ASILA Victoire

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Internship Report 4C0I1

Development of Copper-Catalyzed Aminothiolation of Dienes with N-Fluorobenzenesulfonimide and Thiols

Academic advisor:

Dr. Anne-Lise DHIMANE

Tutor:

Pr. Yasushi NISHIHARA

Location:

OKAYAMA UNIVERSITY

Professor Yasushi NISHIHARA's laboratory

Division of Earth, Life and Molecular Sciences, Graduate School of Natural Science and Technology
3-1-1 Tsushimanaka, Kita-ku,

Okayama 700-8530, Japan

AKNOWLEGMENTS

This internship was done in one of the laboratory of the faculty of science in Okayama University, Japan.

First of all, I would like to thank Prof. Nishihara for welcoming me in his laboratory, helping me through the administrative procedures that allowed me to come to Japan, supporting me financially and for integrating me into his team. I would also like to thank Dr. Iwasaki, Dr. Mori and all of the laboratory's students who helped me and gave me great advice either in the Chemistry field, in the way to use the laboratory equipments or on the Japanese way of life.

I would like to specifically thank Dr. Iwasaki for guiding me in my research topic, who always have been available when needed, and Ms. Miki who has been of great help when I arrived and took her precious time to help me do all of the necessary official documents I needed to stay in Okayama.

Therefore, I would like to thank the Japan Student Servie Organization (JASSO) for their financial support during the month of March.

Also, I would like to thank all of the Okayama University staff for their availability and their understanding toward me, especially since I don't speak Japanese. Moreover, I would like to thank Japanese citizen for making this internship one of the most incredible experience in my life.

Of course, I would like to thank UPMC, the Chemistry Master and Dr. Dhimane who made it possible for me to come to Okayama and has always been helpful and of good guidance.

Last but not least, I would like to thank deeply my family and my friends who supported me all along this journey.

SUMMARY

INTRODUCTION

Okayama University is a top-class national university in Japan with over 140 years of history. It has 11 faculties, 7 graduate schools and various programs (Figure 1).[1]

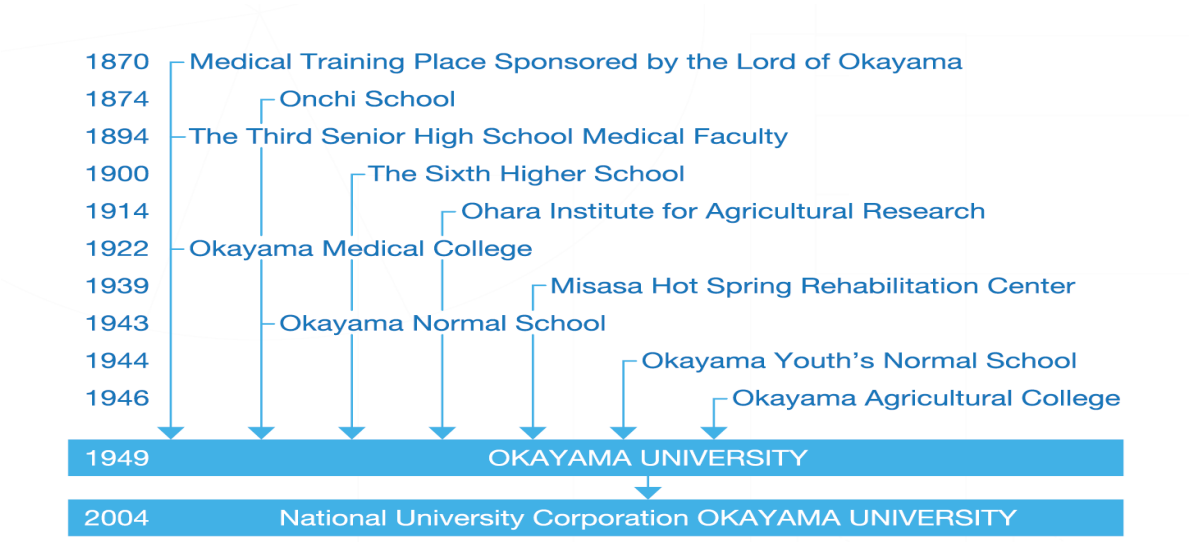


Figure 1: History of Okayama University

13000 students are enrolled in this University including approximatively 600 international students. Indeed, 1600 teachers and staff are engaged for the "Creation of advanced knowledge and inheritance of precise knowledge."[1]

Prof. Nishihara's laboratory is the functional organic chemistry laboratory of the faculty of science of the university and intends to the development of synthetic organic reactions catalyzed by organometallic complexes and their application to functional materials. More detailed by using transition-metal catalysts, they develop organometallic reagents which show interesting reactivities and selectivities different than the ones conventionally observed in chemistry. These reagents would be used for the development of new carbon-carbon bond formation reactions which is a basis for synthetic organic reactions. As it is explained on their website they are also working on the development of: « environmentally friendly reactions for "Green Chemistry" which is one of the most important task for chemists in the 21th century. »[2][3]

As for my research subject, the difunctionalization of dienes is historically an attractive method to install molecular complexity into simple and abundant molecular structures. Despite the prevalence of these transformations, the ability to introduce nitrogen and sulfur functional groups is an enduring challenge due to their diverse

and conflicting reactivity. Such a transformation would find greater applications in the medicinal and material sciences fields.[4]

My main goal is to conduct copper-catalyzed aminothiolation reactions with N-fluorobenzenesulfonimide and thiols and then to demonstrate that the reactions proceed through a radical pathway.

First, I will introduce my laboratory and more precisely my research subject. Then, I will present my work by explaining the conducted experiments Following that, I will present my results and analyze them. Finally, I will conclude this internship report by answering the problematic posed by this subject.

I. Presentation of the Internship

1) Presentation of the laboratory

The Nishihara's laboratory is the functional organic chemistry laboratory of Okayama's University It has eighteen members (myself included) and the team is currently composed of Professor Nishihara, 2 Assistant Professors Iwasaki and Mori, 3 Ph.D's students, 6 master's students, 4 undergraduate students and me as a temporary special research student. In fact, the laboratory is subdivided in two laboratories (Figure2):

- laboratory 1 under Dr. Iwasaki supervision. It is specialized in catalytic synthesis and 7 students are working there (including me).[2]

- laboratory 2 under Dr. Mori supervision. It is specialized in organic polymers synthesis and characterization. Actually, 7 students are working there.

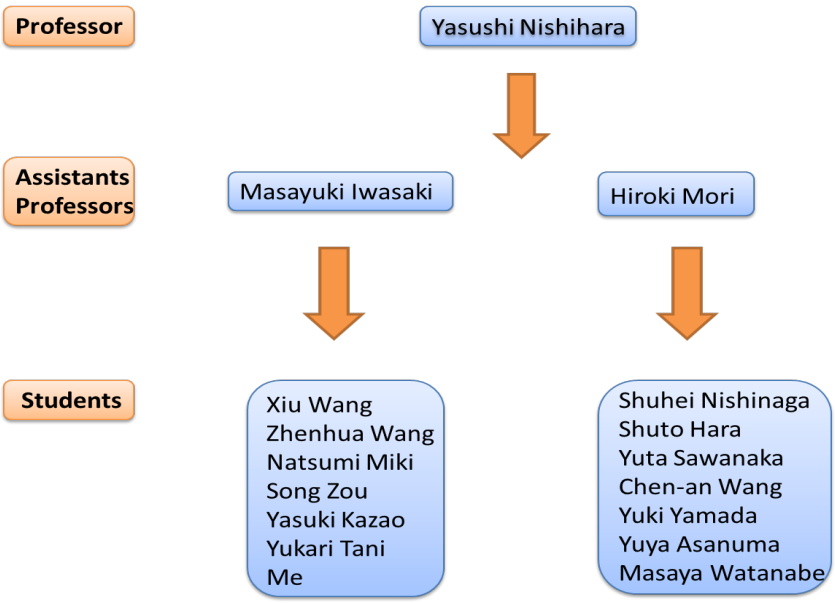


Figure 2 : Organization Chart of the Nishihara's Lab

In these laboratories, they are working on the development of new synthetic organic reactions and methodologies by means of organometallic compounds toward new types of organic molecules and polymers for functional materials, for example, solar cells. They have a particular interest in catalytic coupling reactions with good regio-, stereo-, and chemoselectivities to construct carbon-carbon bonds and are aiming at the activation of various unreactive chemical bonds.[3]

The whole team is very dynamic and is trying to be as much productive as possible. Indeed, every two weeks each member of the laboratory has to submit a BWR which is a report of the work carried out over the last two weeks. During a meeting they discuss with the professors about their latest advances and their future plans.

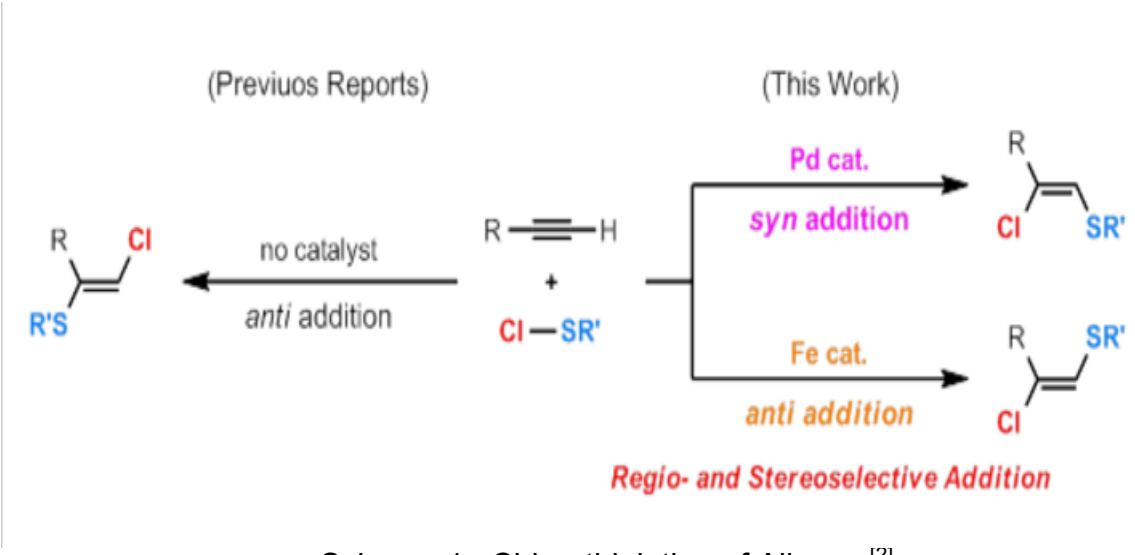
Moreover, each student has to be aware of the latest finding concerning their research subject. Then, once a month they have to choose interesting articles and present them to the team.

Finally, Nishihara's team is committed to seek for reactions that can afford 100% atom efficiency. Furthermore, they strictly regulate the use of compounds and their recycling process so as to respect the principles of Green Chemistry.[2]

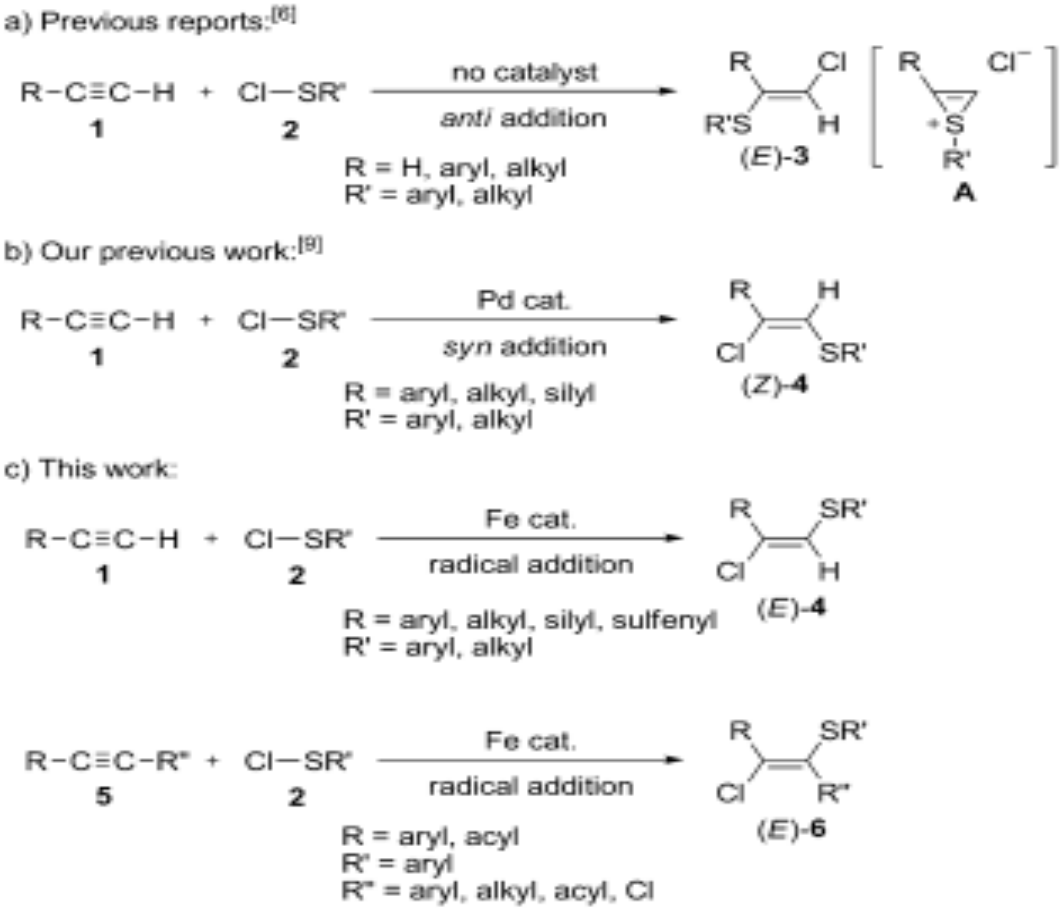
2) Introduction to the Research Topic

My research topic is about aminothiolation of dienes. Before getting interested in this particular reaction, the laboratory explored other types of difunctionalization reactions, for example, the transition-metal-catalyzed regio- and stereoselective halothiolation of alkynes or the transition-metal-catalyzed aminothiolation of alkenes.

Indeed, in 2014, the laboratory published two papers about the halothiolation of alkynes. They were able to reveal that transition-metal-catalysts could control the selectivity of the chlorothiolation of alkynes with high selectivities (Scheme 1 and 2).

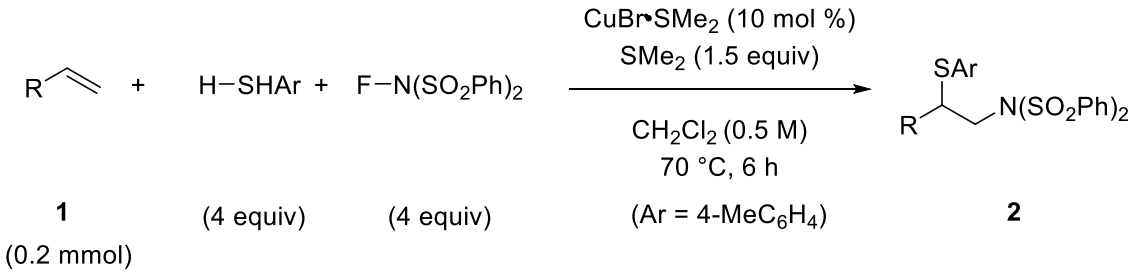


Scheme 1 : Chlorothiolation of Alkynes[2]



Scheme 2 : *Iron-Induced Regio- and Stereoselective Addition of Sulfenyl Chlorides to Alkynes via a Radical Pathway.* [5][6]

More recently they worked on the aminothiolation of alkenes (Scheme 3). Mr. Zou achieved the reaction of styrene (**1a**, R= Ph) to give product **2a** in 89% yield. Then they were able to prove that the reaction proceed through a radical pathway. They are currently working on expanding the substrate scope of the reaction and find ways to further optimize it.



Scheme 3 : Aminothiolation of Alkenes

Actually, my research is really similar to the previous one. The main difference being that I work with dienes and not alkenes. Thereby, I started my work with all the previous informations.

II. Working Process and Experimental Procedures

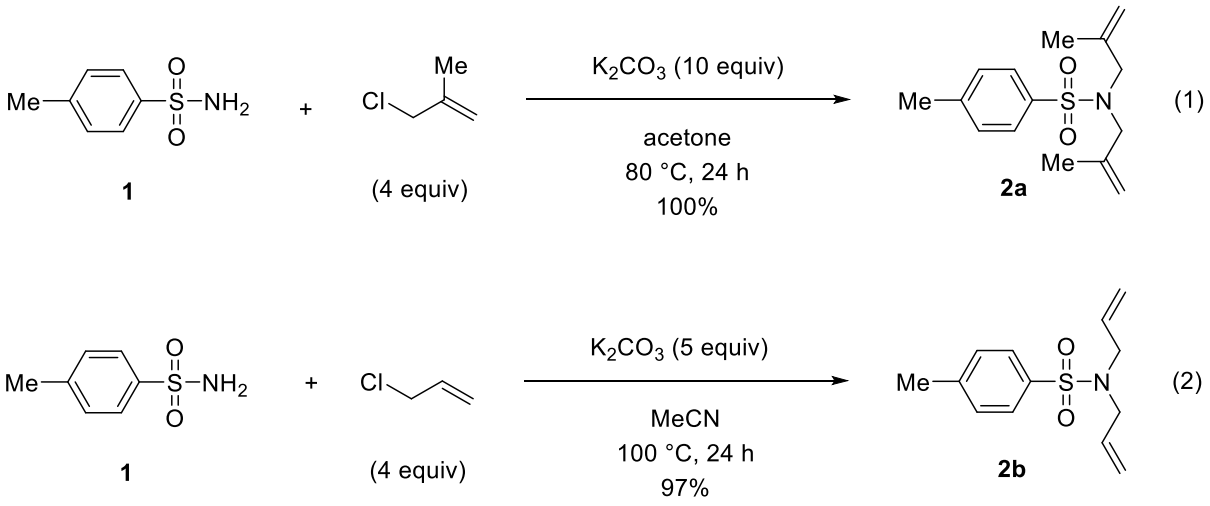
1) Preparation of Starting Materials

For my first experiments in the laboratory I was asked to prepare starting compounds.

Thus, I carried out synthesis of two dienes which are 4-methyl-N,N-di(2-methylallyl)benzenesulfonamide (**2a**) and N,N-diallyl-4-methylbenzenesulfonamide (**2b**) as shown in equation 1 and 2.

As a result, product **2a** was obtained in 100% yield (439.5 mg) as a colorless oil after a silica gel column chromatography. The purity of **2a** was confirmed by TLC analysis with hexane:ethyl acetate (5:1) as an eluant and by ^{1}H NMR spectroscopic analysis. In addition, product **2b** was obtained in 97% yield (4426.7 mg) as a colorless oil after two silica gel column chromatography. After the first purification, a yellow oil was obtained, which is different from what was reported in the paper. Although TLC analysis showed the single spot, a further purification was conducted with column chromatopraphy. I was not sure of the purity of **2b** because the reference shows that **2b** should be colorless.

The allylation of tosylamide (**1**) proceeded very efficiently. The only thing I had to be carefull about was to make sure to keep the reaction under an argon atmosphere. The isolation process was also quite easy since there was almost no impurities in the reaction mixture. :

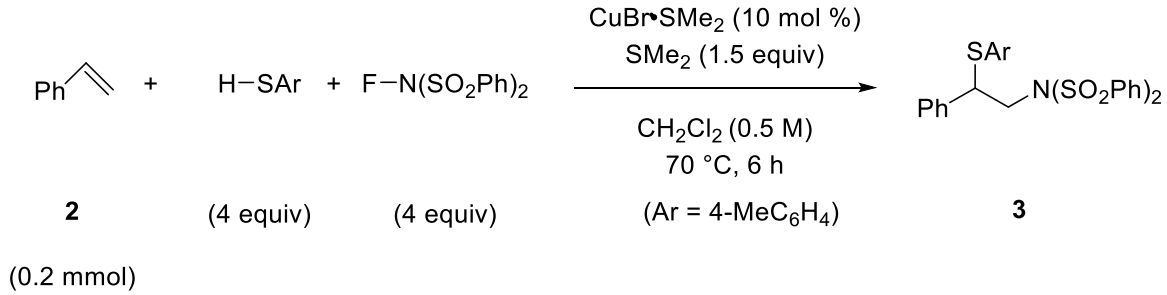


Scheme 4 : Preparation of Starting Materials **2a** and **2b** [7][8]

2) Aminothiolation of Dienes

A) Ring-Closing Aminothiolation of Dienes

After preparation of starting materials, I had to carry out a reproducible experiment. I conducted aminothiolation of styrene (**2**) (Scheme 5).

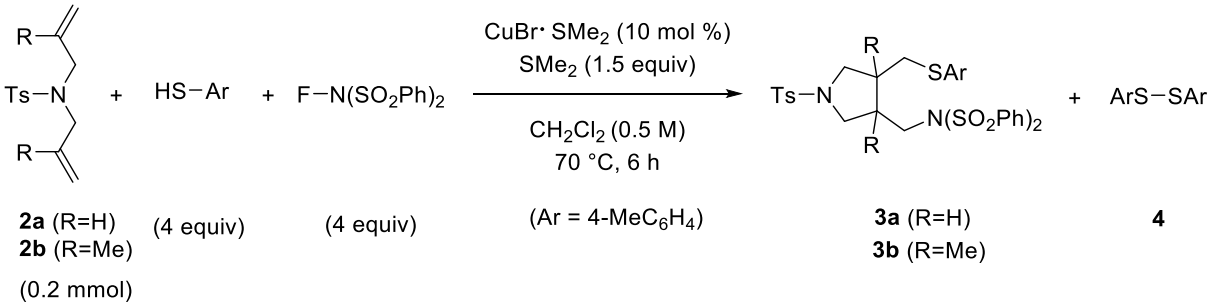


Scheme 5 : Reproducible Experiment

Previously, Mr. Zou reported that the targeted product **3** was obtained in 89% isolated yield. When I tried to reproduce the reaction a first time and the product **3** was only obtained in 45% NMR yield. The same reaction was conducted again, but the yield was decreased to 34% NMR yield. Since the yields were really low compared to the one reported by Mr. Zou, I tried to figure out why the results were not as good as expected. First possible reason was the solvent volume. Indeed, Mr.Zou conducted the reaction with 0.5 mL of CH_2Cl_2 but I used 1 mL of the solvent. Second possible reason was the formation of byproduct, disulfide, due to oxidation. We concluded that we had to avoid incoming air inside the reactor. Moreover, the catalyst used in this reaction is really sensitive to oxidation.

After decreasing solvent volume to 0.5 ml and avoiding air from the reaction flask, the reaction was carried out. Finally, the desired product **3** was obtained in 100% NMR yield.

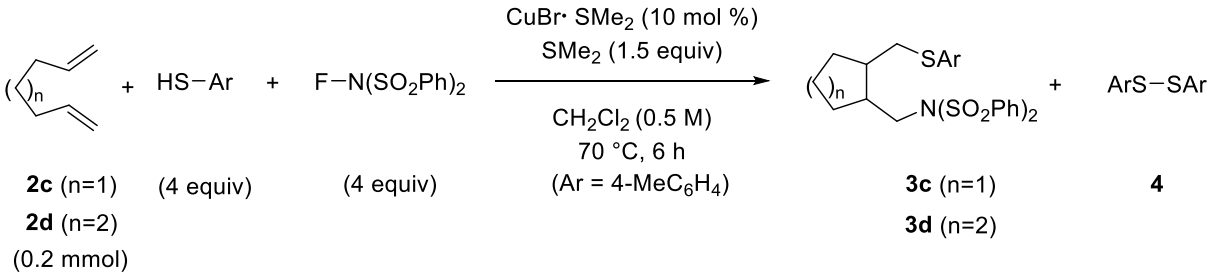
After the reproducibility of the reaction of styrene **2** was confirmed. I used the synthesized dienes **2a** and **2b** to carry out the aminothiolation with NFSI and p-toluenethiol (Scheme 6). We expected ring-closing aminothiolation of dienes proceeds in the presence of a copper catalyst through a radical pathway to give compounds **3a** and **3b**.



Scheme 6 : Aminothiolation of **2a** and **2b**

The reaction of diene **2a** was conducted. After separation of the crude mixture by silica gel column chromatography with CH_2Cl_2 : hexane (1:2) as the eluant, ^{1}H NMR measurements and mass spectroscopy revealed that the targeted product **3a** was not generated. Neither experiments with 0.5 mL or 1 mL of solvent did not give **3a**. Next, the diene **2b** was employed. 1 mL of solvent seemed to give better results than 0.5 mL of solvent from ^{1}H NMR analysis of the crude mixture. The reaction provided the desired adduct **3b** and disulfide in 6% and 37% NMR yield, respectively. Nevertheless, the product still needs further purification because even after two columns there are still some remaining impurities. Fully characterization of **3b** is ongoing.

Later, the reaction of 1,6-octadiene (**2c**) and 1,6-heptadiene (**2d**) were investigated (Scheme 7). Under the identical reaction conditions aminothiolation of diene **2c** did not give the product **3c** and disulfide **4** was only detected. On the other hand, reaction of **2d** gave the product **3d** in 13% NMR yield, along with disulfide 4 in 32% yield. It seemed that the yield with 1 mL solvent was better than the one with 0.5 mL. However, the product is still under purification.



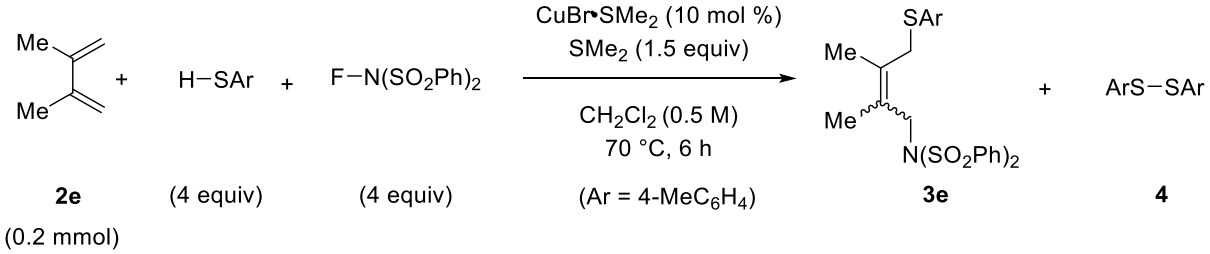
Scheme 7 : Aminothiolation of **2c** and **2d**

B) Aminothiolation of Conjugated Dienes **2e** and **2f**

Since ring-closing aminothiolation products seemed to be hard. We focused on aminothiolation of conjugated dienes.

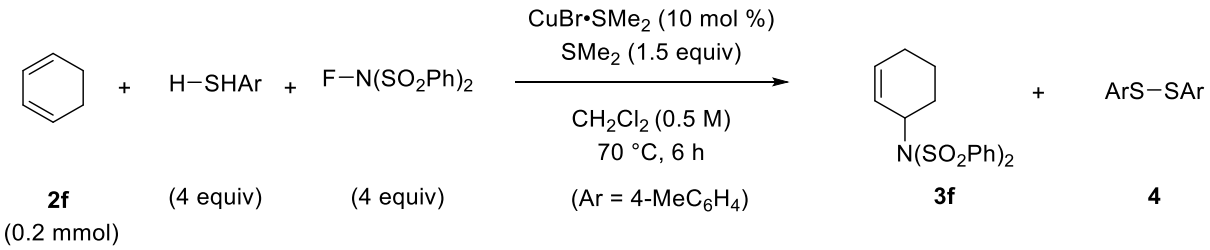
First of all, I carried out the reaction of 2,3-dimethyl-1,3-butadiene (**2e**) as a starting material. After two silica gel column chromatography, the first one with CH_2Cl_2 : hexane (1:2) and the second one with CH_2Cl_2 : hexane (1:3) as the eluent, it was not pure yet. Disulfide **4** was isolated in 34% yield as a byproduct. Further purification was performed by HPLC and **3e** was finally isolated in 9% yield which is a 2.6:1 mixture of isomers.

This is the only example where the desired product was isolated out of all the aminothiolation reactions carried out from now. Since the yield is quite low, further optimization of reactions conditions is necessary.



Scheme 8 : Aminothiolation of **2e**

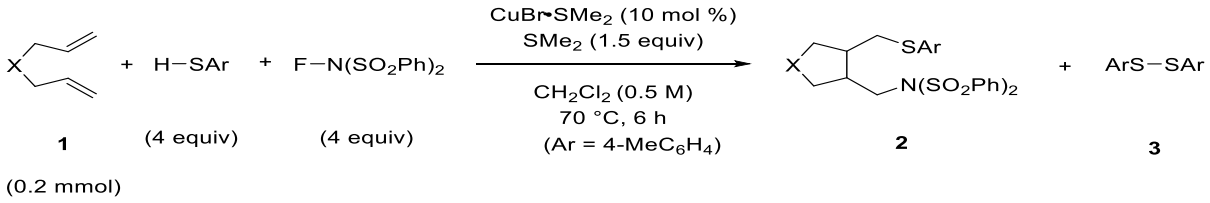
The same reaction was carried out with cyclohexadiene (**2f**) as a starting material (Scheme 9). As a result, the desired product **3f** was obtained in 44% NMR yield. Purification by silca gel column chromatography did not give the pure compound. Further purification is needed to identify **3f**. Simultaneously, disulfide **4** was obtained in 29% yield



Scheme 9 : Aminothiolation of **2f**

III. Results : Analysis and Interpretation

The results of ring-closing aminothiolation of dienes are summerized in table 1.



		NMR yield (%)	
entry	X (**2**)	**3**	**4**
1	NTs (**2b**)	6	45 (37*)
2	CH_2CH_2 (**2d**)	13	— (32*)

* Isolated yields are shownin parentheses.

Table 1 : Aminothiolation of Dienes **2b** and **2d**

The reaction might proceed through a radical pathway as shown in figure 3. First of all, through a single electron transfer, a nitrogen-centered radical specie is generated from NFSI. Then the formed radical specie attacks the more reactive position of the diene to generate a carbon centered radical. Subsequently, 5-exo cyclization provides an alkyl radical, which reacts with thiol to give the product.

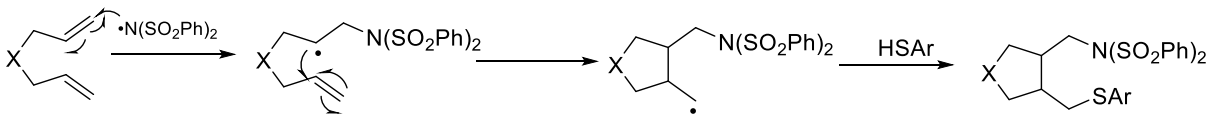


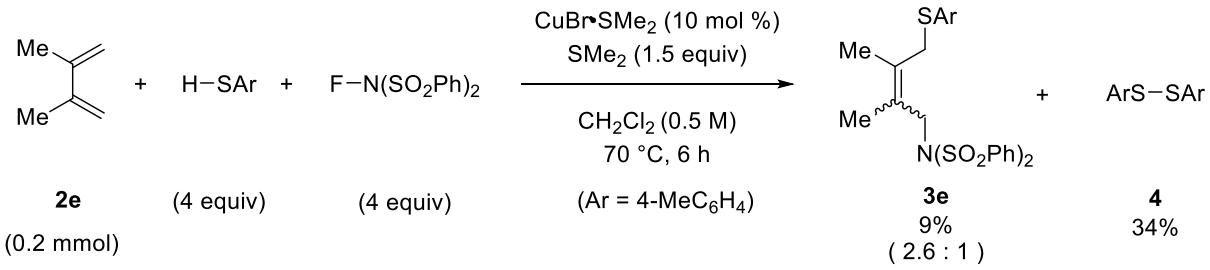
Figure 3 : Possible Radical Pathway

^{1}H NMR analysis revealed that the targeted products were obtained, but it is hard to isolate them even after several purifications above mentioned. At present, therefore, the product yields were not determined. In addition, the formation of a plenty amount of disulfide as a byproduct was confirmed. Effort to decrease the amount of disulfide

by preventing air from the reaction mixture, which would act as an oxidant, did not give better results. In fact, the undesired side reaction occurs because NFSI does not only acts as an amination reagent but also as an oxidant. Hence, it is difficult to avoid the formation of disulfide in the present reaction system.

During investigation to improve the product yield, the solvent quantity was found to have a significant impact on the product yield. Indeed, the reactions shown in table 1 gave better results with 1 mL of solvent than with 0.5 mL. The reason why it has such an impact is not clear yet.

The obtained results lend us to focus on aminothiolation of conjugated dienes which did not involve the cyclization process. The reaction pathway would be similar to the one above mentioned. Fortunately, the desired product **2e** was isolated in 9% yield (Scheme 10). Moreover, ^{1}H NMR analysis confirmed the presence of stereoisomers in the proportions of 2.6:1. 2D NMR measurement is neccesary to know which regioisomer is mejor product. We propose that the reaction proceeds through radical pathway. Further experiments such as radical clock experiment is needed to confirm the radical mechanism.

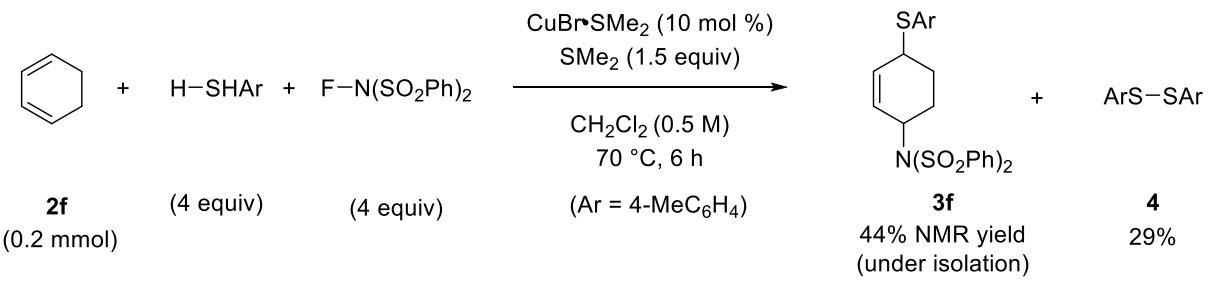


Scheme 10 : Aminothiolation of Diene **2e**

In the same idea, the reaction of diene **2f** was investigated (Scheme 11).

NMR analysis revealed that the desired product **3f** seemed to be formed, but full characterization of **3f** has yet to be achieved due to the contamination of impurities. Although the solvent was dried out from the reaction mixture for better visibility on the NMR chart it did not change a lot. When the internal standard in the NMR sample was changed from dibromomethane to dibenzyl ether to identify some characteristics signals of **3f**, NMR yields was drastically decreased, which did not correspond to the one obtained from dibromomethane.

Therefore, I decided to reproduce this experiment to see if the same results are obtained again and if further purification is needed. If the second run does not give reasonable results I better consider investigation of other dienes.



Scheme 11 : Aminothiolation of Diene **2f**

Achieving these reactions lies on several factors, but the catalyst employed is one of the most important factors. CuBr•SMe_2 was used in the present reaction, which is widely used to generate organocopper reagents (for example, for the addition of alkyl, alkenyl, and aryl Grignard reagents to fullerenes). The catalyst It is formed by the reduction of copper(II) bromide with sulfite. It should not be kept under reduced pressure, as it will lose the sulfide ligand and the copper(I) is easily oxidized in air.

I tried to figure out how the copper catalyst could react and catalyze the present reaction. Taking the mechanism of aminothiolation of alkenes as an example, we propose reaction mechanism for the synthesis of **3e** as shown in scheme 11:

First of all, a nitrogen-centerd radical species is generated through a single electron transfer from copper(I) to NFSI. Simultaneously, the fluoride anion combines with the formed copper(II). Subsequently, the amyl radical reacts with diene to generate a carbon-centered radical species. The generated secondary allyl radical undergoes isomerization to give less-hindered primary allyl radical intermediate, from which recombination with copper(II) complex to give a copper(III). Finally, ligand exchange between fruoride and thiol, followedby reductive elimination provides **3e** and regenerates the initial copper(I) species.

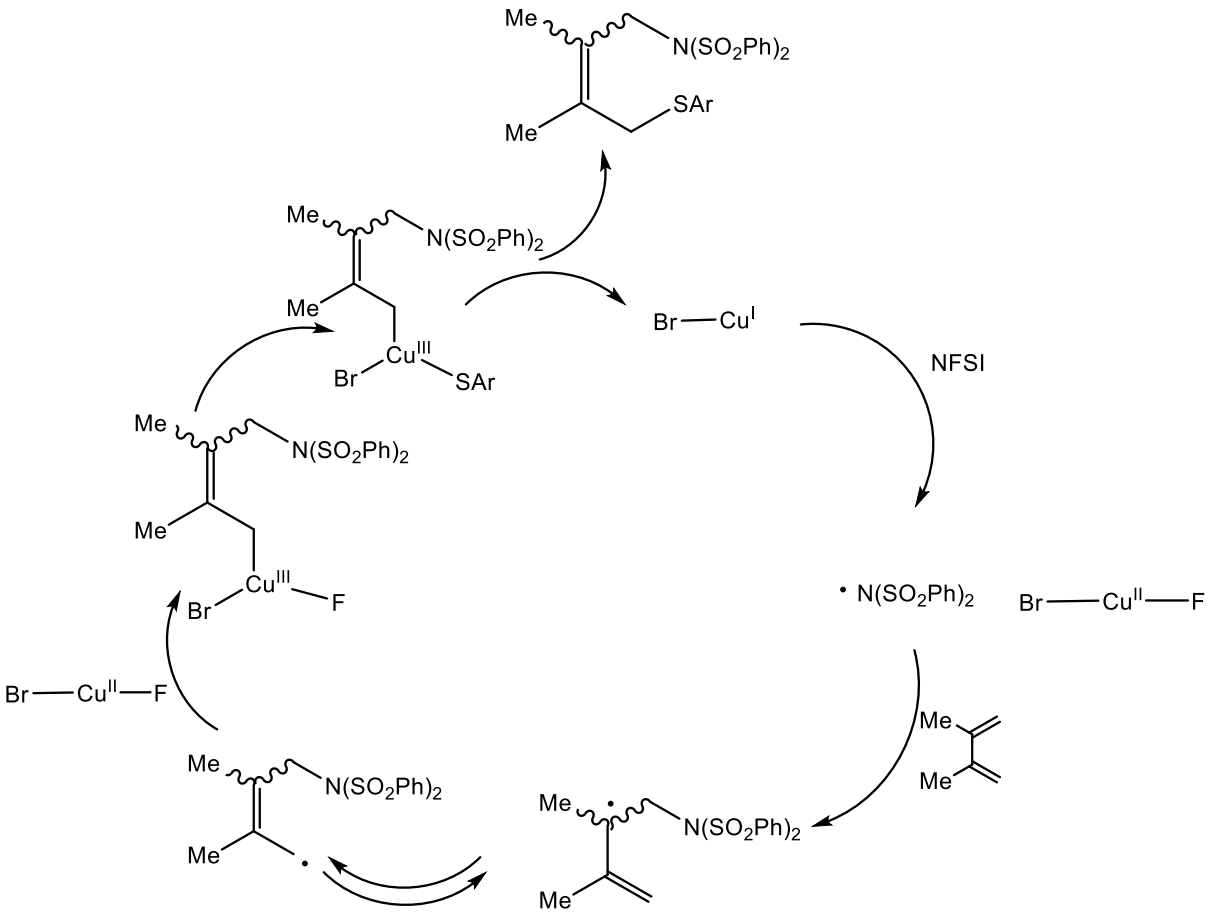
Then the amino radical reacts with the diene to generate a radical specie which through re-arrangments gives an alkene radical specie.

Next, by oxidative addition it bonds to the copper II complex to give a copper III complex.

Then there is a ligand exchange between the Fluor anion and the aryl sulfide.

Finally, through reductive elimination **2e** is created and our copper catalyst form the beginning is regenerated.

Making as a hypothesis that the reaction proceed through a radical pathway this could be a possible mechanism.



Scheme 12 : A Proposed Reaction Pathway

CONCLUSION

The goal of my internship is, for now, to carry out aminothiolation of dienes. So far, I carried out the reaction of seven different dienes, including two dienes prepared by myself.

Concerning reproducible experiments, I was able to achieve good yields and the aminothiolation of alkenes helped me to identify the limiting factors.

Furthermore, during investigation of new reactions, even though I tried a lot of different experiments, only few of them were successful.

I still do not have all the keys to understand why some of the reactions worked better than the others but I learned that exploring unknown reactions is always a difficult task. To this end, I need to conduct further research and experiments. Hopefully, I will find some interesting transformations by the end of my internship.

Besides, I gained a lot of ability thanks to this internship. I learned how to use different analytic techniques and I am more at ease in a laboratory thanks to the laboratory members.

I developed my scientifical knowledge in a dynamic team and I adapted quite well to laboratory life. Indeed, in Japan students are encouraged to develop their practical skills in chemistry. They spend more time in the laboratory than in classes compared to us in France.

I also learned how to cope with the failures and how to keep going on because this is the daily life of a researcher.

Moreover, I developed my ability to read scientifical papers, present the results, and discuss about them.

Not only in the scientific field but in general this internship allowed me to have a personal growth.

Living in a foreign country alone which culture is so different from mine required to adapt quickly to the new environment. In this country I was able to travel and discover a lot of different landscapes all following the Japanese tradition.

I was reassured by the fact that having an experience in a foreign country is clearly an advantage for a student.

Last but not least, even though I am far from my objectives, I am currently doing my best to develop my knowledge in Japanese language so that even after my return in France I can keep on learning and gain a new ability.