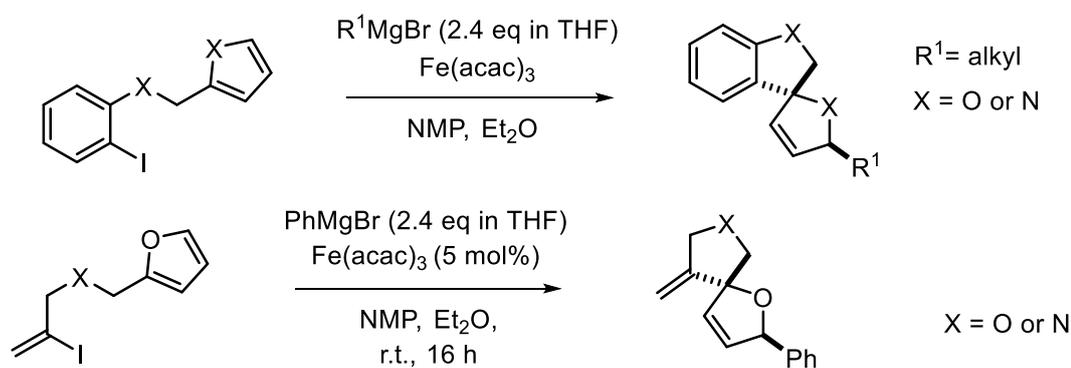


Iron-catalyzed Spirocyclization Project

This thesis is submitted for the degree of Masters by Research in
chemistry.



Weronika Michalska MChem

Supervisors: Professor Joe Sweeney and Anthony Ball PhD

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Center for Global Eco-Innovation

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ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetone
Alk	Alkyl
Ar	Aryl
aq	Aqueous
Bn	Benzyl
^t Bu	<i>tert</i> -Butyl
cod	1,5-Cyclooctadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
dbm	Dibenzoylmethane
DCE	Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DMEDA	1,2-Dimethylethylenediamine
dpm	Dipropylene
dr	Diastereomeric ratio
E _a	Activation energy
EDG	Electron-donating group
ee	Enantiomeric excess
eq	Equivalent
Et	Ethyl
EWG	Electron-withdrawing group
h	Hour

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ⁿ Hex	<i>n</i> -Hexyl
Me	Methyl
min	Minutes
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
PG	Protecting group
ppm	Parts per million
Ph	Phenyl
r.t.	Room temperature
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
Ts	Tosyl

ACKNOWLEDGMENTS

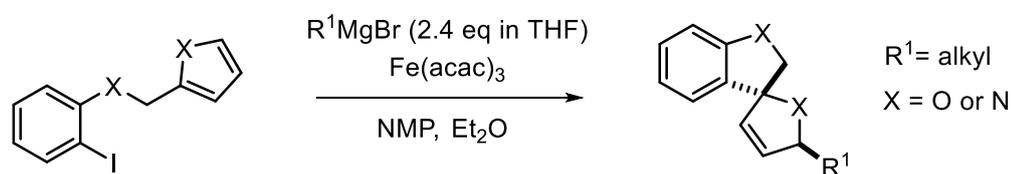
Firstly, I would like to thank Prof. Joe Sweeney for giving me this opportunity and ChiroChem for sponsoring it, especially Dr Ilaria Proietti Silvestri and Dr Paul Colbon. Many thanks to all the people in the Department of Chemistry at Lancaster University, Dr Anthony Ball and Dr Julien Doucet, who helped me with laboratory work, and especially Dr Mike Coogan who always offered his advice and guidance.

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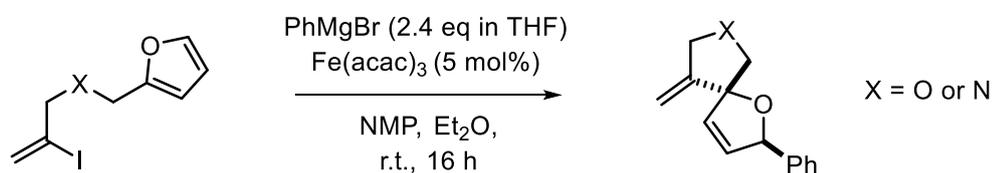
ABSTRACT

This project focuses on iron-catalyzed heterospirocyclization reactions of aryl iodide substrates using Grignard reagents. Specifically, alkyl Grignard reagents were used, in an extension to previous work using aryl Grignard reagents.

The first stage of the project included the formation of heterospirocycles from 2-[(2-iodophenoxy)methyl]-furan (X=O) in the presence of alkyl Grignard reagents. Optimisation of the reaction was not successful, but yielded six novel heterospirocycles in low yield (5-35 %). Next, new amine (X=N) systems were designed to undergo the spirocyclization reaction. However, none of the pathways were successful.



Thirdly, the project included the design and synthesis of novel vinyl iodide reagents. The vinyl iodide reagent underwent the spirocyclization reaction in the presence of phenylmagnesium bromide (PhMgBr) to yield five novel heterospirocycles in 5-50% yield.

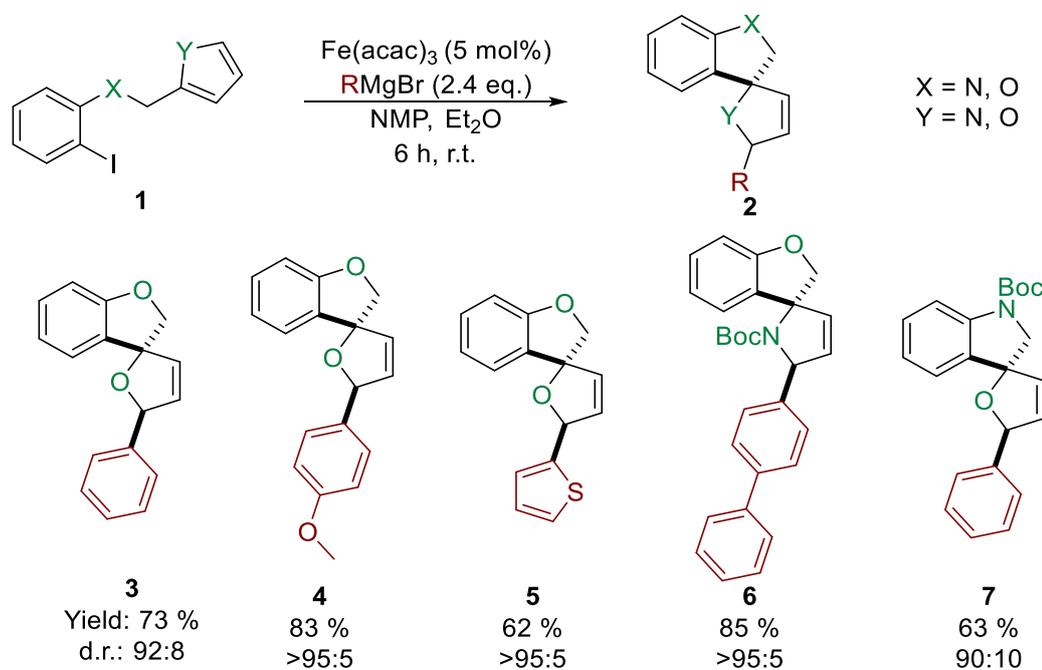


1. LITERATURE REVIEW

1.1 INTRODUCTION

Both industry and academia are interested in the formation of spirocycles. Spirocycles are very interesting structures, containing a quaternary substituted carbon centre and are often chiral. They are found both in pharmaceuticals and natural products^{2,3,4}. This project was funded by ChiroChem, a company based in Liverpool that researches and produces different compounds that can be used as building blocks for the formation of drugs.

The aim of this project is to optimise one spirocyclization methodology that can be used to synthesise a large library of spirocycles containing multiple heteroatoms and comprising different substitution patterns. This research is based on previous work performed within the Sweeney group, in which aromatic Grignard reagents and a cheap iron catalyst were used to form heterospirocycles (Scheme 1)¹. During this project, the spirocyclization reaction will be investigated with different types of Grignard reagents, and with different precursors, for the formation of many different types of heterospirocycles. The precursors will involve substituted amines, ethers, as well as vinyl iodides, which will increase the library of possible heterospirocycles.



Scheme 1: Previous work performed by the Sweeney group with examples of heterospirocycles formed.

1.2 CATALYSIS

Catalysis is a chemical process that increases the rate of a reaction. The catalyst is not consumed during the reaction, so it can be recovered and reused. Catalysts lower the activation energy of a reaction; this can be achieved by formation of (a) new transition state(s) (Figure 1). Catalytic reactions are often quicker and can take place under milder conditions compared to non-catalytic reactions. Catalysis is often used in many chemical processes to reduce the cost, time and energy needed for the reaction to take place. Industry uses catalysis for many processes; some of the best known ones are formation of ammonia with iron (Haber process), or catalytic cracking of gas oil to form fuel oil, petrol, ethane etc. In 2014, it was estimated that US \$ 33.5 billion was spent on catalysts (Global Catalyst Market, 2015).

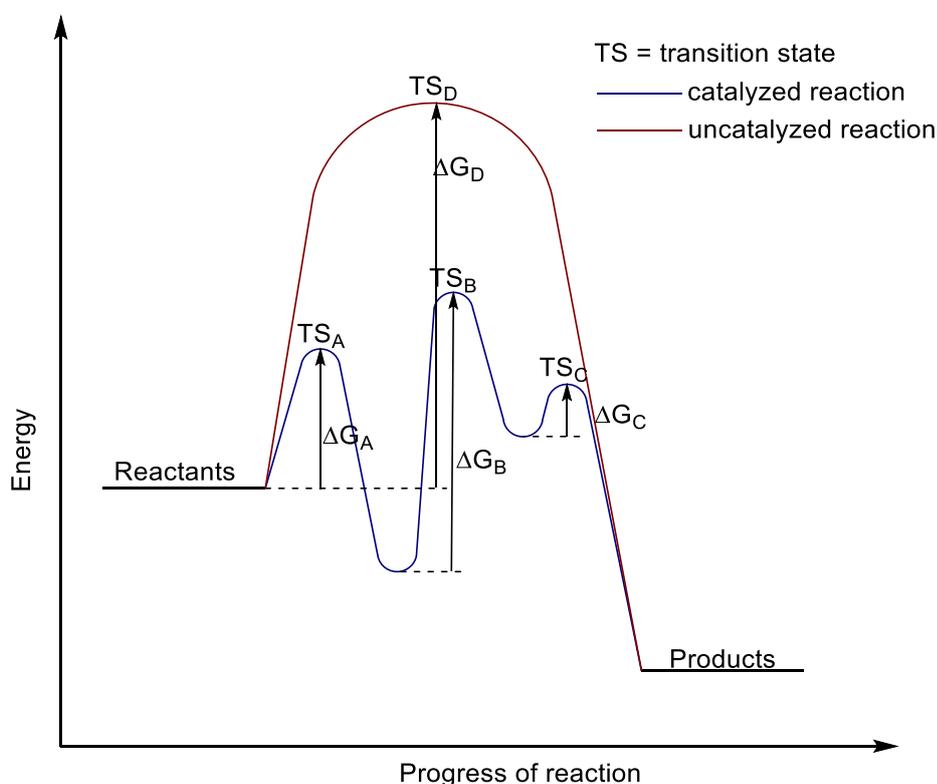


Figure 1: Gibbs energy profile.

1.3 GRIGNARD REAGENTS

Grignard reagents are one of the best known reagents in chemistry and were first reported in 1900⁵ by François Auguste Victor Grignard, who in 1912 won a Nobel Prize. The generic formula is R-Mg-X, where X is a halogen and R is an organic group. A Grignard reagent is a simple way of introducing an R group into a molecule, and is formed by reacting an organic halide with magnesium metal. Pure Grignard reagents are solids and are very

reactive, however often they are synthesised and used in solution, with the concentration of these solutions determined by titration.

The Schlenk equilibrium (Equation 1) is a chemical equilibrium which takes place in a solution of Grignard reagents and Hauser bases (also called magnesium amide bases). The position of the equilibrium can be influenced by various factors, including solvent and temperature. It is known that THF and diethyl ether often coordinate to RMgX. The equilibrium can often stabilise the various mono- and dinuclear Mg complexes present in the reaction⁶.

Equation 1: Schlenk equilibrium.



1.4 IRON

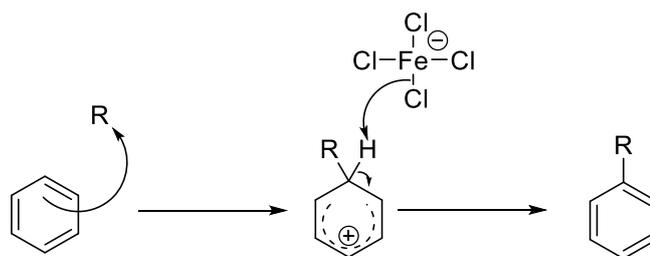
1.4.1 Properties and general uses

Iron is one of the most common elements on Earth⁷. It is a transition metal, located in group 8 of the periodic table between manganese and cobalt. Iron is one of the most used metals in the world, which is due to excellent properties: iron is soft, malleable, ductile and strong. Most of its forms are generally not dangerous to the environment, with the exception of a few iron compounds that can be harmful; for example, iron(III)-O-arsenite ($\text{As}_2\text{Fe}_2\text{O}_6 \cdot \text{Fe}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$) forms iron and arsenic fumes on heating⁸.

Iron's oxidation states range from -2 to +7, all of which have a wide range of use in different reactions, from the Haber process to substitution⁹, isomerisation¹⁰ and rearrangement¹¹ reactions. The most common are bivalent and trivalent iron compounds, however the other oxidation states can also be used, for example Collman's reagent ($\text{Na}_2[\text{Fe}(\text{CO})_4]$), in which iron (-2) is used as solvate (e.g. with THF) to synthesise aldehydes¹². Iron will also react with oxygen in the air to form many forms of oxides (eg. rust) and other hydroxide compounds.

1.4.2 History of iron catalysis

Iron-catalyzed Friedel-Crafts alkylation is one of the oldest known iron-catalyzed reactions. The reaction was developed in 1877 and uses FeCl_3 or AlCl_3 ¹³. In this reaction, the substitution happens at the sp^3 carbon centre,¹⁴ which is very common for iron-catalyzed reactions.



Scheme 2: General mechanism for the Friedel-Crafts alkylation.

It was not until relatively recently that the field of iron catalysis expanded. From 2004, there was significant progress and research about iron-catalyzed cross-coupling reactions (Figure 2)¹⁵.

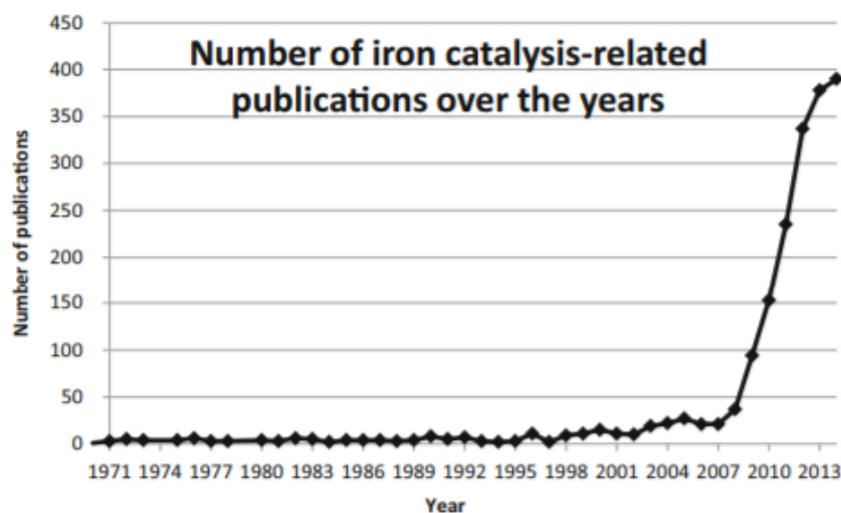


Figure 2: Publication activity in iron catalysis over the years (Graph copied from Iron Catalysis II).

1.5 METAL-CATALYZED CROSS-COUPLING REACTIONS

Transition metals are most often used in cross-coupling reactions. One of the first cross-coupling reactions reported was the Glaser reaction in 1869¹⁶, which used a copper catalyst to form a C-C bond between two alkynes. Following this, more reactions were discovered using transition metal catalysts, the best known being the Suzuki, Sonogashira and Tsuji-Trost reactions. All of these reactions use one of the most commonly used transition metal used in catalysts – palladium. These palladium-catalyzed reactions are well understood, with the mechanism including oxidative addition, reductive elimination, transmetalation and in some cases beta-hydride elimination (Figure 3)¹⁷.

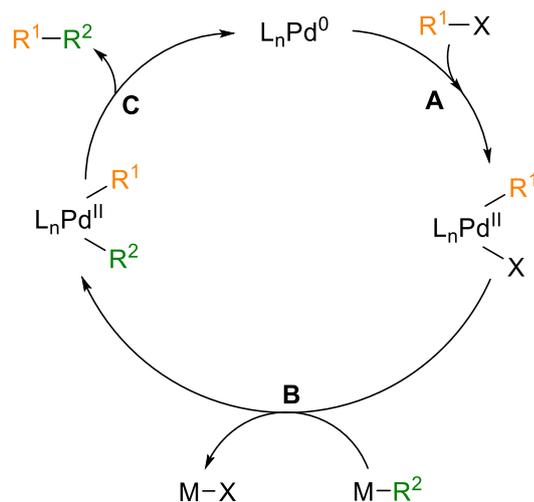
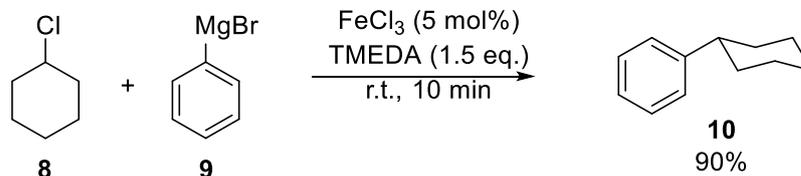


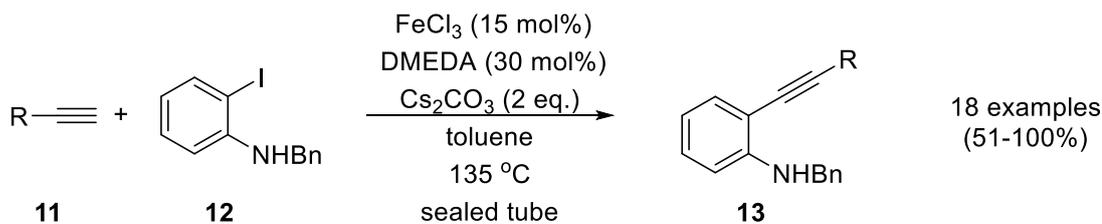
Figure 3: Catalytic cycle for palladium-catalyzed cross-coupling of organohalides with organometallic reagents; A = oxidative addition, B = transmetalation, C = reductive elimination.

One of the cross-coupling reactions that uses iron as its transition metal is the Kumada-Corriu reaction. In this reaction, primary and secondary alkyl halides are coupled with Grignard reagents (Scheme 3).¹⁸ Tetramethylethylenediamine (TMEDA) is a vital part of this reaction as it suppresses the undesirable formation of the olefin, which forms by the loss of the hydrogen chloride from the halide substrate (**8**).



Scheme 3: Iron-catalyzed cross-coupling reaction of primary and secondary alkyl halide with a Grignard reagent in the presence of TMEDA.

The Sonogashira coupling traditionally uses a palladium catalyst with a copper co-catalyst. However, the reaction has been reported to work using other catalytic systems involving an iron catalyst¹⁹. Bolm and co-workers reported reactions between terminal alkynes and aryl and heteroaryl iodides in the presence of iron(III) chloride and using 1,2-dimethylethylenediamine (DMEDA) as a ligand to give good to quantitative yields of cross-coupled products (Scheme 4)¹⁹.

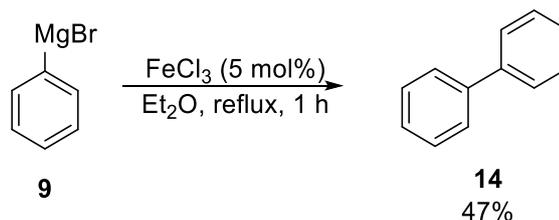


Scheme 4: Sonogashira coupling by Bolm and co-workers.

Around the same time, a ligand-free iron-copper version the Sonogashira reaction was investigated by Liu and co-workers. In that case iron(III) acetate ($\text{Fe}(\text{acac})_3$) was used with CuI or Fe_2O_3 with $\text{Cu}(\text{acac})_2$. Those two methods successfully formed aliphatic alkynes as well as alkynylated arenes and heteroarenes, all in high yields²⁰.

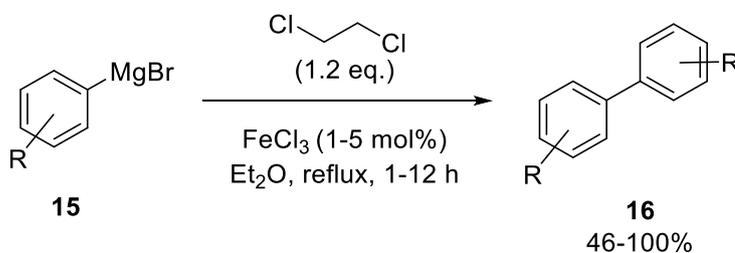
1.5.1 Iron-catalyzed homocoupling reactions of Grignard reagents

The first iron-catalyzed homocoupling reaction was published in 1941 by Kharasch and Fields²¹. In the reaction, a phenylmagnesium bromide can homocouple to itself, using a catalytic amount of iron(III) chloride (Scheme 5).



Scheme 5: Iron(III) chloride catalyzed homocoupling of phenylmagnesium bromide (12) to give biphenyl (13).

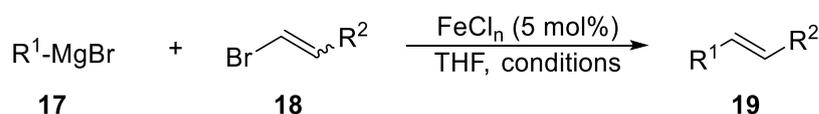
It took many years for this work to be expanded; in 2005 Nagano and Hayashi²² published their results for the reaction of iron(III) chloride with arylmagnesium bromide reagents, in the presence of 1,2-dichloroethane as an oxidant (Scheme 6).



Scheme 6: Reaction of FeCl_3 with arylmagnesium bromides reagents, using 1,2-dichloroethane as oxidant.

1.5.2 Iron-catalyzed cross coupling reactions with Grignard reagents

After the initial reports from Kharasch and Fields, Vavon and colleagues demonstrated an example of iron-catalyzed cross-coupling with alkylmagnesium bromide reagents and benzylbromide in 1945²³. Around the same time Cook and co-workers²⁴ extended the scope of the electrophile coupling partners to acetyl chloride. In 1971, Kochi and Tamura²⁵ reported stereoselective cross-coupling of alkenyl bromides with alkylmagnesium bromide reagents. They used both iron(II) and (III) chloride salts, which delivered high catalytic activity. The time of the reactions varied depending on the substrates used. For example, (*E*)-but-2-ene was formed in 89% yield in 45 minutes while (*Z*)-but-2-ene took 12h) (Table 1; Entry 1 and 2). Another limitation of this reaction was the necessary use of excess alkenyl electrophiles to combat homocoupling.

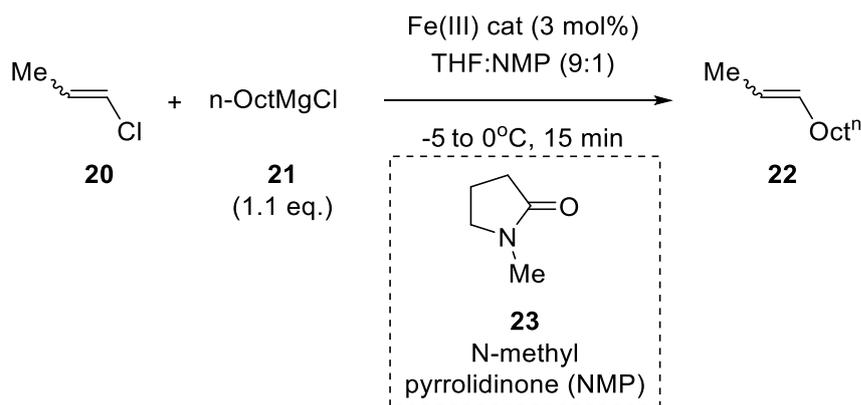


Entry	R ¹ MgBr (eq.)	Br-CH=CH-R ² (eq.)	Time (h)	T (°C)	Product	Isolated yield (%)
1	CH ₃ MgBr (1.0)	<i>trans</i> -CH ₃ CH=CHBr (3.0)	0.75	2	(<i>E</i>)-but-2-ene	89
2	CH ₃ MgBr (1.0)	<i>cis</i> -CH ₃ CH=CHBr (3.0)	12	2	(<i>Z</i>)-but-2-ene	71
3	CH ₃ (CH ₂) ₅ MgBr (1.0)	CH ₂ =CHBr (5.1)	4	0	Oct-1-ene	83

Table 1: Kochi and Tamura's reaction conditions and substrate scope.

In 1982 the scope of this reaction was expanded by Julia and co-workers²⁶, who used Fe(acac)₃ to cross-couple phenylmagnesium bromide with vinylic sulfones. Despite expansion of the field, these methods could not compete with cross-coupling reactions that used other catalysts such as palladium and nickel, which gave a higher stereo- and chemoselectivity. Lower yields were observed due to formation of the non-desired reductive dehalogenated starting material and homocoupled Grignard by-products.

Cahiez in 1998²⁷ reported using an additive in the reaction to improve stereoselective product formation. He used a mixture of THF and NMP (**23**) to form substituted olefin (**20**) in good to excellent yields and with exceptional stereoselectivity (>99.5% *de*) (Scheme 7). Different iron(III) salts were investigated, giving very similar yields (Table 2, Entry 1-4) with the exception of Fe₂(SO₄)₃, which isn't soluble in ethereal solvents (Table 2, entry 5).

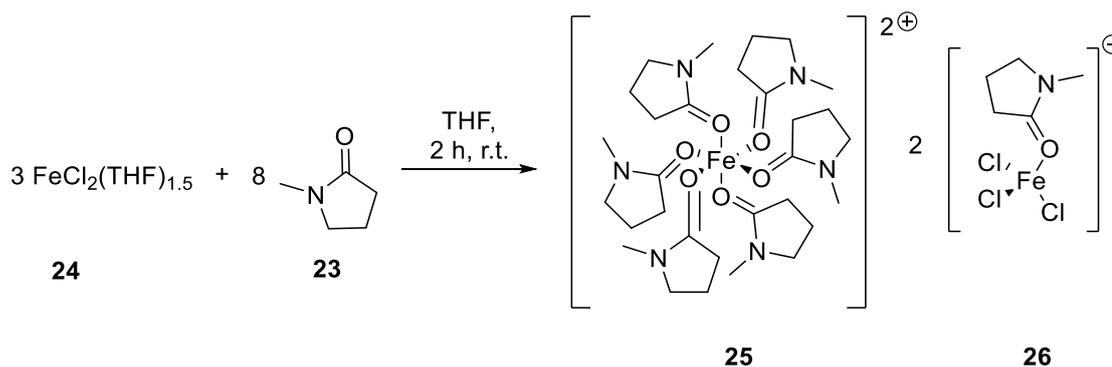


Scheme 7: Formation of substituted olefin by Cabiez, with the use of a mixture of THF and NMP (23).

Entry	Catalyst	Yield (%)
1	Fe(acac) ₃	87
2	Fe(dbm) ₃	87
3	Fe(dpm) ₃	88
4	FeCl ₃	88
5	Fe ₂ (SO ₄) ₃	31

Table 2: Effect of the precatalytic iron(III) salt on final isolated yield of substituted olefin.

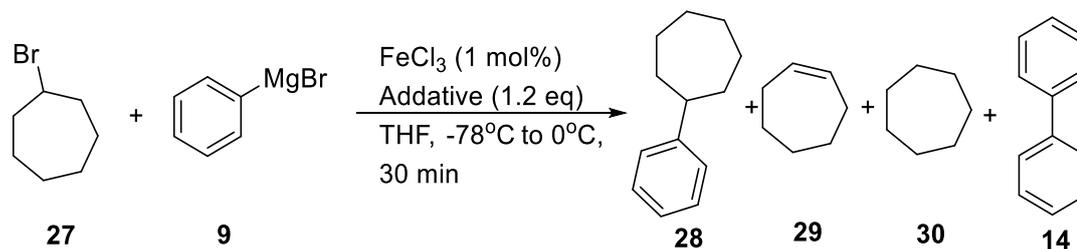
NMP was further confirmed to have a positive role in iron-catalyzed cross-coupling reactions by Holland and co-workers²⁸. They managed to isolate iron(II)-NMP species (**25** and **26**) (Scheme 8). This has led to the addition of NMP (**23**) in multiple cross-coupling reactions.



Scheme 8: Formation of an NMP-coordinated, Fe(II) iron pair.

Nakamura measured the effect of additives on a cross-coupling of primary and secondary alkyl halides with arylmagnesium bromides.²⁹ The idea was to minimise the non-desired β -hydride elimination process. NEt₃, for example, decreased the yield to 3% when added (Table 3; Entry 2) compared to when the reaction had no additive (Table 3; Entry 1). TMEDA was shown to suppress the β -hydride elimination based on the product

distribution with the desired product formed in much greater yield compared to the other additives used (Table 3, Entry 6).



Entry	Additive	Yield (%)				
		28	29	30	14	27
1	None	5	79	0	4	6
2	NEt ₃	3	78	0	11	5
3	N-Methylmorpholine	8	72	0	4	5
4	DABCO	20	2	0	75	3
5	NMP	15	3	Trace	79	4
6	TMEDA	71	19	3	Trace	10

Table 3: Nakamura's solvent additive modifications improve chemoselective product formation²⁹.

The main four coupling partners that can be used in this homocoupling reaction with the iron catalyst are alkenyl, acyl, aryl and alkyl electrophiles (Figure 4). In the case of the alkyl electrophiles, a competitive reaction can take place (β -elimination), which can give rise to multiple products.

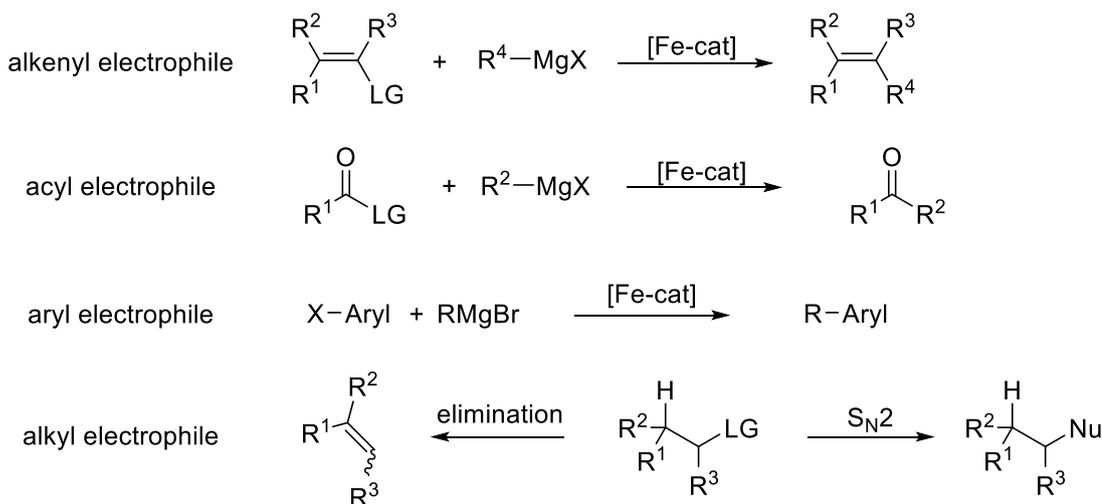
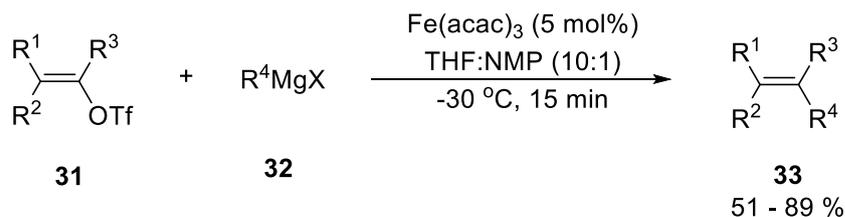


Figure 4: General scheme of homocoupling with alkenyl, acyl, aryl and alkyl electrophiles.

1.5.2.1 Alkenyl electrophiles

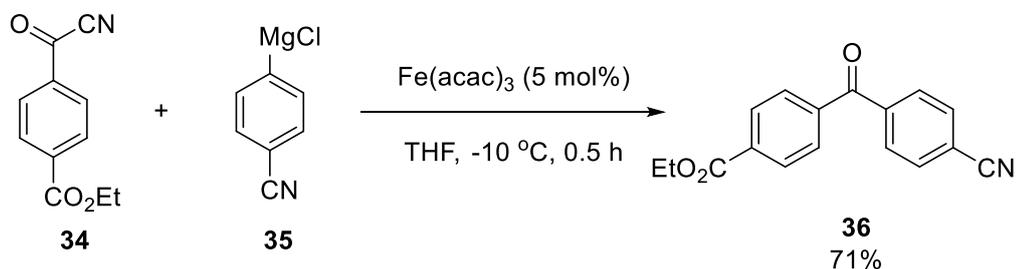
One of the methods, that expanded the use of Grignard reagents was Krause and Furstner's³⁰ iron-catalyzed cross coupling reaction of alkenyl triflates with a range of Grignard reagents. The Grignard reagents used in this reaction included aromatic Grignards such as PhMgBr, as well as alkyl Grignards eg. MeMgBr, BuMgBr etc. Functional groups such as esters, enones, ether, carbamates, acetals and lactones were tolerated in the reaction (Scheme 9).



Scheme 9: Iron-catalyzed cross coupling reactions of alkenyl triflates with Grignard reagents.

1.5.2.2 Acyl electrophiles

Formation of new functionalised ketones is very important and can be often be achieved in the absence of transition metals, but that process can potentially result in bis-alkylation and formation of tertiary alcohol products instead. The first example of formation of functionalised ketones using iron catalysis was reported by Cook and co-workers in 1953²⁴. The reaction used FeCl₃ to achieve a monoalkylation with yields between 31 and 70%. Acyl cyanides were shown to be better acylating agents compared to acyl chlorides and acyl cyanides were used by Knochel *et. al.* in the reaction providing the corresponding ketones in high yields³¹ (Scheme 10).

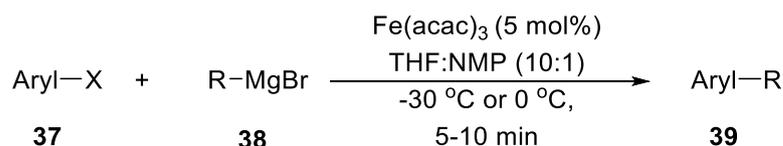


Scheme 10: Acyl cyanide reaction with a Grignard reagent by Knochel *et. al.*

1.5.2.3 Aryl electrophiles

Aryl reagents work very well in iron catalyzed cross-coupling reaction. The Fürstner group showed coupling between functionalised aryl halides with alkyl or phenyl magnesium bromides³². (Table 4).

Iron-Catalyzed Spirocyclization Project



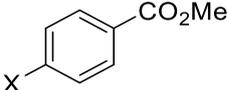
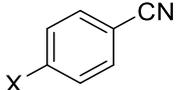
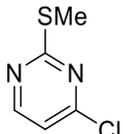
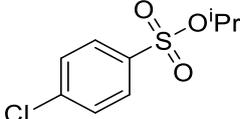
Entry	Ar-X	R-MgBr	Ar-R (yield %)
1		n-C ₆ H ₁₃ MgBr	91% (X=Cl)
			87% (X=OTf)
		PhMgBr	83% (X=OTs)
2		n-C ₁₄ H ₂₉ MgBr	28%
			91% (X=Cl)
			80% (X=OTf)
4		n-C ₁₄ H ₂₉ MgBr	74% (X=OTs)
		PhMgBr	89%
5		n-C ₆ H ₁₃ MgBr	53%
			85%

Table 4: Summary of the Fürstner results for the coupling reaction between functionalised aryl halides and alkyl or phenyl magnesium.

These conditions gave rise to a library of compounds and a methodology for formation of montipyridine (Figure 5) was reported.

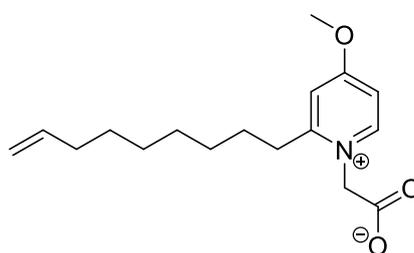
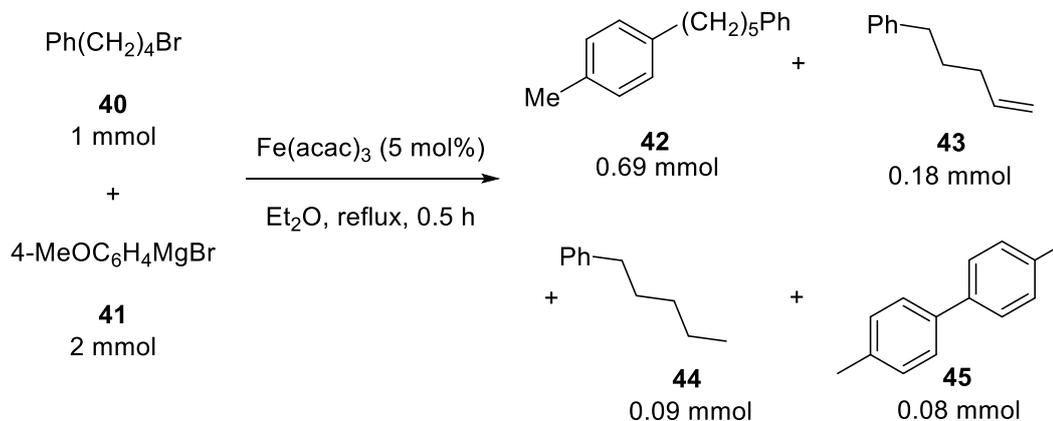


Figure 5: Structure of montipyridine.

1.5.2.4 Alkyl reactions

The first reaction that used an alkyl electrophile was reported by Nagano and Hayashi, who demonstrated that Fe(acac)₃ could be used as a catalyst for the cross-coupling of 1-bromo-4-phenylbutane (**40**) and 4-methoxyphenylmagnesium (**41**). A mixture of products (**42-45**)

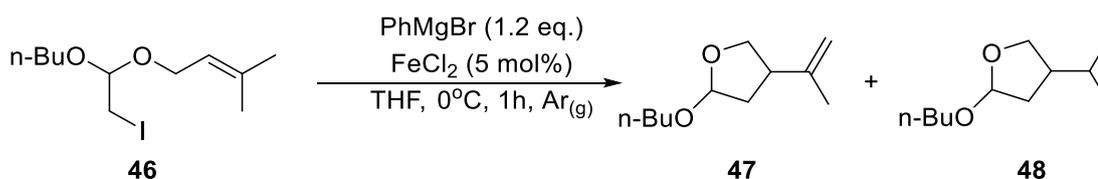
was formed depending on the solvent used in the reaction and temperature of the reaction. The best result was given by heating at reflux in diethyl ether (Scheme 11)³³.



Scheme 11: Product distribution of the reaction between of 1-bromo-4-phenylbutane and 4-methoxyphenylmagnesium bromide.

1.6 IRON-CATALYZED CYCLIZATION REACTIONS INVOLVING GRIGNARD REAGENTS

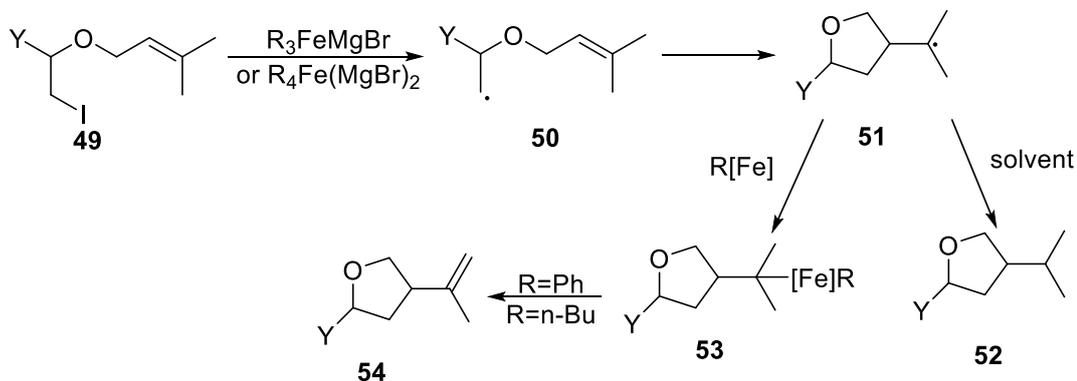
Oshima and co-workers reported the first recorded radical cyclization using iron as a catalyst in 1998. The Grignard reagent (in this case PhMgBr) was used as a reductant with FeCl_2 as a catalyst³⁴. The yield of the reaction was low, 52% and 13% for products **47** and **48** respectively (Scheme 12).



*Scheme 12: Iron(II)-catalyzed radical-cyclization conditions giving substituted tetrahydrofuran compounds (**47**) and (**48**).*

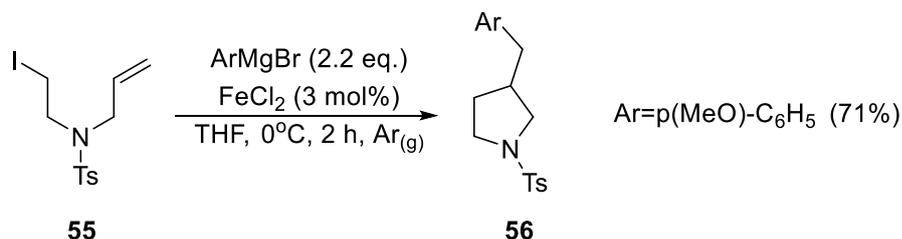
Oshima and co-workers (Scheme 13)³⁴ proposed that a single electron transfer from an iron ate complex (R_3FeMgBr or R_4FeMgBr) to starting material (**49**) could form a corresponding alkyl radical (**50**). This would induce 5-exo mode radical cyclization and form intermediate (**51**). Radical intermediate (**51**) could then recombine with a reduced form of alkylated iron species, $\text{R}[\text{Fe}]$, to form another intermediate (**53**). This is followed by dehydrometallation generating product (**54**). There have been many speculations about the mechanism involved in these sorts of reactions over the years. It was also speculated

that a reduced magnesium cluster is formed $[\text{Fe}(\text{MgX})_2]_n$, which has been reported by Fürstner and co-workers³⁰.



Scheme 13: Oshima's postulated mechanistic pathway for the radical cyclization.

In 2015 the aryl capture methodology was applied by Kang *et. al.* to alkyl iodide substrate³⁵, affording compound (**56**) in 71% yield (Scheme 14). In this reaction the radical cyclization is followed by arylative capture, providing a new route for the formation of arylmethyl substituted pyrrolidines and tetrahydrofuran compounds.



Scheme 14: Radical cyclization with Fe(II) catalyst to form arylmethyl-substituted pyrrolidines.

1.7 HETEROSPIROCYCLES

1.7.1 Background

Spirocyclic compounds are named based on the number of connected atoms contained in the smaller ring followed by the number of atoms in the larger ring. The classification of several all-carbon spirocyclic compounds is shown below (Figure 4).

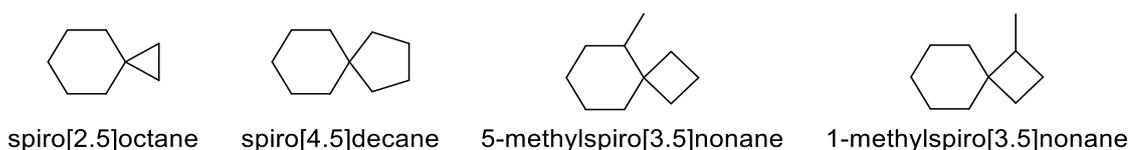


Figure 4: Carbon spiroalkane nomenclature.

Spiro compounds consist of at least two rings that are linked by a single atom. A heterospirocycle contains at least one heteroatom for example: nitrogen, oxygen or sulfur. Spirocycles and heterospirocycles are often a part of natural products, drugs and ligands (57-60) (Figure 6) ^{2,3,4}.

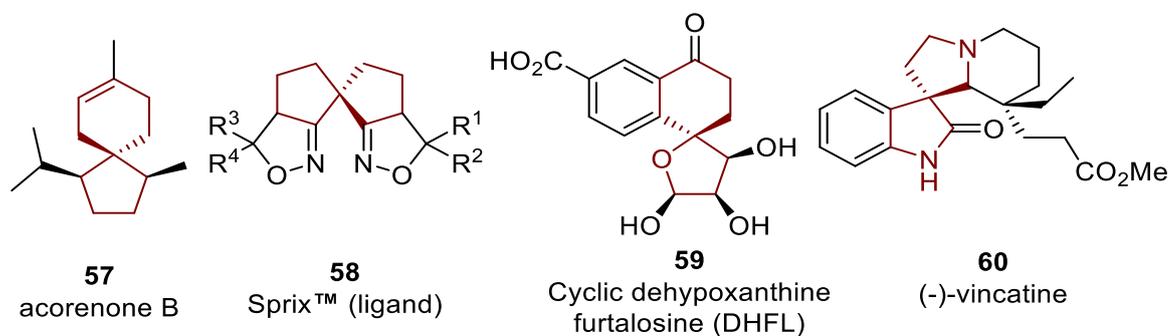


Figure 6: Selected examples of spirocyclic compounds.

1.7.2 Synthesis of spirocycles

There are six main methods for formation of spirocycles: alkylation, radical cyclization, rearrangement, transition-metal based ring closure, ring closure and cycloaddition (Figure 7). Most of the methods for formation of spirocycles have problems with functional group incompatibility, which makes it more difficult to create a large library of compounds based on one set of reaction conditions.

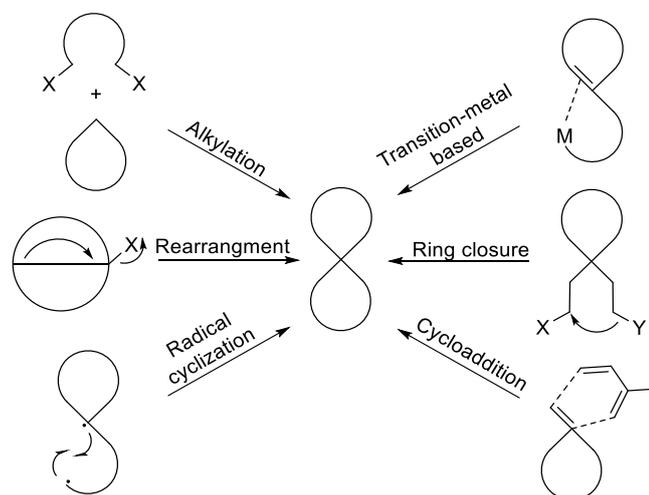
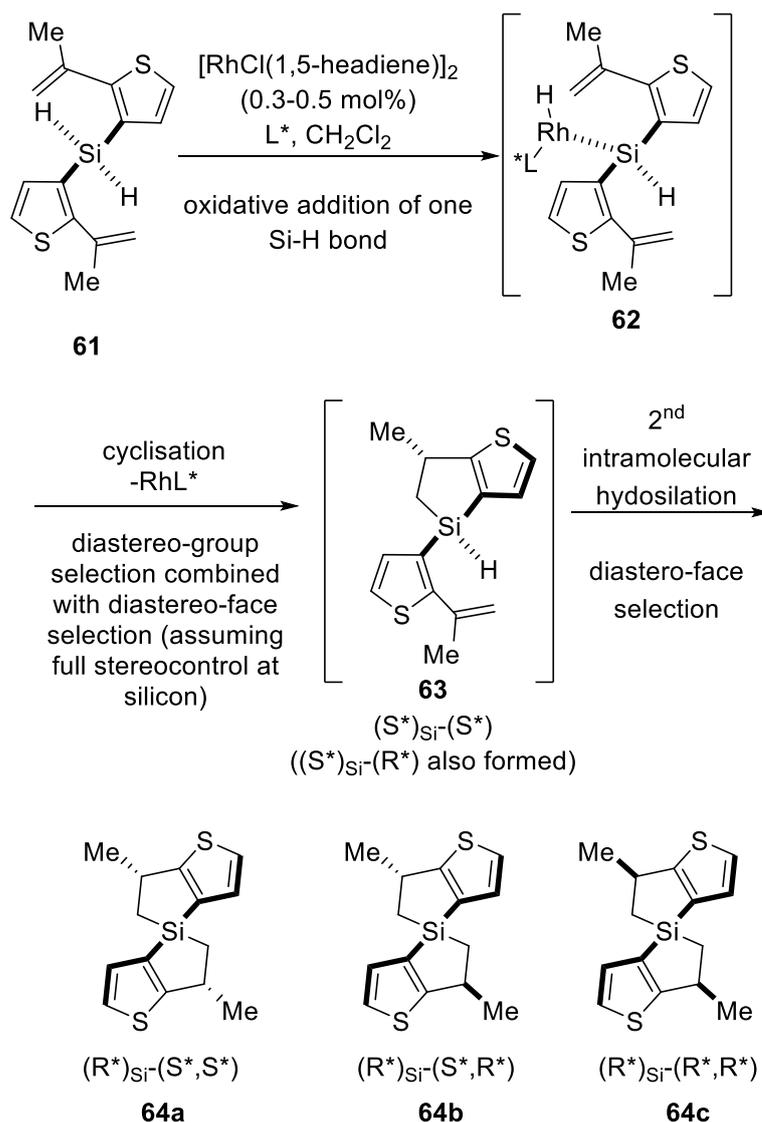


Figure 7: Different methods of formation of spirocycles (Diagram adapted from Ref. ³⁶).

Formation of enantioriched spirocyclic compounds was first described in 1996 by Tamao *et al.*³⁷. The first enantioselective compound that was synthesised did not have a carbon spirocenter, instead it was a spirosilane (Scheme 15)³⁷. However only compound (64) was reported to be synthesised using this method.

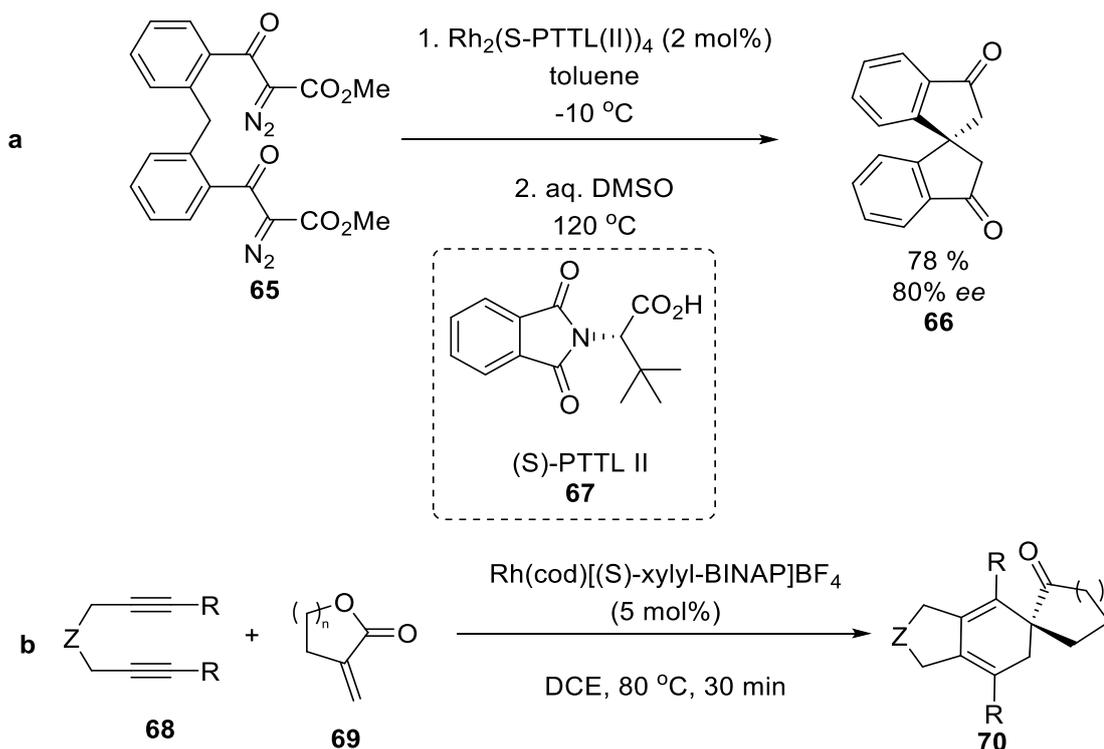
Iron-Catalyzed Spirocyclization Project



Scheme 15: Synthesis of the first spirobeteorocycle: 6,6'-Dimethyl-4,4'-spirobi(siloleno[3,2-b]thiophene) (64), where L = (R)-BINAP.

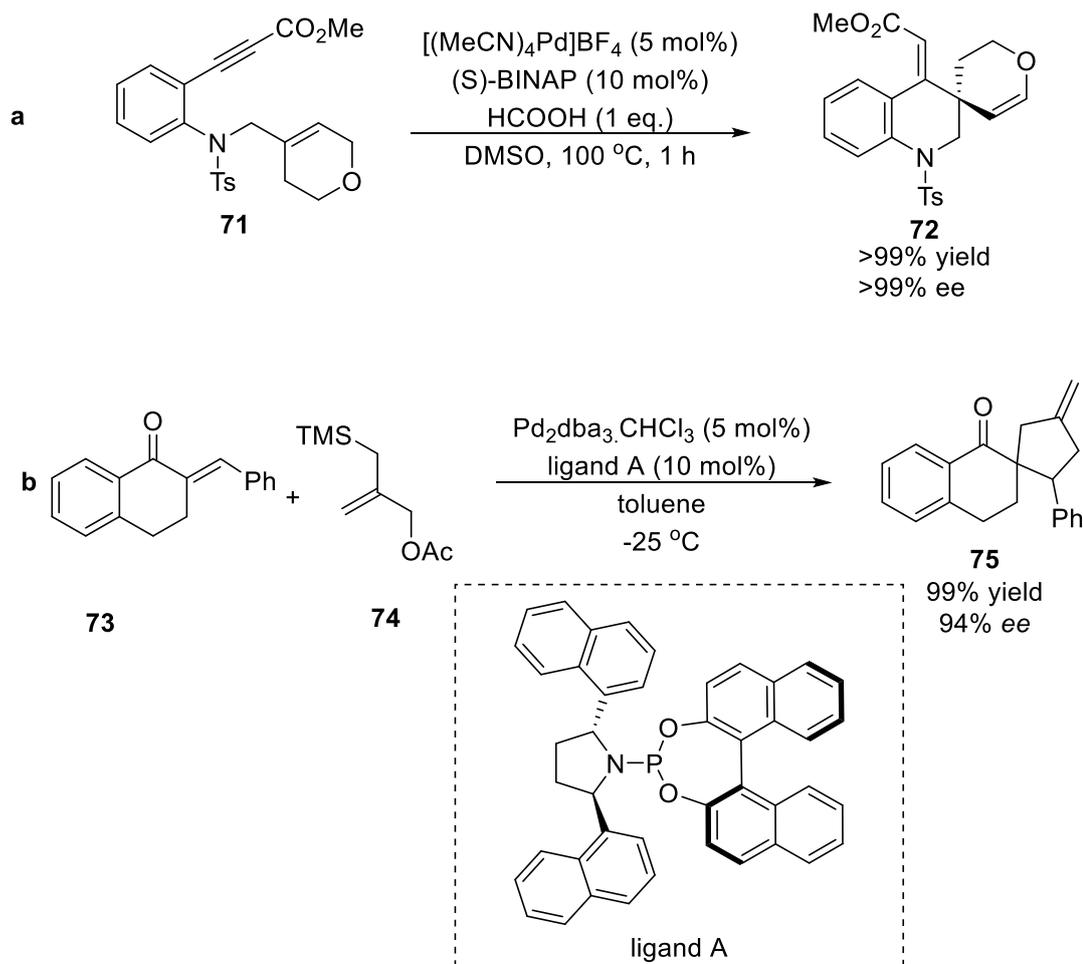
The first all-carbon spirocycle formed by an enantioselective methodology was formed in 2001 by Hashimoto *et al.*⁶⁸. This method involved intermolecular C-H insertion, utilizing a rhodium (II) catalyst followed by decarboxylation at an elevated temperature. This reaction gave yield of 78% and *ee* of 80% (Scheme 16). Another method of formation of spirocycles formation is based on [2+2+2] addition, using Rh(I) catalysis. Shibata *et al.* reported an example of this type in 2007. The method developed by these authors used diynes (**68**) and exo-methylene compound (**69**) in the presence of Rh(cod)[(S)-xylyl-BINAP]BF₄ catalyst (Scheme 16).

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*Scheme 16: a: an enantioselective method of formation of all-carbon stereocentre (**66**); b: formation of spirocycles (**70**) with rhodium catalysts is based on [2+2+2] addition.*

Palladium-mediated approaches to these reactions were reported around the same time, starting with Mikami et al in 2002³⁹, who used a method involving quinolone synthesis via ene-type cyclization of 1,7-enynes. They used a cationic BINAP-Pd(II) complex yielding the desired compound (**72**) in a quantitative yield and high enantioselectivity (Scheme 17, Reaction a). Enyne (**71**), which was involved in the reaction, had a cyclic olefin and the size of the ring influenced the reaction. The five-membered rings gave a moderate enantioselectivity (71 % *ee*) as well as forming an achiral by-product; the six-membered ring, on the other hand, gave high yields and very good enantioselectivity. In 2007, Trost *et al.*⁴⁰ reported a new methodology; it involving [3+2] cycloaddition with use of palladium-catalyzed trimethylenemethane. Optimisation showed that ligand A gave the best results. (Scheme 17, Reaction b).

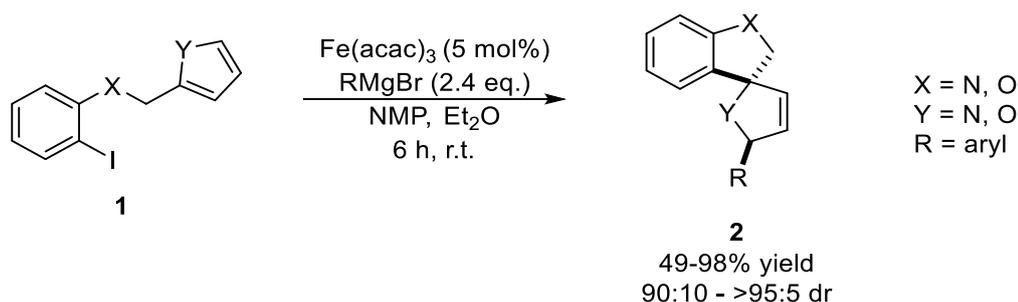


Scheme 17: **a**: Synthesis via ene-type cyclization by Makimi et. al. **b**: Trost et. al. [3+2] cycloaddition with a using palladium catalysis.

1.7.2.1 Synthesis of spirocycles with the use of an iron catalyst

Most of the catalysts used in these reactions are precious metals and therefore expensive and potentially require careful handling. There is a need for a method of formation of heterospirocycles in a simple and effective way using cheap, easy to use catalysts. The synthesis of heterospirocycles with a using an iron catalyst is not well known. The Sweeney group¹ in 2017 published a method for formation of heterospirocycles with the use of $\text{Fe}(\text{acac})_3$ catalyst in the presence of a bromide Grignard reagent in NMP and Et_2O at room temperature (Scheme 18). The method involves formation of a bis-heterocycle (**2**) in a cascade reaction using (2-halo)aryl ether and amines. Different catalysts were investigated with $\text{Fe}(\text{acac})_3$ giving the highest isolated yields. The current scope of the reaction includes aryl Grignard reagents and aromatic iodides and an example of an alkyl Grignard reagent (Scheme 18).

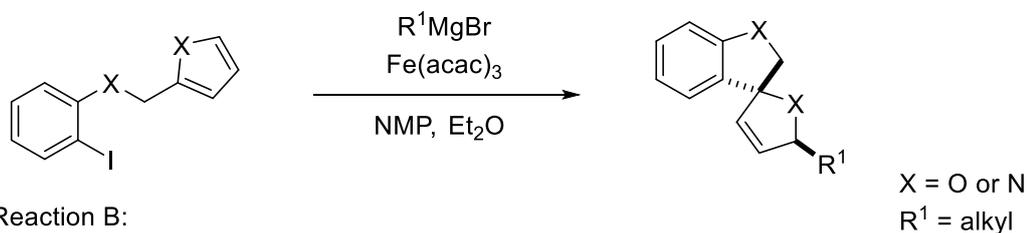
Previous work:



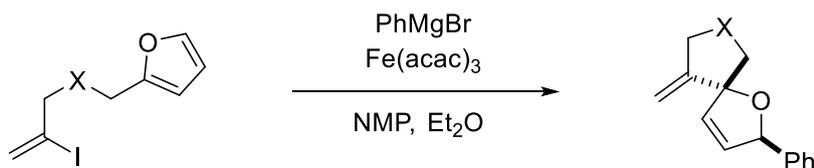
Scheme 18: Previous work on iron-catalyzed spirocyclization reaction.

There are two main aims of this project (Scheme 19). Firstly, using the precursor used previously by the Sweeney group ($\text{X}=\text{O}$), the reaction conditions will be changed by using an alkyl Grignard reagent instead of an aryl one (Scheme 19; Reaction A), as well as using an amine precursor in the spirocyclization reaction (Scheme 19; Reaction A; $\text{X} = \text{NR}$). Reaction B is focused on completely changing the precursor of the reaction to a vinyl iodide, in this case spirocyclization reaction will take place with PhMgBr to ensure the best result.

Reaction A:



Reaction B:



Scheme 19: Aim of the project.

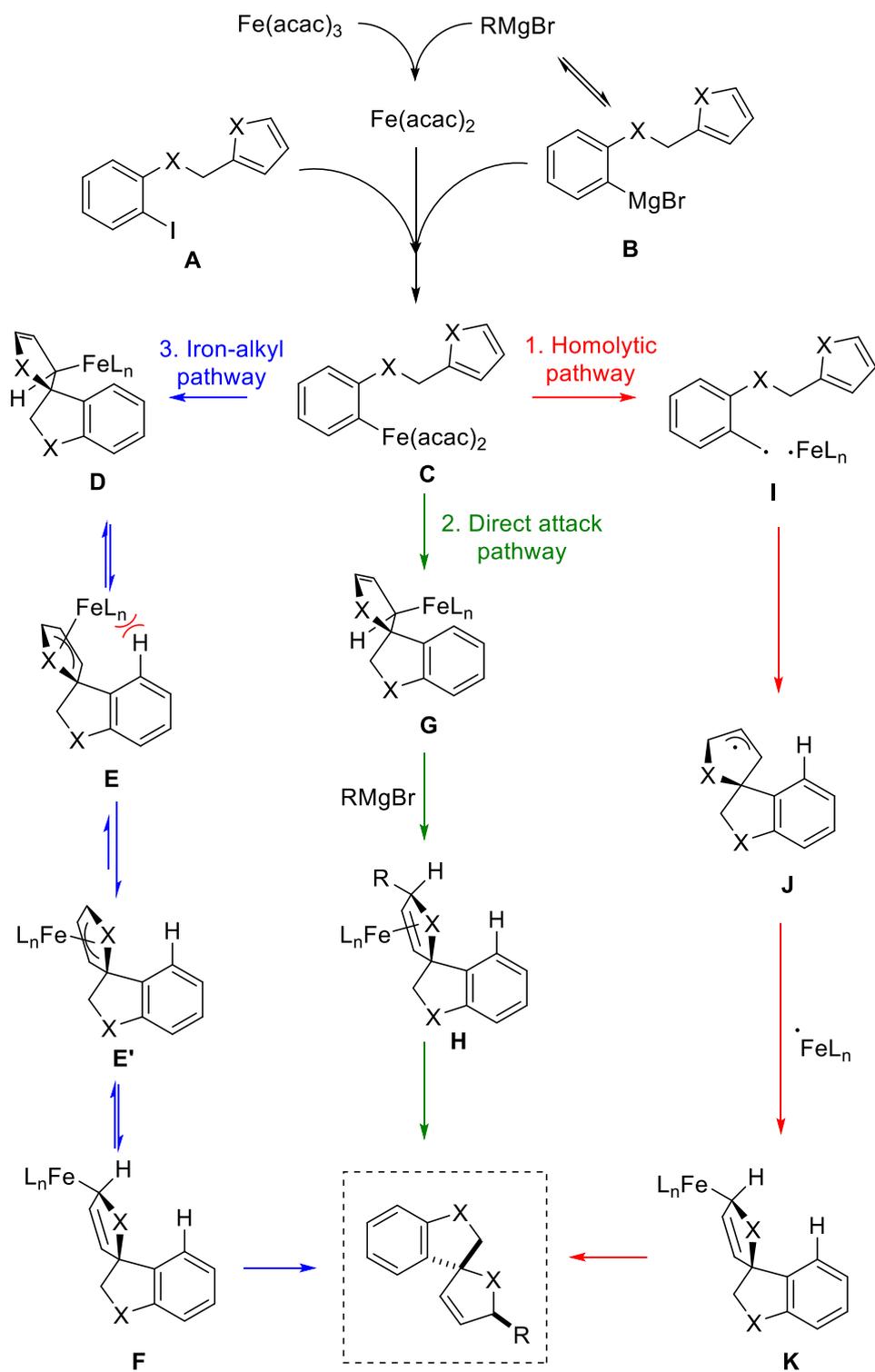
1.7.2.1.1 Proposed mechanism pathways

It is believed this reaction takes place via an $\text{Fe}(\text{II})$ species, suggesting the first step is the reduction of the catalyst with the Grignard reagent. The $\text{Fe}(\text{II})$ species forms the intermediate **C** by either transmetalation or oxidative addition. The side products of this step include homo-coupled Grignard compounds. From intermediate **C** there are 3 possible pathways for the mechanism: homolytic, iron-alkyl and direct attack pathway (Scheme 20)¹.

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The most likely pathway is the iron-alkyl pathway, which again involves formation of intermediate **D**, which is in equilibrium with **E**. **D** is then able to undergo isomerization due to the repulsive forces to form intermediate **E'**, which is less hindered. **F** can be then the Grignard to form the final product via reductive elimination. The second possibility is the direct anti-attack to form intermediate **G**, which then undergoes decomplexation to form the final product. A radical pathway is the last possibility: the Fe-C bond is homolytically broken and makes radical species **I** and $\cdot\text{FeL}_n$ in the process, **I** then cyclizes to give intermediate **J**. After radical recombination an intermediate **K** is formed which reacts with the Grignard again to form the final product. This pathway is unlikely and previously experiments with radical inhibitors (such as TEMPO or BHT) were performed and the results were not affected.

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Scheme 20: Proposed mechanisms pathways: 1. Homolytic attack pathway; 2. Direct attack pathway 3. Iron-alkyl pathway.

2. RESULTS AND DISCUSSION

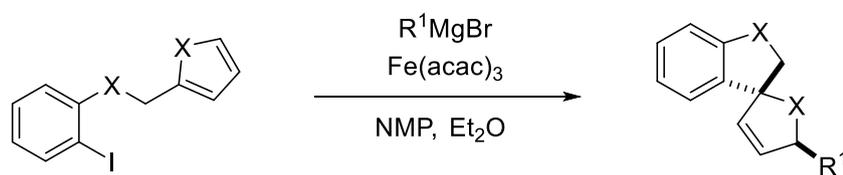
2.1 AIM OF THE PROJECT

The aim of the project is to expand on the current scope of this spirocyclization reaction (Scheme 21). Previously, the heteroatoms present in the precursors in the reaction were oxygen, as well as the combination of oxygen and nitrogen in the X positions. Previously, the Grignard reagent used for the spirocyclization reaction had an aryl R group.

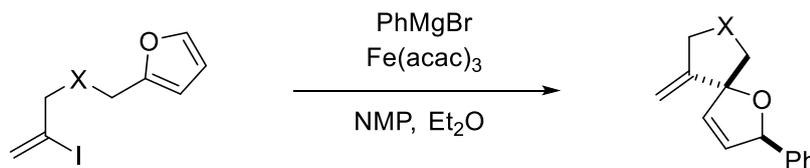
Firstly, this project will investigate the use of alkyl Grignard reagents during spirocyclization (Scheme 21; Reaction A; X = O). Next, a series of amine precursor species will be designed and synthesised, with different protecting groups on each nitrogen atom that can tolerate the spirocyclization reaction, based on previous work done by the Sweeney group (Scheme 21; Reaction A; X = N).

The second reaction will be the spirocyclization reaction using vinyl iodides as starting materials (Scheme 21; Reaction B). This reaction will use PhMgBr to form a library of new heterospirocycles.

Reaction A:



Reaction B:



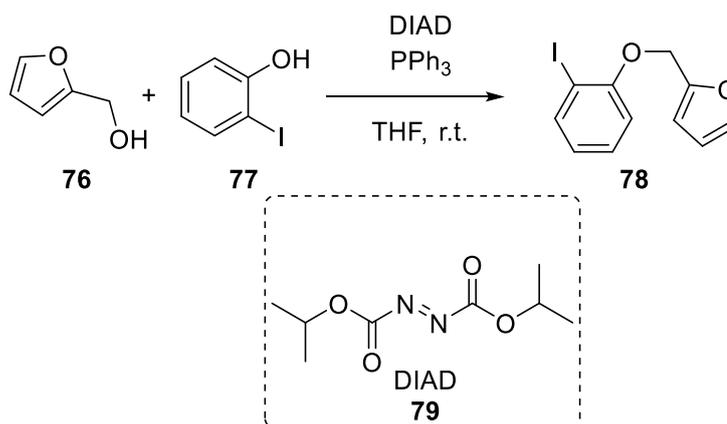
X = O or N
R¹ = alkyl

Scheme 21: Aim of the project.

2.2 SYNTHESIS OF SPIROCYCLIZATION PRECURSORS

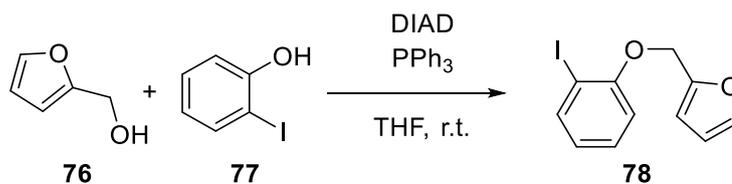
2.2.1 Synthesis and optimisation of 2-[(2-iodophenoxy)methyl]-furan

Precursor (**78**) was synthesised via a Mitsunobu reaction. Furfuryl alcohol (**76**) and iodophenol (**77**) were reacted together in the presence of DIAD (diisopropyl azodicarboxylate, **79**) and PPh₃ (triphenylphosphine)⁴¹ (Scheme 22).



*Scheme 22: The general scheme for the synthesis of 2-[(2-iodophenoxy)methyl]-furan (**68**)⁴¹.*

Initially the limiting reagent of the reaction was furfuryl alcohol (**76**), using this method the reaction gave 12% yield of the product (**78**) (Table 5, Entry 1). The optimization of this reaction started with the use of a sonicator⁴², which could potentially improve the % yield of product. In this case, the sonication did not increase the yield of the reaction (Table 5, Entry 2) it did however decrease the time of the reaction. The reaction was then investigated with an excess of furfuryl alcohol (5 equivalents), but yielded no product (Table 5, Entry 3). Next iodophenol (**77**) was investigated as limiting reagent by increasing amount of the PPh₃ and DIAD (**79**) and the furfuryl alcohol (**76**) to 3.75 equivalents (Table 5, Entry 4). The reaction gave a much higher yield of 32%. Increasing the scale of the reaction meant increasing the time needed for consumption of the starting material. After 16 h (Table 5, Entry 5) a higher isolated yield of 52% of 2-[(2-iodophenoxy)methyl]-furan (**78**) was obtained. Leaving the reaction for 66 h (Table 5, Entry 6) did not help to increase the yield. The downside of increasing the equivalents of DIAD and PPh₃ as well as furfuryl alcohol (**76**) meant that the purification of the reaction was more challenging and often required two chromatography columns, which had a negative effect on isolated yield.



Entry	Furfuryl alcohol (76) (eq.)	Scale	Iodophenol (77) (eq.)	DIAD (79) (eq.)	PPh ₃ (eq.)	Time (h)	% yield (78)
1	1.00	5 mmol	1.10	1.10	1.10	16	12
2	1.00	5 mmol	1.10	1.10	1.10	0.3	12
3	5.00	5 mmol	1.10	1.10	1.10	16	0
4	3.75	5 mmol	1.00	3.75	3.75	2	32
5	3.75	20 mmol	1.00	3.75	3.75	16	52
6	3.75	20 mmol	1.00	3.75	3.75	66	48

Table 5: Optimisation of the synthesis of 2-[(2-iodophenoxy)methyl]-furan (**78**).

2.2.2 Synthesis of vinyl iodide ether precursors

Three novel vinyl iodide reagents (**80**, **81** and **82**) were designed (Figure 8), and different synthetic pathways to these target molecules were proposed. The synthesis of all three of these reagents took place in parallel and the main focus was on the pathway that gave the highest yield of the vinyl iodide product.

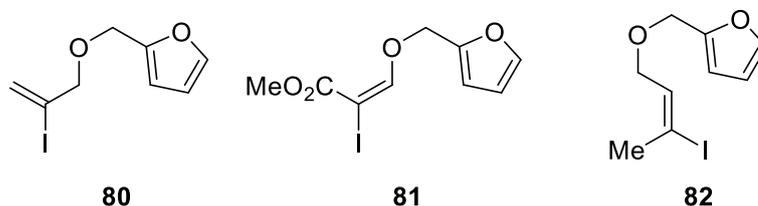
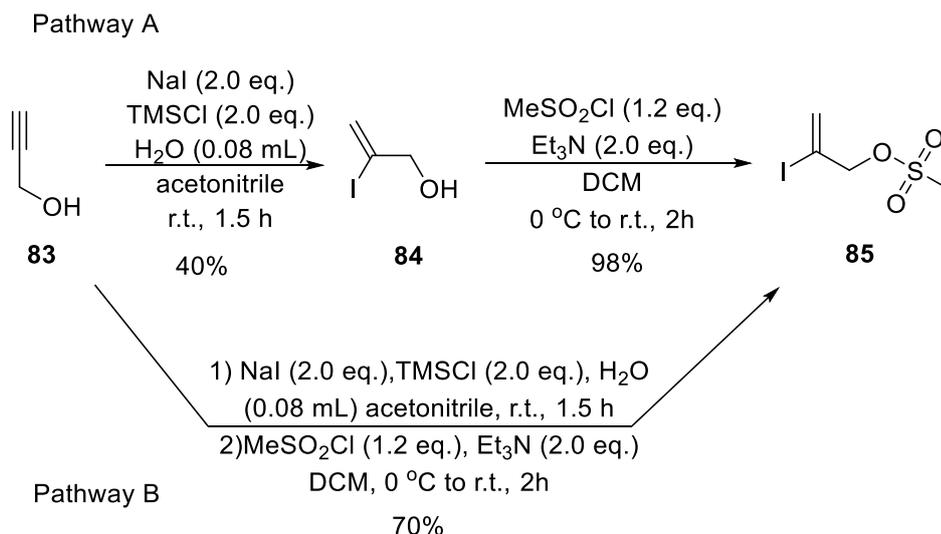


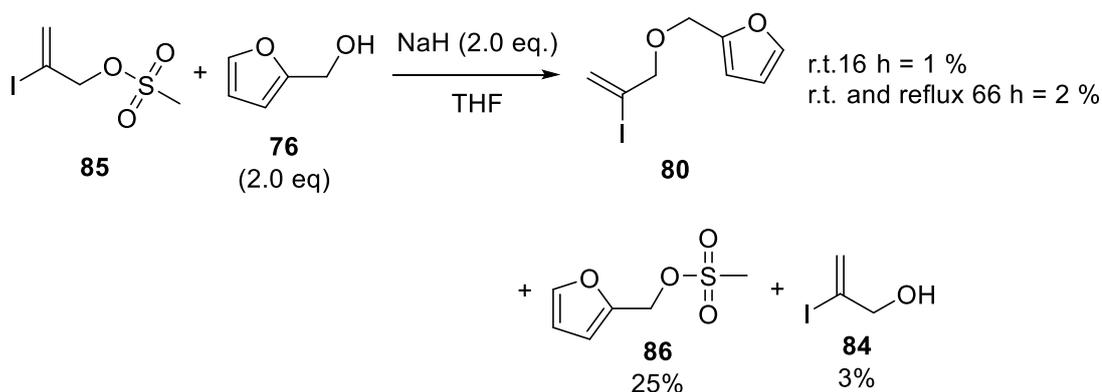
Figure 8: Proposed structures for novel vinyl iodine ether precursors (**80-82**).

The synthesis of (**80**) started with a known reaction of propargyl alcohol (**83**) to form 2-iodo-2-propen-1-ol (**84**)⁴. The 2-iodo-2-propen-1-ol (**84**) was isolated but due to its volatility the yield of the reaction was much lower than expected. The hydroxyl group underwent mesylation⁴³ to make it a better leaving group. The mesylation reaction gave 98% yield if performed on purified 2-iodo-2-propen-1-yl methanesulfonate (**85**) (Scheme 23, Pathway A). However, a quicker way of making 2-iodo-2-propen-1-yl methanesulfonate was to not isolate compound (**84**) and use the crude mixture directly in the mesylation reaction, this pathway increased the overall yield to 70% (Scheme 23, Pathway B).



Scheme 23: Synthesis of 2-iodo-2-propen-1-yl methanesulfonate (**85**)^{44,43}.

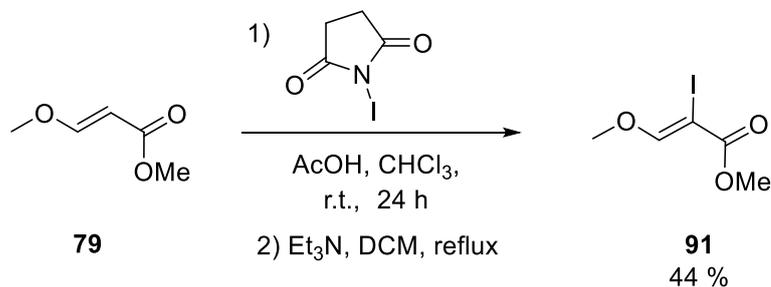
The second step of the synthesis of compound (**80**) involved addition of the furyl group. Mesylated alcohol (**85**) was reacted with furfuryl alcohol (**76**) in the presence of NaH. The desired product (**80**) was only formed in 1-2 % yield, depending on the reaction time and temperature. The main material isolated was recovered furfuryl alcohol (**76**) (60%) along with demesylated starting material (**84**) and mesyl transfer product (**86**) (Scheme 24). Due to the large scale of the reaction, enough product was isolated to investigate the spirocyclization reaction. A possible improvement for this reaction would be an addition of KI, which was done on a small scale but unfortunately based on ¹H NMR analysis of the crude product, the reaction was not improved, and only traces of the desired product (**80**) were visible.



Scheme 24: The synthesis of 2-((2-iodoallyl)oxy)methylfuran (**80**) and the side products of the reaction.

The synthesis pathway to vinyl iodide (**82**) was inspired by a known reaction, which introduces the iodine atom in the desired position by reacting starting material (**79**) in the presence of *N*-iodosuccinimide (NIS) and acetic acid in chloroform, which formed a

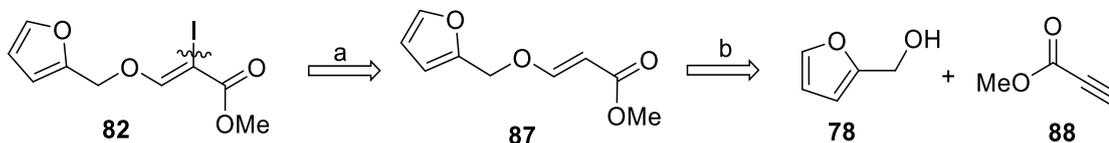
diastereomeric mixture of product (**91**) (Scheme 25). Triethylamine was used to isolate only the *Z* isomer of the product (**91**). This reaction was performed and gave 44% yield of the desired product.



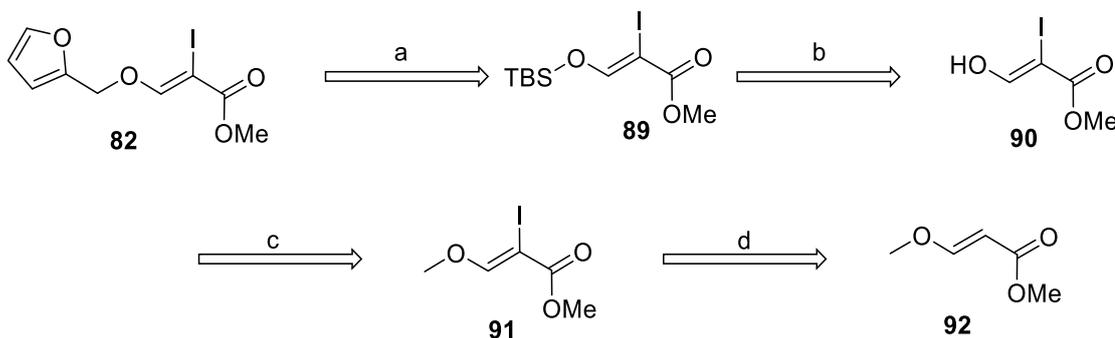
Scheme 25: Synthesis of 2-iodo-3-methoxy-2-propenoic acid methyl ester (**91**).

To shorten the synthetic pathway to (**82**) it was proposed to introduce the iodine atom as the last step of the synthesis (Scheme 26, Pathway A). Alternatively, a second retrosynthesis pathway was designed, which involved addition of the furyl ring as the last step of the synthesis (Scheme 26, Pathway B). Pathway B was twice as long, so pathway A was prioritised.

Pathway A:



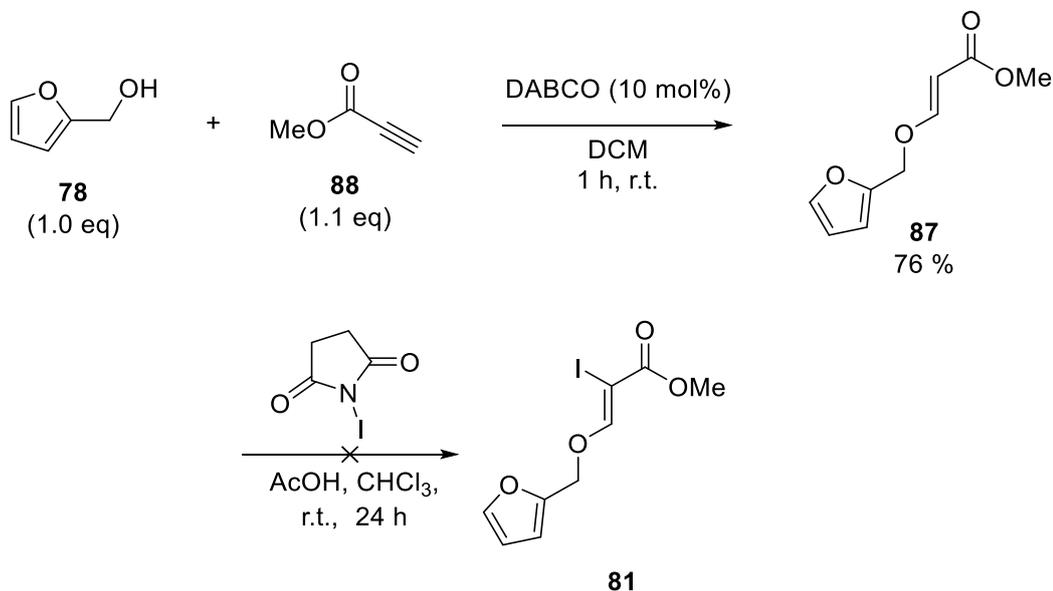
Pathway B:



Scheme 26: Possible retrosynthesis of methyl (*Z*)-3-(furan-2-ylmethoxy)-2-iodoacrylate (**82**).

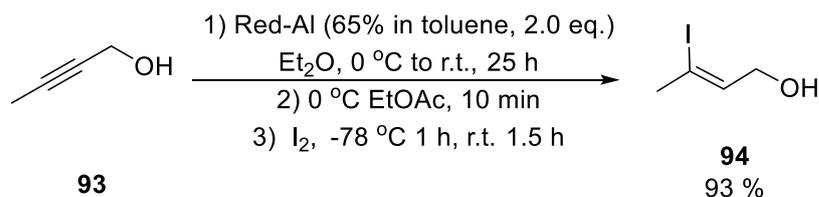
The reaction of furfuryl alcohol (**78**) with methyl propiolate (**88**) had been previously reported in the literature using DABCO as a catalyst, yielding desired (**87**) in 76% yield (Scheme 27)⁴⁵. The second reaction conditions were based on literature but the starting material did not have the furyl group, instead it was a methyl ether⁴⁶. The TLC of the

reaction showed multiple compounds and there was no visible product by ^1H NMR of the crude sample. Due to the failure of this reaction, the purification was not carried out, and the synthetic pathway was changed. Due to time constraints, it was ultimately decided to use the other precursors as they required fewer reactions to synthesise.



*Scheme 27: First attempt of synthesis of 3-(2-furanylmethoxy)-2-iodo-2-propenoic acid ethyl ester (**81**)⁴⁶ via formation of methyl (Z)-3-(furan-2-ylmethoxy)-2-iodoacrylate (**87**)⁴⁰.*

Precursor (**82**) can exist as two different isomers (E and Z) which may react differently in the spirocyclization reaction. For this reason, it would be better to synthesise each isomer selectively. Synthetic pathways were researched for both, and it was decided to focus on the Z isomer, as it required fewer synthetic steps to synthesised (Z)-3-iodo-2-buten-1-ol (**94**). The synthesis of precursor (**82**) was based on the same idea as the synthesis of (**80**). The formed alcohol would be mesylated and then reacted with furfuryl alcohol under basic conditions. The first reaction was the synthesis of (2Z)-3-iodo-2-buten-1-ol (**94**) (Scheme 28). The desired alcohol (**94**) was isolated in high yield although purification proved difficult as left-over aluminium salts were difficult to remove, as they coordinated to the product.



*Scheme 28: The synthesis of (2Z)-3-iodo-2-buten-1-ol (**94**)⁴⁷.*

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^1H NMR analysis showed 3 signals between 3 and 4 ppm (Figure 9; Spectrum 1; Region A), as well as the lack of the OH peak of the desired product. This indicated a left over Red-Al complex potentially binding to the product. The work up was repeated two more times to remove the Red-Al complex, which was proven by analysis of the ^1H NMR spectrum. The OH peak also was visible after the additional purification in region B (Figure 9; Spectrum 1-3).

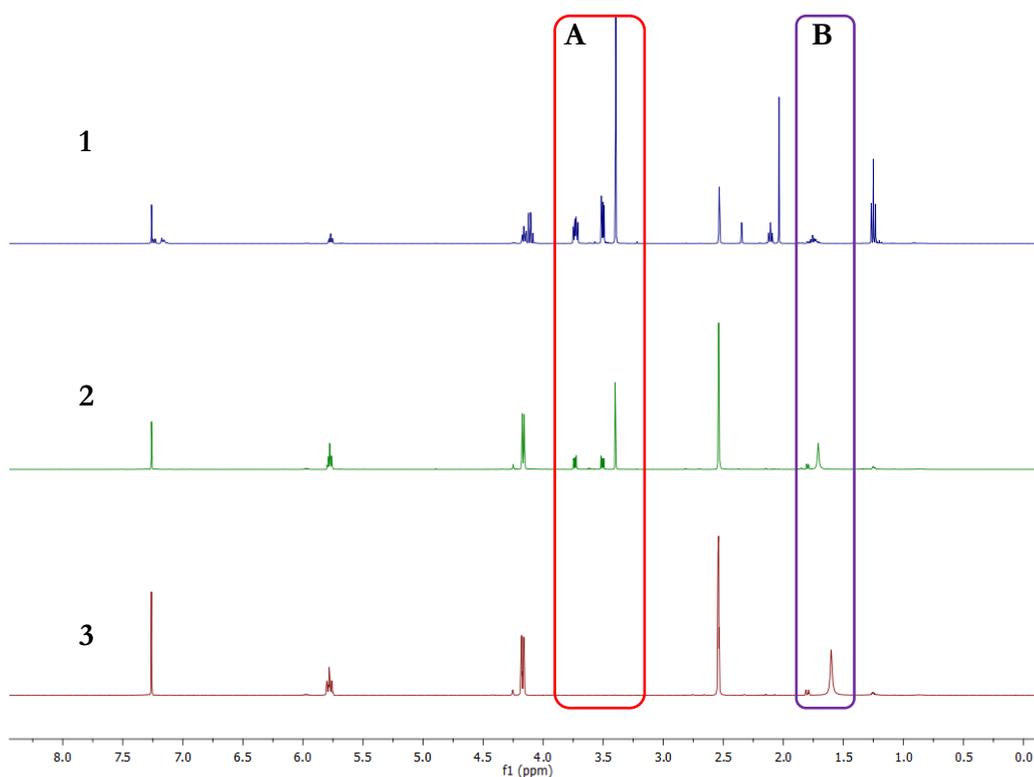


Figure 9: ^1H NMR comparison of (2Z)-3-iodo-2-buten-1-ol (**82**) at different stages of purity.

The majority of the product was the *Z* isomer, but based on ^1H NMR spectroscopy there are traces of the *E* isomer. The difference between the two can easily be seen when looking at proton A, which has a characteristic triplet of quartet splitting due to protons B and C. The shift downfield might have been caused by the iodine atom being next to the proton A in the *E* isomer (Figure 10).

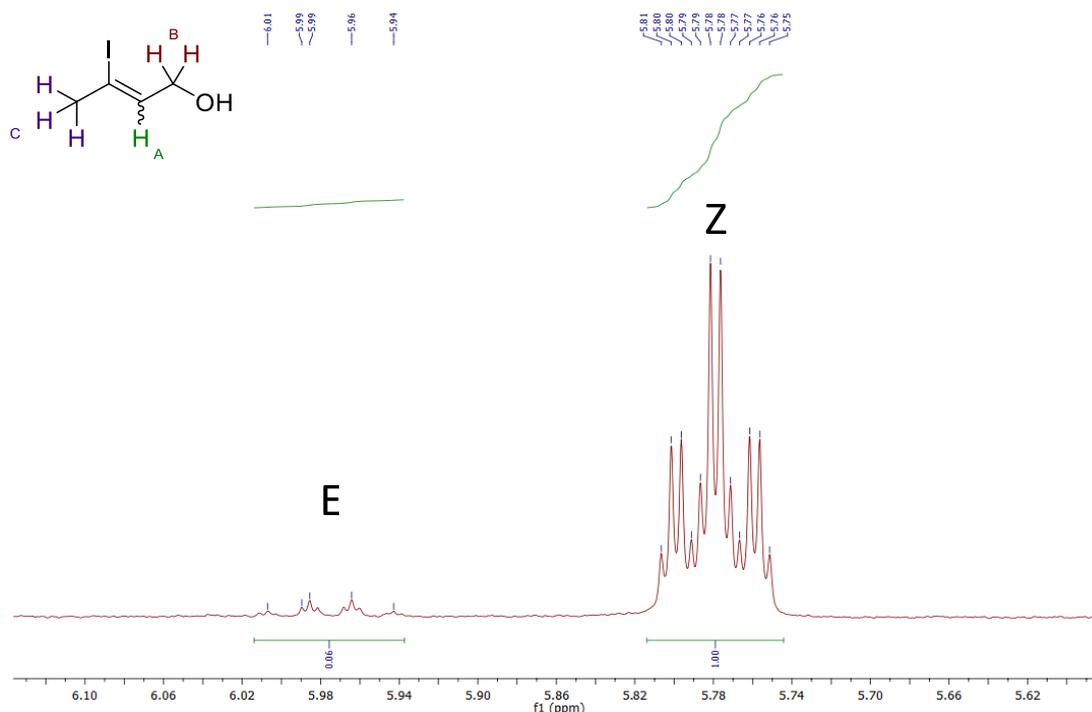
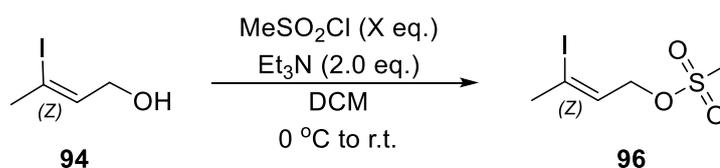


Figure 10: ¹H NMR fragment showing the triplet of quartet in 3-iodo- 2-buten-1-ol.

The next step was mesylation of the alcohol (**94**). However, mesylation was not as simple as previously investigated. The first two reactions were performed on the impure crude product containing complex (<10%), this potentially could have caused a failure of the reaction. The last entry (Table 6, Entry 3) used the 100 % pure alcohol (**94**), but it still was not successful. Based on the ¹H NMR spectrum only starting material (**94**) was present after the reaction. Due to the lack of time left on the project this reaction was abandoned.

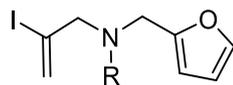


Entry	MeO ₂ Cl eq.	Results
1	2	47 % of SM recovered
2	5	Only MeSO ₂ Cl based on ¹ H NMR
3	2	Only SM based on ¹ H NMR

Table 6: Attempted mesylation of (2Z)- 3-iodo- 2-buten-1-ol (**95**).

2.2.3 Synthesis of (N, O) precursors

Due to difficulties in the formation of the desired vinyl iodide ether precursor, a series of amines were designed instead due to multiple reaction pathways to synthesise secondary and tertiary amines (**97**) (Figure 11).

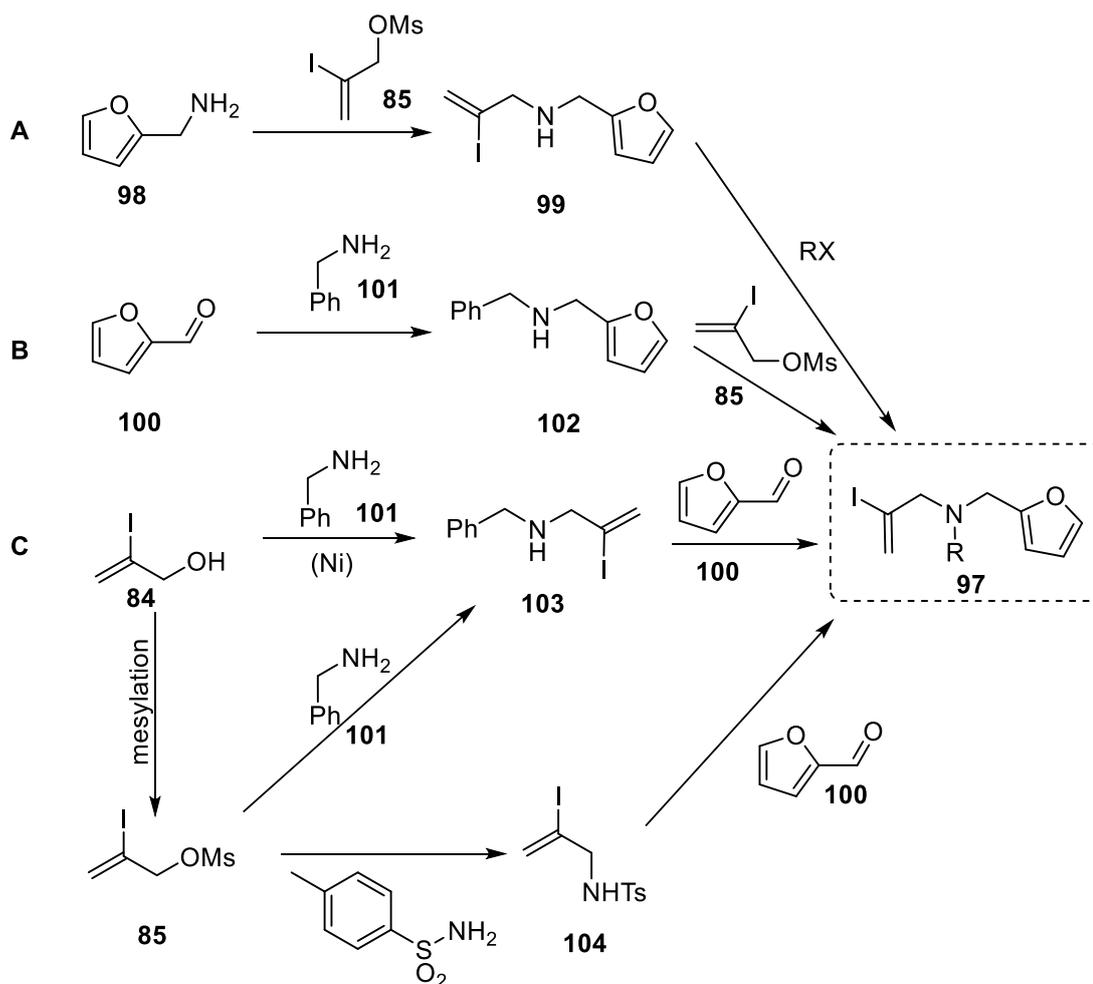
**97**

R = Ts, Boc, Allyl, Me, Bn

Figure 11: Proposed structure of the vinyl iodide amine precursor.

One of the easiest methods for formation of amines is reductive amination. This method involves formation of an imine intermediate from a ketone or an aldehyde and a substituted amine. The reaction then uses mild reducing agent such as: NaCNBH_3 and $\text{NaBH}(\text{OAc})_3$ to yield the desired amine product. Reductive amination reactions can be split into two types: secondary and primary amination.

There are many possible pathways of synthesis for the precursors (**97**) (Scheme 29) but the synthesis trials were focused on 4 pathways, starting from 3 different starting materials: furfuryl amine (**98**), furfural aldehyde (**100**) and 2-iodo-2-propenol (**84**). The first pathway (Scheme 29; Pathway A) was the most desirable way of making these precursors due to the possible diversity of the second step. The pathway starts with the synthesis of *N*-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (**99**) from furfuryl amine (**98**) by simple $\text{S}_{\text{N}}2$ displacement. Amine (**99**) can be protected with multiple groups. Lack of a protection group could cause a failure of a spirocyclization reaction due to the nucleophilicity of the nitrogen. Pathway B (Scheme 29; Pathway B) consists of two reactions: the reductive amination of furfuryl aldehyde (**100**) and benzyl amine (**101**) yielding a *N*-(phenylmethyl)-2-furanmethanamine (**102**) which can then react with compound (**85**) to form the Bn-protected version of the precursor. The third starting material (Scheme 29; Pathway C) (**84**) can directly be used in the allylation reaction with the amine using a nickel catalyst to form the desired intermediate (**103**) which can then undergo reductive amination to form the Bn version of the precursor. If that is not possible the vinyl iodide alcohol (**84**) can be mesylated (**85**) and reacted with benzyl amine (**101**) to form the desired secondary amine (**103**). The second possibility is the conversion of the mesylated iodide amine into tosyl-protected amine (**104**) which later can undergo reductive amination with furfuryl aldehyde (**100**).

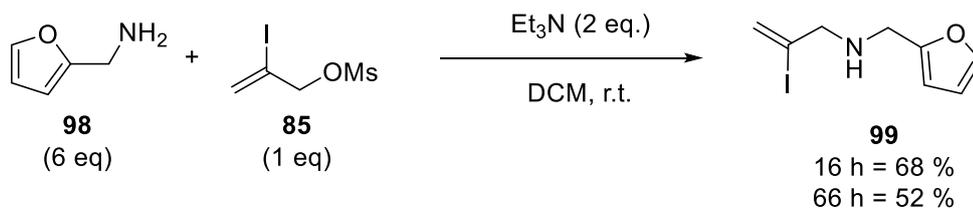


R=Ts, Boc, Allyl, Me, Bn

Scheme 29: Possible pathways (A-C) for the formation of different vinyl iodide amine precursors.

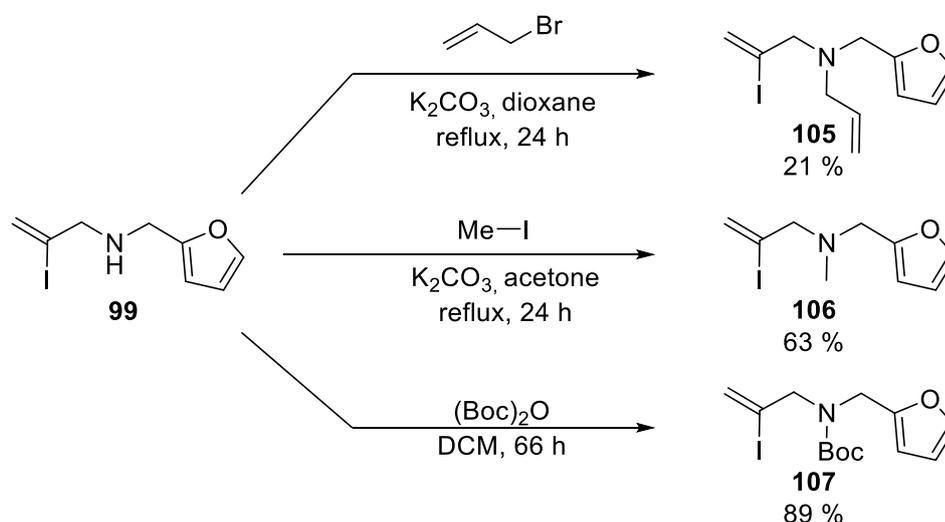
The first reaction of path A involved the synthesis of compound (**99**) using Et₃N in DCM at room temperature (Scheme 30). The product was isolated after purification by flash chromatography on silica gel giving a 68% yield of (**99**) after 16 h. Based on the TLC analysis there was some of the vinyl iodide mesylate left in the reaction so when the reaction was run the second time it was left for 66 h to help with the consumption of the starting material. This however did not help and the yield decreased to 52%, showing the compound to be potentially unstable under reaction conditions; a possible improvement would be decreasing the time of the reaction.

Iron-Catalyzed Spirocyclization Project



Scheme 30: Synthesis of N-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (99).

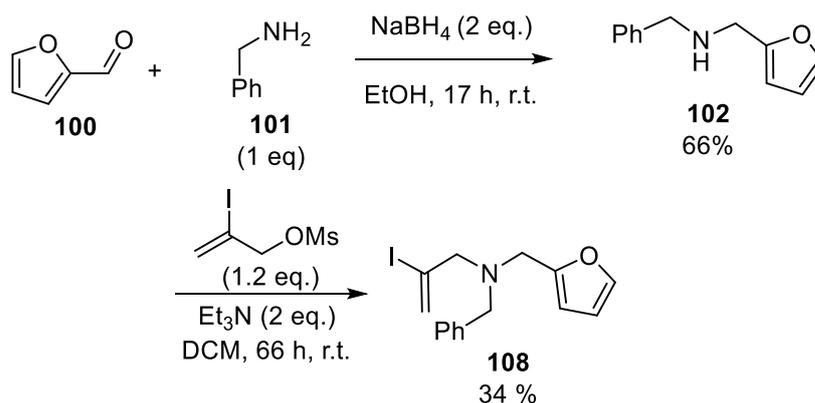
Amine (**99**) can be protected with a number of protecting groups, in this case three were chosen: allyl, Me and Boc. All of these reactions worked, giving a range of yields (Scheme 31). All three of the final compounds (**105-107**) were further investigated in the spirocyclization reaction.



Scheme 31: Protection reactions, the synthesis of (105, 106 and 107).

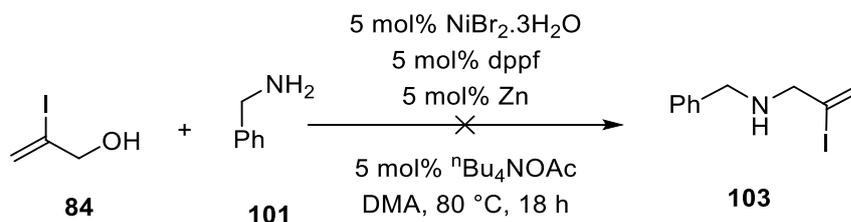
Pathway B started from furfuryl aldehyde (**100**) which was reacted with benzyl amine (**101**) in the presence of NaBH_4 in ethanol for 17 h to give the desired secondary amine (**102**) in 66% yield (Scheme 32). Secondary amine (**102**) was added in the reaction with 2-iodo-2-propen-1-yl methanesulfonate (**85**) to form the desired final product, N-benzyl-N-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (**108**) in 34% yield, with 48% of the secondary amine being recovered from the reaction (Scheme 32). A possible way of increasing the yield of the second reaction would be increasing the equivalents of the 2-iodo-2-propen-1-yl methanesulfonate (**85**) for the full consumption of amine (**102**).

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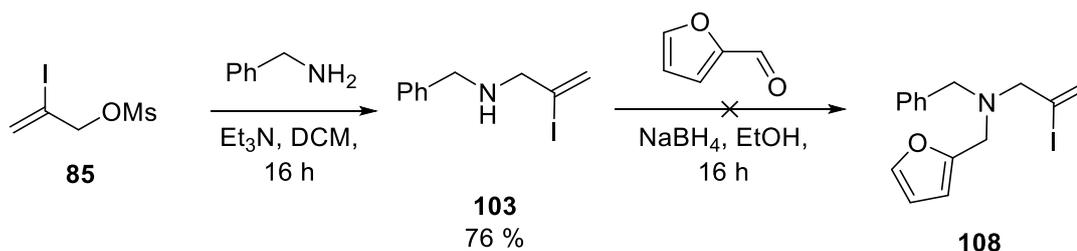
Scheme 32: Synthesis of (**108**) using the B pathway via formation of (**102**)⁴⁸.

Path C is divided into three pathways: the shortest pathway was based on the reaction of the 2-iodo-2-propen-1-ol (**84**) with the benzyl amine (**101**) to form *N*-benzyl-2-iodoprop-2-en-1-amine (**103**) in the presence of a nickel catalyst system that was previously reported by the Sweeney group (Scheme 33)⁴⁹. This reaction, however, did not give any desired product, with the only observed material being compound (**84**) by ¹H NMR spectroscopy of the crude product.



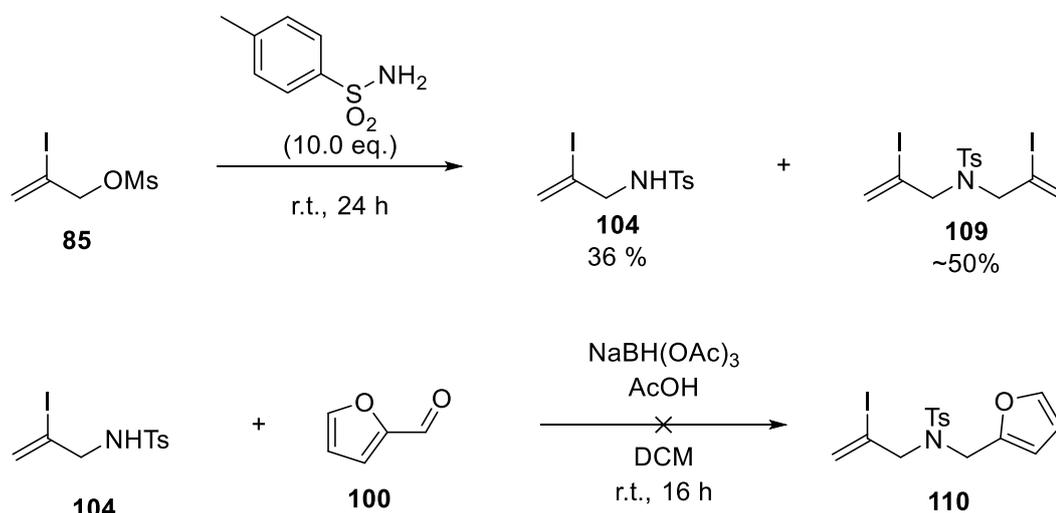
Scheme 33: Nickel-catalyzed amination reaction to form *N*-benzyl-2-iodoprop-2-en-1-amine (**103**).

An alternative route was to use mesylate (**85**) in the same way as before followed by reductive amination with benzyl amine (**101**). This reaction proceeded well yielding the desired amine (**103**) in 76% yield (Scheme 34). The next step in the reaction was the addition of the furfuryl group. The reaction conditions were based on the synthesis of (**102**) however there was no visible product (**108**) by ¹H NMR. This reaction could potentially be improved by increasing the temperature to force the formation of the imine.



Scheme 34: Synthesis of *N*-benzyl-*N*-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (**108**).

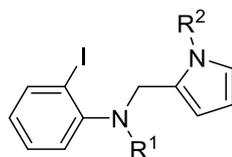
The last side of pathway C involved formation of the tosyl-protected tertiary amine (**104**). This started by the substitution of the –OMs group with a –NHTs group. This reaction worked, giving 36 % yield of the desired product (**104**) as well as 50% of the disubstituted product (**109**) (Scheme 35). Potentially, the amount of side product could be decreased by increasing the amount of the *p*-toluenesulfonamide. From there, a reductive amination reaction was performed with only the mono-substituted amine (**104**) in the presence of furfuryl aldehyde (**100**), NaBH(OAc)₃ and acetic acid was then investigated. TLC analysis showed no product formation after 24 h at room temperature hence the reaction was heated at reflux for an additional 24 h. The ¹H NMR spectrum of the crude product showed only the mixture of the starting materials, 85 % of starting material (**104**) present was recovered. The failure of the reaction was due to the starting material being a sulfonamide, thus the necessary imine needed for reductive amination was not formed.



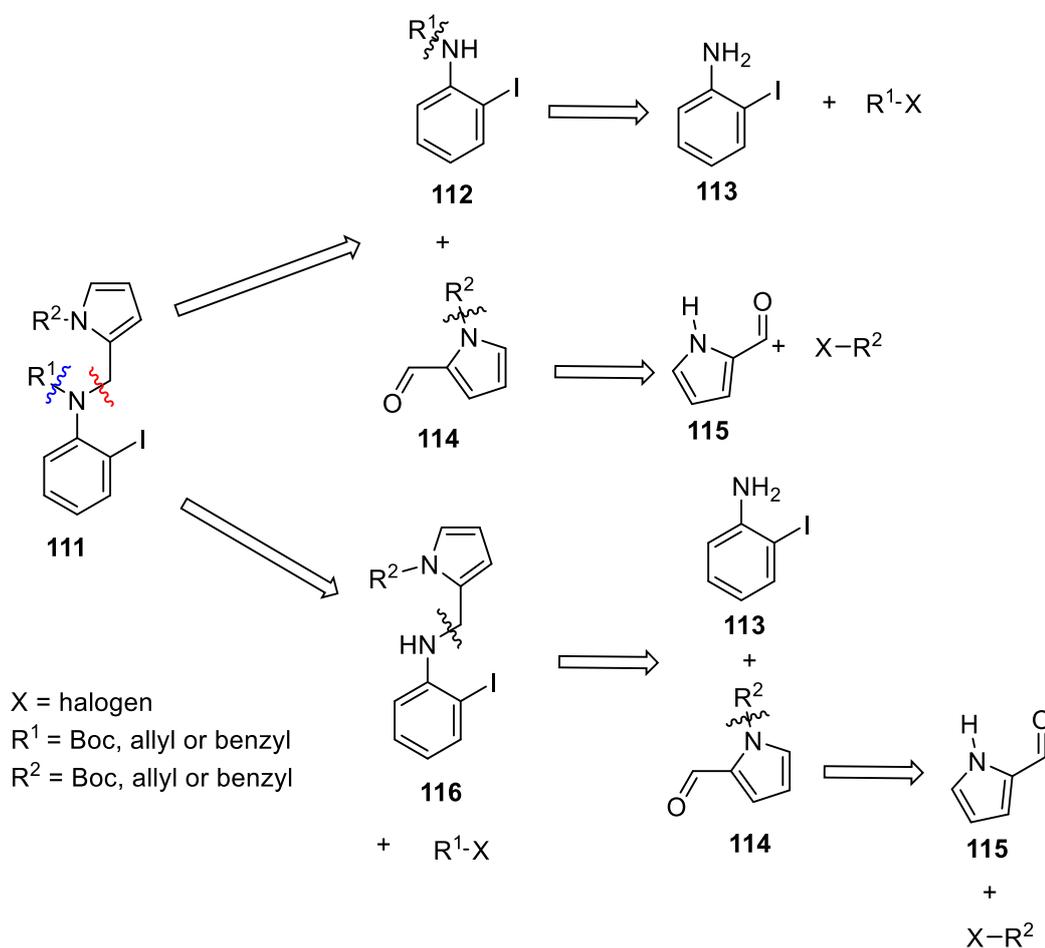
*Scheme 35: Synthesis of the N-(2-iodoallyl)-4-methylbenzenesulfonamide (**104**)⁵⁰ and the attempt of reductive amination to form the final precursor (**110**).*

2.2.4 Synthesis of (N, N) precursors

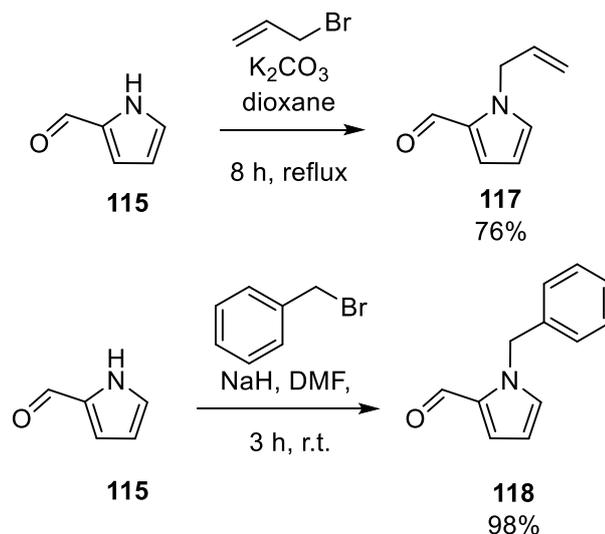
Different (N,N) precursors (**111**) were designed (Figure 11), and the protecting groups used on the nitrogen atoms were chosen based on previous work done by the group and with the use of Greene's book of protecting groups^{1,51}. From previous work it was known that the *tert*-butyloxycarbonyl (Boc) group can withstand the spirocyclization reaction, while tosyl (Ts) protection groups potentially inhibited the reaction. Allyl and benzyl protecting groups were chosen as second protecting groups as they are very easy to selectively deprotect.


111
 $R^1 = \text{Boc, allyl or Bn}; R^2 = \text{Boc, allyl or Bn}$
Figure 12: Proposed structure of the precursor (111).

Possible pathways involve reductive amination of primary and secondary amines (Figure 13). The starting materials for all of these pathways involved 2-iodoaniline and a protected pyrrole-2-carboxaldehyde with either an allyl, benzyl or a Boc protecting group.


Figure 13: Retrosynthesis plan for the (N,N) precursors (111).

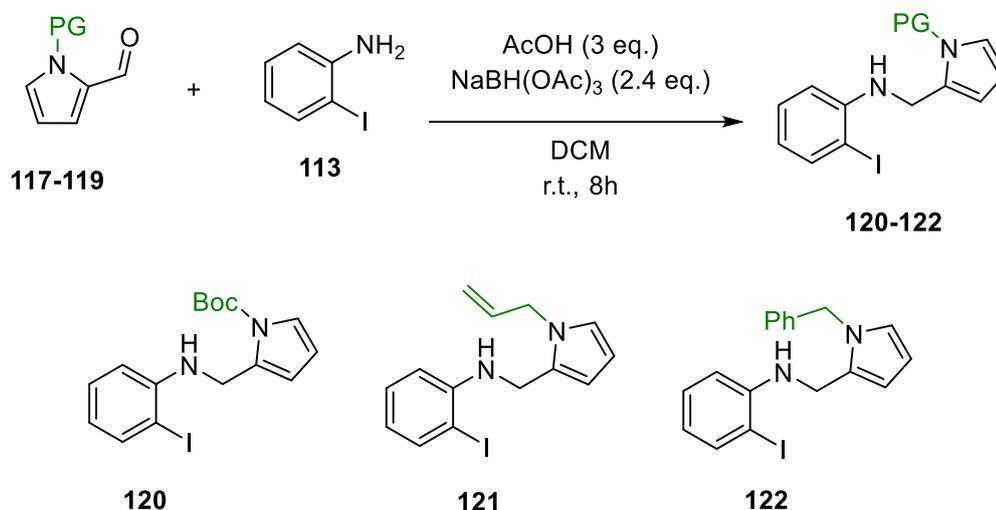
Protection of pyrrole-2-carboxaldehyde (**115**) was the first step in both pathways. The protections with benzyl and allyl groups worked well and isolated yields of 98% and 76% yield respectively (Scheme 36) were achieved.



Scheme 36: Allyl² and benzyl³ protection of pyrrole-2-carboxaldehyde to form (**117**) and (**118**).

2.2.4.1 Reductive amination of primary amines

The next step in the synthesis was the reaction of 2-iodoaniline (**113**) with the protected pyrrole-2-carboxaldehyde (**117**, **118** and **119**). Three parallel reactions were set up using the same reaction conditions to yield the three target compounds (**120-122**) (Scheme 37).



Scheme 37: Reductive amination of primary amine and target compounds (**120-122**)

2.2.4.1.1 Purification and NMR analysis

Analysis of the crude three products looked promising as determined by 1H NMR spectroscopy. Amine (**120**) was recrystallized from hexane and acetone, yielding a product in 70% yield in high purity (Figure 14; Spectrum 1). 1H NMR analysis involved a signal at around 4.2-4.6 ppm which corresponded to the methylene group between the pyrrole and the aniline for each compound. In the cases of (**121**) and (**122**) left over protected pyrrole

carboxylate (**117** and **118**) was observed (peak at ~ 9.5 ppm) showing the reaction may not have gone to completion.

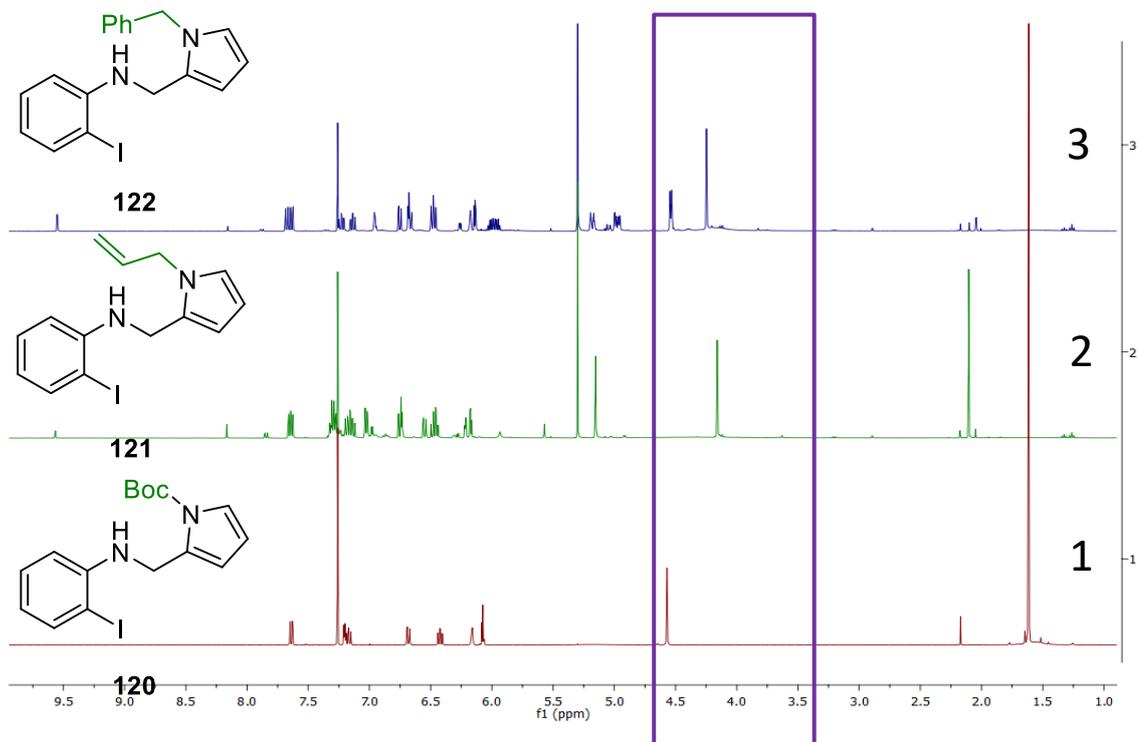


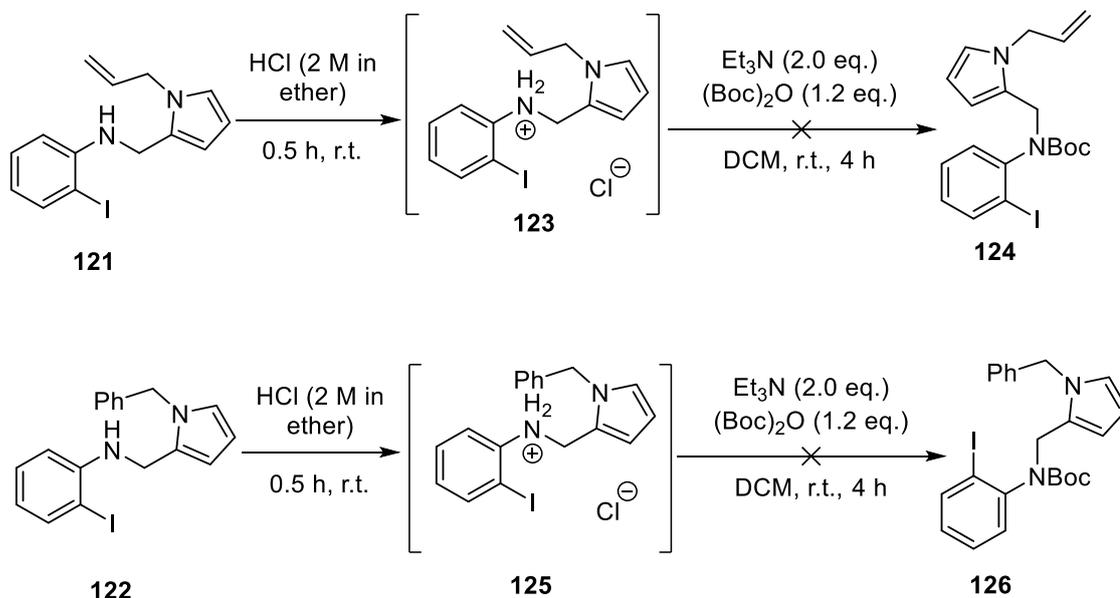
Figure 14: ^1H NMR of the crude products of **120-122** showing the possible formation of the products

Purification of compounds (**121**) and (**122**) was attempted by flash chromatography on silica gel after failing to recrystallize them in a range of solvents; however, no desired product (**121**) and (**122**) was recovered. Both dry and wet loading techniques were used but no material was isolated in either case. This could be due to the lack of stability of the pyrrole on the silica gel.

A potential way purifying (**121**) and (**122**) is formation of a HCl salt (Scheme 38), which can crystallize out of solution and is easy to handle. However, attempted formation of these salts proved difficult and they were difficult to analyse, as they were not very soluble in the common NMR solvents. In the case of the allyl protecting group, a brown powder was isolated and after analysis it was proven to be 2-iodoaniline (**113**). Based on the ^1H NMR analysis there were traces of product, but it cannot be confirmed if it was the pyrrole starting material or the desired product.

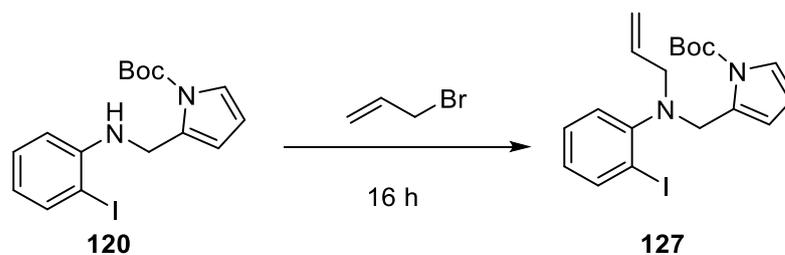
The two salts (**123** and **125**) were further treated with Et_3N and protected with Boc_2O to yield the final precursors. The reaction was tried at a 50 mg scale in both cases. After 4 h the reaction was quenched with NaHCO_3 saturated solution and extracted with ethyl acetate. These reactions did not give positive results. In both cases analysis of crude

reaction mixture by ^1H NMR showed a failure of the reactions. In the case of the desired product (**124**) there was no shift of peaks suggesting the lack of addition of the Boc group on the nitrogen. For the desired product (**126**) the reaction mixture had no peak corresponding to the Boc protecting group at ~ 1.50 ppm, suggesting the lack of the Boc group (Scheme 38).



*Scheme 38: Formation of salts (**123** and **125**) and Boc protection (**124** and **126**).*

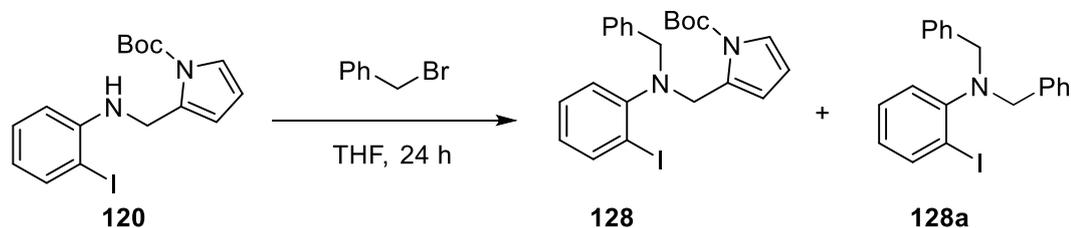
At the same time, the protection of amine (**120**) was attempted with both an allyl or a benzyl group. Attempted allyl protection resulted in recovery of the starting material in $>95\%$ yield when original conditions were used (Table 7, Entry 1). A stronger base, NaH, was used to encourage the deprotonation of the starting material (Table 7, Entry 2 and 3); but at $0\text{ }^\circ\text{C}$ there was no change based on TLC analysis so the reaction was warmed to room temperature. After 3 h the reaction mixture contained no starting material based on TLC. The crude mixture was washed with hexane and the starting material (**120**) was recovered in 11% yield as colourless crystals, the filtrate was concentrated and further purified using column chromatography. Even though there was significant separation by TLC, isolation was not successful and gave a mixture of compounds. The initial ^1H NMR analysis showed peaks that could indicate the product; however, it was not possible to separate it completely from side products. As the work on this crude product continued, more and more starting material precipitated, in total 30 % of the starting material was recovered. This could indicate the decomposition of the product back to the starting material.



Entry	Base	Temperature	Solvent	Results
1	K ₂ CO ₃	Reflux (100 °C)	Dioxane	Starting material (120) recovered in <95%
2	NaH	0°C	THF	After 1 h no conversion based on TLC
3	NaH	r.t.	THF	Cannot separate the desired product

Table 7: Allyl protection conditions and results.

Initially original conditions for benzyl protections were used (NaH, DMF, 3 h, r.t.) (Table 9, Entry 1), which led to decomposition of starting material and the formation of a side product (**128a**). Lowering the temperature seemed to help the reaction and based on crude ¹H NMR spectroscopy of the crude product, the desired product was formed. However, during column chromatography the product decomposed and no desired product was isolated.



Entry	Temperature	Results
1	r.t.	Decomposition and formation of side product (128a)
2	0°C	Decomposition on the column

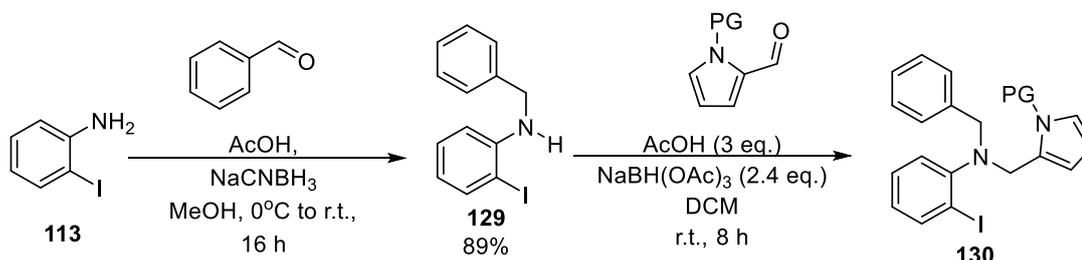
Table 8: Benzyl protection of conditions and results.

It is possible that these compounds are decomposing due to the presence of the pyrrole ring. One way of overcoming this undesired reaction is formation of the pyrrole ring at the end of the synthetic pathway.

2.2.4.2 Reductive amination on secondary amine

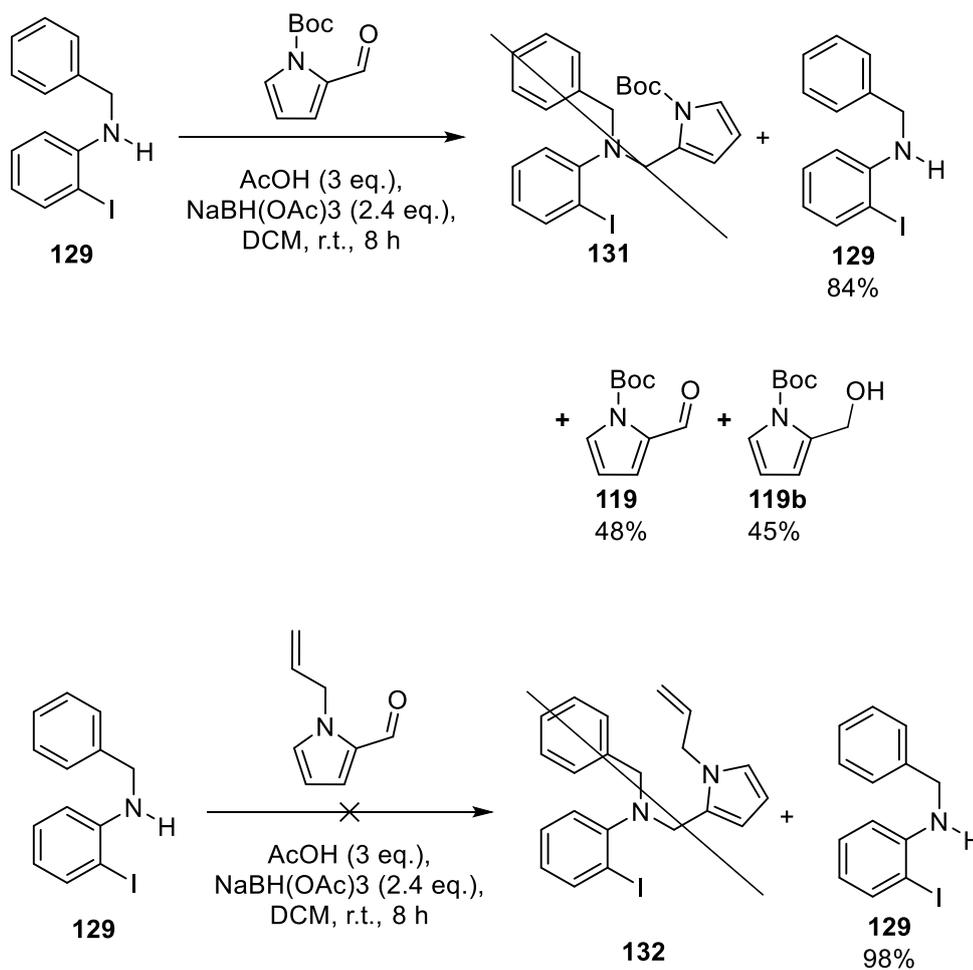
Another approach was needed to form these compounds, which involved the reaction of 2-iodoaniline (**113**) with benzaldehyde to form *N*-benzyl-2-iodoaniline (**129**) in 89 % yield.

Protected pyrrole (Scheme 39) could then be reacted with compound (**129**), using the same reductive amination conditions generating the desired product.



Scheme 39: Formation of secondary amine and its reductive amination reactions.

The reductive amination using previous conditions yielded no product. Attempted Boc protection yielded recovered starting material (**129**) in 84% yield, plus 48% of *N*-Boc-pyrrole-2-carboxaldehyde (**119**) and 45% of the aldehyde was isolated as the reduced alcohol (**119b**). Based on the ¹H NMR spectrum of the crude product of the allyl protection reaction, the desired product (**132**) was not formed, instead 98% of the starting material (**129**) was recovered (Scheme 40).



Scheme 40: Reductive amination to form (**131** and **132**).

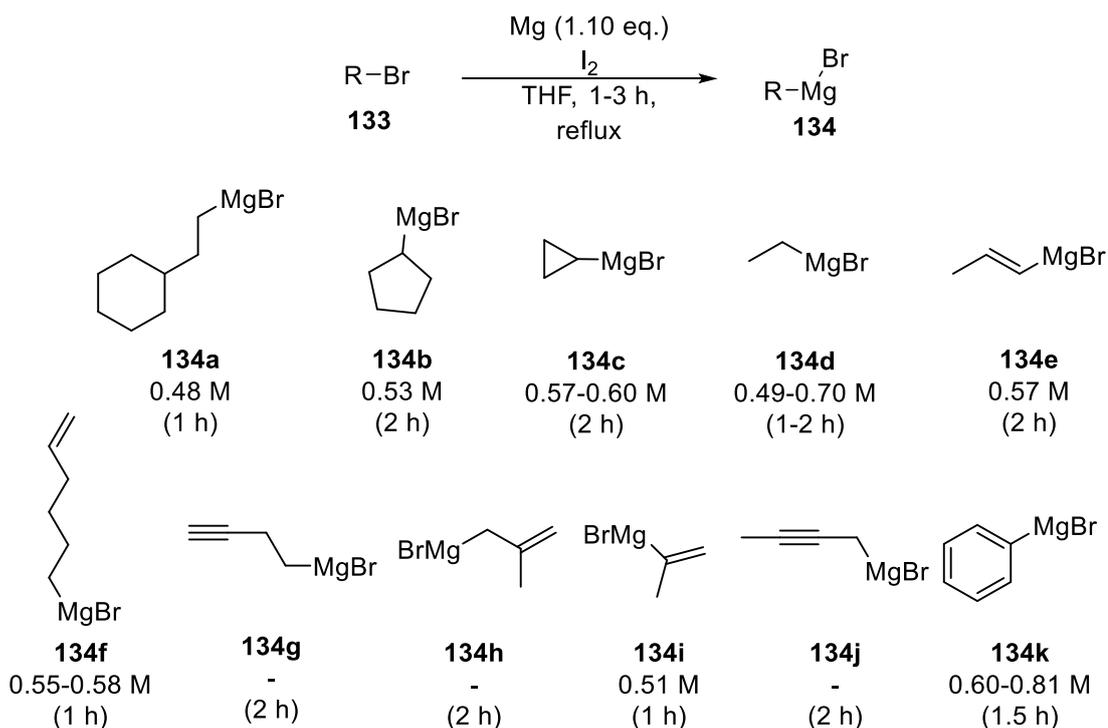
A Dean-Stark apparatus was then used to drive the imine formation to completion then the reducing agent was added afterwards to avoid reduction of an aldehyde. The reaction was performed with *N*-Boc-pyrrole-2-carboxaldehyde using benzene as a solvent and after 16 h under reflux, a sample of the mixture was worked up and analysed by ¹H NMR spectroscopy. However, based on the spectra there was no change, only starting material was present. *p*-Toluenesulfonic acid (10 mol%) was added to push the reaction, however after additional 20 h under reflux the desired product was not formed. This suggests that steric hindrance plays a large part in the reaction and another method may be necessary to form this tertiary amine.

Due to time constraints, these compounds were not pursued further. Different possible synthesis pathways are discussed in the further work section, however they also have their challenges and require multiple steps. With multiple cyclization precursors available, this project was moved to the iron-catalyzed cyclization reaction.

2.3 SPIROCYCLIZATION REACTIONS

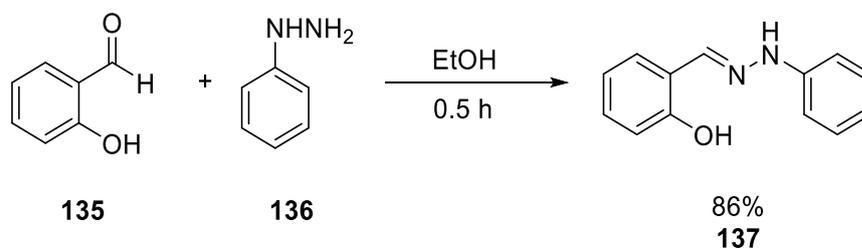
2.3.1 Formation and titration of Grignard reagents

Grignard reagents can be very easy to synthesize (Scheme 39). During the project, all of the spirocyclization reactions required synthesis and titration of a Grignard reagent beforehand. The majority of the Grignards reagents were formed without problems. However, some bromides did not react as planned forming magnesium salts that made both the titration and addition of the Grignard reagent not possible (Scheme 39; **134g**). In some cases (Scheme 39; **134h**, **134j**) when the bromide solution was added to the suspension of Mg in THF, the expected colour change from yellow to colourless did not occur.



Scheme 41: General conditions for formation of a Grignard reagent and list of the Grignard reagent made during the project.

The concentration of the Grignard reagent was measured by titration using salicylaldehyde phenylhydrazone (**137**), which was prepared by reaction of phenylhydrazine with salicylaldehyde in ethanol to yield the desired product (**137**) in 86% yield (Scheme 40).



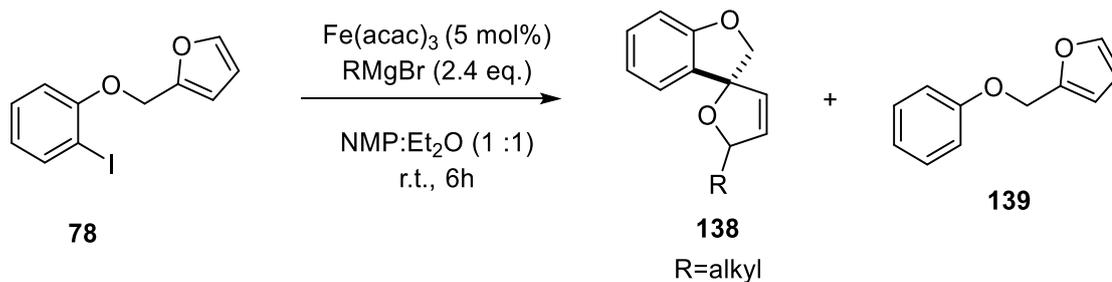
*Scheme 42 Synthesis of salicylaldehyde phenylhydrazone (**137**).⁵⁴*

2.3.2 Iron-catalyzed alkylative spirocyclization using (O,O) precursor

2.3.2.1 Initial scope

First, the spirocyclization reaction was investigated using the reported conditions (Scheme 41)¹.

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Scheme 43: Spirocyclization reaction using the reported conditions with an alkyl Grignard reagent.

Six reactions were performed yielding six new spirocycles (Figure 15; **138a-f**). However, the yield of these reactions was much lower the previously reported for the other substrates, and the products proved difficult to purify by chromatography. The best example was (**138e**), which was obtained in 19% yield, using the Grignard reagent derived from 1-bromoprop-1-ene. The main problem with the reaction was the formation of the deiodinated starting material (**139**). The ratios of the side product (**139**) to the desired products (**138**) are shown below the percentage yield of each spirocycles; this ratio was determined by ^1H NMR analysis of the crude reaction mixture. Due to the small amount of material isolated most of these were only analysed by NMR spectroscopy. IR spectroscopy and mass spectroscopy were not performed at this stage, as the reaction needed to be optimised first to generate material for the analysis. The yields of products (**138b**) and (**138c**) were approximated by analysis of the ^1H NMR spectrum of the crude product mixture.

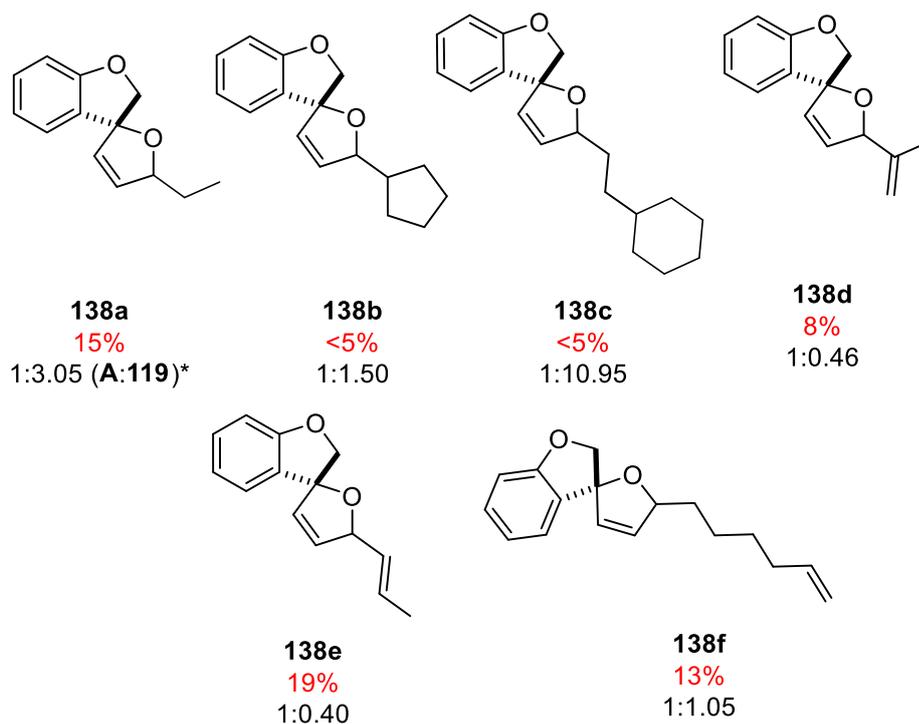
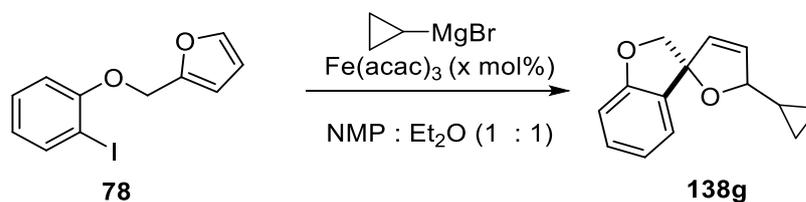


Figure 15: Initial scope of the spiroheterocyclization reaction (**138a-f**). * ratio based on ^1H NMR analysis of the crude product.

2.3.2.2 Optimisation of alkyl spirocyclizations

The effect of the temperature on the reaction was first investigated using a Grignard reagent derived from bromocyclopropane (Table 9). Due to using Et_2O as the solvent, the highest temperature that the reaction could be performed at without sealing the vessel was $40\text{ }^\circ\text{C}$ (Table 9, Entry 3), the reaction was also left stirring for longer. Traces of product were observed in the crude mixture when the amount of catalyst was doubled, however the temperature had no effect on the reaction (Table 9, Entry 4).

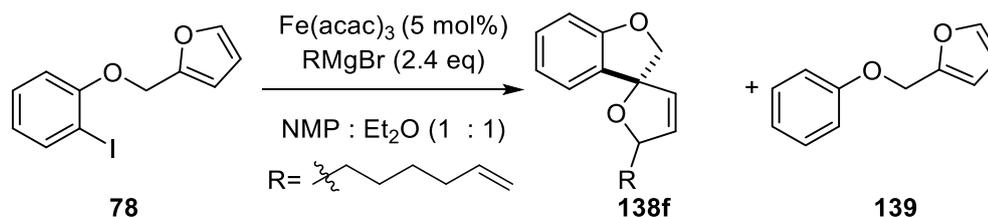


Entry	Time	Fe(acac)_3 (mol %)	Temperature ($^\circ\text{C}$)	% Yield of (138g)
1	24	5	r.t.	-
2	24	5	35	-
3	16	5	reflux	-
4	16	10	r.t.	Traces

Table 9: Effect of the temperature and amount of catalyst on the spirocyclization reaction.

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Next, the investigation into the time of the reaction was performed; in this case the spirocycle (**138f**) was made. Every 2 hours, an aliquot of the reaction mixture was taken (2 mL) and usual worked up. ¹H NMR spectra of crude product at 2 hours, 4 hours, 6 hours and 22 hours were recorded and compared (Table 10; Entry 1-4), and no starting material was observed. Based on the results, it was decided not to leave the reaction for longer than 3 hours because the ratio between the desired product and side product was similar at every stage.

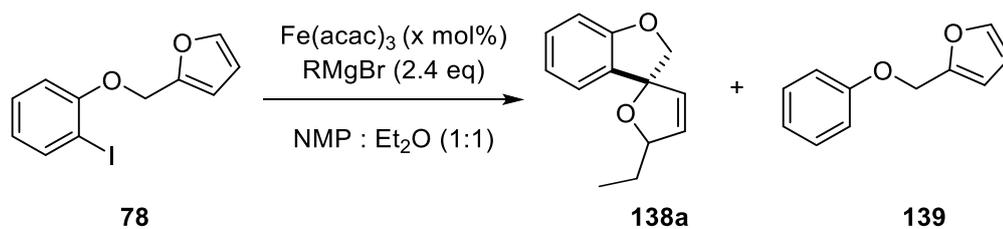


Entry	Time (h)	Ratio 138f:139
1	2	1:1.88
2	4	1:1.73
3	6	1:1.43
4	22	1:1.83

Table 10: Investigation of the effect of the time on the reaction.

The following optimisation was performed using EtMgBr. The main optimisation of the reaction involved increasing the amount of catalyst. This however, did not increase the reaction yield as much as was hoped. The yield of product was still the best at 10 mol% loading of the catalyst (Table 11; Entry 2). The reaction time was changed from 22 h to 3 h based on the results from the timed reaction. The reaction with 30 mol% loading of the catalyst was carried out twice (Table 11, Entry 6 and 7) giving very different results; this suggests the reaction may not be very reliable. In all of the cases, the starting material was observed by ¹H NMR analysis of the crude product mixture.

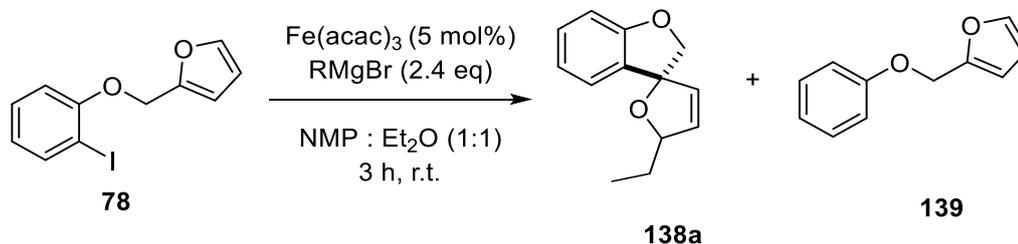
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Entry	$\text{Fe}(\text{acac})_3$ (mol %)	Concentration of Grignard reagent	Reaction time (h)	138a:139 ratio ¹	% yield of 138a
1	5	0.65 M	22	1:3.09	15
2	10	0.65 M	22	1:1.85	34
3	15	0.64 M	3	1:1.94	8
4	20	0.64 M	3	1:1.56	9
5	25	0.64 M	3	1:1.26	9
6	30	0.64 M	3	1:1.56	11
7	30	0.59 M	3	1:1.09	27
8	40	0.59 M	3	1:1.70	10

Table 11: Changing the % mol of the catalyst. (¹= based on ¹H NMR)

Li_2CuCl_4 can change the reactivity of alkyl Grignards by forming an organocuprate specie. It was used as an additive in the reaction. When added, the yield was increased from 15 % to 34 %. Reaction with just the Li_2CuCl_4 was also performed to confirm that the $\text{Fe}(\text{acac})_3$ is performing the reaction (Table 12).



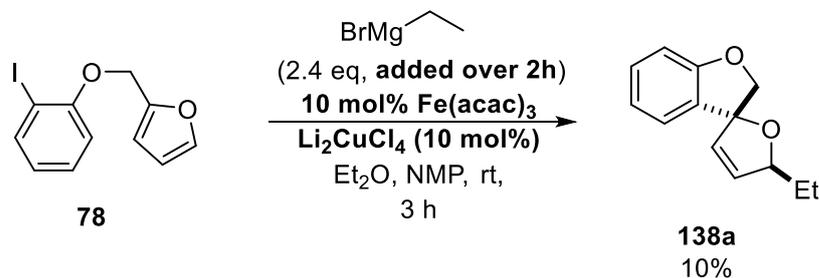
Entry	$\text{Fe}(\text{acac})_3$ (mol %)	Additive	Concentration of Grignard reagent	138a:139 ratio ¹	% yield of 138a
1	5	Li_2CuCl_4 (10 mol%)	0.65 M	1:1.90	35
2	0	Li_2CuCl_4 (10 mol%)	0.59 M	-	0

Table 12: Effect of Li_2CuCl_4 on the spirocyclization reaction (¹= based on ¹H NMR).

The addition rate of the Grignard also plays a major role in the reaction, as when the Grignard reagent is added slower, the product yield improved (from 15 to 36% yield). To control the addition of the Grignard reagent at a slower rate, a syringe pump was used. The addition took place over to 2 h using 5 mol% of $\text{Fe}(\text{acac})_3$, and stirring for an additional 1 hour allowed the reaction to go to completion.

Based on all of the results, a reaction implementing all of the changes that increased the yield was performed (Scheme 42). This however did not improve the reaction, giving only

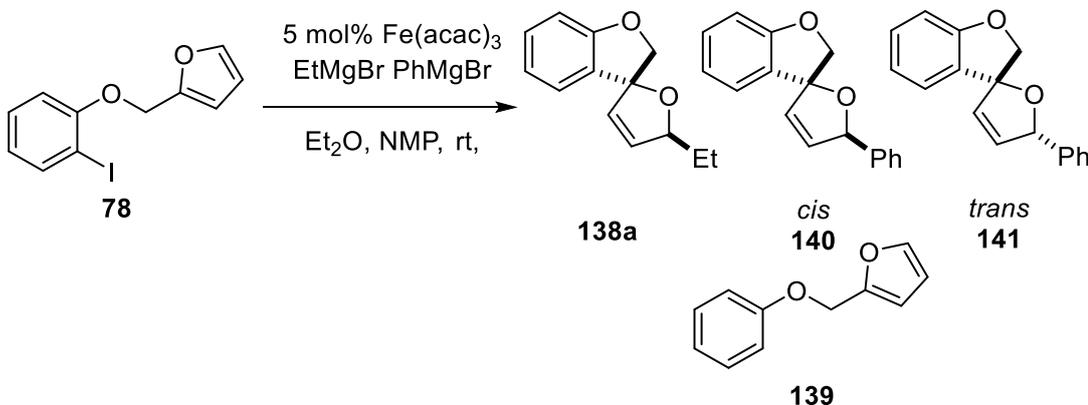
10% yield of product (**138a**). In conclusion, the alkyl Grignards do not work well in the spirocyclization reaction using $\text{Fe}(\text{acac})_3$ catalysis. The normal methods of optimisation had little to no effect and more drastic changes would be necessary.



Scheme 44: Implementing all changes into the reaction conditions.

2.3.2.2.1 Competition reactions: aromatic vs alkyl Grignard reagents

A series of reactions with PhMgBr and EtMgBr was performed to investigate the reactivity of the two different Grignard reagents and investigate why EtMgBr performs much worse in the reaction. Different ratios of the two Grignards were used (total of 2.4 eq.) (Table 13).



Entry	Eq. ratio $\text{PhMgBr}:\text{EtMgBr}$	140 (%) yield)	141 (%) yield)	138a (%) yield)	139 (%) yield)
1	2.4 : 0	73	0	0	5
2	1.8 : 0.6	40	-	-	12
3	1.6 : 0.8	61	6	10	14
4	1.2 : 1.2	35	1	6	17
5	0.8 : 1.6	39	2	14	20
6	0.6 : 1.8	30	1	13	25
7	0 : 2.4	0	0	14	43

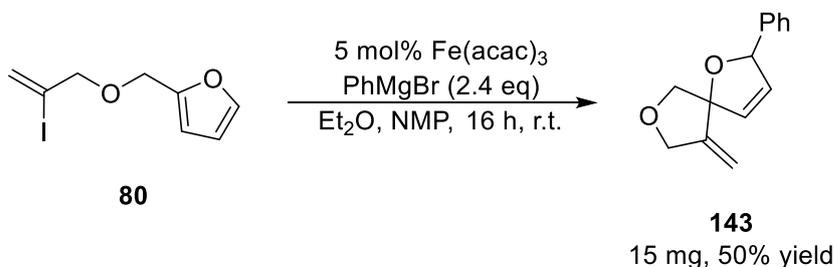
Table 13: Competition reaction between PhMgBr and EtMgBr .

Surprisingly, based on crude ^1H NMR analysis of the crude reaction mixtures, 4 products were observed when both Grignard reagents were used. The reaction used 5 mol% of

catalyst and was left stirring for 6 h. The 4 products formed were **138a**, **140**, **141** and **139**. The amount of the deiodinated side product (**139**) that was formed when only alkyl Grignard was being used was significant (43%, Table 13, Entry 7). This decreased as the equivalents of the PhMgBr increased in the reaction to 5% (Table 13, Entry 1). The separation of the three spirocycles was difficult due to their very similar structures. It was possible to separate **140** from the other two spirocycles but the **141** and **138a** spirocycles were impossible to separate by flash chromatography on silica gel (further NMR analysis of the products is given in section 2.2.4.2.). The yields were based on the ^1H NMR analysis. The 1:1 ratio reaction shows that the aromatic Grignard will form the desired product in good yield, while the alkyl Grignard will only give traces of product. The mechanism of the reaction was discussed before (Section 1.7.2.1.1), and it shows two points at which a Grignard reagent is used: the reduction of the $\text{Fe}(\text{acac})_3$ catalyst and substitution with Fe – spiro complex at the end of the reaction. In reactions with 1:2 and 1:3 ratio of PhMgBr:EtMgBr it was expected to see more **138a** product than **140**. The opposite was recorded, which suggests that most of the PhMgBr was used in the final step of the reaction and EtMgBr is used to recycle the catalyst.

2.3.3 Iron-catalyzed alkylative spirocyclization using vinyl iodides precursors

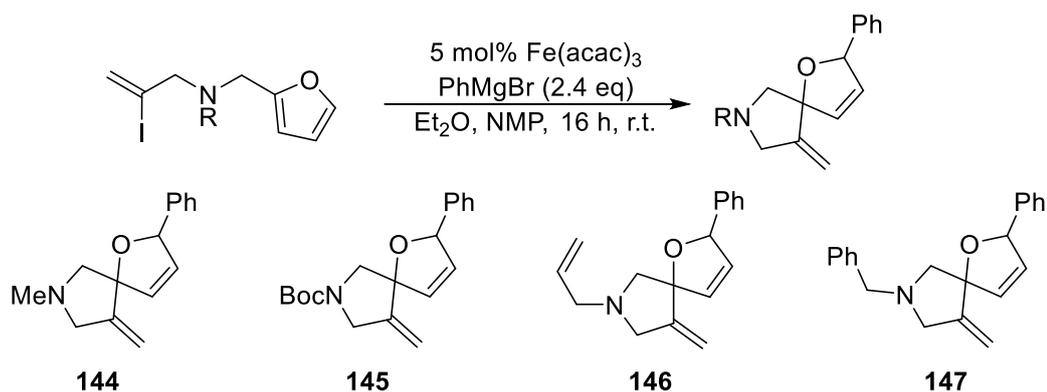
As previously discussed, a number of novel vinyl iodide precursors were prepared. The first one was the (O,O) precursor (**80**), but as only 35 milligrams of the ether was isolated, the spirocyclization reaction was performed on a very small scale. The reaction has worked, yielding 50% of the desired product, 9-methylene-2-phenyl-1,7-dioxaspiro[4.4]non-3-ene (**143**) (Scheme 43). However, due to the low yield during the synthesis of the precursor (**80**) the reaction was not further explored, and this would need to be optimised further before more spirocyclization reactions can be investigated.



*Scheme 45: Iron-catalyzed alkylative spirocyclization using vinyl iodide ether precursor; formation of 9-methylene-2-phenyl-1,7-dioxaspiro[4.4]non-3-ene (**143**).*

The amine vinyl iodide precursors were easier to prepare due to the nitrogen connection instead of oxygen. The formation of the amine vinyl iodide precursors worked well. Some of them were prepared on smaller scale due to lower yields and small scale of the synthesis. One of the main differences between the spirocycles formed from vinyl iodides compared to the aromatic precursors is the lack of a very characteristic peak in ^1H NMR (pair of roofing doublets at $\sim 4.5\text{ppm}$) (discussed in section 2.3.4.). This meant that crude ^1H NMR spectroscopy on the crude products was less useful in the evaluation of the reaction.

As expected, when $\text{R}=\text{H}$ (Table 14, Entry 1) the reaction did not work, and the only isolated compounds were NMP and side products from the Grignard reagent. The starting material was not visible on the ^1H NMR spectrum of the crude product. This could be due to the unprotected nitrogen poisoning the catalyst, and causing the reaction to not progress. The other substrates gave the desired products; starting with the methyl group (Table 14, Entry 2), the reaction gave very low yield of 7-methyl-9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene. As expected, the Boc-protected amine worked well (Table 14, Entry 3) giving 50 % yield of the product (a Boc group was previously used in an aromatic amine precursor). Due to the difficulties with the purification, some fractions collected contained some impurities along with the desired product *tert*-butyl 9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene-7-carboxylate (**145**), decreasing its purity. The allyl protecting group was performed on the smallest scale and only 1 milligram of 7-allyl-9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene (**146**) was isolated (Table 14, Entry 4). Lastly the precursor (**108**) (Table 14, Entry 5) gave the product 7-benzyl-9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene (**147**) in 35% yield. The benzyl protecting group (**147**) gave a lower yield than the Boc protecting group (**145**) – this might be due to the nitrogen being less nucleophilic when a Boc group is attached compared to benzyl group.



Entry	R	Product	Scale (mmol)	Isolated % yield	Purity
1	H	-	0.5	-	-
2	Me	144	0.9	5	50%
3	Boc	145	1.2	50	83%
4	Allyl	146	0.3	<1	90%
5	Bn	147	1.0	35	95%

Table 14: Results of the iron-catalyzed alkylative spirocyclization using vinyl iodide amine precursor and the spirocycles formed during the reaction.

2.3.4 ^1H NMR analysis of spirocycles

One of the most characteristic signals observed by ^1H NMR spectroscopy is a pair of roofing doublets at ~ 4.40 ppm which is caused by an AB system (Figure 16). Both protons A and B are bonded to the same carbon atom, however they are in different environments which gives rise to two signals, and second-order effects cause the roofing of the signals.

The identification of the *cis* isomer and *trans* isomer analysis was based on the previous work done by the group which indicated that the *trans* isomer has a higher coupling constant between two doublets (8 Hz), whilst the *cis* isomers have a coupling constant of 12 Hz. This is observed when a mixture of heterospirocycles are present (Figure 16).

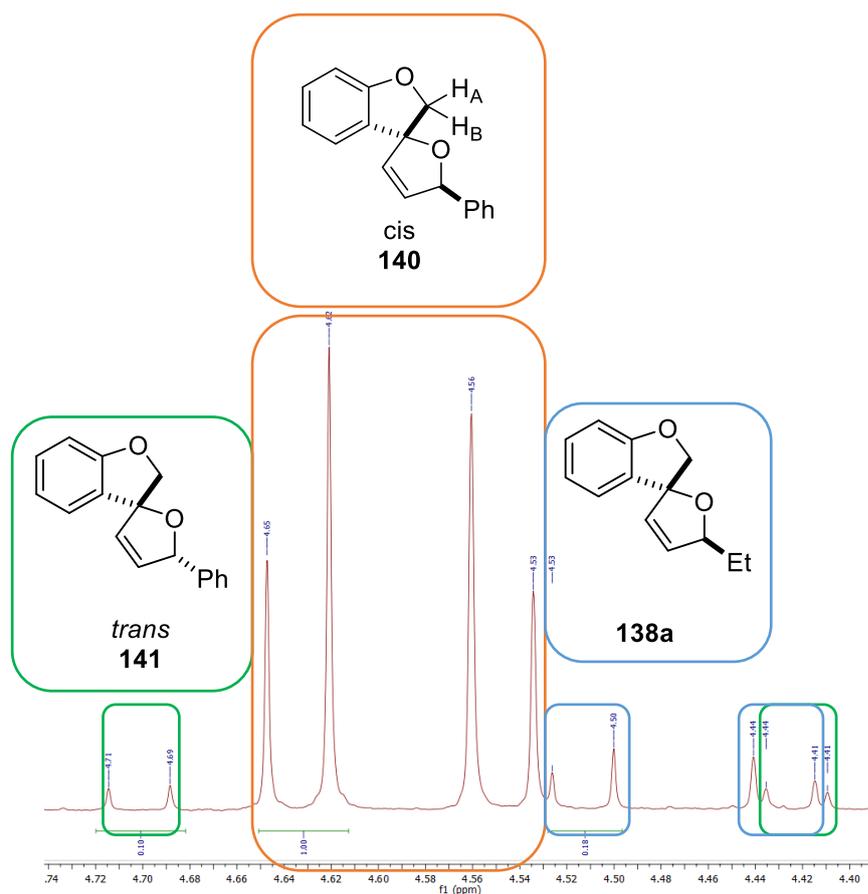


Figure 16: Comparison of the sets of doublets in the competition reaction.

2.3.4.1 COSY analysis of 7-benzyl-9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene (147)

To confirm the structures of the newly formed spirocycles, a correlation spectroscopy (COSY) analysis was performed. COSY (Figure 18) can show spin-spin couplings between nuclei. As an example, the spirocycles (147) will be discussed. The main correlations are summarised in the Table 15, showing the number of bonds the two protons were away (Table 15).

Table 15 Summary of the COSY NMR signals for 127.

Correlation	Proton environment	Proton environment
	1	2
1	A	Ph ₁
2	E/F	B
3	D	C
4	E/F	G

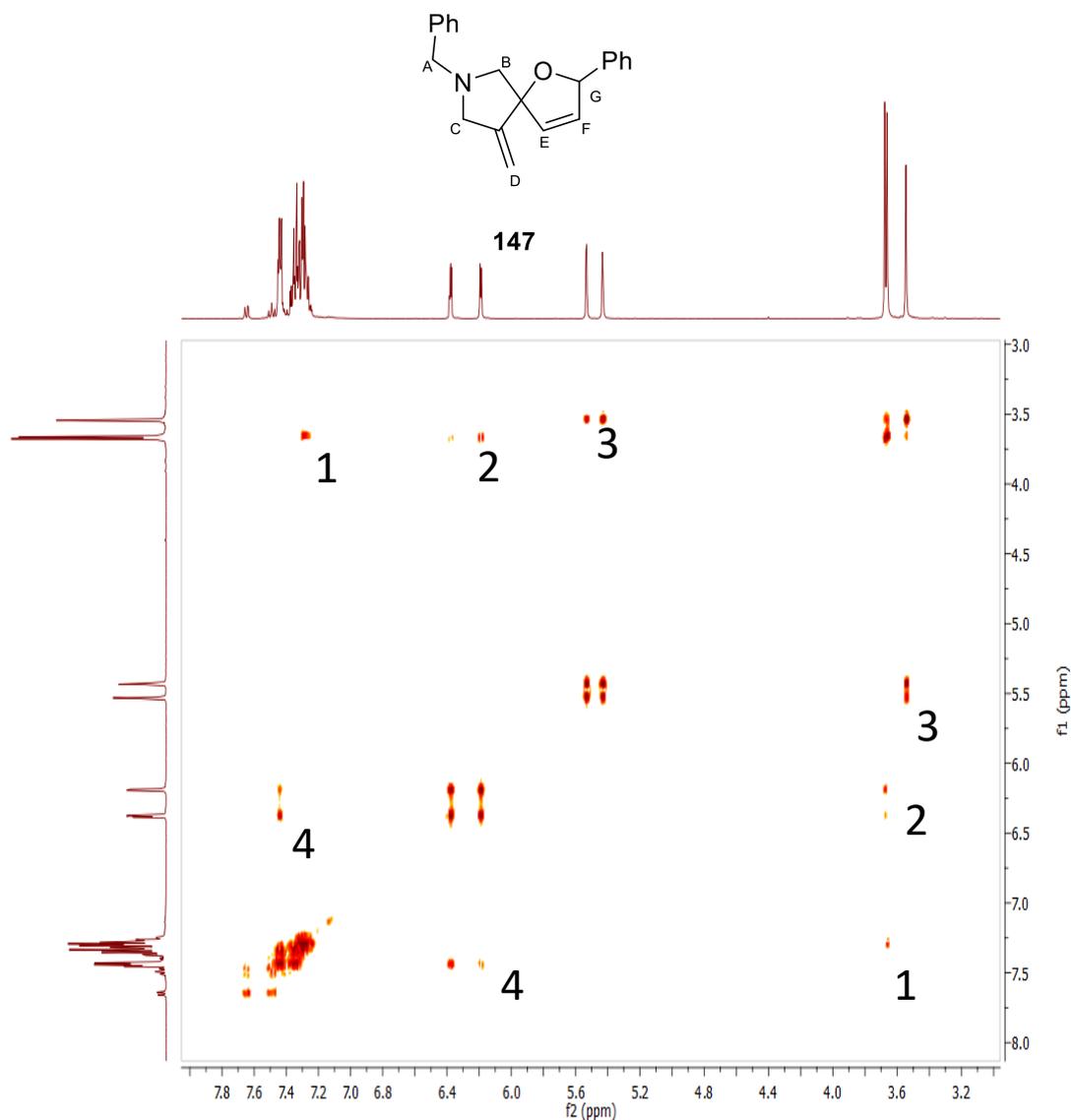


Figure 17: COSY of *-benzyl-9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene* **147**.

In the case of the *tert*-butyl 9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene-7-carboxylate (**145**), the ^1H NMR signals were broad. This made it very difficult to assign the signals to the protons. To help with that a variable temperature NMR was performed to improve the signal quality. This however, did not improve the spectra and as the temperature was increased the signals became even broader (Figure 19). This was not possible in the aromatic spirocycles due to more rigid system.

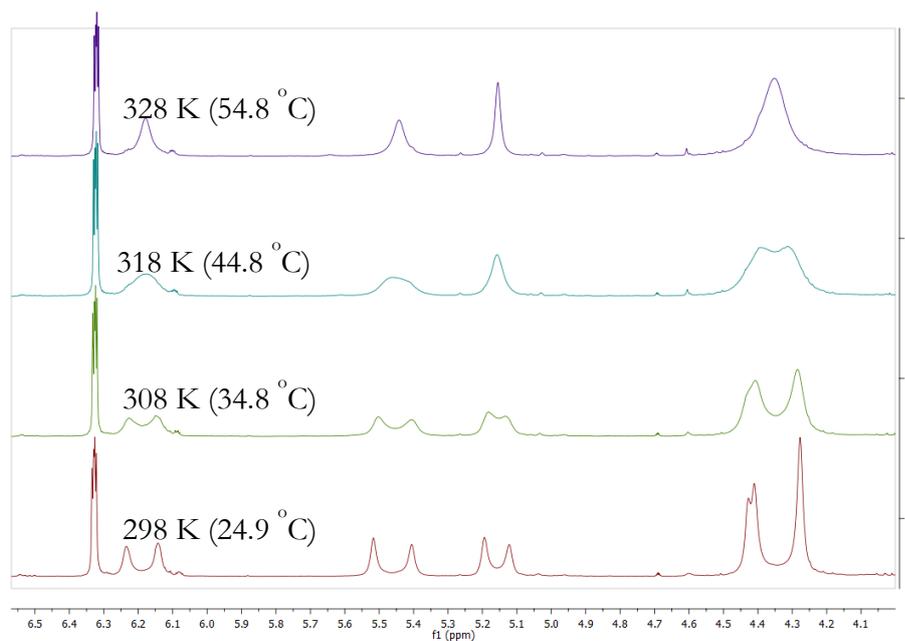


Figure 18: Varied temperature ^1H NMR of **125**.

2.3.4.2 Side product **139**

One of the main problems with the alkylative spirocyclization reaction was the formation of the side product (**139**). This compound had the same R_f value as the starting material, so the reaction could not be tracked by TLC analysis. ^1H NMR spectra, however, showed the differences clearly. When comparing the side product (**139**) with the starting material (**78**) we can see two new signals: a doublet of doublets, and a doublet of triplets (Figure 20). These signals arise when the iodine atom is present on the aromatic ring. The side product does not have those peaks. When looking at the ^1H NMR spectrum of the crude product, we can clearly see the lack of the starting material by the decrease of these two peaks.

Iron-Catalyzed Spirocyclization Project

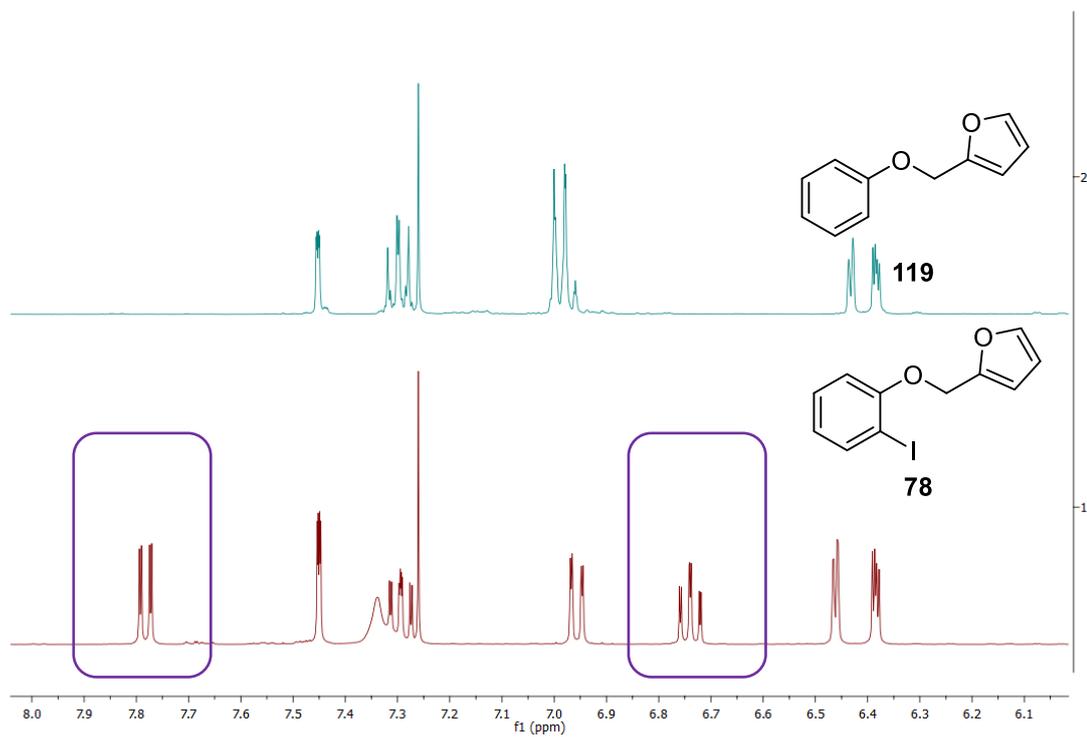


Figure 19: ¹H NMR spectra of **139** and **78**.

3. CONCLUSION AND FURTHER WORK

In total eleven novel spirocycles were made (Figure 22). Much of the time was spent designing new precursors for the reaction and developing synthetic pathways for their preparation.

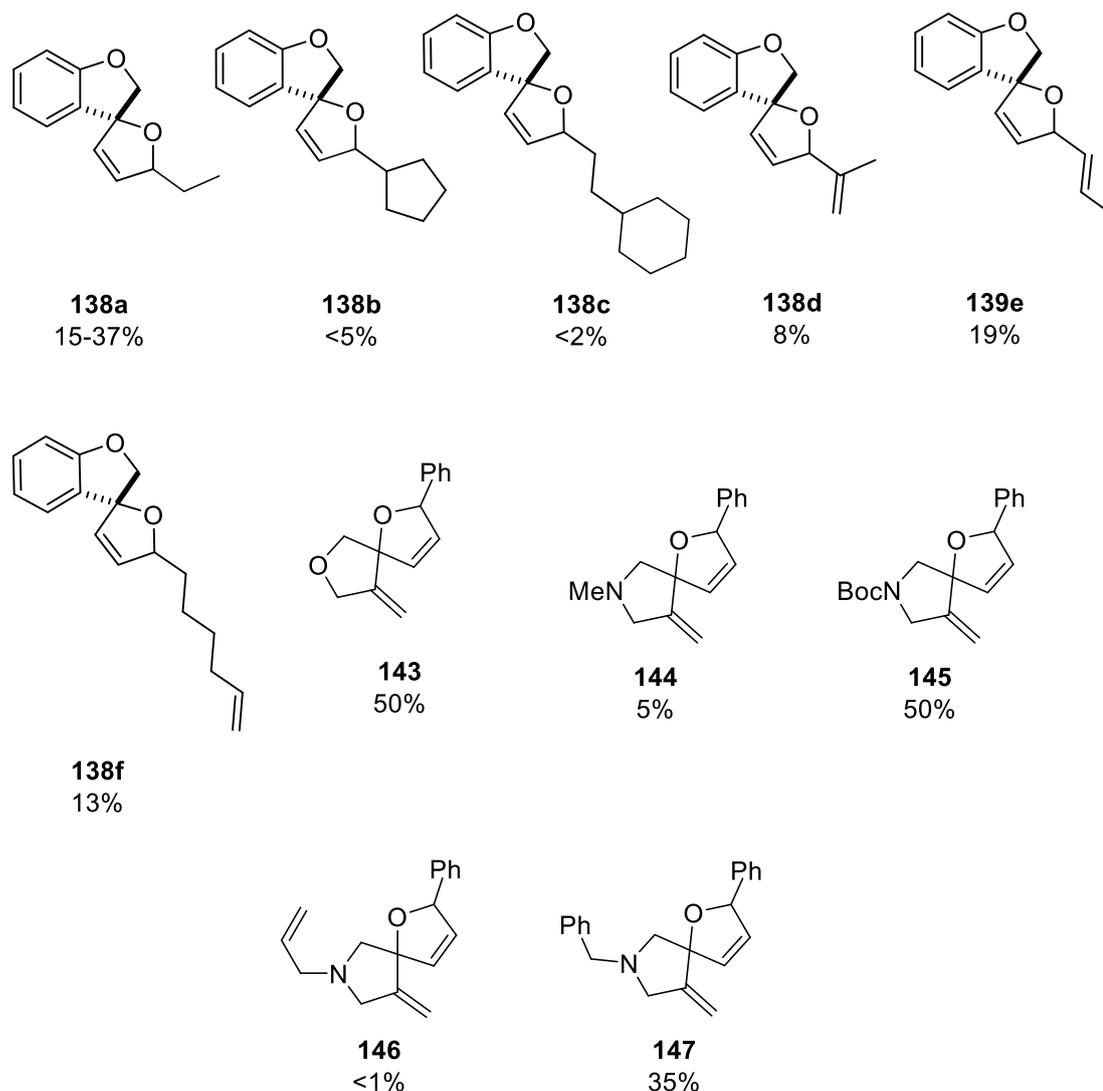


Figure 20: List of heterospirocycles made during the project and their yield.

One of the biggest challenges in this project was not the spirocyclization reaction but the synthesis of the precursors used in the reaction. The yield of the original precursor (**78**) that was used in the alkyl Grignard reagent part of the project was increased from 32 to 52% over the course of the project. Alkyl Grignard reagents were used in the spirocyclization reactions, but optimisation proved difficult with many different factors leading to mixed results. Competition reactions confirmed the lack of reactivity of the alkyl

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Grignard compared to the aromatic Grignard in the reaction. A group of novel vinyl iodide reagents were made and new spirocycles were made from them in a low to good yield. These results show promise and when a method is found to synthesise the precursors efficiently the spirocyclization reaction can be expanded further.

Further work would focus on formation of the precursors and finding new and better yielding pathways to form them. In the case of the aromatic amines, one of the methods of forming the final product would be formation of the pyrrole ring last, possibly by Paal-Knorr synthesis, which uses a 1,4-diketone⁵⁵. Similar approaches could be used in the formation of vinyl iodide ethers⁵⁶. The furyl ring can be very reactive and can inhibit reaction. Forming the furan ring last could help with this problem.

The spirocycles formed from vinyl iodide amines can be further explored by using different protecting groups as well as trying to optimize the conditions of the reaction to achieve higher yields. Addition of other functional groups on to the spirocycles could also be possible. Results from this project show promise and when a method is found to synthesise the precursors more efficiently the spirocyclization reaction can be expanded further.

4. EXPERIMENTAL

4.1 GENERAL INFORMATION

4.1.1 Nuclear magnetic resonance spectroscopy

Nuclear magnetic resonance spectra were recorded using a Bruker AVANCE III (400 MHz) NMR spectrometer (Bruker UK Ltd., Coventry, UK) at 298K and referenced to TMS. NMR spectra were viewed and analysed using Bruker Topspin NMR software.

4.1.2 Infra-red spectroscopy

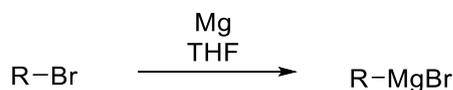
Infra-red spectroscopy data was recorded using an Agilent Technologies Cary 630 FTIR instrument (Agilent Technologies Ltd., Cheshire, UK) from 4000-650 cm^{-1} .

4.1.3 Mass spectrometry

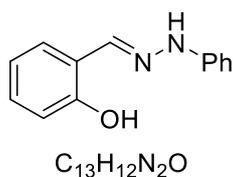
Mass Spectrometry data was recorded using a Shimadzu LCMS-IT-TOF (Shimadzu UK Ltd., Milton Keynes, UK) spectrometer which is was fronted by a Shimadzu NexeraX2 UHPLC system (Shimadzu UK Ltd., Milton Keynes, UK).

4.2 SYNTHESIS AND TITRATION OF THE GRIGNARD REAGENTS

One of the titration methods is the use of menthol and 1,10-phenanthroline in dry (THF) solution, the end point being a dark violet solution which is easily observable⁵⁷. Another method is the use of salicylaldehyde phenylhydrazone in dry THF, in this case the end point colour of this titration is golden orange colour⁵⁴.



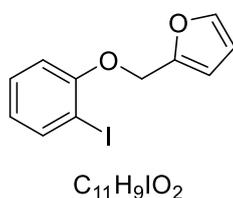
To an oven dried round-bottomed flask was added Mg (1.1 eq) and an iodine crystal under nitrogen. THF was added to the flask. The bromide (1.0 eq) was dissolved in THF and added dropwise to the flask. The reaction was heated to reflux and stirred for 1h. The Grignard reagent was titrated against salicylaldehyde phenylhydrazone (60 mg) in THF (10 mL) to calculate the Grignard reagent's concentration.

Salicylaldehyde Phenylhydrazone (137)⁵⁴

Phenylhydrazine (2.92 g, 27.0 mmol) was dissolved in ethanol (10 mL) and stirred. A solution of salicylaldehyde (3.30 g, 27.0 mmol) in ethanol (15 mL) was added. The solution was stirred for 30 min at room temperature and then cooled to $-15\text{ }^{\circ}\text{C}$. The white solid was collected by vacuum filtration and washed with ice-cold ethanol to give the desired product (**137**) (3.65 g, 67 % yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.90 (s, 1H, N-H), 7.86 (s, 1H, N=C-H), 7.37 – 7.30 (m, 2H, ArH), 7.30 – 7.24 (m, 1H, ArH), 7.17 (dd, $J = 7.7, 1.5$ Hz, 1H, ArH), 7.06 – 6.90 (m, 5H, ArH).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 157.1 (C-OH), 143.4 (N=C-H), 141.2 (CAr), 130.1 (CAr), 129.6 (CAr), 129.4 (CAr), 120.9 (CAr), 119.5 (CAr), 118.5 (CAr), 116.6 (CAr), 112.7 (CAr).

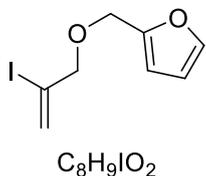
4.3 SYNTHESIS OF PRECURSORS**2-[(2-Iodophenoxy)methyl]-furan (78)**⁵⁸

To an oven dried round bottom flask was added PPh_3 (19.7 g, 75.0 mmol), 2-iodophenol (4.40 g, 20.0 mmol), THF (100 mL) and furfuryl alcohol (7.35 g, 75.0 mmol) under nitrogen. Next, DIAD (15.2 g, 75.0 mmol) was added dropwise at $0\text{ }^{\circ}\text{C}$. The reaction was stirred at $0\text{ }^{\circ}\text{C}$ for 30 minutes and then warmed up to room temperature until the starting material was completely consumed. The reaction was concentrated under reduced pressure, the residue was dissolved in CH_2Cl_2 (75 mL) then washed with 2M NaOH (75 mL), water (75 mL) and brine (75 mL). The organic layer was dried (MgSO_4) and concentrated under reduced pressure. The residue was dissolved in Et_2O , next hexane was added dropwise, and triphenylphosphine oxide was removed by filtration. The filtrate was concentrated under reduced pressure and the product was purified by column chromatography on silica eluting with hexane: CH_2Cl_2 (2:1) to give the desired product (**78**) as colourless oil (3.10 g, 52 %).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 (dd, $J = 7.8, 1.6$ Hz, 1H, Ar-H), 7.45 (dd, $J = 1.8, 0.8$ Hz, 1H, ArH), 7.29 (ddd, $J = 8.2, 7.4, 1.6$ Hz, 1H, ArH), 6.96 (dd, $J = 8.2, 1.3$ Hz, 1H, ArH), 6.78 – 6.70 (m, 1H, ArH), 6.46 (dd, $J = 3.3, 0.7$ Hz, 1H, ArH), 6.38 (dd, $J = 3.2, 1.9$ Hz, 1H, ArH), 5.07 (s, 2H, CH_2).

^{13}C NMR (101 MHz, CDCl_3) δ 157.2 ($\underline{\text{C}}\text{Ar}$), 149.93 ($\underline{\text{C}}\text{Ar}$), 143.0 ($\underline{\text{C}}\text{Ar}$), 139.7 ($\underline{\text{C}}\text{Ar}$), 129.4 ($\underline{\text{C}}\text{Ar}$), 123.3 ($\underline{\text{C}}\text{Ar}$), 113.6 ($\underline{\text{C}}\text{Ar}$), 110.6 ($\underline{\text{C}}\text{Ar}$), 110.1 ($\underline{\text{C}}\text{Ar}$), 87.30 ($\underline{\text{C}}\text{Ar}$), 64.0 (CH_2).

2-(((2-iodoallyl)oxy)methyl)furan (**80**)



To a suspension of dry NaH (420 mg, 10.5 mmol, 60 % suspension in oil) in THF (25 mL) was added a solution of 2-iodo-2-propen-1-methanesulfonate (1.86 g, 7.00 mmol) in THF (5 mL) at 0 °C under nitrogen. Next, furfuryl alcohol (1.03 g, 10.5 mmol) was added dropwise. The mixture was slowly warmed to room temperature and stirred for 66 h. After removal of the solvent, the mixture was redissolved in Et_2O (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried (MgSO_4), filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica eluting with EtOAc :hexane (1:20 \rightarrow 1:10) to give the desired product (**80**) as a yellow oil (40 mg, 2%).

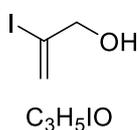
Due to the small amount of the product obtained, mass spectrometry was not performed.

^1H NMR (400 MHz, CDCl_3) δ 7.42 (dd, $J = 1.7, 1.0$ Hz, 1H, ArH), 6.42 (q, $J = 1.6$ Hz, 1H, $\text{C}=\underline{\text{CH}}_2$), 6.35 (d, $J = 1.8$ Hz, 2H, Ar-H-C=C-H), 5.93 (dd, $J = 2.7, 1.2$ Hz, 1H, $\text{C}=\underline{\text{CH}}_2$), 4.49 (s, 2H, O- $\underline{\text{CH}}_2$), 4.09 – 4.07 (m, 2H, O- $\underline{\text{CH}}_2$).

^{13}C NMR (101 MHz, CDCl_3) δ 143.0 (q $\underline{\text{C}}=\text{C}$), 126.3 (O-U=C), 110.3 (C- $\underline{\text{C}}=\text{C}$), 109.8 (C- $\underline{\text{C}}=\text{C}$), 63.6 (C=C), 31.6 ($\underline{\text{C}}\text{-I}$), 22.7 (O- $\underline{\text{C}}\text{H}_2$), 14.1 (O- $\underline{\text{C}}\text{H}_2$).

IR: $\nu_{\text{max}} = 2920$ cm^{-1} (C-H stretch), 1625 cm^{-1} (C=C, stretch), 1069 cm^{-1} (aliphatic C-O, stretch)

2-Iodo-2-propen-1-ol (**84**)⁴⁴



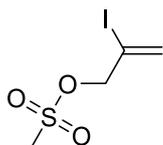
To a solution of NaI (1.20 g, 8.00 mmol) in acetonitrile (10 mL) was added TMSCl (869 mg, 8.00 mmol), followed by water (0.06 mL). The mixture was stirred for 10 minutes, then propargyl alcohol (283 mg, 5.00 mmol) was added dropwise to the reaction. The reaction was stirred at room temperature for 3h. The reaction was quenched with water, and extracted with Et_2O (3×10 mL). The organic layer was washed with a saturated solution of $\text{Na}_2\text{S}_3\text{O}_2$ (10 mL) and brine (10 mL). The resulting organic layer was dried (MgSO_4) and concentrated under reduced pressure. The product was purified by column chromatography on silica, eluting with Et_2O :hexane (1:3) to give

the desired product (**84**) as pink oil (272 mg, 35 %). Due to volatility of this product the crude product was often used in the next reaction without purification.

¹H NMR (400 MHz, CDCl₃) δ 6.40 (q, *J* = 1.7 Hz, 1H, C=CH₂), 5.91 – 5.83 (m, 1H, C=CH₂), 4.18 (dd, *J* = 1.9, 0.8 Hz, 2H, CH₂), 1.90 (s, 1H, OH).

¹³C NMR (101 MHz, CDCl₃) δ 124.5 (C=C₂H₂), 110.5 (C-I), 71.1 (CH₂).

2-Iodo-2-propen-1-methanesulfonate (**85**)⁴³

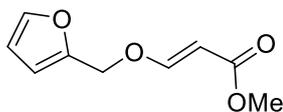


To a solution of 2-iodo-2-propen-1-ol (**84**) (183 mg, 1.00 mmol) in dry CH₂Cl₂ (5 mL) was added triethylamine (203 mg, 2.00 mmol), followed by MeSO₄Cl (137 mg, 1.20 mmol) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 30 minutes and then allowed to warm up to room temperature. The reaction was stirred for 3h at room temperature. The reaction was quenched with water and extracted with CH₂Cl₂ (3 × 10 mL). The organic layers was washed with water (10 mL) and brine (10 mL). The organic layers were dried (MgSO₄) and concentrated under reduced pressure. The product was purified by column chromatography on silica, eluting with Et₂O:hexane (1:3) to give the desired product (**85**) as yellow oil (253 mg, 97 %).

¹H NMR (400 MHz, CDCl₃) δ 6.53 (d, *J* = 1.8 Hz, 1H, C=CH₂), 6.05 (dd, *J* = 1.5, 0.6 Hz, 1H, C=CH₂), 4.78 (d, *J* = 0.9 Hz, 2H, O-CH₂), 3.09 (s, 3H, S-CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 129.7 (C=C₂H₂), 99.2 (C=C-I), 75.5 (CH₂), 38.7 (CH₃).

Methyl (E)-3-(furan-2-ylmethoxy)acrylate (**87**)⁴⁰

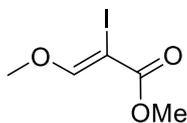


To a solution of furfuryl alcohol (490 mg, 5.00 mmol) and methyl acrylate (462 mg; 5.50 mmol) in anhydrous CH₂Cl₂ (12 mL) was added DABCO (56.0 mg, 0.50 mmol). The reaction mixture was stirred for 1 h or less (TLC control) then the solvent was removed under reduced pressure. The product was purified by column chromatography on silica, eluting with EtOAc:hexane (1:9) to give the desired product (**87**) as pale yellow solid (676 mg, 74%).

¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, *J* = 12.6 Hz, 1H, O-C-H), 7.45 (dd, *J* = 1.8, 0.8 Hz, 1H, C=C-H), 6.45 (d, *J* = 3.2 Hz, 1H, C=C-H), 6.38 (dd, *J* = 3.3, 1.9 Hz, 1H, C=C-H), 5.34 (d, *J* = 12.6 Hz, 1H, C=C-H), 4.84 (s, 2H, O-CH₂), 3.70 (s, 3H, O-CH₃).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 168.0 ($\underline{\text{C}}=\text{O}$), 161.6 (C-O), 148.6 (O- $\underline{\text{C}}=\text{C}$), 143.8 (C= $\underline{\text{C}}$ -O(furyl ring)), 111.1 (C= $\underline{\text{C}}$), 110.7 (C= $\underline{\text{C}}$), 97.4 (C= $\underline{\text{C}}$ - CO_2Me), 64.9 ($\underline{\text{C}}\text{H}_2$), 51.2 (O- $\underline{\text{C}}\text{H}_3$).

2-Iodo-3-methoxy-2-propenoic acid methyl ester (**91**)⁴⁶

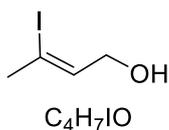


To a solution of NIS (877 mg, 3.90 mmol) in chloroform (12 mL) was added 3-methoxy-2-propenoic acid methyl ester (348 mg, 3.00 mmol). Next, AcOH (360 mg, 6.00 mmol) was added. The reaction was stirred for 24 h at room temperature, then chloroform was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (12 mL) and Et_3N (910 mg, 9.00 mmol) was added. The mixture was heated at reflux for 24 h. The reaction was cooled down, diluted with water (15 mL) and extracted with Et_2O (2×15 mL). The organic layer was washed with saturated sodium thiosulfate (10 mL), water (15 mL), brine (15 mL), dried (MgSO_4) and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica, eluting with EtOAc :hexane (1:9 \rightarrow 1:4) to give the desired product (**91**) as pale yellow crystals (320 mg, 44%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.68 (s, 1H, O-C- $\underline{\text{H}}$), 4.00 (s, 3H, O- $\underline{\text{C}}\text{H}_3$), 3.79 (s, 3H, $\text{CO}_2\text{C}\underline{\text{H}}_3$).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 164.5 (C=O), 164.4 (O- $\underline{\text{C}}=\text{C}$), 65.0 (C-I), (O $\underline{\text{C}}\text{H}_3$), 53.0 (O $\underline{\text{C}}\text{H}_3$).

(Z)-3-Iodobut-2-en-1-ol (**94**)⁴⁷

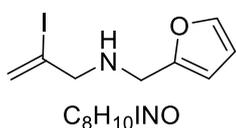


To a suspension of Red-Al (65% in toluene, 25.0 mL, 80.2 mmol) in diethyl ether (100 mL) was added dropwise 2-buten-1-ol (3.00 mL, 40.1 mmol) at 0 °C under nitrogen. The resulting clear solution was allowed to warm to room temperature and stirred for 25 h, during which time a white precipitate was observed. After cooling to 0 °C, ethyl acetate (4 mL) was added and the resulting mixture was stirred for 10 min. The solution was cooled to -78 °C and iodine (15.3 g, 60.0 mmol) was added in one portion. After stirring at -78 °C for 1 h and then at room temperature for 1.5 h, a saturated aqueous solution of sodium thiosulfate (100 mL) was added, and the mixture was stored at 0 °C overnight. The organic phase was decanted. Aqueous layer was extracted with ethyl acetate (3 x 25 mL). The organic layers were combined and dried (Na_2SO_4) and concentrated. The resulting yellow oil (7.55 g, 90%,) was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃) δ 5.78 (ddd, *J* = 7.5, 4.5, 1.5 Hz, 1H, C=CH), 4.17 (dq, *J* = 6.0, 1.2 Hz, 2H, CH₂), 2.54 (dd, *J* = 2.7, 1.3 Hz, 3H, CH₃), 1.71 (s, 1H, OH).

¹³C NMR (101 MHz, CDCl₃) δ 134.1 (C=C), 102.3 (I-C=C), 67.4 (CH₂), 33.7 (CH₃).

***N*-(Furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (99)**



To a solution of furfuryl amine (1.12 g, 12.0 mmol) and 2-iodo-2-propen-1-methanesulfonate (524 mg, 2.00 mmol) in dry CH₂Cl₂ (10 mL) was added Et₃N (404 mg, 4.00 mmol) dropwise under nitrogen, and the resulting mixture was stirred for 16 h. The mixture was diluted with water then extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (10 mL), dried (MgSO₄) and concentrated under reduced pressure. The product was purified by column chromatography on silica, eluting with Et₂O:hexane (1:3) to give the desired product (**99**) as yellow oil (356 mg, 68 %).

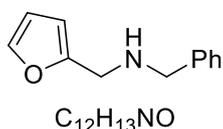
¹H NMR (400 MHz, CDCl₃) δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H, O-CH), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H, C=CH), 6.27 (dd, *J* = 3.0, 1.4 Hz, 1H, C=CH₂), 6.18 (dd, *J* = 3.2, 0.7 Hz, 1H, C=CH), 5.89 (dt, *J* = 1.5, 0.7 Hz, 1H, C=CH₂), 3.73 (s, 2H, N-CH₂), 3.37 (dd, *J* = 1.3, 0.8 Hz, 2H, N-CH₂), 1.78 (s, 2H, N-H).

Due to the NMR probe being broken, no ¹³C NMR was performed.

IR: ν_{max} = 2922 cm⁻¹ (C-H, stretch), 1613 cm⁻¹ (C=C stretch), 1146 cm⁻¹ (C-O, stretch), 732 cm⁻¹ (C=C, bending)

ESI-MS: Calculated for C₈H₁₀IN[M+H]: 263.9880 found at 263.9870.

***N*-(Phenylmethyl)-2-furanmethanamine (102)⁴⁸**

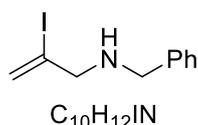


A solution of benzylamine (535 mg, 5.00 mmol) and furfuryl aldehyde (480 mg, 5.00 mmol) in ethanol (9 mL) was stirred under nitrogen for 1 h, after which sodium borohydride (378 mg, 10.0 mmol) was added, and the resulting mixture was stirred for a further 16 h. The reaction was then diluted with deionized water (12 mL), adjusted to pH 1 with 1M hydrochloric acid and washed with CH₂Cl₂ (3 × 10 mL). The aqueous phase was then adjusted to pH 10 with 1 M aqueous sodium hydroxide, after which the product was extracted with CH₂Cl₂ (3 × 8 mL) and washed with brine (3 × 8 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give product as yellow oil (618 mg, 66 %).

¹H NMR (400 MHz, CDCl₃) δ 7.38 (dd, *J* = 1.8, 0.8 Hz, 1H, O-CH), 7.33 (d, *J* = 4.4 Hz, 4H, ArH), 7.29 – 7.23 (m, 1H, ArH), 6.33 (dd, *J* = 3.1, 1.9 Hz, 1H, C=C-H), 6.19 (dd, *J* = 3.2, 0.7 Hz, 1H, C=C-H), 3.80 (s, 4H, H₂C-N-CH₂).

¹³C NMR (101 MHz, CDCl₃) δ 153.8 (q-C-O), 141.9 (C-C=C), 139.8 (qCAr), 128.4 (CAr), 128.3 (CAr), 127.1 (CAr), 110.1 (C-C=C (ring)), 107.1 (C-C=C (ring)), 52.8 (CH₂), 45.4 (CH₂).

***N*-Benzyl-2-iodoprop-2-en-1-amine (103)**



To a solution of 2-iodo-2-propen-1-methanesulfonate (524 mg, 2.00 mmol) and benzylamine (1.29 g, 12.0 mmol) in anhydrous CH₂Cl₂ (10 mL) was added Et₃N (404 mg, 4 mmol) dropwise. The reaction was stirred for 6 h at room temperature. The mixture was diluted with water (10 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine and dried over MgSO₄, the solvent was removed in vacuo. The product was purified by column chromatography eluting with Et₂O:hexane (SiO₂, 1:3) to yield the desired product (**103**) as yellow oil (356 mg, 68 %).

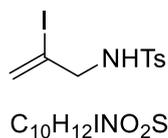
¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.30 (m, 4H, ArH), 7.28 – 7.23 (m, *J* = 7.0 Hz, 1H, ArH), 6.27 (dd, *J* = 3.0, 1.4 Hz, 1H, C=CH₂), 5.90 (dt, *J* = 1.5, 0.7 Hz, 1H, C=CH₂), 3.71 (s, 2H, C=CH₂), 3.38 (dd, *J* = 1.3, 0.8 Hz, 2H, C=CH₂).

Due to the NMR probe being broken, no ¹³C NMR was performed.

IR: ν_{max} = 3324 cm⁻¹ (N-H, secondary amine, stretch), 3024 cm⁻¹ (C-H, alkane stretch), 1615 cm⁻¹ (C=C, stretch), 898 cm⁻¹ (C=C, bend).

ESI-MS: Calculated for C₁₀H₁₂IN[M+H]: 274.0082 found at 274.0082.

***N*-(2-Iodo-2-propen-1-yl)-4-methyl-benzenesulfonamide (104)⁵⁰**



To a solution of 2-iodo-2-propen-1-methanesulfonate (867 mg, 3.30 mmol) and *p*-toluenesulfonamide (5.64 g, 33.0 mmol) in acetone (25 mL) was added K₂CO₃ (455 mg, 3.30 mmol) at room temperature, and the reaction mixture was heated at reflux for 18 h. After removal of the solvent, the mixture was extracted with Et₂O (15 mL), washed with brine (10 mL), dried (MgSO₄) and concentrated under reduced pressure. The product was purified by column chromatography on silica eluting with EtOAc:hexane (1:4) to yield the desired product (**104**) as pale yellow solid (352 mg, 36%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 – 7.72 (m, 2H, ArH), 7.31 (dd, $J = 8.6, 0.6$ Hz, 2H, ArH), 6.25 (dd, $J = 3.6, 1.5$ Hz, 1H, C=CH_{2(A)}), 5.76 (dt, $J = 2.1, 1.0$ Hz, 1H, C=CH_{2(B)}), 4.86 (t, $J = 6.3$ Hz, 1H, N-H), 3.83 – 3.80 (m, 2H, CH₂), 2.43 (s, 3H, CH₃).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 143.8 (q-CAr), 137.1 (q-CAr), 129.7 (CAr), 127.5 (C=CH₂), 127.3 (CAr), 60.4 (C-I), 54.5 (CH₂), 21.6 (CH₃).

***N*-Allyl-*N*-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (105)**



To a solution of *N*-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (**86**) (394 mg, 1.50 mmol) in dioxane (10 mL) were added allyl bromide (227 g, 1.90 mmol) and K_2CO_3 (414 mg, 3.00 mmol), and the mixture was heated at reflux for 8 h. The mixture was cooled to room temperature, and cyclohexane (40 mL) was added. The resulting suspension was filtered through Celite, and the filtrate was concentrated under reduced pressure. The product was purified by column chromatography on silica eluting with Et_2O :hexane (1:4) to yield the desired (**105**) as yellow oil (92 mg, 20%).

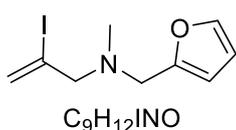
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.37 (dd, $J = 1.8, 0.8$ Hz, 1H, O-CH), 6.40 (s, 1H, C=C-H), 6.32 (dd, $J = 3.2, 1.9$ Hz, 1H, C=CH₂), 6.19 (d, $J = 3.0$ Hz, 1H, C=C-H), 5.88 (m, 2H, overlapped, HC=CH₂), 5.23 (ddd, $J = 17.2, 3.3, 1.5$ Hz, 1H, C=CH₂), 5.17 (dd, $J = 10.6, 1.3$ Hz, 1H, C=CH₂), 3.70 (s, 2H, N-CH₂), 3.18 (s, 2H, N-CH₂), 3.14 (d, $J = 6.3$ Hz, 2H, N-CH₂).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 152.1 (q-C-O), 149.2 (O-C=C), 142.0 (I-C=CH₂), 135.4 (CH=CH₂), 126.8 (C-C (ring)), 117.9 (C-C (ring)), 110.1 (C=CH₂), 108.8 (C-I), 64.2 (CH₂), 55.9 (CH₂), 48.8 (CH₂).

IR: $\nu_{\text{max}} = 2920$ cm^{-1} (C-H, stretch), 1615 cm^{-1} (C=C, stretch), 1146 cm^{-1} (C-N, stretch)

ESI-MS: Calculated for $\text{C}_{11}\text{H}_{14}\text{IN}[\text{M}+\text{H}]$: 304.0193 found at 304.0188.

***N*-(Furan-2-ylmethyl)-2-iodo-*N*-methylprop-2-en-1-amine (106)**



To a solution of *N*-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (**86**) (395 mg, 1.50 mmol) and MeI (265 mg, 1.88 mmol), in acetone (10 mL) was added K_2CO_3 (207 mg, 1.50 mmol) under nitrogen. The reaction was stirred at reflux for 16 h. The mixture was cooled and concentrated under reduced pressure. The product was purified by column chromatography on silica eluting with Et_2O :hexane (1:4) to yield the desired product (**106**) as yellow oil (262 mg, 63%).

The product was used directly in the spirocyclization reaction. Due to small amount of product left only ^1H NMR, ^{13}C NMR and MS were performed.

^1H NMR (400 MHz, CDCl_3) δ 7.38 (dd, $J = 1.8, 0.8$ Hz, 1H, O-CH), 6.35 (d, $J = 1.3$ Hz, 1H, C=CH₂), 6.33 (dd, $J = 3.2, 1.9$ Hz, 1H, C=C-H), 6.21 (dd, $J = 3.1, 0.5$ Hz, 1H, C=C-H), 5.90 (d, $J = 1.1$ Hz, 1H, C=CH₂), 3.64 (s, 2H, N-CH₂), 3.12 (s, 2H, N-CH₂), 2.28 (s, 3H, N-CH₃).

^{13}C NMR (101 MHz, CDCl_3) δ 142.1 (q-C-O), 110.1 (C-O), 108.8 (C=CH₂), 67.8 (C-C (ring)), 52.5 (C-C (ring)), 41.4 (C-I), 31.6 (CH₂), 22.6 (CH₂), 14.1 (CH₃).

ESI-MS: Calculated for $\text{C}_9\text{H}_{12}\text{IN}$ [M+H]: 278.0036 found at 278.0027.

***tert*-Butyl (furan-2-ylmethyl)(2-iodoallyl)carbamate (107)**



To a solution of *N*-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (**86**) (356 mg, 1.35 mmol) in CH_2Cl_2 (10 mL) was added Boc_2O (1.47 g, 6.75 mmol). The reaction was stirred at room temperature for 66 h.

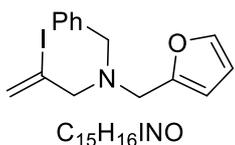
The mixture was washed with water (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic layer was washed with brine (10 mL), dried (MgSO_4) and concentrated under reduced pressure. The product was purified by column chromatography on silica eluting with CH_2Cl_2 :hexane (1:4) to yield the desired product (**107**) as yellow oil (438 mg, 89%).

^1H NMR (400 MHz, CDCl_3) δ 7.35 (s, 1H, O-C-H), 6.31 (dd, $J = 3.2, 1.9$ Hz, 1H, C=CH₂), 6.18 (dd, $J = 25.6, 13.1$ Hz, 2H, C=CH), 5.86 (d, $J = 10.6$ Hz, 1H, C=CH₂), 4.39 (d, $J = 36.9$ Hz, 2H, N-CH₂), 4.05 (d, $J = 33.6$ Hz, 2H, N-CH₂), 1.48 (s, 9H, O-C(CH₃)₃).

^{13}C NMR (101 MHz, CDCl_3) δ 151.1 (C=O), 142.3 (q-C-O), 126.3 (O-C(ring)), 125.6 (C=CH₂), 108.5 (C-C (ring)), 107.0 (C-C (ring)), 80.67 (C-I), 57.4 (C(CH₃)₃), 42.8 (CH₂), 42.1 (CH₂), 28.3 (CH₃).

IR: $\nu_{\text{max}} = 2976$ cm^{-1} (C-H, stretch), 1694 cm^{-1} (C=O, stretch), 1449 cm^{-1} (C-H, alkene stretch), 1248 cm^{-1} (C-O, stretch).

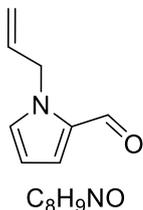
The product was use directly in the spirocyclization reaction. Due to small amount of product left only ^1H NMR, ^{13}C NMR and IR were performed.

***N*-Benzyl-*N*-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (108)**

To a solution of *N*-(furan-2-ylmethyl)-2-iodoprop-2-en-1-amine (618 g, 3.3 mmol) and 2-iodo-2-propen-1-methanesulfonate (1.05 g, 4.00 mmol) in anhydrous CH_2Cl_2 (20 mL) was added Et_3N (667 mg, 6.6 mmol) dropwise under nitrogen. The reaction was stirred for 66 h. The mixture was diluted with water (20 mL) then extracted with $EtOAc$ (3×20 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography on silica eluting with Et_2O :hexane (1:2) to yield the desired product (**108**) as yellow oil (356 mg, 34 %).

The product was used directly in the spirocyclization reaction. Due to the small amount of product left, only 1H NMR spectroscopy was performed.

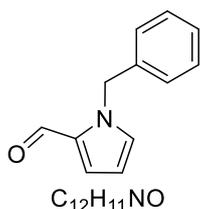
1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, $J = 7.8, 1.0$ Hz, 2H, ArH), 7.39 (dd, $J = 1.8, 0.8$ Hz, 1H, O-CH), 7.37 – 7.27 (m, 3H, ArH), 6.44 (d, $J = 1.3$ Hz, 1H, C=CH₂), 6.34 (dd, $J = 3.1, 1.9$ Hz, 1H, C=CH), 6.20 (d, $J = 2.7$ Hz, 1H, C=CH), 5.92 (d, $J = 1.0$ Hz, 1H, C=CH₂), 3.66 (s, 2H, N-CH₂), 3.63 (s, 2H, N-CH₂), 3.21 (s, 2H, N-CH₂).

1-(2-Propen-1-yl)-1*H*-Pyrrole-2-carboxaldehyde (117)

To a solution of 2-pyrrolecarbaldehyde (951 mg, 10 mmol) in dioxane (16 mL) were added allyl bromide (3.629 g, 30 mmol) and K_2CO_3 (4.837 g, 35 mmol), and the mixture was stirred at the reflux temperature for 8 h. The mixture was cooled to room temperature, and cyclohexane (40 mL) was added. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The product was purified by column chromatography on silica eluting with $EtOAc$:hexane (1:9) to yield the desired product (**117**) as a yellow oil (1.133 g, 84 %).

1H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, $J = 1.0$ Hz, 1H, COH), 7.00 – 6.89 (m, 2H, N-CH₂), 6.25 (dd, $J = 3.9, 2.6$ Hz, 1H, C=CH), 5.99 (ddd, $J = 10.2, 7.9, 4.7$ Hz, 1H, HC=CH₂), 5.16 (ddd, $J = 10.2, 2.6, 1.4$ Hz, 1H, C=CH), 5.03 (dd, $J = 2.9, 1.6$ Hz, 1H, C=CH), 4.97 (ddd, $J = 5.5, 3.1, 1.5$ Hz, 2H, C=CH₂), 3.70 (s, 1H, C=CH).

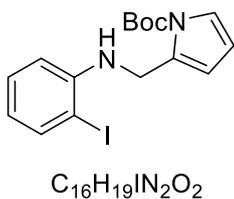
^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4 (C=O), 134.0 (q-C-N(ring)), 131.4 (C-C (ring)), 131.0 (C-C (ring)), 124.6 (C-N), 117.1 (C=CH), 109.9 (C=CH₂), 50.9 (CH₂).

1-(Phenylmethyl)- 1*H*-Pyrrole-2-carboxaldehyde (118)

To a suspension of dry NaH (768 mg, 20.0 mmol) in anhydrous DMF (20 mL) was added pyrrole-2-carboxaldehyde (951 mg, 10.0 mmol) at 0 °C under argon. After 20 minutes, benzyl bromide (3.42 g, 10.0 mmol) was added dropwise. The reaction was slowly warmed up to room temperature and stirred for 3 hours. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (20 mL \times 4), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography on silica eluting with EtOAc:hexane (1:9) to yield the desired product (**118**) as yellow oil (1.82 g, 98 %).

Due to the NMR probe being broken, no ^{13}C NMR was performed.

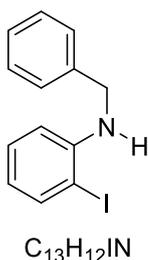
1H NMR (400 MHz, $CDCl_3$) δ 9.61 – 9.52 (m, 1H), 7.35 – 7.23 (m, 3H), 7.18 – 7.10 (m, 2H), 6.98 (d, J = 3.5 Hz, 2H), 6.35 – 6.21 (m, 1H), 5.57 (s, 2H).

***tert*-Butyl 2-(((2-iodophenyl)amino)methyl)-1*H*-pyrrole-1-carboxylate (**120**)⁵⁸**

To a solution of N-Boc-pyrrole-2-carboxaldehyde (1.00 g, 5.00 mmol) in anhydrous CH_2Cl_2 (40 mL) was added AcOH (0.86 mL, 15.0 mmol) under nitrogen. Next, 2-iodoaniline (860 mg, 4.00 mmol) and sodium triacetoxyborohydride (2.50 g, 10.0 mmol) were added, and the reaction was stirred for 16 h at room temperature. The reaction mixture was poured into saturated $NaHCO_3$ solution (40 mL) and extracted with CH_2Cl_2 (2 \times 40 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford the crude product. The product was purified by repeated recrystallization from hexane:acetone (1:1) to yield the desired product (**120**) as a colourless microcrystalline solid (1.10 g, 55%).

1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.8, 1.5 Hz, 1H, O-CH), 7.23 – 7.18 (m, 1H, ArH), 7.18 – 7.13 (m, 1H, ArH), 6.68 (dd, J = 8.2, 1.4 Hz, 1H, ArH), 6.47 – 6.37 (m, 1H, ArH), 6.19 – 6.13 (m, 1H, C=CH), 6.07 (t, J = 3.3 Hz, 1H, C=CH), 4.57 (s, 2H, N-CH₂), 1.62 (s, 9H, O-C(CH₃)₃).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4 (C=O), 146.9 (qArC), 139.1 (ArC-H), 131.9 (C=C), 129.2 (ArC-H), 121.8 (ArC-H), 118.7 (N-C=C), 113.4 (ArC-H), 111.2 (C=C), 110.1 (C=C-H), 85.6 (ArC-I), 84.1 (OC(CH₃)₃), 41.8 (N-CH₂), 28.1 (CH₃).

***N*-(2-Iodophenyl)-benzenemethanamine (**129**)**⁵⁹

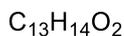
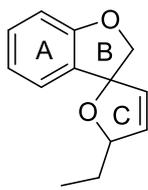
To a solution of 2-iodoaniline (1.09 g, 5.00 mmol) and benzylaldehyde (795 mg, 7.50 mmol) in MeOH (20 mL) was added acetic acid (450 mg, 7.50 mmol), and the reaction was stirred at room temperature for 30 min. Next, the reaction was cooled down to 0 °C and sodium cyanoborohydride (408 mg, 6.50 mmol) was added in two portions over 30 min. The reaction was stirred and allowed to warm from 0 °C to room temperature overnight. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate (30 mL) and extracted with Et₂O (3 × 30 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The product was purified by column chromatography on silica eluting with EtOAc:hexane (1:19) to yield the desired product (**129**) as a yellow oil (1.37 g, 89 %).

¹H NMR (400 MHz, CDCl₃) δ 7.70 (dd, *J* = 7.8, 1.5 Hz, 1H, ArH), 7.38 (dd, *J* = 3.6, 2.0 Hz, 4H, ArH), 7.34 – 7.28 (m, 1H, ArH), 7.17 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H, ArH), 6.57 (dd, *J* = 8.2, 1.4 Hz, 1H, ArH), 6.52 – 6.44 (m, 1H, ArH), 4.42 (s, 2H, N-CH₂).

¹³C NMR (101 MHz, CDCl₃) δ 147.0 (q-ArC), 139.0 (ArC), 138.6 (q-ArC), 129.5 (ArC), 128.8 (ArC), 127.4 (ArC), 127.2 (ArC), 118.9 (ArC), 111.0 (ArC), 85.3 (Ar-C-H), 48.4 (CH₂).

4.4 GENERAL METHOD FOR SPIROCYCLIZATION REACTION

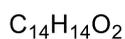
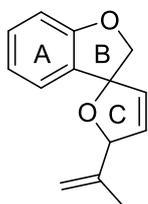
To an oven dried flask was added the desired iodobenzene derivative (1.0 eq) and Fe(III) catalyst (5-10 mol%). The flask was evacuated then refilled with nitrogen (× 3). Anhydrous Et₂O (2.5 mL/mmol) and NMP (2.5 mL/mmol) were added. The appropriate Grignard reagent (~0.5 M in THF, 2.4 eq) was added dropwise at room temperature and the resulting mixture was stirred at room temperature for 3-16 h. The reaction mixture was diluted with ethyl acetate (25 mL/mmol) and the resulting solution was washed with 2M hydrochloric acid (20 mL/mmol), water (20 mL/mmol) and brine (20 mL/mmol). The organic layer was dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (various eluent systems) to yield the desired product.

5'-Ethyl-2H,5'H-spiro[benzofuran-3,2'-furan] (138a)⁵⁸

Following the general procedure: 10 mol% of Fe(acac)₃ was used and the reaction was stirred at room temperature for 16 h. The product was purified by column chromatography on silica eluting with CH₂Cl₂:hexane (2:1) to yield the desired product (**138a**) as yellow oil (34 %).

¹H NMR (400 MHz, CDCl₃) δ 7.24 (ddd, *J* = 8.1, 7.4, 1.3 Hz, 1H, A: ArH), 7.17 (ddd, *J* = 7.4, 1.3, 0.4 Hz, 1H, A: ArH), 6.93 (td, *J* = 7.4, 0.9 Hz, 1H, A: ArH), 6.86 (d, *J* = 8.1 Hz, 1H, A: ArH), 6.08 (dd, *J* = 5.9, 1.4 Hz, 1H, C: C=CH), 5.81 (dd, *J* = 5.9, 2.2 Hz, 1H, C: C=CH), 5.02 – 4.92 (m, 1H C: CH), 4.49 (d, *J* = 10.4 Hz, 1H, B: CH), 4.41 (d, *J* = 10.4 Hz, 1H, B: CH), 1.62 (ddt, *J* = 14.6, 13.7, 6.6 Hz, 2H, CH₂), 0.95 (t, *J* = 7.4 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 160.0 (A/B ArC), 132.3 (C:C=C-H), 130.5 (C:C=C-H), 128.6 3 (ArC-H), 128.6 (A/B: ArC), 124.4 (A: ArC), 121.0 (A: ArC), 110.6 (C=C=CH₂), 95.2 (B/C qC), 87.0 (C: C-C(q)-H), 80.8 (B: CH₂), 29.3 (CH₂), 9.3 (CH₃).

5'-(prop-1-en-2-yl)-2H,5'H-spiro[benzofuran-3,2'-furan] (138d)

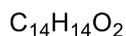
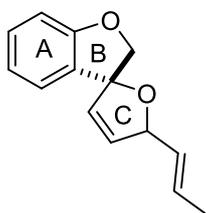
Following the general procedure: 5 mol% of Fe(acac)₃ was used and the reaction was stirred at room temperature for 16 h. The product was purified by column chromatography on silica eluting with CH₂Cl₂:hexane (1:1 → 3:1) to yield the desired product (**138d**) as a yellow oil (19 mg, 8 %).

Due to the small amount of isolated product, only ¹H NMR, ¹³C NMR and IR were performed.

¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.22 (m, 1H, A: ArH), 7.18 (ddd, *J* = 7.5, 1.4, 0.5 Hz, 1H, A: ArH), 6.93 (td, *J* = 7.4, 0.9 Hz, 1H, A: ArH), 6.89 – 6.84 (m, 1H, A: ArH), 6.03 (dd, *J* = 5.9, 1.6 Hz, 1H, C: C=CH), 5.89 (dd, *J* = 5.9, 2.4 Hz, 1H, C: C=CH), 5.40 (s, 1H, C: CH), 5.03 (dt, *J* = 1.8, 0.9 Hz, 1H, C=CH₂), 4.92 – 4.86 (m, 1H, C=CH₂), 4.57 (d, *J* = 10.5 Hz, 1H, B: CH₂), 4.44 (d, *J* = 10.5 Hz, 1H, B: CH₂), 1.75 – 1.66 (m, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 160.0 (A/B ArC), 144.2 (C=C), 131.1 (C:C=C-H), 130.6 (C:C=C-H), 129.3 (ArC-H), 128.4 (A/B: ArC), 124.4 (A: ArC), 121.0 (A: ArC), 112.7 (C=C=CH₂), 110.6 (A: ArC), 95.9 (B/C qC), 89.5 (C: C-C(q)-H), 80.3 (B: CH₂), 17.5 (CH₃).

IR: ν_{max} = 2976 cm⁻¹ (C-H stretch), 1599 cm⁻¹ (C=C cyclic stretch), 1476 cm⁻¹ (alkane, methylene group stretch)

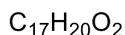
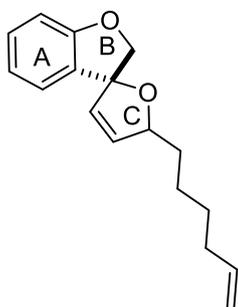
(E)-5'-(Prop-1-en-1-yl)-2H,5'H-spiro[benzofuran-3,2'-furan] (138e)

Following the general procedure: 5 mol% of Fe(acac)₃ was used and the reaction was stirred at room temperature for 16 h. The product was purified by column chromatography on silica eluting with CH₂Cl₂:hexane (1:2) to yield the desired product (**138e**) as a yellow oil (2 %).

Due to the small amount of isolated product, only ¹H NMR and IR were performed.

¹H NMR (400 MHz, CDCl₃) δ 7.26 – 7.16 (m, 2H, A: ArH), 6.94 (d, *J* = 0.9 Hz, 1H, A: ArH), 6.89 – 6.84 (m, 1H, A: ArH), 6.01 (ddd, *J* = 12.9, 5.8, 1.6 Hz, 1H, C: C=CH), 5.87 – 5.82 (m, 1H, C: C=CH), 5.81 – 5.75 (m, 1H, C: CH), 5.63 (ddd, *J* = 10.8, 7.0, 1.3 Hz, 1H, HC=CH₂), 5.36 – 5.24 (m, 1H, C: C-H), 4.51 (dd, *J* = 10.5, 1.1 Hz, 1H, B: CH₂), 4.44 – 4.40 (m, 1H, B: CH₂), 1.73 (td, *J* = 7.1, 1.6 Hz, 3H, CH₃).

IR: ν_{max} = 3019 cm⁻¹ (C-H alkene stretch), 1597 cm⁻¹ (C=C, cyclic stretch), 1476 cm⁻¹ (C-H alkane stretch, methylene group), 1282 cm⁻¹ (C-O stretch).

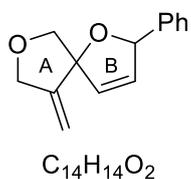
5'-(Hex-5-en-1-yl)-2H,5'H-spiro[benzofuran-3,2'-furan] (138f)

Following the general procedure: 5 mol% of Fe(acac)₃ was used and the reaction was stirred at room temperature for 16 h. The product was purified by column chromatography eluting with CH₂Cl₂:hexane (1:2) to yield the desired product (**138f**) as a yellow oil (33 mg, 13 %).

Due to the small amount of isolated product, only ¹H NMR and IR were performed.

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.21 (m, 1H, A: ArH), 7.16 (ddd, *J* = 7.5, 1.4, 0.5 Hz, 1H, A: ArH), 6.92 (td, *J* = 7.4, 0.9 Hz, 1H, A: ArH), 6.88 – 6.83 (m, 1H, A: ArH), 6.08 (dd, *J* = 5.9, 1.4 Hz, 1H, C: C=CH), 5.86 – 5.74 (m, 2H, overlap: C=CH, C: CH), 5.03 – 4.92 (m, 3H, C=CH₂, CH=CH₂), 4.48 (d, *J* = 10.4 Hz, 1H, B: CH₂), 4.40 (d, *J* = 10.4 Hz, 1H, B: CH₂), 2.12 – 1.98 (m, 2H, CH₂), 1.61 – 1.53 (m, 3H, CH₂), 1.42 (ddd, *J* = 8.9, 5.6, 2.5 Hz, 4H, CH₂).

IR: ν_{max} = 3075 cm⁻¹ (C-H, alkene stretch), 2923 cm⁻¹ (C-H, alkane stretch), 1600 cm⁻¹ (C=C cyclic stretch), 1476 cm⁻¹ (C-H alkane, methylene group stretch).

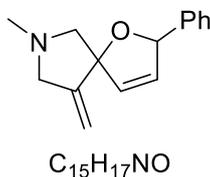
5'-Ethyl-2H,5'H-spiro[benzofuran-3,2'-furan] (143)

Following the general procedure: 5 mol% of $Fe(acac)_3$ was used and the reaction was stirred at room temperature for 16 h. The product was purified by column chromatography on silica eluting with CH_2Cl_2 :hexane (1:2) to yield the desired product (**143**) as a colourless oil (14 mg, 50 %).

Due to small amount of isolated product, only 1H NMR and ^{13}C NMR spectroscopy were performed.

1H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H, ArH), 7.42 (dd, $J = 1.8, 0.8$ Hz, 1H, Ar-C-H), 7.36 – 7.28 (m, 3H, ArH), 6.37 – 6.29 (m, 2H, HC=CH), 5.56 (s, 1H, C=CH₂), 5.37 (d, $J = 1.3$ Hz, 1H, C=CH₂), 4.51 (s, 2H, O-CH₂), 4.41 (d, $J = 0.7$ Hz, 2H, O-CH₂).

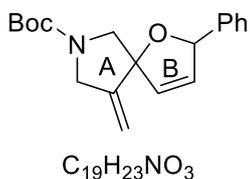
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (C_q=CH₂), 143.9 (CH=C), 142.8 (C_q-Ar), 138.7 (CH=C), 128.4 (CAr), 127.8 (CAr), 126.1 (CAr), 114.79 (C=CH₂), 110.3 (C_q-O), 109.4 (O-CH₂), 100.0 (O-CH-Ar), 71.7 (O-CH₂).

7-Methyl-9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene (144)

Following the general procedure: 5 mol% of $Fe(acac)_3$ was used and the reaction was stirred at room temperature for 16 h. The product was purified by column chromatography on silica eluting with Et_2O :hexane (1:5) to yield the desired product (**144**) as a colourless oil (10 mg, 4 %).

Due to the small amount of isolated product, only 1H NMR spectroscopy was performed.

1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H, ArH), 7.39 (dd, $J = 1.8, 0.8$ Hz, 1H, Ar-C-H), 7.30 (dt, $J = 8.1, 6.8$ Hz, 3H, ArH), 6.34 (dd, $J = 3.1, 1.9$ Hz, 1H, C=CH), 6.20 (d, $J = 3.2$ Hz, 1H, C=CH), 5.48 (d, $J = 1.5$ Hz, 1H, C=CH₂), 3.62 (broad m, 2H, N-CH₂), 3.41 (broad m, 2H, N-CH₂), 2.27 (s, 3H, CH₃).

***tert*-Butyl 9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene-7-carboxylate (145)**

Following the general procedure: 5 mol% of $Fe(acac)_3$ was used and the reaction was stirred at room temperature for 16 h. The product was purified by column chromatography on silica eluting with

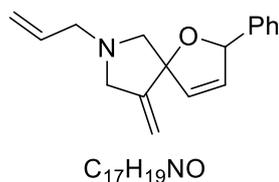
CH₂Cl₂:hexane (1:1) to yield the desired product (**145**) as a yellow oil (185 mg, 50%).

¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1H, B:O-CH), 7.40 – 7.27 (m, 5H, ArH), 6.30 (dd, *J* = 3.1, 1.9 Hz, 1H, Ar-C-H), 6.16 (d, *J* = 36.8 Hz, 1H, C=CH₂), 5.44 (d, *J* = 44.4 Hz, 1H, C=CH), 5.13 (d, *J* = 28.9 Hz, 1H, C=CH₂), 4.39 (broad m, *J* = 6.8 Hz, 2H, N-CH₂), 4.25 (broad m, 2H, N-CH₂), 1.46 (s, 9H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 155.4 (C=O), 143.9 (CH=CH), 141.9 (C_qAr), 141.8 (CH=CH), 128.3 (C_qAr), 127.9 (C_qAr), 126.4 (C_qAr), 114.3 (C=CH₂), 113.5 (O-C_q (Boc group)), 108.1 (C_q-O), 80.1 (O-CH-Ar), 49.8 (N-CH₂), 49.1 (N-CH₂), 28.4 (CH₃).

IR: ν_{max} = 2976 cm⁻¹ (C-H stretch), 1686 cm⁻¹ (C=C, stretch), 1366 cm⁻¹ (C-H, alkene stretch), 1157 cm⁻¹ (N-C stretch).

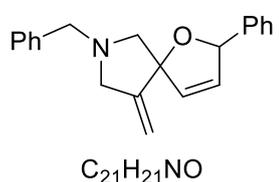
7-Allyl-9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene (**146**)



Following the general procedure: 5 mol% of Fe(acac)₃ was used and the reaction was stirred at room temperature for 16 h. The product was purified by column chromatography on silica eluting with Et₂O:hexane (1:5) to yield the desired product (**146**) (1 mg, <1%). Due to isolating only 1 mg of the compound, only ¹H NMR spectroscopy was performed.

¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.41 (m, *J* = 6.9 Hz, 1H, ArH), 7.38 (s, 1H, ArH), 7.34 – 7.27 (m, *J* = 7.6 Hz, 1H, Ar-C-H), 6.32 (s, 1H,), 6.14 (s, 1H), 5.90 – 5.79 (m, 1H), 5.47 (s, 1H), 5.33 (s, 1H), 5.17 (dd, *J* = 19.2, 14.1 Hz, 1H), 3.66 (broad m, 1H), 3.45 (broad m, 1H), 3.13 (d, *J* = 5.9 Hz, 1H).

7-Benzyl-9-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]non-3-ene (**147**)



Following the general procedure: 5 mol% of Fe(acac)₃ was used and the reaction was stirred at room temperature for 16 h. The product was purified by column chromatography on silica eluting with CH₂Cl₂:hexane (2:3) to yield the desired product (**147**) as a yellow oil (95 mg, <35%).

¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.42 (m, 3H, ArH), 7.38 – 7.24 (m, 9H, ArH and Ar-C-H), 6.38 (dd, *J* = 3.1, 1.9 Hz, 1H, C=CH₂), 6.19 (dd, *J* = 3.1, 0.5 Hz, 1H, C=CH), 5.53 (d, *J* = 1.7 Hz, 1H, C=CH), 5.43 (d, *J* = 1.5 Hz, 1H, C=CH₂), 3.68 (broad m, 2H, N-CH₂), 3.66 (broad m, 2H, N-CH₂), 3.54 (broad m, 2H, N-CH₂).

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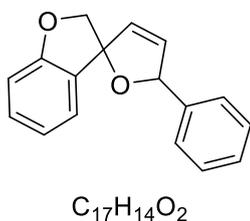
^{13}C NMR (101 MHz, CDCl_3) δ 152.7 (C_{Ar}), 145.6 (C_{Ar}), 141.9 (C_qAr), 140.2 (C_{H=CH}), 139.3 (C_{H=CH}), 129.0 (C_qAr), 128.8 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.4 (C_{Ar}), 115.3 (C=C_{H2}), 108.7 (C_q-O), 57.8 (O-C_H-Ar), 57.4 (N-C_{H2}), 49.0 (N-C_{H2}), 29.7 (N-C_{H2}).

IR: ν_{max} = 3058 cm^{-1} (C-H, alkene stretch), 2924 cm^{-1} (C-H, alkane stretch), 1146 cm^{-1} (C-O stretch), 732 cm^{-1} (C=C, alkene, bending).

General procedure for the competition reaction

To an oven dried flask were added the iodobenzene derivative (1.0 eq) and $\text{Fe}(\text{acac})_3$ (5 mol %), then the flask was purged with nitrogen gas. Anhydrous Et_2O (2.5 mL/mmol) and NMP (2.5 mL/mmol) was added and the flask was evacuated then refilled with nitrogen ($\times 3$). PhMgBr and EtMgBr (total 2.4 eq) were added at the same time dropwise at room temperature and the resulting mixture was subsequently stirred for 16 h. The reaction mixture was diluted with ethyl acetate (25 mL/mmol) and the resulting solution washed with 2M hydrochloric acid (20 mL/mmol), water (20 mL/mmol) and brine (20 mL/mmol). The organic layer was dried (MgSO_4) and concentrated under reduced pressure. The products were purified by column chromatography on silica eluting with hexane: CH_2Cl_2 (1:1 \rightarrow 2:3) to yield products: **139b**, **140** and **141**.

(2' *R*, 5' *R*)-*rel*-5'-phenyl-2'(5' *H*)-furan]-spiro[benzofuran-3(2*H*) (140)⁵⁸



^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.35 (m, 2H, Ar_H), 7.34 – 7.27 (m, 4H, Ar_H), 6.97 (td, $J = 7.4, 0.8$ Hz, 1H, Ar_H), 6.89 (dd, $J = 8.5, 0.8$ Hz, 1H, Ar_H), 6.23 – 6.15 (m, 1H, Ar-C_H), 5.99 (dd, $J = 4.3, 2.6$ Hz, 2H, C=C_H), 4.61 (d, $J = 10.5$ Hz, 1H, C_{H2}), 4.52 (d, $J = 10.5$ Hz, 1H, C_{H2}).

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