Novel copper-catalysed coupling reactions of diphenylmethane

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Contents

Abbreviations

GTP – Guanosine triphosphate

GDP – Guanosine diphosphate

MLC – Myosin Light Chain

CCB – Calcium Channel Blocker

HOMO – Highest occupied molecular orbital

LUMO – Lowest unoccupied molecular orbital

ee – Enantiomeric excess

Abstract

In this thesis, a novel synthesis of the drug fendiline was attempted. Fendiline was sold commercially as an angina therapeutic, and recent studies have shown that it is also anti-malarial and has activity against cancers with a high mortality rate. The novel synthesis attempted involved using lithiated diphenylmethane as the precursor to a Gilman reagent to perform a soft nucleophilic attack on *N*-α-phenylethyl aziridine. Upon carrying out this reaction, no desired product was formed, even with the addition of a Lewis acid. A review of the NMR spectra of the crude reaction mixture indicated that significant amounts of both diphenylpentane and tetraphenyl ethane were present as side products of the coupling reaction. After failing multiple attempts to synthesise fendiline using the proposed synthetic route, the focus of the project shifted to the research and development of hetero- and homo- cross-coupling reactions of the Gilman reagent. Different amounts of the reagents were used to find the ideal stoichiometric quantity, and results from the development only showed small amounts of the coupled products, diphenylpentane and tetraphenyl ethane were synthesised. It has been suggested that a way to improve the yield of this reaction might be to investigate analogues with stronger electron-withdrawing groups substituted on the aryl rings.

Chapter 1: Introduction

2.1 The background, synthesis, and biological activity of fendiline

Fendiline is a small molecule known for having many applications including: an antagonist of L-type calcium channels, disrupting localisation of oncogenic K-Ras and an effective anti-malarial (Rajab et al., 2018; van der Hoeven et al., 2013). Fendiline is categorised as a diphenyl alkyl amine, many under this category have activity against L-type calcium channels. Structurally, it has the possibility of forming 2 optical isomers, which can be controlled in some synthetic routes by using chiral reagents to coordinate the reaction (Huy et al., 2016; Rische & Eilbracht, 1999; Wakchaure et al., 2015)

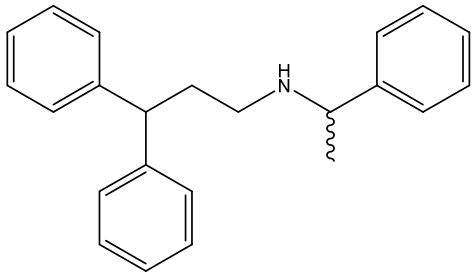


Figure 1: The structure of (+/-)-Fendiline

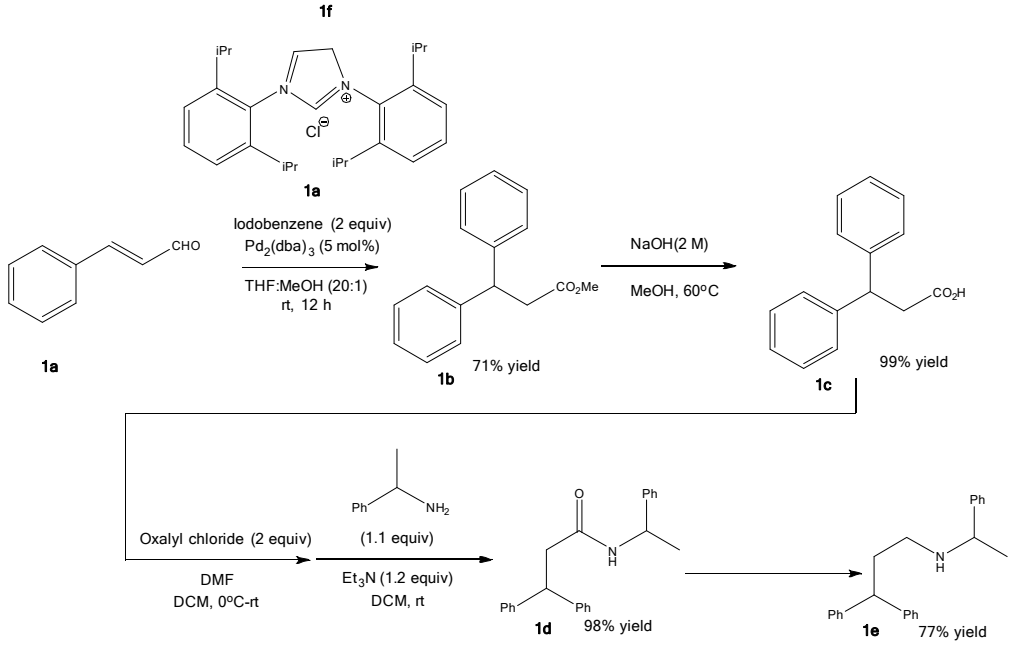
Fendiline has been known for a large period of time as a therapeutic for angina, which is a medical condition defined as a reduction of blood flow to the heart muscles, usually caused by fatty deposits which subsequently can cause a drastic increase in systolic blood pressure (Boden et al., 2007). One way to counteract this hypertension is with calcium channel blockers such as fendiline. Calcium channel blockers can help relax blood vessel stiffness and allow a greater increase in blood throughput. In a regular case, calcium is excreted from an activated synapse and is taken up by the opposing synapse *via* surface calcium channel proteins (Hemmings & Girault, 2006). Once the calcium ions enter the cell they associate with the protein calmodulin. The downstream effect of this is the phosphorylation of the myosin light chain (MLC) kinase which causes the smooth muscle cell to contract (Stevens, 1983). Fendiline disrupts this pathway of muscle contraction in 2 major modes of action, firstly it inhibits the uptake of calcium ions into the corresponding synapse, causing a drastically reduced uptake of calcium ions. Secondly, it acts as an antagonist for calmodulin which reduces the smooth muscles cells sensitivity to calcium and prevents the downstream effect of muscle contraction, this in consequence causes the smooth muscle cells surrounding the blood vessels to relax, leading to a reduction in systolic pressure (Bayer & Mannhold, 1987).

Ras is a large family of proteins that respond to intracellular signals such as growth factors, this family of proteins are essential in the proliferation and cell survival (Simanshu et al., 2017; Tetlow & Tamanoi, 2013). Ras proteins frequently alternate between a guanosine triphosphate (GTP) bound state whereby the protein is active and guanosine diphosphate (GDP) bound whereby it is deactivated. One protein known as K-Ras has an overabundant presence in several carcinomas: 90% pancreatic, 45% colorectal and 35% pulmonary (Bos, 1989). This specific oncogenic mutation causes the protein to be stuck permanently in an activated state, requiring no signal protein to activate it

and consequently causing the downstream effects of this protein to be constitutive (Prior et al., 2012). Due to the high regularity of this specific mutation, being able to selectively block this oncogenic protein is highly sought after. In a recent study, it was found that fendiline possesses activity against the oncogenic K-Ras mutation by a mechanism that prevented the surface proteins from localising on the negatively charged surface membrane of the cell. Due to fendiline being known as an L-type calcium channel blocker (Bayer & Mannhold, 1987), the same malignant cells were screened against other L-type calcium channel blockers. It was concluded in the study that the mechanism is not related to the same mechanism used by L-type calcium channel blockers but is a new pharmacological trait that fendiline possessed. Later in the study, it was observed that the malignant cells form a resistance against fendiline, expressing oncogenic N-Ras proteins instead of oncogenic K-Ras surface proteins (van der Hoeven et al., 2013).

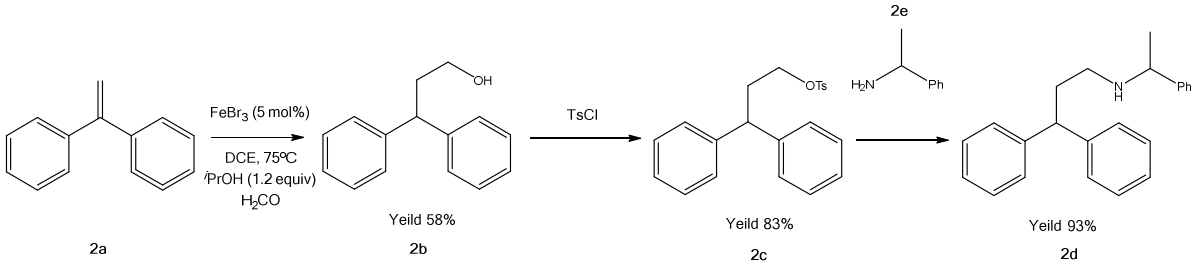
Malaria is a type of illness caused by a parasitic microorganism known as protozoa, the most common and fatal malaria species is the *Plasmodium falciparum*. Plasmodia infect the red blood cells (RBCs) of their host to maturate and proliferate. In summary, the life cycle of malaria in humans is in 2 main stages of infection. Firstly, when the protozoa are initially in the bloodstream, they will localise in the liver and infect the liver cells to maturate. Once the protozoa cells have matured, they will liberate from the liver and begin to infect red blood cells as an environment to proliferate, and this is the stage of the life cycle where the symptoms of malaria take effect. However, the life cycle of malaria is unpredictable and can take anywhere from a week to years. In a study, it was found that infected RBCs had an abnormal concentration of calcium in the cytosol (around 300 times more than usual). It is believed that an excessive amount of calcium is present due to the RBC being larger than normal. Calcium is required for the life cycle of the protozoa and so being able to disrupt the amount of exposure malaria has to calcium could affect its mortality. Fendiline in combination with chloroquine has shown to have a synergetic effect of the fendiline lowering the resistance of malaria and chloroquine being able to treat the parasitic infection. (Gething et al., 2016; Menezes et al., 2003; Rajab et al., 2018).

Recently, a palladium-catalyzed umpolung 1,4-addition reaction of aryl iodides to enals was described to afford biologically active compounds (Yang et al., 2020), including fendiline (Scheme 1).



Scheme 1: Synthesis of fendiline synthesised reported by Yang et al.

Using iodobenzene as the iodinated reagent and cinnamaldehyde as the enal, the biphenyl species 2 are obtained in 71% yield. Compound 2 is then saponified (99% yield) and then reductively aminated. The resulting compound 4 is then reduced with lithium aluminium anhydride to produce fendiline with a 77% yield. Considering the versatility and reliability of the synthetic method, it opens the possibility for the production of a wide variety of pharmaceuticals with thiophene and diphenyl pharmacophores. It is highlighted in the paper that this palladium catalyst is not moisture sensitive and only requires a small amount of the catalyst, around 5 mol for a 15 mol scale reaction, to carry out this reaction, again furthering its economic viability.

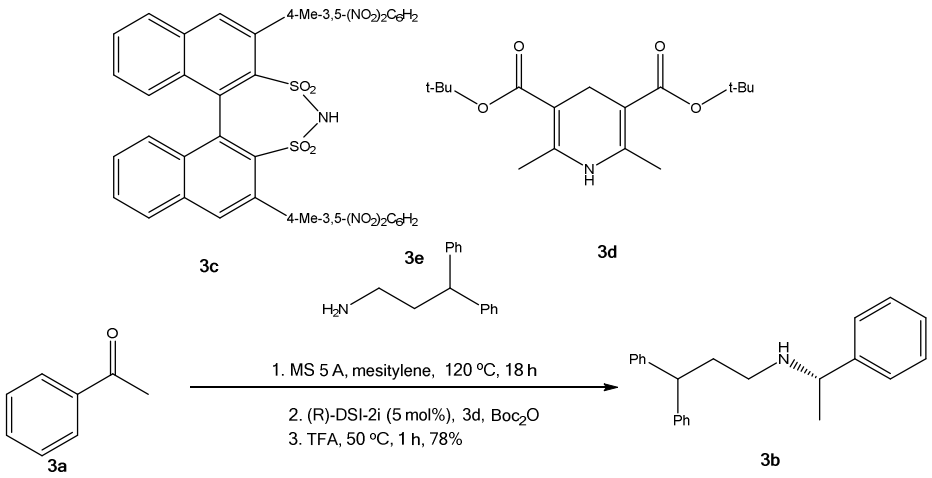


Scheme 2: Synthesis of fendiline using iron-catalysis coupled with reductive amination

Fendiline has also been synthetised by regioselective addition of alcohols onto unactivated alkenes using ferric chloride (Scheme 2).(Zheng et al., 2016) . The alkene (2a) is transformed into the alcohol (2b) and is then substituted with toluene sulfonic acid chloride, which is a good leaving group for converting alcohols into amines. The toluene sulfonic acid (2c) was then substituted for the amine (2d, shown in scheme 2) to afford fendiline with a yield of 93%. This impressively high yield and short method can easily afford a gram-scale synthesis of the pharmaceutical. In addition to fendiline, this methodology allows the synthesis of the drug tolterodine in 98% yield by using $^{i}Pr_2NH$ in place of the amine used (2e) to synthesise fendiline. The mild conditions used to carry out this synthesis for both

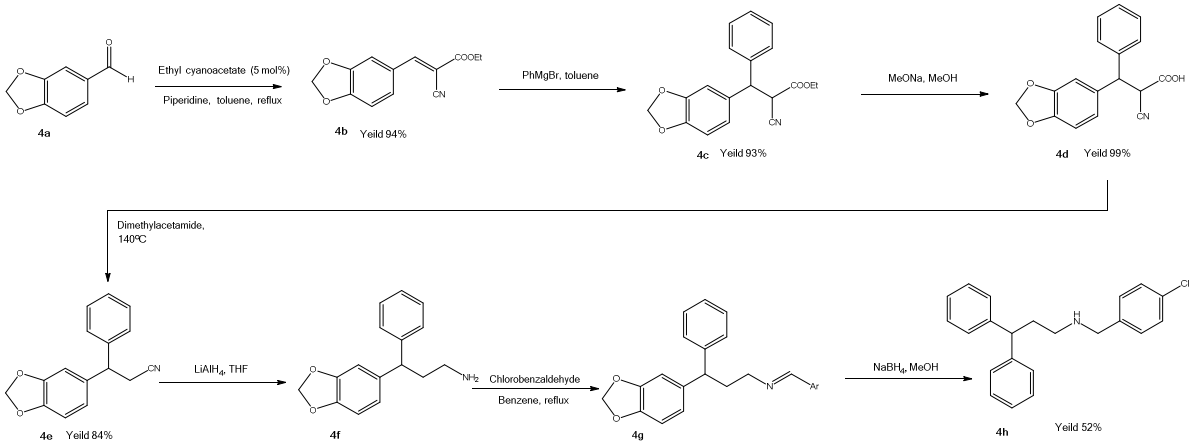
pharmaceuticals and the high conversion, low concentration catalyst, needed to carry out this synthesis afford a low cost to carry out this reaction and additionally can produce pharmaceuticals with an exceptional yield.

While exploring the viability of several catalysts and their usage in performing chiral hydroamination reactions, Wackchaure also reported an alternative synthesis of fendiline (Wakchaure et al., 2015). A disulfonamide catalyst (Figure 2)is needed to perform the chiral hydroamination reaction of ketones.



Scheme 3: Asymmetric reductive amination of a ketone to produce (*R*)-fendiline

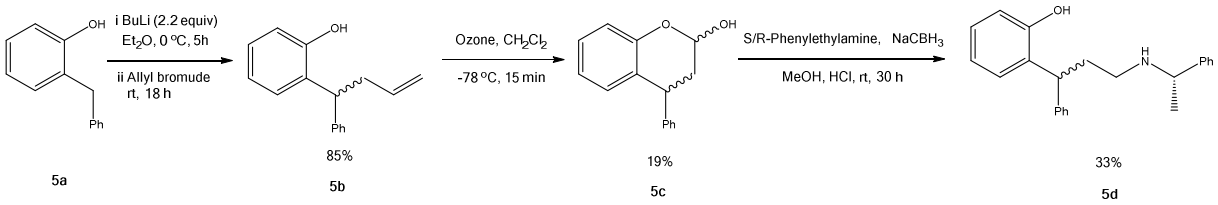
This method allows the synthesis of (*R*)-fendiline in 78% yield and 97.5:2.5 enantiomeric ratio . The methodology is also applicable to the synthesis of (*S*)-rivastigmine, an Alzheimer's and Parkinson's pharmaceutical (in 98% yield and 99.6:0.4 enantiomeric ratio) and NPS R-568 hydrochloride (82% yield and 99.7:0.3 enantiomeric ratio).



Scheme 4: Synthesis fendiline analogue 1-diphenylpropyl-3-1,3-chlorophenylmethylamine

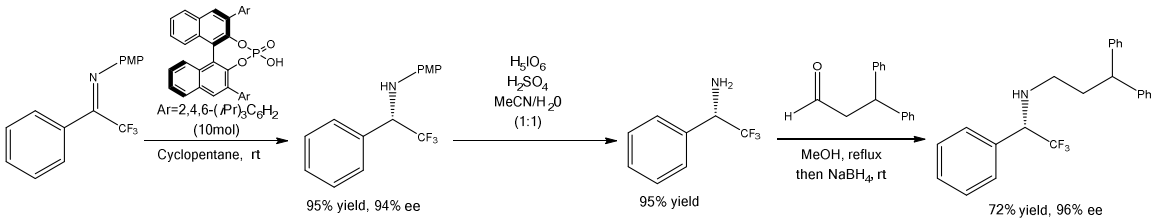
In a paper by Koyama et al (2020) a complete synthesis of a fendiline analogue 1a was reported (Scheme 4). The synthesis includes a reductive amination with 3,3-diphenylpropylamine and 4-

chlorobenzaldehyde. The drugs bioactivity against malaria was explored in the paper by (Rajab, 2018).



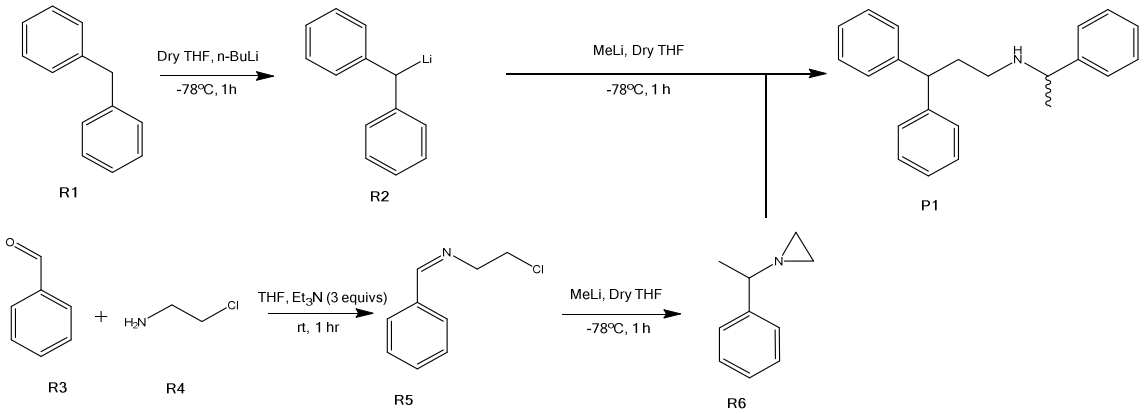
Scheme 5: *ortho*-Substituted hydroxy-fendiline

Wilkinson et al (2007) carried out a study to synthesise 2-hydroxy fendiline and test its ability as a cardiovascular drug. Fendiline, as previously discussed, has been known to act as an angina therapeutic and so the potency of this analogue was to be tested. The synthetic pathway consists on the allylation of 2-hydroxydiphenylmethane using *tert*-butyllithium followed by a cyclisation reaction. Ozone is used in this reaction to cleave the terminal vinyl group see on compound 3 (seen in scheme 5) and is reported with a yield of only 19%. The final step of this reaction can produce 2 different optical isomers, depending on which optical isomer of the reagent is used controls what the optical isomerism of the final product will be. In this case using the S isomer of the reagent phenylethylamine would produce the S isomer of the final product only, this is vice versa for the R optical isomer as well. In the biological study carried out on 2-hydroxy fendiline, it was found that S-hydroxy-fendiline was more potent as a cardiovascular therapeutic than fendiline (Wilkinson et al., 2007).



Scheme 6: Synthesis of trifluoro methylated analogue of fendiline

He, et al (2021) have developed a catalytic asymmetric reduction of α-trifluoro methylated imines, which, as a proof of concept, has been applied to a novel synthesis of trifluoromethyl fendiline in 72% yield and 96% ee. The reduction requires an organocatalyst, in contrast to previous asymmetric catalysts which usually contain a metal centre. The focus on trifluoro methylated analogues in this paper is due to their commonality in pharmaceutically active and agriculturally active compounds. The paper reports high yields (c.a. 95%) and a high enantiomeric excesses, meaning that this newer asymmetric catalyst is highly viable as a more affordable way for asymmetric reduction.

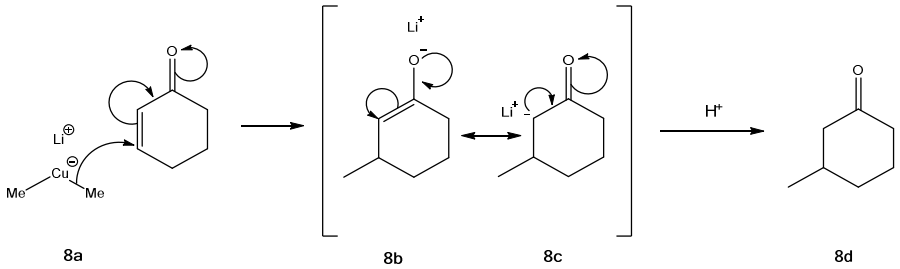


Scheme 7: Proposed synthetic route to fendiline.

The synthetic route proposed in this paper is a cost-effective, versatile, one-pot synthesis for fendiline. Whereas most cross-coupling reactions involve the use of palladium or nickel, here, the use of copper has been opted to help drive down the cost of this reaction and to help produce a novel synthesis for fendiline. This reaction proposal shows promise to be a versatile method, with the potential of the aziridine group and diphenyl reagent to be substituted with different analogues to produce a variety of diphenyl-based compounds. Many modern pharmaceuticals have diphenyl-based pharmacophores and as such this reaction pathway could open up more viable and affordable routes to manufacture these modern pharmaceuticals (Bemis & Murcko, 1996).

2.2 The history and theory of organocuprates

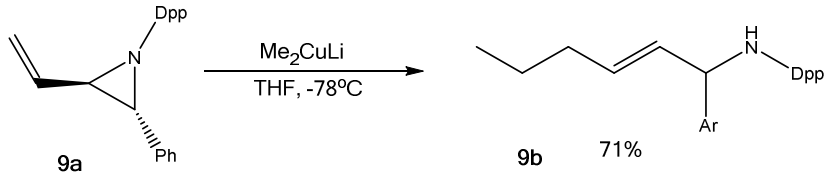
Organocuprates were first discovered in 1952 by Henry Gilman when he first synthesised methyl copper (Gilman et al., 1952). It was found that reacting organo-lithium compounds with a copper halide produced an organocuprate. Organocuprates are reactive to oxygen and water, forming copper oxide. They are also thermally unstable which is why they are mainly generated and used *in situ*. Due to the natural electronegativity of copper, there is a reduction in nucleophilicity for the α-carbon meaning that the attached ligand can undergo soft nucleophilic attacks.



Scheme 8: Reaction mechanism of dimethyl organocuprate (Gilman) reacting with an α, β-unsaturated carbonyl.

A typified example of a soft nucleophilic attack is a conjugate addition of the organocuprate and an α, β-unsaturated carbonyl compound (Scheme 8). The soft nucleophilic attack will selectively react with the β-carbon *via* a conjugate addition and form a sp^3 centre, this is because of a better orbital overlap between the LUMO of the organocuprate and the HOMO carbonyl's β-carbon. In contrariwise, a hard nucleophile, like methyl lithium, would instead attack the αcarbon, as it is the dipole with the highest positive charge. Hard attacks involve atoms that have the greatest electrostatic attraction and soft attacks involve π-bonds with the greatest orbital coefficient (Posner, 2011). Organocuprates are also able to undergo coupling reactions by substituting a leaving group for the organocuprate (Normant, 1972).

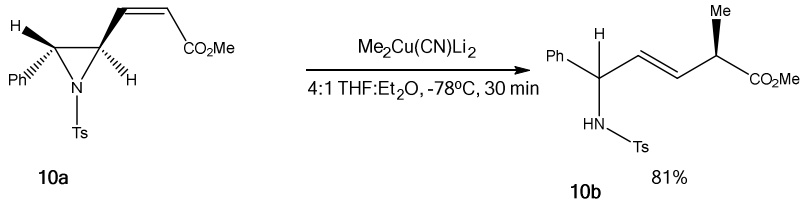
The affordability of copper reagent is far better than the more common palladium and nickel catalysts used in favour of cross-coupling reactions. Also, the selectivity of this reagent presents many positive points. Unfortunately, however, copper lithium reagents are very unstable and reactive, as such, using the reagent on a large scale would not be feasible, firstly due to the drastically increased risk of using lithiated compounds and secondly by using an extreme temperature and an inert atmosphere. Palladium and nickel catalysts do not require lithiated compounds and can run under much milder conditions, and this is the main reason why copper lithium is not used as frequently in cross-coupling reactions.



Scheme 9: Ring-opening of aziridine using a Gilman reagent, methyl copper lithium

Gilman reagents can also perform ring-openings on aziridines to form amine-based compounds. One such example from the group of Sweeney (Jarvis et al., 2013) shows the use of a Gilman reagent to open aziridine rings regioselectively (Scheme 9). The paper explores a variety of nucleophiles, most of which were Gilman reagents, alongside different substituents on the aziridine ring, reporting yields from 44% to of 74%.

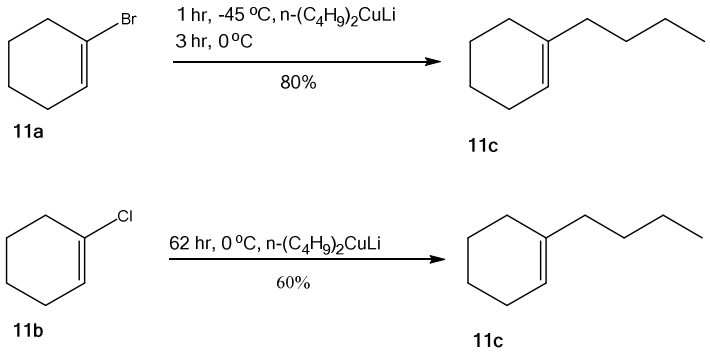
Gilman reagents are excellent at undergoing SN2 reactions and can easily alkylate alkyl bromides and also perform aziridine ring-openings. In contrast, a hard nucleophile like a Grignard reagent cannot carry out SN2 reactions well and would not be able to alkylate the alkene (Scheme 8, 8a) (Corey & Posner, 1968).



Scheme 10: Ring-opening of aziridine bearing an ester group using an organocuprate reagent.

Another instance in which aziridines were opening using a Gilman reagent can be found in the paper by (Fujii et al., 1995). This work explores the use of organometallic reagents with different ligands to produce α,β-unsaturated esters by opening aziridine rings (Scheme 10). It was found that this

reaction produced both trans and cis products depending on the reaction conditions and whether the reaction would either undergo a SN2 reaction or an anti-SN2 reaction, of the variety of ligands tested it was found that the best yield for anti-SN2 reactions was 95% and the worst yield being 81%. These impressive anti-SN2 ring-openings produce high yields, in contrast the reactions what underwent SN2 conditions reported 15% as the best yield from this reaction and 2% and the worst yield from this reaction.

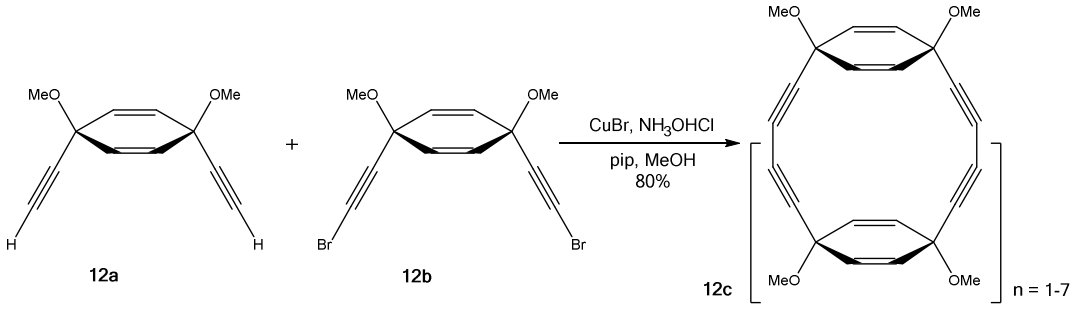


Scheme 11: Two examples of the cross-coupling reactions carried out with a Gilman reagent

In the paper by (Corey & Posner, 1968) they investigated carbon-carbon cross-coupling of organohalides with organocopper lithium. The paper describes the use of different coupling reagents to produce alkylated products reporting that primary halides, on average, produced better yields than secondary halides. In addition, it was also reported that brominated partners produces better yields than the chlorinated analogues. In the paper, it is also discussed that organolithiums can give better yields than organocuprates due to the fact that organocuprates form a metal-halide complex. to the methodology allows the alkylation of 1-bromocyclohex-1-ene and 1-chlorocyclohex-1-ene with 80% and 60% yield respectively using *n*-butyl copper lithium to alkylate the organohalides (Scheme 11).

In recent years, copper has grown more popular largely due to cost and the development of green chemistry. The Ullman reaction was the first reaction of its kind with copper as the catalyst for cross-coupling reactions (Fanta, 1974). There has not been extensive research into Ullman or other copper catalysts when compared to platinum or nickel-based coupling reactions. In recent years, the research into copper-based coupling reactions has increased, this can again be contributed to green chemistry's rising popularity and also due to the affordability of copper compared to palladium family metals . The Ullman reaction affords cross-coupling reactions but comes with some major limitations to its scope. Firstly, the reactivity of iodine substituted phenyl functional groups works better than bromine and even more so than chlorine meaning that iodine-based reagents are the only viable option. Secondly, the Ullman reaction can be hindered by the steric properties of the reagent used (Norrby, 2010; Xu & Wolf, 2009).

The Ullman reaction can couple aryl halide with aliphatic amines, both secondary and primary, which are also known as C-N cross-coupling reactions. Development around these reactions has helped to drastically reduce the harsh reaction conditions used when Ullman reactions were first discovered (Fanta, 1974).

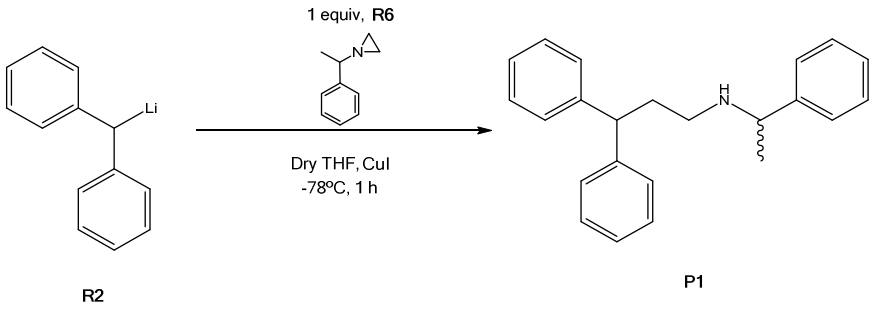


Scheme 12: Cross-coupling of 1,4-diethylnyl-1,4-dimethoxycyclohexa-2,5-diene and 1,4-bis(bromoethylnyl)-1,4-dimethoxycyclohexa-2,5-diene under Cadiot-Chodkiewicz reaction conditions

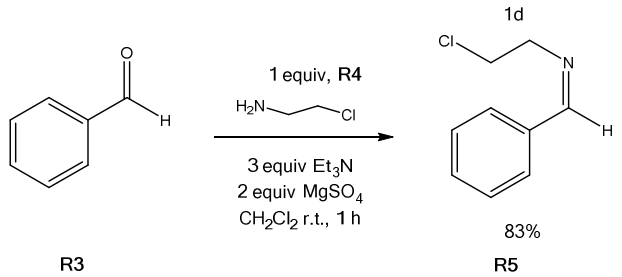
Another coupling method, the Cadiot-Chodkiewicz coupling reaction, does not require harsh conditions to carry out but has a greatly reduced scope. The coupling reaction involves the use of a primary alkyne with a haloalkyne. An example of this coupling reaction can be found in the paper by Bandyopadhyay, et al (2006) where they carried out a Cadiot-Chodkiewicz coupling reaction of 1,4-diethylnyl-1,4-dimethoxycyclohexa-2,5-diene with its brominated counterpart to produce a macrocyclic molecule. The reaction conditions include copper bromide, hydroxylammonium chloride, piperidine and methanol to produce a variety of oligomers with yields ranging from 2.5% (heptamer) to 32% (tetramer).

Chapter 2: Results and Discussion

The purpose of this thesis was to investigate the potential synthesis of fendiline that would also be very versatile. Reagents used in the paper, for example benzaldehyde, have a wide range of derivatives and can afford a large variety of compounds for this reaction. It is also possible to change the methyllithium used in the aziridine formation to another organolithium, the diphenylmethane also has other derivatives that can also be changed, or a different organolithium reagent can be chosen for this part of the reaction altogether. The reaction pathway here suggested demonstrates a very large amount of potential, especially since most of the reagents used were affordable and the main cross-coupling agent is a copper-based Gilman reagent. In addition to its versatility, the reaction conditions needed are easy to carry out and the time needed for the reaction to go to completion is short, meaning that the entire reaction could be carried out in a day depending on the scale of the reaction.

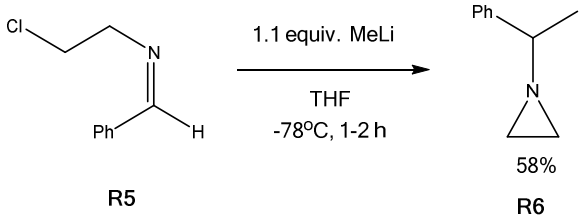


Scheme 13: Proposed synthesis of fendiline using diphenyl methyl lithium and *N*- α-Phenylethyl aziridine.



Scheme 14: Imine formation from benzaldehyde (De Kimpe & De Smaele, 1994)

The first step of the synthetic route involved the imine formation from benzaldehyde (R3) using 2-chloroethylamine (R4), whereby the aldehyde is reduced to a hydroxy group and the amine reagent attacks the carbon to eliminate the just formed hydroxy group (Scheme 14). The average yield from this step was 83% and comparing this value against reported yields in the paper De Kimpe & De Smaele (1994) with a yield of 98%, there is a significant difference between these two figures. Several attempts were made to help improve the yield of this step. It was noted that similar methodologies used 3 equivalents of triethylamine to improve yield and lower the run time of the reaction (D'Hooghe et al., 2008). After implementing the new reaction conditions from 1 equivalent of triethylamine to 3 equivalents of triethylamine, a significant improvement was made to the yield, going from <20% yield to 83%. However, even with the new reaction conditions, the attempt to replicate the 98% yield reported in the De Kimpe paper was unsuccessful. A possible reason why the yield for this step is lower than what most papers report is due to the 2-chloroethylamine used being past its shelf life, as such the quality of this compound is likely to have deteriorated over the years. It was assumed that the reagent was of a lower quality than stated in the bottle and as such, an excess of the compound was used to help mitigate this. If an improvement were to be made on this step, it would be to first use a new stock of 2-chloroethyamine. Other suggested improvements to the reaction would be to use molecular sieves instead of anhydrous magnesium sulphate. As magnesium sulphate has a slightly acidic pKa that could affect the yield, it would be better to use molecular sieves to help remove the water generated and help favour the reaction, it could also be possible to use a dead stark trap instead of using a drying agent.



Scheme 15: Synthesis of aziridine using methyl lithium (De Kimpe & De Smaele, 1994)

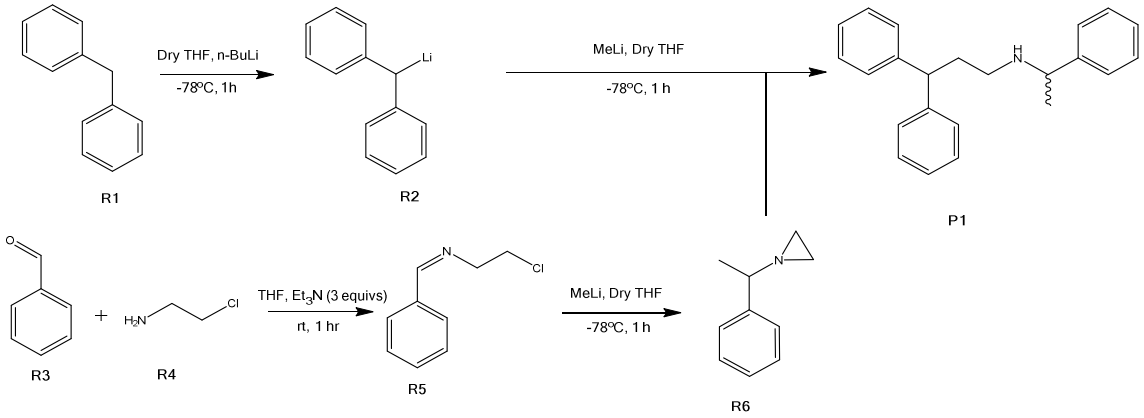
The second step involved the intramolecular cyclisation of *N*-(phenylmethyl diene)-2-chloroethylamine (R5) to produce an aziridine (Scheme 15, R6). The yield from this step was 58%, in accordance with the yield reported by De Kimpe & De Smaele (1994). This low yield would drastically affect the overall yield of the synthesis of fendiline. There is no obvious improvement that can be made to this step as it has been demonstrated in other papers that aziridine formations produce low

yields unless the aziridine ring has substituents attached, the only way to improve this particular step would be to revise the reaction to use a different electrophile (De Kimpe & De Smaele, 1994; Sternativo et al., 2010).

The lithiation of diphenylmethane has been described in the literature several times, with yields of around 80% (Eisch et al., 2012; Bank et al., 1983; Jaun et al., 1980).

The last step of the synthetic route involved the attempted coupling of diphenyl methyllithium and *N*-α-phenylethyl aziridine with the intermediary of a Gilman reagent. Due to the reactive nature of lithiated compounds, the entire reaction was carried out under an argon atmosphere to allow a completely anhydrous environment, the solvent used in this reaction was also anhydrous. The first attempt at this synthesis was carried out under the conditions shown in scheme 12. The 1H NMR spectra of the reaction mixture indicated that no fendiline was produced from this reaction, 2 more attempts were made to confirm that the synthesis of this reaction could not work under these reaction conditions. It was hypothesised that the addition of a Lewis acid would help coordinate the Gilman reagent to attack the aziridine by associating with the nitrogen to make the carbons on the aziridine ring more nucleophilic.

The first attempt at the fendiline synthesis did not yield any of the desired product, and it was suggested that using a Lewis acid alongside the aziridine would help better coordinate the ring-opening to attack the diphenyl lithium. The second attempt for the fendiline synthesis was carried out using the lithiated diphenylmethane and the aziridine reagent, following this, the copper iodide was added and left to mix for half an hour. Afterwards, borotrifluoro etherate, a Lewis acid, was added to the reaction mixture and an immediate change in the reaction vessel occurred. The colour produced from the lithiated diphenylmethane disappeared, heat was generated, and slight effervescence occurred in the reaction vessel.



Scheme 16: Proposed synthesis of fendiline

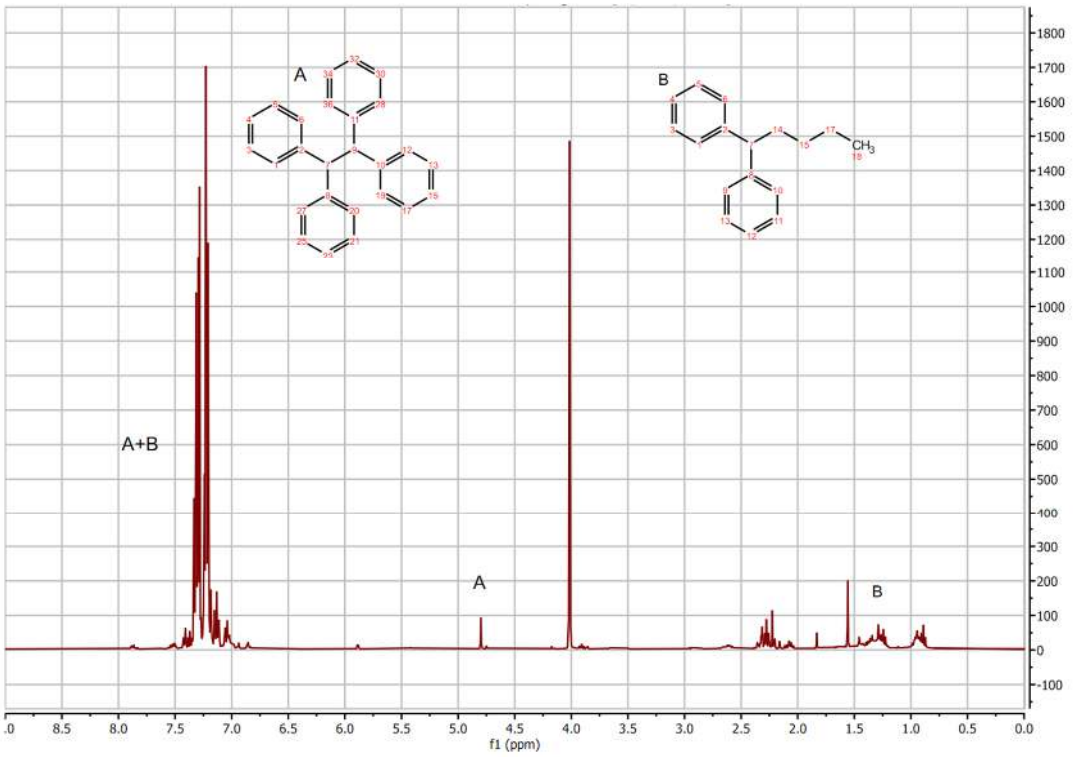
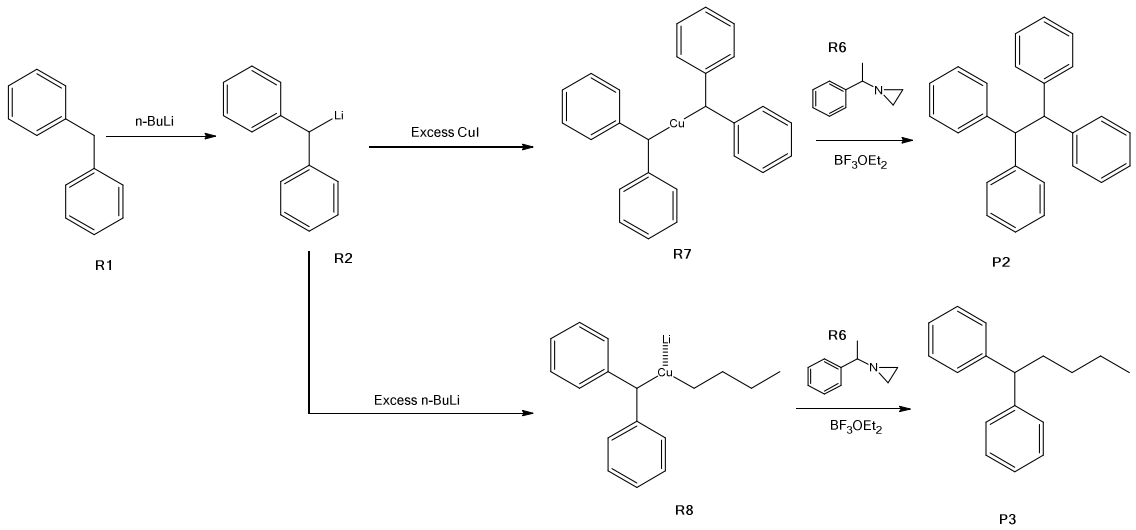


Figure 4: 1H NMR spectra of the crude mixture from attempted fendiline reaction and their assigned peaks

Upon reviewing the results from the reaction there was no evidence that fendiline was produced, if there were, a doublet at 1.5 ppm would be expected, as well as a quartet at 2 ppm, a triplet at 3 ppm and a multiplet at 4 ppm. There are no discernible peaks around 3 ppm. It was evident that a large amount of side-product was present in the reaction mixture instead of the desired product due to the remaining peaks in the NMR spectra. Upon review of the NMR spectra, it was determined that the side-product was tetraphenyl ethane, with the strong peak at 5 ppm being ethane protons from tetraphenyl ethane, deduced upon comparison with the literature Sahoo (2016), and diphenylpentane, recognised by the peaks downstream on the spectrum. An explanation for the presence of tetraphenylethane in this reaction mixture could only be explained as a side product from the reaction carried out. It was hypothesised that the copper iodide associated with 2 lithiated diphenylmethane's and reductively eliminated itself to produce a cross-coupled product, tetraphenylethane. The presence of diphenylpentane, a cross-coupling product was speculatively explained as arising from a mixed cuprate with a butyl group as well as a diphenylmethane group attached to the copper centre (Scheme 17). This was suspected to have been formed due to the excess of *n*-butyllithium used in the formation of the lithiated diphenylmethane and being carried through into the reaction vessel. This formation of this cross-coupled product must then have been reductively eliminated with the same mechanism as with the tetraphenyl ethane which then led to the product, diphenyl pentane, being formed. This kind of unique cross-coupling reaction leads to the idea that the mixed cuprate can have different substituents around the copper centre, i.e., instead of *n*-butyllithium being used we could opt for another organolithium or even substitute the diphenylmethane for a diphenylmethane analogue with different functional groups on its aryl rings. In addition to there being diphenyl pentane and tetraphenyl ethane present in the NMR spectra it is

also believed that the other side products from this reaction were unreacted diphenylmethane and an unknown side product formed from the N-α-phenylethyl aziridine.



Scheme 17: A proposed synthetic route for the synthesis of diphenylmethane and tetraphenyl ethane

After realising that the reaction we carried out produced both tetra phenylethane and diphenylpentane it was realised that a mixed cuprate was likely forming, reductively eliminating when the reaction was quenched to produce 2 major side products. A hypothesised route to produce either product is shown in Scheme 17. It is believed that with an excess of n-BuLi alongside the presence of lithiated diphenylmethane, the diphenylpentane product is produced. But when there is excess CuI instead of n-BuLi, tetraphenyl ethane is more likely produce instead.

Entry	Equivalents of diphenylmethane	Equivalents of copper iodide	Equivalents of boron trifluoride etherate	Equivalents of triethylamine	Equivalents of butyl lithium	Tetra phenylethane (I%)	Diphenyl pentane (I%)	Diphenyl methane (I%)
1	1	1	0	1	1.1	16.10	9.35	74.55
2	1	1	0	1	2	3.98	N/A	96.02
3	1	1	1	1	2	15.39	4.08	80.53
4	1	0.5	1	0	1.1	6.51	2.09	91.40
5	1	0.5	1	0	2	6.34	3.37	90.29
6	1	0.5	0	0	2	8.74	N/A	91.88

Table 1: Attempts to optimise the cross and homo-coupling reactions of diphenylmethane.

The intensity percentage is gathered by percentage difference from the peak height of the methane peak of diphenyl methane and ethane peak of tetraphenyl ethane. The calculation for this value is shown below in this formula.

$$\frac{peak\ height\ of\ tetraphenylethane\ (ethane\ peak)}{peak\ height\ of\ diphenylmethane\ (methane\ peak)} \times 100 = \%\ Intensity$$

After producing this hypothesis an effort was made to increase the yield of the cross-coupled products. The first variable that was explored was the desired stoichiometric amount of reagent to see if the yield would increase but to also see if the reaction could be steered to favour the production of either product. For this, the copper iodide, diphenylmethane and *n*-butyllithium were all altered to see if there would be a significant increase in yield and product ratio. The second variable was the amounts of Lewis acid used. Since the addition of Lewis acid in the second reaction produced enough tetraphenyl ethane to be determined, it was suggested that the addition of different amounts of Lewis acid could help to increase the yield. The first reaction attempted (Table 1, entry 1) had only a small excess of butyllithium (1.1 equivalents) and 1 equivalent of copper iodide, in the original reaction where the tetraphenyl ethane was generated, the aziridine compound was present and acted like a Lewis base, for all the reactions that were carried out we opted to use triethylamine in place of the aziridine compound.

Next, we increased the amount of butyllithium to 2 equivalents (entry 2), but the results from this reaction were far lower than that of entry 1.

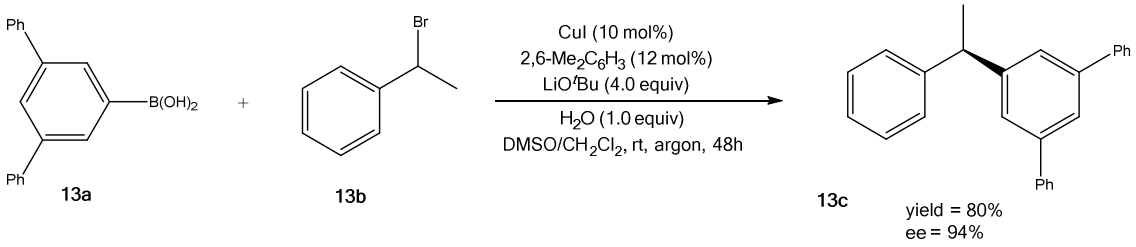
We then decided to use a Lewis acid as well as a Lewis base because both were present in the original reaction, our Lewis acid was boron trifluoro etherate and our Lewis base was triethylamine (entry 3). The results generated from this reaction were far better than previous attempts (entries 1 and 2).

Entries 4 and 5 for table 1 were similar with the exception of entry 5 having a larger excess of n-BuLi, the reaction conditions here were to investigate if Lewis acid could also produce a large amount of the cross-coupled product.

The last reaction, number 6, had neither Lewis base nor Lewis acid and was carried out to see if the cross-coupled products required the presence of a Lewis base or acid at all. The spectra showed that a %intensity of 8.12 was achieved and the cross-coupled product could be formed without the presence of Lewis base or acid.

To summarise, results from table 1 show that when there is a presence of triethylamine in the reaction mixture, there is an increase in the homo coupled product, we can notice a significantly less amount produced when there is no Lewis base. Reaction 2 does not conform to the idea that Lewis base helps increase this yield however, in this reaction an excess of *n*-BuLi is used which would be indicative that an excess of *n*-BuLi is detrimental to the yield of this reaction, but reaction 3 uses the same equivalences with Lewis acid. It would be ideal to run these experiments in triplicate to help prevent any unreliable results skewing the development for the ideal stoichiometric quantity needed as it is believed that the result produced from reaction 2 is an outlier. It can also be observed from table 1 that when there is no presence of Lewis base or acid, the reaction still is able to produce the homo coupled product.

Ideally during the development of the ideal stoichiometric quantity of reagents needed it would be valuable to carry out these reactions with the addition of the original Lewis base used in the original reaction, n-α-phenylethyl aziridine, to see if this base helps improve the yield of either of the cross-coupled products.



Scheme 18: sp^3-sp^2 Coupling using the copper-catalysed Suzuki-Miyaura reaction

The generation of 2 sp^3 centres from this coupling reaction shows a great deal of potential, there have been previous publications that have achieved sp^3-sp^2 coupling like the copper catalysed Suzuki-Miyaura which involves the cross-coupling of an aryl boronic acid (13a) with a haloalkane (13b) to produce a cross-coupled product (13c). It was reported in the paper that one of the compounds achieves homocoupling as a side product for their reaction which can be observed also in this paper(Jiang et al., 2020).

As can be seen from the reviewed literature, most copper-based cross-coupling reactions do not tend to form 2 sp^3 centres and also require a leaving group to be added to the desired reagents firstly. With this reaction that we have found, it is possible to form sp^3-sp^3 carbon-carbon coupling with the addition of no installations of leaving groups on either reagent used, making this reaction a one-pot one-step synthesis for cross-coupling. This possibly rare coupling reaction has the ability to possibly further the scope of copper-based reactions if a more reliable method is developed with a better yield as well.

Chapter 3: Experimental Methods

General:

NMR was carried out under a Bruker 400 MHz, deuterated solvents were sourced from Cambridge Isotopes

Equipment included in this reaction were: a double manifold, 2 necked round bottom flask, magnetic flea, 5ml plungers and syringes, cooling bath, oven (to ensure anhydrous glassware, rubber septas and argon.

Regents were sourced primarily from Acros Organics, Sigma Aldrich, and Alfa Aesar.

3.1 Attempted synthesis of fendiline

3.1.1 Lithiation of diphenylmethane

Under anhydrous conditions, diphenylmethane (0.1682 g, 1 mmol, R1) was added to a 10 mL 2-necked round bottom flask alongside anhydrous THF (2mL). The reaction mixture was charged with argon and after cooling to −78 °C, *n*-butyllithium (1.2 mL, 2 mmol) was slowly added into the

reaction mixture. The reaction mixture will slowly turn red, the reaction mixture was left to stir for 1 hour.

3.1.2 Synthesis of *N*-(phenylmethyl diene)-2-chloroethylamine

2-Chloroethylamine hydrochloride (0.303 g, 2 mmol, R4) was added to a reaction vessel alongside THF (5 mL) and benzaldehyde (0.318 g, 1 mmol, R3). Triethylamine (3 mL, 7.1 mmol) was then added to the reaction mixture and was left to stir for 1 hour.

The crude product was then concentrated under vacuo and the solid was washed with ethyl acetate (10 mL) and 1 deionised water (10 mL). In a separatory funnel, the ethyl acetate layer was washed 3 times with distilled water and then 3 times with brine. The organic layer was then dried with magnesium sulphate and concentrated under vacuo to provided the title compound in 83% yield. ^{1}H NMR (400 MHz, CDCl3) δ 8.26 (d, *J* = 1.2 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.32 (m, 3H), 3.88 (t, J = 6.0 Hz, 2H), 3.79 (t, *J* = 6.0 Hz, 2H). The NMR data is in accordance with the literature Gudun et al., (2020)

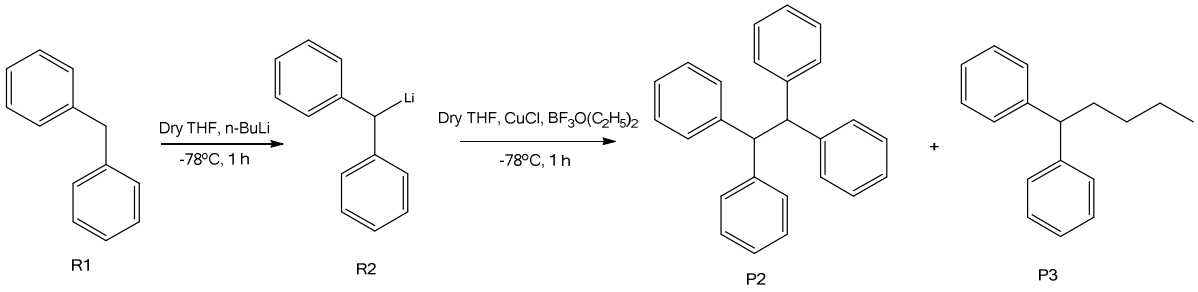
3.1.3 Synthesis of *N*-α-phenylethyl aziridine

The N-(phenylmethyl diene)-2-chloroethylamine (R5) was added to a 2 necked round bottom flask alongside anhydrous THF (5 mL). The reaction vessel was charged with argon and chilled to -78 °C, methyl lithium (1 mL, mL, 1.2 mmol) was added to the round bottom flask and the reaction vessel was left to stir for 1 hour. The crude product was then quenched with ethyl acetate and concentrated under vacuo to provided the title compound in 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.00 (m, 5H), 2.09 (q, *J* = 6.5 Hz, 1H), 1.68 (dd, *J* = 5.8, 4.0 Hz, 1H), 1.46 (dd, *J* = 5.8, 4.0 Hz, 1H), 1.29 – 1.20 (m, 3H), 1.08 (dd, *J* = 7.1, 4.0 Hz, 1H), 0.93 (dd, *J* = 7.1, 4.0 Hz, 1H). The NMR data is in accordance with the literature D'Hooghe, et al., (2008)

3.1.4 Attempted synthesis of fendiline

In the reaction vessel (from 3.1.1), copper iodide (0.5 g, 0.5 mmol) was added alongside boron trifluoride etherate (1 mmol) and left to stir for 30 mins. After this, the aziridine product (R6 from reaction 3.1.3) was added and the reaction mixture was left to stir for a further hour. After this a pale-yellow reaction mixture is presented with black sediment. The reaction was quenched with deionised water (1 mL) and dried with $MgSO_4$. After drying, the mixture was then filtered through filter paper at atmospheric pressure and concentrated under vaccuo.

3.2 Synthesis of homo and hetero coupled products



Scheme 19: A proposed synthetic route for tetra phenylethane.

3.2.1 Synthesis of tetra phenylethane and diphenylpentane

Anhydrous THF (5 mL) was added to a 2 necked round bottom flask and chilled to -78 °C. Diphenylmethane (equivalents used see table 1, R1) was added to the chilled THF alongside *n*-butyllithium (equivalents used see table 1), dropwise. The colour of the reaction mixture changed to a dark purple. To the round bottom flask, boron trifluoride etherate (equivalents used see table 1) was added to the reaction mixture dropwise afterwards triethylamine (equivalents used see table 1). After the reaction has settled a grey precipitate will present. The reaction mixture was then quenched with ethyl acetate (2 mL). The mixture was then vacuum filtered and concentrated under vaccuo. Yield 13% ^{1}H NMR (400 MHz, CDCl3) δ 7.54 – 6.99 (m, 20H), 4.80 (s, 2H). The NMR data produced for the compound tetraphenylethane (P2), conforms to supplementary spectra produced from (Sahoo, 2016)

Chapter 4: Conclusion

To produce *N*-(phenylmethyl diene)-2-chloroethylamine, benzaldehyde was used for an imine formation with 2-chloroethlyamine hydrochloride, however, it was determined that the initial reaction conditions based on the previous works by Dr De Kimpe did not produce the same yield in this experiment and the equivalents of triethylamine were increased from 1 to 3. The yield produced with the increased triethylamine was still lower than reported in papers carrying out the same reaction, however, the reaction could be carried out reliably and still produced an acceptable yield of 80%. The reagent used, 2-chloroethylamine hydrochloride, was an older stock that could have likely deteriorated in quality and as such lowered the reported yield from this reaction. If the reaction were to be repeated it should be under the newer reaction conditions and with the addition of newer 2-chloroethylamine hydrochloride or at the very least, attempts should be made to make the product purer, for instance distillation of the reagent.

For the synthesis of N-α-phenylethyl aziridine the yield produced from this reaction severely bottlenecked the yield of the final synthetic step, producing at best a yield of 40%. A possible improvement to the synthesis of N-α-phenylethyl aziridine would be to either find a catalytic version of the reaction or to opt for an analogue with potentially protecting groups substituted on the aziridine ring.

The lithiation of the diphenylmethane did not have a recorded yield associated with it. This is due to the reactive nature of lithiated species and that there would be no physical way to measure how much lithiated diphenyl methane was produced.

For the synthesis of fendiline, the aziridine and organolithium cuprate did not have the desired effect of cross-coupling the 2 reagents, even with the addition of a Lewis acid. A possible improvement to the synthesis of the desired product could be to opt for a different species of a soft nucleophile or perhaps to try harder nucleophiles. As was observed in the reaction mixture, we can no longer see the characteristic double signals generated by the aziridine ring, it is possible that the ring did open in the reaction mixture but the coordination of the aziridine with the Gilman reagent did not couple the two reagents together.

The tetra-phenylethane was an unexpected product formed from the attempted synthesis of fendiline. The runs from this experiment produced yields with no discernible trend. Some possible improvements to this synthetic step could be to use strong electron-withdrawing groups on the phenyl rings to help make a more electropositive carbon in the alpha position of each of the phenyl rings.

In conclusion on the findings in this paper, if the fendiline synthesis using a Gilman catalyst were to be successfully carried out, it would have afforded a versatile and cost-effective synthesis to a large variety of pharmaceutical compounds. The reaction however could not be carried out due to the aziridine species not performing the ring-opening with the Gilman reagent. In addition to the reaction not working there are limitations if the reaction were to be carried out on a larger scale, firstly lithiated reagents add a higher risk to the reaction which increases depending on the scale carried out, secondly the low yield gained from the formation of the aziridine precursor meant that a large bottleneck would occur downstream of this reaction pathway. The cross-coupled Gilman product afforded a one-pot one-step synthesis to produce tetraphenyl ethane a homo coupled product, and also produced diphenyl methane, a hetero coupled product. If the reaction were to be optimised and the products formed from the reaction could be controlled, it could offer an inexpensive way to cross-couple of aromatic compounds, additionally, it could be possible to use different substituents for Gilman reagent and offer a limited but still flexible scope for cross-coupling.

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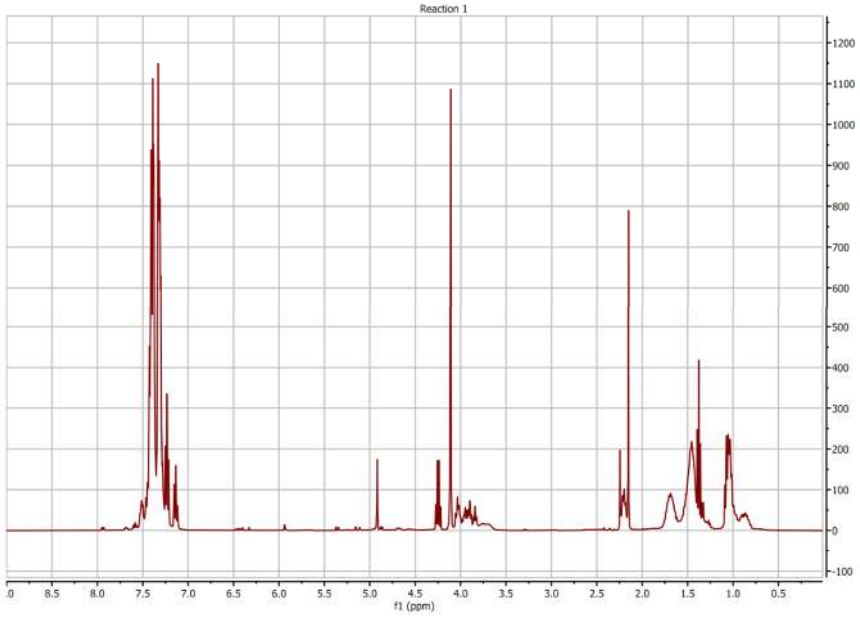
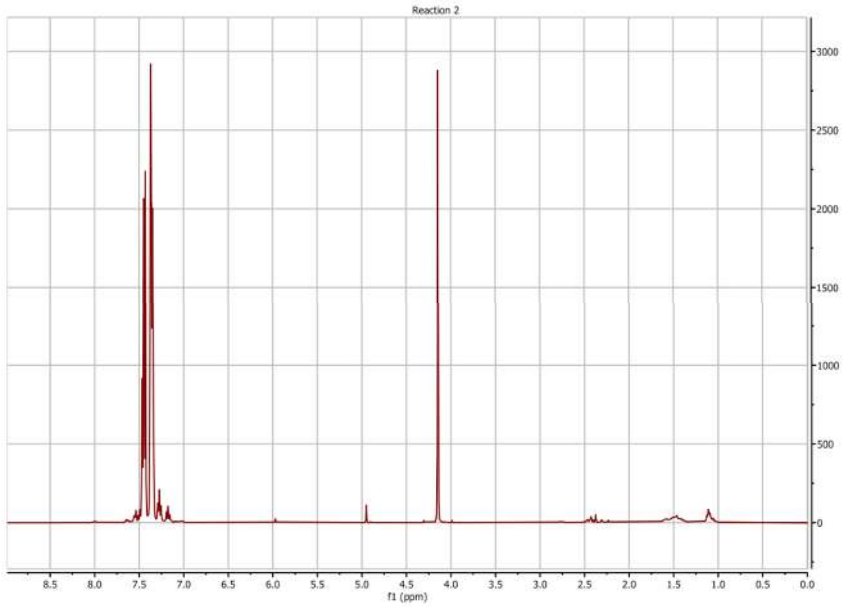
Appendix

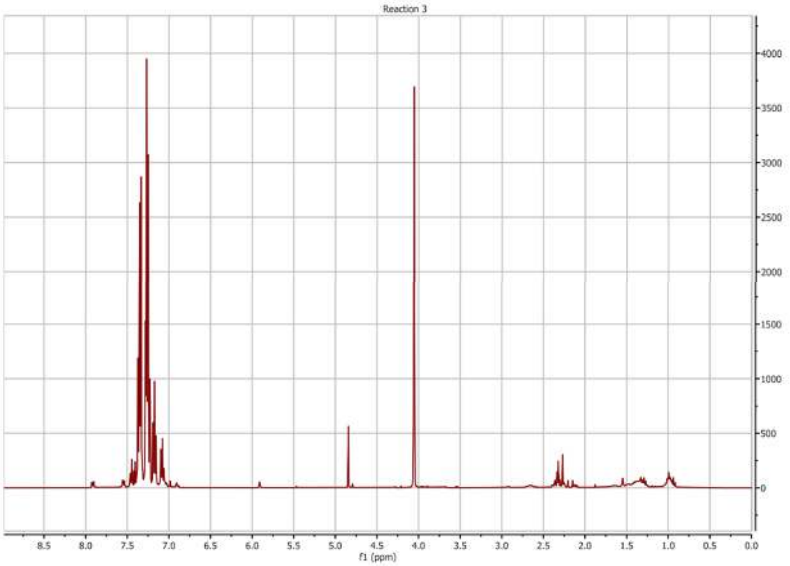
All NMR spectra that have been produced and referenced in this paper are listed below with their relevant title.



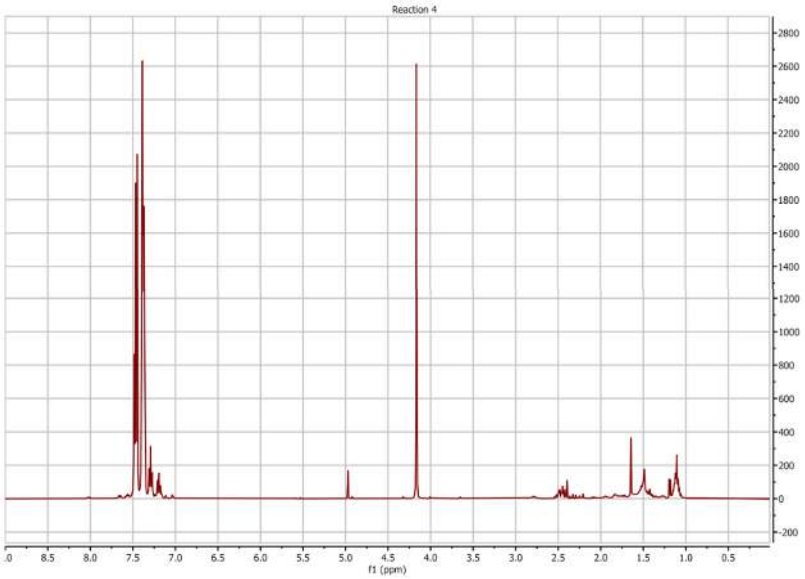
NMR spectra produced from table 1, entry 1.



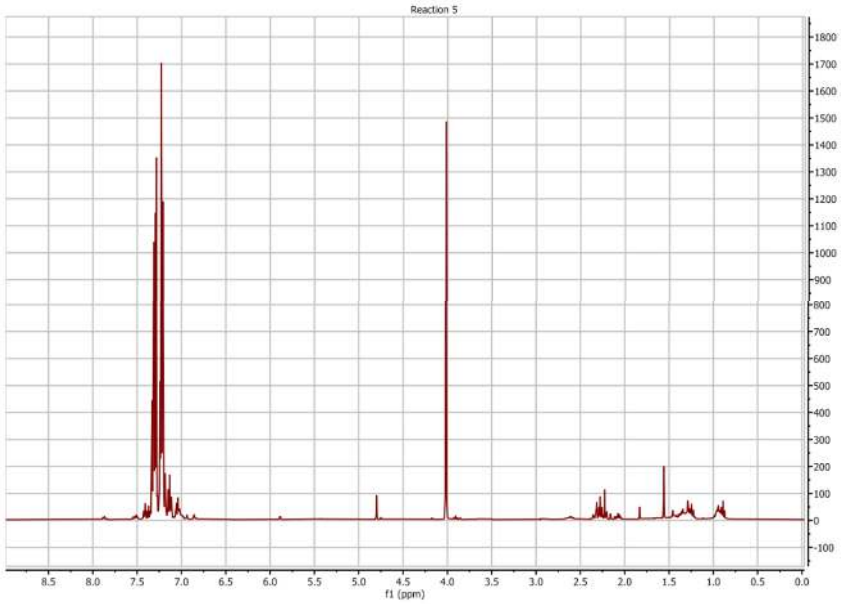
NMR spectra produced from table 1, entry 2.



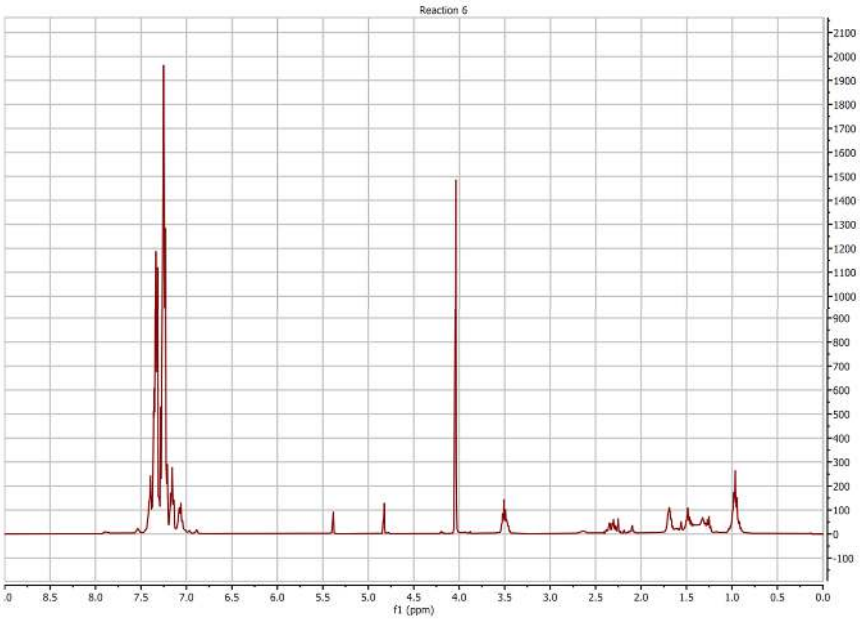
NMR spectra produced from table 1, entry 3.



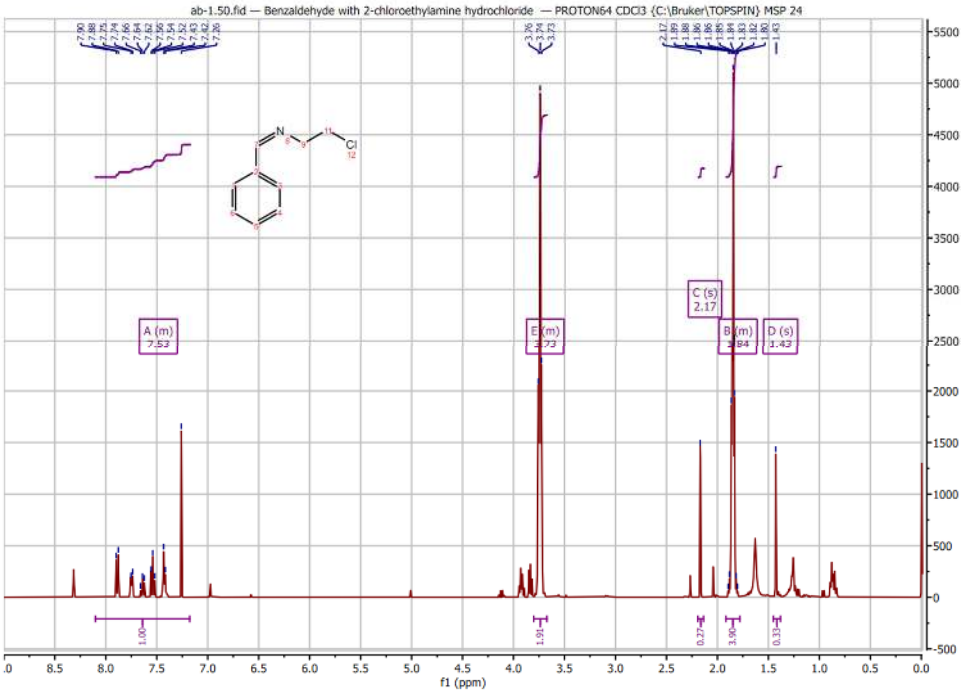
NMR spectra produced from table 1, entry 4.



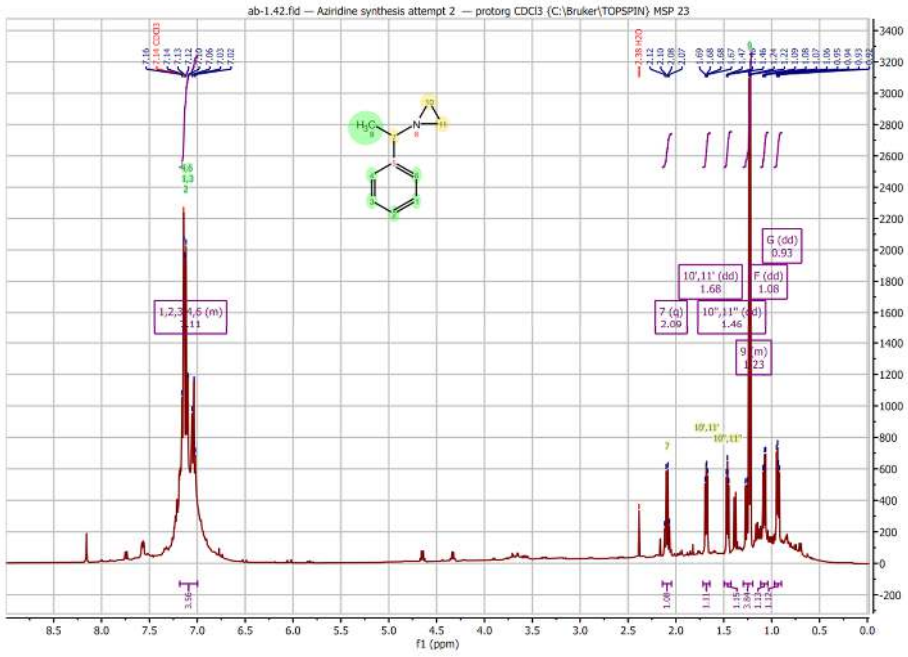
NMR spectra produced from table 1, entry 5



NMR spectra produced from table 1, entry 6.



NMR spectra produced for N-(phenylmethyl diene)-2-chloroethylamine



NMR spectra produced for N-α-phenylethyl aziridine