Applications of Copper-Boryl Reagents in Synthesis

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PhD Thesis

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Statement of copyright

Declaration

The work described in this thesis was carried out in the Department of Chemistry at Durham University between October 2013 and December 2016 under the supervision of Professor Patrick G. Steel and Dr. Eric P. Talbot and has not been submitted previously for a degree at this or any other university.

Part of this thesis was the subject of the following publication:

'A mild copper catalyzed method for the elective deprotection of aryl allyl ethers' *Tetrahedron Letters,* 2017, **58**, 17-20 (David S. Hemming, Eric P. Talbot, Patrick G. Steel)

David S. Hemming April 2017

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Special thanks must go to my supervisor Patrick Steel for all his guidance and support over this project. It was also great to discuss mountain biking and running routes around Durham.

All members of CG1 past and present are thanked for the many laughs we've had in the office and laboratory, as are other members of the department (Miriam especially). Thanks to Raminder and Liz for proofreading sections.

The final group of people to acknowledge is my family, especially Mum and Dad. Having so much support was much appreciated throughout my academic life! Robb thank you so much for being a great brother and keeping me motivated.

Abstract

Previous work into the copper catalysed borylation of alkenyl halides has resulted in the synthesis of cyclic Bpin esters. To date however, the reaction has not been applied to the synthesis of saturated heterocycles nor substituted carbocycles. An overview of the literature precedent for reactions involving copper-boryl complexes is provided in the introduction (chapter 1). Investigations into the reaction were undertaken in an attempt to further expand its scope, and the second chapter outlines preliminary results and investigations into the formation of carbocyclic boronate esters. Application of the borylative cyclisation reaction towards the synthesis of heterocyclic boronate esters is also discussed. The third chapter outlines the development of a copper-boryl mediated deallylation reaction, which was developed as a novel method for the selective deprotection of aryl allyl ethers. Attempts to synthesise chromanyl boronate esters are described in chapter 4, followed by conclusions (chapter 5) and experimental data (chapter 6).

Table of Contents

List of abbreviations

9-BBN = 9-borabicyclo[3.3.1]nonane

ATRC = atom transfer radical cyclisation

Alloc = allyloxycarbonyl

aq = aqueous

Bn = benzyl, $C_6H_5CH_2$-

Boc = *tert*-butoxycarbonyl

B_2pin_2 = bis(pinacolato)diboron

Bpin = boronic acid pinacol ester

Bz = benzoyl, C_6H_5CO-

DCM = dichloromethane

DMA = *N,N*-dimethylacetamide

DMAP = *N,N*-dimethylaminopyridine

DMF = *N,N*-dimethylformamide

dppp = 1,3-bis(diphenylphosphino)propane

ee = enantiomeric excess

eq. = equivalents

EtOAc = ethyl acetate

GC-MS = gas chromatography mass spectrometry

HRMS = high resolution mass spectrometry

HSQC = heteronuclear single quantum coherence spectroscopy

KO^tBu = potassium *tert*-butoxide

LC-MS = liquid chromatography mass spectrometry

MeOH = methanol

MIDA = *N*-methyliminodiacetic acid

NHC = *N*-heterocyclic carbene

NMR = nuclear magnetic resonance

PPh_3 = triphenylphosphine

SET = single electron transfer

SPGS-550-M = β-sitosterol methoxypolyethyleneglycol succinate

TBC = 4-*tert*butylcatechol

tert = tertiary

THF = tetrahydrofuran

TLC = thin layer chromatography

1 Introduction

1.1 Organoboron compounds in the literature

Organoboron compounds are highly important synthetic intermediates that find application in a diverse variety of synthetic processes including both C-X and C-C bond forming transformations. Oxidation (Figure 1, i)), the Suzuki-Miyaura cross coupling (eqn. ii)) and homologation reactions (eqn. iii)) are the most common applications of organoboron reagents.[1-3]

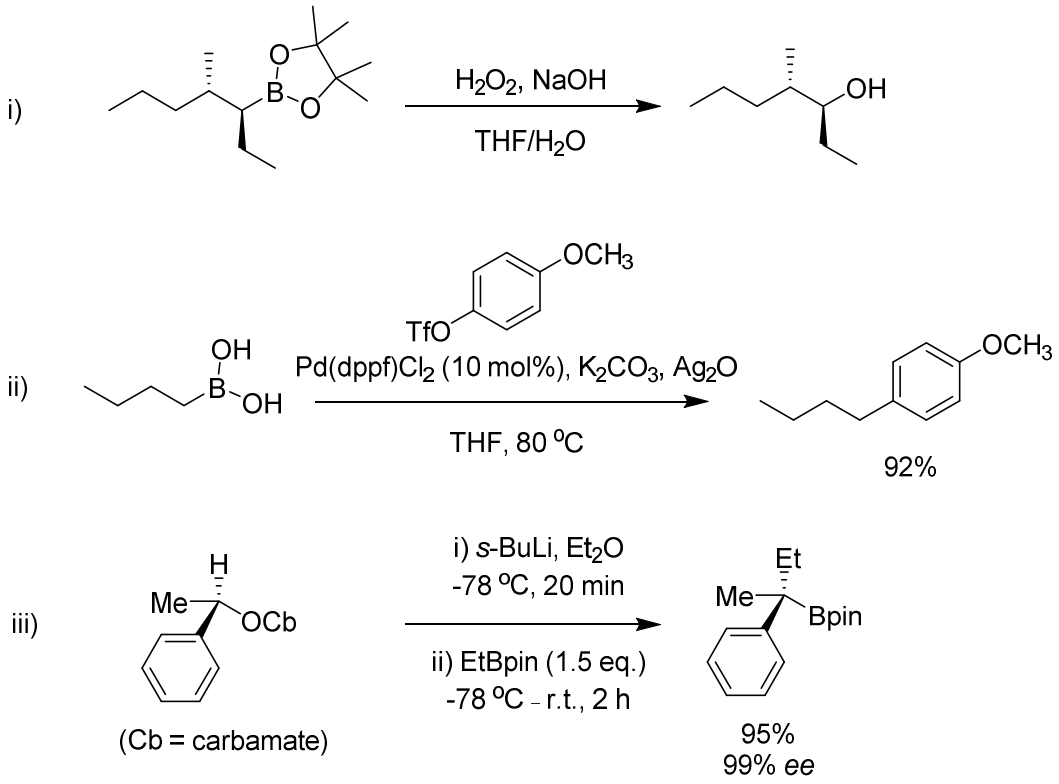


Figure 1: Common uses for (alkyl)organoboron compounds

This has been achieved by using a variety of boron derivatives including alkyl, vinyl and aryl boranes, boronate esters and related compounds. Of these the boronate esters are probably the most versatile being non-toxic, tolerant to air and water,

whilst reacting under relatively mild conditions to produce an inert, benign and easy to separate by-product. Reflecting this, methods for the generation of boronate esters are of considerable current interest. Classically, this is achieved *via* the reaction of hard organometallic reagents with borate esters or through hydroboration strategies. Such methods however have relatively limited substrate scope and more recently, milder catalysed C-H and C-X borylation strategies have emerged.[4-6] Of these, processes mediated by a copper-boryl species are particularly prominent given the mild reaction conditions, good functional group tolerance and low cost of the metal catalyst. In this review, recent developments in this area are examined and the many different transformations possible using these reagents are surveyed.

1.1.1 Boron reagents

The recent commercialisation of diboron reagents has helped to expand the scope of borylation chemistry. These can be categorised into boranes, boronates and diboron reagents. The latter can be further subdivided into symmetrical, unsymmetrical and mixed valence diboron species. The structures of such reagents are shown below (Figure 2, structures 1-9).

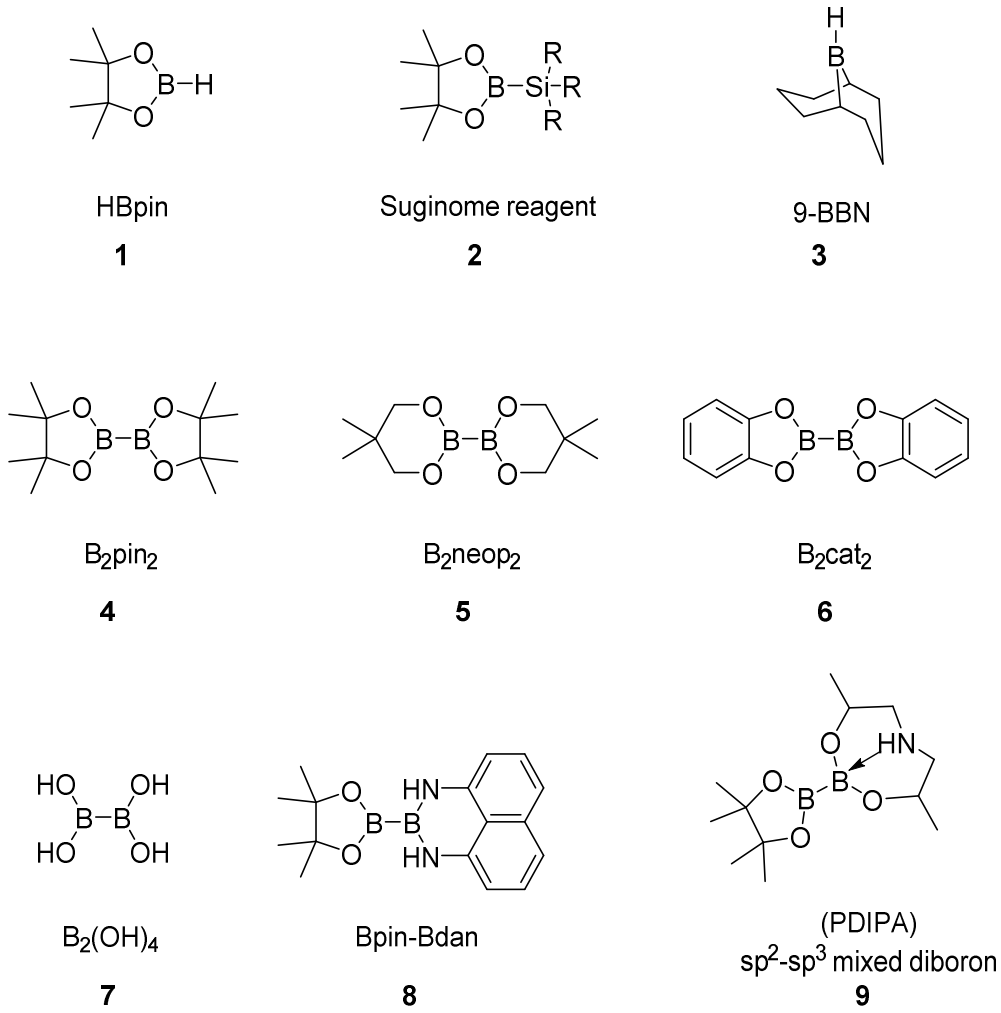


Figure 2: Structures of boron reagents

More recently, preactivated diboron reagents have been developed (9).[7, 8] These species contain mixed sp^2-sp^3 hybridised boron atoms. Co-ordination of the nitrogen atom to the boron lengthens the boron-boron bond and therefore aids transfer of a boryl group to the catalyst, removing the requirement for an alkoxide base in the reaction mixture.[9] For the purposes of this review, the focus will be on the use of diboron compounds with copper catalysts.

1.2 Copper-boryl complexes

The first reported examples of copper-boryl complexes in synthesis were the conjugate additions of a Bpin moiety to enones (10 and 11) as described by Miyuara

and Hosomi, who employed a CuCl/KOAc or a copper(I) phosphine catalyst and a diboron reagent mixture respectively (Figure 3).[10, 11]

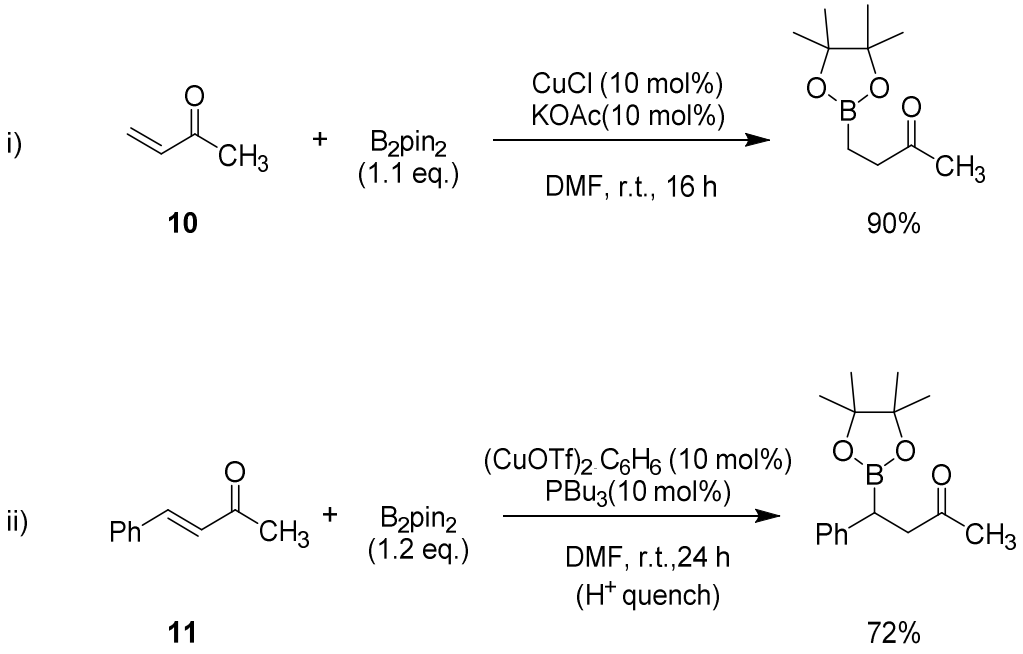


Figure 3: Early reports of reactions mediated by copper-boryl complexes

Since these initial reports, the field has expanded rapidly and a range of transformations have been described. Whilst these have been postulated to proceed through the intermediacy of a copper-boryl complex, isolated examples of these species are rare, with only NHC bound crystal structures having been reported.[12-15] In these examples, a linear arrangement, with the Bpin moiety bound directly opposite to the NHC ligand, was observed. DFT and *in situ* ^{11}B NMR studies also provide some insight into their formation, with the ^{11}B NMR signal for a copper bound boryl moiety observed at δ = 42 ppm.[16-19] It has been calculated that the Cu-B σ* molecular orbital is high in energy, with the filled Cu-B σ-bond being more likely to interact with the substrate.[20]

In the majority of borylation reactions, the active boryl-copper species (11) is generally formed *in situ* by the reaction of a copper(I) salt with an alkoxide base.[21] A metathesis reaction with the diboron reagent (B_2pin_2) then occurs, followed by co-ordination of the substrate and insertion (Figure 4, shown with an alkene), affording a new (boryl)organocopper intermediate (12). Following reaction with an electrophile, ligand exchange with the alkoxide base regenerates the copper alkoxide complex (13).

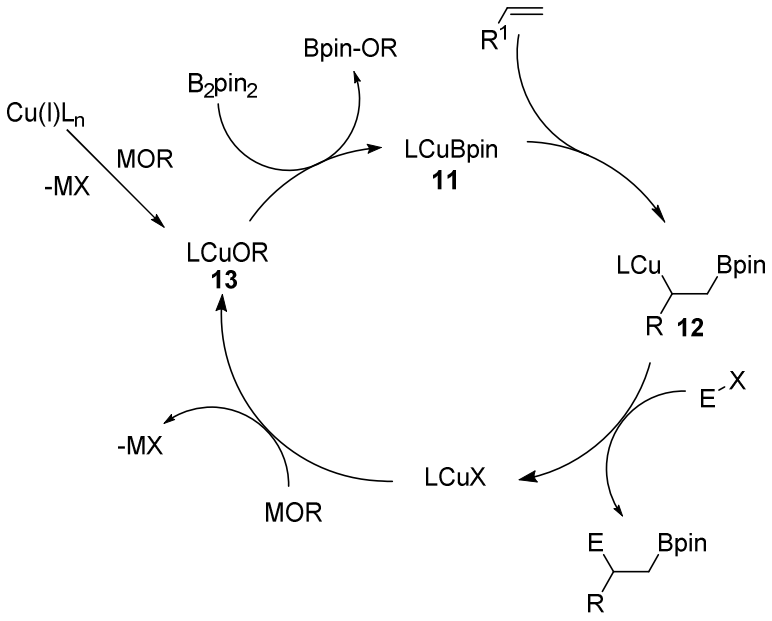
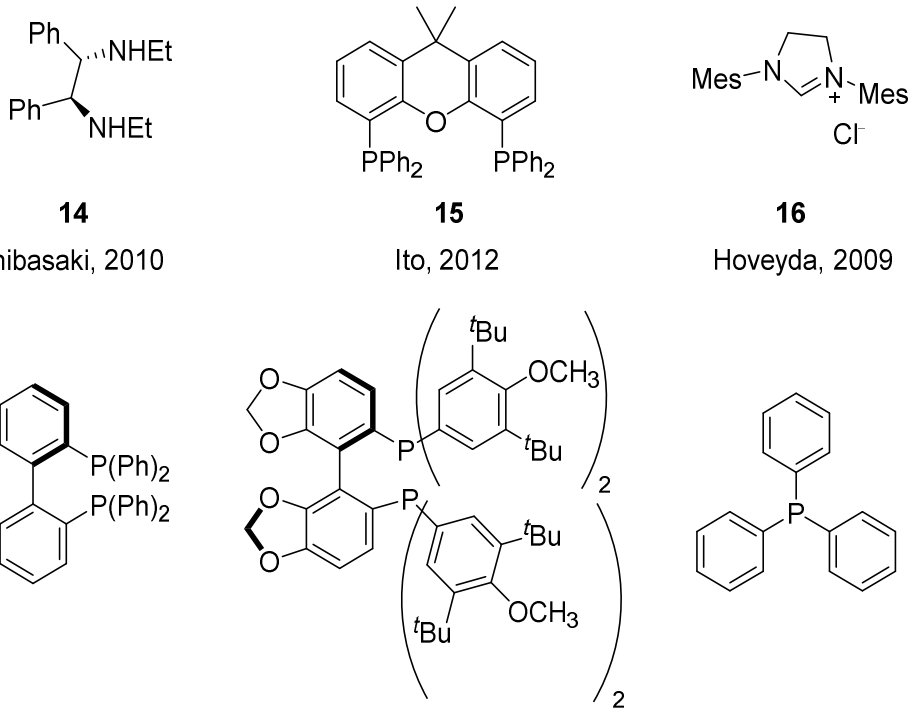


Figure 4: General catalytic cycle for copper-boryl mediated reactions with unsaturated systems

1.3 Synthetic transformations mediated by copper-boryl complexes

The mode of reaction of the copper-boryl complex is largely defined by the nature of the substrate structure and this review is organised along these lines, focussing on issues of chemo-, regio- and stereo selectivity. This has been achieved using a diverse range of ligands, with phosphines (15, 17, 18, 19) being most commonly employed (Figure 5).



14 Shibasaki, 2010 | **15** Ito, 2012 | **16** Hoveyda, 2009

17 Fernandez/Whiting, 2013 | **18** Ito, 2015 | **19** Marder, 2012

Figure 5: Ligands used in copper catalysed borylation[22-27]

1.4 Reactions of copper-boryl species with C-C multiple bonds

Alkenes, allenes and alkynes are amenable to reaction with copper-boryl complexes. These reactions all involve complexation of the π-system to the copper-boryl species, followed by boryl transfer to afford a borylated organocopper intermediate, which is then trapped by a variety of electrophiles (*c.f.* Figure 4). Consequently these processes can be most easily classified by the nature of the overall transformation: hydroboration (E=H, protonation of the copper complex); diboration (E= $B(OR)_2$); carboboration (E = R'-X); aminoboration (E = XNR_2) etc.

1.4.1 Hydroboration of alkenes

In the simplest form, the intermediate formed from addition of a double bond to the copper-boryl complex is trapped by a proton source. Traditionally,

hydroboration (addition of B-H across a π-system) occurs with highly reactive alkyl borane reagents or late transition metal (commonly rhodium) complexes.[28-30] Whilst the mechanism for this is now well established and formally involves a metal boryl species, alternative pathways involving nucleophilic metal boryl complexes are also possible, leading to an intermediate organometallic species which upon protonation affords the formal hydroboration product. Since the first reports, copper-boryl reagents have been widely used with a range of double-bond containing substrates including alkenes, dienes, alkynes and allenes.[31]

With non-polar multiple bond containing substrates, the key issue is the control of regioselectivity. As reactions with simple unactivated alkenes are surprisingly rare, it is difficult to make generic comments as to the intrinsic regioselectivity. For terminal alkenes (20), reaction with a copper Xantphos complex afforded formal anti-Markovnikov borylation (Figure 6, i)) [32] whilst use of a bulky diphosphine ligated complex led to the opposite regiochemistry.[33]

In many substrates, regiochemical control is enabled by inherent structural features. For example, Wen and co-workers reported the copper catalysed borylation of allyl and vinyl arenes[34] in which the Bpin group added to the terminal position in the case of vinyl arenes (21) (Figure 6). Conversely, allylarenes (22) were borylated at the more substituted position of the double bond. Such observations could be attributed to the formation of an η^7 stabilised benzyl copper complex (Figure 6, ii) structure 23) or by co-ordination of the copper to the aromatic π-system (24), respectively (Figure 6, iii)). Further evidence for this coordination

directed mode of addition was seen in the regioselective reaction of hex-5-en-2-one (25, Figure 6, iv)).

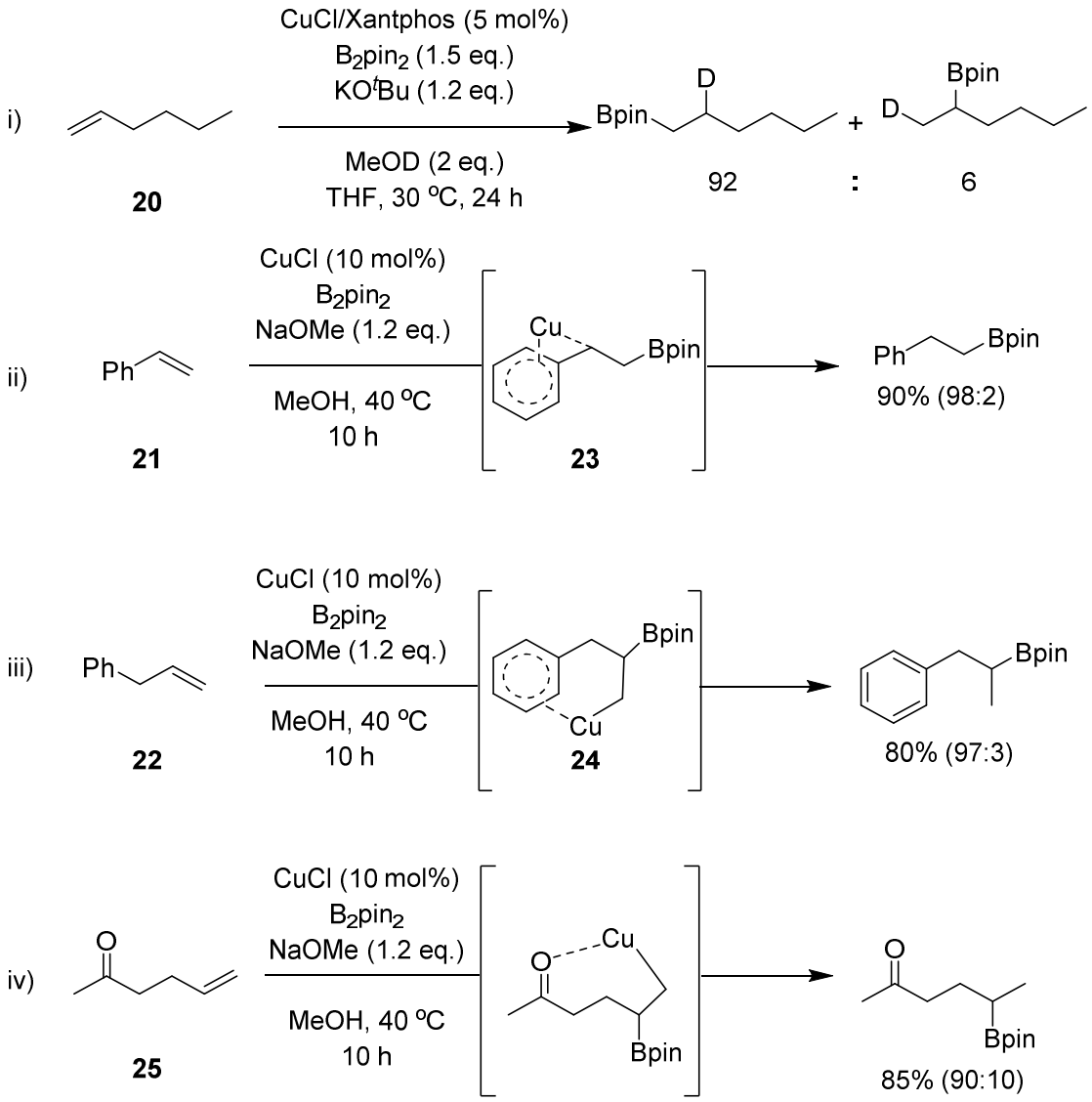
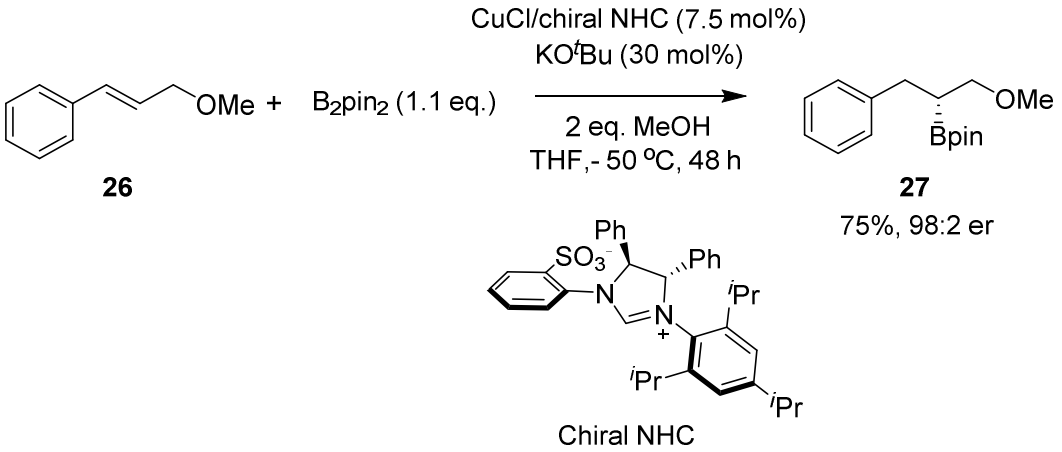


Figure 6: Regiocontrol in the copper catalysed borylation of alkenes

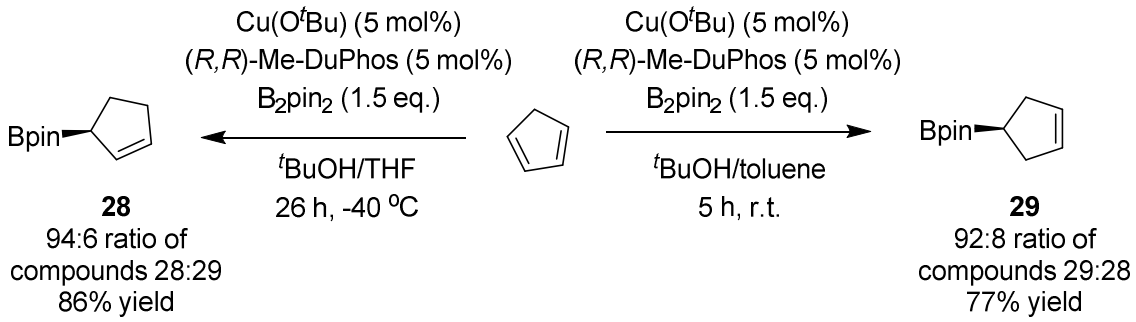
Whilst these substrate based methods are effective, ligand and reagent based control methods are inherently more attractive. Enantioselectivity is a further challenge. In 2009 Hoveyda and co-workers developed an elegant process demonstrating substrate control (formation of a benzylcopper intermediate) and ligand controlled enantioselectivity. Hydroboration of substituted alkenes such as

an allyl ether (26) with a Cu/chiral *N*-heterocyclic carbene (NHC) system afforded the chiral alkyl boronate (27) in good yield and high *ee* (Scheme 1).[24] This remains the benchmark for this transformation.



Scheme 1: Enantioselective hydroboration reported by Hoveyda and co-workers

Dienes can also be borylated enantioselectively, with the first copper-catalysed example being reported in 2010.[35] Similar to the styrene systems discussed above, temperature controlled experiments showed that regiocontrol arose through the kinetically favoured formation of an allylcuprate intermediate at low temperatures. S_E2' protonation of this affords the observed allylboronate product (28). At room temperature, this intermediate rapidly isomerised to a more stable 1,4 boryl copper complex which on protonation, as before, leads to the borylated cyclopentene (29, Scheme 2).



Scheme 2: Enantioselective temperature controlled diene borylation

A particularly elegant example of enantioselective diene hydroboration is the reaction of cyclic dieneamides (30 and 31), generated *in situ* through the reduction of pyridinium and quinolinium salts and enabling the synthesis of a wide range of chiral cyclic amines (Figure 7).[36, 37] As above, the formation of an allyl copper intermediate appears to be the key determinant in the regioselectivity of the process.

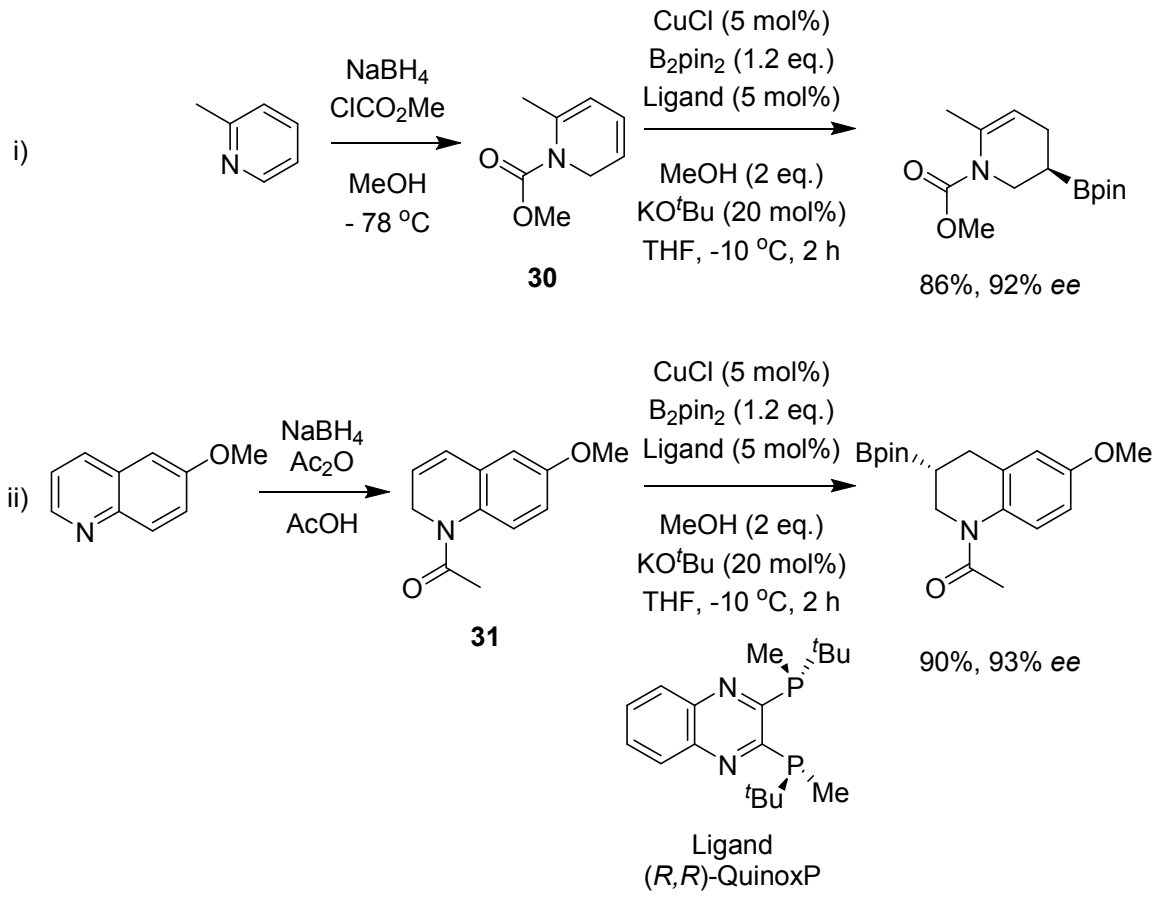


Figure 7: Formation of chiral borylated amines from amino-dienes

Allyl-copper species are also the favoured intermediates generated in the reaction of a copper-boryl reagent with an allene.[38] Regioselective hydroboration of aryl allenes (32) is possible, with either a benzylic or allyl copper intermediate being generated depending on the choice of ligand used in conjunction with a copper (I) catalyst (Figure 8 eqns i) and ii)).[39] Alternatively, varying the nature of the boron source allows selection between allyl and vinyl borane products (33 and 34) according to the nature of the reactive copper species generated (Figure 8 eqns iii) and iv)).[15]

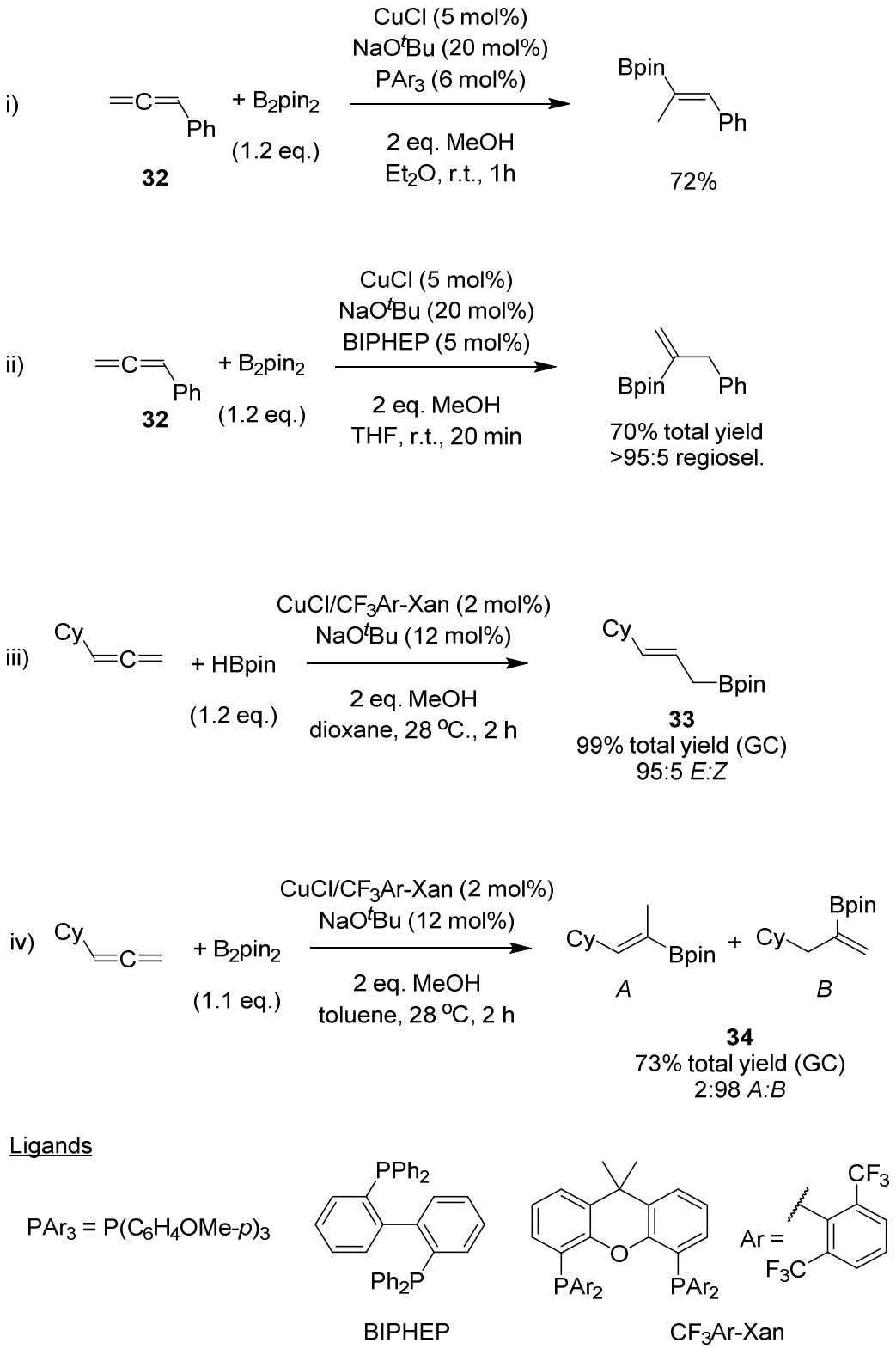
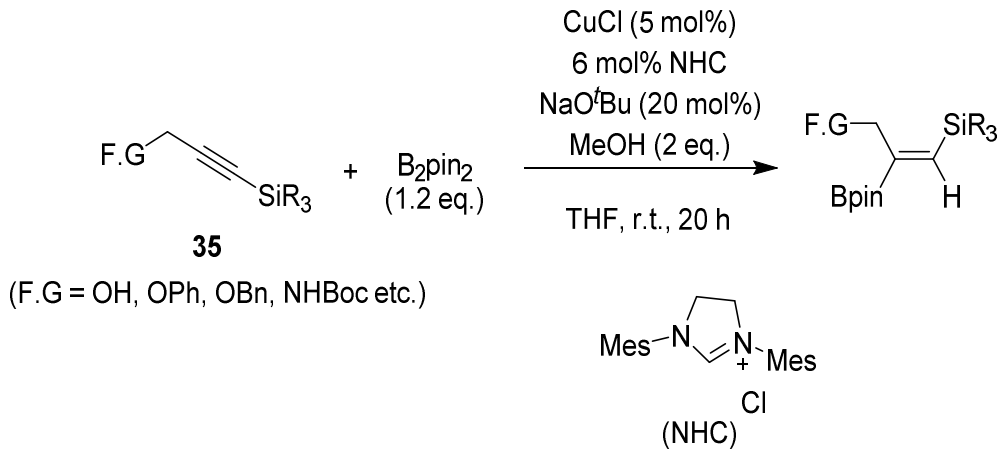


Figure 8: Hydroboration of allenes with different ligands and boryl sources

Akin to the hydroboration of alkenes, copper-catalysed borylation of alkynes, first reported by Miyaura in 2001,[40] is now well established.[31, 41] Good regioselectivities

can be achieved for both simple terminal alkynes and more challenging internal alkynes, with a number of strategies having been described.[42] As with the other functional groups discussed above, substrate based approaches provide the simplest method for achieving regiocontrol.[43, 44] In general, as with alkenes, regioselectivity in the copper-catalyzed alkyne borylation is more effectively achieved by electronic rather than steric factors, for example primary propargylic silyl-alkynes (35) undergo a regioselective copper-boryl mediated reaction (Scheme 3).[45]



Scheme 3: Hydroboration of propargylic silylalkynes

As with the approaches taken for allenyl substrates, different regioisomers can be obtained from the hydroboration of alkynes depending on whether pinacolborane (HBpin) or bispinacolatodiboron (B_2pin_2) is used as the boryl source (Figure 9). As noted above, it was proposed that these reactions were mediated by either a copper hydride or copper-boryl species respectively.[46-48]

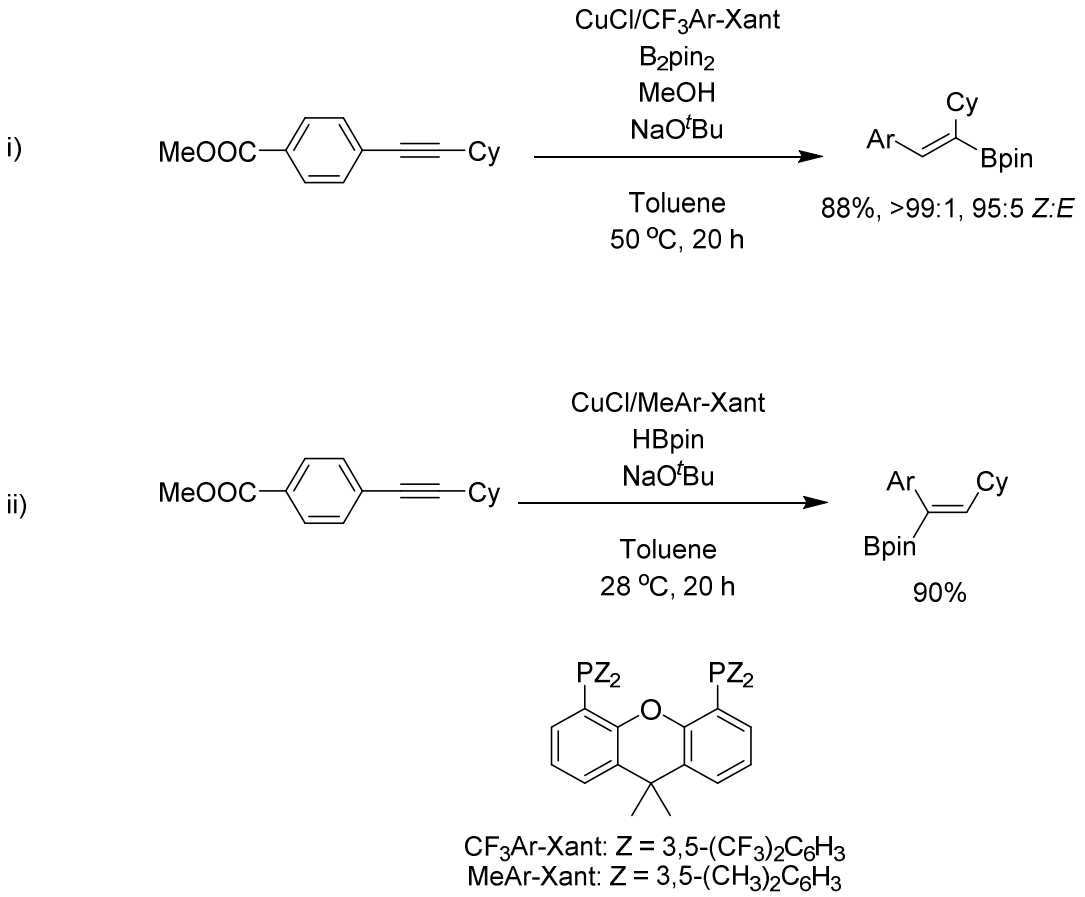
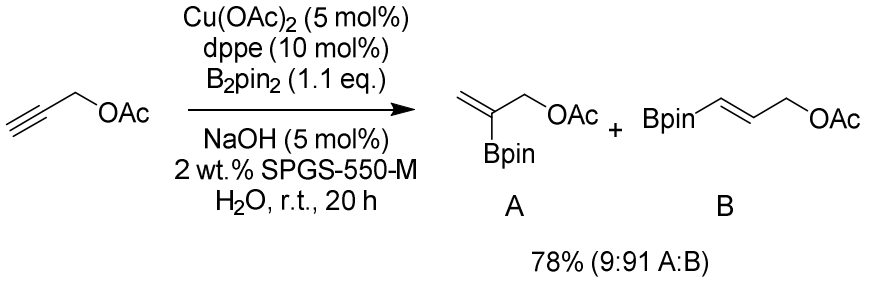


Figure 9: Differing outcomes of alkyne hydroboration depending on the boryl source

Ligand based strategies that provide regiocontrol are also possible.[49-52] One notable example was the borylation of propargylic alcohols, whereby α- or β-boration could be controlled depending on the NHC ligand and its interaction with the substrate.[53] With a simple NHC, electronic effects in the substrate were the main determinant of regiochemistry and gave β-Boration; with a more sterically hindered NHC ligand, the bulk of the catalyst surpassed this electronic bias as the main influence on regiochemistry, yielding α-borylated products.

Although somewhat less developed than Cu(I) mediated transformations, other copper species can also be used to carry out similar (hydro)boration type reactions but with the benefit of increased stability of the catalyst and ligands.[54, 55] For

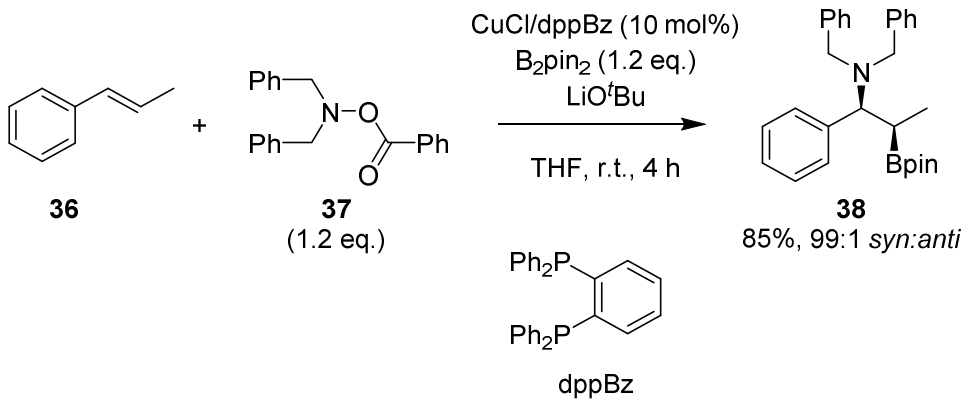
example, Cu (II) catalysed borylation of terminal alkenes and alkynes occurs efficiently to afford β-borylated products with high levels of regioselectivity.[56] With the drive towards more sustainable processes, reactions in water have become more attractive and copper catalysed hydroboration is no exception. Building on early reports of enone borylation described by Santos and others (*vide infra*) [57, 58] there have been reports of alkyne hydroboration under aqueous conditions in which hydroxide rather than alkoxide bases can be used (Scheme 4).[59, 60]



Scheme 4: Cu(II) catalysed hydroboration of propargylic alkynes in water

1.4.2 Aminoboration

Greater structural complexity is possible when the intermediate organoboryl copper complex is intercepted by alternative electrophiles. For example, borylation of styrenes such as 36 with B_2pin_2 and CuCl in the presence of *ortho*-diphenylphosphinobenzene (dppBz), followed by reaction with hydroxylamine ester 37 afforded the aminoborane (38) with high regio and stereoselectivity favouring the *syn* diastereoisomer (Scheme 5).[61] This regiochemistry parallels that observed for hydroboration and is consistent with addition of the boryl fragment to give preferential formation of a benzylcopper intermediate.



36 + **37** (1.2 eq.) → **38** 85%, 99:1 *syn:anti*

Scheme 5: Aminoboration of styrenes

Other activated alkenes, including methylene cyclopropanes (39), cyclopropenes (40, 41) and various strained bicyclic alkenes undergo similar additions, and with appropriate ligands high enantioselectivity be achieved (Figure 10).[62,63,64,65]

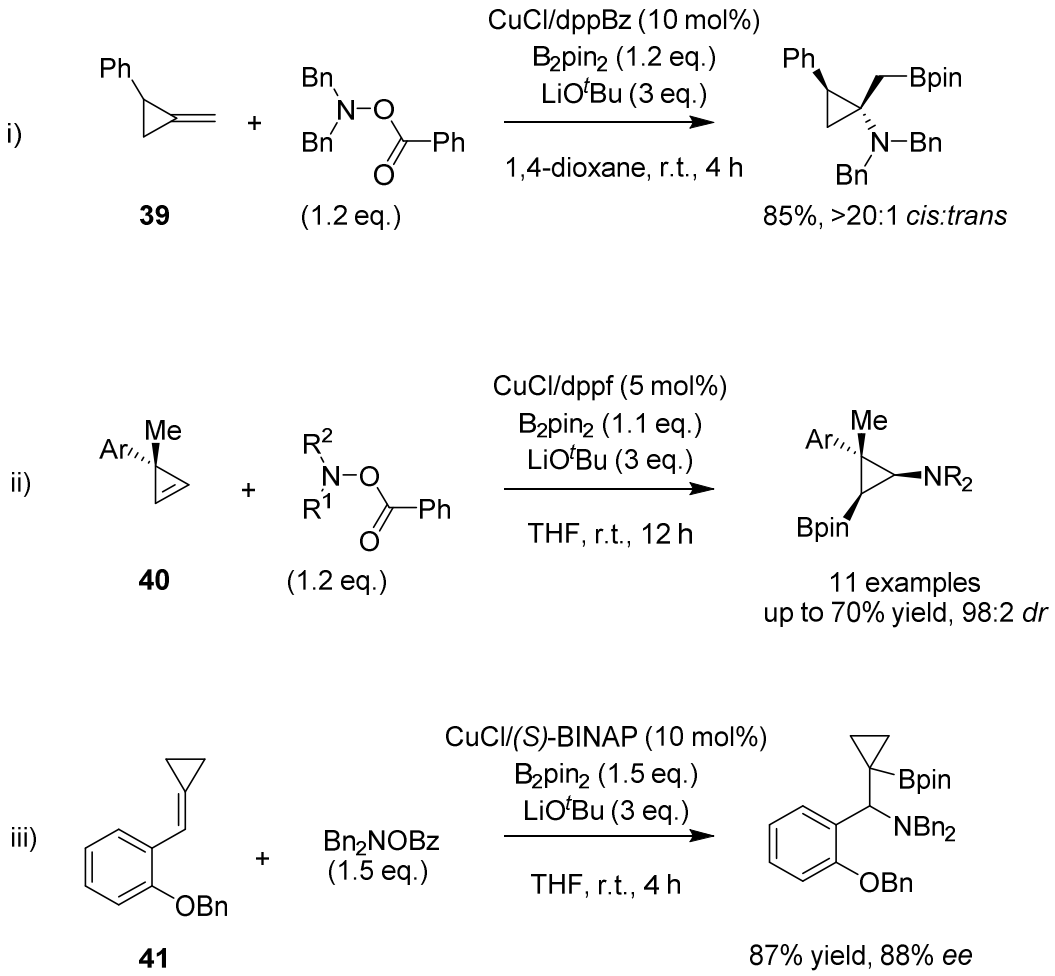


Figure 10: Aminoboration of cyclopropyl derivatives

Unactivated terminal alkenes (42) are also viable substrates.[63] Intriguingly, different regiochemistry was observed depending on the catalyst and diboron reagent combination used (Figure 11, i) and ii)). The rationale for this reversal of regioselectivity is not fully understood, but one possibility is that the bulky NHC ligated Cu complex is only tolerated at the terminal position. Intramolecular reactions are also possible to give borylated cyclic amines such as 43 (Figure 11, iii)).

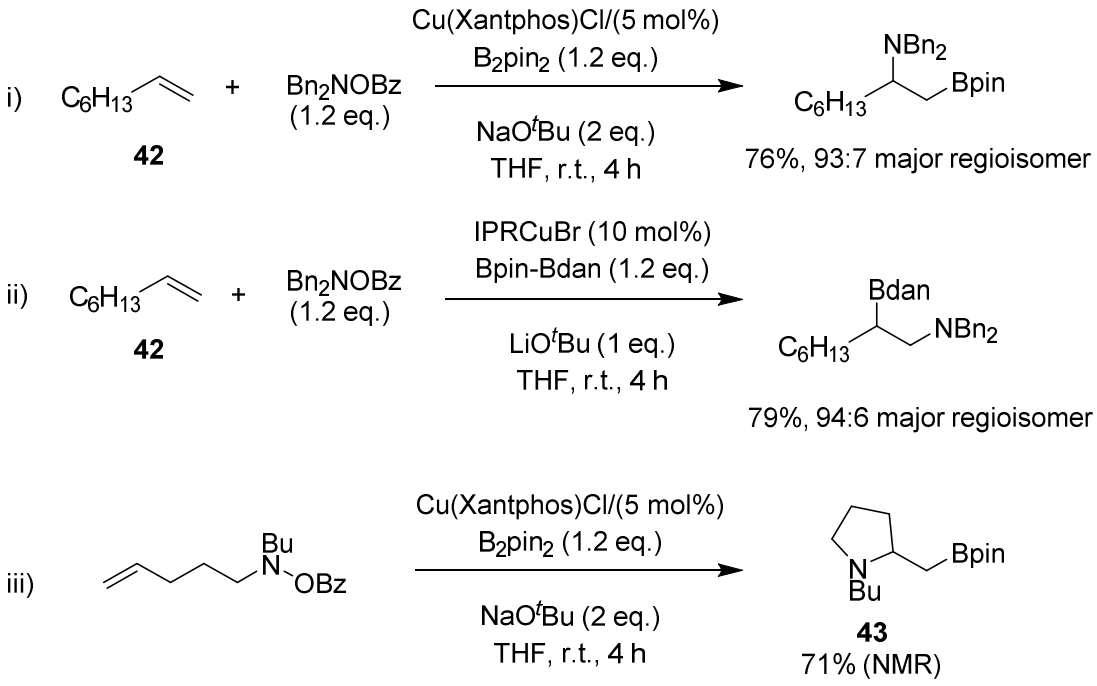


Figure 11: Aminoboration of unactivated terminal alkenes

1.4.3 Carboboration

Carboboration is similar to aminoboration, following an almost identical catalytic cycle but involving the reaction of a carbon centred electrophile with the organocopper-carbon intermediate. The scope of the process is large and diverse with the organocopper generated by activation of an alkene, alkyne or allene by a copper-boryl complex, whilst the electrophile can be either sp^2 or sp^3 based. Many of the earlier examples of this process occur in an intramolecular fashion – for example, a range of cycloalkyl Bpin esters (44, 45) have been synthesised by the stereospecific reaction of homoallylic sulfonates (46, 47) in the presence of a CuCl/dppp catalytic system (Figure 12).[66] The presence of an anion stabilising group, either silane or arene, was required to give synthetically useful silaboronates.

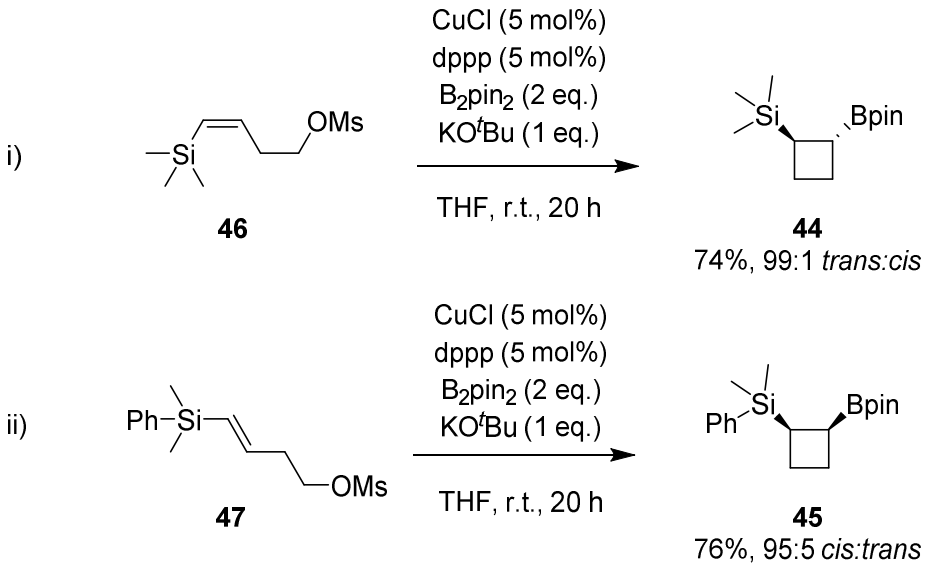


Figure 12: Stereospecific cyclisation of activated alkenes to give cyclobutyl Bpin esters

These transformations are formally related to the borylation of 6-bromo-1-hexene (48) under conditions that lead to simple C-X borylation (see section 1.6), which resulted in a cyclopentylmethyl boronate ester product (49) as opposed to expected linear alkene containing product (50, Figure 13, i)).[27] Alkynes (51, 53) can undergo similar transformations too (Figure 13 eqns. ii) and iii))[67] with regiocontrol being usually dictated by ring strain arguments; although the presence of the silicon atom in (53, Figure 13, iii)) reinforces the *exo* nature of the resulting alkene.

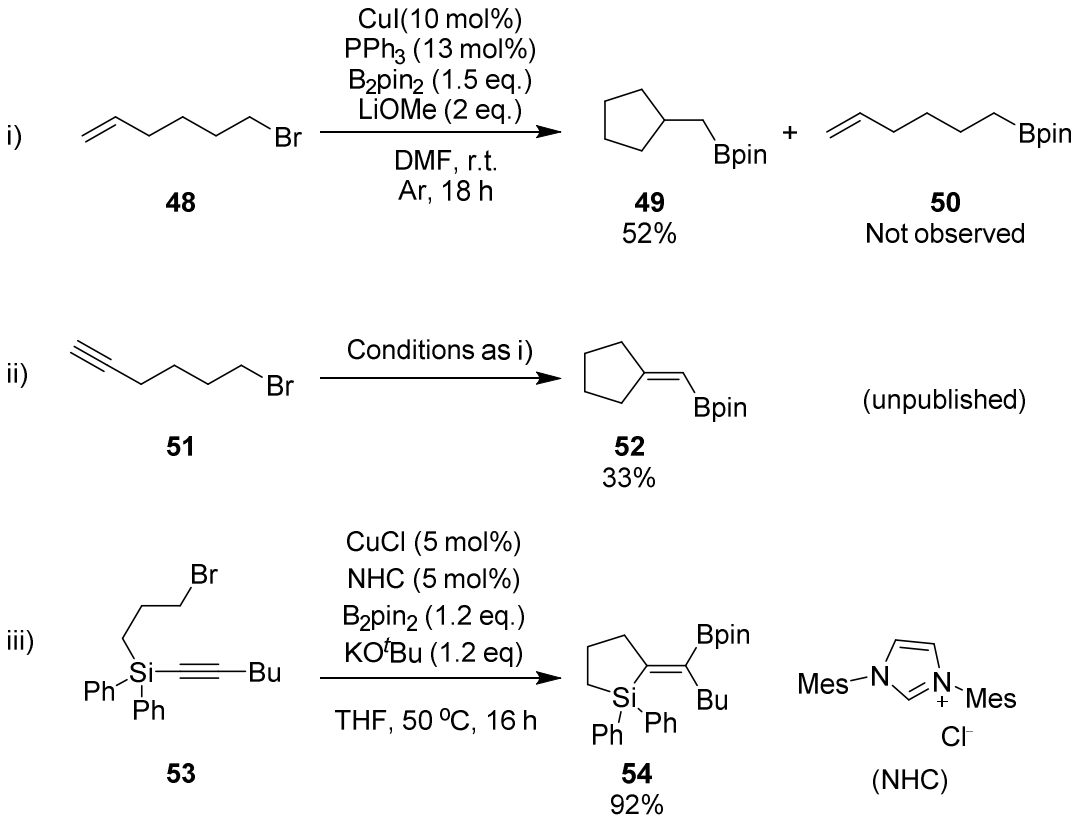
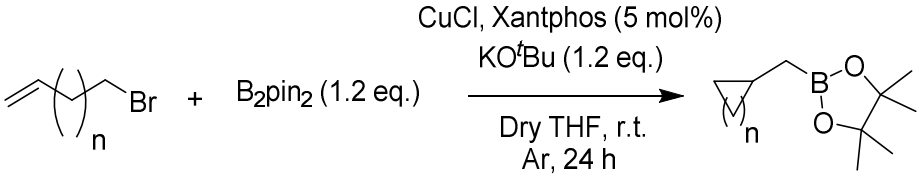
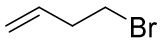
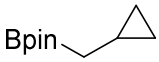
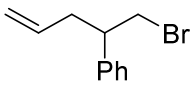
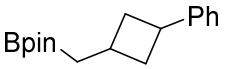
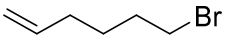
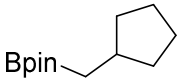
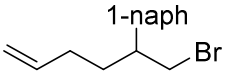
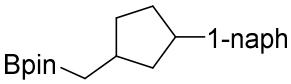
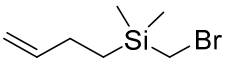
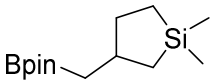
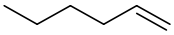


Figure 13: Borylative cyclisation reactions

Concurrent with this report, Ito described a similar process using a Cu(I)/Xantphos/KO^{t}Bu combination.[32] Alkenyl halides could be cyclised with simultaneous C-B bond formation to form a range of cyclic products, arising from formal carboboration of an unactivated alkene (Table 1). The mechanism of the process remains an interesting question as hexen-1-ene (20) was not hydroborated under the reaction conditions (Table 1, entry 6), suggesting that activation of the C-X bond is a prerequisite and thus the potential for radical mediated cyclisation pathways. Counter to this, silyl alkenes (Table 1, entry 5) tend to preferentially form 6-*endo* products upon radical cyclisation as opposed to the observed 5-*exo* product.[68] These mechanistic questions have implications for C-X borylation and are discussed in greater detail below (section 1.6).

Table 1: Intramolecular carboboration substrates reported by Ito



Entry	Substrate	Product	Yield (%)
1			99 (GC)
2			91
3			86
4			87
5			74
6	 **20**	d.n.r.	0

For these transformations, the intramolecular nature of this 'alkylation' reaction is important as there are far fewer examples of copper catalysed *inter*molecular carboboration,[69, 70] with these initially being limited to the more reactive allylic and benzylic alkylating agents. One approach to enhance the scope was to use mixed catalysis, as exemplified in various reports describing co-operative copper/palladium catalysed arylboration of alkenes, allenes and alkynes.[71, 72] In this

process, the initially generated β-borylalkylcopper intermediate undergoes fast transmetallation with an *in situ* generated ArPd(II)(halide) complex, followed by reductive elimination to give the arylboration products. By varying the nature of the phosphine ligand and base, it is possible to change the nature of the transmetallation step from stereoretentive to an invertive pathway, thus enabling either *anti* or *syn*-selective arylboration (55). With chiral ligands good control of enantioselectivity can be achieved (Figure 14).[73, 74] Analogous processes using nickel as the co-catalyst have also been reported.[75]

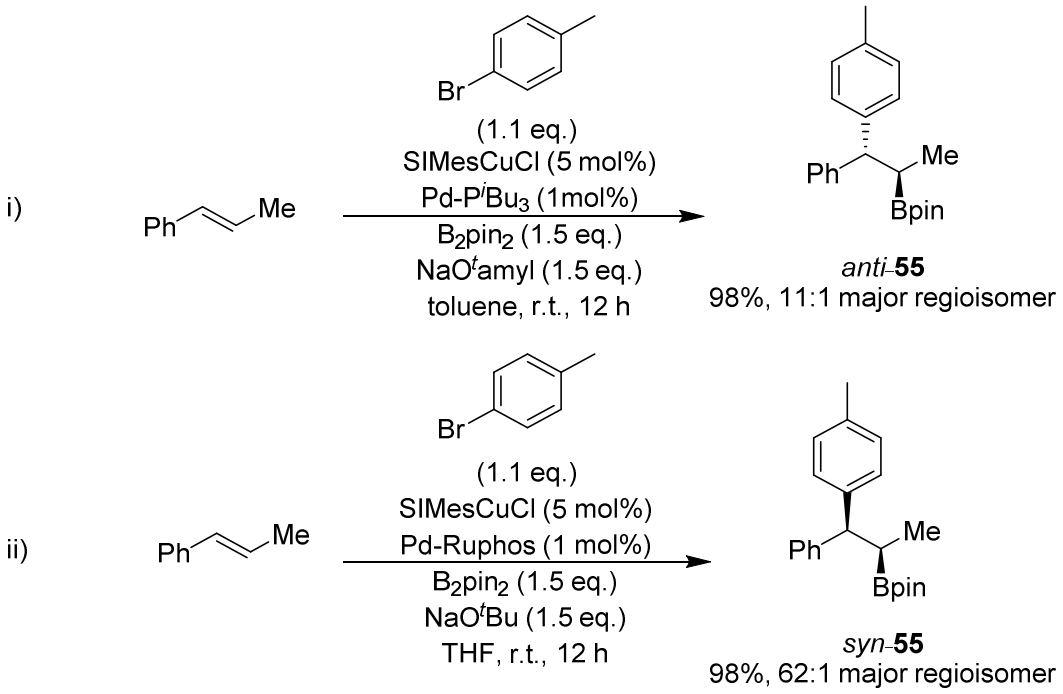


Figure 14: Syn and anti-selectivity and enantioselectivity according to the phosphine ligand and base

With the view to reducing precious metal catalysis, a key development in the area was the development of a purely copper catalysed process. Early studies showed that alkynes could be converted to substituted stilbenes *via* copper catalysed Suzuki-Miyaura couplings with aryl halides, albeit with variable control of

regiochemistry for electronically unbiased (but non-symmetrical) substrates.[76] These studies also demonstrated that simple alkylation with MeI and benzyl bromide were feasible.[77] Such alkylations with sp^3 electrophiles are more challenging as there is the competing direct borylation of the alkyl halide (see section 1.6). Building on earlier work by Sigman,[78] Fu, Xiao & co-workers proposed the use of alkenes with a suitably located proximal coordinating group (heteroatom) to ensure a more rapid insertion and providing an efficient carboboration sequence albeit limited to primary alkyl halide electrophiles (Figure 15).[79] Through choice of ligand (Xantphos or Cy-Xantphos), both the α and β borylated regiosiomers (56 and 57) could be obtained from the same starting material.

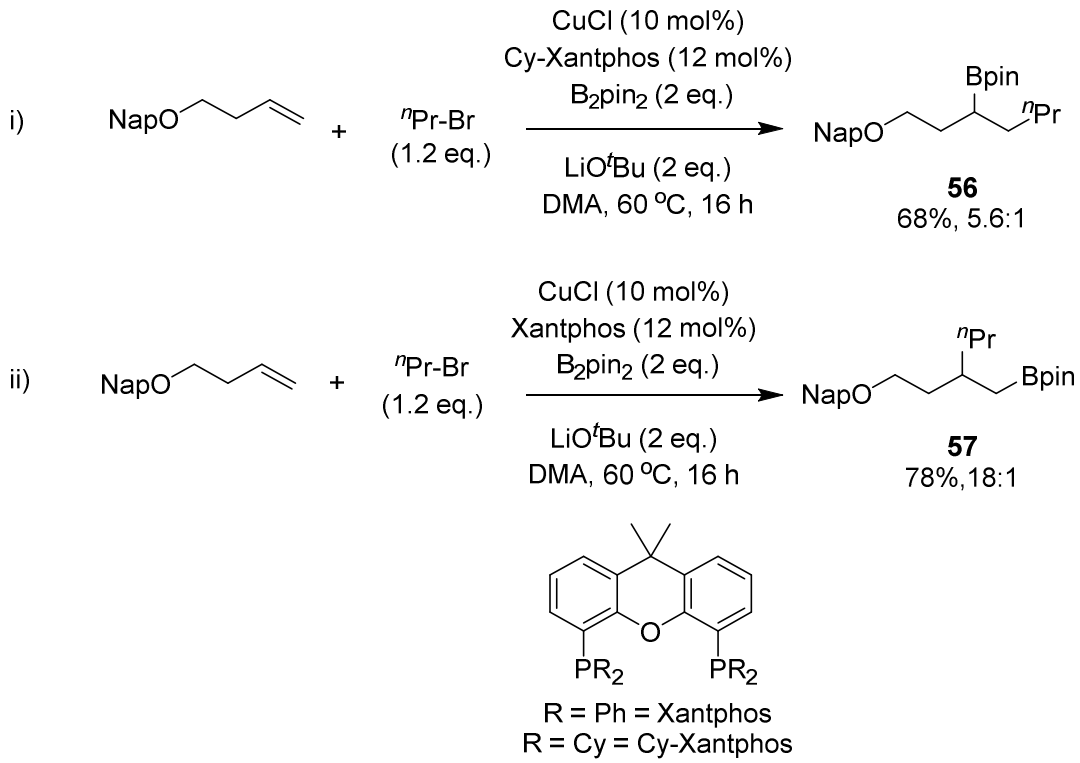
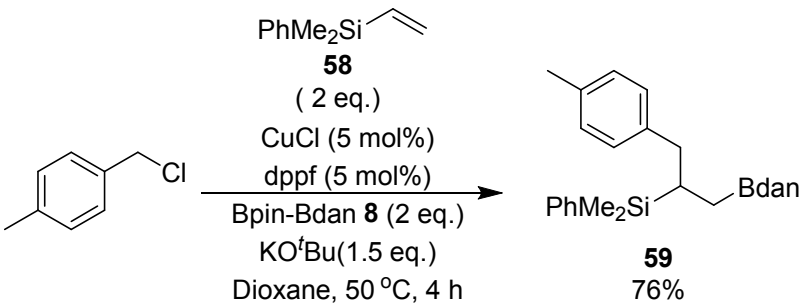


Figure 15: Regioselectivity by choice of ligand in alkylboration

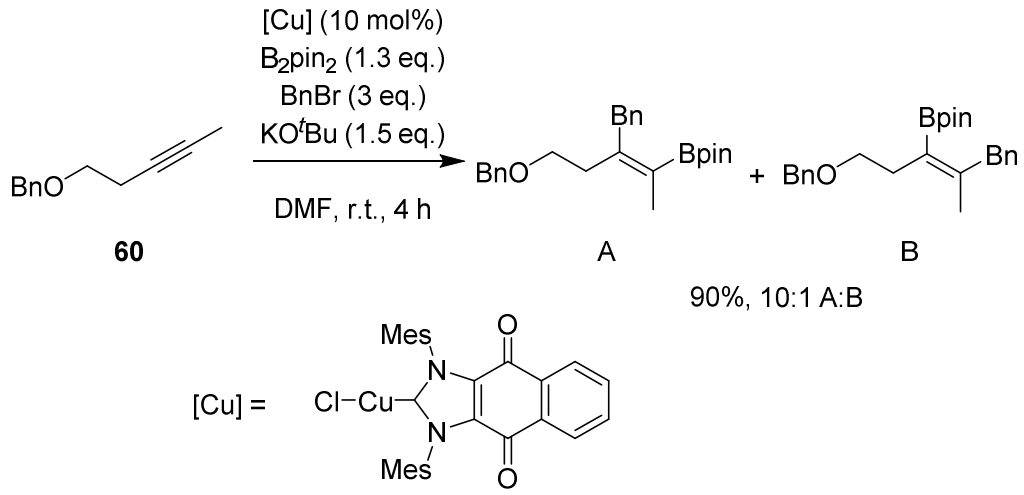
DFT calculations suggest that the regioselectivity is determined during the addition of the alkene to the copper-boryl species.[80] This migratory insertion step was proposed to be irreversible and under kinetic control. Cy-Xantphos, which has a larger steric demand than Xantphos, requires that the less hindered terminal end of the alkene orients closer to the ligand in the active species. Conversely, with Xantphos the alkene orients to minimise unfavourable interactions with the Bpin substituents.

An interesting recent example of intermolecular carboboration was the reaction of vinylsilanes (58) with Bpin-Bdan (8), where the presence of a silicon atom directed the bora-metalation of the double bond, giving exclusively terminal borylated products (59, Scheme 6). Allenes are also amenable to this process.[81]



Scheme 6: Carboboration of silylalkenes with Bpin-Bdan

Similar ligand controlled regioselective bora-alkylations are possible starting from non-symmetrical alkynes (60, Scheme 7).[82, 83] A broad range of alkyl (and aryl) halide electrophiles are tolerated, although the use of secondary alkyl electrophiles remains challenging.



Scheme 7: Regioselective alkylboration of alkynes

Other carbon electrophiles can also be used. For example Hoveyda reported the trapping of the borylated cuprate derived from an allene (61) with aldehydes (62) (Figure 16, eqn i))[84] and more recently dienyl derived allyl copper intermediates have been combined with aldehydes and imines (Figure 16 eqns ii) and iii)).[85, 86]

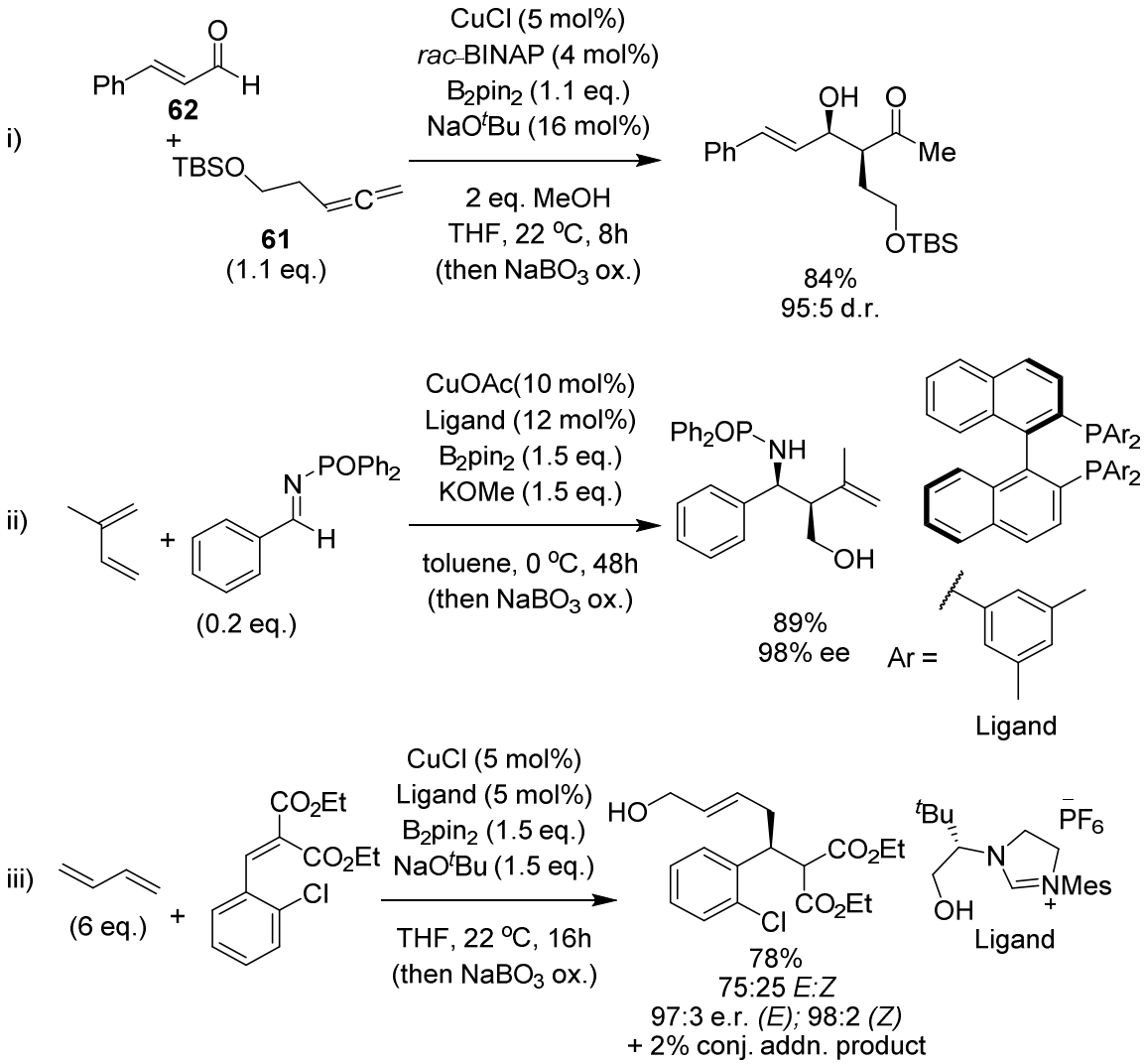
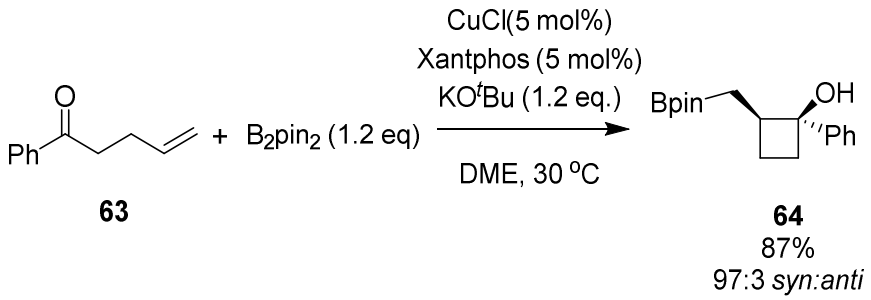


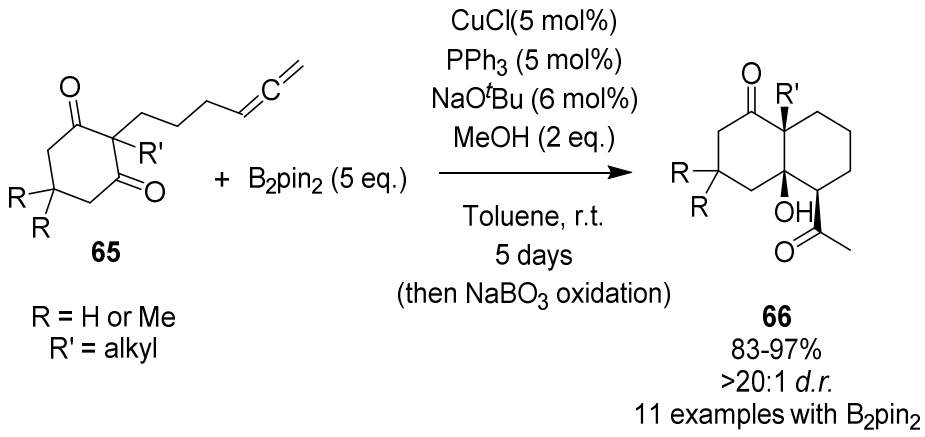
Figure 16: Trapping of allyl copper intermediates

With the alkylations described above the trapping process may be intramolecular and in these cases selectivity for the cyclisation versus the competing direct 1,2 addition to the carbonyl group is key. This is achievable through careful choice of ligand,[87] or may be influenced by the substrate. For example, γ-alkenyl ketones (63) react under CuCl/Xantphos conditions to selectively give cyclobutanes (64, Scheme 8) when an aryl ketone is used as a substrate, whereas alkyl and alkenyl moieties gave complex mixtures, possibly due to competing 1,2-addition amongst other side reactions.[88]



Scheme 8: Borylative cyclisation of a γ-alkenyl ketone

In a similar fashion (albeit with more complex substrates), a number of other elegant borylative cyclisations have been reported,[89] with both alkenyl and alkynyl-ketone derivatives being suitable substrates. Lam and co-workers reported an enantioselective aldol cyclisation from enone diones in the presence of a chiral ferrocenyl ligand,[90] whilst 1,6-enynes underwent asymmetric borylative cyclisation in a similar process.[91] More recently, a cascade borylation/cyclisation of allenyl ketone containing substrates was reported.[92] Initial β-boration of the allene (65) generated an intermediate which then underwent allylic addition and cyclisation to give *cis*-decalinol products (66, Scheme 9). Regiochemistry was controlled by co-ordination of the copper to the carbonyl group and in the presence of suitable ligands good levels of asymmetric induction could be achieved.



Scheme 9: Cyclisation of allenyl ketones to form decalinol products

1.4.4 Diboration & heteroboration of C-C multiple bonds

In the simplest form, the intermediate is trapped by an excess of the diboron reagent, leading to bisborylated products. Whilst copper catalysed diboration of alkenes[93] and alkynes[94, 95] has been described, this is a relatively rare occurrence and is much more common with Pd and Pt based catalysts.[41] Formal copper catalysed diboration is also observed in cascade processes involving allenes, whereby the diborated copper containing intermediate further participates in a cyanoborylation reaction.[96] A number of other examples of heteroboration exist, for example stannylboration and oxyboration, though these are limited in number (Figure 17 eqns i) and ii)).[97-100]

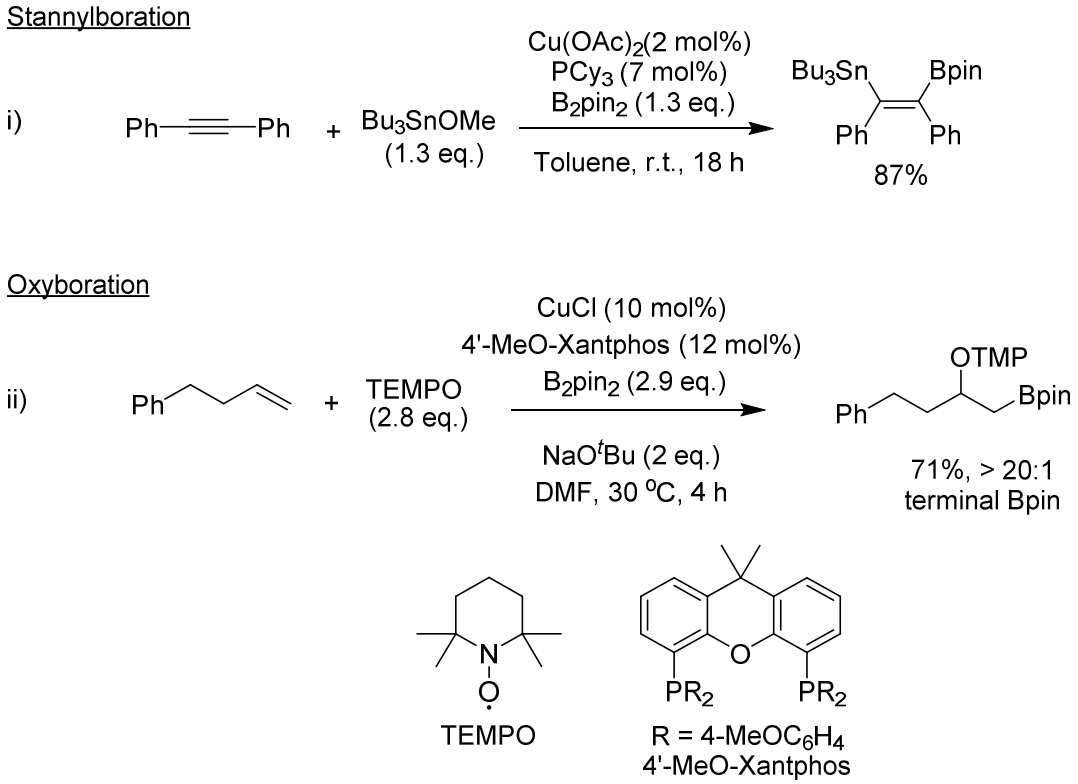
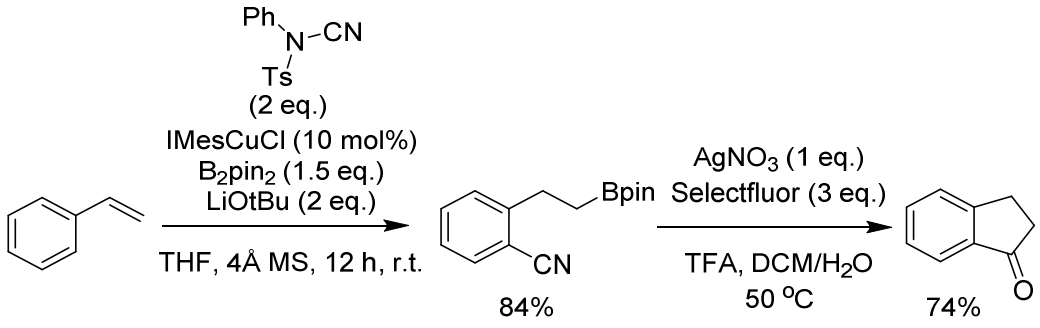


Figure 17: Stannyl and oxyboration

Finally, the α-benzylcopper complex derived from the borylation of styrenes can be trapped with an amino nitrile to afford an intriguing borylative cyanation sequence (Scheme 10).[101,102] This built on previous work by Chatani and co-workers, who pioneered a copper catalysed borylative cyclisation reaction of 2-alkenylaryl isocyanides. The alkene was part of an α,β-unsaturated ester system, giving 2-borylated indole derivatives as the products.



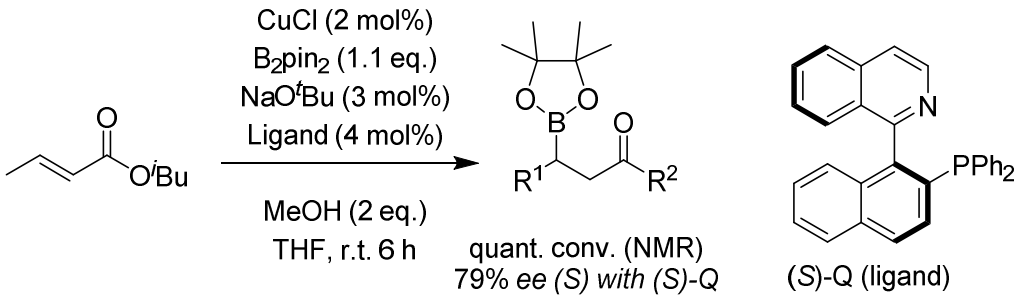
Scheme 10: Cyanoboration/hydroboration and Ag catalysed cyclisation

1.5 Reactions of copper-boryl complexes with polarised multiple bonds

Copper-boryl complexes can also react with polarised π-systems such as enones (1,4-addition) and carbonyl derivatives (1,2-addition). Distinction between these two sites of attack may be minimal and is often conferred by ligand choice (*c.f.* Figure 16, section 1.4.3). As this area has been reviewed by others, only a brief summary of these reactions is provided; for a comprehensive overview the reader is directed to these other sources.[6, 103]

1.5.1 β-Boration of enone derivatives

As previously discussed, the first reported transformations mediated by copper (I)-boryl species were conjugate additions to enones.[10, 11] Since these first reports, the scope of the process has been expanded to include α,β-unsaturated esters and nitriles.[104, 105] Enantioselective borylation of these substrates is also possible *via* chiral ligands (Scheme 11).[106-108]



Scheme 11: Enantioselective conjugate boryl addition to α,β-unsaturated esters

α,β-Unsaturated imines can undergo asymmetric 1,4-addition with copper-boryl complexes (Figure 18, i)).[25] Aldimines (generated *in situ* from aldehydes) could also take part in conjugate addition reactions, though derivatisation of the borylated products was required due to their instability.[109] These were the starting materials

(67) in an efficient synthesis of fluoxetine (68), which had 5 synthetic steps in one-pot (Figure 18, ii)).[110]

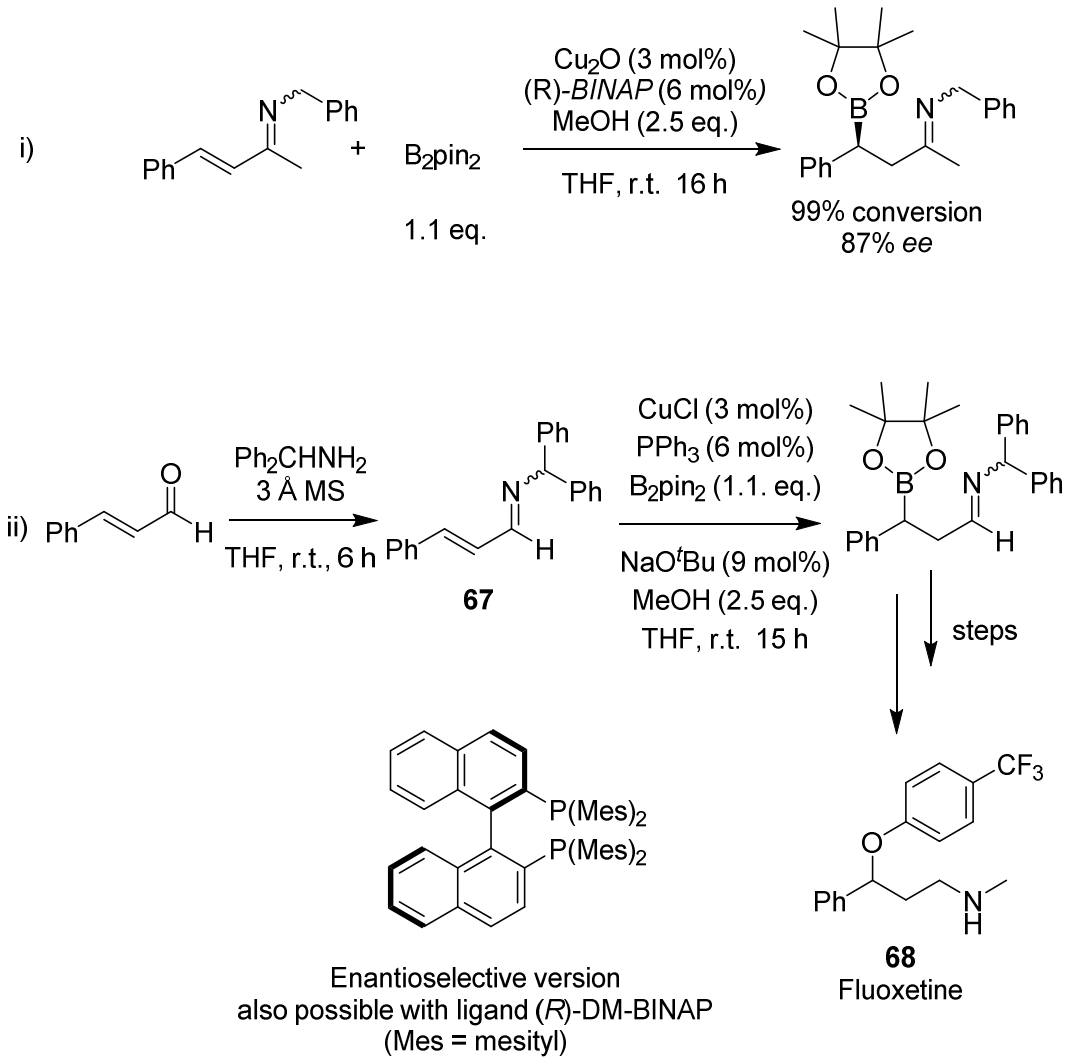


Figure 18: Base free borylation of α,β-unsaturated imines

Copper (II) complexes are also effective catalysts for β-boration processes. With these systems, the optimal solvents are generally protic in nature, including water. Using $Cu(OAc)_2$ as a catalyst,[111] chalcones (69) along with a wide range of aromatic/non-aromatic substrates could be borylated in high yields and with good *ee* (Figure 19, i)). Asymmetrical diboron reagents (e.g. Bpin-Bdan, 8) can also be

incorporated into alkynamides and alkynoates (70); furthermore the reaction could be run open to air (Figure 19, ii)).[112]

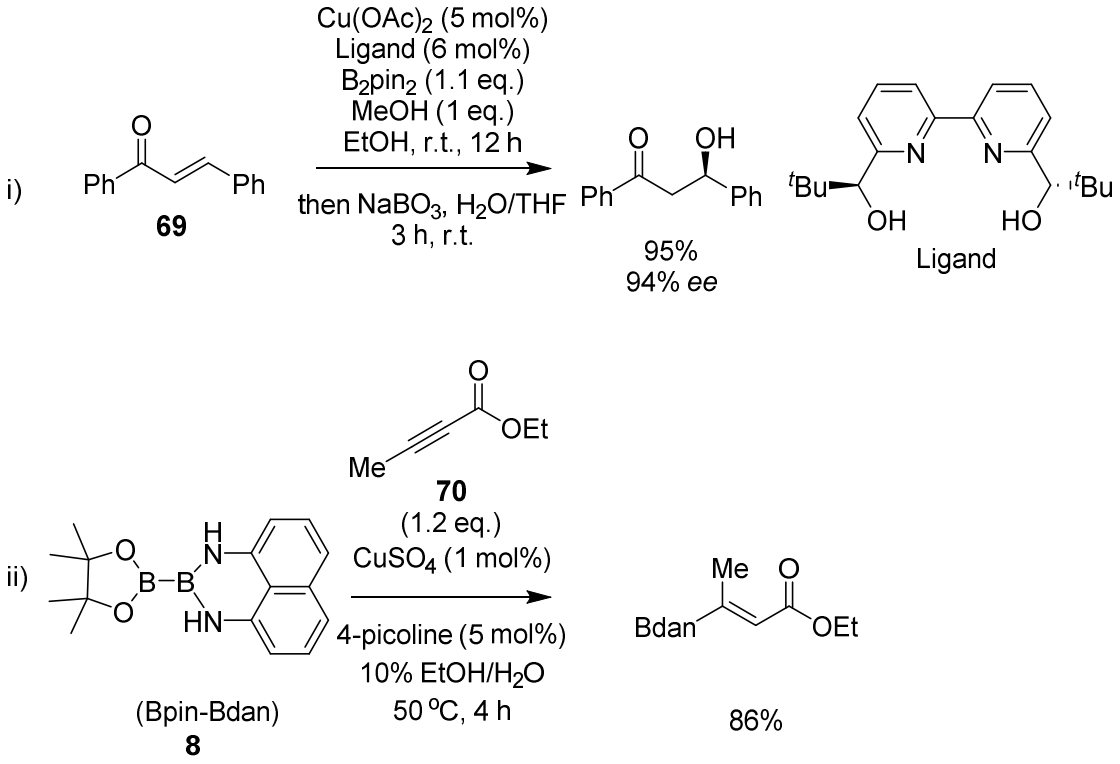


Figure 19: Cu(II) catalysed enantioselective β-borylation

1.5.2 1,2-Addition to carbonyl derivatives

Copper-boryl complexes can also react at the carbonyl carbon in 1,2-addition fashion. The first reported examples resulted in diboration (Figure 20 (i)),[113] though later work allowed the boryl groups on these products to be differentiated (Figure 20, ii)).[114] Ito, Kubota and Yamamoto developed this area by reporting the first enantioselective borylation of carbonyl systems in up to 99% *ee*.[67] The chiral boryl-alcohols were trapped as the silyl ethers (71) to facilitate purification and identification and the reaction could be carried out on a gram scale with high levels of enantioselectivity (Figure 20, iii)).

In these reactions, it has been suggested that regiochemistry is determined by polarisation of the Cu-B bond, with the boryl ligand behaving as a nucleophile,[115] though DFT calculations have suggested that the main reason for the observed mode of addition is due to transition state HOMO-LUMO stabilisation by the copper-boryl complex.[116]

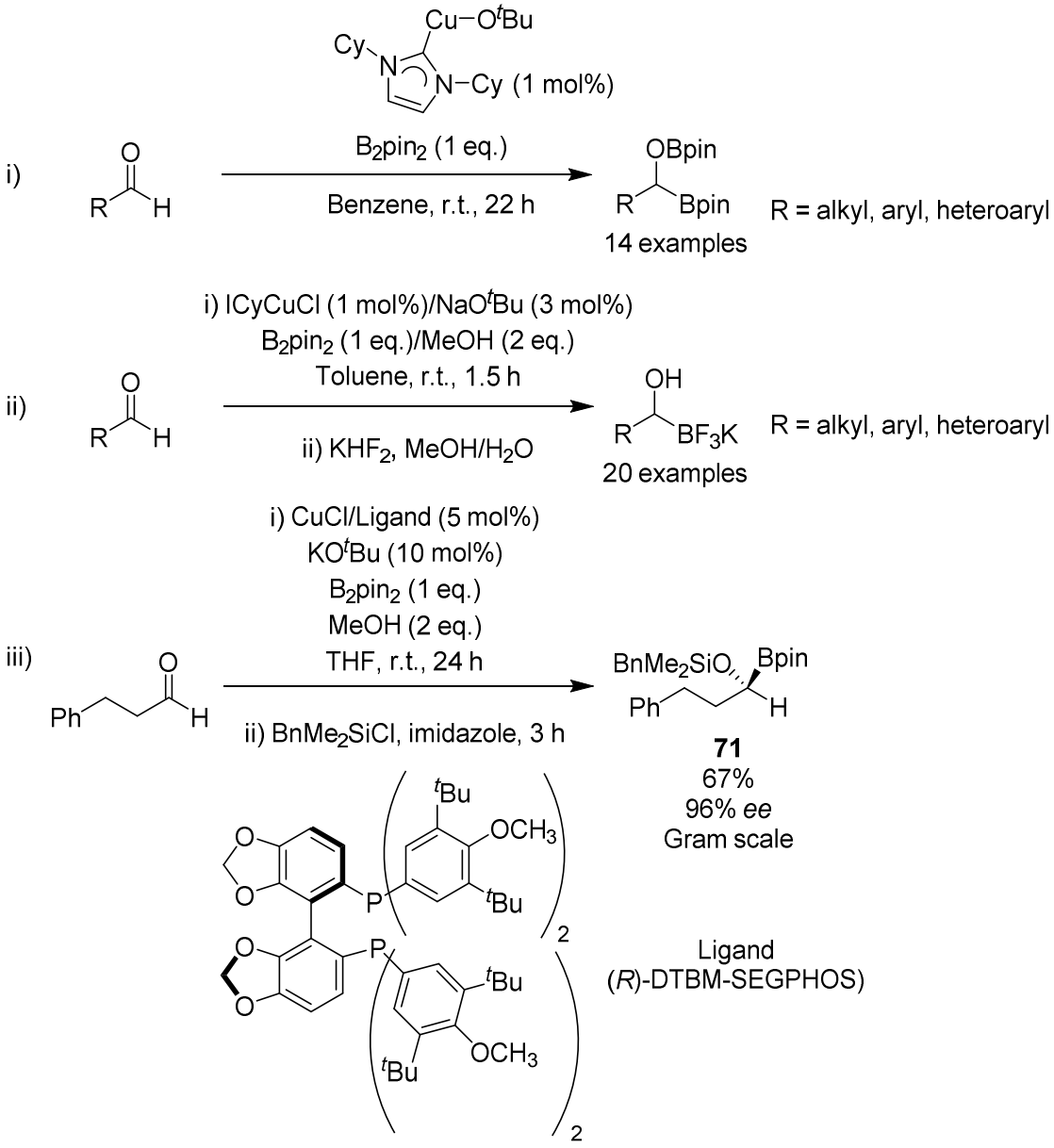


Figure 20: Borylation of aldehydes

Imines can also undergo 1,2-addition, generating α-boryl amines. The asymmetric boration of *N*-*tert*butylsulfinyl aldimines (72) was reported in 2008, whereby a copper/NHC catalyst gave the chiral amine products (73) in >98:2 *dr*.[117] Chirality arose from induction by the *tert*-butyl group in the starting material (Figure 21, i)). In the presence of a chiral sulfoxide based ligand (74), *N*-Boc protected imines (75) also underwent this process.[118] Both enantiomers could be accessed with the same chiral ligand, depending on whether an anionic counter ion (BARF, 76) was added (Figure 21, ii)).

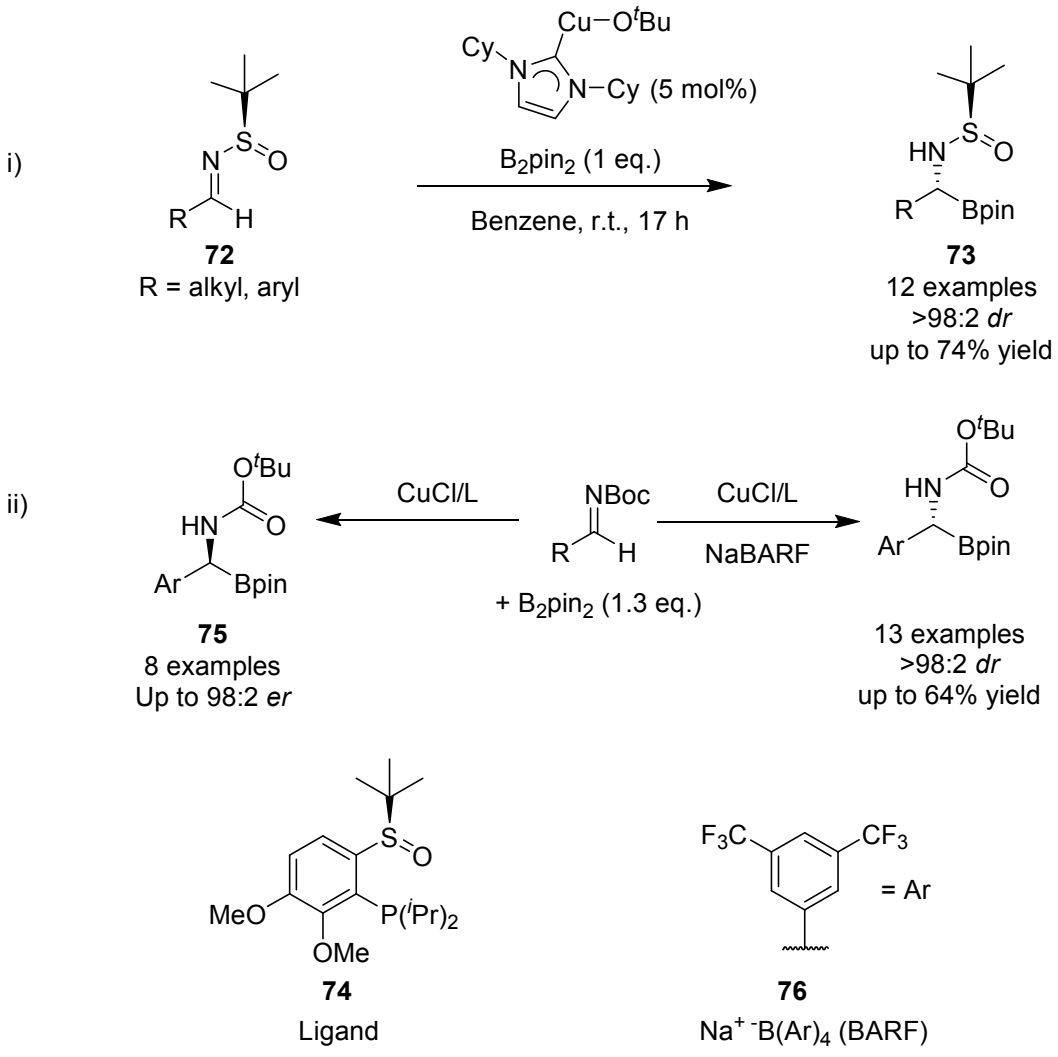


Figure 21: Chiral 1,2-borylation of imines

1.6 Copper catalysed C-X borylation

Building on the analogous palladium catalysed Miyaura borylation[119] and their copper mediated coupling of aryl halides with azides/sulfonates,[120, 121] a study by Zhu and Ma in 2005 found that aryl iodides could be borylated by HBpin (pinacolborane, 1) in the presence of copper iodide and sodium hydride (Figure 22, i)).[122] Subsequently Marder & Lin described the synthesis of aryl boronates *via* the copper catalysed borylation of aryl halides (I/Br) and B_2pin_2 (4, Figure 22, ii)).[18] Recent developments have enabled borylation in shorter reaction times (with bicyclic NHC ligands)[123] and the use of copper nanoparticles as a catalyst.[124]

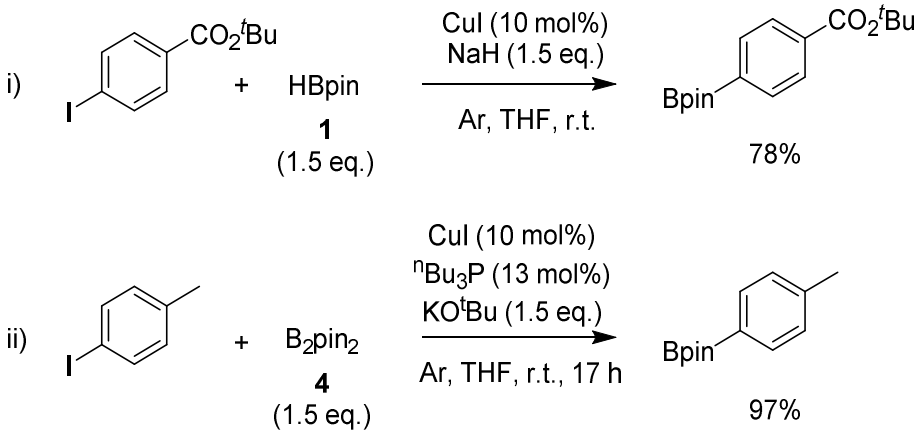
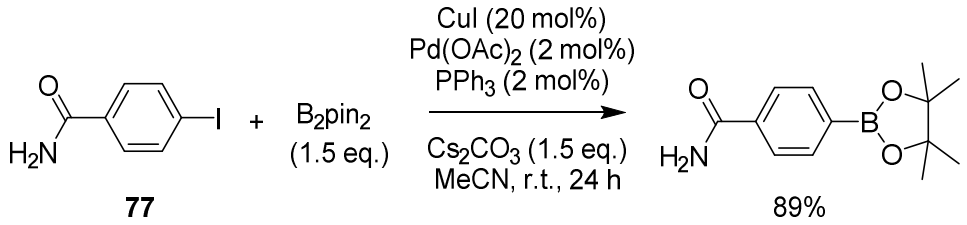


Figure 22: Aryl halide borylation conditions

Marder & Lin proposed that the reaction occurred *via* oxidative addition of the aryl halide to a Cu-Bpin complex. Reductive elimination of the aryl-Bpin moiety then generates the product, with the active copper-boryl species being regenerated *via* halide ligand exchange to give a copper-alkoxide species, followed by substitution with B_2pin_2 (*c.f.* Figure 4). Building on these earlier reports, Ratniyom *et al.* used a Pd/Cu catalytic system to permit the borylation of aryl/heteroaryl iodides open to

the air (Scheme 12).[125] Phenols, esters, ketones and amides (77) were all tolerated under the reaction conditions.



Scheme 12: Borylation under open atmospheric conditions

In a similar fashion, alkyl halides can undergo borylation. First reported in 2012 by Liu, Marder and Steel, mediated by a CuI/PPh_3 catalytic system (Figure 23),[27] and concurrently by Ito with a CuCl/Xantphos catalytic system and similar substrate scope.[23] Other diboron reagents have since been used for this process.[126] The observation that cyclic products formed from a hexenyl bromide substrate in both processes led to the proposition that the mechanism was radical mediated. Counter to this, the addition of radical scavengers had no adverse effect on the outcome of the CuI/PPh_3 mediated reaction.

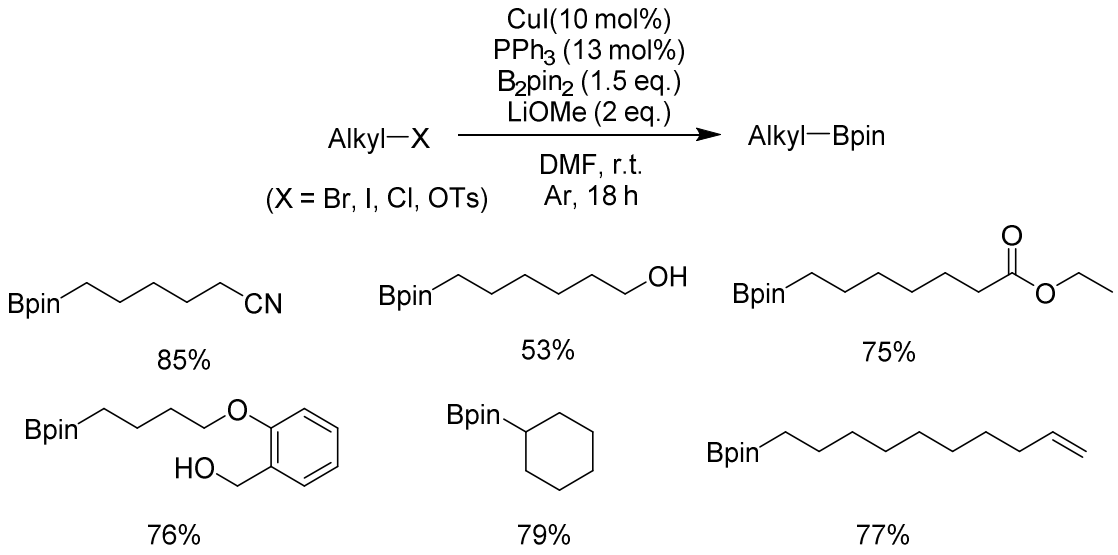


Figure 23: Copper catalysed borylation of alkyl halides

An alternative elimination/hydroboration pathway (Figure 24) could be discounted as base promoted elimination from halide 78 did not occur in the presence of the diboron reagent; furthermore the corresponding alkene (79) did not form hydroborated product 80 under the reaction conditions.

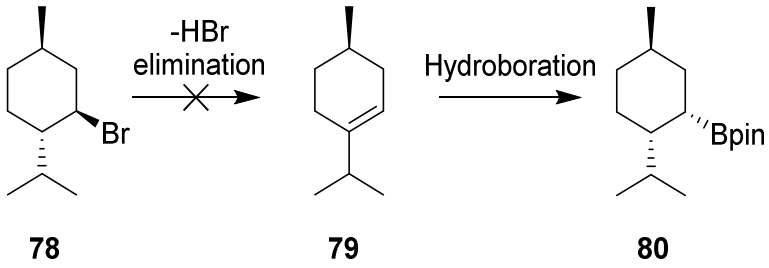


Figure 24: A discounted reaction pathway

Very recently, the analogous Cu(II) catalysed borylation of alkyl halides was reported, enabling alkyl chlorides (81) to be used (Figure 25).[127] Furthermore, the reaction could be carried out open to the atmosphere.

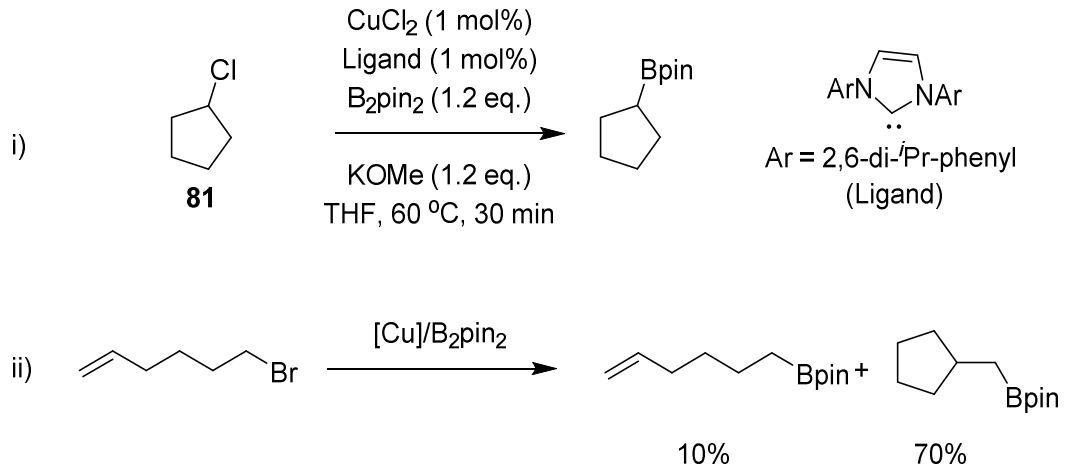


Figure 25: Copper(II) catalysed borylation of alkyl halides

As discussed above (section 1.4.3), with certain alkene substrates cyclisation can compete with direct substitution. Different mechanisms have been proposed, depending on the catalyst/ligand combination. With the CuI/PPh_3 system, a radical generated from the copper catalyst results in cyclisation.[32] Conversely, with the CuCl/Xantphos conditions a metallocycle is invoked as the key intermediate (82). Following addition of a copper-boryl species across the double bond, reaction with a further equivalent of the *tert*-butoxide base then generates an anionic complex (83), with cyclisation upon reductive elimination forming the observed product (49). Larger chain lengths (>7) would be disfavoured in the formation of the metallocycle, accounting for the lack of product formation with these substrates.

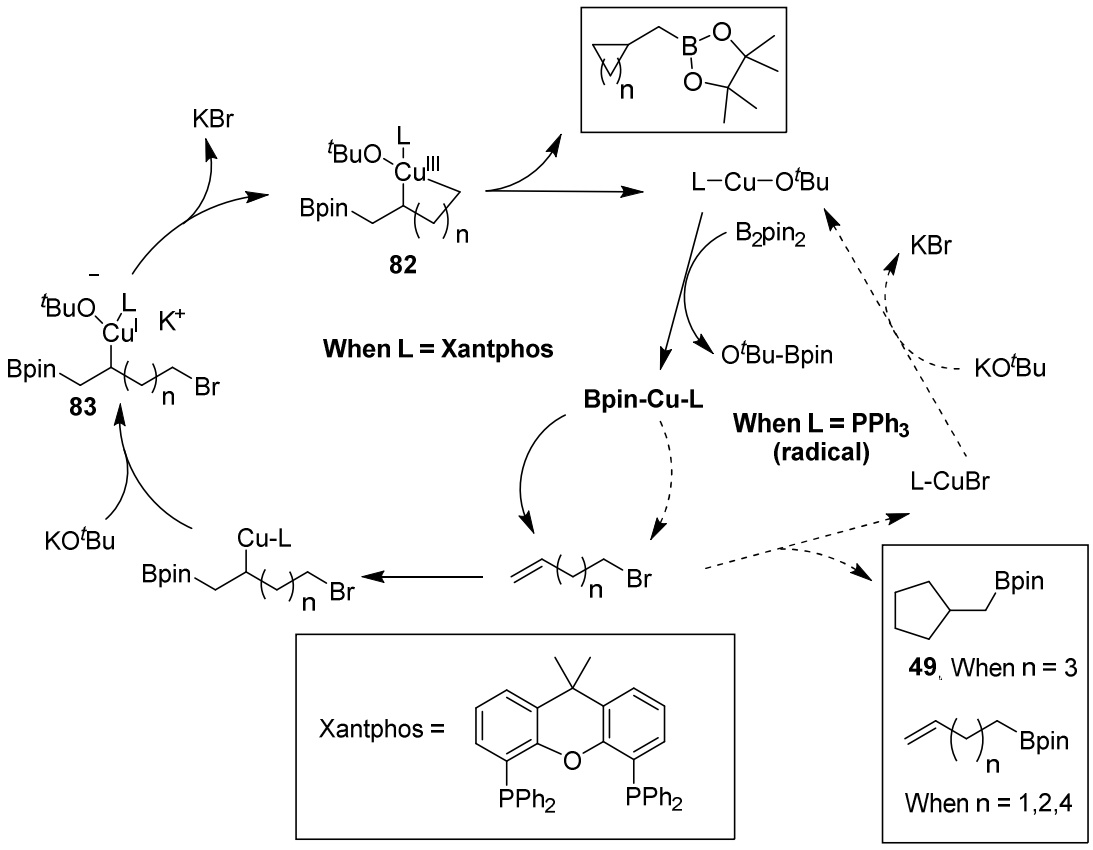
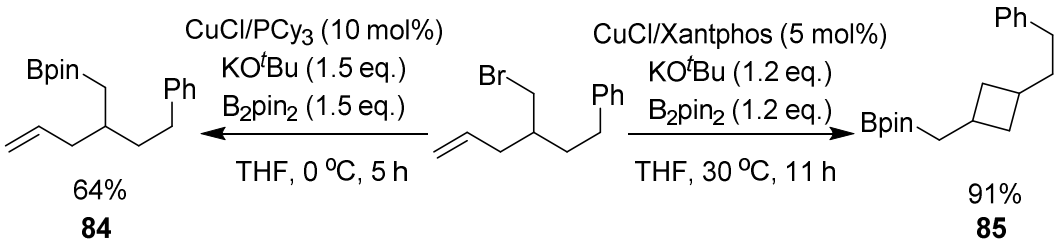


Figure 26: Catalytic cycle for CuCl/Xantphos mediated C-X borylation/cyclisation

Selectivity between cyclisation and direct substitution has since been described.[128] By varying the ligand and the temperature of the reaction, it is possible to obtain the linear alkene containing Bpin product (84) or the corresponding cyclic product (85) in up to >95:5 ratios of the major:minor components (Scheme 13).

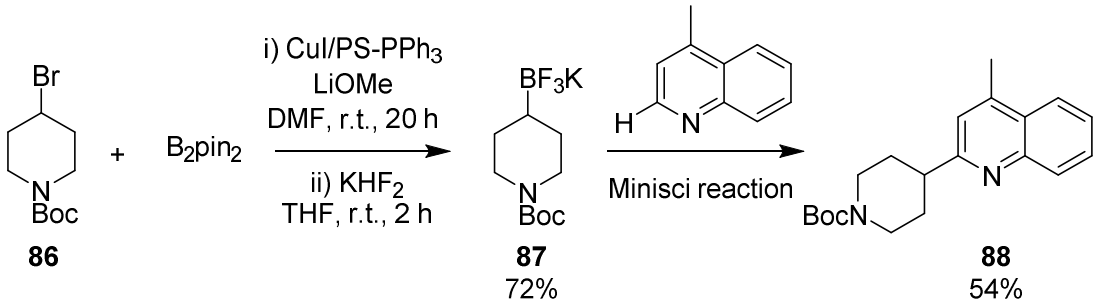


Scheme 13: Site selective borylation by choice of ligand

1.6.1 Borylation of alkyl halides mediated by other copper species

The aforementioned copper catalysed transformations have been proposed to occur *via* Cu(I) catalyst/ligand complexes, however there are several reports of borylation reactions where the active species are copper nanoparticles.[129, 130] These reactions bear similarities to the reactions and outcomes of copper (I) mediated transformations. Such observations raise questions as to the nature of the active catalyst in these copper (I) mediated processes – indeed in their work Steel & Marder speculated that nanoparticles may be responsible for catalytic activity.[27]

Finally, these S_N2 substitution processes have been used as part of more elaborate synthetic strategies. Borylation of heterocyclic alkyl halides (86, Scheme 14), followed by conversion to the more stable potassium trifluoroborate salts (87) was used to generate a number of heterocycles (88) *via* a subsequent Minisci reaction.[131]



Scheme 14: Borylation of heteroaromatic halides and subsequent Minisci reaction

As a result of the of the metal's ability to interact with double bonds, substrates bearing an allylic leaving group can undergo substitution *via* both S_N2 and S_N2' type mechanisms. The first example of a copper-boryl mediated S_N2' reaction was reported by Ramachandran and co-workers, who generated allylboronates (88)

from allylic acetates (89) using a stoichiometric CuCl/KOAc/B_2pin_2 mixture.[132] This strategy has since been expanded (primarily by the Ito group) to include a variety of nucleofuges (carbonates (90-92),[133] phosphates (93),[134] ethers (94)[135, 136], acetals (95)[137] and unsaturated moieties (alkenes,[138] alkynes)[139] and allenes,[140, 141] which can be obtained enantioselectively (Figure 27). The reaction can also lead to the linear or cyclic product. Though it is unclear what factors determine this, the ligand may play a role as with the direct substitution of alkenyl halides.[128]

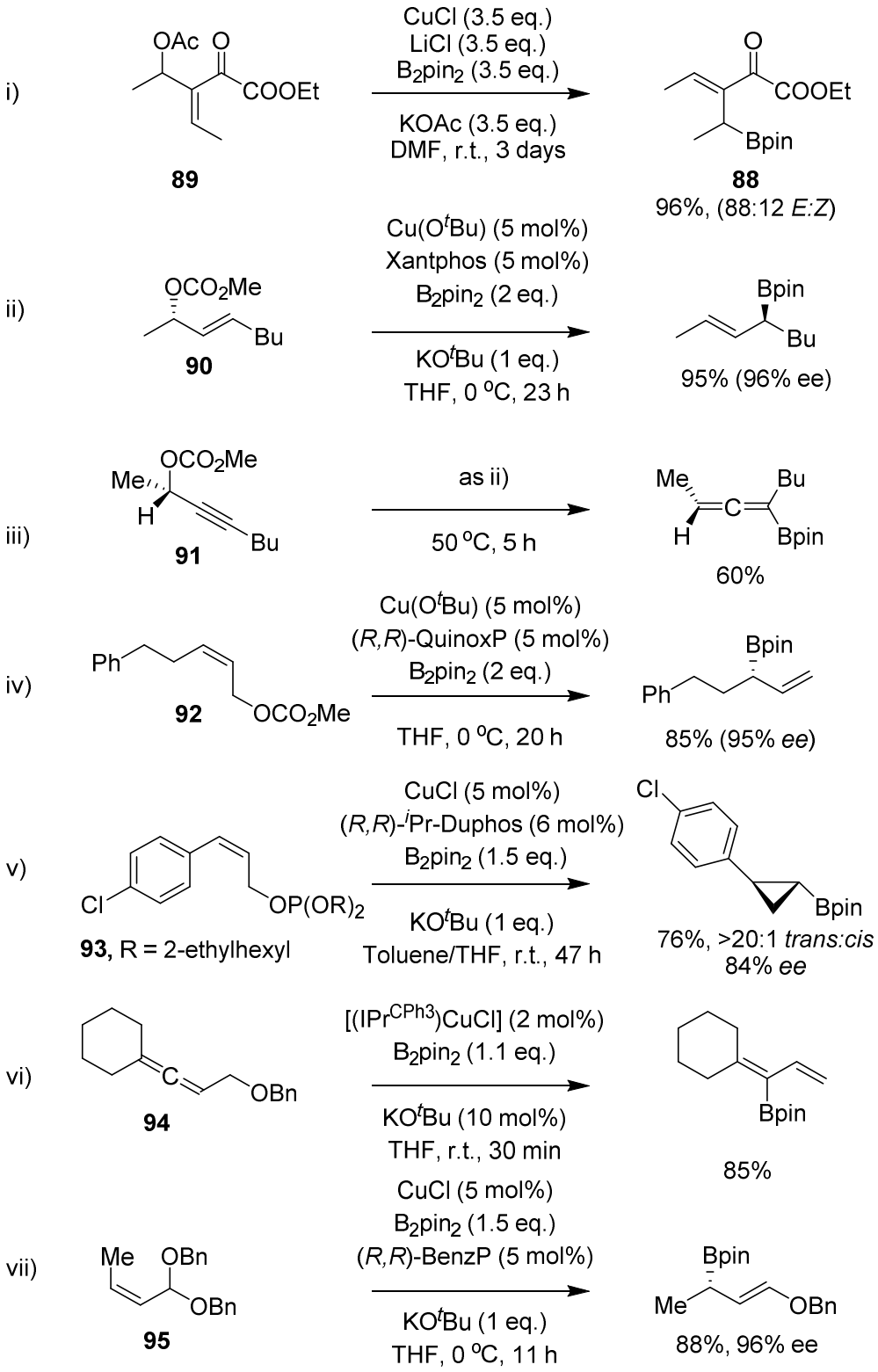


Figure 27: Examples of S_N2' borylative substitution with different leaving groups

1.7 The future of copper-boryl mediated transformations

Thanks to intensive research efforts, copper has been shown to be a viable and more economical alternative to reactions which could previously only be catalysed by precious metal catalysts or under harsh conditions. From the initial reports of enone borylation, a vast number of substrate classes have now been shown to react with copper-boryl complexes including alkenes, alkynes, allenes, carbonyl derivatives and aryl/alkyl halides. Many of these methods have been developed into enantioselective borylation reactions. Given the rapid expansion of the field, it is likely that further exciting discoveries (e.g. copper catalysed C-H borylation) are imminent.

1.8 Previous work within the group and aims of the project

As outlined in section 1.6 and prior to commencement of this project, work undertaken within the group had demonstrated that copper (I) based catalysts could mediate the borylation of alkyl halides under mild conditions.[27] Primary and secondary iodides, bromides, tosylates and chlorides were suitable substrates for the reaction, and a number of functional groups were tolerated (Figure 28).

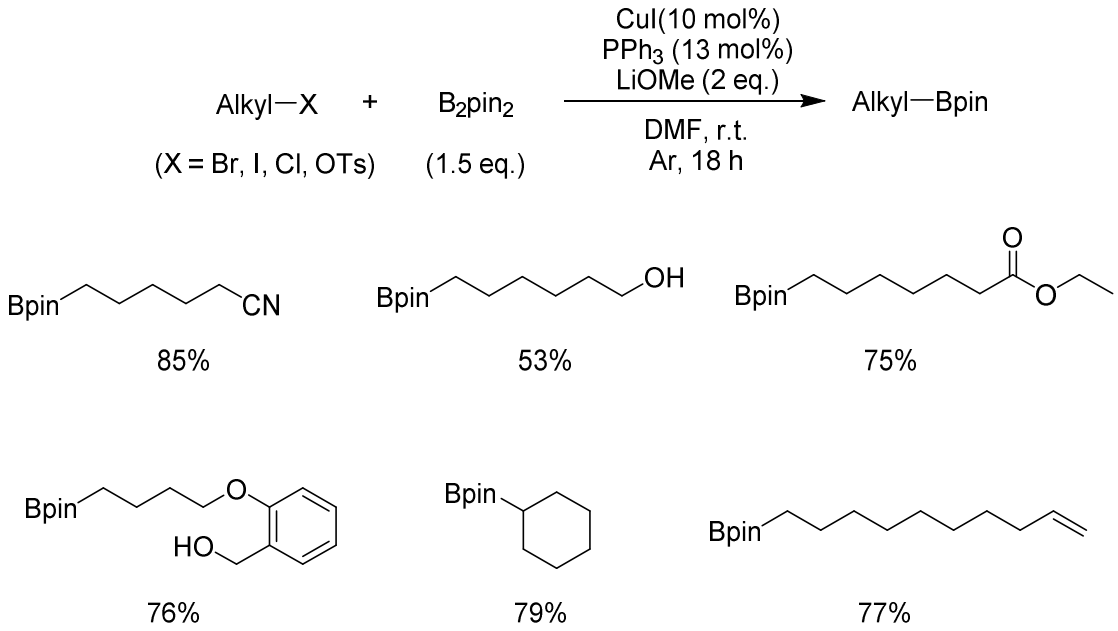


Figure 28: functional groups tolerated by the reaction

A notable result was that the borylation of 6-bromo-1-hexene (48) resulted in a cyclopentylmethyl boronate ester product (49) as opposed to the expected linear alkene containing product (50, Figure 29, i)). This cyclisation reaction led to the hypothesis of a radical mediated reaction. Furthermore, experiments with enantiopure starting materials (96) resulted in racemic mixtures (Figure 29, ii)). Counter to these observations, the borylation was uninhibited by the presence of radical scavengers such as 1,4-cyclohexadiene (97, Figure 29, iii)).[142] The preliminary aim of the project was therefore to gain a better understanding of this mechanism.

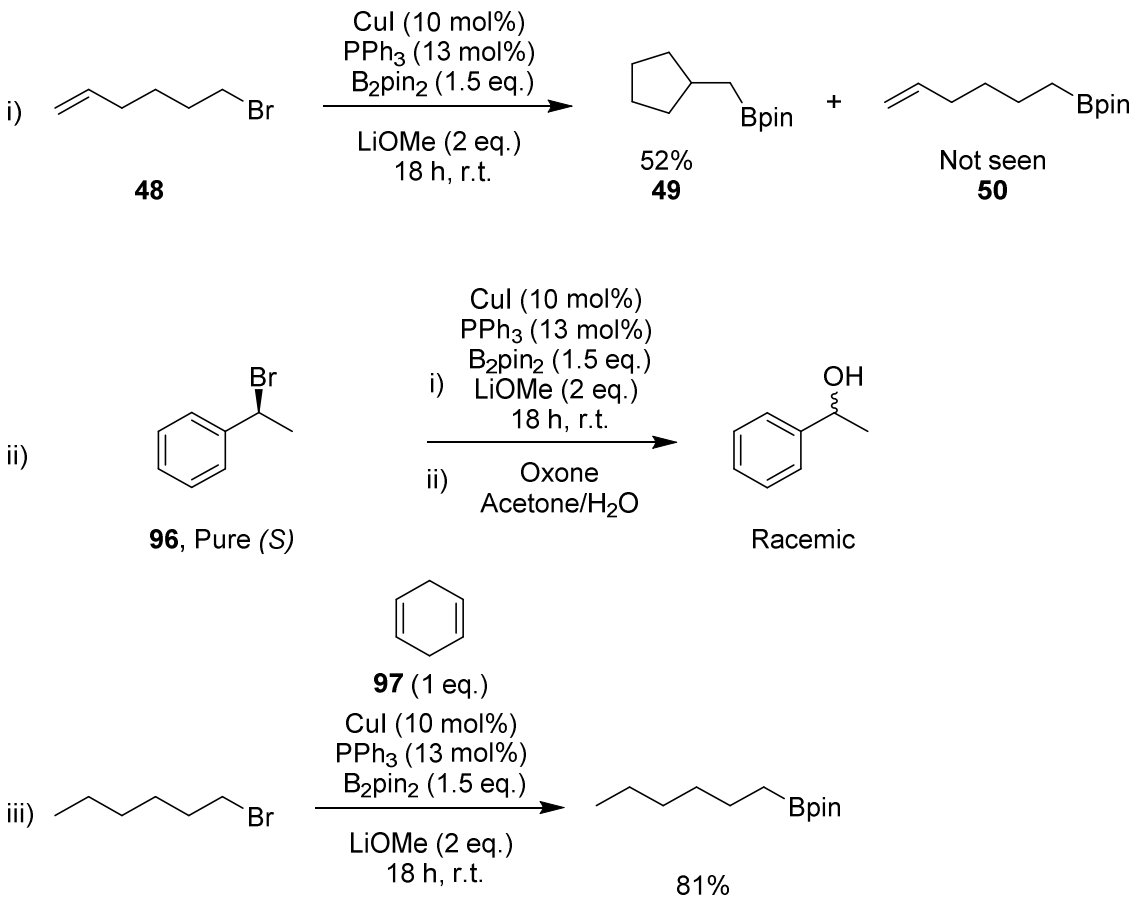


Figure 29: Conflicting evidence of a radical mediated mechanism

Application of the CuI/PPh_3 mediated conditions towards the cyclisation of substituted hexenyl systems was another area of investigation (Figure 30, i)), as the cyclisation had only been reported with a simple hexenyl halide precursor. Finally, as shall be outlined in the following chapter, atom transfer radical cyclisations (ATRCs) have been widely used in the synthesis of heterocyclic systems. Copper has been used as a catalyst for a number of these reactions and it was therefore hypothesised that the borylative cyclisation could be used to synthesise of non-aromatic borylated heterocycles (Figure 30, ii).

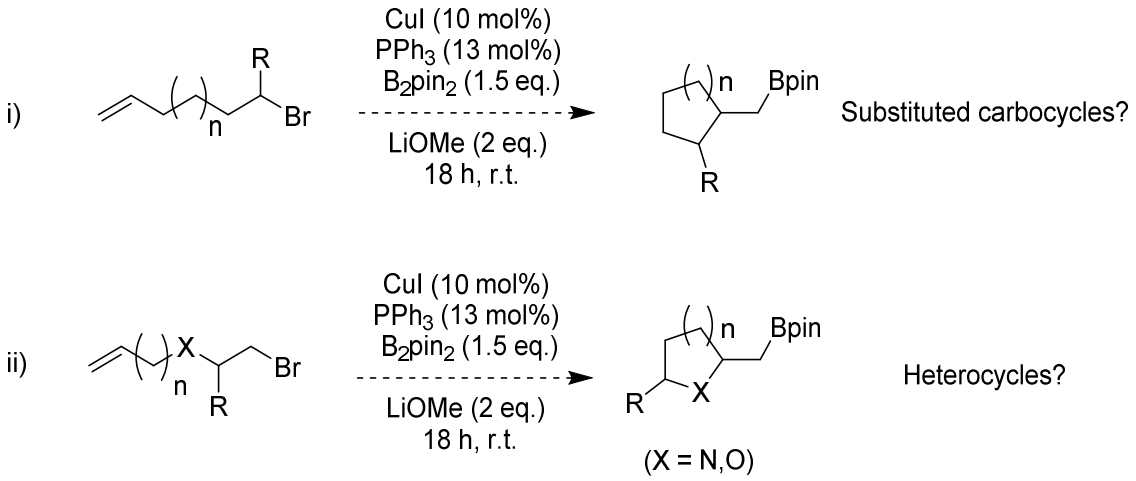


Figure 30: Summary of project aims

2 Carbocyclic and heterocyclic systems

2.1 Introduction

As outlined in section 1.8, a key finding of the work into the copper catalysed borylation of alkyl halides by Tajuddin, Steel and Marder was that 6-bromo-1-hexene (48) gave the cyclisation product (49), rather than linear substitution product (50, Figure 31).[27]

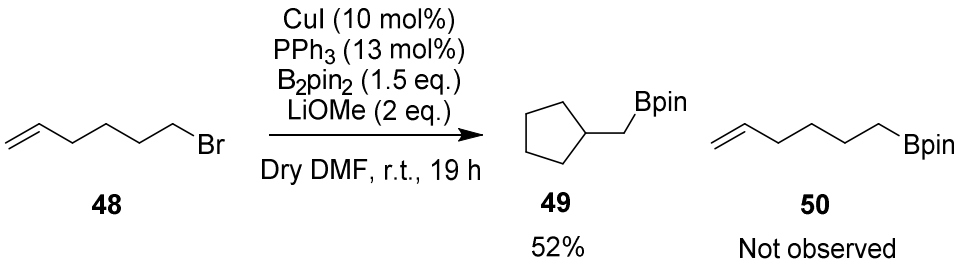
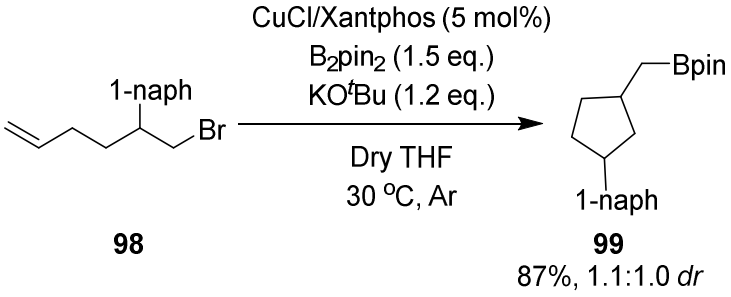


Figure 31: Borylative cyclisation of 6-bromo-1-hexene

Concurrently with these studies, Ito and co-workers described the related *exo*-cyclisation of alkenyl halides.[32] These findings included the cyclisation of a substituted alkene chain precursor (98, Scheme 15), which yielded a diastereomeric mixture of the cyclic product (99).



Scheme 15: Cyclisation of a naphthyl substituted hexenyl bromide reported by Ito[32]

The stereochemical outcomes of related radical cyclisation reactions have been well studied by Beckwith and others,[143-145] with the cyclisations of 2-substituted radical systems giving predominantly the *trans* isomer. This was accounted for by conformational effects in a chair-like transition state, in which conformations placing the substituents in the pseudo-equatorial positions are favoured (Figure 32).[143]

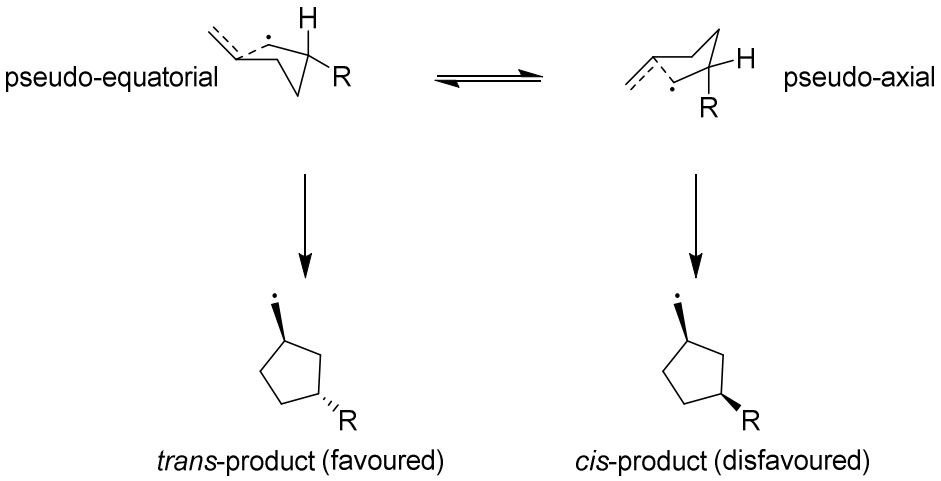


Figure 32: Transition state conformations for substituted systems[143]

The even mixture of *cis/trans* products resulting from the cyclisation reported by Ito suggested that the process was not mediated by radicals. Further studies led to the mechanistic hypothesis previously outlined in section 1.6 (Figure 26), with an ionic metallocycle being invoked as a key intermediate.[32] The authors proposed that larger chain lengths (i.e. heptenyl species) would be disfavoured in the formation of the metallocycle, accounting for the lack of product formation with these chain lengths.

In the case of Marder & Steel's CuI/PPh_3 mediated conditions, it was proposed that the copper-boryl species undergoes a substitution reaction with the bromide. Single electron transfer from the copper would generate a radical, which would then undergo rapid cyclisation. Metathesis with the copper-halide would then regenerate the copper-alkoxide catalyst.[32] If alkyl bromides with chain lengths of 5 and 7 are used then presumably radical cyclisation is less favourable and instead direct substitution occurs to give a linear alkene containing product.

Both of these methods were applied to relatively simple systems, with only one example of a substituted alkene being reported by Ito. The aim of this part of the project was therefore to expand the scope of the methodology (primarily the CuI/PPh_3 catalysed process) towards the cyclisation of substituted hexenyl halides. Doing so would also allow for mechanistic insights into the reaction, as similar stereoselectivity to the radical cyclisations in Figure 32 would give further support to a radical mediated hypothesis.

In tandem with the aforementioned investigations into carbocycles, heterocyclic substrates were also examined during this project. Heterocycles are important structural motifs, found in many pharmaceutical and agrochemical compounds for their physicochemical properties (Figure 33).[146]

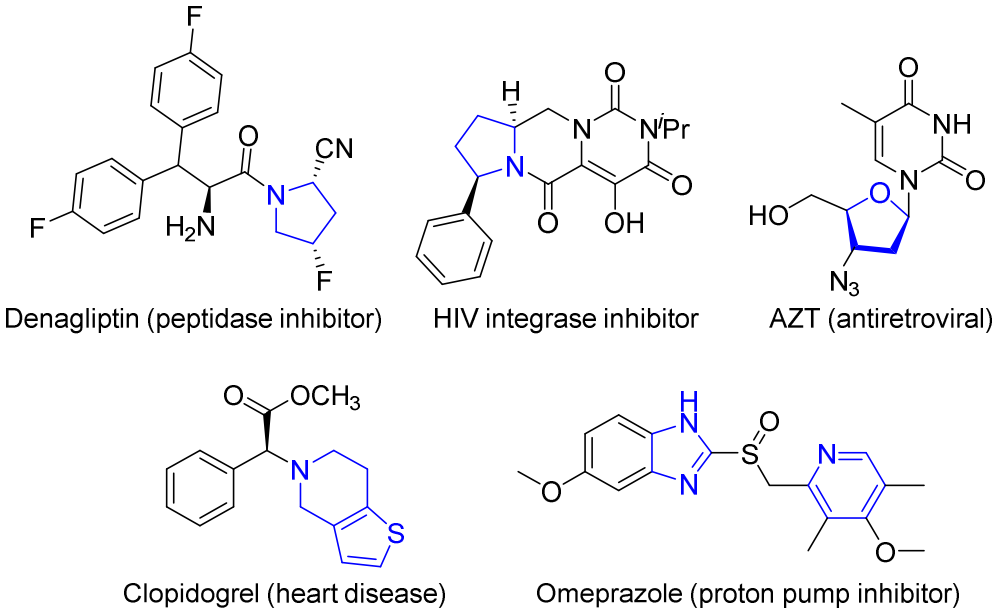


Figure 33: Structures of some heterocycle containing pharmaceuticals

The cyclisation of heteroatom substituted hexenyl radicals has long been established as a means of preparing heterocycles[147, 148] and even today, radical cyclisation remains an effective tool in the synthesis of natural products.[149, 150] Aza- and oxa-hexenyl radicals give predominantly *exo*-products and undergo cyclisation faster than their carbon analogues due to the shorter length of the carbon-heteroatom bond.[143] More recently, copper catalysed atom transfer radical cyclisations (ATRCs) have been developed to prepare a wide range of functionalised hetereocycles.[151-153]

The additional aim of this part of the project therefore was to examine whether trapping of these heterocyclic radicals with a Bpin moiety could be achieved.

2.2 Preliminary results

Given the differences between the Marder/Steel[27] and Ito procedures,[32] verification of these results was an initial objective. A series of simple haloalkenes of varying

chain lengths was subjected to the two different sets of conditions and the relative ratios of the cyclic:linear products were determined.

Initially, the reaction of 6-bromo-1-hexene (48) was undertaken, following the Marder/Steel protocol.[27] 6-bromo-1-hexene was added to a solution of 10 mol% CuI, 13 mol% PPh_3, B_2pin_2 and LiOMe in anhydrous DMF. The reaction turned from yellow in colour to dark blue/purple, indicating that the borylation was proceeding. Purification by column chromatography and subsequent NMR/GC-MS analysis of the fractions indicated that two components had coeluted. Both displayed strong *m/z* peaks of $[M-15]^+$, characteristic of the loss of a methyl group from a Bpin moiety. A peak at 33 ppm in the ^{11}B NMR was indicative of an R-$B(OR)_2$ group.

Analysis of the ^1H NMR spectrum of this fraction also showed two components. The appearance of a ^1H multiplet at δ = 1.95 ppm, corresponding to the proton adjacent to the substitution position on the cyclopentyl ring, confirmed formation of a cyclic product whilst the presence of a linear product was confirmed by multiplet peaks at δ = 5.9 and δ = 5.0 ppm, consistent with a terminal alkene. The integral ratio of the ^1H peak of the linear product at δ = 5.9 ppm relative to the cyclopentyl Bpin product's ^1H signal at δ = 1.95 ppm was approximately 1:7.

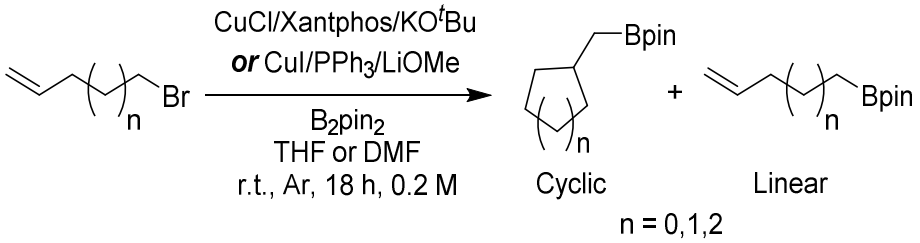
Since the presence of additional alkyl signals complicated ^1H NMR analysis, the mixtures were oxidised. This was achieved by adding oxone (potassium persulfate) to a stirred solution of the Bpin ester in acetone. As a result of oxidation, signals for the α-Bpin methylene group were shifted from δ = 0.84 ppm to δ = 3.51 ppm, as would be expected for carbinol protons. The observed NMR ratio of the cyclic:

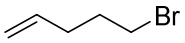
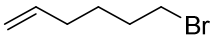
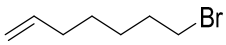
linear product was altered slightly following oxidation, and was most likely due to losses from handling/isolation of the alcohols.

Subsequently, when 6-bromo-1-hexene (48) was subjected to Ito's conditions[32] the cyclic product (49) was formed with only trace amounts of the linear analogue (50, Table 2, row 4). In the absence of a ligand (no PPh_3 or Xantphos), the ratio of cyclic:linear product was 4:1 (3:1 following oxidation; Table 2, row 5).

Having established a standard comparison method, both 5-bromo-1-pentene (100) and 7-bromo-1-hexene (101) were subjected to these reaction conditions. Under Marder & Steel's conditions, 5-bromo-1-pentene gave a single linearly borylated product (100l), as indicated by terminal alkene signals at δ = 5.7 and δ = 4.9 ppm, whilst with Ito's Xantphos protocol only the cyclic product was observed (100c). With 7-bromo-1-heptene (rows 6 & 7), use of Xantphos gave a messy and intractable reaction mixture however under CuI/PPh_3 conditions the linear alkene product (101l) was observed as the major product with only minor quantities of the corresponding cyclic product (101c).

Table 2: Preliminary borylation studies



Substrate	Ligand	Cyclised:Linear	Ratio after ox.[c]	Borylation yield (%)
 **100**	PPh_3	5:95	1:30	91
	Xantphos	>99:1[b]	>99:1	88
 **48**	PPh_3	7:1	8:1	87
	Xantphos	>99:1[b]	-	86
	No ligand	4:1	3:1	n.d.
 **101**	PPh_3	1:6	1:6	38[a]
	Xantphos	Complex mix.	-	-

a) Decreased yield may result from losses during handling,b) literature ratio from Ito et al.[32]; n.d = not determined, c) oxidation was carried out with oxone in 1:1 acetone:H_2O

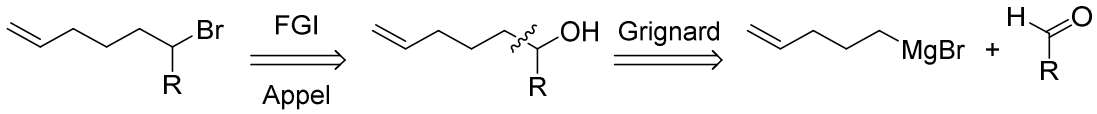
From these results it can be seen that the CuCl/Xantphos conditions favour cyclisation with ring sizes of 4 and 5 being formed, however under Marder & Steel's CuI/PPh_3 conditions, only ring sizes of 5 are formed from the 6-carbon starting material - direct substitution of the halide by Bpin occurring in other cases. These results confirm that two different mechanisms are indeed at play.

2.3 The synthesis of carbocyclic precursors

Following this initial investigation into the two catalytic systems and confirmation of their differing outcomes, attention turned towards the formation of substituted carbocyclic boronate esters.

2.3.1 Hexenyl bromide synthesis

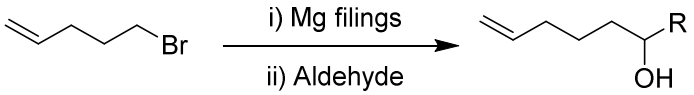
An initial requirement was to develop a simple synthesis towards α-substituted hexenyl halides, as these compounds and their derivatives were not commercially available (Scheme 16).



Scheme 16: Planned route towards α-substituted bromohexenes

2-Bromophenyl-6-hexene was selected as the initial target as this substrate provided a chromophore, aiding identification during chromatography. Following this strategy, generation of the Grignard reagent from 5-bromo-1-pentene and subsequent reaction with benzaldehyde afforded the alcohol in a moderate yield of 54% (Table 3), as confirmed by the appearance of a broad peak (OH) at 3300 cm^{-1} in the IR spectrum of this material.

Table 3: Grignard reaction yields



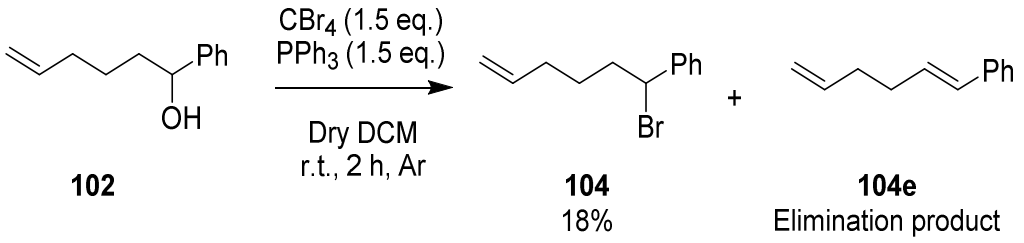
R = (**#**)	Yield (%)	**#**
Ph	54	**102**
^{i}Pr	41	**103**
CH_2Ph	43	**104**
CH_2CH_2Ph	14	**105**

Conditions: i) 5-bromo-1-pentene (1 eq.), Mg filings (1.2 eq.) in dry THF (0.6 M); ii) Aldehyde (1 eq.) dry THF (0.6 M)

To form the alkyl bromide, an Appel reaction was used. Upon addition of CBr_4 to a solution of the alcohol and triphenylphosphine in dry DCM, the reaction mixture turned a bright yellow colour which gradually faded. Following work up and

purification the desired bromide, evidenced by a doublet molecular ion (*m/z* = 238 ($[M^{79}Br]^+$) and 240 ($[M^{81}Br]^+$)) in the GC-MS spectrum, the bromide of the alcohol (102) was obtained in a low yield of 18%.

Further analysis of the crude reaction mixture indicated that elimination of HBr had occurred as a side reaction, giving an elimination product (104e) in addition to the desired bromide (104). No bromine doublet was observed in the mass spectrum of this material, whilst two additional ^{1}H alkene multiplets at δ = 6.45 and 6.25 ppm (multiplet) in the ^{1}H NMR spectrum, characteristic of an internal alkene (Scheme 17) were present. Alternative approaches to form the halide with phosphorus tribromide or to generate the corresponding tosylate were also unsuccessful, and the general lack of success in this area meant that a different target was pursued.



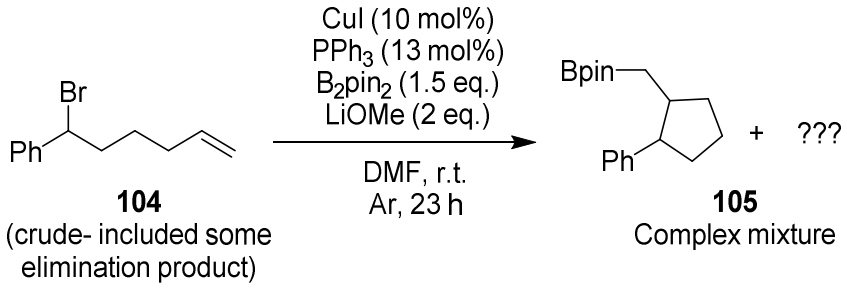
Scheme 17: Appel reaction, resulting in the desired product and an elimination product

2.3.2 Further carbocyclic precursor syntheses

It was hypothesised that the conjugated nature of the alkene was responsible for the elimination occurring so readily. Therefore, attempts were made to replace the phenyl group with a non-aromatic moiety. Although the corresponding alcohols could be prepared in moderate yields (Table 3) attempts to generate substrates with a suitable leaving group were equally inefficient. Despite these challenges, two

1-substituted hexenyl bromides were successfully synthesised and these were tested in the borylation/cyclisation reaction.

Borylation of this phenyl substituted bromide (104) gave a complex mixture by GC-MS (Scheme 18). Several of these peaks had a mass of 286, consistent with the expected product (105) and showing a fragment with *m/z* = 271, indicative of the loss of a methyl group from a Bpin moiety. Owing to the presence of alkenes in the elimination product (104e), it is likely that at least one of these peaks corresponded to a hydroboration product. The structures of the other components in this mixture could not be determined unambiguously.



Scheme 18: Borylation/cyclisation of a phenyl substituted hexenyl bromide

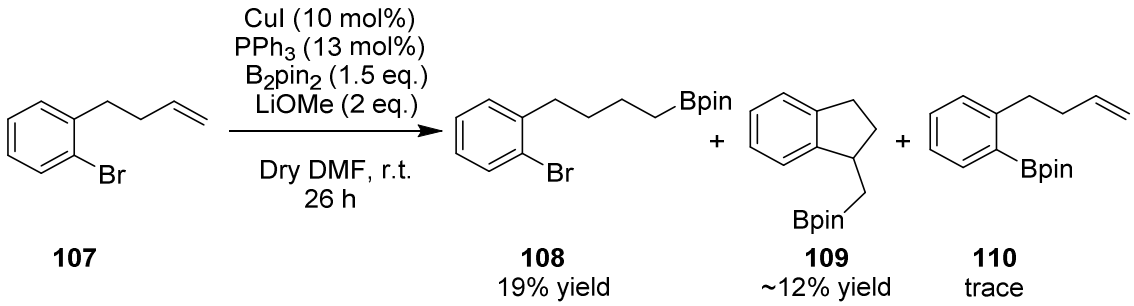
With the benzyl bromide derivative (106, R=CH_2Ph), results were equally poor. Despite full consumption of starting material, GC-MS analysis of the reaction mixture indicated that at least 4 components had the molecular weight of the desired product, with *m/z* = 300 and a fragment with *m/z* 285 (M-CH_3) being observed. The triphenylphosphine ligand coeluted with the mixture of products, hampering efforts towards their identification. Running the reaction at 60 ^{o}C did not show any improvement in product formation, nor did the use of polymer supported PPh_3.

2.3.3 Other carbocyclisations

With these poor results, other ways to improve the likelihood of cyclisation were sought. Preorganisation of the alkenyl chain was one possibility, and would aid cyclisation by bringing the two reactive centres (the alkene and the halide) components into closer proximity with each other. To test this theory, commercially available 4-(2-bromophenyl)-1-butene (107) was used as a substrate. Whilst the nature of the C-Br bond differs (an *aryl* as opposed to an *alkyl* C-Br bond), borylation of such species is possible under conditions similar to those for alkyl C-Br borylation, whereby a CuI/P^{n}Bu$_3$ catalyst combination with KO^{t}Bu as a base provides optimal borylation conditions.[18]

To allow a direct comparison of results with the other borylations, was subjected to the standard CuI/PPh$_3$/LiOMe borylation conditions. The mixture turned a dark purple upon addition of the bromide starting material, consistent with other borylation reactions. After 26 h, GC-MS analysis indicated that a complex mixture with at least 4 components had formed. Whilst significant starting material remained (~50% conversion), two new components, both with strong fragment ions of *m/z* = 258 consistent with the mass of the desired product, were observed.

Following chromatography, mixtures of products were obtained. One of the components, isolated in 19% yield (Scheme 19) with a molecular ion of 338/340 (Br doublet) was assigned as the hydroboration product (108) on the basis of NMR analysis, which showed a new 2H multiplet at δ = 2.74 ppm with the characteristic roofing effect often observed in benzylic signals (Figure 34).



Scheme 19: Formation of a benzofused cyclic Bpin ester

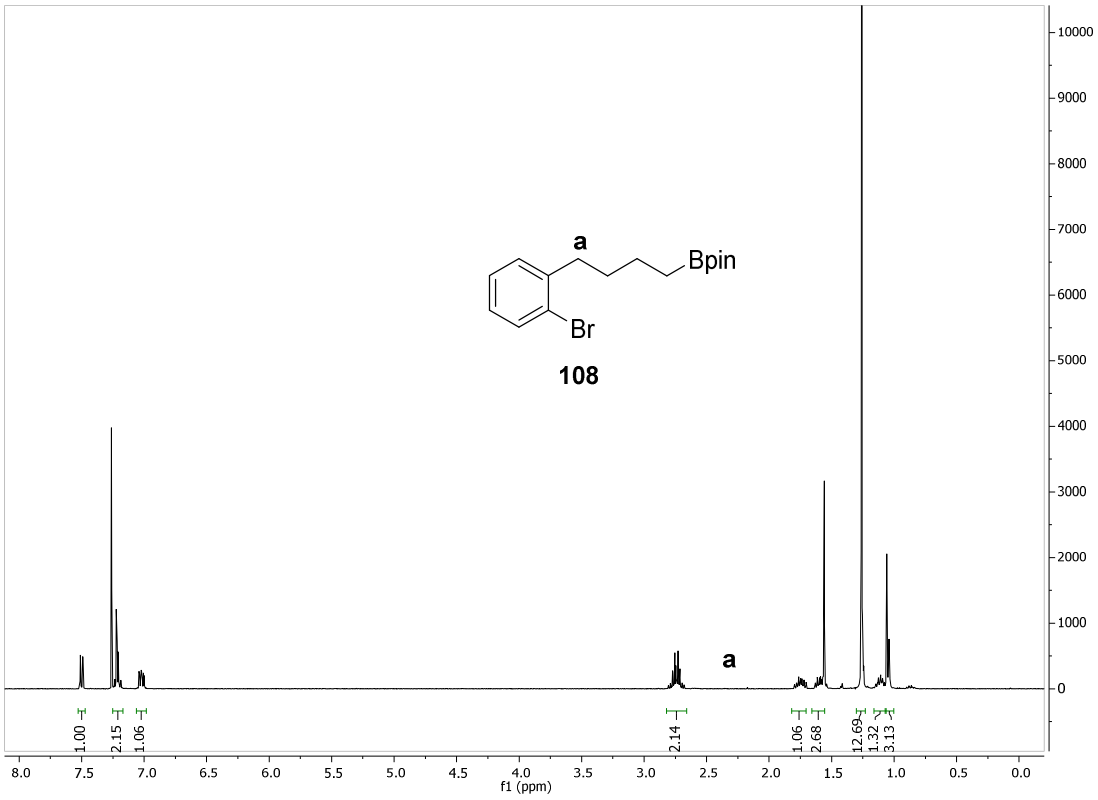


Figure 34: NMR spectrum of the hydroboration product

The other component, with *m/z* = 258 could not be isolated as a single pure compound, however a key diagnostic peak in the ^{1}H NMR spectrum was a multiplet at δ = 3.30 ppm, which corresponded to the shift predicted for the benzylic proton adjacent to the newly formed chiral centre of the cyclic product ((109), labelled b, Figure 35). Formation of this *exo* product is consistent with the expected result for a

radical cyclisation, with alkenylaryl radicals favouring this regiochemistry due to the low entropy change associated with pre-organisation.[144]

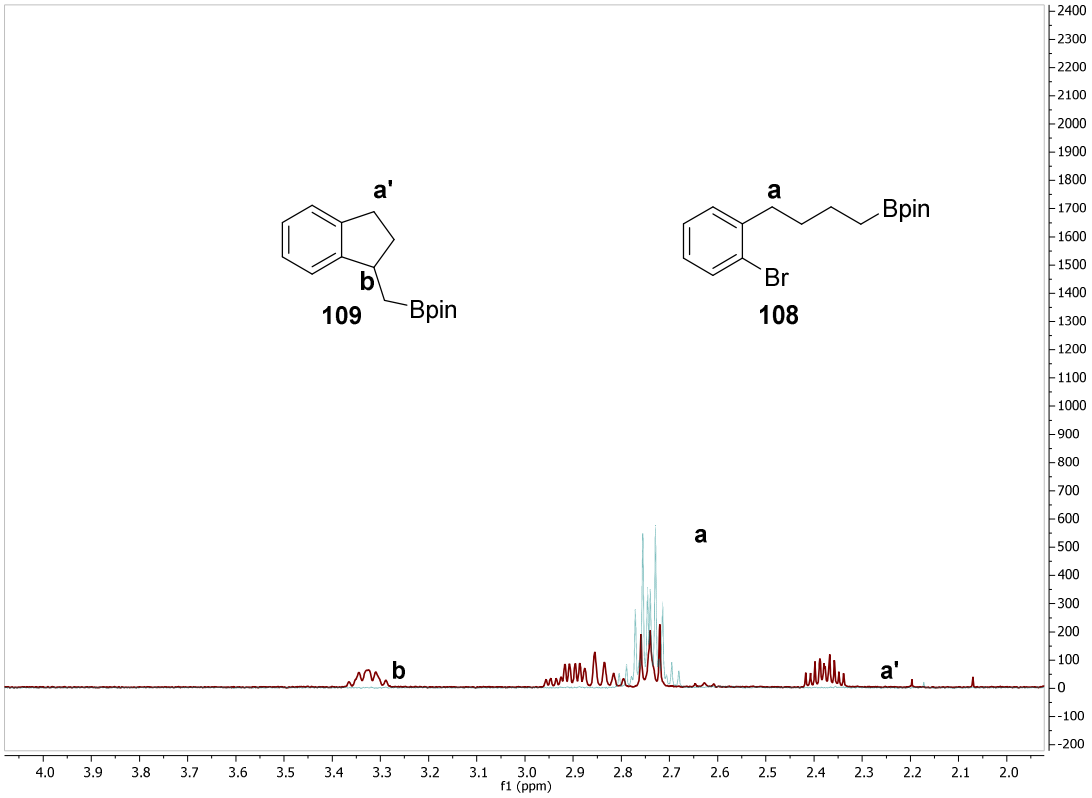
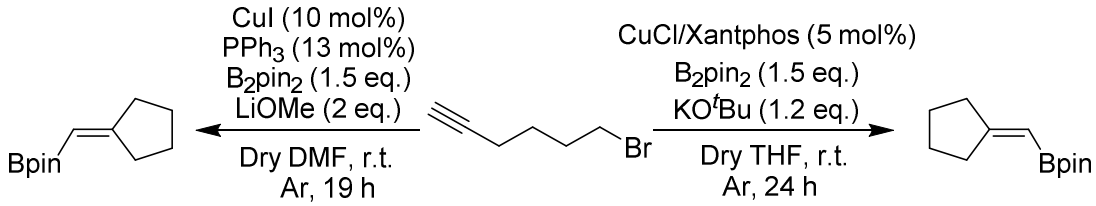


Figure 35: NMR spectrum of the hydroboration product (blue) superimposed on the spectrum of the mixture of cyclic and hydroboration product (red)

No discernible difference was observed under the Marder's conditions for aryl halide borylation (CuI/P^nBu_3/KO^tBu in THF). Interestingly, a Zn/NHC catalytic system has been shown to act on the same substrate to give the cyclic product (109, 21% yield) along with the halide substitution product (110, 37%).[154]

Cyclisation of the analogous alkyne, 6-bromohex-1-yne (51), was also explored. The substrate could be synthesised easily from the Appel reaction of 5-hexyn-1-ol, and was found to cyclise under both CuI/PPh_3 and CuCl/Xantphos conditions (Scheme 20). The appearance of a new alkene signal in the NMR spectrum of a peak at 5.27 ppm was diagnostic of the vinyl proton in (52). Whilst the yields were relatively low

(33% and 15% respectively), the reaction proved that substrates besides alkenes could undergo the cyclisation reaction. Encouragingly, no significant quantities of hydroboration side products could be detected, indicating that cyclisation was the prevalent pathway.



33% **52** **51** 15% **52**

Scheme 20: Borylative cyclisation of an alkyne

2.4 Heterocyclic substrates

Concurrently with the studies into carbocyclic systems, heterocyclic systems were investigated. The results of these experiments are discussed in the following sections.

2.4.1 N-Alkylation of a Boc protected amino acid

Aza-heterocycles were examined first. It was hypothesised that the cyclisation of a nitrogen containing hexenyl radical such as that generated from the bromide (111) would form pyrrolidinyl boronate esters (112, Figure 36) upon trapping with a Bpin moiety.

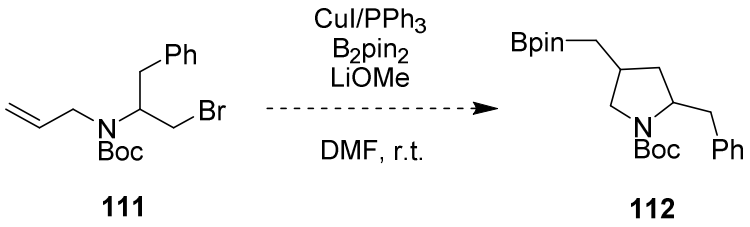


Figure 36: Planned cyclisation to form a pyrrolidinyl Bpin ester

Retrosynthetically, these precursors can be disconnected to the ester of an α-amino acid and commercially available Boc-phenylalanine methyl ester (113) was selected as the initial substrate (Figure 37).

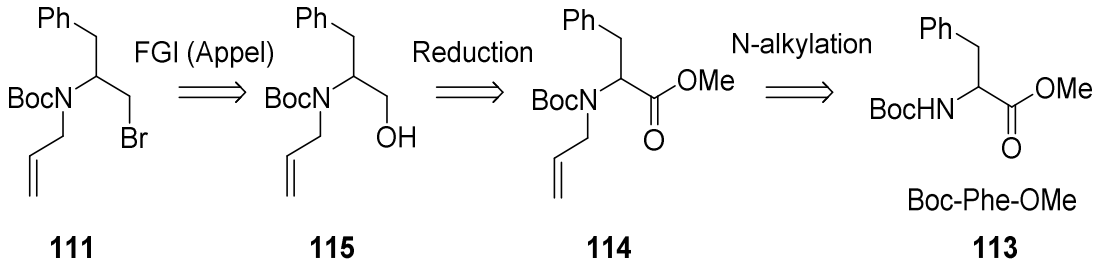
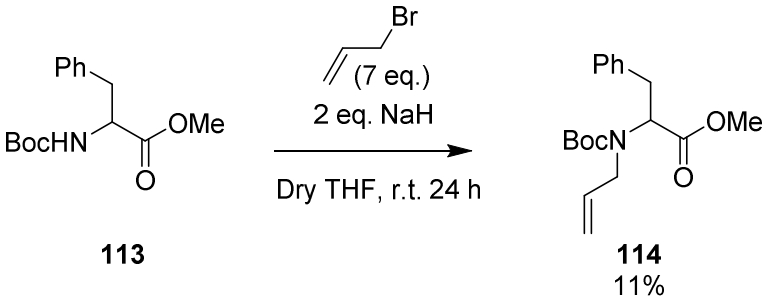


Figure 37: Retrosynthetic analysis of a pyrrolidine precursor

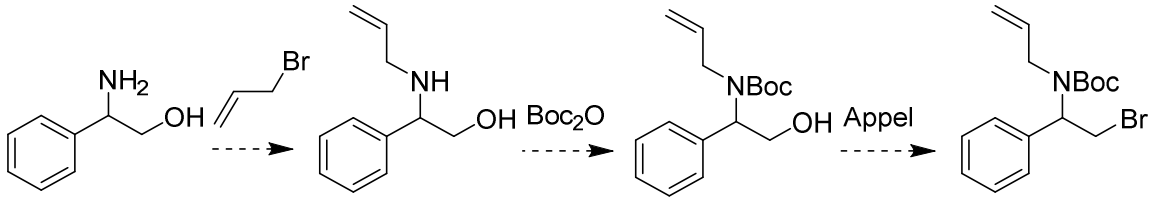
To minimise the possibility of nitrogen mustard formation and poisoning of the catalyst, it was decided that the nitrogen atom of the bromide (111) should be protected as a carbamate. This strategy however lowered the nucleophilicity of the nitrogen, making alkylation more difficult. Attempts to alkylate Boc protected phenylalanine methyl ester (113, Scheme 21) with allyl bromide according to literature procedure resulted in low conversion.[155] A number of reaction conditions were screened, such as the optimal base, solvent (DMF, THF) and temperature of the reaction, however the maximum isolated yield of the product was 11%. The quantity of the *N*-allyl product (114) was insufficient for further chemistry and therefore alternative targets were pursued.



113 **114** 11%

Scheme 21: N-Allylation conditions

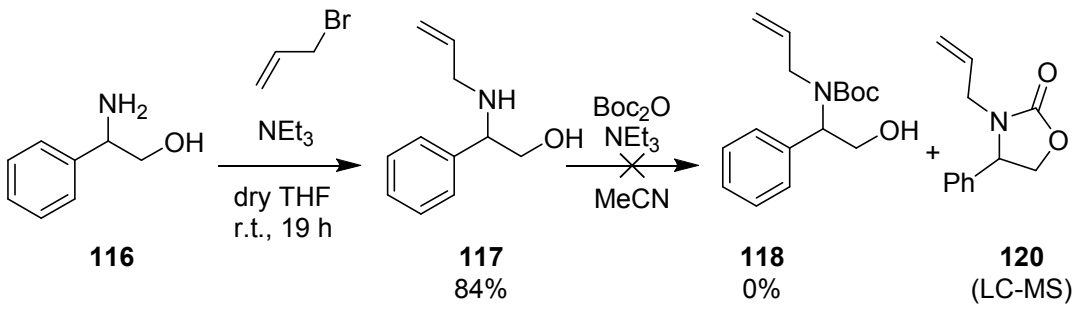
Commercially available phenylglycinol (116) was selected as the starting material for a related synthetic route, with the Boc protection step being planned after *N*-alkylation (Scheme 22).



116 **117** **118** **119** Target Molecule

Scheme 22: Synthetic sequence from phenylglycinol

In the first step, treatment of a solution of phenylglycinol (116) in THF with allyl bromide gave the desired *N*-allylphenylglycinol (117) in 84% yield (Scheme 23), with a broad O-H peak at 3300 cm^{-1} in the IR spectrum confirming that *N* as opposed to *O* alkylation had occurred. Unexpectedly, the Boc protection step to afford the protected amino-alcohol (118) was unsuccessful, with low conversion and the formation of a new component with *m/z* = 203, suspected to be the oxazolidinone (120), being observed in the LC-MS trace.



Scheme 23: Allylation of phenylglycinol

Acetylation and tosylation were also investigated as ways to protect the nitrogen, however these reactions too were unsuccessful and other substrate classes were investigated.

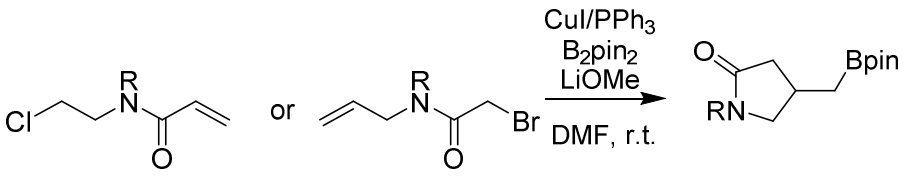
2.4.2 Lactamyl boronate esters

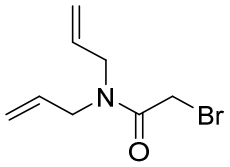
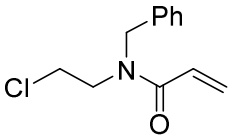
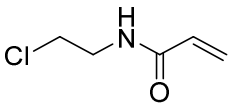
The radical cyclisation of allyl amides has long been used to prepare the corresponding lactams,[156] and it was hypothesised that a similar approach could be taken with the borylative cyclisation. The amide precursors required for these studies could be prepared *via* a simple synthetic route and, furthermore, a protected nitrogen atom was an inherent feature of the substrates. All of the amides in Table 4 were obtained in acceptable yields using a maximum of two synthetic steps, in contrast to the challenging phenylglycinol analogues. The bisallyl compound (121) was chosen as it was thought that the rigidity introduced by the amide group may have affected cyclisation as only amides in the *cis* conformation can undergo radical cyclisation.[147, 157] The protected amide (122) was prepared with an *N*-benzyl group on the amide to enable ease of identification during chromatography *via* its chromophore, and in the hope of providing a 50:50 mixture of *cis/trans* isomers of the amide. Finally, the free amide (123) was included as a

control to verify that the added steric bulk of the benzyl group was not responsible for the failure of the cyclisation.

As can be seen from Table 4 however, all of the borylation reactions gave complex reaction mixtures. Evidence of possible product formation was observed by GC-MS in the case of substrate 123 (entry 3), however this component could not be isolated following chromatography or upon oxidation of the crude reaction mixture. In all of these results, it was surprising not to observe the conjugate addition products.

Table 4: Amide precursors and borylation results



Entry (#)	Substrate	with PPh_3	with Xantphos
1 (**121**)		complex mixture	complex mixture
2 (**122**)		complex mixture[b]	complex mixture
3 (**123**)		complex mixture[b]	complex mixture

Conditions: [PPh_3] = CuI (10 mol%),PPh_3 (13 mol%), B_2pin_2 (1.5 eq.), LiOMe (2 eq.), dry DMF, r.t. 19 h; b) At 60 ^oC with TBAI (1 eq.) added; [Xant] = CuCl/Xantphos (5 mol%); B_2pin_2 (1.2 eq.); KO^tBu (1.2 eq.), dry THF, r.t.19 h reaction mixtures analysed by GC-MS

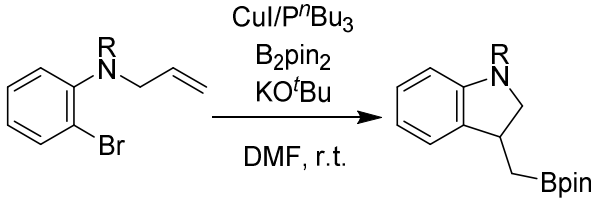
2.4.3 Aniline based substrates

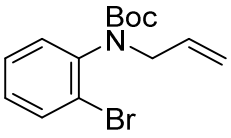
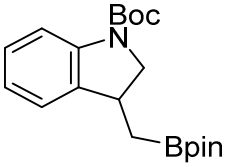
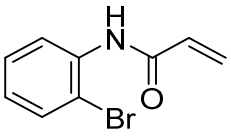
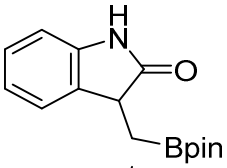
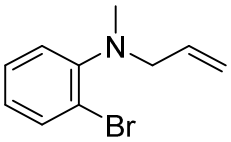
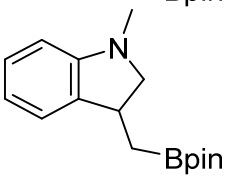
Following a similar hypothesis to the benzofused carbocyclic system discussed previously (Scheme 19), substrates containing an aromatic ring as part of the chain between the halide and the alkene were synthesised. As with fused carbocycles, modified conditions for the borylation of aryl bromides were employed, with a CuI/P^{n}Bu$_3$ catalyst combination and KO^{t}Bu as the alkoxide base.[18]

The synthesis of these substrates was relatively facile. Treatment of commercially available 2-bromoaniline with LiHMDS and subsequent alkylation in the presence of TBAI afforded the *N*-Boc, *N*-allyl bromoaniline (124a) in 18% overall yield (unoptimised). The amide (124b) could be prepared in one step from the coupling of 2-bromoaniline with acrolyl chloride whilst the *N*-methyl, *N*-allyl bromoaniline (124c) was obtained in quantitative yield from the alkylation of commercially available *N*-methyl-2-bromoaniline with allyl bromide in the presence of LiHMDS.

As can be seen in Table 5, only the *N*-methyl derivative (124c) afforded the cyclisation product (125c), although this was as part of a complex reaction mixture. It is interesting to note that the ^{1}H-NMR spectrum of these substrates indicated that various conformations (rotamers) existed, presumably due to the high steric bulk of the Boc group and neighbouring Br atom. This may have affected the ability of these substrates to cyclise.

Table 5: Aniline derivatives and borylation results

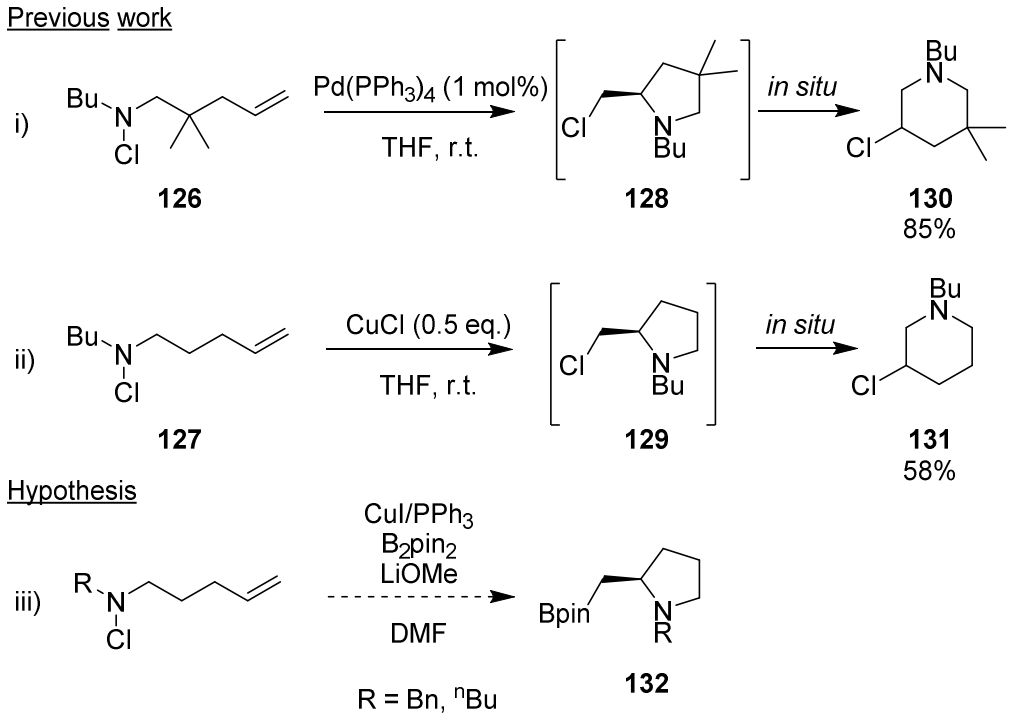


Entry (#)	Substrate (124a-c)	Expected product (125a-c)	Yield (%)[a]
1 (a)			s.m/complex mixture
2 (b)			β-boration (32)[b]
3 (c)			33[b]

Conditions: CuI (10 mol%),P^{n}Bu$_3$ (13 mol%), B$_2$pin$_2$ (1.5 eq.), KO^{t}Bu (2 eq.), dry DMF, r.t. 19 h; a) isolated yields; b) Major components of a complex mixture, containing hydroboration and arylboration products (LC-MS), a similar result was obtained under standard CuI/PPh$_3$ conditions

2.4.4 N-*chloro derivatives*

Several *N*-chlorinated hexenes (126, 127) have been synthesised in the literature where they undergo intramolecular Heck reactions to generate chlorinated piperidines (128, 129) *via* 2-chloromethylpyrrolidines (130, 131), which then rearranged *via* aziridinium ion intermediates (Scheme 24, i)).[158] In a similar fashion, these substrates can also undergo Cu(I) mediated radical cyclisation (Scheme 24, ii)).[159, 160] It was hypothesised that these compounds would also be able to take part in the borylative cyclisation reaction, with trapping of the cyclic radical intermediate occurring with a copper-boryl species to generate heterocyclic boronates (132, Scheme 24, iii)).

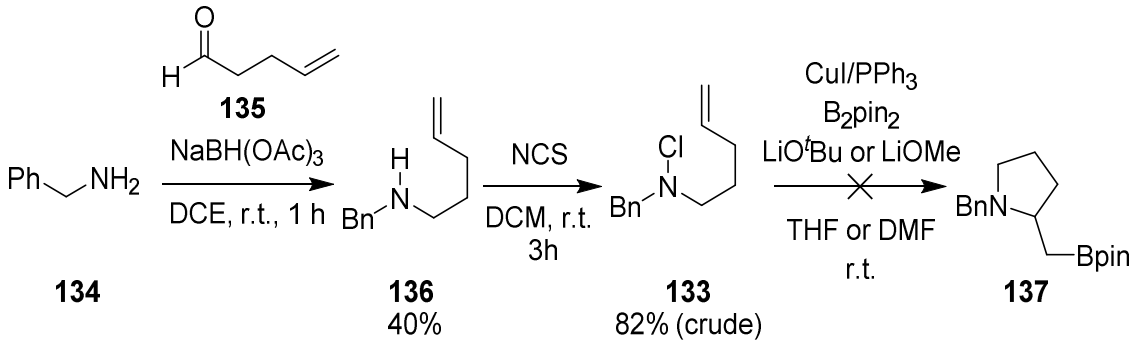


Scheme 24: N-chloro cyclisations in the literature

In addition to the butyl-chloramine (127), an *N*-benzyl derivative (133) was prepared. Reductive amination of benzylamine (134) with 4-pentenal (135) in the

presence of sodium hydride (Scheme 25) proceeded reasonably well to give secondary amine 136, with chlorination by *N*-chlorosuccinimide (NCS) occurring in 3 h at room temperature. The material (133) was not amenable to GC-MS analysis, with ASAP mass spectrometry being used to confirm that *N*-chlorination had been successful.

Owing to concerns over its stability, the chloramine (133) was used immediately without further purification. Whilst the reaction mixtures turned from yellow to dark black as is usual for borylation reactions, no formation of the boronate ester (137) was observed in any of the attempts made with both the *N*-benzyl and *N*-butyl chloramines, nor was there any evidence of any significant side products such as ATRC chlorinated products. Repetitions of the procedure with the flask wrapped in aluminium foil to exclude ambient light did not show any improvement.



Scheme 25: Synthetic route and attempted cyclisation of N-chloro derivatives

A closely related class of compounds, *N,O*-benzoylated amines, have also been shown to be viable substrates in copper catalysed aminoboration.[61, 62, 161, 162] The *N-O* bond is activated by the copper catalyst during the reaction and, whilst intermolecular reports are more common (Figure 38, i)), an intramolecular cyclisation has been reported (*c.f.* section 1.4.2, Figure 38, i)).[63]

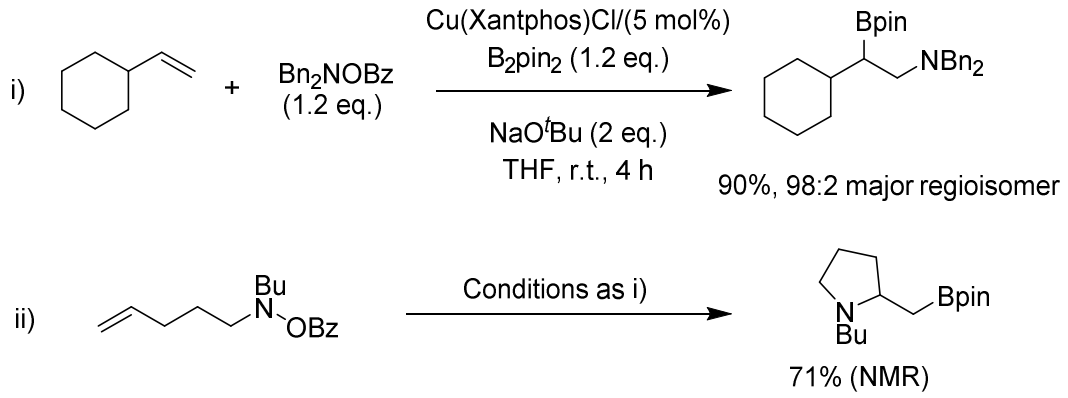
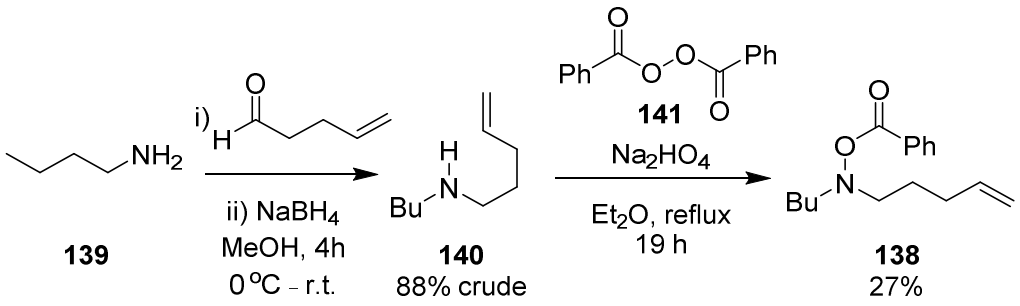


Figure 38: Aminoboration conditions of N,O-benzoylated substrates

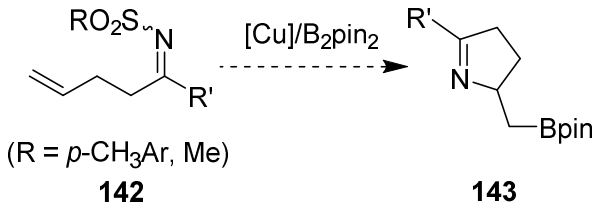
It was thought that such compounds would be suitable cyclisation precursors under these borylation conditions, therefore the *N,O*-benzoylated alkene (138) was synthesised as outlined in Scheme 26 below. Treatment of the secondary amine (140) with dibenzoylperoxide (141) in dry ether afforded the benzoylated alkenylamine product (138) in a yield of 27% (unoptimised). The material was not amenable to analysis by mass spectrometry, but could be characterised by NMR and identified by comparison with literature reports.[163]



Scheme 26: Synthetic route to N-benzoyl compounds

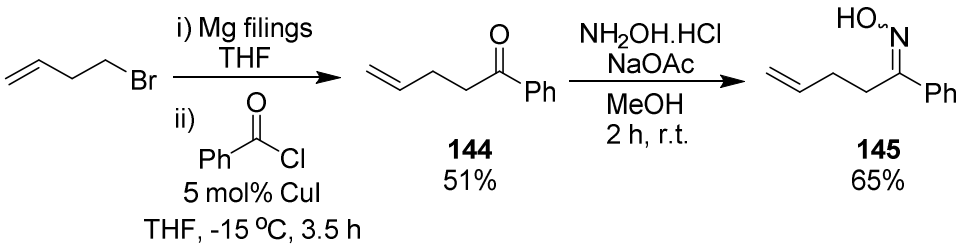
Disappointingly, under the CuI/PPh_3/LiOMe borylation conditions, no identifiable products could be observed or isolated despite complete consumption of the starting material after 3 h.

Pseudohalides are suitable substrates for the borylation reaction and these were also explored. Oxime derivatives (142) were expected to give dihydropyrroles (143) as products (Scheme 27).



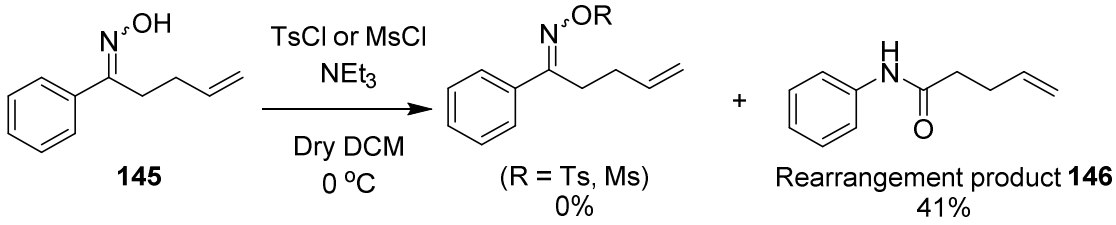
Scheme 27: Expected cyclisation products from oxime derived precursors

A Grignard reaction between butenylmagnesium bromide and benzoyl chloride in the presence of copper iodide afforded the ketone (144) in 51% yield, followed by conversion to the oxime (145) with hydroxylamine hydrochloride salt in 65% yield (Scheme 28).



Scheme 28: Synthetic route to oximes

Tosylation of oxime 145 was attempted next, however this resulted in formation of amide (146) *via* Neber/Beckmann rearrangement, as confirmed by a strong amide C=O band at 1663 cm^{-1} in the IR spectrum of the material (Scheme 29). Mesylation did not yield the desired product either and therefore the approach was abandoned.



Scheme 29: Rearrangement during oxime tosylation/mesylation

2.5 Oxygen based substrates

Due to the challenges in the synthesis of nitrogen based heterocycles, attention turned to oxygen containing substrates. Allyl ethers (147) were expected to give tetrahydrofuranyl (THF) boronate esters upon cyclisation (148, Figure 39) and could be synthesised in two steps *via* ring opening of styrene oxide (149) with allyl alcohol (150) and subsequent Appel reaction of the newly formed alcohol (151).

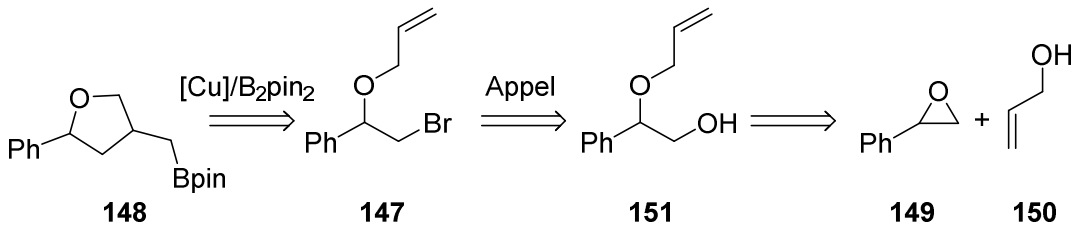
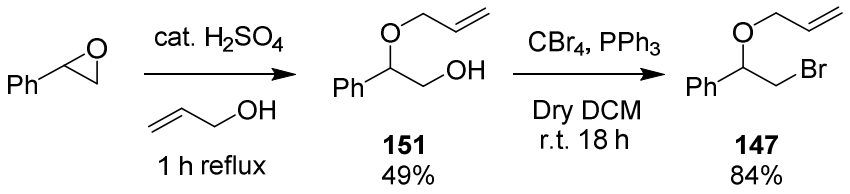


Figure 39: Retrosynthetic analysis of THF precursors

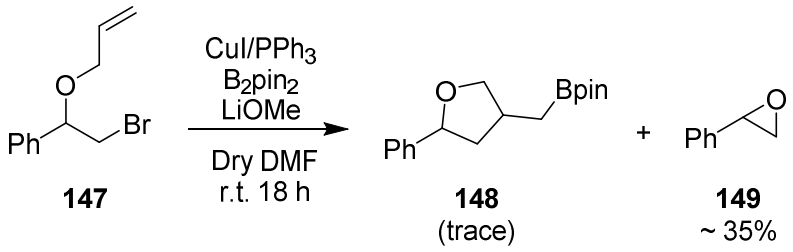
Ring opening of styrene oxide in allyl alcohol with catalytic conc. sulfuric acid under reflux (100 ^{o}C) for 1.5 h afforded allyl ether 151 in 49% yield (Scheme 30). Product formation was confirmed by a broad hydroxyl peak in the IR spectrum and the appearance of alkene signals at δ = 5.9 and δ = 5.2 ppm. An Appel reaction then afforded the alkyl bromide (147) in 84% yield.



Scheme 30: Epoxide ring opening with allyl alcohol

2.5.1 Borylation/cyclisation of aliphatic allyl ethers

With the precursor successfully synthesised, the bromide (147) was subjected to the borylation/cyclisation protocol. Under the standard CuI/PPh_3 borylation conditions, the starting material was completely consumed however only trace amounts of a material consistent with a GC-MS consistent with the boronate ester (148) were obtained and instead styrene oxide (149) was obtained in 35% yield, as confirmed by three non-equivalent protons at δ = 3.9, 3.2 and 2.8 ppm (Scheme 31). Similar results were obtained under CuCl/Xantphos conditions and in the absence of a ligand. Whilst the mechanism for styrene oxide formation is unclear, it may be that activation of the bromide by copper enables intramolecular attack by the ether oxygen, followed by cleavage of the allyl group from this oxonium ion (see following chapter).



Scheme 31: Results of allyl ether borylation/cyclisation

2.6 Other oxygen based heterocycles

As with previous systems, it was hypothesised that pre-organisation of the chain between the alkene and the halide would aid ring formation. This was unsuccessful

with aniline based substrates, however the moderate success with a benzofused carbocyclic precursor (Scheme 19) was encouraging. It was hoped that dihydrobenzofuranyl Bpin esters (153) could also be synthesised by the same approach (Figure 40).

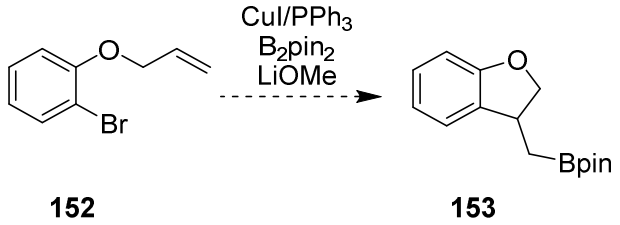
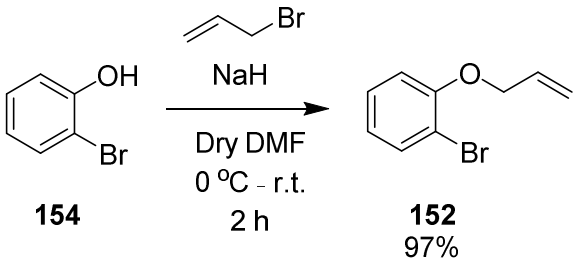


Figure 40: Formation of dihydrobenzofuran Bpin esters

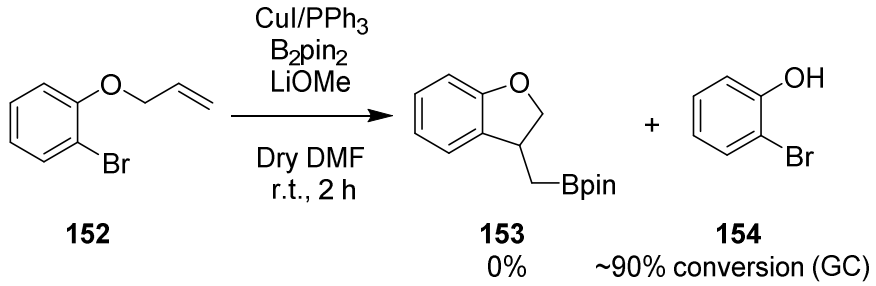
The precursor (152) was synthesised *via* alkylation of commercially available 2-bromophenol (154) with allyl bromide (Scheme 32). Stirring with sodium hydride for 30 minutes followed by addition of allyl bromide gave the product in 97% yield with no requirement for chromatography.[164]



Scheme 32: Alkylation of 2-bromophenol

This material was subjected to the borylation/cyclisation conditions, however unexpectedly, GC-MS analysis indicated formation of 2-bromophenol (~90% conversion), along with a small quantity of an unknown side-product. This competing deallylation process prevailed and no cyclic product was observed in the reaction mixture. After 2 h, all of the starting material had been converted back to

the phenol (154, Scheme 33). The same result occurred under the CuCl/Xantphos conditions, with complete deallylation occurring in 3 h.



Scheme 33: Deallylation of an aryl allyl ether

Deallylation of the substrate was unexpected and the process was further investigated as a novel method for the deprotection of aryl allyl ethers. These results and further studies into this transformation shall be discussed in the following chapter.

2.7 Conclusions

In this section, attempts to prepare substituted carbocycles have been described. It is clear that the challenging syntheses of substrates for the cyclisation were a major issue, and the lack of sufficient quantities of the alkyl halides did not allow for optimisation of the reaction conditions. Further work to develop an alternative route to such precursors would therefore be required in order to fully test the potential of the borylation/carbocyclisation reaction.

In the few cases where starting materials could be synthesised, cyclisation did not occur and the complexity of the reaction mixtures made it difficult to ascribe reasons for the failure of the reactions. Since the radical cyclisation of substituted systems is well documented,[145, 165] these shortcomings were surprising (and raise

further questions as to whether the mechanism is in fact mediated by radicals). The influence of the copper on the transition state cannot be entirely ruled out, as has been reported for the cyclisation of aminyl radicals.[160]

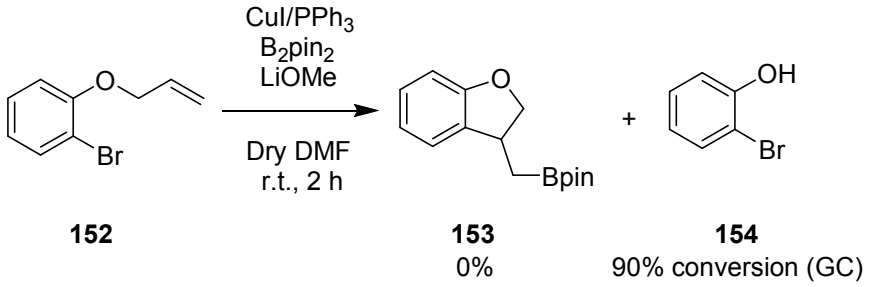
Pre-organisation of the substrate through fusion to an aromatic ring did give the cyclic product, albeit in a low yield. Future attempts could focus on other substrates set up to favour cyclisation, such *gem*-disubstituted precursors. Substituents at other positions along the chain besides the α-position were not investigated, and this is an area for further work.

The synthesis of heterocyclic boronate esters was equally challenging, again due to difficulties in substrate preparation. Once again, relative success was found through pre-organisation of the alkyl chain. Applying this approach to allyl ethers led to deallylation as opposed to cyclisation. Development of this methodology is the focus of the following chapter.

3 Copper catalysed deallylation of aryl allyl ethers

3.1 Introduction

As discussed in the preceding chapter, attempted cyclisation the 2-bromoallyl ether (152) resulted in formation of the phenol (154) rather than desired cyclic product (153, Scheme 33). Allyl groups are commonly used as protecting groups and therefore this observation was further examined and the scope of the reaction expanded. Notably, selective deprotection of an aryl allyl ether was possible in the presence of an *N*-allyl carbamate. These developments are the subject of this chapter.



Scheme 34: Deallylation of an aryl allyl ether

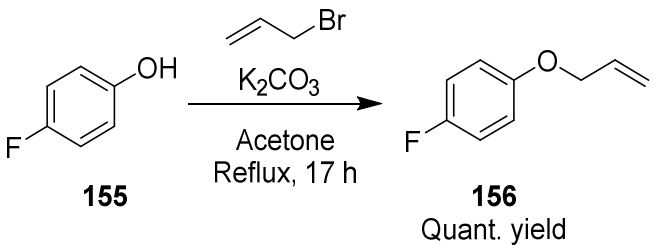
3.2 Development of a copper-boryl mediated deallylation process

Allyl ethers serve as useful protecting groups for alcohols, owing to their stability under a wide pH and a variety of reaction conditions, allowing them to be used in orthogonal protecting group strategies. Many procedures have been established for their removal.[166-170] Such methods give the corresponding free alcohols in high yields and show good functional group tolerance, however the vast majority employ catalysts based on palladium and rhodium. Due to their ever increasing cost and diminishing availability, there is considerable interest in efforts to substitute

processes mediated by palladium group metals (such as cross couplings) with more readily available transition metals.[171-175] This side reaction, which utilised copper as opposed to palladium, was therefore investigated and developed as a new method for the deprotection of allyl ethers.

3.3 Screening of reaction conditions

With the 2-bromophenol system, there was considerable overlap of peaks corresponding to the allyl ether starting material and the free phenol on GC-MS. To enable screening of reaction conditions and quantification of the deallylation procedure, subsequent studies were carried out with 4-fluorophenol (155) and its corresponding allyl ether (156, Scheme 35).



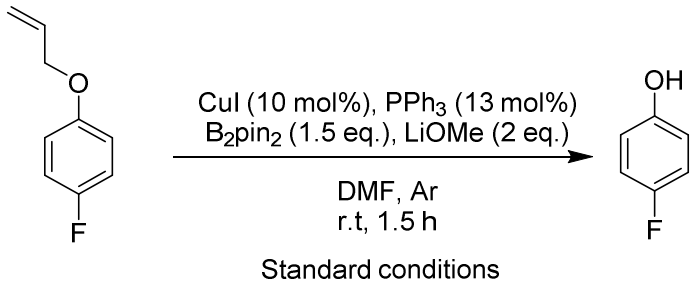
155 **156**
Quant. yield

Scheme 35: Allyl protection of 4-fluorophenol

Applying the standard borylation conditions to 4-fluorophenylallyl ether (156) afforded the parent phenol in good yield (71%) after 1.5 h at room temperature (Table 6, Entry 1). Further examination of the reaction parameters revealed that the presence of the diboron reagent is essential (Entry 2) and no reaction whatsoever occurred in the absence of this component. With 1 eq. B_2pin_2, the reaction did not reach completion within the prescribed time. It was possible to run the reaction with stoichiometric amounts of B_2pin_2 but this required the rigorous exclusion of air and moisture. To achieve this, the reaction was run in a glove box with rigorously

degassed solvent (freeze pump thaw cycles), however it proved more pragmatic to simply use 1.5 equivalents of B_2pin_2. Under these conditions the reaction could even be run open to air with minimal / no loss in yield. This suggested that the excess diboron reagent sequestered trace oxygen and preserved the catalytically active species. The base was also important, with LiOMe proving to be the most effective (Entries 4-9) and no deallylation occurring in its absence. This suggested that the formation of a Bpin-OMe adduct may have been necessary for the reaction to proceed. In the absence of the metal catalyst the reaction did occur, albeit very slowly (Entry 10). This effect was not due to the presence of trace precious metal in the copper source as control reactions using Pd(0) and Pd(II) (Entries 13 and 14) only gave limited conversion, comparable to background reactivity. It was also possible that the copper was simply acting as a Lewis acid, co-ordinating to the ether oxygen and facilitating fragmentation, however the failure of other Lewis acidic metals to catalyse the process ruled this out (Entries 15 and 16). The role of the phosphine ligand was unclear but its presence was important (Entry 17). Given the heterogeneous nature of the reaction mixture, it may have been that the ligand helped to stabilise the metal catalyst, with the active species potentially being copper nanoparticles. To counter this however, the addition of mercury to a reaction mixture did not inhibit the process, suggesting that the active catalytic species remains in solution. In a similar vein to CuI catalysed C-X borylation processes, DMF was found to be the optimal solvent (Entries 20 and 21).

Table 6: Deallylation screening experiments



Entry	Change from standard conditions	Yield (%) after 1 h[a]
1	None	80 (71 isolated)
2	No B_2pin_2	0
3	1 eq. B_2pin_2 (glovebox)	76
4	LiO^tBu	62
5	KO^tBu	s.m. isomerism[b]
6	NaO^tBu	55
7	K_2CO_3	65
8	CsF	59
9	No base	0
10	No metal	15
11	CuCl	62
12	$CuCl_2$	61
13	$Pd(PPh_3)_4$	35[b]
14	$PdCl_2(PPh_3)_2$	12[b]
15	$ZnCl_2$	14
16	$MgCl_2$	5
17	No ligand	Trace
18	Xantphos ligand	78
19	P($^nBu_3$) ligand	72
20	THF	Trace
21	MeCN	20

a) As determined by GC-MS with 1 eq. mesitylene internal standard; b) Suspected to be the corresponding vinyl methyl ether c) 5 mol% Pd was used

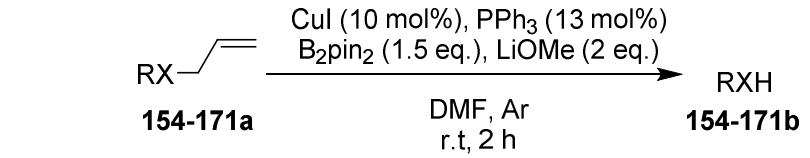
3.4 Substrate scope

Having identified optimal reaction conditions, the substrate scope was next examined (Table 7). All of the substrates could be synthesised by straightforward Williamson-type etherification (as previously described in Scheme 35) whereby a

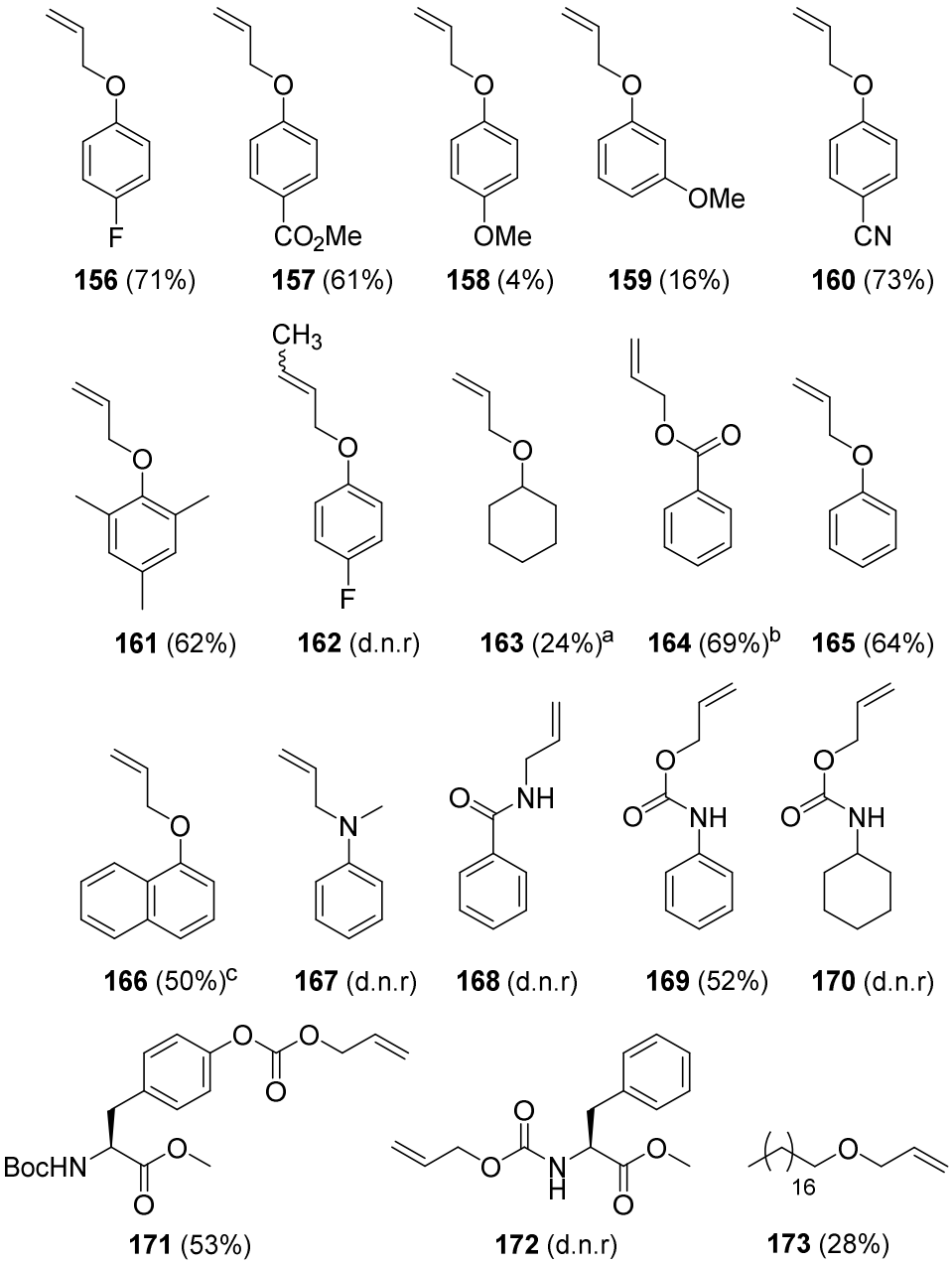
solution of the alcohol/amine was stirred in the presence of base and allyl bromide (or allyl chloroformate). Yields were typically quantitative for this process.

The results of this substrate study revealed that electron deficient phenols were deprotected most readily (157 and 160) whilst very electron rich substrates were only cleaved slowly and in low yields (methoxy-phenols 158 and 159). In these cases a complex reaction mixture resulted, with hydroboration of the alkene being one of the minor isolable products. These outcomes suggested that the pKa of the alkoxide/phenoxide was critical to the process and, consistent with this hypothesis, *alkyl* allyl ethers did not perform well in the reaction (163 and 165). Furthermore, aliphatic allyl carbamates were stable to the reaction conditions (170 and 172). Steric bulk on the aromatic ring was well tolerated (161), however the presence of a terminal methyl group on the alkene (162) was enough to prevent the reaction from occurring, with no reaction even after the mixture was left overnight.

Table 7: Substrate scope of the deallylation reaction



154-171a **154-171b**



156 (71%) **157** (61%) **158** (4%) **159** (16%) **160** (73%)

161 (62%) **162** (d.n.r) **163** (24%)[a] **164** (69%)[b] **165** (64%)

166 (50%)[c] **167** (d.n.r) **168** (d.n.r) **169** (52%) **170** (d.n.r)

171 (53%) **172** (d.n.r) **173** (28%)

Isolated yields for the deprotection reaction in parentheses; d.n.r = did not react; a) After 26 h reaction time, along with coelution of PPh_3; b) After 5 h reaction time; c) Following oxidation with oxone to remove boron impurities

Surprisingly, in view of the pKa correlation for phenoxides, whilst allyl esters were viable substrates (164) the rate of reaction was significantly slower than for simple phenols. It took 5 h for complete consumption of the starting material to occur. It was encouraging to observe that an *O*-alloc group such as that in a tyrosine derivate (171) could be cleaved, as could alloc carbamates of anilines (169).

3.4.1 Purification challenges with deallylation reactions

Conversion to the desired unprotected compounds was good with the vast majority of these reactions. Whilst hydroboration products were sometimes observed, the quantities of such byproducts appeared low by GC-MS analysis (bearing in mind that response factors may vary). Additionally the mass balance was good and there was no significant loss of material after aqueous work up. To check for loss of the product into the aqueous layer (as phenoxide ions), the work up was modified to include acidification of the reaction mixture. This did not affect the yield significantly.

What did cause a problem (and is likely to be the reason for diminished yields) was the co-elution of boron impurities and unreacted B_2pin_2 with the product alcohols. These components were often present throughout the chromatography fractions as a result of their behaviour on silica. The high yield of benzoic acid from substrate 164 was likely due to its ease of purification vs. the phenols.

Attempts were made to modify the work up and facilitate removal of boron derivatives – e.g. by the addition of ethanolamine and subsequent washing of the organic layer, however these did not prove successful. As a result, several

chromatographic runs were often required in order to obtain analytically pure compounds.

Another (imperfect) solution was to oxidise the crude reaction mixture. Using oxone (potassium persulfate), excess B_2pin_2 could be destroyed and subsequently washed out after 20 minutes reaction time. Whilst this was successful, it added another step and work up procedure to the process. The naphthol derivative (166, Table 7) is an example of a substrate where this approach was successful, though the isolated yield was lower than other examples where this approach was not taken.

Given that the reaction required a slight excess of B_2pin_2 in order to reach completion, this fact was unfortunate and something which had to be accepted as a consequence of the reagents used.

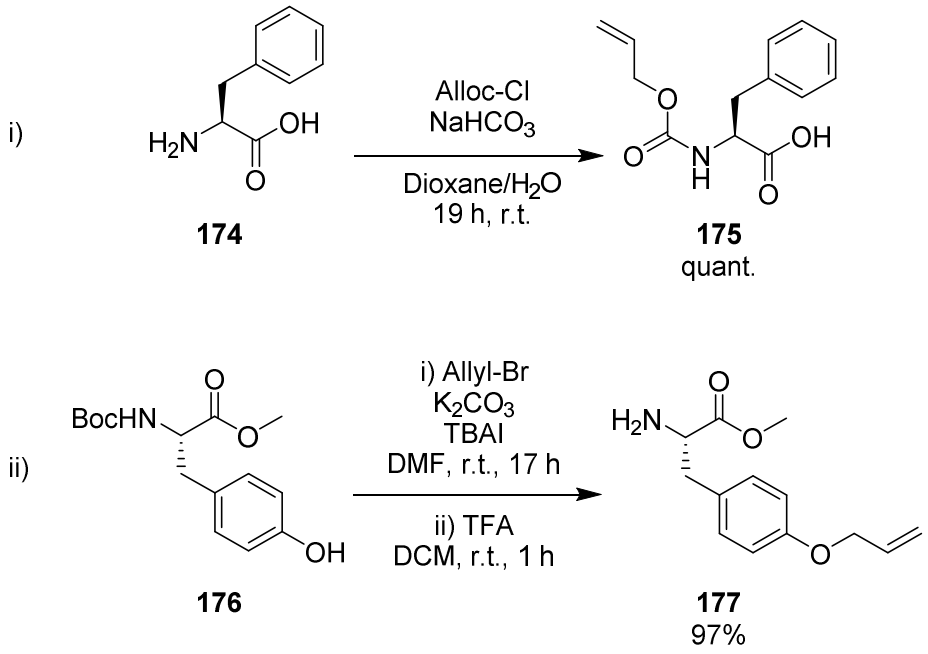
3.5 Selective deprotection reactions

3.5.1 Background

An aromatic carbamate (aniline 169) was successfully deprotected under the reaction conditions and therefore it was surprising to discover that *N*-alloc phenylalanine methyl ester (172, an aliphatic carbamate) was resistant to the cleavage protocol. Given that aromatic allyl ethers *could* undergo deprotection, the observation suggested that the new copper mediated process could have a use in selective deprotection strategies for peptide chemistry. Currently, palladium (0) complexes are the most widely used method for the removal of allyl and alloc protecting groups.[166]

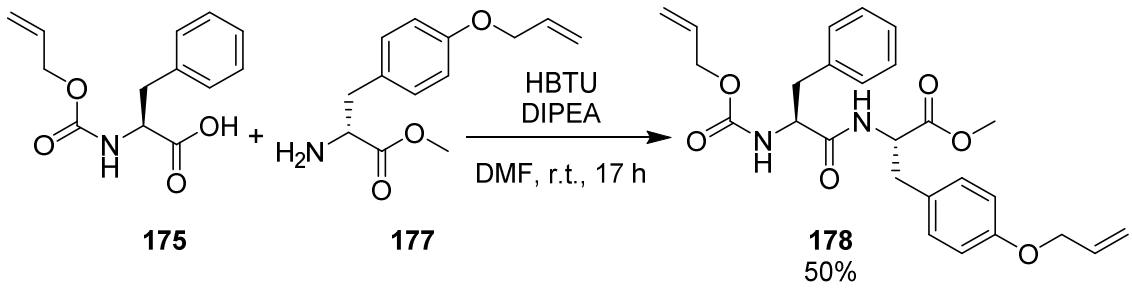
3.5.2 Synthesis of a dipeptide

To test the theory, a dipeptide bearing both an *N*-terminal alloc group and an *O*-allyl tyrosine residue was synthesised. This was possible using a standard amide coupling protocol. Treatment of *L*-phenylalanine (174) with allyl chloroformate gave the *N*-alloc protected acid (175) in quantitative yield (Scheme 36, eqn. i); similarly allyl protection of the phenolic side chain of commercially available *L*-Boc-Tyr-OMe (176), followed by removal of the Boc group gave the free amine (177) in high yield (Scheme 36, eqn. ii). The carboxylic acid of tyrosine was left protected as the methyl ester (known to be stable under the deallylation conditions).



Scheme 36: Preparation of amide coupling partners

Initial attempts to couple the two fragments together under EDCI mediated conditions gave the desired product in a low yield of 11%, however this problem was easily solved by use of the coupling agent HBTU, affording the dipeptide (178) in 50% yield after stirring overnight at room temperature (Scheme 37).

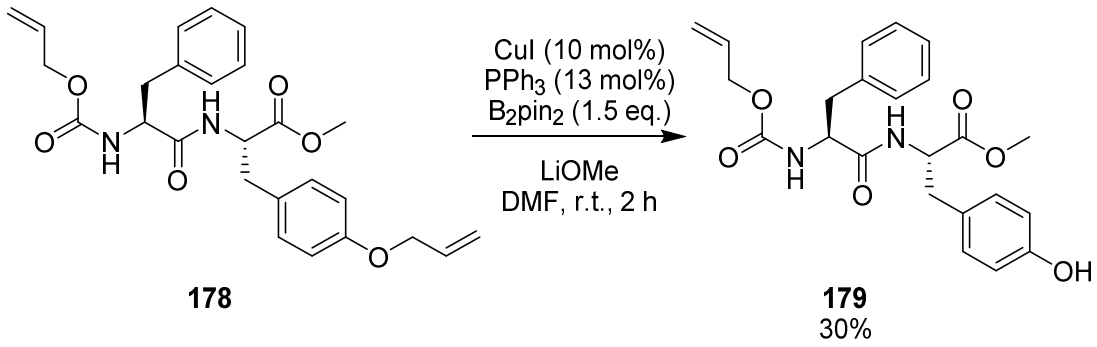


Scheme 37: Amide coupling conditions

With the dipeptide containing both *N*-alloc and *O*-allyl protecting groups in hand, it was then subjected to the cleavage conditions (Scheme 38). Upon monitoring of the reaction mixture by LC-MS, after 2 h complete consumption of starting material was observed along with a new component with *m/z* = 426.

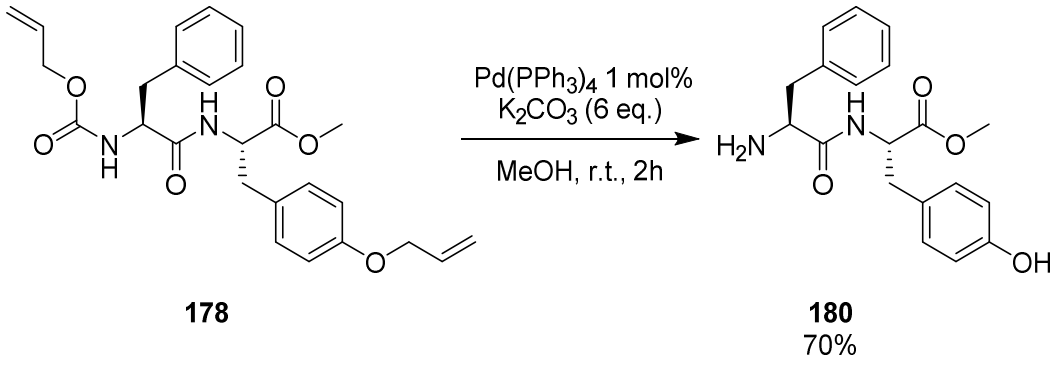
It became apparent that selective cleavage of the *O*-allyl group had occurred, with the *N*-alloc moiety remaining in place to yield the monoprotected dipeptide (179). Small amounts of ester hydrolysis (derived from the product) were also observed, though this may have occurred under LC-MS conditions (formic acid was used in the chromatographic method). Crucially, there was no evidence of any *N*-deprotected material. An experiment was carried out whereby the reaction mixture was left overnight to confirm this.

With good conversion and lack of side products, reasons for the relatively low isolated yield of 30% were, and still remain, unclear. Chromatography was challenging, with boron impurities causing problems once again (*c.f.* phenols). Potentially material could have been lost at the aqueous workup stage however no product was observed in the aqueous layer by LC-MS.



Scheme 38: Selective deprotection of an allyl ether in the presence of an aliphatic N-alloc group

Conversely when standard conditions for Pd catalysed deprotection were employed, after 30 minutes LC-MS analysis indicated that the *N*-alloc group had been cleaved. Leaving the reaction mixture stirring for a further 90 minutes resulted in additional deprotection of the aryl allyl ether (Scheme 39), giving dipeptide Phe-Tyr-OMe (180) in 70% yield.



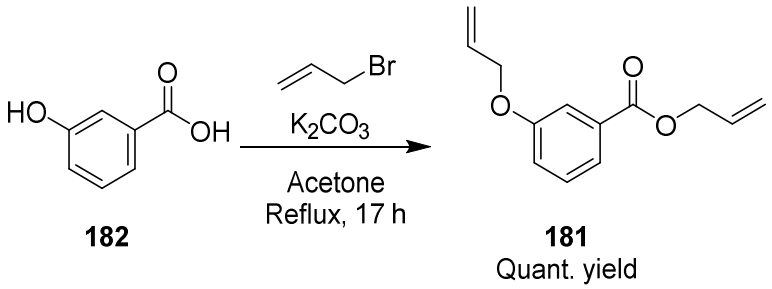
Scheme 39: Pd catalysed conditions cleaved both allyl groups

The newly discovered copper mediated deprotection process is therefore orthogonal to traditional palladium based methods.

3.5.3 Competition experiments with benzyl esters

Given that a benzyl ester (164) took 5 h to be completely deprotected, as opposed to the typical 1.5 h reaction time for allyl ethers, it was hypothesised that selective

deprotection of substrates containing both an allyl ether and an allyl ester would be possible. Preparation of the starting material (181) was simple and achieved through alkylation of 3-hydroxybenzoic acid (182) with an excess of allyl bromide/base in an identical manner to previous allyl protections (Scheme 40). The substance had previously been reported in the literature and a comparison allowed the two allyl groups to be identified.[176] The methylene signals on the allyl group protecting the phenol were reported at δ = 4.6 ppm, whilst those on the ester were present at δ = 4.8 ppm. Thus, the site of deprotection could easily be identified by examination of the ^{1}H NMR peaks (or their absence) in this region.

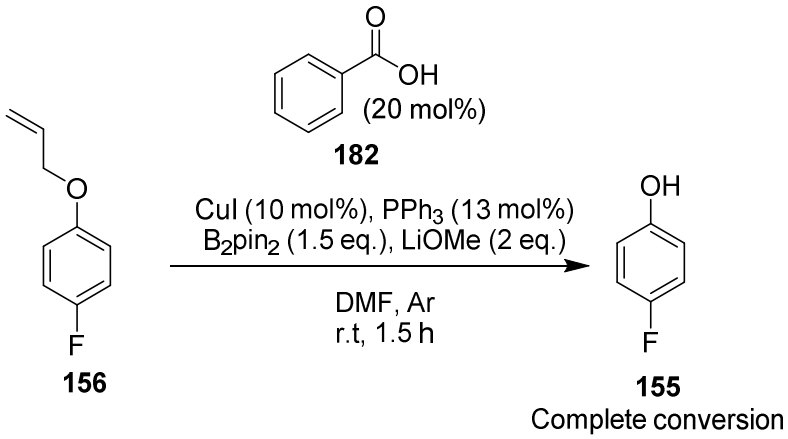


Scheme 40: Synthesis of bisallyl compound 181

The deprotection reaction was then set up as normal and closely monitored by TLC/GC-MS. After 1 h reaction time, it became apparent that selective deprotection had not occurred. A mixture of the starting material and two isomeric compounds had already formed by this point, evidenced by the presence of multiple peaks with *m/z* = 178 in the GC-MS trace of the reaction mixture.

It was thought that the low rate of reactivity of the allyl ester (164) may have been due to complexation of the benzoic acid product to the copper catalyst, thus inhibiting the action of the active species and slowing down the process. To validate

this theory, deallylation of this material (156) was carried out in the presence of 20 mol% benzoic acid (182, Scheme 41).



Scheme 41: Test for inhibition of the catalyst by a benzoic acid product

Contrary to what was expected, the reaction proceeded uninhibited and complete deprotection was observed after the usual reaction time of 1.5 h, ruling out this as a reason for the sluggish reactivity of this material (164). It remains unclear why the allyl ester reacted significantly more slowly than allyl ethers, though the initial rates of reaction did appear similar with relatively minor amounts of the ester starting material remaining after the standard reaction time. Complete consumption then took a further 3 h.

3.5.4 Hydroboration side products

During the deallylation studies on the allyl ether of 4-fluorophenol (156), a related peak with *m/z* = 280, suspected to be the hydroboration product was often observed in GC-MS traces of the reaction mixture (Figure 41). The levels of this peak appeared to fluctuate between reactions, though could not be quantified.

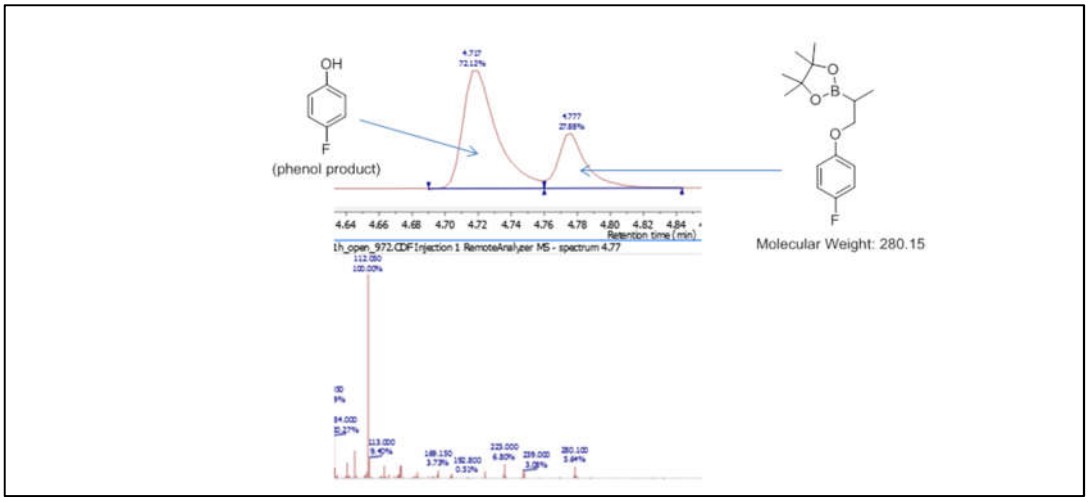
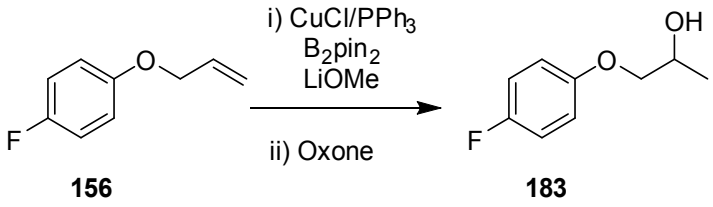


Figure 41: GC-MS trace of the hydroboration side product

When a crude deallylation mixture was oxidised, isolation and subsequent NMR analysis of the alcohol (183) from the hydroborated material indicated that boryl addition had occurred at the position closest to the oxygen of the allyl ether (Scheme 42). This was confirmed by the splitting of the CH_3 signal into a doublet.



Scheme 42: Confirmation of the structure of the hydroboration side product

Owing to the similarity of these conditions to those previously reported for hydroboration,[24] tests were also carried out whereby water (2 eq.) or methanol (2 eq.) was added to the reaction mixture. A comparison between these reactions and the standard reaction conditions did not show a significant drop in the yield of the deprotected product, making it unlikely that formation of the hydroboration product was due to the presence of excess protic species.

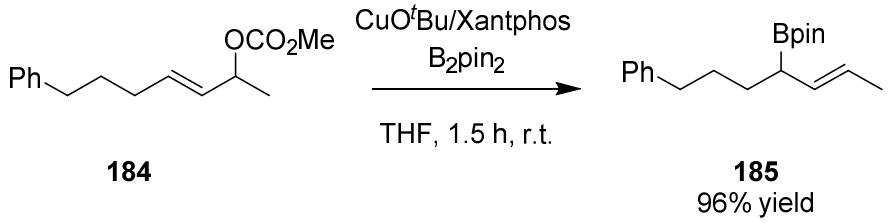
The formation of this hydroboration side product may be accounted for by one of several plausible mechanisms, which willl be discussed in the following section.

3.6 Mechanistic considerations

The mechanism of the deallylation reaction remains an ongoing question. Similar copper-boryl reagent combinations to those described in this section (and indeed this thesis) have been shown to promote a diverse array of transformations, including the hydroboration of alkenes and alkynes,[33, 177-180] the borylation of aldehydes and imines, β-borylation of α,β-unsaturated carbonyl compounds[11, 24, 104, 108, 178] and a variety of C-X borylations to generate aryl, alkyl and allyl boronates.[5, 18, 21, 27, 32, 137] There are several pathways by which the deallylation reaction could proceed.

3.6.1 An S_N2' type displacement pathway

The deallylation reaction has closest parallels with the last transformation (allyl boronate synthesis) for which an S_N2' type displacement is commonly invoked (Scheme 43).[133]



Scheme 43: Allyl Bpin ester formation from carbonates resembles the deallylation of allyl ethers

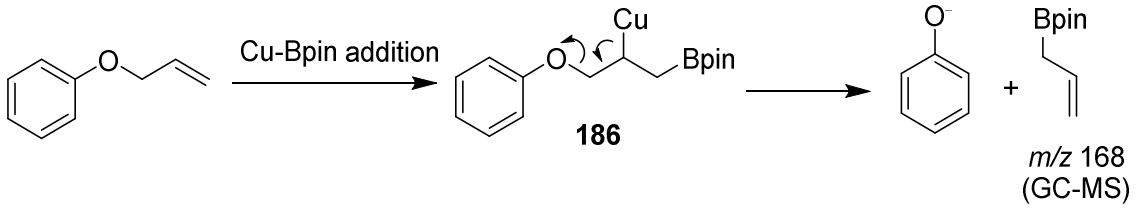
In such a process, formation of a nucleophilic copper-boryl species was proposed. This could then attack the alkene (184). Concurrent double bond isomerisation and

elimination of the carbonate leaving group generated the allylic boronate ester (185).

In line with this hypothesis, GC-MS analysis of the crude reaction mixtures revealed the presence of a signal with *m/z* = 168 corresponding to the formation of allyl-Bpin as a byproduct. Phenoxide (as opposed to carbonate) is the leaving group in this case.

3.6.2 An η-Cu-alkene complex pathway

The second possible pathway could proceed *via* the formation of η-copper-alkene complexes. In a series of elegant studies,[23, 32, 128, 133, 138, 181] Ito provided compelling evidence for the addition of Cu-Bpin species to alkenes, affording η^1-Cu alkyl complexes (i.e. 186) which in this case could then undergo fragmentation to generate the observed phenoxide and allyl-Bpin (Scheme 44).



Scheme 44: Proposed ionic mechanism for deallylation

Alternatively, McQuade and coworkers using electron poor allyl aryl ethers as the leaving group in combination with a chiral copper-NHC/B_2pin_2 system to generate chiral allyl boronates proposed formation of an η^3-complex between copper and the allylic system.[135] It may be that the heteroatom co-ordinates to the copper directing it towards the carbon closest to the oxygen thus facilitating elimination.[79]

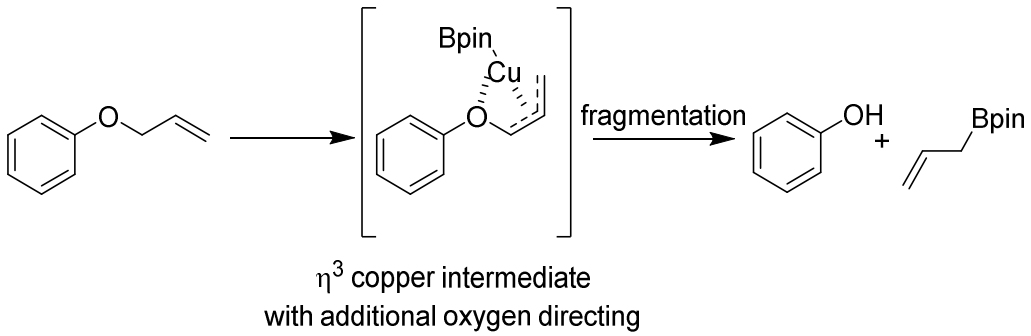


Figure 42: A key intermediate in the mechanism proposed by McQuade and co-workers

The hydroboration side product discussed previously may result from a regioselectivity issue in this step. If Cu-Bpin addition occurs with copper closest to the ether oxygen then rapid elimination can occur. If the Bpin adds closest to the oxygen, then elimination of the phenol cannot occur and protonation of the Cu-C bond may compete, resulting in the observed hydroboration product. On the other hand, competing hydroboration *via* the incorporation of HBpin (generated during the reaction) cannot be completely discounted and may run in parallel with the deallylation process.[33]

Nevertheless, this pathway is consistent with the observation of the higher reactivity of electron deficient aryl arenes compared with their more electron rich analogues, though the lower reactivity of other allyl derivatives with better leaving groups (lower pKa), notably the benzoate obtained from substrate 164, would suggest otherwise.

3.6.3 A radical mediated pathway

A final possibility is that the reaction occurs by reductive cleavage of the C-O bond *via* a single electron transfer (SET) process (Figure 43). The observed selectivities are paralleled by those obtained using a SmI_2/water/amine reagent combination, in

which alkyl allyl ethers reacted more slowly than their aryl counterparts and *N*-allyl amines were not cleaved.[182] Moreover, as with substrate 162 (Table 7), a terminal methyl substituent prevented the reaction from occurring - possibly due to the lower stability of the resulting allyl radical. Counter to this proposal and in common with the CuI catalysed borylation of alkyl halides, attempts to inhibit the reaction by the addition of radical scavengers (cyclohexadiene or dihydroanthracene) had no effect on the reaction of the fluorophenyl ether (156).

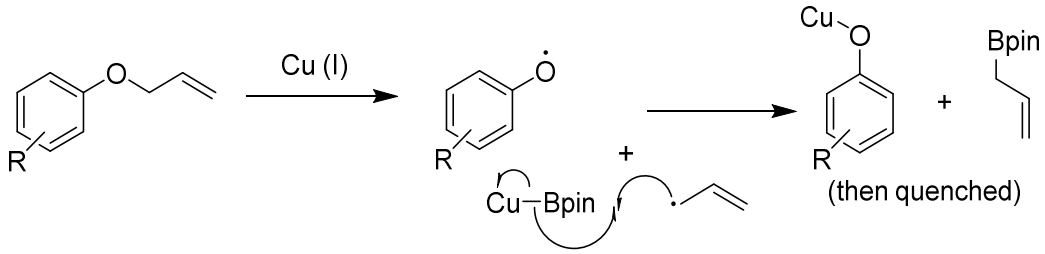


Figure 43: A possible mechanism for a radical mediated pathway

3.7 Conclusions

Initial attempts to form benzofuranyl-type boronate esters were unsuccessful, with cleavage of the allyl ether in the starting material being observed as a competing side reaction. This process was optimised and a copper-boryl catalytic species was able to selectively deprotect a wide range of aryl allyl ethers (including peptides) using chemistry that is orthogonal to established palladium-mediated methods. The procedure was operationally simple, occurring under mild conditions with good functional group tolerance. The mechanism of the reaction could not be definitively proven, though shares many characteristics with a single electron transfer mediated process known to occur with samarium. In common with the borylation

of alkyl halides however, the reaction still proceeds in the presence of radical scavengers.

It should be noted that whilst the cost vs. palladium group metals was lower in terms of the metal catalyst used, the lower yields compared to these processes were not ideal and there is scope for optimisation in future. The conversion to deprotected products was good and it was in fact purification and removal of boron impurities which were the main reason for diminished yields. Nevertheless, the method presents yet another class of substrates amenable to reaction with copper-boryl complexes.

4 Synthesis of chromanyl boronate esters

4.1 Introduction

As outlined in the preceding chapters, application of the borylative cyclisation reaction to substituted carbocyclic and heterocyclic systems was largely unsuccessful. Pre-organisation of the alkene chain did however yield promising results, with tethering of the chain to an aromatic ring affording the cyclic products albeit in low yields (Figure 44 eqns. i) & ii)). Attempts to apply this strategy to allyl ethers were unsuccessful, as these underwent deallylation instead of cyclisation (Figure 44, eqn. iii)).

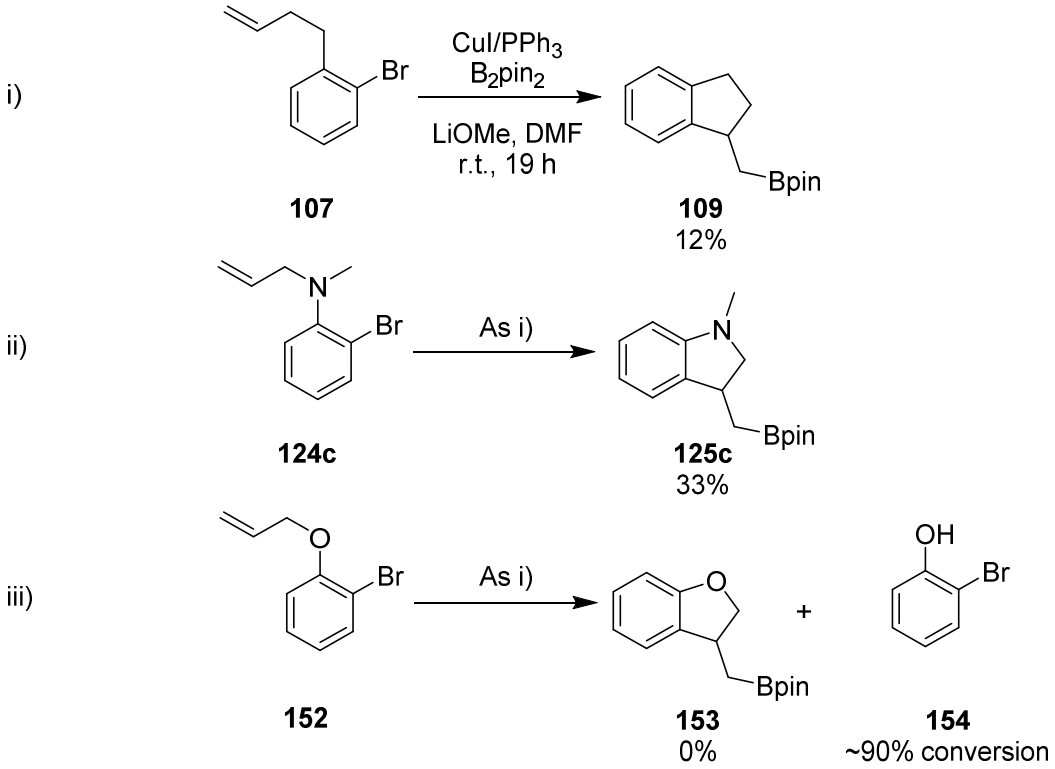


Figure 44: Cyclisations of fused structures

One potential way to circumvent the deallylation reaction was by reordering of the chain of atoms forming the heterocyclic ring. These styrenes (187 and 188) would

be expected to give 5 and 6 membered benzofused boronate esters upon cyclisation.[183] Substrate 187 (R=H, Figure 45, i)) could not be prepared as dimerization occurred *in situ* during its synthesis. Considerably more success was found with chromanes (Figure 45, ii), and these studies are the focus of this chapter.

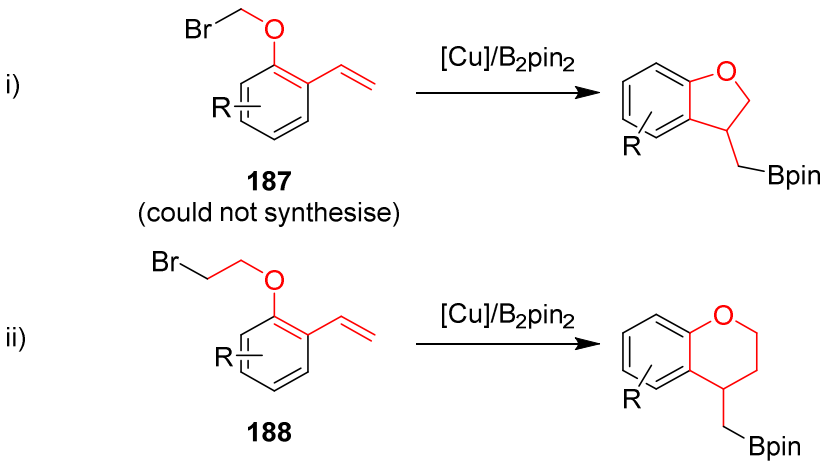


Figure 45: Expected cyclisation products for styrene based substrates

4.2 Chromanes

Chromanes and related compounds are found in many natural products and have widespread biological activity.[184] A number of strategies have been developed for their synthesis such as the cyclocoupling of phenols with dienes (Figure 46, i)),[185, 186] conjugate addition of salicylaldehyde derivatives to α,β-unsaturated systems (Figure 46, ii))[187, 188] and intramolecular coupling reactions mediated by palladium group metals (Figure 46, iii)).[189, 190]

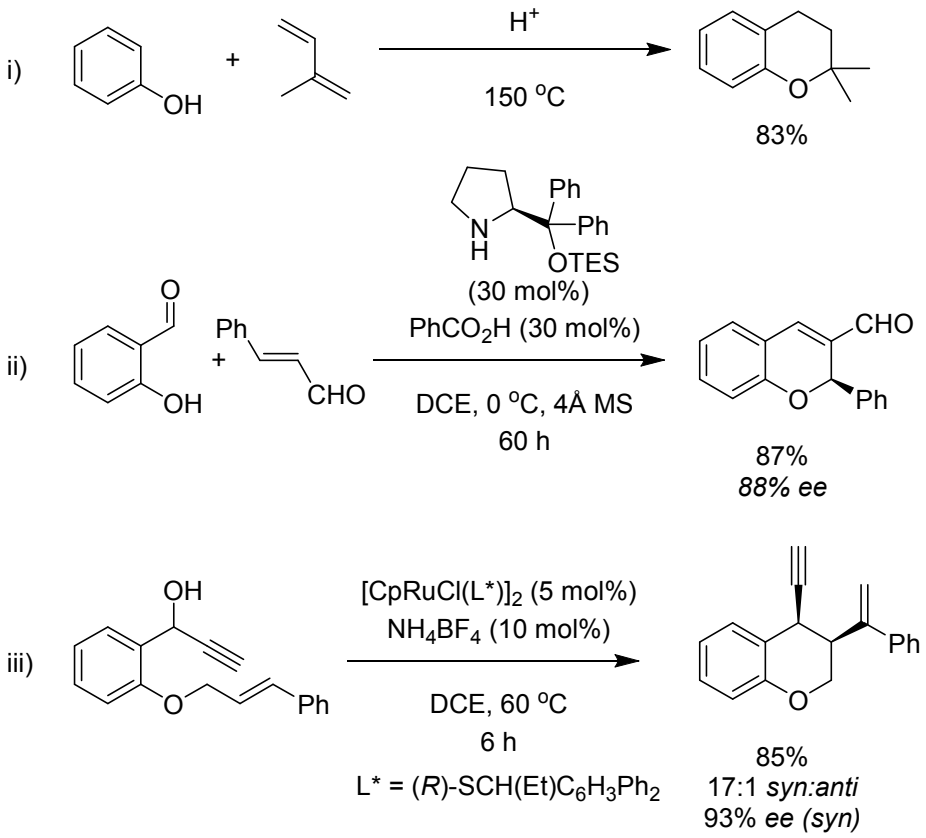


Figure 46: Established routes towards chromanes[185,188, 189]

There are fewer examples of chromanyl boronate esters. Moberg and Xiao recently reported a silaborative cyclisation mediated by palladium to give silicon/boron containing chromane derivatives (189, Figure 47, i)).[191] Additionally, Park, Lautens and co-workers reported a palladium catalysed domino Heck/arylboration sequence, which afforded the boronate esters (190) *via* the trapping of an alkylpalladium intermediate with B_2pin_2 (Figure 47, ii)).[192] Development of a copper catalysed cyclisation reaction would present a more economical route towards these structures, and therefore application of the borylative cyclisation process to these substrates was investigated.

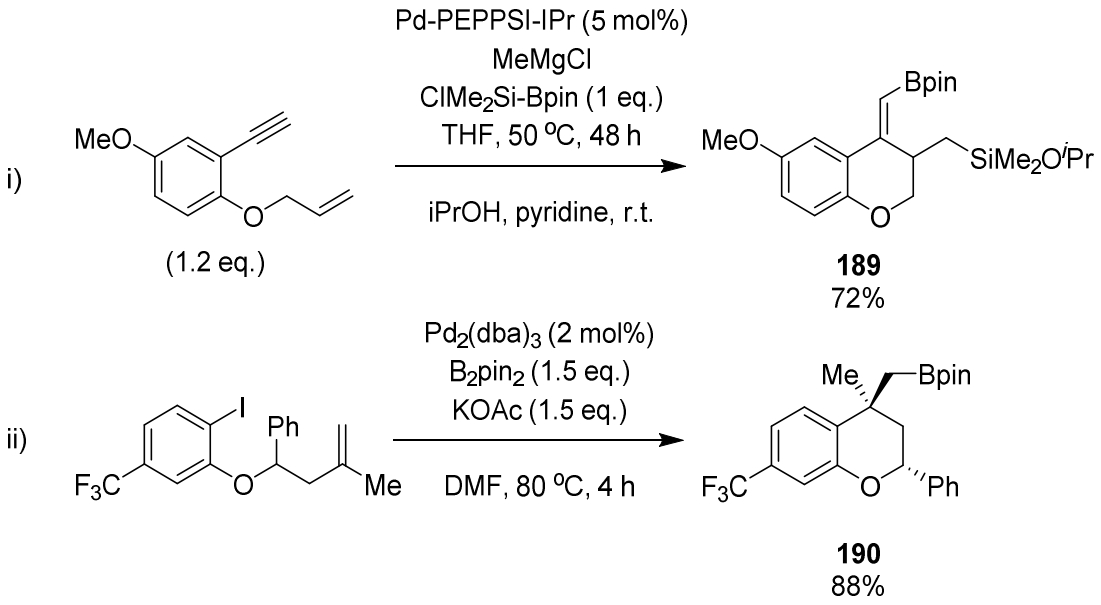


Figure 47: Preparation of borylated chromanes [191, 192]

With the copper catalysed borylative cyclisation of styrenes, it was hypothesised that modifications would be possible at three positions: the aryl ring (denoted R), the 2-position on the alkyl ring (denoted R") and at the *exo*cyclic position (denoted R'). The resulting boronate esters could then undergo transformations such as cross coupling and oxidation reactions (Figure 48).

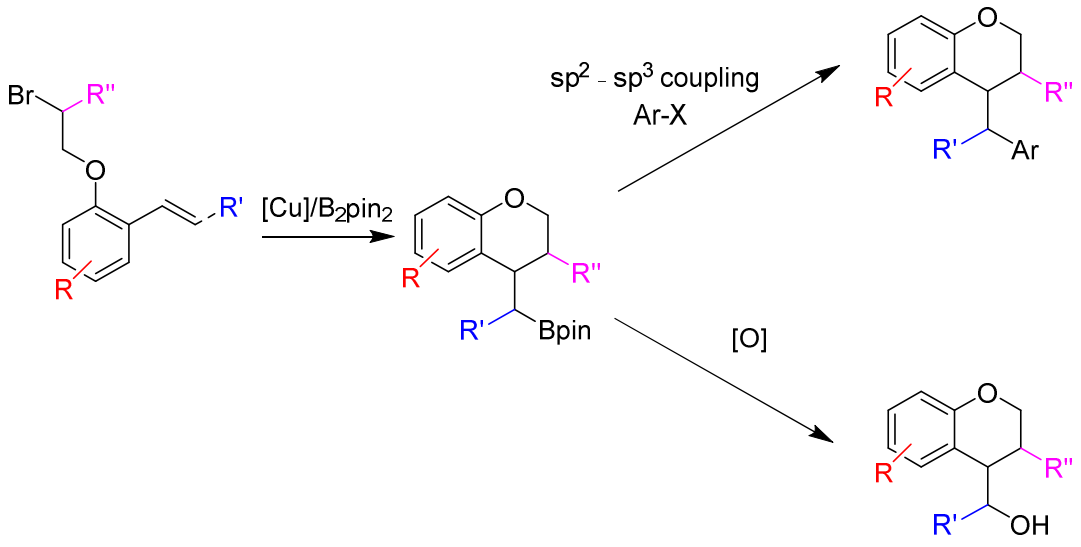
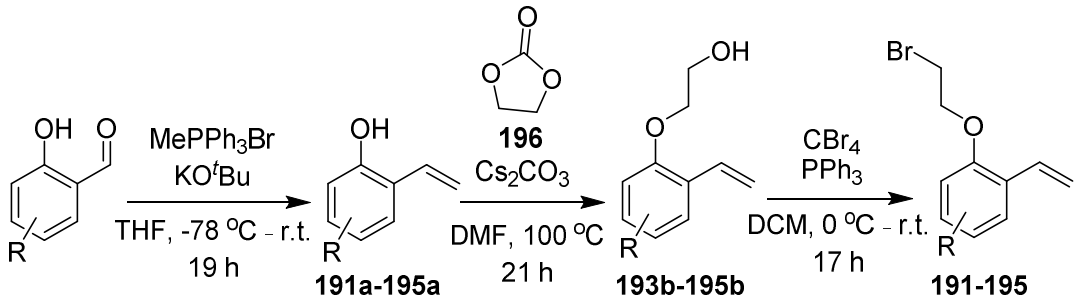


Figure 48: Potential modifications to the chromanyl ring and subsequent reactions

Modifications on the aryl ring were most easily achieved and a general route to such precursors was developed. Alterations to alkyl portions of the molecule were more challenging and required bespoke synthetic routes for each substrate.

4.3 Substrate synthesis

The synthesis of the precursors was relatively straightforward, as outlined in Scheme 45. Beginning with commercially available salicylaldehydes, a Wittig reaction gave the corresponding 2-hydroxystyrenes in good yields. In the original route, the second step was alkylation of the phenol with an excess (10 eq.) of 1,2-dibromoethane, and substrates 191 and 192 were synthesised in 51% and 45% yield respectively *via* this route. Whilst the reactions reached completion, the excess alkylating agent presented issues during purification and other routes were sought. A modification to the process, consisting of ring opening of ethylene carbonate (196, an ethylene oxide surrogate) followed by an Appel reaction was a suitable alternative, despite the additional synthetic step.



Scheme 45: General synthetic route for the synthesis of chromane precursors

Despite the low atom economy (2 out of the 3 steps were mediated by phosphorus), the route proved robust and gave the products in acceptable overall

yields. An overview of the substrates synthesised and corresponding yields is given in Table 8.

Table 8: Summary of yields for chromane precursors

R = (**#**)	Wittig yield (%)**a**	Alkylation yield (%)**b**	Appel yield (%)
H (**191**)	Quant.	51% (dibromoethane)	n/a
p-OCH_3 (**192**)	Quant.	45% (dibromoethane)	n/a
p-F (**193**)	49	87	80
p-CO_2Me (**194**)	76	27	Quant.
m-CH_3 (**195**)	78	83	29

Refers to synthetic steps outlined in figure 2. Alkylation yield refers to ring opening of ethylene carbonate unless otherwise stated; m/p-X = position of the substituent with respect to the phenolic oxygen; a and b denote intermediates in the series e.g. 193a is the 2-hydroxystyrene where R=H; 193b = β*-hydroxyether*

These bromides were relatively unstable – NMR analysis after two weeks in the freezer indicated that decomposition had occurred and therefore each batch had to be freshly prepared prior to use in the borylation reaction.

4.4 Screening of reaction conditions

During the borylation reactions, hydroboration products were frequently observed by GC-MS (Figure 49) in addition to the desired cyclic chromanes (197). Comparison with an authentic sample (prepared *via* Brown hydroboration) confirmed that predominantly the terminal boronate ester (198, see 198a in experimental section) formed. This regiochemistry is consistent with literature reports of styrene hydroboration.[34] In some cases the bisboryl species (199) was also observed *via* GC-MS, presumably *via* further copper catalysed borylative substitution of the alkyl boronate (198).

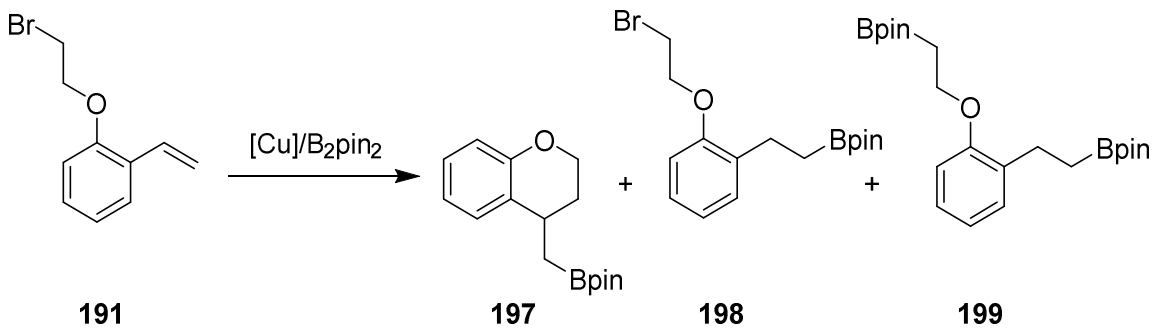
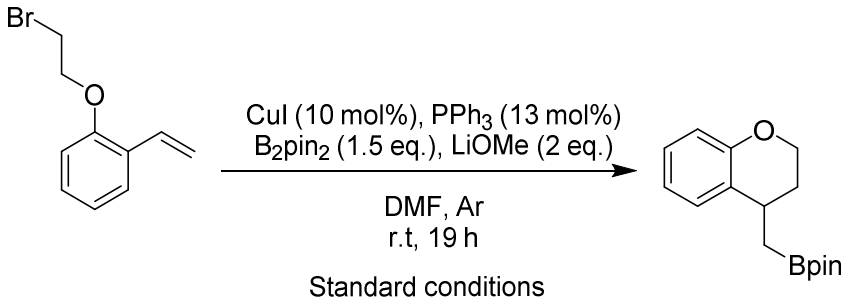


Figure 49: Identifiable products of the cyclisation reaction

Formation of this additional product meant that the actual level of hydroboration side product could not be reliably quantified by GC-MS calibration, as this material was itself consumed. Nevertheless, GC-MS yields for the desired product were still calculated as this was deemed the best way of comparing reaction conditions.

As can be seen from Table 9, a wide range of salts and bases were screened under the borylation conditions. Very low yields were obtained in all cases apart from the standard copper catalysed conditions (entry 1), which even then gave only moderate yields of the cyclic product. The hydroboration product and its bisborylated derivative were present in every reaction mixture, though for reasons described above these levels could not be quantified. Based on comparisons of peak areas, it would appear that the quantities of these byproducts varied between reactions and were significant in some cases (footnote c).

Table 9: Cyclisation screening experiments



Entry	Change from standard conditions	Yield (%) after 19 h[a]
1	None	43 (37)
2	CuCl	3
3	$Cu(OAc)_2$	7
4	LiO^tBu	7
5	KO^tBu	17
6	Na_2CO_3	6
7	Xantphos	5
8	$P(^nBu)_3$	5
9	NHC ligand	18
10	60 ^oC	5
11	0 ^oC	trace[b]
12	Dioxane	0[c]
13	MTBE	0[b]
14	MeCN	0[b]
15	THF	3[c]

a) As determined by GC-MS with 1 eq. mesitylene internal standard; (isolated yield); b) reaction did not reach completion; c) significant levels of hydroboration occurred based on estimations of peak area

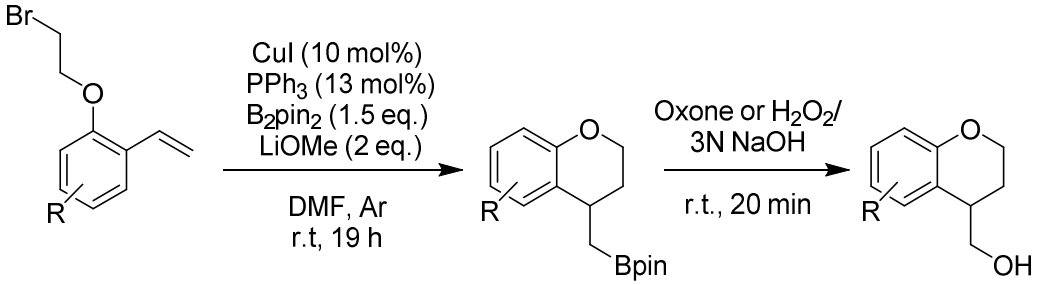
Heating the reaction did not affect the outcome (entry 10) – a much lower yield was obtained than at room temperature, possibly due to starting material decomposition. On the other hand, cooling the reaction mixture (entry 11) meant that the reaction was far from complete after the designated time period. The reactions carried out in MTBE and MeCN (rows 13 and 14) did not turn the usual black colour associated with borylation reactions, remaining white and red respectively and possibly indicating that the active catalytic species did not form.

The low yields obtained during these screening reactions were unexpected, as in most cases complete consumption of the starting material was observed after 19 h. It may be that the levels of the hydroboration product were more significant than expected though, counter to this, these side products could not be isolated in significant quantities. Decomposition during purification cannot be ruled out or, alternatively, it may be that the starting material is consumed by a process undetectable by the analytical techniques employed here. Nevertheless, without a method for *in situ* quantification it was impossible to determine reasons for the poor yields of the cyclic products.

4.5 Aryl substituent studies

Initial studies focussed on an unsubstituted substrate (195), with key NMR signals, such as the diagnostic benzylic proton (a multiplet at δ = 3.1 ppm) being used to confirm that cyclisation had occurred (Table 10, entry 1). The reaction also occurred under CuCl/Xantphos conditions, though in a lower yield (entry 2). Hydroboration side products were frequently observed in the reaction mixtures (GC-MS) and unfortunately these co-eluted alongside the product. To complicate matters further, unreacted B_2pin_2 was also present as a contaminant in the product fractions. As a result, several chromatographic runs were often required in order to obtain pure material and meant that correlations between the nature of the substituent and the reaction outcome were hard to determine (entries 3 - 6). In later attempts, the crude borylation mixtures were oxidised directly to the alcohols.

Table 10: Aryl substituent studies



Entry	R = (**# cyclic Bpin product**)	Borylation yield (%)	Oxidation yield (%)[c,d]
1	H (**197**)	77[a]	54
2	H (**197**)	49[b]	n.d.
3	*p*-OCH_3 (**200**)	70[d]	n.d.
4	*p*-F (**201**)	n.d.	42 (overall)
5	*p*-CO_2Me (**202**)	n/a[d]	n/a
6	*m*-CH_3 (**203**)	n.d.	20 (overall)

n.d. = not determined; a) Product contaminated with up to 30% boron impurities (NMR); b) under Ito's conditions of CuCl/Xantphos (5 mol%), B_2pin_2 (1.2 eq), KO^tBu (1.5 eq.) in THF; c) With oxone or aqueous alkaline peroxide; d) product could not be isolated in sufficient purity following oxidation and acetylation; d) alcohol products are denoted as XXa - for example the oxidation of 197 gives alcohol 197a

4.5.1 Minimisation of hydroboration side products

As discussed in section 4.4 (Table 9) hydroboration side reactions occurred under most of the screened conditions. Given the low yields of cyclisation product, efforts were made to minimise this process by other means, such as by sequestration of excess diboron reagent. The results of these attempts and their rationale are discussed in this section.

Prior to these experiments, the possibility of moisture being responsible for hydroboration was ruled out as hydroboration still occurred when the borylation was carried out under scrupulously dry conditions and with fresh solvent/reagents. The possibility that polymerisation products (undetectable by GC-MS) were responsible for the low yields was countered by the fact that addition of 3 mol% of 4-*tert*butylcatechol (TBC, a commercial polymerisation inhibitor) did not affect the

outcome. The fact that this compound functions by acting as a radical inhibitor, yet the reaction still occurs is also intriguing. Nevertheless, a copper (I) catalyst has been used to initiate styrene polymerisation[193] and such a process cannot be ruled out, though there was no isolable evidence of these products.

Given the similarity of these conditions to copper catalysed hydroboration processes,[32-34, 128] it is possible that the reactivity of the catalyst was simply too general. Excess B_2pin_2 may have allowed this reaction to occur alongside cyclisation and therefore it was hoped that lowering the quantity of diboron reagent would help, however experiments with 1 equivalent of B_2pin_2 did not reach completion.

Another possibility is that the half of the B_2pin_2 not incorporated into the product could take part in the hydroboration. Preactivated sp^2-sp^3 diboron compounds such as 9 have been successfully used by Santos and co-workers in the β-boration of enones (Figure 50, i))[7, 9] and the use of this reagent would ensure that there was no excess Bpin present.

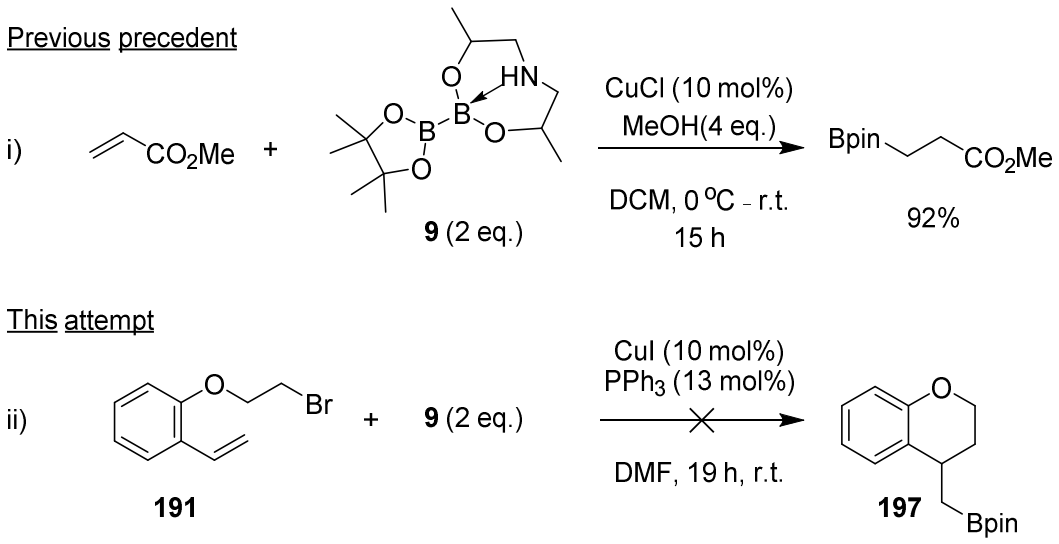
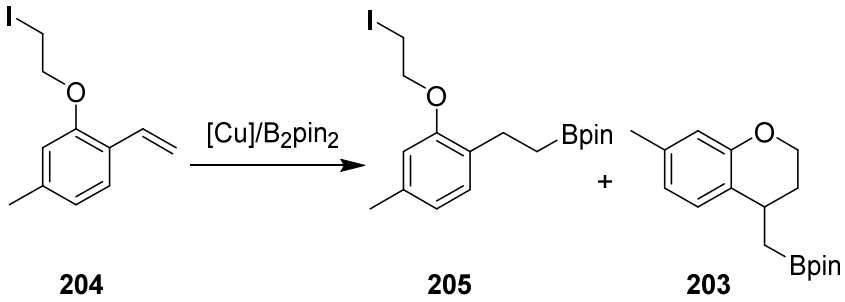


Figure 50: Use of an sp^2-sp^3 diboron reagent in i) enone boration[9] and ii) attempted use in borylative cyclisation

The material (9) was easily prepared from B_2pin_2 in 33% yield, though unfortunately no reaction occurred under the borylation conditions (Figure 50, ii)).

An alternative hypothesis was that cyclisation occurred too slowly relative to hydroboration, with the latter outcompeting the former for consumption of B_2pin_2. Iodides are more reactive than bromides in the borylation reaction and therefore an iodide (204, Scheme 46) was prepared *via* Finkelstein reaction from the corresponding bromide (195) to test this hypothesis. After 4 hours reaction time, the mixture was sampled and a peak corresponding to the iodinated hydroboration product 205 was observed by GC-MS, along with unreacted starting material. This indicated that hydroboration occurred early on in the reaction period and contradicts the hypothesis that excess diboron reagent was responsible for this side product.



Scheme 46: Borylation/cyclisation of an alkyl iodide

Whilst the low *in situ* GC-MS yields (Table 9) indicate that the losses during purification are not the main reason for the low yields of cyclic product, the applicability of this methodology would be greatly improved by a robust means of purification, with product fractions frequently contaminated with boron containing impurities. Unfortunately, the low yield remained a significant and unsolved issue with the reaction.

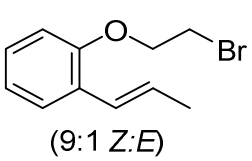
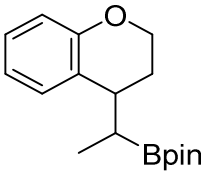
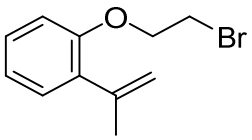
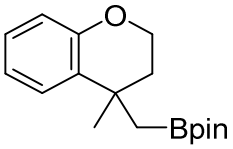
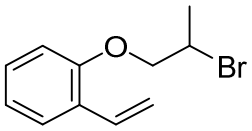
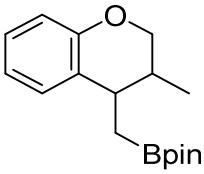
4.6 Further investigations into substrate scope

From these screening attempts, it became clear that the hydroboration side reaction could not be prevented. In spite of this finding, attention turned to the introduction of substituents on other parts of the molecule. Such variations would greatly expand the scope and diversity of the products accessible *via* the cyclisation reaction.

4.6.1 Modifications to the alkyl skeleton

In addition to modifications around the aryl ring, positions along the alkyl chain were also investigated. Synthesis of such substrates required a different linear synthetic route for each example, based on the previously described Wittig/ethylene carbonate/Appel procedure (Scheme 45). As a result of this linearity and poor yields, only limited optimisation of the borylation reaction could be achieved. Due to ease of availability and simplicity when interpreting NMR data, a methyl group was chosen as the alkyl group in these investigations – the precursor substrates and their expected cyclisation products are outlined in Table 5 below.

Table 11: Alkyl chain modifications and borylation results

Entry (#)	Substrate	Expected product	Result[a,b]
1 (**206**)	 (9:1 *Z:E*)		starting material/ complex mixture
2 (**207**)			starting material/ complex mixture
3 (**208**)			starting material

a) Conditions: CuI (10 mol%),PPh_3(13 mol%), B_2pin_2 (1.5 eq.), KO^tBu (2 eq.), dry DMF, r.t. 19 h; b) CuCl/Xantphos (5 mol%), B_2pin_2 (1.2 eq.), KO^tBu (1.5 eq.) in THF; c) reaction was carried out at 37 ^oC; intermediates in substrate synthesis denoted as XXa for the phenol, XXb for the alcohol

In all cases, starting material remained after the standard borylation period of 19 h. There was no appreciable difference between both the CuI/PPh_3 conditions and Ito's CuCl/Xantphos method, with complex mixtures being obtained. Hydroboration side products were not isolated from any of these reaction mixtures, though several components observed by GC-MS analysis of the mixtures did display *m/z* ions consistent with these products.

The secondary bromide (208**,** entry 3) was also subjected to conditions appropriate for secondary halides, which involved heating of the reaction mixture at 37 ^oC. Lack of conversion at this elevated temperature was surprising; a control reaction at room temperature to verify substrate stability did not display any significant differences by GC-MS analysis.

With this final failed attempt, it became clear that substituents on the alkyl portion of the molecule were not tolerated by the borylation reaction, a disappointing result and a significant limitation of the methodology.

4.6.2 Potential mechanism

In previous studies into copper catalysed borylation, copper nanoparticles have been proposed as the active species.[27] In line with this proposal, it may be that a mixture of copper species is responsible for the observed reactivity, accounting for the multitude of side reactions which occur.

Nevertheless, if the active species is indeed a copper(I)-boryl complex, then borylation reactions taking place under CuI, PPh_3, B_2pin_2 and LiOMe mediated conditions would be expected to proceed with the characteristics of a radical type process, as has been previously reported. It should be noted that this reagent combination also displayed behaviour contrary to such a process.

Given the limited substrate scope of the reaction, it is challenging to determine a mechanism. The chromanyl core structure observed here (and the *exo*cyclic nature of the process) is consistent with a radical cyclisation,[183] though Ito's CuCl/Xantphos conditions gave the same *exo*cyclic product despite a different (ionic) mechanism being proposed.[32] Further studies into the nature of the reaction would need to be undertaken before a hypothesis could be developed and shall not be speculated upon here, given the lack of experimental evidence.

4.6.3 Conclusions

These studies with styrene based substrates proved that the borylative cyclisation methodology could be applied towards the synthesis of heterocycles. Nevertheless, there were several issues with the reaction which remain unsolved and greatly limit the application of the methodology.

Hydroboration side products were one of these issues. Given the similarity between these conditions and those previously reported for hydroboration, this is not entirely unexpected. Extensive ligand screening may allow optimal conditions to be found, though issues with obtaining sufficient quantities of the alkyl bromide substrate prevented this. Counter to this, the side products were not isolated in large quantities and it is difficult to account for the low GC-MS yields in the screening studies. This may suggest that other, undetectable side reactions occur.

There appeared to be no correlation between the electronic nature of the aryl substituent and the outcome of the reaction, though the presence of any substituent resulted in a lower yield than the unsubstituted analogue. This variation/lack of correlation may be due to the challenging purification of the boronate esters, and thus isolated yields may not be the most reliable way to compare substituent effects. Other techniques such as *in situ* NMR quantification may have allowed for more accurate quantification, and further exploration of this area could be carried out in the future.

The electronic properties of the alkene are another area for further investigation – addition of an electron withdrawing group for example would result in a better acceptor and possibly influence the cyclic/hydroboration product ratio.

It was disappointing that substituents on the alkyl portion of the molecule were not tolerated. This greatly limited the scope of the reaction and prevented mechanistic studies. The observed *exo*cyclic products are consistent with a radical cyclisation, though the reaction also occurred under Ito's CuCl/Xantphos conditions, which has been proposed as an ionic process and yields *exo*cyclic products. With the limited substrate scope it is difficult to provide further mechanistic insight, though the electronic properties of the double bond were not investigated in these studies and may provide further clues as to the involvement of this component in the reaction.

Despite these challenges, the aim of this part of the project was to expand the scope of the borylation reaction to substrates other than a simple carbocyclic precursor. The successful cyclisation of several aryl substituted styrenes (albeit in low yields) is proof of this concept and provides a basis for further work in this area.

5 Overall conclusions & Future work

Boronate esters and their derivatives are valuable synthetic intermediates. Copper catalysed borylation has emerged as an economical and functional group tolerant method for the synthesis of boronate esters under mild conditions. The suspected radical cyclisation of 6-bromo-1-hexene under the CuI/PPh_3 borylation conditions suggested that application of the methodology towards the synthesis of non-aromatic heterocyclic boronate esters may have been possible, forming the basis of this project.

The preliminary experiments outlined in chapter 2 confirmed that there was a mechanistic difference between the copper iodide/triphenylphosphine mediated borylation of alkyl halides developed by Steel & Marder and the closely related copper chloride/Xantphos system developed by Ito and co-workers. Cyclisation was only observed with a chain length of 6 under the former conditions, whereas other chain lengths underwent cyclisation with the latter.

Attempts to expand the borylation protocol towards the synthesis of substituted carbocyclic precursors were unsuccessful, with the substrate alkyl halides proving difficult to prepare. During the project, this meant that time was often spent developing a synthetic route to the substrates, rather than carrying out borylation studies (the main aim of the project). In cases where a substrate *was* successfully synthesised, the quantities were so minimal that optimisation of the borylation reaction was not possible. If a robust synthesis of the precursor bromides was developed in the future, thorough screening of the reaction conditions may yield better results.

The synthesis of heterocyclic precursors suffered from similar issues to the carbocyclic systems. Amine substrates were challenging to synthesise, with the reasons for this still unclear. Protecting the nitrogen atom in these substrates was a necessity however this made their synthesis more challenging. In the few borylation reactions that were attempted, no cyclisation products could be obtained in significant yield and complex reaction mixtures often resulted.

Oxygen based substrates were easier to synthesise, though these underwent a side reaction rather than borylative cyclisation. This deallylation side reaction was developed and proved useful in the deprotection of aryl allyl ethers as outlined in chapter 3. Furthermore, orthogonal reactivity to palladium was observed in the selective deprotection of a dipeptide.

Throughout the project, the most promising results were obtained when the alkyl chain was preorganised towards cyclisation by fusion to an aromatic ring. This was used to advantage in the synthesis of chromanyl boronate esters, as outlined in chapter 4. The products were obtained in moderately low yields and frequently contaminated with boryl impurities, however the success of the reaction is proof of concept of a copper mediated borylative cyclisation process to yield heterocyclic boronate esters. A competing hydroboration side reaction could not be prevented and the scope of the reaction was limited to substituents on the aryl ring though, as with substituted carbocyclic systems, a detailed screening of reaction conditions may overcome this problem.

Overall, all areas of the project suffered from the same issue of challenging substrate synthesis. It would also appear that the scope of the cyclisation reaction

under CuI/PPh_3 conditions is limited to non-substituted boronate esters. Owing to the general reactivity of a copper (I) catalyst and the multitude of reactions mediated by copper-boryl complexes, as discussed in the introduction to this thesis, side reactions were a problem. These issues may be overcome by the discovery of a highly specific ligand/catalytic system and this is an area for future investigation.

6 Experimental details

General procedures and information

All reactions were carried out under an atmosphere of argon unless stated. Anhydrous solvents were dried using an Innovative Technology Solvent Purification System and stored under argon.

Chemicals: All chemicals obtained from commercial suppliers were used without further purification unless stated.

TLC analysis was carried out on precoated aluminium backed plates (Merck silica gel 60 F_{254}). Visualisation was by UV light (254 and 365 nm) or by staining with potassium permanganate where required.

Flash column chromatography was carried out manually (40 – 63 μm mesh silica) or by using an automated system (Teledyne ISCO Combiflash R_f with prepacked silica Redisep R_f cartridges). Dry loading was carried out by the addition of silica gel to a solution of the crude material, then evaporating to dryness *in vacuo*.

NMR: ^{1}H NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz) or at 700 MHz on a Varian VNMRS-700 (600 MHz on a Varian VNMRS-600). ^{13}C NMR spectra (proton decoupled) were recorded at 101 MHz on a Bruker Avance-400, 176 MHz on a Varian VNMRS-700 or 151 MHz on a Varian VNMRS-600. ^{19}F NMR were recorded at 376 MHz and ^{11}B NMR spectra were recorded at 128 MHz on a Bruker Avance-400 unless otherwise stated. All spectra were acquired in deuterated chloroform ($CDCl_3$) unless otherwise stated. 2D NMR experiments were used to aid assignments. Reported spectra are referenced relative to residual

solvent peaks ($CHCl_3$ = 7.26 ppm (^{1}H); 77.16 ppm (^{13}C)). Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). Multiplicity is as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad peak); app. = apparent. In some cases, the carbon atoms neighbouring boron were not observed due to quadrupolar relaxation.

Gas chromatography mass spectrometry (GC-MS) was performed with an Agilent 6890N gas chromatograph coupled to a 5973 inert mass selective detector (He carrier gas, EI ionisation) or *via* Durham University Mass spectrometry service (Shimadzu QP2010-Ultra GC-MS).

Liquid chromatography mass spectrometry (LC-MS) was carried out on an Acquity UPLC system coupled to a TQD mass spectrometer, with a mobile phase of 0.1 % aqueous formic acid/acetonitrile and an Acquity UPLC BEH C8 1.7µm (2.1mm x 50mm) column.

High resolution mass spectrometry (HRMS) was carried out on a QtoF Premier mass spectrometer (Waters Ltd, UK) with electrospray ionisation or atmospheric solids analysis probe (ASAP) ionisation on an Acquity LCT premier XE (Waters Ltd, UK).

Infrared spectra (IR) were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer (Attenuated total reflection, ATR) over a range of 4000 – 600 cm^{-1}. Peaks are reported in wavenumbers (cm^{-1}).

General procedure for copper catalysed borylation (CuI/PPh_3 conditions):

To an oven dried round bottomed flask/microwave *via*l containing a magnetic stirrer bar was added CuI (10 mol%); PPh_3 (13 mol%); LiOMe (2 eq.) and B_2pin_2 (1.5 eq.). The flask was sealed with a septum then purged under vacuum and backfilled with nitrogen (three cycles). To the sealed vessel *via* syringe was added a solution of the alkyl halide (1 eq.) in anhydrous DMF (0.5 M). The reaction mixture was left to stir for the indicated time. After completion, the crude mixture was diluted with EtOAc and filtered through a silica gel plug, washing with EtOAc. The filtrate was washed 4 times with water and once with brine then dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (DCM/hexane) afforded the title boronate ester.

Xantphos/CuCl borylation conditions:[32]

To an oven dried round bottomed flask/microwave *via*l containing a magnetic stirrer bar was added Xantphos (5 mol%), CuCl (5 mol%), B_2pin_2 (1.2 eq.) and KO^tBu as the base (1.2 eq.). The flask was sealed with a septum then purged under vacuum and backfilled with nitrogen (three cycles). To the sealed vessel *via* syringe was added a solution of the alkyl halide (1 eq.) in anhydrous THF (0.5 M) and the mixture left to stir for the indicated time. The filtrate was washed with water twice then once with brine before drying and concentrating *in vacuo.* Purification by chromatography (DCM/hexane) afforded the title boronate ester.

General procedure for oxidation of boronate esters to alcohols with oxone:

To a solution of the boronate ester in a 1:1 mixture of acetone:water (0.2 M) was added oxone (1 eq.). After stirring at room temperature (around 30 min) the mixture was quenched by the addition of saturated aq. $Na_2S_2O_3$. The solution was extracted with EtOAc 3 times and the combined organic layers were dried over magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography afforded the title alcohol.

General procedure for a Grignard reaction

To an oven dried flask containing magnesium turnings (1.2 eq.) was added dropwise a solution of 5-bromo-1-pentene (1 eq.) in dry THF (0.6 M). After complete addition over 15 minutes, the mixture was stirred at r.t. for a further 45 minutes. The solution was cooled on ice and a solution of the aldehyde (1 eq.) in dry THF (0.6 M) was added dropwise. The mixture was stirred for 2 h then quenched with saturated aq. NH_4Cl and extracted into EtOAc (2 x). The combined organic layers were washed with $NaHCO_3$ then brine and dried over magnesium sulfate. After concentrating *in vacuo*, purification by column chromatography (0 – 40% EtOAc/hexane) afforded the title alcohol.

General procedure for an Appel reaction to prepare alkyl halides from alcohols

To a solution of the alcohol (1 eq.) in dry DCM (0.4 M) at 0 ^{o}C was added CBr_4 (1.5 eq.) followed by PPh_3 (1.5 eq.). The reaction mixture was allowed to warm to room temperature with stirring overnight then concentrated *in vacuo*. Purification by column chromatography afforded the title bromide.

General procedure A for preparation of allyl protected substrates[194]

To a solution of the alcohol/amine (1 eq.) in acetone (0.8 M) was added anhydrous K_2CO_3 (1.2 eq.) followed by allyl bromide (1.5 eq.). The mixture was heated at reflux overnight. After cooling to room temperature, the reaction mixture was filtered, concentrated, redissolved in DCM (or ethyl acetate), washed with 1M aq. NaOH and then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (EtOAc/hexane) afforded the title ether.

General procedure B for preparation of allyl protected substrates[170]

To a solution of the alcohol/amine (1 eq.) in dry THF (1 M) was added sodium hydride (60% dispersion in mineral oil, 1.5 eq.). The mixture was stirred at 0 ^{o}C for 10 minutes and allyl bromide (1.5 eq.) was added. After warming to room temperature, the mixture was heated at reflux overnight then quenched by the addition of sat. aqueous NH_4Cl. The mixture was extracted into ether 3 times and the combined organic layers were washed with brine then dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (EtOAc/hexane) afforded the title ether.

General procedure for deallylation experiments:

To a round bottomed flask/microwave *via*l containing a magnetic stirrer bar was added CuI (0.1 eq); PPh_3 (0.13 eq.); LiOMe (2 eq.) and B_2pin_2 (1.5 eq.). The flask was capped and to the vessel *via* syringe was added a solution of the allyl ether (1 mmol, 1 eq.) in anhydrous DMF (0.5 M). The reaction mixture was left to stir at room temperature for the stated time. After completion, the crude mixture was

diluted with EtOAc and filtered through celite, washing with EtOAc. The filtrate was washed 3 times with water and once with brine then dried over magnesium sulfate and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc/hexane) to give the desired deprotected compound. All spectra and physical properties of the obtained deprotected compounds matched those of authentic samples.

Radical scavenger experiments:

For experiments with radical scavengers, the same procedure as above was carried out in the presence of 1,3-cyclohexadiene (1 eq.) or 9,10-dihydroanthracene (1 eq.). Analysis of both experiments by GC-MS showed that the reaction proceeded as normal with no apparent inhibition.

General procedure for the formation of 2-vinyl phenols (Wittig reaction):

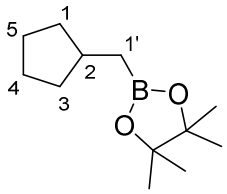
To a solution of methyltriphenylphosphonium bromide (2.3 eq.) in dry THF (50 mL) was added a solution of potassium *tert*-butoxide (2.3 eq.) in dry THF (0.5 M). The mixture was stirred for 2 h at room temperature then cooled to -78 ^{o}C and salicylaldehyde (1 eq.) was added. The mixture was allowed to warm to room temperature and left stirring overnight. After completion, the mixture was quenched with sat. ammonium chloride then concentrated to approx. half volume and extracted 3x with EtOAc. The combined organic layers were washed with brine then dried and concentrated *in vacuo*. Purification by column chromatography (0 – 40% EtOAc/hexane) afforded the title 2-vinyl phenols.

General procedure for the formation of β-substituted alcohols with ethylene carbonate

To a solution of the phenol (1 eq.) in dry DMF (0.5 M) at 0 ^{o}C was added cesium carbonate (0.2 eq.). The mixture was stirred at 0 ^{o}C for 15 minutes then ethylene carbonate (1.2 eq.) was added. The temperature was increased to 100 ^{o}C with stirring overnight. The reaction mixture was allowed to cool then water (10 mL) was added. The mixture was extracted with ether (3 x 10 mL) and the combined organic layers were washed with brine (3 x 10 mL) then dried and concentrated *in vacuo*. Purification by column chromatography (typically 0 – 40% EtOAc/hexane) afforded the title alcohols.

Experimental data for compounds in chapter 2

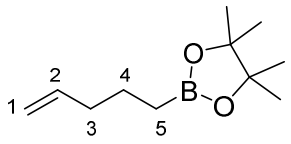
2-(cyclopentylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (49)[27]



Prepared according to the general procedure for CuI/PPh_3 borylation from 6-bromo-hex-1-ene (500 mg, 3.07 mmol), affording the boronate ester as a colourless oil (560 mg, 87%). Trace amounts of the uncyclised borylated material were detected. ν_{max} (ATR): 3005, 2947, 1739, 1371, 1317, 1216, 1145, 968, 907 cm^{-1}; δ_H (400 MHz) 2.02 – 1.89 (1H, m, 2-H), 1.84 – 1.72 (2H, m), 1.66 – 1.57 (2H, m), 1.53 – 1.45 (2H, m), 1.24 (12H, s, CH_3), 1.09 – 1.01 (2H,m), 0.84 (2H, d, *J* = 7.4 Hz, 1'-H); δ_C

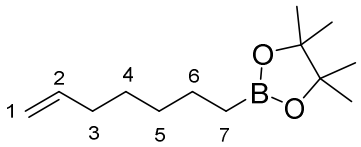
(101 MHz) 83.0 (pin-C), 36.3 (1-C,3-C), 35.2 (4-C, 5-C), 25.3 (2-C), 25.0 (CH_3); δ_B (128 MHz) 33.8; *m/z* (GC-MS, EI) 195 $[M\text{-}CH_3)]^+$.

1-(pentenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane(100l)[27]



Prepared according to the general procedure above for CuI/PPh_3 borylation from 5-bromo-pent-1-ene (500 mg, 3.35 mmol), affording the boronate ester as a colourless oil (597 mg, 91%). ν_{max} (ATR): 2978, 1374, 1320, 1144, 940 cm^{-1}; δ_H (400 MHz) 5.79 (1H, ddt, *J* = 17.0, 10.2, 6.8 Hz, 2-H), 5.04 – 4.89 (2H, m, 1-H), 2.08 – 2.00 (2H, m, 3-H), 1.55 – 1.45 (2H, m, 4-H), 1.24 (12H, s, CH_3), 0.78 (2H, t, *J* = 7.9 Hz, 5-H); δ_C (101 MHz) 139.1 (2-C), 114.6 (1-C), 83.0 (pin-C), 36.5 (3-C), 24.5 (4-C), 23.5 (5-C); δ_B (128 MHz) 34.0; *m/z* (GC-MS, EI) 181 $[M\text{-}CH_3]^+$.

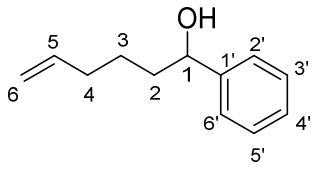
1-(heptenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (101l)



Prepared according to the general procedure above for CuI/PPh_3 borylation from 7-bromo-1-heptene (500 mg, 2.82 mmol), affording the boronate ester as a colourless oil (239 mg, 38%). ν_{max} (ATR): 2980, 2926, 1372, 1318, 1145, 966, 908 cm^{-1}; δ_H (400 MHz) 5.80 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, 2-H), 5.08 – 4.86 (2H, m, 1-H), 2.10 – 1.98 (2H, m, 3-H), 1.45 – 1.28 (6H, m, 4-H, 5-H, 6-H), 1.24 (12H, s, CH_3), 0.77 (2H, t, *J* = 7.7 Hz, 7-H); δ_C (101 MHz) 139.4 (2-H), 114.2 (1-H), 83.0 (pin-C), 36.1 (3-H), 33.9 (4-C),

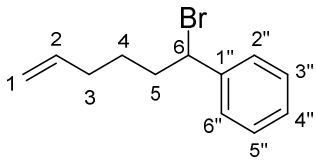
32.0 (5-C), 28.8 (6-C), 25.0 (CH_3), 24.0 (7-C); δ_B (128 MHz) 34.0; *m/z* (GC-MS, EI) 209 $[M\text{-}CH_3]^+$

1-Phenyl-5-hexen-1-ol (102)[195]



Prepared according to the general procedure for a Grignard reaction from benzaldehyde (2.04 mL, 20.1 mmol). affording the title alcohol as a colourless oil (1.64 g, 54%). ν_{max} (ATR): 3322, 2930, 2866, 1614, 1494, 1446, 1064, 990, 903 cm^{-1}; δ_H (400 MHz) 7.32 – 7.17 (5H, m, Ar-H), 5.70 (1H, m, 5-H), 4.96 – 4.82 (2H, m, 6-H), 4.60 (1H, dd, *J* = 7.5, 5.7 Hz, 1-H), 2.00 (2H, tdt, *J* = 7.4, 6.5, 1.4 Hz, 4-H), 1.80 – 1.59 (2H, m, 3-H), 1.52 – 1.38 (1H, m, 2-H), 1.37 – 1.26 (1H, m, 2-H); δ_C (101 MHz) 144.9 (1'-C), 138.7 (5-C), 128.6 (3'-C, 5'-C), 127.7 (2'-C, 6'-C), 126.0 (4'-C), 114.8 (6-C), 74.7 (1-C), 38.6 (2-C), 33.7 (4-C), 25.2 (3-C); *m/z* (GC-MS, EI) 176 $[M]^+$.

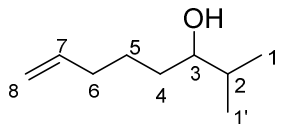
6-bromo-6-phenyl-1-hexene (104)



A solution of the alcohol (1-Phenyl-5-hexen-1-ol, 250 mg, 1.42 mmol) and pyridine (0.23 mL, 2.84 mmol) in dry DCM (2 mL) was cooled to 0 ^oC and to the flask was added a solution of PBr_3 (0.1 mL, 0.99 mmol) in dry DCM (1.5 mL). After stirring at r.t. overnight the mixture was quenched on ice with saturated aq. $NaHCO_3$ (5 mL)

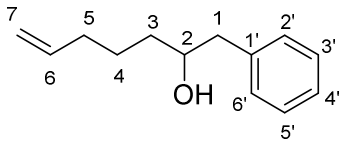
then diluted with DCM (5 mL). The DCM layer was washed with 10% aq. $CuSO_4$ (2 x 10 mL) followed by brine (10 mL) and water (2 x 10 mL), dried through a hydrophobic frit and concentrated *in vacuo*. Owing to instability on silica, the crude mixture (a green oily residue, 188 mg) was used immediately in the next reaction without purification (NMR/GC-MS indicated a mixture of the desired product and corresponding elimination product). For the crude ^{1}H NMR spectrum see page 193.

2-Methyl-7-octen-3-ol (103)[196]



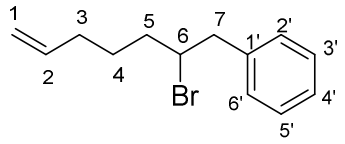
Prepared according to the general procedure for a Grignard reaction, from isobutyraldehyde (1.34 mL, 14.7 mmol, affording the title alcohol as a light orange oil (778 mg, 41%). ν_{max} (ATR): 3375, 2962, 2873, 1740, 1638, 1468, 1362, 1108, 993 cm^{-1}; δ_H (400 MHz) 5.82 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, 7-H), 5.06 – 4.91 (2H, m, 8-H), 3.40 – 3.33 (1H, m, 3-H), 2.09 (2H, m, 4-H), 1.71 – 1.57 (2H, m, 5-H), 1.52 – 1.33 (1H, m, 2-H), 0.91 (6H, m, 1-CH_3, 1'-CH_3); δ_C (101 MHz) 138.9 (7-C), 114.7 (8-C), 33.9 (3-C), 33.7 (6-C), 33.7 (4-C), 25.5 (5-C), 19.0 (2-C), 17.2 (1-C, 1'-C); *m/z* (GC-MS, EI) 142 $[M]^+$.

1-Phenyl-6-hepten-2-ol (104)[197]



Prepared according to the general Grignard reaction procedure from phenylacetaldehyde (1.6 mL, 13.4 mmoL), affording the title alcohol as a light yellow oil (1.1 g, 43%). ν_{max} (ATR): 3366, 2932, 2862, 1640, 1490, 1446, 1082, 990, 908 cm^{-1}**;** δ_H (400 MHz) 7.35 – 7.28 (2H, m, 3'-H, 5'-H), 7.26 – 7.19 (3H, m, 2'-H, 4'-H, 6'-H), 5.82 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, 6-H), 5.05 – 4.93 (2H, m, 7-H), 3.87 – 3.78 (1H, m, 2-H), 2.84 (1H, dd, *J* = 13.5, 4.2 Hz, 1-H), 2.65 (1H, dd, *J* = 13.5, 8.5 Hz, 1-H), 2.14 – 2.04 (2H, m, 3-CH_2), 1.65 – 1.45 (4H, m, 4-CH_2, 5-CH_2); δ_C (176MHz) δ 138.6 (6-C), 138.5 (1'-C), 129.4 (3'-C), 128.5 (4'-C), 126.4 (2'-C, 6'-C), 114.6 (7-C), 72.5 (2-C), 44.1 (1-C), 36.2 (5-C), 33.7 (3-C), 25.0 (4-C); *m/z* (GC-MS, EI) 92 [M – CH_2=$CHCH_2CH_2CH_2CHOH$]$^+$.

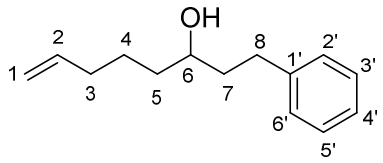
6-bromo-7-phenyl-1-heptene (106)



Following the general procedure for an Appel reaction, 1-Phenyl-6-hepten-2-ol (1.1 g, 5.79 mmol) afforded the title bromide as a colourless oil (428 mg, 31%). ν_{max} (ATR): 3070, 2920, 2900, 2036, 1510, 1442, 992, 902 cm^{-1}; δ_H (400 MHz) 7.36 – 7.26 (2H, m, 3'-H, 5'-H), 7.25 – 7.17 (3H, m, 2'-H, 4'-H, 6'-H), 5.77 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, 2-H), 5.04 – 4.92 (2H, m, 1-H), 4.21 (1H, dtd, *J* = 8.5, 7.2, 4.2 Hz, 6-H), 3.25 –

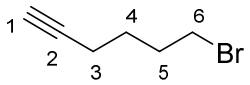
3.10 (2H, m, 7-H), 2.14 – 1.98 (2H, m, 5-H), 1.91 – 1.78 (2H, m, 3-H), 1.76 – 1.68 (1H, m, 4-H), 1.60 – 1.47 (1H, m, 4-H); δ_C (101 MHz) δ 138.7 (2-C), 138.3 (1'-C), 129.4 (3'-C), 128.6 (4'-C), 126.9 (2'-C, 6'-C), 115.1 (1-C), 57.6 (6-C), 45.9 (7-C), 37.7 (3-C), 33.1 (5-C), 26.9 (4-C); *m/z* (GC-MS, EI) 254 $[M(^{81}Br)]^+$, 252 $[M\ (^{79}Br)]^+$.

6-hydroxy-8-phenyl-1-octene (105)[198]



Following the general Grignard reaction procedure from hydrocinnemaldehyde (1 g, 7.46 mmol), the reaction mixture was heated under reflux for 2 h, affording the title alcohol as a colourless oil (214 mg, 14%). ν_{max} (ATR): 3342 (br) 2932, 2858, 1640, 1496, 1454, 1030, 994 cm^{-1}**;** δ_H (400 MHz) 7.29 (2H, td, *J* = 7.3, 1.5 Hz, 3'-H, 5'-H), 7.22 – 7.15 (3H, m, 1'-H, 2'-H, 6'-H), 5.80 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, 2-H), 5.04 – 4.93 (2H, m, 1-H), 3.64 (1H, m, *J* = 8.3, 4.2 Hz, 6-H), 2.80 (1H, ddd, *J* = 15.4, 9.6, 5.9 Hz, 8-H), 2.67 (1H, ddd, *J* = 13.8, 9.6, 6.8 Hz, 8-H), 2.14 – 2.04 (2H, m, 7-H), 1.86 – 1.69 (2H, m, 5-H), 1.60 – 1.38 (4H, m, 3-H, 4-H); δ_C (101 MHz) 142.3 (2-C), 138.8 (1'-C), 128.6 (3'-C, 5'-C), 126.0 (2'-C, 4'-C, 6'-C), 114.8 (1-C), 71.4 (6-C), 39.3 (8-C), 37.1 (3-C), 33.8 (7-C), 32.2 (5-C), 25.0 (4-C); *m/z* (GC-MS, EI) 186 $[M - H_2O]^+$.

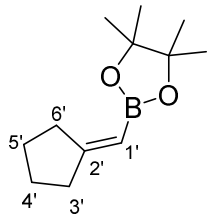
6-bromohex-1-yne (51)[199]



Following the general procedure for an Appel reaction, 5-hexyn-1-ol (0.56 mL, 5.10 mmol) gave the title bromide as a colourless oil (229 mg, 28%). ν_{max} (ATR): 2001,

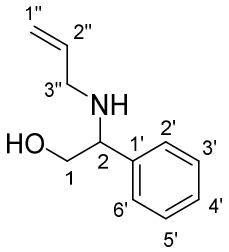
1980, 1742, 1360, 1222 cm^{-1}; δ_H (600 MHz) 3.44 (2H, t, *J* = 6.7 Hz, 6-H), 2.24 (2H, td, *J* = 7.0, 2.6 Hz, 3-H), 2.03 – 1.97 (2H, m, 5-H), 1.97 (1H, t, *J* = 2.7 Hz, 1-H), 1.69 (2H, p, *J* = 7.1 Hz, 4-H); δ_C (151 MHz) 83.8 (2-C), 69.0 (1-C), 33.3 (6-C), 31.7 (5-C), 27.0 (4-C), 17.8 (3-C); *m/z* (GC-MS, EI) 134 $[M(^{81}Br)\text{-}C_2H_2]^+$, 132 $[M(^{79}Br)\text{-}C_2H_2]^+$.

2'-(cyclopentylidenemethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (52)[200]



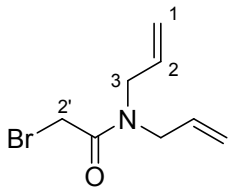
Prepared according to the general procedure for copper catalysed borylation from 6-bromohex-1-yne *via* both Xantphos/CuCl (15% yield) and CuI/PPh_3 (33% yield) conditions. ν_{max} (ATR): 2974, 2872, 1644, 1370, 1258, 1145, 970 cm^{-1}; δ_H (700 MHz) 5.27 (1H, p, *J* = 2.2 Hz, 1'-H), 2.54 – 2.49 (2H, m, 3'-H, 6'-H), 2.40 – 2.34 (2H, m, 3'-H, 6'-H), 1.73 – 1.66 2H, m, 4'-H, 5'-H), 1.66 – 1.59 (2H, m, 4'-H, 5'-H), 1.25 (12H, s, $-CH_3$); δ_C (176 MHz) 172.1 (2'-C), 82.7 (pin-C), 37.7 (3'-C, 6'-C), 33.4 (3'-C, 6'-C), 27.0 (4'-C, 5'-C), 26.0 (4'-C, 5'-C), 25.1 ($-CH_3$); δ_B (128 MHz) 29.8; *m/z* (GC-MS, EI) 208 $[M]^+$.

2-allylamino-2-phenylethanol (117)[201]



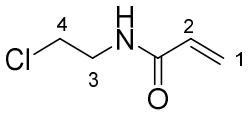
To a stirred solution of phenylglycinol (1.5 g, 10.8 mmol) and triethylamine (1.83 mL, 13 mmol) in dry THF (10 mL) was added dropwise allyl bromide (1.13 mL, 13 mmol). The reaction mixture was stirred at room temperature for 19 h then filtered through celite, washing with EtOAc. The concentrated filtrate was purified by column chromatography (0 – 80% EtOAc/hexane/1% NEt_3) to give the title amino alcohol as a colourless oil (1.6 g, 84%). ν_{max} (ATR): 3320, 2820, 2012, 1884, 1442, 1046, 1020 cm^{-1}; δ_H (400 MHz) 7.39 – 7.26 (5H, m, Ar-H), 5.97 – 5.80 (1H, m, 2''-H), 5.25 – 5.00 (2H, m, 1''-H), 3.82 (1H, dd, *J* = 8.6, 4.4 Hz, 2-H), 3.72 (1H, dd, *J* = 10.8, 4.4 Hz, 1-H), 3.58 (1H, dd, *J* = 10.8, 8.6 Hz, 1-H), 3.22 (1H, ddt, *J* = 14.0, 5.6, 1.5 Hz, 3''-H), 3.08 (1H, ddt, *J* = 14.0, 6.4, 1.3 Hz, 3''-H), 2.68 (2H, br s, OH, NH); δ_C (176 MHz) 140.5 (1'-C), 136.5 (2''-C), 128.8 (3'-C, 5'-C), 127.8 (4'-C), 127.4 (2'-C, 6'-C), 116.4 (1''-C), 66.7 (1-C), 63.9 (2-C), 49.8 (3''-C); *m/z* (GC-MS, EI) 146 $[M - CH_2OH]^+$.

2'-bromo-*N,N*-di(prop-2-en-1-yl)acetamide (121)



To a flask containing a solution of bromoacetyl bromide (0.22 mL, 2.47 mmol) in dry DCM (3 mL) was added at 0 ^{o}C a solution of diallylamine (0.76 mL) in dry 1.5 mL dry DCM. The reaction mixture was allowed to warm to room temperature with stirring over 3 h. Following completion, 10 mL water was added and the organic layer was washed with 1N HCl (10 mL) followed by water (10 mL). After drying over $MgSO_4$ and concentrating *in vacuo* the title amide was obtained as a colourless oil without the need for further purification (452 mg, 83%). ν_{max} (ATR): 3076, 2982, 1642, 1451, 1408, 1286, 1194, 1100, 988, 928 cm^{-1}**;** δ_H (400 MHz) 5.93 – 5.66 (2H, m, 2-H), 5.33 – 5.10 (4H, m, 1-H), 3.99 (4H, ddt, *J* = 6.9, 5.0, 1.7 Hz, 3-H), 3.84 (2H, s, CH_2Br); δ_C (101 MHz) 167.0 (C=O), 132.7, 132.3 (2-C), 117.8, 117.3 (1-C), 50.2, 48.3 (3-C), 26.3 (-CH_2Br); *m/z* (GC-MS, EI) 219 ([M^{81}Br]$^+$) 217 ([M^{79}Br]$^+$).

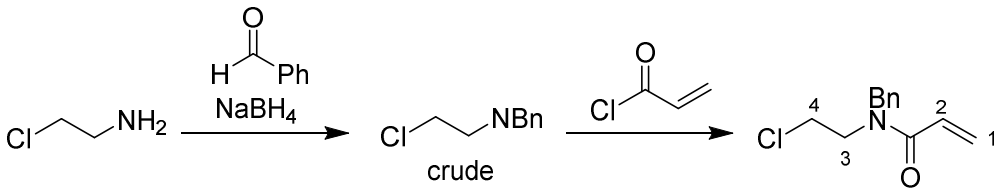
***N*-(2-chloroethyl)prop-2-enamide (123)**



To a solution of 2-chloroethylamine HCl salt (500 mg, 4.31 mmol) in dry DCM (10 mL) was added triethylamine (1.83 mL, 12.93 mmol). After stirring for 5 minutes the reaction mixture was cooled to 0 ^{o}C and acrolyl chloride (0.42 mL, 5.2 mmol) in dry DCM (5 mL) was added dropwise, turning the solution yellow in colour. After 19 h,

the reaction was quenched by the addition of water and the organic layer washed with saturated aq. $NaHCO_3$ (20 mL) and 1N HCl (20 mL). After drying and concentrating *in vacuo*, the resulting oil was suspended in EtOAc and the suspension filtered through a silica plug (eluting with EtOAc) to give the title amide as a light yellow oil (180 mg, 31%) ν_{max} (ATR): 3274, 1974, 1650, 1636, 1626, 1248, 984, 778 cm^{-1}**;** δ_H (400 MHz) 6.32 (1H, dd, *J* = 17.0, 1.4 Hz, 2-H), 6.12 (1H, app. ddt, *J* = 17.0, 10.3 Hz, 1-H_{trans}), 5.99 (1H, s, NH), 5.70 (1H, dd, *J* = 10.3, 1.4 Hz, 1-H_{cis}), 3.75 – 3.59 (4H, m, 3-H, 4-H); δ_C (101 MHz) 165.7 (C=O), 130.5 (2-C), 127.3 (1-C), 44.2 (3-C), 41.4 (4-C); *m/z* (GC-MS, EI) 133 $[M]^+$.

_N_-benzyl-_N_-(2-chloroethyl)prop-2-enamide (122)

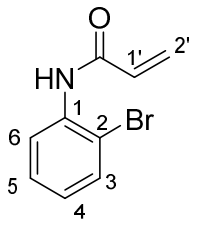


Step 1: To a solution of 2-chloroethylamine HCl salt (1.0 g, 6.25 mmol) in DCE (20 mL) was added triethylamine (0.73 mL, 5.2 mmol). After stirring for 5 minutes, benzaldehyde (0.53 mL, 5.2 mmol) was added followed by $NaBH(OAc)_3$. After 3 h, the reaction was quenched with sat. aqueous $NaHCO_3$ then diluted with DCM. The organic layer was dried over $MgSO_4$ then concentrated *in vacuo* to give a colourless oil (970 mg) which was carried through to the next stage without purification.

Step 2: To a round bottomed flask at – 78 ^oC was added dry THF (5 mL). Under an atmosphere of argon, acrolyl chloride (0.23 mL, 2.83 mmol) was added followed by DIPEA (0.49 mL, 2.83 mmol) and a solution of the crude amine (dropwise). The

reaction mixture was allowed to warm to room temperature and after completion (1.5 h) was concentrated *in vacuo* to remove THF. The residue was redissolved in EtOAc (10 mL) then washed with sat. aqueous $NaHCO_3$ (10 mL), 1N HCl (10 mL), brine (10 mL), dried over $MgSO_4$ then concentrated *in vacuo*. The resulting residue was purified by column chromatography (0 – 30% EtOAc/hexane) to give the title amide as an (impure) colourless oil (364 mg, 26%). ν_{max} (ATR): 2950, 1735, 1638, 1608, 1442, 1416, 1356, 1218, 1176, 970 cm^{-1}**;** *m/z* (GC-MS, EI) 223 [M+], 174 ([M-$CH_2CH_2Cl]^+$); the sample contained unidentifiable impurities (NMR).

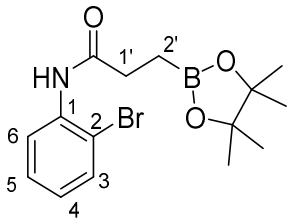
_N_-(2-bromophenyl)prop-2'-enamide (124b)[202]



To a solution of 2-bromoaniline (500 mg, 2.91 mmol) in dry DCM (5 mL) was added triethylamine (0.63 mL, 4.37 mmol). The solution was cooled to 0 ^oC and acrolyl chloride (0.24 mL, 3.2 mmol) was added dropwise. The mixture was allowed to warm to room temperature with stirring overnight and then 1M HCl (10 mL) was added. The organic layer was diluted with DCM (10 mL) then washed with sat. aq. $NaHCO_3$ (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (0 – 30% EtOAc/hexane) to give the title amide as a white solid which melted around room temperature (329 mg, 50%). ν_{max} (ATR) 3277, 1674, 1589, 1518, 1435, 1402, 1313, 1294, 1183, 1026, 975 cm^{-1}; δ_H (700 MHz) 8.46 (1H, d, *J* = 8.3 Hz, 3-H), 7.76 (1H, s, NH), 7.55 (1H, dd, *J* =

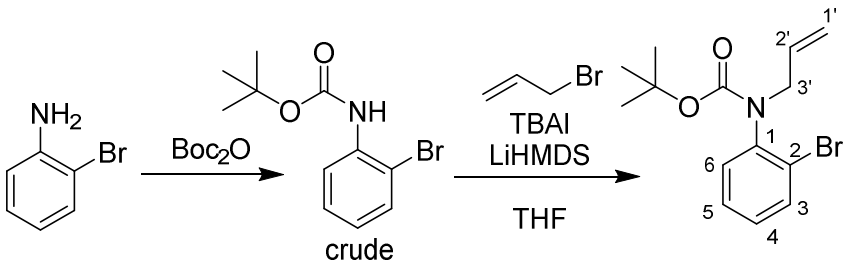
8.1, 1.5 Hz, 6-H), 7.37 – 7.31 (1H, m, 5-H), 7.00 (1H, ddd, *J* = 8.0, 7.4, 1.6 Hz, 4-H), 6.54 – 6.43 (1H, m, 1'-H), 6.31 (1H, dd, *J* = 16.9, 10.2 Hz, 2'-H_{cis}), 5.83 (1H, dd, *J* = 10.2, 1.2 Hz, 2'-H_{trans}); δ_C (101 MHz) 163.5 (C=O), 135.7 (1-C), 132.4 (1'-C), 131.4 (3-C), 128.6 (2'-C), 128.3 (5-C), 125.5 (6-C), 122.0 (2-C), 113.4 (4-C); *m/z* (GC-MS, EI) [227 M(^{81}Br)]$^+$, 225 [M(^{79}Br)]$^+$.

N-(2-bromophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (125b)



Isolated as the main byproduct from the attempted borylative cyclisation of N-(2-bromophenyl)prop-2'-enamide in 32% yield (a colourless oil, 33 mg). ^{1}H NMR data and GC-MS are reported here; the sample contained unknown trace impurities: δ_H (700 MHz) 8.35 (1H, d, *J* = 7.6 Hz, 3-H), 7.72 (1H, s, NH), 7.51 (1H, dd, *J* = 8.0, 1.5 Hz, 6-H), 7.37 – 7.26 (1H, m, 5-H), 6.94 (1H, td, *J* = 7.5, 1.6 Hz, 4-H), 2.56 (2H, t, *J* = 7.6 Hz, 1'-H), 1.25 (12H, s, pinCH_3), 1.16 (2H, t, *J* = 7.6 Hz, 2'-H); *m/z* (GC-MS, EI) [355 M(^{81}Br)]$^+$, 353 [M(^{79}Br)]$^+$.

tert-butyl (2-bromophenyl)prop-2'-en-1'-ylcarbamate (124a)[203]

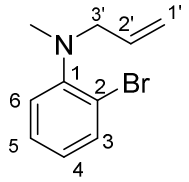


Step 1: To a solution of aniline (500 mg, 2.91 mmol) in dry THF (3 mL) at 0 ^{o}C was added dropwise LiHMDS (3.5 mL of a 1M solution in THF). The mixture was stirred for 30 minutes and Boc_2O (697 mg, 3.20 mmol) and DMAP (36 mg, 0.3 mmol) were added. The mixture was allowed to warm to r.t overnight. The mixture was then concentrated *in vacuo* and purified by column chromatography (0 – 30% EtOAc/hexane) to give an impure mixture (~600 mg) containing the Boc protected material which was used immediately in the next step.

Step 2: To a flask containing the impure Boc protected aniline in dry THF (3 mL) at 0 ^{o}C was added dropwise LiHMDS (3.5 mL of a 1M solution in THF) followed by allyl bromide (0.29 mL, 3.33 mmol) and TBAI (111 mg, 0.3 mmol). After stirring at r.t. overnight, water (10 mL) was added and the mixture concentrated to approx. half volume *in vacuo*. The residue was extracted into DCM (10 mL) which was washed with 1M HCl (10 mL), water (10 mL), dried over $MgSO_4$ then concentrated *in vacuo* and purified by column chromatography to give the product as a yellow oil which solidified on standing (160 mg, 18% over both steps). ν_{max} (ATR) 2978, 1701, 1588, 1477, 1380, 1366, 1304, 1253, 1152, 1030, 862 cm^{-1}; δ_H (600 MHz), indicated a mixture of rotamers (evidenced by splitting of Boc signals around 1.3 ppm and EXSY-NMR experiments) 7.60 (1H, d, *J* = 8.0 Hz, 3-H), 7.28 (app. d, *J* = 8.0 Hz, 5-H),

7.19 – 7.10 (2H, m, 6-H, 4-H), 5.96 – 5.88 (1H, m, 2'-H), 5.15 – 5.04 (2H, m, 1'-H), 4.45 (1H, dd, *J* = 15.2, 5.8 Hz, 3'-H), 3.86 (1H, dd, *J* = 15.2, 7.0 Hz, 3'-H), 1.52 (3H, s, CH_{3minor}), 1.34 (6H, s, CH_{3major}); δ_C (151 MHz) 154.2 (C=O), 141.3 (1-C), 133.8 (2'-C), 133.1 (3-C), 130.7 (5-C) 128.6 (4-C), 127.9 (6-C), 124.1 (2-C), 117.8 (1'-C), 80.4 (-**C**$(CH_3)_3$), 53.3 (3'-C_{minor}) 52.1 (3'-C_{major}), 28.5 (-CH_{3minor}), 28.3 (-CH_{3major}); *m/z* (GC-MS, EI) [257 M(^{81}Br)-^{t}Bu]$^+$, 255 [M(^{79}Br)-^{t}Bu]$^+$.

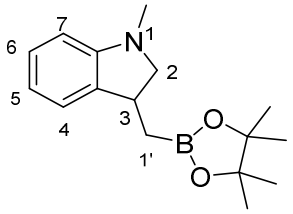
2-bromo-*N*-methyl-*N*-(prop-2'-en-1'-yl)aniline (124c)



To a solution of 2-bromo-*N*-methylaniline (500 mg, 2.91 mmol) in dry THF (3 mL) was added LiHMDS (1.61 mL of a 1M solution in THF). The solution was cooled to 0 ^oC and allyl bromide (0.17 mL, 2.01 mmol) was added dropwise. The mixture was allowed to warm to room temperature with stirring overnight and then water (10 mL) was added. The aqueous layer was extracted into EtOAc (3 x 10 mL) and the combined organic layers were then washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (0 – 10% EtOAc/hexane) to give the title amine as a colourless oil (309 mg, quant.). ν_{max} (ATR) 2981, 1757, 1476, 1368, 1220, 1079, 1038, 907 cm^{-1}; δ_H (400 MHz) 7.56 (1H, dd, *J* = 7.9, 1.5 Hz, 3-H), 7.25 (1H, ddd, *J* = 8.0, 7.3, 1.5 Hz, 5-H) 7.08 (1H, dd, *J* = 8.1, 1.6 Hz, 6-H), 6.89 (1H, ddt, *J* = 7.9, 7.3, 1.6 Hz, 4-H), 5.94 (1H, ddt, *J* = 17.3, 10.1, 6.2 Hz, 2'-H), 5.33 – 5.14 (2H, m, 1'-H), 3.62 (2H, dt, *J* = 6.3, 1.4 Hz, 3'-H), 2.74 (3H, s, -CH_3); δ_C (101 MHz) 151.1 (1'-C), 135.2 (1-C), 134.0 (3-C),

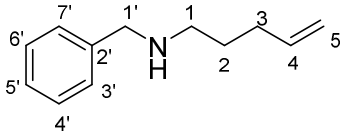
128.0 (5-C), 124.1 (6-C), 121.9 (2-C), 119.9 (4-C), 117.8 (1'-C), 59.60 (3'-C), 40.3 (-CH_3); *m/z* (GC-MS, EI) [227 M(^{81}Br)]$^+$, 225 [M(^{79}Br)]$^+$; HRMS (ASAP) requires 226.0231 (calc. for [M+H]$^+$) found 226.0239 ([$C_{10}H_{12}BrN$]+H).

1-methyl-3-[(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-2,3-dihydro-1H-indole (125c)



Isolated from the copper catalysed borylation of 2-bromo-*N*-methyl-*N*-(prop-2'-en-1'-yl)aniline as described in the general procedure above, affording the title boronate ester as a colourless oil (33%, 39 mg). ^{1}H NMR data and LC-MS are reported here (sample contaminated with acetone): δ_H (700 MHz) 7.10 – 7.02 (2H, m, 4-H, 6-H), 6.67 (1H, app. td, *J* = 7.3, 1.0 Hz, 5-H), 6.46 (1H, d, *J* = 7.7 Hz, 7-H), 3.55 (1H, td, *J* = 8.4, 1.2 Hz, 2-H), 3.36 (1H, m, 3-H), 2.80 (1H, app. t, *J* = 8.6 Hz, 2-H), 2.72 (3H, s, -CH_3), 1.25 (12H, d, J = 4.3 Hz, pinCH_3) 1.03, 0.93 (2H, m, 1'-H); δ_B (128 MHz) 33.6; *m/z* (LC-MS, ESI) 273 [M]$^+$.

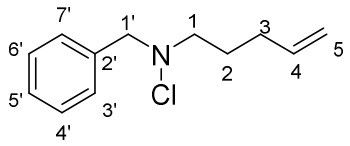
***N*-benzylpent-4-en-1-amine (136)[204]**



To a solution of benzylamine (0.2 mL, 1.87 mmol) in dry methanol (3 mL) was added 4-pentenal (0.19 mL, 1.96 mmol). After 1 h stirring at room temperature, sodium

borohydride (138 mg, 3.74 mmol) was added portionwise (effervescence). After 1 h, the reaction mixture was concentrated *in vacuo* then resuspended in a mixture of DCM/1 N HCl (10 mL). The DCM layer was separated and the aqueous layer basified to pH 14 by the addition of 1 N NaOH. The product was extracted into EtOAc (3 x 10 mL) then dried and concentrated *in vacuo*. Purification by column chromatography (0 – 50% EtOAc/hexane, 1% NEt_3) gave the title amine as a colourless oil (261 mg, 40%). ν_{max} (ATR): 2926, 2849, 1720, 1683, 1456, 1120, 914 cm^{-1}; δ_H (400 MHz) 7.35 – 7.30 (4H, m, Ar-H), 7.28 – 7.23 (1H, m, Ar-H), 5.82 (1H, ddt, *J* = 16.9, 10.2, 6.6 Hz, 4-H), 5.06 – 4.91 (2H, m, 5-H), 3.80 (2H, s, 1'-H), 2.68 – 2.59 (2H, m, 1-H), 2.17 – 2.03 (2H, m, 3-H), 1.69 – 1.56 (2H, m, 2-H); δ_C (101 MHz) 140.7 (2'-C), 138.7 (4-C), 128.5 (Ar-C), 128.3 (Ar-C), 127.0 (Ar-C), 114.8 (5-C), 54.2 (1'-C), 49.1 (1-C), 31.7 (3-C), 29.4 (2-C); *m/z* (GC-MS, EI) 174 $[M-H]^-$.

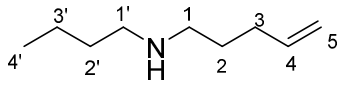
N-benzyl-*N*-chloropent-4-en-1-amine (137)[179]



To a solution of *N*-benzylpent-4-en-1-amine (120 mg, 0.68 mmol) in dry DCM (2 mL) at 0 ^oC was added *N*-chlorosuccinimide (90 mg, 0.68 mmol). After 2 h stirring at room temperature, the reaction mixture was concentrated *in vacuo* then resuspended in hexane. The suspension was filtered to give a colourless oil (146 mg, 100% crude yield). The product was used immediately without further purification. δ_H (400 MHz) 7.41 – 7.28 (5H, m, Ar-H), 5.79 (1H, ddt, *J* = 16.9, 10.2, 6.6 Hz, 4-H), 5.06 – 4.91 (2H, m, 5-H), 4.11 (2H, s, 1'-H), 3.01 – 2.92 (2H, m, 1-H), 2.16 – 2.08 (2H,

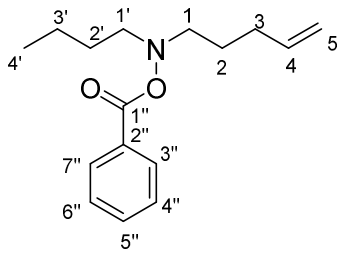
m, 3-H), 1.85 – 1.76 (2H, m, 2-H); δ_C (101 MHz) 138.2 (2'-C), 137.3 (4-C), 129.3 (Ar-C), 128.5 (Ar-C), 128.0 (Ar-C), 115.2 (5-C), 68.5 (1'-C), 62.5 (1-C), 30.9 (3-C), 27.1 (2-C); *m/z* (ASAP) 210 $[M+H]^+$.

_N_-butylpent-4-en-1-amine (140)[205]



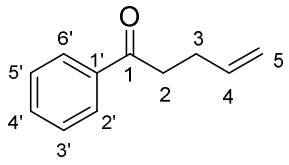
To a solution of butylamine (0.81 mL, 8.19 mmol) in methanol (15 mL) was added 4-pentenal (0.89 mL, 9.01 mL). The mixture was stirred for 1 h at room temperature then cooled to 0 ^oC and sodium borohydride (606 mg, 16.38 mmol) was added portionwise. The reaction mixture was allowed to warm to room temperature with stirring for a further 4 h then concentrated *in vacuo*. The residue was resuspended in a mixture of DCM/1 N HCl (10 mL), the DCM layer was separated and the aqueous layer basified to pH 14 by the addition of 1 N NaOH. The product was extracted into EtOAc (3 x 10 mL) then dried and concentrated *in vacuo*. The residue (a colourless oil/gum) was used without further purification (1.015 g, 88%). ν_{max} (ATR): 2956, 2924, 2792, 1632, 1459, 1128, 991, 907 cm^{-1}; δ_H (400 MHz) 5.78 (1H, ddt, *J* = 16.9, 10.2, 6.6 Hz, 4-H), 5.12 – 4.97 (2H, m, 5-H), 4.12 (1H, br. s, N-H), 2.91 – 2.77 (4H, m, 1'-H, 1-H), 2.15 (2H, m, 3-H), 1.96 – 1.84 (2H, m, 2-H), 1.81 – 1.69 (2H, m, 2'-H), 1.40 (2H, h, *J* = 7.4 Hz, 3'-H), 0.94 (3H, t, *J* = 7.4 Hz, 4'-CH_3); δ_C (101 MHz) 137.0 (4'-C), 116.1 (5'-C), 48.6 (1-C), 48.2 (1'-C), 31.3 (3-C), 29.5 (3'-C), 26.5 (2-C), 20.5 (2'-C), 13.8 (4'-CH_3); *m/z* (GC-MS, EI) 142 $[M]^+$.

(benzyl(pent-4-en-1-yl)amino)oxy(phenyl)methanone (138)[163]



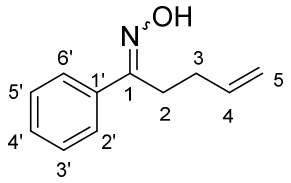
To a solution of Na_2HPO_4 (906 mg, 6.38 mmol) and dibenzoylperoxide (344 mg, 1.42 mmol as a 70% wt. with water solid) in dry ether (10 mL) was added N-butylpent-4-en-1-amine (200 mg, 1.42 mmol) in dry ether (5 mL). The mixture was heated under reflux overnight then concentrated *in vacuo*. The residue was dissolved in DCM (10 mL), washed with sat. sodium bicarbonate (2 x 10 mL), brine (10 mL), dried and concentrated *in vacuo*. Purification by column chromatography (0 – 30% EtOAc/hexane) gave an impure material which required further purification (80% DCM/hexane) to give the title *O*-benzoyl oxime as a colourless oil (100 mg, 27%). The compound's purity and identity was based on NMR data as it was not amenable to mass spectrometry. δ_H (400 MHz) 8.05 – 8.00 (2H, m, 3''-H, 7''-H), 7.61 – 7.53 (1H, m, 5''-H), 7.49 – 7.41 (2H, m, 4''-H, 6''-H), 5.78 (1H, ddt, *J* = 16.9, 10.2, 6.6 Hz, 4-H), 5.05 – 4.91 (2H, m, 5-H), 3.01 – 2.91 (4H, m, 1-H, 1'-H), 2.17 – 2.08 (2H, m, 3-H), 1.76 – 1.65 (2H, m, 2-H), 1.63 – 1.51 (2H, m, 2'-H), 1.45 – 1.32 (2H, m, 3'-H), 0.90 (3H, t, *J* = 7.3 Hz, 4'-CH_3); δ_C (101 MHz) 165.8 (1''-C), 138.2 (4-C), 133.1 (2''-C), 129.7 (3''-C, 7''-C), 128.6 (4''-C, 6''-C), 115.1 (5-C), 59.7 (1-C), 59.3 (1'-C), 31.5 (3-C), 29.1 (3'-C), 26.2 (2-C), 20.6 (2'-C), 14.1 (4'-CH_3).

1-phenylpent-4-en-1-one (144)[206]



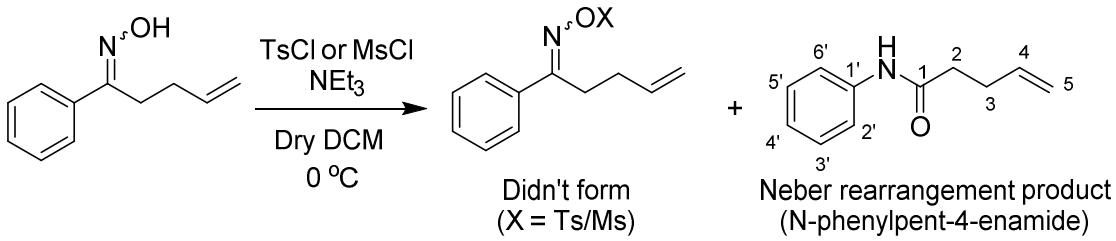
A solution of 4-bromobut-1-ene (0.51 mL, 5 mmol) in dry THF (7 mL) was added dropwise to magnesium turnings (122 mg, 5.1 mmol) in a 3-necked flask. After stirring for approximately 1 h, the solution of the Grignard reagent was transferred *via* syringe to a round bottomed flask (over 10 min, temperature held at -15 ^{o}C) containing a suspension of 5 mol% CuI (48 mg, 0.25 mmol) and benzoyl chloride (0.58 mL, 5 mmol) in dry THF (5 mL). After complete addition the temperature was held at -10 ^{o}C for 1 h then allowed to warm to room temperature. After 3.5 h stirring, the reaction mixture was concentrated, the residue dissolved in DCM (20 mL) then washed with 1 N HCl (10 mL). The organic layer was filtered to remove suspended matter then washed with saturated sodium bicarbonate (10 mL), dried and concentrated *in vacuo*. Purification by column chromatography (0 – 30% EtOAc/pet. ether) gave the title ketone as a colourless oil (405 mg, 51%). ν_{max} (ATR): 3072, 2940, 1708, 1685, 1638, 1584, 1440, 1278, 1198, 1004, 912 cm^{-1}; δ_H (400 MHz) 8.00 – 7.93 (2H, m, 2'-H, 6'-H), 7.61 – 7.54 (1H, m, 4'-H), 7.52 – 7.40 (2H, m, 3'-H, 5'-H), 5.91 (1H, ddt, *J* = 16.8, 10.2, 6.5 Hz, 4-H), 5.15 – 4.97 (2H, m, 5-H), 3.08 (2H, m, 2-H), 2.57 – 2.45 (2H, m, 3-H); δ_C (101 MHz) 199.6 (1-C), 137.5 (4-C), 133.2 (Ar-C), 128.7 (Ar-C), 128.2 (Ar-C), 115.4 (5-C), 37.9 (3-C), 28.3 (2-C); *m/z* (GC-MS, EI) 160 [M]$^{+}$.

_N_-Hydroxy-1-phenylpent-4-en-1-imine (145)[207]



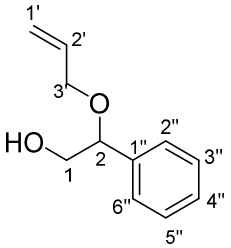
To a solution of 1-phenylpent-4-en-1-one (140 mg, 0.88 mmol) in dry methanol (2.5 mL) was added sequentially sodium acetate (79 mg, 0.96 mmol) and hydroxylamine hydrochloride (92 mg, 1.33 mmol). After stirring for 2 h at room temperature, the reaction mixture was diluted with DCM (10 mL) then washed with water (10 mL). The organic layer was dried and concentrated *in vacuo*. Purification by column chromatography (0 – 30% EtOAc/pet. ether) gave the title oxime (mixture of *E/Z* isomers) as a white waxy solid (100 mg, 65%). ν_{max} (ATR): 3236, 3070, 2920, 1632, 1453, 912 cm^{-1}; δ_H (400 MHz) 7.67 – 7.55 (2H, m, Ar-H), 7.46 – 7.34 (3H, m, Ar-H), 5.87 (1H, ddt, *J* = 16.8, 10.2, 6.6 Hz, 4-H), 5.13 – 4.95 (2H, m, 5-H), 2.96 – 2.86 (2H, m, 2-H), 2.37 – 2.28 (2H, m, 3-H); δ_C (101 MHz) 159.5 (1-C), 137.6 (4-C), 135.7 (Ar-C), 129.4 (Ar-C), 128.7 (Ar-C), 126.5 (Ar-C), 115.3 (5-C), 30.4 (3-C), 25.7 (2-C); *m/z* (GC-MS, EI) 175 $[M]^+$.

N-Phenylpent-4-enamide (146)[208]



N-Phenylpent-4-enamide was obtained as the primary by-product from attempted tosylation and mesylation of *N*-hydroxy-1-phenylpent-4-en-1-imine (41%). ν_{max} (ATR): 3317, 2915, 1663, 1605, 1547, 1440, 1319, 920 cm^{-1}; δ_H (700 MHz) 7.50 (2H, d, *J* = 7.9 Hz, 3'-H, 5'-H), 7.32 (2H, t, *J* = 7.9 Hz, 2'-H, 6'-H), 7.19 (1H, s, N-H), 7.10 (1H, t, *J* = 7.4 Hz, 4'-H), 5.89 (1H, m, 4-H), 5.13 (1H, d, *J* = 17.5 Hz, 4-H_{trans}), 5.06 (1H, d, *J* = 10.1 Hz, 4-H_{cis}), 2.48 (4H, m, 2-H, 3-H); δ_C (176 MHz) 170.6 (C=O), 138.0 (4-C), 137.0 (2'-C, 6'-C), 129.2 (3'-C, 5'-C), 124.4 (4'-C), 120.0 (1'-C), 116.1 (5-C), 37.0 (2-C), 29.6 (3-C); *m/z* (GC-MS, EI) 175 $[M]^+$.

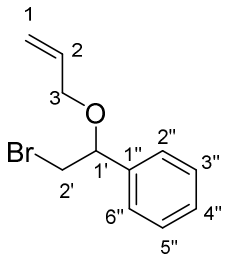
2-(allyloxy)-2-phenylethanol (151)[209]



To a mixture of allyl alcohol (7 mL, 102 mmol) and a catalytic amount of 95% conc. sulfuric acid (0.2 mL) was added dropwise styrene oxide (0.92 mL, 8.44 mmol). The reaction mixture was stirred at r.t. for 1 h then heated at 100 °C for a further 3 h. After allowing to cool, the mixture was basified by the addition of 3N NaOH solution then concentrated *in vacuo*. The residual liquid was diluted with ether (20 mL) then

washed with brine (2 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0 – 50% EtOAc/hexane) gave the title ether as a yellow oil (650 mg, 43%). ν_{max} (ATR): 3438, 3018, 2924, 2858, 2000, 1732, 1434, 1374, 1210 cm^{-1}; δ_H (400 MHz) 7.45 – 7.29 (5H, m, Ar-H), 5.92 (1H,m, 2'-H), 5.32 – 5.16 (2H, m, 1'-H), 4.49 (1H, dd, *J* = 8.5, 3.8 Hz, 2-H), 4.02 (1H, app. ddt, *J* = 12.6, 5.2, 1.5 Hz, 1-H), 3.86 (1H, ddt, *J* = 12.6, 6.2, 1.4 Hz, 1-H), 3.71 (1H, dd, *J* = 11.7, 8.5 Hz, 3'-H), 3.63 (1H, m, 3'-H); δ_C (101 MHz) 138.6 (2-C), 134.6 (1''-C), 128.7 (3''-C, 5''-C), 128.3 (2''-C, 6''-C), 127.0 (4''-C), 117.4 (1'-C), 82.3 (2-C), 70.0 (3'-C), 67.6 (1-C); *m/z* (GC-MS, EI) 147 $[M\text{-}CH_2{=}CHCH_2O]^+$.

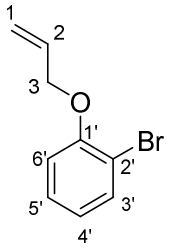
3-(2'-bromo-1'-phenylethoxy)-propene (147)[210]



Following the general procedure for an Appel reaction, 2-(allyloxy)-2-phenylethanol (1.19 g, 6.70 mmol) afforded the title bromide as a colourless oil (1.36 g, 84%). ν_{max} (ATR): 3084, 2858, 1978, 1736, 1202, 1088 cm^{-1}; δ_H (400 MHz) 7.42 – 7.29 (5H, m, Ar-H), 5.92 (1H, dddd, *J* = 17.2, 10.4, 6.2, 5.1 Hz, 2-H), 5.34 – 5.16 (2H, m, 1-H), 4.56 (1H, dd, *J* = 8.2, 4.4 Hz, 1'-H), 4.02 (1H, ddt, *J* = 12.8, 5.1, 1.5 Hz, 2'-H), 3.86 (ddt, *J* = 12.8, 6.2, 1.3 Hz, 2'-H), 3.57 (1H, dd, *J* = 10.6, 8.2 Hz, 3-H), 3.48 (1H, dd, *J* = 10.6, 4.5 Hz, 3-H); δ_C (101 MHz) 139.5 (2-C), 134.5 (1''-C), 128.8 (3''-C, 5''-C), 128.7 (2''-C, 6''-C), 127.0 (4''-C), 117.6 (1-C), 81.0 (1'-C), 70.3 (3-C), 36.5 (2'-C); *m/z* (GC-MS, EI) 185 $[M(^{81}Br)]^+$, 183 $[M\ (^{79}Br)]^+$.

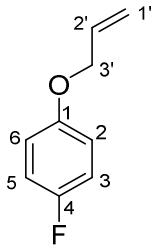
Experimental data for compounds in chapter 3

3-(2'-bromophenoxy)-1-propene (152)[164]



Following general procedure B for allyl protection, 2-bromophenol (0.35 mL, 3 mmol) gave the title ether as a colourless oil (615 mg, 97%). ν_{max} (ATR): 2884, 1470, 1280, 1248, 1103 cm^{-1}**;** δ_H (400 MHz) 7.54 (1H, dd, *J* = 7.9, 1.6 Hz, 5'-H), 7.27-7.22 (1H, m, 3'-H) 6.93 – 6.76 (2H, m, 4'-H, 6'-H), 6.07 (1H, ddt, *J* = 17.3, 10.6, 5.0 Hz, 2-H), 5.49 (1H, dq, *J* = 17.3, 1.7 Hz, 1-H_{trans}), 5.31 (1H, dq, *J* = 10.6, 1.5 Hz, 1-H_{cis}), 4.62 (2H, dt, *J* = 5.0, 1.7 Hz, 3'-H); δ_C (101 MHz) 155.1 (1'-C), 133.6 (2'-C), 132.8 (3'-C), 128.5 (5'-C), 122.1 (6'-C), 117.9 (1-C), 113.8 (4'-C), 112.5 (2'-C), 68.6 (3-C); *m/z* (GC-MS, EI) 214 $[M(^{81}Br)]^+$, 212 $[M\ (^{79}Br)]^+$.

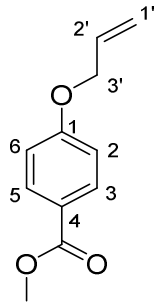
1-(allyloxy)-4-fluorobenzene (156)



Following general procedure A for allyl protection, 4-fluorophenol (3.00 g, 26.8 mmol) gave the title ether as a yellow oil (4.08 g, quant. yield). ν_{max} (ATR): 3011, 1736, 1508, 1372, 1215 cm^{-1}**;** δ_H (400 MHz) 7.03 – 6.92 (2H, m, 3-H, 5-H), 6.90 –

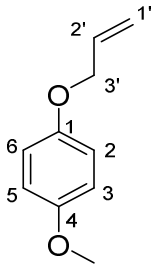
6.81 (2H, m, 2-H, 6-H), 6.04 (1H, ddt, *J* = 17.3, 10.6, 5.3 Hz, 2'-H), 5.46 – 5.25 (2H, m, 1'-H), 4.50 (2H, dt, *J* = 5.3, 1.6 Hz, 3'-H); δ_C (101 MHz) 157.4 (d, *J* = 238 Hz, 4-C), 154.8 (d, *J* = 2.2 Hz, 1-C), 133.3 (2'-C), 117.9 (1'-C), 115.9 (d, *J* = 23 Hz, 3-C, 5-C), 115.8 (d, *J* = 7.9 Hz, 2-C, 6-C), 70.0 (3'-C); δ_F (376 MHz) -124 (app. septet, *J* = 4.4 Hz); *m/z* (GC-MS, EI) 152 $[M]^+$.

methyl 4-[(prop-2'-en-1'-yl)oxy]benzoate (157)



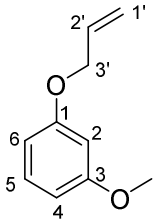
Following general procedure B for allyl protection, 4-methoxyphenol (500 mg, 3.29 mmol) gave the title ether as a yellow oil (487 mg, 77%). ν_{max} (ATR): 2983, 1717, 1606, 1511, 1436, 1280, 1252, 1169, 1106 cm^{-1}; δ_H (700 MHz) 8.01 – 7.95 (2H, m, 3-H, 5-H), 6.95 – 6.89 (2H, m, 2-H, 6-H), 6.05 (1H, ddt, *J* = 17.3, 10.5, 5.3 Hz, 2'-H), 5.43 (1H, dq, *J* = 17.3, 1.6 Hz, 1'-H_{trans}), 5.32 (1H, dq, *J* = 10.5, 1.4 Hz, 1'-H_{cis}), 4.59 (2H, dt, *J* = 5.3, 1.6 Hz, 3'-H), 3.88 (3H, s, CH_3); δ_C (176 MHz) 167 (C=O), 162 (4-C), 132.7 (2'-C), 131.7 (3-C, 5-C), 118.3 (1'-C), 122.9 (1-C), 114.7 (2-C, 6-C), 69.0 (3'-C), 52.0 (CH_3); *m/z* (GC-MS, EI) 192 $[M]^+$.

1-(allyloxy)-4-methoxybenzene (158)



Following general procedure A for allyl protection, 4-methoxyphenol (250 mg, 2.02 mmol) gave the title ether as a colourless oil (247 mg, 75%). ν_{max} (ATR): 2999, 2907, 2834, 1504, 1463, 1227, 1180, 1037, 996 cm^{-1}; δ_H (400 MHz) 6.89 – 6.80 (4H, m, Ar-H), 6.05 (1H, ddt, *J* = 17.2, 10.6, 5.3 Hz, 2'-H), 5.40 (1H, dq, *J* = 17.3, 1.6 Hz, 1'-H_{trans}), 5.27 (1H, dq, *J* = 10.5, 1.4 Hz, 1'-H_{cis}), 4.49 (2H, dt, *J* = 5.3, 1.5 Hz, 3'-H), 3.77 (3H, s, CH_3); δ_C (101 MHz) 154.0 (4-C), 152.9 (1-C), 133.7 (2'-C), 117.6 (1'-C), 115.9, 114.7 (2-C, 3-C, 5-C, 6-C), 69.7 (3'-C), 55.9 (CH_3); *m/z* (GC-MS, EI) 164 $[M]^+$.

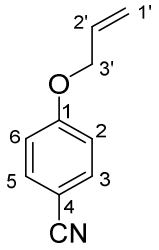
1-methoxy-3-[(prop-2'-en-1'-yl)oxy]benzene (159)



Following general procedure A for allyl protection, 3-methoxyphenol (1.00 g, 8.06 mmol gave the title ether as a colourless oil (876 mg, 66%). ν_{max} (ATR): 1592, 1492, 1452, 1283, 1265, 1200, 1149, 1044 cm^{-1}**;** δ_H (700 MHz) 7.18 (1H, t, *J* = 8.1 Hz, 5-H), 6.53 – 6.51 (2H, m, 4-H, 6-H), 6.49 (1H, app t., *J* = 2.4 Hz, 2-H), 6.06 (1H, ddt, *J* = 17.3, 10.6, 5.3 Hz, 2'-H), 5.42 (1H, dq, *J* = 17.3, 1.6 Hz, 1'-H_{trans}), 5.29 (1H, dq, *J* = 10.5, 1.4 Hz, 1'-H_{cis}), 4.52 (2H, dt, *J* = 5.4, 1.5 Hz, 3'-H), 3.79 (3H, s, CH_3); δ_C (176

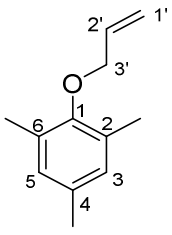
MHz) 161.0 (3-C), 160.0 (1-C), 133.4 (2'-C), 130.0 (5-C), 117.8 (1'-C), 107.0 (6-C), 106.6 (4-C), 101.4 (2-C), 69.0 (3'-C), 55.4 (-CH_3); *m/z* (GC-MS, EI) 164 $[M]^+$.

1-(allyloxy)-4-cyanobenzene (160)



Following general procedure A for allyl protection, 4-cyanophenol (1.00 g, 8.40 mmol) gave the title ether as a fluffy white solid (1.00 g, 75%). ν_{max} (ATR): 1604, 1507, 1305, 1256, 1173, 1236, 1016, 995, 833 cm^{-1}**;** 1H NMR (700 MHz, Chloroform-d) δ 7.60 – 7.56 (2H, m, 3-H, 5-H), 6.98 – 6.94 (2H, m, 2-H, 6-H), 6.03 (1H, ddt, *J* = 17.2, 10.5, 5.3 Hz, 2'-H), 5.42 (1H, dq, *J* = 17.3, 1.6 Hz, 1'-H_{trans}), 5.33 (1H, dq, *J* = 10.5, 1.4 Hz, 1'-H_{cis}), 4.59 (2H, dt, *J* = 5.3, 1.6 Hz, 3'-H). δ_C (176 MHz) 162.0 (1-C), 134.1 (3-C, 5-C), 132.2 (2'-C), 119.3 (-CN), 118.6 (1'-C), 115.6 (2-C, 6-C), 104.3 (4-C), 69.2 (3'-C); *m/z* (GC-MS, EI) 159 $[M]^+$; melting point 40.8 – 41.6 ^oC.

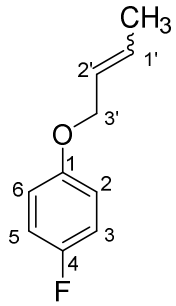
1,3,5-trimethyl-2-[(prop-2'-en-1'-yl)oxy]benzene (161)



Following general procedure A for allyl protection, trimethylphenol (1.00 g, 7.35 mmol) gave the title ether as a colourless oil (575 mg, 44%). ν_{max} (ATR): 2919, 1483, 1421, 1374, 1307, 1213, 1146, 990, 922 cm^{-1}**;** δ_H (600 MHz) 6.83 (2H, d, *J* = 0.7 Hz, 3-

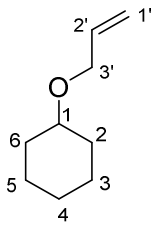
H, 5-H), 6.12 (1H, ddt, *J* = 17.2, 10.4, 5.5 Hz, 2'-H), 5.43 (1H, dq, *J* = 17.2, 1.6 Hz, 1'-H_{trans}), 5.26 (1H, dq, *J* = 10.4, 1.4 Hz, 1'-H_{cis}), 4.29 (2H, dt, *J* = 5.5, 1.5 Hz, 3'-H), 2.25 (6H, s, 2-CH_3, 6-CH_3), 2.24 (3H, s, 4-CH_3); δ_C (151 MHz) 153.8 (1-C), 134.4 (2'-C), 133.2 (4-C), 130.8 (2-C, 6-C), 129.5 (3-C, 5-C), 117.2 (1'-C), 73.3 (3'-C), 20.8 (4-CH_3), 16.4 (2-CH_3, 6-CH_3); *m/z* (GC-MS, EI) 176$[M]^+$.

1-[(but-2'-en-1'-yl)oxy]-4-methyl-benzene (162)



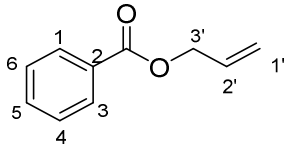
Following general procedure B for allyl protection, 4-fluorophenol (250 mg, 2.23 mmol) and crotyl bromide (0.46 mL, 4.46 mmol) gave the title ether (an 80/20 mixture of *trans/cis* isomers) as a colourless oil (235 mg, 64%). ν_{max} (ATR): 3025, 2920, 2858, 1504, 1483, 1246, 1204, 1097, 1006, 966, 827 cm^{-1}**;** δ_H (700 MHz, peaks listed for major *trans* isomer) 6.99 – 6.93 (2H, m, 3-H, 5-H), 6.87 – 6.82 (2H, m, 2-H, 6-H), 5.85 (1H, dqt, *J* = 15.5, 6.5, 1.3 Hz, 2'-H) 5.74 – 5.68 (1H, m, 1'-H), 4.41 (2H, dt, *J* = 6.1, 1.3 Hz 3'-H), 1.76 (3H, dd, *J* = 6.5, 1.4 Hz, -CH_3); δ_C (176 MHz) 156.7 (1-C), 155.0 (d, *J* = 2.1 Hz, 4-C), 130.8 (2'-C), 126.1 (1'-C), 116.0 (3-C, 5-C), 115.8 (2-C, 6-C), 69.5 (3'-C), 18.0 (-CH_3). δ_F (376 MHz) -124 (septet, *J* = 3.8 Hz); *m/z* (GC-MS, EI) 166 $[M]^+$.

3-(cyclohexyloxy)-1-propene (163)



Following general procedure B for allyl protection, cyclohexanol (500 mg, 5 mmol) gave the title ether as a colourless liquid (248 mg, 35%). ν_{max} (ATR): 2930, 2855, 1450, 1138, 1082, 918 cm^{-1}**;** δ_H (600 MHz) 5.93 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz, 2'-H), 5.35 – 5.07 (2H, m, 1'-H), 4.00 (2H, dt, *J* = 5.6, 1.5 Hz, 3'-H), 3.28 (1H, m, 1-H), 2.00 – 1.84 (2H, m, 2-H_{eq}, 6-H_{eq}), 1.81 – 1.67 (2H, m, 2-H_{ax}, 6-H_{ax}), 1.59 – 1.43 (1H, m, 4-H_{eq}), 1.38 – 1.11 (m,3-H, 5-H, 4-H_{ax}); δ_C (101 MHz) 135.9 (2'-C), 116.4 (1'-C), 68.9 (3'-C), 32.5 (1-C), 26.0 (2'-C, 6'-C), 24.4 (3'-C, 5'-C). 4'-C not observed; *m/z* (GC-MS, EI) 140 $[M]^+$.

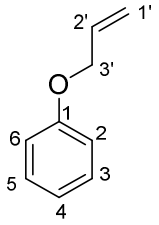
prop-2'-en-1'-yl benzoate (164)



To a solution of benzoyl chloride (0.63 mL, 5.39 mmol) in dry DCM (10 mL) at 0 ^oC was added dry pyridine (0.44 mL, 4.9 mmol) followed by allyl alcohol (0.37 mL, 4.9 mmol). The mixture was allowed to warm to room temperature and stirred for 3 hours then quenched with water (5 mL). After washing twice (10 mL H_2O then brine) the organic layer was dried and evaporated *in vacuo*. Purification by column chromatography (0 – 10% EtOAc/hexane) gave the title ether as a colourless oil

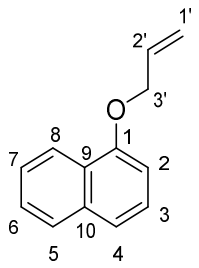
(498 mg, 63%). ν_{max} (ATR): 2983, 2884, 1790, 1717, 1601, 1452, 1361, 1315, 1269, 1175, 1109 cm^{-1}**;** δ_H (700 MHz) 8.09 – 8.04 (2H, m, 1-H, 3-H), 7.59 – 7.53 (1H, m, 5-H), 7.48 – 7.41 (2H, m, 4-H, 6-H), 6.05 (1H, ddt, *J* = 17.2, 10.5, 5.6 Hz, 2'-H), 5.42 (1H, dq, *J* = 17.2, 1.6 Hz, 1'-H_{trans}), 5.29 (1H, dq, *J* = 10.5, 1.3 Hz, 1'-H_{cis}), 4.83 (2H, dt, 3'-H); δ_C (176 MHz) 166.4 (C=O), 133.1 (1-C, 3-C), 132.4 (2'-C), 130.3 (2-C), 129.8 (5-C), 128.5 (4-C, 6-C), 118.4 (1'-C), 65.7 (3'-C); *m/z* (GC-MS, EI) 162 $[M]^+$.

[(prop-2'-en-1'-yl)oxy]benzene (165)



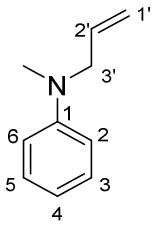
Following general procedure A for allyl protection, phenol (500 mg, 5.32 mmol gave the title ether as a colourless oil (364 mg, 51%). ν_{max} (ATR): 3072, 2927, 2865, 1599, 1495, 1459, 1242, 1222, 1174, 1033 cm^{-1}**;** δ_H (700 MHz) 7.33 – 7.26 (2H, m, 3-H, 5-H), 6.98 – 6.90 (3H, m, 2-H, 4-H, 6-H), 6.07 (1H, ddt, *J* = 17.3, 10.6, 5.3 Hz, 2'-H), 5.42 (1H, dq, *J* = 17.3, 1.6 Hz, 1'-H_{trans}), 5.29 (1H, dq, *J* = 10.6, 1.4 Hz, 1'-H_{cis}), 4.55 (2H, dt, *J* = 5.3, 1.6 Hz, 3'-H); δ_C (176 MHz) 158.7 (1-C), 133.5 (2'-C), 129.6 (3-C, 5-C), 121.0 (4-C), 117.7 (1'-C), 114.9 (2-C, 6-C), 68.8 (3'-C); *m/z* (GC-MS, EI) 134 $[M]^+$.

1-(allyloxy)-naphthalene (166)



Following general procedure A for allyl protection (with the addition of tetrabutylammonium iodide (TBAI) (66 mg, 0.18 mmol), 1-naphthol (250 mg, 1.75 mmol) gave the title ether as a colourless oil (264 mg, 82%). ν_{max} (ATR): 3052, 1595, 1580, 1508, 1267, 1240, 1096 cm^{-1}; δ_H (400 MHz) 8.35 – 8.29 (1H, m, 8-H), 7.84 – 7.76 (1H, m, 5-H), 7.56 – 7.46 (2H, m, 6-H, 7-H), 7.45 – 7.33 (2H, m, 3-H, 4-H), 6.82 (dd, *J* = 7.6, 1H, 1.0 Hz, 2-H), 6.19 (1H, ddt, *J* = 17.2, 10.4, 5.1 Hz, 2'-H), 5.54 (1H, dq, *J* = 17.3, 1.7 Hz, 1'-H_{trans}), 5.35 (1H, dq, *J* = 10.5, 1.5 Hz, 1'-H_{cis}), 4.73 (2H, dt, *J* = 5.1, 1.6 Hz, 3'-H); δ_C (101 MHz) 154.5 (1'-C), 134.7 (2'-C), 133.5 (9-C), 127.6 (5-C), 126.5 (7-C), 125.9 (6-C), 125.3 (3-C), 122.2 (8-C), 120.5 (4-C), 117.5 (1'-C), 105.2 (2-C), 69.1 (3'-C); *m/z* (GC-MS, EI) 184 $[M]^+$.

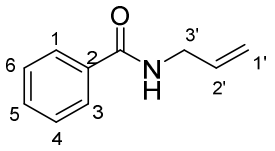
***N*-methyl-*N*-prop-2'-enylaniline (167)**



Following general procedure A for allyl protection, but in ethanol as opposed to acetone, N-methylaniline (535mg, 5 mmol) gave the title ether as a light brown oil (627 mg, 85%). ν_{max} (ATR): 3062, 2894, 1598, 1504, 1367, 1351, 1247, 1209 cm^{-1}**;** δ_H

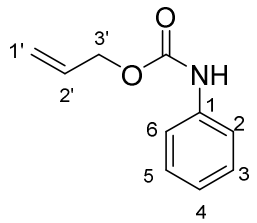
(400 MHz) 7.25 – 7.20 (2H, m, 3-H, 5-H), 6.76 – 6.68 (3H ,m, 2-H, 4-H, 6-H), 5.85 (1H, ddt, *J* = 17.1, 10.2, 5.1 Hz, 2'-H), 5.21 – 5.13 (2H, m, 1'-H), 3.92 (2H, dt, *J* = 5.1, 1.6 Hz, 3'-H), 2.94 (3H, s, CH_3); δ_C (101 MHz) 149.6 (1-C), 133.9 (2'-C), 129.2 (2'-C), 116.6 (3-C, 5-C), 116.3 (1'-C, 6-C), 112.6 (4-C), 55.4 (3'-C), 38.2 (CH_3); *m/z* (GC-MS, EI) 147 $[M]^+$.

_N_-(prop-2'-en-1'-yl)benzamide (168)



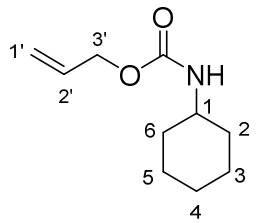
To a solution of benzoyl chloride (0.62 mL, 5.18 mmol) in dry DCM (5 mL) at 0 ^oC was added dropwise over 10 minutes a solution of the amine (0.35 mL, 4.71 mmol) and triethylamine (0.72 mL, 5.18 mmol). The mixture was allowed to warm to room temperature and stirred overnight then quenched with water (5 mL). After extraction into DCM (10 mL), the organic layers were combined, dried and evaporated *in vacuo*. Purification by column chromatography (0 – 40% EtOAc/hexane) gave the title compound as a colourless liquid in quantitative yield. ν_{max} (ATR): 3664, 3316, 2982, 2889, 1640, 1539, 1491, 1264, 1150 cm^{-1}**;** δ_H (700 MHz) 7.83 – 7. 75 (2H, m, 1-H, 3-H), 7.52 – 7.46 (1H, m, 5-H), 7.45 – 7.39 (2H, m, 4-H, 6-H), 6.21 (1H, s, NH), 5.95 (1H, ddt, *J* = 17.2, 10.3, 5.7 Hz, 2'-H), 5.27 (1H, dq, *J* = 17.1, 1.6 Hz, 1'-H_{trans}), 5.19 (1H, dq, *J* = 10.3, 1.4 Hz, 1'-H_{cis}), 4.12 – 4.07 (2H, m, 3'-H); δ_C (176 MHz) 167.4 (C=O), 134.6 (2-C), 134.4 (2'-C), 131.6 (1-C, 3-C), 132.4 (2'-C), 130.3 (2-C), 128.7 (5-C), 127.0 (4-C, 6-C), 116.7 (1'-C), 42.6 (3'-C); *m/z* (GC-MS, EI) 161 $[M]^+$.

prop-2'-en-1'-yl phenylcarbamate (169)



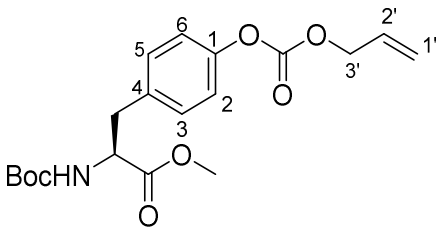
To a solution of aniline (0.98 mL, 10.75 mmol) in dry THF (15 mL) at 0 ^{o}C was added sodium hydride (387 mg, 16.1 mmol, 60% wt. in mineral oil). The mixture was stirred for 30 minutes and allyl chloroformate (1.36 mL, 12.9 mmol added dropwise). The mixture was allowed to warm to room temperature with stirring overnight. 1N HCl (10 mL) was added and the reaction mixture was extracted into EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by column chromatography (0 – 20% EtOAc/hexane) to give the title carbamate as a white solid (1368 mg, 72% yield). ν_{max} (ATR): 3322, 3063, 1706, 1699, 1695, 1602, 1541, 1539, 1445, 1314, 1219, 1059 cm^{-1}**;** δ_H (700 MHz) 7.39 (2H, app. d, 3-H, 5-H), 7.33 – 7.28 (2H, m, 2-H, 6-H), 7.10 – 7.04 (1H, m, 4-H), 6.64 (1H, s, NH), 6.02 – 5.93 (1H, m, 2'-H), 5.37 (1H, dq, *J* = 17.2, 1.5 Hz, 1'-H_{trans}), 5.27 (1H, dt, *J* = 10.4, 1.2, 1'-H_{cis}), 4.67 (2H, dt, *J* = 5.8, 1.4 Hz, 3'-H); δ_C (176 MHz) 153.1 (C=O, weak), 137.9 (1-C), 132.6 (2'-C), 129.2 (3-C, 5-C), 123.7 (4-C), 118.8 (2-C, 6-C), 118.4 (1'-C), 66.0 (3'-C); *m/z* (GC-MS, EI) 177 $[M]^+$ melting point 67.6 – 67.8 ^{o}C.

prop-2'-en-1'-yl cyclohexylcarbamate (170)



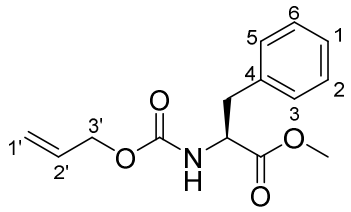
To a solution of cyclohexylamine (1.15 mL, 10.1 mmol) in dry DCM (15 mL) was added pyridine (1.13 mL, 14.1 mmol) followed by allyl chloroformate (1.26 mL, 12.1 mmol). The mixture was stirred overnight then quenched by the addition of sat. aqueous NH_4Cl (10 mL). DCM (10 mL) was added and organic layer was washed with water (10 mL), brine (10 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0 – 15% EtOAc/hexane) gave the title carbamate as a colourless liquid (1.18 g, 64% yield). ν_{max} (ATR): 3323, 2932, 2855, 1694, 1532, 1451, 1315, 1274, 1230 1046 cm^{-1}**;** δ_H (700 MHz) 5.92 (1H, ddt, *J* = 16.3, 10.7, 5.6 Hz, 2'-H), 5.30 (1H, dq, *J* = 17.2, 1.6 Hz, 1'-H_{trans}), 5.20 (1H, dq, *J* = 10.5, 1.4 Hz, 1'-H_{cis}), 4.73 – 4.43 (3H, m, 3'-H, NH), 3.49 (1H, m, 1-H), 1.97 – 1.87 (2H, m), 1.70 – 1.64 (2H, m), 1.42 – 1.29 (2H, m), 1.21 – 1.07 (3H, m); δ_C (176 MHz) 155.5 (C=O), 133.2 (2'-C), 117.7 (1'-C), 65.4 (3'-C), 50.0 (1-C), 33.6 (2-C, 6-C), 25.6 (3-C, 5-C), 24.9 (4-C); *m/z* (GC-MS, EI) 183 $[M]^+$

Boc-Tyr(Alloc)-OMe (171)



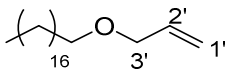
To a solution of Boc-Tyr-OMe (1.00 g, 3.39 mmol) in dry THF (10 mL) was added dry pyridine (0.38 mL, 4.75 mmol) followed by allyl chloroformate (0.43 mL, 4.07 mmol). The reaction mixture was allowed to stir for 17 h and then water (20 mL) was added. Following extraction into EtOAc (3 x 20 mL), the combined organic layers were washed with sat. aq. $NaHCO_3$ and brine then dried and concentrated *in vacuo*. Purification by column chromatography (0 – 30% EtOAc/hexane) gave the product as a colourless oil (527 mg, 41% yield). ν_{max} (ATR): 3385, 2978, 1761, 1714, 1509, 1366, 1242, 1217, 1164, 1055 cm^{-1}**;** ^1H NMR (600 MHz, Chloroform-*d*) δ 7.22 – 6.99 (4H, m, Ar-H), 6.00 (1H, ddt, *J* = 17.2, 10.4, 5.9 Hz, 2'-H), 5.43 (1H, dq, *J* = 17.2, 1.5 Hz, 1'H_{trans}), 5.33 (1H, dq, *J* = 10.4, 1.2 Hz, 1'-H_{cis}), 5.01 – 4.90 (1H, m, NH), 4.73 (2H, dt, *J* = 5.9, 1.3 Hz, 3'-H), 4.64 – 4.50 (1H, m, CH), 3.71 (3H, s, -OCH_3), 3.16 – 2.98 (2H, m, -CH_2), 1.42 (9H, s, Boc-CH_3); δ_C (151 MHz) 172.3 (ester C=O), 155.2 (Boc C=O), 153.6 (Alloc C=O), 150.3 (1-C), 134.1 (4-C), 131.2 (2'-C), 130.5 (Ar-C), 121.2 (Ar-C), 119.7 (1'-C), 80.2 (Boc-C) 69.3 (3'-C), 54.5 (-CH), 52.4 (-OCH_3), 37.9 (-CH_2), 28.4 (Boc-CH_3); *m/z* (LC-MS, ESI) 403 $[M+H+Na]^+$; HRMS (ESI) requires 380.1709 (calc. for $[M+H]^+$) found 380.1727 ($[C_{19}H_{25}NO_7]$+H).

_N_-Alloc-Phe-OMe (172)



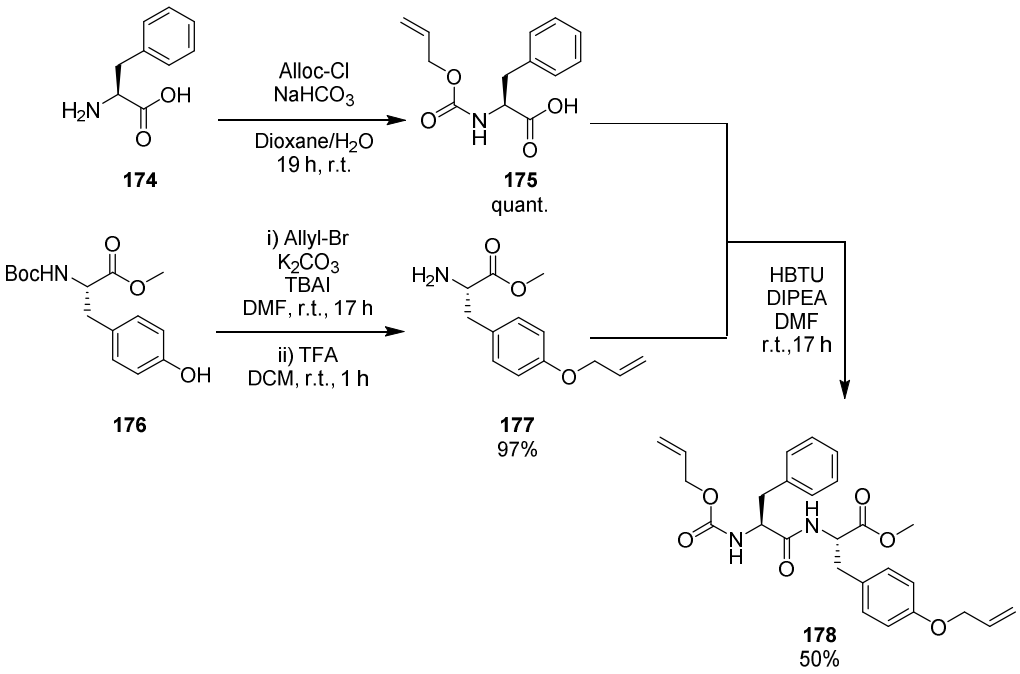
To a solution of *L*-phenylalanine methyl ester hydrochloride (1.00, 4.65 mmol) in 2:1 water/dioxane (30 mL total) and $NaHCO_3$ (1.23 g, 11.6 mmol) at 0 ^oC was added dropwise allyl chloroformate (0.49 mL, 4.65 mmol). The mixture was allowed to warm to room temperature with stirring overnight then extracted into EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by column chromatography (0 – 30% EtOAc/hexane) to give the product as a colourless oil (903 mg, 78% yield). ν_{max} (ATR): 3339, 2952, 1727, 1518, 1498, 1436, 1247, 1210, 1049, 994, 928 cm^{-1}**;** δ_H (700 MHz) 7.31 – 7.20 (3H, m, Ar-H), 7.16 – 7.09 (2H, m, Ar-H), 5.89 (1H, ddt, *J* = 16.4, 10.9, 5.7 Hz, 2'-H), 5.28 (1H, d, *J* = 17.3 Hz, 1'-H), 5.22 – 5.14 (2H, m, 1'-H, N-H), 4.65 (1H, q, *J* = 6.7 Hz, -CH), 4.56 (2H, dt, J = 5.6, 1.4 Hz, 3'-H), 3.72 (3H, s, $-OCH_3$), 3.20 – 3.00 (2H, m $-CH_2Ph$); δ_C (176 MHz) 172.1 (ester C=O), 155.6 (Alloc C=O), 135.9 (4-C), 132.7 (2'-C), 129.4 (2-C, 6-C), 128.8 (3-C, 5-C), 127.3 (1-C), 118.0 (1'-C), 66.0 (3'-C), 54.9 (-CH), 52.5 ($-OCH_3$), 38.4 ($-CH_2$); *m/z* (LC-MS, ESI) 286 $[M+Na]^+$

1-[(prop-2'-en-1'-yl)oxy]octadecane (173)

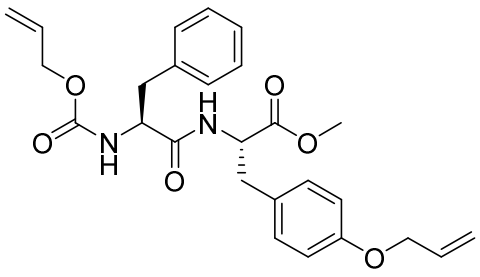


Following general procedure B for allyl protection, octadecan-1-ol (500 mg, 1.85 mmol) gave the title ether as a white waxy solid (108 mg, 19%). ν_{max} (ATR): 2923, 2853, 1466, 1100, 906, 732 cm^{-1}**;** δ_H (400 MHz) 5.92 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz, 2'-H), 5.32 – 5.12 (2H, m, 1'-H), 3.96 (2H, dt, *J* = 5.6, 1.4 Hz, 3'-H), 3.42 (2H, t, CH_2O), 1.63 – 1.55 (2H, m, aliphatic), 1.25 (30H, s, aliphatic), 0.91 – 0.85 (6H, m, aliphatic); δ_C (101 MHz) 135.3, 116.8, 72.0, 70.7, 32.1, 29.94 – 29.5 (6 discrete peaks), 26.3, 22.9, 14.3; *m/z* (GC-MS, EI) 310 $[M]^+$.

Dipeptide synthesis



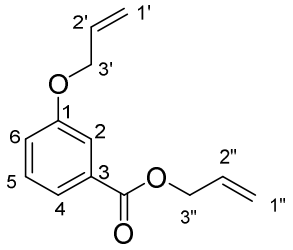
Alloc-Phe-Tyr(Allyl)-OMe (178)



To a solution of *N*-alloc-*L*-phenylalanine (0.97 g, 3.92 mmol) in dry DMF (10 mL) was added HBTU (1.78 g, 4.71 mmol). The mixture was stirred for 10 minutes and then *O*-allyl *L*-tyrosine methyl ester (1.11 g, 4.71 mmol) and DIPEA (1.36 mL, 7.84 mmol) dissolved in dry DMF (5 mL) was added. The mixture was allowed to stir at room temperature overnight then diluted with EtOAc (20 mL). The organic layer was washed with sat. aqueous NH_4Cl (10 mL) followed by saturated aq. $NaHCO_3$ (10 mL) and brine (10 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting

oil was purified by column chromatography (0 – 40% EtOAc/hexane) to give the title compound as a white solid (920 mg, 50% yield). ν_{max} (ATR): 3303, 2949, 1742, 1686, 1663, 1538, 1513, 1286, 1248, 1177, 1040 cm^{-1}**;** δ_H (700 MHz) 7.37 – 7.16 (5H, m), 6.86 (2H, d, *J* = 8.2 Hz), 6.77 (2H, d, *J* = 8.5 Hz), 6.14 (1H, d, *J* = 7.6 Hz, NH), 6.04 (1H, ddt, *J* = 17.1, 10.6, 5.3 Hz), 5.94 – 5.82 (1H, m), 5.40 (1H, dq, *J* = 17.3, 1.7 Hz), 5.34 – 5.14 (4H, m), 4.77 – 4.68 (1H, m), 4.54 (2H, d, *J* = 5.7 Hz), 4.49 (2H, dt, *J* = 5.3, 1.5 Hz), 4.42 – 4.31 (1H, m), 3.68 (3H, s), 3.14 – 2.90 (4H, m); ^{13}C NMR (176 MHz, Chloroform-*d*) δ 171.5, 170.4, 157.9, 133.4, 130.3, 129.5, 128.9, 127.8, 127.2, 118.1, 117.8, 115.0, 68.9, 66.1, 53.6, 52.5, 37.2; *m/z* (LC-MS, ESI) 490 $[M+H+Na]^+$, HRMS (ESI) requires 467.2182 (calc. for $[M+H]^+$) found 467.2172 ($[C_{26}H_{30}N_2O_6]$+H); melting point 131 – 133 ^oC.

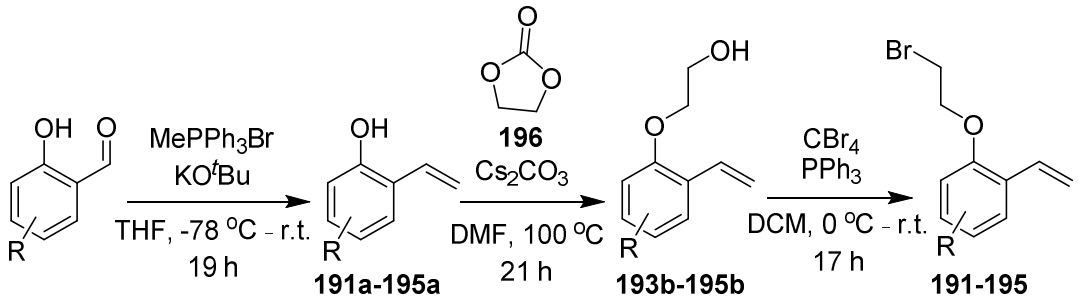
prop-2”-en-1”-yl 3-[(prop-2’-en-1’-yl)oxy]benzene (181)



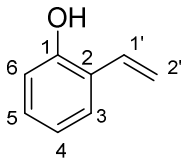
Following general procedure A for allyl protection, with 2 eq. base/allyl bromide, 3-hydroxybenzoic acid (500 mg, 3.62 mmol) gave the title ether as a colourless oil (653 mg, 83%). ν_{max} (ATR): 3087, 2985, 2936, 2876, 1718, 1649, 1585, 1487, 1360, 1287, 1105 cm^{-1}**;** δ_H (700 MHz) 7.66 (1H, dt, *J* = 7.7, 1.2 Hz), 4-H), 7.60 (1H, m, 2-H), 7.35 (1H, t, *J* = 7.9 Hz, 5-H), 7.12 (1H, ddd, J = 8.3, 2.7, 1.0 Hz, 6-H), 6.16 – 5.89 (2H, m, 2’-H, 2”-H), 5.52 – 5.19 (4H, m, 1’-H, 1”-H), 4.82 (2H, dt, J = 5.6, 1.4 Hz, 3”-H) 4.59 (2H, dt, *J* = 5.3, 1.5 Hz, 3’-H); δ_C (101 MHz) 166. 4 (C=O) 158.7 (1-C), 133.0,

132.3, 131.6, 129.6, 122.4, 120.3, 118.4 (1”-C), 118.1 (1’-C), 115.2, 69.1 (3”-C), 65.8 (3’-C); *m/z* (GC-MS, EI) 218 $[M]^+$. For assignment of key methylene NMR signals see[176]

General synthesis of chromane precursors

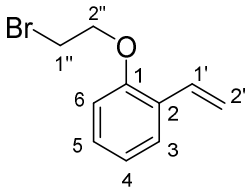


2-ethenylphenol (191a)[211]



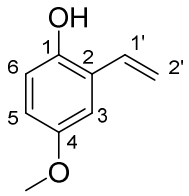
Prepared by a Wittig reaction from salicylaldehyde (1.50 g, 12.27 mmol) as per the general procedure (1.43 g, quant. yield). ν_{max} (ATR): 3432, 1746, 1453, 1370, 1226, 1210, 1094, 1007, 850 cm^{-1}; δ_H (600 MHz) 7.39 (1H, dd, *J* = 7.7, 1.6 Hz, 3-H), 7.15 (1H, td, *J* = 7.7, 1.6 Hz, 4-H), 6.97 – 6.90 (2H, m, 1'-H, 5-H), 6.79 (1H, dd, *J* = 8.0, 1.1 Hz, 6-H), 5.75 (1H, dd, *J* = 17.7, 1.3 Hz, 2'-H_{trans}), 5.37 (1H, dd, *J* = 11.2, 1.3 Hz, 2'-H_{cis}), 4.92 (1H, s, OH); δ_C (151 MHz) 152.9 (1-C), 131.6 (1'-C), 129.0 (4-C), 127.5 (3-C), 124.9 (2-C), 121.1 (5-C), 116.1 (2'-C), 116.0 (6-C); *m/z* (GC-MS, EI) 120 $[M]^+$.

1''-bromoethyl-2-ethenylphenyl ether (191)



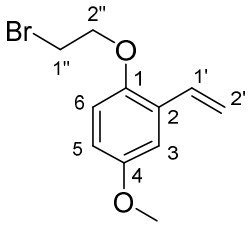
To a solution of 2-ethenylphenol (210 mg, 1.75 mmol) in dry acetonitrile (5 mL) was added potassium carbonate (483 mg, 3.5 mmol). The reaction mixture was stirred at room temperature for 30 minutes then 1,2-dibromoethane (1.51 mL, 17.5 mmol) was added. The mixture was heated under reflux overnight, after which starting material remained. Potassium iodide (29 mg, 0.18 mmol) was added and the mixture heated under reflux for a further 4 h. The reaction was allowed to cool and water (5 mL) was added. The resulting solution was then extracted with chloroform (3 x 10 mL) and the combined organic layers washed with sodium bicarbonate (10 mL) and brine (10 mL), dried and concentrated *in vacuo*. Purification by column chromatography (10 – 20% EtOAc/hexane) afforded the title ether as a colourless oil (203 mg, 51%). ν_{max} (ATR) 2501, 2159, 2026, 1738, 1486, 1450, 1365, 1237, 1109 cm^{-1}; δ_H (400 MHz) 7.50 (1H, dd, *J* = 7.7, 1.7 Hz, 3-H), 7.24 – 7.21 (1H, m, 4-H), 7.09 (1H, dd, *J* = 17.8, 11.2 Hz, 2'-H), 6.98 (1H, t, *J* = 7.6 Hz, 5-H), 6.85 (1H, m, 6-H), 5.78 (1H, dd, *J* = 17.8, 1.4 Hz, 2'-H_{trans}), 5.29 (1H, dd, *J* = 11.2, 1.4 Hz, 2'-H_{cis}), 4.32 (2H, t, *J* = 6.2 Hz, 2''-H), 3.68 (2H, t, *J* = 6.2 Hz, 1''-H). δ_C (176 MHz) 155.4 (1-C), 131.5 (1'-C) , 129.0 (4-C), 127.4 (3-C), 126.9 (2-C), 121.7 (5-C) 114.9 (2'-C), 112.6 (6-C), 68.5 (2''-C), 29.4 (1''-C); *m/z* (GC-MS, EI) [228 M(^{81}Br)]$^+$, 226 [M (^{79}Br)]$^+$; HRMS (ASAP) requires 227.0072 (calc for [M+H]$^+$) found 227.0059 ([$C_{10}H_{11}O_2Br$]+H).

2-ethenyl-4-methoxyphenol (192a)[212]



Prepared by a Wittig reaction from 5-methoxysalicylaldehyde (1.50 g, 9.87 mmol) as per the general procedure (1.50 g, quant. yield). ν_{max} (ATR): 3374, 2960, 2520, 2164, 2023, 1742, 1503, 1466, 1360, 1290, 1210, 1156 cm^{-1}; δ_H (700 MHz) 6.95 – 6.89 (2H, m, 5-H, 6-H), 6.73 – 6.72 (2H, m, 1'-H, 3-H), 5.73 (1H, dd, *J* = 17.7, 1.3 Hz, 2'-H_{trans}), 5.36 (1H, dd, *J* = 11.2, 1.3 Hz, 2'-H_{cis}), 4.68 (1H, s, OH), 3.78 (3H, s, -OCH_3); δ_C (176 MHz) 153.9 (4-C), 147.1 (1-C), 131.6 (1'-C), 125.6 (2-C), 116.9 (5-C), 116.1 (2'-C), 114.8 (3-C), 112.0 (6-C), 55.9 (-OCH_3); *m/z* (GC-MS, EI) 150 $[M]^+$.

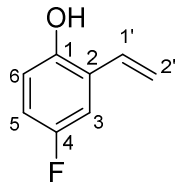
1-(1''-bromoethoxy)-2-ethenyl-4-methoxybenzene (192)



Prepared in an identical way to 1''-bromoethyl-2-ethenylphenyl ether from 2-ethenyl-4-methoxyphenol (50 mg, 0.33 mmol) and 1,2-dibromoethane, a colourless oil (38 mg, 45%). ν_{max} (ATR): 2924, 1730, 1552, 1493, 1421, 1282, 1213, 1026, 912, 801 cm^{-1}; δ_H (700 MHz) 7.10 – 7.03 (2H, m, 3-H, 1'-H), 6.81 (1H, m, 5-H), 6.77 (1H, m, 4-H), 5.75 (1H, dd, *J* = 17.7, 1.3 Hz, 2'-H_{trans}), 5.30 (1H, dd, *J* = 11.1, 1.3 Hz, 2'-H_{cis}), 4.26 (2H, t, *J* = 6.2 Hz, 2''-H), 3.79 (3H, s, -CH_3), 3.64 (2H, t, *J* = 6.2 Hz, 1''-H); δ_C (151 MHz) 154.6 (4-C), 149.8 (1-C), 131.4 (1'-C), 128.7 (2-C), 115.2 (2'-C), 114.9 (5 -C),

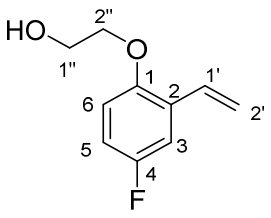
114.1 (4-C), 111.9 (3-C), 69.8 (2''-C), 55.9 (-CH_3), 29.6 (1''-C); *m/z* (GC-MS, EI) [258 M(^{81}Br)]$^+$, 256 [M (^{79}Br)]$^+$; HRMS (ASAP) requires 256.0099 (calc. for [M]$^+$) found 256.0103 ($C_{11}H_{13}O_2Br$).

2-ethenyl-4-fluorophenol (193a)[213]



Prepared by a Wittig reaction from 5-fluorosalicylaldehyde (388 mg, 2.77 mmol) as per the general procedure, giving the title phenol as a pale off white solid (188 mg, 49%). ν_{max} (ATR) 3234, 1618, 1594, 1505, 1438, 1393, 1265, 1171, 1154, 1051, 997, 918, 873, 819 cm^{-1}; δ_H (600 MHz) 7.09 (1H, dd, *J* = 9.4, 3.1 Hz, 6-H), 6.92 – 6.86 (1H, m, 1'-H), 6.86 – 6.82 (1H, m, 5-H), 6.73 (1H, m, 3-H), 5.73 (1H, dd, *J* = 17.7, 1.1 Hz, 2'-H$_{trans}$), 5.40 (1H, app. d, *J* = 11.1 Hz, 2'-H$_{cis}$), 4.78 (1H, s, OH); δ_C (151 MHz) 157.4 (d, *J* = 238 Hz, 4-C), 148.9 (d, *J* = 2.0 Hz), 130.7 (d, *J* = 2.0 Hz, 1'-C), 126.2 (d, *J* = 7.4 Hz), 116.9 (2'-C), 116.8, 115.4 (d, *J* = 23.6 Hz, 5-C), 113.3 (d, *J* = 23.4 Hz, 6-C); δ_F (376 MHz) -123.7 (m), *m/z* (GC-MS, EI) 138 [M]$^+$; melting point: 58.7 – 59.5 ^{o}C.

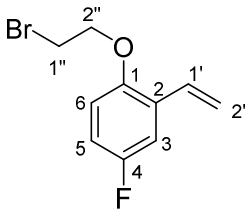
2''-(2-ethenyl-4-fluorophenoxy)ethanol (193b)



Prepared as per the general procedure for alkylation with ethylene carbonate (142 mg, 1.03 mmol), giving the title alcohol as a white solid (163 mg, 87%). ν_{max} (ATR)

3272, 2957, 1589, 1493, 1429, 1258, 1201, 1157, 1076, 1046, 904, 896, 870, 803 cm^{-1}; δ_H (700 MHz) 7.19 (1H, dd, *J* = 9.4, 3.1 Hz, 6-H), 7.02 (1H, app. ddd, *J* = 17.7, 11.1, 1.5 Hz, 1'-H), 6.97 – 6.89 (1H, m, 5-H), 6.82 (1H, m, 3-H), 5.73 (1H, dd, *J* = 17.7, 1.1 Hz, 2'-H_{trans}), 5.33 (1H, dd, *J* = 11.1, 1.1 Hz, 2'-H_{cis}), 4.12 – 4.05 (2H, m, 2"-H), 4.01 – 3.92 (2H, m, 1"-H), 1.97 (1H, t, *J* = 6.3 Hz, OH); δ_C (176 MHz) 157.7 (d, *J* = 239.0 Hz, 4-C), 152.0 (d, *J* = 2.1 Hz, 1-C), 130.7 (d, *J* = 2.1 Hz, 1'-C), 128.8 (d, *J* = 7.4 Hz, 2-C), 116.0 (2'-C), 115.1 (d, *J* = 23.2 Hz, 5-C), 114.1 (d, *J* = 8.4 Hz, 3-C), 112.9 (d, *J* = 23.5 Hz, 6-C), 70.9 (2"-C), 61.7 (1"-C); δ_F (376 MHz) -122.9 (m); *m/z* (GC-MS, EI) 182 $[M]^+$; HRMS (ASAP) requires 182.0743 (calc. for $[M]^+$) found 182.0746, ($C_{10}H_{11}O_2F$); melting point: 69.4 – 70.2 ^oC.

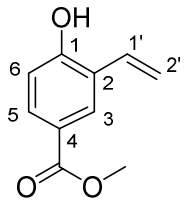
2"-bromoethyl 2-ethenyl-4-fluorophenyl ether (193)



Following the general procedure for an Appel reaction, 2"-(2-ethenyl-4-fluorophenoxy)ethanol (143 mg, 0.79 mmol) afforded the title bromide as a colourless oil (155 mg, 80%). ν_{max} (ATR) 2927, 1589, 1490, 1430, 1254, 1200, 996, 937, 873, 805, 712 cm^{-1}; δ_H (700 MHz) 7.19 (1H, dd, *J* = 9.4, 3.1 Hz, 6-H), 7.05 (1H, app. ddd, *J* = 17.7, 11.1, 1.5 Hz, 1'-H), 6.95 – 6.85 (1H, m, 5-H), 6.80 (1H, m, 3-H), 5.75 (1H, dd, *J* = 17.7, 1.2 Hz, 2'-H_{trans}), 5.34 (1H, dd, *J* = 11.1, 1.1 Hz, 2'-H_{cis}), 4.28 (2H, t, *J* = 6.1 Hz, 2"-H); 3.65 (2H, t, *J* = 6.1 Hz, 1"-H); δ_C (176 MHz) 157.9 (d, *J* = 239.4 Hz, 4-C), 151.5 (d, *J* = 2.2 Hz, 1-C), 130.6 (d, *J* = 2.1 Hz, 1'-C), 129.1 (d, *J* = 7.5 Hz, 2-C), 116.0 (2'-C), 115.0 (d, *J* = 23.2 Hz, 5-C), 114.3 (d, *J* = 8.4 Hz, 3-C), 113.0 (d, *J* =

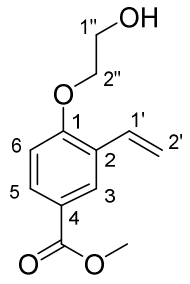
23.5 Hz, 6-C), 69.4 (2”-C), 29.3 (1”-C); δ_F (376 MHz) -122.4 (m); *m/z* (GC-MS, EI) [246 M(^{81}Br)]$^+$, 244 [M (^{79}Br)]$^+$; HRMS (ASAP) requires 244.9977 (calc. for [M+H]$^+$) found 244.9977 ([$C_{10}H_{10}$BrOF]+H).

2-ethenyl-4-methoxycarbonyl phenol (194a)



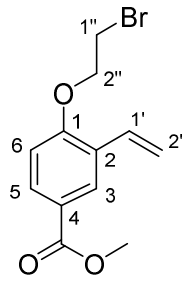
Prepared according to the general procedure for a Wittig reaction from methyl 3-formyl-4-hydroxybenzoate (1.5 g, 8.33 mmol), giving the title phenol as an off white solid (1.12 g, 76%). ν_{max} (ATR): 3361, 2957, 1679, 1675, 1602, 1505, 1431, 1277, 1263, 1133, 999, 753 cm^{-1}; δ_H (600 MHz) 8.11 (1H, d, *J* = 2.1 Hz, 3-H), 7.83 (1H, dd, *J* = 8.5, 2.2 Hz, 5-H), 6.93 (1H, dd, *J* = 17.7, 11.2 Hz, 1’-H), 6.85 (1H, d, *J* = 8.5 Hz, 6-H), 6.11 (1H, br, OH), 5.83 (1H, dd, *J* = 17.8, 1.1 Hz, 2’-H$_{trans}$), 5.41 (1H, dt, *J* = 11.3, 0.8 Hz, 2’-H$_{cis}$), 3.90 (3H, s, -OCH_3); δ_C (167 MHz) 167.3 (C=O), 157.2 (4-C), 130.77 (5-C), 130.76 (1’-C), 129.6 (3-C), 125.0 (1-C), 122.8 (2-C), 117.1 (2’-C), 115.9 (6-C), 52.2 (-OCH_3); *m/z* (GC-MS, EI) 178 [M]$^+$; melting point 105.6 – 106.1 ^{o}C.

2”-(2-ethenyl-4-methoxycarbonyl-phenoxy)ethanol (194b)



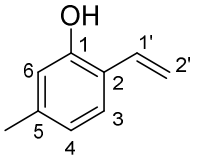
Prepared from alkylation of 2-ethenyl-4-methoxycarbonyl phenol (1.06 g, 5.97 mmol) with ethylene carbonate as per the general procedure, giving the title alcohol as a yellow oil (354 mg, 27%). ν_{max} (ATR): 3425, 2951, 1713, 1699, 1601, 1439, 1255, 1240, 1125, 919 cm^{-1}; δ_H (700 MHz) 8.20 – 8.13 (1H, m, 3-H), 7.93 (1H, dd, *J* = 8.6, 2.2 Hz, 5-H), 7.02 (1H, ddd, *J* = 17.7, 11.2, 0.6 Hz, 1’-H), 6.89 (1H, d, *J* = 8.6 Hz, 6-H), 5.84 (1H, dd, *J* = 17.7, 1.3 Hz, 2’-H_{trans}), 5.34 (1H, dd, *J* = 11.2, 1.3 Hz, 2’-H_{cis}), 4.19 – 4.17 (2H, m, 1’’-H), 4.04 – 3.98 (2H, m, 2’’-H), 3.90 (3H, s, -OCH_3); δ_C (176 MHz) 167.0 (C=O), 159.3 (4-C), 130.9 (5-C), 130.8 (1’-C), 128.5 (3-C), 127.0 (1-C), 123.1 (2-C), 116.1 (2’-C), 111.5 (6-C), 70.0 (1’’-C), 61.5 (2’’-C), 52.1 (-OCH_3); *m/z* (ASAP) 223 $[M+H]^+$; HRMS (ASAP) requires 223.0970 (calc. for $[M+H]^+$) found 223.0995 ($[C_{12}H_{14}O_4]$+H).

2”-bromoethyl-(2-ethenyl-4-methoxycarbonylphenoxy)ether (194)



Following the general procedure for an Appel reaction, 2”-(2-ethenyl-4-methoxycarbonyl-phenoxy)ethanol (354 mg, 1.59 mmol) afforded the title bromide as a white solid (450 mg, quant. yield). ν_{max} (ATR): 2950, 1706, 1626, 1602, 1496, 1421, 1256, 1245, 1137, 915 cm^{-1}; δ_H (700 MHz) 8.20 – 8.17 (1H, m, 3-H), 7.92 (1H, dd, *J* = 8.6, 2.2 Hz, 5-H), 7.08 – 7.02 (1H, m, 1’-H), 6.85 (1H, d, *J* = 8.6 Hz, 6-H), 5.87 (1H, dd, *J* = 17.7, 1.3 Hz, 2’-H_{trans}), 5.36 (1H, dd, *J* = 11.2, 1.2 Hz, 2’-H_{cis}), 4.38 (2H, t, *J* = 6.1 Hz, 1’’-H), 3.90 (3H, s, -OCH_3), 3.70 (2H, t, *J* = 6.1 Hz, 2’’-H); δ_C (176 MHz) 167.0 (C=O), 158.8 (4-C), 130.8 (5-C), 130.7 (1’-C), 128.7 (3-C), 127.2 (1-C), 123.4 (2-C v. weak), 116.3 (2’-C), 111.5 (6-C), 68.3 (2’’-C), 52.1 (-OCH_3), 61.5 (1’’-C); *m/z* (GC-MS, EI) [286 M(^{81}Br)]$^+$, 284 [M (^{79}Br)]$^+$; HRMS (ASAP) requires 284.0048 (calc. for [M]$^+$) found 284.0045 ($C_{12}H_{13}BrO_3$); melting point 78.8 – 80.6 ^oC.

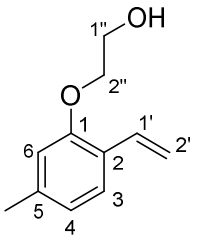
2-ethenyl-5-methylphenol (195a)



Prepared by a Wittig reaction from 5-methylsalicylaldehyde (1.0 g, 7.35 mmol) as per the general procedure, giving the title phenol as a white powder (768 mg, 78%).

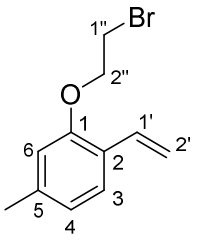
ν_{max} (ATR): 3422, 1622, 1413, 1294, 1214, 1104, 996, 944, 907, 813 cm^{-1}; δ_H (700 MHz) 7.25 (1H, d, *J* = 7.8 Hz, 3-H), 6.88 (1H, dd, *J* = 17.7, 11.2, 1'-H), 6.72 (1H, d, *J* = 8.6, 7.7 Hz, 4-H), 6.60 (1H, s, 6-H), 5.68 (1H, dd, *J* = 17.7, 1.4 Hz, 2'-H_{trans}), 5.29 (1H, dd, *J* = 11.2, 1.4 Hz, 2'-H_{cis}), 4.87 (1H, s, OH), 2.28 (3H, s, CH_3); δ_C (176 MHz) 152.8 (1-C), 139.4 (5-C), 131.6 (1'-C), 127.4 (3-C), 122.1 (2-C), 122.0 (4-C), 116.6 (6-C), 115.0 (2'-C), 21.3 (CH_3); *m/z* (GC-MS, EI) 134 $[M]^+$; HRMS (ASAP) requires 134.0732 (calc. for $[M]^+$) found 134.0726 ($C_9H_{10}O$); melting point: 52.2 – 55.3 ^oC.

2"-(2-ethenyl-5-methylphenoxy)ethanol (195b)



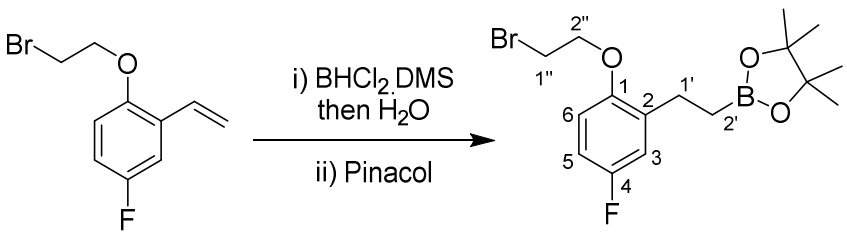
Prepared as per the general procedure, whereby reaction of 2-ethenyl-5-methylphenol (720 mg, 5.37 mmol) with ethylene carbonate afforded the title alcohol as a yellow oil (792 mg, 83%). ν_{max} (ATR) 3342, 2916, 2862, 1623, 1607, 1501, 1415, 1289, 1261, 1168, 1119, 1071, 998, 855 cm^{-1}; δ_H (700 MHz) 7.37 (1H, d, *J* = 7.8 Hz, 3-H), 7.02 (1H, dd, *J* = 17.7, 11.1, 1'-H), 6.78 (1H, ddt, *J* = 7.7, 1.5, 0.7 Hz, 4-H), 6.70 (1H, s, 6-H), 5.71 (1H, dd, *J* = 17.7, 1.5 Hz, 2'-H_{trans}), 5.22 (1H, dd, *J* = 11.1, 1.5 Hz, 2'-H_{cis}), 4.12 – 4.06 (2H, m, 2"-H), 3.98 (2H, t, 1"-H), 2.34 (3H, s, CH_3) 2.09 (1H, s, OH); δ_C (176 MHz) 155.8 (1-C), 139.4 (5-C), 131.5 (1'-C), 126.6 (3-C), 126.6 (2-C), 124.4 (4-C), 113.8 (6-C), 113.4 (2'-C), 70.7 (2"-C), 61.8 (1"-C), 21.7 (CH_3); *m/z* (GC-MS, EI) 178 $[M]^+$; HRMS (ASAP) requires 178.0994 (calc. for $[M]^+$) found 178.0979 ($C_{11}H_{14}O_2$).

2”-bromoethyl 2-ethenyl-5-methylphenyl ether (195)



Following the general procedure for an Appel reaction, 2”-(2-ethenyl-5-methylphenoxy)ethanol (640 mg, 3.59 mmol) afforded the title bromide as a colourless oil (250 mg, 29%). ν_{max} (ATR) 2920, 1609, 1503, 1415, 1289, 1259, 1206, 1119, 997, 906, 816 cm^{-1}; δ_H (700 MHz) 7.38 (1H, d, *J* = 7.8 Hz, 3-H), 7.04 (1H, dd, *J* = 17.8, 11.2, 1’-H), 6.79 (1H, ddt, *J* = 7.8, 1.4, 0.7 Hz, 4-H), 6.76 (1H, s, 6-H), 5.73 (1H, dd, *J* = 17.8, 1.5 Hz, 2’-H_{trans}), 5.23 (1H, dd, *J* = 11.2, 1.5 Hz, 2’-H_{cis}), 4.30 (2H, t, *J* = 6.3 Hz 2”-H), 3.67 (2H, t, *J* = 6.3 Hz, 1”-H), 2.34 (3H, s, CH_3); δ_C (176 MHz) 155.3 (1-C), 139.2 (5-C), 131.4 (1’-C), 126.7 (3-C), 124.6 (2-C), 122.4 (4-C), 113.9 (6-C), 113.5 (2’-C), 68.5 (2”-C), 29.4 (1”-C), 21.7 (CH_3); *m/z* (GC-MS, EI) [242 M(^{81}Br)]$^+$, 240 [M (^{79}Br)]$^+$; HRMS (ASAP) requires 240.0150 (calc. for [M]$^+$) found 240.0157 ($C_{11}H_{13}OBr$).

2’-{2-[2-(2”-bromoethoxy)-4-fluorophenyl]ethyl}-Bpin (198a)

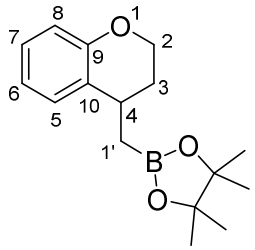


Authentic NMR comparison for the linear side-product 198. To an oven dried flask under Ar atmosphere was added dry DCM (3 mL) followed by $BHCl_2$.DMS complex

(1N solution, 0.41 mmol). To the flask was added *via* syringe a solution of the styrene (100 mg, 0.41 mmol) in dry DCM (2 mL) over 10 minutes. The reaction was refluxed for 5 h and then cooled to 0 ^{o}C and water (5 mL) was added. The reaction mixture was concentrated *in vacuo* and 5 mL water was added, forming a white suspension. The white precipitate was collected then washed with water and hexane to yield 27 mg of a white powder.

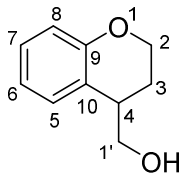
The powder was dissolved in dry toluene (2 mL) and 4Å molecular sieves were added, followed by pinacol (10 mg, 0.08 mmol). The mixture was refluxed overnight then allowed to cool and filtered. The mother liquor was concentrated *in vacuo* and purified by column chromatography (0 – 20% EtOAc/hexane) to afford the title boronate ester as a colourless oil (10 mg, 7% over both steps). ν_{max} (ATR) 2978, 2929,1496, 1379, 1371, 1316, 1202, 1149, 1017, 968, 848, 803 cm^{-1}; δ_H (700 MHz) 6.93 (1H, dd, *J* = 9.3, 3.1 Hz, 6-H), 6.82 – 6.77 (1H, m, 5-H), 6.71 (1H, dd, *J* = 8.9, 4.5 Hz, 3-H), 4.24 (2H, t, *J* = 6.3 Hz, 2”-H), 3.64 (2H, t, *J* = 6.3 Hz, 1”-H), 2.76 – 2.71 (2H, m, 1’-H), 1.22 (12H, s, -pinCH_3), 1.14 – 1.09 (2H, m, 2’-H); δ_C (176 MHz) 152.1, 135.6 116.5, 112.9, 112.8, 112.5, 112.4, 83.3 (1’-C), 68.9 (2”-C), 29.5 (1”-C), 24.9 (-pinC), 24.5 (2’-C); *m/z* (GC-MS, EI) [374 M(^{81}Br)]$^+$, 372 [M (^{79}Br)]$^+$; HRMS (ASAP) requires 371.0944 (calc. for [M]$^+$) found 371.0960 ($C_{16}H_{23}BBrO_3F$).

4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,4-dihydro-2H-chromene (197)[178]



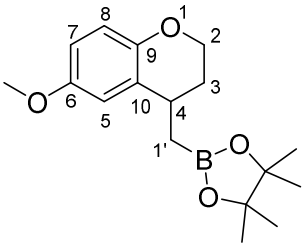
Prepared according to the general procedure for copper catalysed borylation from 2-bromoethyl-2'-ethenylphenyl ether, under both Xantphos/CuCl (49% yield) and CuI/PPh_3 (77% yield) conditions. Both sets of conditions gave the product along with an unknown co-eluting impurity (suspected to be a hydroboration side product, approx. 30% by mass); the material was subsequently oxidised to allow purification and full characterisation. Major peaks corresponding to the desired product in the ^{1}H NMR spectrum are listed below. δ_H (400 MHz) 7.20 (1H, app. d, *J* = 7.8 Hz, 5-H), 7.09 – 7.03 (1H, m, 7-H), 6.84 (1H, app. td, *J* = 7.5, 1.3 Hz, 6-H), 6.76 (1H, app. dd, *J* = 8.2, 1.3 Hz, 8-H), 4.26 – 4.12 (2H, m, 2-H), 3.09 (1H, dq, *J* = 11.1, 5.7 Hz, 4-H), 2.16 – 2.07 (1H, m, 3-H), 1.80 (1H, dtd, *J* = 13.8, 6.9, 3.1 Hz, 3-H), 1.40 – 1.30 (1H, m, 1'-H), 1.26 (12H, s, -CH_3), 1.16 – 1.07 (1H, m, 1'-H); δ_B (128 MHz) 33.7; *m/z* (GC-MS, EI) 274 $[M]^+$.

3,4-dihydro-2H-chromen-4-ylmethanol (197a)[214]



Prepared by oxidation of the crude borylation product (4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,4-dihydro-2H-chromene as per the general procedure for oxidation. The crude boronate ester (93 mg, 0.34 mmol) gave the title alcohol as a colourless oil (30 mg, 54%). ν_{max} (ATR): 3382, 2942, 2880, 1581, 1488, 1451, 1269, 1222, 1118, 1022, 753 cm^{-1}; δ_H (600 MHz) 7.18 (1H, dt, *J* = 7.6, 1.2 Hz, 5-H), 7.13 (1H, ddd, *J* = 8.6, 7.3, 1.7 Hz, 7-H), 6.88 (1H, td, *J* = 7.4, 1.3 Hz, 6-H), 6.83 (1H, dd, *J* = 8.2, 1.3 Hz, 8-H), 4.24 – 4.18 (2H, m, 2-H), 3.91 (1H, m, 1'-H), 3.82 (1H, m, 1'-H), 3.01 (1H, m, 4-H), 2.14 – 2.05 (2H, m, 3-H), 1.46 (1H, t, *J* = 5.6 Hz, OH); δ_C (151 MHz) 155.5 (9-C), 129.3 (5-C), 128.1 (7-C), 122.2 (10-C), 120.5 (6-C), 117.3 (8-C), 66.7 (1'-C), 63.5 (2-C), 36.3 (4-C), 24.6 (3-C); *m/z* (GC-MS, EI) 164 $[M]^+$.

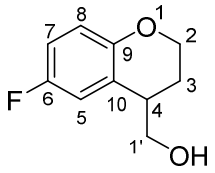
6-methoxy-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,4-dihydro-2H-1-benzopyran (200)



Prepared according to the general procedure for copper catalysed borylation from 1-(1''-bromoethoxy)-2-ethenyl-4-methoxybenzene (30 mg, 0.12 mmol), giving the title boronate ester as a colourless oil (25 mg, ~70% impure yield, significant boron

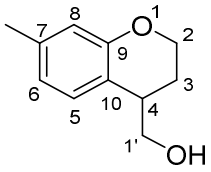
containing impurities and hydroboration product, up to 44%). Purity was insufficient for full characterisation; relevant ^{1}H NMR signals are listed below. δ_H (400 MHz) 6.81 – 6.62 (3H, m, Ar-H), 4.27 – 4.05 (2H, m, 2-H), 3.74 (3H, s, -OCH_3), 3.10 – 3.02 (1H, m, 4-H), 2.15 – 2.15 – 2.04 (1H, m, 3-H), 1.82 – 1.73 (1H, m, 3-H), 1.30 – 1.20 (-pinCH_3), signals for 1'-H were overlapped in broad alkyl region); *m/z* (GC-MS, EI) 304 $[M]^+$.

(6-fluoro-3,4-dihydro-2H-1-benzopyran-4-yl)methanol (201a)



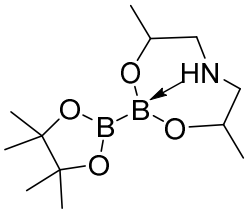
Prepared by borylation of 2"-bromoethyl 2-ethenyl-4-fluorophenyl ether (155 mg, 0.63 mmol) and then oxidation of the corresponding crude borylation product as per the general procedure for oxidation, giving the title alcohol as a colourless oil (48 mg, 42% over both steps, contained some solvent impurities). ν_{max} (ATR): 3344, 2931, 2881, 1493, 1428, 1259, 1201, 1025, 935, 814, 742 cm^{-1}; δ_H (700 MHz) 6.93 – 6.89 (1H, app. dd, 7-H), 6.85 – 6.81 (1H, m, 5-H), 6.78 – 6.74 (1H, m, 8-H), 4.19 – 4.15 (2H, m, 2-H), 3.90 – 3.85 (1H, m, 1'-H), 3.83 – 3.77 (1H, m, 1'-H), 3.00 – 2.95 (1H, m, 4-H), 2.11 – 2.04 (2H, m, 3-H obscured by alkyl impurity); δ_C (176 MHz) 157.5, 156.2, 151.5 (d, J = 1.9 Hz), 118.1 (d, *J* = 8.0 Hz), 115.1 (d, *J* = 22.7 Hz), 114.9 (d, *J* = 23.1 Hz), 66.5 (1'-C), 63.7 (2-C), 36.4 (d, *J* = 1.3 Hz, 4-C), 24.5 (3-C); *m/z* (GC-MS, EI) 182 $[M]^+$; HRMS (ASAP) requires 182.0743 (calc. for $[M]^+$) found 182.0714 ($C_{10}H_{11}O_2F$), -15.9 ppm (outwith 10 ppm limit).

7-methyl-3,4-dihydro-2H-1-benzopyran-4-yl)methanol (203a)



Prepared by borylation of 2”-bromoethyl 2-ethenyl-5-methylphenyl ether (200 mg, 0.84 mmol). The crude mixture was immediately oxidised with oxone as per the general procedure affording the title chromane as a colourless oil (30 mg, 20%, along with traces of a byproduct). ν_{max} (ATR): 3339, 2922, 2876, 1623, 1576, 1505, 1418, 1305, 1131, 1032, 907 cm^{-1}; δ_H (600 MHz) 7.06 (1H, dd, *J* = 7.7, 0.8 Hz, 5-H), 6.71 (1H, dd, *J* = 7.8, 1.7 Hz, 7-H), 6.69 – 6.63 (1H, m, 6-H), 4.20 – 4.15 (2H, m, 2-H), 3.88 (1H, dd, *J* = 10.9, 4.9 Hz, 1’-H), 3.78 (1H, m, *J* = 10.9, 8.0 Hz, 1’-H), 2.96 (1H, app. dq, *J* = 10.4, 5.3 Hz, 4-H), 2.28 (3H, s, $-CH_3$), 2.12 – 2.01 (2H, m, 3-H); δ_C (151 MHz) 155.3 (9-C), 138.1 (5-C), 129.0 (7-C), 121.5 (10-C), 119.1 (6-C), 117.6 (8-C), 66.6 (1’-C), 63.5 (2-C), 35.9 (4-C), 24.7 (3-C), 21.2 ($-CH_3$); *m/z* (GC-MS, EI) 178 $[M]^+$; HRMS (ASAP) requires 179.1072 (calc. for $[M+H]^+$) found 179.1060 ($[C_{11}H_{14}O_2]+H$).

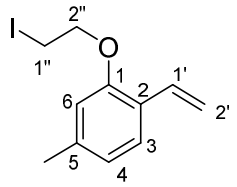
4,8-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,6,2-dioxazaborocane (9)



To a solution of B_2pin_2 (3.33 g, 13.1 mmol) in ether (50 mL) was added bis(2-hydroxypropyl)amine (1.91 g, 14.4 mmol, *cis/trans* mix) in a solution of DCM (10

mL). After 48 h, the suspension was filtered and washed copiously with ether then recrystallized from a 1:2 mixture of DCM:EtOAc, giving the title product as a white crystalline solid (1.16 g, 33%, mixture of *cis/trans* products). ν_{max} (ATR) 3219, 2977, 2932, 2885, 1646, 1459, 1379, 1370, 1115, 1057, 1012, 980, 853, 808 cm^{-1}; δ_H (600 MHz, Acetonitrile-d_3) 5.39 (1H, br. s., NH_{cis}), 5.13 (1H, br. s., NH_{trans}), 4.05 (2H, tdd, *J* = 9.6, 6.1, 4.2 Hz, *cis*), 3.63 (1H, dqd, *J* = 10.5, 6.0, 4.5 Hz, *trans*), 3.26 (1H, ddd, *J* = 11.6, 8.1, 4.6 Hz, *trans*), 2.80 (1H, ddd, *J* = 11.7, 4.6, 1.2 Hz, *cis*), 2.65 (1H, dd, *J* = 11.4, 3.8 Hz, *cis*), 2.45 (1H, ddd, *J* = 11.7, 10.2, 7.4 Hz, *cis*), 2.26 – 2.18 (1H, m, *cis*), 1.88 – 1.82 (1H, m, *trans*), 1.12 (16H, d, *J* = 1.7 Hz, *cis/trans*), 1.08 (4H, dd, J = 8.1, 6.0 Hz *cis/trans* pinCH_3), 1.04 (4H, d, *J* = 6.0 Hz, *cis/trans* pinCH_3); δ_C (151 MHz, Acetonitrile-d_3) 82.3 (*cis*), 82.2 (*trans*), 71.6 (*cis*), 67.6 (*trans*), 58.9 (*trans*), 58.7 (cis), 57.4 (*trans*), 25.6 (*cis*), 21.3 (*cis*), 20.0 (*trans*), 19.2 (*trans*); δ_B (128 MHz, Acetonitrile-d_3) 35.81 (sp^2-B), 9.41 (sp^3-B), *m/z* (ASAP) 270$[M+H]^+$; melting point 191.7 – 196.2 ^oC.

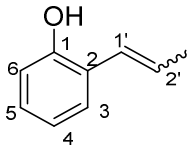
2”-iodoethyl 2-ethenyl-5-methylphenyl ether (204)



To a solution of 2”-bromoethyl 2-ethenyl-5-methylphenyl ether (200 mg, 0.83 mmol) in acetone (2 mL) was added NaI (625 mg, 4.16 mmol). The reaction was heated overnight at 60 ^oC then allowed to cool and filtered, washing with acetone. The filtrate was concentrated then redissolved in EtOAc (10 mL) and washed with sat. $Na_2S_2O_3$ (10 mL), water (10 mL) then brine. After concentrating *in vacuo*, the

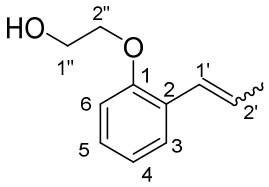
title iodide was obtained as a colourless oil (206 mg, 86%). ν_{max} (ATR): 3084, 2973, 2859, 1624, 1608, 1502, 1415, 1257, 1166, 1118, 1291, 1027, 908, 816 cm^{-1}; δ_H (700 MHz) 7.38 (1H, d, *J* = 7.8 Hz, 3-H), 7.05 (1H, dd, *J* = 17.8, 11.2, 1'-H), 6.78 (1H, ddt, *J* = 7.7, 1.6, 0.7 Hz, 4-H), 6.67 – 6.58 (1H, s, 6-H), 5.72 (1H, dd, *J* = 17.8, 1.5 Hz, 2'-H_{trans}), 5.23 (1H, dd, *J* = 11.1, 1.5 Hz, 2'-H_{cis}), 4.26 (2H, t, *J* = 6.8 Hz 2"-H), 3.50 – 3.38 (2H, m, 1"-H), 2.33 (3H, s, CH_3); δ_C (151 MHz) 155.1 (1-C), 139.2 (5-C), 131.5 (1'-C), 126.6 (3-C), 124.6 (2-C), 122.4 (4-C), 113.9 (6-C), 113.5 (2'-C), 68.5 (2"-C), 21.7 (CH_3), 1.51 (1"-C); *m/z* (GC-MS, EI) 288 ($[M]^+$); HRMS (ASAP) requires 289.0089 (calc. for $[M+H]^+$) found 289.0097 ($[C_{11}H_{13}OI]$+H).

2-[(1'E/Z)-prop-1-en-1-yl]phenol (206a)



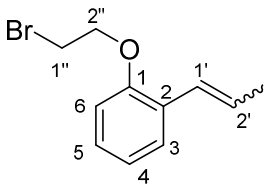
Prepared by a Wittig reaction from salicylaldehyde (2.0 g, 16.4 mmol) as per the general procedure with ethyltriphenylphosphonium bromide (13.99 g, 37.7 mmol), giving the title phenol mixture as a colourless oil (1.85 g, 84%, approx. 9:1 *Z:E* ratio). vmax (ATR): 3421, 2982, 1606, 1577, 1485, 1449, 1367, 1201, 1167, 1034, 928, 840, 751 cm^{-1}; δ_H (600 MHz) NMR peaks listed for major (*Z*) isomer: 7.21 – 7.14 (1H, m, 3-H), 7.14 – 7.08 (1H, m, 4-H), 6.91 (2H, m, 5-H, 6-H), 6.40 (1H, d, J = 11.3, 1'-H_{cis}), 6.03 (1H, dq, *J* = 11.2, 7.0 Hz, 2'-H_{cis}), 4.99 (1H, s, OH), 1.73 (3H, dd, J = 7.0, 1.8 Hz, -CH_3); δ_C (151 MHz) 152.8 (1-C), 131.4 (2'-C), 129.8 (4-C), 128.7 (3-C), 124.2 (1'-C), 123.6 (2-C), 120.4 (5-C), 115.2 (6-C), 14.7 (-CH_3); *m/z* (GC-MS, EI) 134 $[M]^+$; melting point: 58.7 – 59.5 ^oC.

2-(2'-[prop-1"-en-1"-yl]phenoxy)ethanol (206b)



Prepared by alkylation of 2-[(1'E/Z)-prop-1-en-1-yl]phenol (1.5 g, 11.2 mmol) with ethylene carbonate as per the general procedure, giving the title alcohol as a colourless oil (1.71 g, 86%, mixture of 9:1 Z:E isomers). ν_{max} (ATR) 3370, 2936, 2881, 1598, 1579, 1487, 1448, 1368, 1291, 1249, 1111, 1049, 918, 751 cm^{-1}; δ_H (700 MHz) NMR peaks listed for major (*Z*) isomer: 7.28 (1H, dd, *J* = 7.5, 1.7 Hz, 3-H), 7.22 (1H, td, *J* = 7.5, 1.7 Hz 4-H), 6.97 (1H, td, *J* = 7.5, 1.1 Hz, 5-H), 6.93 – 6.87 (1H, m, 6-H) 6.55 (1H, dq, *J* = 11.7, 2.0 Hz, 1'-H_{cis}), 5.84 (1H, dq, *J* = 11.6, 7.1 Hz, 2'-H_{cis}), 4.15 – 4.07 (2H, m, 1"-H), 3.97 – 3.92 (2H, m, 2"-H), 2.07 (1H, t, *J* = 6.4 Hz , OH) 1.83 (3H, dd, J = 7.1, 1.9 Hz, -CH_3); δ_C (176 MHz) 156.1 (1-C), 130.4 (2'-C), 128.1 (4-C), 127.3 (3-C), 127.0 (1'-C), 125.2 (2-C), 120.8 (5-C), 112.4 (6-C), 70.0 (1"-C), 61.7 (2"-C), 14.7 (-CH_3); *m/z* (GC-MS, EI) 178 $[M]^+$

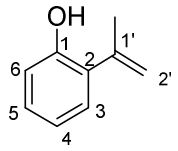
1-(1'-bromoethoxy)-2-[(E/Z)-prop-1'-en-1yl]benzene (206)



Prepared using the general procedure for an Appel reaction, 1.71 g (9.60 mmol) of 2-(2'-[prop-1"-en-1"-yl]phenoxy)ethanol gave the title bromide as a colourless oil (1.34 g, 58%). ν_{max} (ATR) 2971, 1598, 1578, 1487, 1448, 1291, 1245, 1111, 1016,

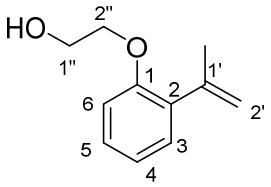
751 cm^{-1}; NMR peaks listed for major (*Z*) isomer: δ_H (600 MHz) 7.30 (1H, dd, *J* = 7.6, 1.6 Hz, 3-H), 7.21 (1H, td, *J* = 7.8, 1.7 Hz 4-H), 7.02 – 6.97 (1H, m, 5-H), 6.87 (1H, dd, J = 8.2, 1.1 Hz, 6-H) 6.59 (1H, dq, *J* = 11.6, 2.0 Hz, 1'-H_{cis}), 5.85 (1H, dq, *J* = 11.6, 7.1 Hz, 2'-H_{cis}), 4.30 (2H, app. t, *J* = 6.9 Hz, 1"-H), 3.65 (2H, app. t, *J* = 6.4 Hz, 2"-H), 1.85 (3H, dd, J = 7.1, 1.8 Hz, -CH_3); δ_C (151 MHz) 155.7 (1-C), 130.5 (2'-C), 128.1 (4-C), 127.2 (3-C), 127.0 (1'-C), 125.1 (2-C), 121.0 (5-C), 112.5 (6-C), 68.5 (2"-C) 29.3 (1"-C), 14.9 (-CH_3); *m/z* (GC-MS, EI) [242 M(^{81}Br)]$^+$, 240 [M (^{79}Br)]$^+$; HRMS (ASAP) requires 240.0150 (calc. for $[M]^+$) found 240.0154 ($C_{11}H_{13}BrO$).

2-(prop-1'-en-2'-yl)phenol (207a)



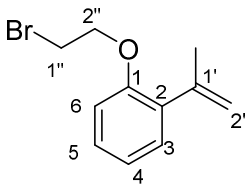
Prepared by a Wittig reaction from 2-hydroxyacetophenone (1.5 g, 11.0 mmol) as per the general procedure, giving the title phenol as a colourless oil (410 mg, 28%). ν_{max} (ATR) 3504, 3084, 2977, 1634, 1576, 1489, 1447, 1344, 1283, 1188, 1089, 908, 831, 751 cm^{-1}; δ_H (600 MHz) 7.21 – 7.08 (2H, m, 3-H, 5-H), 6.98 – 6.84 (2H, m, 4-H, 6-H), 5.67 (1H, s, OH), 5.41 (1H, q, *J* = 1.7 Hz, 2'-H), 5.15 (1H, dt, *J* = 1.9, 0.9 Hz, 2'-H), 2.12 (3H, dt, *J* = 1.7, 0.9 Hz, -CH_3); δ_C (151 MHz) 152.0 (1-C), 142.3 (1'-C), 128.9 (2-C), 128.8 (3-C), 127.9 (5-C), 120.3 (4-C), 115.9 (2'-C), 115.7 (6-C), 24.4 (-CH_3); *m/z* (GC-MS, EI) 134 $[M]^+$.

2-[2-(prop-1'-en-2'-yl)phenoxy]ethan-1"-ol (207b)



Prepared by reaction of 2-(prop-1'-en-2'-yl)phenol (410 mg, 3.06 mmol) with ethylene carbonate as per the general procedure, giving the title alcohol as a colourless oil (415 mg, 76%). ν_{max} (ATR) 3369, 3080, 2925, 2874, 1598, 1490, 1446, 1375, 1237, 1099, 1048, 997, 751 cm^{-1}; δ_H (600 MHz) 7.25 – 7.19 (2H, m, 3-H, 5-H), 6.96 (1H, td, *J* = 7.4, 1.1 Hz, 4-H), 6.90 (1H, dd, *J* = 8.2, 1.1 Hz, 6-H), 5.16 (1H, q, *J* = 1.7 Hz, 2'-H), 5.08 (1H, dd, *J* = 2.1, 1.1 Hz, 2'-H), 4.11 (2H, t, *J* = 6.1 Hz, 1"-H), 3.98 – 3.86 (2H, m, 2"-H), 2.16 – 2.08 (3H, m, $-CH_3$), 2.05 (1H, t, *J* = 6.4 Hz, OH); δ_C (151 MHz) 155.7 (1-C), 144.0 (1'-C), 133.5 (2-C), 129.6 (3-C), 128.5 (5-C), 121.4 (4-C), 115.4 (2'-C), 113.0 (6-C), 70.2 (1"-C), 61.7 (2"-C), 23.6 ($-CH_3$); *m/z* (GC-MS, EI) 178 $[M]^+$, HRMS (ASAP) requires 179.1072 (calc. for $[M+H]^+$) found 179.1066 ($[C_{11}H_{14}O_2]$+H).

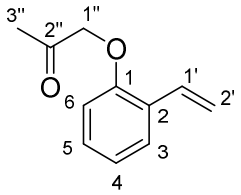
1-(2"-bromoethoxy)-2-(prop-1'-en-2'-yl)benzene (207)



Following the general procedure for an Appel reaction, 2-[2-(prop-1'-en-2'-yl)phenoxy]ethan-1"-ol (411 mg, 2.31 mmol) afforded the title bromide as a white solid which melted around room temperature (301 mg, 54%) ν_{max} (ATR) 3082,

2966, 1631, 1597, 1491, 1446, 1235, 1098, 1020, 897, 751 cm^{-1}; δ_H (700 MHz) 7.26 – 7.17 (2H, m, 3-H, 5-H), 6.96 (1H, td, *J* = 7.4, 1.1 Hz, 4-H), 6.88 – 6.82 (1H, m, 6-H), 5.15 (1H, q, *J* = 2.9, 1.6 Hz, 2'-H), 5.09 (1H, dd, *J* = 2.1, 1.0 Hz, 2'-H), 4.31 (2H, t, *J* = 6.2 Hz, 1"-H), 3.66 (2H, t, *J* = 6.2 Hz, 2"-H), 2.16 (3H, app. dd, *J* = 1.5, 0.9 Hz, $-CH_3$); δ_C (176 MHz) 155.2 (1-C), 144.2 (1'-C), 133.5 (2-C), 129.9 (3-C), 128.5 (5-C), 121.6 (4-C), 115.5 (2'-C), 112.5 (6-C), 68.5 (1"-C), 29.33 (2"-C), 23.49 ($-CH_3$); *m/z* (GC-MS, EI) [242 M(^{81}Br)]$^+$, 240 [M (^{79}Br)]$^+$; HRMS (ASAP) requires 241.0228 (calc. for $[M+H]^+$) found 241.0230 ($[C_{11}H_{13}BrO]$+H).

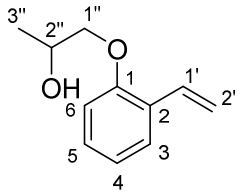
1"-(2-ethenylphenoxy)propan-2"-one (208a)



To a solution of 2-ethenyl phenol (1.0 g, 8.33 mmol) in acetone (15 mL) was added potassium carbonate (1.73 g, 12.5 mmol) followed by chloroacetone (1.0 mL, 12.5 mmol). The reaction mixture was heated at 60 ^oC for 3 h then allowed to cool. The mixture was filtered through a sintered funnel and the filtrate was concentrated *in vacuo*. Purification by column chromatography (0 – 20% EtOAc/hexane) afforded the title ketone as a light yellow oil (1.45 g, quant. yield). ν_{max} (ATR) 2183, 1717, 1486, 1446, 1227, 1113, 751 cm^{-1}; δ_H (700 MHz) 7.53 (1H, dd, *J* = 7.6, 1.5 Hz, 3-H), 7.22 (1H, td, *J* = 8.3, 1.6 Hz, 5-H), 7.13 (1H, dd, *J* = 17.7, 11.1 Hz, 1'-H), 7.00 (1H, app. t, *J* = 7.3 Hz, 4-H), 6.72 (1H, dd, *J* = 8.2 Hz, 6-H), 5.79 (1H, dd, *J* = 17.7, 1.2 Hz, 2'-H_{trans}), 5.32 (1H, dd, *J* = 11.1, 1.2 Hz, 2'-H_{cis}), 4.55 (2H, s, 1''-H), 2.32 (3H, s, 3''-H); δ_C (176 MHz) 206.0 (2"-C), 154.9 (1-C), 131.3 (1'-C), 129.1 (5-C), 127.3 (2-C), 127.0 (3-

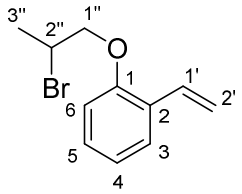
C), 121.9 (4-C), 115.2 (2'-C), 112.0 (6-C), 73.6 (1"-C), 26.9 (3"-C); *m/z* (GC-MS, EI) 176 $[M]^+$; HRMS (ASAP) requires 176.0837 (calc. for $[M]^+$) found 176.0843 ($C_{11}H_{12}O_2$).

1"-(2-ethenylphenoxy)propan-2"-ol (208b)



To a solution of 1"-(2-ethenylphenoxy)propan-2"-one (1.46 g, 8.33 mmol) in ethanol (20 mL) was added at 0 ^oC sodium borohydride (308 mg, 8.33 mmol). The mixture was allowed to warm to room temperature with stirring overnight (17 h) then poured into a mixture of water/ether (10 mL). The product was extracted into ether (4 x 15 mL) then dried and concentrated *in vacuo*. Purification by column chromatography (0 – 30% EtOAc/hexane) afforded the title alcohol as a waxy colourless oil (1.37 g, 93%). vmax (ATR) 3378, 2978, 2928, 1756, 1487, 1451, 1242, 1106, 916, 748 cm-1; δ_H (700 MHz) 7.49 (1H, dd, J = 7.7, 1.7 Hz, 3-H), 7.23 (1H, app. td, J = 8.2, 7.3, 1.1 Hz, 5-H), 7.06 (1H, app. dd, J = 17.7, 11.1 Hz, 1'-H), 6.98 (1H, m, 4-H), 6.87 (1H, dd, J = 8.2, 1.1 Hz, 6-H), 5.78 (1H, dd, J = 17.7, 1.4 Hz, 2'-H_c), 5.28 (1H, dd, J = 11.2, 1.4 Hz, 2'-H_{cis}), 4.20 (1H, m, 2''-H), 3.97 (1H, app. dd, J = 9.2, 3.3 Hz, 1''-H), 3.85 (1H, app. dd, J = 9.2, 7.5 Hz, 1''-H), 2.29 (1H, d, J = 3.5 Hz, OH), 1.31 (3H, d, J = 6.4 Hz, 3''-H). δ_C (176 MHz) 155.8 (1-C), 131.6 (1'-C) , 129.0 (5-C), 127.2 (2-C), 126.8 (3-C), 121.4 (4-C) 114.9 (2'-C), 112.5 (6-C), 74.0 (1''-C), 66.6 (2''-C); 19.02 (3''-C); *m/z* (GC-MS, EI) 178 [M]+; HRMS (ASAP) requires 179.1032 (calc. for $[M+H]^+$) found 179.1073 ($[C_{11}H_{14}O_2]$+H).

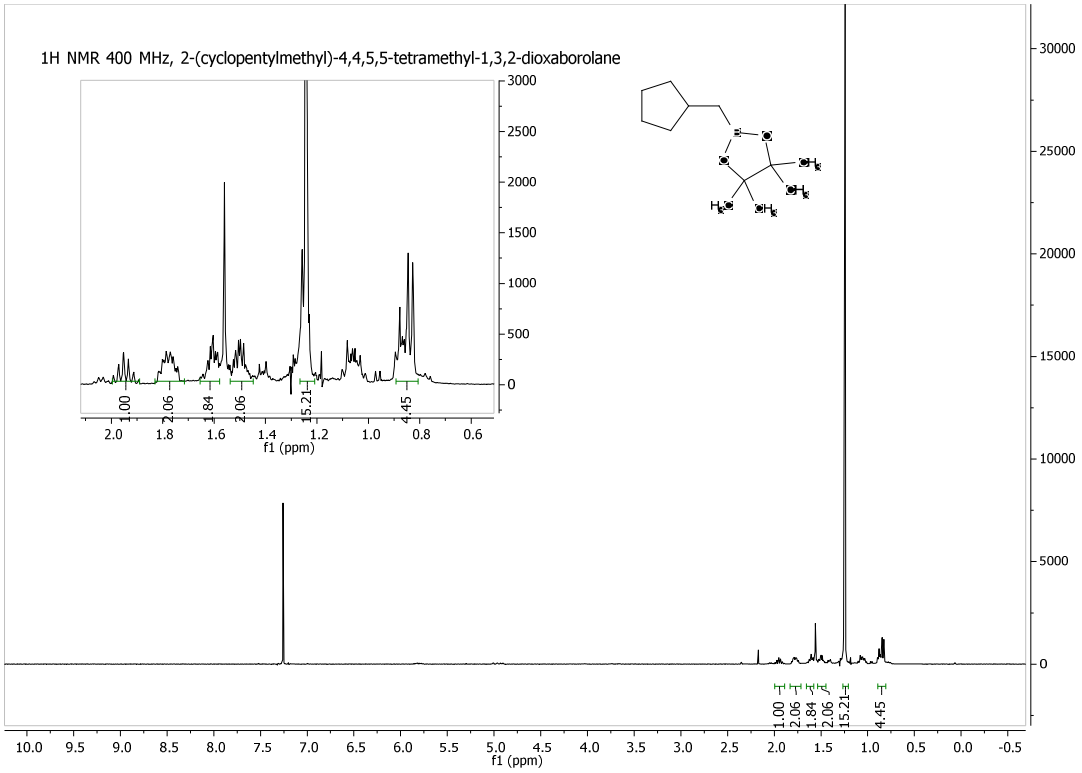
2”-bromopropyl 2-ethenylphenyl ether (208)

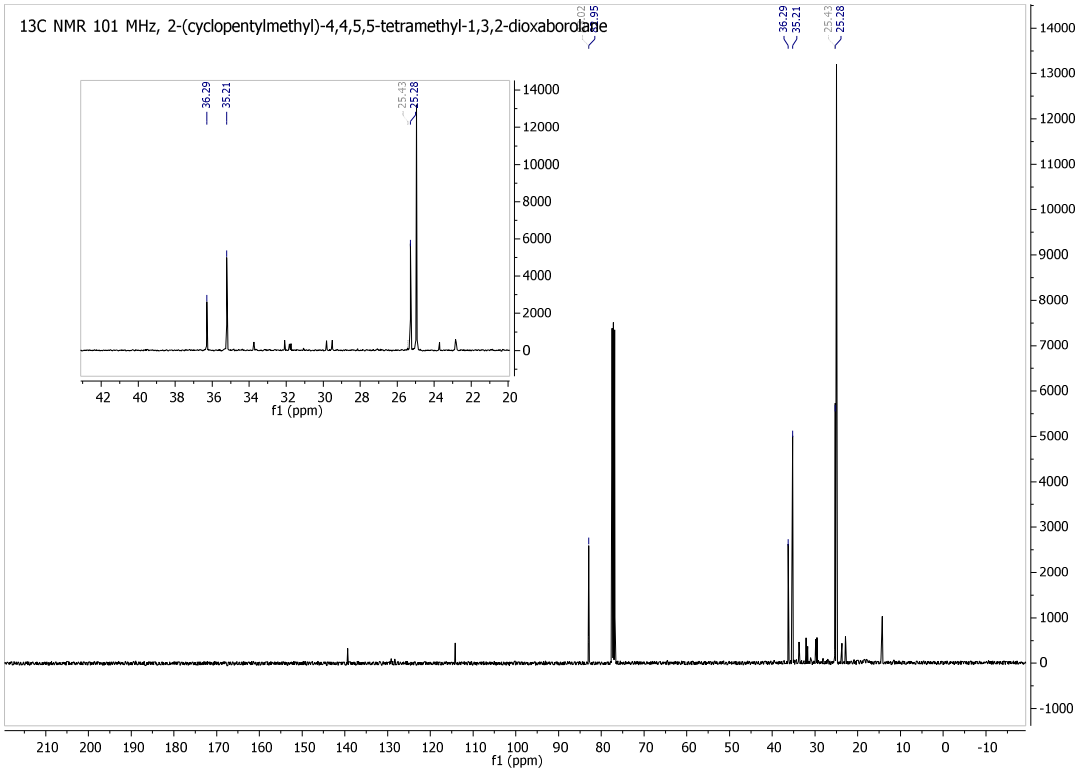


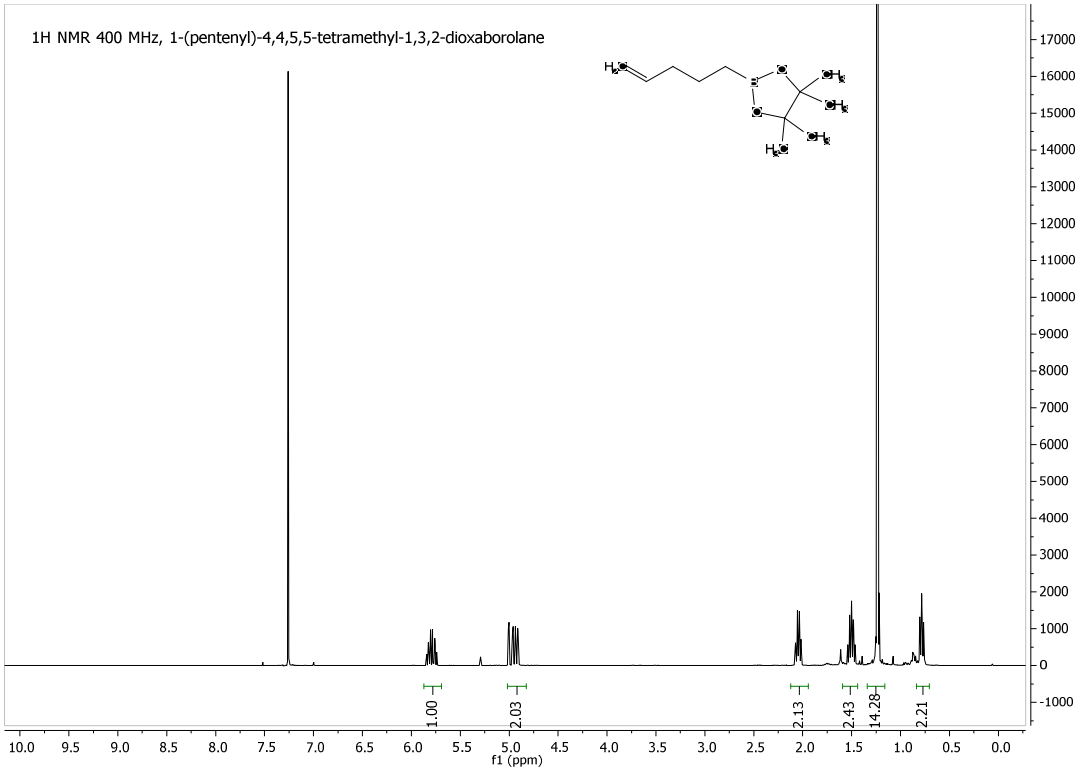
Following the general procedure for an Appel reaction, 1”-(2-ethenylphenoxy)propan-2”-ol (1.15 g, 6.44 mmol) afforded the title bromide as a colourless oil (681 mg, 44%). ν_{max} (ATR) 2968, 1596, 1487, 1451, 1240, 1104, 924, 749 cm^{-1}; δ_H (400 MHz) 7.50 (1H, dd, *J* = 7.7, 1.7 Hz, 3-H), 7.22 (1H, td, J = 8.2, 7.4, 1.7 Hz, 5-H), 7.08 (1H, app. dd, *J* = 17.8, 11.1 Hz, 1’-H), 7.00 – 6.94 (1H, m (app. td), 4-H), 6.87 (1H, dd, *J* = 8.1, 1.0 Hz, 6-H), 5.77 (1H, dd, *J* = 17.8, 1.4 Hz, 2’-H_{trans}), 5.28 (1H, dd, *J* = 11.2, 1.4 Hz, 2’-H_{cis}), 4.40 – 4.34 (1H, m, 2’’-H), 4.24 (1H, dd, *J* = 9.9, 5.6 Hz, 1’’-H), 4.10 (1H, dd, *J* = 9.9, 7.0 Hz, 1’’-H), 1.83 (3H, d, *J* = 6.7 Hz, 3’’-H); δ_C (176 MHz) 155.4 (1-C), 131.5 (1’-C) , 129.0 (5-C), 127.3 (2-C), 126.8 (3-C), 121.5 (4-C) 114.5 (2’-C), 112.4 (6-C), 73.7 (1’’-C), 45.4 (2’’-C); 22.9 (3’’-C); *m/z* (GC-MS, EI) [242 M(^{81}Br)]$^+$, 240 [M (^{79}Br)]$^+$; HRMS (ASAP) requires 240.0150 (calc. for [M]$^+$) found 240.0163 ($C_{11}H_{13}OBr$).

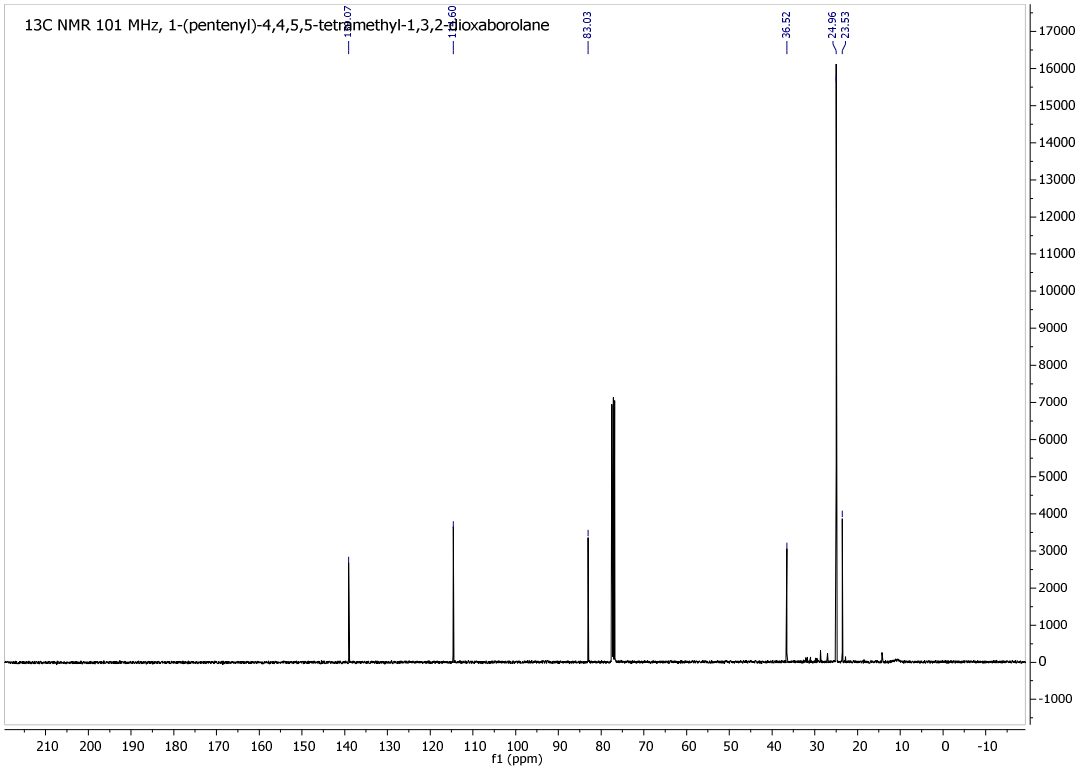
7 Appendix of NMR spectra

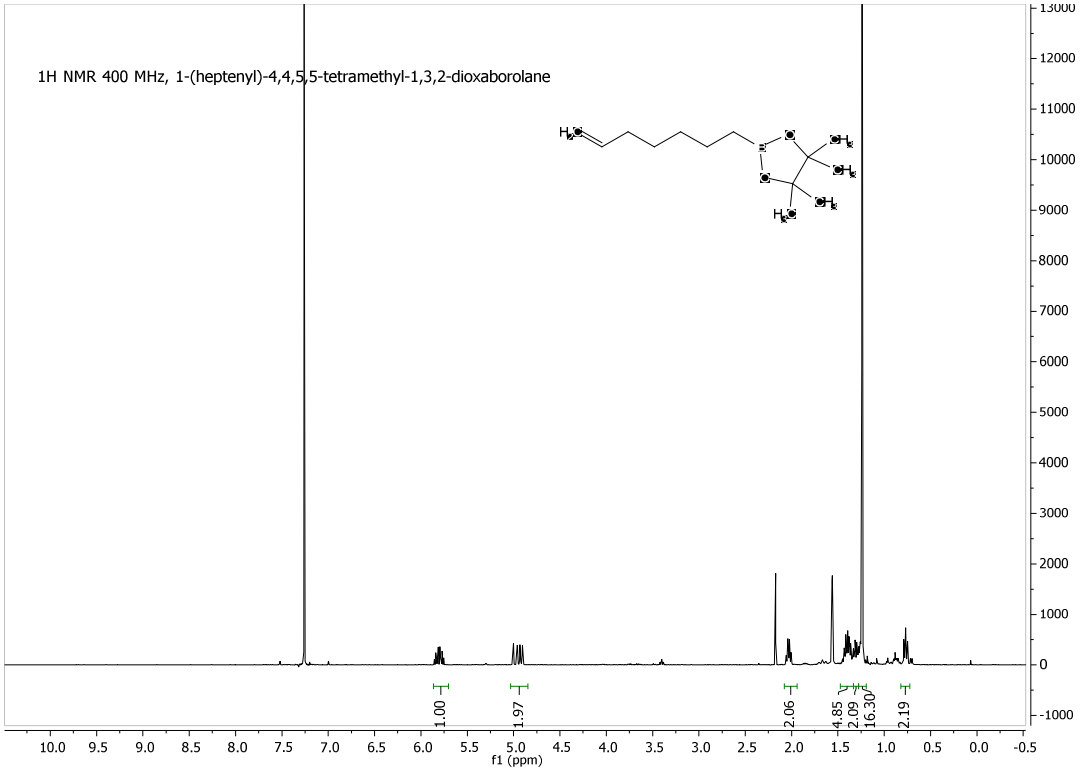
^{1}H & ^{13}C NMR spectra of compounds in chapter 2

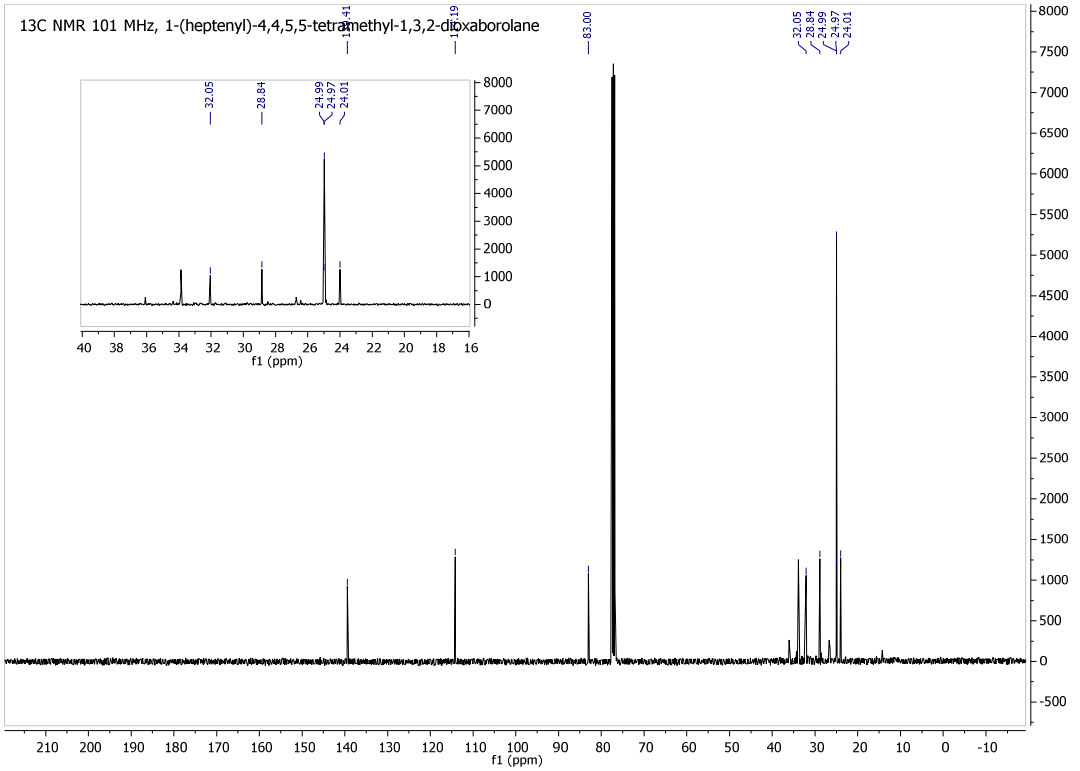


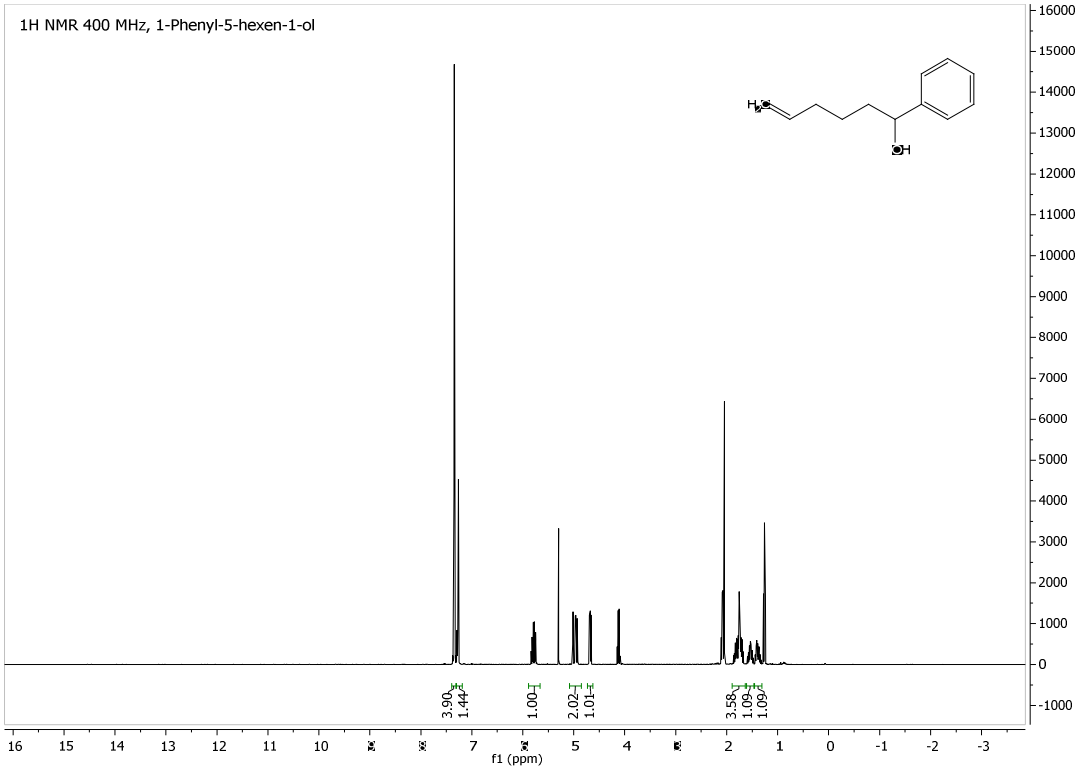


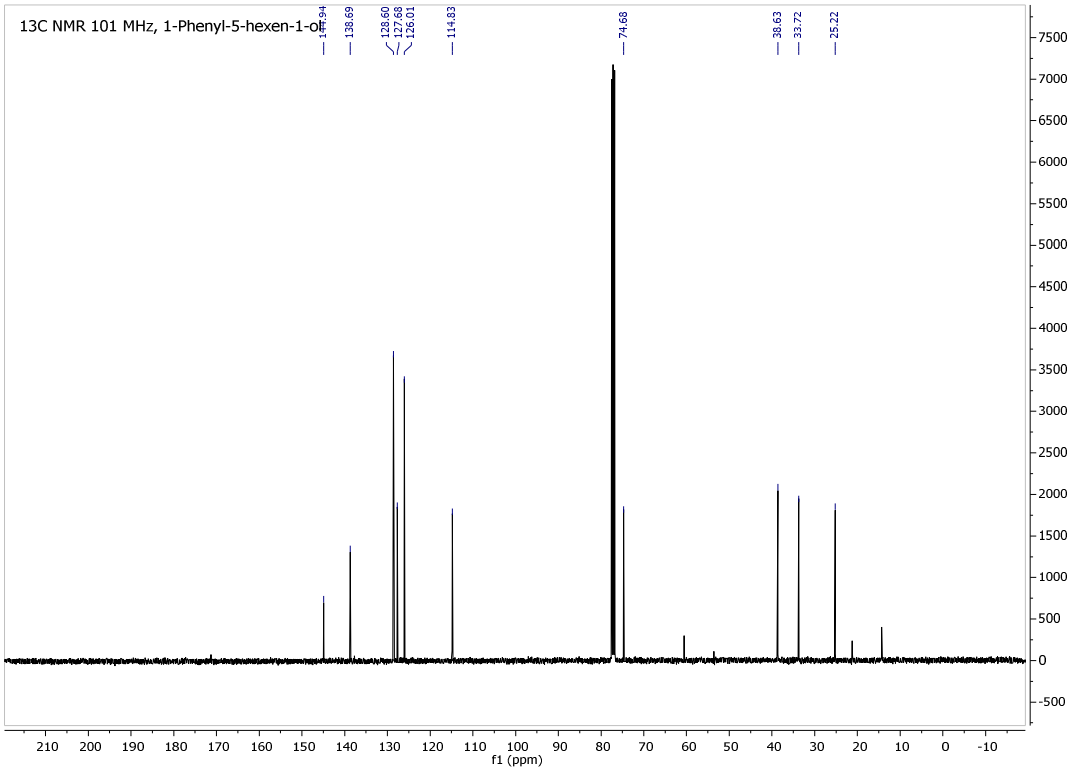

1H NMR 400 MHz, 1-(pentenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
1.00
2.03
2.13
2.43
14.28
2.21
f1 (ppm)

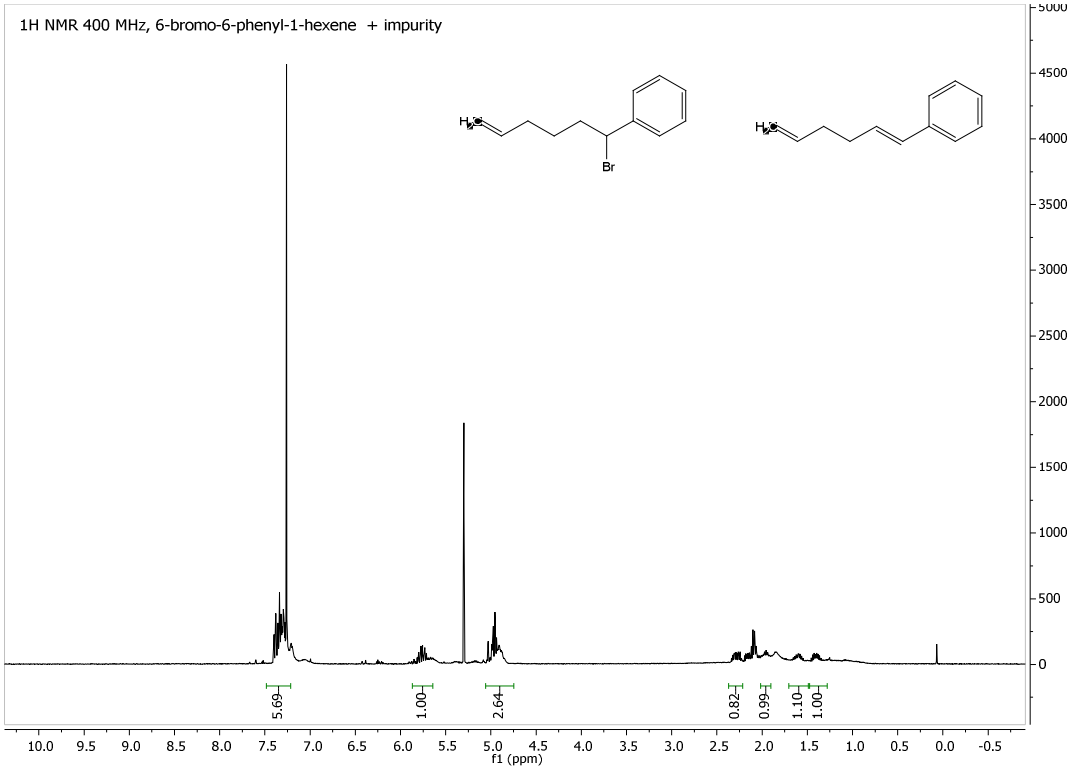

13C NMR 101 MHz, 1-(pentenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
141.07
114.60
83.03
36.52
24.96
23.53
f1 (ppm)

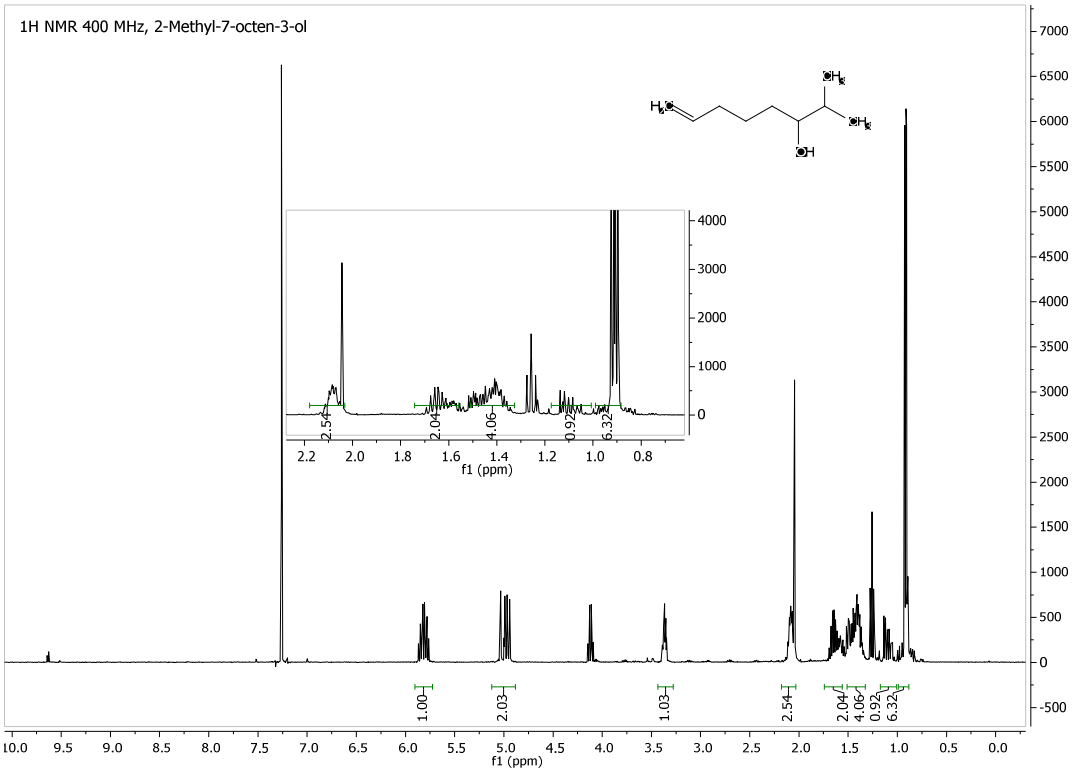

1H NMR 400 MHz, 1-(heptenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
1.00
1.97
2.06
4.85
2.09
16.30
2.19
f1 (ppm)

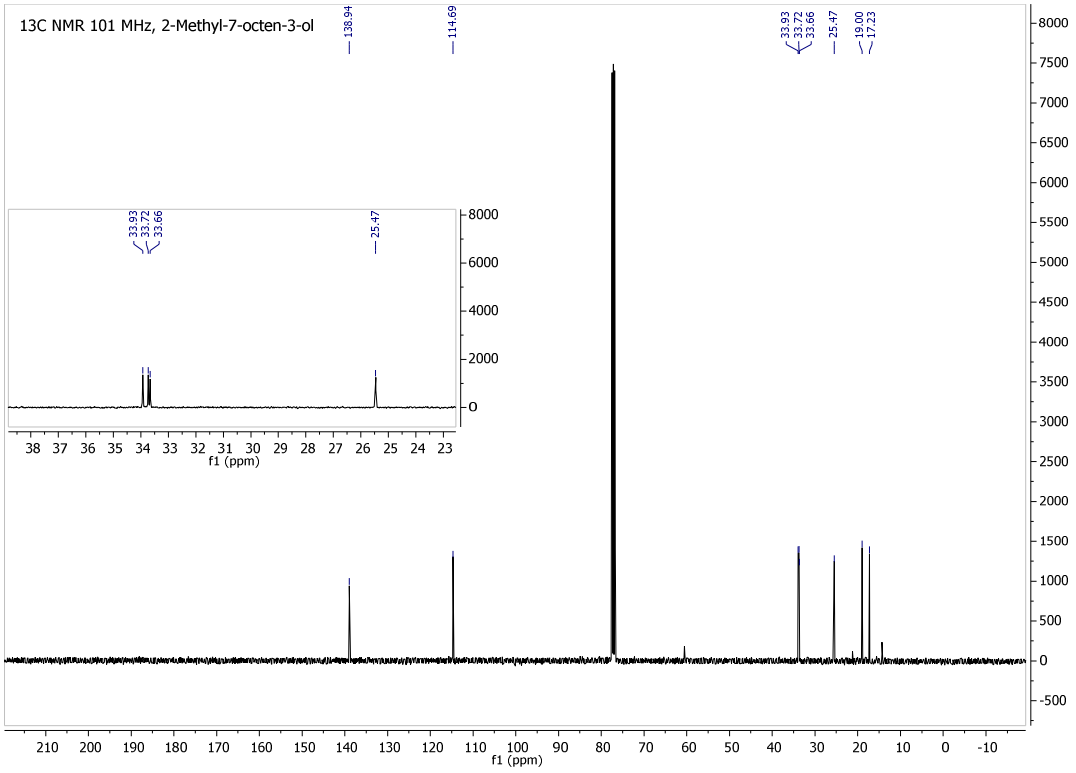

13C NMR 101 MHz, 1-(heptenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
83.00
32.05
28.84
24.99
24.97
24.01
f1 (ppm)

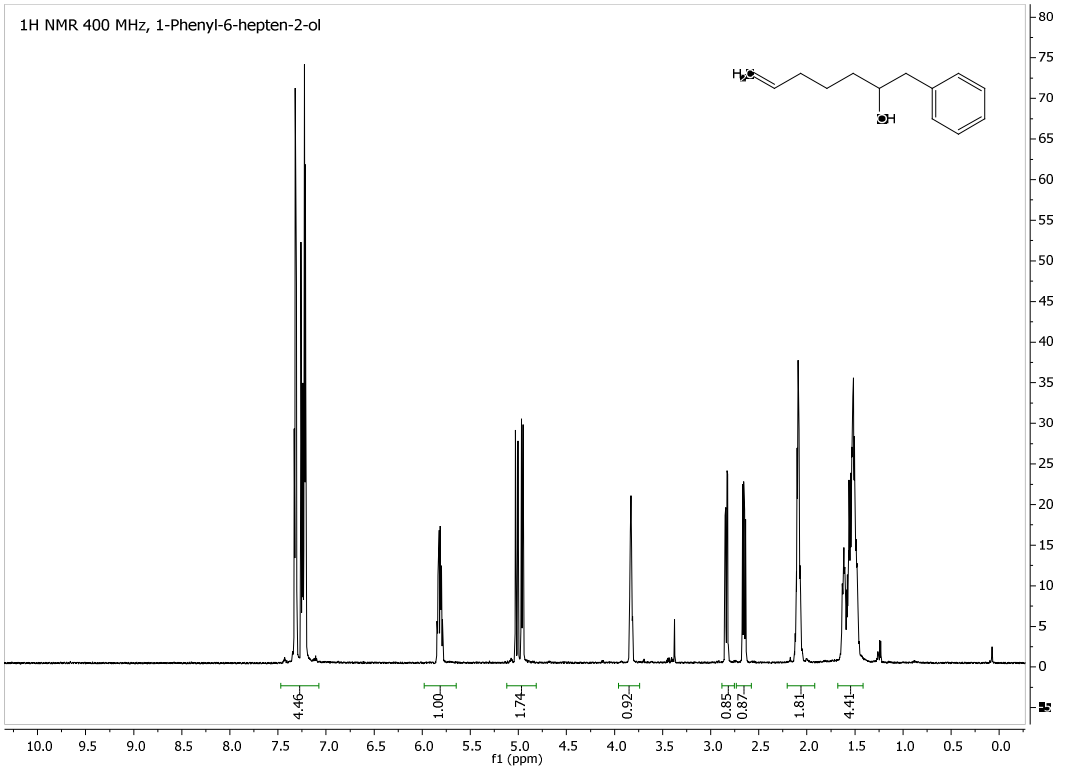

1H NMR 400 MHz, 1-Phenyl-5-hexen-1-ol
3.90
1.44
1.00
2.02
1.01
3.58
1.09
1.09
f1 (ppm)

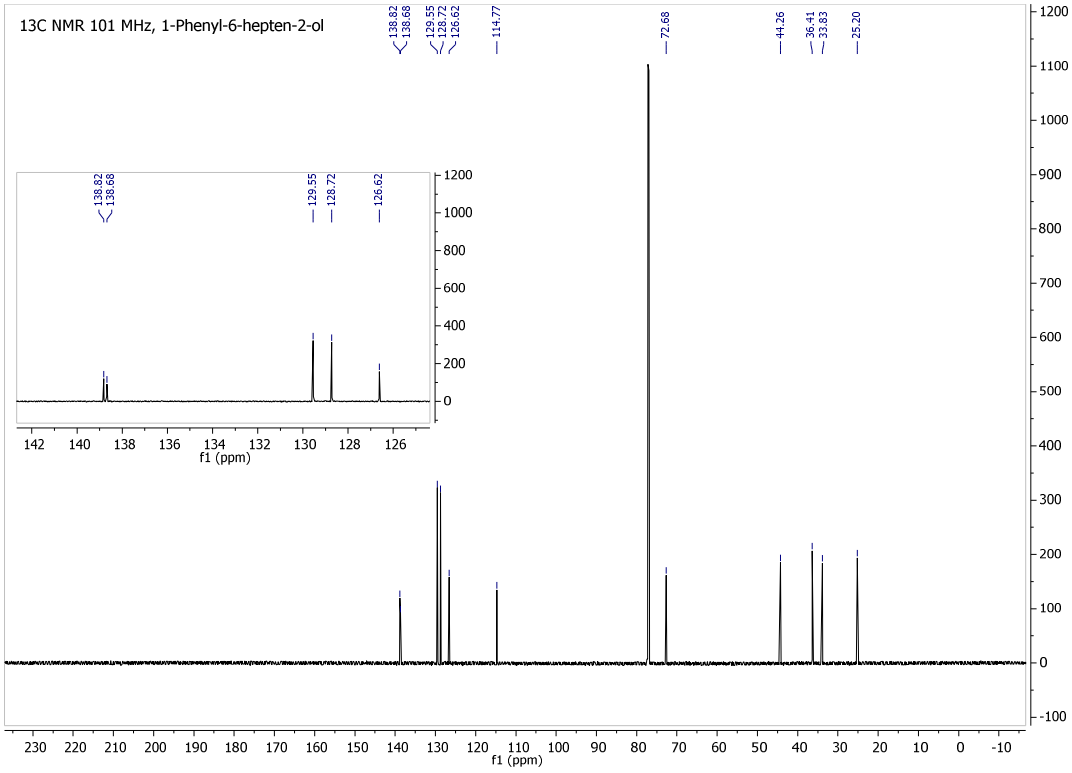

13C NMR 101 MHz, 1-Phenyl-5-hexen-1-ol
144.94
138.69
128.60
127.68
126.01
114.83
74.68
38.63
33.72
25.22
f1 (ppm)

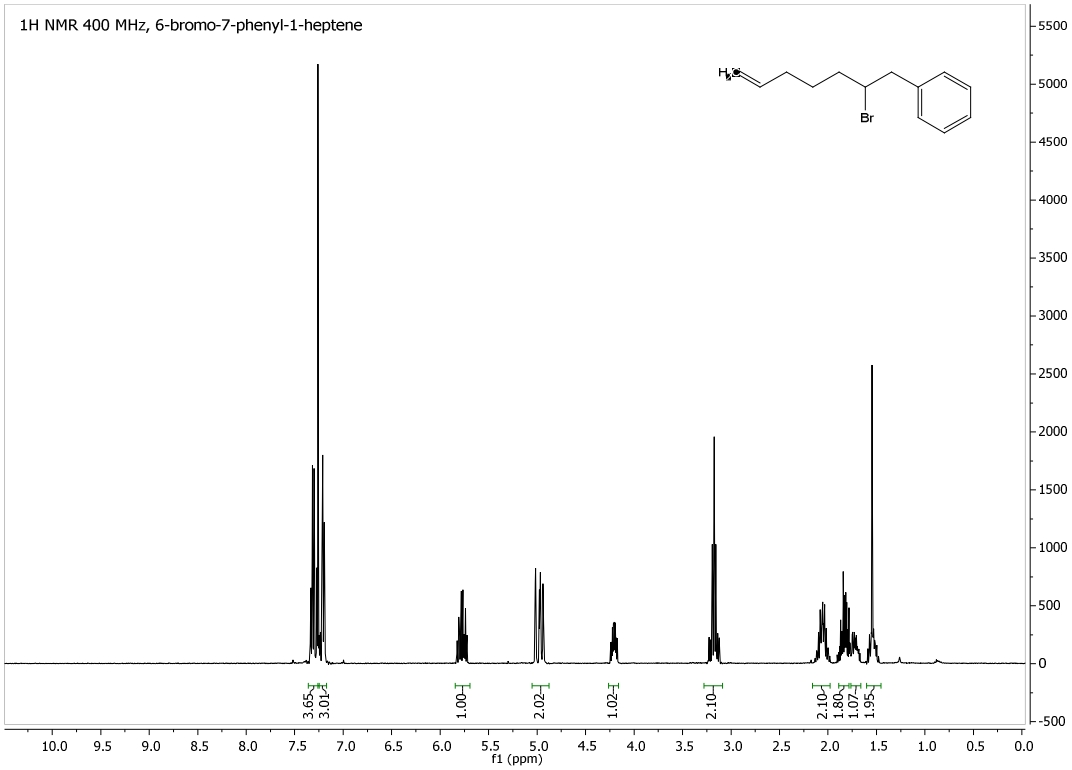

1H NMR 400 MHz, 6-bromo-6-phenyl-1-hexene + impurity
Br
5.69
1.00
2.64
0.82
0.99
1.10
1.00
f1 (ppm)

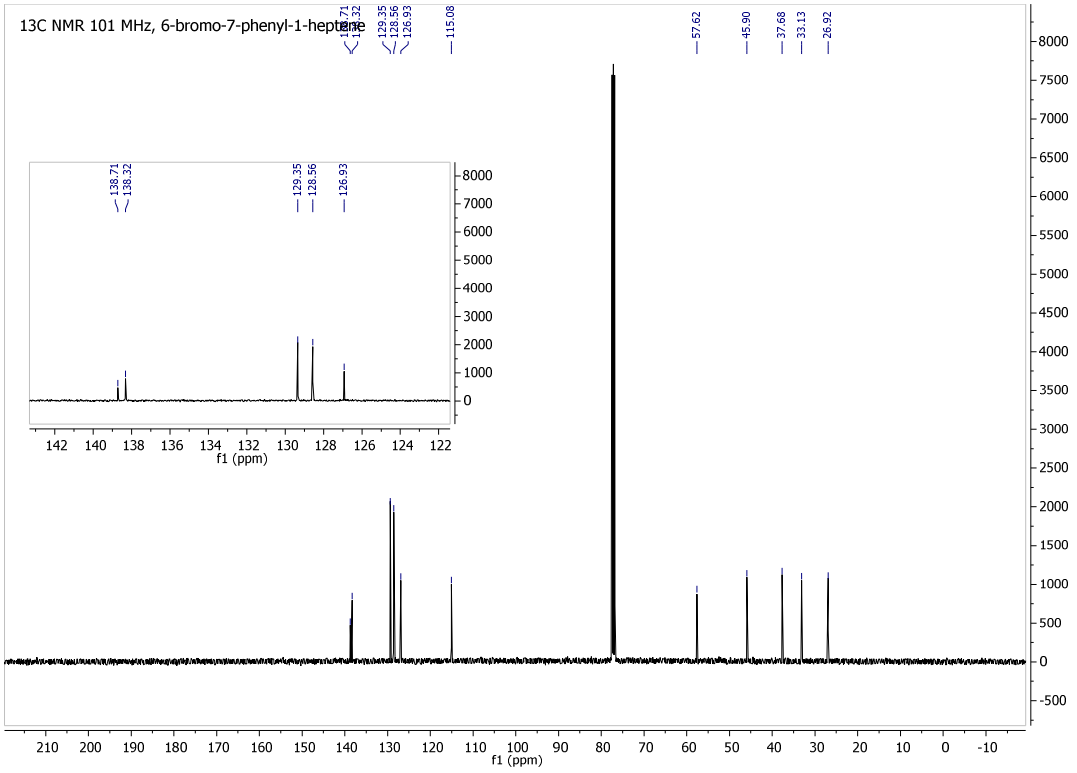

1H NMR 400 MHz, 2-Methyl-7-octen-3-ol
2.54
2.04
4.06
0.92
6.32
f1 (ppm)
1.00
2.03
1.03
2.54
2.04
4.06
0.92
6.32
f1 (ppm)

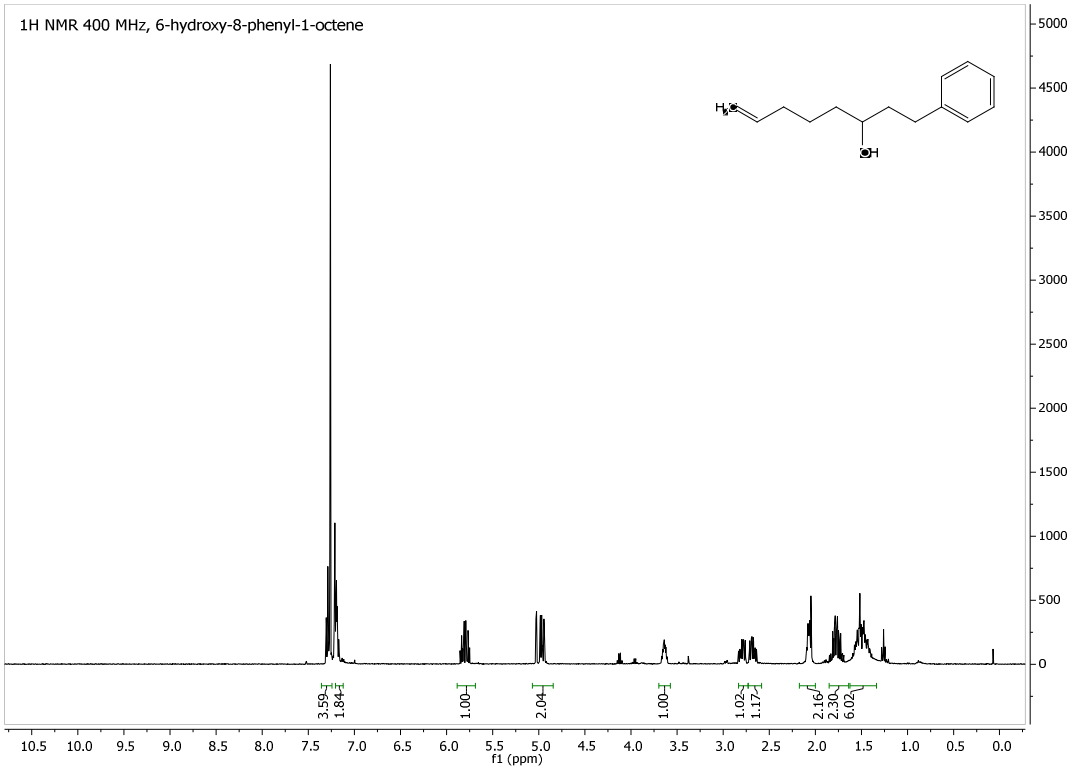

13C NMR 101 MHz, 2-Methyl-7-octen-3-ol
138.94
114.69
33.93
33.72
33.66
25.47
19.00
17.23
f1 (ppm)

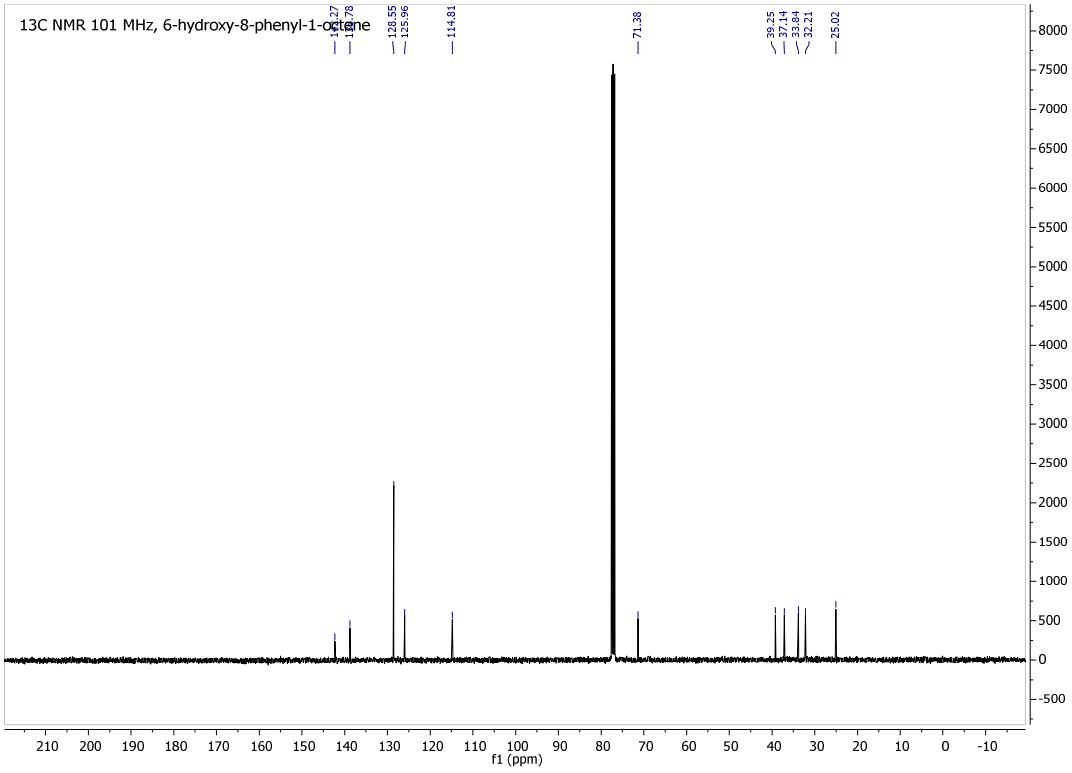

1H NMR 400 MHz, 1-Phenyl-6-hepten-2-ol
4.46
1.00
1.74
0.92
0.85
0.87
1.81
4.41
f1 (ppm)

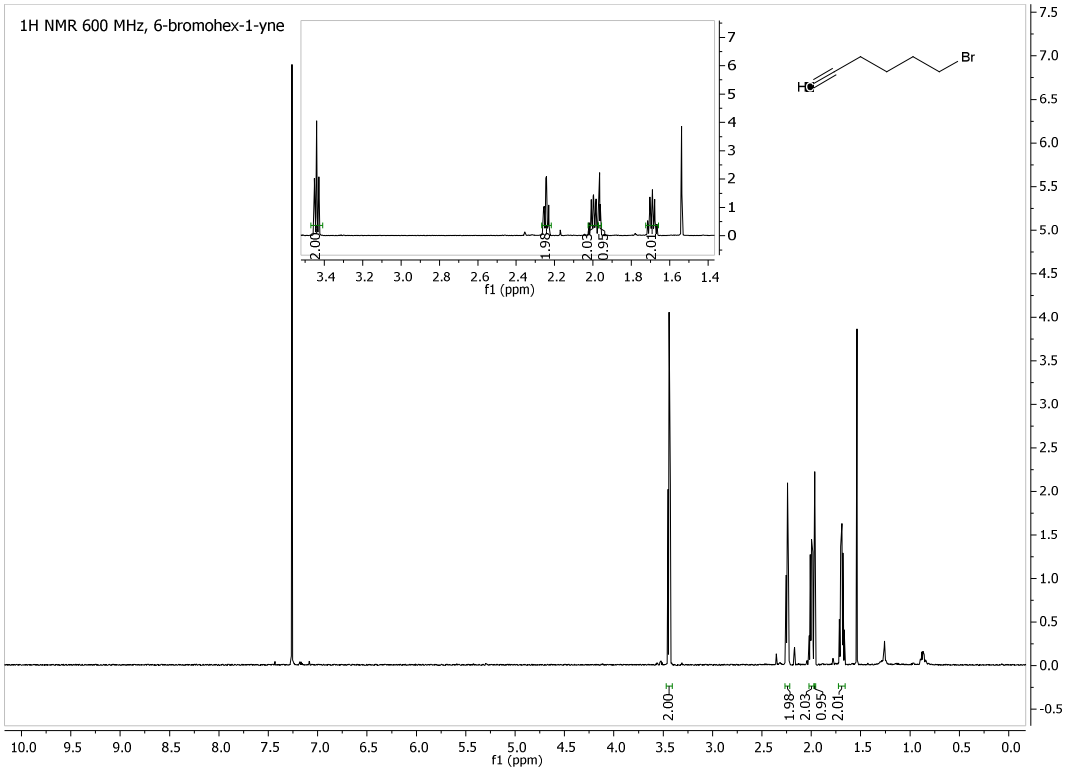

13C NMR 101 MHz, 1-Phenyl-6-hepten-2-ol
138.82
138.68
129.55
128.72
126.62
114.77
72.68
44.26
36.41
33.83
25.20
f1 (ppm)

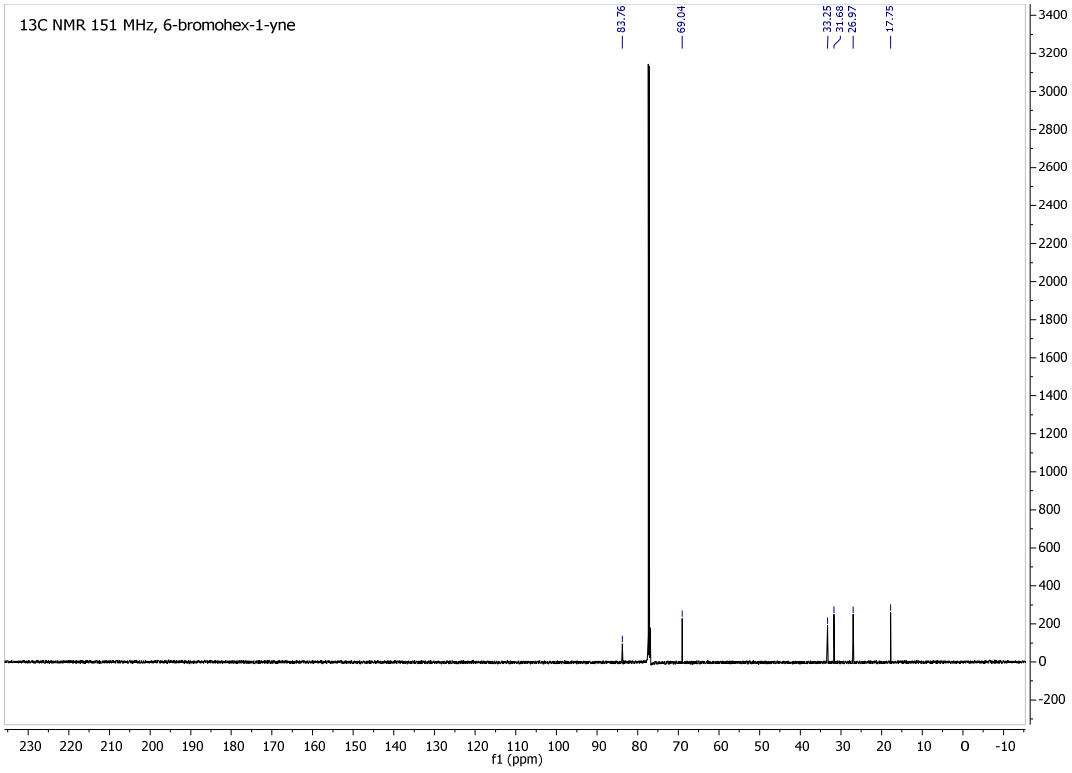

1H NMR 400 MHz, 6-bromo-7-phenyl-1-heptene
Br
3.65
3.01
1.00
2.02
1.02
2.10
2.10
1.80
1.07
1.95
f1 (ppm)

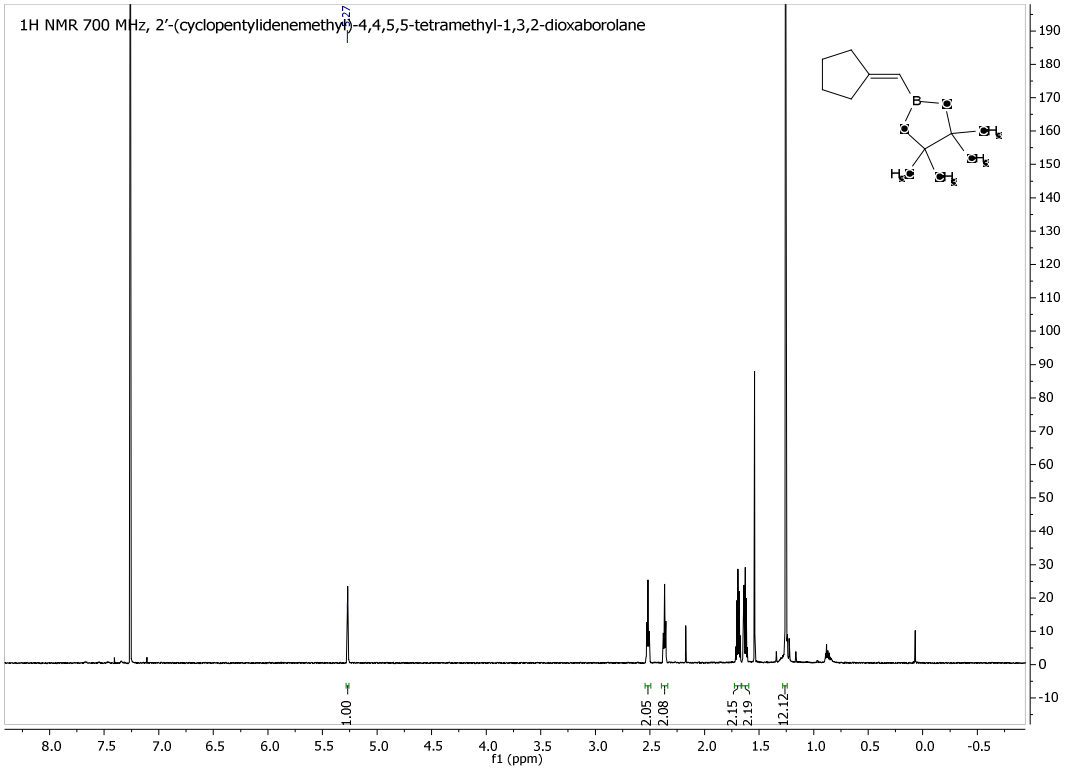

13C NMR 101 MHz, 6-bromo-7-phenyl-1-heptene
138.71
138.32
129.35
128.56
126.93
115.08
57.62
45.90
37.68
33.13
26.92
f1 (ppm)

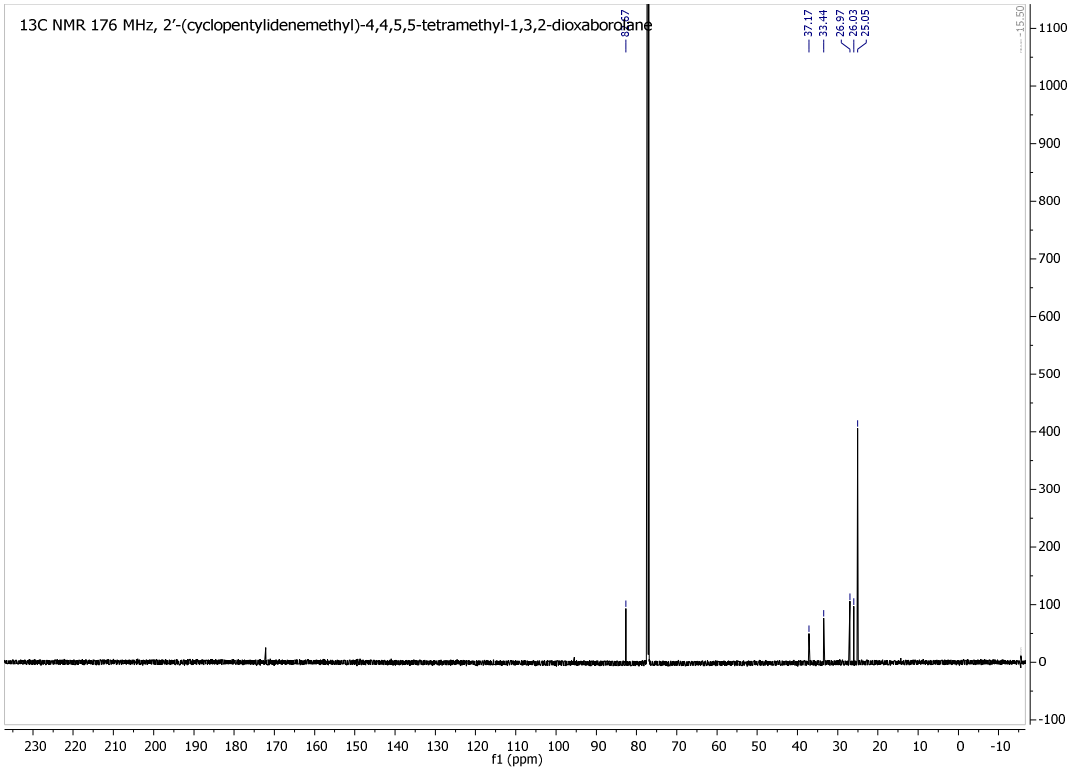

1H NMR 400 MHz, 6-hydroxy-8-phenyl-1-octene
3.59
1.84
1.00
2.04
1.00
1.02
1.17
2.16
2.30
6.02
f1 (ppm)

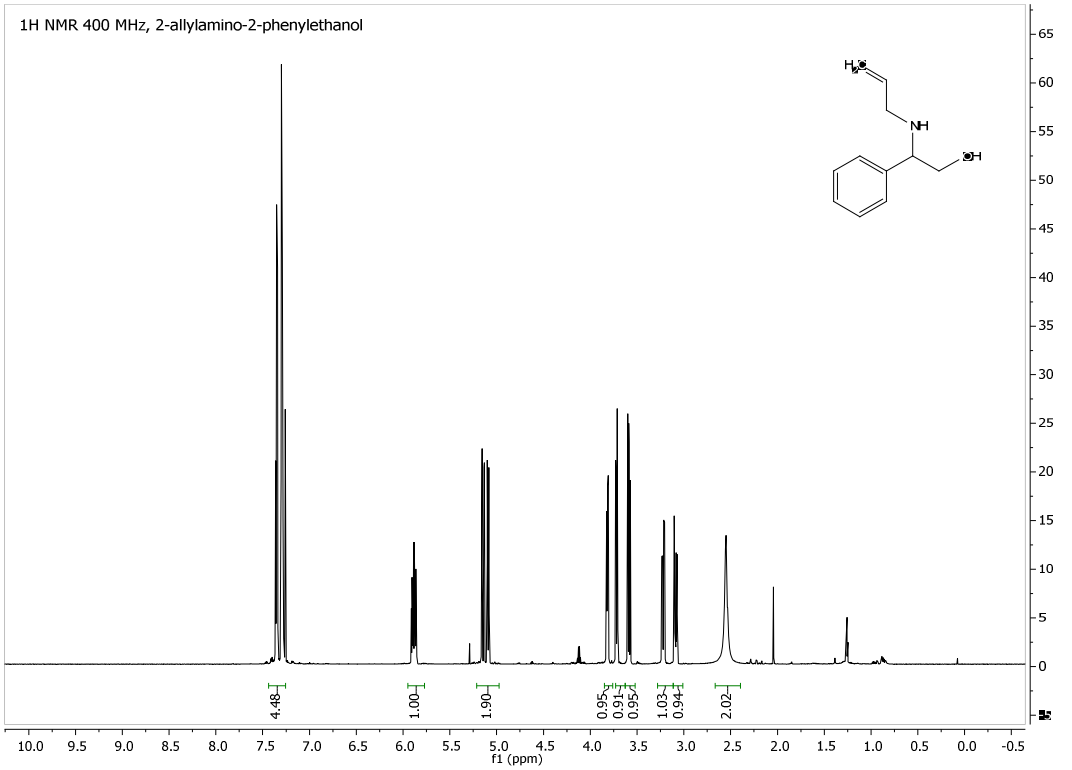

13C NMR 101 MHz, 6-hydroxy-8-phenyl-1-octene
141.27
138.78
128.55
125.96
114.81
71.38
39.25
37.14
33.84
32.21
25.02
f1 (ppm)

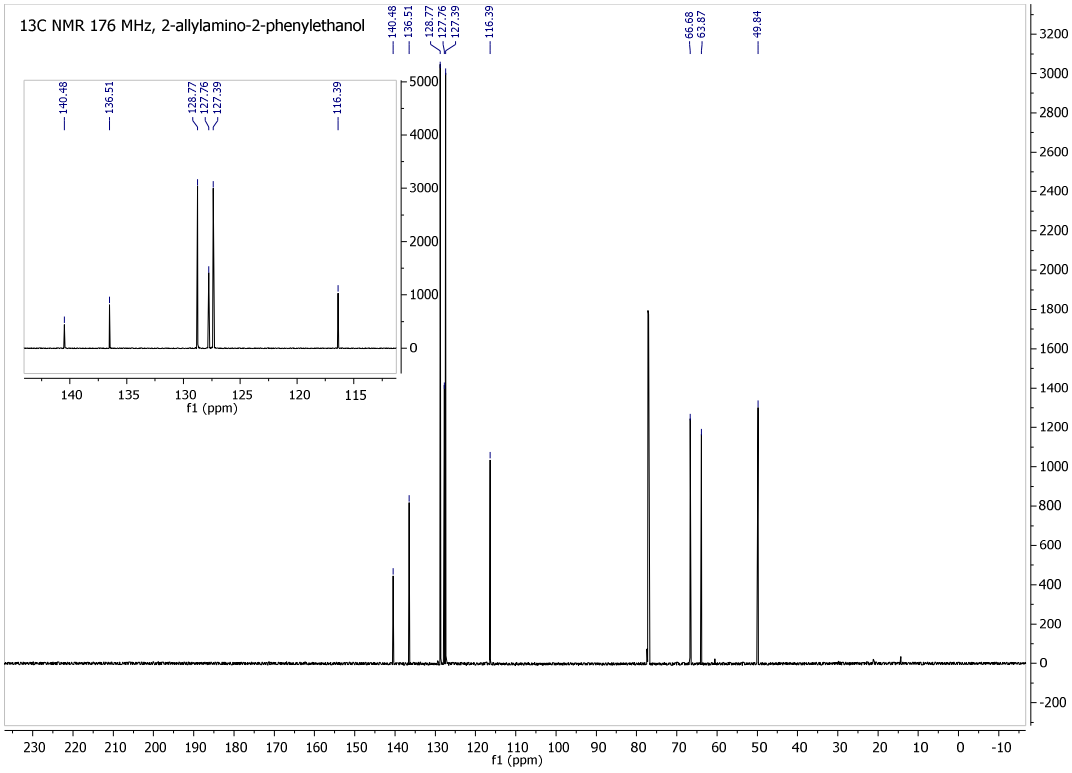

1H NMR 600 MHz, 6-bromohex-1-yne
Br
H
2.00
1.98
2.03
0.95
2.01
f1 (ppm)

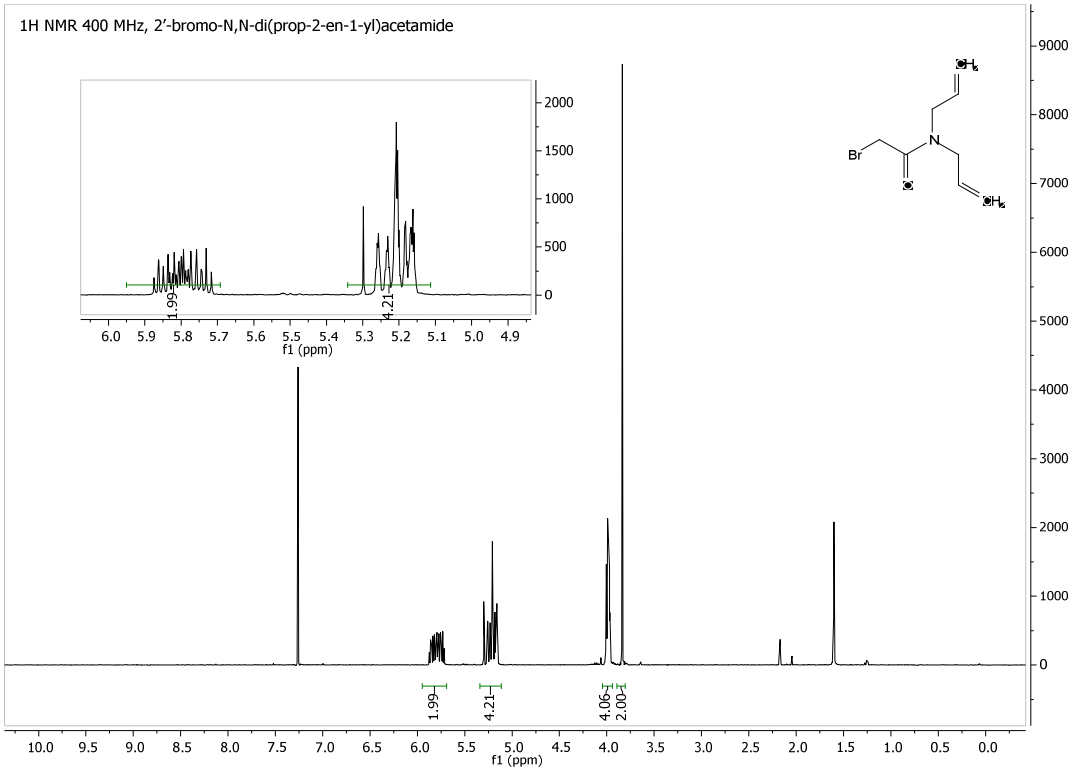

13C NMR 151 MHz, 6-bromohex-1-yne
83.76
69.04
33.25
31.68
26.97
17.75
f1 (ppm)

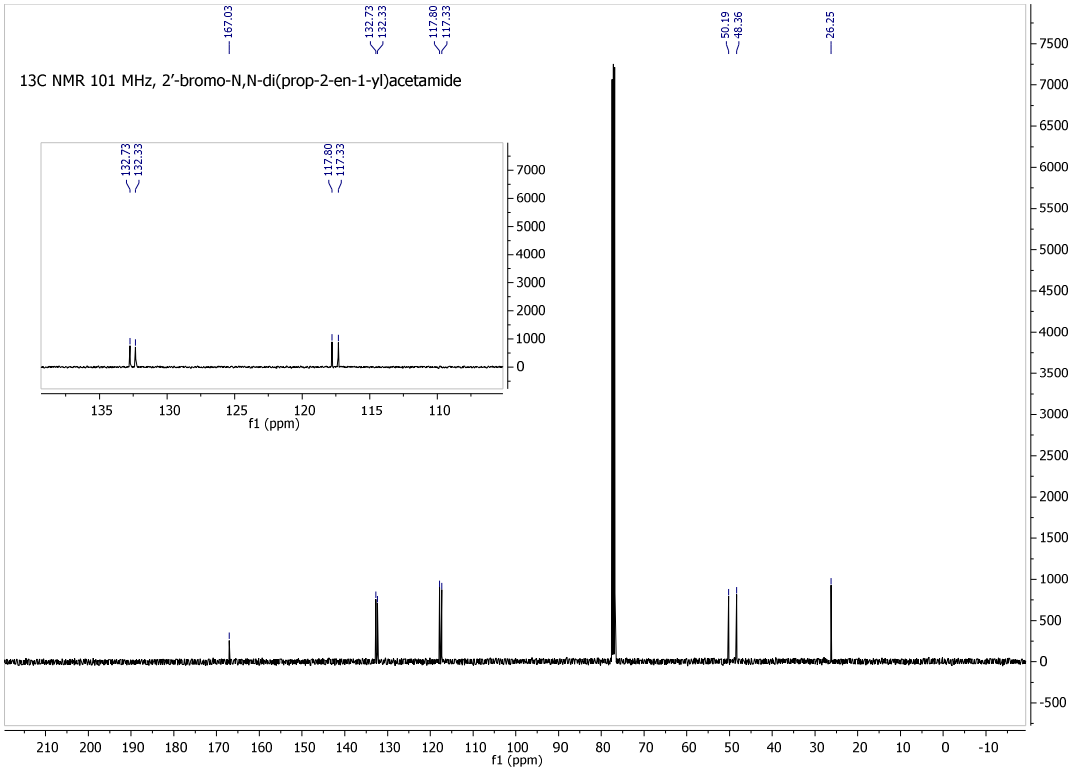

1H NMR 700 MHz, 2'-(cyclopentylidenemethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
1.27
1.00
2.05
2.08
2.15
2.19
12.12
f1 (ppm)

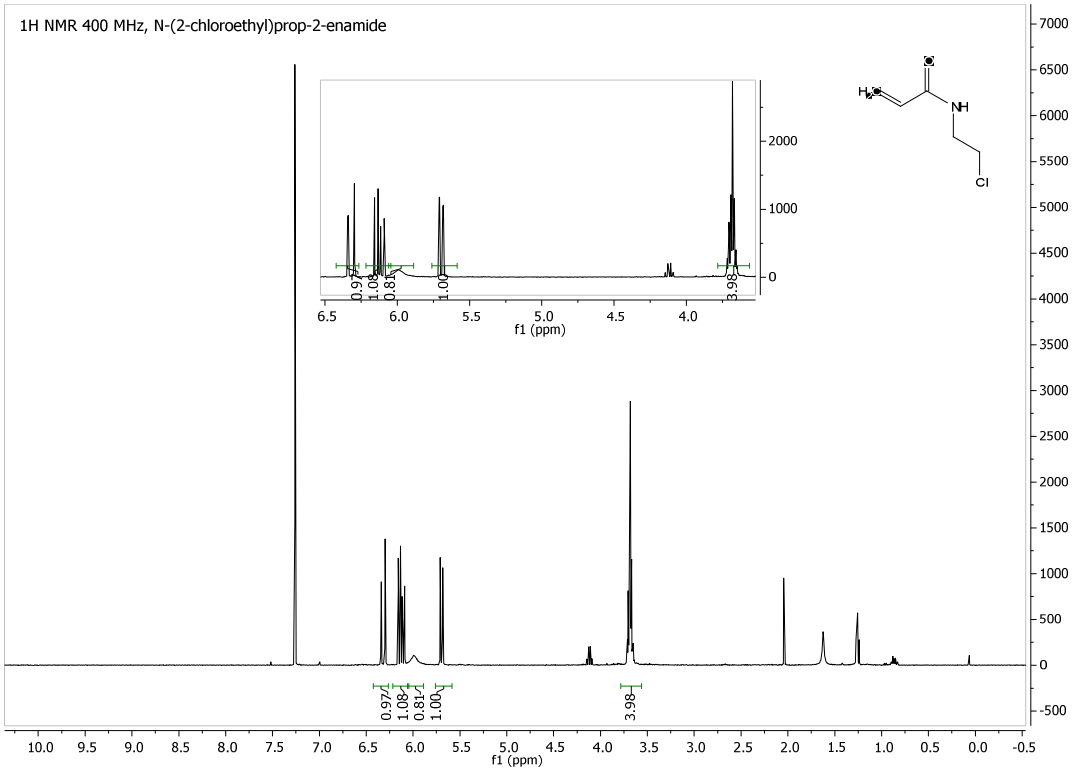

13C NMR 176 MHz, 2′-(cyclopentylidenemethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
83.67
37.17
33.44
26.97
26.03
25.05
f1 (ppm)

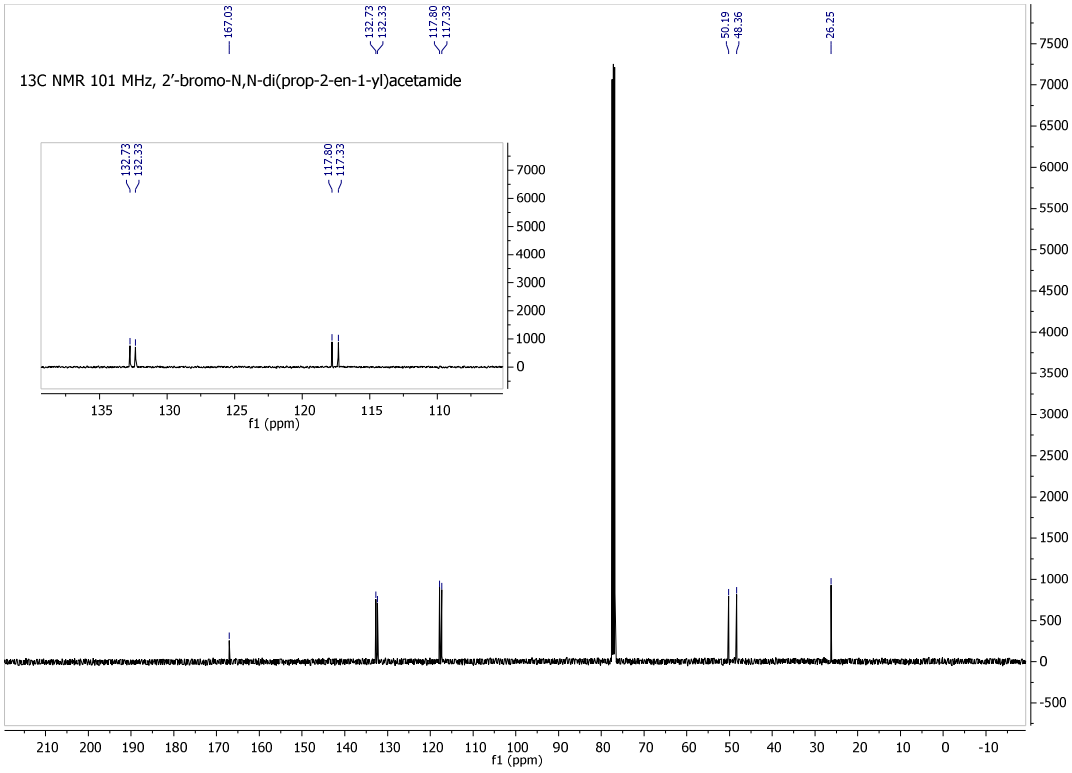

1H NMR 400 MHz, 2-allylamino-2-phenylethanol
NH
OH
4.48
1.00
1.90
0.95
0.91
0.95
1.03
0.94
2.02
f1 (ppm)

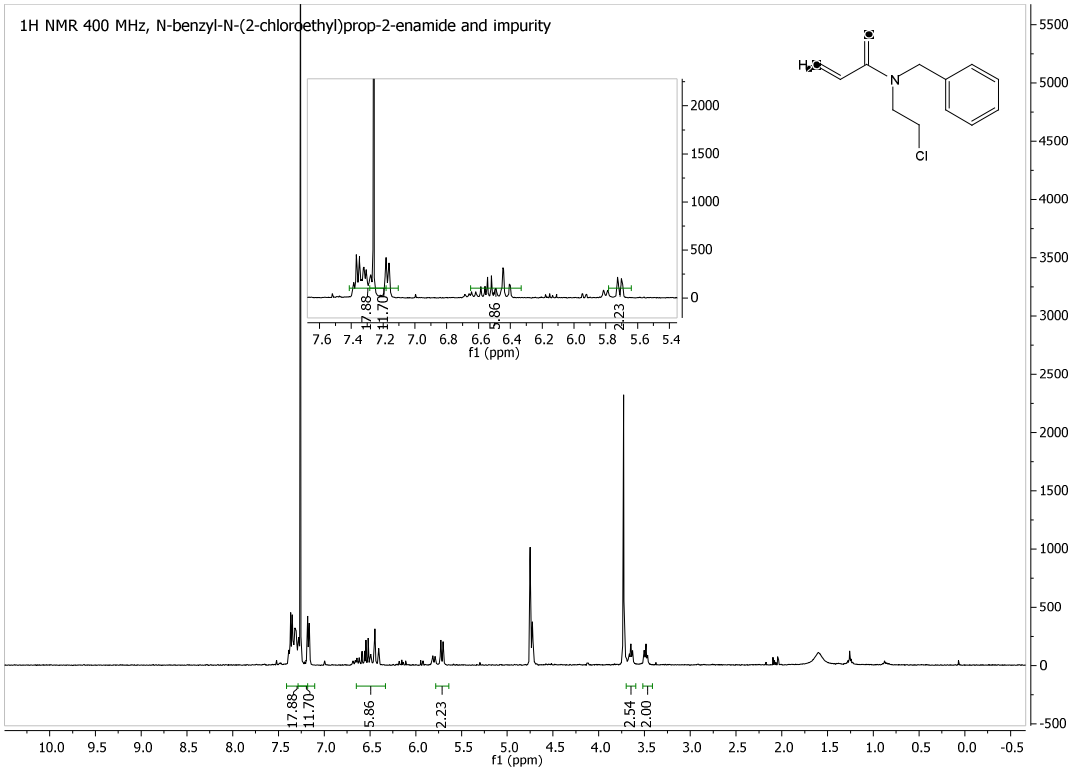

13C NMR 176 MHz, 2-allylamino-2-phenylethanol
140.48
136.51
128.77
127.76
127.39
116.39
66.68
63.87
49.84
f1 (ppm)

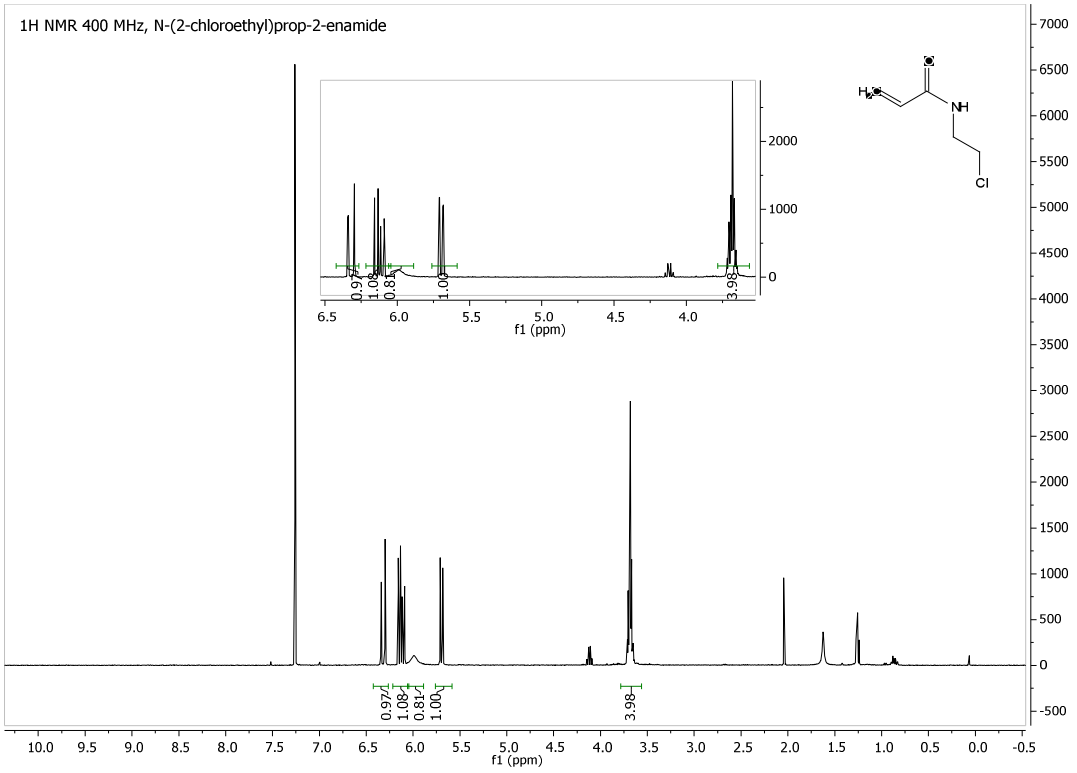

1H NMR 400 MHz, 2'-bromo-N,N-di(prop-2-en-1-yl)acetamide
1.99
4.21
4.06
2.00
f1 (ppm)

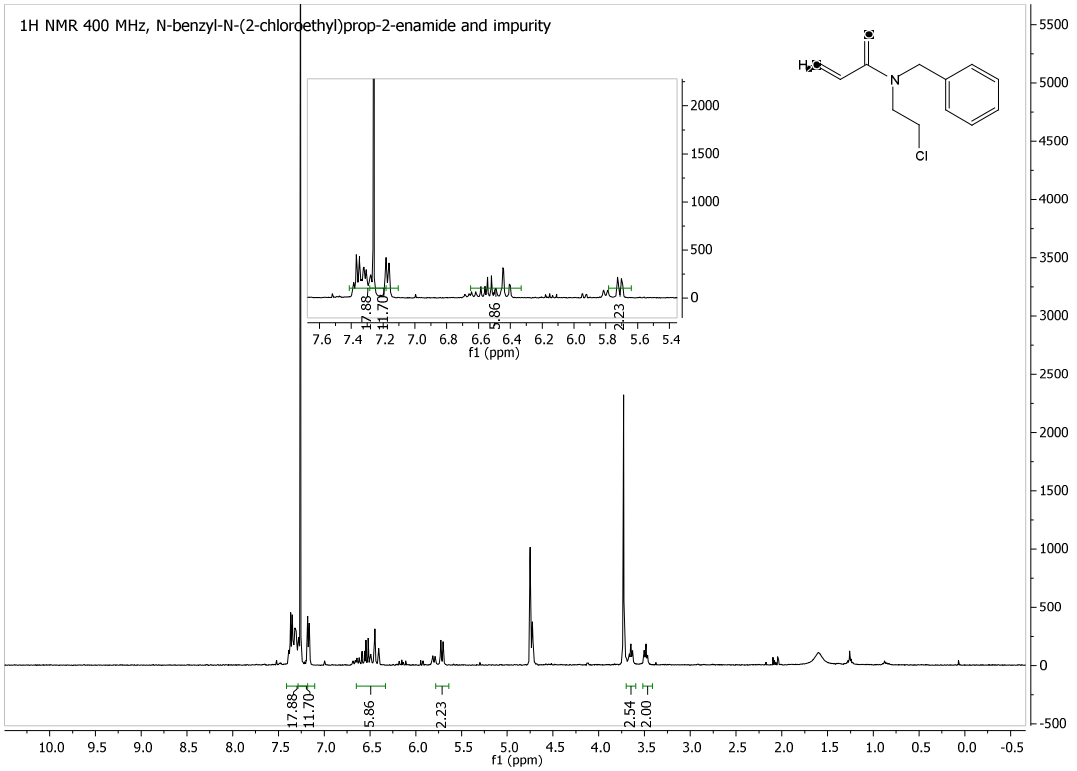

13C NMR 101 MHz, 2'-bromo-N,N-di(prop-2-en-1-yl)acetamide
167.03
132.73
132.33
117.80
117.33
50.19
48.36
26.25
f1 (ppm)

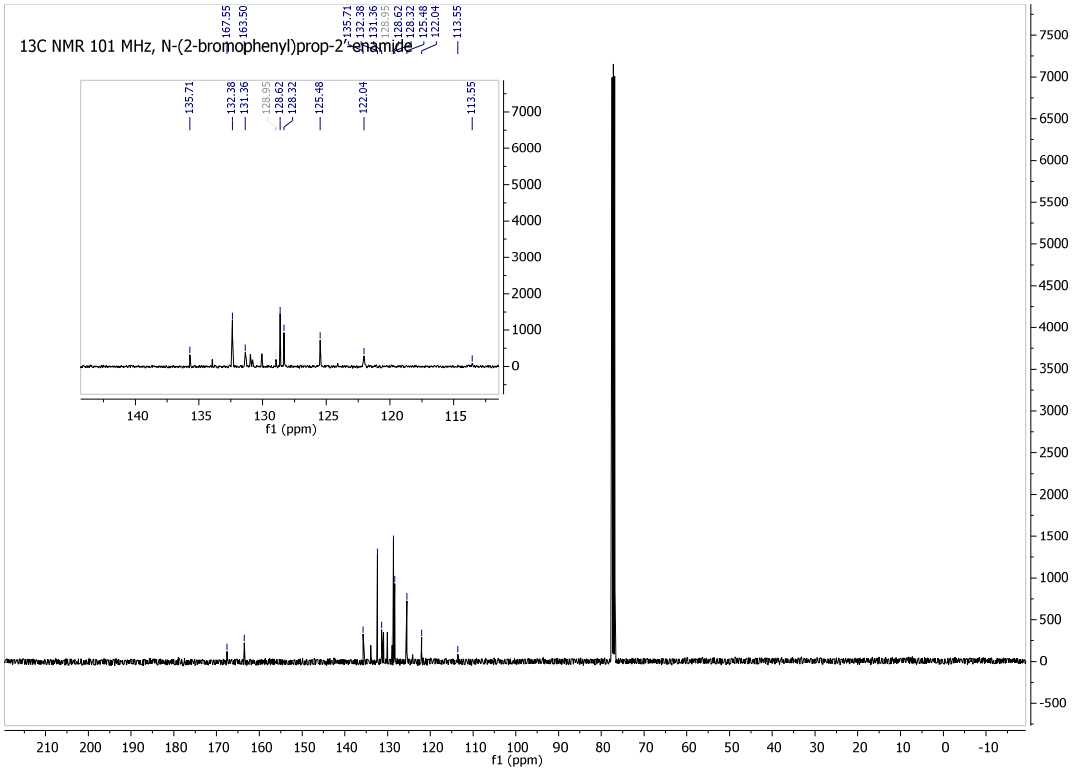

1H NMR 400 MHz, N-(2-chloroethyl)prop-2-enamide
0.97
1.08
0.81
1.00
3.98
NH
Cl
f1 (ppm)

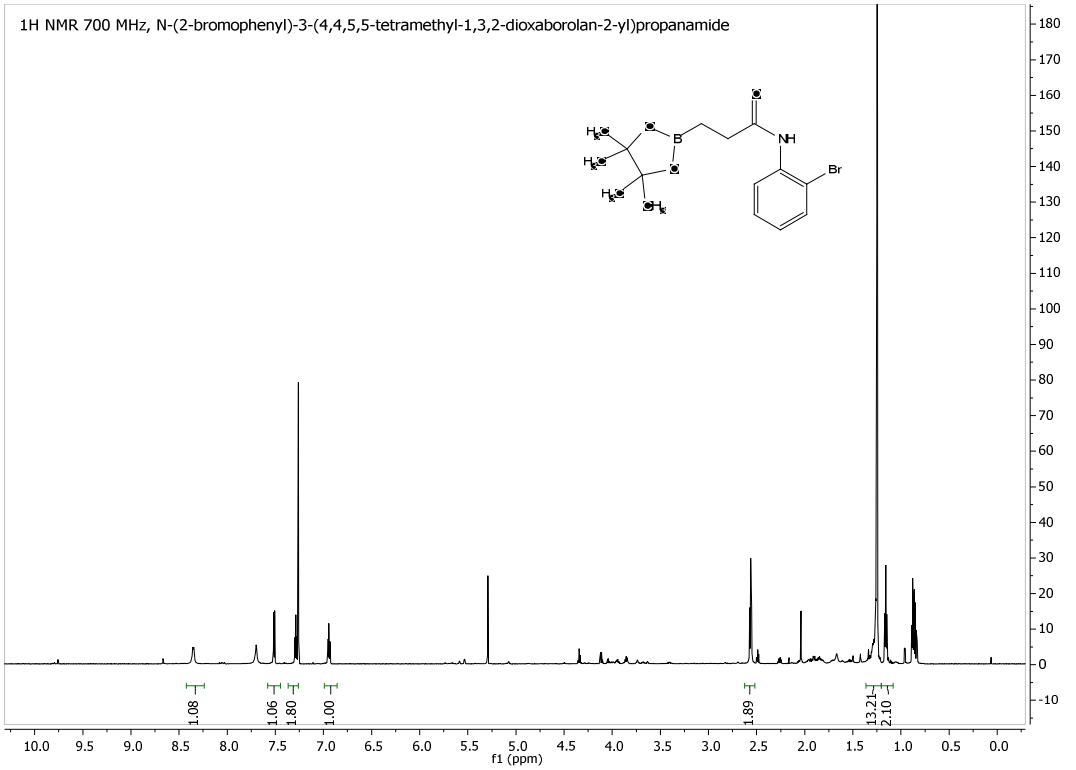

13C NMR 101 MHz, 2'-bromo-N,N-di(prop-2-en-1-yl)acetamide
167.03
132.73
132.33
117.80
117.33
50.19
48.36
26.25
f1 (ppm)

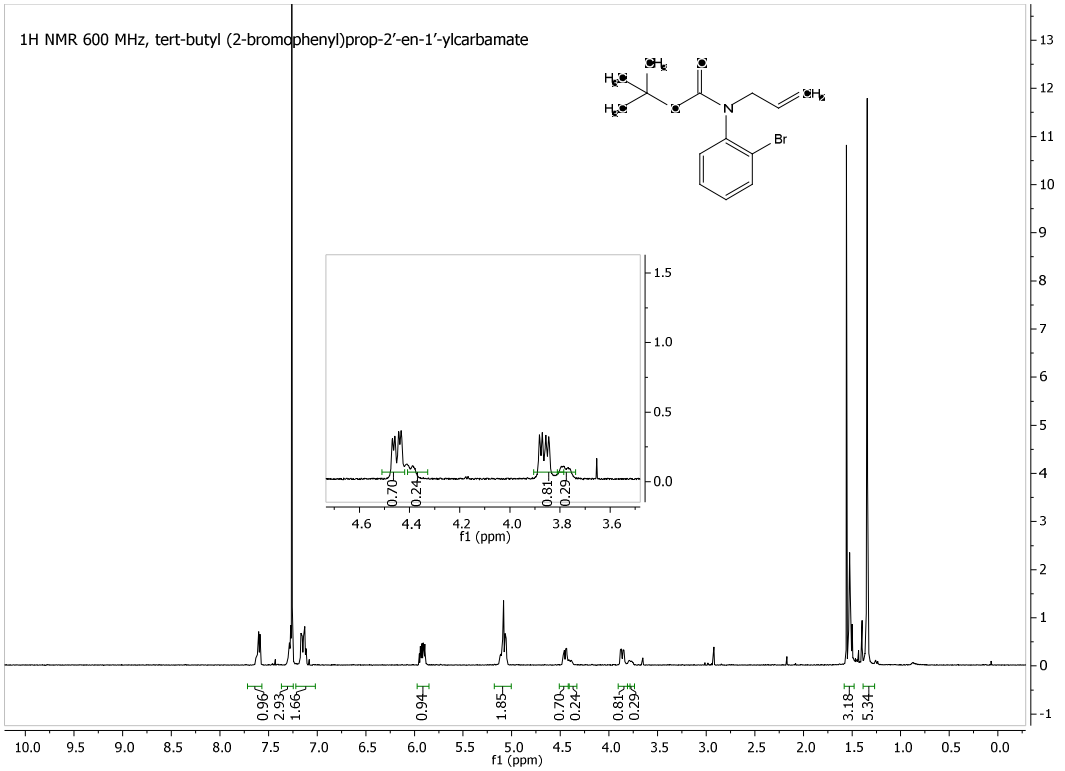

1H NMR 400 MHz, N-benzyl-N-(2-chloroethyl)prop-2-enamide and impurity
17.88
11.70
5.86
2.23
2.54
2.00
f1 (ppm)

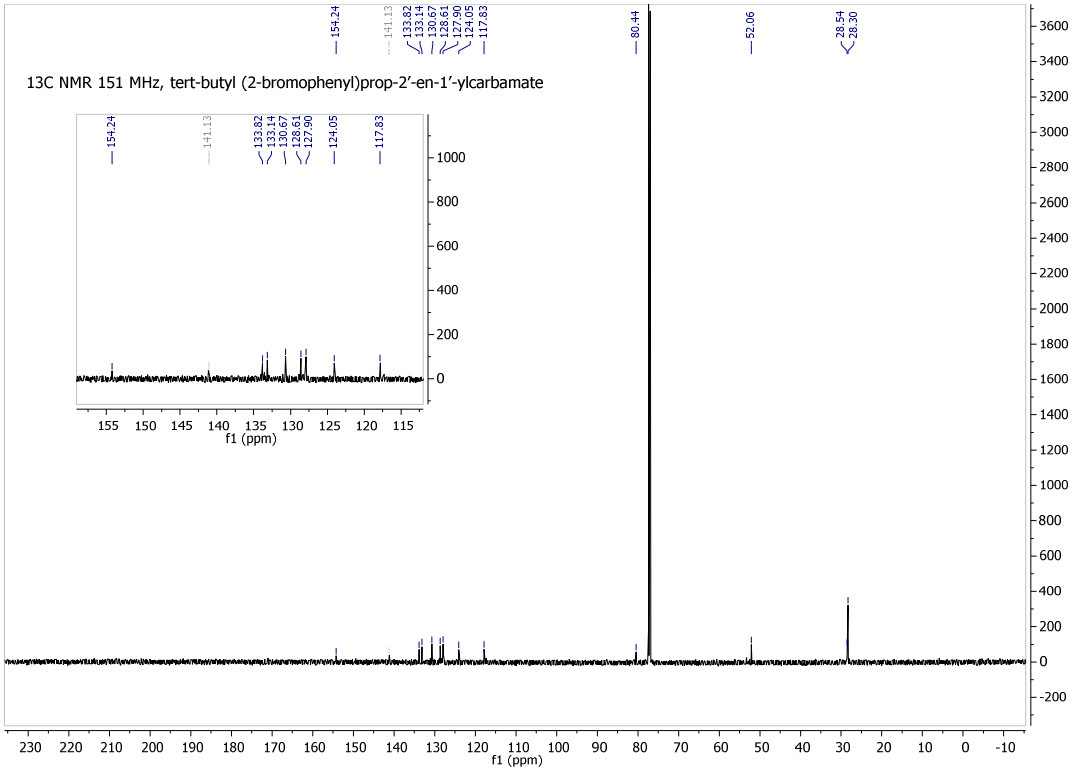

1H NMR 400 MHz, N-(2-chloroethyl)prop-2-enamide
f1 (ppm)

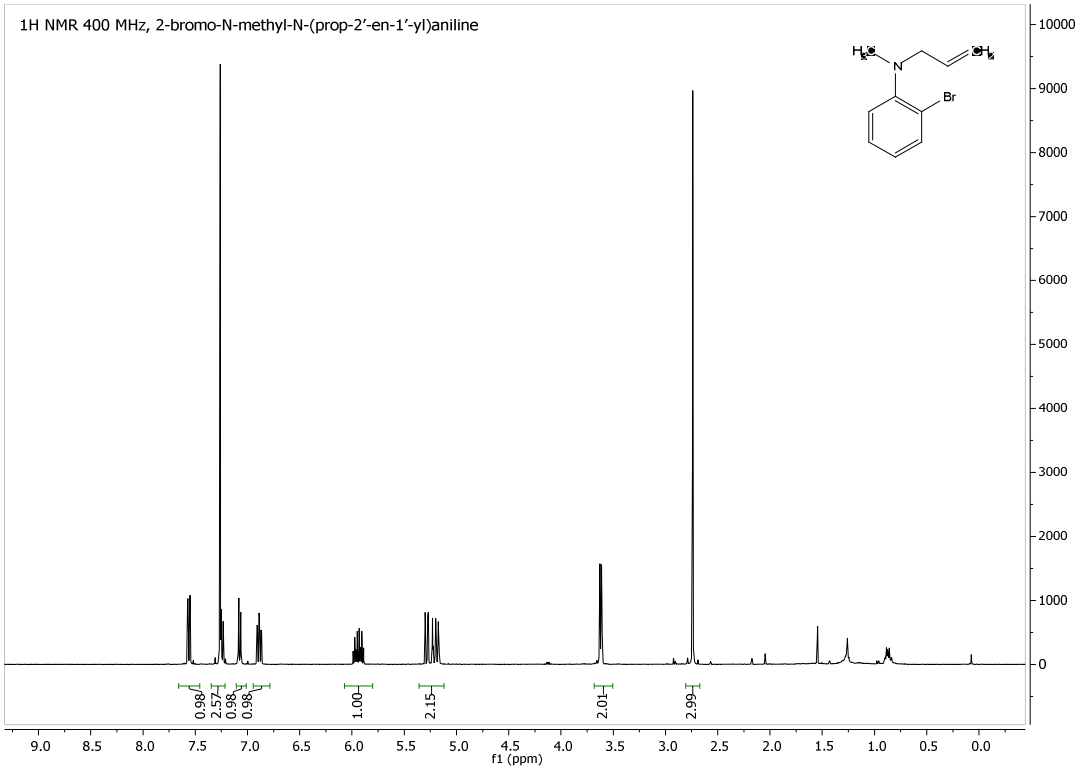

1H NMR 400 MHz, N-benzyl-N-(2-chloroethyl)prop-2-enamide and impurity
f1 (ppm)

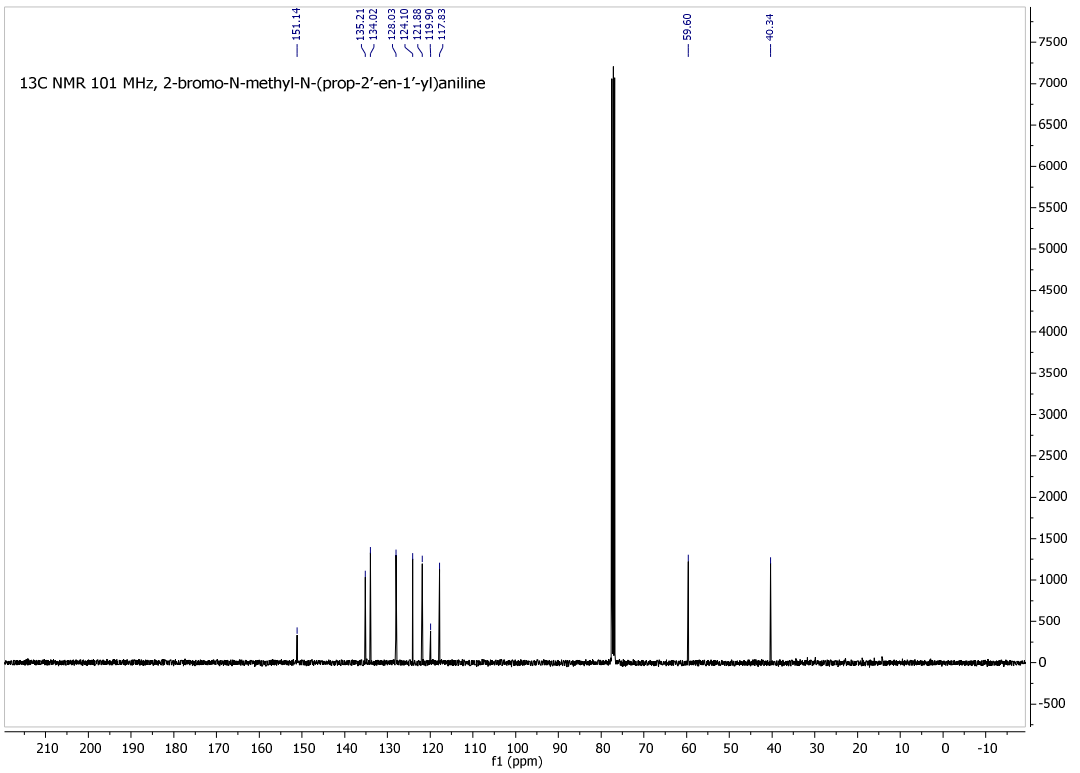

13C NMR 101 MHz, N-(2-bromophenyl)prop-2-enamide
167.55
163.50
135.71
132.38
131.36
128.95
128.62
128.32
125.48
122.04
113.55
f1 (ppm)

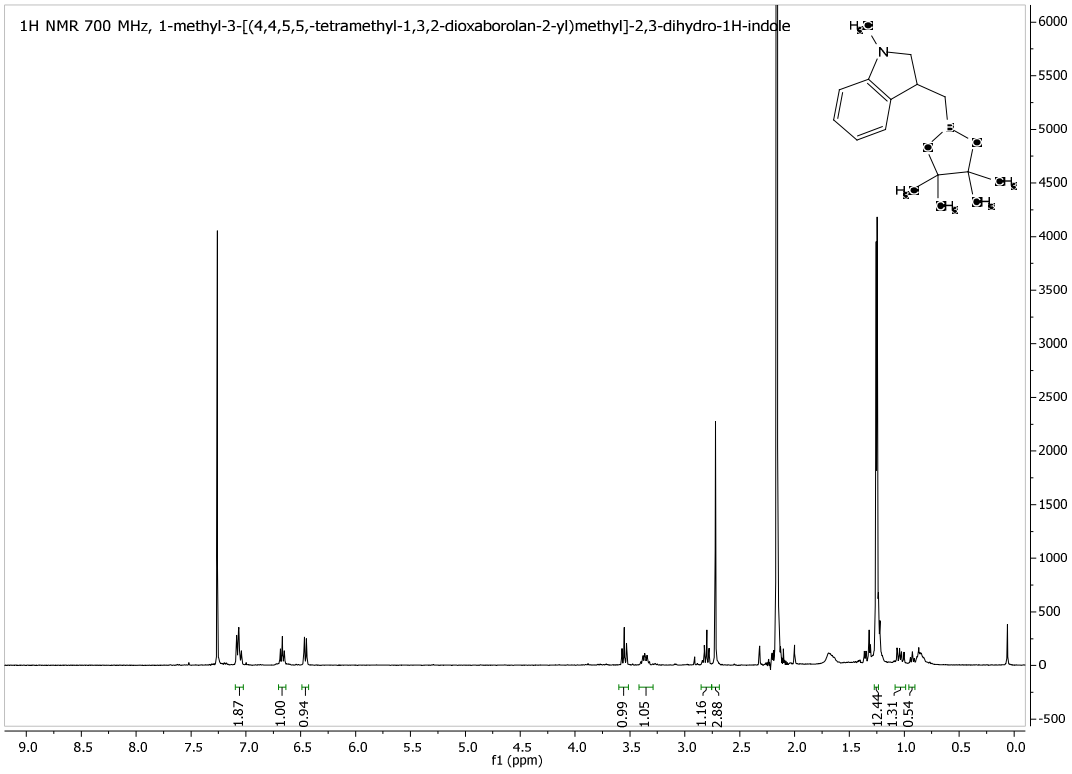

1H NMR 700 MHz, N-(2-bromophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide
B
NH
Br
1.08
1.06
1.80
1.00
1.89
13.21
2.10
f1 (ppm)

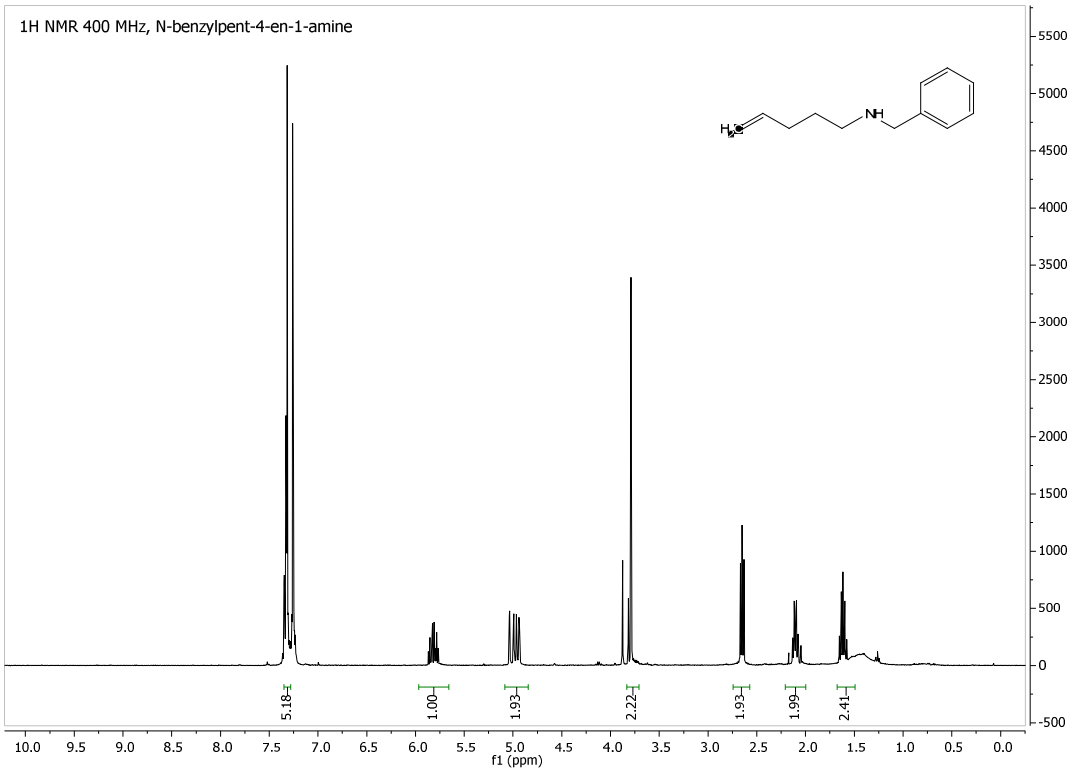

1H NMR 600 MHz, tert-butyl (2-bromophenyl)prop-2′-en-1′-ylcarbamate
Br
0.96
2.93
1.66
0.94
1.85
0.70
0.24
0.81
0.29
3.18
5.34
f1 (ppm)

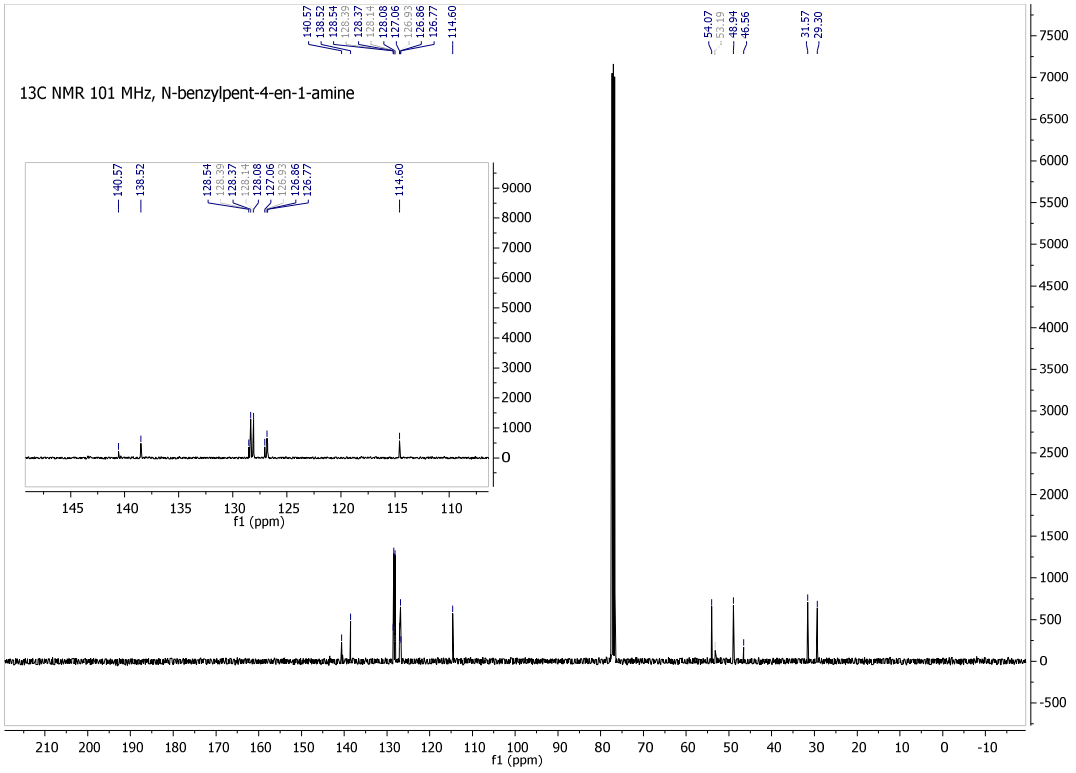

13C NMR 151 MHz, tert-butyl (2-bromophenyl)prop-2′-en-1′-ylcarbamate
154.24
141.13
133.82
133.14
130.67
128.61
127.90
124.05
117.83
80.44
52.06
28.54
28.30
f1 (ppm)

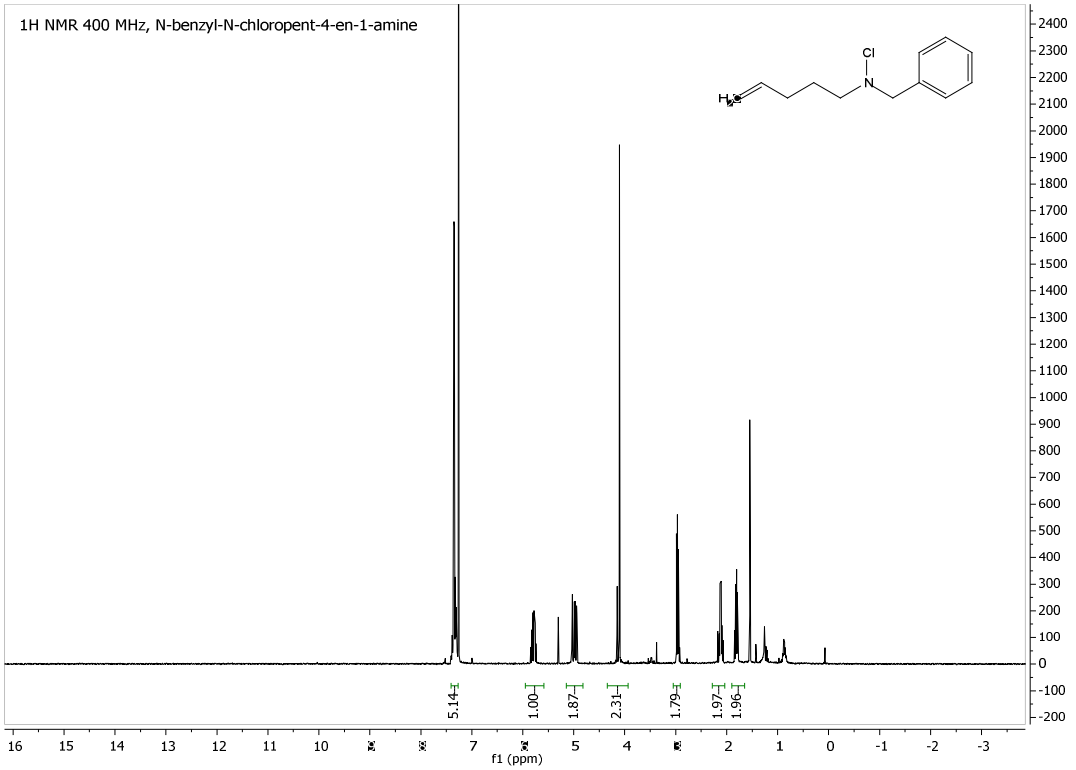

1H NMR 400 MHz, 2-bromo-N-methyl-N-(prop-2′-en-1′-yl)aniline
Br
0.98
2.57
0.98
0.98
1.00
2.15
2.01
2.99
f1 (ppm)

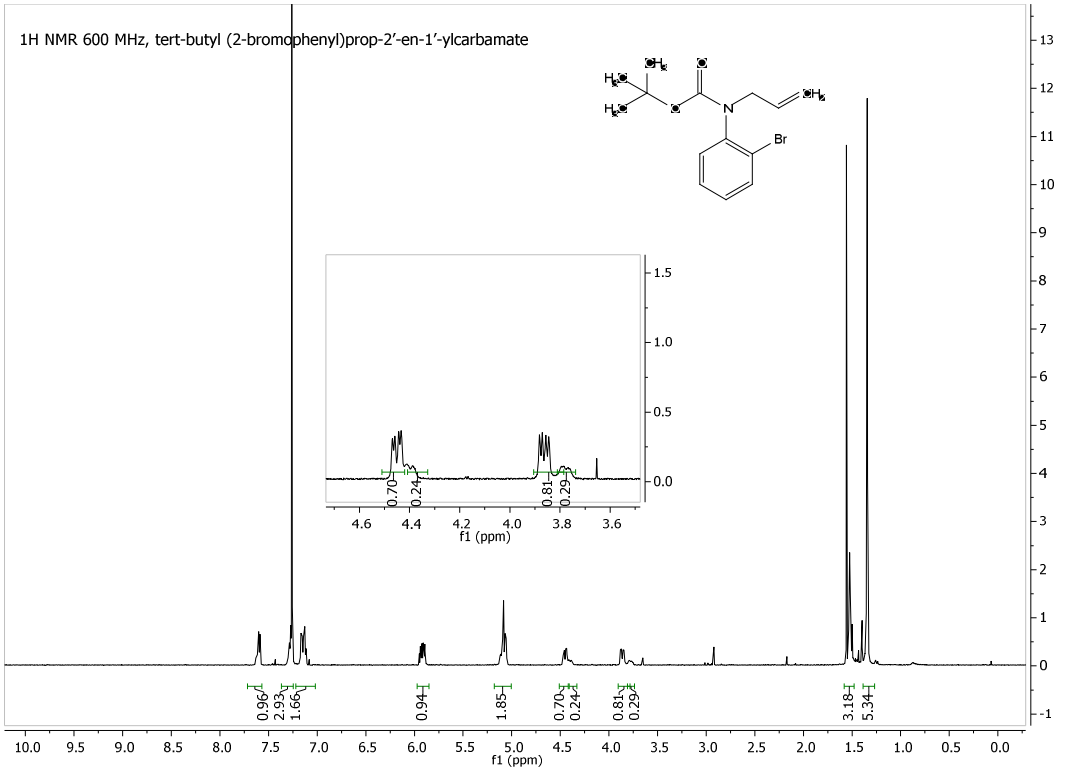

151.14
135.21
134.02
128.03
124.10
123.88
119.60
117.83
59.60
40.34
13C NMR 101 MHz, 2-bromo-N-methyl-N-(prop-2′-en-1′-yl)aniline
f1 (ppm)

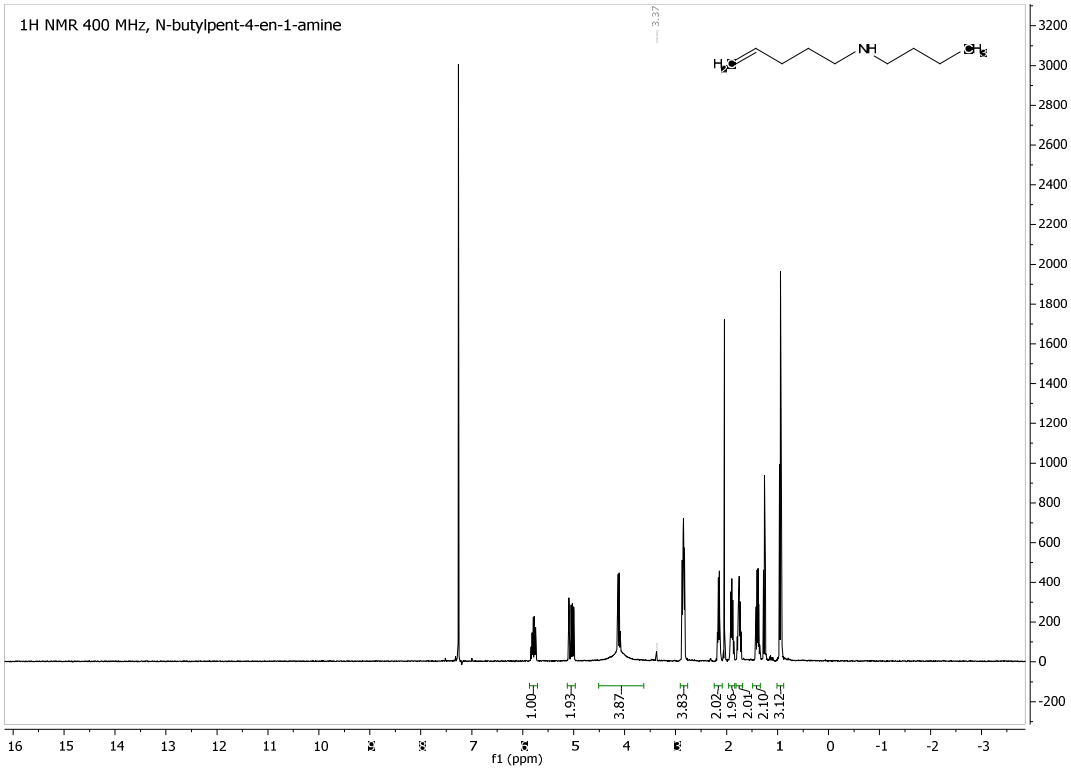

1H NMR 700 MHz, 1-methyl-3-[(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-2,3-dihydro-1H-inddle
1.87
1.00
0.94
0.99
1.05
1.16
2.88
12.44
1.31
0.54
f1 (ppm)

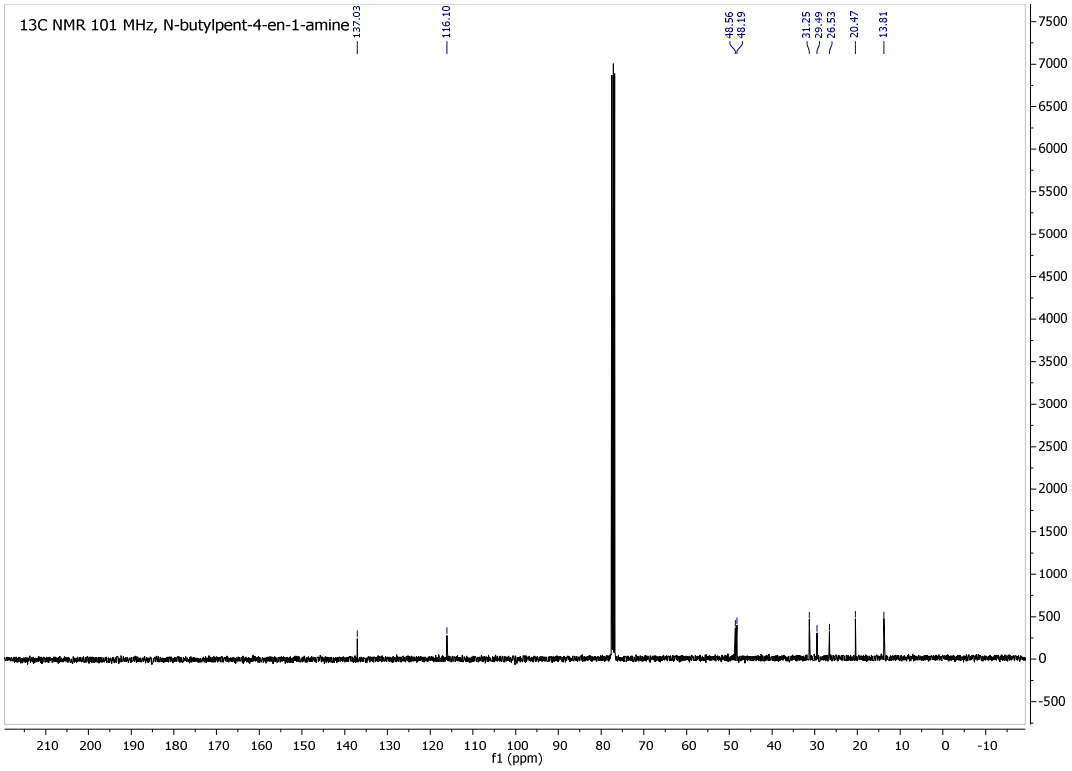

1H NMR 400 MHz, N-benzylpent-4-en-1-amine
5.18
1.00
1.93
2.22
1.93
1.99
2.41
f1 (ppm)

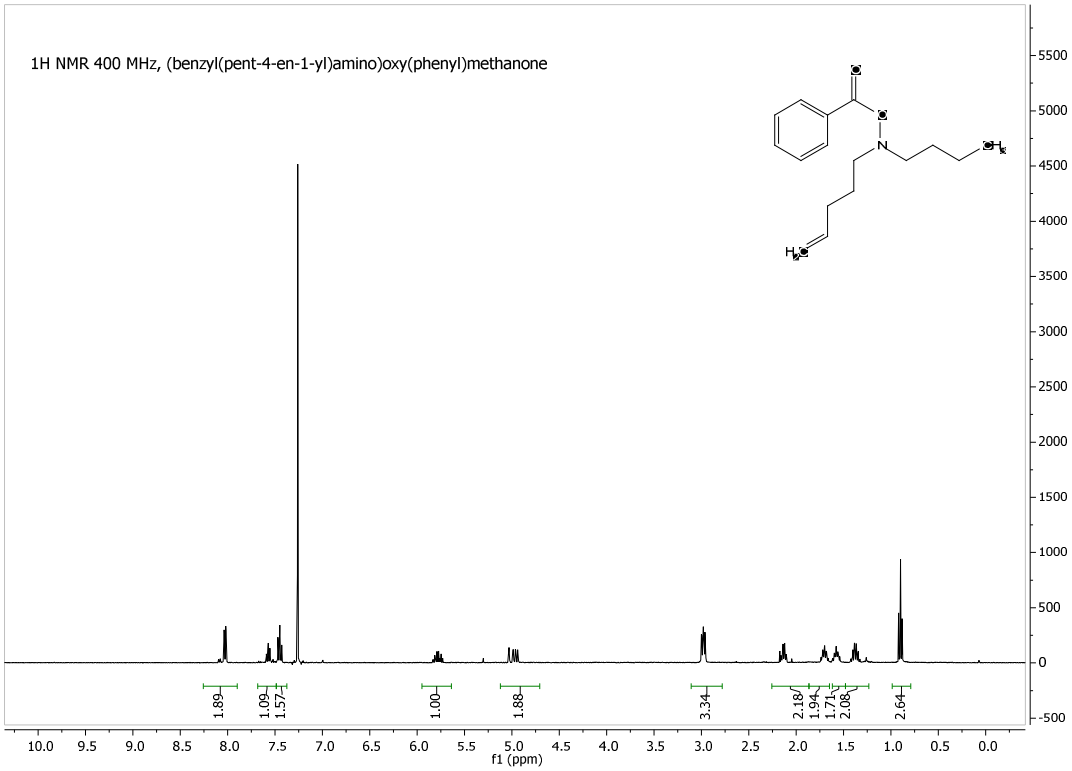

13C NMR 101 MHz, N-benzylpent-4-en-1-amine
140.57
138.52
128.54
128.37
128.08
127.06
126.86
126.77
114.60
54.07
48.94
46.56
31.57
29.30
f1 (ppm)

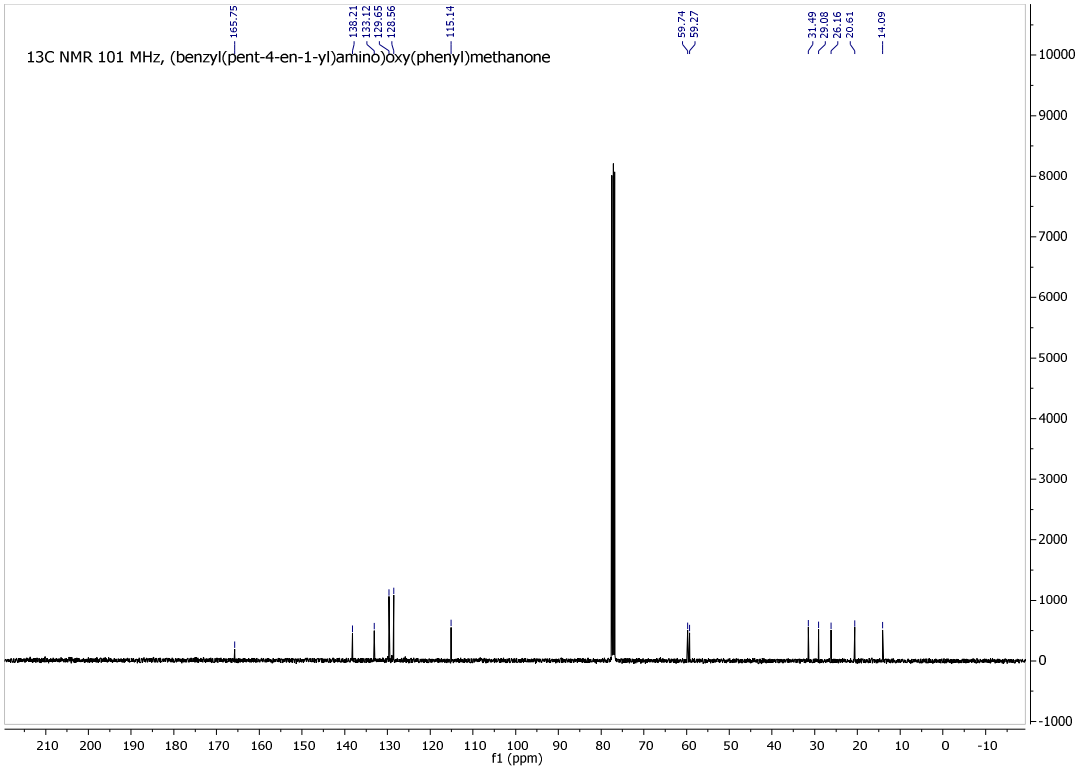

1H NMR 400 MHz, N-benzyl-N-chloropent-4-en-1-amine
Cl
N
5.14
1.00
1.87
2.31
1.79
1.97
1.96
f1 (ppm)

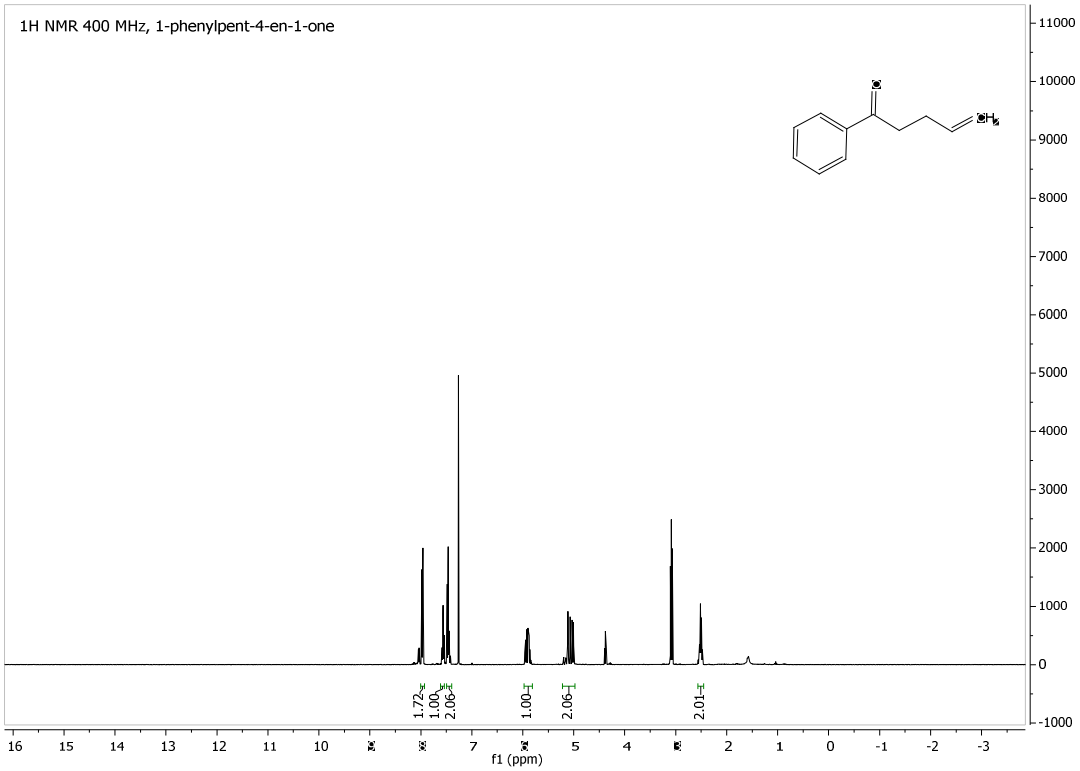

1H NMR 600 MHz, tert-butyl (2-bromophenyl)prop-2′-en-1′-ylcarbamate
Br
f1 (ppm)
0.96
2.93
1.66
0.94
1.85
0.70
0.24
0.81
0.29
3.18
5.34

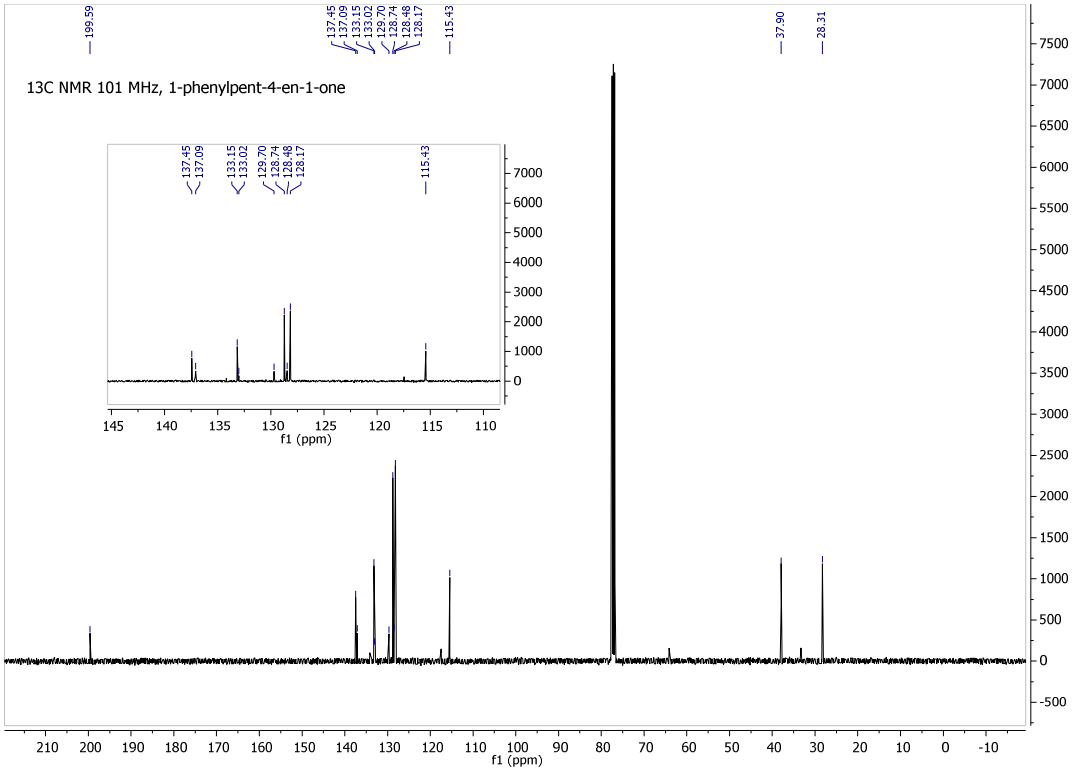

1H NMR 400 MHz, N-butylpent-4-en-1-amine
NH
f1 (ppm)
1.00
1.93
3.87
3.83
2.02
1.96
2.01
2.10
3.12

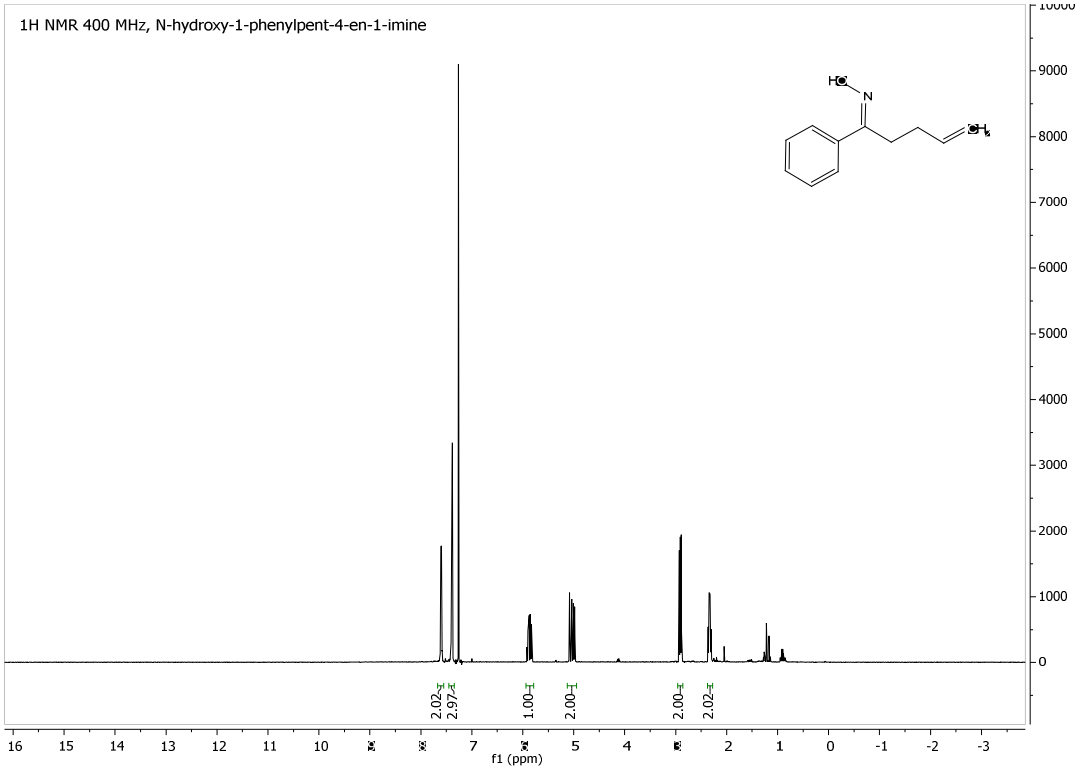

13C NMR 101 MHz, N-butylpent-4-en-1-amine
137.03
116.10
48.56
48.19
31.25
29.49
26.53
20.47
13.81
f1 (ppm)

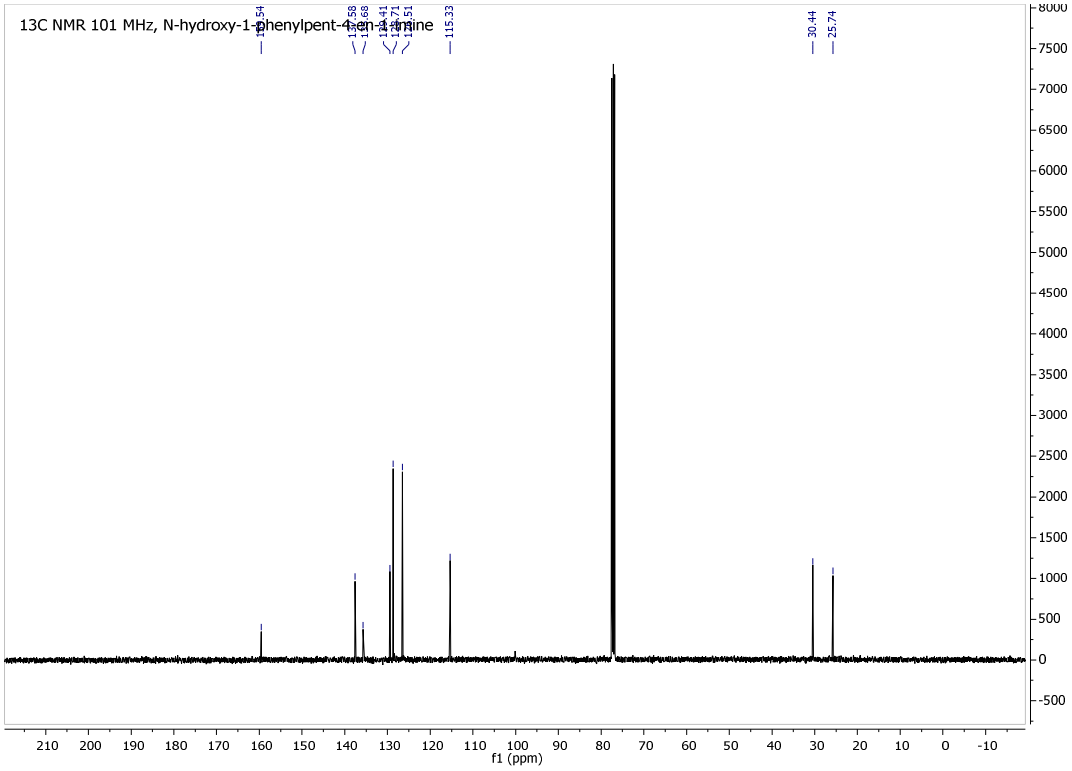

1H NMR 400 MHz, (benzyl(pent-4-en-1-yl)amino)oxy(phenyl)methanone
1.89
1.09
1.57
1.00
1.88
3.34
2.18
1.94
1.71
2.08
2.64
f1 (ppm)

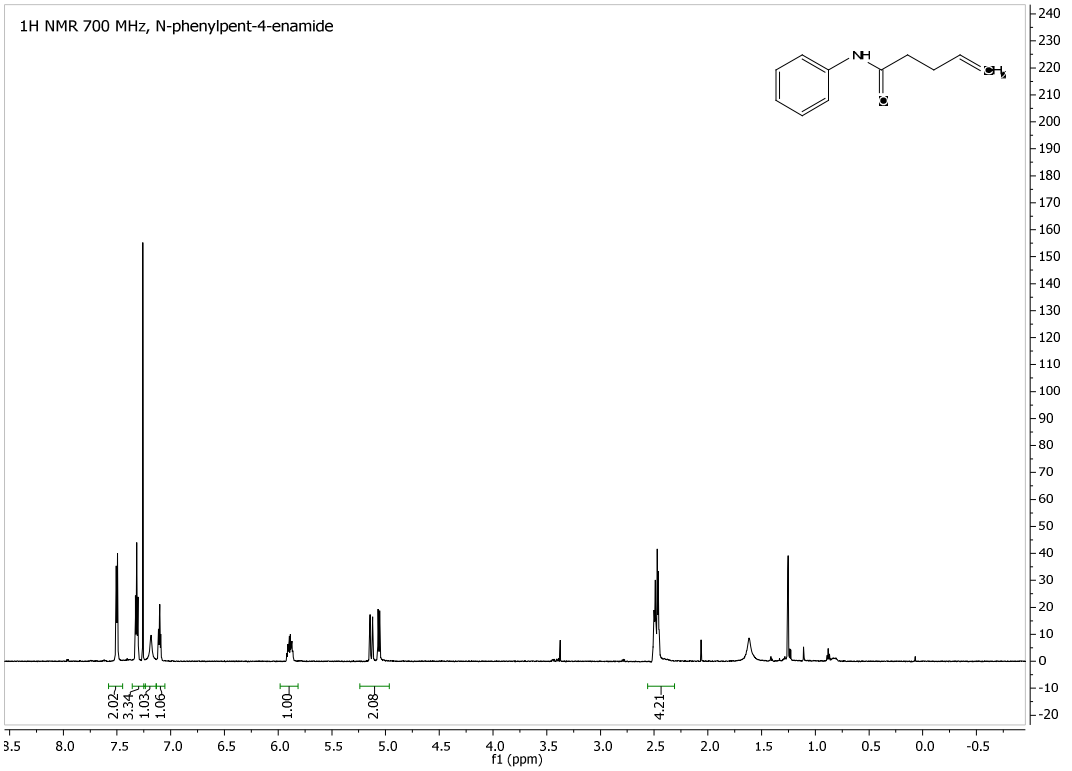

13C NMR 101 MHz, (benzyl(pent-4-en-1-yl)amino)oxy(phenyl)methanone
165.75
138.21
133.12
129.65
128.56
115.14
59.74
59.27
31.49
29.08
26.16
20.61
14.09
f1 (ppm)

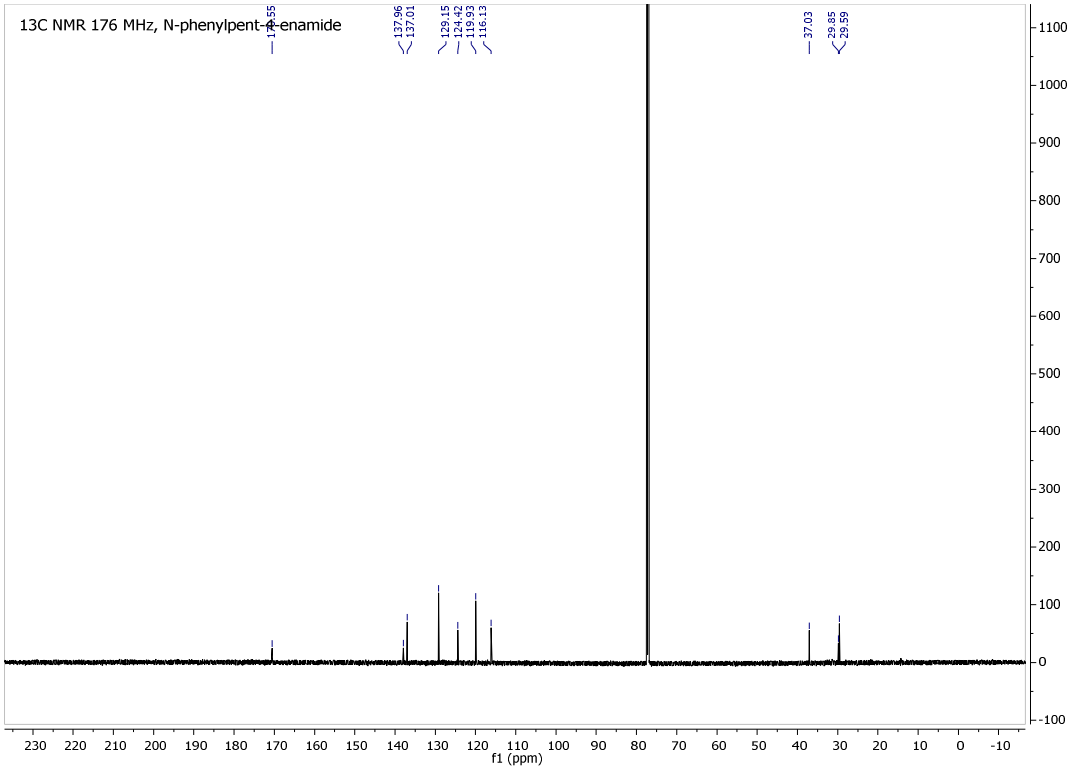

1H NMR 400 MHz, 1-phenylpent-4-en-1-one
1.72
1.00
2.06
1.00
2.06
2.01
f1 (ppm)

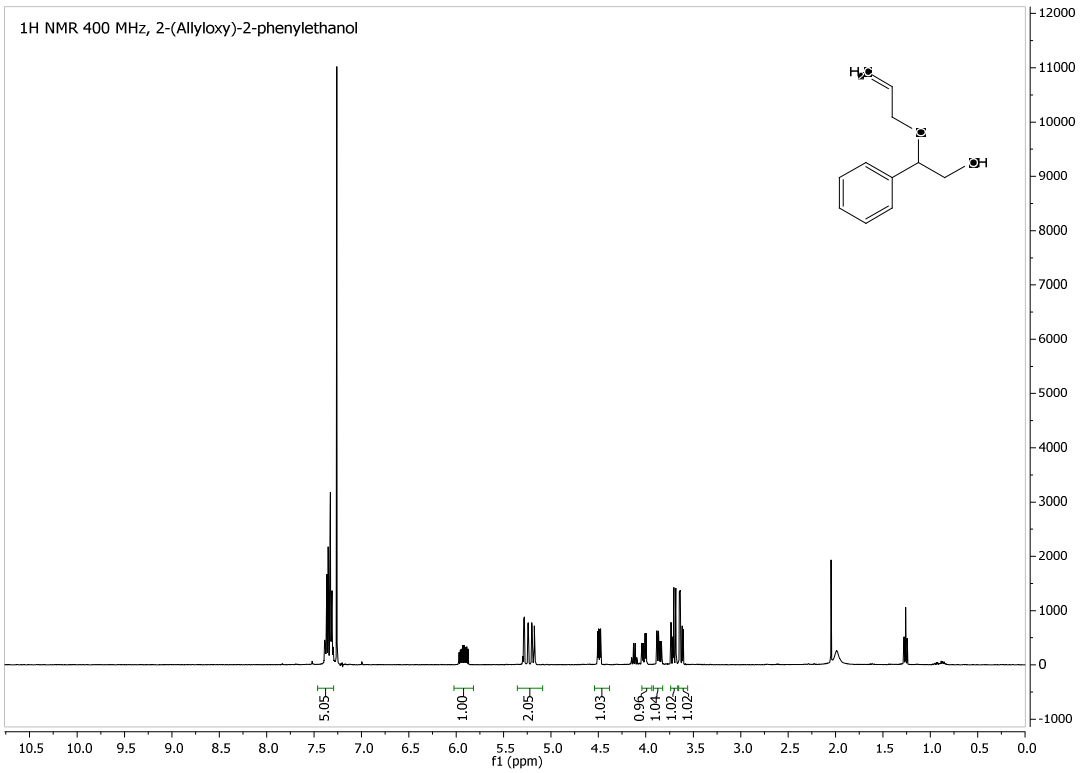

13C NMR 101 MHz, 1-phenylpent-4-en-1-one
199.59
137.45
137.09
133.15
133.02
129.70
128.74
128.48
128.17
115.43
37.90
28.31
f1 (ppm)

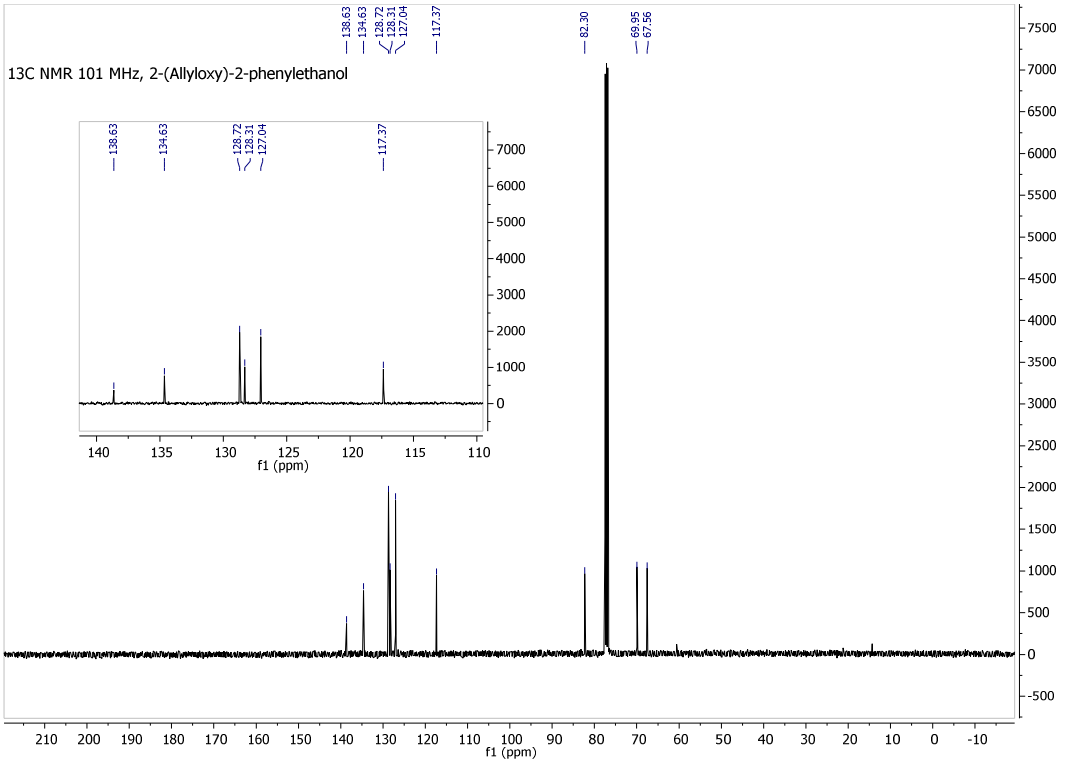

1H NMR 400 MHz, N-hydroxy-1-phenylpent-4-en-1-imine
2.02
2.97
1.00
2.00
2.00
2.02
f1 (ppm)

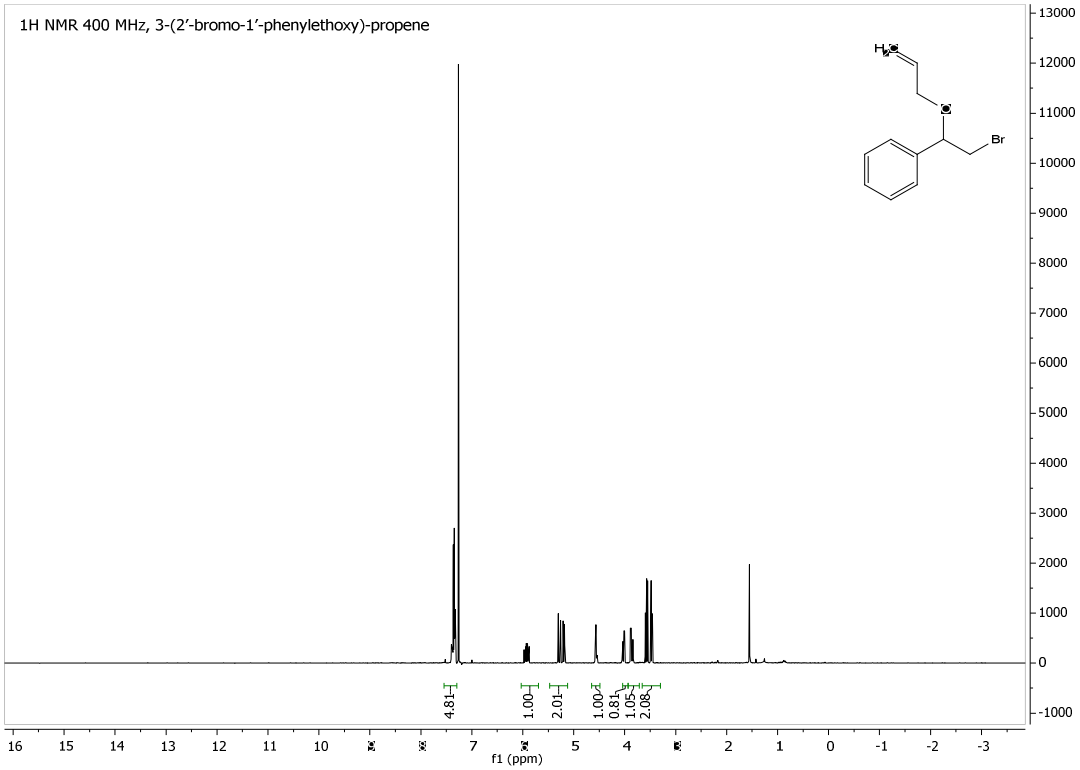

13C NMR 101 MHz, N-hydroxy-1-phenylpent-4-en-1-imine
160.54
142.58
141.68
131.41
130.71
124.51
115.33
30.44
25.74
f1 (ppm)

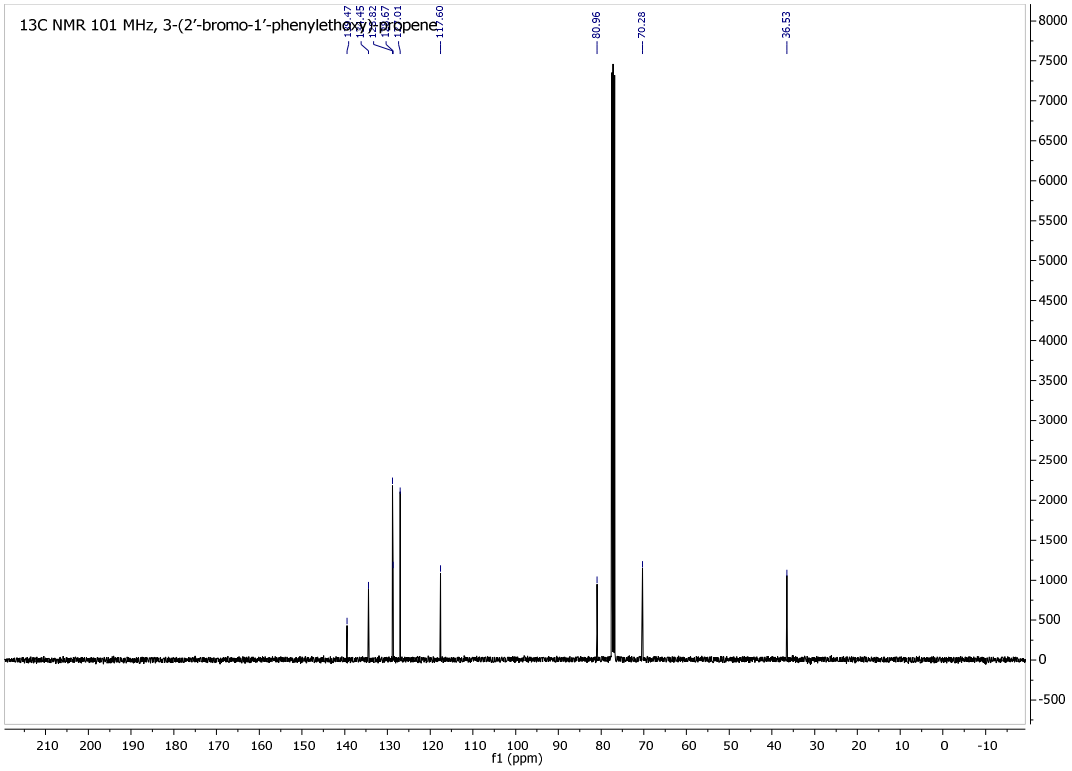

1H NMR 700 MHz, N-phenylpent-4-enamide
NH
O
2.02
3.34
1.03
1.06
1.00
2.08
4.21
f1 (ppm)


13C NMR 176 MHz, N-phenylpent-4-enamide
169.55
137.96
137.01
129.15
124.42
119.93
116.13
37.03
29.85
29.59
f1 (ppm)

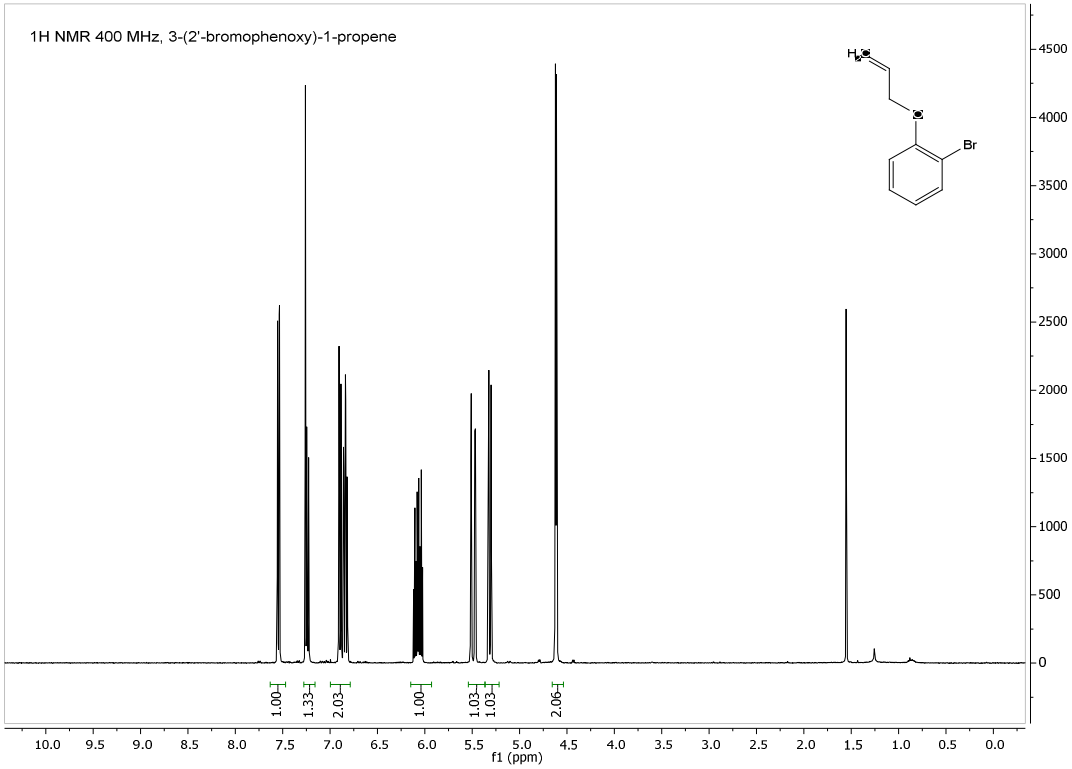

1H NMR 400 MHz, 2-(Allyloxy)-2-phenylethanol
5.05
1.00
2.05
1.03
0.96
1.04
1.02
1.02
f1 (ppm)

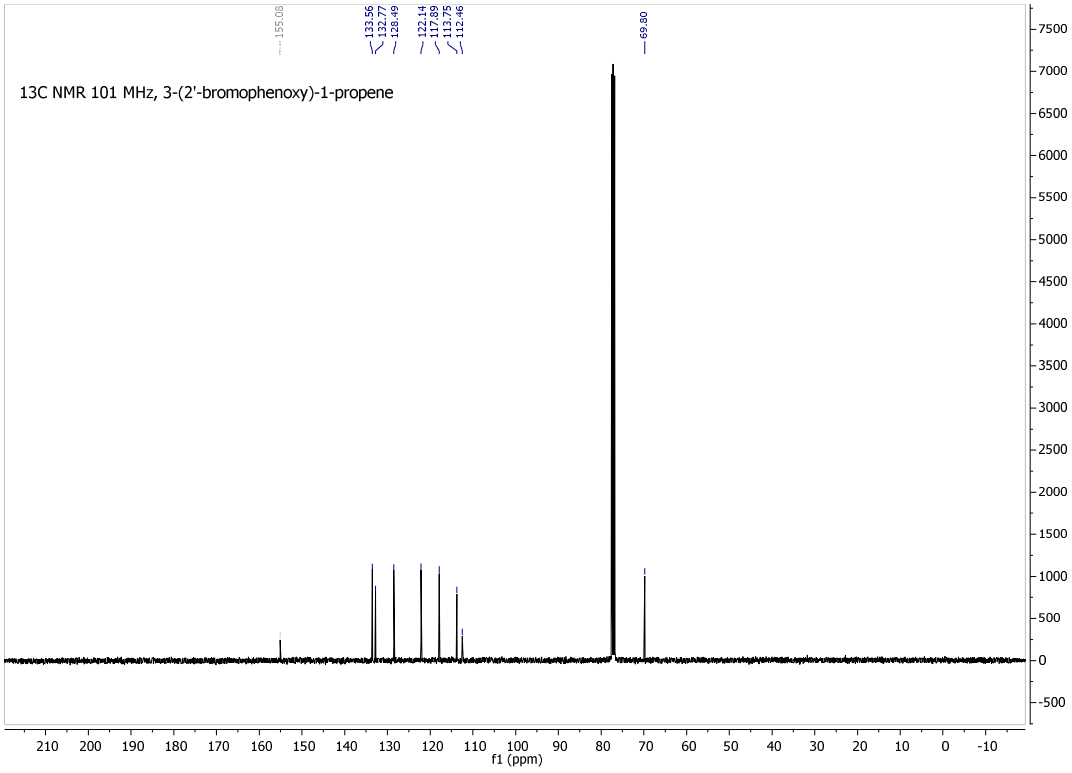

13C NMR 101 MHz, 2-(Allyloxy)-2-phenylethanol
138.63
134.63
128.72
128.31
127.04
117.37
82.30
69.95
67.56
f1 (ppm)

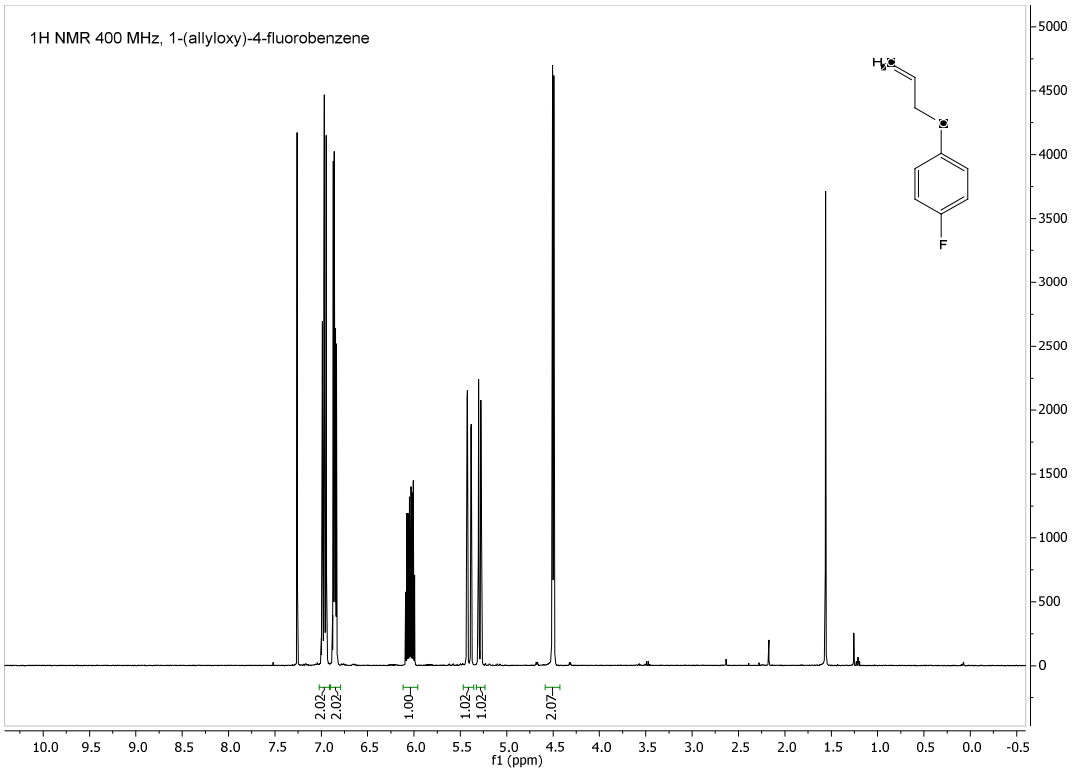

1H NMR 400 MHz, 3-(2′-bromo-1′-phenylethoxy)-propene
Br
4.81
1.00
2.01
1.00
0.81
1.05
2.08
f1 (ppm)

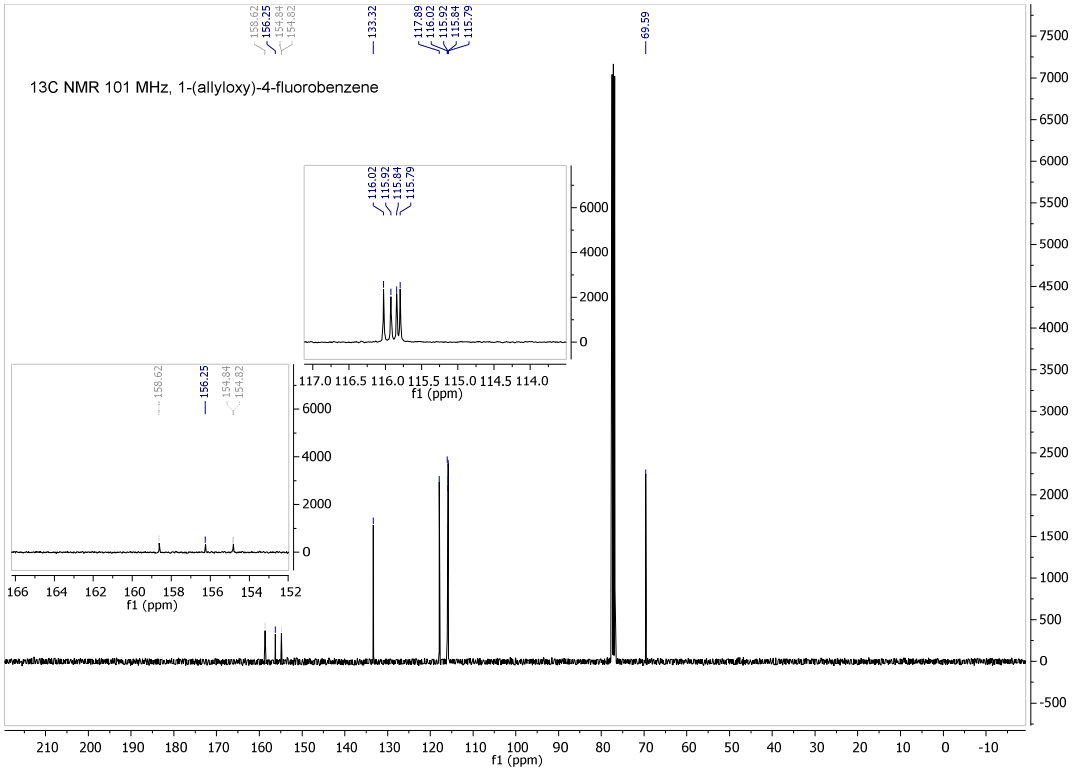


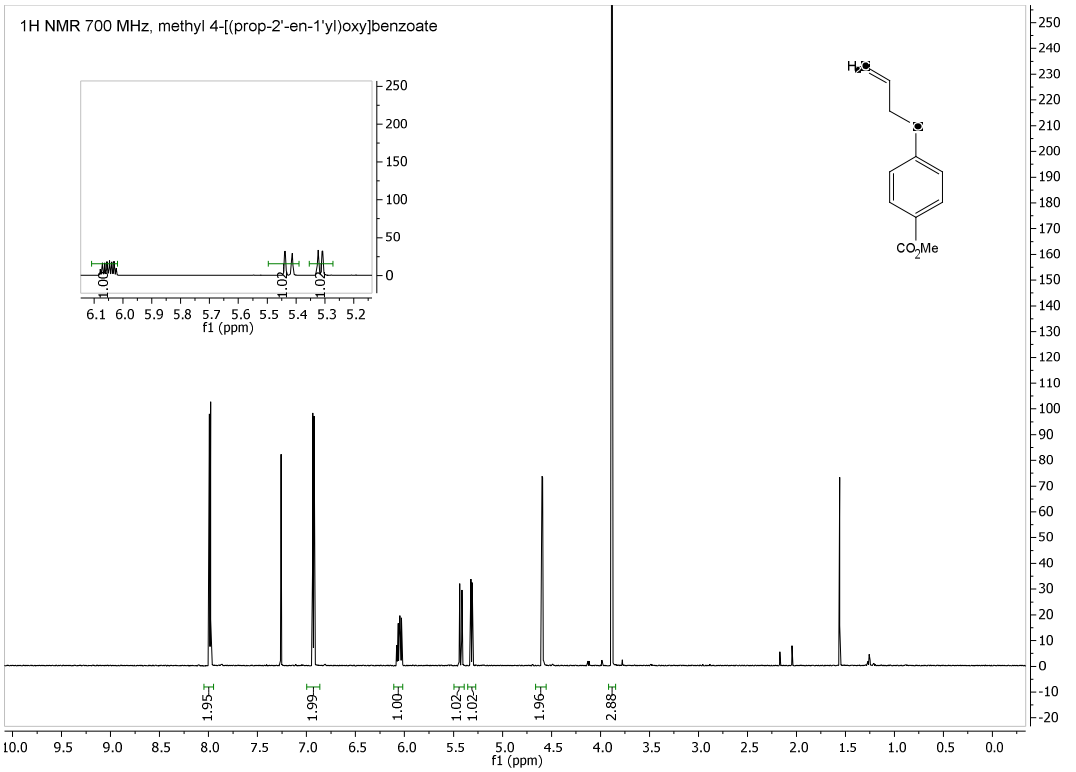
^{1}H & ^{13}C NMR spectra of compounds in chapter 3

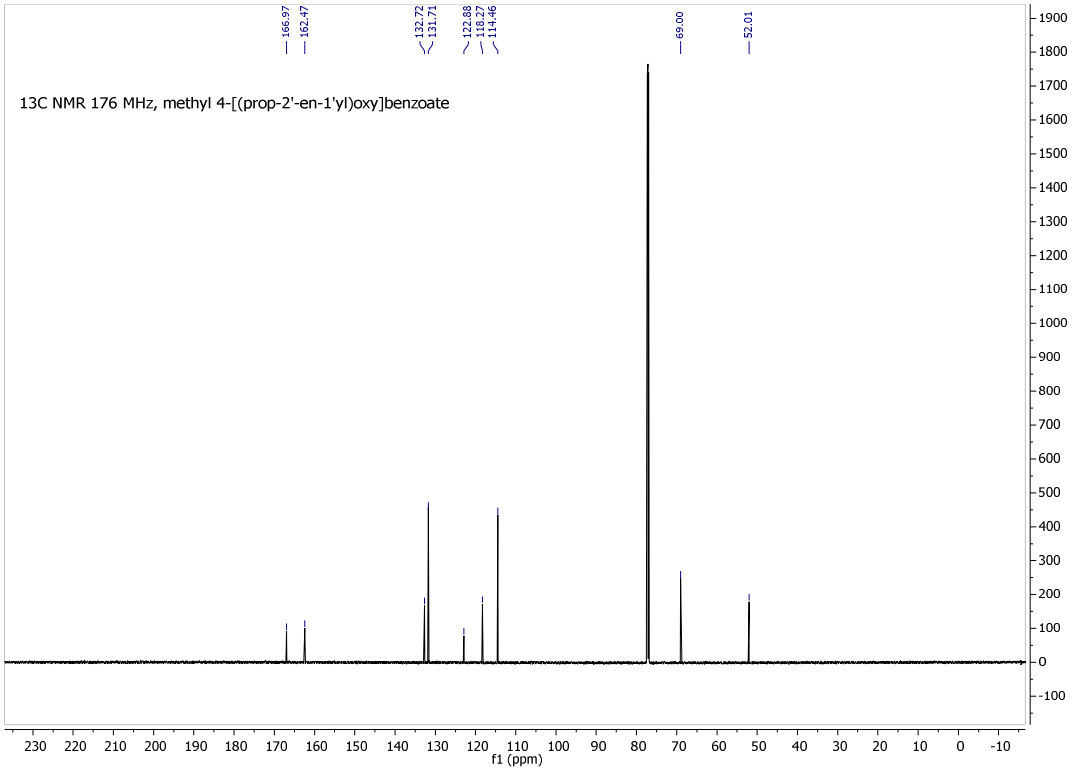


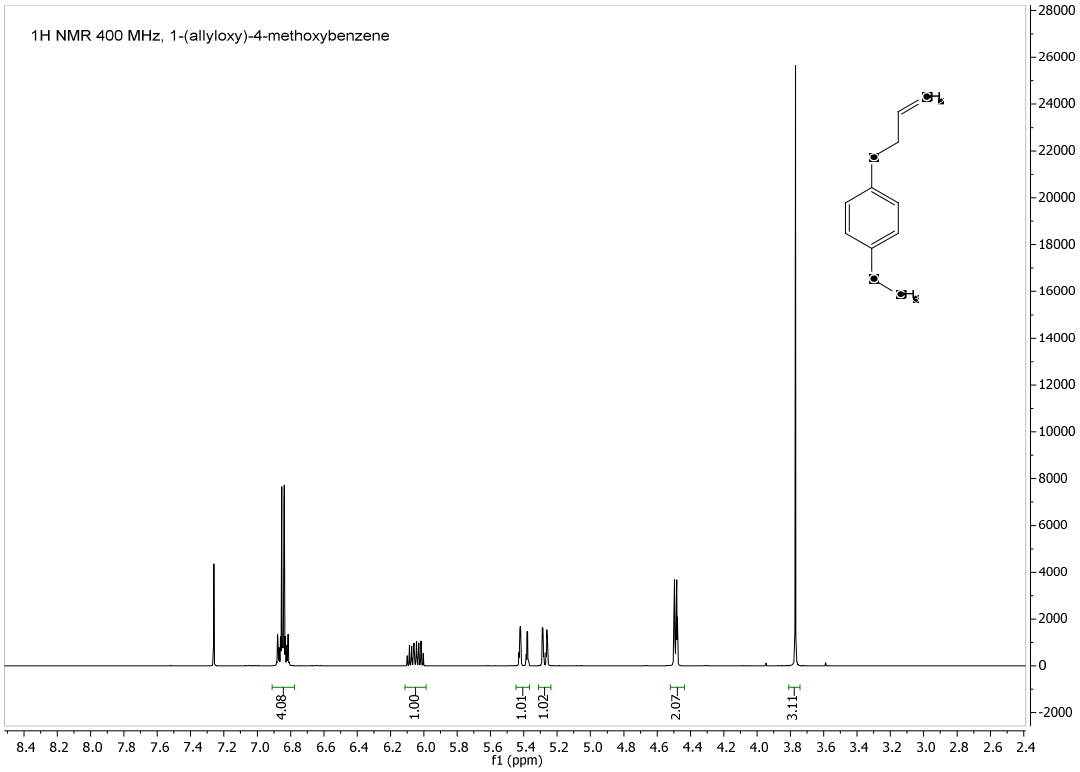

13C NMR 101 MHz, 3-(2'-bromophenoxy)-1-propene
155.08
133.56
132.77
128.49
122.14
117.89
113.75
112.46
69.80
f1 (ppm)

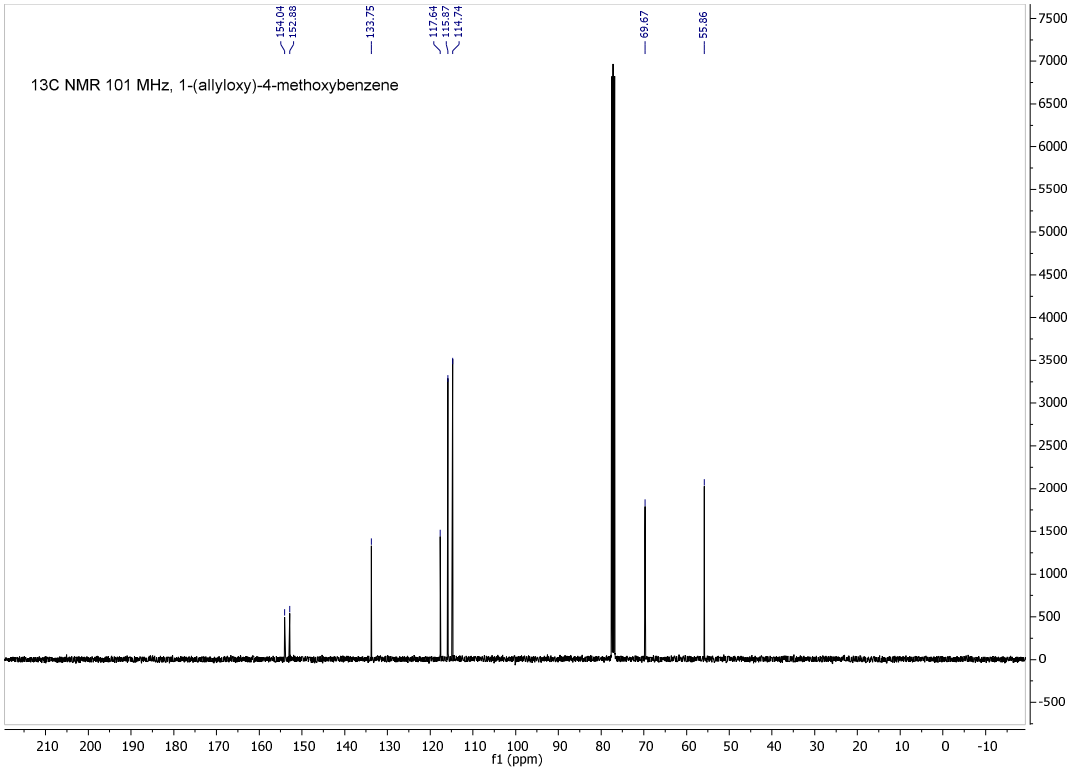

1H NMR 400 MHz, 1-(allyloxy)-4-fluorobenzene
2.02
2.02
1.00
1.02
1.02
2.07
f1 (ppm)

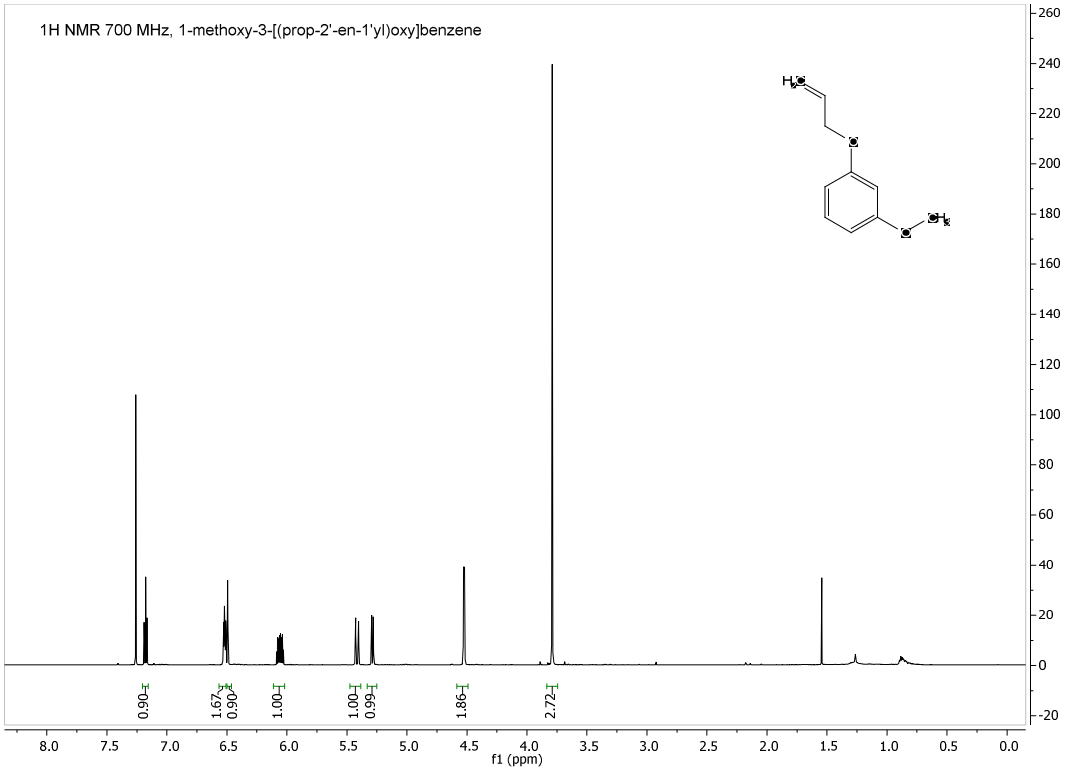

13C NMR 101 MHz, 1-(allyloxy)-4-fluorobenzene
158.62
156.25
154.84
154.82
133.32
117.89
116.02
115.92
115.84
115.79
69.59
f1 (ppm)

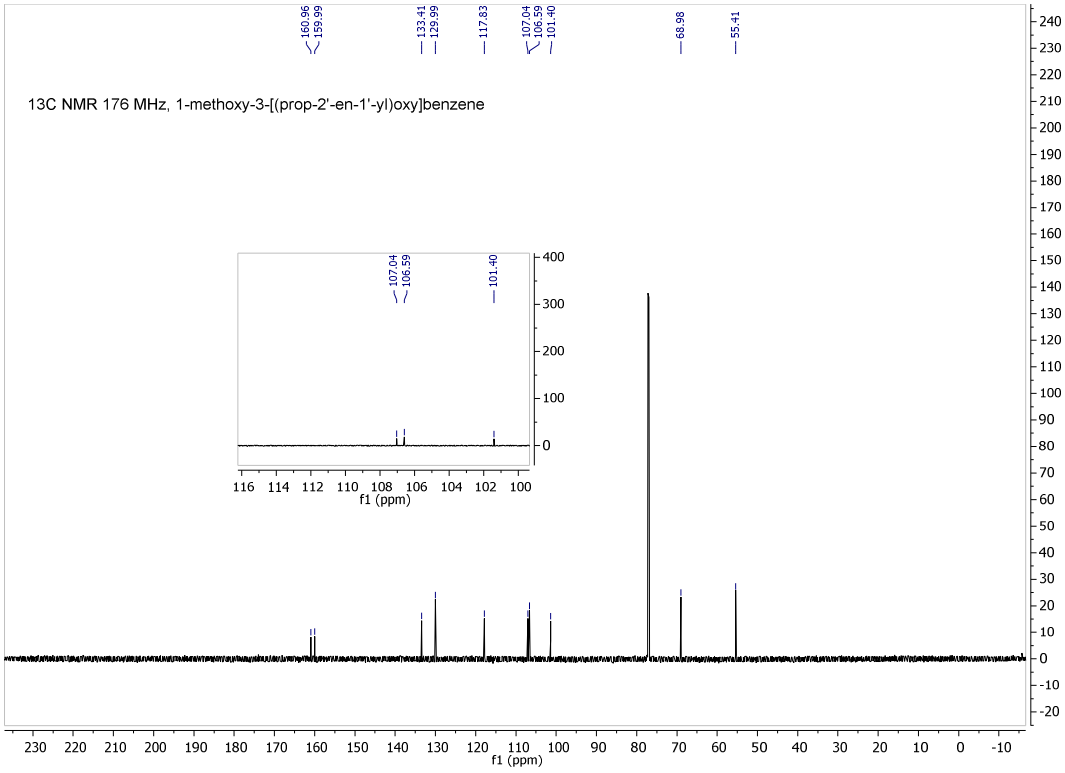

1H NMR 700 MHz, methyl 4-[(prop-2'-en-1'yl)oxy]benzoate
CO2Me
1.00
1.02
1.02
1.95
1.99
1.00
1.02
1.02
1.96
2.88
f1 (ppm)

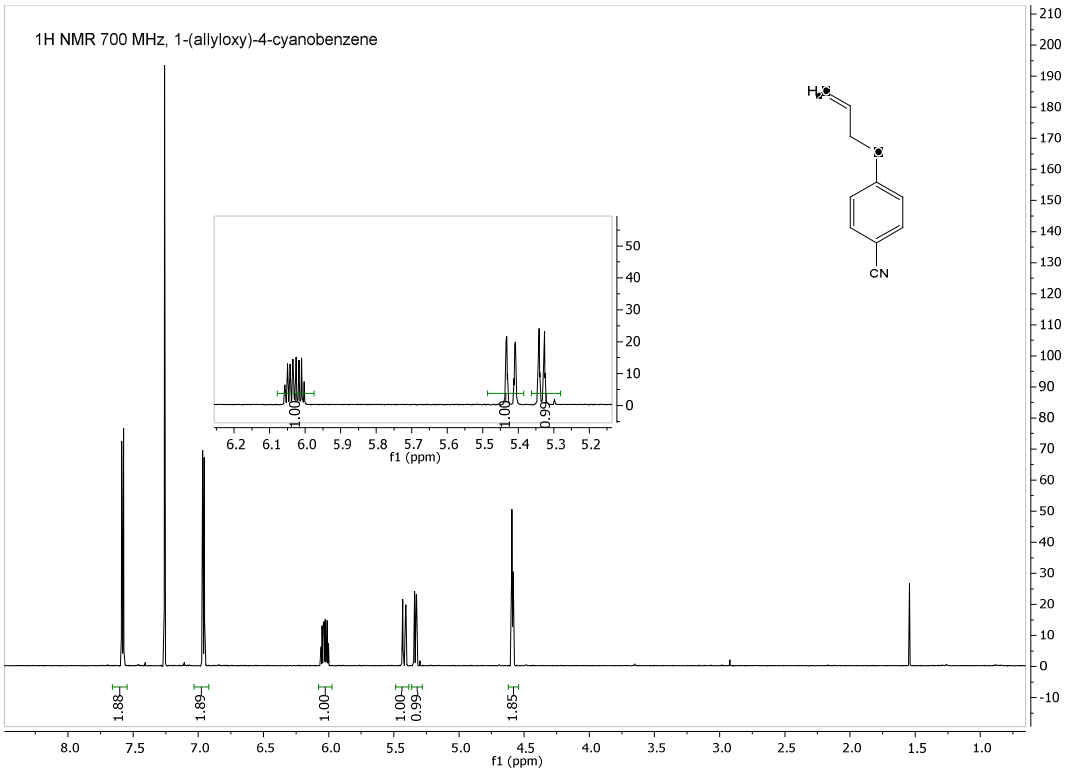

13C NMR 176 MHz, methyl 4-[(prop-2'-en-1'yl)oxy]benzoate
166.97
162.47
132.72
131.71
122.88
118.27
114.46
69.00
52.01
f1 (ppm)

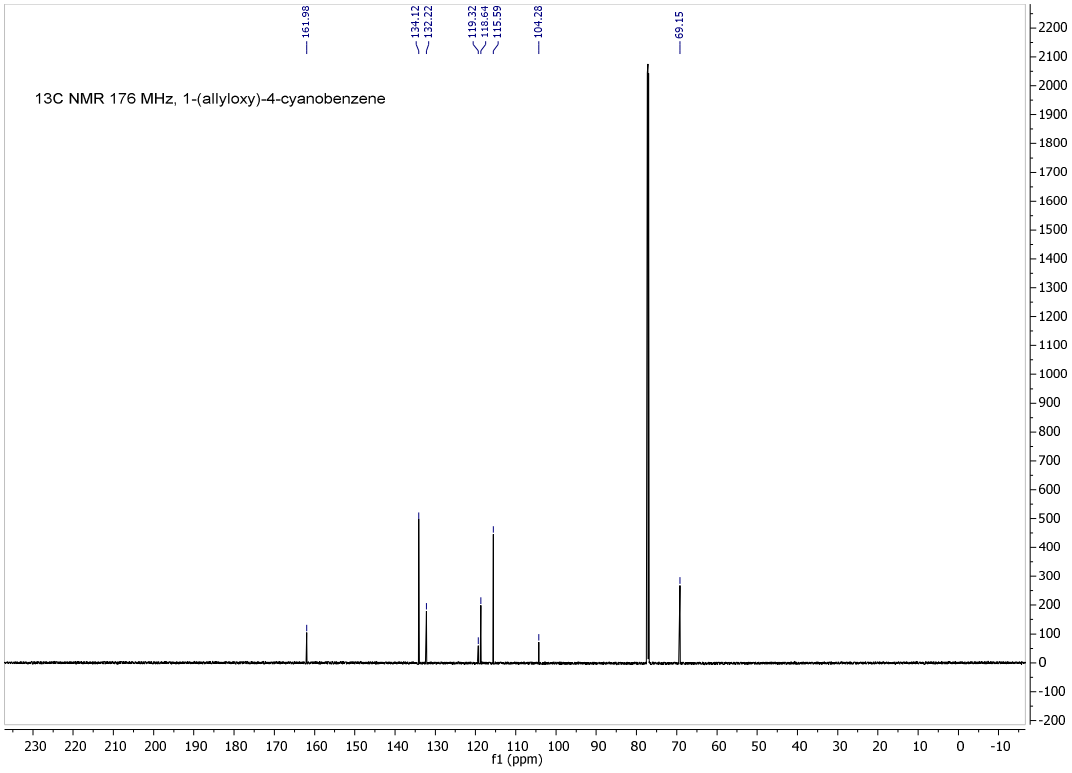

1H NMR 400 MHz, 1-(allyloxy)-4-methoxybenzene
4.08
1.00
1.01
1.02
2.07
3.11
f1 (ppm)

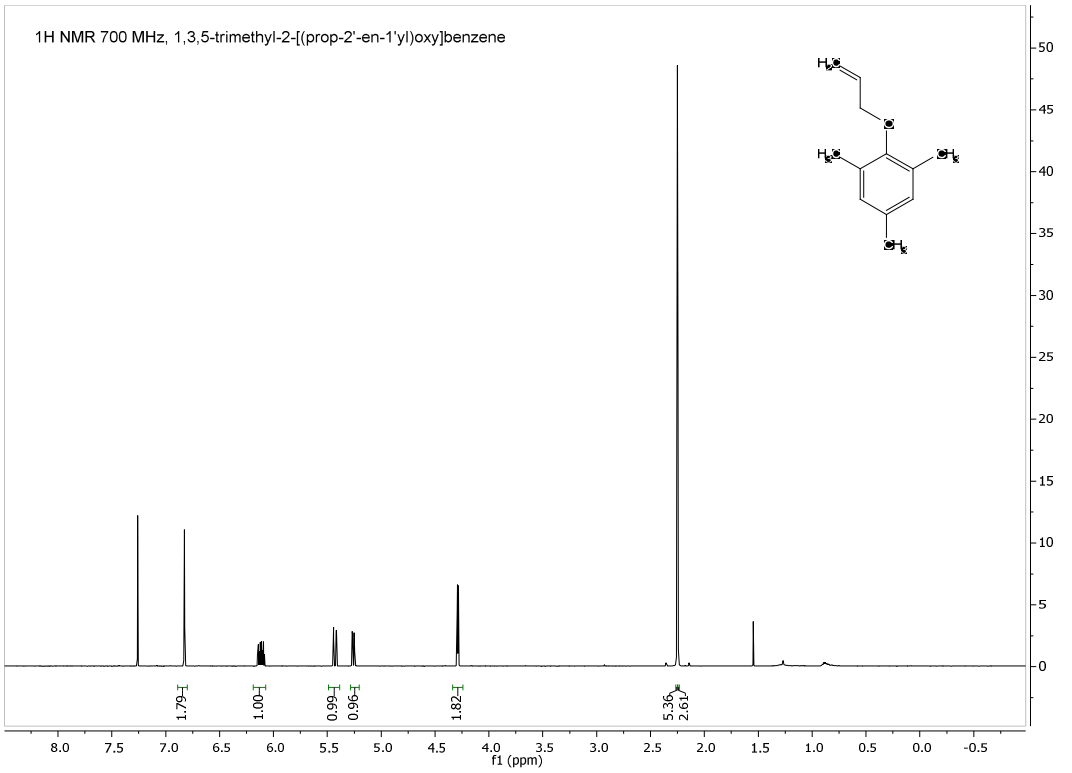

13C NMR 101 MHz, 1-(allyloxy)-4-methoxybenzene
154.04
152.88
133.75
117.64
115.87
114.74
69.67
55.86
f1 (ppm)

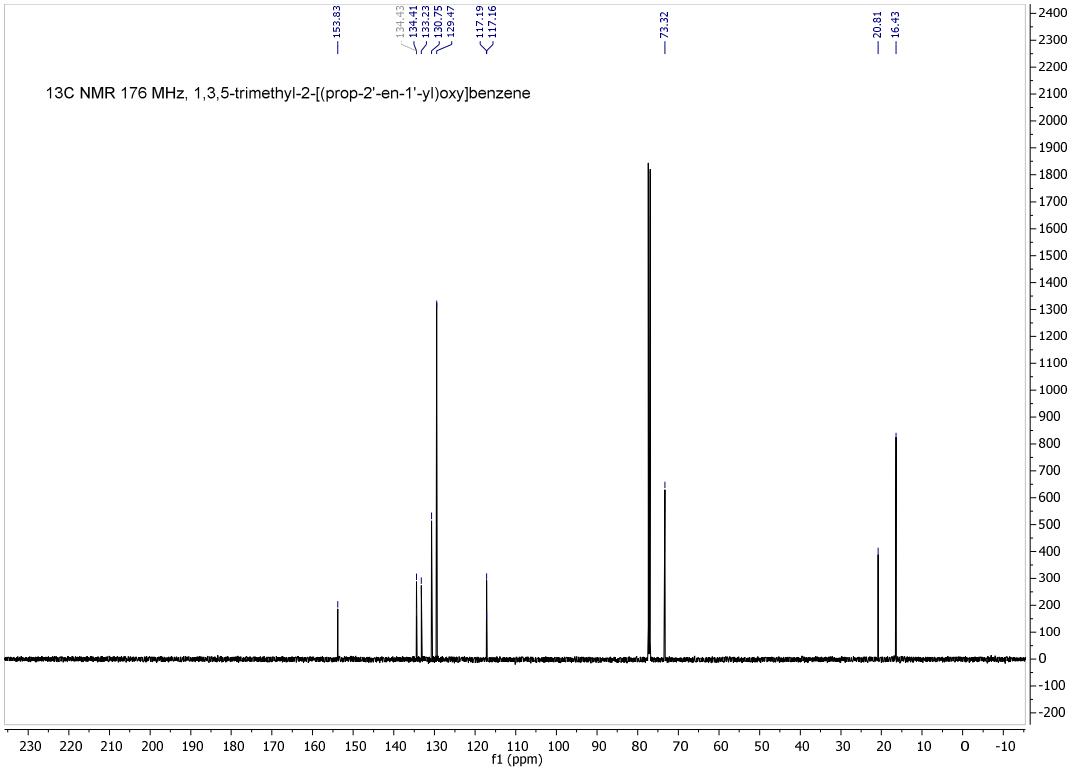

1H NMR 700 MHz, 1-methoxy-3-[(prop-2'-en-1'yl)oxy]benzene
0.90
1.67
0.90
1.00
1.00
0.99
1.86
2.72
f1 (ppm)

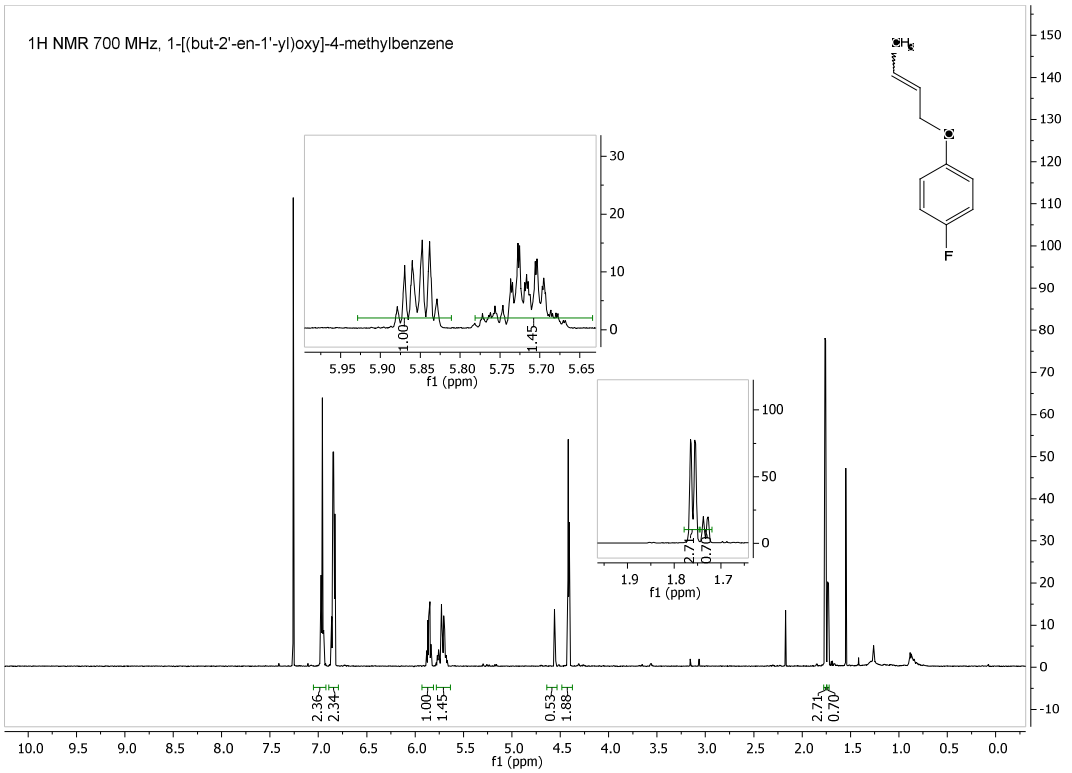

13C NMR 176 MHz, 1-methoxy-3-[(prop-2'-en-1'-yl)oxy]benzene
160.96
159.99
133.41
129.99
117.83
107.04
106.59
101.40
68.98
55.41
f1 (ppm)

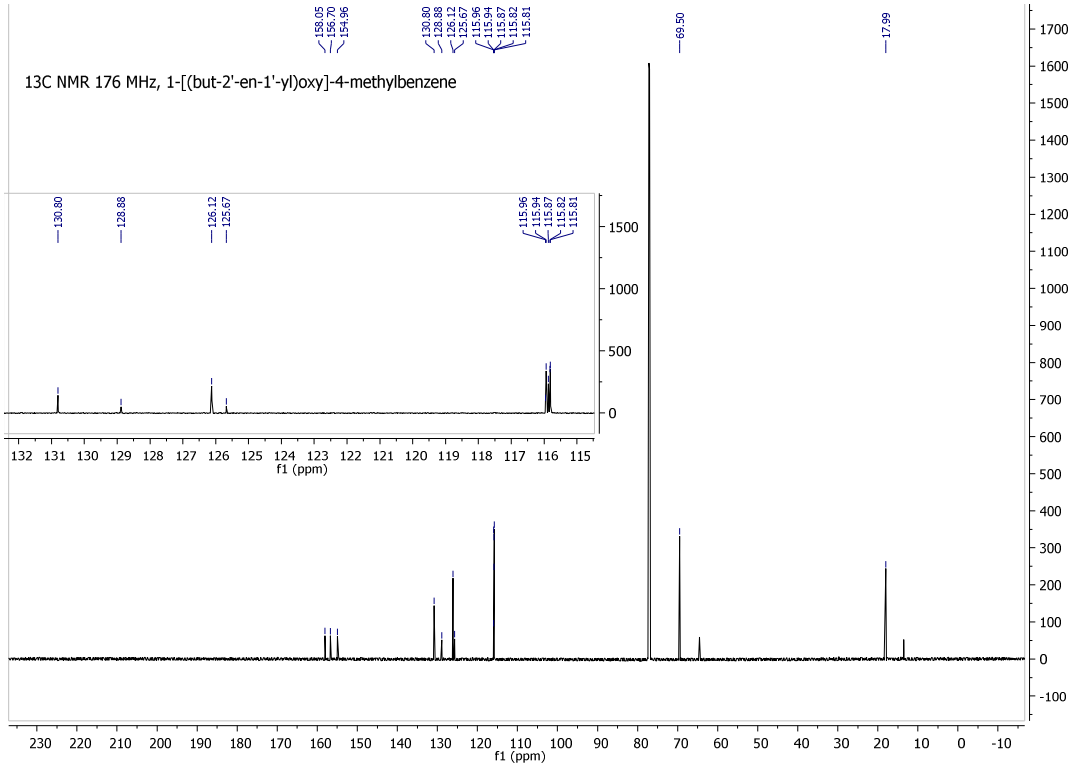

1H NMR 700 MHz, 1-(allyloxy)-4-cyanobenzene
CN
1.88
1.89
1.00
1.00
0.99
1.85
f1 (ppm)

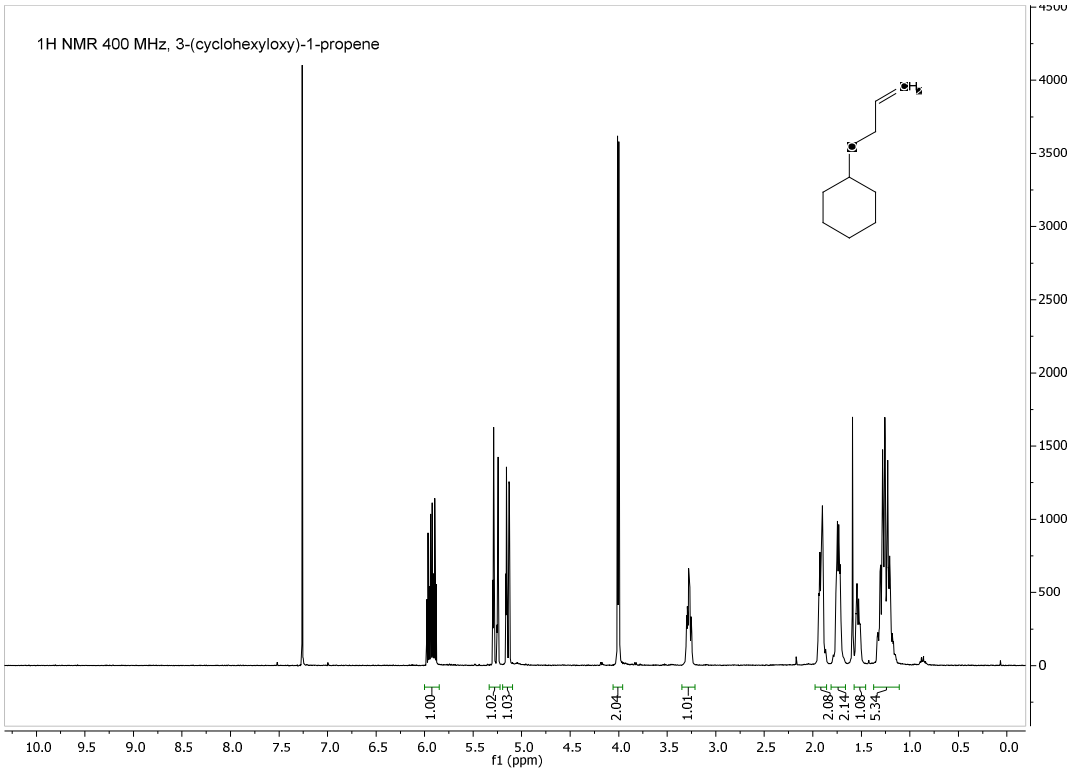

13C NMR 176 MHz, 1-(allyloxy)-4-cyanobenzene
161.98
134.12
132.22
119.32
118.64
115.59
104.28
69.15
f1 (ppm)

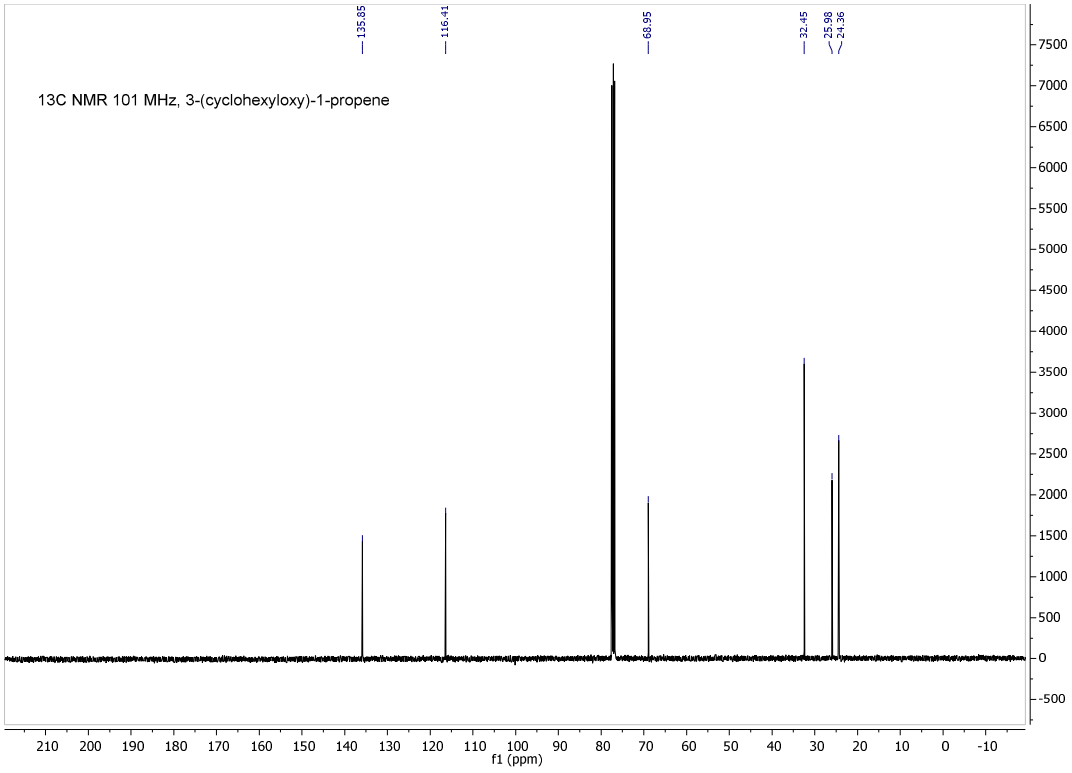

1H NMR 700 MHz, 1,3,5-trimethyl-2-[(prop-2'-en-1'yl)oxy]benzene
1.79
1.00
0.99
0.96
1.82
5.36
2.61
f1 (ppm)

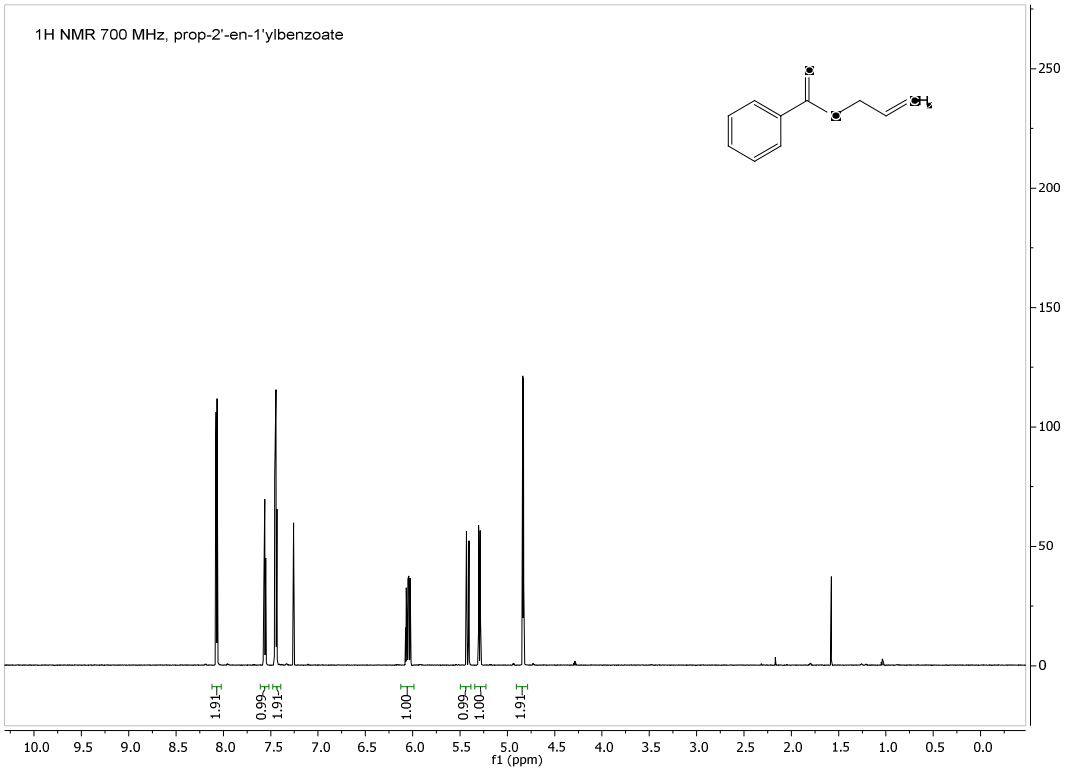

153.83
134.43
134.41
133.23
130.75
129.47
117.19
117.16
73.32
20.81
16.43
13C NMR 176 MHz, 1,3,5-trimethyl-2-[(prop-2'-en-1'-yl)oxy]benzene
f1 (ppm)

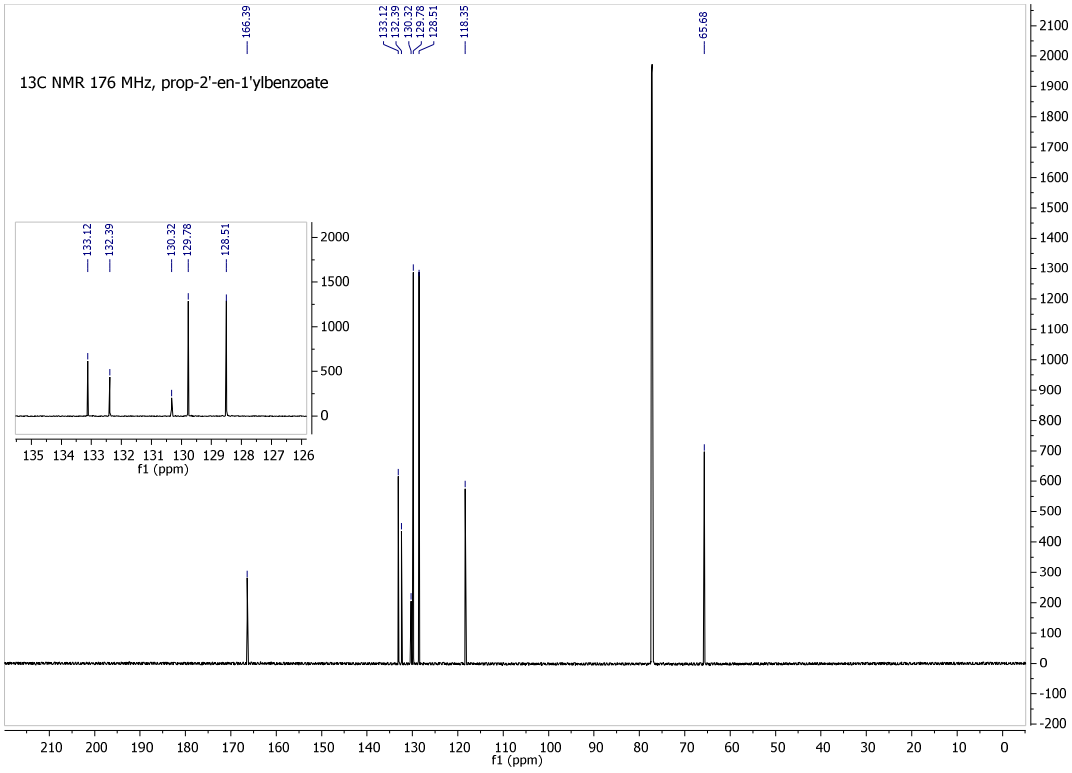

1H NMR 700 MHz, 1-[(but-2'-en-1'-yl)oxy]-4-methylbenzene
2.36
2.34
1.00
1.45
0.53
1.88
2.71
0.70
f1 (ppm)

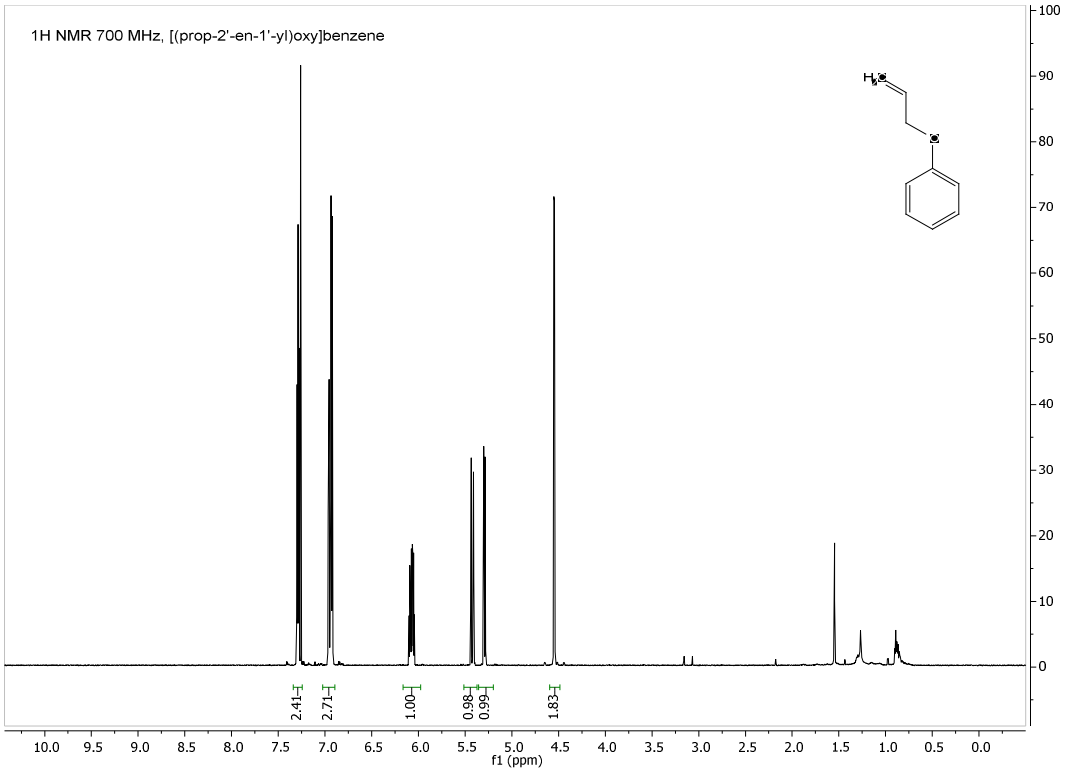

13C NMR 176 MHz, 1-[(but-2'-en-1'-yl)oxy]-4-methylbenzene
158.05
155.70
154.96
130.80
128.88
126.12
125.67
115.96
115.94
115.87
115.82
115.81
69.50
17.99
f1 (ppm)

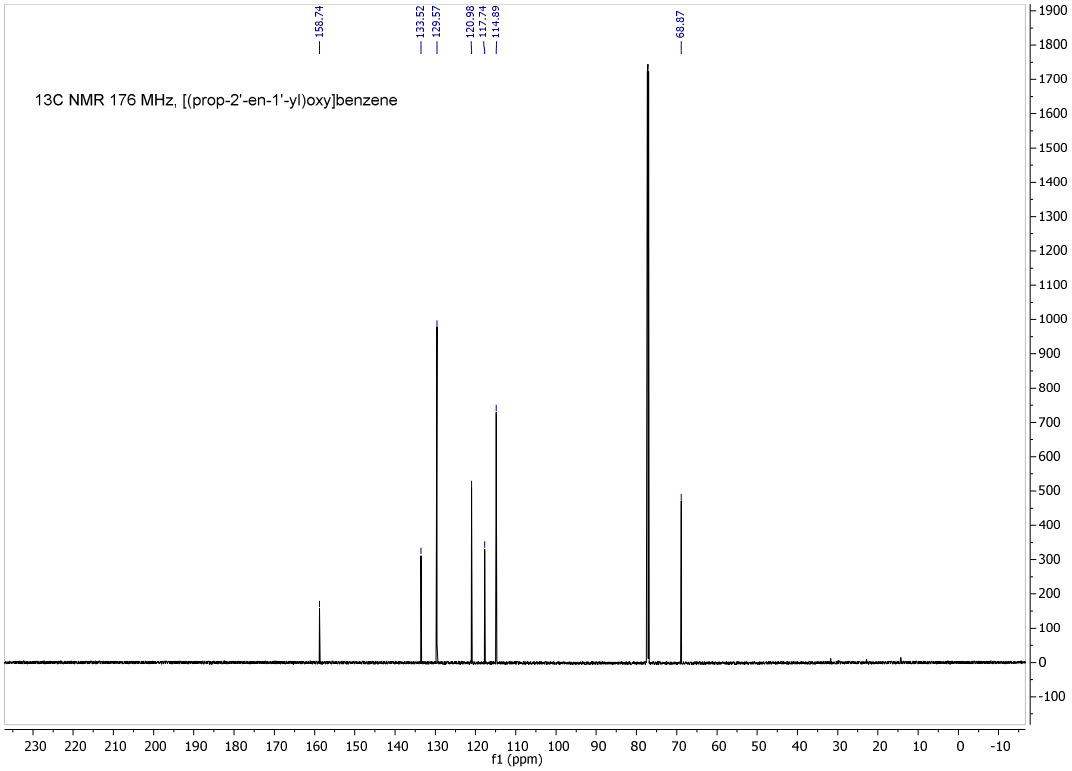

1H NMR 400 MHz, 3-(cyclohexyloxy)-1-propene
1.00
1.02
1.03
2.04
1.01
2.08
2.14
1.08
5.34
f1 (ppm)

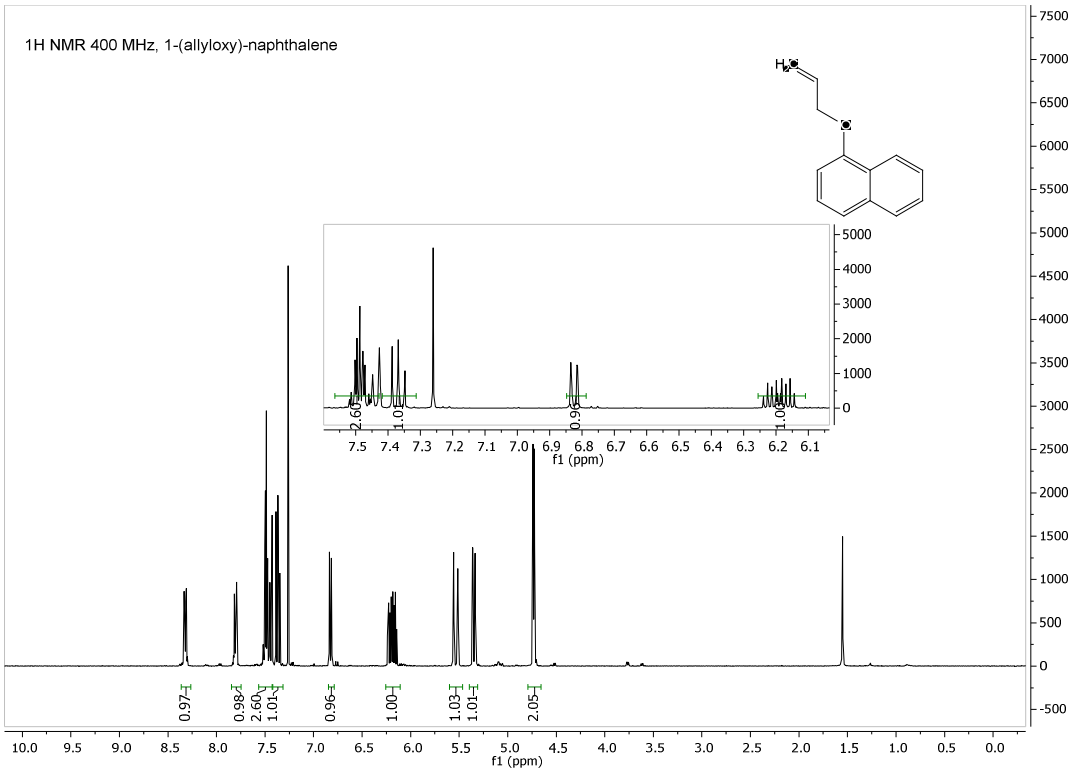

13C NMR 101 MHz, 3-(cyclohexyloxy)-1-propene
135.85
116.41
68.95
32.45
25.98
24.36
f1 (ppm)

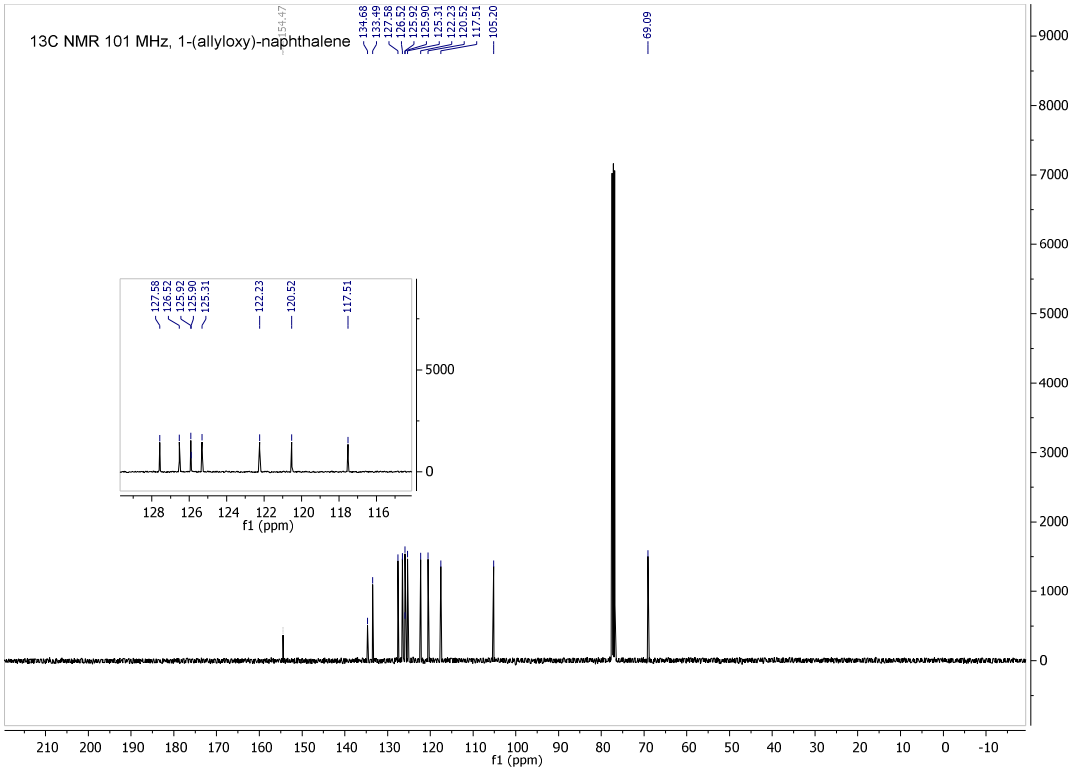

1H NMR 700 MHz, prop-2'-en-1'ylbenzoate
1.91
0.99
1.91
1.00
0.99
1.00
1.91
f1 (ppm)

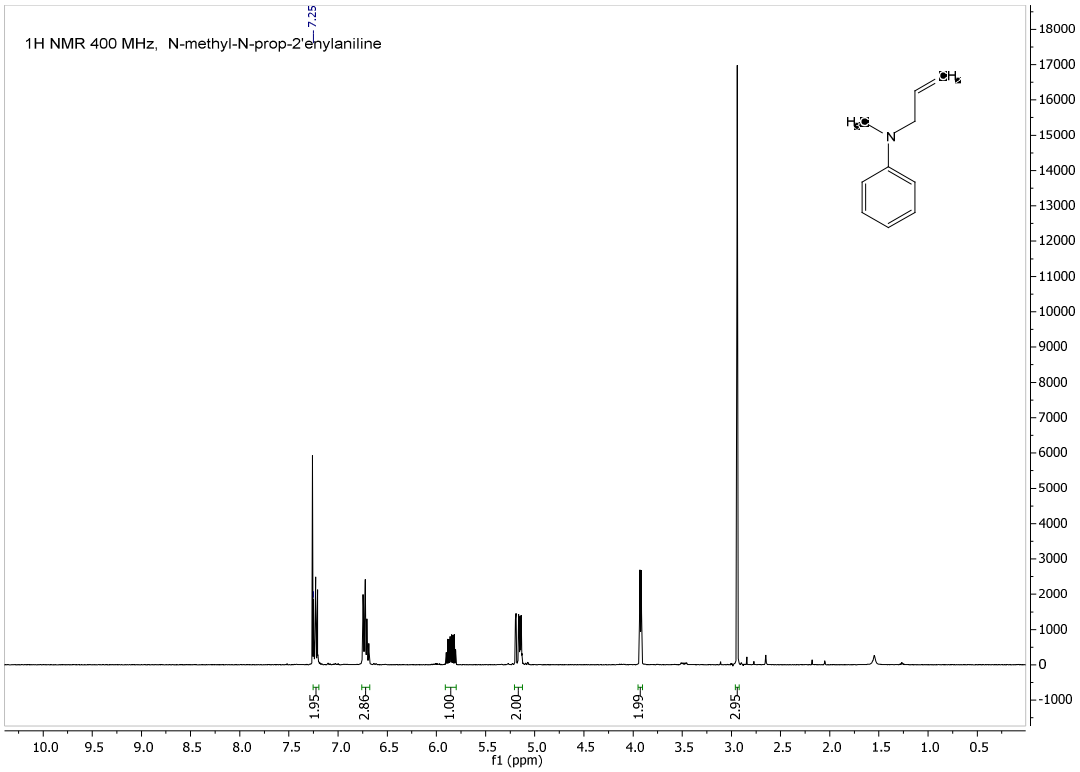

13C NMR 176 MHz, prop-2'-en-1'ylbenzoate
166.39
133.12
132.39
130.32
129.78
128.51
118.35
65.68
f1 (ppm)

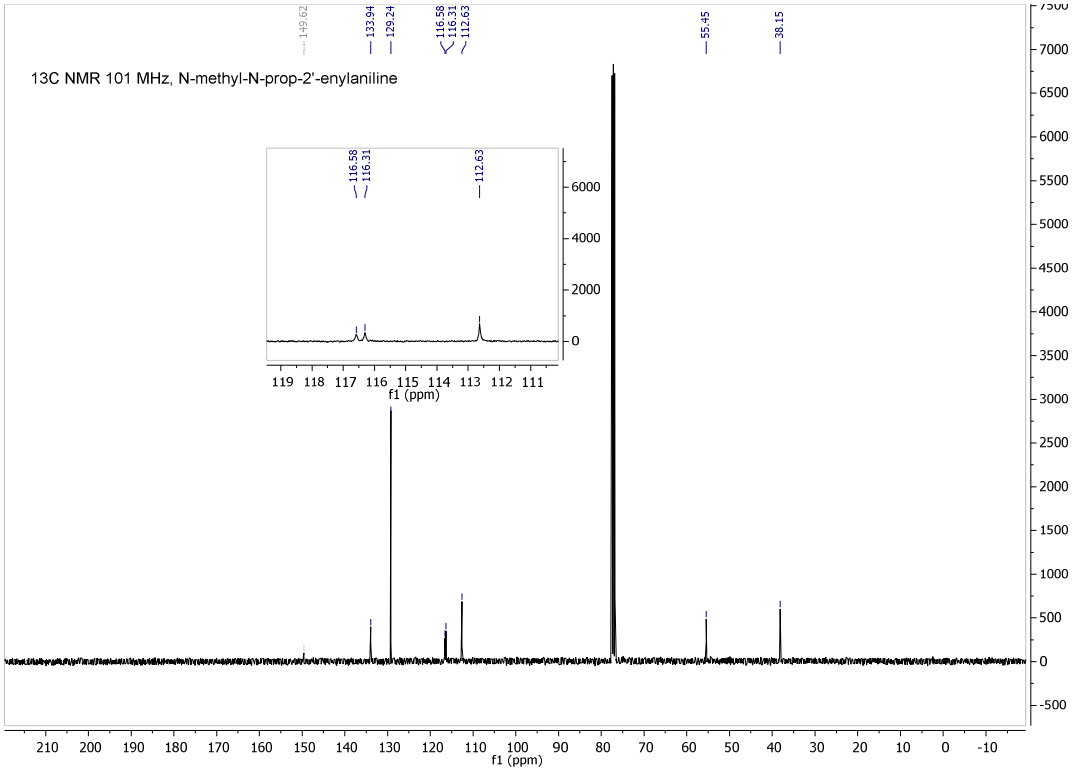

1H NMR 700 MHz, [(prop-2'-en-1'-yl)oxy]benzene
2.41
2.71
1.00
0.98
0.99
1.83
f1 (ppm)

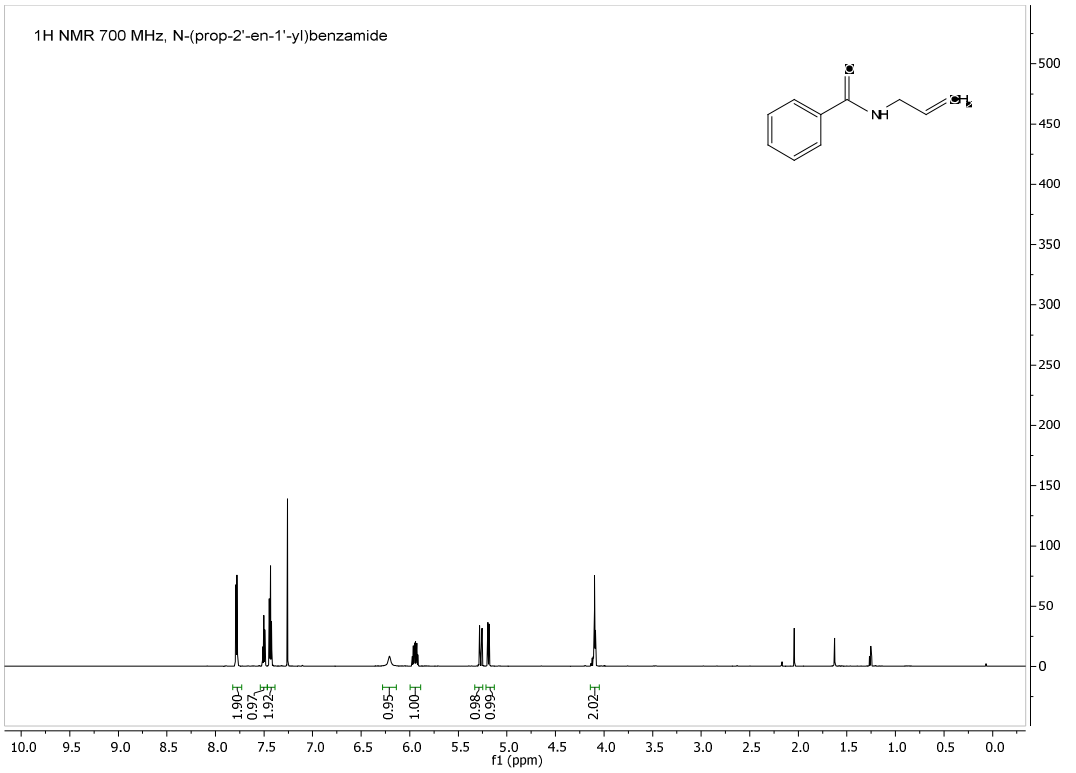

13C NMR 176 MHz, [(prop-2'-en-1'-yl)oxy]benzene
158.74
133.52
129.57
120.98
117.74
114.89
68.87
f1 (ppm)

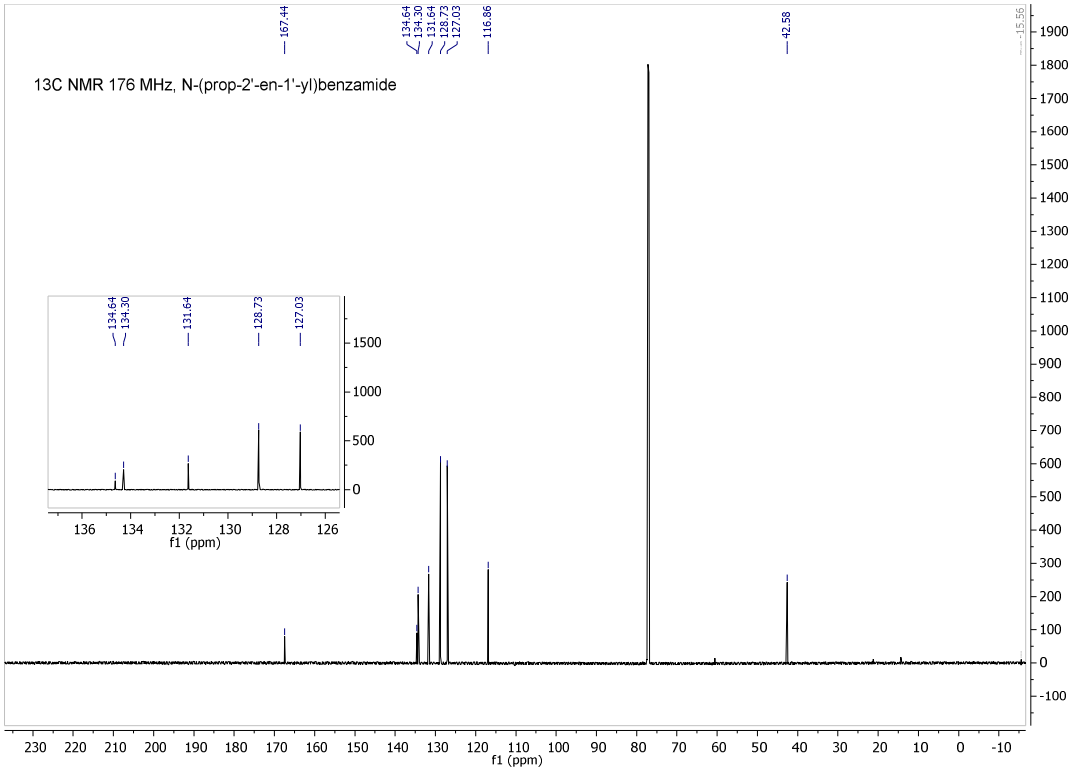

1H NMR 400 MHz, 1-(allyloxy)-naphthalene
0.97
0.98
2.60
1.01
0.96
1.00
1.03
1.01
2.05
2.60
1.00
0.96
1.00
f1 (ppm)

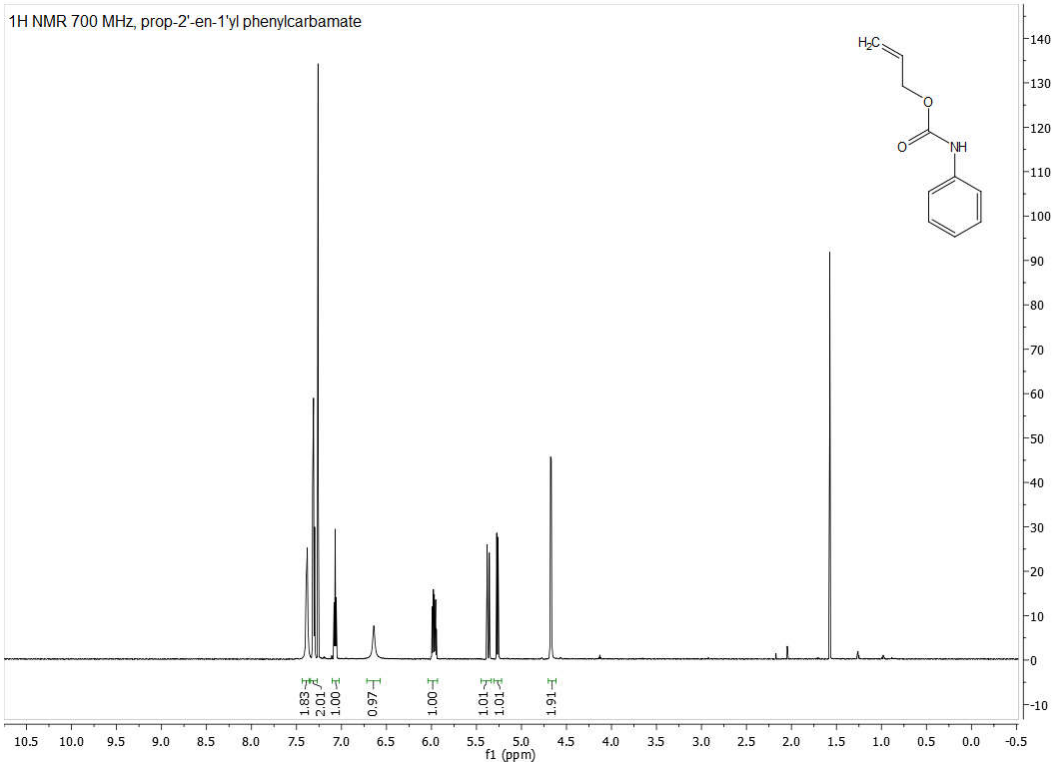

13C NMR 101 MHz, 1-(allyloxy)-naphthalene
154.47
134.68
133.49
127.58
126.52
125.92
125.90
125.31
122.23
120.52
117.51
105.20
69.09
f1 (ppm)

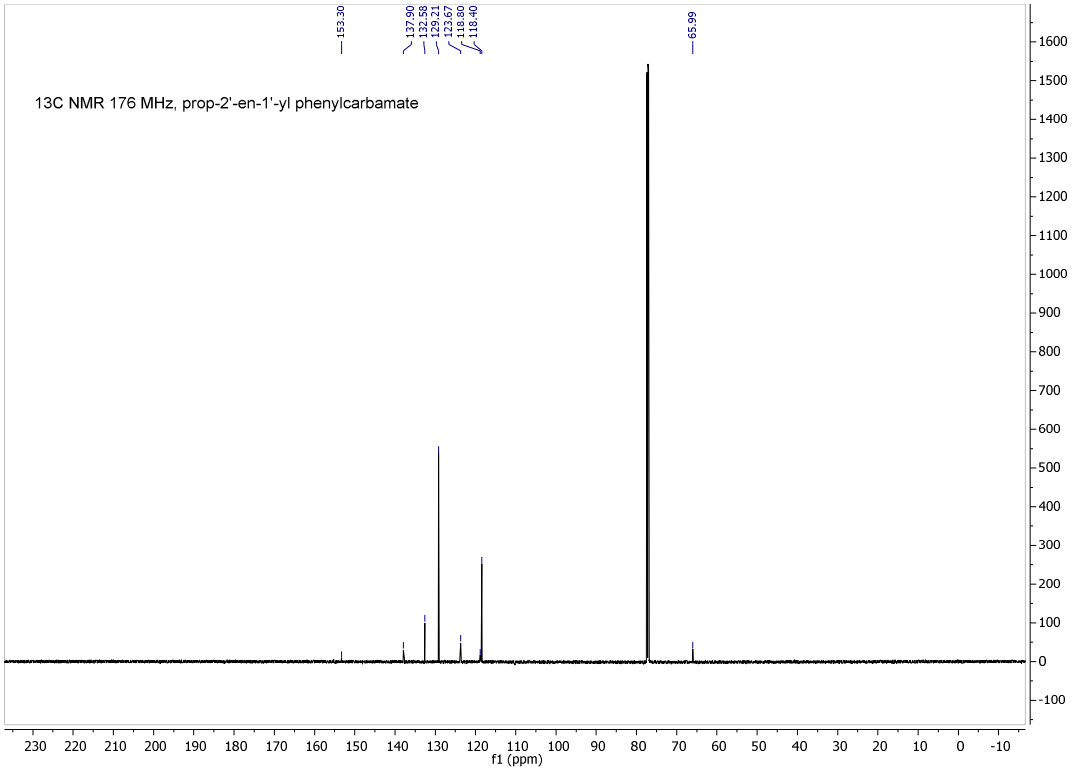

1H NMR 400 MHz, N-methyl-N-prop-2'enylaniline
7.25
1.95
2.86
1.00
2.00
1.99
2.95
f1 (ppm)

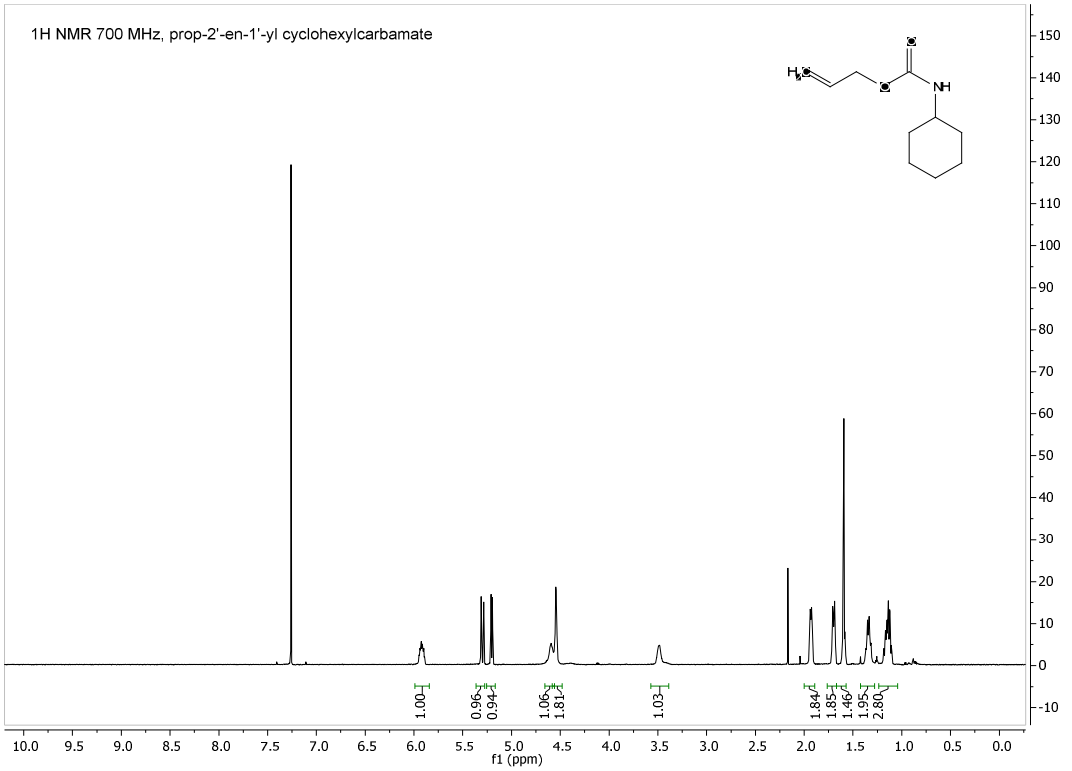

13C NMR 101 MHz, N-methyl-N-prop-2'-enylaniline
149.62
133.94
129.24
116.58
116.31
112.63
55.45
38.15
f1 (ppm)

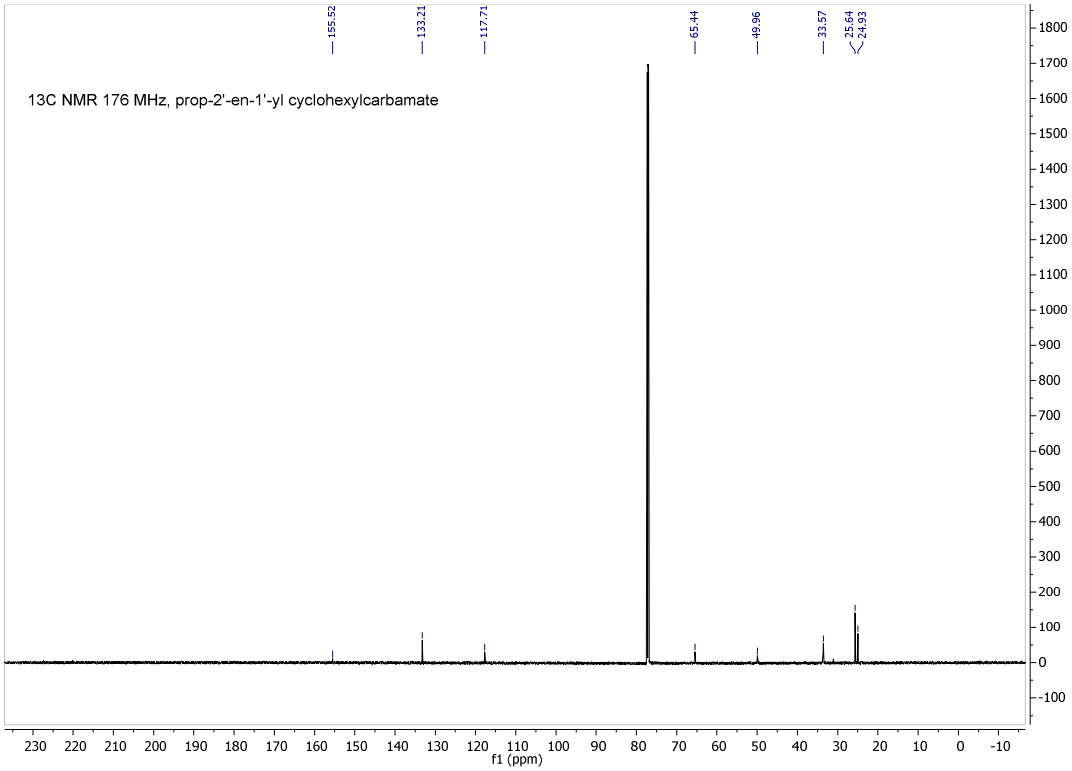

1H NMR 700 MHz, N-(prop-2'-en-1'-yl)benzamide
NH
1.90
0.97
1.92
0.95
1.00
0.98
0.99
2.02
f1 (ppm)

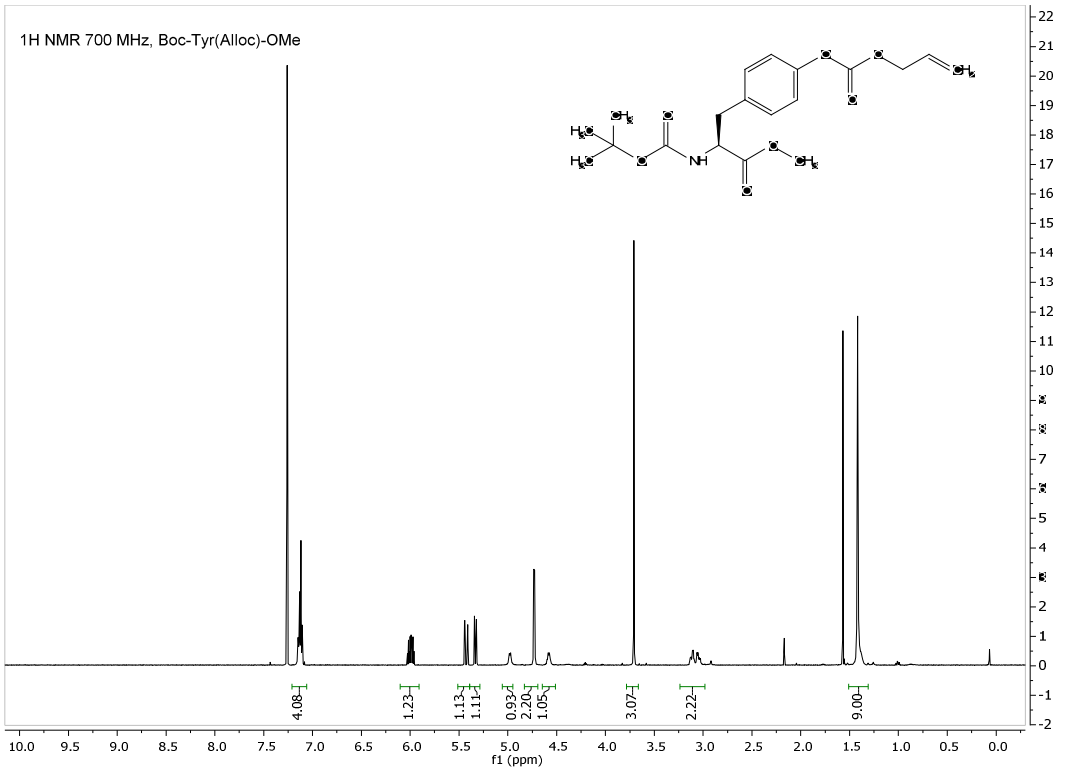

13C NMR 176 MHz, N-(prop-2'-en-1'-yl)benzamide
167.44
134.64
134.30
131.64
128.73
127.03
116.86
42.58
f1 (ppm)

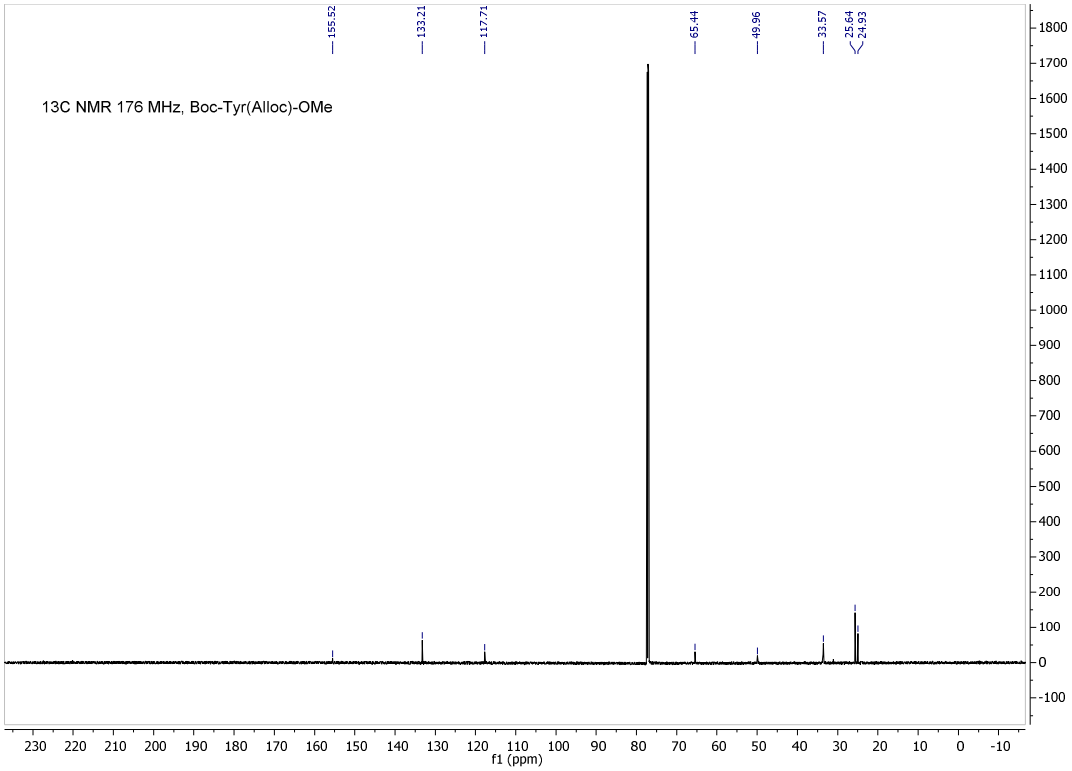

1H NMR 700 MHz, prop-2'-en-1'yl phenylcarbamate
H2C
O
O
NH
1.83
2.01
1.00
0.97
1.00
1.01
1.01
1.91
f1 (ppm)

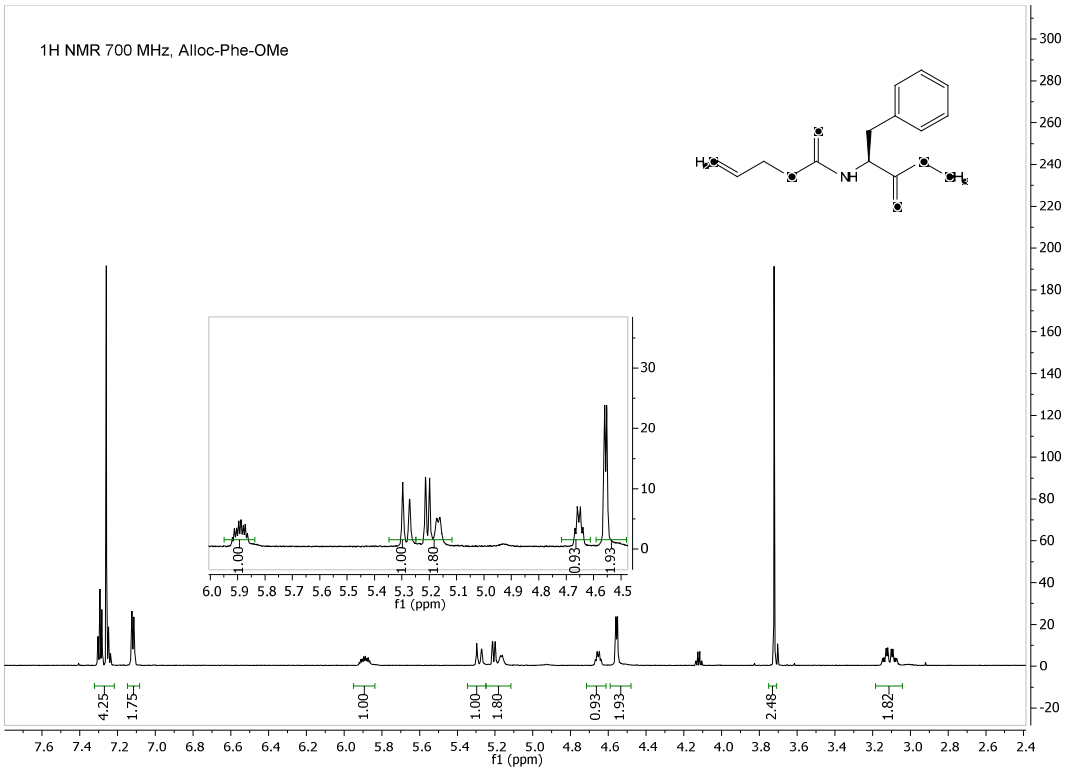

13C NMR 176 MHz, prop-2'-en-1'-yl phenylcarbamate
153.30
137.90
132.58
129.21
123.67
118.80
118.40
65.99
f1 (ppm)

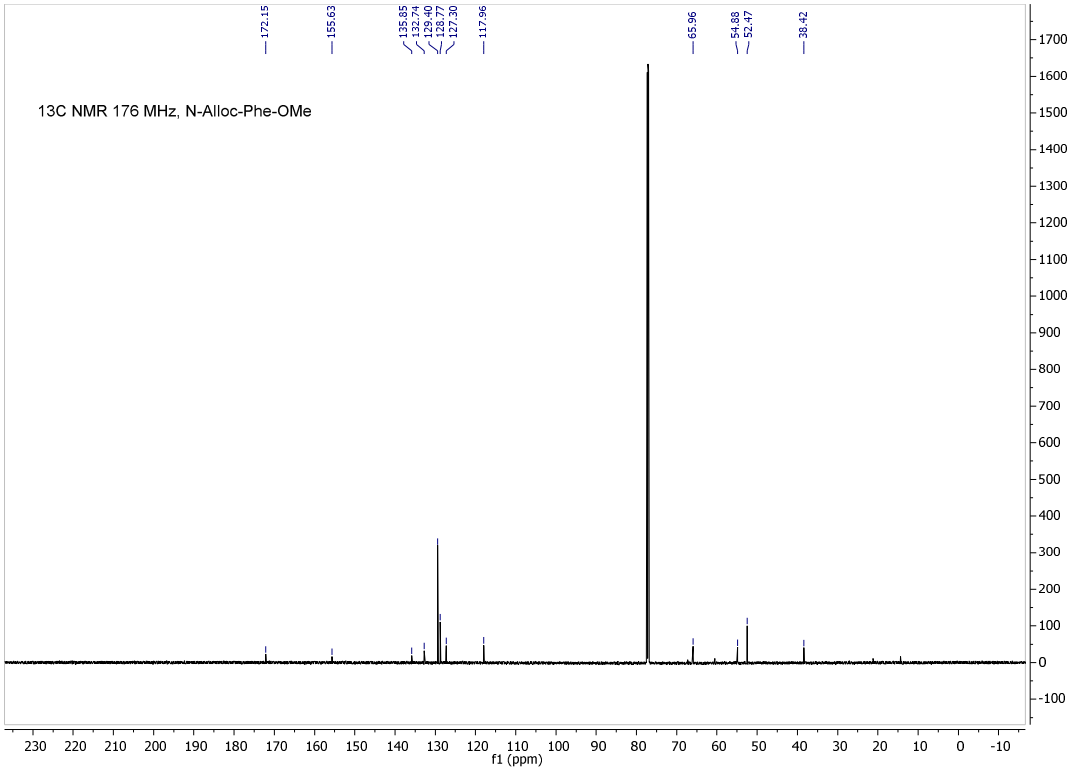

1H NMR 700 MHz, prop-2'-en-1'-yl cyclohexylcarbamate
NH
1.00
0.96
0.94
1.06
1.81
1.03
1.84
1.85
1.46
1.95
2.86
f1 (ppm)

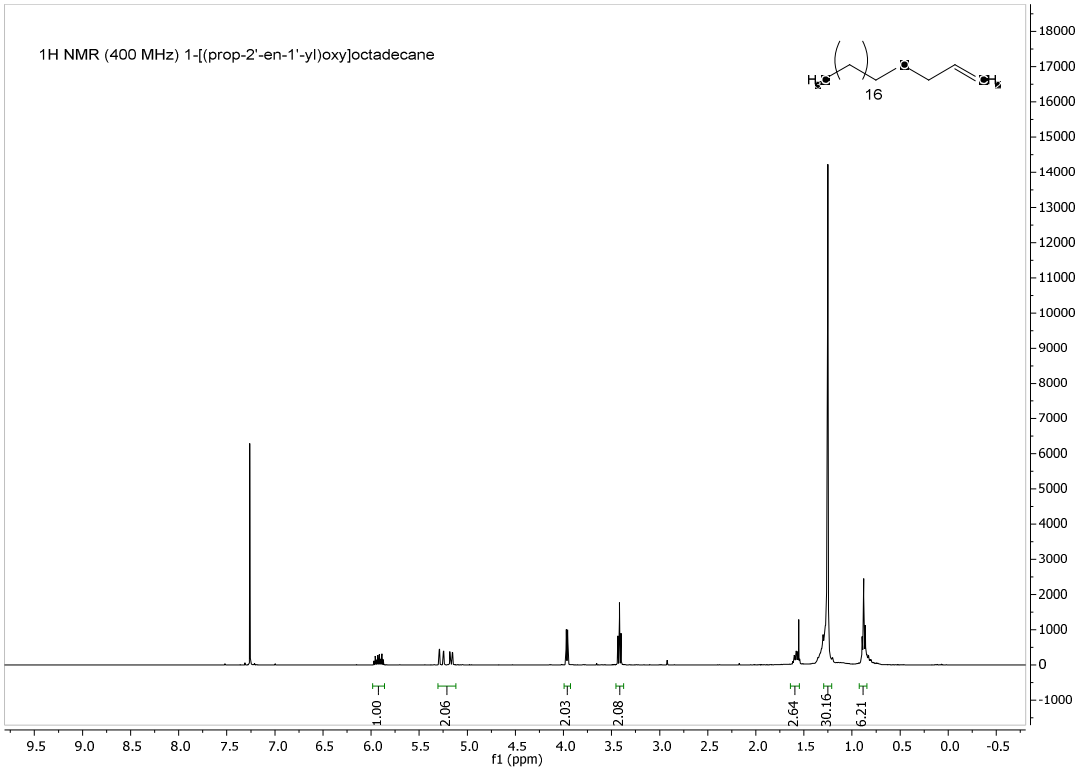

13C NMR 176 MHz, prop-2'-en-1'-yl cyclohexylcarbamate
155.52
133.21
117.71
65.44
49.96
33.57
25.64
24.93
f1 (ppm)

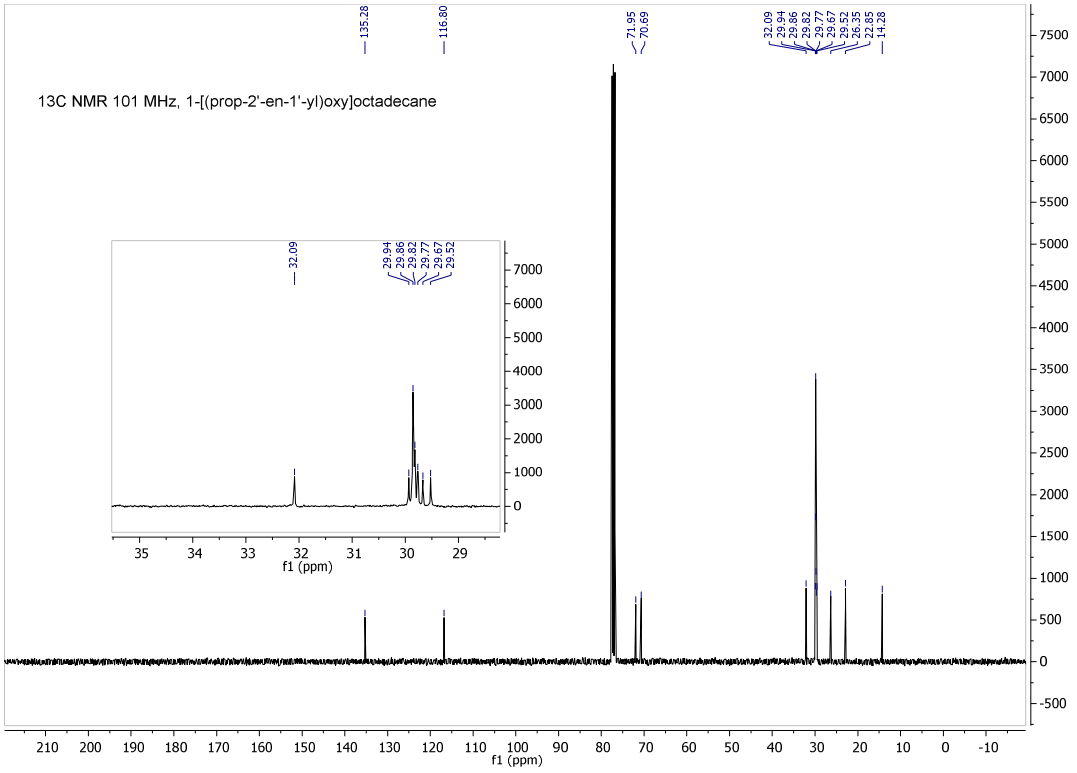

1H NMR 700 MHz, Boc-Tyr(Alloc)-OMe
NH
4.08
1.23
1.13
1.11
0.93
2.20
1.05
3.07
2.22
9.00
f1 (ppm)

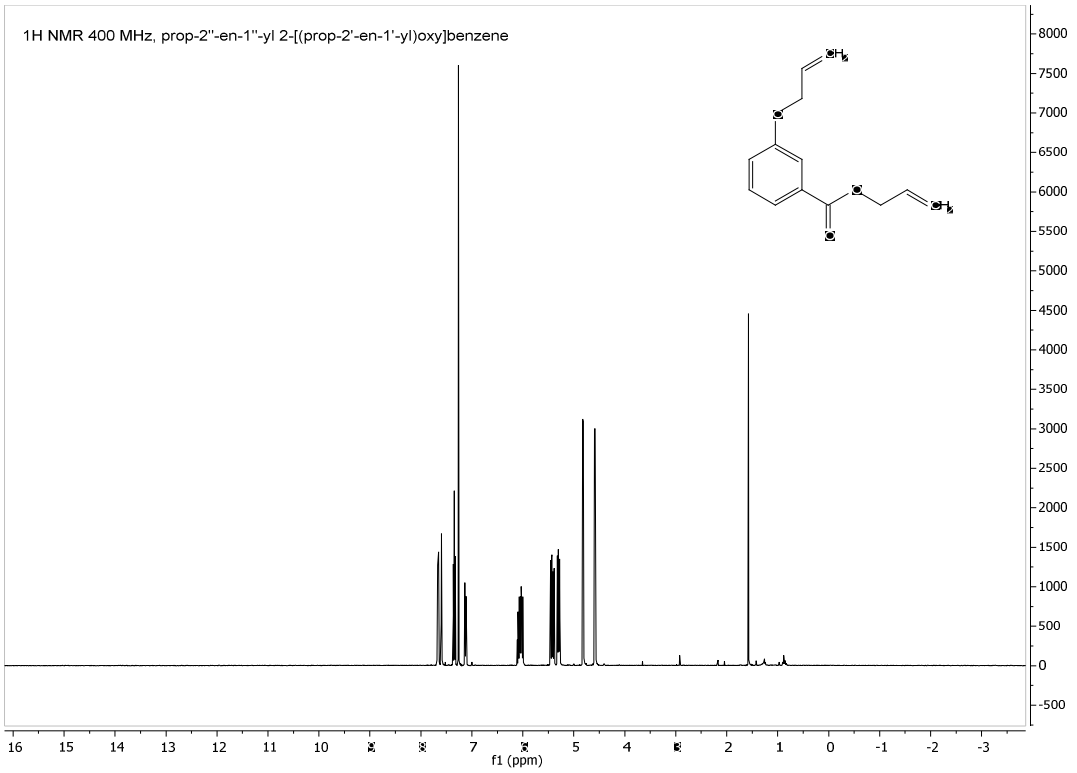

13C NMR 176 MHz, Boc-Tyr(Alloc)-OMe
155.52
133.21
117.71
65.44
49.96
33.57
25.64
24.93
f1 (ppm)

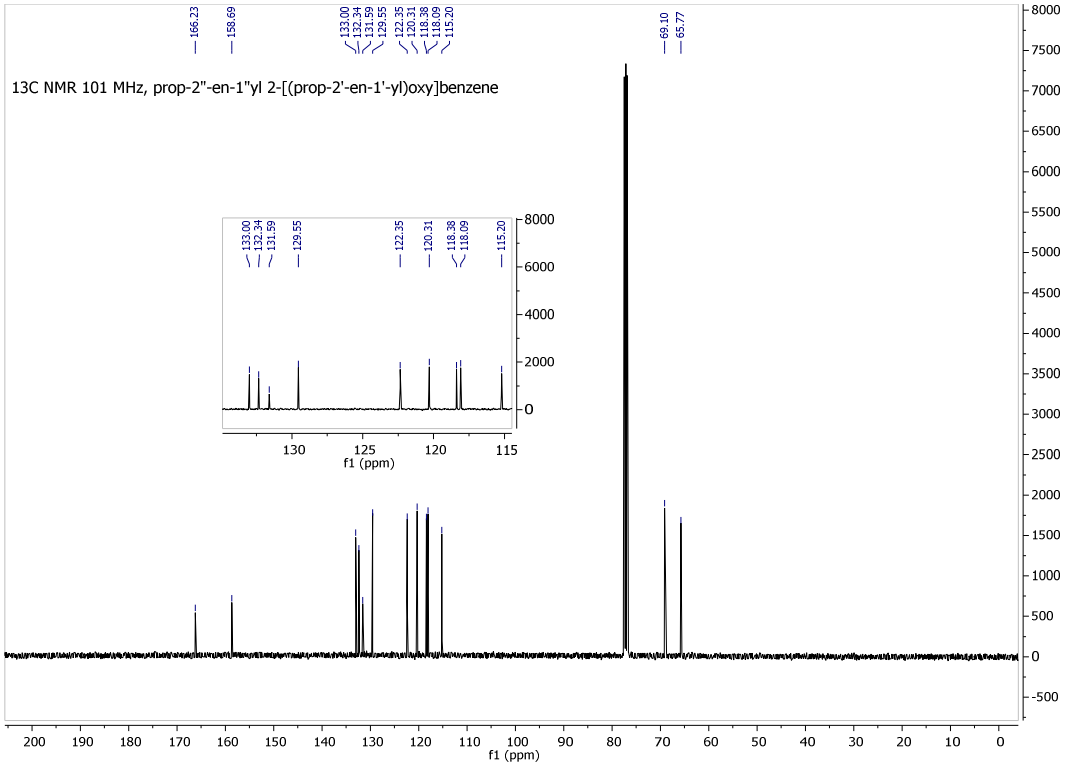

1H NMR 700 MHz, Alloc-Phe-OMe
NH
4.25
1.75
1.00
1.00
1.80
0.93
1.93
2.48
1.82
f1 (ppm)

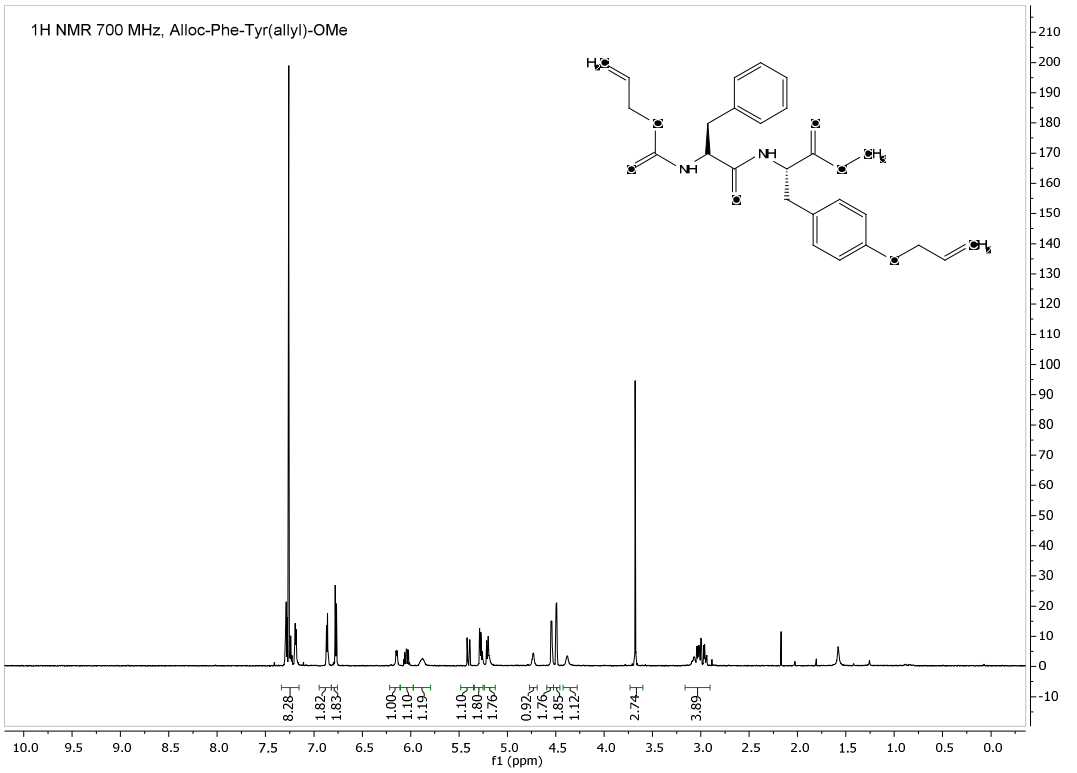

13C NMR 176 MHz, N-Alloc-Phe-OMe
172.15
155.63
135.85
129.40
128.77
127.30
117.96
65.96
54.88
52.47
38.42
f1 (ppm)

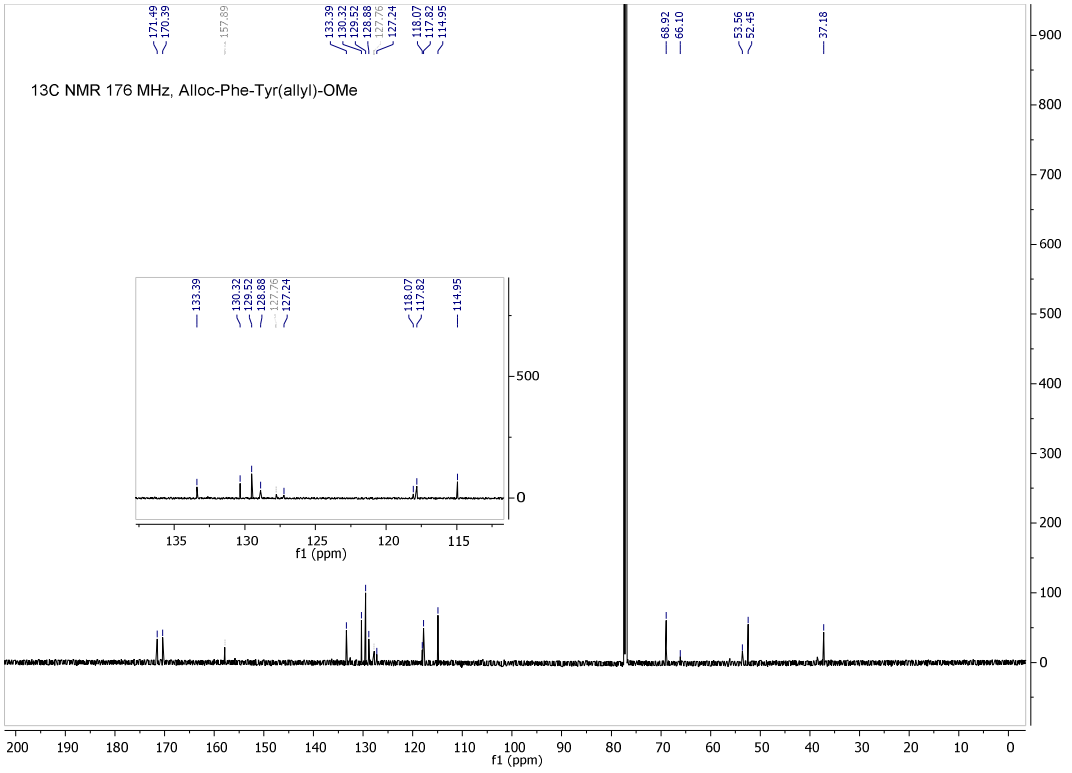

1H NMR (400 MHz) 1-[(prop-2'-en-1'-yl)oxy]octadecane
16
1.00
2.06
2.03
2.08
2.64
30.16
6.21
f1 (ppm)


13C NMR 101 MHz, 1-[(prop-2'-en-1'-yl)oxy]octadecane
135.28
116.80
71.95
70.69
32.09
29.94
29.86
29.82
29.77
29.67
29.52
26.35
22.85
14.28
f1 (ppm)

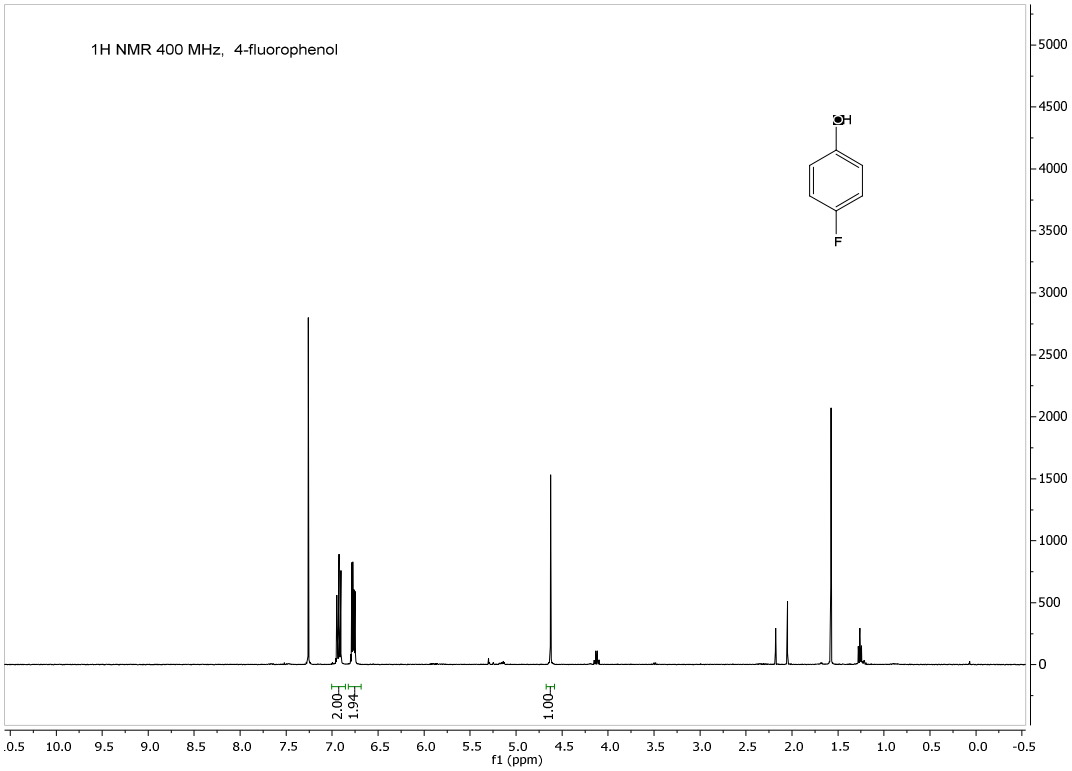

1H NMR 400 MHz, prop-2''-en-1''-yl 2-[(prop-2'-en-1'-yl)oxy]benzene
f1 (ppm)

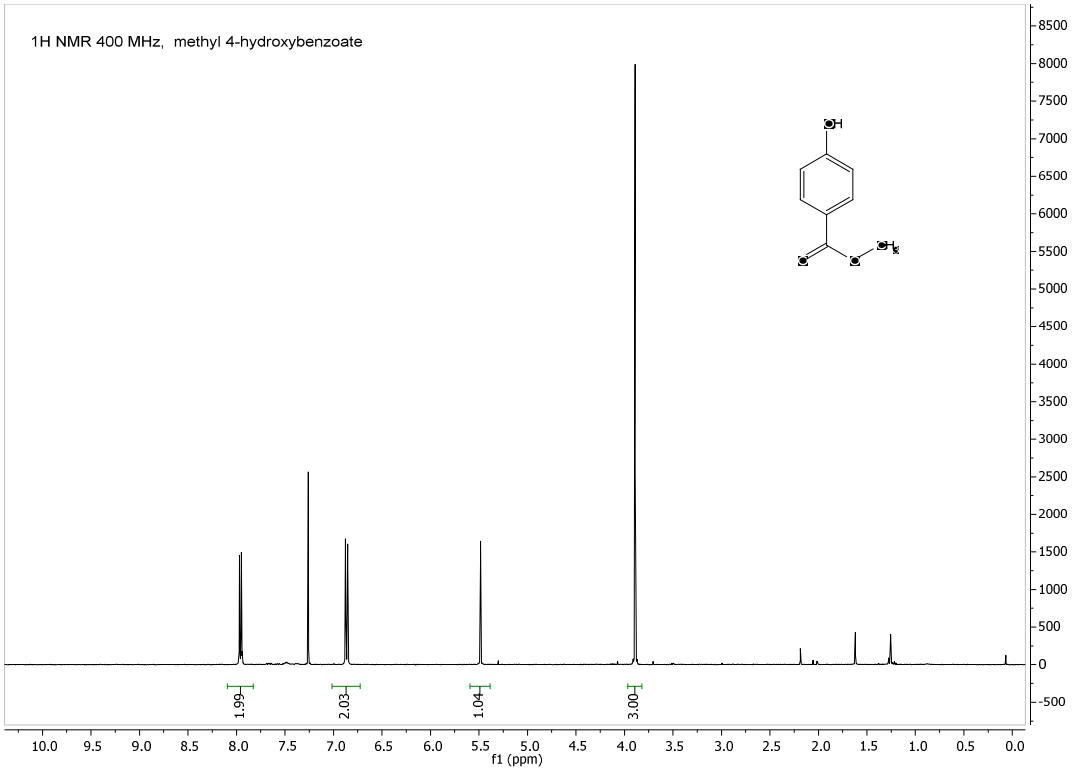

13C NMR 101 MHz, prop-2"-en-1"yl 2-[(prop-2'-en-1'-yl)oxy]benzene
166.23
158.69
133.00
132.34
131.59
129.55
122.35
120.31
118.38
118.09
115.20
69.10
65.77
f1 (ppm)

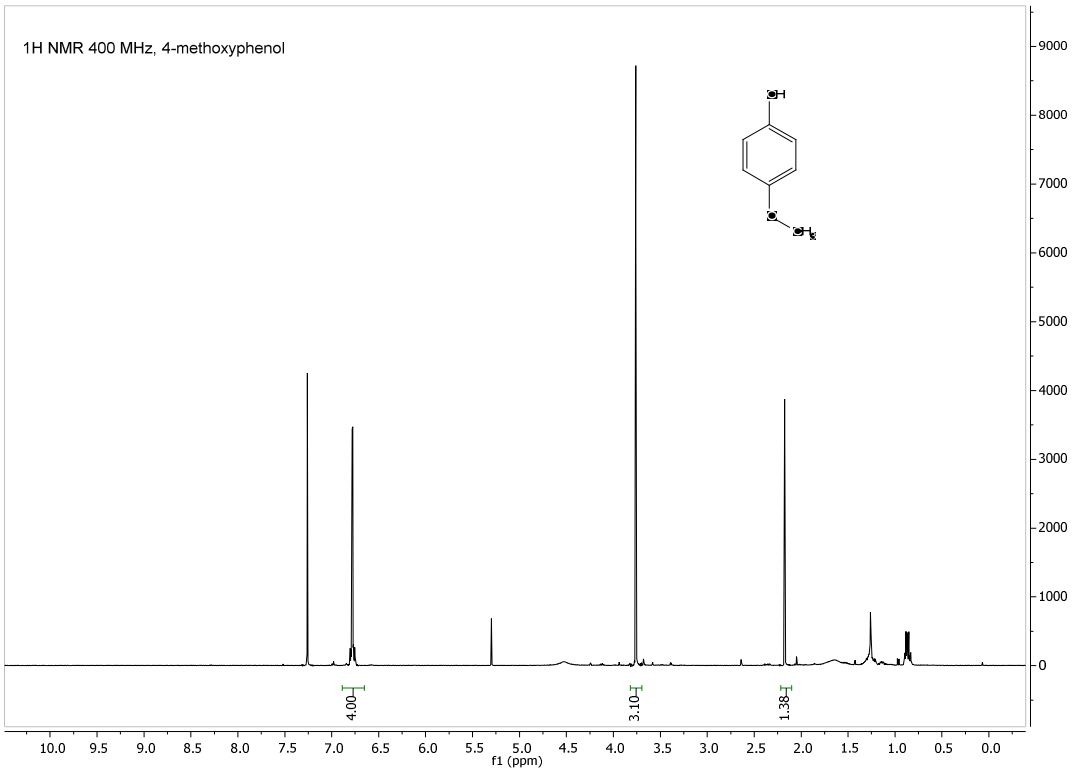

1H NMR 700 MHz, Alloc-Phe-Tyr(allyl)-OMe
NH
NH
8.28
1.82
1.83
1.00
1.10
1.19
1.10
1.80
1.76
0.92
1.76
1.85
1.12
2.74
3.89
f1 (ppm)

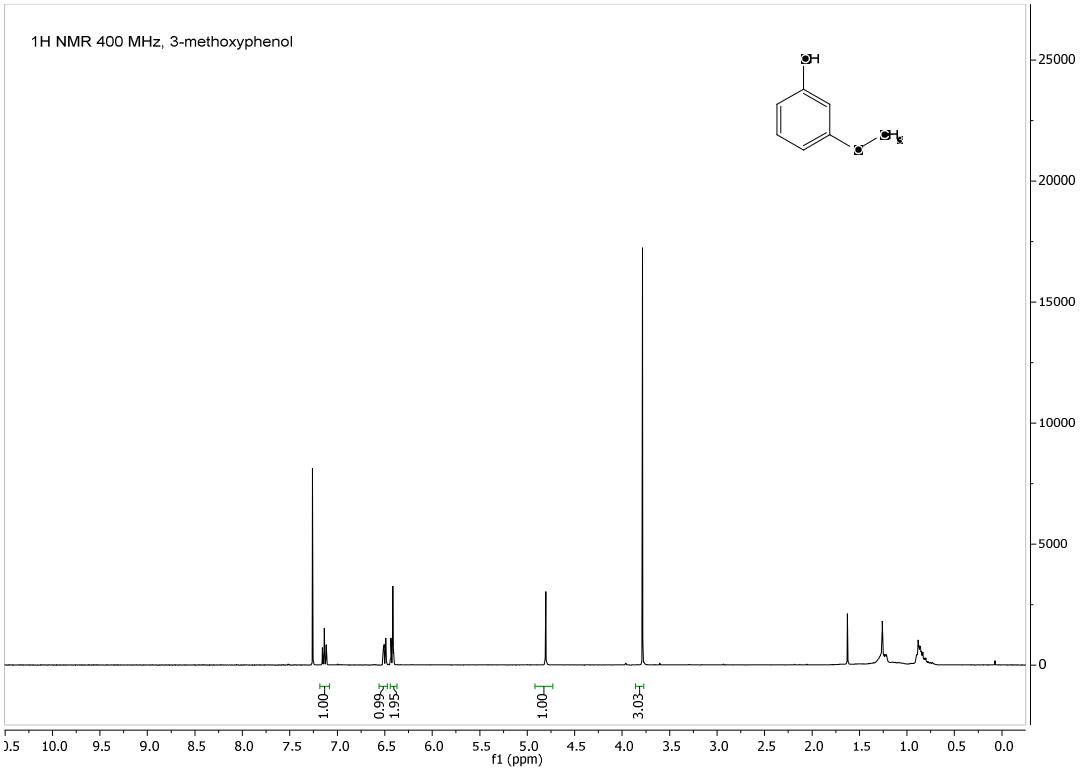


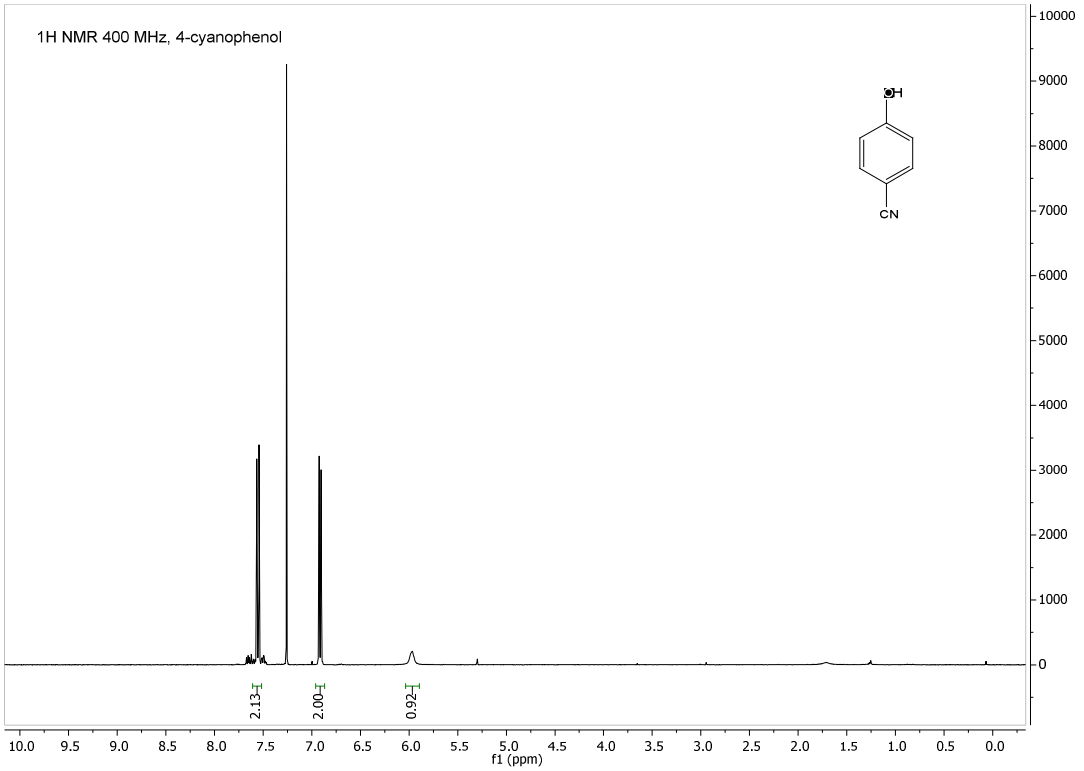
^{1}H NMR spectra of deprotected compounds

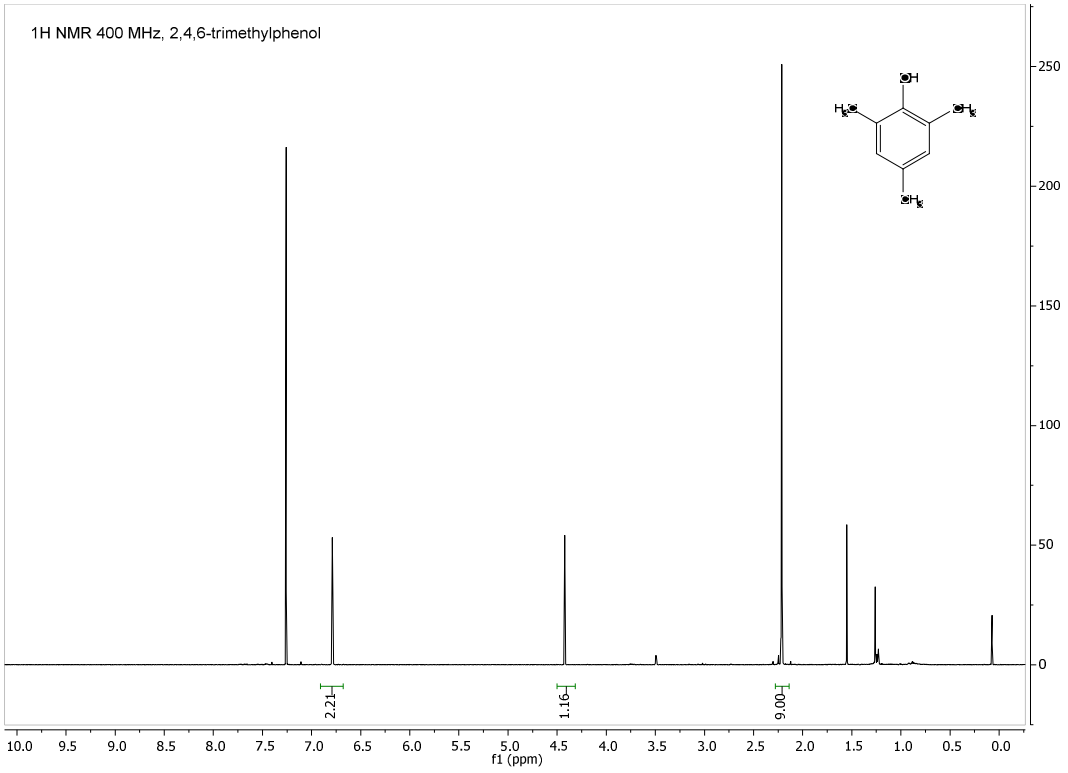


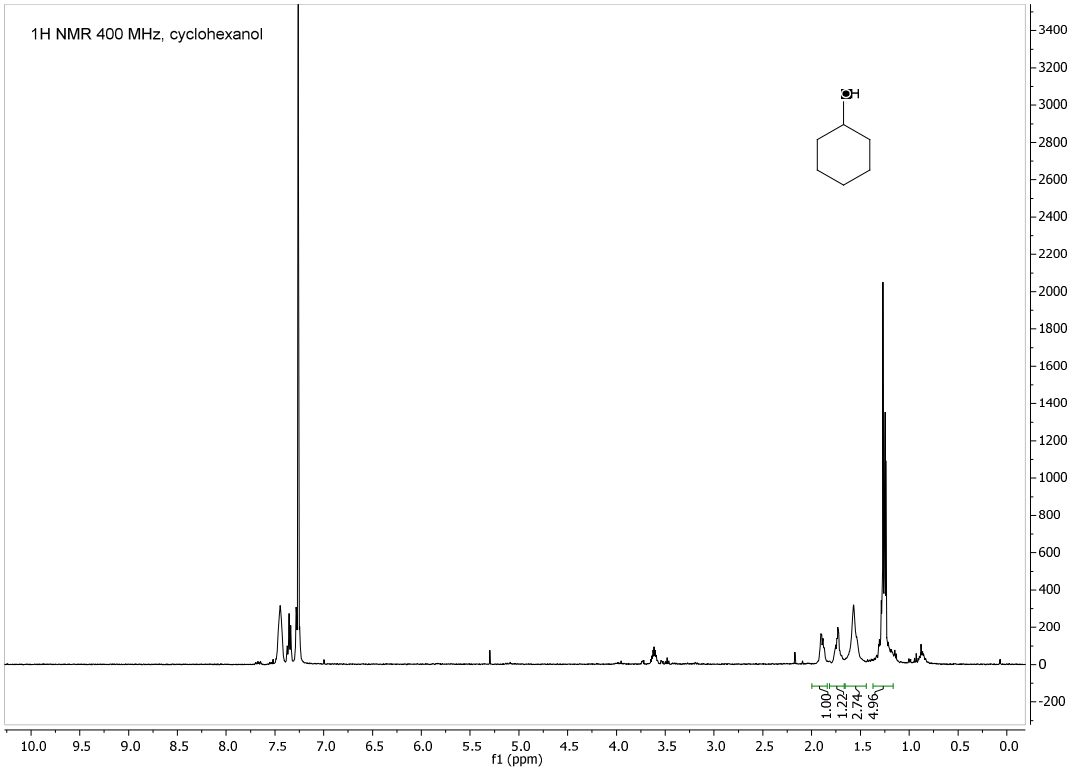

1H NMR 400 MHz, methyl 4-hydroxybenzoate
1.99
2.03
1.04
3.00
f1 (ppm)

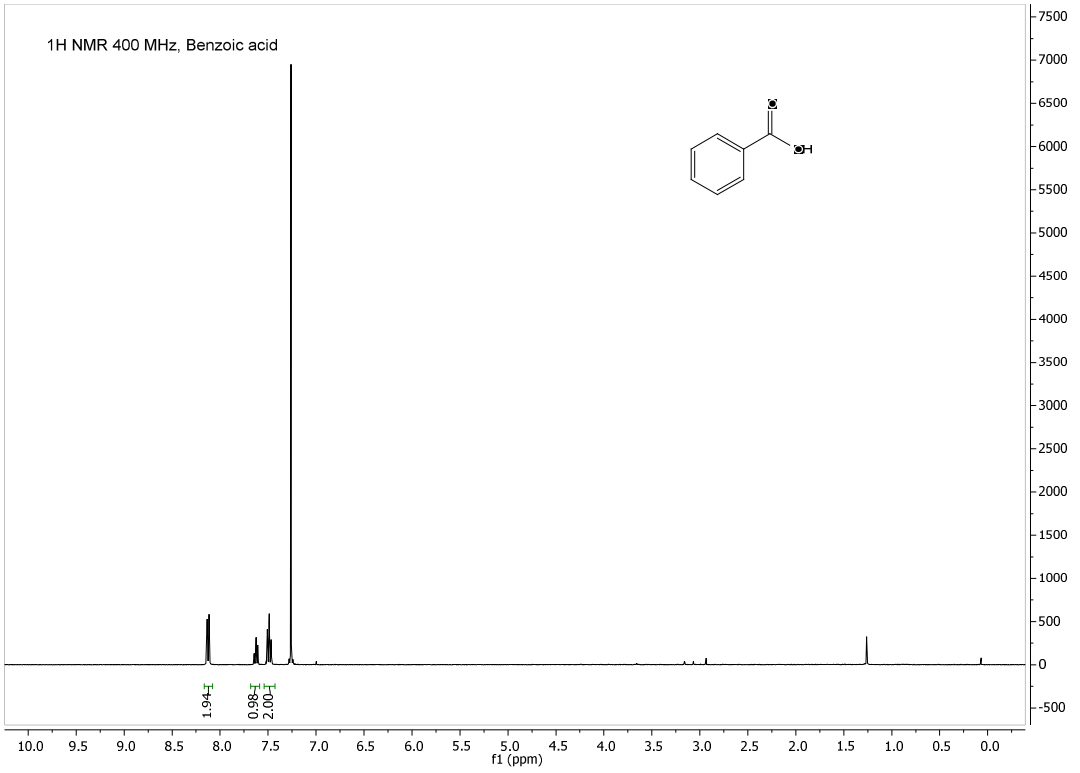

1H NMR 400 MHz, 4-methoxyphenol
4.00
3.10
1.38
f1 (ppm)

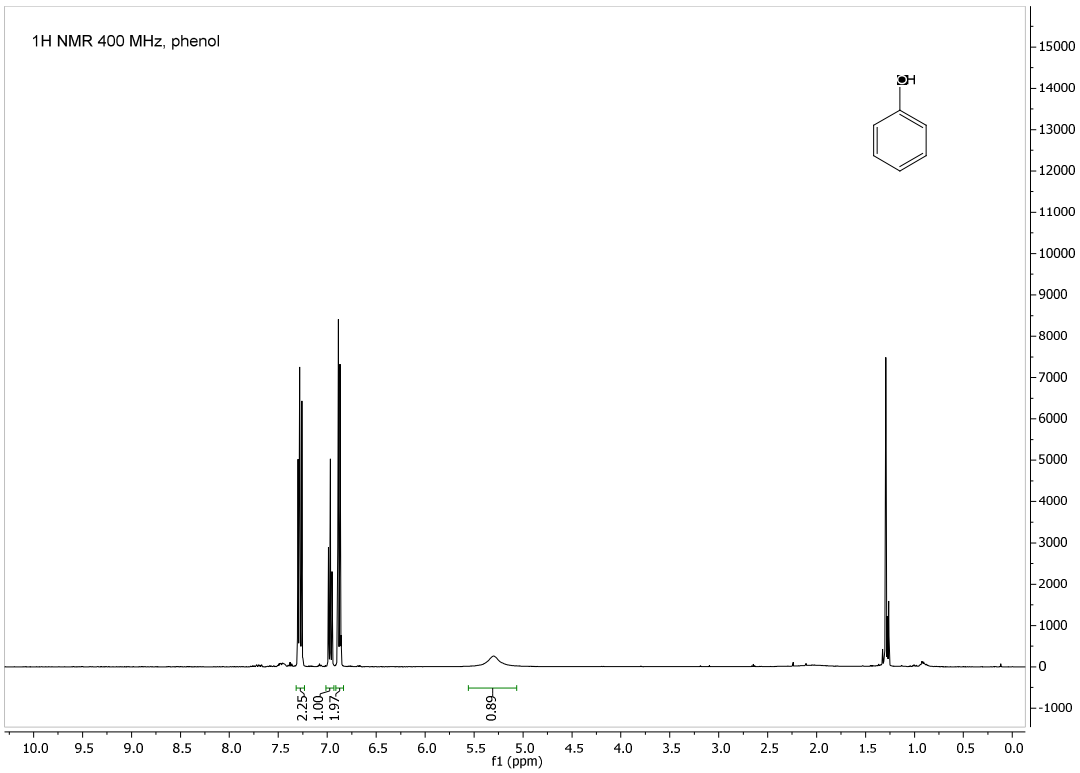

1H NMR 400 MHz, 3-methoxyphenol
1.00
0.99
1.95
1.00
3.03
f1 (ppm)

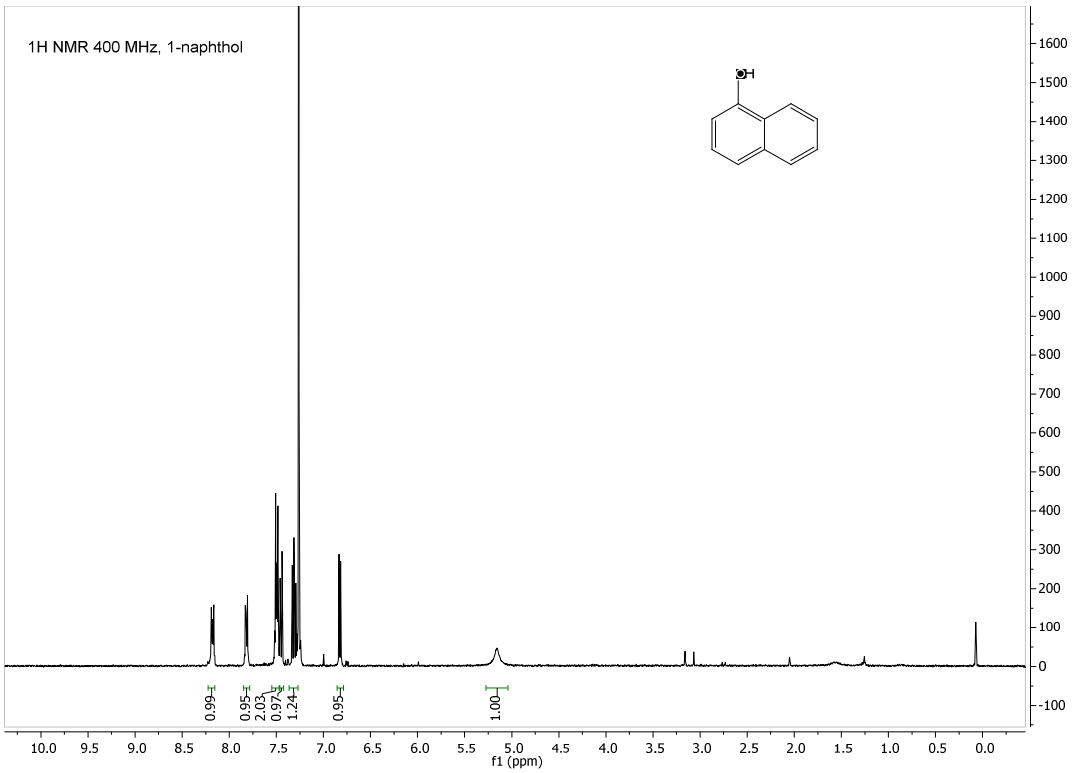

1H NMR 400 MHz, 4-cyanophenol
CN
2.13
2.00
0.92
f1 (ppm)

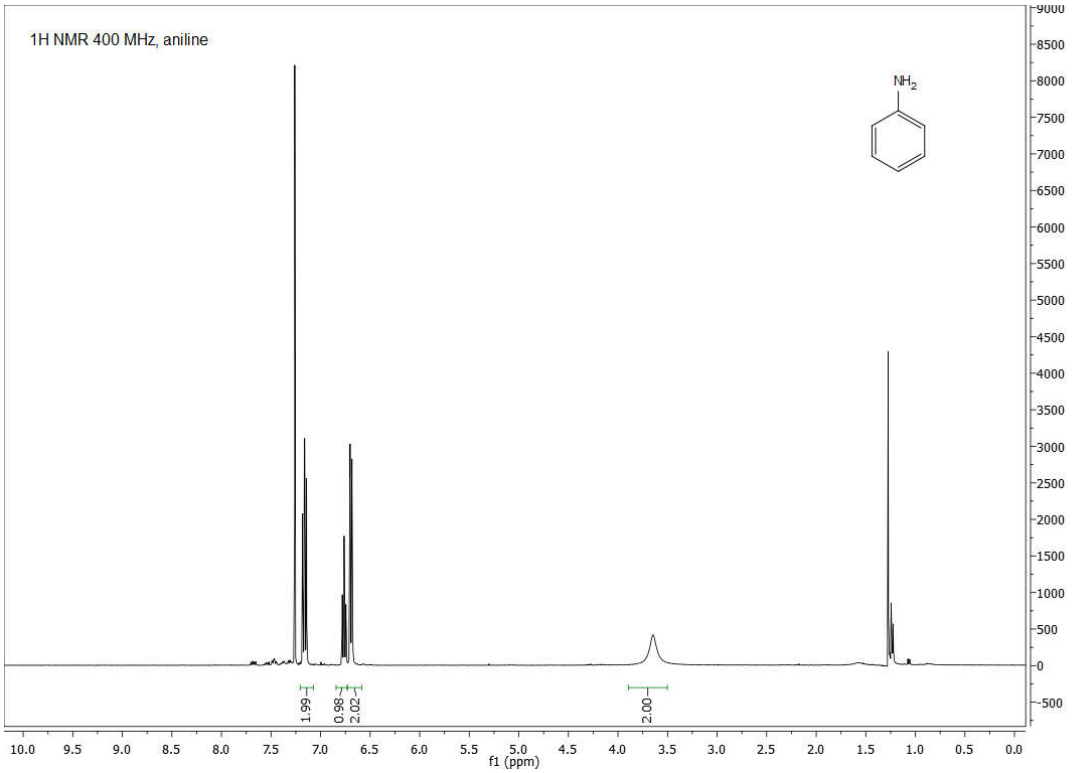

1H NMR 400 MHz, 2,4,6-trimethylphenol
2.21
1.16
9.00
f1 (ppm)

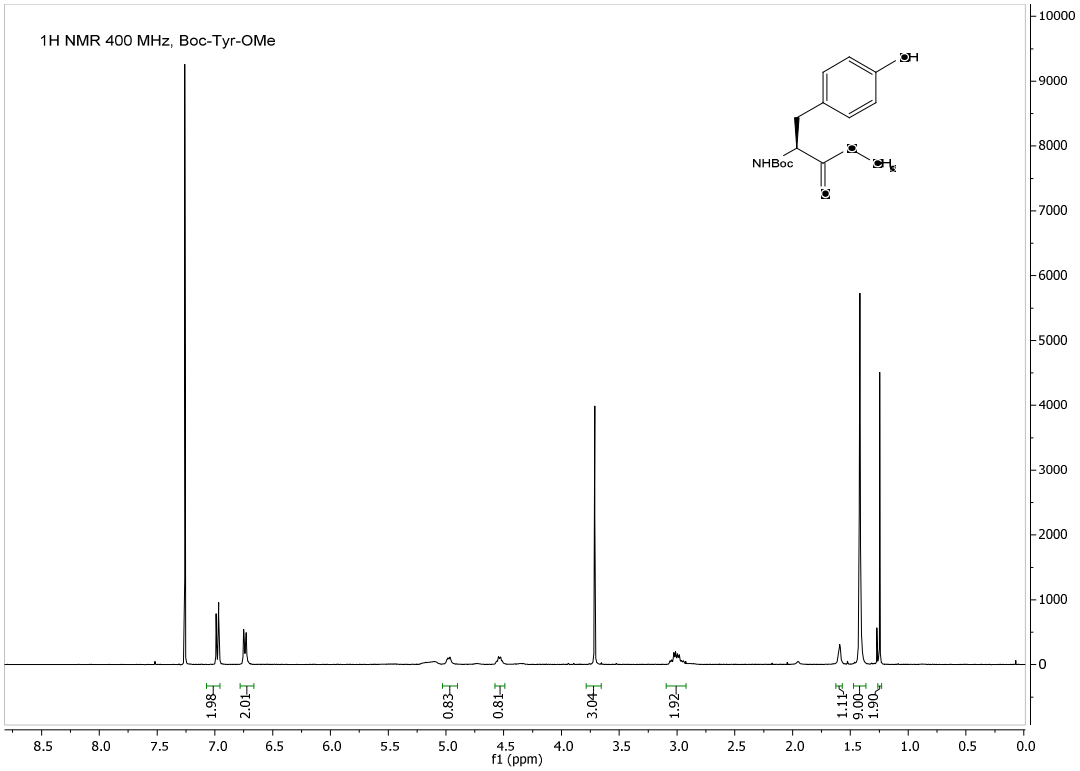

1H NMR 400 MHz, cyclohexanol
1.00
1.22
2.74
4.96
f1 (ppm)

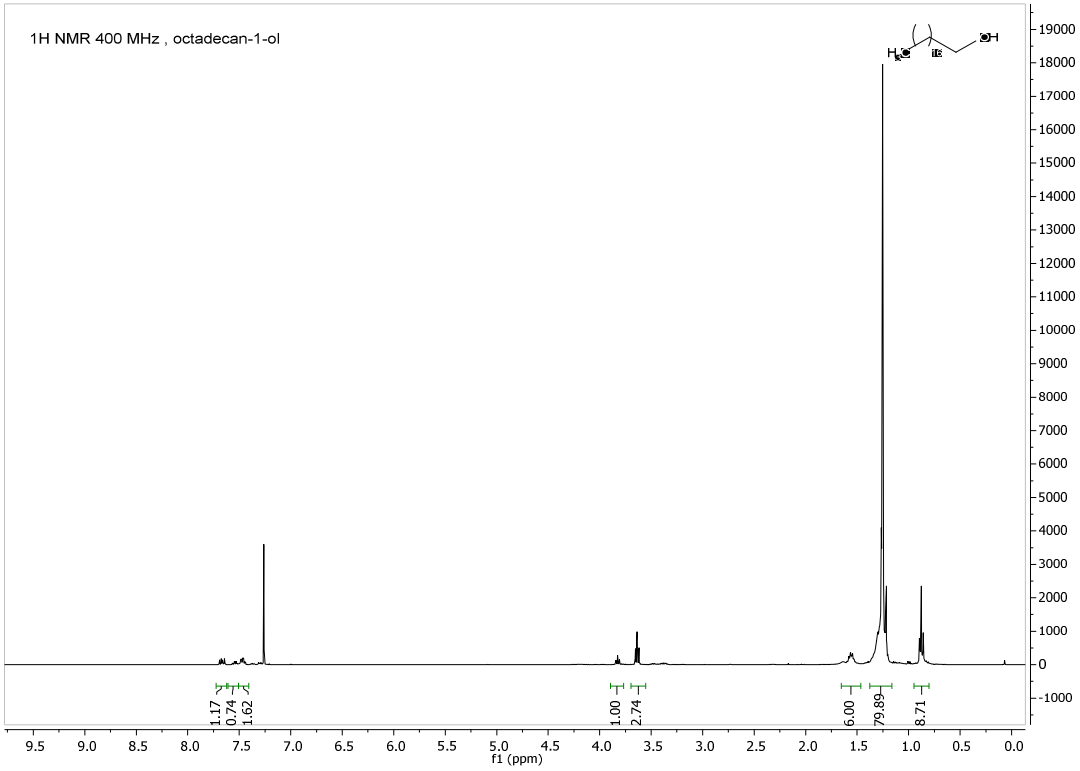

1H NMR 400 MHz, Benzoic acid
1.94
0.98
2.00
f1 (ppm)

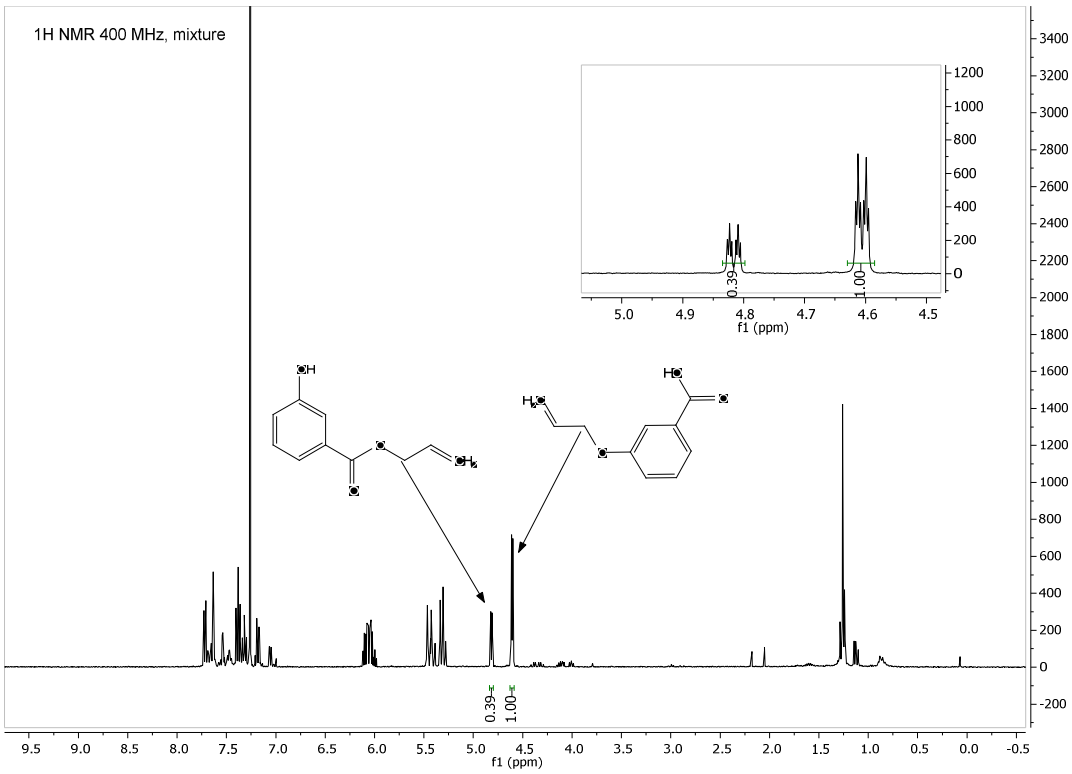

1H NMR 400 MHz, phenol
2.25
1.00
1.97
0.89
f1 (ppm)

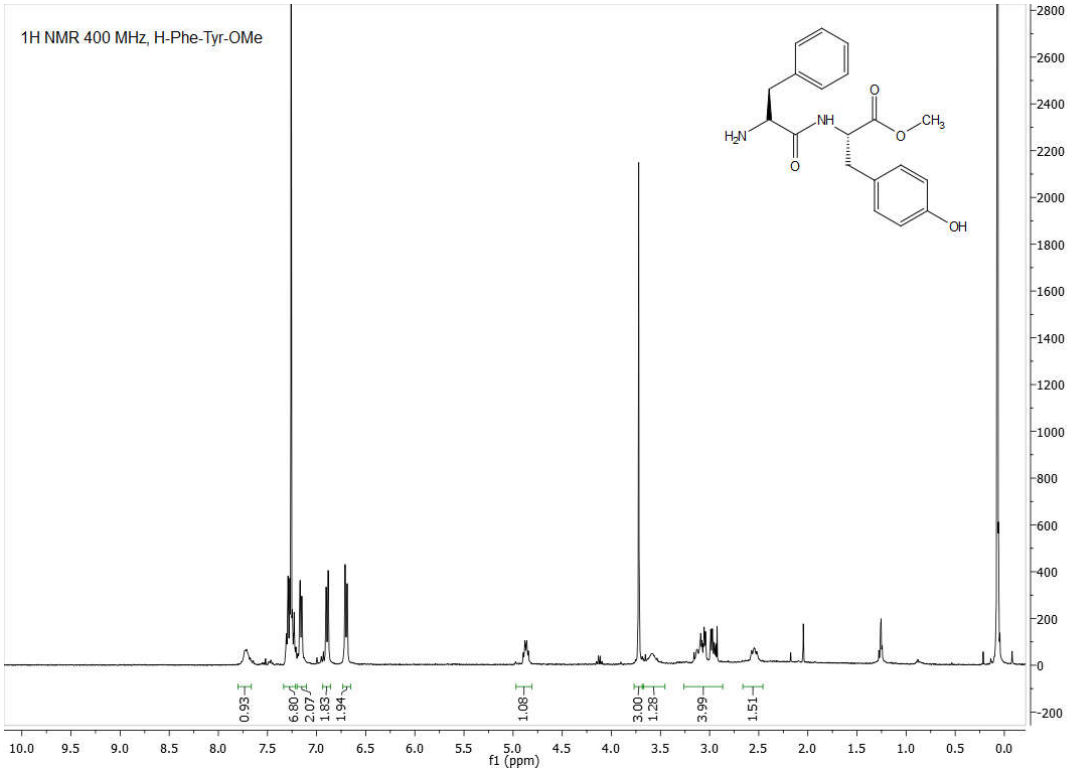

1H NMR 400 MHz, 1-naphthol
OH
0.99
0.95
2.03
0.97
1.24
0.95
1.00
f1 (ppm)

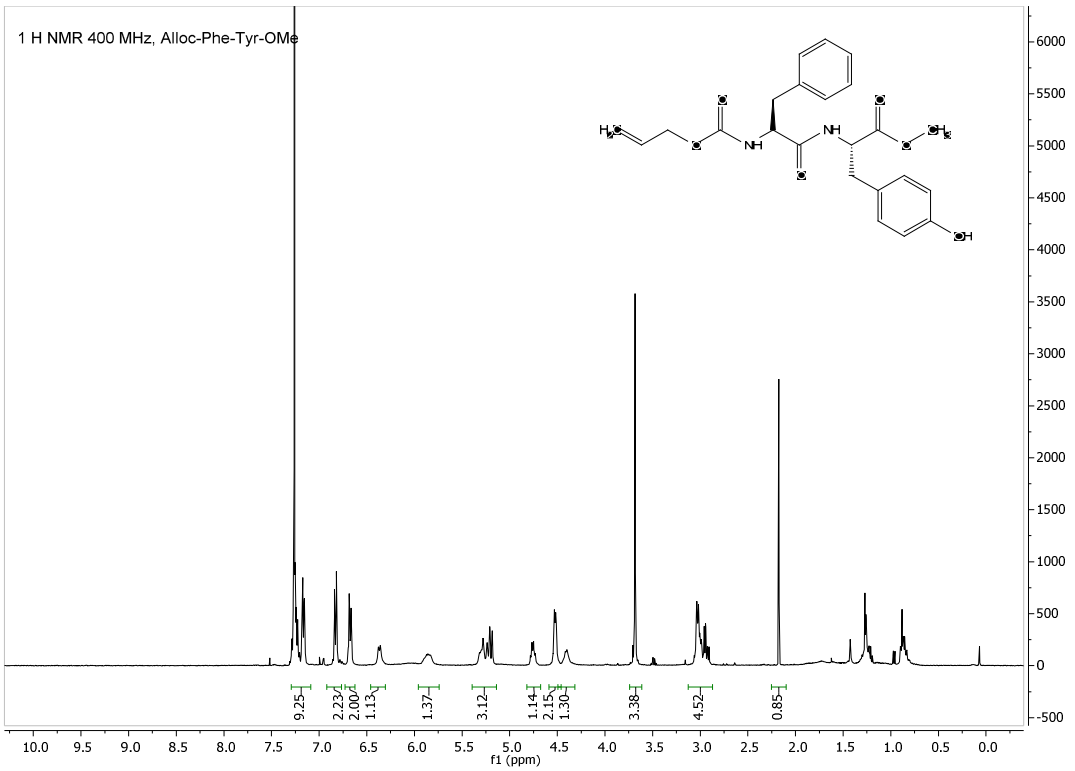

1H NMR 400 MHz, aniline
NH2
1.99
0.98
2.02
2.00
f1 (ppm)


1H NMR 400 MHz, Boc-Tyr-OMe
NHBoc
1.98
2.01
0.83
0.81
3.04
1.92
1.11
9.00
1.90
f1 (ppm)

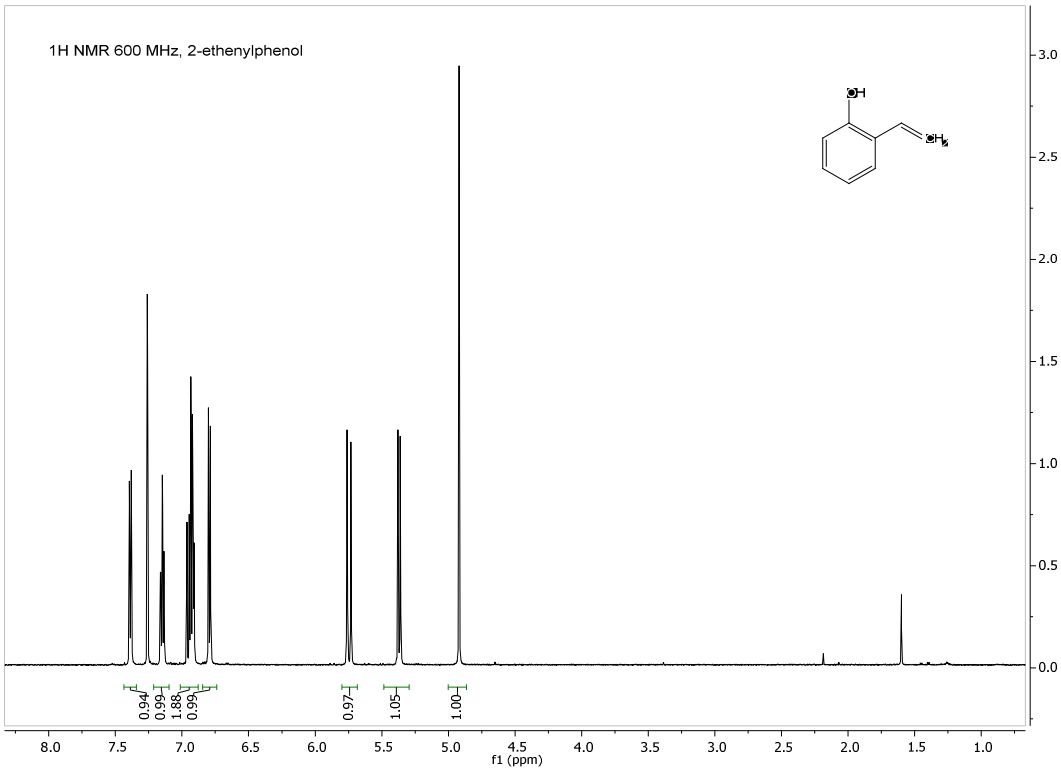

1H NMR 400 MHz , octadecan-1-ol
1.17
0.74
1.62
1.00
2.74
6.00
79.89
8.71
f1 (ppm)

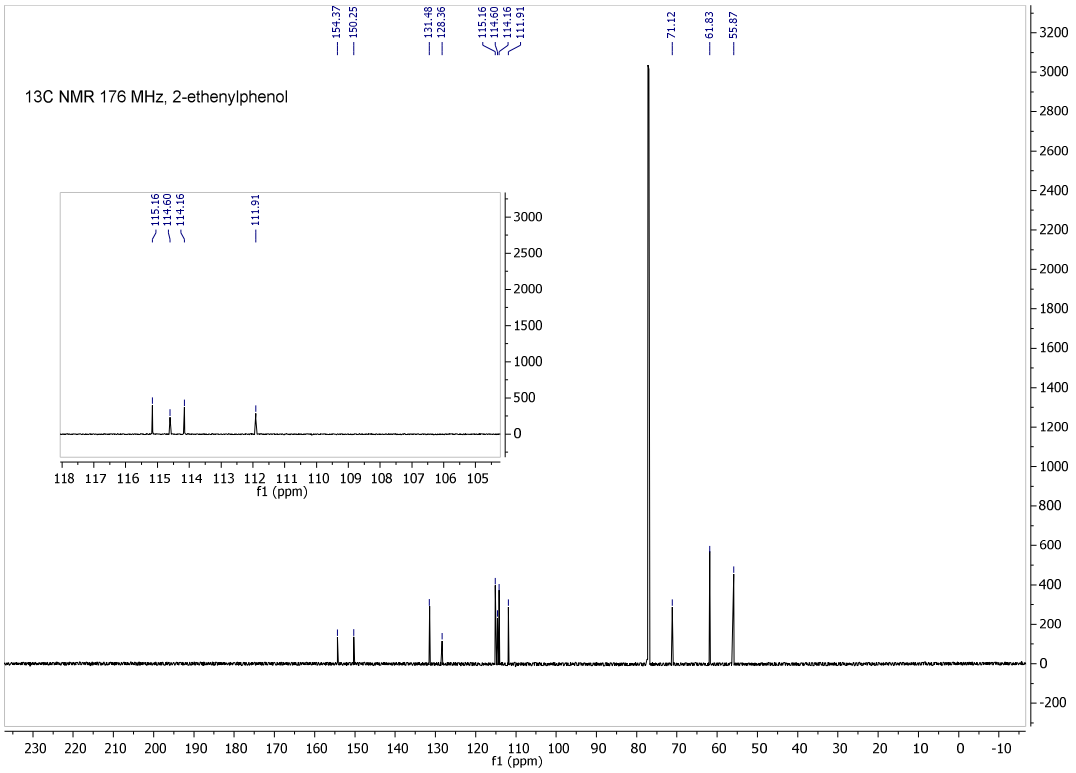

1H NMR 400 MHz, mixture
0.39
1.00
f1 (ppm)

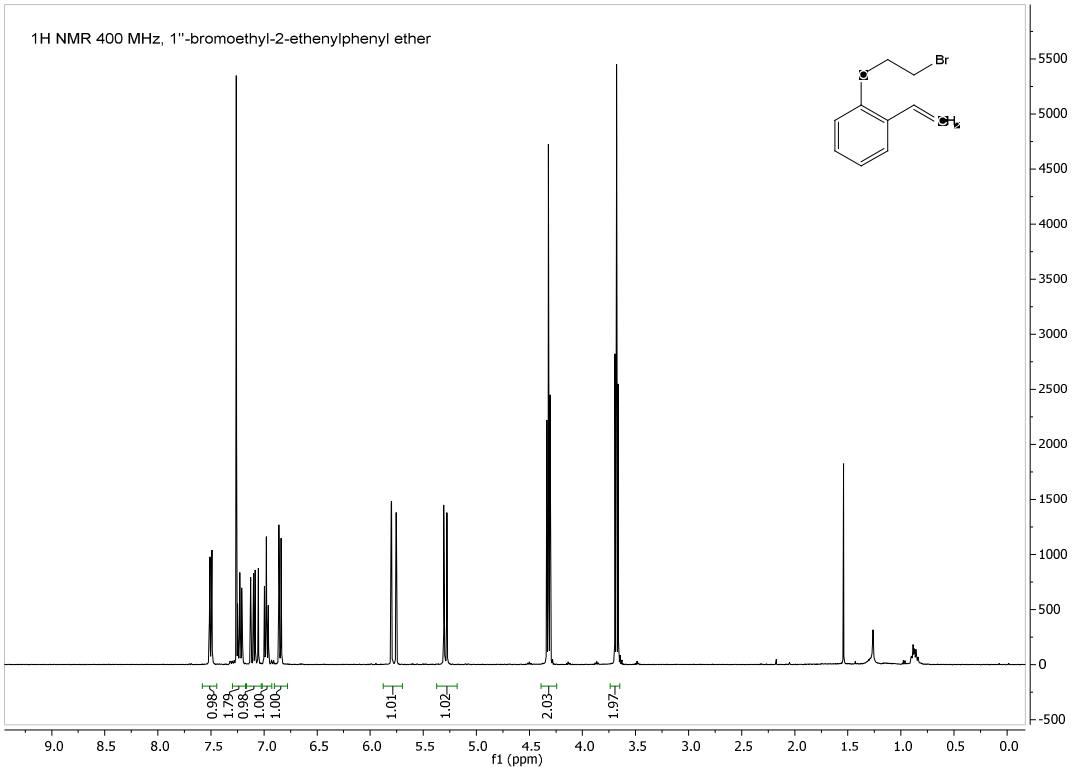

1H NMR 400 MHz, H-Phe-Tyr-OMe
0.93
6.80
2.07
1.83
1.94
1.08
3.00
1.28
3.99
1.51
f1 (ppm)

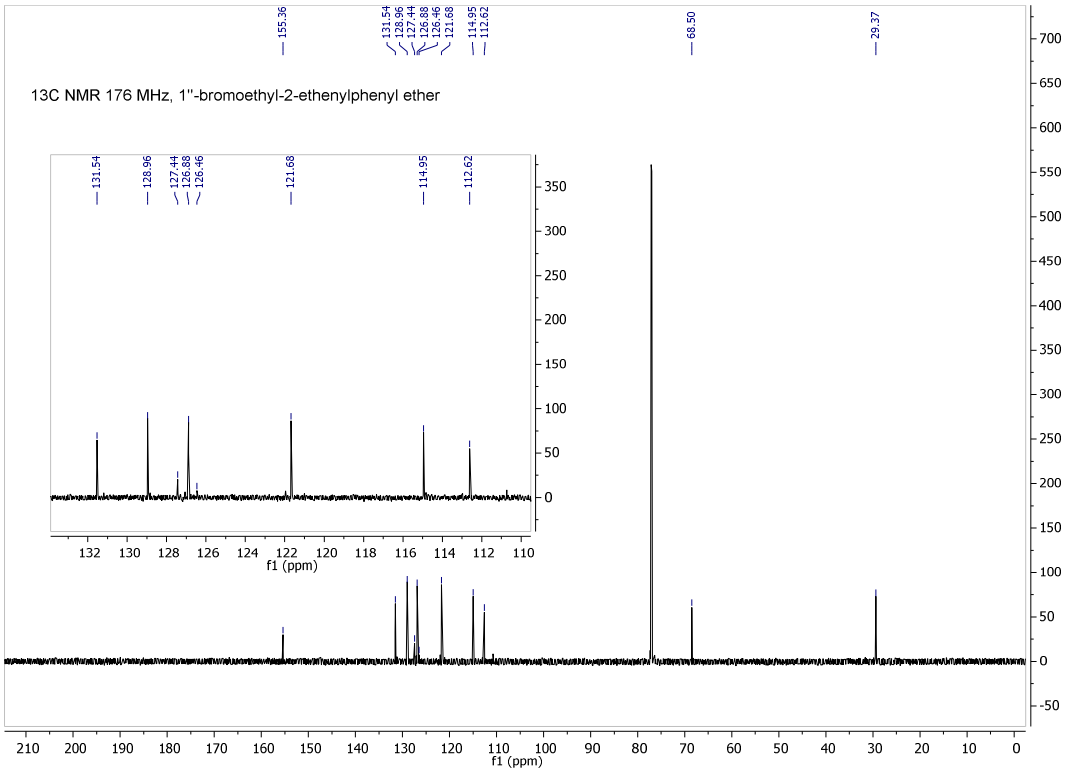


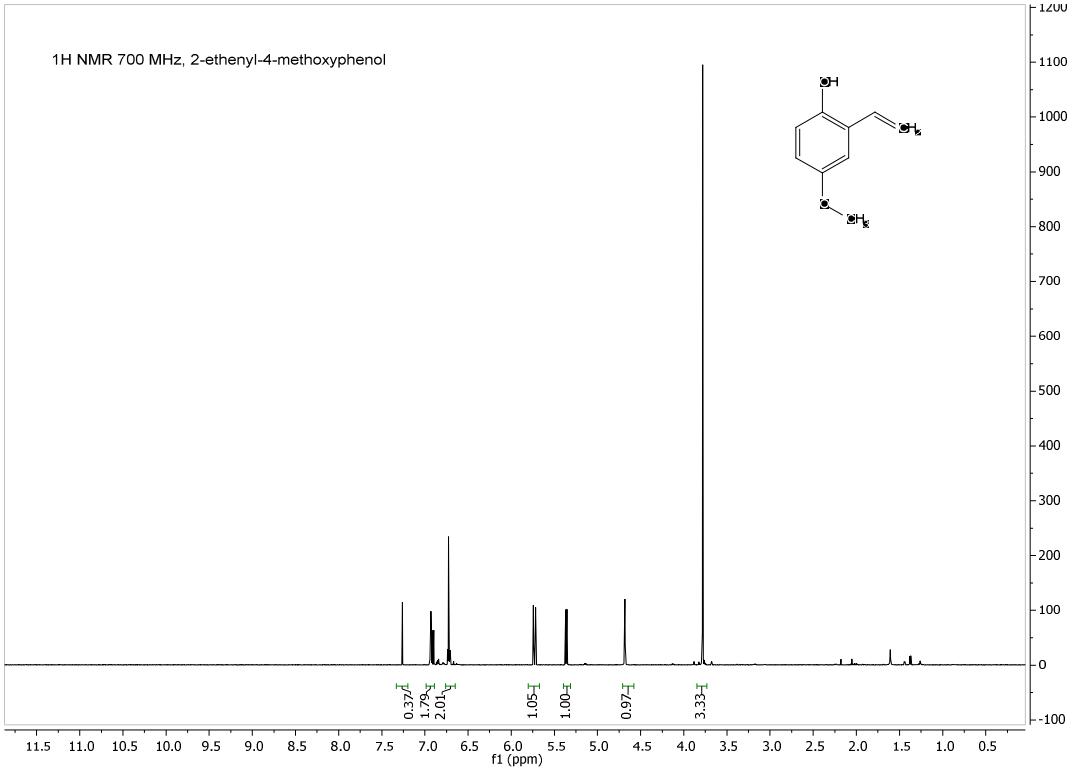
^{1}H & ^{13}C NMR spectra of compounds in chapter 4

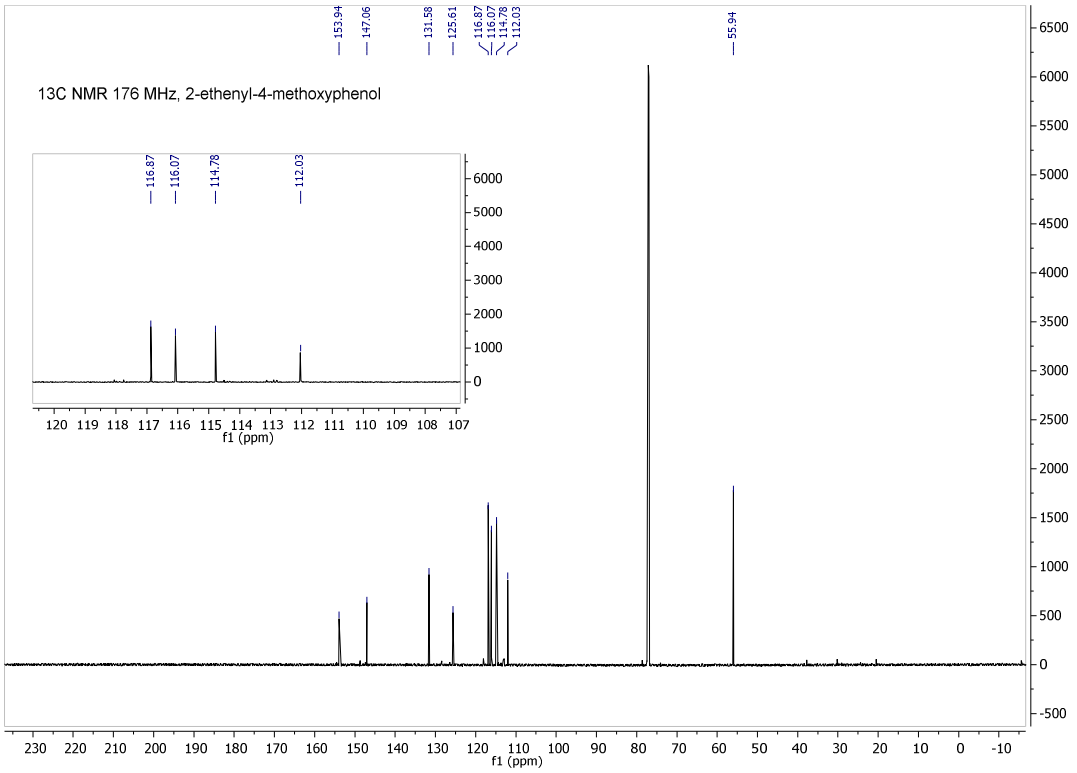


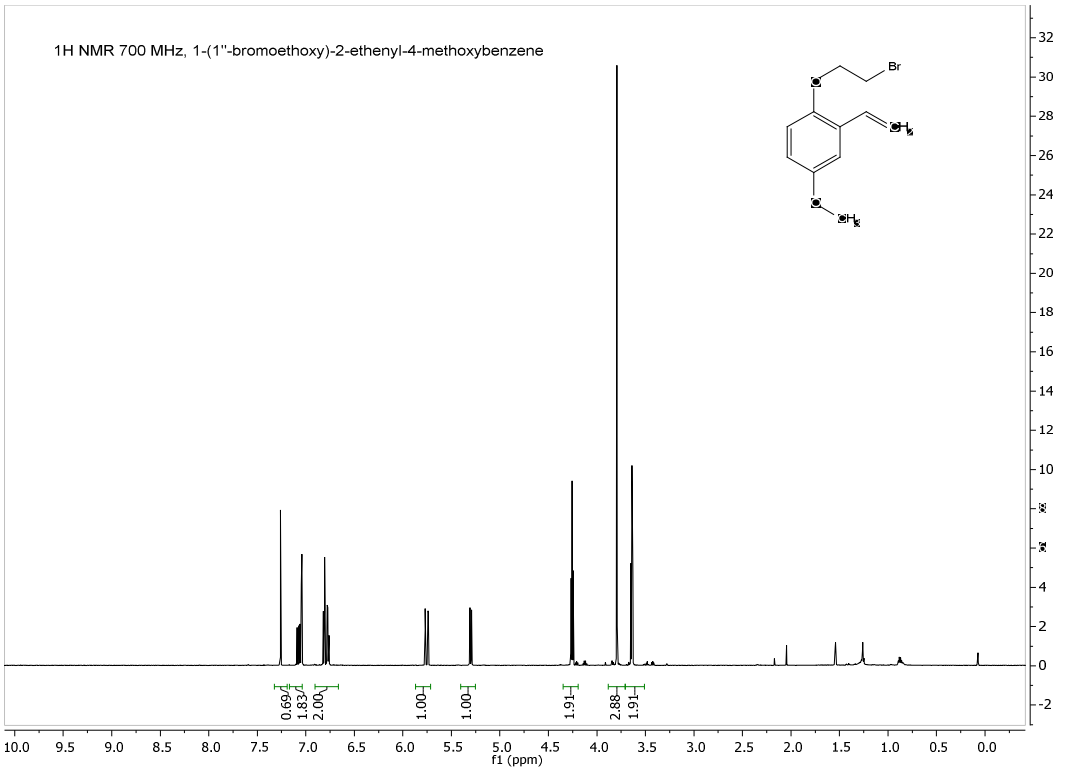

13C NMR 176 MHz, 2-ethenylphenol
154.37
150.25
131.48
128.36
115.16
114.60
114.16
111.91
71.12
61.83
55.87
f1 (ppm)

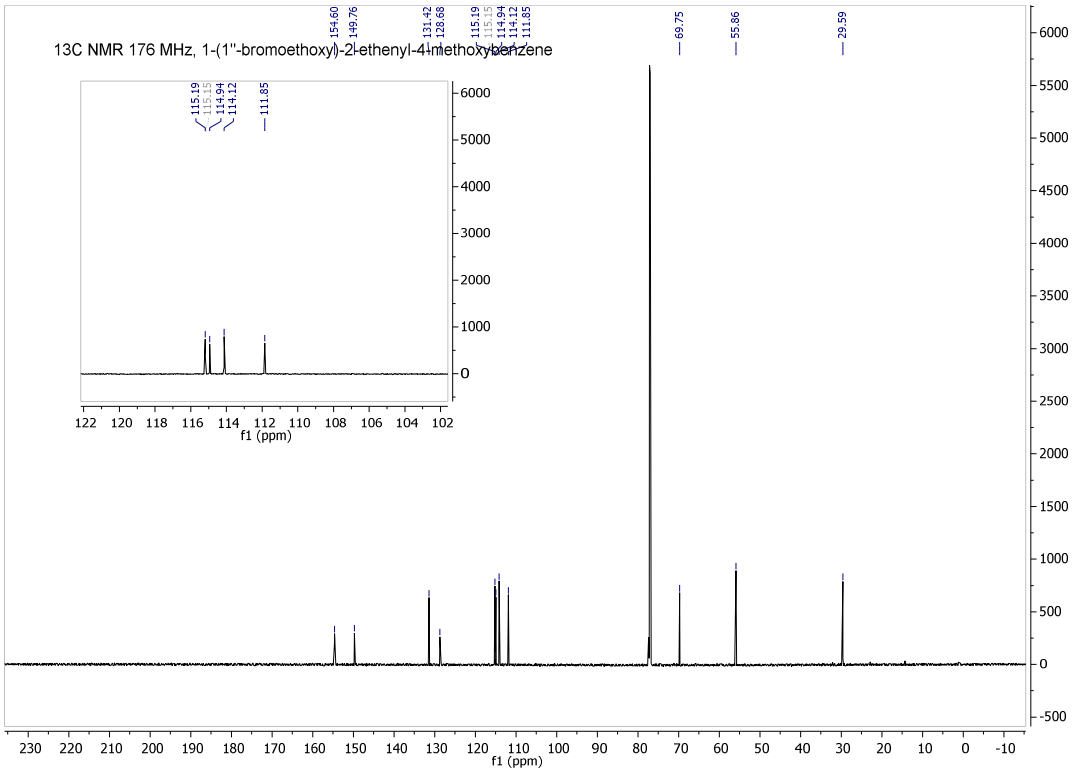

1H NMR 400 MHz, 1''-bromoethyl-2-ethenylphenyl ether
Br
0.98
1.79
0.98
1.00
1.03
1.01
1.02
2.03
1.97
f1 (ppm)

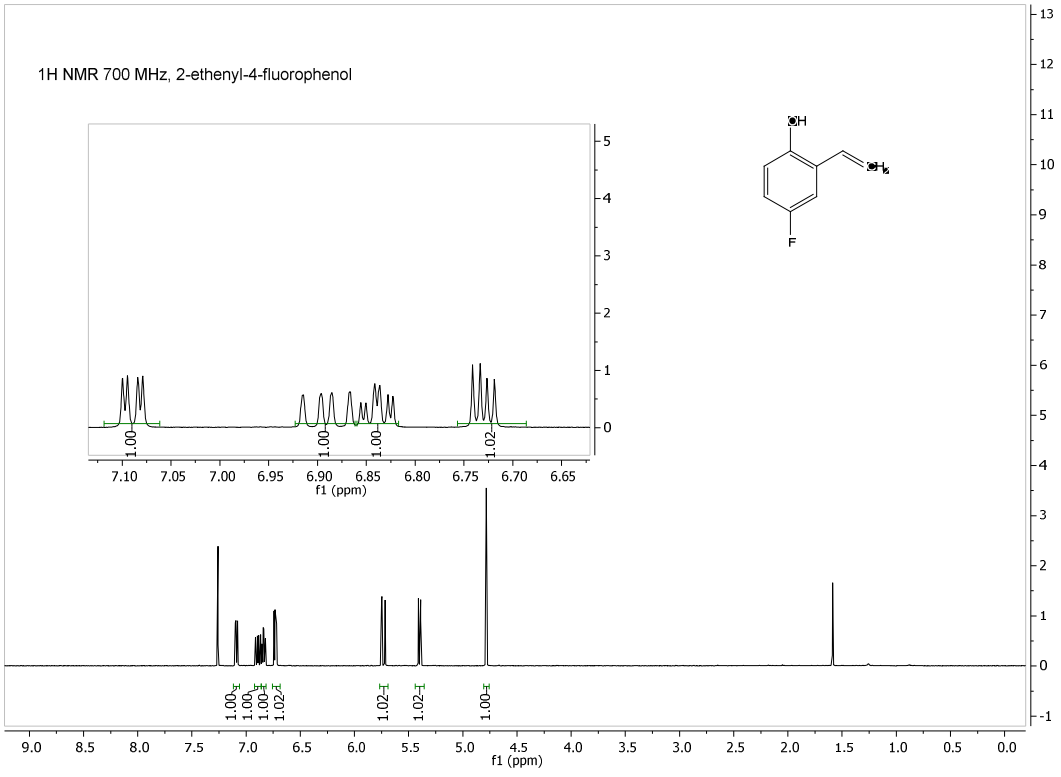

13C NMR 176 MHz, 1''-bromoethyl-2-ethenylphenyl ether
155.36
131.54
128.96
127.44
126.88
126.46
121.68
114.95
112.62
68.50
29.37
f1 (ppm)

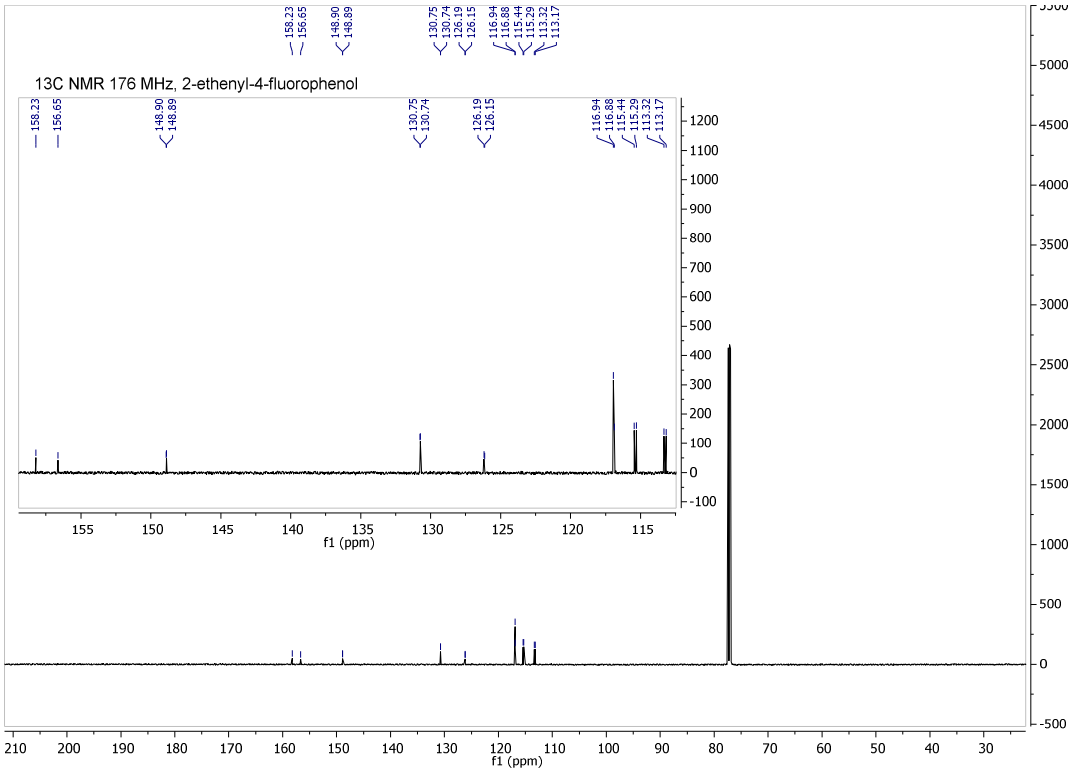

1H NMR 700 MHz, 2-ethenyl-4-methoxyphenol
0.37
1.79
2.01
1.05
1.00
0.97
3.33
f1 (ppm)

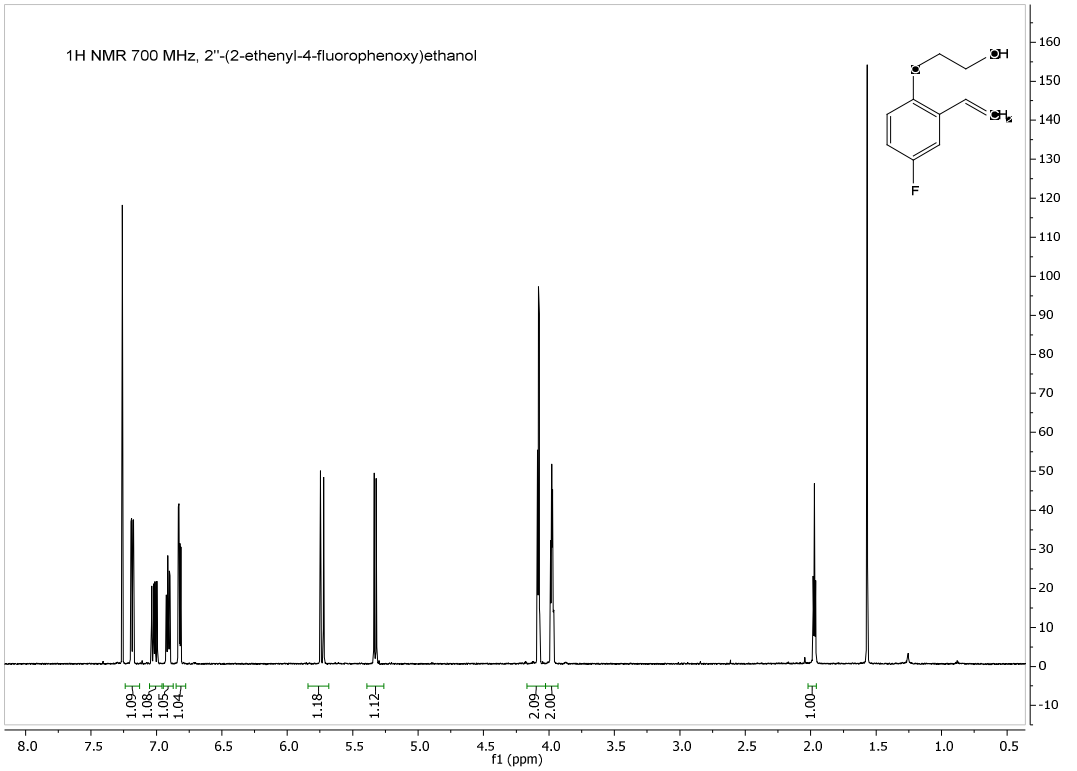

13C NMR 176 MHz, 2-ethenyl-4-methoxyphenol
153.94
147.06
131.58
125.61
116.87
116.07
114.78
112.03
55.94
f1 (ppm)

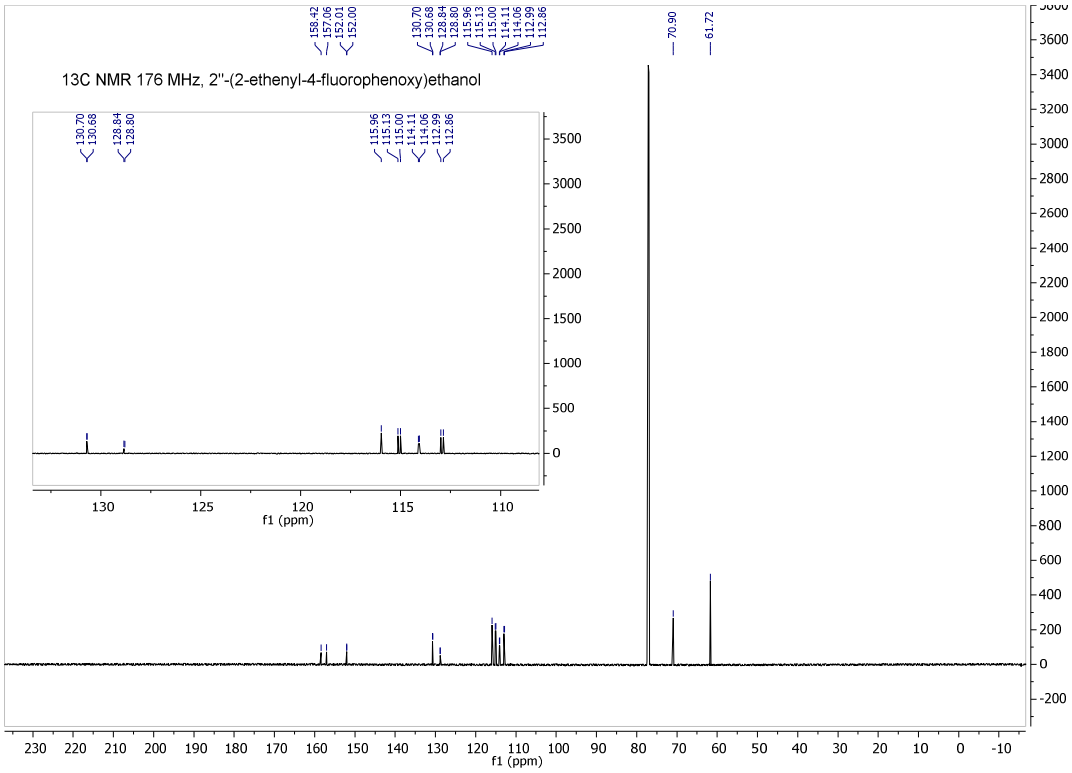

1H NMR 700 MHz, 1-(1''-bromoethoxy)-2-ethenyl-4-methoxybenzene
Br
0.69
1.83
2.00
1.00
1.00
1.91
2.88
1.91
f1 (ppm)

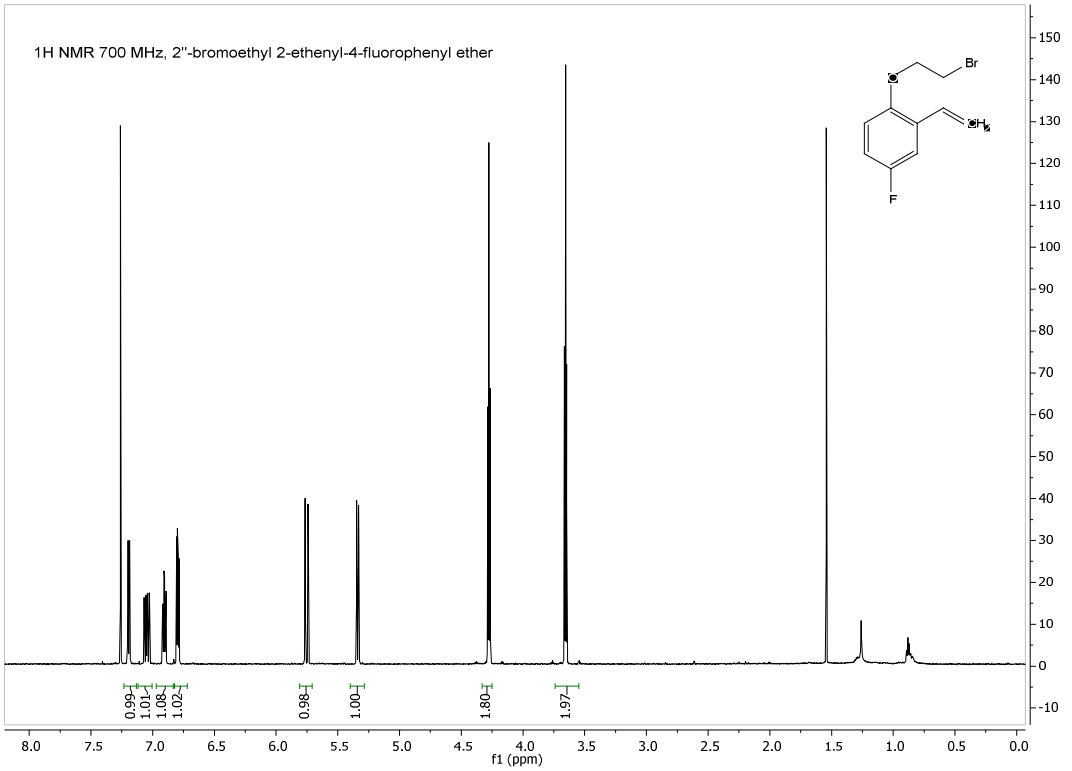

13C NMR 176 MHz, 1-(1''-bromoethoxyl)-2-ethenyl-4-methoxybenzene
154.60
149.76
131.42
128.68
115.19
115.15
114.94
114.12
111.85
69.75
55.86
29.59
f1 (ppm)

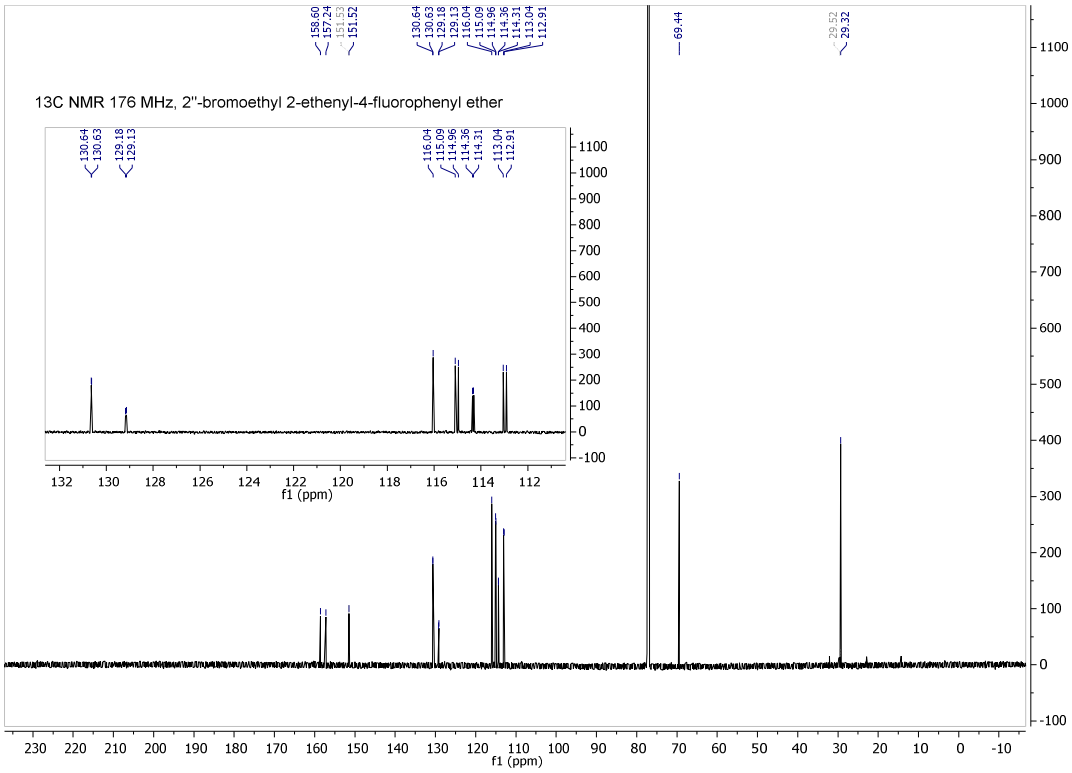

1H NMR 700 MHz, 2-ethenyl-4-fluorophenol
OH
H
H
F
1.00
1.00
1.00
1.02
1.00
1.00
1.02
1.02
1.00
f1 (ppm)

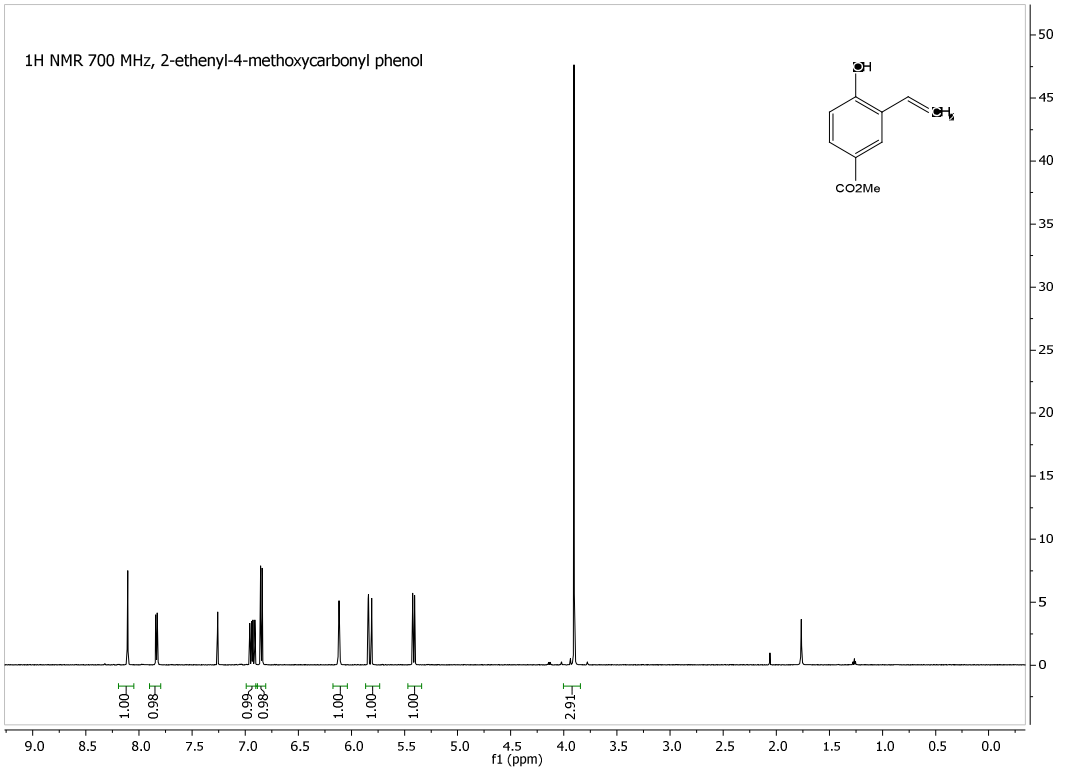

13C NMR 176 MHz, 2-ethenyl-4-fluorophenol
158.23
156.65
148.90
148.89
130.75
130.74
126.19
126.15
116.94
116.88
115.44
115.29
113.32
113.17
f1 (ppm)

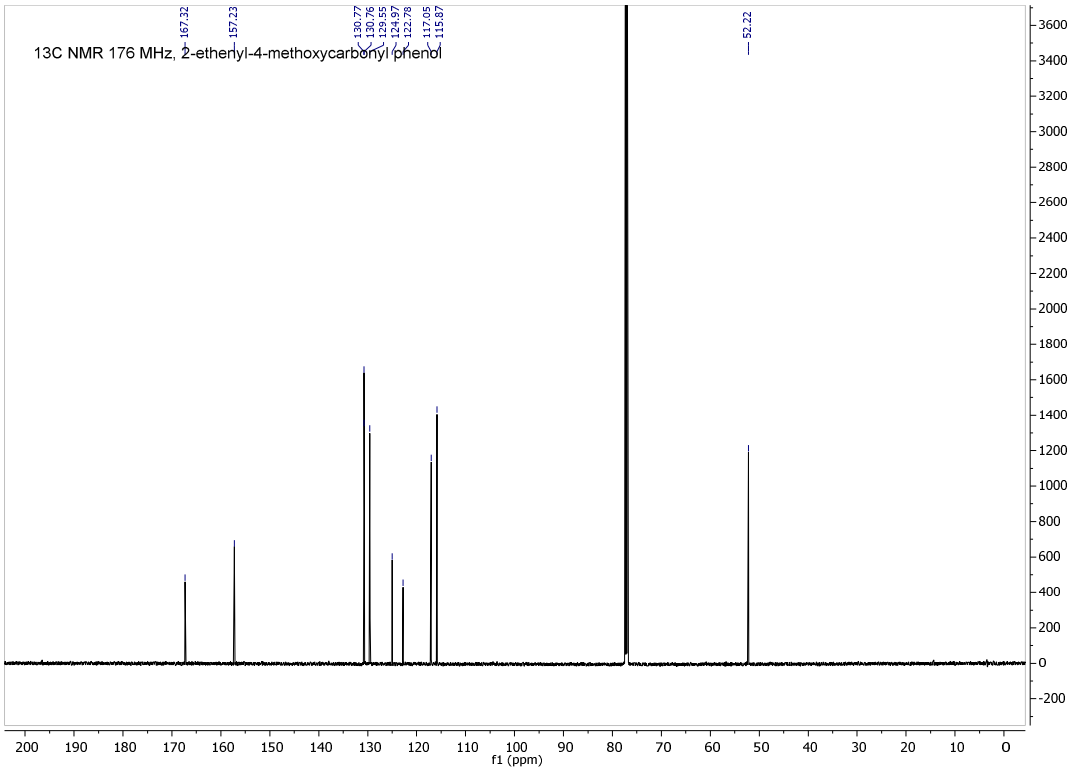

1H NMR 700 MHz, 2''-(2-ethenyl-4-fluorophenoxy)ethanol
1.09
1.08
1.05
1.04
1.18
1.12
2.09
2.00
1.00
f1 (ppm)

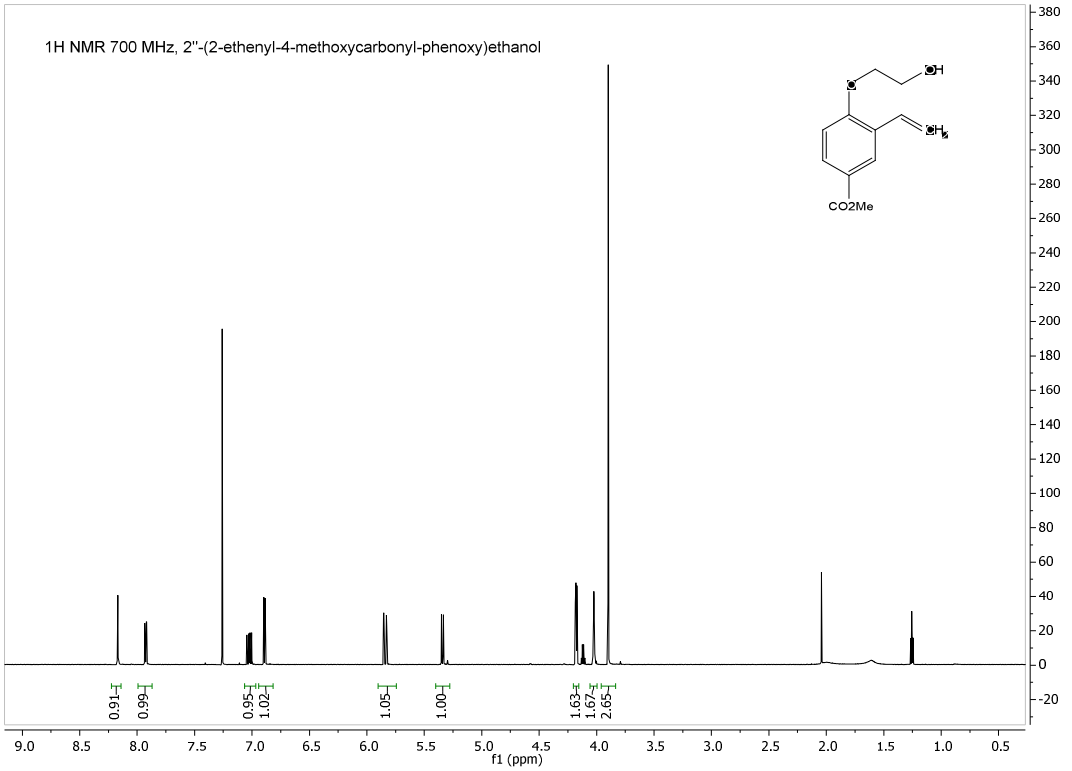

13C NMR 176 MHz, 2''-(2-ethenyl-4-fluorophenoxy)ethanol
158.42
157.06
152.01
152.00
130.70
130.68
128.84
128.80
115.96
115.13
115.00
114.11
114.06
112.99
112.86
70.90
61.72
f1 (ppm)

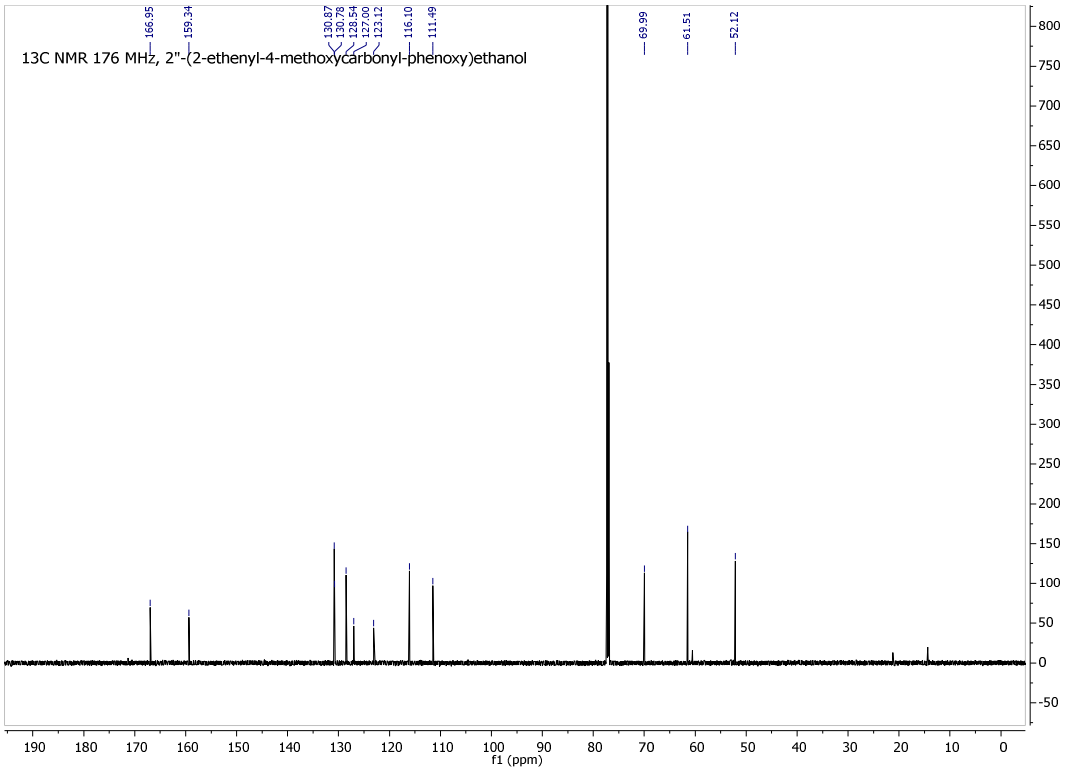

1H NMR 700 MHz, 2''-bromoethyl 2-ethenyl-4-fluorophenyl ether
Br
F
0.99
1.01
1.08
1.02
0.98
1.00
1.80
1.97
f1 (ppm)

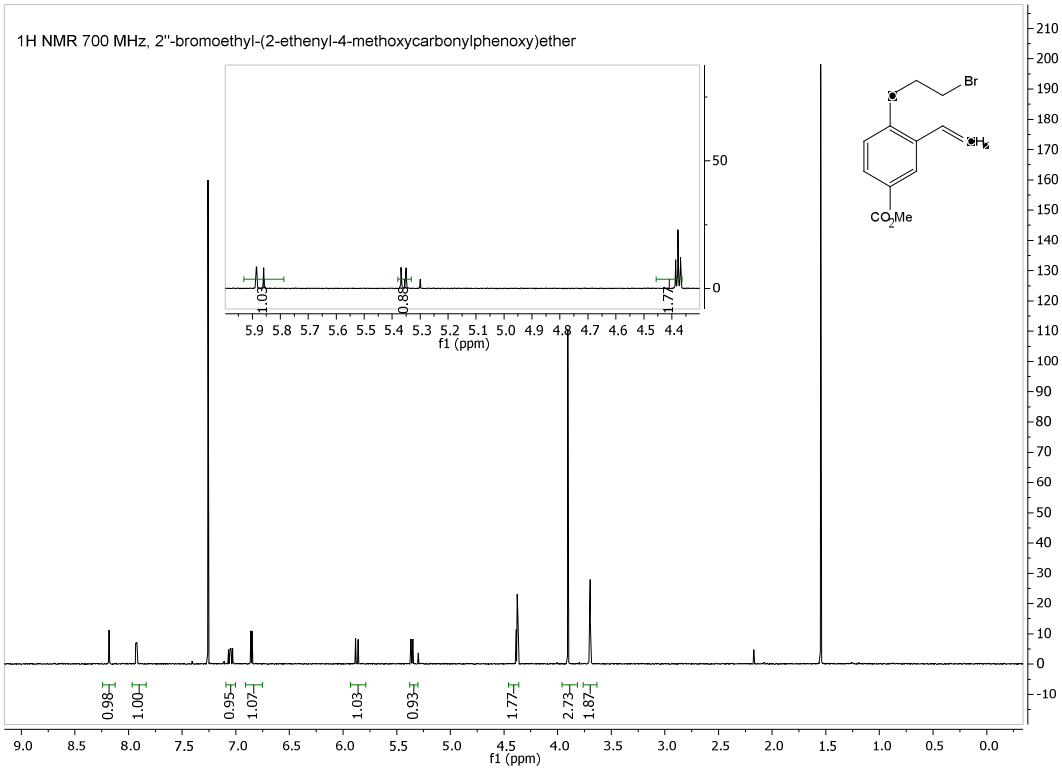

13C NMR 176 MHz, 2''-bromoethyl 2-ethenyl-4-fluorophenyl ether
158.60
157.24
151.53
151.52
130.64
130.63
129.18
129.13
116.04
115.09
114.96
114.36
114.31
113.04
112.91
69.44
29.52
29.32
f1 (ppm)

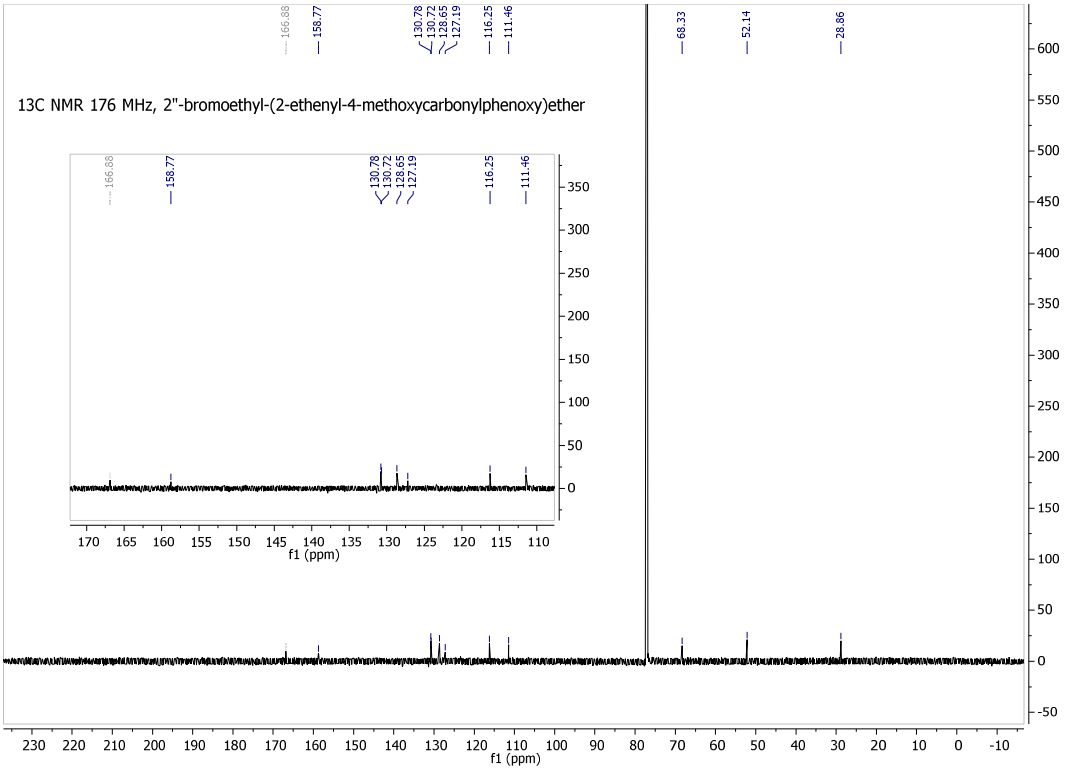

1H NMR 700 MHz, 2-ethenyl-4-methoxycarbonyl phenol
OH
CO2Me
1.00
0.98
0.99
0.98
1.00
1.00
1.00
2.91
f1 (ppm)

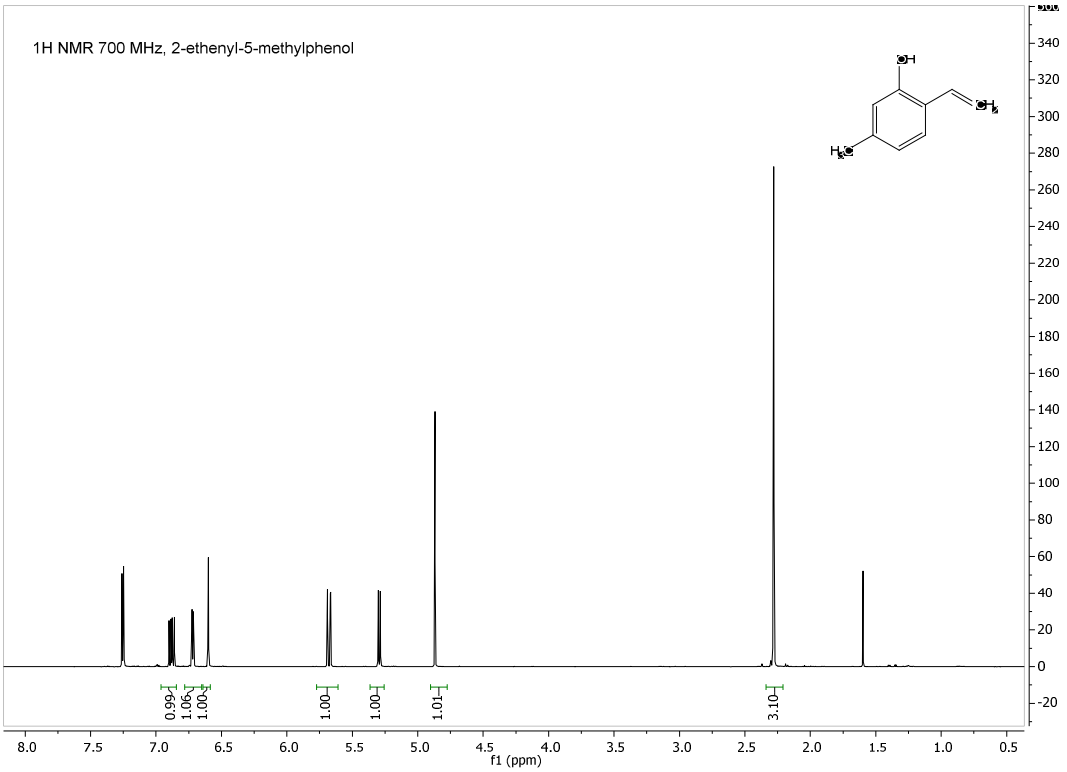

13C NMR 176 MHz, 2-ethenyl-4-methoxycarbonyl phenol
167.32
157.23
130.77
130.76
129.55
124.97
122.78
117.05
115.87
52.22
f1 (ppm)

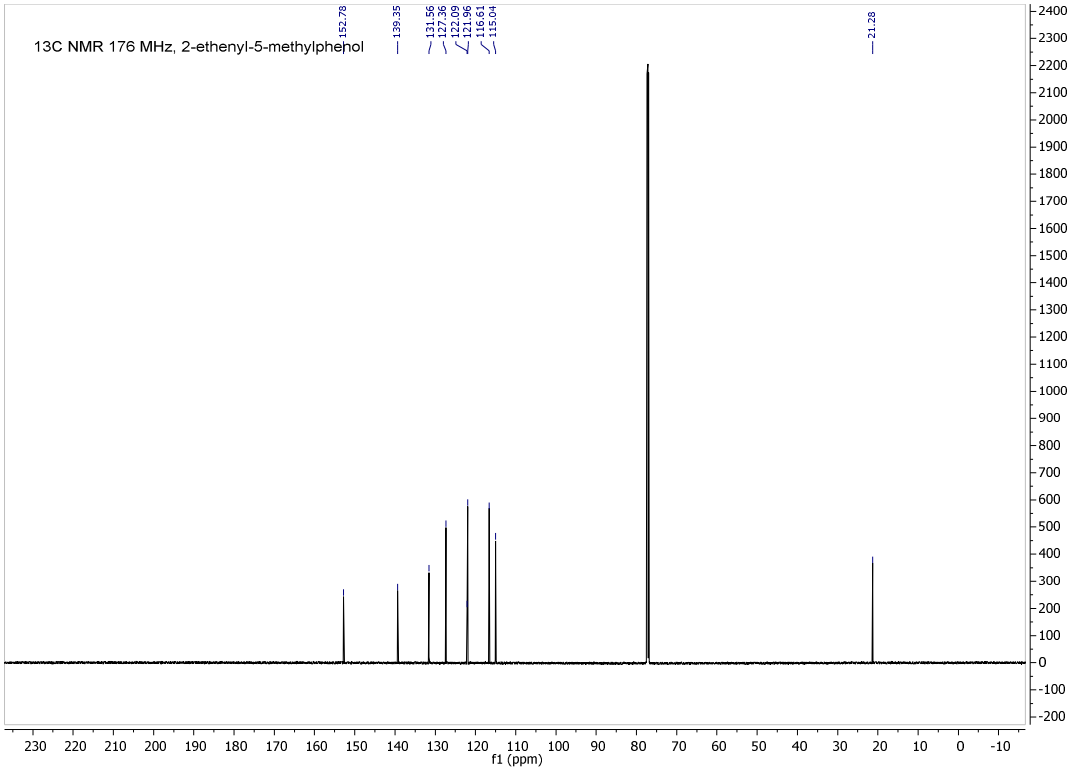

1H NMR 700 MHz, 2''-(2-ethenyl-4-methoxycarbonyl-phenoxy)ethanol
CO2Me
0.91
0.99
0.95
1.02
1.05
1.00
1.63
1.67
2.65
f1 (ppm)

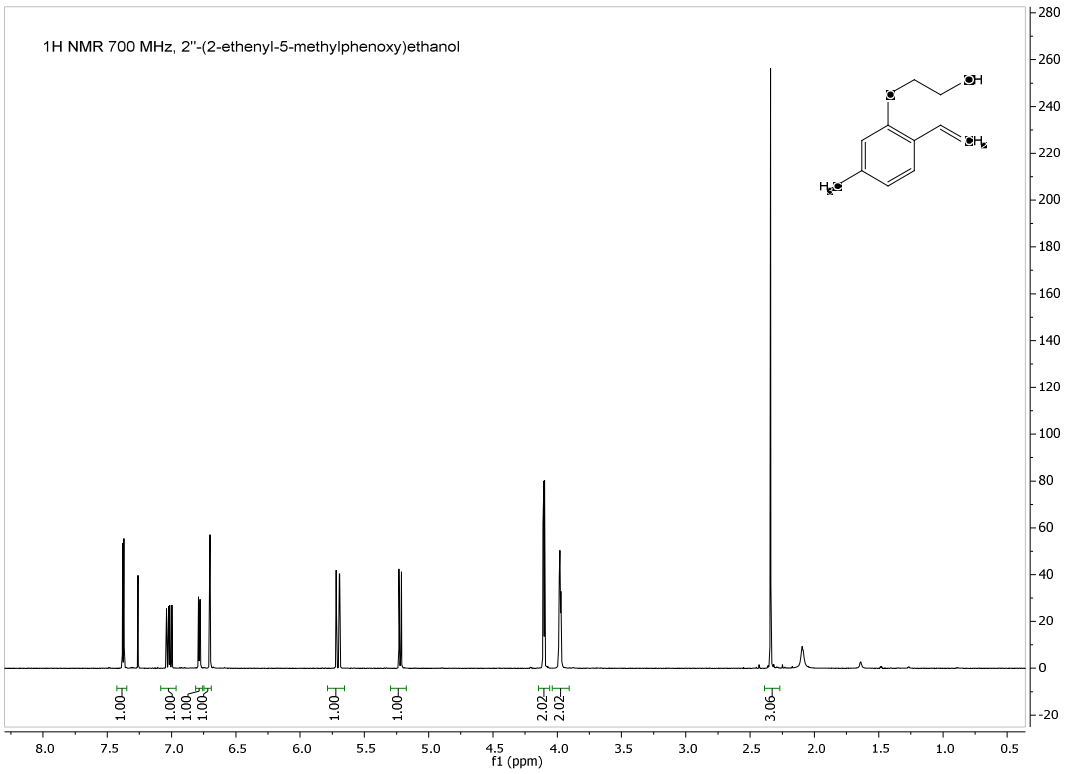

13C NMR 176 MHz, 2"-(2-ethenyl-4-methoxycarbonyl-phenoxy)ethanol
166.95
159.34
130.87
130.78
128.54
127.00
123.12
116.10
111.49
69.99
61.51
52.12
f1 (ppm)

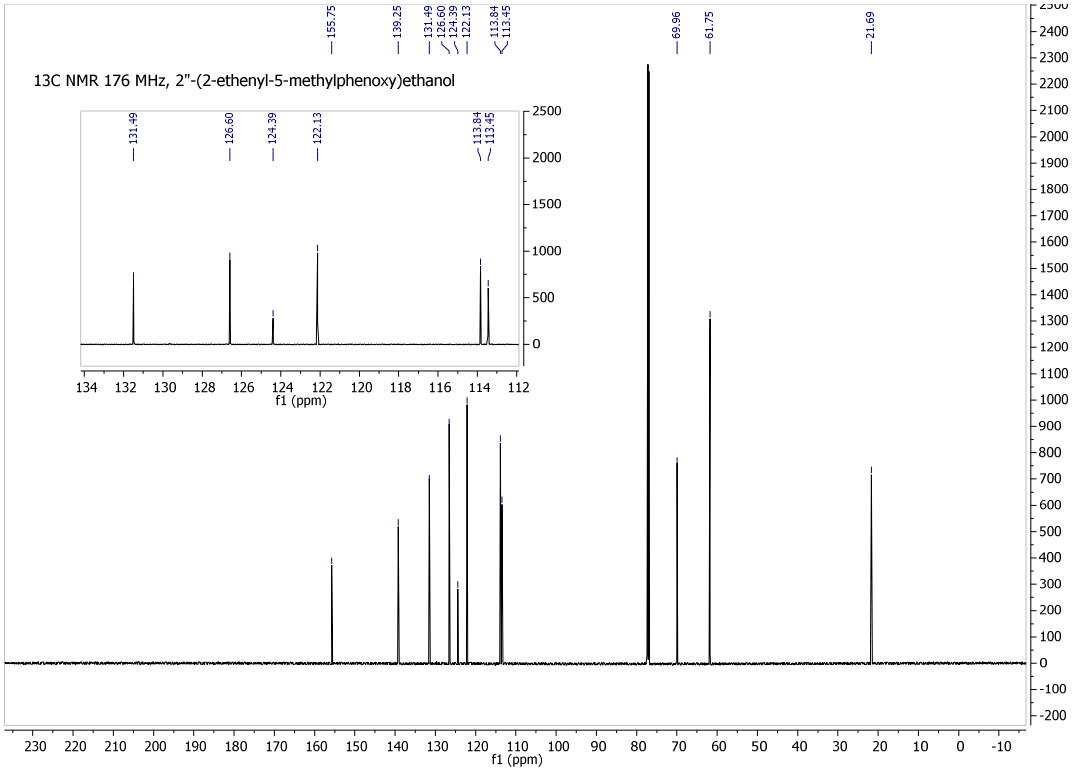

1H NMR 700 MHz, 2"-bromoethyl-(2-ethenyl-4-methoxycarbonylphenoxy)ether
Br
CO2Me
1.03
0.88
1.77
0.98
1.00
0.95
1.07
1.03
0.93
1.77
2.73
1.87
f1 (ppm)

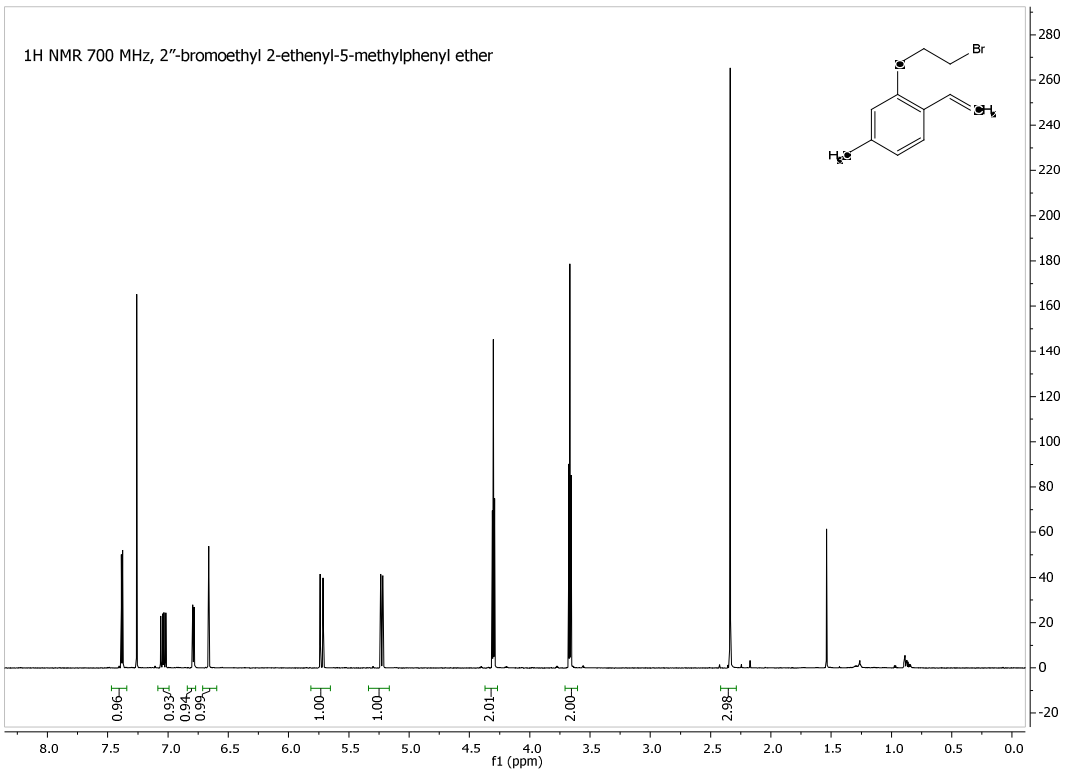

13C NMR 176 MHz, 2"-bromoethyl-(2-ethenyl-4-methoxycarbonylphenoxy)ether
166.88
158.77
130.78
130.72
128.65
127.19
116.25
111.46
68.33
52.14
28.86
f1 (ppm)

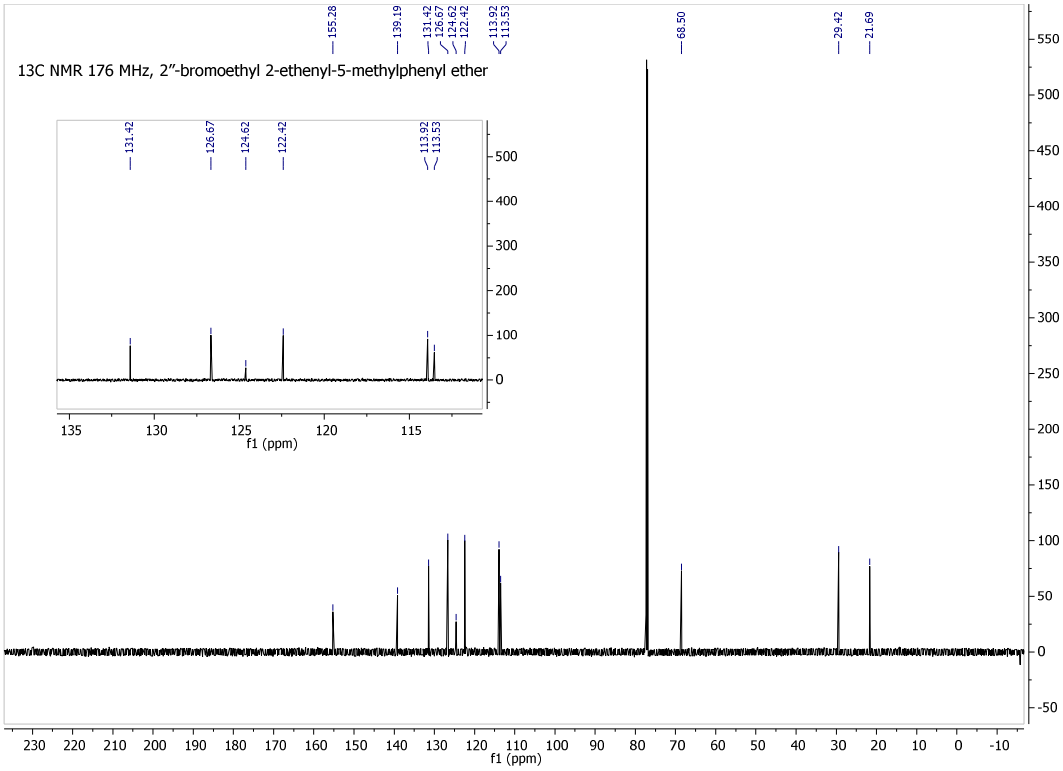

1H NMR 700 MHz, 2-ethenyl-5-methylphenol
0.99
1.06
1.00
1.00
1.00
1.01
3.10
f1 (ppm)

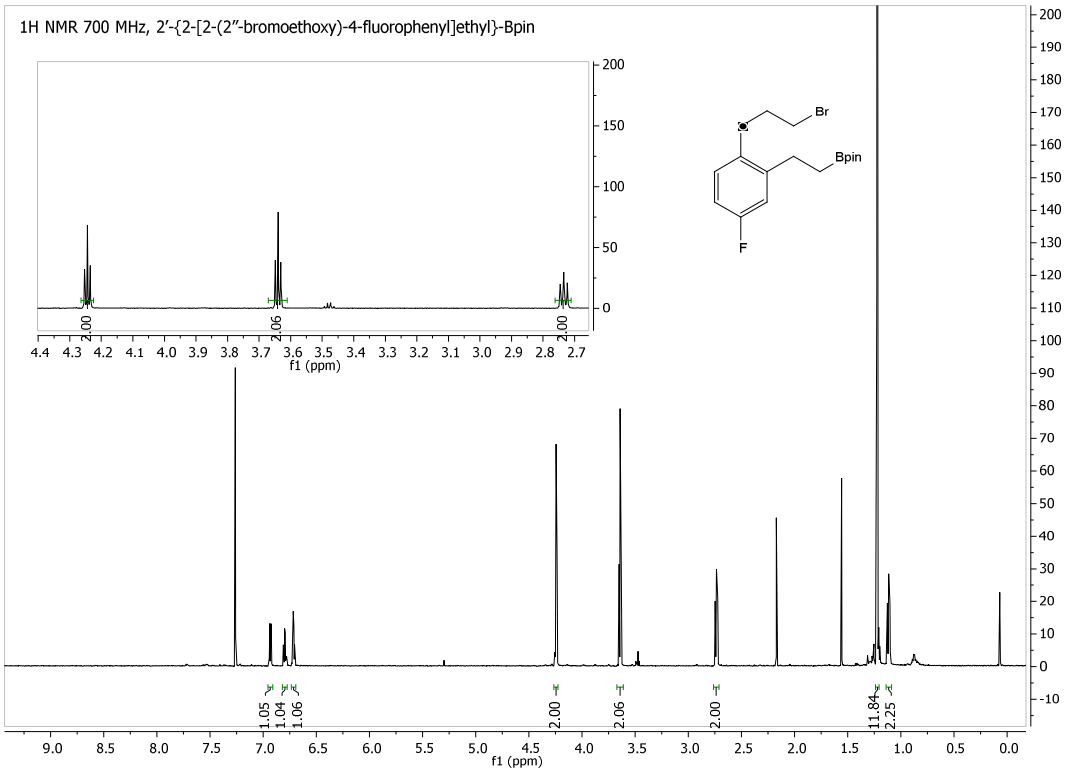

13C NMR 176 MHz, 2-ethenyl-5-methylphenol
152.78
139.35
131.56
127.36
122.09
121.96
116.61
115.04
21.28
f1 (ppm)

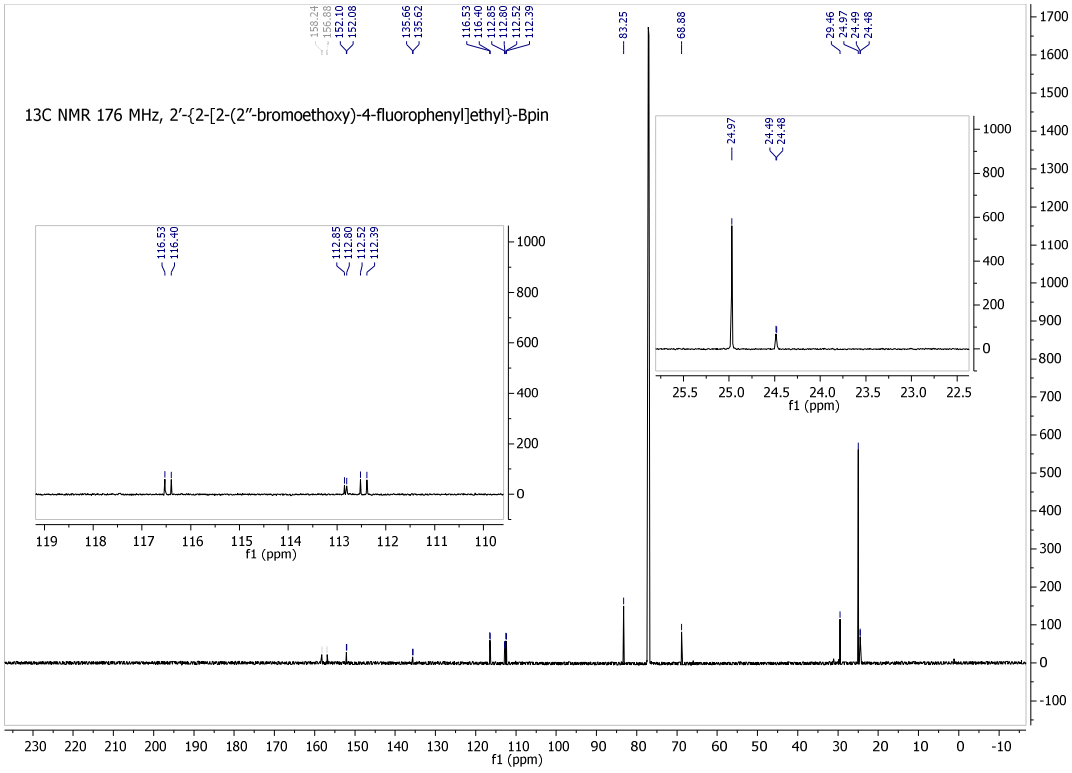

1H NMR 700 MHz, 2''-(2-ethenyl-5-methylphenoxy)ethanol
1.00
1.00
1.00
1.00
1.00
2.02
2.02
3.06
f1 (ppm)

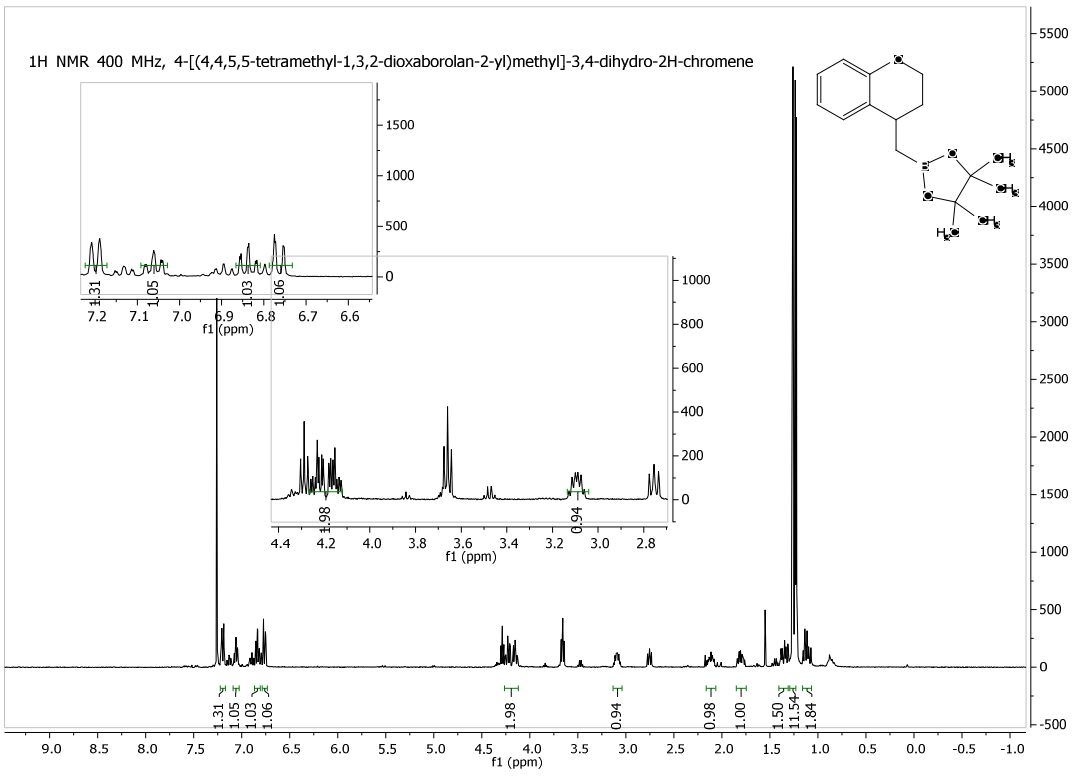

13C NMR 176 MHz, 2"-(2-ethenyl-5-methylphenoxy)ethanol
155.75
139.25
131.49
126.60
124.39
122.13
113.84
113.45
69.96
61.75
21.69
f1 (ppm)

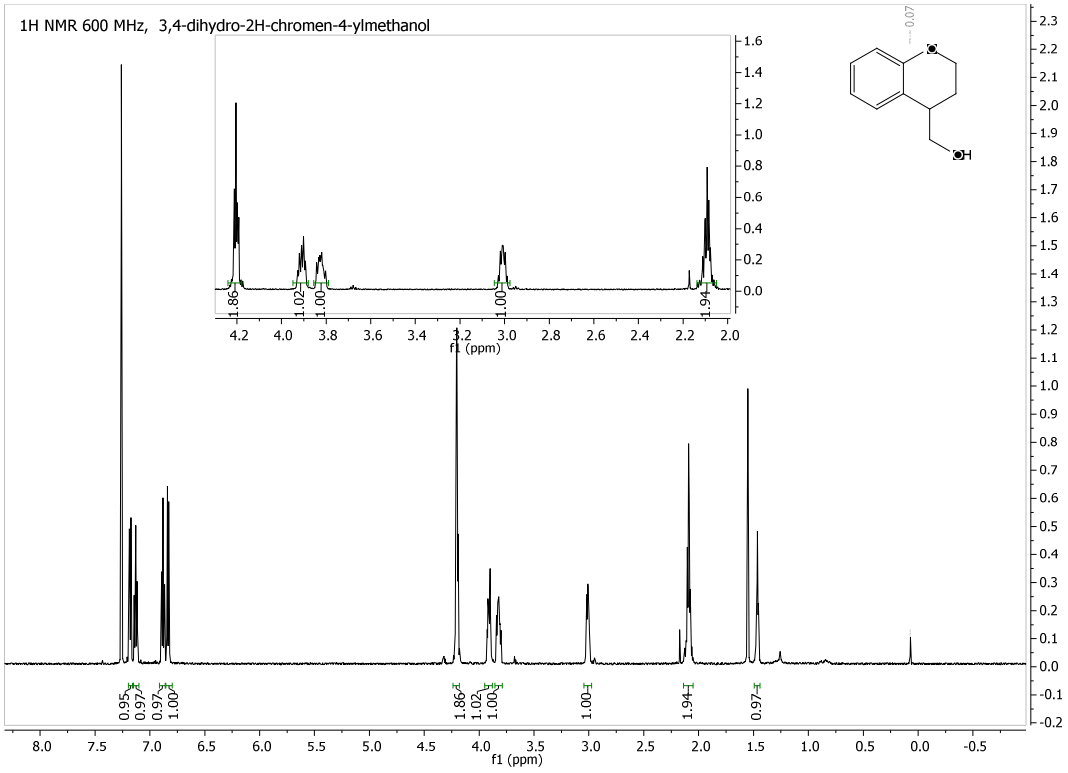

1H NMR 700 MHz, 2"-bromoethyl 2-ethenyl-5-methylphenyl ether
Br
0.96
0.93
0.94
0.99
1.00
1.00
2.01
2.00
2.98
f1 (ppm)

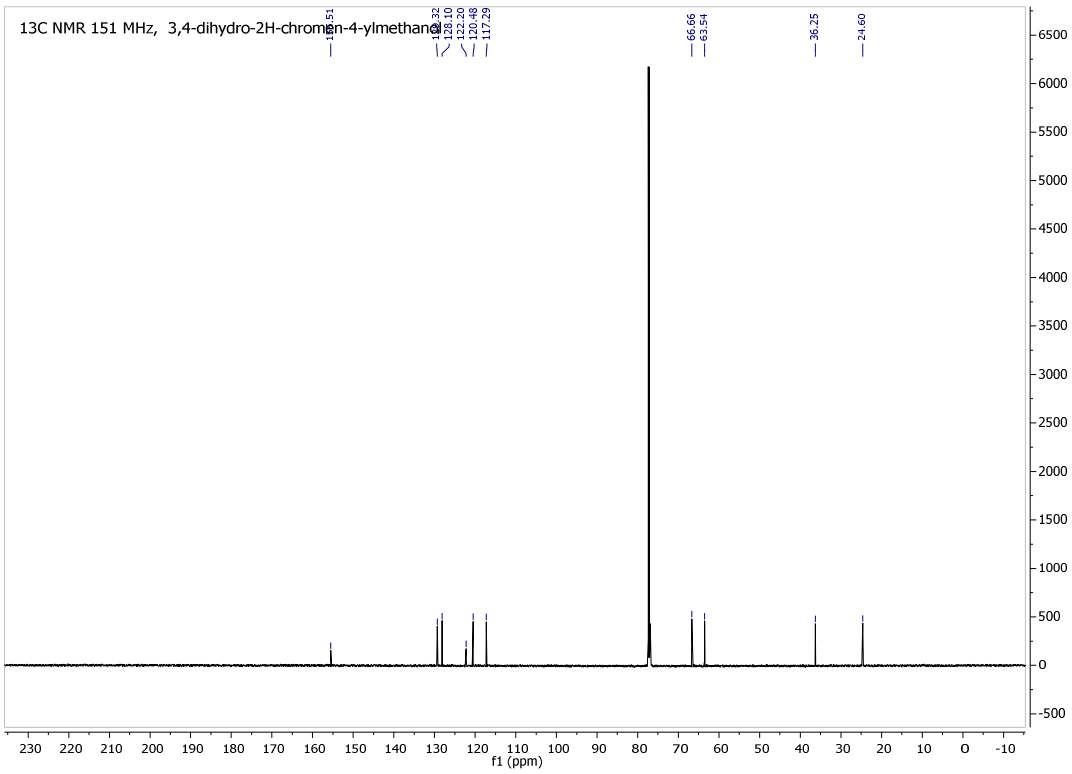

13C NMR 176 MHz, 2″-bromoethyl 2-ethenyl-5-methylphenyl ether
155.28
139.19
131.42
126.67
124.62
122.42
113.92
113.53
68.50
29.42
21.69
f1 (ppm)

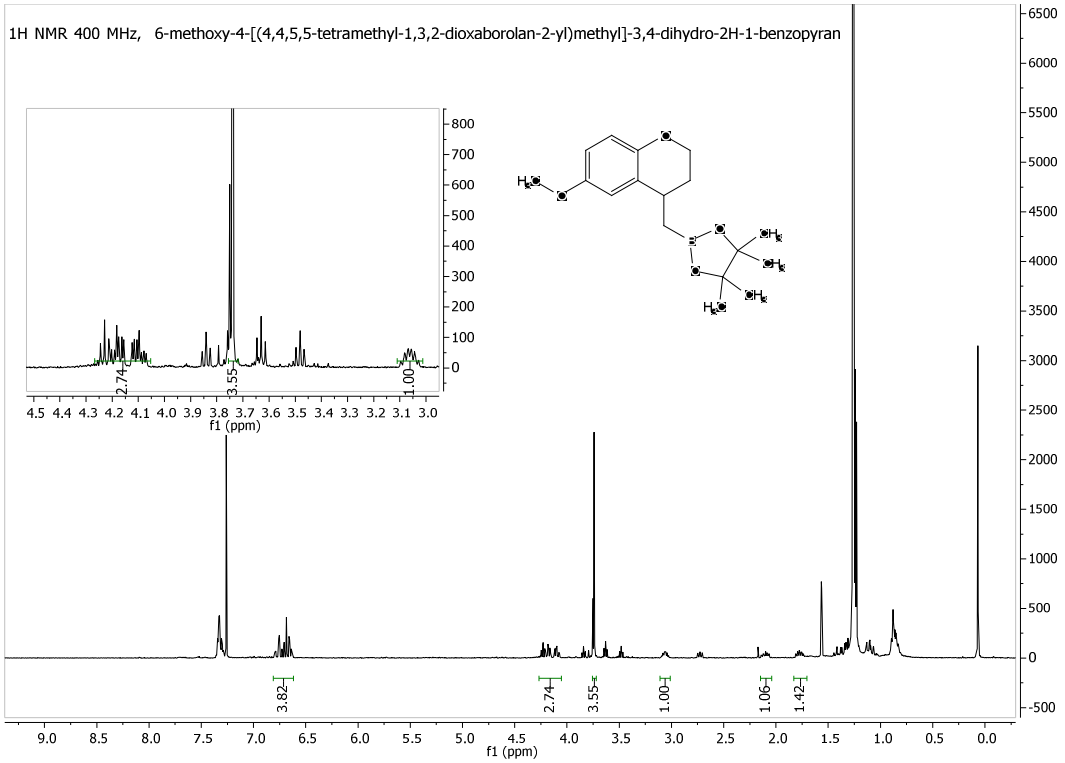

1H NMR 700 MHz, 2′-{2-[2-(2″-bromoethoxy)-4-fluorophenyl]ethyl}-Bpin
Br
Bpin
F
2.00
2.06
2.00
1.05
1.04
1.06
2.00
2.06
2.00
11.84
2.25
f1 (ppm)

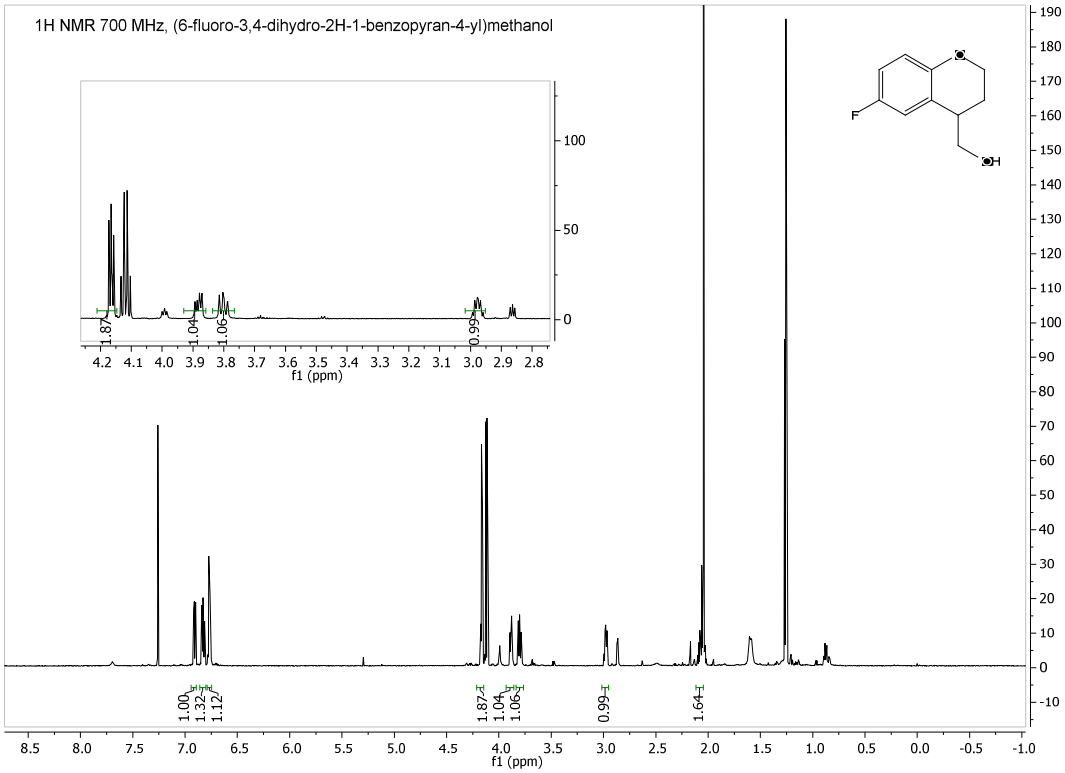

13C NMR 176 MHz, 2'-{2-[2-(2''-bromoethoxy)-4-fluorophenyl]ethyl}-Bpin
158.24
156.88
152.10
152.08
135.66
135.62
116.53
116.40
112.85
112.80
112.52
112.39
83.25
68.88
29.46
24.97
24.49
24.48
f1 (ppm)

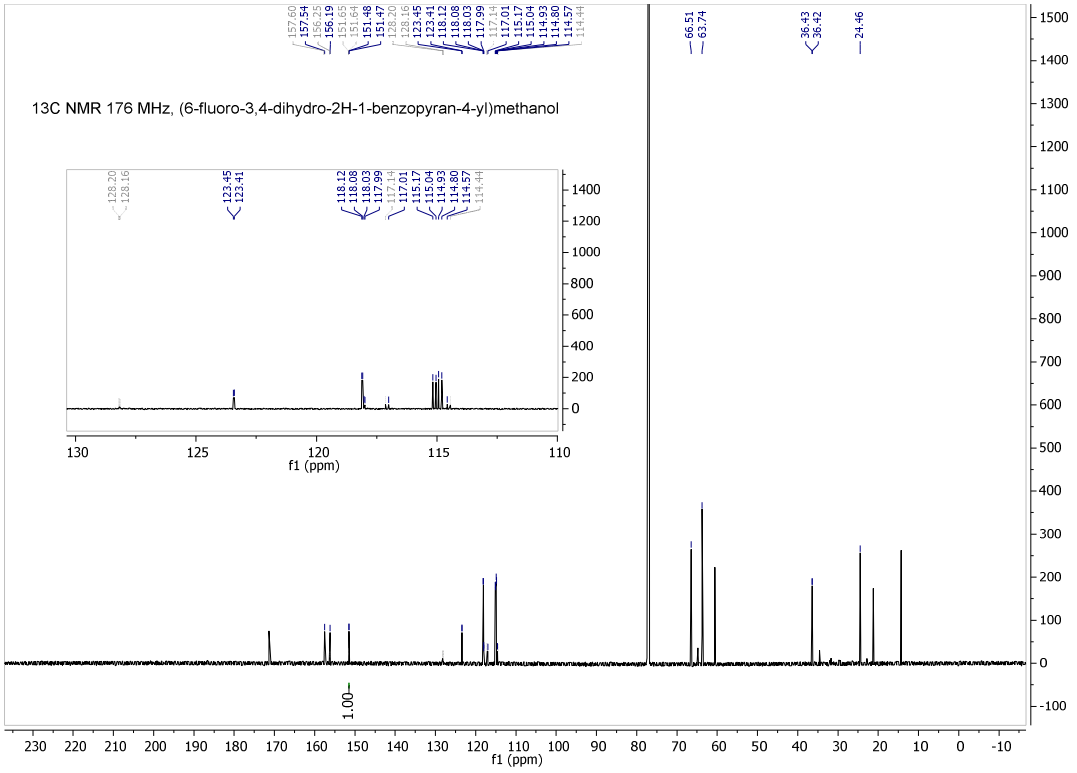

1H NMR 400 MHz, 4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,4-dihydro-2H-chromene
1.31
1.05
1.03
1.06
1.98
0.94
0.98
1.00
1.50
11.54
1.84
f1 (ppm)

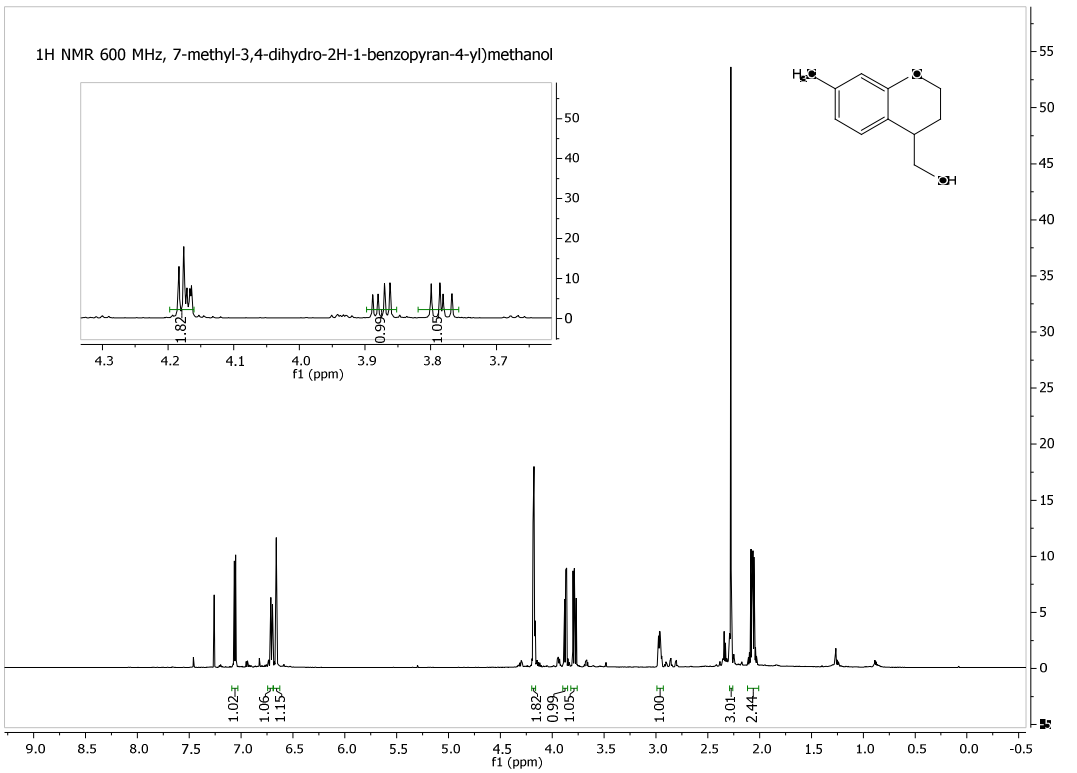

1H NMR 600 MHz, 3,4-dihydro-2H-chromen-4-ylmethanol
f1 (ppm)

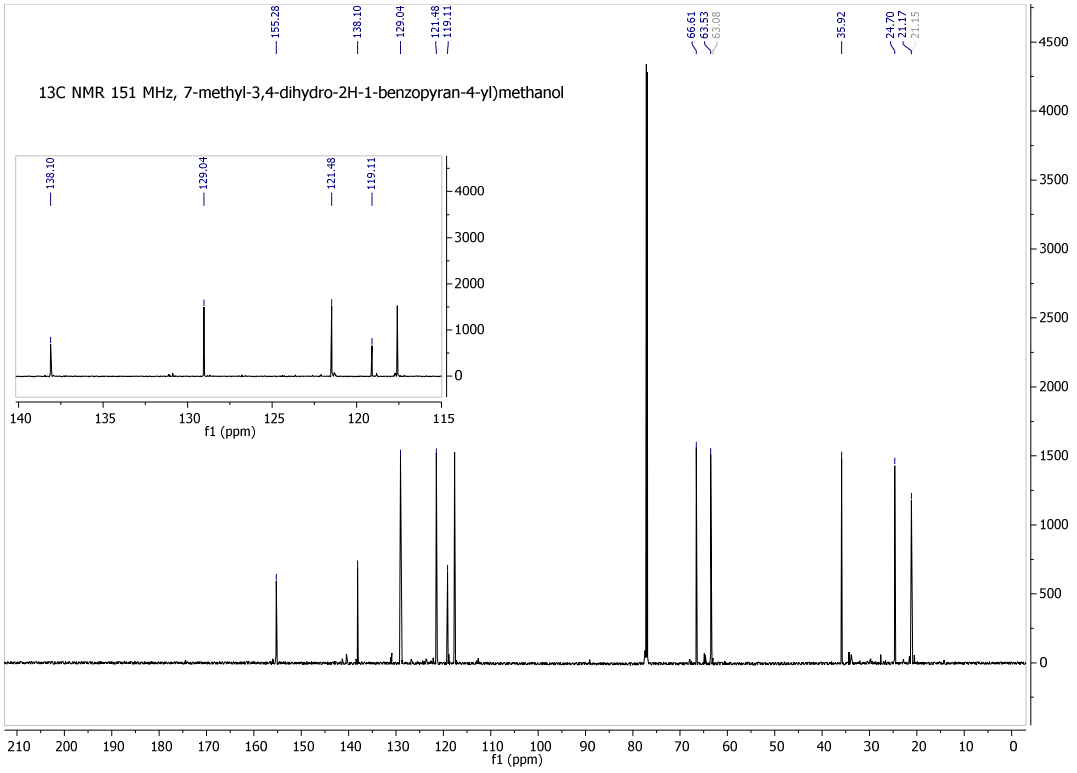

13C NMR 151 MHz, 3,4-dihydro-2H-chromen-4-ylmethanol
f1 (ppm)

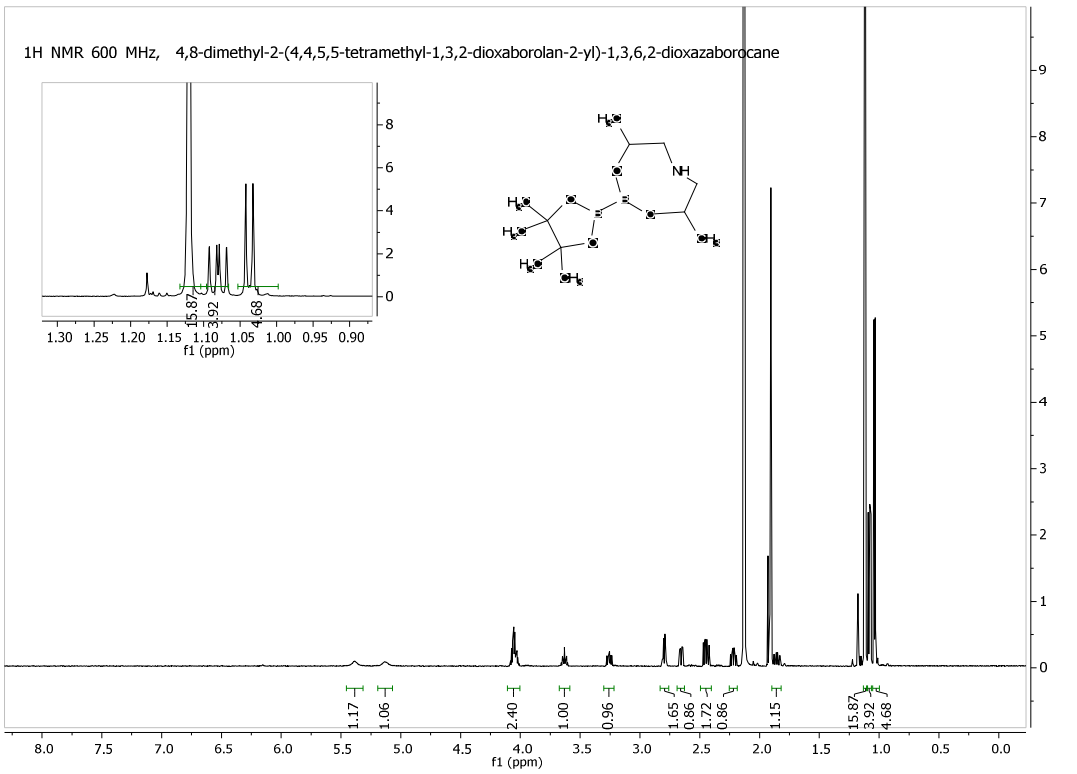

1H NMR 400 MHz, 6-methoxy-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,4-dihydro-2H-1-benzopyran
f1 (ppm)

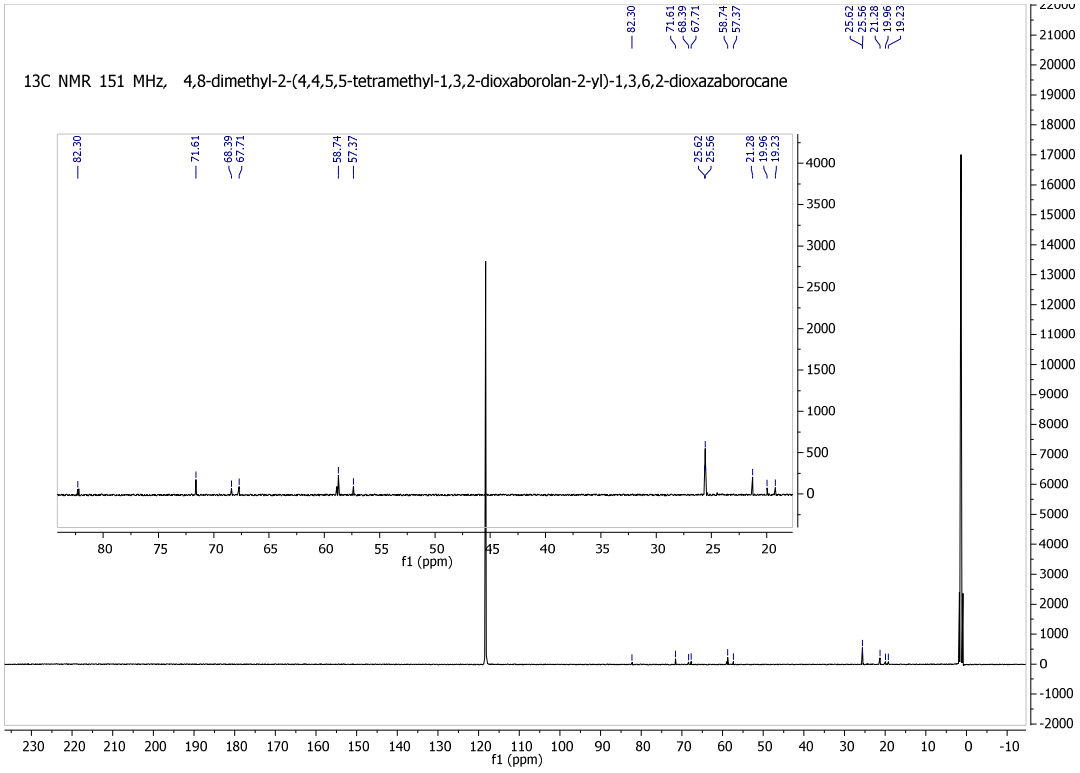

1H NMR 700 MHz, (6-fluoro-3,4-dihydro-2H-1-benzopyran-4-yl)methanol
f1 (ppm)

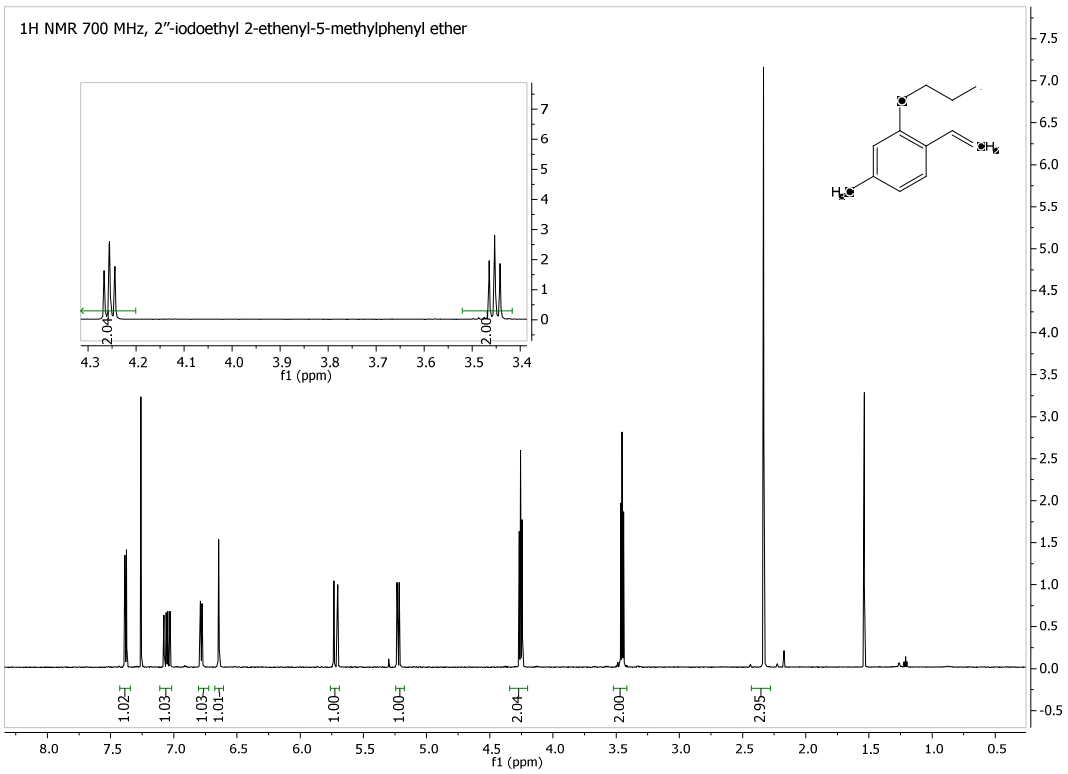

13C NMR 176 MHz, (6-fluoro-3,4-dihydro-2H-1-benzopyran-4-yl)methanol
f1 (ppm)

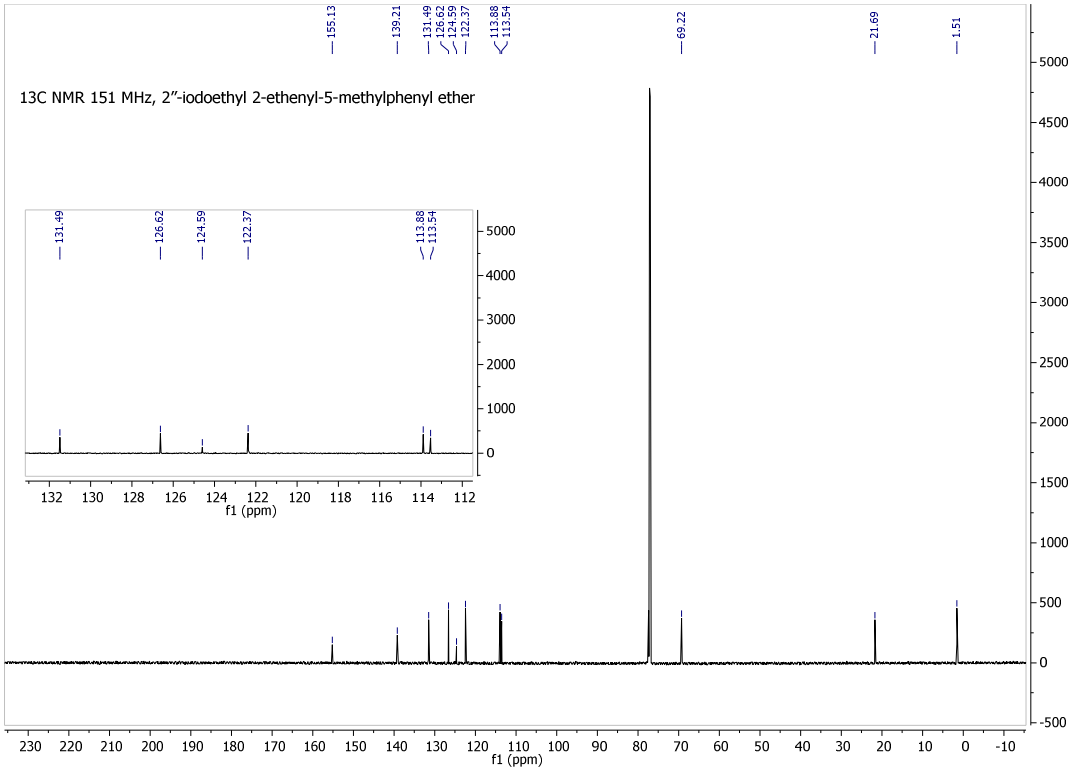

1H NMR 600 MHz, 7-methyl-3,4-dihydro-2H-1-benzopyran-4-yl)methanol
f1 (ppm)

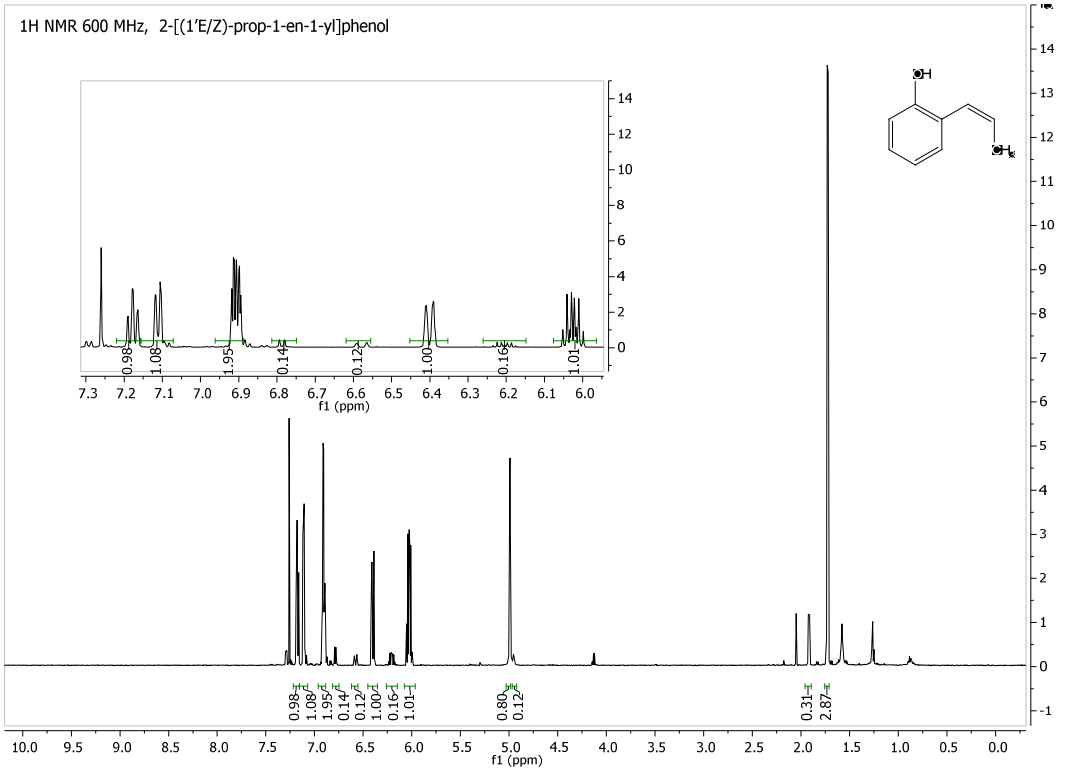

13C NMR 151 MHz, 7-methyl-3,4-dihydro-2H-1-benzopyran-4-yl)methanol
155.28
138.10
129.04
121.48
119.11
66.61
63.53
63.08
35.92
24.70
21.17
21.15
f1 (ppm)

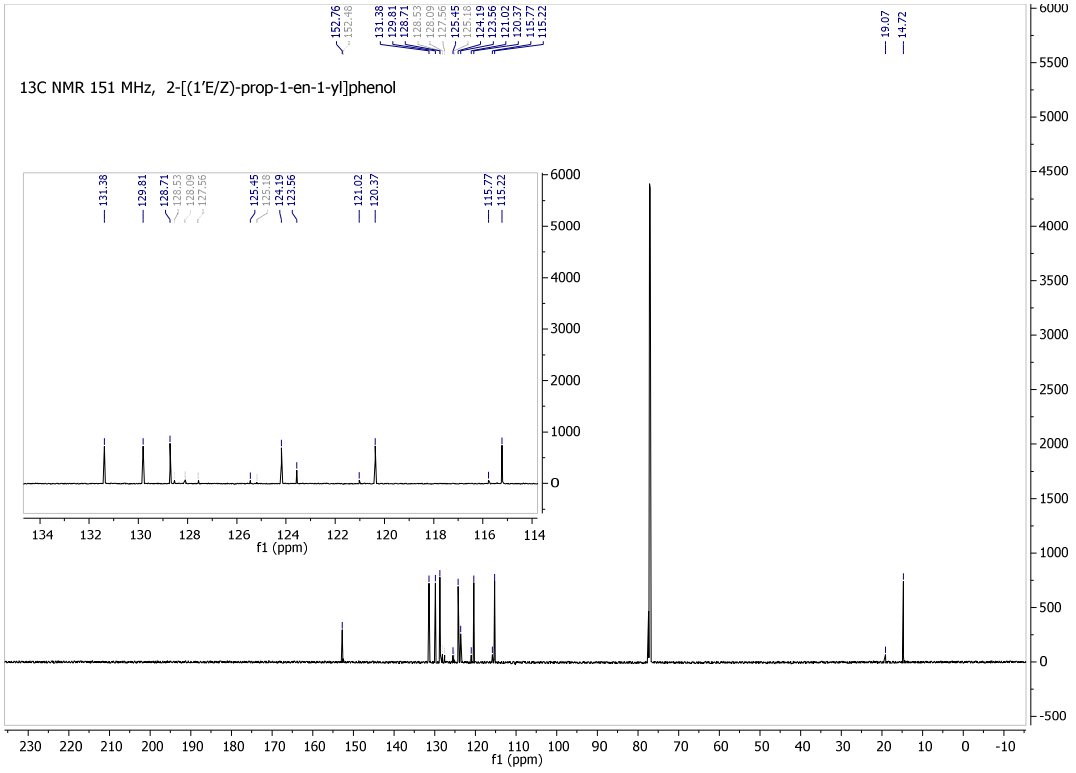

1H NMR 600 MHz, 4,8-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,6,2-dioxazaborocane
NH
15.87
3.92
4.68
1.17
1.06
2.40
1.00
0.96
1.65
0.86
1.72
0.86
1.15
15.87
3.92
4.68
f1 (ppm)

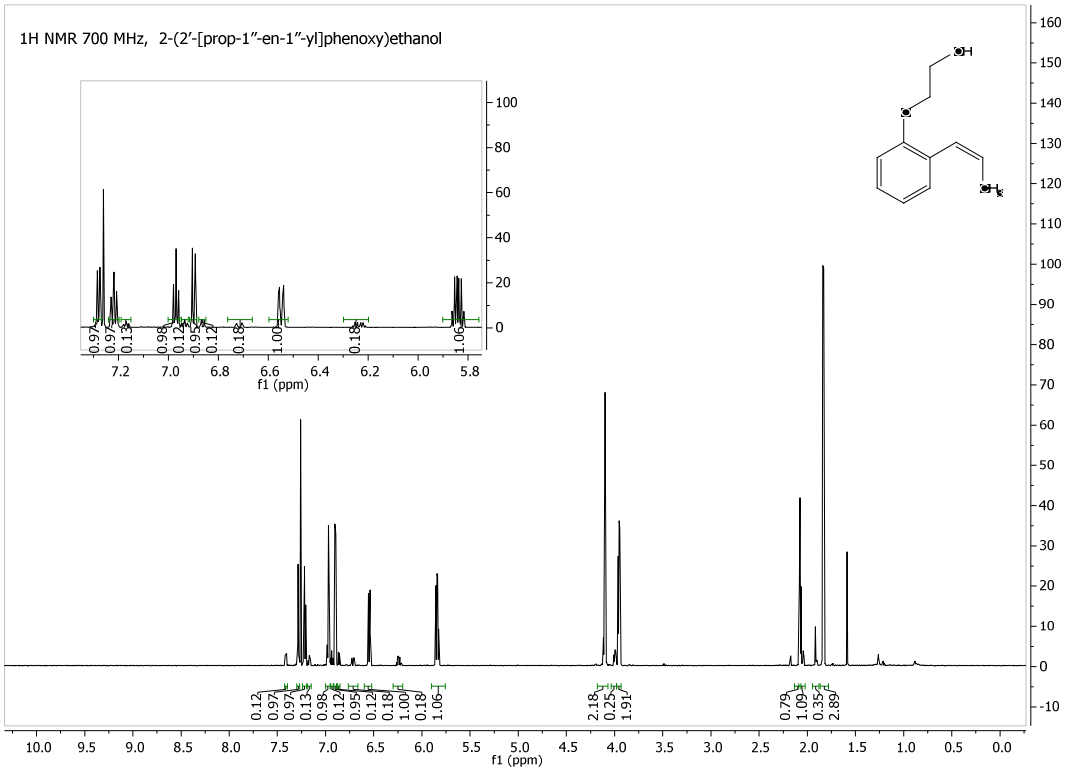

13C NMR 151 MHz, 4,8-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,6,2-dioxazaborocane
82.30
71.61
68.39
67.71
58.74
57.37
25.62
25.56
21.28
19.96
19.23
f1 (ppm)

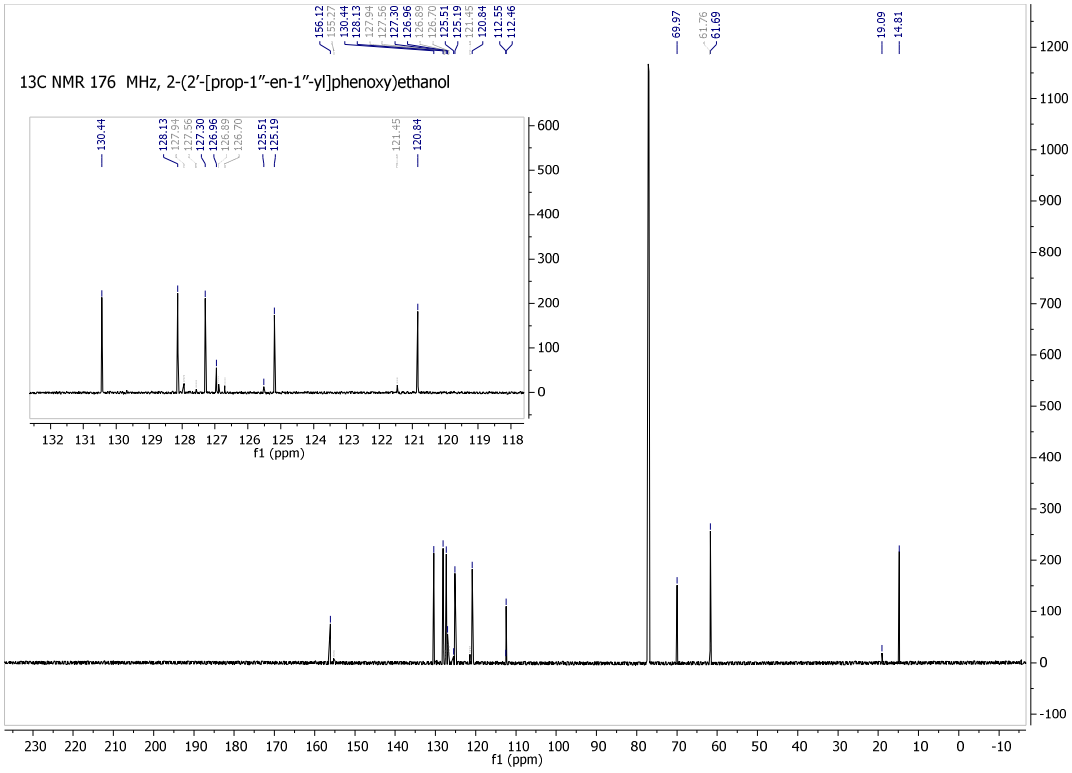

1H NMR 700 MHz, 2''-iodoethyl 2-ethenyl-5-methylphenyl ether
2.04
2.00
1.02
1.03
1.03
1.01
1.00
1.00
2.04
2.00
2.95
f1 (ppm)

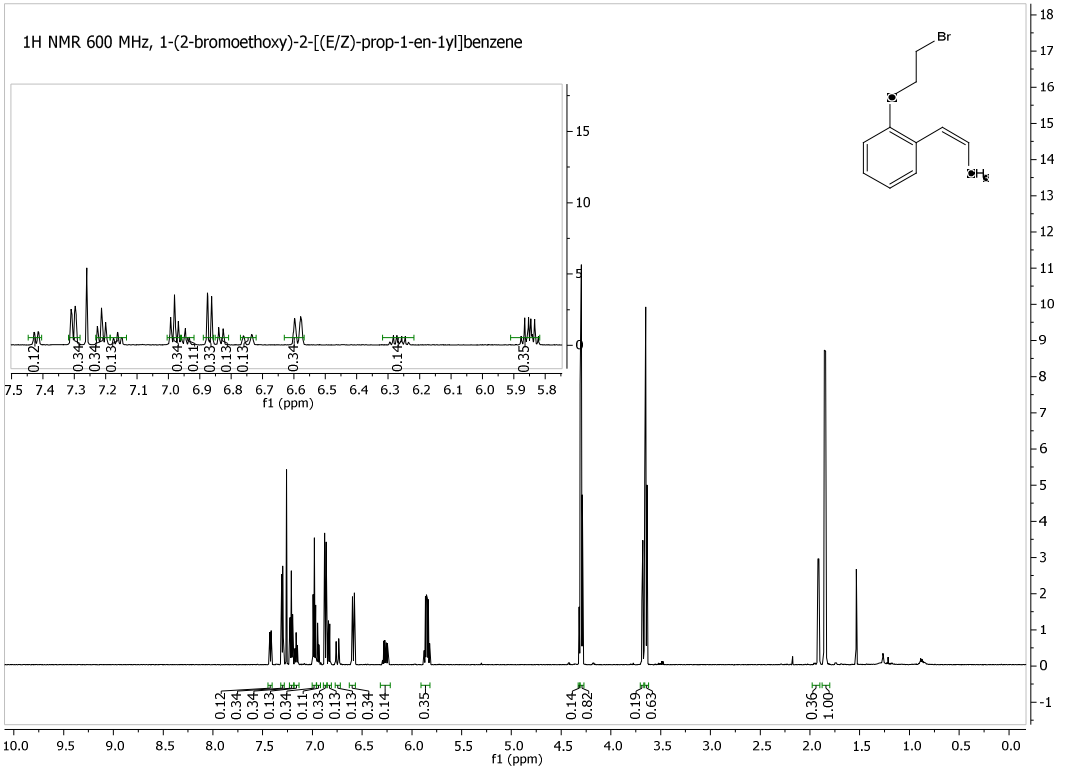

13C NMR 151 MHz, 2''-iodoethyl 2-ethenyl-5-methylphenyl ether
155.13
139.21
131.49
126.62
124.59
122.37
113.88
113.54
69.22
21.69
1.51
f1 (ppm)

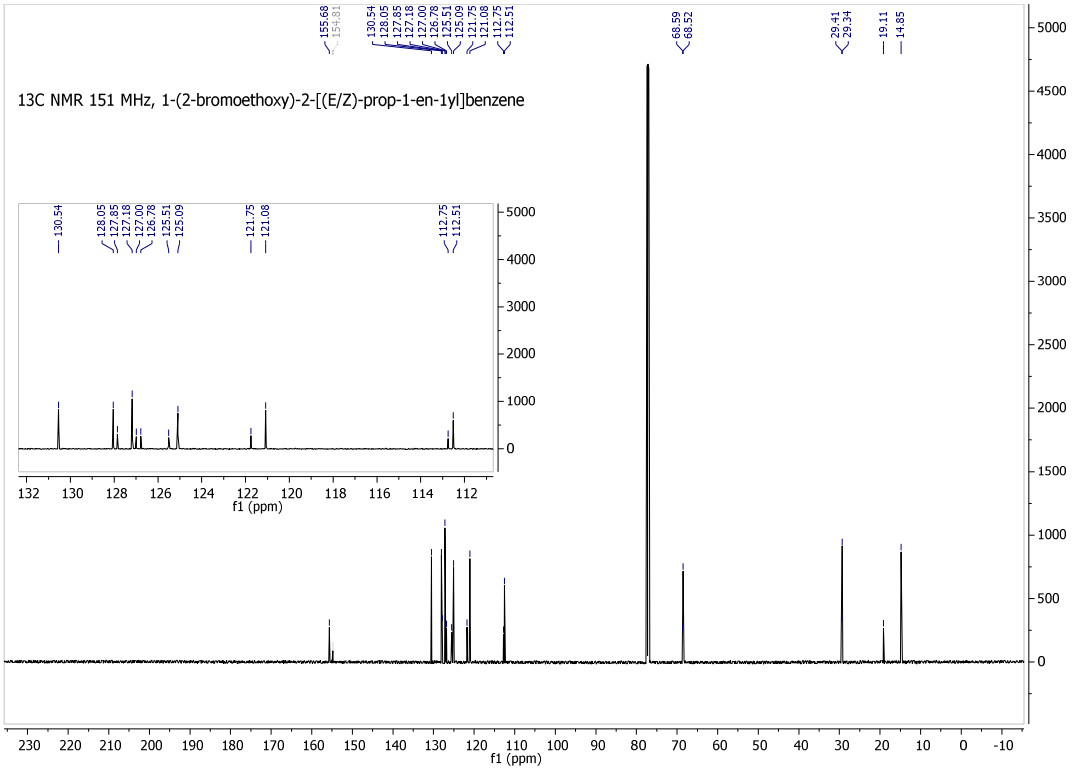

1H NMR 600 MHz, 2-[(1'E/Z)-prop-1-en-1-yl]phenol
0.98
1.08
1.95
0.14
0.12
1.00
0.16
1.01
0.80
0.12
0.31
2.87
f1 (ppm)

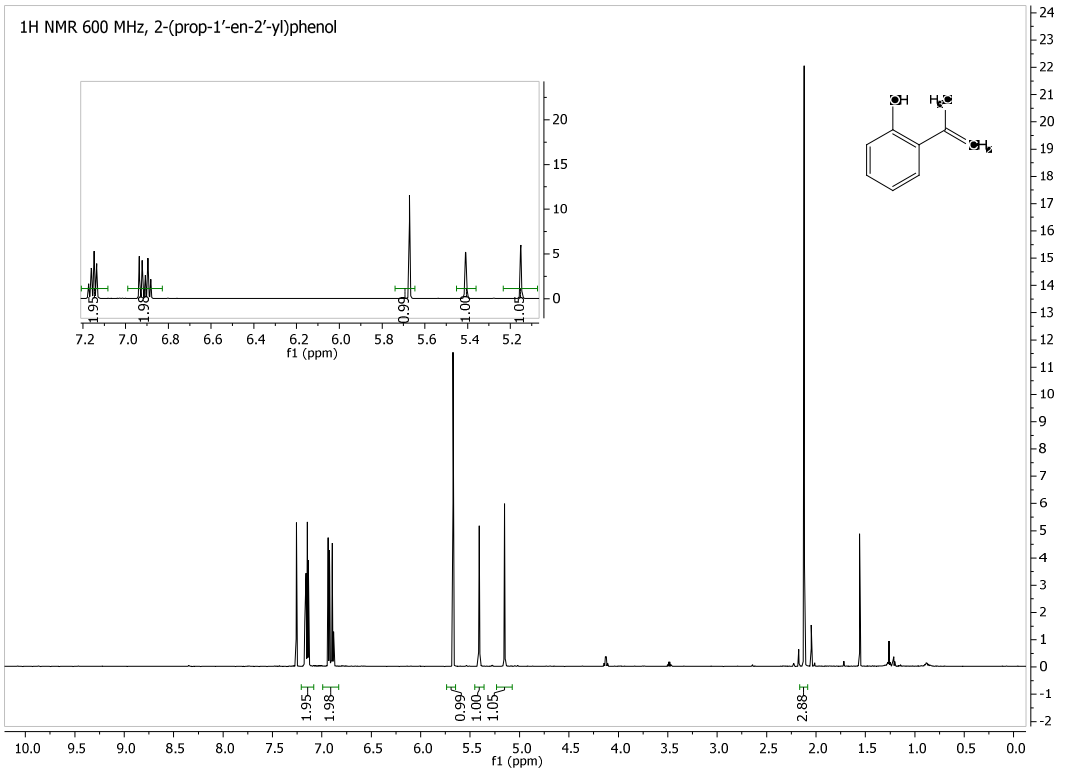

13C NMR 151 MHz, 2-[(1'E/Z)-prop-1-en-1-yl]phenol
f1 (ppm)

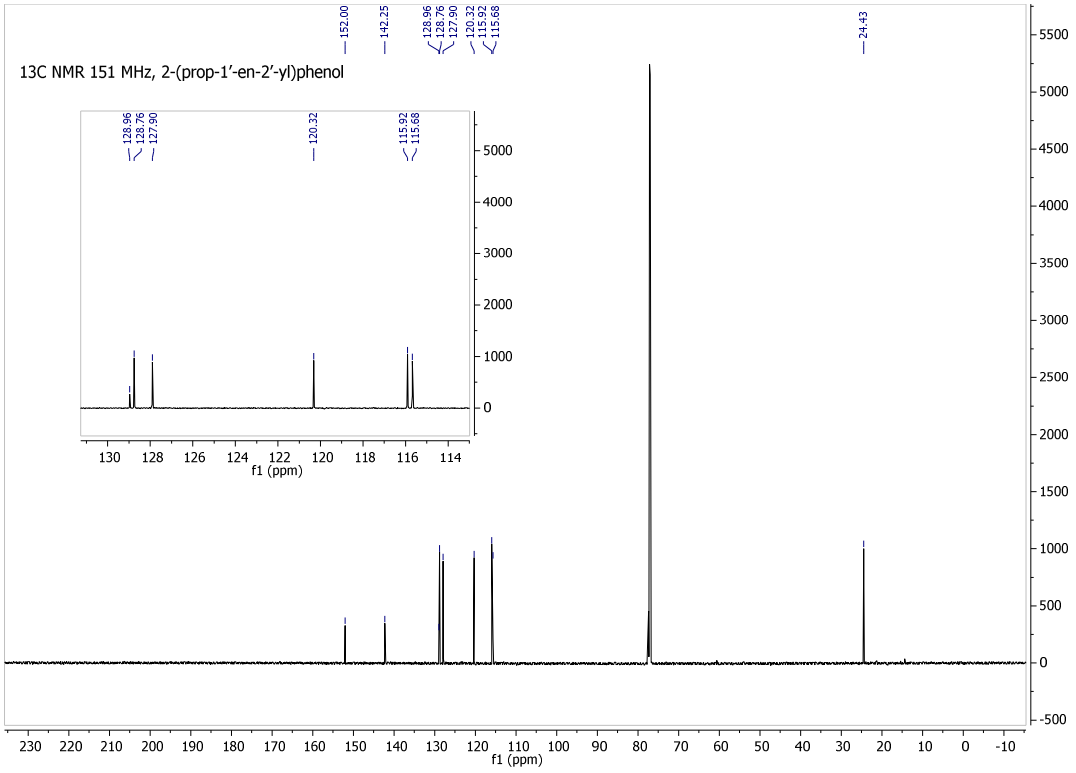

1H NMR 700 MHz, 2-(2'-[prop-1''-en-1''-yl]phenoxy)ethanol
f1 (ppm)

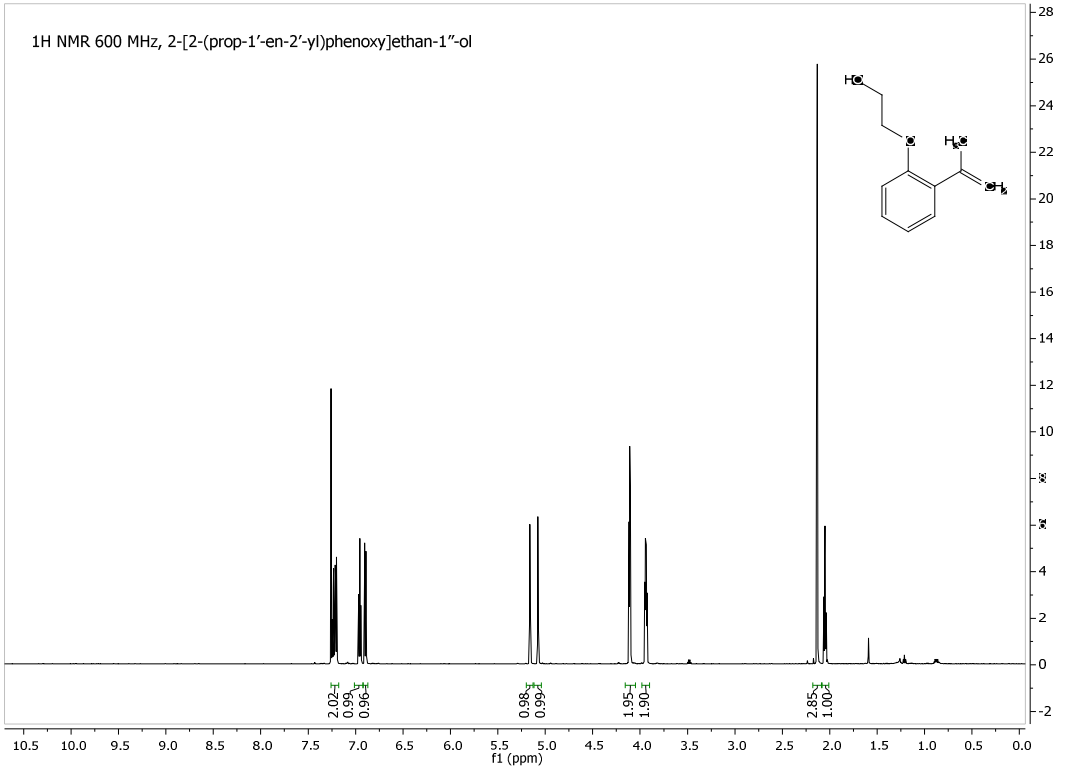

13C NMR 176 MHz, 2-(2′-[prop-1″-en-1″-yl]phenoxy)ethanol
156.12
130.44
128.13
127.30
126.96
125.51
125.19
120.84
112.55
112.46
69.97
61.69
19.09
14.81
f1 (ppm)

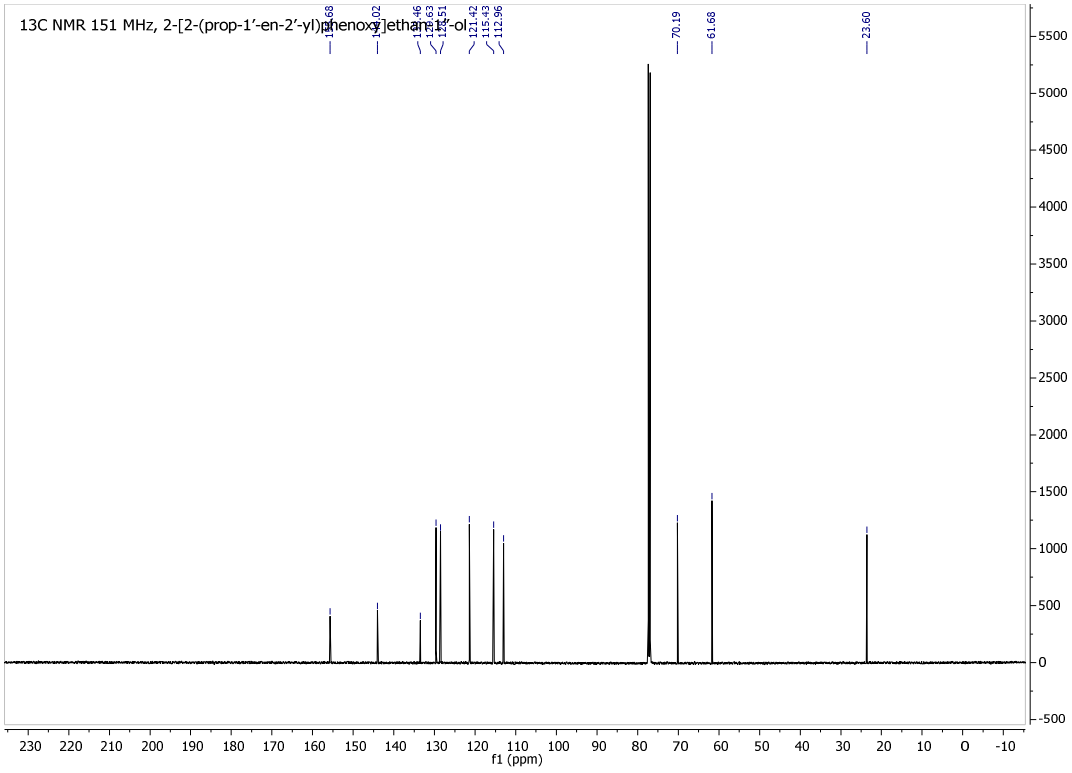

1H NMR 600 MHz, 1-(2-bromoethoxy)-2-[(E/Z)-prop-1-en-1yl]benzene
Br
f1 (ppm)

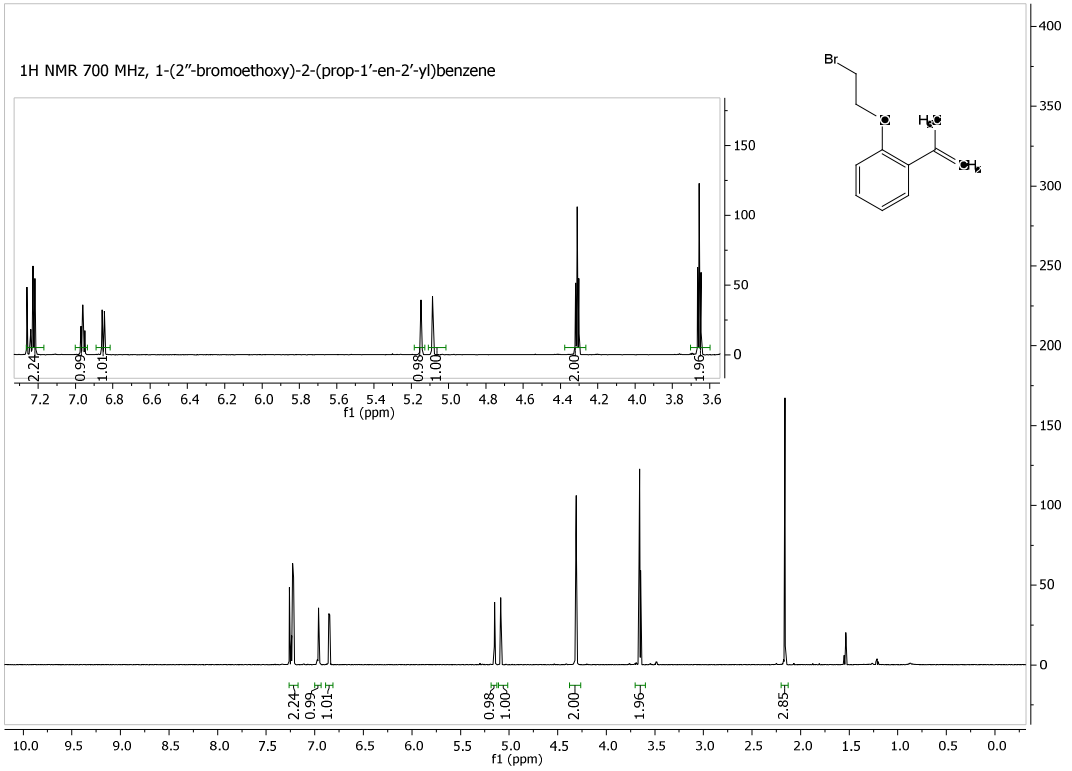

13C NMR 151 MHz, 1-(2-bromoethoxy)-2-[(E/Z)-prop-1-en-1yl]benzene
155.68
154.81
130.54
128.05
127.85
127.18
127.00
126.78
125.51
125.09
121.75
121.08
112.75
112.51
68.59
68.52
29.41
29.34
19.11
14.85
f1 (ppm)

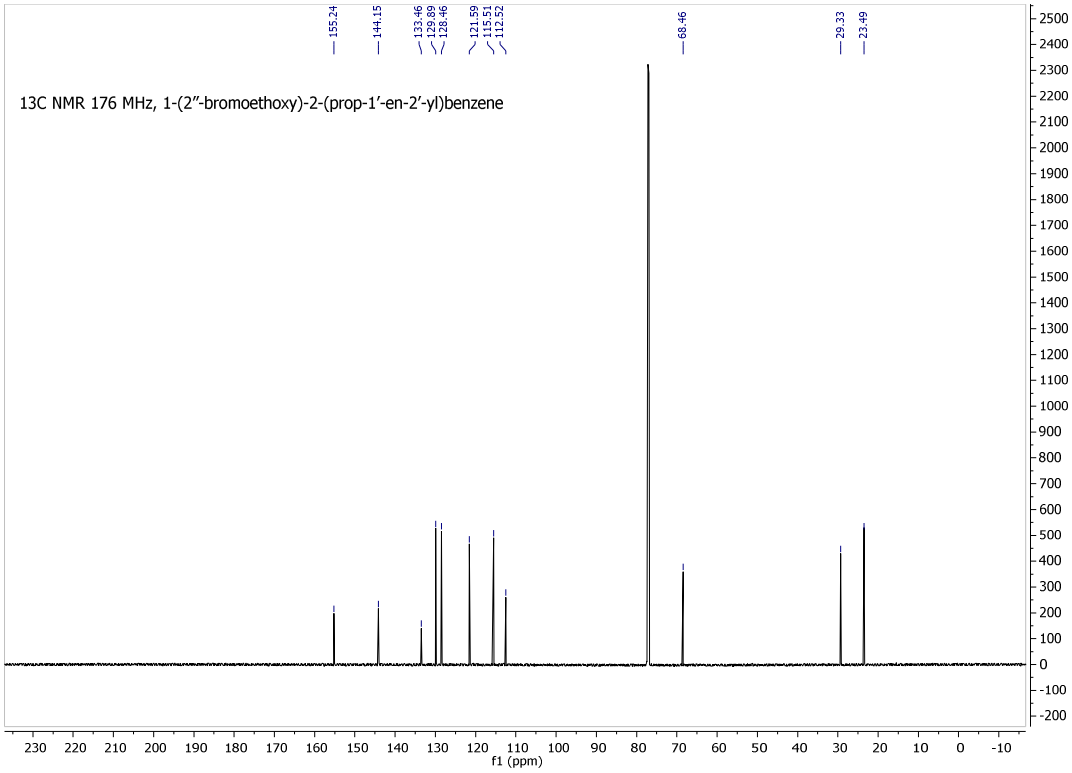

1H NMR 600 MHz, 2-(prop-1'-en-2'-yl)phenol
1.95
1.98
0.99
1.00
1.05
2.88
f1 (ppm)

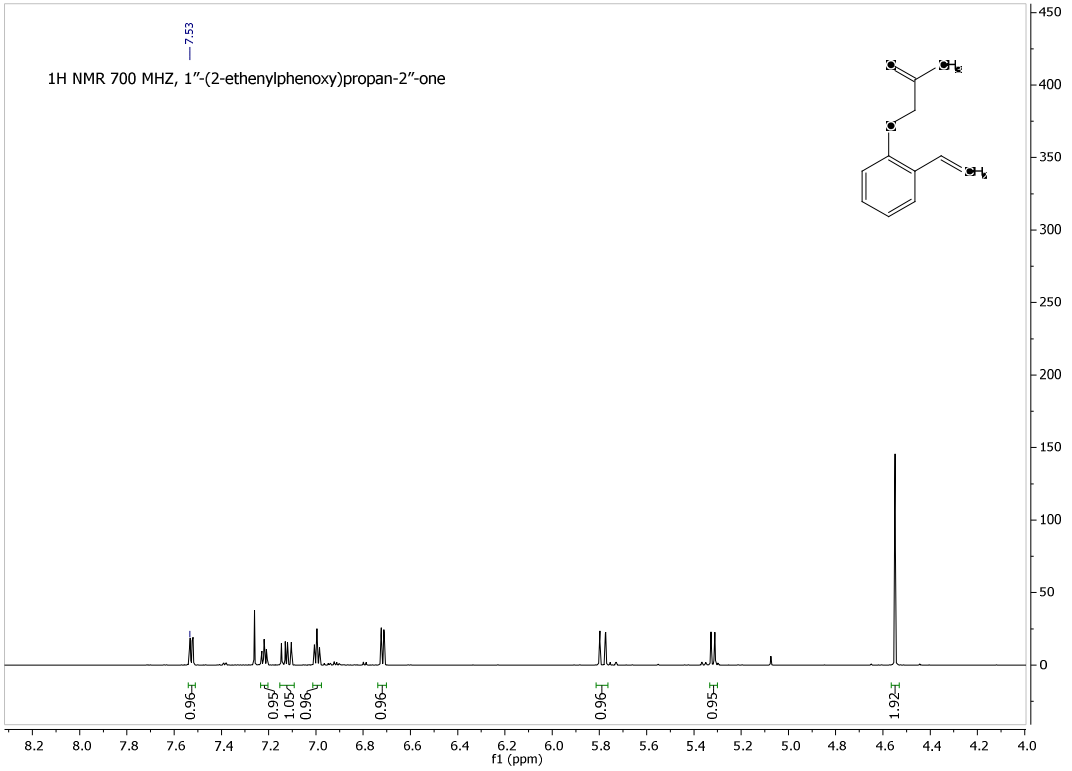

13C NMR 151 MHz, 2-(prop-1′-en-2′-yl)phenol
152.00
142.25
128.96
128.76
127.90
120.32
115.92
115.68
24.43
f1 (ppm)

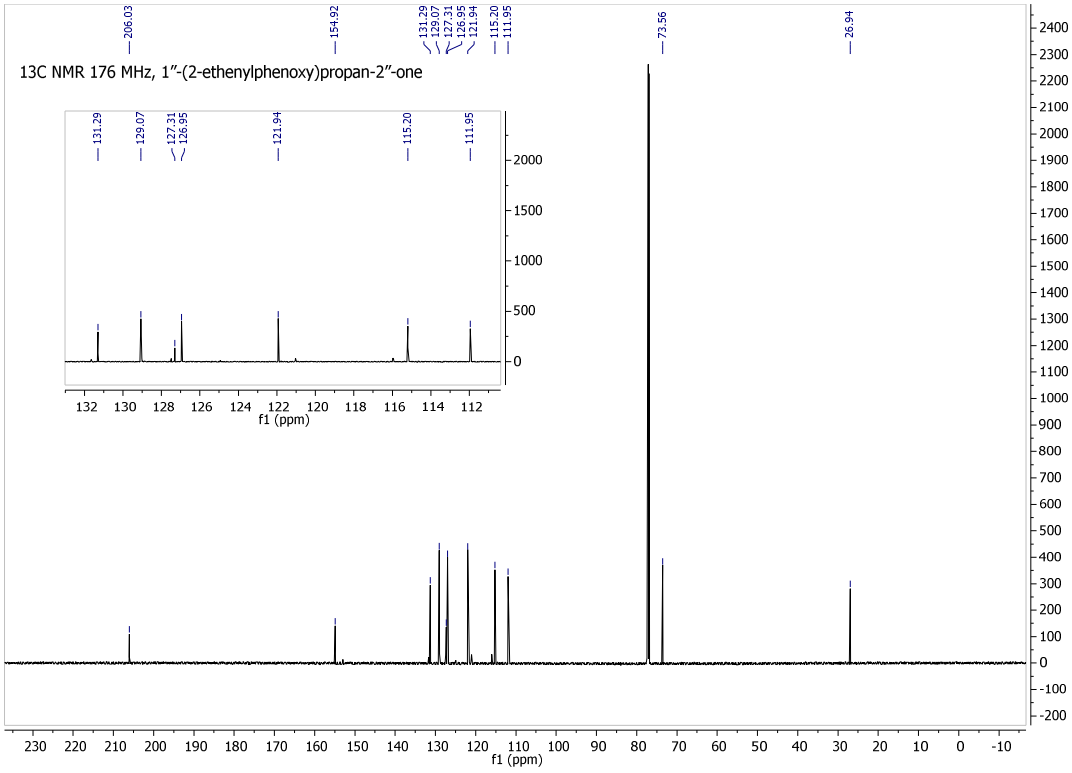

1H NMR 600 MHz, 2-[2-(prop-1′-en-2′-yl)phenoxy]ethan-1″-ol
2.02
0.99
0.96
0.98
0.99
1.95
1.90
2.85
1.00
f1 (ppm)

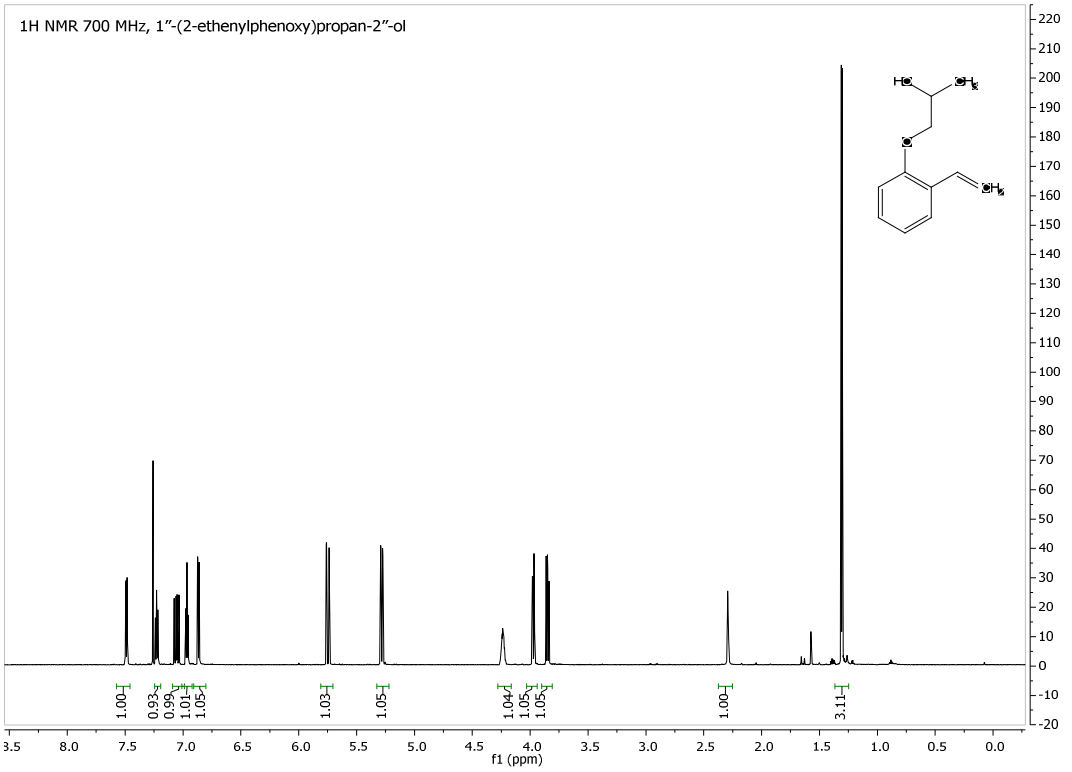

13C NMR 151 MHz, 2-[2-(prop-1′-en-2′-yl)phenoxy]ethan-1-ol
155.68
141.02
130.46
128.63
128.51
121.42
115.43
112.96
70.19
61.68
23.60
f1 (ppm)

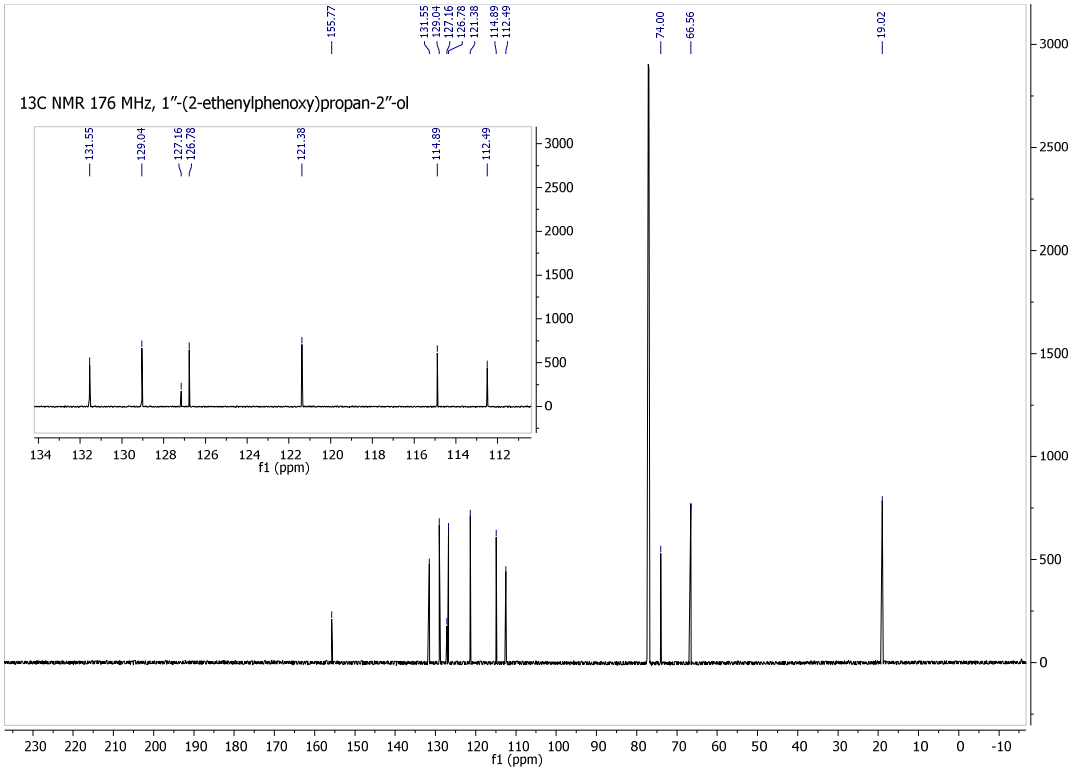

1H NMR 700 MHz, 1-(2″-bromoethoxy)-2-(prop-1′-en-2′-yl)benzene
Br
H
H
2.24
0.99
1.01
0.98
1.00
2.00
1.96
2.85
f1 (ppm)

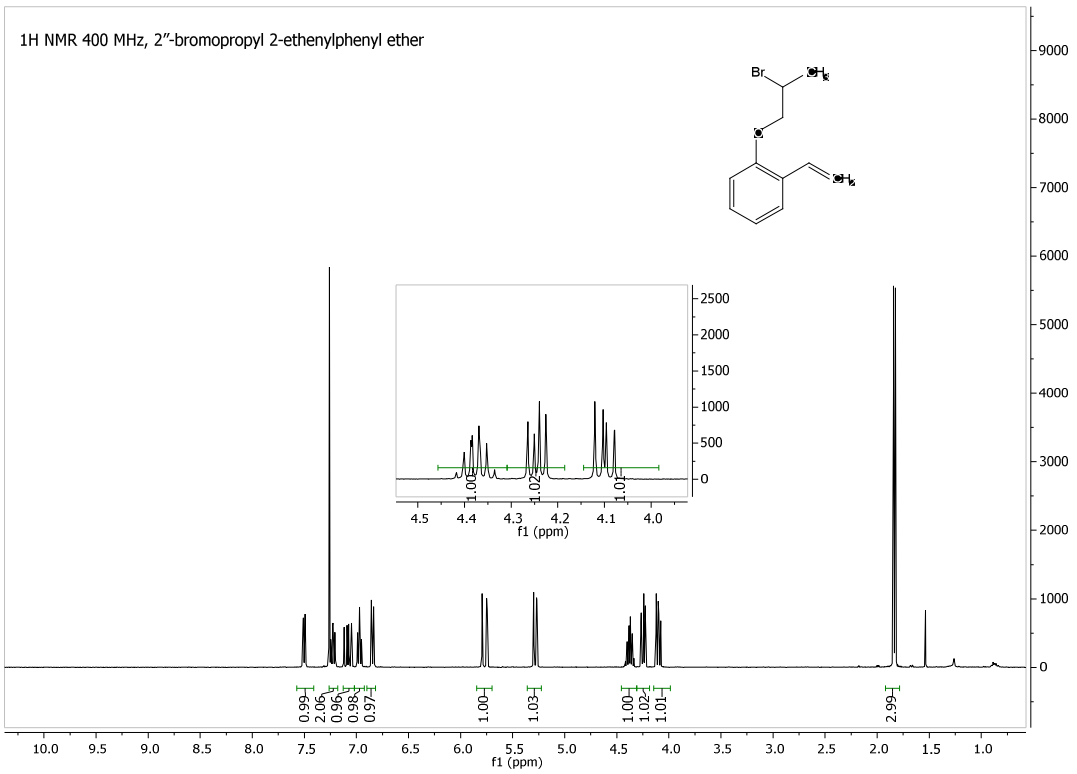

13C NMR 176 MHz, 1-(2''-bromoethoxy)-2-(prop-1'-en-2'-yl)benzene
155.24
144.15
133.46
129.89
128.46
121.59
115.51
112.52
68.46
29.33
23.49
f1 (ppm)

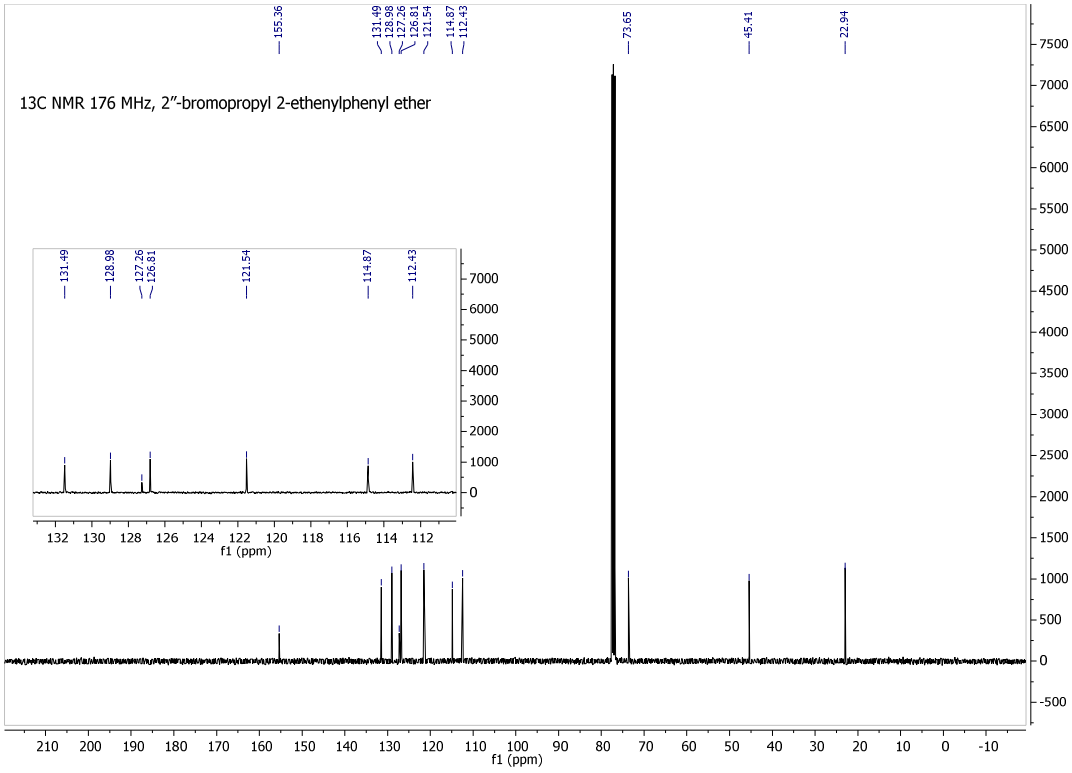

1H NMR 700 MHZ, 1''-(2-ethenylphenoxy)propan-2''-one
7.53
0.96
0.95
1.05
0.96
0.96
0.96
0.95
1.92
f1 (ppm)


13C NMR 176 MHz, 1″-(2-ethenylphenoxy)propan-2″-one
206.03
154.92
131.29
129.07
127.31
126.95
121.94
115.20
111.95
73.56
26.94
f1 (ppm)


1H NMR 700 MHz, 1″-(2-ethenylphenoxy)propan-2″-ol
1.00
0.93
0.99
1.01
1.05
1.03
1.05
1.04
1.05
1.05
1.00
3.11
f1 (ppm)


13C NMR 176 MHz, 1″-(2-ethenylphenoxy)propan-2″-ol
155.77
131.55
129.04
127.16
126.78
121.38
114.89
112.49
74.00
66.56
19.02
f1 (ppm)


1H NMR 400 MHz, 2″-bromopropyl 2-ethenylphenyl ether
Br
OH
f1 (ppm)


13C NMR 176 MHz, 2″-bromopropyl 2-ethenylphenyl ether
155.36
131.49
128.98
127.26
126.81
121.54
114.87
112.43
73.65
45.41
22.94
f1 (ppm)

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