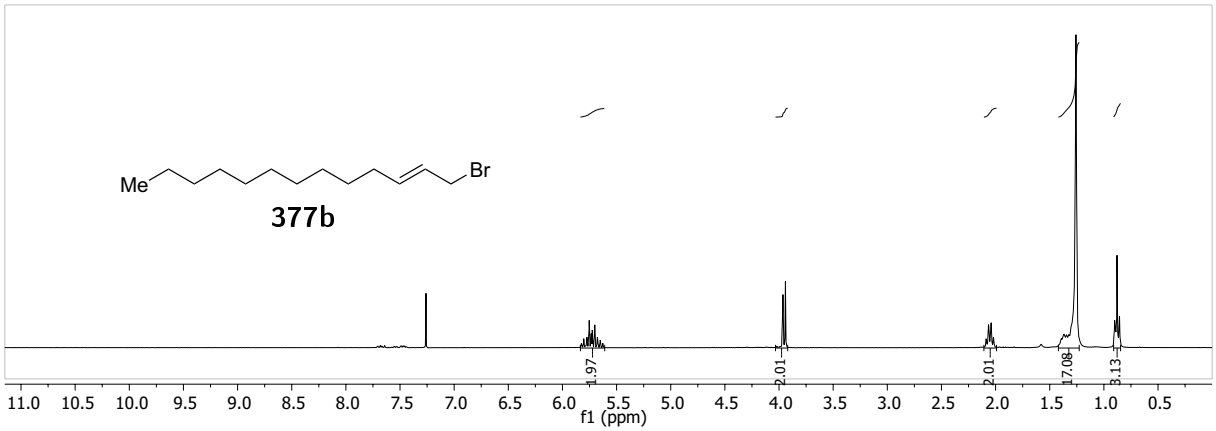


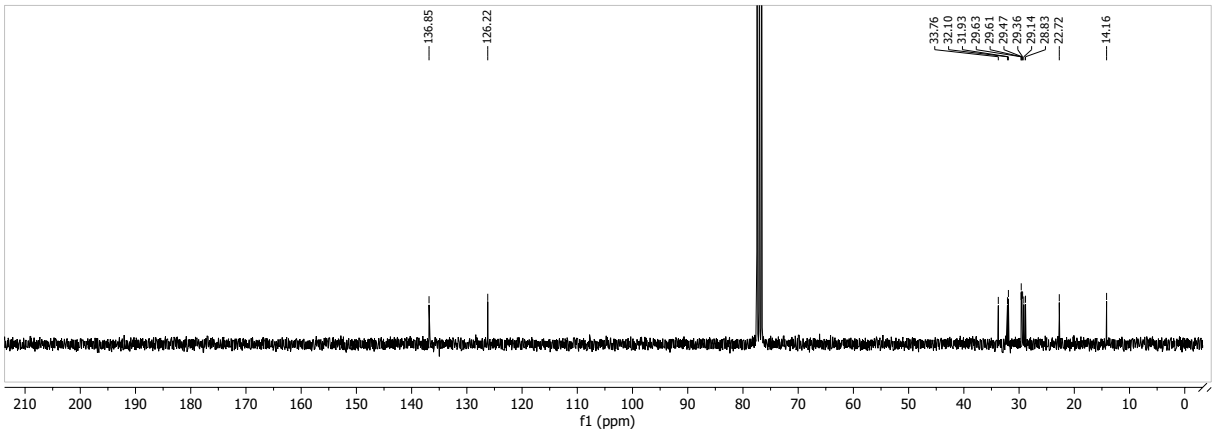


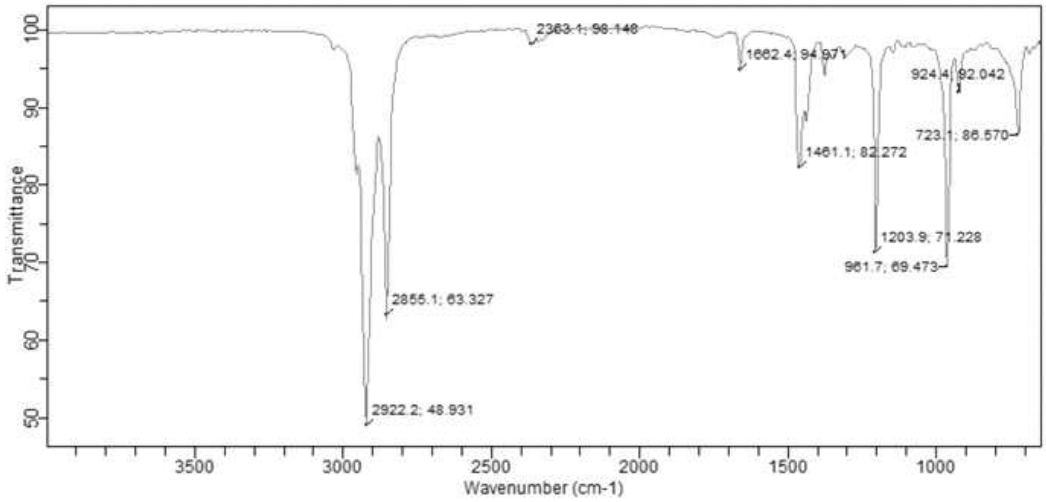




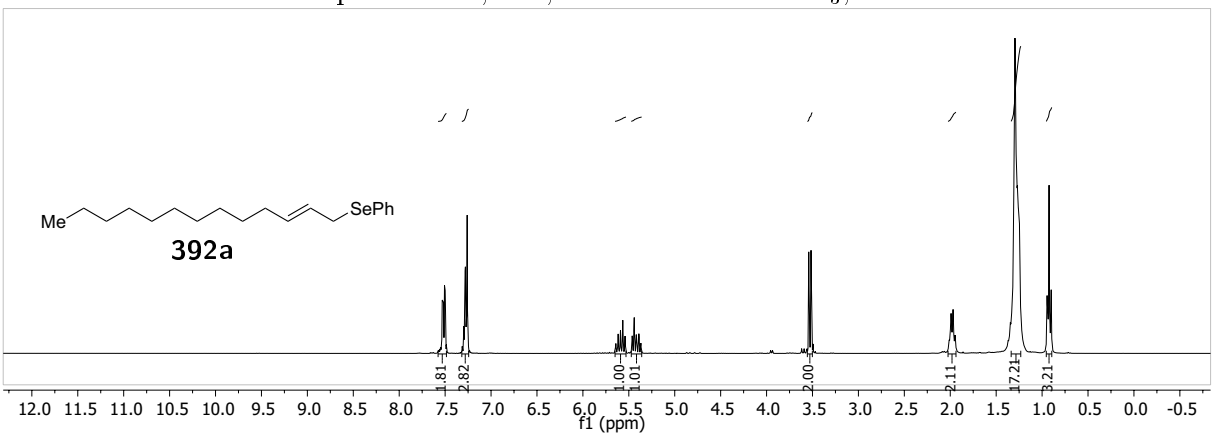
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

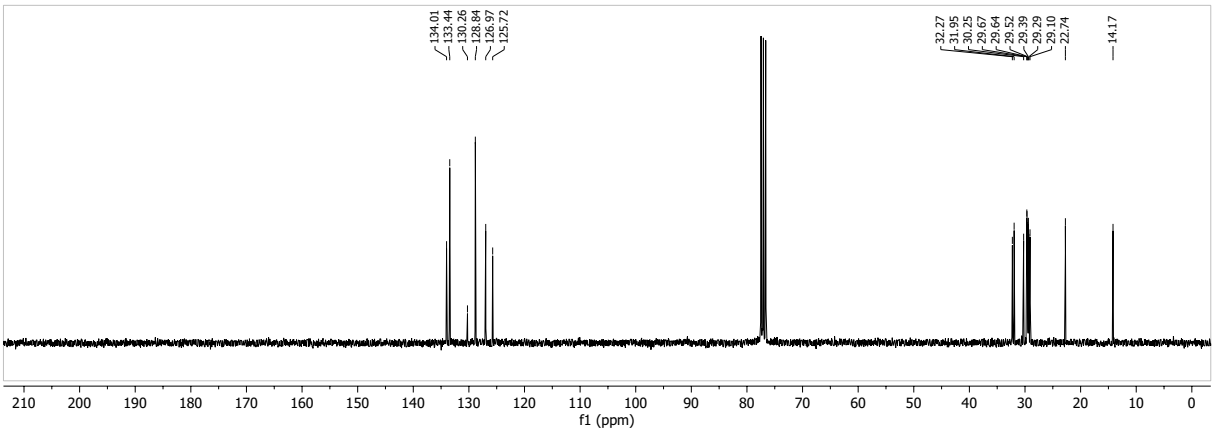


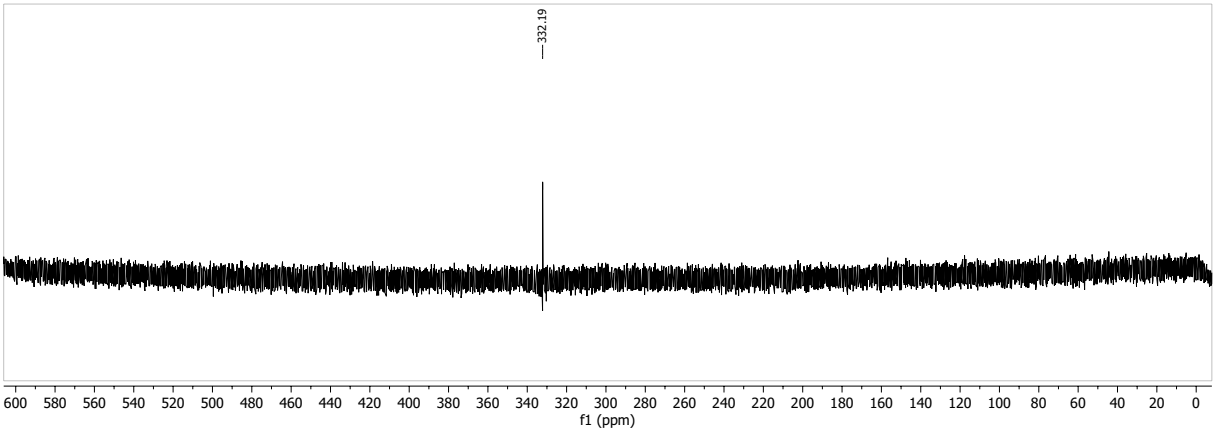


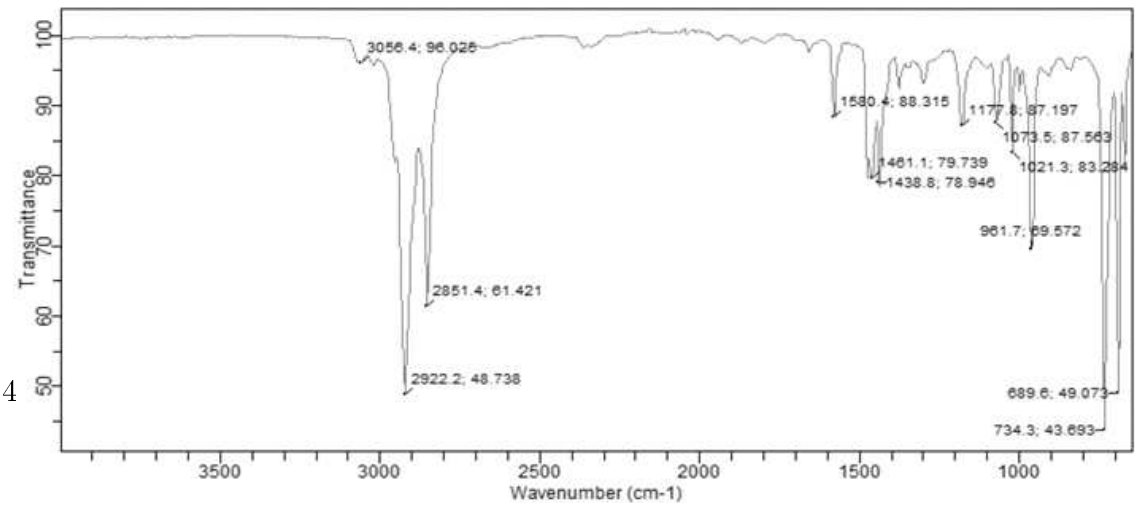


Spectra: ^{1}H, ^{13}C, ^{77}Se NMR in $CDCl_3$; IR

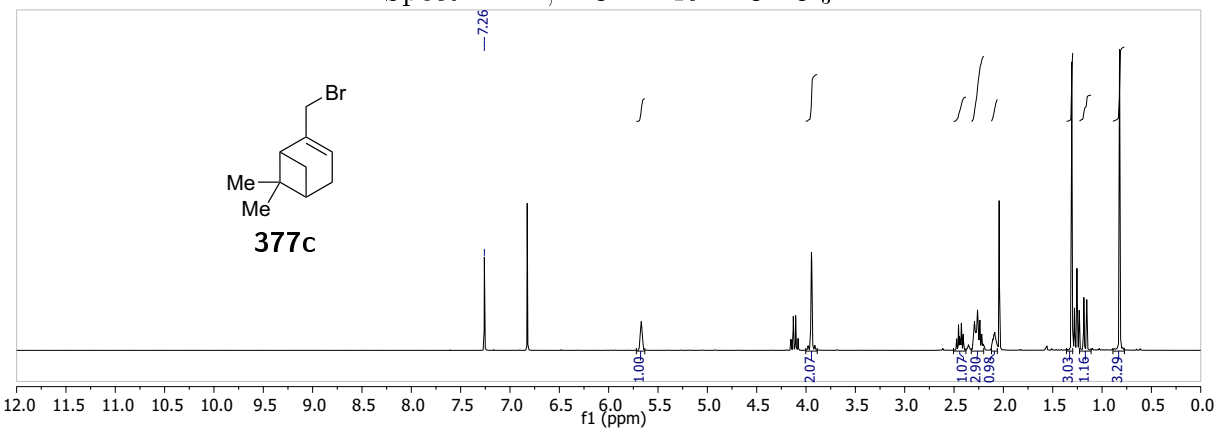


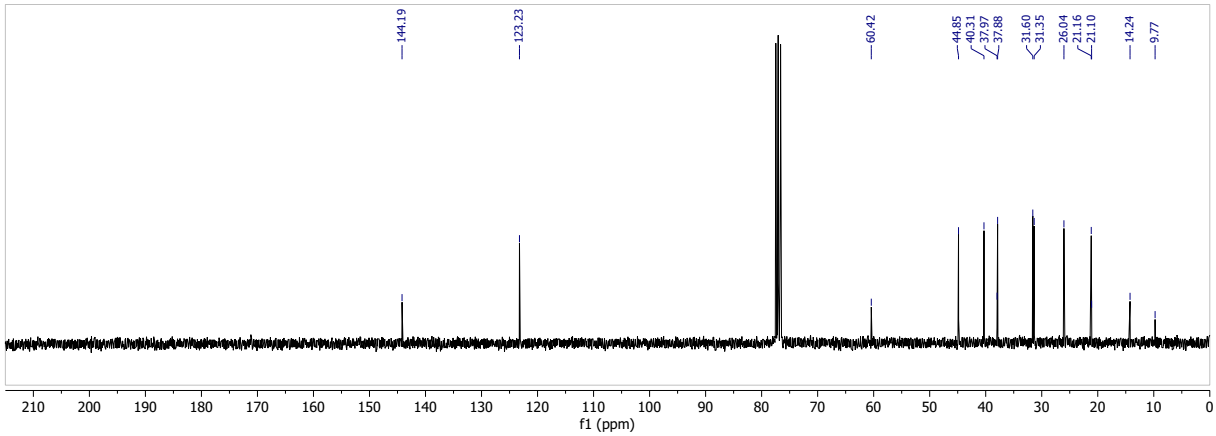




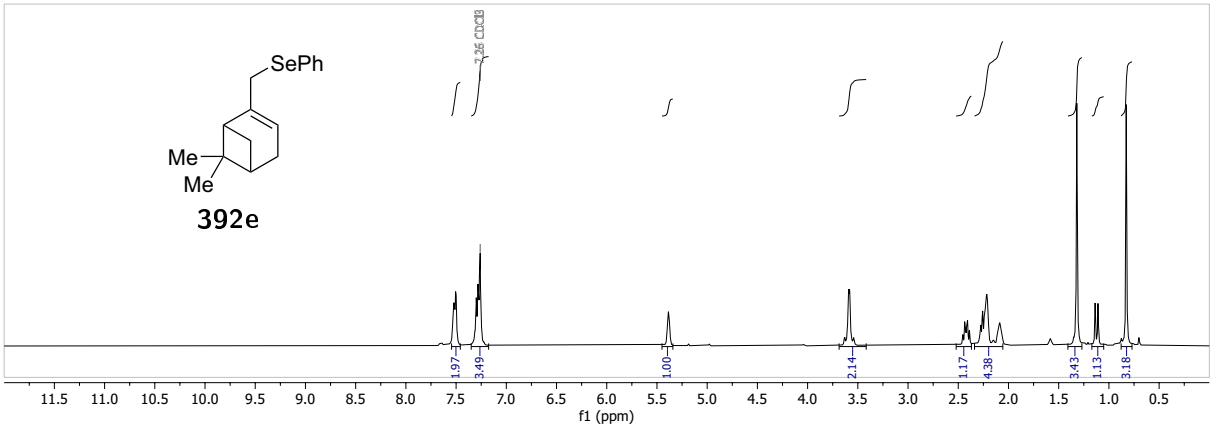


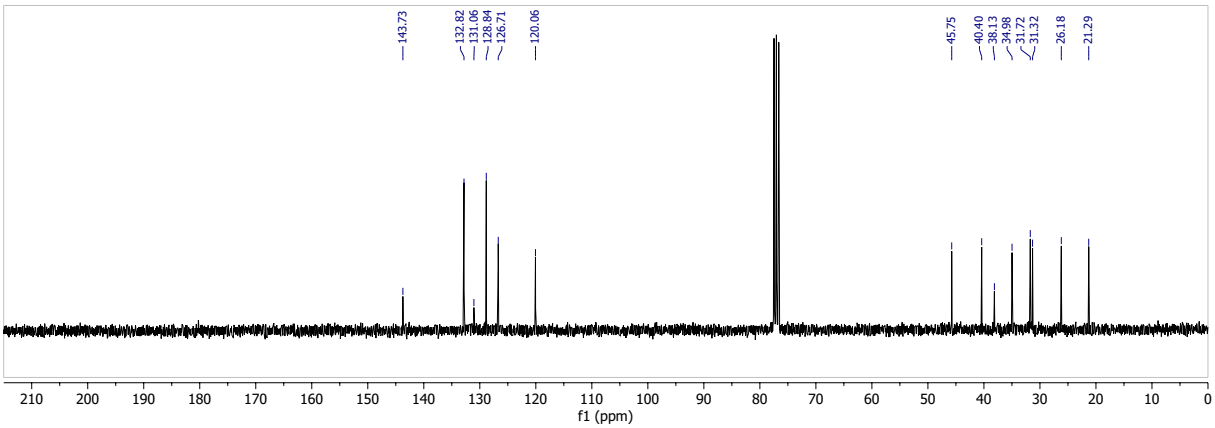
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$

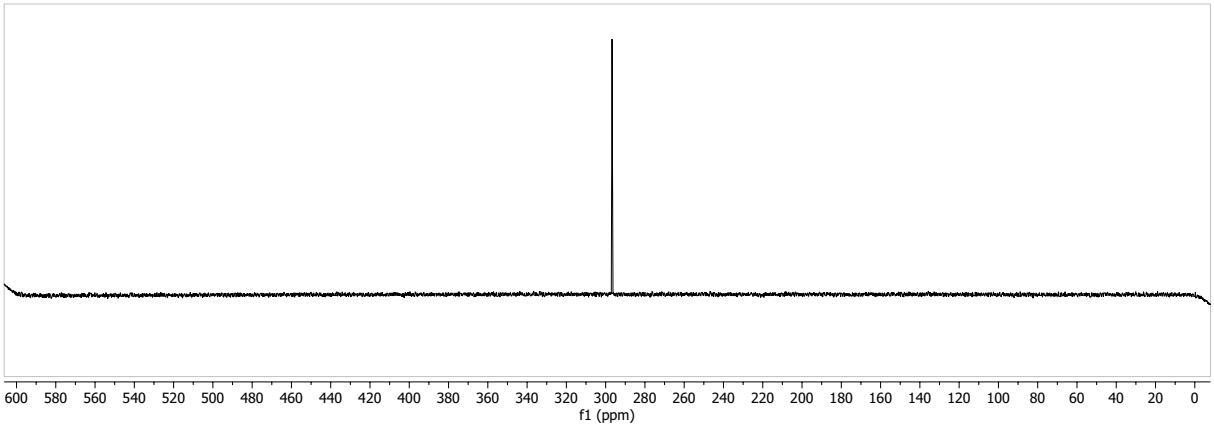


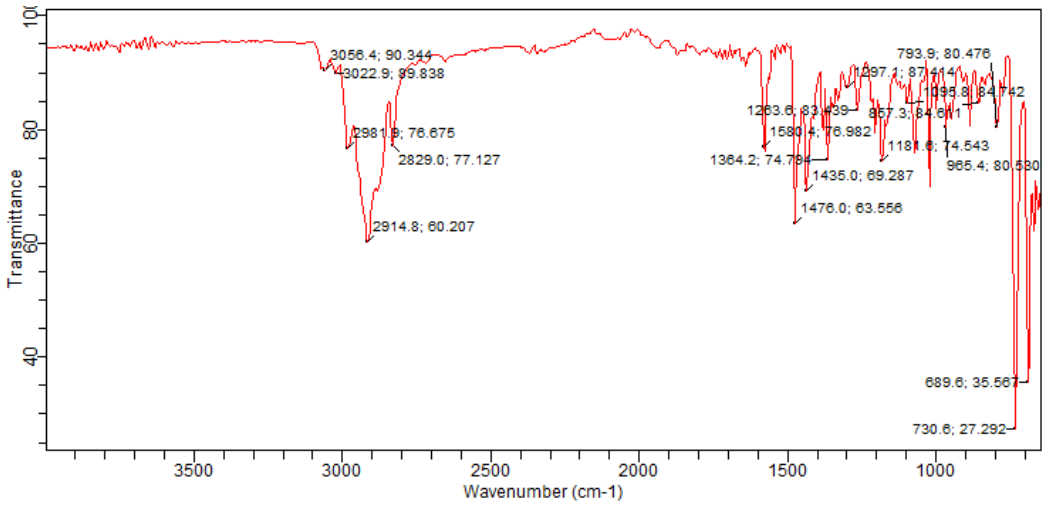


Spectra: ^{1}H, ^{13}C, ^{77}Se NMR in $CDCl_3$; IR

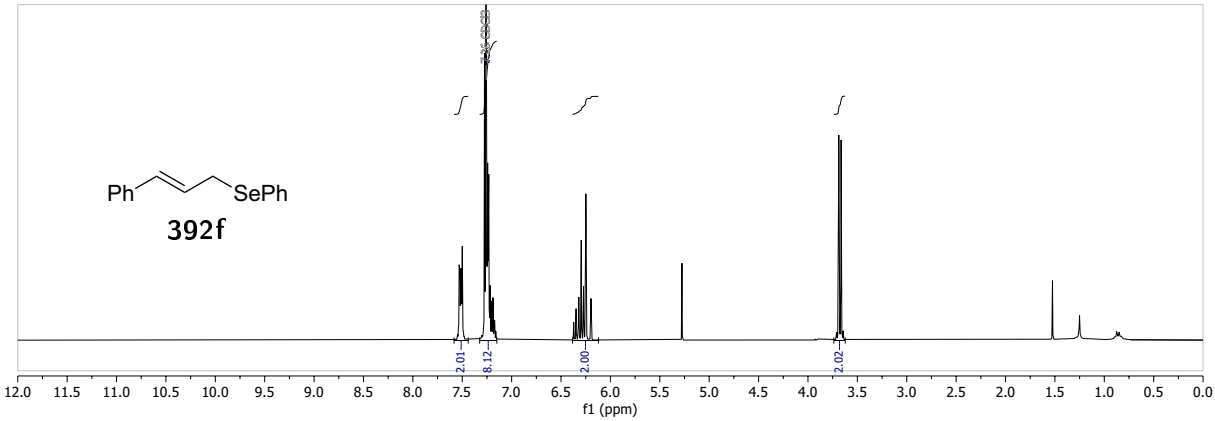


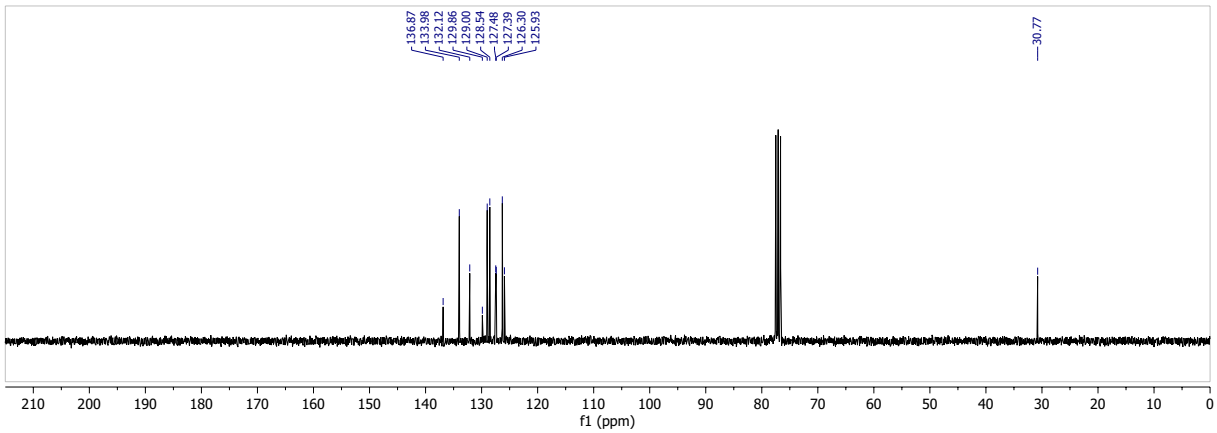


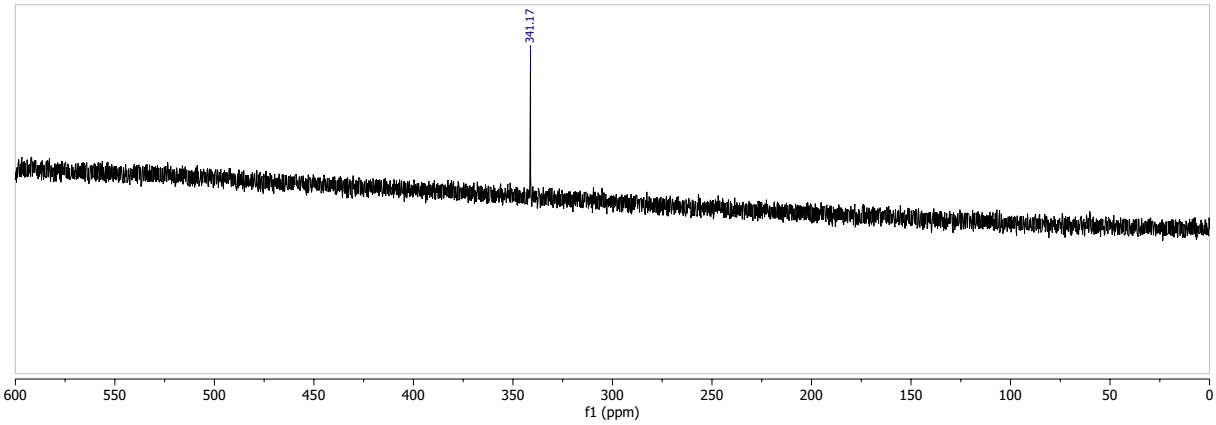


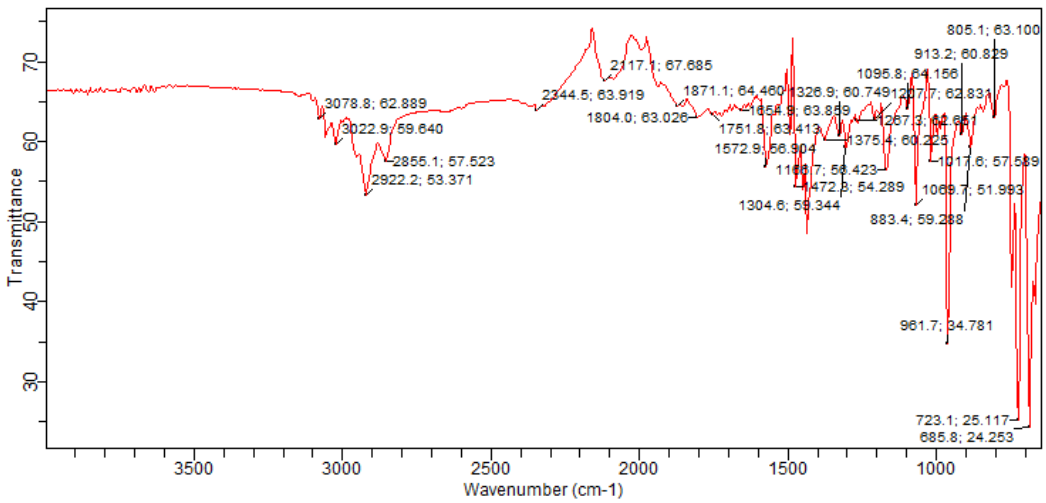


Spectra: ^{1}H, ^{13}C, ^{77}Se NMR in $CDCl_3$; IR









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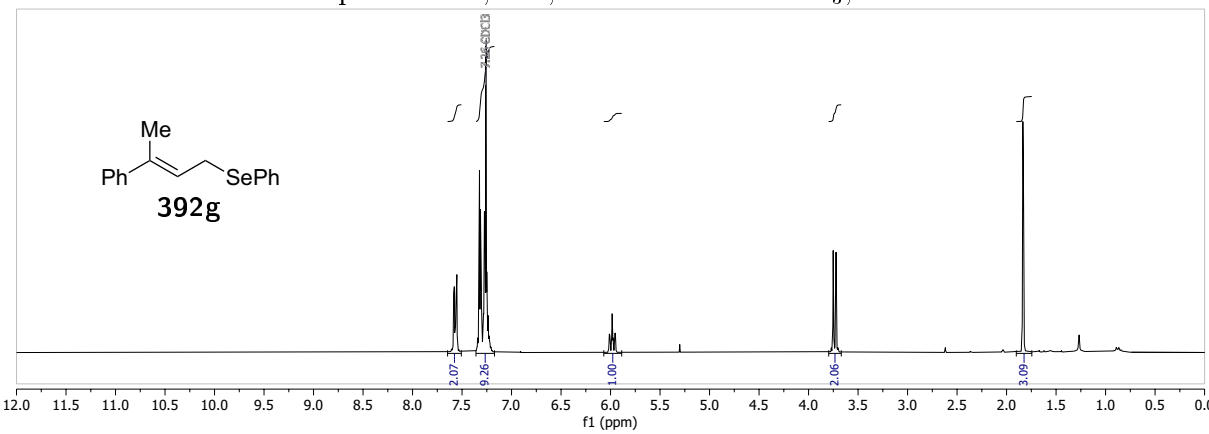

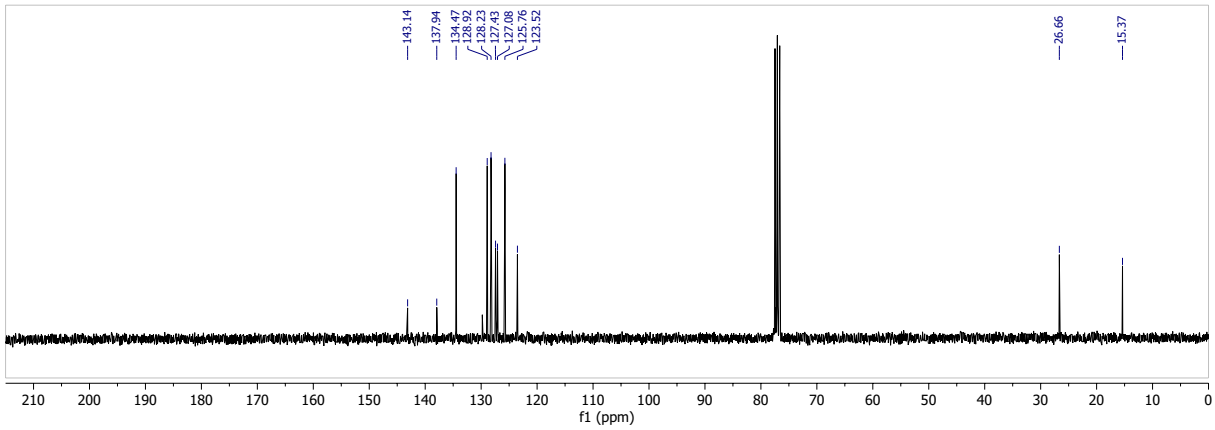

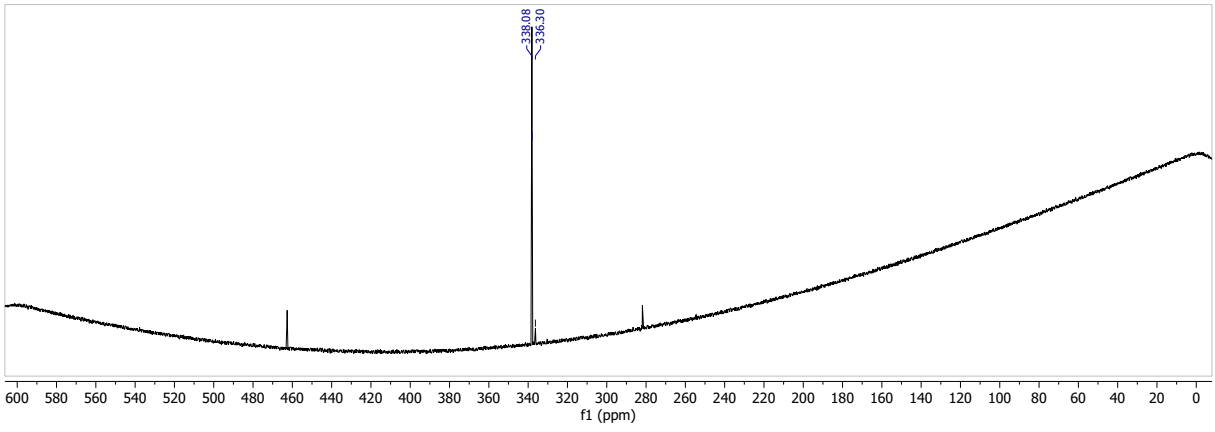

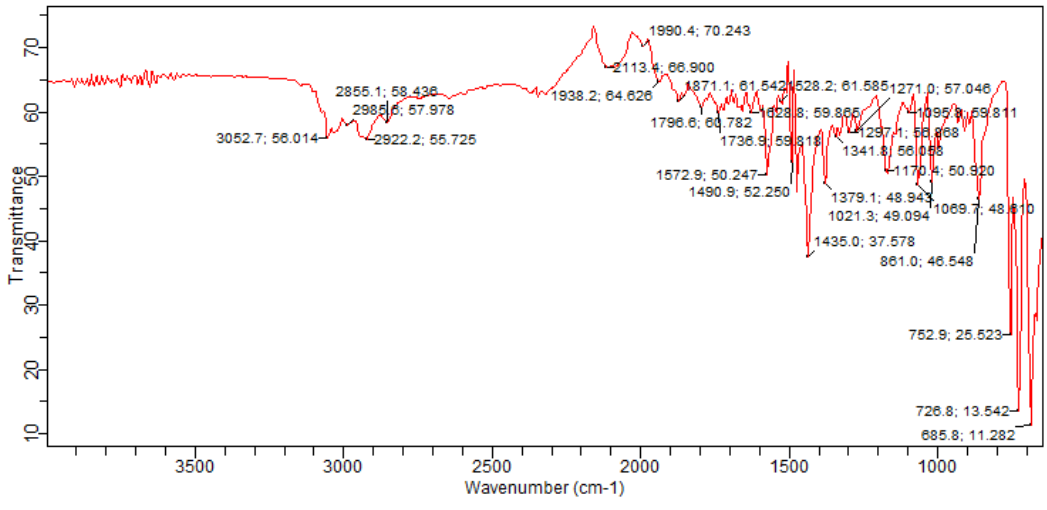

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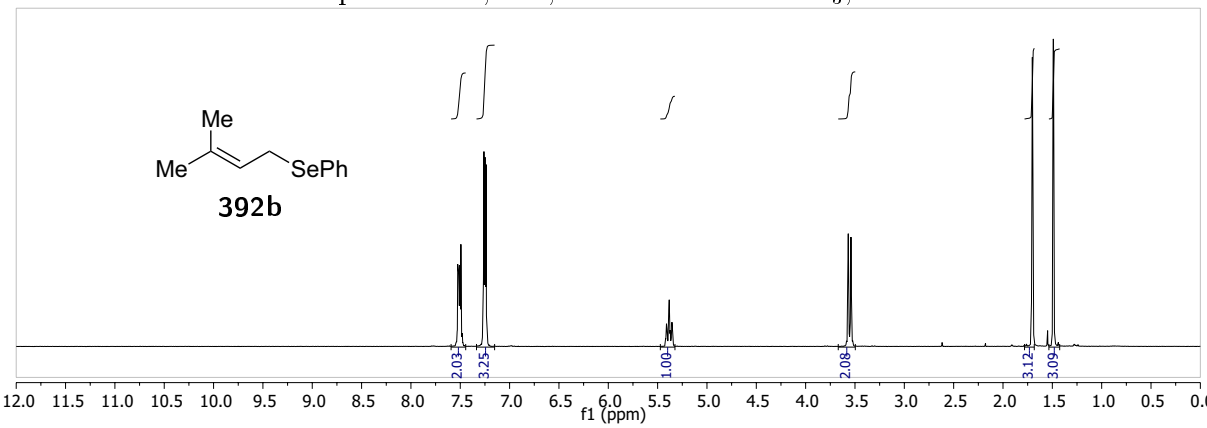

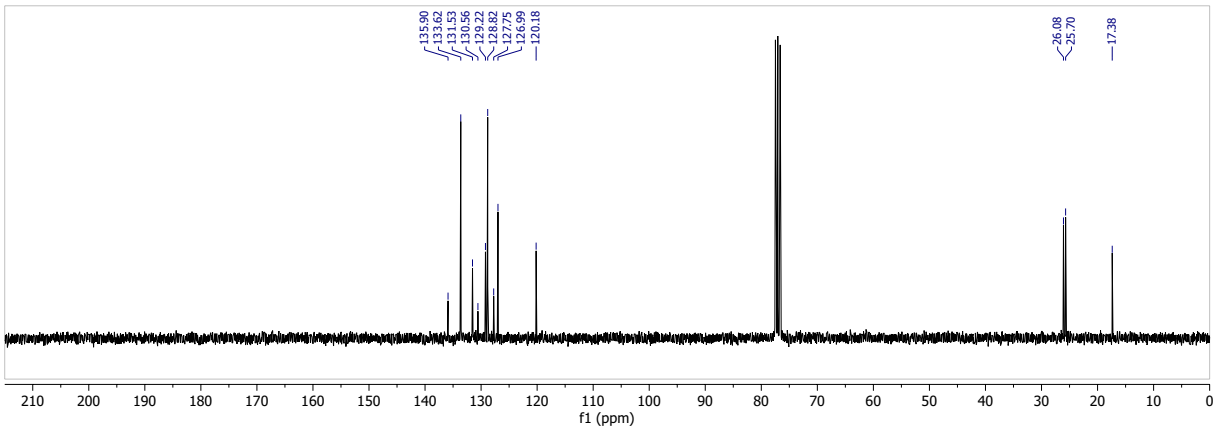

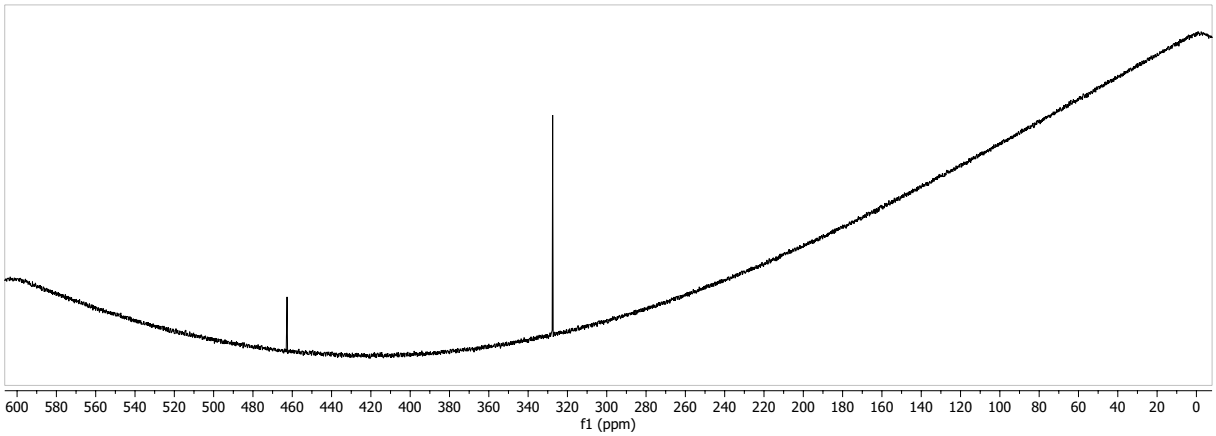

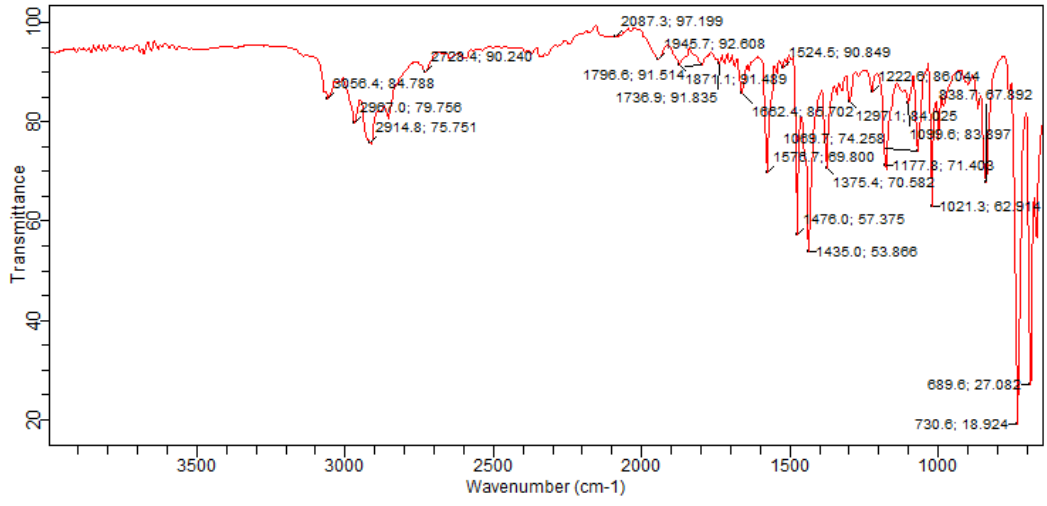

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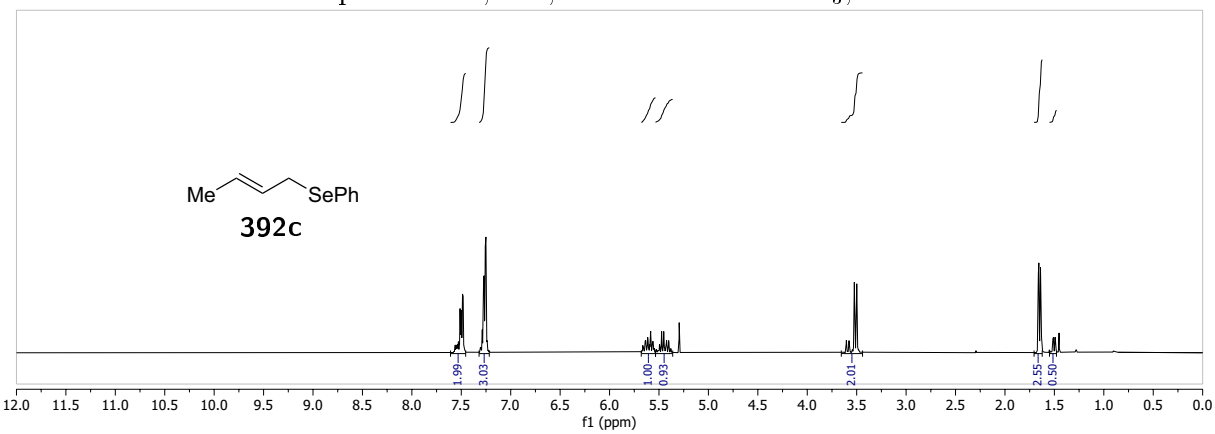

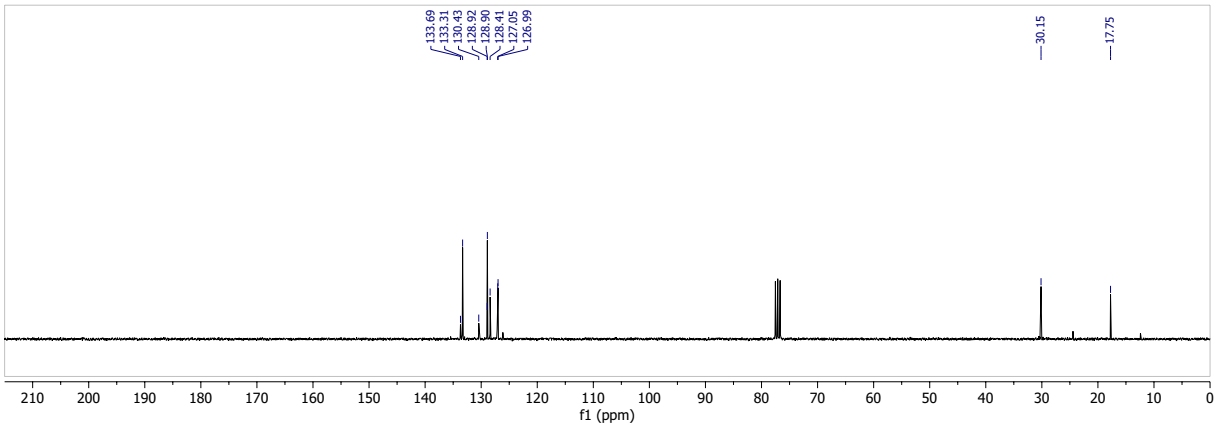

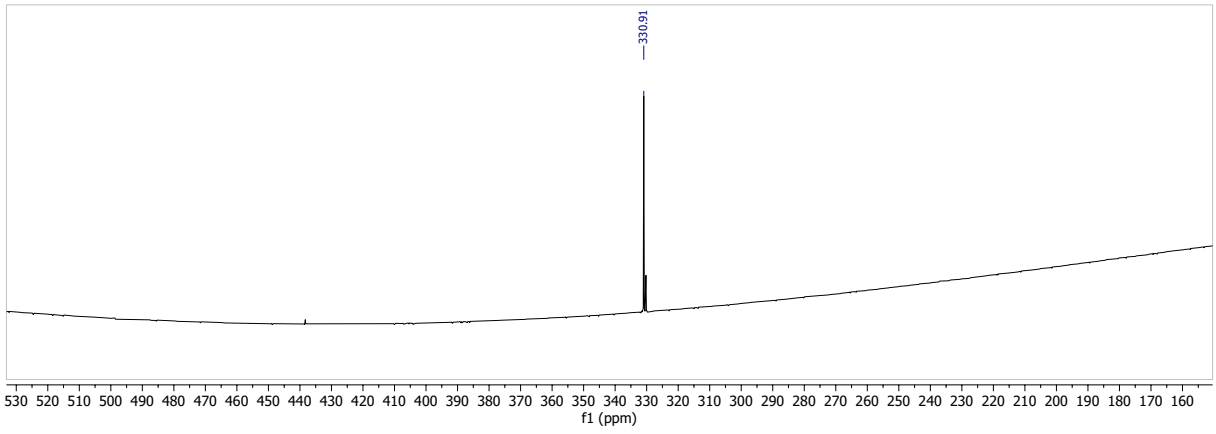

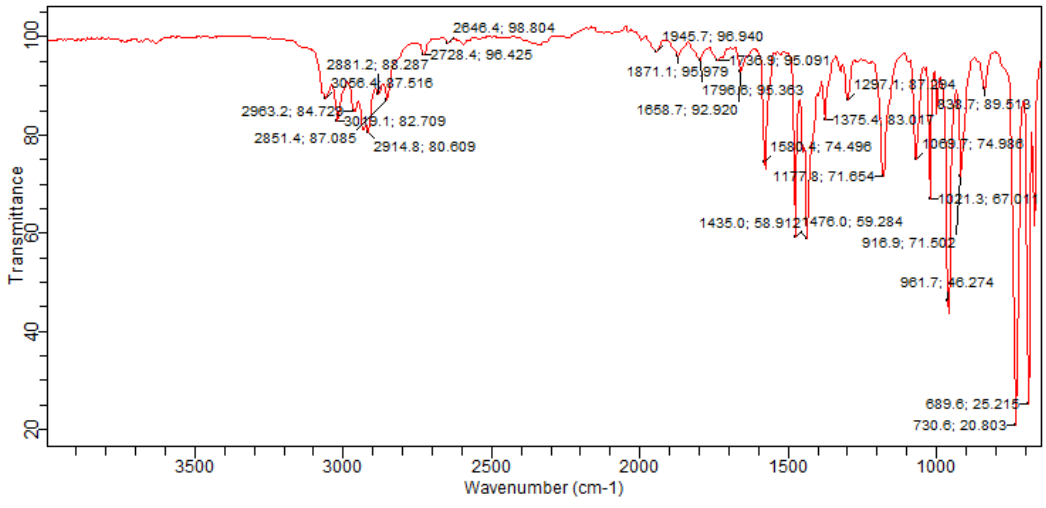

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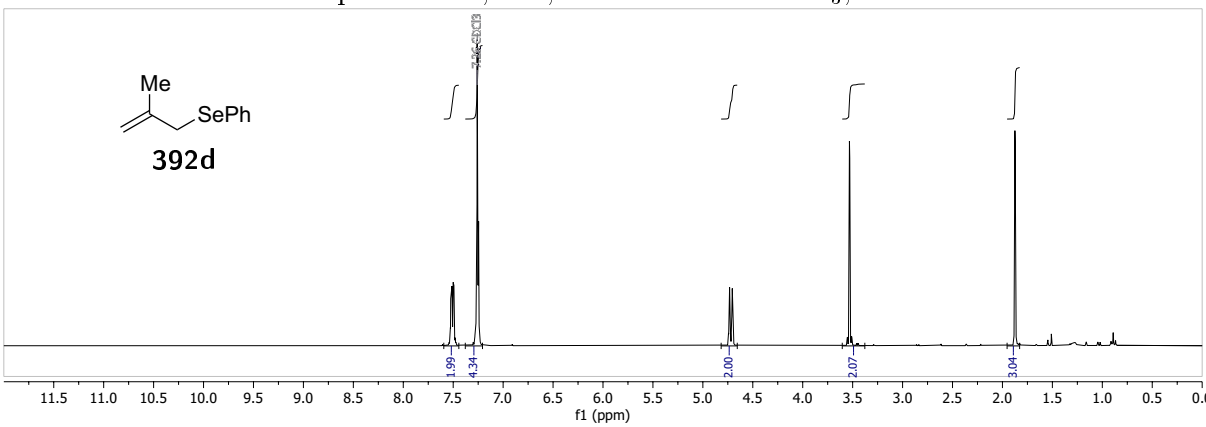

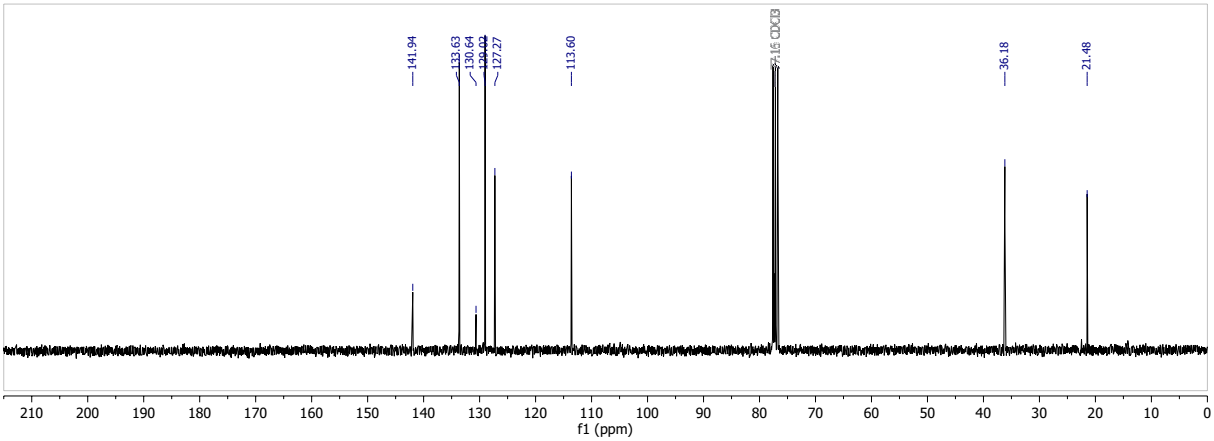

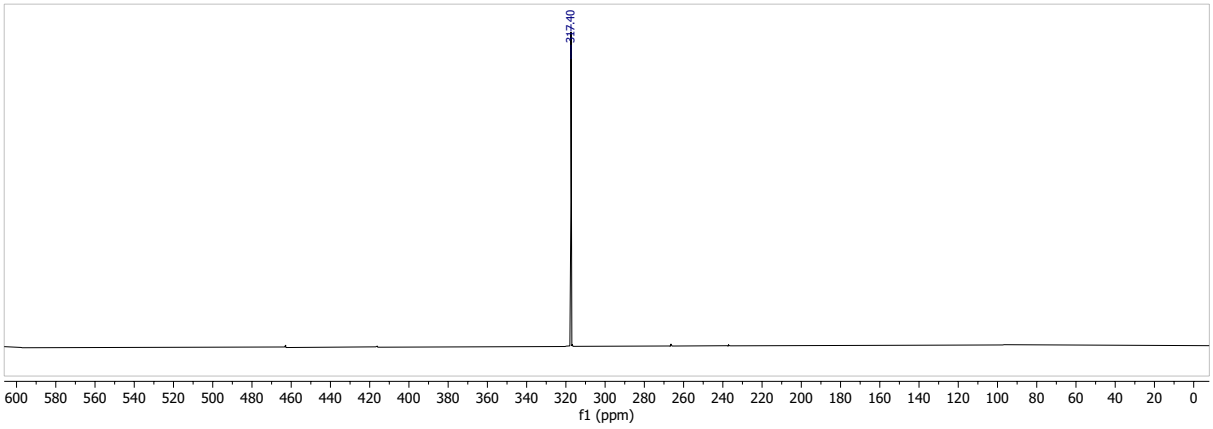

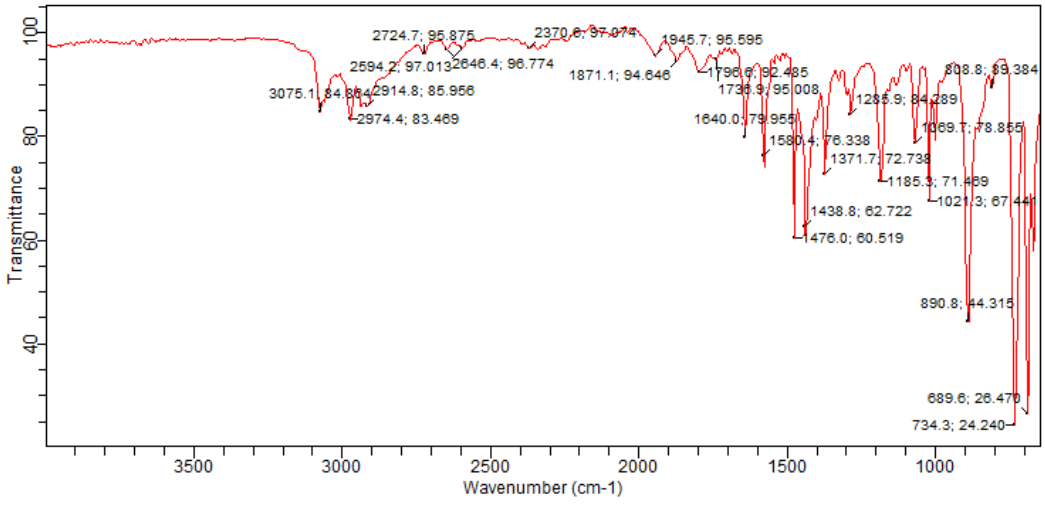

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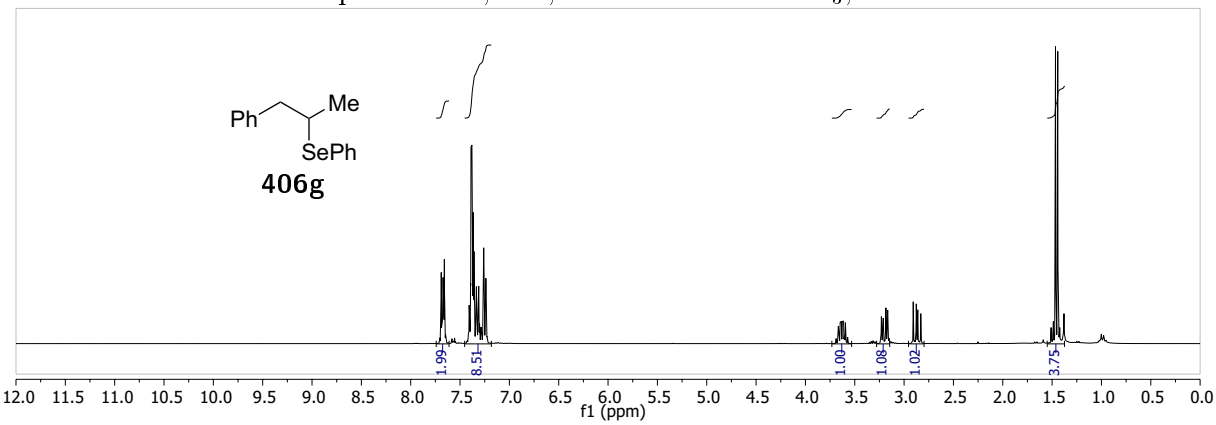

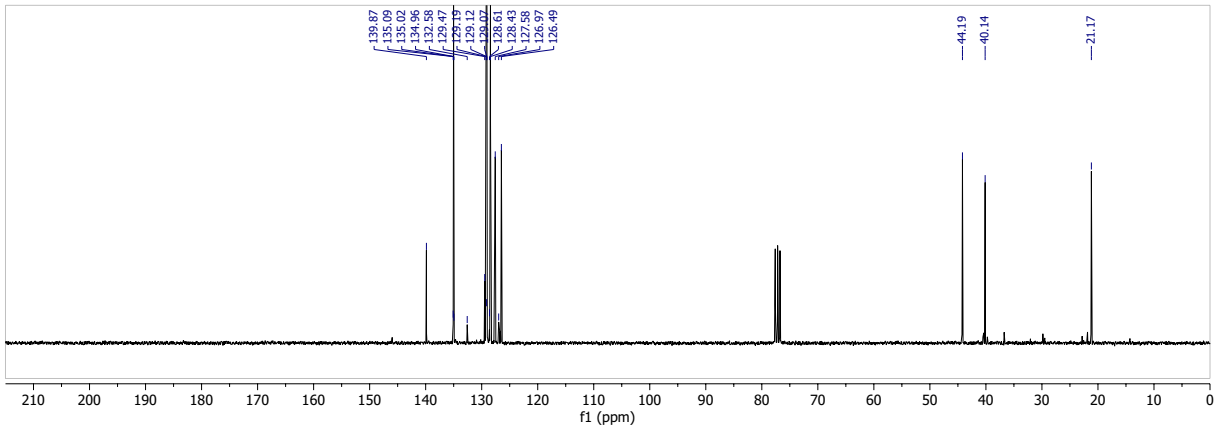

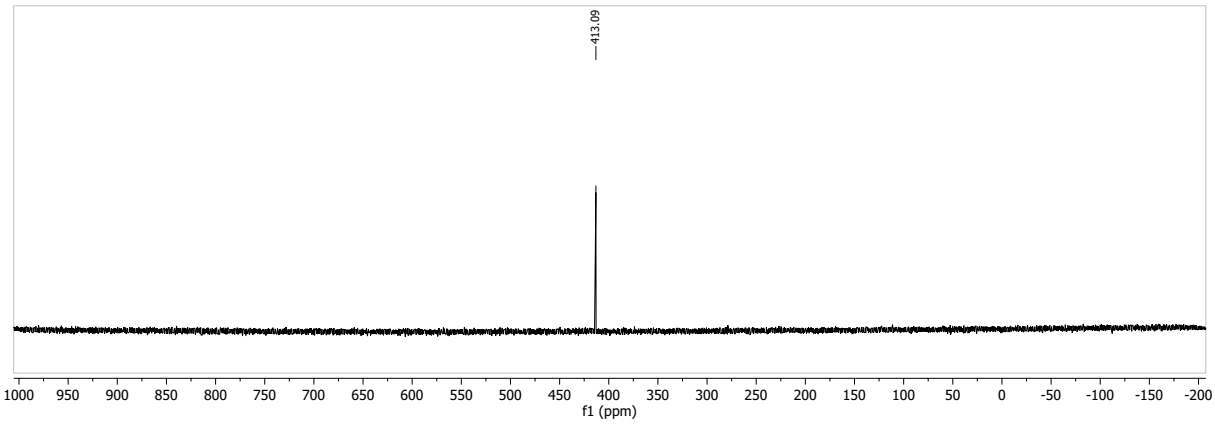

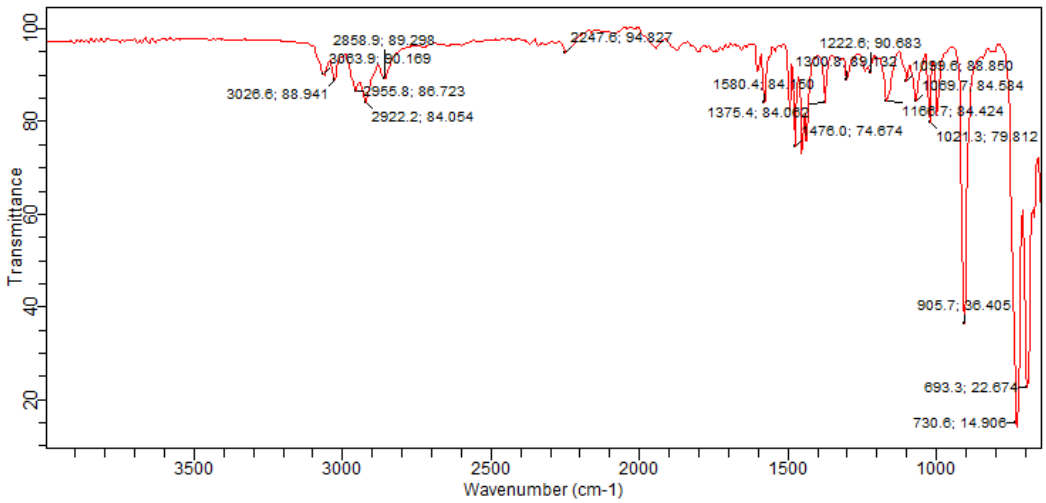

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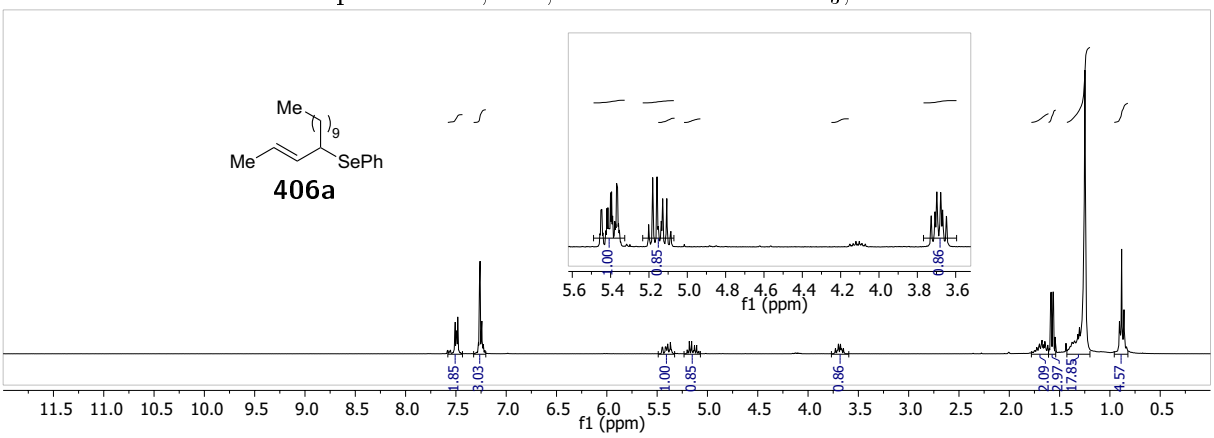

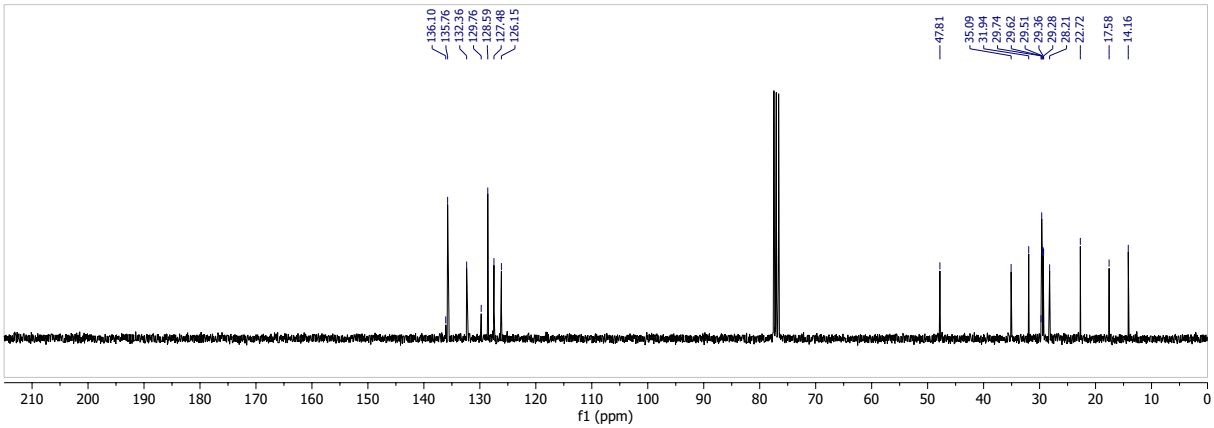

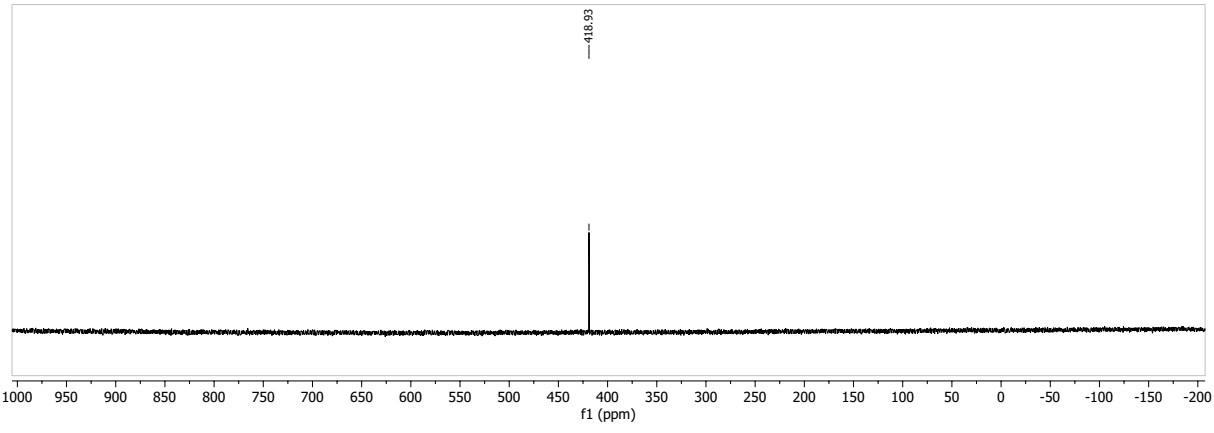

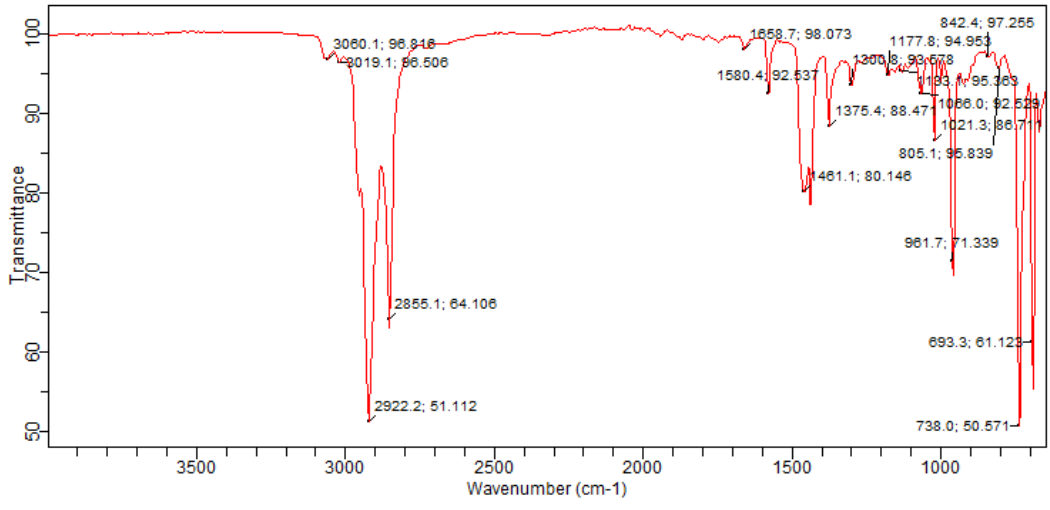

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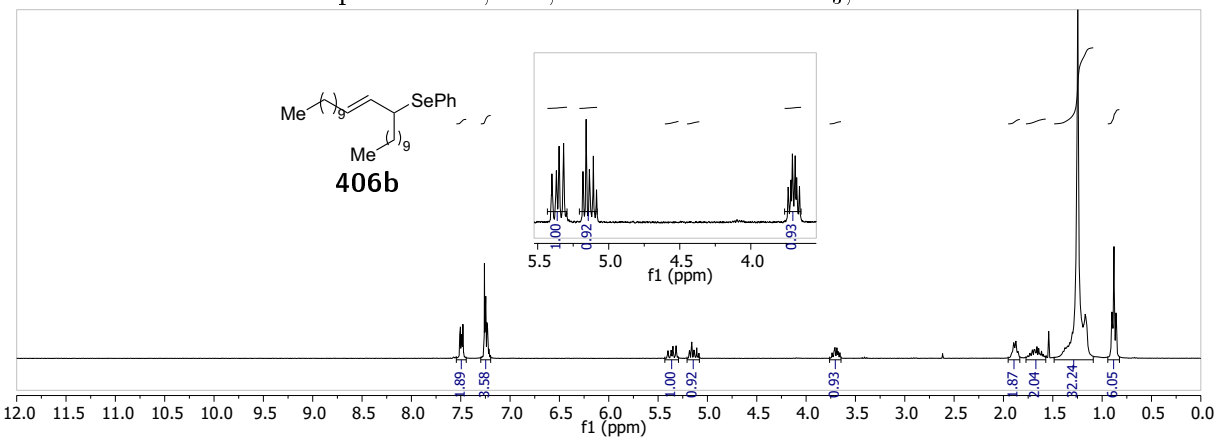

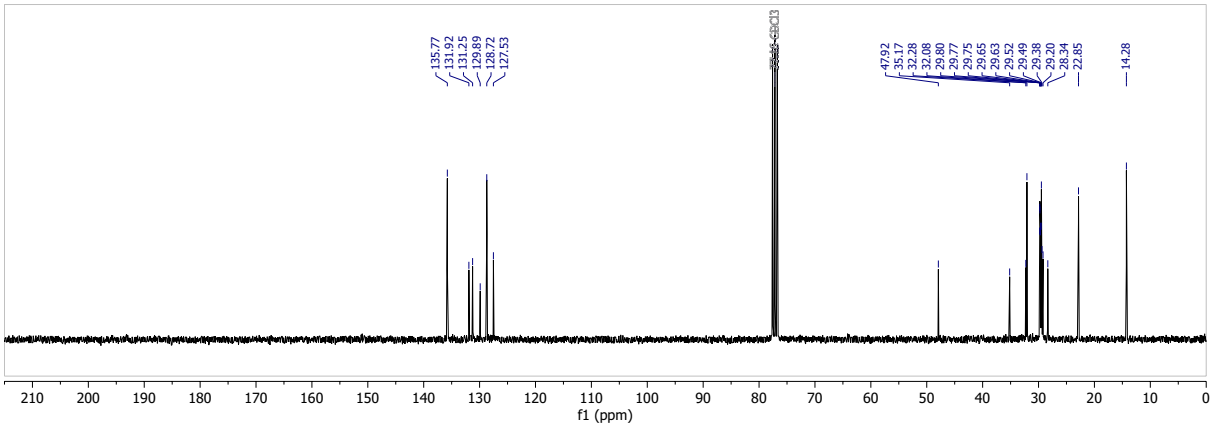

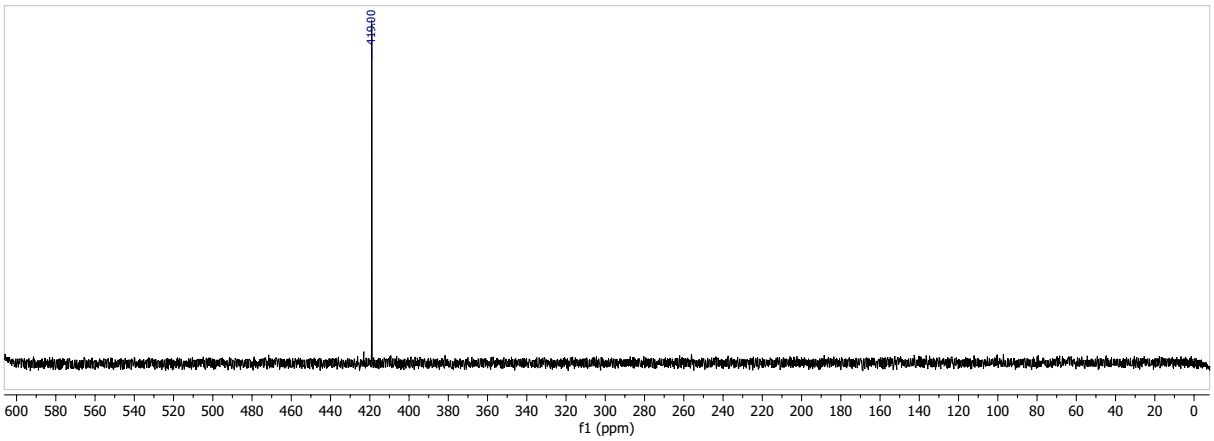

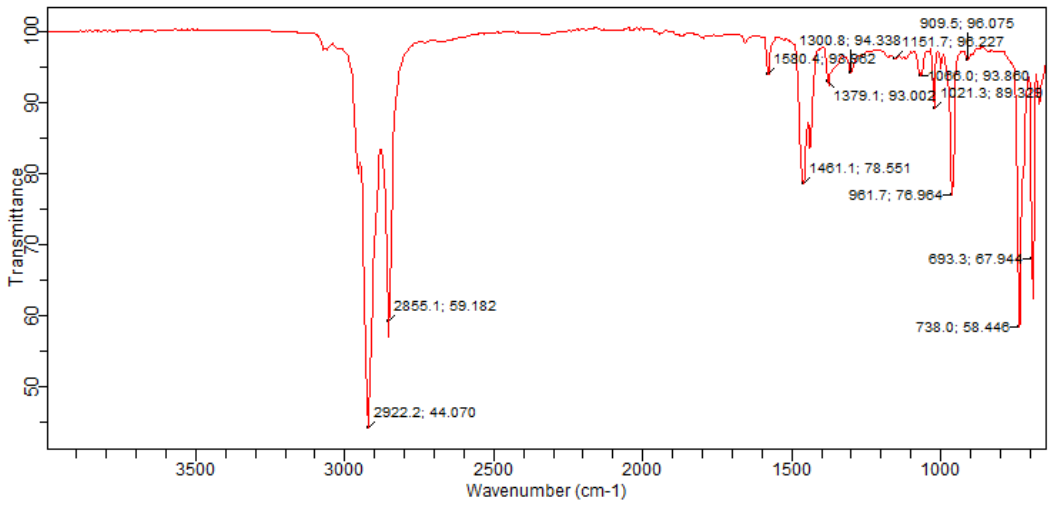

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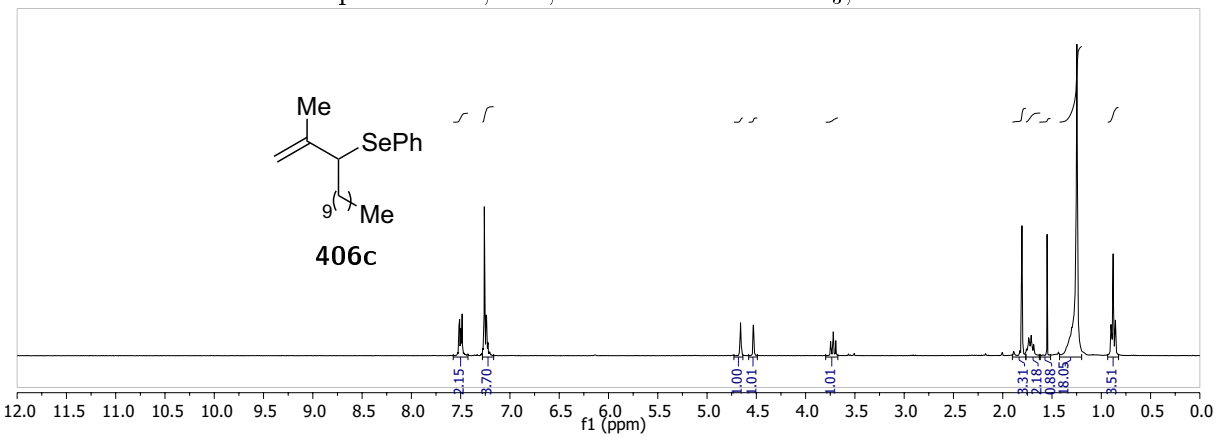

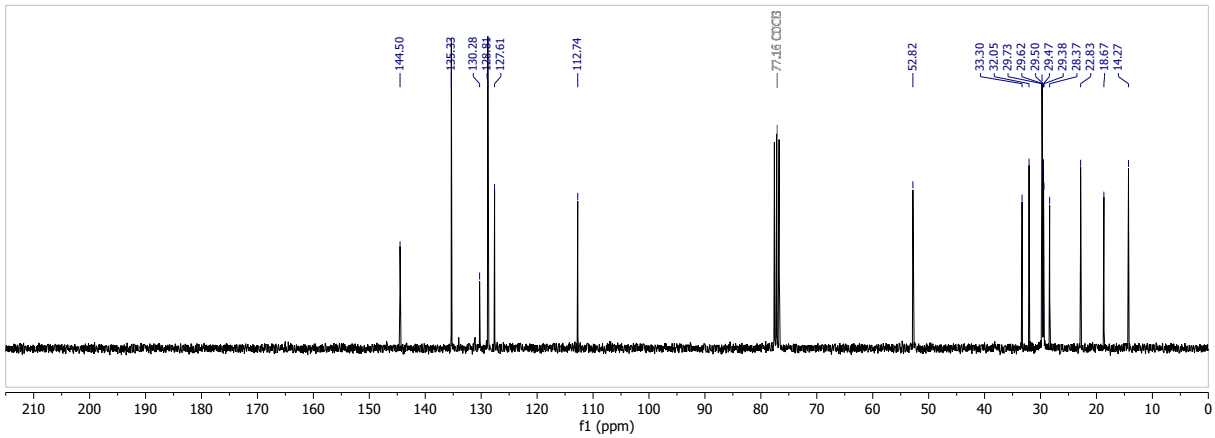

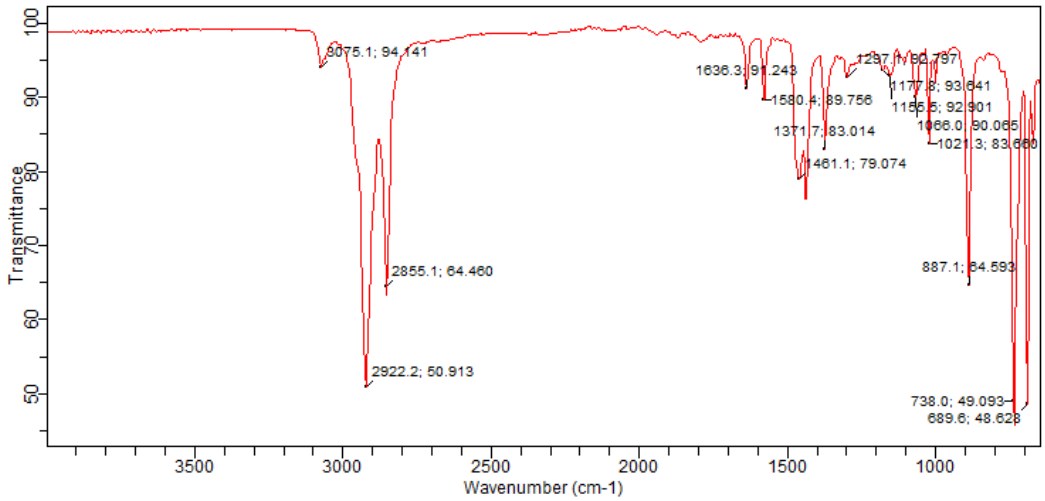

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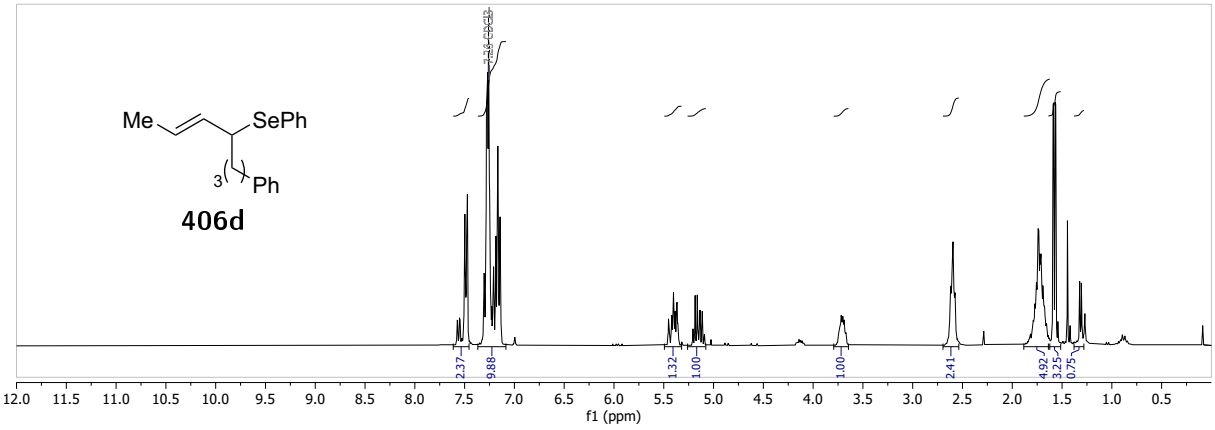

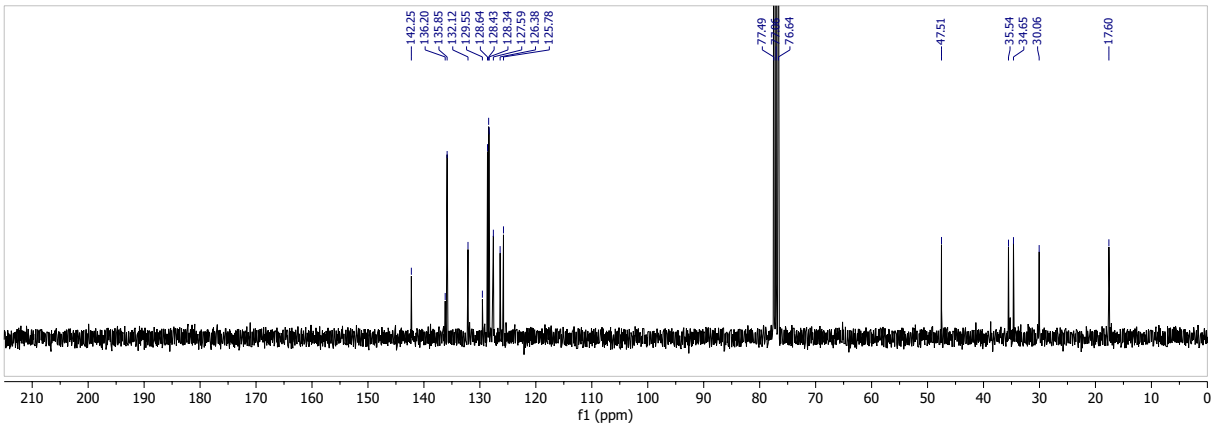

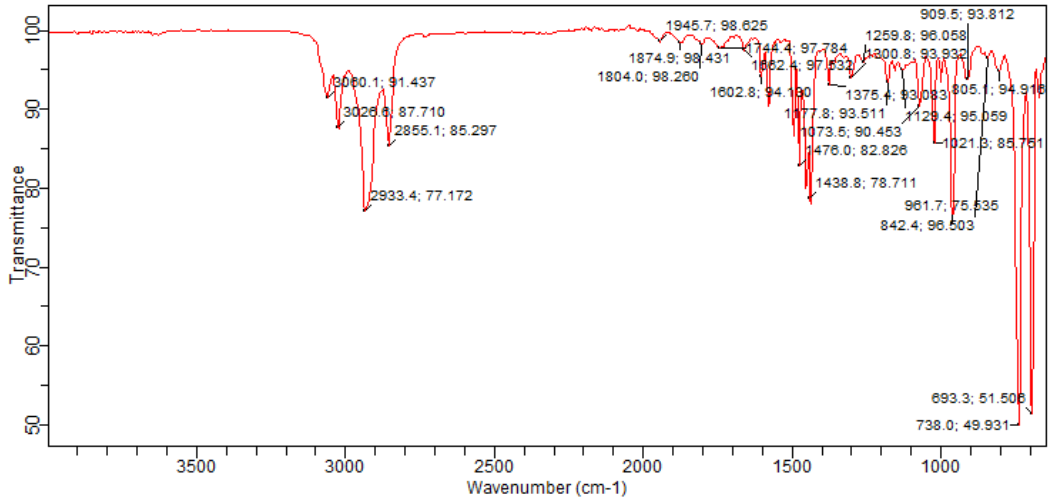

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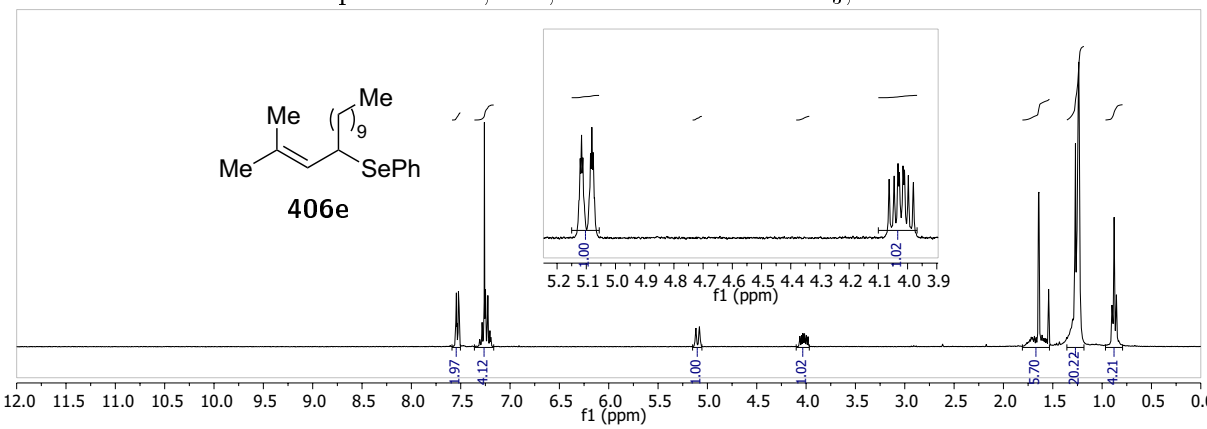

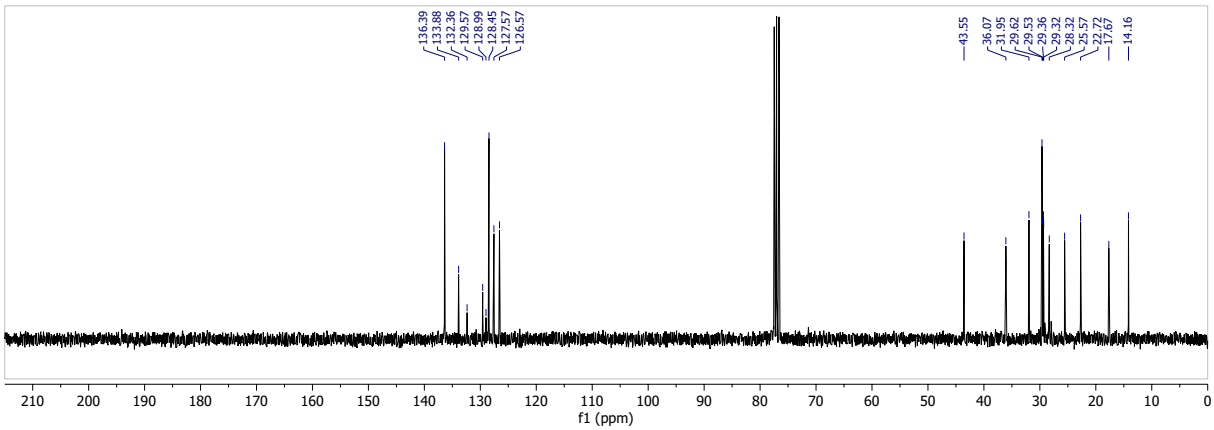

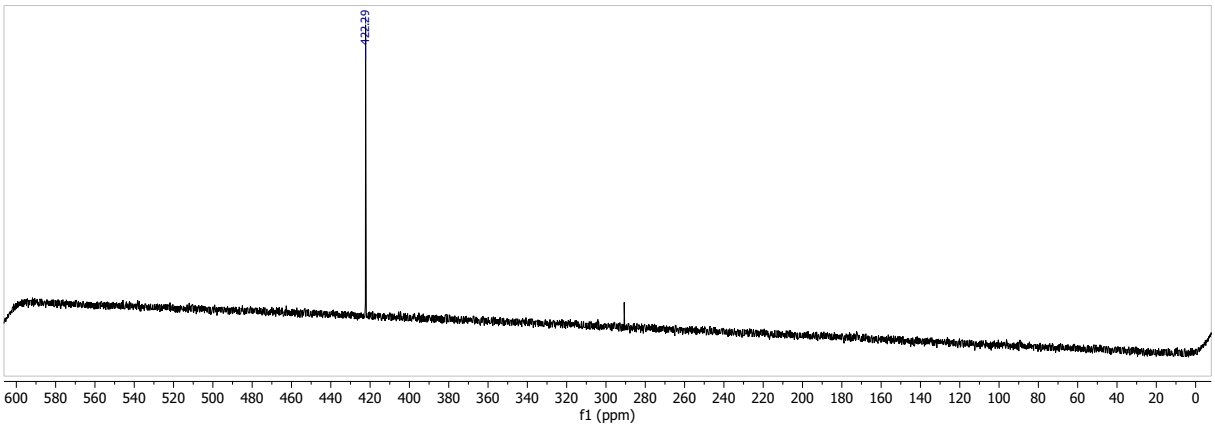

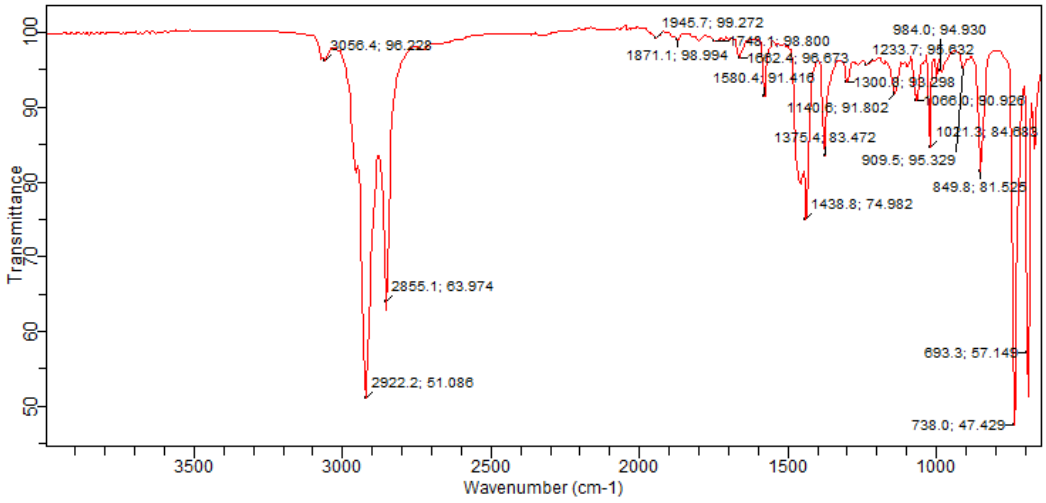

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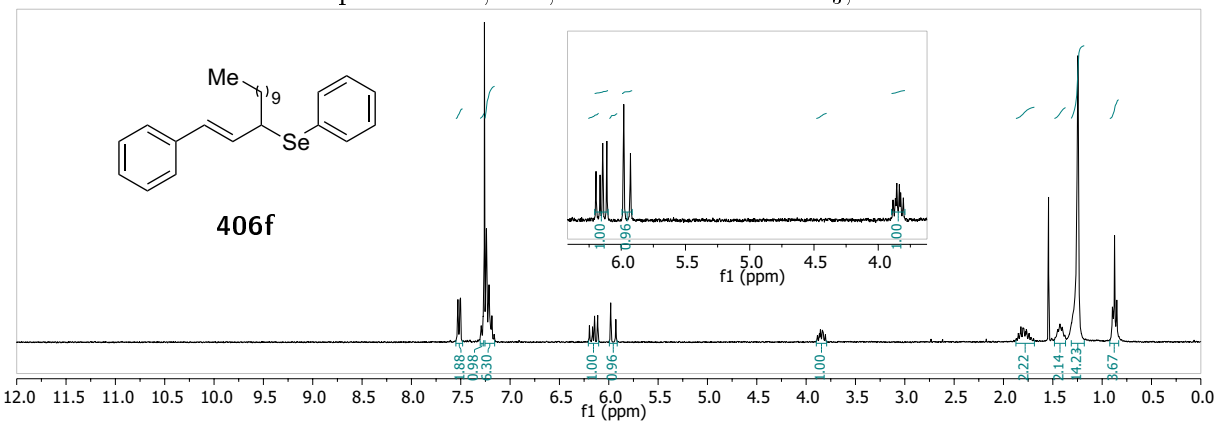

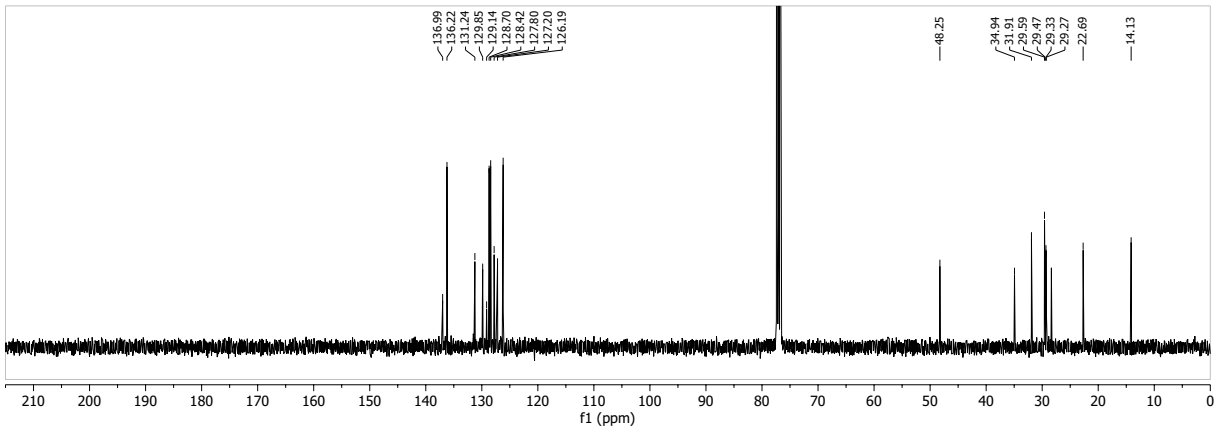

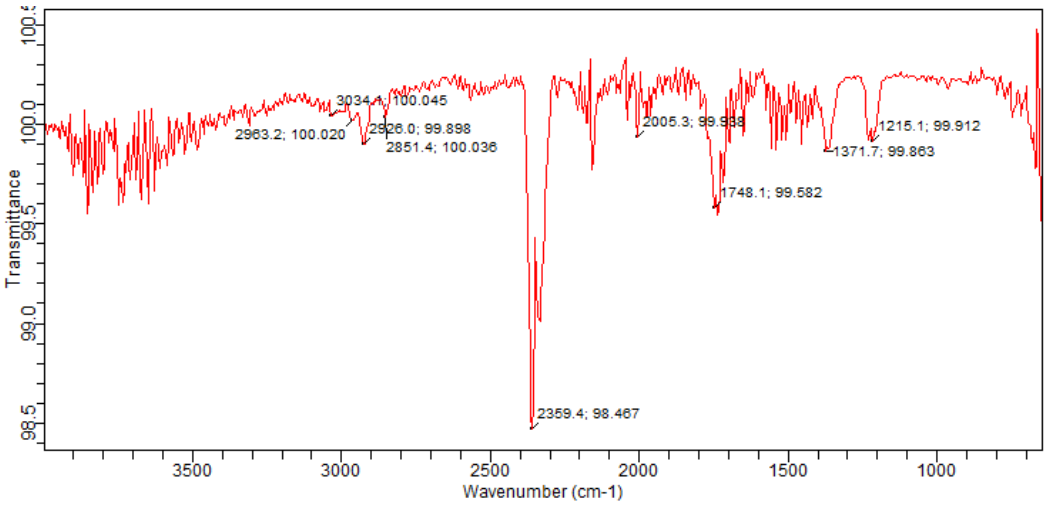

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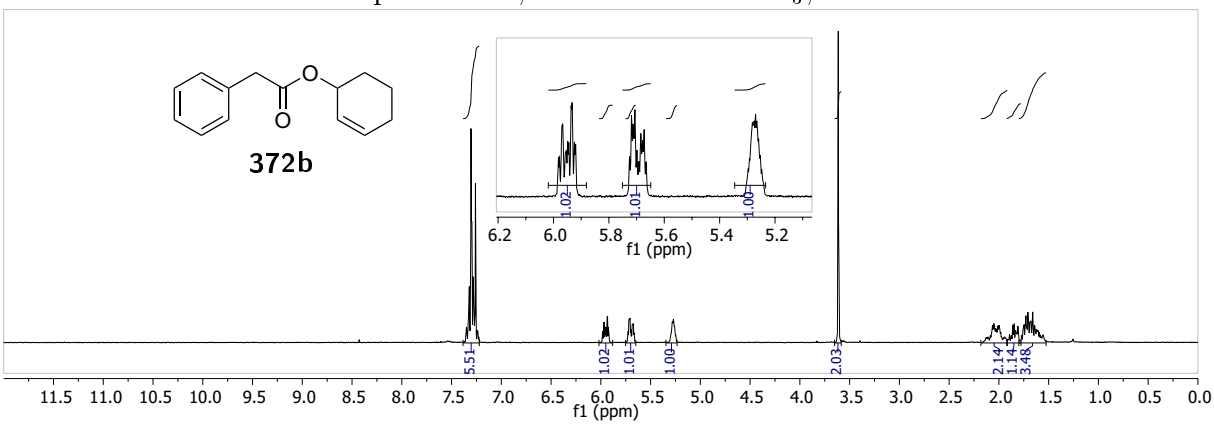

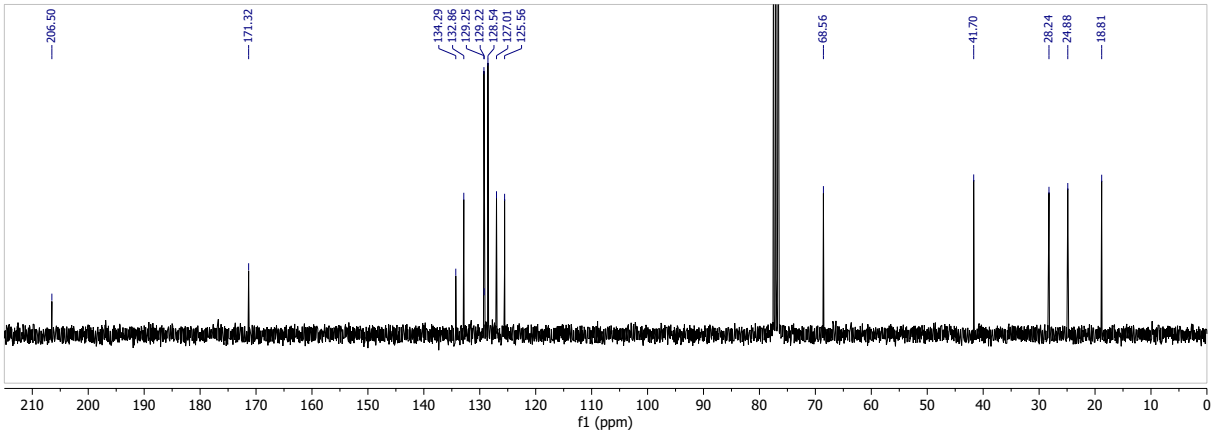

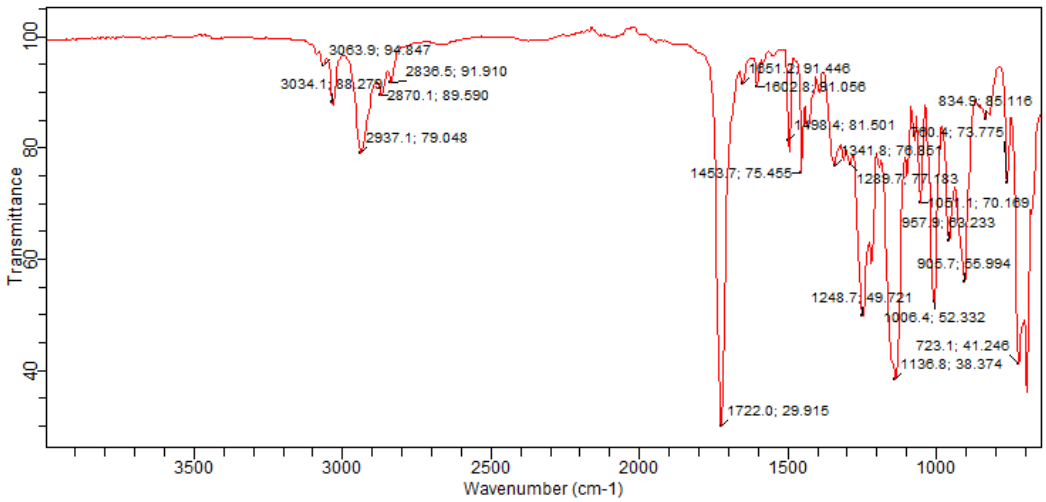

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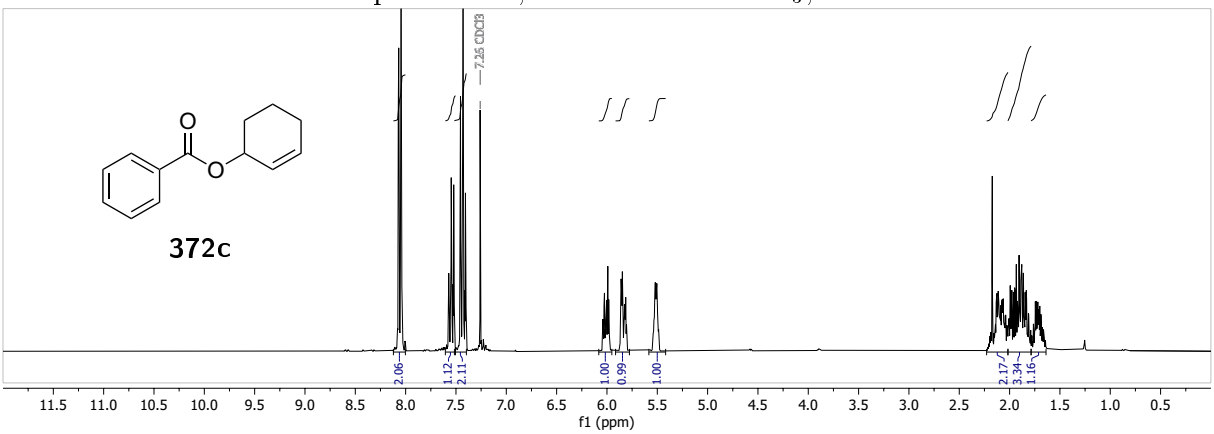

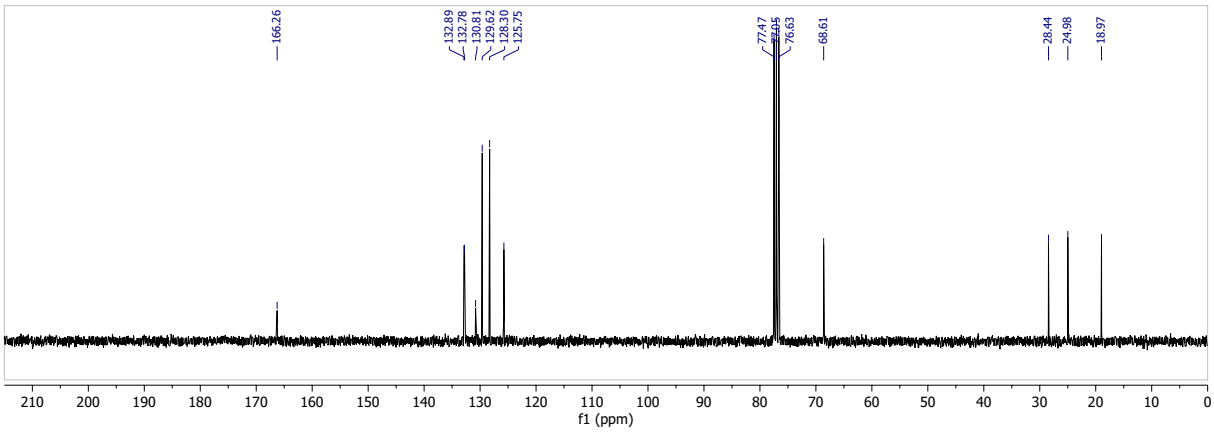

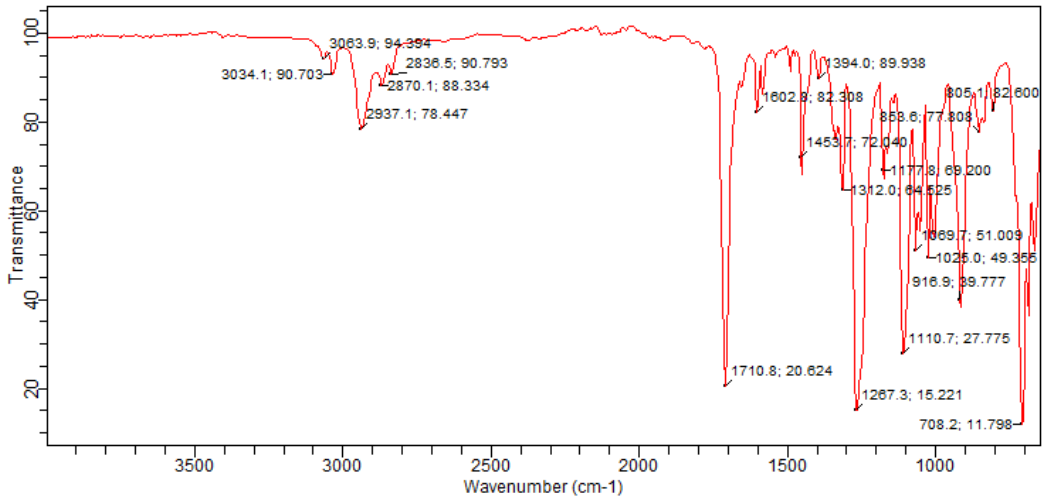

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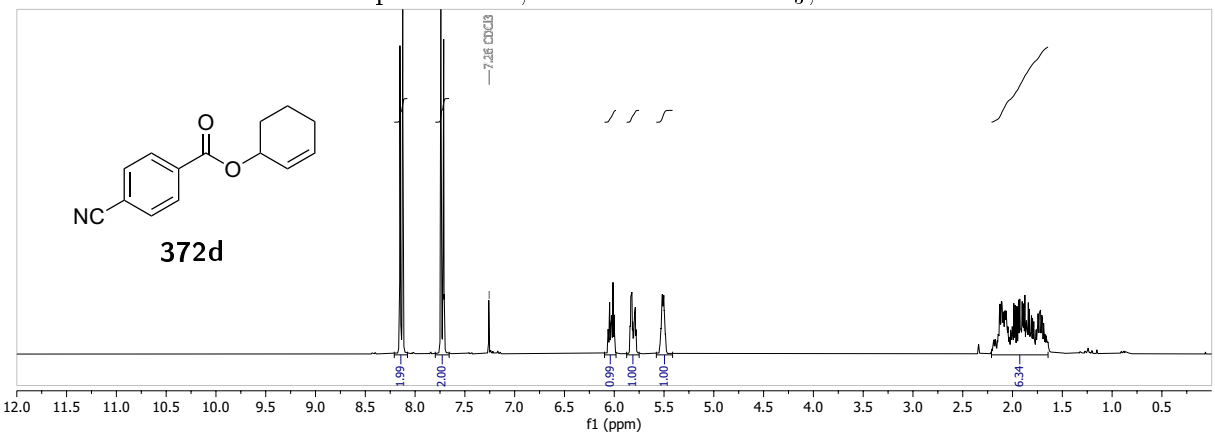
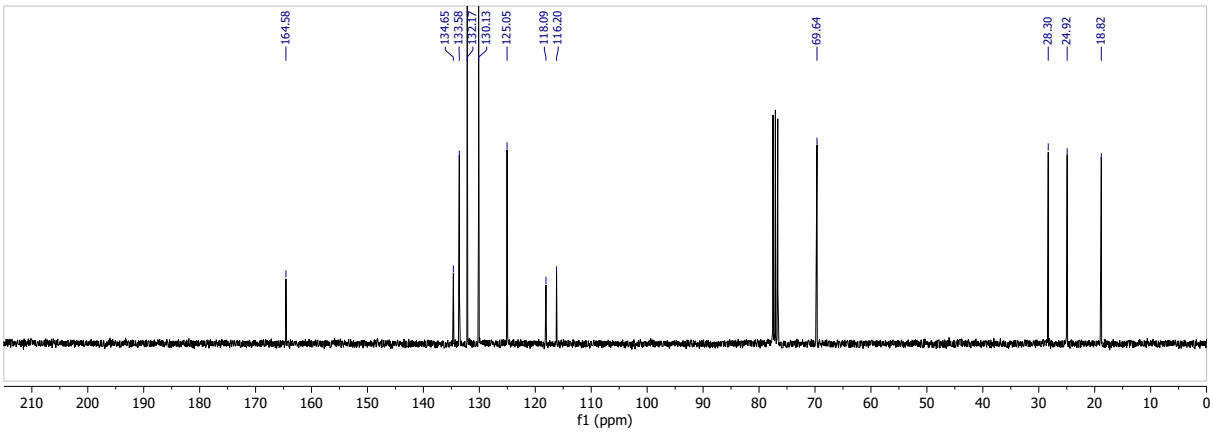
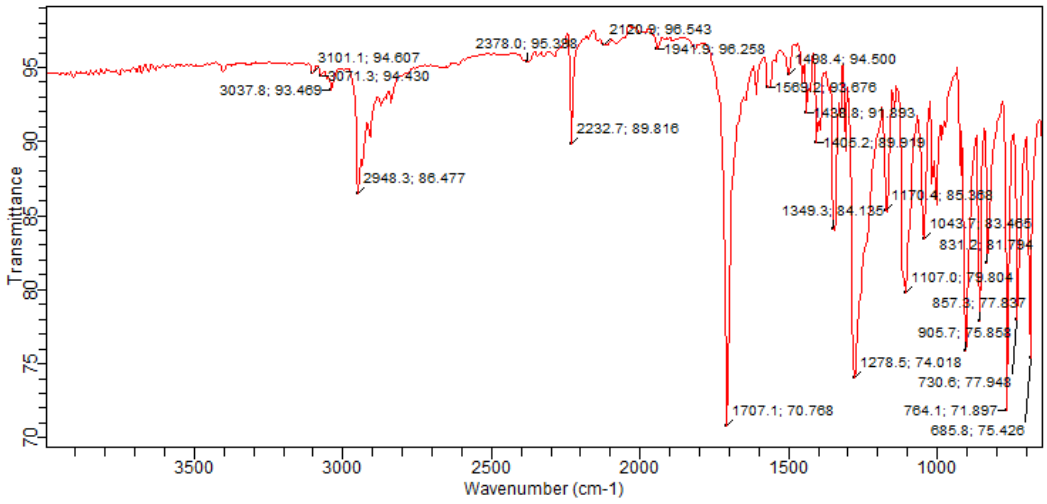
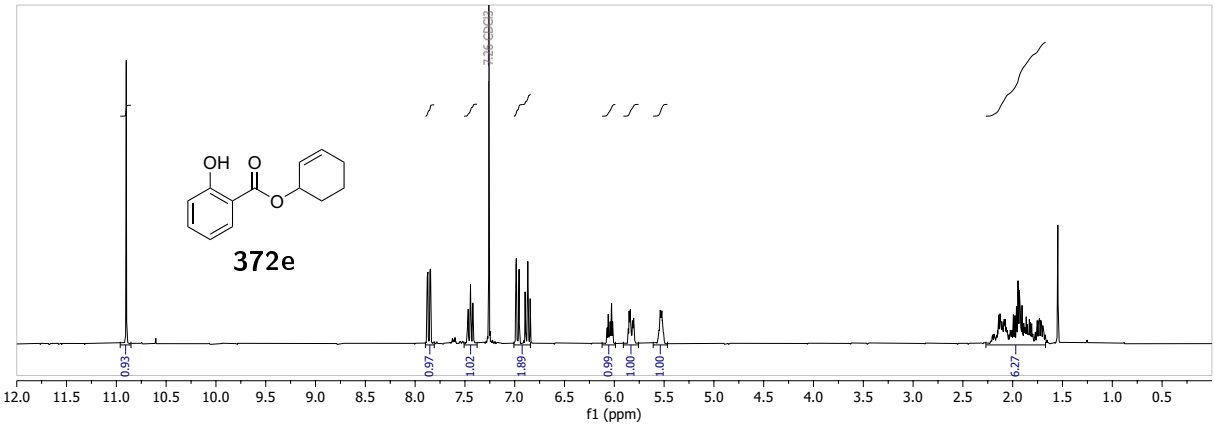
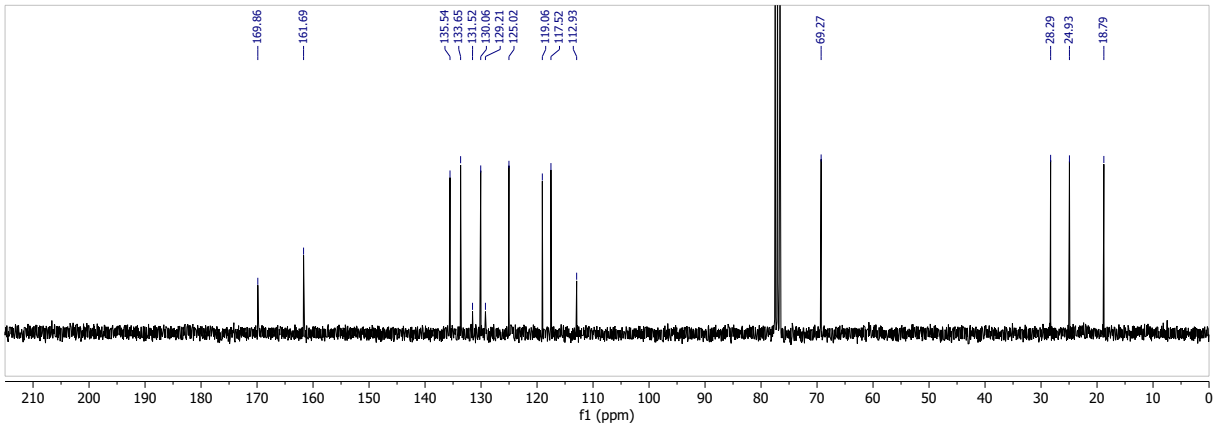


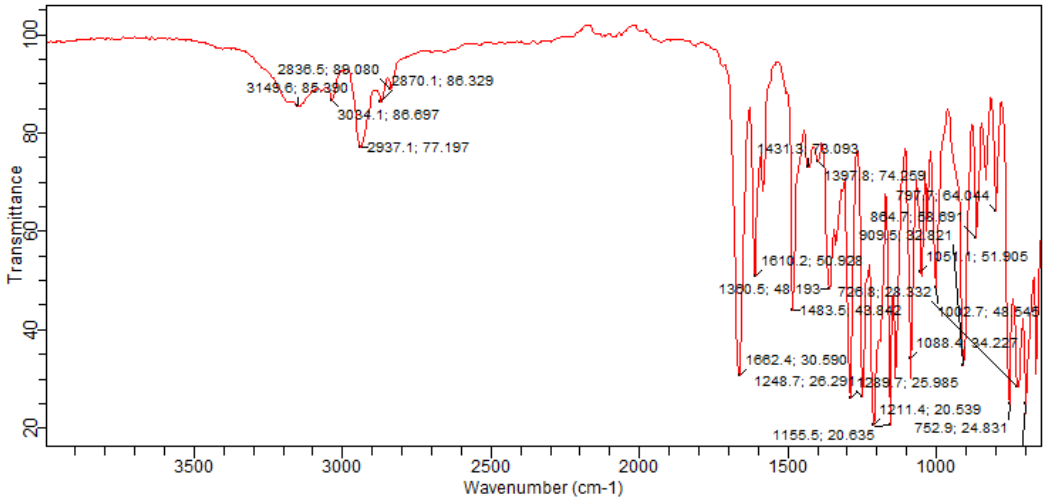




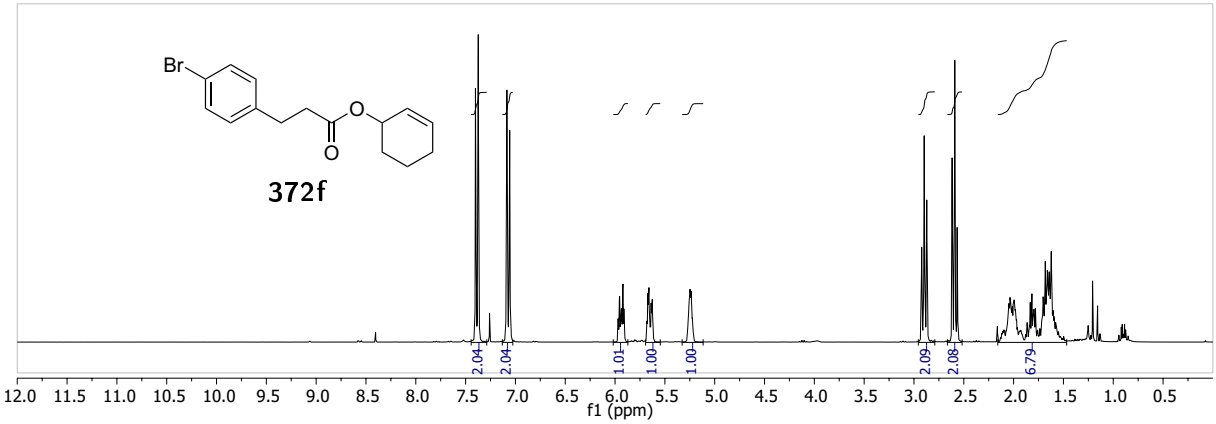
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

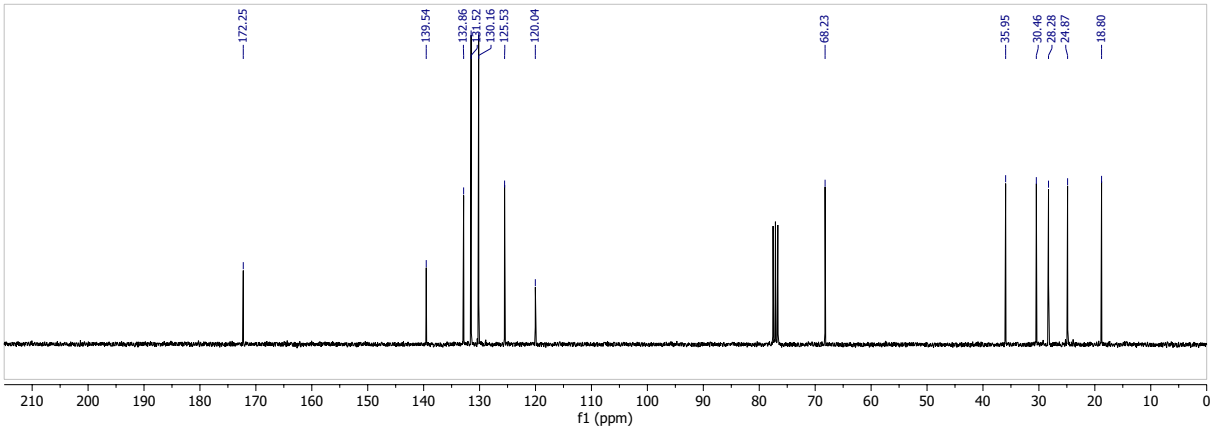


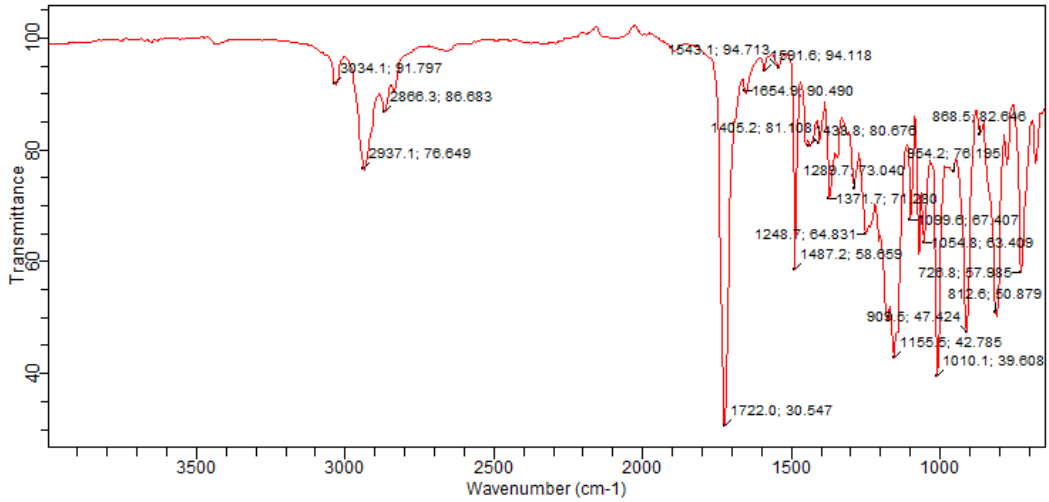




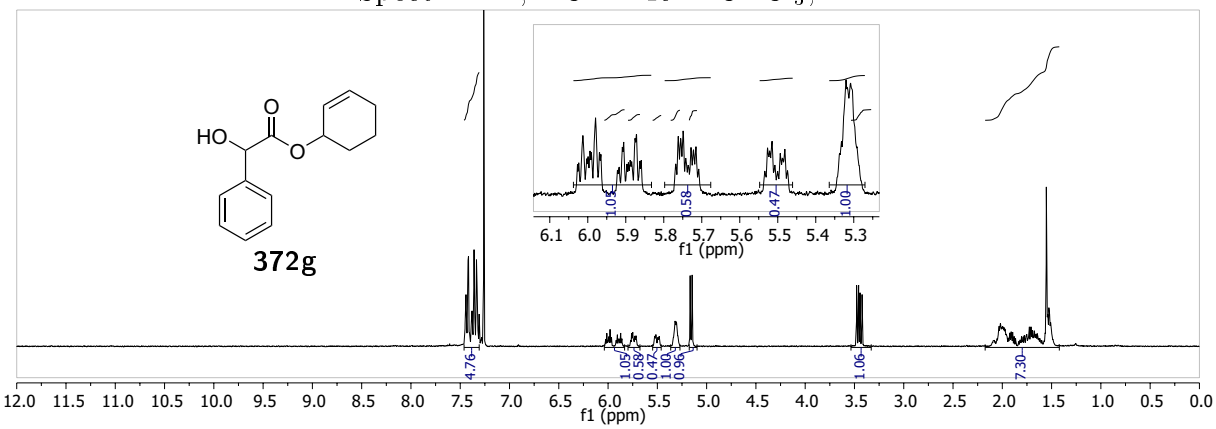
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

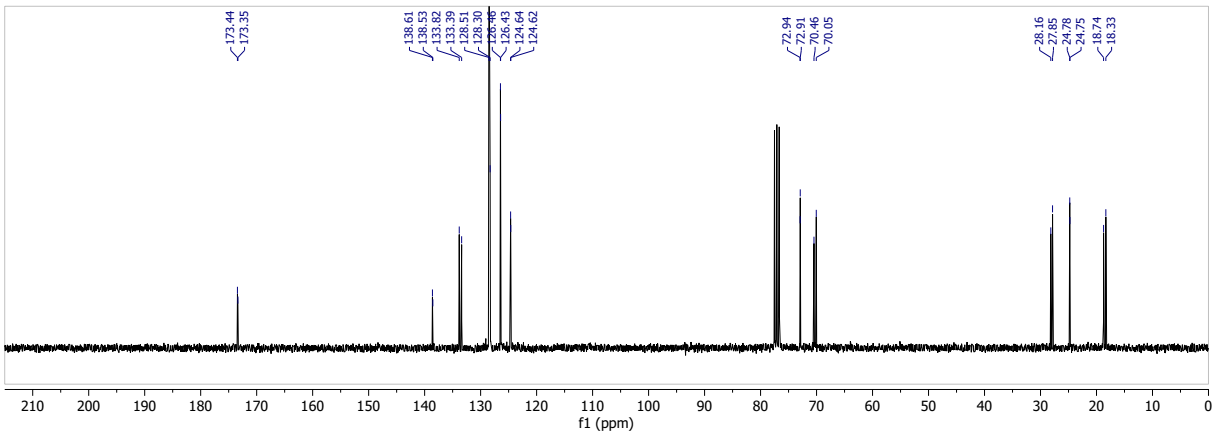


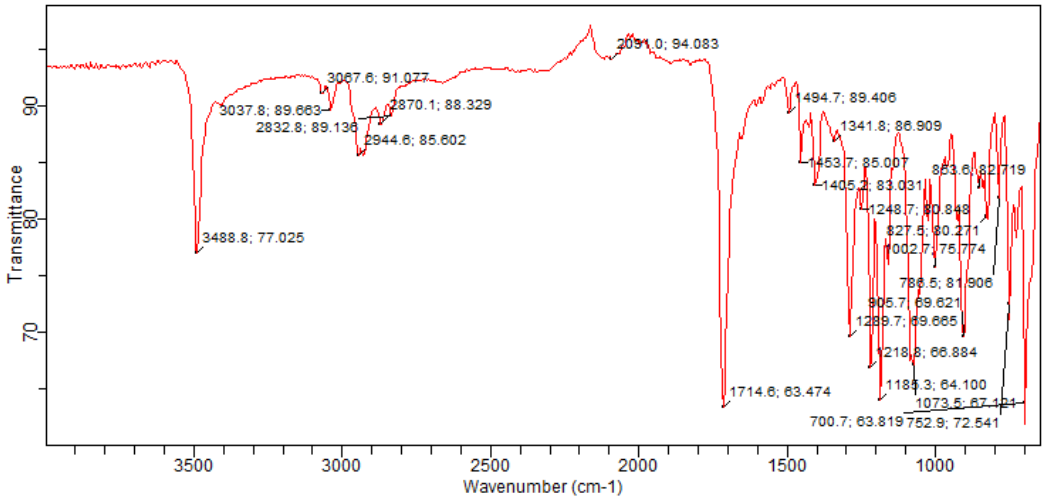




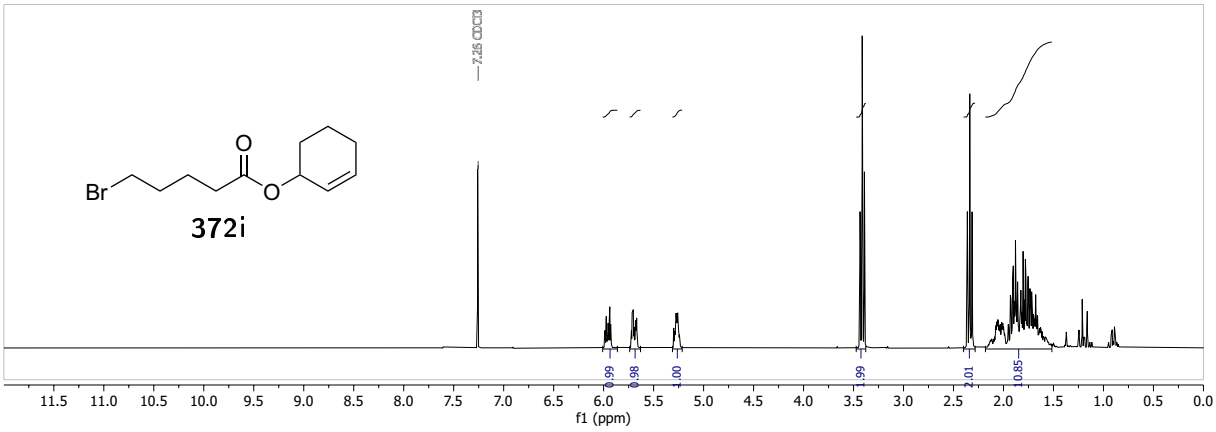
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

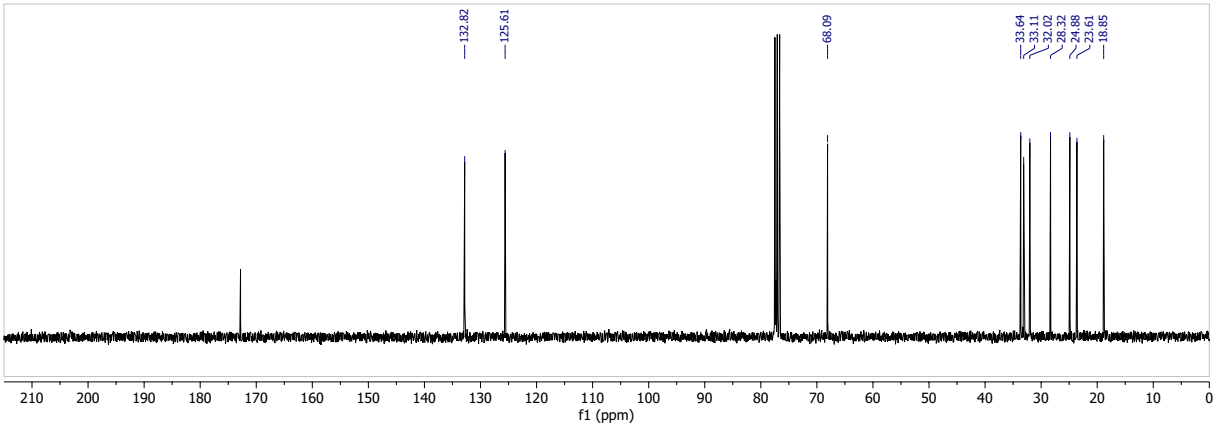


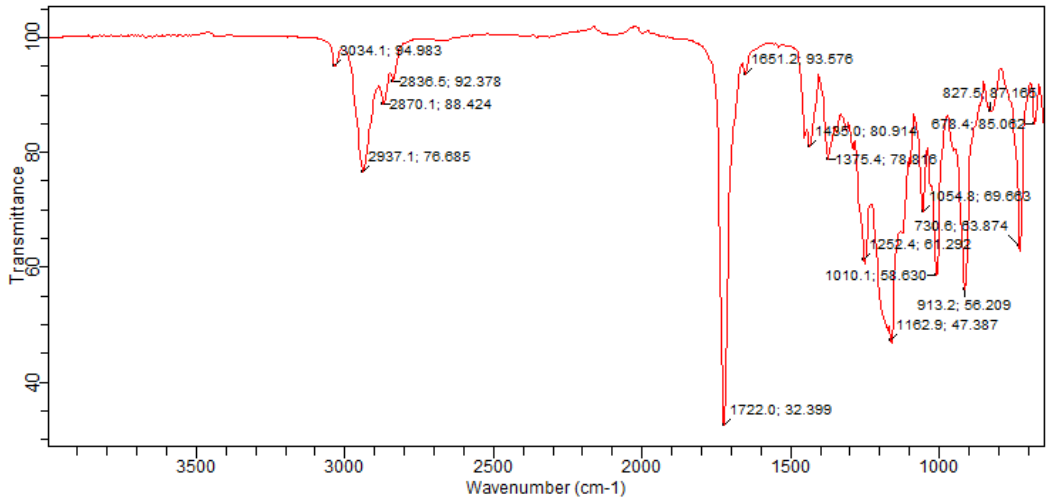




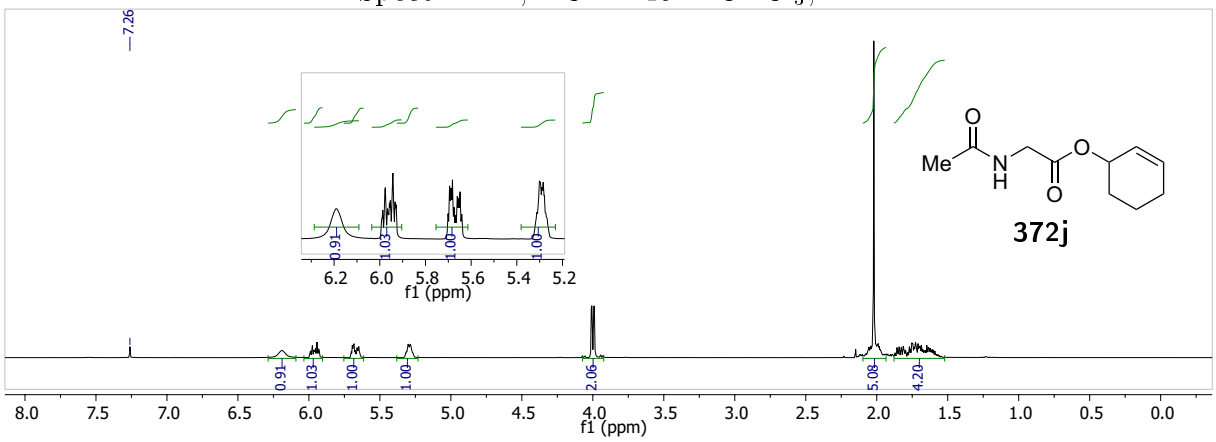
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

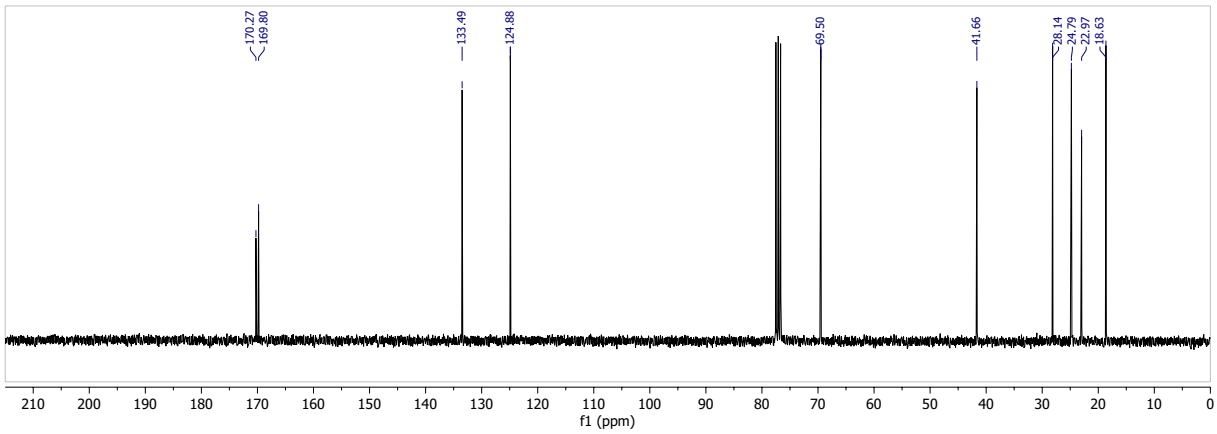


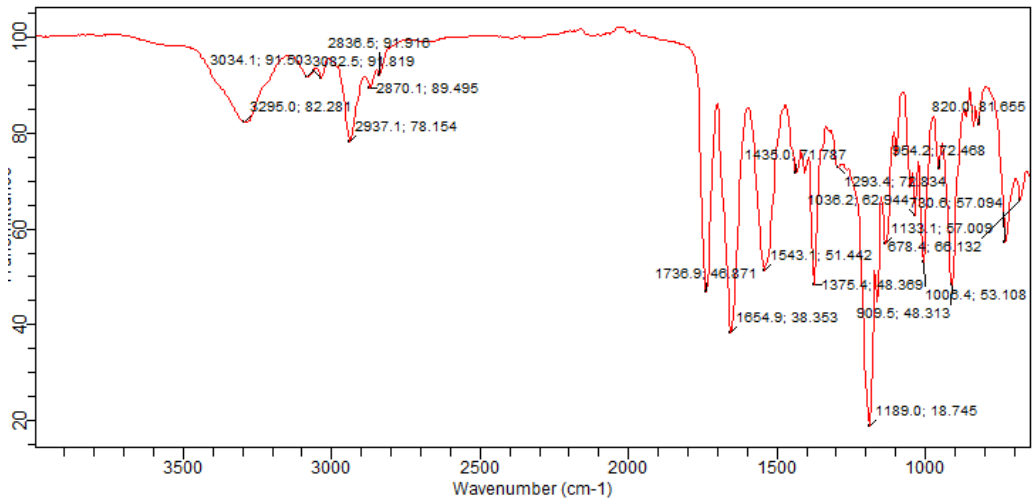




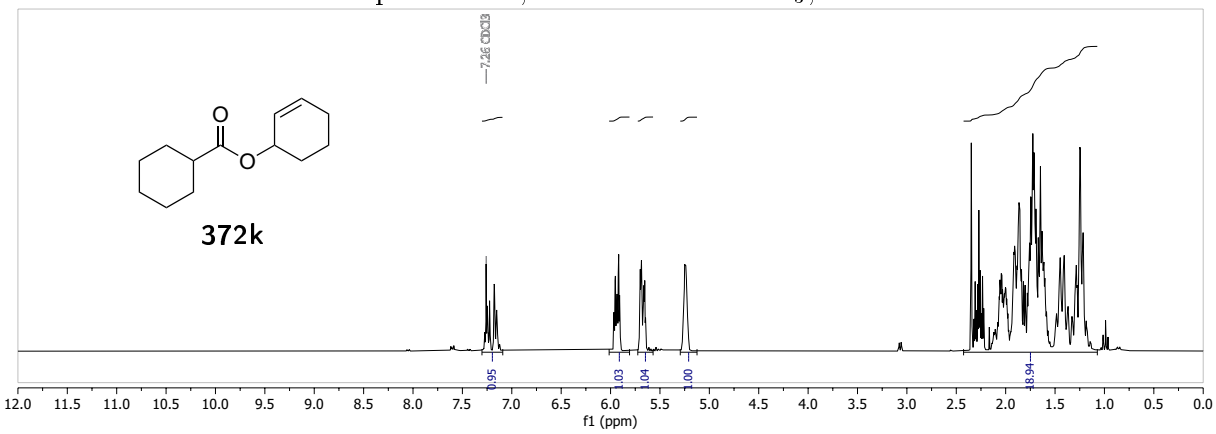
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

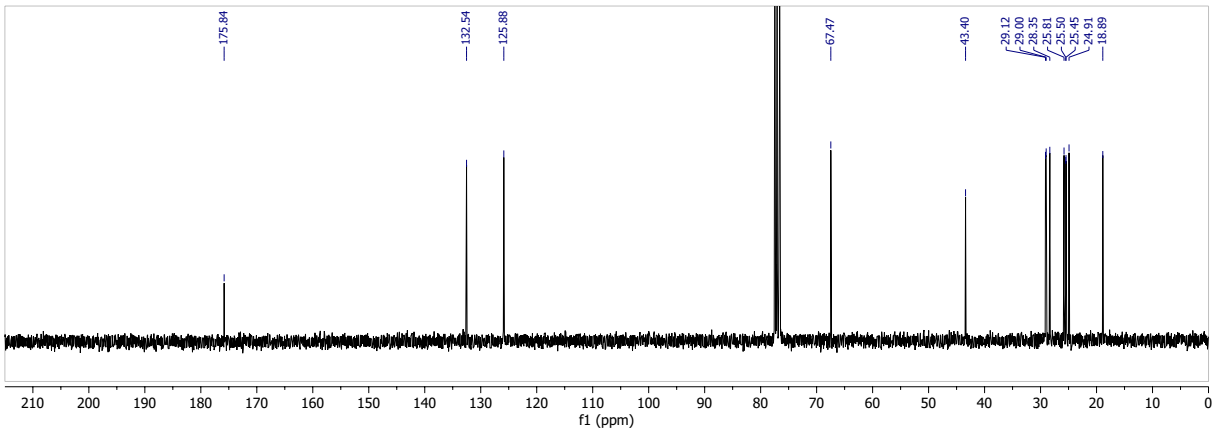


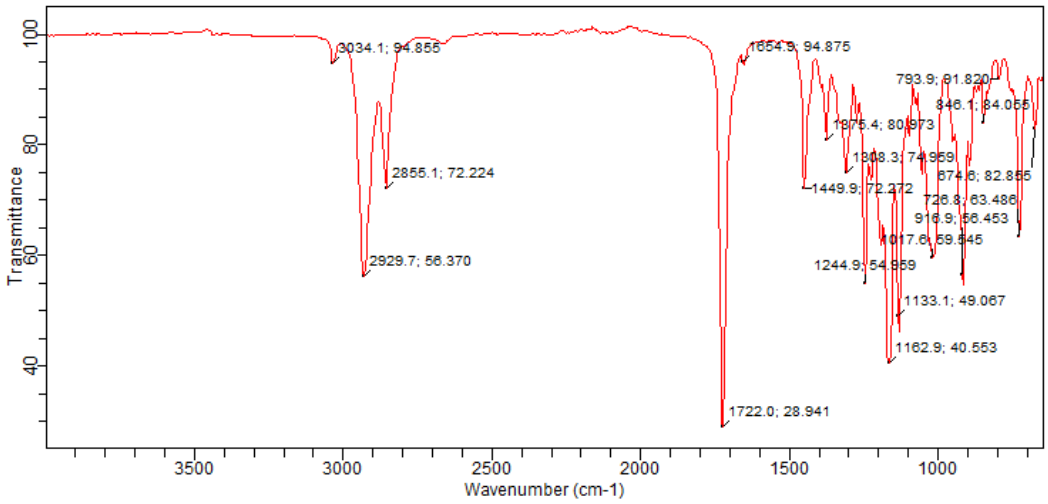




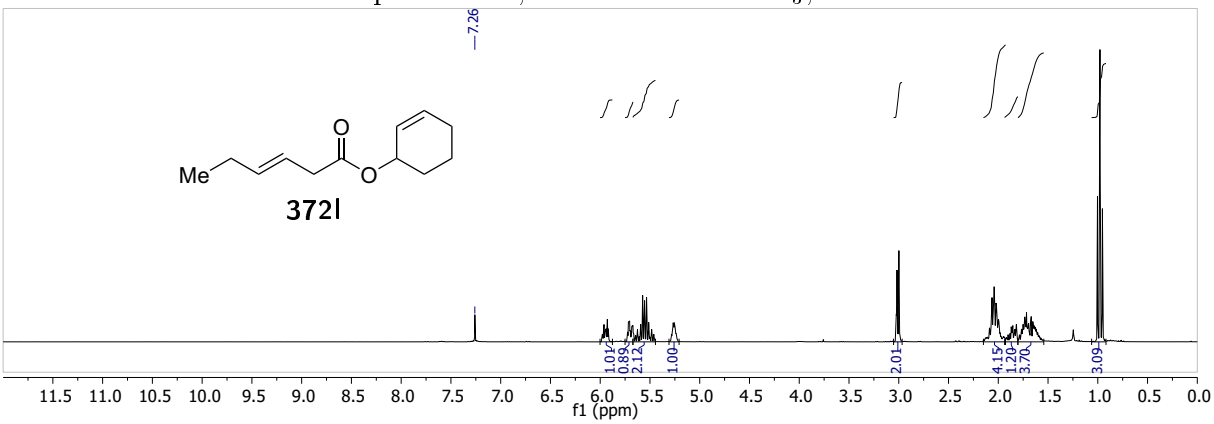
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

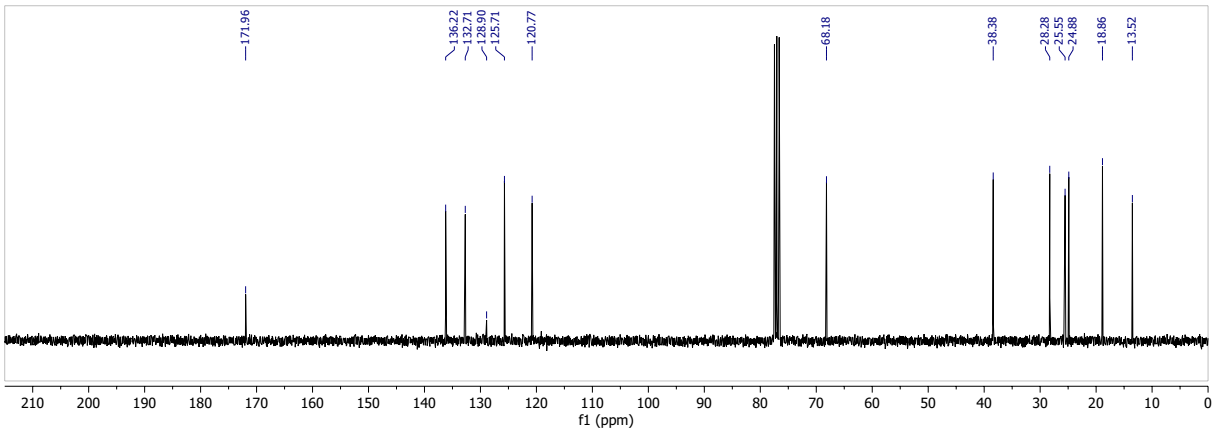


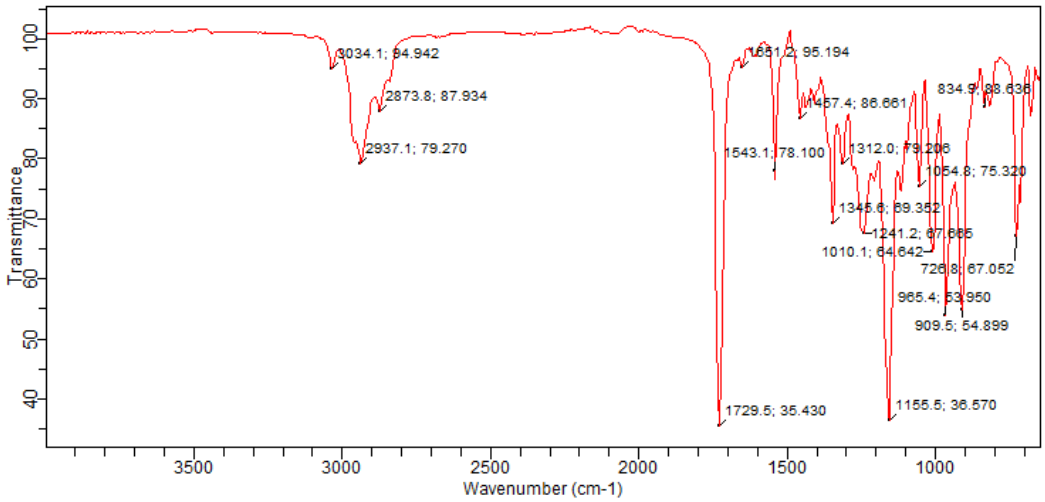




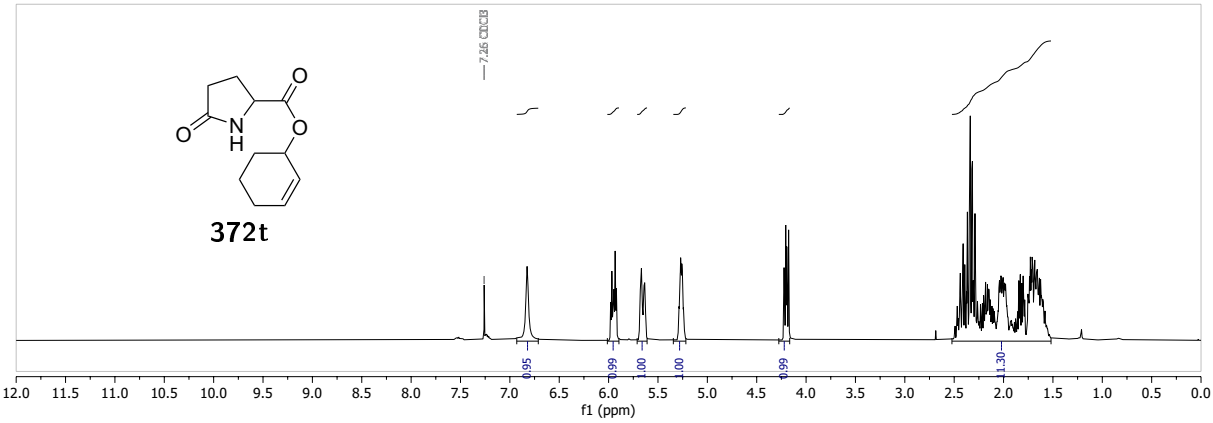
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

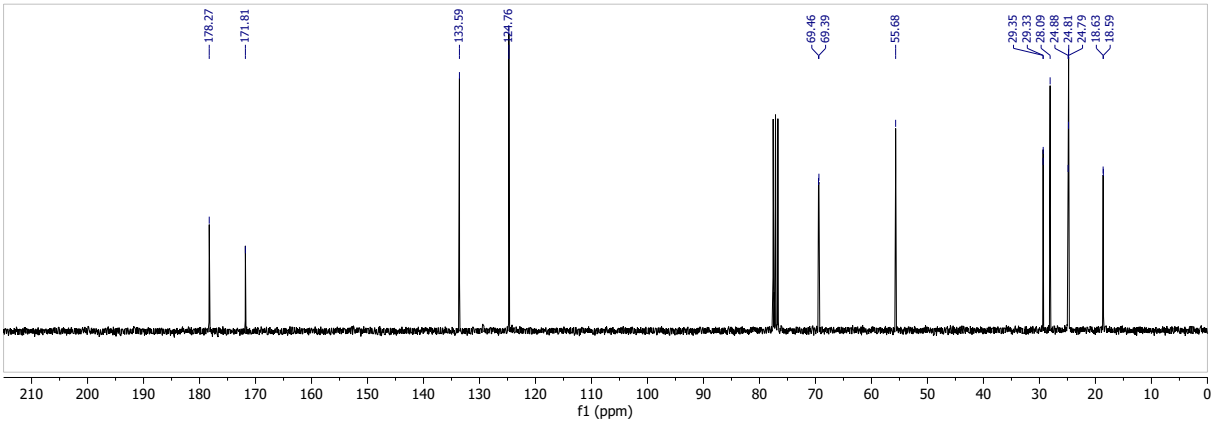


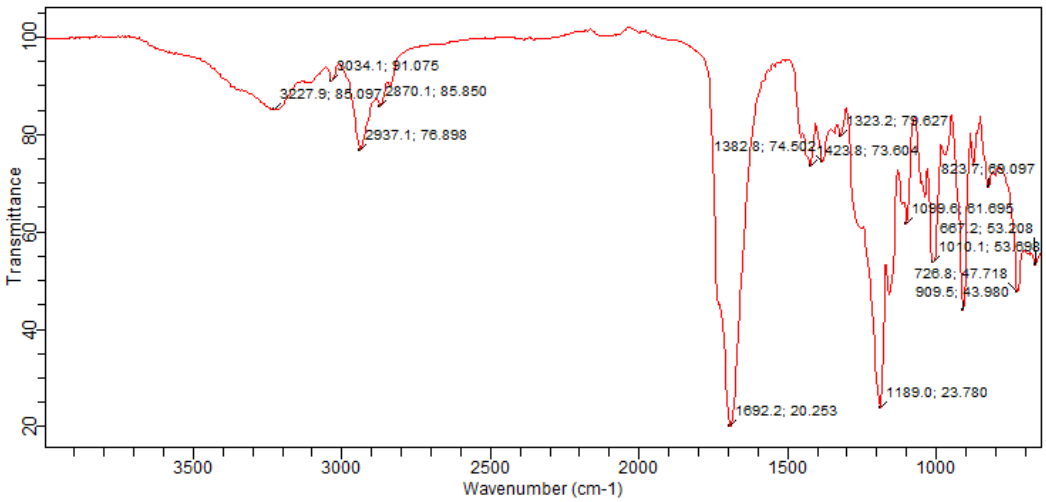




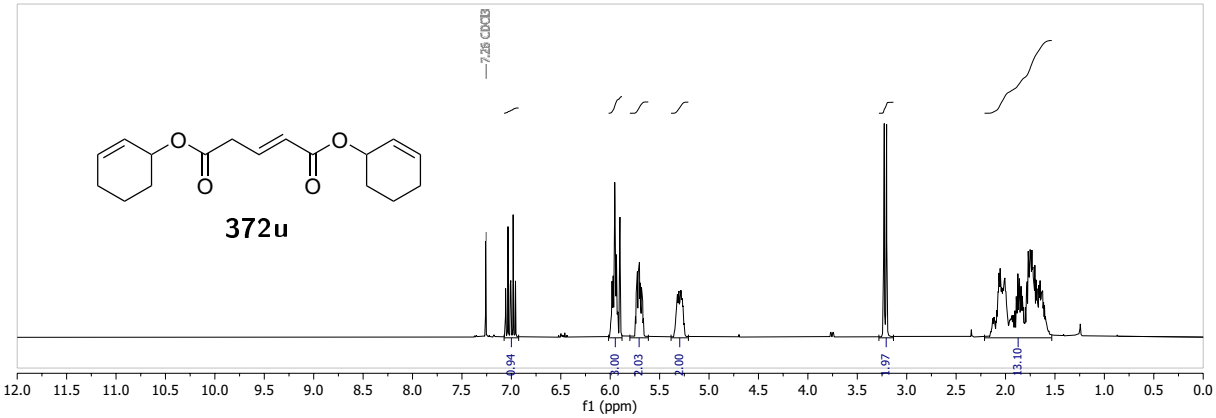
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

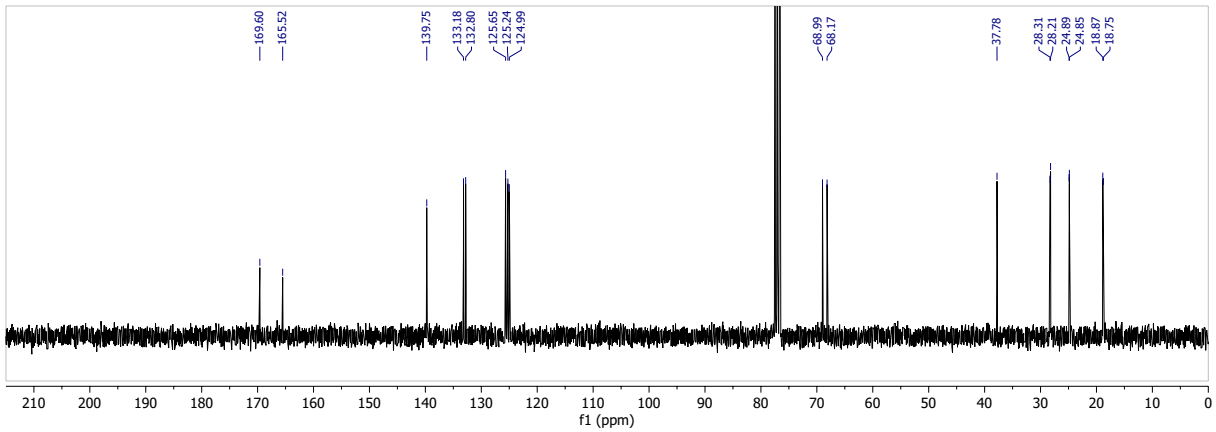


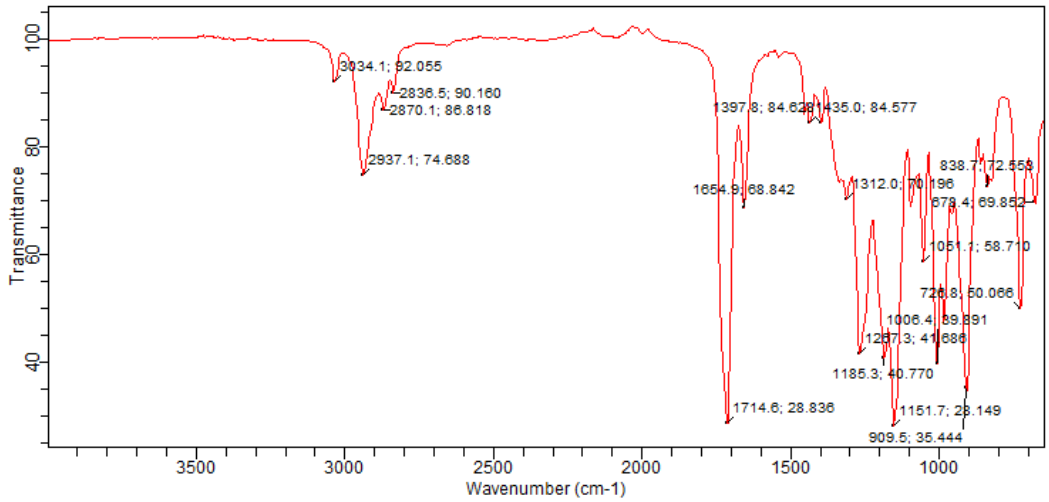




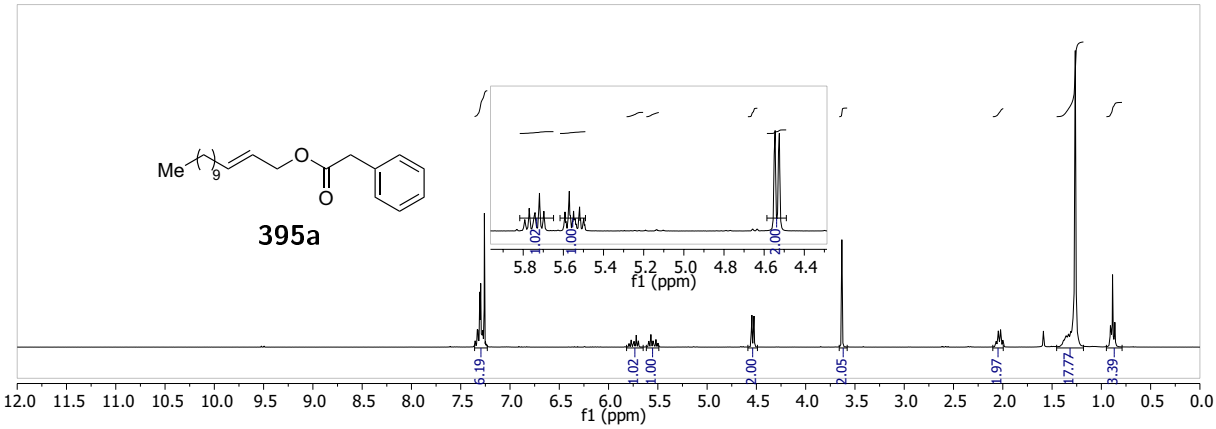
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

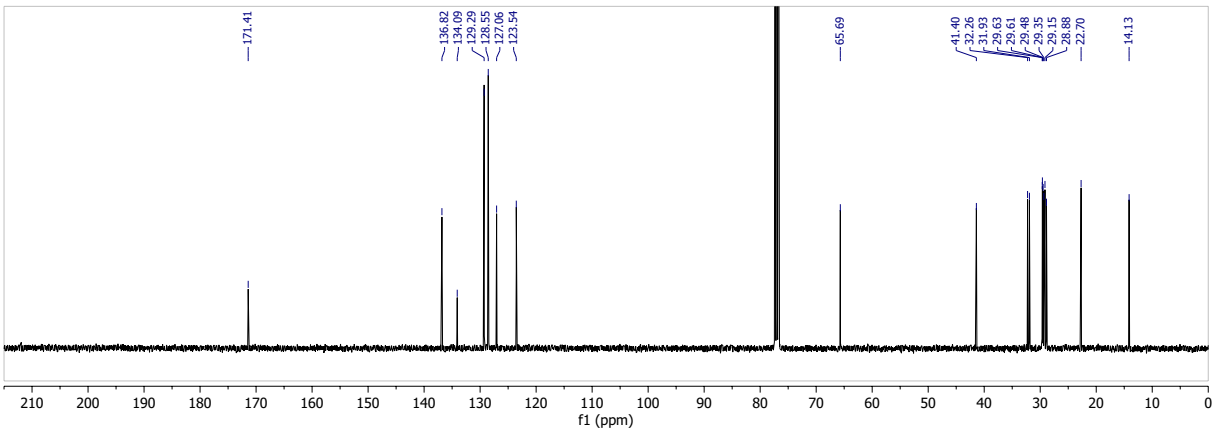


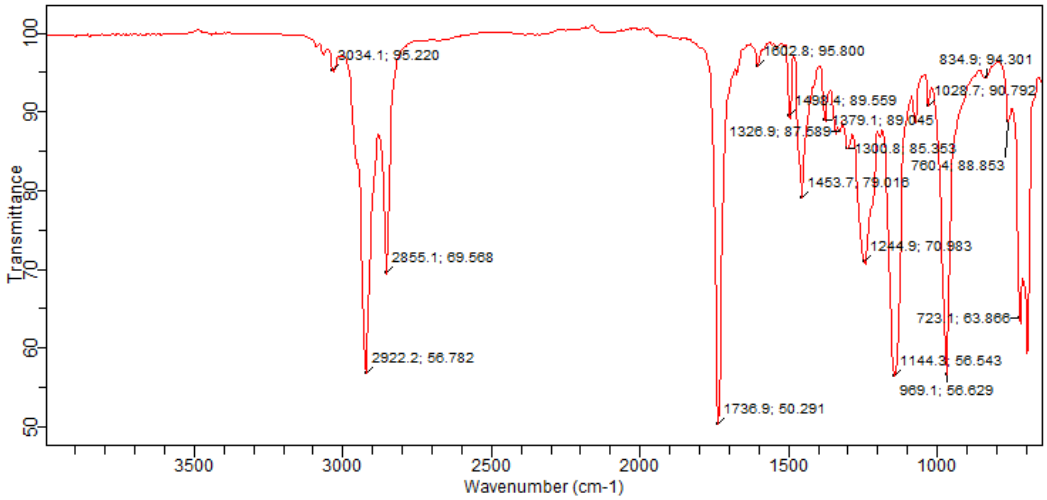




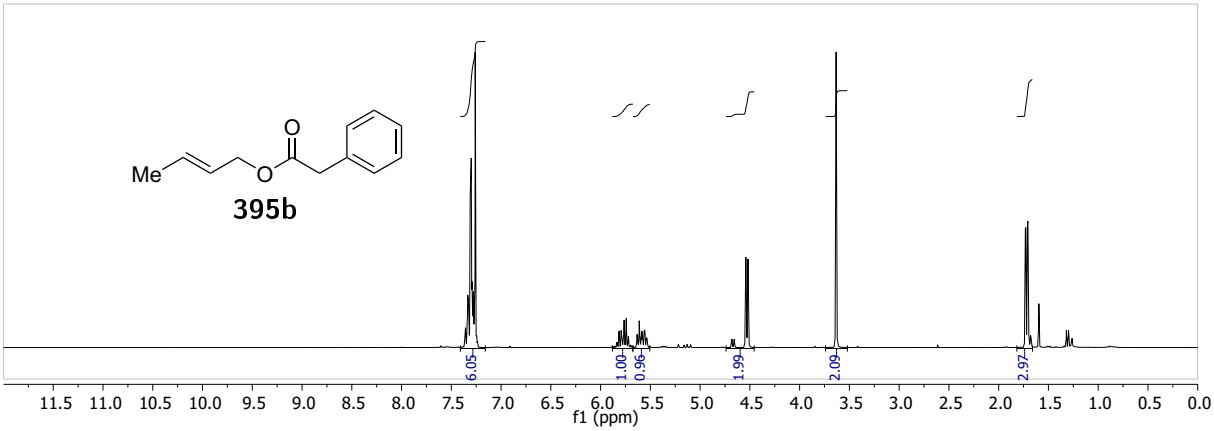
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

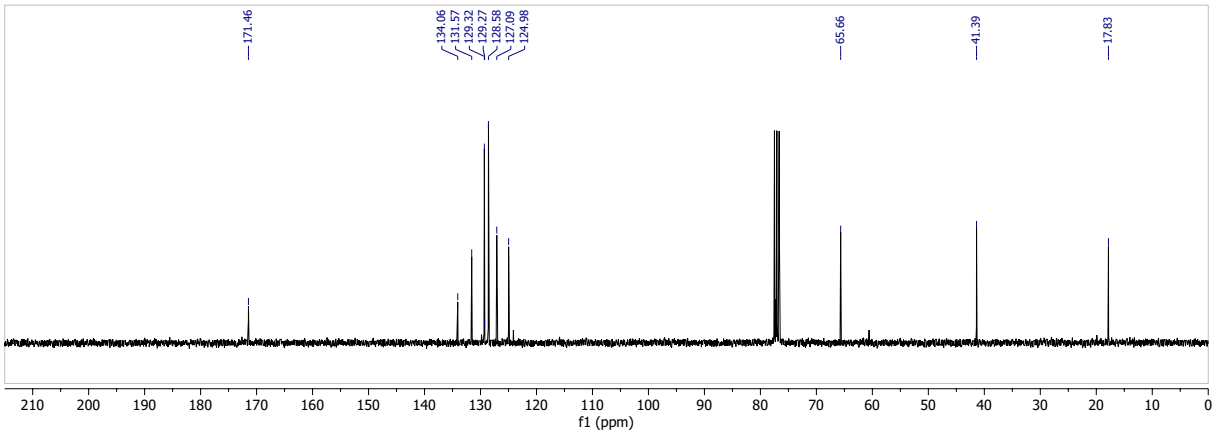


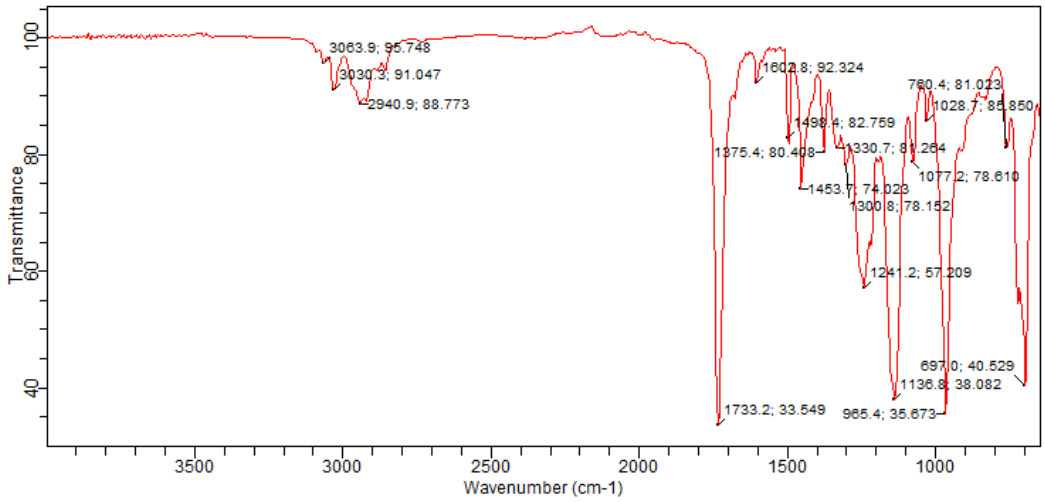




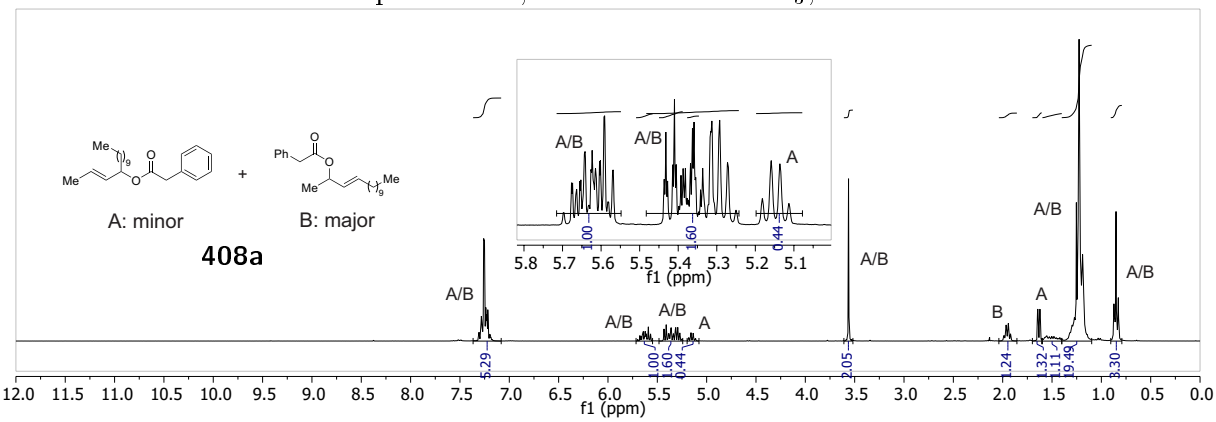
Spectra: ^{1}H, ^{13}C in $CDCl_3$; IR

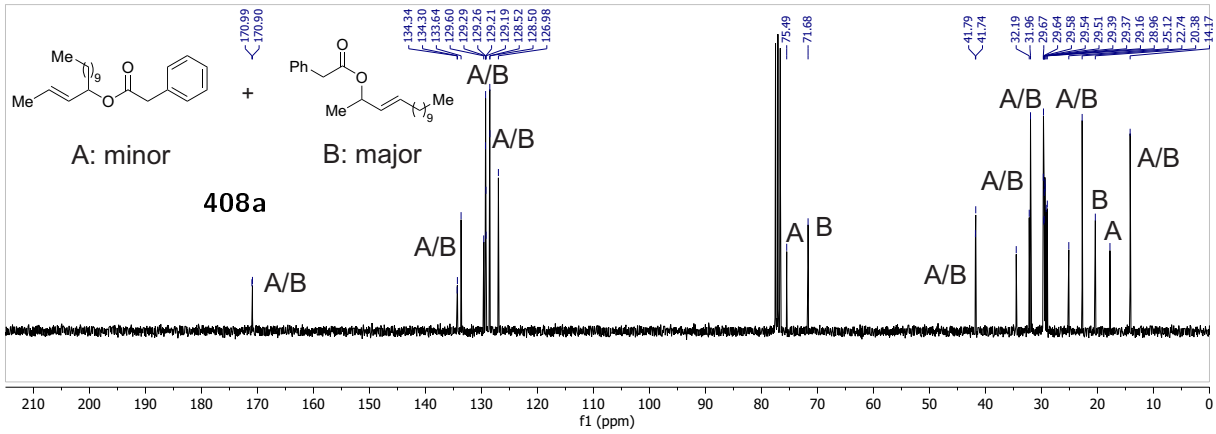


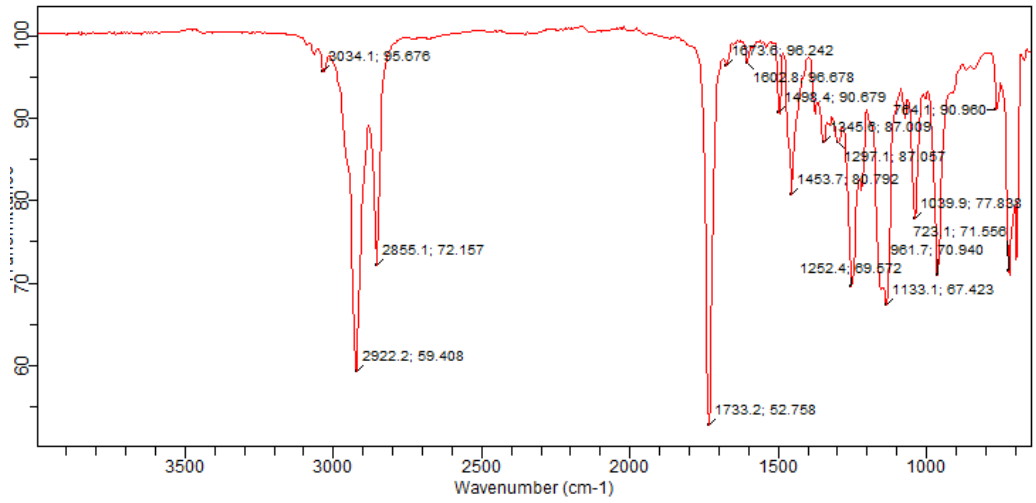




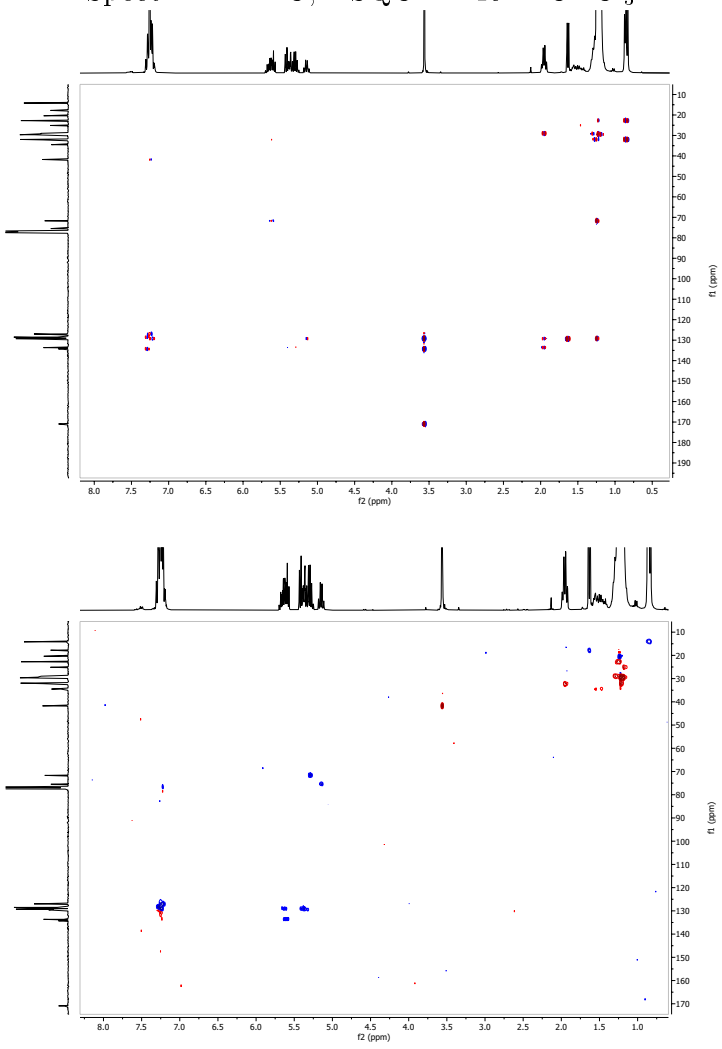
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR



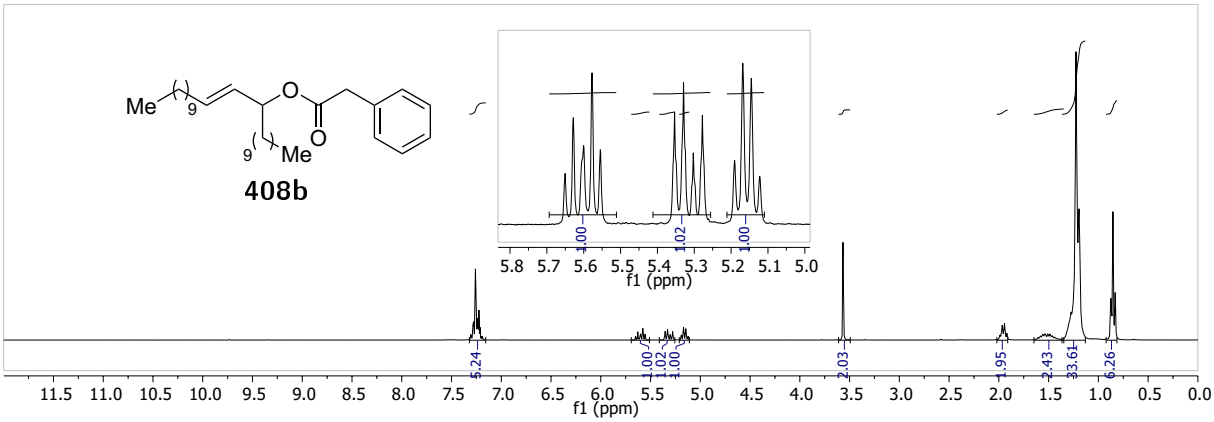


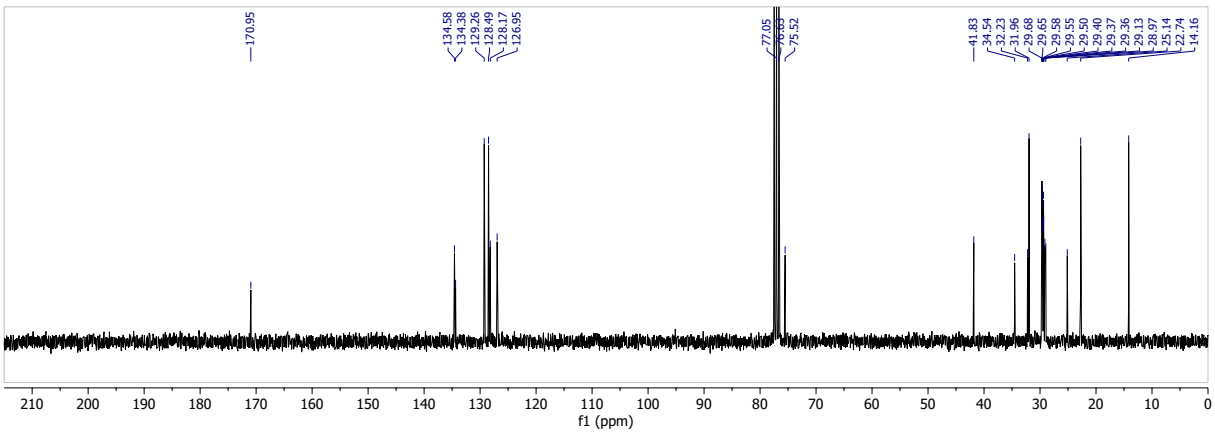


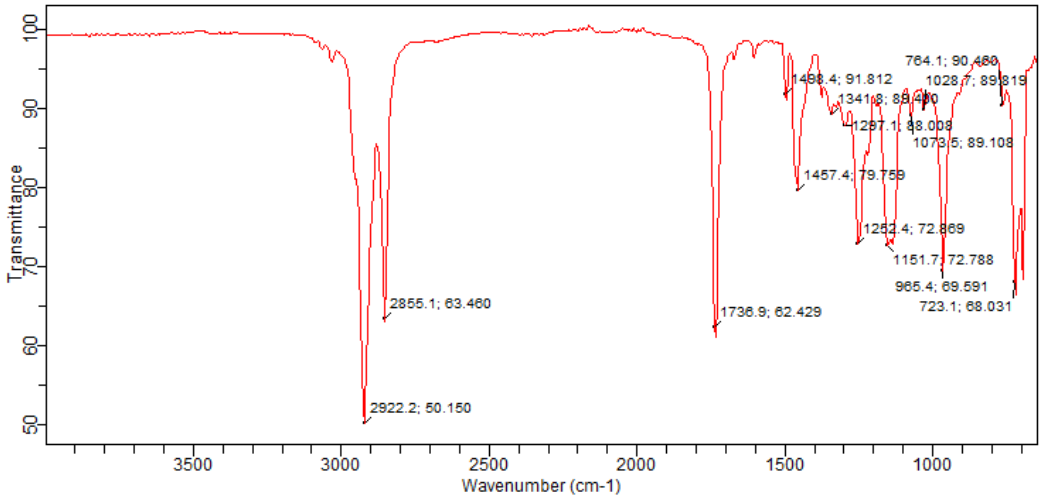
Spectra: HMBC, HSQC NMR in $CDCl_3$



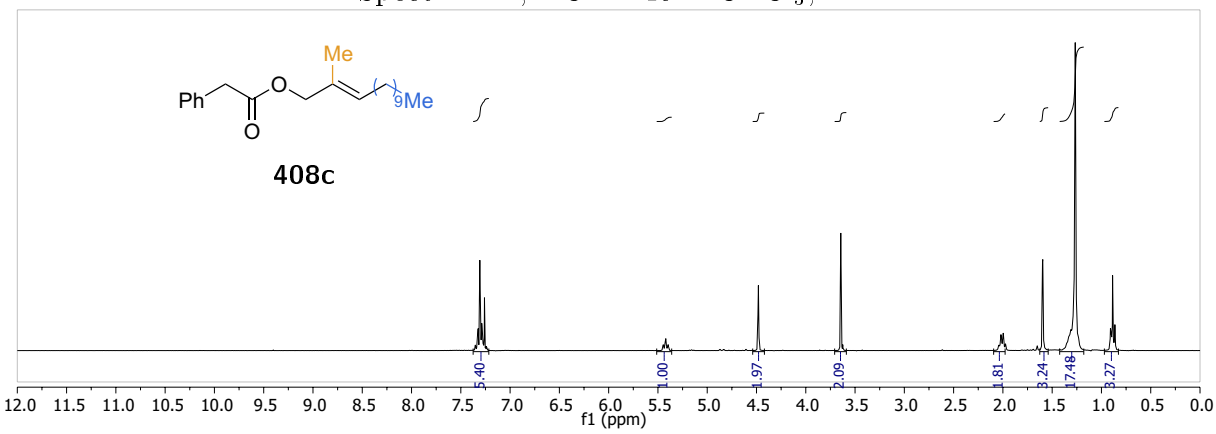
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

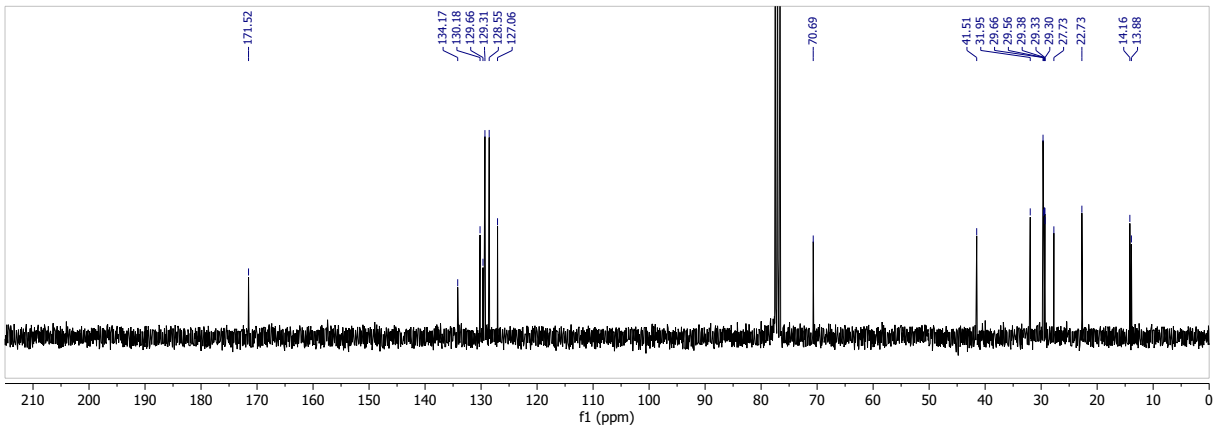


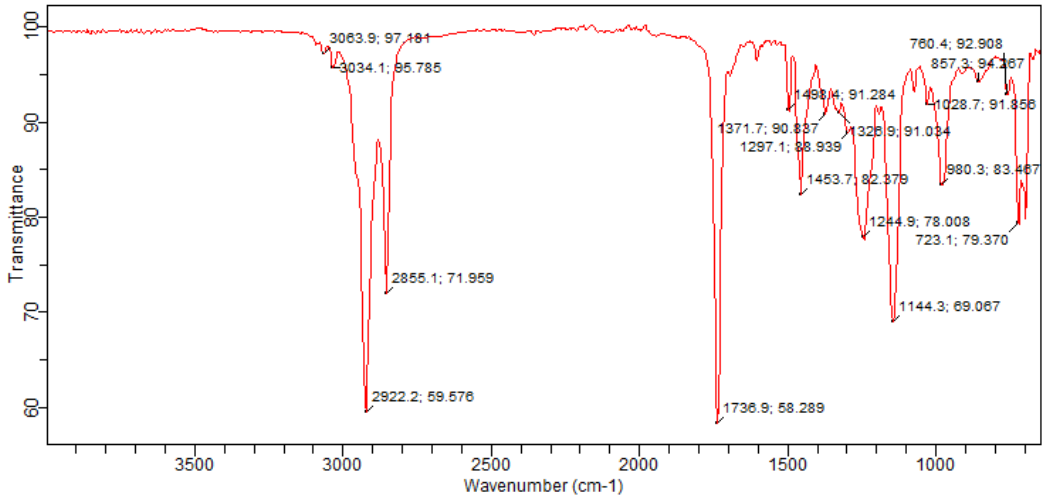




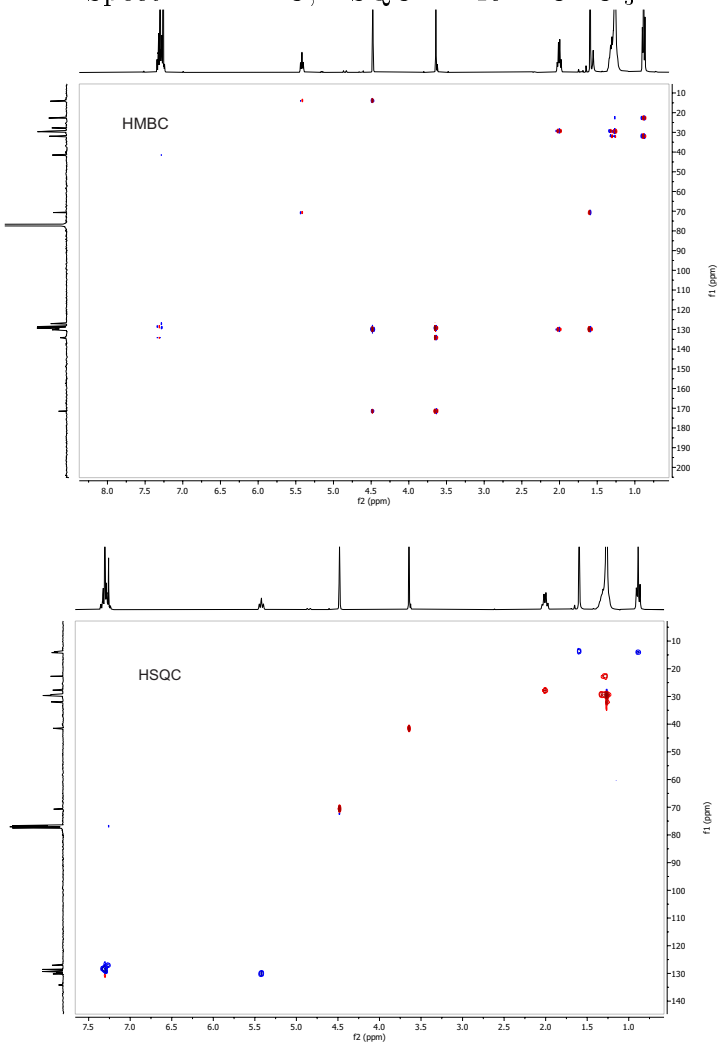
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR



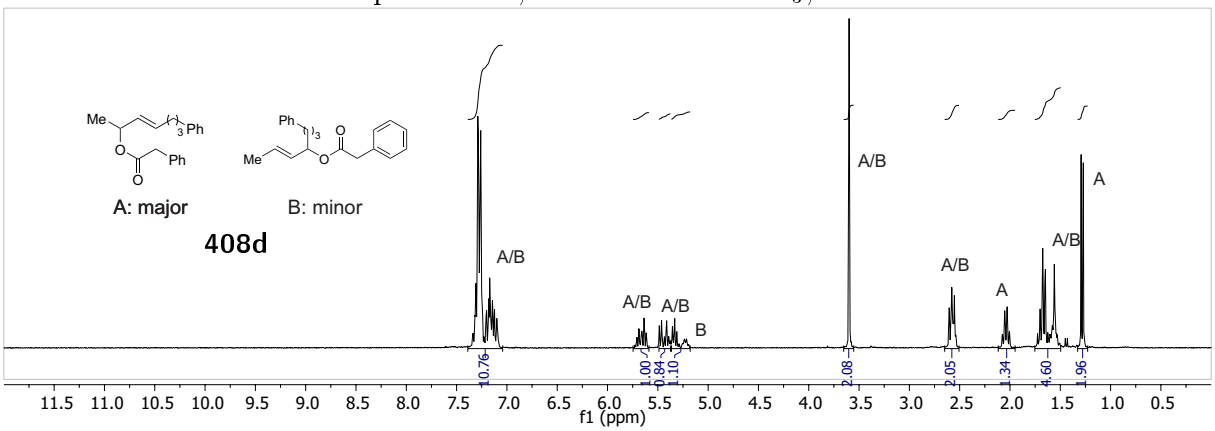


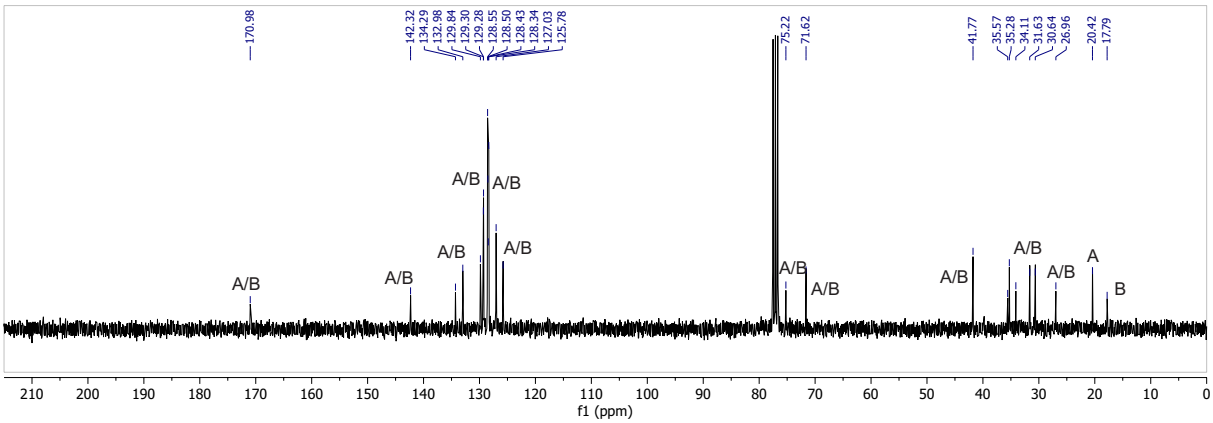


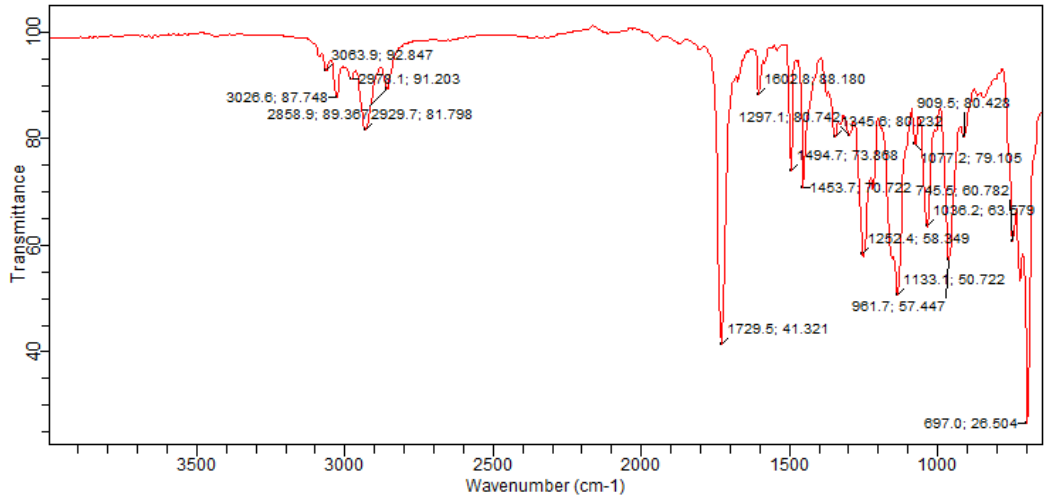
Spectra: HMBC, HSQC NMR in $CDCl_3$



Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR







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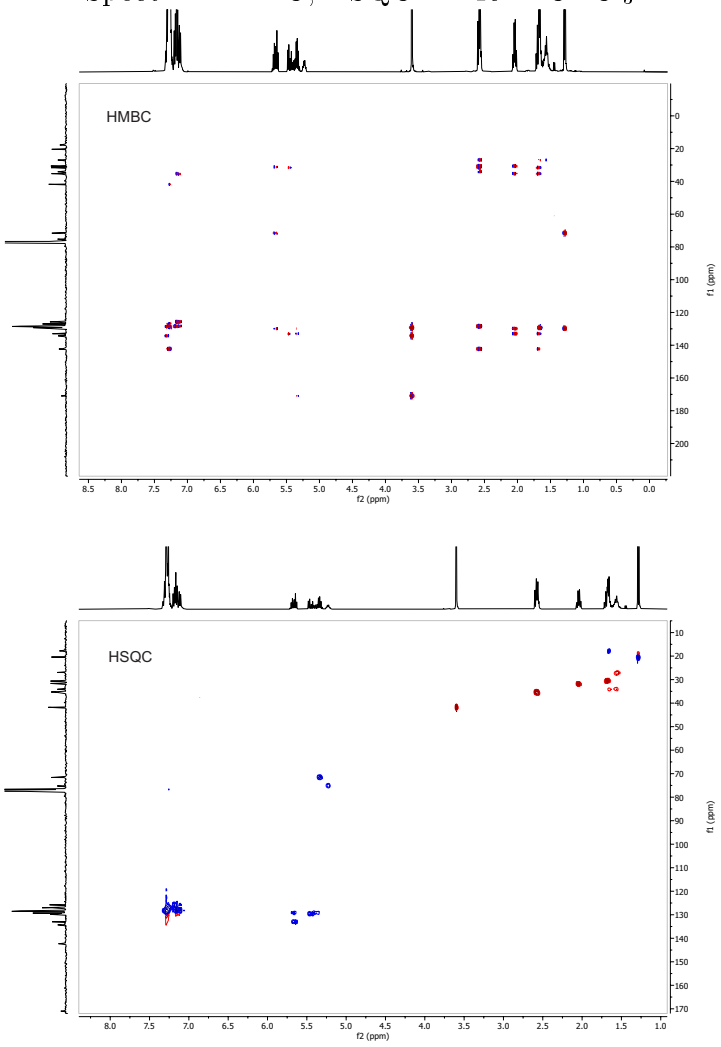
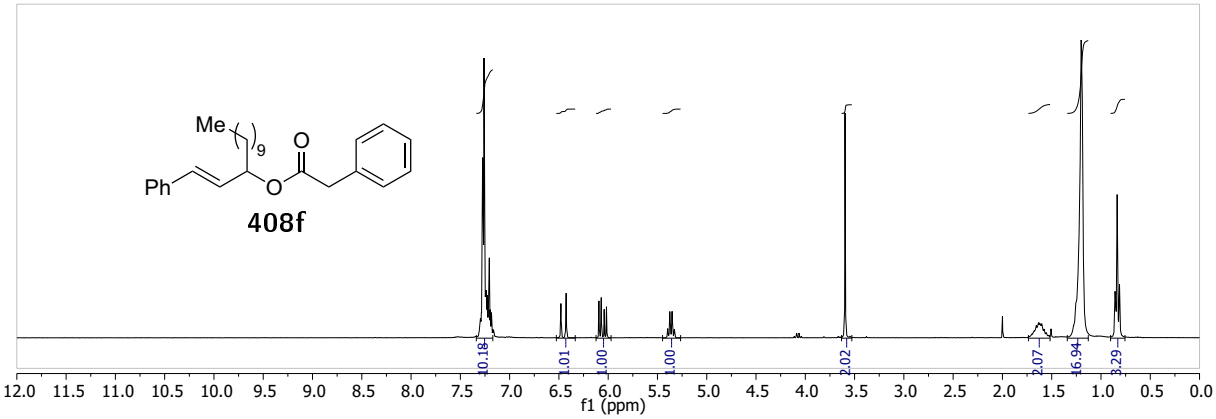
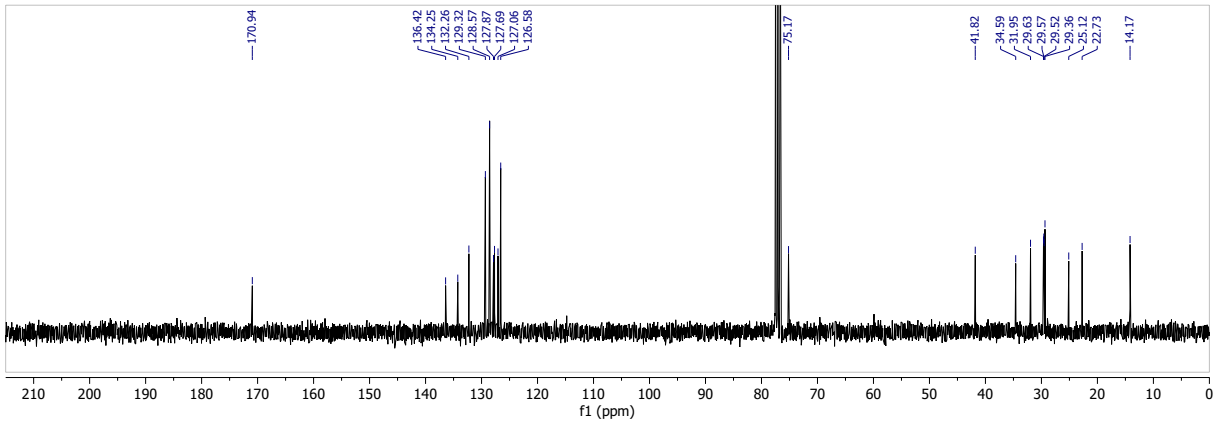
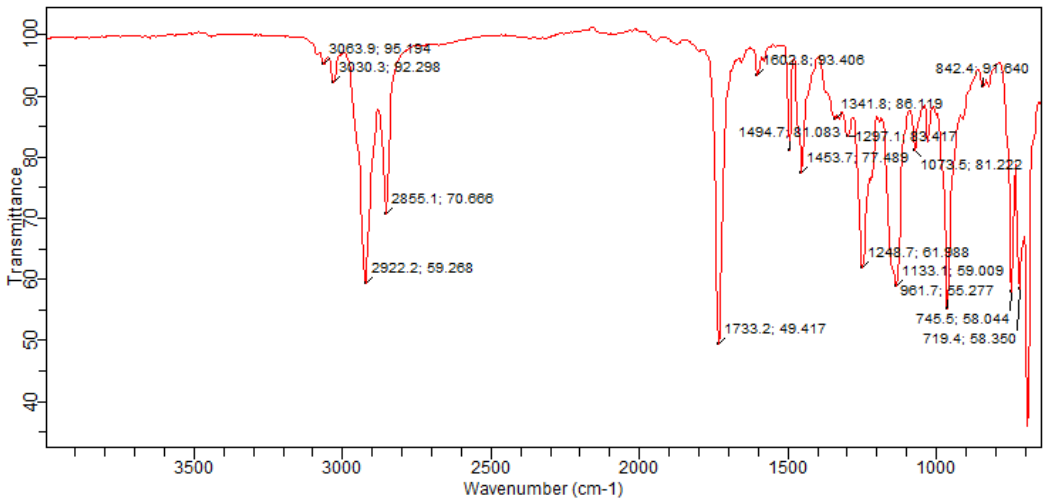


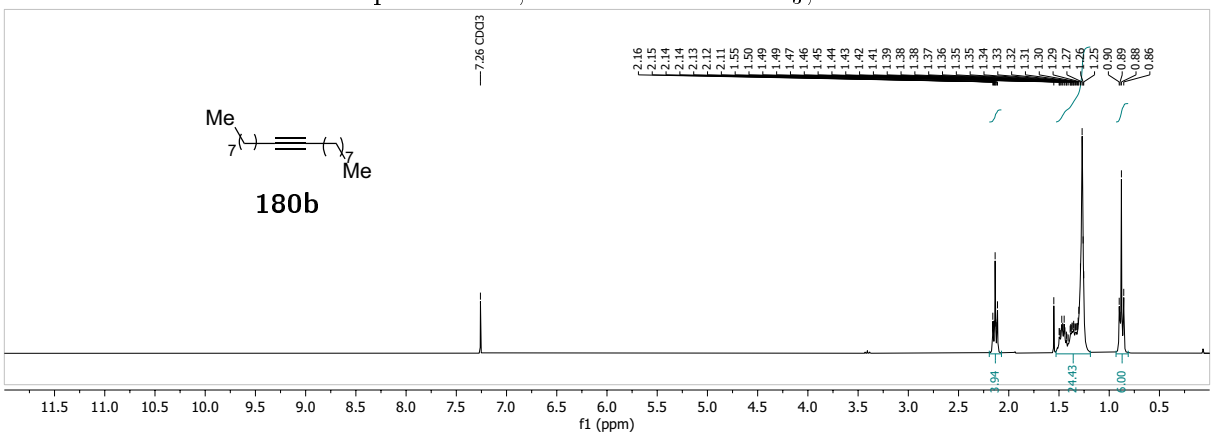
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

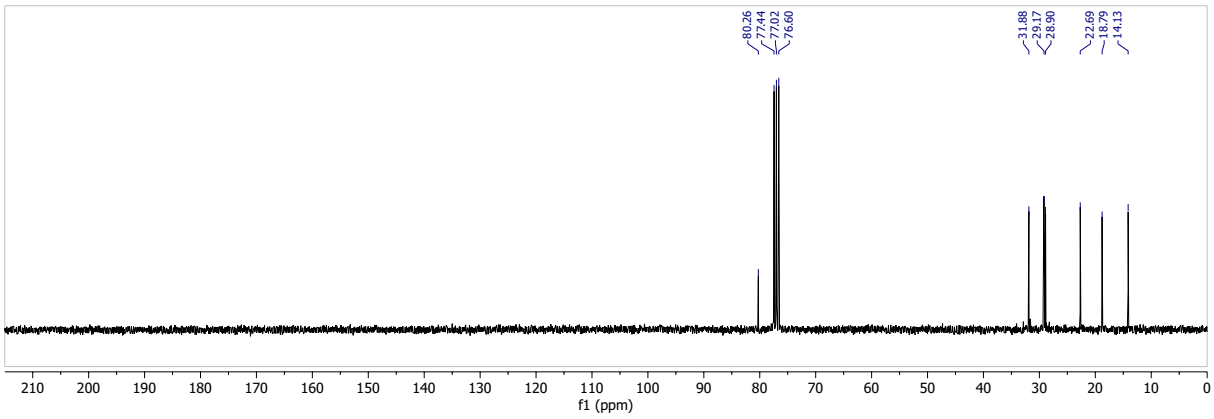


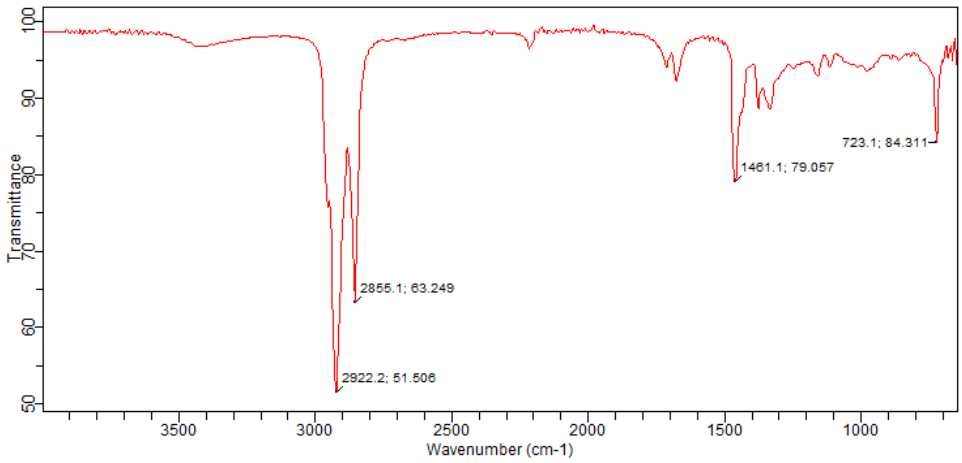




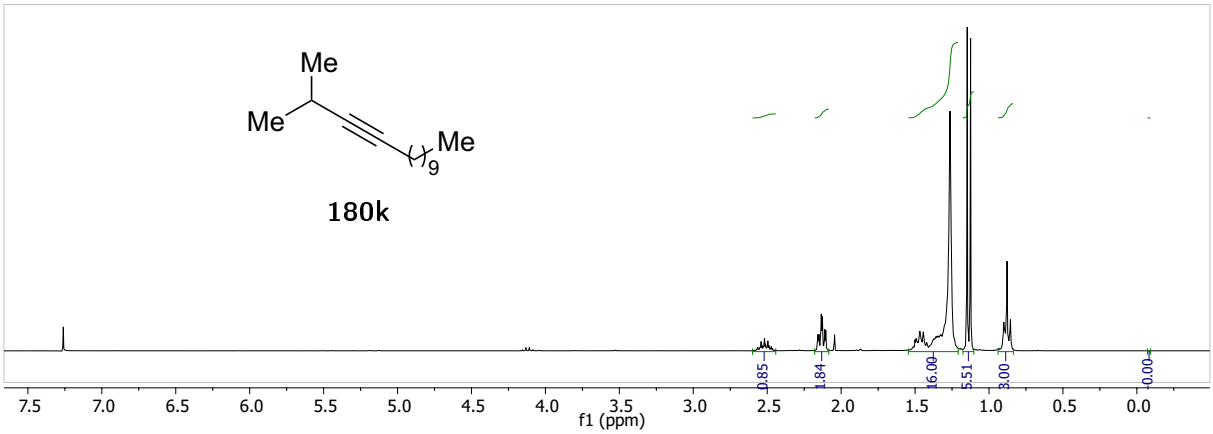
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

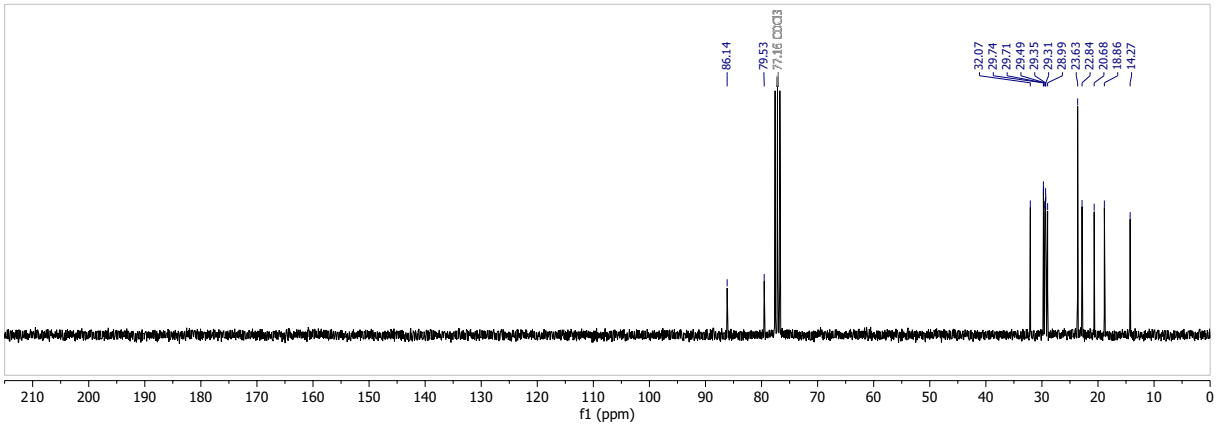


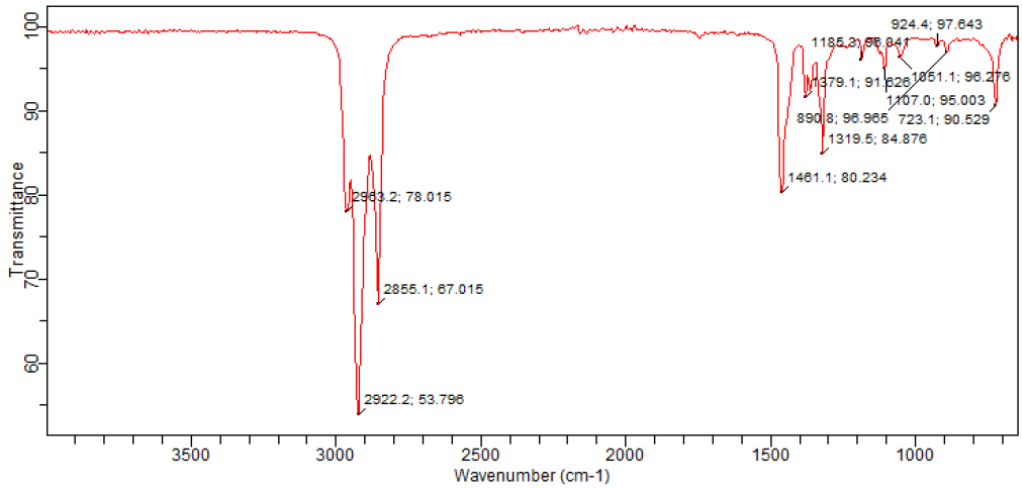




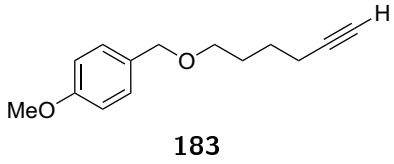
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR







Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR



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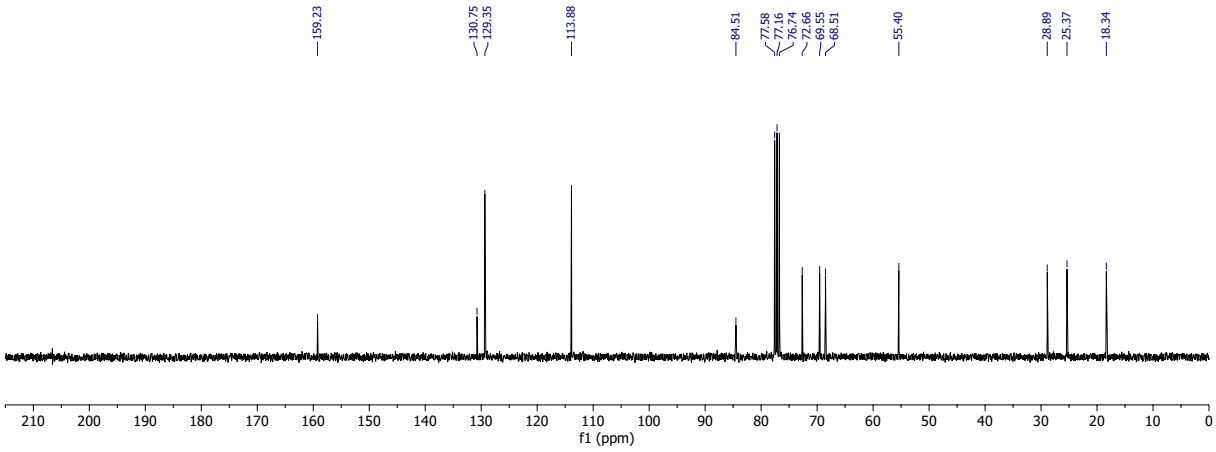
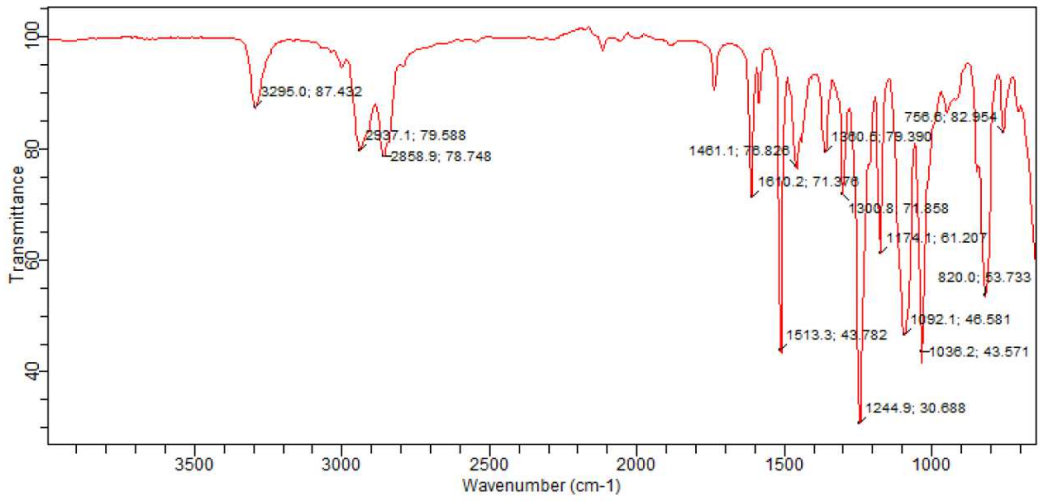
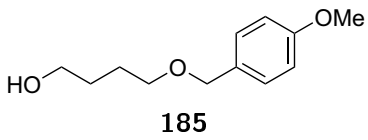




Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR



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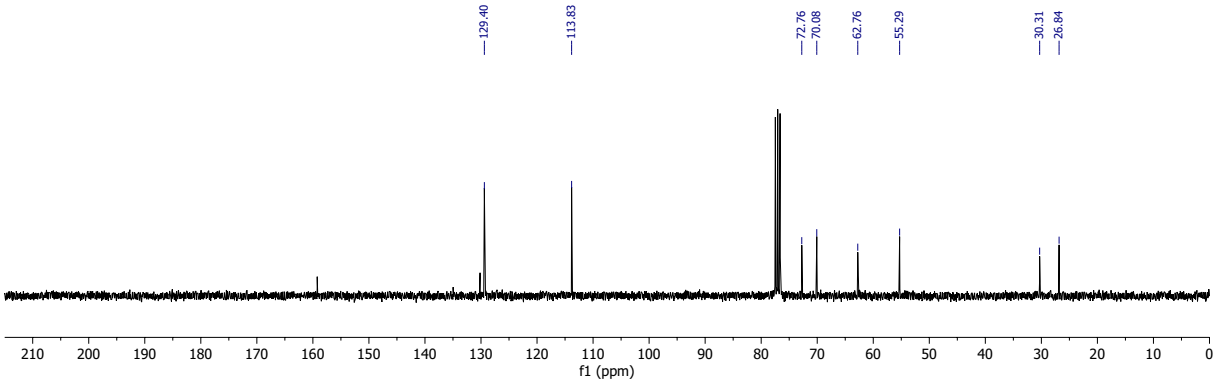
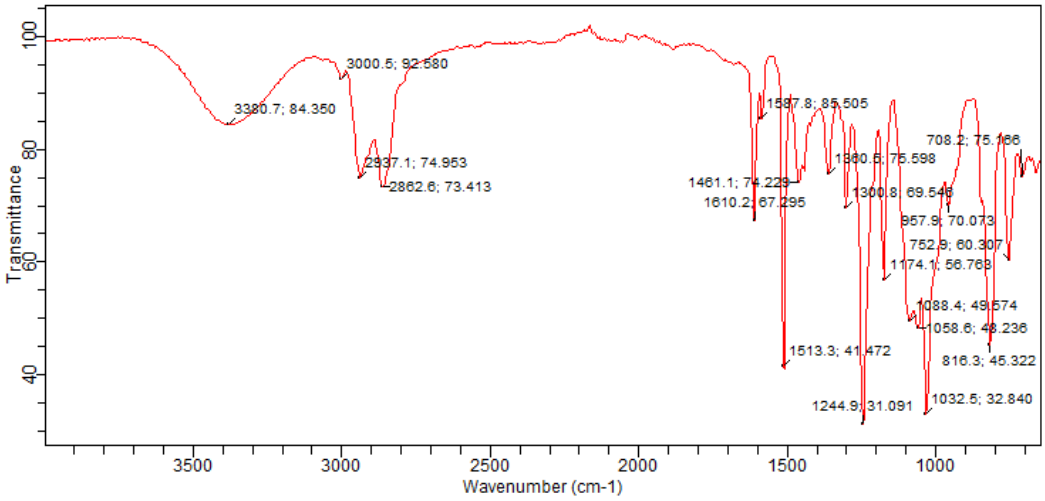
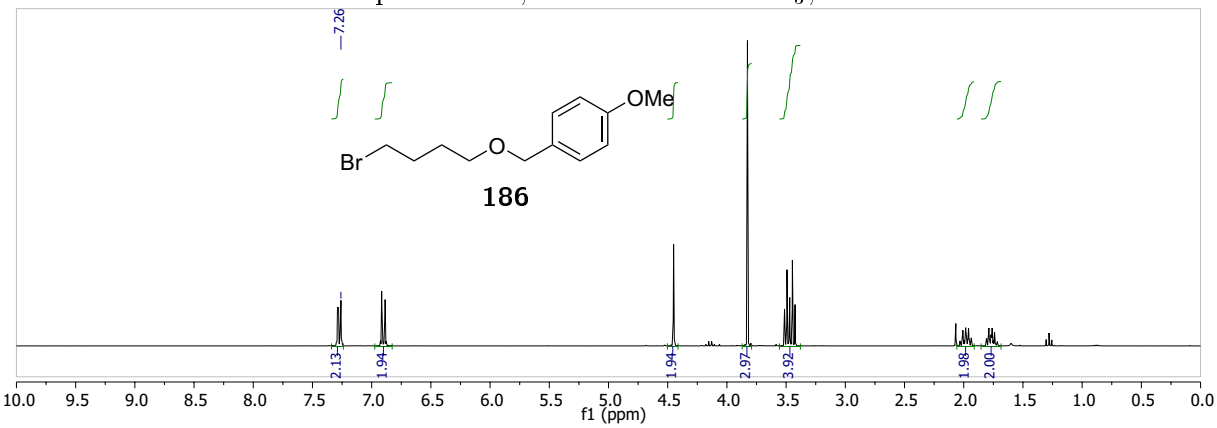
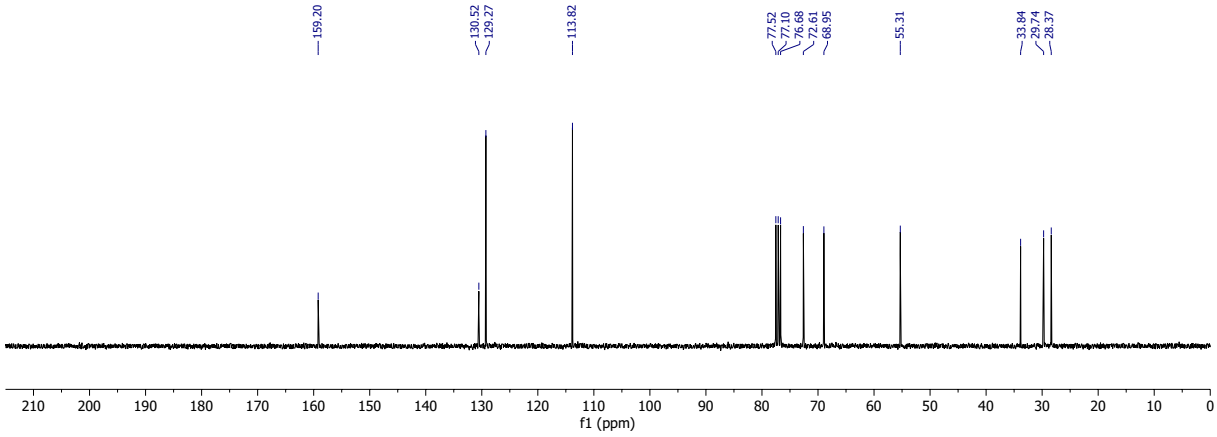
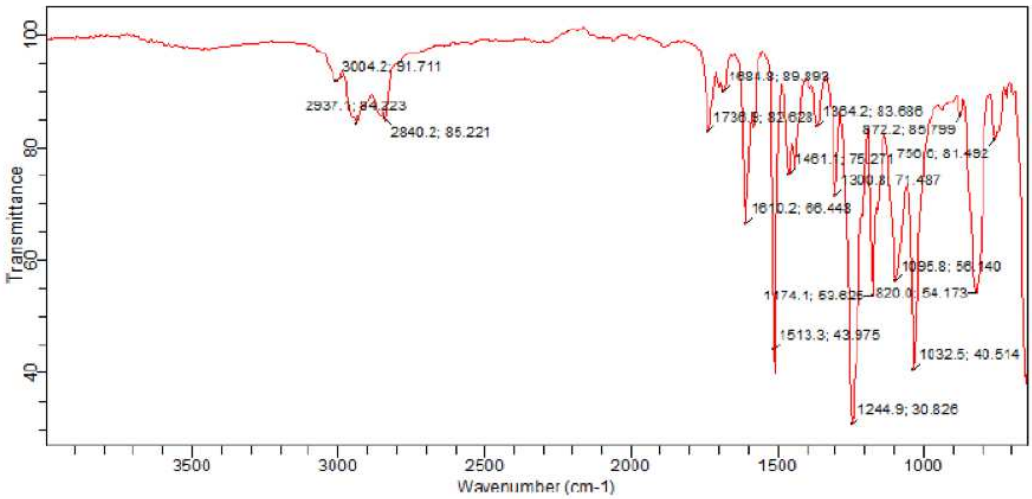




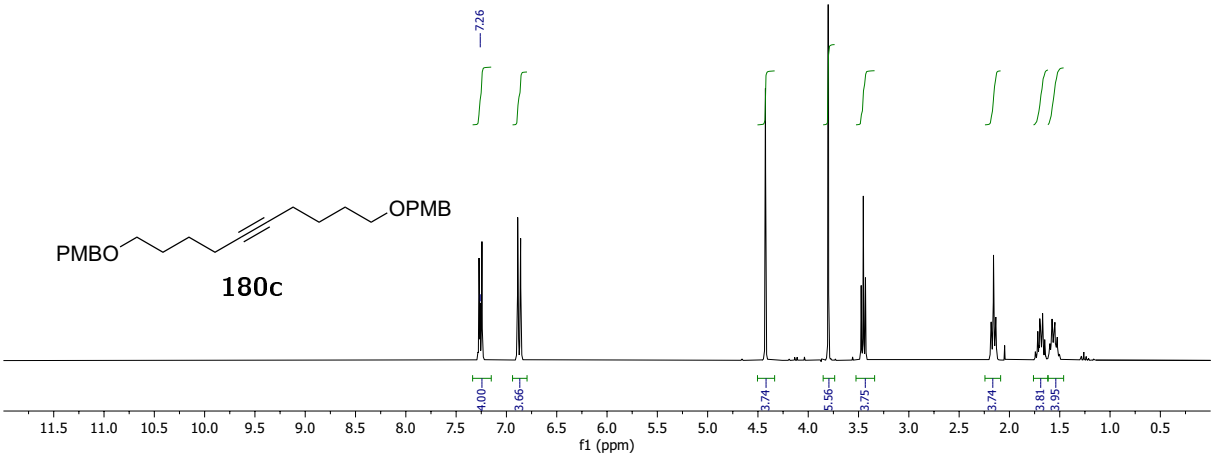
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

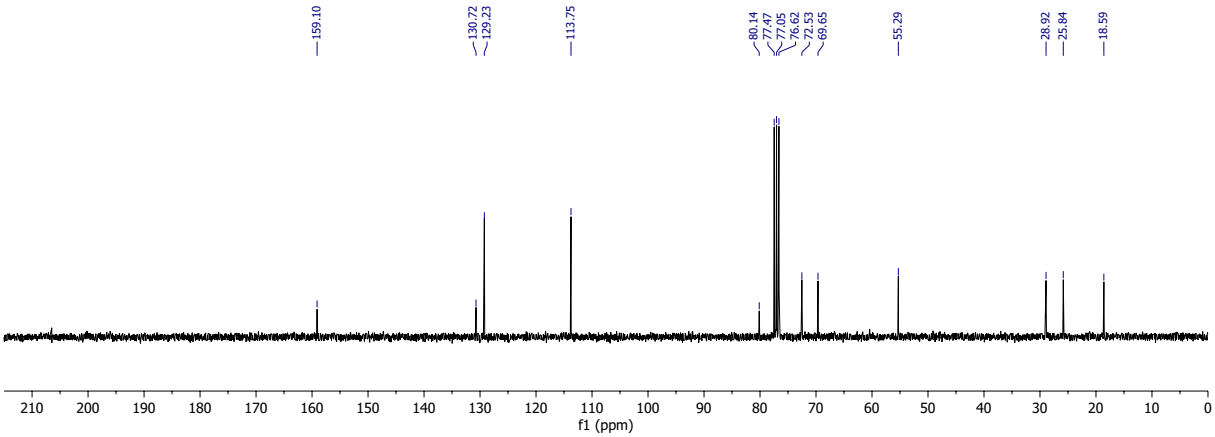


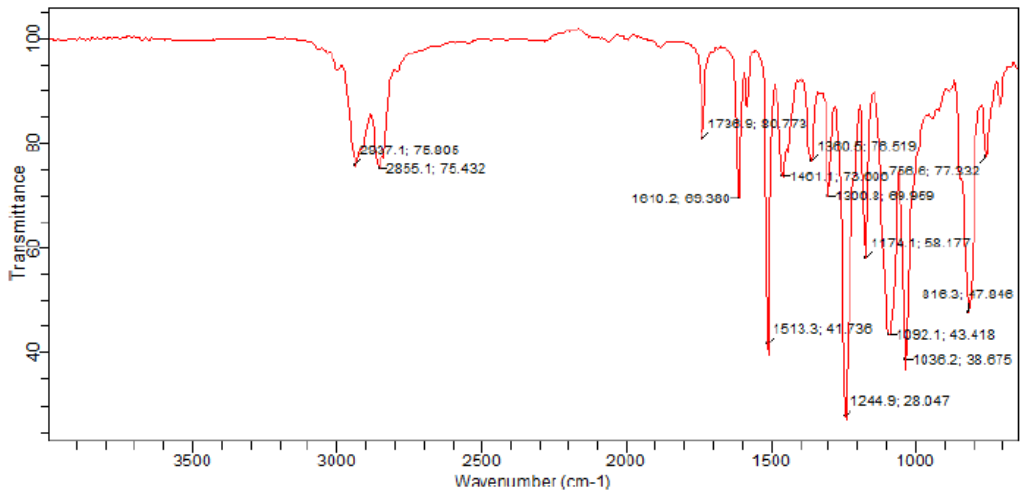




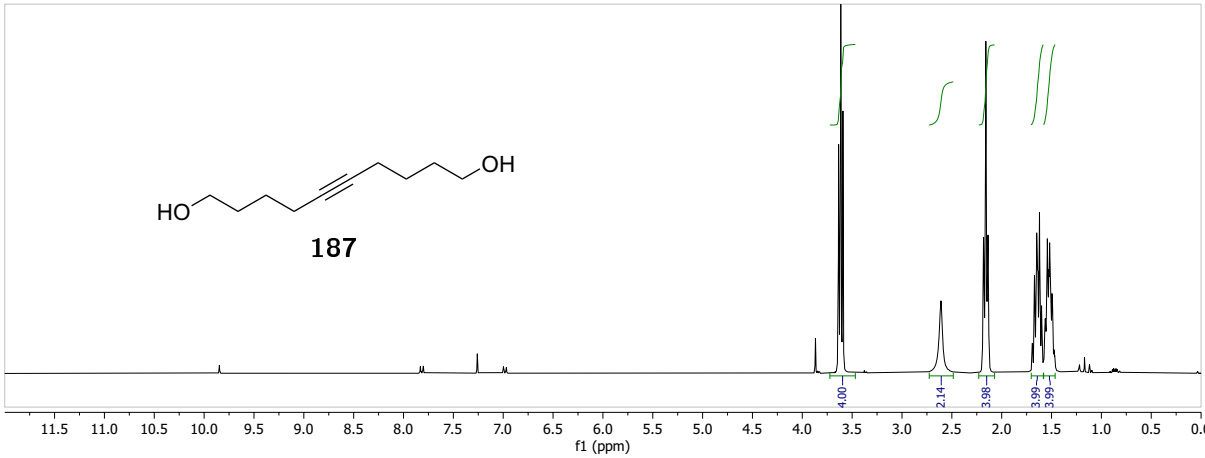
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

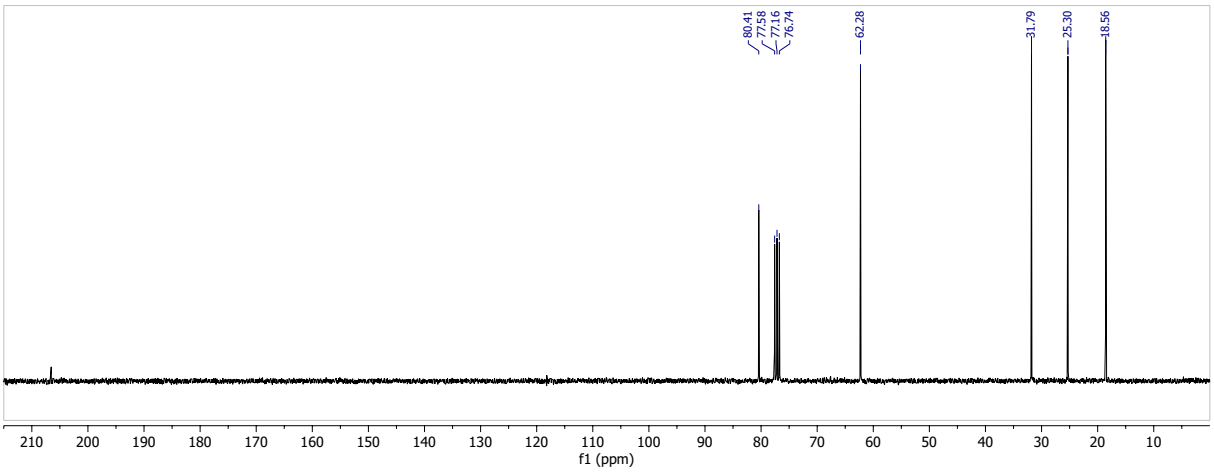


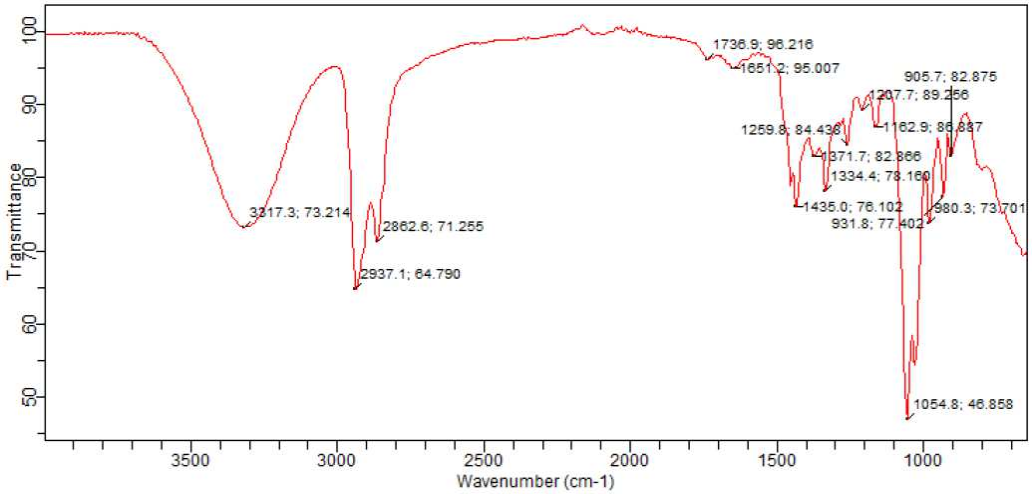




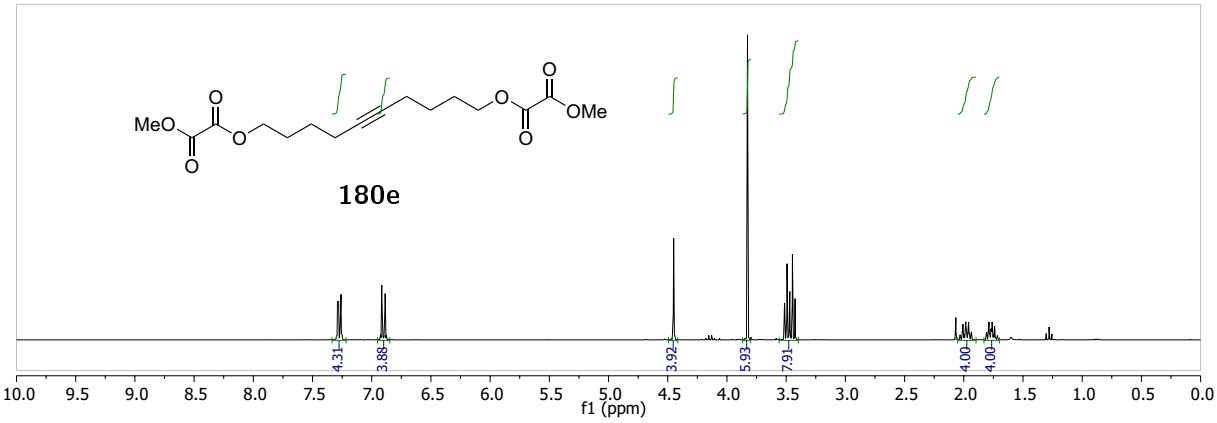
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

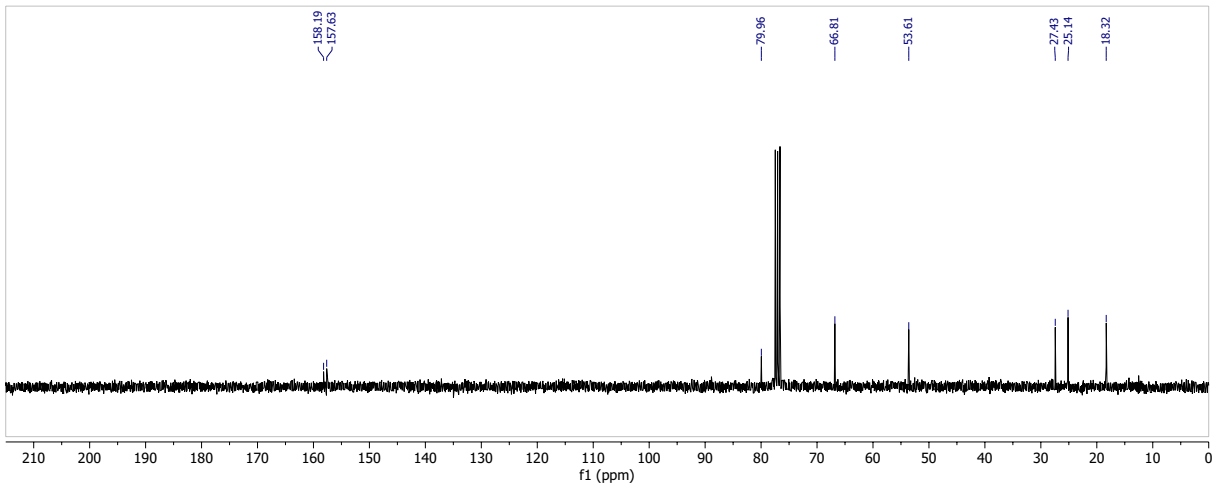


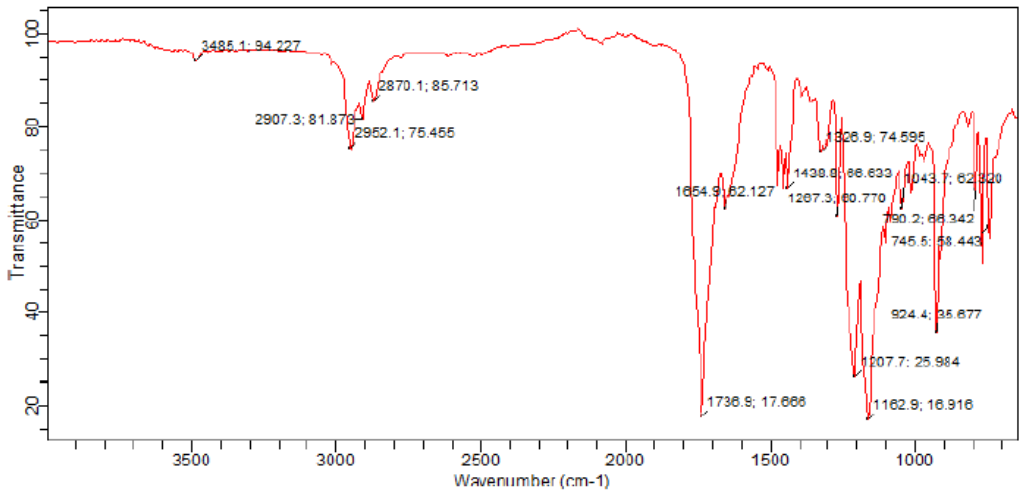




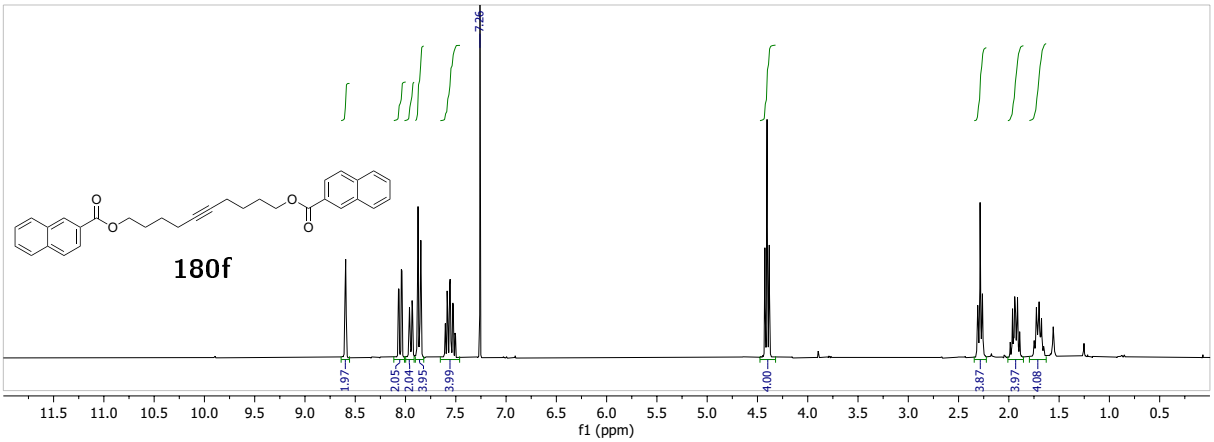
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

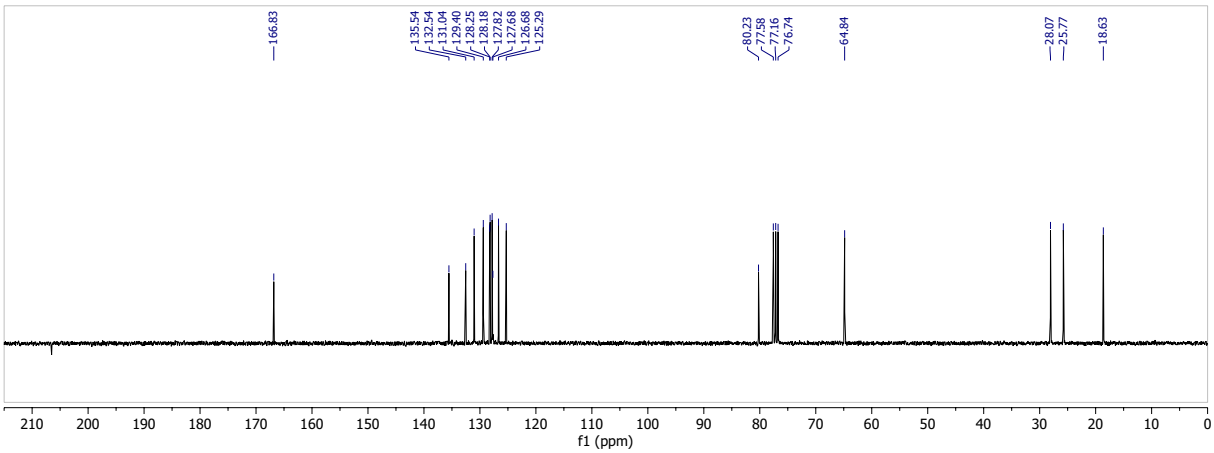


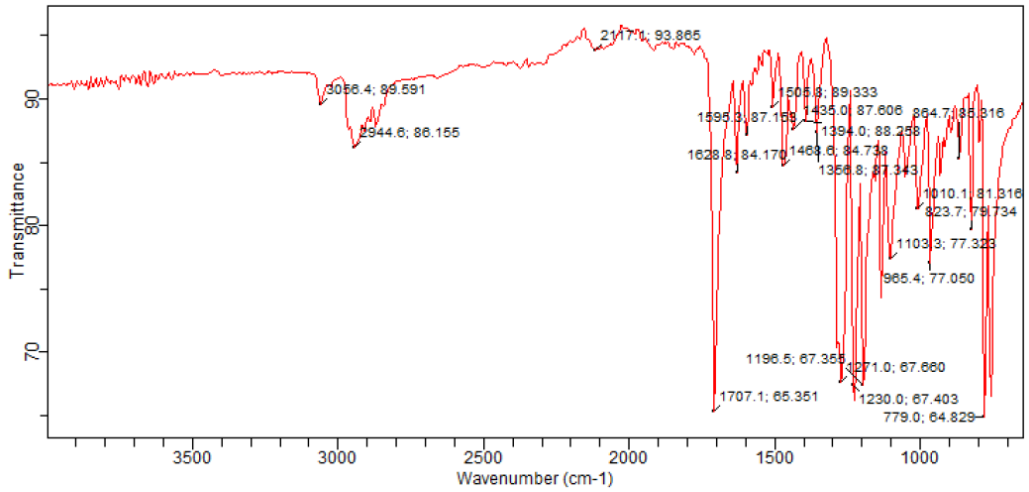




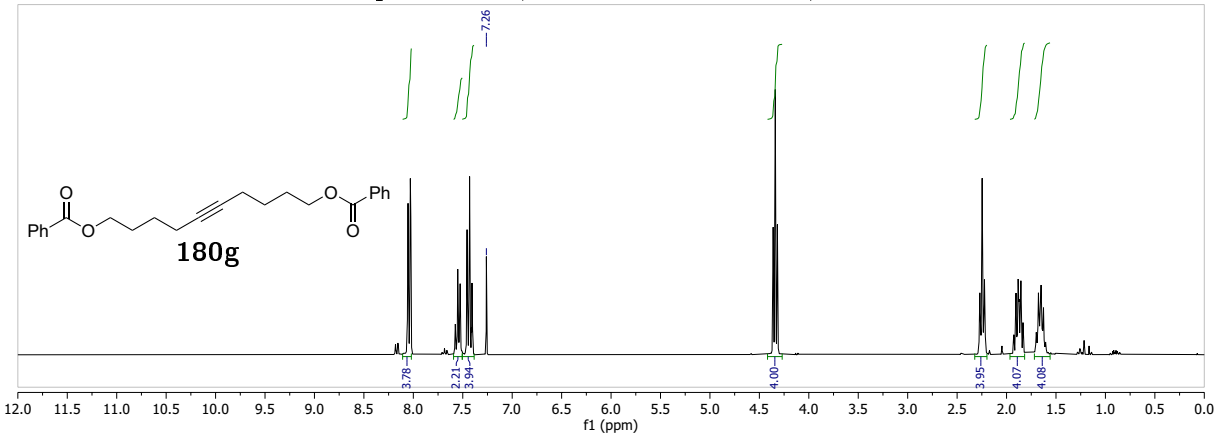
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

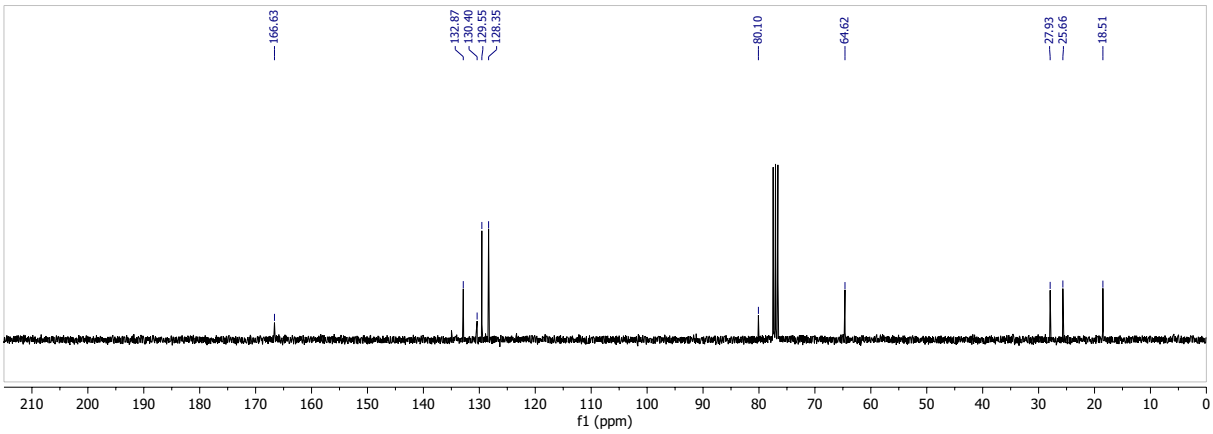


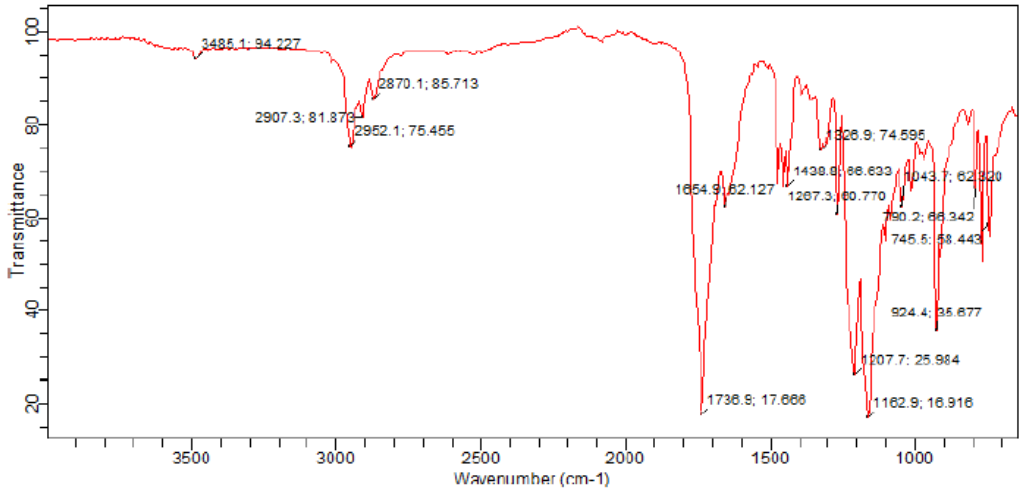




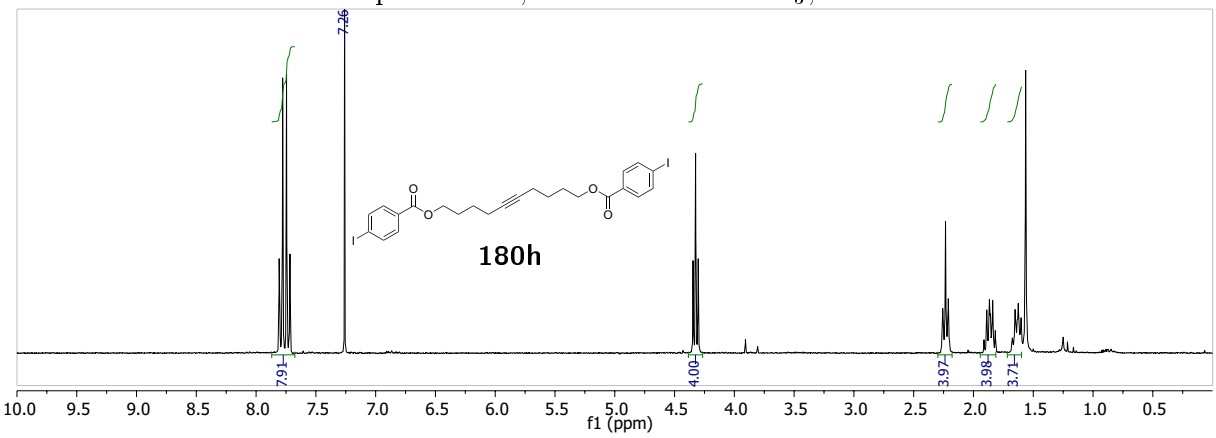
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

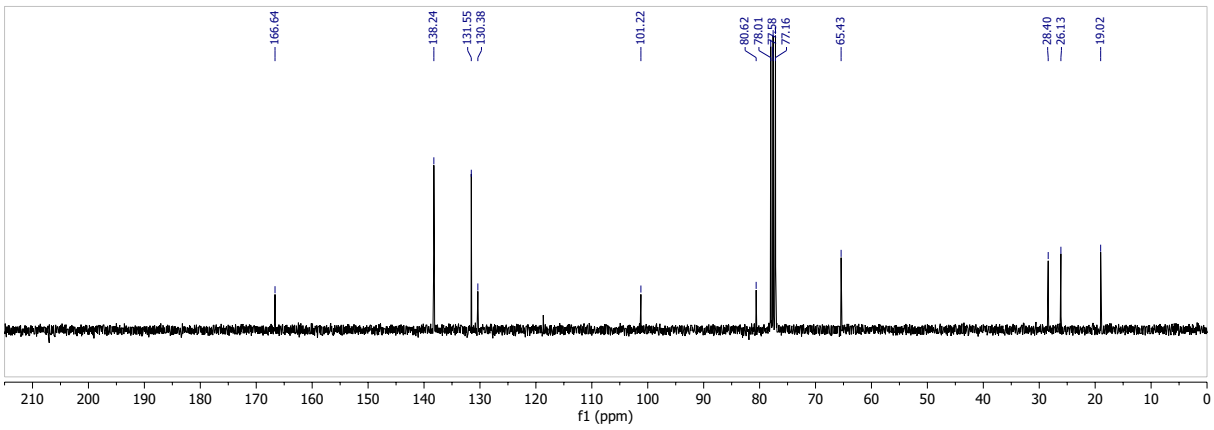


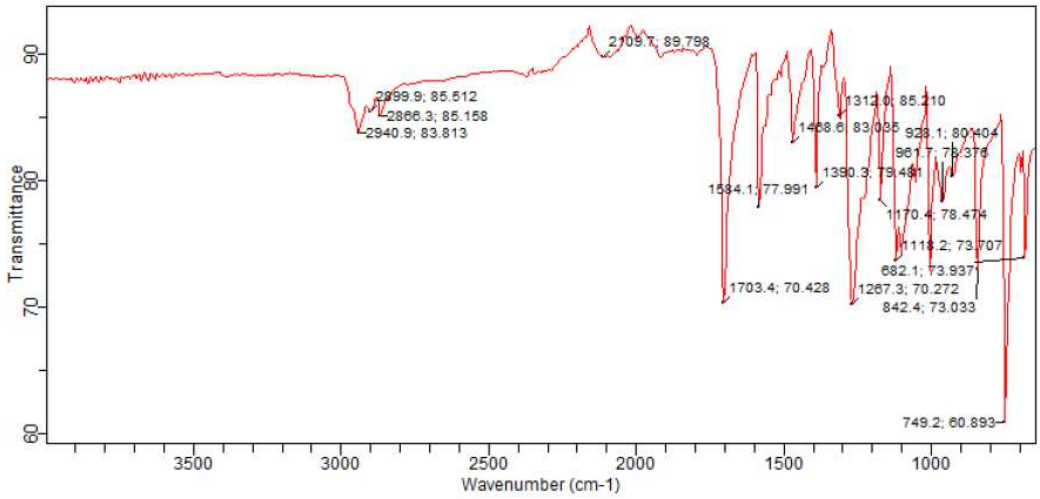




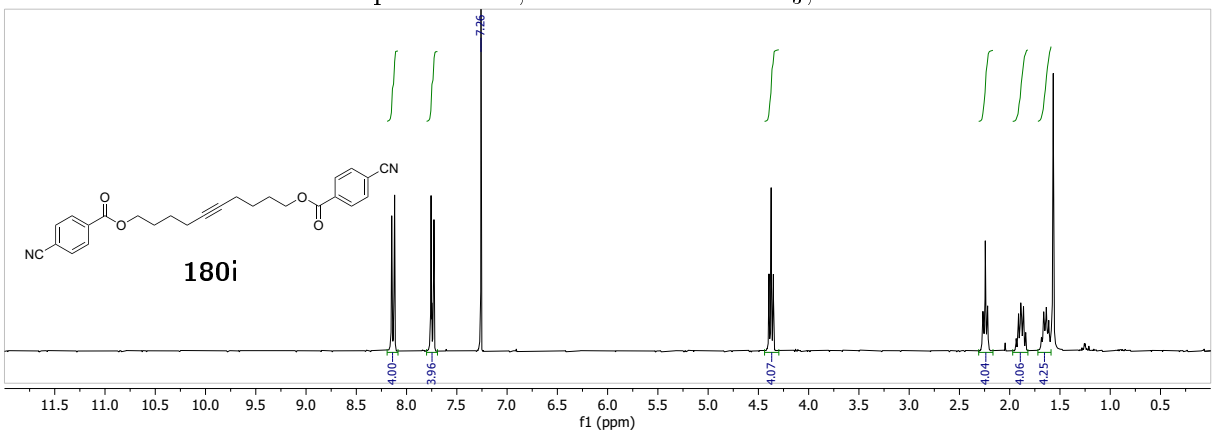
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

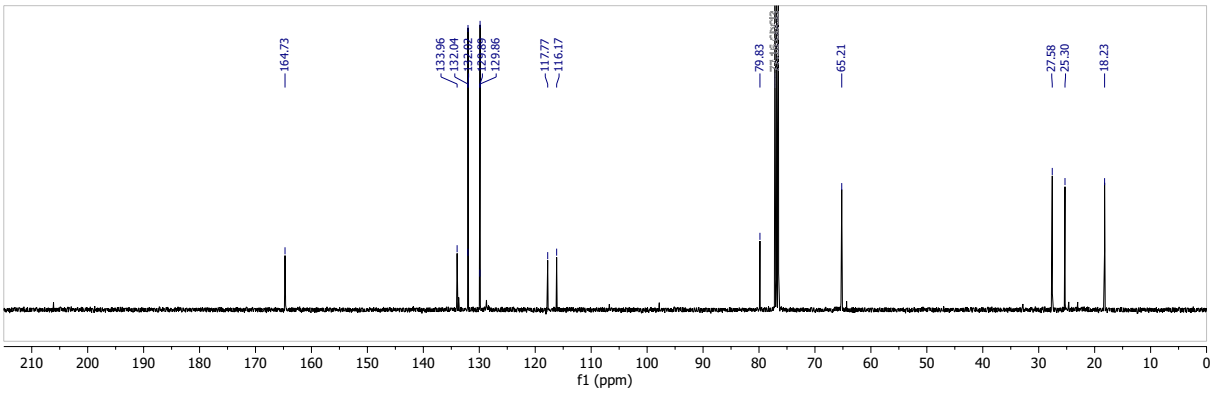


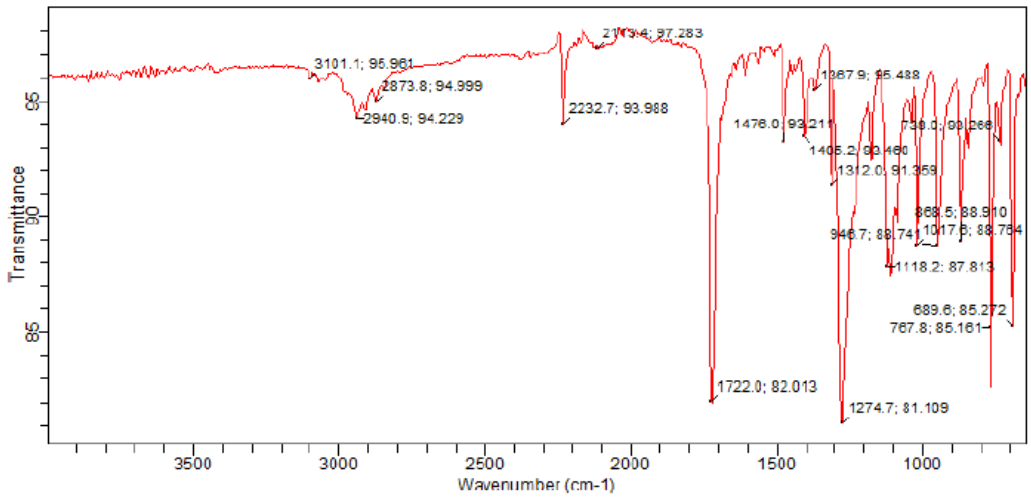




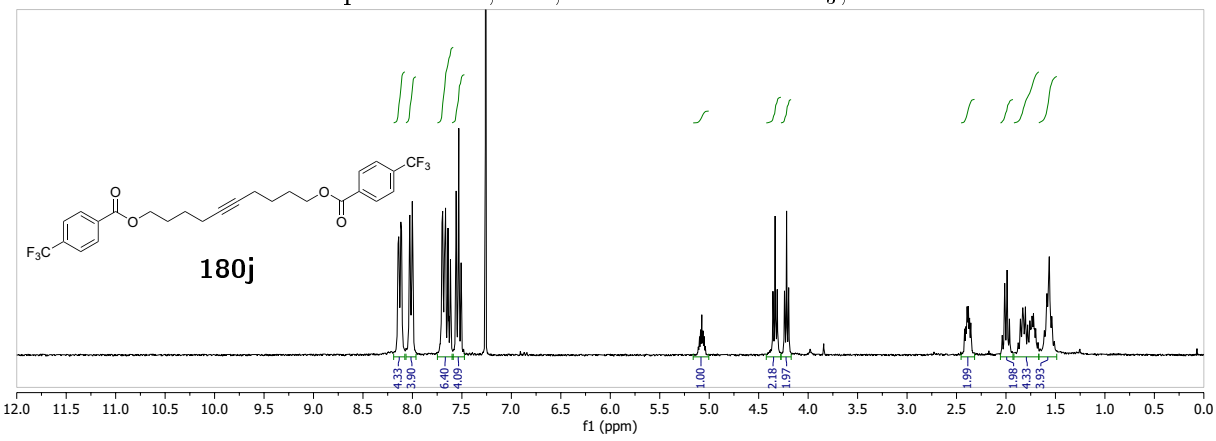
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

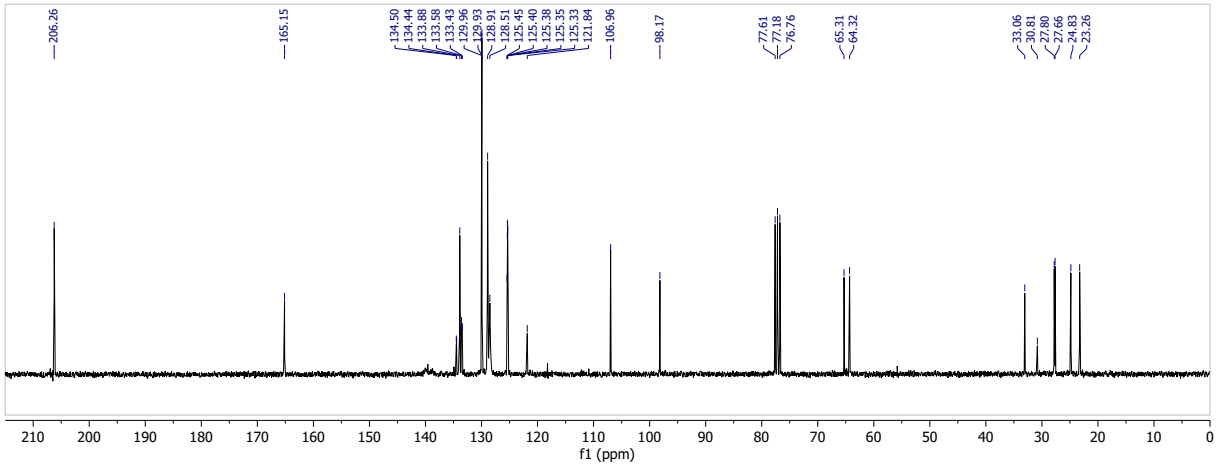


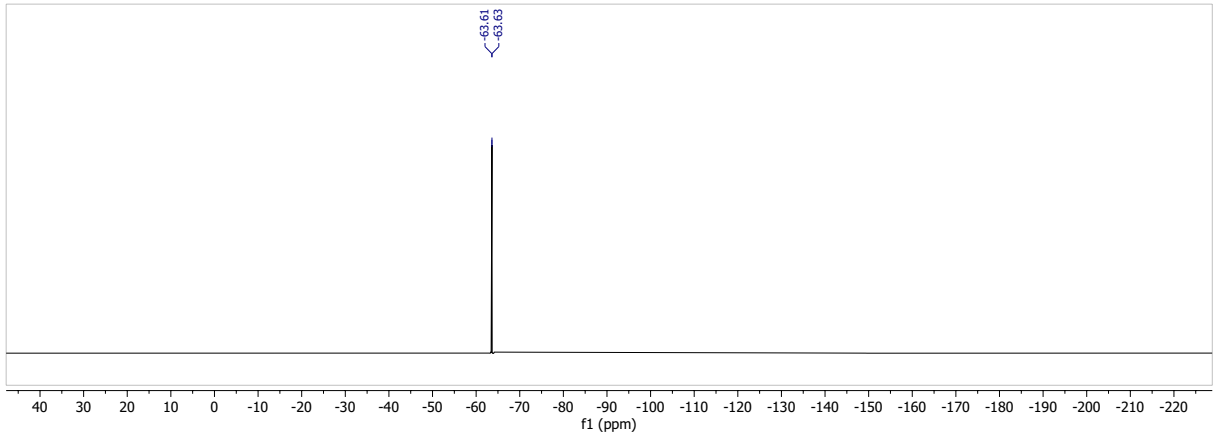


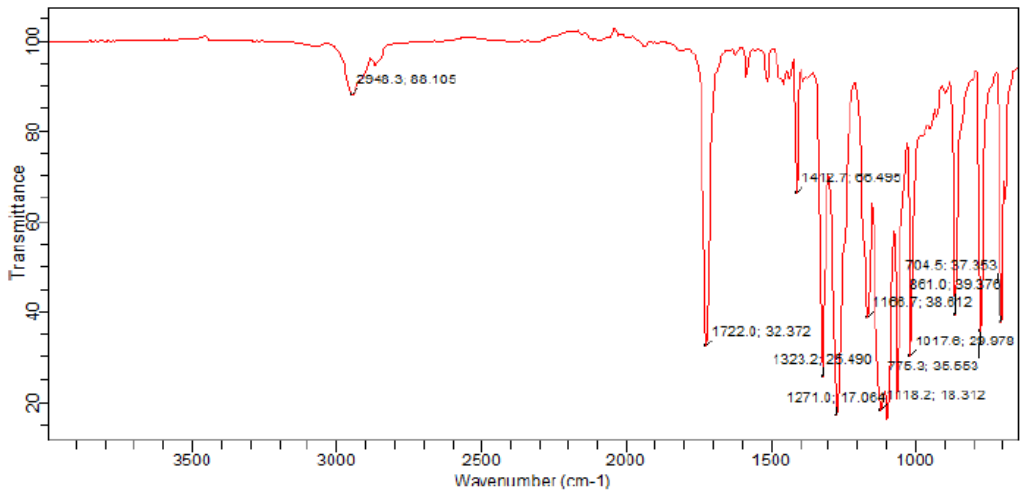


Spectra: ^{1}H, ^{13}C, ^{19}F NMR in $CDCl_3$; IR

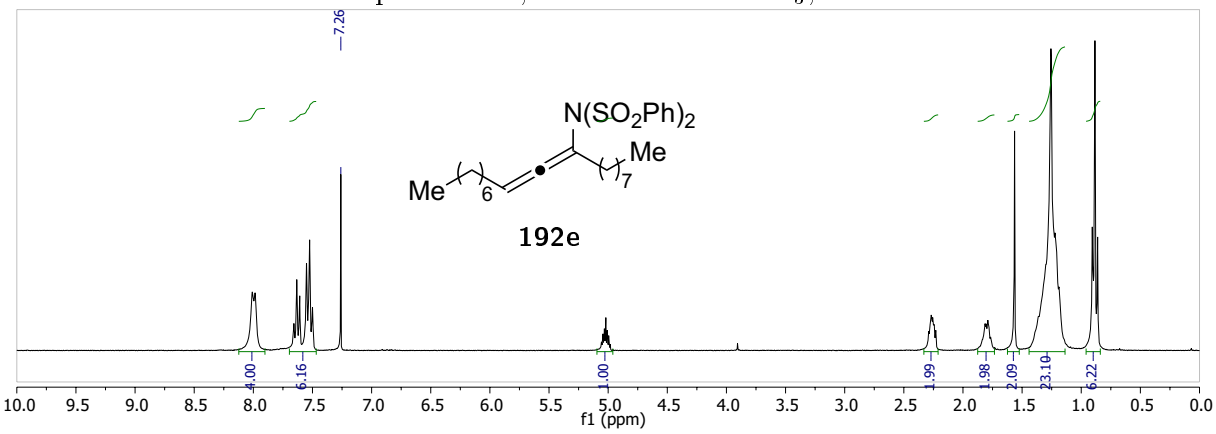


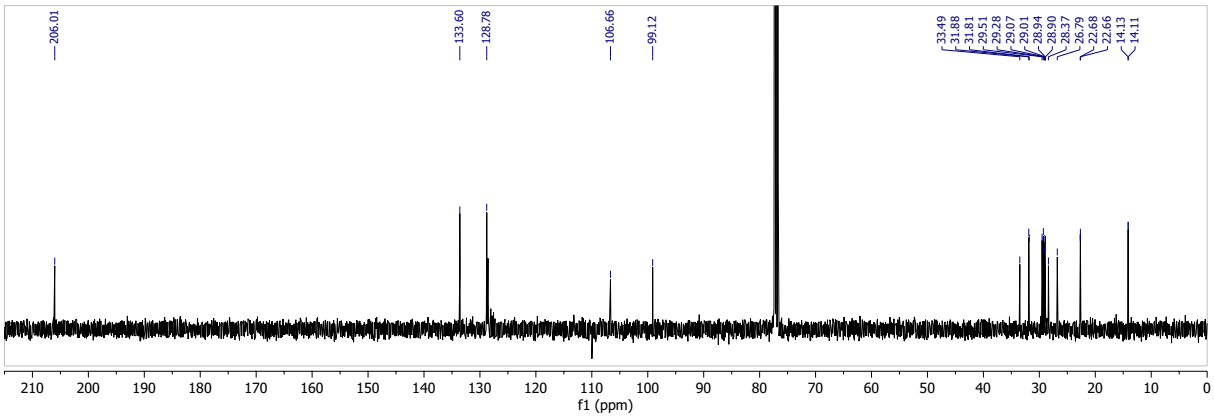


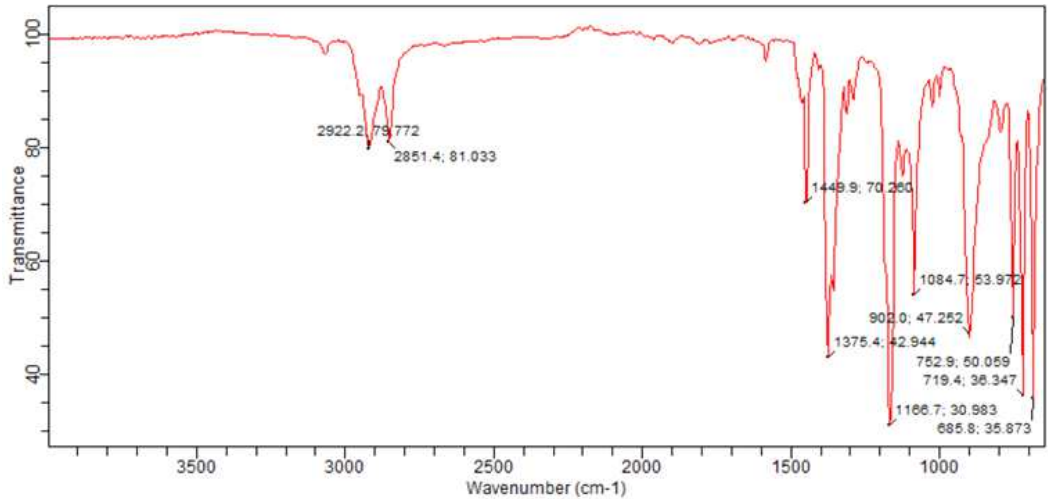




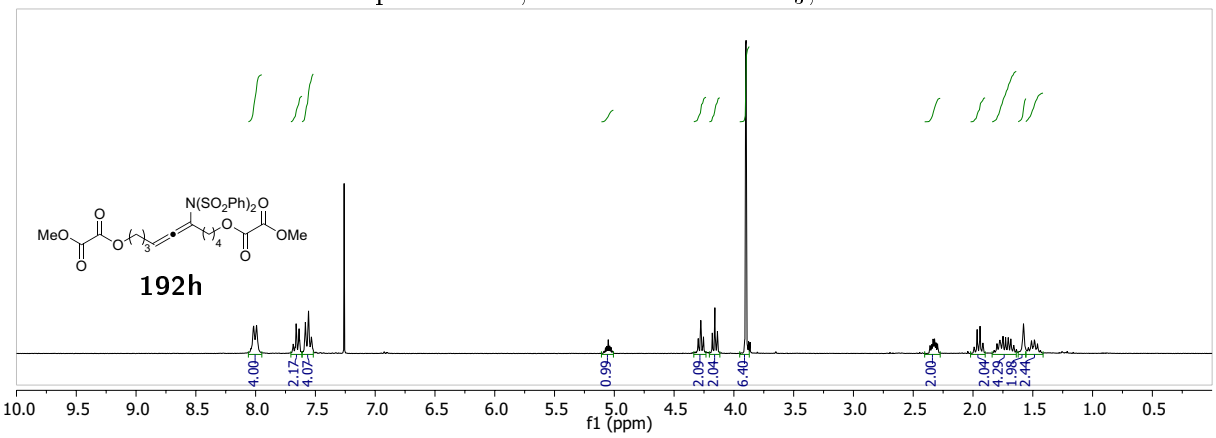
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

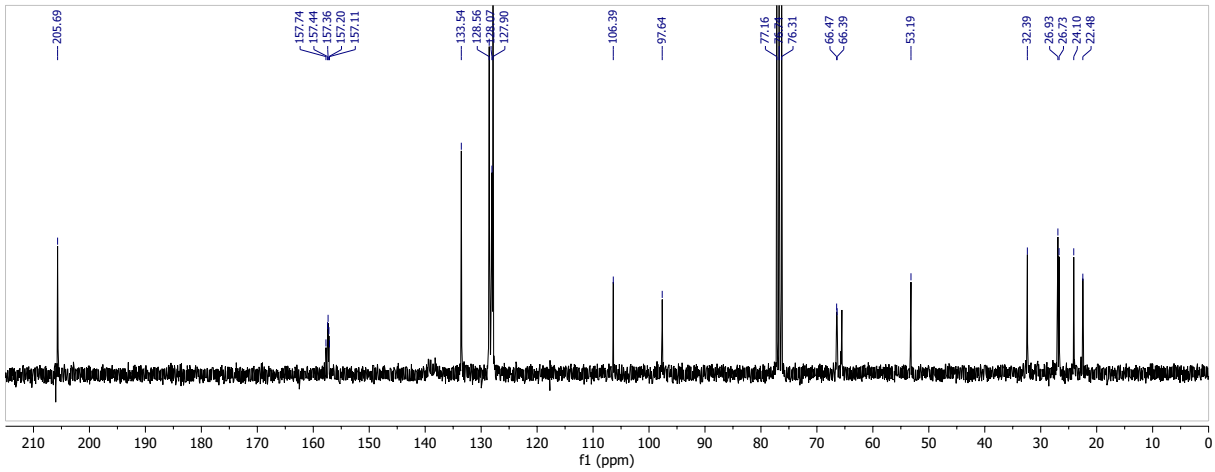


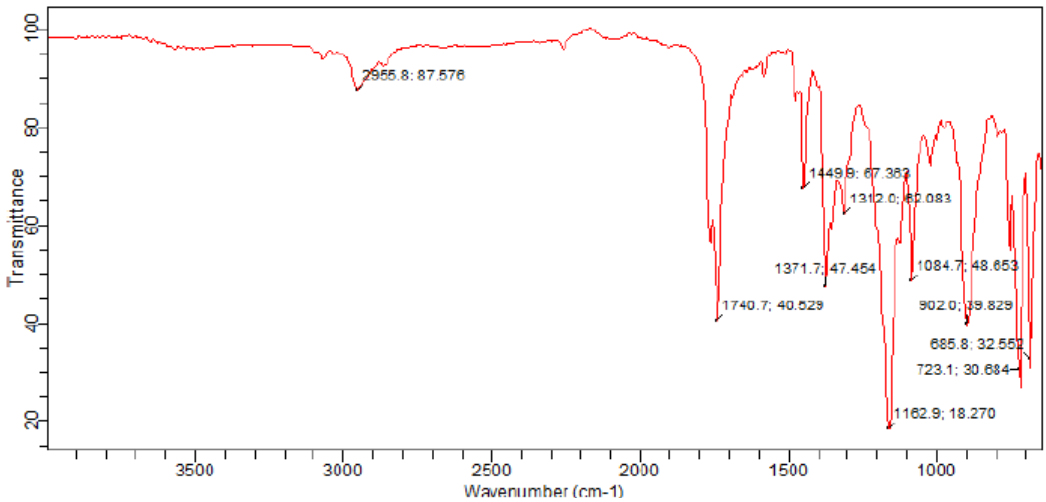




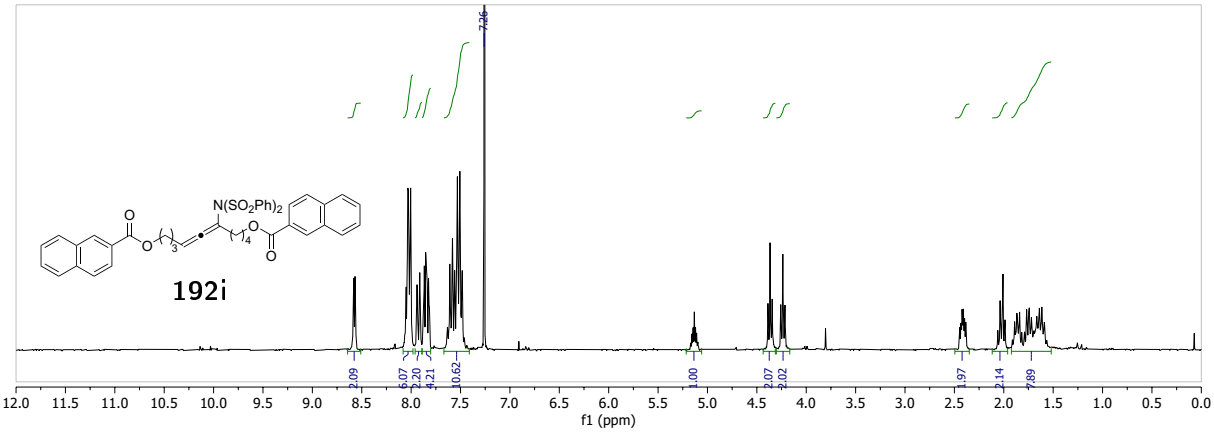
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

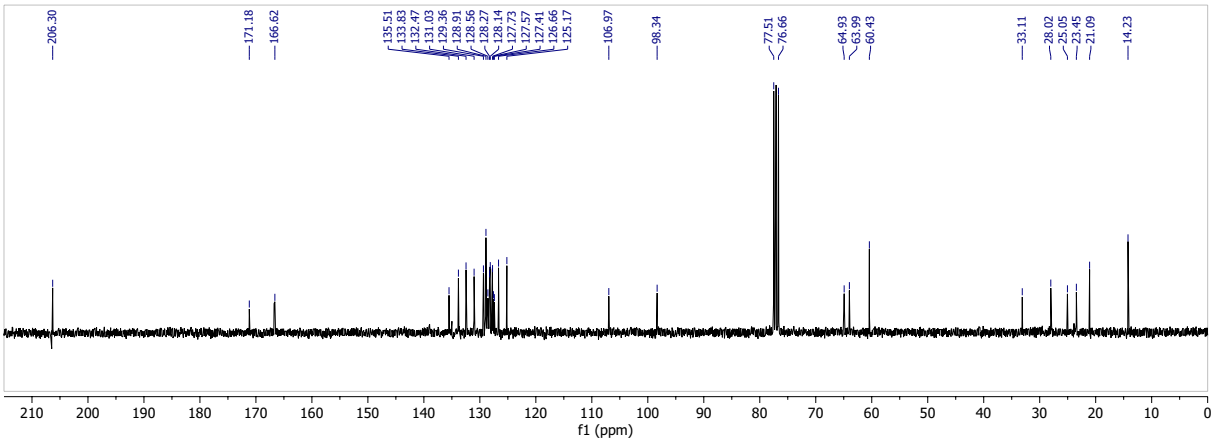


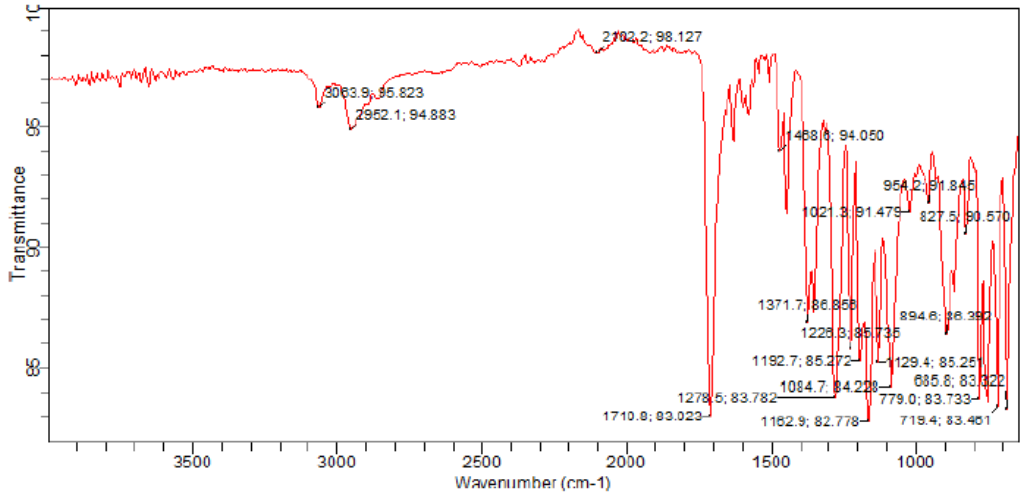




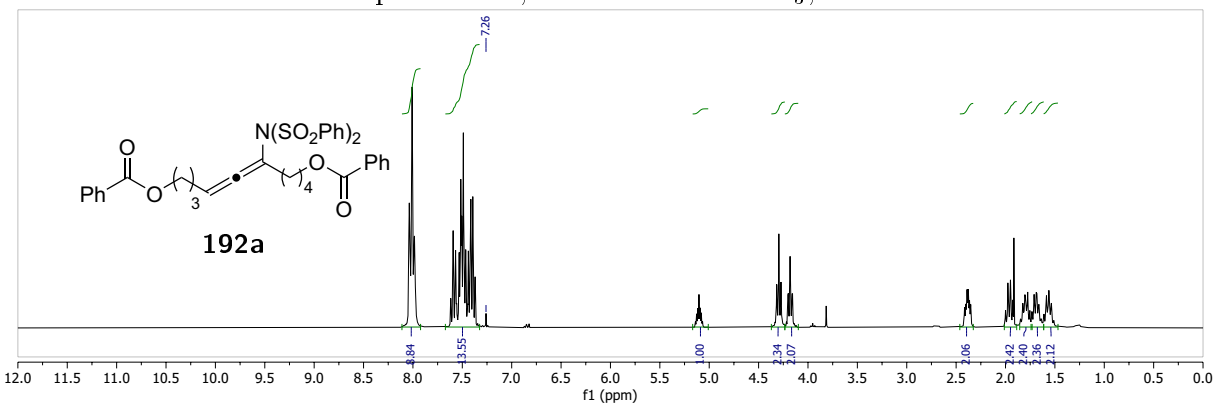
Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR

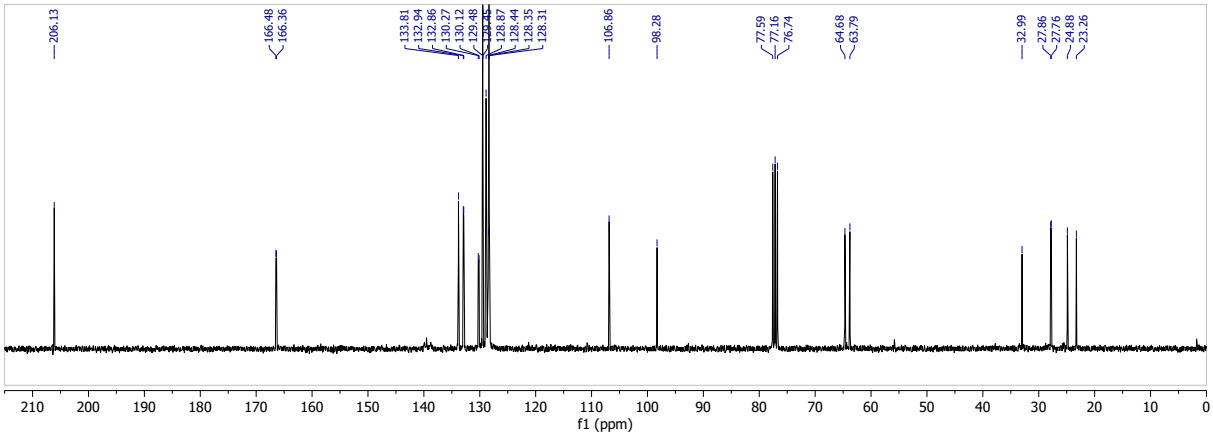


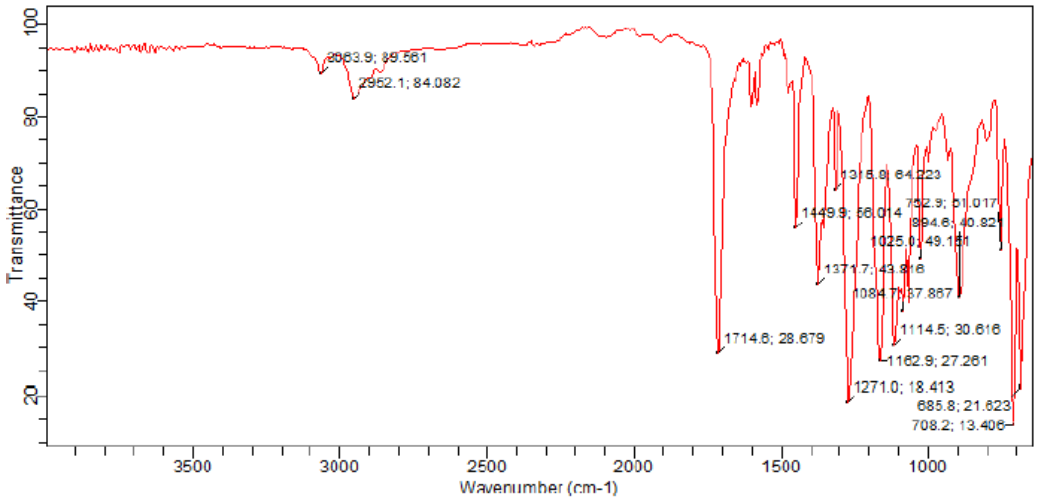




Spectra: ^{1}H, ^{13}C NMR in $CDCl_3$; IR







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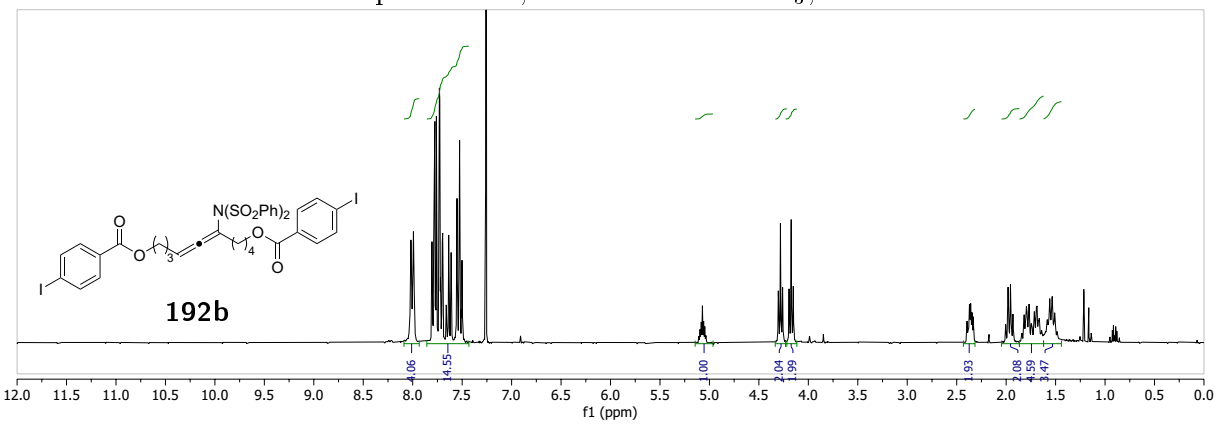

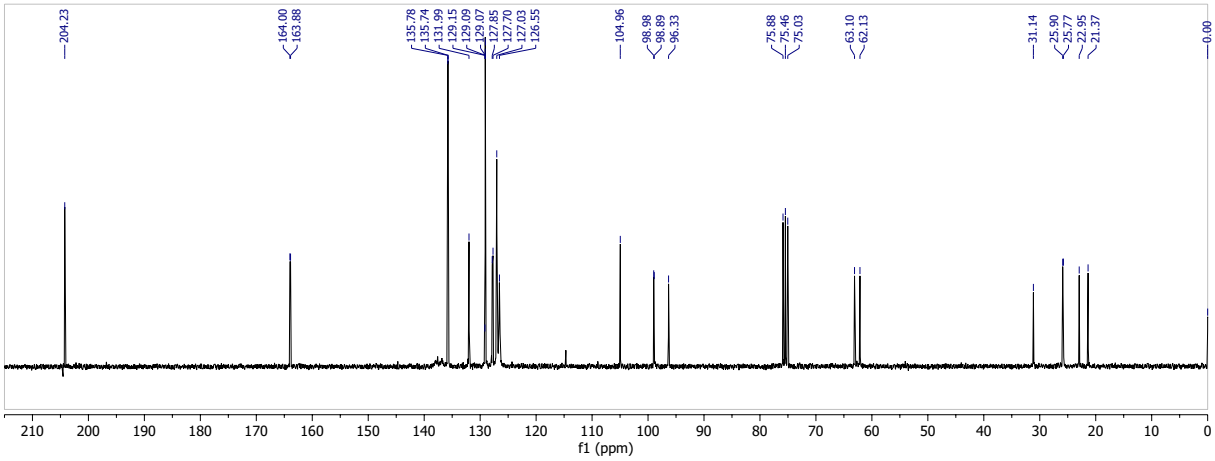

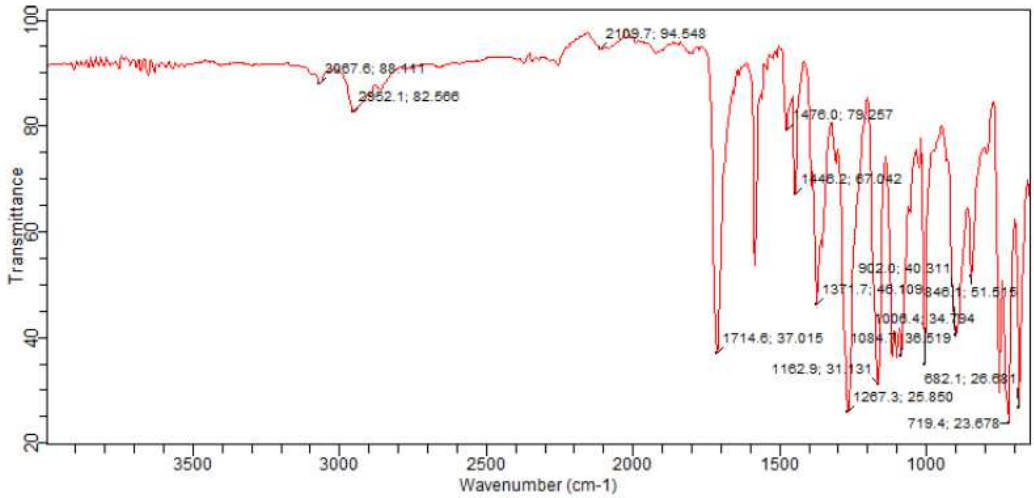

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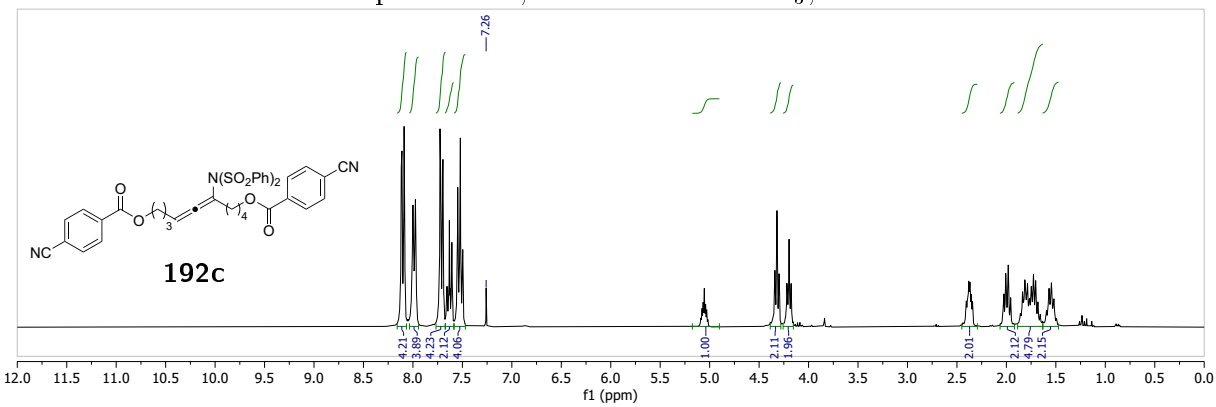

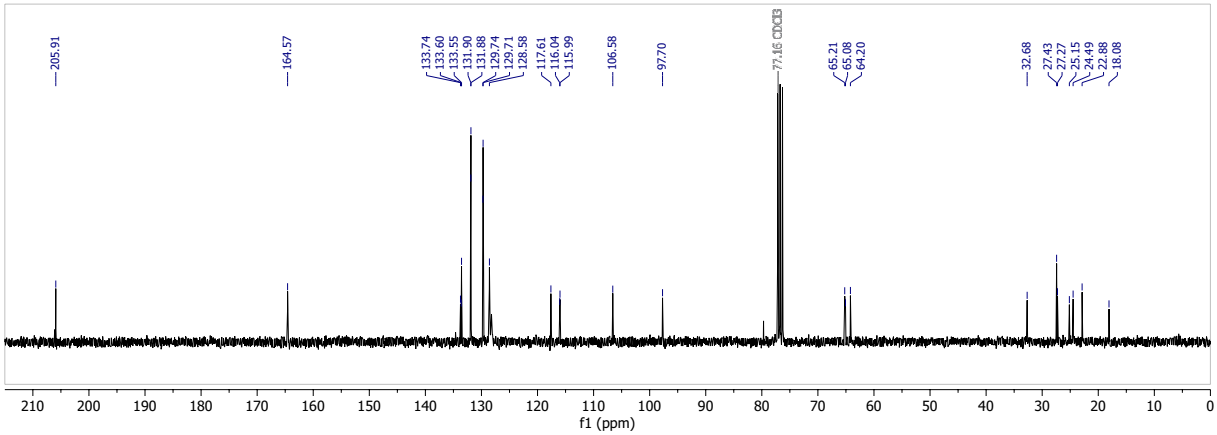

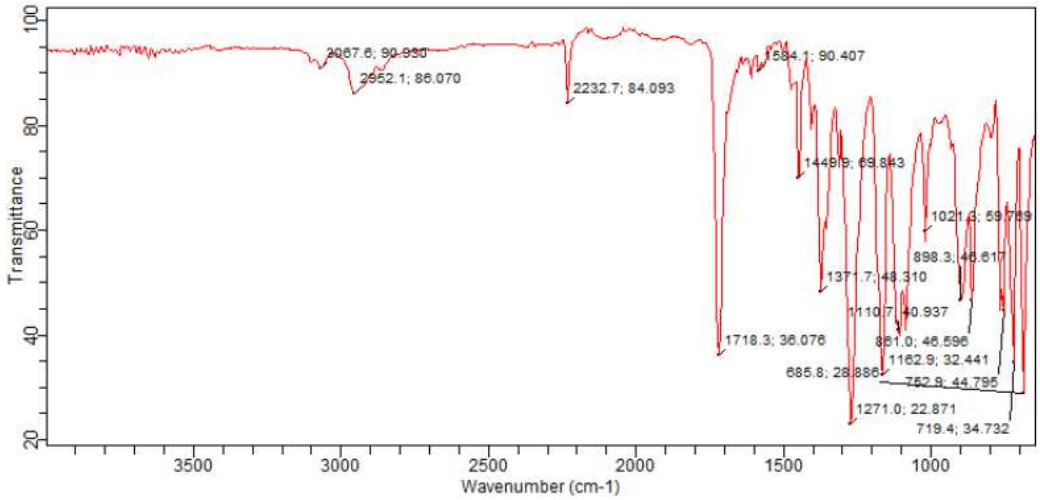

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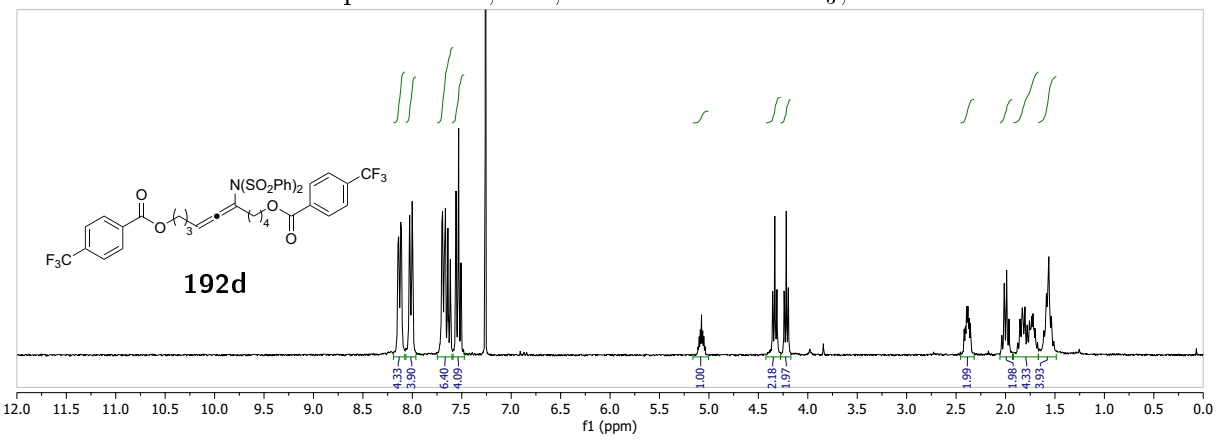

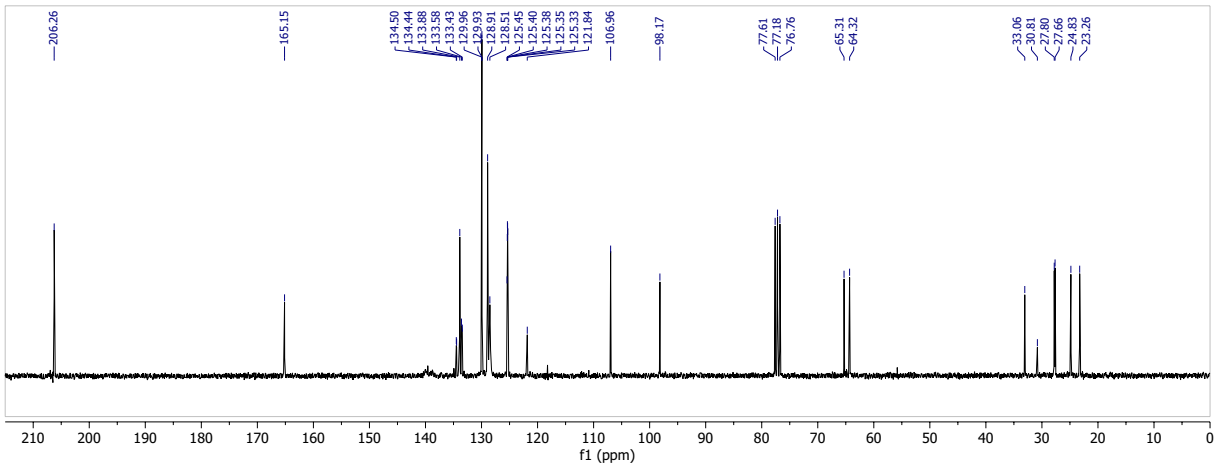

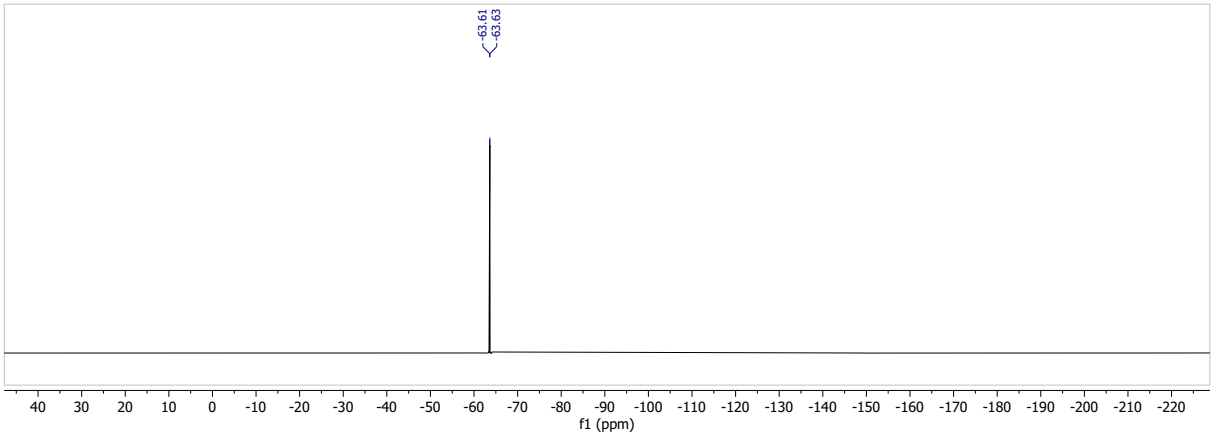

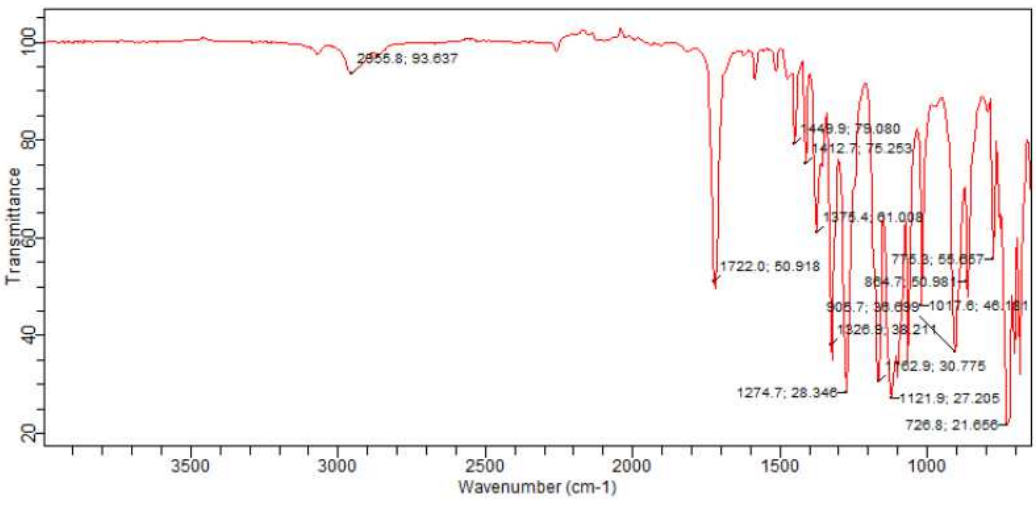

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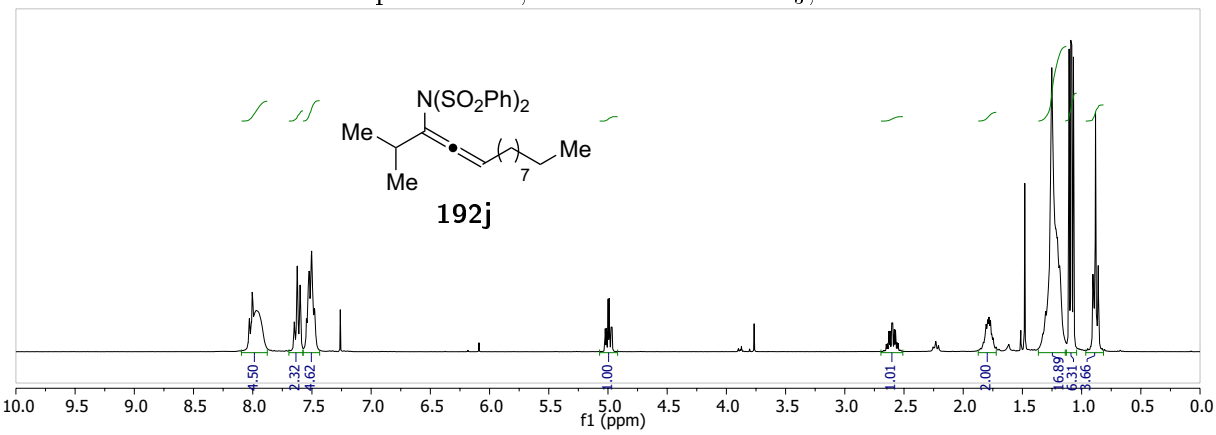

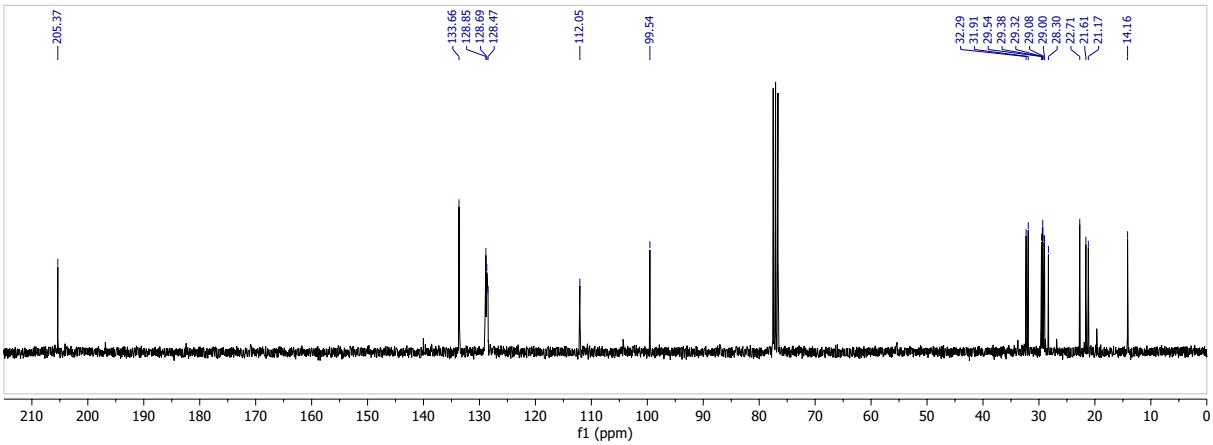

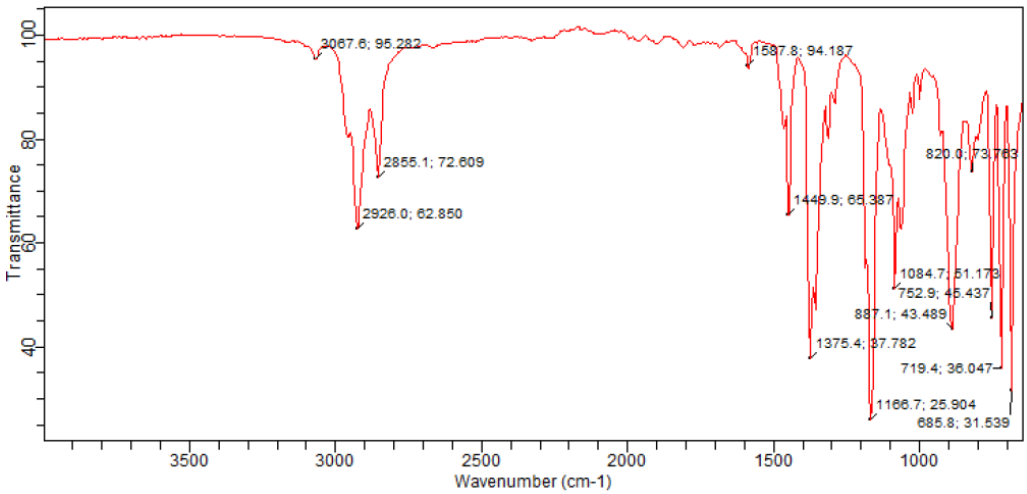

Appendix

List of Abbreviations

1,3-DNB	1,3-dinitrobenzene
1,4-DCNP	1,4-dicyanonaphthalene
ABMO	antibonding molecular orbital
Alk	alkyl
aq.	aqueous
Ar	aryl
BMO	bonding molecular orbital
Bn	benzyl
Boc	tert-butyloxycarbonyl
calc.	calculated
Ch	chalcogen
CIP	contact ion pair
COSY	correlation spectroscopy
CT	charge transfer
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(N,N-dimethylamino)pyridin
DMN	1,5-dimethoxynaphthalene
DMP	Dess-Martin periodinane
E	electrophile
Eox	oxidation potential
equiv / eq.	equivalents
Ered	reduction potential
ESI	electrospray ionizaition
Et	ethyl
Et2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
FRIP	free radical ion pair
HB	hydrogen bond
HBA	hydrogen bond acceptor

HBD	hydrogen bond donor
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation spectroscopy
HR-MS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
int	intermediate
iPr	isopropyl
IR	infrared
LB	lewis base
LDA	lithium diisopropylamide
LED	light emitting diodes
m.p.	melting point
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MS	mass spectrometry or molecular sieves
NBS	N-bromosuccinimide
nBu	n-butyl
NFSI	N-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
NOESY	*nuclear overhauser enhancement spectroscopy*
nr	*no reaction*
Nu	nucleophile
ox	*oxidant*
PC	Photocatalyst
PC*	excited photocatalyst
PCox	oxidised photocatalyst
PCred	reduced photocatalyst
PE	*petroleum ether*
PET	photoinduced electron transfer
PG	*protecting group*
Ph	*phenyl*
PMB	para-methoxybenzyl
PS	photosensitizer
RBME	rose bengal monomethyl ester
RT	room temperature

SEA	sacrificial electron acceptor
SET	single electron transfer
SN	Nucleophilic substitution
SSIP	solvent separated ion pair
T or temp.	temperature
TBAB	tetrabutylammonium bromide
TBS	tert-butyldimethylsilyl
TCE	1,1,2,2-tetrachloroethane
Tf	triflate, trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	1,3,5-trimethoxybenzene
Tol	p-tolyl

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11 Curriculum Vitae

Curriculum Vitae

Poorva Ramadas Narasimhamurthy

Krankenhausstr. 3 84489 Burghausen | rnpoorva@gmail.com | +49(0)157 58683997

DoB: 21.07.1994, Solapur, India

Professional Experience

Since 10/2022	**Scientist** *Clariant Produkte (Deutschland) GmbH, Burgkirchen an der Alz, Germany*
04/2019-11/2021	**Research Associate** *University of Regensburg, Germany*

Education

09/2018-11/2021	**PhD** *AK Prof. Dr. Alexander Breder, University of Regensburg, Germany* Title of PhD thesis: Selenium-mediated allenylation and allylation reactions of N- and O-nucleophiles.
10/2015-05/2018	**MSc in Chemistry** (Grade: 1.3) *Ruhr-University Bochum, Germany* Title of master's thesis: Improved Synthesis of Hemicarcerands
06/2012-04/2015	**BSc in Physics, Chemistry, and Mathematics** *St. Joseph's College (Autonomous), Bangalore, India*

Publications

Net heterolysis of symmetric and homopolar σ-bonds by stimulated doublet-doublet electron transfer- Anna F. Tiefel, Daniel J. Grenda, Carina Allacher, Elias Harrer, Roger J. Kutta, David Hernández-Castillo, Poorva R. Narasimhamurthy, Kirsten Zeitler, Leticia González, Julia Rehbein, Patrick Nuernberger, Alexander Breder, *Nature* **2024** (Manuscript in review)

Enabling Atypical SN1 Reactions by Atom Polarity Quantum-Editing, *Synthesis* **2024** (Manuscript in preparation)

Synthesis of aminoallenes via selenium-π-acid catalyzed cross-coupling of *N*-fluorinated sulfonimides with simple alkynes - Katharina Rode, Poorva Ramadas Narasimhamurthy, Rene Rieger, Felix Krätzschmar, Alexander Breder, *EJOC*. **2021,** 1720-1725.

Awards

2018	**GDCh Master Prize** *Ruhr-University Bochum, Germany*

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Regensburg, den Poorva Ramadas Narasimhamurthy

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