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Rearrangement-driven synthesis of nitrogen heterocycles, cyclobutanes and spirocycles

Rearrangement-driven synthesis of nitrogen heterocycles, cyclobutanes and spirocycles

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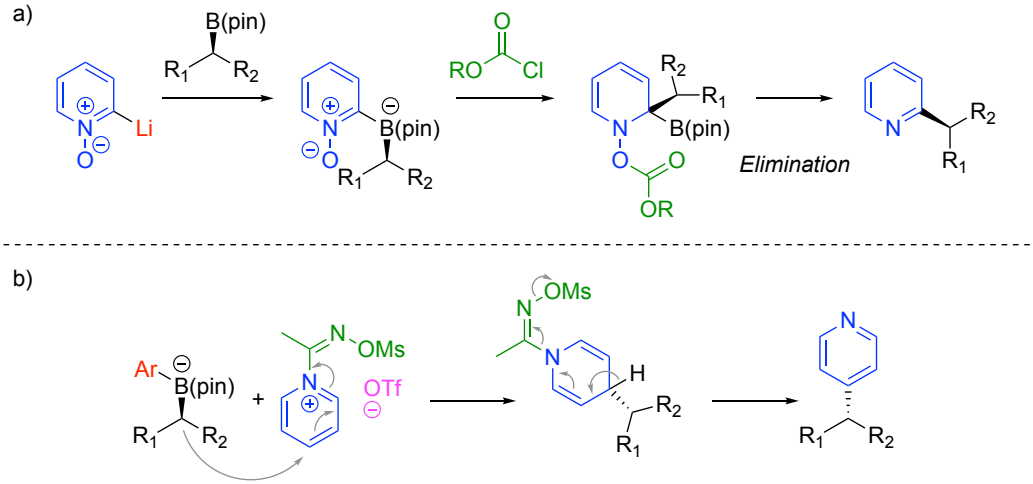
Abstract

Nitrogen-containing heterocycles, particularly pyridines and piperidines, are important components of many bioactive pharmaceuticals and natural products. Furthermore, it has been shown that 3-dimensionality in drug candidates is a key contributor to clinical success: sp^3-rich scaffolds tend to outperform flatter drug candidates, which are frequently explored due to their ease of synthesis by sp^2-sp^2 cross-couplings. The inherent 3-dimensionality and rigidity of cyclobutane rings and spirocyclic scaffolds renders these desirable motifs in drug candidates. This thesis outlines investigations into novel methods of achieving sp^2-sp^3 cross-coupling to pyridines and synthesising cyclobutyl boronic esters and dihydropyridine spirocycles.

1. Cross-coupling to pyridines

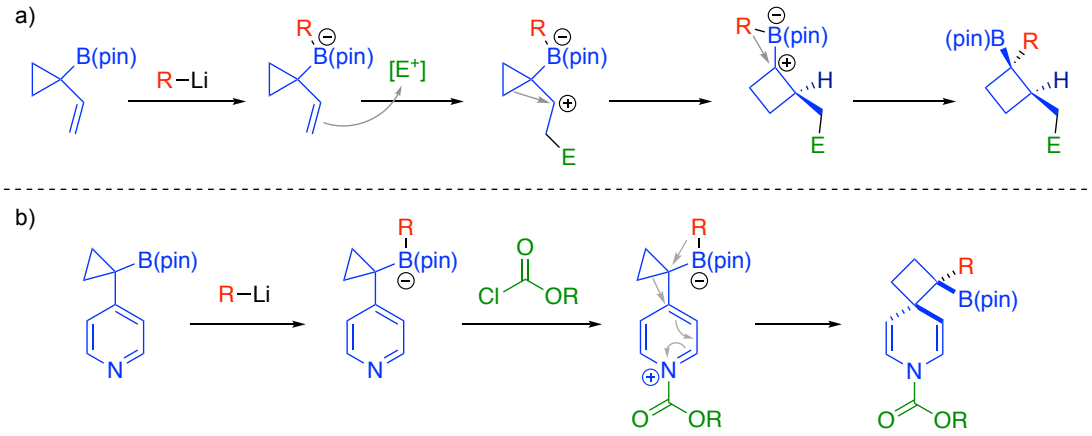
Firstly, investigations into achieving sp^2-sp^3 cross-coupling reactions of boronic esters with pyridines are discussed. These procedures exploit the reactivity of the pyridine nitrogen towards electrophiles or oxidation to facilitate either the intramolecular 1,2-metallate rearrangement of a boron-ate complex (scheme A1, a) or the intermolecular addition of boron-ate nucleophiles to the activated pyridinium species (scheme A1, b)



Scheme A1: a) C2-coupling to pyridines by 1,2-metallate rearrangement of pyridine *N*-oxide-derived boron-ate complexes, b) Nucleophilic addition of boron-ate nucleophiles to activated pyridinium electrophiles

2. Synthesis of cyclobutanes by ring expansion induced 1,2-metallate rearrangement

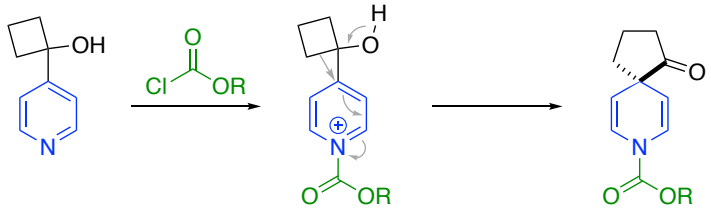
Secondly, the synthesis of cyclobutyl boronic esters by a ring-expansion induced 1,2-metallate rearrangement of vinylcyclopropyl boronic esters was achieved (scheme A2, a). This reaction proceeds by electrophilic activation of the alkene moiety generating a carbocation β- to boron, which triggers a concomitant ring expansion and 1,2-metallate rearrangement to give the cyclobutyl boronic ester product with a high degree of diastereoselectivity. Attempts to expand this methodology to the synthesis of dihydropyridine spirocycles (scheme A2, b) are also briefly discussed.



Scheme A2: a) Ring-expansion induced 1,2-metallate rearrangement of vinylcyclopropyl boron-ate complex to generate cyclobutyl boronic esters, b) Proposed extension of this concept to synthesis of dihydropyridine spirocycles

3. Synthesis of dihydropyridine spirocycles by an electrophile-induced dearomative semi-pinacol rearrangement of hydroxycyloalkylpyridines

Finally, the synthesis of dihydropyridine spirocycles was achieved by an electrophile-induced dearomative semi-pinacol rearrangement of hydroxycyclobutylpyridines (scheme A3). This reaction was successfully applied to a variety of acylating agents and substituted hydroxycycloalkylpyridine substrates.



Scheme A3: Spirocycle synthesis by dearomative semi-pinacol rearrangement of hydroxycyclobutylpyridine

Acknowledgements

First, I would like to thank Varinder for the opportunity to work in his group and for all his patient guidance and advice. I would also like to thank Adam for general advice and chemistry expertise (as well as signing my many COSHH forms) and the past and present members of my sub-groups for their help and suggestions. I would especially like to thank Durga, who led the way on the cyclobutane project and has been a fount of enthusiasm, knowledge and chemistry advice. Furthermore, thanks to Laia, Noelia, Christian and Tom for their contributions to the spirocycle project. Thanks also to Pep and Rob at UCB, for their suggestions and chemistry discussions. The other members of N209 also deserve a mention for their everyday help and advice in the lab and introducing me to their variable tastes in music. Finally, thank you to all my family and friends for their support throughout the past 4 years.

Author's Declaration

"I declare that the work in this dissertation was carried out in accordance with the Regulations of the University of Bristol. The work is original, except where indicated by special reference in the text, and no part of the dissertation has been submitted for any other academic award. Any views expressed in the dissertation are those of the author.

SIGNED: ……Joseph Abell…… DATE:……19th May 2022……"

Acronyms and Abbreviations

The ACS standard List of Abbreviations, found within the 'ACS Style Guide, appendix 10-2', was used with the following additions:

Boc - *tert*-butyloxycarbonyl

bpy - bipyridine

BINAP - (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)

B(neo) - Neopentyl glycol boronic ester

B(pin) - Pinacol boronic ester

Cb - Diisopropyl carbamate

DMI - 1,3-Dimethyl-2-imidazolidinone

E - Electrophile

EDG - Electron donating group

EWG - Electron withdrawing group

eq. - Equivalents

Fmoc - 9*H*-fluorenylmethylcarbonyl

GCMS - Gas chromatography mass spectrometry

HFIP - Hexafluoroisopropanol

[H] - Reduction

[M] - Metal complex

Ms - Methanesulfonyl

[O] - Oxidation

S_EAr - Electrophilic Aromatic Substitution

SEM - [2-(trimethylsilyl)ethoxy] methyl acetal

sp - Sparteine

TES - Triethylsilyl

Tf - Trifluoromethanesulfonyl

TIB - 2,4,6-Triisopropyl benzoate

TMS - Trimethylsilyl

Troc-Cl - Trichloroethyl chloroformate

Contents

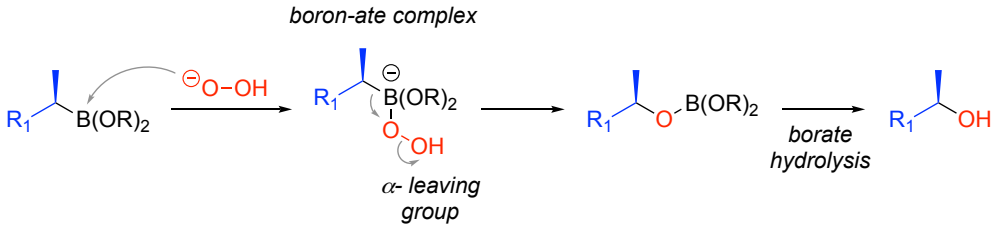
1 Introduction

1.1 Boronic esters in organic synthesis

Boronic esters are useful intermediates in synthetic planning, capable of undergoing a diverse range of transformations forming C-C bonds,[1] C-N bonds,[2,3] C-O bonds[4,5] and other C-heteroatom bonds[6,7] with a high degree of stereospecificity.[8,9] Enantioenriched sp^3 boronic esters are easily accessed by enantioselective hydroboration or lithiation-borylation protocols using chiral ligands.[8] Low toxicity and generally good bench stability of boronic esters, alongside ease of access and wide commercial availability have led to these species being widely used in pharmaceutical industry, particularly for Suzuki-Miyaura cross coupling (which will be discussed in section 2.2.2).[10]

1.2 1,2-metallate rearrangement

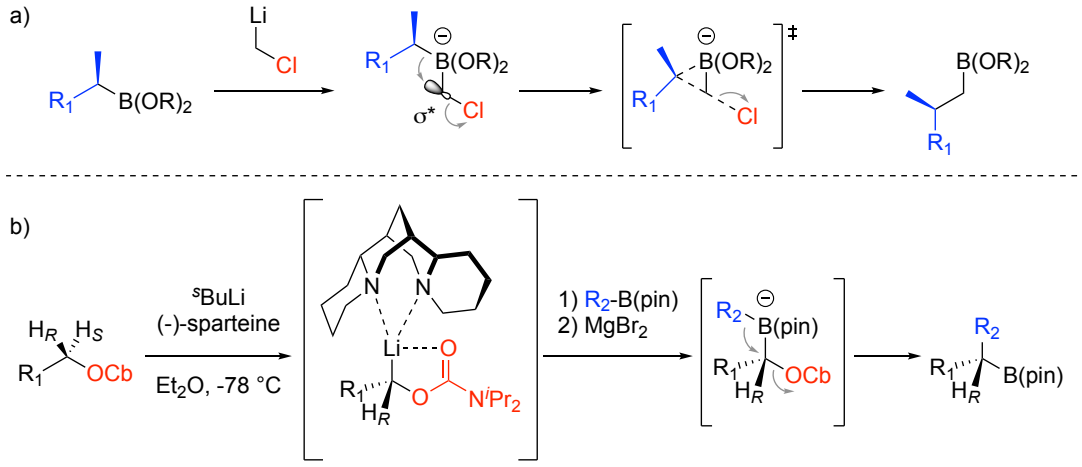
Boron-ate species, generated by attack of electrophilic borane or boronic ester species by a nucleophile, can undergo 1,2-metalate rearrangements if one of the substituents bears a leaving group or carbocation α- to the boron centre.[11–13] 1,2-migration proceeds with retention of configuration at the migrating carbon centre, as demonstrated for the stereoretentive oxidation of boranes and boronic esters using hydrogen peroxides (scheme 1).[4,9]



Scheme 1: Oxidation of enantioenriched boronic ester with hydrogen peroxide and sodium hydroxide, which generate the hydroperoxide anion *in situ*

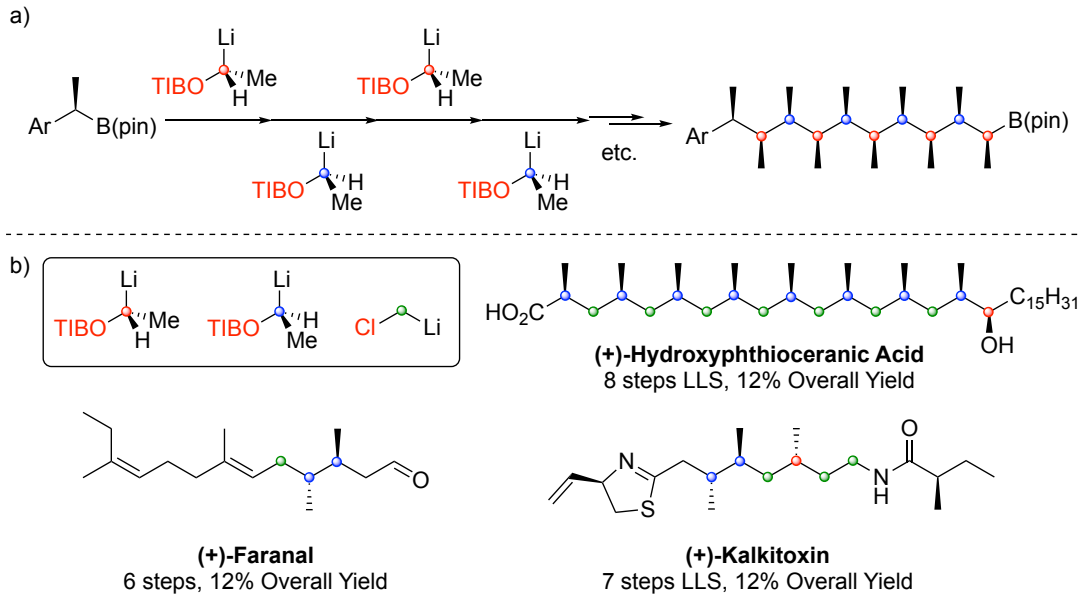
1.2.1 1,2-metallate rearrangement to sp^3 carbon centres

In 1963 Matteson demonstrated that the 1,2-metallate rearrangement could be applied to α-haloalkane boron-ate complexes to form carbon-carbon bonds.[14] 1,2-migration proceeds *via* donation into the σ* orbital of the carbon-halide bond (scheme 2, a), hence an *anti*-periplanar geometry is required in the transition state leading to inversion of configuration at the receiving carbon centre (scheme 2, b).[11,15]



Scheme 2: a) Matteson homologation using (chloromethyl)lithium; b) 'Lithiation-borylation' of a Hoppe carbenoid, demonstrating inversion of configuration at the terminus of the 1,2-migration

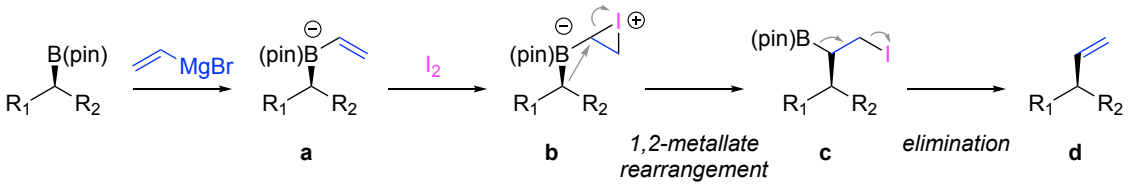
Treatment of an enantioenriched boronic ester with a lithium carbenoid species such as (chloromethyl)lithium can effect a one-carbon homologation (scheme 2, a).[16] The use of chiral lithiated *N*-diisopropylcarbamates, first described by Hoppe,[17] to enact homologations generating a new stereocentre was shown by Aggarwal in 2007 (scheme 2, b).[18] Alongside lithiated 1,3,5-triisopropylbenzoate (TIB) esters, this approach was extended to the iterative synthesis of well-stereodefined alkyl chains and natural products.[19–24] Schemes 3, a and b demonstrate the use of lithiated 1,3,5-triisopropylbenzoate esters as chiral 'building blocks' to install the highlighted carbon stereocentres in the products shown.



Scheme 3: a) Iterative 'assembly-line' synthesis of stereodefined alkyl chain,[22] b) Application of this methodology to synthesis of natural products[21,24]

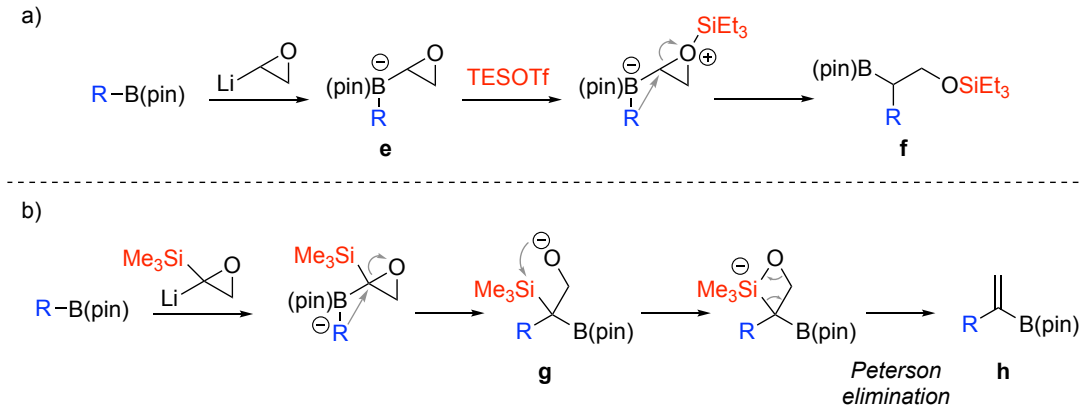
1.2.1.1 1,2-metallate rearrangements to sp^3 centres with ring-opening

A further class of 1,2-metallate rearrangements to sp^3 centres are those that involve the opening of a strained ring. The release of strain from these small rings constitutes a thermodynamic driving force promoting the 1,2-metallate rearrangement.[25] A classic example of this is the Zweifel olefination (scheme 4), in which a 3-membered iodonium ring is generated by treatment of a vinylboron-ate complex **a** (generated by reaction of an alkylboronic ester with vinylmagnesium bromide) with iodine.[26] The zwitterionic species **b** formed subsequently undergoes a 1,2-metallate rearrangement opening this ring, with base-mediated elimination converting the resultant β-iodo boronic ester **c** to an alkene (**d**).

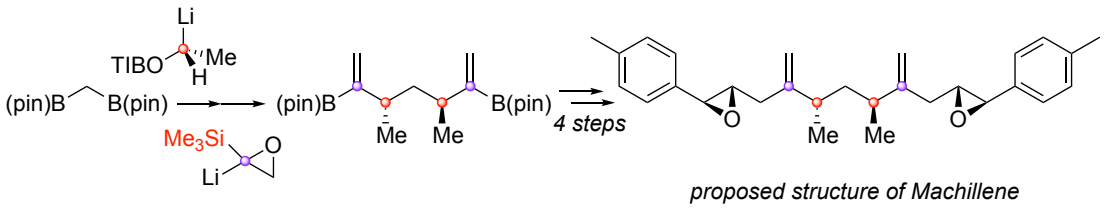


Scheme 4: Zweifel olefination of a pinacol boronic ester

Epoxides and aziridines are also capable of facilitating a 1,2-metallate rearrangement through ring-opening. In these cases, the boron-ate complex required (**e**, scheme 5, a) can be generated by reaction of an alkyl boronic ester with a lithiated epoxide or aziridine.[27–29] Subsequent activation of the heteroatom with a Lewis acid, such as triethylsilyl triflate (TESOTf) enacts the 1,2-metallate rearrangement to give the ring-opened homologation product **f** (scheme 5, a). This reactivity has been exploited by the Aggarwal group for the insertion of methylene groups into carbon-boron bonds, by treating an alkyl boronic ester with a lithiated trimethylsilyl epoxide (scheme 5, b).[30] Following ring-opening, the β-silyl alkoxide species formed (**g**) can undergo a concerted Peterson-type elimination to give the desired vinyl boronic ester product (**h**). This methodology was subsequently applied to the synthesis of the proposed structure of Machillene (scheme 6).[30]

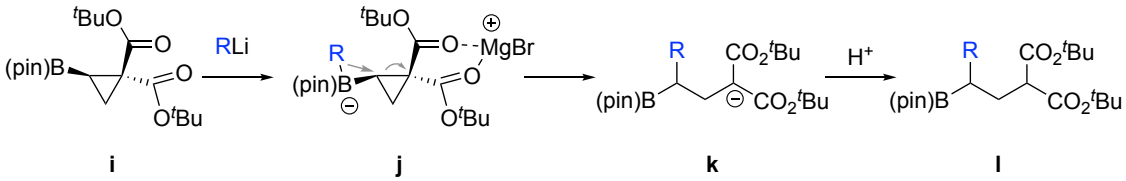


Scheme 5: a) Ring-opening of epoxides by 1,2-metallate rearrangement,[27] b) Vinylidene homologation of boronic esters[30]



Scheme 6: Synthesis of the proposed structure of Machillene, with centres rendered by homologation highlighted[30]

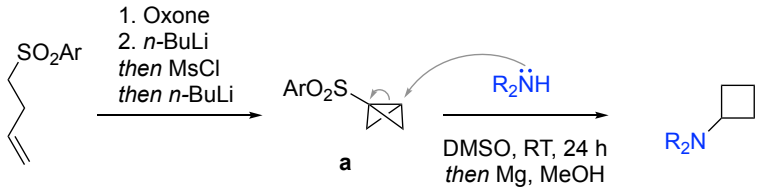
The principle of 1,2-metallate rearrangements promoted by ring-opening has also been applied to the cleavage of C-C bonds in strained rings.[25] 'Donor-acceptor' cyclopropanes are cyclopropanes for which one of the strained carbon-carbon bonds is sufficiently electronically biased by vicinal electron donating and electron withdrawing groups that it is rendered amenable to heterolytic cleavage.[31,32] Cyclopropyl boron-ate complexes bearing two carboxylic esters vicinal to the boron-ate moiety on the cyclopropyl ring can be considered as 'donor-acceptor' cyclopropanes (the boron-ate component being electron donating and the two carboxylic esters electron withdrawing).[25] Following treatment of the parent cyclopropyl boronic ester **i** (scheme 7) with an organolithium to give the boron-ate complex **j**, activation of the two vicinal ester groups with a Lewis acid facilitates the 1,2-metallate rearrangement with opening of the cyclopropane ring.[25] The carbanion formed (**k**), which is stabilised by the two carbonyl groups adjacent, is then protonated to give the open-chain product **l**. It is worthy of note that two ester groups are required at the vicinal carbon for this protocol to work. Attempts at inducing this mechanism with substrates bearing a single ester group failed, due to the reduced amenity of this single ester group to Lewis acid activation compared to the diester.[25]



Scheme 7: 1,2-metallate rearrangement with opening of a cyclopropane ring[25]

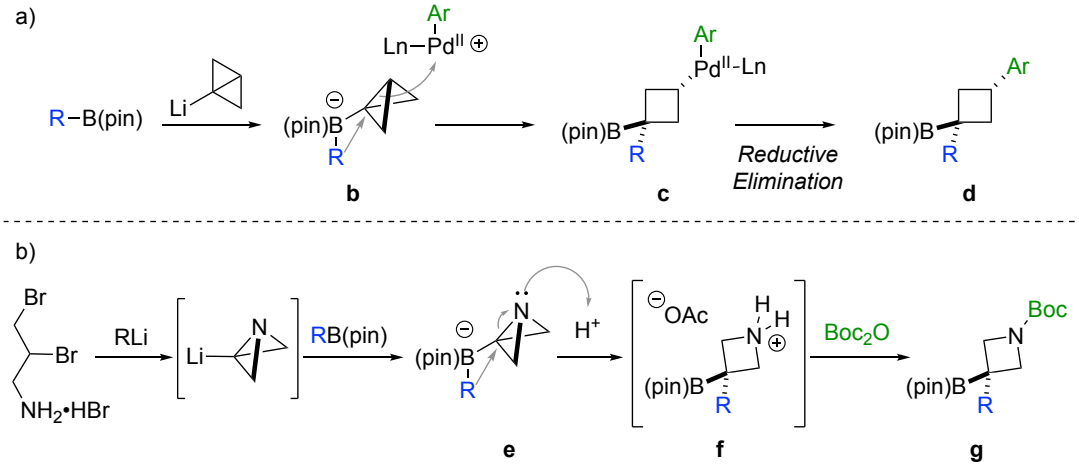
1.2.1.2 Strain-release-driven 1,2-metallate rearrangements from highly strained systems

Bicyclo[1.1.0]butanes (BCBs) may be considered as two edge-fused cyclopropane rings. This constitutes a highly strained molecule. The thermodynamic favourability of releasing this strain renders the central C-C σ bond amenable to being broken to give cyclobutane products. This has been exploited by the Baran group for their 'strain-release' cyclobutylation of amines, in which the central C-C σ bond of a BCB-sulfone (**a**, scheme 8) is broken by the attack of the amine.[33,34] The electron-withdrawing arylsulfonyl group is key for promoting the reactivity of the BCB electrophile towards secondary amines, and is subsequently removed under mild reductive conditions.



Scheme 8: Strain-release cyclobutylation of a secondary amine[33]

Inspired by this work along with Morken's conjuctive cross-coupling of vinylboron-ate complexes[35] (discussed in section 1.2.2), the Aggarwal group sought to demonstrate that bicyclobutylboron-ate complexes can be functionalised across the strained central C-C σ bond by attack of an arylpalladium electrophile.[36] Although C-C σ bonds are generally not known to react with palladium complexes, the ring strain present in the bicyclobutane gives the central C-C σ bond partial π-character – anticipated to facilitate reaction with the organopalladium species. Treatment of a bicyclobutylboron-ate complex (**b**, scheme 9, a), generated by the attack of alkyl or aryl boronic esters by a lithiated bicyclobutane, with arylpalladium electrophiles led to cleavage of the central C-C σ bond alongside the 1,2-metallate rearrangement to furnish a cyclobutyl-aryl-palladium species **c**, which can undergo reductive elimination to give the desired 1,1,3-trisubstituted cyclobutane product **d**. It was proposed that the 1,2-metallate rearrangement from the electron-rich boron-ate moiety and cleavage of the C-C σ bond are concerted, the former providing the 'push' for the latter to occur.[36] The requirement for an *anti*-periplanar relationship of the migrating substituent on boron to the central C-C bond ensures a specific reaction conformation in which the bulky arylpalladium complex coordinates to the less hindered *exo*-face of the bicyclobutane. This gives rise to high diastereoselectivity for the homologation, expected for the concerted mechanism proposed.



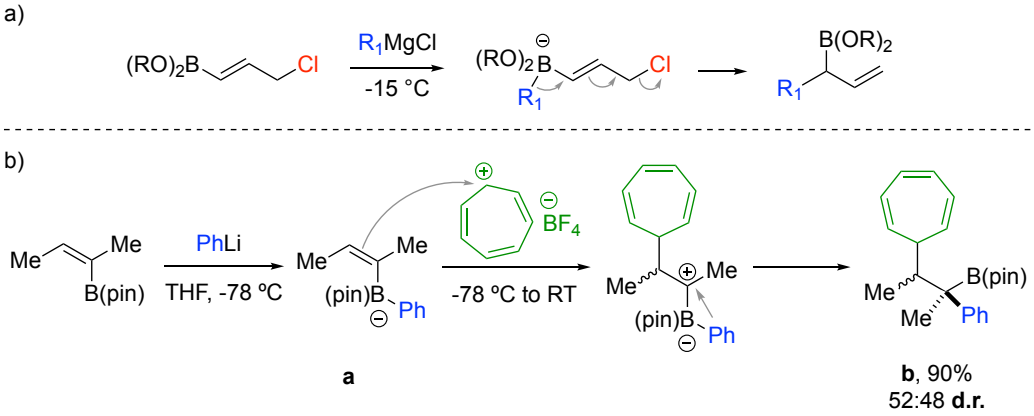
Scheme 9: a) Strain-release 1,2-metallate rearrangement of bicyclobutyl boron-ate complexes with arylpalladium electrophiles;[36] b) Strain-release synthesis of azetidines[37]

Azabicyclo[1.1.0]butane (ABB) can be considered as a heterocyclic analogue to bicyclo[1.1.0]butane in which one of the bridgehead carbon atoms is replaced with a nitrogen atom. The Aggarwal group demonstrated that azabicyclobutane can be lithiated at the bridgehead C-H bond.[37] Treatment of an

alkyl or aryl boronic ester with azabicyclobutyllithium generates a boron-ate complex (**e**, scheme 9, b). This species can be protonated at the bridgehead nitrogen atom by acetic acid, which triggers the opening of the strained central C-N bond and 1,2-migration from the boron-ate moiety to give an azetidine intermediate. This will further protonate under reaction conditions to an azetidinium acetate intermediate **f**, which can then be reacted at nitrogen to furnish an *N*-protected azetidine product (**g**).[37]

1.2.2 1,2-metallate rearrangement to sp^2 carbon centres

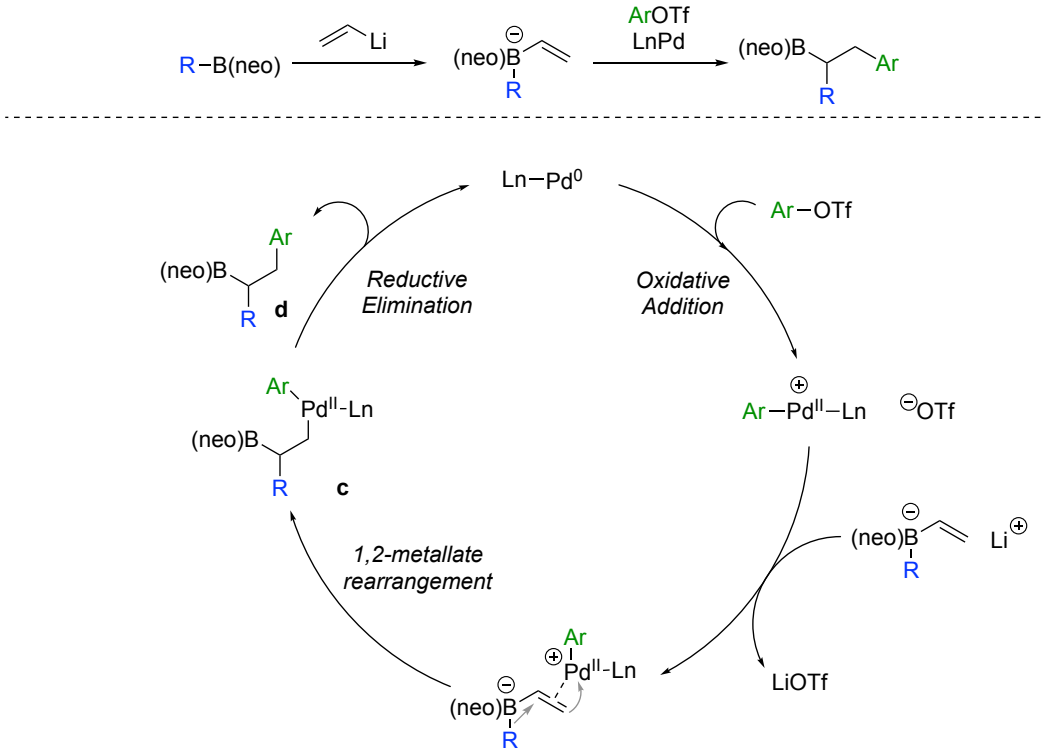
The 1,2-metallate rearrangement into π-systems has been demonstrated for vinylogous homologations of vinyl boron-ate complexes (scheme 10, a), in which the 1,2-migration of the alkyl group from the boron-ate is accompanied with 'migration' of the alkene to eliminate a leaving group γ- to the boron-ate moiety.[38,39] Electrophilic activation of the alkene π-system of vinyl boron-ate complexes, generating a carbocation α- to the boron centre, can also induce a 1,2-metallate rearrangement (scheme 10, b).



Scheme 10: a) Vinylogous homologation giving allylboronic esters; b) 1,2-metallate rearrangement to an α-carbocation generated by electrophilic activation of a vinyl boron-ate complex

Whilst the Zweifel olefination proceeds *via* electrophilic activation of a vinyl boron-ate complex, the invocation of a cyclic iodonium intermediate means this reaction can technically be regarded as a migration to an sp^3 carbon centre, as discussed in section 1.2.1.1. In contrast, the activation of vinyl boron-ate complexes with electrophiles that do not form cyclic intermediates leads to a formal carbocation α- to the boron centre.[40] This species will rapidly undergo a 1,2-metallate rearrangement to give secondary or tertiary alkylboronic esters. In contrast to the high *anti*- diastereoselectivity seen for species that form closed cyclic intermediates, these reactions typically form a mixture of *syn*- and *anti*- products. For example, the reaction of vinyl boron-ate complex **a** (scheme 10, b) with tropylium tetrafluoroborate gives the product **b** as a near equal mixture of diastereomers. This has been attributed to the asynchronous nature of bond formation enabling competing *syn*- migration, eroding the diastereoselectivity.[40]

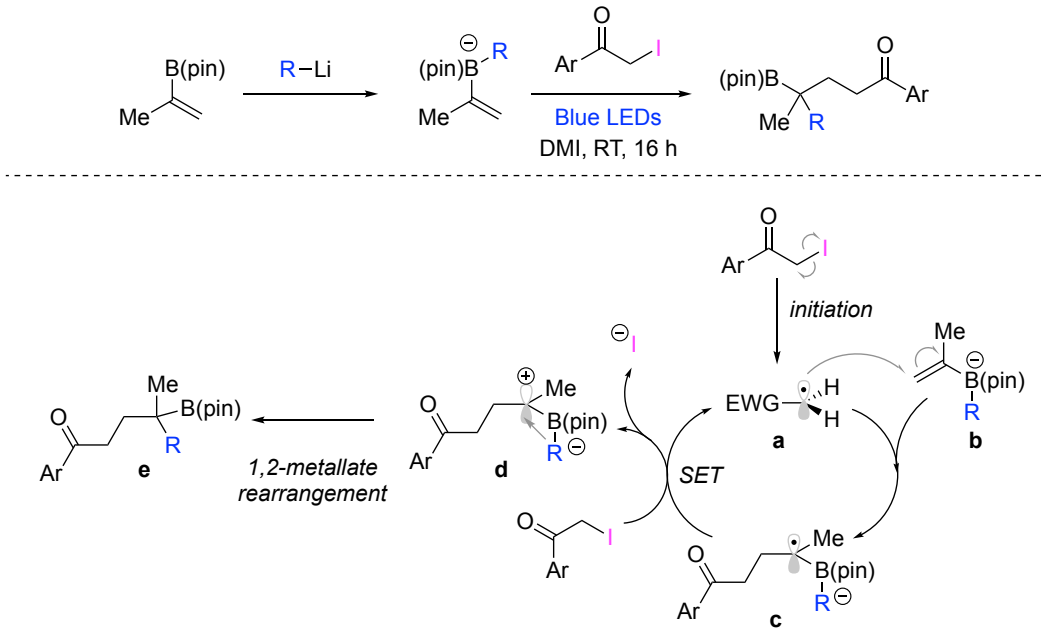
The Morken group has also shown that the alkene π-system of vinyl boron-ate complexes can be activated by arylpalladium electrophiles (scheme 11).[35,41] The subsequent 1,2-metallate rearrangement produces an organopalladium intermediate **c** with a C-Pd σ bond. Reductive elimination from this organopalladium intermediate forms a new carbon-carbon bond (in compound **d**). This reaction may be considered as a formal conjunctive cross-coupling reaction, forming two new carbon-carbon bonds in a single catalytic cycle. The use of chiral ligands on the palladium centre has also enabled the 1,2-metallate rearrangement to occur with high levels of enantioselectivity to form enantioenriched products.[41]



Scheme 11: Morken's conjunctive cross-coupling of vinyl boron-ate complexes with arylpalladium electrophiles[35]

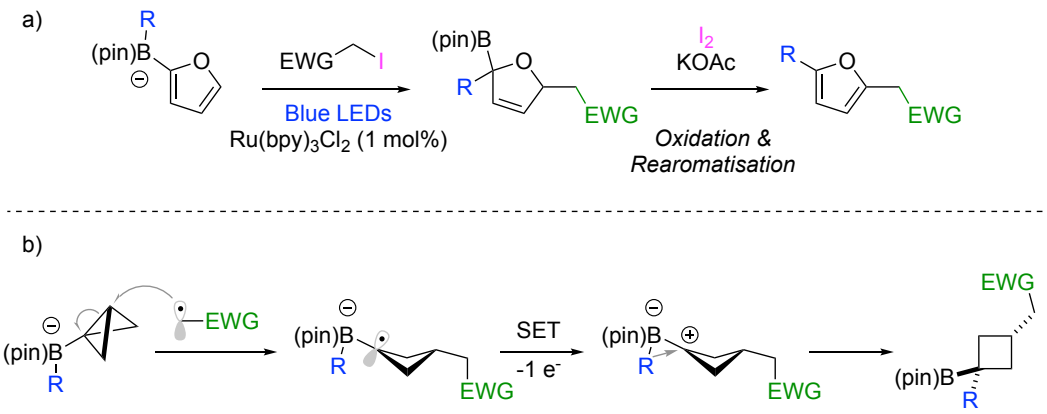
1.2.2.1 Radical-induced 1,2-metallate rearrangements to sp^2 carbon centres

In 2017, the Aggarwal and Studer groups independently reported the induction of 1,2-metallate rearrangements of vinyl boron-ate complexes *via* a radical polar crossover mechanism (scheme 12).[12,13] An α-boryl radical **c** is generated by the addition of an electron-poor alkyl radical **a** to the double bond of the vinyl boron-ate complex **b**, the regioselectivity of this driven by the inductive stabilisation of the radical formed by the electron-rich boron-ate moiety. This radical is then oxidised to an α-boryl carbocation **d** (representing the crossover from a radical to a polar mechanism), which induces the 1,2-metallate rearrangement to give the product **e**.[12,13] This oxidation is proposed to occur by single electron transfer (SET) from the radical intermediate **c** to the alkyl iodide starting material, which regenerates the alkyl radical, thus propagating the cycle.[12]



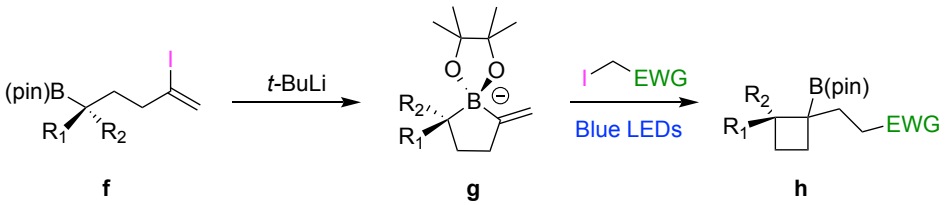
Scheme 12: 1,2-metallate rearrangement induced by a radical-polar crossover mechanism following attack of a vinyl boron-ate complex[12]

The scope of 1,2-metallate rearrangements induced by a radical polar crossover mechanism have been expanded to include three-component alkylations of furans and indoles (scheme 13, a),[42] as well as difunctionalisation across the strained central C-C σ bond of bicyclobutyl boron-ate complexes (scheme 13, b).[43]



Scheme 13: a) 3-component alkylation of furan;[42] b) Addition of radicals to bicyclobutyl boron-ate complexes;[43]

A further interesting application of this chemistry is the visible light-driven strain-increase ring contraction of 5-membered cyclic alkenyl boron-ate complexes to give functionalised cyclobutane products (scheme 14).[44] Cyclobutanes are typically difficult to generate by ring-closure due to the required eclipsed transition state conformation having a high conformational energy barrier. The protocol described here circumvents this barrier by generating a 5-membered boron-ate ring **g** (one of the easiest ring-sizes to make by ring closure of acyclic precursors) from intramolecular attack of a boronic ester **f**, which is then contracted to the more strained cyclobutane ring **h**.[44]

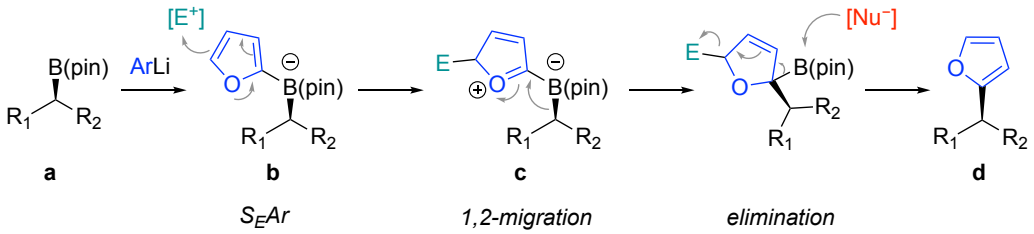


Scheme 14: Strain-increase ring contraction of cyclic boron-ate complexes to give cyclobutanes[44]

1.2.2 Electrophilic activation of aryl boron-ate complexes

1.2.2.1 Electron-rich aromatics

The Suzuki-Miyaura reaction is widely used for the construction of sp^2-sp^2 carbon-carbon bonds but is more limited for sp^2-sp^3 cross-coupling due to competing β-hydride elimination (this will be discussed in section 2.2.2). The Aggarwal group has shown that stereospecific sp^2-sp^3 cross-coupling of aliphatic boronic esters with lithiated aromatics can be achieved by exploiting the tendency of boron-ate species to undergo 1,2-metallate rearrangements to α-carbocations (scheme 15).[45–47] This reaction may be considered as an arene analogue to the Zweifel olefination – both achieving enantiospecific sp^2-sp^3 cross-coupling through electrophilic activation of an sp^2 system to promote the 1,2-metallate rearrangement (with subsequent nucleophile or base induced elimination to give the cross-coupled product).

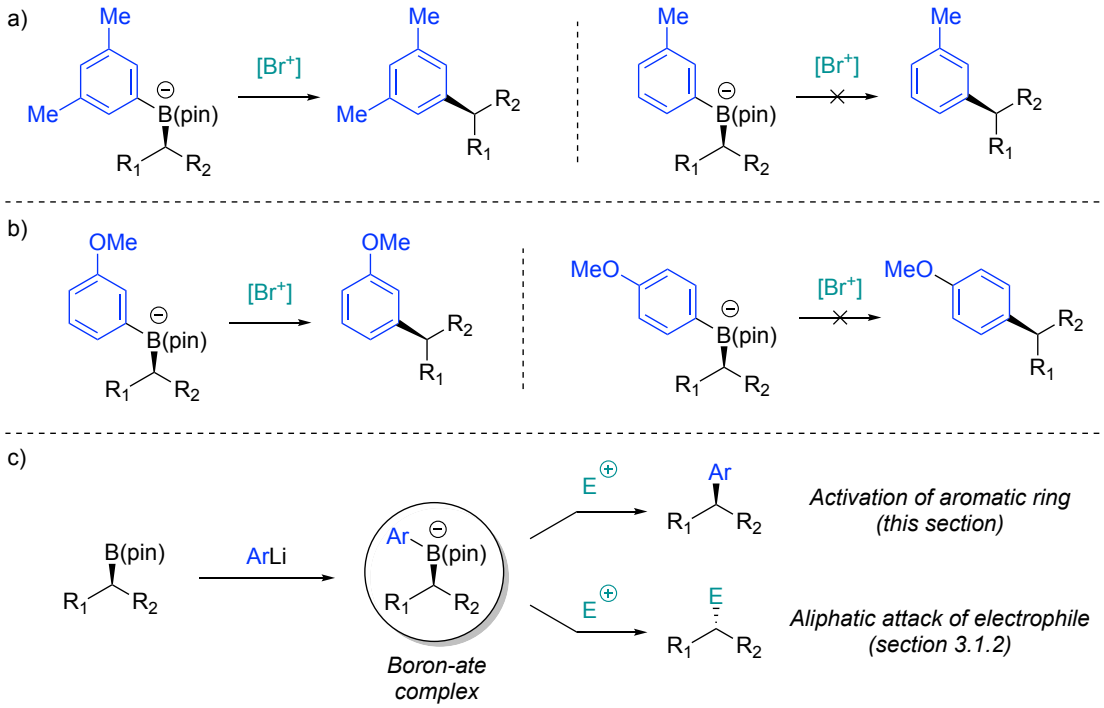


Scheme 15: Aggarwal sp^2-sp^3 cross-coupling to electron rich aromatics[45]

The first step of the cross-coupling is generation of a boron-ate complex **b** (scheme 15) by reaction of the aliphatic boronic ester **a** with a lithiated arene (these two reagents being the two cross-coupling partners).[45] Treatment of boron-ate complexes bearing an electron-rich arene with *N*-bromosuccinimide (or another electrophilic oxidant) activates the aromatic ring in an S_EAr fashion, giving a carbocation adjacent to the boron-ate moiety (**c**).[45,46] Subsequent 1,2-migration followed by elimination of the boronic ester and leaving group (by attack of a nucleophile such as methanol) results in a formal stereospecific sp^2-sp^3 coupling (giving the product **d**).

The arene ring must be sufficiently electron rich to undergo S_EAr activation. Coupling was observed for 3,5-dimethylphenyllithium but not 3-methylphenyllithium (scheme 16, a).[45] Substitution patterns around the ring can also influence the success of this protocol. Cross-coupling to a *meta*-substituted methoxyphenyllithium was achieved, but not to *ortho*- or *para*- methoxyphenyllithium (scheme 16,

b).[45] This is due to a requirement for carbocationic character adjacent to the boron-ate moiety in the activated intermediate to facilitate the 1,2-migration.[45]



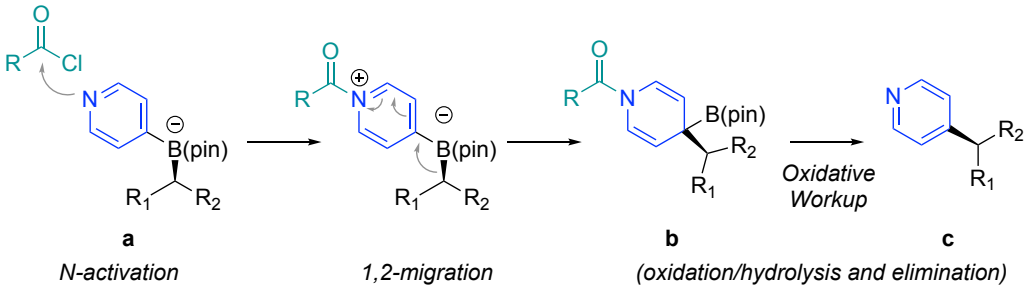
Scheme 16: a) 3,5-dimethylphenyl arene is sufficiently electron rich to undergo cross-coupling, but not 3-phenyl arene, b) 3-methoxyphenyl arene undergoes cross-coupling, whereas competing aliphatic attack of electrophiles dominates for 4-methoxyphenyl arene, c) The two possible pathways, dependent on how amenable the aryl group is to S_EAr

In cases where the aryl group is not amenable to electrophilic activation or 1,2-migration, a competing reaction of boron-ate complexes at the aliphatic carbon substituent is the dominant pathway (scheme 16, c). Depending on the electrophile used, this can occur with complete stereospecificity with inversion of configuration at the carbon centre. This has been exploited by the Aggarwal group in the development of these species as chiral nucleophiles.[6,7,48] This will be discussed in section 3.1.2.

1.2.2.2.2 *N*-heteroaromatic compounds

In contrast with the electron-rich aromatics discussed in the previous section, pyridine is too electron deficient to undergo S_EAr reactions. Therefore, a different approach is required to facilitate the 1,2-migration. Activation of the pyridine nitrogen atom of the pyridyl boron-ate complex **a** (scheme 17) with an acylating agent such as 2,2,2-trichloroethyl chloroformate (Troc-Cl) facilitates the 1,2-migration, forming an *N*-acyl dihydropyridine species **b**. An oxidative work-up is required to hydrolyse the *N*-acyl component and oxidise the boronic ester component to an alcohol, which is then eliminated to give the cross-coupled pyridine product **c**.[47]

Whilst coupling at the C4 position using this protocol is facile for both secondary and tertiary boronic esters, coupling at the C2 position is more capricious. This was assumed to be due to increased steric demand disfavouring reaction at the pyridine nitrogen atom.[47]



Scheme 17: Aggarwal sp^2-sp^3 coupling of boronic esters with lithiated pyridines[47]

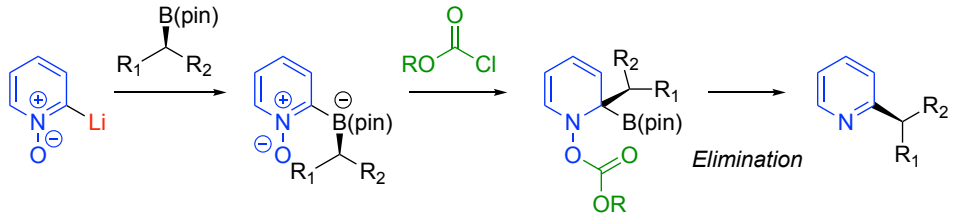
1.3 Project proposals

This report will detail four projects geared towards developing the use of 1,2-metallate rearrangements of boron-ate complexes for the generation of medicinally relevant compounds.

1.3.1 Stereoretentive cross-coupling to pyridines at the C2 position

The cross-coupling of sp^3-rich units to pyridine rings is desirable synthetically for the generation of viable drug-like molecules, particularly if this transformation can introduce or preserve stereochemistry at the sp^3 carbon centre. The Aggarwal group has shown that this transformation can be achieved using the stereospecific migration of alkyl groups from boron-ate complexes to *N*-activated pyridine rings discussed in section 1.2.2.2.2.[47] Although this protocol works well for cross-couplings at the C4 position of pyridine rings, it is considerably less reliable for coupling to the C2 position. This has been attributed to the steric bulk of the boron-ate complex at the C2 carbon blocking or disfavouring the activation of the pyridine nitrogen lone pair by the electrophilic activator.[47]

This project seeks to improve upon this protocol in finding a reliable method for achieving stereospecific C2 couplings to pyridines *via* the 1,2-metallate rearrangement. It is proposed that the use of pyridine *N*-oxides may promote this transformation – the lone pair on oxygen being further from the steric bulk of C2 substituents on pyridine and therefore more available to activation to promote the 1,2-metallate rearrangement (scheme 18).

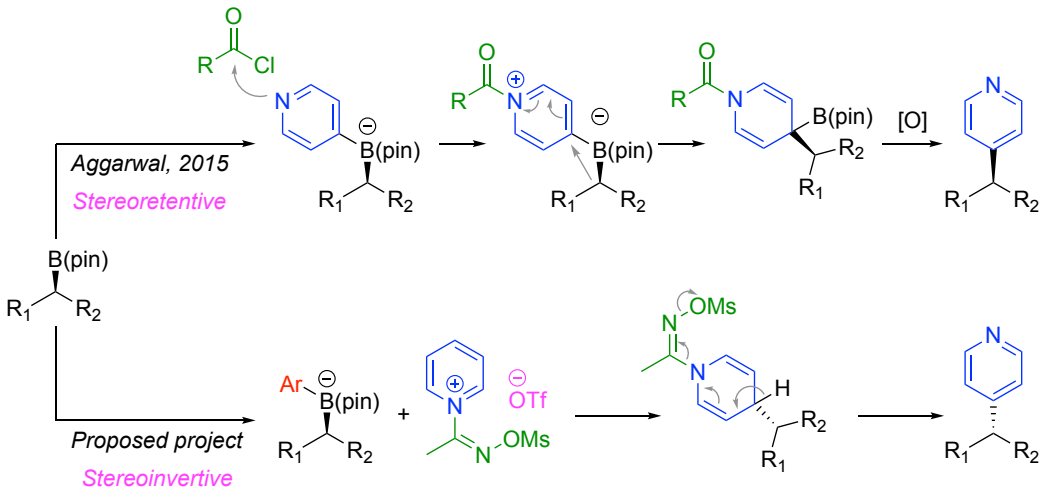


Scheme 18: Proposed coupling to pyridine *N*-oxides

1.3.2 Stereoinvertive cross-coupling to pyridines at the C4 position

As discussed briefly in section 1.2.2.2.1, chiral boron-ate complexes bearing arene groups not capable of undergoing the described S_EAr pathway can react with electrophiles at the aliphatic centre in a stereoinvertive fashion. These chiral boron-ate nucleophiles have been shown to be capable of adding to pyridinium ions generated by *N*-acylation of the pyridine nitrogen to give dihydropyridine products.[48]

Here it is proposed to use of an acylating agent capable of subsequentially acting as a leaving group in a base-promoted elimination following addition of the nucleophile (scheme 19, lower pathway). It is envisaged that this nucleophilic addition-elimination pathway will be a stereoinvertive cross-coupling. This would be complementary to the cross-coupling of enenatioenriched boronic esters with lithiated pyridines described in section 1.2.2.2.2,[47] enabling the synthesis of both product enantiomers from a single enantiomer of the starting boronic ester (scheme 19).

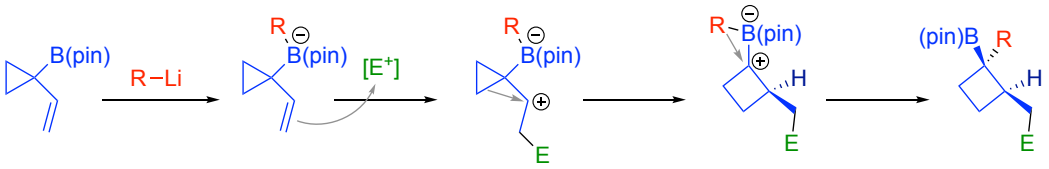


Scheme 19: Reported stereoretentive cross-coupling and proposed stereoinvertive cross-coupling

1.3.3 Synthesis of cyclobutanes *via* ring expansion of vinylcyclopropyl boronic esters

The 1,2-metallate rearrangement of boron-ate complexes with an α-carbocation is well established, however it is currently not possible to induce a 1,2-metallate rearrangement by generating a carbocation at the β-carbon. It is envisaged that if the carbon α- to boron is part of a strained ring, a 1,2-alkyl shift expanding the ring (in part relieving the ring strain) will produce a carbocation α- to the boron-ate moiety, enabling the 1,2-metallate rearrangement to occur.

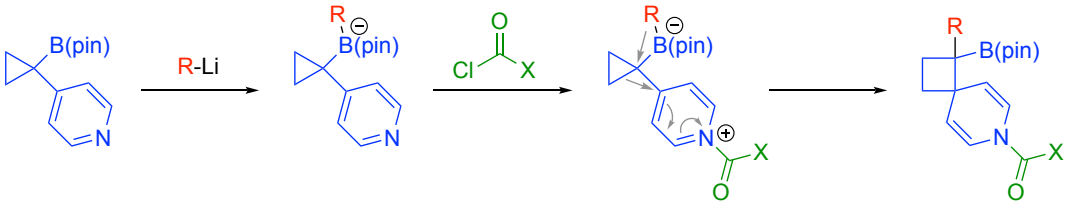
Therefore, this work seeks to develop and demonstrate the scope of a new method for the synthesis of highly substituted cyclobutyl boronic esters by employing a novel strategy to promote 1,2-metallate rearrangements: the ring expansion of electrophile-activated vinylcyclopropyl boron-ate complexes (scheme 20).



Scheme 20: Proposed ring-expansion induced 1,2-metallate rearrangement of vinylcyclopropyl boron-ate complexes

1.3.4 Synthesis of spirocycles by migration-driven dearomatisation of pyridines

Further to the proposed ring-expansion of vinylcyclopropyl boronic esters detailed in section 1.3.3, it is proposed that activation of the pyridine nitrogen atom of pyridylcyclopropyl boron-ate complexes should similarly enact expansion of the cyclopropane ring and 1,2-metallate rearrangement of the boron-ate complex to form complex dihydropyridine spirocycles (scheme 21).



Scheme 21: Proposed ring-expansion induced 1,2-metallate rearrangement of pyridiylcyclopropyl boron-ate complexes to generate dihydropyridine spirocycles

2 Enantiospecific C2-coupling to pyridines

2.1 Importance of *N*-Heterocycles in drug discovery

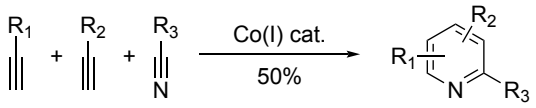
Nitrogen-containing heterocycles are important motifs in bioactive molecules, and are present in 59% of FDA-approved small-molecule pharmaceuticals.[49] Pyridine rings account for a large proportion of these – 10% of the total, and are components in many anti-cancer and anti-malarial drugs.[49,50]

2.2 Synthesis of alkyl-substituted pyridines

Studies have shown that three-dimensional scaffolds comprised of sp^3-rich units (especially if asymmetric) have greater clinical success than flatter achiral molecules, due to improved binding efficiency to target sites and reduced receptor promiscuity (which can influence toxicity).[51,52] This has fuelled a demand for pyridines bearing sp^3-rich substituents (or alternatively, sp^3-rich molecules containing pyridine rings),[53] therefore the synthesis of asymmetric alkyl-substituted pyridines is an important area of organic chemistry.

2.2.1 Multicomponent reactions

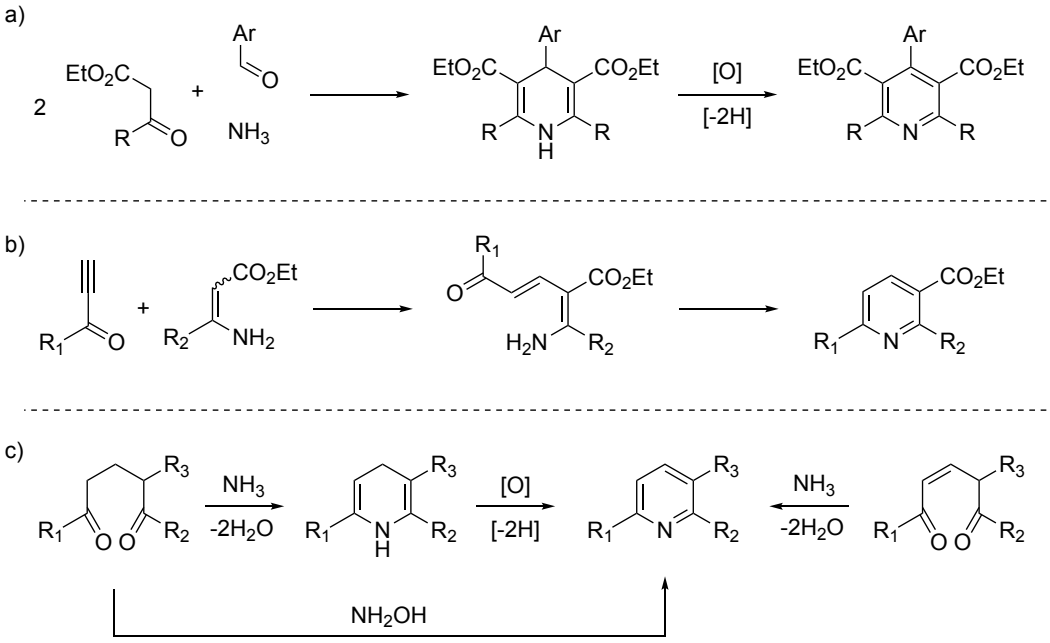
Traditional approaches to syntheses of substituted pyridines have involved multicomponent reactions, forming the pyridine ring from readily available acyclic components.[54] The original laboratory synthesis of pyridine in 1876 was conducted by cyclisation of acetylene and hydrogen cyanide at high temperatures.[54] Cobalt(I)-catalysed variants have superseded this, comprising a commercially important route to simple alkyl-substituted pyridines from readily available alkynes and cyanides (Scheme 22).[55] This approach has enabled the synthesis of a wide variety of multi-substituted pyridines, however a lack of control over regioselectivity limits use of this for target synthesis of specific substitution patterns.[54]



Scheme 22: Cobalt(I)-catalysed alkylpyridine synthesis

More reliable methods for targeted synthesis of pyridines with specific substitution patterns have been developed, typically involving condensation of amines with carbonyls. Classical examples include the Hantzsch synthesis (scheme 23, a) of symmetrically substituted dihydropyridines bearing electron-withdrawing substituents (which are readily oxidised to the respective pyridine),[54,56] and the Bohlmann-Rahtz synthesis of 2,3,6-substituted pyridines (scheme 23, b).[57] The route with most control over the substitution pattern is the condensation of 1,5-dicarbonyl compounds with ammonia (scheme 23, c). This generates dihydropyridines which can be readily oxidised to the respective pyridines, however accessing the 1,5-dicarbonyl starting material can be an issue.[54] Use of unsaturated

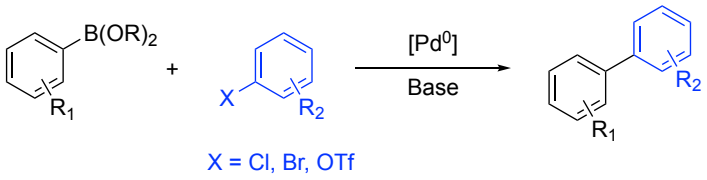
1,5-dicarbonyls, or hydroxylamine in place of ammonia,[58] can directly give the pyridine without the requirement for an additional oxidation step.[54]



Scheme 23: Multicomponent condensations, a) Hantzsch dihydropyridine synthesis and oxidation, b) Bohlmann-Rahtz pyridine synthesis, c) From 1,5-dicarbonyls

2.2.2 Suzuki-Miyaura coupling

Whilst multicomponent routes to substituted pyridines find application in diversity-oriented synthesis of various substituted pyridines,[54] contemporary approaches to target synthesis often employ cross-couplings or functionalisation of pre-formed or existing heteroaromatics.[59–61] The Suzuki-Miyaura reaction – the transition-metal-catalysed cross-coupling of organoboron reagents with organohalides or triflates (scheme 24) – is ubiquitous in pharmaceutical industry as a reliable method for forming sp^2-sp^2 carbon-carbon bonds, in part due to wide availability and low toxicity of organoboron substrates.[10,62]

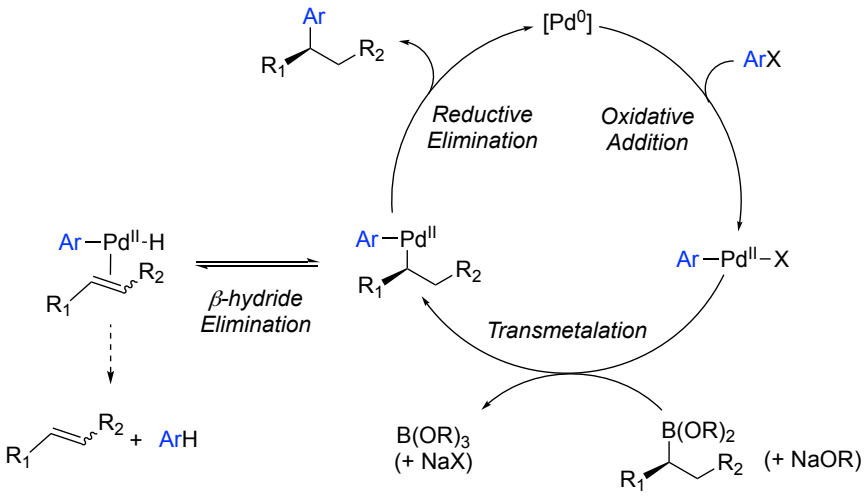


Scheme 24: Biaryl synthesis using the Suzuki-Miyaura reaction

The development of sophisticated protocols have enabled the use of heteroaromatic boronic acids/esters[63,64] and heteroaryl halides[64,65] as coupling partners, however this approach is often unreliable for functionalisation of pyridines.[62] Electron-deficient arylboronic acids tend to suffer slow transmetalation, hence are poor nucleophilic coupling partners for the Suzuki-Miyaura reaction.[62,66]

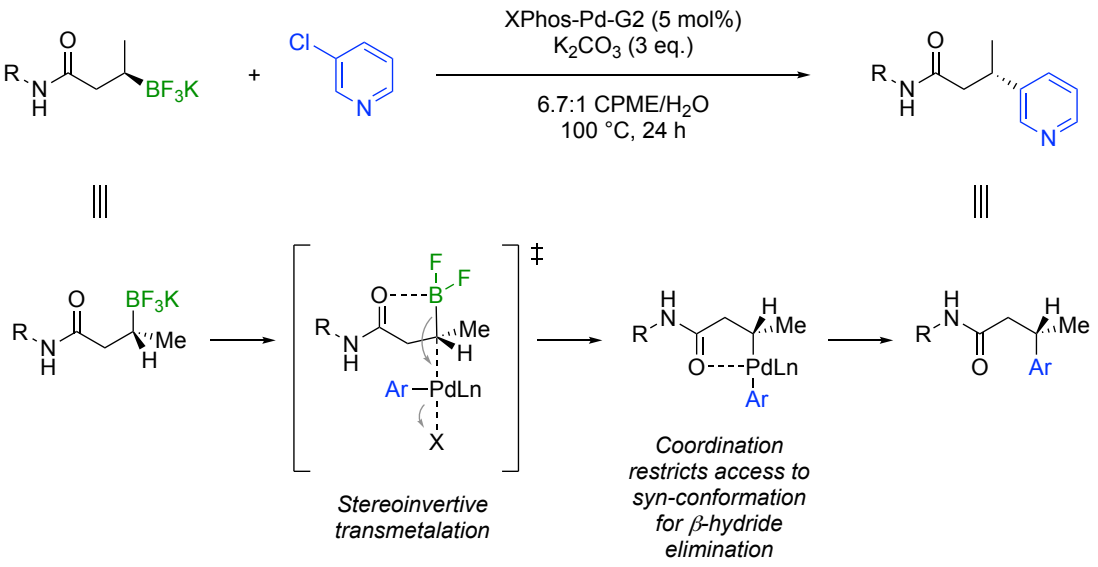
Furthermore, the pyridine nitrogen atom can coordinate to metal catalysts reducing reactivity,[67] or promote protodeboronation of 2-pyridyl boron-ate species.[68]

Whilst sp^2-sp^2 Suzuki-Miyaura couplings to pyridines are well established,[69,70] few examples of sp^2-sp^3 couplings have been reported. A general issue limiting application of the Suzuki-Miyaura reaction towards sp^2-sp^3 coupling is the propensity of alkylpalladium intermediates to undergo β-hydride elimination (scheme 25).[1,71] This is especially pronounced for secondary alkyl groups, for which transmetalation is difficult.[71]



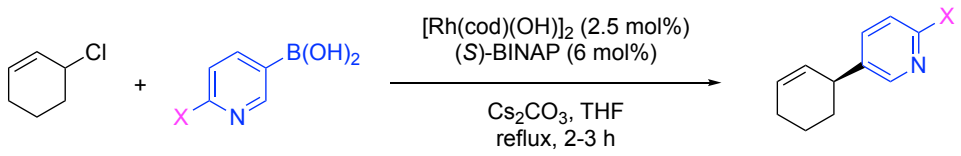
Scheme 25: Mechanism of the Suzuki-Miyaura reaction for sp^3 boronic acids or esters

To achieve stereospecific Suzuki-Miyaura couplings of chiral organoboron species, transmetallation of the boronic ester to the organopalladium intermediate needs to be stereospecific, with reductive elimination sufficiently rapid to outcompete β-hydride elimination (which would cause isomerisation or olefin side-products).[1] Such stereospecific examples have been described using carefully chosen substrates in order to fulfil these criteria. Cyclopropanes have increased π-character, which facilitates transmetallation, whilst β-hydride elimination is disfavoured due to increased ring strain of cyclopropenes.[1,72] Benzylic[73,74] and allylic[75] examples have been reported, these having increased reactivity for transmetallation and fast reductive elimination.[1] Other examples utilise coordinating groups – amides or esters – which facilitate stereospecific transmetallation and conformationally restrict β-hydride elimination (scheme 26).[1,76,77]



Scheme 26: sp^2-sp^3 cross-coupling to 3-chloropyridine with stereoinvertive transmetalation[78]

Examples of stereospecific sp^2-sp^3 Suzuki-Miyaura cross-coupling to pyridines have been achieved using organotrifluoroborate substrates (scheme 26), which are air-stable, non-toxic and are reactive towards transmetalation with minimal competing protodeboronation.[76,78,79] An asymmetric rhodium-catalysed variant of the Suzuki-Miyaura reaction has been reported, allowing coupling of pyridyl boronic acids with cyclic allyl chlorides (scheme 27).[67] Intriguingly a range of pyridylboron species were tested for this protocol, with only pyridyl boronic acids bearing a chlorine or fluorine substituent at the C2 position of the pyridyl ring found to be successful. This substituent effect was attributed to the decreased Lewis basicity of the *N*-atom reducing binding to rhodium which can inhibit the reaction.[67] Overall, examples of stereospecific Suzuki-Miyaura couplings to pyridines are rare and tend to be limited in scope, with a general protocol allowing the coupling of stereoenriched secondary and especially tertiary alkyl species to pyridines remaining a challenging goal.[47]

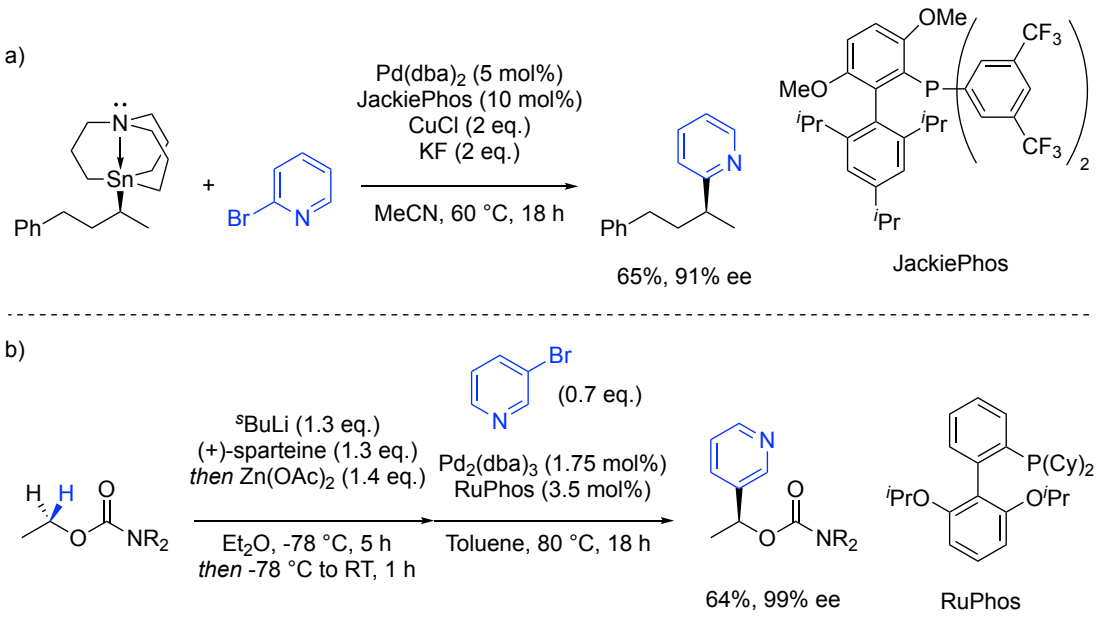


Scheme 27: Asymmetric Rhodium-catalysed Suzuki coupling of cyclic allyl chlorides and heteroaryl boronic acids[67]

2.2.3 Other cross-coupling reactions

Although the Suzuki-Miyaura reaction is generally preferred in industry due to the ease of access to, stability and low toxicity of organoboron compounds, other transition-metal mediated cross-couplings also find use for functionalising pyridines.[10] Stereospecific protocols for Stille[80,81] (scheme 28, a) and Negishi[82,83] (scheme 28, b) couplings to pyridines have been developed. As with Suzuki-Miyaura

coupling, these tend to be limited in scope, with the generation of toxic tin or zinc waste further reducing desirability.[10] Most examples of Negishi coupling form the organozinc reagent by lithiation or magnesiation of a precursor followed by transmetalation to zinc immediately prior to the cross-coupling – this operational complexity a further disadvantage limiting usage.[10]



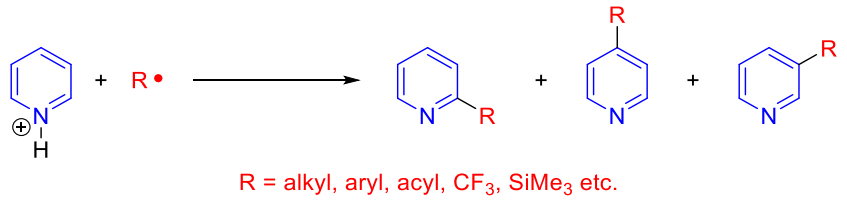
Scheme 28: a) Stereospecific Stille coupling to 2-bromopyridine,[80] b) Enantioselective Negishi coupling to 3-bromopyridine[83]

2.2.4 C-H functionalisation

The cross-couplings discussed in sections 2.2.2 and 2.2.3 all require use of pyridine rings bearing functional substituents – either organometallic species (boronic esters or stannanes) or halogen atoms. Typically, the need for pre-existing functionality in order to perform these reactions delivers the requirement for additional upstream steps in order to introduce these functionalities, with associated synthetic inefficiency.[84] A preferable approach to functionalisation of pyridines is the activation of existing C-H bonds, which has the advantage of improved step and atom economy alongside reduction of upstream waste.[84,85]

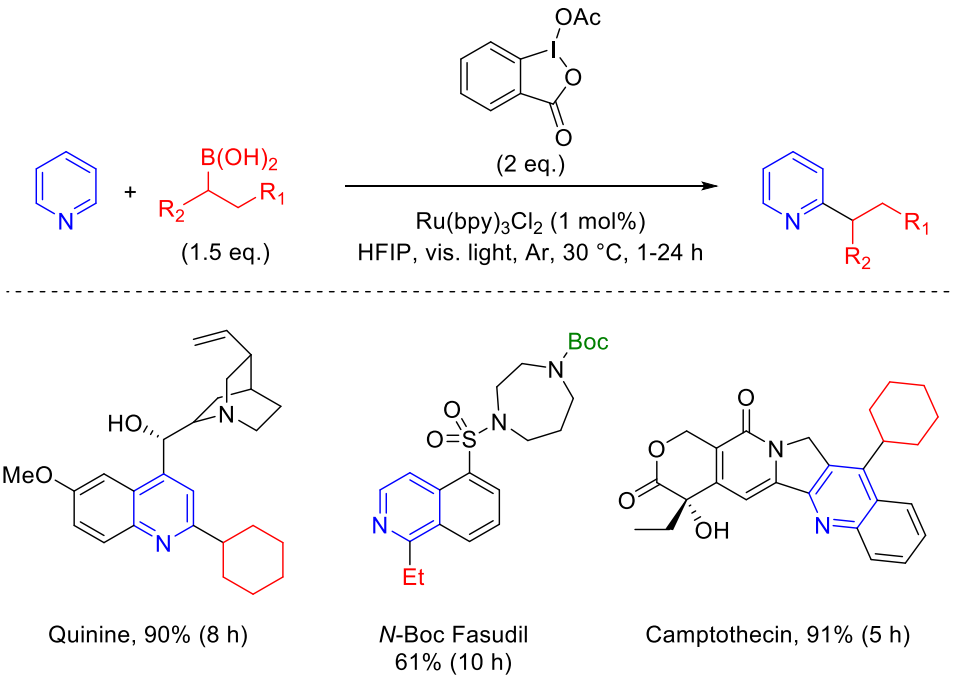
2.2.4.1 Radical-based protocols

The Minisci reaction, first reported in 1968, is a radical-mediated coupling to unfunctionalised pyridines in which alkyl radicals are trapped by a protonated heterocycle (scheme 29).[86] Following formation of the carbon-carbon bond, oxidative re-aromatisation delivers the functionalised pyridine product.[87]



Scheme 29: The Minisci reaction

Minisci reactions constitute a powerful method for C-H functionalisation of pyridines, the high chemoselectivity of carbon-centred radical addition to heteroaromatics in the presence of alcohols or amides (common moieties in drug molecules) allowing Minisci coupling even to complex substrates.[87,88] The scope of radical coupling partners for Minisci-type reactions is broad, with examples using (but not limited to) alkyl,[86,89–92] aryl,[93] fluoroalkyl,[94,95] acyl,[96,97] and silyl[98] radicals reported.[88] A variety of radical precursors can also be used, including alkyl halides,[93] carboxylic acids,[89] boron-ate species,[91] sulfinates[99] and Barton esters.[100] Photoredox catalysis has also enabled Minisci-type reactions using radicals generated from alcohols,[92] ethers[101] and boronic acids[90] under mild conditions. This has enabled late-stage functionalisation of complex molecules avoiding the use of strong oxidants or high temperatures for radical generation (scheme 30).[102]

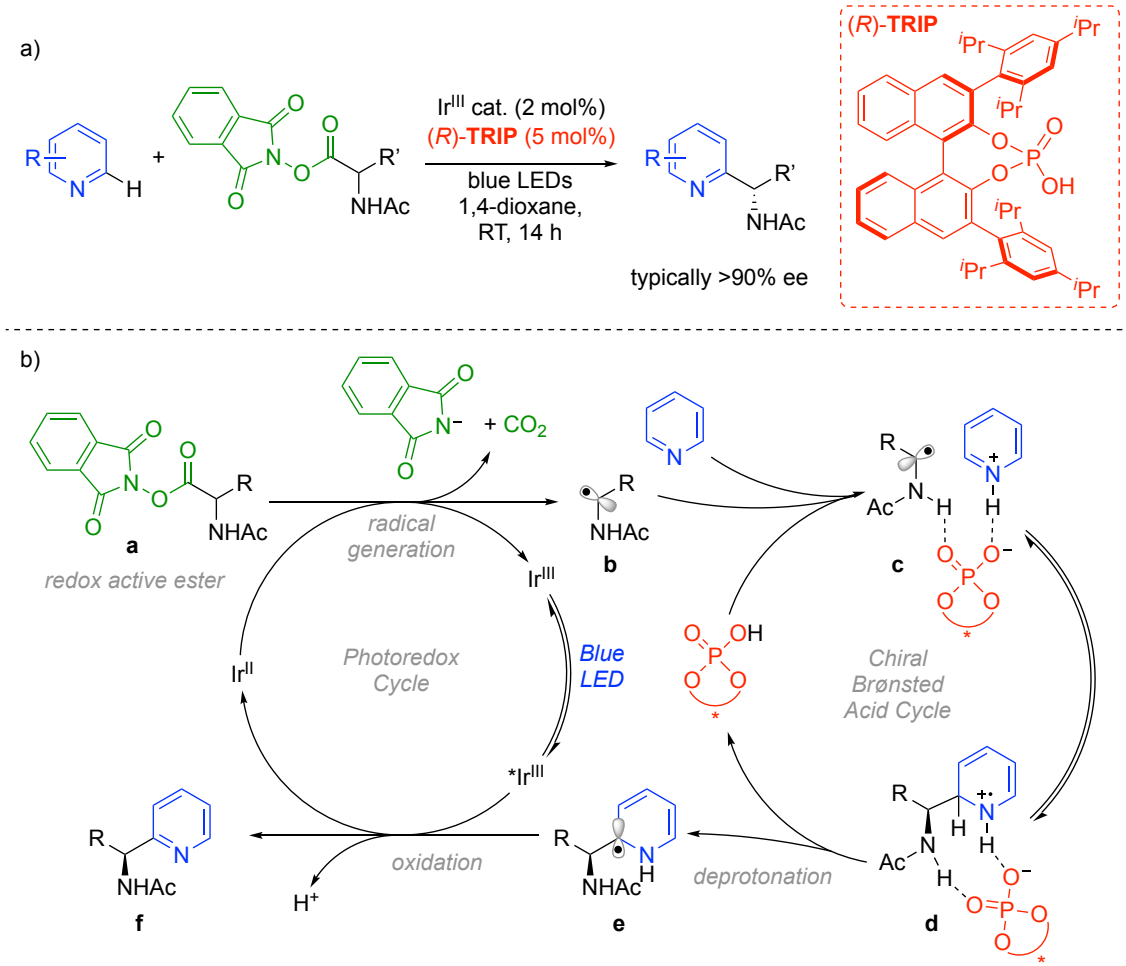


Scheme 30: Photoredox Minisci C-H alkylation and application to complex molecules reported by Liu and Chen[90]

A general limitation of Minisci-type reactions is difficulty controlling regioselectivity, with attack at *ortho*, *meta* and *para* positions of the pyridine ring all possible.[88] This can often result in a mixture of regioisomers or side-products from multiple addition to the pyridine ring, which is undesirable for specific target synthesis. A further limitation is the general inability to render or transfer

stereochemical information through intermolecular radical processes due to the conformational instability of sp^3-centered radicals. There are limited examples of stereoselective radical additions to pyridines driven by the stereochemistry of the sp^3 coupling partner.[91]

The use of an enantiopure chiral Brønsted acid catalyst to coordinate to the pyridine nitrogen, activating the pyridine to radical addition and inducing asymmetry, is a contemporary approach for achieving enantioselective radical addition. This has been utilised by Phipps and co-workers for their enantioselective photoredox Minisci-type addition to pyridines (scheme 31, a).[103]



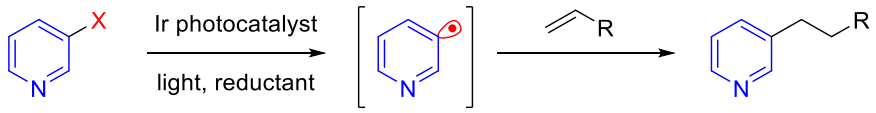
Scheme 31: a) Phipps' catalytic enantioselective Minisci-type addition to pyridines, b) Proposed mechanism

The proposed mechanism for this reaction involves two catalytic cycles: the iridium photoredox cycle, which is responsible for the initial reductive generation of radical **b** (scheme 31, b) from the redox active ester precursor and the oxidation forming the final product **f**, and the chiral phosphoric Brønsted acid cycle which sets the stereochemistry of radical addition to the pyridine substrate.[103] Following the generation of radical **b**, this species coordinates to the chiral Brønsted acid along with the pyridine, forming complex **c**. Minisci-type radical addition within this complex forms radical cation species **d**, which then regenerates the chiral Brønsted acid and forms radical species **e** upon

deprotonation. Finally, oxidation of radical species **e** by the excited Ir^{III} photocatalyst in the photoredox cycle delivers the coupled product **f**.

The chiral phosphoric Brønsted acid plays a highly important role both in ensuring regioselectivity of addition at the C2 position of the pyridine ring (>20:1 regioselectivity for C2 over C4) and inducing a high degree of enantioselectivity. Enantioselectivities of >90% ee were reported for a variety of quinoline and substituted pyridine substrates, with good to excellent yields – typically above 70%. This chemistry represents an important contemporary method for rendering stereocentres adjacent to the C2 position of pyridine rings.

A complementary approach to radical functionalisation of pyridines is to generate the radical on the pyridine ring and trap this with a radical acceptor, such as an olefin. This has been achieved using photoredox-induced reductive radical formation from halopyridines (scheme 32).[87] Subsequent trapping of these radicals with olefins or alkynes delivered alkylated pyridines as single regioisomers.[87] This approach avoids the regioselectivity issues typical for Minisci-type radical additions, but at the cost of a requirement for existing functionality (halogen atoms) on the pyridine ring.

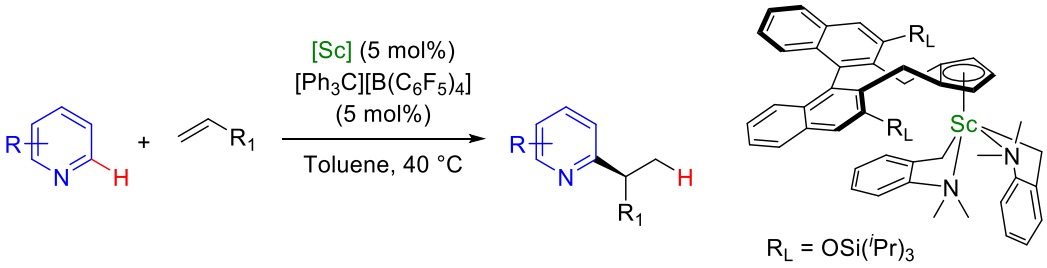


Scheme 32: Regioselective formation of pyridyl radical from halopyridine and trapping

2.2.4.2 Transition-metal catalysed protocols

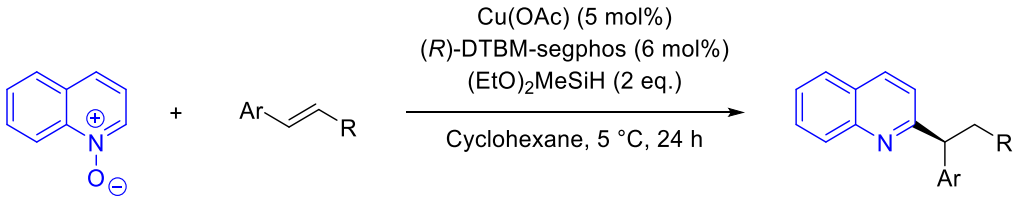
Transition-metal catalysed C-H functionalisation constitutes an important and atom economic method of functionalising aromatic rings,[84] capable of introducing carbon-carbon bonds with high regio- and chemoselectivity.[104] Pyridine rings are capable of undergoing activation at the C2 and C4 positions in the absence of pre-existing functional groups on the ring, however achieving selective activation of the C3 C-H bond typically requires the presence of a directing group at the C4 position to direct the metalation.[104–106]

Activation of the C-H bond at the C2 position of pyridines is favoured by coordination of the pyridine nitrogen lone pair bringing the transition metal catalyst into close proximity with the C2 position, facilitating C2 metalation.[104] Various linear[107,108] and branch-selective[108–110] protocols for C2 alkylation of pyridines *via* C-H activation have been developed, including enantioselective examples (scheme 33).[109,110] Often substituents are required at the C6 position to drive the equilibrium from nitrogen-bound transition metal species towards C2-metalated species, with poor yields in the absence of C6 substituents.[104,107,111]



Scheme 33: Asymmetric C2 alkylation using a chiral half-sandwich scandium catalyst[109]

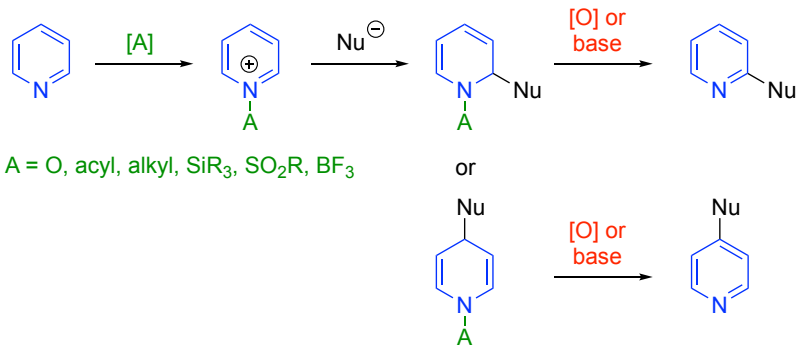
Other examples of transition-metal catalysed cross-couplings at the C2 C-H bonds of pyridines utilise pyridine *N*-oxides[112,113] (scheme 34) or iminopyridinium salts[114] as substrates. These species are electronically activated towards coupling at the C2 position of the pyridine ring through increased ring electron density and acidity of the C-H bond.[115] Inhibitory binding of the pyridine nitrogen lone pair to the transition metal can hinder cross-couplings to pyridines.[67] The use of pyridine *N*-oxides as substrates can avoid this, enabling couplings that would otherwise be difficult.[112,115]



Scheme 34: Selected C2 selective cross-coupling to quinoline *N*-Oxides[112]

2.2.5 Nucleophilic addition to *N*-activated pyridines

Activation of pyridines *via* reaction at the nitrogen lone pair to deliver a pyridinium ion and subsequent nucleophilic attack (scheme 35) has been exploited in numerous cases to build functionality around the pyridine ring.[116] Pyridinium ion intermediates have been shown to be amenable to nucleophilic attack at the C2 and C4 positions.[116]



Scheme 35: Nucleophilic addition to activated pyridines and re-aromatisation

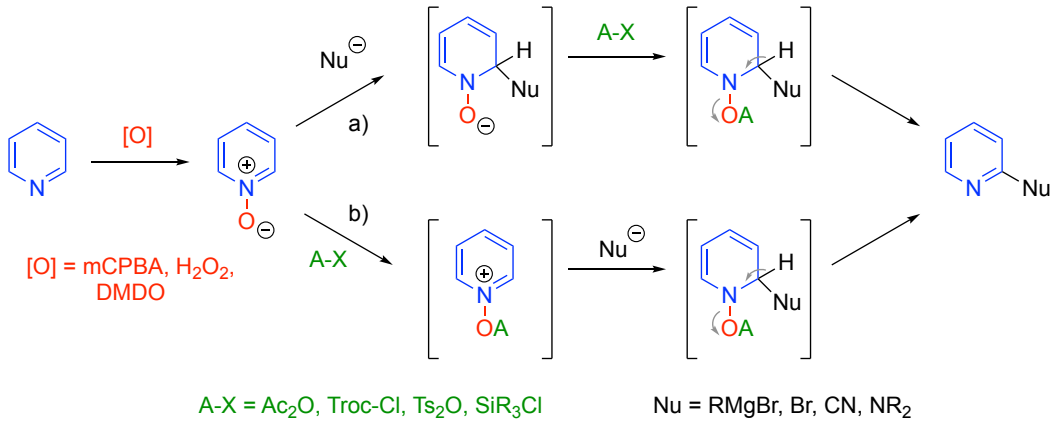
Nucleophilic aromatic substitution reactions can be enacted if there is a leaving group at the position being attacked.[117] In the absence of a leaving group, the dihydropyridine intermediate can be oxidised

to give a pyridine product.[117,118] Where the activating group attached to the nitrogen atom can act as a leaving group, treatment of the product with base can also allow re-aromatisation to give a functionalised pyridine as the product.[119–121]

2.2.5.1 Pyridine *N*-oxides

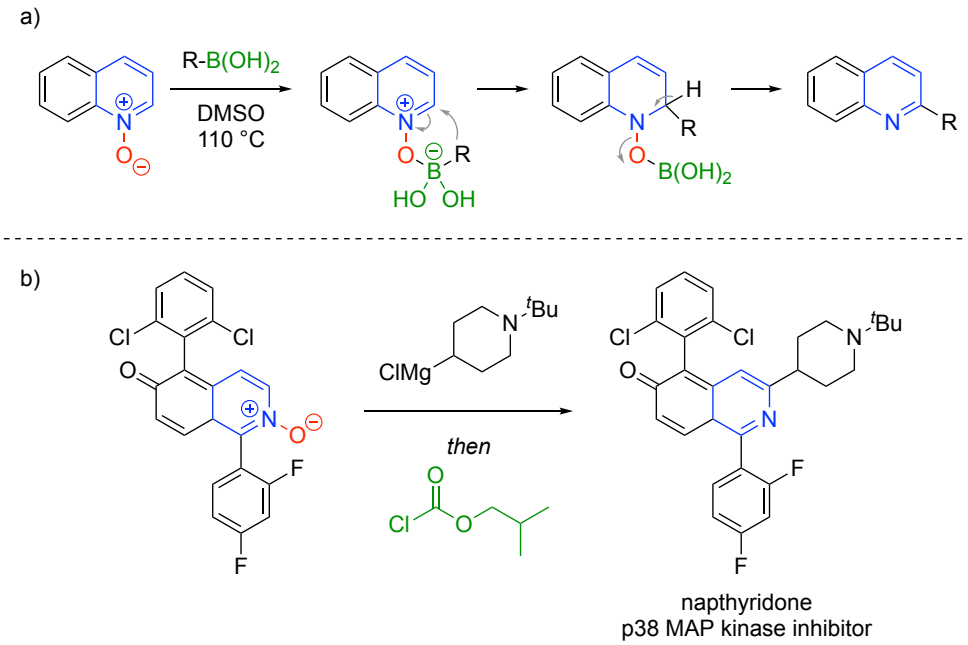
The ease of synthesis of pyridine *N*-oxides and useful reactivity of these species has rendered nucleophilic addition to pyridine *N*-oxides a popular approach to functionalising pyridines.[116] Oxidation of pyridine to the respective *N*-oxide activates the pyridine ring to both nucleophilic and electrophilic attack due to a combination of inductive σ-electron-withdrawing character of the *N*-oxide moiety and π-back-donation of electrons into the aromatic ring.[116,122]

Addition of nucleophiles to pyridine *N*-oxides can occur at the C2 and C4 positions of the pyridine ring, with regioselectivity influenced by steric bulk of the nucleophile and any substituents on the pyridine ring as well as coordination to the *N*-oxide moiety, which can direct attack of organometallic nucleophiles towards the C2 position.[116,123–125]



Scheme 36: Nucleophilic addition to pyridine N-Oxides

Activation of the pyridine *N*-oxide by electrophilic addition to the oxygen atom has been used as a method of promoting N-O bond-cleaving re-aromatisation following nucleophilic attack to give functionalised pyridines (scheme 36, pathway a).[123–130] This can be performed in a stepwise manner by treatment of the product formed by nucleophilic addition to the *N*-oxide with an oxophilic electrophile,[123] although contemporary examples typically use one-pot protocols whereby the electrophile/activating agent is added to a mixture of the *N*-oxide and nucleophile or added alongside the nucleophile – this being useful in cases where the nucleophile is unreactive enough to add directly to the *N*-oxide (scheme 36, pathway b).[126–128] The reaction of arylboronic acids with quinoline *N*-oxides at high temperature has also been found to give C2-coupled pyridines, the C-C bond formation step proposed to occur by migration from the boron-ate species formed by attack of the boron centre by the *N*-oxide (scheme 37, a).[131]



Scheme 37: a) Quinoline *N*-oxide Petasis reaction reported by Bering and Antonchick,[131] b) Application of nucleophilic attack of *N*-oxides in process chemistry[125]

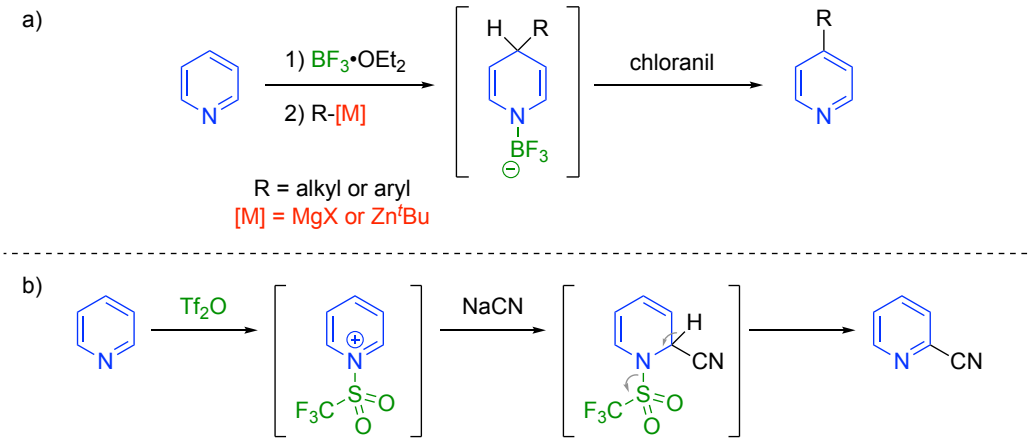
Attack of organometallic nucleophiles on pyridine *N*-oxides constitutes a generally useful method of forming carbon-carbon bonds at the C2 position of pyridine rings, and has been successfully utilised in industry in the multi-kilogram scale synthesis of a napthyridone p38 MAP kinase inhibitor (scheme 37, b).[125]

2.2.5.2 Other *N*-heteroatom activation methods

Less commonly used than *N*-oxides are other *N*-heteroatom activation methods. *N*-amino pyridinium salts can be considered as alternatives to *N*-oxides in which steric bulk and electronic donating/withdrawing nature can be tuned by choice of substituents on the activating amino group.[132,133] Use of bulky substituents has been shown to favour attack of Grignard reagents at the C4 position (as opposed to addition to the C2 position typically seen for pyridine *N*-oxides or *N*-acyl pyridinium species).[133]

The addition of organometallic nucleophiles to pyridine species activated by sterically bulky trialkylsilyl triflates or boron trifluoride (scheme 38, a) followed by subsequent oxidation has also been shown to deliver cross-coupled pyridines, with regioselectivity for the C4 position seen in both cases.[116,118]

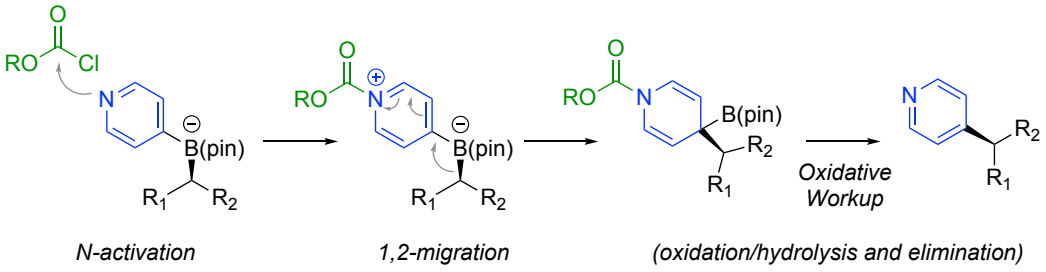
Treatment of pyridines or quinolines with trifluoromethanesulfonic anhydride (scheme 38, b) or the electrophilic fluorinating agent Selectfluor® gives the corresponding pyridinium *N*-triflyl or *N*-fluoride species, both of which have been shown to be amenable to nucleophilic attack with subsequent base-induced re-aromatisation allowing functionalisation of pyridines in one pot.[120,121]



Scheme 38: a) Addition of organometallics to BF_3-activated pyridines and oxidation,[118] b) Cyanation of triflyl-activated pyridines[120]

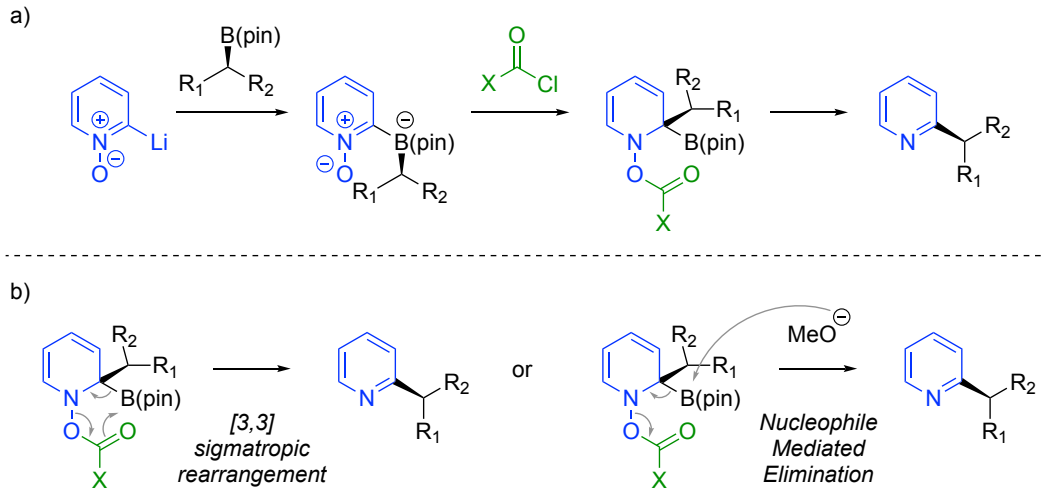
2.3 Proposal

The Aggarwal group has shown that stereospecific sp^2-sp^3 coupling of boronic esters with lithiated pyridines can be achieved by inducing a 1,2-metallate rearrangement of the intermediate boron-ate complex using electrophilic activation of the pyridine nitrogen (with 2,2,2-trichloroethyl chloroformate, Troc-Cl) followed by an oxidative workup to give the pyridine product (scheme 39, also discussed in section 1.2.2.2.2).[47] Although this protocol was demonstrated to work well for cross-couplings at the C4 position of pyridine rings, it is considerably less reliable for coupling to the C2 position. This has been attributed to the steric bulk of the boron-ate complex at the C2 carbon blocking or disfavouring the activation of the pyridine nitrogen lone pair by the electrophilic activator.[47]



Scheme 39: Aggarwal sp^2-sp^3 cross-coupling to pyridines

This project seeks to improve upon this protocol in finding a reliable method for achieving stereospecific C2 couplings to pyridines *via* the 1,2-metallate rearrangement. It is proposed that the use of pyridine *N*-oxides may promote this transformation – the lone pair on oxygen being further from the steric bulk of C2 substituents on pyridine and therefore more available to activation to promote the 1,2-metallate rearrangement (scheme 40, a). An additional advantage over the established protocol is that an oxidative work-up would not be required to induce the elimination needed to re-aromatise to the pyridine. It is envisaged that elimination will be achieved either by a [3,3]-sigmatropic rearrangement or induced by nucleophilic attack at boron (scheme 40, b)



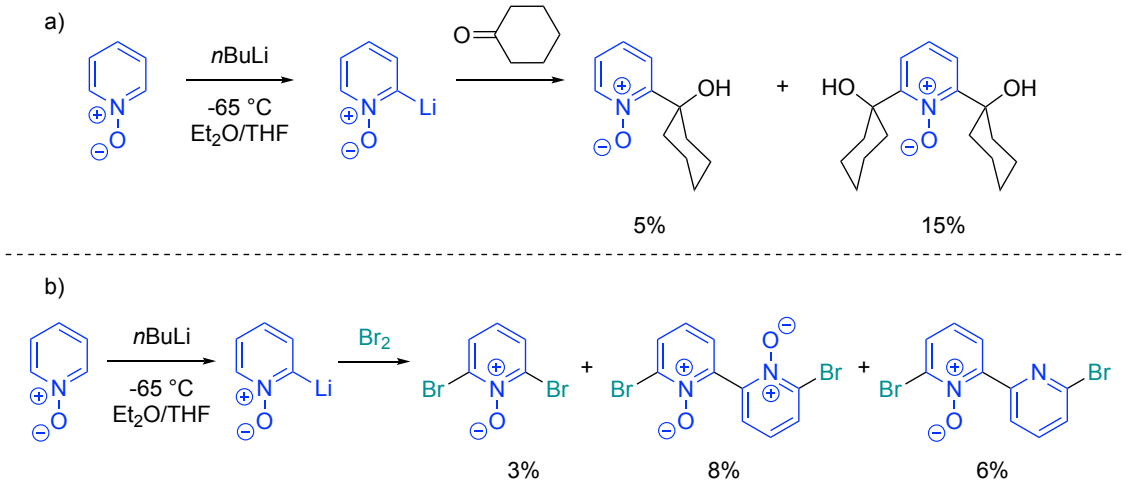
Scheme 40: a) Proposed cross-coupling to pyridine *N*-oxides; b) Potential mechanisms for elimination step

2.4 Results & Discussion

2.4.1 Metallation and boron-ate complex formation

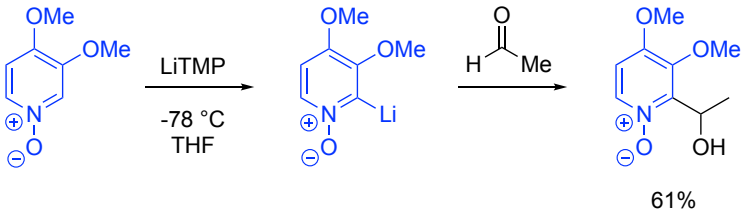
2.4.1.1 Literature precedence for C2-metallation of pyridine *N*-oxides

Direct *ortho*-metallation of pyridine *N*-oxides by deprotonation with organolithium bases is known, however subsequent trapping of these *ortho*-lithiated species with electrophiles tends to result in low yields of product mixtures (scheme 41, a and b).[134,135]



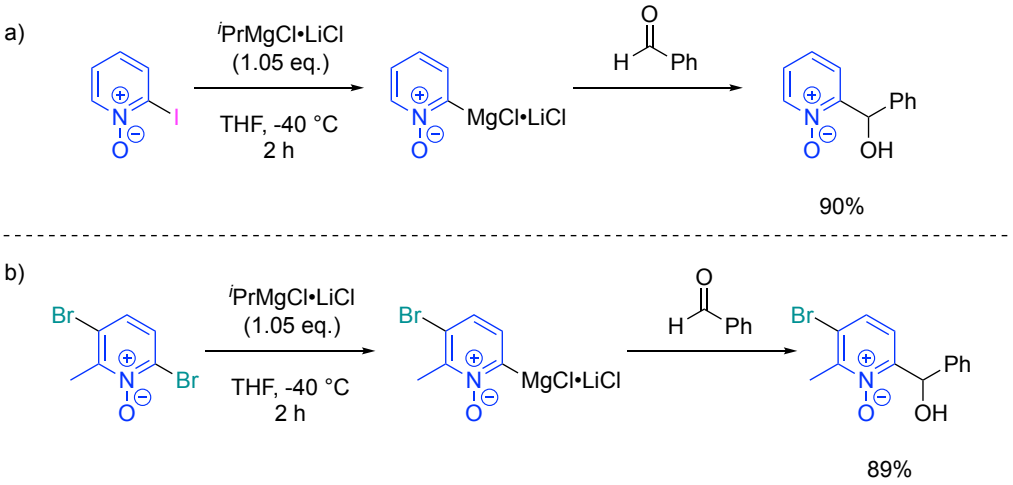
Scheme 41: a) Lithiation of pyridine *N*-oxide and trapping with cyclohexanone, b) Lithiation of pyridine *N*-oxide and trapping with dibromine

A more reliable deprotonation and trapping has been demonstrated for pyridine *N*-oxides in which either the C6 position is blocked or there are coordinating substituents at the C3 position – these aiding stabilisation of the *ortho*-lithiated intermediate (scheme 42).[136] However this approach is not appropriate for a general C2 coupling to pyridines given the limited scope of suitable substituted pyridine *N*-oxides.



Scheme 42: Lithiation and trapping of 3,4-dimethoxypyridine *N*-oxide with acetaldehyde gives a single product

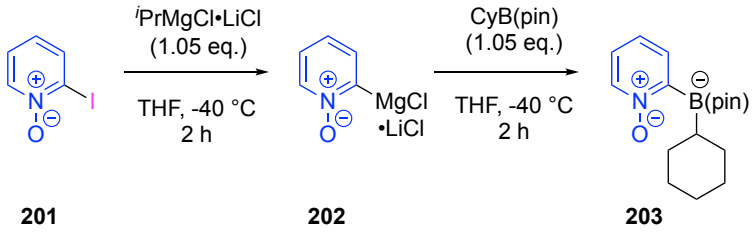
Zhang and co-workers have reported a reliable *ortho*-magnesiation of pyridine *N*-oxides by metal-halogen exchange of the corresponding C2 iodide or bromide, with good yields for subsequent trapping with various electrophiles (scheme 43, a and b).[137] This approach was shown to be regioselective for exchange at the C2 position for pyridine *N*-oxides with multiple bromide substituents (scheme 43, b). Additionally, this approach can be used for pyridines with alkyl substituents, for which competing side-chain lithiation can be an issue with organolithium bases.[137]



Scheme 43: Magnesiation and trapping of a) 2-iodopyridine *N*-oxide and b) 2,5-dibromo-6-methylpyridine *N*-oxide with benzaldehyde

2.4.1.2 Metallation and boron-ate complex formation

Boron-ate complex formation was attempted by the *ortho*-magnesiation of 2-iodopyridine *N*-oxide (accessed by oxidation of commercially available 2-iodopyridine) and subsequent trapping with cyclohexyl boronic acid pinacol ester (hereon referred to as 'cyclohexyl-B(pin)') (scheme 44). A solution of 2-iodopyridine *N*-oxide **201** in THF was treated with turbo Grignard at -40 °C according to the literature procedure and stirred for 2 hours at -40 °C to ensure full magnesiation.[137] Following the addition of cyclohexyl-B(pin), the reaction mixture was stirred at -40 °C with boron-ate complex formation monitored by ^{11}B NMR. The formation of boron-ate complex **203** was found to be complete in 2 hours, observed by depletion of the boronic ester resonance at 32 ppm and formation of a boron-ate resonance at 6 ppm in the ^{11}B NMR spectrum.



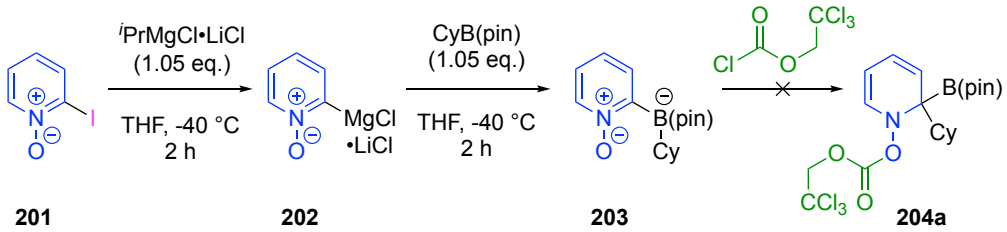
Scheme 44: Formation of boron-ate complex **203**

By contrast, the corresponding lithiation with *n*-butyllithium at -78 °C in THF and subsequent trapping with cyclohexyl-B(pin) only led to around 50% boron-ate complex formation, with 50% of the unreacted boronic ester remaining. Pyridine *N*-oxide **201** is insoluble in diethyl ether; lithiation in this solvent was unsuccessful.

2.4.2 Promoting the 1,2-metallate rearrangement

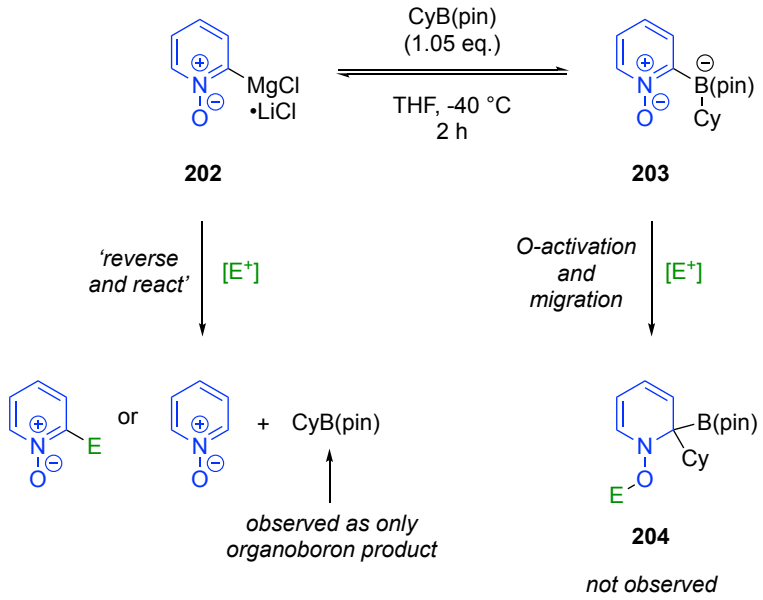
Formation of boron-ate complex **203** by treatment of *ortho*-magnesiated species **202** with cyclohexyl-B(pin) had been observed to go to completion. The next step was to establish conditions for the 1,2-metallate rearrangement and elimination to give the desired cross-coupled product. It was envisaged that these steps could be promoted by reaction of an electrophile reagent with the *N*-oxide moiety – this activating the pyridine *N*-oxide species to enable the 1,2-metallate rearrangement through increasing the local positive charge on nitrogen, whilst also forming a leaving group for subsequent elimination.

The most successful electrophile for activating pyridine boron-ate complexes to 1,2-metallate rearrangements in the previous cross-coupling protocol described in section 1.2.2.2.2 was the acylating agent 2,2,2-Trichloroethyl chloroformate (Troc-Cl).[47] Following formation of boron-ate complex **203**, 1.5 equivalents of Troc-Cl (matching the stoichiometry used in the reported cross-coupling protocol) was added at -40 °C and the reaction stirred at this temperature (scheme 45). Depletion of the boron-ate complex resonance at 6 ppm was followed by ^{11}B NMR: this found to be complete in under 2 hours with a resonance at 32 ppm observed. From GCMS and ^{1}H NMR analysis of the crude reaction mixture (the latter following a protic work-up with a 10% solution of ammonium chloride as the aqueous layer), the only boron-containing species present in the reaction mixture was found to be cyclohexyl-B(pin).



Scheme 45: Attempt to induce 1,2-migration with Troc-Cl

Given that complete formation of boron-ate complex **203** had been observed prior to addition of the electrophile, the observation of cyclohexyl-B(pin) – this species having previously been consumed – indicates that the formation of the boron-ate complex must be reversible in THF. It is likely that the lone pair on the pyridine *N*-oxide oxygen is insufficiently reactive to react with Troc-Cl or does so very slowly, such that this is outcompeted by reaction of the more nucleophilic *ortho*-magnesiated species **202** resulting from reverse of the boron-ate complex formation (scheme 46).



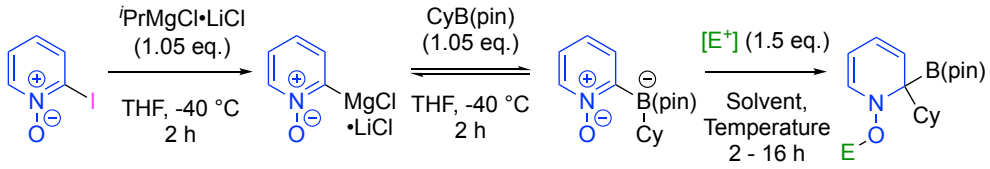
Scheme 46: Reversibility of boron-ate complex formation and products from treatment with electrophile

With the aim of promoting the 1,2-metallate rearrangement over the undesired 'reverse-and-react' pathway, various electrophiles and conditions were screened (table 1 on next page).

Trimethylsilyl chloride (TMSCl) and boron-trifluoride diethyl etherate were assessed as oxophilic electrophiles that may react favourably with the *N*-oxide moiety (entries 2 and 3). In both cases cyclohexyl-B(pin) was observed as the sole boron-containing product indicating dominance of the undesired pathway. Pyridine or pyridine *N*-oxide products were not successfully identified in these cases.

Cyclohexyl-B(pin) was also the sole boron-containing product observed when trifluoroacetic acid anhydride (TFAA) was used as the electrophile (entry 4). Given the dominance of boron-ate complex **203** over the un-complexed organomagnesium (**202**) and boronic ester species in solution (evidenced by the single resonance observed in the ^{11}B NMR of THF solutions of the boron-ate complex) it was hoped that TFAA (which is significantly more electrophilic than Troc-Cl) would react rapidly enough with the large population of boron-ate complex that this pathway could outcompete the undesired decomplexation and reaction. This was found not to be the case, with the 'reverse-and-react' pathway found to dominate in THF.

Table 1: Screen of electrophiles for inducing 1,2-metallate rearrangement



201 **202** **203** **204**

Entry	Solvent	Electrophile	Temperature/°C	Observations (^{1}H NMR, GCMS)[a]
1	THF	Troc-Cl	-40	CyB(pin), no desired product
2	THF	TMSCl	-40	CyB(pin), no desired product
3	THF	BF_3•OEt_2	-40	CyB(pin), no desired product
4	THF	TFAA	-40	CyB(pin), no desired product
5	DCM	TFAA	-40	CyB(pin), no desired product
6	Et_2O	TFAA	-40	CyB(pin), no desired product
7	$CHCl_3$	TFAA	-40	CyB(pin), no desired product
8	$CHCl_3$	None	-40 to RT	CyB(pin), no desired product
9	THF	None	40	CyB(pin), no desired product
10	THF	TFAA	-95	CyB(pin), no desired product
11	THF	Tf_2O[b]	-40 - RT	CyB(pin), no desired product
12	Acetone	Tf_2O[b]	-40 - RT	CyB(pin), no desired product
13	Acetone/ Toluene 2:1	Tf_2O[b]	-40 - RT	CyB(pin), no desired product

a: Analysis of crude reaction mixtures prior to any work-up; *b*: Added as 1 M solution in DCM

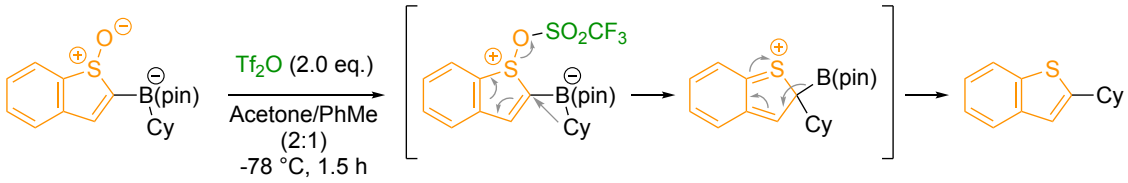
The reversibility was also found to be a problem when solvent switches to diethyl ether, dichloromethane and chloroform were enacted following boron-ate complex formation in THF (entries 5-7). In all cases, cyclohexyl-B(pin) was found to be the major product following addition of TFAA as an electrophile to promote the migration.

Attempts at thermal 1,2-metallate rearrangement in THF and chloroform were also unsuccessful (entries 8 and 9). Decomposition of the *ortho*-magnesiated pyridine *N*-oxide **202** was found to outcompete any migration of the cyclohexyl group in both solvents.

The addition of an electrophile at -95 °C also led to the observation of cyclohexyl-B(pin) (entry 10). It is possible that boron-ate complex formation is reversible down to this temperature. Alternatively,

the *N*-oxide moiety of boron-ate species **203** is insufficiently reactive with TFAA at low temperatures, and upon warming the pathway from the more reactive *ortho*-magnesiated species **202** dominates.

Finally, it was noted that trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O), added as a commercially available 1 M solution in DCM, had been shown to be successful in inducing S-O bond cleavage to trigger a Pummerer-type 1,2-metallate rearrangement from benzothiophene *S*-oxide boron-ate complexes (scheme 47).[138] Additionally, the choice of solvent had been shown to influence the ratio of desired product to undesired 'reverse and react' products for this reaction: acetone or a 2:1 mixture of acetone and toluene were shown to the selectivity towards the desired *O*-sulfonylation and rearrangement pathway.

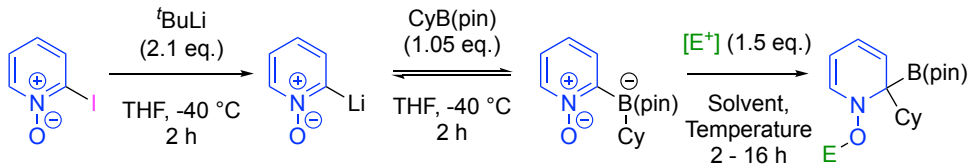


Scheme 47: Triflic anhydride-induced Pummerer-type 1,2-metallate rearrangement from benzothiophene *S*-oxide boron-ate complexes[138]

Unfortunately, the application of these conditions to pyridine *N*-oxide boron-ate complex **203** (table 1, entries 11-13) did not achieve the desired *O*-sulfonylation and rearrangement pathway. Instead, as with the other electrophiles and solvents tried, cyclohexyl-B(pin) was observed as the major product indication a predominance of the 'reverse-and-react' pathway.

It is worth noting that the reversibility is also true of boron-ate formation from the lithiated *N*-oxide species **202'**, with cyclohexyl-B(pin) the major boron-containing component observed following addition of electrophiles to the boron-ate complex generated in this fashion (table 2).

Table 2: Screen of electrophiles for inducing 1,2-metallate rearrangement



201 **202'** **203** **204**

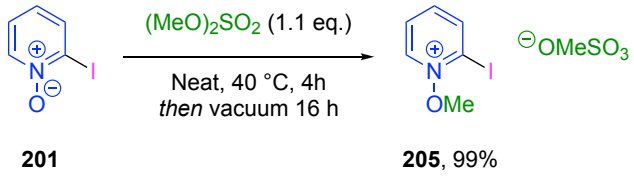
Entry	Solvent	Electrophile	Temperature/°C	Observations (^{1}H NMR, GCMS)[a]
1	THF	Troc-Cl	-78	CyB(pin), no desired product
2	THF	TMSCl	-78	CyB(pin), no desired product
3	THF	TFAA	-78	CyB(pin), no desired product

a: Analysis of crude reaction mixtures prior to any work-up

2.4.3 *Ortho*-metallation and trapping studies with an *N*-methoxypyridinium salt

Given the lack of success at inducing the 1,2-metallate rearrangement by electrophilic activation of the pyridine *N*-oxide boron-ate complex **203**, attention turned to whether a pre-activated species could be used which would promote 1,2-migration directly from the boron-ate complex without the need for additional activation.

N-methoxypyridinium salts can be generated quantitatively from the respective *N*-oxide by reaction with dimethyl sulfate (scheme 48). These can be regarded as a pre-activated pyridine *N*-oxide species.[139]

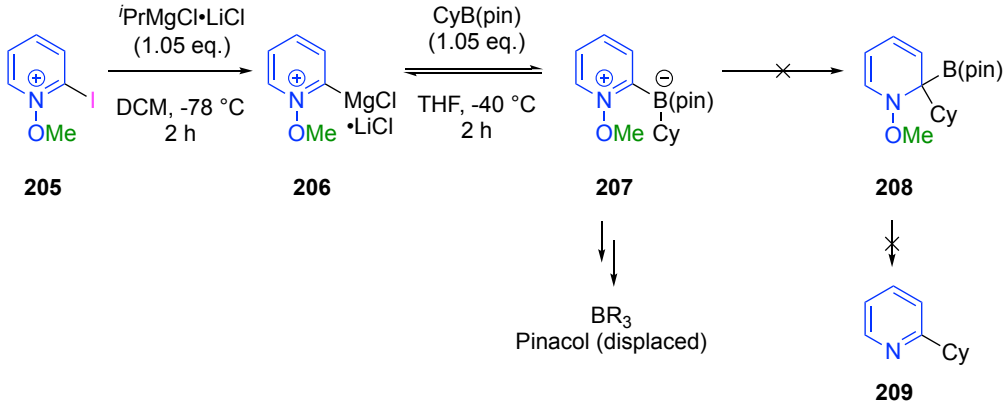


201 **205**, 99%

Scheme 48: Formation of *N*-methoxypyridinium triflate salt **205**

Lithiation of *N*-methoxypyridinium species **205** with *tert*-butyllithium at -78 °C and subsequent trapping with Cyclohexyl-B(pin) in THF was attempted. The *N*-methoxypyridinium salt was found to have little solubility in THF. As a result, formation of the boron-ate complex was unsuccessful, most likely due to failed lithiation resulting from the insolubility.

The *N*-methoxypyridinium salt is soluble in DCM, and so magnesiation of **205** using turbo Grignard was attempted at -78 °C in this solvent (scheme 49). The desired boron-ate complex **207** was not observed by ^{11}B NMR. Instead, a resonance at around 80 ppm was seen (alongside a resonance at 32 ppm for cyclohexyl-B(pin)) corresponding to a trialkylborane species, formed by displacement of the pinacol ligand from boron.



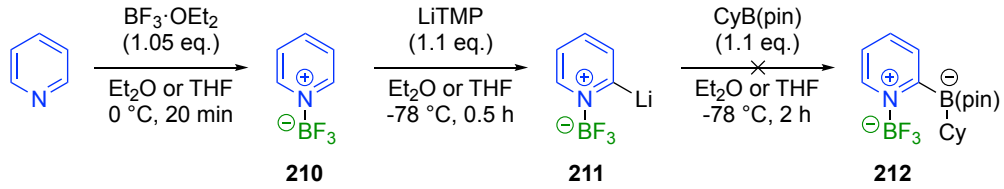
205 **206** **207** **208** **209**

Scheme 49: Attempt at forming boron-ate complex with *N*-methoxypyridinium salt **205** in DCM

2.5 Lithiation and trapping with BF_3-activated pyridines

Given the lack of success in achieving 1,2-metallate rearrangements of pyridine *N*-oxide boron-ate complexes, it was decided to move to a different system. It has been shown that adducts of pyridine with boron trifluoride can be *ortho*-lithiated using LiTMP at -78 °C in diethyl ether or THF.[140,141] This approach has been utilised for the synthesis of α-pyridyl alcohols by subsequent trapping with carbonyls.[140]

Formation of the pyridine-boron trifluoride adduct **210** and lithiation was performed in both diethyl ether and THF (scheme 50). The trapping of *ortho*-lithiated intermediate **211** with cyclohexyl-B(pin) to give boron-ate complex **212** was then attempted. It was hoped that boron-ate complex would undergo the 1,2-metallate rearrangement on warming. Unfortunately, boron-ate complex formation was not observed by ^{11}B NMR in either case. This may be attributable to steric congestion rendering formation of species **212** unfavourable.



Scheme 50: Attempted lithiation and trapping of pyridine-trifluoroborate adduct with cyclohexyl-B(pin)

2.6 Conclusions and future work

To summarise, *ortho*-metallation and trapping of iodopyridine *N*-oxide with cyclohexyl-B(pin) was found to successfully generate a boron-ate complex. Subsequent attempts to trigger 1,2-metallate rearrangement of this boron-ate complex by treatment with various electrophiles were unsuccessful. It was found that boron-ate complex formation was reversible, with the *ortho*-metallated pyridine *N*-oxide intermediate more reactive towards electrophiles than the boron-ate species. Therefore a 'reverse-and-react' pathway predominates, with no 1,2-migration products observed in any case.

It was hoped that the use of *N*-methoxypyridinium salts as 'pre-activated' pyridine *N*-oxide species would enable 1,2-migration of the boron-ate complex without further activation following its formation. The insolubility of *N*-methoxypyridinium triflate in THF and diethyl ether renders these unsuitable substrates for *ortho*-lithiation and trapping.

Additionally, attempts at boron-ate complex formation from *ortho*-lithiated pyridine-boron trifluoride adducts were unsuccessful. This has been attributed to steric hindrance disfavouring the formation of a bulky boron-ate moiety at the C2 position.

Reversibility of boron-ate complex formation presents a major challenge for inducing 1,2-metallate rearrangements to pyridine *N*-oxide boron-ate complexes. It is possible that more electrophilic

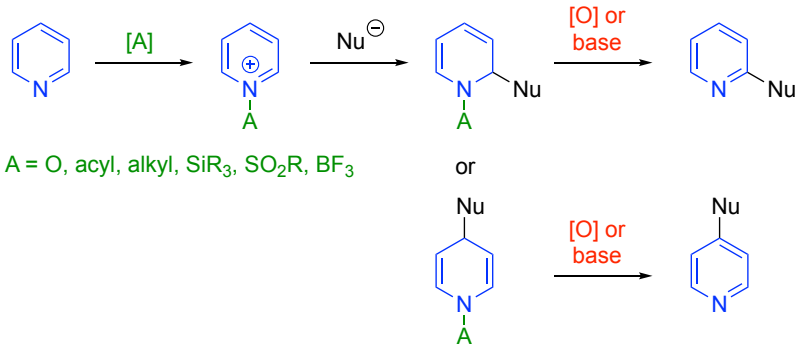
boranes or borinic esters may undergo irreversible boron-ate complex formation with *ortho*-metallated pyridine *N*-oxides. Therefore inducing 1,2-metallate rearrangement may be possible for these species. It is worth noting, however, that these more reactive organoborons tend to be air and moisture sensitive. As a result, the use of these is not as synthetically desirable as use of boronic esters; this may limit the appeal of such a procedure as a useful cross-coupling reaction.

3 Enantiospecific stereoinvertive C4-coupling to pyridines

3.1 Introduction

3.1.1 Nucleophilic addition to *N*-activated pyridines

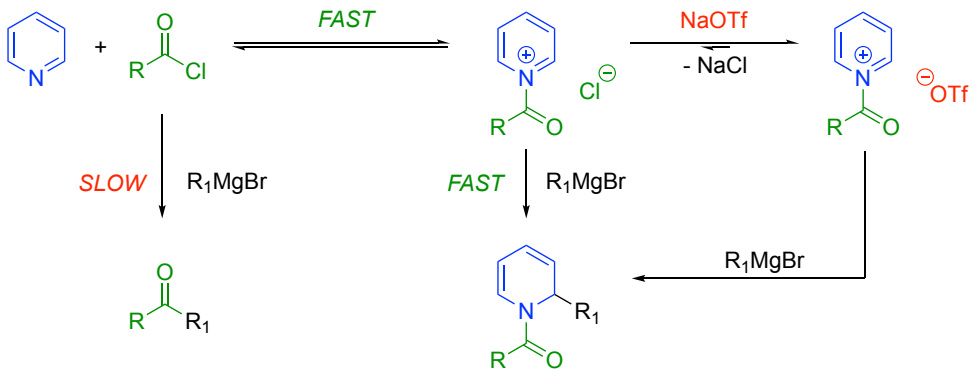
Pyridines are electron-poor aromatic heterocycles, capable of reacting at the nitrogen atom to form electrophilic pyridinium species. These species are amenable to nucleophilic attack at the C2 and C4 positions of the pyridine ring (scheme 51).[116] This reactivity has frequently been exploited in the synthesis of dihydropyridine and piperidine alkaloids.[116,142–144] Furthermore, the possibility of re-aromatisation of dihydropyridine intermediates to the parent pyridine lends this reactivity to enacting cross-couplings and other building of functionality around the pyridine ring. Nucleophilic addition to pyridine *N*-oxides and other *N*-heteroatom species has been discussed in chapter 2, section 2.2.5. The following sections, 3.1.1.1 to 3.1.1.3, will focus on the addition of nucleophiles to *N*-acyl and *N*-alkyl pyridinium species.



Scheme 51: Nucleophilic addition to activated pyridines and re-aromatisation

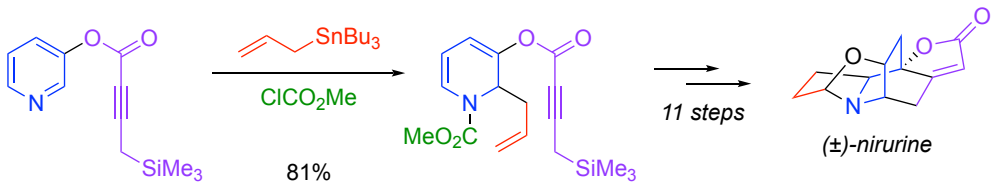
3.1.1.1 *N*-acyl pyridinium salts

Addition of nucleophiles to *N*-acyl pyridinium salts has been used extensively as a straightforward for the synthesis of dihydropyridines, which are also rendered more stable by the *N*-acyl moiety.[116,145] Typically reaction protocols involve addition of the activating reagent to a mixture of the pyridine and nucleophile, although pre-mixing of the activating agent with pyridine is occasionally also used.[116] Activation of pyridines with acylating agents is generally an equilibrium between the activated species and starting materials (scheme 52).[146] The reaction of the activating agent (typically an acyl chloride) with the pyridine and reaction of the nucleophile with the *N*-acyl pyridinium species must both be rapid in order to outcompete attack of the nucleophile on the activating agent.[116] Often equilibria can favour the starting pyridine and acylating agent. It has been found that switching the counter-ion to the less nucleophilic triflate anion can drive the equilibrium towards activated pyridinium formation (scheme 52).[119,146,147] The nucleophile and activating agent can also be chosen to reduce competing side-reactions between these species.[148]



Scheme 52: *N*-acyl activation equilibrium and nucleophilic attack

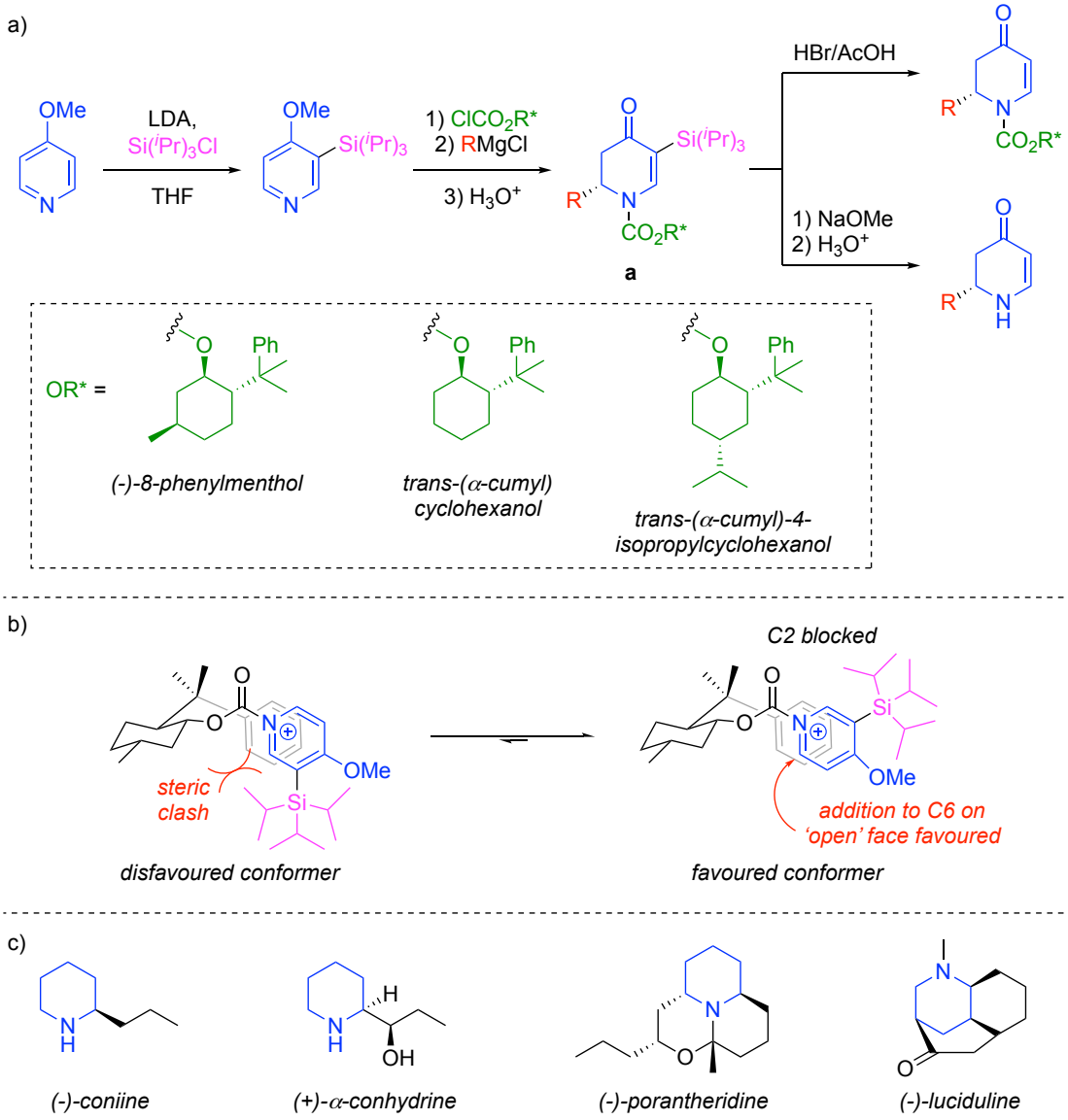
The regioselectivity of addition of organometallic nucleophiles to *N*-acyl pyridinium species has been rationalised using the hard/soft acid/base (HSAB) model.[116,149,150] 'Hard' nucleophiles, including Grignard and organocadmium reagents, tend to attack the C2 position, although sterically bulky nucleophiles often exhibit reduced regioselectivity for C2 over C4 addition due to a steric clash with the *N*-acyl moiety.[150,151] In contrast, 'soft' organocuprates tend to add to the C4 position.[152] The presence of substituents on the pyridine ring can influence the regioselectivity of addition. For example, coordinating groups at the C3 position of the pyridine can bias addition towards the C2 position over C6.[116,153] This directing effect was exploited in a regioselective addition of an allyl stannane nucleophile to an *N*-acylpyridinium intermediate in Matthews' total synthesis of nirurine (scheme 53).[154]



Scheme 53: Addition step in the total synthesis of nirurine[154]

The diastereoselectivity of nucleophilic addition to *N*-acyl pyridinium species can be biased by the use of chiral auxiliaries either on the acylating agent[142,155] or as a substituent at the C3 position of the pyridine ring.[156] The use of menthol- or cumene-derived chloroformates as acylating agents bearing chiral auxiliaries is a common feature of alkaloid syntheses pioneered by Comins (scheme 54, a), alongside the use of bulky trialkylsilyl blocking groups at the C3 position to direct regioselective addition at C6.[116,142] The mode of influence of the chiral auxiliary is a π-stacking interaction between a phenyl group on the auxiliary and the pyridinium cation, which blocks one of the faces of the pyridine ring to nucleophilic attack (scheme 54, b). The silyl blocking group ensures that one conformation of the pyridinium intermediate is favoured over the other and that the C2 position is blocked, ensuring that nucleophilic addition is favoured at the C6 position from the 'open' face of the pyridium ion.

The diastereo- and regioselective addition of a Grignard nucleophile to the chiral pyridinium salt intermediate is immediately followed by hydrolysis of the methoxy-enol component of the dihydropyridine formed (typically in the work-up) to give the α,β-unsaturated ketone species **a** (scheme 54, a). Subsequently, the silyl blocking group and chiral auxiliary can be selectively removed as required for the given alkaloid synthesis. This general approach has been used for the synthesis of numerous piperidine and tetrahydropyridine alkaloids, from the simpler (-)-coniine and (+)-α-conhydrine to the more complex polycyclic alkaloids (-)-porantheridine and (-)-luciduline (scheme 54, c).[116,157–160]



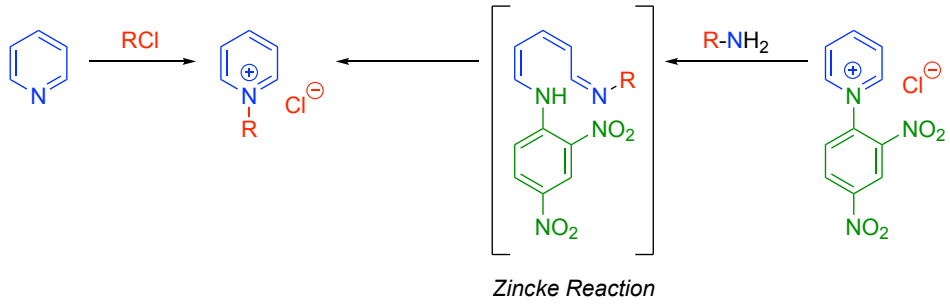
Scheme 54: a) Installation and removal of C3 blocking group, and use of chiral auxiliary in enacting regio- and diastereoselective nucleophilic addition in Comin's alkaloid syntheses, b) Origin of stereo- and regioselectivity with (-)-8-phenylmenthol chiral auxiliary and triisopropylsilyl blocking group, c) Examples of alkaloids rendered by this approach

The addition of nucleophiles to *N*-acylpyridinium intermediates has been commonly used for the synthesis of dihydropyridines, tetrahydropyridines and piperidines. However, re-aromatisation of

N-acyl dihydropyridines to the parent pyridine following nucleophilic addition to enact overall coupling to pyridine is less common. Oxidative re-aromatisation of dihydropyridines or dihydroquinolines formed by 1,4-addition has been described in limited cases using the mild oxidant chloranil (tetrachloro-1,4-benzoquinone) or by heating with elemental sulfur.[48,161]

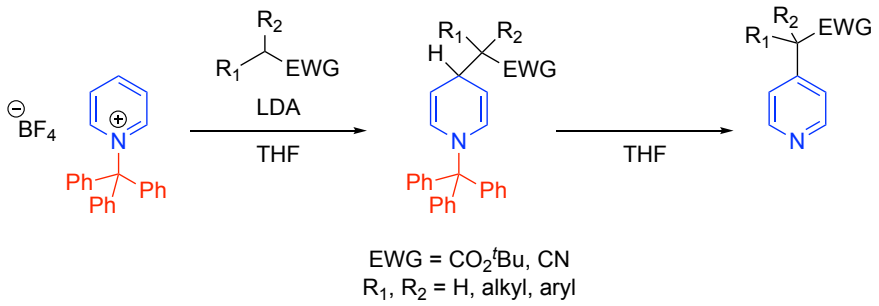
3.1.1.2 *N*-alkyl pyridinium salts

Pyridines can also be activated by alkylation of the pyridine nitrogen. The π-systems of *N*-alkyl pyridinium salts are less electrophilically activated than the corresponding *N*-acyl pyridinium salts.[116] As a result additions of nucleophiles to *N*-alkyl pyridinium salts typically require harsher conditions than for respective *N*-acyl pyridinium salts.[116] In contrast to *N*-acyl pyridinium species, *N*-alkyl species are typically pre-formed, either by reaction of the pyridine with an alkyl halide or synthesis *via* the Zincke reaction (scheme 55).[116,162,163]



Scheme 55: Synthesis of *N*-alkyl pyridinium salts

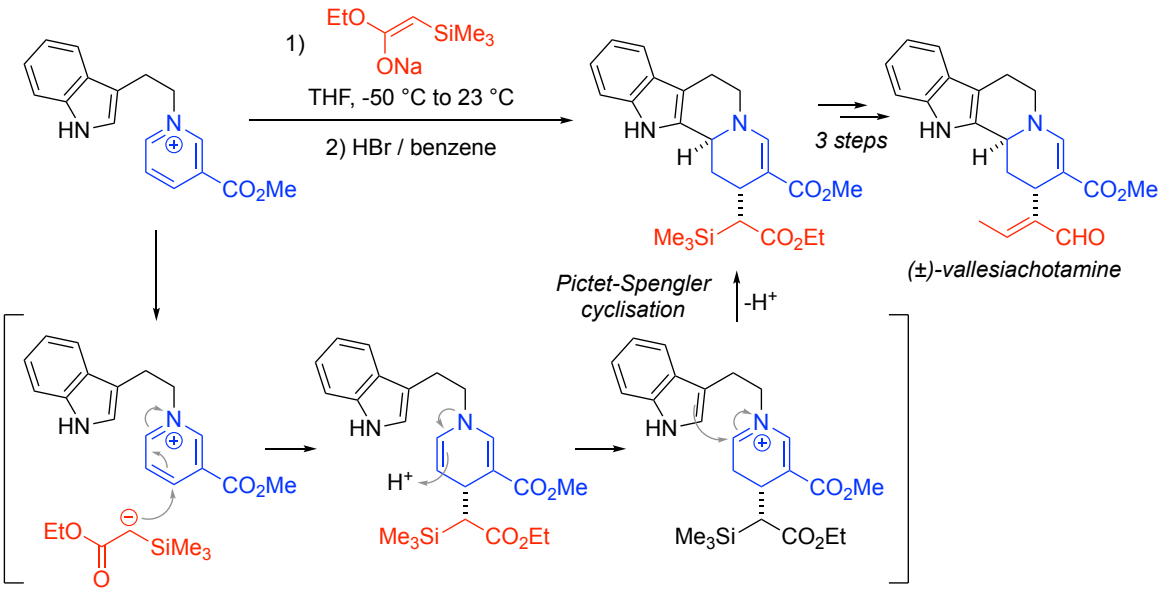
Examples of functionalised heterocycle synthesis by nucleophilic attack of *N*-alkyl pyridinium salts are more limited than for *N*-acyl pyridinium salts or pyridine *N*-oxides. In the absence of electron withdrawing substituents on the heterocycle, dihydropyridine species formed are unstable, displaying reactivity as cyclic enamines.[116] As a result nucleophilic attack at unfunctionalized positions followed by re-aromatisation to give pyridine products is not practicable, except in rare cases where spontaneous oxidation of the dihydropyridine formed is rapid (scheme 56).[164]



Scheme 56: Nuclophilic addition to *N*-trityl salts and subsequent re-aromatisation

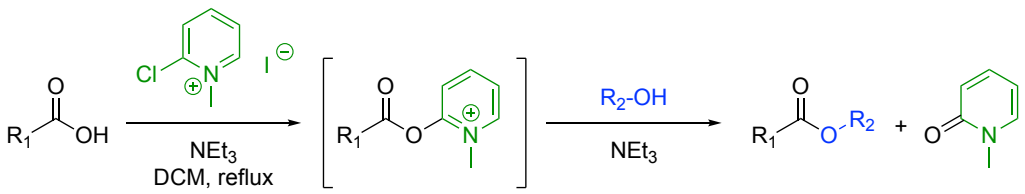
The enamine reactivity of the dihydropyridines formed following nucleophilic addition to *N*-alkylpyridines has been exploited by Wenkert in a cascade synthesis of the indole alkaloid

vallesiachotamine (scheme 57).[143,144,165] In this case, the *N*-alkyl group on the pyridinium nitrogen bears a pendant indole nucleophile. Following the nucleophilic addition of an enolate at the C4 position of the pyridinium salt, the more electron rich enamine in the dihydropyridine intermediate undergoes protonation to form an iminium moiety at the C6 position of the ring. This iminium ion is attacked by the pendant indole nucleophile in a concomitant Pictet-Spengler reaction to construct the tetracyclic backbone of vallesiachotamine.



Scheme 57: Key cascade step in Wenkert's synthesis of vallesiachotamine[143]

Finally, *N*-alkyl pyridinium salts bearing a leaving group at the C2 or C4 positions are capable of undergoing S_NAr reactions. The Mukaiyama reagent, 2-chloro-1-methylpyridinium iodide, is widely used to activate alcohol or carboxylic acid hydroxyl groups in lactonisation, esterification and amidation reactions – these proceeding *via* S_NAr displacement of the chloride (scheme 58).[166,167]



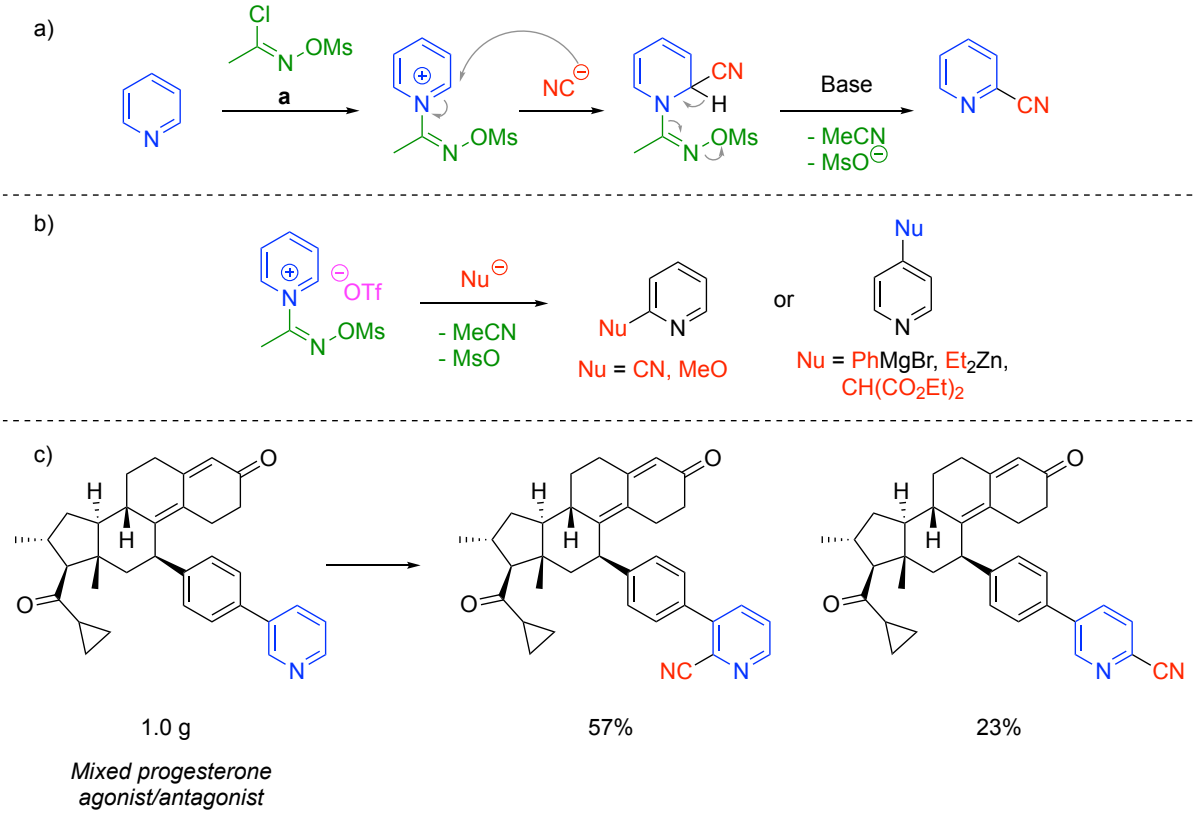
Scheme 58: Mukaiyama esterification

3.1.1.3 Fier activating agent

In 2017, Fier reported the cyanation of pyridines using a bifunctional reagent acting both as an activating agent and leaving group.[119] This reagent, the α-chloro *O*-sulfonyl aldehyde oxime species **a** (scheme 59, a), is bench-stable and easily synthesised on scale from inexpensive aldehyde oxime starting materials. Following attack of a nucleophile on the activated pyridine ring, re-aromatisation was achieved by base-induced elimination of the activating species, proposed to occur in a concerted

manner producing non-toxic and aqueous-soluble acetonitrile and mesylate byproducts (scheme 59, a). This protocol was shown to be C2 selective for cyanide, consistent with regioselectivity seen for addition of hard nucleophiles to *N*-acyl pyridinium species.[116] Cursory investigation into other nucleophiles demonstrated mixture of C2 and C4 selectivities depending on the nucleophile (scheme 59, b).

It is worth noting that this bifunctional oxime reagent is an alternative to the use of pyridine *N*-oxides for nucleophilic addition and re-aromatisation (discussed in chapter 2, section 2.2.5.1). The chemoselectivity of oxidation to access pyridine *N*-oxides can be an issue limiting their use in this type of chemistry given the potential for oxidants to oxidise other functional groups such as tertiary amines and electron-rich alkenes. In contrast, this protocol is mild, enabling its use even on complex molecules bearing multiple functional groups. The efficacy of this protocol for late-stage functionalisation of pyridines in complex pharmaceuticals was demonstrated by gram-scale cyanation of a mixed progesterone agonist/antagonist (scheme 59, c).[119]

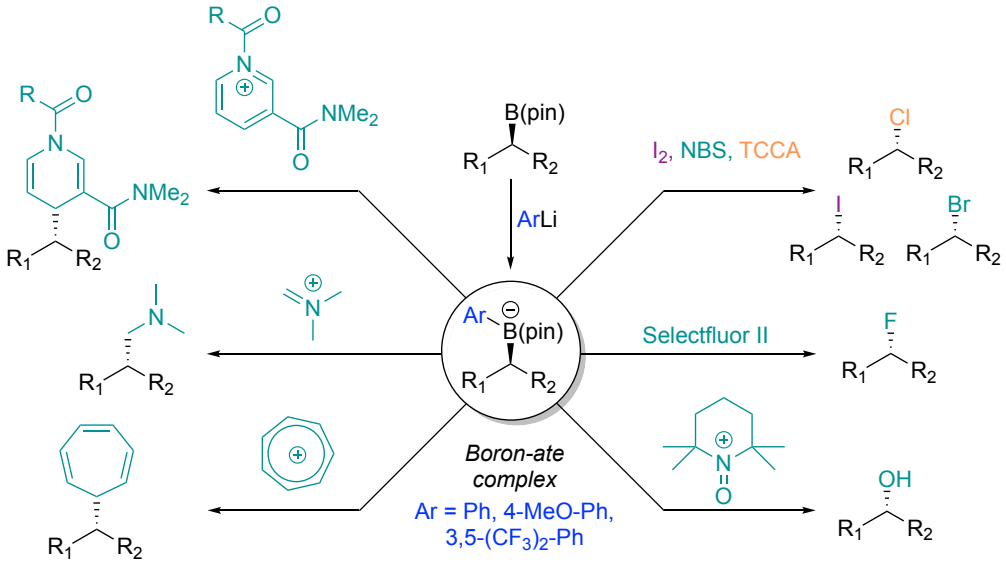


Scheme 59: a) Cyanation of pyridines described by Fier, b) Cursory investigation of other nucleophiles, c) Application to complex drug molecule

3.1.2 Boron-ate complexes as nucleophiles

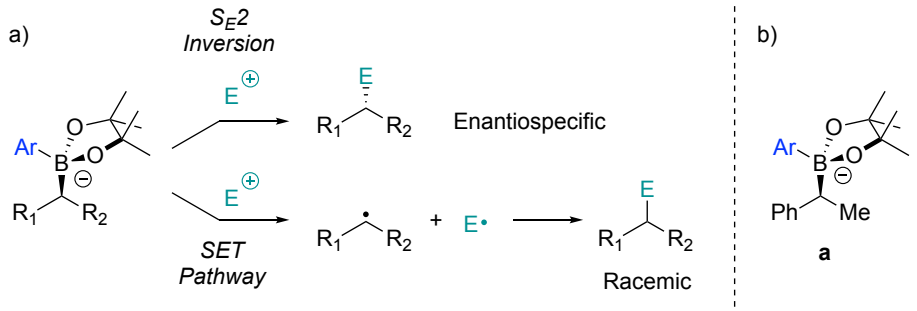
The reactivity of aryl boron-ate complexes generated by treatment of an aliphatic boronic ester with a lithiated arene species was discussed in chapter 1, section 1.2.2.2. In the cases previously discussed, the aryl component is either sufficiently electron rich to react directly with electrophiles in an electrophilic aromatic substitution (S_EAr) pathway or – in the pyridine case – capable of reacting with electrophiles at the nitrogen atom to enact the cross-coupling pathway.

In cases where the aryl group is not amenable to electrophilic activation or 1,2-migration, reaction of boron-ate complexes at the aliphatic carbon substituent is the dominant pathway. The Aggarwal group has exploited this in the development of chiral boron-ate nucleophiles.[6] In contrast to other organometallic nucleophiles (Grignard and organolithium reagents), these species are configurationally stable and have been shown to react with various electrophiles in a stereospecific fashion with inversion of configuration at the carbon centre (scheme 60).[6,7,48]



Scheme 60: Generation and stereoinvertive reactions of boron-ate nucleophiles with electrophiles[6,7,48]

In addition to avoiding the S_EAr/cross-coupling reaction pathway detailed in section 1.2.2.2.1, the choice of aryl group was found to be important for ensuring stereospecificity. A competing single electron transfer (SET) pathway (scheme 61, a) resulting in racemisation was observed for some electrophiles. Use of an electron deficient arene was found to limit this pathway by discouraging electron transfer from the carbon-boron bond; performing the reaction with 3,5-bis(trifluoromethyl)phenyllithium as the aryllithium gave good stereospecificity where racemisation was observed for 4-methoxyphenyllithium.[6]

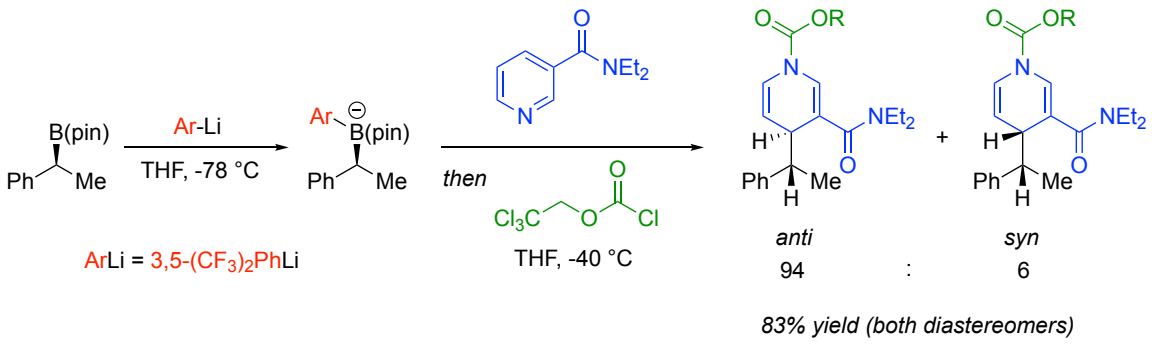


Scheme 61: a) Alternative SET pathway leading to racemisation, b) Secondary benzylic boron-ate complex

Quantitative assessment of structure-activity relationships of boron-ate complexes derived from aryllithiums and boronic esters has been achieved by reaction of various boron-ate nucleophiles with benzhydrylium electrophiles.[168] It was found that the nucleophilicity of the boron-ate complex at the aliphatic centre decreases with increased electron-withdrawing character of the aryl unit attached to the boron centre: the boron-ate complex **a** (scheme 61, b) with Ar = phenyl was found to be 61 times more reactive than the more electron withdrawing Ar = 3,5-bis(trifluoromethyl)phenyl. A boron-ate complex bearing a neopentyl glycol ligand was found to be 100-fold more reactive than that with a pinacol ligand. In addition, a trend was seen for the nature of the sp^3 substituent, with secondary benzylic found to be the most nucleophilic, followed in turn by primary alkyl, primary benzyl and secondary alkyl groups.[168]

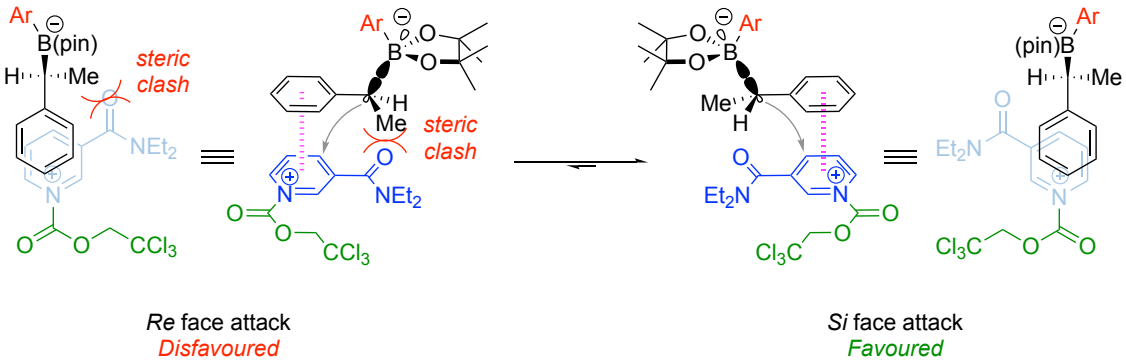
3.1.2.1 Asymmetric addition of chiral boron-ate complexes to cyclic iminium ions

Chiral boron-ate complexes derived from secondary benzylic boronic esters have been demonstrated to add to *N*-acylpyridinium salts derived from activation of *N*,*N*-diethylnicotinamide with 2,2,2-trichloroethyl chloroformate (scheme 62).[48] This reaction was found to be completely enantiospecific, with inversion of configuration at the benzylic centre. Furthermore, the reaction was found to be highly diastereoselective, favouring formation of the *anti*- diastereomer over the *syn*-diastereomer (scheme 62).



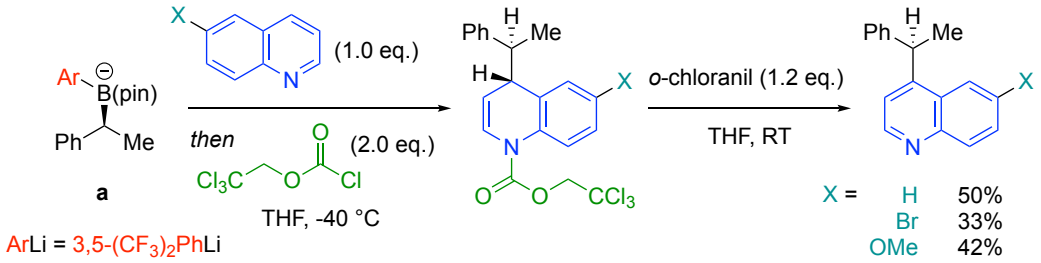
Scheme 62: Asymmetric addition of chiral boron-ate nuclephiles to cyclic iminium ions

The origin for this high diastereoselectivity was attributed to a strong π-cation interaction between the phenyl group on the boron-ate nucleophile and the pyridinium cation (scheme 63), akin to that described for the chiral auxiliaries used in Comin's alkaloid syntheses (discussed in section 3.1.1.1). Attack of the *Re* face of the pyridinium ring is disfavoured by a steric clash between the methyl group of the boron-ate nucleophile and the diethylamide substituent on the pyridinium electrophile. This steric clash is much reduced for attack of the *Si* face of the pyridinium (for which the amide carbonyl is on the same side as a hydrogen atom rather than a methyl group), thus attack at this face is favoured leading to the major (*anti*-) diastereomer.[48]



Scheme 63: Model for origin of diastereoselectivity in the addition

A two-step [1,4]-addition-oxidation sequence was cursorily explored for the synthesis of chiral quinolines in a one-pot process.[48] Following the addition of boron-ate complex **a** (scheme 64) to 2,2,2-trichloromethyl-chloroformate-activated quinolines, the reaction mixture was treated with the mild oxidant *o*-chloranil (3,4,5,6-tetrachlorocyclohexa-3,5-diene-1,2-dione). This protocol was successful in achieving the desired cross-coupling with 100% enantiospecificity for all three of the substrates explored, however the yield of the one-pot addition-oxidation sequence was low to mediocre: below 50% for both C6-substituted quinolines tried.



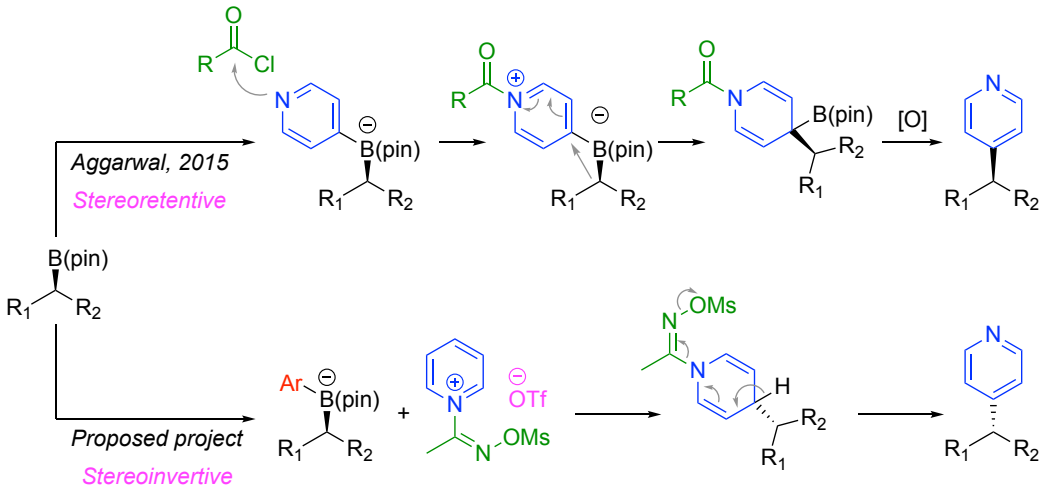
Scheme 64: Addition to quinolines and oxidation in *one pot* to enact C4 coupling

3.2 Project proposal

Enantiospecific cross-coupling of pyridines with enantioenriched boronic esters is a desirable transformation, particularly given the ease of access to enantioenriched boronic esters by enantioselective hydroboration or lithiation-borylation. An enantiospecific transition-metal-free cross-coupling of lithiated pyridines with enantioenriched boronic esters has previously been described by Aggarwal, and was discussed in chapter 1, section 1.2.2.2.2.[47] In this case the reaction is *stereoretentive* – the configuration at the boron centre on the migrating alkyl group is preserved through the reaction.

Given the addition of boron-ate nucleophiles to *N*-acylpyridinium salts has been shown to be *stereoinvertive* (and proceed with complete enantiospecificity), it is envisaged that a successful addition and rearomatisation utilising these nucleophiles would be complementary to the stereoretentive cross-coupling previously described. Therefore, such a protocol would enable expedient access to both enantiomers of the cross-coupled pyridine product from the same enantiomer of the boronic ester starting material.

The limited examples of re-aromatisation of quinolines using *o*-chloranil following the 1,4-addition (described in section 3.1.2.1) suffered from poor yields.[48] It is proposed that a 1,4-addition-elimination pathway, in which the species used to activate the nitrogen atom of the pyridine subsequently acts as a leaving group in a base-promoted elimination step, may exhibit more success for achieving the stereoinvertive cross-coupling (scheme 65). It is envisaged that the bifunctional α-chloro *O*-sulfonyl aldehyde oxime reagent described by Fier (discussed in section 3.1.1.3) would be ideal for this protocol.[119]

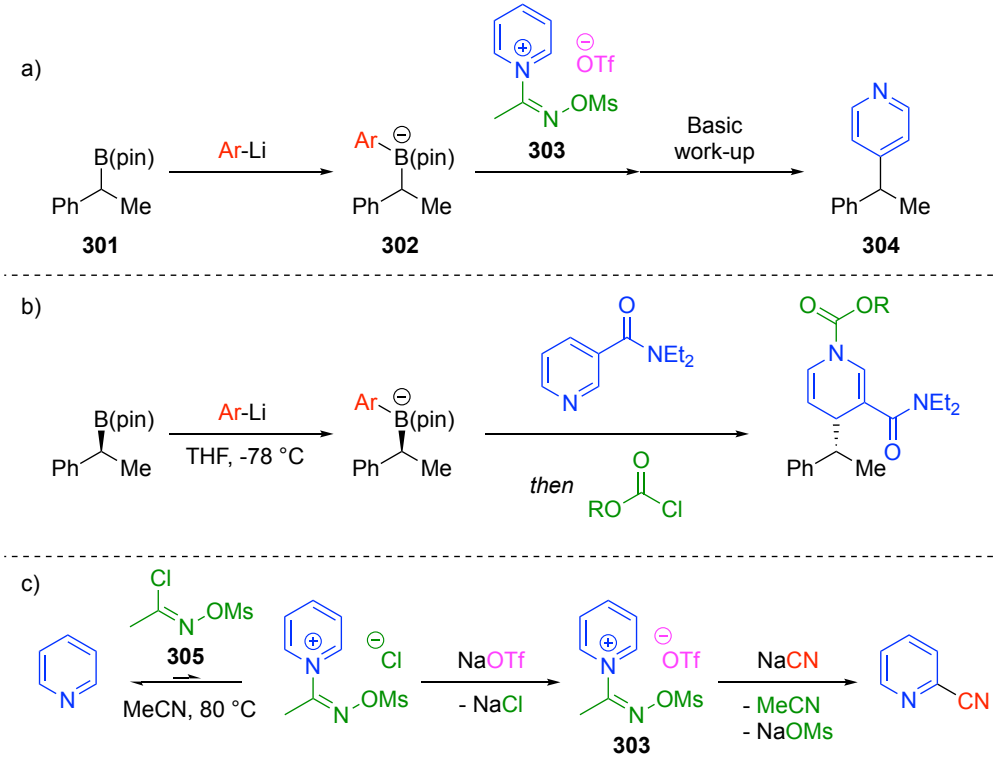


Scheme 65: Reported stereoretentive cross-coupling and proposed stereoinvertive cross-coupling

3.3 Initial studies

Initial studies were carried out with the aim of coupling pyridine with racemic phenyl ethyl boronic ester **301** (scheme 66, a). The previously reported addition of boron-ate nucleophiles to pyridinium electrophiles described in section 3.1.2.1 proceeded by first forming the boron-ate complex before adding the pyridine substrate followed by the chloroformate acylating agent (scheme 66, b).[48] In contrast, the reported cyanation of pyridines with Fier's α-chloro *O*-sulfonyl aldehyde oxime reagent (**305**) first activated the pyridine before adding the nucleophile.[119] Furthermore, a cation switch from chloride to triflate was found to be important to this chemistry in promoting the formation of the activated pyridinium species (scheme 66, c).

To achieve the desired cross-coupling, it was decided to initially approach the reaction in a manner more akin to the previous work with boron-ate nucleophiles. The boron-ate complex **302** would be made first, before adding the activated pyridine electrophile **303** to the reaction. Given the elevated temperatures required to convert the pyridine to the activated pyridinium electrophile **303** (scheme 66, c) would likely decompose the boron-ate complex, it was proposed that the activated pyridinium electrophile could be synthesised in a separate step and isolated before adding to the reaction.

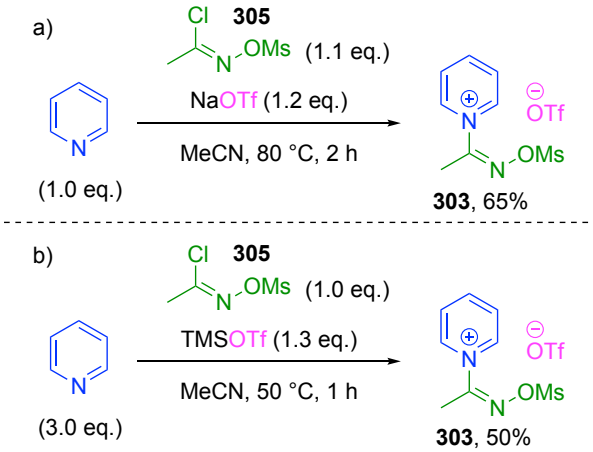


Scheme 66: a) Proposed cross-coupling of boron-ate nucleophile and pyridinium electrophile, b) Reported addition of boron-ate nucleophiles to cyclic iminium ions, c) Reported cyanation of pyridines with bifunctional reagent

3.3.1 Synthesis of activated pyridines[a]

To perform the envisaged protocol, in which the activated pyridinium species is added to the prepared boron-ate complex, the activated pyridine species would first need to be formed separately and isolated. Isolation of activated pyridine intermediates was not described in the 2017 paper,[119] however reaction of the α-chloro *O*-sulfonyl aldehyde oxime activating agent **305** with pyridine in MeCN at 80 °C (with sodium triflate added to drive the reaction forward by precipitation of sodium chloride by-product), followed by filtration and washing with Et_2O and THF was found to deliver the activated pyridine as an off-white solid in a moderate 65% yield (scheme 67, a). An alternative unpublished protocol described by Fier was also attempted (scheme 67, b), which had the activating agent **305** as the limiting reagent (with 3 equivalents of pyridine employed) and used TMSOTf rather than NaOTf as the source of triflate counter-ion at a lower temperature (50 °C rather than 80 °C). This procedure gave a reduced yield (50%), and the excess of pyridine employed is undesirable, hence the former procedure (scheme 67, a) was preferred.

DMF was found to be the best solvent for dissolving the activated pyridine species (**303**) formed. The activated pyridine salt **303** was found to be insoluble in THF and only partially soluble in MeCN.

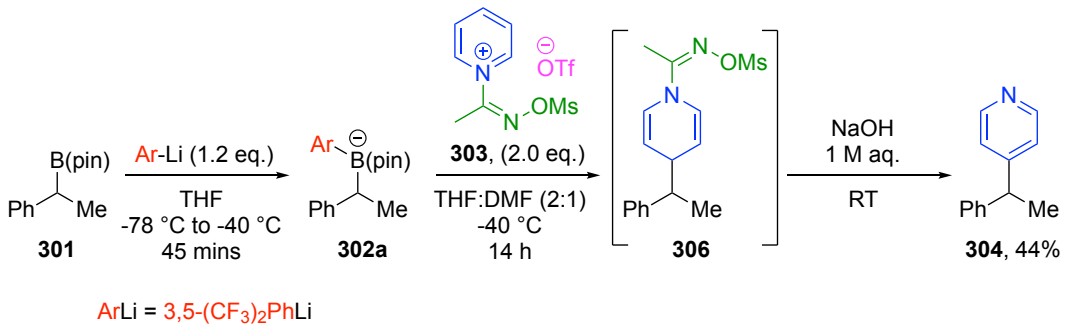


Scheme 67: Synthesis of activated pyridine **303**

[a] The studies described in sections 3.3.1 – 3.3.3 were carried out by Luke Lewis-Borrell

3.3.2 Initial testing of the protocol[b]

The boron-ate complex **302a** was first prepared by dropwise addition of 3,5-(trifluoromethyl)phenyllithium (prepared by lithium halogen exchange with *n*-BuLi from the corresponding aryl bromide) to the starting boronic ester **301** in THF at -78 °C and stirring for 30 minutes at this temperature (scheme 68). The reaction mixture was then warmed to -40 °C and 2 equivalents of the pyridinium electrophile **303** added dropwise as a solution in DMF (this maintaining the stoichiometry of boron-ate nucleophile to pyridinium electrophile utilised in the previously reported addition to cyclic iminium ions).[48] The reaction was stirred overnight at -40 °C before warming to room temperature and performing a basic work-up with 1 M sodium hydroxide.



Scheme 68: Protocol used for initial testing, ArLi = 3,5-bis(trifluoromethyl)phenyllithium, formed by lithium halogen exchange from the corresponding aryl bromide with *n*-BuLi

Formation of a cross-coupled product was successful, with a 44% yield observed for this reaction. In contrast to the cyanation described in section 3.1.1.3[119] the reaction was found to be completely regioselective for addition to the C4 position. This matches the regioselectivity seen for the previously reported addition of boron-ate nucleophiles to *N*-acyl pyridinium electrophiles.[48] It is assumed that the observed selectivity is due to a steric preference for the less hindered position, avoiding a steric clash between the bulky nucleophile and activating group.

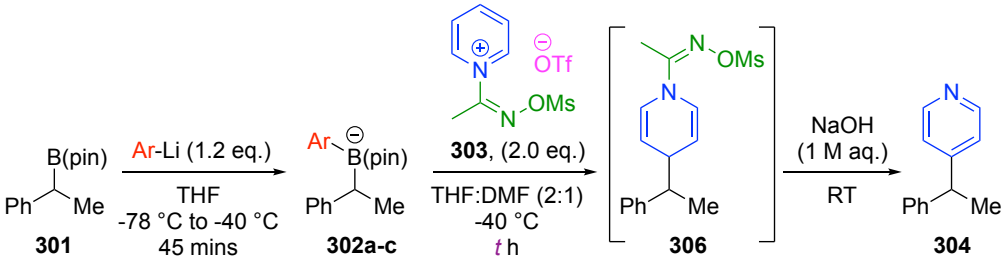
3.3.3 Choice of aryllithium species[c]

In addition to the electron-withdrawing 3,5-bis(trifluoromethyl)phenyl group, 4-methoxyphenyl and phenyl groups were also tested. More electron-rich aryl groups have been shown to increase the nucleophilicity of boron-ate complexes,[168] so it was hoped that moving to a more electron rich aryl group would improve the yield. However, a drop in yield from 44% to 14% was observed for the 4-methoxyphenyl variant (table 3 entry 3), whilst a negligible decrease in yield (42%) was observed when phenyllithium was employed as the aryllithium reagent (table 3 entry 2).

[b] The studies described in sections 3.3.1 – 3.3.3 were carried out by Luke Lewis-Borrell

[c] The studies described in sections 3.3.1 – 3.3.3 were carried out by Luke Lewis-Borrell

Table 3: Screen of aryllithiums



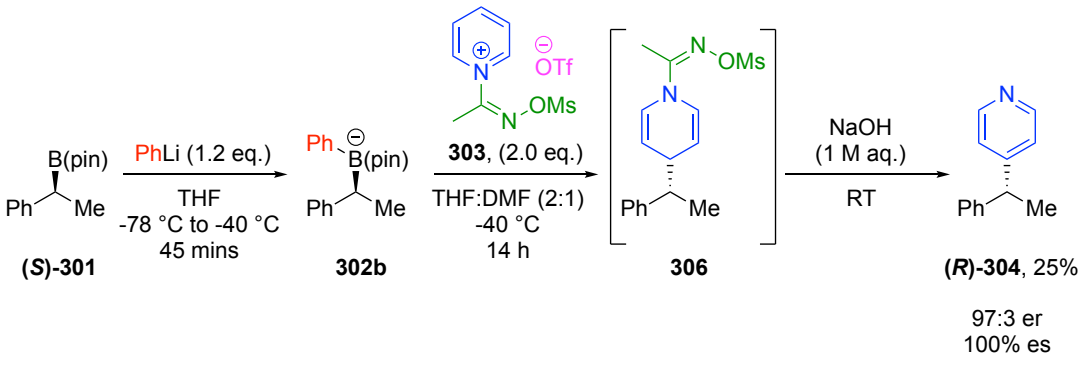
Entry	ArLi	Reaction time *t* / h	Yield[a] / %
1	3,5-$(CF_3)_2$PhLi	14	44
2	PhLi	14	42
3	4-(MeO)PhLi	14	14

a: NMR yield with 1,3,5-trimethoxybenzene internal standard

Phenyllithium is commercially available as a preformed solution in dibutyl ether. Therefore, use of this reagent removes the requirement for an additional lithium-halogen exchange step, reducing overall reaction times and complexity of setup. Hence this reagent was used for further studies.

3.4 Testing reaction enantiospecificity

With regioselectivity of the reaction established for the C4 position of the pyridine, work set out to confirm the enantiospecificity of the cross-coupling. Boronic ester **301** was synthesised in an enantioenriched (96:4 er, (*S*)-enantiomer major product) form by enantioselective hydroboration of styrene. The cross-coupling reaction (scheme 69) was performed under the established reaction conditions. HPLC analysis of the cross-coupling product **304** demonstrated 97:3 er, indicating that the reaction proceeds with complete enantiospecificity (100% es). It is assumed that the reaction proceeds with inversion of configuration, as observed in previous studies of boron-ate nucleophiles.[6,7,48]

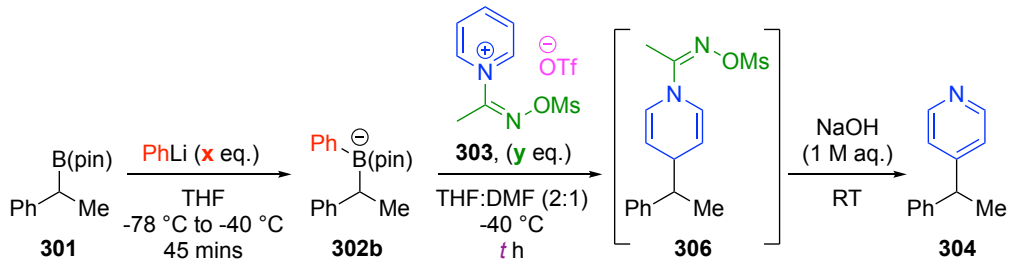


Scheme 69: Cross-coupling using enantioenriched boronic ester starting material **(*S*)-301**

3.5 Optimisation of stoichiometry (1)

With a view to improving the mediocre yield of the reaction, the stoichiometry of the starting boronic ester, phenyllithium and activating agent were optimised.

Table 4: Optimisation of stoichiometry



Entry	Eq. **301**	Eq. PhLi	Eq. **303**	Reaction time *t* / h	Yield[a] / %
1	1	1.2	2	14	42
2	1	1.2	1	14	46
3	2	2.4	1	14	14
4	1	1	1	14	37
5	1.2	1.2	1	14	42
6	1.2	1.4	1	14	47
7	1	1.2	1	2	17

a: NMR yield with 1,3,5-trimethoxybenzene internal standard

Decreasing the stoichiometry of the activated pyridine **303** from 2.0 equivalents to 1.0 equivalents was found to slightly improve the yield of the reaction (table 4, entries 1 and 2). In contrast, a 2:1 excess of boronic ester to activated pyridine led to a marked drop in yield, to 14% (entry 3). A possible reason considered for this was the excess phenyllithium reacting with the activated pyridine, and so the reaction was attempted with equistoichiometric ratios of boronic ester **301** and phenyllithium (entries 4 and 5). The 9% drop in yield observed for entry 4 compared to entry 2 suggests that the slight excess of phenyllithium is necessary to facilitate complete conversion of the boronic ester to the boron-ate intermediate **302**. A move to a slight excess of boronic ester **301** (entries 5 and 6) was not found to significantly improve the yield of the reaction.

Having established an equistoichiometric ratio of boronic ester **301** and activated pyridine **303** (with a slight excess of phenyllithium to form the boron-ate intermediate **302**) as ideal conditions, the reaction was also attempted on a much shorter timescale (entry 7). A lower yield was observed, indicating that the reaction requires longer than 2 hours to reach completion under these conditions.

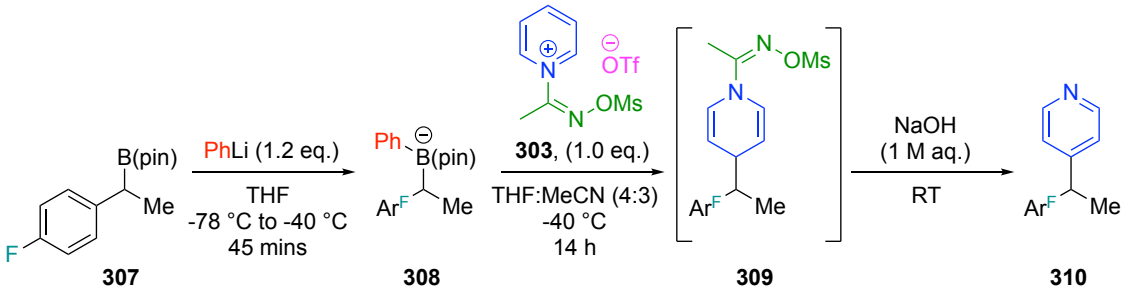
Furthermore, it was found that MeCN was able to fully dissolve the reduced amounts of activated pyridine **303** used for the equistoichiometric protocol. Use of MeCN was deemed preferable to DMF due to ease of removal in the work-up.

3.6 Further optimisation studies

Even with reaction stoichiometry optimised, the highest observed yields observed for this protocol were limited to under 50%. Given the multi-step nature of the reaction, it was unclear which stage was limiting the yield.

3.6.1 ^{19}F NMR studies

To better understand the reaction, a fluorinated variant of the starting boronic ester, **307**, was synthesised and ^{19}F NMR employed to track the formation and consumption of reaction intermediates (scheme 70).



Scheme 70: Reaction protocol for ^{19}F NMR studies

The formation of the boron-ate complex by dropwise addition of phenyllithium to a solution of boronic ester **307** in THF was found to be facile and complete in under 30 minutes at -78 °C, seen by full consumption of the boronic ester starting material (resonance at -120.0 ppm in THF, relative to 1,4-difluorobenzene internal standard resonance at -120.5 ppm) and the appearance of a peak at -125.1 ppm corresponding to boron-ate complex **308** (figure 1, next page).

Following addition of the activated pyridine electrophile as a solution in MeCN and stirring for 16 h at -40 °C, the boron-ate complex resonance at -125.5 ppm (in THF:MeCN, shift relative to the triflate anion at -79 ppm) was almost fully diminished (figure 2, next page). A new resonance observed at -118.4 ppm, corresponding to the intermediate **309** formed by attack of the boron-ate nucleophile **308** at the C4 position of the activated pyridine **303**. A further previously unseen resonance was observed at -117.7 ppm, however this was found to be that of the alcohol **311** resulting from oxidation of boron-ate complex **308**. The formation of the re-aromatised product was not seen in THF:MeCN, so it was presumed that the re-aromatisation step forming the product occurs during the basic work-up.

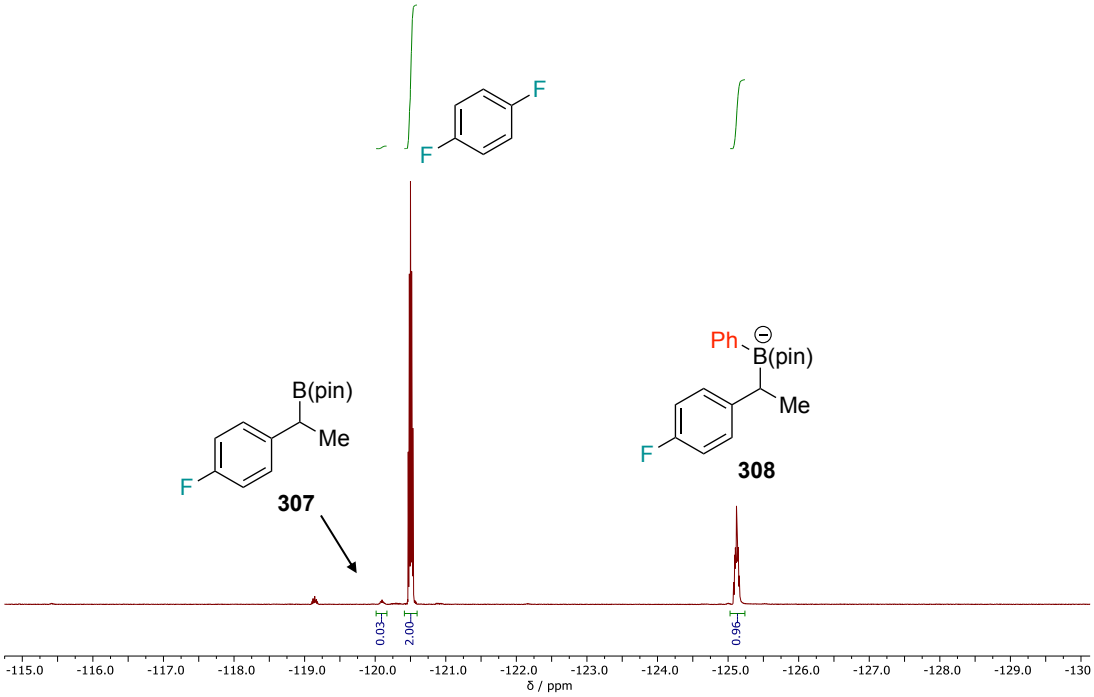


Figure 1: Formation of boron-ate complex **308** in THF (^{19}F, 400 MHz, 30 s relaxation delay)

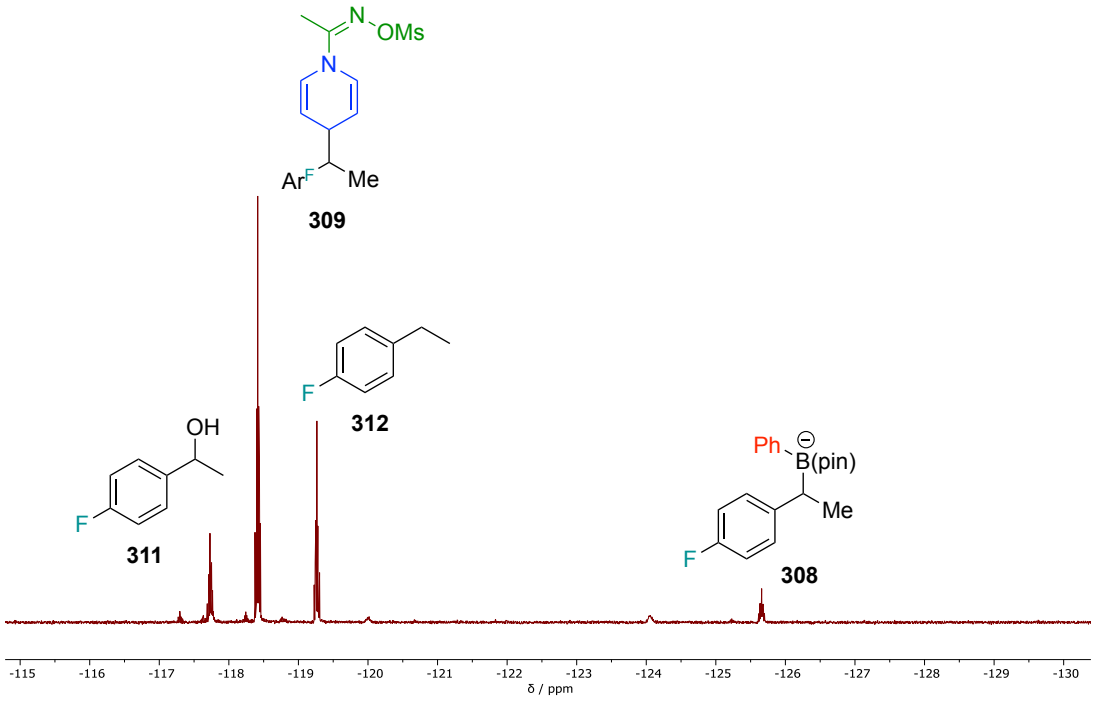
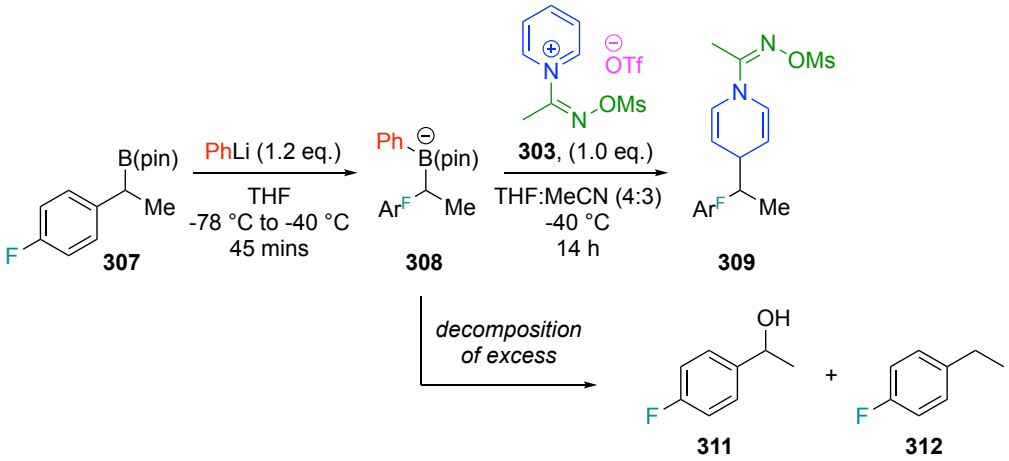


Figure 2: Formation of intermediate **309** and undesired side-products **311** and **312** in 4:3 THF:MeCN (^{19}F, 400 MHz)

To ensure that the formation of side products wasn't resultant of reaction with the electrophile, the stability of boron-ate complex **308** was tested under reaction conditions. The boron-ate complex **308** formed was found to be stable in THF at both -40 °C and room temperature for up to 18 h. However,

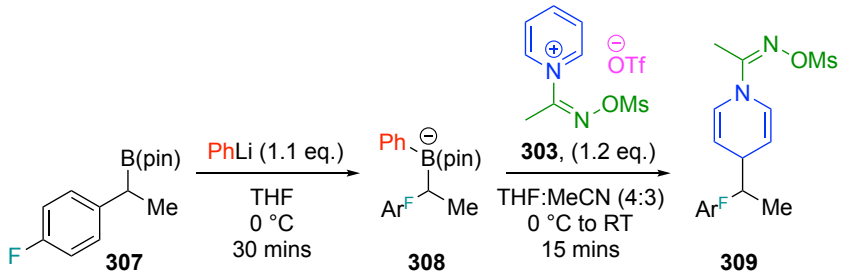
in a 4:3 solution of THF and MeCN (the reaction conditions without the electrophile present), partial decomposition of boron-ate complex **308** to the alcohol side-product **311** was observed after 18 h at both temperatures. Use of freeze-pump-thaw-degassed THF and MeCN was found to decrease the formation of the alcohol side-product **311**, however partial decomposition of the boron-ate complex **308** to a previously unseen side-product (resonance observed at -119.3 ppm) was observed, assumed to be the result of protodeboronation of boron-ate complex **308** (scheme 71, compound **312**).



Scheme 71: Decomposition of excess boron-ate complex giving side-products

It was noted that formation of boron-ate complexes at 0 °C using phenyllithium had been employed in previous work,[7] and so was also tested here. Formation of boron-ate complex **308** was found to be complete after 25 minutes at 0 °C, with negligible formation of any unwanted side-products. Addition of activated pyridine **303** over 5 minutes at 0 °C, followed by allowing the reaction mixture to warm to room temperature delivered the intermediate **309** after just 15 minutes of stirring, with almost full conversion of boron-ate complex **308**. After 16 h, the boron-ate complex was completely consumed with no further change seen in the integral of intermediate **309**, however some formation of the previously seen alcohol and protodeboronation side-products was observed. This implies that the nucleophilic attack step is complete after 15 minutes at room temperature, with any excess boron-ate complex decomposing more slowly to the side-products.

To minimise formation of these side-products, the stoichiometry was re-optimised. Given that a 1:1 stoichiometry of boronic ester **307** and activated pyridine **303** had resulted in excess boron-ate complex **308**, it was suggested that the excess of phenyllithium might be reacting with the activated pyridine, reducing the amount of activated pyridine **303** available to react with the boron-ate complex. A slight excess of activated pyridine **303**, 1.2 equivalents with respect to boronic ester **307**, alongside a reduced excess of phenyllithium (1.1 equivalents as opposed to 1.2 equivalents) delivered near full conversion of the boron-ate complex after 15 minutes at room temperature following addition of the electrophile (scheme 72).



Scheme 72: Optimised stoichiometry for formation of intermediate **309**

3.6.2 Re-aromatisation step optimisation

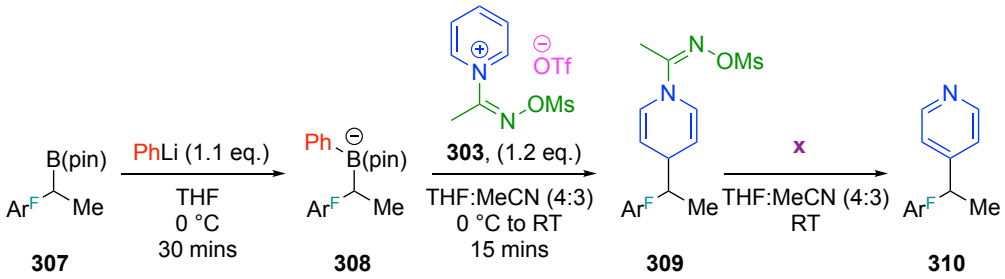
With ^{19}F NMR studies indicating that nucleophilic attack forming intermediate **309** is rapid and near quantitative, it was clear that yield limitation arises either in the re-aromatisation step or loss of reaction species in the work-up. Whilst formation of the cross-coupled product **304** had been observed in previous studies following a basic work-up (using 1 M sodium hydroxide), product formation was not observed immediately following the work-up in repeats of the reaction using either DMF or MeCN to introduce the activated pyridine salt (**303**). A repeat of the reaction under the 'original' conditions with phenyllithium outlined in section 3.3.3 (boron-ate complex formation at -78 °C, electrophile addition in DMF at -40 °C and stirring for 14 h at -40 °C before basic work-up) did not show product formation immediately after work-up either. The de-aromatised intermediate **309** was the major species seen in ^{1}H NMR analysis of the crude residue.

Due to this reproducibility issue, a more reliable method for driving conversion of the intermediate to the re-aromatised product was sought.

3.6.2.1 Bases

The expected mechanism for re-aromatisation to give the cross-coupled product was a base-assisted elimination of the leaving group, in line with the mechanism reported for the cyanation of pyridines.[119] In theory, this should be brought about under basic conditions during the work-up, however this was not seen in repeats using 1 M sodium hydroxide as the aqueous agent. 5 M aqueous sodium hydroxide did not bring about conversion either (table 5, entries 6 and 7).

Table 5: Screen of bases in THF:MeCN



Entry	Reagents/conditions **x**	Time / h	Observations (^{19}F NMR)	Yield[a] / %
1	NEt_3 (1.2 eq.)	18	**309** only	0
2	Pyridine (1.2 eq.)	18	**309** only	0
3	DBU (1.2 eq.)	18	New resonances, not **310**	0
4	KO^{t}Bu (1 eq.)	18	New resonances, not **310**	0
5	KO^{t}Bu (2 eq.)	18	New resonances, not **310**	0
6	NaOH (1 M aq.)	(work-up)	**309** only	0
7	NaOH (5 M aq.)	(work-up)	**309** only	0

a: Yield by ^{19}F NMR relative to 1,4-difluorobenzene internal standard

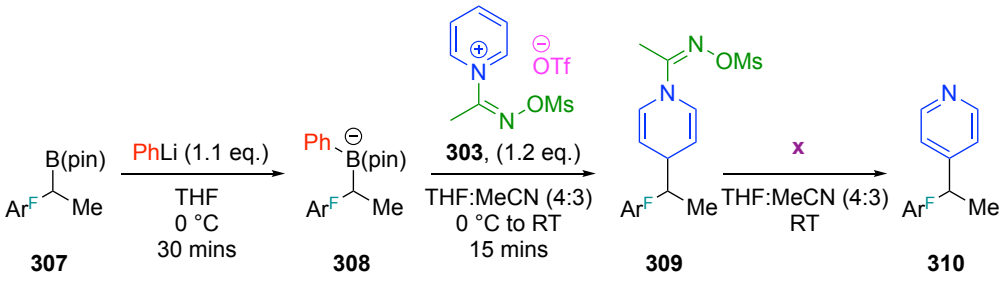
To evaluate whether base-assisted re-aromatisation could be brought about prior to work-up, by addition of base to the reaction medium, a series of bases were screened. ^{19}F NMR was used to track completion of the nucleophilic attack step to form intermediate **309**, before addition of base and stirring at room temperature. No change was observed in ^{19}F NMR spectra after 16 h at room temperature with slight excesses (1.2 equivalents) of triethylamine or pyridine (table 5, entrie 1 and 2). Heating these reaction mixtures to 60 °C for 1 h was not found to bring about any conversion of the intermediate (**309**). Use of stoichiometric amounts of stronger bases, DBU or potassium *tert*-butoxide (the latter supplied as a solution in THF) did bring about formation of a new resonance at -118.2 ppm in the ^{19}F NMR spectrum after 18 h (table 5, entries 3 and 4), however conversion was minimal, even after heating at 60 °C for 1 h. Use of an excess of potassium *tert*-butoxide (entry 5), 2 equivalents (with respect to the boronic ester starting material), did bring about near full conversion of the resonance corresponding to intermediate **309** to this resonance after 18 h, however the species formed was not identified as the desired product **310**.

The lack of efficacy of bases for the re-aromatisation step for this chemistry contrasts with the precedent cyanation, in which re-aromatisation under basic conditions is facile.[119] In the case of the cyanation reaction, the presence of the adjacent cyanide group acidifies the proton rendering a base-induced elimination of the activating/leaving group straightforward. For the cross-coupling protocol explored here, there is no additional acidifying effect, which disfavours this deprotonation-elimination pathway.

3.6.2.2 Other conditions in reaction solvent system or work-up

Attempts to isolate intermediate **309** in previous studies had proved unsuccessful, due to decomposition of this compound on silica gel resulting in formation of the re-aromatised product even where this species had not been identified in crude reaction mixtures. Addition of silica to the reaction mixture was attempted to see if this would bring about the conversion in the reaction medium, however formation of product **310** was not seen under these conditions after stirring for 16 h at room temperature (table 6, entry 1). One possibility is that decomposition of intermediate **309** during column chromatography was due to oxidation when exposed to air over time, however vigorous stirring of the reaction mixture in air did not result in product formation or decomposition of the intermediate otherwise (table 6, entry 2). Chloranil (tetrachloro-1,4-benzoquinone) had been successfully used as a stoichiometric oxidant for aromatisation of *N*-acyl dihydropyridines in previous work,[48] however the pyridine product was not observed following addition of chloranil to the reaction mixture and stirring at room temperature overnight (table 6, entry 3).

Table 6: Other conditions in THF:MeCN



307 **308** **309** **310**

Entry	Reagents/conditions **x**	Time / h	Observations (^{19}F NMR)	Yield / %
1	Silica gel (excess)	16	**309** only	0
2	Rapid stirring in air	16	**309** only	0
3	*p*-chloranil (1.2 eq.)	16	Messy spectrum Product not identified	-
4	*p*-TsOH (1.2 eq.)	16	Messy spectrum Product not identified	-
5	*p*-TsOH (10 mol%)	16	**309** only	0
		112 (5 days)	Product **310** formed	50[a]
6	HCl (1 M aq.)	(work-up)	Product **310** formed	30[a]
7	Heat to 50 °C	1	**309** only	0

a: Yield by ^{1}H NMR relative to 1,3,5-trimethoxybenzene internal standard

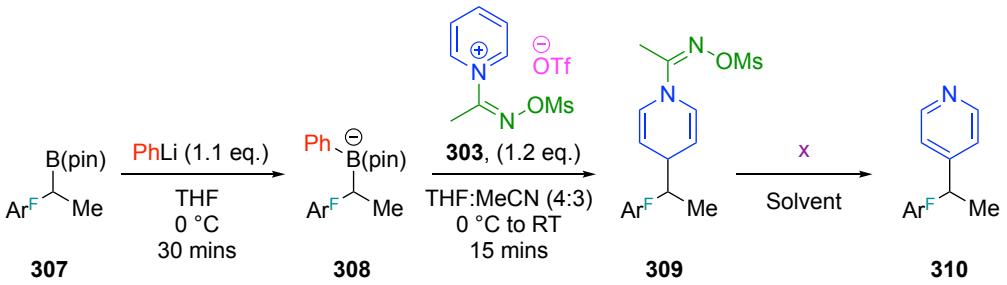
Silica is slightly acidic, so addition of acid in both stoichiometric and catalytic amounts to the reaction mixture following formation of intermediate **309** were also tested (table 6, entries 4 and 5), with reaction mixtures stirred at ambient temperature. Product formation could not be determined in the stoichiometric case (with decomposition to a mixture of unidentified fluorine-containing compounds).

Although a negligible change was seen in ^{19}F NMR analysis of the reaction mixture after 16 h (intermediate **309** was the only identifiable aromatic fluorine-containing species, with a resonance at -118.4 ppm), analysis after 5 days showed an additional resonance at -116.8 ppm, which was identified as the desired product **310** in moderate yield (50%), suggesting that re-aromatisation might be an acid-catalysed process. Performing the reaction with an acidic work-up (using 1 M hydrochloric acid as the aqueous phase) delivered the product in 34% yield, although some of intermediate **309** remained (8%).

3.6.2.3 Solvent switch

A breakthrough was made when it was noticed that full conversion of intermediate **309** to the pyridine product **310** could be observed in NMR samples that had been left overnight, indicating that re-aromatisation is spontaneous in chloroform. Switching solvent from THF:MeCN (4:3) to chloroform was evaluated for the re-aromatisation step by removing volatiles *in vacuo* following formation of the intermediate then taking up the crude residue in (deuterated) chloroform and stirring at room temperature. Conversion of intermediate **309** to product **310** was then tracked by both ^{19}F and ^{1}H NMR, this found to be complete after 16 h at RT in 60% yield (table 7, entry 1). Addition of base or acid to reaction mixtures in chloroform was not found to improve yield (table 7, entries 2 and 3).

Table 7: Solvent exchange optimisation



307 **308** **309** **310**

Entry	Solvent	Reagents/conditions **x**	Time / h	Observations	Yield[a] / %
1	$CDCl_3$	*No additional reagents*	16	Full conversion	60 (54)[b]
2	$CDCl_3$	NEt_3 (1.2 eq.)	17	42% **309** remaining	22
3	$CDCl_3$	*p*-TsOH (10 mol%)	17	15% **309** remaining	17
4	DCM	*No additional reagents*	16	No conversion	0
5	Toluene	*No additional reagents*	16	No conversion	0
6	$CDCl_3$	*No additional reagents*	20	Full conversion	74
7	$CDCl_3$	Heated to 50 °C	2	Full conversion	66
8[c]	$CDCl_3$	Heated to 50 °C	2	Full conversion	60

a: Yield by ^{19}F NMR relative to 4-fluorotoluene internal standard
b: Isolated yield
c: Aqueous workup prior to solvent exchange

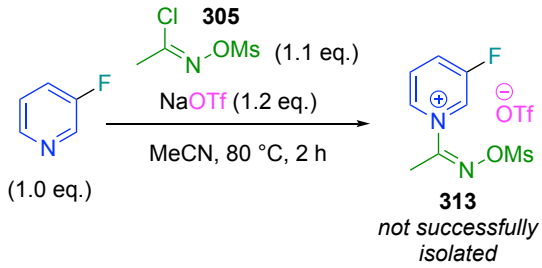
Repeats of this procedure gave a range of yields, with a best yield of 74% (table 7, entry 6). The inconsistency and decreased yield compared to the that of intermediate **309** was attributed to chloroform not fully dissolving the residue following removal of THF:MeCN, accounting for a loss of mass balance through the solvent exchange. Heating the reaction mixture to 50 °C to better dissolve intermediate **309** did not improve the yield, however full conversion was complete within 2 h (table 7, entry 7).

It was surmised that aggregation of the intermediate with insoluble lithium triflate by-product may account for intermediate **309** not being fully dissolved in chloroform. Sonication of the reaction mixture in chloroform was not found (by analysis of the reaction mixture before and after) to increase the total amount of intermediate **309** and product **310** in solution. Performing an aqueous work-up under basic conditions prior to dissolving in chloroform to remove the lithium triflate by-product (and so avoid potential aggregates) was not found to improve yield of the product, with repeats of this procedure consistently giving a 60% yield (entry 8).

Given the inability of chloroform to fully dissolve the reaction mixture, solvent switches to toluene and DCM were also attempted. However, the residue following removal of THF and MeCN was only sparingly soluble in toluene and did not fully dissolve in DCM either. Formation of product **310** was not observed in either case (entries 4 and 5).

3.7 Attempt at alternative 'one-pot' pyridine activation and boron-ate attack

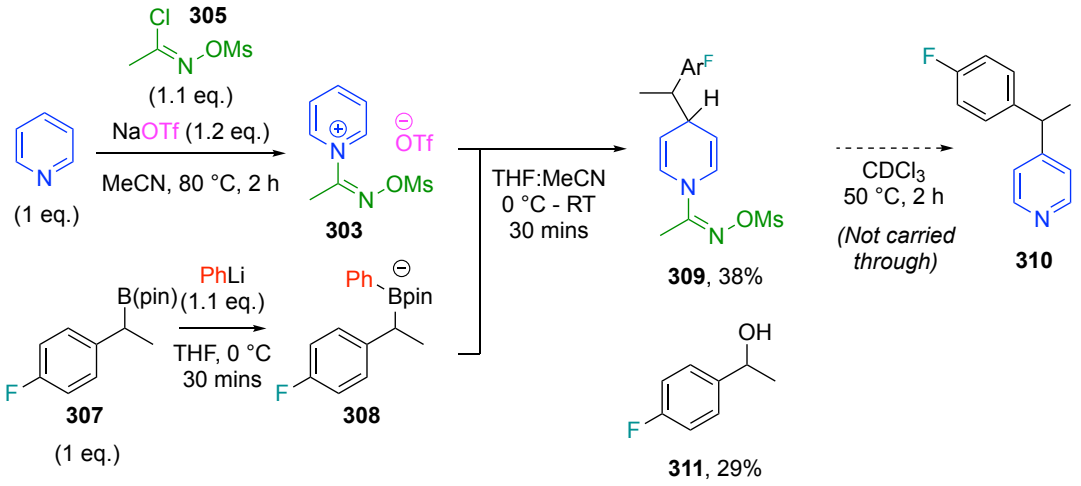
To study the consumption of the pyridinium electrophile by ^{19}F NMR, the synthesis of a 3-fluoropyridinium electrophile **313** was attempted (scheme 73). Unfortunately, attempts to isolate this compound by filtration/solvent washes and recrystallisation were unsuccessful. This led to the realisation that the need to isolate the activated pyridinium electrophile in a separate step was a drawback of this methodology.



Scheme 73: Attempt to synthesise 3-fluoropyridinium electrophile **313**

Therefore, one-pot protocol whereby the pyridine is activated *in situ* before addition of the boron-ate nucleophile **307** would be preferable. Activation of the pyridine *in situ* followed by addition of the

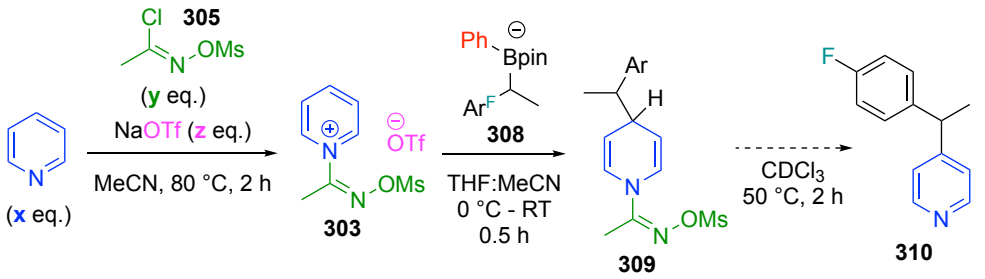
nucleophile was described for the cyanation of pyridines,[119] and it was hoped that adopting this protocol with a boron-ate nucleophile rather than cyanide would also be successful.



Scheme 74: Initial test of alternative 'one-pot' protocol

For the initial test of this protocol (scheme 74), a 1:1 stoichiometry of pyridine and boronic ester starting materials was employed, with formation of intermediate **309** tracked by ^{19}F NMR. In contrast to the previously established protocol (section 3.6.1, scheme 72), the intermediate was formed in only 38% yield after 0.5 hours, alongside a 29% yield of the alcohol by-product **311** (boron-ate complex **308** was completely consumed at this time) (table 8, entry 1). Increasing the amount of pyridine and activating agent was found to improve the yield of intermediate **309** to 63%, with a final yield of 28% for the re-aromatised product **310** following solvent switch to chloroform and stirring for 2 h at 50 °C (table 8, entry 2). On the basis that excess activating agent **303** may be reacting with the boron-ate nucleophile **308** limiting the yield, the reaction was repeated with reduced equivalents of activating agent **305** and sodium triflate (table 8, entry 3). This was not found to improve the yield.

Table 8: Optimisation of stoichiometry for 'one-pot' procedure (equivalents relative to boronic ester starting material)



Entry	Eq. **x**	Eq. **y**	Eq. **z**	Intermediate **309** Yield[a] / %	Product **310** Yield[b] / %
1	1	1.1	1.2	38	-
2	1.5	1.7	1.8	63	28
3	1.5	1.4	1.5	63	-

a: Yield by ^{19}F NMR relative to 1,4-difluorobenzene internal standard
b: Yield by ^{1}H NMR relative to 1,3,5-trimethoxybenzene internal standard

3.8 Summary and conclusions

The development of an enantiospecific sp^2-sp^3 cross coupling, regioselective for the C4 position of pyridines has been achieved by reaction of boron-ate nucleophiles with activated pyridine species. Using a fluorine-labelled boronic ester substrate **307**, the formation of intermediate **309** and product **310** was tracked using ^{19}F NMR spectroscopy. Reaction of the boron-ate complex **308** with the activated pyridinium electrophile **303** was found to proceed rapidly and cleanly, producing a de-aromatised intermediate **309** in near-quantitative yield. This species displayed surprising stability with respect to re-aromatisation to the pyridine product in a mixture of THF and MeCN under a variety of conditions, with a solvent switch to chloroform required to bring about this process. Conversion of intermediate to the pyridine product **310** in chloroform was observed proceed cleanly by ^{19}F NMR, however yields were limited, with loss of mass balance due to insolubility of the reaction mixture in chloroform.

3.9 Future work

Although a solvent switch to chloroform has been shown to facilitate conversion of intermediate **309** to the desired product **310**, further optimisation may be necessary to improve the yield and reproducibility of the reaction. Use of a co-solvent with chloroform, such as methanol may fully solubilise the reaction mixture while facilitating conversion of intermediate **309** to product **310**. Higher temperatures may also improve the conversion of intermediate **309** to product **310**.

The reaction protocol in which a pre-formed activated pyridine electrophile **303** is suitable for exploring the scope of benzylic boronic esters (once the conversion of the dihydropyridine intermediate **309** to cross-coupled pyridine product **310** is optimised). However, the requirement for isolating the activated pyridinium electrophile was found to be a problem when isolation of substituted 3-fluoropyridinium electrophile was attempted. To enable application of the reaction to a scope of substituted pyridines, either isolation of the activated pyridinium electrophile must be optimised (although the influence of any substituents on solubility in different solvents could pose a problem for this) or the alternative protocol explored in section 3.7 should be optimised.

4 Synthesis of cyclobutanes by a 1,2-metallate rearrangement-induced ring expansion of vinylcyclopropyl boronic esters

4.1 Introduction

4.1.1 Cyclobutanes in medicinal chemistry and natural products

Cyclobutanes are present in numerous natural products, including the sesquiterpene antibiotic punctatin A and indole alkaloid welwitindolinone A (figure 3, a). A review in 2008 showed that more than 210 cyclobutane-containing compounds have been confirmed to have antimicrobial, anticancer and other biological activities.[169] This has led to considerable recent interest in the use of cyclobutane compounds as potential drug leads or drug scaffolds.[170,171] Additionally, the well-defined rigid structure of cyclobutane rings has led to interest in their use in ligands for biomedical applications and organic synthesis.[172,173] It was shown by Bianchini that the use of the more rigid 'cyclo-tetraphos' ligand in place of 1,2-bis diphenylphosphinoethylene (dppe) renders Pd(II) catalysts that are 10 times more efficient for ethylene/carbon monoxide co-polymerization (figure 3, b).[173]

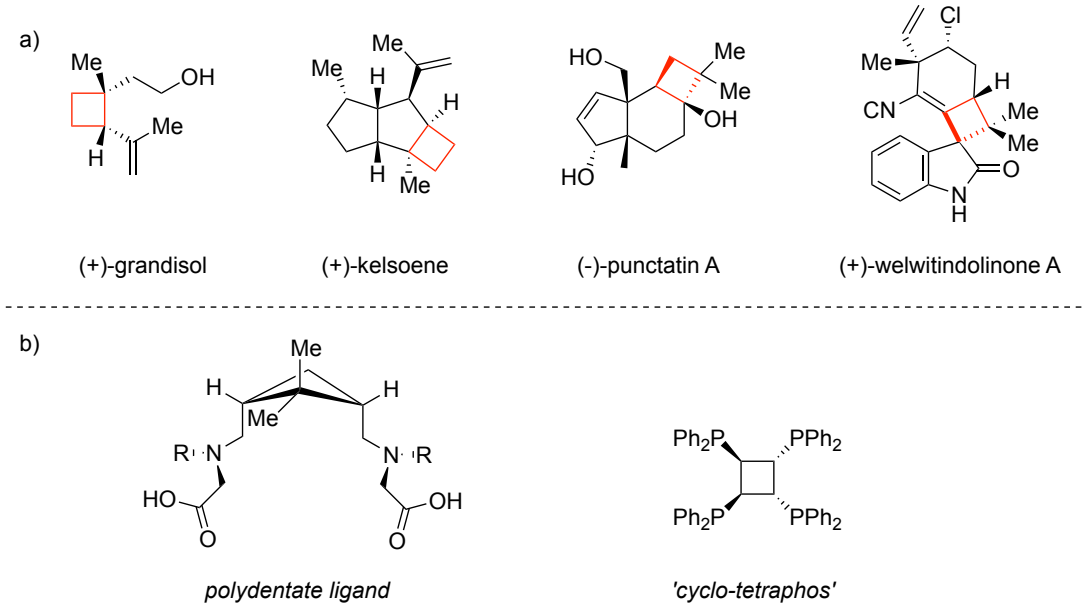
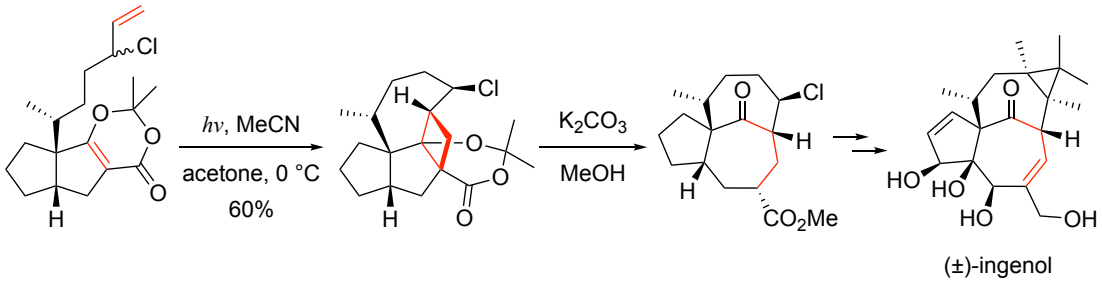


Figure 3: a) Selected cyclobutane natural products; b) Selected examples of cyclobutane ligands used in metal cation complexation[172] and organometallic catalysis[173]

4.1.2 Cyclobutanes as reactive intermediates

Cyclobutanes are inherently highly strained rings. The relief of this ring strain is a driving force for a wide range of useful transformations.[174] In particular, ring-opening and ring-expansion reactions have been utilised in organic synthesis and especially total synthesis for the generation of complex structures.[174] For example the formation by [2+2] cycloaddition and subsequent fragmentation of a cyclobutane ring has been used to generate the bridged 7-membered rings of (±)-ingenol, establishing critical intra-bridgehead stereochemistry (scheme 75).[175,176]



Scheme 75: Base-induced fragmentation of cyclobutane ring as key step in total synthesis of (±)-ingenol

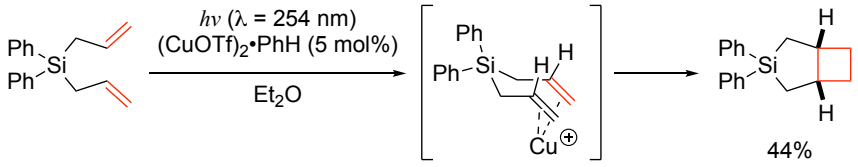
4.1.3 Synthesis of cyclobutanes

Given current interest in cyclobutanes as scaffolds in medicinal chemistry, the synthesis of cyclobutanes is an important topic in contemporary organic synthesis. The recent development of strain-release of bicyclo[1.1.0]butanes, discussed in chapter 1, section 1.2.1.2, has enabled rapid access to 1,3-substituted cyclobutanes – often with high diastereoselectivity.[33,34,36,43] This approach is currently limited to the synthesis of 1,3-substituted cyclobutanes due to the difficulty of building substitution at the bridging carbons in the synthesis of the bicylo[1.1.0]butane starting materials. Traditional approaches to cyclobutane synthesis, each with their own sets of limitations, include [2+2] cycloadditions, 1,4-cyclisations of acyclic substrates and ring contractions or expansions of five- or three-membered rings respectively.[177] These will be discussed in sections 4.1.3.1 to 4.1.3.4.

4.1.3.1 [2+2] Cycloadditions

The most popular method for the construction of cyclobutanes from acyclic substrates is the [2+2] cycloaddition of two alkenes.[177] Orbital symmetry considerations dictate that the thermal [2+2] cycloaddition is forbidden, whilst the photochemical [2+2] cycloaddition is allowed. Non-conjugated alkenes possess a high-lying S_1 singlet state (typically greater than 600 kJmol^{-1})[d], to which excitation is not feasible using commercially available irradiation sources.[178] In contrast, conjugated alkenes and enones can be excited by UV light. The excitation of non-conjugated alkenes by UV irradiation has been enabled by the use of sensitizers or complexation to transition metal catalysts, the latter enabling excitation *via* ligand-to-metal or metal-to-ligand charge transfer.[178] For example, Koenig reported the intramolecular photocycloaddition of two non-conjugated alkenes in the presence of a copper catalyst (scheme 76).[179]

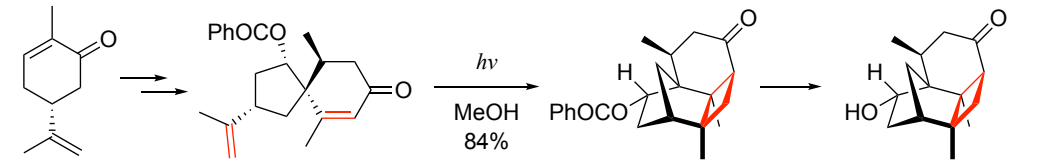
[d] 600 kJmol^{-1} corresponds to the energy of a 200 nm photon. Commercial irradiation sources are typically $\lambda \geq 250$ nm (the wavelength of a photon is inversely proportional to the energy).[178]



Scheme 76: Intramolecular photocycloaddition enabled by complexation to copper described by Koenig

For intermolecular [2+2] cycloadditions, regioselectivity is typically driven by electronic factors, which can lead to a mixture of regioisomers if the two ends of the alkene are insufficiently electronically differentiated.[177] Dimerization of the excited alkene can also compete with the cross-cycloaddition. Frequently, photochemically induced [2+2] cycloadditions are performed by biradical species (formed by intersystem crossing from a singlet to triplet excited state). Biradicals readily undergo stereochemical equilibration, which can limit the ability to influence the stereochemistry of the cyclobutane product by appropriate choice of cis or trans alkene substrates.[177]

Intramolecular [2+2] cycloadditions have been used to generate cyclobutane rings in total syntheses; the regio- and stereochemistry of the cyclobutane ring being set by the stereochemistry of the acyclic precursor.[180] For example, a [2+2] cycloaddition was used by Ramasastry as the penultimate step to construct the highly strained edge-fused cyclobutane ring of (+)-2β-hydroxysolanascone, the aglycone of a phytoalexin natural product (scheme 77).[181]

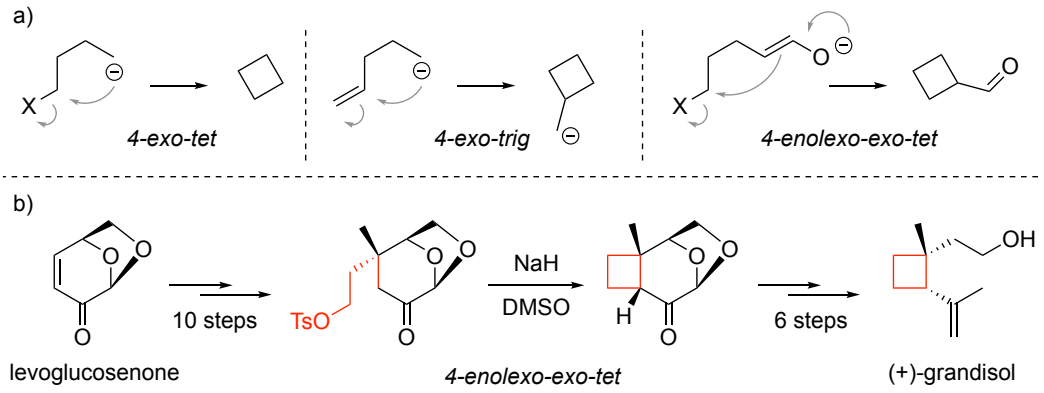


(*R*)-carvone (+)-2β-hydroxysolanascone

Scheme 77: Total synthesis of (+)-2β-hydroxysolanascone

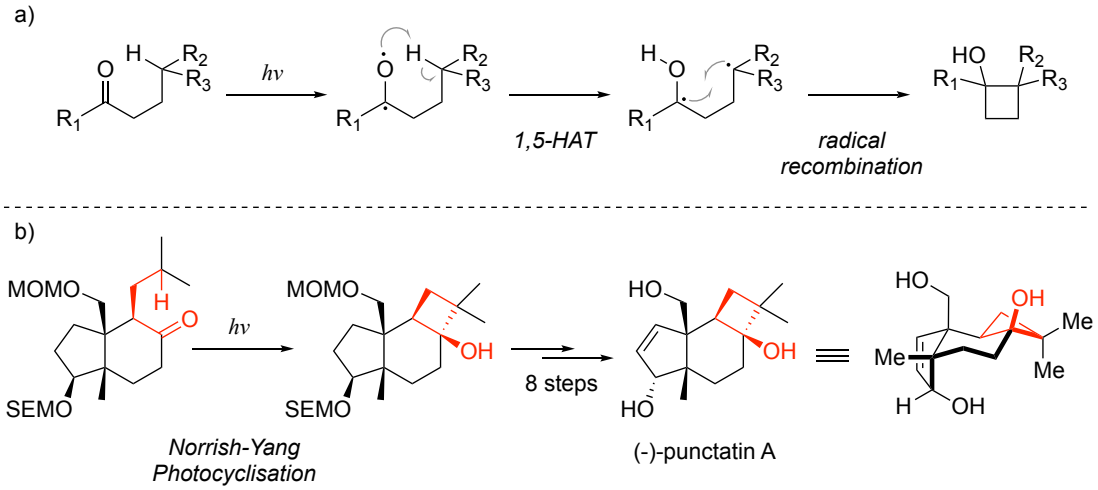
4.1.3.2 1,4-cyclisation of acyclic substrates

The cyclisation of acyclic substrates represents a convenient route to cyclobutanes. The 4-*exo-tet*, 4-*exo-trig* and 4-*endo-dig* cyclisations are all regarded as 'favoured' according to Baldwin's rules for ring closure, as are the corresponding *enolexo* cyclisations of enolates (scheme 78, a).[182] In practise, the conformational energy barrier to access the required eclipsed transition state conformation limits the general efficacy of these cyclisations. Nonetheless, intramolecular S_N2 reactions have been used to generate enantioenriched cyclobutanes from enantioenriched acyclic precursors.[177] This approach has also been used as the key cyclobutane-forming step in the total synthesis of (+)-grandisol from levoglucosenone (scheme 78, b).[183]



Scheme 78: a) 'Favoured' Baldwin cyclisations to generate cyclobutanes; b) Use of cyclisation in total synthesis of grandisol

The Norrish-Yang photocyclisation is a useful method for the synthesis of cyclobutanols. Irradiation of a carbonyl followed by 1,5-hydrogen atom transfer (HAT) gives a 1,4-biradical species, which can recombine to give the cyclobutanol product (scheme 79, a).[180,184] This approach has been utilised as a key step in the total synthesis of (-)-punctatin A, unusually forming a *trans*-fused cyclobutane ring in which both sides of the ring sit equatorial to the adjacent cyclohexane ring (scheme 79, b).[185]

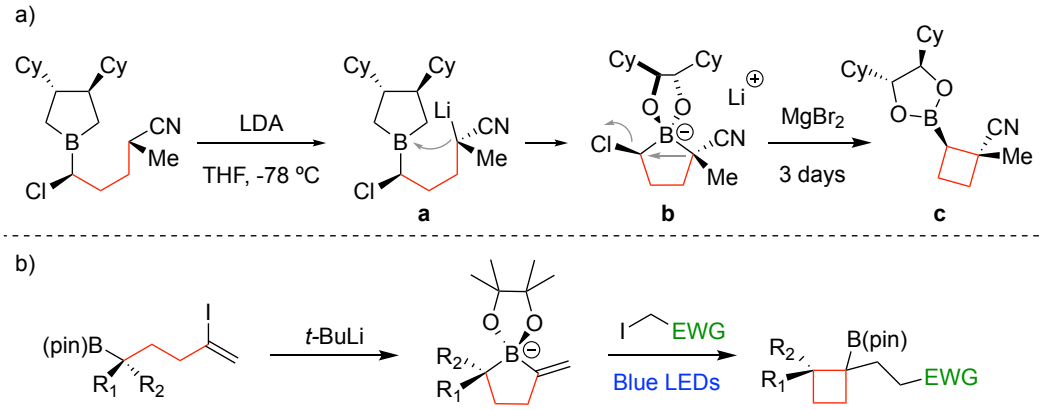


Scheme 79: a) Mechanism of the Norrish-Yang photocyclisation; b) Application in the total synthesis of (-)-punctatin A

4.1.3.3 Ring contraction of 5-membered rings

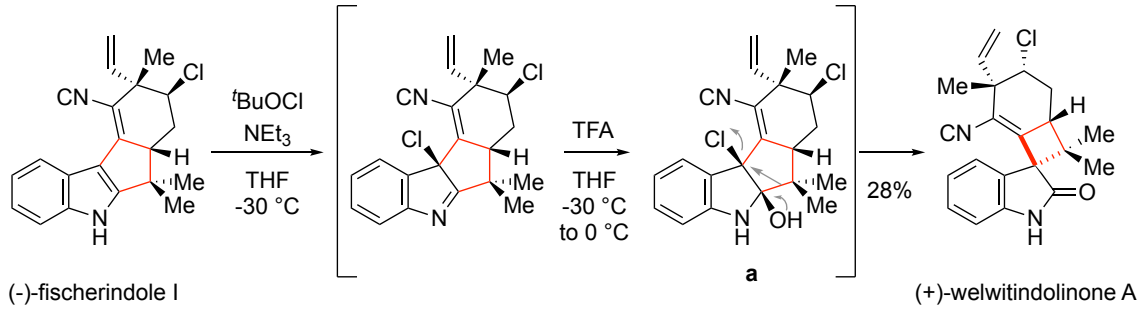
The contraction of 5-membered rings is a powerful tool for the synthesis of cyclobutanes. Matteson showed that deprotonated species **a** (scheme 80, a) can cyclise by intramolecular attack of the alpha-halo boronic ester. The cyclic boron-ate complex formed, **b**, can then undergo a 1,2-metallate rearrangement to generate cyclobutane **c**. A similar approach was utilised by Aggarwal for the strain-increase ring contraction of cyclic vinylboron-ate complexes previously discussed in chapter 1, section 1.2.2.1 (scheme 80, b).[44] For the Matteson reaction, the long reaction time for the 1,2-metallate rearrangement is tantamount to the energetic unfavourability of increasing the strain in the molecule. The addition of magnesium bromide is required to promote this step by coordination to the chloride leaving group, rendering it more amenable to displacement. The Aggarwal methodology circumvents

this difficulty by utilising a much more facile 1,2-metallate rearrangement to a carbocation generated through a radical-polar crossover mechanism – this having a lower energy barrier for the migration.



Scheme 80: a) Matteson's ring contraction of an alpha-chloro boron-ate complex;[186] b) Aggarwal strain-increase synthesis of cyclobutyl boronic esters[44]

Semi-pinacol rearrangements have also been used to contract 5-membered rings to give cyclobutane products. This approach was used as the final step in Baran's 2005 total synthesis of (+)-welwitindolinone A (scheme 81). The 5-membered ring of (-)-fischerindole I (formed in 7 steps from (*S*)-carvone oxide) was converted in one step to a spiro-cyclobutane product by treatment with *tert*-butyl hypochlorite followed by addition of dilute trifluoroacetic acid, giving a *beta*-chloro alcohol intermediate **a** which can undergo a semi-pinacol rearrangement upon warming to furnish the cyclobutane ring.

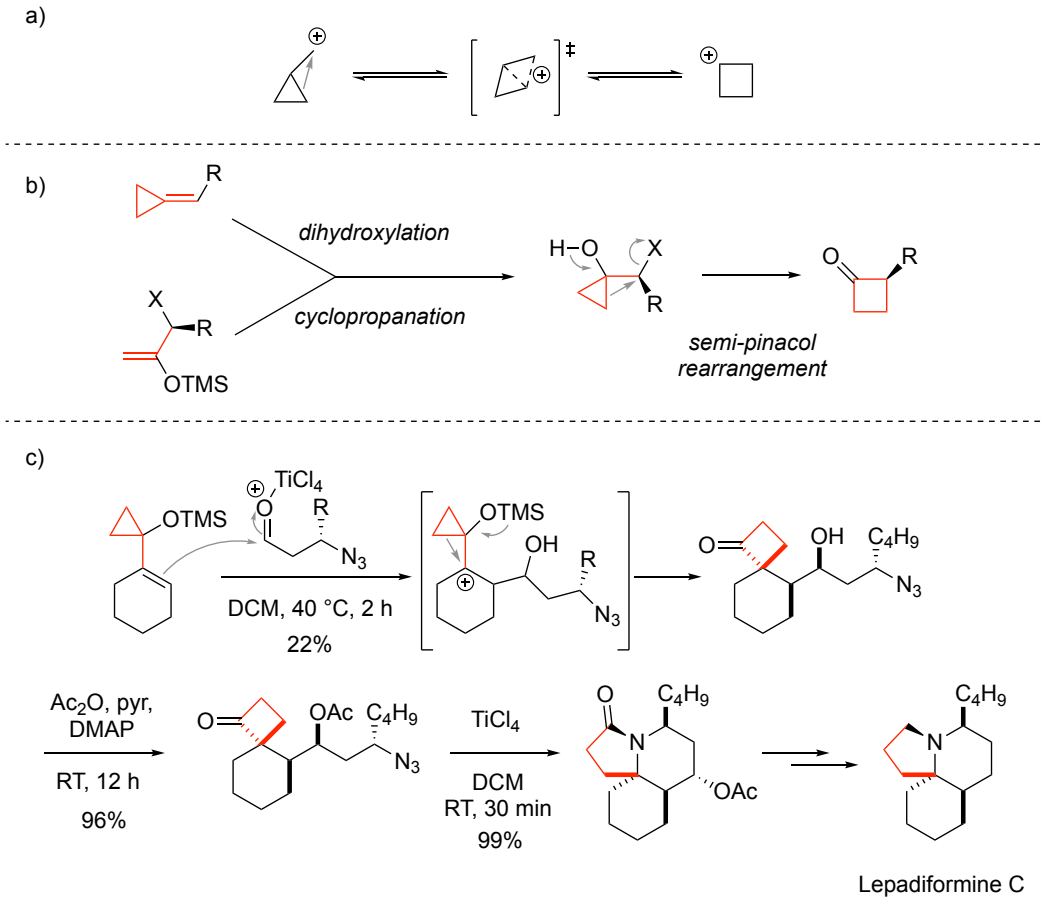


Scheme 81: Semi-pinacol rearrangement to generate the cyclobutane ring of (+)-welwitindolinone A

4.1.3.4 Ring expansion of 3-membered rings

Cyclopropylmethyl cations can be regarded as non-classical carbocations that readily rearrange to a cyclobutyl cation *via* a bicyclobutonium ion (scheme 82, a).[177] The quenching of these species with nucleophiles is not a reliable approach to cyclobutane synthesis given the propensity for stereo- and regiochemical scrambling, however placement of an electron donating group at the C1 position of the cyclopropane ring can enhance the selectivity for cyclobutane formation.[177] The semi-pinacol rearrangement of 1-hydroxycyclopropylmethanol derivatives to give substituted cyclobutanes is well established, these substrates being readily produced by dihydroxylation of alkylidenecyclopropanes

or cyclopropanation of enol ethers (scheme 82, b).[177,187,188] Migration typically proceeds with retention of stereochemistry at the migrating carbon and inversion at the terminus of migration, hence this constitutes a powerful method for enantiospecific synthesis of cyclobutanones.[177] Additionally, semi-pinacol rearrangements with a carbonyl as the migration terminus can be rendered asymmetric if a chiral Lewis acid is used to activate the carbonyl.[187] The semi-pinacol rearrangement of vinylcyclopropanols can also be induced by electrophilic activation of the alkene moiety.[189–191] This approach has also been applied as a key step in the total synthesis of Lepadiformines A and C (scheme 82, c).[192]

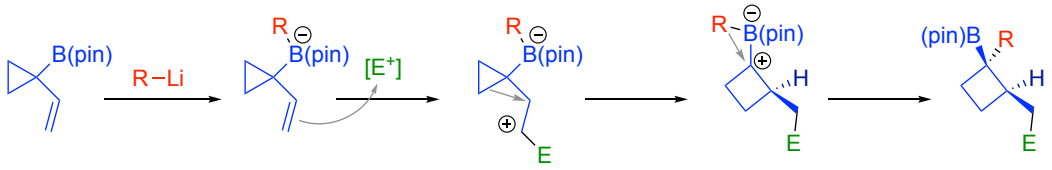


Scheme 82: a) Rearrangement of cyclopropylmethyl carbocation; b) Semi-pinacol rearrangement of 1-hydroxycyclopropylmethanol derivatives; c) Semi-pinacol rearrangement as key step in total synthesis of lepadiformine C

4.2 Project proposal

The project described in this chapter seeks to develop the ring expansion of cyclopropanes to cyclobutanes as a trigger for the 1,2-metallate rearrangement of boron-ate complexes (scheme 83). It is proposed that electrophilic activation of the double bond of a vinylcyclopropyl boron-ate complex will generate a carbocation at the β-position (with respect to the boron-ate moiety). This intermediate will undergo a 1,2-alkyl shift (Wagner-Meerwein rearrangement) expanding the cyclopropyl ring to a cyclobutyl ring and moving the carbocation α- to the boron-ate moiety, triggering the 1,2-metallate

rearrangement (scheme 83). This approach may be considered as a boron analogue to the semi-pinacol reactions described in section 4.1.3.4, for which the 1,2-metallate rearrangement replaces the formation of a ketone as the driving force for the ring-expansion.



Scheme 83: Proposed ring-expansion induced 1,2-metallate rearrangement giving cyclobutyl boronic ester products

This will generate α,β- substituted cyclobutyl boronic esters, which are desirable targets given the ability of the boronic ester to be stereospecifically transformed into a wide variety of functional groups.[9]

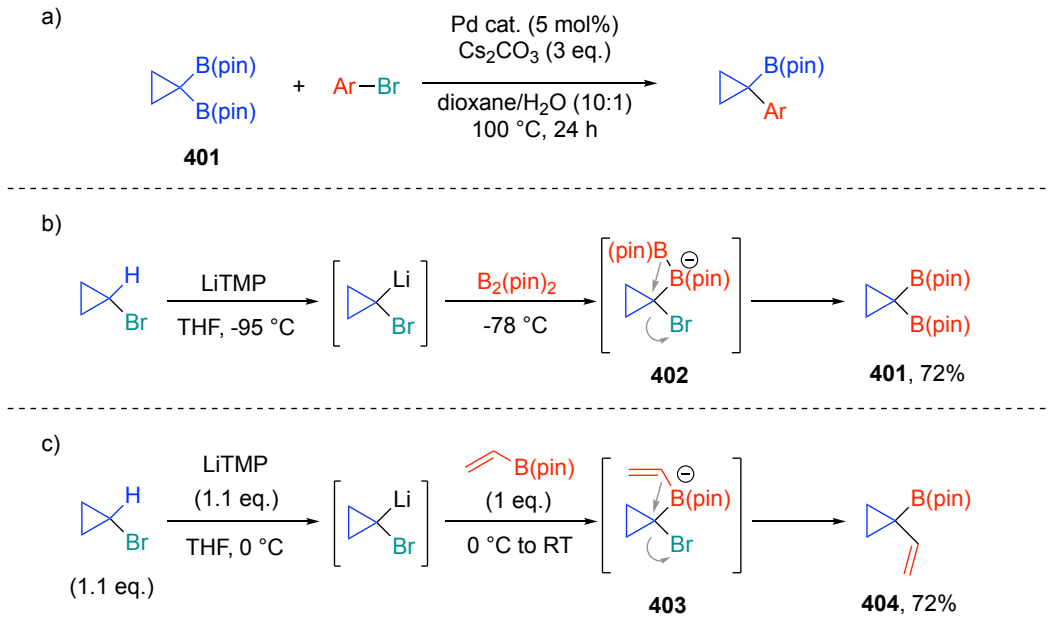
The work outlined in this chapter is described in the following publication: Durga Prasad Hari, Joseph C. Abell, Valerio Fasano and Varinder K. Aggarwal, *J. Am. Chem. Soc.* **2020**, 142, 5515-5520.[193] Contributions of co-authors are briefly described in sections 4.3 and 4.9 in order to give a full account of this project.

4.3 Development of the reaction, electrophile scope and rationale for diasteroeselectivity[e]

4.3.1 Synthesis of vinylcyclopropyl boronic ester

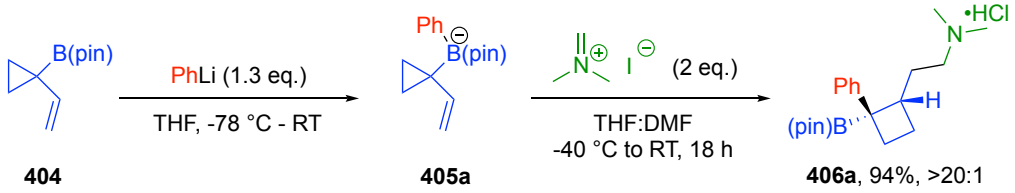
It was anticipated that vinylcyclopropyl boronic esters could be accessed by the known Suzuki coupling of cyclopropane bis-boronic ester species **401** with vinyl bromides (scheme 84, a).[194] The reported synthesis of **401** involves the lithation and trapping of bis-pinacolatodiboron (B_2pin_2) with cyclopropyl bromide (scheme 84, b). It was noted that the proposed mechanism for this procedure resembles that of the Matteson homologation, in which 1,2-migration of a boron-ate complex intermediate **402** with a halide leaving group delivers the product. It was proposed that this methodology could be applied with vinylboronic ester in place of $B_2(pin)_2$ to directly access the desired vinylcyclopropyl boronic ester **404** (scheme 84, c). This was successful. Optimised conditions for the protocol are shown in scheme 84, c). Cyclopropyl bromide is lithiated with lithium tetramethylpiperidide and trapped with vinylboronic acid pinacol ester at 0 °C to form the boron-ate complex **403**. The reaction mixture then allowed to warm to ambient temperature overnight to facilitate the 1,2-metallate rearrangement. This method was successfully applied to the synthesis of vinycyclopropyl boronic ester **404** on a 15 mmol scale.

[e] The chemistry described in sections 4.3.1 to 4.3.3 was performed by Dr. Durga Hari.



Scheme 84: a) Suzuki reaction of gem-bis-boronic ester to give arylcyclopropyl boronic esters; b) Literature synthesis of gem-bis-boronic ester; c) Optimised synthesis of vinylcyclopropyl boronic acid pinacol ester

Optimisation studies for the ring expansion of vinylcyclopropyl boronic ester **404** were conducted using phenyllithium as the organolithium reagent to generate boron-ate complex **405a** in THF. Eschenmoser's salt (dimethylmethylideneammonium iodide) was used as the electrophile to activate the double bond and induce the ring-expansion and subsequent 1,2-metallate rearrangement. It was found that the reaction proceeds with high diastereoselectivity. The desired cyclobutane product **406a** was produced in 94% yield under optimised conditions, in which 2 equivalents of Eschenmoser's salt is used with a 1:1 mixture of THF and DMF as the solvent for this step (scheme 85). Purification of the cyclobutane product was straightforwardly performed by precipitation of the hydrochloride salt from diethyl ether following treatment with dilute hydrochloric acid.



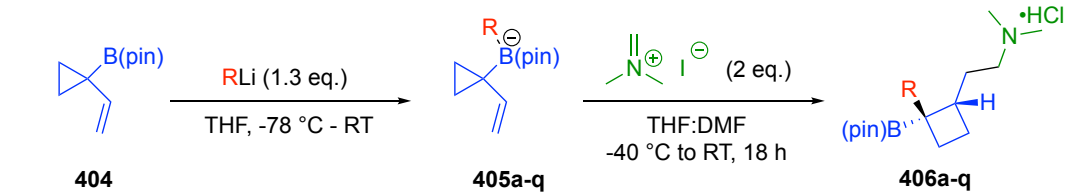
Scheme 85: Ring expansion of vinylcyclopropyl boronic ester with phenyllithium and Eschenmoser's salt

4.3.2 Scope of organolithiums, Grignard reagents and electrophiles

Under optimised conditions with Eschenmoser's salt as the electrophile the reaction was performed with a variety of organolithium reagents (table 9, a). Aryllithiums were generally successful in delivering cyclobutane products with high yields and diastereoselectivity. Additionally, vinyllithiums were also successfully employed with high selectivity for generation of cyclobutanes over any competing electrophilic activation of the vinylboron-ate moiety. Primary and secondary alkyllithiums, including cyclopropyllithium and cyclobutyllithium also performed well in the reaction. The methyl

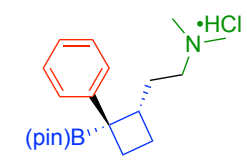
group is notorious for being a poor migrating group,[195] so the success of methyllithium for this protocol demonstrates the favourability of forming the cyclobutane product. In addition to organolithiums, some Grignard reagents, activated with lithium chloride (1.5 equivalents), were also successfully employed for the reaction (table 9, b).

Table 9: a) Scope of organolithiums; b) Scope of Grignard reagents (LiCl used as additive to promote nucleophilicity)

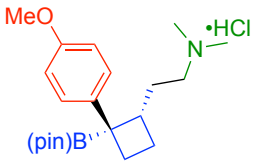


404 **405a-q** **406a-q**

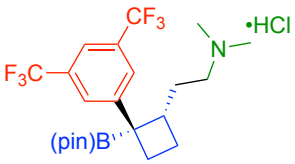
a)



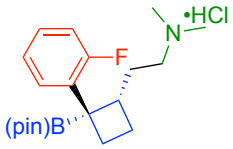
406a, 94%, >20:1



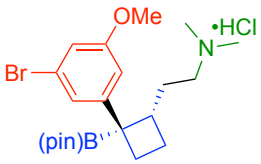
406b, 81%, >20:1



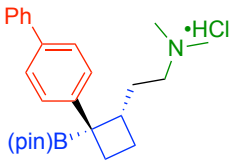
406c, 91%, >20:1



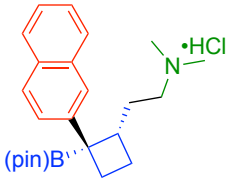
406d, 92%, >20:1



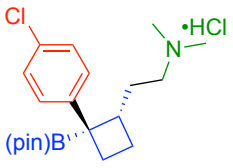
406e, 80%, >20:1



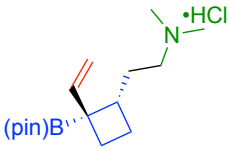
406f, 96%, >20:1



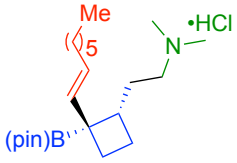
406g, 94%, >20:1



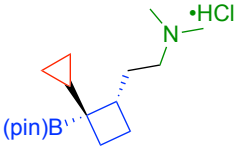
406h, 84%, >20:1



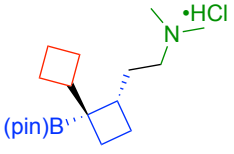
406i, 87%, >20:1



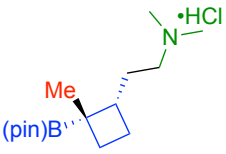
406j, 61%, >20:1



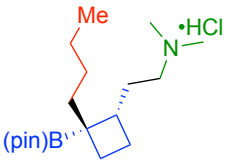
406n, 73%, 12:1



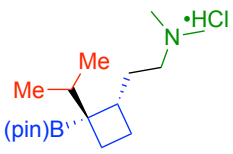
406o, 63%, 13:1



406k, 62%, >20:1

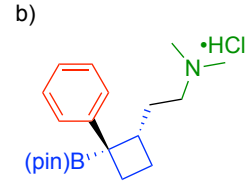


406l, 81%, >20:1

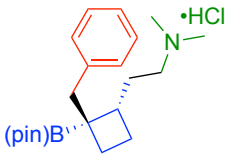


406m, 78%, >20:1

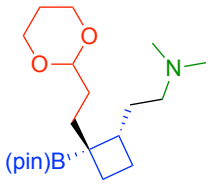
b)



406a, 91%, >20:1



406p, 81%, >20:1

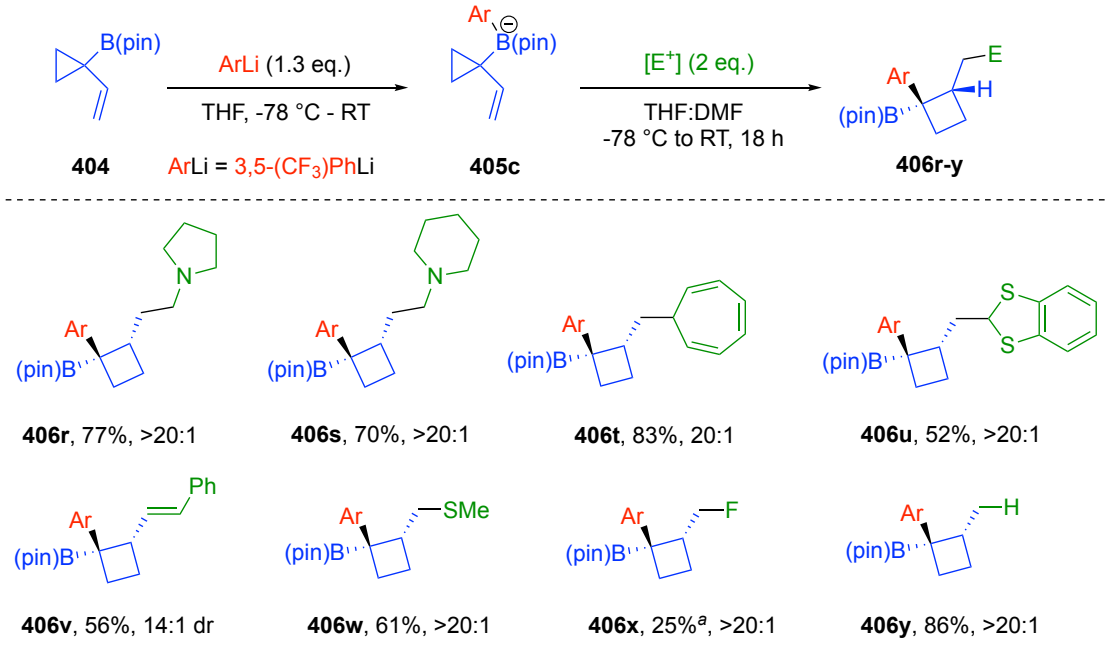


406q, 61%, >20:1

The ring expansion of vinylcyclopropyl boron-ate complex **405a** has been shown to successfully be induced by various electrophiles (table 10). In addition to Eschenmoser's salt the reaction was

performed with cyclic methylidene ammonium salts to give cyclobutanes **406r** and **406s** with similarly high diastereoselectivity. The reaction was extended to other carbon electrophiles, with tropylium tetrafluoroborate and dithiolylium tetrafluoroborate delivering cyclobutane products **406t** and **406u** in high yields and diastereoselectivity. The dimethoxy acetal of benzaldehyde activated with triethylsilyl triflate was also successful in inducing the ring-expansion and 1,2-metallate rearrangement. In this case the alcohol formed subsequently underwent elimination, giving styrene **406v** as the product. Heteroatom-based electrophiles were also successful in generating cyclobutanes with new C-S and C-F bonds with high diastereoselectivity. Finally, HBF_4 was successful in achieving formation of cyclobutane product **406y** in high yield and diastereoselectivity without competing protodeboronation (which dominated when other Brønsted acids were used).

Table 10: Scope of electrophiles (Ar = 3,5-$(CF_3)_2C_6H_3$)



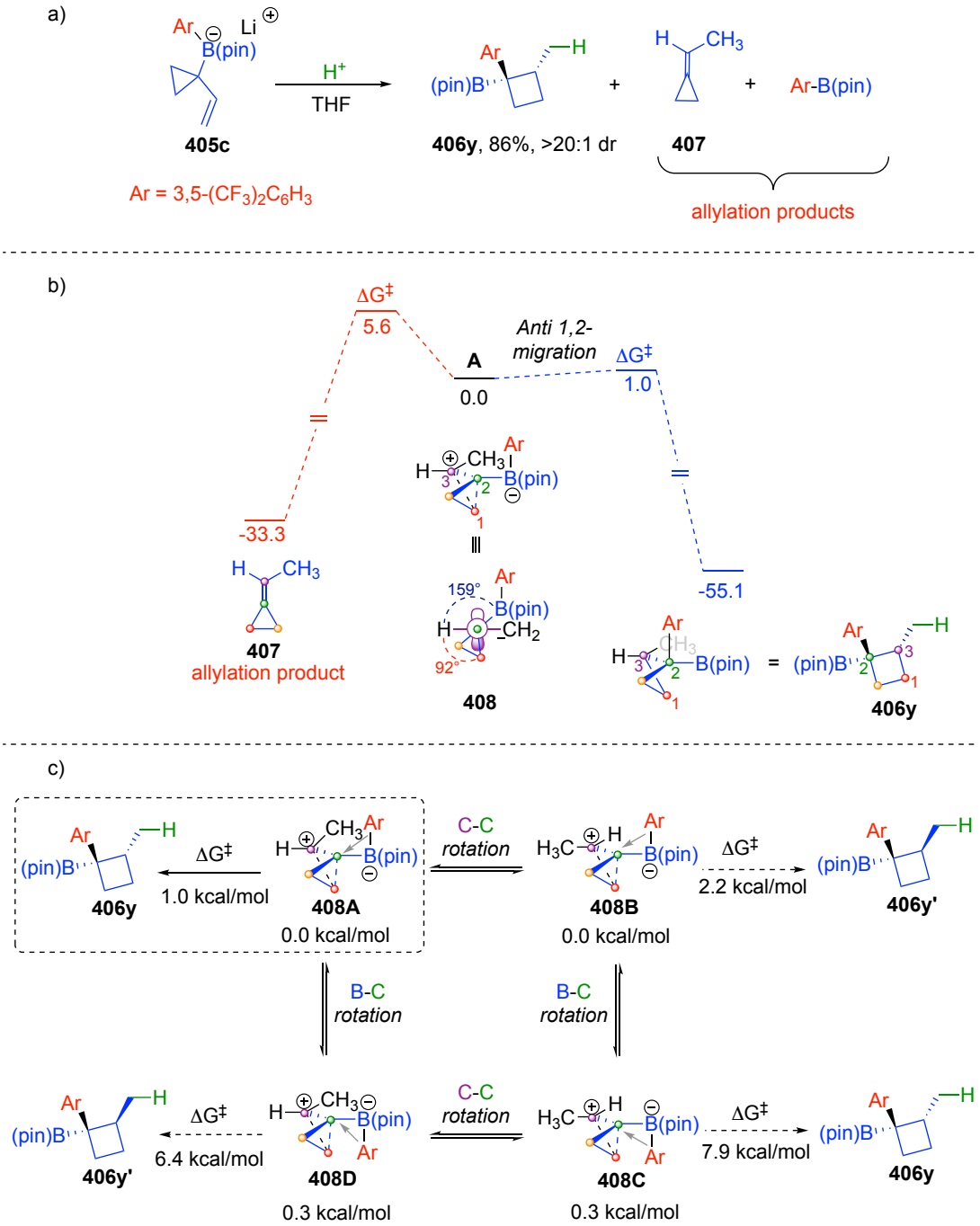
a: a solution of boron-ate complex **405c** in MeCN was added to a solution of selectfluor in MeCN at -40 °C

4.3.3 Model for diastereoselectivity[f]

In most cases with various organolithiums and electrophiles the ring expansion reaction proceeded with greater than 20:1 dr. DFT calculations were performed to gain insight into the mechanism of the reaction and the origin of this diastereoselectivity.[193] Transition state energies for migration and allylation from the zwitterionic intermediate **408** following electrophilic activation of vinylcyclopropylboron-ate complex **405c** with a simple proton were calculated (scheme 86, a and b).

[f] DFT Calculations performed by Dr. Valerio Fasano. Accompanying experiments performed by Dr. Durga Hari

The transition state for 1,2-migration giving ring-expansion was found to be lower than that for allylation, consistent with the observed selectivity for cyclobutane products.



Scheme 86: a) Model reaction studied, b) Transition state energies for 1,2-migration and allylation from zwitterionic intermediate **408**, c) Calculated energies for rotamers of carbocation intermediate with dominant reaction pathway highlighted

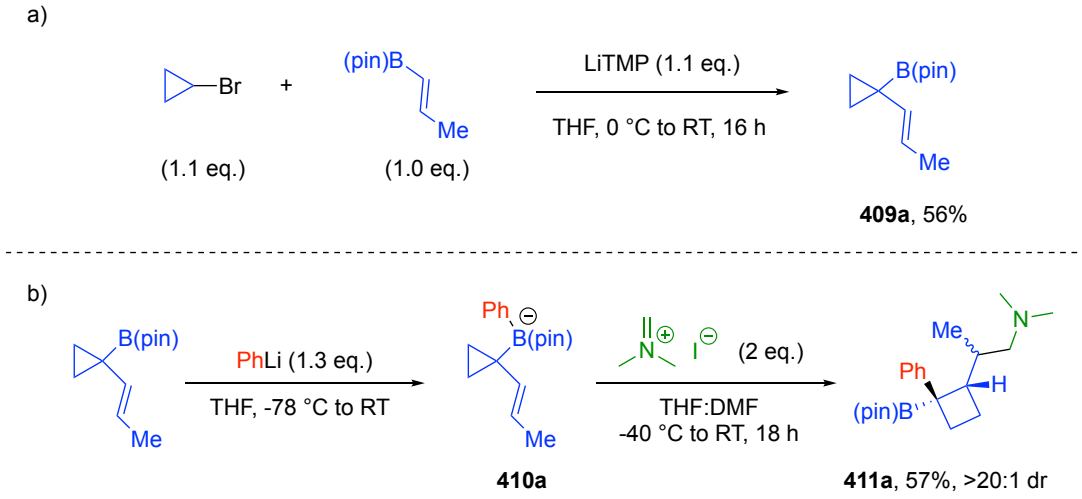
The energies of all possible rotamers of the carbocation intermediate following electrophilic activation of the double bond and the activation barriers for *syn*- and *anti*- migration from these were calculated (scheme 86, c). It was found that energy barriers for *anti*- migration are significantly lower than those for *syn*- migration. Additionally, there is a lower energy barrier for *anti*- migration from intermediate

408A than intermediate **408B** (these being differentiated by rotation around the C-C bond between the carbon atoms highlighted purple and green in scheme 86, c). The preference for this lower energy pathway accounts for the high diastereoselectivity of the reaction.

4.4 Substituted vinylcyclopropyl boronic esters

In addition to varying the organolithium reagent and electrophile used, substitution on the starting vinylcyclopropyl boronic ester provides a third point of differentiation in constructing cyclobutane scaffolds using this methodology. Where the substitution is at the β- position of the alkene in the vinylcyclopropyl boronic ester starting material, this gives rise to an additional stereocentre in the cyclobutane product. It was hoped that the construction of this additional stereocentre would match the high diastereoselectivity observed for the formation of the two cyclobutane stereocentres.

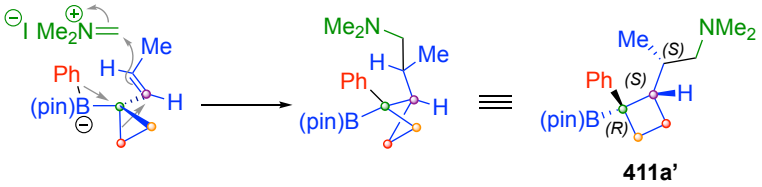
Trans-propenylcyclopropyl boronic ester **409a** was obtained in 56% yield from commercially available *trans*-propen-1-yl boronic acid pinacol ester using the established cyclopropyl homologation methodology (scheme 87, a). Boronic ester **409a** was then subjected to the optimised conditions for ring expansion, with phenyllithium as the organolithium reagent and Eschenmoser's salt as the electrophile (scheme 87, b). GCMS and ^{13}C NMR analysis of the crude reaction mixture showed that the cyclobutane product **411a** had been formed with greater than 20:1 dr demonstrating a high degree of diastereoselectivity for formation of the three contiguous stereocentres in **411a**. The cyclobutane product **411a** was isolated in 57% yield.



Scheme 87: a) Synthesis of trans-propenylcyclopropyl boronic ester **409a**; b) Ring expansion of **409a** to give **411a**

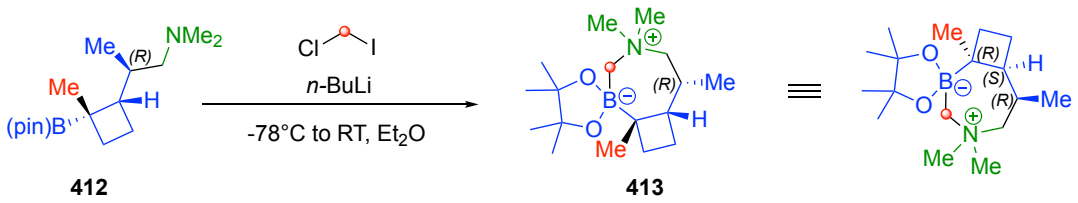
Originally, the high diastereoselectivity for this reaction was rationalised by considering the model shown in scheme 88. It was considered that there may be a preference for an *anti- anti-* relationship between the migrating aryl group on boron, the migrating methylene group of the cyclopropane ring and the approach of the electrophile to the double bond. This would result in the relative

stereochemistry shown, in which the adjacent stereocentres have (*R*), (*S*), (*S*) configurations from left to right in structure **411a'** (*S*, *R*, *R* for the opposite enantiomer). The reaction is believed to occur in a stepwise rather than concerted fashion based on the calculations described in section 4.3.3, therefore the observed diastereoselectivity in this model is a consequence of consecutive rapid 1,2-migrations from the preferred intermediate conformation following electrophilic activation of the double bond.

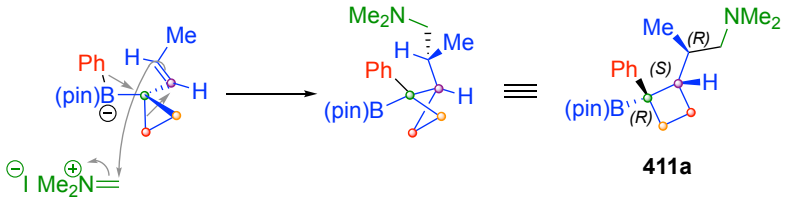


Scheme 88: Original model proposed for formation of single diastereomer

This stereochemistry was later shown to be incorrect. A Matteson homologation was attempted from compound **412**,[g] however intramolecular attack of the amine nitrogen on the chloromethyl component of the boron-ate intermediate resulted in formation of zwitterionic compound **413** (scheme 89). A crystal structure of **413** was obtained demonstrating a clear (*R*), (*S*), (*R*) relationship of the three stereocentres (figure 4, next page). Given that the stereocentre at the side-chain carbon is not affected by the Matteson homologation conditions, this indicates that the stereochemistry of the ring-expansion product is that shown in compound **412** (scheme 89). Therefore, the stereochemistry cannot be set according to the model shown in scheme 88, which delivers the wrong diastereomer. The simplest alternative model that may account for this would be that shown in scheme 90, in which the approach of Eschenmoser's salt occurs at the bottom face of the double bond.



Scheme 89: Formation of zwitterionic species **413**



Scheme 90: Model for formation of product diastereomer

[g] Performed by Dr. Durga Hari

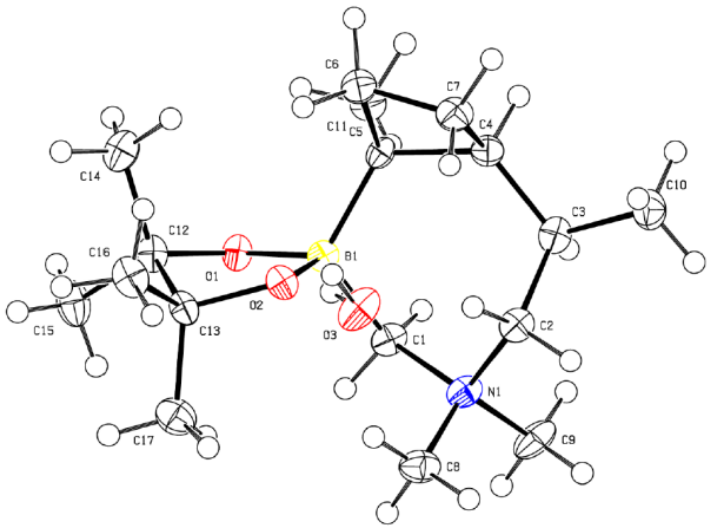
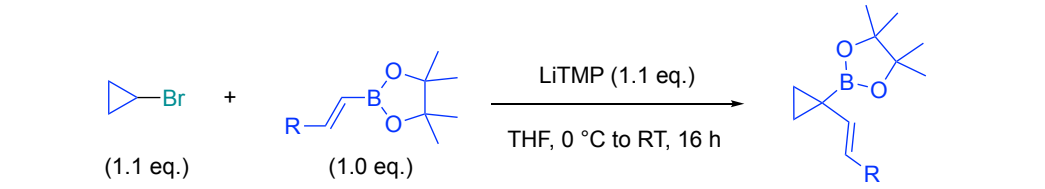


Figure 4: X-ray structure of **413** + water molecule, CCDC 1985237

4.5 Scope of vinylcyclopropyl boronic ester substrates for ring expansion reaction

In addition to *trans*-propenylcyclopropyl boronic ester **409a**, a variety of other substituted vinylcyclopropylboronic esters were synthesised and applied to the ring expansion reaction. Vinylcyclopropyl boronic esters bearing phenyl, butyl, cyclopropyl and other alkyl substituents at the β- position of the double bond *trans*- to the cyclopropylboronic ester were all successfully synthesised in good yields from the respective vinylboronic esters (table 11).

Table 11: Vinylcyclopropyl boronic esters synthesised



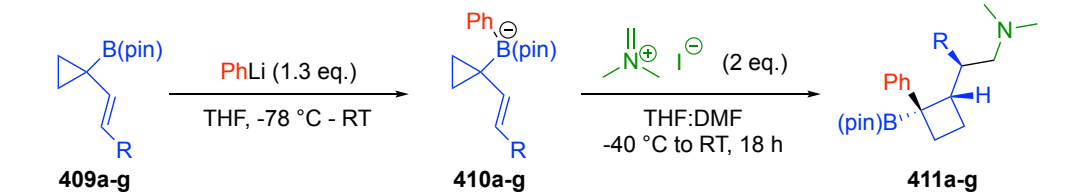
404, 72% **409a**, 56% **409b**, 56% **409c**, 60%

409d, 74% **409e**, 73% **409f**, 62% **409g**, 71%

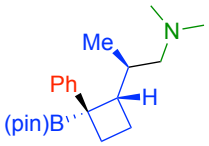
409h, 82% **409i**, 27% **409j**, 7% **409k**, 32%

With the vinycyclopropyl boronic esters in hand, these were subjected to the optimised conditions for ring expansion (table 12). Vinylcyclopropyl boronic esters bearing phenyl, butyl, cyclopropyl and other alkyl substituents at the β- position of the double bond *trans*- to the cyclopropylboronic ester were all successfully converted to cyclobutane products with excellent diastereoselectivity and good yields. A substrate bearing a TBS-protected alcohol, **409e**, underwent deprotection during purification by column chromatography on silica gel to give alcohol product **411e**.

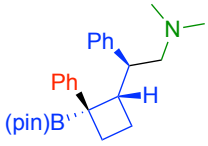
Table 12: Scope of successful vinylcyclopropyl boronic esters in ring espansion reaction



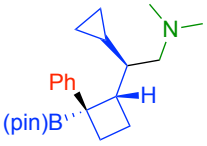
409a-g **410a-g** **411a-g**



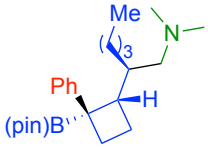
411a, 57%, >20:1



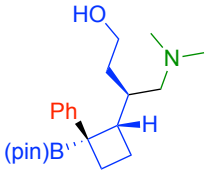
411b, 54%, >20:1



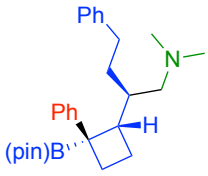
411c, 81%, >20:1



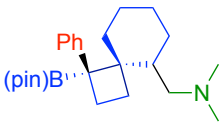
411d, 84%, >20:1



411e, 84%, >20:1



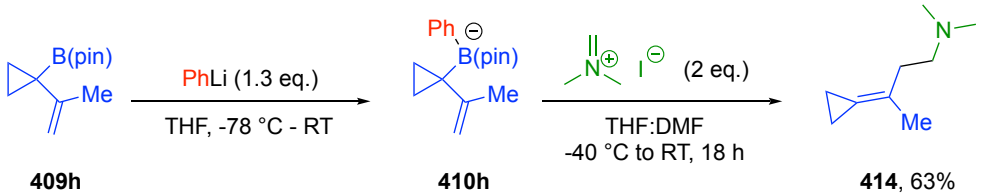
411f, 54%, >20:1



411g, 77%, >20:1

4.5.1 Unsuccessful substrates

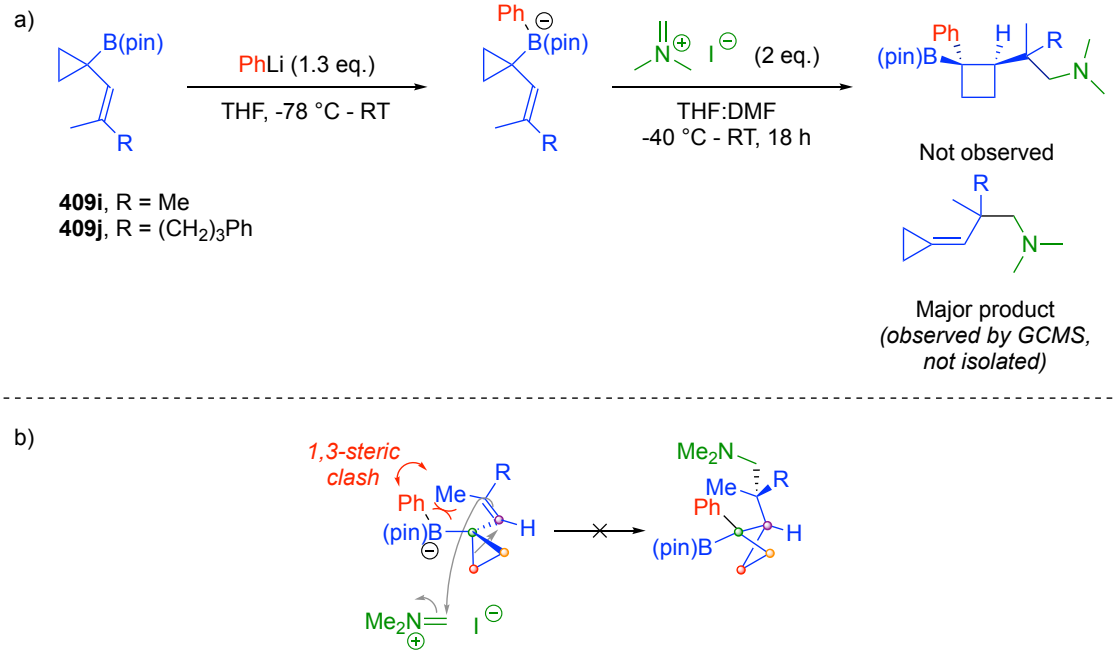
In contrast to the good yields and high diastereoselectivities of cyclobutane products formed from β-substituted vinylcyclopropyl boronic esters, allylation product **414** was the sole product obtained when reaction conditions were applied to the α-substituted propen-2-ylcyclopropyl boronic ester **409h** (scheme 91). It was rationalised that the preference for the allylation pathway in this case arises from the additional stabilisation of the initial carbocation intermediate by the alkyl inductive effect from the adjacent methyl group. This additional stabilisation reduces the propensity of this carbocation to undergo an alkyl migration expanding the cyclopropane ring, allowing the allylation pathway to dominate.



409h **410h** **414**, 63%

Scheme 91: Formation of allylation product **414** from propen 2 ylcyclopropyl boronic ester **409h**

Whilst the reaction tolerates β-substituents *trans*- to the cyclopropyl boronic ester moiety, no cyclobutane product formation was observed for β,β-substituted substrates **409i** and **409j** (scheme 92, a). It appears that the reaction has a limited tolerance for steric bulk around the alkene, especially *cis*- to the cyclopropylboronic ester. This can be considered in terms of the model discussed in section 4.3.3, in which a *cis*-substituent would experience 1,3-allylic strain with the boron-ate moiety in the proposed reaction conformation (scheme 92, b). Steric bulk at this position raises the energy of the transition state for ring-expansion. This causes the allylation pathway to dominate.



409i, R = Me
409j, R = $(CH_2)_3Ph$

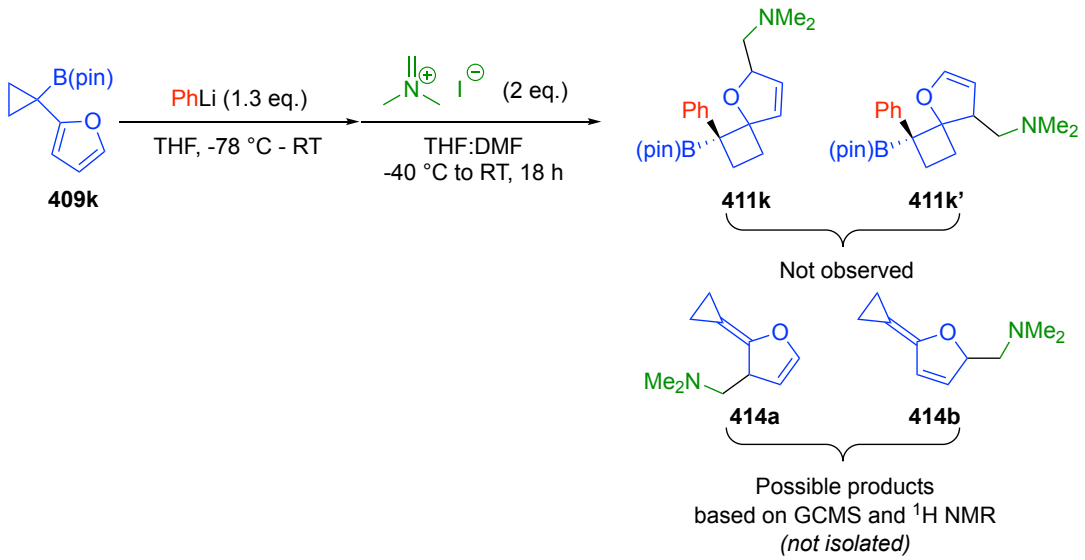
Scheme 92: a) Failed ring expansions with β,β-substituted substrates; b) 1,3-steric clash in proposed reaction conformation

4.6 Synthesis and attempt at ring expansion using furylcyclopropyl boronic ester

Electrophilic activation of a furan ring to trigger a 1,2-metallate rearrangements are known – this protocol having been used to enact enantiospecific sp^2-sp^3 cross-couplings to furan rings (chapter 1, section 1.2.2.2.1). It was anticipated that similar activation of a furylcyclopropyl boron-ate complex with Eschenmoser's salt would trigger a ring expansion and 1,2-metallate rearrangement to produce spiro-compound **411k**. It was anticipated that electrophilic activation of the furan ring with Eschenmoser's salt would occur in the 5-position based on the regioselectivity displayed for 3-component couplings with electrophilic radicals (discussed in chapter 1, section 1.2.2.1).

Alternatively, activation of the furan ring could occur at the 3-position like the cyclopropylvinyl boronic esters in section 4.5 (scheme 93, giving compound **411k'**).

Furylcyclopropyl boronic ester **409k** was subjected to the established conditions for the ring-expansion protocol. Analysis of the crude reaction mixture by GCMS showed no formation of the desired spiro-product **411k** from ring expansion, however a significant quantity of phenyl-B(pin) was observed indicating that the undesired allylation pathway dominates in this case. This was confirmed by ^{1}H NMR of the crude showing phenyl-B(pin) as the only boronic ester species present alongside alkene proton signals corresponding to the undesired product (**414a** or **414b**, scheme 93).

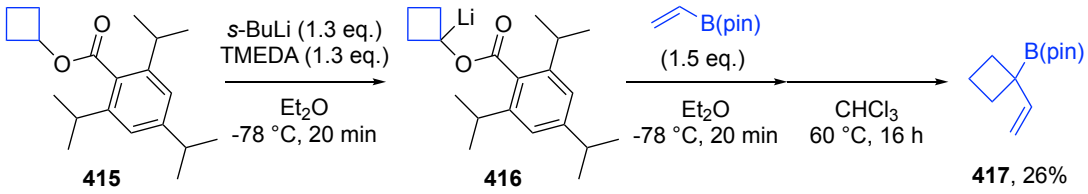


Scheme 93: Attempt at ring expansion of furylcyclopropyl boron-ate complex to give spiro-product(s)

4.7 Synthesis and attempt at ring expansion using vinylcyclobutyl boronic ester

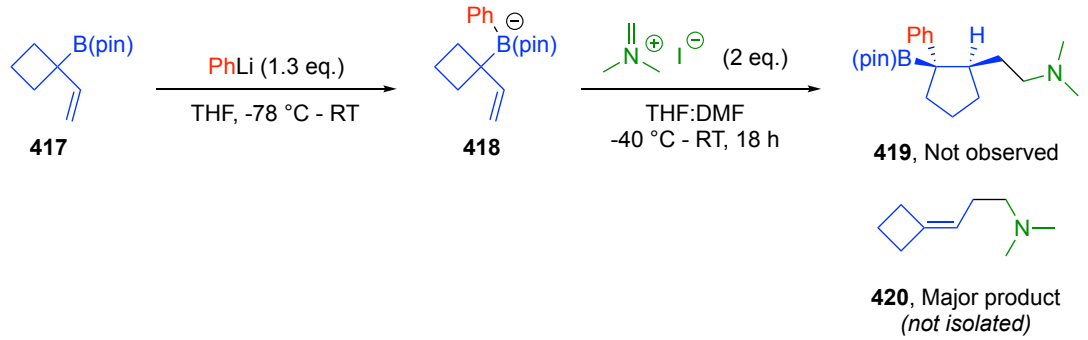
Given the success of the protocol for expanding vinylcyclopropyl boronic esters to give highly substituted cyclobutanes, it was anticipated that this protocol could also be applied to the expansion of vinylcyclobutyl boronic esters to give 1,2-substituted cyclopentane products. Although this is less interesting synthetically than the synthesis of cyclobutanes (given the multitude of existing syntheses of cyclopentane rings), the 4 -> 5 ring expansion was attempted here as a proof-of-concept. In theory, the thermodynamic driving force for ring expansion should be higher for 4 -> 5 ring expansion than 3 -> 4 given the greater decrease in ring strain.[196]

The synthesis of 1,1-cyclobutyl boronic esters has been reported by 1,2-metallate rearrangement of boron-ate complexes generated by trapping boronic esters with lithiated cyclobutyl triisopropylbenzoate (TIB) esters.[197] In contrast to the equivalent reaction with cyclopropyl TIB esters, the 1,2-metallate rearrangement is facile for cyclobutane rings. This method was successfully applied to the synthesis of vinylcyclobutyl boronic ester **417**, which was isolated in 26% yield (scheme 94).



Scheme 94: Synthesis of vinylcyclobutyl boronic ester **417**

Vinylcyclobutyl boronic ester **417** was subjected to the conditions established for the ring-expansion protocol with vinylcyclopropyl boronic esters (scheme 95). Analysis of the crude reaction mixture by GCMS showed no formation of the desired cyclopentane product **419**, however a significant quantity of phenyl-B(pin) was observed indicating that the undesired allylation pathway dominates in this case. This was confirmed by ^{1}H NMR of the crude showing phenyl-B(pin) as the only boronic ester species present alongside an alkene proton signal corresponding to the cyclobutylidene product **420**. The formation of this product is surprising given the anticipated thermodynamic favourability of ring-expansion of the cyclobutane ring to a cyclopentane reducing the ring-strain. It is not known why the allylation pathway dominates in this case – it may be possible that the different shape of the cyclobutane ring promotes the transition state conformation for allylation over that for ring expansion, rendering the allylation product as the kinetic product under the reaction conditions.

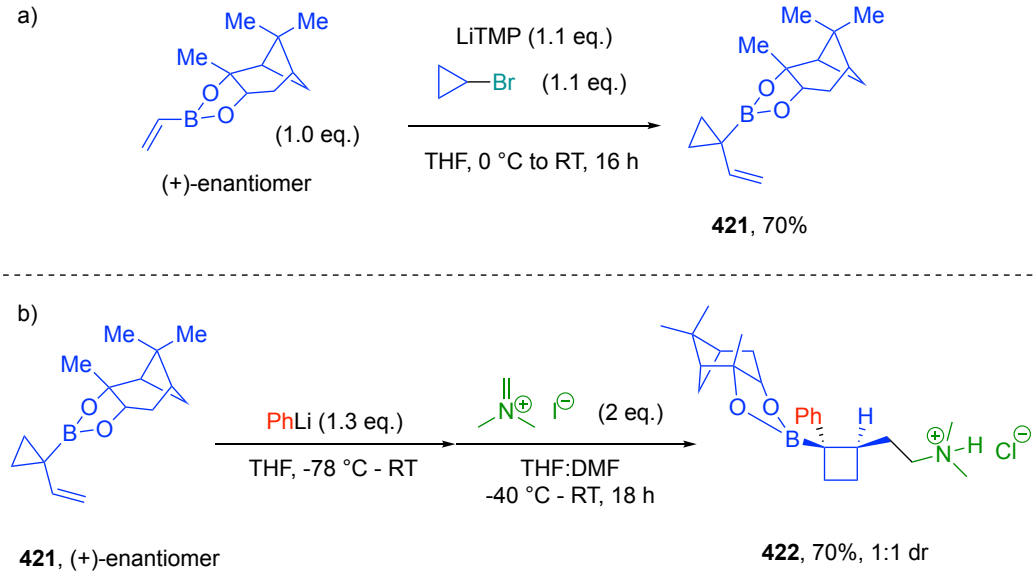


Scheme 95: Attempted ring expansion of vinylcyclobutyl boron-ate complex with allylation product shown

4.8 Use of chiral boronic ester in attempt at enantiospecific reaction

The enantioenriched vinycyclopropyl boronic ester **421** bearing a pinanediol ligand on boron was synthesised from commercially available (+)-vinylboronic acid pinanediol ester and treated to the ring expansion conditions with phenyllithium and Eschenmoser's salt as the electrophile (scheme 96, a and b). GCMS analysis of the crude mixture indicated the desired cyclobutane product **422** had been formed, however ^{1}H and ^{13}C NMR analysis of the crude demonstrated that this was a 1:1 mixture of diastereomers. Given that the chiral pinanediol ligand on boron remains a chiral centre in the product, the two diastereomers here correspond to what would be two enantiomers with an achiral ligand on boron (the two cyclobutane stereocentres being set according to the model for diastereoselectivity

discussed in section 4.3.3). The even ratio of diastereomers here indicates that no additional enantioselectivity is imparted on the reaction by the chiral ligand on boron.



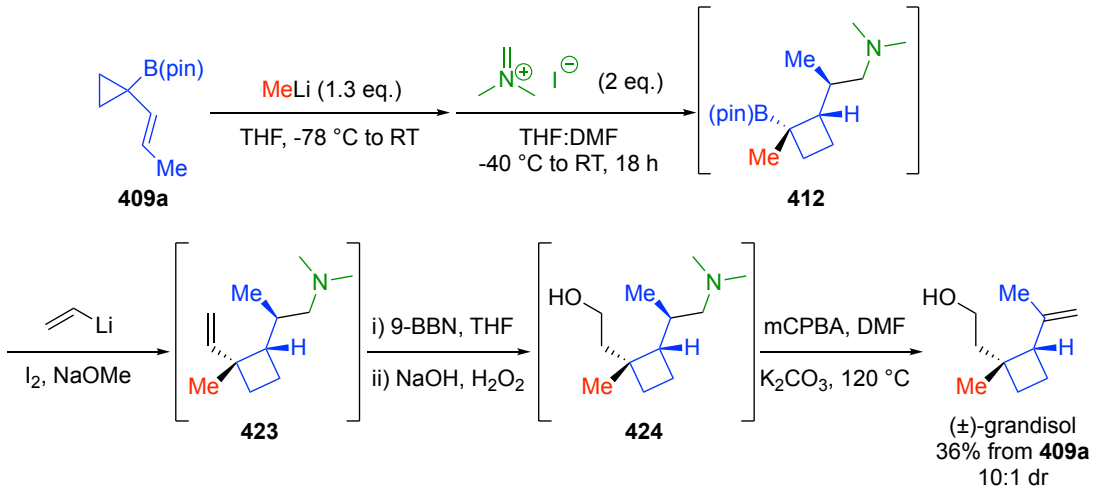
Scheme 96: a) Synthesis of pinanediol-derived vinylcyclopropyl boronic ester; b) Ring expansion reaction

A variety of chiral ligands have been utilised for enantioselective chemistry involving boronic esters, including the C2 symmetric diols employed for the Roush allylation.[198] It is possible that the use of a different chiral ligand may allow the ring-expansion protocol to be performed enantioselectively, however it is not obvious what the mechanism responsible for biasing the stereochemistry of the reaction would be. Given the lack of influence of the pinanediol ligand on the stereochemistry and lack of a feasible stereochemical model it was decided not to test other chiral ligands for this protocol.

4.9 Total synthesis of (±)-grandisol[h]

The utility of the ring expansion reaction was demonstrated with a 5-step synthesis of the pheromone natural product (±)-grandisol from the *trans*-propenylcyclopropyl boronic ester substrate **409a** (scheme 97). Following the ring expansion step with methyllithium and Eschenmoser's salt to access the cyclobutyl boronic ester **412**, a Zweifel olefination, hydroboration and oxidation sequence was enacted to convert **412** to alcohol **424**. Finally, oxidation of the tertiary amine with *meta*-chloroperoxybenzoic acid (mCPBA) and a subsequent Cope elimination in DMF at 120 °C furnished the alkene of (±)-grandisol. The 5-step sequence was performed without purification of intermediates, obtaining (±)-grandisol in 36% yield with 10:1 dr. **409a** was synthesised in 56% yield from commercially available *trans*-propenyl boronic acid pinacol ester (discussed in section 4.4). Therefore, the overall 6-step total synthesis produced (±)-grandisol in 20% yield from the commercially available boronic ester.

[h] Work in section 4.9 performed by Dr. Durga Hari. Briefly discussed here to 'complete the story' of the project.



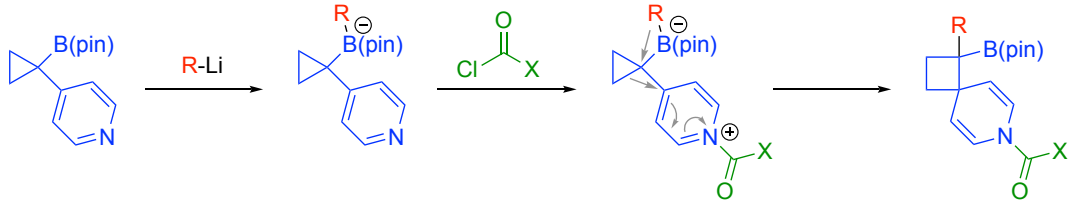
Scheme 97: 5-step total synthesis of (±)-grandisol from **409a**

4.10 Conclusions and future work

In conclusion, an electrophile-induced ring expansion of vinylcyclopropyl boron-ate complexes giving substituted cyclobutyl boronic ester products was successfully extended to vinylcyclopropyl boronic ester substrates bearing a *trans*- substituent on the alkene moiety. This was found to proceed with high diastereoselectivity for various substituents including methyl, cyclopropyl and phenyl groups. This high diastereoselectivity was attributed to a preferred reaction conformation with an *anti*-, *anti*-, *syn*-periplanar relationship of migrating groups and recipient electrophile.

A competing elimination/allylation pathway was found to dominate for some substrates, particularly for more substituted and/or sterically encumbered vinylcyclopropyl boronic ester substrates. Furthermore, this pathway was found to dominate when the expansion of a vinylcyclobutyl boron-ate complex to form a cyclopentane was attempted. Additionally, the use of a chiral pinanediol-derived vinylcyclopropyl boronic ester was not found to impart any enantioselectivity onto the formation of the contiguous stereocentres in the reaction.

It was envisaged that the principal of electrophile-initiated ring-expansion-induced 1,2-metallate rearrangements to generate cyclobutyl boronic esters could be extended to pyridylcyclopropylboron-ate complexes to form spirocyclic dihydropyridine products (scheme 98). Attempts to enact this will be discussed in chapter 5.



Scheme 98: Proposed generation of dihydropyridine spirocycles by ring expansion of pyridylcyclopropyl boronic esters

5 Synthesis of spirocycles by migration-driven dearomatisation of pyridines

5.1 Introduction

5.1.1 Importance of spirocycles in drug discovery

Rigid, three-dimensional structures have been shown to have greater clinical success in drug development programs than flatter counterparts.[51,52] In part this is due to reduced drug receptor promiscuity – a more complex three-dimensional structure will bind more specifically to a target site, and is less likely to bind elsewhere causing adverse side effects (which often leads to failure in clinical trials).[52] The binding of a drug molecule to a receptor inherently carries an entropy cost due to the loss of 'freedom' of the molecule in being forced into the binding conformation. This conformational entropy cost on binding is reduced for more rigid drug molecule structures given that the conformation entropy of these more rigid structures in solution is significantly lower than that for less rigid counterparts (and so there is less conformational entropy to lose on binding).[199] The spiro-arrangement of two rings in a molecule constitutes an inherently well-defined three-dimensional structure. Therefore, spirocyclic compounds are desirable scaffolds for drug molecules and thus are increasingly being explored as candidates in drug discovery programs.[199,200]

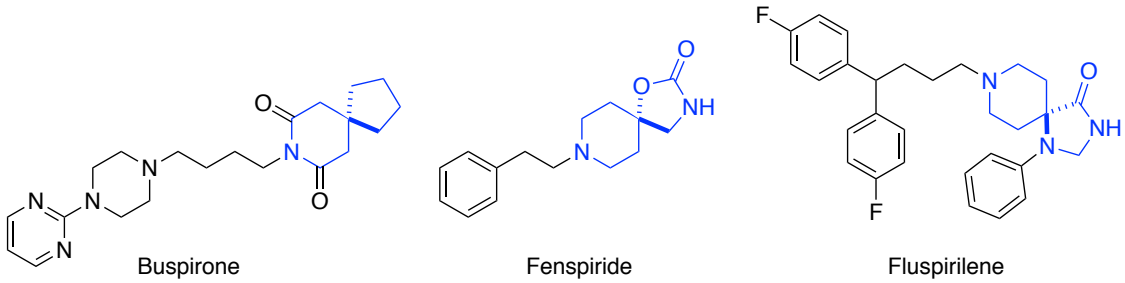


Figure 5: Pharmaceuticals containing piperidine spirocycles

Nitrogen heterocycles are ubiquitous in pharmaceutical agents: 59% of US FDA approved small molecule drugs as of 2014 contain a nitrogen heterocycle, with piperidine rings amongst the most prevalent.[49] As such, spirocyclic compounds which include piperidine or other 6-membered nitrogen heterocycles as part of the spirocycle are highly promising drug scaffolds. Commercially available piperidine spirocycle-based drugs include the respiratory disease medication fenspiride and anti-psychotic drug fluspirilene (figure 5). Furthermore, spiro-piperidine drug candidates have been explored as promising leads in drug discovery programs. LaMarche and co-workers developed spirocyclic 2-oxa-8-azaspiro[4.5]decane compounds as allosteric inhibitors for the cancer-associated oncoprotein SHP2 (figure 6, a). Using structure-based design and structure-activity relationships based on models with the allosteric binding pocket of SHP2, drug candidates SHP389 and SHP394 were

identified as potent orally efficacious inhibitors of SHP2.[201,202] Figure 6, b shows how an analogue of these drug candidates featuring the spirocycle component fits into the allosteric binding pocket of SHP2. This demonstrates how the rigidity imparted by the spirocyclic system helps configure this molecule towards key binding interactions in the pharmacophore binding pocket, in particular the primary amine on the tetrahydrofuran ring of the spirocycle being oriented towards favourable binding interactions with components E110, F113 and T108 of the pharmacophore.

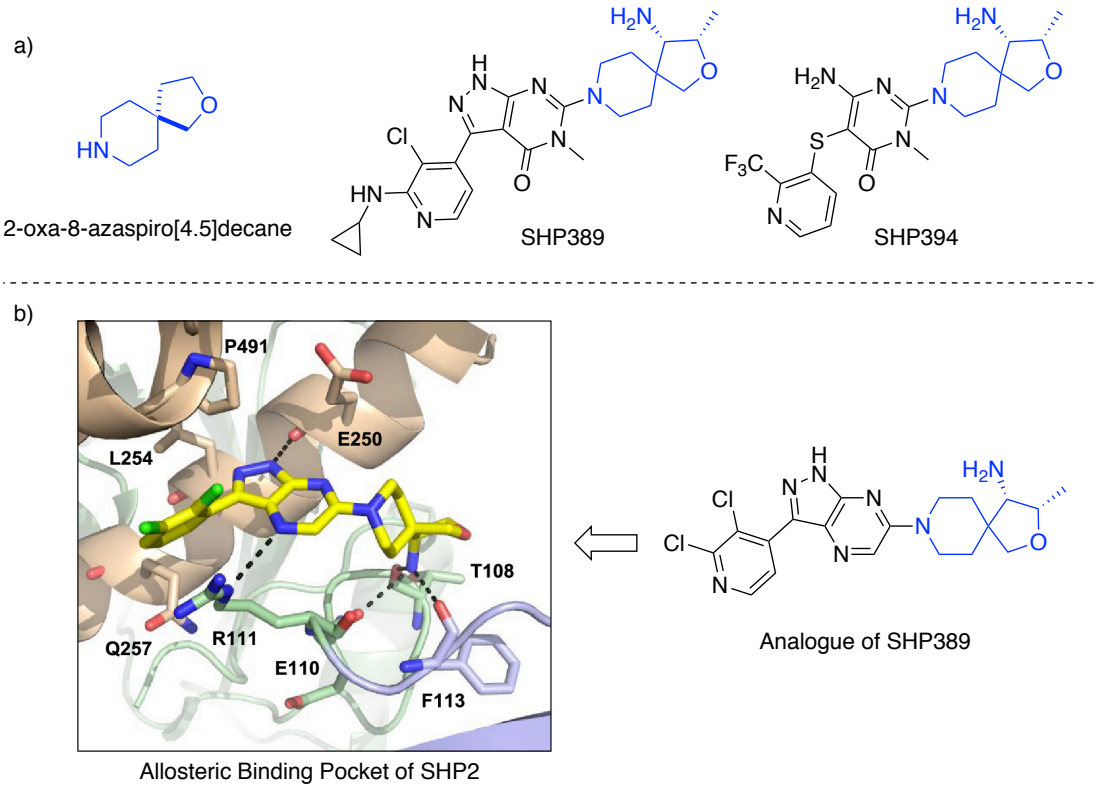


Figure 6: a) 2-oxa-8-azaspiro[4.5]decane inhibitors of SHP2, b) Fitting of SHP389 to the allosteric binding pocket of SHP2[201,202]

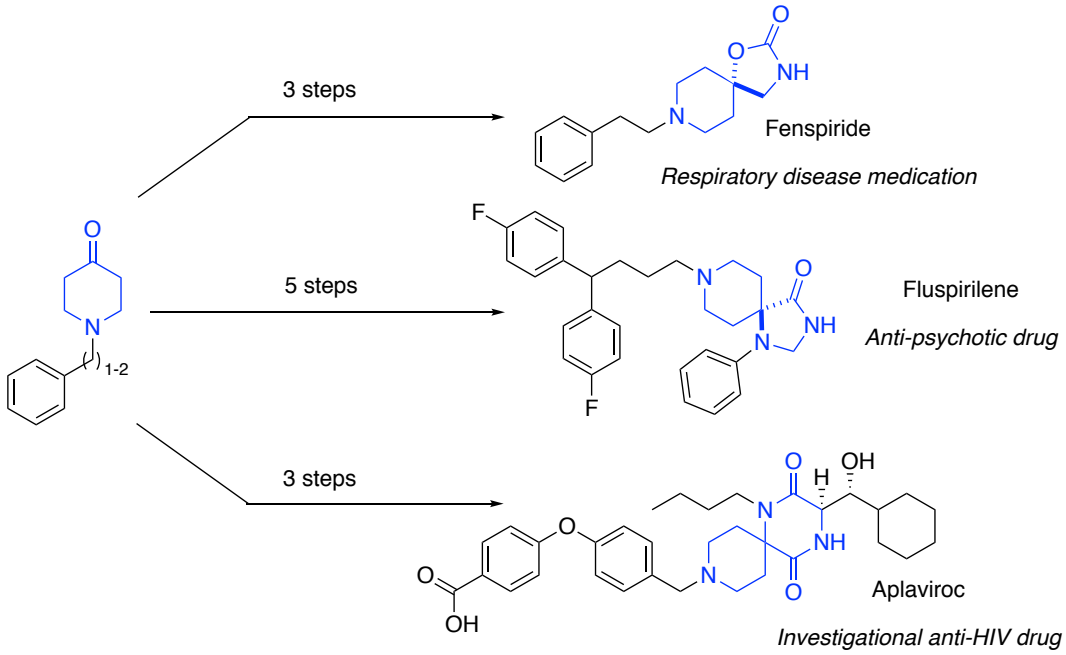
5.1.2 Synthesis of piperidine and dihydropyridine spirocycles

A diverse range of spirocycle moieties exist in natural products and pharmaceuticals. As such the array of methods used to synthesise spirocycles is similarly diverse and encompasses various ring-closing methods, cycloadditions and rearrangement steps.[203] This section will focus on the synthesis of spirocycles containing piperidine and dihydropyridine rings, although mention will be made of other spirocycles where relevant.

5.1.2.1 Spirocycles by heterocycle synthesis

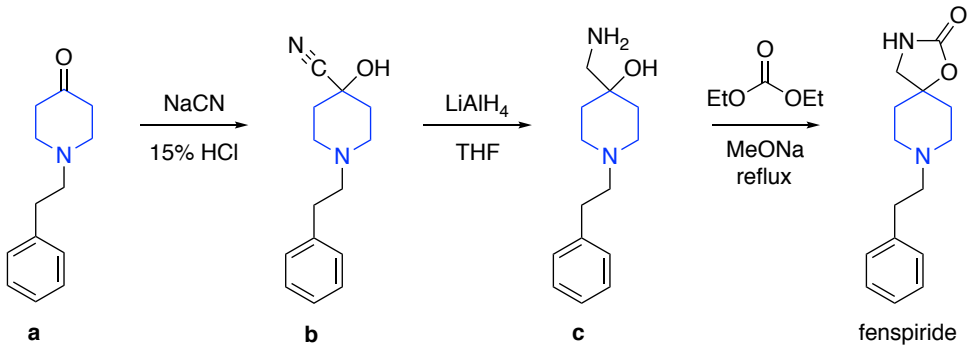
A common route to commercially available piperidine spirocycle drugs is to start with a piperidine precursor and form the second ring of the spirocycle by known heterocycle syntheses. Commercial

routes to fenspiride, fluspirilene and aplaviroc all start from similar *N*-benzyl or *N*-phenethylpiperidin-4-one precursors (scheme 99).[60,204]



Scheme 99: Synthetic routes to pharmaceuticals from *N*-benzyl or *N*-phenethyl piperidin-4-one precursors

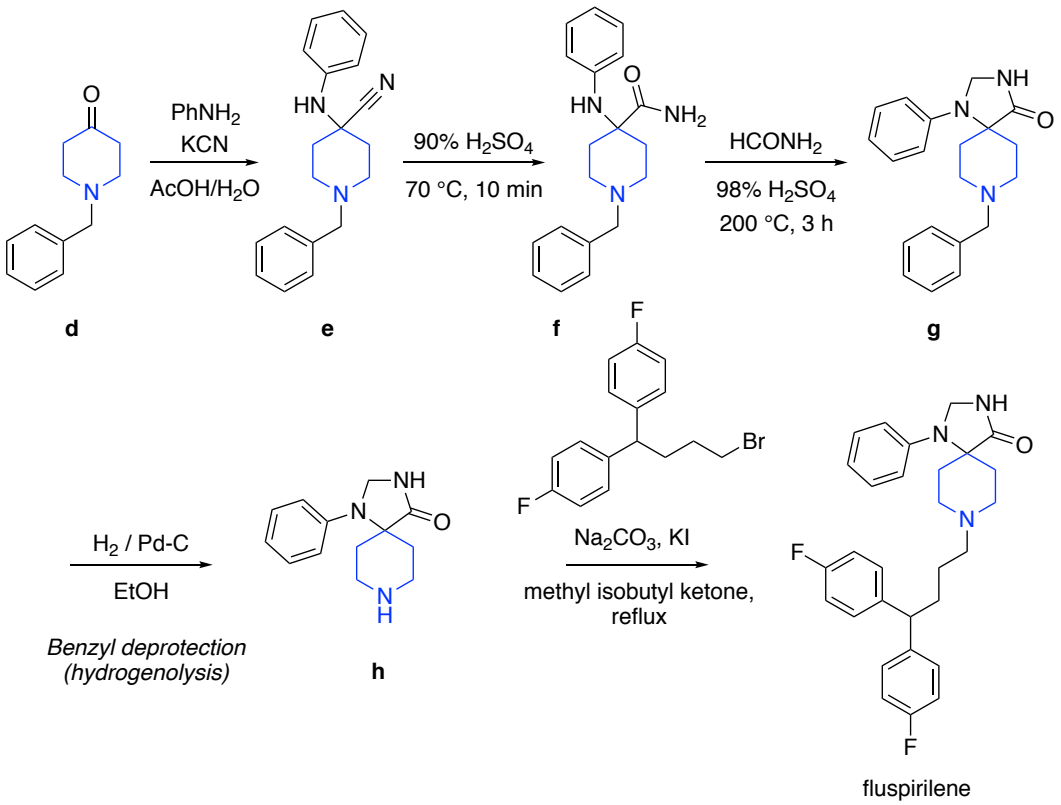
The synthesis of fenspiride can be achieved by the route shown in scheme 100.[204] The first step in this route is attack of the carbonyl of piperidinone **a** with sodium cyanide. The nitrile group in the intermediate **b** formed is then reduced with lithium aluminium hydride to a primary amine which, along with the hydroxyl group, is then cyclised with diethyl carbonate to form the second ring of the fenspiride spirocycle.



Scheme 100: Synthesis of fenspiride

The synthesis of fluspirilene (scheme 101) involves a similar sequence.[204] *N*-benzylpiperidin-4-one **d** is converted to intermediate **e** by imine formation and trapping with potassium cyanide before acid-mediated conversion of the nitrile to a primary amide. Intermediate **f** is then cyclized with formamide under acidic conditions at high temperature to form the imidazolidinone ring of the spirocycle (**g**). In

this case benzyl deprotection followed by reaction at the piperidine nitrogen is required to furnish the fluspirilene product.



Scheme 101: Synthesis of fluspirilene

Multicomponent reactions employing a cyclic starting material are also capable of generating spirocycles. GlaxoSmithKline's investigational anti-HIV drug aplaviroc features a spirodiketopiperazine moiety as a key structural component that mimics a type-I β-turn of polypeptides as shown in figure 7.[60,205] The synthesis of this spirocycle employs an Ugi multicomponent reaction to generate the piperazine-2,5-dione ring, with *N*-benzylpiperidin-4-one providing the piperidine ring of this spirocyclic structure (scheme 102). As with the synthesis of fluspirilene, removal of the benzyl protecting group and reaction at the piperidine nitrogen is used to further functionalise the spirocycle product to generate aplaviroc analogues.

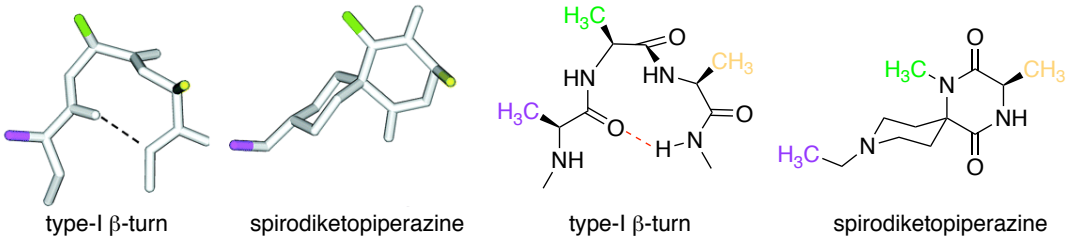
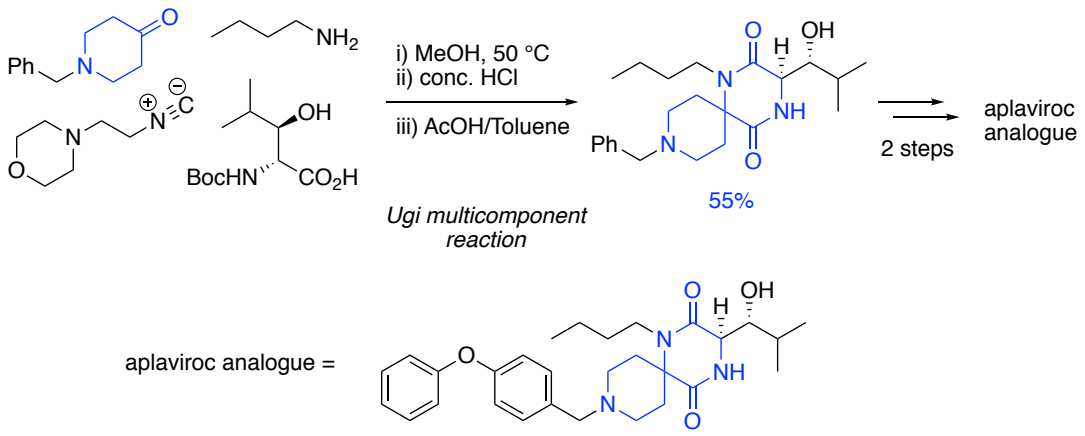
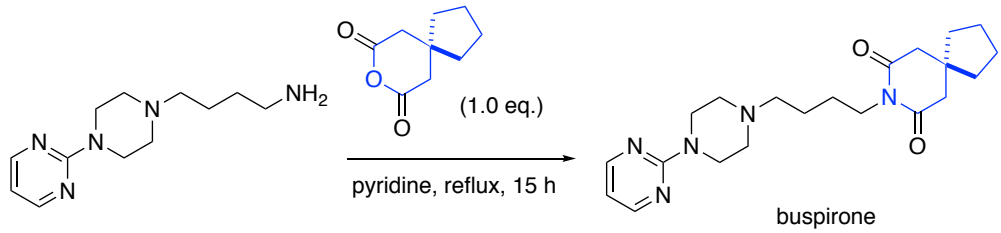


Figure 7: Comparison of spiroketopiperazine mimic with type-I β-turn



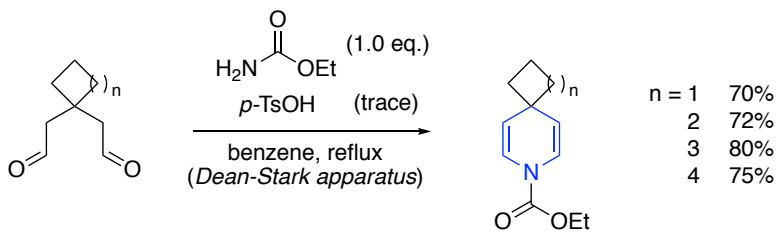
Scheme 102: Synthesis of spiroketopiperazine spirocycle by Ugi multicomponent reaction

Finally, an alternative approach is to construct the piperidine or dihydropyridine ring of the spirocycle with the other ring of the spirocycle pre-formed. This approach is utilised in the synthesis of buspirone, in which a spirocyclic anhydride (formed by dehydration of the parent dicarboxylic acid) is condensed with an amine to form the piperidine-2,6-dione ring (scheme 103).[206,207] In buspirone this ring is kept as-is, however conversion of piperidine-2,6-diones to piperidines by means of borohydride or lithium aluminium hydride reduction of the imide is straightforward.[208]

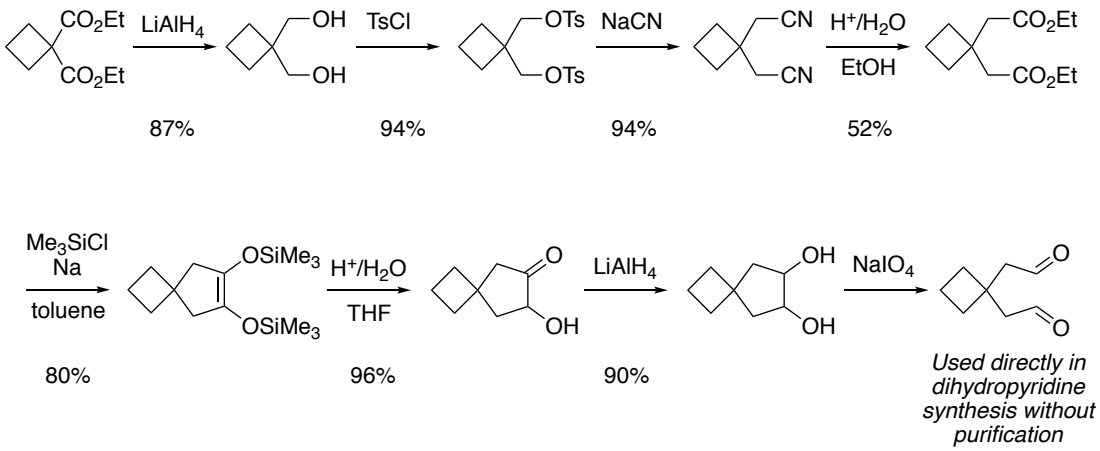


Scheme 103: a) Synthesis of buspirone

Spirocyclic dihydropyridines have also been constructed by condensation of carbamates with substituted glutaraldehydes (1,5-dialdehydes) to generate the dihydropyridine ring (scheme 104).[209] It should be noted that access to the glutaraldehyde starting materials from commercially available precursors typically require multi-step syntheses such as that shown in scheme 105 (next page),[209] which somewhat reduces the appeal of this synthetic approach to dihydropyridine spirocycles in combinatorial drug discovery programs.



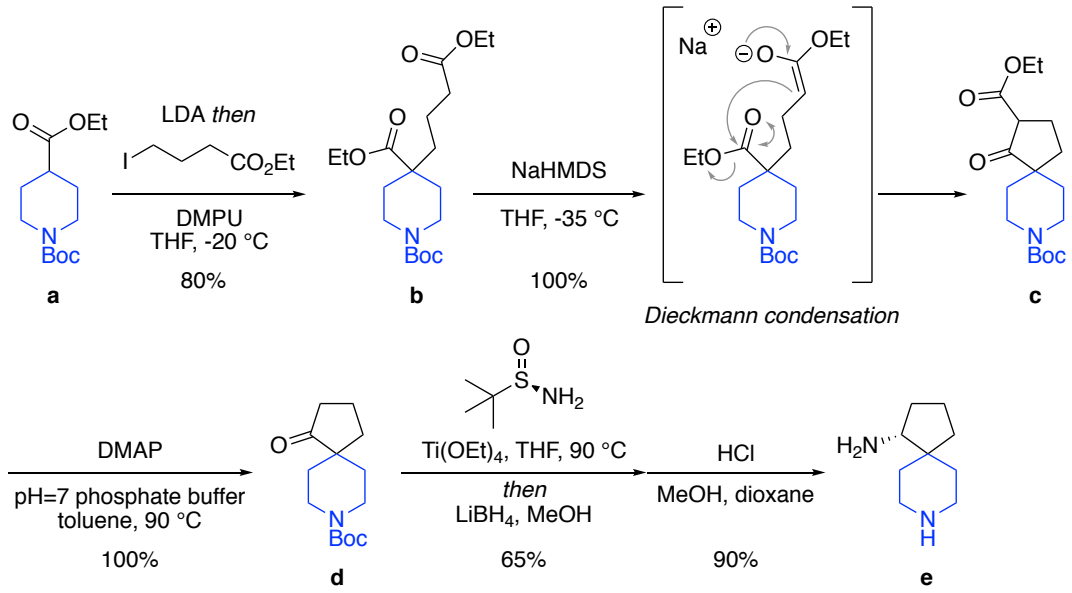
Scheme 104: Spiro-dihydropyridine synthesis by condensation of 1,5-dialdehyde



Scheme 105: Synthetic route to 1,5-dialdehyde precursor used in scheme 104

5.1.2.2 Aldol and Claisen condensations

Intramolecular aldol reactions and Claisen condensations are useful methods for constructing carbon-carbon bonds in carbocycles. Both methods have been applied in the synthesis of spirocyclic natural products and pharmaceuticals.[201,203] An intramolecular Claisen condensation (also known as the Dieckmann condensation) was the key ring-forming step in the synthesis of spirocycle **e** (scheme 106), which was included in the screen of SHP2 inhibitors discussed in section 5.1.1.[201]



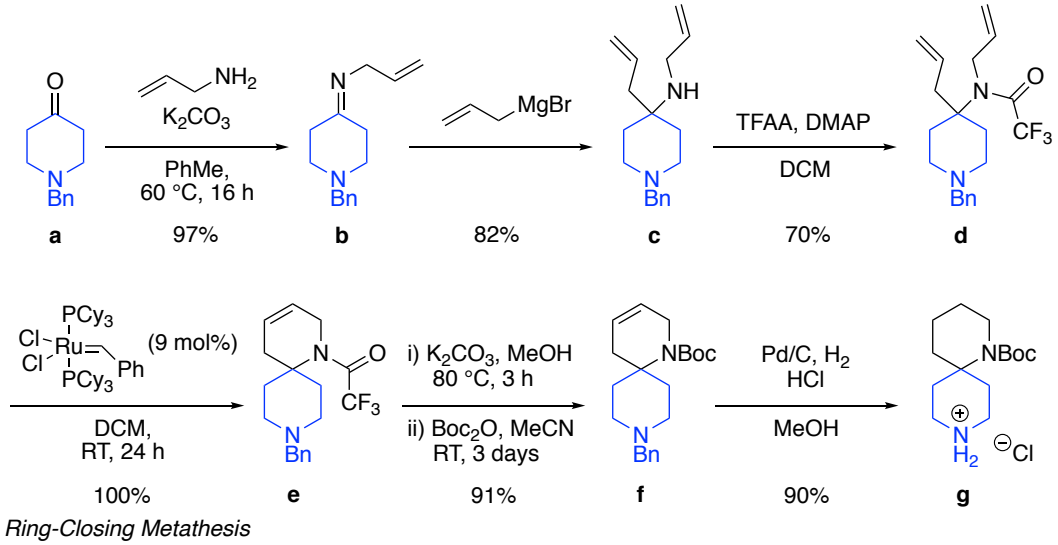
Scheme 106: Synthesis of piperidine spirocycle of SHP2 inhibitor candidate with Dieckmann condensation

In this case amine spirocycle **e** was accessed in 5 steps from *N*-Boc protected ethyl piperidine-4-carboxylate **a** by first forming the quaternary centre by deprotonating α- to the ester and trapping with ethyl 4-iodobutanoate, followed by a Dieckmann condensation of the two ester groups to form the spirocyclic β-keto ester **c** (scheme 106). Subsequently decarboxylative removal of the

ester, stereoselective reduction of the ketone and acid deprotection of the Boc protecting group on the piperidine are used to produce the spirocycle **e** in 47% yield over the 5-step sequence.

5.1.2.3 Ring-closing metathesis

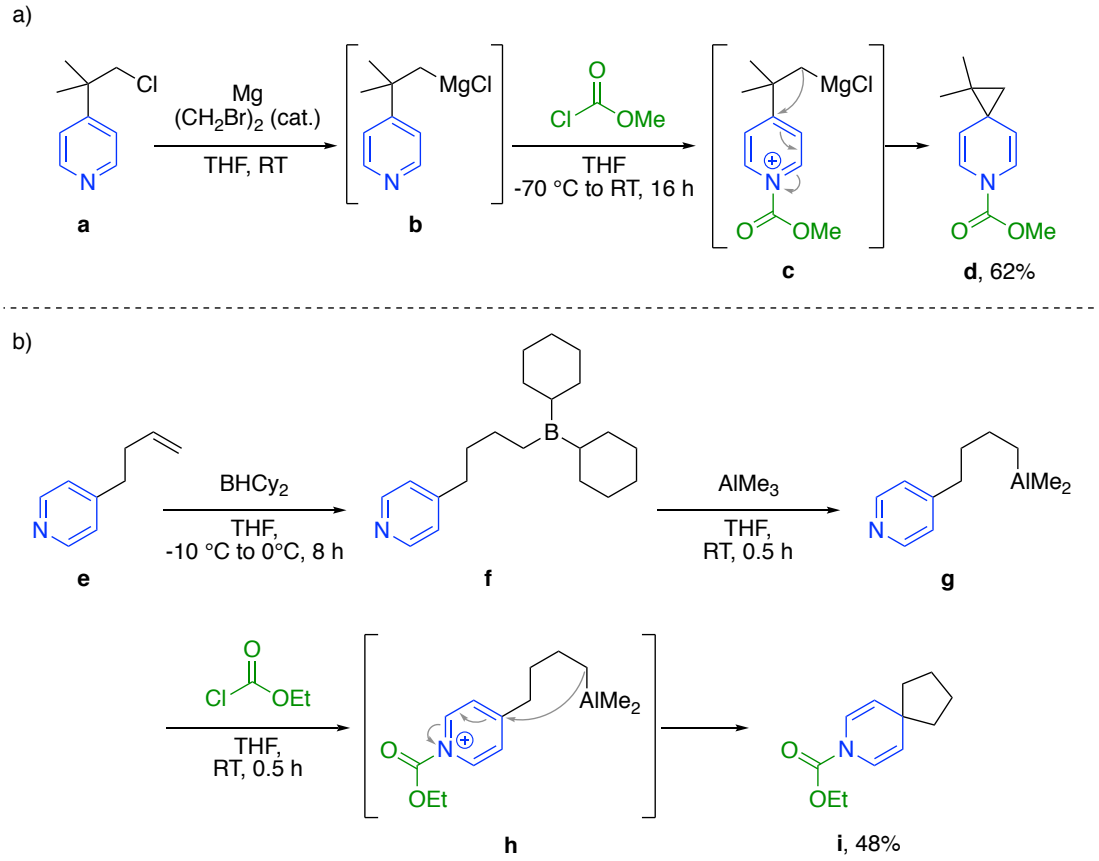
The ring-closing metathesis of two pendant alkenes is a commonly used strategy to construct carbocycles in natural product and pharmaceutical synthesis, and can be applied to the construction of spirocycles.[203,210] The synthesis of the spirocyclic dipiperidine scaffold **g** (scheme 107) involves a ring-closing metathesis as the key ring-forming step, following sequential installation of the pendant terminal alkenes required by imine formation and attack with allymagnesium bromide.[210]



Scheme 107: Spirocycle synthesis by ring-closing metathesis

5.1.2.4 Dihydropyridine spirocycles by pyridine dearomatisation

The dearomative synthesis of dihydropyridines by nucleophilic attack of *N*-acylpyridinium intermediates is well established, and has been discussed in chapter 3, section 3.1.1.1. This principle has been utilised to generate dihydropyridine spirocycles by intramolecular attack of *N*-acylpyridinium intermediates by pendant organometallic nucleophiles.[211,212] Generation of pendant Grignard **b** (scheme 108, a) by treatment of 4-(1-chloro-2-methylpropan-2-yl)pyridine **a** with magnesium, followed by addition of methyl chloroformate at low temperature followed by warming to ambient temperature delivered dimethylcyclopropyl dihydropyridine spirocycle **d** in 62% yield.[211] The 4-(1-chloro-2-methylpropan-2-yl)pyridine starting material in this case is synthesised in two steps from 4-isopropylpyridine by first condensing with formaldehyde followed by treating the primary alcohol formed with thionyl chloride to convert it to the chloride.



Scheme 108: a) Dearomative intramolecular attack of *N*-acylpyridinium species by Grignard to form dihydropyridine spirocycle; b) Formation of cyclopentane ring of spirocycle by intramolecular attack of pyridinium intermediate

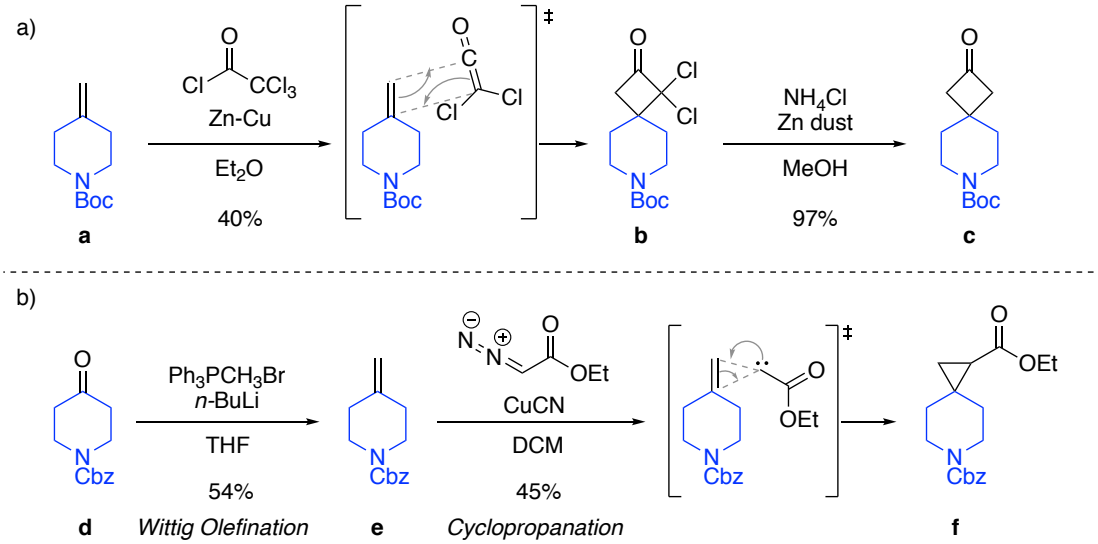
An attempt to apply this approach with 4-(4-chlorobutyl)pyridine to construct a cyclopentane spirocycle was found to be low yielding, with competing protonation of the pendant Grignard nucleophile a problem.[212] Instead, trialkylaluminium species **g** (scheme 108, b), generated by hydroboration of 4-(but-3-en-1-yl)pyridine **e** with dicyclohexylborane and metal exchange to aluminium in one pot, undergoes *N*-acylation and dearomative cyclisation when treated with ethyl chloroformate to give the dihydropyridine carbamate spirocycle **i** in 48% yield from the starting alkenylpyridine.[212]

5.1.2.5 Cycloadditions

The syntheses in sections 5.1.2.1 to 5.1.2.4 all rely on ring closing steps that are subject to Baldwin's rules for ring closure.[182] As such, these approaches are limited when it comes to generating smaller rings – particularly cyclobutane spirocycles – for which there is a conformational energy barrier disfavouring the formation of 4-membered rings.[182]

The [2+2] cycloaddition of two alkenes, discussed in chapter 4, section 4.1.3.1, is a common approach to constructing cyclobutane rings. However, this approach has not been extensively applied to the synthesis of piperidine spirocycles. The cycloaddition of dichloroketene with *N*-Boc protected

4-methylenepiperidine has been utilised in the development of spirocyclic histamine-3 agonists.[213] Dichloroketene is generated *in situ* by zinc insertion into trichloroacetyl chloride and readily undergoes a [2+2] cycloaddition with the exocyclic alkene of *N*-Boc 4-methylenepiperidine **a** (scheme 109, a) (accessible by Wittig olefination of the parent 2-piperidinone) to give species **b**, which is easily converted by zinc mediated dehalogenation to spirocyclic ketone **c**.



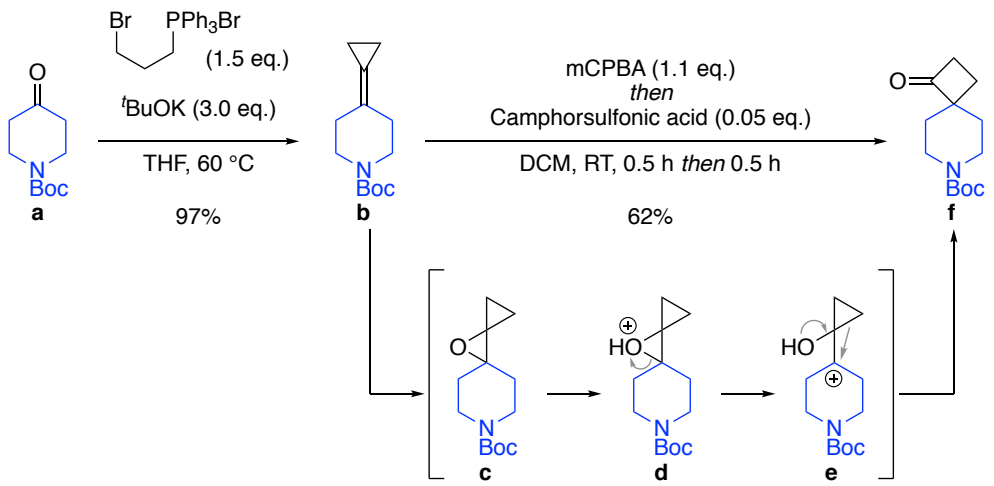
Scheme 109: a) Spirocycle formation by [2+2] cycloaddition; b) Spirocycle formation by cyclopropanation of alkene

The synthesis of 6-azaspiro[2.5]octanes can also be achieved by cyclopropanation of the exocyclic alkene of *N*-protected 4-methylenepiperidine **e** (scheme 109, b).[213] It should be noted that the [2+2] cycloaddition and cyclopropanation examples above both have mediocre yields for the spirocycle-forming step as well as the Wittig olefination to access the starting materials **a** and **e**.

5.1.2.6 Synthesis of small rings and spirocycles by pinacol and semi-pinacol rearrangements

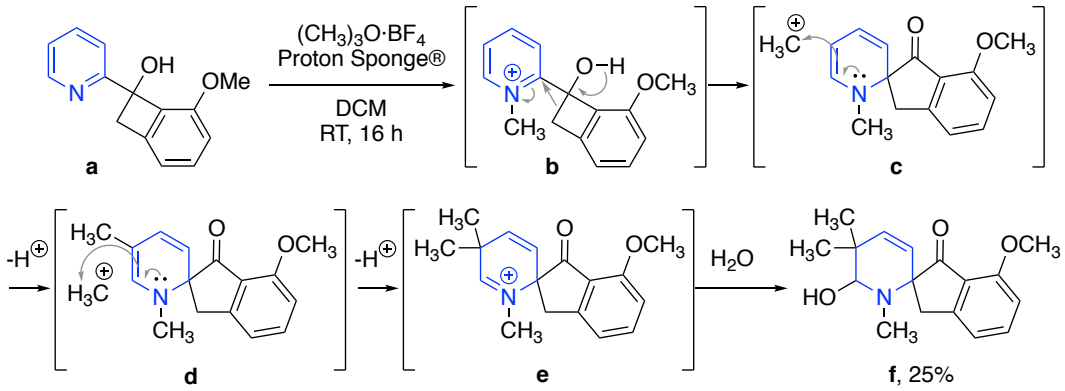
Another way of circumventing the limitations of ring-closing cyclisations is to employ rearrangements of existing rings. The semi-pinacol rearrangement, in which the formation of a carbocation vicinal to an alcohol triggers alkyl migration accompanied by conversion of said alcohol to a ketone, is a well-known and well-utilised rearrangement that has seen extensive application in natural product synthesis and spirocycle formation.[192,214]

The semi-pinacol rearrangement has been used by Ferrié to generate cyclobutanone spirocycles (scheme 110, next page).[215] In this example, *N*-Boc piperidin-4-one **a** is converted to the corresponding cyclopropylalkylidene **b** by Wittig olefination with a cyclopropyl ylide (generated *in situ* from 1-bromopropyl-3-triphenylphosphonium bromide). Treatment of **b** with *meta*-chloroperoxybenzoic acid (mCPBA) converts it to the spiro epoxide **c**, which readily rearranges to the spiro-cyclobutanone **f** in the presence of trace amounts of acid.[215,216]

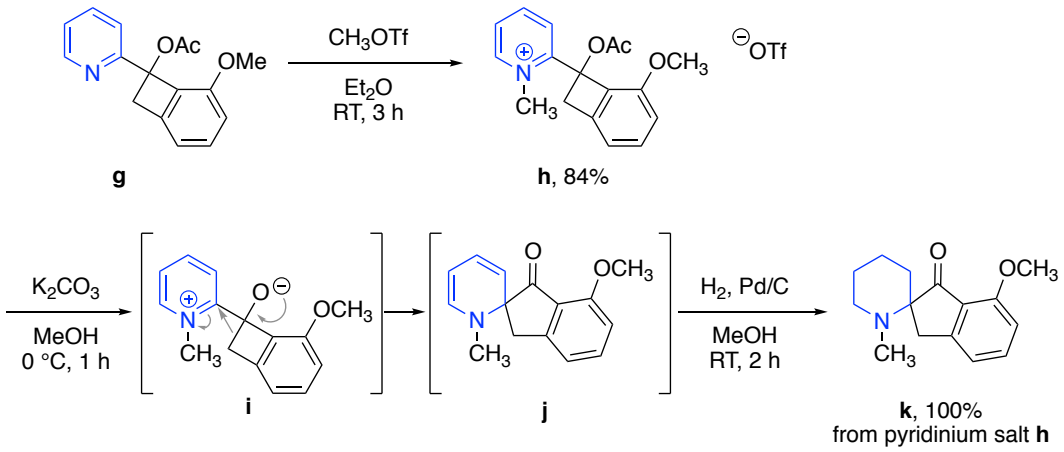


Scheme 110: Semi-pinacol rearrangement of unstable spiro-epoxide forming cyclobutanone spirocycle

The semi-pinacol rearrangement of strained carbocycles has been shown to be capable of dearomatizing pyridinium species as a key step in the synthesis of azaspiro[4.5]decane scaffolds by Hayashi and co-workers.[217] Pyridyl benzocyclobutanol species **a** is capable of undergoing a semi-pinacol rearrangement following methylation of the pyridine nitrogen (by treatment with Meerwein salt), generating a spiro-dihydropyridine **c** (scheme 111). However, this dihydropyridine intermediate is liable to further react as an enamine with the methylating agent, resulting in the synthesis of tetrahydropyridine-2-ol species **f**. It was found that this undesired pathway could be prevented by separating the methylation step from the semi-pinacol step (scheme 112, next page). This was achieved by forming the *N*-methylpyridinium salt with an *O*-acyl protected starting material **g**, and then inducing the semi-pinacol rearrangement in a separate step by deprotection of the alcohol. Given the propensity of the dihydropyridine formed to react as an enamine, this species was not isolated. Instead, the dihydropyridine double bonds were hydrogenated in one pot to give the piperidine spirocycle **k** as the product. The semi-pinacol rearrangement in this case was found to be selective for migration of the benzylic CH_2 moiety over the phenyl group.



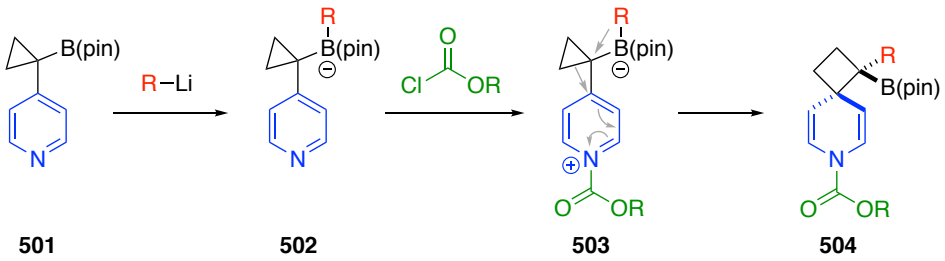
Scheme 111: Treatment of pyridine species **a** with methylating agent leads to over-reaction giving species **f**



Scheme 112: Controlled spirocycle formation following deprotection of hydroxy group and subseqeuent reduction to piperidine

5.1.3 Project proposal

Having established the synthesis of substituted cyclobutyl boronic esters by electrophilic activation of vinylcyclopropylboron-ate complexes (chapter 4), it was envisaged that the principle of ring expansion-induced migration could be applied to pyridylcyclopropylboron-ate complexes to generate complex dihydropyridine spirocycles that would constitute medicinally interesting drug scaffolds (scheme 113). It was anticipated that the pyridylcyclopropylboron-ate complexes (**502**) could be synthesised by treatment of pyridylcyclopropylboronic ester **501** with an organolithium reagent. The ring expansion and 1,2-metallate rearrangement would be invoked by acylation of the pyridine nitrogen atom to generate a pyridinium intermediate **503**, akin to the triggering of the 1,2-metallate rearrangement of pyridylboron-ate complexes discussed in chapter 1, section 1.2.2.2.2.[47]



Scheme 113: Proposed dearomative spirocycle formation with ring-expansion-induced 1,2-metallate rearrangement

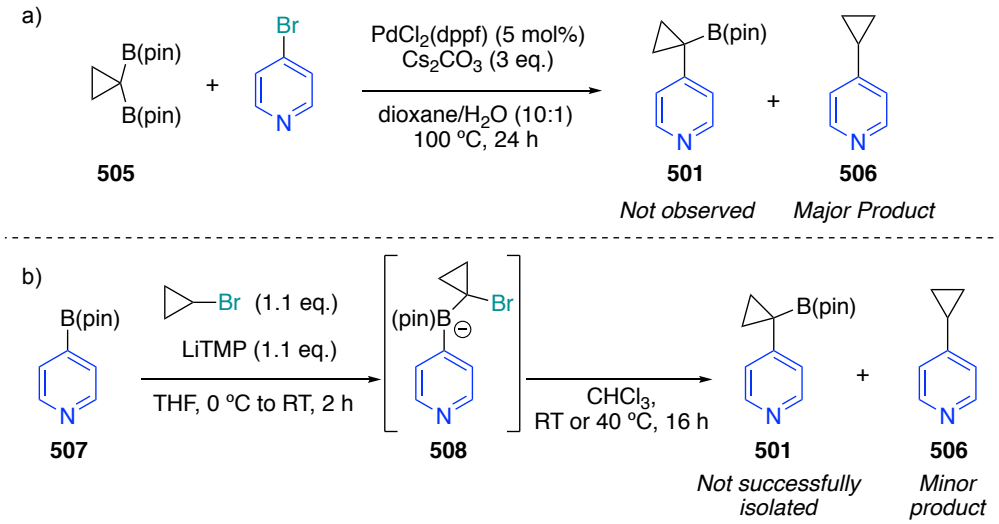
5.2 Ring expansion of pyridylcyclopropyl boron-ate complexes

5.2.1 Synthesis of pyridylcyclopropyl boronic ester starting material

The synthesis of arylcyclopropyl boronic esters using a palladium-mediated Suzuki coupling of bis-boronic ester **505** with aryl bromides has been reported by M. R. Harris, although the target starting material **501** (scheme 114, a) was not reported.[194] The synthesis of pyridylcyclopropyl boronic ester **501** was attempted using the literature conditions with 4-bromopyridine, however the desired

product **501** was not obtained. Instead, 4-cyclopropylpyridine **506** was obtained as the only pyridine-containing product.

It was noted that 4-cyclopropylpyridine can be obtained by protodeboronation of **501**. Given the high temperature and presence of moisture in the reaction it is possible that this occurs under the Suzuki reaction conditions.



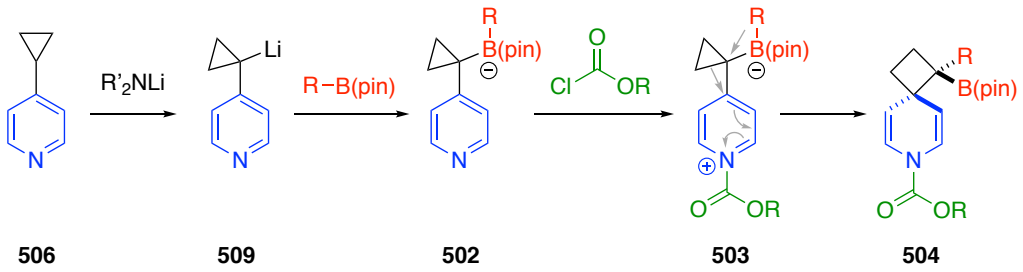
Scheme 114: a) Attempted Suzuki coupling resulting in protodeboronation; b) Attempted cyclopropyl homologation

The alternative to the Suzuki coupling approach was to apply the cyclopropyl homologation conditions described in chapter 4 sections 4.3.1 and 4.5 to 4'-pyridyl boronic ester **507**. Treatment of **507** with 1.1 equivalents each of cyclopropyl bromide and lithium tetramethylpiperidide in THF at 0 °C and allowing the reaction to warm to ambient temperature gave near-full conversion of **507** to boron-ate complex **508** (observed as a resonance at 6 ppm in ^{11}B NMR) after 2 hours. A solvent switch to chloroform was performed and the reaction stirred overnight at ambient temperature, however conversion of the boron-ate complex was not observed after 16 hours. Instead, heating the reaction mixture in chloroform to 40 °C overnight delivered the desired product **501** alongside the protodeboronation product 4-cyclopropylpyridine (**506**) and some remaining starting material (**507**). Unfortunately, isolation of **501** by flash column chromatography was unsuccessful due to a tendency for the product to undergo rapid protodeboronation on silica. Attempts to purify **501** by column chromatography on basic alumna were also unsuccessful.

5.2.2 Lithiation and trapping of 4-cyclopropylpyridine

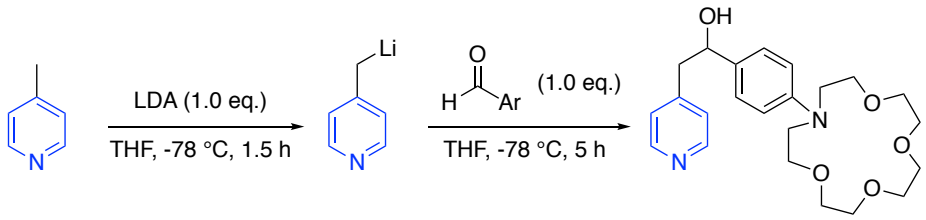
Given the propensity for starting material **501** to undergo protodeboronation, attention was instead focussed on an alternative approach in which 4-cyclopropylpyridine is lithiated at the benzylic position and trapped with a boronic ester to give a boron-ate complex intermediate **502** (scheme 115) which would then hopefully undergo migratory ring expansion to give spirocycle **504** upon electrophilic

activation of the pyridine nitrogen atom. This approach directly utilises boronic esters as the source of the migrating group in the reaction as opposed to organolithium reagents. Given the ease of synthesis of a wide variety of boronic esters, this significantly increases the potential scope of the reaction; especially with enantioenriched migrating groups.



Scheme 115: Lithiation and trapping of 4-cyclopropylpyridine and subsequent ring-expansion/migration of boron-ate complex to give spirocycle

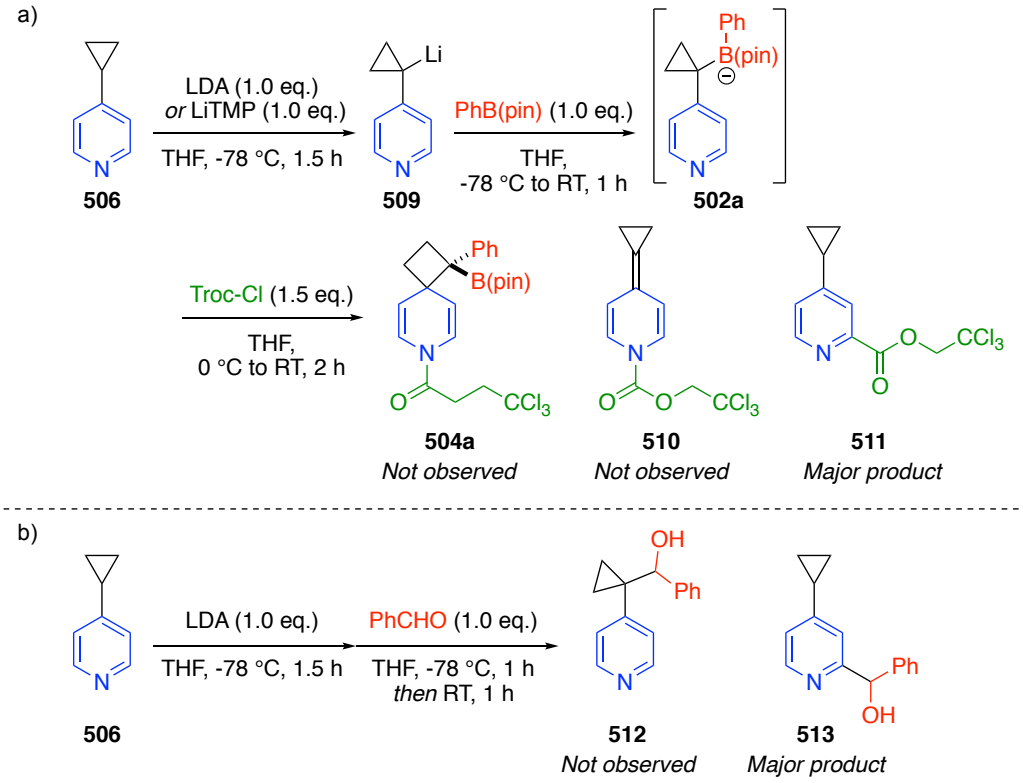
Whilst there was no literature precedence for the lithiation of cyclopropylpyridine at the benzylic position, there was precedence for the lithiation and trapping of 4-picoline (4-methylpyridine) and subsequent trapping with aldehydes, using either lithium diisopropylamide (LDA) in THF at -78 °C or lithium tetramethylpiperidide (LiTMP) in diethyl ether at -78 °C (scheme 116).[140,218]



Scheme 116: Literature lithiation and trapping of 4-picoline

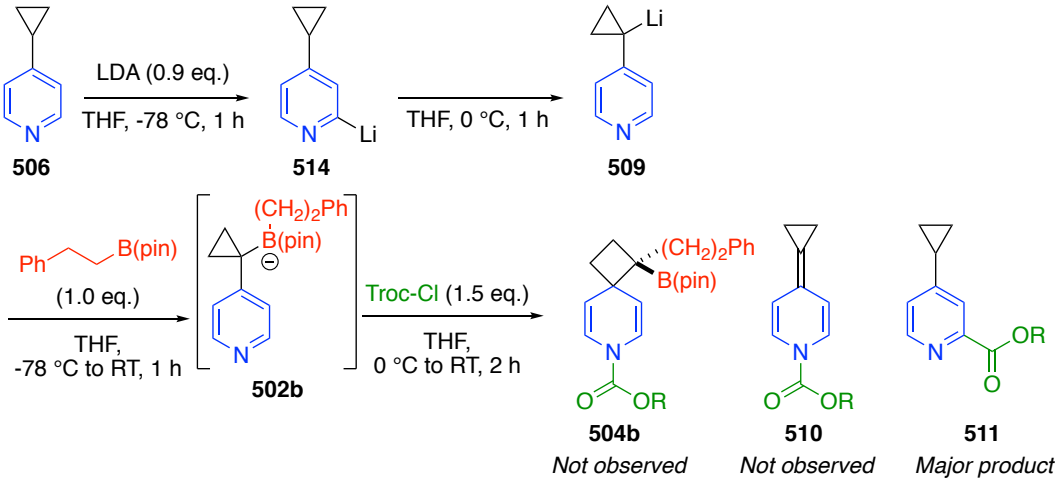
It was anticipated that these conditions should also selectively lithiate the benzylic position of cyclopropylpyridine. Cyclopropylpyridine was treated with LDA or LiTMP (1 eq. with respect to cyclopropylpyridine) in THF at -78 °C and stirred for 1.5 h before trapping with 1 equivalent of phenyl boronic acid pinacol ester (PhBpin) (scheme 117, a). After allowing the reaction to warm to 0 °C over 1 h, full conversion of the boronic ester to boron-ate complex was observed by the presence of a resonance at 8 ppm in ^{11}B NMR. This was speculated to be the desired boron-ate complex **502a**, however following the addition of 2,2,2-trichloroethyl chloroformate (Troc-Cl) and allowing the reaction to warm from 0 °C to ambient temperature over 2 hours, neither the desired product **504a** or the potential undesired elimination product **510** were observed. Instead, the major product identified was **511**, indicating that lithiation and trapping had occurred at the C2 position of the pyridine ring. This was further confirmed with lithiation and trapping studies with benzaldehyde (scheme 117, b), which exclusively formed the C2-trapped product **513** and not the desired product

512. No reaction was observed when deprotonation of cyclopropylpyridine with LiHMDS (lithium bis(trimethylsilyl)amide) or NaHMDS at 0 °C and trapping with benzaldehyde were attempted.



Scheme 117: a) Attempted lithiation and trapping of 4-cyclopropylpyridine with phenylboronic acid pinacol ester, b) Lithiation and trapping of 4-cyclopropylpyridine with benzaldehyde

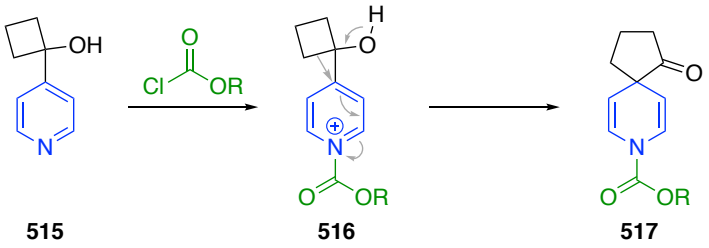
It was hypothesised that the C2 lithiation was the kinetic lithiation and that lithiation at the benzylic position would be thermodynamic. Therefore, it was hoped that use of a sub-stoichiometric amount of LDA at -78 °C and allowing the reaction to warm to 0 °C would enable the deprotonation to 'hop' from the kinetic C2 position (**514**) to the assumed thermodynamic benzylic position (**509**) (scheme 118, next page). Cyclopropylpyridine was treated with LDA at -78 °C and stirred for 1 h before allowing the reaction to warm to 0 °C and stirring for a further 1 h. The reaction was then cooled back down to -78 °C and trapped with phenethyl boronic acid pinacol ester before warming to room temperature to ensure boron-ate complex formation. Following cooling to -78 °C, addition of Troc-Cl and warming back to ambient temperature, neither of the anticipated products from desired migration-ring-expansion (**504b**) or elimination (**510**) pathways were observed. Instead, species **511** was identified indicating that the deprotonation and trapping occurred exclusively at the C2 position.



Scheme 118: Further attempt at achieving lithiation of cyclopropyl ring of 4-cyclopropylpyridine

5.2.3 Revisited proposal

Given the lack of success in achieving the formation of pyridylcyclopropylboron-ate complexes, attention was refocussed to the construction of dihydropyridine spirocycles by a dearomative semi-pinacol rearrangement of hydroxycycloalkylpyridines. It was noted that while dearomative semi-pinacol rearrangements of alkypyridinium salts have been used to construct spirocycles, discussed in section 5.1.2.6, the dihydropyridine spirocycles were non-isolable due to their reactivity (instead direct hydrogenation to the piperidine was employed) and the scope of this protocol was limited to just a few examples.[217] It was envisaged that the use of acylating agents (rather than alkylating agents) would enable the formation of isolable dihydropyridine spirocycles (**517**) in a simple one-step procedure from hydroxycycloalkylpyridines (**515**) without the need to protect the alcohol (scheme 119).



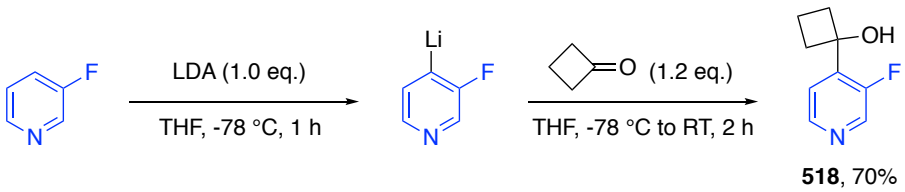
Scheme 119: Proposed formation of dihydropyridine spirocycles by semi-pinacol rearrangement of hydroxycycloalkylpyridinium intermediates accessed by *N*-acylation of hydroxycycloalkylpyridines

5.3 Synthesis of spirocycles by semi-pinacol rearrangement of pyridylcyclobutanols

5.3.1 Initial studies

It was decided to initially study the reaction by using ^{19}F spectroscopy to monitor conversion of a fluorinated starting material. To this end, the 3-fluoro-substituted hydroxycyclobutylpyridine **518** was

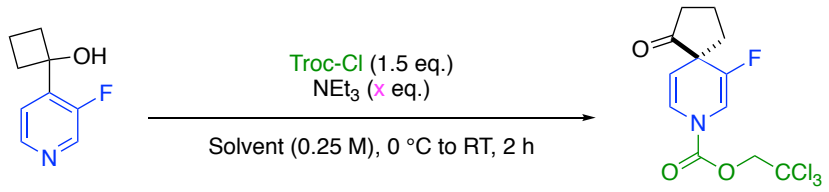
synthesised by deprotonating 3-fluoropyridine at the C4 position with lithium diisopropylamide (LDA) and trapping with cyclobutanone (scheme 120).



Scheme 120: Synthesis of 3-fluoro substrate **518**

An initial screen of conditions was undertaken using 2,2,2-trichloroethyl chloroformate (Troc-Cl) as the acylating agent, added as a solution in the reaction solvent at 0 °C before allowing the reaction to warm to room temperature (table 13). Conversion of the starting material **518** (^{19}F resonance at -129 ppm relative to the 4-fluorotoluene internal standard resonance set at -118.5 ppm) to product species monitored by ^{19}F NMR. In the absence of base (table 13, entries 1-3) a significant amount of precipitation was observed after 2 hours in THF, with a moderate amount of precipitate in DCM and chloroform. Loss of mass balance seen in the ^{19}F NMR spectra of the reaction mixtures indicated that the precipitate was an organofluorine compound.

Table 13: Initial conditions screen with 2,2,2-trichloroethyl chloroformate



518 **519a**

Entry	Solvent	Equivalents x	Precipitation	^{19}F NMR observations
1	THF	0	White solid	**518** only (-129 ppm)
2	DCM	0	White solid	**518** only (-129 ppm)
3	$CHCl_3$	0	White solid	-129 ppm (**518**), -143.75 ppm, -144.25 ppm
4	THF	1.0	White solid	**518** only (-129 ppm)
5	DCM	1.0	None	-129 ppm (**518**), -126 ppm, -143.75 ppm, -144.25 ppm
6	$CHCl_3$	1.0	None	-129 ppm (**518**), -126 ppm, -143.75 ppm, -144.25 ppm

It was noted that for the proposed reaction pathway (scheme 119, previous page), one equivalent of hydrochloric acid would be generated alongside the product, which would result in protonation of the pyridine starting material (which was presumed to be the precipitate observed). With one equivalent of triethylamine (with respect to starting material) present, precipitation was not observed when the reaction was conducted in chloroform or dichloromethane (table 13, entries 5 & 6).

Conversion of the starting material (**518**) resonance at -129 ppm to new resonances at -126 ppm (49% integral relative to 4-fluorotoluene and hexafluorobenzene internal standards) and two resonances at -143.75 ppm and -144.25 ppm (31% integral across both peaks) was observed in chloroform after stirring at ambient temperature for 2 hours (figure 8; table 14 on next page, entry 1). Following isolation by column chromatography, the two resonances at -143.75 and -144.25 ppm were identified as two rotamers of the desired spirocyclic product **519a** (with rotation around the carbamate C-N bond giving two species observed on the NMR timescale). The resonance at -126 ppm was identified as the product of direct acylation of the hydroxy group (**520a**).

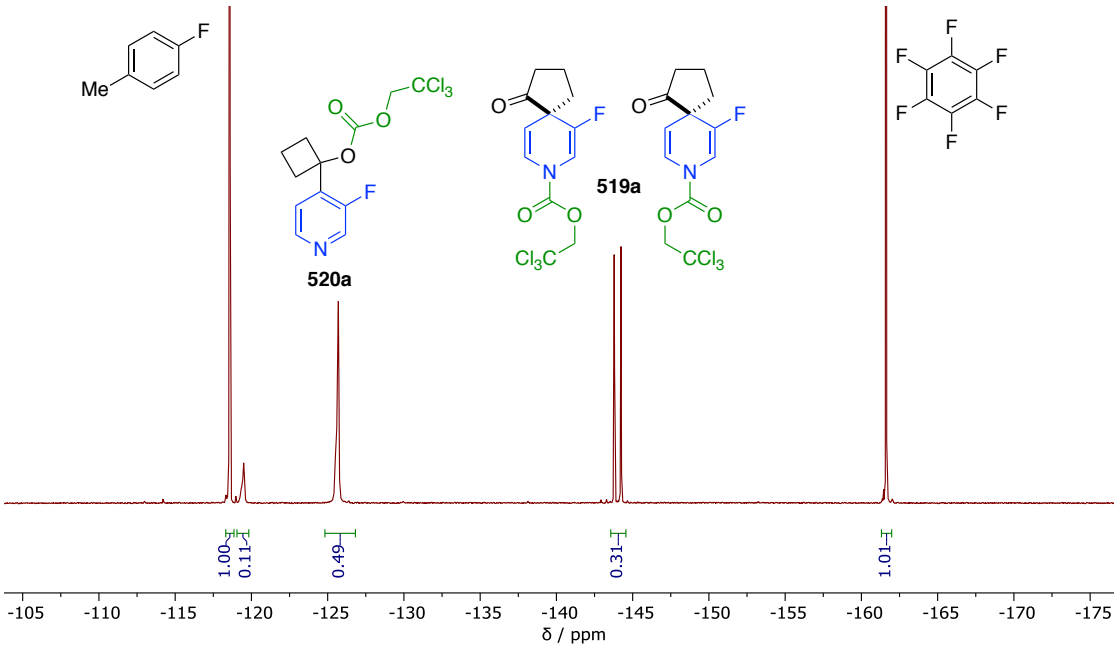
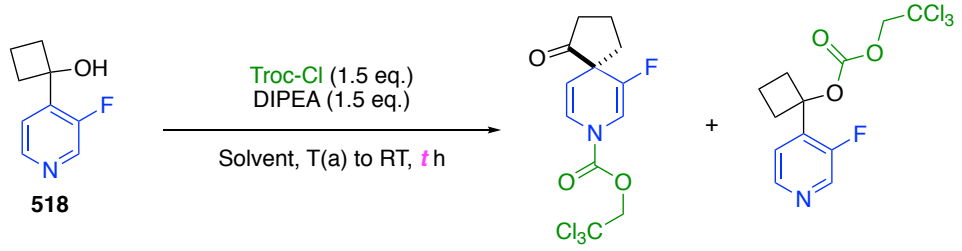


Figure 8: Species identified in reaction mixture after 2 h at RT (^{19}F, 400 MHz, 20 s relaxation delay)

Optimisation of reaction conditions was undertaken with the aim of improving yield and selectivity for the desired *N*-acylation and ring expansion pathway over the undesired *O*-acylation pathway (table 14). It was found that switching the base from triethylamine to diisopropylethylamine (Hünig's base, DIPEA) and increasing the equivalents to match that of the chloroformate (1.5 equivalents) improved the selectivity in favour of the desired product **519a**, delivering this in a 60% yield (table 14, entries 1 and 2).

Decreasing the temperature at which the chloroformate was added to -40 °C was found to reduce the selectivity (compared to adding the chloroformate at 0 °C) and indeed the yield of **519a** (table 14, entry 3). The reaction had a higher yield of **519a** and more favourable selectivity when performed in chloroform compared to acetonitrile, *tert*-butyl methyl ether (TBME) or dichloromethane (table 14, entries 4 to 6).

Table 14: Further condition optimisation with Troc-Cl



Entry	Solvent	T(a) /°C	*t* /h	Remaining SM /%[a]	Yield **519a** /%[a]	Yield **520a** /%[a]	Ratio **519a**:**520a**	Comments
1	$CHCl_3$	0	3	0	31	49	3:5	1.0 eq. NEt_3
2	$CHCl_3$	0	3	0	60 (52[b])	10 (9[b])	6:1	
3	$CHCl_3$	-40	3	0	35	37	1:1	
4	MeCN	0	19	9	35	48	7:10	
5	TBME	0	3	46	4	19	1:5	messy reaction
6	DCM	0	17	0	47	27	5:3	

[a]Yield by ^{19}F NMR integral with respect to 4-fluorotoluene internal standard; [b]isolated yield

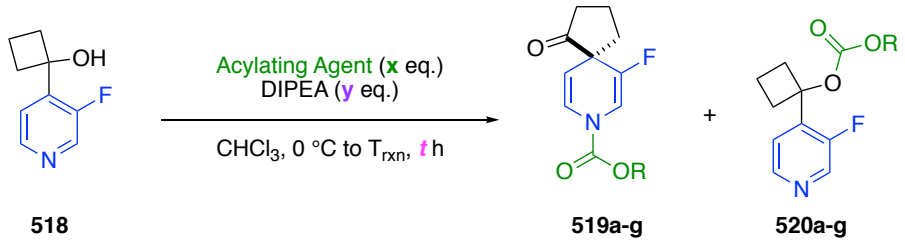
5.3.2 Acylating agent screen

It was noted that the tertiary alcohol is more sterically encumbered than the pyridine nitrogen. It was surmised that this might disfavour *O*-acylation if a sterically bulky acylating agent was used, and therefore improve the selectivity for the desired *N*-acylation and ring expansion pathway. This hypothesis was tested by screening various chloroformates and acylating agents (table 15, next page).

Methyl chloroformate (table 15, entry 2) was found to have a similar selectivity for *N*-acylation/ring expansion as 2,2,2-trichloroethyl chloroformate (Troc-Cl, entry 1), while benzyl chloroformate (Cbz-Cl) gave almost exclusively the spirocycle product **519c** with very little *O*-acylation (entry 3). The more sterically bulky 1,1-dimethyl-2,2,2-trichloroethyl chloroformate (Me_2Troc-Cl, entry 4) and fluorenylmethyl chloroformate (Fmoc-Cl, entries 5 and 6) were found to exclusively give spirocyclic products **519d** and **e** without any competing *O*-acylation. An increased stoichiometry of Fmoc-Cl and a longer reaction time were required to ensure the reaction went to completion (entry 5). In contrast, reaction with trifluoroacetic anhydride (TFAA) gave exclusively the undesired *O*-acylation product **520f** (entry 6). No reaction was observed between the starting material and di-*tert*-butyl dicarbonate (Boc anhydride/Boc_2O) at ambient temperature (entry 8). Heating the reaction to 65 °C gave full conversion of the starting material **518** after 3 days to give an 85% yield (by ^{19}F NMR) of the spirocyclic product **519g** (entry 9). In this case the expected by-products of the reaction would be carbon dioxide and

tert-butanol as opposed to hydrogen chloride or trifluoroacetic acid formed in entries 1 to 7, and so DIPEA was not required in the reaction.

Table 15: Screen of acylating agents



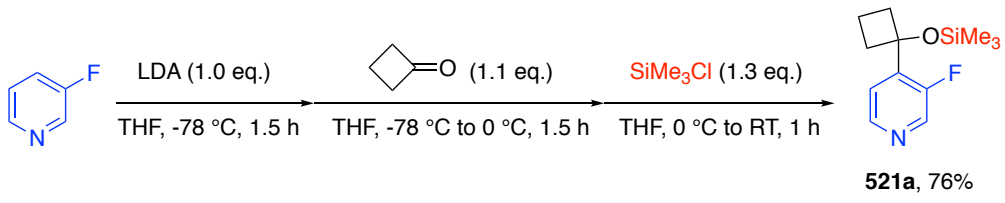
518 **519a-g** **520a-g**

Entry	Acylating Agent	Eq. **x**	Eq. **y**	T_{rxn} /°C	*t* /h	Remaining **518** /%[a]	Yield **519** /%[a]	Yield **520** /%[a]
1	Troc-Cl	1.5	1.5	RT	3	0	60 (52[b])	10 (9[b])
2	MeOCOCl	1.5	1.5	RT	3	0	64	11
3	Cbz-Cl	1.5	1.5	RT	18	0	86 (80)	3
4	Me_2TrocCl	1.5	1.5	RT	3	0	85	0
5	Fmoc-Cl	1.5	1.5	RT	18	27	65	0
6	Fmoc-Cl	2.0	2.0	RT	18	0	85 (73[b])	0
7	TFAA	1.5	1.5	RT	18	0	0	97
8	Boc_2O	1.5	0	RT	17	96	0	0
9	Boc_2O	1.5	0	65	72	0	85 (69[b])	0

[a]Yield by ^{19}F NMR integral with respect to 4-fluorotoluene internal standard; [b]isolated yield

5.3.2.1 Can *O*-Acylation be blocked using silyl protecting groups on alcohol?

It was considered that it may be possible to prevent the competing *O*-acylation pathway by protecting the hydroxy group with a silyl protecting group. To test this, substrate **521a** bearing a trimethylsilyl protecting group on the alcohol was synthesised (scheme 121).

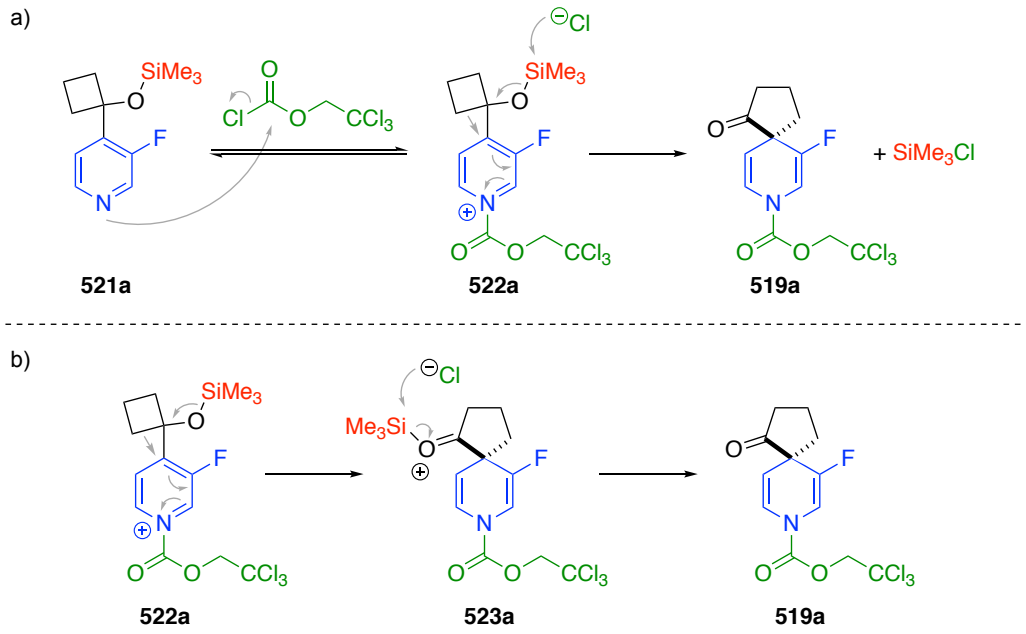


521a, 76%

Scheme 121: Synthesis of TMS-protected starting material **521a**

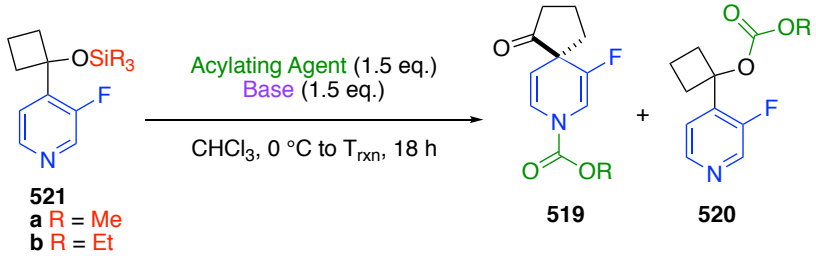
It had been hoped that the chloride anion produced following *N*-acylation would act as a nucleophile either to trigger a concerted deprotection and migratory ring expansion process (scheme 122, a, next page), or 'mop up' the trimethylsilane group following migratory ring expansion of the pyridinium intermediate **522a** (scheme 122, b). However, there was no conversion of the starting material **521a**

when 2,2,2-trichloromethyl chloroformate was used as the acylating agent, even when the reaction was heated to reflux in chloroform (table 16 on next page, entries 1 and 2).



Scheme 122: Possible pathways for spirocycle formation from silyl-protected starting material

Table 16: Conditions screen with silyl-protected starting materials



521
a R = Me
b R = Et

519 **520**

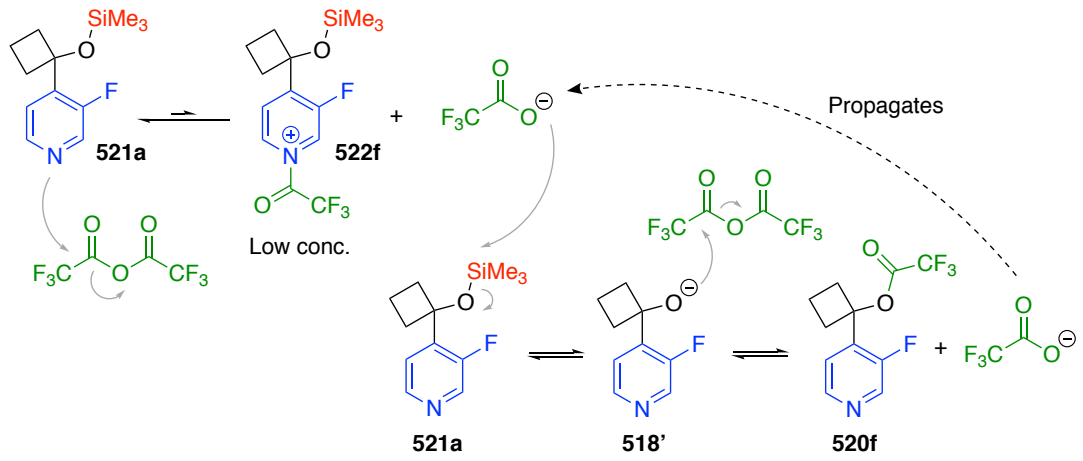
Entry	Protecting group	Acylating Agent	Base	T_{rxn} /°C	Observed Species[a]
1	$SiMe_3$	Troc-Cl	DIPEA	RT	SM (**521a**) only
2	$SiMe_3$	Troc-Cl	DIPEA	65	SM (**521a**) only
3	$SiMe_3$	Ac_2O	DIPEA	RT	SM (**521a**) only
4	$SiMe_3$	Ac_2O	DIPEA	65	SM, **520**
5	$SiMe_3$	TFAA	DIPEA	RT	SM, **520**
6	$SiMe_3$	TFAA	DTBMP	65	SM, **520**
7	$SiEt_3$	TFAA	DIPEA	RT	SM, **520**
8	$SiEt_3$	TFAA	DTBMP	65	SM, **520**

[a]Based on ^{19}F NMR shift with respect to 4-fluorotoluene internal standard

It was hoped that in contrast to the chloride anion formed following *N*-acylation with a chloroformate, the carboxylate anion formed following *N*-acylation with an anhydride would be sufficiently nucleophilic towards the silyl group to enact the semi-pinacol ring expansion process. Whilst acetic anhydride did not react with the starting material **521a** at room temperature, some conversion of the starting material to the *O*-acylation product **520h** was observed at 65 °C (table 16, entries 3 and 4). The more electrophilic trifluoroacetic anhydride (TFAA) reacted with the starting material at room temperature to produce the *O*-acylation product **520f** (table 16, entry 5).

It was considered that the diisopropylethylamine base may be sufficiently nucleophilic to react with TFAA at room temperature, generating enough of the carboxylate species to then deprotect the starting material enabling the formation of the *O*-acylation product. Changing the base to the more sterically encumbered (and thus less nucleophilic) 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) led to only negligible formation of the *O*-acylation product being observed at ambient temperature, however considerable formation of this species was observed at 65 °C, with no formation of the desired spirocyclic product **519f** (table 16, entry 6).

The observation that only the *O*-acylation product is formed can be rationalised by considering the reaction pathway shown in scheme 123. The equilibrium between the starting pyridine **521a** and the pyridinium species **522f** formed by *N*-acylation is heavily biased towards the un-acylated starting material, such that at any given time the concentration of the pyridinium species is very low compared to that of the starting material. Provided the difference in reactivity of **521a** and **522f** towards deprotection by the carboxylate anion isn't large enough to enable the deprotection of the pyridinium species to dominate, the difference in concentration of the two species leads to substantial deprotection of the starting material to give alcohol/alkoxide **518'**. This can then react with another equivalent of TFAA to form the *O*-acylation product **520f**. It should be noted that this then generates the carboxylate, which can then propagate to deprotect more of the starting material.

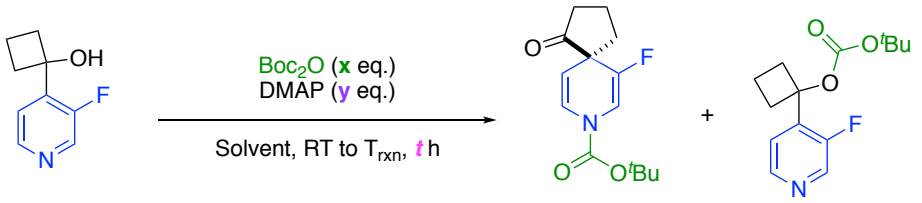


Scheme 123: Proposed mechanism for deprotection of TMS protecting group and *O*-acylation

Finally, it was hoped that using the more robust triethylsilyl protecting group would prevent the deprotection of the starting material whilst allowing deprotection of the pyridinium intermediate. Unfortunately, this was not found to be the case, with the *O*-acylation product being observed when either DIPEA or DTBMP were used as the base (table 16, entries 7 and 8).

5.3.3 Optimisation with Boc anhydride[i]

Table 17: Optimisation of reaction with Boc anhydride



518 **519g** **520g**

Entry	Solvent	Eq. **x**	Eq. **y**	T_{rxn} /°C	***t*** /h	Remaining SM /%[a]	Yield **519g** /%[a]	Yield **520g** /%[a]
1	$CHCl_3$	1.5	0	65	72	0	85 (69[b])	0
2	$CHCl_3$	1.5	0	65	7 days	0	81	0
3	$CHCl_3$	1.5	0.3	65	18	0	0	96
4	$CHCl_3$	5	0	65	6 days	0	88	0
5	1,2-DCB	1.5	0	120	18	82	3	0
6	1,2-DCE	1.5	0	85	48	75	25	0
7	1,4-dioxane	1.5	0	100	48	83	17	0
8	MeCN	1.5	0	85	48	56	44	0
9	MeCN	5	0	85	24	*NR*	85	0
10	EtCN	5	0	100	24	*NR*	83	0
11	EtCN[c]	5	0	100	24	*NR*	41	0
12	PhCN[c]	5	0	120	24	*NR*	15	0

[a]Yield by ^{19}F NMR integral with respect to 4-fluorotoluene internal standard; [b]isolated yield, [c]non-anhydrous solvents; *NR* = not recorded

The *tert*-butyloxycarbonyl (Boc) group is a well-established and widely used protecting group for amines, with deprotection of this group well known. This renders the use of di-*tert*-butyl dicarbonate (Boc anhydride) very attractive for this chemistry. However, in contrast to the chloroformates this acylating agent is relatively unreactive, with full conversion of hydroxycyclobutylpyridine **518** to spirocyclic product **519g** taking 3 days in chloroform at 65 °C (table 17, entry 1). Furthermore, a repeat

[i] Optimisation of equivalents of Boc anhydride and solvents performed by Laia Vicens I Serra

of the reaction took 7 days to go to completion (table 17, entry 2), suggesting an issue with reproducibility for these conditions. Therefore, further optimisation with Boc anhydride as the acylating agent was undertaken with the aim of decreasing the reaction time and making this a more viable and attractive process (table 17).

Addition of a sub-stoichiometric amount of 4-dimethylaminopyridine (DMAP) is commonly used to speed up or improve the yield of Boc protection of alcohols and amines.[219] It was found that with 0.3 equivalents of DMAP in the reaction (entry 3), the electivity of the reaction was reversed completely in favour of the *O*-acylation product **520g** rather than the spirocycle **519g**. Increasing the stoichiometry of Boc anhydride (Boc_2O) to 5 equivalents was found to have little impact on the rate of reaction in chloroform, with the reaction taking 6 days for full conversion of starting material **518** (entry 4).

Different solvents were screened for the reaction. Conversion of starting material **518** was negligible after 18 hours at 120 °C in 1,2-dichlorobenzene (1,2-DCB) (entry 5). Low conversion was also observed after 48 hours at reflux in 1,2-dichloroethane (1,2-DCE) and 1,4-dioxane (entries 6 and 7), however the conversion was higher in acetonitrile (MeCN, entry 8).

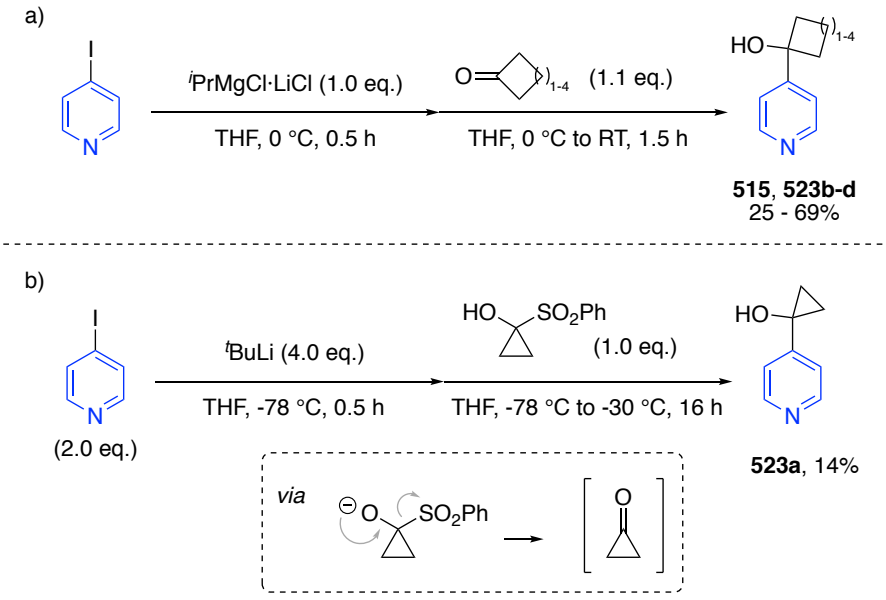
Increasing to 5 equivalents of Boc anhydride in acetonitrile was found to drastically improve the rate of reaction, giving full conversion of the starting material **518** and an 85% yield of spirocyclic product **519g** after 24 hours at 85 °C. Switching to propionitrile (EtCN) and heating to 100 °C was not found to improve the rate of the reaction or yield of **519g** (entry 10). Furthermore, the yield of **519g** fell dramatically when moisture was present (entries 11 and 12, which use non-anhydrous solvents), demonstrating the need for anhydrous solvents for this reaction.

5.3.4 Scope with Boc anhydride

The use of 5.0 equivalents of di-*tert*-butyl dicarbonate (Boc anhydride) in acetonitrile at 85 °C for 24 h were identified as optimal for the reaction. Therefore, the scope of the reaction was explored using these conditions.

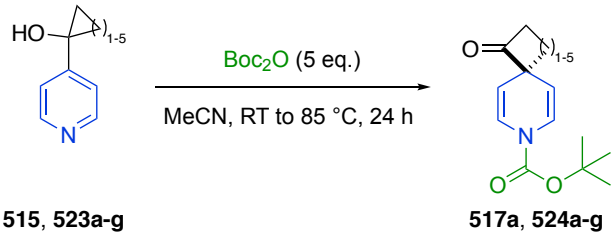
5.3.4.1 Expansions of different ring sizes, heterocycles and substituted aliphatic rings

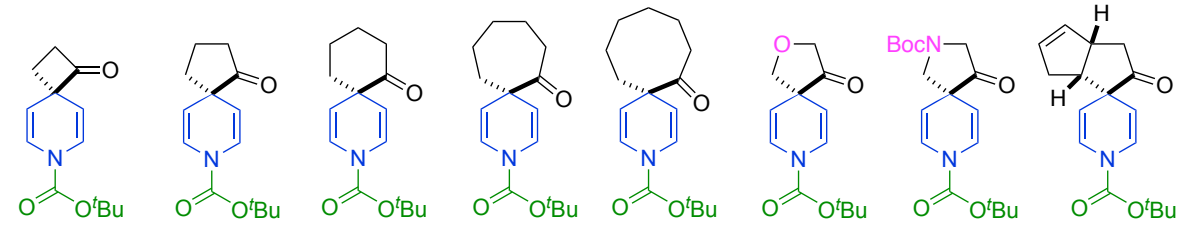
Hydroxycycloalkylpyridines were synthesised by magnesiation of 4-iodopyridine using turbo Grignard (isopropyl magnesium chloride lithium chloride complex) and trapping with respective cyclic ketones (scheme 124, a). Unlike the bench-stable and commercially available 4-7-membered cyclic ketones, cyclopropanone is not stable or isolable. Therefore, this species was produced *in situ* from phenylsulfonylcyclopropanol as established by Lindsay and co-workers.[220,221] In this case an extra equivalent of the metallated pyridine was required to deprotonate the cyclopropanone precursor (scheme 124, b).



Scheme 124: a) Synthesis of 4-7-membered pyridylcycloalkanol substrates **515** and **523b-d**, b) Synthesis of 1-pyridylcyclopropan-1-ol **523a**

Table 18: Scope of ring expansions





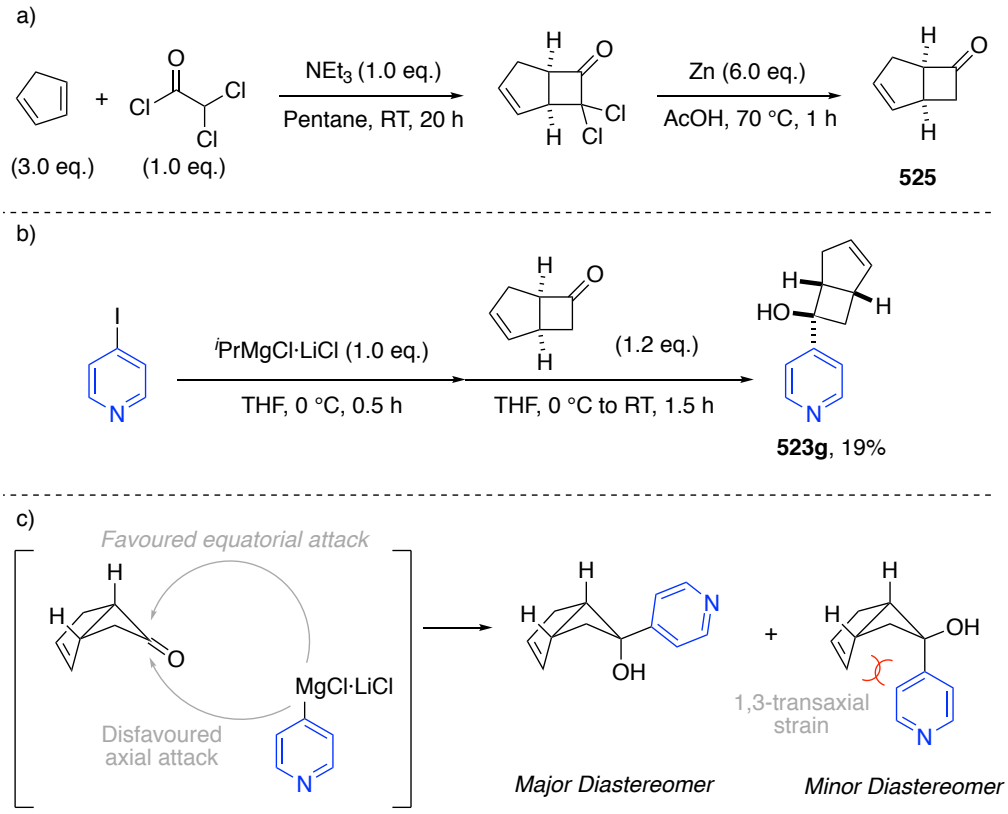
524a	**517a**	**524b**	**524c**	**524d**	**524e**	**524f**	**524g**
64%[a] (73%)[b]	96% (100%)	45% (50%)	- (<10%)	- (<10%)	78% (80%)	64% (78%)	86% (86%)

a: isolated yield; *b*: ^{1}H NMR yield of crude with dibromomethane internal standard

The reaction was found to work well for the expansion of smaller, more strained rings (table 18). The expansion of pyridylcyclopropanol **523a** to cyclobutanone spirocycle **524a** and the expansion of pyridylcyclobutanol **515** to cyclopentanone spirocycle **517a** both proceeded with good to excellent yields: the latter being quantitative. The expansion of the 5-membered pyridylcyclopentanol substrate **523b** to the cyclohexanone spirocycle **524b** had a lower yield. The ring expansions of 6- and 7-membered pyridylcycloalkanols **523c** and **d** to 7- and 8-membered cyclic ketone spirocycles **524c** and **d** respectively were not successful, even when the reaction stoichiometry was upped to 15 equivalents

of Boc anhydride (whilst keeping the reaction temperature at 85 °C).[j] LCMS and ^{1}H NMR analysis of the crude after 24 h determined that some *O*-acylation had occurred alongside the formation of small amounts of the spirocyclic product (**524c** or **524d**) in both cases, in addition to side-products identified as coming from reaction of Boc anhydride with acetonitrile. This indicates that both the spirocycle-forming reaction and *O*-acylation pathway are very slow for these substrates such that they compete. Unfortunately, the spirocyclic products **524c** and **d** were not successfully isolated and so an accurate yield of these could not be determined.

In addition to the expansion of aliphatic rings, the reaction was found to tolerate heteroatoms in the expanding ring. The 3-oxetanone- and *N*-Boc-protected 3-azetidinone-derived substrates **523e** and **523f** both gave good yields of the respective spirocycle products **524e** and **524f**, 78% and 64% respectively.

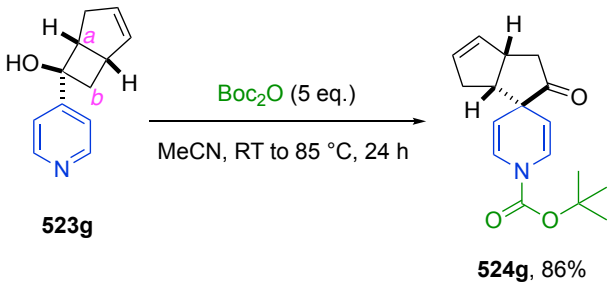


Scheme 125: a) Synthesis of bicyclic cyclobutanone species **525**; b) Synthesis of substrate **523g**; c) Model accounting for favoured diastereomer formation

Bicyclic cyclobutanone species **525** was readily prepared by cycloaddition of a chloroketene species with cyclopentadiene and then a zinc/acid mediated reduction according to literature conditions (scheme 125, a).[222,223] This bicyclic cyclobutanone was then trapped with 4-magnesiated pyridine to give the pyridylcyclobutanol species **523g** in 19% yield (scheme 125, b). Product **523g** was obtained as

[j] Repeats with increased equivalents of Boc anhydride were performed and analysed by Dr. Christian Bold

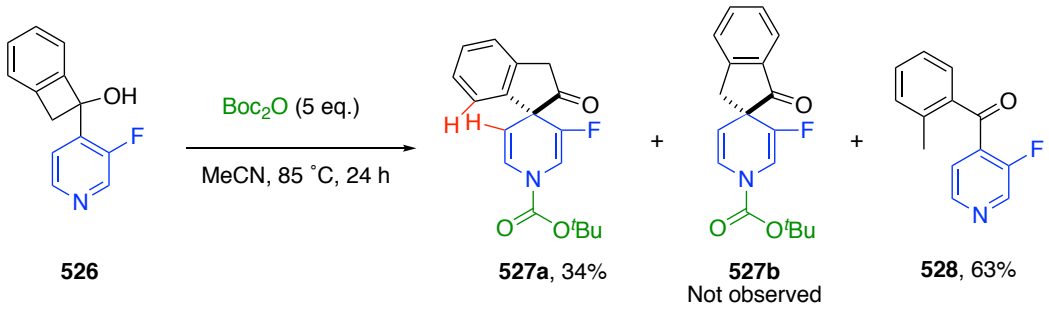
a single diastereomer. A possible explanation for this is a strong preference for equatorial attack of the ketone over axial attack in the model shown in scheme 125, c.



Scheme 126: Ring expansion of species **523g** giving spirocycle **524g**

The reaction of species **523g** with Boc anhydride successfully yielded the spirocyclic product **524g** as a single diastereomer in 86% yield (scheme 126). The reaction was regioselective for migration of the more substituted tertiary carbon centre *a* over the CH_2 moiety *b*. This is attributed to the increased stabilisation of positive charge in the transition state by alkyl inductive effects for *a* migrating compared to *b*, rendering this the lower energy pathway and thus the favoured migration.

5.3.4.2 Benzocyclobutanol ring expansion[k]



Scheme 127: Reaction of benzocyclobutenol species **526** with Boc anhydride gives two products **527a** and **528**

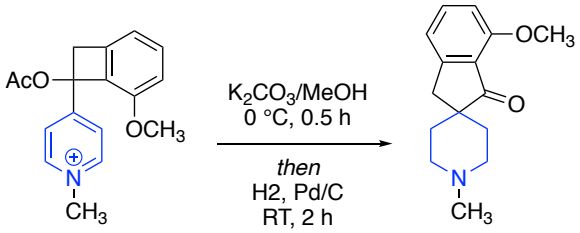
Under the developed reaction conditions shown in scheme 127, benzocyclobutenol substrate **526**, derived from trapping of benzocyclobutenone with 4-lithiated 3-fluoropyridine,[l] gave two products. Product **527a** was the expected spirocyclic product, identified as that coming from migration of the phenyl group carbon of the benzocyclobutenol moiety of the starting material based on the geminal coupling constant of the protons on the carbon α- to the ketone as well as NOESY spectroscopy demonstrating close proximity of the two protons shown in red on compound **527a**, scheme 127. The other product formed was identified as species **528**, indicating that opening of the benzocyclobutenol

[k] 1-(3'-fluoropyridyl)benzocyclobutenol substrate 526 prepared by Laia Vicens I Serra; Ring expansion reaction and identification of products performed by Noelia Velasco Perez

[l] This pyridylcyclobutanol starting material was formed in a low 7% yield. Attempts to synthesise the substrate without the fluorine atom were unsuccessful.

ring (a thermal decomposition pathway of **526**) competes with *N*-acylation and ring expansion/migration under the reaction conditions.

The observation contrasts with the observation by Hayashi and co-workers that the semi-pinacol rearrangement of species **529** (scheme 128) exclusively gave the benzyl group migration product **530** (note in this case the dihydropyridine spirocycle intermediate formed is directly hydrogenated to the piperidine).[217] It isn't obvious why the selectivity would be the opposite to this for the reaction shown in scheme 127. It's possible that the increased electrophilicity of the *N*-acylpyridinium intermediate compared to the *N*-methylpyridinium intermediate enables the phenyl group migration to compete with the benzyl group migration, although it isn't clear why this pathway would dominate to the extent that the benzyl migration product **527b** was not observed.



529 **530**, 85%

Scheme 128: Reported dearomative semi-pinacol rearrangement by Hayashi and co-workers[217]

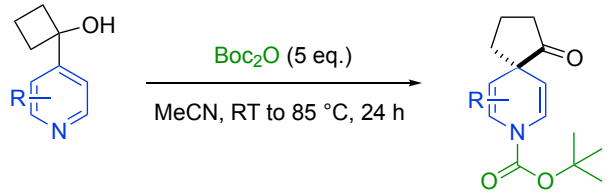
5.3.4.3 Scope of substituted pyridines and quinolines[m]

A series of hydroxyclobutylpyridine and hydroxycyclobutylquinoline substrates were synthesised by lithiation or magnesiation of 4-bromo- or 4-iodopyridine precursors (in some cases deprotonation with LDA was feasible) and trapping with cyclobutanone. These substrates were applied to the established ring expansion conditions with Boc anhydride (table 19).

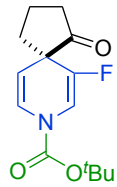
The developed reaction conditions using 5 equivalents of Boc anhydride in acetonitrile and stirring for 24 h at 85 °C were found to work well for pyridylcyclobutanol substrates bearing a substituent at the C3 position of the pyridine ring. Spirocycles **519f**, **524h** and **524i**, bearing 3-fluoro, 3-bromo and 3-diisopropylamide substituents respectively were isolated in yields of 69%, 50% and 67%. The reaction worked less well with a 3-phenyl substituent (forming **524j** in 33% yield).

[m] Substrates 524h, 524i, 524k, 524l, 524m, 524n and 524p were studied by Noelia Velasco Perez; A repeat of the reaction forming 524h was performed by Tom Jentsch

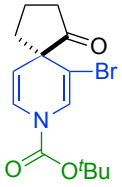
Table 19: Scope of substituted pyridines and quinolines



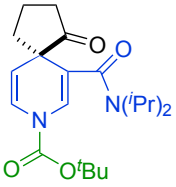
518, 523h-p **519f, 524h-p**



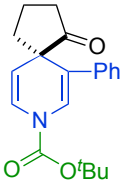
519f
69%[a] (85%)[b]



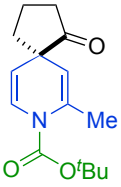
524h
50% (70%)



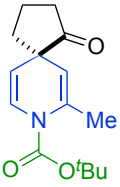
524i
67%



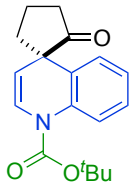
524j
33% (34%)



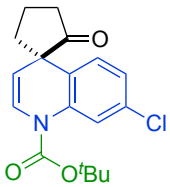
524k
47% (59%)



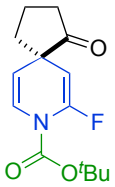
524k[c]
86% (94%)



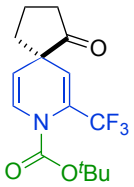
524l
24%



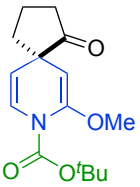
524m
19%



524n
0%



524o
0%



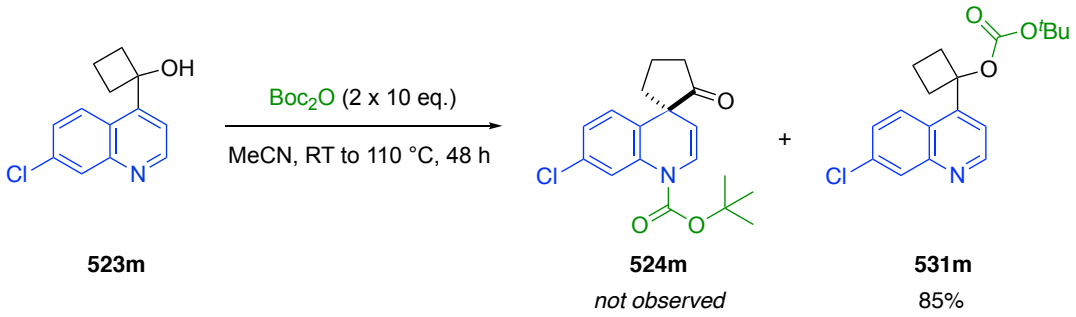
524p
0%

a: isolated yield; *b*: ^{1}H NMR yield of crude with dibromomethane internal standard;
c: An additional 5.0 eq. Boc_2O were added after 12 h of reaction time

Pyridines bearing a C2 substituent were found not to perform well in the ring expansion reaction. Substrate **523k**, bearing a 2-methyl substituent, had only a 59% conversion of starting material to the spirocycle product **524k** under the standard reaction conditions after 24 h. Increasing the equivalents of Boc anhydride in the starting reaction mixture to 10 equivalents was not found to significantly improve the conversion. However, it was found that staggering the addition of Boc anhydride, such that 5 equivalents were included in the starting reaction mixture with an additional 5 equivalents added after 12 h of reaction, significantly improved the conversion of **523k** to product **524k** (to 94%), with an isolated yield of 86%. This result was attributed to the gradual decomposition of Boc anhydride under the reaction conditions competing with the reaction of Boc anhydride with the substrate (which is slower for **523k** due to the steric hindrance pyridine nitrogen by the adjacent 2-methyl group). Introducing additional Boc anhydride halfway through the reaction rather than at the start ensures a higher concentration of Boc anhydride later in the reaction to enable complete conversion of the pyridylcyclobutanol substrate.

Unfortunately, the spirocycles **524n**, **524o** and **524p** were not successfully formed from their respective 2-substituted pyridylcyclobutanol substrates, with no conversion of the respective 2-substituted starting materials (**523n-p**) under the standard reaction conditions. Increasing the equivalents of Boc anhydride was not found to improve conversion, whilst *O*-acylation was found to dominate when the temperature was increased to 110 °C. It was considered that the presence of electron withdrawing fluorine or trifluoromethyl groups adjacent to the pyridine nitrogen reduces the electron density at the pyridine nitrogen, rendering it less nucleophilic towards the Boc anhydride electrophile. Therefore, the *O*-acylation pathway can compete with *N*-acylation, particularly at 110 °C.

The dihydriquinoline spirocycles **524l** and **524m** were both produced in low yields, 24% and 19% respectively under the standard reaction conditions. As with the 2-methyl substrate **523k**, there was incomplete conversion of starting material to the spirocycle product under the standard reaction conditions. Increasing the equivalents of Boc anhydride, even in a staggered fashion (for example 10 equivalents in the starting reaction mixture and a further 10 equivalents added after 24 h) was not found to significantly improve the conversion. Furthermore, increasing the temperature to 110 °C resulted in the formation of exclusively the *O*-acylation product **531m** from substrate **523m** (scheme 129).



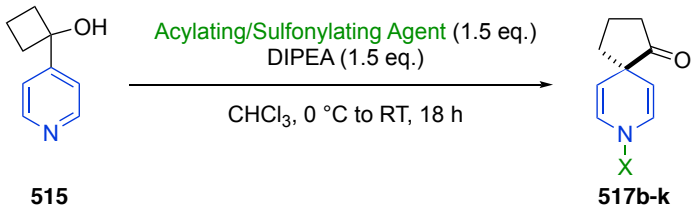
523m | **524m** *not observed* | **531m** 85%

Scheme 129: Reaction of substrate **523m** at 110 °C giving *O*-acylation product **531m**

5.3.5 Scope of acylating and sulfonylating agents

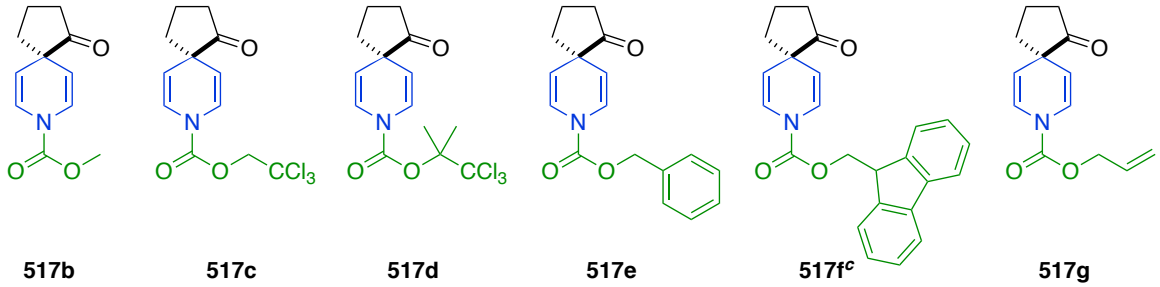
The scope of acylating agents (previously screened with fluorine-labelled substrate **518** in section 5.3.2) was revisited with the simplest hydroxycyclobutylpyridine substrate **515** (table 20).

Table 20: Scope of acylating and sulfonylating agents



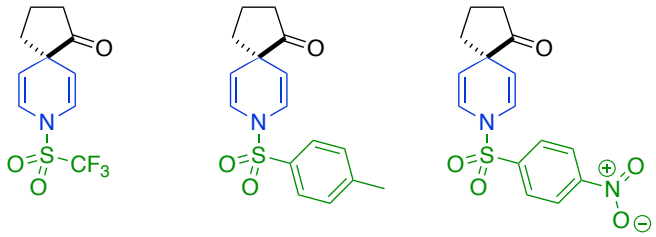
515 **517b-k**

Chloroformates:



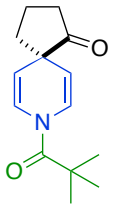
517b	**517c**	**517d**	**517e**	**517f**[c]	**517g**
57%[a] (60%)[b]	52% (60%)	93% (93%)	71% (71%)	74% (-%)	68% (73%)
O-acylation: 27% (28%)	*O-acylation:* 23% (28%)	*O-acylation:* Not observed	*O-acylation:* 16% (17%)	*O-acylation:* Not Observed	*O-acylation:* 9% (13%)

Sulfonic anhydrides/sulfonyl chlorides:



517h	**517i**	**517j**
78% (100%)	66% (75%)	35% (33%)

Acyl chlorides:



517k
35% (35%)

a: isolated yield; *b*: ^{1}H NMR yield of crude with dibromomethane internal standard
c: 2 equivalents of Fmoc-Cl and DIPEA were used

5.3.5.1 Chloroformates

The reaction worked well for a variety of chloroformates. Chloroform was found to be a superior solvent to acetonitrile for these reactions (in contrast with the result for the less reactive Boc anhydride), with 1.5 equivalents of diisopropylethylamine (DIPEA) present to 'mop up' the hydrochloric acid by-product of the reaction. For the less sterically bulky methyl chloroformate and 2,2,2-trichloroethyl chloroformate the *O*-acylation pathway was competitive with the desired spirocyclisation pathway. This resulted in a mixture of spirocycle (**517b** and **c**, table 20) and *O*-acylation

products (**532b** and **c**, not shown in table) in the crude in approximate 2:1 ratios. The spirocycle products **517b** and **517c** were isolated in 57% and 52% yield respectively. The *O*-acylation pathway competed to a lesser extent for benzyl and allyl chloroformate, with the desired spirocycle products **517e** and **517g** obtained in good yields around 70%. The reaction with the more sterically bulky 9*H*-fluorenylmethyl chloroformate (Fmoc-Cl) proceeded without any competing *O*-acylation, the spirocyclic product **517f** obtained in a 74% yield (with 2 equivalents of Fmoc-Cl and DIPEA). Finally, product **517d** was obtained in an excellent 93% yield without any competing *O*-acylation when 1,1-dimethyl-2,2,2-trichloroethyl chloroformate was used as the acylating agent.

5.3.5.2 Sulfonylating agents

Trifluoromethanesulfonic anhydride (Tf_2O), added as a commercially available 1 M solution in dichloromethane, was found to give full conversion of the hydroxycyclobutylpyridine starting material to the desired dihydropyridine product **517h** without any competing *O*-acylation after 18 h at room temperature in chloroform. As with the chloroformates, 1.5 equivalents of Hünig's base (DIPEA) was included to 'mop up' the trifluoromethanesulfonic acid by-product. The product was subsequently isolated in 78% yield.

The reaction was also performed with toluenesulfonyl chloride (tosyl chloridel) and 4-nitrophenylsulfonyl chloride (nosyl chloride) under the same conditions, with the sulfonyl chlorides added in solution in chloroform. Product **517i** was isolated in 66% yield (with 75% conversion of starting material to **517i** determined by NMR integral analysis of the crude with dibromomethane internal standard) when tosyl chloride was used as the sulfonylating agent. Nosyl chloride was found to be only sparingly soluble in chloroform. This led to a smaller amount being added to the reaction than needed, which was reflected in a low (35%) conversion and yield of **517j**.

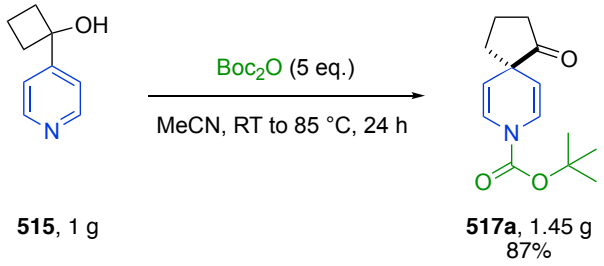
5.3.5.3 Acyl chlorides

Trifluoroacetic anhydride (TFAA) had been found to give exclusively *O*-acylation in the acylating agent screen in section 5.3.2. Similarly, benzoyl chloride was found to also favour this pathway, with no dihydropyridine product observed from the reaction in chloroform at ambient temperature or heating to 65 °C.

The more sterically bulky pivaloyl chloride gave no conversion of the starting material to either the *O*-acylation or ring expansion products at ambient temperature. After 18 h at 65 °C, a 35% yield of dihydropyridine spirocycle product **517k** was obtained. In contrast to TFAA and benzoyl chloride there was no *O*-acylation at either RT or 65 °C.

5.3.6 Gram-scale reaction

To demonstrate the scalability of this chemistry, a gram-scale reaction was performed with hydroxycyclobutylpyridine **515** and Boc anhydride (scheme 130). This constituted a 27-fold scale-up of the 0.25 mmol scale reaction performed in the optimisation/scope, which had a 96% yield.



515, 1 g

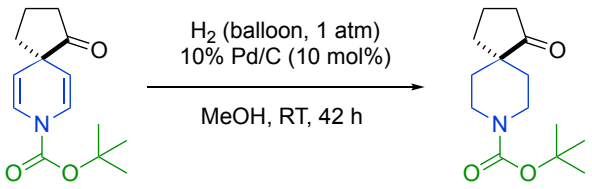
517a, 1.45 g
87%

Scheme 130: Gram-scale synthesis of dihydropyridine spirocycle **517a**

Product **517a** was isolated in 87% yield from the gram-scale reaction. Although slightly lower than the 96% yield obtained for the small-scale reaction, the yield is still very high, demonstrating that the chemistry is scalable.

5.3.7 Hydrogenation of product 517a[n]

As discussed in section 5.1.1, piperidines are important moieties in drug molecules. The reduction of dihydropyridines to piperidines using hydrogen gas over a heterogenous palladium on carbon catalyst in methanol is well established.[224] Application of conditions reported by Liu and co-workers[224] to the dihydropyridine product **517a** from the gram-scale reaction yielded the reduced piperidine product **533** in 89% yield (scheme 131).



517a

533, 89%

Scheme 131: Reduction of **517a** to piperidine spirocycle **533**

5.4 Conclusions and future Work

5.4.1 Semi-pinacol rearrangement of 4(1'hydroxycyclobutyl)pyridines and quinolines

In summary, an operationally simple synthesis of 8-azaspiro[4.5]deca-6,9-diene spirocycles (dihydropyridine spirocycles) by an acylating agent-triggered semi-pinacol rearrangement of 4-(1'-hydroxycyclobutyl)pyridines has been developed. The 4-(1'-hydroxycyclobutyl)pyridine

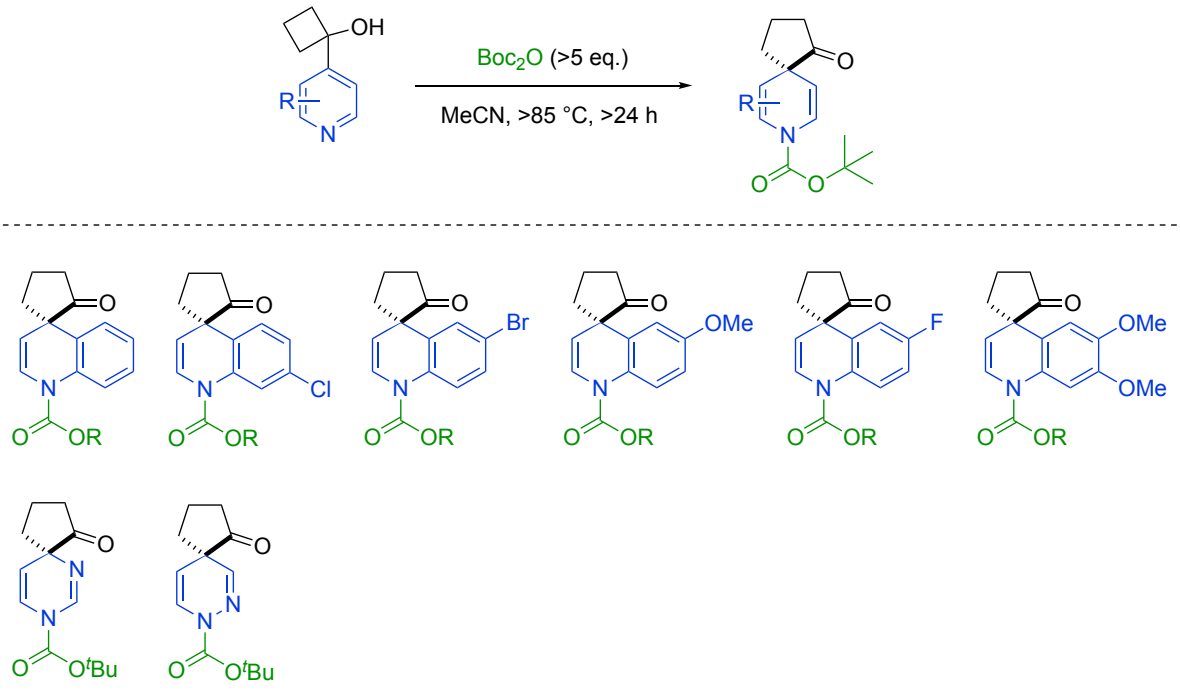
[n] Performed by Dr. Christian Bold.

substrates are readily accessed by lithiation of pyridines and trapping with cyclobutanone. The semi-pinacol rearrangement was found to be successfully triggered by *N*-acylation of the pyridine with a variety of chloroformates, sulfonylating agents and Boc anhydride. It was found that steric bulk on the acylating agent can help minimise a competing pathway in which the tertiary alcohol is directly *O*-acylated.

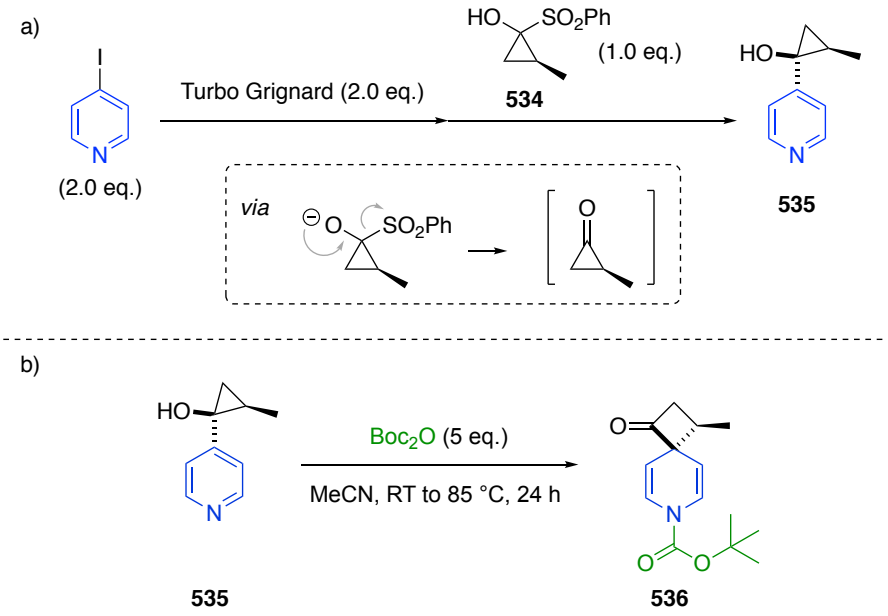
The scope of this protocol with Boc anhydride as the acylating agent was extended to a variety of substituted pyridines and quinolines, in addition to the expansion of different aliphatic cycloalkanol rings and rings containing heteroatoms. The competing *O*-acylation pathway was found to dominate for some substrates bearing bulky or electron withdrawing groups in proximity to the pyridine nitrogen. Furthermore, the reaction was found to be very slow for quinolines and substrates bearing substituents at the C2 position of the pyridine ring due to the steric hinderance of the pyridine nitrogen. Boc anhydride slowly decomposes under the reaction conditions (in acetonitrile at 85 °C), and so the addition of more equivalents of Boc anhydride as the reaction progresses is required to ensure conversion of the starting material over longer reaction times.

Some re-optimisation for these challenging substrates is required to ensure full conversion of starting material and improved yields. The scope of the reaction should be extended further to more examples of substituted pyridines and quinolines (table 21). The reaction could be further extended to 4-(1'-hydroxycyclobutyl)pyrimidines and 4-(1'-hydroxycyclobutyl)pyrazines (table 21, bottom row).

Table 21: Projected further scope of quinolines and other heterocycles



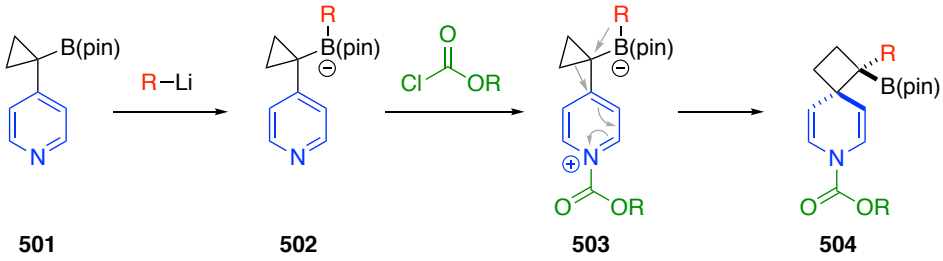
The enantiospecificity of the migration could be demonstrated using the 2-methyl-1-(4'-pyridyl)-cyclopropan-1-ol substrate **535**, generated from the chiral 1-hydroxy-2-methylcyclopropyl phenyl sulfone reagent **534** described by Poteat and co-workers (scheme 132, a and b).[220,221] This would showcase the capability of this methodology for generating enantoenriched spirocycles.



Scheme 132: a) Proposed synthesis of substrate **535**, b) Proposed enantiospecific synthesis of spirocycle **536**

5.4.2 Ring expansion of pyridylcyclopropyl boron-ate complexes

It was proposed that *N*-acylation of pyridylcyclopropylboron-ate complexes would trigger expansion of the cyclopropane ring and a 1,2-metallate rearrangement to form spirocyclic dihydropyridine-cyclobutyl boronic esters (**504**, scheme 133).



Scheme 133: Proposed dearomative spirocycle formation with ring-expansion-induced 1,2-metallate rearrangement

Unfortunately, the pyridylcyclopropylboronic ester starting material **501** was found to be unstable with respect to protodeboronation, particularly during attempted purification by column chromatography on silica or neutral/basic alumina.

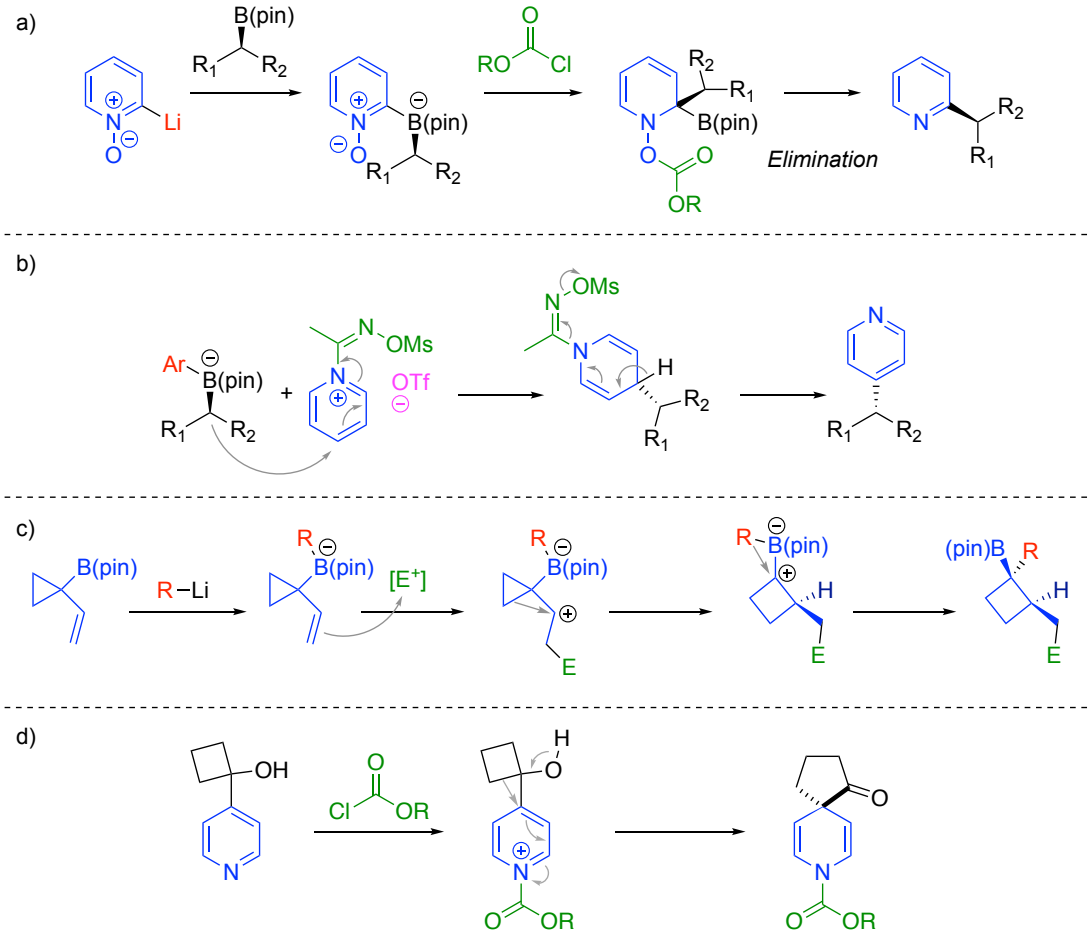
Limited attempts at an alternative approach in which 4-cyclopropylpyridine is lithiated at the benzylic position and trapped with a boronic ester to generate the boron-ate complex **502** were also unsuccessful, with lithiation at the kinetic C2 position of the pyridine found to dominate without any

benzylic lithiation when lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide were used as the organolithium base.

Further screening of organolithium bases and solvents should be undertaken to find appropriate lithiation conditions for benzylic lithiation of 4-cyclopropylpyridine, before applying these to boron-ate complex formation and the envisioned reaction protocol in scheme 133. Alternatively, finding a suitable method for purifying the pyridylcyclopropyl boronic ester starting material **501** (such as recrystallisation from the crude residue) could also enable the potential of this project to be further explored.

6 Summary and conclusions

This thesis has detailed investigations into sp^2-sp^3 cross-couplings of pyridines with boronic esters, the ring-expansion induced 1,2-metallate rearrangement of vinylcyclopropylboronic esters to generate cyclobutanes and the dearomative semi-pinacol rearrangement of hydroxycyclobutylpyridines to form dihydropyridine spirocycles. The reaction pathways discussed are summarised in scheme 134 below.



Scheme 134: a) Proposed stereoretentive C2 cross-coupling of pyridines with boronic esters, b) Stereoinvertive addition of boron-ate nucleophiles to activated pyridinium electrophiles, c) Synthesis of cyclobutyl boronic esters by a ring-expansion induced 1,2-metallate rearrangement of vinylcyclopropyl boron-ate complexes, d) Synthesis of dihydropyridine spirocycles by an electrophile-induced dearomative semi-pinacol rearrangement of hydroxycyclobutylpyridines

Firstly, investigations into achieving C2 cross-coupling to pyridines were undertaken (scheme 134, a). It was proposed that an electrophile-promoted 1,2-metallate rearrangement of boron-ate complexes generated by trapping boronic esters with *ortho*-metallated pyridine *N*-oxides, followed by a rearomative elimination, could achieve this cross-coupling. Unfortunately, reversibility of formation of the boron-ate complex was found to result in direct reaction of the metallated pyridine *N*-oxide with electrophiles. This resulted in a lack of success for the cross-coupling protocol.

Second, a steroinvertive cross-coupling of boronic esters with pyridines was explored, by addition of boron-ate nucleophiles (generated by treatment of secondary benzylic boronic esters with

phenyllithium) to pyridinium electrophiles generated by treatment of pyridines with an aldehyde oxime activating agent (scheme 134, b). The activating agent used would subsequently act as a leaving group in a rearomative elimination. A solvent switch to chloroform following formation of the dihydropyridine intermediate in a combination of tetrahydrofuran and acetonitrile was found to be key for inducing the re-aromatisation to the desired pyridine product. Difficulty purifying activated pyridinium species led to trying the reaction with an alternative protocol in which the activated pyridinium species is generated *in situ* before adding the boron-ate nucleophile. However, this had a lower yield than the earlier, more limited, protocol utilised. Further optimisation of this reaction could render it a feasible method of cross-coupling benzylic boronic esters to pyridines.

Thirdly, an electrophile-induced ring expansion of vinylcyclopropyl boron-ate complexes giving substituted cyclobutyl boronic ester products (scheme 134, c) was successfully extended to vinylcyclopropyl boronic ester substrates bearing a *trans*- β- substituent on the alkene moiety. This was found to proceed with high diastereoselectivity for a variety of *trans*- β- substituents. This high diastereoselectivity was attributed to concomitant ring expansion and 1,2-metallate rearrangement with a preferred *anti*-, *anti*-, *syn*-periplanar relationship of migrating groups and recipient electrophile. A competing elimination/allylation reaction was found to dominate when ring expansion was attempted with α-substituted or β,β- disubstituted vinylcyclopropylboronic ester substrates in addition to furylcyclopropylboronic ester and vinylcyclobutylboronic ester. Attempts to extend this reaction pathway to the synthesis of dihydropyridine spirocycles by electrophilic activation of the pyridine nitrogen atom of pyridylcyclopropyl boron-ate complexes were unsuccessful due to a lack of stability of the boronic ester starting material to protodeboronation.

Finally, the synthesis of dihydropyridine spirocycles was achieved by an electrophile-induced dearomative semi-pinacol rearrangement of hydroxycyclobutylpyridines (scheme 134, d). The proposed pathway was enacted with a variety of chloroformates and Boc anhydride. The use of sterically bulky acylating agents was found to minimise a competing direct *O*-acylation of the tertiary alcohol moiety. The scope of the reaction with various hydroxycycloalkylpyridines and quinolines was explored with Boc anhydride. The reaction was found to work well for expansion of 3-, 4- and 5-membered rings in addition to 4-membered rings containing heteroatoms. The reaction also tolerated substitution at the C3 position of the pyridine ring, however bulky or electron withdrawing C2 substituents led to the competing *O*-acylation pathway being favoured. Further optimisation of the reaction for hydroxycyclobutylquinolines is needed to ensure conversion of the starting material to spirocycle products, and the scope of quinolines explored for the reaction.

7 Experimental

7.1 General directions

Unless otherwise stated, all reactions were conducted under an inert atmosphere of nitrogen in flame-dried glassware using standard Schlenk techniques. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe into the reaction vessels through rubber septa. Unless otherwise specified, all reagents were purchased at highest commercial quality and used as received. Non-anhydrous solvents were purchased (unless specified) at the highest commercial quality and used as received. Anhydrous DMF, 1,2-dichloroethane and pyridine were purchased from Acros and used as received. CH_2Cl_2 and THF were dried on an Anhydrous Engineering alumina column drying system. Temperatures described below −10 °C were achieved using Thermo Fisher Scientific EK-90 or Huber TC100E cryostats or appropriate solvent/dry ice baths.

7.1.1 Analytical directions

Chromatography: Flash column chromatography was carried out using Sigma-Aldrich silica gel (60 Å, 230-400 mesh, 40-63 µm) or a Biotage Isolera^{TM} flash purification system. Reactions were followed by thin-layer chromatography (TLC) where practical, using aluminium-backed Merck Kieselgel 60 F_{254} fluorescent treated silica gel plates, which were visualised under UV light or by staining with aqueous basic potassium permanganate, acidic p-anisaldehyde solution in ethanol, or phosphomolybdic acid solution in ethanol.

NMR yields: ^{1}H NMR: Following work up, 1,1-dibromomethane or 1,3,5-trimethoxybenzene (1 eq. relative to limiting SM) was added to the crude residue. The resultant mixture was dissolved in $CDCl_3$ (5 mL), and a 0.6 mL sample of the resultant solution taken for ^{1}H NMR analysis. Yields were calculated based on the integrals of known product resonances relative to the 1,1-dibromomethane resonance at 4.9 ppm in $CDCl_3$ (2H) or the 1,3,5-trimethoxybenzene resonance at 3.77 ppm in $CDCl_3$ (9H). **^{19}F NMR:** 4-fluorotoluene (1 eq. with respect to the limiting SM) was added to reaction mixtures as a 1 M solution in the reaction solvent (prepared by diluting 5 mmol of 4-fluorotoluene in the reaction solvent in a 5 mL volumetric flask). Yields calculated by integrals of product resonances relative to the 4-fluorotoluene reference (typically around -119 ppm in externally referenced ^{19}F NMR spectra).

IR: IR spectra were recorded on neat compounds using a Perkin Elmer (Spectrum One) FT-IR spectrometer (ATR sampling accessory). Selected absorbances (ν_{max}, expressed in cm^{-1}) are reported and denoted br. (broad), w. (weak), m. (medium) or s. (strong).

^{1}H NMR: Spectra were recorded on Jeol ECS (400 MHz), Jeol ECZ (400 MHz) or Bruker Avance (400 MHz or 500 MHz) instruments. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to

the appropriate NMR solvent peak(s) and are assigned in accordance with numbered diagrams; with resonances described as s (singlets), d (doublets), t (triplets), q (quartets), p (pentets), combinations thereof (i.e. td indicates a triplet of doublets) or m (multiplets). 2D NMR experiments COSY, DEPT-edited HSQC and HMBC were used where necessary in assigning NMR spectra. Spin-spin coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.5 Hz.

^{13}C NMR: Spectra were recorded on a Bruker Avance (101 MHz or 126 MHz) instrument. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s) and are assigned in accordance with numbered diagrams. 2D NMR experiments COSY, DEPT-edited HSQC and HMBC were used where necessary in assigning NMR spectra.

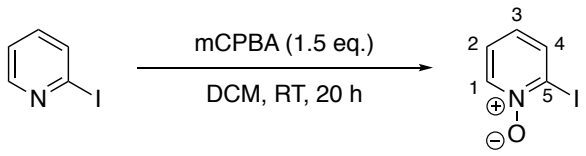
HRMS: High resolution mass spectra were recorded on a Bruker Daltronics MicroTOF II (ESI), Thermo Scientific Orbitrap (ESI, APCI) or Thermo Scientific QExactive (EI). Only molecular ion ($[M+H]^+$ or $[M+Na]^+$ for ESI and APCI; M^+ for EI) peaks are reported.

Naming of Compounds: Compound names are those generated by ChemBioDraw 16.0 or 20.0 software (PerkinElmer), following IUPAC nomenclature.

7.2 Experimental details for chapter 2

7.2.1 Synthesis of pyridine *N*-oxides

7.2.1.1 2-Iodopyridine *N*-oxide (201)



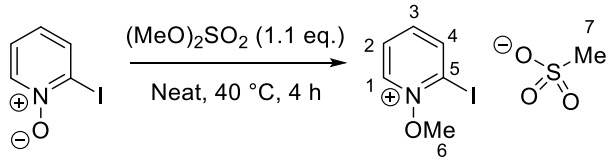
Synthesised using literature procedure.[137]

To a stirring solution of 2-iodopyridine (1.1 g, 5 mmol, 1 eq.) in DCM (25 mL) was added 3-chloroperoxybenzoic acid (77% purity, 1.68 g, 7.5 mmol, 1.5 eq.) in one portion. The reaction mixture was stirred for 16 h at RT. A saturated aqueous Na_2CO_3 solution (10 mL) was added until the resulting mixture became basic. The aqueous layer was extracted with DCM (2 × 20 mL) and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was washed with Et_2O to give the product as an off-white solid (22%, 238 mg, 1.1 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, 1H, J = 8.0 Hz, C_1H), 7.83 (d, 1H, J = 8.0 Hz, C_4H), 7.21 (t, 1H, J = 8.0 Hz, C_3H), 6.89 (t, 1H, J = 8.0 Hz, C_2H)

^{1}H NMR data matches literature.[225]

7.2.1.2 *N*-Methoxy 2-iodopyridinium methylsulfate (205)



Synthesised according to literature procedure.[139]

A 10-mL round-bottomed flask fitted with a rubber septum was charged with 2-iodopyridine *N*-oxide (116 mg, 0.525 mmol, 1 eq.). The reaction vessel was evacuated and refilled using a balloon of argon. This process was repeated twice and the reaction vessel was cooled to 0 °C. Dimethylsulfate (55 µL, 0.58 mmol, 1.1 eq.) was added to the reaction vessel dropwise over a period of 5 min. The reaction vessel was placed in an oil bath that had been preheated to 40 °C. The reaction mixture was stirred for 4 h at 40 °C. The product mixture was concentrated on high vacuum overnight to afford *N*-methoxy 2-iodopyridinium methylsulfate as a thick brown gum (99%, 183 mg, 0.52 mmol).

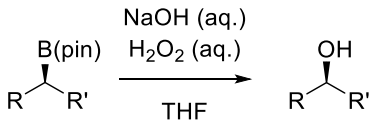
^{1}H NMR (400 MHz, CD_3OD) δ 9.50 (d, 1H, J = 8.0 Hz, C_1H), 8.66 (d, 1H, J = 8.0 Hz, C_4H), 8.19 (t, 1H, J = 8.0 Hz, C_2H), 8.14 (t, 1H, J = 8.0 Hz, C_3H), 4.44 (s, 3H, C_6H), 3.67 (s, 3H, C_7H)

^{1}H NMR data matches literature.[139]

7.3 Experimental details for Chapter 3

7.3.1 General procedures

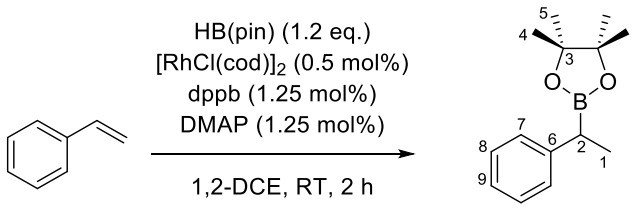
7.3.1.1 GP1: Oxidation of boronic esters to alcohols



To a solution of boronic ester (30 mg) in THF (1 mL) were added ice-cold aqueous solutions of NaOH (2 M, 0.5 mL) and H_2O_2 (30%, 0.5 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to RT and vigorously stirred for 1 – 16 h. The reaction mixture was diluted with water (5 mL) and extracted with ether (4 x 10 mL). Combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography to yield the alcohol.

7.3.2 Synthesis of boronic esters

7.3.2.1 (±)-3,3,4,4-Tetramethyl-1-(1-phenylethyl)borolane (301)



Adapted literature procedures.[226,227]

To a solution of $[RhCl(cod)]_2$ (50 mg, 0.1 mmol, 0.5 mol%), dppb (104 mg, 0.25 mmol, 1.25 mol%) and DMAP (30 mg, 0.25 mmol, 1.25 mol%) in 1,2-dichloroethane (21 mL) was added styrene (3.8 mL, 40.6 mmol, 1 eq.) and pinacolborane (7.1 mL, 48.7 mmol, 1.2 eq.) at RT. The resulting solution was stirred at RT for 1.5 h, then filtered through a plug of silica gel with Et_2O (50 mL) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (24:1 Hexane/Et_2O) to give the boronic ester as a clear colourless oil (80% yield, 7.56 g, 32.6 mmol).

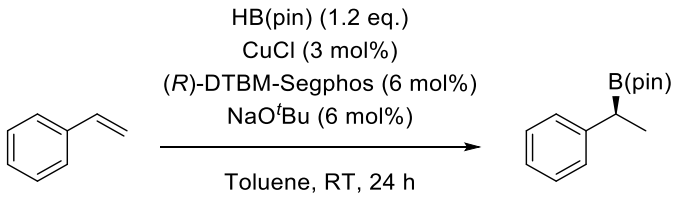
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 4H, ArH), 7.15 – 7.10 (m, 1H, C_9H), 2.43 (q, *J* = 7.5 Hz, 1H, C_2H), 1.33 (d, *J* = 7.5 Hz, 3H, C_1H), 1.21 (s, 6H, $C_{4/5}H$), 1.20 (s, 6H, $C_{4/5}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.12 (C_6), 128.42 (C_8), 127.92 (C_7), 125.20 (C_9), 83.41 (C_3), 24.78 ($C_{4/5}$), 24.74 ($C_{4/5}$), 17.19 (C_1)

ν_{max} /cm^{-1} (neat) 2977 (m.), 2931 (w.), 1451 (m.), 1378 (s.), 1353 (s.), 1319 (s.), 1142 (s.), 844 (m.)

HRMS m/z (ESI+) $C_{14}H_{21}BO_2Na$ $[M+Na]^+$ requires: 255.1529; found: 255.1530

7.3.2.2 (*S*)-3,3,4,4-Tetramethyl-1-(1-phenylethyl)borolane ((*S*)-301)



Adapted literature procedure.[228]

A mixture of CuCl (6 mg, 0.06 mmol, 3 mol%), NaOtBu (12 mg, 0.12 mmol, 6 mol%) and (*R*)-DTBM-Segphos (70.8 mg, 0.12 mmol, 3 mol%) in anhydrous toluene (0.8 mL) was stirred for 10 min in a Schlenk tube under N_2. Pinacolborane (0.36 mL, 2.4 mmol, 1.2 eq.) was added to the reaction mixture and stirred for 10 min at room temperature. Styrene (0.228 mL, 2.0 mmol, 1.0 eq.) was added, and the Schlenk flask was washed with further toluene (1.2 mL), sealed and stirred at RT, with progress

monitored by TLC. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The product was purified by flash column chromatography (24:1 Hexane:Et_2O) to give the boronic ester as a clear colourless oil (92% yield, 0.425 g, 1.83 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 4H), 7.15 – 7.09 (m, 1H), 2.43 (q, *J* = 7.5 Hz, 1H), 1.33 (d, *J* = 7.5 Hz, 3H), 1.21 (s, 6H), 1.20 (s, 6H)

^{1}H NMR data matches that of racemate (7.3.2.1).

HPLC:

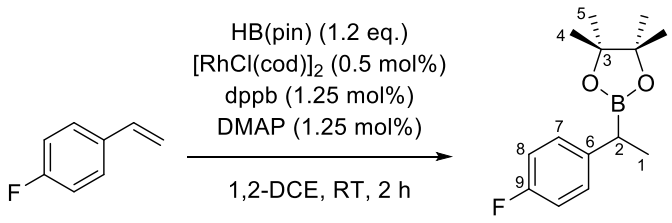
Boronic ester (30 mg) oxidised to alcohol according to **GP1** (Column conditions: 4:1 Hexane:Et_2O). Formation of 1-phenyl-ethanol confirmed by ^{1}H NMR matching literature.[229]

HPLC Separation Conditions (lit.[229]): ChiralCel OD-H, 0.5 mL min^{-1}, 95:5 Hexane:2-propanol

Retention times: 15.5 min (*minor*, (*R*)-(+)-enantiomer), 18.3 min (*major*, (*S*)-(-)-enantiomer)

er: 96:4

7.3.2.3 (±)-3,3,4,4-Tetramethyl-1-(1-(4-fluorophenyl)ethyl)borolane (307)



Adapted literature procedures.[226,227]

To a solution of $[RhCl(cod)]_2$ (9.9 mg, 0.02 mmol, 0.5 mol%), dppb (21.3 mg, 0.05 mmol, 1.25 mol%) and DMAP (6.1 mg, 0.05 mmol, 1.25 mol%) in 1,2-dichloroethane (3 mL) was added 4-fluorostyrene (0.5 mL, 4.0 mmol, 1 eq.) and pinacolborane (0.54 mL, 4.8 mmol, 1.2 eq.) at RT. The resulting solution was stirred at RT for 2 h, then filtered through a plug of silica gel with Et_2O (50 mL) and concentrated *in vacuo*. The product was purified by flash column chromatography (19:1 Pet. Ether/Et_2O) to give the boronic ester as a clear colourless oil (81% yield, 0.81 g, 3.24 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 2H, C_7H), 6.98 – 6.90 (tt, J = 9.0, 2.5 Hz, 2H, ArH), 2.41 (q, J = 7.5 Hz, 1H, C_2H), 1.30 (d, J = 7.5 Hz, 3H, C_1H), 1.21 (s, 6H, $C_{4/5}H$), 1.20 (s, 6H, $C_{4/5}H$)

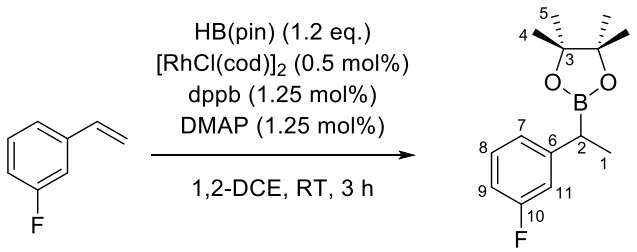
^{13}C NMR (101 MHz, $CDCl_3$) δ 129.2, 129.1, 115.2, 115.0, 83.5 (C_3), 24.8 ($C_{4/5}$), 24.7 ($C_{4/5}$), 17.4 (C_1)

^{19}F NMR (377 MHz, $CDCl_3$) δ -119.05 (tt, J = 9.0, 5.5 Hz)

ν_{max} /cm^{-1} (neat) 2978 (m.), 2932 (w.). 1508 (s.), 1322 (s.), 1219 (m.), 1142 (s.), 847 (m.)

Characterisation data matches literature.[230]

7.3.2.4 (±)-3,3,4,4-Tetramethyl-1-(1-(3-fluorophenyl)ethyl)borolane



Adapted literature procedures.[226,227]

To a solution of $[RhCl(cod)]_2$ (19.72 mg, 0.04 mmol, 0.5 mol%), dppb (42,6 mg, 0.1 mmol, 1.25 mol%) and DMAP (12.2 mg, 0.1 mmol, 1.25 mol%) in 1,2-dichloroethane (4 mL) was added 4-fluorostyrene (1.0 mL, 8.0 mmol, 1 eq.) and pinacolborane (1.1 mL, 9.6 mmol, 1.2 eq.) at RT. The resulting solution was stirred at RT for 3 h, then filtered through a plug of silica gel with Et_2O (50 mL) and concentrated *in vacuo*. The product was purified by flash column chromatography (19:1 Pentane/Et_2O) to give the boronic ester as a clear colourless oil (89% yield, 1,79 g, 7.1 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (ddd, J = 8.0, 8.0, 6.0 Hz, 1H, C_8H), 6.98 (d, J = 8.0 Hz, 1H, C_7H), 6.93 (ddd, J = 10.5, 2.0, 2.0 Hz, 1H, $C_{11}H$), 6.82 (ddd, J = 8.5, 8.5, 2.5 Hz, 1H, C_9H), 2.44 (q, J = 7.5 Hz, 1H, C_2H), 1.32 (d, J = 7.5 Hz, 3H, C_1H), 1.21 (s, 6H, $C_{4/5}H$), 1.20 (s, 6H, $C_{4/5}H$)

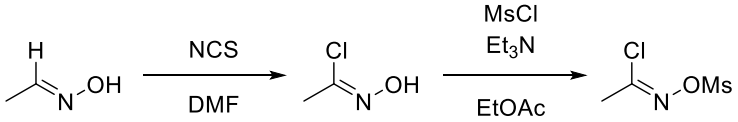
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (d, J = 244.5 Hz, C_{10}), 147.8 (d, J = 7.2 Hz, C_6), 129.7 (d, J = 8.4 Hz, C_8), 123.6 (d, J = 2.6 Hz, C_7), 114.7 (d, J = 21.1 Hz, C_{11}), 112.0 (d, J = 21.1 Hz, C_9), 83.6 (C_2), 24.8 ($C_{4/5}$), 24.7 ($C_{4/5}$), 16.9 (C_1)

^{19}F NMR (377 MHz, $CDCl_3$) δ -114.1 (ddd, J = 15.2, 9.0, 6.5 Hz)

NMR data matches literature.[230]

7.3.3 Synthesis of activated pyridines

7.3.3.1 (*Z*)-*N*-((Methylsulfonyl)oxy)acetimidoyl chloride ('activating agent') (305)



Prepared according to literature procedure.[119]

Acetaldehyde oxime (25.0 g, 423 mmol, 1.00 eq.) was dissolved in DMF (200 mL) at room temperature. *N*-chlorosuccinimide (59.3 g, 444 mmol, 1.05 eq.) was added as a solid in 5 portions over approximately 1 h. The addition rate was such that the internal temperature of the reaction was

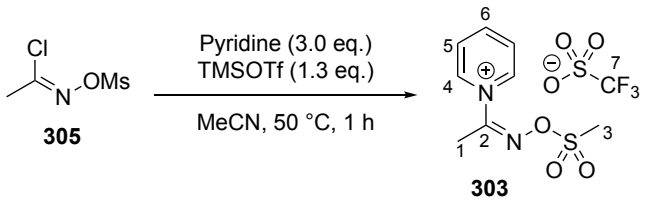
maintained between 25 °C and 50 °C. After complete addition, the reaction mixture was aged for 20 minutes, and then poured into EtOAc (500 mL). The mixture was washed with brine (2 x 150 mL), water (2 x 250 mL) and brine (1 x 150 mL). The organic solution was dried over $MgSO_4$ and concentrated *in vacuo* to approximately 100 mL (Note: extensive concentration was avoided due to the potential loss of the product). The mixture was transferred to a 3 L, 3-neck round bottom flask equipped with an overhead stirrer (note: overhead stirring is strongly encouraged for the 2nd step of this synthesis). The mixture was diluted with EtOAc (1.0 L) and cooled in an ice bath to 0-5 °C. Triethylamine (130 mL, 930 mmol, 2.2 eq.) was added *via* an addition funnel over approximately 10 minutes. During this time, a thick slurry is formed, which cannot be stirred efficiently with a stirrer bar. Methanesulfonyl chloride (36 mL, 470 mmol, 1.1 eq.) was added *via* syringe over approximately 20 minutes, maintaining an internal temperature below 10 °C. After complete addition, the white solid (Et_3N-HCl) was filtered away and rinsed with EtOAc. The filtrate was transferred to a separatory funnel and washed with water (2 x 400 mL) and brine (1 x 150 mL). The organic solution was dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was mixed well with heptane to afford a solid suspension. The solid was collected and washed twice with heptane and dried to afford a pale yellow crystalline solid (23.4 g, 137 mmol, 32% overall yield).

^{1}H NMR (400 MHz, CD_3CN) δ 3.21 (s, 3H), 2.41 (s, 3H)

^{13}C NMR (101 MHz, CD_3CN) δ 149.8, 37.3, 23.9

NMR data matches literature.[119]

7.3.3.2 (*Z*)-1-(1-(((Methylsulfonyl)oxy)imino)ethyl)pyridine-1-ium triflate (303)



Prepared according to unpublished procedure by Fier.

'Pyridine activator' **305** (1.00 g, 5.83 mmol, 1 eq.) was dissolved in MeCN (3 mL) in a flame dried Schlenk tube under N_2. Pyridine (1.38 g, 1.41 mL, 17.48 mmol, 3 eq.) was added followed by TMSOTf (1.68 g, 1.37 mL, 7.78 mmol, 1.3 eq.) dropwise at RT. The reaction mixture was then heated to 50 °C and stirred for 1 h. The solvent was then removed under reduced pressure to give a red oil. This was mixed thoroughly with TBME (30 mL) to form a red-brown aggregate which was filtered and washed with TBME (2 x 20mL) and THF (5 x 20mL) to give the activated pyridine salt **303** as a crystalline beige solid (50% yield, 1.07 g, 2.93 mmol).

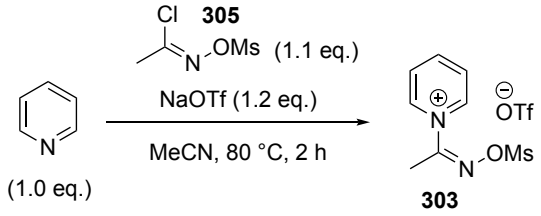
^{1}H NMR (400 MHz, DMSO) δ 9.32 (m, 2H, C_4H), 8.90 (tt, *J* = 8.0, 1.5 Hz, 1H, C_6H), 8.42 (m, 2H, C_5H), 3.50 (s, 3H, C_3H), 2.75 (s, 3H, C_1H)

^{13}C NMR (101 MHz, DMSO) δ 152.7 (C_2), 149.6 (C_4), 143.3 (C_6), 128.3 (C_5), 37.1 (C_3), 19.8 (C_1) *(C_7 not observed at sample concentration due to ^{19}F splitting)*

ν_{max} /cm^{-1} (neat) 3136 (w.), 3080 (w.), 1625 (m.), 1473 (m.), 1376 (s.), 1255 (s.), 1159 (s.), 1025 (s.)

HRMS m/z (ESI+) $C_8H_{11}N_2O_3S$ $[M+H]^+$ requires: 215.0485; found: 215.0493

7.3.3.3 (*Z*)-1-(1-(((Methylsulfonyl)oxy)imino)ethyl)pyridine-1-ium triflate (303)



Prepared according to modification of procedure by Fier.[119]

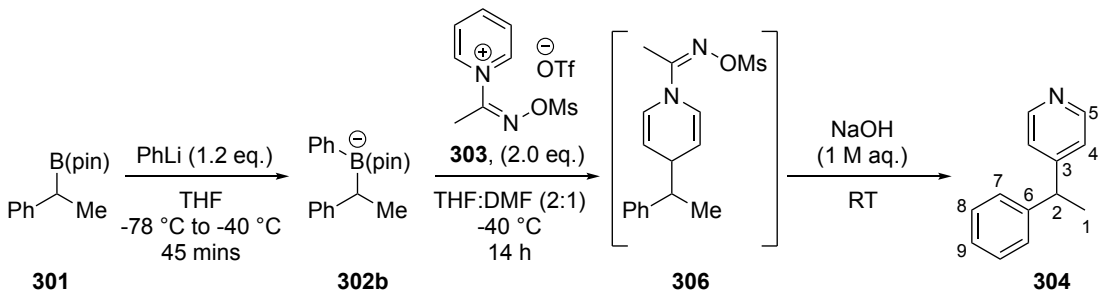
To a solution of activating agent **305** (0.6 g, 3.48 mmol, 1.1 eq.) and NaOTf (0.65 g, 3.8 mmol, 1.2 eq.) in MeCN (6 mL) was added pyridine (0.25 g, 0.25 mL, 3.15 mmol, 1.0 eq.). The reaction mixture was heated to 80 °C and stirred for 2 h. The precipitate formed during the reaction was filtered and washed with MeCN (2 x 10mL) and EtOAc (3 x 15 mL). The filtrate was concentrated *in vacuo* and Et_2O (20 mL) added. The resultant brown solid was washed with Et_2O (3 x 10 mL) and THF (3 x 20 mL) to give a beige solid, which was then rinsed with acetone (50 mL). Solvent was removed from the filtrate to give the activated pyridine as an off-white solid (65% Yield, 0.74 g, 2.05 mmol).

^{1}H NMR (400 MHz, DMSO) δ 9.32 (m, 2H), 8.90 (m, 1H), 8.42 (m, 2H), 3.50 (s, 3H), 2.75 (s, 3H)

^{1}H NMR matches that of activated pyridine produced by TMSOTf method (7.3.3.2).

7.3.4 Cross-couplings

7.3.4.1 (±)-4-(1-Phenylethyl)pyridine (304)



301 302b 306 304

To a solution of boronic ester **301** (46.4 mg, 0.20 mmol, 1.0 eq.) in THF (2 mL) was added phenyllithium (0.13 mL of commercial 1.9 M soln. in dibutyl ether, 2.4 mmol, 1.2 eq.) dropwise at -78 °C. The reaction

mixture was stirred for 30 min at -78 °C and 15 min at -40 °C to give the 'ate'-complex solution. Activated pyridine **303** (145.7 mg, 0.4 mmol, 2.0 eq.) dissolved in DMF (1 mL) was added dropwise. The mixture was stirred at -40 °C overnight. The reaction mixture was allowed to warm to RT and diluted with Et_2O (5 mL). Aqueous NaOH (1 M, 5 mL) was added and the resultant biphasic solution stirred for 5 minutes at RT. The reaction mixture was then extracted with Et_2O (4 x 10 mL) and washed with water (1 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (3% MeOH/DCM) to give the desired alkylated pyridine **304** as a yellow oil (14% yield, 5.1 mg, 0.03 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (m, 2H, C_5H), 7.35 – 7.28 (m, 2H, $C_{7/8}H$), 7.25 – 7.17 (m, 3H, $C_{7/8}H$, C_9H), 7.15 (m, 2H, C_4H), 4.12 (q, *J* = 7.0 Hz, 1H, C_2H), 1.64 (d, *J* = 7.0 Hz, 3H, C_1H)

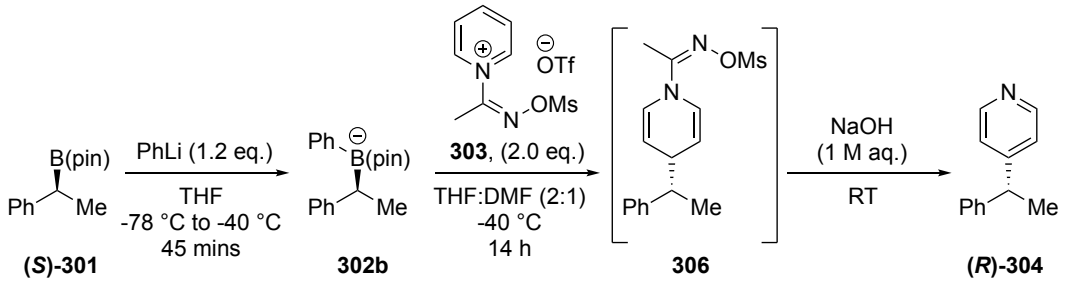
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 (C_3), 149.9 (C_5), 144.5 (C_6), 128.8 (C_8), 127.8 (C_7), 126.8 (C_9), 123.2 (C_4), 44.4 (C_2), 21.2 (C_1)

ν_{max} /cm^{-1} (neat) 3027 (w.), 2969 (w.), 1595 (s.), 1494 (m.), 1413 (m.), 700 (s.)

HRMS m/z (ESI+) $C_{13}H_{14}N$ $[M+H]^+$ requires: 184.1121; found: 184.1130

Characterisation data of product matches literature.[231]

7.3.4.2 (*R*)-4-(1-Phenylethyl)pyridine ((*R*)-304)



To a solution of boronic ester **(*S*)-301** (46.4 mg, 0.20 mmol, 1.0 eq.) in THF (2 mL) was added phenyllithium (0.13 mL of commercial 1.9 M soln. in dibutyl ether, 2.4 mmol, 1.2 eq.) dropwise at -78 °C. The reaction mixture was stirred for 30 min at -78 °C and 15 min at -40 °C to give the 'ate'-complex solution. Activated pyridine **303** (145.7 mg, 0.4 mmol, 2.0 eq.) dissolved in DMF (1 mL) was added dropwise. The mixture was stirred at -40 °C overnight. The reaction mixture was allowed to warm to RT and diluted with Et_2O (5 mL). Aqueous NaOH (1 M, 5 mL) was added and the resultant biphasic solution stirred for 5 minutes at RT. The reaction mixture was then extracted with Et_2O (4 x 10 mL) and washed with water (1 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography

(0 - 5 % MeOH/DCM) to give the desired alkylated pyridine **(*R*)-304** as a yellow oil (25% yield, 9.3 mg, 0.05 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (m, 2H), 7.35 – 7.29 (m, 2H), 7.26 – 7.18 (m, 3H), 7.15 (m, 2H), 4.12 (q, *J* = 7.0 Hz, 1H), 1.64 (d, *J* = 7.0 Hz, 3H)

^{1}H NMR matches that of racemate (7.3.4.1)

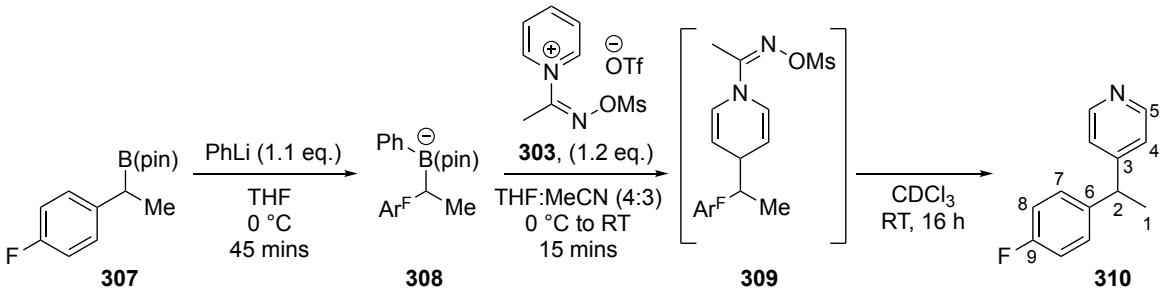
HPLC:

HPLC Separation conditions: ChiralPak AD-H, 1 mL min^{-1}, 95:5 Hexane:2-propanol

Retention times: 11.1 min (*minor*), 11.8 min (*major*)

er: 97:3; **ee:** 94%; **es:** 100%

7.3.4.3 4-(1-(4-Fluorophenyl)ethyl)pyridine (310)



To a solution of boronic ester **307** (50.0 mg, 0.20 mmol, 1.0 eq.) in THF (2 mL) was added phenyllithium (0.12 mL of commercial 1.9 M soln. in dibutyl ether, 2.2 mmol, 1.1 eq.) dropwise at -78 °C. The reaction mixture was stirred for 30 min at 0 °C to give the 'ate'-complex solution. Activated pyridine **303** (87.4 mg, 0.24 mmol, 1.2 eq.) dissolved in MeCN (1.5 mL) was added dropwise. The mixture was allowed to warm to RT and stirred for 20 minutes. Solvents were removed *in vacuo* and the reaction mixture taken up in $CDCl_3$ and stirred for 6 h. The reaction mixture was then extracted with Et_2O (4 x 10 mL) and washed with water (1 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (1% NEt_3/Et_2O) to give **310** as a yellow oil (54% yield, 21.6 mg, 0.11 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.5 Hz, 2H, C_5H), 7.17 – 7.08 (m, 4H, Ph-H), 7.03 – 6.95 (m, 2H, Ph-H), 4.10 (q, *J* = 7.0 Hz, 1H, C_2H), 1.62 (d, *J* = 7.0 Hz, 3H, C_1H)

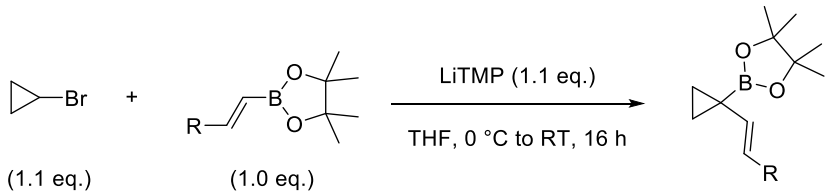
^{19}F NMR (377 MHz, $CDCl_3$) δ -116.3 (tt, *J* = 8.5, 5.5 Hz)

NMR of product matches literature.[232]

7.4 Experimental details for chapter 4

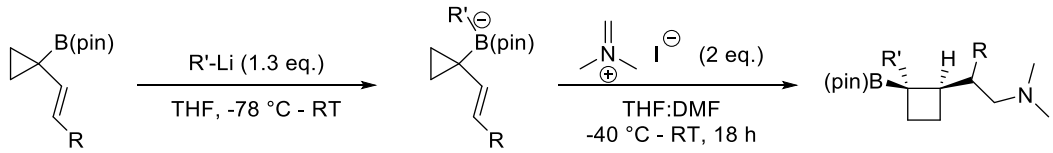
7.4.1 General procedures

7.4.1.1 GP1: Synthesis of cyclopropyl vinyl boronic esters



A solution of vinyl boronic ester (1.0 eq.) and cyclopropylbromide (1.1 eq.) in THF (0.4 M) was prepared and cooled to 0 °C. To this was added a freshly prepared solution of LiTMP (1.1 eq.) in THF (0.4 M) dropwise over 10 minutes. The reaction mixture was allowed to warm slowly to RT overnight, with progress monitored by TLC. Following completion, the reaction was quenched by addition of sat. $NaHCO_3$ (5 mL) and extracted with Et_2O (3 x 20 mL). The organic phases were combined, dried over $MgSO_4$ and solvent removed in vacuo. Crude residues were purified by flash column chromatography.

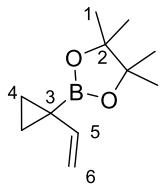
7.4.1.2 GP2: Synthesis of cyclobutanes



A solution of vinylcyclopropyl boronic ester **409a-k** (0.3 mmol, 1.0 eq.) in THF (2 mL) was prepared and cooled to -78 °C. Phenyllithium (0.39 mmol, 1.3 eq.) was added dropwise over 10 minutes, after which the reaction mixture was stirred for 1 h at -78 °C then 1 h at RT. The reaction mixture was diluted with DMF (2 mL) and cooled to -40 °C. Eschenmoser's salt (111 mg, 0.6 mmol, 2.0 eq.) was added in one portion and the reaction mixture stirred for 2 h at -40 °C before being allowed to warm slowly to RT overnight. After 18 h the reaction was quenched by addition of 0.5 M aqueous NaOH (20 mL). The mixture was extracted with Et_2O (3 x 20 mL), organic layers combined and washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and solvent removed *in vacuo*. Crude residues were purified by flash column chromatography.

7.4.2 Synthesis of vinylcyclopropyl boronic esters[o]

7.4.2.1 4,4,5,5-Tetramethyl-2-(1-vinylcyclopropyl)-1,3,2-dioxaborolane (404)[p]



Synthesised using **GP1** on a 5.0 mmol scale using 4,5,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (770 mg, 5.0 mmol, 1.0 eq.). Purified by flash column chromatography (10:1 Pentane/DCM) to give the product as a clear colourless liquid (72%, 704 mg, 3.63 mmol). Extensive exposure to vacuum was avoided due to concerns about product volatility.

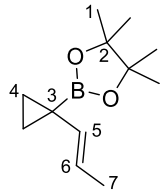
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dq, *J* = 17.5, 10.5 Hz, 1H, C_5H), 5.10 (dd, *J* = 17.5, 1.5 Hz, 1H, C_6H_a), 4.87 (dd, *J* = 10.5, 1.5 Hz, 1H, C_6H_b), 1.22 (s, 12H, C_1H), 0.99 – 0.90 (m 2H, C_4H_a), 0.72 – 0.62 (m, 2H, C_4H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (C_5), 111.6 (C_6), 83.1 (C_2), 24.7 (C_1), 14.0 (C_4)

vmax /cm^{-1} (neat) 2978 (s.), 2927 (m.), 1633 (m.), 1421 (m.), 1388 (s.), 1139 (s.), 854 (m.)

HRMS m/z (APCI) $C_{11}H_{20}O_2B$ $[M+H]^+$ requires: 195.1551; found: 195.1547

7.4.2.2 (*E*)-4,4,5,5-Tetramethyl-2-(1-(prop-1-en-1-yl)cyclopropyl)-1,3,2-dioxaborolane (409a)



Synthesised using **GP1** on a 2.5 mmol scale using (*E*)-4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane (420 mg, 2.5 mmol, 1.0 eq.). Purified by flash column chromatography (150:1 Pentane/Et_2O) to give the product as a clear colourless oil (56%, 289 mg, 1.4 mmol). Extensive exposure to vacuum was avoided due to concerns about product volatility.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (dq, *J* = 15.5, 6.5 Hz, 1H, C_6H), 5.37 (dd, *J* = 15.5, 6.5 Hz, 1H, C_5H), 1.63 (dd, *J* = 6.5, 1.5 Hz, 3H, C_7H), 1.22 (s, 12H), 0.88 (ddd, *J* = 3.5, 3.5, 3.5 Hz, 2H, C_4H_a), 0.60 (ddd, *J* = 3.5, 3.5, 3.5 Hz, 2H, C_4H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0 (C_5), 122.4 (C_6), 83.2 (C_2), 24.8 (C_1), 18.2 (C_7), 13.9 (C_4)

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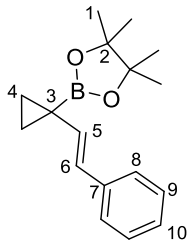
[o] Compounds **404** and **409a-h** were reported in the following paper: Durga Prasad Hari, Joseph C. Abell, Valerio Fasano and Varinder K. Aggarwal, *J. Am. Chem. Soc.* **2020**, 142, 5515-5520[193]

[p] Synthesised by Dr. Durga Hari

vmax /cm^{-1} (neat) 2979 (m.), 1730 (m.), 1372 (w.), 1321 (w.), 1140 (s.), 854 (w.)

HRMS m/z (EI) $C_{12}H_{21}O_2B$ $[M]^+$ requires: 208.1629; found: 208.1628

7.4.2.3 (*E*)-4,4,5,5-Tetramethyl-2-(1-styrylcyclopropyl)-1,3,2-dioxaborolane (409b)



Synthesised using **GP1** on a 2.5 mmol scale using (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (575 mg, 2.5 mmol, 1.0 eq.). Purified by flash column chromatography (150:1 Pentane/Et_2O) to give the product as a white solid (56%, 377 mg, 1.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H, C_8H), 7.29 – 7.22 (m, 2H, C_9H), 7.14 (tt, *J* = 7.0, 1.5 Hz, 1H, $C_{10}H$), 6.50 (d, *J* = 16.0 Hz, 1H, C_6H), 6.16 (d, *J* = 16.0 Hz, 1H, C_5H), 1.25 (s, 12H, C_1H), 1.06 (ddd, *J* = 3.5, 3.5, 3.5 Hz, 2H, C_4H_a), 0.80 (ddd, *J* = 3.5, 3.5, 3.5 Hz, 2H, C_4H_b)

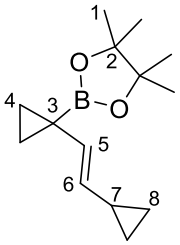
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5 (C_7), 135.4 (C_5), 128.5 (C_9), 127.1 (C_6), 126.5 (C_{10}), 125.9 (C_8), 83.4 (C_2), 24.9 (C_1), 14.9 (C_4)

vmax /cm^{-1} (neat) 2979 (m.), 2932 (w.), 1645 (w.), 1402 (m.), 1321 (m.), 1135 (s.), 967 (m.), 854 (m.), 744 (m.), 693 (m.)

HRMS m/z (EI) $C_{17}H_{23}O_2B$ $[M]^+$ requires: 270.1786; found: 270.1784

m.p./°C 45 – 50

7.4.2.4 (*E*)-2-(1-(2-Cyclopropylvinyl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (409c)



Synthesised using **GP1** on a 2.5 mmol scale using (*E*)-2-(2-cyclopropylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (485 mg, 2.5 mmol, 1.0 eq.). Purified by flash column chromatography (5-40% DCM/Pentane) to give the product as a clear colourless oil (49%, 286 mg, 1.21 mmol).

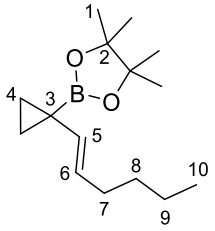
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (d, *J* = 15.5 Hz, 1H, C_5H), 5.03 (dd, *J* = 15.5, 8.5 Hz, 1H, C_6H), 1.38 – 1.27 (m, 1H, C_7H), 1.20 (s, 12H, C_1H), 0.87 (ddd, *J* = 3.5, 3.5, 3.5 Hz, 2H, C_4H_a), 0.62 (m, 2H, C_8H_a), 0.58 (ddd, *J* = 3.5, 3.5, 3.5 Hz, 2H, C_4H_b), 0.31 – 0.24 (m, 2H, C_8H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 131.8 (C_5), 131.3 (C_6), 83.15 (C_2), 24.8 (C_1), 14.1 (C_7), 13.9 (C_4), 6.6 (C_8)

vmax /cm^{-1} (neat) 2979 (m.), 1407 (m.), 1315 (m.), 1136 (s.), 967 (m.), 854 (m.), 682 (m.)

HRMS m/z (APCI) $C_{14}H_{23}O_2B$ $[M+H]^+$ requires: 235.1864; found: 235.1861

7.4.2.5 (*E*)-2-(1-(Hex-1-en-1-yl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (409d)



Synthesised using **GP1** on a 5.0 mmol scale using (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.05 g, 5.0 mmol, 1.0 eq.). Purified by flash column chromatography (1:10 DCM/Pentane) to give the product as a clear colourless oil (74%, 924 mg, 3.7 mmol).

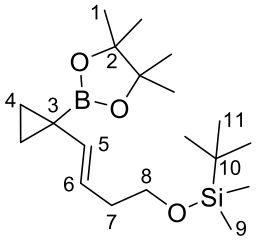
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (dt, *J* = 15.5, 6.5 Hz, 1H, C_6H), 5.38 (d, *J* = 15.5 Hz, 1H, C_5H), 2.01 – 1.87 (m, 2H, C_7H), 1.34 – 1.24 (m, 4H, $C_{8/9}H$), 1.22 (s, 12H, C_1H), 0.89 – 0.84 (m, 5H, C_4H_a, $C_{10}H$), 0.67 – 0.53 (m, 2H, C_4H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.6 (C_5), 127.7 (C_6), 83.0 (C_2), 32.4, 32.0, 24.7 (C_1), 22.2, 14.0, 14.0

vmax /cm^{-1} (neat) 2977 (m.), 2925 (m.), 1404 (m.), 1315 (m.), 1138 (s.), 967 (m.), 854 (w.)

HRMS m/z (ESI) $C_{15}H_{31}BNO_2^+$ $[M+NH_4]^+$ requires: 268.2445; found: 268.2437

7.4.2.6 (*E*)-*tert*-Butyldimethyl((4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)but-3-en-1-yl)oxy)silane (409e)



Synthesised using **GP1** on a 2.5 mmol scale using (*E*)-*tert*-butyldimethyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)oxy)silane (781 mg, 2.5 mmol, 1.0 eq.). Purified by flash column chromatography (10-100% DCM/Pet. Ether) to give the product as a clear colourless oil (60%, 646 mg, 1.8 mmol).

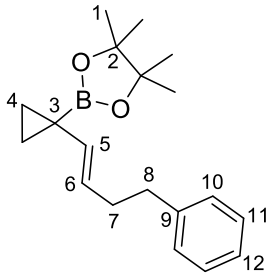
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (dt, *J* = 15.5, 7.0 Hz, 1H, C_6H), 5.40 (dt, *J* = 15.5, 1.0 Hz, 1H, C_5H), 3.58 (t, *J* = 7.0 Hz, 2H, C_8H), 2.19 (qd, *J* = 7.0, 1.0 Hz, 2H, C_7H), 1.21 (s, 12H, C_1H), 0.89 (s, 9H, $C_{11}H$), 0.89 (ddd, *J* = 3.5, 3.5, 3.5 Hz, 2H, C_4H_a) 0.60 (ddd, *J* = 3.5, 3.5, 3.5 Hz, C_4H_b), 0.04 (s, 6H, C_9H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2 (C_6), 123.9 (C_5), 83.2 (C_2), 63.6 (C_8), 36.6 (C_7), 26.1 (C_{11}), 24.8 (C_1), 18.5 (C_{10}), 14.2 (C_4), -5.06 (C_9)

vmax /cm^{-1} (neat) 2978 (s.), 2929 (s.), 1406 (s.), 1255 (m.), 1141 (s.), 1079 (s.), 835 (m.), 775 (m.)

HRMS m/z (APCI) $C_{19}H_{37}O_2BSi$ $[M+H]^+$ requires: 353.2678; found: 353.2670

7.4.2.7 (*E*)-4,4,5,5-Tetramethyl-2-(1-(4-phenylbut-1-en-1-yl)cyclopropyl)-1,3,2-dioxaborolane (409f)



Synthesised using **GP1** on a 2.5 mmol scale using (*E*)-4,4,5,5-tetramethyl-2-(4-phenylbut-1-en-1-yl)-1,3,2-dioxaborolane (645 mg, 2.5 mmol, 1.0 eq.). Purified by flash column chromatography (5-50% DCM/Pentane) to give the product as a clear colourless oil (61%, 452 mg, 1.51 mmol).

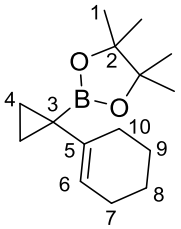
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H, $C_{10/11}H$), 7.20 – 7.14 (m, 3H, $C_{10/11}H$, $C_{12}H$), 5.55 (dt, *J* = 15.5, 6.5 Hz, 1H, C_6H), 5.42 (dt, *J* = 15.5, 1.5 Hz, 1H, C_5H), 2.68 – 2.61 (m, 2H, C_8H), 2.28 (dtd, *J* = 9.0, 6.5, 1.5 Hz, 2H, C_7H), 1.22 (s, 12H, C_1H), 0.89 (ddd, *J* = 3.5, 3.5, 3.5 Hz, 2H, C_4H_a), 0.59 (ddd, *J* = 3.5, 3.5, 3.5 Hz, 2H, C_4H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.51 (C_9), 134.59 (C_5), 128.66 ($C_{10/11}$), 128.32 ($C_{10/11}$), 126.95 (C_6), 125.74 (C_{12}), 83.20 (C_2), 36.45 (C_8), 34.78 (C_7), 24.82 (C_1), 14.14 (C_4)

vmax /cm^{-1} (neat) 2978 (w.), 2028 (w.), 1403 (m.), 1318 (m.), 1136 (s.), 967 (m.) 855 (m.), 746 (w.), 699 (m.)

HRMS m/z (APCI) $C_{19}H_{27}O_2B$ $[M+H]^+$ requires: 299.2177; found: 299.2174

7.4.2.8 2-(1-(Cyclohex-1-en-1-yl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (409g)



Synthesised using **GP1** on a 5.0 mmol scale using 2-(1-cyclohexenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.04 g, 5.0 mmol, 1.0 eq.). Purified by flash column chromatography (1:10 DCM/Pentane) to give the product as a colourless liquid (71%, 770 mg, 3.55 mmol).

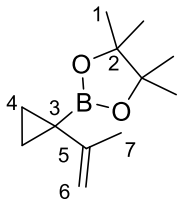
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (tt, *J* = 3.5, 1.5 Hz, 1H, C_6H), 2.07 – 2.02 (m, 2H, $C_{7/10}H$), 1.99 – 1.93 (m, 2H, $C_{7/10}H$), 1.63 – 1.56 (m, 2H, $C_{8/9}H$), 1.55 – 1.50 (m, 2H, $C_{8/9}H$), 1.20 (s, 12H, C_1H), 0.78 – 0.69 (m, 2H, C_4H_a), 0.61 – 0.51 (m, 2H, C_4H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (C_5), 120.2 (C_6), 82.9 (C_2), 29.1 ($C_{7/10}$), 25.2 ($C_{7/10}$), 24.6 (C_1), 23.3 ($C_{8/9}$), 22.7 ($C_{8/9}$), 11.0 (C_4)

vmax /cm^{-1} (neat) 2977 (m.), 2925 (m.), 1426 (m.), 1387 (s.), 1312 (m.), 1165 (m.), 1141 (s), 854 (m.)

HRMS m/z (APCI) $C_{15}H_{26}O_2B$ $[M+H]^+$ requires: 249.2020; found: 249.2010

7.4.2.9 4,4,5,5-Tetramethyl-2-(1-(prop-1-en-2-yl)cyclopropyl)-1,3,2-dioxaborolane (409h)



Synthesised using **GP1** on a 5.0 mmol scale using 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (840 mg, 5.0 mmol, 1.0 eq.). Purified by flash column chromatography (1:10 DCM/Pentane) to give the product as a white solid (82%, 852 mg, 4.09 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (p, *J* = 1.5 Hz, 1H, C_6H_a), 4.68 – 4.69 (m, 1H, C_6H_b), 1.83 – 1.80 (m, 3H, C_7H), 1.21 (s, 12H, C_1H), 0.86 – 0.77 (m, 2H, C_4H_a), 0.69 – 0.55 (m, 2H, C_4H_b)

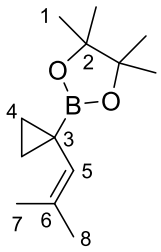
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6 (C_5), 109.7 (C_6), 83.1 (C_2), 24.6 (C_1), 23.0 (C_7), 11.7 (C_4)

vmax /cm^{-1} (neat) 2980 (s.), 1421 (m.), 1368 (s.), 1325 (s.), 1155 (m.), 1127 (s.), 1023 (m.), 885 (s.)

HRMS m/z (APCI) $C_{12}H_{22}O_2B$ $[M+H]^+$ requires: 209.1707; found: 209.1703

m.p./°C 39 – 44

7.4.2.10 4,4,5,5-Tetramethyl-2-(1-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,2-dioxaborolane (409i)



Synthesised using **GP1** on a 3.0 mmol scale using 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (546 mg, 3.0 mmol, 1.0 eq.). Purified by flash column chromatography (1:10 Et_2O/Pentane) to give the product as a colourless liquid (27%, 181 mg, 0.82 mmol).

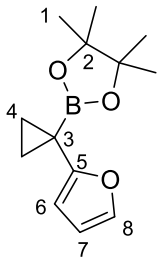
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H, C_5H), 1.67 (s, 6H, C_7H, C_8H), 1.20 (s, 12H, C_1H), 0.91 (q, J = 3.0 Hz, 2H, C_4H_a), 0.51 (q, J = 3.0 Hz, 2H, C_4H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (C_6), 128.0 (C_5), 83.1 (C_2), 25.5 ($C_{7/8}$), 24.7 (C_1), 19.3 ($C_{7/8}$), 14.5 (C_4)

vmax /cm^{-1} (neat) 2978 (w.), 1388 (m.), 1305 (m.), 1140 (s.), 968 (w.), 860 (m.), 683 (m.)

HRMS m/z (EI) $C_{13}H_{23}O_2B$ $[M]^+$ requires: 222.1786; found: 222.1787

7.4.2.11 2-(1-(Furan-2-yl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (409k)



Synthesised using **GP1** on a 2.75 mmol scale using 2-(furan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (534 mg, 2.75 mmol, 1.0 eq.). Purified by flash column chromatography (1-10% DCM/Pentane) to give the product as a low-melting white solid (24%, 157 mg, 0.66 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) 7.20 – 7.16 (m, 1H, C_8H), 6.27 – 6.22 (m, 2H, C_6H, C_7H), 1.27 – 1.21 (m, 12H, C_1H), 1.12 (t, J = 2.0 Hz, 2H, C_4H_a), 1.10 (t, J = 2.0 Hz, 2H, C_4H_b)

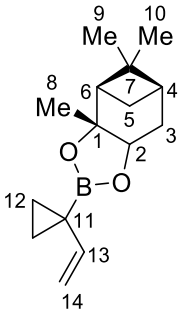
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (C_5), 139.8 (C_8), 110.4 ($C_{6/7}$), 105.0 ($C_{6/7}$), 83.6 (C_2), 24.8 (C_1), 13.9 (C_4)

vmax /cm^{-1} (neat) 2979 (w.), 1418 (m.), 1367 (m.), 1320 (m.), 1143 (s.), 1077 (m.), 1008 (w.), 864 (w.), 690 (w.)

HRMS m/z (EI) $C_{13}H_{19}O_2B$ $[M+H]^+$ requires: 234.1422; found: 234.1422

m.p. /°C 25 – 30

7.4.2.12 (3a*R*,4*R*,6*R*)-3a,5,5-Trimethyl-2-(1-vinylcyclopropyl)hexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborole (421)



Synthesised using **GP1** on a 2.43 mmol scale using (+)-vinylboronic acid pinanediol ester (500 mg, 2.43 mmol, 1.0 eq.). Purified by flash column chromatography (1-10% DCM/Pentane) to give the product as a colourless oil (70%, 419 mg, 1.7 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (dd, J = 17.5, 10.5 Hz, 1H, $C_{13}H$), 5.11 (dd, J = 17.5, 1.5 Hz, 1H, $C_{14}H_a$), 4.88 (dd, J = 10.5, 1.5 Hz, 1H, $C_{14}H_b$), 4.26 (dd, J = 8.5, 1.0 Hz, 1H, C_2H), 2.32 (ddt, J = 14.0, 9.0, 2.5 Hz, 1H, C_3H_a), 2.24 – 2.16 (m, 1H, C_5H_a), 2.03 (t, J = 5.5 Hz, 1H, C_6H), 1.90 (tt, J = 5.5, 3.0 Hz, 1H, C_4H), 1.87

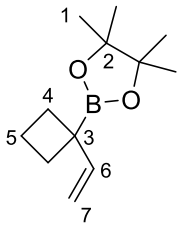
– 1.80 (m, 1H, C_3H_b), 1.36 (s, 3H, C_8H), 1.28 (s, 3H, C_9H), 1.13 (d, J = 11.0 Hz, 1H, C_5H_b), 0.99 – 0.93 (m, 2H, $C_{12}H_a$), 0.83 (s, 3H, $C_{10}H$), 0.74 – 0.65 (m, 2H, $C_{12}H_b$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6 (C_{13}), 111.9 (C_{14}), 85.7 (C_1), 78.1 (C_2), 51.5 (C_6), 39.6 (C_4), 38.3 (C_7), 35.8 (C_3), 28.7 (C_8), 27.2 (C_9), 26.6 (C_5), 24.1 (C_{10}), 14.4 (C_{12}), 14.1 ($C_{12'}$)

vmax /cm^{-1} (neat) 2978 (w.), 2928 (w.), 1428 (w.), 1388 (m.), 1306 (m.), 1140 (s.), 968 (w.), 860 (m.), 823 (w.), 683 (m.)

HRMS m/z (EI) $C_{15}H_{23}O_2B$ $[M]^+$ requires: 246.1786; found: 246.1787

7.4.2.13 4,4,5,5-Tetramethyl-2-(1-vinylcyclobutyl)-1,3,2-dioxaborolane (417)[q]



Synthesised according to literature protocol.[197]

Cyclobutyl-2,4,6-triisopropylbenzoate[r] (1.2 g, 4.0 mmol, 1.0 eq.) and TMEDA (0.80 mL, 5.2 mmol, 1.3 eq.) were dissolved in Et_2O (20 mL) in a Schlenk tube and cooled to -78 °C. *s*-BuLi (1.3M, 4.0 mL, 5.2 mmol, 1.3 eq.) was added dropwise at -78 °C over 20 minutes before stirring for 20 min at −78 °C. A solution of vinylboronic acid pinacol ester (2.04 mL, 12.0 mmol, 3.0 eq.) in Et_2O (12 mL) was then added dropwise over 20 minutes at -78 °C. After 20 min, the reaction was warmed to room temperature, solvent and volatiles removed *in vacuo* and $CHCl_3$ (40 mL) added. The resultant reaction mixture was heated to 60 °C and stirred overnight. The crude reaction mixture was filtered through a silica plug and washed with Et_2O (50 mL), before concentrating *in vacuo*. The crude residue/oil was distilled using a Kugelrohr at 90 °C at <10 mbar pressure (high vacuum) and then further purified by flash column chromatography (2-20% DCM/Pentane) to obtain the product as a colourless oil (19%, 159 mg, 0.77 mmol).

^{1}H NMR (400 MHz, $CDCl_3$)): δ 6.04 (dd, J = 17.5, 10.5 Hz, 1H, C_6H), 5.01 – 4.86 (m, 2H, C_7H), 2.28 – 2.16 (m, 2H, C_5H), 2.04 – 1.91 (m, 3H), 1.89 – 1.78 (m, 1H), 1.27 (s, 12H, C_1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 (C_6), 110.2 (C_7), 83.2 (C_2), 29.9 (C_4), 24.6 (C_1), 18.3 (C_5)

vmax /cm^{-1} (neat) 2975 (w.), 2932, 1473, 1453, 1371, 1327, 1145, 982, 860, 674

HRMS m/z (ESI) $C_{12}H_{22}O_2B$ $[M+H]^+$ requires: 209.1707; found: 209.1701

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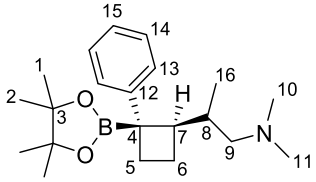
[q] Compound **417** was subsequently re-synthesized by Dr. Durga Hari and reported in the following publication: Durga Prasad Hari, Rudrakshula Madhavachary, Valerio Fasano, Jack Haire and Varinder K. Aggarwal, J. *Am. Chem. Soc.* **2021**, 143, 7462-7470[237]

[r] Cyclobutyl-2,4,6-triisopropylbenzoate was synthesised using the literature procedure.[197]

7.4.3 Synthesis of cyclobutanes[s]

7.4.3.1 *N,N*-Dimethyl-2-((1*r*,2*s*)-2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)propan-1-amine (411a)



Synthesised using **GP2** with **409a** on a 0.3 mmol scale. Purified by flash column chromatography (20:1 DCM/MeOH) to give the product as a white solid (57%, 59 mg, 0.17 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 2H), 7.15 – 7.06 (m, 3H), 2.54 – 2.38 (m, 2H), 2.45 (s, 6H, $C_{10/11}$H), 2.37 – 2.31 (m, 2H, C_9H), 2.10 – 1.96 (m, 2H, C_8H,), 1.94 – 1.75 (m, 2H), 1.23 (s, 6H, C_1H), 1.21 (s, 6H, C_2H), 1.19 (d, *J* = 6.5 Hz, 3H, C_{16}H)

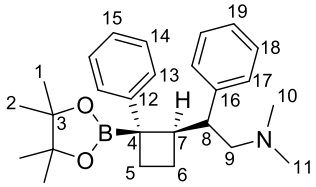
^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5 (C_{12}), 128.0 (C_{13} or C_{14}), 126.2 (C_{13} or C_{14}), 124.8 (C_{15}), 83.6 (C_3), 63.7 (C_9), 48.1 (C_7), 45.2 ($C_{10/11}$), 36.8 (C_8), 30.5 (C_5), 24.9 (C_1), 24.8 (C_2), 24.7 (C_6), 17.8 (C_{16})

vmax /cm^{-1} (neat) 2974 (m.), 1462 (w.), 1344 (m.), 1309 (m.), 1142 (s.), 846 (m.), 699 (s.)

HRMS m/z (ESI) $C_{21}H_{34}NO_2B$ $[M+H]^+$ requires: 344.2755; found: 344.2743

m.p./°C 57 – 62

7.4.3.2 (*s*)-*N,N*-Dimethyl-2-phenyl-2-((1*s*,2*r*)-2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)ethan-1-amine (411b)



Synthesised using **GP2** with **409b** on a 0.3 mmol scale. Purified by flash column chromatography (1-12% MeOH/DCM) to give the product as a white solid (54%, 45 mg, 0.11 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.17 (m, 5H), 6.91 – 6.85 (m, 3H), 6.30 – 6.24 (m, 2H), 3.48 (td, *J* = 11.0, 3.5 Hz, 1H, C_8H), 2.66 (t, J = 11.6 Hz, 1H), 2.54 (td, *J* = 10.5, 7.5 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.34 – 2.25 (m, 1H), 2.19 (s, 6H, $C_{10/11}$H), 2.16 – 1.95 (m, 3H), 1.28 (s, 12H, $C_{1/2}$H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5 (C_{12}), 143.4 (C_{16}), 128.8, 128.6, 127.5, 126.7, 126.5, 124.4, 83.4 (C_3), 62.6 (C_9), 52.3, 46.9 (C_8), 45.5, 28.4 (C_5), 25.0 (C_6), 24.9 ($C_{1/2}$)

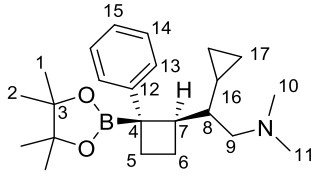
[s] Compounds **411a-g** were reported in the following paper: Durga Prasad Hari, Joseph C. Abell, Valerio Fasano and Varinder K. Aggarwal, *J. Am. Chem. Soc.* **2020**, 142, 5515-5520[193]

vmax /cm^{-1} (neat) 2974 (w.), 1348 (m.), 1143 (s.), 847 (w.), 698 (s.)

HRMS m/z (ESI) $C_{26}H_{36}NO_2B$ $[M+H]^+$ requires: 406.2912; found: 406.2900

m.p./°C 98 – 103

7.4.3.3 (*r*)-2-Cyclopropyl-*N*,*N*-dimethyl-2-((1*s*,2*r*)-2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)ethan-1-amine (411c)



Synthesised using **GP2** with **409c** on a 0.3 mmol scale. Purified by flash column chromatography (1:15 MeOH/DCM) to give the product as a colourless liquid (81%, 89.5 mg, 0.242 mmol).

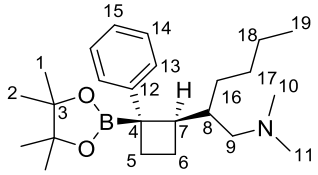
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H, ArH), 7.26 – 7.20 (m, 2H, ArH), 7.11 – 7.05 (m, 1H, ArH), 2.68 (td, *J* = 10.3, 8.5 Hz, 1H), 2.48 – 2.37 (m, 1H), 2.20 (s, 6H, $C_{10/11}H$), 2.15 – 2.05 (m, 2H), 2.04 – 1.91 (m, 2H), 1.88 – 1.81 (m, 1H), 1.64 – 1.57 (m, 1H), 1.24 (s, 6H, C_1H), 1.23 (s, 6H, C_2H), 0.71– 0.80 (m, 1H), 0.55 – 0.39 (m, 2H), 0.33 (tdd, *J* = 8.5, 5.5, 4.0 Hz, 1H), 0.19 (dtd, *J* = 9.5, 5.5, 4.0 Hz, 1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1 (C_{12}), 127.6, 126.5, 124.3, 83.1 (C_3), 62.0 ($C_{10/11}$), 48.4, 46.4, 43.1, 31.5, 25.1, 24.8, 24.4, 14.3, 3.9, 2.9

vmax /cm^{-1} (neat) 3075 (w.), 2974 (s.), 2940 (s.), 1459 (s.), 1370 (s.), 1143 (s.), 1020 (m.), 848 (w.)

HRMS m/z (ESI) $C_{23}H_{37}BNO_2$ $[M+H]^+$ requires: 370.2916; found: 370.2918

7.4.3.4 (*r*)-*N*,*N*-Dimethyl-2-((1*s*,2*r*)-2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)hexan-1-amine (411d)



Synthesised using **GP2** with **409d** on a 0.3 mmol scale. Purified by flash column chromatography (1:15 MeOH/DCM) to give the product as a colourless liquid (84%, 96.5 mg, 0.25 mmol).

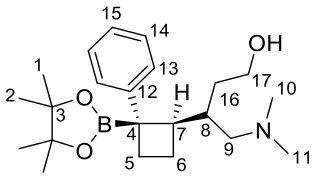
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 2H, ArH), 7.20 – 7.15 (m, 2H, ArH), 7.11 – 7.06 (m, 1H), 2.59 (q, *J* = 10.0, 9.4 Hz, 1H), 2.48 – 2.38 (m, 1H), 2.20 (s, 6H, $C_{10/11}H$), 2.07 – 2.00 (m, 1H), 1.99 – 1.93 (m, 1H), 1.90 – 1.80 (m, 3H), 1.61 – 1.49 (m, 1H), 1.39 – 1.12 (m, 18H), 0.84 (t, *J* = 7.0 Hz, 3H, $C_{19}H$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9 (C_{12}), 127.8, 126.3, 124.4, 83.1 (C_3), 62.1 ($C_{10/11}$), 47.6, 46.4, 41.3, 30.8, 30.7, 28.4, 25.1, 24.7, 24.6, 23.4, 14.3

vmax /cm^{-1} (neat) 2954 (m.), 2931 (s.), 2857 (w.), 1443 (m.), 1378 (m.), 1307 (s.), 1143 (s.), 846 (s.)

HRMS m/z (ESI) $C_{24}H_{41}BNO_2$ $[M+H]^+$ requires: 386.3225; found: 386.3218

7.4.3.5 (*s*)-4-(Dimethylamino)-3-((1*s*,2*r*)-2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)butan-1-ol (411e)



Synthesised using **GP2** with **409e** on a 0.3 mmol scale. Purified by flash column chromatography (1:10 MeOH/DCM) to give the product as a white amorphous solid (92%, 103 mg, 0.276 mmol).

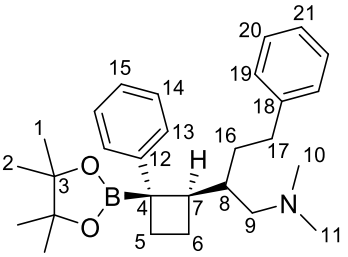
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 2H, ArH), 7.17 – 7.06 (m, 3H, ArH), 3.68 (ddd, *J* = 11.6, 4.7, 2.7 Hz, 1H, $C_{17}H_a$), 3.49 – 3.43 (m, 1H, $C_{17}H_b$), 2.60 – 2.40 (m, 2H), 2.27 (s, 6H, $C_{10/11}H$), 2.25 – 2.14 (m, 1H), 2.11 – 1.97 (m, 3H), 1.94 – 1.82 (m, 1H), 1.82 – 1.70 (m, 2H), 1.41 – 1.27 (m, 1H), 1.25 (s, 6H, C_1H), 1.24 (s, 6H, C_2H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2 (C_{12}), 128.0, 126.1, 124.7, 83.4 (C_3), 63.2, 62.2, 46.2, 45.2, 44.6, 37.9, 30.8, 25.4, 25.1 (C_1), 24.6 (C_2)

νmax /cm^{-1} (neat) 2975 (s.), 1464 (m.), 1443 (m.), 1379 (m.), 1308 (s.), 1237 (m.), 1142 (s.), 1076 (s.), 846 (s.)

HRMS m/z (ESI) $C_{22}H_{37}BNO_3$ $[M+H]^+$ requires: 374.2865; found: 374.2860

7.4.3.6 (*r*)-*N*,*N*-Dimethyl-4-phenyl-2-((1*s*,2*r*)-2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)butan-1-amine (411f)



Synthesised using **GP2** with **409f** on a 0.3 mmol scale. Purified by flash column chromatography (12:1 DCM/MeOH) to give the product as a white solid (54%, 70 mg, 0.16 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 6H, ArH), 7.15 – 7.07 (m, 4H, ArH), 2.72 – 2.62 (m, 2H, $C_{17}H_a$, C_7H), 2.61 – 2.52 (m, 1H, $C_{17}H_b$), 2.51 – 2.39 (m, 1H, C_8H), 2.33 – 2.28 (m, 1H, C_9H_a), 2.25 (s, 6H, $C_{10/11}H$), 2.14 (dd, J = 12.5, 4.0 Hz, 1H, C_9H_b), 2.06 – 1.95 (m, 2H), 1.95 – 1.81 (m, 2H, $C_{16}H$), 1.63 (tdd, J = 12.0, 6.5, 5.0 Hz, 1H, C_8H), 1.26 (s, 6H, C_1H), 1.25 (s, 6H, C_2H)

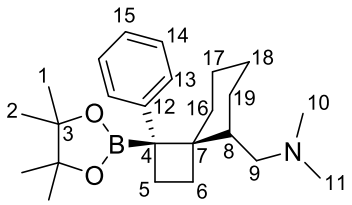
^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5 (C_{12}), 143.6 (C_{18}), 128.6, 128.2, 128.1, 126.6, 125.5, 124.8, 83.4 (C_3), 62.2 (C_9), 48.0 (C_7), 46.4 ($C_{10/11}$), 41.5 (C_8), 33.4 (C_{17}), 32.7 (C_{16}), 30.8 (C_5), 25.2 (C_1), 24.9 (C_2), 24.8 (C_6)

vmax /cm^{-1} (neat) 2974 (m.), 2935 (m.), 1308 (m.), 1143 (s.), 1032 (w.), 847 (w.), 698 (s.)

HRMS m/z (ESI) $C_{28}H_{41}NO_2B$ $[M+Na]^+$ requires: 434.322987; found: 434.322327

m.p./°C 87 – 92

7.4.3.7 *N*,*N*-Dimethyl-1-((1*r*,4*r*,5*s*)-1-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.5]nonan-5-yl)methanamine (411g)



Synthesised using **GP2** with **409g** on a 0.3 mmol scale. Purified by flash column chromatography (12:1 DCM/MeOH) to give the product as a colourless liquid (77%, 88 mg, 0.23 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H, ArH), 7.24 (t, *J* = 7.5 Hz, 2H, ArH), 7.16 – 7.08 (m, 1H, $C_{15}H$), 2.52 – 2.41 (m, 2H), 2.29– 2.19 (m, 7H), 2.18 – 2.02 (m, 2H), 1.97 – 1.73 (m, 2H), 1.57 (dt, *J* = 13.9, 5.0 Hz, 1H), 1.49 – 1.27 (m, 4H), 1.21 (s, 6H, C_1H), 1.19 (s, 6H, C_2H), 1.10 – 1.02 (m, 1H), 0.99 – 0.91 (m, 1H), 0.68 – 0.56 (m, 1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (C_{12}), 129.3, 127.2, 124.9, 83.0 (C_3), 58.6, 49.4, 45.9, 40.6, 31.8, 29.0, 25.1 (C_1), 24.8 (C_2), 24.3, 22.8, 21.3, 21.1

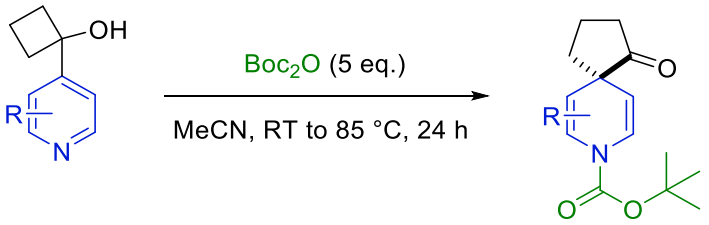
vmax /cm^{-1} (neat) 2974 (m.), 2928 (s.), 2854 (w.), 1444 (m.), 1377 (m.), 1337 (s.), 1299 (s)., 1142 (s.), 1127 (m.), 964 (m.), 851 (m.)

HRMS m/z (ESI) $C_{24}H_{39}BNO_2$ $[M+H]^+$ requires: 384.3068; found: 384.3602

7.5 Experimental procedures for chapter 5

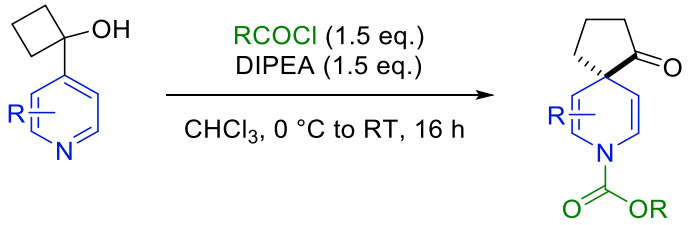
7.5.1 General procedures

7.5.1.1 GP1: Ring expansion with Boc_2O



A flame-dried microwave tube was charged with hydroxycycloalkylpyridine **515/518/523a-p** (0.25 mmol, 1.0 eq.) and anhydrous MeCN (1.4 mL, 0.18 M). To this was added, dropwise at RT, a solution of di-*tert*-butyl dicarbonate (273 mg, 1.25 mmol, 5.0 eq.) in MeCN (0.7 mL. 1.8 M w.r.t. Boc_2O). The reaction mixture was then heated to 85 °C and stirred for 24 h. The reaction was then quenched with H_2O (5 mL) and extracted with DCM (3 x 5 mL). Organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Crude residues were purified by flash column chromatography.

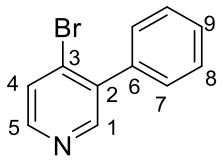
7.5.1.2 GP2: Ring expansion with chloroformates, sulfonylating agents and acyl chlorides



A flame-dried microwave tube was charged with hydroxycycloalkylpyridine **515** or **518** (0.25 mmol, 1.0 eq.), diisopropylethylamine (DIPEA, 65 µL, 0.375 mmol, 1.5 eq.) and anhydrous $CHCl_3$ (1.4 mL, 0.18 M), and cooled to 0 °C using an ice bath. To this was added, dropwise at 0 °C, a solution of chloroformate (0.375 mmol, 1.5 eq.) in $CHCl_3$ (0.7 mL). The reaction mixture was then warmed to RT and stirred for 16 h. The reaction was then quenched with H_2O (5 mL) and extracted with DCM (3 x 5 mL). Organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Crude residues were purified by flash column chromatography.

7.5.2 Literature compounds

7.5.2.1 4-Bromo-3-phenylpyridine



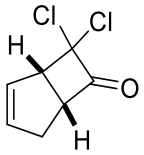
Prepared according to literature procedure.[233]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H, C_1H), 8.36 (d, J = 5.5 Hz, 1H, C_5H), 7.62 (d, J = 5.5 Hz, 1H, C_4H), 7.51 – 7.38 (m, 5H, PhH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 150.8, 149.1, 138.7, 137.2, 133.0, 129.6, 128.6, 128.5, 128.2, 127.4

NMR matches literature data.[233]

7.5.2.2 (1*S*,5*R*)-7,7-Dichlorobicyclo[3.2.0]hept-2-en-6-one



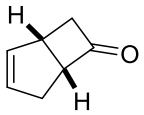
Prepared according to literature procedure.[222,223]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (dq, J = 6.0, 2.0 Hz, 1H), 5.80 (dq, J = 4.5, 2.5 Hz, 1H), 4.37 – 4.19 (m, 1H), 4.07 (ddt, J = 7.5, 5.0, 2.0 Hz, 1H), 2.91 – 2.68 (m, 1H), 2.68 – 2.39 (m, 1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 137.0, 128.6, 88.2, 59.7, 58.7, 35.3

NMR matches literature data.[234]

7.5.2.3 (1*S*,5*R*)-Bicyclo[3.2.0]hept-2-en-6-one (525)



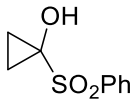
Prepared according to literature procedure.[222]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dq, J = 6.5, 2.0 Hz, 1H), 5.82 – 5.76 (m, 1H), 3.87 (ddtd, J = 7.5, 6.0, 3.0, 1.5 Hz, 1H), 3.48 (dddt, J = 8.5, 5.5, 3.5, 1.9 Hz, 1H), 3.38 – 3.24 (m, 1H), 2.76 – 2.63 (m, 2H), 2.48 (ddq, J = 17.0, 10.0, 2.0 Hz, 1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.5, 133.0, 132.4, 62.1, 54.4, 37.0, 35.1

NMR matches literature data.[235]

7.5.2.4 1-(Phenylsulfonyl)cyclopropan-1-ol



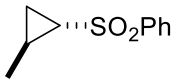
Prepared according to literature procedure.[220]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H, PhH), 7.72 – 7.64 (m, 1H, PhH), 7.58 (t, J = 7.5 Hz, 2H, PhH), 3.95 (s, 1H, OH), 1.69 – 1.61 (m, 2H, CH_2), 1.26 – 1.19 (m, 2H, CH_2)

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (Ph), 134.0 (Ph), 129.3 (Ph), 129.1 (Ph), 71.5 (COH), 13.7 (CH_2)

NMR matches literature data.[220]

7.5.2.5 (((1*S*,2*S*)-2-Methylcyclopropyl)sulfonyl)benzene



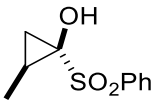
Prepared according to literature procedure.[220]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 2H, PhH), 7.67 – 7.60 (m, 1H, PhH), 7.55 (tt, J = 6.5, 1.5 Hz, 2H, PhH), 2.17 (dt, J = 8.0, 4.5 Hz, 1H, $CHSO_2Ph$), 1.77 (dtd, J = 9.5, 6.0, 4.5 Hz, 1H, CH_2), 1.47 (dt, J = 9.6, 5.0 Hz, 1H, CH), 1.11 (d, J = 6.0 Hz, 3H, CH_3), 0.84 (ddd, J = 8.0, 6.5, 5.5 Hz, 1H, CH_2)

^{13}C NMR (101 MHz, $CDCl_3$) 141.0 (Ph), 133.3 (Ph), 129.2 (Ph), 127.3 (Ph), 40.0 ($PhSO_2C$), 16.8 (CH_3), 14.8 (CH_2), 14.0 (CH)

NMR matches literature data.[236]

7.5.2.6 (1*S*,2*S*)-2-Methyl-1-(phenylsulfonyl)cyclopropan-1-ol



Prepared according to literature procedure.[220]

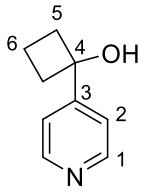
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dt, J = 8.5, 1.5 Hz, 2H), 7.70 – 7.62 (m, 1H), 7.61 – 7.53 (m, 2H), 1.99 (ddd, J = 14.0, 7.5, 4.5 Hz, 1H), 1.69 (dd, J = 10.5, 6.0 Hz, 1H), 1.18 (d, J = 6.5 Hz, 3H, CH_3), 0.79 (t, J = 7.0 Hz, 1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (Ph), 133.8 (Ph), 129.3 (Ph), 129.2 (Ph), 128.9 (Ph), 127.6 (Ph), 73.9 ($COHSO_2Ph$), 19.5 (CH_3), 18.6 (CH), 11.4 (CH_2)

NMR matches literature data.[220]

7.5.3 Synthesis of hydroxycycloalkylpyridines and hydroxycyclobutylquinolines

7.5.3.1 1-(Pyridin-4-yl)cyclobutan-1-ol (515)



To a solution of 4-iodopyridine (615 mg, 3.0 mmol, 1.0 eq.) in THF (10 mL), cooled to 0 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.31 mL, 3.0 mmol, 1.0 eq.) dropwise over 20 minutes. The reaction was stirred for a further 30 minutes at 0 °C before adding cyclobutanone (0.25 mL, 3.3 mmol, 1.1 eq.) as a solution in THF (2.0 mL) dropwise over 20 minutes. The reaction was then stirred at 0 °C for 1 h before removing the ice bath and allowing the reaction to warm to ambient temperature over 30 minutes. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 12-100% Acetone/Petroleum Ether. Product obtained as a white solid (69%, 307 mg, 2.06 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.36 (m, 2H, C_1H), 7.48 – 7.35 (m, 2H, C_2H), 4.31 (s, 1H, OH), 2.56 – 2.28 (m, 4H, C_5H), 2.18 – 1.93 (m, 1H, C_6H_a), 1.78 (m, 1H, C_6H_b)

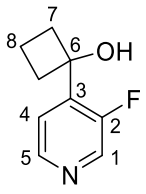
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (C_3), 149.4 (C_1), 120.2 (C_2), 75.5 (C_4), 37.3 (C_5), 13.1 (C_6)

vmax /cm^{-1} (neat) 3203 (br.), 2988 (w.), 2940 (w.), 1602 (s.), 1411 (s.), 1250 (m.), 1147 (s.)

HRMS m/z (ESI) $C_9H_{12}NO$ $[M+H]^+$ requires: 150.0913; found: 150.0921

m.p./°C 102 – 107

7.5.3.2 1-(3-Fluoropyridin-4-yl)cyclobutan-1-ol (518)



A solution of LDA in THF was prepared by dropwise addition of *n*-BuLi (3.75 mL of 1.6 M soln, 6.0 mmol, 1.0 eq.) to a solution of diisopropylamine (0.84 mL, 6.0 mmol, 1 eq.) in THF (10 mL) at -78 °C and stirring for 1 h at this temperature. To the LDA solution was added, dropwise over 20 minutes at -78 °C, a solution of 3-fluoropyridine (0.52 mL, 6.0 mmol, 1.0 eq.) in THF (2.5 mL). The reaction was stirred for

2 h at -78 °C, before dropwise addition of a solution of cyclobutanone (0.48 mL, 6.6 mmol, 1.1 eq.) in THF (2.5 mL). The reaction was then warmed to 0 °C and stirred for 2 h at this temperature, before warming to RT and quenching with sat. aq. NH_4Cl (20 mL). The reaction was extracted with EtOAc (3 x 20 mL), organic layers combined and washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (7-60% acetone/pentane) to give the product as a white solid (70%, 4.2 mmol, 703 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 3.0 Hz, 1H, C_1H), 8.38 (dd, J = 5.0, 1.0 Hz, 1H, C_5H), 7.33 (dd, J = 7.0, 5.0 Hz, 1H, C_4H), 2.75 – 2.57 (m, 3H, OH, C_7H_a), 2.46 – 2.30 (m, 2H, C_7H_b), 2.18 (m, 1H, C_8H_a), 1.90 – 1.76 (m, 1H. C_8H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (d, J = 256 Hz, C_2), 145.8 (d, J = 11.5 Hz, C_5), 141.2 (d, J = 25 Hz, C_3), 138.5 (d, J = 26.5 Hz, C_1), 121.3 (d, J = 9 Hz, C_4), 74.7 (C_6), 35.7 (C_7), 14.1 (C_8)

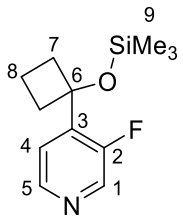
^{19}F NMR (101 MHz, $CDCl_3$) δ -129.6

vmax /cm^{-1} (neat) 3256 (br.), 2992 (w.), 2950 (w.), 1416 (s.), 1220 (m.), 1133 (m.), 1060 (w.)

HRMS m/z (ESI) $C_9H_{11}NOF$ $[M+H]^+$ requires: 168.0819; found: 168.0813

m.p./°C 55 - 60

7.5.3.3 3-Fluoro-4-(1-((trimethylsilyl)oxy)cyclobutyl)pyridine (521a)



A solution of LDA in THF was prepared by dropwise addition of *n*-BuLi (3.75 mL of 1.6 M soln., 6.0 mmol, 1.0 eq.) to a solution of diisopropylamine (0.84 mL, 6.0 mmol, 1.0 eq.) in THF (10 mL) at -78 °C and stirring for 1 h at this temperature. To the LDA solution was added, dropwise over 20 minutes at -78 °C, a solution of 3-fluoropyridine (0.52 mL, 6.0 mmol, 1.0 eq.) in THF (2.5 mL). The reaction was stirred for 2 h at -78 °C, before dropwise addition of a solution of cyclobutanone (0.48 mL, 6.6 mmol, 1.1 eq.) in THF (2.5 mL). The reaction was then warmed to 0 °C and stirred for 1 h at this temperature. A solution of chlorotrimethylsilane (1.0 mL, 7.8 mmol, 1.3 eq.) in THF (2.5 mL) was added dropwise over 20 minutes at 0 °C. The reaction mixture was then warmed to RT and stirred for 45 minutes before quenching with sat. aq. NH_4Cl (20 mL). The reaction was extracted with EtOAc (3 x 20 mL), organic layers combined and washed with brine (20 mL), dried over $MgSO_4$ and

concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2-20% acetone/pentane) to give the product as a colourless oil (64%, 3.85 mmol, 852 mg)

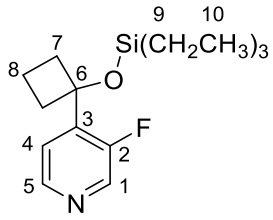
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 3.0 Hz, 1H), 8.40 (dd, J = 5.0, 0.5 Hz, 1H), 7.36 (dd, J = 7.0, 5.0 Hz, 1H), 2.69 – 2.56 (m, 2H, C_7H_a), 2.49 (dt, J = 13.0, 9.0 Hz, 2H, C_7H_b), 1.95 (ddt, J = 11.0, 9.5, 5.0 Hz, 1H, C_8H_a), 1.62 (dp, J = 11.0, 8.5 Hz, 1H, C_8H_b), 0.00 (s, 9H, C_9H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7 (d, J = 5 Hz, C_5), 139.2 (d, J = 26 Hz, C_1), 121.6 (C_4), 75.8 (C_6), 37.0 (C_7), 35.7 (C_{7a}), 13.5 (C_8), 1.6 (C_9)

vmax /cm^{-1} (neat) 2955 (m.), 1485 (w.), 1414 (s.), 1236 (s.), 1219 (m.), 1141 (s.), 1064 (w.)

HRMS m/z (ESI) $C_{12}H_{19}NOFSi$ $[M+H]^+$ requires: 240.1214; found: 240.1212

7.5.3.4 3-Fluoro-4-(1-((triethylsilyl)oxy)cyclobutyl)pyridine (521b)



A solution of LDA in THF was prepared by dropwise addition of *n*-BuLi (3.75 mL of 1.6 M soln., 6.0 mmol, 1.0 eq.) to a solution of diisopropylamine (0.84 mL, 6.0 mmol, 1.0 eq.) in THF (10 mL) at -78 °C and stirring for 1 h at this temperature. To the LDA solution was added, dropwise over 20 minutes at -78 °C, a solution of 3-fluoropyridine (0.52 mL, 6.0 mmol, 1.0 eq.) in THF (2.5 mL). The reaction was stirred for 2 h at -78 °C, before dropwise addition of a solution of cyclobutanone (0.48 mL, 6.6 mmol, 1.1 eq.) in THF (2.5 mL). The reaction was then warmed to 0 °C and stirred for 1 h at this temperature. A solution of chlorotriethylsilane (8.0 mL of a 1 M soln in THF, 8.0 mmol, 1.3 eq.) was added dropwise over 20 minutes at 0 °C. The reaction mixture was then warmed to RT and stirred for 45 minutes before quenching with sat. aq. NH_4Cl (20 mL). The reaction was extracted with EtOAc (3 x 20 mL), organic layers combined and washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5-40% acetone/pentane) to give the product as a colourless oil (61%, 3.64 mmol, 1.02 g)

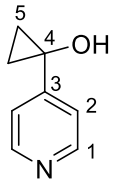
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 3.0 Hz, 1H, C_1H), 8.38 (d, J = 5.0 Hz, 1H, C_5H), 7.34 (dd, J = 7.0, 5.0 Hz, 1H, C_4H), 2.68 – 2.57 (m, 2H, C_7H_a), 2.46 (m, 2H, C_7H_b), 1.94 (m, 1H, C_8H_a), 1.68 – 1.54 (m, 1H, C_8H_b), 0.86 (t, J = 8.0 Hz, 9H, $C_{10}H$), 0.47 (q, J = 8.0 Hz, 6H, C_9H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (d, J = 259.0 Hz, C_2), 145.6 (d, J = 5.5 Hz, C_5), 141.6 (d, J = 10.5 Hz, C_3), 139.1 (d, J = 25.5 Hz, C_1), 121.6 (d, J = 1.5 Hz, C_4), 75.5 (C_6), 37.1 (C_7), 13.4 (C_8), 6.8 (C_{10}) 6.0 (C_9)

vmax /cm^{-1} (neat) 2954 (m.), 2876 (m.), 1484 (w.), 1458 (w.), 1413 (s.), 1296 (w.), 1241 (m.), 1142 (s.), 1064 (w.), 1002 (s.)

HRMS m/z (ESI) $C_{15}H_{25}NOFSi$ $[M+H]^+$ requires: 240.1214; found: 240.1212

7.5.3.5 1-(Pyridin-4-yl)cyclopropan-1-ol (523a)



To a solution of 4-iodopyridine (1230 mg, 6.0 mmol, 2.0 eq.) in THF (16 mL), cooled to -78 °C was added *t*-butyllithium (8.1 mL, 1.48 M, 12.0 mmol, 4.0 eq.) dropwise over 30 minutes. The reaction was then stirred for 2 h at -78 °C before adding 1-(phenylsulfonyl)cyclopropanol (595 mg, 3.0 mmol, 1.0 eq.) as a solution in THF (4 mL) dropwise over 20 minutes. The reaction was then warmed to -30 °C and stirred for 2 hours. The reaction mixture was then warmed to RT and quenched with sat. aq. NH4Cl. The layers were separated and to product extracted with EtOAc. The combined organic phases were dried over MgSO4 and concentrated in vacuo to give a crude residue. This was purified by flash column chromatography (12-100% Acetone/Petroleum Ether) to give the product as a beige solid (14%, 58 mg, 0.43 mmol)

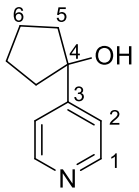
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.40 (m, 2H, C_1H), 7.16 – 7.12 (m, 2H, C_2H), 1.44 – 1.38 (m, 2H, C_5H_a), 1.14 – 1.08 (m, 2H, C_5H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (C_3), 149.3 (C_1), 118.7 (C_2), 54.9 (C_4), 20.4 (C_5)

vmax /cm^{-1} (neat) 3193 (br.), 3079 (w.), 2861 (w.), 1603 (s.), 1438 (m.), 1413 (m.) 1262 (m.), 1120 (m.)

HRMS m/z (ESI) C_8H_9NO $[M+H]^+$ requires: 136.0755; found: 136.0754

7.5.3.6 1-(Pyridin-4-yl)cyclopentan-1-ol (523b)



To a solution of 4-iodopyridine (615 mg, 3.0 mmol, 1.0 eq.) in THF (10 mL), cooled to -30 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.80 mL, 3.6 mmol, 1.2 eq.) dropwise over 20 minutes. The reaction was allowed to warm to -15 °C over 30 minutes before adding cyclopentanone (0.40 mL, 4.5 mmol, 1.5 eq.) as a solution in THF (2.5 mL)

dropwise over 20 minutes. The reaction was then allowed to warm to ambient temperature over 2 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 12-100% Acetone/Petroleum Ether. Product obtained as a white solid (21%, 104 mg, 0.64 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 – 8.41 (m, 2H, C_1H), 7.39 (m, 2H, C_2H), 2.08 – 1.81 (m, 8H, $C_{5/6}H$)

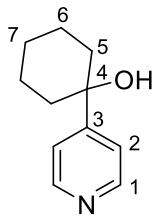
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C_3), 149.7 (C_1), 120.4 (C_2), 82.7 (C_4), 42.6 (C_5), 24.3 (C_6)

vmax /cm^{-1} (neat) 3164 (br.), 2965 (m.), 1403 (m.), 1601 (s.), 1407 (m.), 1240 (m.), 1003 (m.)

HRMS m/z (ESI) $C_{10}H_{13}NO$ $[M+H]^+$ requires: 164.1070; found: 164.1066

m.p./°C 84 – 89

7.5.3.7 1-(Pyridin-4-yl)cyclohexan-1-ol (523c)



To a solution of 4-iodopyridine (615 mg, 3.0 mmol, 1.0 eq.) in THF (10 mL), cooled to 0 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.31 mL, 3.0 mmol, 1.0 eq.) dropwise over 20 minutes. The reaction was stirred at 0 °C for 30 minutes before adding cyclohexanone (0.38 mL, 3.6 mmol, 1.2 eq.) neat, dropwise over 10 minutes. The reaction was then stirred at 0 °C for 30 minutes before warming to ambient temperature and stirring for 1 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 12-100% Acetone/Petroleum Ether. Product obtained as a white solid (43%, 231 mg, 1.30 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.38 (m, 2H, C_1H), 7.48 – 7.31 (m, 2H, C_2H), 2.68 – 2.12 (br. s, 1H, OH), 1.85 – 1.57 (m, 9H, $C_{5/6/7}H$), 1.38 – 1.20 (m, 1H, $C_{6/7}H_b$)

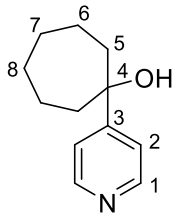
^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8 (C_1), 149.7 (C_3), 120.0 (C_2), 72.8 (C_4), 38.4 (C_5), 25.4 ($C_{6/7}$), 21.9 ($C_{6/7}$)

vmax /cm^{-1} (neat) 3206 (br., m.), 2935 (m.), 2914 (m.), 2858 (w.), 1597 (s.), 1410 (s.), 1268 (m.), 988 (s.), 816 (s.), 725 (w.), 643 (s.), 559 (s.)

HRMS m/z (ESI) $C_{11}H_{15}NO$ $[M+H]^+$ requires: 178.1226; found: 178.1221

m.p./°C 146 – 151

7.5.3.8 1-(Pyridin-4-yl)cycloheptan-1-ol (523d)



To a solution of 4-iodopyridine (615 mg, 3.0 mmol, 1.0 eq.) in THF (10 mL), cooled to 0 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.31 mL, 3.0 mmol, 1.0 eq.) dropwise over 20 minutes. The reaction was stirred at 0 °C for 30 minutes before adding cycloheptanone (0.43 mL, 3.6 mmol, 1.2 eq.) neat, dropwise over 10 minutes. The reaction was then stirred at 0 °C for 30 minutes before warming to ambient temperature and stirring for 1 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 12-100% Acetone/Petroleum Ether. Product obtained as a white solid (35%, 202 mg, 1.06 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 6.0 Hz, 2H, C_1H), 7.47 – 7.34 (m, 2H, C_2H), 2.33 (br. s, 1H, OH), 1.98 (ddd, J = 14.5, 10.5, 1.5 Hz, 2H, C_5H), 1.91 – 1.67 (m, 6H, $C_{6/7/8}H$), 1.61 (m, 4H, $C_{6/7/8}H$)

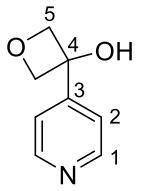
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (C_3), 149.7 (C_1), 119.8 (C_2), 76.2 (C_4), 42.9 (C_5), 29.0 ($C_{6/7/8}$), 22.5 ($C_{6/7/8}$)

vmax /cm^{-1} (neat) 3200 (br., m.), 2928 (s.), 2858 (m.), 1600 (s.), 1411 (m.), 1229 (w.) 1064 (m.), 1003 (m.), 812 (m.), 643 (w.), 561 (w.)

HRMS m/z (ESI) $C_{12}H_{17}NO$ $[M+H]^+$ requires: 192.1383; found: 192.1376

m.p./°C 91 – 96

7.5.3.9 3-(Pyridin-4-yl)oxetan-3-ol (523e)



To a solution of 4-iodopyridine (615 mg, 3.0 mmol, 1.0 eq.) in THF (10 mL), cooled to 0 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.31 mL, 3.0 mmol, 1.0 eq.) dropwise over 20 minutes. The reaction was stirred at 0 °C for 30 minutes before adding 3-oxetanone (0.22 mL, 3.6 mmol, 1.2 eq.) neat, dropwise over 10 minutes. The reaction was then stirred at 0 °C for 30 minutes before warming to ambient temperature and stirring for 1 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 12-100% Acetone/Petroleum Ether. Product obtained as a white solid (34%, 155 mg, 1.03 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.56 (m, 2H, C_1H), 7.66 – 7.58 (m, 2H, C_2H), 4.99 – 4.90 (m, 2H, C_5H_a), 4.86 – 4.78 (m, 2H, C_5H_b)

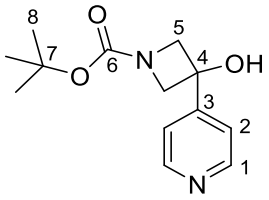
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (C_3), 150.1 (C_1), 119.5 (C_2), 85.9 (C_5), 74.6 (C_4)

vmax /cm^{-1} (neat) 3158 (br., w.), 2923 (s.), 2852 (m.), 1734 (w.), 1265 (w.), 1261 (m.) 750 (s.)

HRMS m/z (ESI) $C_8H_9NO_2$ $[M+H]^+$ requires: 152.0706; found: 152.0703

m.p./°C 172 – 177

7.5.3.10 *tert*-Butyl 3-hydroxy-3-(pyridin-4-yl)azetidine-1-carboxylate (523f)



To a solution of 4-iodopyridine (615 mg, 3.0 mmol, 1.0 eq.) in THF (10 mL), cooled to -30 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.54 mL, 3.3 mmol, 1.1 eq.) dropwise over 20 minutes. The reaction was allowed to stirred at -30 °C for 30 minutes before adding *tert*-butyl 3-oxoazetidine-1-carboxylate (668 mg, 3.9 mmol, 1.3 eq.) as a solution in THF (2.5 mL) dropwise over 20 minutes. The reaction was then allowed to warm to ambient

temperature over 1.5 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 12-100% Acetone/Petroleum Ether. Product obtained as a white solid (21%, 104 mg, 0.64 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 – 8.47 (m, 2H, C_1H), 7.49 (m, 2H, C_2H), 4.26 – 4.04 (m, 4H, C_5H), 1.46 (s, 9H, C_8H)

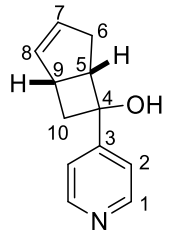
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C_3), 153.8 (C_6), 149.4 (C_1), 119.9 (C_2), 80.5 (C_4), 69.5 (C_5), 28.5 (C_8) *(C_7 not observed)*

νmax /cm^{-1} (neat) 3142 (br.), 2976 (w.), 2882 (w.), 1699 (s.), 1674 (m.), 1605 (w.), 1390 (s.), 1366 (s.), 1250 (w.), 1165 (m.), 1113 (m.)

HRMS m/z (ESI) $C_{13}H_{18}NO_3$ $[M+H]^+$ requires: 251.1390; found: 251.1383

m.p./°C 162 – 167

7.5.3.11 (1*R*,5*S*)-6-(Pyridin-4-yl)bicyclo[3.2.0]hept-2-en-6-ol (523g)



To a solution of 4-iodopyridine (615 mg, 3.0 mmol, 1.0 eq.) in THF (10 mL), cooled to 0 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.31 mL, 3.0 mmol, 1.0 eq.) dropwise over 20 minutes. The reaction was stirred at 0 °C for 30 minutes before adding (1*S*,5*R*)-bicyclo[3.2.0]hept-2-en-6-one **525** (389 mg, 3.6 mmol, 1.2 eq.) as a solution in THF (2.5 mL), dropwise over 15 minutes. The reaction was then stirred at 0 °C for 30 minutes before warming to ambient temperature and stirring for 1 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 7-60% Acetone/Petroleum Ether. Product obtained as a beige solid (19%, 106 mg, 0.57 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.45 (m, 2H, C_1H), 7.47 – 7.35 (m, 2H, C_2H), 5.96 (m, 2H, C_7H, C_8H), 3.31 – 3.19 (m, 2H, C_5H, C_9H), 2.92 – 2.85 (m, 1H, $C_{10}H_a$), 2.85 – 2.77 (m, 1H, C_6H_a), 2.49 (dddd, J = 15.5, 7.5, 4.0, 2.0 Hz, 1H, C_6H_b), 2.06 (dd, J = 13.5, 2.5 Hz, 1H, $C_{10}H_b$)

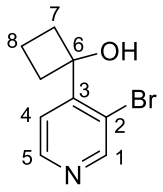
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (C_3), 149.7 (C_1), 135.5 ($C_{7/8}$), 133.0 ($C_{7/8}$), 119.8 (C_2), 75.5 (C_4), 48.6 (C_9), 45.1 (C_{10}), 39.7 (C_5), 32.9 (C_6)

νmax /cm^{-1} (neat) 3173 (br.), 3047 (m.), 2930 (m.), 2845 (w.), 1601 (s.), 1413 (m.) 1239 (w.), 1003 (w.)

HRMS m/z (ESI) $C_{12}H_{14}NO$ $[M+H]^+$ requires: 188.1070; found: 188.1064

m.p./°C 76 – 81

7.5.3.12 1-(3-Bromopyridin-4-yl)cyclobutan-1-ol (523h)[t]



To a solution of 2,2,6,6-tetramethylpiperidine (1.12 mL, 6.6 mmol, 1.1 eq.) in THF (12 mL) was added *n*-BuLi (1.6 M in hexanes, 4.13 mL, 6.6 mmol, 1.1 eq.) dropwise over 20 minutes at -40 °C. The reaction mixture was then warmed to -5 °C and stirred for 15 minutes at this temperature. The reaction mixture was then cooled to -85 °C and a solution of 3-bromopyridine (578 µL, 948 mg, 6 mmol, 1.0 eq.) in THF (2.5 mL) added dropwise over 20 minutes. The reaction was then stirred at 25 °C for 25 minutes before adding a solution of cyclobutanone (986 µL, 13.2 mmol, 2.2 eq.) in THF (1 mL) in one portion. The reaction mixture was stirred at -85 °C for 15 minutes and then warmed to ambient temperature. The reaction was quenched with sat. $NaHCO_3$ (15 mL), extracted with EtOAc (3 x 20 mL), and organic layers combined and washed with brine (20 mL). Organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a crude residue. Purification by flash column chromatography on alumina (2:8 EtOAc/Pet. Ether) to give the product as a white solid (15%, 205 mg, 0.9 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H, C_1H), 8.47 (dd, J = 5.0, 1.0 Hz, 1H, C_5H), 7.28 (d, J = 5.0 Hz, 1H, C_4H), 3.20 (s, 1H, OH), 2.71 – 2.58 (m, 2H, C_7H_a), 2.52 – 2.41 (m, 2H, C_7H_b), 2.26 – 2.11 (m, 1H, C_8H_a), 1.71 (dtt, J = 11.0, 9.0, 5.5 Hz, 1H, C_8H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2 (C_1), 151.7 (C_3), 148.8 (C_5), 121.9 (C_4), 120.3 (C_2), 78.1 (C_6), 34.9 (C_7), 14.4 (C_8)

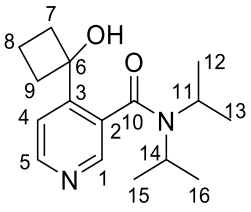
νmax /cm^{-1} (neat) 3260 (br.), 2988 (m.), 2948 (m.), 1585 (m.), 1398 (s.), 1141 (s.) 1030 (s.)

HRMS m/z (ESI) $C_9H_{11}NOBr$ $[M+H]^+$ requires: 228.0019; found: 228.0028

m.p./°C 85 – 90

[t] Prepared by Laia Vicens I Serra

7.5.3.13 4-(1-Hydroxycyclobutyl)-*N*,*N*-diisopropylnicotinamide (523i)[u]



A solution of lithium 2,2,6,6-tetramethylpyridide (LiTMP) in THF was prepared by dropwise addition of *n*-BuLi (5.62 mL of 1.6 M soln, 9.0 mmol, 3.0 eq.) to a solution of 2,2,6,6-tetramethylpiperidine (1.53 mL, 9.0 mmol, 3 eq.) in THF (9 mL) at -78 °C and stirring for 1 h at this temperature. To the LiTMP solution was added, dropwise over 20 minutes at -78 °C, a solution of *N*,*N*-diisopropylnicotinamide (619 mg, 3.0 mmol, 1.0 eq.) in THF (9.0 mL). The reaction was stirred for 3 h at -78 °C, before dropwise addition over 20 minutes of cyclobutanone (0.79 mL, 10.5 mmol, 3.5 eq.). The reaction was then warmed to RT and stirred for 1 h at this temperature, before quenching with sat. aq. NH_4Cl (20 mL). The reaction was extracted with DCM (3 x 20 mL), organic layers combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (60% EtOAc/pet. ether) to give the product as a white solid (38%, 1.14 mmol, 316 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 8.56 (d, J = 5.0 Hz, 1H, C_5H), 8.41 (s, 1H, C_1H), 7.29 (d, J = 5.0 Hz, 1H, C_4H), 5.07 (s, 1H, OH), 3.93 (qq, J = 7.0, 7.0 Hz, 1H, $C_{11}H$), 3.55 (qq, J = 7.0 Hz, 1H, $C_{14}H$), 2.68 – 2.55 (m, 1H, C_7H_a), 2.40 – 2.18 (m, 4H, C_7H, C_9H, C_8H_a), 1.79 – 1.67 (m, 1H, C_8H_b), 1.55 (d, J = 7.0 Hz, 3H, $C_{12}H$), 1.51 (d, J = 7.0 Hz, 3H, $C_{13}H$), 1.29 (d, J = 7.0 Hz, 3H, $C_{15}H$), 1.17 (d, J = 7.0 Hz, 3H, $C_{16}H$)

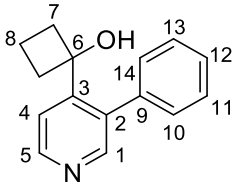
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (C_{10}), 153.3 (C_3), 150.9 (C_5), 146.9 (C_1), 130.8 (C_2), 120.9 (C_4), 76.5 (C_6), 51.9 (C_{11}), 46.7 (C_{14}), 36.2 (C_7), 32.4 (C_9), 21.00 (C_{15}), 20.97 (C_{16}), 20.34 (C_{12}), 20.28 (C_{13}), 15.0 (C_8)

νmax /cm^{-1} (neat) 3353 (br.), 2972 (m.), 1609 (s.), 1444 (m.), 1370 (m.), 1344 (s.), 1032 (m.)

HRMS m/z (ESI) $C_{16}H_{25}N_2O_2$ $[M+H]^+$ requires: 277.1911; found: 277.1904

m.p./°C 113 – 118

7.5.3.14 1-(3-Phenylpyridin-4-yl)cyclobutan-1-ol (523j)



[u] Prepared by Laia Vicens I Serra

To a solution of 4-bromo-3-phenylpyridine (700 mg, 2.9 mmol, 1.0 eq.) in THF (6 mL), cooled to -10 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.45 mL, 3.2 mmol, 1.1 eq.) dropwise over 20 minutes. The reaction was stirred for a further 30 minutes at -10 °C before adding cyclobutanone (0.33 mL, 4,35 mmol, 1.5 eq.) as a solution in THF (1.5 mL) dropwise over 20 minutes. The reaction was then allowed to warm to ambient temperature over 1 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 7-60% Acetone/Petroleum Ether. Product obtained as a white solid (39%, 252 mg, 1.12 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 5.0 Hz, 1H, C_5H), 8.40 (s, 1H, C_1H), 7.51 – 7.33 (m, 5H, PhH), 7.28 (d, J = 5.0 Hz, 1H, C_4H), 3.21 (br. s, 0H), 2.36 – 2.25 (m, 2H, C_7H_a), 2.17 – 2.03 (m, 1H, C_8H_a), 2.01 – 1.90 (m, 2H, C_7H_b), 1.67 – 1.55 (m, 1H, C_8H_b)

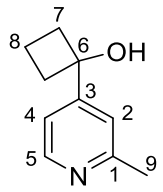
^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C_3), 151.4 (C_1), 148.6 (C_5), 138.3 (C_9), 136.4 (C_2), 129.9 ($C_{10/11}$), 128.3 ($C_{10/11}$), 128.1 (C_{12}), 120.7 (C_4), 77.9 (C_6), 36.0 (C_7), 15.2 (C_8)

νmax /cm^{-1} (neat) 2946 (m.), 1592 (w.), 1401 (m.), 1234 (m.), 1135 (m.), 756 (m.), 700 (s.)

HRMS m/z (EI) $C_{15}H_{15}NO$ $[M]^+$ requires: 225.1148; found: 225.1146

m.p./°C 97 – 102

7.5.3.15 1-(2-Methylpyridin-4-yl)cyclobutan-1-ol (523k)[v]



To a solution of 4-bromo-2-methylpyridine (145 mg, 0.84 mmol, 1.0 eq.) in Et_2O (50 mL, 0.02 M) cooled to -78 °C was added *n*-butyllithium (0.95 mL, 1.6 M, 1.52 mmol, 1.8 eq.) dropwise over 20 minutes. The reaction mixture was then stirred at -78 °C for 15 minutes before adding a solution of cyclobutanone (0.13 mL, 1.68 mmol, 2.0 eq.) in Et_2O (2.5 mL) dropwise over 20 minutes at -78 °C. The reaction was then warmed to ambient temperature and stirred for 1 hour, before quenching the reaction with sat. aq. NH_4Cl, extracting with EtOAc (3 x 20 mL), drying over $MgSO_4$ and concentrating

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in vacuo. The crude residue was purified by flash column chromatography (30-50% EtOAc/pet. ether) to give the product as a white solid (66%, 90 mg, 0.54 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, J = 5.0, 1.0 Hz, 1H, C_5H), 7.28 (dd, J = 1.5, 1.0 Hz, 1H, C_2H), 7.21 (ddd, J = 5.0, 1.5, 0.5 Hz, 1H, C_4H), 3.80 (s, 1H, OH), 2.51 (s, 3H, C_9H), 2.50 – 2.43 (m, 2H, C_7H_a), 2.43 – 2.33 (m, 2H, C_7H_b), 2.12 – 1.99 (m, 1H, C_8H_a), 1.76 (m, 1H, C_8H_b)

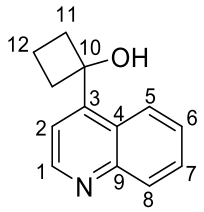
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C_1), 156.3 (C_3), 148.9 (C_5), 119.6 (C_2), 117.2 (C_4), 75.7 (C_6), 37.2 (C_7), 24.4 (C_9), 13.1 (C_8)

vmax /cm^{-1} (neat) 3201 (br.), 2986 (w.), 2940 (w.), 1606 (s.), 1553 (w.), 1385 (m.), 1249 (m.), 1141 (m.)

HRMS m/z (ESI) $C_{10}H_{14}NO$ $[M+H]^+$ requires: 164.1070; found: 164.1075

m.p./°C 60 – 65

7.5.3.16 1-(Quinolin-4-yl)cyclobutan-1-ol (523l)[w]



To a solution of 4-bromoquinoline (396.7 mg, 1.91 mmol) in Et_2O (6.5, 0.3 M), cooled to -100 °C was added *n*-butyllithium (1.31 mL, 1.6 M, 2.1 mmol) dropwise over 30 minutes. The reaction was then stirred for 2 h at -100 °C before warming to -78 °C and adding cyclobutanone (171 µL, 2.29 mmol) as a solution in THF (4 mL, 0.6 M) dropwise over 20 minutes. The reaction was then stirred at -78 °C for 1.5 h before allowing the reaction to warm to RT and quenching with sat. aq. NH4Cl. The layers were separated and to product extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a crude residue. This was purified by flash column chromatography (1:1 EtOAc/Petroleum Ether) to give the product as a white solid (20%, 75.9 mg, 0.38 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 4.5 Hz, 1H, C_1H), 8.29 (dd, J = 8.5, 1.5 Hz, 1H, C_8H), 8.05 (dd, J = 8.5, 1.5 Hz, 1H, C_5H), 7.66 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H, C_6H), 7.52 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H, C_7H), 7.32 – 7.19 (m, 1H, C_2H), 3.35 (s, 1H, OH), 2.86 – 2.68 (m, 2H, $C_{11}H_a$), 2.60 (ddd, J = 12.5, 9.0, 7.0 Hz, 2H, $C_{11}H_b$), 2.15 (dddd, J = 11.0, 9.5, 5.5, 3.5 Hz, 1H, $C_{12}H_a$), 1.69 (dddd, J = 13.0, 8.5, 6.5, 4.5 Hz, 1H, $C_{12}H_b$)

[w] Prepared by Laia Vicens I Serra

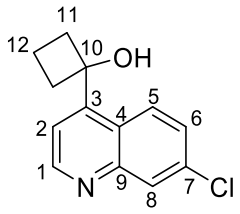
^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9 (C_1), 149.7 (C_3), 149.2 (C_9), 130.2 (C_5), 129.2 (C_6), 126.5 (C_8), 126.3 (C_7), 126.1 (C_4), 117.3 (C_2), 77.4 (C_{10}), 36.5 (C_{11}), 14.4 (C_{12})

vmax /cm^{-1} (neat) 3205 (br.), 1587 (w.), 1397 (m.), 1291 (w.), 1233 (m.) 1146 (s.), 1034 (s.)

HRMS m/z (ESI) $C_{13}H_{13}NONa$ $[M+Na]^+$ requires: 222.0889; found: 222.0884

m.p./°C 60 – 65

7.5.3.17 1-(7-Chloroquinolin-4-yl)cyclobutan-1-ol (523m)[x]



To a solution of 7-chloro-4-iodoquinoline (579 mg, 2.0 mmol, 1.0 eq.) in THF (8.0 mL), cooled to 0 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (1.54 mL, 2.0 mmol, 1.0 eq.) dropwise over 20 minutes. The reaction was stirred for a further 10 minutes at 0 °C before adding cyclobutanone (0.15 mL, 2 mmol, 1.0 eq.) neat, dropwise over 5 minutes. The reaction was then stirred at 0 °C for 1 h before quenching with saturated aqueous NH_4Cl (10 mL) and extracting with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography (33 – 50% EtOAc/Hexane). Product obtained as a white solid (58%, 264 mg, 1.16 mmol).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.89 (d, J = 4.5 Hz, 1H, C_1H), 8.36 (d, J = 9.0 Hz, 1H, C_5H), 8.08 (d, J = 2.5 Hz, 1H, C_8H), 7.63 (dd, J = 9.0, 2.5 Hz, 1H, C_6H), 7.54 (d, J = 4.5 Hz, 1H, C_2H), 6.04 (s, 1H, OH), 2.70 – 2.56 (m, 2H, $C_{11}H_a$), 2.49 – 2.40 (m, 1H, $C_{11}H_b$), 2.05 – 1.87 (m, 1H), 1.54 (m, 1H)

^{13}C NMR (101 MHz, DMSO-d6) δ 151.6 (C_1), 150.6 (C_3), 149.3 (C_9), 133.3 (C_5), 129.1 (C_6), 128.2 (C_8), 126.3 (C_7), 124.5 (C_4), 117.8 (C_2), 75.6 (C_{10}), 36.1 (C_{11}), 13.7 (C_{12})

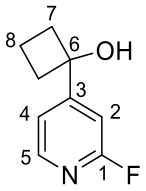
vmax /cm^{-1} (neat) 3284 (br.), 2985 (m.), 2950 (m.), 1769 (w.), 1604 (m.), 1588 (m.) 1275 (m.), 1251 (m.), 1078 (s.)

HRMS m/z (ESI) $C_{13}H_{13}NOCl$ $[M+H]^+$ requires: 234.0680; found: 234.0677

m.p./°C 160 – 165

[x] Prepared by Noeila Velasco Perez

7.5.3.18 1-(2-Fluoropyridin-4-yl)cyclobutan-1-ol (523n)



To a solution of 2-fluoro-4-iodopyridine (1000 mg, 4.48 mmol, 1.0 eq.) in THF (10 mL), cooled to -78 °C, was added *n*-butyllithium (1.6 M in THF) (3.75 mL, 5.38 mmol, 1.2 eq.) dropwise over 20 minutes. The reaction was stirred for a further 1 h at -78 °C before adding cyclobutanone (0.40 mL, 5.38 mmol, 1.2 eq.) as a solution in THF (4 mL). The reaction was then stirred at -78 °C for 30 minutes before replacing the acetone/dry ice bath with an ice bath and allowing the reaction to warm to 0 °C for 1 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 7-60% Acetone/Petroleum Ether. Product obtained as a pale yellow oil (77%, 575 mg, 3.44 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.16 (m, 1H, C_5H), 7.32 (ddd, J = 5.5, 2.0, 1.5 Hz, 1H, C_2H), 7.07 (td, J = 1.5, 0.5 Hz, 1H, C_4H), 2.57 – 2.47 (m, 2H, C_7H_a), 2.46 – 2.36 (m, 2H, C_7H_b)), 2.24 (s, 1H, OH), 2.17 – 2.04 (m, 1H, C_8H_a), 1.83 (m, 1H, C_8H_b)

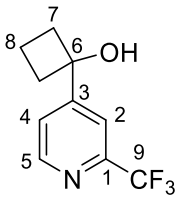
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9 (d, J = 15 Hz, C_5), 117.8 (d, J = 4 Hz, C_4), 105.7 (d, J = 37.5 Hz, C_2), 76.0 (C_6), 37.6 (C_7), 13.1 (C_8) (*C_1 and C_3 not observed)*

^{19}F NMR (101 MHz, $CDCl_3$) δ -67.9

vmax /cm^{-1} (neat) 3350 (br.), 2947 (w.), 1774 (w.), 1614 (s.), 1557 (m.), 1403 (s.) 1295 (w.), 1141 (w.)

HRMS m/z (ESI) $C_9H_{11}NOF$ $[M+H]^+$ requires: 168.0819; found: 168.0821

7.5.3.19 1-(2-Trifluoromethylpyridin-4-yl)cyclobutan-1-ol (523o)



To a solution of 4-bromo-2-trifluoromethylpyridine (590 mg, 2.6 mmol, 1.0 eq.) in THF (5.0 mL), cooled to 0 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.21 mL, 2.87 mmol, 1.1 eq.) dropwise over 20 minutes. The reaction was stirred for a further

1 h at 0 °C before adding cyclobutanone (0.29 mL, 3.9 mmol, 1.5 eq.) as a solution in THF (1.5 mL). The reaction was then stirred at 0 °C for 1 h before removing the ice bath and allowing the reaction to warm to ambient temperature over 30 minutes. The reaction was then quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography eluting with a gradient of 5-40% Acetone/Petroleum Ether. Product obtained as a white solid (56%, 314 mg, 1.45 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.64 (m, 1H, C_5H), 7.84 (dd, J = 2.0, 1.0 Hz, 1H, C_2H), 7.63 (ddd, J = 5.0, 2.0, 0.5 Hz, 1H, C_4H), 2.80 (s, 1H, OH), 2.60 – 2.50 (m, 2H, C_7H_a), 2.50 – 2.38 (m, 2H, C_7H_b), 2.22 – 2.09 (m, 1H, C_8H_a), 1.86 (dtt, J = 12.0, 9.0, 7.5 Hz, 1H, C_8H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (C_3), 150.3 (C_5), 122.5 (C_4), 116.9 (C_2), 75.9 (C_6), 37.7 (C_7), 13.1 (C_8) (*C_1 and C_9 not observed)*

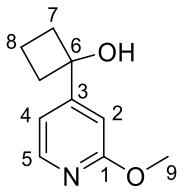
^{19}F NMR (101 MHz, $CDCl_3$) δ -67.8

vmax /cm^{-1} (neat) 3337 (br.), 2993 (w.), 2945 (w.), 1610 (w.), 1424 (w.), 1328 (m.), 1266 (w.), 1180 (m.), 1133 (s.), 1085 (m.)

HRMS m/z (ESI) $C_{10}H_{11}NOF_3$ $[M+H]^+$ requires: 218.0787; found: 218.0779

m.p./°C 54 – 60

7.5.3.20 1-(2-Methoxypyridin-4-yl)cyclobutan-1-ol (523p)[y]



To a solution of 4-bromo-2-methoxypyridine (564 mg, 3.0 mmol, 1.0 eq.) in THF (12.5 mL) cooled to -78 °C was added *n*-butyllithium (1.88 mL, 1.6 M, 3.0 mmol, 1.0 eq.) dropwise over 20 minutes. The reaction mixture was then stirred at -78 °C for 45 minutes before adding a solution of cyclobutanone (0.27 mL, 3.6 mmol, 1.2 eq.) in THF (2.5 mL) dropwise over 20 minutes at -78 °C. The reaction was then warmed to 0 °C and stirred for 2 hours, before warming to RT and quenching the reaction with sat. aq. NH_4Cl, extracting with EtOAc (3 x 20 mL), drying over $MgSO_4$ and concentrating *in vacuo*. The crude residue was purified by flash column chromatography on silica (30% EtOAc/pet. ether) followed by

[y] Prepared by Laia Vicens I Serra

flash column chromatography on alumina (40% EtOAc/pet. ether) to give the product as a colourless oil (22%, 117 mg, 0.66 mmol).

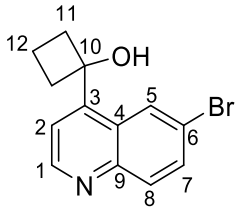
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, J = 5.5, 0.5 Hz, 1H, C_5H), 7.01 (ddd, J = 5.5, 1.5 Hz, 1H, C_4H), 6.85 (m, 1H, C_2H), 3.93 (s, 3H, C_9H), 2.54 – 2.43 (m, 2H, C_7H_a), 2.41 – 2.30 (m, 2H, C_7H_b), 2.11 – 1.98 (m, 1H, C_8H_a), 1.82 – 1.69 (m, 1H, C_8H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (C_1), 158.1 (C_3), 147.2 (C_5), 113.7 (C_4), 106.7 (C_2), 76.1 (C_6), 53.6 (C_9), 37.1 (C_7), 13.1 (C_8)

vmax /cm^{-1} (neat) 3328 (br.), 2986 (w.), 2946 (w.), 1609 (m.), 1555 (m.), 1388 (s.), 1321 (m.), 1139 (w.), 1038 (m.)

HRMS m/z (ESI) $C_{10}H_{14}NO_2$ $[M+H]^+$ requires: 202.0838; found: 202.0829

7.5.3.21 1-(6-Bromoquinolin-4-yl)cyclobutan-1-ol (523q)[z]



To a solution of 6-bromo-4-iodoquinoline (668 mg, 2.0 mmol, 1.0 eq.) in THF (8.0 mL), cooled to 0 °C, was added turbo Grignard (isopropyl magnesium chloride lithium chloride complex, 1.3 M in THF) (2.31 mL, 3.0 mmol, 1.5 eq.) dropwise over 20 minutes. The reaction was stirred for a further 10 minutes at 0 °C before adding cyclobutanone (0.25 mL, 3 mmol, 1.5 eq.) neat, dropwise over 5 minutes. The reaction was then stirred at 0 °C for 1 h before quenching with saturated aqueous NH_4Cl (10 mL) and extracting with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was purified by flash column chromatography (33 – 50% EtOAc/Hexane). Product obtained as an amorphous white solid (53%, 287 mg, 1.06 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 4.5 Hz, 1H, C_1H), 8.48 (d, J = 2.0 Hz, 1H, C_5H), 7.98 (d, J = 9.0 Hz, 1H, C_8H), 7.77 (dd, J = 9.0, 2.0 Hz, 1H, C_7H), 7.38 (d, J = 4.5 Hz, 1H, C_2H), 2.88 – 2.69 (m, 2H, $C_{11}H_a$), 2.60 (ddd, J = 12.5, 9.5, 7.0 Hz, 2H, $C_{11}H_b$), 2.44 (s, 1H, OH), 2.17 (dddd, J = 11.0, 9.0, 5.5, 3.5 Hz, 1H, $C_{12}H_a$), 1.72 (dddd, J = 11.0, 8.5, 7.0, 1.5 Hz, 1H, $C_{12}H_b$)

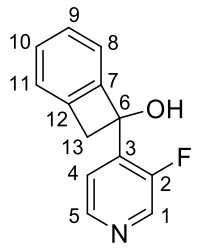
^{13}C NMR (101 MHz, CD_3OD) δ 151.9 (C_9), 151.6 (C_1), 148.5 (C_3). 133.8 ($C_{5/7/8}$), 131.9 ($C_{5/7/8}$), 130.6 ($C_{5/7/8}$), 128.8 (C_6), 121.1 (C_4), 119.6 (C_2), 77.5 (C_{10}), 37.3 (C_{11}), 14.9 (C_{12})

[z] Prepared by Noelia Velasco Perez

vmax /cm^{-1} (neat) 3208 (br.), 2984 (w.), 2949 (w.), 1590 (m.), 1509 (m.), 1249 (m.), 1153 (m.), 1116 (m.), 845 (m.), 761 (s.)

HRMS m/z (ESI) $C_{13}H_{13}NOBr$ $[M+H]^+$ requires: 278.0175; found: 278.0174

7.5.3.22 7-(3-Fluoropyridin-4-yl)bicyclo[4.2.0]octa-1(6),2,4-trien-7-ol (526)[aa]



A solution of LDA in THF was prepared by dropwise addition of *n*-BuLi (3.75 mL of 1.6 M soln, 6.0 mmol, 1.0 eq.) to a solution of diisopropylamine (0.84 mL, 6.0 mmol, 2 eq.) in THF (12 mL) at -78 °C and stirring for 1 h at this temperature. To the LDA solution was added, dropwise over 20 minutes at -78 °C, a solution of 3-fluoropyridine (0.52 mL, 6.0 mmol, 2.0 eq.) in THF (6 mL). The reaction was stirred for 1 h at -78 °C, before dropwise addition of a solution of benzocyclobutenone (0.30 mL, 3.0 mmol, 1.0 eq.) in THF (4 mL). The reaction was then stirred for 40 minutes at -78 °C before warming to RT and quenching with sat. aq. NH_4Cl (20 mL). The reaction was extracted with EtOAc (3 x 20 mL), organic layers combined and washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20-30% EtOAc/pet. ether) to give the product as a white solid (7%, 0.21 mmol, 45 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 2.5 Hz, 1H, C_1H), 8.32 (dd, J = 5.0, 1.0 Hz, 1H, C_5H), 7.43 (dd, J = 6.5, 5.0 Hz, 1H, C_4H), 7.39 – 7.30 (m, 3H, $C_{8/9/10/11}H$), 7.24 (dq, J = 7.0, 1.0 Hz, 1H, $C_{8/9/10/11}H$), 3.83 (d, J = 14.5 Hz, 1H, $C_{13}H_a$), 3.63 (d, J = 14.5 Hz, 1H, $C_{13}H_b$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (d, J = 258 Hz, C_2), 146.8 ($C_{7/12}$), 145.8 (d, J = 5 Hz, C_5), 142.0 ($C_{7/12}$), 138.6 (d, J = 25 Hz, C_1), 130.6 ($C_{8/9/10/11}$), 128.0 ($C_{8/9/10/11}$), 124.5 ($C_{8/9/10/11}$), 122.7 ($C_{8/9/10/11}$), 122.2 (d, J = 2 Hz, C_4), 78.5 (C_6), 48.5 (C_{13})

^{19}F NMR (101 MHz, $CDCl_3$) δ -128.8

vmax /cm^{-1} (neat) 2923 (s.), 2851 (m.), 1403 (m.), 1604 (w.), 1460 (w.), 1416 (m.) 1203 (m.), 1057 (w.)

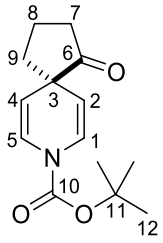
HRMS m/z (ESI) $C_{13}H_{11}FNO$ $[M+H]^+$ requires: 216.0819; found: 216.0819

m.p./°C 130 – 135

[aa] Prepared by Laia Vicens I Serra

7.5.4 Boc anhydride protocol scope

7.5.4.1 *tert*-Butyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517a)



Synthesised using **GP1** with **515** on a 0.25 mmol scale. Purified by flash column chromatography (1:4 EtOAc/Petroleum Ether) to give the product as a pale yellow solid (96%, 57 mg, 0.24 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.5 Hz, 1H, $C_{1/5}H$), 6.87 (d, J = 8.5 Hz, 1H, $C_{1/5}H$), 4.68 (d, J = 8.5 Hz, 1H, $C_{2/4}H$), 4.55 (d, J = 8.5 Hz, 1H, $C_{2/4}H$), 2.33 (td, J = 7.2, 3.5 Hz, 2H, C_7H), 2.06 – 1.84 (m, 4H, C_8H, C_9H), 1.49 (s, 9H, $C_{12}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 218.2 (C_6), 149.7 (C_{10}), 124.2 ($C_{1/5}$), 123.5 ($C_{1/5}$), 106.4 ($C_{2/4}$), 106.0 ($C_{2/4}$), 82.5 (C_{11}), 50.4 (C_3), 40.7 (C_7), 35.8 ($C_{8/9}$), 28.1 (C_{12}), 18.4 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2975 (w.), 1716 (s.), 1686 (m.), 1367 (m.), 1335 (s.), 1318 (s.), 1163 (m.), 1116 (m.), 964 (m.), 857 (w.), 736 (m.)

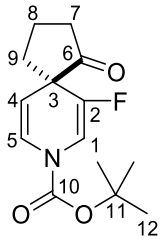
HRMS m/z (ESI) $C_{14}H_{19}NO_3Na$ $[M+Na]^+$ requires: 272.1257; found: 272.1255

m.p./°C 85 – 90

Gram scale:

A 400 mL Schlenk tube was charged with 4-(1'-hydroxycyclobutyl)pyridine **515** (1.0 g, 6.7 mmol, 1.0 eq.) and anhydrous MeCN (40 mL). To this was added, dropwise over 10 minutes at RT, a solution of di-*tert*-butyl dicarbonate (7.8 mL, 33.5 mmol, 5.0 eq.) in MeCN (10 mL). The reaction mixture was then heated to 85 °C and stirred for 24 h. The reaction was then quenched with H_2O (50 mL) and extracted with DCM (3 x 50 mL). Organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2-20% acetone/pentane) to give the product as a pale yellow solid (87%, 5.83 mmol, 1.45 g).

7.5.4.2 *tert*-Butyl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519g)[bb]



Synthesised using **GP1** with **518** on a 0.25 mmol scale. Purified by flash column chromatography (1:4 EtOAc/Petroleum Ether) to give the product as a yellow oil (68%, 46 mg, 0.17 mmol).

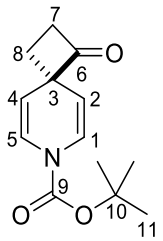
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (m, 2H, C_1H, C_5H), 4.84 – 4.53 (m, 1H, C_4H), 2.49 – 2.23 (m, 3H, C_7, $C_{8/9}H$), 2.10 – 1.88 (m, 3H, $C_{8/9}H$), 1.47 (s, 9H, $C_{12}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.4 (C_6), 216.1 ($C_{6'}$), 123.2 (C_5), 122.6 ($C_{5'}$), 109.9 (d, J = 44 Hz, C_1), 109.0 (J = 44 Hz, $C_{1'}$), 106.4 (d, J = 11.5 Hz, C_4), 106.2 (d, J = 10.5, $C_{4'}$), 83.1 (C_{11}), 52.9 (C_3), 52.6 ($C_{3'}$), 36.9 (C_7), 36.8 ($C_{7'}$), 36.6 ($C_{8/9}$), 36.3 ($C_{8'/9'}$), 28.2 (C_{12}), 19.1 ($C_{8/9}$), 19.0 ($C_{8'/9'}$) (*2 rotamers – assigned here as C_n and $C_{n'}$)*

vmax /cm^{-1} (neat) 2973 (w.), 2932 (w.), 1749 (m.), 1718 (s.), 1399 (m.), 1371 (m.), 1331 (s.), 1313 (s.), 1157 (m.), 1103 (m.)

HRMS m/z (APCI) $C_{15}H_{18}NO_3F$ $[M+H]^+$ requires: 268.1343; found: 268.1344

7.5.4.3 *tert*-Butyl 1-oxo-7-azaspiro[3.5]nona-5,8-diene-7-carboxylate (524a)



Synthesised using **GP1** with **523a** on a 0.25 mmol scale. Purified by flash column chromatography (5-40% Acetone/Pentane) to give the product as an off-white solid (64%, 38 mg, 0.16 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (m, 1H, $C_{1/5}H$), 6.79 (m, 1H, $C_{1/5}H$), 4.90 (m, 1H, $C_{2/4}H$), 4.80 (m, 1H, $C_{2/4}H$), 3.02 (ddd, J = 8.5, 8.5, 2.5 Hz, 2H, $C_7H_{a/b}$), 2.04 (dd, J = 8.5, 8.5 Hz, 2H, C_8H), 1.49 (s, 9H, $C_{11}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.3 (C_6), 149.7 (C_{10}), 124.0 ($C_{1/5}$), 123.5 ($C_{1/5}$), 106.0 ($C_{2/4}$), 105.3 ($C_{2/4}$), 82.8 (C_{10}), 64.6 (C_3), 42.8 (C_7), 31.2 (C_8), 28.2 (C_{11})

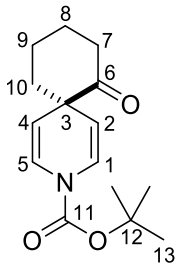
[bb] Prepared by Laia Vicens I Serra and Noelia Velasco Perez

vmax /cm^{-1} (neat) 2979 (w.), 1780 (m.), 1722 (s.), 1681 (m.), 1371 (m.), 1336 (s.), 1319 (s.), 1164 (m.), 1134 (m.)

HRMS m/z (APCI) $C_{23}H_{18}NO_3$ $[M+H]^+$ requires: 236.1281; found: 236.1289

m.p./°C 93 – 98

7.5.4.4 *tert*-Butyl 7-oxo-3-azaspiro[5.5]undeca-1,4-diene-3-carboxylate (524b)



Synthesised using **GP1** with **523b** on a 0.25 mmol scale. Purified by flash column chromatography (5-40% Acetone/Pentane) to give the product as an amorphous off-white solid (45%, 30 mg, 0.11 mmol).

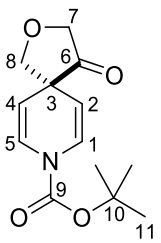
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, J = 8.5 Hz, 1H, $C_{1/5}H$), 6.81 (d, J = 8.5 Hz, 1H, $C_{1/5}H$), 5.03 (d, J = 8.5 Hz, 1H, $C_{2/4}H$), 4.85 (d, J = 8.5 Hz, 1H, $C_{2/4}H$), 2.44 (m, 2H, C_7H), 1.97 – 1.66 (m, 6H, $C_{8/9/10}H$), 1.48 (s, 9H, $C_{13}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.9 (C_6), 150.0 (C_{11}), 123.4 ($C_{1/5}$), 123.0 ($C_{1/5}$), 107.2 (C_2 and C_4), 82.5 (C_{12}), 50.1 (C_3), 43.5 ($C_{7/10}$), 37.9 ($C_{7/10}$), 28.2 (C_{13}), 27.8 ($C_{8/9}$), 19.9 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2976 (w.), 2934 (w.), 2865 (w.), 1708 (s.), 1686 (m.), 1369 (m.), 1334 (s.), 1317 (s.), 1137 (m.), 1121 (m.)

HRMS m/z (APCI) $C_{15}H_{22}NO_3$ $[M+H]^+$ requires: 264.1594; found: 264.1602

7.5.4.5 *tert*-Butyl 4-oxo-2-oxa-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524e)



Synthesised using **GP1** with **523e** on a 0.25 mmol scale. Purified by flash column chromatography (5-40% Acetone/Pentane) to give the product as a pale yellow oil (78%, 49 mg, 0.19 mmol).

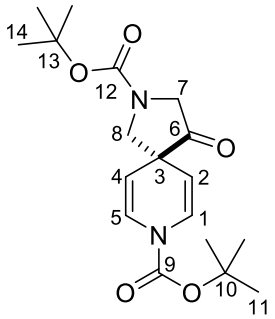
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 1H, $C_{1/5}H$), 6.95 (m, 1H, $C_{1/5}H$), 4.75 (m, 1H, $C_{2/4}H$), 4.64 (m, 1H, $C_{2/4}H$), 4.06 (s, 2H, C_7H), 3.92 (s, 2H, C_8H), 1.50 (s, 9H, $C_{11}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.4 (C_6), 149.6 (C_9), 125.8 ($C_{1/5}$), 125.2 ($C_{1/5}$), 103.3 ($C_{2/4}$), 102.6 ($C_{2/4}$), 83.0 (C_{12}), 79.7 (C_7), 69.7 (C_8), 50.4 (C_3), 28.2 (C_{11})

vmax /cm^{-1} (neat) 2978 (w.), 2870 (w.), 1762 (m.), 1720 (s.), 1333 (s.), 1317 (s.), 1166 (m.), 1129 (m.)

HRMS m/z (APCI) $C_{13}H_{17}NO_4$ $[M+H]^+$ requires: 252.1230; found: 252.1240

7.5.4.6 Di-*tert*-Butyl 4-oxo-2,8-diazaspiro[4.5]deca-6,9-diene-2,8-dicarboxylate (524f)



Synthesised using **GP1** with **523f** on a 0.25 mmol scale. Purified by flash column chromatography (5-40% Acetone/Pentane) to give the product as an off-white solid (64%, 56 mg, 0.16 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (m, 1H, $C_{1/5}H$), 6.94 (m, 1H, $C_{1/5}H$)z, 4.73 (m, 1H, $C_{2/4}H$), 4.60 (m, 1H, $C_{2/4}H$), 3.89 (m, 2H, C_7H), 3.54 (s, 2H, C_8H), 1.49 (s, 9H, $C_{11/14}H$), 1.47 (s, 9H, $C_{11/14}H$)

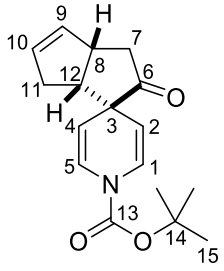
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 ($C_{9/12}$), 149.6 ($C_{9/12}$), 125.6 ($C_{1/5}$), 124.9 ($C_{1/5}$), 103.9 ($C_{2/4}$), 103.1 ($C_{2/4}$), 83.1 (C_7), 80.8 (C_8), 77.4 ($C_{10/13}$), 51.0 (C_3), 28.5 ($C_{11/14}$), 28.2 ($C_{11/14}$)

vmax /cm^{-1} (neat) 2978 (w.), 1763 (m.), 1699 (s.), 1687 (s.), 1368 (s.), 1334 (s.), 1317 (s.), 1160 (s.), 1127 (s.)

HRMS m/z (ESI) $C_{18}H_{26}N_2O_5$ $[M+H]^+$ requires: 351.1914; found: 351.1922

m.p./°C 127 – 132

7.5.4.7 *tert*-Butyl (3a*S*,6a*R*)-2-oxo-3,3a,6,6a-tetrahydro-1'H,2H-spiro[pentalene-1,4'-pyridine]-1'-carboxylate (524g)



Synthesised using **GP1** with **523g** on a 0.25 mmol scale. Purified by flash column chromatography (5-40% Acetone/Pentane) to give the product as a viscous orange oil (87%, 63 mg, 0.22 mmol).

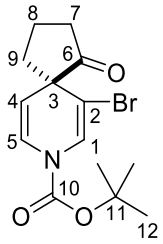
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 7.5 Hz, 1H, $C_{1/5}H$), 6.87 (d, J = 7.5 Hz, 1H, $C_{1/5}H$), 5.79 – 5.67 (m, 2H, C_9H, $C_{10}H$), 4.62 (m, 1H, $C_{2/4}H$), 4.51 (m, 1H, $C_{2/4}H$), 3.34 (m, 1H, C_8H), 2.71 – 2.17 (m, 5H, C_7H, $C_{11}H$, $C_{12}H$), 1.47 (s, 9H, $C_{15}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.0 (C_6), 168.6 (C_{13}), 149.8, 134.5 ($C_{9/10}$), 131.9 ($C_{9/10}$), 125.0 ($C_{1/5}$), 124.4 ($C_{1/5}$), 124.3 ($C_{1'/5'}$), 123.5 ($C_{1'/5'}$), 107.8 ($C_{2/4}$), 107.1 ($C_{2/4}$), 104.6 ($C_{2'/4'}$), 104.0 ($C_{2'/4'}$), 82.6 (C_{14}), 82.4 ($C_{14'}$), 57.8 ($C_{3'}$), 54.2 (C_3), 51.7 (C_{11}), 51.3 ($C_{11'}$), 42.5 (C_8), 42.3 ($C_{8'}$), 38.8 (C_7), 33.8 ($C_{7'}$), 28.23 ($C_{15'}$), 28.16 (C_{15}), 28.0 ($C_{12'}$), 27.5 (C_{12}) *(2 rotamers – assigned as C_n and $C_{n'}$)*

νmax /cm^{-1} (neat) 2977 (w.), 1716 (s.), 1684 (m.), 1368 (m.), 1318 (s.), 1161 (m.), 1121 (m.), 971 (m.), 739 (m.)

HRMS m/z (APCI) $C_{12}H_{13}NO$ $[M\text{-Boc}+H]^+$ requires: 188.1070; found: 188.1070

7.5.4.8 *tert*-Butyl (±)-6-bromo-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524h)[cc]



Synthesised using **GP1** with **523h** on a 0.25 mmol scale. Purified by flash column chromatography (1:10 Acetone/Petroleum Ether) to give the product as a yellow oil (50%, 41 mg, 0.13 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.17 (m, 1H, $C_{1/1'}H$), 6.84 (m, 1H, $C_{5/5'}H$), 4.67 (m, 1H, $C_{4/4'}H$), 2.52 (tdd, J = 13.0, 6.0, 3.0 Hz, 1H, C_7H_a), 2.44 – 2.34 (m, 1H, C_7H_b), 2.27 (dt, J = 19.0, 9.5 Hz, 1H, $C_{8/9}H_a$), 2.09 (tdd, J = 10.5, 8.5, 7.0, 4.5 Hz, 1H, $C_{8/9}H_b$), 1.99 – 1.86 (m, 2H, $C_{8/9}H$), 1.49 (s, 9H, $C_{12}H$)

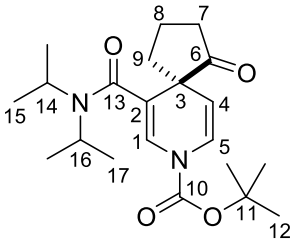
^{13}C NMR (126 MHz, $CDCl_3$) δ 216.2 (C_6), 216.0 ($C_{6'}$), 148.8 (C_{10}), 126.5 (C_1), 125.9 ($C_{1'}$), 122.3 (C_5), 121.8 ($C_{5'}$), 105.7 (C_4), 105.3 ($C_{4'}$), 104.8, 83.5 (C_{11}), 83.4 ($C_{11'}$), 55.5 (C_3), 38.3 ($C_{8/9}$), 38.2 ($C_{8'/9'}$), 36.9 (C_7), 36.7 ($C_{7'}$), 28.2 (C_{12}), 28.1 ($C_{12'}$), 18.9 ($C_{8/9}$), 18.8 ($C_{8'/9'}$)

νmax /cm^{-1} (neat) 2975 (w.), 2930 (w.), 1722 (s.), 1680 (w.), 1630 (w.), 1356 (m.), 1315 (s.), 1160 (m.), 1129 (m.), 990 (m.), 857 (w.), 760 (w.)

HRMS m/z (ESI) $C_{14}H_{19}NO_3Br$ $[M+H]^+$ requires: 328.0543; found: 328.0553

[cc] Prepared by Tom Jentsch

7.5.4.9 *tert*-Butyl (±)-6-(diisopropylcarbamoyl)-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524i)[dd]



Synthesised using **GP1** with **523i** on a 0.25 mmol scale. Purified by flash column chromatography (3:1 EtOAc/Petroleum Ether) to give the product as a colourless oil (67%, 64 mg, 0.17 mmol).

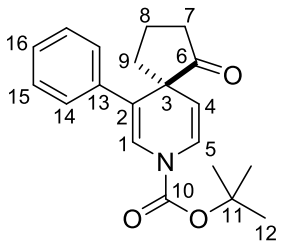
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (m, 1H, C_1H), 6.86 (m, 1H, C_5H), 4.66 (m, 1H, C_4H), 2.59 – 2.44 (m, 1H, $C_{7/8/9/14/16}H$), 2.33 – 2.08 (m, 2H, $C_{7/8/9/14/16}H$), 1.99 – 1.90 (m, 3H, $C_{7/8/9/14/16}H$), 1.90 – 1.80 (m, 2H, $C_{7/8/9}H$), 1.48 (s, 9H, $C_{12}H$), 1.34 – 1.20 (m, 12H, $C_{15}H$, $C_{17}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.5 (C_6), 217.3 ($C_{6'}$), 168.4 ($C_{13/13'}$), 149.6 (C_{10}), 149.4 ($C_{10'}$), 124.2 (C_1), 123.3 ($C_{1'}$), 122.7 (C_5), 122.1 ($C_{5'}$), 116.5 (C_2), 115.6 ($C_{2'}$), 109.1 (C_4), 108.6 ($C_{4'}$), 83.1 (C_{11}), 50.7 (C_3), 48.6 ($C_{14/16}$), 48.5 ($C_{14/16}$), 38.9 ($C_{8/9}$), 38.7 ($C_{8'/9'}$), 36.6 (C_7), 36.5 ($C_{7'}$), 29.8, 28.2 (C_{12}), 21.2 ($C_{15/17}$), 20.7 ($C_{15/17}$), 19.4 ($C_{8/9}$), 14.3 ($C_{8'/9'}$)

vmax /cm^{-1} (neat) 2969 (m.), 1721 (s.), 1615 (m.), 1365 (m.), 1296 (s.), 1146 (s.), 760 (m.)

HRMS m/z (ESI) $C_{20}H_{33}N_2O_5$ $[M+H]^+$ requires: 377.2435; found: 377.2428

7.5.4.10 *tert*-Butyl (±)-6-(phenyl)-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524j)



Synthesised using **GP1** with **523j** on a 0.25 mmol scale. Purified by flash column chromatography (2-20% Acetone/Petroleum Ether) to give the product as an amorphous off-white solid (33%, 27 mg, 0.08 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.07 (m, 5H, $C_{14/15/16}H$), 7.05 – 6.78 (m, 2H, $C_{1/5}H$), 4.73 (m, 1H, C_4H), 2.50 – 2.34 (m, 1H, C_7H), 2.23 – 2.04 (m, 2H, $C_{7/8/9}H$), 1.92 – 1.76 (m, 2H, $C_{8/9}H$), 1.73 – 1.62 (m, 1H, $C_{8/9}H$), 1.50 (s, 9H, $C_{12}H$)

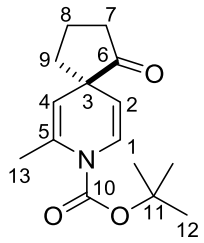
[dd] Prepared by Noelia Velasco Perez

^{13}C NMR (101 MHz, $CDCl_3$) δ 218.7 (C_6), 149.8 (C_{10}), 138.8 (C_2), 138.6 ($C_{2'}$), 129.3 ($C_{14/15/16}$), 129.1 (C_{13}), 128.4 ($C_{14/15/16}$), 127.4 ($C_{14/15/16}$), 123.9 (C_1), 123.5 ($C_{1'}$), 122.8 (C_5), 122.4 ($C_{5'}$), 119.9 (C_2), 119.2 ($C_{2'}$), 107.1 (C_4), 106.7 ($C_{4'}$), 84.0 (C_{11}), 82.8 ($C_{11'}$), 57.8 (C_3), 54.1 ($C_{3'}$), 37.3 ($C_{8/9}$), 37.2 ($C_{8'/9'}$), 37.0 (C_7), 36.9 ($C_{7'}$), 28.2 (C_{12}), 27.5 ($C_{12'}$), 24.7 ($C_{8/9}$), 18.7 ($C_{8'/9'}$)

vmax /cm^{-1} (neat) 2976 (w.), 1715 (s.), 1682 (m.), 1394 (m.), 1353 (s.), 1326 (s.), 1253 (s.), 1154 (s.), 1121 (m.), 990 (s.), 763 (m.), 735 (m.), 702 (m.)

HRMS m/z (ESI) $C_{20}H_{23}NO$ $[M+H]^+$ requires: 326.1751; found: 326.1742

7.5.4.11 *tert*-Butyl (±)-7-methyl-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524k)[ee]



Synthesised using a modified **GP1** with **523k** on a 0.25 mmol scale. 5 eq. Boc_2O added at start, a further 5 eq. added after 10 h. Purified by flash column chromatography (1:5 EtOAc/Petroleum Ether) to give the product as a pale yellow oil (86%, 32 mg, 0.22 mmol).

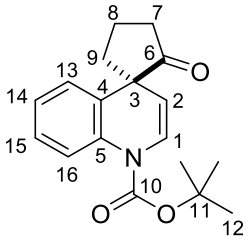
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (m, 1H, C_1H), 4.65 (m, 1H, C_2H), 4.44 (m, 1H, C_4H), 2.29 (m, 2H, C_7H), 2.17 (s, 3H, $C_{13}H$), 1.94 (m, 2H, $C_{8/9}H$), 1.86 (m, 2H, $C_{8/9}H$), 1.48 (s, 9H, $C_{12}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 218.3 (C_6), 150.9 (C_{10}), 134.6 (C_5), 127.0 (C_1), 108.5 (C_2), 107.0 (C_4), 82.4 (C_{11}), 51.4 (C_3), 40.1 ($C_{8/9}$), 35.9 (C_7), 28.3 (C_{12}), 23.0 (C_{13}), 18.4 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2977 (w.), 1743 (s.), 1613 (w.), 1403 (m.), 1285 (s.), 1252 (m.), 1165 (m.), 1127 (m.), 1111 (m.)

HRMS m/z (ESI) $C_{15}H_{21}NO_3Na$ $[M+Na]^+$ requires: 286.1414; found: 286.1409

7.5.4.12 *tert*-Butyl (±)-2-oxo-1'H-spiro[cyclopentane-1,4'-quinoline]-1'-carboxylate (524l)[ff]



[ee] Prepared by Noelia Velasco Perez
[ff] Prepared by Noelia Velasco Perez

Synthesised using **GP1** with **523l** on a 0.25 mmol scale. Purified by flash column chromatography (1:5 EtOAc/Petroleum Ether) to give the product as a pale yellow oil (24%, 18 mg, 0.06 mmol).

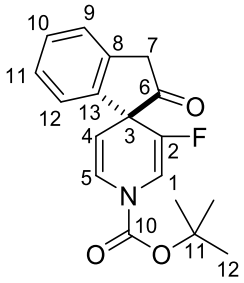
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.0, 1.5 Hz, 1H, $C_{16}H$), 7.23 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, $C_{14}H$), 7.10 (ddd, J = 8.0, 8.0, 1.5 Hz, $C_{15}H$), 7.08 (d, J = 8.0 Hz, 1H, $C_{13}H$), 6.95 (dd, J = 8.0 Hz, 1H, C_1H), 5.04 (d, J = 8.0 Hz, 1H, C_2H), 2.56 – 2.28 (m, 3H, C_7H, $C_{8/9}H$), 2.20 – 2.03 (m, 3H, C_8H, C_9H), 1.57 (s, 9H, $C_{12}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.8 (C_6), 151.3 (C_{10}), 136.6 (C_5), 130.1 (C_4), 127.3 (C_1), 127.0 (C_{16}), 125.9 (C_{14}), 124.8 (C_{15}), 121.9 (C_{13}), 110.3 (C_2), 82.7 (C_{11}), 53.2 (C_3), 39.6 (C_7), 37.4 ($C_{8/9}$), 28.4 (C_{12}), 18.9 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2980 (w.), 1742 (s.), 1592 (w.), 1492 (m.), 1279 (s.), 1250 (s.), 1151 (m.), 1104 (m.), 845 (m.)

HRMS m/z (ESI) $C_{18}H_{22}NO_3Na$ $[M+Na]^+$ requires: 322.1404; found: 322.1408

7.5.4.13 *tert*-Butyl (*R*)-3'-fluoro-2-oxo-2,3-dihydro-1'H-spiro[indene-1,4'-pyridine]-1'-carboxylate (527a)[gg]



Synthesised using **GP1** with **526** on a 0.25 mmol scale. Purified by flash column chromatography (10-100% Acetone/Pentane) to give the product as an amorphous off-white solid (36%, 25.6 mg, 0.09 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 1H, C_1H), 7.69 – 7.59 (m, 1H, C_5H), 7.43 (m, 2H, $C_{9/10/11/12}H$), 7.25 – 6.90 (m, 2H, $C_{9/10/11/12}H$), 4.81 – 4.54 (m, 1H, C_4H), 3.60 (d, J = 17.5 Hz, 1H, C_7H_a), 3.05 (d, J = 17.5 Hz, 1H, C_7H_b), 1.51 (s, 9H, $C_{12}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.1 (C_6), 152.4 (C_{10}), 135.8 ($C_{9/10/11/12}$), 134.1 ($C_{8/13}$), 128.3 ($C_{9/10/11/12}$), 126.5 ($C_{9/10/11/12}$), 125.2 ($C_{9/10/11/12}$), 123.8 (C_5), 123.2 ($C_{5'}$), 110.5 (d, J = 43 Hz, C_1), 109.6 (d, J = 45 Hz, $C_{1'}$), 107.9 (d, J = 11 Hz, C_4), 107.4 (d, J = 11 Hz $C_{4'}$), 83.2 (C_{11}), 52.9 (d, J = 25 Hz, C_3), 41.8 (C_7), 28.3 (C_{12}), 28.2 ($C_{12'}$)

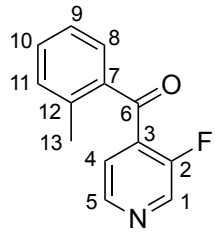
^{19}F NMR (101 MHz, $CDCl_3$) δ -147.8, -148.5

vmax /cm^{-1} (neat) 2943 (w.), 2832 (w.), 1021 (s.), 737 (w.), 621 (w.)

[gg] Prepared by Noelia Velasco Perez

HRMS m/z (APCI) $C_{13}H_{11}FNO$ $[M\text{-}Boc+H]^+$ requires: 216.0819; found: 216.0820

7.5.4.14 (3-Fluoropyridin-4-yl)(*o*-tolyl)methanone (528)[hh]



Synthesised (side-product) using **GP1** with **526** on a 0.25 mmol scale. Purified by flash column chromatography (10-100% Acetone/Pentane) to give the product as an amorphous off-white solid (63%, 31.5 mg, 0.16 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) 8.65 – 8.48 (m, 2H, C_1H, C_5H), 7.44 (m, 2H, $C_{8/9/10/11}H$), 7.38 – 7.29 (m, 2H, $C_{8/9/10/11}$), 7.27 – 7.19 (m, 1H, C_4H), 2.56 (m, 3H, $C_{13}H$)

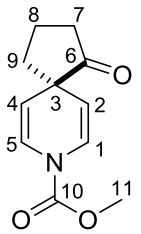
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3 (C_6), 156.0 (d, J = 260 Hz, C_2), 146.3 (d, J = 5 Hz, C_5), 139.8 (d, J = 25 Hz, C_1), 139.7 ($C_{7/12}$), 136.1 ($C_{7/12}$), 134.6 (d, J = 11 Hz, C_3), 132.9 ($C_{8/9/10/11}$), 132.2 ($C_{8/9/10/11}$), 131.3 ($C_{8/9/10/11}$), 125.9 ($C_{8/9/10/11}$), 123.5 (C_4), 21.3 (C_{13})

vmax /cm^{-1} (neat) 2978 (w.), 2932 (w.), 1714 (s.), 1369 (m.), 1324 (s.), 1312 (s.), 1153 (s.), 944 (s.), 756 (m.), 730 (m.)

HRMS m/z (ESI) $C_{13}H_{11}FNO$ $[M+H]^+$ requires: 216.0819; found: 216.0813

7.5.5 Scope of acylating agents

7.5.5.1 Methyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517b)



Synthesised using **GP2** with **515** on a 0.25 mmol scale using methyl chloroformate (30 µL,, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a white solid (57%, 29 mg, 0.14 mmol).

[hh] Prepared by Noelia Velasco Perez

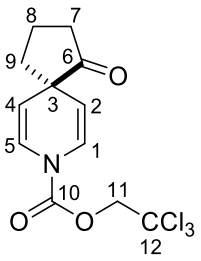
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.0 Hz, 1H, $C_{1/5}H$), 6.94 – 6.82 (d, J = 8.0 Hz, 1H, $C_{1/5}H$), 4.72 (d, J = 8.0 Hz, 1H, $C_{2/4}H$), 4.61 (d, J = 8.0 Hz, 1H, $C_{2/4}H$), 3.80 (s, 3H, $C_{11}H$), 2.32 (m, 2H, C_7H), 2.05 – 1.81 (m, 4H, $C_{8/9}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.8 (C_6), 151.7 (C_{10}), 123.8 ($C_{1/5}$), 123.6 ($C_{1/5}$), 107.3 ($C_{2/4}$), 107.0 ($C_{2/4}$), 53.7 (C_{11}), 50.4 (C_3), 40.5 ($C_{8/9}$), 35.8 (C_7), 18.5 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2958 (w.), 1717 (s.), 1687 (m.), 1627 (w.), 1440 (m.), 1368 (m.), 1334 (s.), 1314 (s.), 1213 (m.), 1118 (m.)

HRMS m/z (ESI) $C_{11}H_{13}NO_3$ $[M+H]^+$ requires: 208.0968; found: 208.0959

7.5.5.2 2,2,2-Trichloroethyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517c)



Synthesised using **GP2** with **515** on a 0.25 mmol scale using 2,2,2-trichloroethyl chloroformate (Troc-Cl, 52 µL, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a white solid (53%, 19 mg, 0.13 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.95 (m, 2H, $C_{1/5}H$), 4.90 – 4.80 (m, 2H, $C_{11}H$), 4.79 – 4.71 (m, 2H, $C_{2/4}H$), 2.36 (m, 2H, C_7H), 2.06 – 1.90 (m, 4H, $C_{8/9}H$)

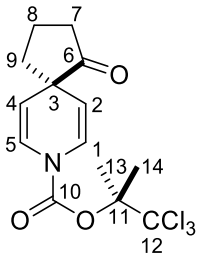
^{13}C NMR (101 MHz, $CDCl_3$) δ 217.4 (C_6), 149.6 (C_{10}), 123.5 ($C_{1/5}$), 123.1 ($C_{1/5}$), 108.8 ($C_{2/4}$), 108.3 ($C_{2/4}$), 94.7 (C_{12}), 75.7 (C_{11}), 50.4 (C_3), 40.3 ($C_{8/9}$), 35.9 (C_7), 18.5 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2960 (w.), 1725 (s.), 1690 (m.), 1629 (w.), 1417 (m.), 1384 (m.), 1333 (m.), 1308 (s.), 1215 (m.), 1121 (m.)

HRMS m/z (ESI) $C_{12}H_{12}Cl_3NO_3$ $[M+H]^+$ requires: 323.9956; found: 323.9953

m.p./°C 102 – 107

7.5.5.3 1,1,1-Trichloro-2-methylpropan-2-yl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517d)



Synthesised using **GP2** with **515** on a 0.25 mmol scale using 2,2,2-trichloro-1,1-dimethylethyl chloroformate (Me_2Troc-Cl, 90 mg, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a white solid (93%, 82 mg, 0.23 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (m, 2H, $C_{1/5}H$), 4.71 (m, 2H, $C_{2/4}H$), 2.35 (dd, J = 8.0, 6.9 Hz, 2H, C_7H), 2.06 – 1.85 (m, 4H, $C_{8/9}H$), 1.95 (s, 3H, $C_{13/14}H$), 1.93 (s, 3H, $C_{13/14}H$)

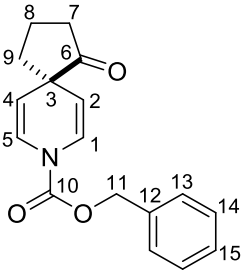
^{13}C NMR (101 MHz, $CDCl_3$) δ 217.9 (C_6), 148.4 (C_{10}), 123.8 ($C_{1/5}$), 123.3 ($C_{1/5}$), 107.9 ($C_{2/4}$), 107.4 ($C_{2/4}$), 106.0 (C_{12}), 90.3 (C_{11}), 50.5 (C_3), 40.6 ($C_{8/9}$), 36.0 (C_7), 21.59 ($C_{13/14}$), 21.50 ($C_{13/14}$), 18.5 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2959 (w.), 1721 (s.), 1689 (m.), 1628 (w.), 1457 (w.), 1367 (m.), 1337 (s.), 1320 (s.), 1157 (m.), 1115 (m.)

HRMS m/z (ESI) $C_{14}H_{16}Cl_3NO_3$ $[M+H]^+$ requires: 352.0269; found: 352.0266

m.p./°C 133 – 138

7.5.5.4 Benzyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517e)



Synthesised using **GP2** with **515** on a 0.25 mmol scale using benzyl chloroformate (60 µL, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a pale yellow solid (71%, 51 mg, 0.18 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H, $C_{13}H$, $C_{14}H$, $C_{15}H$), 7.03 (d, J = 8.5 Hz, 1H, $C_{1/5}H$), 6.94 (d, J = 8.5 Hz, 1H, $C_{1/5}H$), 5.26 – 5.16 (s, 2H, $C_{11}H$), 4.80 – 4.70 (d, J = 8.5 Hz, 1H, $C_{2/4}H$), 4.61 (d, J = 8.5 Hz, 1H, $C_{2/4}H$), 2.33 (td, J = 7.5, 2.5 Hz, 2H, C_7H), 1.95 (m, 4H, $C_{8/9}H$)

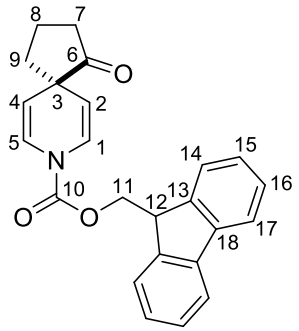
^{13}C NMR (101 MHz, $CDCl_3$) δ 217.8 (C_6), 151.1 (C_{10}), 135.5 (C_{12}), 128.8 ($C_{13/14/15}$), 128.7 ($C_{13/14/15}$), 128.5 ($C_{13/14/15}$), 123.8 ($C_{1/5}$), 123.6 ($C_{1/5}$), 107.5 ($C_{2/4}$), 107.1 ($C_{2/4}$), 68.5 (C_{11}), 50.4 (C_3), 40.5 ($C_{8/9}$), 35.9 (C_7), 18.5 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2959 (w.), 1715 (s.), 1686 (s.), 1387 (m.), 1332 (s.), 1301 (s.), 1212 (m.), 1109 (m.), 957 (m.), 735 (s.)

HRMS m/z (ESI) $C_{17}H_{17}NO_3$ $[M+Na]^+$ requires: 306.1101; found: 306.1095

m.p./°C 102 – 107

7.5.5.5 (9*H*-Fluoren-9-yl)methyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517f)[ii]



Synthesised using a modified **GP2** with **515** on a 0.25 mmol scale, with 9*H*-fluorenylmethyl chloroformate (129.4 mg, 0.5 mmol, 2.0 eq.) and diisopropylethylamine (0.09 mL, 0.5 mmol, 2.0 eq.). Purified by flash column chromatography (1:15 EtOAc/Toluene) to give the product as a white solid (64%, 59 mg, 0.16 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (ddd, J = 7.5, 1.0, 1.0 Hz, 2H, $C_{14/17}H$), 7.57 (ddd, J = 7.5, 1.0, 1.0 Hz, 2H, $C_{14/17}H$)), 7.42 (ddd, J = 7.5, 7.5, 1.0 Hz, 2H, $C_{15/16}H$), 7.33 (ddd, J = 7.5, 7.5, 1.0 Hz, 2H, $C_{15/16}H$), 7.04 (d, J = 8.0 Hz, 1H, $C_{1/5}H$), 6.88 (d, J = 8.0 Hz, 1H, $C_{1/5}H$), 4.76 (d, J = 8.0 Hz, 1H, $C_{2/4}H$), 4.68 (d, J = 8.0 Hz, 1H, $C_{1/5}H$), 4.52 (d, J = 7.0 Hz, 2H, $C_{11}H$), 4.27 (t, J = 7.0 Hz, 1H, $C_{12}H$), 2.39 – 2.32 (m, 2H, C_7H), 2.05 – 1.90 (m, 4H, C_8H, C_9H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.8 (C_6), 151.0 (C_{10}), 143.5 ($C_{13/18}$), 141.4 ($C_{13/18}$), 128.0 ($C_{15/16}$), 127.3 ($C_{15/16}$), 125.0 ($C_{14/17}$), 123.7 ($C_{1/5}$), 123.3 ($C_{1/5}$), 120.2 ($C_{14/17}$), 107.6 ($C_{2/4}$), 107.4 ($C_{2/4}$), 68.7 (C_{11}), 50.4 (C_3), 47.0 (C_{12}), 40.5 ($C_{8/9}$), 35.9 (C_7), 18.5 ($C_{8/9}$)

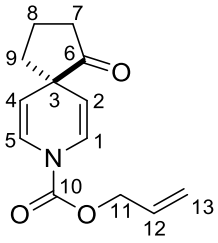
vmax /cm^{-1} (neat) 2958 (w.), 1717 (s.), 1686 (m.), 1391 (m.), 1334 (m.), 1305 (s.), 1212 (m.), 1113 (m.)

HRMS m/z (ESI) $C_{24}H_{21}NO_3Na$ $[M+Na]^+$ requires: 394.1414; found: 394.1429

m.p./°C 102 – 107

[ii] Prepared by Laia Vicens I Serra

7.5.5.6 Allyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517g)



Synthesised using **GP2** with **515** on a 0.25 mmol scale using benzyl chloroformate (30 µL, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a colourless oil (68%, 39 mg, 0.17 mmol).

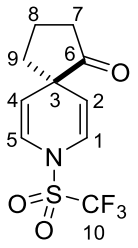
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 7.0 Hz, 1H, $C_{1/5}H$), 6.93 (d, J = 7.0 Hz, 1H, $C_{1/5}H$), 5.92 (ddt, J = 17.0, 10.5, 5.5 Hz, 1H, $C_{12}H$), 5.33 (dq, J = 17.0, 1.5 Hz, 2H, $C_{13}H$), 5.25 (dq, J = 10.5, 1.5 Hz, 1H), 4.73 (d, J = 7.0 Hz, 1H, $C_{2/4}H$), 4.68 (dt, J = 5.5, 1.5 Hz, 2H, $C_{11}H$), 4.65 – 4.56 (d, J = 7.0 Hz, 1H, $C_{2/4}H$), 2.37 – 2.27 (m, 2H, C_7H), 1.95 (m, 4H, C_8H, C_9H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.7 (C_6), 150.9 (C_{10}), 131.9 (C_{12}), 123.6 ($C_{1/5}$), 118.9 (C_{13}), 107.4 ($C_{2/4}$), 107.1 ($C_{2/4}$), 67.3 (C_{11}), 50.4 (C_3), 40.5 ($C_{8/9}$), 35.8 (C_7), 18.5 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2960 (w.), 1716 (s.), 1687 (m.), 1415 (m.), 1378 (s.), 1332 (s.),1305 (s.), 1212 (m.), 1111 (m.), 958 (s.), 736 (s.)

HRMS m/z (EI) $C_{13}H_{15}NO$ $[M]^+$ requires: 233.1046; found: 233.1046

7.5.5.7 8-((Trifluoromethyl)sulfonyl)-8-azaspiro[4.5]deca-6,9-dien-1-one (517h)



Synthesised using a modified **GP2** with **515** on a 0.25 mmol scale using trifluoromethanesulfonic anhydride (0.38 mL of a 1 M soln in DCM, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a colourless oil (68%, 39 mg, 0.17 mmol).

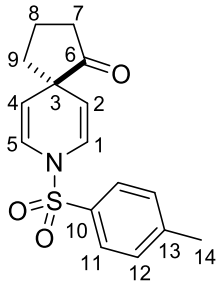
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, J = 8.0 Hz, 2H, $C_{1/5}H$), 4.92 (d, J = 8.0 Hz, 2H, $C_{2/4}H$), 2.36 (td, J = 7.5, 7.0, 1.5 Hz, 2H, C_7H), 2.12 – 1.91 (m, 4H, $C_{8/9}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.5 (C_6), 122.3 ($C_{1/5}$), 111.1 ($C_{2/4}$), 49.7 (C_3), 39.9 ($C_{8/9}$), 35.8 (C_7), 18.6 ($C_{8/9}$) (*C_{10} not observed due to ^{19}F splitting)*

vmax /cm^{-1} (neat) 2967 (w.), 1744 (m.), 1407 (s.), 1229 (s.), 1160 (s.), 1060 (s.), 936 (m.), 703 (m.), 658 (m.), 591 (s.)

HRMS m/z (APCI) $C_{10}H_{11}FNO_3S$ $[M+H]^+$ requires: 282.0406; found: 282.0403

7.5.5.8 8-Tosyl-8-azaspiro[4.5]deca-6,9-dien-1-one (517i)



Synthesised using **GP2** with **515** on a 0.25 mmol scale using *p*-toluenesulfonyl chloride (tosyl chloride, 72 mg, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a yellow solid (66%, 50 mg, 0.17 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.56 (m, 2H, $C_{12}H$), 7.41 – 7.28 (m, 2H, $C_{11}H$), 6.76 – 6.61 (m, 2H, $C_{1/5}H$), 4.74 – 4.58 (m, 2H, $C_{2/4}H$), 2.43 (s, 3H, $C_{14}H$), 2.26 (t, J = 7.5 Hz, 2H, C_7H), 1.92 (dt, J = 14.0, 7.0 Hz, 2H, $C_{8/9}H$), 1.85 – 1.78 (m, 2H, $C_{8/9}H$)

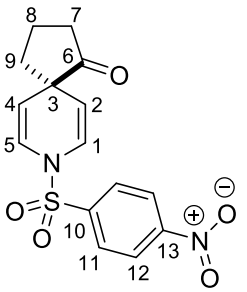
^{13}C NMR (101 MHz, $CDCl_3$) δ 216.7 (C_6), 144.5 (C_{13}), 135.2 (C_{10}), 130.1 (C_{11}), 127.0 (C_{12}), 123.5 ($C_{1/5}$), 108.6 ($C_{2/4}$), 50.0 (C_3), 40.6 ($C_{8/9}$), 35.7 (C_7), 21.8 (C_{14}), 18.4 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2962 (w.), 1741 (m.), 1372 (m.), 1347 (m.), 1170 (s.), 711 (m.), 668 (m.)

HRMS m/z (ESI) $C_{16}H_{17}NO_3S$ $[M+H]^+$ requires: 304.1002; found: 304.0998

m.p./°C 127 – 132

7.5.5.9 8-((4-Nitrophenyl)sulfonyl)-8-azaspiro[4.5]deca-6,9-dien-1-one (517j)



Synthesised using **GP2** with **515** on a 0.25 mmol scale using *p*-nitrophenylsulfonyl chloride (nosyl chloride, 83 mg, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (6-50% acetone/pentane) to give the product as an amorphous orange solid (35%, 29 mg, 0.09 mmol).

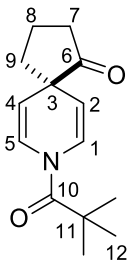
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.28 (m, 2H), 8.09 – 7.90 (m, 2H), 6.67 (d, J = 8.0 Hz, 2H, $C_{1/5}H$), 4.77 (d, J = 8.0 Hz, 2H, $C_{2/4}H$), 2.24 (t, J = 7.5 Hz, 2H, C_7H), 1.98 – 1.89 (m, 2H, $C_{8/9}H$), 1.86 (m, 2H, $C_{8/9}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.8 (C_6), 150.6 (C_{13}), 143.1 (C_{10}), 128.4 (C_{11}), 124.7 (C_{12}), 123.0 ($C_{1/5}$), 111.1 $C_{2/4}$), 50.2 (C_3), 40.0 ($C_{8/9}$), 35.7 (C_7), 18.5 ($C_{8/9}$)

vmax /cm^{-1} (neat) 3106 (w.), 1740 (m.), 1530 (s.), 1377 (m.), 1346 (s.), 1176 (s.), 955 (m.), 739 (s.), 606 (m.)

HRMS m/z (ESI) $C_{15}H_{15}N_2O_5S$ $[M+H]^+$ requires: 335.0696; found: 335.0693

7.5.5.10 8-Pivaloyl-8-azaspiro[4.5]deca-6,9-dien-1-one (517k)



Synthesised using **GP2** with **515** on a 0.25 mmol scale using pivaloyl chloride (50 µL, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as an amorphous white solid (37%, 21 mg, 0.09 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.5 Hz, 2H, $C_{1/5}H$), 4.71 (d, J = 8.5 Hz, 2H, $C_{2/4}H$), 2.33 (t, J = 7.5 Hz, 2H, C_7H), 2.03 – 1.90 (m, 4H, C_8H, C_9H), 1.33 (s, 9H, $C_{12}H$)

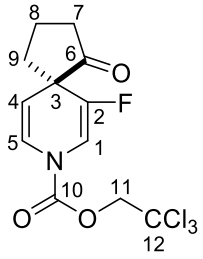
^{13}C NMR (101 MHz, $CDCl_3$) δ 217.5 (C_6), 173.8 (C_{10}), 124.9 ($C_{1/5}$), 107.5 ($C_{2/4}$), 50.6 (C_3), 40.3 ($C_{8/9}$), 39.6 (C_{11}), 36.0 (C_7), 28.3 (C_{12}), 18.5 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2968 (m.), 1743 (s.), 1661 (s.), 1299 (s.), 1195 (s.), 967 (m.), 744 (m.)

HRMS m/z (ESI) $C_{14}H_{19}NO_2$ $[M+H]^+$ requires: 234.2394; found: 234.1479

m.p./°C 113 – 118

7.5.5.11 2,2,2-Trichloroethyl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519a)



Synthesised using **GP2** with **518** on a 0.25 mmol scale using 2,2,2-trichloroethyl chloroformate (Troc-Cl, 52 µL, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (2-30% acetone/pentane) to give the product as a white solid (52%, 45 mg, 0.13 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (ddd, J = 10.0, 5.0, 1.5 Hz, 1H, C_1H), 6.95 (ddt, J = 8.5, 7.0, 1.5 Hz, 1H, C_5H), 4.99 – 4.69 (m, 3H, $C_{11}H$, C_4H), 2.53 – 2.27 (m, 2H, C_7H), 2.17 – 1.90 (m, 4H, $C_{8/9}H$)

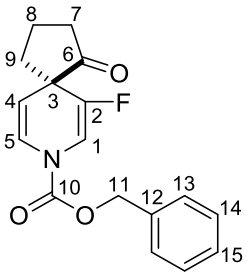
^{13}C NMR (101 MHz, $CDCl_3$) δ 215.5 (C_6), 215.3 ($C_{6'}$), 122.3 (d, J = 48 Hz, C_1), 109.3 (d, J = 17 Hz, C_5), 108.9 (d, J = 17 Hz, $C_{5'}$), 108.7 (d, J = 11 Hz, C_4), 108.3 (d, J = 11 Hz, $C_{4'}$), 94.5 (C_{12}), 75.9 (C_{11}), 75.8 ($C_{11'}$), 52.7 (d, J = 25 Hz, C_3), 52.6 (d, J = 25 Hz, $C_{3'}$), 37.0 ($C_{8/9}$), 36.9 ($C_{8'/9'}$), 36.1 (C_7), 36.0 ($C_{7'}$), 19.2 ($C_{8/9}$), 19.1 ($C_{8'/9'}$) (*C_2 not observed)*

vmax /cm^{-1} (neat) 2964 (w.), 1733 (s.), 1405 (s.), 1309 (s.), 1228 (s.), 1114 (s.), 922 (m.), 822 (m.), 744 (m.), 714 (s.), 569 (m.)

HRMS m/z (APCI) $C_{12}H_{12}NO_3FCl_3$ $[M+H]^+$ requires: 341.9861; found: 341.9850

m.p./°C 52 – 57

7.5.5.12 Benzyl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519c)



Synthesised using **GP2** with **518** on a 0.25 mmol scale using benzyl chloroformate (60 µL, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a pale yellow oil (80%, 60 mg, 0.2 mmol).

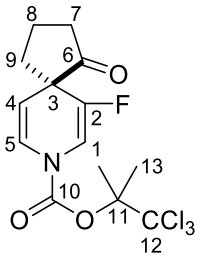
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H, $C_{13/14/15}H$), 7.10 (m, 1H, C_1H, $C_{1'}H$), 6.92 (m, 1H, C_5H, $C_{5'}H$), 5.22 (s, 2H, $C_{11}H$), 4.90 – 4.61 (m, 1H, C_4H, $C_{4'}H$), 2.49 – 2.24 (m, 3H, C_7H, $C_{8/9}H$), 2.14 – 1.84 (m, 3H, $C_{8/9}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.9 (C_6), 215.7 ($C_{6'}$), 150.8 (C_{10}), 150.5 ($C_{10'}$), 135.2 (C_{12}), 128.7 ($C_{13/14/15}$), 122.7 (d, J = 23 Hz, C_1), 109.6 (d, J = 5 Hz, C_5), 109.1 (d, J = 5 Hz, $C_{5'}$), 107.4 (d, J = 11 Hz, C_4), 107.2 (d, J = 11 Hz, $C_{4'}$), 68.8 ($C_{11/11'}$), 52.7 (d, J = 26 Hz, $C_{3/3'}$), 36.9 ($C_{8/9}$), 36.8 ($C_{8'/9'}$), 36.4 (C_7), 36.2 ($C_{7'}$), 19.2 ($C_{8/9}$), 19.0 ($C_{8'/9'}$)

vmax /cm^{-1} (neat) 2965 (w.), 1746 (m.), 1716 (s.), 1642 (w.), 1402 (s.), 1298 (s.), 1230 (m.), 1100 (m.)

HRMS m/z (ESI) $C_{17}H_{16}NO_3F$ $[M+NH_4]^+$ requires: 319.1452; found: 319.1456

7.5.5.13 1,1,1-Trichloro-2-methylpropan-2-yl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519d)



Synthesised using **GP2** with **518** on a 0.25 mmol scale using 2,2,2-trichloro-1,1-dimethylethyl chloroformate (Me_2Troc-Cl, 90 mg, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a white solid (91%, 169 mg, 0.23 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (m, 1H, C_1H), 6.90 (m, 1H, C_5H), 4.79 (m, 1H, C_4H), 2.40 (m, 4H, C_7H, $C_{8/9}H$), 2.18 – 1.89 (m, 8H, $C_{13}H$, $C_{8/9}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.0 ($C_{6/6'}$), 122.5 (d, J = 40 Hz, C_1), 109.6 (d, J = 44 Hz, $C_{1'}$), 109.1 (C_5), 108.7 ($C_{5'}$), 107.8 (d, J = 11 Hz, C_4), 107.5 (d, J = 10 Hz, $C_{4'}$), 90.6 (C_{12}), 52. 8 (d, J = 25 Hz, C_3), 52.7 (d, J = 25 Hz, $C_{3'}$), 37.0 ($C_{8/9}$), 36.9 ($C_{8'/9'}$) 36.3 (C_7), 36.2 ($C_{7'}$), 21.6 (C_{13}), 21.5 ($C_{13'}$), 19.2 ($C_{8/9}$), 19.1 ($C_{8'/9'}$) (*C_2 not observed)*

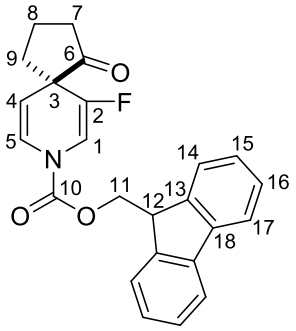
^{19}F NMR (101 MHz, $CDCl_3$) δ -144.8, -145.2

vmax /cm^{-1} (neat) 2964 (w.), 1748 (m.), 1726 (s.), 1643 (w.), 1331 (s.), 1312 (s.), 1152 (s.), 1102 (m.)

HRMS m/z (ESI) $C_{14}H_{16}NO_3FCl_3$ $[M+H]^+$ requires: 370.0174; found: 370.0186

m.p./°C 111 – 116

7.5.5.14 (9*H*-Fluoren-9-yl)methyl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519e)[jj]



Synthesised using a slightly modified **GP2** with **518** on a 0.25 mmol scale using 9*H*-fluorenylmethyl chloroformate (129 mg, 0.5 mmol, 2.0 eq.). Purified by flash column chromatography (5-10% EtOAc/pentane) giving mixture of product and 9*H*-fluorenylmethanol, which was removed by second column (5% EtOAc/Toluene) to give the product as an amorphous white solid (67%, 65 mg, 0.17 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 2H, $C_{14/17}H$), 7.56 (t, J = 6.5 Hz, 2H, $C_{15/16}H$), 7.42 (t, J = 7.5 Hz, 2H, $C_{14/17}H$), 7.34 (q, J = 6.5 Hz, 2H, $C_{15/16}H$), 7.22 – 6.72 (m, 2H, C_1H, $C_{1'}H$, C_5H, $C_{5'}H$), 4.78 (app. dt, J = 40.0, 9.0 Hz, 1H, C_4H, $C_{4'}H$), 4.53 (m, 2H, $C_{11}H$), 4.27 (m, 1H, $C_{12}H$), 2.51 – 2.28 (m, 3H, $C_{7/8/9}H$), 2.14 – 1.91 (m, 3H, $C_{7/8/9}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.8 (C_6), 215.6 ($C_{6'}$), 150.7 (C_{10}), 150.4 ($C_{10'}$), 143.4 ($C_{13/18}$), 141.4 ($C_{13/18}$), 129.2 (C_2), 128.3 ($C_{2'}$), 128.1 ($C_{14/15/16/17}$), 127.4 ($C_{14/15/16/17}$), 125.0 ($C_{14/15/16/17}$), 122.7 (C_5), 122.2 ($C_{5'}$) 120.3 ($C_{14/15/16/17}$), 109.4 (d, J = 18 Hz, C_1), 109.0 (d, J = 18 Hz, $C_{1'}$), 107.5 (d, J = 11 Hz, $C_{4/4'}$), 69.0 ($C_{11/11'}$), 52.7 (d, J = 25 Hz, $C_{3/3'}$), 47.0 ($C_{12/12'}$), 36.9 ($C_{8/9}$), 36.8 ($C_{8'/9'}$), 36.3 (C_7), 36.2 ($C_{7'}$), 19.1 ($C_{8/9}$), 19.0 ($C_{8'/9'}$)

^{19}F NMR (101 MHz, $CDCl_3$) δ -145.2, -145.4

vmax /cm^{-1} (neat) 2963 (w.), 1746 (m.), 1718 (s.), 1642 (w.), 1403 (s.), 1317 (s.), 1231 (m.), 1103 (m.)

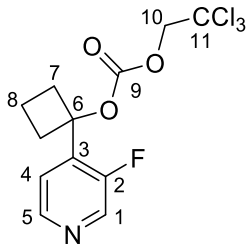
HRMS m/z (ESI) $C_{24}H_{20}NO_3FNa$ $[M+Na]^+$ requires: 412.1319; found: 412.1316

m.p./°C 147 – 152

[jj] Prepared by Laia Vicens I Serra

7.5.6 *O*-acylation products

7.5.6.1 1-(3-Fluoropyridin-4-yl)cyclobutyl (2,2,2-trichloroethyl) carbonate (520a)



Synthesised (side-product) using **GP2** with **518** on a 0.25 mmol scale using 2,2,2-trichloroethyl chloroformate (Troc-Cl, 52 µL, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (2-30% acetone/pentane) to give the product as an amorphous white solid (9%, 8 mg, 0.024 mmol).

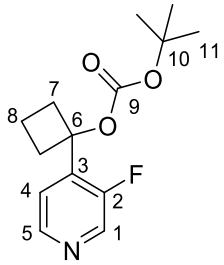
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (m, 1H, C_1H), 8.44 (d, J = 5.0 Hz, 1H, C_5H), 7.44 (dd, J = 6.5, 5.0 Hz, 1H, C_4H), 4.65 (s, 2H, $C_{10}H$), 2.85 – 2.69 (m, 4H, C_7H), 2.14 (m, 1H, C_8H_a), 1.89 – 1.76 (m, 1H, C_8H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (C_9), 145.4 (d, J = 5 Hz, C_5), 139.2 (d, J = 26 Hz, C_1), 136.0 (d, J = 10 Hz, C_3), 122.9 (C_4), 94.4 (C_{11}), 82.3 (C_{10}), 76.6 (C_6), 33.6 (C_7), 14.3 (C_8)

vmax /cm^{-1} (neat) 2958 (w.), 1757 (s.), 1414 (m.), 1239 (s.), 1104 (m.), 1049 (m.), 823 (m.), 731 (m.), 572 (w.)

HRMS m/z (ESI) $C_{12}H_{12}NO_3FCl_3$ $[M+H]^+$ requires: 341.9861; found: 341.9865

7.5.6.2 *tert*-Butyl (1-(3-fluoropyridin-4-yl)cyclobutyl) carbonate (520g)



A flame-dried microwave tube was charged with **518** (43 mg, 0.25 mmol, 1.0 eq.), 4-dimethylaminopyridine (DMAP, 9 mg, 0.075 mmol, 0.3 eq.) and anhydrous $CHCl_3$ (1.5 mL). To this was added, dropwise at RT, a solution of di-*tert*-butyl dicarbonate (83 mg, 0.375 mmol, 1.5 eq.) in MeCN (0.5 mL). The reaction mixture was then stirred for 18 h at RT. The reaction was then quenched with H_2O (5 mL) and extracted with DCM (3 x 5 mL). Organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5-40% acetone/pentane) to give the product as a white solid (85%, 57 mg, 0.21 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 3.0 Hz, 1H, C_1H), 8.42 (d, J = 5.0 Hz, 1H, C_5H), 7.42 (dd, J = 6.5, 5.0 Hz, 1H, C_4H), 2.80 – 2.60 (m, 4H, C_7H), 2.10 (m, 1H, C_8H_a), 1.88 – 1.73 (m, 1H, C_8H_b), 1.39 (s, 9H, $C_{11}H$)

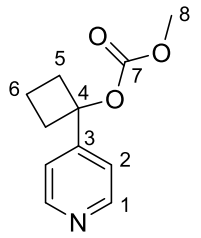
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (C_9), 151.7 (C_3), 145.2 (d, J = 5 Hz, C_5), 138.9 (d, J = 25 Hz, C_1), 122.8 (C_4), 82.9 (C_6), 80.3 (C_{10}), 33.8 (C_7), 27.8 (C_{11}), 14.4 (C_8)

vmax /cm^{-1} (neat) 2983 (w.), 1738 (s.), 1414 (w.), 1369 (w.), 1287 (s.), 1250 (m.), 1163 (m.), 1115 (s.), 850 (w.)

HRMS m/z (ESI) $C_{14}H_{19}NO_3F$ $[M+H]^+$ requires: 268.1343; found: 268.1339

m.p./°C 83 – 88

7.5.6.3 1-(Pyridin-4-yl)cyclobutyl (methyl) carbonate (532b)



Synthesised (side-product) using **GP2** with **515** on a 0.25 mmol scale using methyl chloroformate (30 µL,, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a colourless oil (27%, 14 mg, 0.7 mmol).

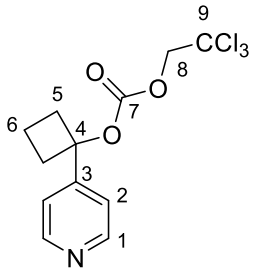
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (m, 2H, C_1H), 7.36 (m, 2H, C_2H), 3.68 (s, 3H, C_8H), 2.72 – 2.51 (m, 4H, C_5H), 2.12 – 1.93 (m, 1H, C_6H_a), 1.78 (m, 2H, C_6H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (C_7), 151.1 (C_3), 150.3 (C_1), 120.1 (C_2), 82.3 (C_4), 54.7 (C_8), 34.2 (C_5), 13.7 (C_6)

vmax /cm^{-1} (neat) 2996 (w.), 2956 (w.), 1747 (s.), 1599 (w.), 1441 (w.), 1271 (s.), 1249 (s.), 1131 (w.), 1056 (w.)

HRMS m/z (ESI) $C_{11}H_{13}NO_3$ $[M+H]^+$ requires: 208.0968; found: 208.0963

7.5.6.4 1-(Pyridin-4-yl)cyclobutyl (2,2,2-trichloroethyl) carbonate (532c)



Synthesised (side-product) using **GP2** with **515** on a 0.25 mmol scale using 2,2,2-trichloroethyl chloroformate (Troc-Cl, 52 µL, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as an amorphous solid (23%, 18 mg, 0.06 mmol).

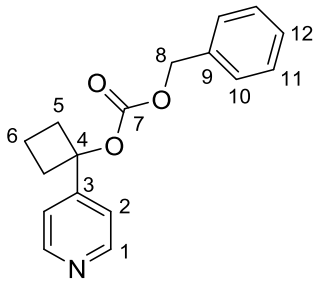
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.53 (m, 2H, C_1H), 7.43 – 7.32 (m, 2H, C_2H), 4.65 (s, 2H, C_8H), 2.80 – 2.55 (m, 4H, C_5H), 2.16 – 1.99 (m, 1H, C_6H_a), 1.90 – 1.72 (m, 1H, C_6H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (C_7), 150.4 (C_1), 120.1 (C_2), 94.4 (C_9), 83.6 (C_4), 76.6 (C_8), 34.2 (C_5), 13.6 (C_6)

vmax /cm^{-1} (neat) 2998 (w.), 2955 (w.), 1759 (s.), 1599 (w.), 1375 (w.), 1238 (s.), 1048 (m.)

HRMS m/z ESI) $C_{12}H_{12}Cl_3NO_3$ $[M+H]^+$ requires: 323.9956; found: 323.9961

7.5.6.5 Benzyl (1-(pyridin-4-yl)cyclobutyl) carbonate (532e)



Synthesised (side-product) using **GP2** with **515** on a 0.25 mmol scale using benzyl chloroformate (60 µL, 0.375 mmol, 1.5 eq.). Purified by flash column chromatography (5-40% acetone/pentane) to give the product as a yellow oil (16%, 11 mg, 0.04 mmol).

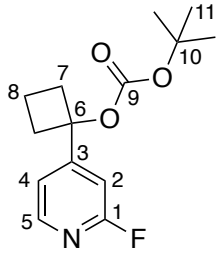
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 – 8.58 (m, 2H, C_1H), 7.38 – 7.28 (m, 7H. C_2H, $C_{10/11/12}H$), 5.05 (s, 2H, C_8H), 2.74 – 2.55 (m, 4H, C_5H), 2.12 – 1.97 (m, 1H, C_6H_a), 1.79 (m, 1H, C_6H_b)

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (C_7), 151.2 (C_3), 150.3 (C_1), 135.1 (C_9), 128.8 $C_{10/11/12}$), 128.4 ($C_{10/11/12}$), 120.1 (C_2), 82.5 (C_4), 69.7 (C_8), 34.3 (C_5), 13.7 (C_6)

vmax /cm^{-1} (neat) 2953 (w.), 1744 (s.), 1747 (s.), 1599 (w.), 1267 (s.), 1244 (s.), 1047 (w.), 698 (w.)

HRMS m/z (ESI) $C_{17}H_{17}NO_3$ $[M+H]^+$ requires: 284.1281; found: 284.1273

7.5.6.6 *tert*-Butyl (1-(2-fluoropyridin-4-yl)cyclobutyl) carbonate (531n)[kk]



Synthesised using a modified **GP1** with **523n** on a 0.25 mmol scale. 10 eq. Boc_2O was added at the start and a further 10 eq. added after 24 h. The reaction was stirred at 110 °C for 48 h. Purified by flash column chromatography (1:1 EtOAc/Petroleum Ether) to give the product as an amorphous white solid (54%, 36 mg, 0.14 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (m, 1H, C_1H), 7.26 – 7.23 (m, 1H, C_2H), 6.99 (m, 1H, C_4H), 2.72 – 2.60 (m, 2H, C_7H_a), 2.56 (m, 2H, C_7H_b), 2.12 – 2.01 (m, 1H, C_8H_a), 1.83 (m, 1H, C_8H_b), 1.40 (s, 9H, $C_{11}H$)

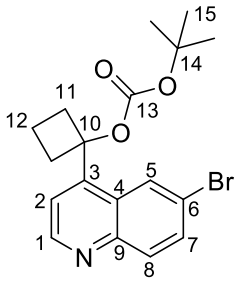
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C_9), 158.3 (C_5), 148.2 (d, 15 Hz, C_3), 117.6 (d, J = 3 Hz, C_4), 105.7 (d, J = 37 Hz, C_2), 83.1 (C_{10}), 81.2 (C_6), 34.5 (C_7), 27.8 (C_{11}), 13.7 (C_8)

νmax /cm^{-1} (neat) 2984 (w.), 1737 (s.), 1373 (m.), 1235 (s.), 1044 (s.)

HRMS m/z (ESI) $C_{15}H_{18}NO_3F$ $[M+H]^+$ requires: 268.1343; found: 268.1340

m.p./°C 65 – 70

7.5.6.7 1-(6-Bromoquinolin-4-yl)cyclobutyl *tert*-butyl carbonate (531q)[ll]



Synthesised using a modified **GP1** with **523q** on a 0.25 mmol scale. 10 eq. Boc_2O was added at the start and a further 10 eq. added after 24 h. The reaction was stirred at 110 °C for 48 h. Purified by flash column chromatography (1:2 EtOAc/Petroleum Ether) to give the product as a white solid (74%, 70 mg, 0.19 mmol).

[kk] Prepared by Noelia Velasco Perez
[ll] Prepared by Noelia Velasco Perez

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 4.5 Hz, 1H, C_1H), 8.35 (d, J = 2.0 Hz, 1H, C_8H), 8.01 (d, J = 9.0 Hz, 1H), 7.76 (dd, J = 9.0, 2.0 Hz, 1H, C_7H), 7.60 (d, J = 4.5 Hz, 1H, C_2H), 2.83 (dd, J = 8.5, 7.0 Hz, 4H, $C_{11}H$), 2.11 (dp, J = 11.5, 7.0 Hz, 1H, $C_{12}H_a$), 1.80 – 1.65 (m, 1H, $C_{12}H_b$), 1.29 (s, 9H, $C_{15}H$)

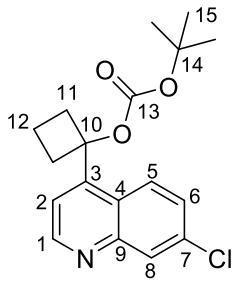
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (C_{13}), 150.3 (C_1), 148.1 (C_9), 145.2 (C_3), 132.7 (C_8), 132.3 (C_5), 128.0 (C_7), 126.6 (C_6), 120.8 (C_4), 120.2 C_2), 82.8 (C_{10}), 82.6 (C_{14}), 34.4 (C_{11a}), 27.8 (C_{15}), 14.6 (C_{12})

vmax /cm^{-1} (neat) 2981 (w.), 1745 (s.), 1593 (w.), 1493 (w.), 1369 (w.), 1280 (s.), 1250 (s.), 1152 (m.), 1107 (s.)

HRMS m/z (ESI) $C_{18}H_{21}NO_3Br$ $[M+H]^+$ requires: 378.0699; found: 378.0698

m.p./°C 160 – 165

7.5.6.8 *tert*-Butyl (1-(7-chloroquinolin-4-yl)cyclobutyl) carbonate (531m)[mm]



Synthesised using **GP2** with **523m** on a 0.25 mmol scale. 2 x 10 eq. Boc_2O over 48 h at 110 °C Purified by flash column chromatography (1:2 EtOAc/Petroleum Ether) to give the product as a white solid (85%, 71 mg, 0.21 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 4.5 Hz, 1H, C_1H), 8.15 (d, J = 6.5 Hz, 1H, C_5H), 8.14 (s, 1H, C_8H), 7.58 (d, J = 4.5 Hz, 1H, C_2H), 7.50 (m, 1H, C_6H), 2.83 (dd, J = 8.5, 7.0 Hz, 4H, $C_{11}H$), 2.19 – 2.01 (m, 1H, $C_{12}H_a$), 1.74 (m, 1H, $C_{12}H_b$), 1.28 (s, 9H, $C_{15}H$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1 (C_{13}), 150.1 (C_1), 135.0 (C_5), 129.5 (C_6), 127.5 (C_8), 127.3 (C_7), 119.6 (C_2), 82.8 (C_{14}), 82.6 (C_{10}), 34.4 (C_{14}), 27.8 (C_{15}), 14.6 (C_{12}) (*C_3, C_4 and C_9 not observed)*

vmax /cm^{-1} (neat) 2980 (w.), 2928 (w.), 1744 (s.), 1593 (w.), 1496 (w.), 1369 (w.), 1293 (s.), 1280 (s.), 1252 (m.), 1143 (m.), 1164 (m.), 1105 (m.), 882 (w.)

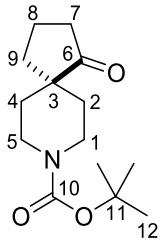
HRMS m/z (ESI) $C_{18}H_{21}NO_3Cl$ $[M+H]^+$ requires: 334.1204; found: 334.1203

m.p./°C 117 – 122

[mm] Prepared by Noelia Velasco Perez

7.5.7 Hydrogenation product

7.5.7.1 *tert*-Butyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (533)[nn]



Hydrogenation based on literature hydrogenation of dihydropyridines by Liu et. al.[224]

In a 50 mL round-bottom flask, *tert*-butyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate **517a** (100 mg, 0.401 mmol, 1.0 equiv) was dissolved in dry methanol (10 mL). To the pale-yellow solution Pd/C (10 wt%, 42.7 mg, 40.1 µmol, 10 mol%) was added and the reaction vessel was three times evacuated and vented with N_2. Then the reaction vessel was three times evacuated and vented with H_2 (balloon). The resulting black suspension was stirred under an H_2 atmosphere for 42 h at ambient temperature. The reaction mixture was filtered through a celite pad (2 cm). The residue was washed with EtOAc (150 mL). The filtrate was concentrated under reduced pressure to give the product as a white solid (89%, 90.0 mg, 0.357 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (dt, J = 13.5, 4.5 Hz, 2H, $C_{1/5}H_a$), 3.05 (ddd, J = 13.5, 10.5, 3.5 Hz, 2H, $C_{1/5}H_b$), 2.35 – 2.22 (m, 2H, C_7H), 1.96 – 1.85 (m, 4H, $C_{8/9}H$), 1.64 (ddd, J = 13.5, 10.5, 4.5 Hz, 2H, $C_{2/4}H_a$), 1.44 (s, 9H, $C_{12}H$), 1.32 (dddd, J = 13.5, 5.0, 3.5, 1.5 Hz, 2H, $C_{2/4}H_b$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 222.0 (C_6), 154.9 (C_{10}), 79.6 (C_{11}), 47.4 (C_3), 40.2 ($C_{1/5}$), 37.9 (C_7), 34.2 ($C_{2/4}$), 31.8 ($C_{8/9}$), 28.6 (C_{12}), 18.8 ($C_{8/9}$)

vmax /cm^{-1} (neat) 2969 (w.), 2935 (w.), 2867 (w.), 1732 (m.), 1687 (s.), 1421 (m.), 1365 (m.), 1249 (m.), 1148 (s.)

HRMS m/z (ESI) $C_{14}H_{23}NO_3Na$ $[M+Na]^+$ requires: 276.1576; found: 276.1577

m.p./°C 70 – 75

[nn] Prepared by Dr. Christian Bold

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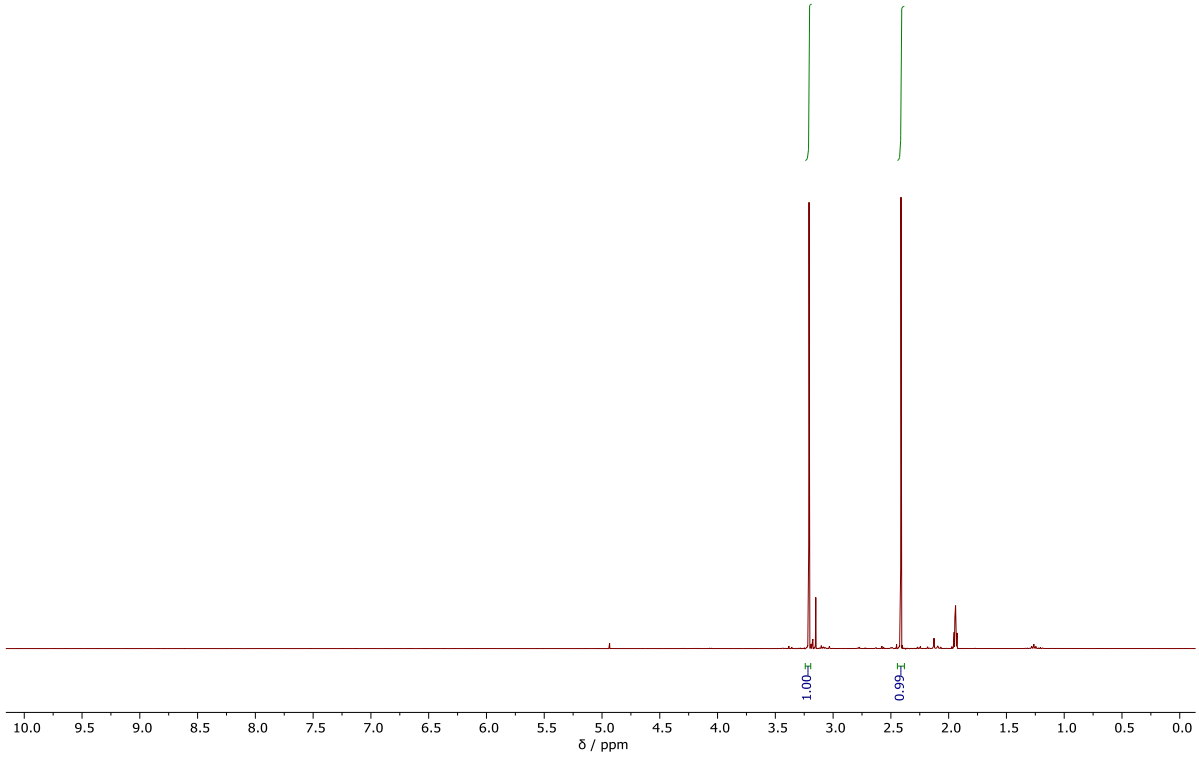
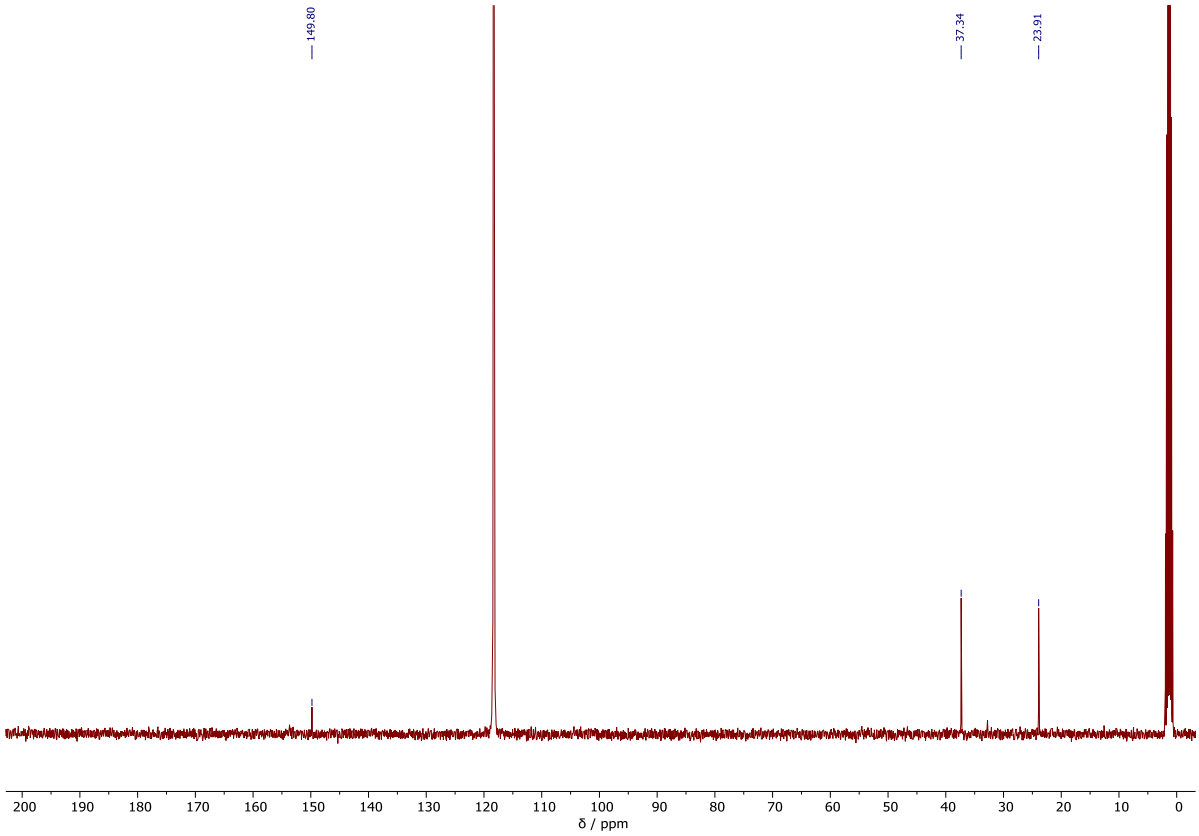
9 APPENDIX: NMR spectra and HPLC traces

9.1 Selected NMR spectra and HPLC traces for section 7.3

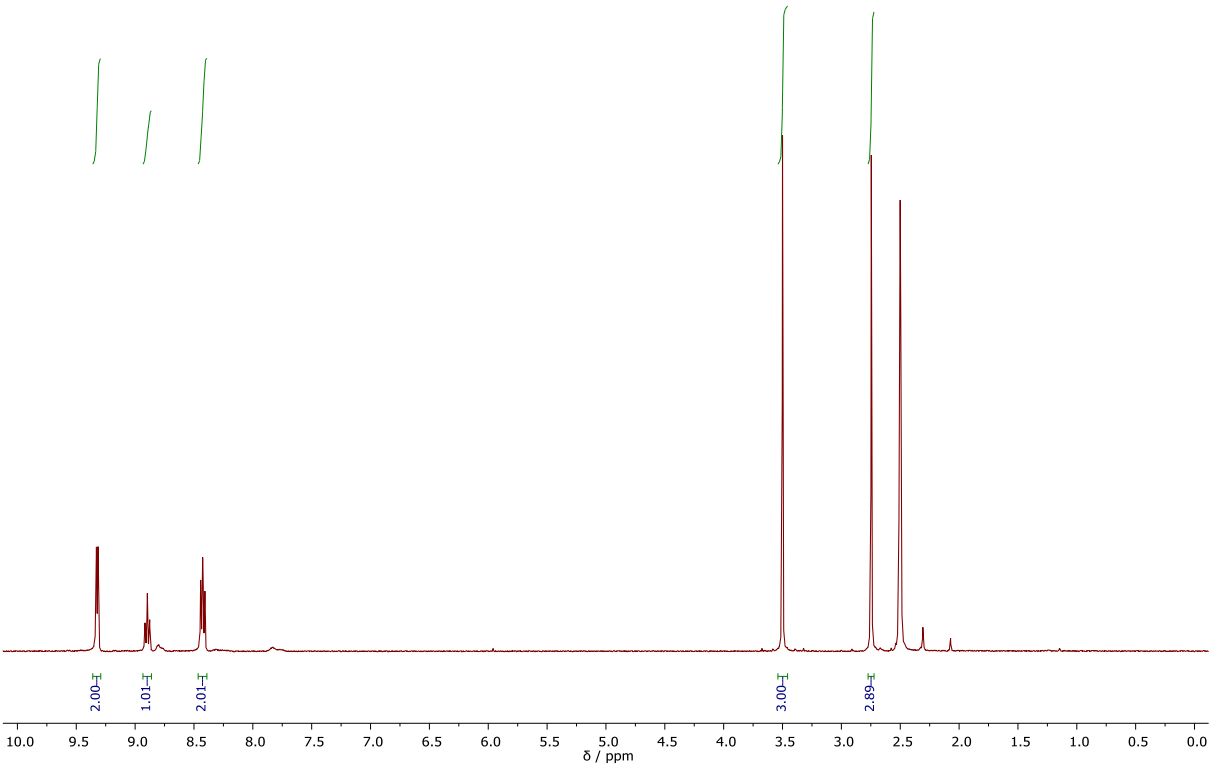
9.1.1 Selected NMR spectra for section 7.3

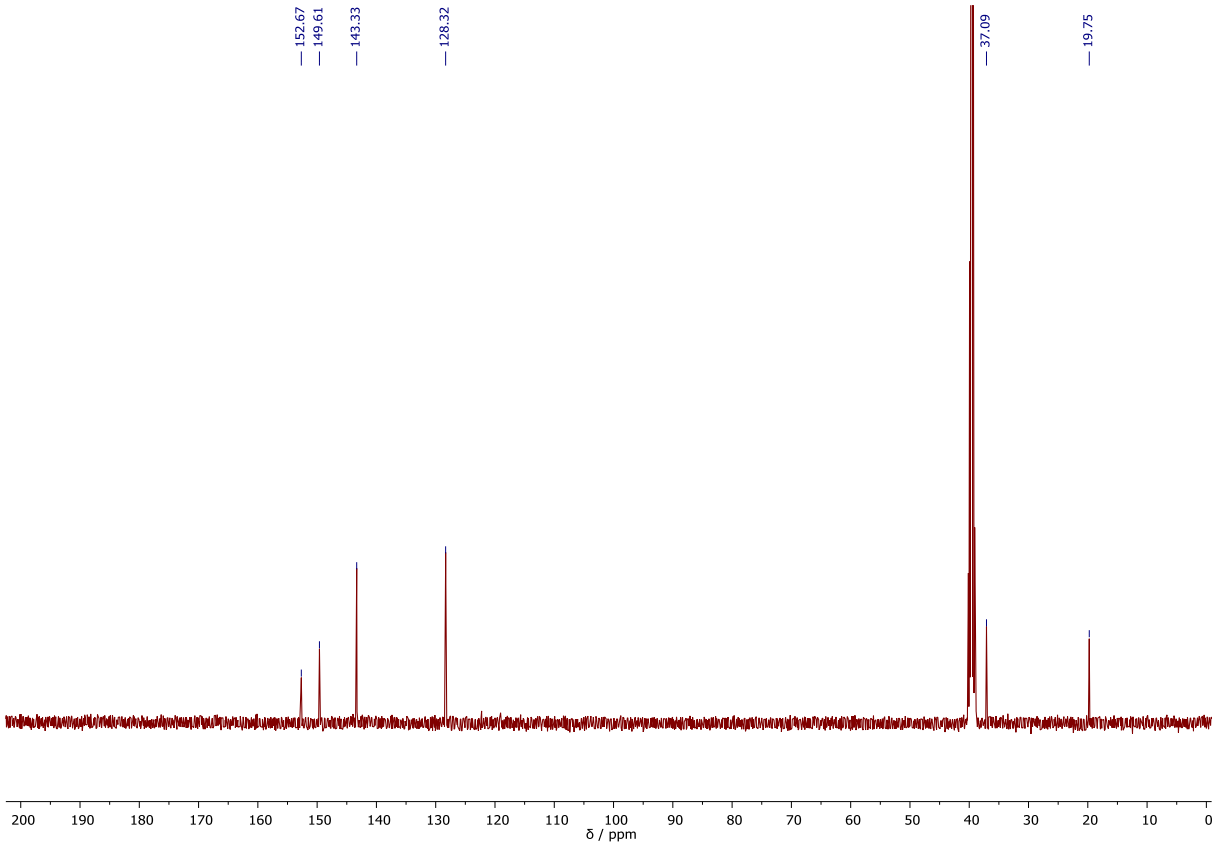
9.1.1.1 (*Z*)-*N*-((Methylsulfonyl)oxy)acetimidoyl chloride ('activating agent') (305)



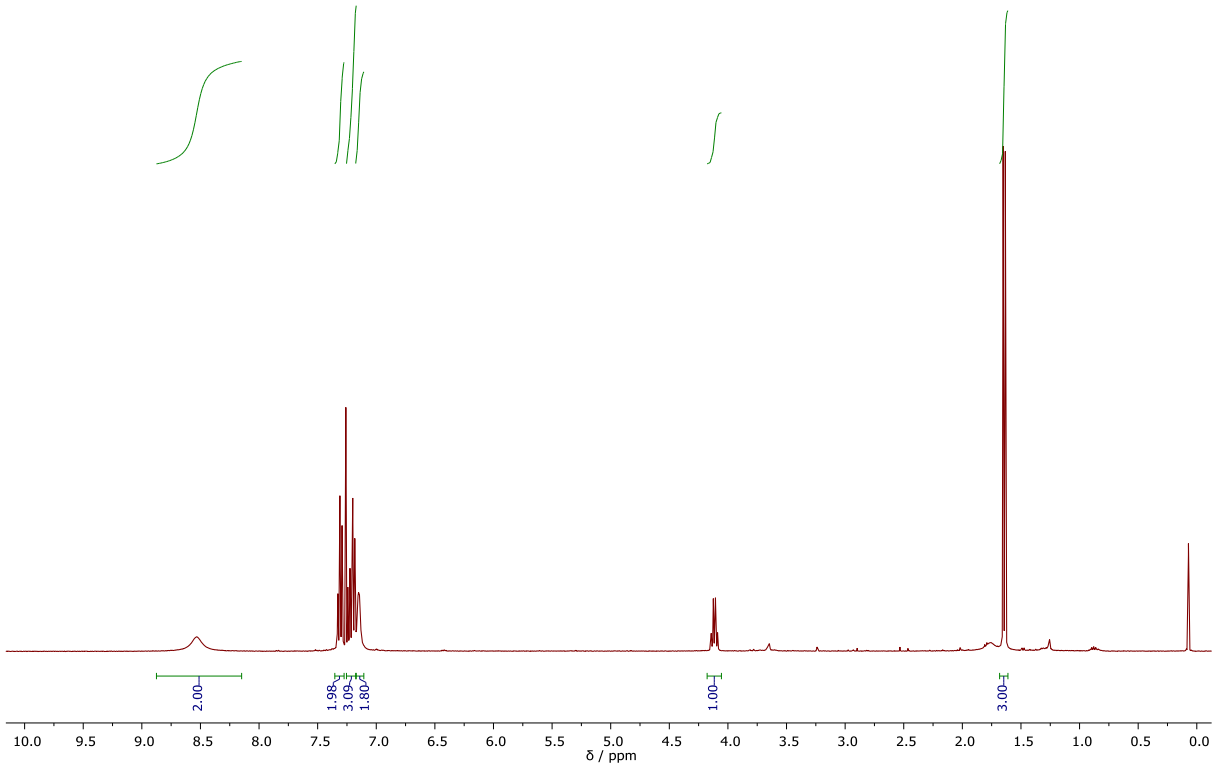


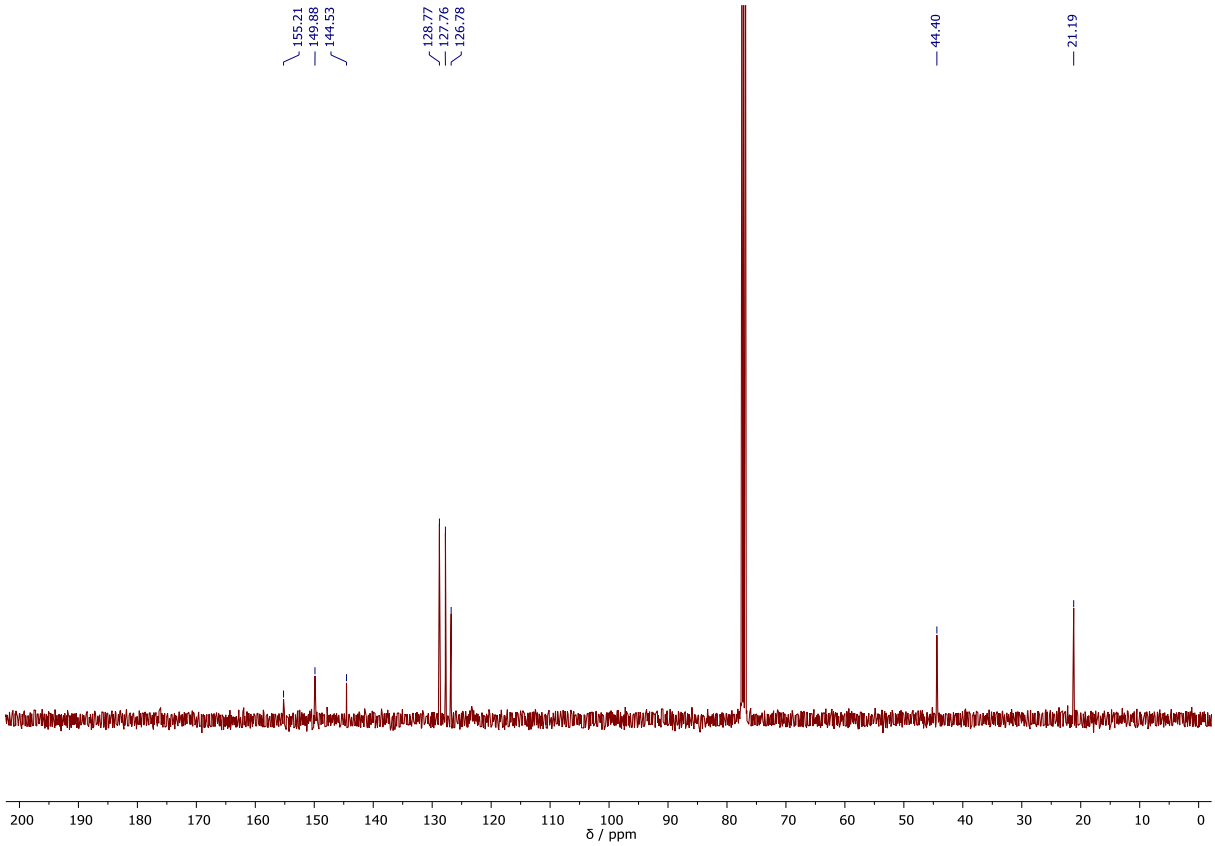
9.1.1.2 (*Z*)-1-(1-(((Methylsulfonyl)oxy)imino)ethyl)pyridine-1-ium triflate (303)



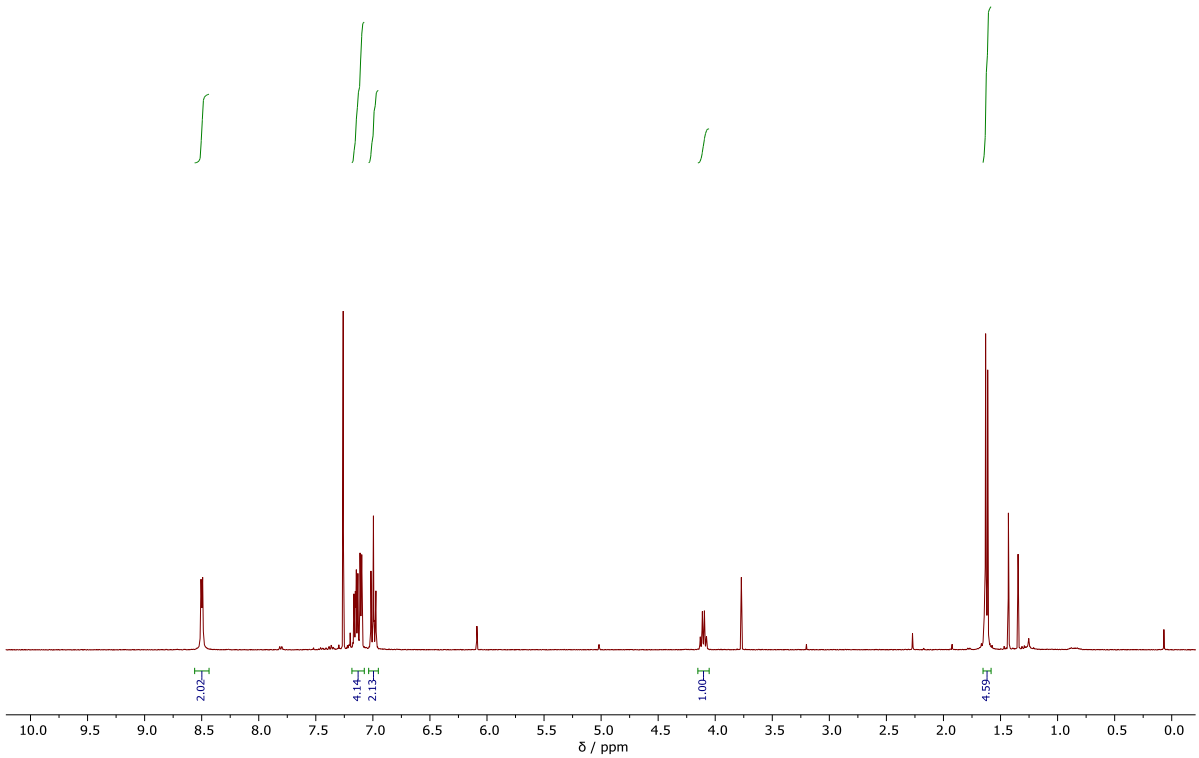


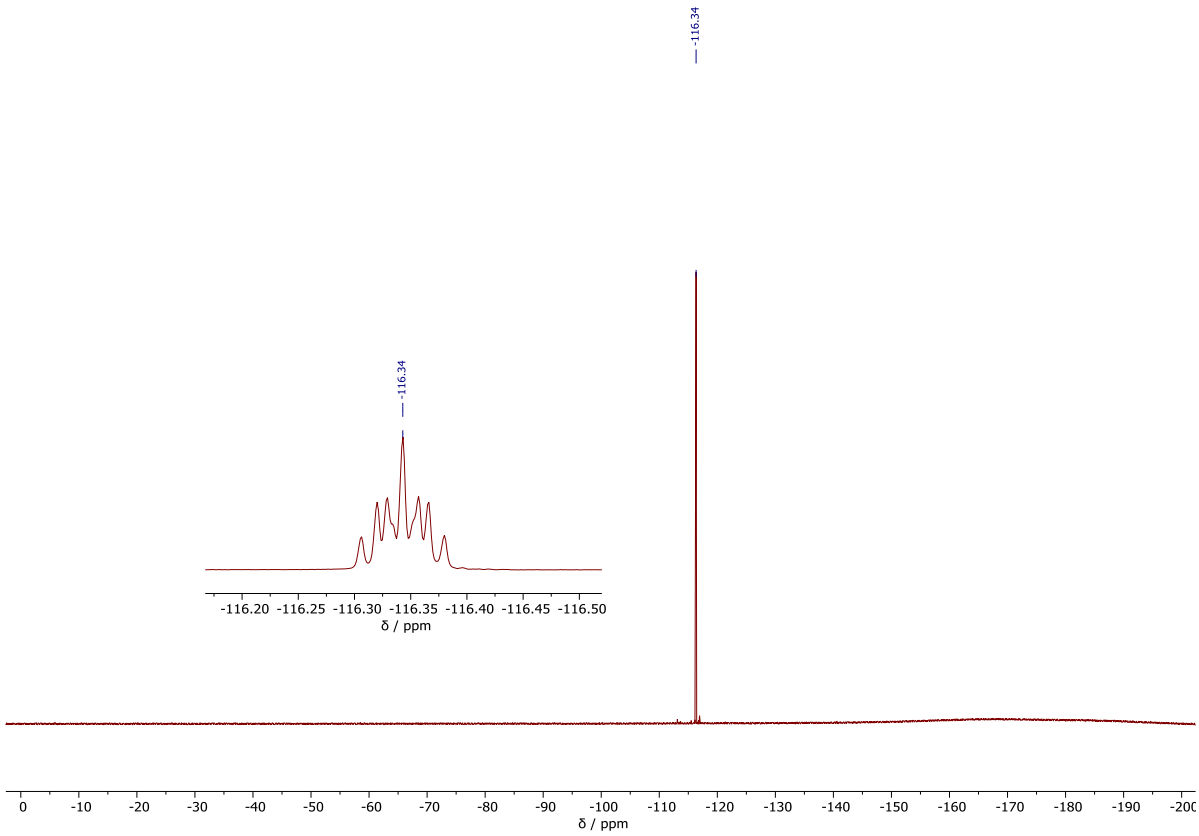
9.1.1.3 4-(1-Phenylethyl)pyridine (304)





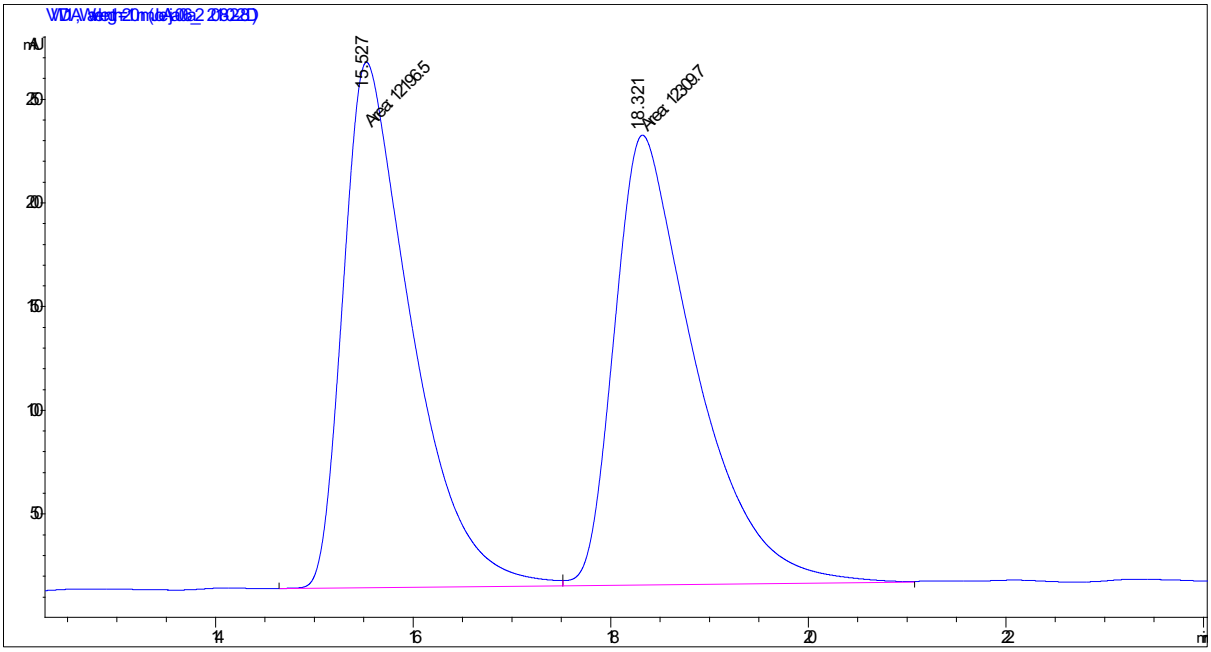
9.1.1.4 4-(1-(4-Fluorophenyl)ethyl)pyridine (310)



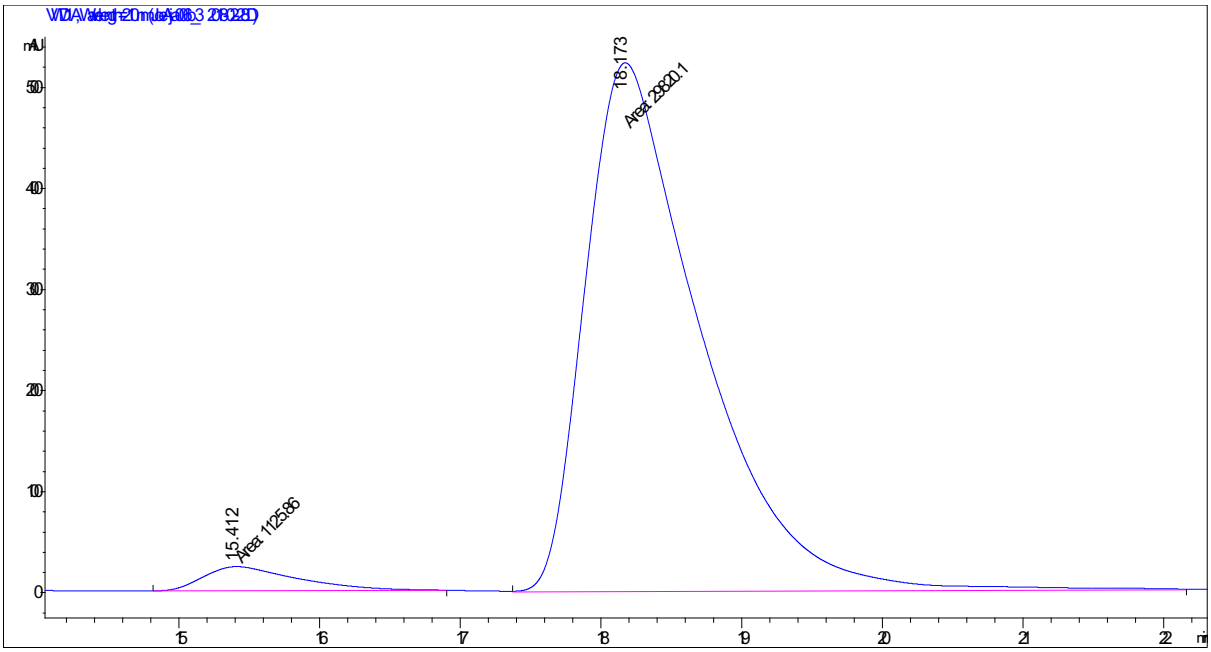

-116.34
-116.34
-116.20 -116.25 -116.30 -116.35 -116.40 -116.45 -116.50
δ / ppm
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
δ / ppm

9.1.2 HPLC traces for section 7.3

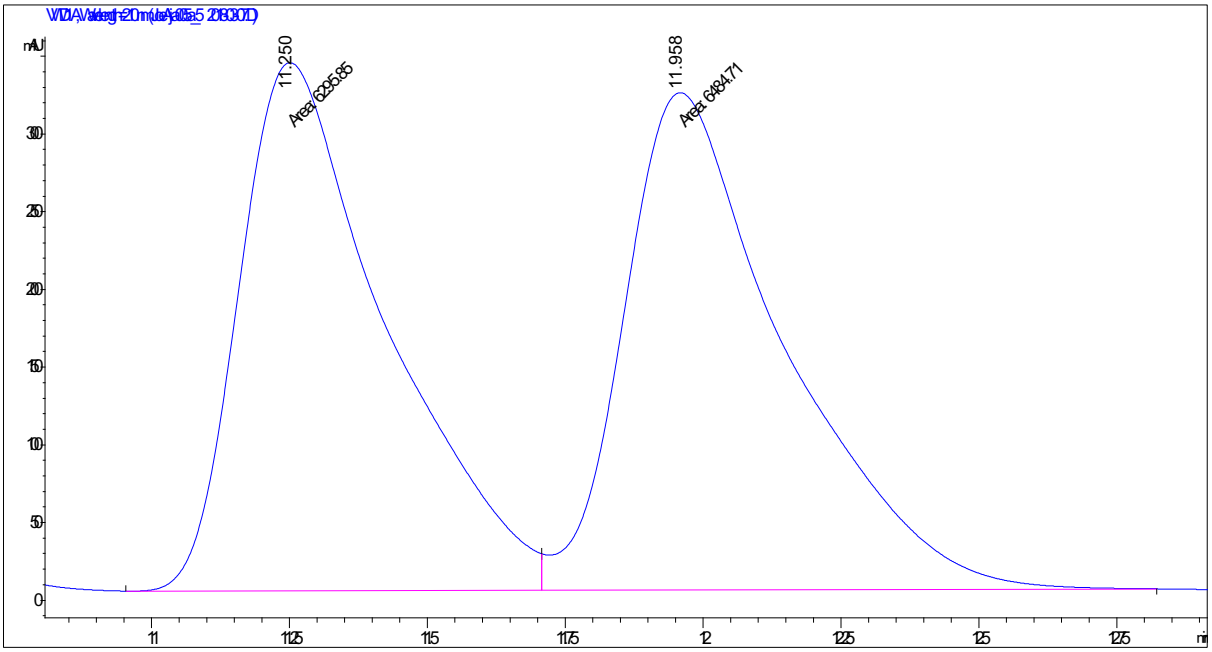
9.1.2.1 (±)-1-Phenylethanol from stereoretentive oxidation of (±)-3,3,4,4-Tetramethyl-1-(1-phenylethyl)borolane (301)



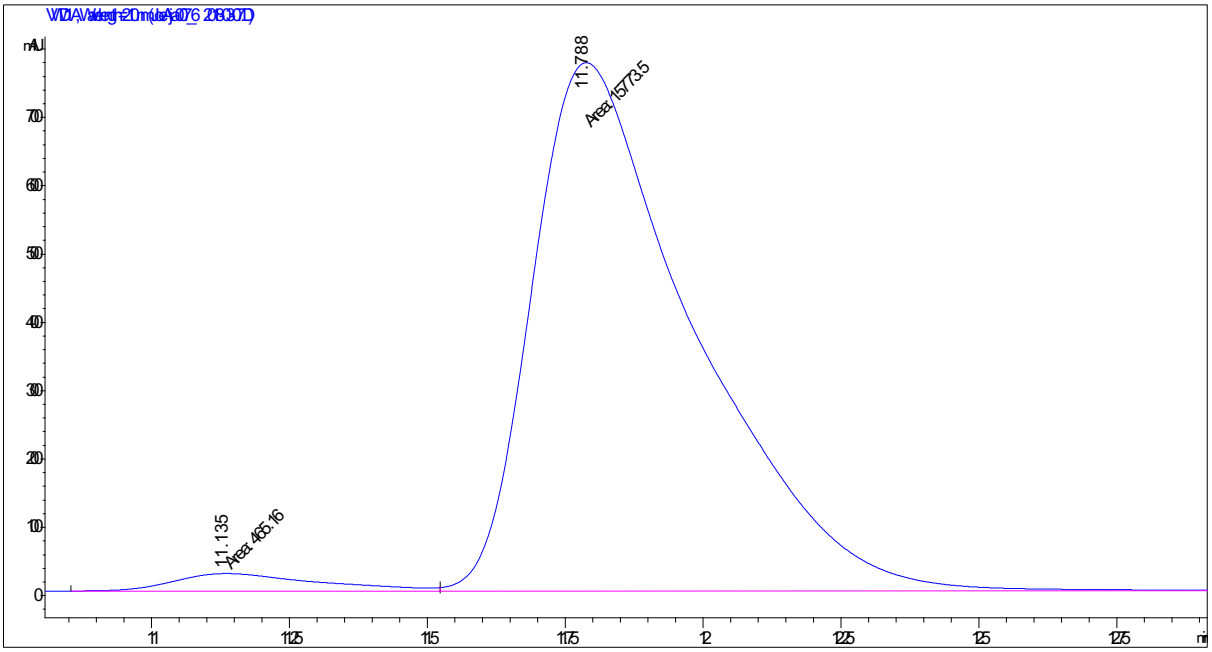
9.1.2.2 (*S*)-1-Phenylethanol from stereoretentive oxidation of (*S*)-3,3,4,4-Tetramethyl-1-(1-phenylethyl)borolane ((*S*)-301)



9.1.2.3 (±)-4-(1-Phenylethyl)pyridine (304)



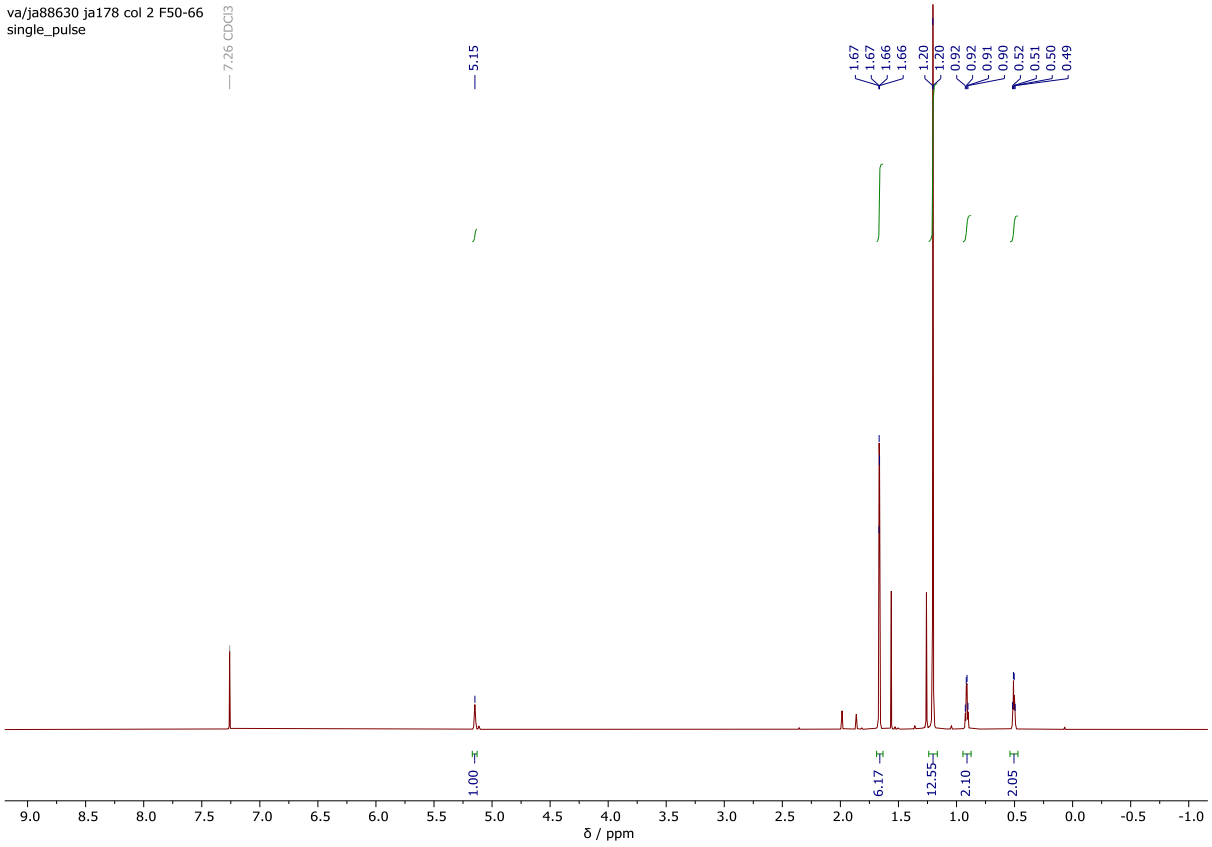
9.1.2.4 (*R*)-4-(1-Phenylethyl)pyridine ((*R*)-304)



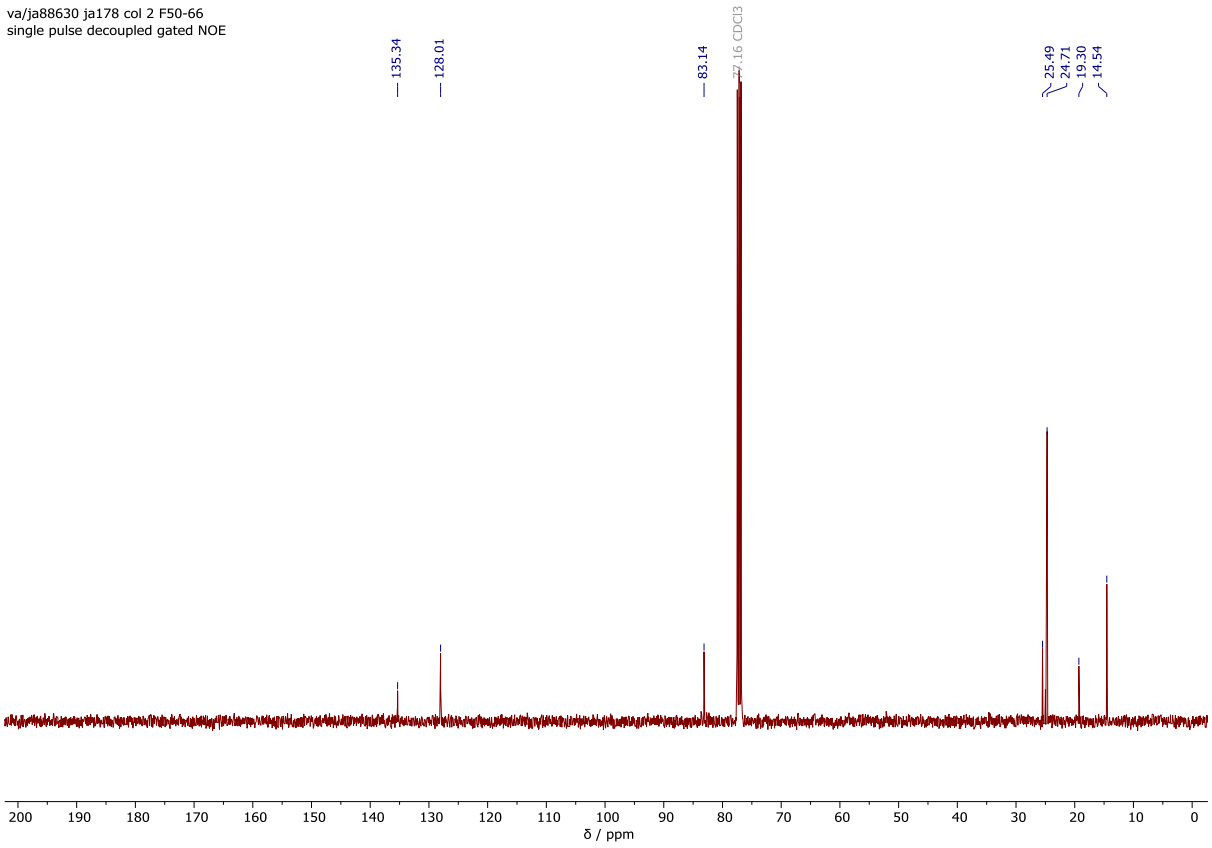
9.2 Selected NMR spectra for section 7.4[oo]

9.2.1 Cyclopropyl vinyl boronic esters

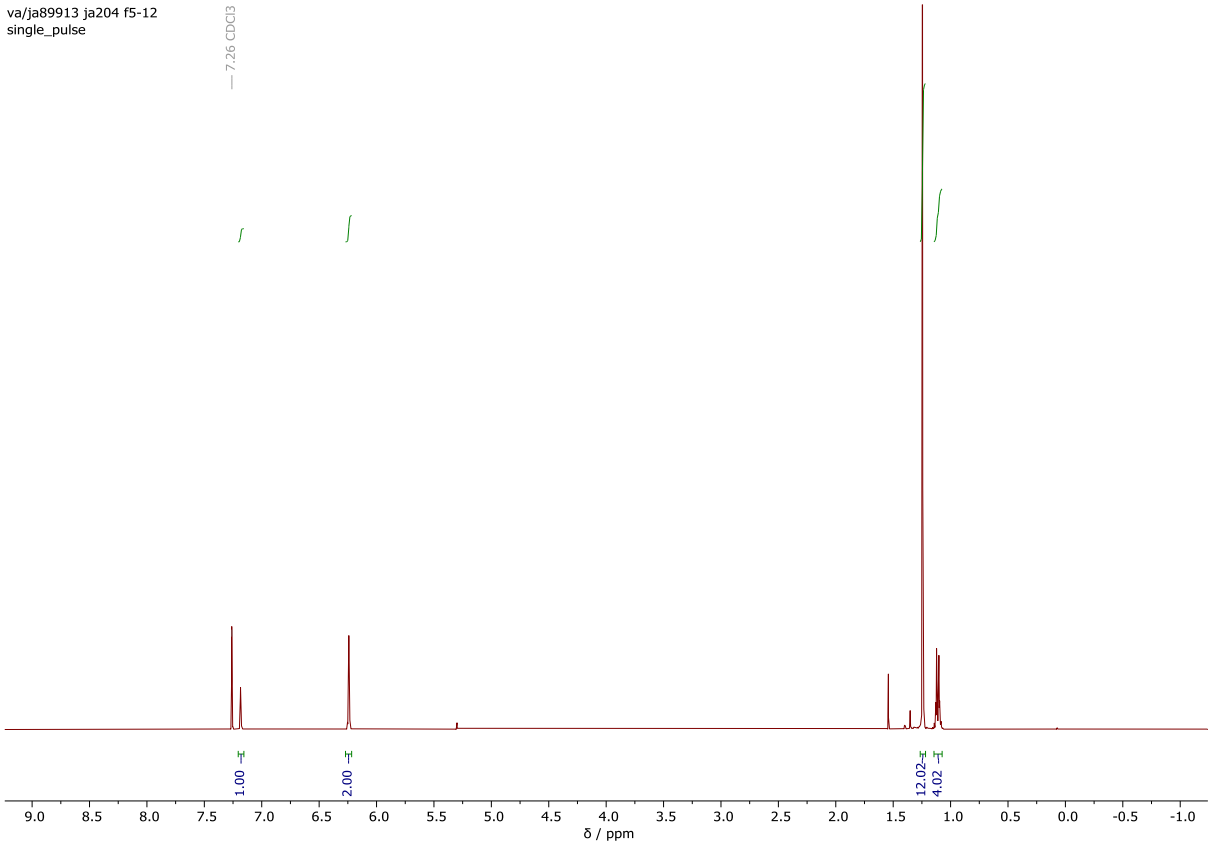
9.2.1.1 4,4,5,5-Tetramethyl-2-(1-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,2-dioxaborolane (409i)

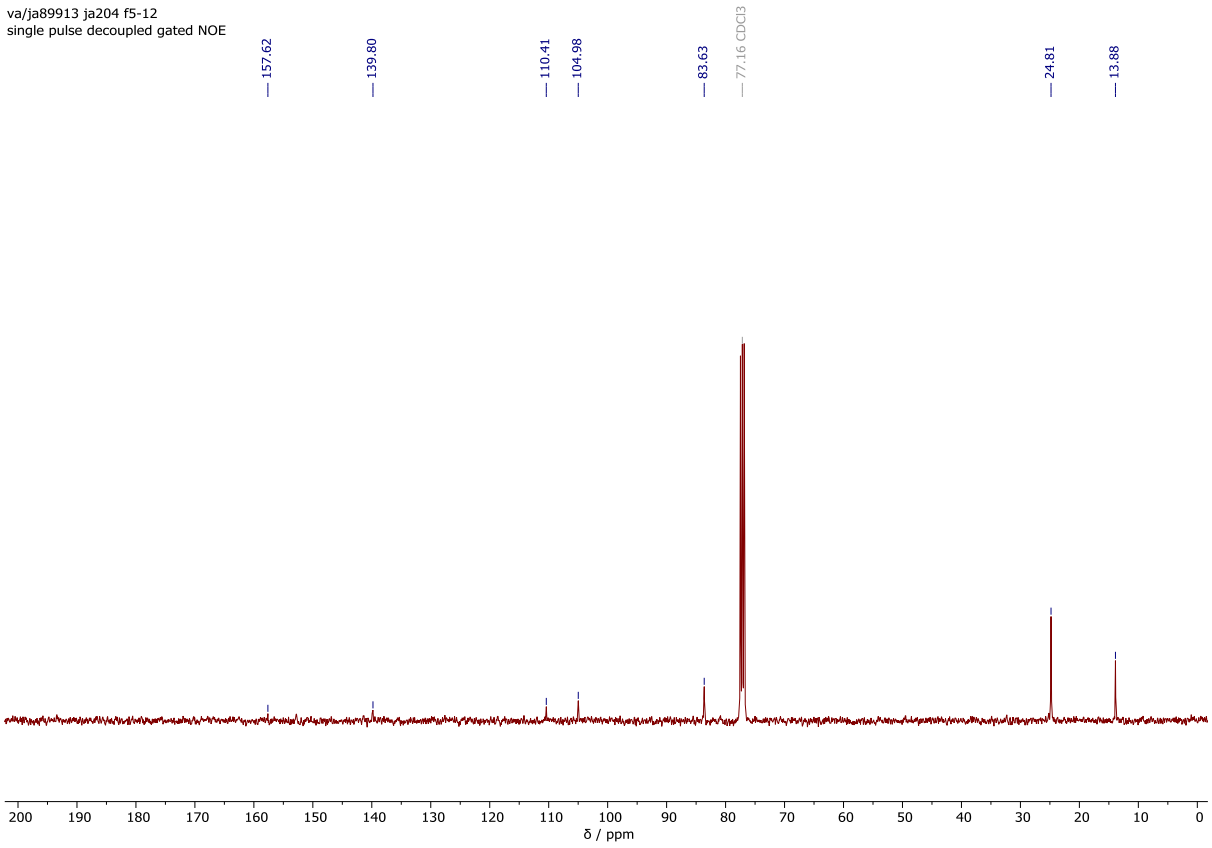


[oo] NMR spectra for compounds **404**, **409a-h** and **411a-g** can be found in the following publication: Durga Prasad Hari, Joseph C. Abell, Valerio Fasano and Varinder K. Aggarwal, *J. Am. Chem. Soc.,* **2020**, 142, 5515-5520
NMR spectra for compound **417** can be found in the following publication: Durga Prasad Hari, Rudrakshula Madhavachary, Valerio Fasano, Jack Haire and Varinder K. Aggarwal, *J. Am. Chem. Soc*., **2021**, 143, 7462-7470

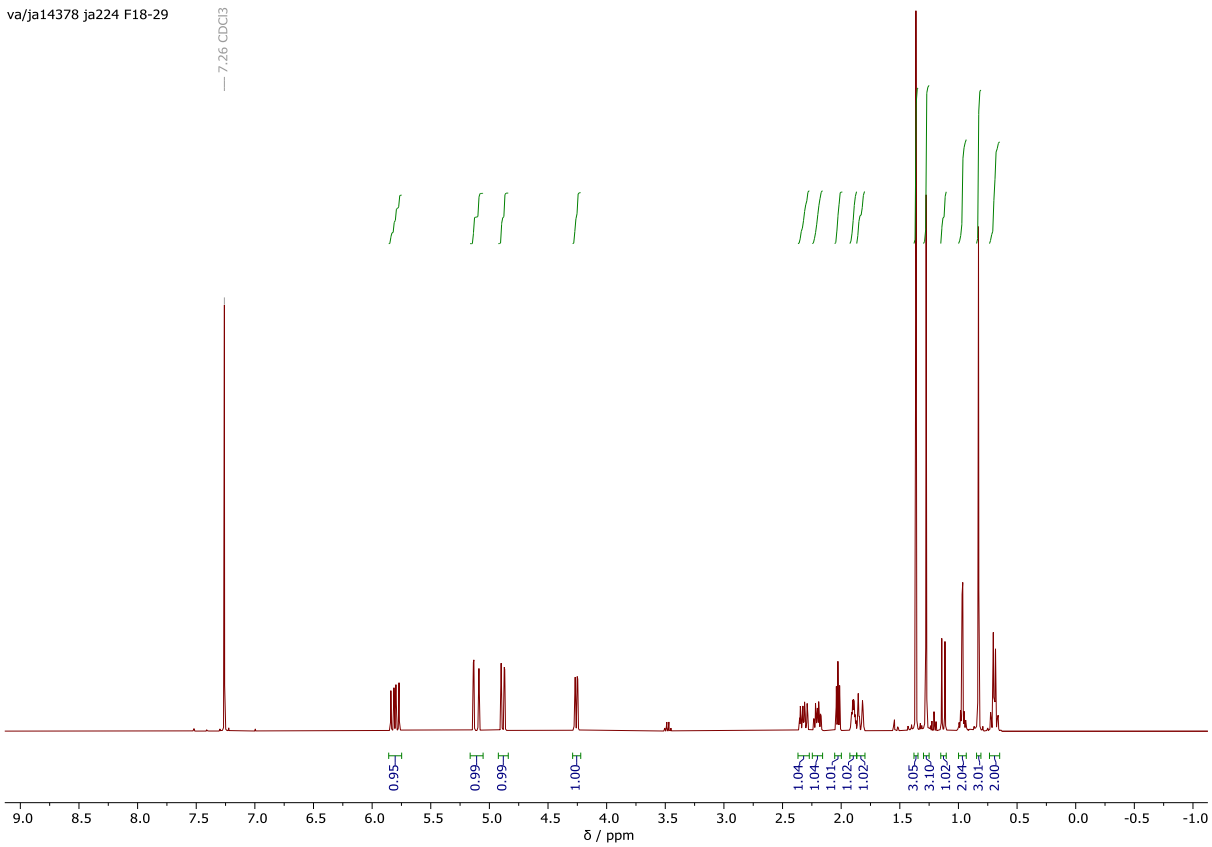


9.2.1.2 2-(1-(Furan-2-yl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (409k)

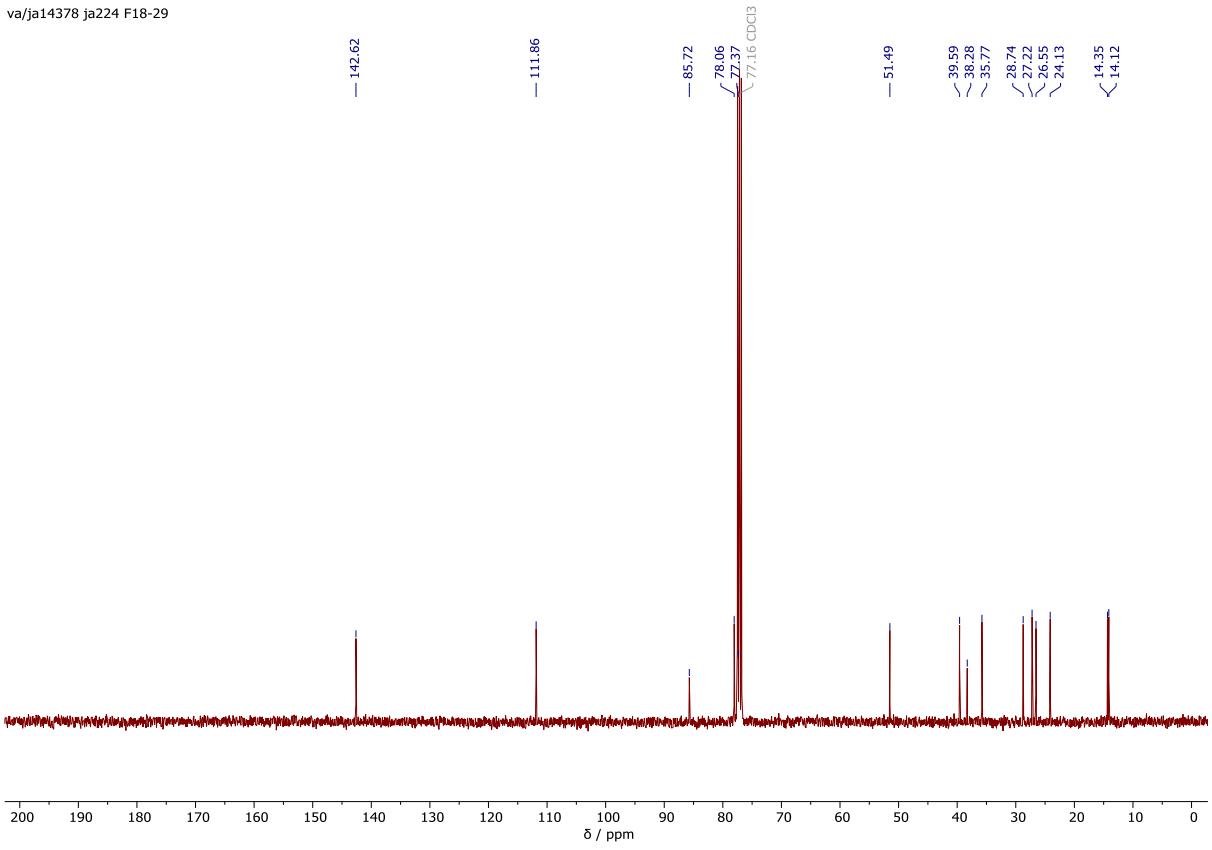




9.2.1.3 (3a*R*,4*R*,6*R*)-3a,5,5-Trimethyl-2-(1-vinylcyclopropyl)hexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborole (421)



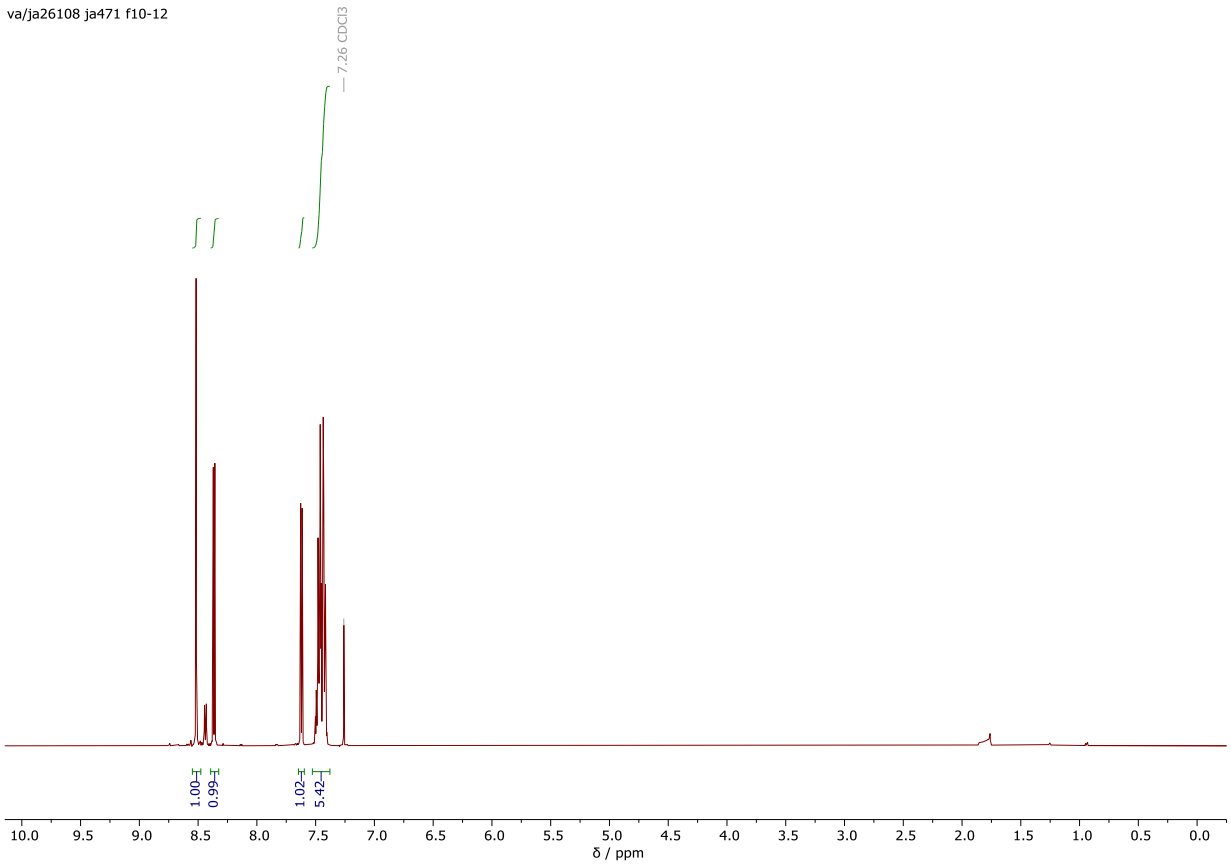
va/ja14378 ja224 F18-29

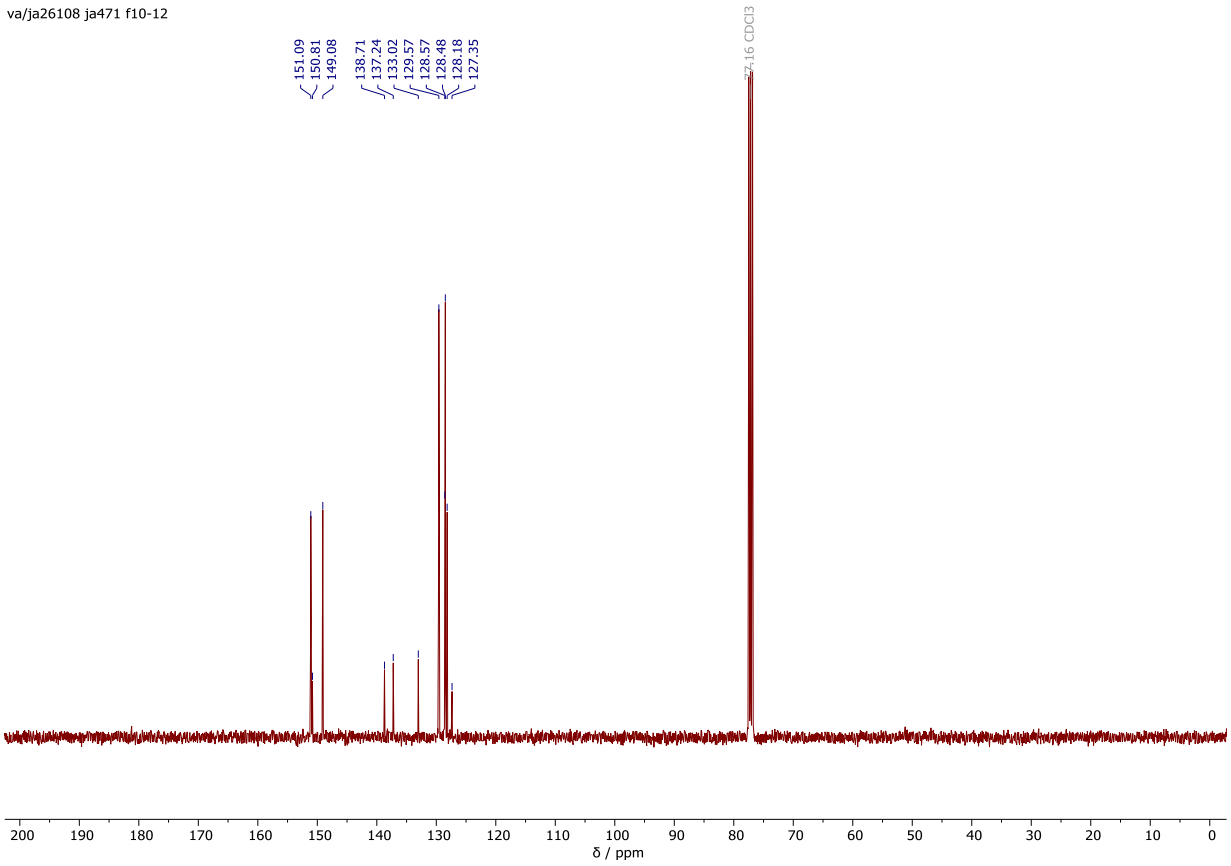


9.3 NMR spectra for section 7.5

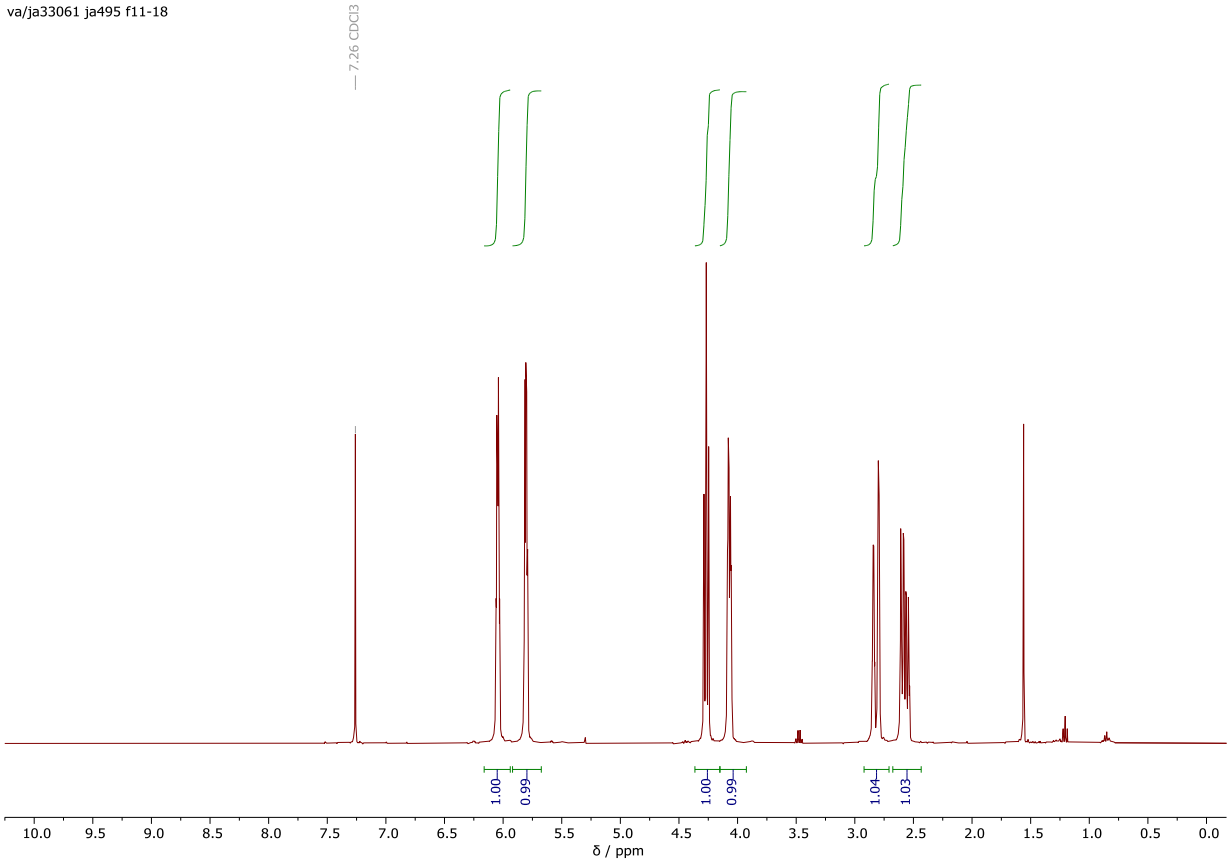
9.3.1 Literature compounds

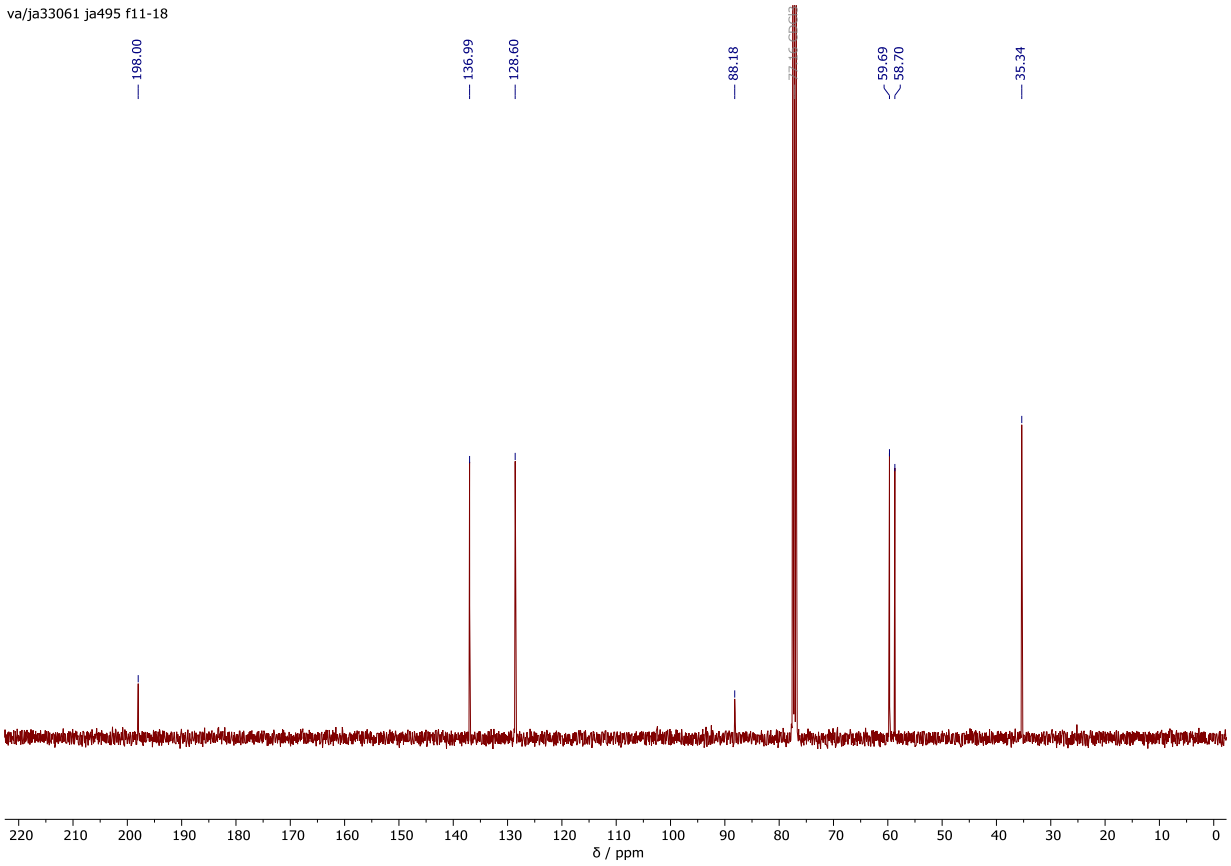
9.3.1.1 4-Bromo-3-phenylpyridine



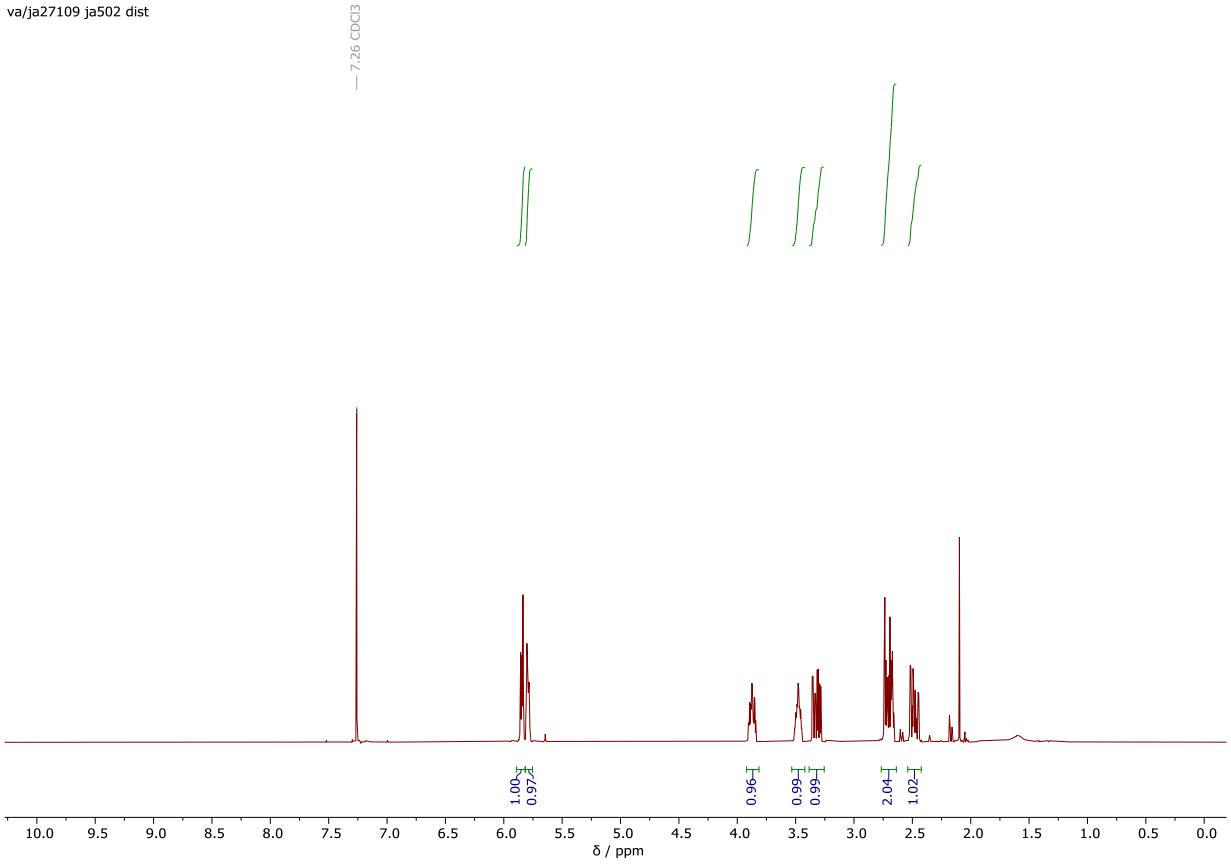


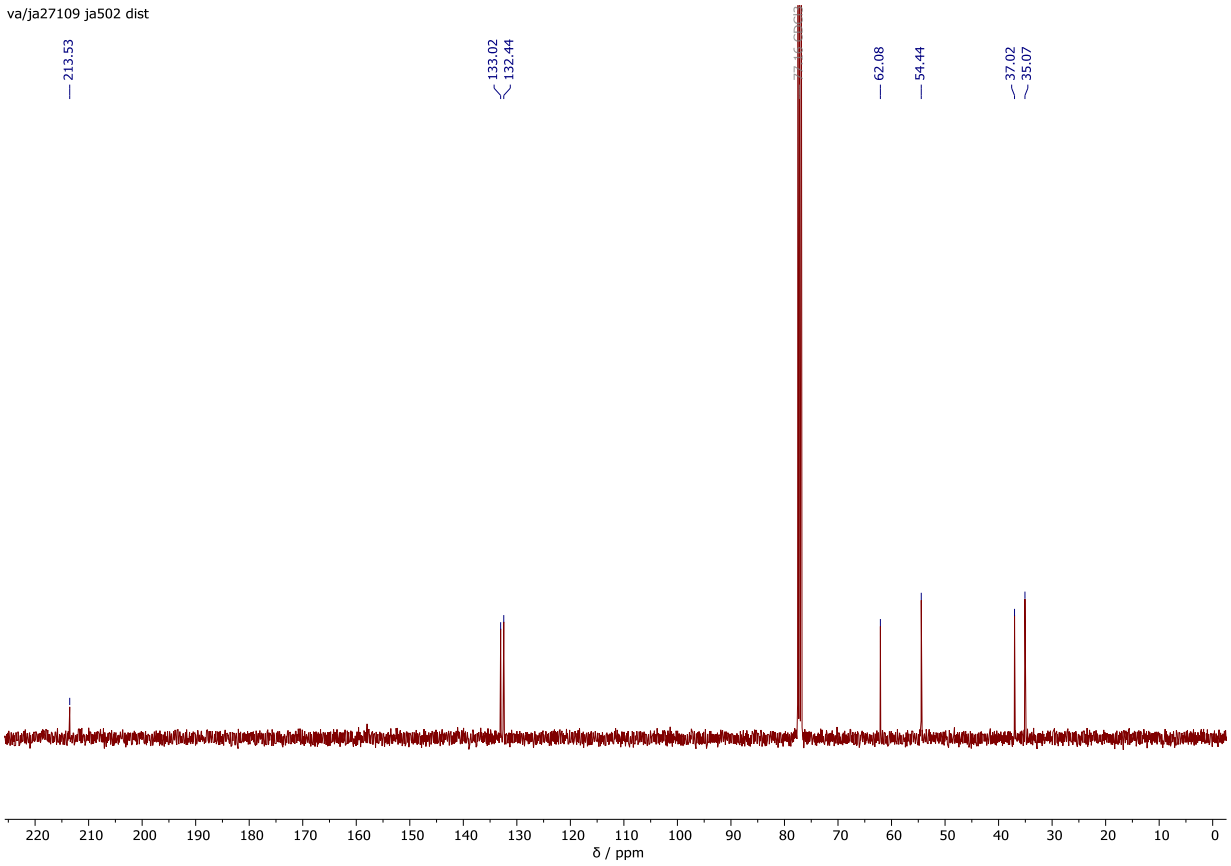
9.3.1.2 (1*S*,5*R*)-7,7-Dichlorobicyclo[3.2.0]hept-2-en-6-one



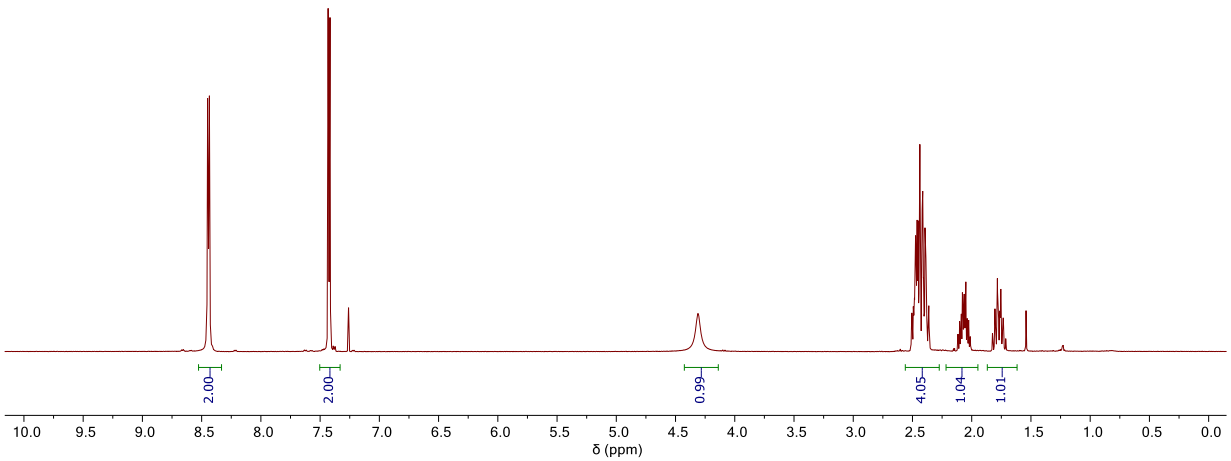


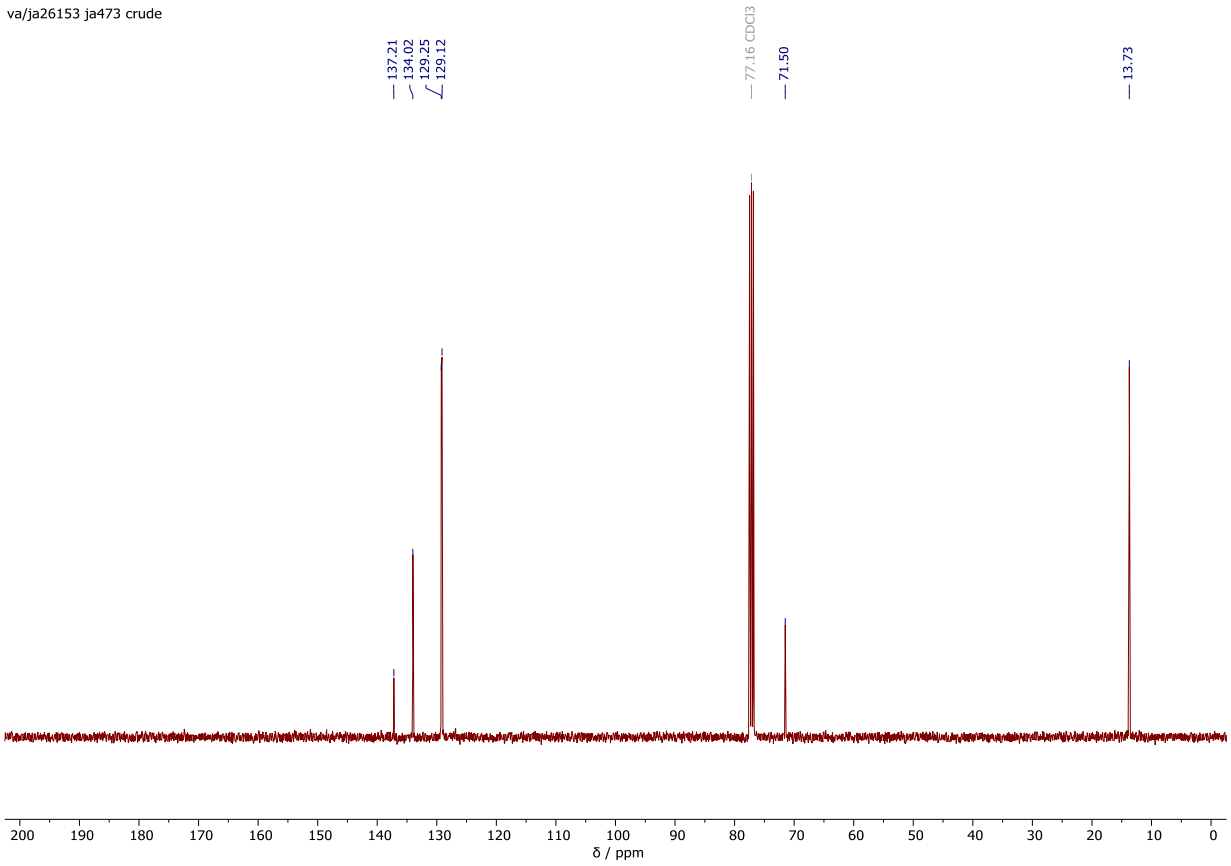
9.3.1.3 (1*S*,5*R*)-Bicyclo[3.2.0]hept-2-en-6-one (525)



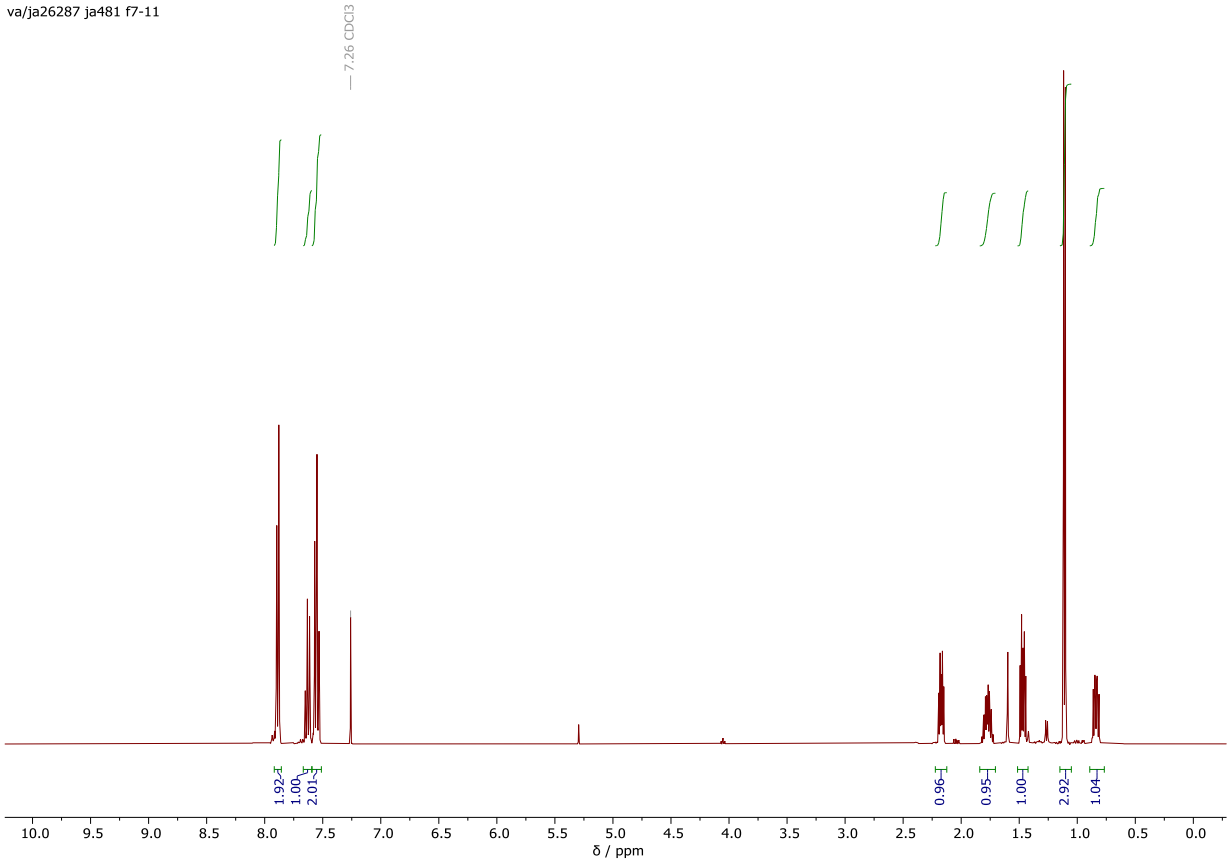


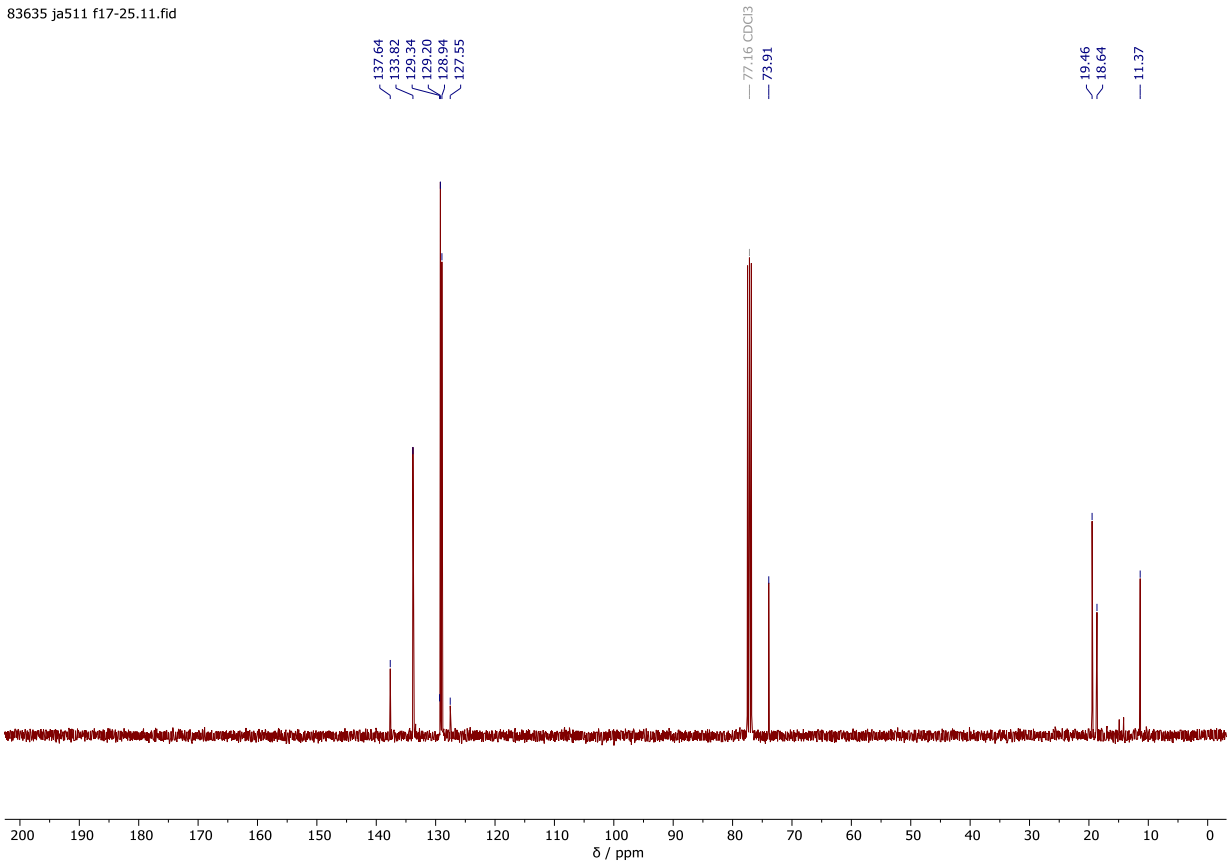
9.3.1.4 1-(Phenylsulfonyl)cyclopropan-1-ol





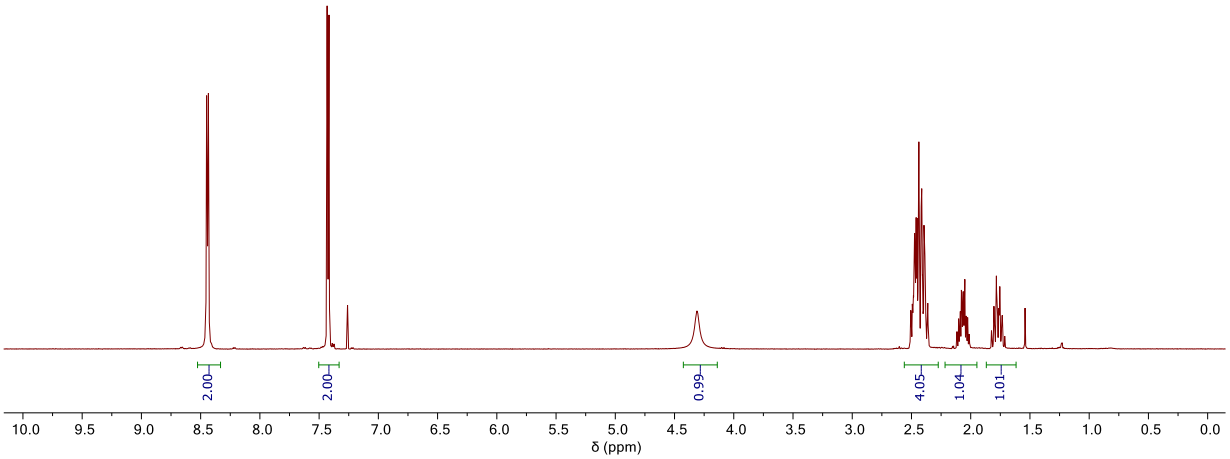
9.3.1.5 (((1*S*,2*S*)-2-Methylcyclopropyl)sulfonyl)benzene

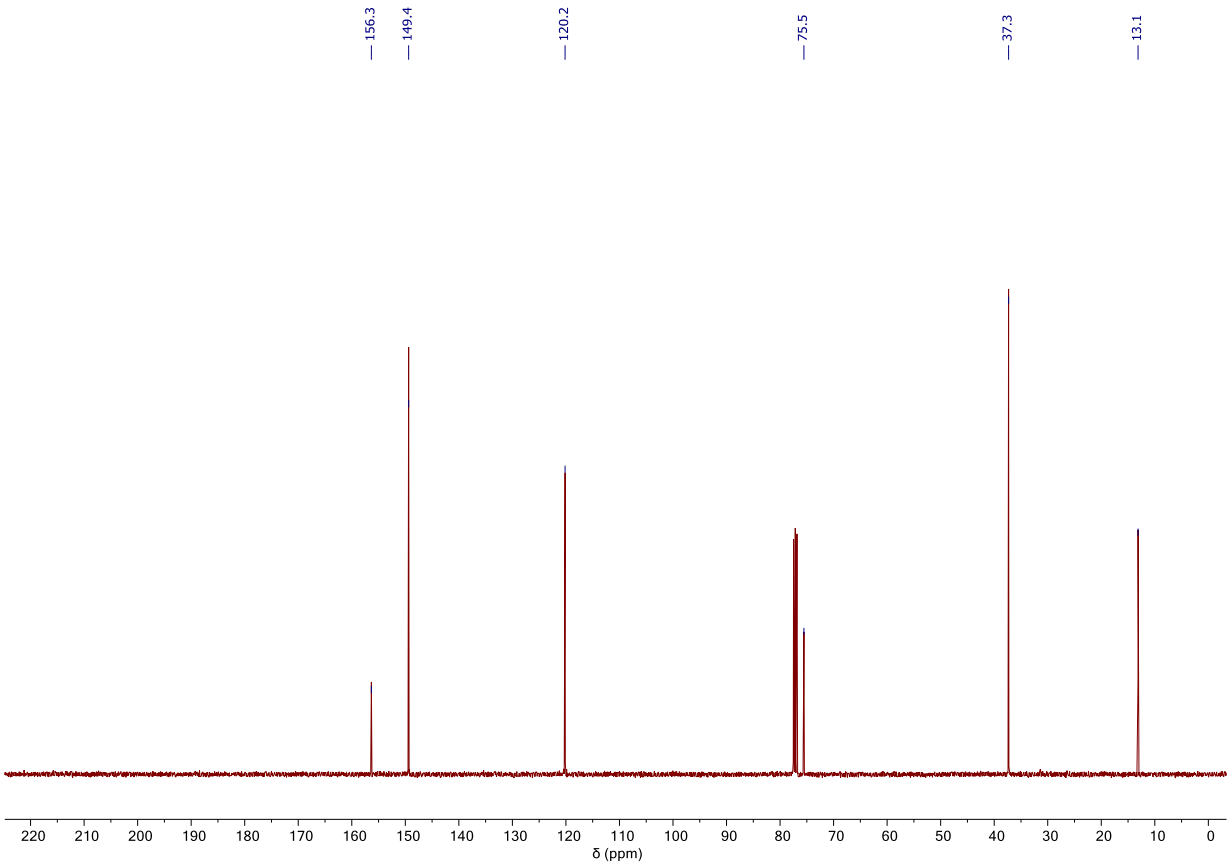



83635 ja511 f17-25.11.fid
137.64
133.82
129.34
129.20
128.94
127.55
77.16 CDCl3
73.91
19.46
18.64
11.37
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
δ / ppm

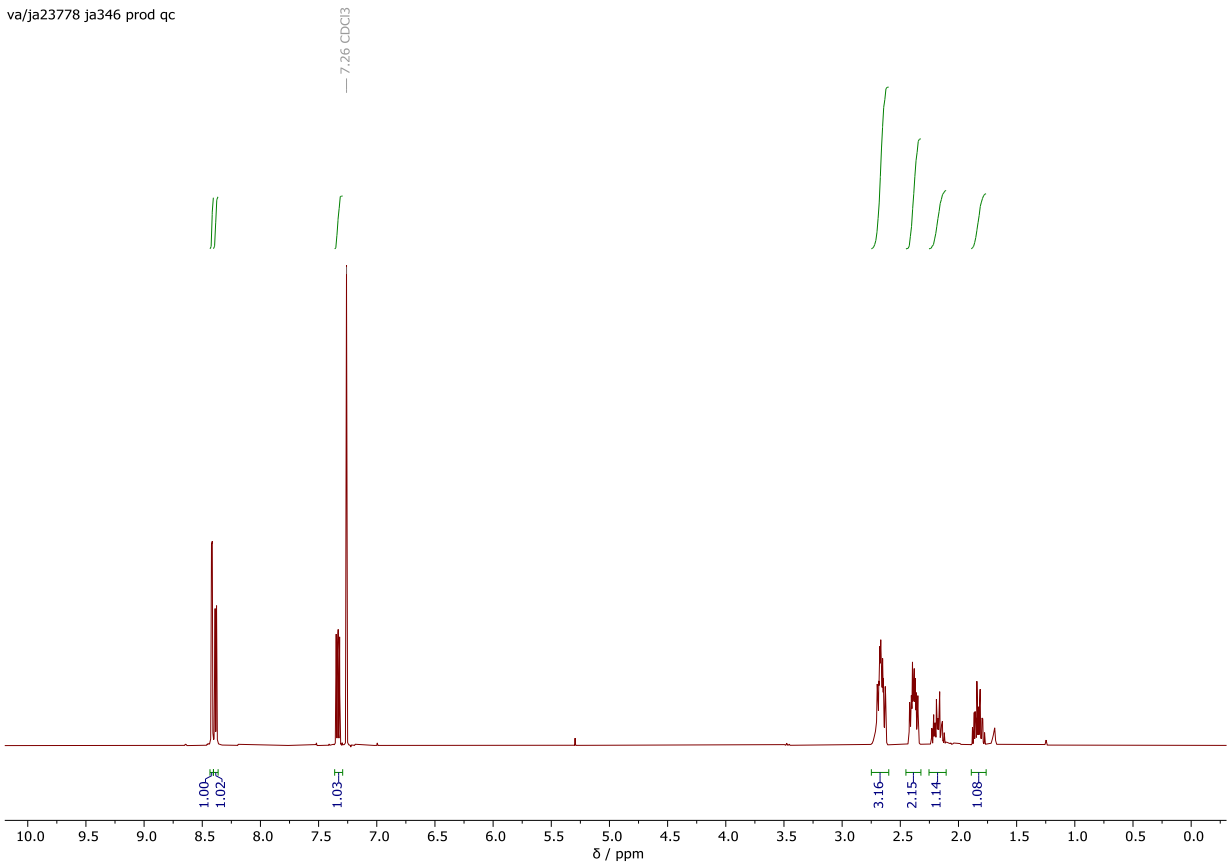
9.3.2 Synthesis of hydroxycyclobutylpyridines and hydroxycyclobutylquinolines

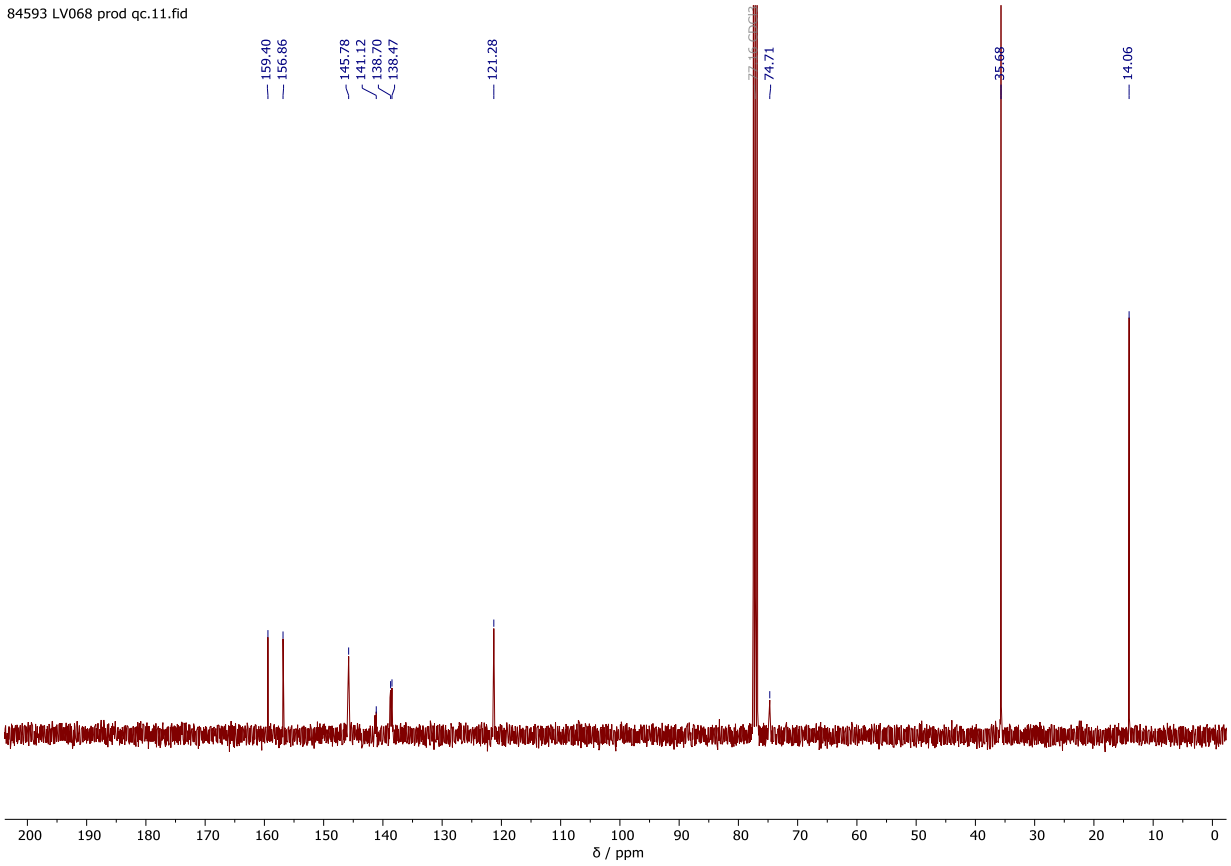
9.3.2.1 1-(Pyridin-4-yl)cyclobutan-1-ol (515)

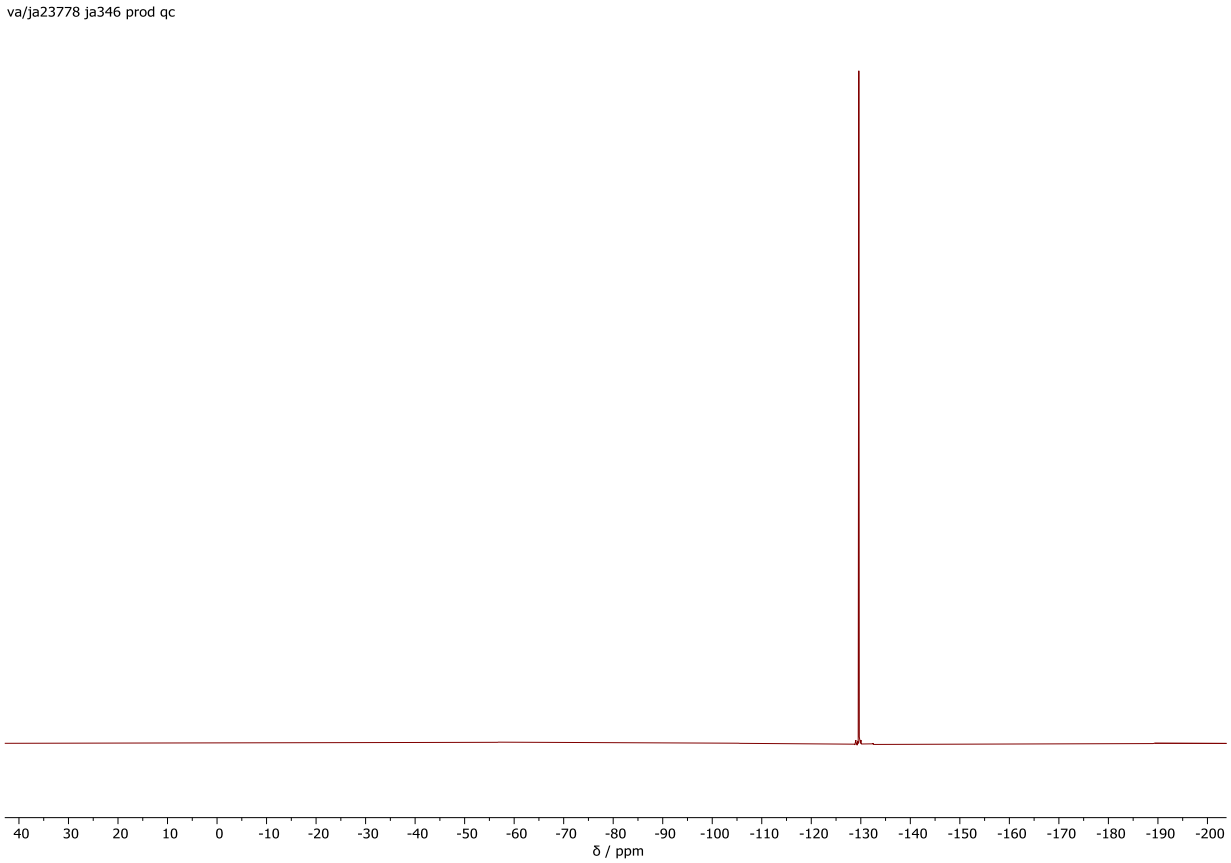




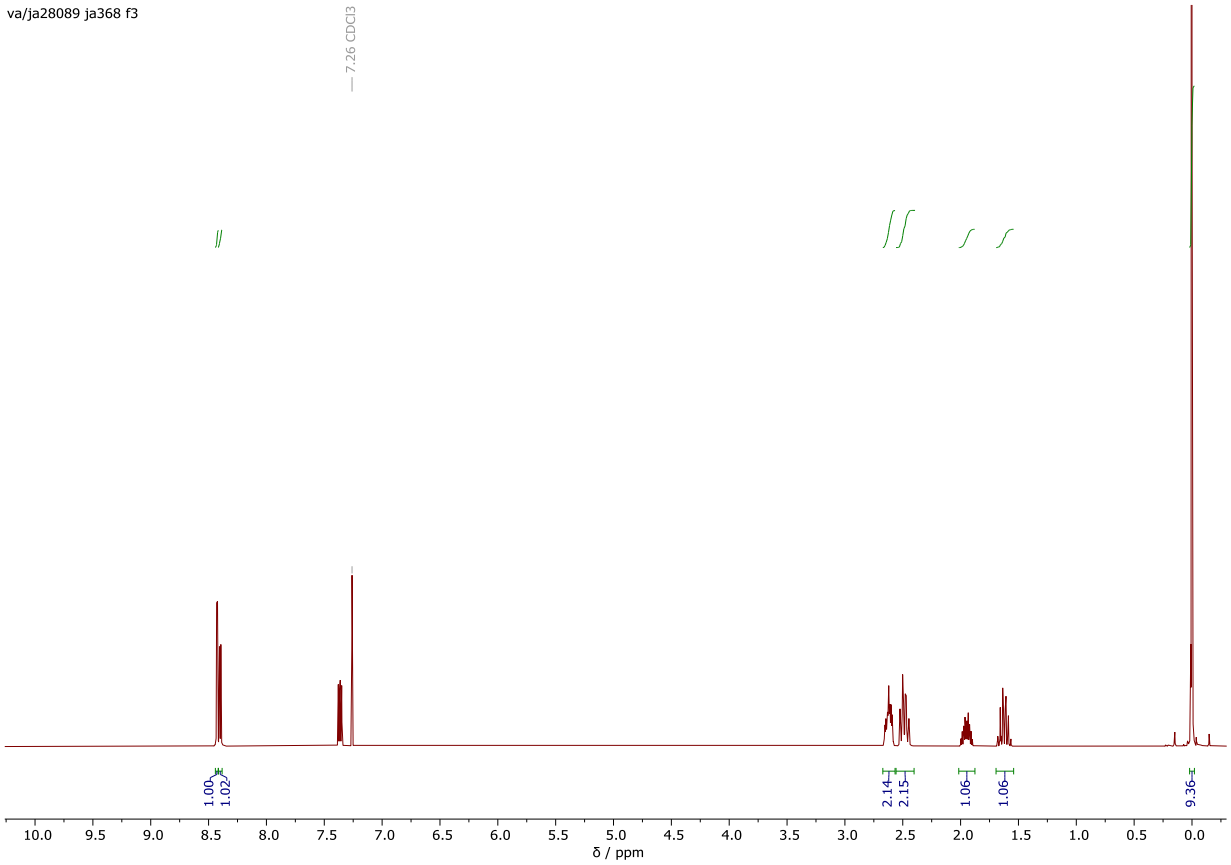
9.3.2.2 1-(3-Fluoropyridin-4-yl)cyclobutan-1-ol (518)

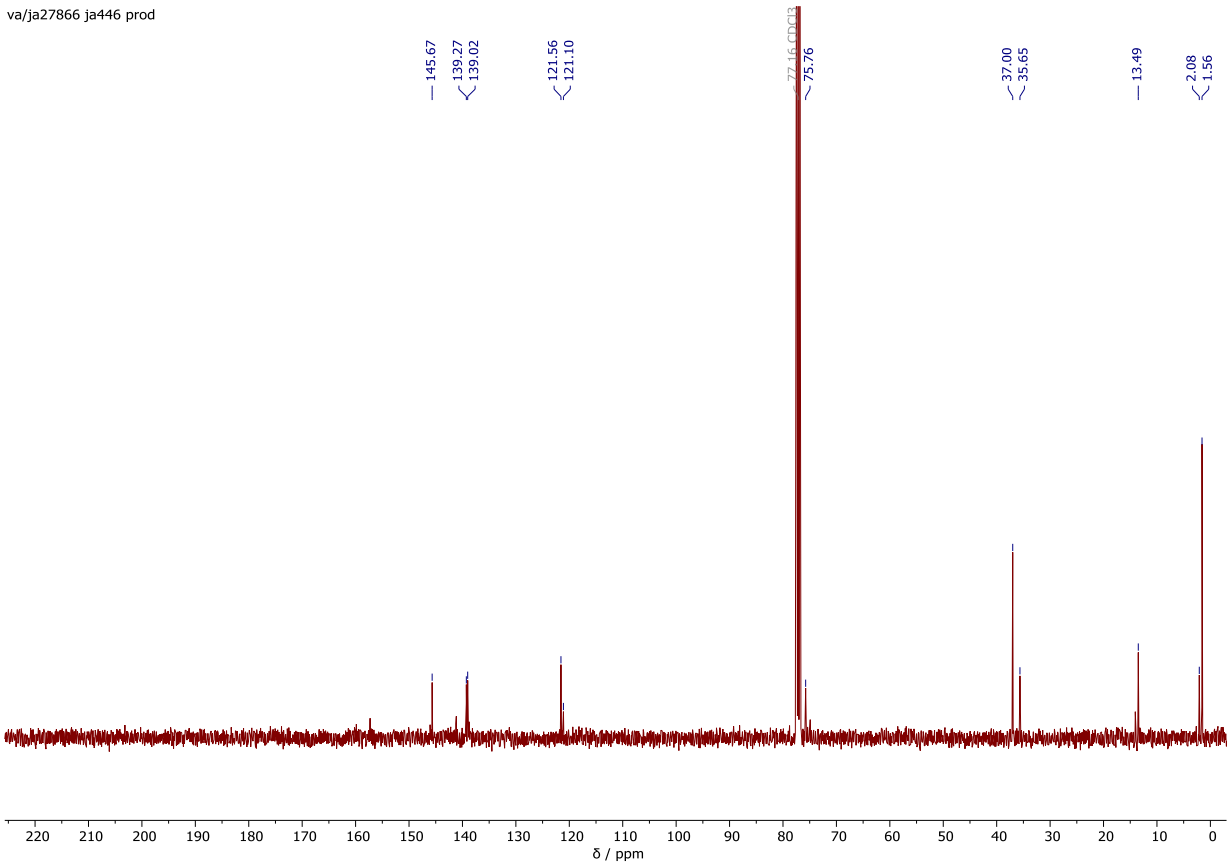



84593 LV068 prod qc.11.fid
159.40
156.86
145.78
141.12
138.70
138.47
121.28
77.16 CDCl3
74.71
35.68
14.06
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
δ / ppm

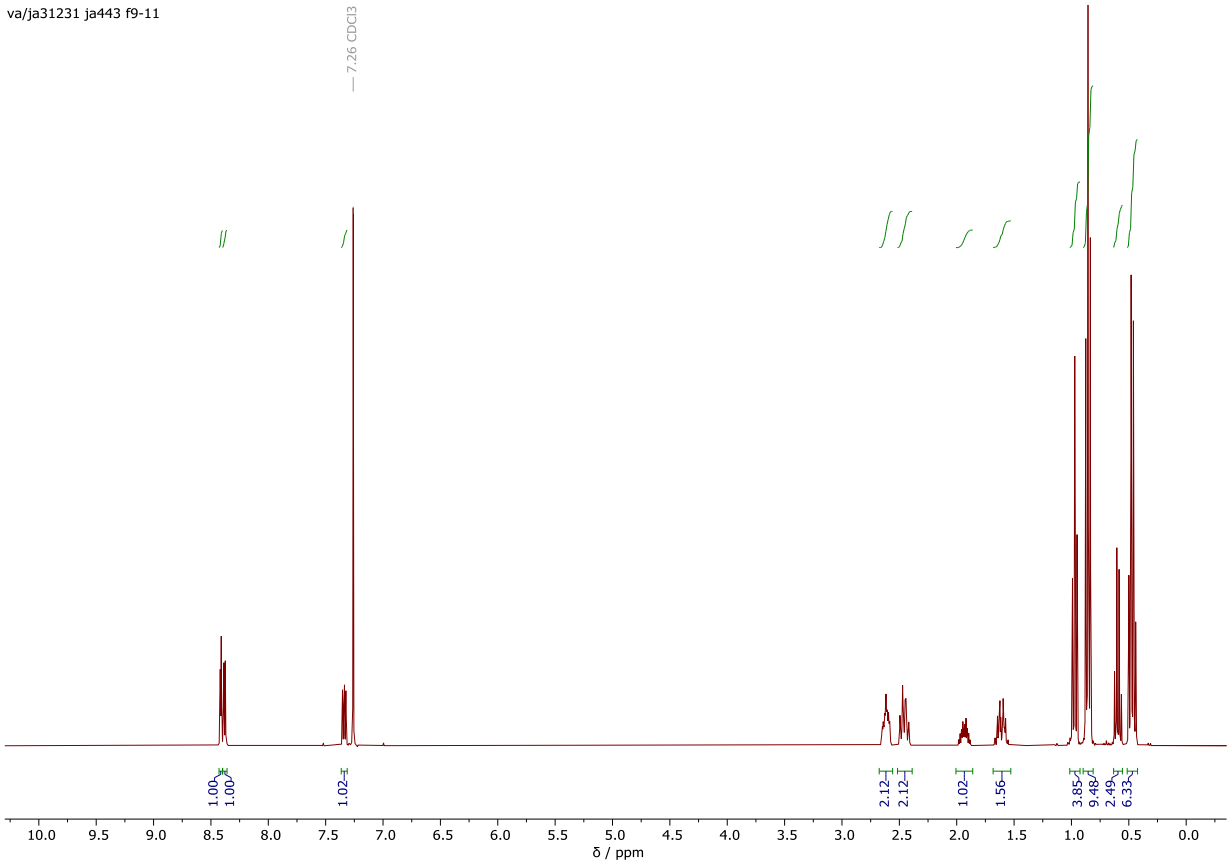

va/ja23778 ja346 prod qc
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
δ / ppm

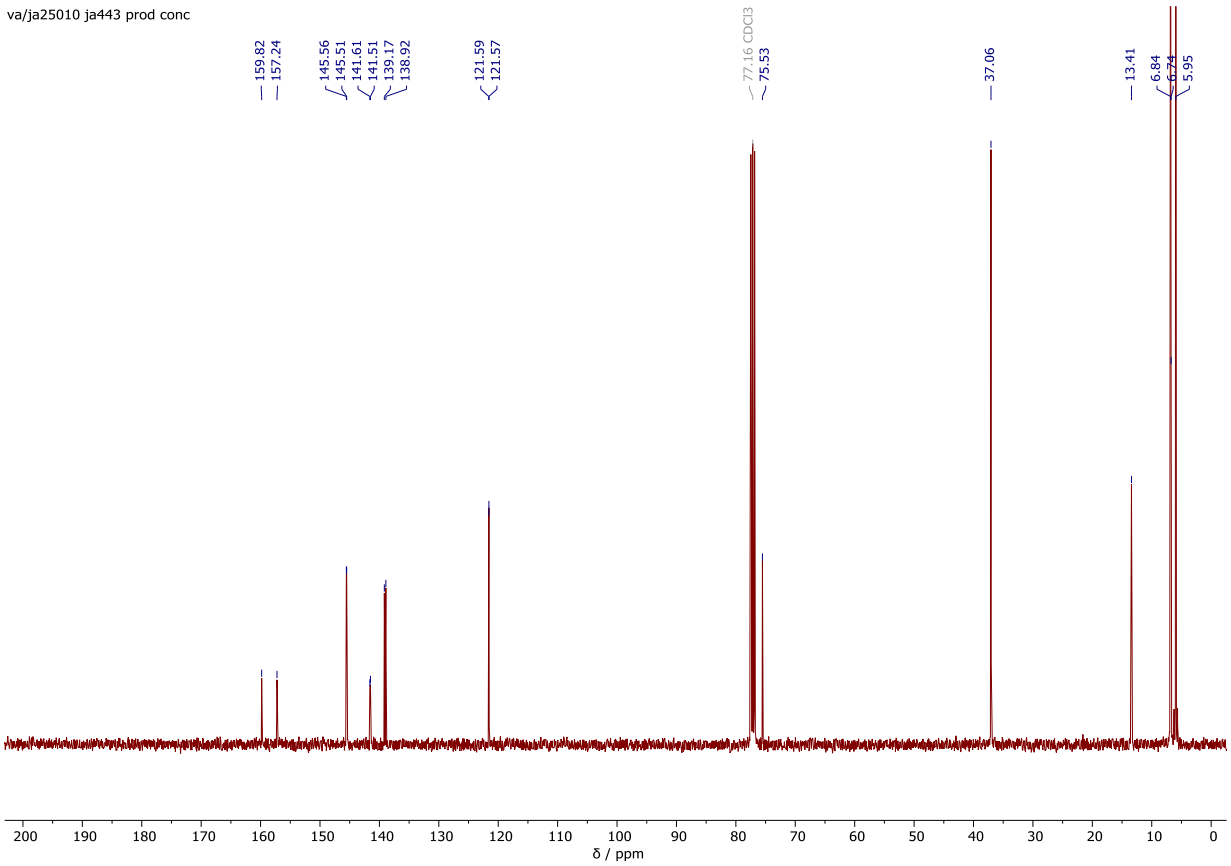
9.3.2.3 3-Fluoro-4-(1-((trimethylsilyl)oxy)cyclobutyl)pyridine (521a)



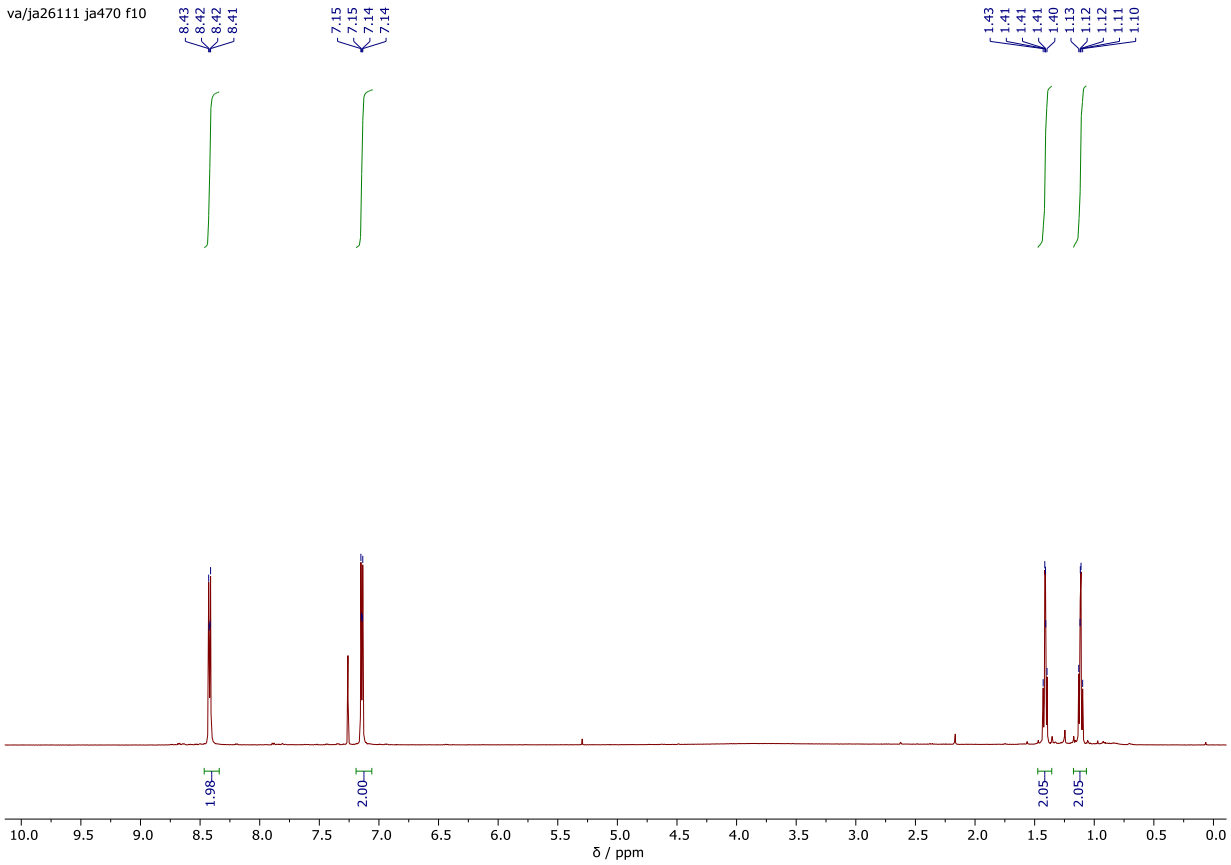


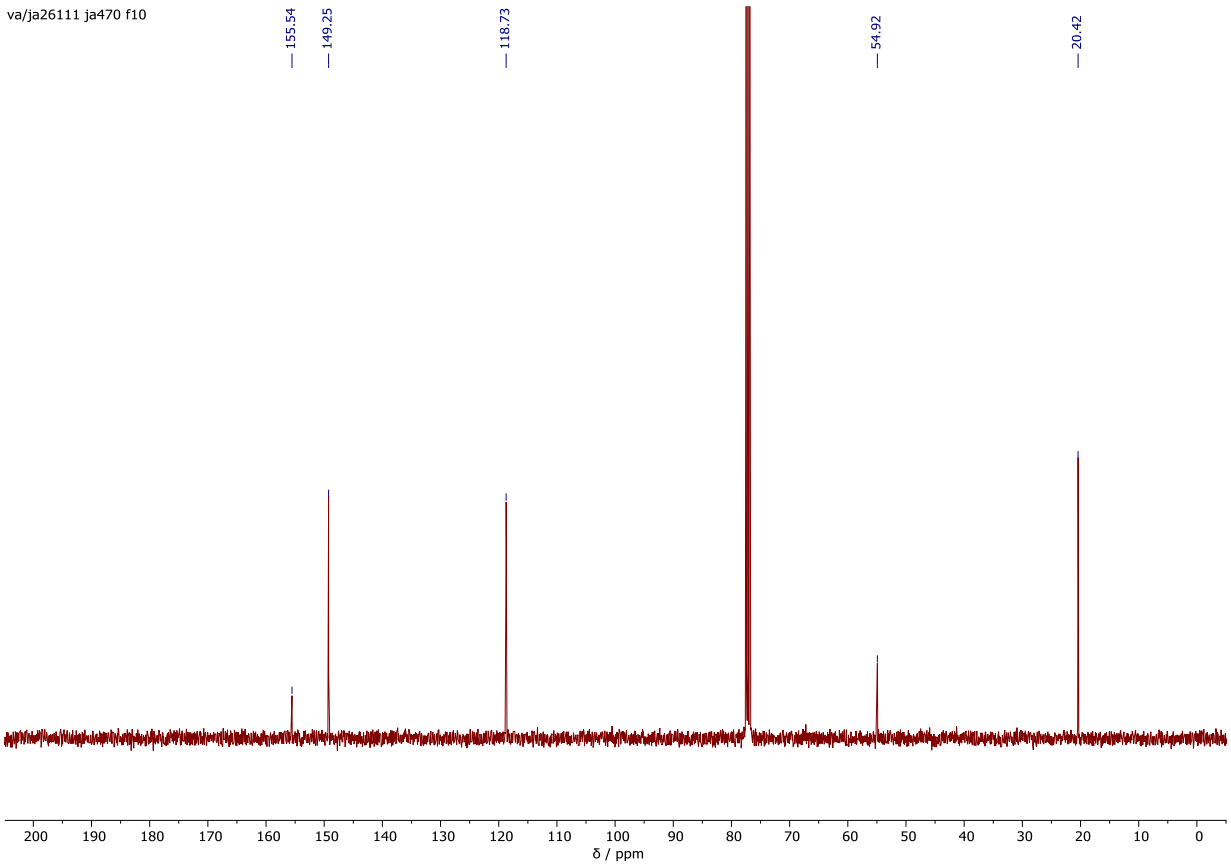
9.3.2.4 3-Fluoro-4-(1-((triethylsilyl)oxy)cyclobutyl)pyridine (521b)





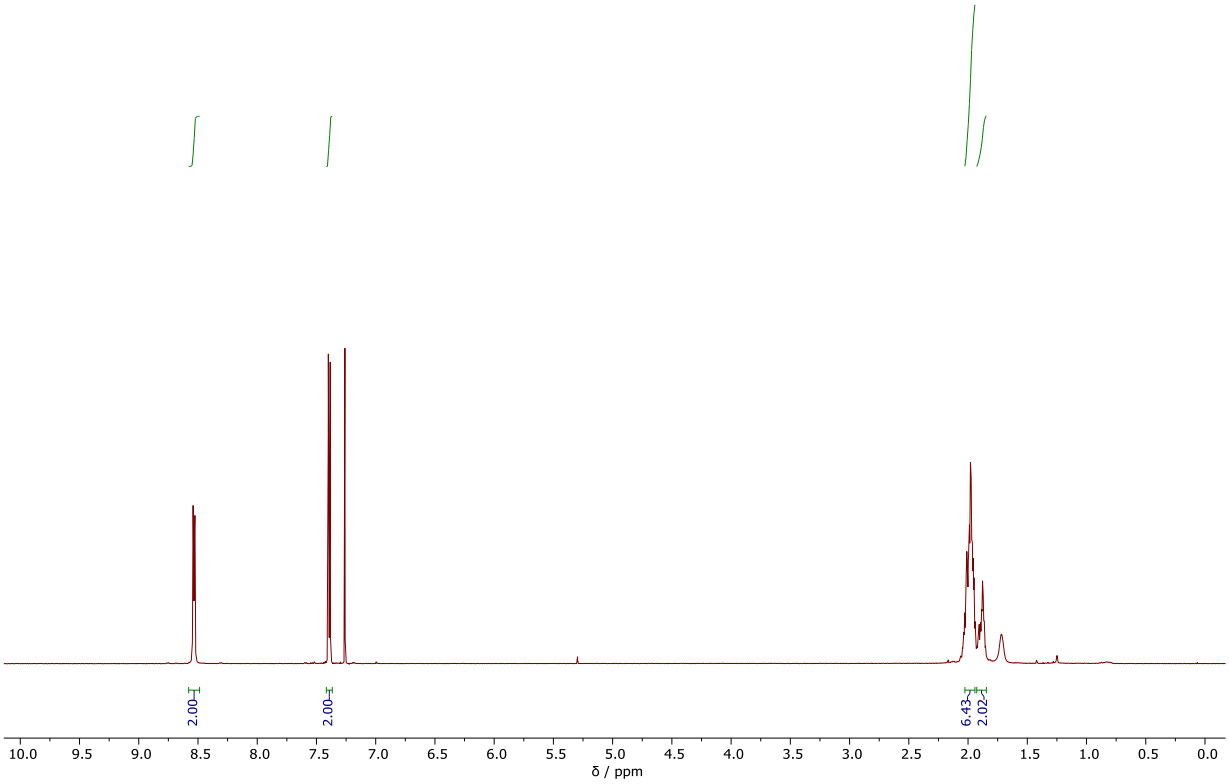
9.3.2.5 1-(Pyridin-4-yl)cyclopropan-1-ol (523a)



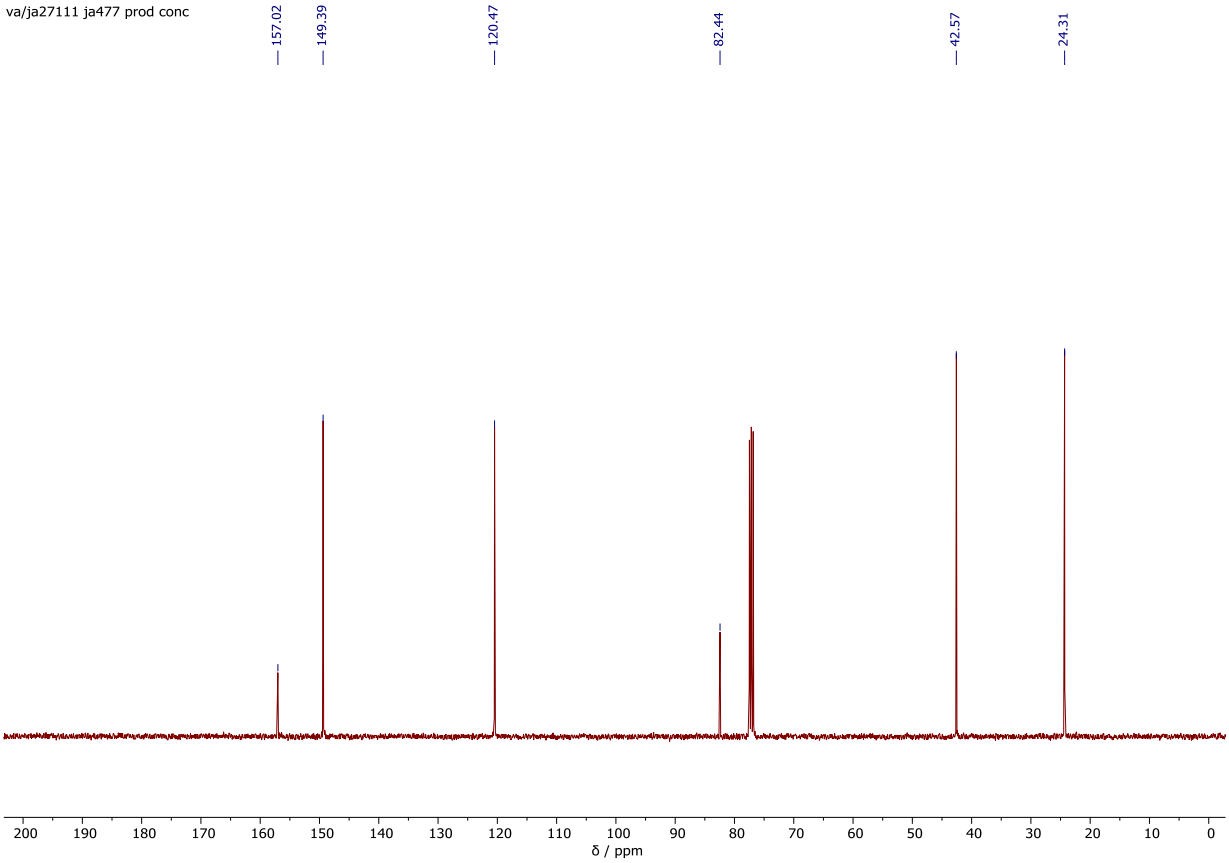


9.3.2.6 1-(Pyridin-4-yl)cyclopentan-1-ol (523b)

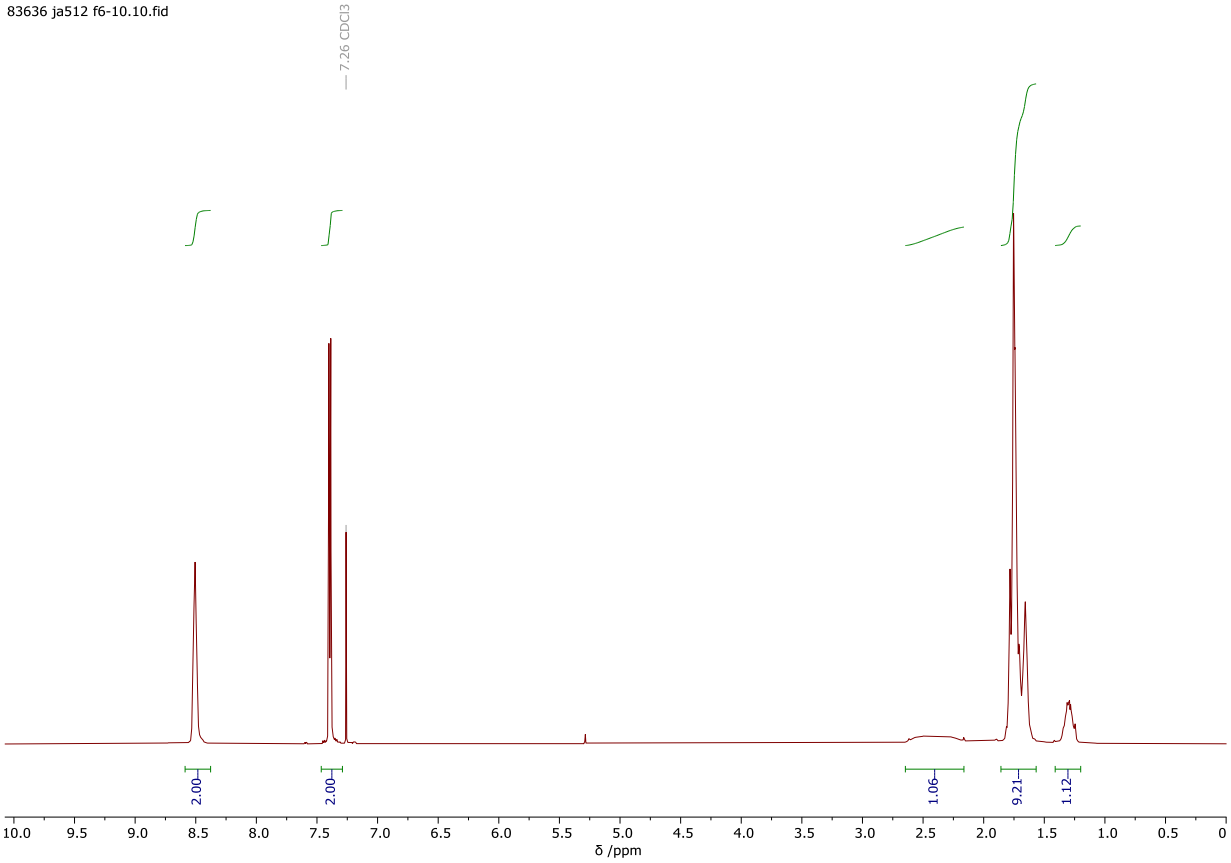
va/ja27313 ja477 prod dilute

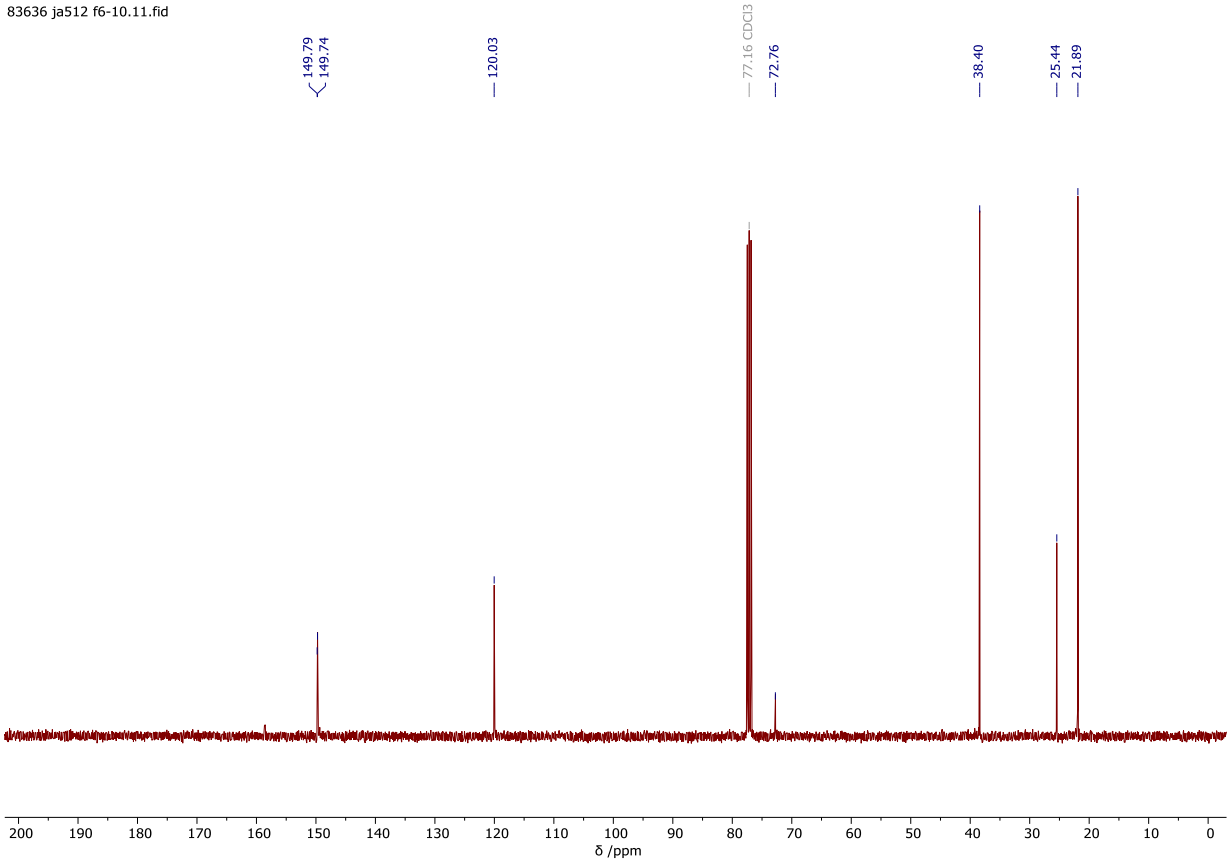


va/ja27111 ja477 prod conc

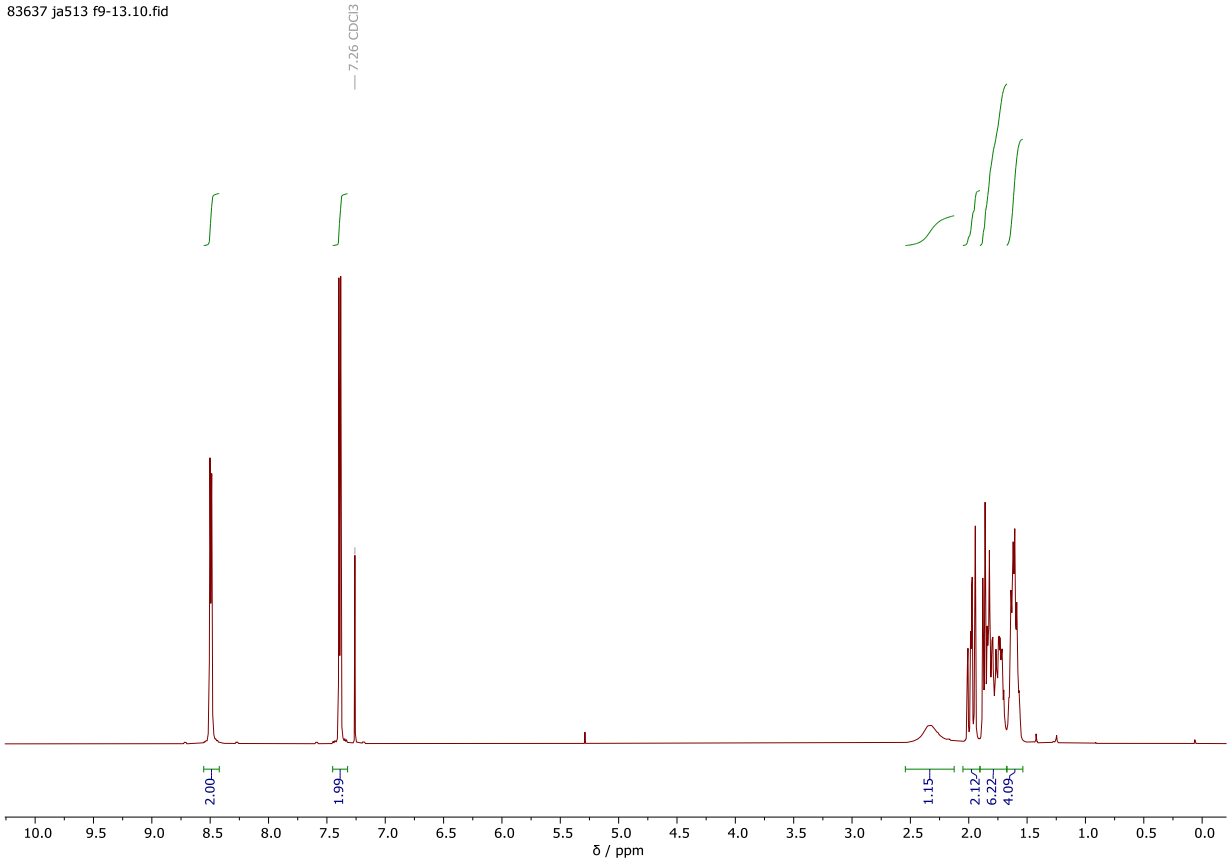


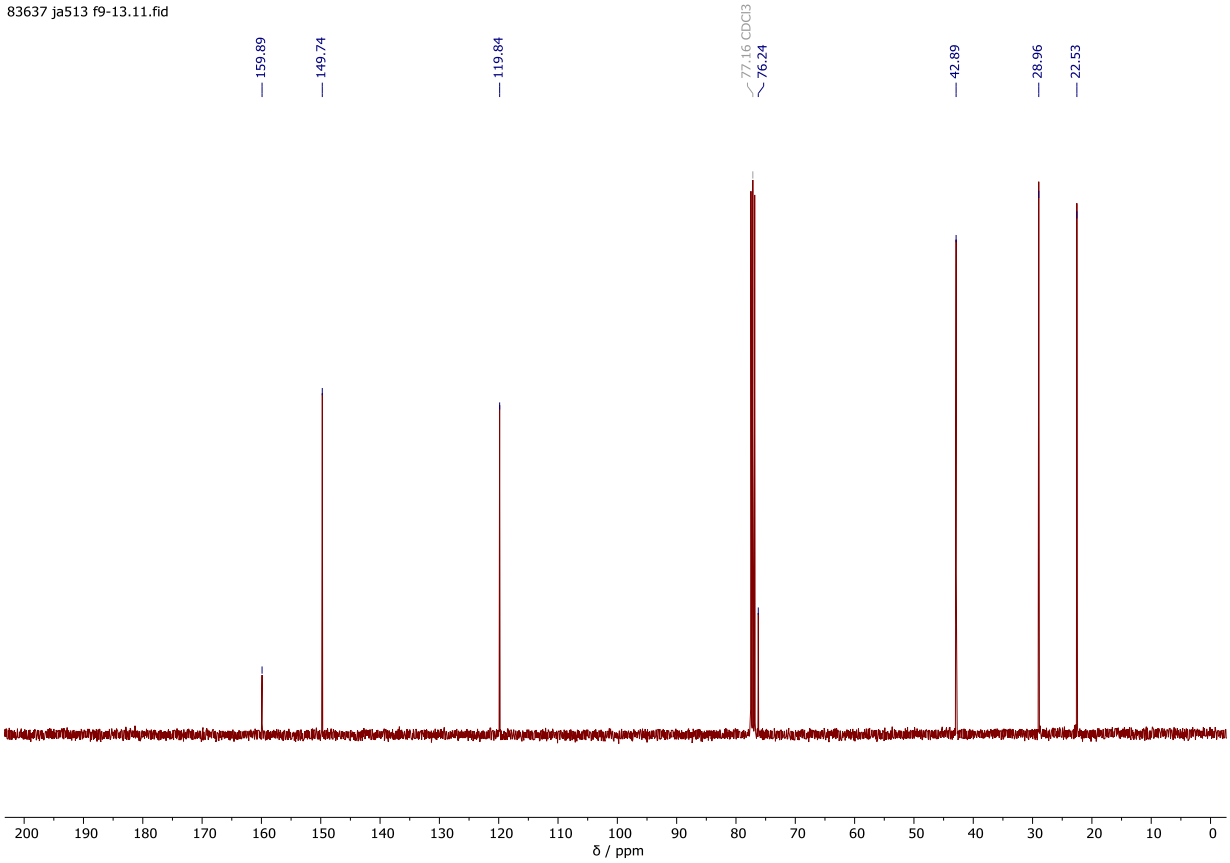
9.3.2.7 1-(Pyridin-4-yl)cyclohexan-1-ol (523c)



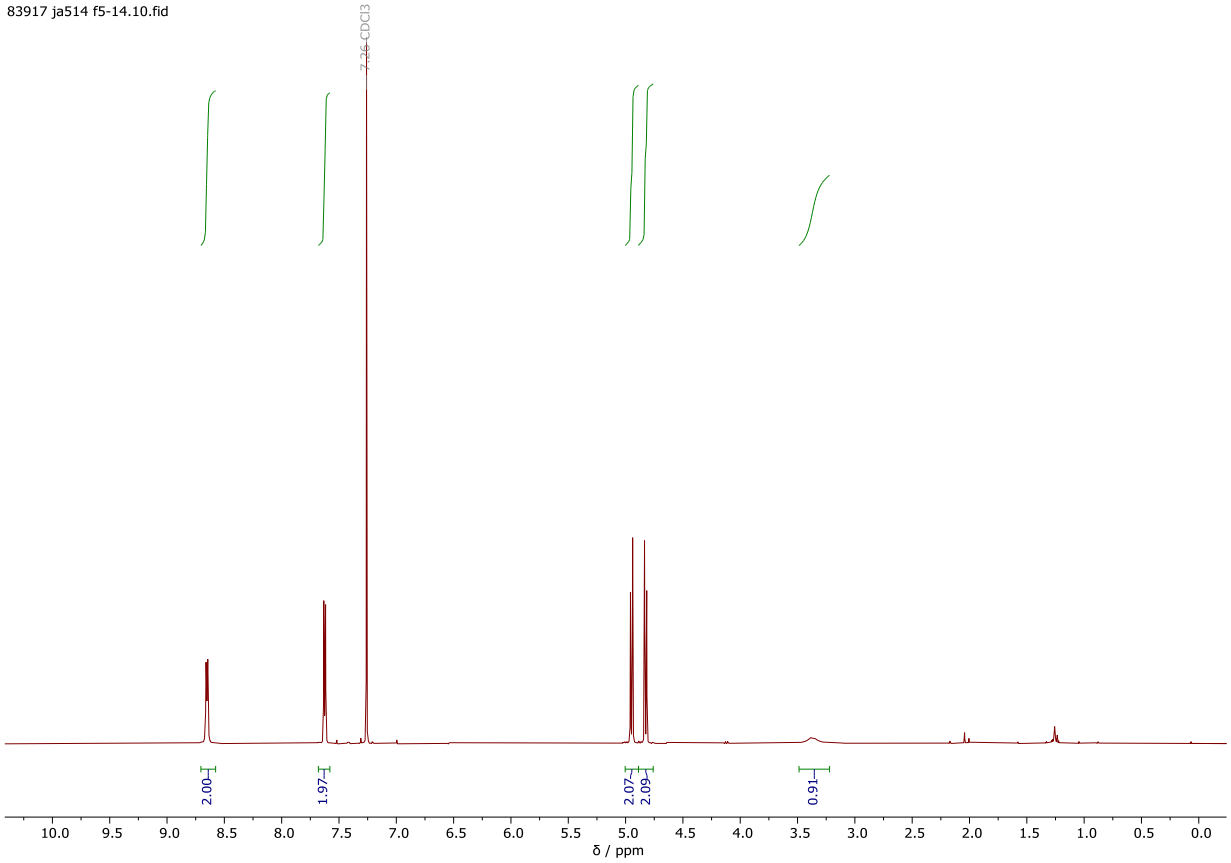


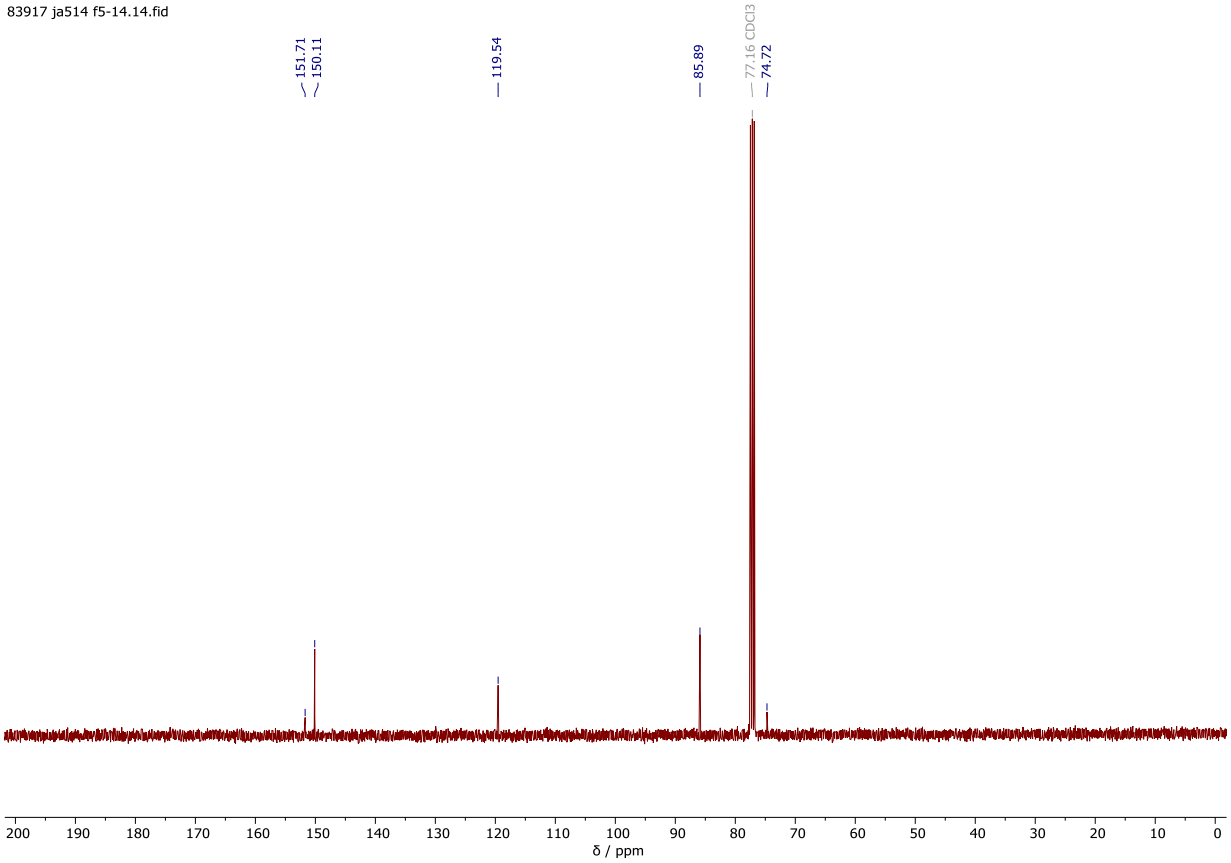
9.3.2.8 1-(Pyridin-4-yl)cycloheptan-1-ol (523d)





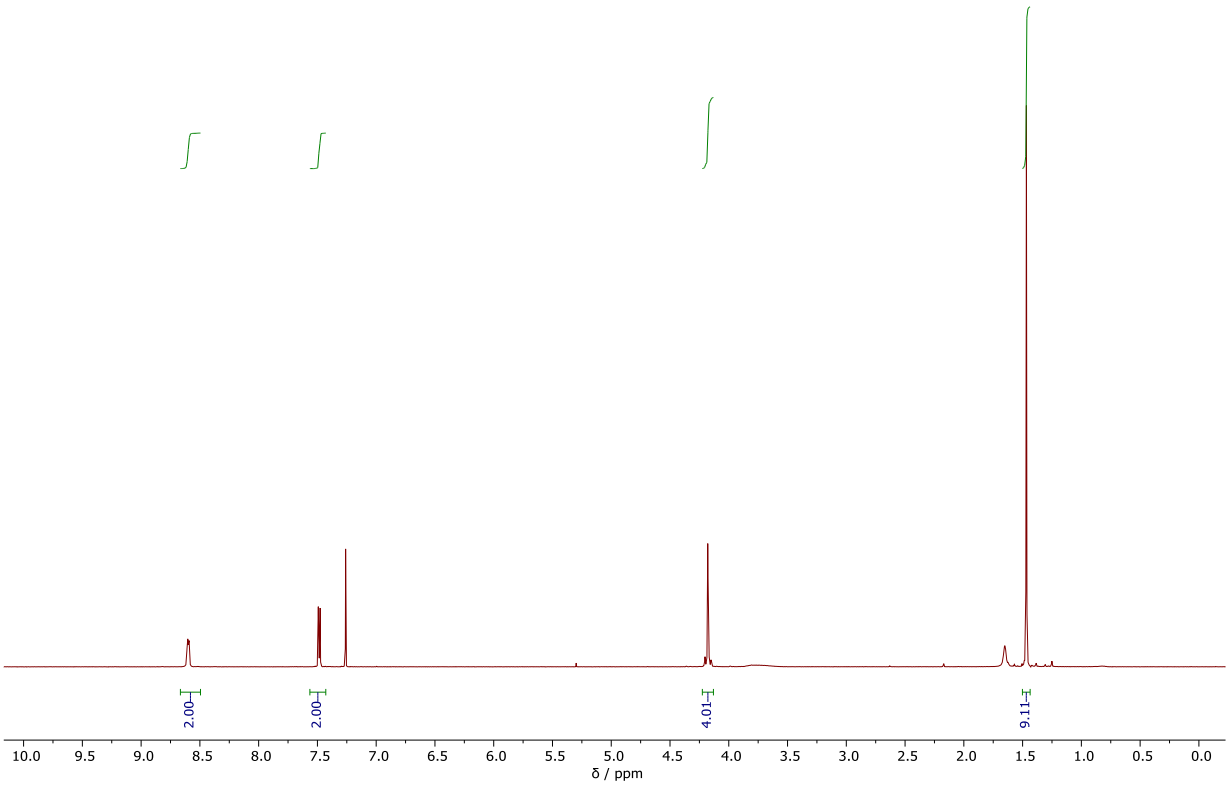
9.3.2.9 3-(Pyridin-4-yl)oxetan-3-ol (523e)



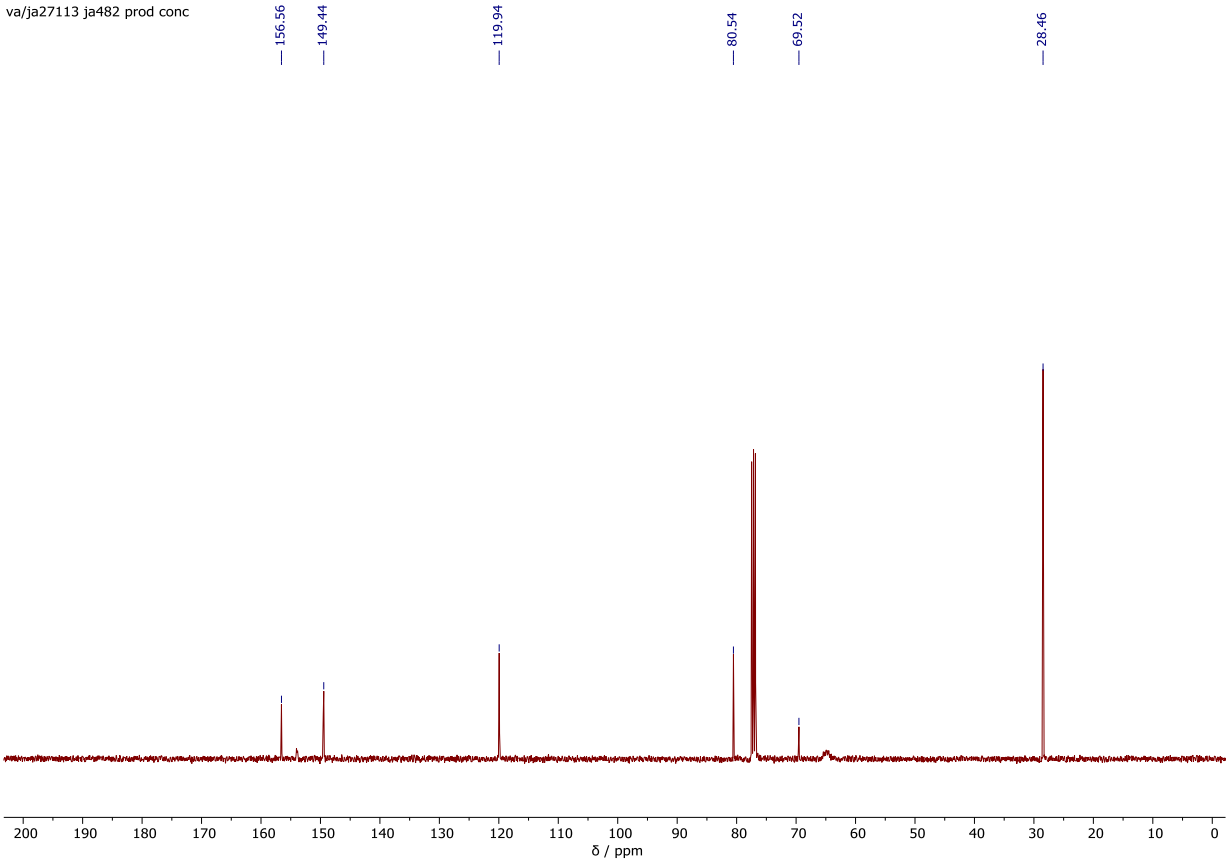


9.3.2.10 *tert*-Butyl 3-hydroxy-3-(pyridin-4-yl)azetidine-1-carboxylate (523f)

va/ja27314 ja482 prod dilute

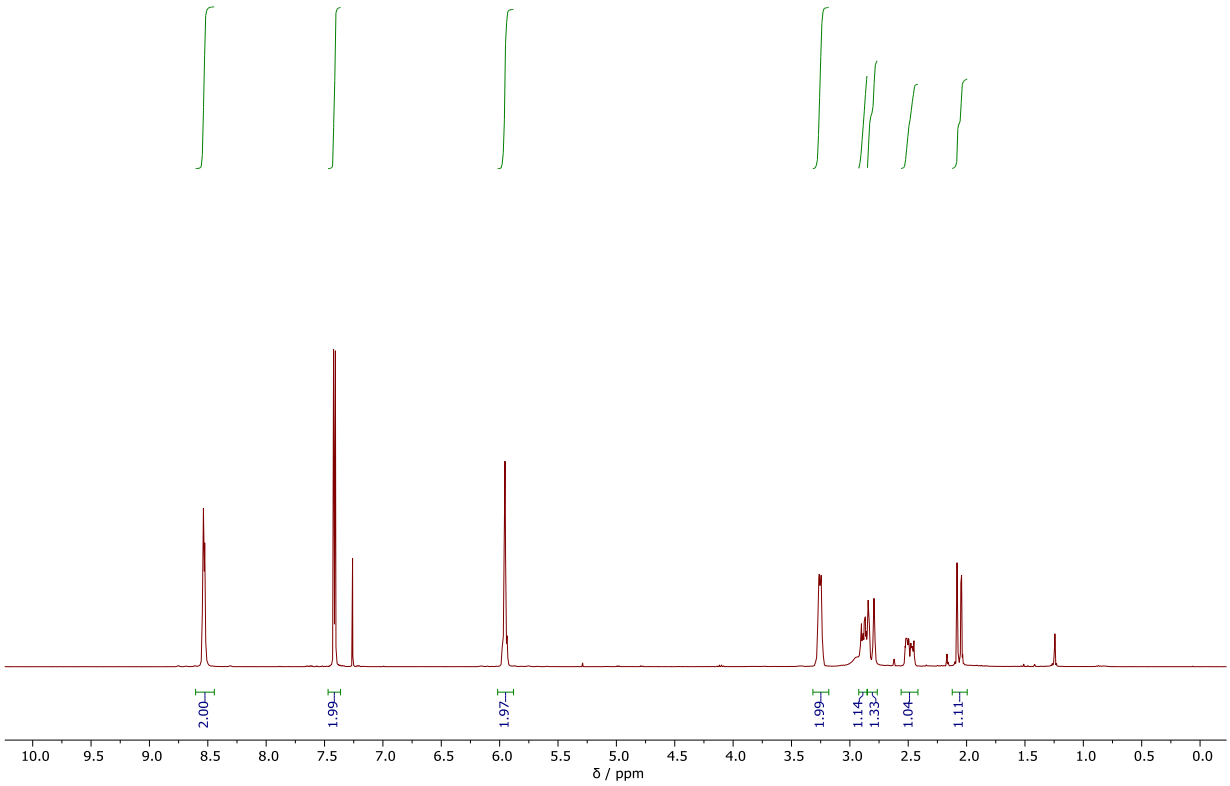


va/ja27113 ja482 prod conc

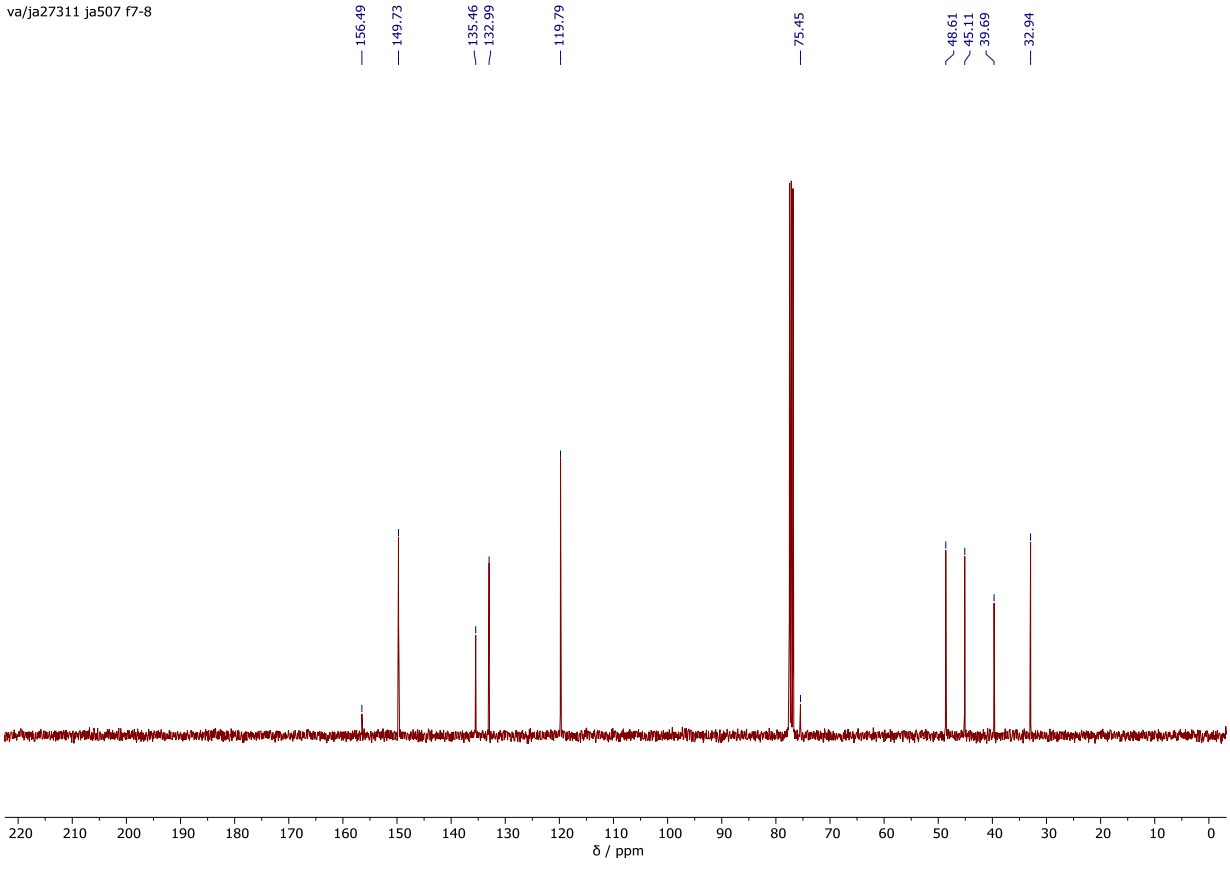


9.3.2.11 (1*R*,5*S*)-6-(Pyridin-4-yl)bicyclo[3.2.0]hept-2-en-6-ol (523g)

va/ja27311 ja507 f7-8

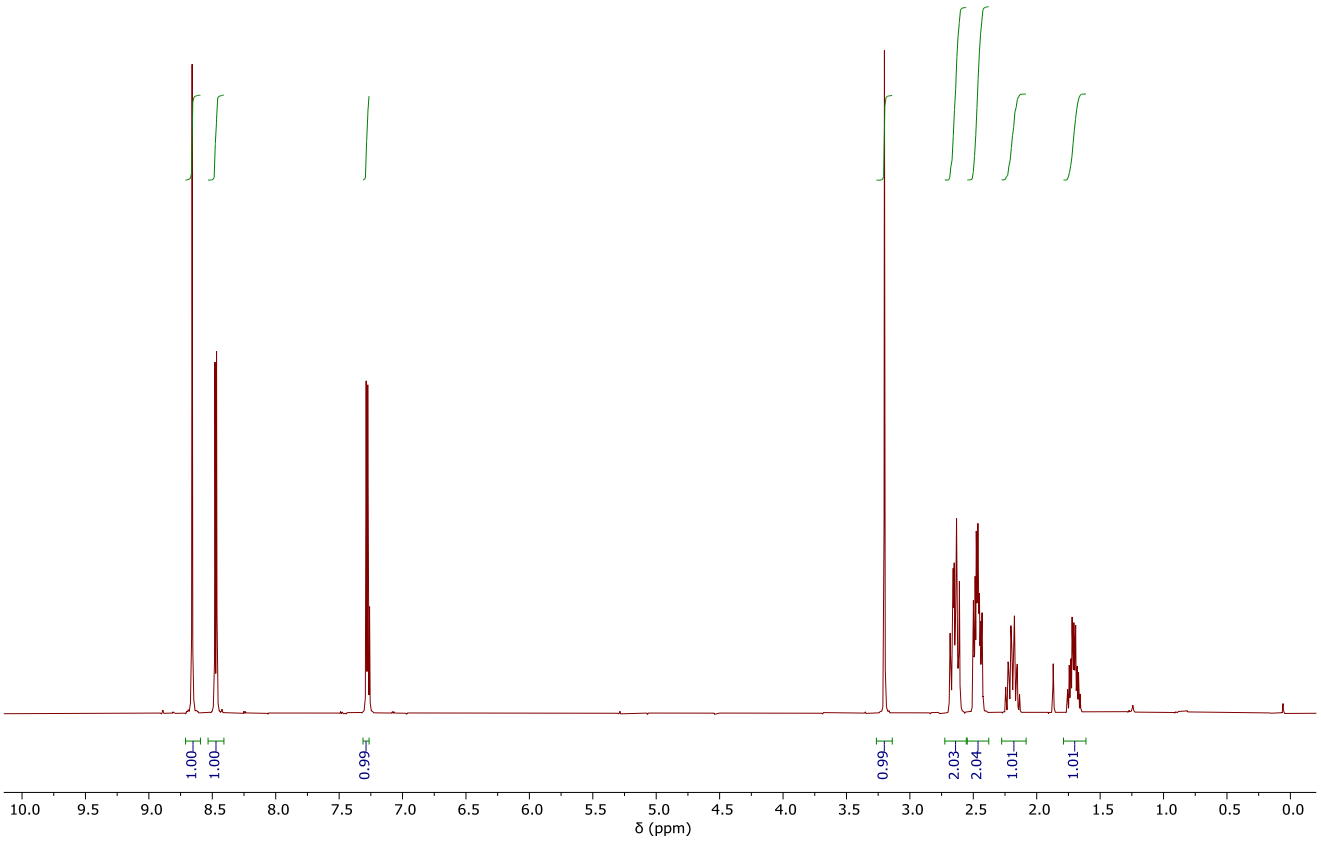


va/ja27311 ja507 f7-8

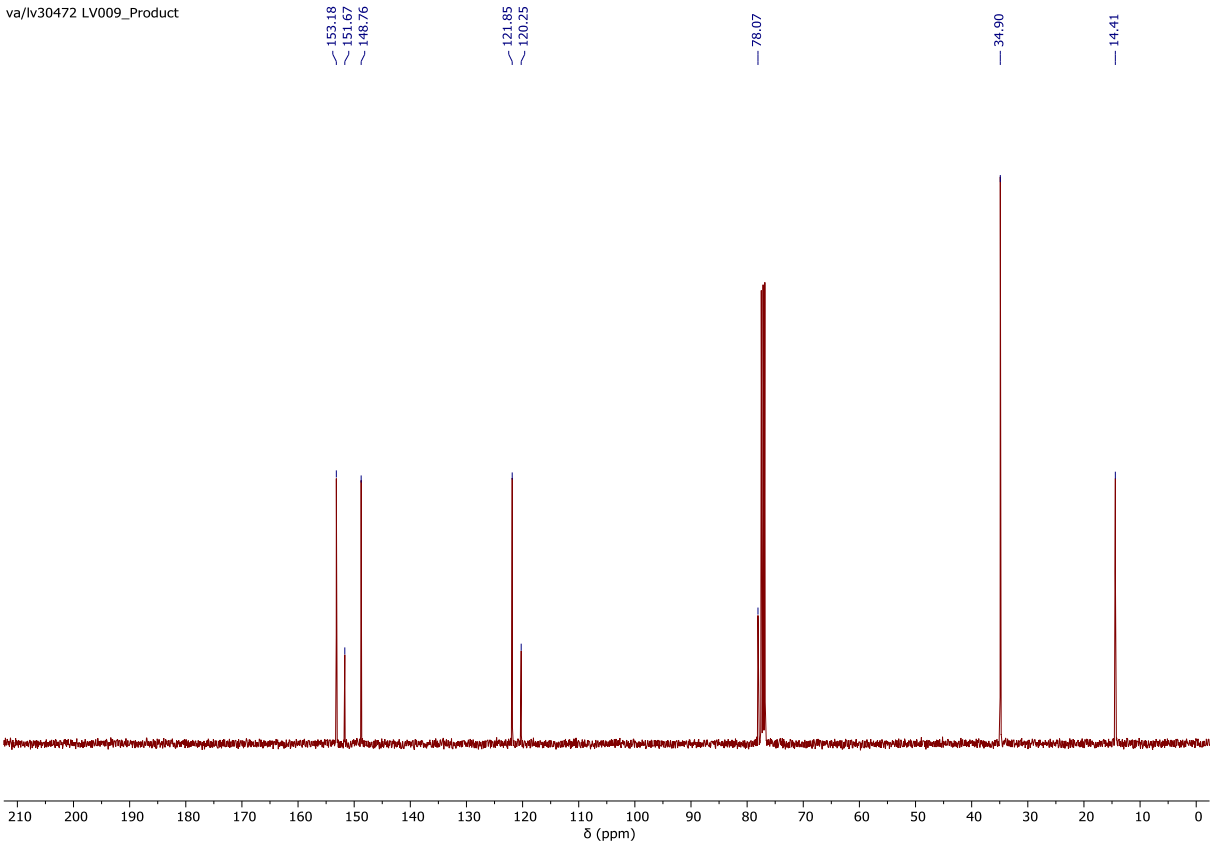


9.3.2.12 1-(3-Bromopyridin-4-yl)cyclobutan-1-ol (523h)

va/lv30472 LV009_Product

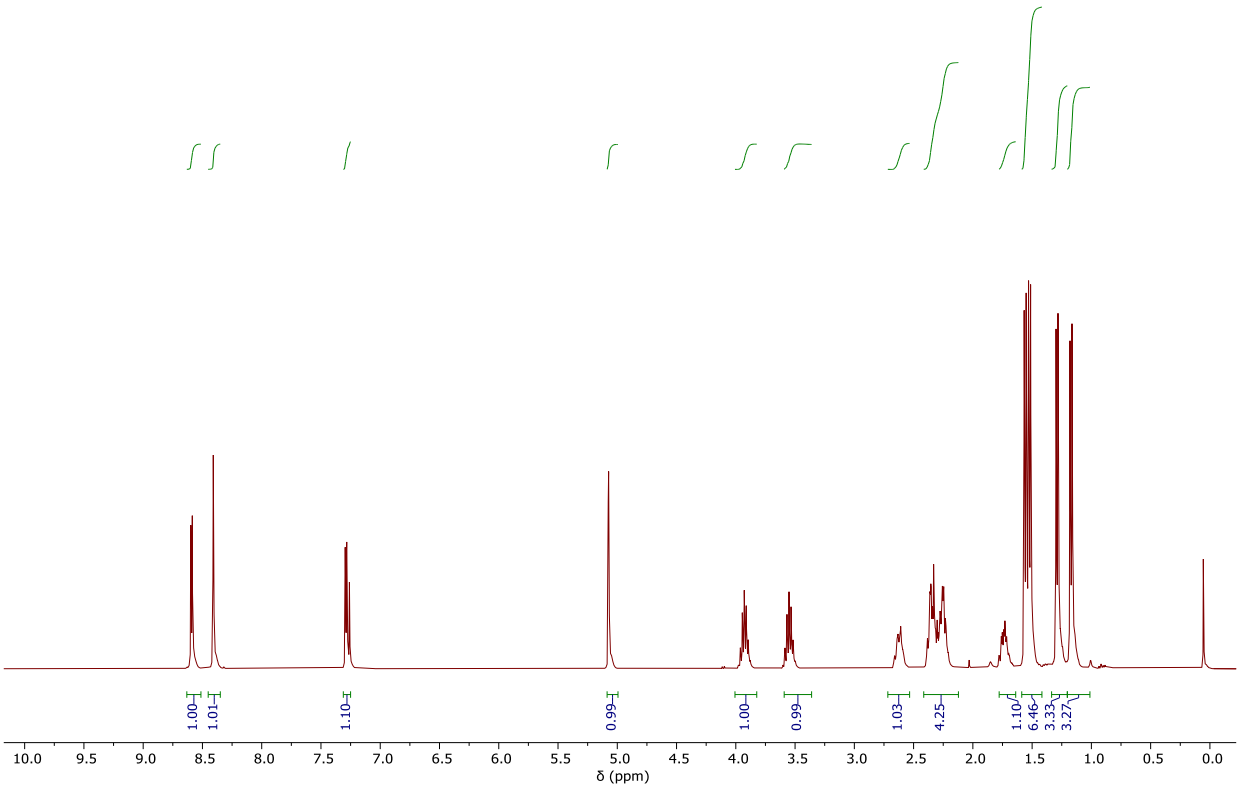


va/lv30472 LV009_Product

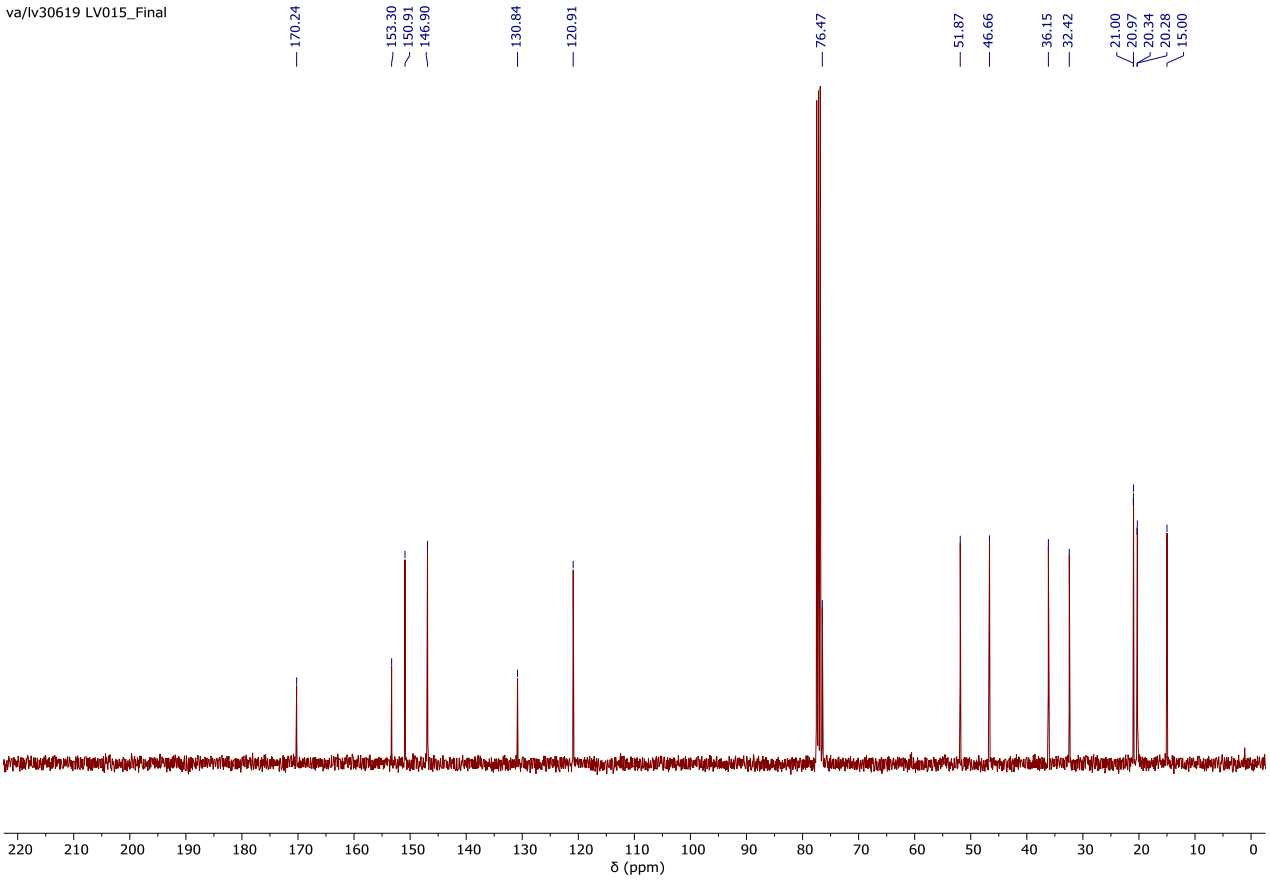


9.3.2.13 4-(1-Hydroxycyclobutyl)-*N*,*N*-diisopropylnicotinamide (523i)

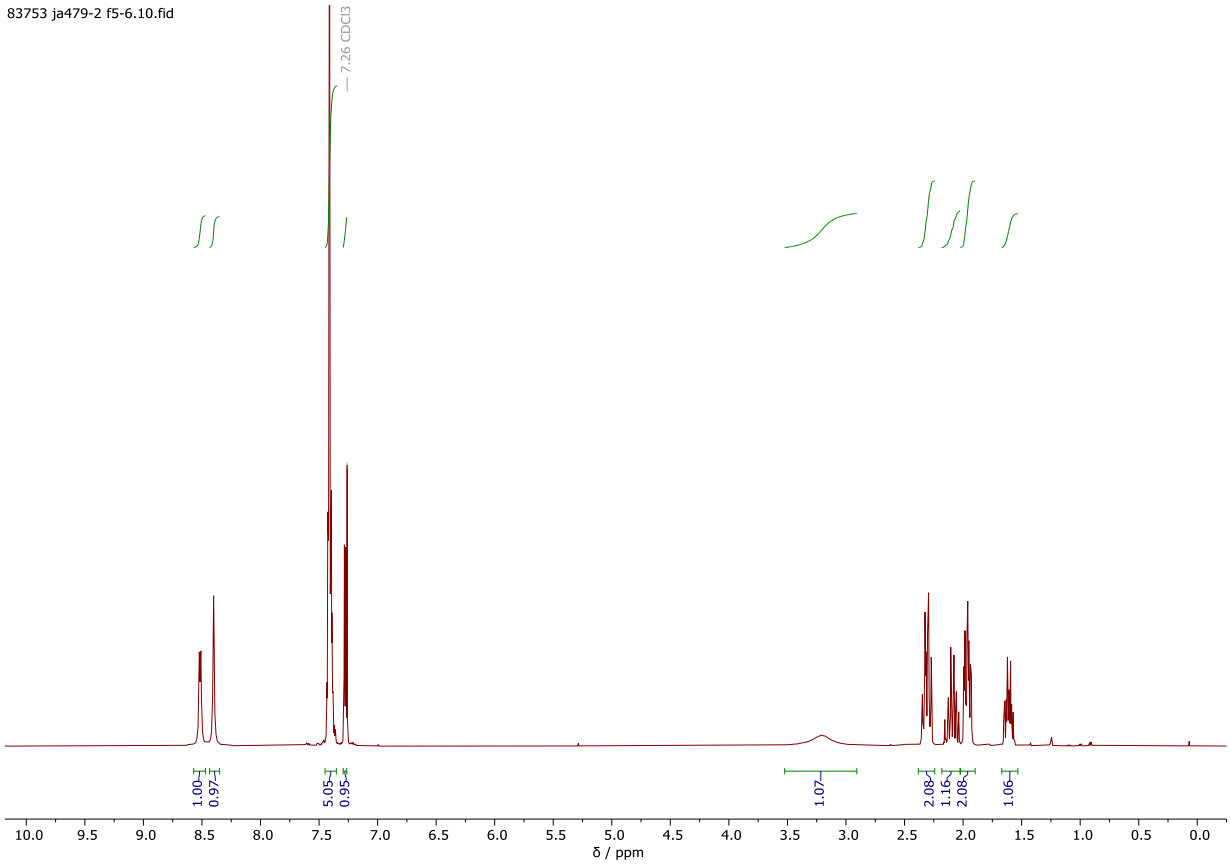
va/lv30619 LV015(2)_Final

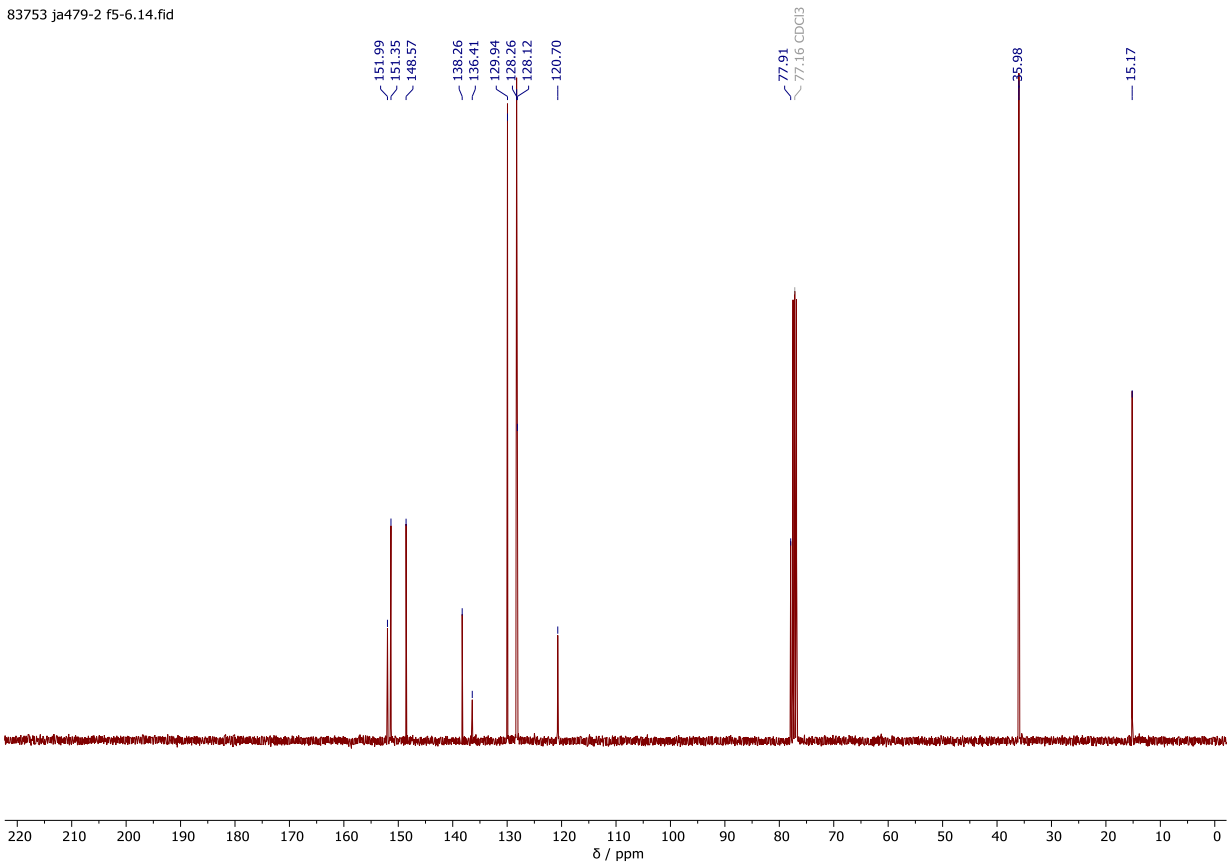


va/lv30619 LV015_Final

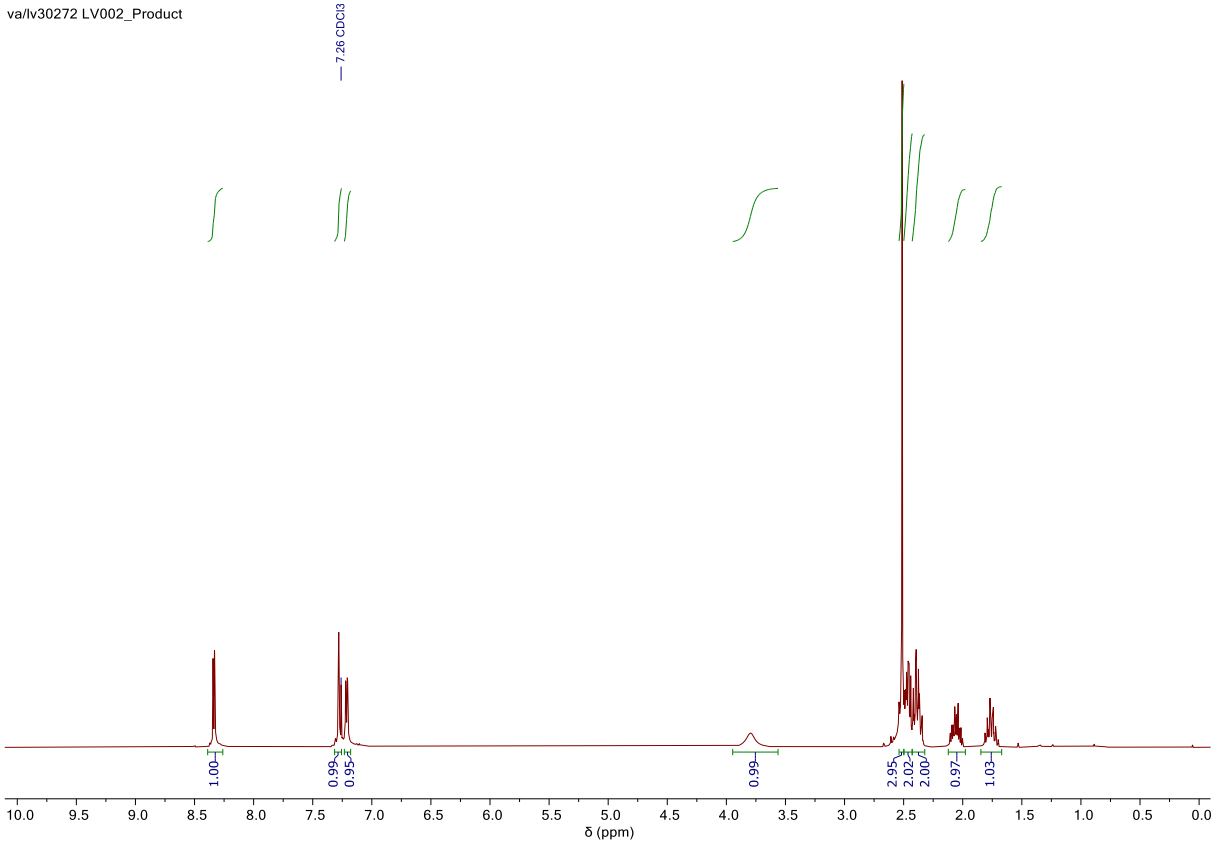


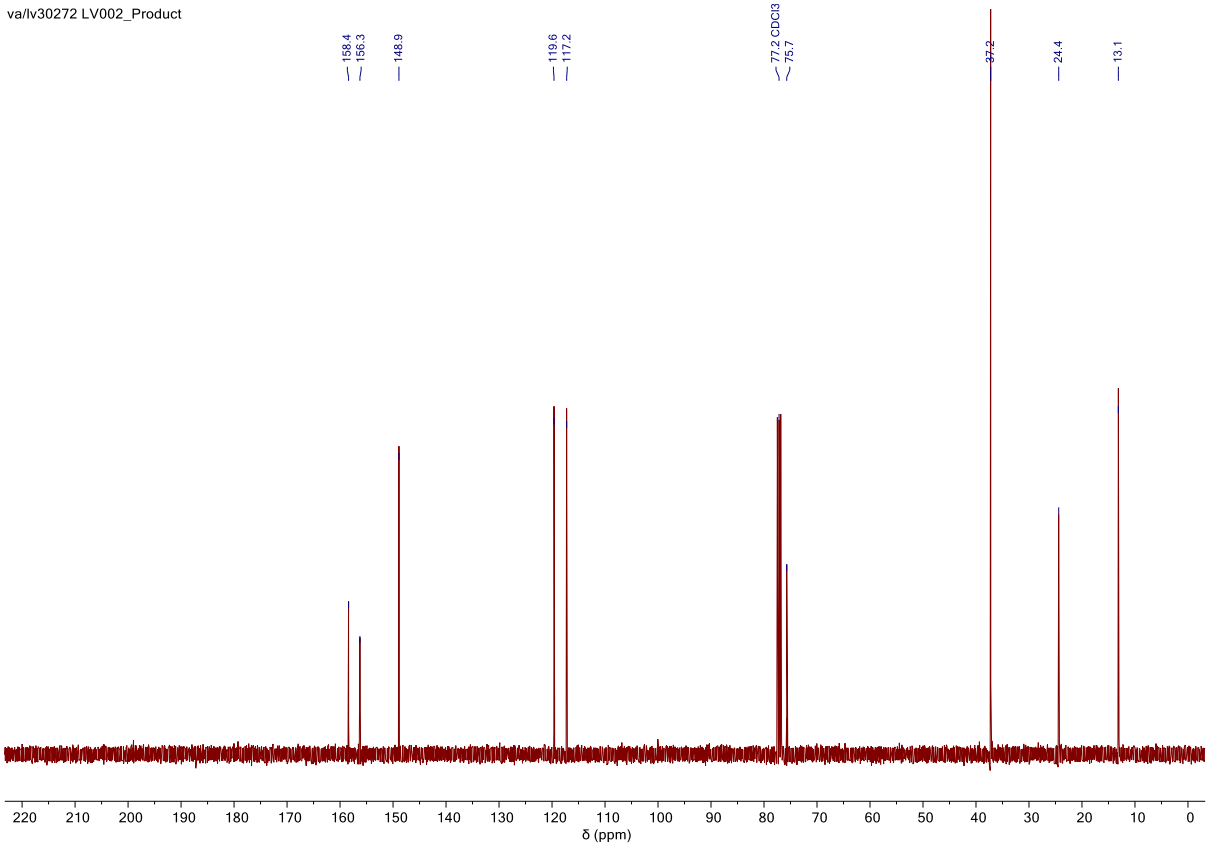
9.3.2.14 1-(3-Phenylpyridin-4-yl)cyclobutan-1-ol (523j)



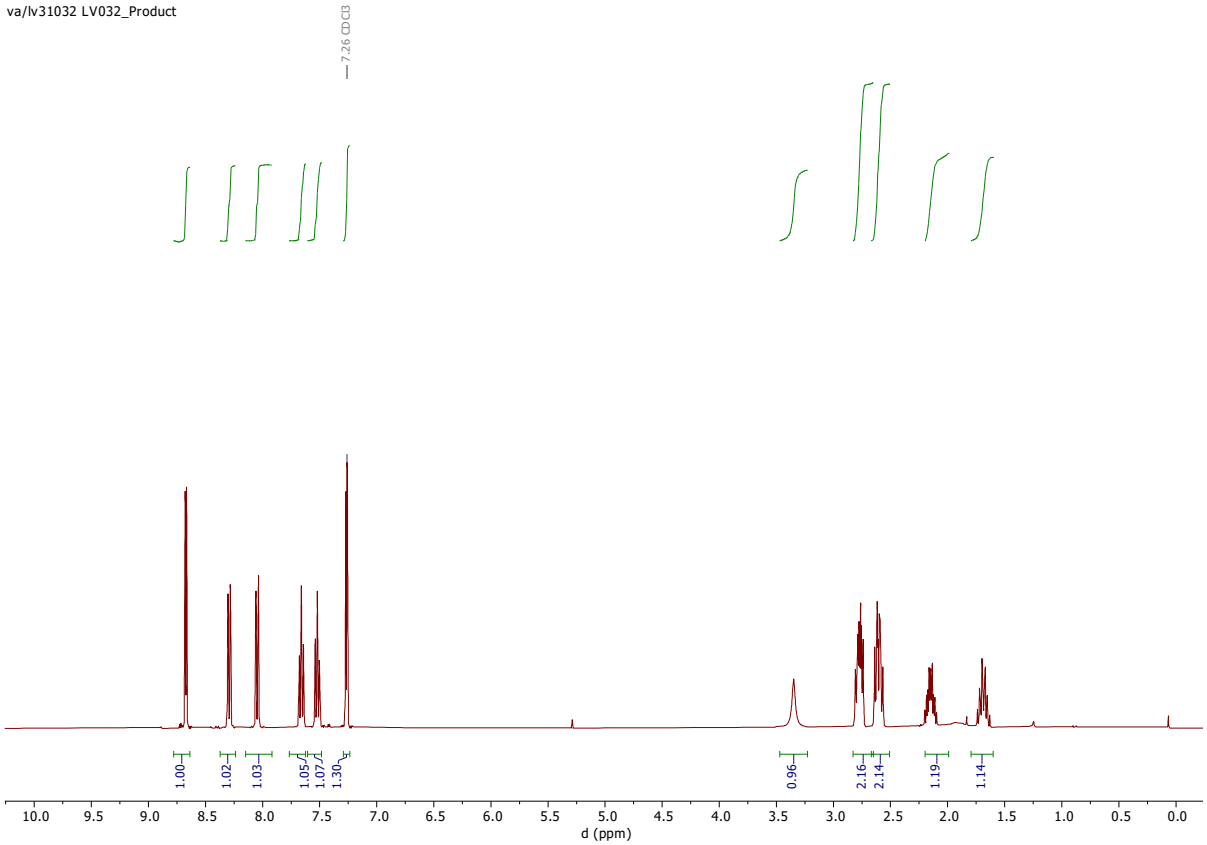


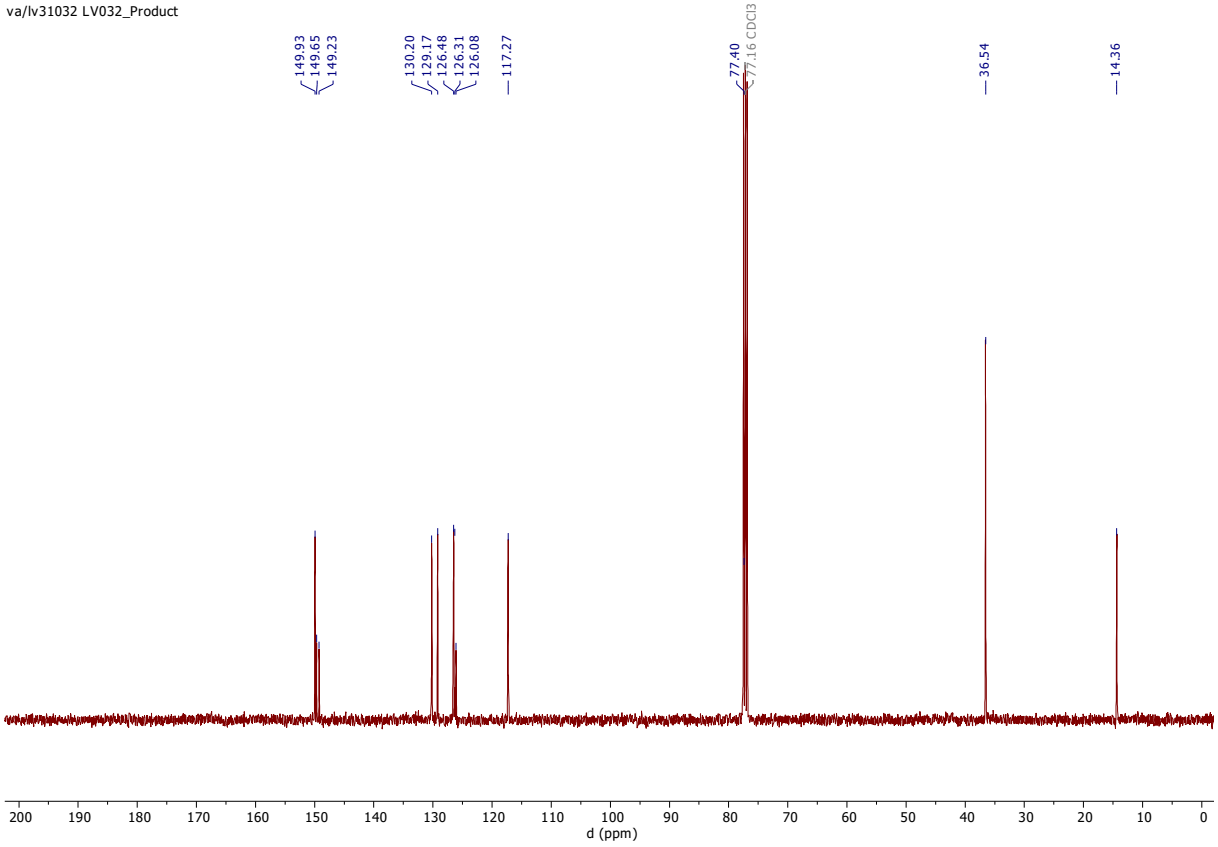
9.3.2.15 1-(2-Methylpyridin-4-yl)cyclobutan-1-ol (523k)



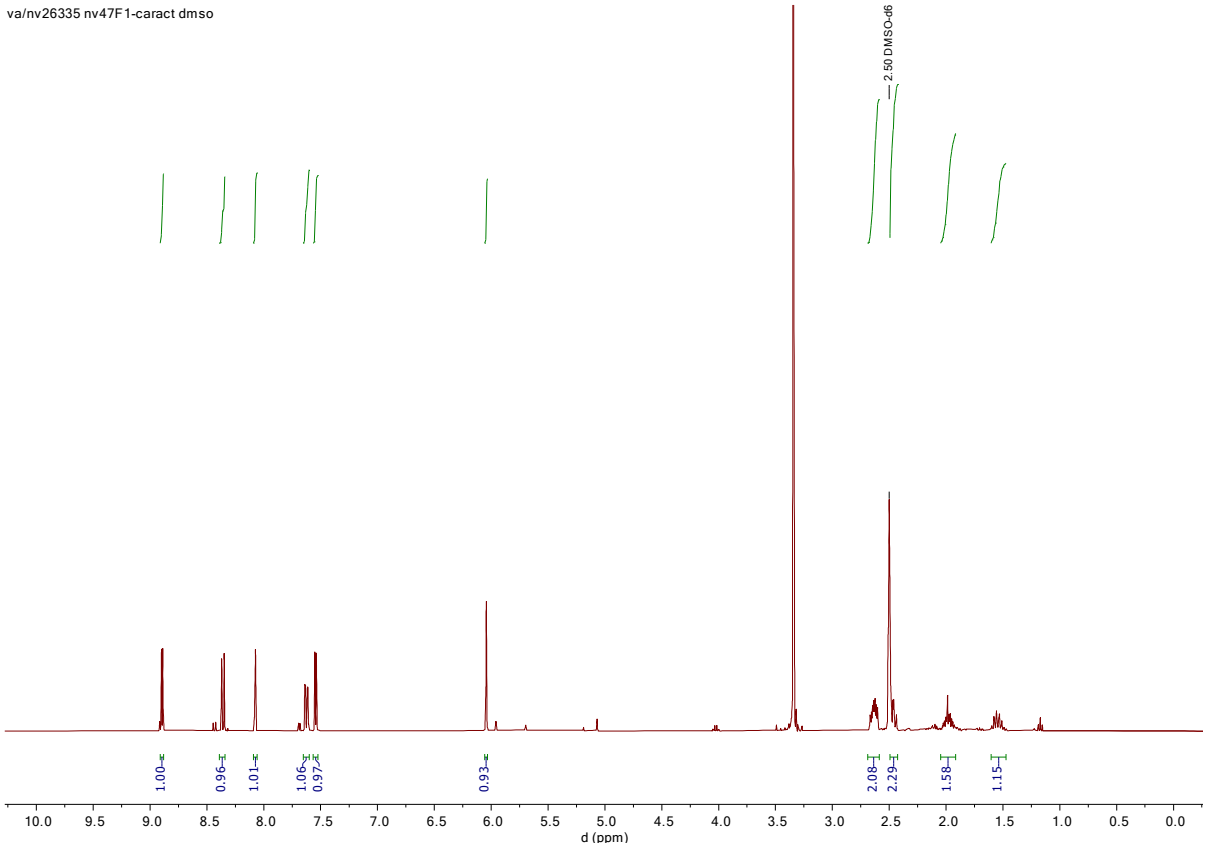


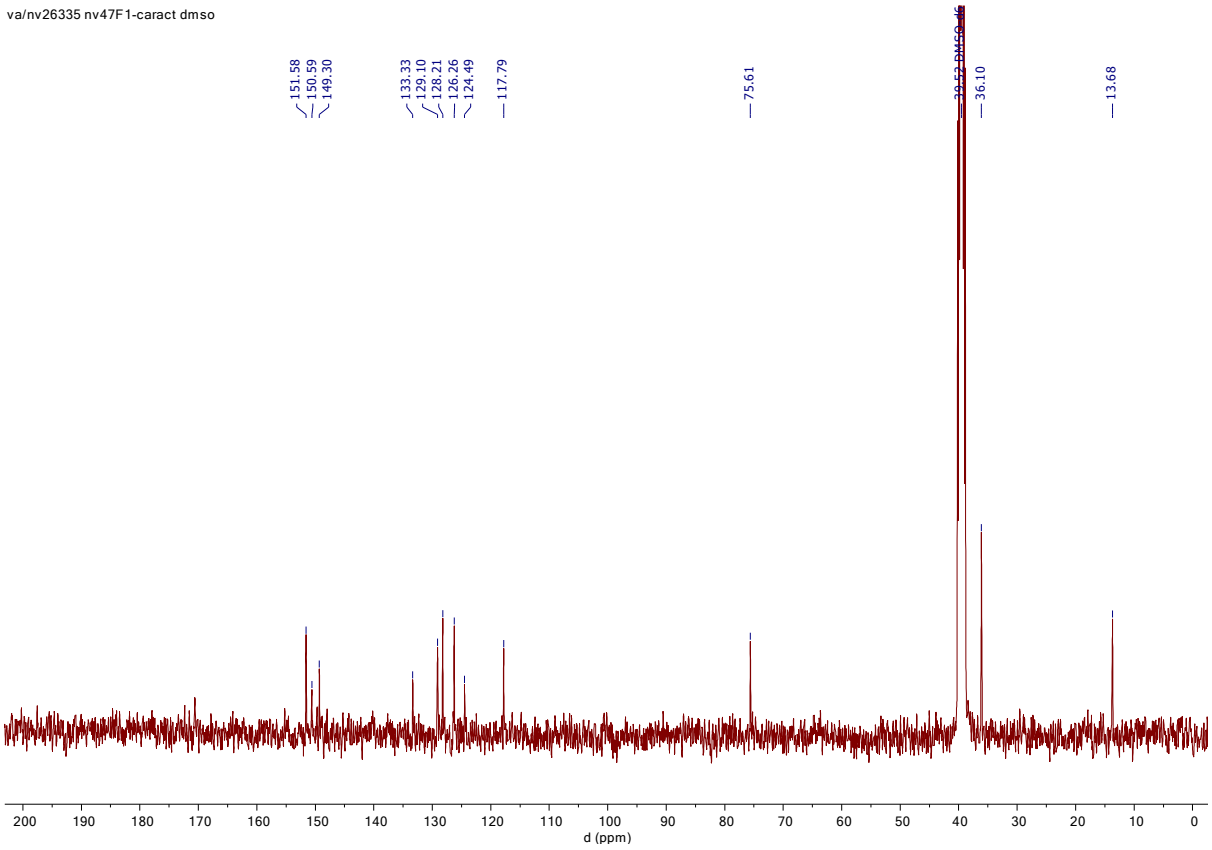
9.3.2.16 1-(Quinolin-4-yl)cyclobutan-1-ol (523l)



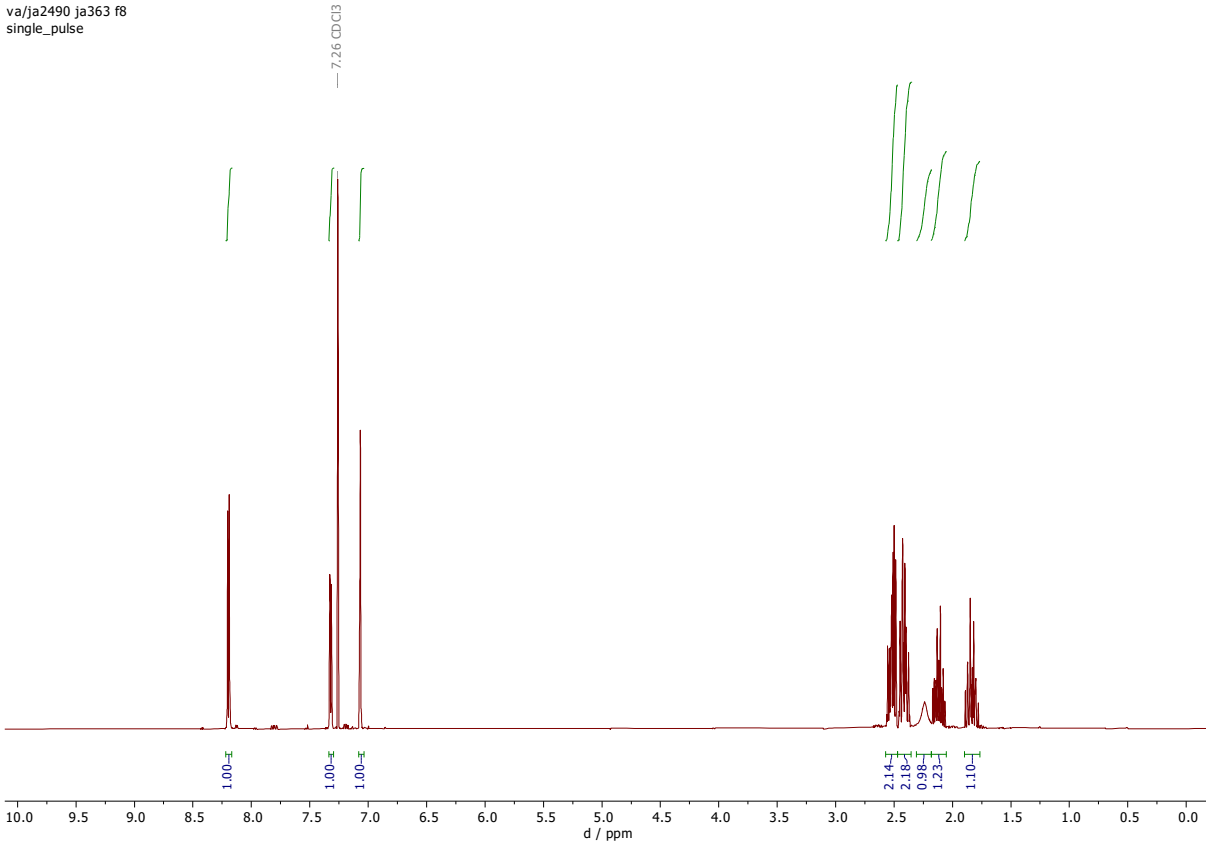


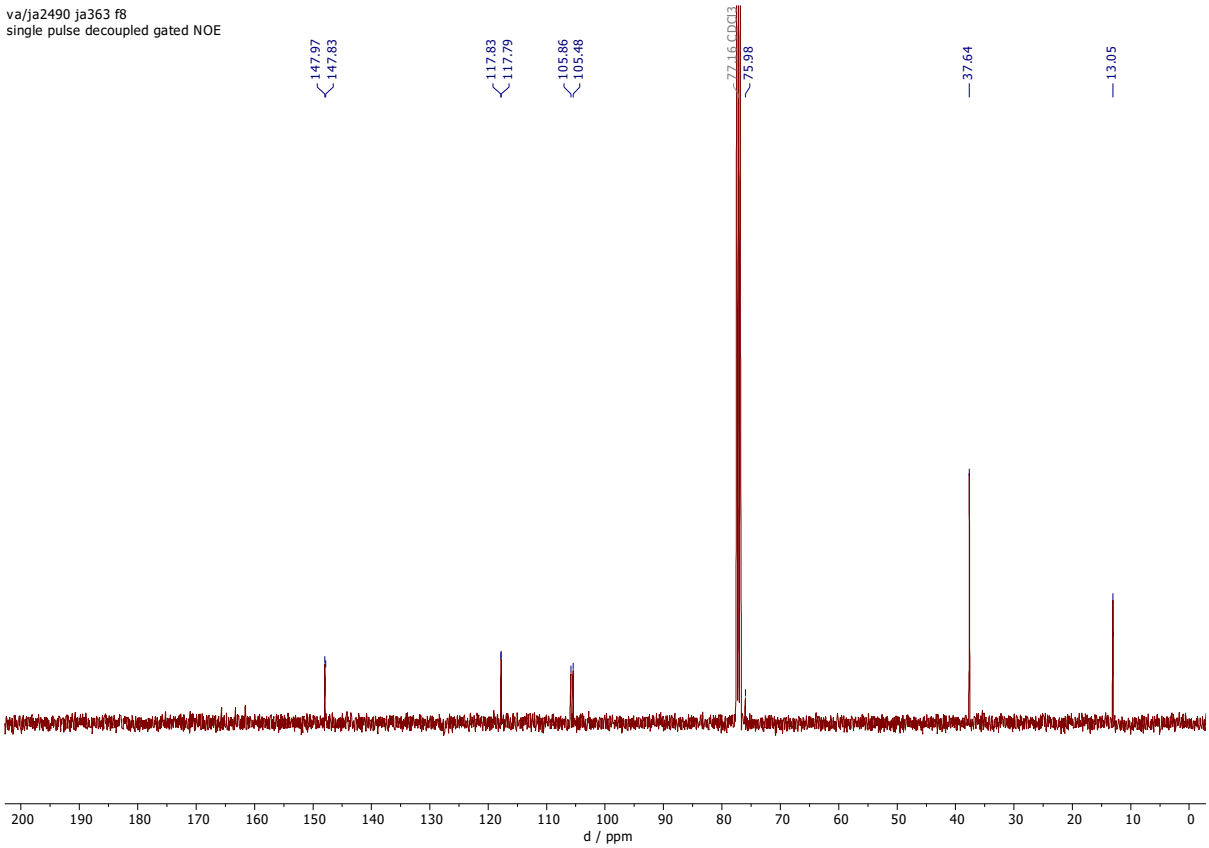
9.3.2.17 1-(7-Chloroquinolin-4-yl)cyclobutan-1-ol (523m)



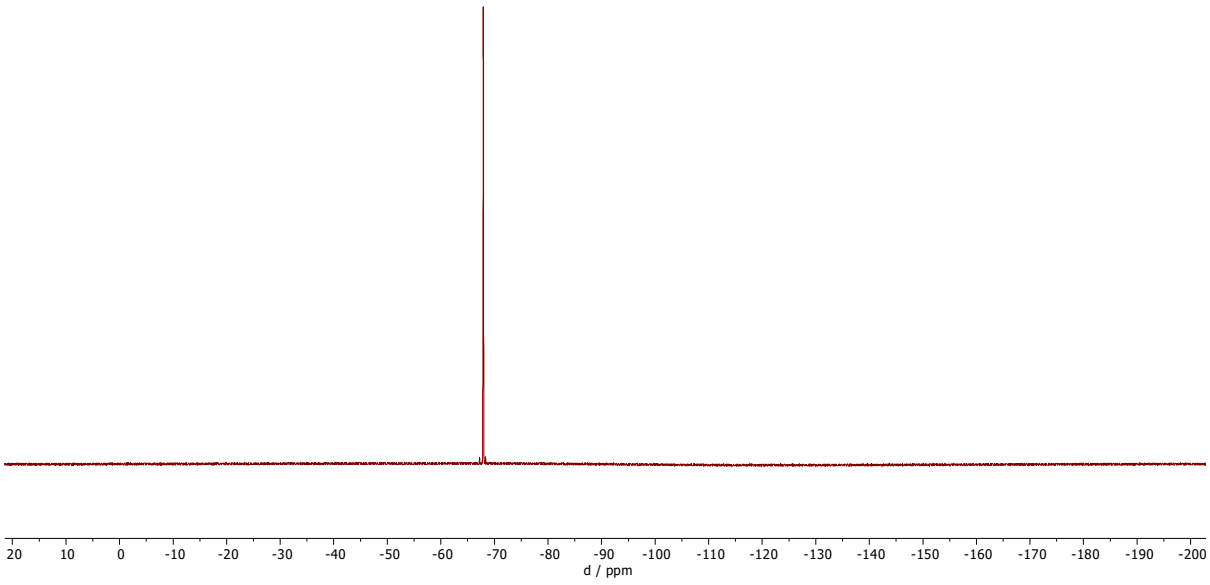


9.3.2.18 1-(2-Fluoropyridin-4-yl)cyclobutan-1-ol (523n)



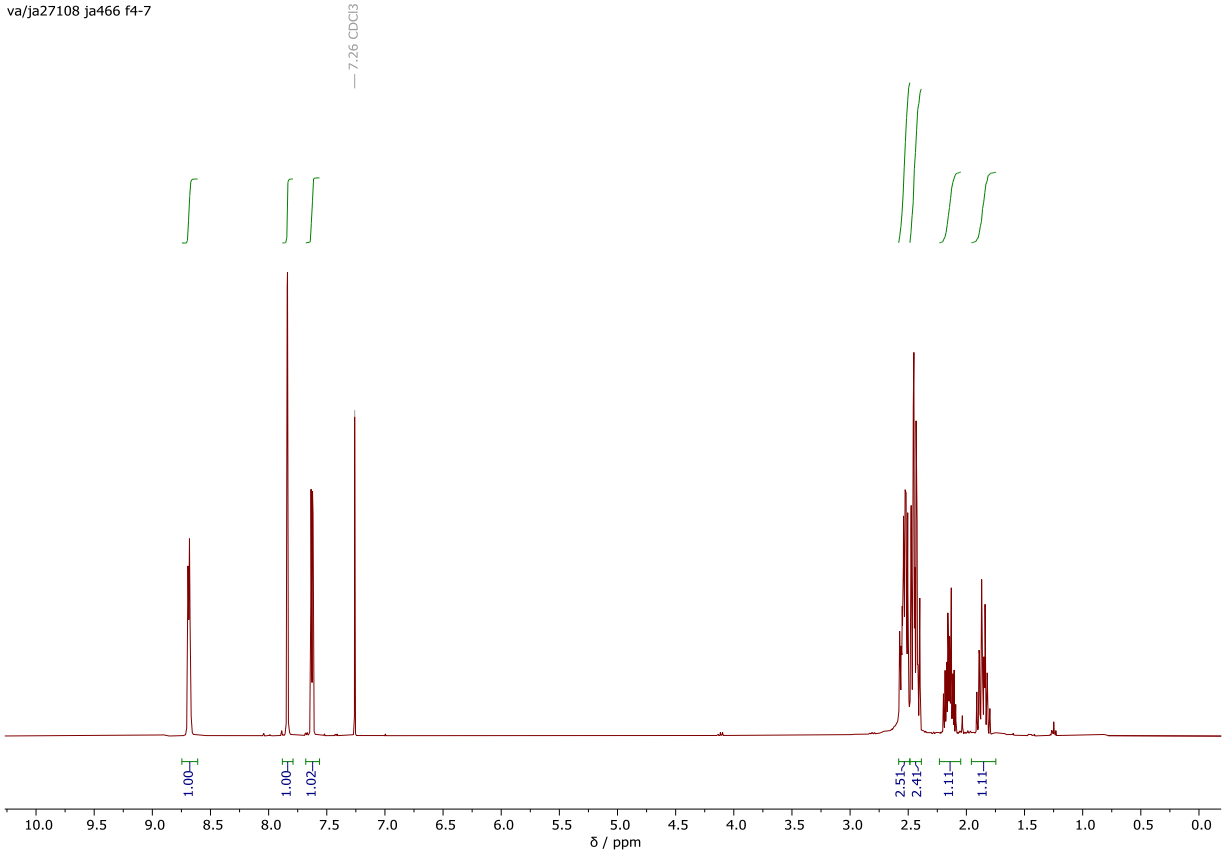


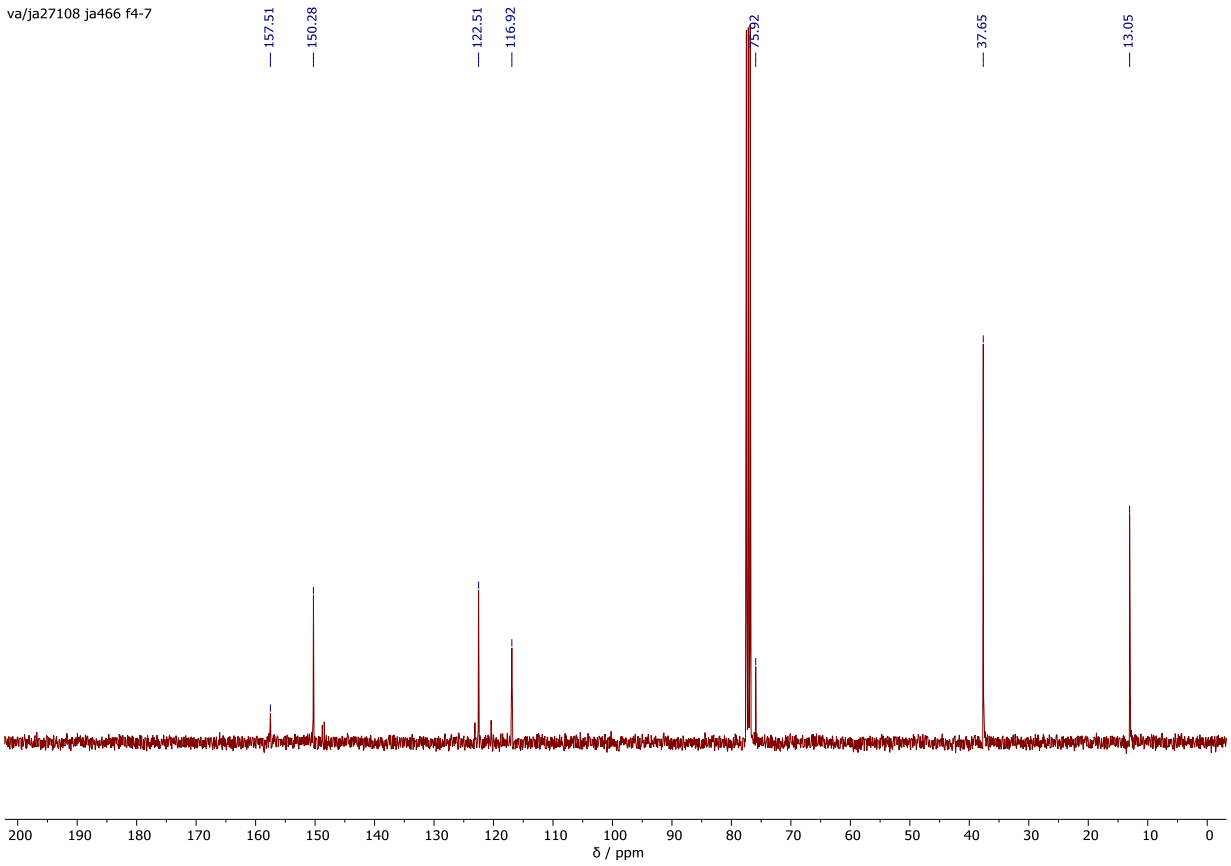
va/ja2490 ja363 f8
19F_single_pulse



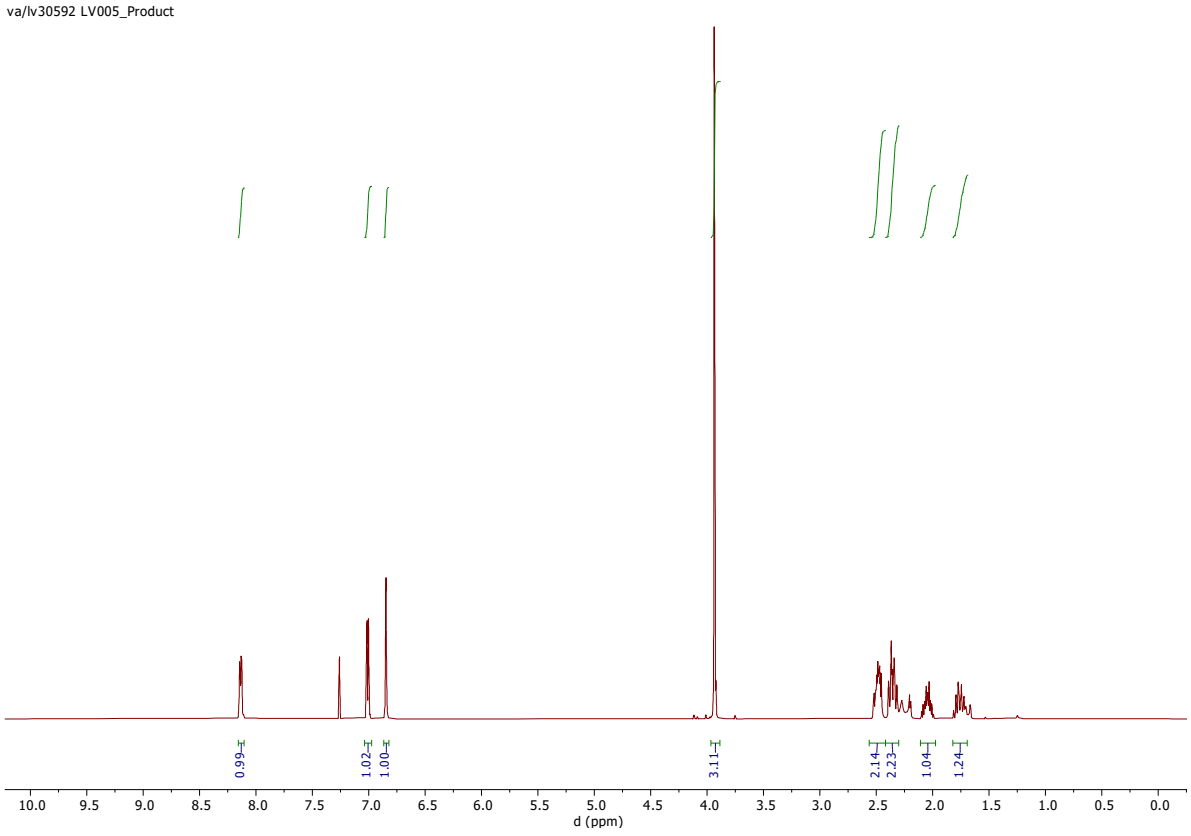
9.3.2.19 1-(2-Trifluoromethylpyridin-4-yl)cyclobutan-1-ol (523o)

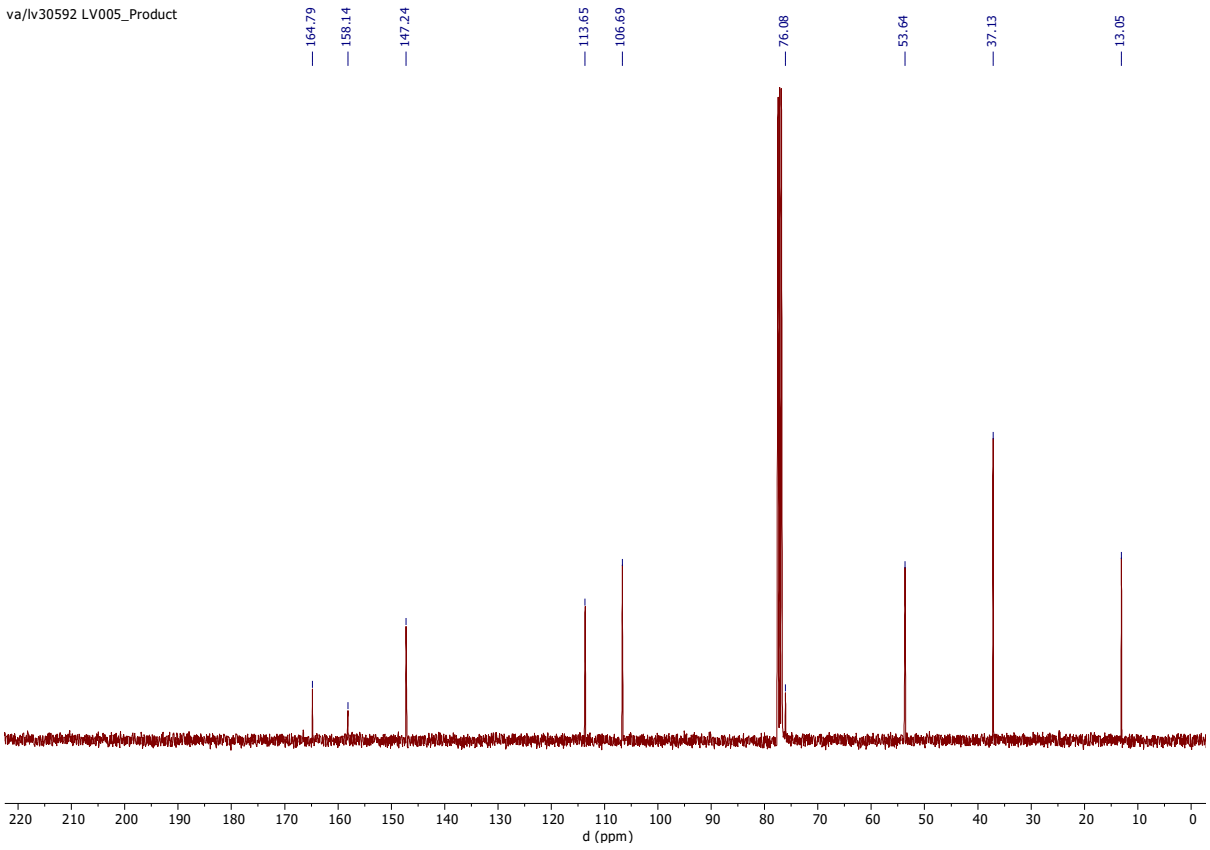
va/ja27108 ja466 f4-7



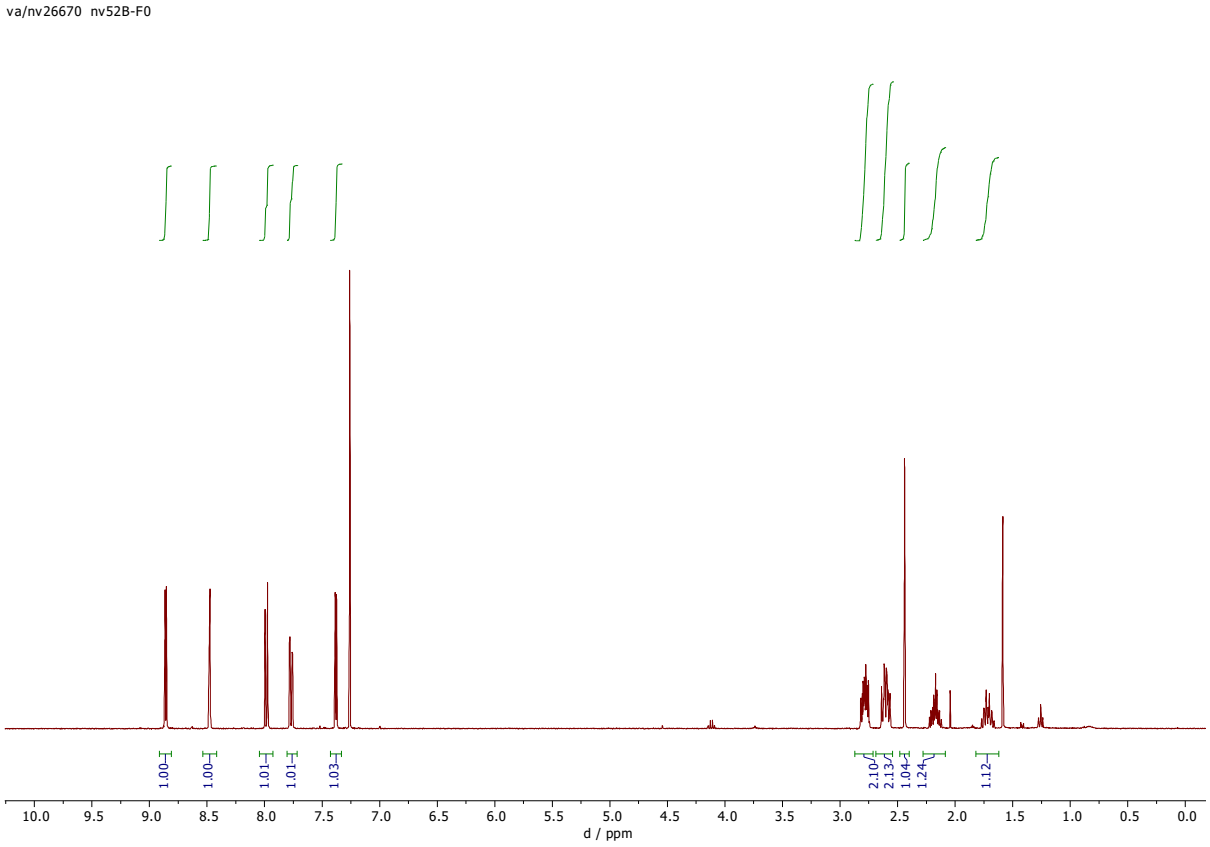


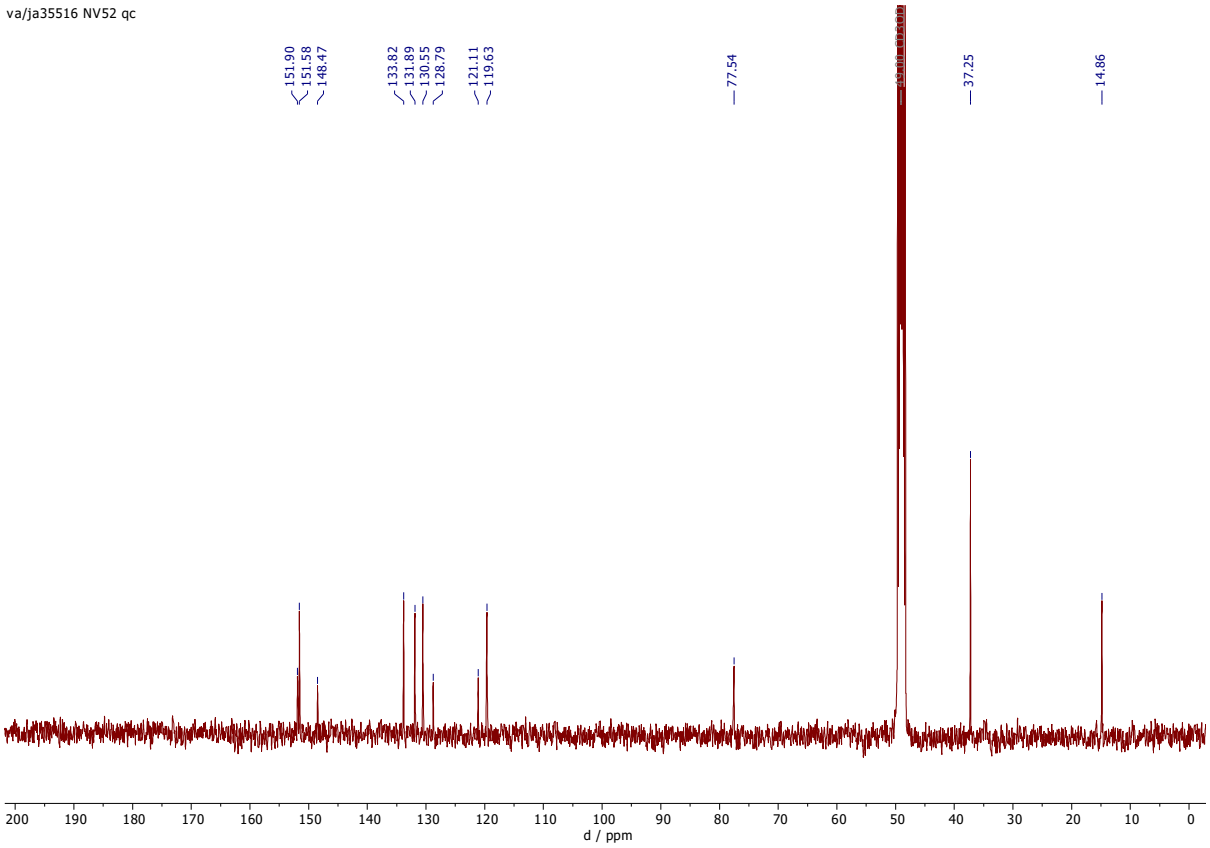
9.3.2.20 1-(2-Methoxypyridin-4-yl)cyclobutan-1-ol (523p)





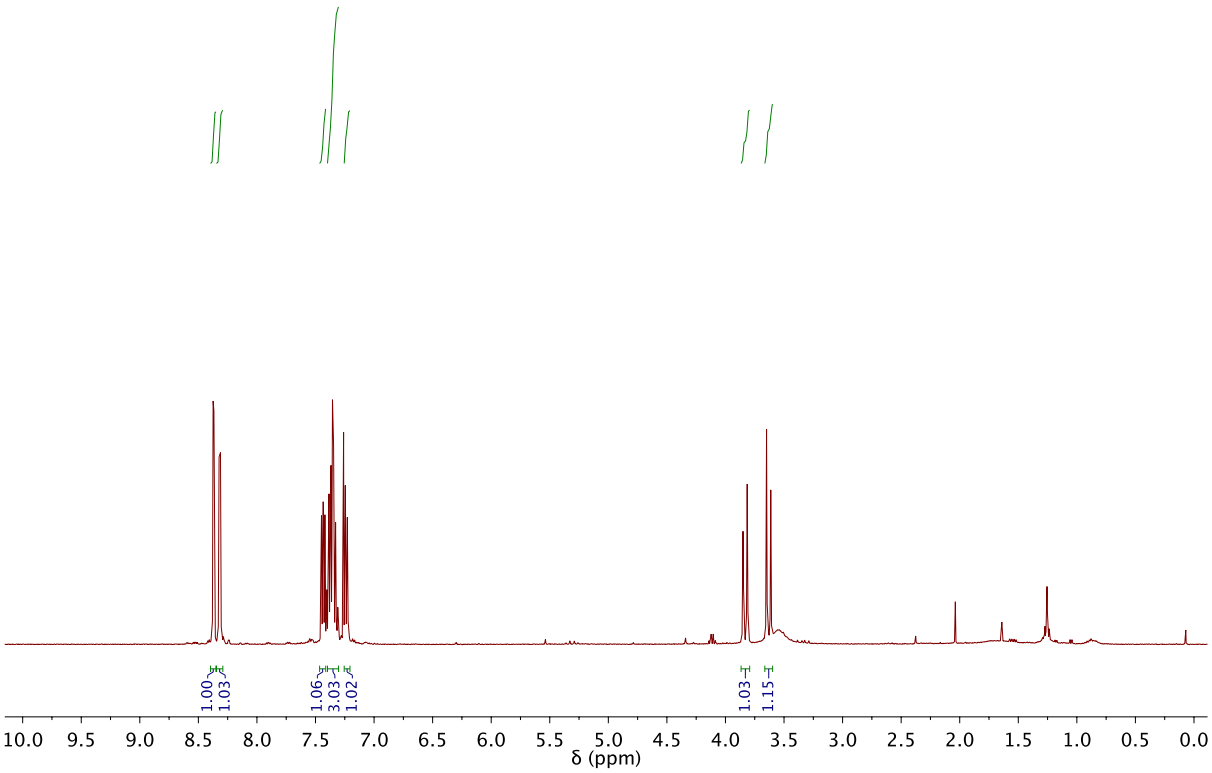
9.3.2.21 1-(6-Bromoquinolin-4-yl)cyclobutan-1-ol (523q)



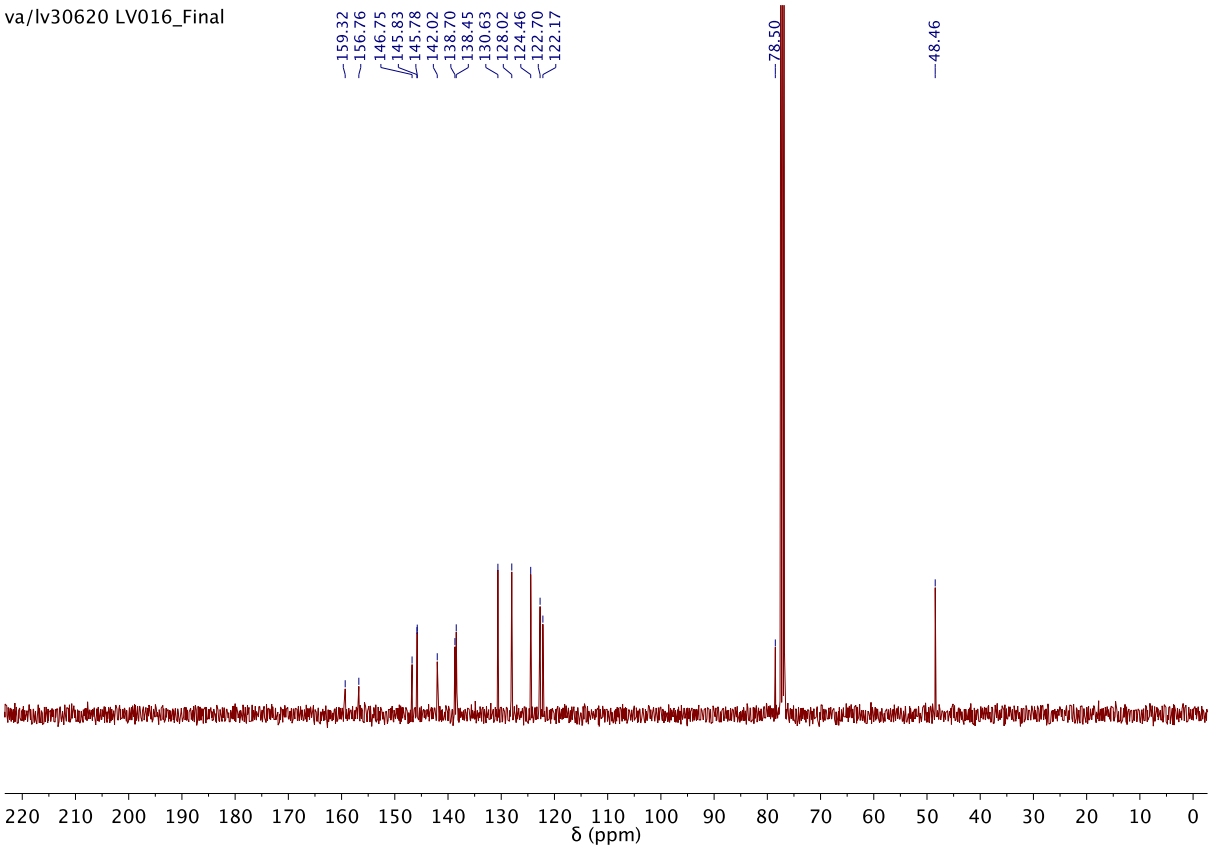


9.3.2.22 7-(3-Fluoropyridin-4-yl)bicyclo[4.2.0]octa-1(6),2,4-trien-7-ol (526)

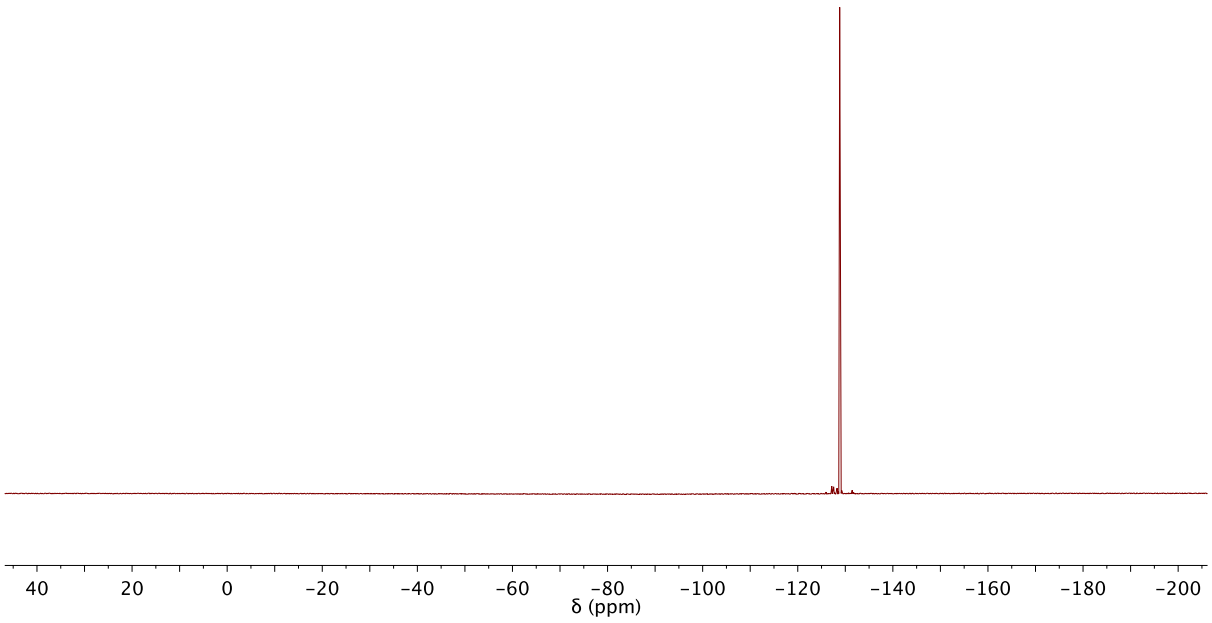
va/lv30620 LV016_Final



va/lv30620 LV016_Final

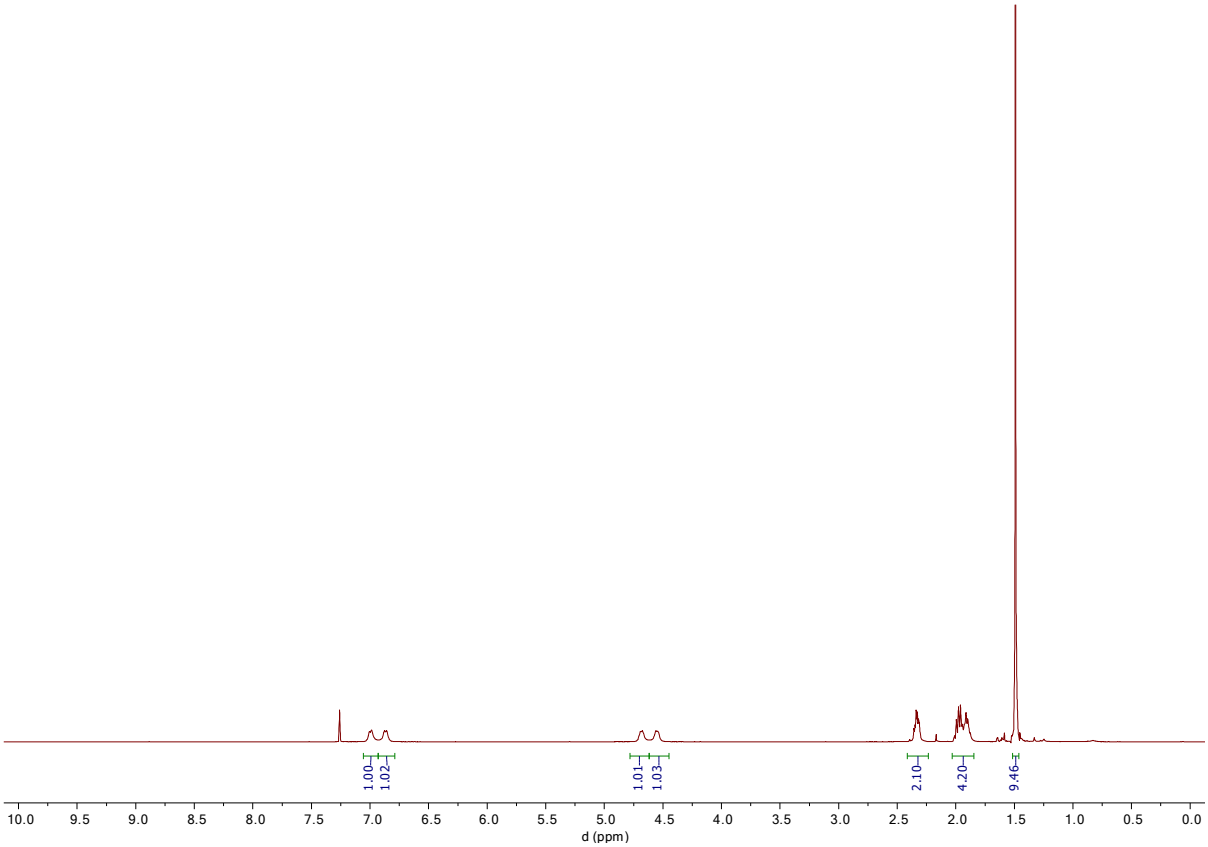


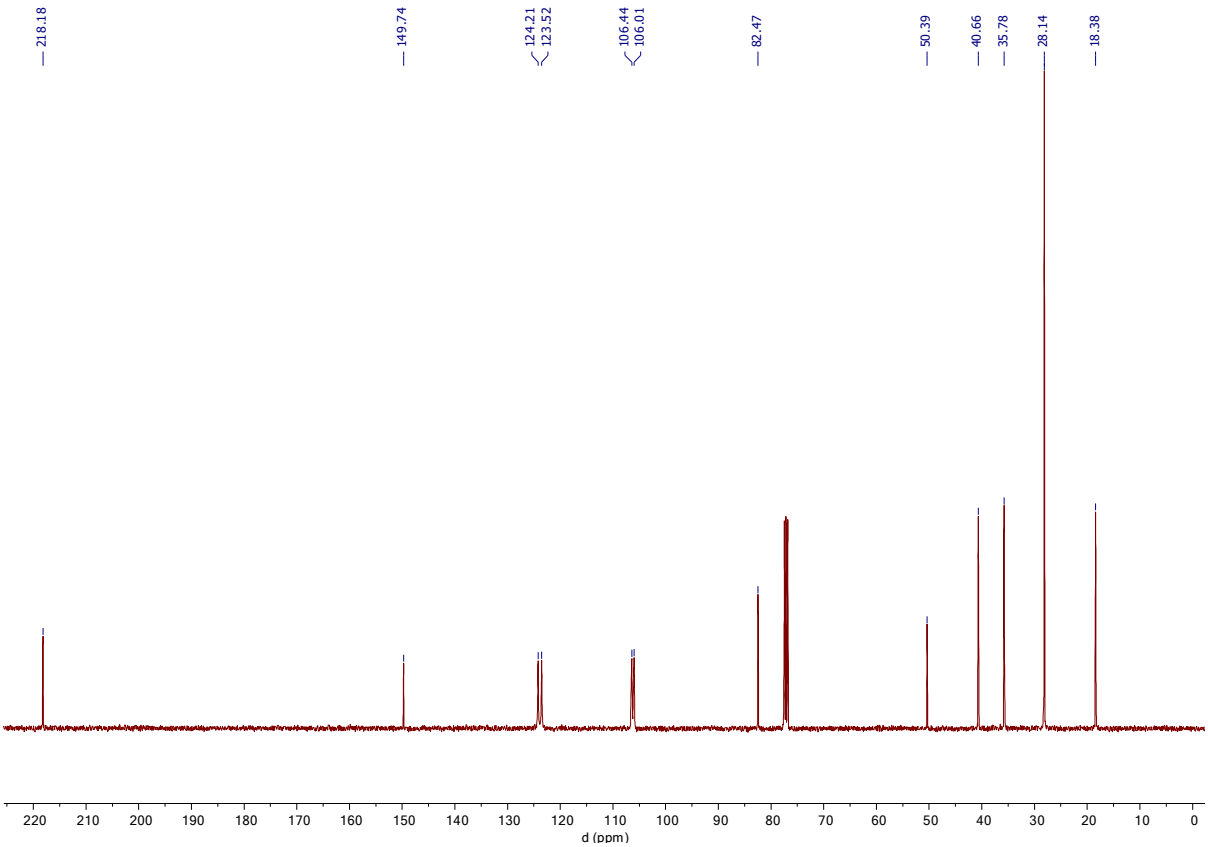
va/lv30620 LV016_Final



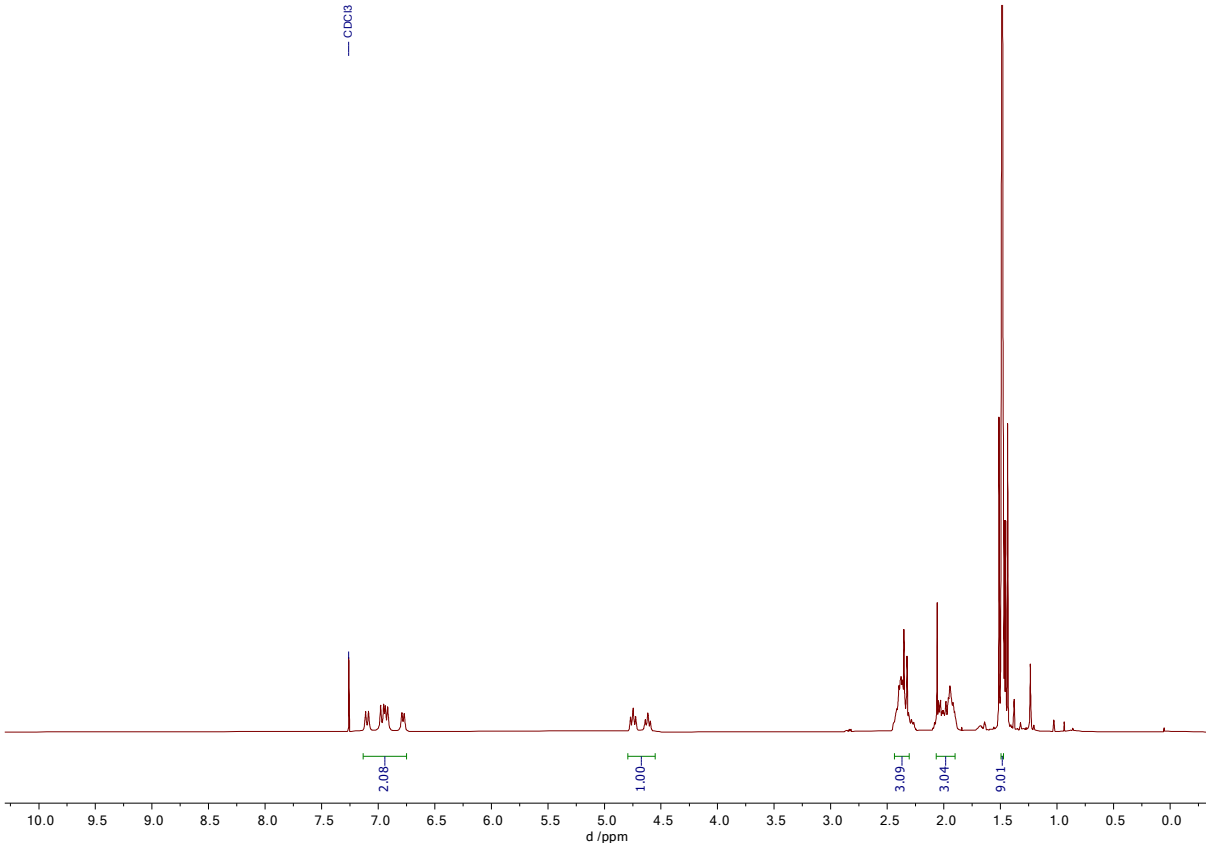
9.3.3 Boc anhydride protocol scope

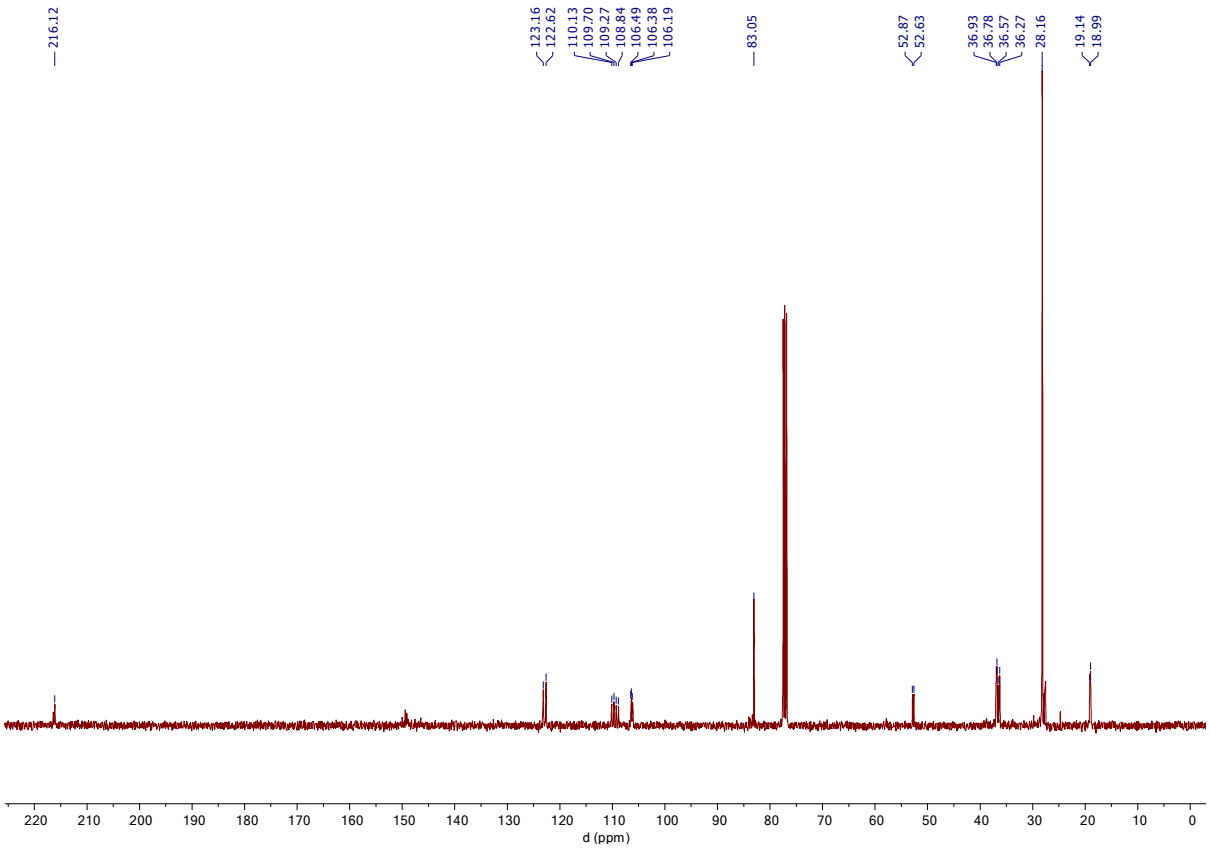
9.3.3.1 *tert*-Butyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517a)



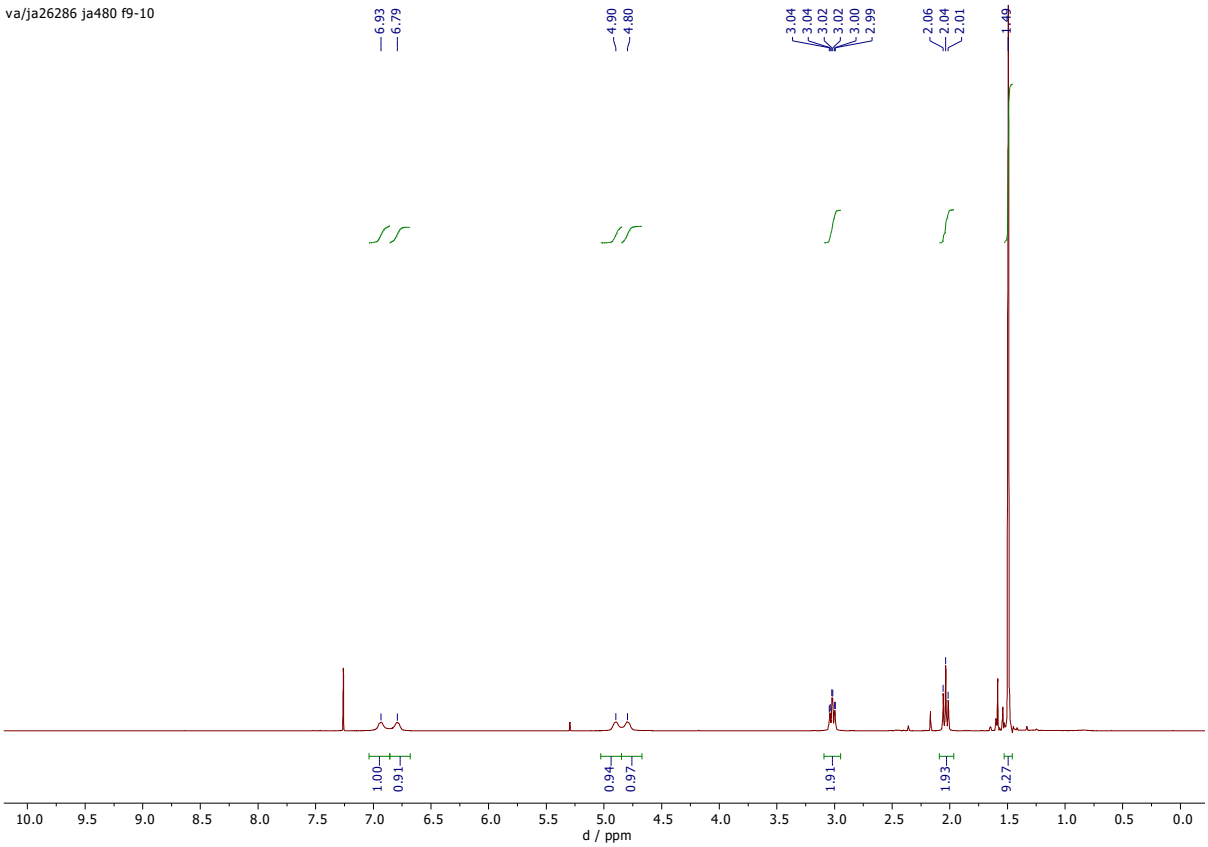


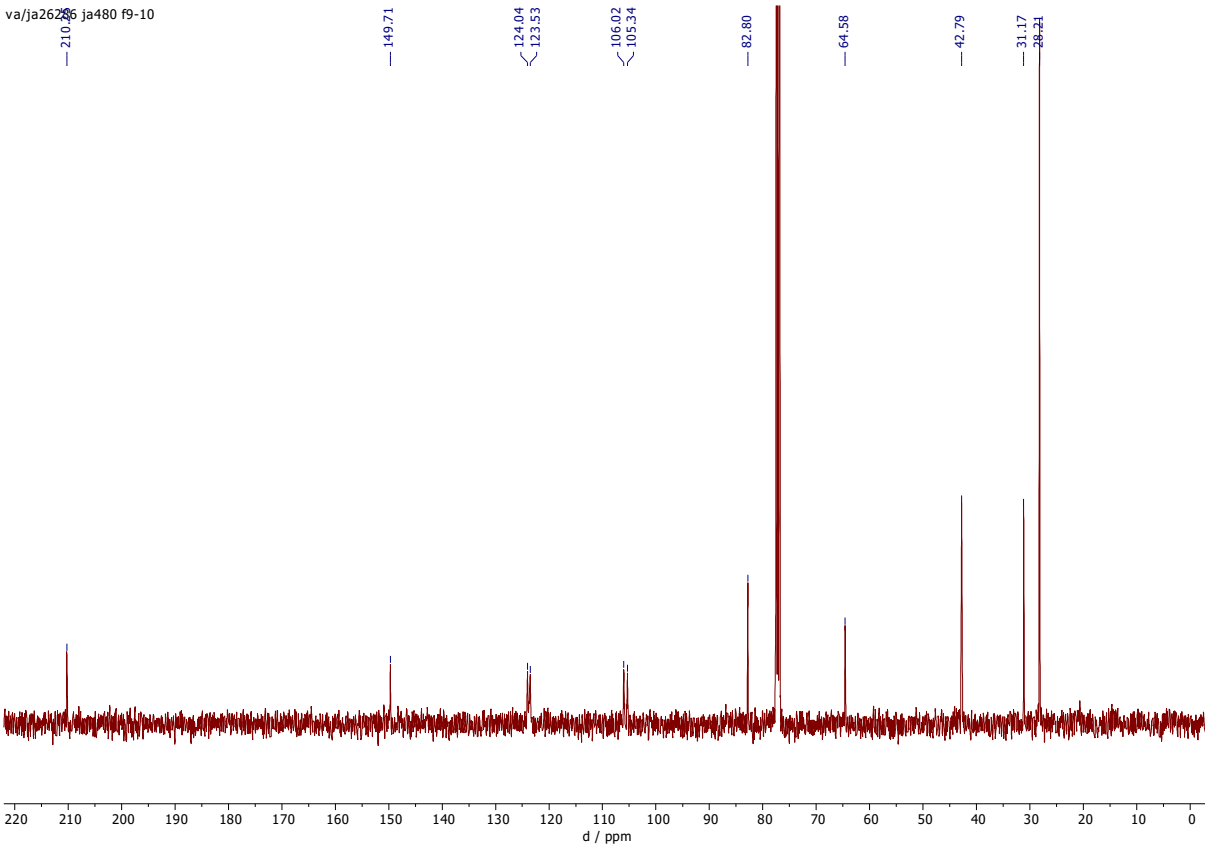
9.3.3.2 *tert*-Butyl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519g)



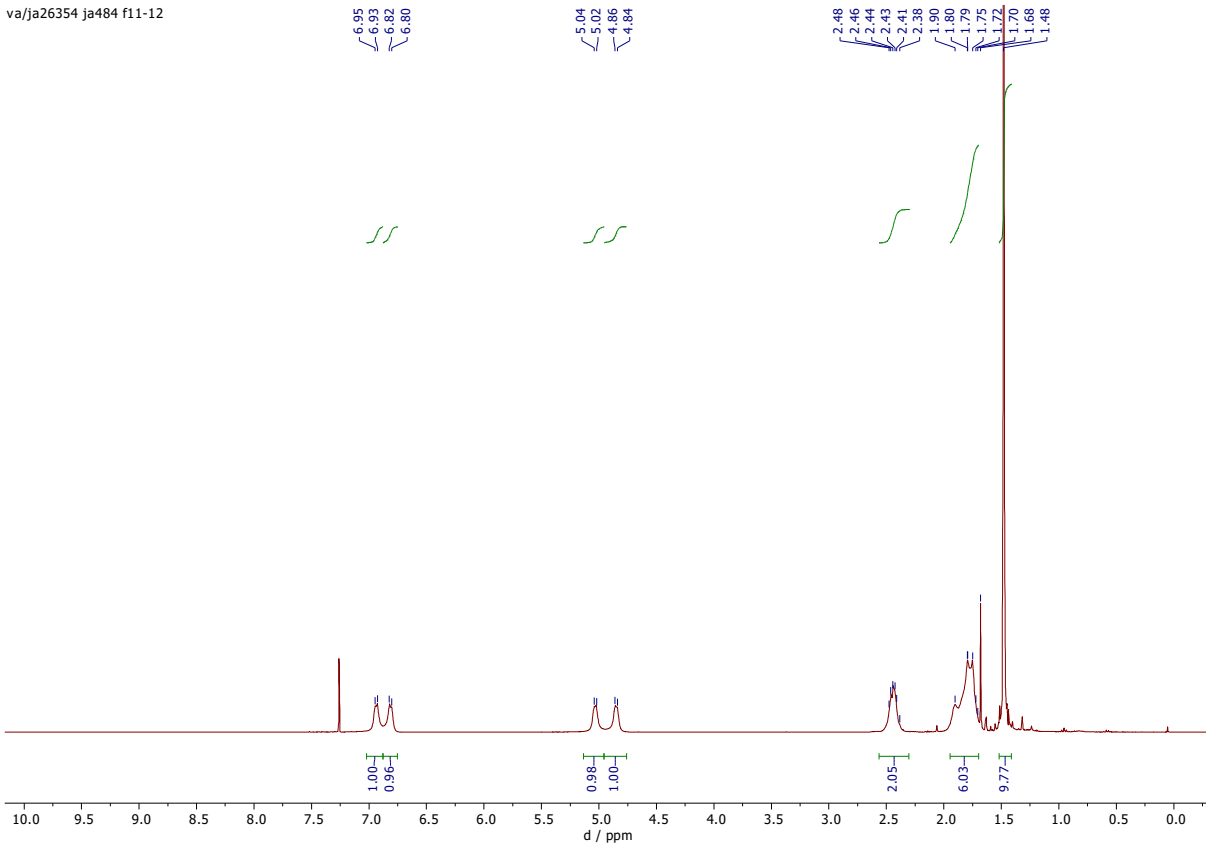


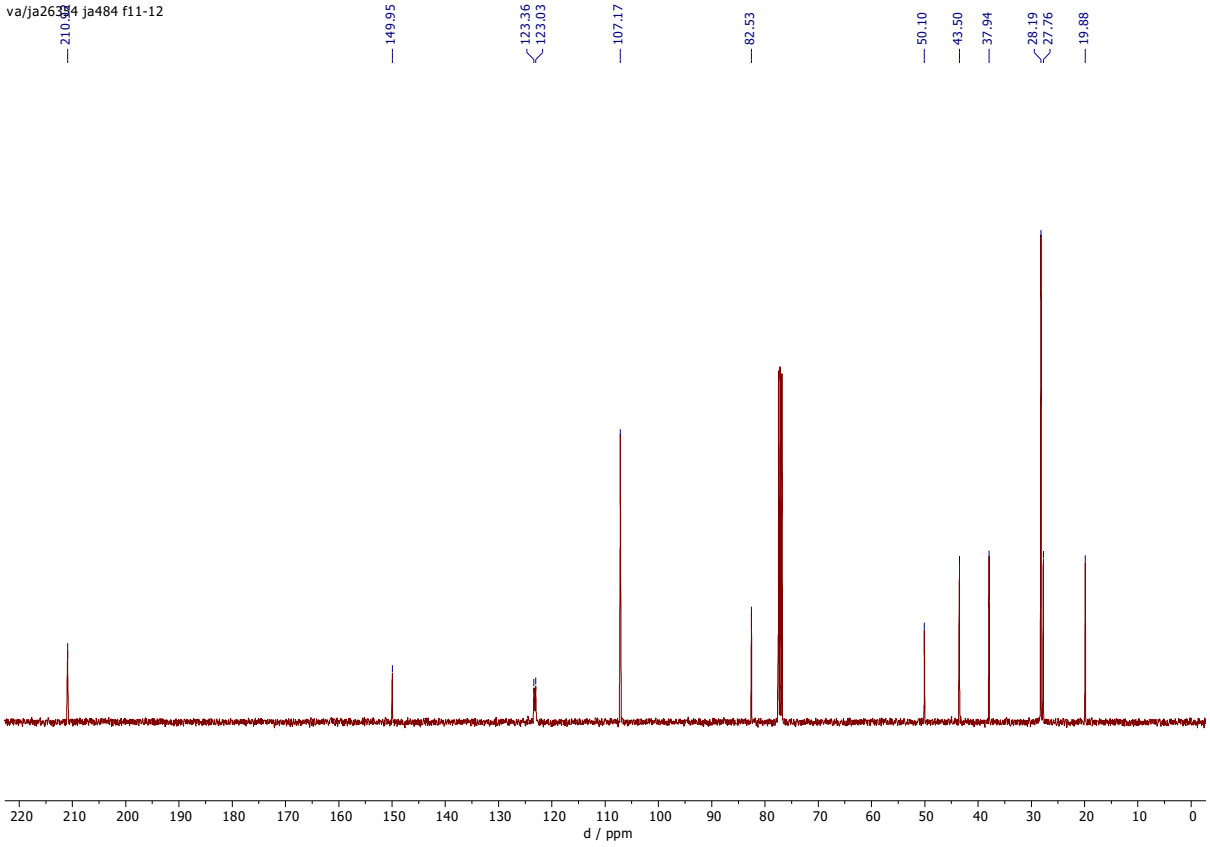
9.3.3.3 *tert*-Butyl 1-oxo-7-azaspiro[3.5]nona-5,8-diene-7-carboxylate (524a)



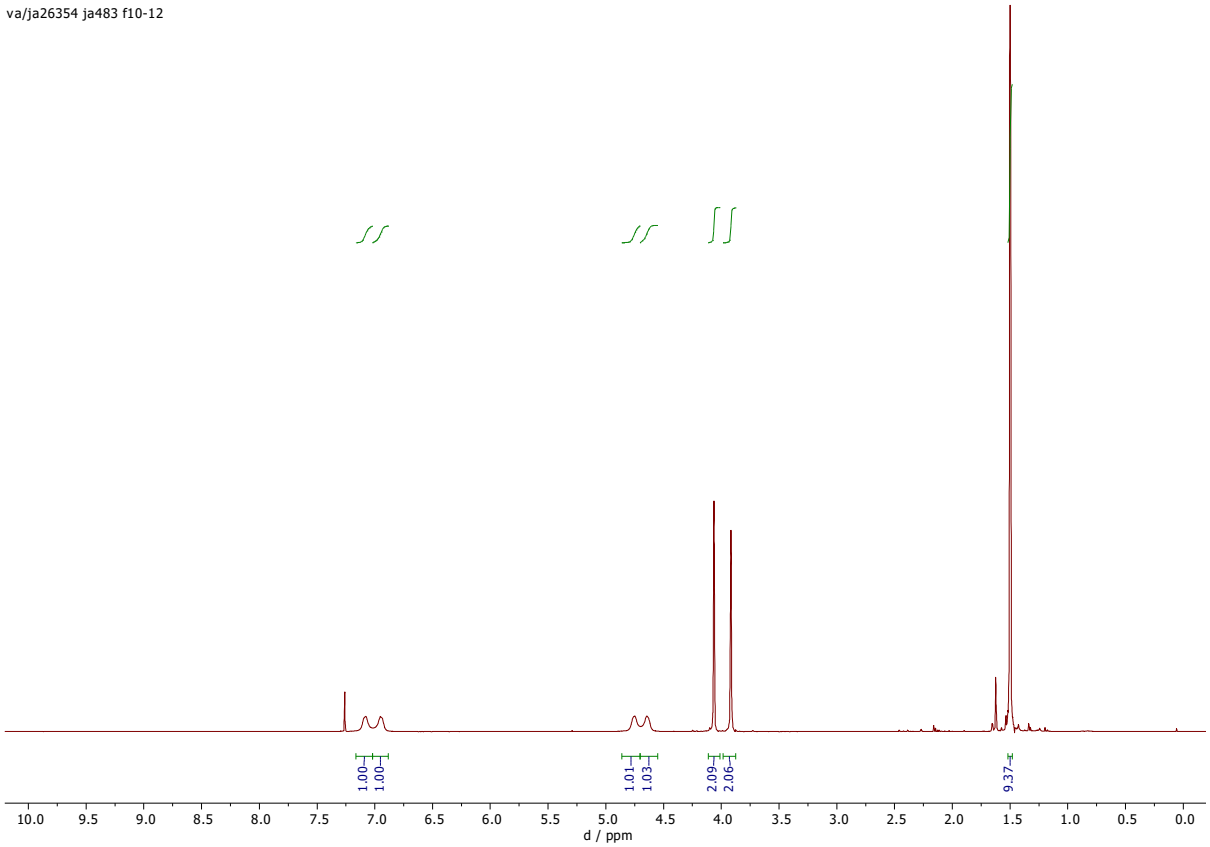


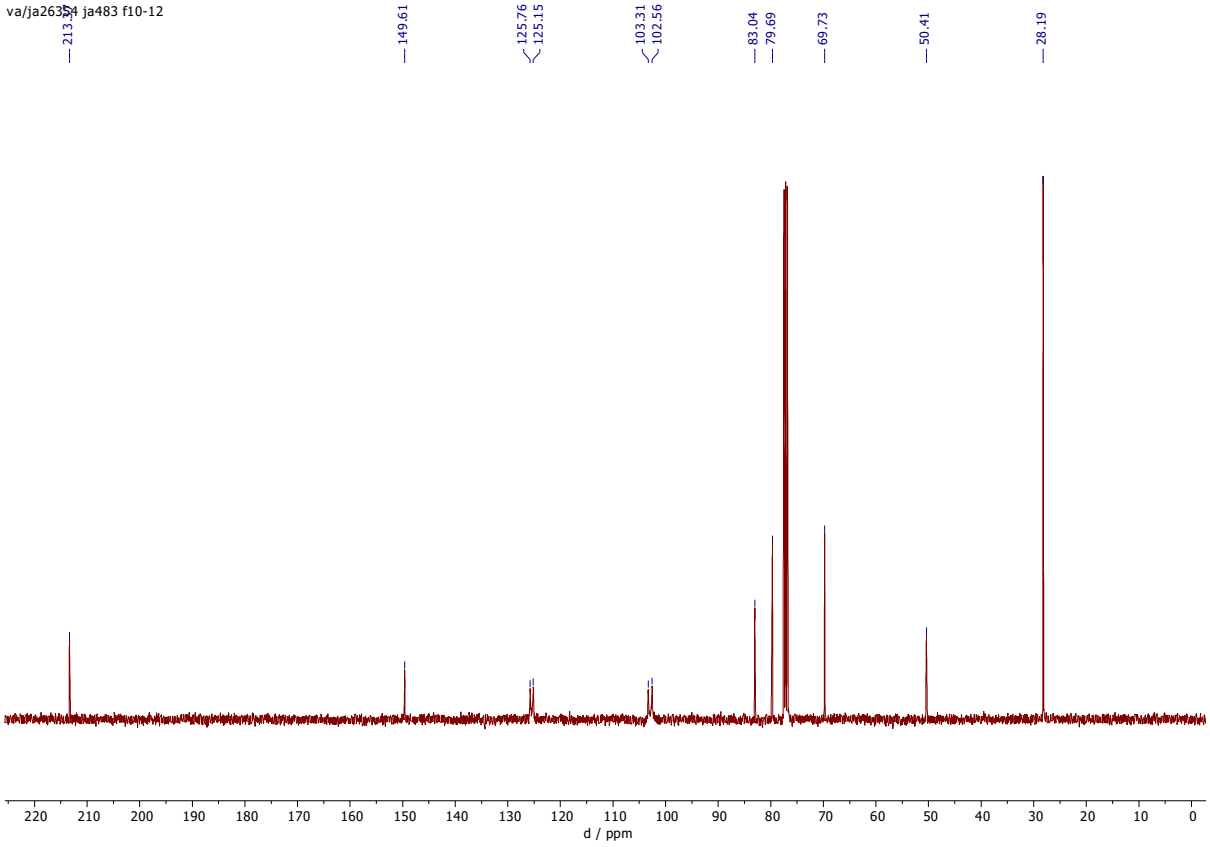
9.3.3.4 *tert*-Butyl 7-oxo-3-azaspiro[5.5]undeca-1,4-diene-3-carboxylate (524b)



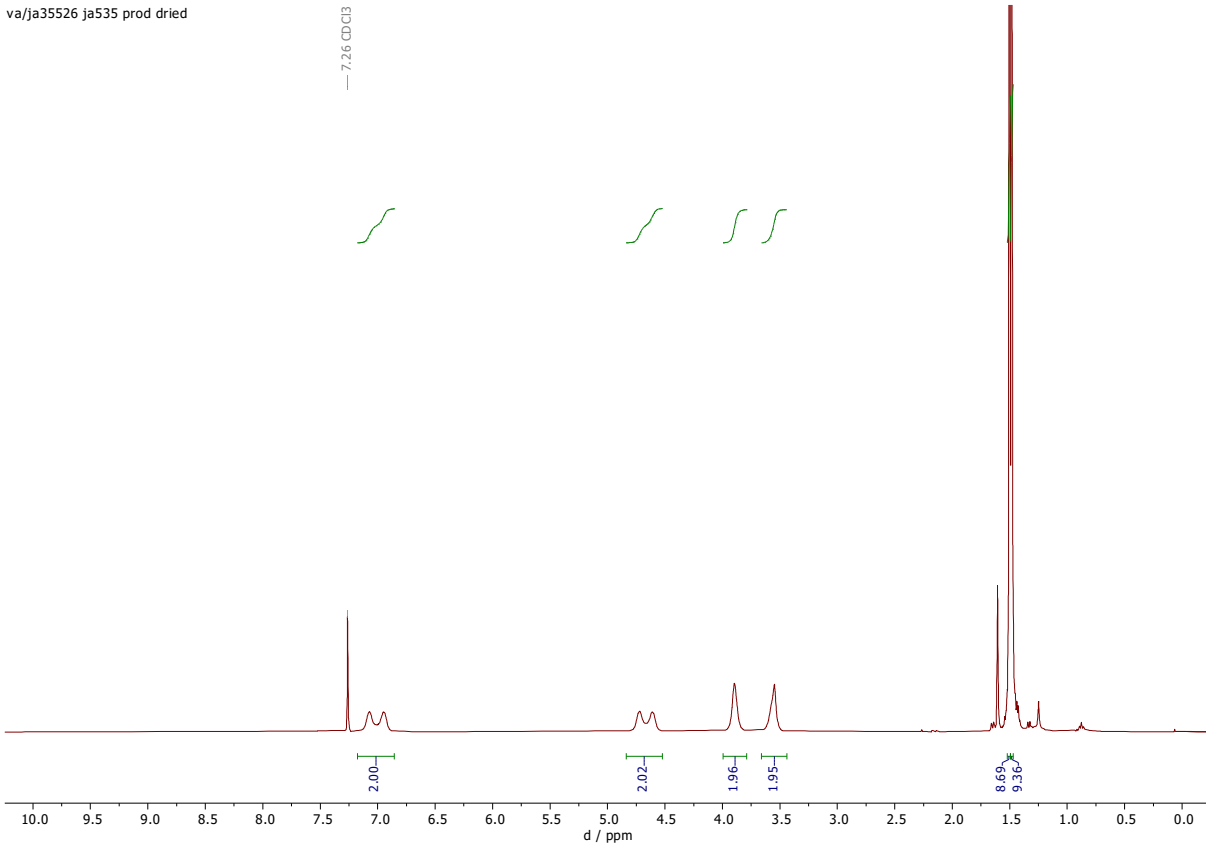


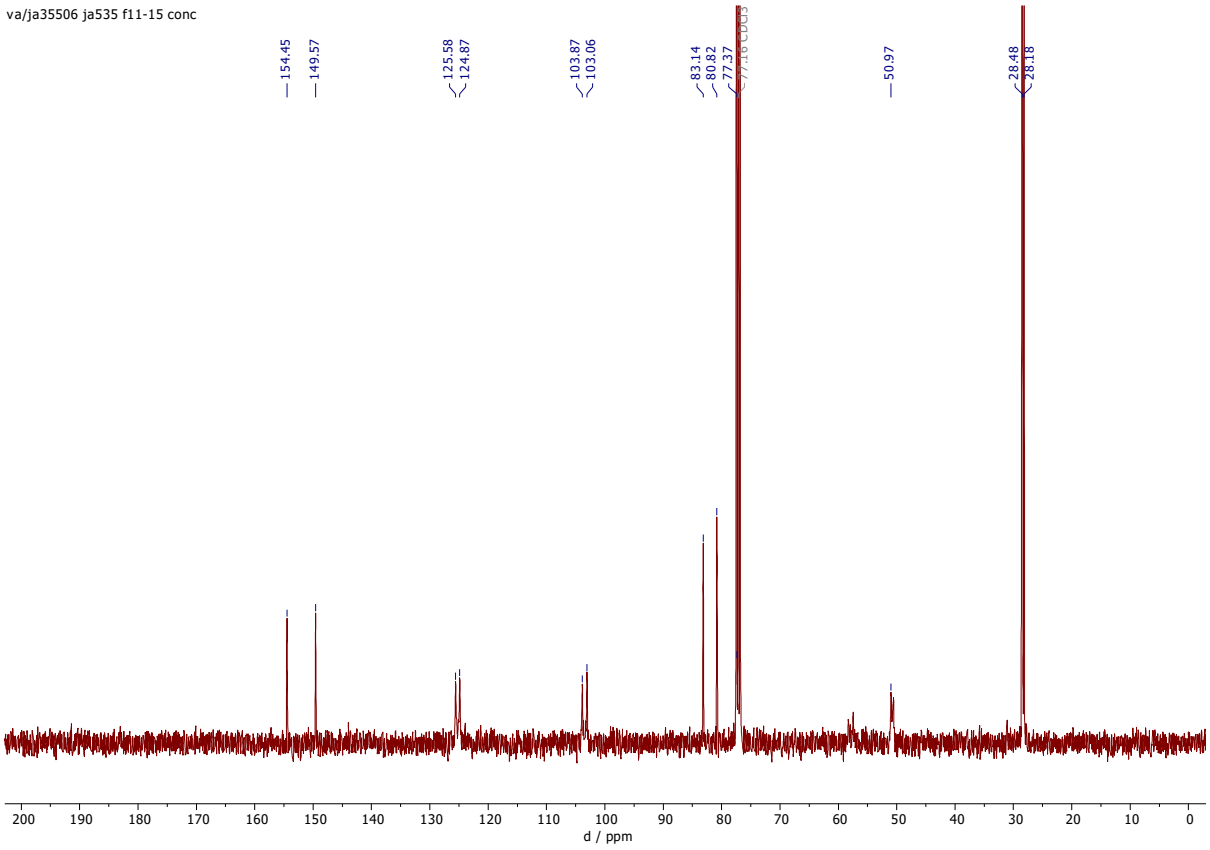
9.3.3.5 *tert*-Butyl 4-oxo-2-oxa-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524e)



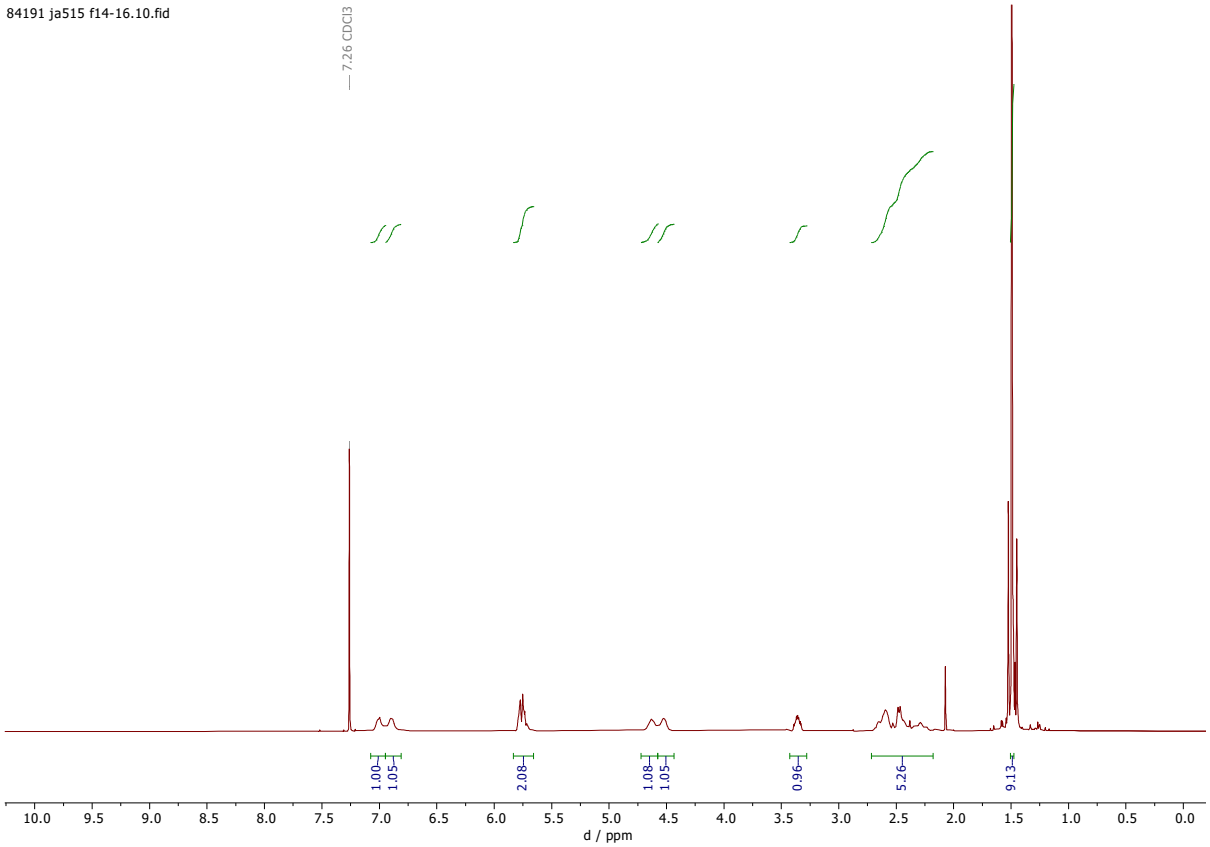


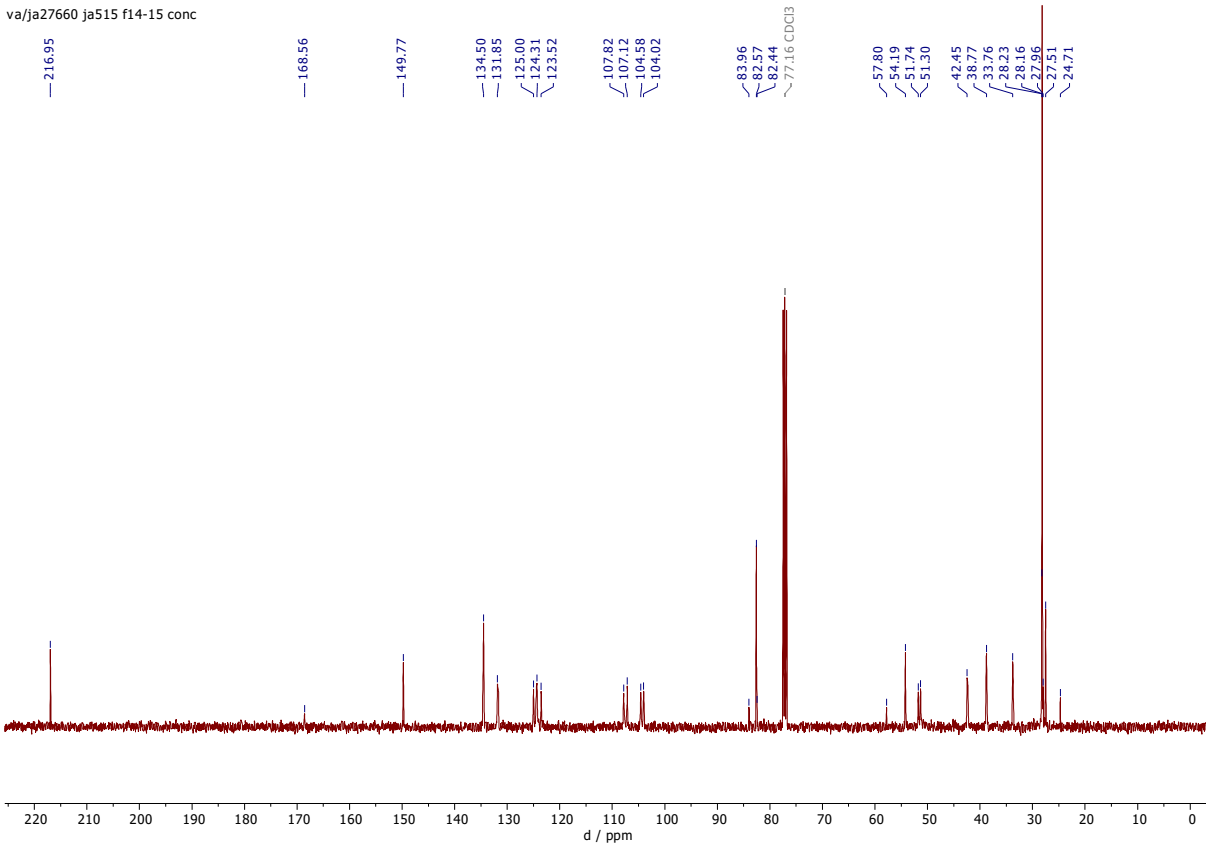
9.3.3.6 Di-*tert*-Butyl 4-oxo-2,8-diazaspiro[4.5]deca-6,9-diene-2,8-dicarboxylate (524f)



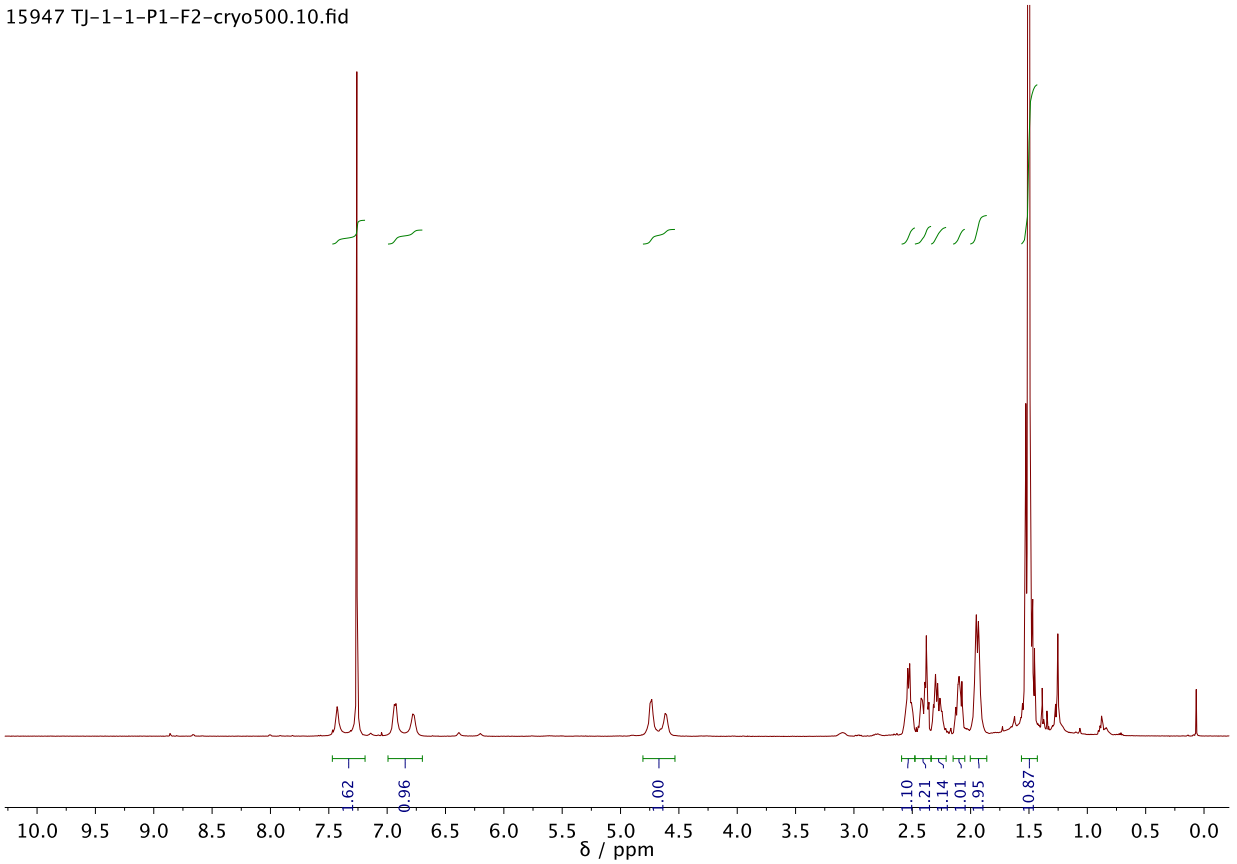


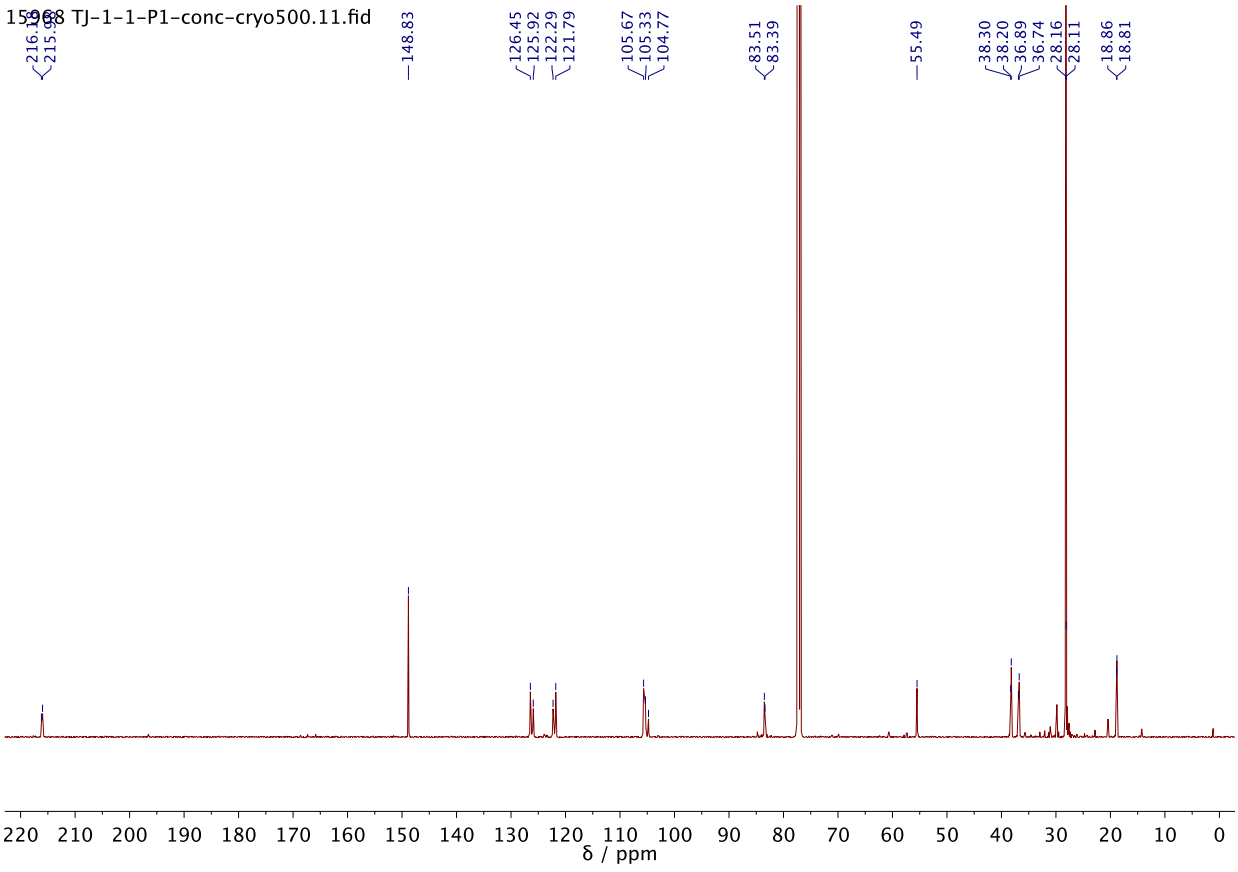
9.3.3.7 *tert*-Butyl (3a*S*,6a*R*)-2-oxo-3,3a,6,6a-tetrahydro-1'*H*,2*H*-spiro[pentalene-1,4'-pyridine]-1'-carboxylate (524g)



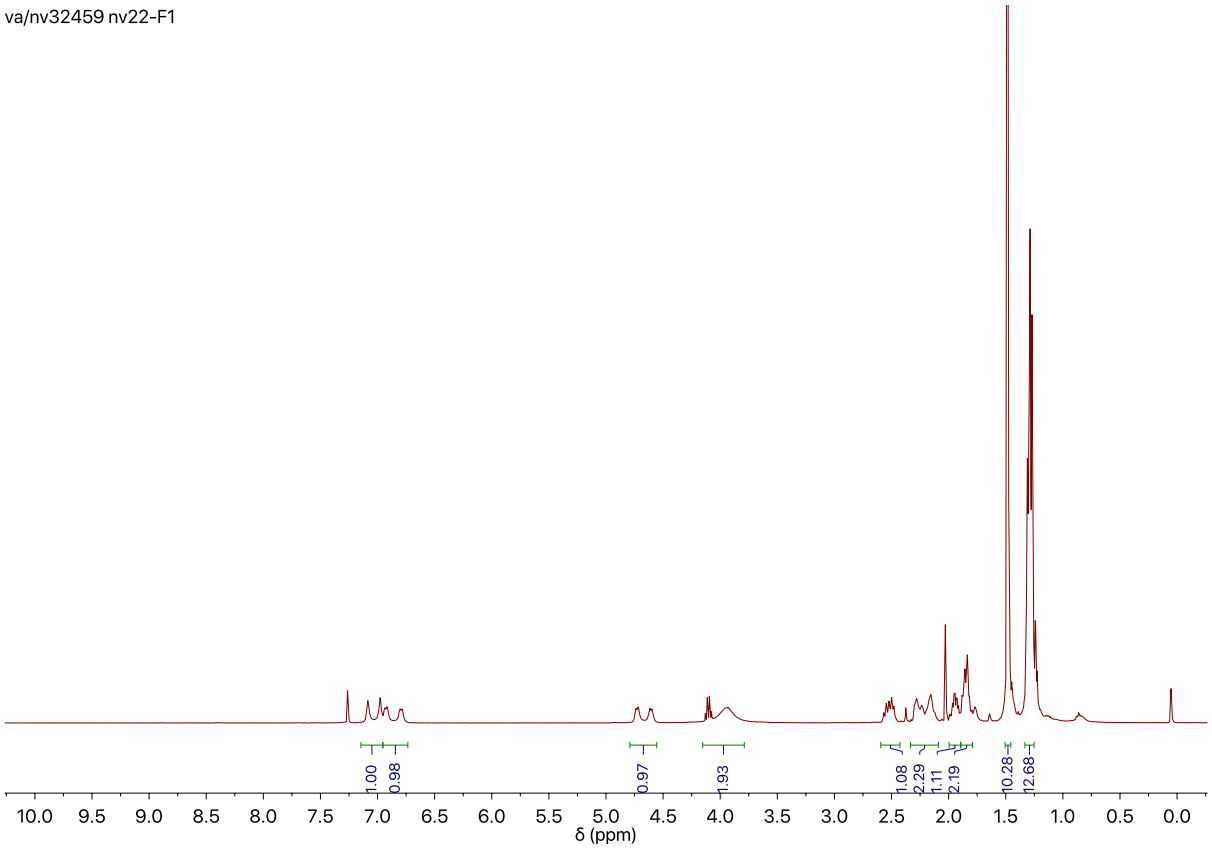


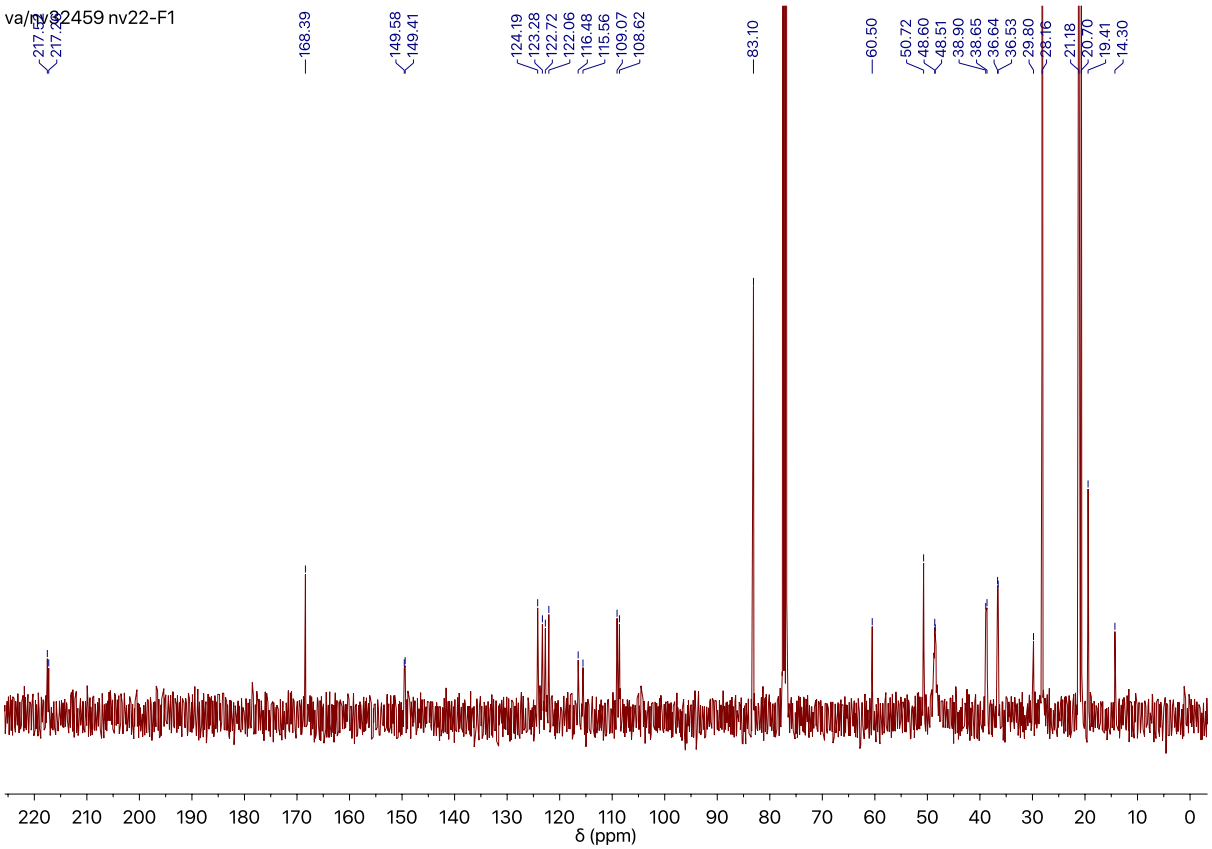
9.3.3.8 *tert*-Butyl (±)-6-bromo-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524h)



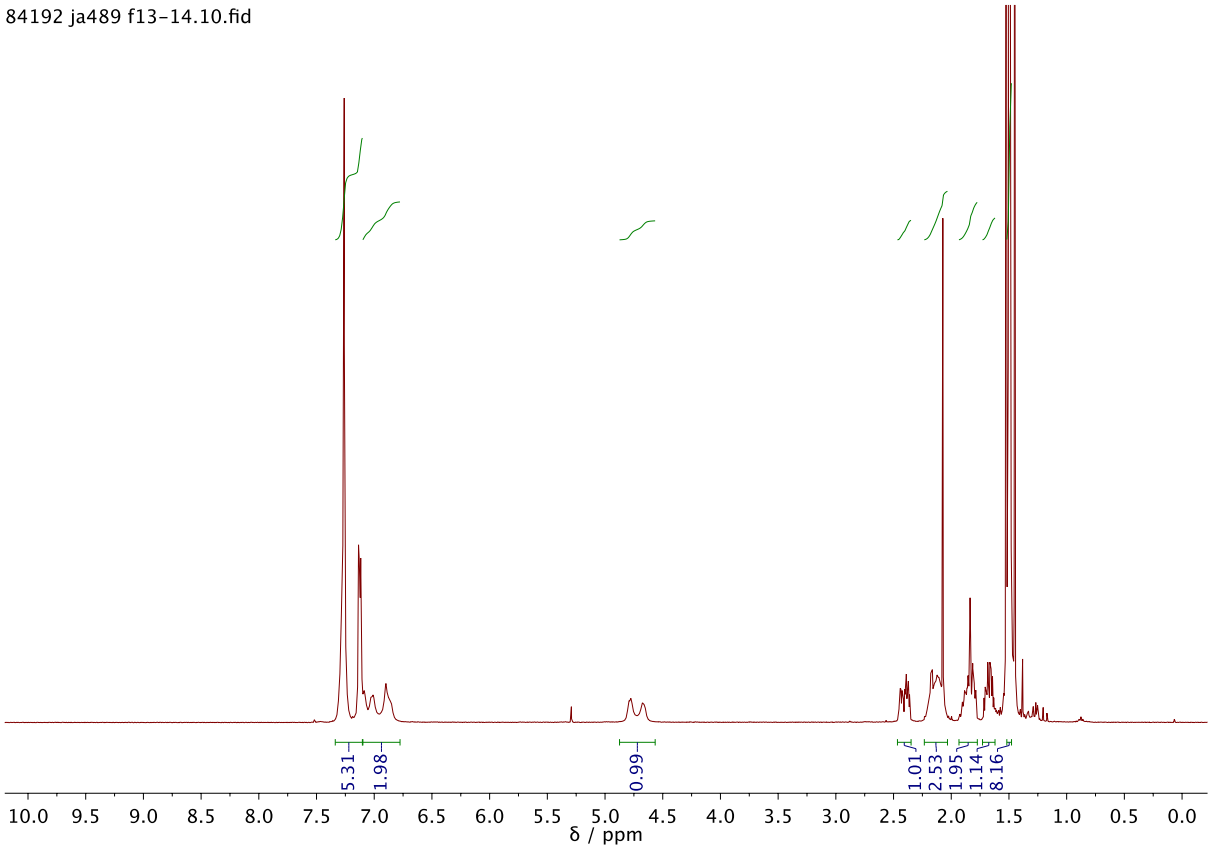


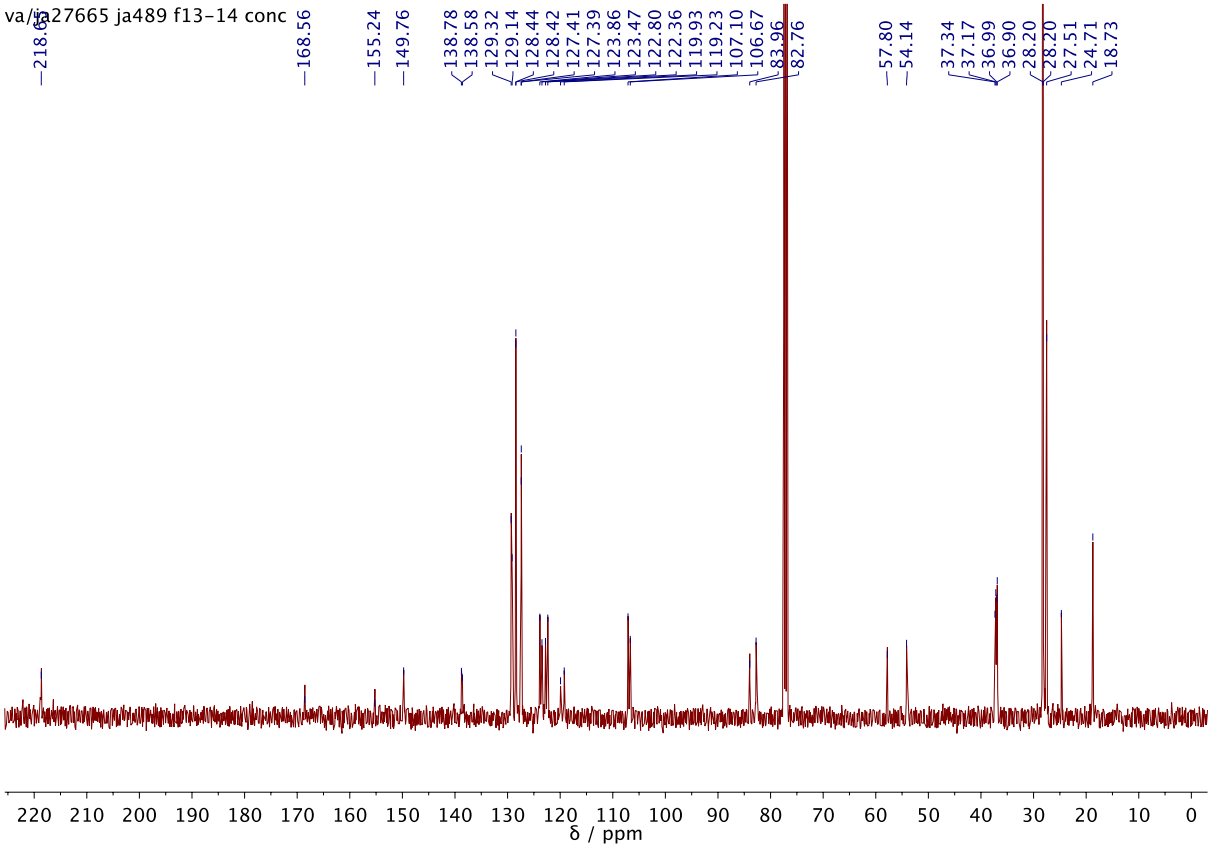
9.3.3.9 *tert*-Butyl (±)-6-(diisopropylcarbamoyl)-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524i)





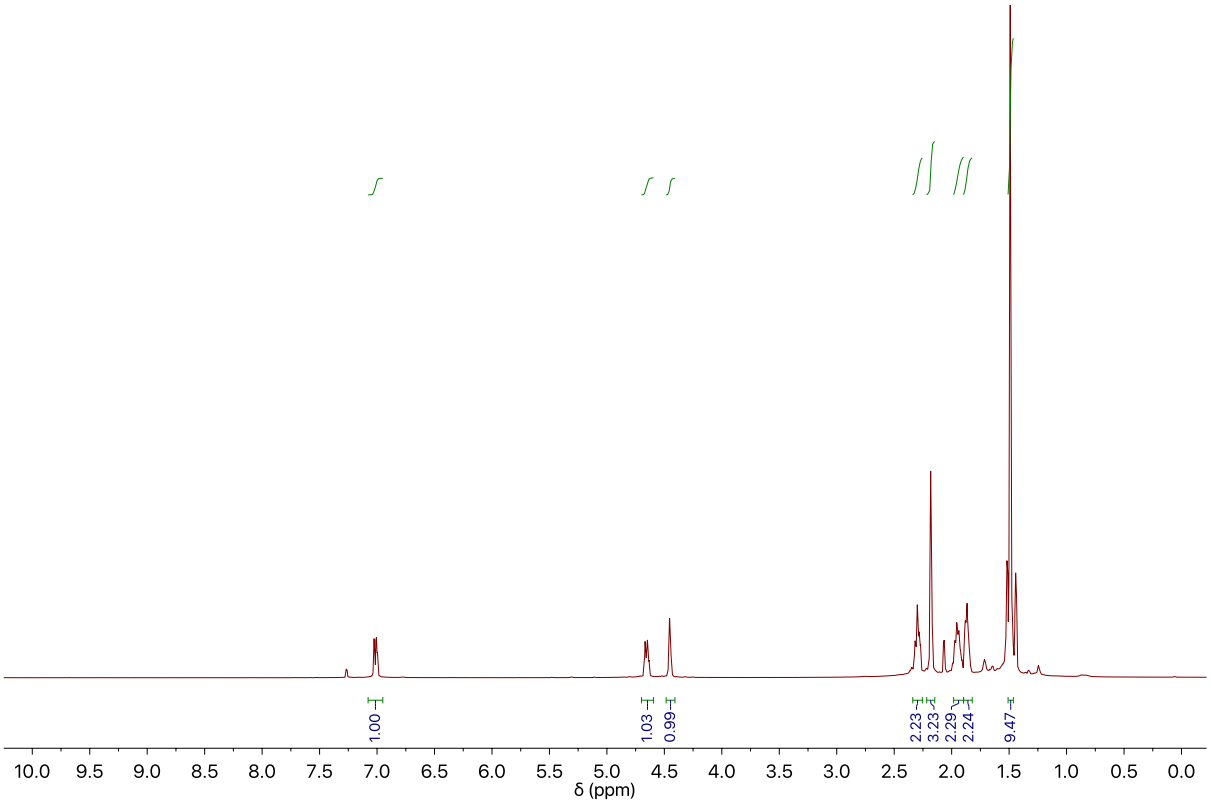
9.3.3.10 *tert*-Butyl (±)-6-(phenyl)-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524j)



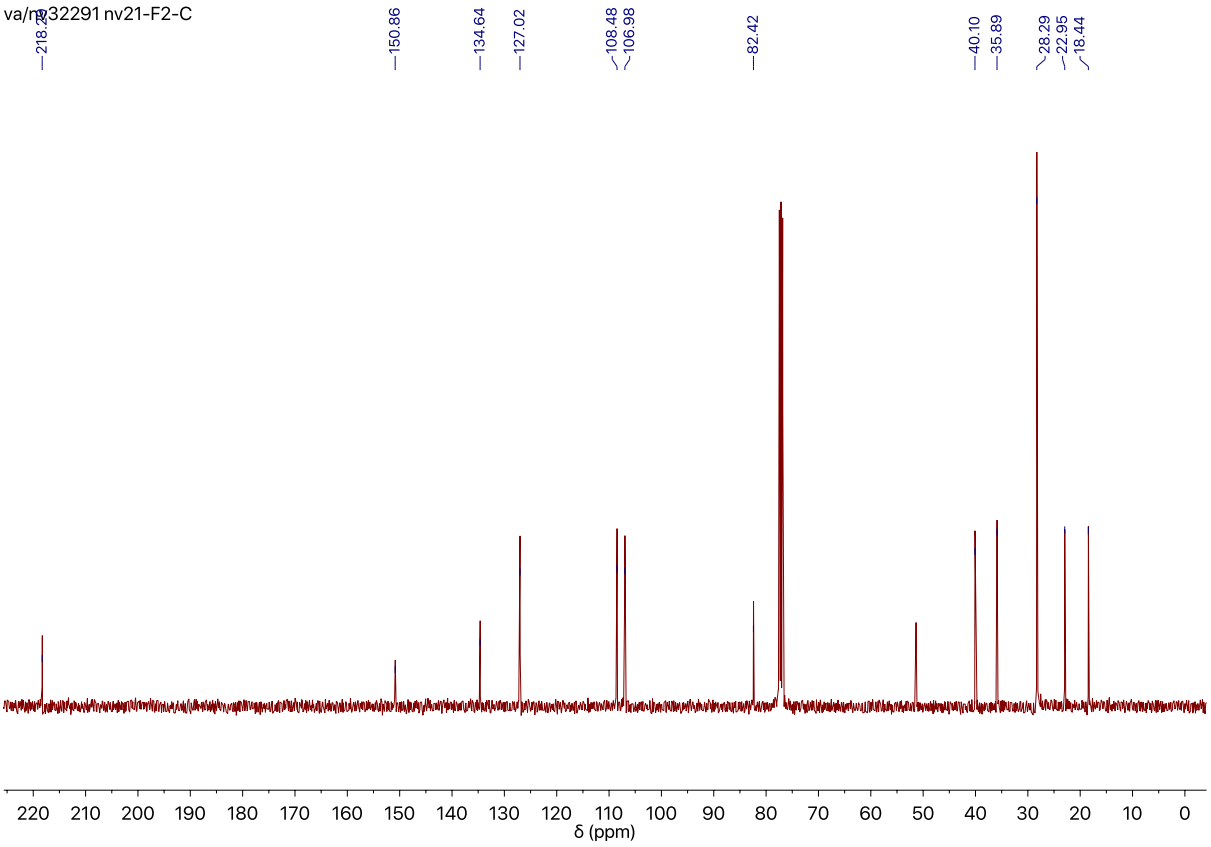


9.3.3.11 *tert*-Butyl (±)-7-methyl-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (524k)

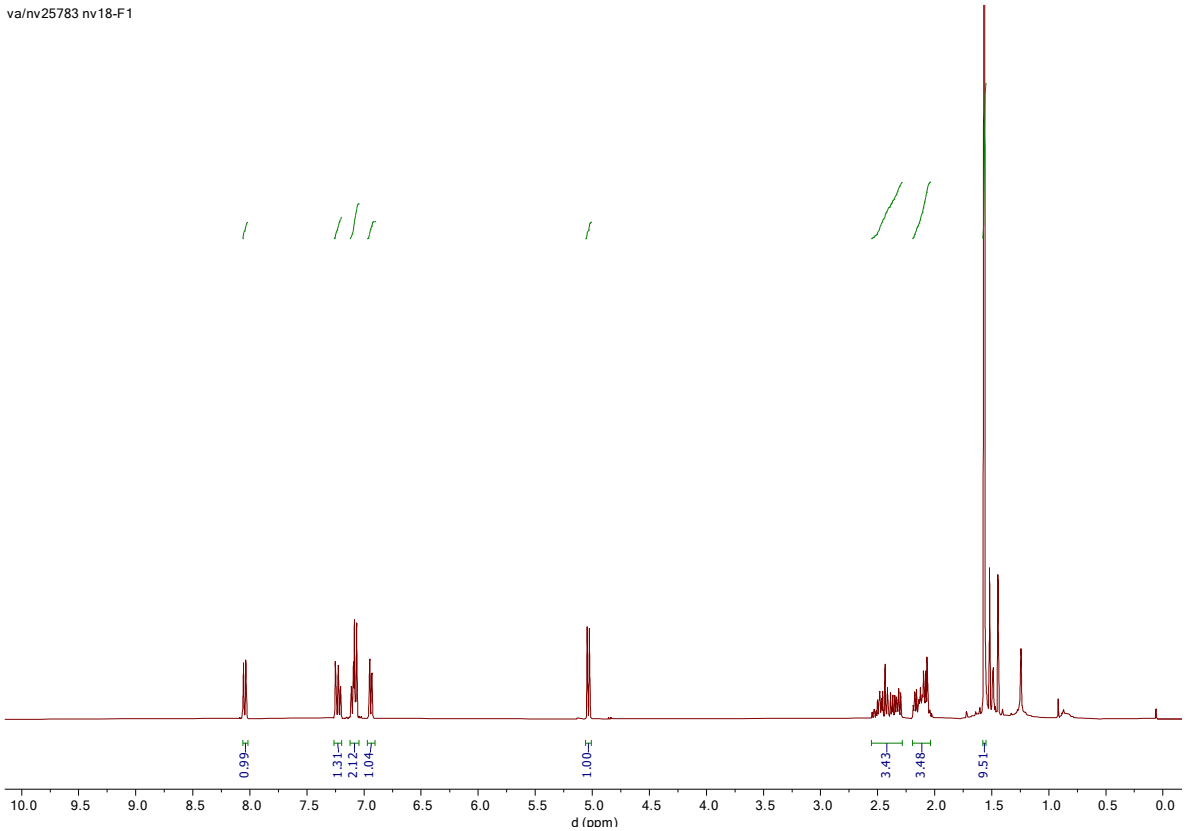
va/nv25780 nv15-F

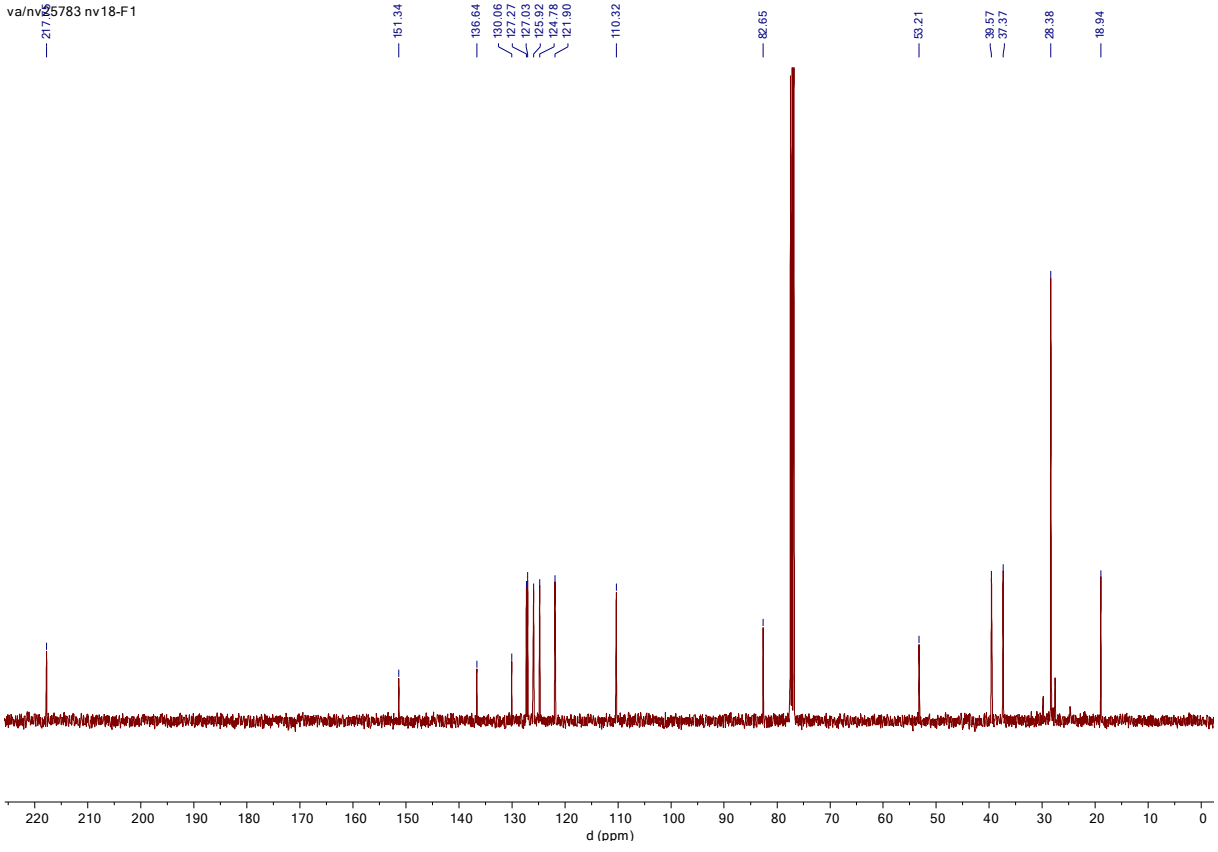


va/nv32291 nv21-F2-C

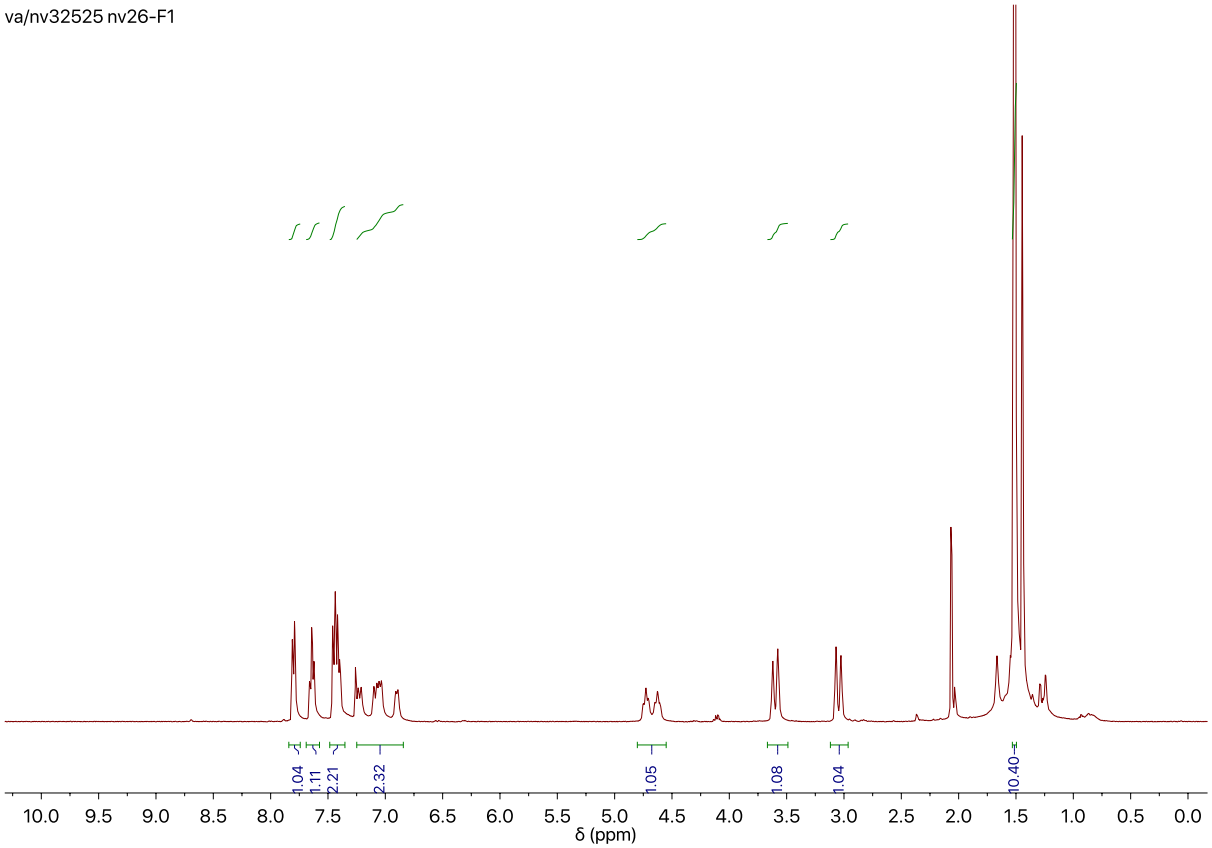


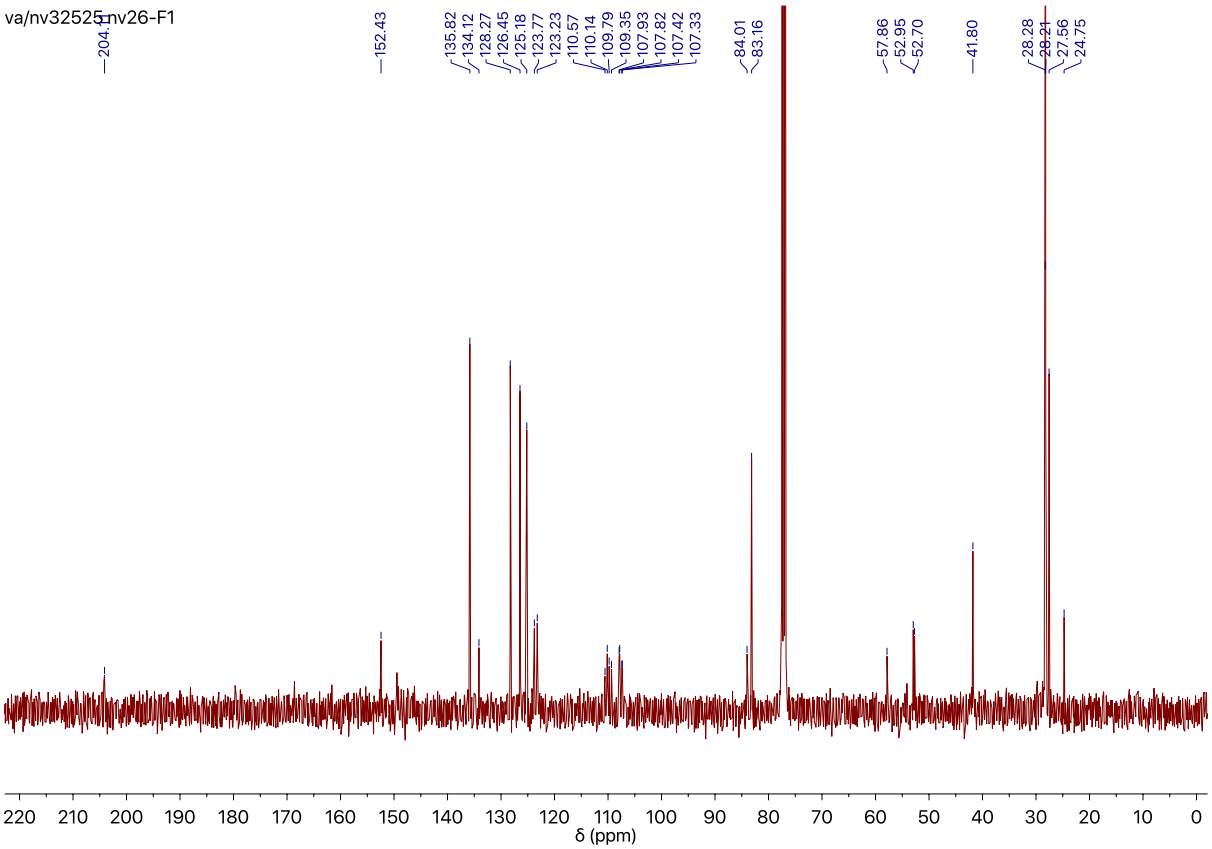
9.3.3.12 *tert*-Butyl (±)-2-oxo-1'H-spiro[cyclopentane-1,4'-quinoline]-1'-carboxylate (524l)

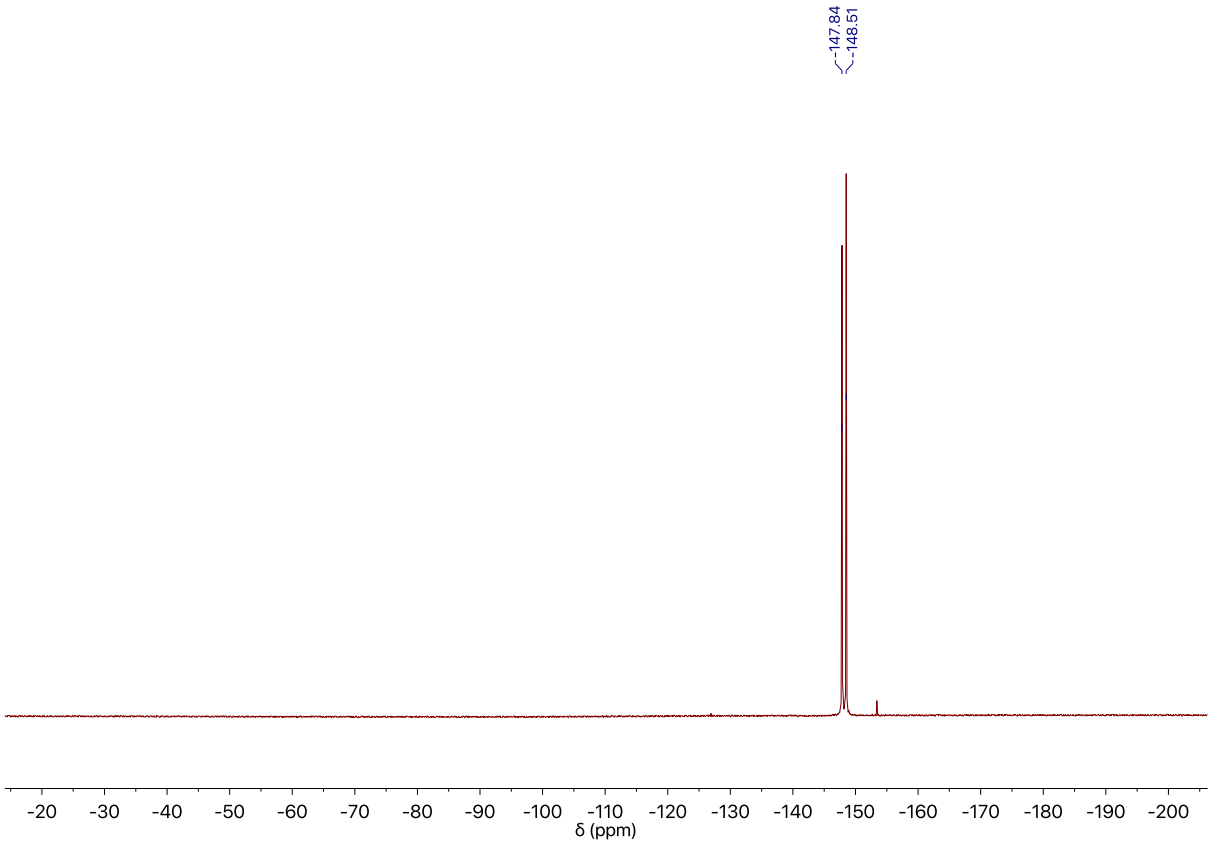




9.3.3.13 *tert*-Butyl (*R*)-3'-fluoro-2-oxo-2,3-dihydro-1'*H*-spiro[indene-1,4'-pyridine]-1'-carboxylate (527a)

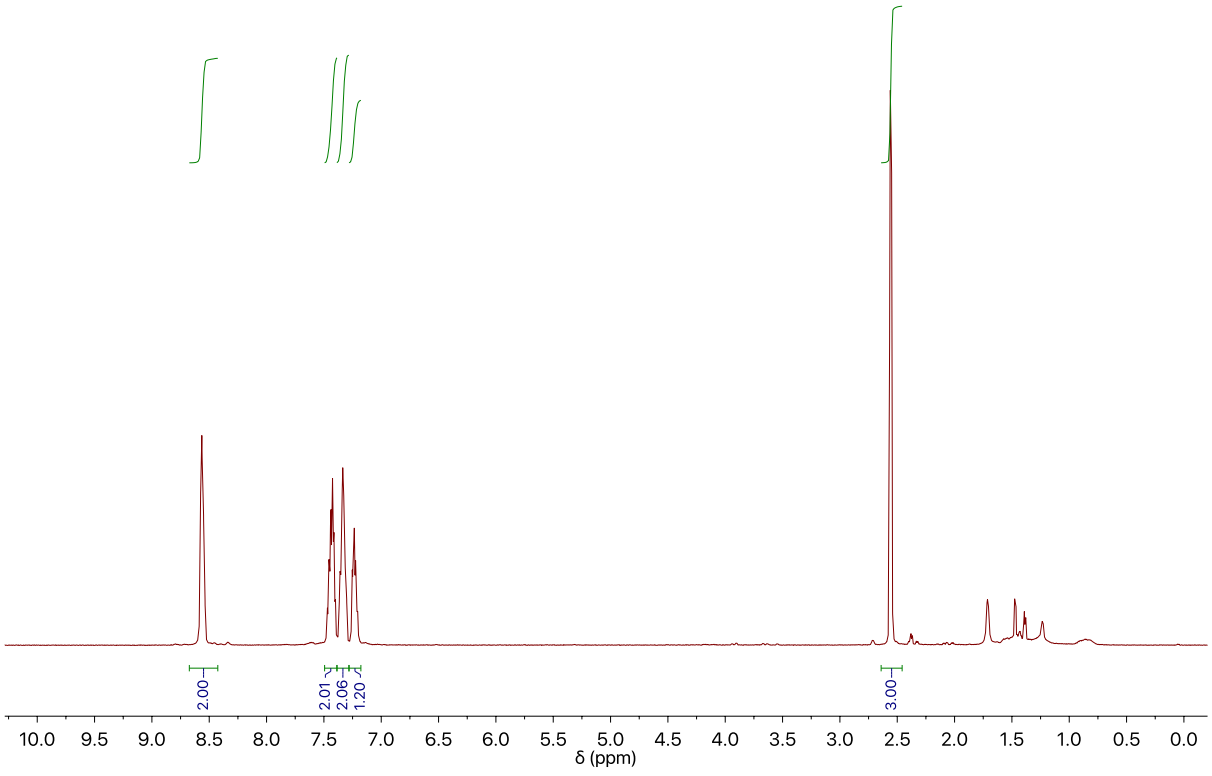


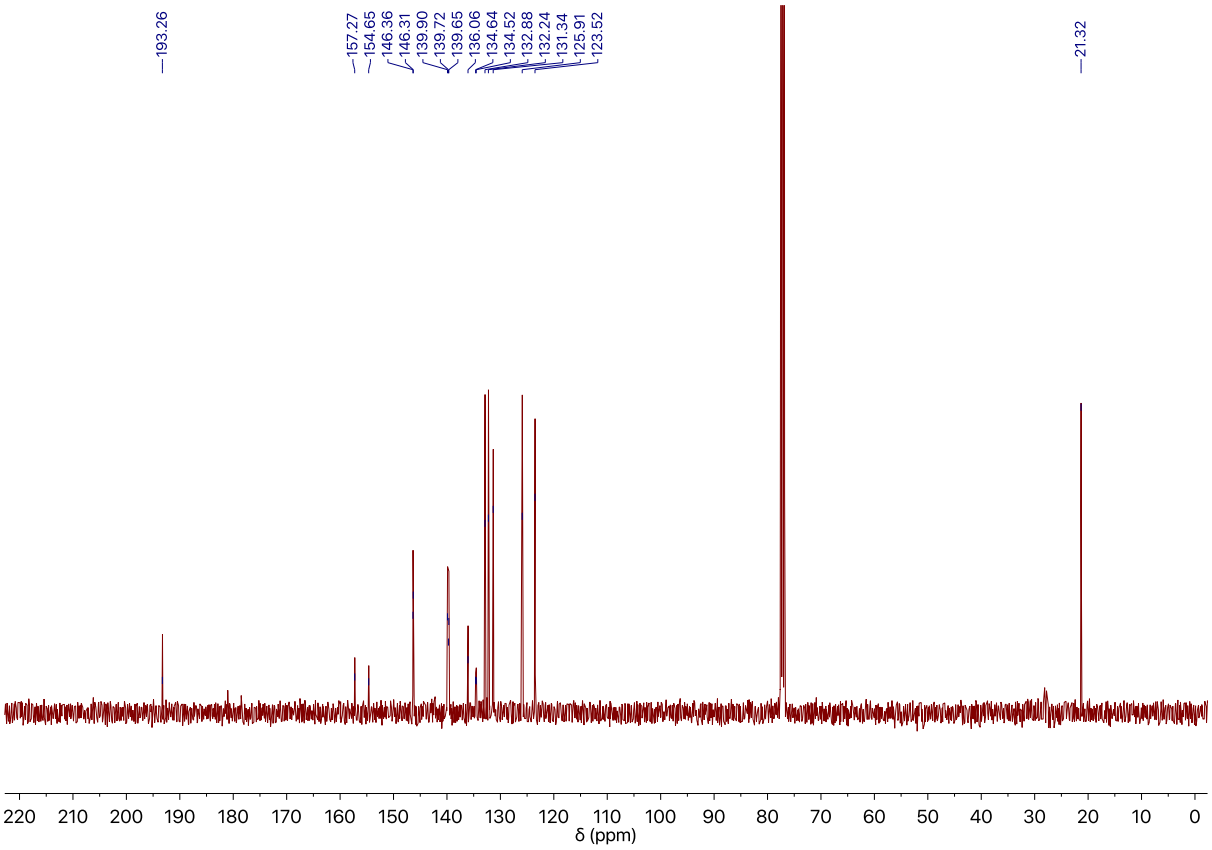


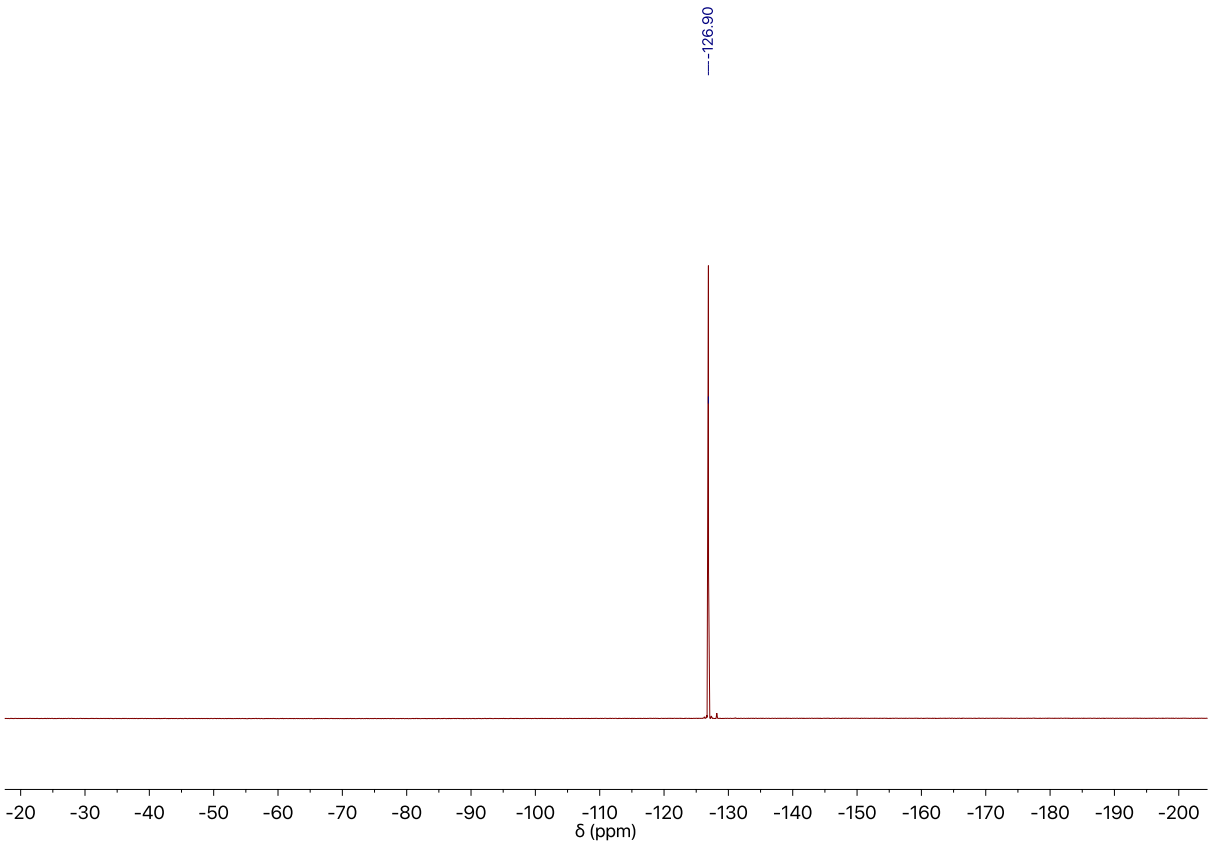


9.3.3.14 (3-Fluoropyridin-4-yl)(o-tolyl)methanone (528)

va/nv32526 nv26-F2

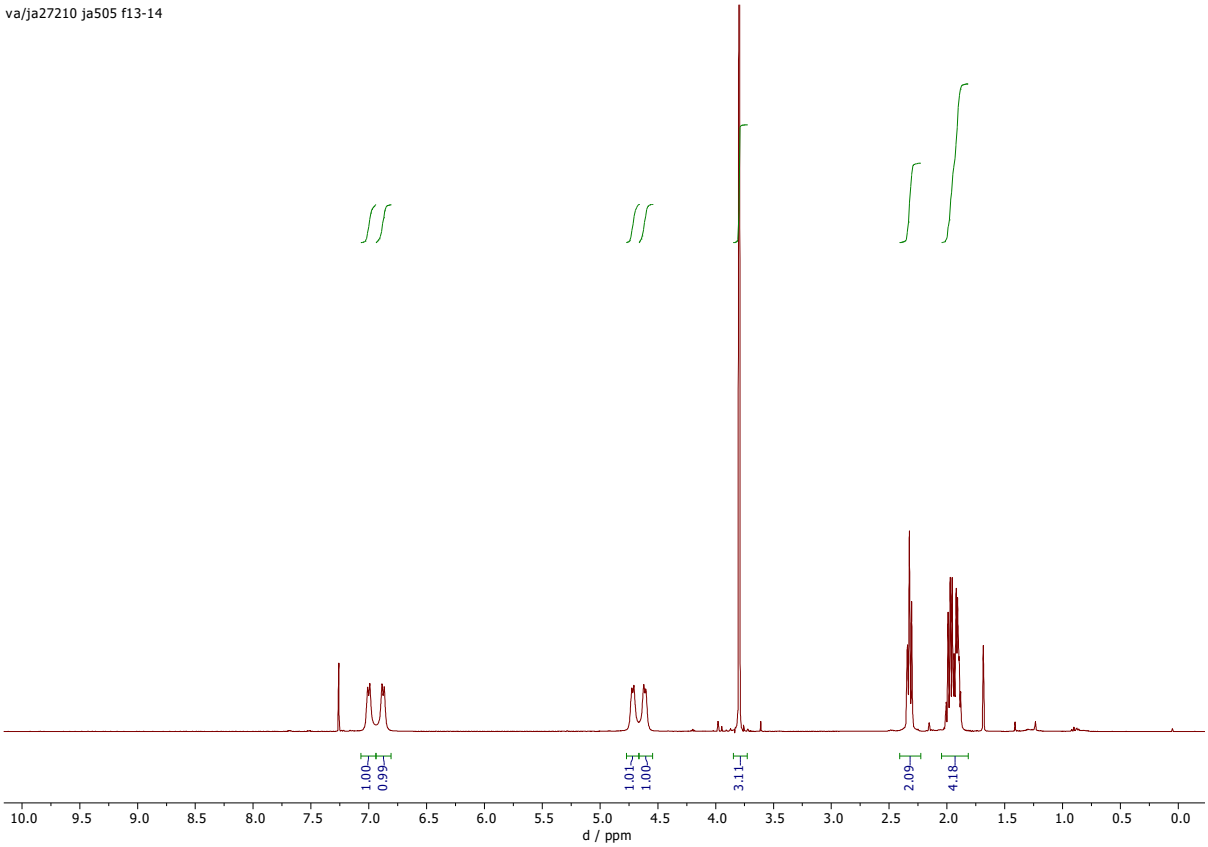


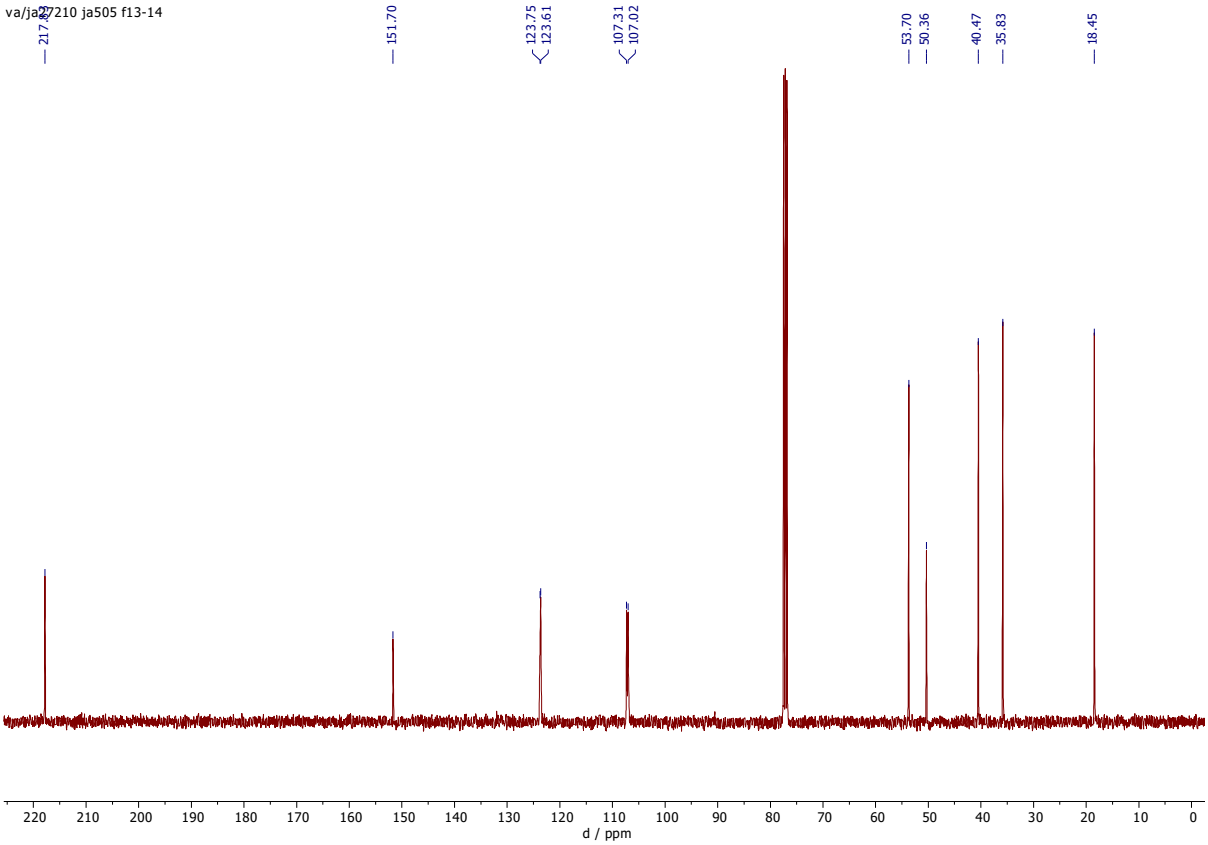

193.26
157.27
154.65
146.36
146.31
139.90
139.72
139.65
136.06
134.64
134.52
132.88
132.24
131.34
125.91
123.52
21.32
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
δ (ppm)


-126.90
-20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
δ (ppm)

9.3.4 Scope of acylating agents

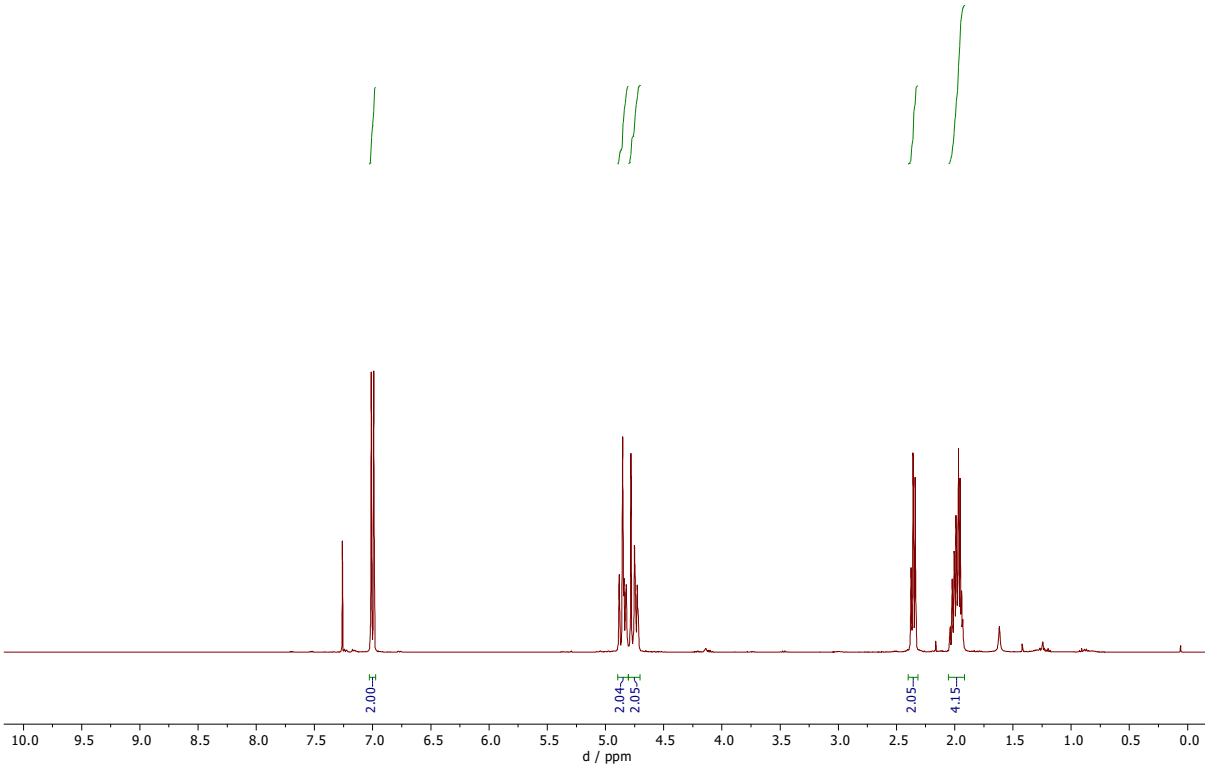
9.3.4.1 Methyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517b)



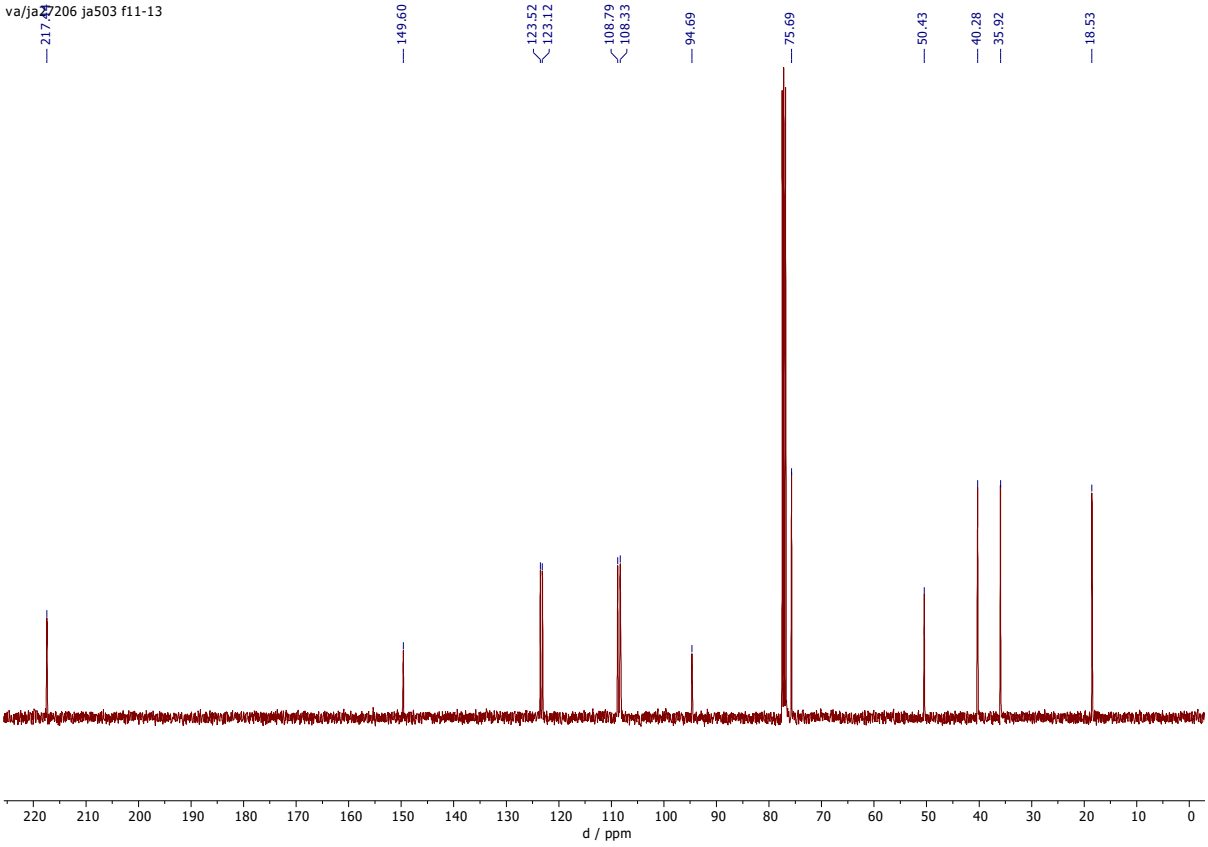


9.3.4.2 2,2,2-Trichloroethyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517c)

va/ja27206 ja503 f11-13

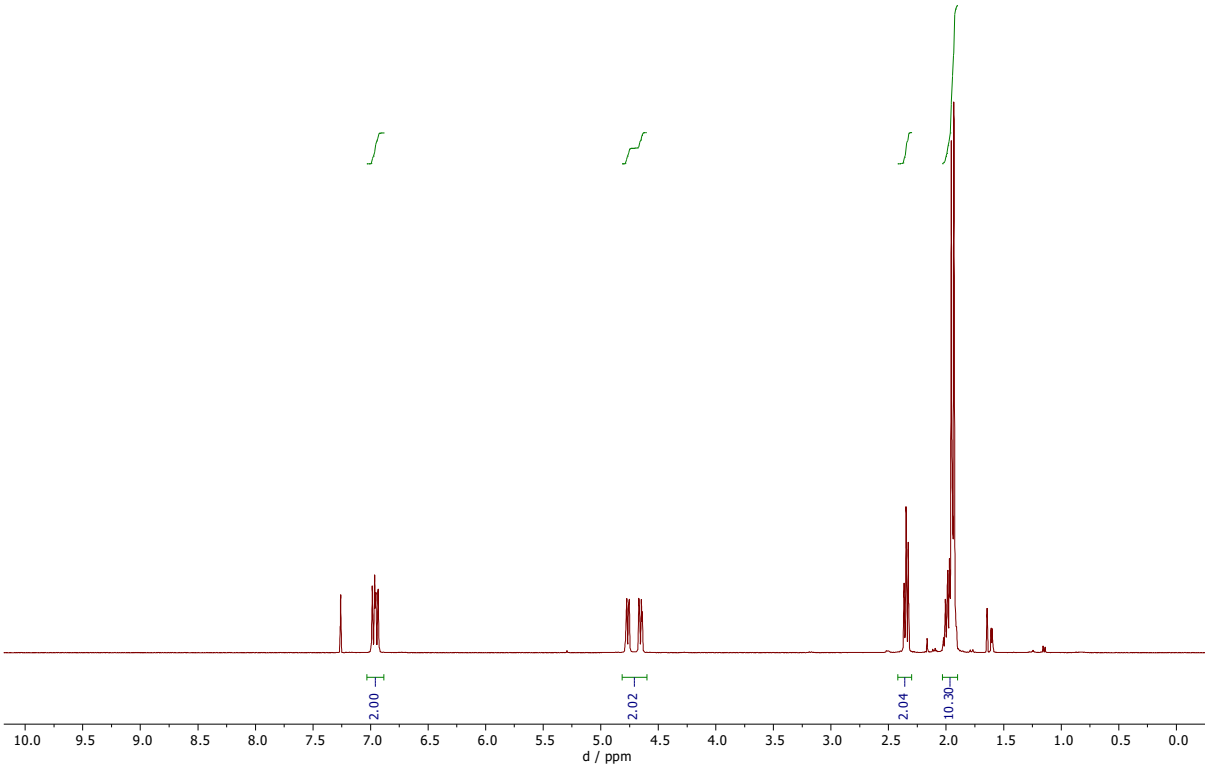


va/ja27206 ja503 f11-13

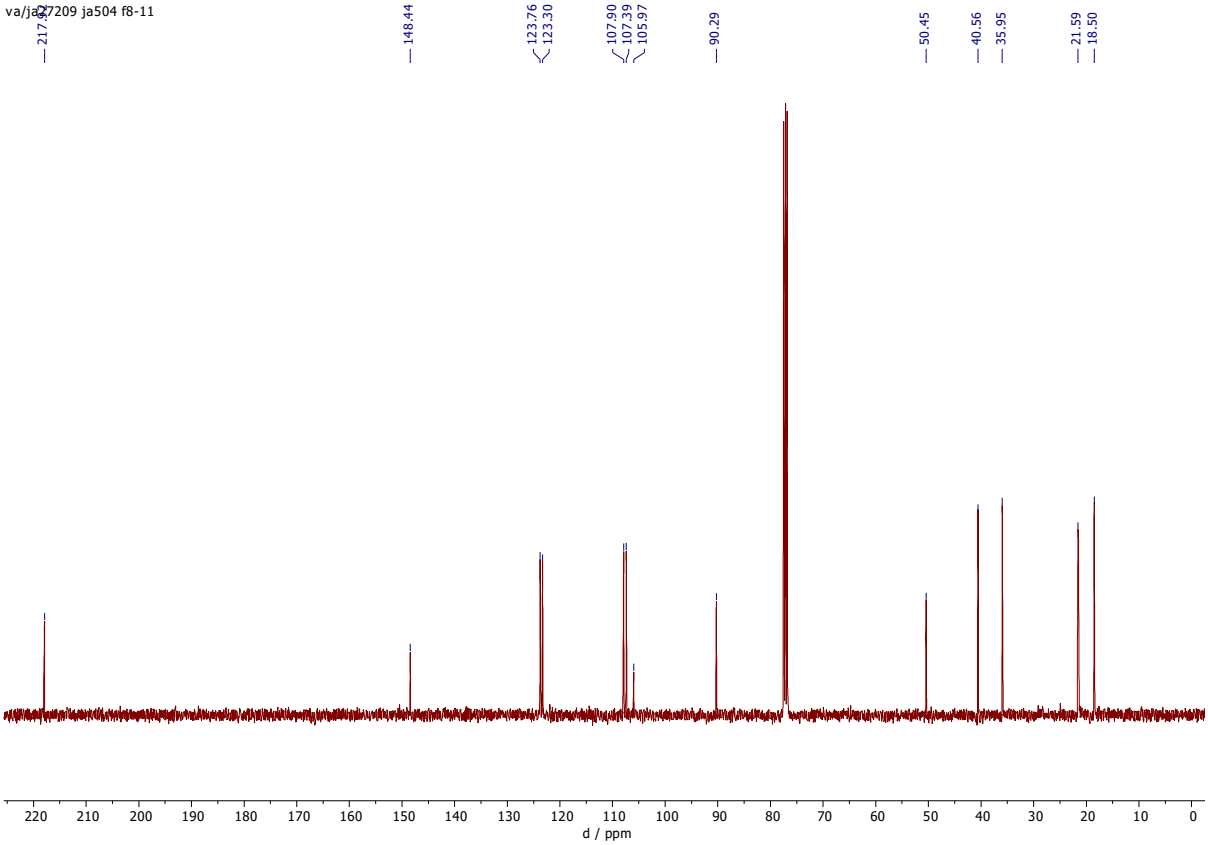


9.3.4.3 1,1,1-Trichloro-2-methylpropan-2-yl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517d)

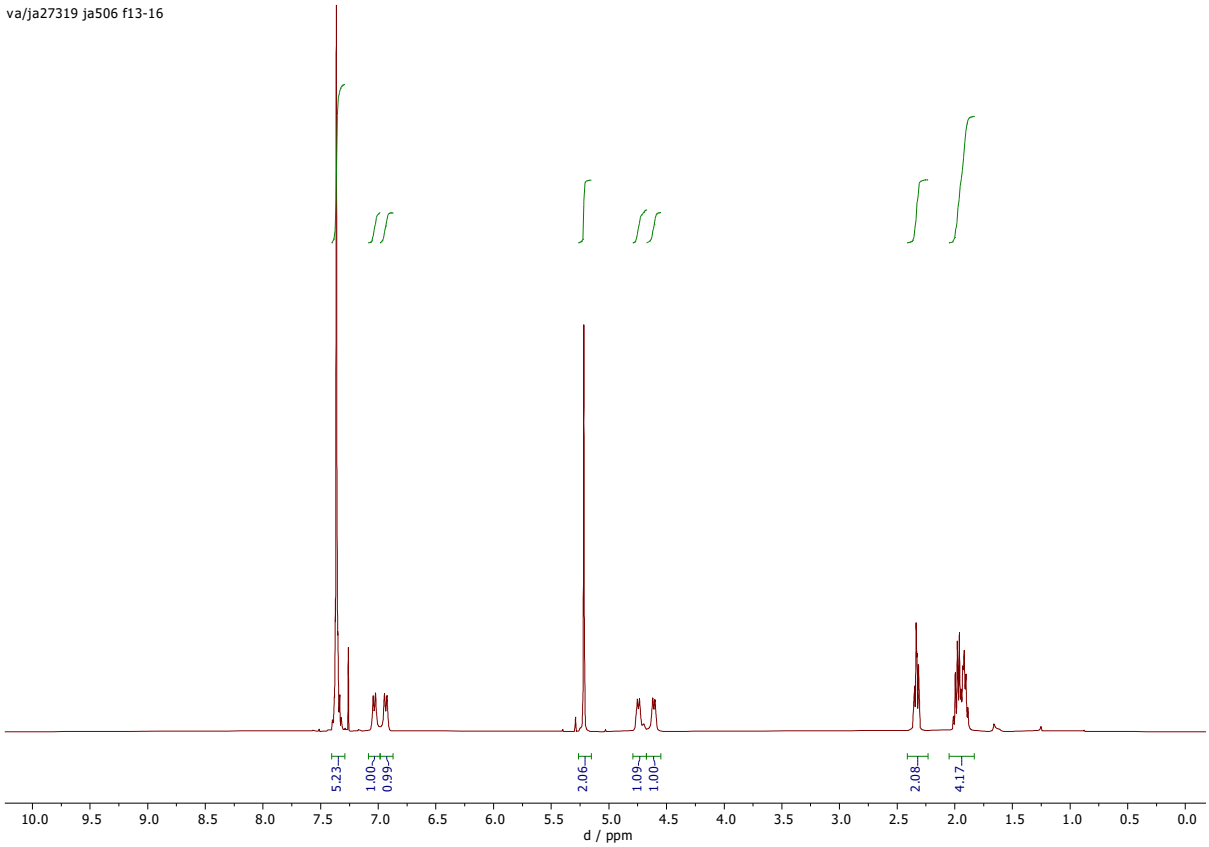
va/ja27209 ja504 f8-11

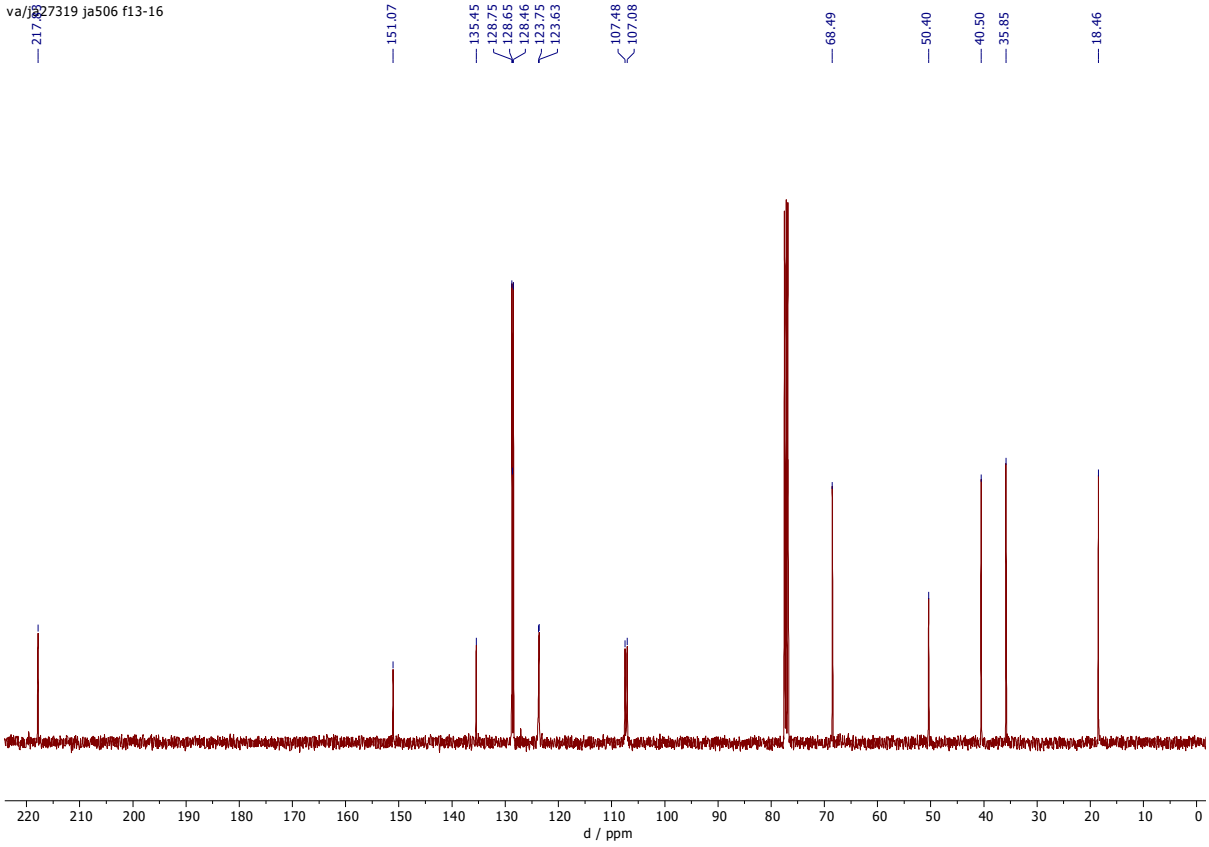


va/ja27209 ja504 f8-11

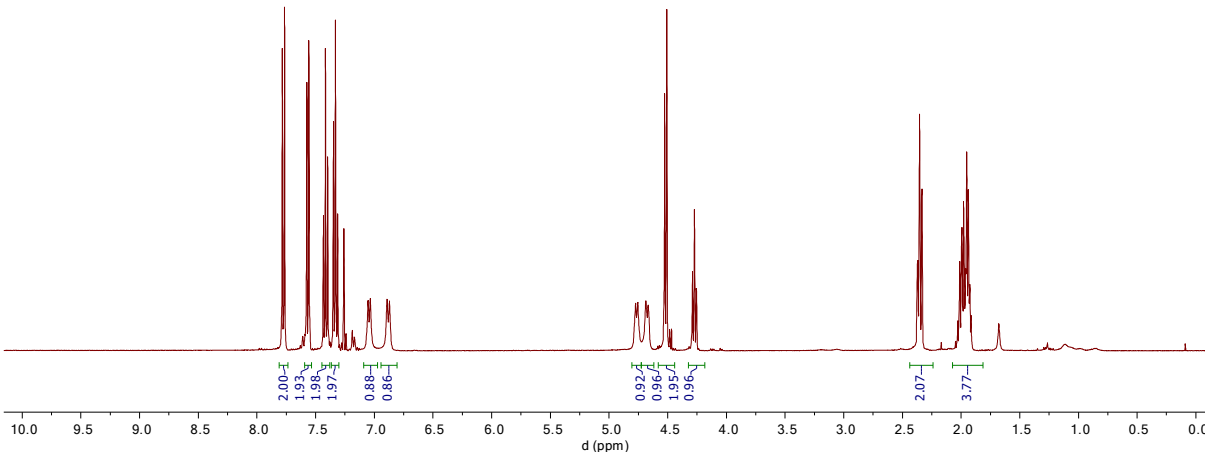


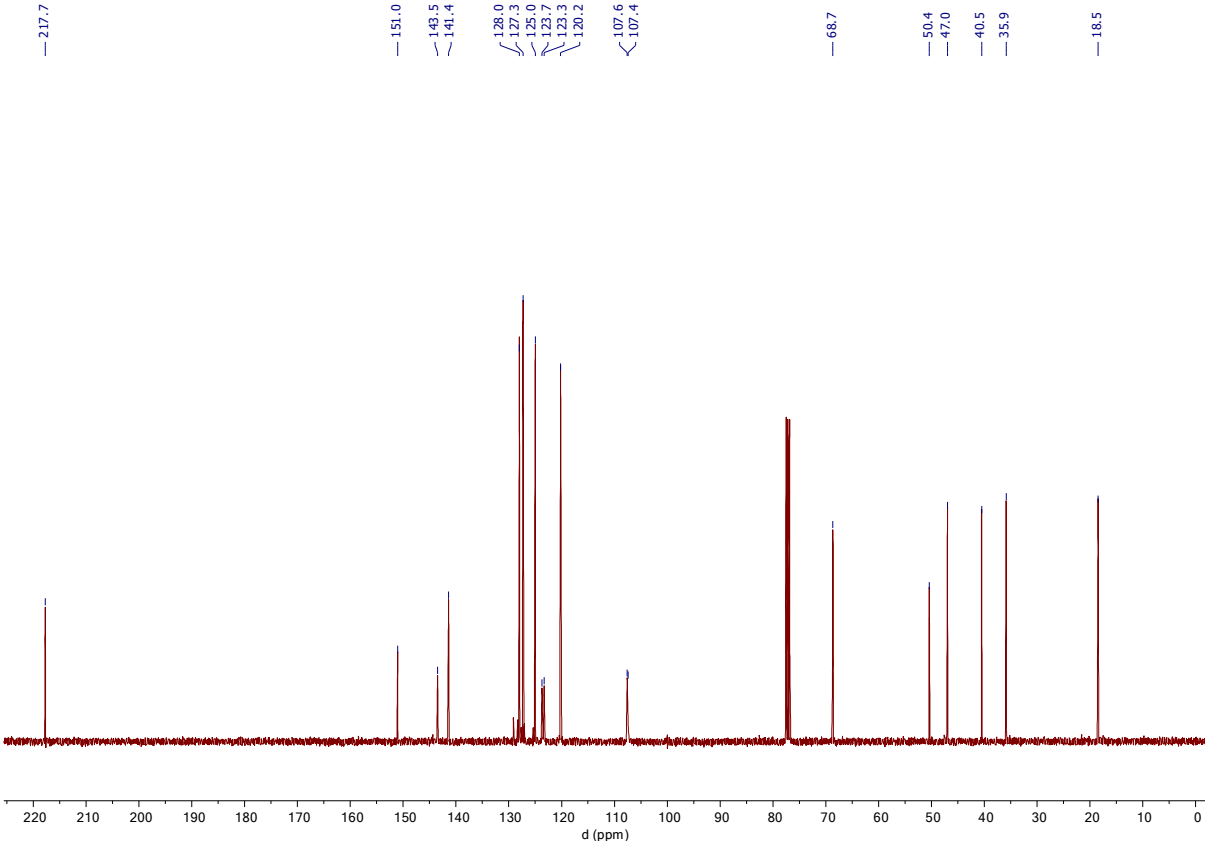
9.3.4.4 Benzyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517e)



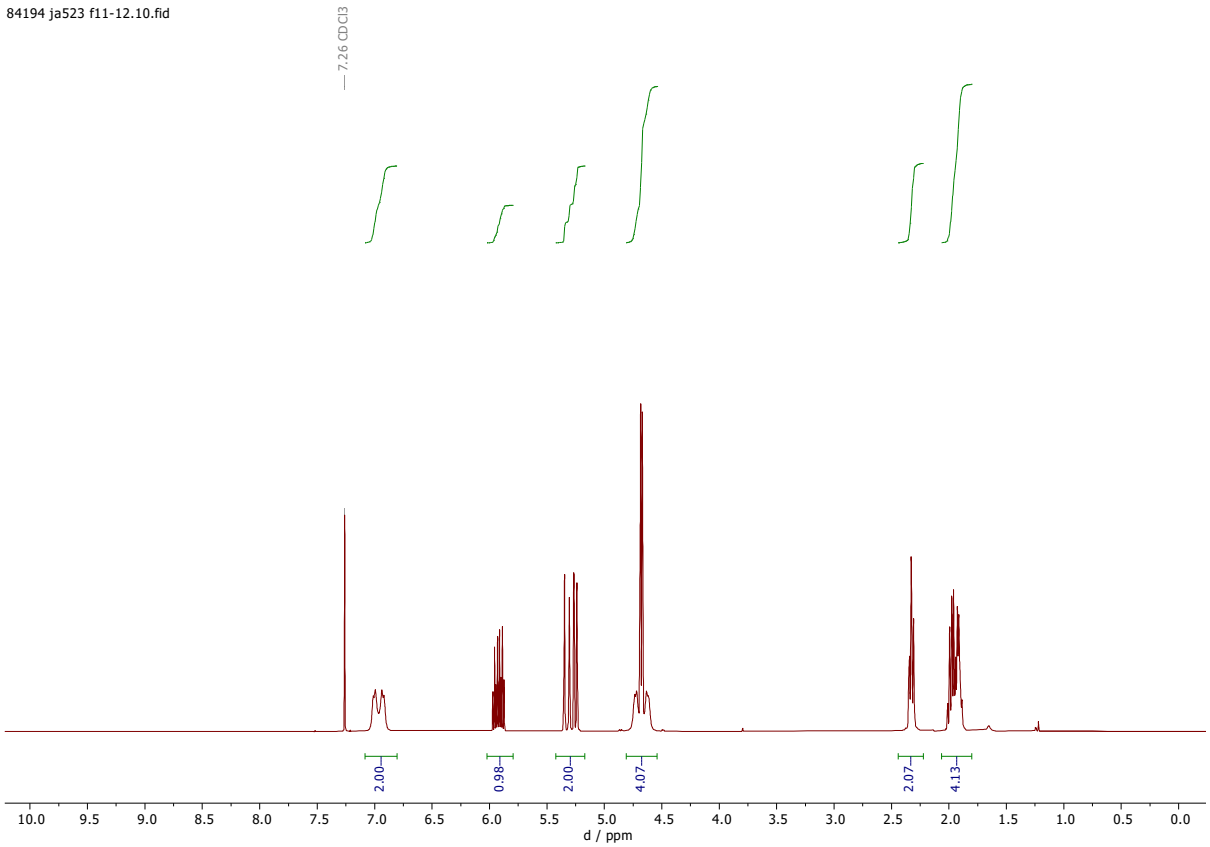


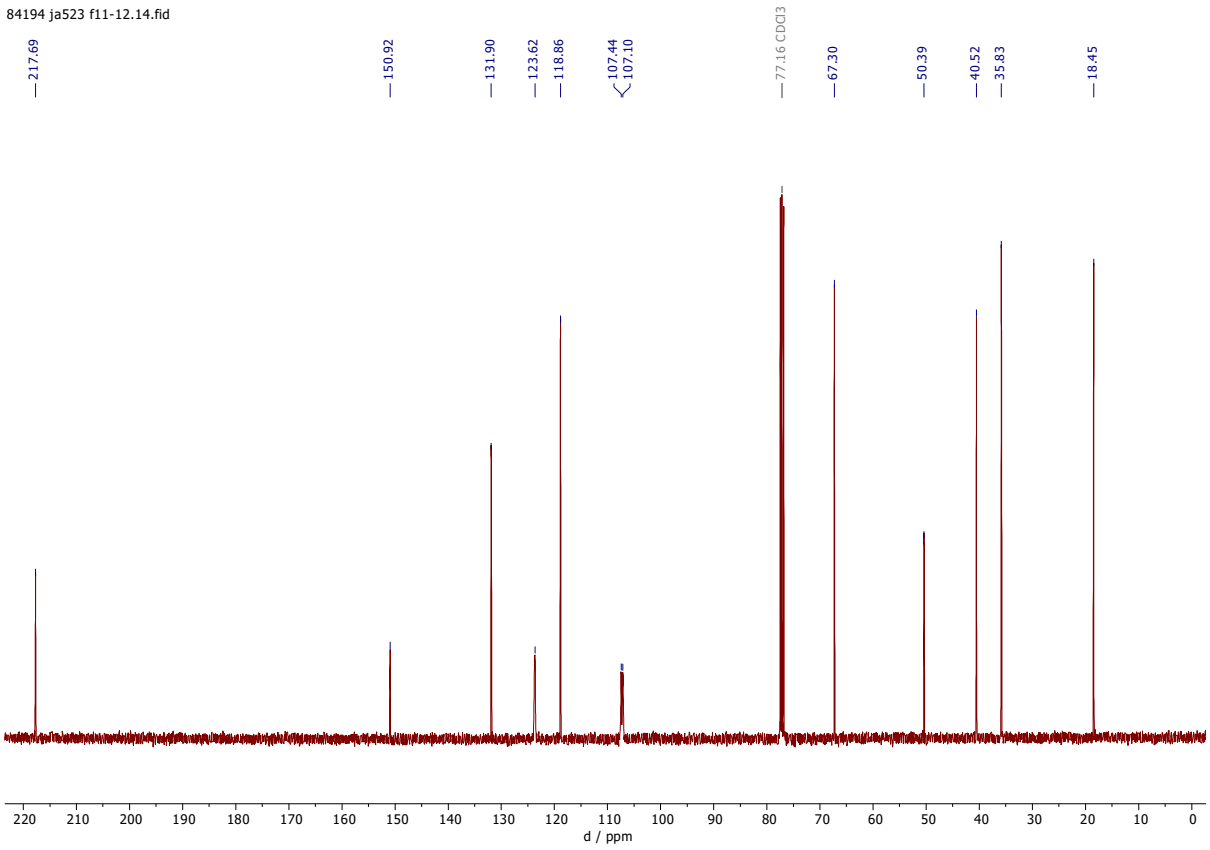
9.3.4.5 (9*H*-Fluoren-9-yl)methyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517f)



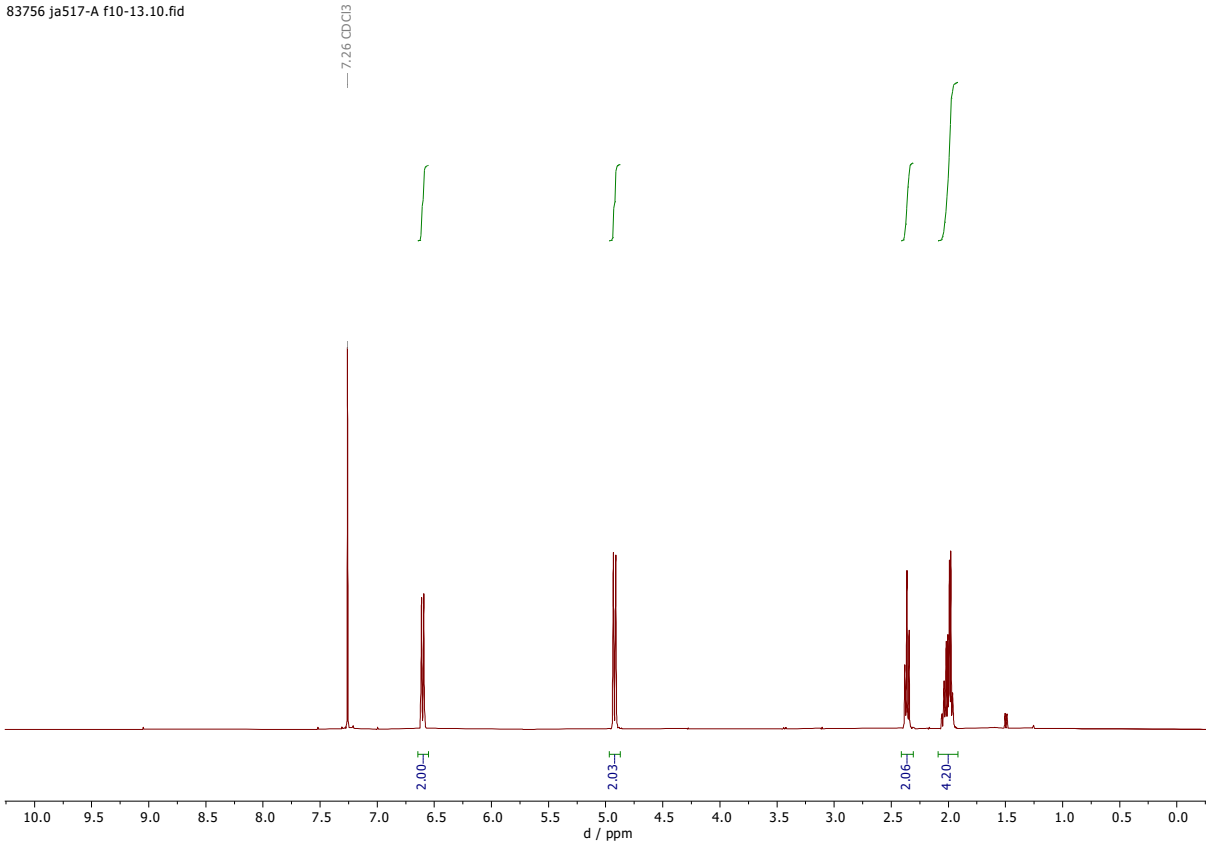


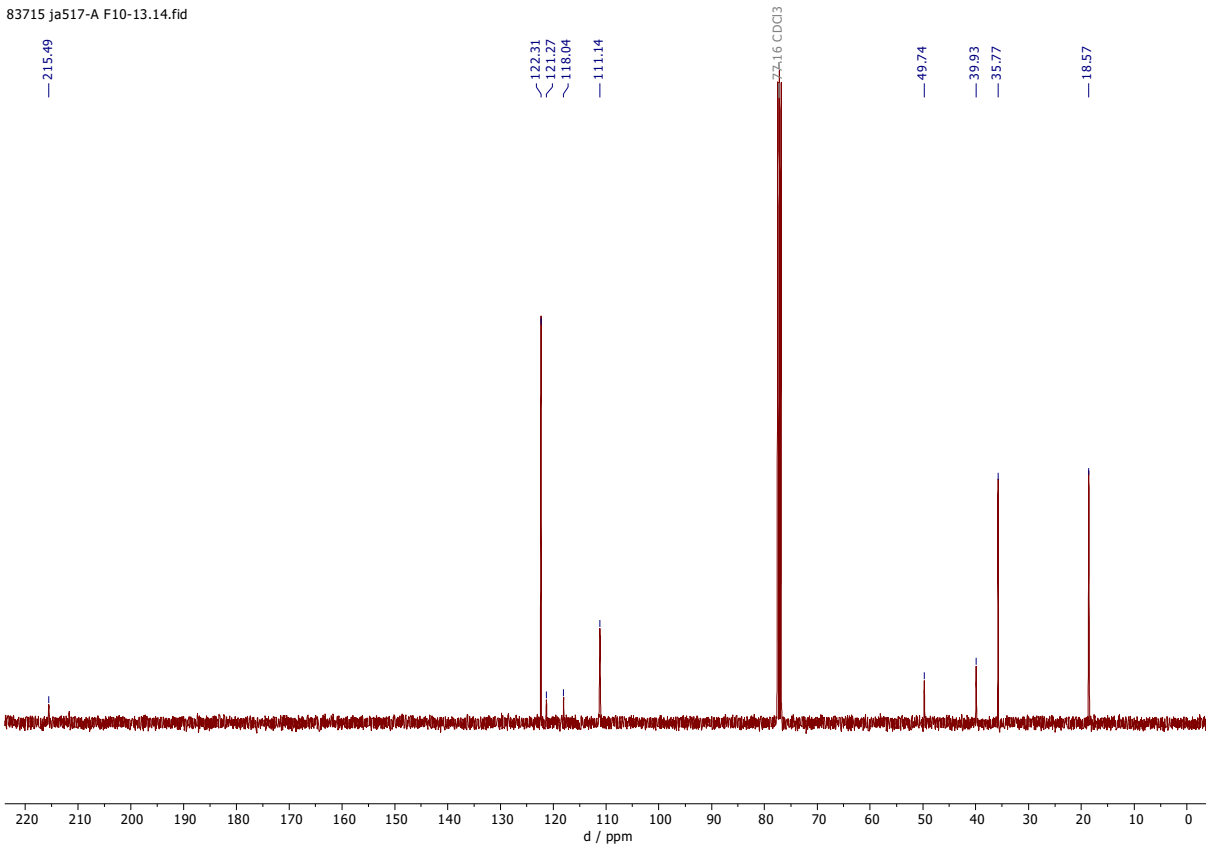
9.3.4.6 Allyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (517g)



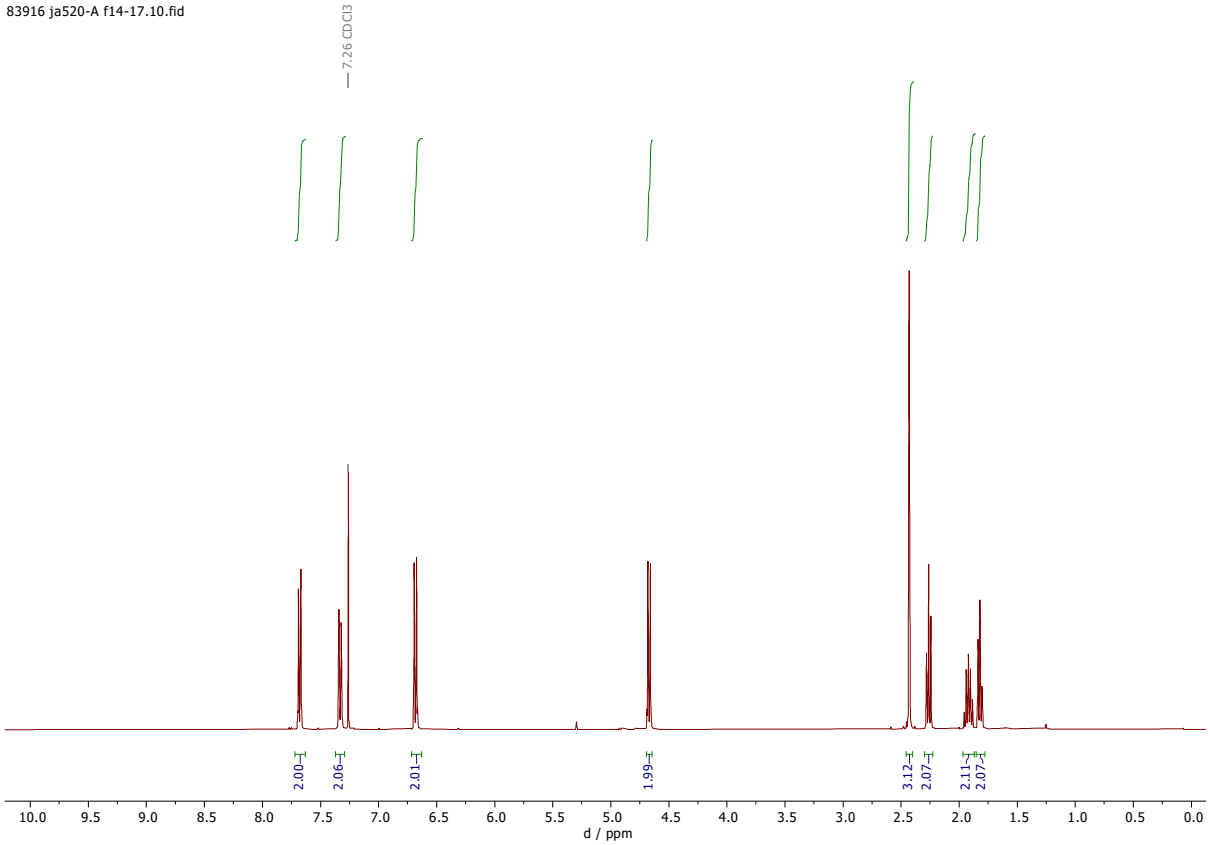


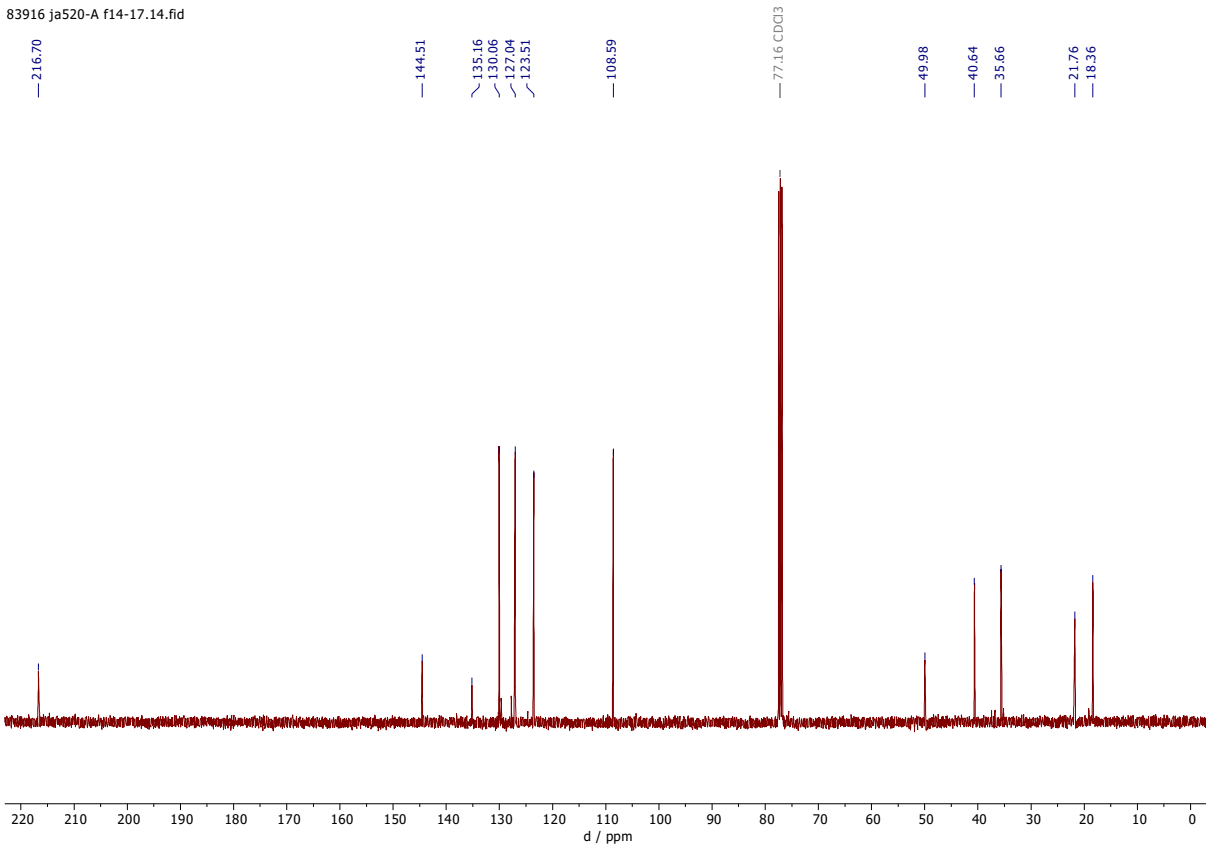
9.3.4.7 8-((Trifluoromethyl)sulfonyl)-8-azaspiro[4.5]deca-6,9-dien-1-one (517h)



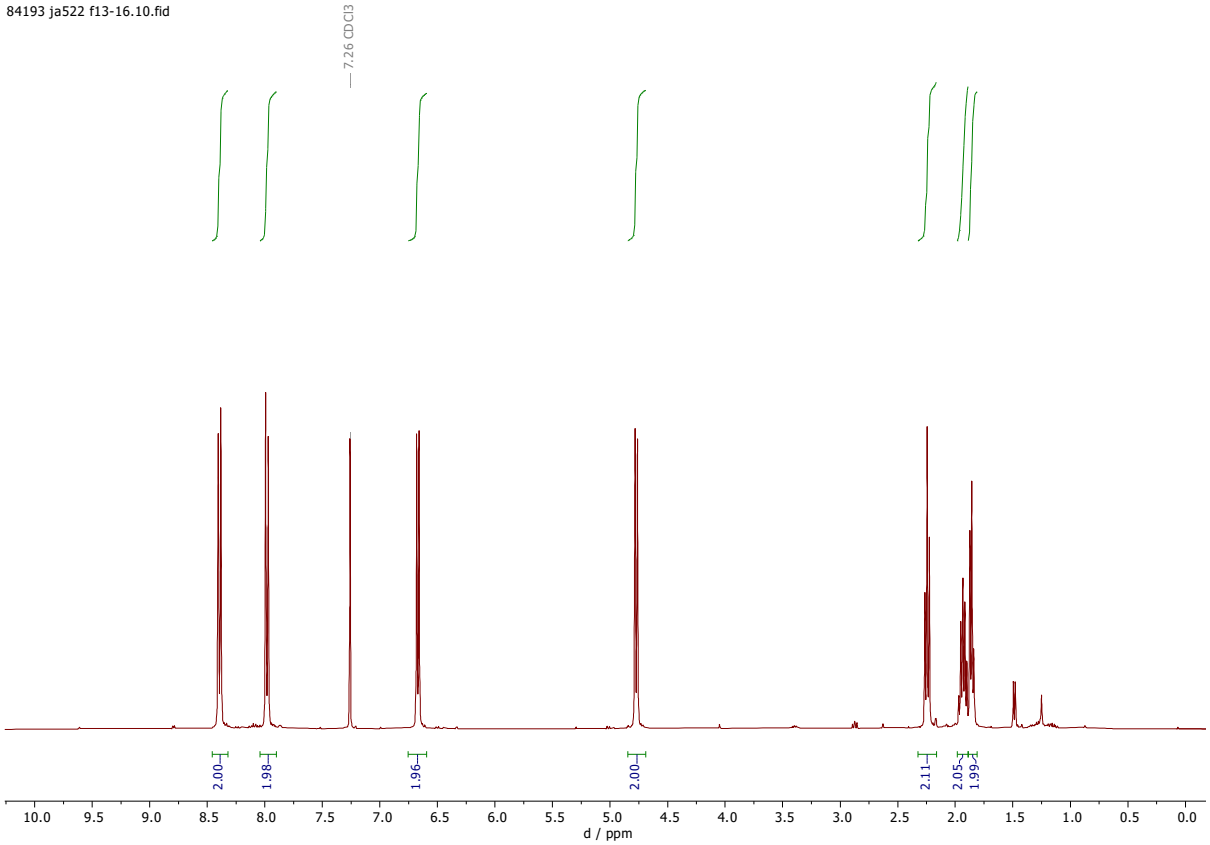


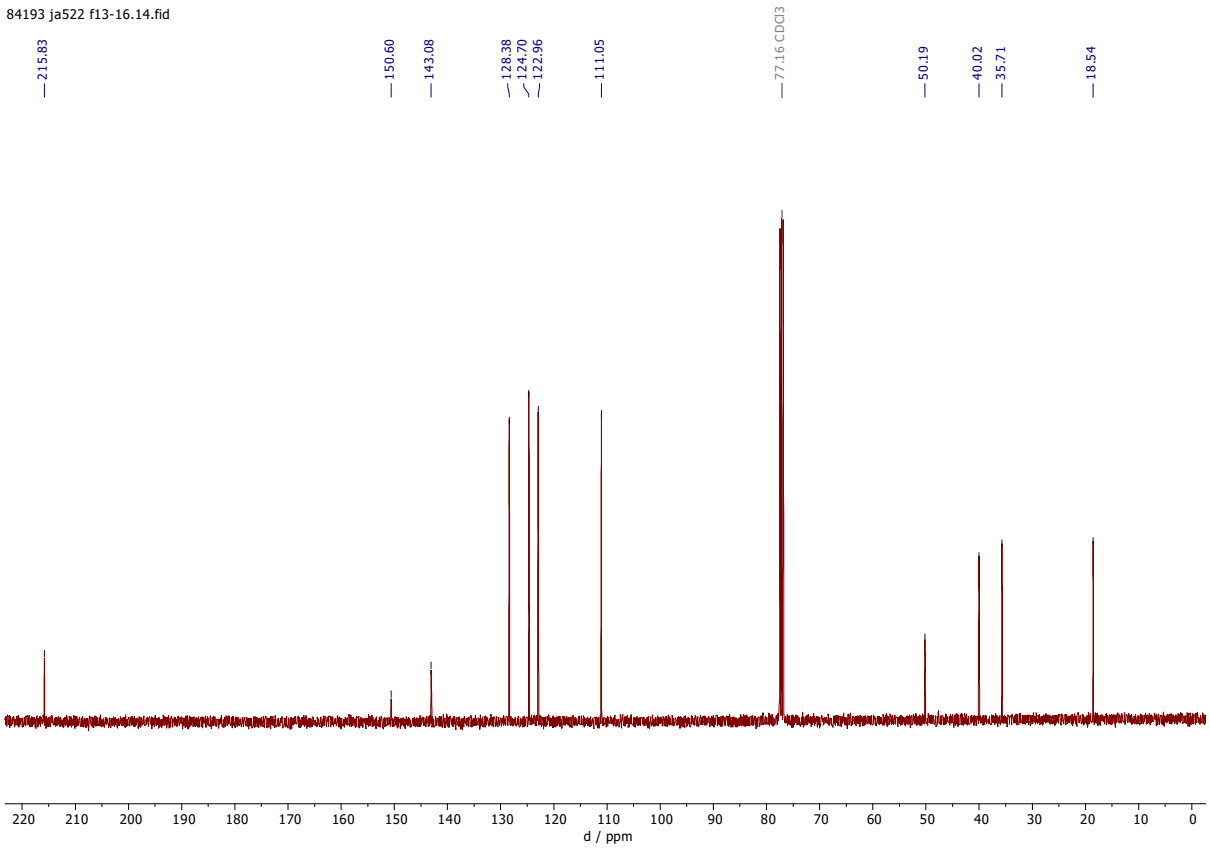
9.3.4.8 8-Tosyl-8-azaspiro[4.5]deca-6,9-dien-1-one (517i)



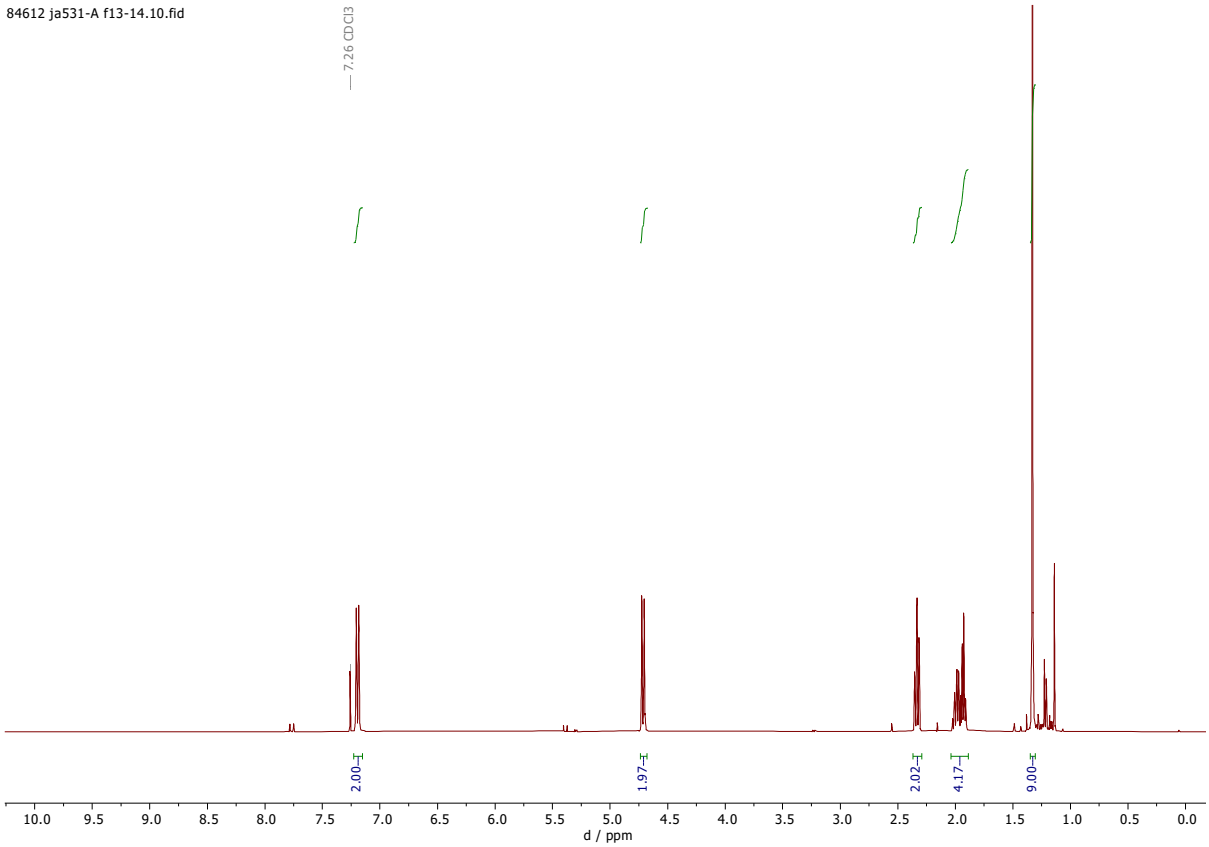


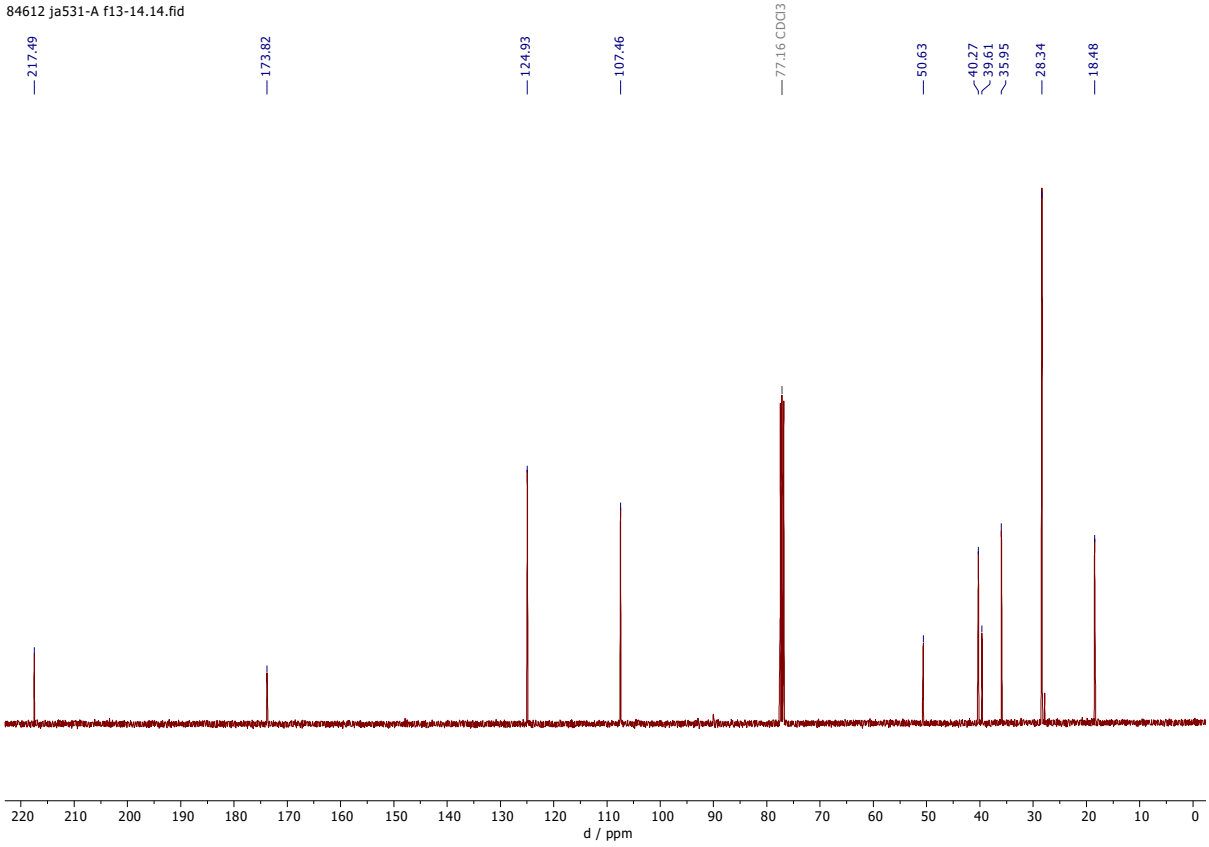
9.3.4.9 8-((4-Nitrophenyl)sulfonyl)-8-azaspiro[4.5]deca-6,9-dien-1-one (517j)



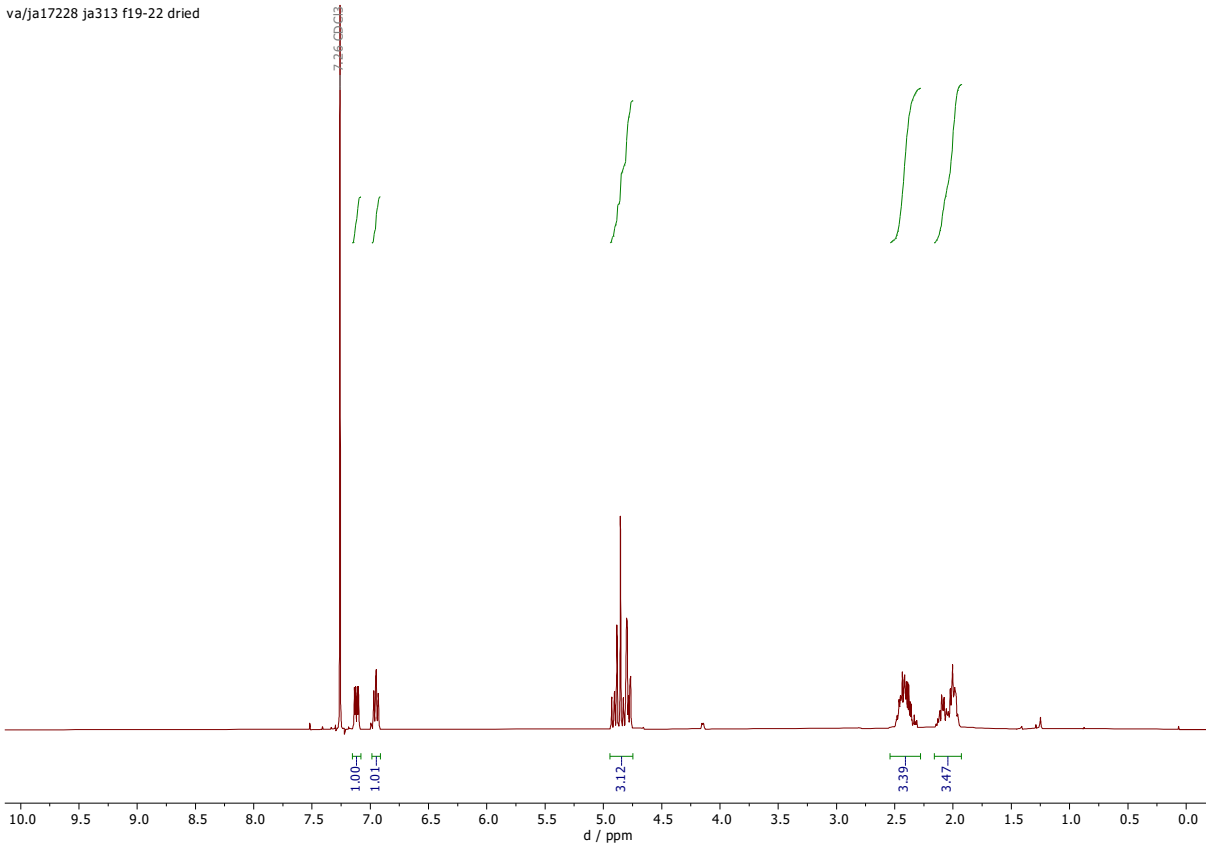


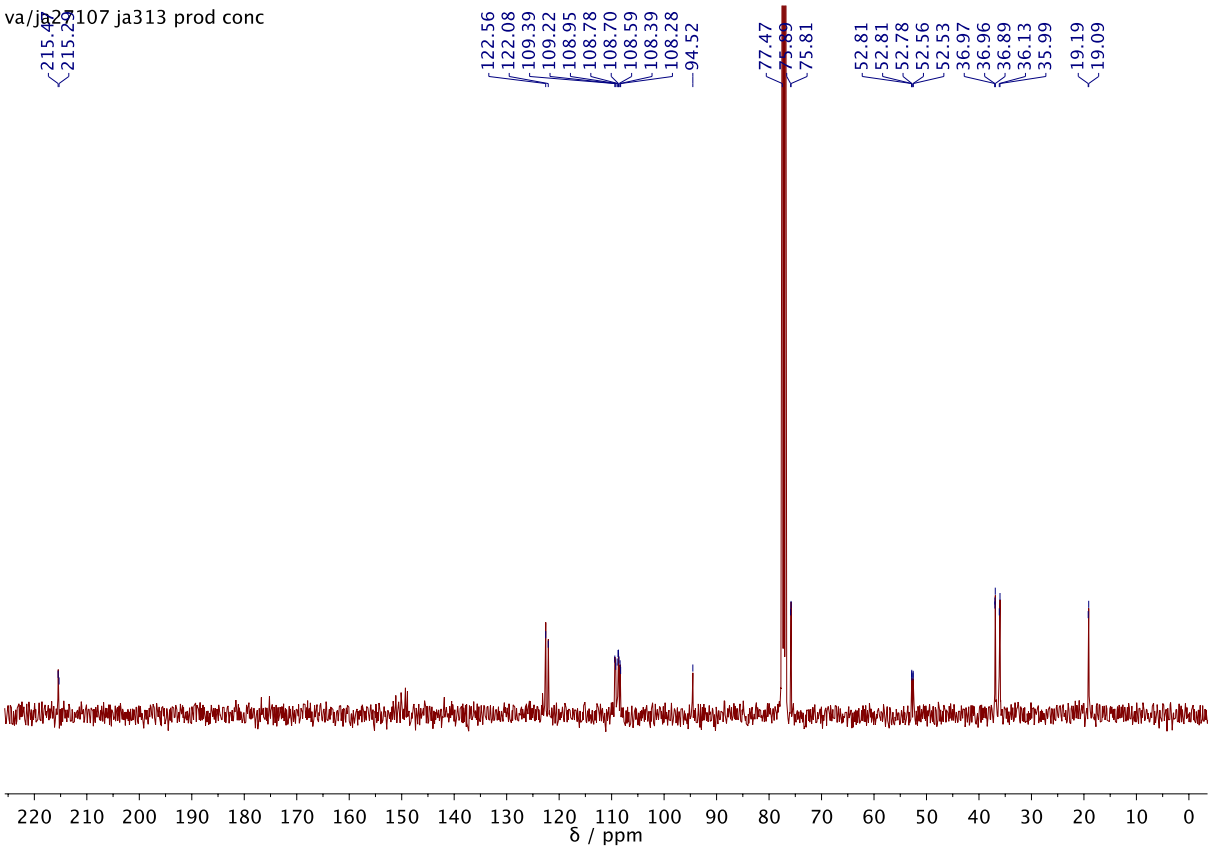
9.3.4.10 8-Pivaloyl-8-azaspiro[4.5]deca-6,9-dien-1-one (517k)



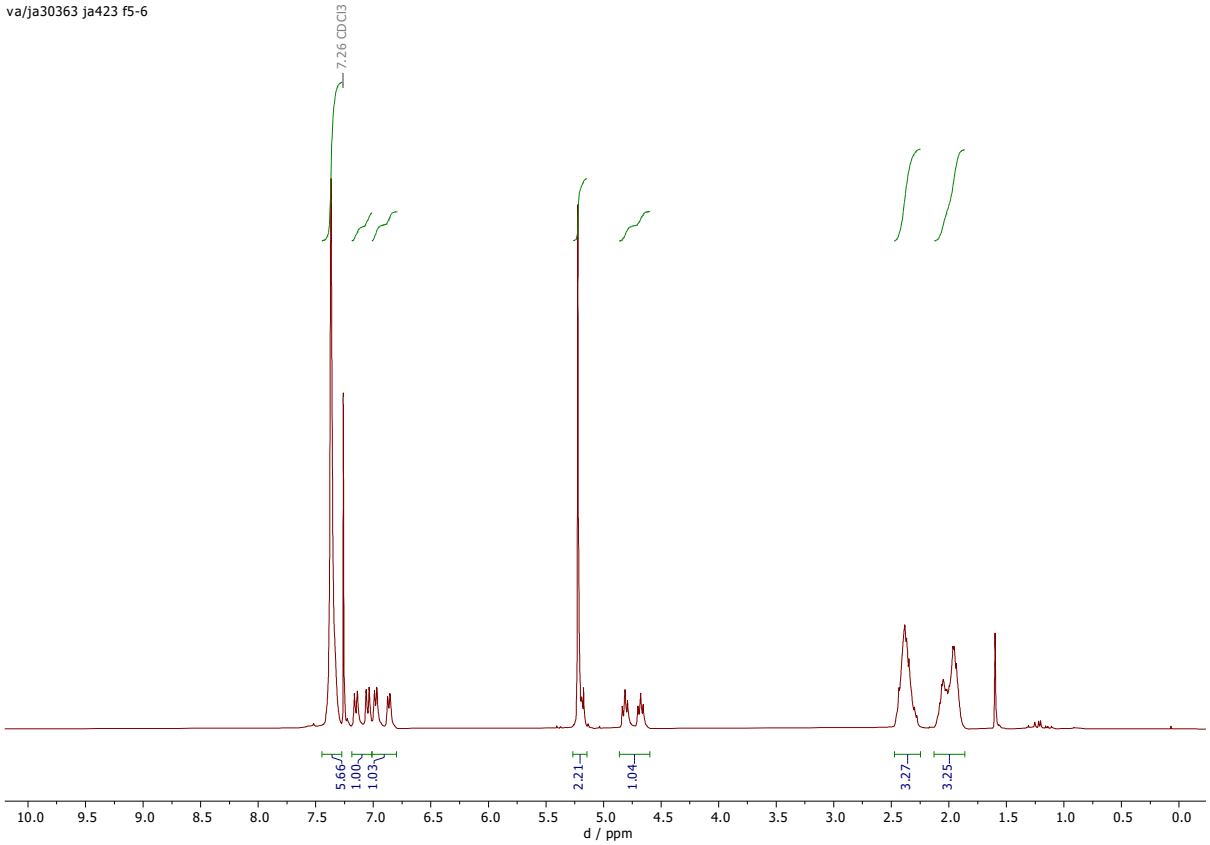


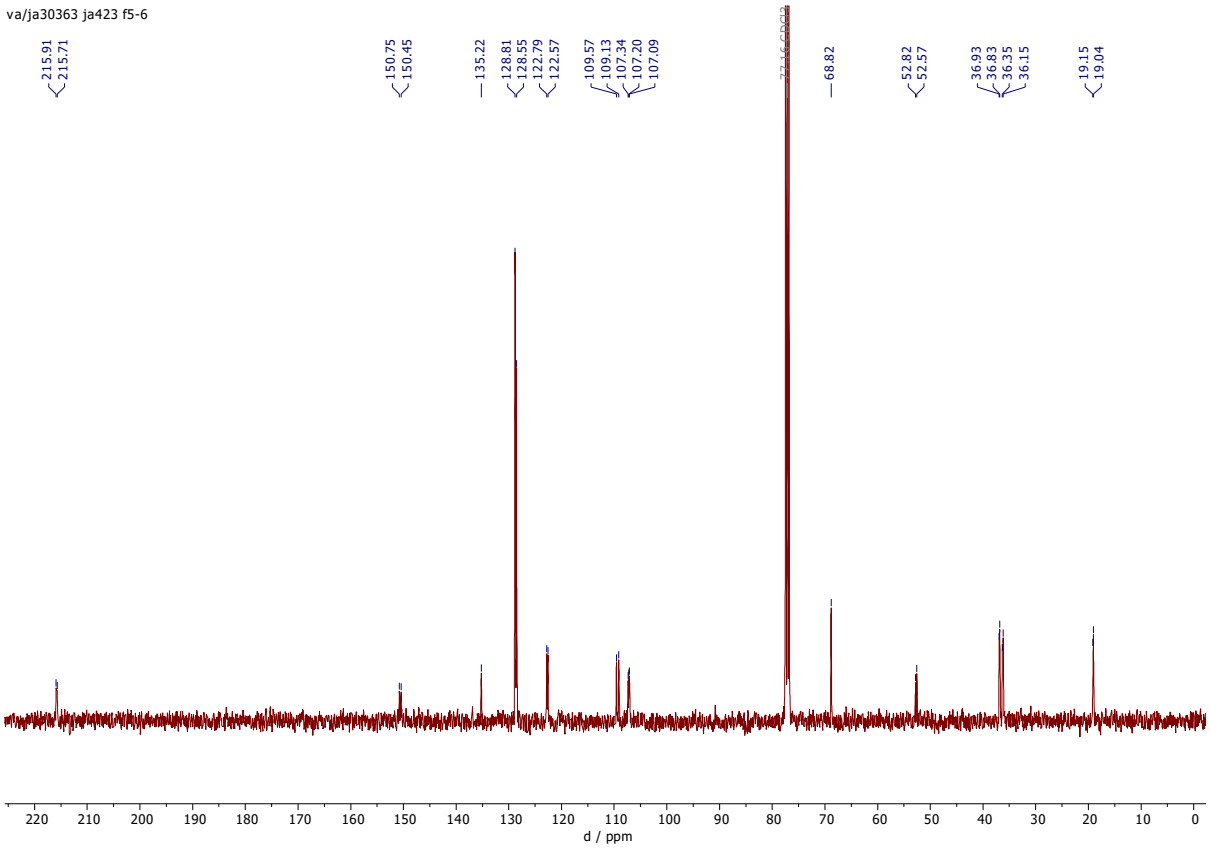
9.3.4.11 2,2,2-Trichloroethyl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519a)



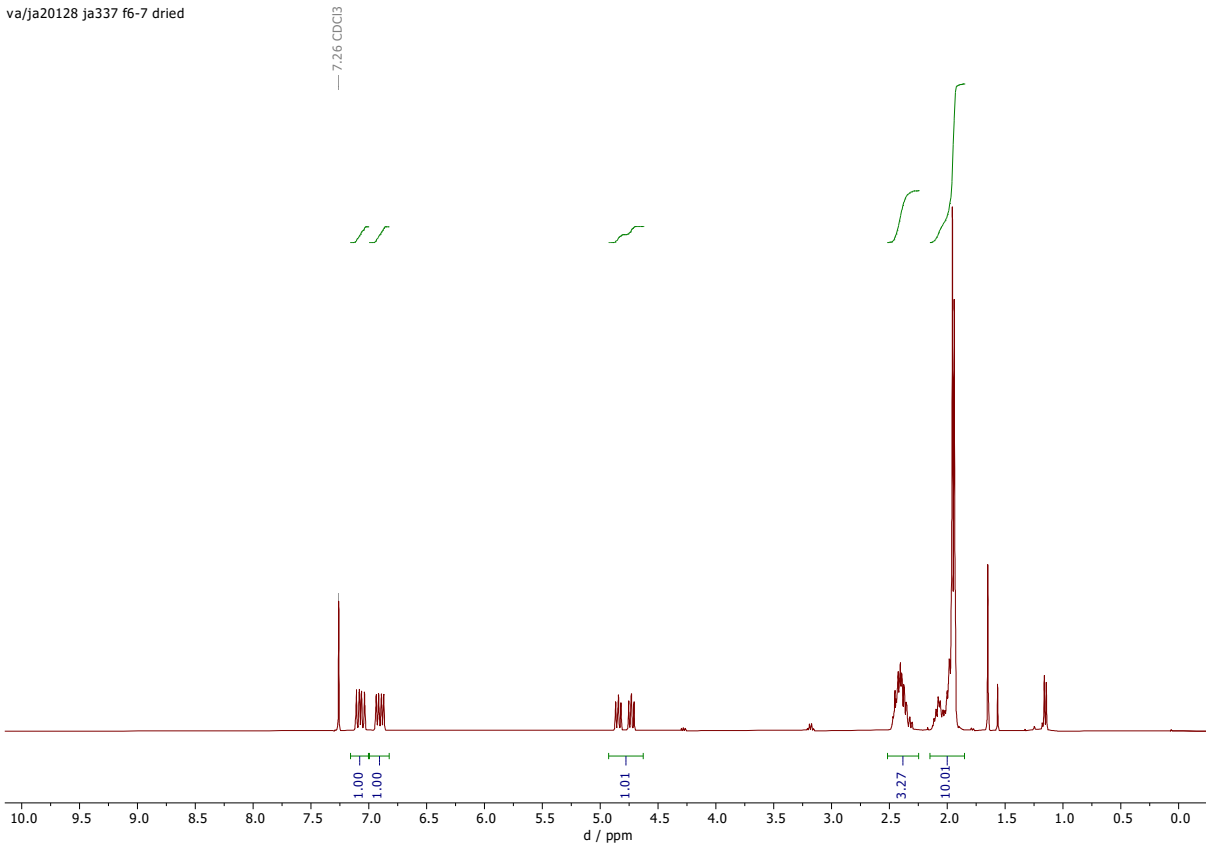


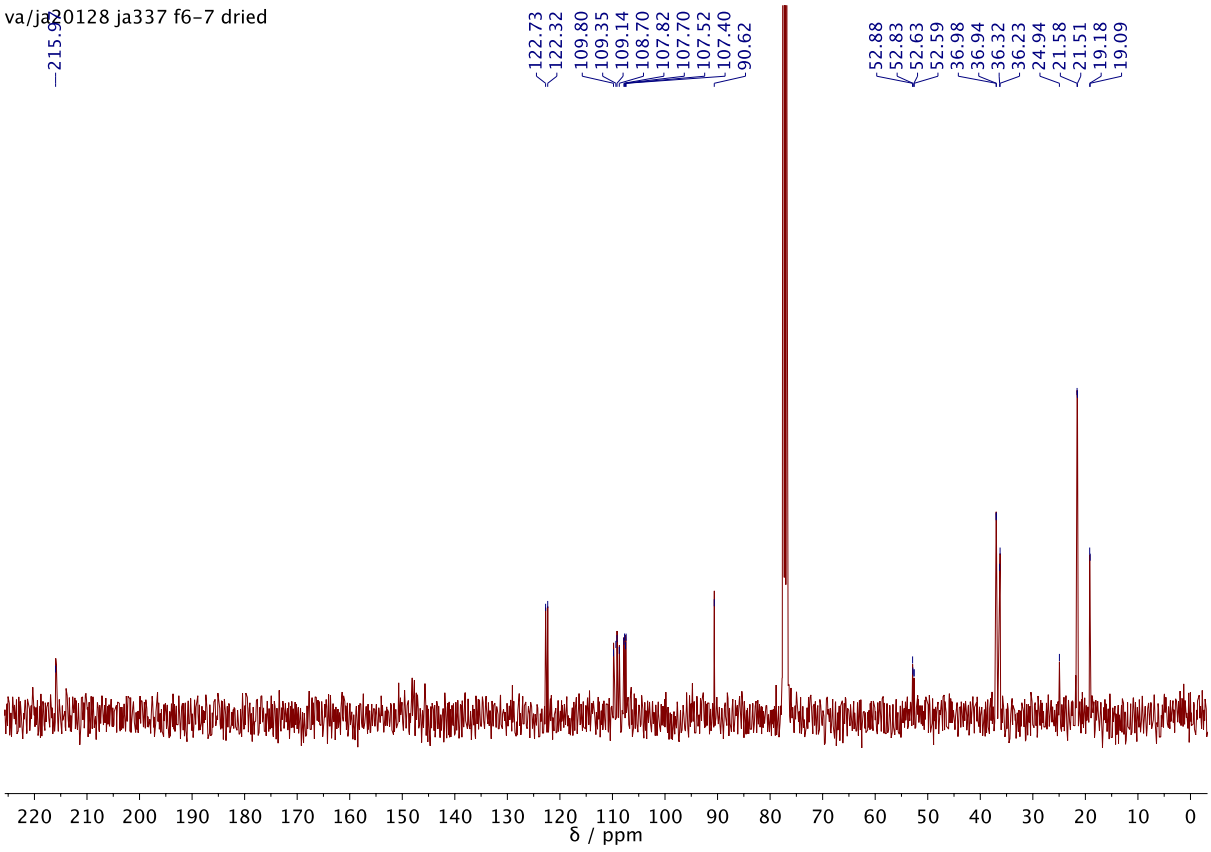
9.3.4.12 Benzyl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519c)





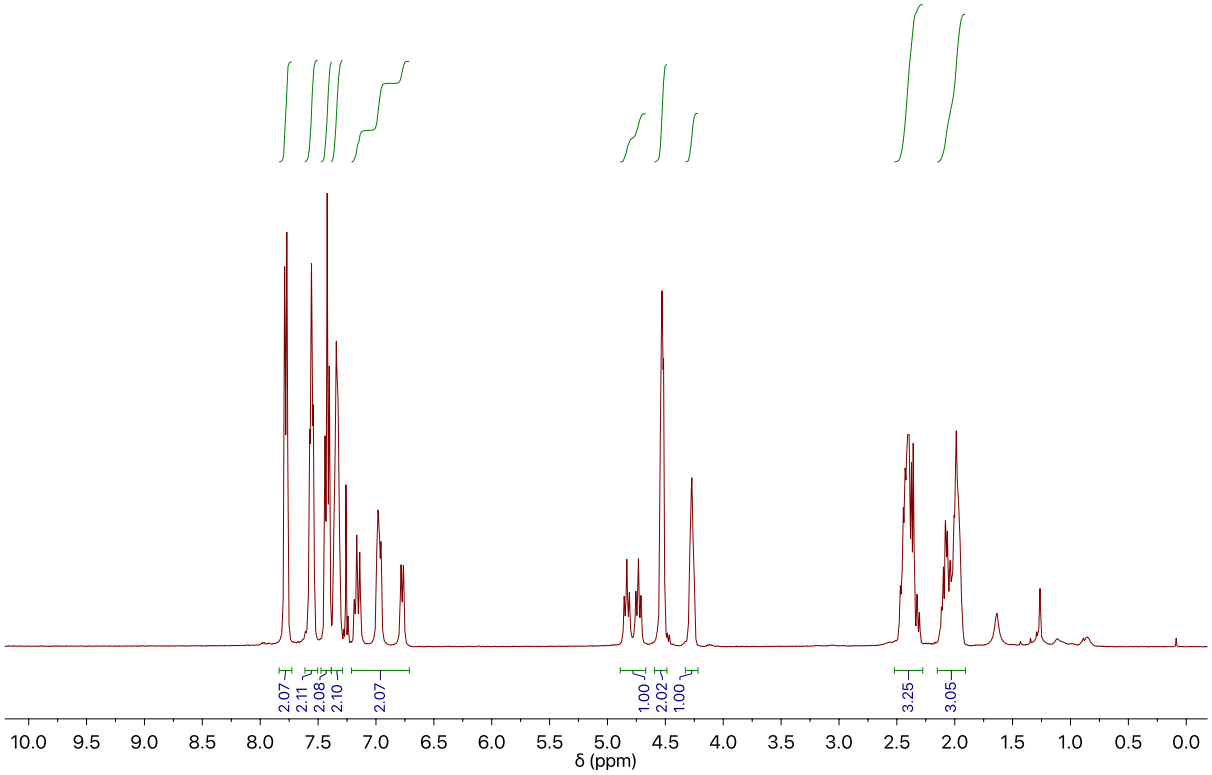
9.3.4.13 1,1,1-Trichloro-2-methylpropan-2-yl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519d)





9.3.4.14 (9*H*-Fluoren-9-yl)methyl (±)-6-fluoro-1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (519e)

va30172/lv LV001_product



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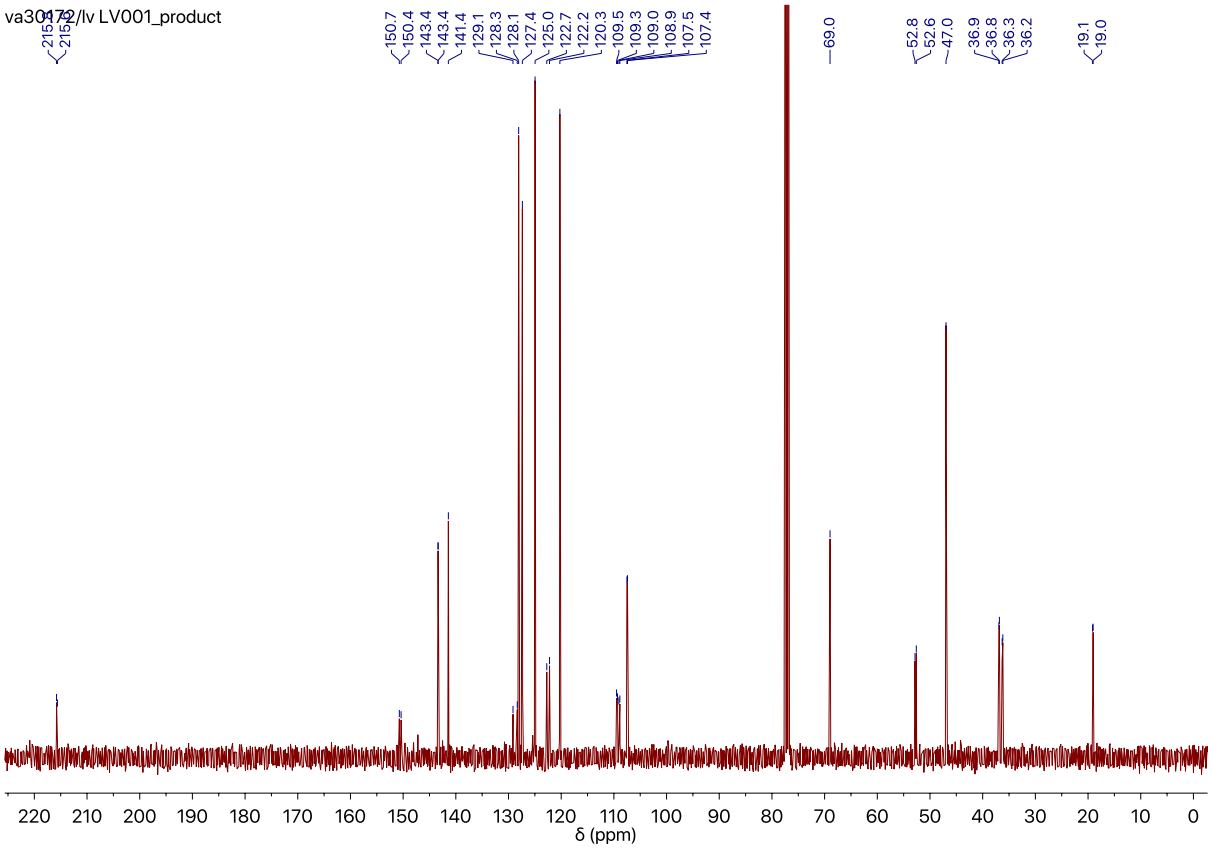
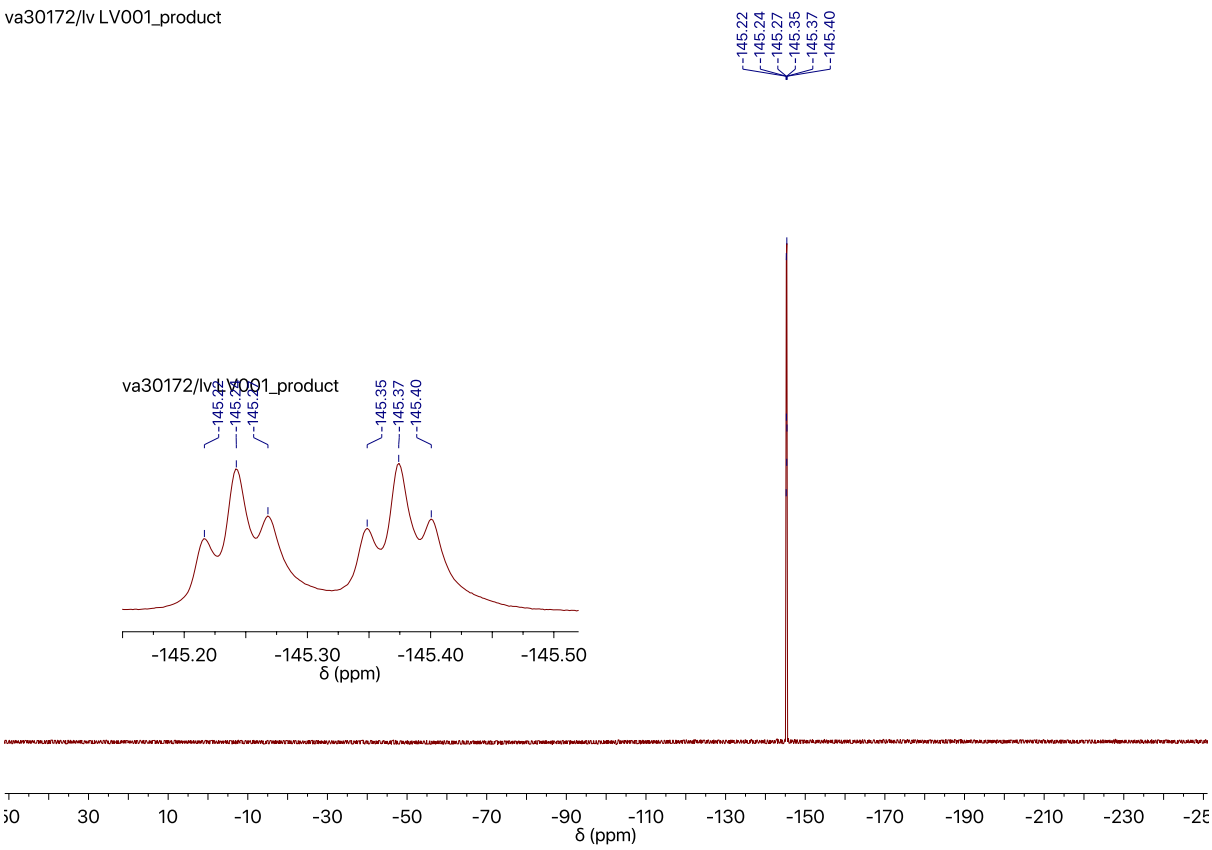
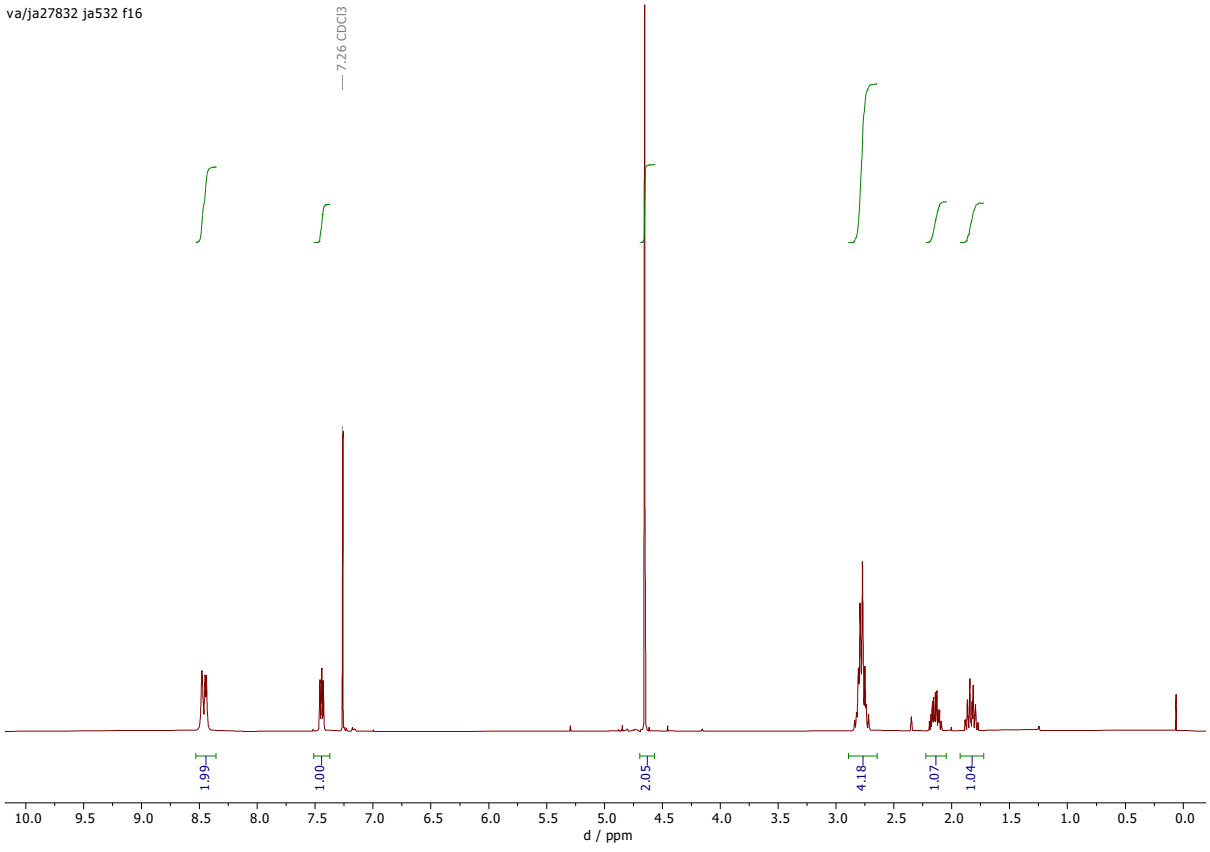
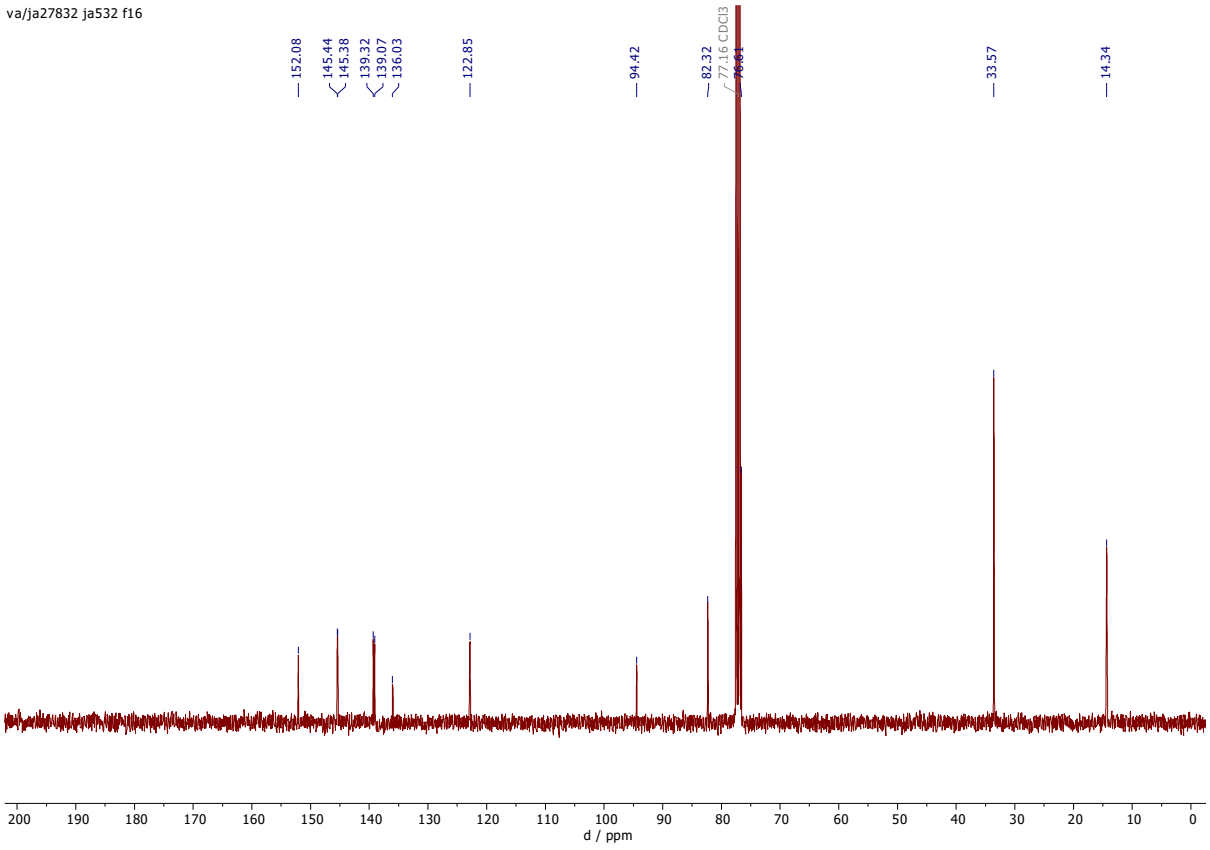




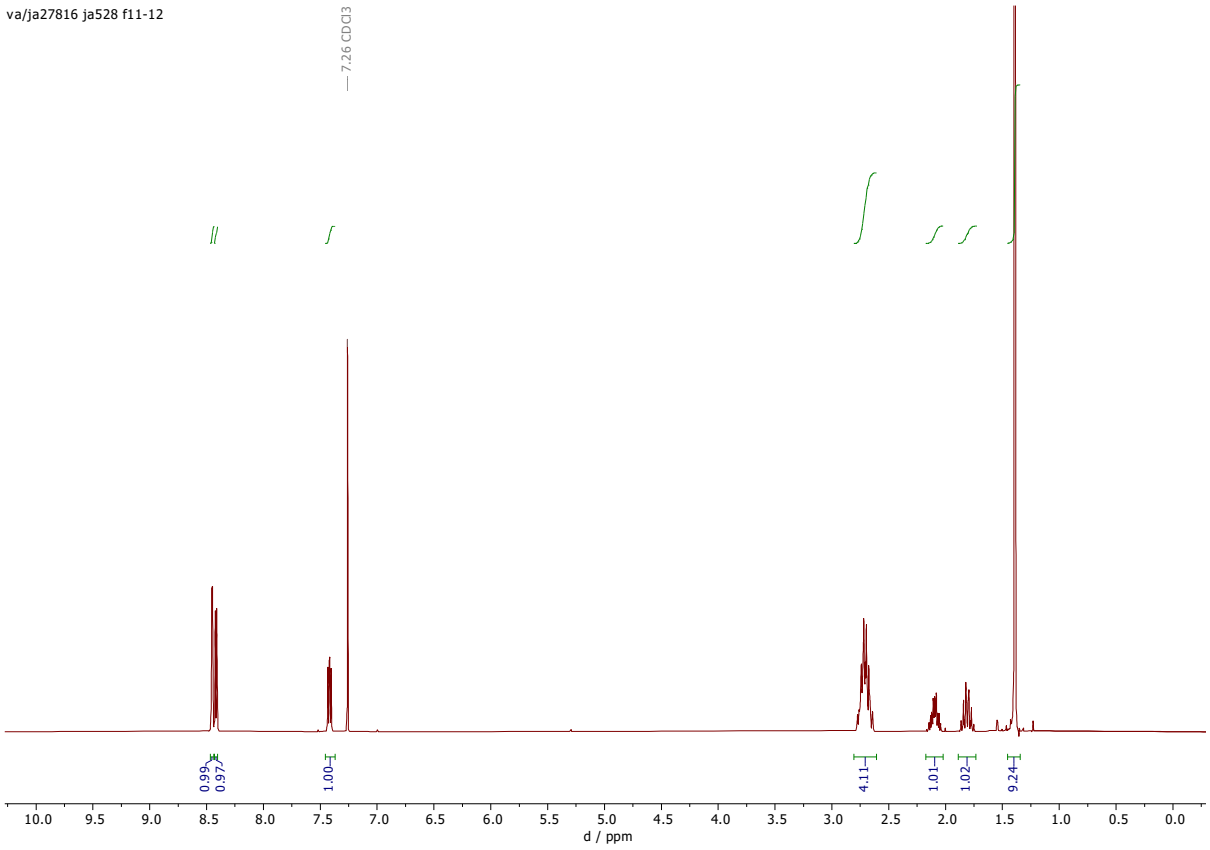
9.3.5 *O*-acylation products

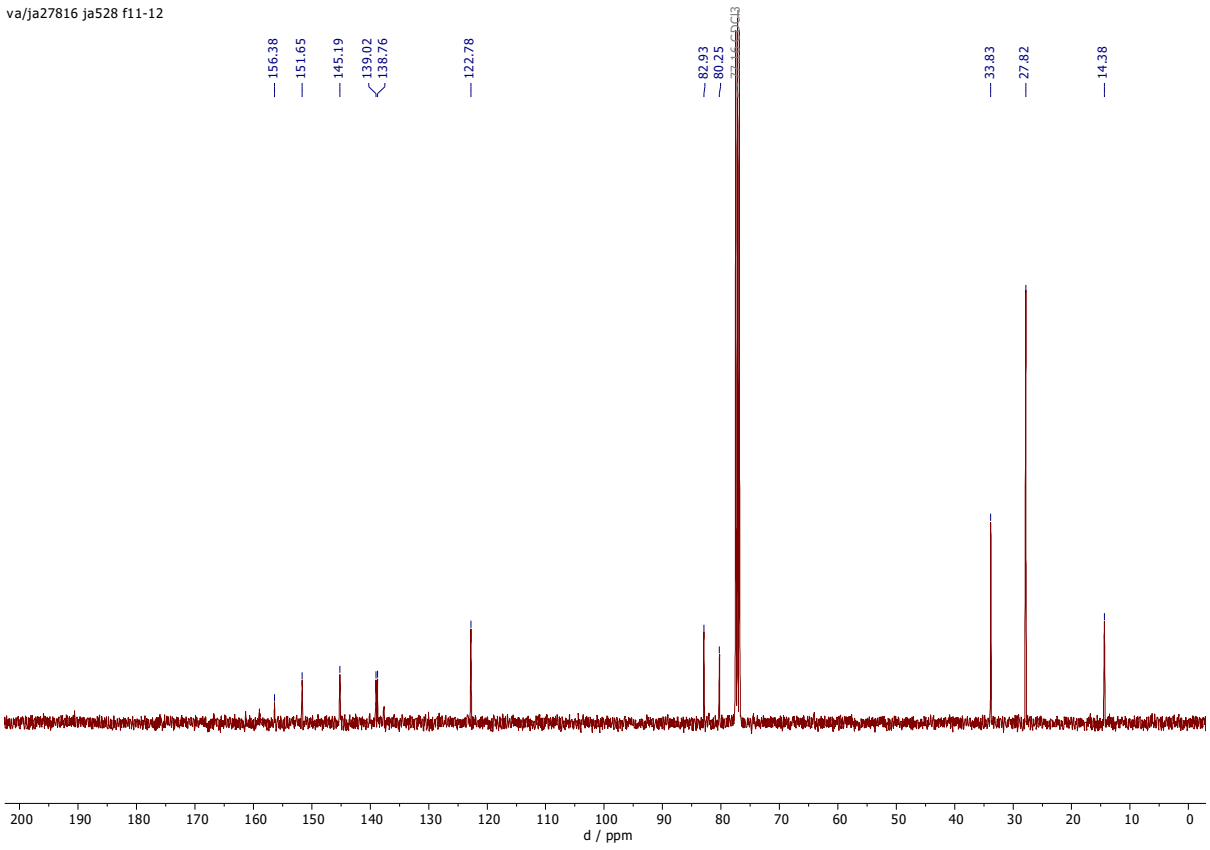
9.3.5.1 1-(3-Fluoropyridin-4-yl)cyclobutyl (2,2,2-trichloroethyl) carbonate (520a)



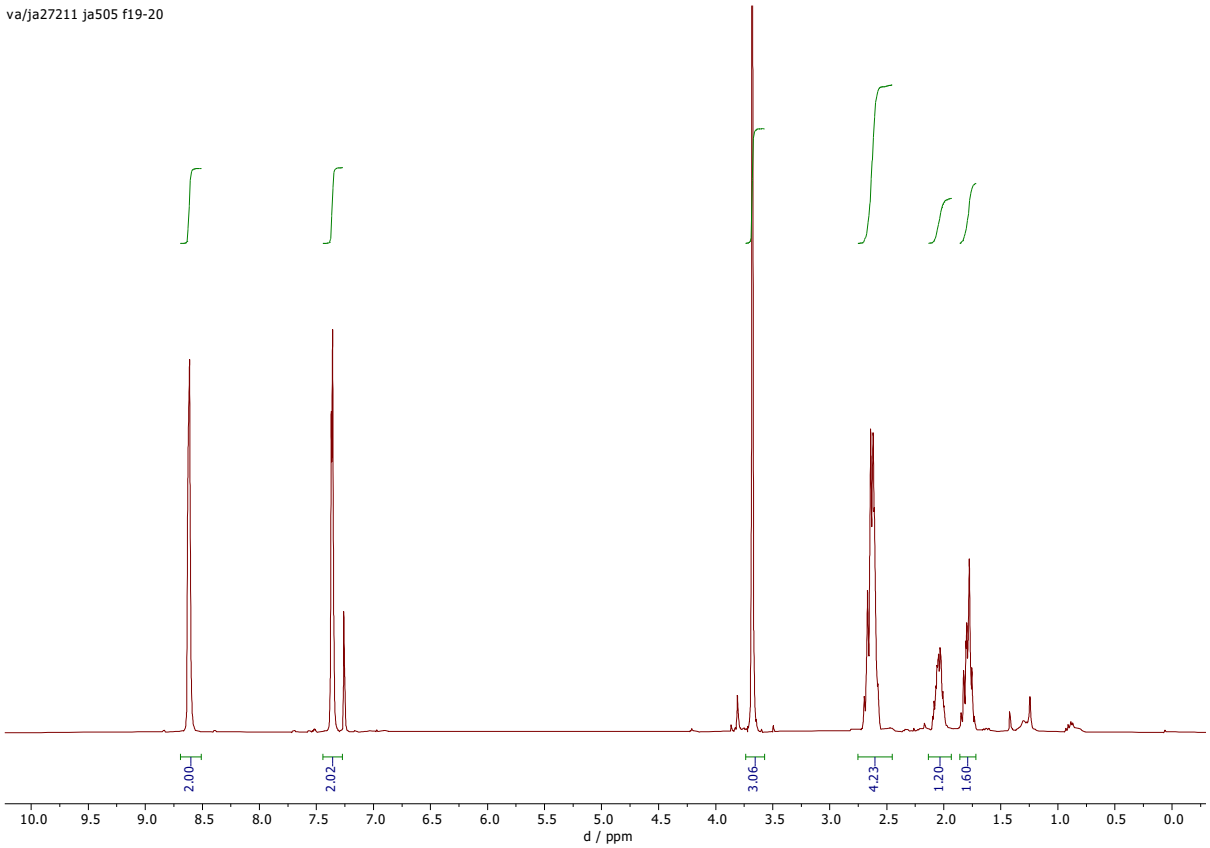


9.3.5.2 *tert*-Butyl (1-(3-fluoropyridin-4-yl)cyclobutyl) carbonate (520g)

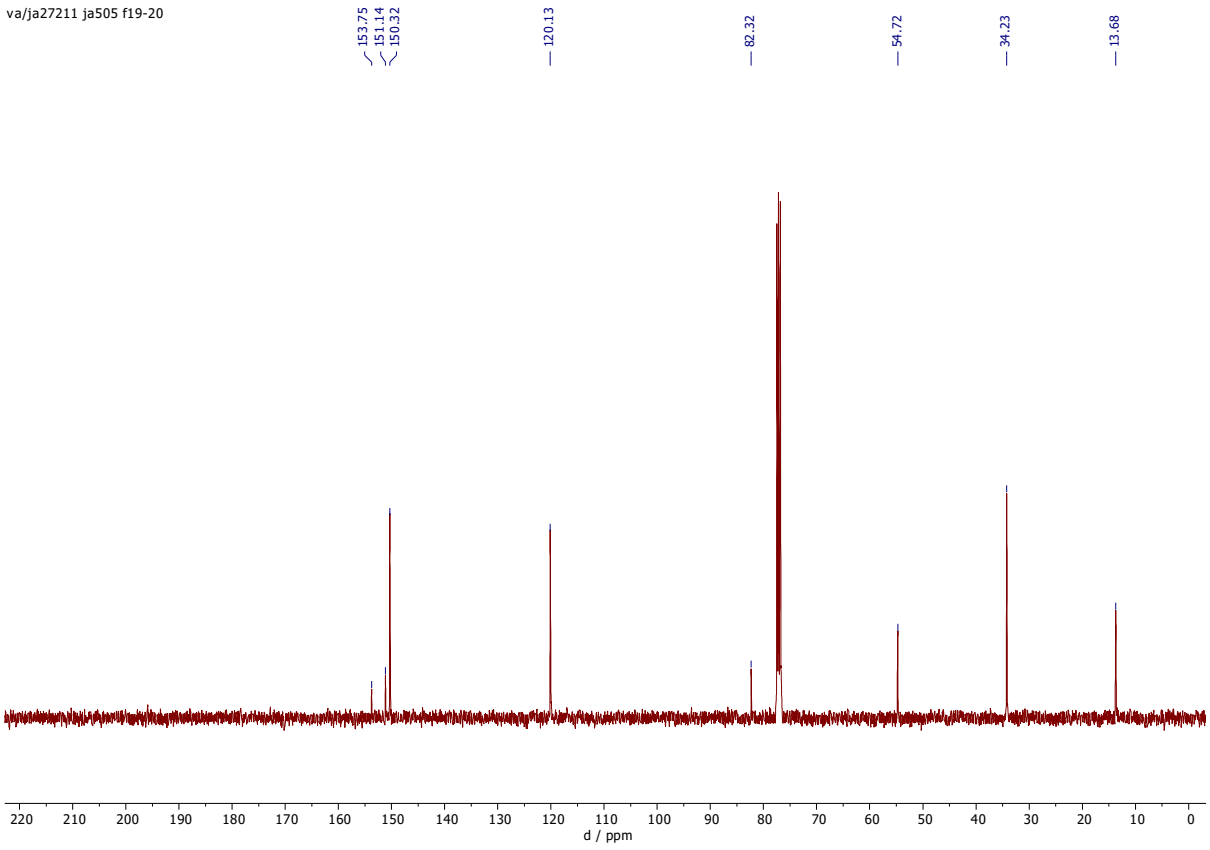




9.3.5.3 1-(Pyridin-4-yl)cyclobutyl (methyl) carbonate (532b)

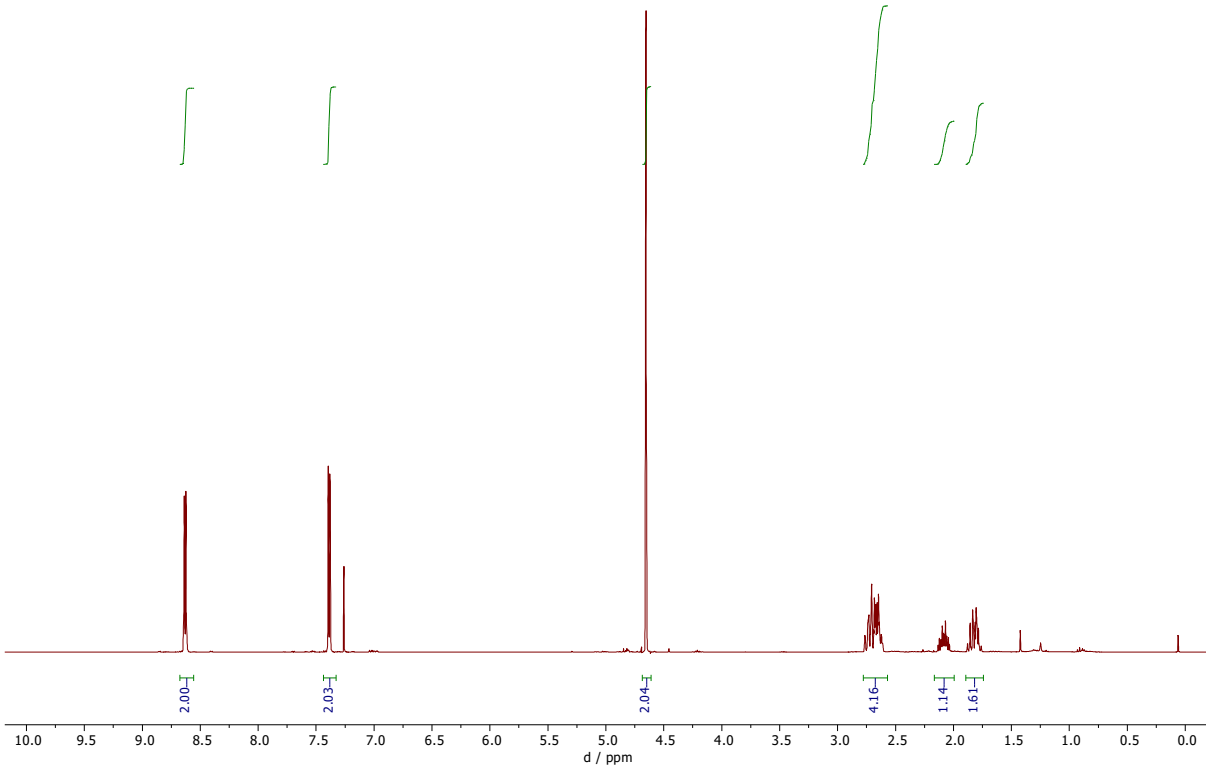


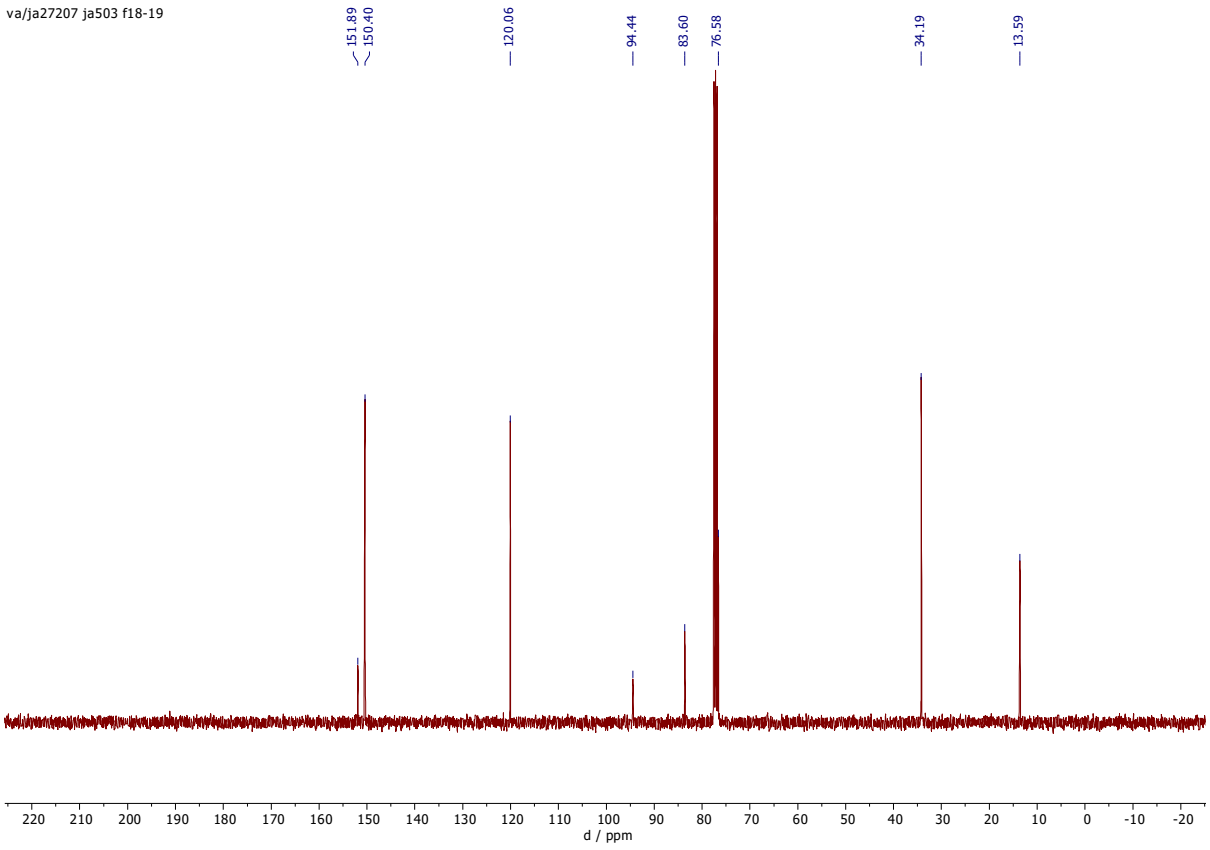
va/ja27211 ja505 f19-20



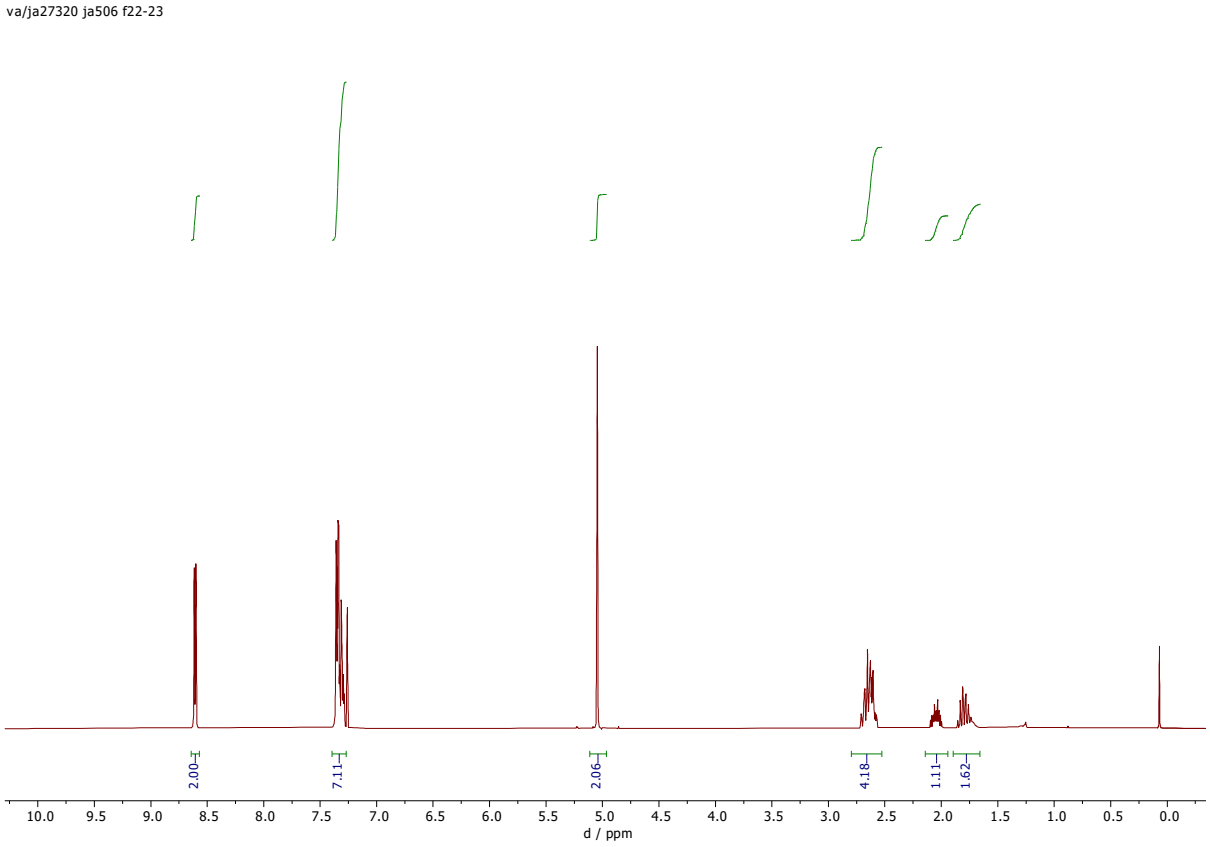
9.3.5.4 1-(Pyridin-4-yl)cyclobutyl (2,2,2-trichloroethyl) carbonate (532c)

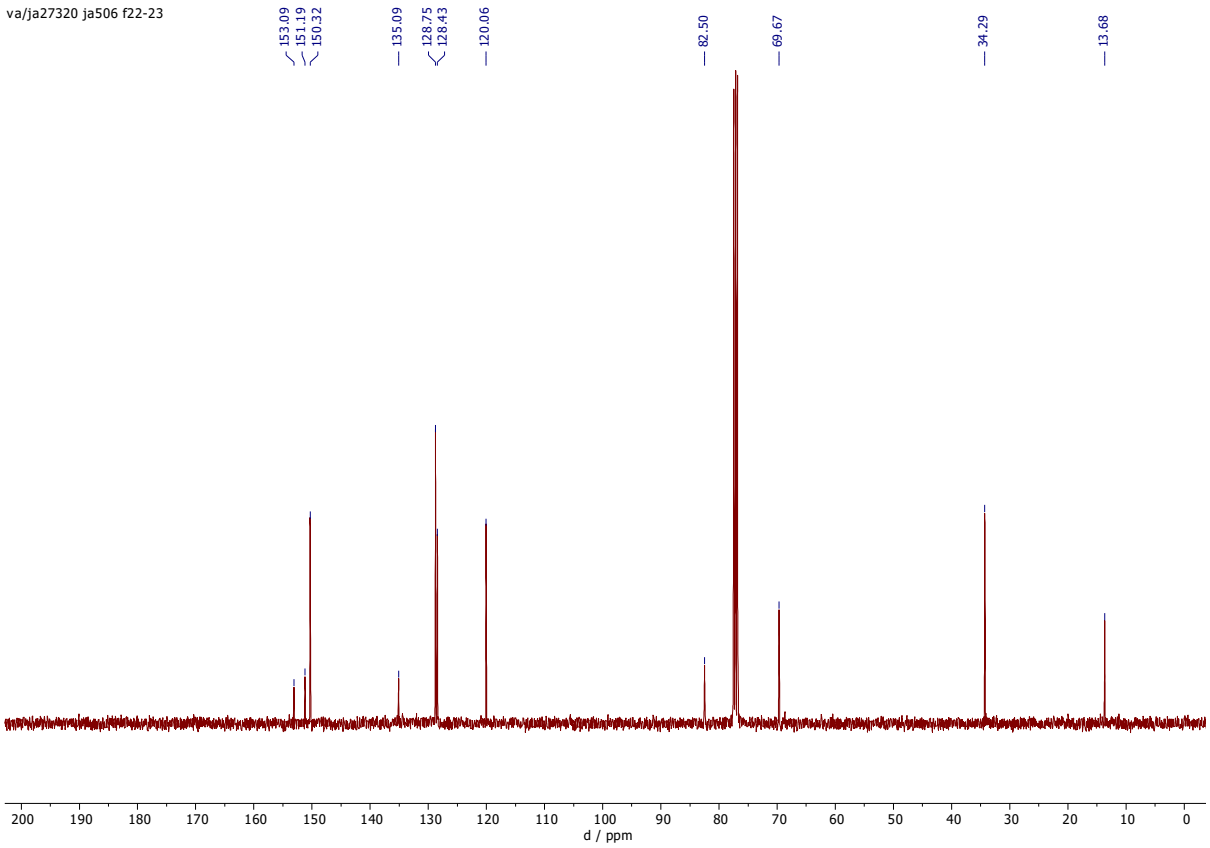
va/ja27207 ja503 f18-19



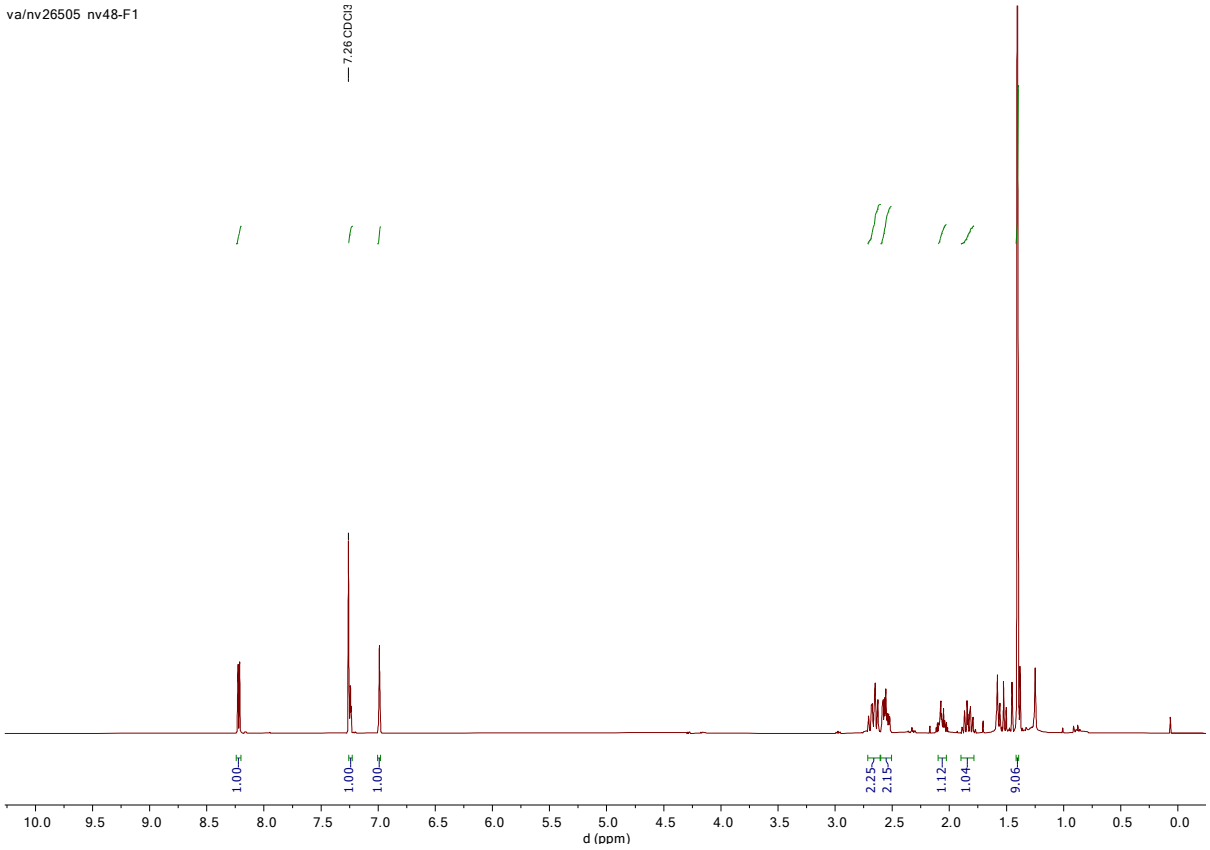


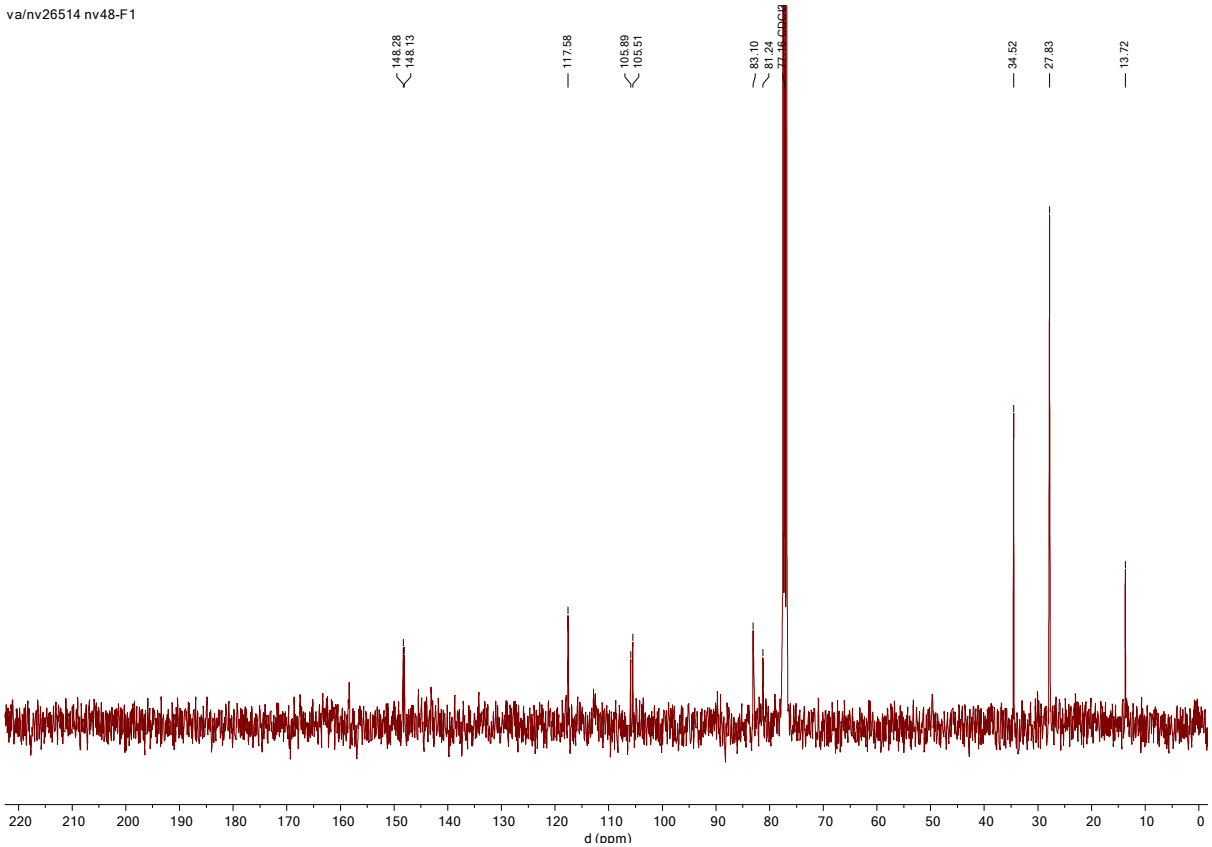
9.3.5.5 Benzyl (1-(pyridin-4-yl)cyclobutyl) carbonate (532e)



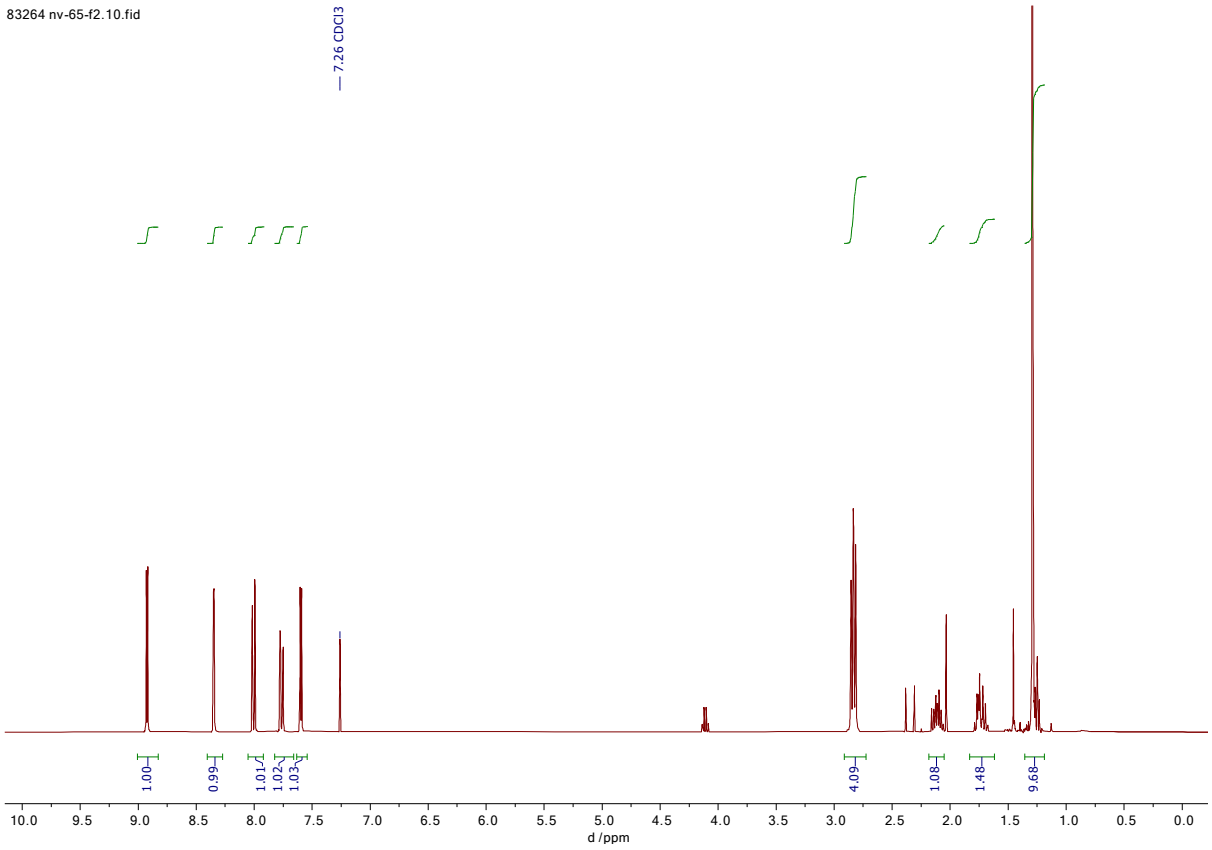


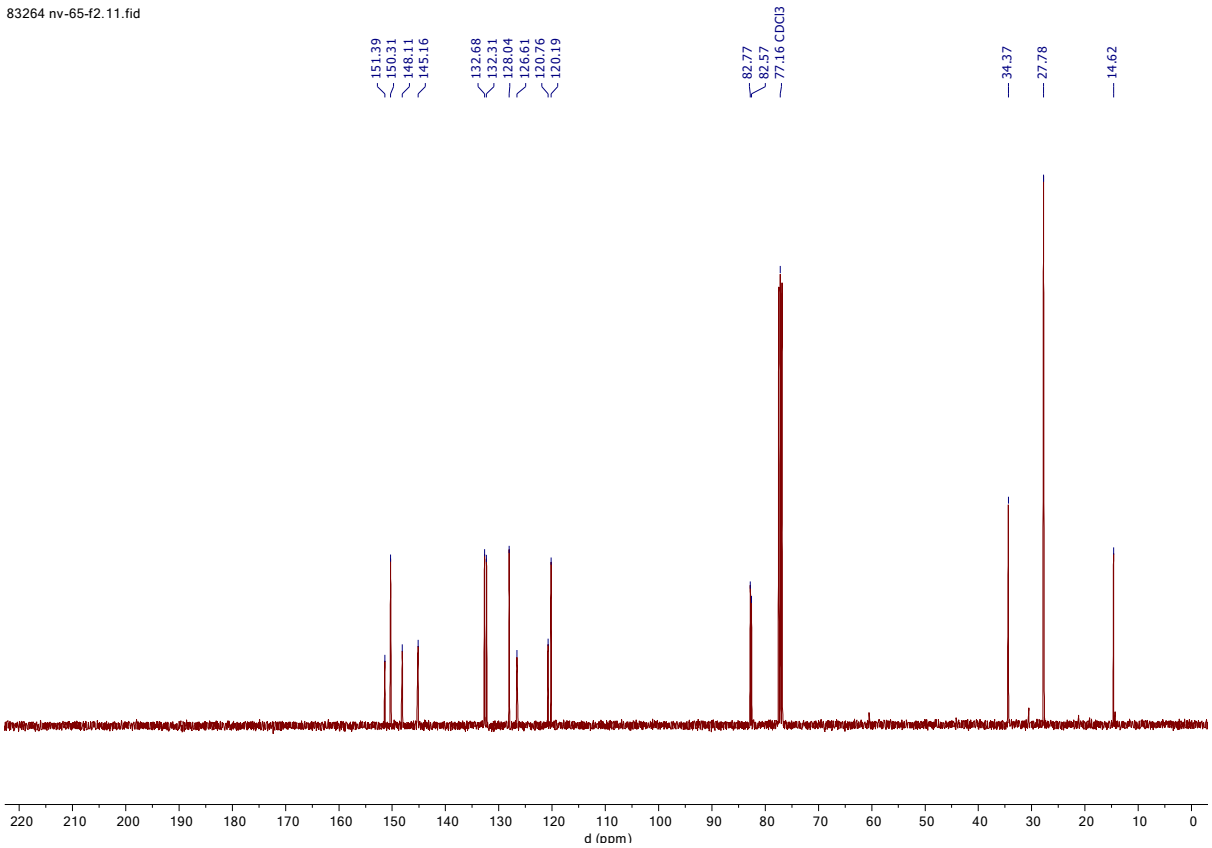
9.3.5.6 *tert*-Butyl (1-(2-fluoropyridin-4-yl)cyclobutyl) carbonate (531n)



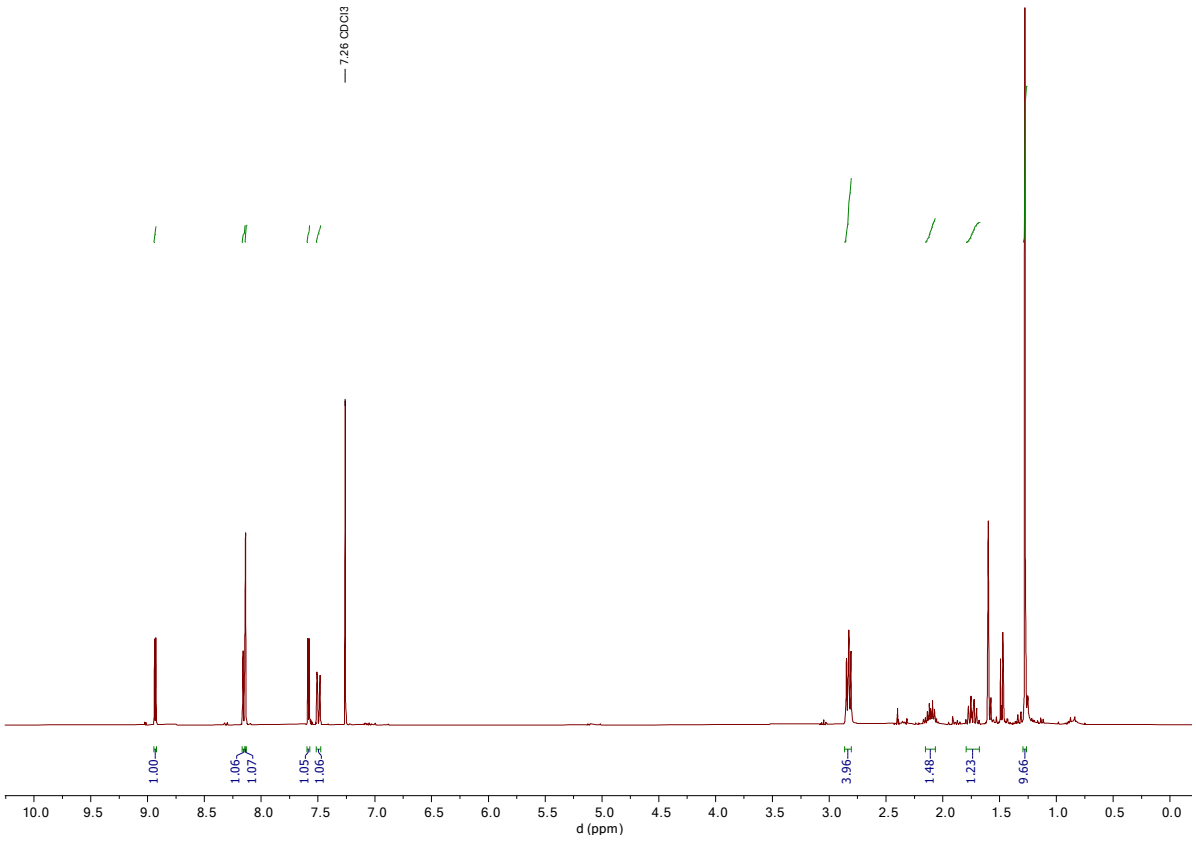


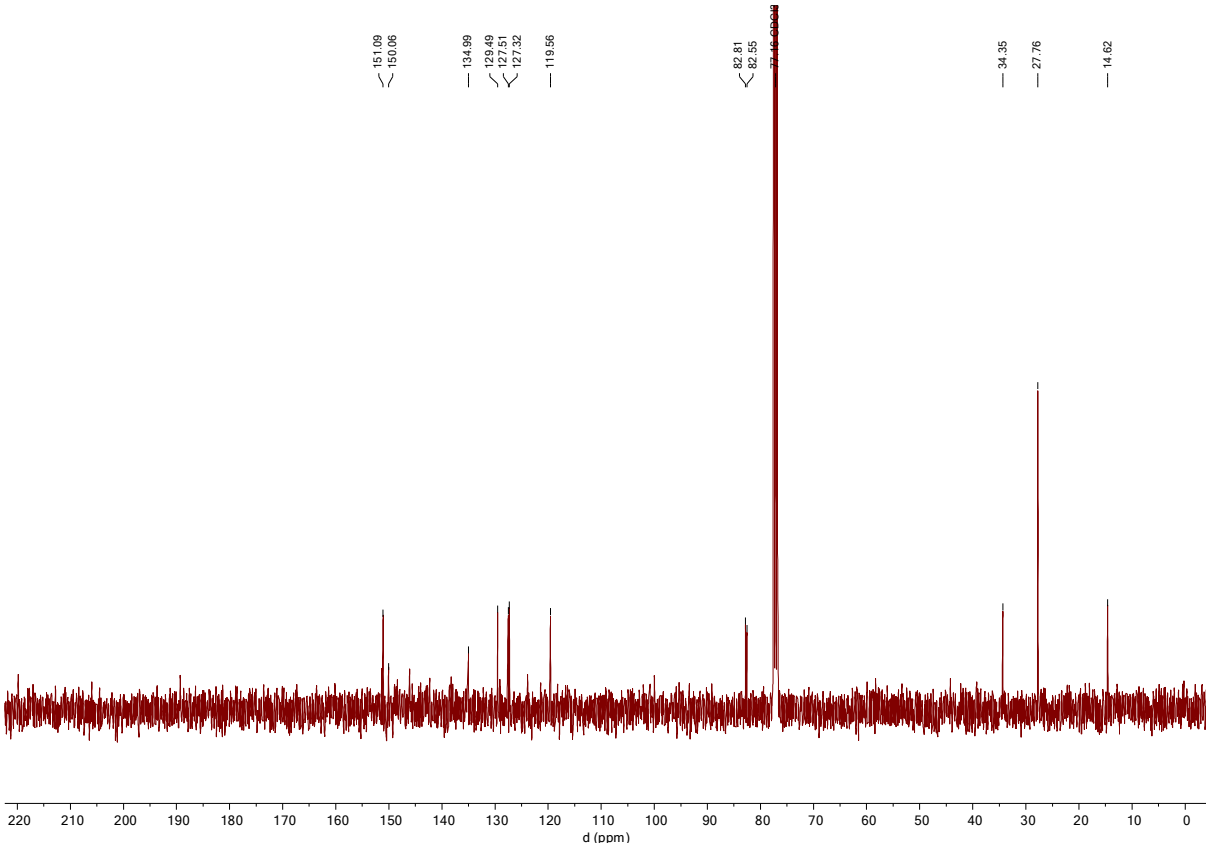
9.3.5.7 1-(6-Bromoquinolin-4-yl)cyclobutyl *tert*-butyl carbonate (531q)





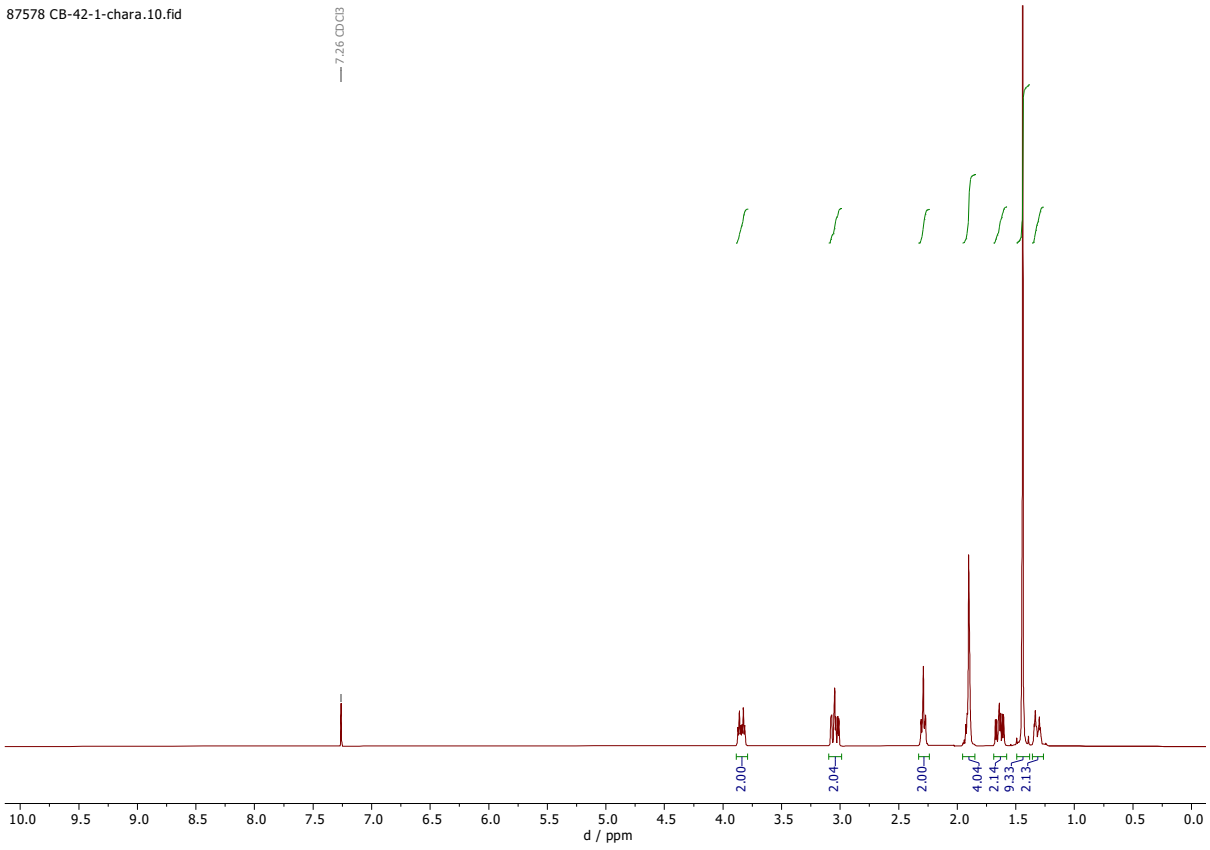
9.3.5.8 *tert*-Butyl (1-(7-chloroquinolin-4-yl)cyclobutyl) carbonate (531m)

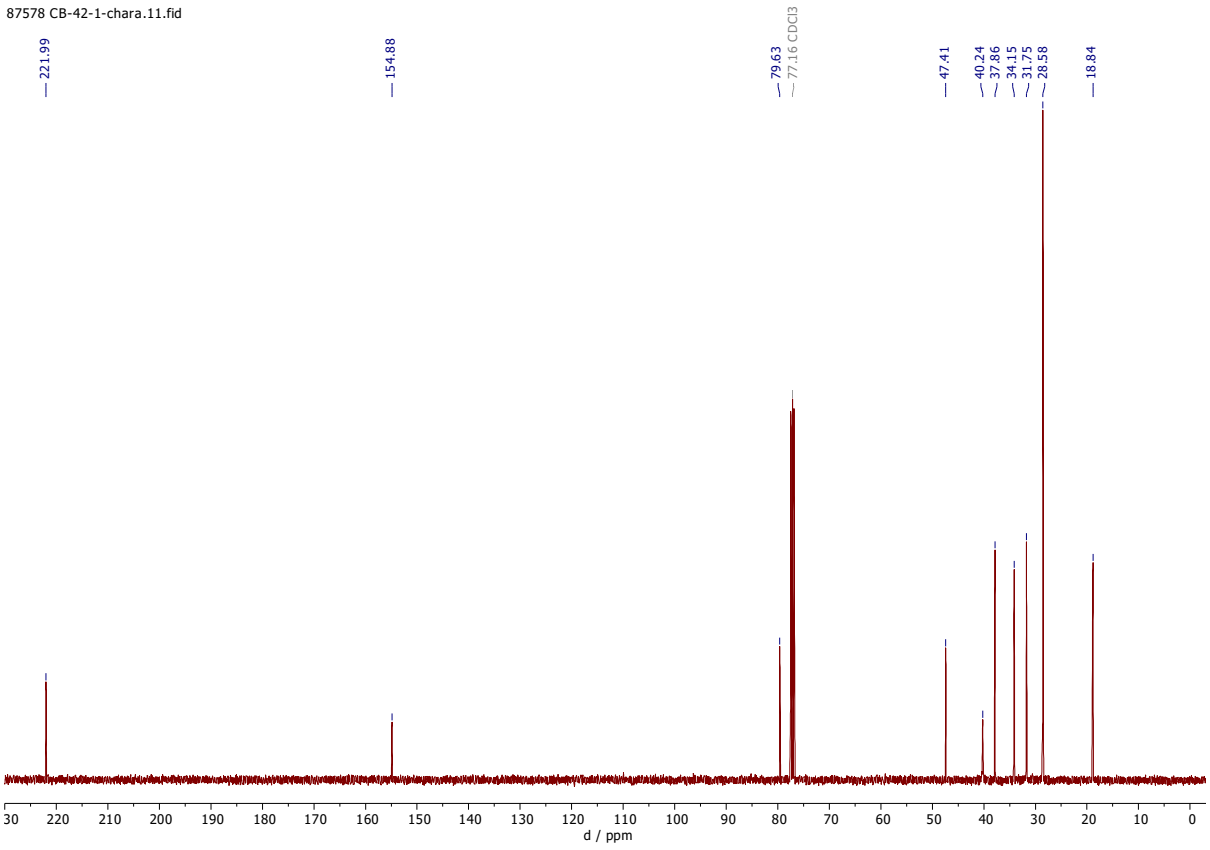




9.3.6 Hydrogenation product

9.3.6.1 *tert*-Butyl 1-oxo-8-azaspiro[4.5]deca-6,9-diene-8-carboxylate (533)

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d / ppm