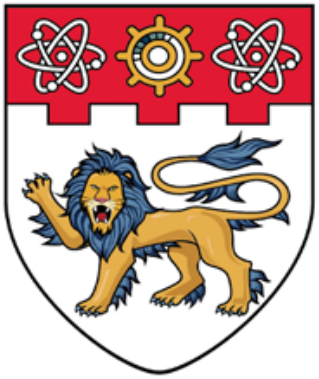


NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

CM5071 Final Report

AY23/24 Special Term

July 25, 2024

Project Title: **Unsaturated Imines with a Rigid Backbone**

Supervisor: Professor Kinjo Rei

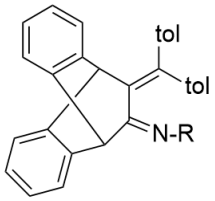
Student mentor: Ms. Kavita Devi

Submitted by: Isaac Ng En Xin (U2340664K)

Contents

1 Overview

This document shall report on the current progress of the synthesis of the final ligand derivative **8a,b**.



8a,b

Figure 1: Final ligand derivative **8a,b**

As of July 25, 2024, the following synthesis pathway has been conducted to reach **3**, which is a step in the pathway of synthesizing **8a,b**.

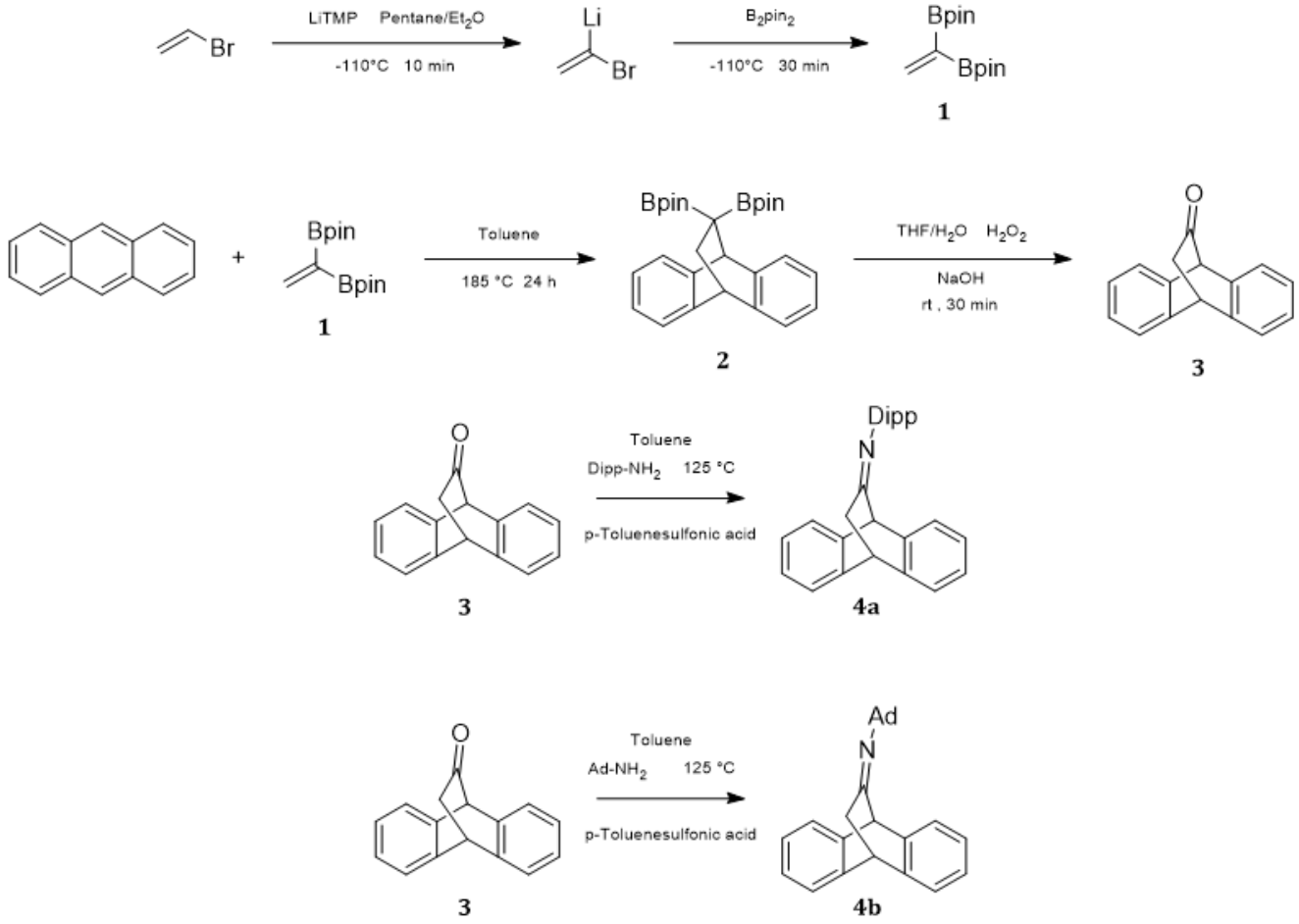
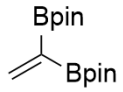


Figure 2: Progress of Synthesis

All current procedures of synthesis are obtained from the supplementary information portion of pre-existing literature.[1] Some portions of the prescribed procedures have been modified and will be reported accordingly.

2 Synthesis of Dienophile (1)

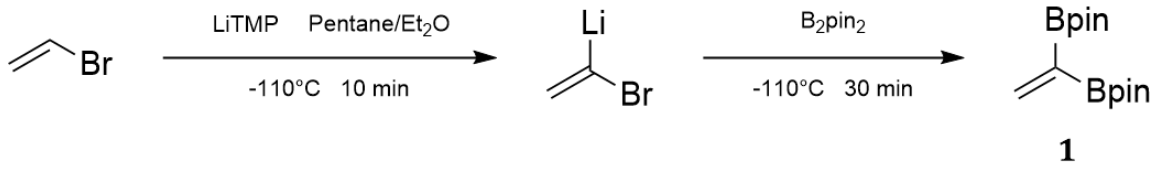
The structure of the Dienophile **1** is given below:



1

Figure 3: Dienophile **1**

2.1 Experimental Procedure



1

Figure 4: Synthesis of **1**

Under argon glove box conditions, solid Bis(pinacolato)diboron (B_2pin_2) (10 g, 40.00 mmol) and solid Lithium tetramethylpiperidide (LiTMP) (8.8 g, 60.00 mmol) were added into seperate Schlenk flasks. The flasks were later transported out of the glove box tightly plugged and connected to a Schlenk line. Then, from a solvent drying-reflux system, 120 ml of dry Et_2O and 30 ml of dry Pentane were injected via syringe and septum into the flask containing B_2pin_2. From the same system, 40 ml of dry Et_2O was injected into the flask containing LiTMP and both flasks were stirred until all solids have dissolved (The B_2pin_2 solution is colorless while the LiTMP solution is opaque light brown). 1.0 M Vinyl Bromide solution in THF (60 ml, 60.00 mmol) was then taken from the fridge and injected into the flask containing B_2pin_2(the reaction flask) via syringe and septum, and the flask was cooled down to -110°C by using an ethanol and liquid nitrogen bath. After keeping the reaction flask at -110°C for 10 minutes, the freshly prepared LiTMP solution from the other flask was added dropwise into the reaction flask via a cannula. Upon addition of the LiTMP solution, the reaction mixture should gradually turn pale yellow. The reaction flask is then left for 30 minutes at -110°C, and then cooled down to room temperature, giving a transparent yellow reaction mixture.

The reaction mixture is then quenched with 100 ml of 10% $NaHSO_4$ solution and 100 ml of water, which brings it to around neutral pH. More $NaHSO_4$ solution may be added until the reaction mix reaches a desired neutral pH. As the 10% $NaHSO_4$ solution is added, some white solids form, making the reaction mix turn slightly opaque. Then, the organic layer is extracted with repeated washings of the aqeuous layer in a seperatory funnel using around 500 ml of Et_2O. The extracted organic layer is then washed with brine solution and dried with $MgSO_4$ powder after the brine solution has been drained. The remaining organic layer is then filtered and concentrated via a rotory evaporator to yield the crude product which is a pale yellow solid. The crude product is purified via silica gel column chromatography using 10% EtOAc in hexane as the eluent. The product **1** is a white solid where the final yield is 72%.

2.1.1 Procedural modifications and Discussion

The literature[1] used a scale of 5.00 mmol of B_2pin_2, but we have used a larger scale of 40 mmol. Nonetheless, the reaction seems to proceed without affecting the yield much. Furthermore, subsequent NMR spectra have shown that B_2pin_2 is still remaining after the reaction is completed. Moreover, the residual B_2pin_2 does not show up in TLC and is difficult to remove from the product mixture although it does not seem to interfere with subsequent reactions. Potentially, the amount of vinyl bromide or LiTMP used could be increased to mitigate this.

2.2 NMR Spectra

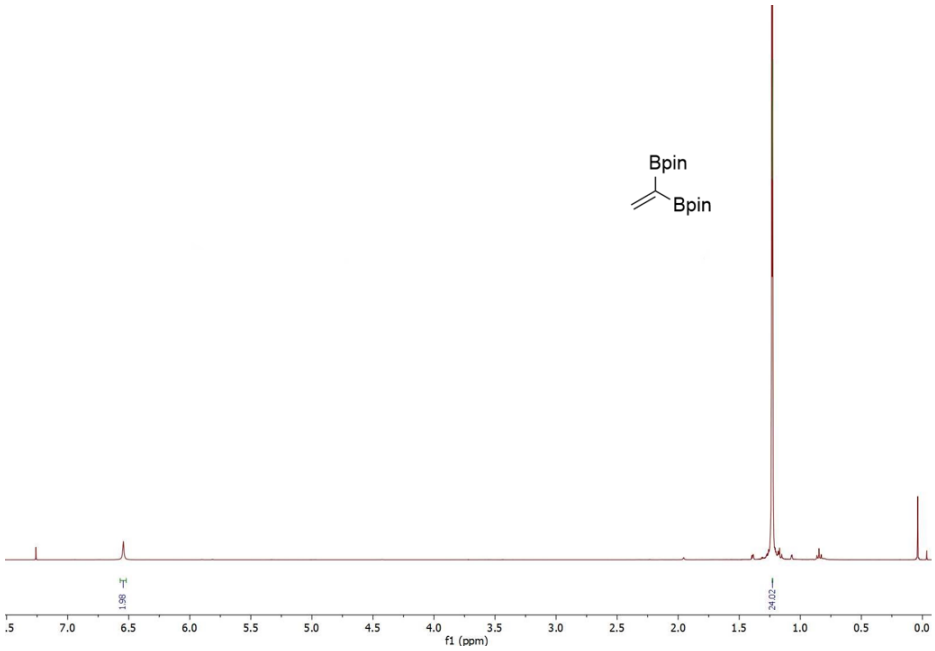


Figure 5: ^{1}H NMR spectra of dienophile **1**

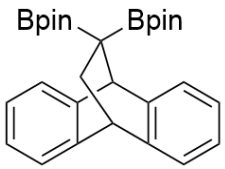
Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.58 (s, 2H), 1.26 (s, 24H).

The 24H singlet at 1.26 ppm corresponds to the hydrogens attached to the methyl groups in Bpin. The 2H singlet at 6.58 ppm corresponds to the hydrogens connected to the double bonded carbon.

A small multiplet at 1.26 ppm is believed to be residual n-hexane that was not evaporated fully. Additionally, the 2 singlets close to 0 ppm are believed to be silicone grease that has entered the reaction mixture. Otherwise, The ^{1}H NMR spectra of the product **1** matches the literature[1] given spectral data.

3 Diels-Alder Synthesis of (2)

The structure of **2** is given below:



2

Figure 6: Product **2**

3.1 Experimental Procedure

1 **2**

Figure 7: Synthesis of **2**

The solid powder form of the dienophile **1** (1 eq, 4 g, 14.60 mmol) and Anthracene powder (1.5 eq, 3.9 g, 21.90 mmol) is added into a pressure tube and the pressure tube was put under inert conditions using a Schlenk line. Then, 150 ml of dry toluene is collected from a solvent drying-reflux system and injected into the pressure tube via syringe and septum. The pressure tube is then sealed and heated up to 185 °C using an oil bath and left to react while stirring for 2-3 days.

After 2-3 days of heating, the reaction vessel is left to cool to room temperature and a white solid will start to crystalize out, this is mostly excess anthracene as verified by NMR. The reaction mixture will be pale yellow and can be decanted or filtered out and the anthracene crystals can be washed with more toluene to extract all the residual crude product. The crude product is then concentrated via rotary evaporator to form a yellow solid. The crude product can be then purified via silica gel column chromatography with 10% Ethyl Acetate in Hexane as the eluent. The final product **2** is a white solid with a yield of 52%.

3.1.1 Procedural modifications and Discussion

The literature[1] reported scale is 0.3 mmol for this reaction, but we have used a much larger scale of 14.60 mmol. The reaction seemed to proceed nonetheless albeit with a reduced yield (52%) compared to the literature[1] reported yield (65%). It is not known why the yield is smaller, potentially due to mistakes in the work-up process.

Additionally, the literature[1] reported reaction time of 24 hours is not achievable as the NMR monitoring reveals that the reaction is still incomplete after 24 hours and will instead take up to 2-3 days. Furthermore, the large excess of anthracene used makes it difficult to isolate the product **2** out of the crude product in the column chromatography. We have deployed a few methods so far to mitigate this:

1. To use 1.5 equivalents (we have also successfully tried 1.2 equivalents) of anthracene instead of the literature[1]-reported 3 equivalents, resulting in a reaction time that is between 2-3 days.
2. Using hexane as the eluent first to flush out the anthracene in the column (because **2** does not seem to move when hexane is the eluent). And when the anthracene is mostly removed from the column, the eluent of 10% EtOAc in Hexane is used to collect the remaining product **2**. However, anthracene is sparingly soluble in hexane and large amounts of hexane (our attempt used roughly 2.5 litres) is required to completely flush all the anthracene down the column.

3. Using a mechanochemical reactor to see if it will shorten the reaction time. However, even after reacting for 2 hours, NMR shows that the reaction is not progressing.
4. Using a Microwave reactor at 80 °C to see if it will shorten the reaction time. However, even after 4-5 hours of reaction, NMR shows that the reaction is not progressing.

3.2 NMR Spectra

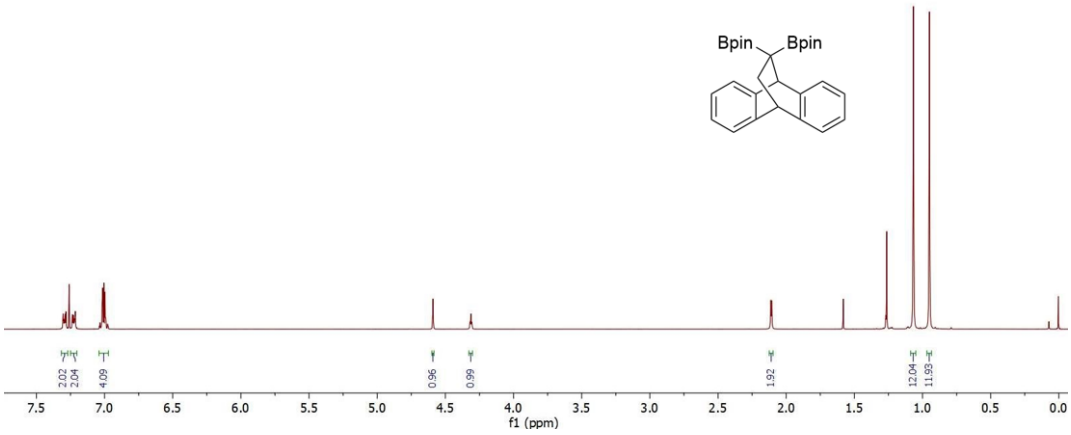


Figure 8: ^{1}H NMR spectra of **2**

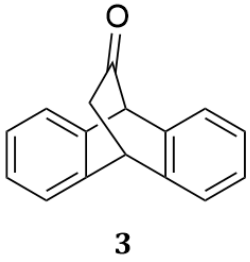
Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.23-7.21 (m, 2H), 7.16-7.14 (m, 2H), 6.94-6.92 (m, 4H), 4.52 (s, 1H), 4.23 (t, J = 2.6 Hz, 1H), 2.04 (d, J = 2.7 Hz, 2H), 0.99 (s, 12H), 0.88 (s, 12H).

Both the 12H singlets at 0.88 and 0.99 ppm are the hydrogens from the methyl groups in Bpin, the difference in shift is caused by the difference in proximity to the aromatic region. The 2H doublet at 2.04 ppm are the hydrogens attached to the carbon adjacent to the carbon attached to B_2pin_2. The 1H triplet at 4.23 ppm is the hydrogen attached to the carbon adjacent to the 2 benzene rings and the alkyl CH_2 carbon. The 1H singlet at 4.52 ppm is the other hydrogen that is also adjacent the 2 benzene rings. The remaining 2H, 2H and 4H multiplets at 7.23-7.21 ppm, 7.16-7.14 ppm and 6.94-6.92 ppm are the hydrogens attached to the benzene rings.

Additionally, the 2 singlets close to 0 ppm are believed to be silicone grease that has entered the reaction mixture. The singlet near 1.25 ppm is believed to be residual B_2pin_2. The singlet near 1.6 ppm is believed to be water that we failed to dry out of the product. Otherwise, The ^{1}H NMR spectra of the product **1** matches the literature[1] given spectral data.

4 Synthesis of Ketone (3)

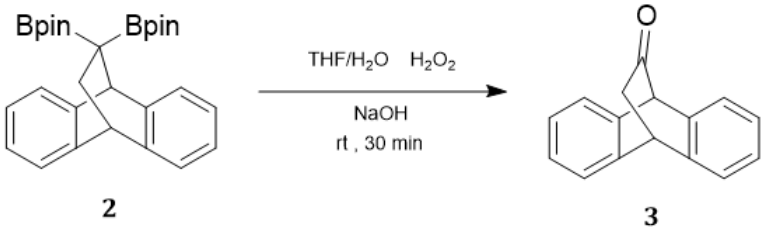
The structure of **3** is given below:



3

Figure 9: Ketone **3**

4.1 Experimental Procedure



2 **3**

Figure 10: Synthesis of **3**

2 g (4.37 mmol) of **2** is added into a flask and dissolved in 90 ml of water and 90 ml of THF (Taken from bottle). Then, 80.8 ml of 30wt% H_2O_2 and 7.3 ml of 3 M NaOH solution (5eq) was added to the flask and the reaction was left to stir at room temperature for 30 minutes. Note that the reaction is time-sensitive, leaving the reaction for a prolonged time will decompose the products.

Then, the reaction mixture is washed with a copious amount of brine (to dry the mixture and to quench the H_2O_2) and the aqeuous phase was washed repeatedly with around 300 ml of CH_2Cl_2 (DCM) via separatory funnel. The final organic layer is dried with $MgSO_4$ powder and then filtered and concentrated via rotary evaporator. The final crude product is a pale yellow liquid.

The crude product can be then purified via silica gel column chromatography with 10% Ethyl Acetate in Hexane as the eluent.

4.1.1 Procedural modifications and Discussion

The literature[1] reported scale is 0.1 mmol for this reaction, but we have used a much larger scale of 4.37 mmol. Since we only have the crude product as of now without any final yield, we have not observed the effects of this change of scale.

The purification step via column chromatography also cannot be perfectly carried out as it is difficult to seperate the product spot and a few other impurity spots. We found that most impurities would move down the column when using hexane as the eluent, leaving behind the ketone product **3**. However, the final isolated ketone still shows some impurities even after performing a hexane run to flush out the impurities. Furthermore, the literature[1] reported the ketone **3** to be a white solid. However, we have isolated yellow crystals instead which may indicate an imperfect purification.

This procedure was also repeated with scales of 3.5 g and subsequently 5.0 g of starting material **2**. The combined yield was calculated to be a low 25% in stark contrast to the literature[1] reported 90%. It is believed that the purification step for **2** was impecfect and left a large residue of B_2pin_2 which caused the yield calculation to be inaccurate.

4.2 NMR Spectra

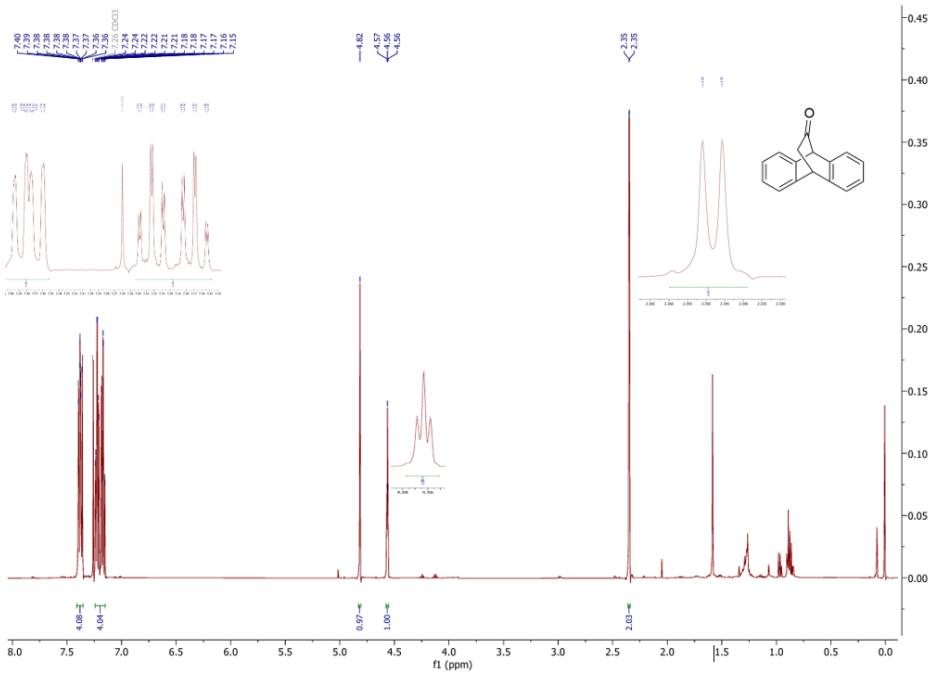


Figure 11: ^{1}H NMR spectra of crude **3**
Spectral data(product only): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 (td, J = 7.3, 0.6 Hz, 4H), 7.26-7.15 (m, 4H), 4.82 (s, 1H), 4.57 (t, J = 2.6 Hz, 1H), 2.35 (d, J = 2.6 Hz, 2H).

The 2H doublet at 2.35 ppm are the hydrogens attached to the CH_2 carbon adjacent to the ketone carbon. The 1H triplet at 4.57 ppm is the hydrogen attached to the carbon adjacent to the 2 benzene rings and the alkyl CH_2 carbon. The 1H singlet at 4.82 ppm is the other hydrogen that is adjacent both the 2 benzene rings and the ketone carbon. The remaining 4H, 4H multiplets at 7.3 ppm and 7.26-7.15 ppm are the hydrogens attached to the benzene rings.

Additionally, the 2 singlets close to 0 ppm are believed to be silicone grease that has entered the reaction mixture. The multiplets near 1.8 and 3.75 ppm are impurities that potentially correspond to residual THF. The large singlet near 1.25 is believed to be residual B_2pin_2 that we find difficult to remove since it does not show up in TLC but fortunately does not seem to interfere with the reaction. The singlet near 5.25 ppm is believed to be residual DCM that we failed to evaporate fully.

Literature[1] reports a 1H singlet at 7.19 ppm but we are not able to locate it from our spectrum. Otherwise, The ^{1}H NMR spectra of the product **1** matches the literature[1] given spectral data.

5 Synthesis of Imine (4a)

The structure of imine **4a** is given below:

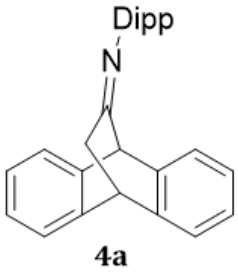


Figure 12: Imine **4a**

5.1 Experimental Procedure

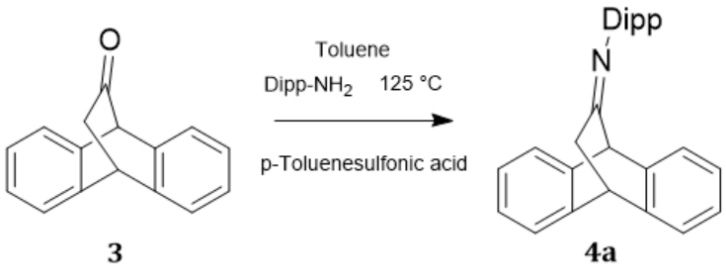


Figure 13: Synthesis of **4a**

Ketone **3** (0.1g , 0.454 mmol), 2,6-diisopropylaniline (0.097 g , 0.545 mmol , 1.2 eq.), a catalytic amount of p-toluenesulphonic acid (0.02 eq.), $MgSO_4$ (3 eq.), and toluene (10-15 ml) were added into a reaction flask to stir at 125 °C under argon atmosphere. Depending on the reaction setup, the time taken for the reaction to complete may vary. As the reaction progresses towards completion, the reaction mixture gradually turns from light reddish-brown to a darker hue of reddish-brown.

5.1.1 Procedural modifications and Discussion

As previously mentioned, this procedure has not been documented yet in any literature. However, we are able to find literature[2] that reports a partially similar procedure that uses a diketone instead of a monoketone like our compound **3**. We have mostly followed the steps provided by the literature[2] with a few exceptions:

1. We have used 1.2 equivalents of 2,6-diisopropylaniline while the literature[2]-reported amount was 3 equivalents.
2. We have used $MgSO_4$ as a drying agent in the reaction mix while this addition was absent in the literature[2]-reported procedure.
3. We have used an argon atmosphere instead of the literature[2]-reported nitrogen atmosphere.
4. We have used a scale of 0.454 mmol of starting ketone instead of the literature[2]-reported 2.0 mmol.

We have tried this reaction in 3 different conditions. Namely, using a pressure tube, a reflux setup and also a Dean-Stark setup. The following summarizes the observations:

Table 1: Observations from different reaction conditions for synthesis of **4a**

Reaction Condition	**Observations**
Pressure tube	After 1 week, reaction progress is Slowest overall.
Reflux setup	After 1 week, reaction progress is faster than the pressure tube setup.
Dean-Stark Setup	After 1 week, reaction progress is fastest overall.

In conclusion, the observations show that using a Dean-Stark setup gives the fastest reaction progress by monitoring the decrease of the size of the reactant peak in the NMR spectra. In the reflux and Dean-Stark setup, the reactant peak decreases in size after a few days of reacting. However, the peak then comes to a halt in change and stays constant even after a whole week of reacting. Because of this, we are unable to confirm whether the reaction comes to completion or not.

The literature[2] reported a reaction time of 24 hours by using a reflux setup. However, our reaction seems to be taking much longer than that. We are not sure why this is the case.

As of July 25, 2024, we have not yet completed the purification of **4a** (literature[2] reports the use of recrystallization for purification) and are unable to report on the yield of the procedure.

5.2 NMR Spectra

The NMR spectra of crude **4a** is given below:

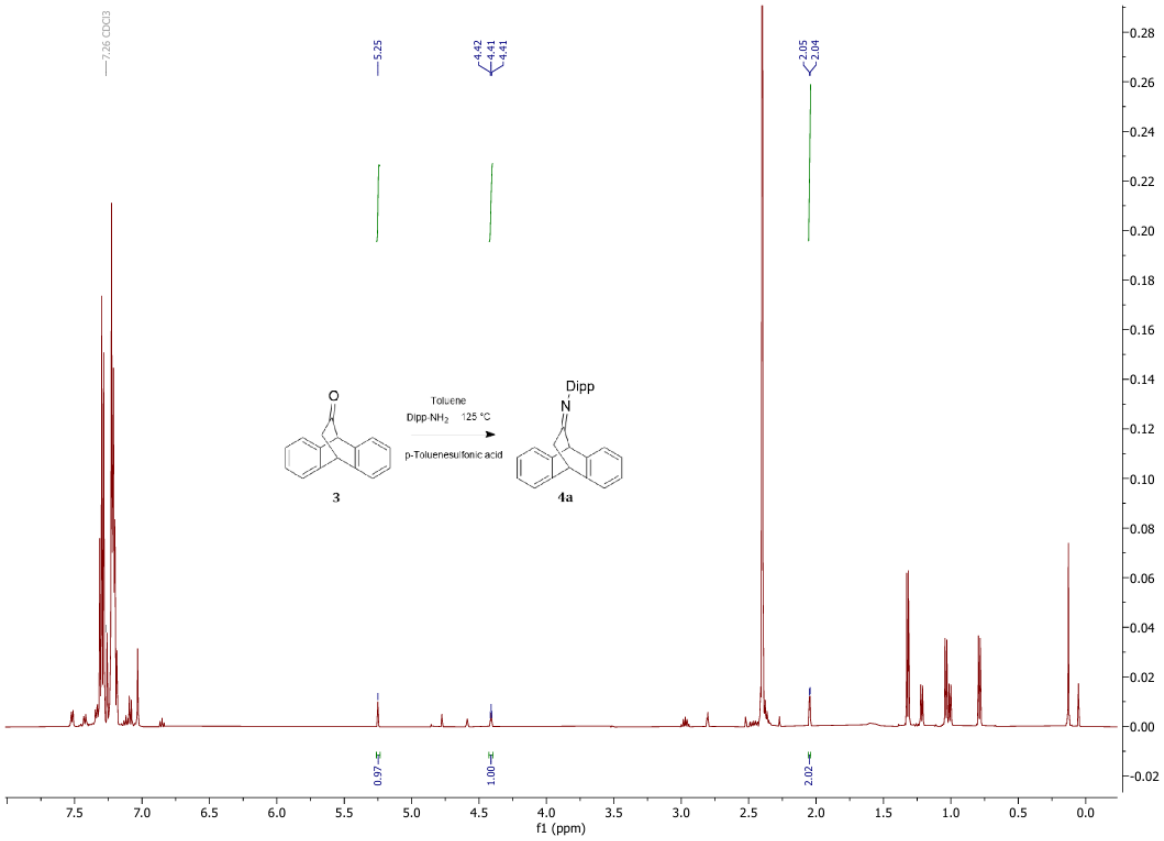


Figure 14: ^{1}H NMR spectra of crude **4a**

The NMR spectrum of the crude product contains many impurity peaks and residual solvent peaks (Toluene is present in a large proportion). This crude NMR spectrum was recorded from the Dean-Stark setup while the reaction was still incomplete, resulting in the presence of our starting ketone **3** and also excess 2,6-diisopropylaniline. Thus, it is not so simple to identify all the peaks of the imine product **4a**. Noting our limitations, we believe we still have managed to identify a few peaks that indicate our imine product:

1. A doublet at 2.05 ppm is believed to correspond to the two hydrogens attached to the carbon that is adjacent to the carbon that is double bonded to the nitrogen atom.
2. A singlet at 5.25 ppm is believed to correspond to the hydrogen atom attached to the carbon that is adjacent to the carbon that is double bonded to the nitrogen atom and also adjacent two aromatic benzene groups.
3. A doublet at 4.41 ppm is believed to correspond to the hydrogen atom attached to the other carbon that is also adjacent the two aromatic benzene groups.

The crystal structure **4a** was obtained via X-ray crystallography and given below:

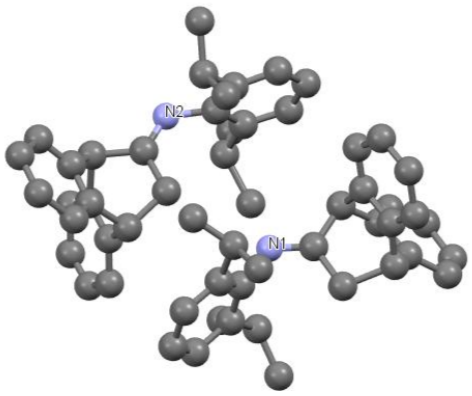


Figure 15: Crystal structure of Imine **4a**

6 Synthesis of Imine (4b)

The structure of imine **4b** is given below:

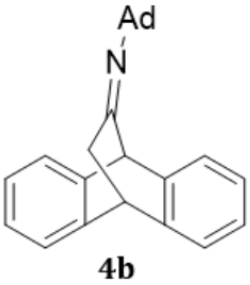


Figure 16: Imine **4b**

6.1 Experimental Procedure

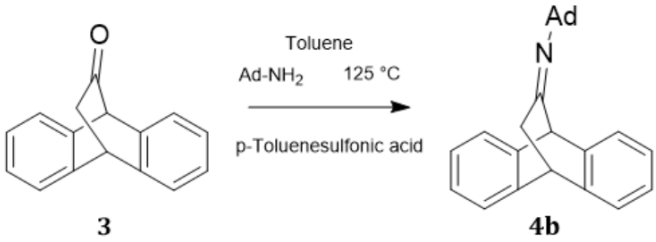


Figure 17: Synthesis of **4b**

Ketone **3** (0.1g , 0.454 mmol), Adamantan-1-amine (0.082 g , 0.545 mmol , 1.2 eq.), a catalytic amount of p-toluenesulphonic acid (0.02 eq.), $MgSO_4$ (3 eq.), and toluene (10-15 ml) were added into a reaction flask to stir at 125 °C under argon atmosphere. Depending on the reaction setup, the time taken for the reaction to complete may vary. As the reaction progresses towards completion, the reaction mixture gradually turns from colorless to light yellow.

6.1.1 Procedural modifications and Discussion

This procedure is similar to the synthesis of **4a** with the exception of using Adamantan-1-amine instead of 2,6-diisopropylaniline. Other than that, all other proportions are similar to the synthesis of **4a**. The usage of Adamant-1-amine in this procedure is undocumented in literature as of now. Furthermore, the literature[2] we are referencing only reported the procedure in which 2,6-diisopropylaniline was used.

After running trials, we have found the formation of **4b** to be slower and more difficult than the formation of **4a**. We have tried the reaction in 3 different conditions. Namely, using a pressure tube, a reflux setup and also a Dean-Stark setup. The following summarizes the observations:

Table 2: Observations from different reaction conditions for synthesis of **4b**

Reaction Condition	**Observations**
Pressure tube	Reaction does not proceed
Reflux setup	Reaction does not proceed
Dean-Stark Setup	After 1 week, reaction proceeds but progress is slow

In conclusion, it is only feasible to use a Dean-Stark setup. Even so, reaction progress is slow and anticipated to take much longer than just a week.

As of July 25, 2024, we have not yet completed the purification of **4a** and are unable to report on the yield of the procedure.

6.2 NMR Spectra

The NMR spectra of crude **4a** is given below:

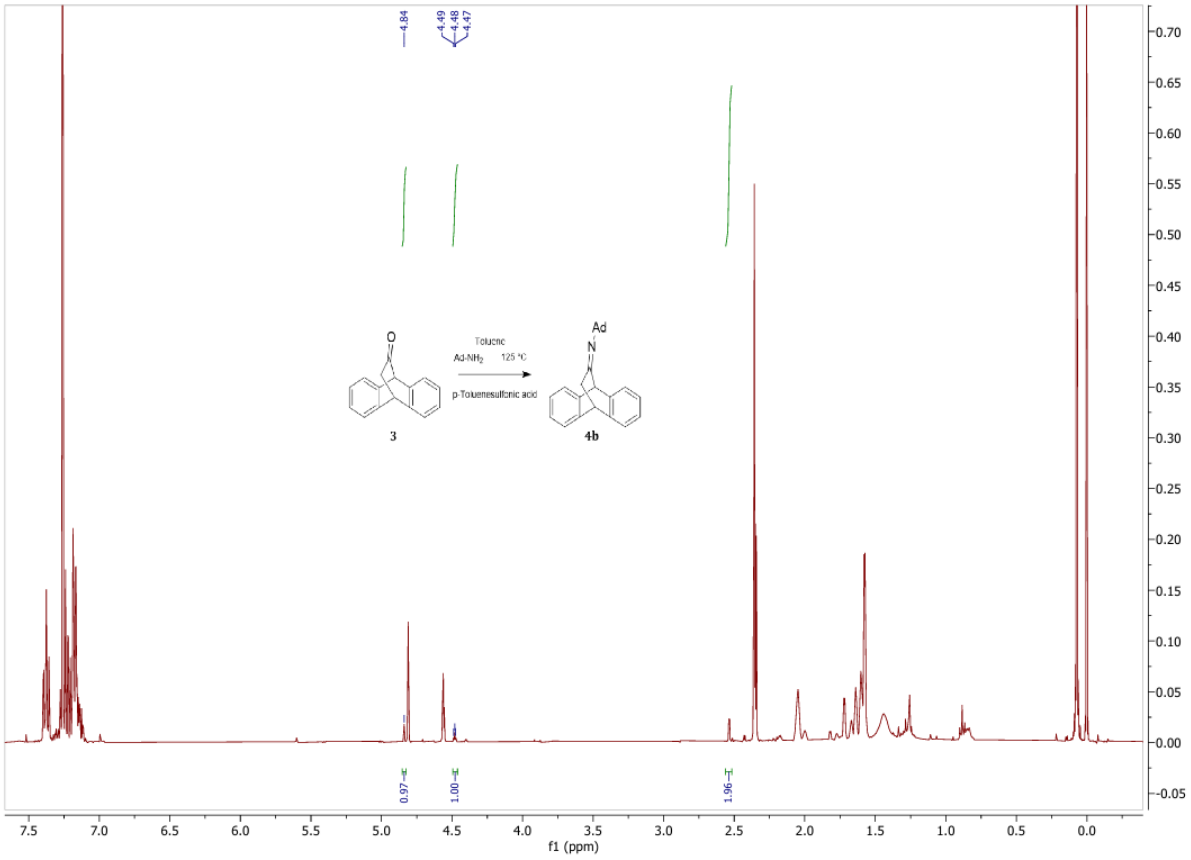


Figure 18: ^{1}H NMR spectra of crude **4b**

The NMR spectrum of the crude product contains many impurity peaks and residual solvent peaks (Toluene is present in a large proportion). This crude NMR spectrum was recorded from the Dean-Stark setup while the reaction was still incomplete, resulting in the presence of our starting ketone **3** and also excess Adamantan-1-amine. Thus, it is not so simple to identify all the peaks of the imine product **4b**. Noting our limitations, we believe we still have managed to identify a few peaks that indicate our imine product:

1. A doublet at 2.54 ppm is believed to correspond to the two hydrogens attached to the carbon that is adjacent to the carbon that is double bonded to the nitrogen atom.
2. A singlet at 4.84 ppm is believed to correspond to the hydrogen atom attached to the carbon that is adjacent to the carbon that is double bonded to the nitrogen atom and also adjacent two aromatic benzene groups.
3. A doublet at 4.48 ppm is believed to correspond to the hydrogen atom attached to the other carbon that is also adjacent the two aromatic benzene groups.

7 Conclusion

For this term of 10 weeks or so, we have been able to synthesize the compounds **1** , **2** and **3** by following the procedures given by known literature[1] with minor modifications. Furthermore, we have also conducted imine synthesis for the compounds **4a** and its variant **4b** by referencing literature[2] that reports a partially similar process. While we have conducted the imine reactions, we have not yet been able to affirm the completion of the reactions and also have not been able conduct a complete purification and the pure NMR spectra. However, we can still confirm the presence of our target imine via X-Ray crystallography.

As of July 25, 2024we have unfortunately yet to be able to reach the desired ligand product of **8a,b**.

Acknowledgements

I would like to show thanks to Professor Kinjo Rei for being accomodative and understanding in my term of CM5071 summer research. I would also like to thank my mentor Ms. Kavita Devi for the support and guidance throughout the entire term.

References

(1) Eghbarieh, N.; Hanania, N.; Zamir, A.; Nassir, M.; Stein, T.; Masarwa, A. *Journal of the American Chemical Society* **2021**, *143*, 6211–6220.

(2) Huo, P.; Liu, W.; He, X.; Wang, H.; Chen, Y. *Organometallics* **2013**, *32*, 2291–2299.